Associations between interleukin-10 gene polymorphisms and systemic lupus erythematosus risk: a meta-analysis with trial sequential analysis

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Abstract

Objective

Interleukin-10 (IL-10) polymorphisms have been reported to be associated with systemic lupus erythematosus (SLE), however, the results are controversial. Therefore, we conducted a meta-analysis with trial sequential analysis to evaluate a more accurate estimation of the associations.

Methods

Eligible studies were retrieved by searching PubMed, Embase, Google Scholar, VIP, Wan Fang and China National Knowledge Infrastructure databases. Hardy-Weinberg equilibrium (HWE) was evaluated. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Heterogeneity was evaluated by Q statistic and I^2 statistic. Sensitivity analysis and subgroup analysis (stratified by HWE, region, event sample size, source of controls, genotyping method) were conducted and the potential for publication bias was assessed. Trial sequential analysis was introduced to assess the information size and the positive results.

Results

Twenty case-control studies were included. Overall results from IL10-1082A/G polymorphism showed increased risk of systemic lupus erythematosus, but no significant associations were observed in both IL10-819C/T and IL10-592C/A polymorphism. Increased risk of SLE was also observed in IL10A/G polymorphism in Asian population, hospital-based and PCR-RFLP (polymerase chain reaction restriction fragment length polymorphism) subgroups. In addition, decreased risk of SLE was widely detected in IL10-819C/T and IL10-592C/A polymorphisms in subgroup analysis.

Conclusion

Our study suggests that the IL10-1082A/G polymorphism is a risk factor in systemic lupus erythematosus. A decreased risk of SLE in the IL10-819C/T and IL10-592C/A polymorphisms in subgroups was also observed, but further rigorously studies are needed to confirm these results.

Key words

IL-10 gene polymorphism, systemic lupus erythematosus, meta-analysis, trial sequential analysis

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterised by the production of autoantibodies leading to intense inflammation and multiple organ destruction (1, 2). The aetiology of SLE is not fully clear. Gene susceptibility plays an important role in the pathogenesis of SLE (3, 4). Cytokines are crucial immunomodulatory molecules that mediate immune response and inflammation (5). Some cytokine gene polymorphisms, like tumour necrosis factor-α (TNF-α) (3), interferon-γ (IFN-γ) (6), interleukin-1 (IL-1) (7), interleukin-4 (IL-4) (8), interleukin-10 (IL-10) (9), are reported to be involved in the cytokine gene transcription and translation, which might imply a potential relationship between cytokine gene polymorphism with susceptibility, severity and clinical features of SLE.

Gene polymorphisms can affect the gene expression and IL10 promoter is highly polymorphic. Three common single nucleotide polymorphisms (SNPs) in the IL-10 promoter were widely studied: a G to A substitution at position -1081, a C to T at -819 and a C to A at -592. Many case-control studies and meta-analyses were conducted to seek the associations between these three IL-10 polymorphisms and SLE risk, however, the results are controversial. This inconsistency may be due to the small sample size and the low statistical power of individual case-control studies. In the previous meta-analysis, adjusted alpha was not assessed for multiple tests, besides, random error and information size should also be evaluated in meta-analysis (10). Therefore, we carried out this updated meta-analysis with trial sequential analysis to pool current evidence together for a more accurate evaluation of the associations between IL-10 polymorphisms and SLE risk.

Methods

This meta-analysis was written on the basis of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist (11).

Identification of the related studies

We conducted systematic search in PubMed, Embase, Google Scholar, VIP, Wan fang and China National Knowledge Infrastructure databases to identify potential studies about the relationships between the interleukin-10 gene polymorphisms and systemic lupus erythematosus risk. The last literature search update was performed on December 20th, 2017. The terms "systemic lupus erythematosus," "SLE," "interleukin-10," "IL-10," "variant," "polymorphism," and "polymorphisms" were used. No language limitations were applied. Reference list was also screened.

Inclusion and exclusion criteria

Studies met the following inclusion criteria were included: (1) evaluation of the associations between the interleukin-10 gene polymorphisms and systemic lupus erythematosus; (2) case-control study or cohort design; (3) detailed genotype data could be acquired to calculate odds ratios (ORs), 95% confidence intervals (CIs) and *p*-value for Hardy-Weinberg equilibrium; exclusion criteria: (1) duplication of previous publications; (2) comment, review and editorial; (3) study without detailed genotype data. Two investigators independently conducted the comprehensive literature search to obtain the potential included studies by screening the title, abstract and full-text. Any disagreement was solved by group discussion.

Data extraction

The following data were independently extracted by the first two investigators using a standardised form from the eligible studies: first author's last name, year of publication, study country, study region, genotyping methods, sample size, source of controls, Hardy-Weinberg equilibrium, number of cases and controls, and genotype frequency in cases and controls for interleukin-10 gene. Consensus was reached by discussion.

Quality assessment

Two reviewers independently assessed the quality of the included studies, according to a set of criteria (shown in Table S3) modified based on the Newcastle-Ottawa quality assessment scale.

Table I. Characteristics of included studies about the associations between IL10 polymorphism and SLE

Study	Year	Country	Region	Sample Size		SLE			Control			Controls Source	Genotyping Method	Quality Score	HWE*
				SLE	Control	AA	GA	GG	AA	GA	GG				
IL10-1082A/G polymorphism															
Manolova	2018	Bugaria	Europe	154	224	55	72	27	74	124	26	PB	ARMS-PCR	7	0.016 **
Talaat	2016	Egypt	Africa	100	119	40	42	18	30	78	11	HB	PCR-SSP	8	0.000 **
Rezaei	2015	Iran	Asian	59	140	20	37	2	53	75	12	PB	PCR-SSP	9	0.042**
Palafox-Sanchez	2015	Mexico	America	125	260	62	50	13	133	103	24	PB	PCR-SSP	9	0.532
da Silva	2014	Brazil	America	90	100	8	81	1	20	72	8	HB	ARMS-PCR	7	0.000 **
Rianthavorn1	2013	Thailand	Asian	71	160	56	14	1	139	21	0	HB	PCR-RFLP	8	0.374
Rianthavorn2	2013	Thailand	Asian	57	160	43	13	1	139	21	0	HB	PCR-RFLP	7	0.374
Lin	2010	China	Asian	172	215	158	14	0	194	21	0	PB	PCR-Taqman	9	0.452
Rosado	2008	Spain	Europe	116	151	38	55	23	65	72	14	HB	PCR-RFLP	8	0.348
Guarnizo-Zuccardi	2007	Colombia	America	120	102	56	50	14	51	42	9	HB	PCR-SSP	8	0.933
Suarez	2005	Spain	Europe	192	343	69	86	37	134	158	51	HB	PCR-Taqman	8	0.692
Hrycek	2005	Poland	Europe	24	36	6	14	4	11	18	7	HB	PCR-SSP	7	0.940
Khoa	2005	Japan	Asian	64	57	15	31	18	21	30	6	PB	ARMS-PCR	9	0.323
Guzowski	2005	USA	America	36	25	25	4	7	9	12	4	PB	PCR-DHPLC	9	0.999
Chong	2004	China	Asian	554	708	501	51	2	652	56	0	PB	PCR-Taqman	9	0.273
Fei	2004	Sweden	Europe	52	26	15	24	13	8	10	8	PB	ARMS-PCR	9	0.239
Dijstelbloem	2002	Netherland	Europe	180	163	44	94	42	41	72	50	PB	ARMS-PCR	8	0.146
Rood	1999	Netherland	Europe	92	162	21	47	24	34	78	50	PB	PCR-SSP	8	0.726
Crawley	1999	UK	Europe	120	274	28	65	27	80	124	70	PB	PCR-SSP	8	0.121
Lazarus	1997	UK	Europe	76	119	14	36	26	35	47	37	HB	PCR-SSP	7	0.022**
IL10-819TC/T polymorphism						CC	CT	TT	CC	CT	TT				
Talaat	2016	Egypt	Africa	100	119	22	70	8	60	53	6	HB	PCR-SSP	8	0.184
Rezaei	2015	Iran	Asian	58	140	23	31	4	71	57	12	PB	PCR-SSP	9	0.907
Palafox-Sanchez	2015	Mexico	America	125	260	46	61	18	96	124	40	PB	PCR-SSP	9	0.997
Rianthavorn1	2013	Thailand	Asian	71	160	11	31	29	10	70	80	HB	PCR-RFLP	8	0.299
Rianthavorn2	2013	Thailand	Asian	57	160	8	26	23	10	70	80	HB	PCR-RFLP	7	0.299
Guzowski	2005	USA	America	51	25	18	24	9	15	10	1	PB	PCR-DHPLC	9	0.671
Chong	2004	China	Asian	554	708	64	241	249	47	322	339	PB	PCR-Taqman	9	0.011 **
IL10-592C/A polymorphism						CC	AC	AA	CC	AC	AA				
Rezaei	2015	Iran	Asian	58	140	19	35	4	71	57	12	PB	PCR-SSP	9	0.907
Palafox-Sanchez	2015	Mexico	America	125	260	49	60	16	100	125	35	PB	PCR-SSP	9	0.679
Rianthavorn1	2013	Thailand	Asian	71	161	11	31	29	10	70	81	HB	PCR-RFLP	8	0.313
Rianthavorn2	2013	Thailand	Asian	57	161	8	26	23	10	70	81	HB	PCR-RFLP	7	0.313
Zhu	2005	China	Asian	265	100	21	119	125	12	47	41	PB	PCR-RFLP	9	0.792
Guzowski	2005	USA	America	51	25	21	21	9	13	11	2	PB	PCR-DHPLC	9	0.876
Chong	2004	China	Asian	554	708	64	241	249	47	322	339	PB	PCR-Taqman	9	0.011

SLE: systemic lupus erythematosus; HB: Hospital Based=Population Based; PCR: Polymerase Chain Reaction; PCR-SSP: Polymerase Chain Reaction primer sequence specific; PCR-RFLP: Polymerase Chain Reaction Restriction Fragment Length Polymorphism; ARMS-PCR: Refractory Mutation System Polymerase Chain Reaction; PCR-DHPLC: Polymerase Chain Reaction Denaturing high-performance liquid chromatography. *p-value for Hardy-Weinberg equilibrium test in controls; ** Studies using departure from Hardy-Weinberg equilibrium.

Table II. Results of meta-analysis of associations between IL10 polymorphisms and SLE risk.

Genetic model	Numbers of Studies	Statistical method	OR[95%CI]	$P_{meta\text{-}analysis}$*	BON	FDR	I2 (%)	$P_{heterogeneity}$#
IL10-1082A/G polymorphism								
G VS A	20	**Odds ratio (M-H, Fixed, 95% CI)**	**1.11 [1.01, 1.21]**	**0.030**	0.150	0.067	25	**0.150**
GG+GA VS AA	20	**Odds ratio (M-H, Fixed, 95% CI)**	**1.14 [1.01, 1.30]**	**0.040**	0.200	0.067	39	**0.040**
GG VS GA+AA	20	Odds ratio (M-H, Random, 95% CI)	1.10 [0.81, 1.49]	0.550	1.000	0.550	58	0.000
GA VS AA	20	Odds ratio (M-H, Fixed, 95% CI)	1.11 [0.97, 1.26]	0.140	0.700	0.175	48	0.009
GG VS AA	20	**Odds ratio (M-H, Fixed, 95% CI)**	**1.26 [1.04, 1.54]**	**0.020**	0.100	0.067	19	**0.230**
IL10-819C/T polymorphism								
T VS C	7	Odds ratio (M-H, Random, 95% CI)	1.05 [0.78, 1.42]	0.730	1.000	0.930	78	0.000
TT+TC VS CC	7	Odds ratio (M-H, Random, 95% CI)	1.03 [0.56, 1.90]	0.930	1.000	0.930	85	0.000
TT VS TC+CC	7	Odds ratio (M-H, Random, 95% CI)	0.82 [0.48, 1.40]	0.460	1.000	0.930	78	0.000
TC VS CC	7	Odds ratio (M-H, Random, 95% CI)	1.05 [0.58, 1.91]	0.870	1.000	0.930	83	0.000
TT VSCC	7	Odds ratio (M-H, Random, 95% CI)	0.85 [0.46, 1.56]	0.590	1.000	0.930	68	0.004
IL10-592C/A polymorphism								
A VS C	7	Odds ratio (M-H, Random, 95% CI)	0.95 [0.77, 1.18]	0.660	1.000	0.820	59	0.020
AA+AC VS CC	7	Odds ratio (M-H, Random, 95% CI)	0.88 [0.55, 1.41]	0.590	1.000	0.820	73	0.001
AA VS AC+CC	7	Odds ratio (M-H, Random, 95% CI)	1.09 [0.51, 2.33]	0.820	1.000	0.820	93	0.000
AC VS CC	7	Odds ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.42]	0.620	1.000	0.820	69	0.004
AA VS CC	7	Odds ratio (M-H, Random, 95% CI)	0.78 [0.47, 1.29]	0.330	1.000	0.820	60	0.020

SLE: systemic lupus eythematosus; OR: odds ratio; CI: Confidence Interval.
#*p*-value for meta-analysis; **p*-value for between-study heterogeneity based on Q test. Significant results are marked in bold.

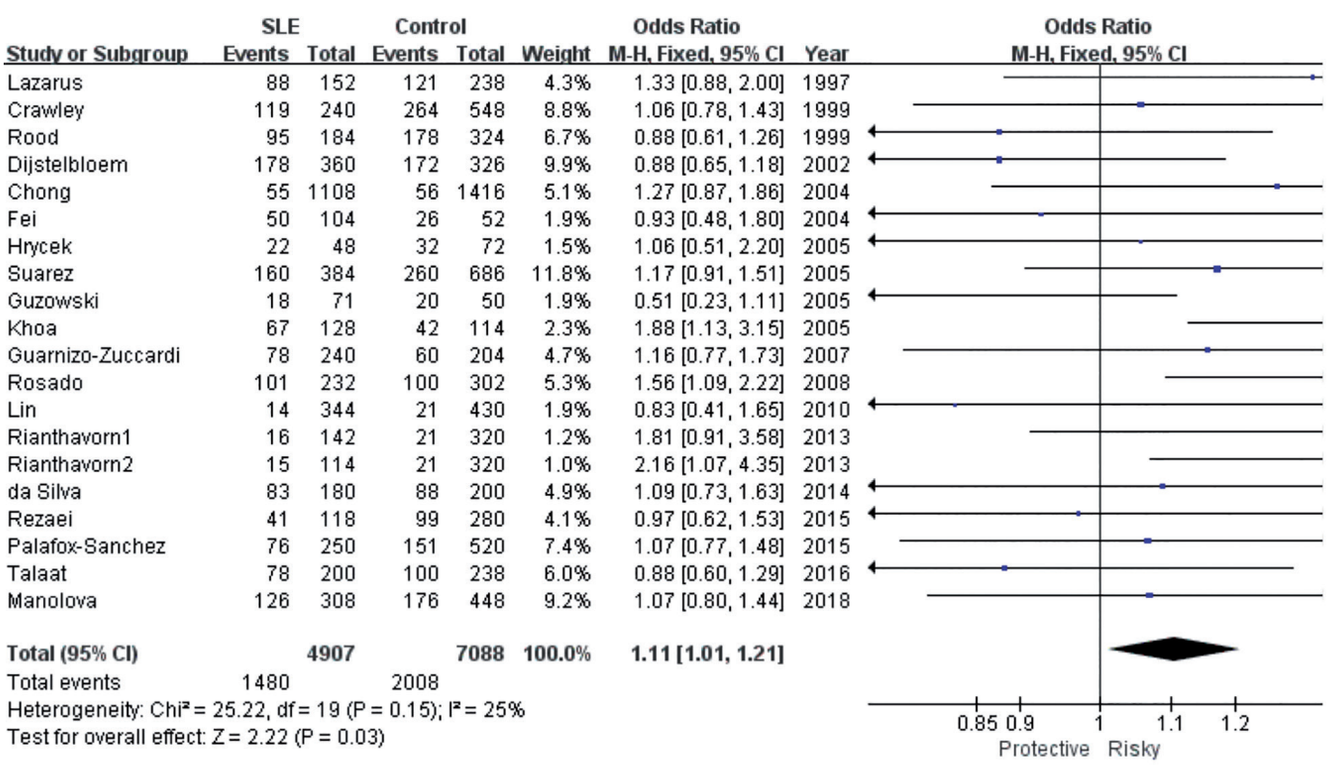


Fig. 1. Forest plot of SLE risk associated with the G allele compared with the A allele in IL10-1082/G polymorphism. OR: odds ratio; CI: confidence interval.

Statistics analysis

Hardy-Weinberg equilibrium (HWE) was evaluated for each study by Chi-square test in control groups, and $p<0.05$ was considered as a significant departure from HWE. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the strength of the association between interleukin-10 gene polymorphisms and systemic lupus erythematosus risk. ORs and 95%CIs were performed for the allelic model (-1082A/G: G *vs*. A; -819C/T: T VS C; -592C/A: A VS C), recessive model (-1082A/G: GG *vs*. GA+AA; -819C/T:

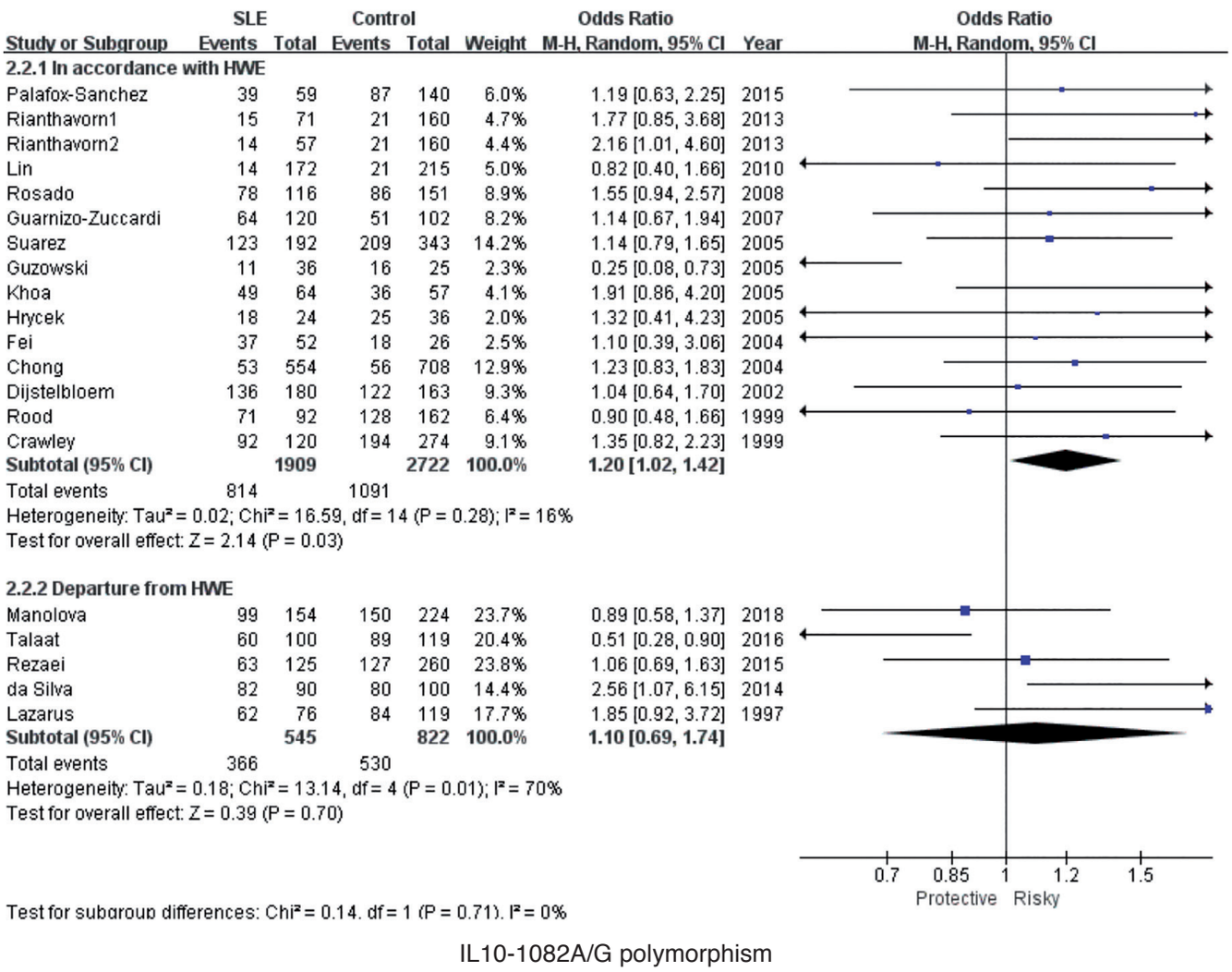


Fig. 2. Subgroup analysis (HWE) of SLE risk associated with IL10-1082A/G polymorphism. HWE: Hardy-Weinberg Equilibration; OR: odds ratio; CI: confidence interval.

TT VS TC+CC; -592C/A: AA VS AC+CC), dominant model (-1082A/G: GG+GA *vs*. AA; -819C/T: TT+TC VS CC; -592C/A: AA+AC VS CC), heterozygote model (-1082A/G: GA *vs*. AA; -819C/T: TC VS CC; -592C/A: AC VS CC), and homozygote model (-1082A/G: GG *vs*. AA; -819C/T: TT VS CC; -592C/A: AA VS CC), respectively. Heterogeneity was evaluated by Q statistic (significance level of $p<0.1$) and I^2 statistic (greater than 50% as evidence of significant inconsistency). In heterogeneity evaluation, when the I^2 <50%, the fixed-effects model would be used; if the I^2=50% to 90%, a random-effects model was used; if the I^2 >90%, the studies would not be pooled (12). Sensitivity analysis was performed to detect the heterogeneity by omitting one study in each turn. Subgroup analysis were stratified by HWE (In accordance with or departure from HWE), region (Asian, Europe, America and Africa), event sample size (<100 as small and ≥100 as large), source of controls (Population-based or Hospital-based) and genotyping method (PCR-SSP (Polymerase Chain Reaction primer sequence specific), PCR-TaqMan (Polymerase Chain Reaction-TaqMan), PCR-RFLP (Polymerase Chain Reaction Restriction Fragment Length Polymorphism), ARMS-PCR (Refractory Mutation System Polymerase Chain Reaction) and PCR-DHPLC (Polymerase Chain Reaction Denaturing high-performance liquid chromatography)). The potential for publication bias was assessed with Begg's funnel plot and Egg's test. All the tests in this meta-analysis were conducted with the RevMan 5.3 and the STATA 11.0 software packages. The Bonferroni method which control for the false discovery rate was adopted to adjust for multiple comparisons (13). The power of meta-analysis for SNP to detect some effect size was estimated according to the method recommended by Hedges and Piggott, given a significant value of 0.05 (14).

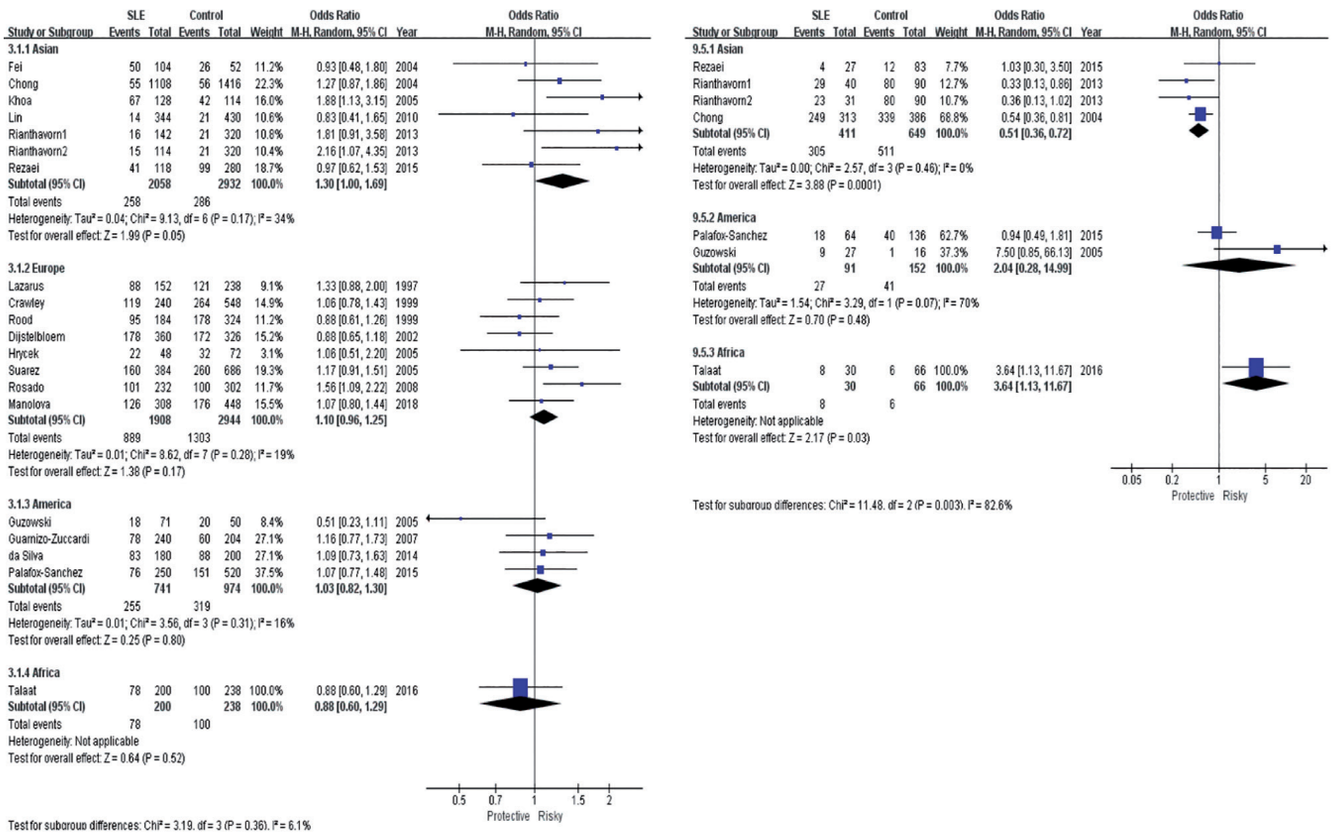
Trial sequential analysis

In order to reduce the risk of type I errors, we performed the trial sequential analysis (TSA) by using the trial sequential analysis software (Copenhagen Trial Unit, Copenhagen, Denmark). TSA is a method in combining an information size calculation from cumulated sample sizes for a meta-analysis with the threshold of statistical significance (http://www.ctu.dk/tsa). The required

Table III. Stratified analysis of the associations of IL10 polymorphisms with SLE risk

Subgroup	N	Allelic genetic model				Dominant genetic model				Recessive genetic model				Heterozygote genetic model				Homozygote genetic model			
		OR[95%CI]	P*	I2	P#	OR[95%CI]	P*	I2	P#	OR[95%CI]	P*	I2	P#	OR[95%CI]	P*	I2	P#	OR[95%CI]	P*	I2	P#
IL10-1082A/G polymorphism	20	G VS A				GG+GA VS AA				GG VS GA+AA				GA VS AA				GG VS AA			
HWE																					
In accordance with HWE	15	1.14 [0.99, 1.31]	0.080	38.0	0.070	**1.20 [1.02, 1.42]**	**0.030**	**16.0**	**0.280**	1.17 [0.82, 1.67]	0.390	58.0	0.004	1.19 [0.99, 1.41]	0.060	15.0	0.280	1.30 [0.96, 1.75]	0.090	29.0	0.150
Departure from HWE	5	1.06 [0.89, 1.25]	0.510	0.0	0.700	1.10 [0.69, 1.74]	0.700	70.0	0.010	0.85 [0.41, 1.73]	0.650	67.0	0.020	1.05 [0.60, 1.84]	0.860	77.0	0.001	1.27 [0.84, 1.92]	0.260	0.0	0.260
Region																					
Asian	7	**1.30 [1.00, 1.69]**	**0.050**	**34.0**	**0.170**	**1.27 [1.02, 1.59]**	**0.040**	**0.0**	**0.430**	1.77 [0.57, 5.48]	0.320	60.0	0.030	1.21 [0.97, 1.53]	0.100	0.0	0.660	2.03 [0.72, 5.67]	0.180	44.0	0.110
Europe	8	1.10 [0.96, 1.25]	0.170	19.0	0.280	1.17 [0.97, 1.40]	0.100	0.0	0.570	0.94 [0.70, 1.26]	0.670	48.0	0.060	1.14 [0.94, 1.39]	0.170	0.0	0.500	1.26 [0.94, 1.67]	0.120	26.0	0.220
America	4	1.03 [0.82, 1.30]	0.800	16.0	0.310	1.03 [0.51, 2.10]	0.930	73.0	0.010	0.91 [0.35, 2.32]	0.840	65.0	0.040	0.97 [0.40, 2.32]	0.940	80.0	0.002	1.07 [0.63, 1.79]	0.810	0.0	0.550
Africa	1	0.88 [0.60, 1.29]	0.520	NA	NA	0.51 [0.28, 0.90]	0.020	NA	NA	2.00 [0.89, 4.46]	0.090	NA	NA	0.40 [0.22, 0.74]	0.003	NA	NA	1.23 [0.51, 2.98]	0.650	NA	NA
Sample size																					
Small(<100)	10	1.16 [0.93, 1.46]	0.190	44.0	0.060	1.33 [0.94, 1.87]	0.100	50.0	0.040	1.06 [0.57, 1.96]	0.850	62.0	0.005	1.31 [0.90, 1.90]	0.160	53.0	0.020	1.18 [0.69, 2.01]	0.540	34.0	0.130
Large(≥100)	10	1.09 [0.98, 1.22]	0.110	0.0	0.460	1.07 [0.90, 1.28]	0.430	22.0	0.240	1.10 [0.77, 1.55]	0.610	58.0	0.010	1.03 [0.83, 1.27]	0.810	41.0	0.090	**1.29 [1.01, 1.65]**	**0.040**	**3.0**	**0.410**
Source of controls																					
Population based	12	1.05 [0.92, 1.19]	0.500	19.0	0.260	1.09 [0.90, 1.32]	0.390	24.0	0.210	1.02 [0.68, 1.52]	0.920	66.0	0.001	1.09 [0.87, 1.37]	0.460	37.0	0.090	1.13 [0.84, 1.52]	0.420	21.0	0.240
Hospital based	8	**1.23 [1.03, 1.46]**	**0.020**	**22.0**	**0.250**	1.30 [0.93, 1.82]	0.120	56.0	0.030	1.29 [0.80, 2.07]	0.300	39.0	0.120	1.22 [0.84, 1.78]	0.300	63.0	0.008	**1.56 [1.11, 2.20]**	**0.010**	**1.0**	**0.420**
Genotyping method																					
PCR-SSP	8	1.04 [0.90, 1.19]	0.610	0.0	0.850	1.07 [0.83, 1.38]	0.590	32.0	0.170	0.80 [0.52, 1.23]	0.310	59.0	0.020	1.08 [0.78, 1.49]	0.640	52.0	0.040	1.12 [0.83, 1.52]	0.440	0.0	0.800
PCR-TaqMan	3	1.16 [0.95, 1.42]	0.150	0.0	0.570	1.13 [0.88, 1.45]	0.340	0.0	0.610	1.08 [0.38, 3.05]	0.890	17.0	0.270	1.07 [0.83, 1.39]	0.600	0.0	0.670	1.47 [0.89, 2.44]	0.140	0.0	0.330
PCR-RFLP	3	**1.69 [1.27, 2.25]**	**0.000**	**0.0**	**0.700**	**1.73 [1.20, 2.49]**	**0.003**	**0.0**	**0.780**	**2.12 [1.07, 4.21]**	**0.030**	**0.0**	**0.950**	**1.54 [1.05, 2.24]**	**0.030**	**0.0**	**0.660**	**3.15 [1.51, 6.57]**	**0.002**	**0.0**	**0.660**
ARMS-PCR	5	1.09 [0.86, 1.37]	0.480	39.0	0.160	1.24 [0.85, 1.79]	0.260	37.0	0.180	1.42 [0.76, 2.67]	0.280	65.0	0.020	1.25 [0.82, 1.90]	0.290	44.0	0.130	1.19 [0.64, 2.23]	0.580	53.0	0.080
PCR-DHPLC	1	0.51 [0.23, 1.11]	0.090	NA	NA	0.25 [0.08, 0.73]	0.010	NA	NA	2.17 [0.58, 8.15]	0.250	NA	NA	0.12 [0.03, 0.47]	0.002	NA	NA	0.63 [0.15, 2.67]	0.530	NA	NA
IL10-819C/T polymorphism	7	T VS C				TT+TC VS CC				TT VS TC+CC				TC VS CC				TT VS CC			
HWE																					
In accordance with HWE	6	1.12 [0.76, 1.65]	0.560	79.0	0.000	1.17 [0.60, 2.27]	0.650	82.0	0.000	0.69 [0.41, 1.16]	0.160	56.0	0.050	1.20 [0.64, 2.26]	0.570	78.0	0.000	0.99 [0.44, 2.22]	0.990	70.0	0.006
Departure from HWE	1	0.83 [0.70, 0.99]	0.030	NA	NA	0.54 [0.37, 0.81]	0.003	NA	NA	1.33 [1.08, 1.65]	0.009	NA	NA	0.55 [0.36, 0.83]	0.004	NA	NA	0.54 [0.36, 0.81]	0.003	NA	NA
Region																					
Asian	4	**0.82 [0.71, 0.95]**	**0.007**	**5.0**	**0.370**	0.63 [0.33, 1.20]	0.160	72.0	0.010	0.68 [0.35, 1.32]	0.250	82.0	0.000	**0.63 [0.41, 0.98]**	**0.040**	**47.0**	**0.130**	**0.51 [0.36, 0.72]**	**0.000**	**0.0**	**0.460**
America	2	1.56 [0.88, 2.76]	0.130	44.0	0.180	1.36 [0.62, 3.01]	0.440	58.0	0.120	2.03 [0.10, 42.26]	0.650	87.0	0.005	**1.73 [1.01, 2.98]**	**0.050**	**0.0**	**0.860**	2.04 [0.28, 14.99]	0.480	70.0	0.070
Africa	1	2.01 [1.35, 2.99]	0.000	NA	NA	3.61 [1.99, 6.53]	0.000	NA	NA	1.45 [0.48, 4.34]	0.510	NA	NA	3.60 [1.97, 6.60]	0.000	NA	NA	3.64 [1.13, 11.67]	0.030	NA	NA
Sample size																					
Small(<100)	4	0.92 [0.61, 1.38]	0.670	69.0	0.020	0.88 [0.36, 2.13]	0.770	77.0	0.005	0.68 [0.31, 1.48]	0.330	66.0	0.030	0.80 [0.43, 1.49]	0.490	54.0	0.090	0.72 [0.25, 2.08]	0.550	65.0	0.030
Large(≥100)	3	1.25 [0.71, 2.20]	0.440	88.0	0.000	1.23 [0.45, 3.32]	0.690	93.0	0.000	0.99 [0.50, 1.95]	0.980	75.0	0.020	1.47 [0.46, 4.72]	0.520	93.0	0.000	1.05 [0.43, 2.56]	0.910	80.0	0.007
Source of controls																					
Population based	4	1.07 [0.79, 1.45]	0.660	65.0	0.040	1.08 [0.60, 1.94]	0.790	77.0	0.004	0.96 [0.40, 2.28]	0.930	81.0	0.001	1.06 [0.60, 1.87]	0.840	74.0	0.010	0.90 [0.46, 1.75]	0.750	59.0	0.060
Hospital based	3	0.96 [0.46, 2.03]	0.920	89.0	0.000	0.84 [0.16, 4.35]	0.840	92.0	0.000	0.65 [0.39, 1.06]	0.090	32.0	0.230	0.91 [0.19, 4.38]	0.910	90.0	0.000	0.73 [0.17, 3.16]	0.680	83.0	0.003
Genotyping method																					
PCR-SSP	3	1.33 [0.86, 2.07]	0.200	74.0	0.020	1.75 [0.82, 3.74]	0.150	83.0	0.003	0.63 [0.31, 1.27]	0.200	41.0	0.180	1.81 [0.86, 3.81]	0.120	81.0	0.006	1.40 [0.62, 3.17]	0.410	51.0	0.130
PCR-RFLP	2	**0.66 [0.49, 0.90]**	**0.009**	**0.0**	**0.950**	**0.38 [0.20, 0.75]**	**0.005**	**0.0**	**0.870**	**0.55 [0.36, 0.84]**	**0.006**	**0.0**	**0.580**	**0.43 [0.21, 0.87]**	**0.020**	**0.0**	**0.840**	**0.34 [0.17, 0.69]**	**0.003**	**0.0**	**0.900**
PCR-DHPLC	1	2.27 [1.07, 4.85]	0.030	NA	NA	2.33 [0.88, 6.19]	0.090	NA	NA	10.93 [1.33, 89.78]	0.030	NA	NA	1.87 [0.68, 5.16]	0.230	NA	NA	7.50 [0.85, 66.13]	0.070	NA	NA
PCR-Taqman	1	0.83 [0.70, 0.99]	0.030	NA	NA	0.54 [0.37, 0.81]	0.003	NA	NA	1.33 [1.08, 1.65]	0.009	NA	NA	0.55 [0.36, 0.83]	0.004	NA	NA	0.54 [0.36, 0.81]	0.030	NA	NA
IL10-592C/A polymorphism	7	A VS C				AA+AC VS CC				AA VS AC+CC				AC VS CC				AA VS CC			
HWE																					
In accordance with HWE	6	0.99 [0.76, 1.31]	0.970	60.0	0.030	0.98 [0.58, 1.65]	0.940	67.0	0.010	1.06 [0.34, 3.29]	0.920	94.0	0.000	1.00 [0.61, 1.65]	0.990	60.0	0.030	0.87 [0.46, 1.63]	0.650	59.0	0.030
Departure from HWE	1	0.83 [0.70, 0.99]	0.030	NA	NA	0.54 [0.37, 0.81]	0.003	NA	NA	1.33 [1.08, 1.65]	0.009	NA	NA	0.55 [0.36, 0.83]	0.004	NA	NA	0.54 [0.36, 0.81]	0.003	NA	NA
Region																					
Asian	5	0.92 [0.70, 1.21]	0.540	68.0	0.010	0.79 [0.40, 1.59]	0.510	80.0	0.000	1.02 [0.42, 2.50]	0.960	94.0	0.000	0.83 [0.42, 1.66]	0.600	78.0	0.001	0.66 [0.36, 1.22]	0.190	64.0	0.030
America	2	1.03 [0.78, 1.38]	0.830	0.0	0.320	1.02 [0.69, 1.52]	0.920	0.0	0.570	1.51 [0.15, 15.08]	0.730	86.0	0.007	1.00 [0.66, 1.52]	0.990	0.0	0.850	1.22 [0.48, 3.07]	0.670	29.0	0.240
Sample size																					
Small(<100)	4	0.94 [0.60, 1.47]	0.790	69.0	0.020	0.83 [0.33, 2.07]	0.690	78.0	0.003	0.69 [0.33, 1.47]	0.340	66.0	0.030	0.87 [0.36, 2.11]	0.750	74.0	0.008	0.68 [0.27, 1.69]	0.400	58.0	0.070
Large(≥100)	3	0.97 [0.77, 1.23]	0.810	57.0	0.100	0.88 [0.50, 1.56]	0.670	74.0	0.020	1.62 [0.51, 5.18]	0.410	96.0	0.000	0.86 [0.50, 1.46]	0.580	67.0	0.050	0.90 [0.45, 1.76]	0.750	72.0	0.030
Source of controls																					
Population based	5	1.08 [0.85, 1.36]	0.550	58.0	0.050	1.12 [0.67, 1.89]	0.670	75.0	0.003	1.49 [0.57, 3.87]	0.420	93.0	0.000	1.10 [0.65, 1.86]	0.740	73.0	0.005	1.03 [0.58, 1.85]	0.910	60.0	0.040
Hospital based	2	**0.66 [0.48, 0.89]**	**0.007**	**0.0**	**0.950**	**0.38 [0.20, 0.74]**	**0.005**	**0.0**	**0.870**	**0.54 [0.36, 0.83]**	**0.005**	**0.0**	**0.580**	**0.43 [0.21, 0.87]**	**0.020**	**0.0**	**0.840**	**0.34 [0.17, 0.68]**	**0.003**	**0.0**	**0.900**
Genotyping method																					
PCR-SSP	2	1.14 [0.78, 1.68]	0.500	50.0	0.160	1.38 [0.65, 2.95]	0.410	74.0	0.050	**0.48 [0.27, 0.85]**	**0.010**	**0.0**	**0.580**	1.45 [0.63, 3.33]	0.380	77.0	0.040	1.00 [0.55, 1.82]	0.990	0.0	0.690
PCR-RFLP	3	0.83 [0.53, 1.31]	0.430	74.0	0.020	0.64 [0.23, 1.73]	0.380	74.0	0.020	1.20 [0.22, 6.63]	0.840	97.0	0.000	0.68 [0.29, 1.59]	0.370	61.0	0.080	0.61 [0.19, 1.91]	0.390	78.0	0.010
PCR-Taqman	1	0.83 [0.70, 0.99]	0.030	NA	NA	0.54 [0.37, 0.81]	0.003	NA	NA	1.33 [1.08, 1.65]	0.009	NA	NA	0.55 [0.36, 0.83]	0.004	NA	NA	0.54 [0.36, 0.81]	0.003	NA	NA
PCR-DHPLC	1	1.44 [0.70, 2.98]	0.320	NA	NA	1.32 [0.50, 3.45]	0.570	NA	NA	5.46 [1.12, 26.68]	0.040	NA	NA	1.09 [0.39, 3.02]	0.870	NA	NA	2.79 [0.52, 14.96]	0.230	NA	NA

OR: odds ratio; CI: Confidence Interval; HB: Hospital Based; PB: Population Based. #*p*-value for meta-analysis; **p*-value for between-study heterogeneity based on Q test. Significant results are marked in bold.



A. IL-10-1082A/G polymorphism **B.** IL-10-819C/T polymorphism

Fig. 3. Subgroup analysis (region) of SLE risk associated with IL10-1082A/G and IL10-819C/T. polymorphism. OR: odds ratio; CI: confidence interval.

information size was calculated to an overall type-I error of 5%, a power of 80% and a relative risk reduction (RRR) assumption of 20%, and a continuity correction of 0.5 was also applied in zero-event trials.

Results

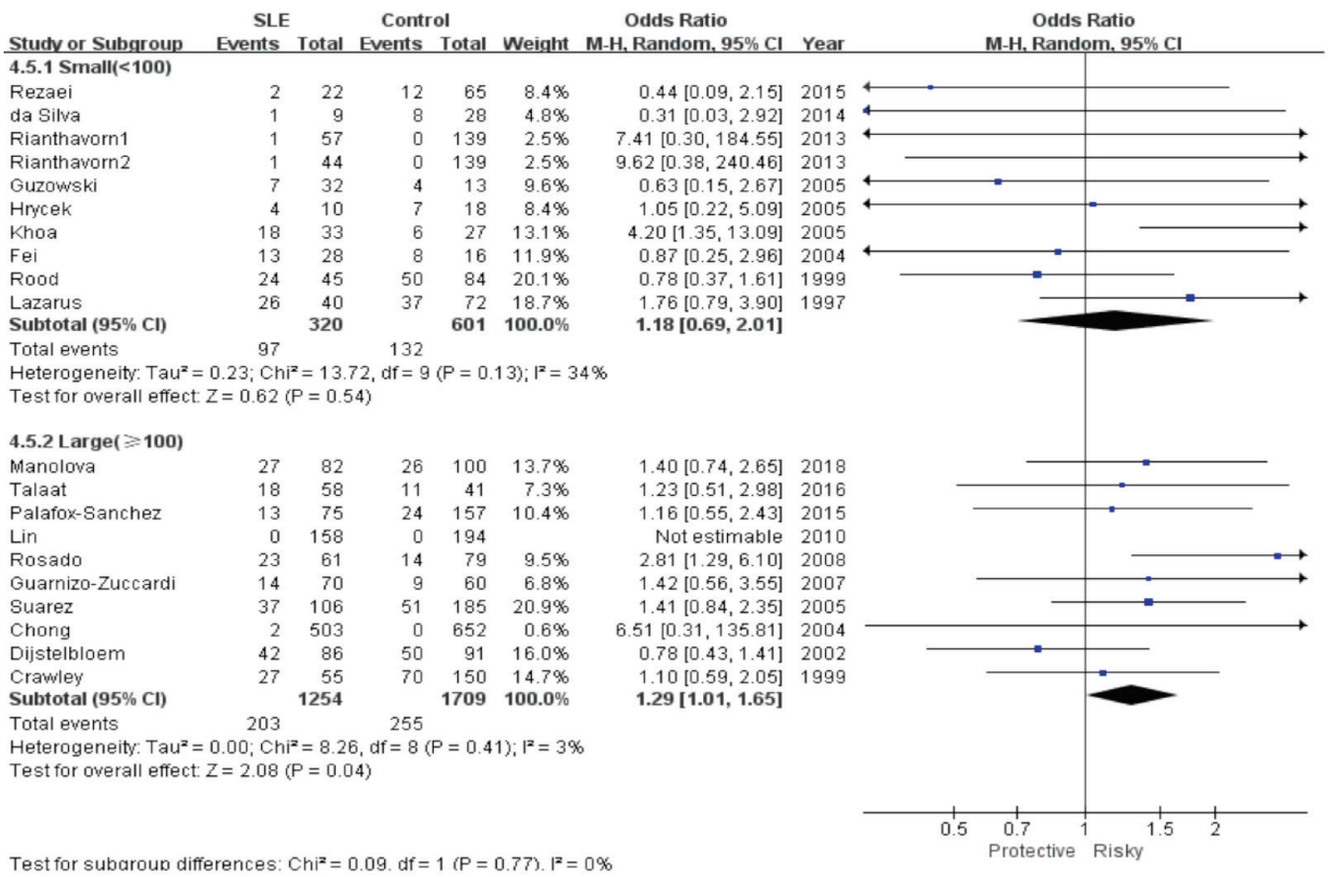
The characteristics of the included studies

A total of 326 articles were obtained by searching foreign databases (PubMed, Embase and Google scholar) and Chinese databases (CNKI, VIP and Wan Fang) respectively. After removing duplicates and screening the title and abstract, 32 articles were selected. After screening full-text articles, eighteen articles were included in qualitative synthesis. Finally, a total of twenty published articles (15-34), involving twenty studies for the IL10-1082A/G polymorphism, seven studies for the IL10-819C/T polymorphism and seven studies for the IL10-592C/A polymorphism in this meta-analysis (Seen in the Table S1 PRISMA Flow Diagram). The characteristics of all the included articles are summarised in Table I.

Meta-analysis results and heterogeneity analysis

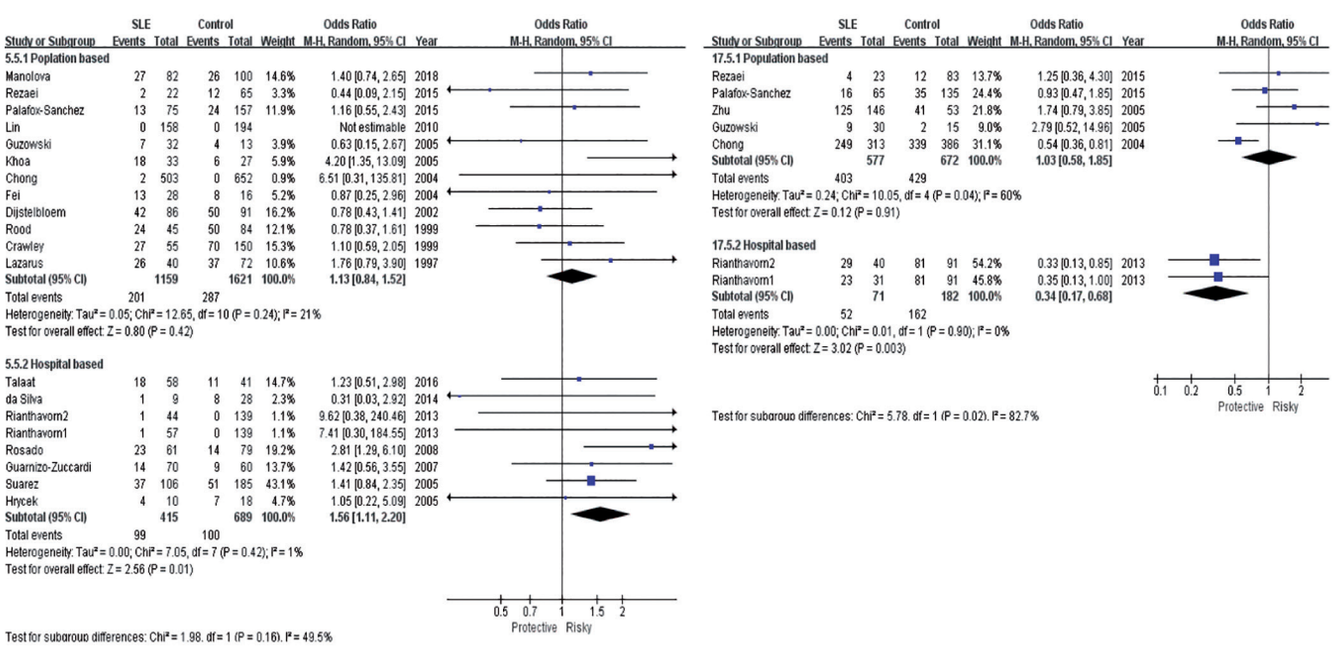
Table II shows the main results of this meta-analysis and the heterogeneity of the interleukin-10 gene polymorphisms and systemic lupus erythematosus risk. The -1082A/G polymorphism was associated with increased risk of systemic lupus erythematosus in the allelic model (G VS A: OR=1.21, 95%CI=1.01–1.25) (Fig. 1), dominant model (GG+GA VS AA: OR=1.07, 95%CI=1.01–1.13), and homozygote model (GG VS AA: OR=1.27, 95%CI=1.01–1.60). However, association was not detected in the IL10-819C/T and IL10-592C/A polymorphisms.

Subgroup analysis was introduced to uncover some potential details concerning associations between IL10 polymorphisms and systemic lupus erythematosus risk. Table III summarises the results of the subgroup analysis. For the subgroup analysis stratified by HWE, significant associations were only detected in IL10-1082A/G polymorphism in dominant genetic model (GG+GA VS AA: OR=1.20, 95%CI=1.02–1.42), but for IL10-819C/T and -592C/A polymorphisms, no associations were observed. As stratified by region, significant associations were found in Asian subgroup both IL-1082A/G and IL10-819C/T polymorphisms (IL10-1082A/G polymorphism: G VS A: OR=1.30, 95%CI=1.00–1.69; GG+GA VS AA: OR=1.27, 95%CI=1.02–1.59, IL10-819C/T polymorphism: T VS C: OR=0.82, 95%CI=0.71–0.95; TC VS CC: OR=0.63, 95%CI=0.41–0.98; TT VS CC: OR=0.51, 95%CI=0.36–0.72). No associations were detected in the three polymorphisms in subgroup analysis stratified by sample size. Interesting significant associations were detected in hospital-based subgroup of both IL10-1082A/G and IL10-592C/A polymorphisms (IL10-1082A/G polymorphism: G VS A: OR=1.23, 95%CI=1.03–1.46; GG VS AA: OR=1.56, 95%CI=1.11–2.20, IL10-592C/A polymorphism:



IL-10-1082A/G polymorphism

Fig. 4. Subgroup analysis (event sample size) of SLE risk associated risk associated with IL10-1082A/G. polymorphism.
OR: odds ratio; CI: confidence interval.



A. IL-10-1082A/G polymorphism

B. IL-10-592C/A polymorphism

Fig. 5. Subgroup analysis (source of controls) of SLE risk associated risk associated with IL10-1082A/G and IL10-592C/A. polymorphism.
OR: odds ratio; CI: confidence interval.

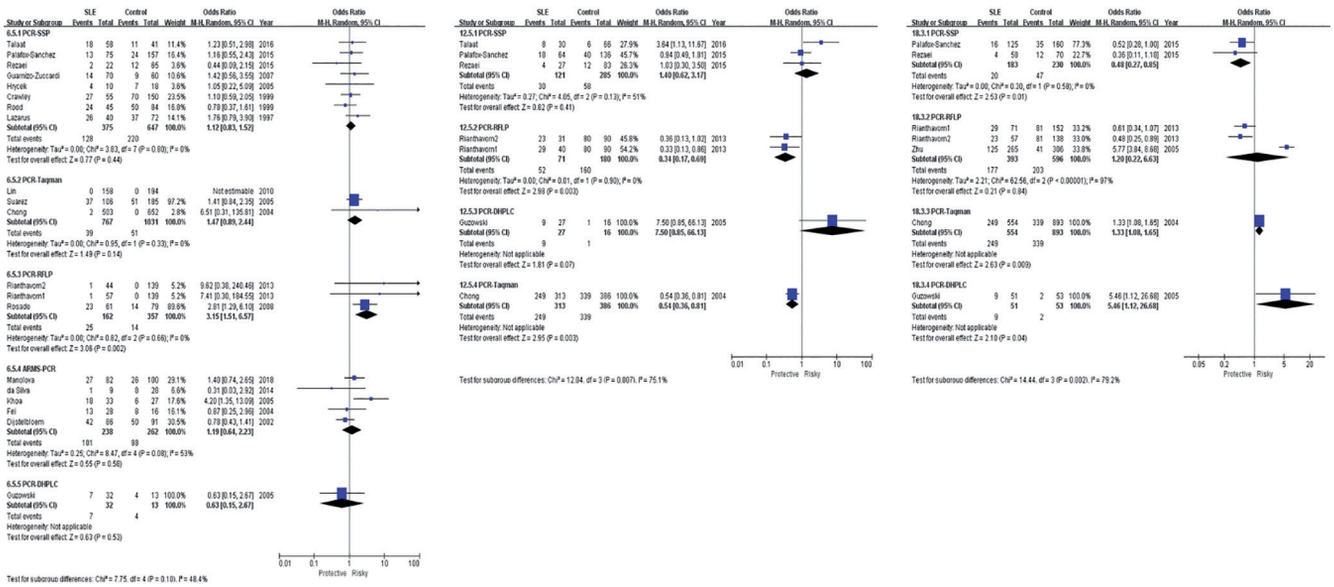


Fig. 6. Subgroup analysis (genotyping method) of SLE risk associated risk associated with IL10-1082A/G, IL10-819C/T and IL10-592C/A polymorphism. OR: odds ratio; CI: confidence interval.

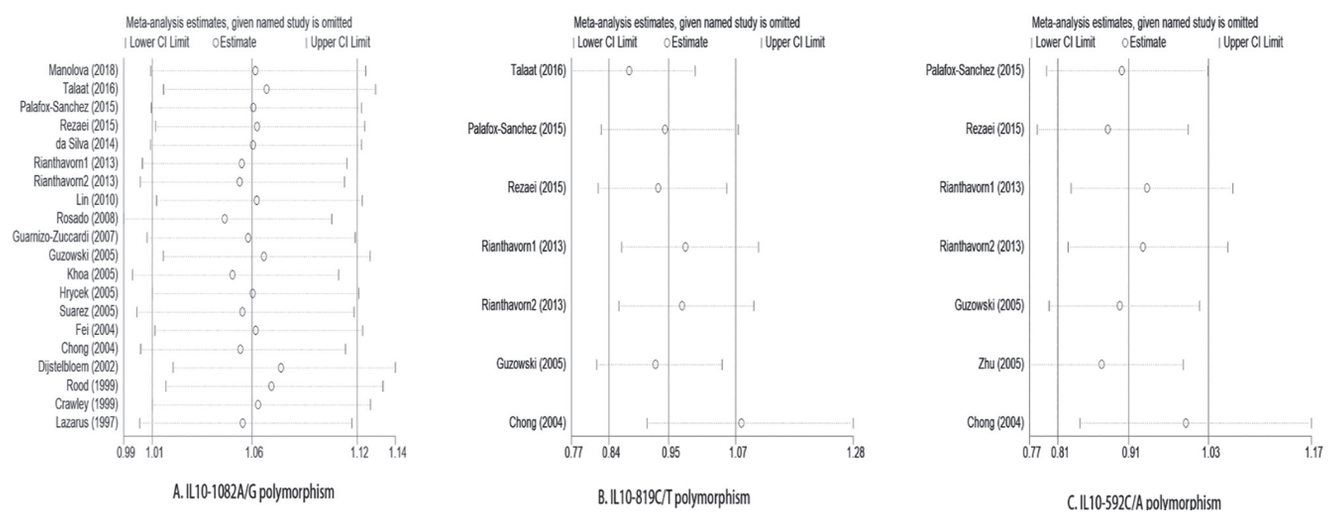


Fig. 7. Sensitivity analysis of SLE risk associated risk associated with IL10-1082A/G, IL10-819C/T and IL10-592C/A polymorphism. OR: odds ratio; CI: confidence interval.

A VS C: OR=0.66, 95%CI=0.48–0.89; AA+AC VS CC: OR=0.38, 95%CI=0.20–0.74;AA VS AC+CC: OR=0.54, 95%CI=0.36–0.83;AC VS CC: OR=0.43, 95%CI=0.21–0.87;AA VS CC: OR=0.34, 95%CI=0.17–0.68). As for the subgroup analysis stratified by genotyping method, wide significant associations were observed in the PCR-RFLP subgroup in IL10-1082A/G and -819C/T polymorphisms (IL1082A/G: G VS A: OR=1.69, 95%CI=1.27–1.2.25; GG+GA VS AA: OR=1.73, 95%CI=1.20–1.2.49; GG VS GA+AA: OR=2.12, 95%CI=1.07–4.21;GA VS AA: OR=1.54, 95%CI=1.05–2.24; GG VS AA: OR=3.15, 95%CI=1.51–6.57, IL10-819C/T: T VS C: OR=0.66, 95%CI=0.49–0.90; TT+TC VS CC: OR=0.38, 95%CI=0.20–0.75; TT VS TC+CC: OR=0.55, 95%CI=0.36–0.84; TC VS CC: OR=0.43, 95%CI=0.21–0.87; TT VS CC: OR=0.34, 95%CI=0.17–0.69).

Sensitivity analysis

In order to detect the influence of each study on the overall meta-analysis, sensitivity analysis was performed by sequentially omitting one individual study. No substantial change of data on all five-genetic models were observed, therefore, our results of our meta-analysis were relatively stable and credible.

Publication bias

No publication bias was detected in the five genetic models among studies regarding the associations between the IL10-1082A/G polymorphism and systemic lupus erythematosus risk. For IL10-819C/T and IL10-592C/A polymorphisms, publication bias was not observed because the number of studies of each subgroup was less than 10 (35).

Trial sequential analysis

Our results show the number of patients included in the meta-analysis for IL10-1082A/G polymorphism not only exceeded the Z line but also passed the TSA line, which indicated the numbers in case-control studies reach the minimum sample size.

Discussion

The IL10 gene is located on chromosome 1 at position 1q31-1q32, which is a major SLE susceptibility locus (36). The increased production of IL-10 in SLE patients was reported and the up-production of IL-10 might influence the biosynthesis of autoantibodies in SLE subjects (37). Moreover, down-regulation of IL-10 expression by an anti-IL10 monoclonal antibody resulted in amelioration of clinical manifestation in SLE patients (38), which implied a pivotal role of IL-10 in the pathogenesis of SLE. Three common IL10 gene polymorphisms which are IL10-1082A/G, -819C/T and -592C/A polymorphisms have been widely studied in the past years. Four meta-analyses have already been published regarding the correlation between IL10 polymorphisms and SLE risk (39-43). Most included studies in the previous meta-analysis were before 2013, and several new studies after 2013 draw inconsistent results (27, 28). In addition, adjusted *p*-value and type I error were not evaluated in the previous studies. Therefore, we performed an updated meta-analysis with trial sequential analysis to analyse these associations.

In our meta-analysis, significant increased risk of SLE was observed in IL10-1082G/A polymorphism from the overall analysis, but no associations were observed in the IL10-819C/T and IL10-592C/A polymorphisms. The trial sequential analysis confirms the positive results of the IL10-1082G/A polymorphism, which indicates case-control studies or meta-analysis regarding the associations between this polymorphism and SLE risk are no more necessary. Subgroup analysis stratified by HWE, Region, sample size, source of controls and genotyping method were conducted and interesting associations were revealed. For the IL10-1082A/G polymorphism, increased risk of SLE was extensively detected in Asian population, hospital-based and PCR-RFLP subgroups. However, decreased risks of SLE were observed in the IL10-819C/T and IL10-592/A polymorphisms. In the Asian population, the T allele, TC genotype and TT genotype of IL10-819C/T polymorphism show 18%, 37% and 49% decreased risk of SLE. In the hospital-based subgroup of IL10-592C/A polymorphism, decreased risk of SLE was observed in all genetic models. As for the subgroup analysis stratified by genotyping method, decreased risk was widely detected in the PCR-RFLP subgroup of IL10-819C/T polymorphism and a 52% decreased SLE risk of AA genotype compared to AC and CC genotype was observed in IL10-592C/A polymorphism. The decreased risk of SLE in IL10-819C/T and IL10-

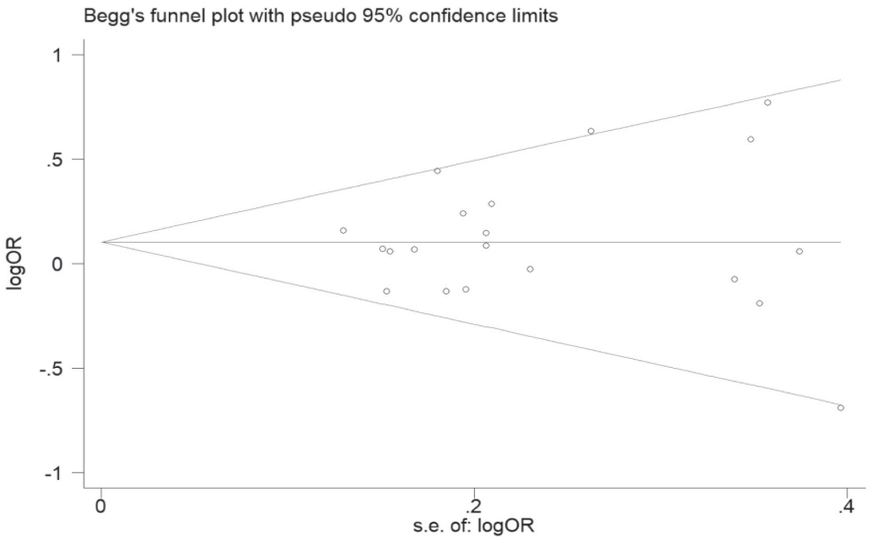


Fig. 8. Publication bias of SLE risk associated with IL10-1082A/G polymorphism.
OR: odds ratio; CI: confidence interval.

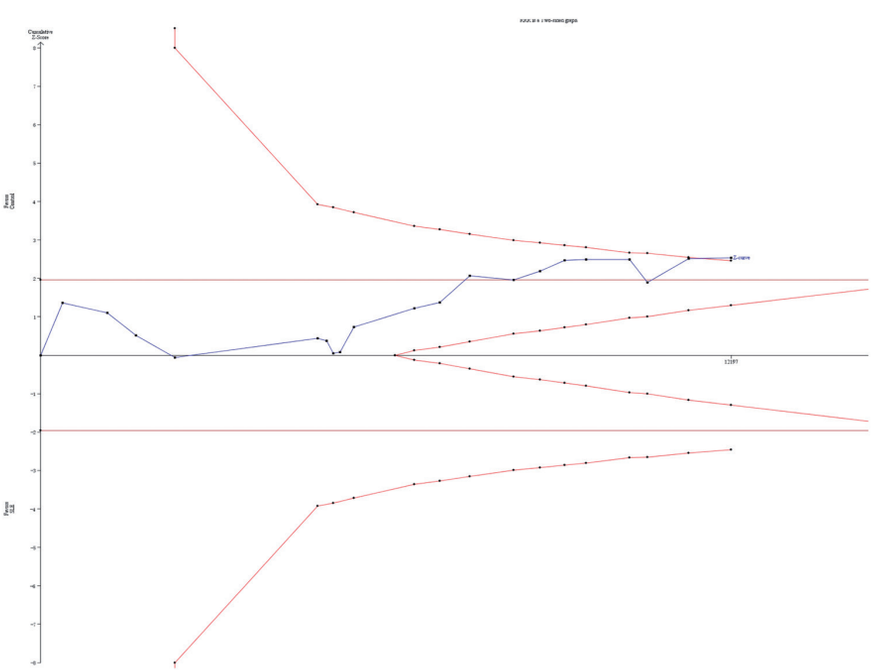


Fig. 9. Trial sequential analysis of SLE risk associated with IL10-1082A/G polymorphism.
OR: odds ratio; CI: confidence interval.

592C/A polymorphisms was observed in our study, studies included in some subgroups were relatively small and the decreased risk need to be interpreted with cautions. Our subgroup analysis indicated HWE, geography information, different source of controls and genotyping methods had an important influence on the source of heterogeneity and recovering the potential associations, moreover, the risk factor role of IL-10 polymorphisms would have a great clinical importance in SLE genetic prevention and therapy.

For the SLE patients, associations between IL-10 gene polymorphisms and clinical manifestations have attracted great attention. In the study reported by Lazarus *et al*. in 1997 (24), the IL10-1082G allele was increased in population with Ro antiantibodies and renal involvement. In the following years, many researchers reported the IL10-1082G/A polymorphism was associated with clinical manifestations in SLE. In the study reported by Rood *et al*. (30), the SLE subjects with neuropsychiatric manifestations were found to be associated with the IL-10 promoter haplotype ATA but less frequent in GCC haplotype. However, in different population, conflicting results were observed. In a Brazilian population, no relationship between clinical features and IL10-1082G/A was detected (17). The discrepancy may be due to different population characteristics (sample size, individual disease feature heterogeneity, environmental factors). Although differences were found, the IL10-1082G/A polymorphism may be associated with clinical manifestations, which also needs further study.

Furthermore, haplotype also played an important role in the susceptibility to disease. The GCC haplotype of the IL-10 gene associated with an increased risk of SLE in Spanish population was reported by Rosado *et al*. (31), moreover, the GCC haplotype was found to be related with high IL10 producers in the USA population (21). However, lack of association between the haplotype GCC/ATA polymorphism and SLE risk was reported by the meta-analysis of Wang *et al*. (41), which suggests that the associations between the IL-10 polymorphism haplotypes and SLE risk needs further research.

There were several limitations in this meta-analysis. Firstly, although we did not set a language limitation, only English and Chinese articles were recruited based on our search strategy. Similar researches in other languages may also exist, which could have an influence on our results. Secondly, individual patient heterogeneity and confounding factors might have distorted the analysis. Thirdly, the sample size of some included studies was relatively small in some subgroups, thus the results should be interpreted with caution. Fourth, the only one study from Africa included was consistent with our results, but used departure from Hardy-Weinberg equilibrium, so it was not pooled into our meta-analysis, which would require further researches in the African population in the future. In addition, the issue of environment factors on genes is worthy of consideration.

In conclusion, our study suggests that the IL10-1082A/G polymorphism is associated with an increased risk of systemic lupus erythematosus. Significant decreased risk of SLE in the IL10-819C/T and IL10-592C/A polymorphisms in some subgroups was also observed, but further rigorously studies are needed to confirm our results.

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