Correlations of Three Polymorphisms in Beta2-Adrenergic Receptor Gene with Chronic Obstructive Pulmonary Disease Risk and Related Phenotypes: A Meta-Analysis

Type

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polymorphism, gene, meta-analysis, chronic obstructive pulmonary disease, β 2-adrenergic receptor

Abstract

Introduction

The gene encoding β 2-adrenergic receptor (ADRB2) is a candidate gene for chronic obstructive pulmonary disease (COPD), yet the results are not often reproducible. We aimed to assess the association of ADRB2 genetic polymorphisms (rs1042713, rs1042714, and rs1800888) with COPD risk and COPD-related phenotypes via a meta-analysis.

Material and methods

Literature search, quality evaluation, and data extraction were completed independently and in duplicate. Effect-size estimation is expressed as odds ratio (OR) or weighted mean difference (WMD) with 95% confidence interval (CI).

Results

Total 15 articles were meta-analyzed, including 12 articles (2917/8807 patients/controls) for COPD risk, and 6 articles (18350 subjects) for COPD-related phenotypes. Overall, there was no detectable significance for the association of rs1042713 (OR, 95% CI: 1.02, 0.88-1.19) and rs1042714 (1.01, 0.85-1.20) with COPD risk, and only marginal significance retained for rs1800888 (1.31, 1.00-1.72). In subsidiary analyses, the association of rs1042713 and rs1042714 with COPD risk was significant in populations of Asian origin (OR: 1.66 and 1.351, 95% CI: 1.13-2.44 and 1.02-1.79). Additionally, carriers of rs1042713 AA genotype had significantly lower levels of FEV1 (WMD, 95% CI: -0.011 L, -0.026 to -0.004) than carriers of GG genotypes, and FVC% predicted levels were significantly increased for the comparisons of rs1042713 AA genotype (6.914, 4.829 to 8.999) and AG genotype (4.249, 2.925 to 5.573) with GG genotype. There were low probabilities of publication bias.

Conclusions

Our findings suggest that contribution of ADRB2 genetic polymorphisms to COPD risk is small and ethnicity-dependent, and to COPD-related phenotypes is significant.

Correlations of Three Polymorphisms in Beta2-Adrenergic Receptor Gene with Chronic Obstructive Pulmonary Disease Risk and Related Phenotypes: A Meta-Analysis

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ABSTRACT

The gene encoding β 2-adrenergic receptor (*ADRB2*) is a candidate gene for chronic obstructive pulmonary disease (COPD), yet the results are not often reproducible. We aimed to assess the association of *ADRB2* genetic polymorphisms (rs1042713, rs1042714, and rs1800888) with COPD risk and COPD-related phenotypes via a meta-analysis.

Literature search, quality evaluation, and data extraction were completed independently and in duplicate. Effect-size estimation is expressed as odds ratio (OR) or weighted mean difference (WMD) with 95% confidence interval (CI).

Total 15 articles were meta-analyzed, including 12 articles (2917/8807 patients/controls) for COPD risk, and 6 articles (18350 subjects) for COPD-related phenotypes. Overall, there was no detectable significance for the association of rs1042713 (OR, 95% CI: 1.02, 0.88-1.19) and rs1042714 (1.01, 0.85-1.20) with COPD risk, and only marginal significance retained for rs1800888 (1.31, 1.00-1.72). In subsidiary analyses, the association of rs1042713 and rs1042714 with COPD risk was significant in populations of Asian origin (OR: 1.66 and 1.351, 95% CI: 1.13-2.44 and 1.02-1.79). Additionally, carriers of rs1042713 AA genotype had significantly lower levels of FEV1 (WMD, 95% CI: -0.011 L, -0.026 to -0.004) than carriers of GG genotypes, and FVC% predicted levels were significantly increased for the comparisons of rs1042713 AA genotype (6.914, 4.829 to 8.999) and AG genotype (4.249, 2.925 to 5.573) with GG genotype. There were low probabilities of publication bias.

Our findings suggest that contribution of *ADRB2* genetic polymorphisms to COPD risk is small and ethnicity-dependent, and to COPD-related phenotypes is significant.

Key Words: Chronic obstructive pulmonary disease; β 2-adrenergic receptor; Gene; Polymorphism; Meta-analysis.

INTRODUCTION

It is widely believed that the development of chronic obstructive pulmonary disease (COPD) is largely under genetic control.¹ COPD is a complex disease of high prevalence, and it has become the third leading cause of morbidity and mortality worldwide.² As reported by the Global Burden of Disease (GBD) study, an estimated 174.5 million adults have prevalent COPD in 2015.³ Our recent national survey indicated that in China, the estimated total number of COPD patients aged 20 years or older was 99.9 million in 2015.⁴ Currently, debates concerning how to early identify subjects at risk for COPD are still ongoing and unsettled.⁵ Identification of genetic markers hence, has proven to be feasible and effective, as heritability of COPD affection status was estimated to be 37.7%.⁶

A considerable number of genes and polymorphisms have been assessed as candidate determinants of the risk for COPD in current literature.^{7,8} Many case-control studies have addressed in particular the putative contribution of β 2-adrenergic receptor (*ADRB2*) gene to COPD susceptibility. *ADRB2* is a member of the G protein-coupled receptor superfamily. Several polymorphisms in *ADRB2* gene have been widely evaluated in association with COPD risk, including rs1800888 (Thr164Ile), rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu). For instance, Ho and colleagues⁹ for the first time focused on *ADRB2* gene and found that Gly16 allele increased the susceptibility to the development of COPD, and Gln27 was associated with the severity of COPD in a Chinese population. Another study in Germans by Vacca and colleagues¹⁰ showed that Gly16 allele predisposed to COPD development, yet no relevance was noted for Gln27Glu polymorphism. A thorny issue facing human geneticists is the inconsistent findings across different studies, possibly due to diverse genetic backgrounds, heterogeneous subject characteristics or insufficient study power of individual studies.¹¹ To shed some light on this issue, we employed the meta-analytical method and tested the hypothesis that *ADRB2* genetic polymorphisms are potential candidates in predisposition to the development of COPD.

To be specific, we reviewed medical literature to identify eligible articles that assessed the association of genetic polymorphisms in *ADRB2* gene with the risk of having COPD, pooled the results and explored possible causes of between-study heterogeneity. Meanwhile, we also interrogated the association of three polymorphisms (rs1042713, rs1042714, and rs1800888) with COPD-related phenotypes.

METHODS

The meta-analysis was conducted according to the guidelines of the Preferred

Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹² The PRISMA checklist and flow diagram are presented in Supplementary Table 1 and Figure 1, respectively.

Search Strategy

We searched all potentially eligible studies from PubMed, EMBASE, Web of Science, and Google Scholar published before August 29, 2020. We used the title or abstract search strategy with following entries: ('ADRB2' OR 'β2-adrenergic receptor' OR 'β2 adrenergic receptor' OR 'beta2-adrenergic receptor' OR 'beta2 adrenergic receptor' OR 'β-2-adrenergic receptor' OR 'ADRB2R' OR 'B2AR' OR 'BETA2AR' OR 'ADRB2R' OR 'β-2-adrenergic receptor' OR 'adrenoceptor') AND ('polymorphism' OR 'variant' OR 'variation' OR 'mutation' OR 'allele' OR 'genotype' OR 'SNP') AND ('chronic obstructive pulmonary' OR 'COPD' OR 'obstructive pulmonary'). We also checked reference lists of identified publications for other potentially relevant studies. Literature search was completed by two authors (Guan Wang and Yang Wang). All citations were combined, and duplicates were manually excluded.

Selection Criteria

Articles were inclusive if a) the genotype or allele counts of *ADRB2* genetic polymorphisms were provided in both COPD patients and controls; b) the mean and standard deviation or standard error or quartile or 95% confidence interval (CI) of COPD-related phenotypes (including FEV1%Pred or FEV1 or FVC or FVC% or FEV1/FVC) and genotype counts were available; c) COPD was diagnosed by generally accepted standards; d) polymorphisms were genotyped using validated methods. Only articles published in the English language and conducted in populations were included, and articles published in form of conference abstract, letter to the editor or correspondence, case reports or case series, or reviews or meta-analyses were excluded.

Per the selection criteria formulated above, two authors (Guan Wang and Yang Wang) independently assessed the eligibility of each potential article for inclusion, and the results were compared and disagreement was resolved by consensus.

Data Extraction

The following data were extracted from each eligible study into an unified designed table: the first author's surname, year of publication, country, ethnicity of the study subjects, study design, sample size, diagnosis of COPD, source of cases and controls, age, gender, match, body mass index, smoking status, pack years of smoking, forced expiratory volume in one second (FEV1), forced expiratory volume in one second % predicted (FEV1/Pred%),

forced vital capacity (FVC), forced vital capacity % predicted (FVC/Pred%), the ratio of forced expiratory volume to forced vital capacity in one second (FEV1/FVC), the number of subjects with different genotypes of *ADRB2* genetic polymorphisms in both COPD patients and controls. Data abstracted by the two authors (Guan Wang and Yang Wang) were checked for coherence, and any divergence was resolved by resorting to original context until a consensus was reached.

Quality score assessment

The quality of each study was independently assessed by two authors (Guan and Yang) according to the score system by Thakkestian^{13,14} displayed in Supplementary Table 2. The quality scores were based on both traditional epidemiologic considerations and genetic issues.¹⁴ The total scores ranged from 0 to 15.

Statistical Analyses

Statistical analyses were conducted by the STATA software Release 14.1 (Stata Corp, College Station, TX). Considering the limited number of minor homozygous genotypes, COPD risk prediction is evaluated under the allele and dominant models of inheritance only. The association between three polymorphisms in *ADRB2* gene and COPD risk was evaluated by weighted odds ratio (OR) with 95% CI in COPD patients relative to controls. The secondary outcome of this meta-analysis was the difference in COPD-related phenotypes across genotypes, as expressed as weighted mean difference (WMD) with 95% CI. Summary OR and WMD were calculated under the random-effects model, due to assumption of clinical and methodological heterogeneity across studies, which can often cause statistical heterogeneity. Additionally, in case of no statistical heterogeneity, both fixed-effects model and random-effects model yield very similar results, and when statistical heterogeneity is present, random-effects model is preferred.¹⁵

Statistical heterogeneity was quantified using the inconsistency index (I^2) statistic (ranging from 0.0% to 100.0%), which is defined as the percentage of observed between-study variability that is due to heterogeneity rather than chance. If I^2 exceeds 50% or χ^2 -based probability is less than 10%, it indicates significant heterogeneity.

Cumulative and sensitivity analyses were performed to identify the influence of individual studies on overall estimation.

Funnel plots were used to assess the probability of publication bias and small-study effect. If funnel shape was asymmetric, it might suggest an association between pooled estimate and study size (publication bias or small study bias). The Egger's test was used to objectively assess funnel asymmetry, and the trim-and-fill method was used to calculate

probable missing studies due to publication bias. On the side, to estimate the extent to which one or more covariates explain heterogeneity, meta-regression was employed as an extension to random-effects meta-analysis.

RESULTS

Qualified Studies

Initial literature search retrieved 53 articles published in the English language, and two additional articles were identified through the other sources. Based on predefined inclusion and exclusion criteria, 15 articles were eligible for analysis.^{9,10,16-28} There were 12 articles involving 15 studies (2917 patients and 8807 controls) that focused on the association of *ADRB2* genetic polymorphisms (rs1042713 [Arg16Gly], rs1042714 [Gln27Glu], and rs1800888 [Thr164Ile]) with the risk for COPD, and 6 articles involving 10 studies (18350 subjects) that focused on the changes in either FEV1 or FEV1%Pred or FVC or FVC%Pred or FEV1/FVC across genotypes of *ADRB2* genetic polymorphisms, if available. The score of involved studies was greater than or equal to 10.

Baseline Characteristics

Baseline characteristics of eligible studies are presented in Table 1. All studies were published between 2001 and 2018. Total sample size ranged from 106 to 8470. Five studies were prospective in design, and 9 studies were retrospective. COPD was diagnosed according to the GOLD²⁹ guideline in all, but two (according to ATS³⁰) studies.

Overall Association with COPD Risk

Figure 2 shows the forest plots of three polymorphisms in *ADRB2* gene associated with the risk for COPD under the allele model of inheritance. There are 13, 12, and 2 studies eligible for rs1042713, rs1042714, and rs1800888, respectively. Overall, there was no detectable significance for the association of rs1042713 (OR: 1.02, 95% CI: 0.88 to 1.19) and rs1042714 (OR: 1.01, 95% CI: 0.85 to 1.20) with COPD risk, with moderate evidence of heterogeneity (I^2 : 60.2% and 66.5%, respectively). As for rs1800888, the mutant allele of this polymorphism was significantly associated with a 31% increased risk of COPD (OR: 1.31, 95% CI: 1.00 to 1.72), without heterogeneity (I^2 : 0.0%).

Subsidiary Association with COPD Risk

Table 2 shows the effect size estimates by subgrouping studies according to sample size, ethnicity, study design, matched status, COPD diagnosis, and sources of cases and controls respectively under both allele and dominant models. Because of the limited number of eligible studies for rs1800888, subsidiary analyses were only conducted for rs1042713 and

rs1042714. Under the allele model, no hint of significance was observed for both polymorphisms across all subgroups. By contrast, under the dominant model, the association of both polymorphisms with COPD risk was significant in populations of Asian origin (for rs1042713, OR: 1.66, 95% CI: 1.13 to 2.44; for rs1042714, OR: 1.35, 95% CI: 1.02 to 1.79), without heterogeneity (I^2 : 0.0% and 1.7%, respectively). In addition, rs1042713 was associated with ATS-diagnosed COPD under the dominant model (OR: 2.17, 95% CI: 1.14 to 4.12, I^2 : 0.0%).

Cumulative and Influential Analyses

The plots of cumulative and influential analyses on the association of three studied polymorphisms in *ADRB2* gene with COPD risk are displayed in Supplementary Figure 1.

Publication Bias

Begg's and filled funnel plots of three polymorphisms in *ADRB2* gene associated with COPD risk are displayed in Figure 3. The probability of publication bias was low, as reflected the seemingly symmetry of Begg's funnel plots and as confirmed by Egger's tests (all $p > 0.1$). Filled funnel plots revealed that only one study was assumed to be missing to make the funnel plot symmetrical for the association between rs1042713 and COPD risk.

Overall and Subsidiary Association with COPD-Related Phenotypes

Table 3 shows the association of two polymorphisms (rs1042713 and rs1042714) in *ADRB2* gene with COPD-related phenotypes in both overall and subsidiary analyses.

In overall analyses, carriers of rs1042713 AA genotype had significantly lower levels of FEV1 (WMD: -0.011 L, 95% CI: -0.026 to -0.004) than carriers of GG genotypes, with no evidence of heterogeneity (both I^2 : 0.0%). Levels of FVC% predicted were significantly increased for the comparisons of rs1042713 AA genotype (WMD: 6.914, 95% CI: 4.829 to 8.999) and AG genotype (WMD: 4.249, 95% CI: 2.925 to 5.573) with GG genotype. Significant increase in FEV1/FVC was also found for the comparison of rs1042714 CC genotype with GG genotype (WMD: 3.098, 95% CI: 0.102 to 6.095).

In subsidiary analyses, FVC% predicted was significantly increased in carriers of rs1042713 AA genotype (WMD: 6.990, 95% CI: 4.897 to 9.083) and AG genotype (WMD: 4.250, 95% CI: 2.923 to 5.577) related to GG genotype in populations of Caucasian origin. Significant increase in FEV1/FVC was also observed for the comparison of rs1042714 CC genotype with GG genotype in Caucasians (WMD: 3.120, 95% CI: 0.010 to 6.230).

Meta-regression Analyses

To further account for between-study heterogeneity within a multivariable frame-work, we performed meta-regression analyses by incorporating various study-level

covariates including averaged levels of FEV1%Pred, FVC%Pred, FEV1, FVC, and FEV1/FVC ratio between *ADRB2* gene polymorphisms and controls. In Figure 4, we interestingly and exclusively observed that study design was a significant source of between-study heterogeneity by rs1042713 (FEV1%Pred (P=0.009), FVC%Pred (P=0.048)) and rs1042714 (FEV1 (P=0.035), FEV1/FVC ratio (P=0.000)) .

Although overall analyses failed to detect any significance for rs1042713 and rs1042714, subsidiary analyses indicated that both polymorphisms were potential candidate loci in susceptibility to COPD in Asians. In further genotype-phenotype analyses, carriers of mutant allele of rs1042713 had significantly higher levels of FVC% predicted than those with the wild genotype, and homozygous mutant genotype of rs1042714 was associated with significantly increased FEV1/FVC levels relative to the corresponding homozygous wild genotype, and the effects were more obvious in Caucasians.

DISCUSSION

In 2014, Wei and colleagues³¹ conducted a meta-analysis of 10 articles and found that *ADRB2* gene rs1042713 was a potential risk factor for the development of COPD in smoking Asian populations, but not in European descendents. In 2017, Nielsen and colleagues³² updated this meta-analysis by including 16 articles and additionally assessing the association of *ADRB2* gene three polymorphisms as the present study examined with therapeutic response to inhaled beta2-agonists in COPD, and they found null associations with COPD risk and treatment response. Extending the results of previous meta-analyses, we made more efforts to explore possible causes of between-study heterogeneity by subsidiary analyses, and additionally interrogated data on changes of COPD-related phenotypes across *ADRB2* genotypes. On one hand, although our overall analyses consolidated previous results, subsidiary analyses revealed that the association between *ADRB2* gene and COPD risk may be depended on ethnicity and diagnosis of COPD. In view of ethnic differences, we agree that it is of importance to construct a database of genetic determinants related to COPD in each ethnic group, and deciphering the difference in the genetic profiles of different ethnic groups will help in unravelling the molecular mechanisms involved in COPD. Nevertheless, because of a small effect expected from studied polymorphisms in *ADRB2* gene, studies of multiple genes and polymorphisms are needed to test a new hypothesis.

On the other hand, our genotype-phenotype analyses indicated that *ADRB2* genetic defects might lead to changes in FVC% and FEV1/FVC. It is widely believed that COPD is a complex polygenic disease, which is the result of combinations of genetic and non-genetic

factors, each of which contributes to a tiny fraction of disease risk. It might be speculated that the modulatory effect of a single locus in *ADRB2* gene on COPD-related phenotypes is not strong enough to result in a statistically significant risk for COPD. Also, we agree that success in characterizing genetic underpinning of COPD will depend on our capability to assess nonlinearities in the genotype-phenotype association, as well as possible gene-gene and locus-locus interactions known as epistasis.

Our findings are biologically plausible. There is experimental evidence suggesting that *ADRB2* has a strong correlation with airway bronchodilation, and a predominant role in the treatment of obstructive pulmonary diseases via mediating the function of β_2 -adrenergic agonists.³³ The β_2 -adrenergic agonists may inhibit the proliferation of human airway smooth muscle cells and neutrophil accumulation, and so the responsiveness of *ADRB2* to β_2 -adrenergic agonists thereby may play a vital role in regulating bronchial hyperresponsiveness and the development of COPD.³¹

Our results indicated that *ADRB2* gene rs1042713 and rs1042714 were potential candidate loci in susceptibility to COPD in Asians. It has been proved that *ACE* DD genotype³⁴ and *TNF-alpha* +489 G/A genotype³⁵⁻³⁸ were also risk factors specially in Asians. More bench works could be conducted to find whether synergistic effects of the three polymorphisms exist on COPD risk in Asians. Furthermore, more researches on genome-wide association study (GWAS) and epigenetics should be considered to help decipher the pathogenesis of COPD.³⁵

There are several possible limitations for this present meta-analysis. Firstly, only studies published in English were retrieved, and selection bias is likely. It is estimated that grey literature may result in an overestimate of an association impact by an average of 12%.³⁹ Secondly, our analyses were based on cross-sectional observational data, which obviated comment on causality between *ADRB2* gene and COPD risk, as well as COPD-related phenotypes. Thirdly, eligible studies on the association between rs1800888 and COPD are limited, and although this association was statistically significant, more studies are needed. Fourthly, a large panel of subsidiary analyses were conducted to appraise heterogeneity, as it is estimated that small sample size may lead to low statistical efficiency.

In conclusion, our findings suggest that the contribution of *ADRB2* genetic polymorphisms to COPD risk is small and ethnicity-dependent, yet the contribution to COPD-related phenotypes is significant but requires further confirmation. For practical reasons, further investigations in large, well-designed studies are required to elucidate the association between *ADRB2* genetic polymorphisms and COPD and its relevant phenotypes,

as well as the molecular mechanisms of these polymorphisms in the pathogenesis of COPD.

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Conflict of Interest Statement: None declared.

Specific Author Contributions: W.N. and G.W. planned and designed the study; G.W. and Y.W. searched literature, selected articles and abstracted data; D.H., L.S., H.J., L.Y., and S.Z. did data preparation, quality control and data analyses; G.W. and W.N. wrote the manuscript.

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Table 1. The baseline characteristics of all involved studies in this meta-analysis.

First author	Year	Country	Ethnicity	Sample size	Matched condition	Study design	COPD diagnosis	COPD stage	Features of controls
Ho, L. I	2001	China	East Asian	106	YES	Prospective	ATS	I-III	NA
Hegab, A. E. (Japan)	2004	Japan	East Asian	149	YES	Retrospective	GOLD	I-IV	Smoke
Hegab, A. E. (Egypt)	2004	Egypt	African	178	YES	Retrospective	GOLD	I-IV	Smoke
Brogger, J.	2006	Norway	Caucasian	492	NA	Prospective	GOLD	I-IV	Smoke
Matheson, M. C.	2006	Australia	Caucasian	260	NA	Retrospective	ATS	I-III	Mixed
Ferdinands, J. M. (American-African)	2007	America	American-African	63	NA	Prospective	GOLD	I-IV	Mixed
Ferdinands, J. M. (Caucasian)	2007	America	Caucasian	189	NA	Prospective	GOLD	I-IV	Mixed
Vacca, G.	2009	German	Caucasian	362	YES	Retrospective	GOLD	I-IV	Smoke
Papatheodorou, A.	2010	Greece	European	218	NA	Retrospective	GOLD	I-IV	Smoke
Thomsen, M.	2012	Denmark	Caucasian	8470	NA	Prospective	GOLD	I-IV	NA
Ganbold, C.	2016	Mongolia	Middle Asian	200	YES	Retrospective	GOLD	I-IV	NA
Hussein, M. H.	2017	Egypt	African	115	YES	Retrospective	GOLD	I-IV	Mixed
Zhao, H.	2017	China	East Asian	500	NA	Retrospective	GOLD	I-IV	NA
Li, J. X.	2018	China	East Asian	422	YES	Retrospective	GOLD	I-IV	Smoke

(Continued)

Sources		Age (years)		Male		Pack-years		FEV1/Predicted (%)		FEV1		FEV1/FVC		FEV1/FVC%		FVC	
Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Hospital	Hospital	71.2	71.2	60	NA	NA	NA	45.2	NA	45.2	NA	NA	NA	NA	NA	NA	NA
Population	Population	66.9	67.8	85	60	60.1	53.3	46.7	96.2	46.7	96.2	77.4	97.1	47.1	81.4	NA	NA
Population	Population	62.5	59	106	72	52.5	49.5	30.3	85.9	30.3	85.9	56.3	92.3	44.3	78.3	NA	NA
Hospital	Population	58.4	54.9	144	128	28.8	19.1	50	95.4	50	95.4	76	97.9	52	80	3.16	4.15
Population	Population	62.7	56.9	21	128	36	33	71.2	113.6	71.2	113.6	97	113.2	56.5	79	3.63	4.53
Population	Population	54.6	53.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Population	Population	56.4	54.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hospital	Hospital	62.66	65.29	124	93	33.52	25.38	51.31	94.16	51.31	94.16	70.87	98	57.2	78.78	NA	NA
Hospital	Hospital	69.4	63	40	54	76.1	44.3	48.5	100.7	48.5	100.7	70.8	101.6	53	83	NA	NA
Population	Population	59.8	59.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Hospital	Hospital	62.2	60.3	57	54	31	29.2	44.5	82.4	44.5	82.4	49.9	94.9	53	86	NA	NA
Hospital	Hospital	62	60.91	60	51	72.9	30.5	32.9	91.6	32.9	91.6	48.6	86.4	53.2	85.1	NA	NA
Hospital	Hospital	63.17	61.77	172	146	27.15	22.9	52.99	91.22	52.99	91.22	NA	NA	51.86	83.54	NA	NA
Hospital	Hospital	69.9	67.9	163	160	30.6	28.8	54	95	54	95	NA	NA	49	86	NA	NA

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV1/ Predicted%, forced expiratory volume in 1 second % predicted; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ATS, American Thoracic Society; NA, not available.

Table 2. Subsidiary association of two polymorphisms in *ADRB2* gene with COPD risk under both allele and dominant models.

Subgroups	Studies (cases/ controls), n (n/n)	Allele model			Dominant model		
		OR (95% CI)	I ²	p	OR (95% CI)	I ²	p
rs1042713							
By sample size							
Sample size <164	4 (258/175)	1.02 (0.62 to 1.68)	67.5%	0.026	1.27 (0.80 to 2.03)	0.0%	0.570
Sample size ≥164	9 (2389/8398)	1.03 (0.87 to 1.20)	61.9%	0.007	1.07 (0.82 to 1.41)	70.4%	0.001
By ethnicity							
African	3 (211/145)	0.82 (0.47 to 1.41)	65.4%	0.056	0.74 (0.46 to 1.17)	0.0%	0.544
Asian	3 (355/324)	1.09 (0.72 to 1.64)	64.6%	0.059	1.660 (1.13 to 2.44)	0.0%	0.967
Caucasian	7 (2081/8104)	1.07 (0.89 to 1.30)	65.2%	0.008	1.073 (0.79 to 1.46)	70.6%	0.002
By study design							
Retrospective	8 (897/1019)	1.09 (0.85 to 1.39)	69.0%	0.002	1.06 (0.71 to 1.57)	69.6%	0.002
Prospective	5 (1750/7554)	0.99 (0.80 to 1.21)	47.7%	0.105	1.16 (0.87 to 1.55)	42.4%	0.139
By matched status							
YES	6 (610/511)	0.92 (0.69 to 1.22)	62.5%	0.021	0.83 (0.56 to 1.2)	47.0%	0.093
NA	7 (2037/8062)	1.13 (0.93 to 1.37)	62.3%	0.014	1.33 (0.99 to 1.77)	61.8%	0.015
By COPD diagnosis							
ATS	2 (104/262)	1.21 (0.42 to 3.53)	88.0%	0.004	2.17 (1.14 to 4.12)	0.0%	0.389
GOLD	11 (2543/8311)	1.01 (0.88 to 1.16)	51.2%	0.025	1.03 (0.81 to 1.29)	57.8%	0.008
By case source							
Hospital	7 (967/945)	0.99 (0.84 to 1.15)	28.3%	0.212	1.02 (0.73 to 1.42)	59.0%	0.023
Population	6 (1680/7628)	1.13 (0.80 to 1.60)	77.9%	<0.0001	1.24 (0.81 to 1.92)	67.4%	0.009
By control source							
Hospital	6 (729/706)	0.95 (0.79 to 1.15)	31.2%	0.201	0.99 (0.64 to 1.46)	61.8%	0.023
Population	7 (1918/7867)	1.13 (0.87 to 1.46)	74.3%	0.001	1.23 (0.88 to 1.70)	63.9%	0.011
rs1042714							
By sample size							
Sample size <164	3 (213/156)	0.93 (0.45 to 1.89)	65.2%	0.056	0.88 (0.26 to 2.93)	81.7%	0.004
Sample size ≥164	9 (2536/8591)	1.07 (0.89 to 1.27)	67.6%	0.002	1.07 (0.84 to 1.37)	67.0%	0.002

By ethnicity								
African	2 (167/126)	1.20 (0.27 to 5.44)	93.2%	<0.0001	0.98 (0.09 to 10.35)	95.3%	<0.0001	
Asian	4 (613/563)	1.27 (0.92 to 1.73)	28.8%	0.239	1.35 (1.02 to 1.79)	1.7%	0.384	
Caucasian	6 (1969/8058)	0.95 (0.81 to 1.11)	50.8%	0.071	0.89 (0.71 to 1.13)	49.1%	0.081	
By study design								
Retrospective	9 (1187/1247)	1.08 (0.81 to 1.45)	74.1%	<0.0001	1.03 (0.68 to 1.56)	78.1%	<0.0001	
Prospective	3 (1562/7500)	1.05 (0.97 to 1.13)	0.0%	0.482	1.09 (0.96 to 1.23)	0.0%	0.661	
By matched status								
YES	8 (609/500)	1.041 (0.655 to 1.655)	79.1%	<0.0001	0.977 (0.494 to 1.932)	83.5%	<0.0001	
NA	4 (2140/8247)	1.054 (0.919 to 1.210)	35.6%	0.170	1.100 (0.965 to 1.254)	6.7%	0.374	
By COPD diagnosis								
ATS	2 (138/262)	0.78 (0.57 to 1.08)	0.0%	0.741	0.82 (0.52 to 1.31)	0.0%	0.549	
GOLD	10 (2611/8485)	1.08 (0.89 to 1.31)	69.0%	0.001	1.05 (0.79 to 1.40)	75.0%	<0.0001	
By case source								
Hospital	8 (1230/1179)	0.96 (0.78 to 1.18)	54.3%	0.032	0.87 (0.63 to 1.20)	65.5%	0.005	
Population	4 (1519/7568)	1.32 (0.83 to 2.10)	80.7%	0.001	1.48 (0.82 to 2.65)	78.6%	0.003	
By control source								
Hospital	7 (986/934)	0.96 (0.75 to 1.24)	60.3%	0.019	0.85 (0.58 to 1.26)	70.4%	0.002	
Population	5 (1763/7813)	1.15 (0.86 to 1.55)	76.1%	0.002	1.27 (0.85 to 1.90)	73.4%	0.005	

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; I^2 , inconsistency index; NA, not available.

Table 3. Overall and subgroup analyses of *ADRB2* gene polymorphisms with COPD-related phenotypes.

Groups	rs1042713									
	AA vs. GG					AG vs. GG				
	Studies (total samples), n (n)	WMD	95% CI	<i>I</i> ²	<i>p</i>	Studies (total samples), n (n)	WMD	95% CI	<i>I</i> ²	<i>p</i>
FEV1 (L) (Overall)	4 (1625)	-0.011	-0.026 to -0.004	0.0%	0.767	4 (2550)	0.007	-0.016 to 0.030	0.0%	0.786
FEV1 (L) by ethnicity										
Asian	2 (79)	-0.095	-0.322 to 0.132	0.0%	0.477	2 (122)	0.038	-0.150 to 0.226	0.0%	0.564
Mixed	2 (1546)	-0.011	-0.026 to 0.004	0.0%	0.738	2 (2428)	0.006	-0.017 to 0.030	0.0%	0.429
FEV1 (L) by group										
COPD patients	4 (1625)	-0.011	-0.026 to 0.004	0.0%	0.767	4 (2550)	0.007	-0.016 to 0.030	0.0%	0.786
FEV1% predicted (Overall)	8 (9383)	0.991	-0.602 to 2.583	70.8%	0.001	8 (15095)	1.175	-0.515 to 2.866	86.6%	0.000
FEV1%predicted by ethnicity										
Asian	1 (17)	-12.0	-32.927 to 8.927	NA	NA	1 (56)	1.000	-19.852 to 21.852	NA	NA
African	2 (2039)	10.396	-12.912 to 33.705	86.3%	0.007	2 (3045)	0.108	-1.662 to 1.878	0.0%	0.537
Caucasian	2 (5781)	2.466	-2.156 to 7.087	85.7%	0.001	3 (9566)	1.896	-3.152 to 6.943	95.8%	<0.0001
Mixed	2 (1546)	0.044	-0.995 to 1.083	0.0%	0.777	2 (2428)	0.284	-0.500 to 1.067	9.3%	0.294
FEV1% predicted by group										
COPD patients	5 (1692)	0.415	-1.959 to 2.789	54.7%	0.066	5 (2698)	0.279	-0.461 to 1.018	0.0%	0.778
Controls	1 (67)	0.000	-0.949 to 0.949	0.0%	1.00	2 (12300)	0.000	-0.657 to 0.657	0.0%	1.000
Both	2 (7624)	5.360	2.781 to 7.939	NA	NA	1 (97)	5.930	4.400 to 7.460	NA	NA
FVC% predicted (Overall)	2 (84)	6.914	4.829 to 8.999	0.0%	0.414	2 (154)	4.249	2.925 to 5.573	0.0%	0.982
FVC% predicted by ethnicity										
Asian	1 (17)	-3.00	-26.884 to 20.884	NA	NA	1 (56)	4.000	-17.783 to 25.783	NA	NA
Caucasian	1 (67)	6.990	4.897 to 9.083	NA	NA	1 (98)	4.250	2.923 to 5.577	NA	NA
FVC% predicted by group										
COPD patients	1 (17)	0.415	-1.959 to 2.789	54.7%	0.066	1 (56)	4.000	-17.783 to 25.783	NA	NA
Both	1 (67)	5.360	2.781 to 7.939	NA	NA	1 (98)	4.250	2.923 to 5.577	NA	NA
FEV1/FVC (%)	6 (7837)	-0.144	-0.993 to 0.706	37.2%	0.158	6 (12666)	0.373	-0.296 to 1.043	45.6%	0.102
FEV1/FVC (%) by ethnicity										
Asian	1 (17)	-12.000	-27.090 to 3.090	NA	NA	1 (56)	-1.000	-14.368 to 12.368	NA	NA

African	2 (2039)	3.258	-5.219 to 11.735	72.1%	0.058	2 (3045)	0.010	-0.674 to 0.695	0.0%	0.773
Caucasian	3 (5781)	-0.162	-0.846 to 0.523	0.0%	0.407	3 (9565)	0.558	-0.738 to 1.854	76.2%	0.015
FEV1/FVC (%) by group										
COPD patients	3 (146)	0.917	-8.278 to 10.112	64.2%	0.061	3 (270)	-0.433	-4.041 to 3.176	0.0%	0.887
Controls	2 (7624)	0.000	-0.508 to 0.508	0.0%	1.000	2 (12300)	0.000	-0.406 to 0.406	0.0%	1.000
Both	1 (67)	-1.330	-3.218 to 0.558	NA	NA	1 (96)	1.460	0.586 to 2.334	NA	NA
(Continued)										
rs1042714										
Groups	CC vs. GG					CG vs. GG				
	Studies (total samples), n (n)	WMD	95% CI	I ²	p	Studies (total samples), n (n)	WMD	95% CI	I ²	p
FEV1 (L) (Overall)	2 (130)	-0.091	-0.40 to 0.218	12.7%	0.284	2 (49)	-0.058	-0.355 to 0.240	0.0%	0.562
FEV1 (L) by ethnicity										
Asian	2 (130)	-0.091	-0.400 to 0.218	12.7%	0.284	2 (49)	-0.058	-0.355 to 0.240	0.0%	0.562
FEV1 (L) by group										
COPD patients	2 (130)	-0.091	-0.400 to 0.218	12.7%	0.284	2 (49)	-0.058	-0.355 to 0.240	0.0%	0.562
FEV1% predicted (Overall)	3 (325)	-10.003	-27.128 to 7.122	87%	0.000	3 (142)	1.906	-2.654 to 6.466	0.0%	0.583
FEV1% predicted by ethnicity										
Asian	2 (253)	-17.615	-37.387 to 2.158	75.1%	0.045	2 (84)	-3.001	-13.491 to 7.488	0.0%	0.838
Caucasian	1 (72)	2.640	-2.394 to 7.674	NA	NA	1 (58)	3.050	-2.014 to 8.114	NA	NA
FEV1% predicted by group										
COPD patients	2 (253)	-17.615	-37.387 to 2.158	75.1%	0.045	1 (84)	-3.001	-13.491 to 7.488	0.0%	0.838
Both	1 (72)	2.640	-2.394 to 7.674	NA	NA	1 (58)	3.050	-2.014 to 8.114	NA	NA
FVC% predicted (Overall)	2 (118)	-3.017	-13.136 to 7.102	63.3%	0.099	2 (85)	-1.042	-9.909 to 7.826	50.4%	0.156
FVC% predicted by ethnicity										
Asian	1 (45)	-10.000	-22.165 to 2.165	NA	NA	1 (27)	-8.000	-21.030 to 5.30	NA	NA
Caucasian	1 (73)	0.800	-3.280 to 4.880	NA	NA	1 (58)	1.900	-2.228 to 6.028	NA	NA
FVC% predicted by group										
COPD patients	1 (45)	-10.000	-22.165 to 2.165	NA	NA	1 (27)	-8.000	-21.030 to 5.30	NA	NA
Both	1 (73)	0.800	-3.280 to 4.880	NA	NA	1 (58)	1.900	-2.228 to 6.028	NA	NA
FEV1/FVC (%) (Overall)	3 (325)	3.098	0.102 to 6.095	0.0%	0.634	3 (141)	0.122	-2.912 to 3.157	0.0%	0.819

FEV1/FVC (%) by ethnicity										
Asian	2 (253)	2.820	-8.342 to 13.982	0.0%	0.341	2 (84)	1.516	-9.589 to 12.620	0.0%	0.563
Caucasian	1 (72)	3.120	0.010 to 6.230	NA	NA	1 (57)	0.010	-3.145 to 3.165	NA	NA
FEV1/FVC (%) by group										
COPD patients	2 (253)	2.820	-8.342 to 13.982	0.0%	0.341	2 (84)	1.516	-9.589 to 12.620	0.0%	0.563
Both	1 (72)	3.120	0.010 to 6.230	NA	NA	1 (57)	0.010	-3.145 to 3.165	NA	NA

Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; I^2 , inconsistency index; NA, not available.

Supplementary Table 1. The PRISMA checklist for this present meta-analysis.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7;14-15 Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figure 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Figure 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7-9;16-20 Supplementary Figure1, Table2, Table 3, Figure4
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

Supplementary Table 2. The quality scores of all involved studies in this present meta-analysis.

First author(year)	Representativeness of cases	Representativeness of controls	Ascertainment of COPD	Ascertainment of controls	Genotyping examination	Hardy-Weinberg equilibrium	Association assessment	Response rate	Total
Ho, L. I.(2001)	2	2	2	1	0	0	1	2	10
Hegab, A. E. (Japan) (2004)	2	2	2	0	0	2	1	2	11
Hegab, A. E. (Egypt) (2004)	2	2	2	0	0	2	1	2	11
Brogger, J.(2006)	2	2	2	2	0	2	2	0	12
Matheson, M. C. (2006)	2	2	2	2	1	2	2	2	15
Ferdinands, J. M. (2007) (American-African)	2	2	2	2	1	2	2	2	15
Ferdinands, J. M. (2007) (Caucasian)	2	2	2	2	1	2	2	2	15
Vacca, G.(2009)	2	2	2	2	0	2	1	2	13
Papatheodorou, A. (2010)	2	2	2	1	0	2	1	2	12
Thomsen, M.(2012)	2	2	2	2	1	2	2	2	15
Ganbold, C.(2016)	2	2	2	1	0	2	2	2	13
Hussein, M. H.(2017)	2	2	2	1	0	2	2	2	13
Zhao, H.(2017)	2	2	2	2	0	2	1	2	13
Li, J. X.(2018)	2	2	2	2	0	2	2	2	14

Supplementary Figure 1. Cumulative and influential plots of three polymorphisms in *ADRB2* gene associated with the risk of chronic obstructive pulmonary disease.

A. rs1042713

B. rs1042713

C. rs1042714

D. rs1042714

E. rs1800888

F. rs1800888

Figure 1. Flow Diagram of study selection for the meta-analysis

Figure 2. Forest plots of three polymorphisms in *ADRB2* associated with COPD under the allele model.

A. rs1042713

B. rs1042714

C. rs1800888

Figure 3. Begg's and filled funnel plots of three polymorphisms in *ADRB2* gene associated with COPD under the allele model.

A. rs1042713 Begg's funnel plot

B. rs1042713 filled funnel plot

C. rs1042714 Begg's funnel plot

D. rs1042714 filled funnel plot

E. rs1800888 Begg's funnel plot

F. rs1800888 filled funnel plot

Figure 4. Meta-regression analyses of rs1042713 and rs1042714 polymorphisms in *ADRB2* with COPD-relevant phenotypes.

A. Average FEV1%Pred by rs1042713

B. Average FVC%Pred levels by rs1042713

C. Average FEV1 levels by rs1042714

D. Average FEV1/FVC ratio levels by rs1042714