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The associations between interleukin 10 polymorphisms and susceptibility to autoimmune uveitis – a meta-analysis

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Abstract

Autoimmune uveitis is an ocular inflammatory disease that is associated with genetic factors. Interleukin 10 (IL-10) is an immune-regulatory cytokine of autoimmune diseases. IL-10 is considered a candidate gene for uveitis. We evaluate the association of IL-10 with susceptibility to autoimmune uveitis. The results from seven studies were pooled in the meta-analysis, covering a total of 2893 cases of uveitis and 4873 controls. Published literature from MEDLINE and Embase was retrieved. Meta-analyses were conducted on the associations between autoimmune uveitis and the -1082 A/G and -819 C/T polymorphisms of the IL-10 gene. The meta-analysis revealed no association between uveitis and the IL-10 -1082 A allele (OR = 0.91, 95% CI = 0.64-1.30, p = 0.62). The recessive, dominant, and homozygous models of the IL-10 -1082 A/G allele also suggested no association between autoimmune uveitis and each genotype. The meta-analysis revealed significant association between uveitis and the -892 C allele (OR = 0.81, 95% CI = 0.67-0.98, p = 0.03). In addition, significant association was found in homozygous models (OR = 0.58, 95% CI = 0.36-0.92, p = 0.02). However, the dominant and recessive models of the IL-10 -819 C/T polymorphisms showed no association between uveitis and each genotype. This meta-analysis showed that the -1082 A/G polymorphisms of IL-10 were not associated with autoimmune uveitis, but the -819 C/T polymorphisms were significantly associated with uveitis.

Key words: *polymorphism, meta-analysis, interleukin-10, autoimmune uveitis.*

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Introduction

Uveitis is an inflammatory disease of the uvea, which includes three highly vascularised and pigmented areas: the iris, ciliary body, and choroid [1]. Uveitis is an important ocular disease because it is one of the leading causes of blindness next to cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration [2]. It can result from both infectious and non-infectious or autoimmune causes. Autoimmune uveitis is often accompanied by a systemic inflammatory condition, such as Behçet's disease (BD), ankylosing spondylitis (AS), and Vogt-Koyanagi-Harada (VKH) disease [3].

Previous studies indicate that cytokines affect the development of autoimmune uveitis; biologic agents such as tumour necrosis factor α (TNF-α) blocker have been used to treat uveitis [4-6]. Interleukin 10 (IL-10) is an immunosuppressive cytokine that inhibits chemokine production [7]. IL-10 promotes immune tolerance, resolution of inflammation, and apoptosis in both systemic and ocular diseases [8]. IL-10 polymorphisms are also associated with autoimmune diseases that can involve ocular symptoms such as AS and BD [9, 10]. IL-10 is considered a strong candidate gene for ocular inflammatory disease based on its chromosomal location and functional relevance. This cytokine contains three of the most well characterised single-nucleotide polymorphisms (SNPs): -1082 A/G (rs1800896), -819 C/T (rs1800871), and -592 C/A (rs1800872) [10].

Autoimmune uveitis has an unknown aetiology. Some uveitic entities are associated with systemic autoimmune diseases, whereas others are limited to the eye [11]. Uveitis is classified anatomically as anterior, intermediate, posterior, or panuveitis, and the location of the inflammation depends mainly on the type of systemic disease. Although the features of uveitis vary, they all develop due to ocular inflammation and inflammatory processes. IL-10, an anti-inflammatory cytokine, may affect the development of uveitis. Therefore, we investigated the genetic associations between IL-10 polymorphisms and the susceptibility to autoimmune uveitis, using a meta-analysis.

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Material and methods

Study selection

We searched MEDLINE and Embase for studies of the association between IL-10 and uveitis using the terms (interleukin-10 OR IL-10) AND (uveitis OR ocular inflammation OR autoimmune uveitis) AND (polymorphisms OR variant OR mutation OR genotype) in articles published through November 2016. References cited in the retrieved articles were also screened manually. No restrictions were placed on race, language, ethnicity, or geographic area.

Inclusion and exclusion criteria

The inclusion criteria for this investigation included case-control studies that determined the distributions of the IL-10 -1082 A/G, -819 C/T, and -592 C/A polymorphisms and uveitis, and detailed data for both the case and control groups, or any other data from which the desired numbers could be calculated. Studies were excluded based on the following criteria: those that contained overlapping data; studies in which the number of null and wild genotypes or alleles could not be ascertained; and investigations that were review articles or only contained abstracts.

Data extraction

The following information was obtained from each article: the first author, year of publication, ethnicity of the study population, demographics, numbers of cases and controls, Hardy-Weinberg equilibrium (HWE), and allele and genotype frequencies of the IL-10 -1082 A/G, -819 C/T, and -592 C/A alleles. Because IL-10 -819 C/T and -592 C/A exhibit complete linkage disequilibrium and data of -819 C/T were larger in number than those of -592 C/A, we excluded the -592 C/A in this meta-analysis. In cases of duplicated publications from the same study group, the study with a larger sample size was retained. This meta-analysis was reported based on the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines [12].

Statistical analyses

The raw data for allele contrast and genotype frequencies without adjustment were used for the meta-analysis. A chi-squared test was conducted to detect whether the controls in each study conformed to HWE. The strength of each association between IL-10 polymorphism and susceptibility to autoimmune uveitis was estimated using the crude odds ratio (OR) and 95% confidence interval (CI).

The meta-analyses were performed on the following genetic models: allelic contrast, recessive (-1082 A/G: AA vs. AG + GG; -892 C/T: CC vs. CT + TT), dominant (-1082 A/G: AA + AG vs. GG; -892 C/T: CC + CT vs. TT), and homozygous (-1082 A/G: AA vs. GG; -892 C/T: CC vs. TT).

Heterogeneity between studies was assessed with the Cochran Q test, in which a p-value < 0.10 was considered as statistically significant heterogeneity, and the heterogeneity among studies was tested by the I_{χ} statistic, in which $I_{\chi} > 50\%$ was considered as statistically significant heterogeneity [13]. A fixed-effect model was employed in cases with no significant heterogeneity [14]. Otherwise, a random-effect model was used [15]. Forest plots were drawn to visualise the overall effect. Data were analysed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study characteristics

In total, 90 studies were identified through our electronic and manual searches. Of these investigations, 26 were selected for full-text review based on their titles and abstracts. Nineteen studies were excluded because they were review articles or meta-analyses, had the potential for overlapping data, lacked genotype data or suitable control data, or contained other polymorphisms. Thus, seven studies met the inclusion criteria (Fig. 1). Because two of these studies contained data on two different groups, we analysed these groups independently [16, 17]. Finally, this meta-analysis considered nine separate comparisons, including 2893 patients and 4873 controls [8, 16-21].

Two studies (three different groups) contained only minor allele data [8, 17]. Thus, in the meta-analysis for -1082 A/G, allelic contrast and recessive and homozygous models included five studies, and the dominant model included seven studies. In the meta-analysis for -819 C/T, allelic

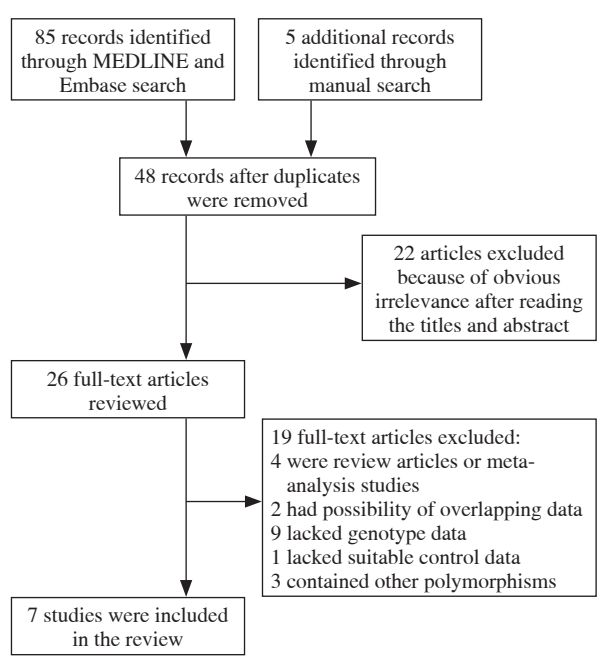


Fig. 1. Flow chart of the study's inclusion/exclusion process

Table 1. Characteristics of the individual studies included in our systemic review and meta-analysis

First author	Year	Country	Disease	Number of cases	Characteristics of cases	Number of controls	Characteristics of controls	Gene	Genotyping method	HWE *p*-value
Yu [21]	2017	China	BD	1206	Diagnosed at the department of ophthalmology	2475	Matched for sex and age Same ethnic background and geographic area	-819 C/T	PCR-SSP	0.4817
Hu [16]	2015	China	BD VKH syndrome	718 300	Diagnosed at the ophthalmology	1,753	No genetic connection to the patients Same ethnic background	-1082 A/G -819 C/T -592 C/A	PCR-RFLP	0.3238 0.0957/0.9872 0.0902
Talaat [18]	2014	Egypt	BD	55	Complete ophthalmic examination and fundus fluorescein angiography	97	Matched for age	-1082 A/G -819 C/T	PCR-SSP	0.164 0.5261
Lindner [17]	2013	Austria	HLA-B27 associated uveitis Intermediate uveitis	159 85	Diagnosed at the department of ophthalmology	235	Same ethnic background and geographic area	-1082 A/G -819 C/T -592 C/A	PCR-HRM	> 0.05 > 0.05 > 0.05
Atan [8]	2010	UK	Non-infectious uveitis	192	Full ophthalmic examination	92	Matched for sex and age	-819 C/T	PCR-SSP	> 0.05
Dilek [19]	2009	Turkey	BD	53	Diagnosed according to international study group for BD	124	Matched for sex and age Same ethnic background and geographic area	-1082 A/G -819 C/T -592 C/A	PCR-SSP	0.3452 0.3294 0.3294
Stanford [20]	2005	UK	Idiopathic intermediate uveitis	125	Diagnosed at the department of ophthalmology	98	Same ethnic background	-1082 A/G -819 C/T	PCR-SSP	0.2258 0.2463

HWE – Hardy-Weinberg equilibrium, UK – United Kingdom, BD – Behçet's disease, VKH – Vogt-Koyanagi-Harada, PCR – polymerase chain reaction, RFLP – restriction fragment length polymorphisms, SSP – sequence specific primers, HRM – high-resolution melting

contrast and recessive and homozygous models included six studies, and the dominant model included eight studies.

The case group included all types of autoimmune uveitis, and uveitis was diagnosed in the department of ophthalmology or using objective tools. The control group was healthy, mostly of the same ethnicity or geographic area, and matched for age and sex, or had similar characteristics to the case groups. The selected characteristics of these studies with respect to the associations between IL-10 polymorphisms and uveitis are summarised in Table 1.

Meta-analysis of the IL-10 -1082 A/G and -892 C/T polymorphisms and susceptibility of autoimmune uveitis

The meta-analysis revealed no association between uveitis and the IL-10 -1082 A allele (OR = 0.91, 95% CI = 0.64-1.30, $p = 0.62$). In addition, no association was found using the pooled results for all of the models of the IL-10 -1082 A/G polymorphisms. The meta-analysis revealed significant association between uveitis and the -892 C allele (OR = 0.81, 95% CI = 0.67-0.98, $p = 0.03$; Fig. 2A). In addition, significant association was found in homozygous models (OR = 0.58, 95% CI = 0.36-0.92, $p = 0.02$; Fig. 2D). However, the dominant and recessive models of the IL-10 -819 C/T polymorphisms showed no association between uveitis and each genotype (Figs. 2B and 2C). The meta-analysis findings concerning the associations between IL-10 polymorphisms and uveitis are provided in Table 2.

Four studies were conducted on BD, and subgroup analysis was conducted on BD. In the IL-10 -1082 A/G polymorphisms there were no associations among uveitis of BD, allelic contrast, and any of the models. However, there were significant associations among uveitis of BD, allelic contrast, and all of the models of the IL-10 -819 C/T polymorphisms (Table 3 and Fig. 3).

Heterogeneity and publication bias

Some heterogeneity was found in this meta-analysis of the IL-10 -1082 A/G and -819 C/T polymorphisms (Table 2). Except for the dominant model of -1082 A/G, there was no change in the effect model used. Publication bias was examined using a funnel plot. Figure 4 shows the funnel plots for positive results. The funnel plots did not appear to be exactly symmetric.

Discussion

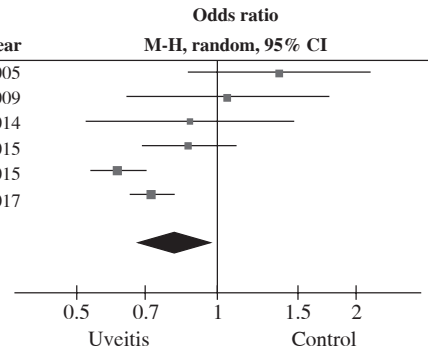
IL-10 is a potent anti-inflammatory cytokine produced by T cells, macrophages, and retinal cells [22]. Functional studies of IL-10 promoter polymorphisms have suggested that some genotypes or haplotypes are linked to down-regulation of IL-10 production [23]. This meta-analysis indicated that IL-10 -819 C/T polymorphisms were significantly associated with susceptibility to autoimmune uveitis.

A

Study or subgroup	Uveitis Events	Uveitis Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI	Year
Stanford *et al.*	202	250	148	196	10.8%	1.36 (0.87, 2.15)	2005
Dan *et al.*	76	106	175	248	9.4%	1.06 (0.64, 1.75)	2009
Talat *et al.*	77	110	141	194	9.1%	0.88 (0.52, 1.47)	2014
Hu *et al.* (VKH)	194	600	248	700	20.0%	0.87 (0.69, 1.10)	2015
Hu *et al.* (BD)	367	1436	1259	3506	24.8%	0.61 (0.53, 0.70)	2015
Yu *et al.*	631	2412	1630	4950	26.1%	0.72 (0.65, 0.80)	2017
Total (95% CI)		4914		9794	100.0%	0.81 (0.67, 0.98)	
Total events	1547		3601				

Heterogeneity: $Tau^2 = 0.03$, $\chi^2 = 18.38$, $df = 5$ ($p = 0.003$), $I^2 = 73\%$

Test for overall effect: $Z = 2.16$ ($p = 0.03$)

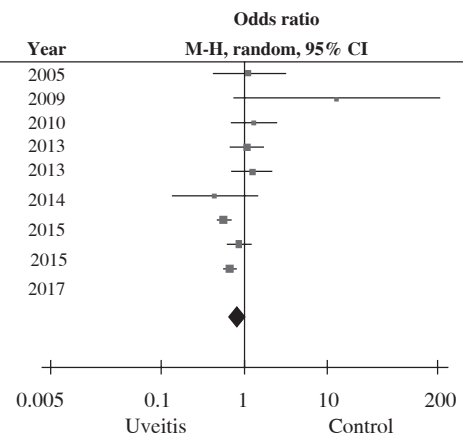


B

Study or subgroup	Uveitis Events	Uveitis Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI	Year
Stanford *et al.*	116	125	90	98	4.5%	1.15 (0.43, 3.09)	2005
Dilek *et al.*	53	53	111	124	0.7%	12.96 (0.76, 222.05)	2009
Alan *et al.*	157	192	71	92	9.0%	1.33 (0.72, 2.44)	2010
Lindner *et al.* (HLA)	113	159	163	235	12.8%	1.09 (0.70, 1.69)	2013
Lindner *et al.* (Int)	63	85	163	235	10.0%	1.26 (0.72, 2.21)	2013
Talat *et al.*	48	55	91	97	3.5%	0.45 (0.14, 1.42)	2014
Hu *et al.* (BD)	334	718	1049	1753	20.9%	0.58 (0.49, 0.70)	2015
Hu *et al.* (VKH)	166	300	204	350	16.7%	0.89 (0.65, 1.21)	2015
Yu *et al.*	545	1206	1354	2475	21.9%	0.68 (0.59, 0.78)	2017
Total (95% CI)		2893		5459	100.0%	0.85 (0.67, 1.07)	
Total events	1595		3296				

Heterogeneity: $Tau^2 = 0.06$, $\chi^2 = 24.31$, $df = 8$ ($p = 0.002$), $I^2 = 67\%$

Test for overall effect: $Z = 1.37$ ($p = 0.17$)

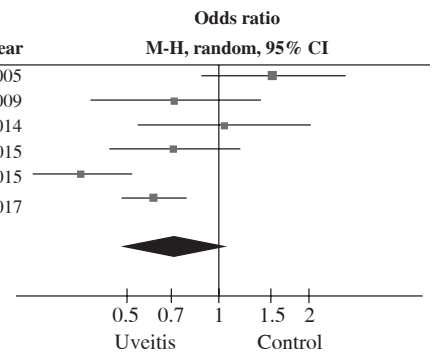


C

Study or subgroup	Uveitis Events	Uveitis Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI	Year
Stanford *et al.*	86	125	58	98	15.7%	1.52 (0.88, 2.64)	2005
Dilek *et al.*	23	53	64	124	14.1%	0.72 (0.38, 1.37)	2009
Talat *et al.*	29	55	50	97	13.8%	1.05 (0.54, 2.03)	2014
Hu *et al.* (VKH)	28	300	44	350	16.6%	0.72 (0.43, 1.18)	2015
Hu *et al.* (BD)	33	718	210	1753	18.9%	0.35 (0.24, 0.52)	2015
Yu *et al.*	86	1206	276	2475	20.9%	0.61 (0.48, 0.79)	2017
Total (95% CI)		2457		4897	100.0%	0.72 (0.49, 1.06)	
Total events	285		702				

Heterogeneity: $Tau^2 = 0.17$, $\chi^2 = 21.56$, $df = 5$ ($p = 0.0006$), $I^2 = 77\%$

Test for overall effect: $Z = 1.65$ ($p = 0.10$)



D

Study or subgroup	Uveitis Events	Uveitis Total	Control Events	Control Total	Weight	Odds ratio M-H, random, 95% CI
Dilek *et al.*	23	23	64	77	2.5%	9.84 (0.56, 172.10)
Hu *et al.* (BD)	33	417	210	914	25.0%	0.29 (0.20, 0.42)
Hu *et al.* (VKH)	28	162	44	190	21.8%	0.69 (0.41, 1.18)
Stanford *et al.*	86	95	58	66	12.6%	1.32 (0.48, 3.61)
Talat *et al.*	29	36	50	56	10.4%	0.50 (0.15, 1.62)
Yu *et al.*	86	747	276	1397	27.6%	0.53 (0.41, 0.69)
Total (95% CI)		1480		2700	100.0%	0.58 (0.36, 0.92)
Total events	285		702			

Heterogeneity: $Tau^2 = 0.19$, $\chi^2 = 17.11$, $df = 5$ ($p = 0.004$), $I^2 = 71\%$

Test for overall effect: $Z = 2.29$ ($p = 0.02$)

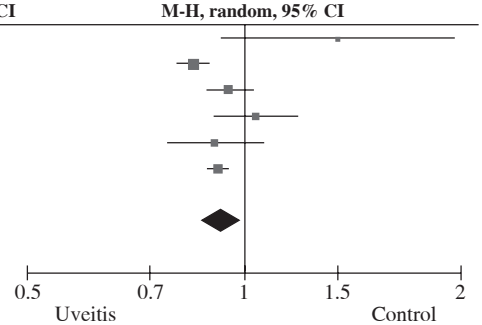


Fig. 2. ORs and 95% CIs of the IL-10 -819 C/T polymorphisms and autoimmune uveitis. Allelic contrast **(A)**, dominant **(B)**, recessive **(C)**, and homozygous **(D)** models

Table 2. Meta-analysis of the associations between the IL-10 polymorphisms and autoimmune uveitis

Polymorphism		Test of association			Test of heterogeneity		
		OR	95% CI	*p*-value	Model	*p*-value	I^2 (%)
-1082 A/G	A vs. G	0.91	0.64-1.30	0.62	R	0.01	69
	AA+AG vs. GG	0.86	0.66-1.10	0.23	F	0.22	27
	AA vs. AG+GG	0.78	0.35-1.73	0.54	R	< 0.0001	87
	AA vs. GG	0.66	0.39-1.09	0.10	F	0.49	0
-819 C/T	C vs. T	0.81	0.67-0.98	0.03	R	0.003	73
	CC+CT vs. TT	0.85	0.67-1.07	0.17	R	0.002	67
	CC vs. CT+TT	0.72	0.49-1.06	0.10	R	0.0006	77
	CC vs. TT	0.58	0.36-0.92	0.02	R	0.004	71

OR – odds ratio, CI – confidence interval, R – random effects model, F – fixed effects model

Table 3. Meta-analysis of the associations between the IL-10 polymorphisms and autoimmune uveitis of Behçet's disease

Polymorphism		Test of association			Test of heterogeneity		
		OR	95% CI	*p*-value	Model	*p*-value	I^2 (%)
-1082 A/G	A vs. G	0.90	0.46-1.77	0.76	R	0.002	84
	AA+AG vs. GG	0.91	0.18-4.55	0.91	R	0.005	66
	AA vs. AG+GG	0.69	0.19-2.47	0.57	R	< 0.00001	92
	AA vs. GG	0.53	0.25-1.13	0.10	F	0.32	12
-819 C/T	C vs. T	0.71	0.60-0.84	< 0.0001	R	0.07	58
	CC+CT vs. TT	0.64	0.51-0.80	0.0001	R	0.09	54
	CC vs. CT+TT	0.60	0.40-0.90	0.01	R	0.02	71
	CC vs. TT	0.47	0.26-0.84	0.01	R	0.01	73

Autoimmune uveitis comprises a heterogeneous group of disorders diagnosed using clinical characteristics and is accompanied by multiple systemic diseases; therefore, multiple genetic factors and cytokines may affect the development of uveitis in each condition. This meta-analysis contained various types of uveitis including BD, VKH syndrome, HLA-B27-associated uveitis, intermediate uveitis, sarcoidosis, sympathetic ophthalmia, and white dot with or without inflammation.

In this study, the -819 C allele and CC genotype were associated with low risk of uveitis. Although not statistically significant, the C allele in the dominant and recessive models also showed a trend toward lower risk of uveitis. In uveitis of BD, the -819 C/T allelic contrast and all genotype models showed that the C allele was significantly associated with lower risk. This result is consistent with the results from the previous meta-analysis on BD [10]. However, for diseases other than BD, subgroup analysis was not performed because the number of studies was less than two. Therefore, further studies on these diseases are necessary.

Several previous studies have suggested that IL-10 polymorphisms are related to the clinical manifestations of uveitis, such as severity, recurrence rate, and treatment response [20, 22]. In addition, pro-inflammatory cytokines influence autoimmune uveitis, and blocking agents of the pro-inflammatory cytokine pathway, especially TNF-α inhibitors, have been used to treat this disorder [2, 5, 24, 25]. TNF-α blocking agents are reportedly effective in treating AS, BD, and sarcoidosis accompanying uveitis [26-28]. As a result, IL-10 may down-regulate TNF-α production and has been correlated with disease severity [25-29]; thus, IL-10 can affect disease severity and the treatment response of uveitis.

As with any meta-analysis, there were some limitations to this study, and its results should be interpreted with caution. First, each case of uveitis has different clinical and pathological characteristics. The heterogeneity and confounding factors may have distorted the meta-analysis. We did not perform a subgroup analysis by disease category except BD due to the small number of published studies available on this topic. Second, stratification for ethnicity was also impossible because of the small number of cases. Therefore, well-designed and large-scale studies are required for further analyses. Third, IL-10 polymorphisms may be associated with disease severity and treatment response as well as susceptibility; however, we did not perform a meta-analysis to determine this association. Fourth, we did not conduct a haplotype study because only

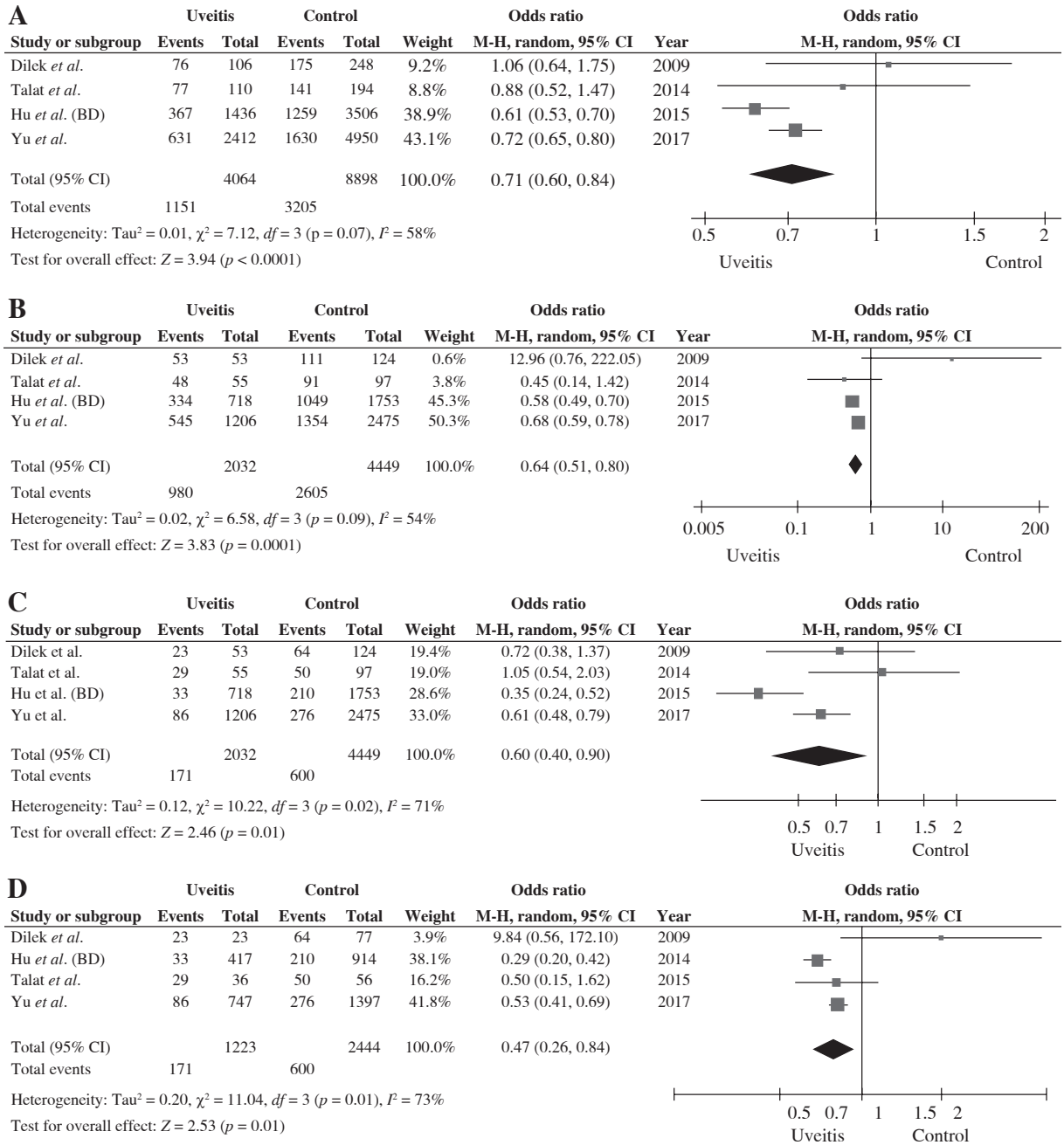


Fig. 3. ORs and 95% CIs of the IL-10 -819 C/T polymorphisms and autoimmune uveitis of BD. Allelic contrast **(A)**, dominant **(B)**, recessive **(C)**, and homozygous **(D)** models

one study contained haplotype data. Finally, publication bias could not be completely excluded.

The pathogenesis of autoimmune uveitis remains incompletely understood; however, cytokines seem to be critical mediators in this process. Cytokines act in a complex manner to mediate immune responses, and IL-10 has an anti-inflammatory effect on the inflammatory process [30].

This meta-analysis showed that the -1082 A/G polymorphisms of IL-10 were not associated with autoimmune uveitis, but the -819 C/T polymorphisms were significantly associated with uveitis. However, these results should be interpreted with caution given the study's limitations. Further studies with larger sample sizes that also include polymorphisms of other cytokines are needed.

The authors declare no conflict of interest.

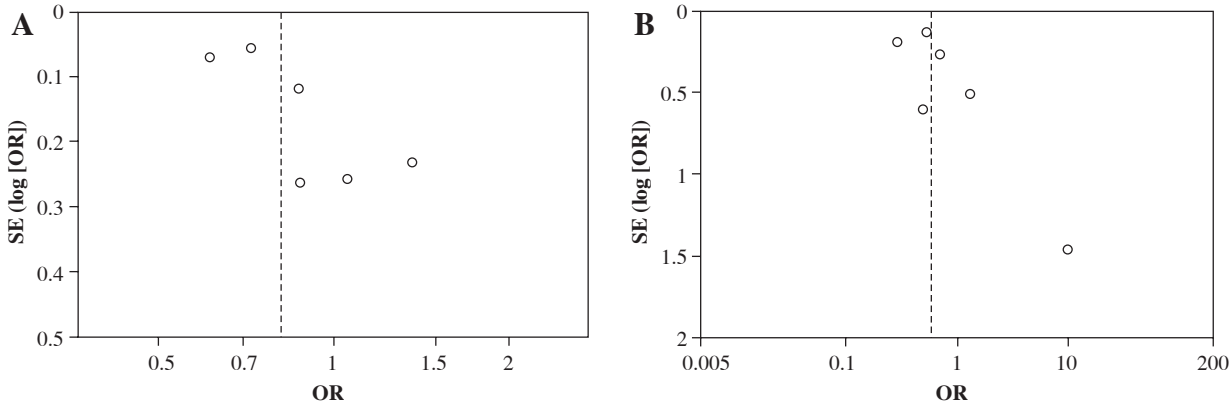


Fig. 4. Funnel plot of autoimmune uveitis and the -819 C allele (**A**) and CC vs. TT polymorphisms (**B**)

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