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REVIEW

Interleukin-10 Gene Promoter Polymorphisms and Susceptibility to Asthma: Systematic Review and Meta-analysis

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Abstract

Several studies have previously assessed the association between *interleukin* (*IL*)-*10* gene polymorphisms and the risk of asthma, leading to conflicting results. To resolve the incongruent outcomes yielded from different single studies, we conducted the most up-to-date meta-analysis of the *IL-10* gene rs1800896, rs1800871, and rs1800872 single-nucleotide polymorphisms (SNPs) and susceptibility to asthma. A systematic literature search performed until April 2020, and the pooled odds ratio (OR) and their corresponding 95% confidence interval (CI) were calculated to determine the association strength. Thirty articles comprising 5678 asthmatic patients and 6079 controls met the inclusion criteria. No significant association was found between rs1800872 SNP and susceptibility to asthma across all genetic models in the overall and subgroup analyses. The rs1800871 SNP had only significant association with a decreased risk of asthma in Europeans (OR 0.66, CI 0.53–0.82, $P < 0.001$). However, rs1800896 SNP was significantly associated with a decreased risk of asthma by dominant (OR 0.67, CI 0.50–0.90, $P < 0.001$) and heterozygote (OR 0.66, CI 0.49–0.88, $P < 0.001$) models in the overall analysis. Subgroup analyses indicated significant association of rs1800896 SNP by dominant (OR 0.45, CI 0.28–0.72, $P < 0.001$) and heterozygote (OR 0.43, CI 0.26–0.70, $P < 0.001$) models in the African population. The *IL-10* rs1800896 SNP confers protection against the risk of asthma, especially in Africans. Additionally, rs1800871 SNP has a protective role against asthma in Europeans.

Keywords Asthma · Interleukin-10 · Polymorphism · Gene association · Meta-analysis

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Abbreviations

IL-10	Interleukin-10
SNP	Single-nucleotide polymorphism
IL	Interleukin
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
NOS	Newcastle–Ottawa Scale
OR	Odds ratio
CI	Confidence interval
AHR	Airway hyperresponsiveness
Ig	Immunoglobulin
Th2	Helper T
Treg	Regulatory T
IBS	Irritable bowel syndrome
HWE	Hardy–Weinberg equilibrium
FEM	Fixed-effect model
REM	Random-effects models

Introduction

Asthma is a chronic inflammatory disease that is characterized by recurrent attacks of breathlessness, wheezing, chest tightness, airflow obstruction, and airway hyperresponsiveness (AHR). The disease affects children and young adults with varying severity and frequency (Boulet et al. 2012; Makoui et al. 2020). Asthma is the most common allergic disease, and the prevalence of this disease has been increased markedly across the world, with an approximately 250,000–345,000 death cases annually (Bahadori et al. 2009). The pathogenesis of asthma is complex, and several studies implicated that traditional risk factors, including age, allergen, pollution, infections, and smoking interact with susceptibility genetic factors during asthma development (Maddox and Schwartz 2002; Miller and Ho 2008).

A bulk of cytokines and immune cells promote an inflammatory setting in the asthmatic patients (Kim et al. 2010). The disease displays an inflammatory immune response with a noticeable rise in the level of serum immunoglobulin (Ig) E and helper T (Th2) cytokines, including interleukin (IL)-4 and IL-13. These cytokines, in turn, promote class switching of antibody to IgE and further production of this antibody class by B cells (Fahy 2015). Regulatory T (Treg) cells play a pivotal role in coordinating immune responses to maintain and acquire tolerance toward allergens through several mediators, especially IL-10 (Rivas and Chatila 2016). IL-10 is a cytokine that illustrates pleiotropic immunoregulatory and anti-inflammatory effects and contributes to the homeostasis of immune system (Barnes 2008).

To date, scientists have found many candidate genes associated with asthma susceptibility. Among these risk genes, researchers extensively studied *IL-10* single-nucleotide polymorphisms (SNPs) (Huang et al. 2016). Studies have reported several polymorphic sites within the promoter region of the *IL-10* gene. Growing evidence suggests that three SNPs of the *IL-10* gene at positions 1082A/G (rs1800896 or −1087A/G or −1117A/G), 819T/C (rs1800871 or −892C/T or −854C/T), and

592C/A (rs1800872 or −571C/A or −597C/A or −627C/A) located in the transcription initiation site are involved in regulation of the expression of *IL-10* gene (Lazarus et al. 2002; Vázquez-Villamar et al. 2016). The A allele of rs1800896 SNP correlates with low IL-10 levels, whereas G allele of this polymorphism associates with increased IL-10 transcription (Barnes 2008; Nie et al. 2012; Turner et al. 1997). Additionally, IL-10 levels in the plasma and peripheral blood mononuclear cells (PBMCs) of the irritable bowel syndrome (IBS) subjects with CT genotype for rs1800896 were significantly higher than those in the TT genotype subjects (Zhu et al. 2019). The −819 C-to-T substitution is a dimorphic polymorphism and may change an estrogen-responsive factor (Lazarus et al. 1997). Also, the C-to-T shift at position −819T/C (rs1800871) was associated with a high level of the total serum IgE by decreasing the expression of *IL-10* gene (Zhang et al. 2002). The −592C/A variation is a C-to-A substitution that lies within a region that plays a negative regulatory function in the transcription of *IL-10* gene (Kube et al. 1995). This polymorphism was shown to be correlated with increased total serum IgE level in homozygote or heterozygote asthmatics (Hobbs et al. 1998), while the CC genotype was associated with a higher level of serum IL-10 than AA genotype (Jin et al. 2013).

Several studies examined the association between polymorphisms of the *IL-10* gene and susceptibility to asthma. However, the results of these researches were inconclusive due to small sample sizes, clinical heterogeneity, and low statistical power (Hyun et al. 2013; Nie et al. 2012; Zheng et al. 2010). To offset these limitations, we performed the most up-to-date meta-analysis (by including several recent original works) to investigate whether *IL-10* gene polymorphisms play a significant role in susceptibility to asthma.

Methods

The present meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2010). This article does not contain any study involving human participants or animals.

Search Strategy

In order to retrieve all potential publications that consider the association between *IL-10* gene polymorphisms (rs1800872, rs1800871, and rs1800896) and susceptibility to asthma, we conducted a comprehensive search through Scopus and Medline. The search covered publications from inception to April 2020. We use combination of the following keywords and medical subject headings (MeSH) terms during search in databases: ("asthma" [MeSH] OR "asthmatic") AND ("interleukin-10" OR "*IL10*" OR "IL-10") AND ("single-nucleotide polymorphism" OR "SNP" OR "polymorphisms" OR "mutation" OR "variation"). Besides, we screened references of eligible studies for additional potentially relevant studies.

Inclusion and Exclusion Criteria

Publications considered eligible if they met the following inclusion criteria: (a) publications with case and control groups (case–control design and cohort design); (b) publications reporting sufficient data to extract or to calculate risk estimates with 95% CI; (c) publications that evaluate the association between *IL-10* gene polymorphism and the risk of asthma as the primary outcome; and (d) publications that report genotype or allele distributions of the case and healthy individuals. We excluded duplicated articles as well as those that were reviews, irrelevant, meta-analysis, and book chapters. The application of these criteria results in 22, 11, and18 qualified studies for rs1800872, rs1800871, and rs1800896, respectively.

Data Extraction and Quality Assessment

We exported all retrieved publications to an EndNote library and final eligible studies were selected after duplicates exclusion. Two independent reviewers performed article screening and data extraction. The publications were screened by title, abstract, and full-text examination. Eventually, the data of the eligible studies were extracted as follows: the first author's last name, journal, year of publication, country of origin, ethnicity, number of subjects in the case and control groups, mean or range of age, genotyping method, and genotype counts in both case and control groups. In case the final extracted file by two reviewers was not similar, they discussed to resolve the discrepancies by consensus. The quality of each study was assessed using the Newcastle–Ottawa Scale (NOS) (Stang 2010). Studies with scores 0–3, 4–6, or 7–9 were considered of low, moderate, or high-quality, respectively.

Statistical Analysis

We conducted Pearson's χ^2 test to examine Hardy–Weinberg equilibrium (HWE) in the healthy control group. The strength of the association between SNPs and asthma risk was assessed by estimating odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) in five genetic models for each SNP: dominant model (AA+AC vs. CC), recessive model (AA vs. CC+CA), allelic model (A vs. C), homozygote model (AA vs. CC), and heterozygotes model (CA vs. CC) for rs1800872 SNP; dominant model (TT+TC vs. CC), recessive model (TT vs. CC+CT), allelic model (T vs. C), homozygote model (TT vs. CC), and heterozygotes model (CT vs. CC) for rs1800871 SNP; dominant model (GG+GA vs. AA), recessive model (GG vs. GA+AA), allelic model (G vs. A), homozygote model (GG vs. AA), and heterozygotes model (AG vs. AA) for rs1800896 SNP. A chi-square-based *Q*-test and I^2 test were used to estimate the between-study heterogeneity. In case of heterogeneity (*P*-value of <0.1 for the *Q*-test or $I^2>50\%$), the random-effects models (REM) was employed for meta-analysis; otherwise, fixed-effect model (FEM) was applied (DerSimonian and Laird 1986; Mantel and Haenszel 1959). We performed subgroup analysis and meta-regression analysis based on

year of publication and ethnicity to assess the pre-defined sources of heterogeneity among included studies. Potential publication bias was estimated using both Begg's test and Egger's test (Begg and Mazumdar 1994; Egger et al. 1997). Furthermore, the funnel plot asymmetry was assessed according to the Begg's test (P-value < 0.05 considered statistically significant). We applied sensitivity analysis in order to evaluate the influence of individual studies on the pooled OR. Stata statistical software (version 14.0; Stata Corporation, College Station, TX, USA) was used for quantitative analysis and preparation of figures and calculation of OR was conducted using SPSS (version 23.0; SPSS, Inc. Chicago, IL, USA).

Results

Study Characteristics

The search and screening process were conducted based on the PRISMA statement depicted in the Fig. 1. In detail, the initial search generated 640 publications. Then, duplicates ($n = 72$), which were the same among the databases, were omitted, and the remaining articles were excluded either by title and abstracts ($n = 473$) or full-text ($n = 65$) evaluations. Ultimately, 30 publications were recognized as eligible and were included in the quantitative analysis (Bo et al. 2011; Cárdaba et al. 2014; Chatterjee et al. 2005; Daley et al. 2009; Gaddam et al. 2012; Hakimizadeh et al. 2012; Hákonarson et al. 2001; Hang et al. 2003; Hsia et al. 2015; Hussein et al. 2011, 2014; Jahromi et al. 2015; Ji et al. 2004; Kadhem and Darweesh 2017; Karjalainen et al. 2003; Kim et al. 2011; Li et al. 2006, 2007; Lim et al. 1998; Movahedi et al. 2008; Park et al. 2004; Schubert et al. 2006; Smolnikova et al. 2013; Trajkov et al. 2008; Undarmaa et al. 2010; Xie 2012; Xu et al. 2014; Yucesoy et al. 2016; Zedan et al. 2008; Zhang et al. 2002). The references of all eligible publications were cross-checked, and no further records were found to meet the inclusion criteria. All eligible studies were published between 2001 and 2017 and had an overall good methodological quality with NOS scores ranging from 6 to 8. Tables 1 and 2 summarize the characteristics and genotype frequency of the included studies, respectively.

Quantitative Synthesis

Meta-analysis of rs1800872 and the Risk of Asthma

Twenty-two studies involving 3629 cases and 4255 controls were included in the final analysis of association between rs1800872 SNP and risk of asthma (Bo et al. 2011; Cárdaba et al. 2014; Chatterjee et al. 2005; Daley et al. 2009; Gaddam et al. 2012; Hakimizadeh et al. 2012; Hákonarson et al. 2001; Hang et al. 2003; Hsia et al. 2015; Ji et al. 2004; Karjalainen et al. 2003; Kim et al. 2011; Li et al. 2006, 2007; Movahedi et al. 2008; Park et al. 2004; Schubert et al. 2006; Smolnikova et al. 2013; Trajkov et al. 2008; Undarmaa et al. 2010; Xie 2012). Among these studies, 15 studies were carried out on Asians, 6 studies on Europeans,

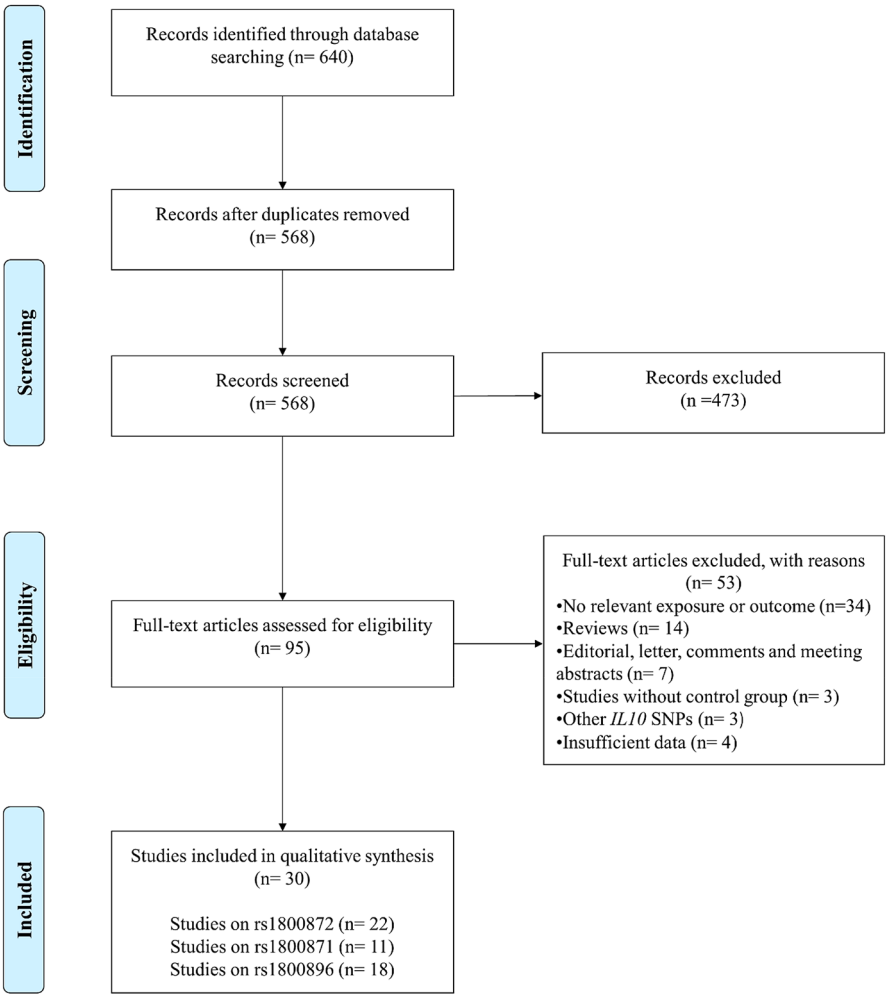

Fig. 1 Flow diagram of the study selection process

and 1 study on Australians. Since there was only one study from Australia, it was omitted from subgroup analysis. The pooled OR did not show association between rs18000872 SNP and asthma risk under all genotype models, including dominant model (OR 1.03, 95% CI 0.81–1.30, $P = 0.80$; Fig. 2a), recessive model (OR 1.10, 95% CI 0.86–1.40, $P = 0.45$), allelic model (OR 1.07, 95% CI 0.91–1.26, $P = 0.38$), homozygote model (OR 1.07, 95% CI 0.79–1.44, $P = 0.67$), and heterozygote model (OR 0.95, 95% CI 0.73–1.23, $P = 0.68$). The results also indicated that there were no significant associations between rs18000872 SNP and asthma risk in the subgroup analysis based on atopic status and ethnicity. The results of pooled ORs, heterogeneity tests, and publication bias tests in different analysis models are shown in the Table 3.

Table 1 Characteristics of studies included in a meta-analysis of overall asthma

Study author	Year	Country	Ethnicity	Atopic status	Total cases/controls	Age Case/control (Mean)	Quality score
IL-10 (rs 1800872)							
Hakonarson et al.	2001	Iceland	European	Atopic	94/94	38/NR	5
Hang et al.	2003	China	Asian	Atopic	117/60	22.7 ± 16.6/20.8 ± 2.7	5
Karjalainen et al.	2003	Finland	European	Non-atopic	242/395	59 ± 11/60 ± 11	7
Ji et al.	2004	China	Asian	Non-atopic	147/184	NR/NR	6
Park et al.	2004	Korea	Asian	Mixed	532/170	37.2/28.7	7
Chatterjee et al.	2005	India	Asian	Atopic	167/304	22.96 ± 12/30.05 ± 15	7
Li et al.	2006	China	Asian	Non-atopic	50/36	NR/NR	5
Schubert et al.	2006	Germany	European	Non-atopic	231/273	5–18/NR	7
Li et al.	2007	China	Asian	Non-atopic	30/26	NR/NR	5
Movahedi et al.	2008	Iran	Asian	Non-atopic	59/140	NR/NR	5
Trajkov et al.	2008	Macedonia	European	Non-atopic	74/299	NR/NR	6
Daley et al.	2009	Australia	Oceania	Non-atopic	643/750	NR/NR	8
Undarmaa et al.(i)	2010	Japan	Asian	Atopic	325/336	NR/NR	8
Undarmaa et al.(ii)	2010	Japan	Asian	Atopic	367/676	NR/NR	8
Kim et al.	2011	Korea	Asian	Atopic	333/248	11.48 ± 4.06/11.40 ± 4.33	7
Wei et al.	2011	China	Asian	NR	186/198	NR/NR	6
Hakimzadeh et al.	2012	Iran	Asian	Non-atopic	100/100	48 ± 12/43 ± 14	5
Gaddam et al.	2012	India	Asian	NR	94/100	32.4/NR	5
Xie et al.	2012	China	Asian	NR	110/63	NR/NR	5
Smolnikova et al.	2013	Russia	European	Atopic	64/50	13.36 ± 2.24/14.8 ± 0.68	5
Cardaba et al.	2014	Spain	European	Atopic	109/50	22.9 ± 7.1/NR	5
Hsia et al.	2015	China	Asian	NR	198/453	> 25/> 25	7

Table 1 (continued)

Study author	Year	Country	Ethnicity	Atopic status	Total cases/controls	Age Case/control (Mean)	Quality score
IL-10 (rs1800871)							
Zhang et al.	2002	China	Asian	Non-atopic	336/106	NR/NR	5
Karjalainen et al.	2003	Finland	European	Non-atopic	242/395	59 ± 11/60 ± 11	7
Chatterjee et al.	2005	India	Asian	Atopic	269/305	22.96 ± 12/30.05 ± 15	7
Li et al.	2007	China	Asian	Non-atopic	30/26	NR/NR	5
Movahedi et al.	2008	Iran	Asian	Non-atopic	59/140	NR/NR	5
Trajkov et al.	2008	Macedonia	European	Non-atopic	74/299	NR/NR	6
Kim et al.	2011	Korea	Asian	Atopic	333/248	11.48 ± 4.06/11.40 ± 4.33	7
Xu et al.	2014	China	Asian	NR	200/189	NR/NR	7
Hsia et al.	2015	China	Asian	NR	198/453	> 25/> 25	7
Raeiszadeh et al.	2015	India	Asian	Mixed	419/393	NR/NR	8
Yucesoy et al.	2015	Canada	American	NR	93/141	42.4 ± 1.24/30.4 ± 0.63	5
IL-10 (rs 1800896)							
Zhang et al.	2002	China	Asian	Non-atopic	336/106	NR/NR	5
Karjalainen et al.	2003	Finland	European	Non-atopic	242/395	59 ± 11/60 ± 11	7
Park et al.	2004	Korea	Asian	Mixed	532/170	37.2/28.7	7
Chatterjee et al.	2005	India	Asian	Atopic	265/295	22.96 ± 12/30.05 ± 15	7
Li et al.	2007	China	Asian	Non-atopic	30/26	NR/NR	5
Movahedi et al.	2008	Iran	Asian	Non-atopic	59/122	NR/NR	5
Trajkov et al.	2008	Macedonia	European	Non-atopic	74/299	NR/NR	6
Zedan et al.	2008	Egypt	African	Atopic	69/98	NR/NR	5
Daley et al.	2009	Australia	Oceania	Non-atopic	643/751	NR/NR	8
Hussein et al.	2011	Egypt	African	Mixed	220/110	8.6 ± 2.7/10.5 ± 2.3	6
Kim et al.	2011	Korea	Asian	Atopic	333/248	11.48 ± 4.06/11.40 ± 4.33	7

Table 1 (continued)

Study author	Year	Country	Ethnicity	Atopic status	Total cases/controls	Age Case/control (Mean)	Quality score
Cardaba et al.	2014	Spain	European	Atopic	109/50	22.9 ± 7.1/NR	5
Hussein et al.	2014	Saudi Arabia	Asian	Atopic	200/50	10.12 ± 2.24/10.83 ± 2.65	6
Xu et al.	2014	China	Asian	NR	200/189	NR/NR	7
Hsia et al.	2015	China	Asian	NR	198/435	> 25/> 25	7
Raeiszadeh et al.	2015	India	Asian	Mixed	419/393	NR/NR	8
Yucesoy et al.	2015	Canada	American	NR	93/142	42.4 ± 1.24/30.4 ± 0.63	5
Kadhem and Darweesh	2017	Iraq	Asian	NR	40/40	14–50/14–48	5

NR not reported

Table 2 Distribution of genotype and allele among asthma patients and controls

Study author	Asthma cases					Healthy control					P-HWE	MAF
	CC	CA	AA	C	A	CC	CA	AA	C	A		
IL-10 (rs 1800872)												
Hakonarson et al.	59	31	4	149	39	61	30	3	152	36	0/765	0/191
Hang et al.	6	58	53	70	164	11	22	27	44	76	0/102	0/633
Karjalainen et al.	146	84	12	376	108	232	142	21	606	184	0/904	0/233
Ji et al.	74	49	24	197	97	117	54	13	288	80	0/062	0/217
Park et al.	58	235	239	351	713	22	78	70	122	218	0/97	0/641
Chatterjee et al.	79	36	52	194	140	115	141	48	371	237	0/662	0/390
Li et al.	6	24	20	36	64	3	17	16	23	49	0/605	0/681
Schubert et al.	131	86	14	348	114	145	109	19	399	147	0/808	0/269
Li et al.	6	17	7	29	31	7	9	10	23	29	0/128	0/558
Movahedi et al.	1	58	0	60	58	71	57	12	199	81	0/907	0/289
Trajkov et al.	35	33	6	103	45	154	117	28	425	173	0/402	0/289
Daley et al.	372	233	38	977	309	461	254	35	1176	324	0/996	0/659
Undarmaa et al.(i)	30	141	154	201	449	39	151	146	229	443	0/935	0/653
Undarmaa et al.(ii)	44	167	156	255	479	81	307	288	469	883	0/47	0/661
Kim et al.	44	143	146	231	435	31	106	111	168	328	0/068	0/669
Wei et al.	22	89	75	133	239	16	99	83	131	265	0/23	0/500
Hakimzadeh et al.	69	21	10	159	41	22	56	22	100	100	0/338	0/440
Gaddam et al.	19	12	63	50	138	29	54	17	112	88	0/004	0/667
Xie et al.	9	78	23	96	124	2	38	23	42	84	0/29	0/130
Smolnikova et al.	40	19	5	99	29	37	13	0	87	13	0/448	0/280
Cardaba et al.	62	43	4	167	51	27	18	5	72	28	0/136	0/709
Hsia et al.	21	79	98	121	275	45	174	234	264	642	0/765	0/191
Study author	Asthma cases					Healthy control					P-HWE	MAF
	CC	CT	TT	C	T	CC	CT	TT	C	T		
IL-10 (rs1800871)												
Zhang et al.	*	*	*	126	210	*	*	*	42	64	–	0/650
Karjalainen et al.	146	84	12	376	108	232	142	21	606	249	0/904	0/233
Chatterjee et al.	76	144	49	296	242	107	147	51	361	29	0/966	0/408
Li et al.	6	17	7	29	31	7	9	10	23	81	0/128	0/558
Movahedi et al.	2	57	0	61	57	71	57	12	199	163	0/907	0/289
Trajkov et al.	35	32	7	102	46	155	125	19	435	334	0/348	0/273
Kim et al.	40	138	155	218	448	27	108	113	162	265	0/875	0/673
Xu et al.	20	87	93	127	273	18	77	94	113	645	0/700	0/701
Hsia et al.	9	64	125	82	314	48	165	240	261	356	0/017	0/712
Raeiszadeh et al.	138	195	86	471	367	126	178	89	430	81	0/088	0/453
Yucesoy et al.	56	31	6	143	43	72	57	12	201	0	0/879	0/287

Table 2 (continued)

Study author	Asthma cases					Healthy control					P-HWE	MAF
	AA	AG	GG	A	G	AA	AG	GG	A	G		
IL-10 (rs 1800896)												
Zhang et al.	*	*	*	299	37	*	*	*	94	12	–	0/127
Karjalainen et al.	72	121	49	265	219	123	201	71	447	343	0/478	0/434
Park et al.	460	69	3	989	75	135	33	2	303	37	0/991	0/109
Chatterjee et al.	159	91	15	409	121	150	122	23	422	168	0/792	0/285
Li et al.	20	8	2	48	12	16	7	3	39	13	0/150	0/25
Movahedi et al.	0	59	0	59	59	53	57	12	163	81	0/555	0/332
Trajkov et al.	31	32	11	94	54	70	212	17	352	246	≤0.001	0/411
Zedan et al.	11	39	19	61	77	8	85	5	101	95	≤0.001	0/485
Daley et al.	160	320	163	640	646	186	376	189	748	754	0/970	0/502
Hussein et al.	82	90	48	254	186	23	54	33	100	120	0/916	0/545
Kim et al.	291	40	2	622	44	215	30	3	460	36	0/110	0/073
Cardaba et al.	39	42	28	120	98	21	22	7	64	36	0/749	0/36
Hussein et al.	75	86	39	236	164	8	25	17	41	59	0/812	0/59
Xu et al.	161	39	0	361	39	73	108	8	254	124	≤0.001	0/328
Hsia et al.	151	38	9	340	56	353	83	17	789	117	≤0.001	0/129
Raeiszadeh et al.	244	148	27	636	202	238	135	20	611	175	0/879	0/223
Yucesoy et al.	21	45	27	87	99	22	81	39	125	159	0/060	0/56
Kadhem and Darweesh	2	29	9	33	47	3	17	20	23	57	0/813	0/713

P-HWE the *P*-value for Hardy–Weinberg equilibrium, *MAF* the minor allele frequency of the control group

*Only allele frequency available

Meta-analysis of rs1800871 and the Risk of Asthma

Overall, 11 studies containing 1917 cases and 2589 healthy controls were found to be eligible and included for quantitative analysis of association between rs1800871 SNP and asthma risk (Chatterjee et al. 2005; Hsia et al. 2015; Jahromi et al. 2015; Karjalainen et al. 2003; Kim et al. 2010; Li et al. 2006; Movahedi et al. 2008; Trajkov et al. 2008; Xu et al. 2014; Yucesoy et al. 2016; Zhang et al. 2002). Among them, eight studies were on Asians, two studies on Europeans, and only one study on Americans, which was excluded from the subgroup analysis. The pooled OR showed no significant association between rs1800871 SNP and asthma risk across all genotype models, including dominant model (OR 1.23, 95% CI 0.90–1.68, $P=0.19$; Fig. 2b), recessive model (OR 1.05, 95% CI 0.90–1.22, $P=0.52$), allelic model (OR 1.25, 95% CI 0.67–2.35, $P=0.47$), homozygote model (OR 1.07, 95% CI 0.87–1.33, $P=0.50$), and heterozygote model (OR 1.26, 95% CI 0.91–1.74, $P=0.17$). Additionally, the results of subgroup analysis (based on ethnicity and atopic status) were not statistically significant and rejected the association between rs1800871 SNP and asthma risk,

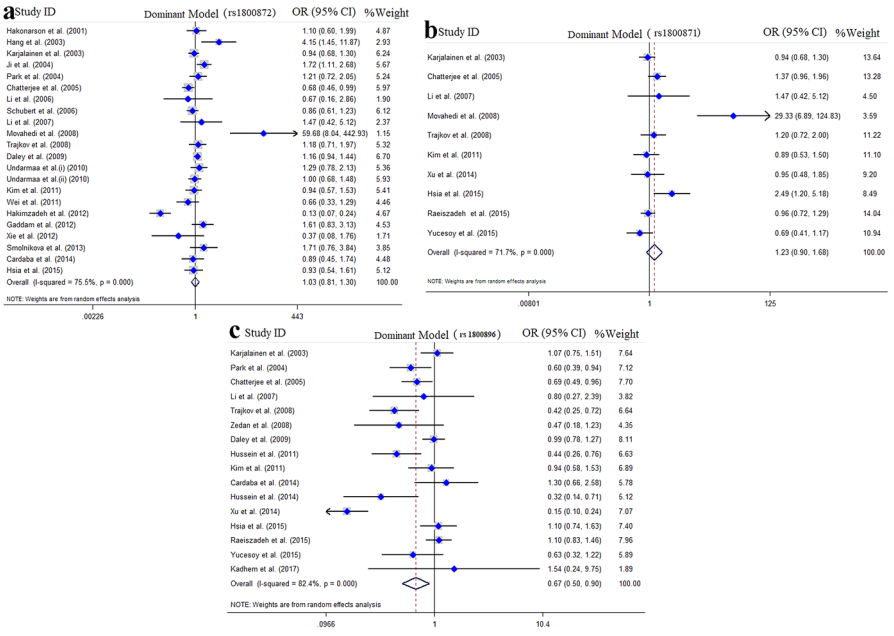

Fig. 2 Pooled odds OR and 95% confidence interval of individual studies and pooled data for the association between *IL-10* gene polymorphism and the risk of asthma in overall populations. The dashed vertical line is the overall OR. **a** Dominant model (rs1800872), **b** dominant model (rs1800871), **c** dominant model (rs1800896)

except for significant association of the allelic model of rs1800871 SNP with a decreased risk of asthma in Europeans (OR 0.66, CI 0.53–0.82, $P < 0.001$). The results of pooled ORs, heterogeneity tests, and publication bias tests in different analytic models are shown in the Table 3.

Meta-analysis of rs1800896 and the Risk of Asthma

Herein, 18 studies were included for analysis of association between rs1800896 SNP and risk of asthma (Cárdaba et al. 2014; Chatterjee et al. 2005; Daley et al. 2009; Hsia et al. 2015; Hussein et al. 2014; Hussein et al. 2011; Jahromi et al. 2015; Kadhem and Darweesh 2017; Karjalainen et al. 2003; Kim et al. 2011; Li et al. 2007; Movahedi et al. 2008; Park et al. 2004; Trajkov et al. 2008; Xu et al. 2014; Yucesoy et al. 2016; Zedan et al. 2008; Zhang et al. 2002). A total of 3894 cases and 3884 controls were included in the quantitative analysis. Of eligible studies, 11 studies were on Asians, 2 studies on Africans, 3 studies on Europeans, and one study was on each Australian and American populations. Since there was only one study from Australia and America, they were omitted from subgroup analysis. Our results showed that rs1800896 SNP was associated with decrease risk of asthma across dominant model (OR 0.67, 95% CI 0.50–0.90, $P < 0.001$; Fig. 2c) and heterozygote model (OR 0.66, 95% CI 0.49–0.88, $P < 0.001$), but not recessive model (OR 1.03, 95% CI 0.79–1.40, $P = 0.19$), allelic model (OR

Table 3 Main results of pooled ORs in a meta-analysis of *IL-10* gene polymorphisms

Subgroup	Genetic model	Sample size	Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
		Case/control	OR	95% CI (*P*-value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
IL-10 (rs 1800872)										
Overall	Dominant model	4272/5005	1.03	0.81–1.30 (0.80)	75.5	≤0.001	− 1.88	0.06	− 1.02	0.13
	Recessive model	4272/5005	1.10	0.86–1.40 (0.45)	76.2	≤0.001	− 1.88	0.06	− 1.42	0.06
	Allelic model	4272/5005	1.07	0.91–1.26 (0.38)	80.6	≤0.001	− 1.52	0.12	− 1.90	0.09
	Homozygote model	4272/5005	1.07	0.79–1.44 (0.67)	69.7	≤0.001	− 0.68	0.49	− 0.59	0.61
	Heterozygote model	4272/5005	0.95	0.73–1.23 (0.68)	77.6	≤0.001	0.45	0.65	0.54	0.61
Subgroup										
Asian	Dominant model	2815/3094	1.04	0.70–1.55 (0.83)	82.6	≤0.001	− 0.15	0.88	0.23	0.83
	Recessive model	2815/3094	1.16	0.86–1.56 (0.33)	82.2	≤0.001	1.35	0.17	1.24	0.26
	Allelic model	2815/3094	1.08	0.86–1.35 (0.50)	86.2	≤0.001	0.60	0.54	0.48	0.64
	Homozygote model	2815/3094	1.11	0.75–1.66 (0.59)	77.6	≤0.001	0.48	0.62	0.68	0.50
	Heterozygote model	2815/3094	0.93	0.59–1.45 (0.74)	83.9	≤0.001	1.39	0.16	1.89	0.07
European	Dominant model	814/1161	0.99	0.82–1.19 (0.90)	0	0.68	0.02	0.98	− 0.23	0.81
	Recessive model	814/1161	0.84	0.56–1.26 (0.39)	0	0.71	0.91	0.35	1.15	0.26
	Allelic model	814/1161	0.98	0.84–1.15 (0.81)	4	0.39	− 0.52	0.60	− 1.20	0.44
	Homozygote model	814/1161	0.84	0.55–1.27 (0.39)	0	0.72	− 0.68	0.49	− 0.59	0.61
	Heterozygote model	814/1161	1	0.82–1.21 (0.97)	0	0.87	0.45	0.65	0.54	0.61
Atopic	Dominant model	1576/1818	1.08	0.82–1.43 (57)	49.9	0.05	1.34	0.18	0.23	0.82
	Recessive model	1576/1818	1.15	0.86–1.54 (0.34)	62.3	0.01	1.46	0.14	1.35	0.22
	Allelic model	1576/1818	1.07	0.96–1.19(0.22)	0	0.44	− 1.36	0.17	− 1.69	0.22
	Homozygote model	1576/1818	1.22	0.88–1.69 (0.24)	40.5	0.12	0.49	0.62	− 0.28	0.79
	Heterozygote model	1576/1818	1.04	0.69–1.56 (0.84)	72.6	≤0.001	1.24	0.21	0.74	0.48
Non-atopic	Dominant model	1576/2203	1.01	0.63–1.63 (96)	87.9	≤0.001	1.48	0.13	0.81	0.44

Table 3 (continued)

Subgroup	Genetic model	Sample size	Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
		Case/control	OR	95% CI (*P*-value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
	Recessive model	1576/2203	0.94	0.64–1.39 (0.75)	52.9	0.03	0	1	− 0.34	0.75
	Allelic model	1576/2203	0.99	0.71–1.38 (0.94)	87.6	≤0.001	0.49	0.62	− 0.56	0.61
	Homozygote model	1576/2203	0.86	0.47–1.56 (0.61)	75.5	≤0.001	1.57	0.11	1.09	0.29
	Heterozygote model	1576/2203	1.03	0.64–1.67 (0.90)	86.6	≤0.001	1.24	0.21	0.39	0.70
IL-10 (rs1800871)										
Overall	Dominant model	1917/2589	1.23	0.90–1.68 (0.19)	71.7	≤0.001	0.37	0.10	1.84	0.13
	Recessive model	1917/2589	1.05	0.90–1.22 (0.52)	13.8	0.31	0.94	0.34	1.64	0.17
	Allelic model	1917/2589	1.25	0.67–2.35 (0.47)	97.2	≤0.001	0.98	0.32	2.59	0.08
	Homozygote model	1917/2589	1.07	0.87–1.33 (0.50)	25.4	0.21	0.56	0.57	1.87	0.13
	Heterozygote model	1917/2589	1.26	0.91–1.74 (0.17)	71.4	≤0.001	0.52	0.60	0.94	0.52
Subgroup										
Asian	Dominant model	1508/1754	1.53	0.96–2.43 (0.07)	77.8	≤0.001	1.05	0.29	2.26	0.07
	Recessive model	1508/1754	1.05	0.90–1.24 (0.52)	37.8	0.15	0.63	0.53	0.31	0.76
	Allelic model	1508/1754	1.48	0.71–3.12 (0.29)	97.3	≤0.001	0.09	0.92	− 0.12	0.90
	Homozygote model	1508/1754	1.09	0.87–1.38 (0.45)	43.2	0.11	0.25	0.80	0.33	0.75
	Heterozygote model	1508/1754	1.60	0.98–2.62 (0.06)	77.7	≤0.001	0	1	− 0.38	0.71
European	Dominant model	316/694	1.01	0.76–1.32 (0.96)	0	0.42	0.98	0.32	2.19	0.08
	Recessive model	316/694	1.13	0.64–2 (0.66)	27.2	0.19	0.56	0.57	1.87	0.13
	Allelic model	316/694	**0.66**	**0.53–0.82 (≤0.001)**	**0**	**0.45**	0.49	0.62	2	0.13
	Homozygote model	316/694	1.14	0.64–2.03 (0.66)	0	0.33	0.94	0.34	1.27	0.27
	Heterozygote model	316/694	0.99	0.74–1.32 (0.95)	0	0.56	0.52	0.60	0.63	0.64

Table 3 (continued)

Subgroup	Genetic model	Sample size	Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
		Case/control	OR	95% CI (*P*-value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
Atopic	Dominant model	602/553	1.16	0.77–1.74 (0.48)	43.8	0.18	0.52	0.60	1.18	0.44
	Recessive model	602/553	1.07	0.82–1.38 (0.63)	0	0.81	0.98	0.32	2.01	0.08
	Allelic model	602/553	3.55	0.46–27 (0.22)	98.6	≤0.001	1.98	0.04	2.44	0.02
	Homozygote model	602/553	1.14	0.79–1.64 (0.47)	2.7	0.31	1.87	0.06	1.79	0.08
	Heterozygote model	602/553	1.14	0.73–1.79 (0.56)	47.9	0.16	1.14	0.25	0.72	0.48
Non-atopic	Dominant model	405/860	2.05	0.83–5.10 (0.12)	85.7	≤0.001	− 0.68	0.49	− 0.59	0.61
	Recessive model	405/860	0.96	0.58–1.60 (0.88)	15.7	0.30	0.45	0.65	0.54	0.61
	Allelic model	405/860	0.72	0.51–1.03 (0.07)	73.7	≤0.001	1.55	0.11	0.60	0.16
	Homozygote model	405/860	1.09	0.63–1.86 (0.76)	0	0.57	1.01	0.31	1.44	0.18
	Heterozygote model	405/860	2.38	0.87–6.52 (0.09)	87.3	≤0.001	0.83	0.40	0.64	0.54
IL-10 (rs 1800896)										
Overall	Dominant model	3894 /3884	**0.67**	**0.50–0.90 (≤0.001)**	**82.4**	≤0.001	1.47	0.14	2.01	0.13
	Recessive model	3894 /3884	1.03	0.76–1.40 (0.19)	65.5	≤0.001	2.47	0.01	2.38	0.1
	Allelic model	3894 /3884	0.85	0.69–1.03 (0.09)	82.5	≤0.001	− 0.42	0.67	− 0.48	0.64
	Homozygote model	3894 /3884	0.93	0.77–1.11 (0.39)	48.2	0.01	− 0.68	0.49	− 0.85	0.48
	Heterozygote model	3894 /3884	**0.66**	**0.49–0.88 (≤0.001)**	**80.8**	≤0.001	0.68	0.49	0.48	0.67
Subgroup										
Asian	Dominant model	2444/2039	0.64	0.40–1.02 (0.09)	87.5	≤0.001	1.95	0.05	2.33	0.06
	Recessive model	2444/2039	0.69	0.46–1.04 (0.07)	33.6	0.16	0.17	0.86	− 0.25	0.80
	Allelic model	2444/2039	0.76	0.54–1.07 (0.11)	86.9	≤0.001	0.83	0.40	0.62	0.54
	Homozygote model	2444/2039	0.69	0.43–1.12 (0.13)	38.3	0.12	1.65	0.09	2.40	0.06

Table 3 (continued)

Subgroup	Genetic model	Sample size	Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
		Case/control	OR	95% CI (*P*-value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
	Heterozygote model	2444/2039	0.68	0.43–1.07 (0.09)	85.8	≤0.001	− 0.88	0.38	− 0.52	0.60
European	Dominant model	425/744	0.83	0.44–1.59 (0.57)	79.2	≤0.001	0.46	0.64	− 0.04	0.96
	Recessive model	425/744	1.76	0.96–3.22 (0.06)	57.2	0.09	− 0.10	0.92	0.49	0.63
	Allelic model	425/744	1.06	0.81–1.37 (0.67)	41.2	0.10	− 0.19	0.85	− 0.40	0.70
	Homozygote model	425/744	1.34	0.92–1.96 (0.12)	0	0.54	− 0.52	0.60	− 2.24	0.26
	Heterozygote model	425/744	0.71	0.34–1.49 (0.36)	81.8	≤0.001	− 0.56	0.57	− 0.79	0.47
African	Dominant model	289/208	**0.45**	**0.28–0.72 (≤0.001)**	0	0.92	*	*	*	*
	Recessive model	289/208	2.05	0.20–21 (0.54)	93.8	≤0.001	*	*	*	*
	Allelic model	289/208	0.89	0.41–1.93 (0.77)	87.5	≤0.001	*	*	*	*
	Homozygote model	289/208	0.97	0.15–6.24 (0.97)	84.3	0.01	*	*	*	*
	Heterozygote model	289/208	**0.43**	**0.26–0.70 (≤0.001)**	0	0.56	*	*	*	*
Atopic	Dominant model	976/741	0.71	0.48–1.06 (0.30)	54.3	0.06	0.39	0.69	2.61	0.02
	Recessive model	976/741	1.22	0.46–3.21 (0.68)	82.2	≤0.001	2.41	0.01	2.76	0.02
	Allelic model	976/741	0.90	0.62–1.30 (0.57)	75	≤0.001	− 1.36	0.17	− 5.95	0.02
	Homozygote model	976/741	0.83	0.34–2.03 (0.68)	71.8	≤0.001	0.68	0.49	0.48	0.67
	Heterozygote model	976/741	0.69	0.48–1.00 (0.04)	43.8	0.13	− 1.36	0.17	− 1.69	0.23
Non-atopic	Dominant model	1216/1646	0.82	0.55–1.20 (0.09)	67.5	0.02	1.05	0.29	1.40	0.22
	Recessive model	1216/1646	1.23	0.82–1.85 (0.30)	54.6	0.08	− 0.45	0.65	0.24	0.82
	Allelic model	1216/1646	1.07	0.87–1.32 (0.53)	53.5	0.05	0.45	0.65	0.87	0.39
	Homozygote model	1216/1646	1.07	0.84–1.35 (0.60)	0	0.71	1.73	0.07	1.21	0.08
	Heterozygote model	1216/1646	0.76	0.47–1.23 (0.27)	75.8	≤0.001	0.45	0.65	2.37	0.05

Table 3 (continued)

Subgroup	Genetic model	Sample size	Test of association		Test of heterogeneity		Test of publication bias (Begg's test)		Test of publication bias (Egger's test)	
		Case/control	OR	95% CI (*P*-value)	I^2 (%)	*P*	*Z*	*P*	*T*	*P*
Mixed	Dominant model	1171/673	0.69	0.39–1.21 (0.19)	81.9	≤ 0.001	− 0.88	0.38	− 0.52	0.60
	Recessive model	1171/673	0.85	0.49–1.47 (0.55)	38.7	0.19	0.46	0.64	− 0.04	0.96
	Allelic model	1171/673	0.76	0.49–1.18 (0.22)	82.3	≤ 0.001	0.17	0.86	− 0.25	0.80
	Homozygote model	1171/673	0.67	0.27–1.71 (0.40)	71.9	0.02	0.83	0.40	0.62	0.54
	Heterozygote model	1171/673	0.70	0.42–1.17 (0.17)	76.1	0.01	0.22	0.82	− 0.14	0.89

Bold values indicate statistically significant

0.85, 95% CI 0.69–1.03, $P=0.09$), and homozygote model (OR 0.93, 95% CI 0.77–1.11, $P=0.39$). Additionally, the results of subgroup analysis based on ethnicity and atopic status reject association between rs1800896 and asthma risk except for Africans in dominant model (OR 0.45, 95% CI 0.28–0.72, $P<0.001$) and heterozygote model (OR 0.43, 95% CI 0.26–0.70, $P<0.001$). The results of pooled ORs, heterogeneity tests, and publication bias tests in different analysis models are shown in Table 3.

Publication Bias

We estimate publication bias using funnel plot, Begg's and Egger's tests. Except in some models, no evidence of publication bias was observed for the overall population and subgroup analysis under all genetic models (Table 3). Additionally, the shape of the funnel plot (just for dominant models of three SNPs) appeared to be symmetrical, demonstrating no significant publication bias (Fig. 3).

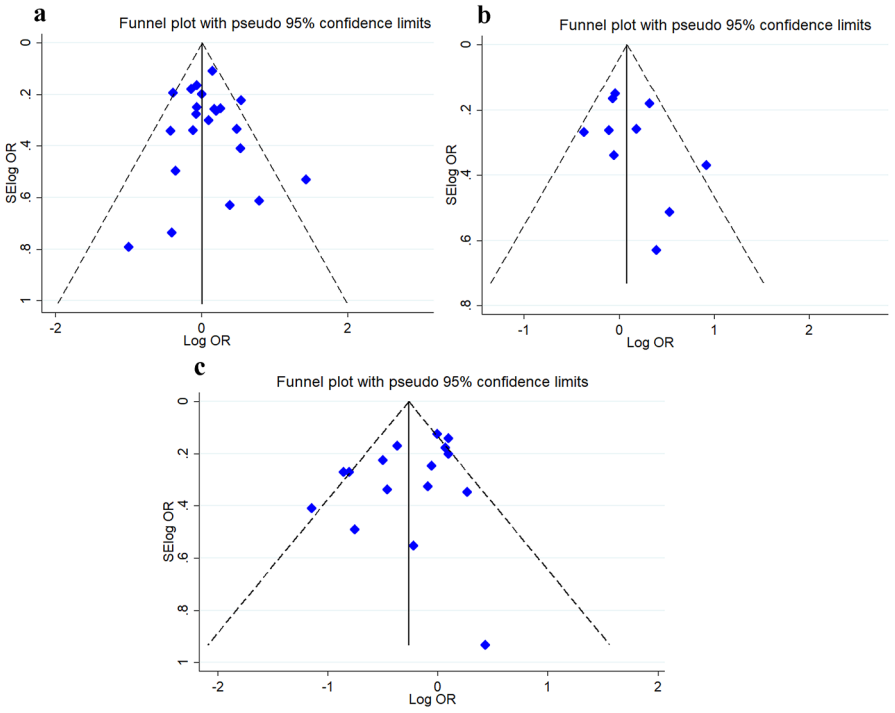

Fig. 3 Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. **a** Dominant model (rs 1800872), **b** dominant model (rs1800871), **c** dominant model (rs 1800896)

Sensitivity Analysis

The leave-one-out method was used in the sensitivity analysis to explore the effect of individual data on the pooled ORs. The significance level of ORs was not altered through omitting any single study in the dominant model for rs1800872, rs1800871, and rs1800896, indicating that our results were statistically robust (Fig. 4).

Meta-regression Analyses

Meta-regression analysis was performed to explore potential sources of heterogeneity among the included studies (Table 4). The findings indicated that none of the potential parameters, including publication year and ethnicity, were a source of heterogeneity (Fig. 5).

Discussion

Asthma is a chronic inflammatory disease and AHR and airway remodeling are the main hallmarks of the disease (Murphy and O'Byrne 2010). Although the pathogenesis of asthma is unknown, many studies have demonstrated that genetic background is involved in susceptibility to asthma (Kim et al. 2010). Our previous studies also

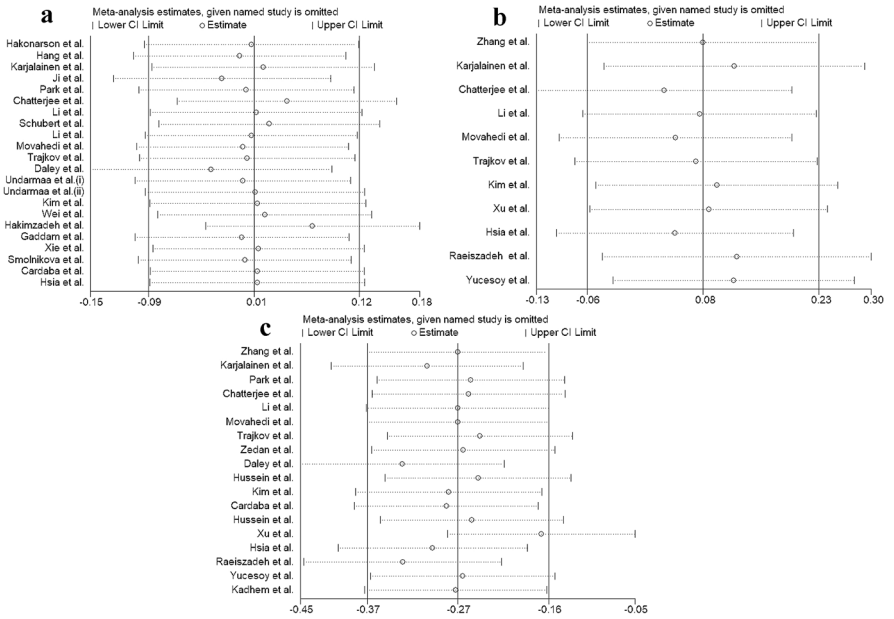

Fig. 4 Sensitivity analysis in present meta-analysis investigates the individual influence of studies on pooled results. **a** Dominant model (rs1800872), **b** dominant model (rs1800871), **c** dominant model (rs1800896)

Table 4 Meta-regression analyses of a potential source of heterogeneity

Heterogeneity factor	Genetic model	Coefficient	SE	*T*-test	*P*-value	95% CI	
						UL	LL
IL-10 (rs 1800872)							
Publication year	Dominant model	− 0.128	0.70	− 0.18	0.85	− 1.59	1.33
	Recessive model	0.044	0.12	0.36	0.72	− 0.21	0.29
	Allelic model	0.002	0.038	0.06	0.95	− 0.077	0.081
	Homozygote model	− 0.05	0.076	− 0.72	0.48	− 0.21	0.10
	Heterozygote model	− 0.16	0.85	− 0.19	0.85	− 1.94	1.61
Ethnicity	Dominant model	− 2.13	3.7	− 0.57	0.57	− 9.99	5.71
	Recessive model	− 0.34	0.64	− 0.53	0.60	− 1.68	1
	Allelic model	− 0.06	0.20	− 0.35	0.73	− 0.48	0.34
	Homozygote model	− 0.23	0.39	− 0.59	0.56	− 1.06	0.59
	Heterozygote model	− 2.59	4.58	− 0.57	0.57	− 12.14	6.95
IL-10 (rs1800871)							
Publication year	Dominant model	− 0.31	0.68	− 0.46	0.66	− 1.89	1.27
	Recessive model	0.05	0.02	0.20	0.85	− 0.05	0.06
	Allelic model	− 0.02	0.22	− 0.09	0.92	− 0.53	0.49
	Homozygote model	0.01	0.05	0.33	0.75	− 0.10	0.14
	Heterozygote model	− 0.40	0.83	− 0.48	0.64	− 2.33	1.52
Ethnicity	Dominant model	− 1.33	2.43	− 0.55	0.59	− 6.95	4.28
	Recessive model	− 0.05	0.13	− 0.43	0.67	− 0.36	0.25
	Allelic model	− 2.02	2.43	− 0.83	0.43	− 7.64	3.60
	Homozygote model	− 0.15	0.19	− 0.76	0.47	− 0.62	0.31
	Heterozygote model	− 1.60	2.97	− 0.54	0.60	− 8.46	5.24
IL-10 (rs 1800896)							
Publication year	Dominant model	0.006	0.02	0.29	0.77	− 0.03	0.05
	Recessive model	− 0.05	0.10	− 0.53	0.60	− 0.27	0.16
	Allelic model	− 0.01	0.02	− 0.52	0.61	− 0.05	0.03
	Homozygote model	0.001	0.03	0.04	0.97	− 0.07	0.08
	Heterozygote model	0.006	0.02	0.31	0.76	− 0.03	0.05
Ethnicity	Dominant model	0.001	0.07	0.02	0.98	− 0.16	0.16
	Recessive model	0.35	0.34	1.01	0.33	− 0.40	1.10
	Allelic model	0.02	0.07	0.33	0.74	− 0.14	0.19
	Homozygote model	0.01	0.12	0.09	0.93	− 0.25	0.27
	Heterozygote model	− 0.01	0.07	− 0.15	0.88	− 0.17	0.15

indicated association of genetic polymorphisms in the critical cytokines involved in asthma pathogenesis, namely IL-4 (Kousha et al. 2020) and IL-13 (Omraninava et al. 2020) with the risk of asthma. Moreover, inflammation plays a significant role in the incidence and development of the disease (Noutsios and Floros 2014). On the other hand, IL-10 is a critical anti-inflammatory cytokine that suppresses the immune responses (Kurowski et al. 2018). A significant reduction of *IL-10*

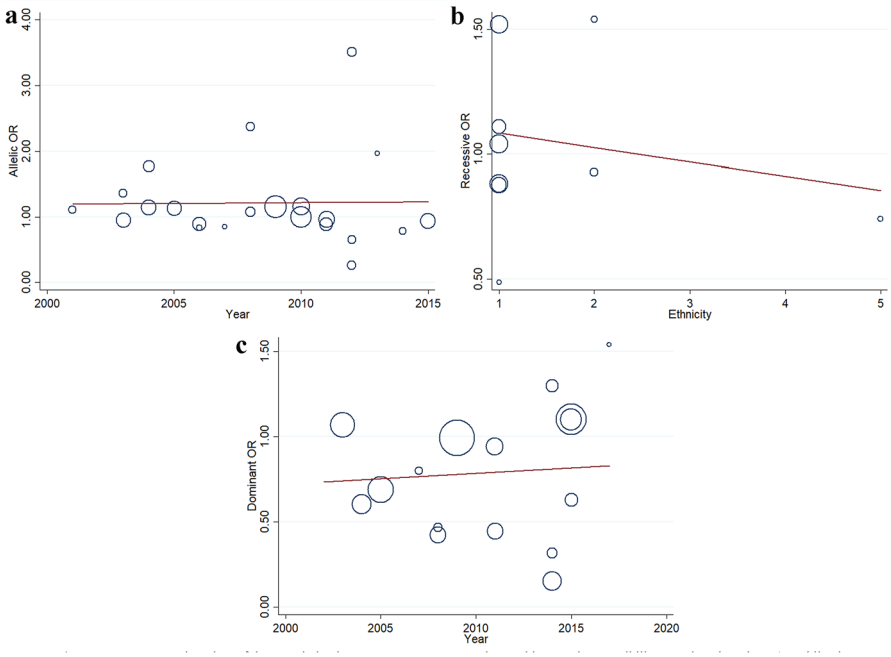

Fig. 5 Meta-regression plots of the association between IL-10 promoter polymorphisms and susceptibility to asthma based on **a** publication year (rs 1800872), **b** ethnicity (rs1800871), and **c** publication year (rs 1800896)

expression in asthmatics suggests that IL-10 plays a crucial role in the pathogenesis of asthma (Raeiszadeh Jahromi et al. 2014). The results of previous studies on the association between *IL-10* polymorphisms and asthma risk were inconsistent. The reasons for this contradiction may underly in the demographic differences and small sample size the low statistical power of the individual studies. Consequently, meta-analysis can help to obtain a more accurate finding of the association of *IL-10* gene polymorphisms with risk of asthma.

Nie et al. (2012) performed the first meta-analysis in 2012 by including 17 studies (containing 4478 cases and 4803 controls) and indicated that rs1800896 and rs1800872, but not rs1800871, were associated with asthma risk. Similarly, the meta-analysis by Zheng et al. (2014) in 2014 on a total of 23 studies (22 articles) involving 4716 asthmatic patients and 5093 controls reported that rs1800896 and rs1800872 (but not rs1800871) had significant association with asthma risk. However, Hyun et al.'s (2013) meta-analysis in 2013 on 11 studies (containing 2215 asthma patients and 2170 controls) revealed an association between rs1800896 (but not rs1800871 and rs1800872) and asthma in adults. The meta-analysis by Huang et al. (2016) in 2016 on 16 studies (comprising 2494 cases and 2160 controls) showed no significant association between these three SNPs and pediatric asthma risk.

In order to update and provide a more precise evaluation of the association between *IL-10* promoter rs1800896, rs1800871, and rs1800872 SNPs and asthma susceptibility,

we conducted a meta-analysis of the studies on all articles published up to April 2020. Our meta-analysis consisted of 30 eligible case–control studies comprising 5678 asthmatic patients and 6079 controls. We observed that there was no association between rs1800872 and susceptibility to asthma in all genetic models both in the overall analysis and in thesubgroup analyses based on ethnicity and atopic status. Although rs1800871 had no significant association with asthma risk in the overall analysis, the results of subgroup analysis indicated a significant association of the allelic model of this SNP with a decreased risk of asthma in Europeans. However, analyses indicated that rs1800896 was associated with a decreased risk of asthma among dominant and heterozygote genetic models with no association across recessive, allelic, and homozygote models. The subgroup analysis based on ethnicity revealed that the dominant and heterozygote models had a significant association with decreased susceptibility to asthma in Africans.

The demonstrated association between rs1800896 polymorphism and asthma risk in Africans should be interpreted with caution. Although we applied sensitivity analysis for studies in HWE to explore the effect of individual data on pooled results and revealed significant associations, there were only two studies in HWE, which contained small sample sizes. Furthermore, we found no evidence of a significant association between rs1800871 (11 eligible studies) and rs1800872 (22 eligible studies) polymorphisms and risk of asthma under different genetic models with subgroup analysis based on atopic status and ethnicity. Our result disagrees with four previous meta-analysis studies (Huang et al. 2016; Hyun et al. 2013; Nie et al. 2012; Zheng et al. 2014), which may due to inclusion of more studies in the analysis. However, inclusion of more studies implies to higher sample size with more statistical power, suggesting that our findings are more valid. Compared to the previous meta-analysis studies, we identified thirty relevant papers using a robust retrieval method, far more than the number of studies included in previous analyses. Hence our analyses' statistical power is higher.

Some limitations have to be taken into account when interpreting our findings. First, the heterogeneity of asthma can influence the analysis. Various criteria for inclusion and diagnosis of asthmatic patients and selection of the control group without screening test for asthma may distort the results. Second, the limited number of available studies possibly accounts for the observed results, implying that the polymorphisms of *IL-10* may be associated with asthma susceptibility if more original data become available in the future. Although the subgroup analysis performed based on ethnicity, a small number of studies were found in the Europeans and African populations. Third, although we estimated publication bias using a funnel plot, Begg's and Egger's tests, their results in most of groups had *P*-value higher than < 0.05. However, the results for some subgroups showed significant publication bias and we think possible unpublished studies or many unknown reasons can be the source.

Conclusion

Our findings showed that rs1800896 SNP (by dominant and heterozygote genetic models) plays a protective role against asthma risk. Also, the rs1800896 SNP was associated with decreased risk of asthma in Africans. We found no association

between rs1800872 SNP and asthma risk. Despite rs1800871 had no significant association with asthma risk in the overall analysis, this SNP had a protective role against asthma risk in Europeans. Nevertheless, due to the limited number of available studies in the subgroup analyses, the findings should be interpreted cautiously. Hopefully, further original works will contribute to our understanding of the association between *IL-10* gene polymorphisms and risk of asthma.

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Author Contributions DI and ND generated the idea. AP, SH, and BR searched the literature and analyzed and interpreted the data. FA, SS, and MHH prepared the original draft. MA, ND, BR, MM, and SA wrote and critically revised the paper. DI supervised the project. All authors read and approved the final manuscript.

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Declarations

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