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Correlates of chronic hepatitis B virus infection in the general adult population of China: Systematic review and meta-analysis

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Abstract

Chronic infection with hepatitis B virus (HBV) is a significant public health issue in China. Understanding factors associated with chronic HBV is important to enable targeted screening and education and to improve early diagnosis and prevention of disease progression. This systematic review and meta-analysis aimed to identify and describe correlates of chronic HBV among Chinese adults. Searches were conducted in MEDLINE, EMBASE and grey literature up to 25 June 2020. Eligible papers included observational studies in adults of the general population in China that reported factors associated with chronic HBV, measured by Hepatitis B surface antigen (HBsAg). Meta-analysis was performed using fixed-effect models of HBsAg prevalence among factors, and of adjusted odds ratios (ORs) for chronic HBV associated with each factor. Overall 39 articles were included, covering 22 factors, including a range of sociodemographic, behavioural and medical factors. In meta-analysis of eligible studies, a range of factors were significantly associated with higher HBsAg prevalence, including middle age, male sex, being married, rural residence, lower education, smoking, having a HBsAg positive household contact, family history of HBV, history of surgery or blood transfusion. The adjusted ORs varied, from 1.11 (95% CI 1.05–1.18) for

smoking to 5.13 (95% CI 4.99–5.26) for having a HBsAg positive household contact. In Chinese adults, a range of factors are associated with chronic HBV infection, which may help inform targeted screening in the general population.

KEYWORDS
China, chronic hepatitis B infection, hepatitis B surface antigen, prevalence, risk factors

1 | INTRODUCTION

Hepatitis B virus (HBV) is one of the most common chronic viral infections in the world, affecting 240 million people globally.[1] China has the highest burden of chronic HBV infection in the world,[1] despite progress in controlling HBV, largely through vaccination of newborns being freely accessible since 2005.[2] It is coined a 'silent epidemic', due to its high disease burden and prolonged asymptomatic disease course, compounded by lack of screening, diagnosis and education.[1] Among adults with chronic HBV, up to one in four will progress to cirrhosis or liver cancer,[2,3] and an estimated 10 million people living with HBV in China will die by 2030 from largely avoidable liver cancers.[4]

In order to eliminate chronic HBV infection as a public health threat in China, increasing the rate of diagnosis from the current status (19% of cases diagnosed) to the World Health Organization's target of 90% by 2030 is a key priority.[5,6] Although several chronic hepatitis B correlates have been reported in past studies,[7–11] many are constrained by relatively small sample size,[12–16] limited geographic areas[10,12,17–19] or breadth and depth of the risk factors selected.[14,15,17,20–22] Consequently, there is still uncertainty about the relevance, both qualitatively and quantitatively, of a range of factors in relation to chronic HBV infection among adults in China. In China, up to half of HBV transmission occurs at birth from mother to child or horizontally in early childhood[23]; however, it can also occur via horizontal transmission routes later in life. Given the temporality between chronic HBV infection and 'risk factors' is often unclear, we refer to these as 'factors' or 'correlates' in this review. Appropriate understanding of correlates of HBV chronicity can help inform targeted education and testing, to increase the diagnosis rate and capture infected individuals on the chronic HBV care continuum so they can be monitored and treated. Through conducting a systematic review and meta-analysis of published studies, this paper aims to identify and assess correlates of chronic hepatitis B infection in the general adult population of China.

2 | METHODS

2.1 | Search strategy

This systematic review follows the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines[24] (eTable 1; PROSPERO registration: CRD42020197502). In June 2020 we searched Medline, Embase and grey literature sources for studies published from 1992 to 25 June 2020. In collaboration with a librarian, we developed a literature search strategy related to 'hepatitis B', 'China', 'risk factor' and 'prevalence' (eTable 2 for search strategy) and used filters for observational studies as specified by the Scottish Intercollegiate Guidelines Network (SIGN).[25] All identified references were stored in Endnote and Covidence software.[26]

2.2 | Inclusion and exclusion criteria

Observational studies on adult participants of the general population in mainland China were included, where at least one factor in relation to chronic HBV as measured by Hepatitis B surface antigen (HBsAg) was reported. Adults were defined as ≥15 years given many studies categorized age groups from ≥15 years, and studies including children were eligible if adult-specific estimates could be extracted. Studies using the same serosurvey were eligible if they reported data from a different timeframe, location, or additional chronic HBV correlates—otherwise the largest study was included. No language restriction was applied (eTable 3 for detailed criteria).

2.3 | Selection procedure, data extraction and quality assessment

Two reviewers (EH, WR) screened all articles and performed full text eligibility assessment. At least two authors (EH, WR, AS) independently extracted qualitative (study methodology details; characteristics of study population; correlates reported, measurement of HBV; statistical methods), and quantitative data (number of participants; categorization of correlates; HBsAg prevalence; effect estimate; variables included in multivariable model). Quality assessment (EH, AS) was conducted using a modified Newcastle Ottawa Scale[27] (NOS) (eTable 4) for assessing quality of nonrandomized studies, which assesses quality under three domains: selection, comparability, and outcomes. Articles were scored as 'good', 'fair' or 'poor' based on scores in each domain. Two Chinese language reviewers completed this process of study selection (YY, SN) and quality assessment (YY, JZ) for Chinese language articles.

2.4 | Data synthesis and meta-analysis

Qualitative data synthesis of chronic HBV correlates included tabulating the number of studies reporting each correlate, where they

were reported by ≥3 studies. Two separate meta-analyses were conducted to be as inclusive as possible, as several studies reported either HBsAg prevalence or odds ratios (ORs). First, a meta-analysis of adult specific HBsAg prevalence estimates among comparable variables was performed to generate overall pooled HBsAg prevalence. Second, a meta-analysis was conducted of ORs relating variables to chronic HBV, where there was adjustment for age or sex at a minimum. Since most of the studies reported ORs, we treated the risk ratios reported in two studies[8,28] as ORs given the relatively low prevalence of HBsAg.[29] Meta-analysis was not performed if (1) the requisite number of studies (≥3 studies) was not met, and/or (2) categories of a factor were not comparable among studies.

Fixed effect meta-analysis using the inverse-variance weighted method was conducted. Heterogeneity between study subgroups was assessed using Cochrane's Q test of heterogeneity and the I^2 statistic. In meta-analysis of studies reporting HBsAg prevalence, the parameter estimate was pooled HBsAg prevalence with 95% confidence interval (CI), while for meta-analysis of studies reporting ORs, the parameter estimate was pooled OR (pOR) and 95% CI. In the presence of moderate heterogeneity ($I^2 \geq 50\%$), random effects meta-analysis was also conducted. Publication bias was assessed by visual inspection of funnel plots and Egger's test if at least 10 studies reported a risk factor.[30] Subgroup analysis of HBsAg prevalence by study year (<2006; 2007–2012; ≥2013); region (central; eastern; north-eastern; south; western; nationwide) and study quality (poor; fair; good) was performed. Sensitivity analyses excluding 'poor' quality studies were conducted. The significance threshold was $p < .05$ and meta-analysis were conducted using R version 4.1.0 using the 'meta' package.

3 | RESULTS

3.1 | Selection and study characteristics

A total of 6944 articles were identified in the initial search. Following removal of duplicates along with title and abstract screening, full-text assessment of 264 articles was completed (eTable 5), resulting in 39 articles (Figure 1) being included in the systematic review. Of these 39 articles (see Table 1), 35 published data from participants recruited from 2006 onwards, and 22 were from Eastern China. The sample size ranged from ≈500[15,31] to ≈2 million adults,[7] with an age range of 15–80 years. One study recruited pregnant women[32] and two studies[7,11] included men or women of reproductive age residing in rural areas, as part of the National Free Preconception Health Examination Project (NFPHEP), which provides free preconception health examinations and counselling services for reproductively aged couples. Of these 39 articles, 20 reported HBsAg prevalence estimates, and 24 studies used logistic regression to report ORs relating baseline factors to chronic HBV infection.
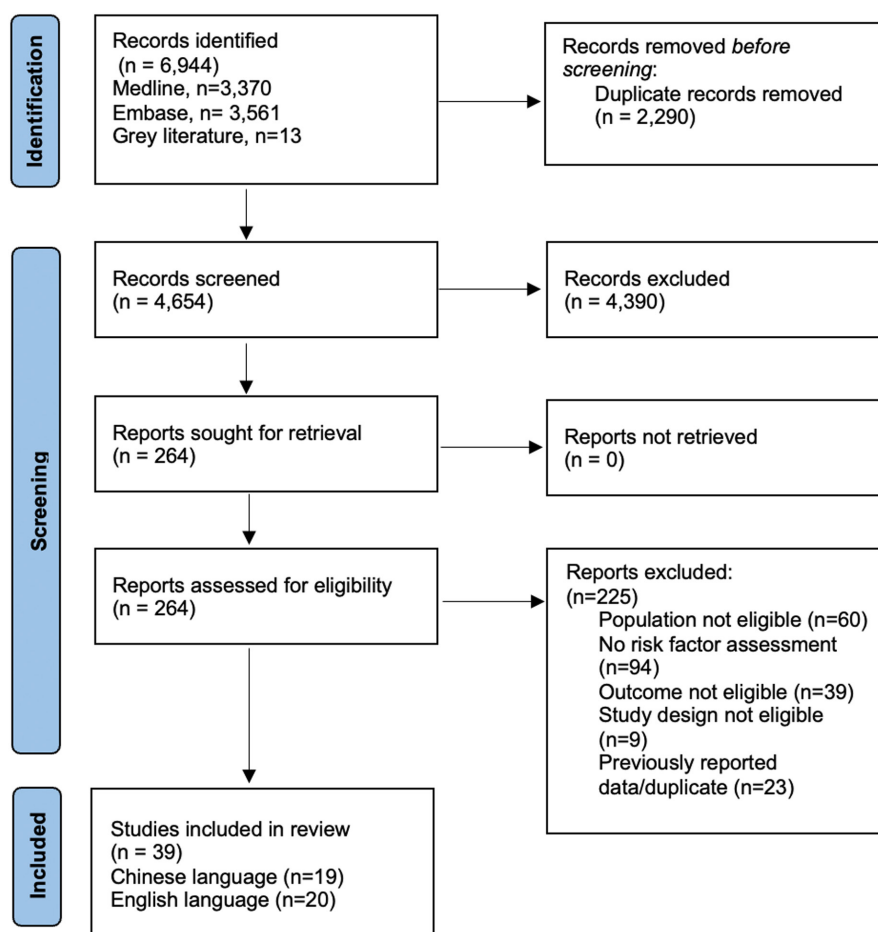

FIGURE 1 PRISMA flow diagram for study selection.

TABLE 1 Characteristics of studies included in systematic review.

Study ID	Setting	Study date	Recruitment method	Study population				Baseline factor ascertainment	HBsAg measurement	Statistical analysis
				No. adults	HBsAg prevalence	Men (%)	Age[a], mean (SD)/range (years)			
Che 2017	Quanzhou City, Fujian Province	2015	Stratified multi-stage cluster sampling, Population-based	3676	9.7	50	15–59	Interviewer-administered questionnaire	ELISA	Prevalence, Multivariable logistic regression OR (95% CI)
Chen 2018	Mianyang city, Sichuan province	2009–2012	All participants in three areas, Population-based	409,408	8.0	46	46 (17)	Interviewer-administered questionnaire	ELISA	Prevalence, Multivariable logistic regression OR (95% CI)
Cheng 2013	Shenzen City, Guangdong province	2010	Stratified multi-stage cluster sampling, Population-based	2005	10.7	49	20–59	Interviewer-administered questionnaire	ELISA	Standardized prevalence
Deng 2013	Hua County, Henan Province	2006–2009	Stratified multi-stage cluster sampling, Population-based	5104	5.1	51	44 (25–65)	Interviewer-administered questionnaire	GICA	Prevalence, Multivariable logistic regression OR (95% CI)
Du 2009	Sichuan province	2006	Stratified multi-stage cluster sampling, Population-based	1319	11.6	NR	15–59	Interviewer-administered questionnaire	ELISA	Standardized prevalence
Fang 2012	Guangxi Province	2011	Random selection from five counties, Population-based	2805	9.9	48	15–≥60	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Multivariable logistic regression OR (95% CI)
Gao 2016	Beijing	2013–2014	Stratified multi-stage cluster sampling, Population-based	5710	3.1	47	15–≥60	Interviewer-administered questionnaire	CMIA	Standardized prevalence
Guo 2020	Beijing	2014	Consecutive sampling, Population-based	4496	4.7	48	47(16–≥60)	NR	ELISA	Prevalence, Logistic regression RR (95% CI)
He 2014	Tianjin City	NR	Stratified multi-stage cluster sampling, Population-based	1030	3.2	51	15–59	Self-administered questionnaire	ELISA	Standardized prevalence
Huang 2015	Jiangsu province	2011	Stratified multi-stage cluster sampling, Population-based	119,710	9.2	45	≥20	Interviewer-administered questionnaire	ELISA	Prevalence, Multivariable logistic regression OR (95% CI)
Ji 2014	Wuwei City, Gansu Province	2010	Stratified multi-stage cluster sampling, Population-based	24,071	7.8	44	15–≥70	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Multivariable logistic regression OR (95% CI)
Li 2012	Anhui province	2006	Stratified multi-stage cluster sampling, Population-based	7901	8.0	43	15–≥60	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Multivariable logistic regression OR (95% CI)

TABLE 1 (Continued)

Study ID	Setting	Study date	Recruitment method	No. adults	HBsAg prevalence	Men (%)	Age[a], mean (SD)/range (years)	Baseline factor ascertainment	HBsAg measurement	Statistical analysis
Liang 2009	Nationwide (31 provinces)	2006	Stratified multi-stage cluster sampling, Population-based	41,646	8.7	48	15–59	Interviewer-administered questionnaire	ELISA	Standardized prevalence, multivariable logistic regression
Liu 2016	Nationwide (31 provinces)	2010–2012	Convenience sampling (NHPHEP), Men in rural couple planning pregnancy	1,966,013	6.3	100	21–49	Interviewer-administered questionnaire	ELISA	Prevalence
Liu 2017	Mianyang City, Sichuan Province	2014–2015	Stratified multi-stage cluster sampling, Population-based	260,950	6.1	43.4	47.7 (18–≥65)	Interviewer-administered questionnaire	ELISA	Prevalence, Multivariable logistic regression OR (95% CI)
Pang 2012	Chaoyang District, Beijing City	2010	Stratified multi-stage cluster sampling for families, Population-based	12,846	2.7[b]	53	15–70	Questionnaire (administration NR)	CMIA	Prevalence, Multivariable logistic regression OR (95% CI)
Qian 2008	Wuxi City, Jiangsu Province	2007	All participants in a given area, Population-based	3744	4.4	44	53 (20–98)	Interviewer-administered questionnaire	ELISA	Standardized prevalence
Ren 2013	Shanghai City	2011–2012	Stratified multi-stage cluster sampling, Population-based	1980	7.8	46	15–≥60	Interviewer-administered questionnaire	ELISA	Standardized prevalence
Sheng 2018	Shenyang, Liaoning Province	2016	Pregnant women visiting hospital	14,314	3.1	0	≥19	Self-administered questionnaire	ELISA	Standardized prevalence
Su 2015	Jiangyin City, Jiangsu Province	NR	Convenience sampling, Population-based	9262	6.9	50	15–≥60	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Logistic regression OR (95% CI)
Tao 2018	Changchun City, Jilin Province	2016	Stratified multi-stage cluster sampling, Population-based	537	3.2	47	15–59	Interviewer-administered questionnaire	ELISA	Prevalence
Wang 2002	Zaozhuang City, Shandong Province	2000	Stratified multi-stage cluster sampling, Population-based	514	7.6	43	15–59	Interviewer-administered questionnaire	RIA	Standardized prevalence, Univariate logistic regression OR (95% CI)
Wang 2015	Chaoyang District, Beijing City	2015	Stratified multi-stage cluster sampling, Population-based	74,854	2.2	42	53 (18–≥75)	Interviewer-administered questionnaire	ELISA	Prevalence, Multivariable logistic regression OR (95% CI)

(Continues)

TABLE 1 (Continued)

| Study ID | Setting | Study date | Recruitment method | Study population | | | | Baseline factor ascertainment | HBsAg measurement | Statistical analysis |
				No. adults	HBsAg prevalence	Men (%)	Age[a], mean (SD)/range (years)			
Wu 2007	Beijing City	2003	Stratified multi-stage cluster sampling, Population-based	4362	4.0	47	15–≥60	Self-administered questionnaire	EIA	Standardized prevalence
Xi 2017	Mianyang, Sichuan province	2013–2014	Stratified multi-stage cluster sampling, Population-based	182,977	7.5	46	18–≥58	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Multivariable logistic regression OR (95% CI)
Xia 1996	Nationwide	1992	Stratified multi-stage cluster sampling, Population-based	41,061	13.9	48	15–59	Self-administered questionnaire	SPRIA	Standardized prevalence
Xin 2016	Nationwide (31 provinces)	2014	Convenience sampling (NHPHEP), Women of child-bearing age	764,460	5.7	0	20–50	Interviewer-administered questionnaire	ELISA	Prevalence
Yang 2012	Zhejiang province	2005	Volunteer, Population-based	728,986	7.4	41	20–≥60	Health records	ELISA	Standardized prevalence Risk Ratios
Yang 2015	Zhejiang province	2008–2014	Stratified multi-stage cluster sampling, Population-based	309,752	6.9	40	15–≥80	Health records	NR	Standardized prevalence, Multivariable logistic regression OR (95% CI)
Yang 2016	Shanghai	1997–2006	Shanghai men's and women's health surveys, Community based	3864	6.3	65	59(40–≥70)	Interviewer-administered questionnaire	CMIA	Prevalence, Multivariable logistic regression OR (95% CI)
Yang 2017	Zhejiang province	2014–2015	Stratified multi-stage cluster sampling, Population-based from rural communities	16,601	4.0	47	40 (19)	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Multivariable logistic regression OR (95% CI)
Yong 2017	Henan province	2011–2013	Stratified multi-stage cluster sampling, Population-based	16,685	3.9	44	18–74	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Multivariable logistic regression OR (95% CI)
Zeng 2016	Guandong province	2014–2015	Stratified multi-stage cluster sampling, Population-based	120,129	10.4	32	23–≥60	Interviewer-administered questionnaire	ELISA	Prevalence, Multivariable logistic regression OR (95% CI)

TABLE 1 (Continued)

Study ID	Setting	Study date	Recruitment method	No. adults	HBsAg prevalence	Men (%)	Age[a], mean (SD)/range (years)	Baseline factor ascertainment	HBsAg measurement	Statistical analysis
				Study population						
Zhai 2010	Shanxi province	2006	Stratified multi-stage cluster sampling, Population-based	1613	3.6	NR	15–59	Interviewer-administered questionnaire	ELISA	Prevalence
Zhang 2011	Dehui, JiLin	2007	Stratified multi-stage cluster sampling, Population-based	3833	4.4	46	≥18	Interviewer-administered questionnaire	ELISA	Prevalence, Multivariable logistic regression OR (95% CI)
Zhang 2012	Chaoyang District, Beijing	2010	Stratified multi-stage cluster sampling, Population-based	14,491	2.9	42	18–≥70	Interviewer-administered questionnaire	ELISA	Prevalence
Zhang 2013	Hainan province	2007–2008	Stratified multi-stage cluster sampling, Women of child-bearing age	12,393	9.5	0	32 (15–49)	Self-administered questionnaire	ELISA	Prevalence, Logistic regression OR (95% CI)
Zhang 2016	JiLin region	2010–2013	Volunteer, Population-based	215,460	6.4	61	15–≥65	Self-administered questionnaire	ELISA	Prevalence
Zhu 2014	Jiangsu Province	2009–2010	Stratified multi-stage cluster sampling, Population-based	86,732	9.9	42	20–59	Interviewer-administered questionnaire	ELISA	Standardized prevalence, Multivariable logistic regression OR (95% CI)

Abbreviations: CMIA, Chemiluminescence Microparticle Immuno Assay; ELISA, enzyme-linked immunosorbent assay; GICA, gold immunochromatography; HBsAg, hepatitis B surface antigen; NR, not reported; SPRIA, solid phase radioimmunoassay.

[a]Where possible mean and SD reported, otherwise age-range provided.

[b]In overall population aged 1–70 years.

TABLE 2 Modified Newcastle-Ottawa quality assessment of included studies.[a]

	Individual criterion							Overall domain			
	Represent-ativeness (2 star)	Sample size (1 star)	Non-respondents (1 star)	Risk factor ascertainment (2 star)	Comparability (2 star)	Assessment of outcome (2 star)	Statistical test (1 star)	Selection (6 star)	Comparability (2 star)	Outcome (3 star)	Overall
Che 2017	2	0	1	2	2	2	1	5	2	3	Good
Chen 2018	1	1	0	2	2	2	1	4	2	3	Good
Cheng 2013	2	1	1	2	1	2	1	6	1	3	Fair
Deng 2013	2	1	1	2	2	1	1	6	2	2	Good
Du 2009	2	0	0	2	1	2	1	4	1	3	Fair
Fang 2012	2	0	1	2	2	2	1	5	2	3	Fair
Gao 2016	2	1	0	2	1	2	1	5	1	3	Fair
Gao 2020	2	0	1	0	0	2	1	3	1	3	Poor
He 2014	2	0	0	1	0	2	0	3	1	2	Poor
Huang 2015	2	1	0	2	2	2	1	5	2	3	Fair
Ji 2014	2	1	0	2	2	2	1	5	2	3	Fair
Li 2012	2	1	1	2	2	2	1	6	2	3	Good
Liang 2009	2	1	1	2	2	2	1	6	2	3	Good
Liu 2016	2	1	1	2	0	2	1	6	1	3	Fair
Liu 2017	2	1	1	2	2	2	1	6	2	3	Good
Pang 2012	2	1	0	1	2	2	1	4	2	3	Fair
Qian 2008	2	0	1	2	1	2	1	5	1	3	Fair
Ren 2013	2	0	1	2	1	2	1	5	1	3	Fair
Sheng 2018	1	1	1	1	1	1	1	4	1	2	Fair
Su 2015	1	1	0	2	1	2	1	4	1	3	Fair
Tao 2018	2	0	0	2	1	2	0	4	1	2	Fair
Wang 2002	2	1	1	2	1	1	1	6	1	2	Fair
Wang 2015	2	1	0	2	2	2	1	5	2	3	Fair
Wu 2007	2	1	0	1	1	2	1	4	1	3	Fair
Xi 2017	2	1	1	2	2	2	1	6	2	3	Good
Xia 1996	2	0	1	1	1	1	1	4	1	2	Fair
Xin 2016	1	1	1	2	1	2	1	5	1	3	Fair
Yang 2012	2	1	1	2	1	2	1	6	1	3	Fair
Yang 2015	2	0	1	2	2	0	1	5	2	1	Fair
Yang 2016	1	1	2	2	2	1	1	6	2	2	Good
Yang 2017	2	1	1	2	2	2	1	6	2	3	Good
Yong 2017	2	1	1	2	2	2	1	6	2	3	Good

TABLE 2 (Continued)

	Individual criterion							Overall domain			
	Represent-ativeness (2 star)	Sample size (1 star)	Non-respondents (1 star)	Risk factor ascertainment (2 star)	Comparability (2 star)	Assessment of outcome (2 star)	Statistical test (1 star)	Selection (6 star)	Comparability (2 star)	Outcome (3 star)	Overall
Zeng 2016	2	1	1	2	2	2	1	6	2	3	Good
Zhai 2010	2	0	0	2	0	2	0	4	1	2	Fair
Zhang 2011	2	1	2	2	2	2	1	7	2	3	Good
Zhang 2012	2	1	1	2	0	2	0	6	1	2	Fair
Zhang 2013	2	0	0	1	0	2	1	3	1	3	Poor
Zhang 2016	1	0	1	1	0	2	1	3	1	3	Poor
Zhu 2014	2	1	1	2	2	2	1	6	2	3	Good

aNumbers represent stars awarded for each criterion and overall domain, where the maximum number of stars possible is in brackets in the heading. Detailed criteria and information about generating the overall rating is in eTable 2.

Colours for overall rating are green (good), yellow (fair) and red (poor).

3.2 | Quality assessment

Overall, 13, 22, and 4 of the 39 included studies were assessed as 'good', 'fair', and 'poor' quality, respectively (Table 2). The most frequent limitation was in the 'selection' domain in the 'non-respondents' criteria, whereby one-third of studies did not report information about non-respondents or provide a response rate. The most common method of recruitment was stratified multi-cluster sampling (71.8%, $n = 28$) and most studies (74.4%, $n = 29$) used inter-viewer administered questionnaires to assess baseline factors, while six used self-administered questionnaires,[9,17,33–36] two used hospital records[8,37] and two did not report the method used.[18,28]

To detect HBsAg, 34 studies used a gold standard test (i.e. laboratory-based ELISA or CMIA), while, one used a rapid diagnostic test,[31] one did not report the method used[38] and three used other methods[36,39,40] such as solid phase radioimmunoassay or gold immu-nochromatography. Among 24 studies reporting ORs, 19 provided estimates that were adjusted for demographic in addition to socio-economic or medical factors, two[8,31] provided estimates adjusted only for age and sex, while three[28,35,41] did not specify what covari-ates were adjusted for in the model.

3.3 | Chronic HBV correlates

Overall, 22 factors were reported across 39 studies, including a range of sociodemographic, behavioural and medical factors (Figure 2). Of these 22 factors, 15 were included in meta-analysis of HBsAg prevalence estimates (Table 3), and nine of 22 factors were included meta-analysis of ORs (Figure 3A–I). Seven factors (ethnicity, region, occupation, income, piercing, sharing needles and acupuncture) were only included in the qualitative synthesis due to insufficient number of studies reporting HBsAg prevalence or ORs, or inconsist-ency in categorization of factors between different studies.

3.4 | Sociodemographic factors

3.4.1 | Age

Of the 35 studies reporting age, 22 showed an inverted U-shaped association with chronic HBV prevalence, where HBsAg prevalence peaked in middle-age, mainly at 30–39 years ($n = 11$).[9,13,21,31,33,35,36,42–45] On the other hand, seven studies ob-served an inverse correlation between age and HBsAg preva-lence,[7,8,14,19,39,46,47] three found a positive correlation,[11,17,48] one showed similar prevalence across different age-groups,[32] and two had dual peaks of HBsAg prevalence in both young and middle-aged adults.[16,40] In meta-analysis of HBsAg prevalence among age groups, the lowest pooled prevalence was at age 20–29 years (5.70%, 95% CI 5.68%–5.74%), reaching a peak at 50–59 years (8.14%, 95% CI 8.02%–8.26%) and decreasing afterwards in ≥60 years (6.10%, 95% CI 6.00%–6.19%) (Test for subgroup differences: $\chi^2 = 3533.6$, df = 5,

Chronic HBV correlate	Studies reporting chronic HBV correlate
Age (n=35)	1 3 4 5 6 7 8 9 10 11 13 14 15 17 18 19 20 21 22 23 24 25 26 27 28 30 31 32 33 34 35 36 37 38 39
Occupation (n=23)	1 3 4 7 9 10 11 12 13 14 15 17 18 23 24 25 27 28 29 32 33 35 37
HBV Vaccination (n=18)	2 7 8 10 11 12 13 14 15 17 18 25 27 29 33 35 37 39
Sex (n=17)	2 3 4 8 10 11 12 13 15 17 23 25 29 31 32 35 39
Education (n=15)	1 2 3 4 10 11 12 13 14 27 29 32 33 36 37
Surgical history (n=11)	2 8 10 11 12 15 16 25 29 33 37
Blood transfusion (n=11)	2 8 10 11 12 15 16 23 25 29 37
Marital status (n=10)	2 4 10 11 12 15 25 29 33 37
Ethnicity (n=8)	11 12 13 14 25 27 32 37
Region (n=7)	14 15 23 27 28 29 39
Household + contact (n=7)	10 11 15 16 31 32 37
Alcohol use (n=5)	4 25 28 33 35
HBV family history (n=5)	2 25 28 29 35
Urban/Rural (n=5)	8 11 12 13 32
Dental therapy (n=5)	8 10 11 16 37
Sharing needles (n=5)	8 10 12 16 32
Endoscopy (n=4)	10 11 16 37
Smoking (n=4)	4 25 28 35
Tattoo (n=4)	8 10 16 37
Piercing (n=3)	8 10 37
Income (n=3)	32 35 37

FIGURE 2 Chronic HBV correlates reported by studies in systematic review.[†] [†]Each number represents one of 39 studies included in the review: [1]Che 2017; [2]Chen 2018; [3]Cheng 2013; [4]Deng 2011; [5]Du 2009; [6]Fang 2012; [7]Gao 2016; [8]Guo 2020; [9]He 2014; [10]Huang 2015; [11]Ji 2014; [12]Li 2012; [13]Liang 2009; [14]Liu 2016; [15]Liu 2017; [16]Pang 2012; [17]Qian 2008; [18]Ren 2011; [19]Sheng 2018; [20]Su 2015; [21]Tao 2018; [22]Wang 2002; [23]Wang 2015; [24]Wu 2007; [25]Xi 2017; [26]Xia 1996; [27]Xin 2016; [28]Yang 2012; [29]Yang 2017; [30]Yang 2015; [31]Yang 2016; [32]Yong 2017; [33]Zeng 2016; [34]Zhai 2010; [35]Zhang 2011; [36]Zhang 2016; [37]Zhang 2013; [38]Zhang 2012; [39]Zhu 2014.

$p < .01$ (Table 3). Meta-analysis of ORs were not performed due to insufficient number of studies reporting this.

3.4.2 | Sex

Of 17 studies reporting male sex, 15 found it was correlated with chronic HBV, while two studies[20,45] reported no significant difference in chronic HBV risk by sex. In meta-analysis of nine studies reporting HBsAg prevalence, the pooled HBsAg prevalence among men was 8.40% (95% CI 8.28%–8.52%), compared to 6.15% (95% CI 6.06%–6.24%) among women (Test for subgroup differences: $\chi^2 = 864.2$, df = 1, $p < .01$) (Table 3). Likewise, in meta-analysis of 14 studies, the pOR of chronic HBV for men compared to women was 1.35 (95% CI 1.33–1.37, $I^2 = 79\%$, $p_{het} < .01$) (Figure 3A).

3.4.3 | Ethnicity

In eight studies reporting ethnicity,[7,11,35,48–52] four[35,49–51] reported lower HBsAg prevalence in participants of Han than of non-Han ethnicity, including Li,[35] Uigar[49] and Zhuang[51] ethnicities, where the latter had a HBsAg prevalence of 13.4% compared to 7.2% in Han ethnic people in the 2006 National serosurvey.[51] By contrast, the remaining four[7,11,48,52] studies reported higher HBsAg prevalence among Han than non-Han ethnic participants, but these studies only included very small numbers of non-Han ethnic participants (≈8.5% overall). Categories of ethnicity reported in different studies were not comparable, and thus meta-analysis was not performed.

3.4.4 | Urban or rural residence

Of five studies reporting urban or rural residence, four[28,48,49,51] found higher HBsAg prevalence among rural compared to urban residents, while one study found no difference.[53] In meta-analysis of five studies, pooled HBsAg prevalence was 7.11% (95% CI 6.93%–7.29%) and 6.46% (95% CI 6.26%–6.67%) in rural and urban sites, respectively (Test for subgroup differences: $p < .01$) (Table 3). In meta-analysis of three studies reporting ORs (Figure 3B),[48,49,51] the pOR of chronic HBV for rural residents was 1.24 (95% CI 1.09–1.41, $I^2 = 72\%$, $p_{het} = .03$) times than of urban counterparts.

3.4.5 | Region

Of seven studies reporting chronic HBV by region, all showed variation in HBsAg prevalence. Two nationwide studies[7,11] found the

TABLE 3 Fixed effects meta-analysis of HBsAg prevalence among baseline correlates.

Variable	N people	N studies	Pooled HBsAg prevalence (95% CI)	I^2 (%)	p_{het}	Test for subgroup differences		
						χ^2	df	p-value
Age (years)						3533.6	5	<.01
15–19	12,773	12	5.71 (5.29–6.17)	93	<.01			
20–29	1,982,226	23	5.70 (5.68–5.74)	99	<.01			
30–39	1,088,444	23	6.64 (6.60–6.69)	99	<.01			
40–49	382,269	24	7.52 (7.44–7.61)	99	<.01			
50–59	223,920	21	8.14 (8.02–8.26)	99	<.01			
60+	243,678	13	6.10 (6.00–6.19)	99	<.01			
Sex						864.2	1	<.01
Male	220,546	9	8.40 (8.28–8.52)	99	<.01			
Female	283,149	9	6.15 (6.06–6.24)	99	<.01			
Urban/rural						21.8	1	<.01
Urban	58,673	5	6.46 (6.26–6.67)	97	<.01			
Rural	78,147	5	7.11 (6.93–7.29)	97	<.01			
Marital status						1826.0	1	<.01
Not married	341,635	10	5.61 (5.53–5.70)	99	<.01			
Married	908,746	10	8.14 (8.08–8.19)	99	<.01			
Education						1870.2	2	<.01
Illiterate/primary	661,102	13	7.92 (7.85–7.99)	99	<.01			
Junior/highschool	2,483,401	13	6.45 (6.41–6.48)	99	<.01			
College or above	505,907	11	6.40 (6.33–6.47)	99	<.01			
Alcohol						1296.5	1	<.01
Non-drinker	560,670	4	6.82 (6.75–6.89)	99	<.01			
Drinker	110,193	4	9.96 (9.78–10.14)	99	<.01			
Smoking						1989.0	1	<.01
Non-smoker	560,004	4	6.67 (6.60–6.74)	99	<.01			
Smoker	111,786	4	10.55 (10.37–10.73)	98	<.01			
Tattoo						5.32	1	.02
No	20,618	3	7.19 (6.82–7.58)	99	<.01			
Yes	5934	3	6.23 (5.57–6.96)	99	<.01			
HBV vaccination						2798.3	1	<.01
No	2,623,756	12	7.33 (7.30–7.36)	99	<.01			
Yes	1,062,466	12	5.19 (5.15–5.23)	99	<.01			
Family history HBV						2867.2	1	<.01
No	1,068,411	5	6.26 (6.21–6.30)	99	<.01			
Yes	108,988	5	10.52 (10.34–10.71)	99	<.01			
Household contact						1544.4	1	<.01
No	338,847	4	5.80 (5.72–5.88)	99	<.01			
Yes	6235	4	18.92 (17.95–19.94)	97	<.01			
Blood transfusion						94.9	1	<.01
No	1,090,579	9	6.55 (6.50–6.60)	99	<.01			
Yes	12,679	9	8.82 (8.32–9.36)	94	<.01			
Surgical history						428.9	1	<.01
No	958,286	9	6.43 (6.39–6.48)	99	<.01			
Yes	139,491	9	7.92 (7.78–8.07)	98	<.01			

(Continues)

TABLE 3 (Continued)

Variable	N people	N studies	Pooled HBsAg prevalence (95% CI)	I^2 (%)	p_{het}	Test for subgroup differences		
						χ^2	df	p-value
Endoscopy history						0.76	1	.39
No	23,149	3	6.94 (6.59–7.30)	99	<.01			
Yes	3424	3	7.38 (6.49–8.39)	97	<.01			
Dental treatment						6.6	1	.01
No	38,165	4	7.27 (7.01–7.54)	99	<.01			
Yes	16,400	4	6.63 (6.23–7.04)	99	<.01			

Abbreviations: df, degree of freedom; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; N, number.

highest HBsAg prevalence in eastern China (men: 8.0%; women: 6.3%), and lowest in central China (men: 5.5%; women: 5.0%); while the 2006 National serosurvey[51] found participants in western China had the highest HBsAg prevalence at 8.3%, compared to counterparts in eastern (6.5%) and central China (6.7%). One study[21] comparing Beijing to non-Beijing residents found that non-Beijing residents had a 69% (95% CI 50%–90%) increased relative risk of chronic HBV, two studies[8,45] comparing residents living in coastal to non-coastal areas reported higher prevalence among coastal residents, while a further two studies[44,54] found higher HBsAg prevalence in areas with lower economic development on the outskirts of the city compared to those with higher economic development. Categories of regions reported in different studies were not comparable, and thus meta-analysis was not performed.

3.4.6 | Marital status

Marital status was reported in 10 studies[10,18,28,35,43,45,47,49,50,52,54] and overall 73% of participants across studies were married. Meta-analysis of these 10 studies showed higher pooled HBsAg prevalence in married than un-married participants (8.14%, 95% CI 8.08%–8.19% vs. 5.61%, 95% CI 5.53%–5.70%; Test for subgroup differences: $\chi^2 = 1862.0$, df = 1, $p < .01$) (Table 3). Similarly, in meta-analysis of six studies reporting ORs, the pOR comparing married versus unmarried was 1.38 (95% CI 1.32–1.45; $I^2 = 90$%, $p_{het} < .01$) (Figure 3C).

3.4.7 | Education

Of 15 studies reporting education, 10 reported inverse associations between education level and chronic HBV.[9–12,19,35,43,45,48,51] In meta-analysis of studying reporting HBsAg prevalence among levels of education (Table 3), pooled prevalence of HBsAg was 7.92% (95% CI 7.85%–7.99%), 6.45% (95% CI 6.41%–6.48%) and 6.40% (95% CI 6.33%–6.47%) in those with illiterate/primary ($n_{studies} = 13$), junior/high school ($n_{studies} = 13$) and college or above ($n_{studies} = 11$), respectively (Test for subgroup differences: $\chi^2 = 1870.2$, df = 2, $p < .01$) (Table 3). Meta-analysis of ORs were not performed due to insufficient number of studies reporting this.

3.4.8 | Occupation

Occupation was reported in 23 studies, with somewhat heterogeneous classification of occupational categories. Overall, participants in agricultural or farming occupations tended to have a higher HBsAg prevalence[12,17,19,21,33,36,39,43,47,48] ranging from 8.5%[51] to 24.1%,[12] while students generally had lower HBsAg prevalence ranging from <1%[32,35] to 7.1%[48] compared to other occupations.[20,36,45] In seven studies reporting healthcare workers (HCW) as an occupation, five ($n_{studies} = 5$[48,49,51,52,54]) found they had 39%[54] to 50%[51] lower relative risk of HBsAg positivity after multivariable adjustment compared to the baseline occupational category, while two studies[14,50] found HCW had the highest HBsAg prevalence among reported occupations. Other occupations associated with higher relative risk of chronic HBV included 'workers',[7,8,11,17,20,21,50,51] truck driving[8,33] and business.[12,20,21,46] Categories of occupation reported in different studies were not comparable, and thus meta-analysis was not performed.

3.4.9 | Income

Of three studies reporting income, two[35,48] found higher income was inversely correlated with chronic HBV, while one found no difference by income level.[46] One study[48] compared participants reporting income of <50,000, 50–100,000, ≥100,000 RMB/year with HBsAg prevalence of 4.1%, 3.2% and 2.8% respectively, while another study[25] found those in the lower income group (<2000 RMB/month) had a 23% (95% CI 8%–42%) higher relative risk of chronic HBV than the higher income group (≥2000 RMB/month). In another study[46] there was no significant difference in HBsAg prevalence between participants earning <800 and ≥800 RMB/year. Meta-analysis was not performed due to insufficient number of studies reporting either HBsAg prevalence or ORs.

3.5 | Behavioural factors
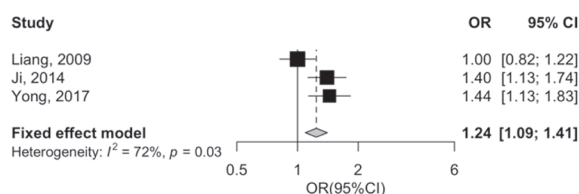
3.5.1 | Alcohol

Alcohol intake was reported in five studies,[8,39,46,47,52] with mixed findings relating to chronic HBV Xi et al.[52] found a J-shaped
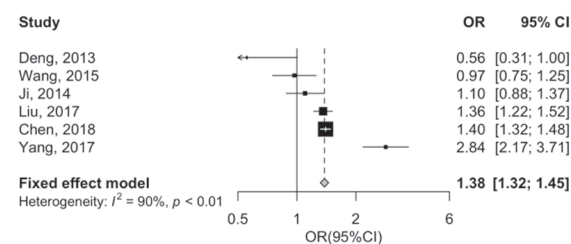
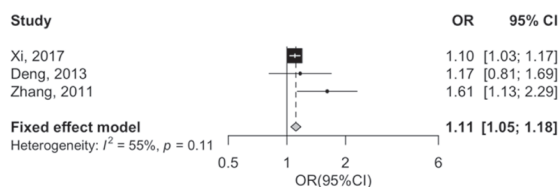**(A) Sex: men vs. women**
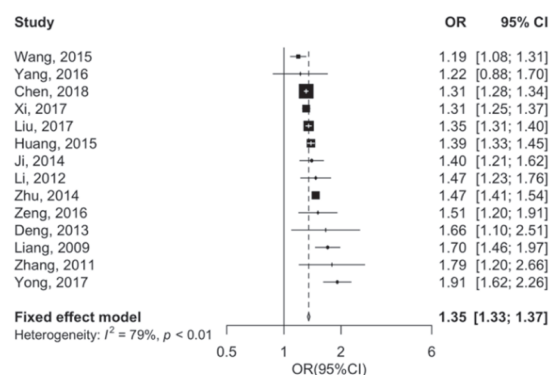
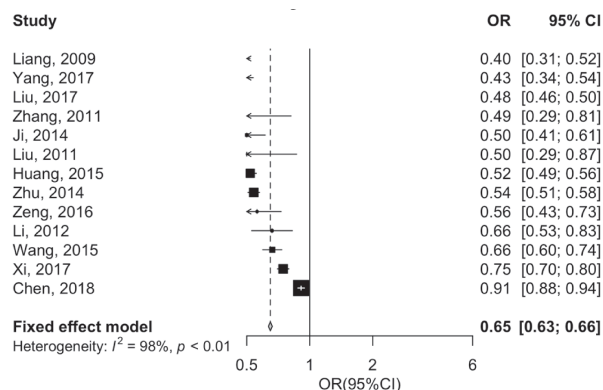Egger's test p-value=0.08

(B) Rural vs. urban location

(C) Married vs. not married

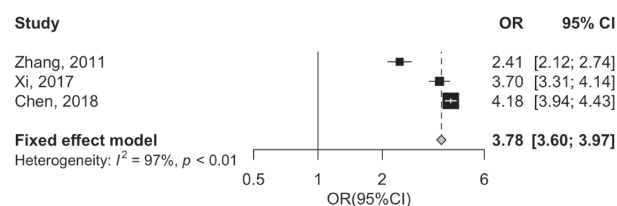**(D) Smoker vs. non-smoker**
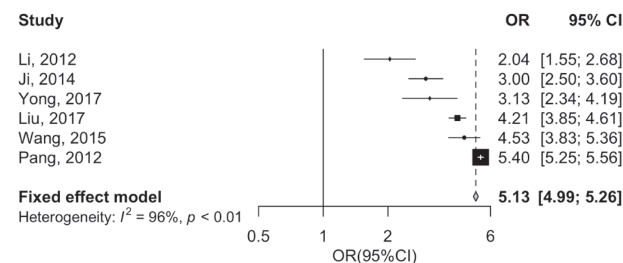

(E) HBV Vaccination: yes. vs. no
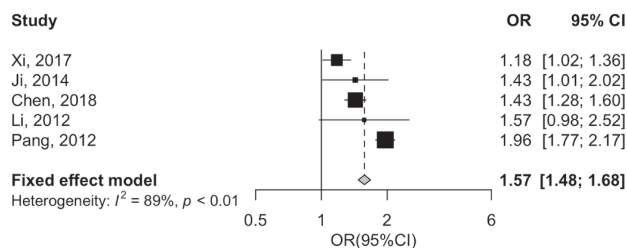

Egger's test p-value=0.37

(F) HBV Family history: yes vs. no

(G) Householdcontact: yes vs. no

(H) Blood Transfusion: yes vs. no
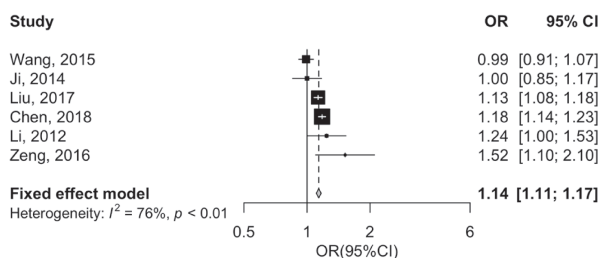

(I) Surgical history: yes vs. no

FIGURE 3   (A–I) Meta-analysis of odds ratios for baseline correlates and chronic HBV.

association between alcohol intake and chronic HBV, where low (0–20 mL/day) intake was associated with a 11% (95% CI 7%–16%) lower risk of chronic HBV relative to never drinkers, and each category of higher alcohol intake was associated with higher odds of chronic HBV, greatest in participants in the highest category of alcohol intake (≥80 mL/day) compared to never drinkers (OR: 1.20, 95% CI 1.06–1.36). Zeng et al.[47] also found lower chronic HBV risk in 'occasional' alcohol drinkers compared to never drinkers (OR: 0.62, 95% CI 0.41–0.93), with participants in the 'often' and 'every day' group having non-significantly lower risk of chronic HBV. Other studies investigated alcohol as a binary variable, where one[8] found a 30% (95% CI 27%–34%) higher odds of chronic HBV in drinkers compared to non-drinkers, while the other two studies[39,46] found a non-significant association between drinking and HBsAg status. Meta-analysis of four studies yielded a pooled HBsAg prevalence of 9.96% (95% CI 9.78%–10.14%) and 6.82% (95% CI 6.75%–6.89%) for drinkers and non-drinkers, respectively (Test for subgroup differences: $\chi^2 = 1296.5$, df = 1, $p < .01$) (Table 3). Meta-analysis of ORs was not performed due to insufficient number of studies reporting this.

3.5.2 | Smoking

Smoking was reported in four studies[8,39,46,52] where all reported higher HBsAg prevalence in smokers compared to non-smokers. Meta-analysis of four studies reporting HBsAg prevalence by smoking status found smokers had a significantly higher prevalence (10.55%, 95% CI 10.37%–10.73%) than non-smokers (6.67%, 95% CI 6.60%–6.74%) (Test for subgroup differences: $\chi^2 = 1989.0$, df = 1, $p < .01$) (Table 3). Meta-analysis of three studies reporting odds of chronic HBV among smokers versus non-smokers yielded a pOR of 1.11 (95% CI 1.05–1.18, $I^2 = 55\%$, $p_{het} = .11$) (Figure 3D).

3.5.3 | Tattooing

Three of four[18,28,35,43] studies reporting tattooing found no significant association between tattooing and chronic HBV, where history of tattooing varied between 6.3%[28] to 33.2%[18] of participants. Meta-analysis of HBsAg prevalence among participants with and without tattoos in three studies[18,28,35] yielded pooled prevalence of 6.23% (95% CI 5.57%–6.96%) and 7.19% (95% CI 6.82%–7.58%), respectively (Test for subgroup differences: $\chi^2 = 1870.2$, df = 1, $p = .02$) (Table 3). Meta-analysis of ORs was not performed due to insufficient number of studies reporting this.

3.5.4 | Piercing

Of three studies[28,35,43] that investigated piercing, all found there was no significant association with chronic HBV. Piercing was relatively common, reported in 24.9%[28] and 77.3%[35] of participants. One[43] study reported piercing compared to no piercing was associated with

a non-significant decrease in chronic HBV while two[28,35] found a non-significant increase. Meta-analysis was not performed due to insufficient number of studies reporting either HBsAg prevalence or ORs.

3.5.5 | Sharing syringes

Of five studies reporting sharing syringes,[18,28,41,43,48] the frequency of sharing syringes was reported in two studies at 1.2%[18] and 17.7%[28] of the total study population. All five studies found greater chronic HBV risk among those reporting shared syringe-use, remaining significant after multivariable adjustment in two studies.[43,48] These latter studies reported a higher odds of chronic HBV of 28% (95% CI 3%–57%)[48] and 44% (95% CI 12%–86%)[43] in participants reporting sharing syringes compared to those not. One study reported a non-significant association with chronic HBV after multivariable adjustment,[41] while a further study[28] with an unreported adjustment level reported an OR of 2.07 (95% CI 1.26–3.41). Meta-analysis was not performed due to insufficient number of studies reporting either HBsAg prevalence or ORs.

3.6 | Medical factors

3.6.1 | HBV vaccination

HBV vaccination was inversely associated with chronic HBV in all 18 studies reporting this,[7,10,11,14,20,28,33,35,43–47,49–52,54] with the lower risk of chronic HBV varying from 9% to 60% among vaccinated compared to non-vaccinated individuals. In meta-analysis of 12 studies the pooled HBsAg prevalence among non-vaccinated participants was ≈2.0% higher than vaccinated individuals vaccinated 5.19% (95% CI 5.15%–5.23%) versus not vaccinated 7.33% (95% CI 7.30%–7.36%) (Test for subgroup differences: $\chi^2 = 2798.3$, df = 1, $p < .01$) (Table 3). Meta-analysis of 13 studies reporting ORs yielded a pOR of 0.65 (95% CI 0.63–0.66) in vaccinated compared to non-vaccinated individuals ($I^2 = 98\%$, $p_{het} < .01$) (Figure 3E).

3.6.2 | Family history of HBV

Five studies[8,10,45,46,52] found having a positive family history was related to higher chronic HBV risk. The frequency of participants reporting a family history of HBV varied among studies—two studies found a family history of HBV was reported in 14.9%[46] and 22.4%[10] of participants, while the remaining three studies reported this in <3%[8,45,52] of participants. Meta-analysis of HBsAg prevalence by family HBV history status among five studies[8,10,45,46,52] yielded a pooled HBsAg prevalence of 10.52% (95% CI 10.34%–10.71%) and 6.26% (95% CI 6.21%–6.30%) in those with and without a family history of HBV, respectively (Test for subgroup differences: $\chi^2 = 2867.2$, df = 1, $p < .01$) (Table 3). Meta-analysis of ORs reported in three studies[10,46,52] yielded a pOR of 3.78 (95% CI 3.60–3.97, $I^2 = 97\%$, $p_{het} < .01$) (Figure 3F).

3.6.3 | Household HBsAg positive contact

Seven studies[18,21,42,48,49,54] reported a positive correlation between chronic HBV and having a household HBsAg positive contact. Among studies the frequency of participants reporting a household positive contact ranged from 1.2%[54] to 14.6%.[35] Meta-analysis of four studies[18,21,35,54] reporting HBsAg prevalence yielded a pooled prevalence of 18.92% (95% CI 17.95%–19.94%) and 5.80% (95% CI 5.72%–5.88%) in those with and without a HBsAg positive contact (Test for subgroup differences: $\chi^2 = 1554.4$, df = 1, $p < .01$) (Table 3). Meta-analysis of odds of chronic HBV among those with a HBsAg positive contact compared to those without among six studies yielded a pOR of 5.13 (95% CI 4.99–5.26, $I^2 = 96\%$, $p_{het} < .01$) (Figure 3G).

3.6.4 | Blood transfusion

Of 11[10,18,21,28,35,43,45,49,50,52,54] studies reporting the association between blood transfusion and chronic HBV, six reported a positive correlation with chronic HBV. Blood transfusion was uncommon, reported in only ≈1% of participants across studies. In meta-analysis of nine studies,[10,18,21,28,45,49,52,54] the pooled HBsAg prevalence was 8.82% (95% CI 8.32%–9.36%) and 6.55% (95% CI 6.50%–6.60%) in those with and without a history of blood transfusion, respectively (Test for subgroup differences: $\chi^2 = 94.9$, df = 1, $p < .01$) (Table 3). Meta-analysis of five studies[10,18,49,50,52] reporting ORs, yielded a pOR of 1.57 (95% CI 1.48–1.68, $I^2 = 81$, $p_{het} < .01$) in participants with a blood transfusion compared to those without (Figure 3H).

3.6.5 | Surgical history

There were 11 studies reporting surgical history in association with chronic HBV. Surgical history was reported in ≈13% of overall participants. In nine studies included in meta-analysis of HBsAg prevalence,[1,18,21,28,35,45,49,52,54] the pooled HBsAg prevalence was 7.92% (95% CI 7.78%–8.07%) and 6.43% (95% CI 6.39%–6.48%) in those with and without a surgical history, respectively (Test for subgroup differences: $\chi^2 = 428.9$, df = 1, $p < .01$) (Table 3). Meta-analysis of six studies[10,21,47,49,50,54] reporting ORs for chronic HBV in participants with a surgical history compared to their counterparts yielded a pOR of 1.14 (95% CI 1.11–1.17, $I^2 = 76\%$, $p_{het} < .01$) (Figure 3I).

3.6.6 | Dental therapy

Of five studies[18,28,35,43,49] reporting dental therapy in relation to chronic HBV, none found an association with chronic HBV. Dental therapy was relatively common, reported in 20.3%[49] to 57.8%[18] of participants across studies. In four studies[18,28,35,49] included

meta-analysis of HBsAg prevalence the pooled HBsAg prevalence was 6.63% (95% CI 6.23%–7.04%) and 7.27% (95% CI 7.01%–7.54%) in those those with and without a history of dental therapy, respectively (Test for subgroup differences: $\chi^2 = 6.6$, df = 1, $p = .01$) (Table 3). Meta-analysis of ORs were not performed due to insufficient number of studies reporting this.

3.6.7 | Endoscopy

Of four studies reporting history of endoscopy,[18,28,35,49] endoscopy history was present in 7.9%[49] to 12.9%[18] of participants, and none found an association with chronic HBV. Meta-analysis of three studies[18,28,35] reporting HBsAg prevalence yielded no significant difference by endoscopy status, with a pooled HBsAg prevalence of 7.38% (95% CI 6.49%–8.39%) and 6.94% (95% CI 6.59%–7.30%) in those with and without a history of endoscopy, respectively (Test for subgroup differences: $\chi^2 = 0.79$, df = 1, $p = .39$) (Table 3). Meta-analysis of ORs were not performed due to insufficient number of studies reporting this.

3.6.8 | Acupuncture

Of three studies[18,43,49] reporting acupuncture related to HBsAg status, none reported an association with chronic HBV. Frequency of acupuncture was 8.0%[49] and 28.0%[18] in two studies reporting this information. Meta-analysis was not performed due to insufficient number of studies reporting either HBsAg prevalence or ORs.

3.7 | Publication bias, heterogeneity and sensitivity analyses

Funnel plots (eFigure 1) for did not demonstrate obvious asymmetry, other than for household contact. This may reflect geographic variation in risk reported by included studies, where two[18,21] conducted in the same Beijing district found a four-to-five-fold increased risk of chronic HBV among those with positive contacts, while other studies[48–50] conducted in different regions of China found a two-to-three-fold increased risk. Interpretation of funnel plots is limited by low number of studies for many factors. Egger's tests for age and HBV vaccination were not significant (Figure 3A,E). Tests for subgroup heterogeneity were significant for all factors other than endoscopy, while between-study heterogeneity (I^2) was high for all factors. In meta-analysis of select study characteristics (eFigures 2–4), there was significant subgroup heterogeneity by region (lower HBsAg prevalence in studies in central and north-eastern China); study date (lower HBsAg prevalence in more recent studies) and quality (highest prevalence in high quality studies). Analyses excluding 'poor' quality studies (eTable 6), and random effect meta-analysis (eTable 7, eFigure 5) did not materially alter the observed associations.

4 | DISCUSSION

Through this systematic review we identified that a wide range of factors are correlated with chronic HBV infection among adults of the general population in China. These correlates included middle age, male sex, being married, rural residence, lower education, smoking, having a HBsAg positive household contact, family history of HBV, lack of HBV vaccination and history of surgery or blood transfusion.

It is well established that mother to child transmission of HBV is key route of transmission in China, responsible for up to 50% of incident cases of chronic HBV infection,[55,56] which has been reduced significantly through universal free vaccination at birth and pre-natal HBsAg screening. Horizontal transmission during childhood is also a common route of transmission,[57] especially among unvaccinated children, and risk of progression to chronic HBV is highest among neonates and young children, compared to infection as an adult.[58] The present review showed that both family history and having a current positive household contact were correlated with chronic HBV among adults.

Our findings regarding the association between age and chronic HBV infection are consistent with findings in large nationwide studies included in this review,[7,11,40,51] and a recent meta-analysis of HBsAg prevalence in the general Chinese population.[59] They reported ongoing intermediate-high levels of chronic HBV infection among middle-aged adults, with HBsAg prevalence peaking in several studies in participants of childbearing age.[9,13,21,31,33,35,36,42–45] This demonstrates the birth cohort effect of adults of the 'pre-vaccination at birth era', in addition to the widespread implementation of pre-natal HBsAg screening, blood screening and harm minimization programs. The relatively high HBsAg prevalence in young and middle aged adults is of public health importance for several reasons: this cohort will be responsible for the largest burden of disease and death related to chronic HBV in coming decades, they are key contributors to the workforce, and are of child-bearing age, where 1 million babies every year are born to HBsAg positive mothers,[60] resulting in an ongoing neonatal infection despite vaccination and immunoglobulin treatment availability. A recent economic evaluation[55] on the cost-effectiveness of universal screening chronic HBV in China highlighted the importance of age considerations in progressing to elimination of HBV, where they found adults aged 18–30 years would benefit most from screening, because identifying younger people who need vaccination would result in the greatest quality of life years gained. Greater chronic HBV prevalence among men is hypothesized to be related to the role sex hormones play in regulation of the immune response and response to exogenous pathogens, where immune clearance of HBsAg is achieved in a higher proportion of women than men, and women gain better protection from HBV vaccination.[61]

Geographic variation in chronic HBV prevalence has been attributed to multiple factors, including host, viral and environmental factors. Historically, rates of chronic HBV have been higher in rural, western regions of China, but with widespread urbanization and mass migration of rural workers to large coastal cities and eastern provinces, these patterns have been shifting.[62] Although we found rural residence was correlated with chronic HBV, recent studies show a reduced absolute difference in HBsAg prevalence between urban and rural dwellers, highlighted by the findings of the 2006 National serosurvey[51] which reported no difference in relative risk of chronic HBV after multivariable adjustment (1.00, 95% CI 0.83–1.22). This may reflect the expansion of vaccination to rural, removal of a user fee for vaccination, better access to healthcare and HBV screening and access to education in rural areas. Higher HBsAg prevalence in certain outskirt districts or coastal areas, warrants further investigation and may relate to differences in socioeconomic status, occupational hazards and behavioural factors. This review has a disproportionate number of studies performed in Eastern China, with further research required in diverse areas.

Like many other infectious diseases, socioeconomic factors including education and occupation, are associated with chronic HBV. This may reflect differences in social development increasing risk of exposure to chronic HBV, differences in access to healthcare, in addition to geographic factors. Historically, the two-tiered system of health insurance in China means that poorer Chinese have less access to healthcare and incur large out of pocket expenses,[1] where attendance to health facilities for HBV screening, monitoring and treatment incurs a large financial barrier. Furthermore, implementation of practices to reduce contaminated blood products and unsafe injections, which were correlates identified in this study, was slower in areas that were less economically developed and have a higher proportion of less educated people. In terms of occupation, the higher prevalence of chronic HBV among agricultural workers in our review may also be related to socioeconomic factors and rural residence, while the apparent lower prevalence in HCW may relate to better screening practices. Further research into relevant behavioural factors among businessmen and truck-drivers is needed, including sexual practices and injecting drug use (IDU). Although we found sharing syringes to be correlated with chronic HBV, IDU was not explicitly explored, and factors related to sexual practices were not included in this review due to lack of studies reporting this. The relative importance of these transmission routes in China (which are key in low-endemic settings[63]) may shift in coming decades in the context of universal vaccination coverage in children, and have been highlighted as an area requiring more attention, particularly due to the higher HBsAg prevalence in a sexually active population.[64]

This study adds to the literature a synthesis of factors associated with chronic HBV among Chinese adults, providing both pooled HBsAg prevalence and pooled ORs. Although past studies have meta-analysed the overall and age-sex and region specific prevalence of HBsAg in China,[59,65] other factors have not been explored, and these reviews included children, who have a substantially lower prevalence of chronic HBV due to vaccination. We used a broad search filter with no language restriction, used Chinese language reviewers to maximize inclusion of relevant articles and

ensured only studies reporting adult specific estimates were included in analyses. Nevertheless, several limitations exist. First, this review includes observational studies where temporality between baseline factors and chronic HBV infection is unclear—thus the direction of the associations and potential causality cannot be inferred. Further research investigating factors associated with incident HBV infection is warranted, where targeting of risk factors may alter chronic HBV disease risk. Second, the categorization of factors between studies varied (e.g. occupation, region, ethnicity) preventing meta-analysis. Third, heterogeneity was high between studies in our meta-analyses. Clinical heterogeneity may arise from variability in the timeframe of studies and geographic variation in relative importance of different risk factors, while methodological heterogeneity may arise from differences in study design and risk of bias of included studies. Fourth, we were not able to clarify the relevance of some factors to chronic HBV, such as smoking, piercing and sharing syringes, due to few studies reporting these factors. Finally, the review spanned an 18-year time period in the context of changing landscape with the introduction of HBV vaccination at birth, blood screening and peri-natal HBV interventions, so some correlates identified may not be contemporarily relevant (e.g. blood transfusion and surgical history).

In summary, this systematic review identified a range of correlates of chronic HBV infection among adults in the general population of China. While some of these factors have been reported separately in previous studies, this has been inconsistent and the evidence has not been synthesized to date. As the patterns and relative importance of historic risk factors for chronic HBV evolve in China, ongoing research in this area is needed. Greater representation from people of non-Han ethnic origin, as well as study of the role of genetic factors, and their interaction with non-genetic factors on chronic HBV risk is also warranted. More detailed knowledge of chronic HBV correlates can help inform targeted chronic HBV screening and provision of tailored education, to help increase the diagnosis rate, an important target for reaching elimination of HBV in China in the coming decades.

CONFLICT OF INTEREST STATEMENT
None of the authors have any conflicts of interest in relation to this report.

DATA AVAILABILITY STATEMENT
Data used is publicly available from respective studies.

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