Correlations of three polymorphisms in β_2-adrenergic receptor gene with chronic obstructive pulmonary disease risk and related phenotypes: a meta-analysis

Guan Wang[1,2], Danni He[3], Yang Wang[4], Haifeng Jin[1], Lijie Yao[1], Yang Jiang[1], Deshan Zhou[2], Lei Shen[1], Wenquan Niu[3,5]

[1]Department of Anatomy, Qiqihar Medical University, Qiqihar, Heilongjiang, China
[2]Department of Histology and Embryology, School of Basic Medical Sciences, Capital Medical University, Beijing, China
[3]Institute of Clinical Medical Sciences, China-Japan Friendship Hospital, Beijing, China
[4]Department of Medical Service Supervision, Qiqihar Health Inspection Bureau, Qiqihar, Heilongjiang, China
[5]National Clinical Research Center for Respiratory Diseases, Beijing, China

Submitted: 10 October 2020; **Accepted:** 3 March 2021
Online publication: 20 March 2021

Arch Med Sci
DOI: https://doi.org/10.5114/aoms/133901

Corresponding authors:
Wenquan Niu, PhD
Institute of Clinical Medical Sciences
China-Japan Friendship Hospital
No. 2 Yinghua East St
Chaoyang District
Beijing 100029, China
Tel./fax: 86-01-8420 6414
E-mail: niuwenquan_shcn@163.com

Lei Shen, PhD
Department of Anatomy
Qiqihar Medical University
No.333 Bukui North St
Jianhua District
Qiqihar 161006, China
Tel./fax: 86-452-2663809
E-mali: shenlei815@yahoo.com

Abstract

Introduction: The gene encoding the 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 the odds ratio (OR) or weighted mean difference (WMD) with a 95% confidence interval (CI).

Results: In 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 higher for rs1042713 AA genotype (6.914, 4.829 to 8.999) and AG genotype (4.249, 2.925–5.573) compared with GG genotype. There were low probabilities of publication bias.

Conclusions: Our findings suggest that the 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 had 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 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 recent literature [7, 8]. Many case-control studies have addressed in particular the putative contribution of the β_2-adrenergic receptor (ADRB2) gene to COPD susceptibility. ADRB2 is a member of the G protein-coupled receptor superfamily. Several polymorphisms in the *ADRB2* gene have been widely evaluated in association with COPD risk, including rs1800888 (Thr164Ile), rs1042713 (Arg16Gly) and rs1042714 (Gln27Glu). For instance, Ho and colleagues [9] for the first time focused on the *ADRB2* gene and found that the 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 on Germans by Vacca and colleagues [10] showed that the 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 the *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.

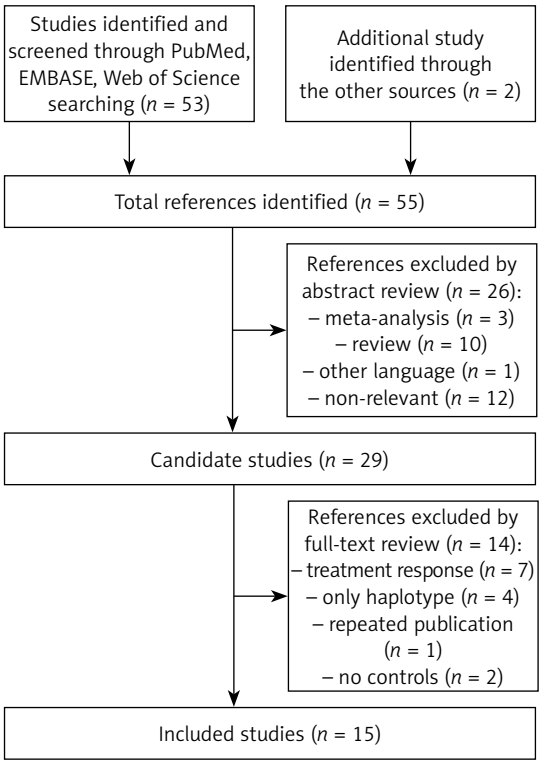

Figure 1. Flow diagram of study selection for the meta-analysis

Material and 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 SI 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 the following entries: ('ADRB2' OR 'β2-adrenergic receptor' OR 'β2 adrenergic receptor' OR 'beta2-adrenergic receptor' OR 'beta2 adrenergic receptor' OR 'beta-2-adrenergic receptor' OR 'ADRBR' 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. The 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 the form of conference abstracts, letters to the editor or correspondence, case reports or case series, or reviews or meta-analyses were excluded.

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

Data extraction

The following data were extracted from each eligible study into a 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 the 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 Thakkinstian [13, 14] displayed in Supplementary Table SII. 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 the *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 the assumption of clinical and methodological heterogeneity across studies, which can often cause statistical heterogeneity. Additionally, in the case of no statistical heterogeneity, a fixed-effects model and a random-effects model yield very similar results, and when statistical heterogeneity is present, a 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). 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. 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

The initial literature search retrieved 53 articles published in the English language, and two additional articles were identified through 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 included studies was greater than or equal to 10.

Baseline characteristics

Baseline characteristics of eligible studies are presented in Table I. All studies were published between 2001 and 2018. Total sample size ranged

Table I. Baseline characteristics of all studies included in this meta-analysis

First author	Year	Country	Ethnicity	Sample size	Matched condition	Study design	COPD diagnosis	COPD stage	Features of controls
Ho LI	2001	China	East Asian	106	Yes	prospective	ATS	I –III	NA
Hegab AE (Japan)	2004	Japan	East Asian	149	Yes	retrospective	GOLD	I –IV	smoke
Hegab AE (Egypt)	2004	Egypt	African	178	Yes	retrospective	GOLD	I –IV	smoke
Brogger J	2006	Norway	Caucasian	492	NA	prospective	GOLD	I –IV	smoke
Matheson MC	2006	Australia	Caucasian	260	NA	retrospective	ATS	I –III	mixed
Ferdinands JM (American-African)	2007	America	American-African	63	NA	prospective	GOLD	I –IV	mixed
Ferdinands JM (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 MH	2017	Egypt	African	115	Yes	retrospective	GOLD	I –IV	mixed
Zhao H	2017	China	East Asian	500	NA	retrospective	GOLD	I –IV	NA
Li JX	2018	China	East Asian	422	Yes	retrospective	GOLD	I –IV	smoke

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

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.

from 106 to 8470. Five studies were prospective in design, and 9 studies were retrospective. COPD was diagnosed according to the GOLD [29] guideline in all but two (according to ATS [30]) studies.

Overall association with COPD risk

Figure 2 shows the forest plots of three polymorphisms in the *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: 0.88–1.19) and rs1042714 (OR: 1.01, 95% CI: 0.85–1.20) with COPD risk, with moderate evidence of heterogeneity (I^2: 60.2% and 66.5%, respectively). As for rs1800888, the mutant allele

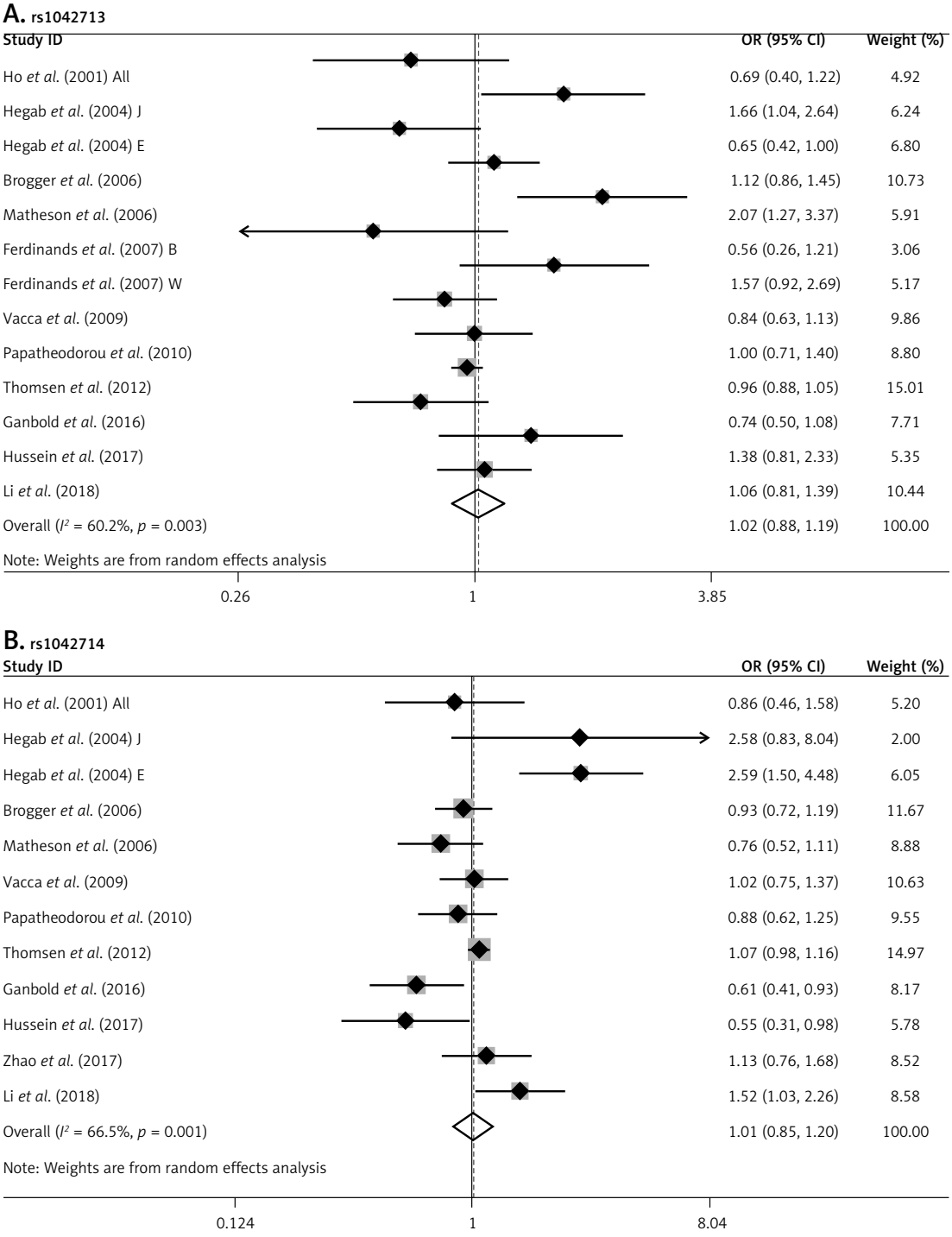

Figure 2. Forest plots of three polymorphisms in *ADRB2* associated with COPD under the allele model

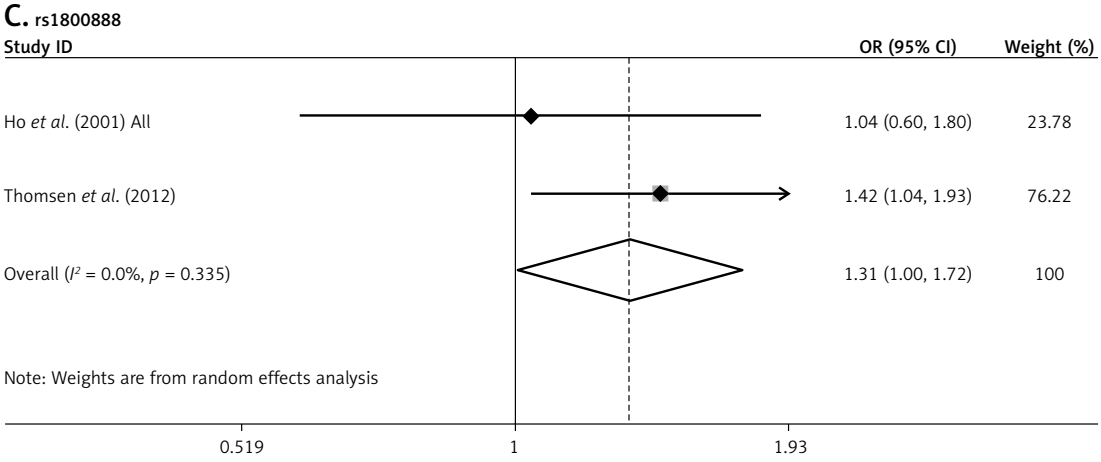

Figure 2. Cont.

of this polymorphism was significantly associated with a 31% increased risk of COPD (OR: 1.31, 95% CI: 1.00–1.72), without heterogeneity (I^2: 0.0%).

Subsidiary association with COPD risk

Table II 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 significance was observed for either polymorphism 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: 1.13–2.44; for rs1042714, OR: 1.35, 95% CI: 1.02–1.79), 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: 1.14–4.12, I^2: 0.0%).

Cumulative and influential analyses

The plots of cumulative and influential analyses on the association of three studied polymorphisms in the *ADRB2* gene with COPD risk are displayed in Supplementary Figure S1.

Publication bias

Begg's and filled funnel plots of three polymorphisms in the *ADRB2* gene associated with COPD risk are displayed in Figure 3. The probability of publication bias was low, as reflected by the seeming 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 III shows the association of two polymorphisms (rs1042713 and rs1042714) in the *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 higher for rs1042713 AA genotype (WMD: 6.914, 95% CI: 4.829–8.999) and AG genotype (WMD: 4.249, 95% CI: 2.925–5.573) compared with GG genotype. Significantly higher FEV1/FVC was also found for the comparison of rs1042714 CC genotype with GG genotype (WMD: 3.098, 95% CI: 0.102–6.095).

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

Meta-regression analyses

To further account for between-study heterogeneity within a multivariable framework, 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 het-

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

Table II. Cont.

Subgroups	Studies (cases/controls), *n* (*n*/*n*)	Allele model			Dominant model		
		OR (95% CI)	I^2	*p*	OR (95% CI)	I^2	*p*
rs1042714							
By sample size:							
Sample size < 164	3 (213/156)	0.93 (0.45–1.89)	65.2%	0.056	0.88 (0.26–2.93)	81.7%	0.004
Sample size ≥ 164	9 (2536/8591)	1.07 (0.89–1.27)	67.6%	0.002	1.07 (0.84–1.37)	67.0%	0.002
By ethnicity:							
African	2 (167/126)	1.20 (0.27–5.44)	93.2%	< 0.0001	0.98 (0.09–10.35)	95.3%	< 0.0001
Asian	4 (613/563)	1.27 (0.92–1.73)	28.8%	0.239	1.35 (1.02–1.79)	1.7%	0.384
Caucasian	6 (1969/8058)	0.95 (0.81–1.11)	50.8%	0.071	0.89 (0.71–1.13)	49.1%	0.081
By study design:							
Retrospective	9 (1187/1247)	1.08 (0.81–1.45)	74.1%	< 0.0001	1.03 (0.68–1.56)	78.1%	< 0.0001
Prospective	3 (1562/7500)	1.05 (0.97–1.13)	0.0%	0.482	1.09 (0.96–1.23)	0.0%	0.661
By matched status:							
Yes	8 (609/500)	1.041 (0.655–1.655)	79.1%	< 0.0001	0.977 (0.494–1.932)	83.5%	< 0.0001
NA	4 (2140/8247)	1.054 (0.919–1.210)	35.6%	0.170	1.100 (0.965–1.254)	6.7%	0.374
By COPD diagnosis:							
ATS	2 (138/262)	0.78 (0.57–1.08)	0.0%	0.741	0.82 (0.52–1.31)	0.0%	0.549
GOLD	10 (2611/8485)	1.08 (0.89–1.31)	69.0%	0.001	1.05 (0.79–1.40)	75.0%	< 0.0001
By case source:							
Hospital	8 (1230/1179)	0.96 (0.78–1.18)	54.3%	0.032	0.87 (0.63–1.20)	65.5%	0.005
Population	4 (1519/7568)	1.32 (0.83–2.10)	80.7%	0.001	1.48 (0.82–2.65)	78.6%	0.003
By control source:							
Hospital	7 (986/934)	0.96 (0.75–1.24)	60.3%	0.019	0.85 (0.58–1.26)	70.4%	0.002
Population	5 (1763/7813)	1.15 (0.86–1.55)	76.1%	0.002	1.27 (0.85–1.90)	73.4%	0.005

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

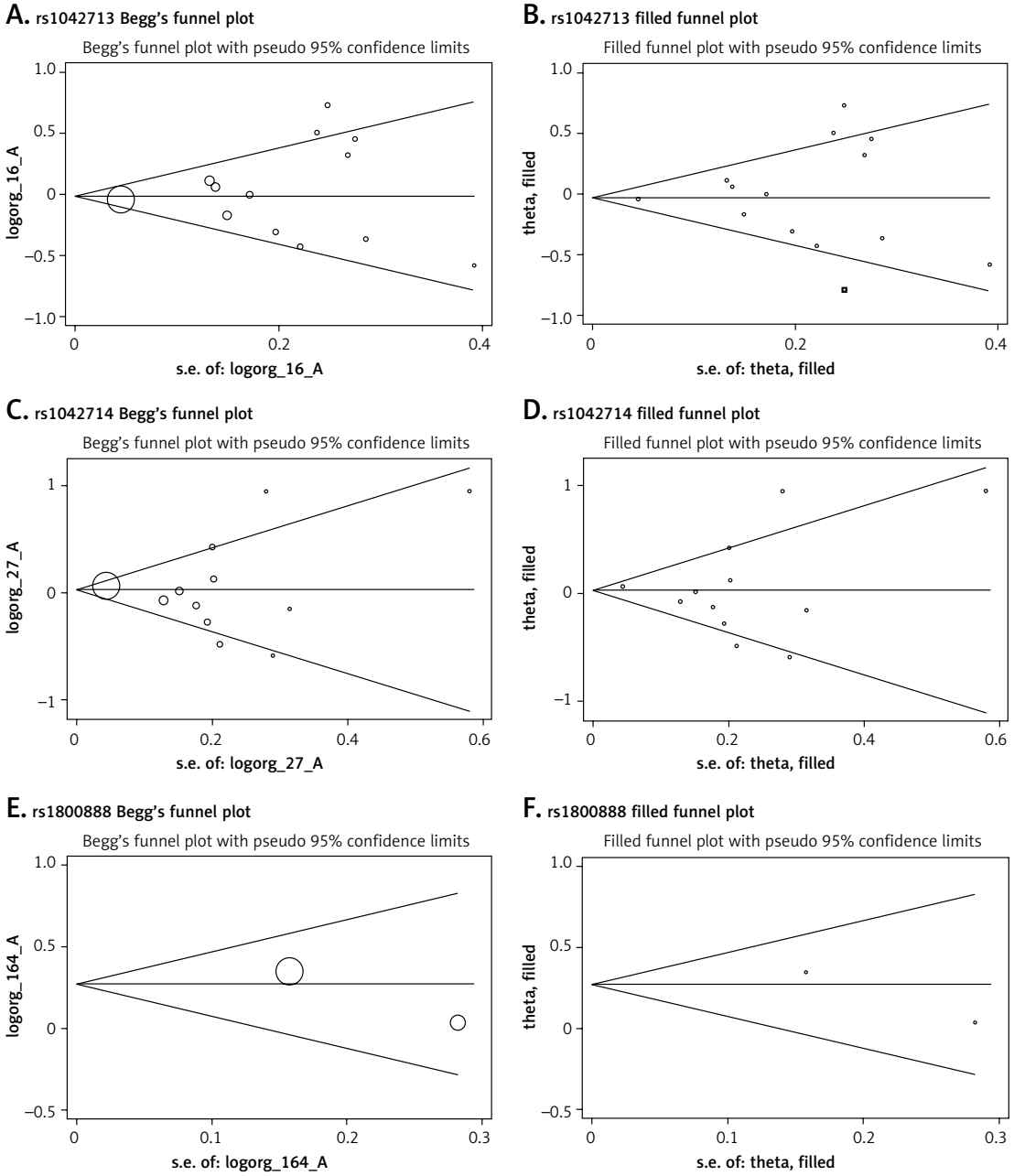

Figure 3. Begg's and filled funnel plots of three polymorphisms in *ADRB2* gene associated with COPD under the allele model

erogeneity 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 the 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 higher FEV1/FVC levels relative to the corresponding homozygous wild genotype, and the effects were more obvious in Caucasians.

Discussion

In 2014, Wei and colleagues [31] 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 descendants. In 2017, Nielsen and colleagues [32] updated this meta-analysis by including 16 articles and additionally assessing the association of three *ADRB2* gene polymorphisms, like the present study, examined with therapeutic response

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

Table III. Cont.

Groups	rs1042713									
	AA vs. GG					AG 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/FVC (%) by ethnicity:										
Asian	1 (17)	–12.000	–27.090–3.090	NA	NA	1 (56)	–1.000	–14.368–12.368	NA	NA
African	2 (2039)	3.258	–5.219–11.735	72.1%	0.058	2 (3045)	0.010	–0.674–0.695	0.0%	0.773
Caucasian	3 (5781)	–0.162	–0.846–0.523	0.0%	0.407	3 (9565)	0.558	–0.738–1.854	76.2%	0.015
FEV1/FVC (%) by group:										
COPD patients	3 (146)	0.917	–8.278–10.112	64.2%	0.061	3 (270)	–0.433	–4.041–3.176	0.0%	0.887
Controls	2 (7624)	0.000	–0.508–0.508	0.0%	1.000	2 (12300)	0.000	–0.406–0.406	0.0%	1.000
Both	1 (67)	–1.330	–3.218–0.558	NA	NA	1 (96)	1.460	0.586–2.334	NA	NA

Groups	rs1042714									
	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	–0.40–0.218	12.7%	0.284	2 (49)	–0.058	–0.355–0.240	0.0%	0.562
FEV1 (L) by ethnicity:										
Asian	2 (130)	–0.091	–0.400–0.218	12.7%	0.284	2 (49)	–0.058	–0.355–0.240	0.0%	0.562
FEV1 (L) by group:										
COPD patients	2 (130)	–0.091	–0.400–0.218	12.7%	0.284	2 (49)	–0.058	–0.355–0.240	0.0%	0.562
FEV1% predicted (overall)	3 (325)	–10.003	–27.128–7.122	87%	0.000	3 (142)	1.906	–2.654–6.466	0.0%	0.583
FEV1% predicted by ethnicity:										
Asian	2 (253)	–17.615	–37.387–2.158	75.1%	0.045	2 (84)	–3.001	–13.491–7.488	0.0%	0.838
Caucasian	1 (72)	2.640	–2.394–7.674	NA	NA	1 (58)	3.050	–2.014–8.114	NA	NA
FEV1% predicted by group:										
COPD patients	2 (253)	–17.615	–37.387–2.158	75.1%	0.045	1 (84)	–3.001	–13.491–7.488	0.0%	0.838
Both	1 (72)	2.640	–2.394–7.674	NA	NA	1 (58)	3.050	–2.014–8.114	NA	NA
FVC% predicted (overall)	2 (118)	–3.017	–13.136–7.102	63.3%	0.099	2 (85)	–1.042	–9.909–7.826	50.4%	0.156

Table III. Cont.

Groups	rs1042714									
	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*
FVC% predicted by ethnicity:										
Asian	1 (45)	–10.000	–22.165–2.165	NA	NA	1 (27)	–8.000	–21.030–5.30	NA	NA
Caucasian	1 (73)	0.800	–3.280–4.880	NA	NA	1 (58)	1.900	–2.228–6.028	NA	NA
FVC% predicted by group:										
COPD patients	1 (45)	–10.000	–22.165–2.165	NA	NA	1 (27)	–8.000	–21.030–5.30	NA	NA
Both	1 (73)	0.800	–3.280–4.880	NA	NA	1 (58)	1.900	–2.228–6.028	NA	NA
FEV1/FVC (%) (verall)	3 (325)	3.098	0.102–6.095	0.0%	0.634	3 (141)	0.122	–2.912–3.157	0.0%	0.819
FEV1/FVC (%) by ethnicity:										
Asian	2 (253)	2.820	–8.342–13.982	0.0%	0.341	2 (84)	1.516	–9.589–12.620	0.0%	0.563
Caucasian	1 (72)	3.120	0.010–6.230	NA	NA	1 (57)	0.010	–3.145–3.165	NA	NA
FEV1/FVC (%) by group										
COPD patients	2 (253)	2.820	–8.342–13.982	0.0%	0.341	2 (84)	1.516	–9.589–12.620	0.0%	0.563
Both	1 (72)	3.120	0.010–6.230	NA	NA	1 (57)	0.010	–3.145–3.165	NA	NA

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

to inhaled β_2-agonists in COPD, and they found no associations with COPD risk or 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 the *ADRB2* gene and COPD risk may be dependent on ethnicity and diagnosis of COPD. In view of ethnic differences, we agree that it is important 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 the *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 the *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 the 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 are potential candidate loci in susceptibility to COPD in Asians. It has been proved that *ACE* DD genotype [34] and *TNF-alpha* +489 G/A genotype [35–38] are also risk factors specially in Asians. More bench works could be

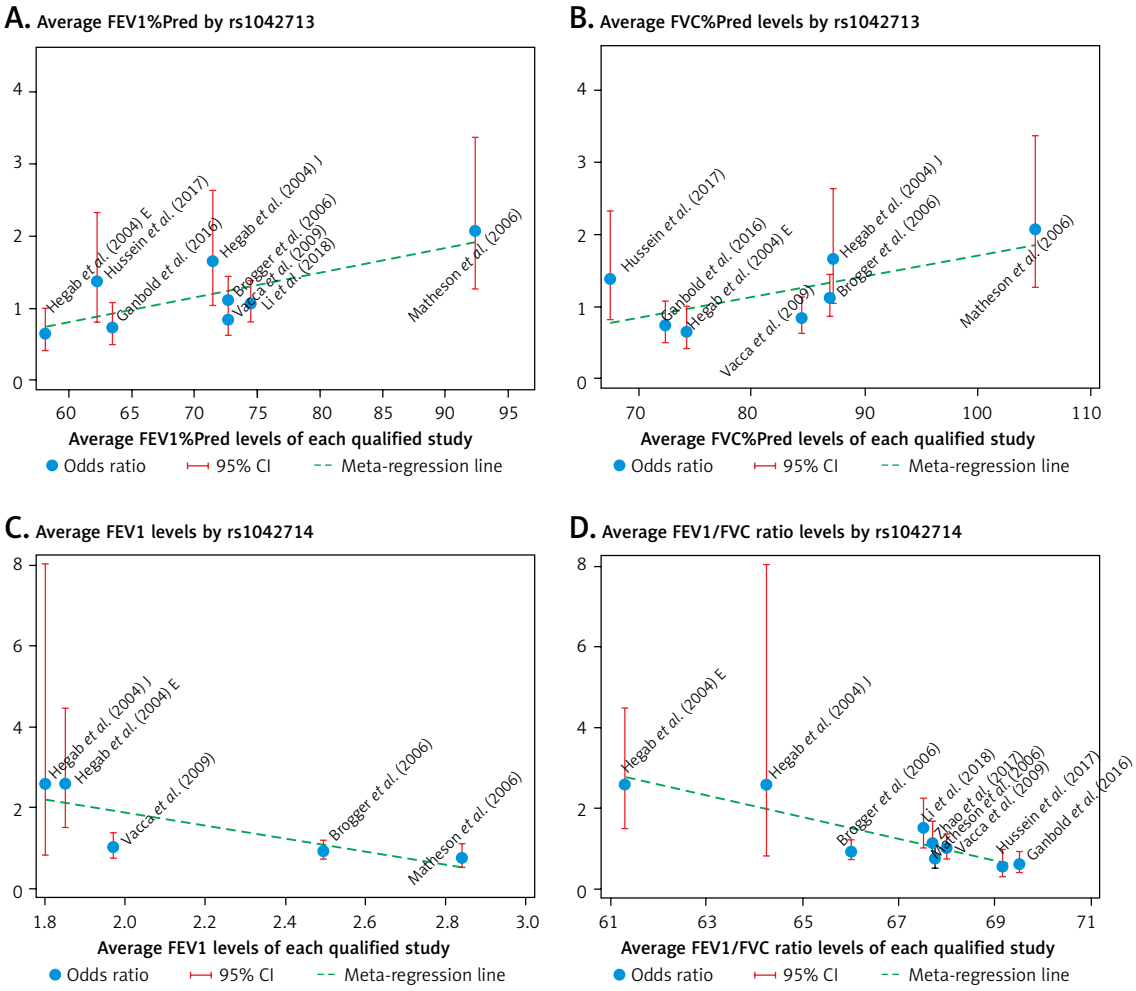

Figure 4. Meta-regression analyses of rs1042713 and rs1042714 polymorphisms in *ADRB2* with COPD-relevant phenotypes

conducted to find out whether there exist synergistic effects of the three polymorphisms on COPD risk in Asians. Furthermore, more research including genome-wide association study (GWAS) and epigenetics should be considered to help decipher the pathogenesis of COPD [35].

There are several possible limitations of 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 precluded comment on causality between the *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.

Acknowledgment

Guan Wang, Danni He and Yang Wang contributed equally to this work.

This work was supported by the Science Research Foundation of Qiqihar Medical University (Grant No. QY2017Q-06) and the National Natural Science Foundation of China (Grant No. 81970042).

Conflict of interest

The authors declare no conflict of interest.

References

1. Kurche JS, Schwartz DA. Deciphering the genetics of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2019; 199: 4-5.
2. Starkey MR, Plank MW, Casolari P, et al. IL-22 and its receptors are increased in human and experimental COPD and contribute to pathogenesis. Eur Respir J. 2019; 54: 1800174.
3. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017; 5: 691-706.
4. Wang C, Xu J, Yang L, et al. Prevalence and risk factors of chronic obstructive pulmonary disease in China (the China Pulmonary Health [CPH] study): a national cross-sectional study. Lancet 2018; 391: 1706-17.
5. Baraldo S. Advances in chronic obstructive pulmonary disease genetics: building the picture one piece at a time. Lancet Respir Med 2019; 7: 371-2.
6. Zhou JJ, Cho MH, Castaldi PJ, Hersh CP, Silverman EK, Laird NM. Heritability of chronic obstructive pulmonary disease and related phenotypes in smokers. Am J Respir Crit Care Med 2013; 188: 941-7.
7. Hardin M, Silverman EK. Chronic obstructive pulmonary disease genetics: a review of the past and a look into the future. Chronic Obstr Pulm Dis 2014; 1: 33-46.
8. Korytina GF, Akhmadishina LZ, Aznabaeva YG, et al. Associations of the NRF2/KEAP1 pathway and antioxidant defense gene polymorphisms with chronic obstructive pulmonary disease. Gene. 2019; 692: 102-12.
9. Ho LI, Harn HJ, Chen CJ, Tsai NM. Polymorphism of the beta(2)-adrenoceptor in COPD in Chinese subjects. Chest 2001; 120: 1493-9.
10. Vacca G, Schwabe K, Duck R, et al. Polymorphisms of the beta2 adrenoreceptor gene in chronic obstructive pulmonary disease. Ther Adv Respir Dis 2009; 3: 3-10.
11. Niu W, Qi Y. Matrix metalloproteinase family gene polymorphisms and risk for coronary artery disease: systematic review and meta-analysis. Heart 2012; 98: 1483-91.
12. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015; 313: 1657-65.
13. Thakkinstian A, McEvoy M, Minelli C, et al. Systematic review and meta-analysis of the association between {beta}2-adrenoceptor polymorphisms and asthma: a HuGE review. Am J Epidemiol 2005; 162: 201-11.
14. Attia J, Thakkinstian A, D'Este C. Meta-analyses of molecular association studies: methodologic lessons for genetic epidemiology. J Clin Epidemiol 2003; 56: 297-303.
15. Cohn LD, Becker BJ. How meta-analysis increases statistical power. Psychol Methods 2003; 8: 243-53.
16. Hegab AE, Sakamoto T, Saitoh W, et al. Polymorphisms of IL4, IL13, and ADRB2 genes in COPD. Chest 2004; 126: 1832-9.
17. Brogger J, Steen VM, Eiken HG, Gulsvik A, Bakke P. Genetic association between COPD and polymorphisms in TNF, ADRB2 and EPHX1. Eur Respir J 2006; 27: 682-8.
18. Matheson MC, Ellis JA, Raven J, Johns DP, Walters EH, Abramson MJ. Beta2-adrenergic receptor polymorphisms are associated with asthma and COPD in adults. J Hum Genet 2006; 51: 943-51.
19. Ferdinands JM, Mannino DM, Gwinn ML, Bray MS. ADRB2 Arg16Gly polymorphism, lung function, and mortality: results from the Atherosclerosis Risk in Communities study. PloS One 2007; 2: e289.
20. Kim WJ, Oh YM, Sung J, et al. Lung function response to 12-week treatment with combined inhalation of long-acting beta2 agonist and glucocorticoid according to ADRB2 polymorphism in patients with chronic obstructive pulmonary disease. Lung 2008; 186: 381-6.
21. Papatheodorou A, Makrythanasis P, Kaliakatsos M, et al. Development of novel microarray methodology for the study of mutations in the SERPINA1 and ADRB2 genes – their association with obstructive pulmonary disease and disseminated bronchiectasis in Greek patients. Clin Biochem 2010; 43: 43-50.
22. Bleecker ER, Meyers DA, Bailey WC, et al. ADRB2 polymorphisms and budesonide/formoterol responses in COPD. Chest 2012; 142: 320-8.
23. Marson FA, Bertuzzo CS, Ribeiro AF, Ribeiro JD. Polymorphisms in ADRB2 gene can modulate the response to bronchodilators and the severity of cystic fibrosis. BMC Pulm Med 2012; 12: 50.
24. Thomsen M, Nordestgaard BG, Sethi AA, Tybjaerg-Hansen A, Dahl M. Beta2-adrenergic receptor polymorphisms, asthma and COPD: two large population-based studies. Eur Respir J 2012; 39: 558-66.
25. Ganbold C, Jamyansuren J, Puntsag O, Batjargal O, Dashtseren I, Jav S. ADRB2 and ACE gene polymorphisms in COPD susceptibility. Cent Asian J Med Sci 2016; 2: 127-33.
26. Hussein MH, Sobhy KE, Sabry IM, El Serafi AT, Toraih EA. Beta2-adrenergic receptor gene haplotypes and bronchodilator response in Egyptian patients with chronic obstructive pulmonary disease. Adv Med Sci 2017; 62: 193-201.
27. Zhao H, Wu X, Dong CL, Wang BY, Zhao J, Cao XE. Association between ADRB2 genetic polymorphisms and the risk of chronic obstructive pulmonary disease: a case-control study in a Chinese population. Genet Test Mol Biomarkers 2017; 21: 491-6.
28. Li JX, Fu WP, Zhang J, et al. A functional SNP upstream of the ADRB2 gene is associated with COPD. Int J Chron Obstruct Pulmon Dis 2018; 13: 917-25.
29. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, Committee GS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001; 163: 1256-76.
30. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. Am J Respir Crit Care Med 1995; 152 (5 Pt 2): S77-121.
31. Wang W, Li P, Chen Y, Yang J. Association between beta2-Adrenergic Receptor-16Arg/Gly gene polymorphism and chronic obstructive pulmonary disease risk: systematic review and meta-analysis. Iran J Public Health 2014; 43: 877-88.
32. Nielsen AO, Jensen CS, Arredouani MS, Dahl R, Dahl M. Variants of the ADRB2 gene in COPD: Systematic review and meta-analyses of disease risk and treatment response. COPD 2017; 14: 451-60.
33. Sampsonas F, Karkoulias K, Kaparianos A, Spiropoulos K. Genetics of chronic obstructive pulmonary disease, beyond a1-antitrypsin deficiency. Curr Med Chem 2006; 13: 2857-73.
34. Mlak R, Homa-Mlak I, Powrozek T, et al. Impact of I/D polymorphism of ACE gene on risk of development and

course of chronic obstructive pulmonary disease. Arch Med Sci 2016; 12: 279-87.
35. Cui K, Ge XY, Ma HL. Association of the TNF-alpha+489 G/A polymorphism with chronic obstructive pulmonary disease risk in Asians: meta-analysis. Genet Mol Res 2015; 14: 5210-20.
36. Murdaca G, Gulli R, Spano F, et al. TNF-alpha gene polymorphisms: association with disease susceptibility and response to anti-TNF-alpha treatment in psoriatic arthritis. J Invest Dermatol 2014; 134: 2503-9.
37. Murdaca G, Gulli R, Spano F, Mandich P, Puppo F. Pharmacogenetics and future therapeutic scenarios: what affects the prediction of response to treatment with etanercept? Drug Dev Res 2014; 75 Suppl. 1: S7-10.
38. Murdaca G, Spano F, Contatore M, Guastalla A, Magnani O, Puppo F. Pharmacogenetics of etanercept: role of TNF-alpha gene polymorphisms in improving its efficacy. Expert Opin Drug Metab Toxicol 2014; 10: 1703-10.
39. McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses? Lancet 2000; 356: 1228-31.