Systematic Review and Meta-Analysis

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Association between polymorphisms in the interleukin-10 gene and susceptibility to human immunodeficiency virus-1 infection

A systematic review and meta-analysis

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Abstract

Background: This study meta-analyzed the literature on possible association of 3 polymorphisms (-592, -1082, -819) in the interleukin-10 (IL-10) gene with susceptibility to human immunodeficiency virus (HIV)-1 infection.

Methods: PubMed, EMBASE, MEDLINE and Google Scholar were systematically searched to identify relevant studies in English. Meta-analyses were performed to examine the association of IL-10 polymorphisms -592, -1082, and -819 with susceptibility to HIV-1 infection.

Results: A significant association between the -592 polymorphism and susceptibility to HIV-1 infection was found in the total population (recessive model, odds ratios (OR) = 1.44, 95% CI = 1.06–1.96, $P = .02$; homozygous model, OR = 1.44, 95% CI = 1.02–2.02, $P = .04$). However, these results were not observed in subgroups based on ethnicity. The -1082 polymorphism was significantly associated with susceptibility to HIV-1 infection in Caucasians (OR = 1.30, 95% CI = 1.05–1.62, $P = .02$; recessive model, OR = 1.49, 95% CI = 1.09–2.03, $P = .01$; homozygous model, OR = 1.58, 95% CI = 1.01–2.46, $P = .04$), but not in Asians or the total population. None of the 5 genetic models suggested a significant association between the -819 polymorphism and HIV-1 infection.

Conclusion: The available evidence indicates that the AA genotype of IL-10 -592 may confer increased susceptibility to HIV-1 infection, and that the AA genotype of -1082 may confer increased susceptibility in Caucasians. In contrast, the -819 polymorphism may not be associated with HIV-1 infection risk. These conclusions should be verified in large, well-designed studies.

Abbreviations: AIDS = acquired immune deficiency syndrome, HIV = human immunodeficiency virus, IL = interleukin, OR = odds ratios.

Keywords: human immunodeficiency virus-1, interleukin -10, meta-analysis, polymorphism, susceptibility

1. Introduction

Increasing data on the genes in infected hosts has widened our vision regarding the importance of host factors in mediating pathogenesis and limiting the progression of disease to acquired immune deficiency syndrome (AIDS).[1] In order to effectively prevent and treat human immunodeficiency virus (HIV), understanding the etiology of HIV infection and how it may be influenced by genetic variation in the host genome is of vital importance. Recent evidence has indicated that HIV infection and progression to AIDS in humans are significantly associated with host genetic factors, such as the cytokines.[2] Moreover, it has been suggested that cytokines play a vital role in regulating the homoeostasis of the immune system and alterations in their relative levels play critical roles in the immune response against HIV-1 infection and the progression of HIV-1 infection to clinical AIDS.[3]

Interleukin (IL)-10 is an immunoregulatory cytokine produced mainly by monocytes, macrophages, T-helper 2 cells and B lymphocytes. It can inhibit secretion of interferon γ (IFN- γ) and IL-2 from T cells, as well as IL-1, IL-6, IL-8 and tumor necrosis factor α (TNF-α) from monocytes and macrophages. IL-10 also inhibits different immune reactions such as antigen presentation, macrophage activation, antigen-specific T cell proliferation and cell-mediated immunity.[4,5] Increasing evidence has suggested

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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that IL-10 can have beneficial but also detrimental effects during HIV-1 infection. The timing and cellular source of IL-10 production are essential for the balance between successful pathogen clearance by innate and adaptive responses and the prevention of immune pathology.[6] Several previous reports have suggested that IL10 production was associated with genetic variations.[7–10]

Numerous case-control studies[6–16] have investigated whether -592, -1082, -819 polymorphisms in the IL-10 gene influence susceptibility to HIV-1 infection. The results have been inconclusive and contradictory, prompting us to perform this comprehensive meta-analysis of all available evidence on these potential associations. To the best of our knowledge, this is the largest meta-analysis concerning the 3 polymorphisms and susceptibility to HIV-1 infection.

2. Materials and Methods

2.1. Ethics statement

This study was approved by the Institutional Review Board of Tumor Hospital Affiliated to Guangxi Medical University.

2.2. Search strategy

All clinical and experimental case–control studies of polymorphisms in the IL-10 gene and HIV-1 infection published in English through May 20, 2020 were identified through systematic searches in PubMed, EMBASE, MEDLINE and Google Scholar. The search terms used were: interleukin-10; IL-10; these 2 terms in combination with polymorphism, polymorphisms, SNP, variant, variants, variation, genotype, genetic or mutation; and all of the above terms in combination with acquired immune deficiency syndrome, human immunodeficiency virus 1 or HIV-1. Reference lists in identified articles and reviews were also searched manually to identify additional eligible studies.

2.3. Inclusion criteria

To be included in our review and meta-analysis, studies had to

(1) have a case-control design for assessing the association of HIV-1 infection risk with IL-10 -592, -1082 and -819 polymorphisms;
(2) be accessible as a full-text article and report sufficient data for estimating odds ratios (ORs) with 95% confidence intervals (CIs);
(3) report genotype frequencies; and
(4) involve humans rather than animal models.

2.4. Data extraction

Two authors (DHF and WJD) independently extracted the following data from included studies: first author's family name, year of publication, ethnicity, testing methods, control source, age, sex, *P* value for Hardy-Weinberg equilibrium (HWE) in controls, numbers and genotypes of cases and controls, and frequencies of genotypes in cases and controls. Discrepancies were resolved by consensus. Only those studies that met the predetermined inclusion criteria were included.

2.5. Assessment of methodological quality

To assess the quality of the studies included in this analysis, the Newcastle–Ottawa Scale was applied independently by 2 assessors (DHF and WJD)[18] (Table 1). On the 10-point Newcastle–Ottawa Scale, scores of 5 to 9 points (stars) are considered to indicate generally high methodological quality, while scores of 0 to 4 stars are considered to indicate poor quality.[19] Any disagreements about Newcastle–Ottawa scores were resolved by other authors following a comprehensive reassessment. Only high-quality studies were included in the meta-analysis.

2.6. Statistical analysis

Unadjusted ORs with 95% confidence intervals (CIs) were used to assess the strength of the association of HIV-1 infection risk with IL-10 -592, -1082 and -819 polymorphisms based on genotype frequencies in cases and controls. The significance of pooled ORs was determined using the *Z* test, with $P < .05$ defined

Table 1

Methodological quality of studies included in the meta-analysis, based on the Newcastle–Ottawa Scale for assessing the quality of case–control studies.

	Selection (score)				Comparability (score)	Exposure (score)			
Study	Adequate definition of patient cases	Representativeness of patient cases	Selection of controls	Definition of controls	Control for important factor or additional factor	Ascertainment of exposure (blinding)	Same method of ascertainment for participants	Non-response rate*	Total Score†
Erikstrup[7]	1	1	1	1	1	0	1	1	7
Chatterjee[8]	1	1	0	1	1	0	1	1	6
Naicker[9]	1	1	0	1	1	0	1	1	6
Sobti[10]	1	1	0	1	1	0	1	1	6
Sunder[11]	1	1	0	1	1	0	1	1	6
Corchado[12]	1	1	0	1	2	0	1	1	7
Piddubna[13]	1	1	1	1	0	0	1	1	6
Freitas[14]	1	1	0	1	1	0	1	1	6
Ramezani[15]	1	1	0	1	2	0	1	1	7
Kallas[16]	1	1	1	1	0	0	1	1	6
Singh[17]	1	1	1	1	2	0	1	1	8

* When there was no significant difference in the response rate between both groups based on a chi-squared test ($P > .05$), 1 point was awarded.
† Total score was calculated by adding up the points awarded for each item.

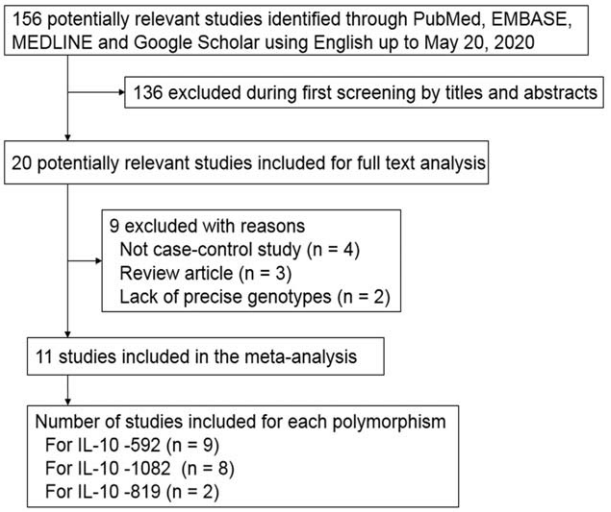

Figure 1. Flowchart of study selection.

as the significance threshold. Meta-analysis was conducted using a fixed-effect model when $P > .10$ for the Q test, indicating lack of heterogeneity among studies; otherwise, a random-effect model was used. All these statistical tests were performed using Review Manager 5.2 (Cochrane Collaboration).

Publication bias was assessed using Begg funnel plots and Egger weighted regression in Stata 12.0 (Stata Corp., College Station, TX), with $P < .05$ considered statistically significant.

3. Results

3.1. Description of studies

Fig. 1 is a flowchart illustrating the process of searching for and selecting studies. A total of 184 potentially relevant publications were identified. Of these, we excluded 156 studies during initial screening based on review of the titles and abstracts. During analysis of the full text of the remaining articles, 4 studies were excluded for not being case-control studies, 3 studies were excluded because they were review articles, and 2 studies were excluded because they did not report precise genotypes.

In the end, 11 studies[7–17] were included in this meta-analysis based on our search strategy and inclusion criteria. Their characteristics are summarized in Table 2. Of these, 9 studies[7–10,12,13,15–17] (Table 4) involving 1,405 cases and 1,842 controls evaluated the association between -592 polymorphism and HIV-1 infection risk. Eight studies[6–9,11,14–17] (Table 4) involving 1,278 cases and 1,858 controls evaluated the association between -1082 polymorphism and HIV-1 infection risk. Two studies[8,17] (Table 4) involving 440 cases and 565 controls evaluated -819 polymorphism and HIV-1 infection risk. The distribution of genotypes in controls was consistent with HWE ($P > .05$) in all studies. The overall quality of the included studies was adequate, and the mean Newcastle-Ottawa score for the included studies was 6.45 (Table 1).

3.2. Quantitative data synthesis

3.2.1. HIV-1 infection risk and IL-10 -592 polymorphism. The overall results for IL-10 -592 are summarized in Table 4 and Figure 2. On the basis of 1,405 cases and 1,842 controls from 9 studies,[7–10,12,13,15–17] the overall results indicated that the AA genotype of -592 may be associated with increased HIV-1 infection risk according to the recessive model (OR = 1.20, 95% CI = 1.02–1.42, $P = .03$, Fig. 2B) and homozygous model (OR = 1.44, 95% CI = 1.02–2.02, $P = .04$, Fig. 2D).

Next we meta-analyzed data for subgroups based on ethnicity. Meta-analysis of 4 studies[8,10,15,17] involving 809 Asian cases and 896 Asian controls showed no evidence of a significant association between -592 polymorphism and HIV-1 infection risk in any of the 5 genetic models (Table 4): allelic model, OR = 1.16, 95% CI 1.00–1.33, $P = .05$; recessive model, OR = 1.25, 95% CI = 0.99–1.59, $P = 0.06$; dominant model, OR = 0.86, 95% CI = 0.69–1.07, $P = .19$; homozygous model, OR = 1.33, 95% CI = 0.98–1.79, $P = .07$; and heterozygous model, OR = 1.08, 95% CI = 0.85–1.36, $P = .54$. Similarly, no evidence of an association was identified in meta-analysis of 4 studies[9,12,13,16] involving 402 Caucasian cases and 772 Caucasian controls (Table 3): allelic model, OR = 1.43, 95% CI = 0.82–2.50, $P = .21$; recessive model, OR = 1.74, 95% CI = 0.72–4.19, $P = .22$; dominant model, OR = 0.74, 95% CI = 0.41–1.32, $P = .31$; homozygous model, OR = 1.79, 95% CI = 0.69–4.68, $P = .23$; and heterozygous model, OR = 1.14, 95% CI = 0.70–1.83, $P = .60$.

Table 2

Characteristics of studies included in the meta-analysis.

First author	Year	Ethnicity	Country	Testing method	Control source	Sample size (n)		SNP
						Cases	Controls	
Erikstrup[7]	2007	African	Zimbabwe	PCR	Population-based healthy volunteers	198	180	IL-10 -1082
Chatterjee[8]	2009	Asian	India	PCR-RFLP	Hospital-based healthy volunteers	180	305	IL-10 -592; IL-10 -1082; IL-10 -819
Naicker[9]	2009	Caucasian	South Africa	ARMS-PCR	Hospital-based healthy volunteers	64	195	IL-10 -592; IL-10 -1082
Sobti[10]	2010	Asian	India	PCR-RFLP	Hospital-based healthy volunteers	300	300	IL-10 -592; IL-10 -1082
Sunder[11]	2012	Asian	India	PCR-RFLP	Hospital-based healthy volunteers	121	102	IL-10 -1082
Corchado[12]	2013	Caucasian	Spain	PCR	Hospital-based healthy volunteers	91	55	IL-10 -592
Piddubna[13]	2013	Caucasian	Ukraine	PCR-RFLP	Population-based healthy volunteers	78	100	IL-10 -592
Freitas[14]	2015	Mixed	Brazil	PCR-RFLP	Hospital-based healthy volunteers	216	294	IL-10 -1082
Ramezani[15]	2015	Asian	Iran	PCR	Hospital-based healthy volunteers	70	31	IL-10 -592
Kallas[16]	2015	Caucasian	Estonia	TaqMan	Population-based healthy volunteers	172	496	IL-10 -592; IL-10 -1082
Singh[17]	2016	Asian	India	PCR-RFLP	Population-based healthy volunteers	260	260	IL-10 -592; IL-10 -1082; IL-10 -819

ARMS = amplification refractory mutation system, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SNP = single-nucleotide polymorphism.

Table 3

Distributions of IL-10 -592, -1082, and -819 genotypes.

First author	Year		*P* for HWE	Sample size (Cases/Controls)	No. of cases			Allele frequencies in cases, n, (%)		No. of controls			Allele frequencies in controls, n, (%)	
IL-10 -592					**CC**	**CA**	**AA**	**C**	**A**	**CC**	**CA**	**AA**	**C**	**A**
Erikstrup[7]	2007	African	0.912	194/174	80	71	43	231 (59.5)	157 (40.5)	68	81	25	217 (62.4)	131 (37.6)
Chatterjee[8]	2009	Asian	0.055	180/305	67	74	39	208 (57.8)	152 (42.2)	140	122	43	402 (65.9)	208 (34.1)
Naicker[9]	2009	Caucasian	0.798	64/195	24	23	17	71 (55.5)	57 (44.5)	97	80	18	274 (70.3)	116 (29.7)
Sobti[10]	2010	Asian	0.295	299/300	36	136	127	208 (34.8)	390 (65.2)	34	146	120	214 (35.7)	386 (64.3)
Corchado[12]	2013	Caucasian	0.672	88/51	43	38	7	124 (70.5)	52 (29.5)	24	21	6	69 (67.6)	33 (32.4)
Piddubna[13]	2013	Caucasian	0.619	78/30	42	28	8	112 (71.8)	44 (28.2)	25	5	0	55 (91.7)	5 (8.3)
Ramezani[15]	2015	Asian	0.358	70/31	31	35	4	97 (69.3)	43 (30.7)	16	11	4	43 (69.4)	19 (30.6)
Kallas[16]	2015	Caucasian	0.972	172/496	113	49	10	275 (79.9)	69 (20.1)	306	167	23	779 (78.5)	213 (21.5)
Singh[17]	2016	Asian	0.555	260/260	106	115	39	327 (62.9)	193 (37.1)	109	122	29	340 (65.4)	180 (34.6)
IL-10 -1082					**GG**	**GA**	**AA**	**G**	**A**	**GG**	**GA**	**AA**	**G**	**A**
Erikstrup[7]	2007	African	0.448	195/175	22	73	100	117 (30.0)	273 (70.0)	17	82	76	116 (33.1)	234 (66.9)
Chatterjee[8]	2009	Asian	0.653	180/305	20	60	100	100 (27.8)	260 (72.2)	27	122	156	176 (28.9)	434 (71.1)
Naicker[9]	2009	Caucasian	0.206	64/195	5	22	37	32 (25.0)	96 (75.0)	27	80	88	134 (34.3)	256 (65.6)
Sunder[11]	2012	Asian	0.057	121/303	2	83	36	87 (36.0)	155 (64.0)	2	43	57	47 (23.0)	157 (77.0)
Freitas[14]	2015	Mixed	0.459	216/294	14	79	123	107 (24.8)	325 (75.2)	24	111	159	159 (27.0)	429 (73.0)
Ramezani[15]	2015	Asian	0.655	70/31	10	32	28	52 (37.1)	88 (62.9)	3	15	13	21 (33.9)	41 (66.1)
Kallas[16]	2015	Caucasian	0.692	172/496	32	78	62	142 (41.3)	202 (58.7)	104	251	141	459 (46.3)	533 (53.7)
Singh[17]	2016	Asian	0.098	260/260	21	119	120	161 (31.0)	359 (69.0)	21	125	114	167 (32.1)	353 (67.9)
IL-10 -819					**TT**	**TC**	**CC**	**T**	**C**	**TT**	**TC**	**CC**	**T**	**C**
Chatterjee[8]	2009	Asian	0.327	180/305	39	74	67	152 (42.2)	208 (57.8)	43	122	140	495 (34.1)	251 (65.9)
Singh[17]	2016	Asian	0.398	260/260	29	122	109	180 (34.6)	340 (65.4)	39	115	106	193 (37.1)	327 (62.9)

HWE = Hardy-Weinberg equilibrium.

Table 4

Overall meta-analysis of the association between HIV-1 infection and IL-10 -592, -1082, and -819 polymorphisms.

Genetic model	OR [95% CI]	*Z* (*P* value)	Heterogeneity of study design			Analysis model
			$\chi 2$	df (*P* value)	I^2 (%)	
IL-10 -592 in total population from 9 case control studies (1405 cases and 1,842 controls)						
Allelic model (A-allele vs. C-allele)	1.10 [0.99, 1.44]	1.90 (.06)	19.02	8 (.01)	58	Random
Recessive model (AA vs. CA + CC)	1.44 [1.06, 1.96]	2.31 (.02)	15.00	8 (.06)	47	Random
Dominant model (CC vs. CA + AA)	0.88 [0.70, 1.10]	1.14 (.25)	13.89	8 (.08)	42	Random
Homozygous model (AA vs. CC)	1.44 [1.02, 2.02]	2.09 (.04)	14.09	8 (.08)	43	Random
Heterozygous model (CA vs. CC)	1.00 [0.84, 1.18]	0.01 (.99)	10.72	8 (.22)	25	Fixed
IL-10 -592 in Asian population from 4 case-control studies (809 cases and 896 controls)						
Allelic model (A-allele vs. C-allele)	1.16 [1.00, 1.33]	2.00 (.05)	3.18	3 (.36)	6	Fixed
Recessive model (AA vs. CA + CC)	1.25 [0.99, 1.59]	1.89 (.06)	4.48	3 (.21)	33	Fixed
Dominant model (CC vs. CA + AA)	0.86 [0.69, 1.07]	1.32 (.19)	2.35	3 (.50)	0	Fixed
Homozygous model (AA vs. CC)	1.33[0.98, 1.79]	1.84 (.07)	4.40	3 (.22)	32	Fixed
Heterozygous model (CA vs. CC)	1.08 [0.85, 1.36]	0.61 (.54)	2.32	3 (.51)	0	Fixed
IL-10 -592 in Caucasian population from 4 case-control studies (402 cases and 772 controls)						
Allelic model (A-allele vs C-allele)	1.43 [0.82, 2.50]	1.27 (0.21)	15.73	3 (.001)	81	Random
Recessive model (AA vs. CA + CC)	1.74 [0.72, 4.19]	1.23 (.22)	8.03	3 (.05)	63	Random
Dominant model (CC vs. CA + AA)	0.74 [0.41, 1.32]	1.02 (.31)	10.58	3 (.01)	72	Random
Homozygous model (AA vs CC)	1.79 [0.69, 4.68]	1.20 (.23)	8.72	3 (.03)	66	Random
Heterozygous model (CA vs CC)	1.14 [0.70, 1.83]	0.52 (.60)	6.43	3 (.09)	53	Random
IL-10 -1082 in total population from 8 case-control studies (1278 cases and 1858 controls)						
Allelic model (A-allele vs. G-allele)	1.06 [0.89, 1.26]	0.63 (.53)	15.35	7 (.03)	54	Random
Recessive model (AA vs. GA + GG)	1.08 [0.81, 1.43]	0.54 (.59)	23.14	7 (.002)	70	Random
Dominant model (GG vs. GA +AA)	0.95 [0.75, 1.21]	0.40 (.69)	3.74	7 (.81)	0	Fixed
Homozygous model (AA vs. GG)	1.18 [0.91, 1.52]	1.24 (.22)	4.49	7 (.72)	0	Fixed
IL-10 -1082 in Asian population from 4 case-control studies (631 cases and 698 controls)						
Allelic model (A-allele vs. G-allele)	0.87 [0.64, 1.19]	0.86 (.39)	8.44	3 (.04)	64	Random
Recessive model (AA vs. GA + GG)	0.81 [0.47, 1.41]	0.73 (.46)	15.83	3 (.001)	81	Random
Dominant model (GG vs. GA +AA)	1.16 [0.77, 1.74]	0.70 (.48)	0.60	3 (.90)	0	Fixed
Homozygous model (AA vs. GG)	0.90 [0.59, 1.38]	0.48 (.63)	0.55	3 (.91)	0	Fixed
Heterozygous model (GA vs. GG)	0.81 [0.53, 1.25]	0.95 (.34)	1.42	3 (.70)	0	Fixed

(*continued*)

Table 4

(continued).

Genetic model	OR [95% CI]	Z (P value)	Heterogeneity of study design			Analysis model
			$\chi 2$	df (P value)	I^2 (%)	
IL-10 -1082 in Caucasian population from 2 case-control studies (236 cases and 691 controls)						
Allelic model (A-allele vs G-allele)	1.30 [1.05, 1.62]	2.37 (.02)	0.89	1 (.34)	0	Fixed
Recessive model (AA vs GA + GG)	1.49 [1.09, 2.03]	2.53 (.01)	0.22	1 (.64)	0	Fixed
Dominant model (GG vs GA +AA)	0.79 [0.53, 1.18]	1.16 (.24)	0.78	1 (.38)	0	Fixed
Homozygous model (AA vs GG)	1,58 [1.01, 2.46]	2.01 (.04)	0.63	1 (.43)	0	Fixed
Heterozygous model (GA vs GG)	1.08 [0.70, 1.66]	0.35 (.73)	0.42	1 (.52)	0	Fixed
IL-10 -819 in total population from 2 case-control studies (440 cases and 565 controls)						
Allelic model (C-allele vs T-allele)	1.73 [0.73, 4.12]	1.25 (.21)	22.90	1 < .001)	96	Random
Recessive model (CC vs TC + TT)	0.86 [0.58, 1.28]	0.73 (.46)	2.40	1 (.12)	58	Random
Dominant model (TT vs TC + CC)	1.10 [0.47, 2.56]	0.22 (.82)	5.78	1 (.02)	83	Random
Homozygous model (CC vs TT)	0.85 [0.33, 2.19]	0.34 (.74)	6.20	1 (.01)	84	Random
Heterozygous model (TC vs TT)	0.97 [0.46, 2.04]	0.07 (.94)	0.89	1 (.05)	74	Random

95%CI = 95% confidence interval, OR = odds ratios.

3.2.2. HIV-1 infection risk and IL-10 -1082 polymorphism.

The overall results are summarized in Table 4 and Fig. 3. On the basis of 1,278 cases and 1,858 controls from 8 studies,[7–9,11,14–17] IL-10 -1082 polymorphism did not show significant association with HIV-1 infection risk in any of the 5 genetic models: allelic model, OR = 1.06, 95% CI = 0.89–1.26, $P = .53$ (Fig. 3A); recessive model, OR = 1.08, 95% CI = 0.81–1.43, $P = .59$ (Fig. 3B); dominant model, OR = 0.95, 95% CI = 0.75–1.21, $P = .69$ (Fig. 3C); homozygous model, OR = 1.18, 95% CI = 0.91–1.52, $P = .22$ (Fig. 3D); or heterozygous model, OR = 0.93, 95% CI = 0.72–1.21, $P = .59$ (Fig. 3E).

Similarly, no significant association was observed for the subgroup of 631 Asian cases and 698 Asian controls in 4 studies[8,11,15,17] (Table 4): allelic model, OR = 0.87, 95% CI 0.64–1.19, $P = .39$; recessive model, OR = 0.81, 95% CI = 0.47–1.41, $P = .46$; dominant model, OR = 1.16, 95% CI = 0.77–1.74, $P = .48$; homozygous model, OR = 0.90, 95% CI = 0.59–1.38, $P = .63$; and heterozygous model, OR = 0.81, 95% CI = 0.53–1.25, $P = .34$. However, meta-analysis of 2 studies[9,16] involving 236 Caucasian cases and 691 Caucasian controls indicated that the AA genotype of -1082 may be associated with increased HIV-1 infection risk according to the allelic model (OR = 1.30, 95% CI = 1.05–1.62, $P = .02$), recessive model (OR = 1.49, 95% CI = 1.09–2.03, $P = .01$) and homozygous model (OR = 1.58, 95% CI = 1.01–2.46, $P = .04$)

3.2.3. HIV-1 infection risk and IL-10 -819 polymorphism.

The overall results are summarized in Table 4 and Figure 4. On the basis of 440 cases and 565 controls from 2 studies,[8,17] IL-10 -819 polymorphism did not show significant association with HIV-1 infection risk in any of the 5 genetic models: allelic model, OR = 1.73, 95% CI = 0.73–4.12, $P = .21$ (Fig. 4A); recessive model, OR = 0.86, 95% CI = 0.58–1.28, $P = .46$ (Fig. 4B); dominant model, OR = 1.10, 95% CI = 0.47–2.56, $P = .82$ (Fig. 4C); homozygous model, OR = 0.85, 95% CI = 0.33–2.19, $P = .74$ (Fig. 4D); or heterozygous model, OR = 0.97, 95% CI = 0.46–2.04, $P = .94$ (Fig. 4E).

3.3. Publication bias

Potential publication bias in this meta-analysis was assessed using Begg funnel plot and Egger test. No obvious asymmetry was observed in Begg funnel plots of the recessive models of the -592 polymorphism (Fig. 5A) or -1082 polymorphism (Fig. 5C). *P* values for Egger tests were greater than 0.05 for -592 polymorphism (Fig. 5B) and -1082 polymorphism (Fig. 5D). These results suggest no potential publication bias. Begg funnel plot and Egger test for the -819 polymorphism were not performed because they involved only 2 studies.

4. Discussion

IL-10 is an important anti-inflammatory, immunosuppressive and immunomodulatory cytokine that is associated with many diseases[20] and is involved in the regulation of inflammatory response, autoimmunity, infection progression, tumorigenesis and transplantation tolerance.[21–23] Interleukin 10 is a major regulator of innate immunity and prevents the development of immunopathological lesions that result from exacerbated protective immune response to acute and chronic infections.[24] It has been reported that HIV-1-infected individuals with a particular IL-10 promoter haplotype may progress to AIDS more rapidly, but with a late effect manifested primarily about 5 years post-HIV-1 seroconversion.[25] IL-10 may promote viral persistence by inactivation of effect or immune mechanisms.[26] And it has been indicated that IL-10 acts as a general inhibitor of proliferative and cytokine responses of both T-helper-Th1 and Th2 cells in vitro and in vivo.[10] IL-10 could limit viral replication in vivo by inducing secretion of inflammatory cytokines and limiting replication of T cells. In addition, Previous studies have demonstrated that IL-10 can affect several aspects of immune reaction and suppress HIV replication in vivo.[8] Increasing evidence has suggested that polymorphisms in IL-10 may influence susceptibility to HIV infection and rate of progression to AIDS.[7–17,27,28] Nevertheless, some of those literatures have shown IL-10 polymorphisms were protective factors against HIV infection.[7,9,10] While the others have got different conclusions.[8,11–17] Limited sample size and ethnic differences among the various populations examined have contributed to a lack of consensus in this literature. Therefore, we conducted the present meta-analysis on all eligible studies to provide a more precise estimate of the association of HIV-1 infection risk with IL-10 -592, -1082, and -819 polymorphisms.

A recent meta-analysis by Tsiara et al[24] found no significant association of -592 or -1082 polymorphism with HIV susceptibility. Our meta-analysis, in contrast, suggests that the AA

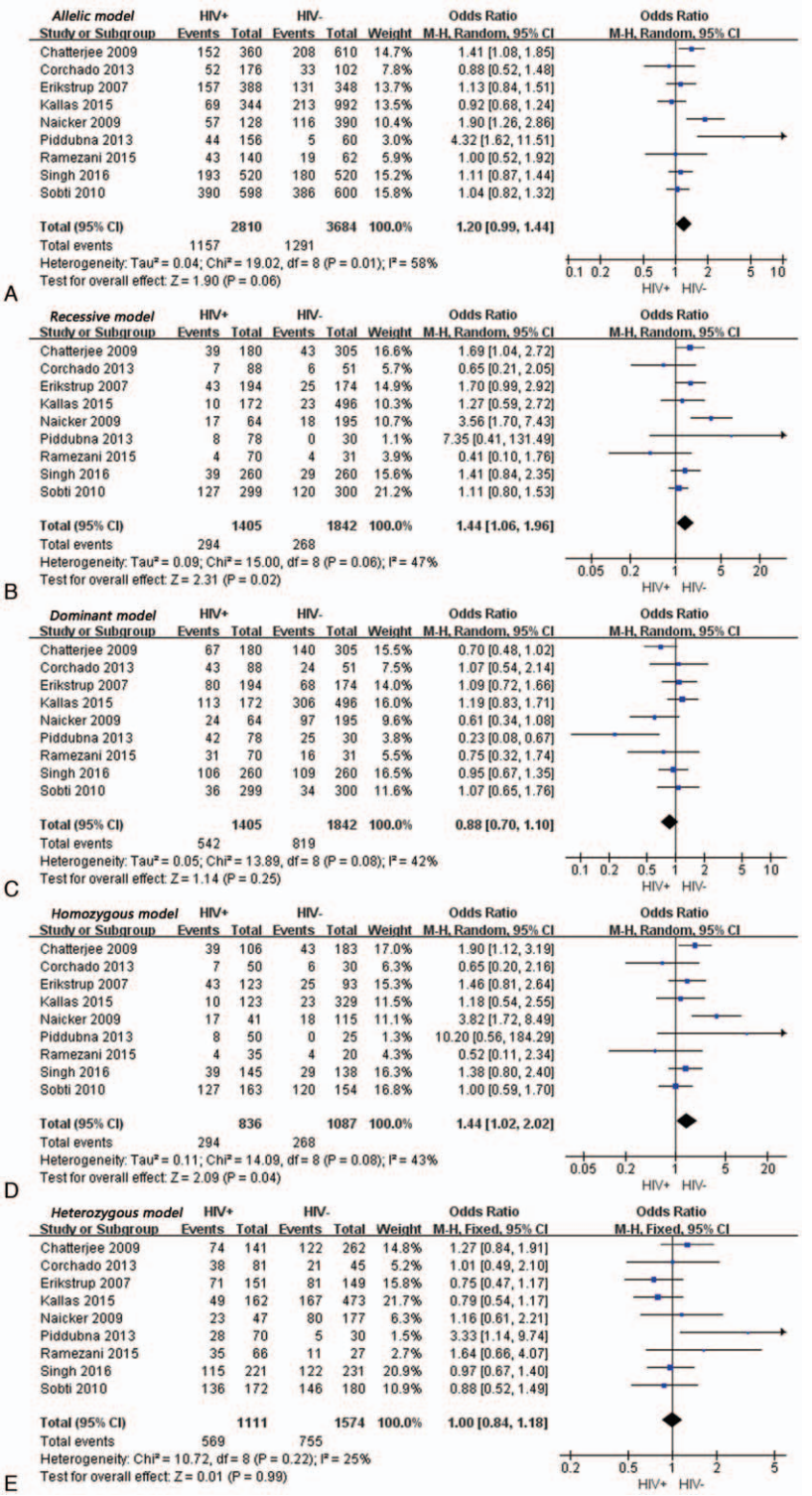

Figure 2. Forest plot describing the association between the IL-10 -592 polymorphism and HIV-1 infection risk according to different genetic models: (A) allelic, (B) recessive, (C) dominant, (D) homozygous and (E) heterozygous.

genotype of IL-10 -592 may increase susceptibility to HIV-1 infection in the total population, though not specifically in Asian or Caucasian subpopulations. This suggests that the association may not depend on ethnicity. In contrast, our meta-analysis found a significant association between the -1082 polymorphism and susceptibility to HIV-1 infection in Caucasians, but not in Asians or the total population. Our results may be more reliable than those of Tsiara et al[24] because of our larger sample, which can increase the statistical power for detecting significant correlations. Our meta-analysis did not identify a significant

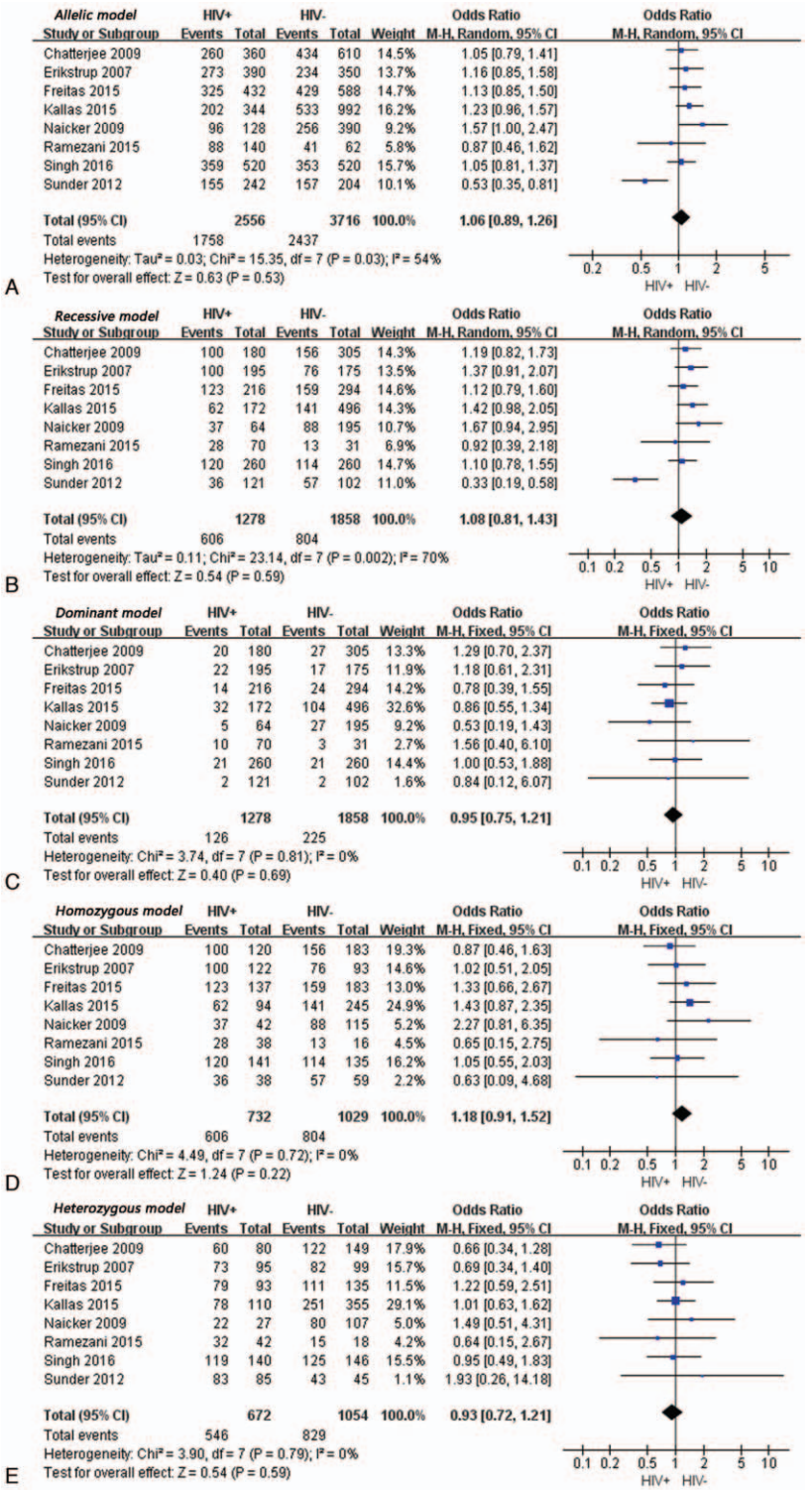

Figure 3. Forest plot describing the association between the IL-10 -1082 polymorphism and HIV-1 infection risk according to different genetic models: (A) allelic, (B) recessive, (C) dominant, (D) homozygous and (E) heterozygous.

relationship between IL-10 -819 polymorphism and HIV-1 infection risk.

To the best of our knowledge, this is the largest meta-analysis so far investigating the possible association between polymorphisms in interleukin-10 gene and susceptibility to HIV-1 infection. Nevertheless, the meta-analysis is limited by the designs of the included studies. First, the results may be affected by both genetic and environmental factors, but most studies did not report environmental exposure, making it impossible to include them in the meta-analysis. Second, the studies may be

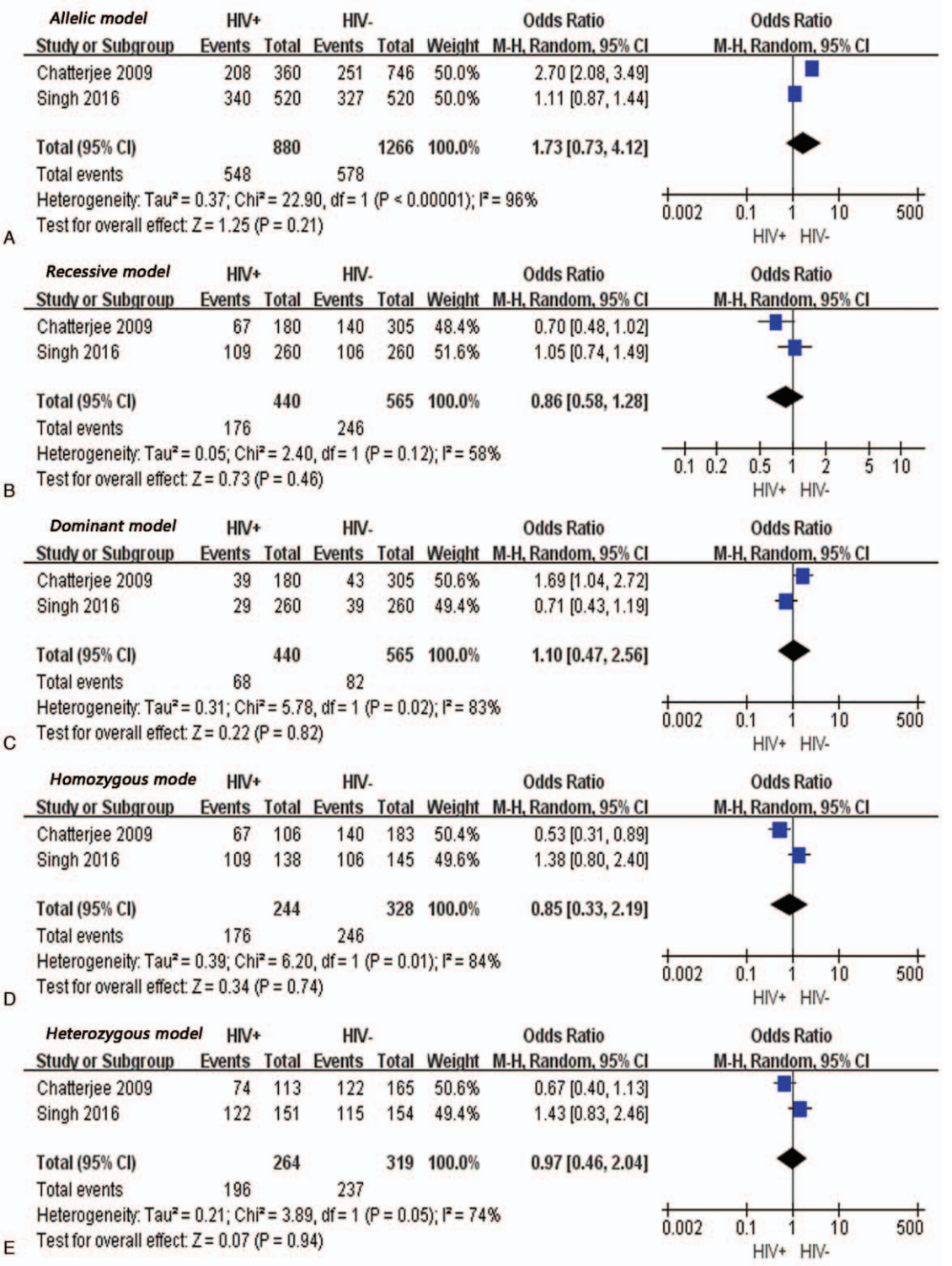

Figure 4. Forest plot describing the association between the IL-10 -819 polymorphism and HIV-1 infection risk according to different genetic models: (A) allelic, (B) recessive, (C) dominant, (D) homozygous and (E) heterozygous.

subject to performance, attrition and reporting biases, although Newcastle-Ottawa scores were at least 6 for all 11 studies, indicating high quality. Third, our exclusion of unpublished data and of papers published in languages other than English may have biased our results. Fourth, there were only 2 case-control studies[8,17] concerning IL-10 -819 polymorphism, and all subjects in those studies were Asian. The relatively small Asian sample in our meta-analysis may bias our results and limit the relevance of our results. Finally, for lack of data, we were unable to examine whether any of the genetic associations varied with

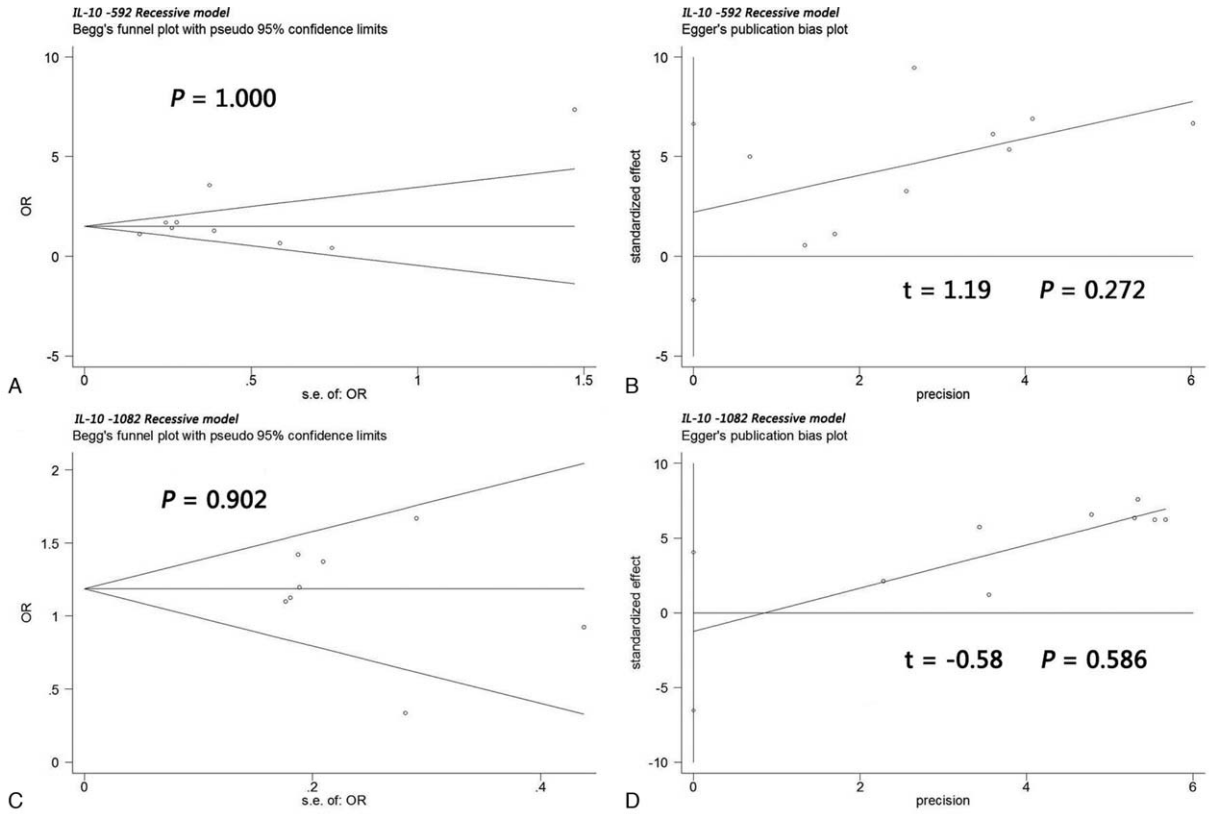

Figure 5. Begg funnel plot and Egger test to assess publication bias in the meta-analysis of potential associations between HIV-1 infection risk and (A, B) IL-10 -592 polymorphism or (C, D) IL-10 -1082 polymorphism. All analyses were performed using a recessive genetic model.

age, sex, HIV-1 subtype, or family history of HIV infection. Future studies should examine these additional factors.

Despite these limitations, this meta-analysis provides evidence that the AA genotype of IL-10 -592 may confer increased susceptibility to HIV-1 infection, and that the AA genotype of -1082 may be associated with increased HIV-1 infection risk in Caucasians. However, the -819 polymorphism may not be associated with HIV-1 infection risk. These conclusions should be verified in large, well-designed studies.

Author contributions

Designed the study: Dan-Ke Su and Dan-Hui Fu. Searched databases and collected full-text papers: Wen-Juan Deng, Zhi Yang, Sen Hong. Extracted and analyzed the data: Qian-Lin Ding, Yang Zhao. Statistical analyses: Jia Chen. Wrote the manuscript: Dan-Hui Fu. All authors reviewed the manuscript.

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