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Association of RANTES gene polymorphisms with susceptibility to childhood asthma
A meta-analysis

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Abstract

Background: Previous investigations have illustrated that regulated upon activation, normal T-cell expressed and secreted (RANTES) polymorphisms are linked to susceptibility to childhood asthma; nevertheless, the findings continue to be controversial. Accordingly, we conducted the present meta-analysis to clarify the impact of RANTES genetic polymorphisms (-403G/A and -28C/G) on childhood asthma vulnerability.

Methods: A search for published literature was performed using the PubMed, EMBASE, Chinese National Infrastructure, Cochrane Library, Scopus, Web of Science, and WanFang databases and selected in the form of PICOS (participants, interventions, comparisons, outcomes, and study design) to identify all eligible research works. The link between RANTES genetic polymorphisms and childhood asthma susceptibility was evaluated by a pooled odds ratio with a 95% confidence interval.

Results: In total, 14 case–control studies were included in the analysis. No significant association existed between risk of childhood asthma and the -403G/A polymorphism subjected to any genetic framework in the overall population. In the stratified analysis, according to ethnicity, the -403G/A polymorphism was linked to augmented vulnerability to childhood asthma in Caucasians (allelic model: odds ratio [OR] = 1.63, 95% confidence interval [CI] = 1.04–2.57, $P = .034$; codominant model: OR = 2.20, 95% CI = 1.28–3.78, $P = .004$; dominant model: OR = 1.78, 95% CI = 1.01–3.13, $P = .047$; and recessive model: OR = 1.92, 95% CI = 1.11–3.30, $P = .019$). For the stratified analysis by atopic status, the -403G/A polymorphism was linked to augmented childhood asthma in the codominant (OR = 1.39, 95% CI = 1.02–1.91, $P = .037$) and dominant models (OR = 1.43, 95% CI = 1.02–2.01, $P = .037$) in atopic asthma. For the -28C/G polymorphism, there was a significant association between childhood asthma and the -28C/G variant (allelic model: OR = 1.33, 95% CI = 1.08–1.65, $P = .009$; codominant framework: OR = 2.14, 95% CI = 1.47–3.10, $P < .001$; dominant model: OR = 1.44, 95% CI = 1.07–1.93, $P = .017$; and recessive model: OR = 2.08, 95% CI = 1.44–3.02, $P < .001$). Stratified analysis based on ethnicity and the -28C/G polymorphism was linked to augmented vulnerability to childhood asthma in Asian and Caucasian populations. For the subgroup analysis by atopic status, no association was found in atopic and non-atopic asthma.

Conclusion: The present meta-analysis indicated that the RANTES -403G/A and -28C/G polymorphisms contributed to the development of childhood asthma.

Abbreviations: ADAM33 = a disintegrin and metalloprotease 33, CCL5 = CC motif chemokine ligand 5, CI = confidence interval, CNKI = Chinese National Knowledge Infrastructure, FEV_1 = forced expiratory volume in 1-s, HWE = Hardy-Weinberg equilibrium, IL-7 = Interleukin-7, OR = odds ratio, RANTES = regulated upon activation normal T-cell expressed and secreted.

Keywords: asthma, childhood, meta-analysis, polymorphism, regulated upon activation, normal T-cell expressed and secreted

1. Introduction

Asthma is among the most frequent chronic respiratory ailments in children, which is characterized by airway hyper-responsiveness and intermittent airflow obstruction due to chronic inflammation of the airways.[1] The prevalence of pediatric asthma has been increasing in various countries worldwide over the last 2 decades, accompanied by burdensome fiscal issues to not just the family but also to society, resulting in extensive clinical expenses.[2–4] Increasing evidence has revealed that asthma is a result of an intricate interaction between genetic and environmental factors.[5] Recently, a number of studies have placed emphasis on the connection between genetic polymorphisms and susceptibility to childhood asthma, including interleukin-7 (IL-7), a disintegrin and metalloprotease 33 (ADAM33), and regulated upon activation, normal T-cell expressed and secreted (RANTES).[6–8]

RANTES, also known as CC motif chemokine ligand 5 (CCL5), is a potent chemoattractant for eosinophils, lymphocytes,

monocytes, and basophils.[9,10] It has been suggested that RANTES stimulates the recruitment of eosinophils to sites of inflammation; accordingly, it is involved in different kinds of allergic and immune disorders.[9,11–14] As indicated, many common single nucleotide polymorphisms in the RANTES gene have been observed to affect promoter activity and increase the expression of RANTES, including -403G/A and -28C/G in the promoter region.[15,16] Therefore, these 2 RANTES genetic polymorphisms are likely to exert an impact on the course of childhood asthma susceptibility by modulating not only the transcription, but also the expression of the RANTES gene.

Although previous case–control investigations have studied the potential contribution of the RANTES gene to childhood asthma susceptibility, the findings of these investigations continue to be controversial and inconclusive. We hypothesize that these inconsistent results are likely to be due to limited sample sizes, clinical heterogeneity, or a combination of the 2. Accordingly, we performed the current meta-analysis to examine the association between RANTES variants and susceptibility to asthma in children.

2. Methods and materials

2.1. Search strategy

Literature searches were carried out using the PubMed, EMBASE, Chinese National Knowledge Infrastructure, Cochrane Library, Scopus, Web of Science, and WanFang databases. We have used the following strategy: #1 asthma OR asthmatic OR (bronchial asthma) OR (bronchial hyperreactivity) OR allergy OR atopy; #2 RANTES OR (regulated upon the activation normal T-cell expressed and secreted) OR CCL5 OR (-403 G/A) OR (-28 C/G) OR rs2107538 OR rs2280788; #3 polymorphism* OR mutation* OR variant*. #1 AND #2 AND #3. In PubMed, we have used "asthma" as Mesh term. In EMBASE, we have used "asthma" as EMTREE term. All analyses were based on published studies, therefore no ethical approval and patient consent are required.

2.2. Inclusion and exclusion criteria

The qualified research studies adhered to the criteria as follows: they concerned the correlation between RANTES polymorphisms and childhood asthma susceptibility; all patients were diagnosed with asthma; case–control studies were in human beings; and studies provided sufficient information to estimate the odds ratios (ORs) with 95% confidence intervals (CIs). The following were excluded: studies with no control groups; insufficient information for the evaluation of the ORs with 95% CI; abstract, reviews, and animal studies.

In the form of PICOS (P, participants; I, interventions; C, comparisons; O, outcomes; S, study design),[17] the study was described as follows: P, patients with childhood asthma; I, mutant RANTES polymorphisms; C, health control groups; O, RANTES polymorphisms including -403 G/A or -28 C/G; S: case–control study.

2.3. Data extraction and quality assessment

Data extraction from the included studies according to the above-mentioned criteria comprised: first author's name, year of publication, country, ethnicity, atopic status, genotyping meth-

od, and genotype numbers in both the cases and controls. The independent extraction of the information from all included studies was carried out by 2 reviewers. Any potential disagreement was settled by discussion. The quality of the included studies was estimated using the Newcastle-Ottawa Scale (NOS).[18]

2.4. Statistical analysis

The evaluation of the P-value of Hardy-Weinberg equilibrium (HWE) among the control groups was carried out by the chi-squared test; a P-value >.001 demonstrated that the population was in genetic equilibrium. ORs with 95% CIs were adopted for the purpose of calculating the robustness of the link between childhood asthma susceptibility and the RANTES polymorphisms. The Z-test was conducted to evaluate the statistical significance of the accumulated ORs. Furthermore, the calculation of the between-study heterogeneity was conducted with the help of the Q test and I^2 statistics. The random-effects model was adopted if there was statistical heterogeneity $(I^2 > 50\%)$[19]; otherwise, the fixed-effects model was applied.[20] Sensitivity analysis was conducted through the emission of a single study every time to evaluate the robustness of the results. In addition, the assessment of potential publication bias was carried out using Begg funnel plot and Egger linear regression test.[21,22] All statistical analyses were carried out using the STATA version 15.0 software (Stata Corporation, College Station, TX). Furthermore, a P-value <.05 was considered statistically significant.

3. Results

3.1. Study characteristics

The literature retrieval mechanism is presented in Fig. 1. In total, 297 potentially related studies were identified with the help of a preliminary search of databases. Subsequent to the systematic literature search and in accordance with the inclusion criteria, 14 case–control research studies, which included 2943 asthma patients and 2402 controls subjects, were identified to assess the association of RANTES genetic variants with susceptibility to asthma in children.[8,23–35] Nine investigations were carried out in Asian populations and 5 were conducted in Caucasian populations. Five studies included atopic asthma in children, whereas 4 studies counted non-atopic asthma in children. The quality of the included studies was estimated via the NOS, and the scores for the included studies ranged from 6 to 9, revealing that the enrolled studies were of relatively high quality. The key characteristics of the individual studies are summarized in Table 1.

3.2. RANTES -403G/A polymorphism and susceptibility to asthma in children

The correlation between the RANTES −403G/A polymorphism and susceptibility to patients with childhood asthma was evaluated in 12 studies. The results demonstrate that there is no statistically significant connection between the −403G/A polymorphism and susceptibility to asthma in children in any genetic model, as shown in Fig. 2. With regard to the stratified analysis in accordance with ethnicity, as shown in Fig. 3, a substantial link is observed in Caucasian individuals in the allelic
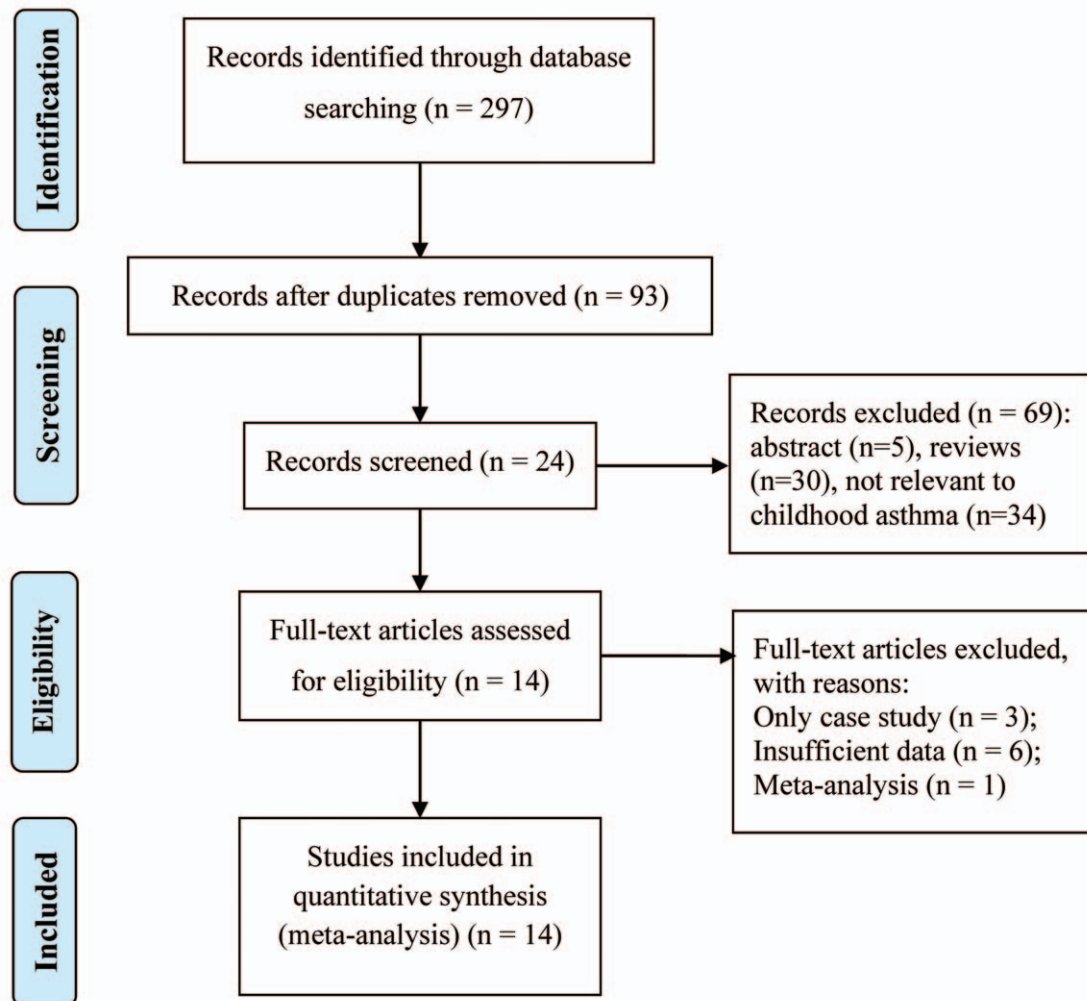
Figure 1. Flow diagram of included and excluded studies.

genetic model (OR = 1.63, 95% CI = 1.04–2.57, P = .034), dominant genetic model (OR = 1.78, 95% CI = 1.01–3.13, P = .047), codominant genetic model (OR = 2.20, 95% CI = 1.28–3.78, P = .004), and recessive genetic model (OR = 1.92, 95% CI = 1.11–3.30, P = .019). Moreover, the stratification analysis by atopic status reveals that the -403G/A polymorphism has an association with significantly augmented susceptibility to atopic asthma among children in the dominant genetic framework (OR = 1.43, 95% CI = 1.02–2.01, P = .037) as well as the codominant framework (OR = 1.39, 95% CI = 1.02–1.91, P = .037), as shown in Fig. 4. The main results are listed in Table 2.

3.3. RANTES -28C/G polymorphism and susceptibility to asthma in children

There were 10 case–control studies that investigated the relationship between the −28C/G polymorphism and suscepti-bility to asthma in children. Among children, there is a substantial link between the −28C/G polymorphism and vulnerability to asthma in the allelic genetic framework

(OR = 1.33, 95% CI = 1.08–1.65, P = .009), dominant genetic framework (OR = 1.44, 95% CI = 1.07–1.93, P = .017), codom-inant genetic model (OR = 2.14, 95% CI = 1.47–3.10, P < .001), and recessive genetic model (OR = 2.08, 95% CI = 1.44–3.02, P < .001), as shown in Fig. 5. With regard to the stratified analysis in accordance with the ethnicity of the research population, the results reveal that the −28C/G polymorphism has an association with augmented susceptibili-ty to childhood asthma in Asian individuals in the codominant genetic model (OR = 2.06, 95% CI = 1.38–3.06, P < .001) and recessive genetic model (OR = 2.01, 95% CI = 1.36–2.99, P = .001), as shown in Fig. 6A and B. However, significantly increased susceptibility to asthma is also observed in Caucasian populations in the allelic genetic framework (OR = 1.55, 95% CI = 1.11–2.16, P = .010) as well as the dominant genetic framework (OR = 2.47, 95% CI = 1.05–5.82, P = .038), as shown in Fig. 6C and D. Additionally, with regard to the subgroup analysis conducted in accordance with atopic status, no substantial link was found between the −28C/G polymor-phism and vulnerability to asthma in children with atopic asthma or non-atopic asthma in any of the genetic models.

Table 1

Main characteristics of included studies in this meta-analysis.

Author	Year	Country	Ethnicity	Atopic status	Case (n)	Control (n)	Distribution of genotype (case/control)			Genotyping methods	NOS	HWE in controls
							MM	MW	WW			
−403G/A												
Liu[8]	2013	China	Asian	Mixed	384	384	148/149	186/183	50/52	PCR	7	0.723
Undarmaa[23]	2010	Japan	Asian	Atopic	325	336	144/145	145/152	36/39	TaqMan	8	0.934
Sohn[24]	2008	Korea	Asian	Mixed	326	253	109/97	146/107	71/49	PCR-RFLP	7	0.051
Ungvari[25]	2007	Hungary	Caucasian	Mixed	254	260	188/199	59/56	7/5	PCR-RFLP	8	0.649
Lachheb[26]	2007	Tunisia	Caucasian	Mixed	210	224	140/174	50/40	20/10	PCR-RFLP	6	0.005
Tolgyesi[27]	2006	Hungary	Caucasian	Mixed	144	174	107/131	34/40	3/3	PCR-RFLP	8	0.978
Liu[28]	2005	China	Asian	Mixed	32	32	17/16	13/14	2//2	PCR	7	0.642
Liu[29]	2005	China	Asian	Mixed	287	53	102/15	141/32	44/6	PCR-RFLP	7	0.076
Leung[30]	2005	China	Asian	Mixed	129	66	60/37	53/21	16/8	PCR-RFLP	8	0.086
Al-Abdulhadi[32]	2005	UK	Caucasian	Mixed	83	38	30/35	47/2	6/1	PCR-RFLP	9	0.004
Yao[34]	2003	China	Asian	Mixed	298	311	146/140	108/137	44/34	PCR-RFLP	7	0.955
Szalai[35]	2001	Hungary	Caucasian	Mixed	120	74	75/51	39/21	6/2	PCR	7	0.926
−28C/G												
Liu[8]	2013	China	Asian	Mixed	384	384	282/310	63/60	39/14	PCR	7	<0.001
Undarmaa[23]	2010	Japan	Asian	Atopic	325	336	250/243	67/86	8/7	TaqMan	8	0.849
Sohn[24]	2008	Korea	Asian	Mixed	326	253	218/174	93/66	15/13	PCR-RFLP	7	0.050
Lachheb[26]	2007	Tunisia	Caucasian	Mixed	210	224	163/190	35/29	12/5	PCR-RFLP	6	0.005
Liu[28]	2005	China	Asian	Mixed	32	32	25/29	6/3	1/0	PCR	7	0.781
Liu[29]	2005	China	Asian	Mixed	58	53	44/40	14/13	0/0	PCR-RFLP	7	0.309
Huang[31]	2005	China	Asian	Mixed	251	107	189/83	53/23	9/1	NR	7	0.666
Wang[33]	2004	China	Asian	Mixed	100	90	65/72	31/17	41	PCR-RFLP	6	0.997
Yao[34]	2003	China	Asian	Mixed	182	107	134/83	39/23	9/1	PCR-RFLP	7	0.666
Szalai[35]	2001	Hungary	Caucasian	Mixed	160	303	144/284	16/19	0/0	PCR	7	0.573

HWE = Hardy-Weinberg equilibrium, MM = wild genotype, MW = heterozygous genotype, NOS = Newcastle-Ottawa Scale, NR = not reported, PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, WW = homozygous genotype.
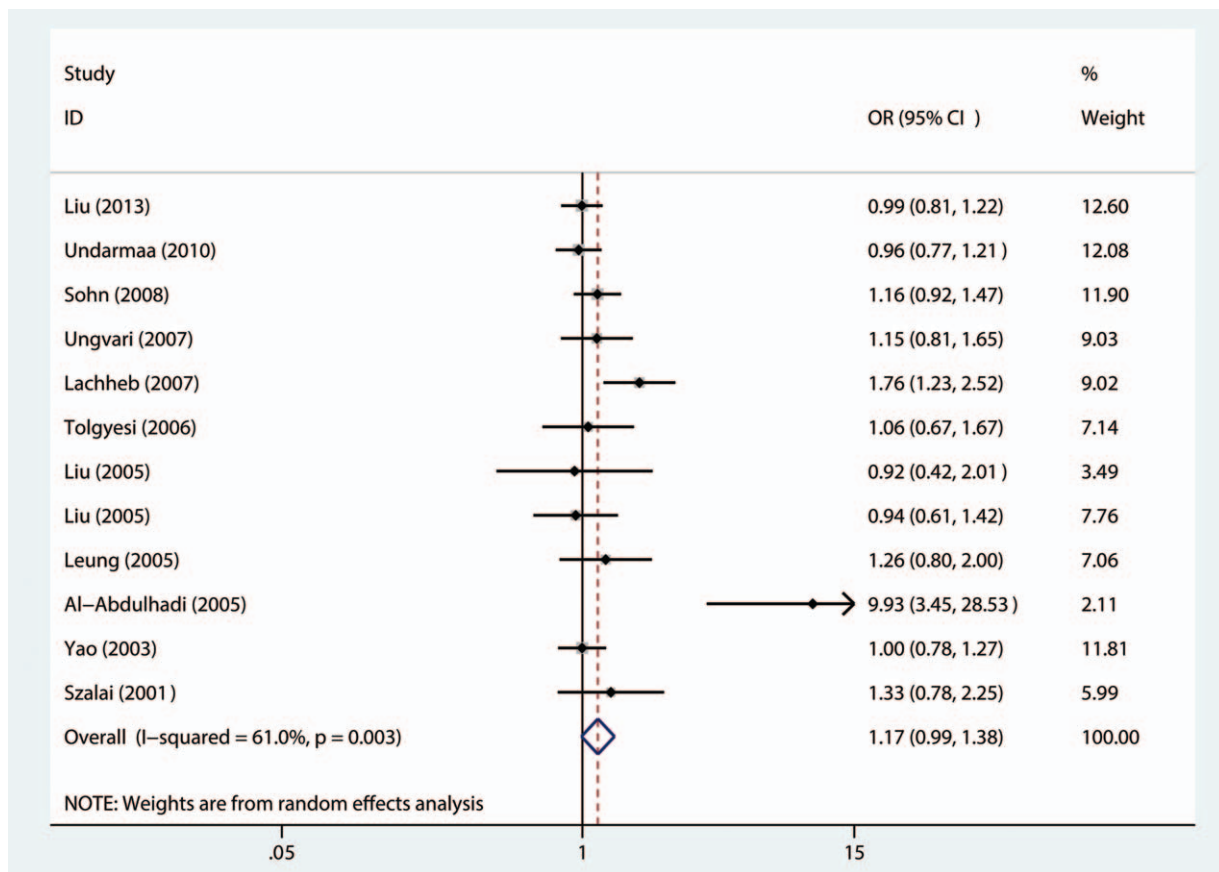

Figure 2. Meta-analysis for the association between asthma susceptibility and the RANTES -403G/A polymorphism among the allelic model (A vs G). RANTES = regulated upon activation normal T-cell expressed and secreted.
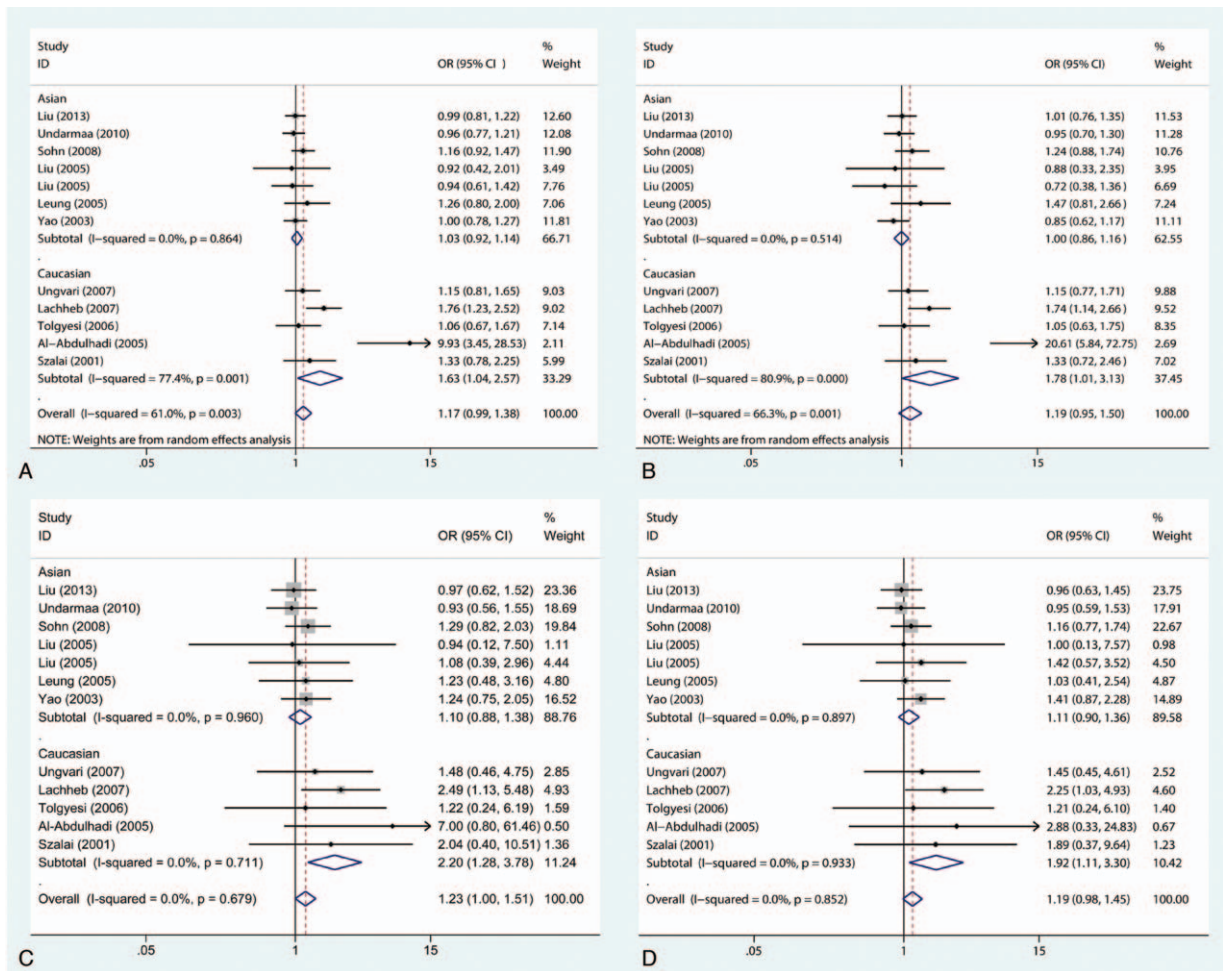
Figure 3. Meta-analysis for the association between asthma susceptibility and the RANTES -403G/A polymorphism: subgroup analysis by ethnicity. (A) For allelic model: A versus G; (B) for dominant model: GA+AA versus GG; (C) for codominant model: AA versus GG; (D) for recessive model: AA versus GG+GA. RANTES = regulated upon activation normal T-cell expressed and secreted.
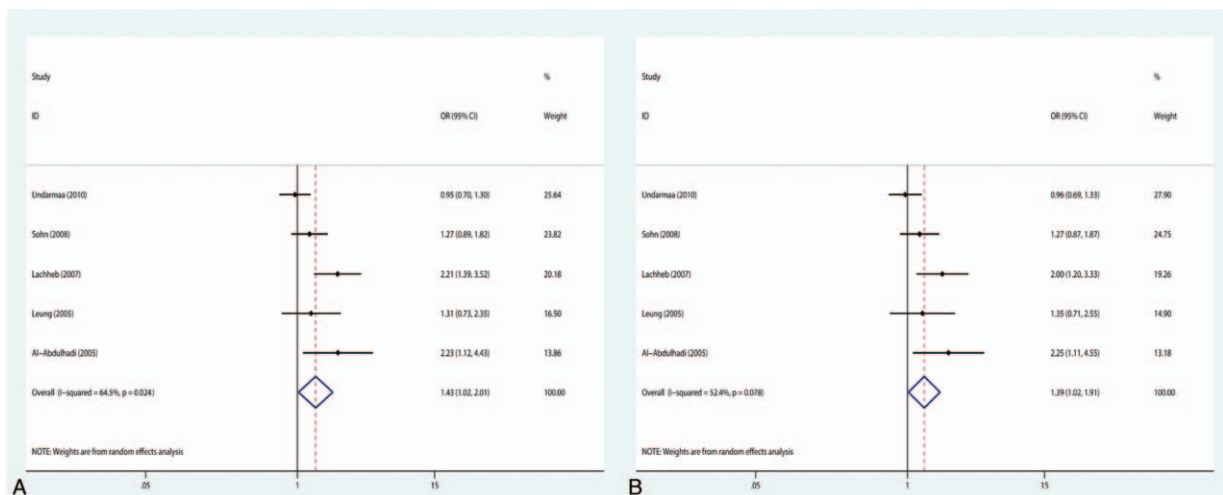

Figure 4. Meta-analysis for the association between asthma susceptibility and the RANTES -403G/A polymorphism: subgroup analysis by atopic status. (A) For dominant model: GA+AA versus GG; (B) for codominant model: GA versus GG. RANTES = regulated upon activation normal T-cell expressed and secreted.

Summary ORs and 95% CI of the association between RANTES -403G/A polymorphism and pediatric asthma susceptibility.

Genetic models	Study subjects	No. of studies	OR (95% CI)	P-meta	I^2 (%)	P-value	Model	Test of Egger
						Test of heterogeneity		
A versus G	Overall	12	1.17 (0.99–1.38)	.066	61.0	.003	R	0.049
	Asian	7	1.03 (0.92–1.14)	.623	0	.864	R	
	Caucasian	5	**1.63 (1.04–2.57)**	**.034**	77.4	.001	R	
	Atopic asthma	5	1.32 (0.99–1.74)	.054	70.6	.009	R	
	Non-atopic asthma	4	1.22 (0.94–1.57)	.132	0	.936	F	
GA versus GG	Overall	12	1.13 (0.90–1.43)	.296	62.7	.002	R	0.071
	Asian	7	0.97 (0.82–1.16)	.757	15.0	.316	R	
	Caucasian	5	1.65 (0.94–2.90)	.084	78.1	.001	R	
	Atopic asthma	5	**1.39 (1.02–1.91)**	**.037**	52.4	.078	R	
	Non-atopic asthma	4	1.11 (0.76–1.61)	.591	0	.645	F	
AA versus GG	Overall	12	1.23 (1.00–151)	.052	0	.679	F	0.108
	Asian	7	1.10 (0.88–1.38)	.394	0	.960	F	
	Caucasian	5	**2.20 (1.28–3.78)**	**.004**	0	.711	F	
	Atopic asthma	5	1.29 (0.96–1.73)	.094	33.3	.200	F	
	Non-atopic asthma	4	1.46 (0.87–2.42)	.149	0	.765	F	
AA+GA versus GG	Overall	12	1.19 (0.95–1.50)	.139	66.3	.001	R	0.080
	Asian	7	1.00 (0.86–1.16)	.994	0	.514	R	
	Caucasian	5	**1.78 (1.01–3.13)**	**.047**	80.9	<.001	R	
	Atopic asthma	5	**1.43 (1.02–2.01)**	**.037**	64.5	.024	R	
	Non-atopic asthma	4	1.20 (0.85–1.68)	.300	0	.838	F	
AA versus GG+GA	Overall	12	1.19 (0.98–1.45)	.073	0	.852	F	0.135
	Asian	7	1.11 (0.90–1.36)	.327	0	.897	F	
	Caucasian	5	**1.92 (1.11–3.30)**	**.019**	0	.933	F	
	Atopic asthma	5	1.16 (0.88–1.53)	.288	8.0	.361	F	
	Non-atopic asthma	4	1.39 (0.86–2.25)	.173	0	.653	F	

AA = mutation genotype, CI = confidence interval, F = fixed-effect model, GA = heterozygous genotype, GG = wild genotype, OR = odds ratio, P-meta = P-value of pooled effect, R = random-effect model, RANTES = regulated upon activation normal T-cell expressed and secreted.
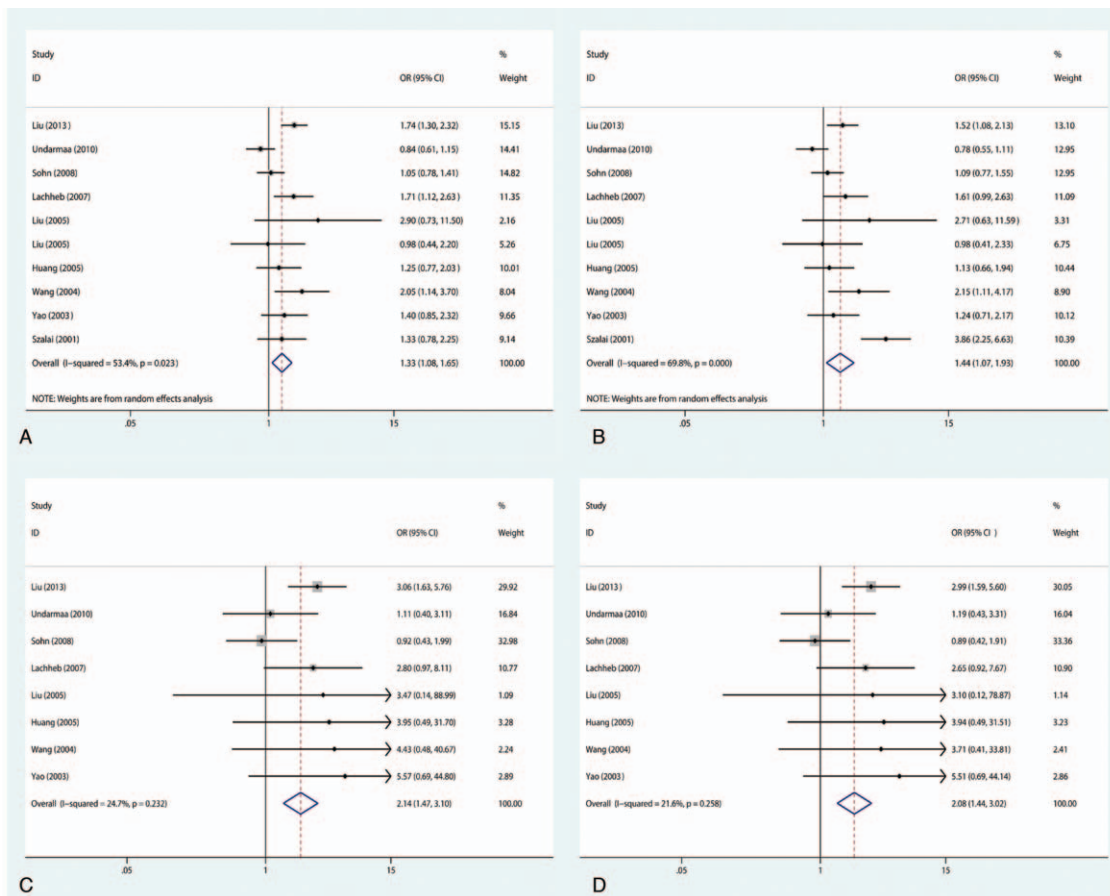Bold values indicate statistically significant results.

Figure 5. Meta-analysis for the association between asthma susceptibility and the RANTES -28C/G polymorphism. (A) For allelic model: G versus C; (B) for dominant model: CG+CC versus GG; (C) for codominant model: GG versus CC; (D) for recessive model: GG versus CC+CG. RANTES = regulated upon activation normal T-cell expressed and secreted.
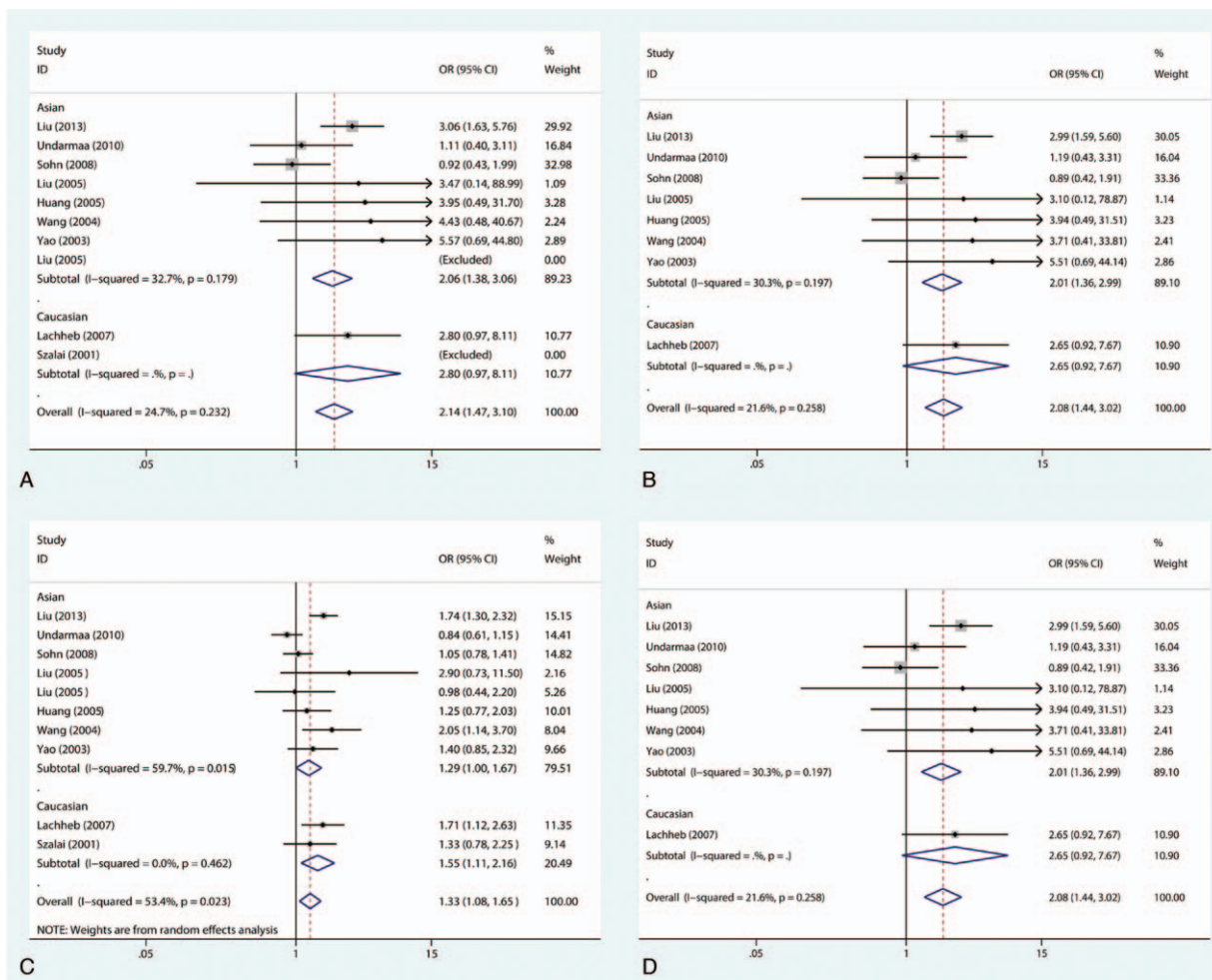
Figure 6. Meta-analysis for the association between asthma susceptibility and the RANTES -28C/G polymorphism: subgroup analysis by ethnicity. (A) For codominant model in Asian: GG versus CC; (B) for recessive model in Asian: GG versus CC+CG; (C) for allelic model in Caucasian: G versus C; (D) for recessive model in Caucasian: GG versus CC+CG. RANTES = regulated upon activation normal T-cell expressed and secreted.

3.4. Sensitivity analysis and publication bias

Sensitivity analysis was carried out to assess the stability of the findings through the sequential removal of individuals. As the findings suggest, the accumulated ORs do not have a significant impact, as shown in Fig. 7. Moreover, both the Begg funnel plot and Egger test were applied to evaluate potential publication bias. The shape of the funnel plot shows symmetry, which suggests that no significant publication bias is present, as shown in Fig. 8. The Egger test was also used to evaluate potential publication bias (Tables 2 and 3); there was no publication bias in the present meta-analysis.

4. Discussion

Earlier research has shown that asthma vulnerability is determined not only by the infectious agent and environmental determinants, but also by host genetics.[3,5] Several candidate genes have been studied for accessing the likely connection between the modulations of asthma risk across various populations. Despite comprehensively stating the recruitment criteria, sample size, characteristics of participants, and genotyping methodologies, most of the studies were short of the proper conclusion. Hence, to improve the statistical power, together with determining the effect size of the RANTES -403G/A and -28C/G polymorphisms, a meta-analysis was carried out with the updated data of 14 studies to determine a more concrete correlation between the RANTES -403G/A and -28C/G polymorphisms and the occurrence of asthma susceptibility.

As far we know, this is the most detailed and systematic meta-analysis performed to date, meant to assess the potential link between the RANTES -403G/A and -28C/G polymorphisms and asthma susceptibility in childhood. Meta-analysis data revealed that the RANTES -28C/G polymorphism was significantly associated with augmented asthma susceptibility in childhood. Compared with the wild type C allele and homozygous CC genotype, the subjects with a G allele and 2 variant GG alleles had 1.33- and 2.14-fold increased risk of the development of asthma, respectively. With regard to the stratified analysis based on ethnicity, the C28G polymorphism was linked to augmented susceptibility to childhood asthma in Asian and Caucasian populations. We also carried out a subgroup analysis in
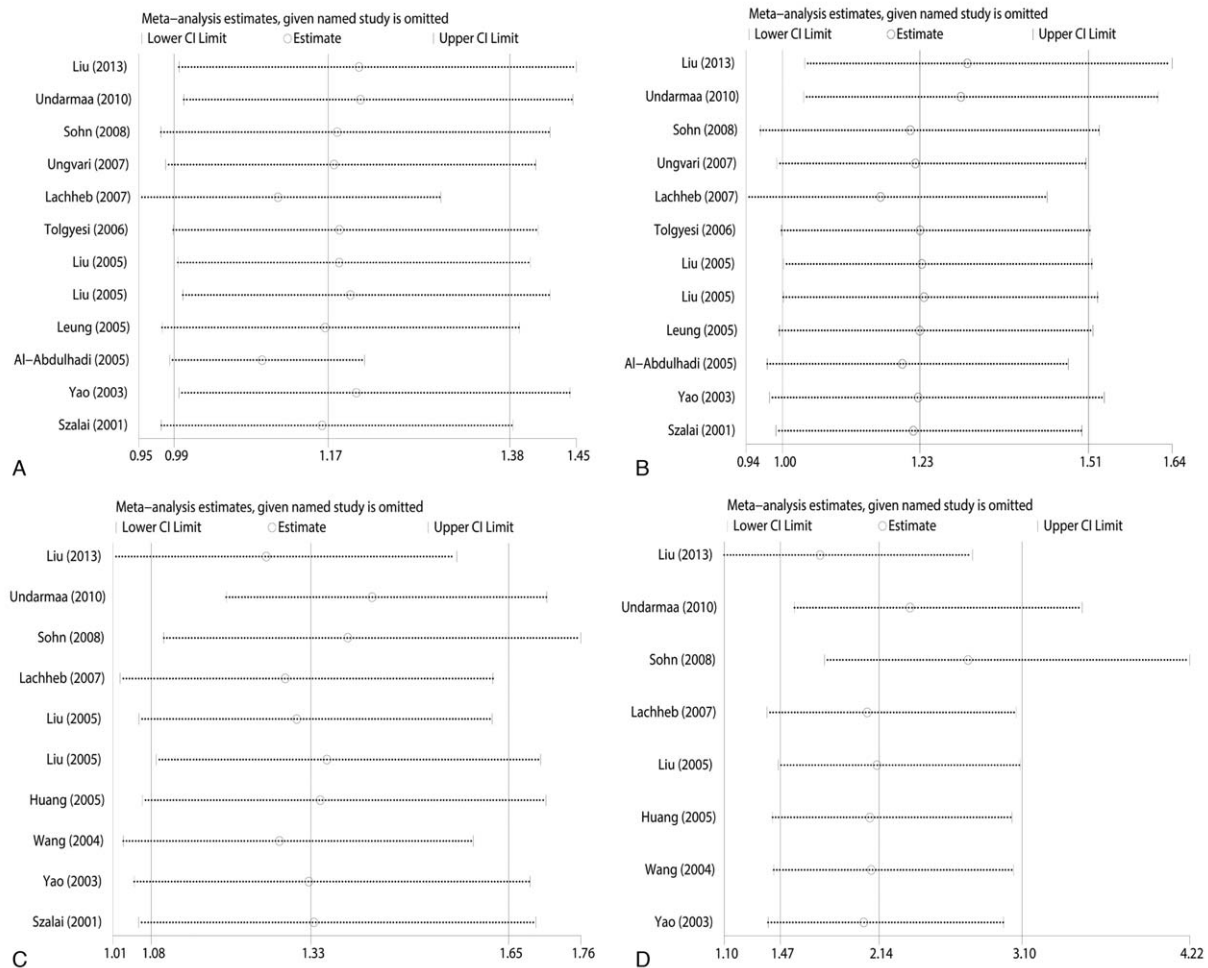
Figure 7. Sensitivity analysis on the association between RANTES polymorphisms and susceptibility asthma. For allelic (A) and codominant (B) model of -403G/A polymorphism; and for allelic (C) and codominant (D) model of -28C/G polymorphism. RANTES = regulated upon activation normal T-cell expressed and secreted.

accordance with atopic status; no significant association was found in atopic and non-atopic asthma. In addition, the data showed that the RANTES -403G/A polymorphism did not have a statistical association with asthma susceptibility in childhood. Nevertheless, for the stratified analysis according to ethnicity, the subjects with an A allele, together with 2 variant AA alleles, had 1.63- and 2.20-fold augmented susceptibility to the development of asthma, compared with the wild type G allele and homozygous GG genotype in Caucasian children, respectively. In the same manner, with regard to the stratified analysis by atopic status, dominant and codominant models indicated the increased risk of atopic asthma. Based on the above data and the significance of RANTES polymorphisms in the pathogenesis of asthma in children, it is biologically plausible that both the -403G/A and -28C/G polymorphisms are likely to modulate the risk of asthma, in addition to being a genetic determinant for the inter-individual discrepancies in vulnerability to asthma in children.

From previous reports, we know that RANTES constitutes a key chemotactic determinant created through asthmatic feed-back, and contributes to the deterioration of allergic airway inflammation.[36–38] There are substantially high concentrations of RANTES in asthmatic patients, together with asthma severity,

demonstrating the pivotal function of RANTES in the pathogenesis of this disorder.[37,39,40] Serum RANTES is likely to be a helpful noninvasive diagnostic marker for monitoring asthma severity. Identifying and hampering RANTES and/or its receptor are likely to constitute a potential therapeutic methodology for asthmatic patients.[41] In the study by Leung et al,[30] the -403G/A polymorphism is linked to allergen sensitization and forced expiratory volume in 1-s (FEV_1), and there is an association with the -28C/G polymorphism. In contrast, Liu et al[8] found that the -28C/G polymorphism has a substantial association with increased asthma susceptibility in childhood. Contrary to these results, -403G/A and -28C/G polymorphisms have no detectable impact on asthma susceptibility.[35] Several previous meta-analyses have shown controversial findings regarding the association between these 2 polymorphisms and asthma susceptibility.[42–44] In comparison with the earlier research works, the current meta-analysis offered a comprehensive and systematic meta-analysis to assess the potential association between the RANTES -403G/A and -28C/G polymorphisms and asthma susceptibility in childhood.

The genetic susceptibility to asthma in children is polygenic; hence, a single genetic variant is typically not suitable for the
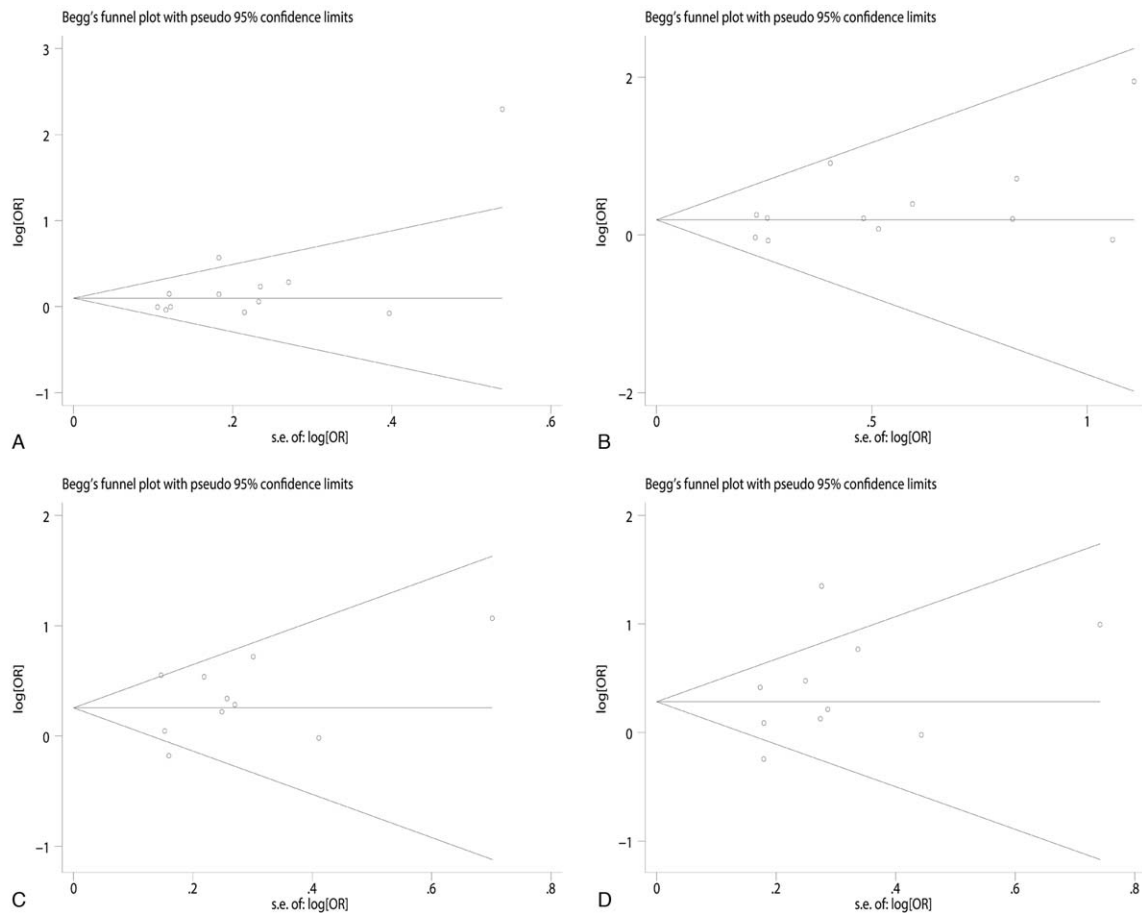
Figure 8. Funnel plot analysis to examine publication bias. For allelic (A) and codominant (B) model of -403G/A polymorphism; and for allelic (C) and codominant (D) model of -28C/G polymorphism.

Table 3

Summary ORs and 95% CI of the association between RANTES -28C/G polymorphism and pediatric asthma susceptibility.

Genetic models	Study subjects	No. of studies	OR (95% CI)	*P*-value	I^2 (%)	*P*-value	Model	Test of Egger
					Test of heterogeneity			
G versus C	Overall	10	**1.33 (1.08–1.65)**	**.009**	53.4	.023	R	0.391
	Asian	8	1.29 (1.00–1.67)	.051	59.7	.015	R	
	Caucasian	2	**1.55 (1.11–2.16)**	**.010**	0	.462	R	
	Atopic asthma	3	1.05 (0.67–1.65)	.816	69.6	.037	R	
	Non-atopic asthma	2	1.32 (0.90–1.94)	.162	0	.537	F	
GC versus CC	Overall	10	1.11 (0.95–1.31)	.194	13.9	.315	F	0.081
	Asian	8	1.06 (0.89–1.27)	.522	13.9	.322	F	
	Caucasian	2	1.49 (0.98–2.28)	.064	0	.710	F	
	Atopic asthma	3	0.96 (0.63–1.47)	.855	50.6	.132	R	
	Non-atopic asthma	2	1.33 (0.82–2.16)	.441	0	.854	F	
GG versus CC	Overall	10	**2.14 (1.47–3.10)**	**<.001**	24.7	.232	F	0.439
	Asian	8	**2.06 (1.38–3.06)**	**<.001**	32.7	.179	F	
	Caucasian	2	2.80 (0.97–8.11)	.058	NA	NA	F	
	Atopic asthma	3	1.32 (0.67–2.58)	.420	0	.389	F	
	Non-atopic asthma	2	1.46 (0.56–3.83)	.441	0	.566	F	
GG+GC versus CC	Overall	10	**1.44 (1.07–1.93)**	**.017**	69.8	<.001	R	0.280
	Asian	8	1.21 (0.95–1.53)	.124	42.3	.096	R	
	Caucasian	2	**2.47 (1.05–5.82)**	**.038**	81.9	.019	R	
	Atopic asthma	3	1.01 (0.63–1.62)	.958	63.9	.063	R	
	Non-atopic asthma	2	1.36 (0.86–2.14)	.186	0	.709	F	
GG versus CC+CG	Overall	10	**2.08 (1.44–3.02)**	**<.001**	21.6	.258	F	0.456
	Asian	8	**2.01 (1.36–2.99)**	**.001**	30.3	.197	F	
	Caucasian	2	2.65 (0.92–7.67)	.071	NA	NA	F	
	Atopic asthma	3	1.34 (0.69–2.61)	.393	0	.472	F	
	Non-atopic asthma	2	1.36 (0.53–3.54)	.524	0	.548	F	

CC = wild genotype, CG = heterozygous genotype, CI = confidence interval, F = fixed-effect model, GG = mutation genotype, NA = not available, OR = odds ratio, *P*-meta = *P*-value of pooled effect, R = random-effect model.
Bold values indicate statistically significant results.

prediction of the susceptibility of this disease. The most pivotal attribute of these gene polymorphisms suggests that their occurrence has the potential to vary significantly between various racial or ethnic populations. Before reaching a conclusion, limitations of this study should be addressed. First, just research works, authored in English or Chinese, were included in the meta-analysis. This suggests that qualified research works published in other languages were likely to have been neglected, which likely introduced selection bias. Second, the sample size of some research works had limitations; in addition, the findings required careful interpretation. Third, the current research work had statistical heterogeneity, despite the fact that this is extensively frequent in the meta-analysis of genetic association research. Accordingly, we carried out a subgroup analysis for the purpose of identifying all factors that contributed to the heterogeneity. Ultimately, other determinants, such as sex, environment, and lifestyle, which were likely to exert an impact on the contact of RANTES polymorphisms with asthma susceptibility in children, could not be analyzed due to the lack of data.

5. Conclusions

To summarize, the present meta-analysis revealed that the RANTES -403G/A and -28C/G polymorphisms appear to be associated with the susceptibility to childhood asthma. However, prospective, well-designed, large research studies will likely be beneficial for the validation of this association in various populations, including consideration of environmental factors responsible for the vulnerability to asthma in children.

Author contributions

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