



The association between vitamin D receptor gene polymorphisms and asthma: a systematic review and meta-analysis

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Background: Numerous studies have reported on the genetic factors related to asthma. In recent years, the vitamin D receptor (VDR) has been identified as one of the asthma susceptibility genes that is closely associated with the pathogenesis of asthma.

Methods: Randomized controlled trials (RCTs) related to asthma and the VDR were identified from the Chinese and English databases. The following keywords were used as search terms: “asthma”, “vitamin D receptor”, “VDR”, “polymorphism”, and “mutation”. Meta-analysis was performed using RevMan 5.3 and Stata 13 software provided by the Cochrane system.

Results: A total of 7 RCTs were included in this meta-analysis, 6 of which described the correct random allocation methods, 6 described the allocation plan in detail, and 4 used the blinding method. The frequency of the CC + CA dominant genotype at the *Apa I* locus and the GG + GA genotype frequency at the *Bsm I* locus of the VDR gene were significantly higher in asthmatic patients compared to control healthy patients [odds ratio (OR) =0.81, 95% confidence interval (CI): 0.68 to 0.98, P=0.03<0.05; and OR =2.05, 95% CI: 1.23 to 3.41, P=0.006<0.05, respectively]. There were no significant differences between the CC, CT, and TT genotype frequencies at the *Fok I* site of the VDR gene in the experimental group and the CC, CT, TT genotype frequencies at the *Taq I* site and the control group (P>0.05). There was no significant difference between the genotype frequencies.

Discussion: Meta-analysis confirmed that VDR gene polymorphisms are closely related to the onset of asthma, and the gene expression of the *Fok I*, *Bsm I*, *Apa I*, and *Taq I* loci directly affects the incidence of asthma.

Keywords: Vitamin D receptor (VDR); gene polymorphism; asthma; meta-analysis

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Introduction

Bronchial asthma is a chronic inflammation of the airways, often accompanied by extensive and variable airflow obstruction. Patients often present with shortness of breath, chest tightness or chest pain, sleep difficulties, whistling or wheezing on exhalation, and coughing which can occur

at night and/or early in the morning. In severe cases, dyspnea or even sudden death may occur (1). The disease is common, with a high incidence mainly in young adults and children (2). The global prevalence of asthma has increased by 20–50% every decade, and the prevalence of asthma in Chinese adults is 1.09% (3). Asthma can often be complicated by bacterial infection and severe asthma can

cause pulmonary edema and even death. The main forms of treatments include anti-airway inflammation drugs (such as glucocorticoids), bronchodilators (such as salbutamol aerosol), and specific immunotherapy (4).

While the etiology of asthma is still not fully understood, it is believed to be closely associated with genetic and environmental factors (such as inhalation of mites, dust, drugs, and other allergens). It can also be related to factors such as air pollution, smoking, respiratory virus infection, strenuous exercise, inhalation of copious amounts of cold air, and allergic physique of the mother during the fetal period (5). The current global research data on asthma susceptibility shows that there are more than one hundred known asthma-related genes. In addition, many studies suggest that asthma and its specific phenotypes are linked to multiple regions in the genome and involve multiple biological pathways. Cytokine genes, such as tumor necrosis factor (TNF), interleukin (IL)-4 and IL-3, transforming growth factor (TGF), intercellular adhesion molecule (ICAM)-1, and human leukocyte antigen (HLA) genes, as well as membrane receptor genes, such as prostaglandin D2 receptor, IgE receptor, and vitamin D receptor (VDR), have been suggested to be associated with the pathogenesis of asthma. Furthermore, other types of genes including interferon (IFN)- γ , ADAM33, and others may also play a role in asthma. Some studies have pointed out that Th9, Treg cell ratio, serum IL-9, and TGF- β in patients with asthma- β . According to the stage of asthma and the severity of lung infection, the proportion of Th9 and Treg cells in peripheral blood, serum IL-9, and TGF- β had significant differences in cytokine levels, such as Th9, Treg cell ratio, IL-9, and TGF- β . The level has a weak negative correlation with pulmonary function indexes, which may be caused by the interaction between inflammatory response and structural cells mediated by immune cells involved in innate and acquired immunity, so as to affect the action mode of various cytokines in the immune pathway of asthmatic patients (6).

On this basis, in recent reports, a variety of gene polymorphisms have been confirmed to be highly related to the susceptibility of asthma, such as β 2 adrenergic receptor (β 2-drenergic receptor, ADRB2) gene, cytotoxicity T lymphocyte-associated antigen 4 (CTLA-4) gene, IL-17A gene, glucocorticoid induced transcript 1, GLCCI1 gene, TNF- α Gene, chitinase 3-like protein 1 (CHI3L1) gene, and methylenetetrahydrofolate reductase (MTHFR) gene (7,8).

Vitamin D (Vit D) is a steroid derivative, and its

activated form 1,25-(OH) $_2$ D $_3$ can regulate blood calcium and tissue cell differentiation (9). Activation of Vit D requires the combined action of the liver and kidney hydroxylase. Current research believes that there is a strong correlation between Vit D gene polymorphism and gestational diabetes, autoimmune thyroid disease, osteoporotic fractures, chronic kidney disease, lung infectious diseases, and asthma-like respiratory diseases. It is believed that Vit D can affect embryonic lung development and participate in the regulatory processes involved in the body's immune system (10). Vit D does not directly act on target organs, but works by binding to the VDR, which is located in the q13-14 region of the long arm of human chromosome 12. Studies have found that the q arm of chromosome 12 where VDR is located is similar to the asthma-related region, and polymorphisms in this region are a good indicator of the occurrence of asthma. Genome scanning has also revealed that the VDR is a candidate gene associated with asthma (11). To date, four single nucleotide polymorphism (SNP) sites have been reported in the VDR gene and these are located in the *Fok I* locus, *Bsm I* locus, *Apa I* locus, and *Taq I* locus (12,13).

Although there have been many studies on VDR gene polymorphisms in asthma patients, the relationship between asthma susceptibility and polymorphisms at different VDR loci is unclear. Therefore, this research innovatively conducts a meta-analysis of the current clinical research content involving the correlation between asthma patients and VDR gene polymorphisms, hoping to compare the overall correlation of various VDR locus polymorphisms with asthma susceptibility. To track the genetic causes of asthma, more high-quality randomized controlled trials (RCTs) should be included for systematic reviews and meta-analysis. This study is a systematic evaluation and meta-analysis to study the correlation between the polymorphism of different VDR gene loci and asthma, and hope to provide a certain scientific basis for tracking the genetic causes of asthma. We present the following article in accordance with the PRISMA reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-3797/rc>).

Methods

Literature search

The China National Knowledge Internet (CNKI), Chinese Biomedical Literature Database, Cochrane Library, Medline, and Embase databases were searched for RCTs

and journal literature related to the incidence of asthma and VDR gene polymorphisms published from inception of database to April 2021. The compound logic retrieval and Boolean logic retrieval methods were used to select related documents. The following search terms were used alone or in combination: “randomized controlled trial”, “asthma”, “vitamin D receptor or VDR”, “gene polymorphism”, “polymorphism”, “SNP”, and “mutation”. The RevMan 5.3 and Stata 13 software provided by the Cochrane system were used for meta-analysis.

The documents retrieved were initially screened by reading the titles and abstracts, and inconsistent documents were excluded. The second screening was performed according to the inclusion and exclusion criteria, and search engines were used to trace the included literatures. Finally, a review of the full text was performed to evaluate the quality of the studies.

Literature inclusion and exclusion criteria

The following inclusion criteria were applied: (I) the study design was a RCT; (II) literature published in domestic and foreign journals; (III) studies examining the relationship between the polymorphisms of at least one of the above VDR loci and asthma susceptibility; (IV) the study included an experimental group and a control group; (V) complete basic clinical data and observation indicators were included in the study; (VI) the frequency of each genotype in the experimental group and the control group were provided or could be calculated; and (VII) the control group was non-asthmatic and had no relationship with the patients.

The following exclusion criteria were applied: (I) duplicate subjects; (II) case reports, reviews, or non-population studies; (III) studies with family as the research subject; (IV) the genotype distribution of the control group did not meet the Hardy-Weinberg genetic balance test; and (V) the Jadad score of literature quality was less than three.

Observation indicators

The main research indicators used in this study included frequency and distribution of the genotypes of the VDR gene SNP locus *Fok I* (rs2228570), *Bsm I* (rs1544410), *Apa I* (rs7975232), and *Taq I* (rs731236). The secondary research indicators included the country and ethnic distribution of the research subjects, as well as the age distribution.

Data extraction

Two experts used a Microsoft Excel spreadsheet for independent data extraction. Any inconsistencies were resolved through discussion. The data collated included the following: (I) basic information of the included research such as first author, research title, research time, sample size, and grouping situation; (II) the ethnic composition and age distribution of the research subjects; and (III) the frequency and distribution of genotypes at *Fok I*, *Bsm I*, *Apa I*, and *Taq I* in the VDR gene SNP sites of the experimental group and the control group.

Risk of bias and quality assessment

Two experts independently screened the literature according to inclusion and exclusion criteria. The risk of bias included in the RCTs was assessed using the Cochrane Handbook of RCT risk assessment tool. Specifically, it included whether the random allocation method was correct; whether the allocation scheme was hidden and whether the method was correct; whether study subjects, treatment regimens, and study results were blinded; selective reporting of research results; and study data integrity. The above items were judged as “high risk bias”, “low risk bias”, or “unclear”.

Statistical methods

Statistical analysis was performed using the Stata SE 12.0 software (College Station, USA). The risk of bias assessment chart under RevMan 5.3 software was used to assess the risk bias of the included references. The results of continuous variables, discrete variables, and non-continuous variables (NOA) were expressed using mean difference (MD), standardized mean difference (SMD), and odds ratio (OR), respectively. Each effect was represented by a 95% confidence interval (CI). When $P > 0.01$ and $I^2 < 50\%$, the fixed effects model (FEM) was used for meta-analysis. When $P < 0.01$ and $I^2 > 50\%$, the random effects model (REM) was used for meta-analysis.

Results

Search results and basic information of the included documents

A total of 1,013 articles were retrieved from the database searches, and 823 articles remained after the preliminary

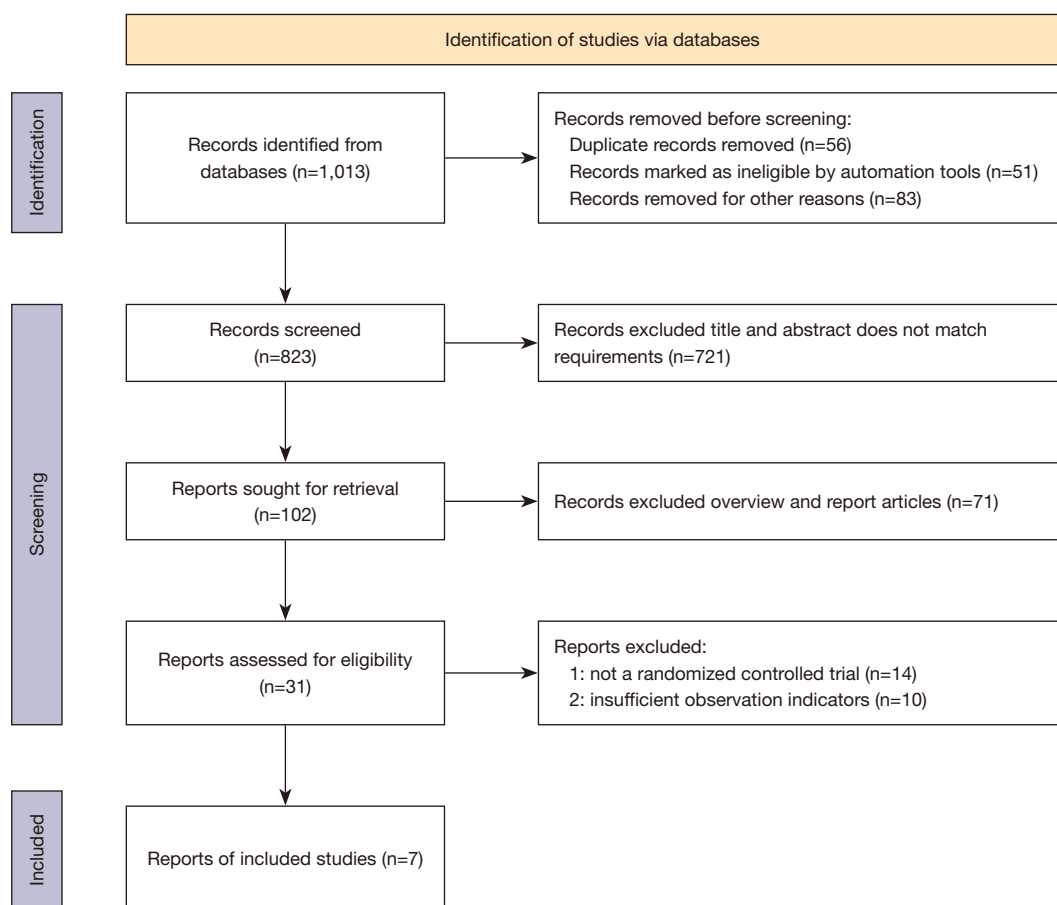


Figure 1 A flowchart showing the literature retrieval process.

elimination. A further 721 articles were excluded after reading the abstracts and titles, 71 articles such as review articles and research reports were eliminated, and 31 articles remained. After the full texts were read, the articles which were not RCTs were eliminated (14 articles), and 10 articles with insufficient observation indicators were excluded. Finally, a total of 7 publications were included in this study (Figure 1).

A total of 7 articles (14-20), including 3,865 patient cases, were included in this investigation. The sample sizes in these 7 articles varied significantly, ranging from 33 cases to 567 cases. In these 7 articles, the sample size, patient age group, grouping situation, multiple related genes of VDR gene (including *Apa I* gene, *Fok I* gene, *Bsm I* gene, *Taq I* gene distribution, and VDR genotype) were described in detail, including the detection methods and diagnostic criteria. Table 1 shows the basic characteristics of the included articles.

Results of risk bias evaluation of the included literatures

Figures 2,3 show the results of multiple risk bias evaluations of the included articles drawn using the RevMan 5.3 software. In this study, among the 7 RCTs, 6 articles (85.7%) described the correct random allocation method, and 6 articles (85.7%) described the concealed allocation plan in detail. In addition, there were 4 articles (57.1%) that used the blinding method and no blinding method was used in the remaining articles.

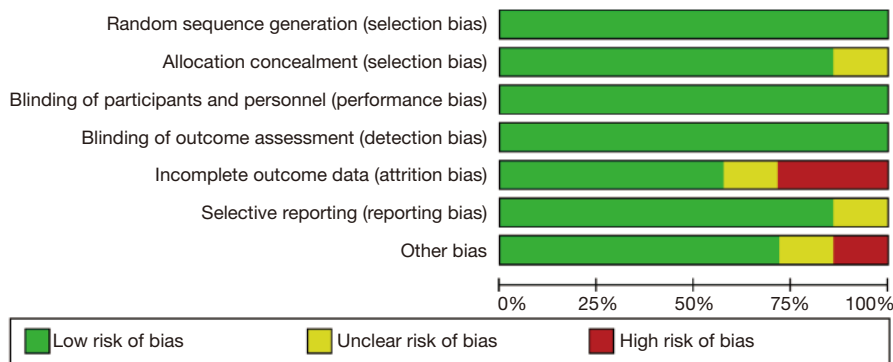
Meta-analysis of the genotype of the *Apa I* locus

The data related to distribution of the CC genotype at the *Apa I* locus did not show obvious heterogeneity [chi-square (χ^2) = 1.99; degrees of freedom (df) = 3; I^2 = 0% < 50%; P = 0.57]. Meta-analysis using the FEM showed that the frequency of the CC genotype at the *Apa I* locus was significantly

Table 1 Basic characteristics of included articles

First author	Publish year	Age	Case numbers		VDR gene type				Detection method	Diagnostic criteria
			Experimental group	Control group	<i>Apa I</i>	<i>Fok I</i>	<i>Bsm I</i>	<i>Taq I</i>		
Fang WL	2009 (14)	Adults	101	206	–	NS	NS	–	PCR-RFLP	1
Ismail MF	2013 (15)	Children	51	33	–	S	–	–	TaqMan	4
Li F	2011 (16)	Adults	467	288	–	NS	–	–	Direct sequencing	3
Maalmi H	2013 (17)	Children	155	225	NS	S	S	S	PCR-RFLP	2
Pillai DK	2011 (18)	Teenagers	139	74	NS	NS	–	NS	TaqMan	Other
Raby BA	2004 (19)	Adults	517	519	S	NS	–	S	TaqMan	Other
Saadi A	2009 (20)	Adults	567	523	S	NS	NS	NS	PCR-RFLP	Other

“S” indicates that the difference between the experimental group and the control group is statistically significant, and “NS” indicates that the difference is not statistically significant. The diagnostic criteria were as follows: “1” indicates the GINA 2008 asthma prevention and treatment guidelines; “2” represents the diagnosis and care of patients with COPD and asthma; “3” represents the ATS criteria, and “4” represents the GINA prevention and treatment. VDR, vitamin D receptor; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; GINA, Global Initiative for Asthma; COPD, chronic obstructive pulmonary disease; ATS, American Thoracic Society.

**Figure 2** Risk bias assessment of the included literature.

different between the experimental group and the control group (OR =0.76; 95% CI: 0.64 to 0.91; $P=0.003<0.05$; *Figure 4*).

The results related to the frequency distribution of the CA genotype at the *Apa I* locus did not show obvious heterogeneity ($c^2=2.32$; $df=3$; $I^2=0\%<50\%$; $P=0.51$). Meta-analysis using the FEM revealed that there was no significant difference between the experimental group and the control group in the CA genotype frequency at *Apa I* (OR =1.06; 95% CI: 0.90 to 1.23; $P=0.50>0.05$; *Figure 5*).

The data related to the AA genotype at the *Apa I* locus showed no obvious heterogeneity ($c^2=2.02$, $df=3$;

$I^2=0\%<50\%$; $P=0.57$) and the FEM was used. Meta-analysis demonstrated that the frequency of the AA genotype at the *Apa I* site was not significantly different between the experimental group and the control group (OR =1.32; 95% CI: 1.09 to 1.59; $P=0.004<0.05$; *Figure 6*).

The results related to the CC + CA genotype at the *Apa I* locus showed no obvious heterogeneity ($c^2=3.13$; $df=3$; $I^2=4\%<50\%$; $P=0.37$) and the FEM was used. Interestingly, meta-analysis showed that the CC + CA genotype frequency at the *Apa I* locus differed significantly between the experimental group and the control group (OR =0.81; 95% CI: 0.68 to 0.98; $P=0.03<0.05$; *Figure 7*).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Fang WL, 2009	+	+	+	+	+	+	+
Ismail MF, 2013	+	+	+	+	+	?	+
Li F, 2011	+	?	+	+	-	+	+
Maalmi H, 2013	+	+	+	+	-	+	+
Pillai DK, 2011	+	+	+	+	?	+	-
Raby BA, 2004	+	+	+	+	+	+	?
Saadi A, 2009	+	+	+	+	+	+	+

Figure 3 Multiple risk bias evaluation results corresponding to the included studies. “+” denotes low risk bias; “-” denotes high risk bias; and “?” denotes unclear risk bias.

Meta-analysis of the *Fok I* locus genotype

Data related to the frequency distribution of the CC genotype at the *Fok I* locus was significantly heterogeneous ($c^2=21.02$; $df=6$; $I^2=71\%>50\%$; $P=0.002$). Meta-analysis using the REM showed that the frequency of the CC genotype at *Fok I* locus was not significantly different between the experimental group and the control group (OR =0.98; 95% CI: 0.71 to 1.35; $P=0.92$; *Figure 8*).

Data related to the CT genotype at the *Fok I* locus showed obvious heterogeneity ($c^2=30.44$; $df=6$; $I^2=80\%>50\%$; $P<0.0001$) and the REM was used. Meta-analysis found no significant difference in the CT genotype frequency at the *Fok I* locus between the experimental group and the control group (OR =0.85; 95% CI: 0.61 to 1.17; $P=0.32$; *Figure 9*).

Results relating to the TT genotype at the *Fok I* locus showed obvious heterogeneity ($c^2=28.45$; $df=6$; $I^2=79\%>50\%$; $P<0.0001$) and the REM was used. Meta-analysis revealed that the frequency of the TT genotype at

the *Fok I* locus was not significantly different between the experimental group and the control group (OR =0.78; 95% CI: 0.52 to 1.17; $P=0.24$; *Figure 10*).

Results related to the CC + CT genotype at the *Fok I* locus showed obvious heterogeneity ($c^2=68.55$; $df=6$; $I^2=91\%>50\%$; $P<0.00001$) and the REM was used. Meta-analysis showed that the difference in the frequency of the CT genotype at the *Fok I* locus was not statistically different between the experimental group and the control group (OR =0.93; 95% CI: 0.53 to 1.64; $P=0.80$; *Figure 11*).

Meta-analysis of *Bsm I* locus genotype

Data regarding the frequency of the GG genotype at the *Bsm I* locus did not show obvious heterogeneity ($c^2=2.17$; $df=2$; $I^2=8\%<50\%$; $P=0.34$). Meta-analysis using the FEM showed that there was no significant difference in the GG genotype frequency at *Bsm I* between the experimental group and the control group (OR =0.88; 95% CI: 0.67 to 1.14; $P=0.33$; *Figure 12*).

Data regarding the frequency of the GA genotype at the *Bsm I* locus showed obvious heterogeneity ($c^2=4.28$; $df=2$; $I^2=53\%>50\%$; $P=0.12$). Meta-analysis using the REM found that the difference in the GA genotype frequency at the *Bsm I* locus was not significantly different between the experimental group and the control group (OR =1.02; 95% CI: 0.69 to 1.50; $P=0.92$; *Figure 13*).

Results related to the frequency of the AA genotype at the *Bsm I* locus showed no obvious heterogeneity ($c^2=1.25$; $df=2$; $I^2=0\%<50\%$; $P=0.54$). Interestingly, meta-analysis using the FEM found that the frequency of the AA genotype was significantly different between the experimental group and the control group (OR =0.47; 95% CI: 0.28 to 0.79; $P=0.004<0.05$; *Figure 14*).

Data related to the GG + GA genotype at the *Bsm I* locus showed no obvious heterogeneity ($c^2=1.81$; $df=2$; $I^2=0\%<50\%$; $P=0.41$). The FEM was used for meta-analysis and the frequency of the GG + GA genotype at *Bsm I* locus was found to be statistically different between the experimental group and the control group (OR =2.05; 95% CI: 1.23 to 3.41; $P=0.006<0.05$; *Figure 15*).

Meta-analysis of the *Taq I* locus genotype

Results related to the frequency of the CC genotype at the *Taq I* locus showed obvious heterogeneity ($c^2=7.09$; $df=3$; $I^2=58\%>50\%$; $P=0.07$) and the REM was used. Meta-analysis showed that there was no significant difference between the

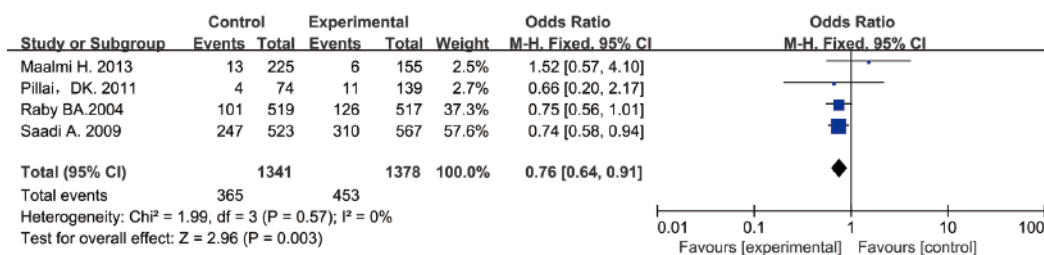


Figure 4 Forest plot of the CC genotype at the *Apa I* locus. CI, confidence interval.

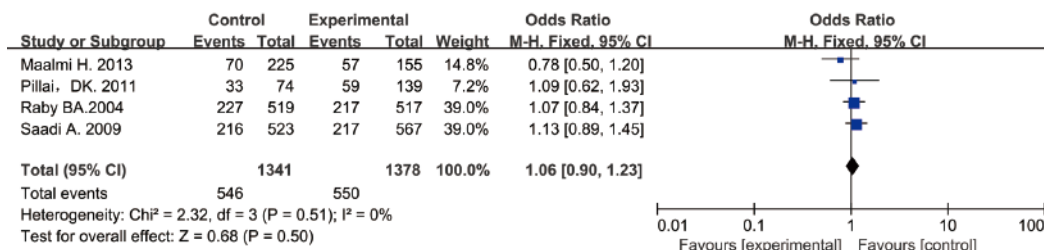


Figure 5 Forest plot of the CA genotype at the *Apa I* locus. CI, confidence interval.

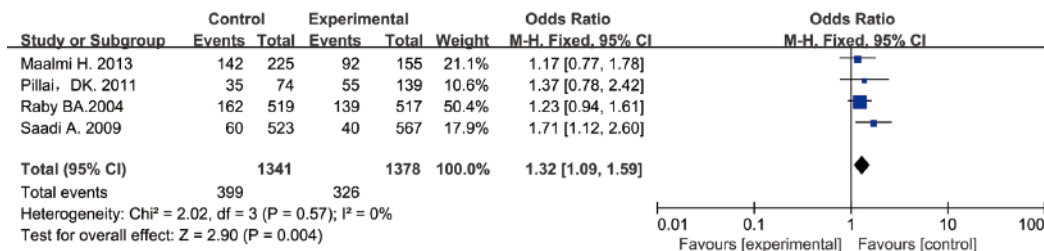


Figure 6 Forest plot of the AA genotype at the *Apa I* locus. CI, confidence interval.

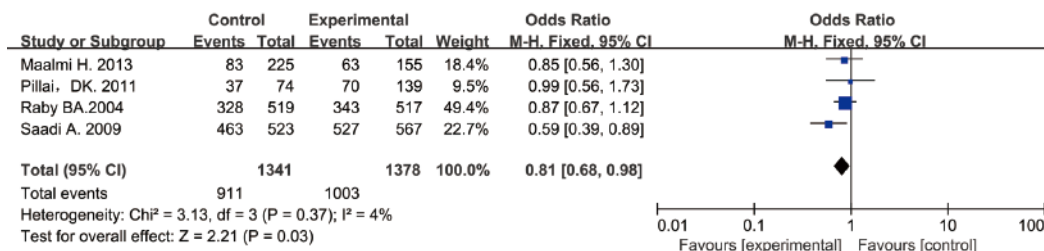


Figure 7 Forest plot of the CC + CA genotype at the *Apa I* locus. CI, confidence interval.

experimental group and the control group in the frequency of the CC genotype at the *Taq I* locus (OR =1.28; 95% CI: 0.68 to 2.39; $P=0.44$; Figure 16).

Data examining the frequency of the CT genotype at

the *Taq I* locus showed obvious heterogeneity ($c^2=1.95$; $\text{df}=3$; $I^2=0\%<50\%$; $P=0.58$). Meta-analysis using the REM showed that there was no significant difference in the frequency of the CT genotype at the *Taq I* locus between

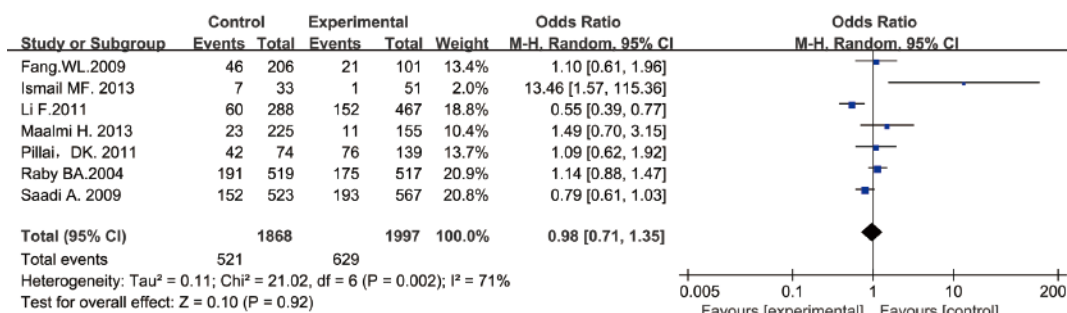


Figure 8 Forest plot of the CC genotype at the *Fok I* locus. CI, confidence interval.

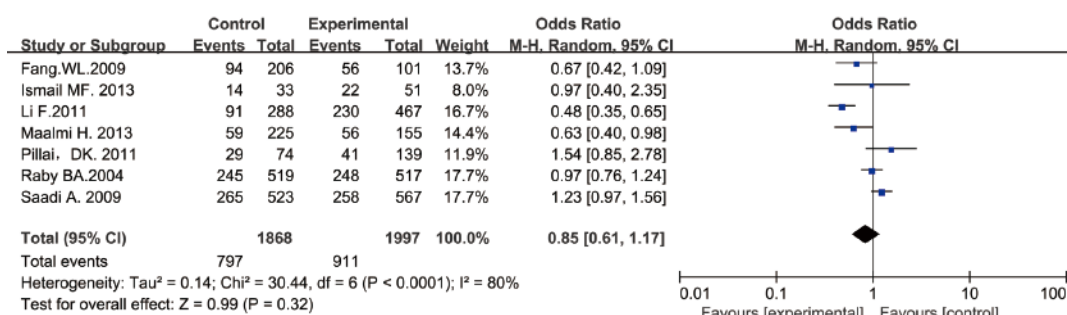


Figure 9 Forest plot of the CT genotype at the *Fok I* locus. CI, confidence interval.

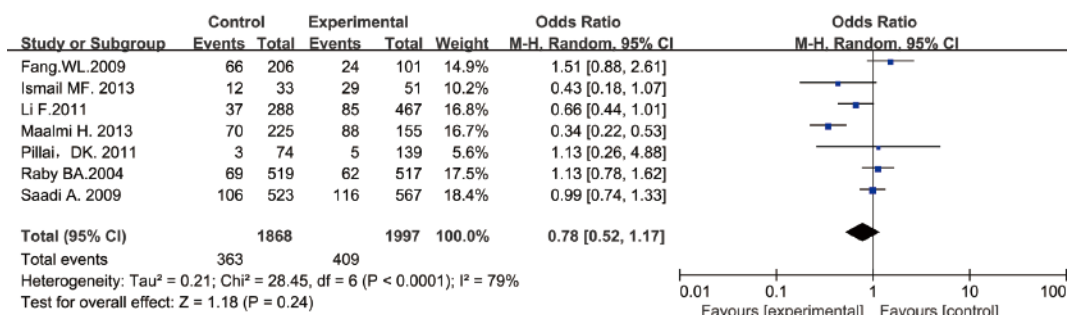


Figure 10 Forest plot of the TT genotype at the *Fok I* locus. CI, confidence interval.

the experimental group and the control group (OR =0.96; 95% CI: 0.80 to 1.15; P=0.65; Figure 17).

Data regarding the TT genotype frequency at the *Taq I* locus showed heterogeneity ($c^2=7.45$; $df=3$; $I^2=60\%>50\%$; P=0.06). Meta-analysis using the REM revealed that the difference in the frequency of the TT genotype at the *Taq I* locus was not significantly different between the experimental group and the control group (OR =1.03; 95% CI: 0.76 to 1.41; P=0.85; Figure 18).

Results related to the frequency of CC + CT genotype

at the *Taq I* locus showed heterogeneity ($c^2=10.71$; $df=3$; $I^2=72\%>50\%$; P=0.01) Meta-analysis using the REM found that the difference in the CC + CT genotype frequency at the *Taq I* locus was not statistically significant between the experimental group and the control group (OR =1.04; 95% CI: 0.72 to 1.51; P=0.82; Figure 19).

Publication of biased results

Figures 20-23 show the funnel charts of publication bias

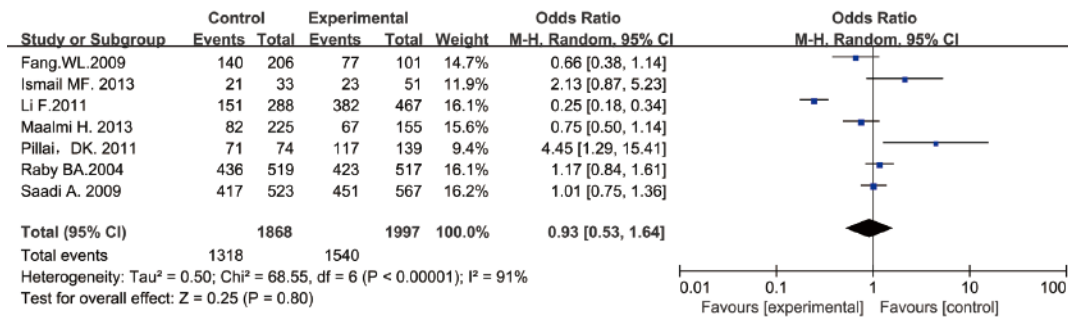


Figure 11 Forest plot of the CC + CT genotype at the *Fok I* locus. CI, confidence interval.

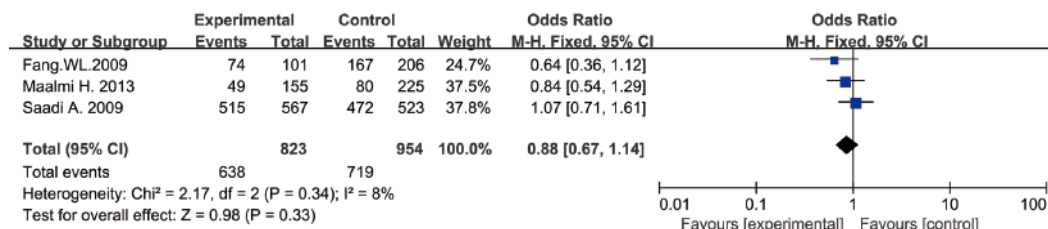


Figure 12 Forest plot of the GG genotype at the *Bsm I* locus. CI, confidence interval.

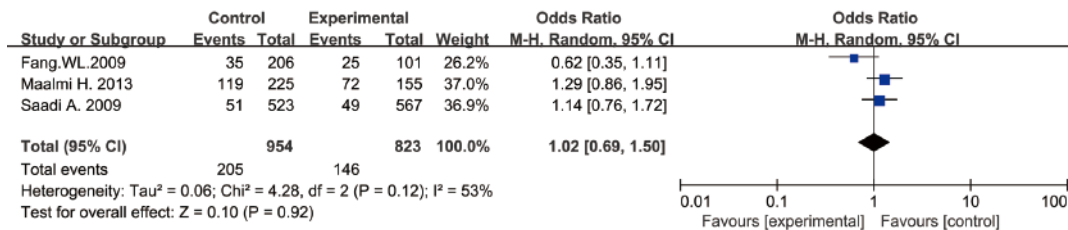


Figure 13 Forest plot of the GA genotype at the *Bsm I* locus. CI, confidence interval.

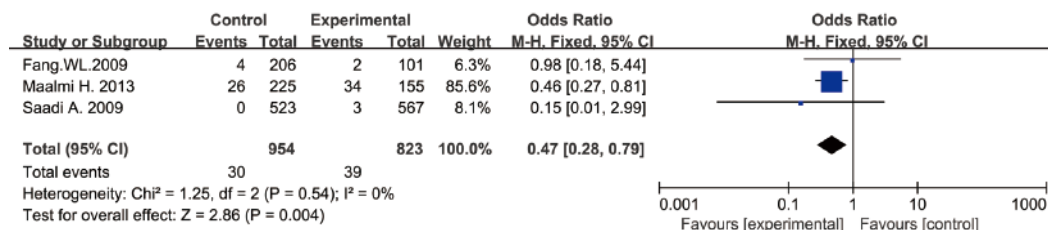


Figure 14 Forest plot of the AA genotype at the *Bsm I* locus. CI, confidence interval.

for the distribution of the *Apa I*, *Fok I*, *Bsm I*, and *Taq I* genotypes involved in asthma attacks. The funnel charts showed that the circles in some studies were basically

concentrated on the midline and were roughly symmetrical to the midline, indicating that there was no bias in the publication of the included literature, and the conclusions

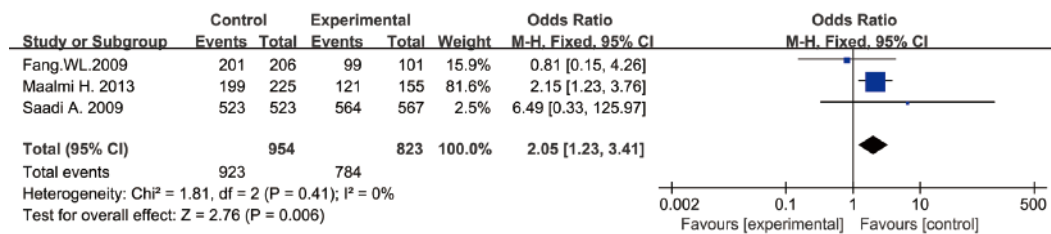


Figure 15 Forest plot of the GG + GA genotype at the *Bsm I* locus. CI, confidence interval.

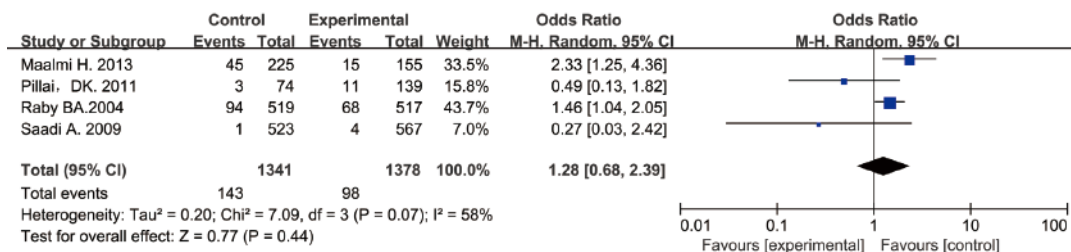


Figure 16 Forest plot of the CC genotype at the *Taq I* locus. CI, confidence interval.

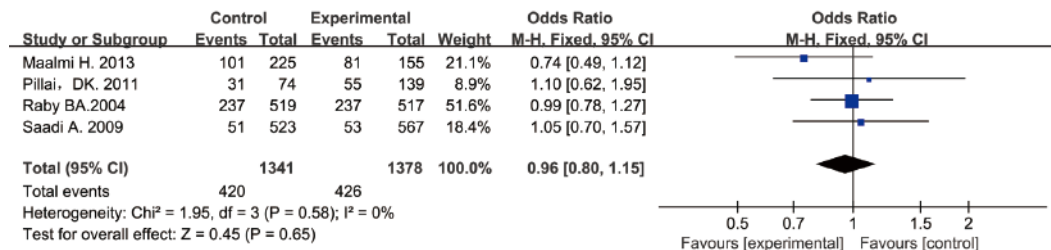


Figure 17 Forest plot of the CT genotype at the *Taq I* locus. CI, confidence interval.

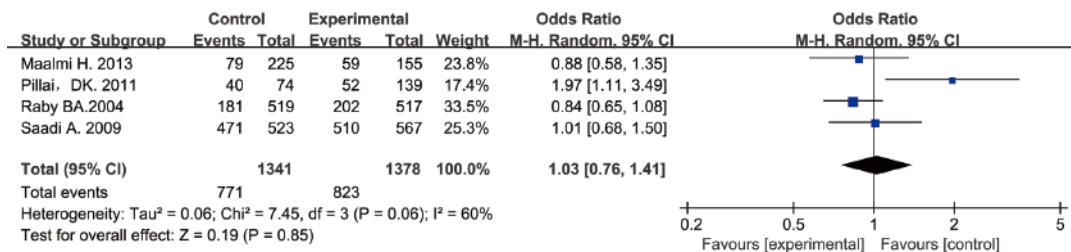


Figure 18 Forest plot of the TT genotype at the *Taq I* locus. CI, confidence interval.

drawn were relatively reliable.

Discussion

A total of 7 articles were included in this systematic review

and meta-analysis evaluating the relationship between VDR gene polymorphisms and the onset of asthma. Among them, 6 articles described the correct random allocation method, 6 articles described the concealment of allocation plan in detail, and 4 articles used the blinding method. The

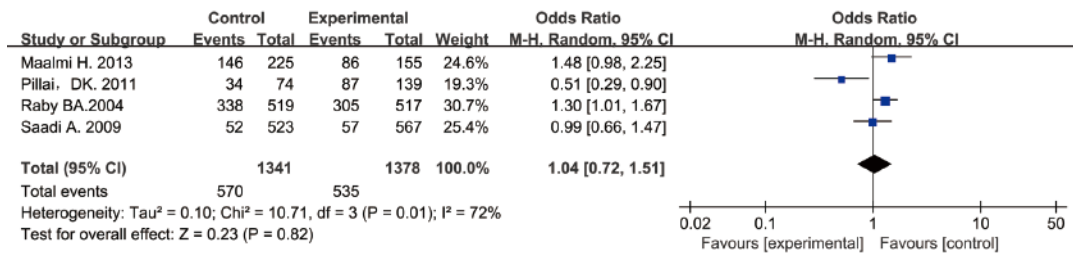


Figure 19 Forest plot of the CC + CT genotype at the *Taq I* locus. CI, confidence interval.

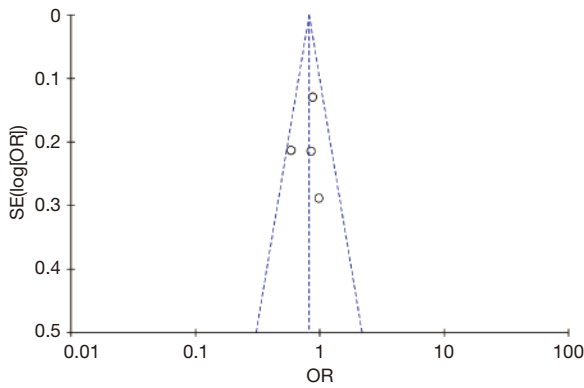


Figure 20 Funnel chart showing the publication bias of *Apa I* genotype distribution in the included literature. SE, standard error; OR, odds ratio.

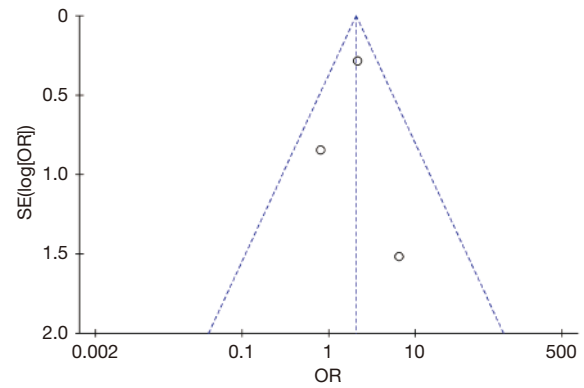


Figure 22 Funnel chart showing the publication bias of the *Bsm I* genotype distribution in the included literature. SE, standard error; OR, odds ratio.

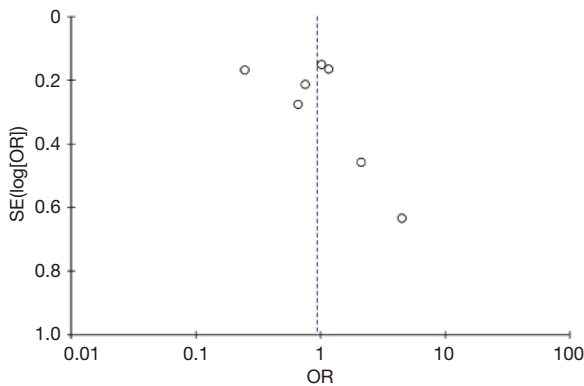


Figure 21 Funnel chart showing the publication bias of the *Fok I* genotype distribution in the included literature. SE, standard error; OR, odds ratio.

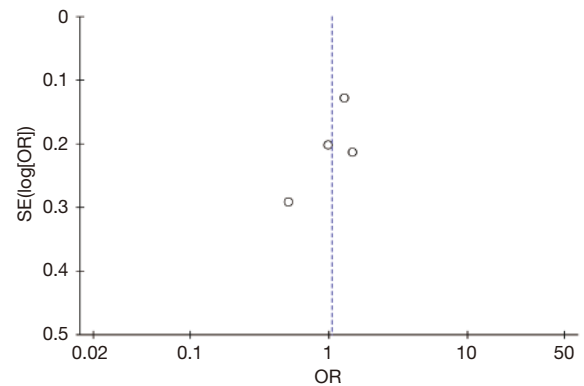


Figure 23 Funnel chart showing the publication bias of the *Taq I* genotype distribution in the included literature. SE, standard error; OR, odds ratio.

reason for the bias may be the unclear method of random allocation in the study and the bias caused by experimental error (21).

This investigation showed that the frequency of the CC

+ CA dominant genotype at the *Apa I* locus was significantly higher in the experimental group consisting of asthmatic patients compared to control healthy participants. The frequency of the CC + CT dominant genotype at the *Fok*

I locus of the experimental group was not significantly different from that of the control group. The frequency of the GG + GA genotype at the *Bsm I* locus in asthmatic patients was significantly higher than that in non-asthmatic participants. Furthermore, the frequency of the CC + CT genotype at the *Taq I* locus was comparable between the experimental group and the control group. These results suggested that VDR gene polymorphisms at the *Apa I* site and the *Bsm I* site are closely related to the genetic susceptibility of asthma. Indeed, an increase in the dominant expression significantly elevated the probability of suffering from asthma. These results are consistent with the reports of Corren *et al.* [2017] (22). Other studies have suggested that the VDR may improve T helper 2 (Th2) lymphocyte immunity by increasing the levels of eosinophils and Th2 cells (23). In addition, animal experiments have demonstrated that Vit D can inhibit Th1 lymphocytes and enhance the function of Th2 lymphocytes, which may be related to the occurrence and development of asthma (24). This further supports the relationship between the VDR receptor and the occurrence of asthma. The gene polymorphisms at *Fok I*, *Bsm I*, *Apa I*, and the dominant gene expression of the *TaqI* locus may increase a patient's genetic susceptibility to asthma. The activated form of Vit D, 1,25-(OH)₂D₃, may act as an immunomodulator and combined with VDR to jointly regulate the function of T and B lymphocytes and maintain the balance of Th1/Th2 cells (25,26). The genetic polymorphisms of VDR may directly affect its normal interaction with 1,25-(OH)₂D₃, thereby inducing asthma.

The gene polymorphism of *Fok I*, *Bsm I* and *Apa I* loci of Vit D gene and the dominant gene expression of tag I locus may increase the genetic susceptibility of patients to asthma. The activated form of Vit D is 1,25-(OH)₂D₃; it may be used as an immune regulator to combine with VDR to jointly regulate the function of T and B lymphocytes and maintain the balance of Th1/Th2 cells (27,28). The genetic polymorphism of VDR may directly affect its normal interaction with 1,25-(OH)₂D₃, so as to induce asthma.

The results of the current research on asthma and DNA methylation show that environmental factors can affect the DNA methylation of multiple CpG sites in asthma patients (28), which explains the apparent gene-environment interaction. Genetic factors can affect the symptoms of asthma patients, which provides new research ideas for the genetic attribution of asthma.

Conclusions

In this study, 7 relevant literatures were included for meta-analysis to explore the genetic association of VDR gene polymorphisms and asthma. The results showed that the *Fok I* locus, *Bsm I* locus, *Apa I* locus, and *Taq I* locus in the VDR gene polymorphism sites were closely related to the genetic susceptibility of asthma. The increase in its dominant expression evidently increased the probability of suffering from asthma. However, this study may have been limited by the heterogeneity among some included literatures, which may have a certain impact on the results, and further study is warranted to verify our data. In conclusion, this study provides a reference for future clinical studies examining VDR gene polymorphic loci involved in the pathogenesis of asthma.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

- Zihlif M, Zihlif N, Obeidat NM, et al. Association between ADAM33 polymorphisms and susceptibility with adult and childhood asthma among Jordanians. *Genet Test Mol Biomarkers* 2014;18:767-74.
- Qiu W, Guo F, Glass K, et al. Differential connectivity of gene regulatory networks distinguishes corticosteroid response in asthma. *J Allergy Clin Immunol* 2018;141:1250-8.
- Wenzel SE. Severe Adult Asthmas: Integrating Clinical Features, Biology, and Therapeutics to Improve Outcomes. *Am J Respir Crit Care Med* 2021;203:809-21.
- Randolph AG, Yip WK, Falkenstein-Hagander K, et al. Vitamin D-binding protein haplotype is associated with hospitalization for RSV bronchiolitis. *Clin Exp Allergy* 2014;44:231-7.
- Livingstone KM, Celis-Morales C, Hoeller U, et al. Weekday sunlight exposure, but not vitamin D intake, influences the association between vitamin D receptor genotype and circulating concentration 25-hydroxyvitamin D in a pan-European population: the Food4Me study. *Mol Nutr Food Res* 2017. doi: 10.1002/mnfr.201600476.
- Awasthi N, Awasthi S, Pandey S, et al. Association of vitamin D receptor gene polymorphisms in North Indian children with asthma: a case-control study. *Int J Mol Epidemiol Genet* 2021;12:24-34.
- Pavón-Romero GF, Reséndiz-Hernández JM, Ramírez-Jiménez F, et al. Single nucleotide polymorphisms in TNF are associated with susceptibility to aspirin-exacerbated respiratory disease but not to cytokine levels: a study in Mexican mestizo population. *Biomark Med* 2017;11:1047-55.
- Holster A, Teräsjärvi J, Lauhkonen E, et al. IL-17A gene polymorphism rs2275913 is associated with the development of asthma after bronchiolitis in infancy. *Allergol Int* 2018;67:109-13.
- Graser A, Ekici AB, Sopel N, et al. Rhinovirus inhibits IL-17A and the downstream immune responses in allergic asthma. *Mucosal Immunol* 2016;9:1183-92.
- Kilic M, Ecin S, Taskin E, et al. The Vitamin D Receptor Gene Polymorphisms in Asthmatic Children: A Case-Control Study. *Pediatr Allergy Immunol Pulmonol* 2019;32:63-9.
- Yick CY, Zwinderman AH, Kunst PW, et al. Glucocorticoid-induced changes in gene expression of airway smooth muscle in patients with asthma. *Am J Respir Crit Care Med* 2013;187:1076-84.
- Mirzakhani H, Al-Garawi AA, Carey VJ, et al. Expression network analysis reveals cord blood vitamin D-associated genes affecting risk of early life wheeze. *Thorax* 2019;74:200-2.
- Alkhatatbeh MJ, Almomani HS, Abdul-Razzak KK, et al. Association of asthma with low serum vitamin D and its related musculoskeletal and psychological symptoms in adults: a case-control study. *NPJ Prim Care Respir Med* 2021;31:27.
- Fang WL, Gao LB, Liang WB, et al. Association analysis of vitamin D receptor gene polymorphisms in Chinese population with asthma. *Iran J Allergy Asthma Immunol* 2009;8:141-7.
- Ismail MF, Elnady HG, Fouda EM. Genetic variants in vitamin D pathway in Egyptian asthmatic children: a pilot study. *Hum Immunol* 2013;74:1659-64.
- Li F, Jiang L, Willis-Owen SA, et al. Vitamin D binding protein variants associate with asthma susceptibility in the Chinese Han population. *BMC Med Genet* 2011;12:103.
- Maalmi H, Sassi FH, Berraies A, et al. Association of vitamin D receptor gene polymorphisms with susceptibility to asthma in Tunisian children: A case control study. *Hum Immunol* 2013;74:234-40.
- Pillai DK, Iqbal SF, Benton AS, et al. Associations between genetic variants in vitamin D metabolism and asthma characteristics in young African Americans: a pilot study. *J Investig Med* 2011;59:938-46.
- Raby BA, Lazarus R, Silverman EK, et al. Association of vitamin D receptor gene polymorphisms with childhood and adult asthma. *Am J Respir Crit Care Med* 2004;170:1057-65.
- Saadi A, Gao G, Li H, et al. 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.
- Munkhbayarlakh S, Kao HF, Hou YI, et al. Vitamin D plasma concentration and vitamin D receptor genetic variants confer risk of asthma: A comparison study of Taiwanese and Mongolian populations. *World Allergy Organ J* 2019;12:100076.
- Corren J, Parnes JR, Wang L, et al. Tezepelumab in Adults with Uncontrolled Asthma. *N Engl J Med* 2017;377:936-46.
- Rabe KF, Nair P, Brusselle G, et al. Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma. *N Engl J Med* 2018;378:2475-85.
- FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as

- add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388:2128-41.
25. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and Comorbid Features of Patients with Severe Asthma and Frequent Exacerbations. *Am J Respir Crit Care Med* 2017;195:302-13.
26. Taylor SL, Leong LEX, Choo JM, et al. Inflammatory phenotypes in patients with severe asthma are associated with distinct airway microbiology. *J Allergy Clin Immunol* 2018;141:94-103.e15.
27. Laidlaw TM, Bachert C, Amin N, et al. Dupilumab improves upper and lower airway disease control in chronic rhinosinusitis with nasal polyps and asthma. *Ann Allergy Asthma Immunol* 2021;126:584-92.e1.
28. Jiang R, Jones MJ, Sava F, et al. Short-term diesel exhaust inhalation in a controlled human crossover study is associated with changes in DNA methylation of circulating mononuclear cells in asthmatics. *Part Fibre Toxicol* 2014;11:71.

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