Meta-Analysis of Vitamin D Receptor Gene Polymorphisms in Childhood Asthma

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We conducted the systematic review to investigate the potential relationship between the vitamin polymorphisms of D receptor (VDR) gene and childhood asthma. Relevant studies researching on VDR polymorphisms and asthma susceptibility were searched throughout Embase, PubMed, China Science and technology journal database (CQVIP), etc. till 12 April, 2021. We calculated the pooled odds ratios (OR) and its 95% confidence interval (CI) using RevMan 5.3 software and Stata 11.0. FokI (rs2228570) could significantly affect childhood asthma risk across co dominant model (Ff vs. FF: OR (95%CI) = 0.82 (0.65, 1.02), $P = 0.071$) and dominant model (ff vs. FF: OR (95%CI) = 0.77 (0.63, 0.95), $P = 0.016$), especially among Caucasians in additive model (f vs. F: OR (95%CI) = 0.63 (0.43, 0.92), $P = 0.015$) and dominant model (ff vs. FF: OR (95%CI) = 0.67 (0.51, 0.88), $P = 0.004$). TaqI (rs731236) was significantly related with childhood asthma in additive model (t vs. T: OR (95%CI) = 0.45 (0.23, 0.89), $P = 0.022$), co dominant model (Tt vs. TT: OR (95%CI) = 0.36 (0.17, 0.77), $P = 0.009$), and dominant model (tt vs. TT: OR (95%CI) = 0.36 (0.15, 0.87), $P = 0.024$) among Asian, as well as population-based subgroup in co dominant model (Tt vs. TT: OR (95%CI) = 0.53 (0.31, 0.94), $P = 0.029$). However, no evidence supported the role of ApaI (rs7975232) and BsmI (rs1544410) polymorphisms in childhood asthma. FokI and TaqI polymorphisms were found to be related with the susceptibility of childhood asthma. However, it seems that ApaI and BsmI polymorphisms are not related with childhood asthma susceptibility.

Keywords: vitamin D receptor, polymorphisms, childhood asthma, systematic review, susceptibility

INTRODUCTION

Asthma is recognized as a chronic heterogeneous respiratory disease, which has characterized by airway inflammation and hyper-responsiveness, and the disease affects more than 300 million people worldwide, especially among children (1). The incidence, morbidity, and mortality related with asthma was influenced by several potential risk factors such as environmental factors (2), infancy microbial, biome influences, and genetic background, including vitamin D receptor (VDR) gene (3).

Vitamin D has been shown to have potent immunomodulatory properties, and Vitamin D correlated with the regulation of adaptive and innate immune function through VDR (4). Recently, increasing evidence researched on the effect of vitamin D in asthma and demonstrated that the severity of symptoms was related with vitamin D deficiency (5, 6). Among VDR polymorphisms, four SNPs, including BsmI (rs1544410), ApaI (rs7975232), FokI (rs2228570), and TaqI (rs731236) have been widely researched (7), but the relationship remains inconsistent. For example,
meta-analysis by Makoui et al. showed a statistical significant association between asthma risk and TaqI SNP (7). However, the systematically review by Zhen et al. showed no association between TaqI SNP and asthma risk (8). Additionally, thereafter, some new studies have been published (9–13).

Thus, it is necessary to update the report based on the previous results of researches to further explore the potential role of VDR genes polymorphism in childhood asthma susceptibility. Then, we designed the meta-analysis and explored this relationship in different races and source of controls. Finally, our data demonstrated that FokI and TaqI polymorphisms might be associated with childhood asthma susceptibility. However, ApaI and BsmI polymorphisms are not related with childhood asthma susceptibility.
MATERIALS AND METHODS

Selection Strategy
The published studies were searched from numerous databases including Embase, PubMed, WANGANG data, China National Knowledge Infrastructure (CNKI), China Science and technology journal database (CQVIP), etc. The comprehensive systematic search process was exploited till 12 April, 2021 using the following key words: (“Vitamin D receptor” OR “VDR”) AND (“polymorphisms” OR “polymorphism” OR “variant” OR “mutant”) AND (“children” OR “child” OR “teenager” OR “pediatric”). The selection strategies in Pubmed and Embase were shown in Supplementary Tables 1, 2. Moreover, in order to enroll more researches, print-out literatures, reviews, and the references of included articles were also retrieved.

Study Selection
The following inclusion criteria were designed: (1) the study was designed as a case-control study or cohort study; (2) the subjects in the experiment group were children and/or adolescents with asthma, and subjects in the control group were healthy children and/or adolescents; (3) The study explored the association of VDR ApaI (rs7975232), TaqI (rs731236), BsmI (rs1544410), FokI (rs2228570) gene polymorphisms and asthma susceptibility; (4) genotype data were reported or could be calculated based on information provided in the study.

When the control group and the case group were family members or close family members, the study would be excluded. The non-research articles, such as reviews, comments, and conference summaries, would be excluded. When duplicated studies were found or same data were showed in more than one study, the study with the most specific information would be included in the present study, and other duplicated articles would be excluded.

Data Extraction and Quality Assessment
Based on the designed criteria, studies were screened by two investigators independently. According to the standardized form, the information including year of publication, the name of the first author, research regions, the demographic information (age, sample size, source of the control group), polymorphism detection methods, the ethnicity of the included population, and genotype data, etc.

Newcastle-Ottawa Scale (NOS) criteria was used to assess the methodological quality of included studies, and the scale was assessed according to three aspects including subjects selection, comparability, and exposure (14). The study with a score of five or more would be considered as moderate quality, and the study with a score of four or less would be considered as poor quality.

When data extraction was finished, the extraction form would be exchanged, and the disagreements were solved by discussing.

Statistic Analysis
Firstly, the Hardy-Weinberg equilibrium test (HWE) of the frequency distribution of genotypes among controls was performed. We defined the population were not in the HWE if \(P < 0.05\). For each single nucleotide polymorphisms (SNP), we examined four models, including computational additive model \([m \text{ (mutation)} \text{ vs. } W \text{ (Wild)}]\), co dominant model \((mm \text{ vs. } WW, Wm \text{ vs. } WW)\), dominant model \((mm+ \text{ Wm vs. } WW)\), and recessive model \((mm \text{ vs. } WW + Wm)\). The effect of VDR polymorphisms in the childhood asthma susceptibility was assessed based on the pooled odds ratio (OR) and its 95% confidence interval (95%CI). Heterogeneity among individual studies was assessed using Cochran’s Q test and I\(^2\) test (15). If \(P < 0.05\), and/or I\(^2\) > 50%, suggesting obvious heterogeneity between the studies, the random effects model would be selected to calculate the pooled data; if \(P \geq 0.05\) and/or I\(^2\) \leq 50%, the fixed effect model would be used. RevMan 5.3 software and Stata 11.0 were enrolled to perform all statistical analyses.

RESULTS

Studies Inclusion
The detailed information associated with search process was shown in Figure 1. In this study, a total of 197 studies were firstly searched, including 54 articles in PubMed, 104 articles in Embase, 16 articles in Wanfang data, 18 articles in CNKI, and 5 articles in CQVIP. After removing 55 duplicated documents, there were 142 articles remaining. After that, we excluded 117 articles after browsing the titles and reading the abstract. Then, total 25 articles were fully reviewed, and seven articles were excluded, including five articles with adults as study subjects and two reviews. Finally, 18 articles were included in this meta-analysis (8–13, 16–27).

The Baseline Characteristics and Quality Assessment of Included Studies
As shown in Table 1, total 3,495 subjects including 1,392 cases in asthma group and 2,103 cases in control group were enrolled in the present study. The studies included in the meta-analysis were all published from 2010 to 2020. Among these articles, the subjects in eight studies were Asians, eight articles were Caucasians, one study were Americans, and one study were African-Americans. For subjects in the control group, there were two studies with population-based controls and 16 studies with hospital-based controls.

The genotype data and HWE test results of the case group and the control group were shown in Table 2. NOS scores of all included studies ranged from 5 to 8, suggesting an overall moderate methodological quality (Table 3).

Meta-Analysis of VDR Polymorphism and Asthma

ApaI (rs7975232)

As shown in Figure 2, total 16 articles reported the association between ApaI (rs7975232) and asthma risk (8–12, 16–18, 20–27). Obvious heterogeneity across studies was observed in additive model (a vs. A: \(I^2 = 89\%\), \(P < 0.00001\)), co dominant model (aa vs. AA: \(I^2 = 84\%\), \(P < 0.00001\)); Aa vs. AA: \(I^2 = 63\%\), \(P < 0.00006\)), dominant model (aa+Aa vs. AA: \(I^2 = 77\%\), \(P < 0.00001\)), and recessive model (aa vs. AA+Aa: \(I^2 = 86\%\), \(P < 0.00001\)). No significant association between ApaI (rs7975232) and asthma risk was calculated across additive model (a vs. A: OR (95%CI) = 0.82 (0.56, 1.21), \(P = 0.317\)), co dominant model (aa vs. AA: OR (95%CI) = 0.65 (0.31, 1.38), \(P = 0.263\); Aa vs.
### TABLE 1 | Characteristics of the included studies.

| Study                | Area       | Ethnicity   | Source of control | Diagnostic of asthma | Polymorphisms | Group     | n, M/F | Age, years |
|----------------------|------------|-------------|-------------------|----------------------|---------------|-----------|--------|------------|
| Ahmed et al. (9)     | Egypt      | European    | HB                | GINA guidelines      | ApaI, TaqI, BsmI | Asthma    | 50, 28/22 | 12.66±3.34 |
| Batmaz et al. (16)   | Turkey     | European    | HB                | GINA guidelines      | ApaI, TaqI, FokI, BsmI | Asthma    | 30, 20/10 | 11.74±2.4  |
| Einisman et al. (17) | Chile      | American    | HB                | GINA guidelines      | ApaI, TaqI, FokI | Asthma    | 75, 43/32 | 9.1 (3.5)  |
| Hou et al. (10)      | China      | Asia        | HB                | DPGPBA (2008)        | ApaI, BsmI     | Asthma    | 70, 43/27 | 8.84±3.21  |
| Einisman et al. (17) | Chile      | American    | HB                | GINA guidelines      | ApaI, TaqI, FokI | Asthma    | 44, 23/21 | 8.7 (6–13, 15–17) |
| Ma et al. (21)       | China      | Asia        | PB                | DPGPBA (2008)        | ApaI, TaqI, FokI, BsmI | Asthma    | 127, 82/45 | 8.4±2.3   |
| Kilic et al. (12)    | Turkey     | European    | HB                | GINA guidelines      | ApaI, TaqI, FokI | Asthma    | 33, 18/15 | 7.8±2.6    |
| Liu et al. (23)      | China      | Asia        | HB                | DPGPBA (2008)        | ApaI, TaqI, FokI, BsmI | Asthma    | 41, 24/17 | 3.9±1.2    |
| Maalumi et al. (22)  | Tunisia    | European    | HB                | DPGPBA (2008)        | ApaI, TaqI, FokI, BsmI | Asthma    | 155, 59/96 | 9.1 (6–13, 15–17) |
| Mo et al. (23)       | China      | Asia        | HB                | DPGPBA (2008)        | ApaI, BsmI     | Asthma    | 71, NR   | NR         |
| Papadopoulos et al.  | Cyprus     | European    | PB                | NR                   | ApaI, TaqI, BsmI | Asthma    | 69, 30/39 | 16.9 (15.9–18.1) |
| Pillai et al. (25)   | USA        | African-American | HB | NAEPP (2007) | ApaI, TaqI, FokI | Asthma    | 139, 81/58 | 11.2±3.5   |
| Zhang et al. (26)    | China      | Asia        | HB                | NR                   | ApaI, FokI, BsmI | Asthma    | 143, 86/57 | 7.56±2.39  |
| Zhao et al. (27)     | China      | Asia        | HB                | DPGPBA (2008)        | ApaI, TaqI, FokI, BsmI | Asthma    | 40, 22/18 | 3.41±1.07  |
| Zhen and Wang (8)    | China      | Asia        | HB                | NR                   | ApaI           | Asthma    | 30, 17/13 | 5.70±2.84  |
| Zhu et al. (13)      | China      | Asia        | HB                | DPGPBA (2008)        | FokI, BsmI     | Asthma    | 97, 50/47 | 8.76±1.22  |

$, median (IQR); HB, hospital-based; PB, population-based; PCR, Polymerase chain reaction; RT-PCR, Real time polymerase chain reaction; RFLP, restriction fragment lengths polymorphism; NR, not reported; BMI, body mass index; GINA, the Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program (2007) (28).
| References | Country | Case group | Control group | P_value for HWE |
|------------|---------|------------|---------------|----------------|
|            | N | WW | WM | MM | N | WW | WM | MM |                |
| **ApaI (rs7975232)** | | | | | | | | | |
| Ahmed et al. ([9]) | Egypt | 50 | 25 | 15 | 10 | 50 | 20 | 20 | 10 | 0.2386 |
| Batmaz et al. ([16]) | Turkey | 30 | 5 | 25 | 0 | 30 | 7 | 23 | 0 | 0.0070 |
| Einisman et al. ([17]) | Chile | 70 | 21 | 35 | 14 | 50 | 10 | 28 | 12 | 0.3891 |
| Hou et al. ([10]) | China | 70 | 4 | 30 | 36 | 70 | 0 | 5 | 65 | 0.7567 |
| Hutchinson et al. ([11]) | Ireland | 44 | 11 | 23 | 10 | 57 | 5 | 20 | 32 | 0.4721 |
| Iordanidou et al. ([18]) | Greece | 127 | 41 | 63 | 23 | 91 | 35 | 41 | 15 | 0.6120 |
| Kilic et al. ([12]) | Turkey | 100 | 18 | 60 | 22 | 80 | 26 | 42 | 12 | 0.4569 |
| Liu et al. ([20]) | China | 41 | 7 | 15 | 19 | 41 | 1 | 4 | 36 | 0.1599 |
| Ma et al. ([21]) | China | 60 | 46 | 7 | 7 | 60 | 48 | 4 | 8 | <0.0001 |
| Maalmi et al. ([22]) | Tunisia | 155 | 92 | 57 | 6 | 225 | 142 | 70 | 13 | 0.2729 |
| Mo et al. ([23]) | China | 71 | 4 | 31 | 36 | 71 | 14 | 28 | 29 | 0.1416 |
| Papadopoulou et al. ([24]) | Cyprus | 61 | 19 | 34 | 8 | 633 | 232 | 312 | 89 | 0.3290 |
| Pillai et al. ([25]) | Cyprus | 61 | 19 | 34 | 8 | 633 | 232 | 312 | 89 | 0.3290 |
| Zhang et al. ([26]) | China | 143 | 54 | 75 | 14 | 143 | 8 | 69 | 66 | 0.0637 |
| Zhao et al. ([27]) | China | 40 | 0 | 15 | 25 | 40 | 0 | 27 | 13 | 0.0013 |
| Zhen and Wang ([8]) | China | 30 | 3 | 2 | 25 | 40 | 6 | 14 | 20 | 0.2061 |
| **TaqI (rs731236)** | | | | | | | | | |
| Ahmed et al. ([9]) | Egypt | 50 | 5 | 30 | 15 | 50 | 10 | 40 | 0 | <0.0001 |
| Batmaz et al. ([16]) | Turkey | 30 | 18 | 9 | 3 | 30 | 15 | 10 | 5 | 0.1709 |
| Einisman et al. ([17]) | Chile | 72 | 35 | 34 | 3 | 50 | 24 | 24 | 2 | 0.1780 |
| Hutchinson et al. ([11]) | Ireland | 44 | 17 | 21 | 6 | 57 | 34 | 23 | 0 | 0.0564 |
| Iordanidou et al. ([18]) | Greece | 127 | 43 | 68 | 16 | 91 | 35 | 38 | 12 | 0.1990 |
| Kilic et al. ([12]) | Turkey | 100 | 31 | 61 | 8 | 80 | 28 | 32 | 20 | 0.0861 |
| Liu et al. ([20]) | China | 41 | 6 | 11 | 24 | 41 | 1 | 5 | 35 | 0.1607 |
| Ma et al. ([21]) | China | 60 | 6 | 7 | 47 | 60 | 5 | 6 | 49 | <0.0001 |
| Maalmi et al. ([22]) | Tunisia | 155 | 59 | 81 | 15 | 225 | 79 | 101 | 45 | 0.2230 |
| Papadopoulou et al. ([24]) | Cyprus | 61 | 28 | 20 | 13 | 630 | 224 | 325 | 81 | 0.0276 |
| Pillai et al. ([25]) | Cyprus | 61 | 28 | 20 | 13 | 630 | 224 | 325 | 81 | 0.0276 |
| Zhao et al. ([27]) | China | 40 | 16 | 14 | 0 | 40 | 13 | 27 | 0 | 0.0003 |
| **BsmI (rs1544410)** | | | | | | | | | |
| Ahmed et al. ([9]) | Egypt | 50 | 10 | 25 | 15 | 50 | 20 | 20 | 10 | 0.2386 |
| Batmaz et al. ([16]) | Turkey | 30 | 2 | 12 | 16 | 30 | 5 | 13 | 12 | 0.6477 |
| Hou et al. ([10]) | China | 70 | 0 | 4 | 66 | 70 | 0 | 5 | 65 | 0.7567 |
| Iordanidou et al. ([18]) | Greece | 127 | 20 | 67 | 40 | 91 | 19 | 39 | 33 | 0.2442 |
| Liu et al. ([20]) | China | 41 | 9 | 11 | 21 | 41 | 1 | 4 | 36 | 0.0723 |
| Ma et al. ([21]) | China | 60 | 5 | 10 | 45 | 60 | 6 | 6 | 48 | <0.0001 |
| Maalmi et al. ([22]) | Tunisia | 155 | 34 | 72 | 49 | 225 | 26 | 119 | 80 | 0.0663 |
| Mo et al. ([23]) | China | 71 | 0 | 5 | 66 | 71 | 0 | 4 | 67 | 0.8070 |
| Papadopoulou et al. ([24]) | Cyprus | 63 | 11 | 32 | 20 | 631 | 127 | 327 | 177 | 0.2801 |
| Zhang et al. ([26]) | China | 143 | 56 | 74 | 13 | 143 | 72 | 65 | 6 | 0.0635 |
| Zhao et al. ([27]) | China | 40 | 0 | 23 | 17 | 40 | 0 | 11 | 29 | 0.3133 |
| Zhu et al. ([13]) | China | 97 | 0 | 10 | 87 | 100 | 0 | 2 | 98 | 0.9195 |
| **FokI (rs2228570)** | | | | | | | | | |
| Batmaz et al. ([16]) | Turkey | 30 | 19 | 11 | 0 | 30 | 12 | 12 | 6 | 0.3613 |
| Einisman et al. ([17]) | Chile | 73 | 11 | 62 | 0 | 50 | 5 | 45 | 0 | <0.0001 |
| Iordanidou et al. ([18]) | Greece | 127 | 67 | 54 | 6 | 91 | 38 | 45 | 8 | 0.2958 |

(Continued)
TABLE 2 | Continued

| References        | Country     | Case group | Control group | P-value for HWE |
|-------------------|-------------|------------|---------------|-----------------|
|                   | N WW WM MM | N WW WM MM |               |                 |
| Ismail et al. (19)| Tunisia     | 84 27 43 9 | 92 22 24 10   | 0.668           |
| Klic et al. (12)  | Turkey      | 141 62 49 20 | 127 54 49 20 | 0.808           |
| Liu et al. (20)   | China       | 97 27 48 22 | 100 30 45 25  | 0.3283          |
| Maalmi et al. (21)| Tunisia     | 155 88 56 11 | 152 70 59 23  | 0.0808          |
| Pillai et al. (23) | USA         | 122 76 41 5  | 74 42 29 3     | 0.4636          |
| Zhang et al. (26) | China       | 143 2 49 92 | 143 6 63 74    | 0.0975          |
| Zhao et al. (27)  | China       | 40 19 14 7  | 40 15 16 9     | 0.2508          |
| Zhu et al. (13)   | China       | 97 27 48 22 | 100 30 45 25  | 0.3283          |

TABLE 3 | Quality assessment of the included studies.

| References        | Representativeness | Case definition adequate | Ascertainment of exposure | Same method of ascertainment for cases and controls | Control for important or additional factor | Selection of controls | Definition of controls | Non-response rate | Total quality scores |
|-------------------|--------------------|--------------------------|----------------------------|-----------------------------------------------|-------------------------------------------|-----------------------|----------------------|---------------------|----------------------|
| Ahmed et al. (9)  |                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Batmaz et al. (18)|                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Einisman et al. (17)|                |                          |                            |                                               |                                           |                       |                      |                     | 6                    |
| Hou et al. (10)   |                     |                          |                            |                                               |                                           |                       |                      |                     | 6                    |
| Hutchinson et al. (11)|               |                          |                            |                                               |                                           |                       |                      |                     | 5                    |
| Iordanidou et al. (18)|           |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Ismail et al. (19)|                     |                          |                            |                                               |                                           |                       |                      |                     | 6                    |
| Klic et al. (12)  |                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Liu et al. (20)   |                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Ma et al. (21)    |                     |                          |                            |                                               |                                           |                       |                      |                     | 6                    |
| Maalmi et al. (22)|                     |                          |                            |                                               |                                           |                       |                      |                     | 6                    |
| Mo et al. (23)    |                     |                          |                            |                                               |                                           |                       |                      |                     | 5                    |
| Papadopoulou et al. (24)|          |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Pillai et al. (23)|                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Zhang et al. (26) |                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Zhao et al. (27)  |                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |
| Zhen and Wang (8) |                     |                          |                            |                                               |                                           |                       |                      |                     | 6                    |
| Zhu et al. (13)   |                     |                          |                            |                                               |                                           |                       |                      |                     | 7                    |

AA: OR (95%CI) = 0.97 (0.66, 1.42), P = 0.866, dominant model (aa+Aa vs. AA: OR (95%CI) = 0.86 (0.55, 1.35), P = 0.520), and recessive model (aa vs. AA+Aa: OR (95%CI) = 0.73 (0.40, 1.32), P = 0.295).

The subgroup analysis was performed stratified by ethnicity, HWE, and source of controls (Table 4). No significant association was observed in all subgroup analysis (P>0.05). Meanwhile, the results of heterogeneity analysis showed that ethnicity, HWE, and source of subjects were not the source of heterogeneity.

TaqI (rs731236)
As shown in Figure 3, total 12 articles researched on the role of TaqI (rs731236) in asthma risk (9, 11, 12, 16–18, 20–25, 27). Obvious heterogeneity across studies was observed in additive model (t vs. T: I² = 71%, P < 0.0001), co dominant model (tt vs. TT: I² = 63%, P = 0.002; Tt vs. TT: I² = 50%, P = 0.02), dominant model (tt+Tt vs. TT: I² = 53%, P = 0.82), and recessive model (tt vs. TT+Tt: I² = 73%, P < 0.0001). Thus, the random effects model was used to calculated the pooled data, and the results showed that no significant association between TaqI (rs731236)
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Relationship Between the VDR Gene and Childhood Asthma

FIGURE 2 | Forest plot for meta-analyzing the association between Vitamin D receptor ApaI (rs7975232) polymorphisms and childhood asthma. (A) additive model: a vs. A; (B) co-dominant model: aa vs. AA; (C) co-dominant model: Aa vs. AA; (D) dominant model: aa + Aa vs. AA; (E) recessive model: aa vs. AA + Aa.
### TABLE 4 | Outcomes of the subgroup analysis.

| Model     | No. of studies | Heterogeneity test | Effect size |  |
|-----------|----------------|--------------------|-------------|---|
|           |                | $I^2$ (%) | $P_H$ | OR (95% CI) | $P$ value |
| ApaI (rs7975232) |                |          |     |            |         |
| a vs. A   | 16             | 88.7     | <0.001 | 0.82 (0.56, 1.21) | 0.317 |
| Ethnicity |               |          |     |            |         |
| American  | 1              | NA       | NA   | 0.76 (0.45, 1.26) | 0.285 |
| Asian     | 7              | 93.6     | <0.001 | 0.66 (0.25, 1.70) | 0.378 |
| Caucasians| 7              | 67.3     | 0.005 | 0.98 (0.72, 1.33) | 0.876 |
| African-American | 1        | NA       | NA   | 1.20 (0.77, 1.89) | 0.417 |
| HWE       |                |          |     |            |         |
| Yes       | 13             | 90.3     | <0.001 | 0.73 (0.47, 1.13) | 0.163 |
| No        | 3              | 17.7     | 0.297 | 1.37 (0.88, 2.16) | 0.167 |
| Source    |                |          |     |            |         |
| HB        | 14             | 90.0     | <0.001 | 0.79 (0.50, 1.22) | 0.287 |
| PB        | 2              | 0        | 0.927 | 1.09 (0.78, 1.52) | 0.607 |
| aa vs. AA | 16             | 83.7     | <0.001 | 0.65 (0.31, 1.38) | 0.263 |
| Ethnicity |                |          |     |            |         |
| American  | 1              | NA       | NA   | 0.56 (0.19, 1.63) | 0.265 |
| Asian     | 7              | 90.8     | <0.001 | 0.37 (0.06, 2.48) | 0.205 |
| Caucasians| 7              | 65.2     | 0.013 | 0.89 (0.46, 1.74) | 0.737 |
| African-American | 1        | NA       | NA   | 1.75 (0.52, 5.93) | 0.369 |
| HWE       |                |          |     |            |         |
| Yes       | 13             | 85.0     | <0.001 | 0.63 (0.28, 1.42) | 0.264 |
| No        | 3              | NA       | NA   | 0.91 (0.31, 2.72) | 0.290 |
| Source    |                |          |     |            |         |
| HB        | 14             | 86.0     | <0.001 | 0.59 (0.24, 1.46) | 0.254 |
| PB        | 2              | 0        | 0.795 | 1.02 (0.52, 2.01) | 0.948 |
| Aa vs. AA | 16             | 62.7     | <0.001 | 0.97 (0.66, 1.42) | 0.866 |
| Ethnicity |                |          |     |            |         |
| American  | 1              | NA       | NA   | 0.60 (0.24, 1.47) | 0.260 |
| Asian     | 7              | 72.9     | <0.001 | 0.71 (0.19, 2.67) | 0.615 |
| Caucasians| 7              | 9.2      | 0.358 | 1.24 (0.94, 1.63) | 0.128 |
| African-American | 1        | NA       | NA   | 1.14 (0.62, 2.08) | 0.674 |
| HWE       |                |          |     |            |         |
| Yes       | 13             | 67.0     | <0.001 | 0.90 (0.59, 1.38) | 0.637 |
| No        | 3              | 0        | 0.844 | 1.67 (0.67, 4.14) | 0.272 |
| Source    |                |          |     |            |         |
| HB        | 14             | 66.6     | <0.001 | 0.89 (0.57, 1.39) | 0.612 |
| PB        | 2              | 0        | 0.662 | 1.40 (0.82, 2.40) | 0.213 |
| aa+Aa vs. AA | 16       | 76.9     | <0.001 | 0.86 (0.55, 1.35) | 0.520 |
| Ethnicity |                |          |     |            |         |
| American  | 1              | NA       | NA   | 0.58 (0.25, 1.38) | 0.220 |
| Asian     | 7              | 86.9     | <0.001 | 0.53 (0.12, 2.25) | 0.391 |
| Caucasians| 7              | 46.8     | 0.080 | 1.14 (0.79, 1.62) | 0.488 |
| African-American | 1        | NA       | NA   | 1.20 (0.67, 2.15) | 0.532 |
| HWE       |                |          |     |            |         |
| Yes       | 13             | 79.9     | <0.001 | 0.80 (0.48, 1.33) | 0.393 |
| No        | 3              | 0        | 0.778 | 1.31 (0.64, 2.68) | 0.467 |
| Source    |                |          |     |            |         |
| HB        | 14             | 79.8     | <0.001 | 0.79 (0.47, 1.36) | 0.400 |
| PB        | 2              | 0        | 0.926 | 1.26 (0.78, 2.03) | 0.339 |
| aa vs. AA+AA | 16       | 85.6     | <0.001 | 0.73 (0.40, 1.32) | 0.295 |

(Continued)
TABLE 4 | Continued

| Model | No. of studies | Heterogeneity test | Effect size |
|-------|----------------|--------------------|-------------|
|       |                | $I^2$ (%) | $P_{H}$ | OR (95% CI) | $P$ value |
| Ethnicity |                |          |        |          |           |
| American | 1              | NA       | NA     | 0.79 (0.33, 1.90) | 0.600 |
| Asian    | 7              | 92.5     | <0.001 | 0.60 (0.17, 2.04) | 0.409 |
| Caucasians | 7             | 58.5     | 0.034  | 0.81 (0.48, 1.39) | 0.446 |
| African-American | 1     | NA       | NA     | 1.64 (0.50, 5.36) | 0.412 |
| HWE      |                |          |        |          |           |
| Yes     | 13             | 85.8     | <0.001 | 0.64 (0.34, 1.20) | 0.165 |
| No      | 3              | 72.9     | 0.055  | 1.78 (0.45, 6.96) | 0.409 |
| Source  |                |          |        |          |           |
| HB      | 14             | 87.6     | <0.001 | 0.70 (0.35, 1.40) | 0.319 |
| PB      | 2              | 0.0      | 0.916  | 0.90 (0.48, 1.69) | 0.745 |

TaqI (rs731236)

| Model | No. of studies | Heterogeneity test | Effect size |
|-------|----------------|--------------------|-------------|
|       |                | $I^2$ (%) | $P_{H}$ | OR (95% CI) | $P$ value |
| Ethnicity |                |          |        |          |           |
| American | 1              | NA       | NA     | 0.99 (0.56, 1.75) | 0.970 |
| Asian    | 3              | 55.4     | 0.106  | 0.45 (0.23, 0.89) | 0.022 |
| Caucasians | 7             | 71.5     | 0.002  | 1.06 (0.77, 1.47) | 0.711 |
| African-American | 1     | NA       | NA     | 1.45 (0.92, 2.30) | 0.112 |
| HWE      |                |          |        |          |           |
| Yes     | 8              | 70.8     | 0.001  | 0.91 (0.66, 1.27) | 0.582 |
| No      | 4              | 77.9     | 0.004  | 0.96 (0.52, 1.78) | 0.888 |
| Source  |                |          |        |          |           |
| HB      | 10             | 76.3     | <0.001 | 0.93 (0.66, 1.30) | 0.670 |
| PB      | 2              | 0.0      | 0.699  | 0.93 (0.66, 1.30) | 0.661 |
| tt vs. TT | 12            | 63.5     | 0.002  | 0.92 (0.49, 1.70) | 0.783 |

TaqI (rs731236)

| Model | No. of studies | Heterogeneity test | Effect size |
|-------|----------------|--------------------|-------------|
|       |                | $I^2$ (%) | $P_{H}$ | OR (95% CI) | $P$ value |
| Ethnicity |                |          |        |          |           |
| American | 1              | NA       | NA     | 1.03 (0.16, 6.63) | 0.976 |
| Asian    | 3              | 56.5     | 0.129  | 0.37 (0.06, 2.40) | 0.300 |
| Caucasians | 7             | 71.0     | 0.002  | 0.96 (0.44, 2.09) | 0.912 |
| African-American | 1     | NA       | NA     | 2.82 (0.74, 10.79) | 0.130 |
| HWE      |                |          |        |          |           |
| Yes     | 8              | 56.2     | 0.025  | 0.71 (0.36, 1.40) | 0.320 |
| No      | 4              | 70.6     | 0.033  | 2.01 (0.46, 8.77) | 0.351 |
| Source  |                |          |        |          |           |
| HB      | 10             | 67.7     | 0.002  | 0.93 (0.42, 2.07) | 0.857 |
| PB      | 2              | 3.5      | 0.407  | 1.15 (0.62, 2.12) | 0.665 |
| Tt vs. TT | 12            | 50.2     | 0.024  | 1.00 (0.72, 1.38) | 0.996 |

TaqI (rs731236)

| Model | No. of studies | Heterogeneity test | Effect size |
|-------|----------------|--------------------|-------------|
|       |                | $I^2$ (%) | $P_{H}$ | OR (95% CI) | $P$ value |
| Ethnicity |                |          |        |          |           |
| American | 1              | NA       | NA     | 0.97 (0.46, 2.03) | 0.939 |
| Asian    | 3              | 0.0      | 0.379  | 0.36 (0.17, 0.77) | 0.009 |
| Caucasians | 7             | 48.6     | 0.070  | 1.13 (0.78, 1.65) | 0.513 |
| African-American | 1     | NA       | NA     | 1.36 (0.75, 2.49) | 0.312 |
| HWE      |                |          |        |          |           |
| Yes     | 8              | 0.0      | 0.693  | 1.26 (0.99, 1.60) | 0.064 |
| No      | 4              | 49.2     | 0.116  | 0.57 (0.29, 1.15) | 0.120 |
| Source  |                |          |        |          |           |
| HB      | 10             | 41.4     | 0.082  | 1.11 (0.81, 1.53) | 0.521 |
| PB      | 2              | 0.0      | 0.438  | 0.53 (0.31, 0.94) | 0.029 |
| tt+Tt vs. TT | 12        | 53.3     | 0.015  | 0.96 (0.70, 1.32) | 0.817 |

(Continued)
| Model          | No. of studies | Heterogeneity test  | Effect size      |
|---------------|--------------|-------------------|-----------------|
|               |              | $I^2$ (%) | $P_H$ | OR (95% CI) | $P$ value |
| Ethnicity     |              |          |      |             |            |
| American      | 1            | NA      | NA   | 0.98 (0.47, 2.01) | 0.947       |
| Asian         | 3            | 29.0    | 0.244 | 0.36 (0.15, 0.87) | 0.024       |
| Caucasians    | 7            | 42.7    | 0.106 | 1.08 (0.77, 1.50) | 0.663       |
| African-American | 1          | NA      | NA   | 1.49 (0.83, 2.68) | 0.178       |
| HWE           |              |          |      |             |            |
| Yes           | 8            | 30.6    | 0.184 | 1.12 (0.84, 1.50) | 0.437       |
| No            | 4            | 64.1    | 0.039 | 0.70 (0.32, 1.51) | 0.362       |
| Source        |              |          |      |             |            |
| HB            | 10           | 56.6    | 0.014 | 1.02 (0.71, 1.47) | 0.901       |
| PB            | 2            | 0       | 0.739 | 0.67 (0.41, 1.10) | 0.112       |
| tt vs. TT+Tt  | 12           | 72.6    | <0.001 | 0.87 (0.47, 1.62) | 0.658       |
| Ethnicity     |              |          |      |             |            |
| American      | 1            | NA      | NA   | 1.04 (0.17, 6.48) | 0.964       |
| Asian         | 3            | 65.5    | 0.089 | 0.46 (0.14, 1.50) | 0.198       |
| Caucasians    | 7            | 79.3    | <0.001 | 0.97 (0.41, 2.28) | 0.941       |
| African-American | 1          | NA      | NA   | 2.43 (0.66, 9.03) | 0.184       |
| HWE           |              |          |      |             |            |
| Yes           | 8            | 57.8    | 0.020 | 0.60 (0.32, 1.09) | 0.095       |
| No            | 4            | 73.5    | 0.023 | 2.06 (0.59, 7.27) | 0.259       |
| Source        |              |          |      |             |            |
| HB            | 10           | 69.2    | 0.001 | 0.78 (0.38, 1.61) | 0.503       |
| PB            | 2            | 51.7    | 0.150 | 1.30 (0.59, 2.86) | 0.521       |
| BsmI (rs1544410) |          | 73.2    | <0.001 | 0.87 (0.62, 1.21) | 0.408       |
| Ethnicity     |              |          |      |             |            |
| Asian         | 7            | 79.9    | <0.001 | 0.57 (0.28, 1.17) | 0.128       |
| Caucasians    | 5            | 62.5    | 0.031 | 1.12 (0.82, 1.54) | 0.481       |
| HWE           |              |          |      |             |            |
| Yes           | 11           | 75.6    | <0.001 | 0.86 (0.60, 1.23) | 0.419       |
| No            | 1            | NA      | NA   | 0.88 (0.44, 1.77) | 0.724       |
| Source        |              |          |      |             |            |
| HB            | 10           | 77.6    | <0.001 | 0.81 (0.54, 1.24) | 0.336       |
| PB            | 2            | 0       | 0.527 | 1.08 (0.78, 1.49) | 0.662       |
| bb vs. BB     | 12           | 68.0    | 0.003 | 1.16 (0.61, 2.21) | 0.665       |
| Ethnicity     |              |          |      |             |            |
| Asian         | 7            | 79.5    | 0.008 | 0.74 (0.12, 4.40) | 0.741       |
| Caucasians    | 5            | 66.2    | 0.019 | 1.24 (0.62, 2.50) | 0.539       |
| HWE           |              |          |      |             |            |
| Yes           | 11           | 72.6    | 0.001 | 1.16 (0.56, 2.40) | 0.690       |
| No            | 1            | NA      | NA   | 1.13 (0.32, 3.94) | 0.854       |
| Source        |              |          |      |             |            |
| HB            | 10           | 76.7    | 0.001 | 1.12 (0.45, 2.76) | 0.805       |
| PB            | 2            | 0       | 0.844 | 1.25 (0.65, 2.42) | 0.501       |
| Bb vs. BB     | 12           | 55.6    | 0.027 | 1.22 (0.76, 1.96) | 0.409       |
| Ethnicity     |              |          |      |             |            |
| Asian         | 7            | 0       | 0.401 | 1.42 (0.90, 2.23) | 0.130       |
| Caucasians    | 5            | 68.4    | 0.013 | 1.22 (0.62, 2.40) | 0.561       |
| HWE           |              |          |      |             |            |
| Yes           | 11           | 60.8    | 0.018 | 1.18 (0.71, 1.96) | 0.524       |
| Model | No. of studies | Heterogeneity test | Effect size |
|-------|----------------|-------------------|-------------|
|       |                | $I^2$ (%) | $P_\text{H}$ | OR (95% CI) | $P$ value |
| No    | 1              | NA            | NA          | 2.00 (0.42, 9.52) | 0.384 |
| Source |                |              |             |              |          |
| HB    | 10             | 67.3         | 0.009       | 1.20 (0.64, 2.24) | 0.576 |
| PB    | 2              | 0.0          | 0.514       | 1.25 (0.65, 2.39) | 0.505 |
| bb+Bb vs. BB | 12 | 68.5         | 0.002       | 1.14 (0.67, 1.93) | 0.627 |
| Ethnicity | | | | | |
| Asian | 7              | 70.5         | 0.034       | 0.80 (0.23, 2.81) | 0.732 |
| Caucasians | 5 | 72.2         | 0.006       | 1.25 (0.64, 2.47) | 0.515 |
| HWE   | |              |             |              |          |
| Yes   | 11             | 73.0         | 0.001       | 1.13 (0.63, 2.01) | 0.686 |
| No    | 1              | NA           | NA          | 1.22 (0.35, 4.24) | 0.752 |
| Source |                |              |             |              |          |
| HB    | 10             | 77.4         | <0.001      | 1.10 (0.54, 2.25) | 0.788 |
| PB    | 2              | 0            | 0.972       | 1.20 (0.66, 2.17) | 0.552 |
| bb vs. BB+Bb | 12 | 61.5         | 0.003       | 0.80 (0.54, 1.20) | 0.278 |
| Ethnicity | | | | | |
| Asian | 7              | 69.2         | 0.003       | 0.55 (0.25, 1.18) | 0.124 |
| Caucasians | 5 | 0            | 0.414       | 1.01 (0.77, 1.32) | 0.948 |
| HWE   | |              |             |              |          |
| Yes   | 11             | 64.9         | 0.001       | 0.80 (0.52, 1.24) | 0.326 |
| No    | 1              | NA           | NA          | 0.75 (0.32, 1.77) | 0.513 |
| Source |                |              |             |              |          |
| HB    | 10             | 66.5         | 0.001       | 0.75 (0.46, 1.24) | 0.267 |
| PB    | 2              | 0.0          | 0.375       | 1.04 (0.65, 1.66) | 0.870 |
| FokI (rs2228570) | | | | | |
| f vs. F | 12            | 76.7         | <0.001      | 0.78 (0.57, 1.05) | 0.102 |
| Ethnicity | | | | | |
| American | 1            | NA           | NA          | 0.90 (0.54, 1.51) | 0.694 |
| Asian | 5              | 84.4         | <0.001      | 0.90 (0.50, 1.63) | 0.721 |
| Caucasians | 5 | 62.7         | 0.030       | 0.63 (0.43, 0.92) | 0.015 |
| African-American | 1 | NA | NA | 0.85 (0.52, 1.39) | 0.524 |
| HWE   | |              |             |              |          |
| Yes   | 11             | 78.8         | <0.001      | 0.76 (0.55, 1.06) | 0.107 |
| No    | 1              | NA           | NA          | 0.90 (0.54, 1.51) | 0.694 |
| Source |                |              |             |              |          |
| HB    | 11             | 73.2         | <0.001      | 0.72 (0.54, 0.97) | 0.030 |
| PB    | 1              | NA           | NA          | 1.90 (1.14, 3.17) | 0.015 |
| ff vs. FF | 12            | 67.6         | 0.001       | 0.67 (0.34, 1.34) | 0.260 |
| Ethnicity | | | | | |
| American | 1            | NA           | NA          | NA | NA |
| Asian | 5              | 70.7         | 0.008       | 1.05 (0.38, 2.91) | 0.925 |
| Caucasians | 5 | 62.9         | 0.029       | 0.37 (0.13, 1.07) | 0.067 |
| African-American | 1 | NA | NA | 0.92 (0.21, 4.05) | 0.913 |
| HWE   | |              |             |              |          |
| Yes   | 11             | 67.6         | 0.001       | 0.67 (0.34, 1.34) | 0.260 |
| No    | 1              | NA           | NA          | NA | NA |
| Source |                |              |             |              |          |
| HB    | 11             | 59.3         | 0.008       | 0.57 (0.29, 1.11) | 0.095 |
| PB    | 1              | NA           | NA          | 3.27 (1.18, 9.09) | 0.023 |
| Ff vs. FF | 12            | 0           | 0.890       | 0.82 (0.65, 1.02) | 0.071 |

(Continued)
and asthma risk was observed across additive model (t vs. T: OR (95%CI) = 0.93 (0.70, 1.23), P = 0.608), co dominant model [tt vs. TT: OR (95%CI) = 0.92 (0.49, 1.70), P = 0.783; Tt vs. TT: OR (95%CI) = 1.00 (0.72, 1.38), P = 0.996], dominant model [tt+Tt vs. TT: OR (95%CI) = 0.96 (0.70, 1.32), P = 0.817], and recessive model [tt vs. TT+Tt: OR (95%CI) = 0.87 (0.47, 1.62), P = 0.658].

Further subgroup analysis showed that HWE and source of control were two sources for the obvious heterogeneity across co dominant model (Tt vs. TT). Notably, significant association was found in additive model (b vs. B: I^2 = 73%, P < 0.0001), co dominant model (bb vs. BB: I^2 = 68%, P = 0.003; Bb vs. BB: I^2 = 56%, P = 0.03), dominant model (bb+Bb vs. BB: I^2 = 68%, P = 0.002), and recessive model (bb vs. BB+Bb: I^2 = 62%, P = 0.003). Thus, the random effects model was used to calculated the pooled data, and the results showed that no significant association between BsmI (rs1544410) and asthma risk was observed across additive model (b vs. B: OR (95%CI) = 0.87 (0.62, 1.21), P = 0.408), co dominant model [Tt vs. TT: OR (95%CI) = 0.53 (0.31, 0.94), P = 0.029].

**BsmI (rs1544410)**

As shown in Figure 4, total 12 articles researched on the role of BsmI (rs1544410) in asthma risk (9, 10, 13, 16, 18, 20–24, 26, 27). Obvious heterogeneity across studies was observed in additive model (b vs. B: I^2 = 73%, P < 0.0001), co dominant model (bb vs. BB: I^2 = 68%, P = 0.003; Bb vs. BB: I^2 = 56%, P = 0.03), dominant model (bb+Bb vs. BB: I^2 = 68%, P = 0.002), and recessive model (bb vs. BB+Bb: I^2 = 62%, P = 0.003). Thus, the random effects model was used to calculated the pooled data, and the results showed that no significant association between BsmI (rs1544410) and asthma risk was observed across additive model (b vs. B: OR (95%CI) = 0.87 (0.62, 1.21), P = 0.408), co dominant model [Tt vs. TT: OR (95%CI) = 0.53 (0.31, 0.94), P = 0.029].

As shown in Figure 4, total 12 articles researched on the role of BsmI (rs1544410) in asthma risk (9, 10, 13, 16, 18, 20–24, 26, 27). Obvious heterogeneity across studies was observed in additive model (b vs. B: I^2 = 73%, P < 0.0001), co dominant model (bb vs. BB: I^2 = 68%, P = 0.003; Bb vs. BB: I^2 = 56%, P = 0.03), dominant model (bb+Bb vs. BB: I^2 = 68%, P = 0.002), and recessive model (bb vs. BB+Bb: I^2 = 62%, P = 0.003). Thus, the random effects model was used to calculated the pooled data, and the results showed that no significant association between BsmI (rs1544410) and asthma risk was observed across additive model (b vs. B: OR (95%CI) = 0.87 (0.62, 1.21), P = 0.408), co dominant model [Tt vs. TT: OR (95%CI) = 0.53 (0.31, 0.94), P = 0.029].

As shown in Figure 4, total 12 articles researched on the role of BsmI (rs1544410) in asthma risk (9, 10, 13, 16, 18, 20–24, 26, 27). Obvious heterogeneity across studies was observed in additive model (b vs. B: I^2 = 73%, P < 0.0001), co dominant model (bb vs. BB: I^2 = 68%, P = 0.003; Bb vs. BB: I^2 = 56%, P = 0.03), dominant model (bb+Bb vs. BB: I^2 = 68%, P = 0.002), and recessive model (bb vs. BB+Bb: I^2 = 62%, P = 0.003). Thus, the random effects model was used to calculated the pooled data, and the results showed that no significant association between BsmI (rs1544410) and asthma risk was observed across additive model (b vs. B: OR (95%CI) = 0.87 (0.62, 1.21), P = 0.408), co dominant model [Tt vs. TT: OR (95%CI) = 0.53 (0.31, 0.94), P = 0.029].

As shown in Figure 4, total 12 articles researched on the role of BsmI (rs1544410) in asthma risk (9, 10, 13, 16, 18, 20–24, 26, 27). Obvious heterogeneity across studies was observed in additive model (b vs. B: I^2 = 73%, P < 0.0001), co dominant model (bb vs. BB: I^2 = 68%, P = 0.003; Bb vs. BB: I^2 = 56%, P = 0.03), dominant model (bb+Bb vs. BB: I^2 = 68%, P = 0.002), and recessive model (bb vs. BB+Bb: I^2 = 62%, P = 0.003). Thus, the random effects model was used to calculated the pooled data, and the results showed that no significant association between BsmI (rs1544410) and asthma risk was observed across additive model (b vs. B: OR (95%CI) = 0.87 (0.62, 1.21), P = 0.408), co dominant model [Tt vs. TT: OR (95%CI) = 0.53 (0.31, 0.94), P = 0.029].
dominant model (bb vs. BB: OR (95%CI) = 1.16 (0.61, 2.21), \( P = 0.665 \); Bb vs. BB: OR (95%CI) = 1.22 (0.76, 1.96), \( P = 0.409 \)), dominant model (bb+Bb vs. BB: OR (95%CI) = 1.14 (0.67, 1.93), \( P = 0.627 \)), and recessive model (bb vs. BB+Bb: OR (95%CI) = 0.80 (0.54, 1.20), \( P = 0.278 \)).

Further subgroup analysis showed that no significant association was observed in all subgroup analysis (\( P > 0.05 \)). Meanwhile, the results of heterogeneity analysis showed that ethnicity, HWE, and source of subjects were not the source of heterogeneity.

FokI (rs2228570)
As shown in Figure 5, total 12 articles researched on the role of FokI (rs2228570) in asthma risk (12, 13, 16–22, 25–27). Obvious heterogeneity across studies was observed in additive model (\( \chi^2 = 77\%, P < 0.00001 \)), co dominant model (ff vs. FF: I\(^2\) = 68\%, \( P = 0.0006 \)), and recessive model (ff vs. FF+FF: I\(^2\) = 74\%, \( P < 0.0001 \)). Thus, the random-effects model was used to calculate the pooled data, and the results showed that no significant association between FokI (rs2228570) and asthma risk was observed across additive model (\( \chi^2 = 77\%, P < 0.00001 \)), co dominant model (ff vs. FF: \( P = 0.102 \)), and dominant model (ff vs. FF: OR (95%CI) = 0.67 (0.34, 1.34), \( P = 0.260 \)), and recessive model (ff vs. FF+FF: OR (95%CI) = 0.71 (0.39, 1.29), \( P = 0.266 \)).

No significant obvious heterogeneity across studies was observed in co dominant model (FF vs. FF: I\(^2\) = 0\%, \( P = 0.89 \)) and dominant model (FF+FF vs. FF: I\(^2\) = 35\%, \( P = 0.02 \)), thus, the fixed effect model was used to calculate the pooled data, and the results showed that FokI (rs2228570) could significantly affect the risk of asthma across co dominant model (FF vs. FF: OR (95%CI) = 0.82 (0.65, 1.02), \( P = 0.071 \)) and dominant model (FF+FF vs. FF: OR (95%CI) = 0.77 (0.63, 0.95), \( P = 0.016 \)).

As for FokI (rs2228570), race, source of controls, HWE were not the source for the obvious heterogeneity. Subgroup analysis showed that FokI (rs2228570) SNP was significantly related with the risk of asthma in additive model (\( \chi^2 = 0.43, 0.92, P = 0.015 \)) and dominant model (ff+FF vs. FF: OR (95%CI) = 0.67 (0.51, 0.88), \( P = 0.004 \)) among Caucasians. Meanwhile, significant association was found in additive model (ff vs. FF: OR (95%CI) = 0.72 (0.54, 0.97), \( P = 0.03 \)) and dominant model (ff+FF vs. FF: OR (95%CI) = 0.67 (0.51, 0.88), \( P = 0.004 \)) in the hospital-based subgroup. Significant association was found in additive model (ff vs. FF: OR (95%CI) = 1.90 (1.14, 3.17), \( P = 0.015 \)), co dominant model (ff vs. FF: OR (95%CI) = 3.27 (1.18, 9.09), \( P = 0.023 \)), and recessive model (ff vs. FF+FF: OR (95%CI) = 2.97 (1.29, 6.83), \( P = 0.01 \)) in population-based subgroup.

Publication Bias
No significant publication bias was observed for ApaI (rs7975232), TaqI (rs731236), BsmI (rs1544410), FokI (rs2228570), and TaqI (rs731236), were the main gene locuses (3, 29). Based on the meta-analysis, our data showed that FokI (rs2228570) could significantly affect the risk of childhood asthma across co dominant model and dominant model, especially among Caucasians. Notably, among Asians, significant correction between TaqI (rs731236) and childhood asthma was also found in additive model (t vs. T), co dominant model (Tt vs. TT), and dominant model (tt+Tt vs. TT), as well as population-based subgroup in co dominant model (Tt vs. TT). No relationship was found between childhood asthma and the polymorphisms of ApaI (rs7975232) and BsmI (rs1544410).

Previous evidence showed that the level of Vitamin D was closely related with airway remodeling, the number of T regulatory cells, and expression level of pro-inflammatory cytokines and NF-\( \kappa \)B (30). The connection between the deficiency of Vitamin D and poor asthma outcomes has been previously reported, such as worse symptomatology and poor lung function, and these defects could be reversed for offspring if Vitamin D was supplemented in deficient pregnant rodents (31). Zhen et al. demonstrated that, two out of four VDR polymorphisms could significantly affect the susceptibility of childhood asthma, including FokI and TaqI (8). Similarly, our study supported FokI and TaqI polymorphisms were associated with childhood asthma. Interestingly, it was different from the finding of a previous study (32), which gave support for that VDR gene ApaI (rs7975232) could contribute to asthma susceptibility.

The conflicting results might be explained by the following aspects. Firstly, it is well known that asthma is a clinical syndrome, and no gold standard test have been reported for making the diagnosis. Thus, physicians used multiple algorithms to make the final diagnosis, such as breath shortness, cough history, or wheezing history (33). Meanwhile, other baseline characteristics, such as smoking status, stress, gender, and age, were all related with the diagnosis of asthma (1). Secondly, based on genome-wide analysis studies, the researchers found that over 100 candidate genes were associated with the risk and development of asthma (34). Thirdly, the study designs and different genotyping methods might also account for the conflicting results. The obvious heterogeneity across included studies might also be attributed to these reasons.

There are some limitations should be noted. Firstly, the number of studies included in some subgroups was small, and more high-quality studies would be needed to verify the stability of the results. Secondly, since most of the included studies did not report the family history, living habits and other information of the study subjects, the quantitatively analyze based on these factors could not be performed to determine whether they affect the relationship between VDR gene polymorphisms and the childhood asthma susceptibility. Thirdly, the obvious heterogeneity across included studies could not be ignored. However, the moderate quality suggested that the analysis results had good credibility.

CONCLUSION
In summary, we concluded that FokI and TaqI polymorphisms were associated with childhood asthma susceptibility. However,
**FIGURE 3** | Forest plot for meta-analyzing the association between Vitamin D receptor TaqI (rs731238) polymorphisms and childhood asthma. (A) additive model: t vs. T; (B) co dominant model: tt vs. TT; (C) co dominant model: Tt vs. TT; (D) dominant model: tt + Tt vs. TT; (E) recessive model: tt vs. TT + Tt.
FIGURE 4 | Forest plot for meta-analyzing the association between Vitamin D receptor BsmI (rs1544410) polymorphisms and childhood asthma. (A) additive model: b vs. B; (B) co dominant model: bb vs. BB; (C) co dominant model: Bb vs. BB; (D) dominant model: bb + Bb vs. BB; (E) recessive model: bb vs. BB+Bb.
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FIGURE 5 | Forest plot for meta-analyzing the association between Vitamin D receptor FokI (rs2228570) polymorphisms and childhood asthma. (A) additive model: f vs. F; (B) co dominant model: ff vs. FF; (C) co dominant model: Ff vs. FF; (D) dominant model: ff + Ff vs. FF; (E) recessive model: ff vs. FF+Ff.
it seems that ApaI and BsmI polymorphisms are not related with childhood asthma susceptibility. Due to these limitations, further multi-center study with high quality should be designed to verify the present conclusion.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

YZ: conception and design of the research, acquisition of data, analysis and interpretation of data, and drafting the manuscript. SL: statistical analysis and revision of manuscript for important intellectual content. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.843691/full#supplementary-material

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