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Asthma susceptible genes in children

A meta-analysis

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Abstract

Background: During the last decade, a number of studies have evaluated the potential association between some genetic polymorphisms and childhood asthma risk, however, the results of published studies appear conflicts. The aim of the present study was to investigate association between genetic polymorphisms and pediatric asthma.

Methods: Relevant studies were searched in PubMed, Embase, Web of Science, CNKI (China National Knowledge Infrastructure), Wanfang, and Weipu database. Pooled odds ratios (OR) with 95% confidence interval (CI) were calculated to evaluate the strength of the associations.

Results: Fifty five case-control studies were finally included in this meta-analysis, including 17,971 pediatric asthma cases and 17,500 controls. Eighteen polymorphisms were identified, of which, 9 polymorphisms were found to be associated with asthma risk in overall populations: *IL-13* +2044G/A, *IL-4* -590C/T, *ADAM33* F+1, *ADAM33* T2, *ADAM33* T1, *ADAM33* ST+4,*ORMDL3* rs7216389, *VDR* FokI, *VDR* TaqI. Furthermore, *IL-13* +2044G/A, *IL-4* -590C/T, *ADAM33* T2, *ADAM33* T1, *VDR* BsmI polymorphisms may cause an increased risk of asthma among Chinese children.

Conclusions: This meta-analysis found that *IL-13* +2044G/A, *IL-4* -590C/T, *ADAM33* F+1, *ADAM33* T2, *ADAM33* T1, *ADAM33* ST+4,*ORMDL3* rs7216389, *VDR* FokI, and *VDR* TaqI polymorphisms might be risk factors for childhood asthma. Further study with large population and more ethnicities is needed to estimate these associations.

Abbreviations: ADAM33 = A Disintegrin and Metalloprotease33, ADRB2 = β-2 adrenergic receptor, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CTLA-4 = cytotoxic T lymphocyte associated antigen-4, GWAS = Genome-wide association study, HWE = Hardy–Weinberg equilibrium, IL = interleukin, OR = odds ratio, ORMDL3 = Orosomucoid 1-like 3, SNP = single nucleotide polymorphism, VDR = Vitamin D receptor.

Keywords: gene polymorphisms, meta-analysis, pediatric asthma

1. Introduction

Bronchial asthma, one of the most prevalent chronic diseases in childhood, is a complex disease characterized by reversible airway obstruction and chronic inflammation.[1] Asthma exacerbation is an important cause of childhood morbidity and hospitalization. The prevalence of asthma in children is higher than that in adults and it continues to increase worldwide, particularly in low- and middle-income countries.[2,3] Children experienced asthma symptoms reach to 14.2% all over the world. The global mortality rate for childhood asthma ranges 0 to 0.7 per 100,000 population.[4–6] Lifetime prevalence reaches 14% in children. Asthma affects seriously childhood health and imposes extremely high medical costs on families and society. There is an association between childhood asthma and adult chronic obstructive pulmonary disease (COPD). Children with severe asthma have a high risk of developing adult COPD.[7] Due to the heterogeneity of asthma, there are differences in the clinical manifestations of children at different ages, which may make it harder to diagnose asthma in children.[8] Both genetic and environmental factors contribute to inception and evolution of asthma, while genes play a greater role in pediatric asthma than adults. A genome-wide association study (GWAS) found that the genes associated with childhood asthma are almost 3 times that of adults.[9] GWASs have identified several regions associated with asthma.[6] In recent years, the exploration of genetic susceptibility

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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to asthma has become an important subject worldwide. However, some results remain largely inconsistent, even contradictory. Therefore, we carried out a meta-analysis to assess association between genetic polymorphisms and pediatric asthma.

2. Materials and methods

2.1. Search strategy

Two independent investigators used electronic databases of English (PubMed, Embase, Web of Science) and Chinese (China National Knowledge Infrastructure [CNKI], Wanfang, Weipu) to search relevant studies published between January 2010 and January 2020. The following terms were used for search: "asthma or asthmatic," "gene or genetic," "case-control studies," and "pediatric or childhood." Corresponding Chinese words were used in the Chinese database. The language was no restricted.

2.2. Inclusion and exclusion criteria

Inclusion criteria included: evaluation of the association between genetic variants and pediatric asthma (age ≤18 years); studies published in journals; the patients were clinically diagnosed with asthma; detailed genotype data were available to estimate an odds ratio (OR) with 95% confidence interval (CI) and *P* value in control and case groups; each polymorphism should be studied in at least 3 case-control studies; gene polymorphism characterized as A/B, including genotypes: AA, AB, and BB. When the author published multiple studies on the same topic, only the latest full-text studies were included in the final analysis.

Exclusion criteria included: conference papers, meta-analysis, or review; duplicated data; not present the usable data; genetic variants not characterized as A/B; unavailable full-text.

2.3. Data extraction and quality assessment

Primary search strategy generates 1914 studies, which is exported to Endnote X9. Two researchers (ZR and ZS) independently estimated the studies, extracted the data, and cross-checked based on the inclusion and exclusion criteria. Any disagreement was resolved by discussing or negotiating with a third researcher (HD). Firstly, we browsed the title and abstract of the studies to exclude the obviously irrelevant. Secondly, we determined whether to include these studies by reading full-text. The following contents were collected: name of first author, year of publication, country of origin, ethnicity, mean age, number of cases and controls, genotyping methods, and allele and genotype frequencies in cases and controls. The quality of each study was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). Studies scoring 0 to 3, 4 to 6, or 7 to 9 were defined as low-, moderate-, or high-quality study, respectively. The results of quality assessments were shown in Table 1.

2.4. Statistical analysis

We conducted our meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklists and followed the guideline. Hardy-Weinberg equilibrium (HWE) were carefully calculated by Chi-squared test for each study in control groups ($P < .05$ was defined as departure from HWE). The strength of the association between each gene polymorphism and pediatric asthma was calculated by OR and 95% CI. The pooled OR was determined by Z-test and performed for allelic model, homozygous model, heterozygous model, dominant model, and recessive model, respectively. Heterogeneity was evaluated by Chi-squared-based *Q*-test and I^2. Either fixed-effect or random effects model was used to pool the effect sizes: if $I^2 < 50\%$ and $P \geq .1$, the pooled OR was calculated by the fixed-effects model; otherwise, a random-effects model was applied. Subgroup analyses based on countries were performed for polymorphisms which were investigated in a sufficient number of studies (data were available from at least 3 studies). Funnel plot, Begg test, and Egger test were applied to estimate potential publication bias. Furthermore, the funnel plot asymmetry was assessed with the Begg test. An asymmetric plot and the *P* value of Begg test <.05 was considered a significant publication bias. All statistical analyses were performed with Stata statistical software (version 15.1) and Revman software (version 5.3). A *P* value < .05 was considered statistically significant, while the level of 0.10 were used for the heterogeneity test.

3. Results

3.1. Study inclusion and characteristics

The flow chart of the selection process is shown in Fig. 1. Briefly, a total of 1914 studies were identified after initial search, of which, 868 duplicate studies were removed. After screening the titles and abstracts, 270 articles were selected. The 270 full-text articles were evaluated based on inclusive and exclusive criteria. Finally, 55 studies were included in the meta-analysis, including 17,971 asthma patients and 17,500 controls. The included studies were published between 2010 and 2020 and conducted in 11 countries: China, Indian, Egypt, Jordan, Poland, Mexico, Saudi Arabia, Colombia, Chile, Turkey, and Tunisia. A total of 18 polymorphisms in 7 genes were identified for data synthesis: *IL-13* +2044G/A (rs20541),[10–15] *IL-13* -1112C/T (rs1800925),[11,13,15–19] *IL-13* +1923C/T (rs1295686),[20–22] *IL-4* -590C/T (rs2243250),[12,15–19,21,23–28] *ADRB2* -46 G /A (rs1042713),[11,15,21,29–37] *ADRB2* -79G/C (rs1042713),[29,31–35,38] *ADAM33* F+1 (rs511898),[39–42] *ADAM33* V4 (rs2787094),[39,40,43–45] *ADAM33* S2 (rs528557),[15,39,41,44,45] *ADAM33* T2 (rs2280090),[40,43–46] *ADAM33* T1 (rs2280091),[40,41,44,45] *ADAM33* ST+4 (rs44707),[39,47,48] *ORMDL3* rs7216389,[49–52] *VDR Apa*I (rs7975232),[53–59] *VDR Fok*I (rs2228570),[53–55,57,58,60,61] *VDR* BsmI (rs1544410),[54–57,59,61] *VDR* TaqI (rs731236),[53–55,57,58] and *CTLA-4* +49 G/A (rs231775).[62–64]The detailed characteristics of included studies are given in Table 1. Distribution of genotype and allele among asthma patients and controls are given in Supplementary1, http://links.lww.com/MD/F141.

3.2. Results of meta-analysis

The results of meta-analyses of the association between each polymorphism and the risk of pediatric asthma are shown in Table 2.

3.2.1. IL-13 +2044G/A polymorphism and pediatric asthma risk. The association between *IL-13* +2044G/A polymorphism and pediatric asthma risk was evaluated in 6 case-control studies, including 1022 cases and 1037 controls. The pooled results showed significant association between *IL-13* +2044G/A polymorphism and pediatric asthma risk in dominant model (GA+AA vs GG: OR = 1.73, 95% CI: 1.16–2.56, $P = .01$), allelic model (A

Table 1

Main characteristics of included studies in this meta-analysis.

Studies	Country	Ethnicity	Mean age		Total Case/ Controls	Genotyping methods	Polymorphisms	Quality scores
			Cases	Control				
Awasthi 2011	Indian	Asian	74.39±45.7m (1–15y)	73.61±42.56m (1–15y)	211/137	PCR-RFLP	ADAM33 F+1, V4, ST+4, S2	7
Qu 2011	China	Asian	7.74±2.78 (8–13)	7.52±2.95 (8–13)	412/397	PCR-RFLP	ADAM33 F+1, T+1, T2, T1, V4	8
Wang 2017	China	Asian	3–15	3–15	197/120	PCR-RFLP	ADAM 33 F+1	7
Yu 2011	China	Asian	3.9±3.1	3.3±2.7	123/136	PCR-RFLP	ADAM33 S2	7
Fan 2015	China	Asian	5.27–1.93 (2–10)	5.68–2.17 (3–12)	120/105	PCR-RFLP	ADAM 33 F+1, T1, S2	8
Shalaby 2015	Egypt	African	8.5 (±3.6) (3–14)	8.8 (±2.6) (4–13)	400/200	PCR-RFLP	ADAM33 F+1, ST+4	6
Li 2014	China	Asian	10.4±2.9 (3.1–14.6)	3.1–14.6	299/311	PCR-RFLP	ADAM33 V4, T2, S2, S1, T1	6
Zihlif 2014	Jordan	Asian	5.96–4.63	7.53–4.83	107/115	PCR-RFLP	ADAM33 T1, T2, V4, S2	6
Zhao 2012	China	Asian	14.2±3.4 (3.1–14.8)	14.5±3.5 (3.3–14.9)	110/144	PCR-RFLP	ADAM33 T2, V4	6
Yu 2018	China	Asian	6.26±2.06 (5–12)	6.19±2.03	105/98	Sequencing	ADAM33 ST+4	7
Long 2018	China	Asian	22.98±20.67y	22.51±20.32	101/117	SNaPshot	ADAM33 S2, IL13+2044G/A IL-13-1112C /T IL-4 -590C/T ADRB2-46G /A	8
Ding 2013	China	Asian	6.62±1.90 (1–14)	5.86±2.11 (0.78–14)	90/82	PCR-RFLP	IL-13+2044G/A	7
Guo 2017	China	Asian	5.4±1.8 (1–13)	6.3±2.1 (3–14)	80/112	PCR-RFLP	IL-13+2044G/A IL-13-1112C /T	8
Zhang 2016	China	Asian	5. 68±3. 33	4. 85±3. 69	153/103	Mass Array	IL-13+2044G/A	7
Narozna 2016	Poland	European	11.5±3.6	12.1±33.4	177/194	TaqMan	IL-13+2044G/A IL-4 -590C/T	6
Martínez 2015	Mexico	Mestizo	10.8±2.9	NA	421/430	TaqMan	IL-13-1112C /T ADRB2-46G /A	6
Alghobashy 2018	Egypt	African	6–12	6–11	104/52	PCR-RFLP	ADRB2-46G /A ADRB2 -79G/C	8
Dixit 2014	India	Asian	6.29±3.28 (1–15)	6.08±3.22 (1–15)	275/275	PCR-RFLP	IL-13-1112C /T IL-4 -590C /T	7
Liao 2014	China	Asian	6.30±3.39	4.96±3.61	300/200	PCR-RFLP	IL-13 -1112C /T IL-4-590C/T	7
Huang 2013	China	Asian	48.6±43.2m	40.9±41.5	168/188	Mass Array	ORMDL3 rs7216389	7
Yang 2012	China	Asian	5.872±2.543	6.038±2.526	152/190	Mass Array	ORMDL3 rs7216389	6
Sun 2010	China	Asian	6–14	6–14	178/129	PCR-RFLP	ORMDL3 rs7216389	7
Wei 2016	China	Asian	6.02±1.98	6.31±2.04	128/100	Mass Array	ORMDL3 rs7216389	7
Jia 2013	China	Asian	4.27±2.52	4.15±2.91	77/50	PCR-RFLP	IL-13 +1923	7
Pu 2013	China	Asian	5.8±2.9 (3–12)	5.6±2.6	96/96	PCR-RFLP	IL-13 +1923	7
Ramphul 2014	Mixed	African/Asian	3–12	18–22	M:193/189 C:192/192	PCR-RFLP	IL-13 +1923 IL-4 -590C/T ADRB2 -46G /A	7
Zeng 2015	China	Asian	6. 60±3. 40	4. 91±3. 73	250/200	PCR-RFLP	IL-4-590C/T	7
Smolnikova 2013	Russians	European	13.3±2.24	14.8±0.68	64/50	PCR	IL-4-590C/T	8
Zhang 2010	China	Asian	10. 3±1. 5 (6–13)	10. 1±1. 5 (6–13)	291/668	PCR-RFLP	IL-4 -590C/T	7
Wu 2019	China	Asian	6.8±2.7 (3–12)	6.6±2.5 (3–12)	160/160	PCR-RFLP	IL-13-1112C /T IL-4 -590C/T	6
Li 2014	China	Asian	8.4±2.7 (3–12)	7.9±3.2 (3–12)	500/523	PCR-RFLP	IL-13-1112C /T IL-4 -590C/T	7
Lin 2012	China	Asian	4.4±2.3 (1.4 -13)	7.7±2.5 (3–14)	72/102	PCR-RFLP	IL-4-590C/T	8
Huang 2010	China	Asian	6. 57±2. 76 (2–13)	7. 46±2. 94 (3–14)	100/122	PCR-RFLP	IL-4 -590C/T	6
Yan 2015	China	Asian	6±2. 8 (6m-14y)	7±2. 1 (4–14)	34/30	PCR-RFLP	IL-4 - 590C/T	7
Karam 2013	Egypt	African	10.3±2.4	9.8±2.8	90/110	AS-PCR	ADRB2-46G /A ADRB2 -79G/C	6
Abdullah 2011	Saudi Arabia	Asian	10.4±4.6	12.6±4.2	73/85	PCR-RFLP	ADRB2 -46G/A ADRB2 -79G/C	7
Yang 2012	China	Asian	7.66±2.59	7.69±2.55	212/52	Sequencing	ADRB2-46G /A	7
Zheng 2012	China	Asian	3.5	3.8	198/110	StepOnePlus/TaqMan	ADRB2-46G /A	7
Feng 2018	China	Asian	5.8±2.8 (2–12)	6.3±3.1 (2–12)	173/166	Taqman	ADRB2-46G /A ADRB2 -79G/C	8

(*continued*)

Table 1

(continued).

Studies	Country	Ethnicity	Mean age		Total Case/ Controls	Genotyping methods	Polymorphisms	Quality scores
			Cases	Control				
Isaza 2012	Colombia	Mestizo	(6–17)	(6–17)	109/137	Sequencing	ADRB2 -46G/A ADRB2 -79G/C	8
Qi 2014	China	Asian	1.1–14	2–14	120/117	PCR-RFLP	ADRB2 -79G/C	7
Tian 2016	China	Asian	5.6±10.3 (0.75–16)	5.2±9.8 (2–14)	298/304	TaqMan	ADRB2 -46G/A ADRB2 -79G/C	7
Yang 2017	China	Asian	N/A	N/A	74/110	PCR-RFLP	ADRB2 -46G/A	6
Kilic 2019	Turkey	European	9.5±2.8 (5–16)	9.5±2.5 (5–14)	80/100	StepOnePlus/TaqMan	VDR ApaI, TaqI, FokI	8
Maalmi 2013	Tunisia	African	9.1 (4–16)	9.5 (2–16)	155/225	PCR-RFLP	VDR ApaI, TaqI, FokI, BsmI	7
Mo 2015	China	Asian	NA	NA	71/71	PCR-RFLP	VDR ApaI, BsmI	7
Zhu 2019	China	Asian	8.76±1.22	8.60±1.16	97/100	Sequencing	VDR FokI, BsmI	8
Ismail 2013	Egypt	African	8.6±2.7	7.8±2.6	51/33	TaqMan	VDR FokI	6
Zhao 2015	China	Asian	3.14±1.07 (2–6)	3.37±1.04 (2–6)	40/40	Sequencing	VDR ApaI, TaqI, FokI, BsmI	7
Ma 2014	China	Asian	11	10.6	60/60	PCR-RFLP	VDR ApaI, TaqI, FokI, BsmI	7
Einisman 2015	Chile	American	6-15	2-18	75/227	PCR-RFLP	VDR ApaI, TaqI, FokI	7
Hou 2018	China	Asian	8.84±3.2	8.04±3.01	70/70	PCR-RFLP	VDR ApaI, BsmI	6
Zhang 2010	China	Asian	7.1±2.3	7.1±1.6	118/160	PCR-RFLP	CTLA-4 +49A/G	7
Wang 2014	China	Asian	8m–10y	9m–10y	40/40	Sequencing	CTLA-4 +49 A/G	7
Zhang 2012	China	Asian	1–10	3–7	26/30	PCR-RFLP	CTLA-4 +49 A/G	6

AS-PCR = allele-specific PCR, m = month, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, y = year.

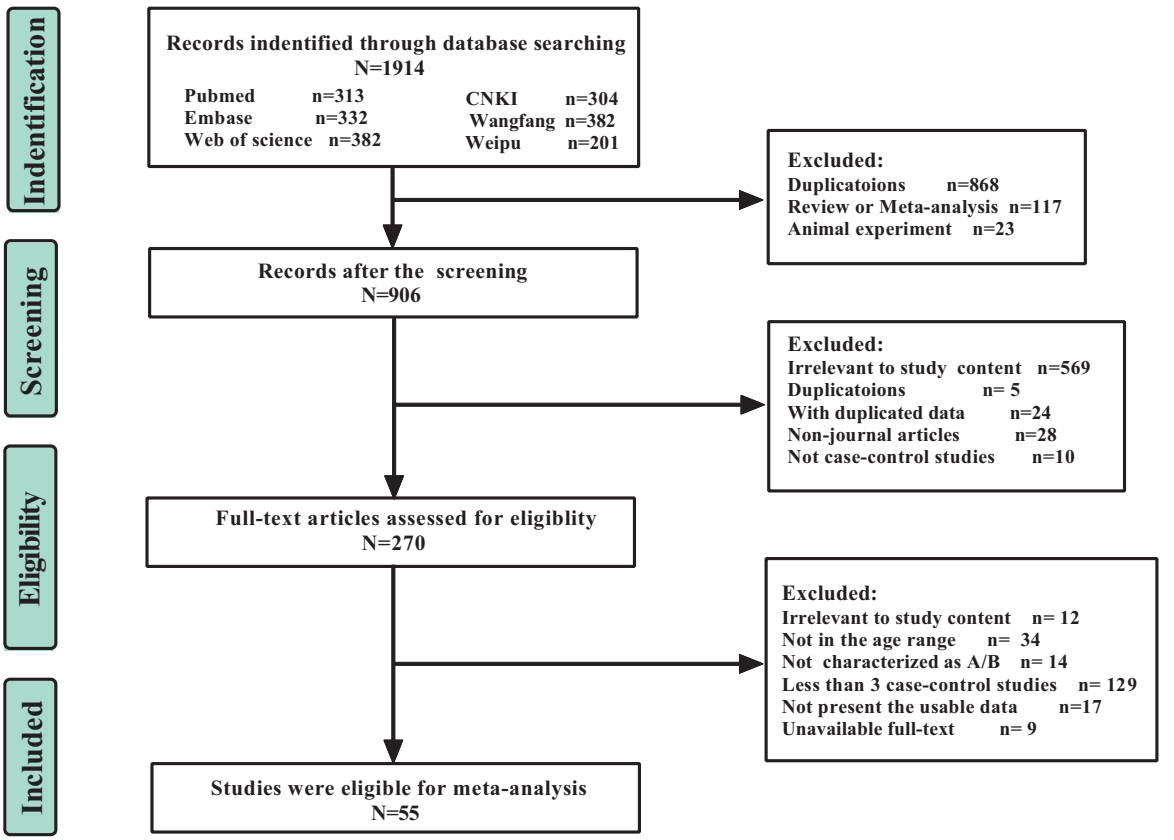

Figure 1. The flow chart of the selection process.

Table 2

Meta-analysis of the association between 18 polymorphisms of 7 genes and pediatric asthma risk.

				Test of association		Test of heterogeneity			Begg test	
Gene	Polymorphism	Comparison	N	OR (95% CI)	P	Model	Ph	I^2/%	z	P
IL-13	+2044G/A	GA+AA vs GG	6	1.73 (1.16–2.56)	.01	R	0.00	70.8	1.32	.26
		AA vs GG+GA		1.04 (0.84–1.20)	.72	F	0.14	39.9	1.13	.26
		A vs G		1.42 (1.05–1.91)	.02	R	0.00	77.5	2.63	.01
		AA vs GG		1.66 (0.98–2.82)	.06	R	0.03	58.4	1.13	.26
		AG vs GG		1.70 (1.18–2.45)	.01	R	0.02	62.6	1.13	.26
	−1112C/T	CT+TT vs CC	6	1.31 (0.72–1.78)	.59	R	0.00	90.0	0.60	.55
		TT vs CC+CT		1.05 (0.59–1.87)	.87	R	0.00	79.7	0.90	.37
		T vs C		1.06 (0.73–1.54)	.75	R	0.00	91.1	0.30	.76
		TT vs CC		1.72 (0.76–3.90)	.20	R	0.00	83.6	1.20	.23
		CT vs CC		1.14 (0.73–1.78)	.56	R	0.00	88.4	0.00	1.00
	+1923C/T	CT+TT vs CC	4	1.09 (0.54–2.21)	.82	R	0.00	85.9	−0.34	1.00
		TT vs CC+CT		1.06 (0.43–2.60)	.91	R	0.00	76.4	−0.34	1.00
		T vs C		1.08 (0.64–1.82)	.78	R	0.00	86.9	−0.34	1.00
		TT vs CC		1.07 (0.37–3.06)	.91	R	0.00	80.4	−0.34	1.00
		CT vs CC		1.09 (0.55–2.14)	.80	R	0.00	83.1	−0.34	1.00
IL-4	−590C/T	CT+TT vs CC	14	1.37 (1.04–1.82)	.03	R	0.02	51.6	0.33	.74
		TT vs CC+CT		1.23 (1.02–1.49)	.03	R	0.01	52.3	1.31	.19
		T vs C		1.24 (1.04–1.48)	.02	R	0.00	70.0	0.55	.58
		TT vs CC		1.49 (1.05–2.12)	.03	R	0.12	50.6	0.11	.91
		CT vs CC		1.26 (1.04–1.52)	.02	F	0.09	35.5	0.55	.58
ADRB2	−46 G /A	GA+GG vs AA	12	1.22 (0.88–1.70)	.24	R	0.00	79.1	1.30	.19
		GG vs GA+AA		0.97 (0.69–1.35)	.84	R	0.00	75.7	0.07	.95
		G vs A		1.10 (0.86–1.40)	.46	R	0.00	84.3	1.17	.24
		GG vs AA		1.09 (0.71–1.67)	.69	R	0.00	78.4	0.62	.54
		GA vs AA		1.26 (0.93–1.73)	.14	R	0.00	72.6	2.54	.01
	−79G/C	GC+GG vs CC	7	1.12 (0.84–1.50)	.44	R	0.05	51.9	1.20	.23
		GG vs GC+CC		1.04 (0.68–1.60)	.85	F	0.77	0.00	0.60	.55
		G vs C		1.08 (0.86–1.36)	.52	R	0.06	50.3	0.90	.37
		GG vs CC		1.12 (0.72–1.72)	.62	F	0.63	0.00	1.50	.13
		GC vs CC		1.10 (0.90–1.35)	.35	F	0.09	45.8	0.60	.55
ADAM33	F+1	CT+TT vs CC		1.24 (1.04–1.48)	.02	F	0.13	44.3	0.24	.81
		TT vs TC+CC		1.67 (0.94–2.97)	.08	R	0.00	79.0	0.24	.81
		T vs C		1.33 (0.99–1.79)	.06	R	0.00	80.0	−0.24	1.00
		TT vs CC		1.81 (0.95–3.44)	.07	R	0.00	79.1	−0.24	1.00
		CT vs CC		1.13 (0.93–1.36)	.21	F	0.93	0.0	0.73	.46
	V4	GC+GG vs CC	5	1.02 (0.47–2.22)	.96	R	0.00	90.4	1.22	.22
		CC vs CG+CC		1.15 (0.44–3.01)	.78	R	0.00	95.2	0.24	.81
		G vs C		0.99 (0.47–2.09)	.99	R	0.00	97.1	−0.24	1.00
		GG vs CC		1.22 (0.34–4.32)	.76	R	0.00	94.2	0.24	.81
		GC vs CC		1.17 (0.66–2.08)	.59	R	0.00	79.3	0.73	.46
	S2	GC+CC vs GG	6	0.99 (0.28–3.43)	.00	R	0.00	92.7	0.38	.71
		CC vs GC+GG		1.40 (0.54–3.60)	.49	R	0.00	95.5	1.50	.13
		C vs G		1.17 (0.57–2.42)	.67	R	0.00	95.8	0.00	1.00
		CC vs GG		1.07 (0.23–4.93)	.93	R	0.00	94.2	0.00	1.00
		GC vs GG		0.99 (0.36–2.69)	.98	R	0.00	87.2	0.75	.45
	T2	AG+AA vs GG	4	1.87 (1.07–3.27)	.03	R	0.00	84.4	−0.34	1.00
		AA vs GA+GG		3.72 (1.98–6.98)	.00	F	0.27	23.1	0.34	.73
		A vs G		1.86 (1.10–3.15)	.02	R	0.00	86.2	−0.34	1.00
		AA vs GG		4.25 (2.27–7.98)	.00	F	0.15	43.4	0.34	.73
		AG vs GG		1.71 (1.03–2.85)	.04	R	0.00	79.2	−0.34	1.00
	T1	GA+GG vs AA	4	2.12 (1.29–3.47)	.00	R	0.01	75.2	1.02	.31
		GG vs GA+AA		1.70 (0.65–4.45)	.28	R	0.00	87.3	0.34	.73
		G vs A		1.54 (0.90–2.65)	.12	R	0.00	90.1	1.70	.90
		GG vs AA		4.11 (2.56–5.90)	.00	F	0.03	67.2	1.02	.31
		GA vs AA		2.05 (1.37–3.08)	.00	R	0.06	60.0	0.34	.73
	ST+4	AC+CC vs AA	3	1.74 (1.37–2.39)	.00	F	0.37	0.0	1.04	.30
		CC vs AC+AA		1.81 (1.31–2.30)	.00	F	0.47	0.0	0.00	1.00
		C vs A		1.57 (1.32–1.87)	.00	F	0.62	0.0	0.00	1.00
		CC vs AA		2.19 (1.55–3.12)	.00	F	0.56	0.0	1.04	.30
		AC vs AA		1.59 (1.18–2.13)	.00	F	0.16	45.2	1.04	.30
ORMDL3	rs7216389	CT+TT vs CC		2.44 (1.68–3.55)	.00	F	0.91	0.00	0.34	.73
		TT vs TC+CC		1.80 (1.43–2.26)	.00	F	0.84	0.0	−0.34	1.00
		T vs C		1.89 (1.57–2.27)	.00	F	0.78	0.0	0.34	.73
		TT vs CC		2.92 (1.98–4.32)	.00	F	0.90	0.0	0.34	.73
		CT vs CC		1.76 (1.14–2.72)	.01	F	0.92	0.0	0.34	.73
VDR	ApaI	CC+CA vs AA	7	1.21 (0.60–2.41)	.60	R	0.00	84.1	0.30	.76
		CC vs AC+AA		0.87 (0.59–1.30)	.51	R	0.08	49.3	0.38	.71
		C vs A		1.11 (0.67–1.84)	.68	R	0.00	83.6	0.00	1.00

(*continued*)

Table 2

(continued).

Gene	Polymorphism	Comparison	N	Test of association		Test of heterogeneity			Begg test	
				OR (95% CI)	*P*	Model	Ph	I^2/%	z	*P*
		CC vs AA		0.93 (0.40–2.14)	.86	R	0.01	66.1	0.38	.71
		CA vs A		1.31 (0.65–2.61)	.45	R	0.00	81.5	0.00	1.00
	FokI	CC+CT vs TT	7	0.74 (0.57–0.96)	.02	F	0.14	37.5	0.30	.76
		CC vs TC+TT		0.76 (0.42–1.38)	.37	R	0.04	57.6	0.00	1.00
		C vs T		0.79 (0.59–1.07)	.13	R	0.02	61.6	0.30	.76
		CC vs TT		0.64 (0.30–1.40)	.27	R	0.01	66.1	0.00	1.00
		CT vs TT		0.79 (0.60–1.04)	.09	F	0.46	0.0	0.00	1.00
	BsmI	GG+GA vs AA	6	1.40 (0.59–3.36)	.45	F	0.00	74.4	0.38	.71
		GG vs GA+AA		0.82 (0.56–1.21)	.31	F	0.82	0.0	0.00	1.00
		G vs A		1.20 (0.59–2.47)	.61	R	0.00	78.0	0.75	.45
		GG vs AA		0.56 (0.32–0.97)	.39	F	0.22	33.5	0.00	1.00
		GA vs AA		1.52 (0.61–3.77)	.37	R	0.00	74.4	0.38	.71
	TaqI	TT+CT vs CC	5	0.86 (0.55–1.35)	.51	R	0.07	53.6	0.24	.81
		TT vs CC+CT		0.45 (0.29–0.71)	.00	F	0.19	37.2	0.34	.73
		T vs C		0.78 (0.64–0.96)	.02	F	0.24	26.7	0.24	.81
		TT vs CC		0.52 (0.32–0.85)	.01	F	0.36	7.2	0.34	.73
		CT vs CC		0.96 (0.55–1.66)	.87	R	0.02	64.3	0.24	.81
CTLA-4	+49 A/G	AG+AA vs GG	3	1.20 (0.50–2.89)	.68	R	0.03	71.1	0.00	1.00
		AA vs AG+GG		1.51 (0.40–5.70)	.54	R	0.02	73.8	0.00	1.00
		A vs G		1.22 (0.52–2.88)	.64	R	0.00	84.3	0.00	1.00
		AA vs GG		1.48 (0.30–7.40)	.63	R	0.01	78.8	0.00	1.00
		AG vs GG		1.28 (0.84–1.95)	.24	F	0.20	37.2	1.04	.30

95% CI = 95% confidence interval, F = fixed-effect model, N = number of studies, OR = odds ratio, R = random-effect model.

vs G: OR = 1.42, 95% CI: 1.05–1.91, *P* = .02), and heterozygous model (AG vs GG: OR = 1.70, 95% CI: 1.18–2.45, *P* = .01). However, no significant association was found in homozygous and recessive models. Additionally, subgroup analysis in Chinese population showed *IL-13* +2044G/A polymorphism increased the risk of pediatric asthma risk in allelic and dominant model (A vs G: OR = 1.70, 95% CI: 1.38–2.09, *P* = .00; GA+AA vs GG: OR = 2.29, 95% CI: 1.69–3.11, *P* = .00) (Table 3).

Table 3

Meta-analysis of the association between 18 polymorphisms of 7 genes and pediatric asthma risk in Chinese.

Gene	Polymorp-hism	Comparison	N	Test of association		Test of heterogeneity			Begg test	
				OR (95%CI)	*P*	Model	Ph	I^2/%	z	*P*
IL-13	+2044G/A	A vs G	4	1.70 (1.38–2.09)	.00	F	0.21	34.3	1.70	.09
		GA+AA vs GG		2.29 (1.69–3.11)	.00	F	0.19	36.7	0.34	.73
	−1112C/T	T vs C	4	1.12 (0.61–2.03)	.72	R	0.00	93.5	−0.24	1.00
		CT+TT vs CC		1.15 (0.58–2.30)	.69	R	0.00	92.5	−0.24	1.00
	+1923C/T	T vs C	3	1.06 (0.46–2.42)	.89	R	0.00	91.2	0.00	1.00
		CT+TT vs CC		1.13 (0.38–3.36)	.82	R	0.00	90.2	0.00	1.00
IL-4	−590C/T	T vs C	10	1.28 (1.01–1.61)	.04	R	0.00	75.1	0.18	.86
		CT+TT vs CC		1.73 (1.34–2.23)	.00	F	0.25	21.0	0.89	.37
ADRB2	−46 G /A	G vs A	7	0.96 (0.67–1.36)	.80	R	0.00	87.1	0.30	.76
		GA+GG vs AA		0.99 (0.65–1.51)	.96	R	0.00	80.1	0.00	1.00
	−79G/C	G vs C	3	1.05 (0.65–1.71)	.83	R	0.01	79.6	0.00	1.00
		GC+GG vs CC		1.12 (0.63–1.98)	.71	R	0.00	79.2	0.00	1.00
ADAM33	F+1	T vs C	3	1.02 (0.87–1.21)	.77	F	0.60	0.0	1.04	.30
		CT+TT vs CC		1.05 (0.85–1.31)	.63	F	0.89	0.0	1.04	.30
	V4	G vs C	3	0.74 (0.22–2.17)	.62	R	0.00	98.2	0.00	1.00
		GC+GG vs CC		0.72 (0.15–3.60)	.69	R	0.00	95.1	0.00	1.00
	S2	C vs G	4	0.80 (0.57–1.12)	.19	R	0.03	67.4	0.34	.74
		GC+CC vs GG		0.52 (0.17–1.60)	.26	R	0.01	76.0	0.34	.73
	T2	A vs G	3	2.26 (1.29–3.94)	.00	R	0.00	84.5	0.00	1.00
		AG+AA vs GG		2.29 (1.25–4.17)	.01	R	0.00	83.4	0.00	1.00
	T1	G vs A	3	1.72 (0.95–3.14)	.07	R	0.00	90.5	0.00	1.00
		GA+GG vs AA		2.92 (2.35–3.63)	.00	F	0.34	8.3	0.00	1.00
VDR	ApaI	C vs A	4	1.23 (0.40–3.77)	.72	R	0.00	90.5	1.02	.31
		CC+CA vs AA		1.28 (0.31–5.18)	.73	R	0.00	90.7	0.73	.46
	FokI	C vs T	3	0.88 (0.53–1.48)	.64	R	0.05	67.3	0.00	1.00
		CC+CT vs TT		0.79 (0.34–1.87)	.59	R	0.05	67.5	0.00	1.00
	BsmI	G vs A	5	2.09 (1.23–3.56)	.01	F	0.20	33.9	0.24	.81
		GG+GA vs AA		1.51 (0.99–2.31)	.06	R	0.11	46.8	0.73	.46

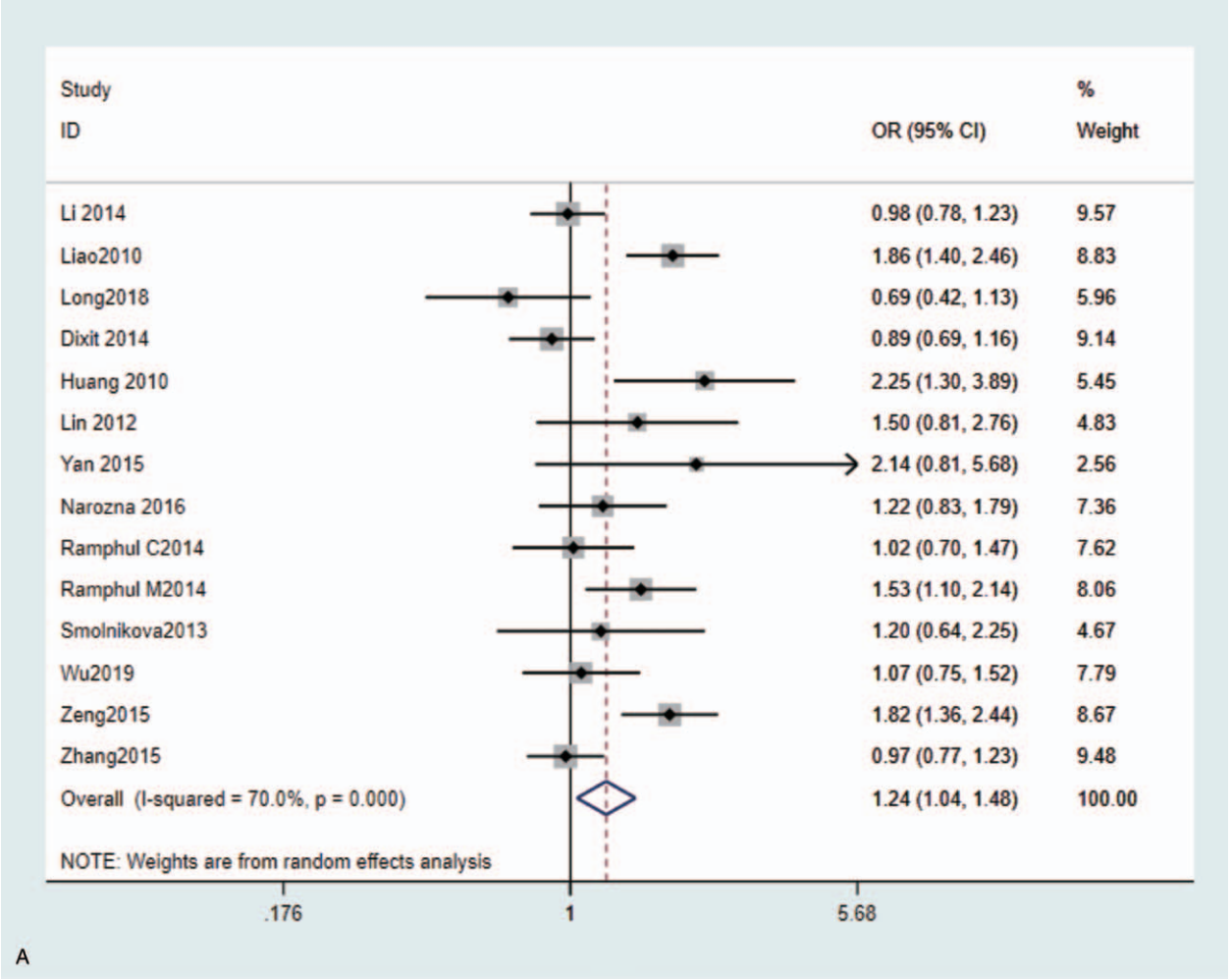

Figure 2. Forest plots of the association between IL-4 -590C/T polymorphism and childhood asthma risk. A: allelic model. B: homozygous model. C: heterozygous model. D: dominant model. E: recessive model.

3.2.2. IL-4 -590C/T polymorphism and pediatric asthma risk. Fourteen case-control studies including 2694 patients and 2994 controls were investigated. A significant increased risk of pediatric asthma risk was observed in all genetic models: allelic model (T vs C: OR = 1.24, 95% CI: 1.04–1.48, $P = .02$), homozygous model (TT vs CC: OR = 1.49, 95% CI: 1.05–2.12, $P = .03$), heterozygous model (CT vs CC: OR = 1.26, 95% CI: 1.04–1.52, $P = .02$), dominant model (CT+TT vs CC: OR = 1.37, 95% CI: 1.04–1.82, $P = .03$), and recessive model (TT vs CT+CC: OR = 1.23, 95% CI: 1.02–1.49, $P = .03$). Furthermore, the results of subgroup analysis in allelic and dominant model remarkably showed that IL-4 -590C/T polymorphism increased the susceptibility of asthma in the Chinese children (T vs C: OR = 1.28, 95% CI: 1.01–1.61, $P = .04$; CT+TT vs CC: OR = 1.73, 95% CI: 1.34–2.33, $P = .00$) (Table 3). Forest plots of the association between the IL-4 -590C/T polymorphism and asthma risk in dominant model were showed Fig. 2.

3.2.3. ADAM33 F+1 polymorphism and pediatric asthma risk. We analyzed 1340 cases and 959 controls from 5 case-control studies. The pooled results revealed that the CT+TT genotypes of *ADAM33* F+1 polymorphism was associated with an increased risk of pediatric asthma (CT+TT vs CC: OR = 1.24, 95% CI: 1.04–1.48, $P = .02$), while no significant association was observed in the allelic model (T vs C: OR = 1.33, 95% CI: 0.99–1.79, $P = .06$), homozygous model (TT vs CC: OR = 1.81, 95% CI: 0.95–3.44, $P = .07$), heterozygous model (TC vs CC: OR = 1.13, 95% CI: 0.93–1.36, $P = .21$), and recessive model (TT vs TC+CC: OR = 1.67, 95% CI: 0.94–2.97, $P = .08$). No evidence of significant association was found between ADAM33 F+1 polymorphism and pediatric asthma risk among Chinese (Table 3). In sensitivity analysis, F+1 polymorphism was significantly associated with childhood asthma after omitting one study (Qu2011)[40]: allelic model (T vs C: OR = 1.48, 95% CI: 1.14–1.92, $P = .003$), homozygous model (TT vs CC: OR = 2.34, 95% CI: 1.40–3.92, $P = .001$), dominant model (TC+TT vs CC: OR = 1.43, 95% CI: 1.13–1.80, $P = .003$), recessive model (TT vs TC+CC: OR = 2.31, 95% CI: 1.74–3.07, $P < .00001$).

3.2.4. ADAM33 T2 polymorphism and pediatric asthma risk. Four studies containing 928 cases and 967 controls were synthesized. The pooled results indicated that an increased risk of childhood asthma was observed in all genetic models: allelic model (A vs G: OR = 1.86, 95% CI: 1.10–3.15, $P = .02$),

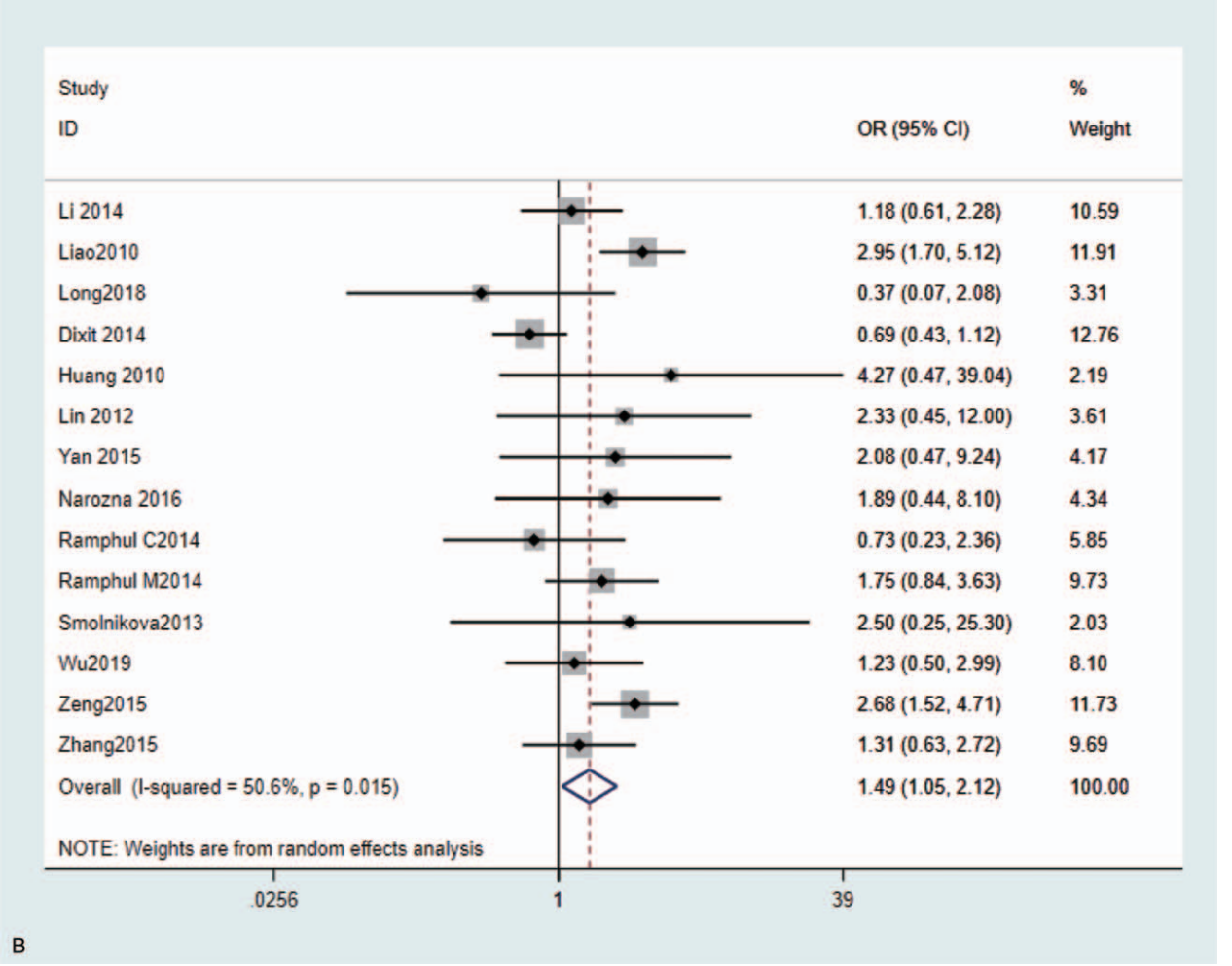

Figure 2. (Continued).

homozygous model (AA vs GG: OR = 4.25, 95% CI: 2.27–7.98, *P* = .00), heterozygous model (AG vs GG: OR = 1.71, 95% CI: 1.03–2.85, *P* = .04), dominant model (AG+AA vs GG: OR = 1.87, 95% CI: 1.07–3.27, *P* = .03), recessive model (AA vs GA+GG: OR = 3.72, 95% CI: 1.98–6.98, *P* = .00). Subgroup analysis showed that the allele A and AG+AA genotype was associated with increased asthma risk in Chinese children (A vs G: OR = 2.26, 95% CI: 1.29–3.94, *P* = .00; AG+AA vs GG: OR = 2.29, 95% CI: 1.25–4.17, *P* = 0.01).

3.2.5. ADAM33 T1 polymorphism and pediatric asthma risk. Four case-control studies included 938 cases and 928 controls. Our result detected a significant association in dominant model, homozygous model, heterozygous model (GA+GG vs AA: OR = 2.12, 95% CI: 1.29–3.47, *P* = .00; GG vs AA: OR = 4.11, 95% CI: 2.56–5.90, *P* = .00; GA vs AA: OR = 2.05, 95% CI: 1.37–3.08, *P* = .00). No association between *ADAM33* T1 polymorphism and asthma risk was found in allelic and recessive models. The results of subgroup analysis showed that GA+GG genotype may increase the risk of childhood asthma in Chinese (GA+GG vs AA: OR = 2.92, 95% CI: 2.35–3.63, *P* = .00) (Table 3).

3.2.6. ADAM33 ST+4 polymorphism and pediatric asthma risk. There were three studies with 716 cases and 435 controls concerning *ADAM33* ST+4 polymorphism and pediatric asthma risk. Our result showed that the correlation between ADAM33 ST+4 polymorphism and pediatric asthma risk was statistically significant in all genetic models under fixed-effects model: allelic model (G vs A: OR = 1.57, 95% CI: 1.32–1.87, *P* = .00), homozygous model (CC vs AA: OR = 2.19, 95% CI: 1.55–3.12, *P* = .00), heterozygous model (AC vs AA: OR = 1.59, 95% CI: 1.18–2.13, *P* = .002), dominant model (AC+CC vs AA: OR = 1.81, 95% CI: 1.37–2.39, *P* = .00), recessive model (CC vs AC +AA: OR = 1.74, 95% CI: 1.31–2.30, *P* = .00).

3.2.7. ORMDL3 rs7216389 polymorphism and pediatric asthma risk. We synthesized 4 studies including 626 cases and 607 controls. The pooled results revealed that *ORMDL3* rs7216389 polymorphism was associated with a high risk of childhood asthma in all genetic model: allelic model (T vs C: OR = 1.89, 95% CI: 1.57–2.27, *P* = .00), homozygous model (TT vs CC: OR = 2.92, 95% CI: 1.98–4.32, *P* = .00), heterozygous model (TC vs CC: OR = 1.76, 95% CI: 1.14–2.72, *P* = .01), dominant model (CT+TT vs CC: OR = 2.44, 95% CI: 1.68–3.55,

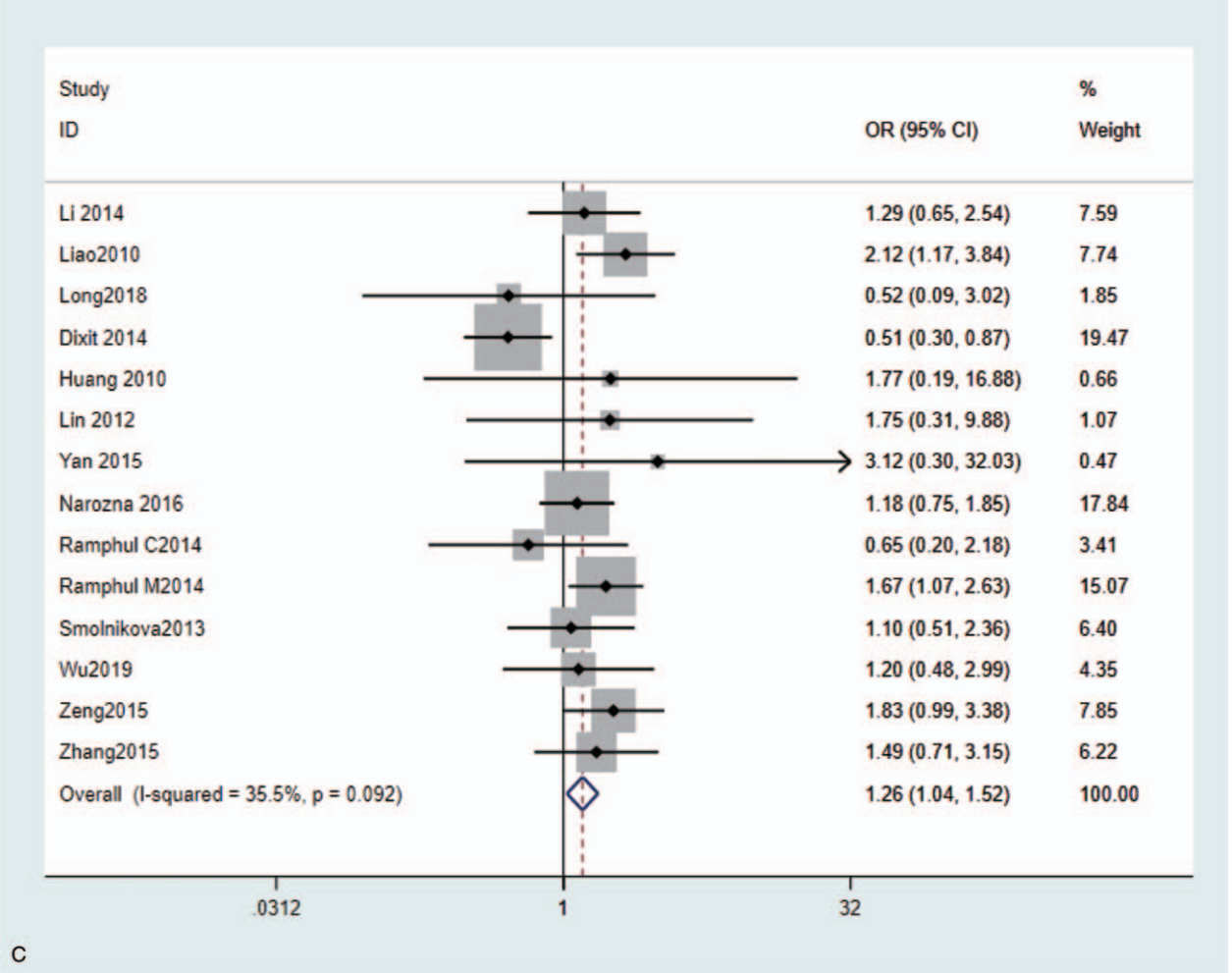

Figure 2. (Continued).

$P = .00$), recessive model (TT vs TC+CC: OR = 1.80, 95% CI: 1.43–2.26, $P = .00$).

3.2.8. VDR FokI polymorphism and pediatric asthma risk. Seven studies included 576 cases and 515 controls. Our results revealed that a significant association in dominant model (CT +CC vs TT: OR = 0.02, 95% CI: 0.57–0.96, $P = .02$). No association was found in other models. Subgroup analysis did not find a significant association in Chinese (Table 3).

3.2.9. VDR BsmI polymorphism and pediatric asthma risk. Six studies included 493 cases and 566 controls. No evidence of significant association between *VDR* BsmI gene polymorphism and asthma risk was observed in the pooled results. However, subgroup analysis showed VDR BsmI polymorphism was related with risk of childhood asthma in Chinese (G vs A: OR = 2.09, 95% CI: 1.23–3.56, $P = .01$) (Table 3).

3.2.10. VDR TaqI polymorphism and pediatric asthma risk. Five studies included 427 cases and 455 controls. The pooled results revealed a significant association in allelic model (T vs C: OR = 0.78, 95% CI: 0.64–0.96, $P = .02$), homozygous model (TT vs CC: OR = 0.52, 95% CI: 0.32–0.85, $P = .01$), recessive model (TT vs CT+CC: OR = 0.45, 95% CI: 0.29–0.71, $P = .00$). Since only 2 studies were conducted in China, we omitted the subgroup analysis.

No association between other 8 gene polymorphisms (*IL-13*-1112C/T, *IL-13*+1923 C/T, *ADRB2* -46 G /A, *ADRB2*-79G/C, *ADAM33* S2, *ADAM33* V4, *VDR* ApaI, *CTLA-4* +49 A/G) and susceptibility to pediatric asthma was found in total population and in Chinese.

3.3. Sensitivity analysis and publication bias

For each synthesized data, sensitivity analysis was performed by systematically omitted each study in turn and recalculated OR to assess the stability of the overall results. We detected that the pooled ORs of *IL-13*-1112C/T, *ADAM33* S2 polymorphisms were remarkable difference in fixed-effects model random-effects model and the result of *ADAM33* F+1 polymorphism was influenced by a single study (Qu, 2011). Sensitivity analysis of other polymorphisms showed that the pooled ORs were not significantly changed. Publication bias was estimated by funnel plot, Begg test, and Egger test (Table 2, Fig. 3). Except for the *ADRB2-46G/A* polymorphism (heterozygous model, $P = .01$), no evidence of publication bias was observed in other polymorphisms.

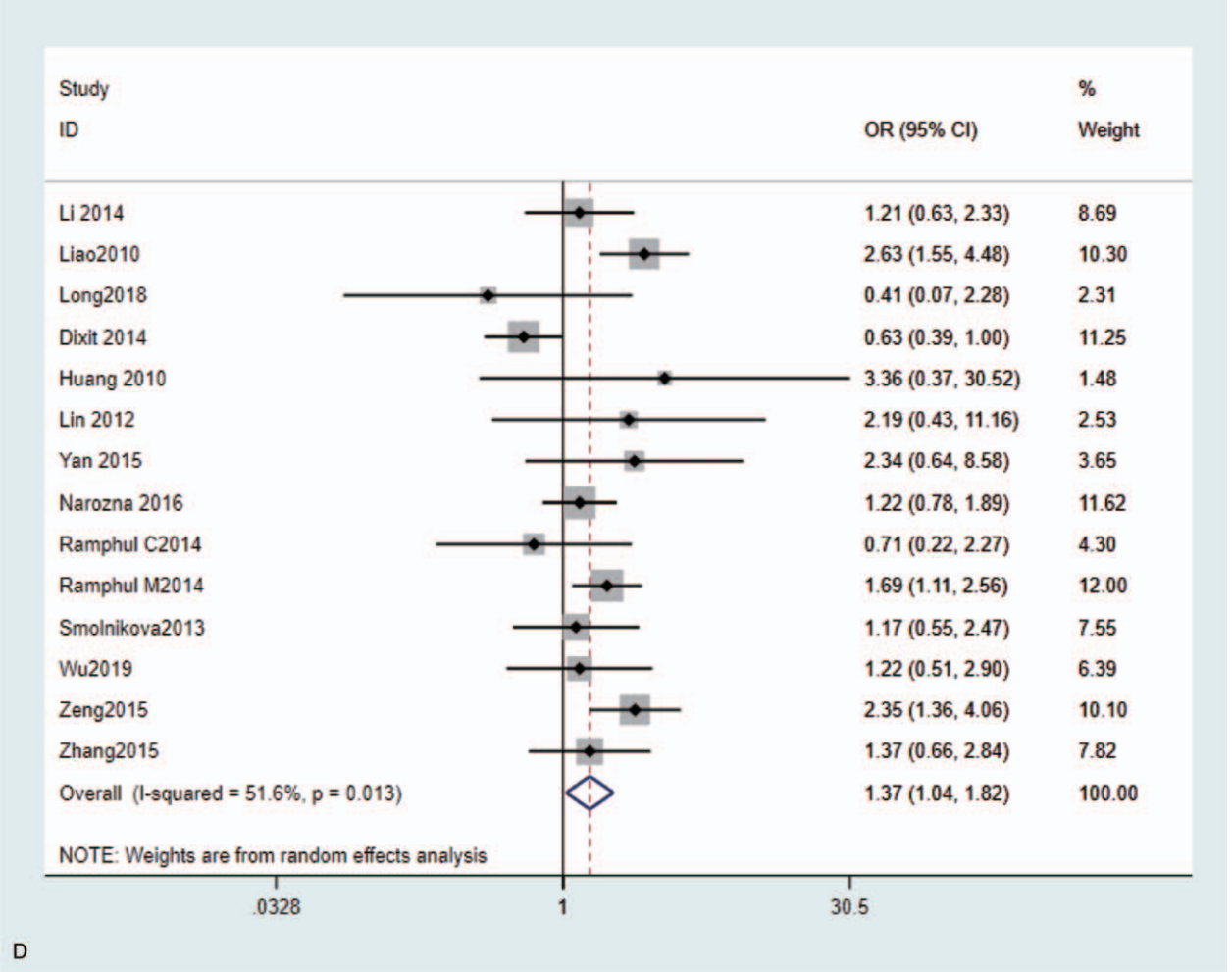

Figure 2. (Continued).

4. Discussion

Single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among people, which are closely associated with susceptibility to individual disease.[65] A number of studies have evaluated the potential association between some genetic polymorphisms and childhood asthma risk, however, the results of published studies appeared conflicts. Meta-analysis is a combination of comparable studies that increase the sample size to get more convincing results. The aim of this study was to analyze the strength of the association between partial polymorphisms and pediatric asthma. We final identified 18 polymorphisms in 7 genes. According to the characteristics of the included studies, we performed subgroup analysis of Chinese. We believe this is the first comprehensive genetic meta-analyses for pediatric asthma.

IL-13 and *IL-4*, with various biological activities, are associated with the inflammatory response and fibrosis in T helper 2 (Th2) inflammation and play an important role in the development of asthma.[66] Biologics targeting *IL-4* and *IL-13* are expected to be a promising treatment for asthma in the future.[67] Our results demonstrated that *IL-13* +2044G/A and *IL-4* -590C/T polymorphisms were associated with asthma risk in total populations and Chinese, while *IL-13* -1112C/T, +1923C/T polymorphisms were not associated with the risk of childhood asthma in any models. These results are partially consistent with the previous meta-analyses: Liu et al[68] and Mei and Qu[69] found that *IL-13*+2044A/G polymorphism was significantly associated with asthma risk in Asian children; Zhang et al[70] found that a strong association between the *IL-4* -590 C/T polymorphism and the risk of childhood asthma; a meta-analysis showed that *IL-4* -590 C/T polymorphism was associated with asthma risk among Chinese children. In line with these findings, we presume *IL-13*+2044 A/G and *IL-4* -590 C/T polymorphisms maybe potential susceptible predictor for pediatric asthma. However, some studies showed that *IL-13* -1112C/T and +1923C/T polymorphisms were correlated with increased risk of asthma in children,[68,69,71] which is different from our results. The reasons may be as follows: on the one hand, a significantly increased risk between *IL-13* -1112C/T and asthma risk was observed by Liu et al[68] in overall populations, but not in Asians or Chinese. The most of studies we included were conducted in China, which probably result from the different retrieval methods and inclusion criteria. Therefore, our results indicated *IL-13* -1112C/T polymorphism is not associated with childhood asthma in Chinese. On the other hand, the instability of the results may also be responsible for the differences. For *IL-13* +1923C/T

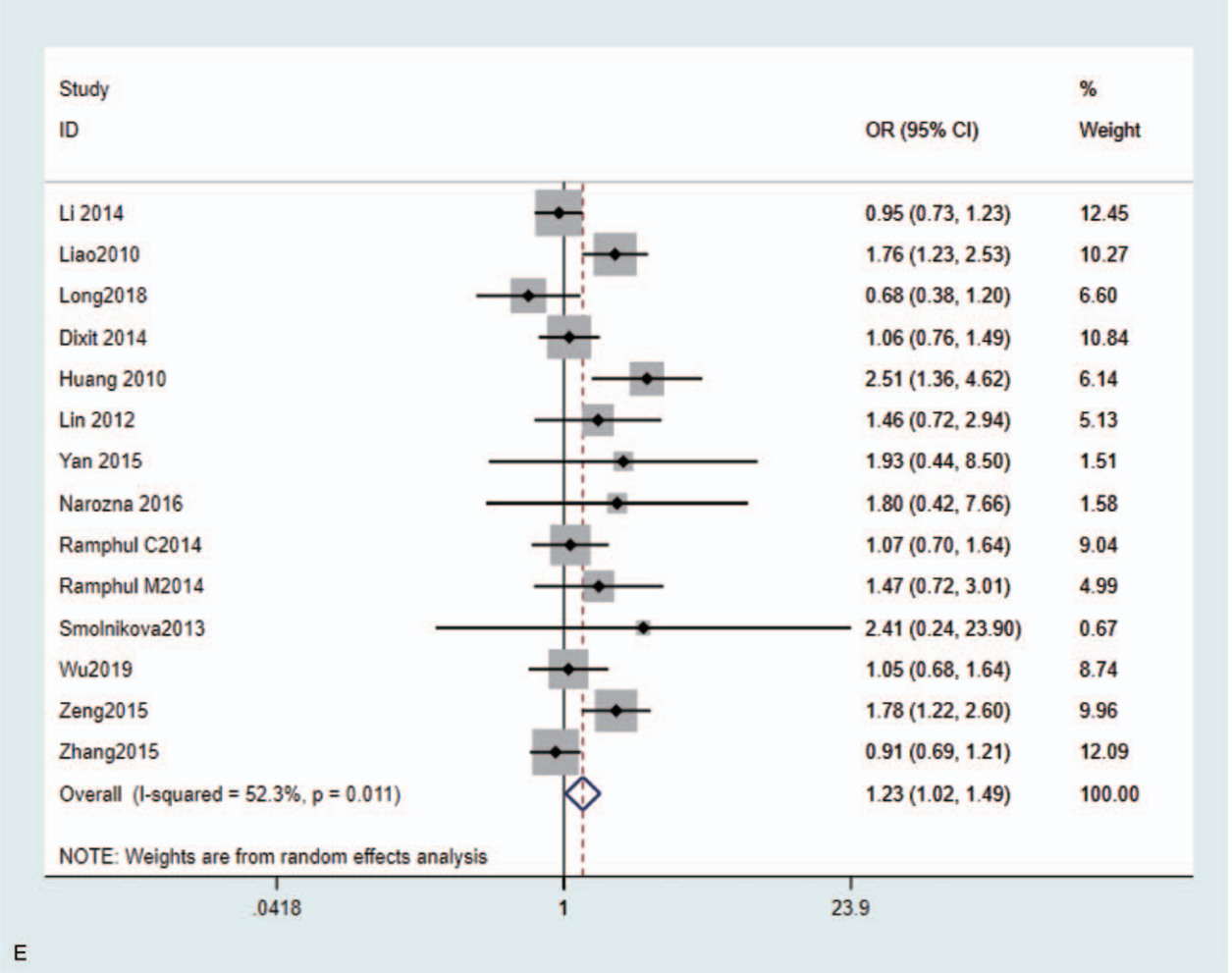

Figure 2. (Continued).

polymorphism, inconsistent results may be due to the small number of studies we included. More data are required to further investigate these associations.

ADAM33 gene has been identified as a susceptibility gene for asthma by positional cloning. This gene, localized on chromosome 20p13, is expressed in human lung fibroblasts and bronchial smooth muscle and plays an important role in airway remodeling and airway hyperresponsiveness in asthma.[72] Our results showed that ST+4, T1, T2, and F+1 polymorphisms of *ADAM33* gene were significantly associated with asthma risk among the overall children and Chinese, which mostly confirm previous studies. A meta-analysis performed by Li et al[73] showed that F+1, ST+4, and T2 polymorphisms were associated with pediatric asthma susceptibility, while S2 and V4 polymorphism were not associated with childhood asthma risk. Deng et al[74] found that T1 polymorphism was associated with asthma risk among Asian children. Therefore, *ADAM33* gene could be proposed as childhood asthma susceptible gene. In view of the result of *ADAM33*F+1 and S2 polymorphisms were unstable in sensitivity analysis, further researches need to be conducted.

Moffatt et al[75] identified *ORMDL3* located at 17q21.1 as a candidate gene for asthma and indicated SNP rs7216389 was the most correlated with asthma. The sequence around rs7216389 contains regions that are homologous to pro-inflammatory transcription factors. Our study and other studies[76–78] have shown a significant association between rs7216389 and susceptibility to childhood asthma.

VDR is associated with the occurrence and development of asthma and is an intranuclear macromolecule that mediates 1,25 (OH) D to exert biological effects. Serum 25 (OH) D level is negatively correlated with asthma, and vitamin D level has a significant relationship with lung function test outcomes in children with asthma.[79] In the past few years, researches on the correlation between *VDR* and asthma has focused on 4 SNPs: ApaI, FokI, BsmI, and TaqI. Our meta-analysis showed that FokI, and TaqI polymorphisms might contribute to childhood asthma susceptibility. There was some evidence of an association between BsmI polymorphism and childhood asthma in Chinese children. Zhao et al[80] suggested that ApaI, BsmI, and FokI polymorphisms might be associated with childhood asthma, while TaqI polymorphism be not. Further studies on larger samples are required to produce more accurate outcomes.

The *ADRB2* gene is abundantly expressed on bronchial smooth muscle and can activate β-adrenergic receptors, thereby regulating the constriction function of bronchial smooth muscle. The amino acid sequence of *ADRB2* gene can affect the function

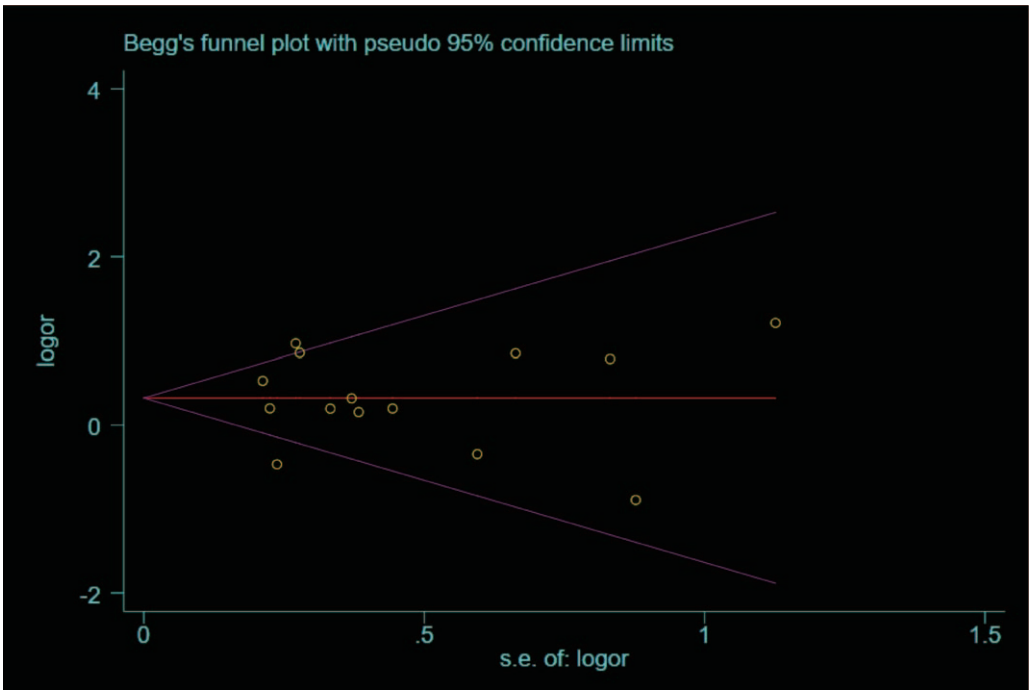

Figure 3. Begg funnel plot for publication bias in studies on IL-13 IL-4 -590C/T polymorphism and childhood asthma in overall populations (dominant model).

of β-adrenergic receptor.[81]*CTLA-4* can improve airway hyperresponsiveness and plays an important role in the pathogenesis of asthma.[82] Our results and Guo et al[83] found -46 G/A and -79G/C polymorphisms of *ADRB2* gene were not associated with a risk of childhood asthma. However, some studies[84,85] indicated that -79G/C polymorphism was associated with a reduced risk for the development of pediatric asthma. Some meta-analysis[86,87] found that *CTLA-4*+49 A/G polymorphism might be a risk factor for asthma susceptibility, which contradicts our results. However, since the 3 the studies on *CTLA-4*+49 A/G polymorphism we included are in conducted in Chinese population, we considered that *CTLA-4*+49 A/G polymorphism was no associated with Chinese Children.

Finally, several limitations to the present study should be considered. First, we searched the literature for the past 10 years, the numbers of published studies were insufficient for a comprehensive analysis, therefore, we only performed a subgroup analysis of Chinese population. Moreover, this study involves fewer ethnicities, and we will conduct a larger sample study in the future. Second, due to the lack of original individual data in the included literature, the unadjusted OR value was used for the combined analysis in this study, which may reduce the accuracy of the results. Third, certain studies have shown that multiple SNPs may act together to increase the risk of asthma. The association between SNP and asthma was influenced by region, ethnicity, age, sex, etc. The effect of individual genes on asthma is small, and many complex causes such as gene–gene interactions and gene–environment interactions contribute to asthma, which need more studies to determine.

In summary, this meta-analysis suggested that 9 gene polymorphisms (*IL-13* +2044G/A, *IL-4* -590C/T, *ADAM33* F +1, *ADAM33* T2, *ADAM33* T1, *ADAM33* ST+4,*ORMDL3* rs7216389, *VDR* FokI, *VDR* TaqI) might be risk factors for pediatric asthma susceptibility in overall populations. Furthermore, *IL-13* +2044G/A, *IL-4* -590C/T, *ADAM33* S2, *ADAM33* T2, *ADAM33* T1, *VDR* BsmI polymorphisms may cause an increased risk of asthma among Chinese children. However, due to some limitations, studies with larger samples are needed for further study in detail.

Author contributions

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