Association of Vitamin D Receptor Gene Polymorphisms With Susceptibility to Childhood Asthma: A Meta-Analysis

Dong-Dong Zhao, MD,[1] Dan-Dan Yu, MD,[1] Qiong-Qiong Ren, MD,[1] Bao Dong, MD,[1] Feng Zhao, MD,[1] and Ye-Huan Sun, PhD[1,2]*

Summary. Background: As for the association of vitamin D receptor (VDR) gene polymorphisms with susceptibility to pediatric asthma, results of published studies yielded conflicts. A systematic review was conducted on the relationship between childhood asthma and VDR gene polymorphisms, including *Apa*I (rs7975232), *Bsm*I (rs1544410), *Fok*I (rs2228570), and *Taq*I (rs731236). Methods: PubMed, Web of Science, CBM (Chinese Biomedical Database), CNKI (China National Knowledge Infrastructure), and Wanfang (Chinese) database were searched for relevant studies. Pooled odds ratios (OR) with 95% confidence interval (CI) were calculated. Results: Overall results suggested that there was a statistically significant association between *Apa*I polymorphism and childhood asthma in homozygote model (OR = 1.674, 95%CI = 1.269–2.208, $P < 0.001$) and allele model (OR = 1.221, 95%CI = 1.084–1.375, $P = 0.001$). Stratification by ethnicity revealed a statistical association in Asians (OR = 1.389, 95%CI = 1.178–1.638, $P < 0.001$). There was some evidence of an association between *Bsm*I polymorphism and childhood asthma in the homozygote (OR = 1.462, 95%CI = 1.016–2.105, $P = 0.041$) and allele models (OR = 1.181, 95%CI = 1.006–1.386, $P = 0.042$). This association reached significance only in the Caucasian group (OR = 1.236, 95%CI = 1.029–1.485, $P = 0.023$). For *Fok*I, a statistical association was detected in dominant model (OR = 1.281, 95%CI = 1.055–1.555, $P = 0.012$); this association was significant in allele model (OR = 1.591, 95%CI = 1.052–2.405, $P = 0.028$) in Caucasian. Conclusion: *Apa*I polymorphism plays a particular role in childhood asthma in Asians. *Fok*I polymorphism may be connected with pediatric asthma in Caucasian population. And *Bsm*I polymorphism marginally contributes to childhood asthma susceptibility, while there might be no association between *Taq*I polymorphism and childhood asthma risk. **Pediatr Pulmonol. 2016; 9999:XX–XX.** © 2016 Wiley Periodicals, Inc.

Key words: pediatric asthma; vitamin D; gene polymorphism.

Funding source: None reported.

INTRODUCTION

Asthma, one of the most common chronic respiratory disorders among children, is characterized by airway inflammation and hyper-responsiveness[1] with typical symptoms such as intermittent attacks of breathlessness, wheezing, and coughing. In the last decade, there has been an increasing prevalence of childhood asthma.[2] A total of 7.1 million children were affected in the US.[3] And it was estimated that at least 250 thousand people died of asthma annually in the early age.[4] Several potential risk factors were studied such as early-life exposure to ambient air pollution,[5] infancy microbial, and metabolic alterations,[6] etc. Furthermore, a growing number of studies suggested that the susceptibility to asthma was influenced by genetic background, including interleukin-17 gene,[7] interleukin-27 gene,[8] and vitamin D receptor (VDR) gene.

Vitamin D not only plays a critical role in bones primarily as a vitamin, but also influences the pathogenesis of immune-mediated disorders as a hormone.[9] VDR is correlated with the function of vitamin D for the most part. As a transcriptional mediator, it regulates the effects

[1]Department of Epidemiology and Health Statistics, Anhui Medical University, Hefei, China.

[2]Centre for Evidence-Based Practice, Anhui Medical University, Hefei, China.

Conflict of interest: none.

*Correspondence to: Ye-Huan Sun, PhD, Department of Epidemiology and Statistics, School of Public Health, Anhui Medical University, No. 81 Meishan Road, Hefei, Anhui 230032, China.
E-mail: yhsun_ahmu_edu@yeah.net

Received 3 May 2016; Revised 19 July 2016; Accepted 26 July 2016.

DOI 10.1002/ppul.23548
Published online in Wiley Online Library (wileyonlinelibrary.com).

of the active form of vitamin D 1,25-dihydroxyvitamin D3 [1, 25(OH) 2D3]. Previous study showed that VDR regulated gene expression in many cell types, including immune cells.[10] A series of restriction fragment length polymorphisms (RFLP) in VDR gene have been reported, including *Bsm*I (rs1544410), *Apa*I (rs7975232), *Fok*I (rs2228570), *Taq*I (rs731236) restriction sites.[11] Of these polymorphic sites, *Apa*I and *Bsm*I have been identified located in intron 8 and *Taq*I in exon 9. Both of them at the 3′ end of the VDR gene which is known to be involved in regulation of gene expression through regulation of mRNA stability and expression level[12]; whereas the *Fok*I in exon 2 which leads to a protein with different size: the shorter form of the protein (424 amino acids) being more active and abundant than the longer one (427 amino acids).[13]

A number of studies have examined the potential contribution caused by VDR genes to pediatric asthma susceptibility. But the results of these articles have been inconsistent due to small sample sizes, clinical heterogeneity, or a combination of above factors. To offset these limitations, this meta-analysis was performed to investigate whether VDR gene polymorphisms play a role in childhood asthma.

METHODS

Identification of Eligible Studies

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement was consulted to report this systematic review.[14] Searches were made electronically in PubMed, Web of Science, CBM (Chinese Biomedical Database), CNKI (China National Knowledge Infrastructure), and Wanfang (Chinese) database (update to January 2016) with following searching terms: (polymorphism*) and (VDR OR vitamin D receptor) and (wheeze or asthma) and (Child* or infant or preschool or adolescent). The references quoted in relevant articles were also reviewed for additional publications. The languages were limited to English and Chinese.

Inclusion Criteria

Studies should fulfill the following inclusive criteria: (1) original study of human participants; (2) case–control or cohort design; (3) allele or phenotype frequencies was available; (4) genotype distribution in controls met the Hardy–Weinberg equilibrium (HWE).

Exclusion Criteria

The exclusive criteria were as follows: (1) insufficient data to ascertain the number of genotypes or odds ratio (OR); (2) review or conference; (3) duplicate or overlapping studies.

Data Extraction

Two investigators filtered the abstracts and collected data independently. In case of any dispute, a third author would assess these articles. The following characteristics of selected articles are shown in Table 1: first author, year of publication, country, ethnicity, number of cases and controls, genotyping method, and studied polymorphisms.

Statistical Method

Meta-analyses were calculated with the aid of STATA 11.0 software, and all of the data extracted from eligible studies were calculated as OR and 95%CI in four models: the allelic model (G vs. C), dominant model (GG + GC vs. CC), recessive model (GG vs. GC + CC), and homozygote model (GG vs. CC). Different genetic backgrounds and environmental factors can affect the sensitivity to particular genomic variants. To evaluate ethnicity-specific effect, subgroup analyses were stratified by ethnicity. HWE in control group of every study was examined, and $P < 0.05$ was defined as departure from HWE.

TABLE 1— Characteristics of the Studies Included in the Meta-Analysis

First author	Year	Country	Ethnicity	Source of control	Case/control	Genotyping methods	Studied polymorphism	HWE	Quality scores
Saadi[16]	2009	China	Asian	HB	567/523	PCR-RFLP	*Apa*I *Bsm*I *Fok*I *Tap*I	Y	6
Zhen[23]	2010	China	Asian	PB	30/40	PCR-RFLP	*Apa*I	Y	6
Pillai[20]	2011	America	African-American	HB	139/74	PCR-RFLP	*Apa*I *Fok*I *Tap*I	Y	7
Ismail[21]	2013	Egypt	Caucasian	PB	51/33	Allele-specific PCR	*Fok*I	Y	6
Maalmi[19]	2013	Tunisia	Caucasian	HB	155/225	PCR-RFLP	*Apa*I *Bsm*I *Fok*I *Tap*I	Y	6
Ma[22]	2014	China	Asian	PB	60/60	PCR-RFLP	*Apa*I *Bsm*I *Fok*I *Tap*I	Y	7
Mo[24]	2015	China	Asian	PB	71/71	PCR-RFLP	*Apa*I *Bsm*I	Y	8
Einisman[18]	2015	Chile	Caucasian	PB	75/227	PCR-RFLP	*Apa*I *Fok*I *Tap*I	Y	6
Papadopoulou[17]	2015	Cyprus	Caucasian	PB	190/671	PCR	*Apa*I *Bsm*I *Tap*I	Y	9

Hb, hospital-based; Pb, population-based.

The heterogeneity of effects across individual studies was evaluated with I^2-statistic ($0\% < I^2 < 25\%$, no heterogeneity; $25\% < I^2 < 50\%$, moderate heterogeneity; $50\% < I^2 < 75\%$, large heterogeneity; and $75\% < I^2 < 100\%$, extreme heterogeneity).[15] If the *P*-value of the heterogeneity test was more than 0.10, the pooled OR was estimated by the fixed-effects model; otherwise, a random-effects model was employed. Moreover, Begg's test and Egger's test were utilized to detect the potential publication bias, which might exist when *P*-value is less than 0.05. To weigh the influence of every single study on the pooled effects, sensitivity analysis was performed.

RESULTS

Study Characteristics

The progress of selecting eligible studies was outlined in Figure 1. A total of 80 potential relevant studies consisting of 20 Chinese articles and 60 English papers were retrieved initially. A total of nine studies were found related VDR polymorphism to childhood asthma after removal of duplicates and those studies did not meet the inclusive criteria.[16–24] There were eight studies on *Apa*I (rs7975232),[16–20,22–24] five on *Bsm*I (rs15444 10),[16,17,19,22,24] six on *Fok*I (rs2228570),[16,18–22] and six involved *Tap*I (rs731236)[16–20,22] separately. The qualities of included studies were estimated according to the Newcastle–Ottawa scale. Main characteristics of individual studies were summarized in Table 1.

*Apa*I Polymorphism and Childhood Asthma Susceptibility

All eight studies encompassing 1,254 cases and 1,674 health controls examined the association of *Apa*I polymorphism with childhood asthma. Results revealed that an increased risk was observed in allele model (G vs. A, OR = 1.221, 95%CI = 1.084–1.375, $P = 0.001$), homozygote model (GG vs. AA, OR = 1.674, 95% CI = 1.269–2.208, $P < 0.001$), dominant model (GG + GA vs. AA, OR = 1.199, 95%CI = 1.026–1.402, $P = 0.023$), and recessive model (GG vs. GA + AA, OR = 1.561, 95%CI = 1.201–2.030, $P = 0.001$) (Fig. 2 and Table 2). Subgroup analysis by ethnicity stratification showed that there was a relationship in Asian population (G vs. A, OR = 1.389, 95%CI = 1.178–1.638, $P < 0.001$) (Table 3).

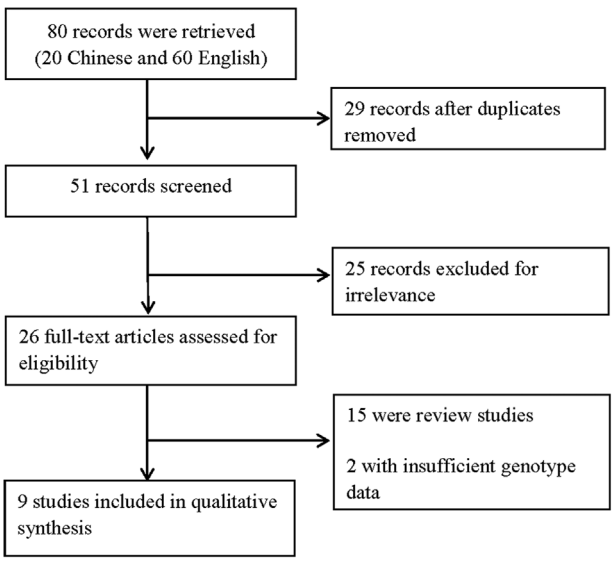

Fig. 1. Study flow diagram.

*Bsm*I Polymorphism and Childhood Asthma Susceptibility

Five studies determined the relationship between *Bsm*I polymorphism and susceptibility to childhood asthma containing 2,541 subjects (1,031 cases and 1,510 controls). This meta-analysis suggested an association in allele model (T vs. C, OR = 1.181, 95%CI = 1.006–1.386, $P = 0.042$), and homozygote model (TT vs. CC, OR = 1.462, 95% CI = 1.016–2.105, $P = 0.041$), but not in other models (TT + TC vs. CC, OR = 1.201, 95%CI = 0.940–1.533, $P = 0.142$; TT vs. TC + CC, OR = 1.286, 95%CI = 0.978–1.691, $P = 0.072$) (Fig. 2 and Table 2). In addition, there was an association in Caucasian group (T vs. C, OR = 1.236, 95%CI = 1.029–1.485, $P = 0.023$) (Table 3).

*Fok*I Polymorphism and Childhood Asthma Susceptibility

Six articles including 1,028 cases and 892 controls identified a probable association in the dominant model (GA + GG vs. AA, OR = 1.281, 95%CI = 1.055–1.555, $P = 0.012$), also in allele model of Caucasian by ethnicity-specific analysis (G vs. A, OR = 1.591, 95%CI = 1.052–2.405, $P = 0.028$) (Table 3). In contrast, the recessive model and homozygote models indicated negative results (Fig. 2 and Table 2).

*Tap*I Polymorphism and Childhood Asthma Susceptibility

We analyzed 1,149 cases and 1,562 controls from six records to assess the relationship between *Tap*I polymorphism and childhood asthma susceptibility. Finally, not only four genetic models (Fig. 2 and Table 2), but also subgroup analysis failed to demonstrate any association (Table 3).

Sensitivity Analysis and Publication Bias

To assess the stability of the results, sensitivity analysis was conducted by excluding each study sequentially. Although, two pilot studies were included, statistical results indicated that only one study[22] was found to play

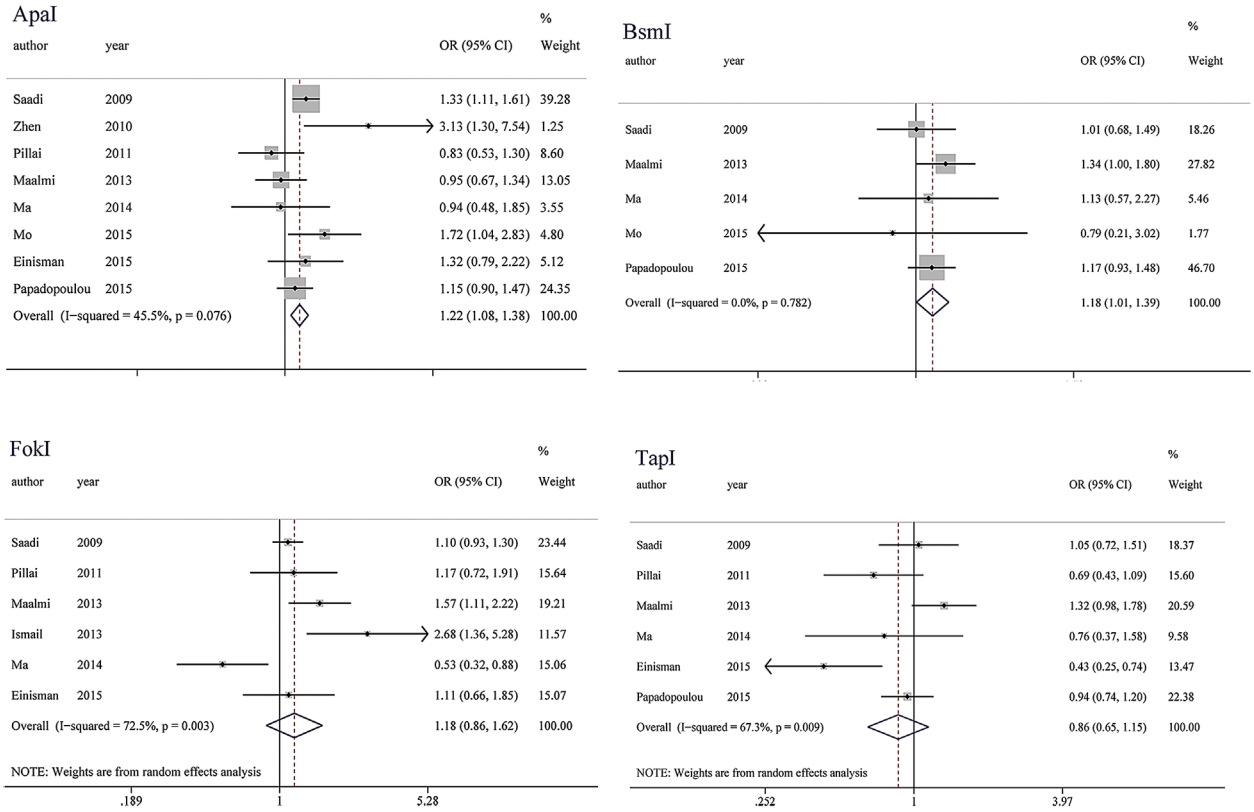

Fig. 2. Odds ratios and 95%CI for each study and pooled data for the association between VDR polymorphisms and childhood asthma.

an excessive role on the pooled OR, and it was limited to the analysis of *Fok*I polymorphism in allele model. There was no evidence of heterogeneity according to Begg's test and Egger's test (Table 2).

DISCUSSION

Based on previous report, Childhood asthma was associated with several factors including intake of vitamin D, eosinophilia, antibiotic exposure during pregnancy, environmental exposures, and predisposition genes.[25–28] The function of vitamin D is influenced by the mediation of VDR gene.[29] Therefore, there was accumulating evidence about the association between pediatric asthma and genetic polymorphism of VDR gene.[16,30] *Apa*I, *Bsm*I, *Fok*I, and *Taq*I were the most common four genes. But the previous results yielded interference. And we performed this meta-analysis to get a better understanding of these contradictory results.

Four polymorphisms of VDR gene were investigated in current meta-analysis. There were nine studies focusing on the association of these genes with childhood asthma in case-control manner. A pooled analysis with a larger sample size, subgroup analysis, sensitivity analysis, and heterogeneity explore aimed to comprehend the conflicts and association. Compared with previous independent studies, our meta-analysis enhanced the statistical power and drew a particularly instructive conclusion.

The pooled results suggested that that there was a significant association between VDR gene rs7975232 polymorphism and childhood asthma susceptibility in dominant model (OR = 1.2), recessive model (OR = 1.6), co-dominant model (OR = 1.7), and allelic model (OR = 1.2). And rs1544410 polymorphism marginally associate with childhood asthma in co-dominant model (OR = 1.5). Interestingly, it was at variance with the finding of a previous study.[31] It gave support for that rs7975232 polymorphism was not candidate for susceptibility to childhood asthma, while rs2228570, and rs731236 polymorphisms contributed to asthma susceptibility. Following reasons may account for the conflicting results: (1) different ages and gender ratios affected the results,[32,33] especially when we focused on children; (2) different studies used different genotyping methods and study designs; (3) though pooled results were closer to the real value, the small number of studies included in both previous meta-analyses may lead to a little bias and reduce the power of revealing the relationship.

Ethnicity-specific analysis suggested that the risk of developing childhood asthma was almost 1.5-fold higher in Asians with *Apa*I G allele (OR = 1.4 95%CI = 1.2–1.6), but not in Caucasians and African-Americans. When it comes to

TABLE 2— Summary of OR and 95%CI for Association Between *Apa*I, *Bsm*I, *Fok*I, and *Taq*I Gene Polymorphisms and Childhood Asthma Risk

	Test of association			Test of heterogeneity					
	OR(95%CI)	Z	*P*	χ^2	*P*	I^2 (%)	Model	Begg's test (*P*)	Egger's test (*P*)
*Apa*I									
G versus A	1.221 (1.084–1.375)	3.29	0.001	12.86	0.076	45.5	F	0.711	0.836
GA + GG versus AA	1.199 (1.026–1.402)	2.28	0.023	13.08	0.070	46.5	F	0.536	0.693
GG versus AA + GA	1.561 (1.201–2.030)	3.32	0.001	5.77	0.567	0.0	F	0.711	0.654
GG versus AA	1.674 (1.269–2.208)	3.65	<0.001	6.71	0.460	0.0	F	0.711	0.755
*Bsm*I									
T versus C	1.181 (1.006–1.386)	2.03	0.042	1.75	0.782	0.0	F	0.462	0.366
TC + TT versus CC	1.201 (0.940–1.533)	1.47	0.142	5.54	0.236	27.8	F	0.462	0.840
TT versus TC + CC	1.286 (0.978–1.691)	1.80	0.072	2.42	0.489	0.0	F	0.308	0.192
TT versus CC	1.462 (1.016–2.105)	2.04	0.041	4.25	0.236	29.4	F	0.308	0.228
*Fok*I									
G versus A	1.181 (0.863–1.618)	1.04	0.299	18.19	0.003	72.5	R	1.000	0.781
GA + GG versus AA	1.281 (1.055–1.555)	2.50	0.012	5.90	0.316	15.2	F	0.707	0.874
GG versus GA + AA	1.174 (0.528–2.610)	0.39	0.694	16.63	0.002	76.0	R	0.462	0.639
GG versus AA	1.324 (0.562–3.121)	0.64	0.522	15.99	0.003	75.0	R	0.462	0.701
*Tap*I									
T versus C	0.865 (0.652–1.146)	1.01	0.312	15.29	0.009	67.3	R	0.260	0.201
TC + TT versus CC	1.027 (0.846–1.246)	0.27	0.790	3.32	0.651	0.0	F	0.133	0.121
TT versus TC + CC	0.934 (0.493–1.767)	0.21	0.833	13.18	0.022	62.1	R	0.707	0.940
TT versus CC	0.980 (0.701–1.369)	0.12	0.905	9.50	0.091	47.4	F	0.707	0.846

F, fixed effects model; R, random effects model.

*Fok*I, our study suggested that the G allele may increase the asthma risk compared with the A allele (OR = 1.6 95% CI = 1.1–2.4) in Caucasian population, but a lack of association in Asians. Diverse roles of the same gene in ethnicity-specific subgroup analysis might be attributed to following aspects: firstly, ethnic differences resulted in the inconsistent outcomes; furthermore, a number of autoimmune diseases containing asthma are caused by interactions of environmental and genetic factors[34,35]; two things can not be ignored are that small sample size of both ethnicity groups and insufficiency of studies included (two in Asians, three in Caucasian). A small sample size and limited small number of studies in the ethnic groups may play noticeable roles in the discrepancy between different ethnic groups. *Apa*I polymorphism has been proposed to be associated with childhood asthma susceptibility in Chinese.[24] Similarly,

TABLE 3— Ethnicity-Stratification Analyses of the Genetic Susceptibility to Childhood Asthma

			Test of association				Test of heterogeneity		
Polymorphisms	Population	No. of studies	OR(95%CI)	Z	*P*	Model	χ2	*P*	I^2 (%)
*Apa*I(rs7975232) G versus A	Overall	8	1.221 (1.084–1.375)	3.29	0.001	F	12.86	0.076	45.5
	Asian	4	1.389 (1.178–1.638)	3.91	<0.001	F	5.44	0.142	44.9
	Caucasian	3	1.107 (0.918–1.335)	1.06	0.288	F	1.31	0.520	0.0
	African-American	1	0.831 (0.530–1.301)	0.81	0.417	NA	NA	NA	NA
*Bsm*I(rs1544410) T versus C	Overall	5	1.181 (1.006–1.386)	2.03	0.042	F	1.75	0.782	0.0
	Asian	3	1.018 (0.732–1.416)	0.11	0.914	F	0.23	0.892	0.0
	Caucasian	2	1.236 (1.029–1.485)	2.27	0.023	F	0.51	0.477	0.0
*Fok*I(rs2228570) G versus A	Overall	6	1.181 (0.863–1.618)	1.04	0.299	R	18.19	0.003	72.5
	Asian	2	0.793 (0.388–1.621)	0.64	0.525	R	7.08	0.008	85.9
	Caucasian	3	1.591 (1.052–2.405)	2.20	0.028	R	4.14	0.126	51.7
	African-American	1	1.172 (0.719–1.911)	0.64	0.524	NA	NA	NA	NA
*Tap*I(rs731236) T versus C	Overall	6	0.865 (0.652–1.146)	1.01	0.312	R	15.29	0.009	67.3
	Asian	2	0.980 (0.705–1.361)	0.12	0.902	F	0.59	0.444	0.0
	Caucasian	3	0.859 (0.526–1.402)	0.61	0.544	R	12.72	0.002	84.3
	African-American	1	0.688 (0.434–1.091)	1.59	0.112	NA	NA	NA	NA

F, fixed effects model; R, random effects model; NA, not available.

another study in Chinese population showed significant difference in allele frequency of *Apa*I polymorphism between patients and controls.[23] However, Ma et al.[22] suggested no statistically significant difference between patients and controls. Owing to that few studies focused on these polymorphisms in Chinese population, these results might be unreliable and should be treated with caution.

Vitamin D is significantly associated with lung function in children with a dose-response effect,[36] and bronchial inflammation is also possibly regulated by vitamin D.[37] Zheng et al.[38] found that 1,25-dihydroxyvitamin D3 as an intermediary could reduce airway inflammatory reaction significantly in pig models. Combination of the previous and present data led tentatively to the prediction that VDR gene *Apa*I polymorphism down-regulate VDR gene expression, then less 1,25-dihydroxyvitamin D3 would combine with VDR. Ultimately, it led to deteriorative control of inflammatory in pediatric asthma.

Several potential limitations of this study should be noted. First, although no publication bias was detected by several statistical methods, it still could exist as a result of that only published articles were included. Language bias should not be ignored, because our literature search was based on English and Chinese. Second, some factors such as different disease status, gender ratio and genotyping method might affect the integration and data interpretation of the included studies. Thirdly, limited number of studies resulted in insufficient statistical power. Finally, insufficient original data prevented us from investigating other potential risk factors, for example, gene–environment interaction.

In summary, results from this meta-analysis suggested that VDR gene *Apa*I polymorphism *was* significantly associated with the increased risk of childhood asthma in Asians. There might be correlation between *Fok*I polymorphism and pediatric asthma in Caucasian. *Bsm*I is marginally associated with childhood asthma susceptibility; while no significant association between *Taq*I polymorphism and childhood asthma risk was identified.

REFERENCES

1. Page TF, Beck-Sague CM, Pinzon-Iregui MC, Cuddihy A, Tyler T, Forno E, Dean AG, Siven J, Pottinger S, Gasana J. Asthma in underserved schoolchildren in Miami, Florida: results of a school- and community-based needs assessment. J Asthma 2013;50:480–487.
2. Lin R, Guan R, Liu X, Zhao B, Guan J, Lu L. Significant rise of the prevalence and clinical features of childhood asthma in Qingdao China: cluster sampling investigation of 10,082 children. BMC Public Health 2014;14:1002.
3. Bloom B, Jones LI, Freeman G. Summary health statistics for U. S. children: National Health Interview Survey, 2012. Vital and health statistics Series 10, Data from the National Health Survey 2013:1–81.
4. Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, Brightling CE, Burney P, Bush A, Busse WW, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. J Allergy Clin Immunol 2010;126:926–938.
5. Deng Q, Lu C, Norback D, Bornehag CG, Zhang Y, Liu W, Yuan H, Sundell J. Early life exposure to ambient air pollution and childhood asthma in China. Environ Res 2015;143:83–92.
6. Arrieta MC, Stiemsma LT, Dimitriu PA, Thorson L, Russell S, Yurist-Doutsch S, Kuzeljevic B, Gold MJ, Britton HM, Lefebvre DL, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. Sci Transl Med 2015;7:307ra152.
7. Du J, Han JC, Zhang YJ, Qi GB, Li HB, Zhang YJ, Cai S. Single-nucleotide polymorphisms of IL-17 gene are associated with asthma susceptibility in an Asian population. Med Sci Monit 2016;22:780–787.
8. Zhang YF, Zhao AD. Common polymorphisms in IL-27 genes may contribute to risk of various human diseases in Asian populations: a meta-analysis. Med Sci Monit 2016;22:766–775.
9. Muehleisen B, Gallo RL. Vitamin D in allergic disease: shedding light on a complex problem. J Allergy Clin Immunol 2013;131:324–329.
10. Booth DR, Ding N, Parnell GP, Shahijanian F, Coulter S, Schibeci SD, Atkins AR, Stewart GJ, Evans RM, Downes M, et al. Cistromic and genetic evidence that the vitamin D receptor mediates susceptibility to latitude-dependent autoimmune diseases. Genes Immun 2016;17:213–219.
11. Kostner K, Denzer N, Muller CS, Klein R, Tilgen W, Reichrath J. The relevance of vitamin D receptor (VDR) gene polymorphisms for cancer: a review of the literature. Anticancer Res 2009;29:3511–3536.
12. Fang Y, van Meurs JB, d'Alesio A, Jhamai M, Zhao H, Rivadeneira F, Hofman A, van Leeuwen JP, Jehan F, Pols HA, et al. Promoter and 3′-untranslated-region haplotypes in the vitamin d receptor gene predispose to osteoporotic fracture: the rotterdam study. Am J Hum Genet 2005;77:807–823.
13. Whitfield GK, Remus LS, Jurutka PW, Zitzer H, Oza AK, Dang HT, Haussler CA, Galligan MA, Thatcher ML, Encinas Dominguez C, et al. Functionally relevant polymorphisms in the human nuclear vitamin D receptor gene. Mol Cell Endocrinol 2001;177:145–159.
14. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) elaboration and explanation. BMJ 2015;349:g7647.
15. Zintzaras E, Ioannidis JP. Heterogeneity testing in meta-analysis of genome searches. Genet Epidemiol 2005;28:123–137.
16. Saadi A, Gao G, Li H, Wei C, Gong Y, Liu Q. Association study between vitamin D receptor gene polymorphisms and asthma in the Chinese Han population: a case-control study. BMC Med Genet 2009;10:71.
17. Papadopoulou A, Kouis P, Middleton N, Kolokotroni O, Karpathios T, Nicolaidou P, Yiallouros PK. Association of vitamin D receptor gene polymorphisms and vitamin D levels with asthma and atopy in Cypriot adolescents: a case-control study. Multidiscip Respir Med 2015;10:26–26.
18. Einisman H, Reyes ML, Angulo J, Cerda J, Lopez-Lastra M, Castro-Rodriguez JA. Vitamin D levels and vitamin D receptor gene polymorphisms in asthmatic children: a case-control study. Pediatr Allergy Immunol 2015;26:545–550.
19. Maalmi H, Sassi FH, Berraies A, Ammar J, Hamzaoui K, Hamzaoui A. Association of vitamin D receptor gene polymorphisms with susceptibility to asthma in Tunisian children: a case control study. Hum Immunol 2013;74:234–240.
20. Pillai DK, Iqbal SF, Benton AS, Lerner J, Wiles A, Foerster M, Ozedirne T, Holbrook HP, Payne PW, Jr., Gordish-Dressman H, et al. Associations between genetic variants in vitamin D

metabolism and asthma characteristics in young African Americans: a pilot study. J Investig Med 2011;59:938–946.
21. Ismail MF, Elnady HG, Fouda EM. Genetic variants in vitamin D pathway in Egyptian asthmatic children: a pilot study. Hum Immunol 2013;74:1659–1664.
22. Ma JH, Tang CC, Zhang XH, Gao Y, Bai H. Correlation between polymorphisms of vitamin receptor gene and asthma in Ningxia Hui children. Ningxia Med J 2014;36:870–874.
23. Zhen YF, Wang L. Association of vitamin D receptor gene polymorphisms w ith children asthma and wheezy. Chin Prev Med 2010;11:1055–1004.
24. Mo LY, Deng YC, Huang CZ, Liu JL. Association between polymorphisms of vitamin D receptor genes and asthma in children. CJCHC 2015;23:742–744.
25. Guilbert TW, Mauger DT, Lemanske RF, Jr. Childhood asthma-predictive phenotype. J Allergy Clin Immunol Pract 2014;2: 664–670.
26. Kamran A, Hanif S, Murtaza G. Risk factors of childhood asthma in children attending Lyari General Hospital. J Pak Med Assoc 2015;65:647–650.
27. Zhao D, Su H, Cheng J, Wang X, Xie M, Li K, Wen L, Yang H. Prenatal antibiotic use and risk of childhood wheeze/asthma: a meta-analysis. Pediatr Allergy Immunol 2015;26:756–764.
28. Chan WC, Sy HY, Kong AP, Wong CK, Tse LY, Hon KL, Chan JC, Wong GW, Leung TF. Childhood asthma is associated with polymorphic markers of PROC on 2q14 in addition to 17q21 locus. Pediatr Allergy Immunol 2015;26: 173–180.
29. Buckberry S, Spronk F, Wilson RL, Laurence JA, Bianco-Miotto T, Leemaqz S, O'Leary S, Anderson PH, Roberts CT. The effect of Vdr gene ablation on global gene expression in the mouse placenta. Genomics Data 2015;6:72–73.
30. Michel S, Liang L, Depner M, Klopp N, Ruether A, Kumar A, Schedel M, Vogelberg C, von Mutius E, von Berg A, et al. Unifying candidate gene and GWAS approaches in asthma. PLoS ONE 2010;5:e13894.
31. Tizaoui K, Berraies A, Hamdi B, Kaabachi W, Hamzaoui K, Hamzaoui A. Association of vitamin D receptor gene polymorphisms with asthma risk: systematic review and updated meta-analysis of case-control studies. Lung 2014;192:955–965.
32. Csaba G, Pallinger E. Gender dependence in the hormone content of the immune cells. Acta Physiol Hung 2009;96:45–50.
33. Malling TH, Sigsgaard T, Andersen HR, Deguchi Y, Brandslund I, Skadhauge L, Thomsen G, Baelum J, Sherson D, Omland O. Differences in associations between markers of antioxidative defense and asthma are sex specific. Gend Med 2010;7:115–124.
34. Bouma G, Strober W. The immunological and genetic basis of inflammatory bowel disease. Nat Rev Immunol 2003;3:521–533.
35. Khoo AL, Joosten I, Michels M, Woestenenk R, Preijers F, He XH, Netea MG, van der Ven AJ, Koenen HJ. 1,25-Dihydroxyvitamin D3 inhibits proliferation but not the suppressive function of regulatory T cells in the absence of antigen-presenting cells. Immunology 2011;134:459–468.
36. Yao TC, Tu YL, Chang SW, Tsai HJ, Gu PW, Ning HC, Hua MC, Liao SL, Tsai MH, Chiu CY, et al. Serum 25-hydroxyvitamin D levels in relation to lung function and exhaled nitric oxide in children. J Pediatr 2014;165:1098–1103. e1091.
37. Miraglia Del Giudice M, Allegorico A, Grandone A, Galdo F, Cuppari C, Capasso M, Maiello N. Vitamin D and bronchial inflammation in asthmatic children. J Biol Regul Homeost Agents 2015;29:125–129.
38. Zheng XH, Zhang GD, Zhang GH, Mai RQ, Shen L. Effect of 1,25-dihydroxyvitamin D3 on mast cells tryptase in asthmatic guinea pigs. Asian Pac J Trop Dis 2015;8:494–497.