

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%Cl) = 0.82 (0.65, 1.02), P = 0.071) and dominant model (ff+Ff vs. FF: OR (95%Cl) = 0.77 (0.63, 0.95), P = 0.016), especially among Caucasians in additive model (f vs. F: OR (95%Cl) = 0.63 (0.43, 0.92), P = 0.015) and dominant model (ff+Ff vs. FF: OR (95%Cl) = 0.67 (0.51, 0.88), P = 0.004). Taql (rs731236) was significantly related with childhood asthma in additive model (t vs. T: OR (95%Cl) = 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+Tt vs. TT: OR (95%Cl) = 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%Cl) = 0.53 (0.31, 0.94), P = 0.029). However, no evidence supported the role of Apal (rs7975232) and Bsml (rs1544410) polymorphisms in childhood asthma. Fokl and Taql polymorphisms were found to be related with the susceptibility of childhood asthma. However, it seems that Apal and Bsml 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, the

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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 metaanalysis 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, WANFANG 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 (mutation) vs. W (Wild)], co dominant model (mm vs. WW, Wm vs. WW), dominant model (mm+ Wm vs. WW), and recessive model (mm 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 I² test (15). If P < 0.05, and/or I² >50%, suggesting obvious heterogeneity between the studies, the random effects model would be selected to calculate the pooled data; If $P \ge 0.05$ and/or I² $\le 50\%$, 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

Apal (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: I² = 89%, P < 0.00001), co dominant model (aa vs. AA: I² = 84%, P < 0.00001; Aa vs. AA: I² = 63%, P < 0.0006), dominant model (aa+Aa vs. AA: I² = 77%, P < 0.00001), and recessive model (aa vs. AA+Aa: I² = 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.

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	Apal, Taql, Bsml	Asthma	50, 28/22	12.66±3.34
						Control	50, 29/21	12.08±3.53
Batmaz et al. (16)	Turkey	European	HB	GINA guidelines	Apal, Taql, Fokl, Bsml	Asthma	30, 20/10	11.74±2.4
						Control	30, 13/17	11.31±2.27
Einisman et al. (17)	Chile	American	HB	GINA guidelines	Apal, Taql, Fokl	Asthma	75, 43/32	9.1 (3.5) \$
						Control	227, 114/113	10.3 (7.9)
Hou et al. (10)	China	Asia	HB	DPGPBA (2008)	Apal, Bsml	Asthma	70, 43/27	8.84±3.21
						Control	70, 37/33	8.04±3.01
Hutchinson et al. (11)	Ireland	European	HB	GINA guidelines	Apal, Taql	Asthma	44, 23/21	8.7 (6–13, 15–17)
						Control	57, NR	NR
lordanidou et al. (18)	Greece	European	HB	GINA guidelines	Apal, Taql, Fokl, Bsml	Asthma	127, 82/45	8.4±2.3
						Control	91, 41/50	9.5±3.8
Ismail et al. (12)	Egypt	European	HB	GINA guidelines	Fokl	Asthma	51, 28/23	8.6±2.7
						Control	33, 18/15	7.8±2.6
Kilic et al. (12)	Turkey	European	HB	GINA guidelines	Apal, Taql, Fokl	Asthma	100, 52/48	9.5±2.8
						Control	80, 42/38	9.5±2.5
Liu et al. (20)	China	Asia	HB	DPGPBA (2008)	Apal, Taql, Fokl, Bsml	Asthma	41, 24/17	3.9±1.2
						Control	41, 23/18	3.7±1.3
Ma et al. (21)	China	Asia	PB	DPGPBA (2008)	Apal, Taql, Fokl, Bsml	Asthma	60, 32/28	10.2
						Control	60, 30/30	10.6
Maalmi et al. (22)	Tunisia	European	HB	DPGPBA (2008)	Apal, Taql, Fokl, Bsml	Asthma	155, 59/96	9.1 (4–13, 15–17)
						Control	225, 99/126	9.5 (2–13, 15–17)
Mo et al. (23)	China	Asia	HB	DPGPBA (2008)	Apal, Bsml	Asthma	71, NR	NR
						Control	71, NR	NR
Papadopoulou et al. (24)	Cyprus	European	PB	NR	Apal, Taql, Bsml	Asthma	69, 30/39	16.9 (15.9-18.1)
						Control	671, 282/389	17.0 (15.9-18.0)
Pillai et al. (25)	USA	African- American	HB	NAEPP (2007)	Apal, Taql, Fokl	Asthma	139, 81/58	11.2±3.5
						Control	74, 26/48	11.8±4.3
Zhang et al. (26)	China	Asia	HB	NR	Apal, Fokl, Bsml	Asthma	143, 86/57	7.56±2.39
						Control	143, 87/56	7.28±2.54
Zhao et al. (27)	China	Asia	HB	DPGPBA (2008)	Apal, Taql, Fokl, Bsml	Asthma	40, 22/18	3.41±1.07
						Control	40, 21/19	3.37±1.04
Zhen and Wang (8)	China	Asia	HB	NR	Apal	Asthma	30, 17/13	5.70±2.84
						Control	40, 22/18	5.53±2.93
Zhu et al. (13)	China	Asia	HB	DPGPBA (2008)	Fokl, Bsml	Asthma	97, 50/47	8.76±1.22
						Control	100, 55/45	8.60±1.16

\$, median (IQR); HB, hospital-based; PB, population-based; PCR, Polymerase chain reaction; RT-PCR, Realtime 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).

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TABLE 2 | Frequency distribution of gene polymorphisms in the experimental group and the control group.

References	Country		Case	group			Contro	ol group		P _{value} for HWE
		N	ww	WM	ММ	N	ww	WM	ММ	
Apal (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
lordanidou 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)	USA	125	55	59	11	72	35	33	4	0.2762
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
Taql (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
lordanidou et al. (18)	Greece	127	43	68	16	91	35	38	18	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)	USA	118	52	55	11	74	40	31	3	0.3137
Zhao et al. (27)	China	40	26	14	0	40	13	27	0	0.0013
Bsml (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
lordanidou 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
Fokl (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
lordanidou et al. (18)	Greece	127	67	54	6	91	38	45	8	0.2958

References	Country		Case	group			Contro	ol group		P _{value} for HWE
		N	ww	WM	ММ	N	ww	WM	ММ	
Ismail et al. (19)	Egypt	51	29	22	0	33	12	14	7	0.4497
Kilic et al. (12)	Turkey	100	58	33	9	80	48	28	4	0.9744
Liu et al. (20)	China	41	8	13	20	41	1	5	35	0.1607
Ma et al. (21)	China	60	12	24	24	60	18	31	11	0.7124
Maalmi et al. (22)	Tunisia	155	88	56	11	152	70	59	23	0.0808
Pillai et al. (25)	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	Representativene of the cases	essCase definition adequate	Ascertainment of exposure	t Same method of ascertainment for cases and controls	Control for important factor or additional factor	Selection of controls	Definition of controls	Non- response rate	Total quality scores
Ahmed et al. (9)	☆	☆	☆	☆	☆	_	☆	☆	7
Batmaz et al. (16)	\overleftrightarrow	\Rightarrow	☆	\overleftrightarrow	\overleftrightarrow	-	\overleftrightarrow	☆	7
Einisman et al. (17)	\diamond	\Rightarrow	☆	\Rightarrow	☆	_	☆	-	6
Hou et al. (10)	${\simeq}$	\Rightarrow	\overleftrightarrow	${\simeq}$	-	_	☆	${\simeq}$	6
Hutchinson et al. (11)	\overleftrightarrow	\Rightarrow	${\leftrightarrow}$	${\simeq}$	-	_	-	${\simeq}$	5
lordanidou et al. (18)	${\simeq}$	${\leftrightarrow}$	${\leftrightarrow}$	${\simeq}$	$\stackrel{\frown}{\simeq}$	_	$\stackrel{\circ}{\simeq}$	${\leftrightarrow}$	7
Ismail et al. (19)	${\simeq}$	${\leftrightarrow}$	${\leftrightarrow}$	${\simeq}$	-	-	$\stackrel{\circ}{\simeq}$	${\leftrightarrow}$	6
Kilic et al. (12)	${\simeq}$	\Rightarrow	\overleftrightarrow	${\simeq}$	☆	_	☆	${\simeq}$	7
Liu et al. (20)	${\simeq}$	${\leftrightarrow}$	${\leftrightarrow}$	${\simeq}$	$\stackrel{\frown}{\simeq}$	_	$\stackrel{\circ}{\simeq}$	${\leftrightarrow}$	7
Ma et al. (21)	${\simeq}$	\Rightarrow	\overleftrightarrow	${\simeq}$	-	☆	☆	${\simeq}$	6
Maalmi et al. (22)	${\simeq}$	\Rightarrow	\overleftrightarrow	${\simeq}$	☆	_	☆	_	6
Mo et al. (23)	-	${\leftrightarrow}$	${\leftrightarrow}$	${\simeq}$	-	_	$\stackrel{\circ}{\simeq}$	${\leftrightarrow}$	5
Papadopoulou et al. (24)	${\leftrightarrow}$	-	${\leftrightarrow}$	${\leftrightarrow}$	\overleftrightarrow	☆	☆	\overleftrightarrow	7
Pillai et al. (25)	\overleftrightarrow	\Rightarrow	${\leftrightarrow}$	${\simeq}$	$\stackrel{\frown}{\simeq}$	_	☆	${\simeq}$	7
Zhang et al. (26)	${\simeq}$	-	\Rightarrow	${\simeq}$	\overleftrightarrow	☆	☆	${\simeq}$	7
Zhao et al. (27)	${\simeq}$	\Rightarrow	\Rightarrow	${\simeq}$	☆	_	☆	\Rightarrow	7
Zhen and Wang (8)	${\simeq}$	-	\Rightarrow	${\simeq}$	\overleftrightarrow	_	☆	${\simeq}$	6
Zhu et al. (13)	${\leftrightarrow}$	${\simeq}$	${\simeq}$	${\leftrightarrow}$	${\simeq}$	-	\overleftrightarrow	${\leftrightarrow}$	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.

Taql (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: $I^2 = 71\%$, P < 0.0001), co dominant model (tt vs. TT: $I^2 = 63\%$, P = 0.002; Tt vs. TT: $I^2 = 50\%$, P = 0.02), dominant model (tt+Tt vs. TT: $I^2 = 53\%$, P = 0.82), and recessive model (tt vs. TT+Tt: $I^2 = 73\%$, P < 0.0001). Thus, the randomed effects model was used to calculated the pooled data, and the results showed that no significant association between TaqI (rs731236)

	Study or Subaroun	Experim	ental Total	Contre	ol Total	Weight	Odds Ratio	Odds Ratio	
	Ahmed, AE 2020	35	100	40	100	6.3%	0.81 [0.46, 1.43]	-+-	
	Batmaz, SB 2017 Einisman H 2015	25 63	60 140	23 52	60 100	5.8%	1.15 [0.55, 2.39]		
	Hou, C 2018	102	140	135	140	5.0%	0.10 [0.04, 0.26]		
	Hutchinson, K 2018 Iordanidou M 2014	43	88 254	84 71	114	6.3%	0.34 [0.19, 0.62]		
	Kilic, M 2019	103	200	66	160	6.8%	1.54 [1.01, 2.35]		
	Liu, Y 2016	53	82 120	76	82	5.1%	0.14 [0.06, 0.37]		
	Maalmi, H 2013	69	310	96	450	7.0%	1.06 [0.74, 1.50]	+	
	Mo, LY 2015	103	142	86	142	6.6%	1.72 [1.04, 2.83]		
	Pillai, DK 2011	81	250	490	144	6.7%	1.20 [0.77, 1.89]		
	Zhang, Y 2017 Zhang, UX 2015	103	286	201	286	7.0%	0.24 [0.17, 0.34]	I	
	Zhao, HX 2015 Zhen, YF 2010	65 52	80 60	53 54	80	5.8%	3.13 [1.30, 7.54]		
	Total (95% CI)		2424		2506	100.0%	0 92 10 56 1 211	•	
	Total events	1078	2434	1588	3300	100.078	0.02 [0.30, 1.21]		
	Heterogeneity: Tau ² = 0.5	2; Chi ² = 1	132.36, d	f = 15 (P	< 0.00	001); I ² = 8	9%	0.05 0.2 1 5	20
R	resciol overall ellect. 2 -	· 1.00 (F =	0.52)					Favours [experimental] Favours [control]	
D	Study or Subgroup	Experim Events	ental Total	Contro Events	ol Total	Weight	Odds Ratio	Odds Ratio IV. Random, 95% Cl	
-	Ahmed, AE 2020	10	35	10	30	7.7%	0.80 [0.28, 2.30]		
	Batmaz, SB 2017 Einieman H 2015	0	5 35	0	7	7.6%	Not estimable		
	Hou, C 2018	36	40	65	65	3.8%	0.06 [0.00, 1.18]		
	Hutchinson, K 2018	10	21	32	37	7.2%	0.14 [0.04, 0.51]		
	Kilic, M 2019	23	40	12	38	7.9%	2.65 [1.05, 6.68]	_ .	
	Liu, Y 2016	19	26	36	37	5.2%	0.08 [0.01, 0.66]		
	Ma, JH 2014 Maalmi, H 2013	6	53 98	13	155	7.6%	0.91 [0.31, 2.72]	_	
	Mo, LY 2015	36	40	29	43	7.3%	4.34 [1.29, 14.63]		
	Papadopoulou, A 2015 Pillai, DK 2011	8 11	27 66	89 4	321 39	8.1% 7.3%	1.10 [U.46, 2.60] 1.75 [0.52, 5.93]	- -	
	Zhang, Y 2017	14	68	66	74	7.9%	0.03 [0.01, 0.08]	_ —	
	Zhao, HX 2015 Zhen, YF 2010	25 25	25 28	13 20	13 26	6.6%	Not estimable 2.50 [0.55, 11.27]	—	
	Total (95% CI) Total events	266	671	424	1013	100.0%	0.65 [0.31, 1.38]		
	Heterogeneity: Tau ² = 1.6	15; Chi² = 1	79.92, df	= 13 (P <	0.000	01); l² = 84	%	0.005 0.1 1 10	200
	Test for overall effect: Z =	: 1.12 (P =	0.26)					Favours [experimental] Favours [control]	200
		Experim	ental	Contr	ol		Odds Ratio	Odds Ratio	
C-	Study or Subgroup	Events 15	Total 40	Events 20	Total 40	Weight 7.5%	IV. Random, 95% C	IV. Random, 95% CI	
	Batmaz, SB 2017	25	30	23	30	5.3%	1.52 [0.42, 5.47]		
	Einisman, H 2015 Hou, C 2018	35 30	56 34	28 5	38 5	7.5% 1.4%	0.60 [0.24, 1.47]		
	Hutchinson, K 2018	23	34	20	25	5.6%	0.52 [0.16, 1.76]		
	lordanidou, M 2014 Kilic, M 2019	63 60	104	41	76	9.7%	1.31 [0.72, 2.39]		
	Liu, Y 2016	15	22	42	5	2.2%	0.54 [0.05, 5.72]		
	Ma, JH 2014 Maalmi H 2012	7	53	4	52	5.2%	1.83 [0.50, 6.66]		
	Mo, LY 2015	31	35	28	42	5.6%	3.88 [1.14, 13.17]		
	Papadopoulou, A 2015	34	53	312	544	9.8%	1.33 [0.74, 2.39]		
	Zhang, Y 2017	75	129	69	77	8.1%	0.16 [0.07, 0.36]	[
	Zhao, HX 2015	15	15	27	27	0.00/	Not estimable		
	211011, 117 2010	2	5	14	20	2.0%	0.29 [0.04, 2.17]		
						100.0%	0.97 [0.66, 1.42]	+	
	Total (95% CI)	546	951	740	1329				
	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3	546 11; Chi² = 3	951 37.50, df	740 = 14 (P =	1329	6); I² = 63%		0.05 0.2 1 5	
	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z =	546 11; Chi² = 3 : 0.17 (P =	951 37.50, df 0.87)	740 = 14 (P =	1329 0.000	6); I² = 63%		0.05 0.2 1 5 Favours [experimental] Favours [control]	20
n	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z =	546 11; Chi ² = 3 0.17 (P = Experim	951 37.50, df 0.87) iental	740 = 14 (P = Contr	1329 0.000	6); I² = 63%	Odds Ratio	0.05 0.2 1 5 Favours [experimental] Favours [control] Odds Ratio	20
D_	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = Study or Subgroup	546 11; Chi ² = 3 0.17 (P = Experim Events	951 37.50, df 0.87) eental <u>Total</u>	740 = 14 (P = Contro Events	1329 0.000 ol <u>Total</u>	6); I ² = 63% Weight	Odds Ratio	0.05 0.2 1 5 Favours [experimental] Favours [control] Odds Ratio	20
D_	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017	546 11; Chi ² = 3 0.17 (P = Experim Events 25 25	951 37.50, df 0.87) ental <u>Total</u> 50 30	740 = 14 (P = Contro Events 30 23	1329 0.000 ol <u>Total</u> 50 30	6); I ² = 63% <u>Weight</u> 7.6% 5.5%	Odds Ratio IV. Random. 95% Cl 0.67 [0.30, 1.47] 1.52 [0.42, 5.47]	0.05 0.2 1 5 Favours [experimental] Favours [control] Odds Ratio IV, Random, 95% Cl	20
D_	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015	546 11; Chi ² = 3 0.17 (P = Experim Events 25 25 25 49	951 37.50, df 0.87) eental <u>Total</u> 50 30 70	740 = 14 (P = Contro Events 30 23 40	1329 0.000 ol <u>Total</u> 50 30 50	6); I ² = 63% <u>Weight</u> 7.6% 5.5% 7.3% 7.3%	Odds Ratio IV. Random. 95% C 0.67 [0.30, 1.47] 1.52 [0.42, 5.47] 0.58 [0.25, 1.38]	0.05 0.2 1 5 Favours [experimental] Favours [control] Odds Ratio IV. Random, 95% Cl	20
D_	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hou, C 2018 Hutchinson, K 2018	546 11; Chi ² = 3 0.17 (P = Experim Events 25 25 49 66 33	951 37.50, df 0.87) eental <u>Total</u> 50 30 70 70 44	740 = 14 (P = Contro Events 30 23 40 70 52	1329 0.000 0I <u>Total</u> 50 50 70 57	6); I ² = 63% <u>Weight</u> 7.6% 5.5% 7.3% 1.9% 6.1%	Odds Ratio IV. Random, <u>95% C</u> 0.67 [0.30, 1.47] 1.52 [0.42, 5.47] 0.58 [0.25, 1.38] 0.10 [0.01, 1.98] 0.29 [0.09, 0.91]	0.05 0.2 1 Favours [experimental] Favours [control] Odds Ratio IV. Random 95% Cl	20
D_	Total (95% CI) Total events Heterogeneity: Tau' = 0.3 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hou, C 2018 Hutchinson, K 2018 Iodranidou, M 2014	546 11; Chi ² = 3 0.17 (P = Experim Events 25 25 49 66 33 86 	951 37.50, df 0.87) eental 50 30 70 70 44 127 127	740 = 14 (P = Contri Events 30 23 40 70 52 56	1329 0.000 0 <u>Total</u> 50 30 50 70 57 91	b); l ² = 63% Weight 7.6% 5.5% 7.3% 1.9% 6.1% 8.6%	Odds Ratio IV. Random, 95% CI 0.67 [0.30, 1.47] 1.52 [0.42, 5.47] 0.58 [0.25, 1.38] 0.10 [0.01, 1.98] 0.29 [0.09, 0.91] 1.31 [0.75, 2.30]	0.05 0.2 1 Favours [experimental] Favours [control] Odds Ratio IV. Random, 85% Cl	20
D	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = <u>Study or Subgroup</u> Anmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Hutchinson, K 2018 Hutching AD 2016	546 11; Chi ² = 3 0.17 (P = Experim Events 25 25 49 66 33 86 82 34	951 37.50, df 0.87) eental 50 30 70 70 44 127 100 41	740 = 14 (P = Contro Events 30 23 40 70 52 52 56 54 40	1329 0.000 0 1 <u>Total</u> 50 30 50 70 57 91 80 41	6); I ² = 63% <u>Weight</u> 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.1% 3.1%	Odds Ratio <u>IV. Random. 95% CI</u> 0.67 [0.30, 1.47] 1.52 [0.42, 5.47] 0.58 [0.25, 1.38] 0.29 [0.09, 0.91] 1.31 [0.75, 2.30] 2.19 [1.10, 4.38] 0.12 [0.01, 1.04]	0.05 0.2 1 Favours [control] Odds Ratio IV. Random. 95% CI	20
D	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = Study or Subgroup Anmed, AE 2020 Batmarc, SB 2017 Einisman, H 2015 Hou, C 2018 Hutchinson, K 2018 Hutchinson, K 2018 Liu, Y 2016 Ma, JH 2014	546 11; Chi ² = 3 5 0.17 (P = Experim 255 25 49 66 33 86 82 34 34 14	951 37.50, df 0.87) eental 50 30 70 70 70 44 127 100 41 60	740 = 14 (P = Contro Events 30 23 40 70 56 56 54 40 12	1329 0.000 0 1 50 50 50 70 57 91 80 41 60	6); ² = 63% <u>Weight</u> 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.1% 3.1% 7.2%	Odds Ratio <u>IV. Random. 95% CI</u> 0.67 [0.30, 1.47] 1.52 [0.42, 5.47] 0.58 [0.25, 1.38] 0.10 [0.01, 1.98] 0.29 [0.09, 0.91] 1.31 [0.75, 2.30] 2.19 [1.10, 4.38] 0.12 [0.01, 1.04] 1.22 [0.51, 2.91]	0.05 0.2 1 Favours [experimental] Favours [control] 0dds Ratio IV. Random 95% Cl	20
D	Total (95% CI) Total events Total events Test for overall effect: 2 = Study or Subproup Ahmed, AE 2020 Balmaz, 98 2017 Enlimana, H 2015 Hou, C 2018 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2015 Manuel, H 2015	546 11; Chi² = 3 0.17 (P = Experim Events 25 25 49 66 33 86 82 23 4 4 9 66 33 33 86 82 23 4 14 63 67	951 37.50, df 0.87) tental 50 30 70 70 44 127 100 41 60 155 71	740 = 14 (P = Contro Events 30 23 40 70 52 56 54 40 12 83 57	1329 0.000 0 <u>Total</u> 50 30 50 70 57 91 80 41 60 225 71	b); I ² = 63% Weight 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.1% 3.1% 7.2% 9.2% 6.0%	Odds Ratio V. Random. 95% Cl 0.67 [0.30, 1.47] 1.52 [0.42, 5.47] 0.58 [0.25, 1.38] 0.10 [0.01, 1.98] 0.29 [0.09, 0.91] 1.31 [0.75, 2.30] 1.31 [0.75, 2.30] 1.21 [0.11, 0.438] 0.12 [0.01, 1.04] 1.22 [0.51, 2.91] 1.71 [0.77, 1.78] 4.11 [1.92 1.300]	0.05 0.2 1 Favours [experimental] Favours [experimental] Favours [control] Odds Ratio	20
D	Total (95% CI) Total events Heterogeneily: Tau* = 0.3 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Enisman, H 2015 Hutchinson, K 2018 Hutchinson, K 2018 Hutchinson, K 2018 Liu, Y 2016 Ma, JH 2013 Mo, LY 2015 Moalmi, H 2013 Mo, LY 2015	546 11; Chi² = 3 0.17 (P = Experim Events 25 25 49 66 33 86 82 34 14 63 67 42	951 37.50, df 0.87) eental 50 30 70 70 70 44 127 100 41 60 55 711 61	740 = 14 (P = Contro Events 30 23 40 70 56 56 54 40 12 83 57 401	1329 0.000 Total 50 30 50 70 57 91 80 41 60 225 71 633	b); I ² = 63% 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.1% 3.1% 7.2% 9.2% 6.0%	Odds Ratio (V. Random. 95%; Cl 0.67 (0.30, 1.47) 1.52 (0.42, 5.47) 0.58 (0.25, 1.38) 0.10 (0.11, 1.98) 0.29 (0.09, 0.91) 1.31 (0.75, 2.30) 2.19 (1.10, 4.38) 0.12 (0.01, 1.04) 1.22 (0.51, 2.91) 1.71 (0.77, 1.78) 4.11 (1.28, 1.320) 1.28 (0.73, 2.25)	0.05 0.2 1 Favours [experimental] Favours [experimental] Favours [control] Odds Ratio	20
D	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = Study or Subgroup Anmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hou, C 2018 Hutchinson, K 2018 Icu, Y 2016 Maa, JH 2014 Maalimi, H 2013 Papadopoulou, A 2015 Papadopoulou, A 2015	546 11; Chi ² = 3 0.17 (P = Experim 225 25 49 66 82 33 86 82 34 414 63 67 7 42 70	951 37.50, df 0.87) eental Total 50 30 70 70 44 127 100 41 60 155 711 61 125	740 = 14 (P = Contro Events 30 23 40 70 52 56 54 40 12 83 57 401 37 37	1329 0.0000 01 Total 50 300 50 50 50 50 50 50 50 50 91 80 41 60 225 71 633 27 1	b); I ² = 63% Weight 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.1% 7.2% 9.2% 6.0% 8.6% 8.6% 8.5% 7.2% 9.2% 9.2	Odds Ratio (V. Random, 95% CI 0.67 (0.30, 1.47) 1.52 (0.42, 5.47) 0.58 (0.25, 4.38) 0.10 (0.01, 1.98) 0.10 (0.01, 1.98) 0.12 (0.01, 75, 2.30) 2.19 (1.10, 3.38) 0.12 (0.01, 1.04) 1.22 (0.51, 2.91) 1.17 (0.77, 1.78) 4.11 (1.28, 13.20) 1.28 (0.73, 2.25) 1.29 (0.67, 2.15) 1.29 (0.67, 2.15)	0.05 0.2 1 Favours [experimental] Favours [control] 0dds Ratio 1V. Random 95% Cl	20
D_	Total (95% CI) Total events Total events Test for overall effect: 2 = Study or Subproug Anmed, AF 2020 Batmaz, SB 2017 Enilaman, H 2015 Hou, C 2018 Hutchinson, K 2018 Iordanidau, M 2014 Klinc, M 2019 Liu, Y 2016 Maa, JH 2014 Maalimi, H 2013 Papadopoulou, A 2015 Papadopoulou, A 2015 Papa, HX 2015	546 11; Chi ² = 3 20.17 (P = Experim 225 25 49 66 82 33 86 82 34 4 14 63 67 7 42 70 89 40	951 37.50, df 0.87) tental Total 50 30 70 70 44 127 100 41 60 155 71 61 125 143 40	740 = 14 (P = Contro Events 30 23 40 70 52 56 54 40 12 83 57 401 37 37 135 40	1329 0.000 0 1 7 0 50 50 50 50 50 70 57 91 80 41 60 225 71 633 72 143 40	 b): I² = 63% Weight 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.6% 8.5% 7.6% 	Odds Ratio U. Random. 95% CI 0.67 (0.30, 147) 1.52 [042, 5.47] 0.56 [0.25, 1.38] 0.29 [0.00, 0.61] 1.31 [0.75, 2.30] 0.21 [0.10, 1.43] 0.21 [0.10, 1.43] 0.12 [0.15, 1.24] 1.77 [0.77, 1.78] 1.22 [0.57, 1.24] 1.22 [0.67, 2.15] 0.10 [0.44, 0.22] Not estimable	0.05 0.2 1 Favours [experimental] Favours [experimental] Favours [control] Odds Ratio	20
D	Total (95% CI) Total events Heterogeneity: Tau" = 0.3 Test for overall effect: Z = <u>Study or Subparoup</u> Anmed, AE 2020 Batmaz, BS 2017 Einisman, H 2015 Hutchinson, K 2018 Hutchinson, K 2014 Kilic, M 2019 Lu, Y 2016 Ma, JH 2013 Mo, LY 2015 Pilal, DK 2011 Zhao, HX 2017 Zhao, HX 2017 Zhao, HX 2017 Zhao, HX 2010	546 11; Chi ² = 3 0.17 (P = Expertim 25 25 25 49 66 33 86 66 82 33 86 66 82 34 14 63 67 42 27 70 89 40 0 27	951 37.50, df 0.87) ental Total 50 30 70 70 70 44 127 100 41 127 100 41 60 155 711 61 125 143 40 30	740 = 14 (P = Contri Events 300 23 40 700 52 56 54 40 12 83 57 401 37 135 40 34	1329 0.000 0 1 7 0 30 50 50 50 50 57 91 80 41 60 225 71 80 41 633 72 143 40 40	b); I ² = 63% Weight 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.1% 3.1% 7.2% 9.2% 6.0% 8.6% 8.5% 7.6% 4.8%	Odds Ratio IV. Random. 95% Cl 0.67 (0.30, 142, 471) 1.52 (0.42, 487) 1.52 (0.42, 612) 0.10 (0.01, 1.98) 0.29 (0.09, 0.91) 1.31 (0.75, 2.30) 2.19 (1.10, 4.38) 0.12 (0.01, 1.04) 1.22 (0.51, 9.21) 1.21 (0.51, 9.21) 1.20 (0.67, 2.15) 1.20 (0.67, 2.15)	0.05 0.2 1 Favours [control] 0.05 0.4 Control] 0.05 0.4 Random .85% Cl IV. Random .85% Cl	20
D	Total (85% CI) Total events Heterogeneity: Tau ² = 0.2 Test for overall effect: Z = Study or Subgroup Anmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hou, C 2018 Hutchinson, K 2018 Luk, 72016 Ma, JH 2015 Maaim, H 2013 Maaim, H 2013 Maaim, H 2013 Maaim, H 2013 Maaim, H 2015 Zhao, YX 2017 Zhao, HX 2015 Zhao, YK 2010 Total (85% CI)	546 11; Chi ² = 3 20.17 (P = Expertim Events 25 25 49 9 66 33 86 66 82 34 14 63 67 42 27 70 89 40 27	951 37.50, df 0.87) ental Total 50 30 70 70 70 44 127 100 41 125 711 61 125 143 40 30 30 30	740 = 14 (P = Contri Events 300 23 40 700 52 56 54 400 12 83 57 401 37 135 400 34	1329 0.0000 Total 50 30 50 50 50 70 57 91 80 41 605 71 633 72 143 40 40 1753	b); I ² = 63% Weight 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.6% 8.6% 8.5% 7.6% 4.8% 100.0%	Odds Ratio 1, Random, 95% Cl 0,67 (10,0,1,47) 1,52 (10,42,547) 1,52 (10,42,547) 0,58 (10,52,30) 1,10 (10,1,1,188) 0,29 (10,90,041) 1,31 (10,75,2,30) 2,19 (1,10,438) 1,21 (0,11,128,13,20) 1,21 (0,	0.05 0.2 1 Pavours [experimental] Favours [control] 0.04s Ratio 1V. Random. 95% Cl	20
D	Total (95% CI) Total events Heterogeneity: Tau* = 0.3 Test for overall effect: Z = Study or Subgroup Anmed. AE 2020 Batmaz, SB 2017 Einisama, H 2015 Hou, C 2018 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Maa, JH 2011 Maalimi, H 2013 Papadopoulou, A 2015 Piala, DK 2015 Zhen, YK 2010 Total (95% CI) Total events	546 11; Chi ² = 3 0.17 (P = Experim Events 25 25 25 49 66 33 86 82 34 14 63 34 14 63 34 14 63 34 14 63 82 70 89 40 27 89 40 80 80 80 80 80 80 80 80 80 8	951 37.50, df 0.87) eental 50 30 70 70 44 127 100 41 125 71 61 125 143 40 30 1217	740 = 14 (P = Contrin Events 30 23 40 0 70 52 56 54 40 12 83 57 401 37 135 400 34	1329 0.0000 0 1 50 30 50 70 57 91 80 41 603 72 143 40 40 1753	Weight 7.6% 5.5% 6.1% 8.6% 8.1% 3.1% 7.2% 9.2% 6.0% 8.6% 8.6% 8.6% 8.6% 8.6% 8.6% 8.6% 8.6% 100.0%	Odds Ratio IV. Random. 95% CI 0.67 (0.30, 1.47) 1.52 (0.42, 6.47) 0.58 (0.25, 1.38) 0.10 (0.01, 1.98) 0.29 (0.08, 0.61) 1.31 (0.76, 2.30) 0.12 (0.01, 1.04) 1.21 (0.71, 2.43) 1.22 (0.51, 2.61) 1.71 (0.77, 1.78) 1.20 (0.67, 2.15) 0.10 (0.40, 0.22) Not estimable 1.59 (0.36, 6.94) 0.86 (0.55, 1.35]	0.05 0.2 1 Favours [experimental] Favours [control] 0 dds Ratio IV. Random 95% Cl	20
D	Total (95% CI) Total events Heterogeneity: Tau" = 0.3 Test for overall effect: 2 = Study or Subproug Anmed, AE 2020 Balmaz, SB 2017 Enilaman, H 2013 Hou, C 2018 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Maa, LH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Papadopoulou, A 2015 Papadopoulou, A 2015 Zhao, HX 2015 Zhao, HX 2015 Zhao, YK 2010 Total (95% CI) Total events Heterogeneity: Tau" = 0.5	546 11; Chi ² = 3 0,17 (P = Experim Events 25 25 25 49 66 33 86 82 34 14 63 34 14 63 82 34 14 63 84 89 40 27 89 40 28 29 66 33 86 82 34 14 67 89 40 89 40 20 89 40 80 80 80 80 80 80 80 80 80 8	951 37.50, df 0.87) iental Total 50 300 70 70 70 44 127 100 41 125 71 100 155 71 143 30 252, df 0, 52, df	740 = 14 (P = Contr Events 30 23 30 70 52 56 54 40 12 83 357 7401 135 54 401 37 34 9 1164 40 9 40 40 9 40 40 9 40 40 40 40 40 40 40 40 40 40 40 40 40	1329 0.0000 01 Total 50 30 50 70 57 91 80 41 60 225 71 633 72 143 40 40 1753 0.0000	Weight 7.6% 5.5% 7.3% 1.9% 8.6% 3.1% 7.2% 9.2% 9.6% 8.6% 8.7% 7.6% 4.8% 100.0% 01); l ² = 77'	Odds Ratio (V. Random, 95% Cl 0.67 (0.30, 1.47) 1.52 (0.42, 4.47) 1.52 (0.42, 4.67) 1.31 (0.75, 2.30) 2.19 (1.10, 4.38) 0.29 (0.96, 9.41) 1.21 (0.07, 1.78) 1.21 (0.07, 1.78) 1.21 (0.07, 1.78) 1.21 (0.07, 2.75) 1.20 (0.67, 2.15) 1.20 (0.67, 2.15) 1.50 (0.66, 6.94) 0.86 (0.55, 1.35]	0.05 0.2 1 5 Favours [experimental] Favours [control] 0 dds Ratio IV. Random 35% Cl	+
D_	Total (85% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = Study or Subgroup Anmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hou, C 2018 Hutchinson, K 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Ma, JH 2015 JH 2016 Ma, JH 2016 Ma, JH 2016 JH 2016 JH 2017 Zhao, HX 2015 Zhao, Y 2017 Zhao, HX 2015 Total (95% CI) Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = 0.5 Test for overall effect: Z =	546 11: Chi ² = 2 25: 25: 25: 25: 25: 25: 25: 25: 25: 25:	951 37.50, df (0.87) tental 50 50 50 70 70 41 127 100 155 71 41 61 125 143 40 30.52, df 1217 1227 143 40 30.52, df 1227	740 = 14 (P = Contribution 23 30 23 340 70 556 56 54 40 12 83 357 400 135 40 34 1164 = 14 (P <	1329 0.0000 ol Total 50 30 50 50 57 91 80 41 60 225 71 143 40 40 1753 0.0000	 b); l² = 63% Weight 7.6% 5.5% 7.3% 6.1% 8.6% 8.1% 9.2% 6.0% 8.6% 8.6% 8.6% 4.8% 100.0% 01); l² = 77⁴ 	Odds Ratio IV. Random. 95% Cl 0.67 (10.30, 147) 1.52 (0.42, 4.67) 1.52 (0.42, 4.67) 1.52 (0.42, 6.7) 1.31 (0.75, 2.30) 2.19 (1.10, 4.38) 0.29 (0.09, 0.91) 1.31 (0.75, 2.30) 2.19 (1.10, 4.38) 0.12 (0.01, 1.04) 1.22 (0.51, 9.31) 1.21 (0.67, 2.15) 1.20 (0.55, 1.35) 1.20 (0.55, 1.35)	0.05 0.2 1 Pavours [experimental] Favours [control] 0.046 Ratio 1V. Random. 95% Cl 	20
D_ E	Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 Test for overall effect: Z = Study or Subgroup Anmed, AE 2020 Batmaz, SB 2017 Einiaman, H 2015 Hou, C 2018 Hutchinson, K 2018 Iduchinson, K 2018 Iduchinson, K 2018 Iduchinson, K 2019 Liu, Y 2016 Maajimi, H 2013 Maajimi, H 2013 Maajimi, H 2013 Chao, HX 2015 Zhen, YF 2010 Total events Heterogeneity, Tau ² = 0.5 Total for yall effect: Z = Study or Suboroup	546 6 11 Chi = 1 22 Chi + 1 24 Chi + 1 25 Chi + 1	951 37.50, df 0.87) ental 50 0 30 70 70 41 127 100 41 61 55 52 143 40 30.52, df 1257 143 40 30.52, df 1217 1257 143 40 30.52, df 1217 1217 1217 1217 1217 1217 1217 121	740 = 14 (P = Contrt Events 30 30 30 30 40 70 56 56 56 54 40 12 83 357 400 34 1164 = 14 (P < Contr T Events 57 60 57 40 34	1329 0.0000 ol Total 50 30 50 50 57 91 80 40 225 71 633 72 143 40 40 1753 0.0000 ol Total Total Total	 b); l² = 63% Weight 7.6% 5.5% 7.3% 1.9% 6.1% 8.6% 8.6% 8.6% 8.6% 8.6% 8.6% 8.6% 4.8% 100.0% 01); l² = 77' Weight 	Odds Ratio IV. Random. 95% CI 0.67 (0.30, 1.47) 1.52 (0.42, 6.47) 0.58 (0.25, 1.38) 0.29 (0.06, 0.51) 2.10 (0.10, 1.48) 0.29 (0.06, 0.51) 1.21 (0.10, 4.38) 0.12 (0.11, 0.4.38) 0.12 (0.11, 0.11,	0.05 0.2 1 Favours [experimental] Favours [control] 0 dds Ratio 0.05 0.1 10 Favours [experimental] Favours [control] 0 dds Ratio 0, Random .95% C1	20
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FIGURE 2 | Forest plot for meta-analyzing the association between Vitamin D receptor Apal (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	Heterog	eneity test	Effect	size
		l² (%)	P _H	OR (95% CI)	P value
Apal (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	0.65 (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)	0.285
Asian	7	90.8	<0.001	0.37 (0.06, 2.48)	0.305
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)	0.280
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	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

Model	No. of studies	Heterog	eneity test	Effect	size
		l² (%)	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
Taql (rs731236)					
t vs. T	12	71.1	<0.001	0.93 (0.70, 1.23)	0.608
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	0.699	0.93 (0.66, 1.30)	0.661
tt vs. TT	12	63.5	0.002	0.92 (0.49, 1.70)	0.783
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
Ethnicity					
American	1	NA	NA	0.97 (0.46, 2.03)	0.939
Asian	3	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	0.693	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
				· · · /	

Model	No. of studies	Heterog	jeneity test	Effect	size
		l² (%)	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
Bsml (rs1544410)				(
b vs. B	12	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
			0.010		5.024

Model	No. of studies	Heterog	eneity test	Effect	size
		l² (%)	P _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
Fokl (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

Model	No. of studies	Heterog	eneity test	Effect	size
		l² (%)	P _H	OR (95% CI)	P value
Ethnicity					
American	1	NA	NA	0.63 (0.20, 1.93)	0.415
Asian	5	72.9	<0.001	1.06 (0.68, 1.65)	0.796
Caucasians	5	32.1	0.172	0.75 (0.56, 1.00)	0.052
African-American	1	NA	NA	0.78 (0.43, 1.43)	0.425
HWE					
Yes	11	0	0.854	0.82 (0.66, 1.03)	0.093
No	1	NA	NA	0.63 (0.20, 1.93)	0.415
Source					
HB	11	0	0.883	0.80 (0.64, 1.00)	0.052
PB	1	NA	NA	1.16 (0.47, 2.87)	0.746
ff+Ff vs. FF	12	34.7	0.112	0.77 (0.63, 0.95)	0.016
Ethnicity					
American	1	NA	NA	0.63 (0.20, 1.93)	0.415
Asian	5	53.6	0.071	1.08 (0.72, 1.63)	0.714
Caucasians	5	11.6	0.340	0.67 (0.51, 0.88)	0.004
African-American	1	NA	NA	0.79 (0.44, 1.43)	0.443
HWE					
Yes	11	40.2	0.081	0.78 (0.63, 0.96)	0.021
No	1	NA	NA	0.63 (0.20, 1.93)	0.415
Source					
HB	11	24.1	0.214	0.73 (0.59, 0.91)	0.005
PB	1	NA	NA	1.71 (0.74, 3.97)	0.208
ff vs. FF+Ff	12	74.2	<0.001	0.71 (0.39, 1.29)	0.266
Ethnicity					
American	1	NA	NA	NA	NA
Asian	5	81.6	<0.001	0.94 (0.42, 2.10)	0.880
Caucasians	5	59.8	0.041	0.43 (0.16, 1.17)	0.099
African-American	1	NA	NA	1.01 (0.23, 4.36)	0.988
HWE					
Yes	11	74.2	<0.001	0.71 (0.39, 1.29)	0.266
No	1	NA	NA	NA	NA
Source					
HB	11	70.7	<0.001	0.60 (0.33, 1.11)	0.103
PB	1	NA	NA	2.97 (1.29, 6.83)	0.010

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 [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+Tt vs. TT: OR (95%CI) = 0.36 (0.15, 0.87), P = 0.024] among Asians. Moreover, significant association was also found in the population-based

subgroup in co dominant model [Tt vs. TT: OR (95%CI) = 0.53 (0.31, 0.94), P = 0.029].

Bsml (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 randomed 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 (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.

Fokl (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 (f vs. F: $I^2 = 77\%$, 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 randomed effects model was used to calculated the pooled data, and the results showed that no significant association between FokI (rs2228570) and asthma risk was observed across additive model (f vs. F: OR (95%CI) = 0.78 (0.57, 1.05), P = 0.102), co 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 (f vs. F: OR (95%CI) = 0.63 (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 (f vs. F: 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 (f vs. F: 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) across the genotype models (P>0.05).

DISCUSSION

Among childhood, asthma is accepted as the most common chronic disease. Recently, accumulating evidence researched the function role of VDR gene polymorphism in childhood asthma, and four SNPs, including BsmI (rs1544410), ApaI (rs7975232), 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- κ 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,

A									
		Experim	ental	Cont	rol		Odds Ratio	Odds	Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% C	I IV. Rando	om, 95% Cl
	Batmaz, SB 2017	60 15	100	40 20	60	8.3% 6.2%	2.25 [1.28, 3.96] 0.67 [0.30, 1.47]		
	Einisman, H 2015	40	144	28	100	8.3%	0.99 [0.56, 1.75]		
	Hutchinson, K 2018 Iordanidou, M 2014	33 100	88 254	23 74	114	7.7%	2.37 [1.27, 4.45]		
	Kilic, M 2019	77	200	72	160	9.8%	0.77 [0.50, 1.17]		+
	Liu, Y 2016 Ma JH 2014	59 101	82 120	75 104	82 120	5.4% 6.9%	0.24 [0.10, 0.60]		
	Maalmi, H 2013	111	310	191	450	11.0%	0.76 [0.56, 1.02]	-	-
	Papadopoulou, A 2015 Pillai DK 2011	46 77	122	487	1260	10.2%	0.96 [0.65, 1.41]		
	Zhao, HX 2015	14	80	27	80	6.7%	0.42 [0.20, 0.87]		
	Total (95% CI)		1796		2856	100.0%	0.93 [0.70, 1.23]	<	
	Total events	733		1178					
	Heterogeneity: Tau ² = 0. Test for overall effect: 7	.16; Chi ² = 3 = 0.51 (P =	38.06, df	= 11 (P	< 0.000	1); l² = 71	%	0.1 0.2 0.5	1 2 5 10
R		0.01 ()	0.01)					Favours [experimental]	Favours [control]
0	Study of Substances	Experime	ental	Contr	ol	Wainht	Odds Ratio	Odds	Ratio
	Ahmed, AE 2020	Events 15	20	Events 0	10(a)	3.4%	59.18 [2.95, 1187.72]	IV, Kando	· · · · · · · · · · · · · · · · · · ·
	Batmaz, SB 2017	3	21	5	20	8.0%	0.50 [0.10, 2.44]		
	Hutchinson, K 2018	6	38 23	2	26 34	6.7% 3.5%	25.63 [1.36, 481.59]		·
	lordanidou, M 2014	16	59	18	53	13.2%	0.72 [0.32, 1.62]		
	Liu, Y 2016	8 24	39 30	20	48 36	12.0%	0.36 [0.14, 0.95]		
	Ma, JH 2014	47	53	49	54	10.0%	0.80 [0.23, 2.80]		
	Papadopoulou, A 2015	15	74 41	45 81	124 305	14.1% 13.9%	1.28 [0.63, 2.60]		-
	Pillai, DK 2011	11	63	3	43	9.5%	2.82 [0.74, 10.79]	-	-
	211a0, HX 2015	U	26	U	13		NOT estimable		
	Total (95% CI)	464	487	050	766	100.0%	0.92 [0.49, 1.70]	•	•
	Heterogeneity: Tau ² = 0.5	161 59; Chi ² = 2	7.36, df	∠58 = 10 (P =	0.002)	; I² = 63%		0.001 0.1	10 1000
~	Test for overall effect: Z =	= 0.28 (P =	0.78)					Favours [experimental]	Favours [control]
C		Experime	ental	Contr	ol		Odds Ratio	Odds	Ratio
	Study or Subgroup Abmed, AE 2020	Events 30	Total 35	Events 40	Total 50	Weight 5.4%	IV, Random, 95% CI 1 50 [0 46, 4 85]	IV, Rando	m, 95% Cl
	Batmaz, SB 2017	9	27	10	25	5.7%	0.75 [0.24, 2.33]		
	Einisman, H 2015 Hutchinson, K 2018	34 21	69 38	24 23	48 57	9.5% 8.4%	0.97 [0.46, 2.03] 1.83 [0.80, 4.19]	_	
	lordanidou, M 2014	68	111	38	73	11.4%	1.46 [0.80, 2.65]	-	
	Kilic, M 2019 Liu, Y 2016	61 11	92 17	32 5	60 6	10.4% 1.7%	1.72 [0.88, 3.35] 0.37 [0.03, 3.91]		·
	Ma, JH 2014	7	13	6	11	3.3%	0.97 [0.19, 4.87]		
	Maalmi, H 2013 Papadopoulou, A 2015	81 20	140 48	101 325	180 549	13.8% 11.4%	1.07 [0.69, 1.68] 0.49 [0.27, 0.90]		
	Pillai, DK 2011	55					4 26 10 75 2 401		-
			107	31	71	11.3%	1.30 [0.75, 2.49]		
	Zhao, HX 2015	14	40	31 27	71 40	11.3% 7.4%	0.26 [0.10, 0.66]		
	Zhao, HX 2015 Total (95% CI)	14	107 40 737	31 27	71 40 1170	11.3% 7.4% 100.0%	1.36 [0.75, 2.49] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38]		•
	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1	14 411 15; Chi² = 2:	107 40 737 2.08, df	31 27 662 = 11 (P =	71 40 1170 : 0.02);	11.3% 7.4% 100.0% I ² = 50%	1.36 [0.73, 2.49] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38]	0.02 0.1	► 10 50
п	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	411 15; Chi ² = 2 = 0.00 (P = 1	107 40 737 2.08, df 1.00)	31 27 662 = 11 (P =	71 40 1170 : 0.02);	11.3% 7.4% 100.0% I ² = 50%	1.36 [0.73, 2.49] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38]	L L L L L L L L L L L L L L L L L L L	Favours [control]
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	411 15; Chi ² = 2; = 0.00 (P = 1) Experime	107 40 737 2.08, df 1.00) ental	31 27 662 = 11 (P = Contr	71 40 1170 = 0.02);	11.3% 7.4% 100.0% I ² = 50%	0.26 [0.10, 0.66] 1.00 [0.72, 1.38] Odds Ratio	0.02 0.1 Favours [experimental]	Favours [control]
D	Zhao, HX 2015 Total (95% Cl) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020	411 15; Chi ² = 2: = 0.00 (P = - Experime Events 45	107 40 737 2.08, df 1.00) ental <u>Total</u> 50	31 27 662 = 11 (P = Contr <u>Events</u> 40	71 40 1170 = 0.02); ol <u>Total</u> 50	11.3% 7.4% 100.0% I ² = 50% <u>Weight</u> 5.3%	0.26 [0.10, 0.66] 1.00 [0.72, 1.38] Odds Ratio <u>IV, Random, 95% CI</u> 2.25 [0.71, 7.14]	0.02 0.1 Favours [experimental] Odds IV. Rando	Favours [control] Ratio m. 95% CI
D	Zhao, HX 2015 Total (95% Cl) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einemone H 2015	411 15; Chi ² = 2: = 0.00 (P = 1 Experime Events 45 12 27	107 40 737 2.08, df 1.00) ental Total 50 30 72	31 27 662 = 11 (P = Contr Events 40 15	71 40 1170 : 0.02); ol <u>Total</u> 50 30	11.3% 7.4% 100.0% I ² = 50% <u>Weight</u> 5.3% 6.2%	0.26 [0.7, 2.49] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] Odds Ratio IV. Random. 95% CI 2.25 [0.71, 7.14] 0.67 [0.24, 1.85]	0.02 0.1 Favours [experimenta] Odds V. Rando	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity. Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018	411 15; Chi ² = 2: = 0.00 (P = 1 Experime Events 45 12 37 27	107 40 737 2.08, df 1.00) ental <u>Total</u> 50 30 72 44	31 27 662 = 11 (P = Contr <u>Events</u> 40 15 26 23	71 40 1170 : 0.02); ol <u>Total</u> 50 30 50 57	11.3% 7.4% 100.0% ² = 50% <u>Weight</u> 5.3% 6.2% 9.1% 8.2%	1.36 [0.7, 2.48] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] Odds Ratio IV. Random. 95% CI 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25]	0.02 0.1 Favours [experimenta] Odds IV. Rando	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Batmaz, BS 2017 Einisman, H 2015 Hutchinson, K 2018 Jordanidou, M 2014	411 15; Chi ² = 2: = 0.00 (P = - Experime Events 45 12 37 27 84 60	107 40 737 2.08, df 1.00) ental <u>Total</u> 50 30 72 44 127	31 27 662 = 11 (P = Contr Events 40 15 26 23 56	71 40 1170 : 0.02); ol <u>Total</u> 50 50 57 91	11.3% 7.4% 100.0% I ² = 50% <u>Weight</u> 5.3% 6.2% 9.1% 8.2% 11.3%	0.26 (0.10, 0.66) 0.26 (0.10, 0.66) 1.00 [0.72, 1.38] V. Random, 95% CI 2.25 (0.71, 7.14) 0.67 (0.24, 1.85) 0.98 [0.47, 2.01] 1.25 [1.05, 5.25] 1.22 [0.70, 2.14]	0.02 0.1 Favours [experimental] Odds IV. Rando	Tavours [control]
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Lordanidou, M 2014 Kilic, M 2016	411 411 15; Chi ² = 2: = 0.00 (P = : Experime Events 45 12 37 27 84 69 935	107 40 737 2.08, df 1.00) ental 50 30 72 44 127 100 41	31 27 662 = 11 (P = Contr Events 40 15 26 23 56 23 56 23 52 40	71 40 1170 = 0.02); ol Total 50 30 50 57 91 80 41	11.3% 7.4% 100.0% I ² = 50% Weight 5.3% 6.2% 9.1% 8.2% 10.4% 10.4% 1.9%	0.26 (0.10, 0.66) 0.26 (0.10, 0.66) 1.00 [0.72, 1.38] V. Random, <u>95% C1</u> 2.25 (0.71, 7.14) 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 (0.70, 2.14] 1.20 [0.64, 2.24] 0.15 [0.02, 1.27]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subproup Ahmed, AE 2020 Batmaz, SB 2017 Enisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014	14 411 15; Chi ² = 2; = 0.00 (P = Experime Events 45 12 37 27 84 69 935 54 54	107 40 737 2.08, df 1.00) ental Total 50 30 72 44 127 100 41 60	31 27 662 = 11 (P = Contr Events 40 15 26 23 56 52 40 55	71 40 1170 : 0.02); ol Total 50 50 50 57 91 80 41 60	11.3% 7.4% 100.0% I ² = 50% <u>Weight</u> 5.3% 6.2% 9.1% 8.2% 11.3% 10.4% 1.9% 4.7%	1.36 [0.7, 2, 43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.25 [0.72, 1.38] 0.25 [0.71, 7.14] 0.67 [0.24, 1.86] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.70, 2.14] 1.20 [0.70, 2.14] 0.15 [0.02, 1.27] 0.88 [0.24, 2.84]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015	14 411 15; Chi ² = 2: = 0.00 (P = Experime <u>Events</u> 45 12 37 27 84 69 35 54 96 33	107 40 737 2.08, df 1.00) ental Total 50 30 72 44 127 100 41 60 155 61	31 27 662 = 11 (P = Contr Events 40 15 26 23 56 52 40 55 146 406	71 40 1170 = 0.02); ol Total 50 30 50 57 91 80 41 60 225 630	11.3% 7.4% 100.0% ² = 50% 5.3% 6.2% 9.1% 8.2% 11.3% 10.4% 1.9% 4.7% 13.3%	0.26 [0.7, 2.48] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.15 [0.02, 1.27] 0.88 [0.58, 1.36] 0.65 [0.38, 1.10]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau* = 0.1 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Hutchinson, K 2018 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pgnadopoluou, A2015 Pillai, DK 2011	411 15; Chi ² = 2: = 0.00 (P = Experime Events 45 12 37 27 84 69 35 54 96 33 66 33 66	107 40 737 2.08, df 1.00) ental <u>Total</u> 50 30 72 44 127 100 41 125 61 118	31 27 662 = 11 (P = Contr Events 40 15 26 23 56 52 40 55 52 40 55 146 406 34	71 40 1170 = 0.02); ol Total 50 50 50 50 57 91 80 60 225 630 74	11.3% 7.4% 100.0% I ² = 50% Weight 5.3% 6.2% 9.1% 8.2% 9.1% 11.3% 10.4% 1.9% 4.7% 10.9% 11.7%	0.26 [0.7, 2.48] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.15 [0.02, 1.27] 0.88 [0.58, 1.36] 0.65 [0.38, 1.10] 0.65 [0.38, 1.10]	0.02 0.1 Favours [experimenta] Odds V. Rando	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau* = 0.1 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pilai, DK 2011 Zhao, HX 2015	411 15; Chi ² = 2: = 0.00 (P = Experime Events 45 12 37 27 84 69 35 54 96 33 66 14	107 40 737 2.08, df 1.00) ental Total 50 30 72 44 127 100 41 127 100 41 125 61 118 40	31 27 662 = 11 (P = Contr Events 40 15 26 23 56 52 40 55 146 406 34 27	71 40 1170 • 0.02); • 0 • 0 • 0 • 0 • 0 • 0 • 0 • 0 • 0 • 0	11.3% 7.4% 100.0% I ² = 50% Weight 5.3% 6.2% 9.1% 8.2% 11.3% 10.4% 1.9% 4.7% 13.3% 11.7% 10.9% 7.0%	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.44, 2.24] 0.15 [0.02, 1.27] 0.88 [0.58, 1.35] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] 8atio m. 95% Cl - - - - - - - - - - -
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kille, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pilala, DK 2015 Total (95% CI)	411 411 15; Chi ^p = 2: e 0.00 (P = Experime Events 45 12 37 27 84 45 37 27 84 69 35 54 96 33 66 14	107 40 737 2.08, df 1.00) ental Total 50 30 72 44 127 100 41 227 100 41 155 61 118 40 898	31 27 662 = 11 (P = Contr Events 40 15 26 52 40 55 55 55 146 406 34 27	71 40 1170 00 70 50 50 50 50 50 50 57 91 80 41 60 225 630 74 40 1428	11.3% 7.4% 100.0% I ² = 50% Veight 5.3% 6.2% 9.1% 8.2% 11.3% 10.4% 1.9% 4.7% 13.3% 11.7% 10.9% 7.0% 100.0%	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 1.20 [0.44, 2.24] 0.15 [0.02, 1.27] 0.82 [0.24, 2.84] 0.15 [0.02, 1.27] 0.82 [0.24, 2.84] 0.65 [0.38, 1.16] 0.65 [0.38, 1.16] 0.65 [0.38, 1.16] 0.48 [0.58, 1.38] 0.66 [0.58, 1.38] 0.66 [0.70, 1.32]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Liordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pilial, DK 2011 Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.4	411 411 15; Chi ^p = 2: e 0.00 (P = Experime Events 45 12 37 27 84 45 37 27 84 69 35 54 96 33 66 14 572 552 15; Chi ² = 2:	10/ 40 737 2.08, df 1.00) ental Total 50 30 72 50 30 72 41 100 41 118 40 898 83, 55 df	31 27 662 = 11 (P = Contrt Events 40 15 26 23 52 40 15 26 52 40 15 26 52 40 15 26 52 40 15 52 40 15 26 52 40 33 52 40 34 23 52 40 34 24 40 34 27 146 406 34 27 146 406 34 27 146 406 34 27 146 406 34 27 167 170	71 40 1170 6 0.02); 50 50 50 50 50 50 50 50 50 50 50 50 41 60 225 630 41 40 41 40 225 630 74 40	11.3% 7.4% 100.0% I ² = 50% Veight 5.3% 6.2% 9.1% 8.2% 10.4% 1.9% 4.7% 13.3% 10.9% 7.0% 10.9% 7.0% 100.0%	1.36 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] V. Random. 95% CI 2.25 [0.7, 1, 7, 14] 0.67 [0.24, 1.86] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.15 [0.02, 1.27] 0.62 [0.24, 2.84] 0.16 [0.02, 1.27] 0.62 [0.34, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32]	0.02 0.1 Favours [experimental] Odds V. Rando	10 50 Favours [control] 80 Ratio 95% Cl - - - - - - - - - - - -
	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Enisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pillai, DK 2011 Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	14 411 15; Chi ² = 2: 0.00 (P = Experime Events 12 37 27 84 69 93 54 96 33 66 66 14 572 15; Chi ² = 2: = 0.23 (P =	107 40 737 2.08, df 1.00) ental <u>Total</u> 50 30 30 30 72 44 127 100 41 100 41 100 41 118 40 898 83.55, df 0.82)	31 27 6622 = 11 (P = Contribution 40 15 23 356 62 23 40 55 240 55 240 40 65 21 40 63 4 27 920 920 921 (P =	71 40 1170 6 0.02); 50 50 50 50 50 57 91 80 0 225 630 225 630 74 40 1428 6.001);	11.3% 7.4% 100.0% ² = 50% (1) 5.3% 6.2% 9.1% 8.2% 11.3% 10.4% 13.3% 11.3% 10.4% 13.3% 11.7% 10.9% 7.0% 100.0% ² = 53%	1.36 [0.7, 2.48] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.26 [0.72, 1.38] 1.00 [0.72, 1.38] 0.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.55 [0.24, 2.84] 0.68 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] Ratio m, 95% Cl
D .	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subproup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Liu, Y 2016 Ma, JH 2014 Maajih, JH 2013 Pajadopoulou, A 2015 Pillai, DK 2011 Zhao, HX 2015 Heterogeneity: Tau ² = 0.1 Total effect: Z =	14 411 15; Chi ² = 2: 0.00 (P = Experime Fvents 45 12 37 27 84 99 35 54 96 33 66 14 572 15; Chi ² = 2: 0.23 (P = 1 Experime	107 40 737 2.08, df 1.00) ental <u>Total</u> 50 30 0 30 30 72 44 127 100 41 100 41 100 41 118 40 898 83.55, df 0.82) ental	31 27 6622 = 11 (P = Contr Events 40 15 26 23 356 52 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 40 55 24 54 54 54 54 54 54 54 54 54 54 54 54 54	71 40 1170 ol Total 50 30 50 50 57 91 80 41 60 225 630 74 40 1428 c 0.01); rol	11.3% 7.4% 100.0% 12 = 50% 12 = 50% 10.4% 10.4% 10.9% 7.0% 10.0% 1	0.26 [0.7, 2.49] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.45 [0.24, 2.84] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32]	0.02 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01	10 50 Favours [control] Ratio
D .	Zhao, HX 2015 Total (95% CI) Total events Heterogeneily: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Killc, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pilla, DK 2011 Zhao, HX 2015 Total (95% CI) Total effect: Z = Study or Subgroup	411 15; Chi ² = 2: = 0.00 (P = Experime Events 45 12 37 27 84 96 33 35 54 96 33 66 14 572 15; Chi ² = 2: = 0.23 (P = I Experime Expe	10/7 40 737 2.08, df 1.00) ental Total 50 30 72 44 127 100 41 60 41 60 41 60 41 898 83, 3.55, df 0.82) ental 108 898	31 27 6622 Contr Events 40 15 26 6 23 35 55 146 406 406 406 406 920 920 920 91(P = 11 (P =	71 40 1170 ol Total 50 30 50 50 30 50 57 91 80 225 630 74 40 1428 50,01); rol 1428	11.3% 7.4% 100.0% 12° = 50% Weight 5.3% 6.2% 9.1% 9.1% 9.1% 9.1% 9.1% 9.1% 9.1% 9.1	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.55 [0.24, 2.84] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] Odds Ratio	0.02 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01 0.01 0.01 0.01 V. Rando	10 50 Favours [control] Ratio
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E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kille, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Polial, DK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015	14 411 15; Chi ² = 2: = 0.00 (P = : Experime 45 12 37 27 84 69 35 54 96 33 66 14 572 15; Chi ² = 2: = 0.23 (P = : Experime Events 15 57 15 16 16 16 16 17 17 16 17 17 17 17 17 17 17 17 17 17	10/7 40 737 2.08, df 11.00) ental 50 30 30 72 44 4127 100 41 100 41 107 43 40 898 8355, df 898 3.55, df 90.82) 10.82 898 898 3.55, df 10.55 10.5	31 27 662 20 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	71 40 1170 c 0.02); ol Total 50 50 50 50 50 50 50 50 41 60 225 630 74 40 1428 c 0.01); rol Total 50 0 50 57 74 40 50 50 50 50 57 74 40 50 50 50 50 50 50 50 50 50 50 50 50 50	11.3% 7.4% 100.0% P = 50% Weight 5.3% 9.1% 8.2% 4.7% 4.7% 4.7% 10.4% 11.3% 4.7% 10.9% 7.0% 100.0% P = 53% Weight 3.6% 7.7% 6.4%	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.45 [0.02, 1.27] 0.82 [0.24, 2.84] 0.88 [0.58, 1.36] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.36 [0.70, 1.32] 0.66 [0.70, 1.32] 0.66 [0.70, 1.32]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] Ratio m. 95% Cl
D .	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Liordanidou, M 2014 Kilić, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pillai, DK 2011 Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Ordanidou, M 2014	14 411 15; Chi ² = 2: = 0.00 (P = Experime 45 12 37 27 84 69 35 54 96 33 66 14 572 15; Chi ² = 2: = 0.23 (P = Experime Experime 53 66 14 572 15; Chi ² = 2: = 0.23 (P = Experime 54 54 55 54 56 56 14 57 25 25 25 25 25 25 25 25 25 25	10/7 40 737 2.08, df 100) ental 50 30 30 72 44 4127 100 41 60 41 118 898 83.55, df 1018 40 898 83.55, df 50 0.82) 1024 1055 61 1186 1187 1082 1082 1082 1082 1082 1082 1082 1082	31 27 6622 = 11 (P = Contr Events. 40 15 26 23 36 6 52 24 00 34 27 920 920 = 11 (P = 920 = 921 (P = 920 = 921 (P = 920 = 920 = 920 (P = 920 = 920 = 920 (P = 920 = 920 (P = 92) (P = 920 (P = 92) (P = 92	71 40 1170 ol <u>Total</u> 50 30 50 50 91 80 41 60 225 630 74 40 1428 c0.01); rol <u>Total</u> 50 30 57 91 80 41 40 225 74 40 50 57 91 80 225 74 91 80 80 80 80 80 80 80 80 80 80 80 80 80	11.3% 7.4% 100.0% P = 50% Weight 5.3% 6.2% 9.1% 6.2% 9.1% 8.2% 11.3% 11.3% 11.3% 11.3% 10.9% 7.0% 10.9% 7.0% 10.0%	1.36 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] V. Random, <u>95% C1</u> 2.25 [0.7, 1, 14] 0.67 [0.24, 1.86] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.15 [0.02, 1.27] 0.62 [0.24, 2.84] 0.48 [0.58, 1.35] 0.65 [0.38, 1.10] 1.48 [0.58, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] Vdds Ratio IV. Random, <u>95% C</u> 44, 10 [2.55, 761.37] 0.56 [0.12, 2.57] 1.04 [0.17, 6.48] 19.42 [1.06, 354, 72]	0.02 0.1 Favours [experimental] Odds IV. Rando	10 50 Favours [control] 80 Ratio 95% Cl - -
E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019	14 411 15; Chi ² = 2: = 0.00 (P = Experime 45 12 37 27 84 49 35 54 96 33 66 14 572 15; Chi ² = 2: = 0.23 (P = 1) Experime 15 572 15; Chi ² = 2: 15; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16; C	10/ 40 737 2.08, df 1.00) Total Total 50 0 0 72 44 41 127 100 898 3.55, df 0.82) Solution 50 30 0 72 44 40 898 50 3.55, df 127 108 127 109 127 100 155 107 100 107 107	31 27 662 = 11 (P = Contr Events 40 15 52 26 55 146 406 406 406 406 406 55 52 147 920 920 920 920 0 55 52 20 0 55 52 147 82 920 0 55 52 11 (P = 11 (P = 1) 82 920 0 55 52 11 (P = 1) 82 92 0 52 11 (P = 1) 82 92 0 52 11 (P = 1) 82 10 10 10 10 10 10 10 10 10 10 10 10 10	71 40 1170 ol <u>Total</u> 50 30 50 57 91 80 41 40 225 630 74 40 1428 c0.01);; rol <u>Total</u> 50 30 57 71 80 30 57 80 74 80 80 80 74 80 80 80 80 80 80 80 80 80 80 80 80 80	11.3% 7.4% 100.0% P = 50% Weight 5.3% 6.2% 9.1% 8.2% 11.3% 10.4% 7.0% 100.0% P = 53% Weight 3.6% 7.7% 3.5% 12.1%	0.26 [0.7, 2.49] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.26 [0.72, 1.38] 0.25 [0.72, 1.38] 0.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.42, 2.24] 0.15 [0.24, 2.24] 0.15 [0.24, 2.24] 0.88 [0.58, 1.36] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.71, 6.48] 19.42 [1.06, 354, 72] 0.58 [0.28, 1.22] 0.58 [0.28, 1.22] 0.58 [0.28, 2.61]	0.02 0.1 Favours [experimental] Odds IV. Rande 0.01 0.1 Favours [experimental] Odds U. Rande	10 50 Favours [control] Ratio
E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Enisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kile, M 2019 Liu, Y 2016 Ma, JH 2014 Maaimi, H 2013 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014	14 411 15; Chi ² = 2: = 0.00 (P = Experime Events 45 12 37 27 84 45 54 96 33 66 14 572 15; Chi ² = 2: 0.23 (P = Experime Experime 572 15; Chi ² = 2: 66 14 572 15; Chi ² = 2: 15; Chi ² = 2: 15; Chi ² = 2: 15; Chi ² = 2: 15; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 17; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16;	10/ 40 737 738, df ff 1.00) ental Total 50 30 30 72 44 127 100 41 128 40 898 838 838 838 50 61 118 40 898 50 3.55, df 50 0.821 100 100 127 100 155 56 1 108 107 107 107 100 155 107 107 107 107 107 107 107 107	31 27 6622 = 11 (P = Contr Events 40 15 266 52 40 406 55 24 40 406 406 34 406 406 27 920 0 920 0 0 5 5 2 2 0 0 0 18 8 20 19 20 19 20 0 19 20 0 10 19 10 19 10 10 10 10 10 10 10 10 10 10 10 10 10	71 40 1170 1170 1 50 50 50 50 57 91 80 41 60 225 630 74 40 1428 630 74 40 1428 630 74 40 1428 630 74 80 50 57 91 80 50 57 91 80 80 80 91 80 91 80 91 80 91 91 80 91 91 80 91 91 91 80 91 91 80 91 91 80 91 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 91 91 80 90 80 91 80 91 80 91 80 91 80 90 80 91 80 91 80 90 80 91 80 90 80 91 80 90 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 80 91 91 80 91 91 80 91 91 80 91 91 91 91 91 91 91 91 91 91 91 91 91	$\begin{array}{c} 11.3\% \\ 7.4\% \\ 7.4\% \\ 100.0\% \\ 9^{2} = 50\% \\ \hline \\ $	0.26 [0.7, 2.49] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.45 [0.24, 2.84] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.41 [0.25, 761, 37] 0.56 [0.12, 2.57] 1.04 [0.7, 5.761, 37] 0.56 [0.12, 2.57] 1.04 [0.7, 65, 5761, 37] 0.56 [0.12, 2.57] 1.04 [0.17, 65, 5761, 37] 0.56 [0.12, 2.57] 1.04 [0.17, 65, 547.2] 0.26 [0.11, 0.63] 0.24 [0.06, 3.70] 0.26 [0.10, 0.63] 0.24 [0.06, 3.70]	0.02 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.04 V. Rando	10 50 Favours [control] Ratio
E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneily: Tau ² = 0.1 Test for overall effect: Z = Study or Subparoup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2013 Pillai, DK 2011 Zhao, HX 2015 Heterogeneily: Tau ² = 0.1 Total events Heterogeneily: Tau ² = 0.1 Total effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SD 2017 Einisman, H 2015 Hotalow, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Maj, JH 2014 Maatmi, H 2013 Mathematical States Study or Subgroup Ahmed, AE 2020 Batmaz, SD 2017 Einisman, H 2015 Hotalow, Z018 Iordanidou, M 2014 Maatmi, H 2013 Mathematical States Study or Subgroup	14 411 15; Chi ² = 2: = 0.00 (P = Experime Experime 45 12 37 27 45 54 96 33 66 14 572 15; Chi ² = 2: 96 33 66 14 572 15; Chi ² = 2: 10; Chi ² = 2: 12; Chi ² = 2: 13; Chi ² = 2: 14; Chi ² = 2: 14; Chi ² = 2: 14; Chi ² = 2: 15; Chi ² = 2: 16; Chi ² = 2: 17; Chi ² = 2: 16; Chi ² = 2: 16; Chi ² = 2: 16; Chi ² = 2: 16; Chi ² = 2:	107/ 40 737 2.08, df Total 700 72 44 127 100 72 44 127 100 41 155 61 155 61 155 61 898 83.55, df 0.82) ************************************	31 27 6622 = 11 (P = Contr Events 26 35 56 52 40 40 65 52 40 40 6 55 52 40 920 0 146 406 406 55 2 146 402 34 40 5 5 5 6 5 2 2 0 0 18 8 19 920 0 10 920 0 10 920 10 10 10 10 10 10 10 10 10 10 10 10 10	71 40 1170 1170 1 50 50 50 50 57 91 60 225 630 74 40 1428 630 74 40 1428 630 74 40 1428 630 74 80 50 57 70 1 1428 60 50 74 1428 60 225 50 50 75 75 70 14 10 50 50 50 50 50 50 50 50 50 50 50 50 50	11.3% 7.4% 100.0% P = 50% Weight 5.3% 6.2% 9.1% 8.2% 8.2% 8.2% 9.1% 9.1% 9.1% 9.1% 9.1% 9.1% 9.1% 9.1	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.15 [0.02, 1.27] 0.82 [0.24, 2.84] 0.88 [0.58, 1.36] 0.26 [0.10, 0.66] 0.26 [0.10, 0.66] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.45 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.58 [0.28, 1.22] 0.58 [0.28, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.58 [0.28, 1.22] 0.58 [0.28, 1.23] 0.58 [0.28, 1	0.02 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01	10 50 Favours [control] Ratio
E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneliy: Tau" = 0.1 Test for overall effect: Z = Study or Stubaroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Total (95% CI) Total events Heterogeneliy: Tau" = 0.1 Colal (95% CI) Total events Heterogeneliy: Tau" = 0.1 Study or Subaroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2013 Patha 2014 Matheway and AE 2020 Batmaz, SB 2017 Einisman, H 2013 Patha 2014 Kilic, M 2014 Maalmi, H 2013 Papadopoulou, A 2015	411 411 15; Chi ² = 2: = 0.00 (P = Experime Events 45 12 37 27 84 69 35 54 66 33 36 66 14 572 15; Chi ² = 2: = 0.23 (P = I Experime Events 15 3 3 6 16 16 8 8 8 8 8 8 8 12 37 37 35 54 14 572 15; Chi ² = 2: 15 15 3 3 6 16 16 16 17 15 15 15 15 15 15 15 15 15 15	107/ 40 737 2.08, df 1.00) ental <u>Total</u> 50 300 72 44 127 100 41 118 40 898 838 61 118 40 8388 61 118 40 8388 61 118 40 8388 61 118 40 8388 61 118 40 8388 61 118 40 8388 83 83 84 127 100 125 100 125 100 125 100 125 100 125 100 125 100 125 100 125 100 125 100 125 100 125 100 100 100 100 100 100 100 100 100 10	31 27 6662 = 11 (P = Contr Events 40 55 52 62 23 35 66 23 34 406 55 24 00 55 52 40 05 5 52 40 05 5 52 2 40 05 5 5 2 8 146 8 20 34 4 5 5 2 8 10 8 20 10 10 10 10 10 10 10 10 10 10 10 10 10	71 40 1170 1170 1170 50 50 50 50 50 50 57 91 80 41 40 2255 630 74 40 1428 50 30 57 74 80 50 57 74 80 50 57 91 80 50 57 91 80 50 50 50 50 50 50 50 50 50 50 50 50 50	11.3% 7.4% 100.0% P = 50% Weight 8.2% 9.1% 8.2% 9.1% 8.2% 10.4% 7.0% 7.0% 7.0% 10.0% 10.9% 10.9% 10.9% 10.9% 11.2% 11.3% 11.2% 12.2%	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.15 [0.22, 1.27] 0.82 [0.24, 2.84] 0.88 [0.58, 1.36] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.48 [0.58, 7.132] 0.49 [0.7, 6.132] 0.49 [0.25, 761.37] 1.04 [0.17, 6.48] 1.9.42 [1.06, 354.72] 0.56 [0.28, 1.22] 0.26 [0.11, 0.63] 0.24 [0.08, 54.72] 0.26 [0.11, 0.63] 0.24 [0.08, 0.70] 0.43 [0.23, 0.80] 1.84 [0.95, 3.54] 2.43 [0.66, 9.03]	0.02 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01	10 50 Favours [control] Ratio
E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maaimi, H 2013 Papadopoulou, A 2015 Pilai, DK 2015 Total (95% CI) Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Matmaz, SB 2017 Einisman, H 2013 Papadopoulou, A 2015 Pilai, DK 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pilai, DK 2018 Iordanidou, M 2014	411 411 15; Chi ² = 2: = 0.00 (P = Experime Events 45 54 96 33 35 54 96 33 35 54 96 33 66 14 572 15; Chi ² = 2: = 0.23 (P = i Experime Events 15 3 3 6 16 8 8 24 4 5 5 14 15 15 15 15 15 15 15 15 15 15	10/ 40 737 2.08, df 1.00) ental Total 50 300 72 44 127 100 155 61 118 40 898 898 898 898 898 898 898 118 40 898 118 40 898 118 40 898 118 40 898 118 40 898 118 40 118 118 40 118 118 40 118 118 40 118 118 40 118 118 40 118 118 40 118 118 118 118 118 118 100 101 118 100 101 101	31 27 6662 = 11 (P = Contr Events 40 55 52 40 05 55 146 406 52 23 40 05 55 146 406 52 24 00 55 52 40 0 5 5 52 40 0 0 5 5 2 8 40 5 5 5 2 6 6 2 1 1 (P = 1 1 (P = 1) 2 6 6 2 3 4 5 5 5 2 6 6 2 3 4 5 5 5 2 6 6 2 3 4 5 5 5 2 6 6 2 3 4 5 5 5 2 6 6 2 3 4 5 5 5 2 6 6 2 3 4 6 5 5 2 6 6 2 3 4 6 5 5 2 6 6 2 3 4 6 5 5 5 2 6 6 2 3 4 6 5 5 5 2 6 6 2 3 4 6 5 5 5 2 6 6 2 3 4 6 5 5 2 7 7 9 20 0 0 5 5 5 2 6 1 5 5 2 6 1 5 5 5 2 6 6 2 3 4 4 0 5 5 5 2 6 6 2 3 4 4 0 5 5 5 2 6 2 6 3 4 4 0 5 5 5 2 2 6 0 0 0 5 5 5 2 2 6 0 0 0 5 5 5 2 2 6 0 0 0 0 0 5 5 5 2 2 6 0 0 0 5 5 5 2 2 6 0 0 0 0 5 5 5 2 2 3 4 4 6 5 5 5 2 2 3 4 4 0 0 0 5 5 5 2 2 2 3 4 6 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	71 40 1170 1170 50 50 50 50 50 50 57 80 41 40 2255 630 74 40 1428 50 30 57 71 80 40 1428 50 30 57 74 40 1428 50 50 57 74 40 225 56 30 0 57 74 40 74 40 74 40 74 74 74 74 74 74 74 74 74 74 74 74 74	11.3% 7.4% 100.0% P = 50% Weight 5.3% 6.2% 9.1% 6.2% 9.1% 8.2% 10.4% 7.0% 7.0% 7.0% 7.0% 10.9% 7.0% 10.9% 7.0% 10.9% 7.7% 6.4% 5.3% 5.3% 10.9% 1	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.71, 7.14] 0.68 [0.48, 2.44] 0.15 [0.02, 1.27] 0.82 [0.24, 2.84] 0.88 [0.58, 1.35] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.26 [0.70, 1.32] 0.46 [0.33, 1.10] 1.49 [0.83, 2.68] 0.26 [0.70, 1.32] 0.56 [0.25, 761.37] 1.04 [0.17, 6.48] 19.42 [1.06, 354.72] 0.56 [0.28, 1.22] 0.56 [0.28, 1.22] 0.56 [0.28, 1.22] 0.26 [0.11, 0.63] 1.44 [0.8, 54.72] 0.26 [0.11, 0.63, 1.29] 0.24 [0.08, 0.70] 0.43 [0.23, 0.80] 1.84 [0.85, 3.54] 2.43 [0.66, 9.03] Not estimable	0.02 0.1 Favours [experimental] 0.01 0.1 Favours [experimental] 0.01 0.01 V. Rando 0.01	10 50 Favours [control] Ratio
E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Mamed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Maalmi, H 2013 Papadopoulou, A 2015 Total (95% CI)	14 411 15; Chi ² = 2: 0.00 (P = Experime Events 45 12 37 27 84 69 35 54 96 63 33 66 14 572 15; Chi ² = 2: e 0.23 (P = 1 Experime Events 15 3 3 6 16 8 24 47 15 3 3 6 16 8 24 47 15 15 15 15 15 15 15 15 15 15	10/ / 40 737 2.08, df 1.00) ental Total 50 50 72 44 127 100 155 61 118 40 898 838 3.55, df 0.82) ental 50 0.82) ental 50 61 118 40 898	31 27 662 Events 400 15 26 65 22 40 15 52 40 406 52 23 40 406 52 23 40 920 0 920 0 0 5 2 2 0 0 18 20 5 2 8 40 920 0 18 34 20 5 2 8 40 9 20 10 920 10 10 10 920 10 10 10 10 10 10 10 10 10 10 10 10 10	71 40 11170 6.0.2); ol <u>Total</u> 50 0 30 50 50 79 1 80 630 74 40 1428 50 0.01); rol <u>Total</u> 630 74 40 1428 50 57 91 80 50 57 91 80 50 74 40 57 50 74 40 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 57 50 50 57 50 50 57 50 50 57 50 50 57 50 50 57 57 50 57 50 57 50 57 50 57 57 50 50 57 57 50 50 57 50 57 50 57 50 57 50 57 50 50 57 50 50 57 57 50 57 50 57 50 57 50 50 57 57 50 57 50 57 50 50 57 50 50 50 57 50 50 50 57 50 50 50 50 50 57 50 50 50 50 50 50 50 50 50 50 50 50 50	11.3% 7.4% 100.0% P = 50% Weight 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3% 5.3%	0.26 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 2.25 [0.71, 7.14] 0.67 [0.24, 1.85] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.71, 7.14] 0.67 [0.24, 1.86] 1.20 [0.64, 2.24] 0.15 [0.02, 1.27] 0.82 [0.24, 2.84] 0.88 [0.58, 1.36] 0.65 [0.38, 1.10] 1.29 [0.64, 2.24] 0.48 [0.58, 1.36] 0.65 [0.38, 1.10] 1.20 [0.64, 2.24] 0.68 [0.58, 1.36] 0.66 [0.38, 1.10] 0.68 [0.24, 2.84] 0.68 [0.58, 1.36] 0.66 [0.70, 1.32] 0.66 [0.70, 1.32] 0.66 [0.70, 1.32] 0.56 [0.12, 2.57] 1.04 [0.17, 6.48] 19.42 [1.06, 354.72] 0.58 [0.28, 1.22] 0.26 [0.11, 0.63] 0.24 [0.08, 0.70] 0.43 [0.23, 0.80] 1.84 [0.95, 3.54] 2.43 [0.66, 9.03] Not estimable 0.87 [0.47, 1.62]	0.02 0.1 Favours [experimenta] 0.01 0.1 Favours [experimenta]] 0dds V. Rando 0.01 0.1 Favours [experimenta]] 0dds V. Rando	10 50 Favours [control] Ratio
E	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Liordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pillai, DK 2011 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Heterogeneity: Tau ² = 0.1 Chiman, K 2018 Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2013 Papadopoulou, A 2015 Pilla, DK 2011 Zhord HX 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Pilla, DK 2011 Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Chiman, JK 2015 Chiman, JK 2015 Chi	14 411 15; Chi ² = 2: = 0.00 (P = Experime Events. 45 12 37 27 84 69 35 54 96 33 66 14 572 15; Chi ² = 2: = 0.23 (P = Experime Experime 54 96 35 54 96 33 66 14 572 15; Chi ² = 2: 15; Chi ² = 2: 15 3 3 6 16 8 24 47 15 15 15 15 15 15 15 15 15 15	10/ / 40 737 2.08, df 1.00) ental Total 50 50 30 72 44 127 70 118 40 898 8355, df 118 40 838 838 8355, df 118 40 838 838 838 838 838 838 839 840 127 100 155 50 30 00 72 44 41 100 118 40 118 118 40 118 118 40 118 118 118 118 118 118 118 118 118 11	31 27 662 Events 400 15 26 62 35 400 52 400 52 400 52 400 52 400 52 24 00 52 20 8 406 52 146 406 52 20 8 400 52 8 11 (P =	71 40 40.02); 50.02); 50.01 Total 50.05 791 80.05 791 80.05 74 40 41 428 50.01); 701 Total 1428 50.001; 701 1428 50.007 74 40 50 57 91 80.007 74 40 50 57 70 50 50 70 74 74 74 74 74 74 74 74 74 74 74 74 74	11.3% 7.4% 100.0% P = 50% Weight 5.3% 6.2% 9.1% 6.2% 9.1% 1.3% 7.0% 7.0% 7.0% 7.0% 7.0% 7.0% 7.0% 7.0	1.36 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] V. Random, <u>95% C1</u> 2.25 [0.7, 7, 14] 0.67 [0.24, 1.86] 0.98 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.64, 2.24] 0.45 [0.02, 1.27] 0.62 [0.24, 2.84] 0.45 [0.02, 1.27] 0.62 [0.24, 2.84] 0.88 [0.58, 1.35] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] Vodds Ratio IV. Random, <u>95% C</u> 44, 10 [2.55, 761.37] 0.56 [0.28, 1.22] 0.58 [0.28, 1.22] 0.40 [0.06, 0.70] 0.81 [0.33, 1.99] 0.43 [0.23, 0.80] 0.44 [0.65, 3.54] 2.43 [0.66, 9.03] Not estimable 0.87 [0.47, 1.62]	0.02 0.1 Favours [experimenta] 0.01 0.1 Favours [experimenta]] 0dds V. Rando 0.01 0.1 Favours [experimenta]] 0dds V. Rando	10 50 Favours [control] Ratio
D.	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: 2 = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Liordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Chamber J. 2018 Buttanz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Liu, Y 2016 Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Liu, Y 2016 Ma, JH 2014 Mail, H 2013 Papadopoulou, A 2015 Pillal, DK 2011 Zhao, HX 2014 Kilic, M 2019 Liu, Y 2016 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overail effect: Z	14 411 15; Chi ² = 2: = 0.00 (P = Experime 45 12 37 27 84 69 35 54 96 33 66 14 572 5; Chi ² = 2: = 0.23 (P = 1 Experime Experime 15; Chi ² = 2: 3 3 6 16 8 24 477 15 13 11 0 16 8 24 477 15 15 15 24 25 24 15 15 15 15 15 15 15 15 15 15	10/ 40 737 2.08, df 11.00) ental Total 50 30 0, 72 44 11.00 155 61 118 40 898 3.55, df 0.82) ental Total 30 0.72 44 127 100 30 0.72 44 128 50 30 0.72 44 128 50 30 0.72 44 128 50 30 0.72 44 128 50 30 0.72 44 128 50 30 0.72 44 128 50 30 0.72 44 128 50 128 50 30 0.72 100 11.00 10.00	31 27 6622 = 11 (P = Contr Events. 400 15 26 65 22 40 15 26 65 22 40 406 55 40 406 406 406 406 406 406 406 40 55 2 40 0 55 2 6 20 8 40 5 2 8 11 (P = 11 (P = 10) 2 10 5 5 2 6 6 2 3 40 40 5 5 2 6 6 2 3 40 6 2 6 2 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 6 2 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 3 40 6 2 9 20 0 0 5 2 2 0 0 0 15 5 2 2 0 0 0 15 5 2 2 0 0 0 0 15 5 2 2 0 0 0 0 0 0 5 2 2 0 0 0 0 0 0 0	71 14 40 1170 1170 1170 1170 1170 10 10 10 10 10 10 10 10 10 1	11.3% 7.4% 100.0% P = 50% Weight 1.53% 6.2% 9.2% 10.4% 1.3% 10.4% 1.3% 10.4% 1.3% 10.4% 1.3% 10.9% 7.0% 100.0% Weight 11.3% 11.3% 11.3% 12.5% 8.8% 100.0%	1.36 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.25 [0.72, 1.38] 1.20 [0.72, 1.14] 0.56 [0.24, 1.85] 0.58 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.42, 2.44] 0.45 [0.02, 1.27] 0.82 [0.24, 2.84] 0.88 [0.58, 1.36] 0.42 [0.24, 2.84] 0.86 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.36 [0.70, 1.32] 0.65 [0.38, 1.10] 1.44 [0.25, 574] 37] 0.56 [0.26, 1.22] 0.56 [0.26, 1.22] 0.56 [0.23, 1.26] 0.56 [0.33, 1.99] 0.43 [0.23, 0.83] 0.24 [0.08, 0.72] 0.58 [0.23, 1.99] 0.43 [0.23, 1.99] 0.44 [0.23	0.02 0.1 Favours [experimental] Odds IV. Rande 0.01 0.1 Favours [experimental] Odds V. Rande 0.01 0.1 Favours [experimental] Odds	10 50 Favours [control] Ratio
D	Zhao, HX 2015 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Hutchinson, K 2018 Iordanidou, M 2014 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Total (95% CI) Total events Heterogeneity: Tau ² = 0.1 Total (95% CI) Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Einisman, H 2015 Heterogeneity: Tau ² = 0.4 Califormic Magnetic Magnet	14 411 15; Chi ² = 2: = 0.00 (P = Experime Events 45 54 96 33 54 96 33 66 14 572 = 0.23 (P = 1 Experime Events 15; Chi ² = 2: 15; Chi ² = 2: 16 8 4 4 7 16 16 8 4 4 7 16 16 16 8 4 4 7 16 16 16 16 8 16 16 16 16 16 16 16 16 16 16	107 40 737 2.08, df 1.00) ental Total 50 30 072 44 4127 100 41 100 41 100 41 100 41 100 41 898 3.55, df 0.62) ental 724 44 127 100 41 118 40 0.62) 898 836.50, df 0.65)	31 27 662 52 52 40 15 52 6 26 52 40 52 40 52 23 56 52 40 52 24 40 52 23 56 52 40 52 24 10 52 20 0 52 20 0 52 20 0 52 20 0 52 20 0 52 20 10 10 10 10 10 10 10 10 10 10 10 10 10	71 140 1170 0.022); ol Total 50 0.30 50 0.225 630 0.225 630 0.225 630 0.1428 0.01); Total 50 30 0 1428 <0.01); 1428 <<0.000; 74 40 1428 <0.01); 1428 <<0.000; 1428 <<0.000; 1428 <<0.000; 1428 <<0.000; 1428 <<0.000; 1428 <<0.000; 1428 0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </0.000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000; 1428 </000;</td <td>11.3% 7.4% 7.4% 100.0% 9 = 50% Weight 1.9% 8.2% 10.4% 1.9% 7.0% 10.9% 7.0% 10.9% 7.0% 10.0% 7.0% 10.0% 7.0% 10.0% 11.3% 11.3% 11.3% 11.2% 8.8% 100.0%</td> <td>1.36 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.25 [0.72, 1.38] 0.25 [0.72, 1.34] 0.85 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.44, 2.24] 0.45 [0.24, 2.24] 0.45 [0.24, 2.24] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.41, 10 [2.55, 761.37] 1.04 [0.17, 6.48] 19.42 [1.06, 354.72] 0.26 [0.11, 0.63] 0.24 [0.08, 0.73] 0.43 [0.23, 0.83] 0.43 [0.23, 0.83] 0.43 [0.23, 0.80] 0.43 [0.23, 0.80] 0.43 [0.23, 0.80] 0.43 [0.53, 544] 2.43 [0.66, 9.03] Not estimable 0.87 [0.47, 1.62]</td> <td>0.02 0.1 Favours [experimental] 0dds IV. Rando 0.01 0.1 Favours [experimental] 0dds VV. Rando 0.01 0.1 Favours [experimental]</td> <td>10 50 Favours [control] Ratio </td>	11.3% 7.4% 7.4% 100.0% 9 = 50% Weight 1.9% 8.2% 10.4% 1.9% 7.0% 10.9% 7.0% 10.9% 7.0% 10.0% 7.0% 10.0% 7.0% 10.0% 11.3% 11.3% 11.3% 11.2% 8.8% 100.0%	1.36 [0.7, 2.43] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.26 [0.10, 0.66] 1.00 [0.72, 1.38] 0.25 [0.72, 1.38] 0.25 [0.72, 1.34] 0.85 [0.47, 2.01] 2.35 [1.05, 5.25] 1.22 [0.70, 2.14] 1.20 [0.44, 2.24] 0.45 [0.24, 2.24] 0.45 [0.24, 2.24] 0.65 [0.38, 1.10] 1.49 [0.83, 2.68] 0.26 [0.10, 0.66] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.96 [0.70, 1.32] 0.41, 10 [2.55, 761.37] 1.04 [0.17, 6.48] 19.42 [1.06, 354.72] 0.26 [0.11, 0.63] 0.24 [0.08, 0.73] 0.43 [0.23, 0.83] 0.43 [0.23, 0.83] 0.43 [0.23, 0.80] 0.43 [0.23, 0.80] 0.43 [0.23, 0.80] 0.43 [0.53, 544] 2.43 [0.66, 9.03] Not estimable 0.87 [0.47, 1.62]	0.02 0.1 Favours [experimental] 0dds IV. Rando 0.01 0.1 Favours [experimental] 0dds VV. Rando 0.01 0.1 Favours [experimental]	10 50 Favours [control] Ratio

FIGURE 3 | Forest plot for meta-analyzing the association between Vitamin D receptor Taql (rs731236) 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.

		Experim	ental	Contr	ol		Odds Ratio	Odds	Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% C	I IV, Rande	om, 95% Cl
	Ahmed, AE 2020 Batmaz SB 2017	55 44	100	40	100	9.9% 7.9%	1.83 [1.05, 3.21]	-	
	Hou, C 2018	136	140	135	140	4.3%	1.26 [0.33, 4.79]		· · · ·
	lordanidou, M 2014	147	254	105	182	11.6%	1.01 [0.69, 1.48]		-
	Liu, Y 2016 Ma JH 2014	53 100	82 120	76 102	120	6.5% 8.6%	0.14 [0.06, 0.37]	·	
	Maalmi, H 2013	170	310	279	450	12.4%	0.74 [0.55, 1.00]	-	
	Mo, LY 2015	137	142	138	142	4.3%	0.79 [0.21, 3.02]		-
	Papadopoulou, A 2015 Zhang, Y 2017	72 100	126 286	681 77	1262 286	11.7% 11.8%	1.14 [0.79, 1.65] 1.46 [1.02, 2.09]		
	Zhao, HX 2015	57	80	69	80	7.6%	0.40 [0.18, 0.88]		
	Zhu, L 2019	184	194	198	200	3.5%	0.19 [0.04, 0.86]		
	Total (95% CI)		1894		3104	100.0%	0.87 [0.62, 1.21]		
	Total events	1255		1937					
	Heterogeneity: Tau ² = 0.2 Test for overall effect: Z =	21; Chi ^z = 4 = 0.83 (P =	1.10, df 0.41)	= 11 (P <	0.000	1); l² = 73	%	0.05 0.2	1 5 20
в			,					Favours [experimental]	Favours [control]
-	Study or Subgroup	Experime	ental Total	Contr	ol Total	Weight	Odds Ratio	Odds I IV Rando	Ratio
	Ahmed, AE 2020	15	25	10	30	12.7%	3.00 [1.00, 9.04]		
	Batmaz, SB 2017	16	18	12	17	7.8%	3.33 [0.55, 20.22]	_	· · ·
	Hou, C 2018 Iordanidou, M 2014	66 40	66 60	65 33	65 52	15.6%	Not estimable 1 15 (0 53, 2 51)		_
	Liu, Y 2016	21	30	36	37	6.3%	0.06 [0.01, 0.55]	· · · · ·	
	Ma, JH 2014	45	50	48	54	11.5%	1.13 [0.32, 3.94]		
	Maalmi, H 2013 Mo. LY 2015	49	83 66	80 67	106	17.0%	0.47 [0.25, 0.87] Not estimable	-	
	Papadopoulou, A 2015	20	31	177	304	15.7%	1.30 [0.60, 2.82]	-	•
	Zhang, Y 2017 Zhao, HX 2015	13	69	6	78	13.4%	2.79 [1.00, 7.79]		-
	Zhao, 11X 2015 Zhu, L 2019	87	87	∠9 98	29 98		Not estimable		
	T-1-1 (050)				0	100			
	Total (95% CI)	455	602	661	937	100.0%	1.16 [0.61, 2.21]		Γ
	Heterogeneity: Tau ² = 0.5	54; Chi ² = 2	1.89, df	= 7 (P =	0.003);	l² = 68%		0.005 0.1	1 10 200
_	Test for overall effect: Z =	= 0.45 (P =	0.66)					Favours [experimental]	Favours [control]
C		Experime	ental	Contr	ol		Odds Ratio	Odds	Ratio
-	Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% C	I IV, Rande	om, 95% Cl
	Batmaz, SB 2017	25 12	35 14	20	40	5.4%	2.30 [0.96, 6.53]		
	Hou, C 2018	4	4	5	5		Not estimable		
	lordanidou, M 2014	67 11	87 20	39	58	16.0%	1.63 [0.78, 3.43]		
	Ma, JH 2014	10	15	6	12	6.8%	2.00 [0.42, 9.52]		
	Maalmi, H 2013	72	106	119	145	18.7%	0.46 [0.26, 0.83]		
	Mo, LY 2015 Papadopoulou A 2015	5 32	5 43	4 327	4 454	16.4%	Not estimable 1 13 (0 55 2 31)		_
	Zhang, Y 2017	74	130	65	137	20.6%	1.46 [0.90, 2.37]	,	
	Zhao, HX 2015	23	23	11	11		Not estimable		
	Zhu, L 2019	10	10	2	2		Not estimable		
	Total (95% CI)		492		891	100.0%	1.22 [0.76, 1.96]	•	•
	Total events Heterogeneity: Tau ² = 0.2	345 22: Chi ² = 1	5.78. df	615 = 7 (P =	0.03): 1	² = 56%		H	l
	Test for overall effect: Z =	= 0.83 (P =	0.41)	,	- // 1			v.uz 0.1 Favours (experimental)	1 10 50 Favours [control]
D		Exporim						i aroaro josponnoni	
-	Study or Subgroup	Experim	ental	Contr	ol		Odds Ratio	Odds	Ratio
	etteraj et europietas	Events	ental Total	Contr Events	ol Total	Weight	Odds Ratio IV, Random, 95% C	Odds I IV, Rande	Ratio pm. 95% Cl
	Ahmed, AE 2020	Events 40	ental Total 50	Contr Events 30	ol <u>Total</u> 50	Weight 13.1%	Odds Ratio IV, Random, 95% C 2.67 [1.09, 6.52]	Odds I IV, Rande	Ratio pm, 95% Cl
	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018	Events 40 28 70	ental <u>Total</u> 50 30 70	Contr Events 30 25 70	ol <u>Total</u> 50 30 70	Weight 13.1% 6.5%	Odds Ratio <u>IV, Random, 95% C</u> 2.67 [1.09, 6.52] 2.80 [0.50, 15.73] Not estimable	Odds I IV. Rando	Ratio pm <u>. 95% Cl</u>
	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014	Experim Events 40 28 70 107	ental <u>Total</u> 50 30 70 127	Contr Events 30 25 70 72	ol <u>Total</u> 50 30 70 91	Weight 13.1% 6.5% 15.4%	Odds Ratio <u>IV, Random, 95% C</u> 2.67 [1.09, 6.52] 2.80 [0.50, 15.73] Not estimable 1.41 [0.70, 2.83]	Odds I IV, Randu	Ratio pm. 95% Cl
	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, IH 2014	Experim Events 40 28 70 107 32 55	ental <u>Total</u> 50 30 70 127 41 60	Contr Events 30 25 70 72 40	ol Total 50 30 70 91 41	Weight 13.1% 6.5% 15.4% 4.8%	Odds Ratio IV. Random, 95% C 2.67 [1.09, 6.52] 2.80 [0.50, 15.73] Not estimable 1.41 [0.70, 2.83] 0.09 [0.01, 0.74] 1.22 (0.25, 4.01)	Odds I IV. Rande	Ratio m. <u>95% Cl</u>
	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013	Events 40 28 70 107 32 55 121	ental <u>Total</u> 50 30 70 127 41 60 155	Contr Events 30 25 70 72 40 54 199	ol <u>Total</u> 50 30 70 91 41 60 225	Weight 13.1% 6.5% 15.4% 4.8% 9.7% 17.0%	Odds Ratio <u>IV. Random, 95% C</u> 2.67 [1.09, 6.52] 2.80 [0.50, 15.73] Not estimable 1.41 [0.70, 2.83] 0.09 [0.01, 0.74] 1.22 [0.35, 4.24] 0.46 [0.27, 0.81]	Odds (bitsing) Odds Odds V. Randa	Ratio m. 95% Cl
	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Mo, LY 2015	Experim 40 28 70 107 32 55 121 71	ental <u>Total</u> 50 30 70 127 41 60 155 71	Contr Events 30 25 70 72 40 54 199 71	ol <u>Total</u> 50 30 70 91 41 60 225 71	Weight 13.1% 6.5% 15.4% 4.8% 9.7% 17.0%	Odds Ratio <u>IV. Random, 95% C</u> 2.60 [1.09, 6.52] 2.80 [0.50, 15.73] Not estimable 1.41 [0.70, 2.83] 0.09 [0.01, 0.74] 1.22 [0.35, 4.24] 0.46 [0.27, 0.81] Not estimable		Ratio m. 95% Cl
	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Mo, LY 2015 Papadopoulou, A 2015 Zhang, Y 2017	Experimi Events 40 28 70 107 32 55 121 71 52 97	ental <u>Total</u> 50 30 70 127 41 60 155 71 63 142	Contr Events 30 25 70 72 40 54 199 71 504 74	ol <u>Total</u> 50 30 70 91 41 60 225 71 631 142	Weight 13.1% 6.5% 15.4% 4.8% 9.7% 17.0% 15.6% 18.0%	Odds Ratio IV. Random, 95% C 2.67 [1.09, 6.52] 2.80 [0.50, 15.73] Not estimable 1.41 [0.70, 2.83] 0.09 [0.01, 0.74] 1.22 [0.35, 4.24] 0.46 [0.27, 0.81] Not estimable 1.19 [0.60, 2.35] 1.58 [0.00, 2.57]		Ratio pm. 95% Cl
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E	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Ma, JH 2014 Ma, JH 2014 Ma, JH 2015 Papadopoulou, A 2015 Zhang, Y 2017 Zhao, HX 2015 Zhu, L 2019 Total (95% CI) Total events Heterogeneity: Tau ^g = 0.3 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Mo, LY 2015	Events 40 28 70 107 107 525 55 121 71 52 87 40 97 800 34; Chi ² = 2 8, 049 (P = Experime Events 15 16 66 40 21 45 40 25 121 15 15 15 15 15 15 121 15 15 15 15 15 15 15 15 15 1	ental <u>Total</u> 50 30 70 127 41 60 155 71 63 143 40 97 947 2.2.1, df 40 97 947 2.2.21, df 50 30 0 70 127 41 63 143 43 43 43 43 43 43 43 43 43	Contribution Contr	ol <u>Total</u> 500 30 70 91 41 60 225 71 631 143 40 100 1552 0.002); ol <u>Total</u> 50 0 70 91 41 40 100 225 71 63 143 40 100 205 71 63 143 40 100 205 71 63 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 50 70 143 143 143 100 70 70 1552 70 100 70 70 100 70 70 100 70 70 70 70 70 70 70 70 70	Weight 13.1% 6.5% 15.4% 4.8% 9.7% 15.6% 18.0% 100.0% 12.6% 100.0% 12.1% 115.6% 12.1% 12.1% 12.2% 7.2% 1.1.7%	Odds Ratio <u>IV. Random, 95% C</u> 2.67 (10.9, 6.52) 2.80 (10.9, 6.53) Not estimable 1.41 (0.70, 2.83) 0.49 (0.70, 24) 1.22 (0.35, 4.24) 0.46 (0.27, 0.81) Not estimable 1.19 (0.60, 2.35) 1.58 (0.99, 2.52) Not estimable 1.14 (0.67, 1.93) Odds Ratio <u>IV. Random, 95% C</u> 1.71 (0.68, 4.30) 0.81 (0.46, 1.43) 0.81 (0.64, 1.43) 0.51 (0.50, 0.45] 0.75 (0.24, 1.77) 0.79 (0.20, 3.64) 0.79 (0.20, 3.64) 0.79 (0.20, 3.64) 1.19 (0.68, 2.68)	0dda IV. Rando V. Rando 0.01 0.1 Favours [experimental] 0dda IV. Rando 	Ratio m. 95% Cl
E.	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Mo, LY 2015 Papadopoulou, A 2015 Zhang, Y 2017 Zhao, HX 2015 Total (95% CI) Total events Heterogeneity. Tau ² = 0.3 Test for overall effect: Z = <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Lorda JH 2014 Maalmi, H 2013 Mo, LY 2015 Papadopoulou, A 2015 Zhang, Y 2017	Events 40 28 70 107 32 55 121 71 52 87 40 97 800 800 97 800 800 97 800 800 97 800 800 800 800 800 800 800 80	ental Total 500 300 707 127 41 600 1555 71 633 1433 443 977 947 2.21, df 707 947 2.21, df 500 300 000 127 411 500 127 411 500 127 127 127 127 127 127 127 127	Contribution Contr	ol <u>Total</u> 500 30 70 91 41 60 225 71 631 143 40 100 1552 0.002); 0l <u>Total</u> 50 0 70 91 41 40 100 225 71 63 143 40 100 205 71 63 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 100 205 71 143 40 205 71 143 143 40 205 70 143 143 143 100 70 70 1552 70 100 70 100 70 70 100 70 100 70 70 100 70 70 70 70 70 70 70 70 70	Weight 13.1% 6.5% 15.4% 9.7% 17.0% 15.6% 18.0% 100.0% 100.0% 18.0% 100.0% 18.4% 7.6% 8.4% 7.6% 8.9% 11.6% 8.9% 11.7% 5.5% 5	Odds Ratio <u>IV. Random. 95% C</u> 2.67 (10.9, 6.52) 2.80 (0.50, 15.73) Not estimable 1.41 (0.70, 2.83) 0.09 (0.01, 0.74) 1.22 (0.35, 4.24) Not estimable 1.19 (0.60, 2.35) 1.58 (0.99, 2.52) Not estimable Not estimable 1.14 (0.67, 1.93) Odds Ratio <u>IV. Random. 95% C</u> 1.71 (0.68, 4.30) 1.71 (0.68, 4.30) 1.72 (0.33, 6.94) 0.75 (0.32, 177) 0.54 (0.54, 4.129) 0.79 (0.20, 3.06) 1.19 (0.68, 2.68) 0.79 (0.20, 3.06) 1.90 (0.68, 4.129) 0.79 (0.20, 3.06) 1.90 (0.64, 6.19) 0.28 (0.64	0.01 0.1 0.01 0.1 Favours (experimental) 0.04 1. V. Randa 0.01 0.1 Favours (experimental) 0.04 1. V. Randa 0.04 1. V. Randa	Ratio m. 95% Cl
E	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2016 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Mo, LY 2015 Papadopoulou, A 2015 Zhang, Y 2017 Zhao, HX 2017 Total (95% CI) Total events Heterogeneity: Tau ² = 0.2 Study or Subgroup Test for overall effect: Z = Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Maa, JH 2014 Maalmi, H 2013 Papadopoulou, A 2015 Zhang, Y 2015	Expertise Events 40 28 70 107 32 55 121 71 52 87 40 097 87 40 16 17 17 17 17 17 17 17 17 17 17	ental Total 50 30 70 127 41 60 155 71 63 34 40 97 947 2.21, df 0.63) ental Total 50 30 70 0.63 ental 55 71 63 155 71 63 165 71 71 63 165 71 71 63 165 71 71 63 165 71 71 63 165 71 71 63 165 71 71 63 165 71 71 63 165 71 71 63 165 71 71 63 165 71 71 71 63 165 71 71 71 71 71 71 71 71 71 71	Contribution Contr	ol Total 500 30 70 91 41 60 225 71 631 143 40 100 1552 0.002); ol Total 50 300 20 50 300 20 50 300 20 50 10 10 10 10 10 10 10 10 10 1	Weight 13.1% 6.5% 15.4% 4.8% 9.7% 15.6% 17.0% 15.6% 11.0% 100.0% 110.0% 10	Odds Ratio V. Random. 95% C 2.67 (10.9, 6.52) 2.80 (10.50, 15.73) Not estimable 1.41 (0.70, 2.83) 0.09 (10.01, 0.74) 1.22 (0.35, 4.24) Not estimable 1.19 (0.60, 2.55) 1.58 (10.99, 2.52) Not estimable Not estimable 1.14 (0.67, 1.93) Odds Ratio V. Random. 95% C V. Ran	0,010,010,000,000,000,000,000,000,000,0	Ratio 95% Cl
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E .	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Mo, LY 2015 Papadopoulou, A 2015 Zhang, Y 2017 Zhao, HX 2015 Zhu, L 2019 Total (95% CI) Total events Study or Subgroup Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2015 Zhao, HX 2015 Zhao, HX 2015 Zhao, HX 2015 Zhao, HX 2015 Zhao, HX 2015 Zhao, LX 2015	Events Events 40 28 70 107 107 121 55 55 121 71 52 87 40 97 87 15 15 15 15 121 15 15 15 15 15 15 15 15 15 1	ental Total 50 50 30 127 41 13 143 40 947 947 2.21, df 0.63) Total 50 30 0.70 127 947 947 947 947	Contribution Contr	ol Total 50 30 70 91 41 60 225 71 631 143 40 100 1552 0.002); ol Total 50 30 07 0 91 143 40 100 1552 71 631 143 40 100 1552 71 631 143 40 100 1552 71 631 141 143 143 143 143 143 143 1	Weight 13.1% 6.5% 15.4% 9.7% 9.7% 17.0% 15.6% 18.0% 100.0% ************************************	Odds Ratio V. Random, 95% C 2.67 (10.9, 6.52) 2.80 (10.9, 6.52) 3.80 (10.9, 6.52) 3.80 (10.9, 6.52) 3.80 (10.9, 6.52) 3.80 (10.7, 4.54) 1.22 (10.35, 4.24) 0.46 (10.27, 0.41) Not estimable 1.19 (10.60, 2.55) 1.58 (10.99, 9.252) Not estimable Not estimable 1.14 (10.67, 1.93) Odds Ratio (V. Random, 95% C 1.71 (10.68, 4.30) 1.71 (10.62, 4.77) 1.27 (10.38, 4.54) 0.81 (10.46, 1.43) 0.75 (10.22, 1.77) 0.84 (10.54, 1.29) 0.79 (10.23, 0.52) 1.19 (10.68, 2.08) 2.28 (10.41, 0.71) 0.28 (10.41, 0.71) 0.28 (10.41, 0.71) 0.28 (10.41, 0.71) 0.28 (10.41, 0.71) 0.38 (10.04, 0.83) 0.80 (0.54, 1.20)	0.01 0.1	Ratio m, 95% Cl
E .	Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Mo, LY 2015 Papadopoulou, A 2015 Zhang, Y 2017 Zhao, HX 2019 Total (95% CI) Total events Heterogeneity: Tau ² = 0.3 <u>Study or Subgroup</u> Ahmed, AE 2020 Batmaz, SB 2017 Hou, C 2018 Iordanidou, M 2014 Liu, Y 2015 Zhao, HX 2015 Zhu, L 2019 Total (95% CI) Total (95% CI)	Events 40 28 70 107 107 55 55 121 71 52 87 40 97 880 34; Chi ² = 2 8, 00 97 8, 00 9, 00 8, 00	ental Total Total 50 30 070 127 41 60 155 71 63 143 443 443 443 97 947 2.21, df 0.63) ental Total 50 30 0 70 127 41 63 143 43 443 443 97 947 947 947 947 947 947 947	Contr Events: 300 255 700 54 199 711 504 710 400 100 1276 6 = 7 (P = Contr Events: 10 10 1276 6 333 36 880 667 177 76 98 80 6611 1(P =	ol Total 50 30 70 91 41 60 225 71 631 143 40 100 1552 0.002); ol Total 50 30 0 70 91 143 40 100 1552 0.002); 14 16 100 1552 100 100 100 1552 100 100 100 100 100 100 100 10	Weight 13.1% 6.5% 15.4% 4.70 15.6% 18.0% 100.0% 100.0% Weight 8.4% 8.9% 1.1.6% 7.6% 5.5% 11.6% 7.0% 12.9% 5.5% 4.7% 100.0% b; P = 62%	Odds Ratio IV. Random. 95% C 2.67 (10.9, 6.52) 2.80 (10.9, 6.52) 3.80 (0.50, 15.73) Not estimable 1.41 (0.70, 2.83) 0.09 (10.01, 0.74) 1.22 (0.35, 4.24) 0.46 (0.27, 0.81) Not estimable 1.19 (0.60, 2.35) 1.58 (0.99, 2.52) Not estimable 1.14 (0.67, 1.93) Odds Ratio IV. Random. 95% C 1.71 (0.68, 4.30) 0.81 (0.46, 1.43) 0.15 (0.05, 0.43) 0.84 (0.54, 1.29) 0.28 (0.14, 0.71) 0.28 (0.14, 0.71)	0.01 0.1 V. Rando	Ratio pm, 95% Cl
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FIGURE 4 | Forest plot for meta-analyzing the association between Vitamin D receptor Bsml (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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-	Study or Subarous	Experim	nental Total	Contro	l Total	Weight	Odds Ratio	Odds Ratio	
	Batmaz SB 2017	<u>= vents</u> 11	<u>10tai</u> 60	24	60	6 1%	0.34 [0.15_0.77		
	Einisman, H 2015	62	146	45	100	8.6%	0.90 [0.54, 1.51		
	Iordanidou, M 2014	66	254	61	182	9.4%	0.70 [0.46, 1.06		
	Ismail, MF 2013 Kilic, M 2019	22 51	102 200	28	66 160	7.3%	0.37 [0.19, 0.74]		
	Liu, Y 2016	53	82	75	82	5.7%	0.17 [0.07, 0.42]		
	Ma, JH 2014	72	120	53	120	8.6%	1.90 [1.14, 3.17]		
	Pillai, DK 2013	78 51	310 244	105	304 148	9.9% 8.8%	0.64 [0.45, 0.90]		
	Zhang, Y 2017	233	286	211	286	9.5%	1.56 [1.05, 2.33	_ 	
	Zhao, HX 2015	28	80	34	80	7.6%	0.73 [0.38, 1.38		
	Znu, L 2019	92	194	95	200	9.6%	1.00 [0.67, 1.48]		
	Total (95% CI)		2078		1788	100.0%	0.78 [0.57, 1.05]	•	
	Total events Heterogeneity: Tau ² =	0 21 · Chi ²	= 47 19	802 df = 11 (P	< 0.00	001)· I ² =	77%		
-	Test for overall effect: $Z = 1.63$ (P = 0.10)							0.1 0.2 0.5 1 2 5 Favours [experimental] Favours [control]	10
в		Experim	ontal	Contro	a		Odds Ratio	Odds Ratio	
_	Study or Subgroup	Events	Total	Events	Total	Weight	IV. Random, 95% 0	IV. Random. 95% Cl	
	Batmaz, SB 2017	0	19	6	18	4.0%	0.05 [0.00, 0.95]	· · · · · · · · · · · · · · · · · · ·	
	Einisman, H 2015 Iordanidou M 2014	0	11 73	0	5 46	10.8%	0 43 [0 14 1 32	_ _	
	Ismail, MF 2013	õ	29	7	19	4.1%	0.03 [0.00, 0.53]		
	Kilic, M 2019	9	67	4	52	10.2%	1.86 [0.54, 6.42]		
	Ma, JH 2014	20	36	11	29	11.4%	3.27 [1.18, 9.09]		
	Maalmi, H 2013	11	99	23	93	12.7%	0.38 [0.17, 0.83	_ -	
	Piliai, DK 2011 Zhang, Y 2017	5 92	81 94	3 74	45 80	9.0% 8.3%	0.92 [0.21, 4.05]		
	Zhao, HX 2015	7	26	9	24	10.5%	0.61 [0.19, 2.03]	i —•+-	
	Zhu, L 2019	22	49	25	55	12.8%	0.98 [0.45, 2.12]	· –	
	Total (95% CI)		612		502	100.0%	0.67 [0.34, 1.34]	•	
	Total events	196	- 00	205		00) 12	00/		
_	Heterogeneity: Tau ² = Test for overall effect:	U.82; Chi ² Z = 1 13 (F	= 30.85, = 0.261	af = 10 (P	= 0.00	U6); l ² = 6	8%	0.002 0.1 1 10	500
С			5.20)					⊢avours [experimental] Favours [control]	
	Study or Subgroup	Experin	nental Total	Contr	ol Total	Weight	Odds Ratio	Odds Ratio	
-	Batmaz, SB 2017	11	30	12	24	4.1%	0.58 [0.19, 1.72]		
	Einisman, H 2015	62	73	45	50	3.8%	0.63 [0.20, 1.93]		
	iordanidou, M 2014 Ismail, MF 2013	54 22	121 51	45 14	83 26	15.5% 5.4%	0.68 [0.39, 1.19] 0.65 [0.25. 1.68]		
	Kilic, M 2019	33	91	28	76	12.2%	0.98 [0.52, 1.84]	_ + _	
	Liu, Y 2016	13	21	5	6	0.9%	0.33 [0.03, 3.31]	·	
	Ma, JH 2014 Maalmi, H 2013	24 56	30 144	59	129	21.0%	0.76 [0.47, 2.87]		
	Pillai, DK 2011	41	117	29	71	13.2%	0.78 [0.43, 1.43]		
	Zhang, Y 2017	49	51	63	69	1.8%	2.33 [0.45, 12.07]		
	Zhao, HX 2015 Zhu, L 2019	48	75	45	75	11.2%	1.19 [0.61, 2.29]		
	T-4-1 (05% OI)		0.40			400.0%	0.00 10.05 4.001		
	Total (95% CI)		843		689	100.0%	0.82 [0.65, 1.02]	•	
	Total events	427		392					+
	Total events Heterogeneity: Chi ² =	427 5.74, df =	11 (P = 0	392 0.89); l² =	0%			0.02 0.1 1 10	50
_	Total events Heterogeneity: Chi ² = Test for overall effect:	427 5.74, df = : Z = 1.80 (11 (P = 0 P = 0.07	392 0.89); I² =)	0%			0.02 0.1 1 10 Favours [experimental] Favours [control]	50
D	Total events Heterogeneity: Chi ² = Test for overall effect:	427 5.74, df = Z = 1.80 (Experin	11 (P = 0 P = 0.07 nental	392 0.89); I² =) Contr	0% ol		Odds Ratio	0.02 0.1 1 10 Favours [experimental] Favours [control] Odds Ratio	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect:	427 5.74, df = Z = 1.80 (Experin Events	11 (P = (P = 0.07 nental <u>Total</u>	392 0.89); I ² =) Contr <u>Events</u>	ol Total	Weight	Odds Ratio IV, Fixed, 95% CI	0.02 0.1 1 10 Favours [experimental] Favours [control] Odds Ratio IV. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015	427 5.74, df = 2 = 1.80 (Experin Events 11 62	11 (P = 0 P = 0.07 nental <u>Total</u> 30 73	392 	0% ol <u>Total</u> 30 50	Weight 4.0% 3.5%	Odds Ratio <u>IV. Fixed, 95% CI</u> 0.39 [0.14, 1.09] 0.63 [0.20, 1.93]	0.02 0.1 10 Favours [experimentai] Favours [control] Odds Ratio IV. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014	427 5.74, df = : Z = 1.80 (Experin Events 11 62 60	11 (P = 0 P = 0.07 nental <u>Total</u> 30 73 127	392 0.89); I ² =) Contr <u>Events</u> 18 45 53	0% ol <u>Total</u> 30 50 91	Weight 4.0% 3.5% 14.8%	Odds Ratio <u>IV. Fixed, 95% CI</u> 0.39 [0.14, 1.09] 0.63 [0.20, 1.93] 0.64 [0.37, 1.11]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013	427 5.74, df = : Z = 1.80 (Experin Events 11 62 60 22	11 (P = 0 P = 0.07 nental Total 30 73 127 51	392 0.89); I ² =) Contr Events 18 45 53 21 20	0% Total 30 50 91 33	Weight 4.0% 3.5% 14.8% 5.4%	Odds Ratio IV. Fixed, 95% CI 0.39 [0.14, 1.09] 0.63 [0.20, 1.93] 0.64 [0.37, 1.11] 0.43 [0.18, 1.07] 1.09 [0.64, 4.03]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio IV, Fixed, 95% Cl	50
D _	Total events Heterogeneity: Ch ^{ip} = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016	427 5.74, df = 2 = 1.80 (Experin Events 11 62 60 22 42 33	11 (P = (P = 0.07 nental <u>Total</u> 30 73 127 51 100 41	392 0.89); I ² =) Contr Events 18 45 53 21 32 40	0% Total 30 50 91 33 80 41	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.0%	Odds Ratio IV. Fixed, 95% CI 0.39 [0.14, 1.09] 0.63 [0.20, 1.93] 0.64 [0.37, 1.11] 0.43 [0.18, 1.07] 1.09 [0.60, 1.98] 0.10 [0.01, 0.87]	0.02 0.1 1 10 Favours [experimental] Favours [control] Odds Ratio IV, Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014	427 5.74, df = Z = 1.80 (Experin Events 11 62 60 22 42 33 48	11 (P = 0.07 nental Total 30 73 127 51 100 41 60	392 0.89); I ² =) Contr Events 18 45 53 21 32 40 42	0% Total 30 50 91 33 80 41 60	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.0% 6.2%	Odds Ratio IV. Fixed, 95% CI 0.39 [0.14, 1.09] 0.63 [0.20, 1.93] 0.64 [0.37, 1.11] 0.43 [0.18, 1.07] 1.09 [0.60, 1.98] 0.10 [0.01, 0.87] 1.71 [0.74, 3.97]	0.02 0.1 10 Favours [experimentai] Favours [control] Odds Ratio V. Fixed .95% Cl	50
D _	Total events Heterogeneity: Chi ^a = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pilai, DK 2014	427 5.74, df = Z = 1.80 (Experin 62 60 22 42 33 48 67	11 (P = 0 P = 0.07 nental 30 73 127 51 100 41 60 155	392 392 30.89); I ² =) Contr Events 18 45 53 21 32 40 42 82 22 22 22 22 22 22 22 22 2	0% Total 30 50 91 33 80 41 60 152 74	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.0% 6.2% 21.6% 12.7°	Odds Ratio IV. Fixed, 95% CI 0.39 [0.14, 1.09] 0.63 [0.20, 1.93] 0.64 [0.37, 1.11] 0.43 [0.18, 1.07] 1.09 [0.60, 1.98] 0.10 [0.01, 0.87] 1.71 [0.74, 3.97] 0.65 [0.41, 1.02] 0.79 [0.44, 4.47]	0.02 0.1 10 Favours [experimentai] Favours [control] Odds Ratio IV. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pillai, DK 2011 Zhang, Y 2017	427 5.74, df = 2 = 1.80 (Experin Events 11 62 60 22 42 42 33 48 67 46 141	11 (P = 0 P = 0.07 nental 30 73 127 51 100 41 60 155 122 143	392 392 30.89); I ² =) Contr Events 18 45 53 21 32 40 42 82 32 40 42 82 32 137	0% Total 30 50 91 33 80 41 60 152 74 143	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 6.2% 6.2% 12.7% 12.7% 1.7%	Odds Ratio IV. Fixed, 95% CI 0.39 [0.14, 1.09] 0.63 [0.20, 1.93] 0.64 [0.37, 1.11] 0.43 [0.18, 1.07] 1.09 [0.60, 1.98] 0.10 [0.01, 0.87] 1.71 [0.74, 3.97] 0.65 [0.41, 1.02] 0.79 [0.44, 1.43] 3.09 [0.61, 15.56]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Fixed, 55% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pillai, DK 2011 Zhao, HX 2015	427 5.74, df = 2 = 1.80 (Experin Events 11 62 60 02 42 42 33 48 67 46 67 46 141 21	11 (P = 0 P = 0.07 nental 30 73 127 51 100 41 60 155 122 143 40	392 0.89); I ² =) Contr Events 18 45 53 21 32 40 42 82 32 40 42 82 32 137 25	0% Total 30 50 91 33 80 41 60 152 74 143 40	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 6.2% 2.6% 12.7% 1.7% 5.5%	Odds Ratio IV. Fixed, 95% CI 0.39 [0.14, 1.09] 0.63 [0.20, 1.93] 0.64 [0.37, 1.11] 0.43 [0.16, 1.07] 1.09 [0.60, 1.98] 0.10 [0.01, 0.87] 1.71 [0.74, 3.97] 0.65 [0.41, 1.02] 0.79 [0.44, 1.43] 3.09 [0.61, 15.56] 0.66 [0.27, 1.62]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Philai, DK 2011 Zhao, HX 2015 Zhu, L 2019	427 5.74, df = : Z = 1.80 (Experin Events 11 62 60 22 42 33 348 67 46 141 21 70	11 (P = 0 P = 0.07 nental 30 73 127 51 100 41 60 155 122 143 40 97	392 0.89); I ² =) Contr Events 18 45 53 21 32 40 42 82 32 32 40 42 82 32 137 25 70	0% Total 30 50 91 33 80 41 60 152 74 143 40 100	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 6.2% 21.6% 12.7% 1.7% 5.5% 11.5%	Odds Ratio IV. Fixed. 95% CI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.37, 1.11) 0.43 (0.18, 1.07) 1.09 (0.60, 1.98) 0.10 (0.01, 0.87) 1.71 (0.74, 3.97) 0.65 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 [0.61, 15.56] 0.66 (0.27, 1.62) 1.11 [0.60, 2.06]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio IV. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Iui, JY 2016 Ma, JH 2016 Ma, JH 2016 Ma, JH 2016 Ma, JH 2011 Zhao, HX 2015 Zhu, L 2019 Total (95% CI)	427 5.74, df = : Z = 1.80 (Experint 62 60 22 42 42 33 3 48 67 46 141 21 70	11 (P = 0 P = 0.07 nental Total 30 73 127 51 100 41 60 155 122 143 40 97 1039	392 0.89); ² =) Contr Events 18 45 53 21 32 40 42 82 32 137 25 70	0% Total 30 50 91 33 80 41 60 152 74 143 40 100 894	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.0% 6.2% 21.6% 12.7% 1.7% 5.5% 11.5% 100.0%	Odds Ratio IV. Fixed. 35% CI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.27, 1.11) 0.93 (0.64, 1.07) 1.09 (0.60, 1.98) 1.71 (0.74, 3.97) 0.65 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 (0.61, 15.56) 0.66 (0.27, 162) 1.11 (0.60, 2.06) 0.77 (0.63, 0.95)	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pillai, DK 2011 Zhang, Y 2017 Zhang, Y 2017	427 5.74, df = . Z = 1.80 (Experin Events 111 62 60 22 42 42 33 48 67 46 141 21 70 623	11 (P = 0 P = 0.07 nental Total 30 73 127 51 100 41 60 155 122 143 40 97 1039	392 0.89); ² =) Contr Events 18 45 53 21 32 40 42 82 32 137 25 70 597	00 00 00 00 00 00 00 00 00 00	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.0% 6.2% 21.6% 12.7% 1.7% 5.5% 11.5% 100.0%	Odds Ratio [V. Fixed. 95% CI 0.39 [0.14, 1.09] 0.64 [0.23, 1.11] 0.43 [0.18, 1.07] 1.09 [0.60, 1.98] 0.10 [0.01, 0.87] 1.71 [0.74, 3.97] 0.65 [0.41, 1.02] 0.79 [0.44, 1.43] 3.09 [0.61, 15.56] 0.66 [0.27, 1.62] 1.11 [0.60, 2.06] 0.77 [0.63, 0.95]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pillai, DK 2011 Zhang, Y 2017 Zhang, Y 2017 Zhang, Y 2017 Zhang, Y 2017 Total (95% CI) Total events: Heterogeneity: Chi ² = Test for overall effect:	427 5.74, df = . Z = 1.80 (Experin Events 111 62 60 22 42 43 48 67 46 141 21 70 623 16.85, df = . Z = 2.41(. Z = 2.41(. Z = 1.80 (. Z = 1.80 (11 (P = 0, 07) nental Total 300 73 127 51 1000 41 60 155 1222 143 40 97 1039 = 11 (P = 0, 02)	392 0.89); ² =) Contr Events 18 45 53 21 32 40 42 82 32 32 32 40 42 82 32 32 57 70 597 0.11); ² =	0% Total Total 300 500 91 333 800 411 600 1522 74 1433 400 1000 894 35%	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 12.2% 12.7% 12.7% 1.7% 5.5% 11.5% 100.0%	Odds Ratio IV. Fixed. 95% CI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.37, 1.11) 0.64 (0.37, 1.11) 0.10 (0.01, 0.67) 1.71 (0.60, 1.98) 0.65 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 [0.61, 1.15.56] 1.11 (0.60, 2.06] 0.77 [0.63, 0.95]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Fixed, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Detmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pillai, DK 2011 Zhao, HX 2015 Zhu, L 2019 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	427 5.74, df = Z = 1.80 (Experin Events 11 62 60 22 42 33 48 67 46 141 21 70 623 16.85, df = Z = 2.41 (11 (P = 0.07 nental Total 30 73 127 51 100 41 60 155 122 143 40 97 1039 = 11 (P = P = 0.02	392 0.89); ² =) Contr Events 18 45 53 21 32 40 42 82 32 32 32 40 42 82 32 57 70 597 0.11); ² =)	0% Total 300 50 91 333 800 411 600 152 74 1433 400 100 894 35%	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.2% 21.6% 12.7% 1.7% 5.5% 11.5% 100.0%	Odds Ratio IV. Fixed. 95% CI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.37, 1.11) 1.09 (0.60, 1.98) 0.10 (0.01, 0.87) 1.71 (0.74, 3.97) 0.55 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 (0.61, 1.556) 0.66 (0.27, 1.62) 1.11 (0.60, 2.06) 0.77 [0.63, 0.95]	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio V. Fixed, 95% Cl 0.01 0.1 10 Favours [experimental] Favours [control]	50
D_	Total events Heterogeneity: Chi ² = Test for overall effect: Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Ismail, MF 2013 Ma, JH 2014 Maalmi, H 2013 Philai, DK 2011 Zhao, HX 2015 Zhu, L 2019 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	427 5.74, df = Z = 1.80 (Experin Events 11 62 60 22 42 33 48 67 46 141 21 70 623 16.85, df = Z = 2.41 (Experins Experins 62 62 62 62 62 62 62 62 62 62	11 (P = 0.07 nental Total 30 73 127 51 100 41 60 155 122 143 40 97 1039 = 11 (P = P = 0.02 mental Tota'	392 0.89); ² =) Contr Events 18 45 53 21 32 40 42 82 32 40 42 82 32 137 25 70 597 0.11); ² =) Contro 597 0.11); ² =	D% D Total 30 50 91 33 80 152 74 143 40 100 894 35%	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.0% 21.6% 12.7% 1.7% 5.5% 11.5%	Odds Ratio IV. Fixed. 35% CI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.37, 1.11) 0.43 (0.18, 1.07) 1.09 (0.60, 1.98) 1.71 (0.74, 3.97) 0.65 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 [0.61, 15.56] 0.66 (0.27, 1.62) 1.11 (0.60, 2.06] 0.77 [0.63, 0.95] Odds Ratio N Pandom 05%	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio V. Fixed .55% Cl .01 0.1 10 Favours [experimental] Favours [control] Odds Ratio Odds Ratio	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Ismail, MF 2013 Ma, JH 2016 Ma, JH 2016 Ma, JH 2016 Ma, JH 2016 Ma, JH 2011 Zhao, HX 2015 Zhu, L 2019 Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017	427 5.74, df = Z = 1.80 (Experint 62 60 60 22 42 33 48 67 46 67 46 623 16.85, df = Z = 2.41 (Experint Experint 0 0 0 0 0 0 0 0 0 0 0 0 0	111 (P = $P = 0.07$ nental Total 300 733 127 51 1000 41 100 155 122 1433 40 97 1039 = 11 (P = $P = 0.02$ nental Total 30	392 0.89); ² =) Contr Events 18 45 53 21 32 40 42 82 32 137 25 70 597 0.11); ² =) Contro Events 6	0% of Total 30 50 91 33 80 141 60 152 74 143 40 100 894 35% 0 Total 30 30 30 30 30 30 30 50 91 33 80 50 91 33 80 50 91 33 80 50 91 33 80 50 91 33 80 50 91 33 80 50 91 33 80 50 91 33 80 50 91 33 80 50 91 33 80 50 91 133 80 50 141 140 100 100 100 100 100 10	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 1.0% 21.6% 12.7% 1.5% 100.0% Weight 3.2%	Odds Ratio IV. Fixed. 35% CI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.27, 1.11) 0.93 (0.18, 1.07) 1.09 (0.60, 1.98) 1.71 (0.74, 3.97) 0.65 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 (0.61, 15.56) 0.66 (0.27, 1.62) 0.77 [0.63, 0.95] Odds Ratio <u>V. Random, 95% 1</u> 0.06 (0.00, 1.15)	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Fixed, 95% Cl 0.01 0.1 10 Favours [experimental] Favours [control] Odds Ratio N. Random, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pillai, DK 2011 Zhao, Y 2017 Zhao, Y 2	427 5.74, df = Z = 1.80 (Experin Events 11 62 60 22 42 33 348 67 46 141 21 70 623 16.85, df = Z = 2.41 (Experin Events 0 0	$\begin{array}{c} 111 \ (P=e \\ P=0.07 \\ \hline \ \ nental \\ \hline \ \ Total \\ 300 \\ 73 \\ 127 \\ 51 \\ 100 \\ 411 \\ 60 \\ 155 \\ 122 \\ 143 \\ 400 \\ 97 \\ \hline \ \ non \\ 97 \\ \hline \ non \\ \ non \ non \\ \ non \ non \\ \ non \\ \ non \\ \ non \ non \\ \ non \ non \ non \\ \ non \ n$	392 392; ² =) Contr Events 18 45 53 21 32 40 42 42 42 42 32 32 137 25 70 597 0.11); ² =) Contro Events 6 0 0	0% b Total 30 50 91 33 80 141 60 152 74 143 40 100 894 35% 1 1 1 2 3 5 1 1 1 1 1 1 1 1	Weight 4.0% 3.5% 14.8% 5.4% 12.2% 21.6% 12.7% 5.5% 11.5% 100.0% Weight 3.2%	Odds Ratio IV. Fixed. 95% CI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.37, 1.11) 0.43 (0.18, 1.07) 1.09 (0.60, 1.98) 0.10 (0.01, 0.87) 1.71 (0.74, 3.97) 0.65 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 (0.61, 1.55.6] 0.66 (0.27, 1.62) 1.11 (0.60, 2.06] 0.77 (0.63, 0.95] Odds Ratio IV. Random, 95% (0.06 (0.00, 1.15) Not estimable	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio IV. Fixed, 95% Cl 0.01 0.1 1 10 Favours [experimental] Favours [control] Odds Ratio IV. Random, 95% Cl	50
D _	Total events Heterogeneity: Chi ² = Test for overall effect: Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014 Ismail, MF 2013 Kilic, M 2019 Liu, Y 2016 Ma, JH 2014 Maalmi, H 2013 Pillai, DK 2011 Zhao, H 2015 Zhu, L 2019 Total (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Study or Subgroup Batmaz, SB 2017 Einisman, H 2015 Iordanidou, M 2014	427 5.74, df = Z = 1.80 (Experin 62 60 22 42 33 48 67 46 141 21 70 623 16.85, df = Z = 2.41 (Experin Events 0 0 6 6	111 (P = $P = 0.07$ neental Total 300 733 127 51 100 401 100 155 122 1433 400 97 1039 97 1039 97 1039 97 1039 97 1039 97 1039 97 1039 97 1039 97 1039 104 105 105 127 105 127 127 127 127 127 127 127 127	392 392 392 392 201 302 302 302 302 302 302 302 302	ov Total 30 50 91 33 80 41 60 152 74 143 40 100 894 335% 0 Total 30 50 91 30 50 91 152 74 155 50 894 30 50 894 30 50 894 30 50 894 30 50 894 30 50 894 30 50 894 30 50 895 805 805 805 805 805 805 805 80	Weight 4.0% 3.5% 14.8% 12.2% 1.0% 5.4% 12.7% 5.5% 11.5% 100.0% Weight 3.2% 9.6% 3.3*	Odds Ratio IV. Fixed. 95% cI 0.39 (0.14, 1.09) 0.63 (0.20, 1.93) 0.64 (0.37, 1.11) 1.09 (0.60, 1.98) 0.10 (0.01, 0.87) 1.71 (0.74, 3.97) 0.65 (0.41, 1.02) 0.79 (0.44, 1.43) 3.09 (0.64, 1.556) 0.66 (0.27, 1.62) 1.11 (0.60, 2.06] 0.77 (0.63, 0.95] Odds Ratio IV. Random, 95% d 0.06 (0.00, 1.15) Not estimably 0.51 (0.71, 1.54) Not estimably 0.51 (0.71, 1.54) 0.03 (0.00, 0.25)	0.02 0.1 10 Favours [experimental] Favours [control] Odds Ratio IV, Fixed, 95% CI 0 0 0 0 0 0 0 0 0 0 0 0 0	50
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FIGURE 5 | Forest plot for meta-analyzing the association between Vitamin D receptor Fokl (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

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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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