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Association between chronic obstructive pulmonary disease and interleukins gene variants: A systematic review and meta-analysis

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ABSTRACT

Interleukins are cytokines involved in systemic inflammation and immune system regulation. Many studies have investigated the association between common genetic variations in interleukin-coding genes and COPD susceptibility. In this study, a systematic review and meta-analysis was performed to evaluate the association between interleukin gene variations and COPD pathogenesis.

Association studies were retrieved from PubMed and Google Scholar databases using the standard systematic search strategy. A total of 26 different studies evaluating eight polymorphisms in four interleukin genes were included in this study.

In overall comparisons, IL1β-rs16944, -rs1143627, -rs1143634, IL13-rs20541 polymorphisms were found not to be associated with the increased risk for developing COPD. However, IL1RN-rs2234663 and IL13-rs1800925 showed a strong association with COPD. We showed that the CC genotype carriers of the IL6-rs1800795 are at significantly higher risk of developing COPD (OR = 1.31, 95% CI: 1.04–1.64, P = 0.01) compared to GG carriers. In case of IL6-rs1800796, individuals with CC and CG genotypes showed a lower risk to develop COPD (OR = 0.46, 95%CI: 0.32–0.66, P > 0.00).

This updated meta-analysis strongly supports the association of IL1RN-rs2234663, IL6-rs1800795, -rs1800795 and IL13-rs1800925 variants with COPD.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease state characterized by a progressive limitation of airflow caused by an abnormal airway inflammatory response to inhaled aerosols [1]. It is estimated that COPD will be the third leading cause of death worldwide in 2030 [2]. Although cigarette smoking is the most widely recognized risk factor of COPD, only 15% of smokers develop COPD, suggesting that apart from environmental risk factors, additional characteristics such as genetic variations contribute to COPD development. Moreover, COPD shows a familial clustering pattern indicating a substantial contribution of genetic factors to COPD [3,4]. A deeper comprehension of the genetic architecture of COPD is crucial for helping to elucidate the pathogenesis mechanisms of the disease and to develop novel therapeutic strategies. To date, many studies have identified specific loci implicated in the genetic predisposition to COPD [3]. Although the pathology of COPD is closely related to a typical chronic inflammatory process including the tissue damage and repair process, it is conceivable that cytokines play a pivotal role in this condition.

Interleukins and cytokines are involved in modulating inflammation and immune system regulation. To date, a large number of genetic epidemiological studies have investigated the association between interleukin coding gene variations and COPD susceptibility [3,5–9], including *IL1A* [7], *IL1β* [5,10–12], *IL1RN* [6,13,14], *IL4* [15], *IL6* [9,16,17], IL8 [18], *IL10* [12,16], *IL12* [19], *IL13* [20–23], *IL17* [24], *IL18* [18] and *IL27* [19], but they have reported inconsistent results. To date, several meta-analyses have analyzed the associations between different interleukin variants and the risk of COPD development, however, there are a number of recently published reports that need to be considered in an updated meta-analysis [25,26]. To further reconcile the conflicting findings regarding the association between interleukin genes variants and COPD susceptibility, we have evaluated and updated the association between the polymorphism of interleukins genes and the susceptibility of COPD using published papers through a systematic review and meta-analysis.

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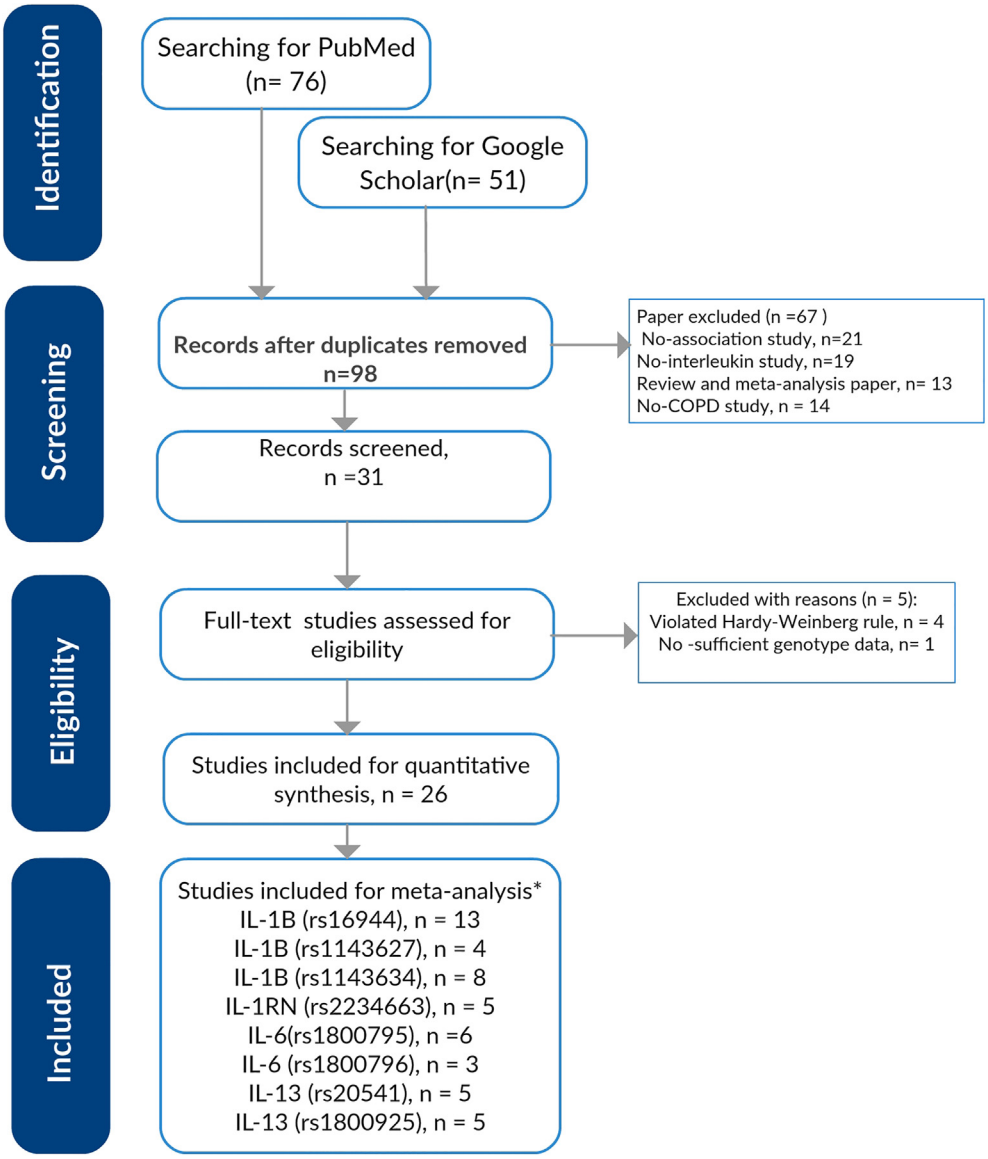

Fig. 1. Flow diagram of the search process. *Some publications include more than one SNP or more than one population.

2. Materials and methods

2.1. Search strategy

We searched in PubMed and Google Scholar until December 2017 with the following search terms: "*interleukin* Or *IL*" And "*gene polymorphism* Or *variant* Or *mutation*" And "*COPD* Or *chronic obstructive pulmonary disease*", on only human conducted studies. No limitation was applied regarding papers language. After the retrieval of articles fulfilling inclusion criteria, a reference cross-check was performed to explore more articles not listed in the searched databases.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) case-control design; (2) sufficient genotype frequency data in case and control groups; (3) studies analyzing the association between interleukin genes polymorphisms and COPD; and (4) subjects in the control group were either healthy individuals or smokers. We excluded review and meta-analysis articles, animal studies, and those investigated any pathologic state other than COPD as a major outcome. In addition, studies or sub-studies violated Hardy-Weinberg equilibrium (HWE) were excluded from final analysis. In addition, we avoided to include variants for which two or fewer reports have been reported.

2.3. Data extraction and quality assessment

Two independent reviewers collected the data according to inclusion and exclusion criteria. Disagreements were resolved through a team discussion. The key extracted characteristics of each study were as follows: the first author's name, year of publication, country and ethnicity of participants, investigated SNP, genotyping technique, number of case and control, and genotype distribution. For studies containing different sub-populations, data were extracted separately.

2.4. Statistical analysis

All statistical tests were performed with metafor (version 1.9–4) [27] packages of R (version 3.1.1) Chi-square test was used to investigate the deviation of genotype distributions from Hardy-Weinberg equilibrium in control groups of each study. For each SNP, meta-analysis was performed under four different genetic models (Allele

contrast, Additive, Dominant and Recessive model). We used Z-test to determine the statistical significance for odds ratio (OR) with the corresponding 95% confidence intervals (CIs). A $P < 0.05$ was considered the statistically significant difference. Between-study heterogeneity was address by the Cochran's Q-statistic (significance at $P_Q < 0.10$) and quantified by the I^2 metric. When heterogeneity was present, the random-effects model (fitted by restricted maximum-likelihood estimator) was used to pool the data; otherwise, the fixed-effects model was used. We used a multivariate meta-regressions in order to find potential sources of heterogeneity among the following moderators: ethnicity (categorized as: Asian, Caucasian, and Others), source of controls (divided into healthy individuals or smokers), and sample size. Sub-group analyses were carried out by the ethnicity and source of controls. A leave-one-out sensitivity analysis was performed by iteratively removing one study at a time in order to evaluate the robustness of acquired *P*-values. Publication bias was considered by funnel plot and Egger regression asymmetry test. For Egger test, the significance of the intercept was determined by *t*-test, as proposed by Egger, with $P < 0.10$ indicative of statistically significant publication bias.

3. Results

3.1. Study description and characteristics

A total of 109 articles were identified in PubMed and Google Scholar updated to December 2017. A total of 26 articles were found to met the inclusion criteria. The main characteristics of the included studies are summarized in supplementary file Tables S1–S4. Totally, eight common variants across four interleukin genes were included in the meta-analysis. A flow diagram of the study identification process is depicted as Fig. 1.

3.2. Quantitative data synthesis

3.2.1. IL1β gene polymorphisms and COPD susceptibility

The main results for the association between *IL1β* polymorphisms and COP risk are listed in Table 1. The forest plots of *IL1β* polymorphisms association with COPD are available as Supplementary file, Figs. S1–S12. For *IL1β*-rs16944 polymorphism, 15 studies from 13 publications [5–7,11–13,20,28–32] including 1764 cases and 2063 controls were included in the meta-analysis (Supplementary file, Table S1). In general, no association was found under any of four genetic models. Similarly, based on the control resources and ethnicity, no association was observed in sub-group analysis.

Five studies from four publications [10,14,29,31] containing 474 COPD cases and 816 controls were identified in order to investigate the association between the *IL1β*-rs1143627 polymorphism and COPD susceptibility (Supplementary file, Table S1). No statistically significant association was found in the overall and also in sub-group analyses. Due to limited available data on ethnicities, the ethnicity-stratified sub-group analysis did not perform.

Four studies from three papers [5,13,29] including 316 COPD patients and 233 control subjects were included in the meta-analysis for *IL1β*-rs1143634 polymorphism (Supplementary file, Table S1). The results implied no association between *IL1β*-rs1143634 polymorphism and COPD risk in the overall and also sub-group analyses.

3.2.2. IL1RN gene polymorphism and COPD susceptibility

Five studies [6,13,14,21,30] containing 322 cases and 365 controls were identified that evaluated the association between the *IL1RN*-rs2234663 polymorphism and COPD risk (Supplementary file, Table S2). The overall pooled estimates evidenced a significant association between COPD and *IL1RN*-rs2234663 polymorphism under Allele contrast model (OR = 0.56, 95% CI: 0.39–0.80, *P* = 0.00), Additive model (OR = 0.34, 95% CI: 0.13–0.85, *P* = 0.02) and Recessive model (OR = 1.79, 95% CI: 1.18–1.70, *P* = 0.00), but not Dominant model (OR = 0.41, 95% CI: 0.16–1.02, *P* = 0.06) (Table 2). The forest plots of *IL1RN*-rs2234663 association with COPD are available as Supplementary file Figs. S13–S16. Limited number of studies in each sub-group of ethnicity and control resource precluded us to perform sub-group analysis.

3.2.3. IL6 gene polymorphisms and COPD susceptibility

For meta-analysis of the association between COPD risk with *IL6*-rs1800795 variant, nine studies from seven articles [4,9,12,14,17,28,33] comprised of 1213 cases and 1968 controls were included (Supplementary file, Table S3). Overall meta-analysis result found a significant association between rs1800795 and COPD susceptibility under Allele and Additive models and also a marginal significance under dominant and recessive models. (Table 3). The forest plots of *IL6*-rs1800795 association with COPD are available as Supplementary file Figs. S17–S20. Stratified by control resources we found that the pooled estimated effect remained significant in healthy controls under Allele contrast (OR = 0.11, 95%CI: 0.012–1.05, *P* = 0.03), Additive (OR = 1.32 95%CI: 1.03–1.71, *P* = 0.02) and Dominant model (OR = 1.20, 95%CI: 1.02–1.42, *P* = 0.02) but not a Recessive model (OR = 0.81 95%CI: 0.65–1.00, *P* = 0.09). Considering smokers as controls, a significant association observed only under Allele contrast model (OR = 0.29, 95%CI: 0.22–0.37, *P* ≤ 0.00). Moreover, in the sub-group analysis stratified by ethnicity, an obvious association existed in Asians under Allele contrast model (OR = 0.00, 95%CI: 0.00–0.38, *P* = 0.02) and in Caucasians under Allele contrast (OR = 0.33, 95%CI: 0.28–0.40, *P* < 0.00), Additive (OR = 1.29, 95%CI: 1.02–1.62, *P* = 0.03) and Dominant model (OR = 1.17, 95%CI:

Table 1
Meta-analysis of IL1β polymorphisms and COPD susceptibility.

SNP	Genetic model	Test for association			Test for heterogeneity		
		OR (95%CI)	Z	*P*	Q	*P*	I^2 (%)
rs16944	Allele contrast (C vs. T)	1.01 (0.81–1.25)	0.11	0.90	52.97	< 0.00	78.54
	Additive (CC vs. TT)	1.04 (0.66–1.64)	0.18	0.85	49.88	< 0.00	77.53
	Dominant (CC + CT vs. TT)	1.10 (0.82–1.47)	0.69	0.49	31.60	0 0.00	62.13
	Recessive (TT + CT vs. CC)	1.05 (0.77–1.44)	0.34	0.73	48.58	< 0.00	73.34
rs1143627	Allele contrast (C vs. T)	1.11 (0.94–1.31)	1.29	0.19	1.07	0.89	0.00
	Additive (CC vs. TT)	1.28 (0.91–1.79)	1.44	0.14	0.65	0.95	0.00
	Dominant (CC + CT vs. TT)	1.26 (0.89–1.79)	1.33	0.18	4.61	0.32	20.75
	Recessive (TT + CT vs. CC)	0.98 (0.66–1.46)	0.76	0.44	11.02	0.02	62.45
rs1143634	Allele contrast (C vs. T)	1.02 (0.72–1.44)	0.14	0.88	1.70	0.63	0.00
	Additive (CC vs. TT)	1.08 (0.41–2.84)	0.16	0.87	0.67	0.87	0.00
	Dominant (CC + CT vs. TT)	1.11 (0.43–2.87)	0.23	0.81	0.38	0.94	0.00
	Recessive (TT + CT vs. CC)	0.98 (0.64–1.49)	−0.71	0.94	1.89	0.59	0.00

Table 2
Meta-analysis of the *IL1RN*-rs2234663 polymorphism with COPD susceptibility.

SNP	Genetic Model	Test for association			Test for heterogeneity		
		OR (95%CI)	Z	*P*	Q	*P*	I^2 (%)
rs2234663	Allele contrast (L vs. 2)	0.56 (0.39–0.80)	−3.16	**0.00**	5.33	0.25	30.25
	Additive (LL vs. 22)	0.34 (0.13–0.85)	−2.28	**0.02**	1.51	0.82	0.00
	Dominant (LL + L2 vs. 22)	0.41 (0.16–1.02)	−1.90	0.06	1.00	0.90	0.00
	Recessive (22 + L2 vs. LL)	1.79 (1.18–2.70)	2.76	**0.00**	5.27	0.26	28.39

1.00–1.36, $P = 0.03$).

Three studies [8,9,33] totaling 574 COPD cases and 862 controls were identified in order to assess the association between the *IL6*-rs1800796 polymorphism and COPD susceptibility (Supplementary file, Table S3). The results evidenced significant association and the overall ORs and 95% CIs were 2.23, 1.46–3.40 ($P < 0.00$) and 2.16, 1.51–3.10 ($P < 0.00$) under Dominant and Recessive models, respectively (Table 3). The forest plots of *IL6*-rs1800796 association with COPD are available as Supplementary file Figs. S21–S24. In this case, we did not perform a sub-group analysis because there were no sufficient sub-groups regarding control resources and ethnicity.

3.2.4. IL13 gene polymorphisms and COPD susceptibility

For the *IL13*-rs20541 polymorphism, six studies [15,21,34–37] with 1330 cases and 703 controls were included in the meta-analysis (Supplementary file, Table S4). Neither in the primary pooled analysis nor in the sub-group analysis we found any significant association under any genetic model (Table 4). The forest plots of *IL13*-rs20541 association with COPD are available as Supplementary file Figs. S25–S28. However, the results indicated a lower frequency of G allele in COPD patients under Allele contrast and Additive model (OR were 0.87 and 0.65, respectively).

Five trials were identified [15,21,23,34,38], for which the genotype status of *IL13*-rs1800925 polymorphism was determined in overall 1035 COPD patients and 502 control subjects (Supplementary file, Table S4). By pooling these studies, the meta-analysis showed a strong association between this polymorphism and COPD risk under all comparison models (Table 4). The forest plots of *IL13*-rs20541 association with COPD are available as Supplementary file Figs. S29–S30. In the sub-group analysis, this significant association was persist in healthy controls (OR = 0.52, 95% CI: 0.37–0.74, $P = 0.00$) and Asian ethnicity (OR = 0.50, 95% CI: 0.33–0.76, $P = 0.00$) under all comparison models.

3.3. Heterogeneity analysis

For *IL1β*-rs16944 polymorphism, there was a significant evidence for between-studies heterogeneity ($P < 0.1$ and $I^2 > 50\%$) under all genetic models. For *IL1β*-rs1143627 polymorphism, heterogeneity was found only under Recessive model (Table 1). For *IL6*-rs1800795 and -rs1800796 polymorphisms, between-study heterogeneity was found only under Allele contrast model (Table 3). No evidence was found for between-studies heterogeneity for *IL1β*-rs1143634, *IL1RN*-rs2234663 or *IL13* rs20541 and -rs1800925 polymorphisms under any genetic model. As detailed in Table 5, meta-regression was done in this study to identify potential sources of between-study heterogeneity. The confounding moderators included ethnicity, source of controls, and study sample size. The meta-regression analysis failed to identify the major source of heterogeneity for *IL1β*-rs16944 and *IL6*-rs1800796 polymorphisms (all *P* values for regression > 0.05). Indeed, the test for residual heterogeneity was significant (QE p < 0.01), possibly indicating that other moderators not considered in the model may affect the observed association.

For *IL1β*-rs1143627 polymorphism, all of the observed heterogeneity may be due to including the ethnicity and study sample size in the model. Moreover, both the control source and sample size had a significant influence on the observed association of COPD and the polymorphism (for both, *P* values = 0.03). In the case of *IL6*-rs1800795 polymorphism, more than 50% of the observed heterogeneity might be attributed to the inclusion of predefined moderators into the model. Also, the results suggest that ethnicity significantly influences the association of COPD with rs1800795 ($P = 0.05$).

3.4. Sensitivity analysis

To assess the stability of results, sensitivity analyses were performed by removing one study at a time (Supplementary file Tables S5–S12). We found that excluding the Antczak et al. study [10] from the analysis changed significantly the P value of *IL1β*-rs1143627 polymorphism association with COPD under Dominant model (OR = 1.48, 95%CI: 1.1–2.00, P = 0.01) (Supplementary file Table S5).

For *IL1RN*-rs2234663 polymorphism, removing each of studies including Shi et al. [30], Hsieh et al. [14], and Issac et al. [6] could change the significance level of obtained P value in Allele contrast, Dominant, and Recessive model analyses (Supplementary file Table S8). For *IL6*-rs1800795 under Allele contrast model, the sequential exclusion of studies did not alter the pooled OR. However, leaving out the study of He et al. [17] under Additive model, studies including He et al. [17], Seifart et al. [16] and Danilko et al. [12] under Dominant model, and also studies including He et al. [17] and Zhou et al. [9] under

Table 3
Meta-analysis of the *IL6* polymorphisms with COPD susceptibility.

SNP	Genetic model	Test for association			Test for heterogeneity		
		OR (95%CI)	Z	p	Q	p	I^2 (%)
rs1800795	Allele contrast (C vs. G)	0.06 (0.00–0.57)	−2.44	0.01	71.56	< 0.00	99.73
	Additive (CC vs. GG)	1.31 (1.04–1.64)	2.32	**0.01**	3.48	0.90	0.00
	Dominant (CC + CG vs. GG)	1.16 (0.99–1.34)	1.95	0.05	5.70	0.68	0.00
	Recessive (GG + CG vs. CC)	0.81 (0.65–1.00)	−1.90	0.05	3.28	0.91	0.00
rs1800796	Allele contrast (C vs. G)	0.07 (0.00–14.29)	−0.96	0.33	911.32	< 0.00	99.72
	Additive (CC vs. GG)	0.49 (0.09–2.61)	0.82	0.40	3.80	0.14	48.76
	Dominant (CC + GC vs. GG)	2.23 (1.46–3.40)	4.21	< **0.00**	1.93	0.38	19.29
	Recessive (GG + GC vs. CC)	2.16 (1.51–3.10)	3.71	< **0.00**	2.88	0.23	0.00

Table 4
Meta-analysis of the IL-13 polymorphisms and COPD susceptibility.

SNP	Genetic model	Test for association			Test for heterogeneity		
		OR (95%CI)	Z	p	Q	p	I^2 (%)
rs20541	Allele contrast (G vs. A)	0.87 (0.74–1.01)	−1.74	0.08	4.51	0.47	5.85
	Additive (GG vs. AA)	0.65 (0.42–1.03)	−1.95	0.06	4.81	0.43	0.00
	Dominant (GG + GA vs. AA)	0.73 (0.48–1.10)	−1.48	0.13	5.31	0.37	0.00
	Recessive (AA + GA vs. GG)	1.13 (0.93–1.37)	1.27	0.20	6.50	0.26	27.85
rs1800925	Allele contrast (C vs. T)	0.70 (0.59–0.84)	−3.85	0.00	9.43	0.12	47.14
	Additive (CC vs. TT)	0.40 (0.23–0.69)	−3.30	0.00	4.39	0.49	13.16
	Dominant (CC + CT vs. TT)	0.45 (0.25–0.73)	−2.60	0.00	3.95	0.55	4.29
	Recessive (TT + CT vs. CC)	1.37 (1.11–1.68)	2.98	0.00	9.31	0.11	48.80

Table 5
The Between-study heterogeneity assessment by meta-regression using ethnicity. The source of controls and the study sample size were considered as confounding variables.

Gene	SNP	Genetic model	Residual heterogeneity		Test of moderators		R^2 (%)
			Q_E	p	Q_M	p	0.00
IL13	rs20541	Allele contrast (C vs. T)	39.48	< 0.00	2.88	0.57	0.00
		Additive (CC vs. TT)	36.51	< 0.00	0.83	0.55	0.00
		Dominant (CC + CT vs. TT)	26.74	0.00	0.67	0.65	0.00
		Recessive (TT + CT vs. CC)	26.74	0.00	0.67	0.65	0.00
IL1β	rs1143627	Recessive (TT + CT vs. CC)	3.88	0.42	4.49	0.09	100
IL6	rs1800795	Allele contrast (C vs. G)	62.98	0.00	3.81	0.09	53.75
	rs1800796	Allele contrast (C vs. G)	90.44	0.00	3.27	0.36	61.04

Recessive model could separately alter the P value to the non-significant level (Supplementary file Table S9). For *IL6*-rs1800796, the exclusion of Zhou et al. study [9] under Allele contrast model and as well as the exclusion of Zhou et al. study [9] and Córdoba et al. study [33] under Dominant model significantly influenced the obtained P values. In contrast, the exclusion of any included studies under the Recessive model at a time did not alter significance levels (Supplementary file Table S10). In the case of *IL13*-rs20541, sensitivity analysis revealed that excluding the study of Wang et al. [36] from Allele contrast, Additive, and Dominant model markedly changed the pooled ORs (Supplementary file Table S11). For *IL13*-rs1800925, sensitivity analysis appreciably changed the results under all compared models (Supplementary file Table S12). Moreover, we found that the omission of Hegab et al. study [21] turned the P value into a significant level for Additive and Recessive model. Similarly, excluding the study of Beghe et al. [34] under the Recessive model markedly changed the association results of IL13-rs1800925 polymorphism with COPD (Supplementary file Table S12).

3.5. Publication bias

Publication bias was examined by Egger's test and funnel plot under all genetic comparisons for tested polymorphisms (Supplementary file, Tables S13–S15, Figs. S33–S40). After combining all studies, an obvious asymmetry was observed for *IL1RN*-rs2234663 polymorphism under all genetic models (Egger P values < 0.10) (Supplementary file, Table S14, Fig. S36). For *IL6*-rs1800795 polymorphism, a significant bias was found under Allele contrast (t = −3.49, P value = 0.01) and Dominant model (t = −2.30, P value = 0.05) (Supplementary file, Table S15, Fig. S37-A and -B). In addition, publication bias was suggested for *IL13*-rs20541 polymorphism under Allele contrast model (t = 2.14, *P* = 0.09) (Supplementary file, Fig. S38-A) and for *IL13*-rs1800925 polymorphism under Additive model (t = −2.43, *P* = 0.09) (Supplementary file, Table S15, Fig. S39-B).

4. Discussion

The main findings of the present meta-analysis, designed to summarize the evidence to date regarding the association between eight polymorphisms (*IL1β*-rs16944, -rs1143627, -rs1143634, *IL1RN*-rs2234663, *IL6*-rs1800795, -rs1800796, *IL13*-rs20541, and rs1800925) and the susceptibility to COPD, include: (1) *IL1β*-rs16944, -rs1143627, -rs1143634, *IL13*-rs20541 polymorphisms are not associated with any increased risk for developing COPD in overall comparisons; (2) compared to the L allele, the 2 alleles of the *IL1RN*-rs2234663 polymorphism is associated with an increased risk for developing COPD in overall comparisons; (3) the CC genotype carriers of the *IL6*-rs1800795 polymorphism are at significantly higher risk of developing COPD (OR = 1.31, 95%CI: 1.04–1.64, *P* = 0.01), compared to GG carrier; (4) individuals with CC and CG genotypes of *IL6*-rs1800796 have a lower risk to develop COPD (OR = 0.46, 95%CI: 0.32–0.66, P > 0.00); and (5) the IL13-rs1800925 polymorphism shows a significant association with COPD risk under all comparison models.

IL1β is a pro-inflammatory cytokine thought to be the main mediator of inflammatory responses to cigarette smoking and COPD [39]. Over the past years, a number of genetic association studies and meta-analyses have been conducted to analyze the association of *IL1β* genes polymorphisms and the risk of COPD [20,25,29,40]. The latest related meta-analyses reported in 2014 [25] and 2015 [41] indicated that *IL1β*-rs16944 and -rs1143627 polymorphisms was not markedly associated with susceptibility to COPD in overall comparisons.

Similarly, our results showed that this polymorphism was not associated with increased risk of COPD. Although Wang et al. [40] and Xie et al. [23] suggested a significant association between the rs16944 polymorphism and COPD in Asian ethnicity, our results indicated not an obvious association. Such discrepancies in findings could partially be explained by arbitrary designation of ethnicity to a country population. For example, despite genetically different, Wang et al. [41] categorized both the Egyptians and Indians as the Caucasian ethnicity. For *IL1β*-rs16944, Wang et al. reported no heterogeneity, however, Xie et al. [25] has reported an inter-study heterogeneity. The meta-regression

analysis revealed that factors other than source of controls, ethnicity, or study sample size are attributed to the heterogeneity. For *IL1β*-rs1143627 under the Recessive model, a moderate degree of between-study heterogeneity was found that are totally attributable to sample size and ethnicity. While the overall results indicated no association between rs1143627 polymorphism and COPD development, the sensitivity analysis showed that the exclusion of Antczak et al. study [10] under Dominant model markedly changed the P value to a significant level (OR = 1.48, 95%CI: 1.1–2, P = 0.01). Such findings emphasize the influence of each included study on the pooled estimate. Similar to a previous meta-analysis [25], our results indicated that the *IL1β*-rs1143634 polymorphism is not associated with the risk of COPD both in overall and sub-group analyses. Although there was an obvious inter-study heterogeneity for rs1143634 polymorphism, we were unable to further identify the exact sources of heterogeneity by meta-regression analysis. In the case of *IL1β* gene polymorphisms (rs16944, rs1143627, rs1143634), considering the present and also previous findings it seems generally that there is no significant association between the *IL1β* gene variations and COPD risk.

The IL-1 Antagonist Receptor (*IL1RN*) gene encodes a protein that belongs to the interleukin 1 cytokine family [42]. This protein has negative regulatory effects on the activities of both *IL-1α* and *IL-1β*. Moreover, *IL1RN* play important roles in *IL1*-related inflammatory responses. The dysregulation of *IL-1* cause abnormal inflammatory activities leading to a tissue damage commonly observed in the pathogenesis of COPD [43,44]. The rs2234663 is a VNTR polymorphism of the *IL1RN* gene that is reported to be associated with increased risk of several diseases such as cancer and COPD [6,25,45]. The *IL1RN* allele 2 has been suggested to be significantly associated with a low IL1-RA/IL1β ratio. In this way, the allele 2 is suggested to elicit a more prolonged and severe pro-inflammatory immune response. Although the *IL1RN* allele 1 has a higher population frequency, the allele 2 is more frequent in patients with autoimmune or inflammatory diseases [44,46]. In this meta-analysis, the *IL1RN* allele 2 was considerably more frequent in COPD patients, indicating a significant contribution of this variation in COPD development. In 2014, Xie et al. [25] suggested that *IL1RN* allele 2 homozygotes had an increased risk for COPD development. They included sub-studies/studies violated HWE (including Heghab et al. [29] on Arabian sub-study, Shukla et al. [47] and Lee et al. [31]) in the final analysis. The significant association was persisted even after excluding sub-studies/studies violated HWE. Interleukin-6 (a cytokine involved in inflammatory disease progression) circulatory levels are significantly elevated in COPD patients and are associated with lung function [48]. A considerable evidences support that genetic variations in *IL6* may contribute to the susceptibility to COPD [7,16,33]. In 2015 [49] and 2017 [50], two meta-analysis studies were performed on the association of *IL6*-rs1800795 and -rs1800796. In 2015, a meta-analysis [49] reported an association between the *IL6*-rs1800795 polymorphism and risk of COPD. In a similar way, our analysis showed an increased risk of COPD in CC genotype carriers compared with GG carriers (OR: 1.31, 95% CI: 1.04–1.64, P = 0.01). In addition, although a significant association was observed for both Asian and Caucasian ethnicities, Xie et al. [49] reported no significant association for Asians. To date, several studies have investigated the association of *IL6*-rs1800796 with COPD development [8,9,33]. Our results are in line with a previous meta-analysis [50], indicating that the C allele acts as a protective factor for COPD development.

IL13 has a variety of functions, including the regulation of pro-inflammatory cytokine expression from macrophages. Based on animal studies, *IL13* has functional roles in COPD development [51]. To date, several studies have evaluated the association of *IL13* variations with COPD development with controversial results. Accordingly, a recent meta-analysis by Liao et al. [52] tried to evaluate the association indicated a non-significant association of rs20541 and COPD in the overall analysis and also in Asian ethnicity. Likewise, we also found no significant association.

However, although Liao et al. [52] found a significant association in Caucasians under a Recessive genetic model, we found no obvious association. For rs1800925, Liao et al. [52] found a significant association in the overall population and also in Asians and Caucasians. Similarly, our results also revealed a significant association under all genetic comparisons. Moreover, an obvious association was seen between Asians and Arabs. The differences between our results and Ning Liao et al. [52] may be due to: (i) they included studies violated HWE (Heghab et al., on Japanese sub-study [21], Liu et al. on Taiwanese study [22] and Jiang et al. on Chinese study [53]); and (ii) they considered the Egyptians as the Caucasian. However, since there is no strong evidence to support this designation, we considered Egyptian as Arabs.

Some limitations should be mentioned in this meta-analysis. We found the between-study heterogeneity in some analyses. The meta-regression analyses were failed to further identify the sources of heterogeneity due to limited available data. It is acknowledged that in a meta-analysis of genetic association studies, some variables such as ethnicity, genotyping method, gender, and the phenotype of disease partially explain the observed heterogeneity. In addition, it seems that the sub-group analysis according to control resources and ethnicity could greatly reduce the heterogeneity. Third, although COPD is genetically regarded as a multifactorial disease, we were unable to take into account gene-gene or gene-environmental interactions such as gender, age, and smoking status which may have changed the associations between IL gene polymorphisms and COPD susceptibility. Moreover, associations of COPD and genetic variations of candidate genes are still unclear. Large sample size and considering gene-environment interactions are required to obtain a deeper comprehension of genetic risk factors for COPD.

5. Conclusions

This updated meta-analysis of 26 studies revealed that *IL1RN*-rs2234663, *IL6*-rs1800796, -rs1800795, and *IL13*-rs1800925 polymorphisms are significantly associated with the risk of COPD. In contrast, three polymorphisms of *IL1β* gene (rs16944, rs1143627, and rs1143634) were not associated with increased risk of COPD. Furthermore, our results were mainly similar to previous meta-analyses. Nevertheless, the findings for *IL1β*-rs16944 and IL13-rs1800925 polymorphisms in different ethnicity differed from those of previous meta-analyses. Accordingly, our results proposed that *IL1β*-rs16944 and *IL13*-rs1800925 polymorphisms may not be a potential risk factor for COPD development even in the Asian or Caucasian ethnicities. In addition, our result evidenced that the *IL13*-rs1800925 polymorphism was associated with COPD risk in pooled comparison, Asians, and Arabs but not in Caucasians.

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Conflict of interest

No conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2019.02.003.

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