

Association between the interleukin-4, interleukin-13 polymorphisms and asthma: a meta-analysis

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Abstract A numbers studies had been reported that the polymorphisms in the Interleukin 4 (*IL-4*) and Interleukin 13 (*IL-13*) genes were associated with susceptibility to asthma. However, the results were inconsistent and inconclusive. We carried out a meta-analysis of case-control genetic association studies to assess whether the combined data showed this association by using a genetic model-free approach. Thirty studies (total 12,781 asthma and 11,500 controls) for the *IL-4* C-33T and C-589T, *IL-13* C-1112T and G+2044A with asthma were included in the meta-analysis. The results indicated that there were an association between the *IL-4* C-33T ($P = 0.006$) and C-589T ($P = 0.04$), *IL-13* C-1112T ($P = 0.002$) and G+2044A ($P = 0.04$) and susceptibility to asthma. And the definition of asthma subgroup meta-analysis demonstrates that the

IL-4 C-33T is not associated with nonatopic or atopic, and *IL-4* C-589T and *IL-13* C-1112T polymorphisms are not associated with atopic. In the ethnicity subgroup meta-analysis, the *IL-4* -589T ($P = 0.003$) and the *IL-13* -1112T ($P < 0.00001$) alleles are associated with asthma among Caucasian, but not on the *IL-13* +2044A allele. In conclusion, *IL-4* C-33T and C-589T, *IL-13* C-1112T and G+2044A could be proposed as asthma susceptible SNPs. Further investigation in larger studies and meta-analysis is required.

Keywords *IL-4* · *IL-13* · Polymorphism · Asthma · Association

Zhen-dong Wang, Duan Lian and Jing-ling Shen contributed equally to this study.

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Introduction

Asthma is one of the most common chronic inflammatory respiratory diseases of variable airway obstruction, and is characterized by bronchial hyper-responsiveness (BHR) with recurring episodes of wheezing, coughing, chest tightness, and shortness of breath [20]. Since the 1970s [49], the prevalence of asthma has increased significantly, and 300 million people are affected all over the world. Asthma also is clinically classified as atopic and non-atopic. According to the etiology, asthma is thought to be a polygenic disease caused by complex interactions between genetic and environmental factors [34].

Interleukin 4 (IL-4) and *Interleukin 13 (IL-13)* are the important proinflammatory cytokine genes in immune regulation produced by activated T helper cells, and promote immunoglobulin E isotype switching in B cells, growth and differentiation of B cells and monocytes [55]. They share a receptor component and signaling pathways, and locate at close proximity on chromosome 5q31 where asthma and

atopy have also been linked [42]. Numerous previously published studies of genetic epidemiology have assessed the association between genetic variants of the *IL-4* (in the promoter region, C-33T, rs number 2070874; C-589T that also referred to as C-590T, rs number 2243250) and *IL-13* (C-1112T in the promoter region, rs1800925, also referred to as C-1111T, C-1055T or C-1024T; G+2044A in exon 4, rs20451, also referred to as Arg130Gln, Arg110Gln, R130Q or R110Q) with asthma in different populations. However, the results are inconsistent and inconclusive.

In the present study, based on a comprehensive search of the literature, we have carried out a meta-analysis to assess whether the combined evidence demonstrates an association between the *IL-4* and *IL-13* polymorphisms and asthma susceptibility, and the reasons of the disagreements are resolved by discussion.

Materials and methods

Search strategy

We considered all of the studies that examined the association of *IL-4* and/or *IL-13* with COPD by using 'PubMed' search engine, Chinese National Knowledge Infrastructure (CNKI) database, Wanfang database, CQVIP database and Google scholar. We used the following terms: 'interleukin-4', '-33 (rs2070874)', '-589 (-590 or rs2243250)', 'interleukin-13', '-1112 (-1111, -1055, -1024 or rs1800925)', '+2044 (rs20541, Arg130Gln, Arg110Gln, R130Q, R110Q)', 'asthma', 'polymorphism' and 'association'. Only English and Chinese language papers were considered. No restrictions were placed on race, ethnicity or geographic area.

Inclusion and exclusion criteria

A study was included in this meta-analysis if it satisfied the following inclusion criteria: (i) the date of publication was before February 2012; (ii) the data were original (independent studies); (iii) studies were case-control design and all the controls were healthy individuals, participants could be of any age and (iv) enough information was provided to calculate the odds ratio (OR).

Data extraction

If a study satisfied the following excluded criteria, it would be excluded: (i) studies in which the number of wild-type genotypes could not be ascertained; (ii) studies that contained overlapping data; (iii) the distribution of genotypes in the control group was not in Hardy-Weinberg equilibrium (HWE) and (iv) the studies which family members had been included. The following information was

extracted from each of the included studies: first author, year of publication, demographics, racial of the study population, and the specific genotype data for case and control groups. Extraction from each study was conducted independently, and consensus was achieved for all data.

Statistical analyses

Using the allele-counting method, we calculated the allele frequencies at the polymorphisms of the *IL-4* and *IL-13* genes from each respective study. We calculated the deviation from HWE for the control groups by Pearson's χ^2 test <http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl>.

We assumed that the '*N*' represented the risk or variant allele and the '*n*' represented the common allele for each SNP of the *IL-4* or *IL-13* gene. All asthma groups were combined for the meta-analysis. Then we examined the contrast of the effect of the *N*- versus *n*-allele. And we also performed for the association with asthma by analyses the dominant (genotypes NN + Nn vs. nn) and recessive (genotype NN vs. Nn + nn) genetic models. To assess the heterogeneity of studies, we analyzed the genotype-specific OR such as genotype NN versus nn (OR₁), Nn versus nn (OR₂), and NN versus Nn (OR₃). And the OR and its 95 % confidence interval (CI) were calculated for each study. In this study, we tested Cochran's *Q*-statistics to assess the within- and between-study heterogeneity [23]. This heterogeneity test assessed the null hypothesis that all studies were evaluating the same effect. If the meta-analysis accepted the null hypothesis, it used to adopt a fixed-effects model since the fixed-effects model assumes that the estimates effect sizes only differ by the sampling error. In contrast, a significant *Q*-statistics ($P < 0.01$), we used a random-effects model to combine the data, with inverse-variance weighting. The random-effects model assumes that different studies may assess different underlying effects and considers both within- and between-study variation [44].

We also used an I^2 index to quantify the effect of heterogeneity: $I^2 = 100 \% \times (Q - df)/Q$ [58]. I^2 measured the degree of inconsistency across studies by calculating the percentage of total between-study variation, because of heterogeneity rather than random variation. We considered low, moderate and large heterogeneity to I^2 values of 25, 50 and 75 % (I^2 range between 0 and 100 %). Assessing the heterogeneity by the *Q*-statistics of OR₁, OR₂, and OR₃, we selected the most appropriate genetic model for the meta-analysis. Subgroup was analyzed based on ethnicity and asthma definition: asthma (atopy status undefined), atopic asthma, and nonatopic asthma.

Publication bias was assessed using the funnel plot. Statistical manipulations were performed using the program Review Manager 5.1.5 (Oxford, UK). We considered the power of each study as the probability of detecting an

Table 1 Characteristics of studies included in meta-analysis

First author [reference]	Years	Country (Ethnicity)	SNP	Age (years)	Male (%)	Characteristics of cases	No. case/ control	Case		Control		G*power	P-HWE controls		
								NN	Nn	NN	Nn				
Amirzargar [2]	2009	Iranian (Asian)	IL-4 C-33T			Asthma	59/139	2	56	1	61	78	0	15.57	<0.0001
			IL-4 C-589T			Asthma		0	59	0	10	129	0	29.06	
Adjers [1]	2005	Finish (Caucasian)	IL-4 C-589T	59 ± 11	38	Asthma	245/405	100	110	35	190	166	49	72.23	0.1764
Berce [7]	2010	Slovenian (Caucasian)	IL-4 C-33T			Nonatopic	28/89	17	8	3	51	35	3	10.79	0.3032
Berce [7]	2010	Slovenian (Caucasian)	IL-4 C-33T			Asthma	106/89	67	31	8	51	35	3	15.39	
Berce [7]	2010	Slovenian (Caucasian)	IL-4 C-33T			Atopic	78/89	50	23	5	51	35	3	13.68	
Beghé [6]	2003	England (Caucasian)	IL-4 C-33T	13	56.9	Asthma	331/182	223	102	6	132	48	2	37.19	0.2994
			IL-4 C-589T			Asthma	331/183	220	105	6	136	45	2	62.07	0.4145
Beghé [6]	2003	England (Caucasian)	IL-4 C-33T	9.9	53.6	Asthma	310/182	217	88	5	132	48	2	35.70	0.2994
			IL-4 C-589T			Asthma	309/183	216	87	6	136	45	2	60.19	0.4145
Bottema [8]	2010	Dutch (Caucasian)	IL-13 +G2044A	31.8 ± 8.3	65.8	Asthma	114/89	57	51	6	62	24	3	15.65	0.7211
			IL-13 C-1112T			Asthma	115/92	67	43	5	65	23	4	16.02	0.3014
Chan [9]	2008	Hongkong (Asian)	IL-13 +G2044A			Asthma	273/141	94	136	43	54	70	17	12.15	0.4308
Chiang [10]	2007	Chinese (Asian)	IL-4 C-589T	46 ± 20	51.5	Asthma	167/111	1	19	147	7	34	70	38.50	0.3105
Cui [11]	2003	Chinese (Asian)	IL-4 C-589T			Allergic	241/175	11	89	141	9	52	114	53.18	0.3447
Cui T-b [12]	2003	Chinese (Asian)	IL-4 C-589T			Allergic	98/103	5	37	56	4	32	67	29.42	0.9415
de Guia [14]	2010	Filipino (Asian)	IL-4 C-589T	25.99 ± 8.94	48	Atopic allergy	102/102	52	39	11	73	23	6	29.78	0.0368
Donfack [15]	2005	American (Caucasian)	IL-4 C-589T			Asthma	126/205	84	35	7	144	55	6	44.42	0.7883
Donfack [15]			IL-13 +G2044A			Asthma	126/205	78	41	7	127	73	5	29.90	0.1412
			IL-13 C-1112T			Asthma	127/205	73	42	12	126	71	8		0.6071
			IL-4 C-589T			Asthma	203/183	24	81	98	24	82	77	50.19	0.7683
			IL-13 +G2044A			Asthma	206/183	132	68	6	126	53	4	27.23	0.5642
			IL-13 C-1112T			Asthma	205/183	69	100	36	66	85	32		0.6089
Gervaziev [17]	2006	Russian (Caucasian)	IL-4 C-33T	39.84 ± 13.78	47.7		109/68	15	26	68	43	20	5	14.28	0.2329
			IL-4 C-589T			Bronchial	109/68	16	75	18	18	43	7	26.50	0.0138
Hosseini-Farahabadi [21]	2007	Iranian (Asian)	IL-4 C-589T	34 ± 11	43.3	Allergic	30/50	17	8	5	38	12	0	14.55	0.3349
Hijazi [19]	2000	Kuwaiti Arab (Asian)	IL-4 C-589T			Asthma	84/47	5	25	54	3	17	27	20.84	0.8832
Hijazi [19]	2000	Kuwaiti Arab (Asian)	IL-4 C-589T			Asthma	84/53	5	25	54	6	14	33	21.58	0.0370
Howard [22]	2001	Dutch (Caucasian)	IL-13 +G2044A	52.1 ± 8.3	62	Asthma	152/120	89	52	11	67	44	9	19.48	0.6366
			IL-13 C-1112T			Asthma	171/119	99	63	9	87	30	2	19.35	0.7483
Howard [22]	2001	Dutch (Caucasian)	IL-13 +G2044A			BHR	186/120	111	60	15	67	44	9	19.48	0.6366
			IL-13 C-1112T			BHR	216/119	126	77	13	87	30	2	19.35	0.7483

Table 1 continued

First author [reference]	Years	Country (Ethnicity)	SNP	Age (years)	Male (%)	Characteristics of cases	No. case/control	Case				Control				G*power	P-HWE controls
								NN	Nn	nn	nn	NN	Nn	nn	nn		
Howard [22]	2001	Dutch (Caucasian)	<i>IL-13</i> +G2044A <i>IL-13</i> C-1112T			Skin test	162/145	89	62	11	89	43	13	22.57	0.0282		
						Skin test	189/147	111	67	11	102	41	4	22.81	0.9605		
Isidoro-Garcia [24]	2005	Caucasian	<i>IL-4</i> C-33T	32 ± 17	42.1	Asthma	133/79	93	39	1	64	15	0	16.45	0.3512		
Kim [28]	2008	Korean (Asian)	<i>IL-13</i> +G2044A <i>IL-13</i> C-1112T	9.13 ± 2.65	65.8	Asthma	709/227	301	318	90	99	100	28	32.54	0.7244		
						Asthma	716/241	455	236	25	155	80	6	34.20	0.2462		
Kim [28]	2008	Korean (Asian)	<i>IL-13</i> +G2044A <i>IL-13</i> C-1112T	9.30 ± 2.64	67.1	Atopic	579/227	248	257	74	99	100	28	32.54	0.7244		
						Atopic	587/241	376	189	22	155	80	6	34.20	0.2462		
Lee [29]	2004	Korean (Asian)	<i>IL-4</i> C-589T		62.5	Asthma	254/100	9	77	168	3	29	68	46.88	0.9655		
Lee [29]	2004	Korean (Asian)	<i>IL-4</i> C-589T	10.9 ± 2.60	63.3	Nonatopic	60/100	4	19	37	3	29	68	24.41			
Lee [29]	2004	Korean (Asian)	<i>IL-4</i> C-589T	11.5 ± 2.60	62.2	Atopic	194/100	5	58	131	3	29	68	40.32			
Liu Lina [31]	2005	Chinese (Asian)	<i>IL-4</i> C-589T			Asthma	76/60	2	29	45	3	23	34	21.45	0.7225		
Mak [33]	2007	Hong kong (Asian)	<i>IL-4</i> C-589T	42.4 ± 16.1	43.8	Asthma	289/292	15	95	179	19	87	186	67.38	0.0505		
Moissidis [37]	2005	American (African)	<i>IL-13</i> C-1112T			Asthma	61/157	13	36	12	62	75	20	24.05	0.7158		
Sandford [40]	2000	White (Caucasian)	<i>IL-4</i> C-589T			Asthma	89/143	64	23	2	100	41	3	33.14	0.3313		
Takabayashi [43]	2000	Japanese (Asian)	<i>IL-4</i> C-589T	2.9 ± 2.6	58	Atopic	100/100	6	43	51	10	39	51	29.30	0.5327		
Van der [46]	1999	Netherlands (Caucasian)	<i>IL-13</i> C-1112T			Allergic	101/107	57	31	13	77	28	2	17.87	0.7654		
Wang [47]	2004	Chinese (Asian)	<i>IL-4</i> C-589T			Asthma	93/62	29	42	22	21	26	15	23.80	0.2272		
Wei Ming [36]	2007	Chinese (Asian)	<i>IL-13</i> +G2044A	43	55.6	Asthma	32/20	18	8	6	15	3	2	7.32	0.0316		
Wu [51]	2010	Chinese (Asian)	<i>IL-4</i> C-589T	8.8		Asthma	252/227	6	83	163	11	84	132	59.04	0.6102		
			<i>IL-13</i> +G2044A			Asthma	105	111	36	125	84	18	32.54	0.4649			
Wang [48]	2009	Taiwanese (Asian)	<i>IL-4</i> C-589T	7.82 ± 3.81	67.03	Asthma	446/508	22	145	279	16	183	309	87.05	0.0727		
			<i>IL-13</i> +G2044A			Asthma	446/505	203	194	49	212	234	59	61.31	0.6467		
			<i>IL-13</i> C-1112T			Asthma	446/511	321	113	12	357	136	18	61.81	0.2651		
Xi [52]	2004	Chinese (Asian)	<i>IL-13</i> +G2044A		53.5	Asthma	43/31	10	25	8	16	13	2	8.62	0.7654		
Xi [52]	2004	Chinese (Asian)	<i>IL-13</i> +G2044A		53.3	Asthma	45/46	15	24	6	23	20	3	10.41	0.6241		
Xue-Xi Yang [55]	2011	Chinese (Asian)	<i>IL-4</i> C-33T	41.59 ± 15.94	50	Asthma	202/205	14	56	132	7	67	131	29.67	0.6591		
			<i>IL-13</i> +G2044A			Asthma	201/203	105	73	23	90	80	33	29.66	0.0397		
			<i>IL-13</i> C-1112T			Asthma	193/204	144	43	6	148	50	6	29.78	0.4837		
Xue-Xi Yang [55]	2011	Chinese (Asian)	<i>IL-4</i> C-33T			Atopic	42/205	4	16	22	7	67	131	18.70			
			<i>IL-13</i> +G2044A			Atopic	41/203	20	15	6	90	80	33	29.66	0.0397		
			<i>IL-13</i> C-1112T			Atopic	41/204	29	10	2	148	50	6	29.78	0.4837		
Xue-Xi Yang [55]	2011	Chinese (Asian)	<i>IL-4</i> C-33T			Nonatopic	47/205	4	14	29	7	67	131	35.49	0.6591		
Yang [54]	2010	Chinese (Asian)	<i>IL-13</i> +G2044A	8 ± 4	60.7	Asthma	178/158	71	60	47	73	66	19	24.17	0.4968		
Zhang Linyuan [32]	2010	Chinese (Asian)	<i>IL-4</i> C-589T	10.3 ± 1.5	56.7	Asthma	291/665	10	112	169	31	233	401	87.12	0.6998		
Zhang Linyuan [32]	2010	Chinese (Asian)	<i>IL-4</i> C-589T			Asthma	166/381	9	65	92	14	135	232	64.76	0.2955		

Table 1 continued

First author [reference]	Years	Country (Ethnicity)	SNP	Age (years)	Male (%)	Characteristics of cases	No. case/ control	Case		Control		G*power	P-HWE controls		
								NN	Nn	NN	Nn				
Zhang Linyuan [32]	2010	Chinese (Asian)	<i>IL-4</i> C-589T			Asthma	126/284	2	47	77	17	98	169	52.59	0.5804
Zhao Kaishu [27]	2005	Chinese (Asian)	<i>IL-13</i> +G2044A		60	Asthma	130/100	18	60	52	8	42	50	17.01	0.8421
Zhu Xiaohua [53]	2002	Chinese (Asian)	<i>IL-4</i> C-589T		66.7	Asthma	27/30	8	3	16	12	1	17	11.74	<0.0001
BHR bronchial hyperresponsiveness															

BHR bronchial hyperresponsiveness

association between the polymorphisms of *IL-4* and *IL-13* genes and asthma, and calculated it at the 0.05 level of significance, assuming a small effect size (0.1). Using the G*power to performed the power analysis (<http://www.psych.uni-duesseldorf.de/aap/projects/gpower>).

Results

Studies included in the meta-analysis

There were fifty studies on the association of the *IL-4* and/or *IL-13* polymorphisms with asthma by the electronic literature [1–19, 21, 22, 24–33, 35–41, 43, 45–48, 50–54, 57]. The mainly investigated genotypes were *IL-4* C-33T and C-589T, *IL-13* C-1112T and G+2044A, which were reported 10, 20, 8 and 12 in studies, respectively. According to above criteria, in the meta-analysis four studies were excluded because their control populations were found to be in accordance with HWE [2, 14, 36, 53]. Thirteen did not report detailed genotype frequencies [3–5, 13, 18, 25, 26, 30, 35, 38, 41, 50, 57], one had overlapping data [45] and two had family-based study designs [16, 39]. Finally, thirty studies remained for the meta-analysis, and total 12,781 asthma and 11,500 controls were included in the meta-analysis (Table 1).

Meta-analysis of available data

Table 2 showed the results of this meta-analysis for the association between the polymorphisms of *IL-4* and *IL-13* and susceptibility to asthma.

IL-4 C-33t

Table 2 showed the results of the meta-analysis for the association between the polymorphism of *IL-4* C-33T and asthma. This meta-analysis indicated that the *IL-4* –33T allele was significantly associated with asthma (T- vs. C-allele: OR = 1.23; 95 % CI = 1.06–1.42; $P = 0.006$), and heterogeneity was found among studies ($Q = 82.45$, $P < 0.00001$, $I^2 = 89$). By comparing the OR₁ (genotype TT vs. CC), OR₂ (genotype CT vs. CC), and OR₃ (genotype TT vs. CT), we chose the dominant model to analysis (genotypes TT + CT vs. CC: OR = 1.07, 95 % CI = 0.64–1.77, $P = 0.8$), it denominated that the carriers of the *IL-4* –33T allele had a 7.0 % increased risk of asthma compared with homozygotes (–33CC) (Fig. 1).

In the subgroup meta-analysis, the *IL-4* C-33T was not significantly associated with Caucasian (T-allele: OR = 1.57, 95 % CI = 0.86–2.87, $P = 0.14$; TT + CT genotypes: OR = 1.44, 95 % CI = 0.82–2.52, $P = 0.2$), nonatopic (T-allele: OR = 0.91, 95 % CI = 0.59–1.39, $P = 0.66$; TT + CT genotypes: OR = 0.67, 95 %

Table 2 Meta-analysis of the *IL-4* and *IL-13* polymorphisms in asthma

SNP	Comparison	Subgroup	OR (95 % CI)	Heterogeneity test			Meta-analysis statistics	
				<i>Q</i>	<i>P</i>	<i>I</i> ² (%)	<i>Z</i>	<i>P</i>
<i>IL-4</i> C-33T	T vs. C	All	1.23(1.06–1.42)	82.45	<0.00001	89	2.75	0.006
		Caucasian	1.57(0.86–2.87)	66.71	<0.00001	91	1.46	0.14
		Nonatopic	0.91(0.59–1.39)	0.52	0.47	0	0.44	0.66
		Atopic	0.75(0.51–1.08)	0.98	0.32	0	1.54	0.12
	TT vs. CC	All	1.61(0.55–4.68)	51.05	<0.00001	82	0.87	0.38
	CT vs. CC	All	0.95(0.65–1.37)	24.43	0.004	63	0.29	0.77
	TT vs. CT	All	1.76(1.03–3.00)	21.35	0.01	58	2.08	0.04
	TT + CT vs. CC	All	1.07(0.64–1.77)	51.57	<0.00001	83	0.25	0.80
		Caucasian	1.44(0.82–2.52)	40.07	<0.00001	85	1.28	0.20
		Nonatopic	0.67(0.33–1.37)	1.11	0.29	10	1.10	0.27
		Atopic	0.64(0.37–1.13)	1.23	0.27	19	1.54	0.12
<i>IL-4</i> C-589T	T vs. C	All	1.12(1.00–1.26)	49.02	0.001	53	2.04	0.04
		Caucasian	1.24(1.08–1.43)	1.86	0.87	0	2.94	0.003
		Atopic	1.05(0.77–1.44)	0.1	0.75	0	0.31	0.75
	TT vs. CC	All	1.26(1.03–1.55)	26.35	0.28	13	2.26	0.02
	CT vs. CC	All	1.21(1.05–1.40)	16.98	0.81	0	2.55	0.01
	TT vs. CT	All	1.03(0.93–1.14)	32.93	0.08	30	0.48	0.63
	TT + CT vs. CC	All	1.24(1.08–1.43)	22.81	0.47	0	3.02	0.003
		Caucasian	1.29(1.07–1.54)	3.48	0.63	0	2.75	0.006
		Atopic	1.52(0.65–3.56)	0.19	0.66	0	0.96	0.34
<i>IL-13</i> G+2044A	A vs. G	All	1.16(1.00–1.34)	34.3	0.001	62	2.03	0.04
		Caucasian	1.09(0.89–1.33)	6.35	0.10	53	0.85	0.40
	AA vs. GG	All	1.26(1.04–1.53)	24.5	0.03	47	2.41	0.02
	AG vs. GG	All	1.07(0.95–1.21)	21.95	0.06	41	1.17	0.24
	AA vs. GA	All	1.17(0.98–1.41)	13.76	0.39	6	1.71	0.09
<i>IL-13</i> C-1112T	T vs. C	All	1.29(1.10–1.51)	29.02	0.004	59	3.11	0.002
		Caucasian	1.65(1.39–1.96)	4.06	0.54	0	5.64	<0.00001
		Atopic	1.06(0.83–1.36)	0.07	0.80	0	0.49	0.62
	TT vs. CC	All	1.59(1.20–2.09)	17.6	0.13	32	3.26	0.001
	CT vs. CC	All	1.16(1.02–1.31)	19.05	0.09	37	2.31	0.02
	TT vs. CT	All	1.31(0.99–1.72)	10.41	0.58	0	1.91	0.06
	TT + CT vs. CC	All	1.29(1.08–1.55)	25.11	0.01	52	2.82	0.005
		Caucasian	1.67(1.36–2.05)	3.47	0.63	0	4.89	<0.00001
		Atopic	1.02(0.77–1.37)	0.04	0.85	0	0.16	0.87

CI = 0.33–1.37, $P = 0.27$), or atopic (T-allele: OR = 0.75, 95 % CI = 0.51–1.08, $P = 0.12$; TT + CT genotypes: OR = 0.64, 95 % CI = 0.37–1.13, $P = 0.12$). And heterogeneity was found in the Caucasian ($Q = 66.71$, $P < 0.00001$, $I^2 = 91$), but not in the nonatopic ($Q = 0.52$, $P = 0.47$, $I^2 = 0$) and atopic ($Q = 0.98$, $P = 0.32$, $I^2 = 0$) (Sup. Fig. 1).

In short, the *IL-4* C-33T was significantly associated with asthma, but not associated with nonatopic or atopic in our meta-analysis. In the subgroup based on ethnicity, there was not an association between the *IL-4* C-33T polymorphism and asthma in the Caucasian population, and

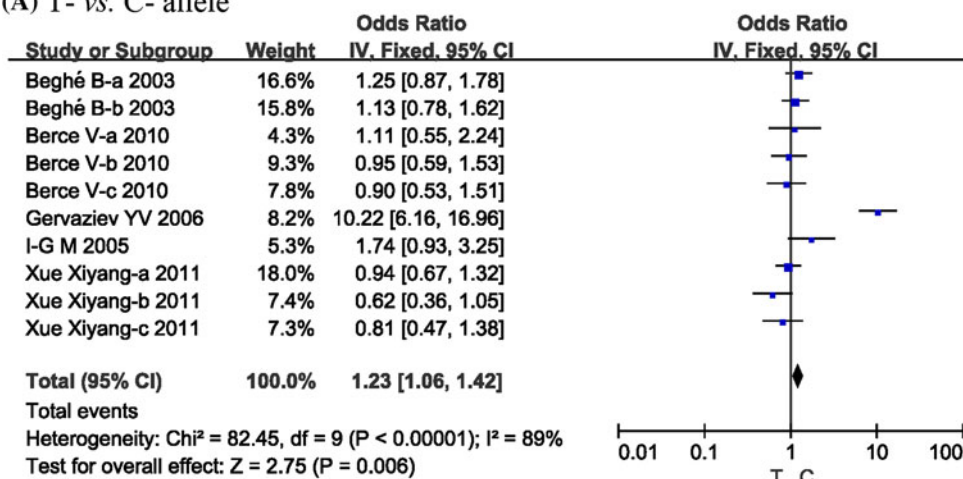
heterogeneity was found. It indicated that the geographical difference was not the one of the numerous reasons leading to heterogeneity among studies.

IL-4 C-589t

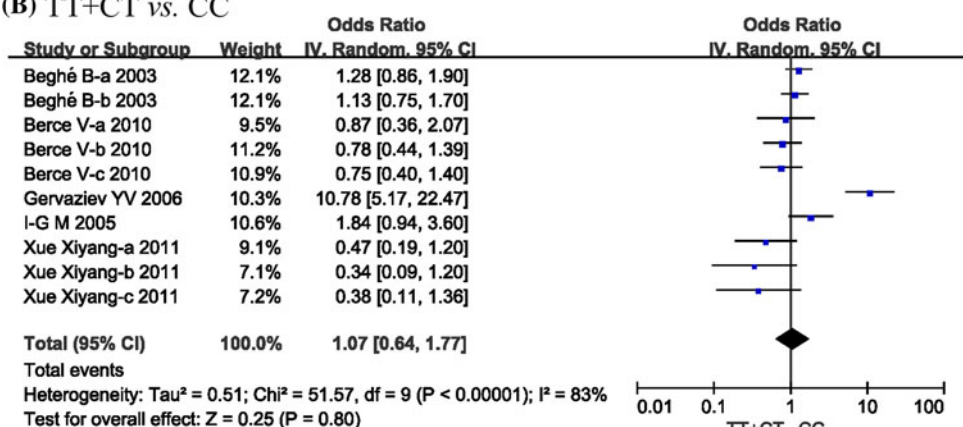
The meta-analysis demonstrated that there was an association between the *IL-4* -589T allele and asthma in the over all population (OR = 1.12, 95 % CI = 1.00–1.26, $P = 0.04$). Heterogeneity was found among studies ($Q = 49.02$, $P = 0.001$, $I^2 = 53$). By exploring further comparisons of OR₁ (genotype TT vs. CC), OR₂ (genotype

Fig. 1 OR and 95 % CI from individual studies testing association of the *IL-4* C-33T polymorphism and asthma: **a** *IL-4* -33 T- vs. C-allele; **b** *IL-4* -33 genotypes TT + CT vs. CC. CI, confidence interval; df, degree of freedom; IV inverse-variance

(A) T- vs. C- allele



(B) TT+CT vs. CC



CT vs. CC), and OR_3 (genotype TT vs. CT), the genetic model was most likely to be dominant (genotypes TT + CT vs. CC) ($OR = 1.24$, 95 % CI = 1.08–1.43, $P = 0.003$). It denominated that the individuals carrying the T allele may have a 24.0 % increased risk of asthma compared with CC homozygote (Fig. 2).

In the subgroup meta-analysis of *IL-4* -589 T- versus C-allele, heterogeneity was not found in the Caucasian ($Q = 1.86$, $P = 0.87$, $I^2 = 0$). And it indicated that there also was an association in the subgroup meta-analysis ($OR = 1.24$, 95 % CI = 1.08–1.43, $P = 0.003$). The overall OR of the dominant model (genotypes TT + CT vs. CC) was 1.29 in the Caucasian meta-analysis (95 % CI = 1.07–1.54, $P = 0.006$). And in the subgroup of atopic, there was no association between the *IL-4* -589T allele and atopic asthma (T-allele: $OR = 1.05$, 95 % CI = 0.77–1.44, $P = 0.75$; TT + CT genotypes: $OR = 1.52$, 95 % CI = 0.65–3.56, $P = 0.34$), and no heterogeneity was found (T-allele: $Q = 0.1$, $P = 0.75$, $I^2 = 0$; TT + CT genotypes: $Q = 0.19$, $P = 0.66$, $I^2 = 0$) (Sup. Fig. 2).

Therefore, this meta-analysis indicated that the *IL-4* C-589T was associated with susceptibility to asthma in all

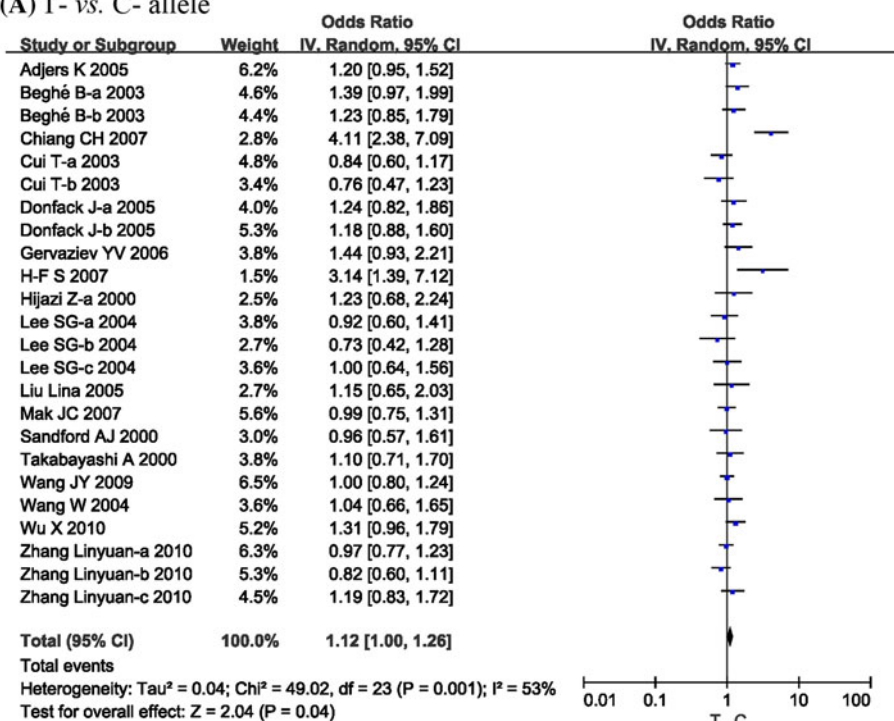
groups and Caucasian populations, but not with atopic. Heterogeneity was found in worldwide populations, but not in the Caucasian populations or atopic, the difference from ethnicity was one of the reasons leading to heterogeneity among studies.

***IL-13* SNP**

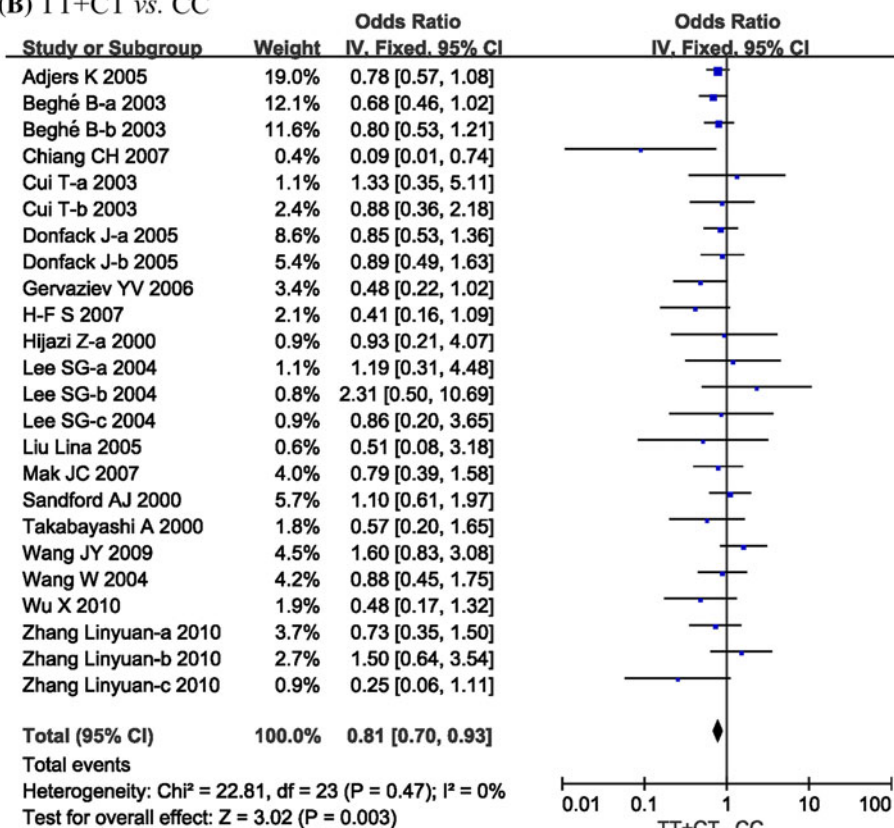
The results of the meta-analyses for the associations between the polymorphisms of the *IL-13* and asthma were showed on the Table 2. Heterogeneity was identified within- and between-studies for the *IL-13* +2044A allele and asthma ($Q = 34.3$, $P = 0.001$, $I^2 = 62$). The overall ORs for the *IL-13* +2044 A- versus G-allele, genotype AA versus GG and GA versus GG for the total population were 1.16 (95 % CI = 1.00–1.34), 1.26 (95 % CI = 1.04–1.53) and 1.07 (95 % CI = 0.95–1.21), respectively. In the Caucasian subgroup, there was no statistical evidence of heterogeneity among studies ($Q = 6.35$, $P = 0.10$, $I^2 = 53$) and no association was found ($OR = 1.09$, 95 % CI = 0.89–1.33, $P = 0.40$) (Sup. Fig. 3).

Fig. 2 OR and 95 % CI from individual studies testing association of the *IL-4* C-589T polymorphism and asthma:
a *IL-4* -589 T- vs. C-allele;
b *IL-4* -589 genotypes TT + CT vs. CC

(A) T- vs. C- allele



(B) TT+CT vs. CC



The overall ORs for the *IL-13* -1112T-allele, genotype TT versus CC (OR₁), genotype CT versus CC (OR₂), and genotype TT versus CT (OR₃) were 1.29 (95 % CI = 1.10–1.51, $P = 0.002$), 1.59 (95 % CI = 1.20–2.09, $P = 0.001$), 1.16 (95 % CI = 1.02–1.31, $P = 0.02$) and 1.31 (95 % CI = 0.99–1.72, $P = 0.06$), respectively. This demonstrated that the *IL-13* -1112T allele was associated with susceptibility to asthma. Heterogeneity within-and between-studies was observed ($Q = 29.02$, $P = 0.004$, $I^2 = 59$). Because OR₁ and OR₂ were significant ($P < 0.05$) while OR₃ was not significant ($P > 0.05$), the genetic model was most likely to be dominant (genotypes TT + CT vs. CC: OR = 1.29, 95 % CI = 1.08–1.55, $P = 0.005$). In the Caucasian subgroup meta-analysis, there was no statistical evidence of heterogeneity among studies (T-allele: $Q = 4.06$, $P = 0.54$, $I^2 = 0$; TT + CT genotypes: $Q = 3.47$, $P = 0.63$, $I^2 = 0$), and there was an association between the polymorphism of the *IL-13* C-1112T and asthma (T-allele: OR = 1.65, 95 % CI = 1.39–1.96, $P < 0.00001$; TT + CT genotypes: OR = 1.67, 95 % CI = 1.36–2.05, $P < 0.00001$). And in the atopic subgroup meta-analysis, heterogeneity was not found (T-allele: $Q = 0.07$, $P = 0.80$, $I^2 = 0$; TT + CT genotypes: $Q = 0.04$, $P = 0.85$, $I^2 = 0$), and the *IL-13* C-1112T did not confer susceptibility to atopic asthma (T-allele: OR = 1.06, 95 % CI = 0.83–1.36, $P = 0.62$; TT + CT genotypes: OR = 1.02, 95 % CI = 0.77–1.37, $P = 0.87$) (Sup. Fig. 4).

In a word, the polymorphisms of *IL-13* G + 2044A and C-1112T were associated with the asthma in our meta-analysis, respectively. In a subgroup analysis by ethnicity, and the *IL-13* +2044A allele was not associated with asthma among Caucasian, and the *IL-13* -1112T allele was associated with asthma among Caucasian, the results was the same to the Haijun Yang's study [56]. And the polymorphism of *IL-13* C-1112T was not associated with atopic asthma in the atopic subgroup meta-analysis.

Publication bias

The funnel plot for the selected studies that the association between the polymorphisms of the *IL-4* and *IL-13* genes and asthma was generated to examine publication bias. The results showed significant symmetry. It indicated that there was no significant publication bias (except the funnel plot of the meta-analysis of the association between the *IL-4* -33T allele and asthma) (Sup. Fig. 5).

Discussion

A number of studies have reported the association between the *IL-4* and *IL-13* polymorphisms and the risk of asthma, and the results have been inconsistent and inconclusive.

Our meta-analysis aimed to combine the evidence which can assess the association between the *IL-4* and *IL-13* polymorphisms and risk of asthma. It included only the extensively investigated SNPs (C-33T and C-589T in the *IL-4* gene, C-1112T and G+2044A in the *IL-13* gene), because the meta-analysis that included a small number of studies could weaken the conclusions. The present results indicated that the SNPs were associated with the asthma, and heterogeneity was found among studies. By performing the Caucasian subgroup meta-analysis, ethnic differences could lead to conflicting results of the association studies between the *IL-4* C-589T, *IL-13* C-1112T and G + 2044A and asthma. And the results suggested *IL-4* C-33T was not associated with nonatopic or atopic, and *IL-4* C-589T and *IL-13* C-1112T was not associated with atopic.

T/A allele acts as risk alleles at *IL-4* C-33T, *IL-4* C-589T, *IL-13* C-1112T and *IL-13* G + 2044A. In vitro experiments have shown that higher total serum IgE levels in T/A allele carriers, as high serum IgE levels being observed in the atopic individuals [26]. At *IL-4* C-589T where is located in the *IL-4* promoter region, T-allele is more facilitily for a transcription factor to bind. Because *IL-4* plays an important role in the inducing from IgM to IgE, higher total serum IgE levels in *IL-4* -589T allele carriers [3, 26]. However, there are no evidences in the producing of IgE at the other SNPs. We can speculate that T/A allele upregulates the expression of *IL-4* or *IL-13* that increasing serum IgE levels. Therefore, *IL-4* and *IL-13* SNPs affect atopic asthma risk.

Then the limitations of the meta-analysis were discussed. First, the publication bias could affect the meta-analysis. Our meta-analysis adopted the funnel plot to analysis whether there was the publication bias. But when there was the small number of studies, we could not draw funnel plots for each meta-analysis. In our meta-analysis, the funnel plots were symmetry except the meta-analysis between the *IL4* -33T allele and susceptibility to asthma, and it indicated that there was no significant publication bias among the selected studies. The language bias was also present because the included studies were published in English or Chinese. Second, heterogeneity might be present to affect the meta-analysis. There was high heterogeneity among all studies. There were some factors which might bring heterogeneity to the meta-analysis. (1) The sample size of included studies could affect the meta-analysis. (2) The difference of choosing sample was present such as there were not exactly standard about the age of case group. (3) The variety of environment and the interaction of the genotype with environment could lead to the difference between studies. But the meta-analysis did not discuss above. (4) In our meta-analysis there were major population of Caucasian and Asian, but little African, this

could bring about the difference of ethnic. Further studies were needed more sample. Third, asthma itself was a complex and heterogeneous disease, and the divergent inclusion criteria for the patient groups might limit the pooling the various studies. In genetic studies, the asthma phenotype was not described in full detail, and details of asthma diagnostic criteria were often scanty. The atopic status of controls should be fully defined in the future studies. The overestimation of the genetic effect for genetic association could lead to publication bias.

In conclusion, results of this meta-analysis indicate that the C-33T and C-589T polymorphisms in the *IL-4* gene, the C-1112T and G+2044A polymorphisms in the *IL-13* gene are significantly associated with a risk of asthma. Depending on the definition of asthma, the subgroup meta-analysis demonstrates that the polymorphism of *IL-4* C-33T is not associated with nonatopic or atopic, and the polymorphisms of the *IL-4* C-589T and *IL-13* C-1112T are not associated with atopic. In the subgroup meta-analysis by ethnicity, the *IL-4* -589T allele and the *IL-13* -1112T allele are associated with asthma among Caucasian, but not on the *IL-13* +2044A allele. Further investigation in larger studies and meta-analysis is required.

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Disclosure No conflicts of interest, financial or otherwise, are declared by the authors.

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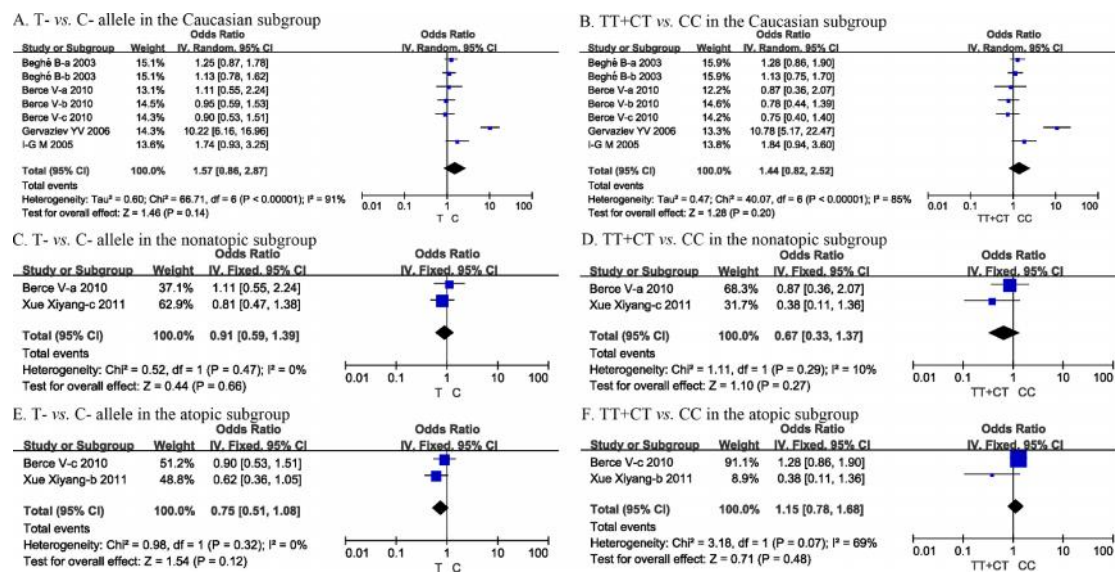
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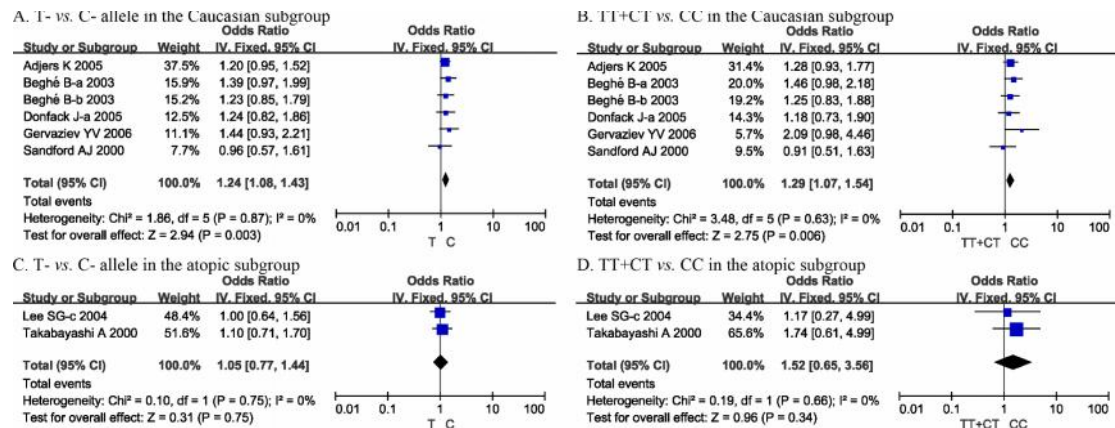
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Association between the interleukin-4, interleukin-13 polymorphisms and asthma: a meta-analysis

Zhen-dong Wang, Duan Lian, Jing-ling Shen, Ruizhen Sun, Wang Xu, Zhang Xin, Lei Lei, Lian-hong Jin, Shou-de Jin

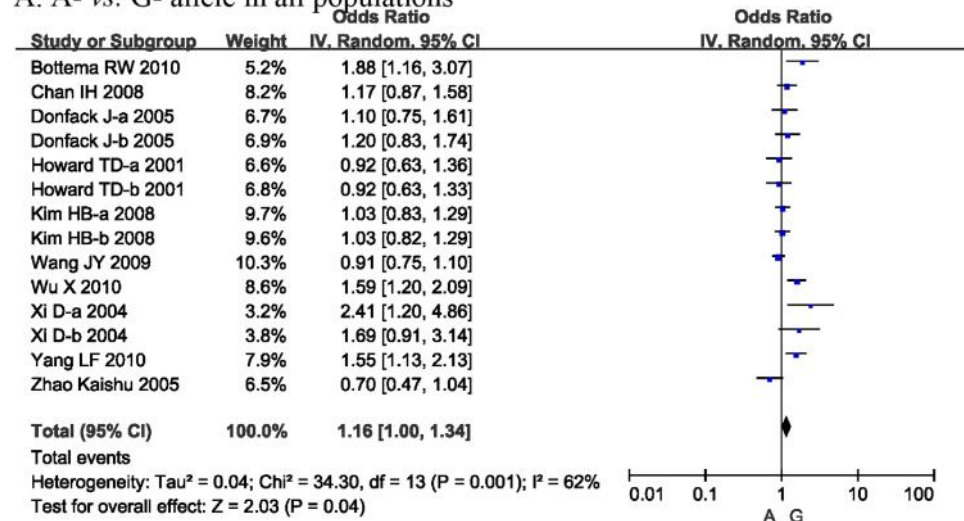


Sup. Fig. 1 OR and 95% CI from individual studies testing association of the *IL4* C-33T polymorphism and asthma in the Caucasian populations, nonatopic, and atopic: (A) *IL4* -33 T- vs. C-allele in the Caucasian subgroup; (B) *IL4* -33 genotypes TT+CT vs. CC in the Caucasian subgroup; (C) *IL4* -33 T- vs. C-allele in the nonatopic subgroup; (D) *IL4* -33 genotypes TT+CT vs. CC in the nonatopic subgroup; (E) *IL4* -33 T- vs. C-allele in the atopic subgroup; (F) *IL4* -33 genotypes TT+CT vs. CC in the atopic subgroup.

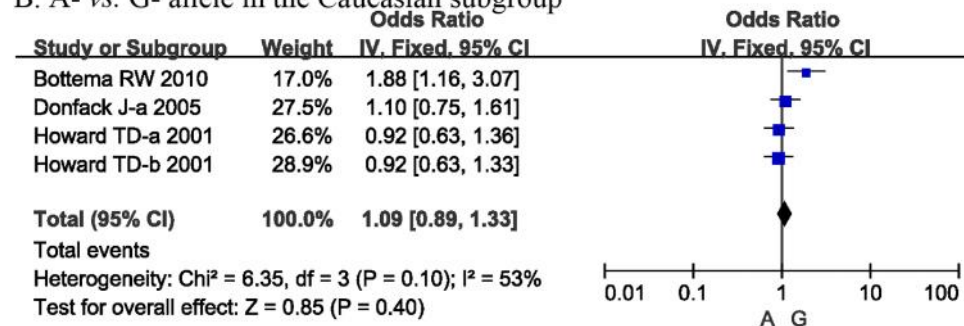


Sup. Fig. 2 OR and 95% CI from individual studies testing association of the *IL4* C-589T polymorphism and asthma in the Caucasian populations and the atopic subgroup: (A) *IL4* -589 T- vs. C-allele in the Caucasian subgroup; (B) *IL4* -589 genotypes TT+CT vs. CC in the Caucasian subgroup; (C) *IL4* -589 T- vs. C-allele in the atopic subgroup; (D) *IL4* -589 genotypes TT+CT vs. CC in the atopic subgroup.

A. A- vs. G- allele in all populations

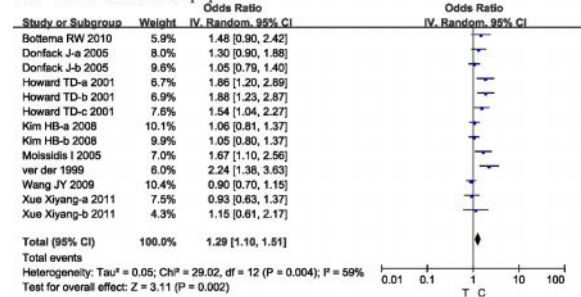


B. A- vs. G- allele in the Caucasian subgroup

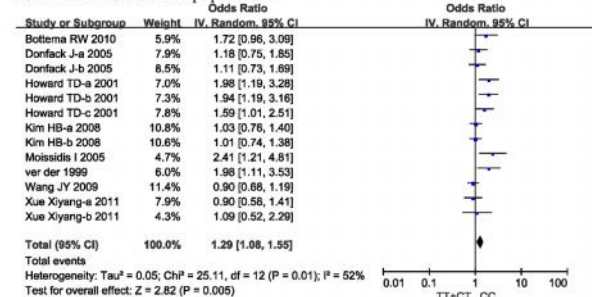


Sup. Fig. 3 OR and 95% CI from individual studies testing association of the *IL13* G+2044A polymorphism A allele and asthma in all and Caucasian populations: (A) *IL13* +2044 A- vs. G-allele in all populations; (B) *IL13* +2044 A- vs. G-allele in the Caucasian populations.

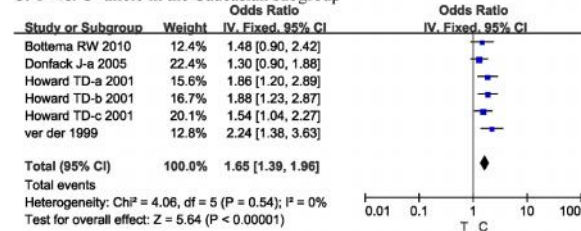
A. T- vs. C- allele in all population



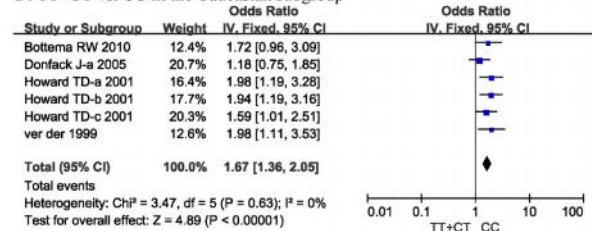
B. TT+CT vs. CC in all population



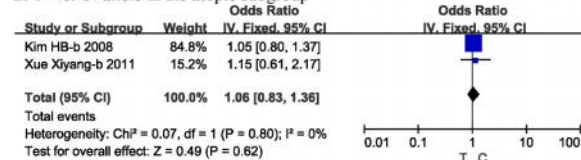
C. T- vs. C- allele in the Caucasian subgroup



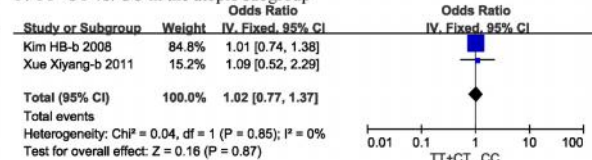
D. TT+CT vs. CC in the Caucasian subgroup



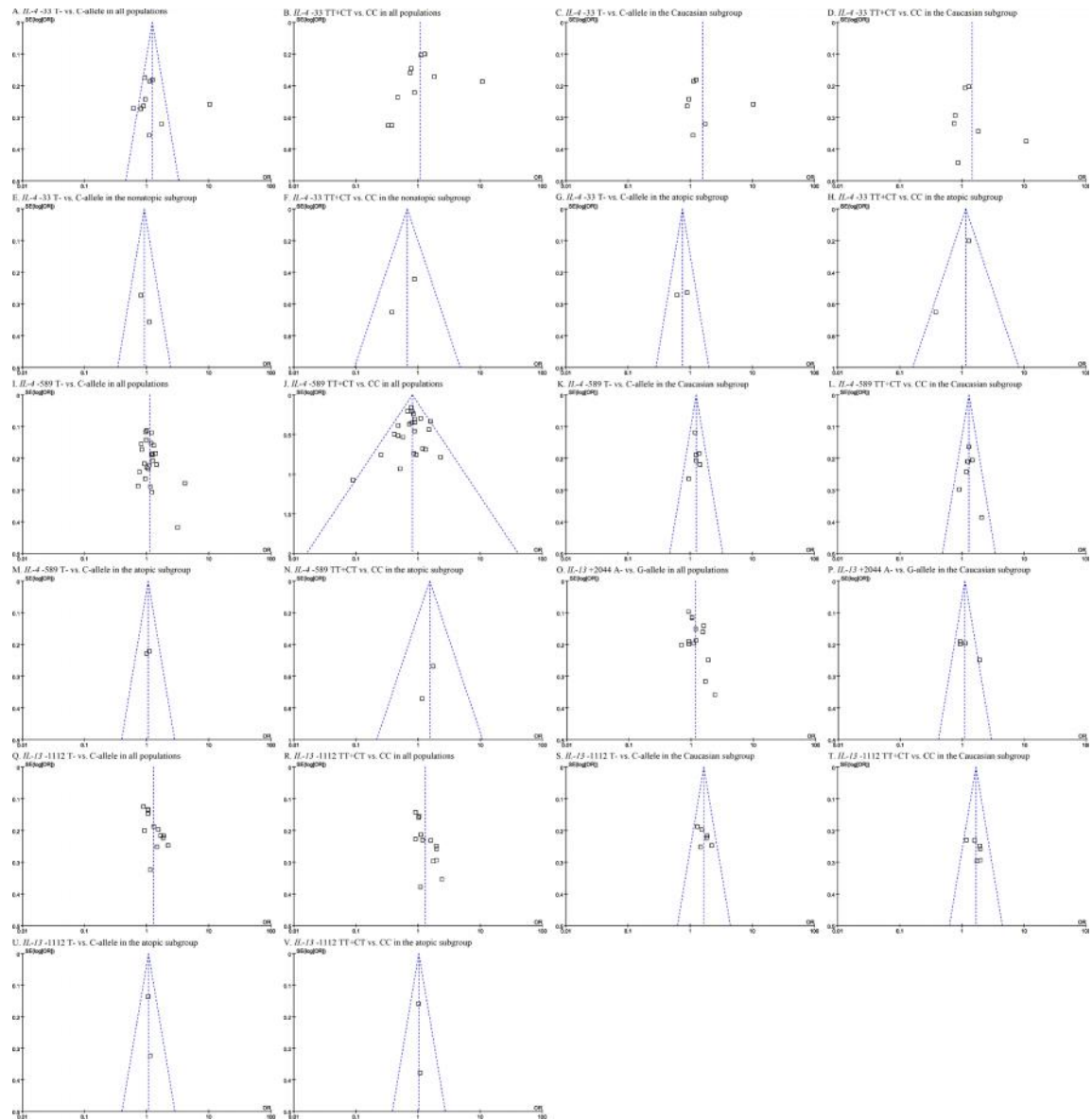
E. T- vs. C- allele in the atopic subgroup



F. TT+CT vs. CC in the atopic subgroup



Sup. Fig. 4 OR and 95% CI from individual studies testing association of the *IL13* C-1112T polymorphism and asthma: (A) *IL13* -1112 T- vs. C-allele in all population; (B) *IL13* -1112 genotypes TT+CT vs. CC in all population; (C) *IL13* -1112 T- vs. C-allele in the Caucasian subgroup; (D) *IL13* -1112 genotypes TT+CT vs. CC in the Caucasian subgroup; (E) *IL13* -1112 T- vs. C-allele in the atopic subgroup; (F) *IL13* -1112 genotypes TT+CT vs. CC in the atopic subgroup.



Sup. Fig. 5 Funnel plot with ORs of all studies on the association between the *IL4* and *IL13* polymorphisms and risk of asthma.