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Correlation study on β2-adrenergic receptor gene polymorphisms and asthma susceptibility: evidence based on 57 case-control studies

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Abstract. – OBJECTIVE: Previous studies have indicated that β2-adrenergic receptor (ADRB2) genetic polymorphism is related to the risk of asthma, but the results still have some controversy and uncertainty. To this end, the meta-analysis was performed, including all studies that can be used to assess the correlation between ADRB2 polymorphism and asthma susceptibility.

MATERIALS AND METHODS: The related papers on ADRB2 polymorphisms and asthma were systematically reviewed in databases of PubMed, EMBASE, Cochrane Library, and Wan-Fang, Odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were measured. The sensitivity analysis and publication bias were evaluated to investigate the correlation.

RESULTS: This meta-analysis included 57 papers in total involving 11,157 cases and 12,281 controls. Results illustrated that the C79G variant genotypes owned a reduced effect on asthma susceptibility (G *vs.* C: OR=0.94, *p*=0.037). In the age stratification analysis, C79G polymorphism owned a reduced effect on asthma risk for children (GG *vs.* CC: OR=0.69, *p*=0.002; GG *vs.* CC+CG: OR=0.65, *p*<0.001). Furthermore, in the ethnic stratification analysis, the C79G variant genotypes also owned a reduced effect on asthma in Asians (GG *vs.* CC: OR=0.80, *p*=0.027; GG *vs.* CC+CG: OR=0.81, *p*=0.02). Besides, for A46G polymorphism, the ethnic stratification analysis demonstrated that the A46G variant owned an increased effect on asthma susceptibility among Caucasians (G *vs.* A: OR=1.15, *p*=0.043). For C491T polymorphism, a considerable reduced effect was found between C491T and asthma susceptibility for children (CT *vs.* CC: OR=0.70, *p*=0.03). In the ethnic stratification analysis, the effect was also considerable in the Caucasian subjects.

CONCLUSIONS: The present meta-analysis demonstrated that C79G and C491T polymorphism may be a defensive factor for asthma, while A46G polymorphism may be a risk factor for asthma among the Caucasian population.

Key Words
Asthma, ADRB2, Polymorphism, Meta-analysis, Susceptibility.

Abbreviations

OR, odds ratios; CI, confidence intervals; ADRB2, β2-adrenergic receptors; NA, not available; HWE, Hardy-Weinberg equilibrium; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; F, fixed-effects model; R, random-effects model.

Introduction

As a common chronic inflammatory respiratory disease, asthma is characterized by the chronic airway hyper-responsiveness and intermittent airflow obstruction, leading to wheezing, chest tightness and shortness of breath[1]. In recent decades, the number of asthma patients has increased worldwide, placing heavy financial burdens to the family and society[2,3]. In etiology, environmental factors such as allergens, genetic variation, and air pollution, are interacted with various susceptibility genes, contributing to asthma diseases[4]. So, far more than 100 candidate genes and single nucleotide polymorphism are reported to be associated with asthma[5,6].

As the superfamily members of G protein-coupled receptors, β2-Adrenergic receptors (ADRB2) mediate the catecholamine-induced activation of the adenylate cyclase signaling cascade, which is a considerable mechanism in smooth muscle relaxation[7]. β2-Adrenergic receptors agonists are adopted as the premiere bronchodilator therapy to asthma because the activated ADRB2 leads to

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the enlargement of small airways. Chromosome 5q31-q32, which is mapped to ADRB2 receptor in the gene encoding, is considered to carry an asthma susceptibility, atopic or bronchial hyper-responsiveness locus[8-10].

Although previous research on the correlation between the A46G, C79G, and C491T of the ADRB2 gene and asthma susceptibility has been studied, results are controvertible and inconclusive[11-17]. It is hypothesized that inconsistent findings may have resulted from either insufficient sample size in a single study or genetic heterogeneity of ADRB2 genetic variants in different populations. Hence, a comprehensive meta-analysis was carried out through all the available studies to investigate the correlation between ADRB2 genetic polymorphisms and asthma susceptibility, concentrating on A46G, C79G, and C491T polymorphism.

Materials and Methods

Search Strategy

The literature search has been conducted in EMBASE, PubMed, Cochrane Library, and WanFang until August 2018. Keywords in electronic searches include terms of "asthma" or "allergic" or "atopy", "polymorphism*" or "variant*" or "mutation", "ADRB2" or "β2-AR" or "β2-adrenergic receptor". In addition, this analysis only focused on studies written in Chinese and English.

Exclusion and Inclusion Standards

Titles and abstracts were examined by two authors to identify the relevance in these studies. If case-control studies have been published in accordance with the following requirements, they have been involved in this meta-analysis: (1) case-control studies on human beings; (2) there are sufficient data for the evaluation of odds ratios (ORs) and 95% confidence interval (CI), and *p*-value; (3) the correlation between asthma susceptibility and ADRB2 genetic variants (A46G, C79G, and C491T) is accessed. Furthermore, (1) duplication of published articles; (2) review articles, letters, and case reports; (3) studies on case groups only, were exclusive in this meta-analysis.

Data Extraction

Data from all available studies were carefully concluded by two independent investigators. The data included the following items: (1) frequency of controls and cases, involved genes and HWE status in controls; (2) detailed information about the published papers, including the publication date, the first author name, age group of the case, country, and ethnicity. If there was a divergence between two investigators, the issue was discussed to reach an agreement.

Statistical Analysis

The correlation strength between asthma susceptibility and ADRB2 genetic variants (A46G, C79G, and C491T) was evaluated by ORs with 95% CI. Stratified analyses were performed based on ethnicity, and age group in cases. The pooled ORs were measured for the following models, namely allelic, dominant, homozygote, recessive, and heterozygote. The Q-test and I^2 statistics were adopted for the quantification of statistical heterogeneity. The random-effect framework was performed if there was a significant heterogeneity ($p<0.05$ or $I^2>50\%$)[18]; or, the fixed effects framework was utilized[19]. The stability of the results was evaluated in the sensitivity analysis by eliminating each eligible study every time. Egger's and Begg's tests ($p<0.05$ was considered significant) were also involved to evaluate the potential publication bias. STATA 15.0 (StataCorp LP, College Station, TX, USA) was used to conduct all the analyses. $p<0.05$ in the two-tail test suggested that the difference had statistical significance.

Results

Collection of Qualified Studies

Figure 1 reveals the process of the qualified study collection. Based on the mentioned searching method, 1056 potential publications were identified from the initial search through PubMed, EMBASE, Cochrane Library, and Wanfang Databases. After removing duplicate papers, titles and abstracts of the remained papers were evaluated based on exclusion and inclusion standards. Finally, 163 studies were left for the following research. With the exclusion of ineligible studies, 57 case-control studies were read, involving 11,157 cases and 12,281 controls[11-14,16,20-70]. The distribution of the ADRB2 gene polymorphism (A46G, C79G, and C491T) in control was inconsistent with HWE in three studies[30,68,71]. The characteristics of each study are shown in Table I.

Correlation of A46G Polymorphism With Asthma Risk

A meta-analysis of the A46G polymorphism comprised 55 studies with 10,621 asthma patients and 12,106 controls. In the overall analysis, no considerable correlation was proved between

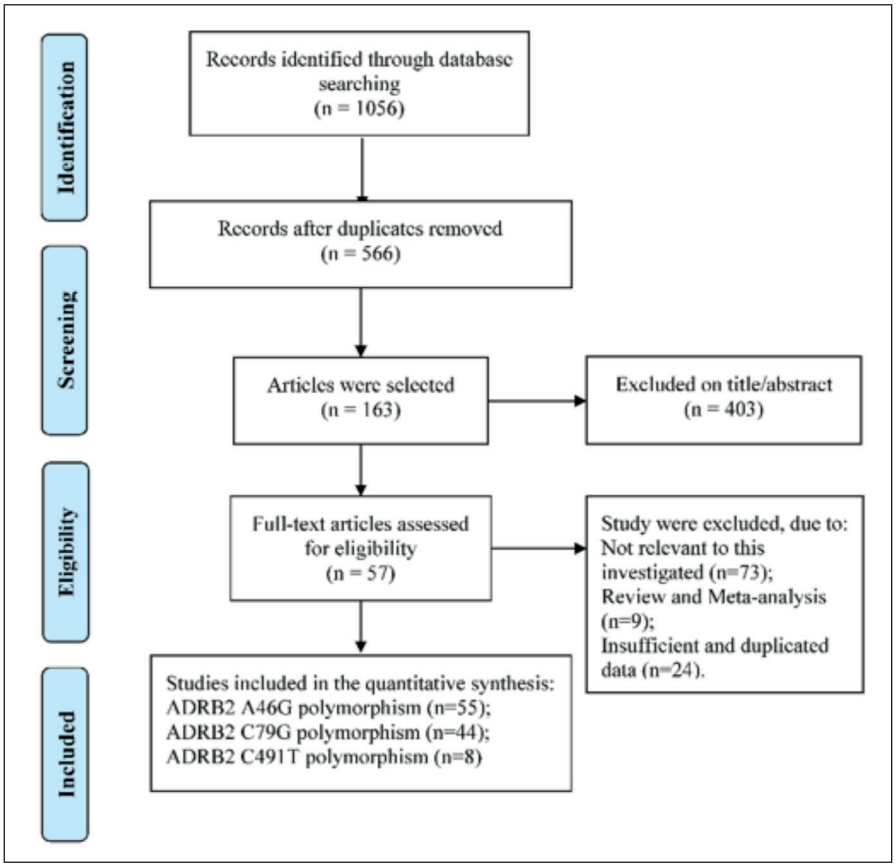

Figure 1. Flow chart of study selection in this meta-analysis.

asthma susceptibility and the A46G polymorphism. In the age stratification analysis, no considerable correlation was discovered between the A46G polymorphism and asthma susceptibility under any model. While in the ethnic stratification analysis, a statistically considerable correlation was proved in Caucasians (G *vs.* A: OR=1.15, p=0.043), as shown in Table II and Figure 2.

Correlation of C79G Polymorphism With Asthma Risk

Totally, 44 studies with 7800 asthma patients and 9214 control subjects were involved to evaluate the correlation between asthma susceptibility and C79G genetic polymorphism. A statistically considerable correlation was detected between C79G and asthma susceptibility in the allelic model (G *vs.* C: OR=0.94, p=0.037). The subgroup analysis of age demonstrated that there was a considerable reduced asthma risk for children (GG *vs.* CC: OR=0.70, 95% CI=0.55-0.90, p=0.005; GG *vs.* CC+CG: OR=0.65, 95% CI=0.52-0.82, p<0.001), as shown in Figures 3 and 4. To further assess the correlation between the C79G and asthma risk, an ethnic subgroup analysis was conducted. C79G polymorphism owned a significantly reduced effect on asthma susceptibility in Asians (GG *vs.* CC: OR=0.80, 95% CI=0.66-0.98, p=0.027; GG *vs.* CC+CG: OR=0.80, 95% CI=0.66-0.97, p=0.02), as shown in Figures 5 and 6. Results are shown in Table III.

Correlation of C491T Polymorphism With Asthma Risk

The correlation between the C491T polymorphism and asthma susceptibility was measured in eight studies containing 2038 asthma patients and 3634 control subjects. No considerable correlation was observed between the C491T polymorphism and asthma susceptibility in any comparison of genetic models in the population, as shown in Table IV. The age stratification analysis suggested that a considerable correlation existed between C491T polymorphism and asthma susceptibility for children (CT *vs.* CC: OR=0.67, 95% CI=0.51-0.89, p=0.005). Besides, the ethnic stratification analysis revealed that, in Caucasian subjects, a statistically considerable correlation of C491T and asthma risk existed in heterozygous models (CT *vs.* CC: OR=0.52, 95% CI=0.29-0.94, p=0.03).

Table I. Main characteristics of studies selected in the meta-analysis.

Author	Year	Country	Ethnicity	Age group	Case	Control	Genotyping methods	HWE
Alghobashy et al[11]	2018	Egypt	Caucasians	Children	104	52	PCR–RFLP	0.010
Ramphul et al[20]	2015	India	Asians	Children	191	188	RT-PCR	0.695
Hua et al1[3]	2016	China	Asians	Children	1000	1000	TaqMan	0.666
Liu et al[22]	2014	China	Asians	Adult	429	483	PCR	0.943
Martinez-Aguilar et al[23]	2015	Mexico	Caucasians	Children	429	430	TaqMan	0.928
Saadi et al1[2]	2013	India	Asians	Mixed	150	150	PCR	0.217
Larocca et al[14]	2013	Venezuela	NA	Adult	105	100	PCR-RFLP	0.018
Chung et al[24]	2014	Australia	Caucasians	Adult	689	2296	PCR	0.494
Telleria et al[25]	2005	Spain	Caucasians	Mixed	80	64	PCR	0.454
Hakonarson et al[26]	2001	Iceland	Caucasians	Mixed	323	181	PCR	0.677
Almomani et al[27]	2016	Jordan	Asians	Adult	248	241	MassARRAY	0.797
Llanes et al[28]	2009	Spain	Caucasians	Adult	108	50	PCR-RFLP	0.813
Kohyama et al[29]	2011	Japan	Asians	Adult	300	100	Sequencing	0.677
Bandaru et al[30]	2015	India	Asians	Adult	398	456	ARMS-PCR	<0.001
Shah et al[31]	2015	India	Asians	Adult	112	127	TaqMan	0.174
Santillan et al[32]	2003	México	Caucasians	Adult	303	604	PCR-RFLP	0.070
Shachor et al[33]	2003	Israel	Asians	Mixed	66	113	PCR-RFLP	0.433
Munakata et al[34]	2006	Japan	Asians	NA	46	100	Sequencing	0.580
Qiu et al[35]	2010	China	Asians	Adult	201	276	PCR	0.924
Li et al[36]	2009	China	Asians	Children	192	192	PCR-RFLP	0.563
Ye et al[37]	2010	Korea	Asians	Adult	101	322	Sequencing	0.441
Fu et al[71]	2011	China	Asians	Adult	238	265	PCR	<0.001
Bhatnagar et al[39]	2005	India	Asians	Adult	101	55	PCR	0.498
Reihsaus et al[40]	1993	USA	Caucasians	Adult	51	56	PCR	0.042
Tian et al[41]	2016	China	Asians	Children	298	304	PCR	0.687
Kotani et al[42]	1999	Japan	Asians	Adult	117	103	PCR	0.201
Wang et al[43]	2009	China	Asians	Children	442	510	RT-PCR	0.837
Chan et al[44]	2008	China	Asians	Children	295	173	PCR-RFLP	0.597
Szczepankiewicz et al[45]	2009	Poland	Caucasians	Children	113	121	PCR-RFLP	0.304

Continued

Table I (Continued). Main characteristics of studies selected in the meta-analysis.

Author	Year	Country	Ethnicity	Age group	Case	Control	Genotyping methods	HWE
Binaei et al[46]	2003	USA	Caucasians	NA	38	155	PCR-RFLP	0.132
Lin et al[47]	2003	China	Asians	Children	80	69	PCR	0.031
Leung et al[48]	2002	China	Asians	Children	76	70	PCR	0.483
Salama et al[49]	2011	Egypt	Caucasians	Children	40	19	PCR-RFLP	0.693
Al-Rubaish et al[50]	2011	Saudi Arabia	Asians	Children	73	85	PCR-RFLP	0.012
Birbian et al[69]	2012	India	Asians	Adult	410	414	PCR-RFLP	0.878
Gao et al[58]	2002	China	Asians	Adult	125	96	PCR-RFLP	0.051
Isaza et al[67]	2012	Colombia	NA	Children	109	137	RT-PCR	0.004
Akkary et al[66]	2012	Egypt	Caucasians	Adult	60	60	PCR-RFLP	0.452
Zhang et al[55]	2008	China	Asians	Children	217	50	PCR	0.814
Liao et al[38]	2001	China	Asians	Children	50	100	PCR-RFLP	0.577
Wang et al[65]	2001	China	Asians	Adult	128	136	AS-PCR	0.499
Guo et al[16]	2016	China	Asians	Children	340	340	PCR	0.010
Ramphul et al[21]	2013	China	Asians	Children	192	192	RT-PCR	0.061
Karam et al[64]	2013	Egypt	Caucasians	Children	90	110	PCR	0.770
Cui et al[63]	2013	China	Asians	Adult	72	60	PCR	0.019
He et al[62]	2007	China	Asians	Adult	171	148	MassARRAY	0.249
Feng et al[61]	2012	China	Asians	Adult	74	39	AS- PCR	0.006
Liu et al[60]	2004	China	Asians	Adult	120	120	Sequencing	0.044
Tuerxun et al[59]	2009	China	Asians	Adult	76	89	SSP- PCR	0.014
Petrovic-Stanojevic et al[68]	2007	Serbia	NA	Adult	171	101	PCR-RFLP	<0.001
Zheng et al[57]	2014	China	Asians	Children	198	110	PCR-RFLP	0.966
Xie et al[56]	2012	China	Asians	Children	57	62	SSP- PCR	0.220
Gao et al[53]	2008	China	Asians	Mixed	58	89	AS-PCR	0.450
Yang et al[52]	2000	China	Asians	Children	212	52	Sequencing	0.880
Tatarskyy et al[70]	2011	Ukraine	NA	Children	58	89	PCR-RFLP	0.035
Holloway et al[51]	2000	New Zealand	Caucasians	Adult	154	91	PCR-RFLP	0.303
Chiang et al[54]	2012	China	Asians	Adult	476	115	PCR-RFLP	0.384

HWE: Hardy-Weinberg equilibrium; PCR: Polymerase chain reaction; RFLP: Restriction fragment length polymorphism.

Table II. Meta-analysis of the association between A46G polymorphism and asthma susceptibility.

Comparison	Subgroup	Studies	Heterogeneity test		Association test		Model	Publication bias
			p-value	I^2 (%)	OR (95%CI)	*p*-value		Egger
G vs. A	Overall	55	0.000	65.7	1.00 (0.93-1.07)	0.914	R	0.059
	Children	22	0.000	76.5	1.02 (0.89-1.17)	0.788	R	
	Adult	26	0.002	50.8	1.00 (0.92-1.09)	0.916	R	
	Caucasian	14	0.010	52.8	**1.15 (1.00-1.31)**	**0.043**	R	
	Asian	38	0.000	65.6	0.94 (0.86-1.02)	0.147	R	
GA vs. AA	Overall	55	0.000	62.9	1.02 (0.91-1.15)	0.724	R	0.003
	Children	22	0.000	72.7	1.13 (0.92-1.39)	0.246	R	
	Adult	26	0.002	49.6	0.98 (0.85-1.14)	0.823	R	
	Caucasian	14	0.001	63.3	1.22 (0.93-1.61)	0.144	R	
	Asian	38	0.000	60.1	0.94 (0.83-1.08)	0.408	R	
GG vs. AA	Overall	55	0.000	58.3	0.96 (0.84-1.10)	0.597	R	0.079
	Children	22	0.000	68.2	0.99 (0.78-1.26)	0.955	R	
	Adult	26	0.003	48.9	0.98 (0.82-1.16)	0.792	R	
	Caucasian	14	0.012	53.3	1.17 (1.02-1.34)	0.066	R	
	Asian	38	0.000	66.3	0.94 (0.86-1.03)	0.109	R	
GG+AG vs. AA	Overall	55	0.000	64.5	1.01 (0.90-1.14)	0.810	R	0.066
	Children	22	0.000	76.2	1.11 (0.90-1.36)	0.322	R	
	Adult	26	0.007	45.1	0.99 (0.87-1.13)	0.866	R	
	Caucasian	14	0.002	59.2	1.27 (1.00-1.61)	0.051	R	
	Asian	38	0.000	62.2	1.00 (0.89-1.12)	0.229	R	
GG vs. AA+AG	Overall	55	0.000	61.3	0.96 (0.86-1.08)	0.538	R	0.361
	Children	22	0.000	58.8	0.92 (0.77-1.10)	0.373	R	
	Adult	26	0.000	64.0	1.02 (0.87-1.21)	0.783	R	
	Caucasian	14	0.092	35.4	1.13 (0.95-1.35)	0.168	R	
	Asian	38	0.000	63.4	0.97 (0.85-1.09)	0.232	R	

OR: Odds ratio; CI: Confidence interval; F: Fixed-effects model; R: Random-effects model; NA: Not available

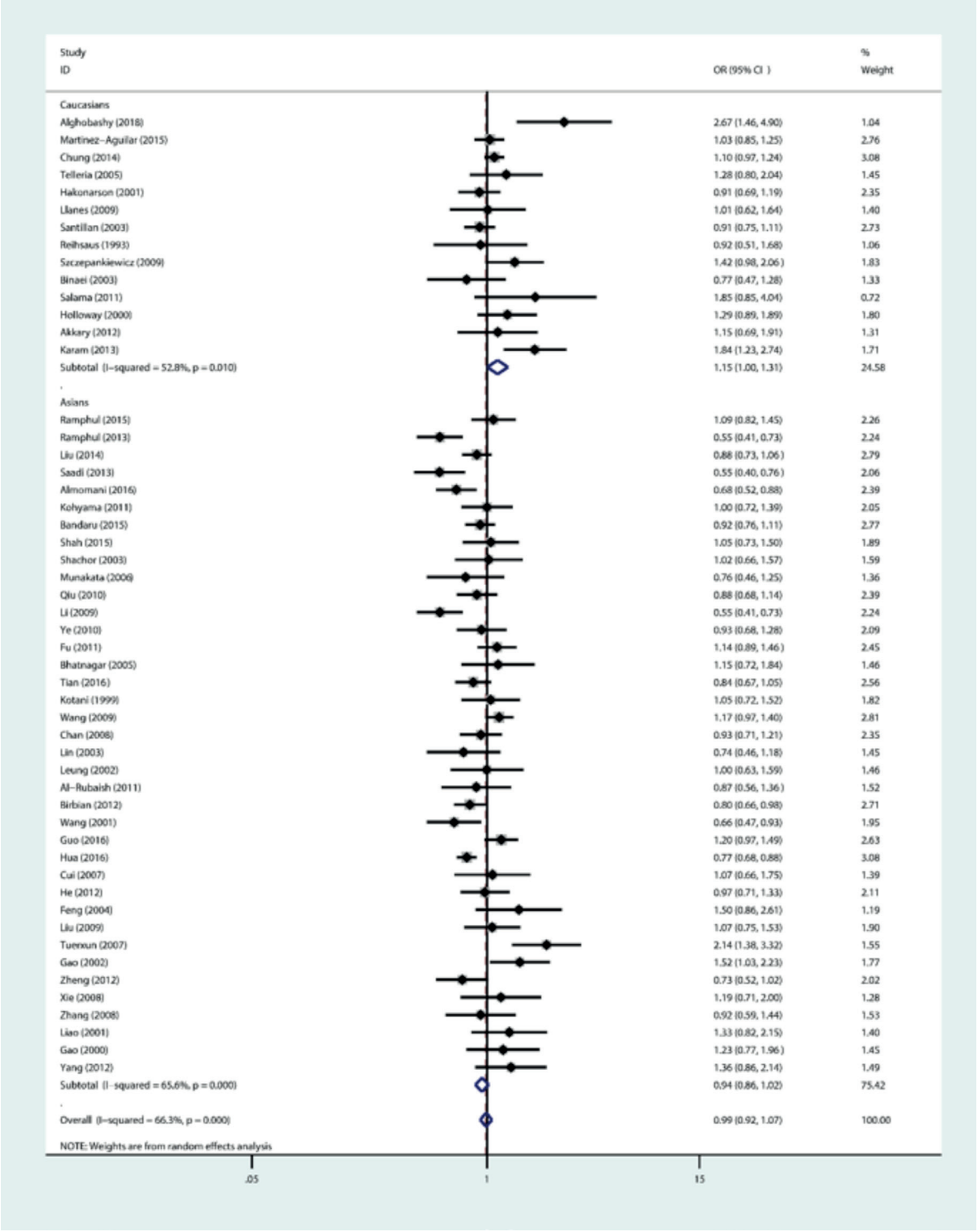

Figure 2. Forest plot on the association between the A46G polymorphism and asthma susceptibility in Caucasians.

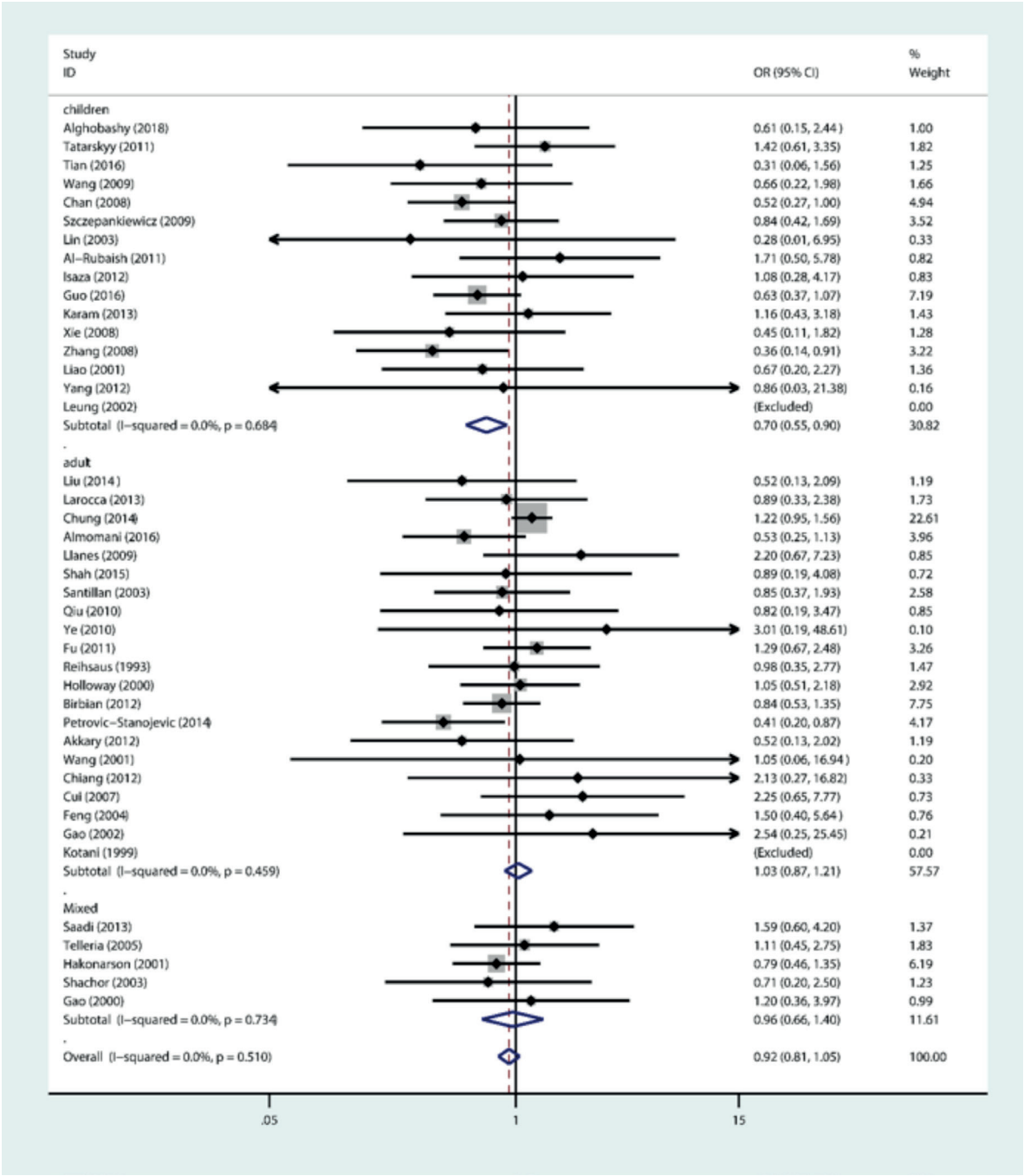

Figure 3. Forest plot on the association between the C79G polymorphism and asthma susceptibility stratified by age group in the co-dominant model.

Sensitivity Analysis and Publication Bias

Sensitivity analysis was performed by excluding any study in sequence. The results showed that these conclusions were accurate and reliable in all genetic models when removing studies that deviated from HWE, as shown in Figure 7. The potential bias of the publication was examined by Begg's and Egger's test[72,73]. As shown in Figure 8, the symmetrical shape of the funnel plot indicated that the publication bias was excluded in any genetic model, except for the co-dominant model of A46G polymorphism. Results are shown in Table II-IV.

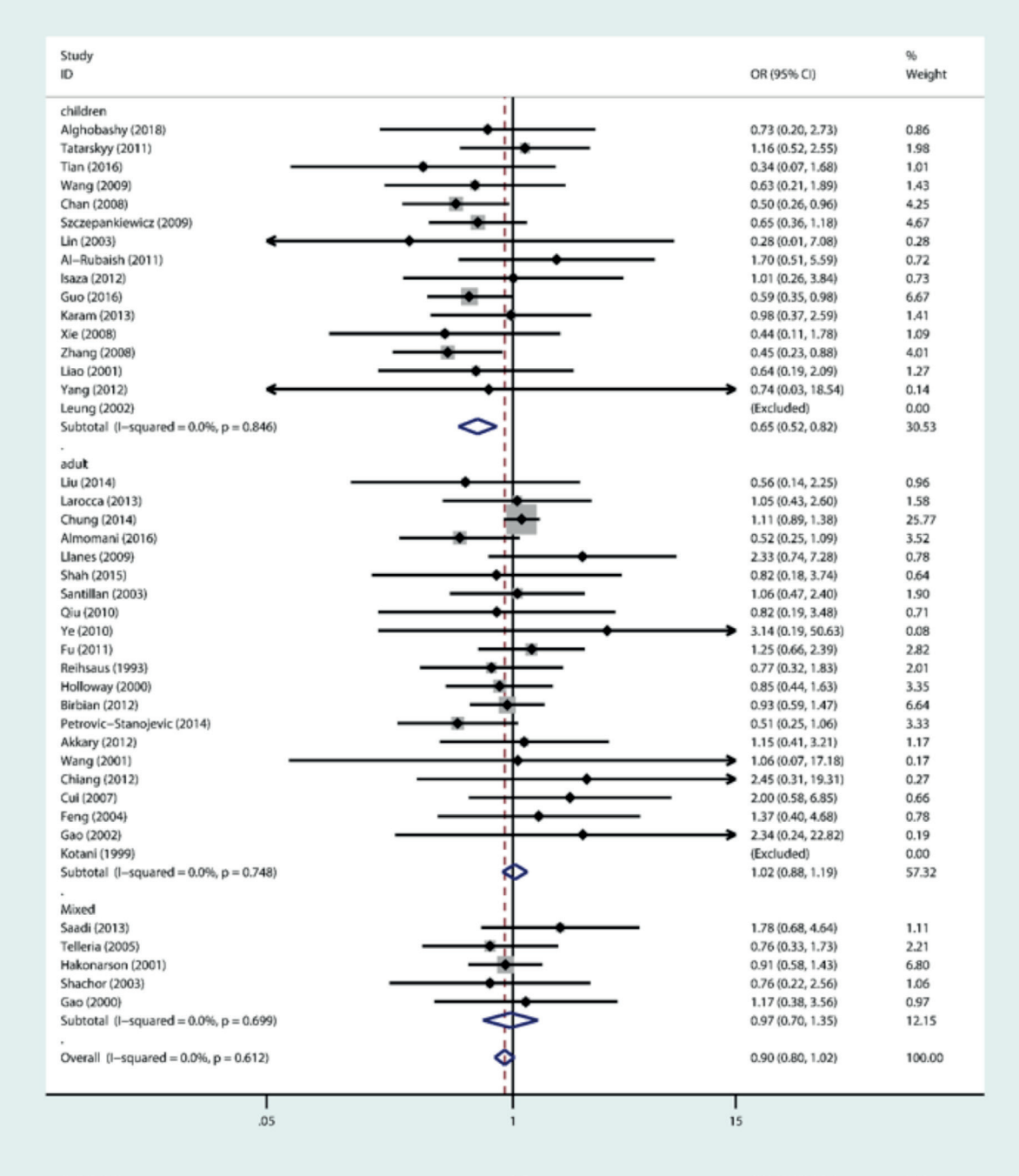

Figure 4. Forest plot on the association between the C79G polymorphism and asthma susceptibility stratified by age group in the recessive model.ww

Discussion

Asthma is a common allergic respiratory disease caused by an intricate interplay of genetic and environmental factors. Several high-risk environmental factors have been recognized, and it has also ben found that several genes are correlated with pathological regulation of asthma[74-76]. ADRB2, which encodes the β2-adrenergic receptor, is a possible risk gene for asthma. This receptor lives in airway smooth muscle cells, resulting in the bronchiectasis caused by interactions between the receptor and the complete set of molecules such as hormones and small molecule compounds[77].

Table III. Meta-analysis of the association between C79G polymorphism and asthma susceptibility.

Comparison	Subgroup	Studies	Heterogeneity test		Association test		Model	Publication bias
			p-value	I^2 (%)	OR (95%CI)	*p*-value		Egger
G vs. A	Overall	44	0.000	47.8	**0.94 (0.89-1.00)**	**0.037**	F	0.954
	Children	16	0.101	32.7	0.92 (0.80-1.06)	0.232	R	
	Adult	21	0.000	65.3	0.92 (0.80-1.06)	0.248	R	
	Caucasian	12	0.009	56.3	0.96 (0.82-1.12)	0.622	R	
	Asian	28	0.089	27.6	0.92 (0.83-1.01)	0.082	R	
GA vs. AA	Overall	44	0.000	55.0	0.97 (0.85-1.10)	0.609	R	0.464
	Children	16	0.300	13.4	1.11 (0.95-1.31)	0.183	R	
	Adult	21	0.000	68.0	0.88 (0.72-1.07)	0.193	R	
	Caucasian	12	0.000	74.7	1.04 (0.76-1.41)	0.823	R	
	Asian	28	0.090	27.5	0.95 (0.84-1.08)	0.429	R	
GG vs. AA	Overall	44	0.533	0	0.92 (0.81-1.05)	0.214	F	0.595
	Children	16	0.684	0	**0.70 (0.55-0.90)**	**0.005**	F	
	Adult	21	0.459	0	1.03 (0.87-1.21)	0.728	F	
	Caucasian	12	0.846	0	1.07 (0.89-1.28)	0.491	F	
	Asian	28	0.557	0	**0.80 (0.66-0.98)**	**0.027**	F	
GG+AG vs. AA	Overall	44	0.000	52.1	0.94 (0.84-1.06)	0.313	R	0.565
	Children	16	0.221	20.4	1.01 (0.86-1.18)	0.903	R	
	Adult	21	0.000	68.4	0.89 (0.74-1.08)	0.237	R	
	Caucasian	12	0.000	70.8	1.00 (0.76-1.31)	0.994	R	
	Asian	28	0.150	21.9	0.93 (0.83-1.04)	0.182	R	
GG vs. AA+AG	Overall	44	0.627	0	0.90 (0.80-1.02)	0.095	F	0.784
	Children	16	0.748	0	**1.02 (0.88-1.19)**	**0.000**	R	
	Adult	21	0.000	64.0	1.02 (0.87-1.21)	0.765	R	
	Caucasian	12	0.823	0	1.00 (0.85-1.17)	0.987	F	
	Asian	28	0.481	0	**0.80 (0.66-0.97)**	**0.020**	F	

OR: Odds ratio; CI: Confidence interval; F: Fixed-effects model; R: Random-effects model; NA: Not available.

Table IV. Meta-analysis of the association between C491T polymorphism and asthma susceptibility.

Comparison	Subgroup	Studies	Heterogeneity test		Association test		Model	Publication bias
			p-value	I^2 (%)	OR (95%CI)	*p*-value		Egger
T vs. C	Overall	8	0.317	14.8	0.97 (0.82-1.14)	0.705	F	0.066
	Children	2	0.831	0	0.54 (0.12-2.38)	0.415	R	
	Adult	4	0.138	45.6	0.95 (0.79-1.13)	0.533	R	
	Caucasian	2	0.310	3.1	0.68 (0.40-1.14)	0.142	R	
	Asian	6	0.401	0.9	1.01 (0.85-1.21)	0.880	R	
TC vs. CC	Overall	8	0.008	65.6	0.86 (0.41-1.77)	0.678	R	0.893
	Children	2	0.879	0	0.93 (0.17-5.01)	0.928	R	
	Adult	4	0.242	28.3	**0.67 (0.51-0.89)**	**0.005**	R	
	Caucasian	2	0.397	0	**0.52 (0.29-0.94)**	**0.030**	R	
	Asian	6	0.007	71.3	1.06 (0.34-3.31)	0.918	R	
TT vs. CC	Overall	8	0.293	19.4	1.07 (0.77-1.48)	0.686	F	0.606
	Children	2	NA	NA	0.33 (0.01-8.19)	0.500	F	
	Adult	4	0.074	68.7	2.69 (0.20-36.25)	0.455	F	
	Caucasian	2	NA	NA	16.5 (0.8-345.02)	0.070	F	
	Asian	6	0.770	0	1.02 (0.73-1.41)	0.914	F	
TT+CT vs. CC	Overall	8	0.000	52.1	0.94 (0.84-1.06)	0.691	R	0.683
	Children	2	0.221	20.4	1.01 (0.86-1.18)	0.631	R	
	Adult	4	0.000	68.4	**0.89 (0.74-1.08)**	**0.048**	R	
	Caucasian	2	0.000	70.8	1.00 (0.76-1.31)	0.074	R	
	Asian	6	0.150	21.9	0.93 (0.83-1.04)	0.947	R	
TT vs. CC+CT	Overall	4	0.063	58.8	0.94 (0.32-2.81)	0.913	F	0.874
	Children	2	NA	NA	0.33 (0.01-8.19)	0.067	R	
	Adult	4	0.087	66.0	2.84 (0.24-33.4)	0.407	R	
	Caucasian	2	NA	NA	16.8 (0.81-350.3)	0.069	F	
	Asian	6	0.123	52.2	0.73 (0.29-1.86)	0.510	F	

OR: Odds ratio; CI: Confidence interval; F: Fixed-effects model; R: Random-effects model; NA: Not available.

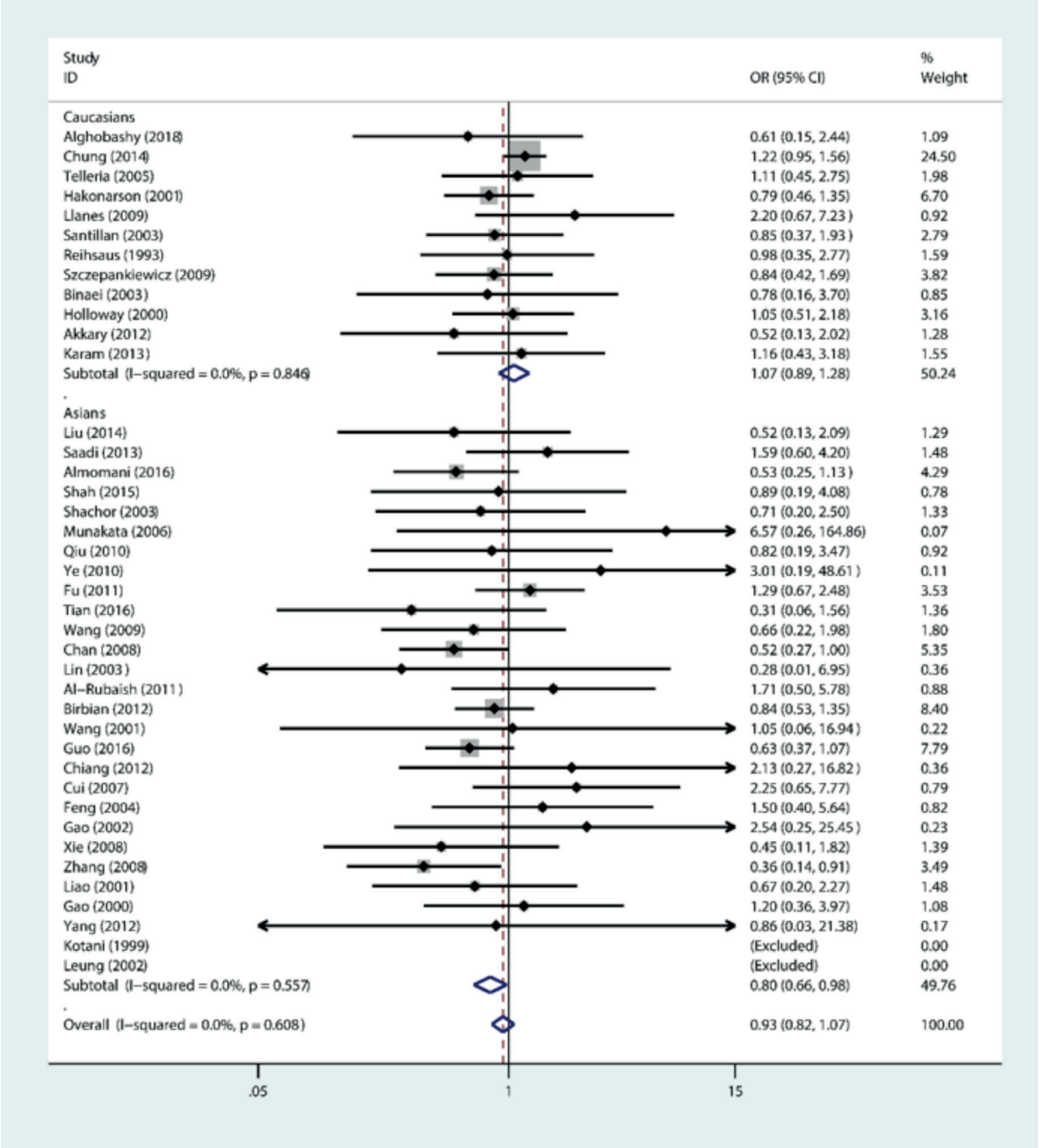

Figure 5. Forest plot on the association between the C79G polymorphism and asthma susceptibility stratified by ethnicity in the co-dominant model.

Previous studies[11-17] have indicated that ADRB2 genetic polymorphism is correlated with asthma susceptibility, but the results were still debatable and controversial. To resolve the contradictory findings, this meta-analysis was conducted to precisely investigate the correlation between asthma susceptibility and the ADRB2 genetic polymorphism.

In the current meta-analysis, 57 case-control studies of 11,157 cases and 12,281 controls were systematically adopted to assess the correlation between the A46G, C79G, and C491T polymorphisms in the ADRB2 gene and asthma susceptibility. By the combined results, A46G, and C491T have not been shown to be correlated with asthma risk in the entire population. In the eth-

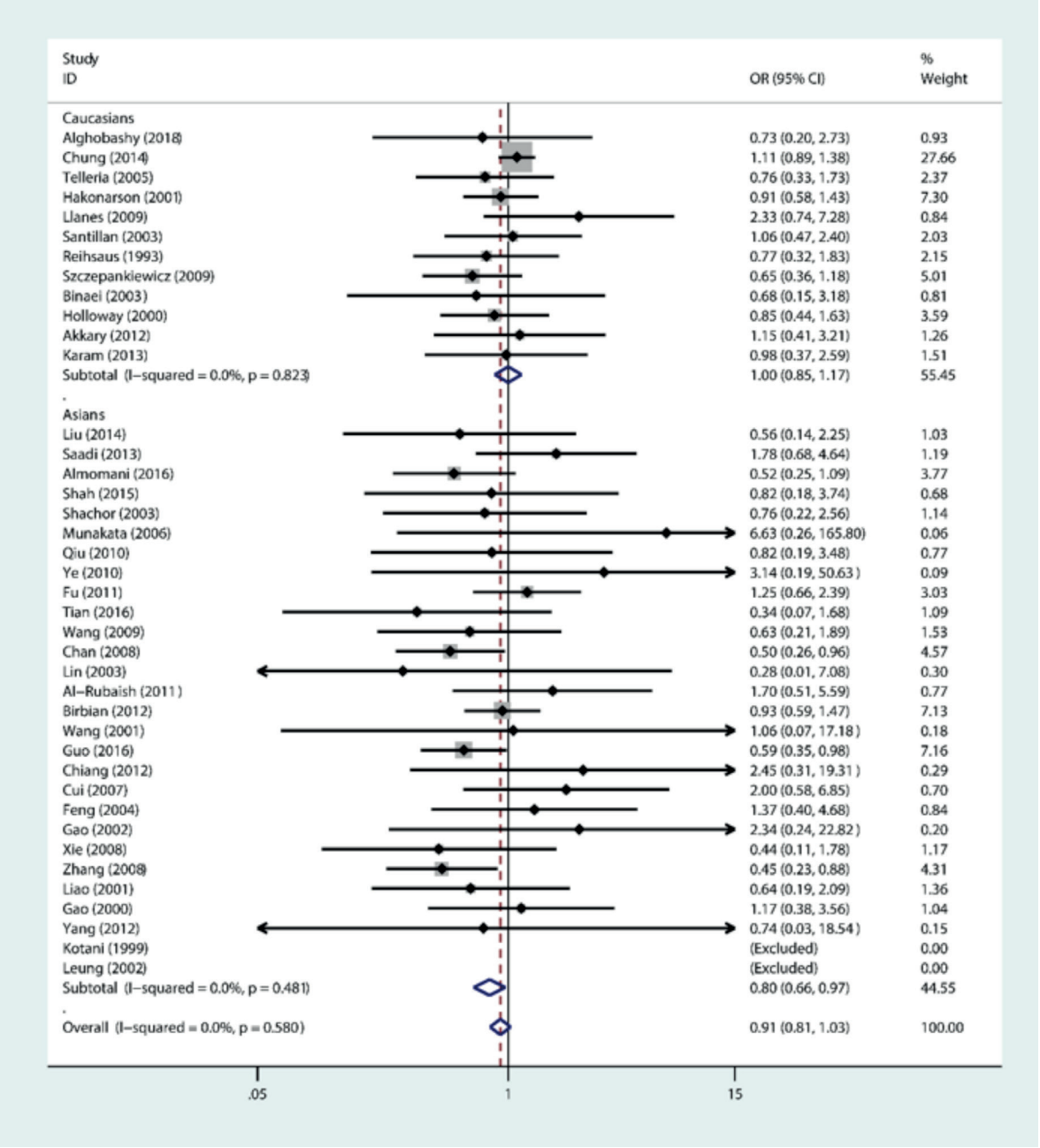

Figure 6. Forest plot on the association between the C79G polymorphism and asthma susceptibility stratified by ethnicity in the recessive model.

nic stratification analysis, an increased asthma susceptibility was only observed with the A46G polymorphism in Caucasians, and the defensive effect of C491T polymorphism was also detected in Caucasians. In the age stratification analysis, a defensive effect was only observed in the C491T polymorphism for adult and only in the co-dominant model. As for the C79G polymorphism, a statistically considerable correlation was detected in the whole population in the allelic model. The ethnic stratification analysis indicated that there was a defensive effect of C79G polymorphism on asthma risk in Asians. Similarly, a defensive effect from the C79G polymorphism was detected for children in the comparison between co-dominant and recessive models.

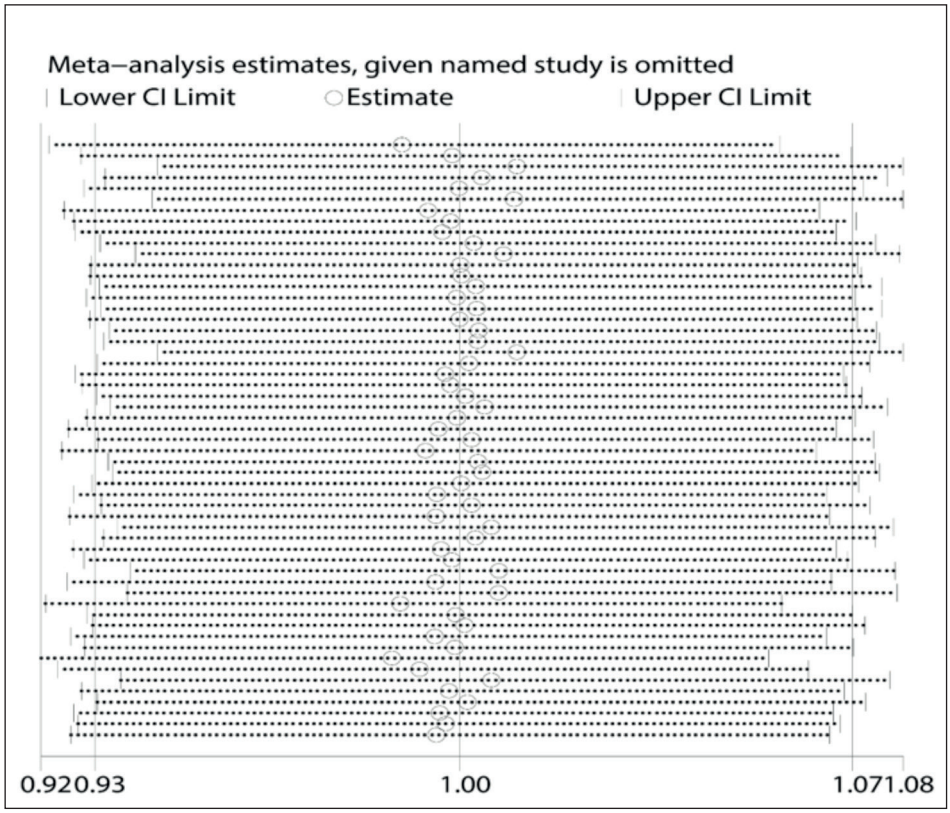

Figure 7. Sensitivity analysis for the influences of the A46G polymorphism and asthma susceptibility under the allele model.

Several meta-analyses have explored the correlation between the ADRB2 polymorphisms and asthma susceptibility. In 2004, the first meta-analysis was conducted to assess the correlation between the two polymorphisms (A46G and C79G) and asthma susceptibility by Migita et al[78]. It was reported that these two common polymorphisms do not contribute to the risk of asthma[78]. However, this conclusion is contradictory to the findings in the current study. A larger systematic meta-analysis was conducted to investigate the correlation between the ADRB2 polymorphisms (A46G and C79G) and asthma susceptibility by Xie et al[17]. According to their work, A46G and C79G are probably risk factors for asthma in Asians and adults, respectively. This conclusion is in contrast with the conclusion of the ethnic or age stratification analyses, in which the A46G polymorphism may increase asthma susceptibility in Caucasians and the C79G polymorphism may have a defensive effect on the asthma risk in Asians and Children. The latest meta-analysis by Khan et al[15] demonstrated that the A46G and C79G polymorphism in the ADRB2 gene does not contribute to the risk for asthma. This result is contradictory with the results of this study.

However, there are some limitations in this meta-analysis. Firstly, the majority populations included in the present study are of Asian ethnicity. Future research needs more people of different races. Secondly, publication bias should be considered. There was almost no publication bias in any genetic model, except for the co-dominant model of A46G polymorphism. Finally, although relevant published articles in other languages were not considered, a language bias might have occurred in this meta-analysis, because it contains only Chinese and English language literature.

Conclusions

We found that the C79G polymorphism may have a defensive effect on asthma risk for Asians and children, the C491T polymorphism may have a defensive factor against asthma in Caucasians and adults. Additionally, the A46G polymorphism is a risk factor for asthma in Caucasians. To further validate the potential function of ADRB2 genetic variation in asthma risk, further large-scale multi-center studies were needed with large sample sizes and well-designed methods.

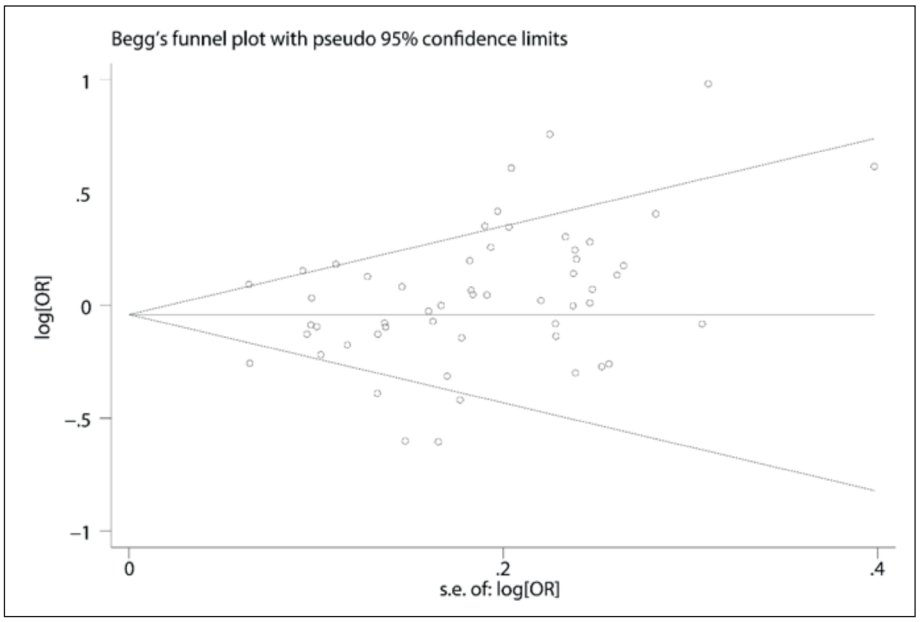

Figure 8. Funnel plot of publication biases on the association between the A46G polymorphism and asthma susceptibility under the allele model.

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Conflict of Interests

The authors declared that they have no conflicts of interests.

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