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META-ANALYSIS

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The C79G Polymorphism of the β2-Adrenergic Receptor Gene, ADRB2, and Susceptibility to Pediatric Asthma: Meta-Analysis from Review of the Literature

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The ADRB2 gene encodes the β2-adrenergic receptor (β2-AR). This study aimed to determine the association between the C79G polymorphism of the ADRB2 gene and its association with pediatric asthma using a meta-analysis of the published data.

Material/Methods: Review of publications up to May 2018 was from the PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), and WanFang databases. The odds ratio (ORs) with 95% confidence interval (CI) were used in evaluating the strength of the reported association between the C79G polymorphism of the ADRB2 gene and pediatric asthma.

Results: There were 18 controlled studies that included 2,982 pediatric cases of asthma and 2,651 controls. Expression of the C79G polymorphism of the ADRB2 gene was significantly associated with risk of pediatric asthma associated with the C or G allele with comparison of the co-dominant model (GG *vs.* CC: OR, 0.69; 95% CI, 0.55–0.88) and the recessive model (GG *vs.* CC+CG: OR, 0.65; 95% CI, 0.53–0.81). Subgroup analysis by ethnicity showed a significantly reduced risk of pediatric asthma in Asian patients for comparison of the co-dominant model (GG *vs.* CC: OR, 0.59; 95% CI, 0.45–0.78), the recessive model (GG *vs.* CC+CG: OR, 0.58; 95% CI, 0.45–0.76), and the allelic model (G *vs.* C: OR, 0.89; 95% CI, 0.79–0.99).

Conclusions: The C79G polymorphism of the ADRB2 gene encoding β2-AR was associated with a reduced risk for the development of pediatric asthma, particularly in the Asian population.

MeSH Keywords: **Asthma • Pediatrics • Polymorphism, Genetic**

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Background

Asthma is a common chronic allergic disease that involves the respiratory tract and affects millions of children worldwide, occurring in up to 10% of children, which makes atopic asthma a global public health problem [1,2]. Asthma is a heterogeneous disease that typically includes chronic inflammation of the airway with symptoms that include cough, shortness of breath, wheeze, chest tightness, and variably reduced expiratory airflow [3]. Several risk factors are now known to exacerbate episodes of asthma and include air pollution, exposure to environmental chemicals, microbes, and allergens, and also exposure to dander from animal fur in children who keep pets [4–6]. Recently published studies have shown that the development of asthma in children depends on genetic predisposition, and have highlighted the role of the IL17A gene that encodes interleukin 17 (IL-17), the ORMDL3 gene that encodes orosomucoid 1-like 3, and the ADRB2 gene that encodes the β2-adrenergic receptor (β2-AR).

The ADRB2 gene is a 1200 bp intron-less gene that encodes a 413 amino acid protein, β2-AR, with a molecular mass of approximately 46.5 kD [7,8]. The β2-adrenergic receptor (β2-AR) is a prototypical G protein-coupled receptor (GPCR) with seven transmembrane domains, an extracellular amino terminus, an intracellular carboxyl terminus, three interconnecting extracellular loops, and three intracellular loops [7,9,10]. Because β2-AR is highly expressed in the lung tissue, mainly in the airway smooth muscles, β2-AR agonists are used as first-line bronchodilator therapy in patients with asthma [11,12]. The gene that encodes this receptor, ADRB2, is found on the long arm of chromosome 5q31-33, and studies have shown that ADRB2 is a major candidate gene in asthma [13,14]. Several polymorphisms of the ADRB2 gene have recently been recognized, including the C79G polymorphism, rs1042714, also known as Gln27Glu.

Previously published controlled clinical have investigated the role of the ADRB2 gene and the gene polymorphisms in the susceptibility to asthma in pediatric patients [10,15–17]. However, these studies have reported inconsistent findings, because of the small number of study participants, the presence of clinical heterogeneity, or due to a combination of both factors. Therefore, this study aimed to investigate the association between the C79G polymorphism of the ADRB2 gene and its association with pediatric asthma using a meta-analysis of the published data.

Material and Methods

Study selection

Two investigators searched the literature using the PubMed, EMBASE, China National Knowledge Infrastructure (CNKI), and WanFang databases to identify controlled studies that had investigated the relationship between the expression of C79G polymorphism of the ADRB2 gene and asthma in children. The electronic literature search was conducted up to May 6 2018 and was limited to publications in the English and Chinese language. Some of the search terms used included asthma or asthmatic and polymorphism or mutation or variant and β2-AR or beta2-AR or β2-adrenergic receptor or ADRB2.

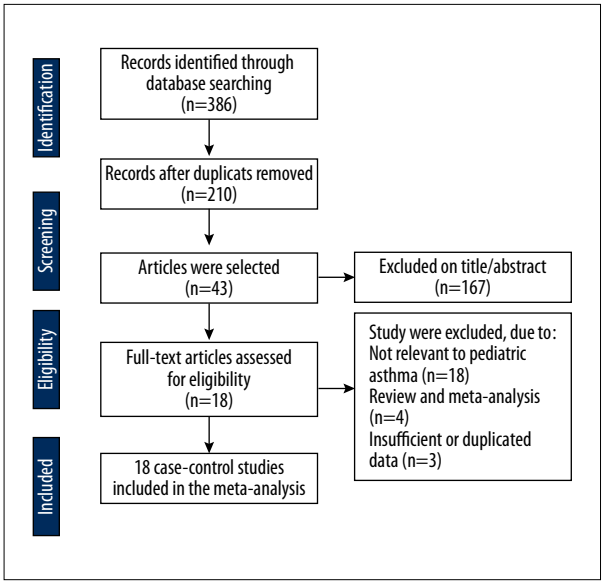

Figure 1. Flowchart of the selection of published studies used in the meta-analysis.

Inclusion and exclusion criteria

The published studies were selected using the following criteria: studies with a controlled design that included an asthmatic and a normal population; studies that evaluated the relationship between the C79G polymorphism of the ADRB2 gene and the risk of pediatric asthma in patients aged <18 years; studies with sufficient data to allow calculation of the odds ratio (OR) and the 95% confidence interval (CI). The following published studies were excluded: case reports; studies without available genotype frequency data; abstracts, comments, review articles, and methodological publications. The largest or most recent publication was chosen where studies had duplicated data.

Data extraction

Data were obtained from all included publications by two authors, and the information retrieved included first author, year of publication, country, ethnicity, distribution of the genotype of cases and controls, and the Hardy-Weinberg equilibrium in the controls. Any disagreement between the two investigators

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Table 1. The main findings from the published studies selected for meta-analysis.

Author	Year	Country	Ethnicity	Case	Control	Genotyping methods	HWE
Alghobashy	2018	Egypt	Caucasians	104	52	PCR–RFLP	0.078
Almomani	2016	Jordan	Asians	249	238	MassARRAY	0.436
Tatarskyy	2011	Ukraine	Caucasians	114	86	PCR-RFLP	0.466
Tian	2016	China	Asians	298	304	PCR	0.660
Wang	2009	China	Asians	448	511	RT-PCR	0.016
Chan	2008	China	Asians	294	173	PCR-RFLP	0.597
Szczepankiewicz	2009	Poland	Caucasians	113	123	PCR-RFLP	0.015
Lin	2003	China	Asians	80	69	PCR	0.932
Leung	2002	China	Asians	76	70	PCR	0.315
Al-Rubaish	2011	Saudi Arabia	Arabia	73	85	PCR-RFLP	0.859
Isaza	2012	Colombia	NA	109	137	RT-PCR	0.119
Guo	2016	China	Asians	340	340	PCR	0.003
Karam	2013	Egypt	Caucasians	90	110	PCR	0.149
Xie	2008	China	Asians	57	62	SSP-PCR	0.220
Zhang	2008	China	Asians	217	50	PCR	0.993
Liao	2001	China	Asians	50	100	PCR-RFLP	0.153
Gao	2000	China	Asians	58	89	AS-PCR	0.077
Yang	2012	China	Asians	212	52	Sequencing	NA

HWE – Hardy-Weinberg equilibrium; PCR – polymerase chain reaction; RFLP – restriction fragment length polymorphism; NA – not available.

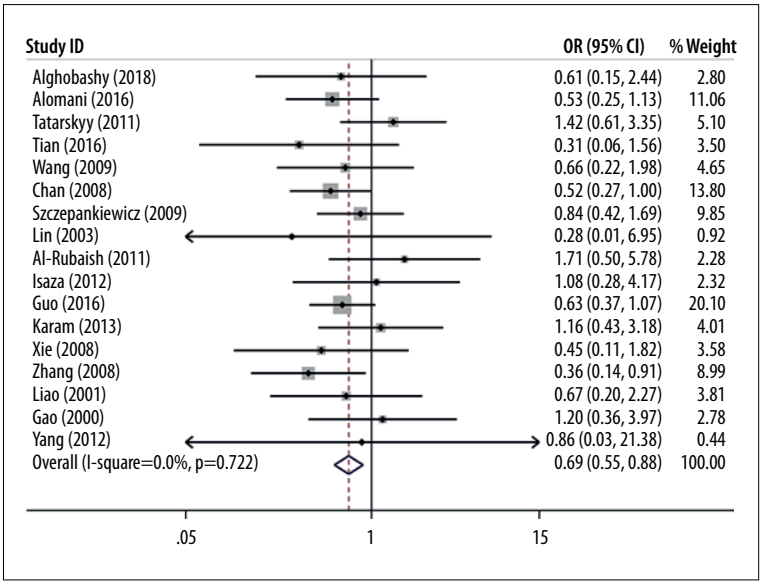

Figure 2. Meta-analysis of the association between the C79G polymorphism of the ADRB2 gene and pediatric asthma in the co-dominant model.

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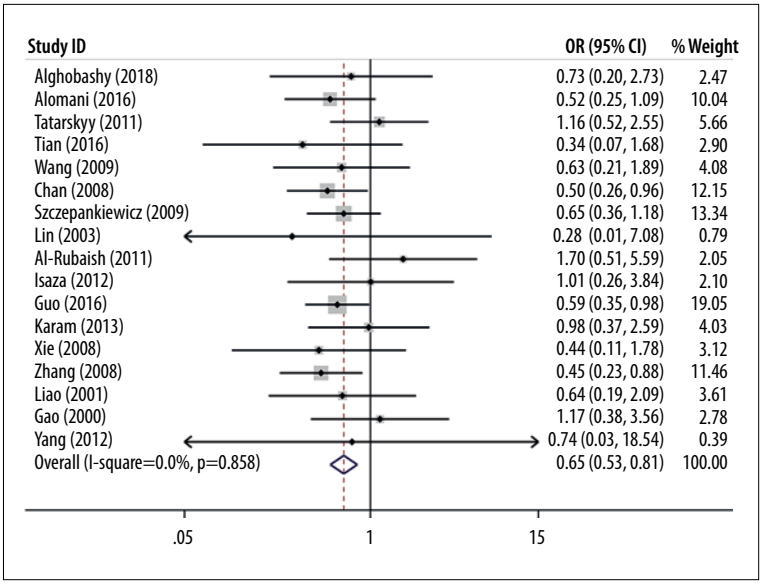

Figure 3. Meta-analysis of the association between the C79G polymorphism of the ADRB2 gene and pediatric asthma in the recessive model.

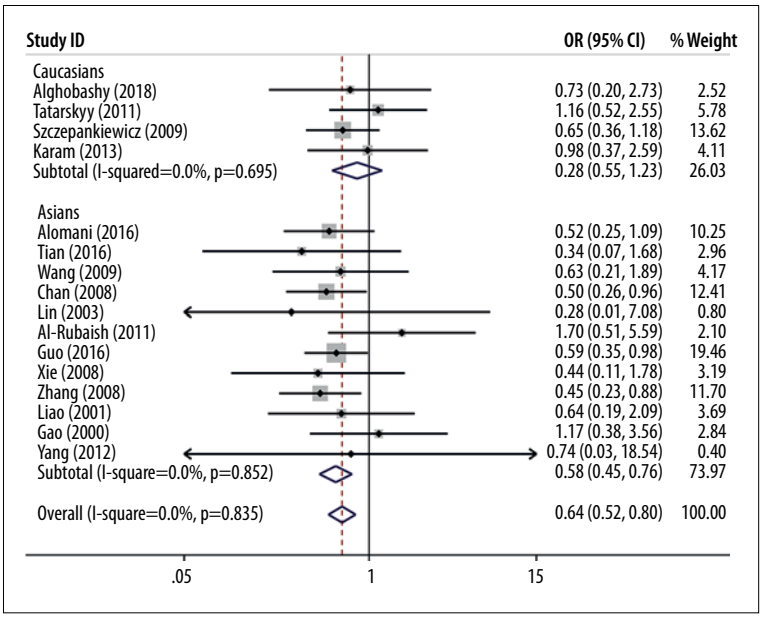

Figure 4. Meta-analysis of the association between the C79G polymorphism of the ADRB2 gene and pediatric asthma stratified by ethnicity in the recessive model.

conducting the publication was resolved by consensus discussion with the other investigators.

Statistical analysis

Data analysis used the Hardy-Weinberg equilibrium. The controls for each of the studies were evaluated by Pearson's chi-squared (χ^2) test and a P-value <0.001 was regarded as a statistically significant to departure from the Hardy-Weinberg equilibrium. The odds ratio (OR) with the 95% confidence interval (CI) was used to evaluate the strength of the relationship between the C79G polymorphism of the ADRB2 gene and the risk of pediatric asthma, which was also assessed using the allelic model (G *vs.* C), the recessive model (GG *vs.* CC+CG), the dominant model (GG+CG *vs.* CC), and the co-dominant model (GG *vs.* CC and CG *vs.* CC), respectively. Stratification analysis was performed using ethnicity and the severity of the disease. Heterogeneity between studies was further analyzed using the χ^2-based Q test and I^2 statistic. The fixed-effects model was used when the Q-test resulted in a P-value >0.1 or the I^2 resulted in a value <50% [18]. Otherwise, the random-effects model was used [19]. Sensitivity analysis was performed by the omission of a single study at each time point to evaluate the robustness of the results. Possible bias in the publication of data were analyzed using Begg's funnel plots and Egger's test [20,21]. Statistical analysis was performed using STATA version 15.0 (Stata Corp, College Station, TX, USA). A P-value <0.05 was considered to be statistically significant.

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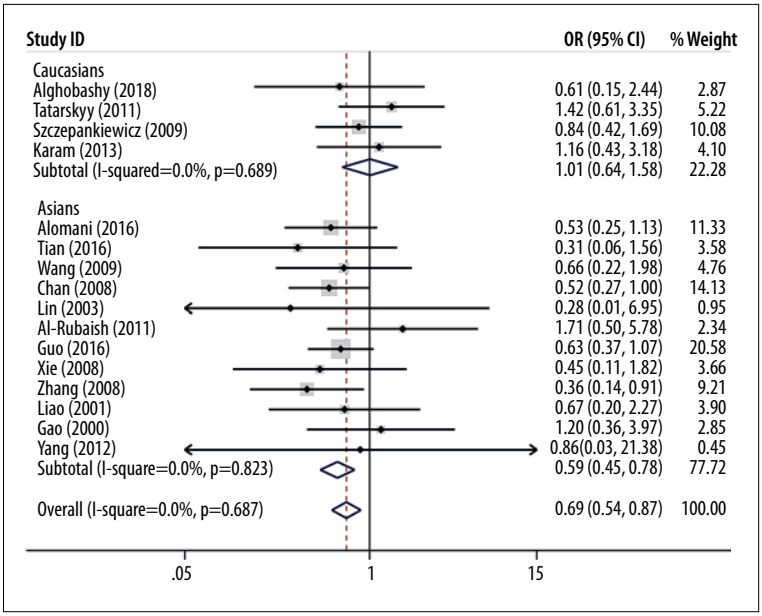

Figure 5. Meta-analysis of the association between the C79G polymorphism of the ADRB2 gene and pediatric asthma stratified by ethnicity in the co-dominant model.

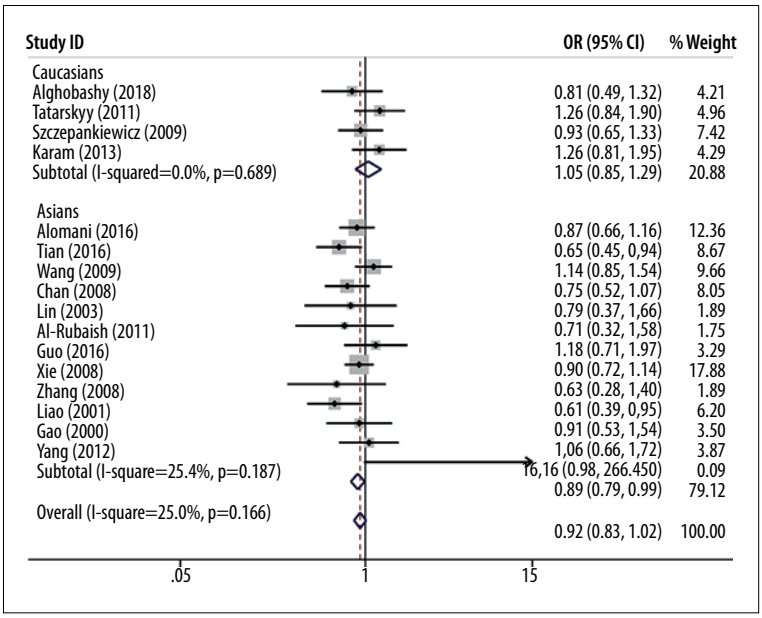

Figure 6. Meta-analysis of the association between the C79G polymorphism of the ADRB2 gene and pediatric asthma stratified by ethnicity in the allelic model.

Results

Characteristics of the published studies

The procedure for selection of the published studies is shown in Figure 1. Initially, there were 386 potentially relevant publications identified during the literature search. Following primary screening using the study exclusion criteria, a total of 167 publications were eliminated, which resulted in a total of 18 controlled studies that included 2,982 pediatric patients with asthma and 2,651 controls [10,15–17,22–35]. The main findings of each study are summarized in Table 1.

Association between the C79G polymorphism of the ADRB2 gene and the risk of pediatric asthma

From the 18 published studies identified (2,982 pediatric patients with asthma and 2,651 controls), the presence of the C79G polymorphism of the ADRB2 gene was significantly associated with the a reduced risk of asthma in pediatric patients using the co-dominant model (GG *vs.* CC: OR, 0.69; 95% CI, 0.55–0.88; P=0.002; I^2=0) (Figure 2) and the recessive model (GG *vs.* CC+CG: OR, 0.65; 95% CI, 0.53–0.81; P=0.000; I^2=0) (Figure 3). There was no significant relationship with the other gene model. For stratification analysis according to the ethnicity, a significant relationship was found for a reduced

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Table 2. Meta-analysis of the association between the C79G polymorphism of the ADRB2 gene and susceptibility to pediatric asthma.

Subgroup	Comparisons	Studies	Heterogeneity test		Association test		Model	Publication bias
			P Value	I^2 (%)	OR (95% CI)	P-Value		Egger's test
Total	G *vs.* A	18	0.158	25.2	0.93 (0.84–1.02)	0.144	F	0.593
	GA *vs.* AA	18	0.425	2.5	1.12 (0.99–1.28)	0.082	F	0.829
	GG *vs.* AA	18	0.722	0	**0.69 (0.55–0.88)**	**0.002**	F	0.523
	GG+AG *vs.* AA	18	0.330	10.4	1.02 (0.90–1.15)	0.734	F	0.721
	GG *vs.* AA+AG	18	0.858	0	**0.65 (0.53–0.81)**	**0.000**	F	0.499
Asian	G *vs.* A	13	0.187	25.4	**0.89 (0.79–0.99)**	**0.033**	F	–
	GA *vs.* AA	13	0.432	1.4	1.07 (0.93–1.24)	0.356	F	–
	GG *vs.* AA	13	0.823	0	**0.59 (0.45–0.78)**	**0.000**	F	–
	GG+AG *vs.* AA	13	0.384	6.2	0.97 (0.84–1.11)	0.637	F	–
	GG *vs.* AA+AG	13	0.852	0	**0.58 (0.45–0.76)**	**0.000**	F	–
Caucasian	G *vs.* A	4	0.400	0	1.05 (0.85–1.29)	0.646	F	–
	GA *vs.* AA	4	0.361	6.3	1.31 (0.96–1.79)	0.089	F	–
	GG *vs.* AA	4	0.689	0	1.01 (0.64–1.58)	0.976	F	–
	GG+AG *vs.* AA	4	0.394	0	1.22 (0.91–1.64)	0.182	F	–
	GG *vs.* AA+AG	4	0.695	0	0.82 (0.55–1.23)	0.344	F	–
Mild to moderate asthma	G *vs.* A	3	0.056	65.3	0.95 (0.53–1.68)	0.855	R	–
	GA *vs.* AA	3	0.837	0	0.67 (0.41–1.09)	0.110	F	–
	GG *vs.* AA	3	0.054	65.8	1.09 (0.28–4.31)	0.898	R	–
	GG+AG *vs.* AA	3	0.407	0	0.77 (0.49–1.21)	0.266	F	–
	GG *vs.* AA+AG	3	0.042	68.5	1.33 (0.34–5.19)	0.679	R	–
Severe asthma	G *vs.* A	3	0.064	63.6	1.73 (0.49–6.11)	0.391	R	–
	GA *vs.* AA	3	0.431	0	1.37 (0.51–3.65)	0.533	F	–
	GG *vs.* AA	3	0.126	51.8	2.79 (0.34–23.22)	0.342	R	–
	GG+AG *vs.* AA	3	0.516	0	1.55 (0.64–3.74)	0.327	F	–
	GG *vs.* AA+AG	3	0.026	72.7	3.41 (0.23–50.28)	0.372	R	–

OR – odds ratio; CI – confidence interval; F – fixed-effects model; R – random-effects model; NA – not available.

risk of pediatric asthma in the Asian population using recessive model (GG *vs.* CC+CG: OR, 0.58; 95% CI, 0.45–0.76; P=0.000; I^2=0) (Figure 4), the co-dominant model (GG *vs.* CC: OR, 0.59; 95% CI, 0.45–0.78; P=0.000; I^2=0) (Figure 5), and the allelic model (G *vs.* C: OR, 0.89; 95% CI, 0.79–0.99; P=0.033; I^2=25.4%) (Figure 6). Stratified analysis by severity of disease showed no significant association between the presence of the C79G polymorphism of the ADRB2 gene and vulnerability to mild to moderate asthma or severe asthma when a comparison was made with the genetic model. The main results of this analysis are shown in Table 2.

Sensitivity analysis and publication bias

Sensitivity analysis was performed to determine whether the results of the meta-analysis were significantly affected by the availability of any particular study. The findings showed that the pooled ORs were not substantially affected, which supported the strength of the results and the stability of the meta-analysis (Figure 7). Begg's funnel plot and Egger's test were used to assess the potential publication bias (Table 2). The symmetrical shape of the funnel plot was indicative of the lack of publication bias in the meta-analysis (Figure 8).

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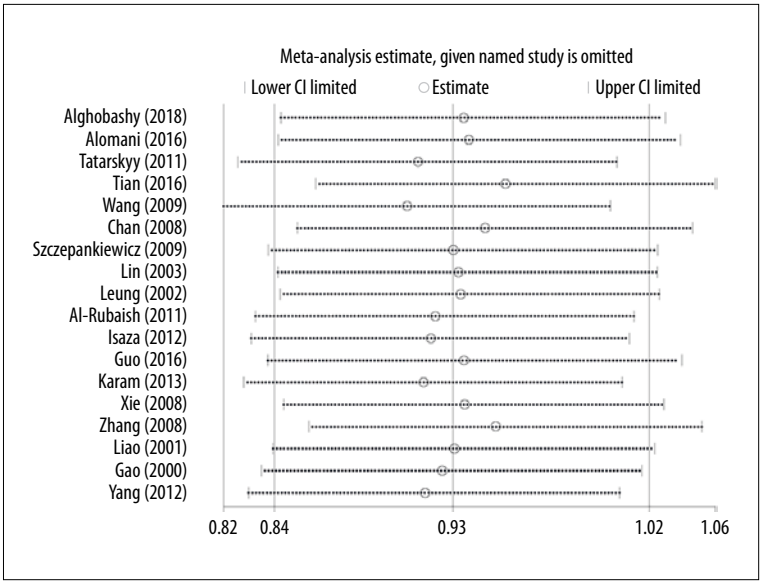

Figure 7. Sensitivity analysis for the influence of the C79G polymorphism of the ADRB2 gene and pediatric asthma in the allele model.

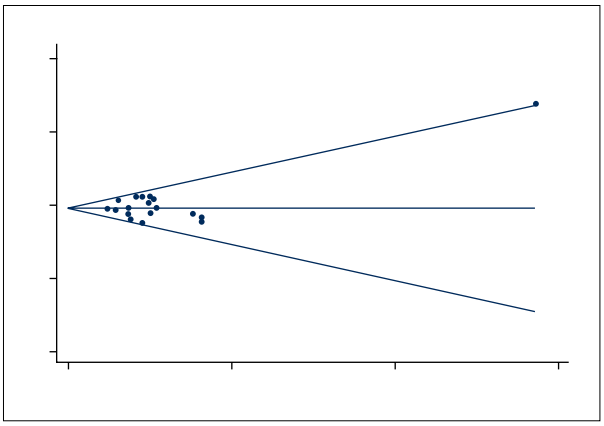

Figure 8. Funnel plot of the publication bias on the association between the C79G polymorphism of the ADRB2 gene and pediatric asthma in the allele model.

Discussion

Worldwide, asthma is a chronic respiratory disease that affects about 300 million people, including more than 10 million children [36,37]. Asthma now imposes an increasing burden on health systems throughout the world [1,38]. A first-line treatment approach for acute asthma is the use of inhaled β2-adrenergic receptor (β2-AR) agonists, due to their good bronchodilator effects, extensive therapeutic range, and few side effects [39]. However, there is significant variation in the degree of individual response to short-acting β2-agonist treatment, which is attributable to gene polymorphism [40,41], particularly in the ADRB2 gene that encodes for β2-AR [10,16,17,42].

The etiology of pediatric asthma remains poorly understood. Although an increasing number of controlled clinical studies have investigated the relationship between variants of the ADRB2 gene with the risk of asthma in children, the impact of the ADRB2 gene on asthma in children remains unclear. In 2002, the finding s from a study in Taiwanese showed that there was no significant association between the presence of the C79G polymorphism of the ADRB2 gene and the risk of asthma in children [43]. This result was inconsistent with the findings of the present study. Also, a study conducted in Egypt on children with asthma showed that the presence of the C79G polymorphism was associated with increased airway hyper-responsiveness to endogenous catecholamine, which result in augmented airway sensitivity to proinflammatory stimuli resulting in long-term airway inflammation [30]. A meta-analysis to evaluate the relationship between ADRB2 gene polymorphisms and the risk of asthma in China showed that the C79G polymorphism was a contributing factor associated with increased vulnerability to asthma in adults, but no significant association was found in children [44].

The present meta-analysis was the first to comprehensively assess the potential relationship between the presence of the C79G polymorphism of the ADRB2 gene and the risk of asthma in children. The findings contradict some of the findings from previously published studies. From this meta-analysis of 18 eligible published studies that included 2,982 pediatric patients with asthma patients and 2,651 controls, the findings were that the presence of the C79G polymorphism of the ADRB2 gene significantly reduced the risk of asthma in children. Stratified analysis according to the ethnicity showed that C79G polymorphism in the ADRB2 gene could be a protective factor for pediatric asthma, particularly in Asian populations. However, stratified analysis by disease severity showed no significant relationship between the presence of the C79G polymorphism of the ADRB2 gene and both the mild to moderate asthma and severe asthma in children.

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This study had several limitations. The majority of the identified published controlled studies involved Caucasians and Asian children with asthma, and the association between the C79G polymorphism of the ADRB2 gene and pediatric asthma in other ethnic groups remains unknown and requires further study. Also, heterogeneity existed in some subgroup analysis. Only published studies with adequate data were included in the meta-analysis. Publication bias might have been undetected by Begg's funnel plot and Egger's test. Finally, asthma is a complex disease that involves the interaction between genetic and environmental factors. Therefore, gene-gene interactions as well as gene-environment interactions should be considered in future controlled studies.

Conclusions

The findings from a meta-analysis of published studies on pediatric asthma showed that the C79G polymorphism of the ADRB2 gene might have a protective role, particularly in Asian populations. This study has highlighted the need for more controlled clinical studies that are well designed, large-scale, that include several ethnic groups, and that investigate environmental as well as genetic factors in the role of the C79G polymorphism of the ADRB2 gene, as well as other gene polymorphisms.

Conflict of interest

None.

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