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Review Article

Association between interleukin-18 gene promoter (rs1946518 and rs187238) polymorphisms and susceptibility to chronic hepatitis B virus infection: a systematic review with meta-analysis

Guoming Su[1], Qili He[2], Tao Kuang[1], Xuemei Zhang[3], Guinian Wang[1], Junbei Xiang[1], Binyang Huang[1], Yuechong Sun[1], Yuxin Han[1]

[1]Sichuan Nursing Vocational College, Chengdu 610100, Sichuan Province, China; [2]Sichuan Center for Disease Control and Prevention, Chengdu 610041, Sichuan Province, China; [3]West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

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Abstract: The aim of our study was to investigate the association between interleukine-18 (IL-18) gene promoter (rs1946518 or rs187238) polymorphisms and susceptibility to chronic hepatitis B virus (HBV) infection. We conducted a search of PubMed, EMBASE, and the Chinese National Knowledge Infrastructure (CNKI) databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were determined as measures of the strength of association between IL-18 gene promoter polymorphisms and chronic HBV infection. Sensitivity analysis and publication bias were evaluated. All analyses were undertaken using the STATA 13.0. A total of 11 studies were included in the meta-analysis. We found a statistically significant association between rs187238 polymorphism and chronic HBV infection in total populations (heterozygous model, OR 0.732, 95% CI 0.539-0.994, *P* = 0.046). Further, results from our stratified analysis showed that there was a robust significant association between rs187238 polymorphism and chronic HBV infection in Asians (allelic model, OR 0.775, 95% CI 0.603-0.995, *P* = 0.045; heterozygous model, OR 0.676, 95% CI 0.513-0.892, *P* = 0.006; dominant model, OR 0.709, 95% CI 0.534-0.940, *P* = 0.017), especially in the Chinese populations (allelic model, OR 0.675, 95% CI 0.540-0.844, *P* = 0.001; heterozygous model, OR 0.557, 95% CI 0.465-0.668, *P*<0.001; dominant model, OR 0.582, 95% CI 0.489-0.692, *P*<0.001). However, no significant association was observed between rs1946518 polymorphism and chronic HBV infection under different comparison models. The present meta-analysis suggested that IL-18 -137 C/G (rs187238) polymorphism in promoter region was associated with chronic HBV infection in Asians, especially in the Chinese populations.

Keywords: Interleukine-18, polymorphisms, HBV, meta-analysis

Introduction

Hepatitis B virus (HBV) infection has become a prominent health obstacle with more than 400 million HBV carriers around the world [1]. HBV is transmitted by exposure to infectious blood or body fluids such as semen and vaginal fluids through blood vessels, skin, or mucous membranes, and perinatally from mother to child [2]. The clinical outcome of HBV infection varies between individuals and possibly includes spontaneous recovery, hepatitis B surface antigen (HBsAg) carriers, chronic hepatitis B (CHB), liver cirrhosis (LC) or hepatocellular carcinoma (HCC) [3].

Cytokines act as pleiotropic polypeptides were closely involved in both innate and adaptive immune response and defense against viral infection. Interleukine-18 (IL-18), a novel pro-inflammatory cytokine, is known as immune activator involved in host defense mechanisms [4]. It was initially recognized as an interferon-γ (IFN-γ)-inducing factor [5]. The human IL-18 gene is located on chromosome 11q22.2-22.3 and consists of five introns and six exons [6]. IL-18 gene expression is regulated by at least two distinct promoter regions, one of which is located upstream of untranslated exon 1 (promoter 1) and the other upstream of exon 2 (promoter 2) [7]. Two single nucleotide polymor-

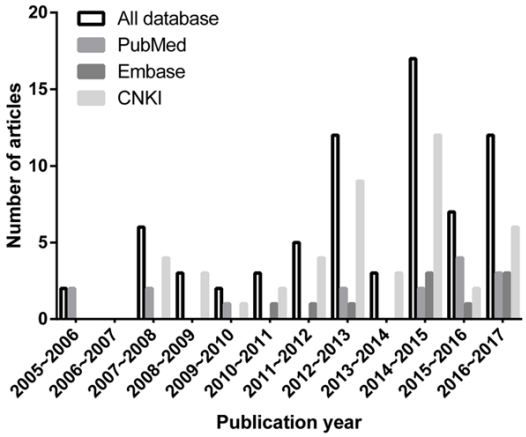


Figure 1. The distribution of topic-related literature in the electronic database over the past decade.

phisms (SNPs) at position IL-18 -607C/A (rs1946518) and IL-18 -137C/G (rs187238) in the IL-18 gene promoter region played a valuable role in altering promoter transcription activity [1], which can influence the level of IL-18 protein production [8]. So, immune status of an individual may be affected by the alteration, consequently making carriers more or less susceptible to the diseases. This may be a potential mechanism of the observed association between IL-18 gene promoter polymorphisms and diverse diseases.

So far, IL-18 gene promoter polymorphisms have been proved associated with various diseases, including tuberculosis [9], systemic lupus erythematosus [10], bladder cancer [11], colorectal cancer [12], oral cancer [13], and breast cancer [14]. Recently, several studies have investigated the association between IL-18 gene promoter polymorphisms and susceptibility to chronic HBV infection [1, 15]. However, results remain controversial, in part because of the differences from the sample sizes, the types of control, and the ethnicity of the patients. Therefore, we performed a meta-analysis to derive a more powerful estimation of the association between IL-18 gene promoter polymorphisms and susceptibility to chronic HBV infection.

Materials and methods

Identification of eligible studies

This meta-analysis was conducted according to PRISMA statement [16] and Cochrane Collaboration guidelines (http://handbook.cochrane.org/). We performed a systematic search using PubMed, Embase, and the Chinese National Knowledge Infrastructure (CNKI) databases with the last search updated on January 2, 2017. The search strategies were based on combinations of the following terms: "interleukin-18 -137 or interleukin-18 -607 or IL-18 -137 or IL-18 -607 or rs187238 or rs1946518" AND "polymorphism or polymorphisms or SNP or variant or variants or variation or genotype or genetic or mutation" AND "hepatitis B or HBV". In addition, reference lists of all identified articles were manually screened and reviewed for relevant studies.

Eligibility criteria

Studies were included in this meta-analysis if they satisfied the following criteria: (1) It was acase-control study in human beings; (2) The study assessed the association between IL-18 gene promoter (rs1946518 or rs187238) polymorphisms and susceptibility to chronic HBV infection; (3) The study provided complete genotypes distribution data; (4) The study fulfilled Hardy-Weinberg equilibrium (HWE) in the control group; (5) Genotyping method in each study was universally acknowledged. If more than one study were published using the same case series, we included the study with the most cases or the most recent analysis. Two reviewers independently identified eligible studies according to the selection criteria. Any disagreement between reviewers was solved by discussion.

Data extraction

Data were extracted by two reviewers independently, and then another reviewer verified them and any discrepancies were resolved by consensus. The following data were extracted from each study: name of first author, year of publication, ethnicity, country of origin, genotyping method, type of controls, HWE in control groups, numbers of cases and controls, genotype frequency in cases and controls, respectively.

Statistical analysis

HWE was evaluated by Pearson's goodness-of-fit χ^2 test for each study in the controls, and a *P* value of less than 0.05 was considered as devi-

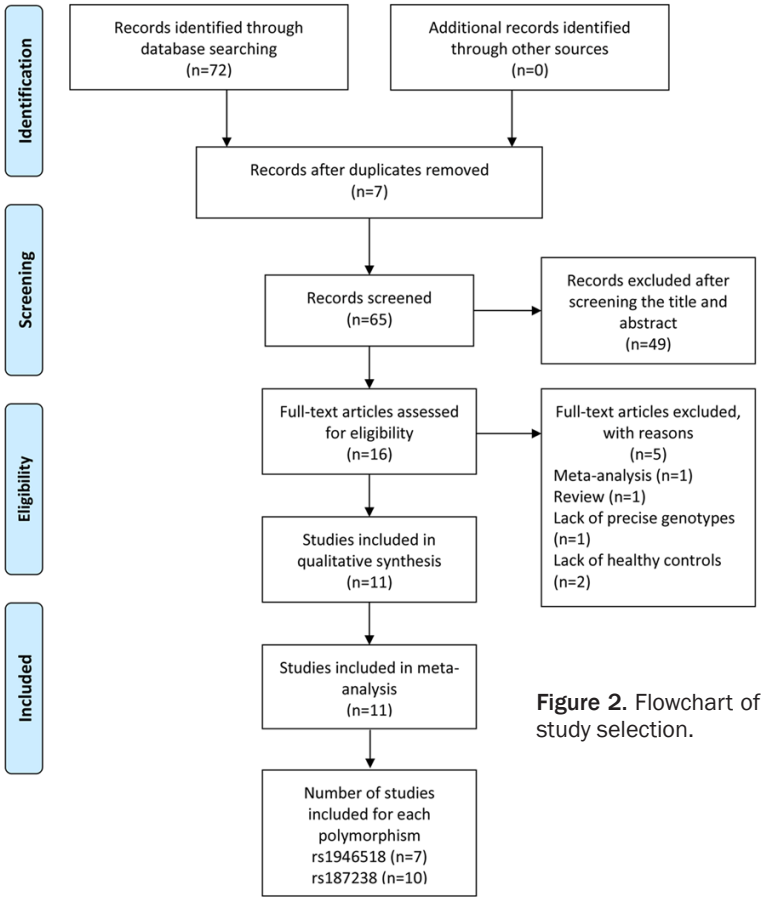


Figure 2. Flowchart of study selection.

ation from HWE [17]. The strength of the association between the IL-18 gene promoter polymorphisms and susceptibility to chronic HBV infection was assessed by calculating crude odds ratios (ORs) along with their 95% confidence intervals (CIs). The pooled ORs (rs1946518) were calculated for the allelic model (C-allele vs. A-allele), heterozygous model (AC vs. AA), homozygous model (CC vs. AA), dominant model (CC+AC vs. AA) and recessive model (CC vs. AC+AA). Similarly, the pooled ORs (rs187238) were calculated for the allelic model (C-allele vs. G-allele), heterozygous model (GC vs. GG), homozygous model (CC vs. GG), dominant model (CC+GC vs. GG) and recessive model (CC vs. GC+GG). Heterogeneity was determined using the Cochrane's Q test and I^2 statistics [18]. When the Q-test showed a $P<0.05$ or I^2 test exhibited >50%, the random-effect model was used for the meta-analysis [19]; otherwise, the fixed-effect model was chosen [20]. We performed stratified analyses based on Asian and Chinese populations. Sensitivity analyses were also carried out by sequential omission of each study one at a time to ensure the stability of our results. Publication bias was assessed using Begg's funnel plot [21] and Egger's linear regression method [22]. All statistical analyses were performed by using STATA version 13.0 (Stata Corpotion, College Station, Texas).

Results

Study characteristics

We give the detailed search strategies and results in the supplemental material (see Table S1). A total of 72 records were initially identified from PubMed, Embase, and CNKI databases. The distribution of the number of topic-related literatures in the electronic databases for the last decade is shown in **Figure 1**. All studies were published from 2005 to 2016, most of which were published in the past two years. Firstly, 7 records were excluded using EndNote X8 due to duplication of records across the databases. Due to unrelated topics, we excluded 49 studies based on review of the titles and abstracts. We excluded another one study because it was a meta-analysis [23], one study because it was a review study [15], one study because it did not report genotypes [24], and two studies because they were lack of healthy controls [25, 26]. Finally, a total of 11 studies (6 studies in English and 5 in Chinese) were included based on our inclusion criteria [1, 27-36]. A total of 10 studies with 1,450 cases and 1,949 controls for the rs187238 polymorphism were performed a meta-analysis [1, 27-32, 34-36]. For the rs187238 polymorphism, the distribution of genotypes in the controls of all studies was in agreement with HWE ($P>0.05$). For the rs1946518 polymorphism, two studies were further excluded due to deviating from HWE [34, 35], and then a total of 7 studies with 1,439 cases and 1,633 controls [1, 27-29, 32, 33, 36]. The flow diagram summarizing the literature review process and final

Table 1. Characteristics of studies in the meta-analysis

First author	Year	Ethnicity	Country	Genotyping method	Type of control	*P* for HWE	Cases/Controls	No. of cases			No. of controls		
IL-18 -607 C/A (rs1946518)								AA	AC	CC	AA	AC	CC
Zhang QX [27]	2016	Asian	China	PCR-LDR	Healthy	0.542	113/127	31	60	22	23	66	38
Li N [33]	2012	Asian	China	Multiplex Snapshot	HBV natural clearance	0.448	501/301	141	239	121	60	156	85
Hirankarn N [35]	2007	Asian	Thailand	PCR-SSP	Healthy	0.012	140/140	39	68	33	18	83	39
Zhang PA [36]	2005	Asian	China	PCR-SSP	Healthy	0.243	231/300	53	116	62	74	160	66
Gao JM [34]	2010	Asian	China	PCR-sequencing	Healthy	0.041	56/193	17	35	4	49	110	34
Lu Y [28]	2015	Asian	China	PCR-RFLP	Healthy	0.278	129/160	32	58	39	40	73	47
Karra VK [1]	2015	Asian	India	PCR-SSP	Healthy	0.120	48/280	10	36	2	102	144	34
Liao Y [32]	2013	Asian	China	PCR-SSP	Healthy	0.429	264/300	56	145	63	83	156	61
Bao J [29]	2015	Asian	China	PCR-RFLP	Healthy	0.322	153/165	37	73	43	41	76	48
IL-18 -137 C/G (rs187238)								GG	GC	CC	GG	GC	CC
Zhang QX [27]	2016	Asian	China	PCR-LDR	Healthy	0.110	113/127	93	17	3	99	24	4
Hirankarn N [35]	2007	Asian	Thailand	PCR-SSP	Healthy	0.999	140/140	105	29	6	102	35	3
Zhang PA [36]	2005	Asian	China	PCR-SSP	Healthy	0.588	231/300	182	45	4	202	90	8
Gao JM [34]	2010	Asian	China	PCR-sequencing	Healthy	0.792	56/193	41	11	4	151	39	3
Lu Y [28]	2015	Asian	China	PCR-RFLP	Healthy	0.611	129/160	100	27	2	103	52	5
Karra VK [1]	2015	Asian	India	PCR-SSP	Healthy	0.320	48/280	19	27	2	159	108	13
Liao Y [32]	2013	Asian	China	PCR-SSP	Healthy	0.183	264/300	182	68	14	173	115	12
Bao J [29]	2015	Asian	China	PCR-RFLP	Healthy	0.548	153/165	122	28	3	106	54	5
Yalcin S [30]	2014	European	Turkey	PCR-sequencing	Noninfected individuals	0.773	40/30	26	12	2	27	3	0
Jiang H [31]	2014	Asian	China	PCR-LDR	Healthy	0.324	276/254	221	51	4	168	80	6

PCR, polymerase chain reaction; LDR, ligase detection reaction; SSP, sequence-specific primer; RFLP, restriction fragment length polymorphism; HWE, Hardy-Weinberg equilibrium.

Table 2. Main results on association between IL-18 gene promoter (-607 C/A and -137 C/G) polymorphisms and chronic HBV infection

Comparisons	No. of Studies	Test of association			Analysis model	Test of heterogeneity			*P-value* (Egger's test)
		OR	95% CI	*P-value*		χ^2	*P-value*	I^2 (%)	
IL-18 -607 (rs1946518) in total populations (1,439 cases and 1,633 controls)									
Allelic (C/A)	7	0.980	0.828-1.161	0.818	Random	14.58	0.024	58.8	0.890
Heterozygous (AC/AA)	7	1.034	0.763-1.402	0.830	Random	15.25	0.018	60.7	0.331
Homozygous (CC/AA)	7	0.909	0.637-1.298	0.600	Random	14.55	0.024	58.8	0.708
Dominant (CC+AC/AA)	7	1.013	0.745-1.376	0.936	Random	17.21	0.009	65.1	0.482
Recessive (CC/AC+AA)	7	0.954	0.804-1.133	0.593	Fixed	10.08	0.121	40.5	0.248
IL-18 -607 (rs1946518) in Chinese populations (1,391 cases and 1,353 controls)									
Allelic (C/A)	6	0.962	0.800-1.156	0.679	Random	13.87	0.016	64.0	0.853
Heterozygous (AC/AA)	6	0.929	0.770-1.120	0.440	Fixed	8.64	0.124	42.1	0.917
Homozygous (CC/AA)	6	0.925	0.635-1.348	0.686	Random	14.25	0.014	64.9	0.848
Dominant (CC+AC/AA)	6	0.933	0.698-1.247	0.640	Random	12.42	0.030	59.7	0.958
Recessive (CC/AC+AA)	6	0.978	0.822-1.164	0.802	Fixed	7.78	0.169	35.7	0.670
IL-18 -137 (rs187238) in total populations (1,450 cases and 1,949 controls)									
Allelic (C/G)	10	0.830	0.630-1.094	0.187	Random	32.64	<0.001	72.4	0.047
Heterozygous (GC/GG)	10	0.732	0.539-0.994	0.046	Random	27.79	0.001	67.6	0.013
Homozygous (CC/GG)	10	0.977	0.649-1.472	0.912	Fixed	10.16	0.338	11.4	0.970
Dominant (CC+GC/GG)	10	0.772	0.564-1.057	0.106	Random	31.72	<0.001	71.6	0.011
Recessive (CC/GC+GG)	10	1.074	0.715-1.612	0.731	Fixed	8.54	0.481	0.0	0.714
IL-18 -137 (rs187238) in Asian populations (1,410 cases and 1,919 controls)									
Allelic (C/G)	9	0.775	0.603-0.995	0.045	Random	24.67	0.002	67.6	0.203
Heterozygous (GC/GG)	9	0.676	0.513-0.892	0.006	Random	20.66	0.008	61.3	0.064
Homozygous (CC/GG)	9	0.934	0.616-1.418	0.750	Fixed	9.02	0.340	11.3	0.970
Dominant (CC+GC/GG)	9	0.709	0.534-0.940	0.017	Random	23.49	0.003	65.9	0.057
Recessive (CC/GC+GG)	9	1.039	0.688-1.570	0.856	Fixed	7.85	0.448	0.0	0.714
IL-18 -137 (rs187238) in Chinese populations (1,222 cases and 1,499 controls)									
Allelic (C/G)	7	0.675	0.540-0.844	0.001	Random	12.08	0.060	50.3	0.406
Heterozygous (GC/GG)	7	0.557	0.465-0.668	<0.001	Fixed	4.49	0.610	0.0	0.109
Homozygous (CC/GG)	7	0.839	0.531-1.326	0.452	Fixed	7.71	0.260	22.1	0.760
Dominant (CC+GC/GG)	7	0.582	0.489-0.692	<0.001	Fixed	8.13	0.229	26.2	0.197
Recessive (CC/GC+GG)	7	0.977	0.620-1.539	0.918	Fixed	6.90	0.330	13.1	0.646

participation is shown in **Figure 2**. Genotype methods used in these studies were PCR-LDR, PCR-SSP, PCR-RFLP, PCR and sequencing, and Multiplex Snapshot technique, which were universally acknowledged. The main characteristics of the selected studies are presented in **Table 1**.

Meta-analysis of data on the rs1946518 polymorphism

A total of 7 studies with 1,439 cases and 1,633 controls for the rs1946518 polymorphism were identified to perform a meta-analysis. The meta-analysis of a possible association between the rs1946518 polymorphism and susceptibility to chronic HBV infection was summarized in **Table 2**. Based on the total populations, none of the five genetic models indicated a significant association: allelic model, OR 0.980, 95% CI 0.828-1.161, *P* = 0.818; heterozygous model, OR 1.034, 95% CI 0.763-1.402, *P* = 0.830; homozygous model, OR 0.909, 95% CI 0.637-1.298, *P* = 0.600; dominant model, OR 1.013, 95% CI 0.745-1.376, *P* = 0.936; recessive model, OR 0.954, 95% CI 0.804-1.133, *P* = 0.593. Similarly, no significant association was observed for the subgroup of Chinese populations in 6 studies (**Table 2**).

Meta-analysis of data on the rs187238 polymorphism

A total of 10 studies with 1,450 cases and 1,949 controls for the rs187238 polymorphism were identified to perform a meta-analysis. The

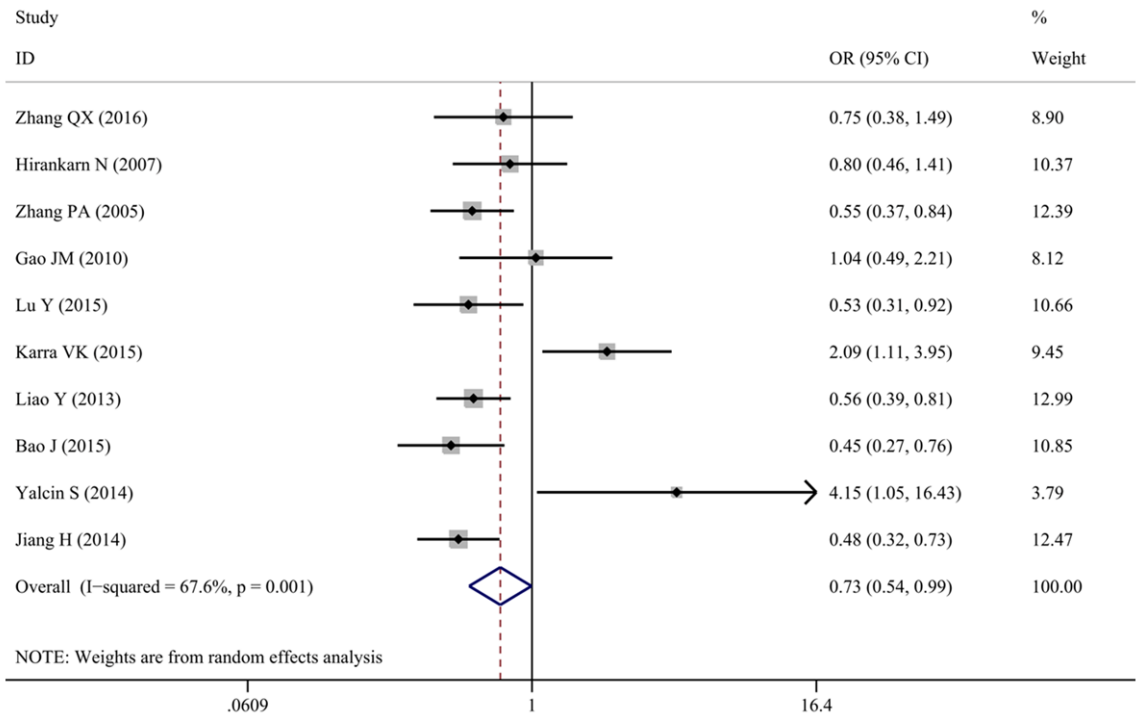


Figure 3. Forest plot describing the association between the rs187238 polymorphism and susceptibility to chronic HBV infection in total populations according to heterozygous model (GC vs. GG).

meta-analysis of a possible association between the rs187238 polymorphism and susceptibility to chronic HBV infection was summarized in **Table 2**. Based on the total populations, the combined results showed that there was a statistically significant association between rs187238 polymorphism and chronic HBV infection under heterozygous model: OR 0.732, 95% CI 0.539-0.994, *P* = 0.046 (**Figure 3**). However, there was no evidence of association between the rs187238 polymorphism and the susceptibility of chronic HBV infection in other four comparison models (**Table 2**).

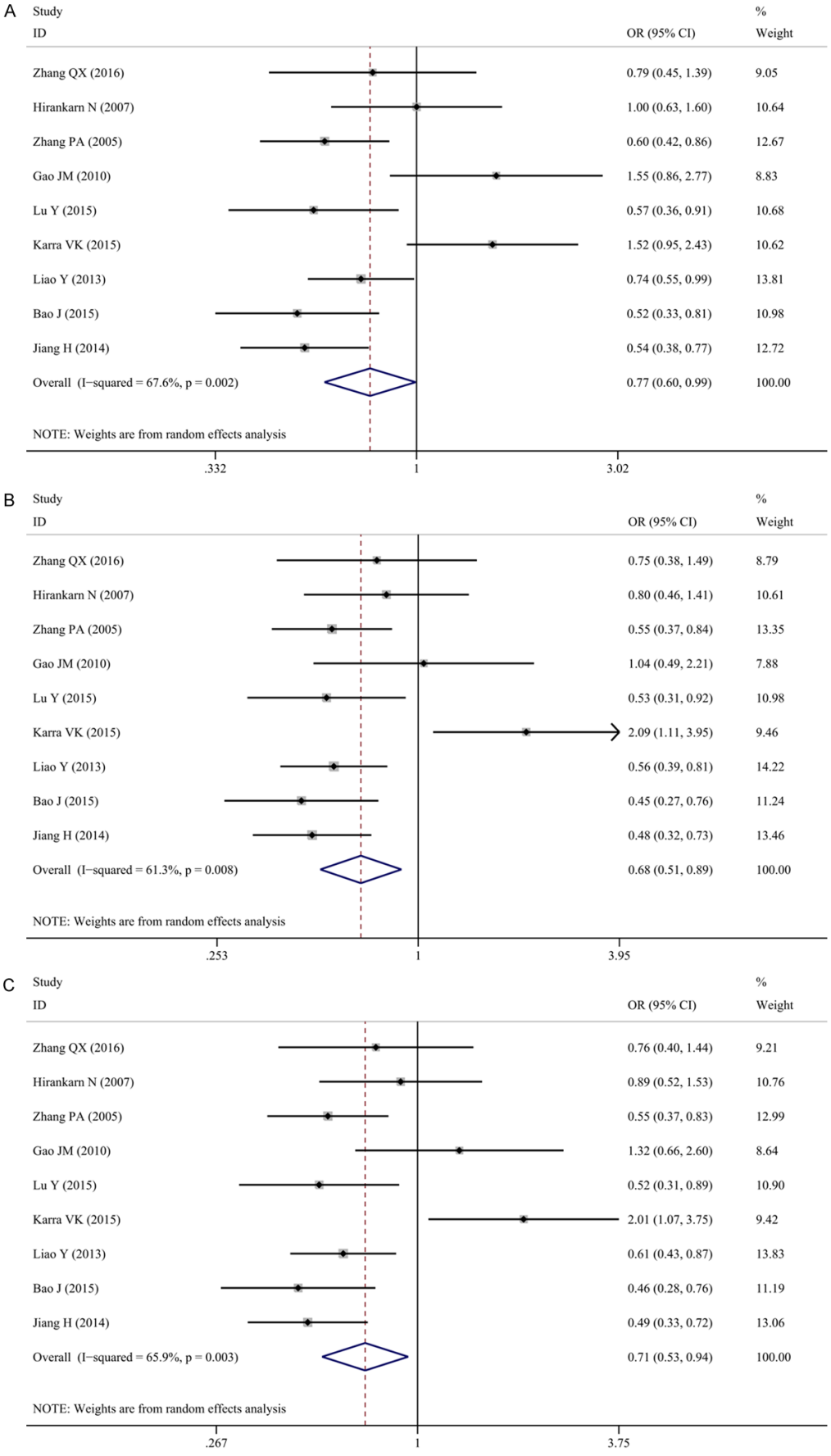
We also performed stratified analysis based on Asian and Chinese populations. In Asians, The combined results showed that there was a robust significant association between rs187-238 polymorphism and chronic HBV infection under three comparison models: allelic model, OR 0.775, 95% CI 0.603-0.995, *P* = 0.045 (**Figure 4A**); heterozygous model, OR 0.676, 95% CI 0.513-0.892, *P* = 0.006 (**Figure 4B**); dominant model, OR 0.709, 95% CI 0.534-0.940, *P* = 0.017 (**Figure 4C**). In Chinese populations, a more robustly significant association between rs187238 polymorphism and chronic HBV infection was also observed under three comparison models: allelic model, OR 0.675, 95% CI 0.540-0.844, *P* = 0.001 (**Figure 5A**); heterozygous model, OR 0.557, 95% CI 0.465-0.668, *P*<0.001 (**Figure 5B**); dominant model, OR 0.582, 95% CI 0.489-0.692, *P*<0.001 (**Figure 5C**).

Sensitivity analysis

In order to assess the robustness of the meta-analysis results, we carried out a sensitivity analysis. Our results showed that pooled ORs were not materially altered, which suggested that noindividual study significantly affected the pooled results.

Publication bias

Begg's funnel plots and Egger's regression method were used to assess publication bias statistically. For the rs1946518 polymorphism, the results of Egger's linear regression test did not provide statistical evidence of publication bias (*P*>0.05) (**Table 2**). Funnel plot analyses were also not generally indicative of any strong publication bias because visual inspection of


A
Study
ID
OR (95% CI)
%
Weight
Zhang QX (2016) 0.79 (0.45, 1.39) 9.05
Hirankarn N (2007) 1.00 (0.63, 1.60) 10.64
Zhang PA (2005) 0.60 (0.42, 0.86) 12.67
Gao JM (2010) 1.55 (0.86, 2.77) 8.83
Lu Y (2015) 0.57 (0.36, 0.91) 10.68
Karra VK (2015) 1.52 (0.95, 2.43) 10.62
Liao Y (2013) 0.74 (0.55, 0.99) 13.81
Bao J (2015) 0.52 (0.33, 0.81) 10.98
Jiang H (2014) 0.54 (0.38, 0.77) 12.72
Overall (I−squared = 67.6%, p = 0.002) 0.77 (0.60, 0.99) 100.00
NOTE: Weights are from random effects analysis
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Study
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OR (95% CI)
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Weight
Zhang QX (2016) 0.75 (0.38, 1.49) 8.79
Hirankarn N (2007) 0.80 (0.46, 1.41) 10.61
Zhang PA (2005) 0.55 (0.37, 0.84) 13.35
Gao JM (2010) 1.04 (0.49, 2.21) 7.88
Lu Y (2015) 0.53 (0.31, 0.92) 10.98
Karra VK (2015) 2.09 (1.11, 3.95) 9.46
Liao Y (2013) 0.56 (0.39, 0.81) 14.22
Bao J (2015) 0.45 (0.27, 0.76) 11.24
Jiang H (2014) 0.48 (0.32, 0.73) 13.46
Overall (I−squared = 61.3%, p = 0.008) 0.68 (0.51, 0.89) 100.00
NOTE: Weights are from random effects analysis
.253
1
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Study
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OR (95% CI)
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Weight
Zhang QX (2016) 0.76 (0.40, 1.44) 9.21
Hirankarn N (2007) 0.89 (0.52, 1.53) 10.76
Zhang PA (2005) 0.55 (0.37, 0.83) 12.99
Gao JM (2010) 1.32 (0.66, 2.60) 8.64
Lu Y (2015) 0.52 (0.31, 0.89) 10.90
Karra VK (2015) 2.01 (1.07, 3.75) 9.42
Liao Y (2013) 0.61 (0.43, 0.87) 13.83
Bao J (2015) 0.46 (0.28, 0.76) 11.19
Jiang H (2014) 0.49 (0.33, 0.72) 13.06
Overall (I−squared = 65.9%, p = 0.003) 0.71 (0.53, 0.94) 100.00
NOTE: Weights are from random effects analysis
.267
1
3.75

Figure 4. Forest plot describing the association between the rs187238 polymorphism and susceptibility to chronic HBV infection in Asians. A: Allelic (C-allele vs. G-allele), B: Heterozygous (GC vs. GG), C: Dominant (GC+ CC vs. GG).

funnel plots did not show asymmetry for all comparison models (**Figure 6**), indicating the strength of the results. For the rs187238 polymorphism, we found that there was a significant publication bias in overall populations, but there was not a publication bias in Asian or Chinese populations (**Table 2**).

Discussion

IL-18 that is part of the pro-inflammatory cytokine network is an essential mediator in innate and adaptive immunity. As noted in the introduction, several SNPs in the IL-18 gene promoter region have been predicted to affect the expression of IL-18 and are involved in the HBV infection. A review study conducted by Motavaf *et al*. [15], which reviewed the association between IL-18 gene promoter single nucleotide polymorphisms (-137 C/G and -607 C/A) and susceptibility to chronic HBV infection, suggested that IL-18 genotype -607 A/A was associated with susceptibility to chronic hepatitis B. However, a previous meta-analysis conducted by Xia *et al*. [23], which reviewed Association of polymorphisms in interleukin-18 and interleukin-28B genes with outcomes of hepatitis B virus infections, showed that there was no evidence for an association between the HBV infections and the variant genotypes of IL-18. Therefore, to provide a more accurate estimate of the association between IL-18 gene promoter (rs1946518 and rs187238) polymorphisms and susceptibility to chronic HBV infection, we conducted a meta-analysis with inclusion of newly published studies in English and Chinese. The present meta-analysis suggested that IL-18 -137 C/G (rs187238) polymorphism in promoter region was associated with chronic HBV infection, but no significant association was observed between IL-18 -607 C/A (rs1946518) polymorphism and susceptibility to chronic HBV infection.

For the IL-18 -607 C/A (rs1946518) polymorphism, we found no strong evidence of association with susceptibility to chronic HBV infection. It was in agreement with the result of Xia *et al*. study [23] in which the pooled data demonstrated that IL-18 rs1946518 was not associated with an increased risk of HBV infection in CHB patients and healthy controls. Furthermore, a recent meta-analysis conducted by Zhu *et al*. [37] suggested no significant association of the IL-18 -607 polymorphism with risk of HCC in general or specifically of HBV-related HCC. As a result, we our findings support the viewpoint that no significant association of the rs1946518 polymorphism with risk of HBV-related HCC. We performed a stratified analysis based on Chinese populations, and the pooled data also demonstrated that there was no evidence of association between the rs1946518 polymorphism and the susceptibility of chronic HBV infection. Sensitivity analysis demonstrated that pooled ORs were not materially altered, indicating that our results were robust and reliable. After evaluating the publication bias by Begg's funnel plots and Egger's regression method, we did not detect a publication bias based on total population or Chinese population, indicating the strength of the results.

However, we found that genotype GC and the allele C of the IL-18 at position -137 C/G (rs187238) were closely associated with the resistance to chronic HBV infection, especially in Chinese populations. It was in agreement with the result of Motavaf *et al*. study [15] in which allele C at position -137 was suggested to play a protective role against development of chronic HBV infection. Furthermore, Lau et al. [38] showed that the correlation between the IL-18 -137 C/G polymorphism and HCC-related HBV infection was a risk factor for vascular invasion. Here our findings cast doubt on the relevance of IL-18 -137 C/G polymorphism in the pathogenesis of HBV-related HCC. However, a recent meta-analysis [37] simply suggested that the IL-18 -137 polymorphism do not affect viral clearance, at least not clearance of HBV, since they found no evidence that either association was associated with risk of HBV-related HCC. So, future large studies should investigate these possibilities. We conducted a test for publication bias in total populations, Asians or Chinese populations. We found that there was a significant publication bias in total populations, but there was not a publication bias in Asians or Chinese populations. However, the significance of results did not change after sen-

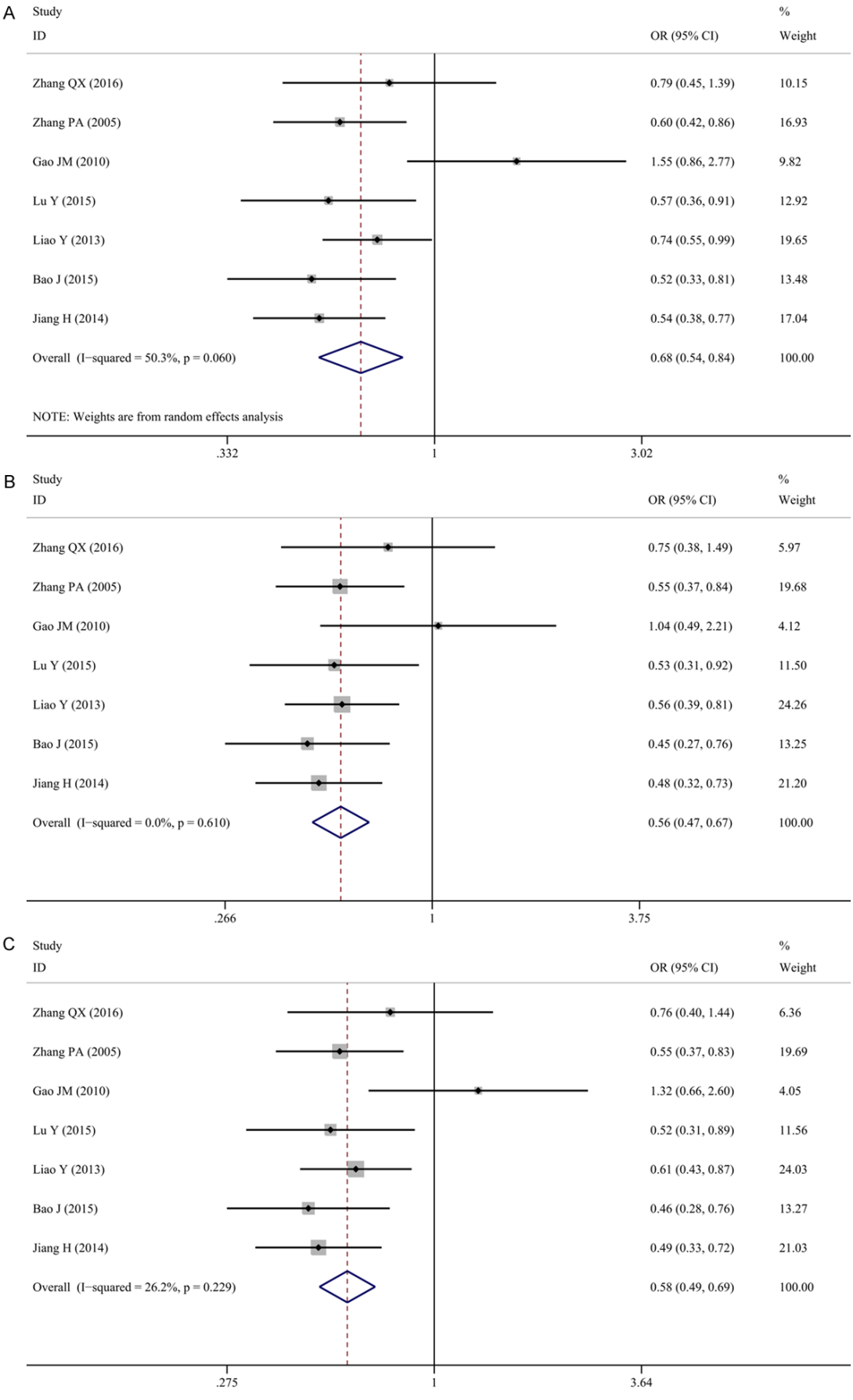
A
Study
ID
OR (95% CI)
%
Weight
Zhang QX (2016)
0.79 (0.45, 1.39)
10.15
Zhang PA (2005)
0.60 (0.42, 0.86)
16.93
Gao JM (2010)
1.55 (0.86, 2.77)
9.82
Lu Y (2015)
0.57 (0.36, 0.91)
12.92
Liao Y (2013)
0.74 (0.55, 0.99)
19.65
Bao J (2015)
0.52 (0.33, 0.81)
13.48
Jiang H (2014)
0.54 (0.38, 0.77)
17.04
Overall (I−squared = 50.3%, p = 0.060)
0.68 (0.54, 0.84)
100.00
NOTE: Weights are from random effects analysis
.332
1
3.02
B
Study
ID
OR (95% CI)
%
Weight
Zhang QX (2016)
0.75 (0.38, 1.49)
5.97
Zhang PA (2005)
0.55 (0.37, 0.84)
19.68
Gao JM (2010)
1.04 (0.49, 2.21)
4.12
Lu Y (2015)
0.53 (0.31, 0.92)
11.50
Liao Y (2013)
0.56 (0.39, 0.81)
24.26
Bao J (2015)
0.45 (0.27, 0.76)
13.25
Jiang H (2014)
0.48 (0.32, 0.73)
21.20
Overall (I−squared = 0.0%, p = 0.610)
0.56 (0.47, 0.67)
100.00
.266
1
3.75
C
Study
ID
OR (95% CI)
%
Weight
Zhang QX (2016)
0.76 (0.40, 1.44)
6.36
Zhang PA (2005)
0.55 (0.37, 0.83)
19.69
Gao JM (2010)
1.32 (0.66, 2.60)
4.05
Lu Y (2015)
0.52 (0.31, 0.89)
11.56
Liao Y (2013)
0.61 (0.43, 0.87)
24.03
Bao J (2015)
0.46 (0.28, 0.76)
13.27
Jiang H (2014)
0.49 (0.33, 0.72)
21.03
Overall (I−squared = 26.2%, p = 0.229)
0.58 (0.49, 0.69)
100.00
.275
1
3.64

Figure 5. Forest plot describing the association between the rs187238 polymorphism and susceptibility to chronic HBV infection in Chinese populations. A: Allelic (C-allele vs. G-allele), B: Heterozygous (GC vs. GG), C: Dominant (GC+CC vs. GG).

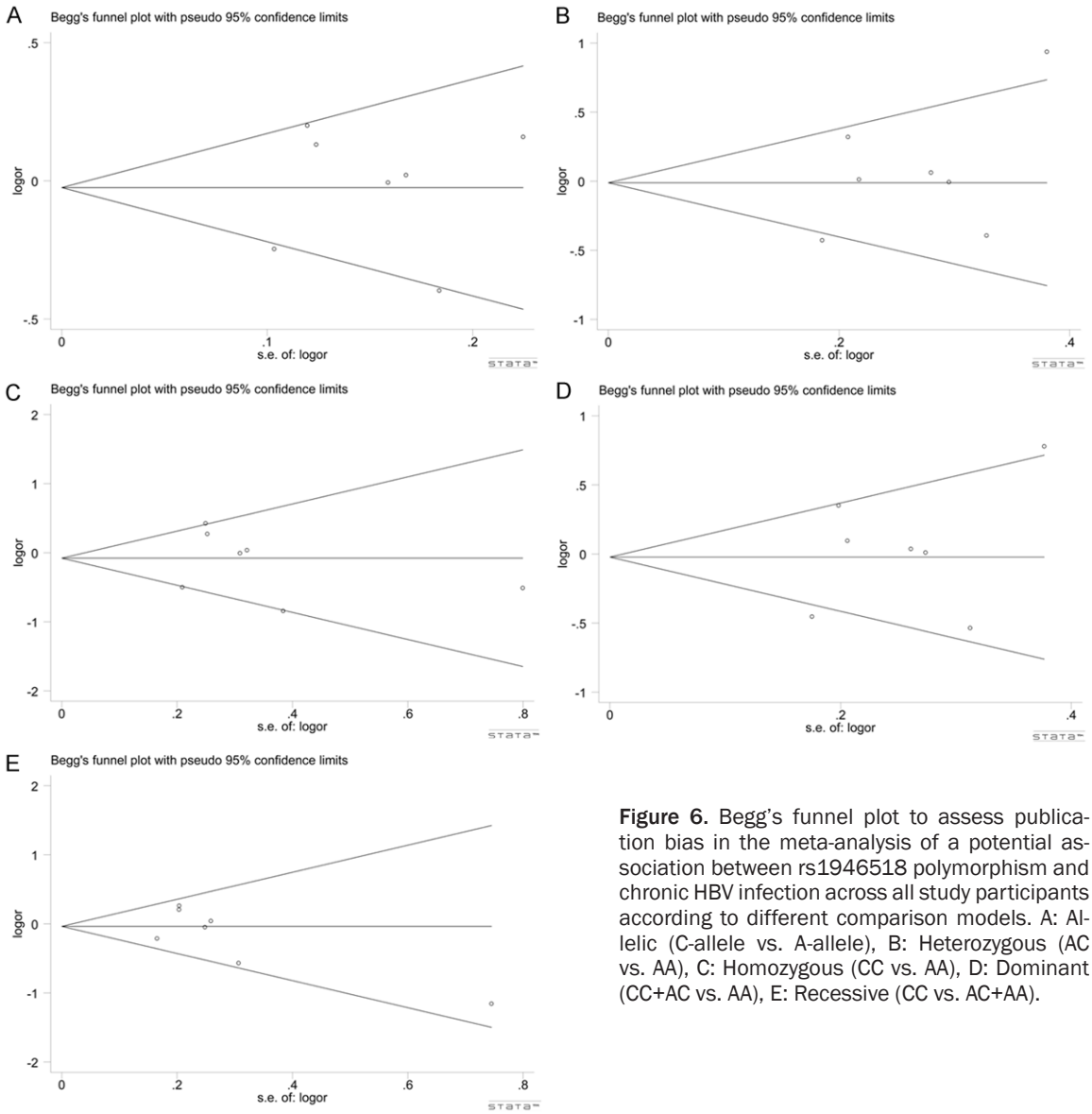

Figure 6. Begg's funnel plot to assess publication bias in the meta-analysis of a potential association between rs1946518 polymorphism and chronic HBV infection across all study participants according to different comparison models. A: Allelic (C-allele vs. A-allele), B: Heterozygous (AC vs. AA), C: Homozygous (CC vs. AA), D: Dominant (CC+AC vs. AA), E: Recessive (CC vs. AC+AA).

sitivity analysis. So our conclusions might be stable for Asians and Chinese populations.

Several limitations of this meta-analysis should be summarized. Firstly, our exclusion of papers published in languages other than English and Chinese might have biased our results. Secondly, the studies in our meta-analysis relied on an array of genotyping methods, including PCR-LDR, PCR-SSP, PCR-RFLP, PCR and sequencing, and Multiplex Snapshot technique, but we did not perform a subgroup analysis based on genotyping methods. Lastly, since this meta-analysis included only one study from European populations, large and well-designed studies in Caucasian and African populations are warranted. However, a more precise analysis should be conducted if there were more detailed individual data, such as age, gender, alcohol consumption and other risk factors.

In conclusion, this meta-analysis suggested that no significant association was observed

between IL-18 -607 C/A (rs1946518) polymorphism and susceptibility to chronic HBV infection under different contrast models. But IL-18 -137 C/G (rs187238) polymorphism in promoter region was associated with susceptibility to chronic HBV infection in Asians, especially in Chinese populations.

Disclosure of conflict of interest

None.

Address correspondence to: Guoming Su, Department of Pharmacy and Laboratory, Sichuan Nursing Vocational College, No. 173 Longdu Road South, Longquanyi District, Chengdu 610100, Sichuan Province, China. E-mail: guomingsu77@163.com

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Table S1. The detailed search strategies and results

Database	Last update	Search strategy	Results
PubMed	January 2, 2017	(((((((“interleukin-18”[MeSH Terms] OR “interleukin-18”[All Fields] OR “interleukin 18”[All Fields]) AND -137[All Fields]) OR ((“interleukin-18”[MeSH Terms] OR “interleukin-18”[All Fields] OR “interleukin 18”[All Fields]) AND -607[All Fields])) OR ((“interleukin-18”[MeSH Terms] OR “interleukin-18”[All Fields] OR “il 18”[All Fields]) AND -137[All Fields])) OR ((“interleukin-18”[MeSH Terms] OR “interleukin-18”[All Fields] OR “il 18”[All Fields]) AND -607[All Fields])) OR rs187238[All Fields]) OR rs1946518[All Fields]) AND ((((((((“polymorphism, genetic”[MeSH Terms] OR (“polymorphism”[All Fields] AND “genetic”[All Fields]) OR “genetic polymorphism”[All Fields] OR “polymorphism”[All Fields]) OR (“polymorphism, genetic”[MeSH Terms] OR (“polymorphism”[All Fields] AND “genetic”[All Fields]) OR “genetic polymorphism”[All Fields] OR “polymorphisms”[All Fields])) OR (“Socioaffect Neurosci Psychol”[Journal] OR “snp”[All Fields])) OR variant[All Fields]) OR variants[All Fields]) OR variation[All Fields]) OR (“genotype”[MeSH Terms] OR “genotype”[All Fields])) OR (“genetic therapy”[MeSH Terms] OR (“genetic”[All Fields] AND “therapy”[All Fields]) OR “genetic therapy”[All Fields] OR “genetic”[All Fields])) OR (“mutation”[MeSH Terms] OR “mutation”[All Fields]))) AND (HBV[All Fields] OR (“hepatitis b”[MeSH Terms] OR “hepatitis b”[All Fields]))	16
Embase	January 2, 2017	‘interleukin-18 -137’ OR ‘interleukin-18 -607’ OR ‘il-18 -137’ OR ‘il-18 -607’ OR ‘rs187238’ OR ‘rs1946518’ AND (polymorphism OR polymorphisms OR snp OR variant OR variants OR variation OR genotype OR genetic OR ‘gene mutation’) AND (‘hepatitis b’ OR hbv)	10
CNKI	January 2, 2017	FT = ‘interleukin-18 -137’ + ‘interleukin-18 -607’ + ‘IL-18 -137’ + ‘IL-18 -607’ + ‘rs187238’ + ‘rs1946518’ AND FT = polymorphism + polymorphisms + snp + variant + variants + variation + genotype + genetic + mutation AND FT = ‘hepatitis B’ + ‘HBV’	44