ORIGINAL ARTICLE

Effects of TNF-α Polymorphisms on Asthma Risk: A Systematic Review and Meta-Analysis

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Abstract

Background: Several studies have examined associations between TNF-α polymorphisms and asthma risk, but the results have been conflicting.
Methods: A search was performed of the PubMed, EMBASE, and Wanfang databases. Data were extracted and pooled ORs with 95% CIs were calculated.
Results: Fifty-four studies were included. A significant association between the *TNFA* -308A/G polymorphism and asthma susceptibility was observed for AA+AG vs GG (OR, 1.39; 95% CI, 1.23-1.58; *P*<.001). This polymorphism was also significantly associated with asthma risk in whites (OR, 1.47; 95% CI, 1.25-1.73; *P*<.001), atopic asthma risk (OR, 1.38; 95% CI, 1.16-1.65; *P*<.001), pediatric asthma risk (OR, 1.48; 95% CI, 1.23-1.79; *P*<.001), and adult asthma risk (OR, 1.35; 95% CI, 1.21-1.52; *P*<.001). There was also a significant association between the TNFA -857C/T polymorphism and asthma risk in the recessive model (OR, 1.25; 95% CI, 1.10-1.43; *P*<.001). In the subgroup analyses, asthma risk was significantly increased in Asians (OR, 1.23; 95% CI, 1.07-1.41; *P*=.004) and atopic individuals (OR, 1.33; 95% CI, 1.13-1.57; *P*<.001). No significant association was found for the *TNFA* -238A/G polymorphism. There were insufficient data to evaluate the associations between *TNFA* -1031T/C and -863C/A polymorphisms and asthma risk.
Conclusions: This meta-analysis suggests that *TNFA* -308A/G and -857C/T polymorphisms are risk factors for asthma.

Key words: Asthma. Tumor necrosis factor-α. Meta-analysis. Polymorphism.

Resumen

Antecedentes: Son varios los estudios que han examinado las asociaciones existentes entre diferentes polimorfismos del factor de necrosis tumoral alfa (TNF-α) con el riesgo de padecer asma. Sin embargo, los resultados han sido contradictorios.
Métodos: Se utilizaron diversas bases de datos para realizar las búsquedas, incluyendo: PubMed, EMBASE y Wanfang. Se calcularon los odd ratios combinados (OR) con intervalos de confianza del 95% (IC).
Resultados: Se incluyeron cincuenta y cuatro estudios. Se encontró una asociación significativa entre el polimorfismo TNFA-308A/G y la susceptibilidad de asma para AA+AG vs GG (OR = 1,39, IC del 95% 1,23-1,58, P <0,00001). Este polimorfismo también se asoció significativamente con el riesgo de asma en los pacientes caucásicos (OR = 1,47, IC del 95%: 1,25 a 1,73, P <0,00001), el riesgo de asma atópica (OR = 1,38, IC del 95%: 1,16 a 1,65, P = 0,0003), el riesgo de asma infantil (OR = 1,48, IC del 95%: 1,23 a 1,79, P <0,0001), y el riesgo de asma en adultos (OR = 1,35, IC del 95%: 1,21 a 1,52, P <0,00001), respectivamente. También hubo una asociación significativa entre el polimorfismo TNFA-857C/T y el riesgo de asma en el modelo recesivo (OR = 1,25, IC del 95%: 1,10 a 1,43, P = 0,0009). En los análisis de subgrupos, el riesgo de asma fue significativamente mayor en los asiáticos (OR = 1,23, IC del 95%: 1,07 a 1,41, P = 0,004) y en los individuos atópicos (OR = 1,33, IC del 95%: 1,13 a 1,57, P = 0,0006). No se encontró asociación significativa para el polimorfismo TNFA-238A/G. No hubo datos suficientes para evaluar asociaciones entre los polimorfismos TNFA-1031T/C y TNFA-863C/A y el riesgo de asma.
Conclusiones: Este meta-análisis sugiere que los polimorfismos TNFA-308A/G y TNFA-857C/T son factores de riesgo para el asma.

Palabras clave: Asma. Factor de necrosis tumoral-alfa. Meta-análisis. Polimorfismo.

1. Introduction

Asthma is one of the most common chronic diseases and affects an estimated 300 million people worldwide. TNF is a proinflammatory cytokine involved in the inflammation of asthmatic airways, and many studies have suggested that TNF-α may play an important role in the pathogenesis of asthma. *TNFA*, the gene encoding TNF-α, is located on chromosome 6p21.3. Several polymorphisms have been identified in *TNFA*, including -308A/G (rs1800629), -238A/G (rs361525), -857C/T (rs1799724), and -1031C/T (rs1799964) (Figure 1). Associations between *TNFA* polymorphisms and asthma risk have been extensively studied [1-54], but with conflicting and inconclusive results. Four meta-analyses have been performed in this field [23,55-57], as single studies may lack the power to draw reliable conclusions. The latest meta-analysis, which included 26 studies, was published by Zhang and colleagues in 2010 [57], but since then, an additional 13 studies with more data have been published [42-54]. A new meta-analysis is thus warranted. In addition, the 4 meta-analyses conducted to date have focused on just a single polymorphism: -308A/G. The aims of the current meta-analysis were to reinvestigate the relationship between the *TNFA* -308A/G polymorphism and asthma risk and assess the effects of other *TNFA* polymorphisms on asthma risk.

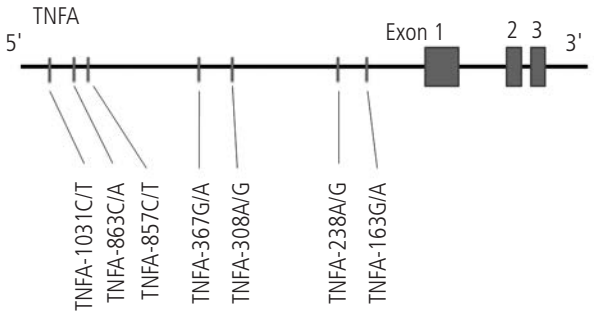

Figure 1. Schematic representation of the *TNFA* gene on chromosome 6 with single nucleotide polymorphism locations. The dark boxes denote exons.

2. Methods

2.1 Publication Search

A comprehensive, computerized literature search was conducted in PubMed, EMBASE, and Wanfang databases from the beginning of indexing for each database to June 1, 2013; the search was performed by 2 independent investigators (Huang and Nie). The search terms used were (asthma or asthmatic) and (TNF-α or tumor necrosis factor-α or TNF-a or tumor necrosis factor-a), and (polymorphism or mutation or variant). We also perused the reference lists of selected research papers and reviews to identify additional relevant studies. No language restrictions were imposed.

2.2 Inclusion and Exclusion Criteria

Two authors (Huang and Nie) independently evaluated all studies retrieved. To be included in the meta-analysis, a study had to meet the following criteria: 1) evaluation of *TNFA* polymorphisms and asthma risk, 2) case-control design, and 3) reporting of genotype distributions for both cases and controls to enable calculation of ORs with a 95% CI. Animal studies, studies that did not address asthma or asthma risk in relation to TNF or *TNFA* polymorphisms, and editorials, reviews, and abstracts were excluded. In the case of multiple studies analyzing the same cases, the one with the most comprehensive population was included. Discrepancies between the authors were resolved by discussion.

2.3 Data Extraction

Two authors (Nie and Qian) extracted the data using standardized data collection forms. The following data were collected from each study: first author's name, year of publication, country of origin, ethnicity, age group, atopic status, sample size, *TNFA* polymorphisms, and genotype numbers in cases and controls.

2.4 Statistical Analysis

When data from more than 3 similar studies were available, a meta-analysis was performed. The strength of the associations between the *TNFA* polymorphisms and asthma risk was measured by ORs and 95% CIs. The statistical significance of the summary OR was determined with the Z test. OR1, OR2, and OR3 were calculated for the following genotypes: *1*) AA vs GG (OR1), AG vs GG (OR2), and AA vs AG (OR3) for the -308A/G and -238A/G polymorphisms, and *2*) CC vs TT (OR1), CT vs TT (OR2), and CC vs CT (OR3) for the -857C/T polymorphism. These pairwise differences were used to indicate the most appropriate genetic model as follows: if OR1 = OR3 ≠ 1 and OR2 = 1, then a recessive model was suggested; if OR1 = OR2 ≠ 1 and OR3 = 1, then a dominant model was suggested; if OR2 = 1/OR3 ≠ 1 and OR1 = 1, then a complete overdominant model was suggested; and if OR1 > OR2 > 1 and OR1 > OR3 > 1 (or OR1 < OR2 < 1 and OR1 < OR3 < 1), then a codominant model was suggested [58]. Once identified, the best genetic model was used to collapse the 3 genotypes into 2 groups (except in the case of the codominant model) and to pool the results.

Departure from Hardy-Weinberg equilibrium (HWE) in controls was tested by the χ^2 test. Studies not in HWE were excluded from the quantitative meta-analysis. Heterogeneity was assessed by the I^2 statistic. We considered low, moderate, and high I^2 values to be 25%, 50%, and 75%, respectively. A χ^2 based Q-test was also performed to check between-study heterogeneity. When a *P* value of over .10 for the Q-test indicated a lack of heterogeneity between the studies, the pooled OR estimate for each study was calculated by the fixed-effects model. Otherwise, the random-effects model was used. To explore the source of the heterogeneity and evaluate ethnic-specific and atopic-specific effects, subgroup analyses were performed according to ethnicity and atopic status. To assess the stability of the meta-analysis, 1-way sensitivity analyses were carried out. A Begg's funnel plot and Egger's plot was used to quantitatively assess potential publication bias [59].

All statistical tests were performed using STATA 11.0 software. The Bonferroni correction of critical *P* values was applied when performing a high number of comparisons.

3. Results

3.1 Study Characteristics

The results of the study selection process are shown in Figure 2. The initial search produced 454 studies from PubMed, Embase, and Wanfang databases. After exclusion of duplicates, 357 potentially eligible studies were selected. After detailed evaluation, 54 studies were selected for inclusion in the meta-analysis [1-54]. Two articles reported 2 cohorts, and each cohort was considered a separate case-control study. There were 52 studies on the -308A/G polymorphism, 9 studies on the -238A/G polymorphism, 6 studies on the -857C/T polymorphism, 4 studies on the -1031T/C polymorphism, and 3 studies on the -863C/A polymorphism. There were 29 studies on Asians, 23 studies on whites, 1 study on Mexicans, and 3 studies on mixed populations. Nineteen studies were performed on adults and 26 on children. Four studies included both adults and children, and 7 studies did not provide this information. Six studies included atopic asthma patients only, 6 studies included both atopic and nonatopic asthma patients (but it was possible to separate these data), and 43 studies did not report detailed information. The characteristics of each study included in the meta-analysis are shown in Table 1. Genotype frequencies and HWE examination results are listed in Table 2.

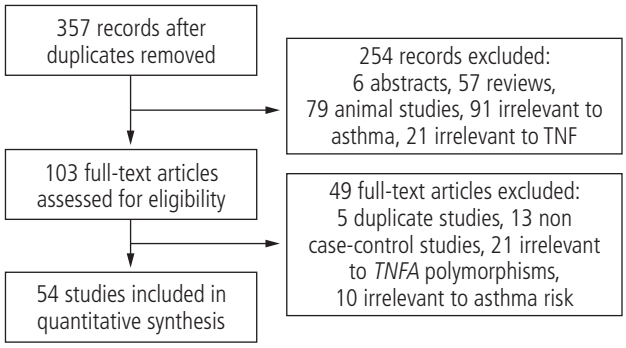

Figure 2. Flow of study identification, inclusion, and exclusion.

Table 1. Characteristics of the Case-Control Studies Included in the Meta-Analysis

First Author	Year	Country	Ethnicity	Age Group	Atopic Status	No. of Cases	No. of Controls	*TNFA* polymorphisms
Moffatt [1]	1997	Australia	White	NA	NA	88	312	-308A/G
Albuquerque [2]	1998	Australia	White	Children	NA	124	50	-308A/G
Chagani [3]	1999	Canada	White	NA	NA	251	43	-308A/G
Tan [4]	1999	Singapore	Asian	NA	NA	105	187	-308A/G
Louis [5]	2000	Belgium	White	Adults	Mixed	95	98	-308A/G
Winchester 1 [6]	2000	UK	White	Children	NA	6	275	-308A/G
Winchester 2 [6]	2000	UK	Asian	Children	NA	20	416	-308A/G
Hakonarson [7]	2001	Iceland	White	Mixed	Atopic	94	94	-308A/G
Buckova [8]	2002	Czech Republic	White	Adults	Atopic	151	155	-308A/G
Witte [9]	2002	USA	Mixed	Adults	NA	235	273	-308A/G
Bahlawan [10]	2003	USA	White	Children	NA	38	231	-308A/G, -238A/G
Gao J [11]	2003	China	Asian	Adults	Mixed	125	96	-308A/G
Li [12]	2003	China	Asian	Children	NA	30	26	-308A/G
Beghe [13]	2004	Italy	White	Adults	NA	142	45	-308A/G
Sandford [14]	2004	China	Asian	Children	NA	106	118	-308A/G
Shin [15]	2004	Korea	Asian	NA	Mixed	534	170	-308A/G, -238A/G -1031T/C, -863C/A -857C/T
Wang [16]	2004	China	Asian	Children	Mixed[a]	191	129	-308A/G
Guo [17]	2004	China	Asian	NA	NA	48	21	-308A/G
Liu [18]	2004	China	Asian	Children	NA	113	126	-308A/G
Zhai [19]	2004	China	Asian	Adults	Mixed	80	64	-308A/G
Bilolikar [20]	2005	UK	Mixed	Children	NA	100	100	-308A/G
Gupta [21]	2005	India	Asian	NA	NA	155	211	-308A/G
Zhao [22]	2005	China	Asian	NA	NA	50	80	-308A/G

Continuation

First Author	Year	Country	Ethnicity	Age Group	Atopic Status	No. of Cases	No. of Controls	*TNFA* polymorphisms
Aoki [23]	2006	Japan	Asian	Children	NA	461	465	-308A/G
Kim S [24]	2006	Korea	Asian	Adults	Mixed	360	257	-308A/G, -238A/G -1031T/C, -863C/A -857C/T
Schubert [25]	2006	Germany	White	Children	NA	231	270	-308A/G, -857C/T
Sharma [26]	2006	India	Asian	Adults	Atopic	488	476	-308A/G, -857C/T -1031T/C, -863C/A
Tolgyesi [27]	2006	Hungary	White	Children	Mixed	144	174	-308A/G
Hong [28]	2007	Korea	Asian	Children	Mixed[a]	635	153	-308A/G
Kamali-Sarvestani [29]	2007	Iran	White	Adults	NA	203	113	-308A/G
Mak [30]	2007	China	Asian	Adults	Mixed[a]	292	292	-308A/G
Kim [31]	2008	Korea	Asian	Children	Mixed[a]	715	240	-308A/G
Kumar [32]	2008	India	Asian	Mixed	Mixed[a]	123	100	-308A/G
Liu [33]	2008	China	Asian	Adults	NA	108	88	-238A/G
Trajkov [34]	2008	Macedonia	White	Adults	NA	74	311	-308A/G, -238A/G
Zedan [35]	2008	Egypt	White	Children	NA	69	98	-308A/G
Aytenkin [36]	2009	Turkey	White	Children	NA	46	67	-308A/G
Castro-Giner [37]	2009	Switzerland	White	Adults	NA	558	8588	-308A/G
Daley [38]	2009	Australia	White	Mixed	NA	643	751	-308A/G, -238A/G
Jimênez-Morales [39]	2009	Mexico	Mexican	Children	NA	226	400	-308A/G, -238A/G
Mahdaviani [40]	2009	Iran	White	Mixed	NA	60	140	-308A/G, -238A/G
Wang [41]	2009	China	Asian	Children	NA	449	512	-308A/G
Michel [42]	2010	Germany	White	Children	NA	703	658	-308A/G
Undarmaa 1 [43]	2010	Japan	Asian	Children	Atopic	325	336	-857C/T
Undarmaa 2 [43]	2010	Japan	Asian	Adults	Atopic	367	676	-857C/T
Cui [44]	2010	China	Asian	Adults	NA	100	104	-308A/G, -238A/G
Dhaouadi [45]	2011	Tunisia	White	Adults	NA	107	168	-308A/G
Jiffri [46]	2011	Egypt	White	Children	NA	120	120	-308A/G, -1031T/C
Murk [47]	2011	USA	Mixed	Children	Atopic	99	480	-308A/G
Gao [48]	2011	China	Asian	Children	NA	105	80	-308A/G
Daneshmandi [49]	2012	Iran	White	Adults	Mixed[a]	81	124	-308A/G
Jia [50]	2012	China	Asian	Children	NA	91	89	-308A/G
Zheng [52]	2012	China	Asian	Children	NA	198	110	-308A/G
Chiang [52]	2013	China	Asian	Adults	NA	217	110	-308A/G
Shaker [53]	2013	Egypt	White	Children	NA	100	100	-308A/G
Li [54]	2013	China	Asian	Adults	NA	65	50	-308A/G

Abbreviation: NA, not available.
[a]It was not possible to extract separate data.

Table 2. Distribution of *TNFA* Polymorphisms Among Patients and Controls

First Author	Asthma Patients			Controls			HWE
TNFA -308A/G	AA	AG	GG	AA	AG	GG	
Moffatt [1]	8	36	44	12	89	211	Yes
Albuquerque [2]	9	40	75	7	19	24	Yes
Chagani [3]	101[a]		150	9[a]		34	Yes
Tan [4]	0	22	83	0	37	150	Yes
Louis [5]	0	31	64	2	27	69	Yes
Winchester 1 [6]	2	9	9	17	116	283	Yes
Winchester 2 [6]	0	2	4	3	33	239	Yes
Hakonarson [7]	3	27	64	2	25	67	Yes
Buckova [8]	3	46	102	1	38	116	Yes
Witte [9]	4	67	164	6	55	212	Yes
Bahlawan [10]	2	5	31	4	45	182	Yes
Gao J [11]	26	52	47	11	41	44	Yes
Li [12]	5	16	9	2	10	14	Yes
Beghe [13]	1	33	108	1	8	36	Yes
Sandford [14]	0	26	80	0	16	102	Yes
Shin [15]	2	50	482	2	37	131	Yes
Wang [16]	2	49	140	0	18	111	Yes
Guo [17]	4	28	16	3	11	7	Yes
Liu [18]	0	15	98	0	22	104	Yes
Zhai [19]	6	14	44	1	12	67	Yes
Bilolikar [20]	7	47	46	6	31	63	Yes
Gupta [21]	3	36	116	1	32	178	Yes
Zhao [22]	0	5	45	0	9	71	Yes
Aoki [23]	1	19	441	1	10	454	No
Kim [24]	1	43	316	0	40	217	Yes
Schubert [25]	6	65	160	6	67	197	Yes
Sharma [26]	2	111	375	4	65	321	Yes
Tolgyesi [27]	4	41	99	5	47	122	Yes
Hong [28]	5	82	548	0	14	139	Yes
Kamali-Sarvestani [29]	0	28	175	1	9	103	Yes
Mak [30]	1	47	244	2	40	250	Yes
Kim [31]	6	95	614	0	21	219	Yes
Kumar [32]	2	35	86	0	18	82	Yes
Trajkov [34]	1	9	64	0	30	251	Yes
Zedan [35]	14	47	8	11	81	6	No
Aytenkin [36]	0	11	35	0	16	51	Yes
Castro-Giner [37]	19	163	347	213	1991	6055	Yes
Daley [38]	25	203	416	23	216	512	Yes
Jimenez-Morales [39]	1	25	200	0	23	377	Yes
Mahdaviani [40]	0	17	10	0	39	98	Yes
Wang [41]	3	100	345	7	94	409	Yes
Michel [42]	23	207	473	13	158	487	Yes

Continuation

First Author	Asthma Patients			Controls			HWE
TNFA -308A/G	AA	AG	GG	AA	AG	GG	
Cui [44]	2	6	92	2	13	89	Yes
Dhaouadi [45]	6	31	70	4	42	122	Yes
Jiffri [46]	0	33	87	0	15	105	Yes
Murk [47]	2	20	78	15	113	359	Yes
Gao [48]	8	26	71	2	8	70	No
Daneshmandi [49]	1	10	70	2	5	117	No
Jia [50]	1	14	76	0	7	82	Yes
Zheng [51]	5	25	168	0	17	93	Yes
Chiang [52]	10	44	163	16	26	68	No
Shaker [53]	8	60	32	4	30	66	Yes
Li [54]	4	16	45	1	6	43	Yes
TNFA -238A/G	AA	AG	GG	AA	AG	GG	
Bahlawan [10]	1	4	33	0	19	212	Yes
Shin [15]	0	38	496	0	14	156	Yes
Kim [24]	2	36	314	1	22	231	Yes
Liu [33]	0	65	43	0	88	0	No
Trajkov [34]	0	27	47	2	23	276	Yes
Daley [38]	2	66	576	3	83	662	Yes
Jimênez-Morales [39]	1	21	204	1	31	368	Yes
Mahdaviani [40]	3	13	11	1	57	79	No
Cui [44]	0	9	91	1	8	95	Yes
TNFA -857C/T	CC	CT	TT	CC	CT	TT	
Shin [15]	377	131	10	118	42	5	Yes
Kim [24]	159	71	11	166	69	8	Yes
Schubert [25]	183	45	3	196	70	6	Yes
Sharma [26]	208	231	49	172	235	69	Yes
Undarmaa 1 [43]	224	92	9	227	99	10	Yes
Undarmaa 2 [43]	266	93	8	422	224	30	Yes
TNFA -1031T/C	CC	CT	TT	CC	CT	TT	
Shin [15]	17	126	258	3	36	119	Yes
Kim [24]	23	129	189	11	85	161	Yes
Sharma [26]	49	231	208	69	235	172	Yes
Jiffri [46]	8	24	88	6	60	54	No
TNFA -863C/A	AA	AC	CC	AA	AC	CC	
Shin [15]	16	160	356	3	35	130	Yes
Kim [24]	17	110	230	8	64	182	Yes
Sharma [26]	34	218	236	60	243	173	Yes

Abbreviation: HWE, Hardy-Weinberg equilibrium.
[a]Combined genotype numbers of AA and AG.

3.2 Quantitative Data Synthesis

3.2.1 TNFA *-308A/G Polymorphism*

Fifty-two studies determined the association between the -308A/G polymorphism and asthma risk. Five studies were not in HWE and were therefore excluded from the final quantitative meta-analysis. Thus, the sample sizes for the case and control groups were 9634 and 17 616, respectively. The estimated OR1, OR2, and OR3 were 1.56 (*P*<.001), 1.35 (*P*<.001), and 1.16, respectively (*P*=.16) (Table 3). These estimates suggested a dominant genetic model; therefore AA and AG were combined and compared with GG. The pooled OR was 1.39 (95% CI, 1.23-1.58; *P*<.001) (Figure 3). There was high heterogeneity (I^2=60%, *P*<.001). In the stratified analysis by ethnicity, a statistically significant association was found for studies in whites (OR, 1.47; 95% CI, 1.25-1.73; *P*<.001). However, no significant association was observed in Asians after Bonferroni correction (OR, 1.30; 95% CI, 1.05-1.62; *P*=.02) (Table 3). In the subgroup analysis by atopic status, the *TNFA* -308A/G polymorphism was significantly associated with risk of atopic asthma (OR, 1.38; 95% CI, 1.16-1.65; *P*<.001) but not with nonatopic asthma risk (OR, 1.28; 95% CI, 0.97-1.68; *P*=.08). Of note, heterogeneity was significantly decreased in the atopic asthma subgroup and nonatopic asthma subgroups (I^2=0%, *P*=.48 and I^2=21%, *P*=.28, respectively). In the subgroup analysis according to age, the *TNFA* -308A/G polymorphism was significantly associated with both pediatric asthma risk (OR, 1.48; 95% CI, 1.23-1.79; *P*<.001) and adult asthma risk (OR, 1.35; 95% CI, 1.21-1.52; *P*<.001).

We conducted 1-way sensitivity analysis to evaluate the stability of the meta-analysis. The statistical significance of the results was not altered when any single study was omitted (data not shown). The funnel plot was symmetrical (Figure 4), and Egger's test did not indicate any significant publication bias (*P*=.302).

3.2.2 TNFA *-238A/G Polymorphism*

Nine case-control studies identified an association between the *TNFA* -238A/G polymorphism and asthma risk. Two studies were not in HWE. Therefore, a total of 1968 cases and 2208 controls were included in this meta-analysis. The estimated OR1, OR2, and OR3 were 1.30 (*P*=.60), 1.43 (*P*=.20), and 0.91 (*P*=.84), respectively (Table 3). These estimates suggested that the *TNFA* -238A/G polymorphism was not significantly associated with asthma risk.

3.2.3 TNFA *-857C/T Polymorphism*

The association between the *TNFA* -857C/T polymorphism and asthma risk was investigated in 6 case-control studies with a total of 2170 cases and 2168 controls. The estimated OR1, OR2, and OR3 were 1.56 (*P*=.003), 1.29 (*P*=.09), and 1.22 (*P*=.005), respectively (Table 3). These estimates suggested a recessive genetic model, and therefore TT and CT were combined and compared with CC. The pooled OR was 1.25 (95% CI, 1.10-1.43) and the Z test for overall effect was 3.33 (*P*<.001) (Figure 5). There was moderate heterogeneity (I^2=38%, *P*=.15). In the subgroup analysis by ethnicity, a significant association was found among Asians

Table 3. Determination of the Genetic Effects of TNFA Polymorphisms on Asthma and Subgroup Analysis

Polymorphisms	Study	Sample Size Cases	Controls	No. of studies	Test of Association OR (95% CI)	Z	*P* Value[a]	Model	Heterogeneity χ^2	*P* Value	I^2 (%)
TNFA -308A/G											
AA vs GG	Overall	7240	13711	40	1.56 (1.27-1.91)	4.26	<.001	F	42.27	.33	8.0
AG vs GG	Overall	9169	17192	46	1.35 (1.19-1.53)	4.79	<.001	R	104.72	<.001	56.0
AA vs AG	Overall	2357	4243	40	1.16 (0.94-1.43)	1.40	.16	F	26.91	.93	0.0
AA+AG vs GG	Overall	9634	17616	48	1.39 (1.23-1.58)	5.24	<.001	R	116.43	<.001	60.0
AA+AG vs GG	Asian	5042	3814	23	1.30 (1.05-1.62)	2.40	.02	R	62.29	<.001	65.0
AA+AG vs GG	Caucasian	3931	12542	21	1.47 (1.25-1.73)	4.69	<.001	R	42.95	.002	53.0
AA+AG vs GG	Atopic	2325	1769	9	1.38 (1.16-1.65)	3.65	<.001	F	7.58	.48	0.0
AA+AG vs GG	Non-atopic	427	737	5	1.32 (0.92-1.89)	1.50	.13	F	5.07	.28	21.0
AA+AG vs GG	Children	4485	4849	22	1.48 (1.23-1.79)	4.04	<.001	R	49.59	. <.001	58.0
AA+AG vs GG	Adults	3030	10661	15	1.35 (1.21-1.52)	5.17	<.001	F	16.16	.30	13.0
TNFA -238A/G											
AA vs GG	Overall	1767	2008	6	1.30 (0.49-3.44)	0.52	.60	F	3.72	.59	0.0
AG vs GG	Overall	1962	2200	7	1.43 (0.83-2.47)	1.29	.20	R	32.30	<.001	81.0
AA vs AG	Overall	207	208	6	0.91 (0.34-2.38)	0.20	.84	F	4.14	.53	0.0
TNFA -857C/T											
CC vs TT	Overall	1507	1429	6	1.56 (1.16-2.11)	2.94	.003	F	4.70	.45	0.0
CT vs TT	Overall	753	867	6	1.29 (0.96-1.75)	1.68	.09	F	1.85	.87	0.0
CC vs CT	Overall	2080	2040	6	1.22 (1.06-1.40)	2.79	.005	F	6.04	.30	17.0
CC vs CT+TT	Overall	2170	2168	6	1.25 (1.10-1.43)	3.33	<.001	F	8.05	.15	38.0
CC vs CT+TT	Asian	1939	1896	5	1.23 (1.07-1.41)	2.88	.004	F	7.35	.12	46.0
CC vs CT+TT	Atopic	1180	1488	3	1.33 (1.13-1.57)	3.45	<.001	F	3.32	.19	40.0

Abbreviations: F, fixed-effects model; R, random-effects model.
[a]Bonferroni correction was applied (*P*<.005).

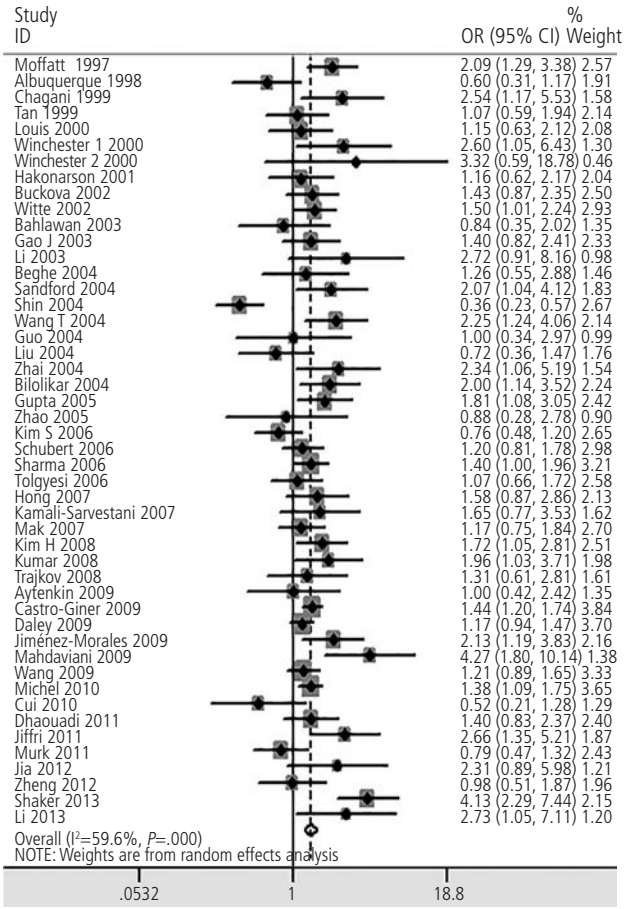

Figure 3. Forest plot of asthma risk associated with *TNFA* -308A/G polymorphism (AA+AG vs GG) by the random effects model. For each study, the estimates of ORs and 95% CIs were plotted with a box and a horizontal line. The filled diamond symbol indicates the pooled OR and corresponding 95% CI.

(OR, 1.23; 95% CI, 1.07-1.41; *P*=.004). In the subgroup analysis by atopic status, a significant association was found among atopic asthma patients (OR, 1.33; 95% CI, 1.13-1.57; *P*<.001). A summary of the results of the comparisons is shown in Table 3.

In order to assess the stability of the results of the meta-analysis, we performed a sensitivity analysis through sequentially excluded individual studies. Statistically similar results were obtained after sequentially excluding each study (data not shown). The shape of the funnel plot was symmetric (Figure 6), indicating an absence of publication bias. Furthermore, no significant publication bias was detected by Egger's test (*P*=.325).

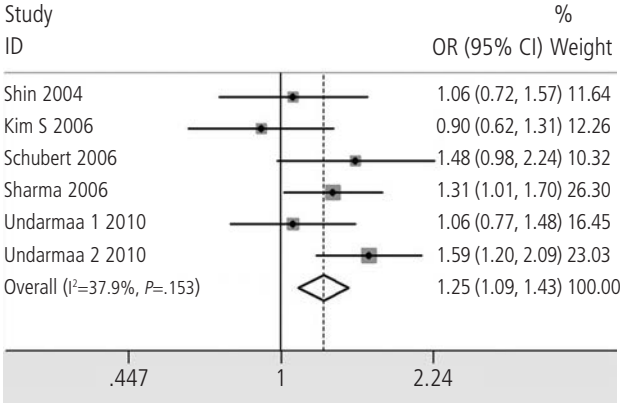

Figure 5. Forest plot of asthma risk associated with the *TNFA* -857C/T polymorphism (CC vs CT+TT) by the random effects model. For each study, the estimates of ORs and 95% CIs were plotted with a box and a horizontal line. The filled diamond symbol indicates the pooled OR and 95% CI.

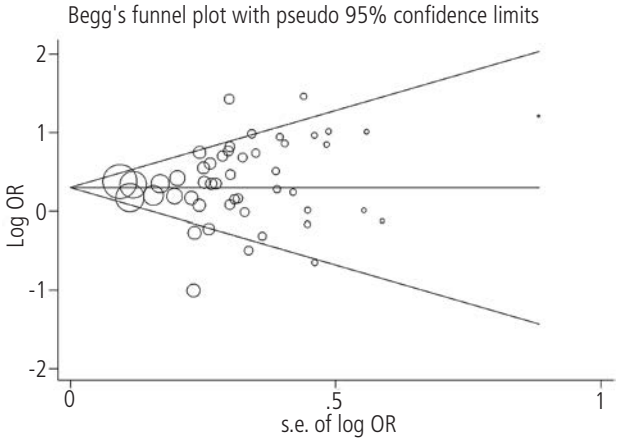

Figure 4. Funnel plot for studies of the association between asthma and the *TNFA* -308A/G polymorphism (AA+AG vs GG). The horizontal and vertical axes correspond to the OR and 95% CI.

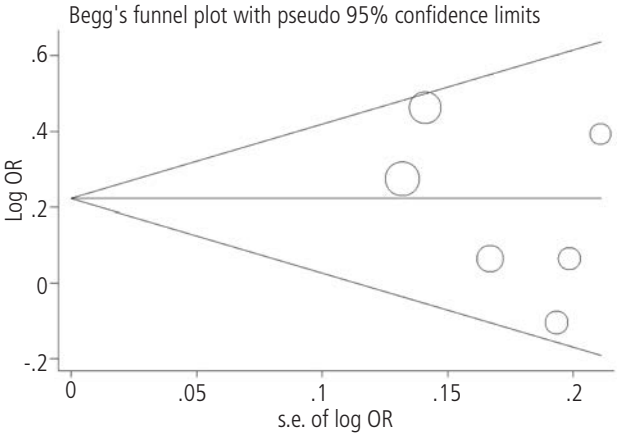

Figure 6. Funnel plot for studies of the association between asthma and the *TNFA* -857C/T polymorphism (CC vs CT+TT). The horizontal and vertical axis correspond to the OR and 95% CI.

4. Discussion

This meta-analysis of 54 case-control studies systematically evaluated the associations between *TNFA* polymorphisms and asthma risk. We found that the -308A/G polymorphism was a modest risk factor for the development of asthma in the overall study population. This result suggests that individuals with AA or AG genotypes have increased asthma risk compared with GG homozygotes. In the subgroup analysis, we found that AA or AG genotype carriers had an increased asthma risk in the case of whites but not Asians, suggesting that interactions between different ethnicities and genetic variants may contribute to asthma risk. However, a recent meta-analysis by Zhang et al [57] found that the -308A/G polymorphism was associated with asthma risk in Asians, but not whites. There are several potential explanations for the different results. First, Zhang et al included 29 case-control studies comprising 4717 cases and 5012 controls in their meta-analysis, compared with 48 case-control studies involving 9634 cases and 17 616 controls in ours. Differences in statistical power might therefore be one explanation for the discrepancy in results. Second, the average allele frequency of -308A is 6% in Asians but 14% in whites (data from http://asia.ensembl.org/). This might also explain the different incidence of asthma in AA or AG genotype carriers between Asians and whites. Third, Zhang et al did not correct their *P* values, ie, if they had applied the Bonferroni correction, their results would have lost their statistical significance. In the subgroup analysis by atopic status, we observed a significant association between the *TNFA* -308A/G polymorphism and atopic asthma. This result was consistent with the meta-analysis by Zhang et al. We also carried out a subgroup analysis according to age and found that the *TNFA* -308A/G polymorphism was associated with increased pediatric asthma risk and adult asthma risk, suggesting that -308A/G has the same effect on the pathogenesis and occurrence of asthma in different age groups. We also found the *TNFA* -857C/T polymorphism to be significantly associated with asthma risk. Subgroup analyses were performed according to ethnicity and atopic status. Significantly increased asthma risk was found in Asians and atopic individuals who carried the CC genotype. As for the -238A/G polymorphism, no evidence supported the association between this polymorphism and risk of asthma. Since only 7 case-control studies were included in this meta-analysis, a positive association between -238A/G and asthma cannot be ruled out because studies with small sample sizes may have insufficient statistical power to detect a slight effect. Four studies investigated the association between the *TNFA* -1031T/C polymorphism and asthma risk. However, as 1 of these [46] was not in HWE, a quantitative meta-analysis was not performed. Similarly, a quantitative meta-analysis was not conducted for -863C/A, as only 3 studies estimated the association between this polymorphism and asthma. More studies are needed to determine the associations between these 2 polymorphisms and asthma risk.

TNF-α is one of the most widely studied pleiotropic cytokines and it is an important cytokine in the innate immune response. Several lines of evidence support a role for TNF-α in asthma and airway hyperresponsiveness. TNF-α may have an essential role in the pathogenesis of asthma and *TNFA* may be a candidate gene for asthma. A previous study indicated that the presence of a G-to-A polymorphism at position -308 in the promoter region of the *TNFA* gene could increase transcription 6- to 7-fold [60]. Thus, it is biologically plausible that the A allele of the -308A/G polymorphism could increase susceptibility to asthma. Our findings support this speculation. Puthothu et al [61] reported a serum concentration of 526.32 pg/mL for TNF-α from asthmatic children with CC homozygous for -857C/T compared with a concentration of 135.9 pg/mL in heterozygous children. Our meta-analysis showed that the -857CC genotype was significantly associated with asthma risk. It is possible that this genotype produces more TNF-α than other genotypes, but the exact mechanism remains unclear. Functional studies of the -857CC polymorphism in asthma are needed. As for the -238A/G polymorphism, Cui and colleagues [62] found no association with serum TNF-α levels in 376 unrelated individuals. However, other researchers have suggested that peripheral blood mononuclear cells carrying the -238A allele produced significantly less TNF-α after stimulation with T-cell mitogens and streptococcal antigens in comparison with controls [63]. They also found that -238A showed significantly decreased transcriptional activity. Therefore, the relationship between the -238A/G polymorphism and TNF-α production is still unclear, and whether or not this polymorphism influences asthma risk remains to be elucidated.

Asthma is a highly heterogeneous disease and conventional treatments are not effective in all patients. Genetic factors are thought to be important determinants of drug efficacy. Pharmacogenetics focuses on the prediction of response to standard therapy by genetic profiling and thereby allows selection of the most appropriate medication at optimal doses for individual patients. However, only a few genes have been identified for the various asthma drug response phenotypes. Therefore, more studies should be designed to predict individual response to anti-asthma therapies.

We should acknowledge the importance of publication bias and heterogeneity, which may influence the results of a meta-analysis. Significant heterogeneity was detected in studies of the -308A/G polymorphism and asthma risk in our meta-analysis. We used subgroup analysis to find the main source of heterogeneity. After subgroup analysis by atopic status, heterogeneity decreased significantly in the atopic subgroup and nonatopic subgroup, suggesting that the high heterogeneity might be a result of atopic status. No evidence of publication bias was shown by Begg's funnel plot or Egger's test.

There are some limitations that should be considered when interpreting our results. First, only studies that were indexed in the selected databases were included in our data analysis, and we therefore may have missed some relevant published studies or unpublished studies with null results. Second, our results were based on unadjusted estimates, whereas a more precise analysis could be performed if individual data were available to allow adjustment. Third, a lack of original data in eligible studies limited the evaluation of the effects of the haplotype of *TNFA*, gene-gene interactions, and gene-environment interactions in asthma. Fourth, most of the case-control studies were conducted in Asians and whites and thus our results may only be applicable to these ethnic groups.

To our knowledge, this is the most comprehensive meta-analysis to data to assess the relationship between *TNFA* polymorphisms and asthma susceptibility. We found that the *TNFA* -308A/G and -857C/T polymorphisms were moderately associated with an increased risk of asthma.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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