The characteristics of the frequent exacerbator with chronic bronchitis phenotype and non-exacerbator phenotype in patients with chronic obstructive pulmonary disease: a meta-analysis and system review

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Abstract

Objective: To investigate the clinical characteristics between the frequent exacerbator with chronic bronchitis (FE-CB) phenotype and the non-exacerbator (NE) phenotype among patients with chronic obstructive pulmonary disease (COPD). Methods: We searched CNKI, Wan fang, Chongqing VIP, China Biology Medicine disc, PubMed, Cochrane Library, and EMBASE databases for relevant studies published as of April 30, 2019. All studies that investigated COPD patients with the FE-CB and NE phenotypes and which qualified the inclusion criteria were included. Cross-Sectional/Prevalence Study Quality recommendations were used to measure methodological quality. RevMan5.3 software was used for meta-analysis. Results: Ten case-control studies (n=8848) were included. Compared with the NE phenotype, patients with the FE-CB phenotype showed significantly lower forced vital capacity percent predicted (FVC%pred) [mean difference (MD) -6.69, 95% confidence interval (CI) -7.73–-5.65, P<0.001, I2=5%], forced expiratory volume in one second percent predicted (FEV1%pred) (MD -8.50, 95% CI -11.36–-5.65, P<0.001, I2=91%), and forced expiratory volume in one second/forced vital capacity (FEV1/FVC) (MD -3.76, 95% CI -4.58–-2.95,P<0.001, I2=0%); in contrast, the quantity of cigarettes smoked (pack-years) (MD 3.09, 95% CI 1.60–4.58, P<0.001, I2=41%), COPD assessment test (CAT) score (MD 5.61, 95% CI 4.62–6.60, P<0.001, I2=80%), modified Medical British Research Council (mMRC) score (MD 0.72, 95% CI 0.63–0.82, P<0.001, I2=57%), exacerbations in previous year (2.65, 95% CI 2.32–2.97, P<0.001, I2=91%), body mass index (BMI), obstruction, dyspnea, exacerbations (BODEx) (MD 1.78, 95% CI 1.28–2.28, P<0.001, I2=91%), I2=34%), and Charlson comorbidity index (MD 0.47, 95% CI 0.37–0.58, P<0.001, I2=0] were significantly higher in patients with FE-CB phenotype. No significant between-group difference was observed with respect to BMI (MD-0.14, 95% CI -0.70–0.42, P=0.62, I2=75%). Conclusion: COPD patients with the FE-CB phenotype had poorer pulmonary function and higher CAT score, the quantity of cigarettes smoked (pack-years), frequency of acute exacerbations, and mMRC scores than those with the NE phenotype.

Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease[1-3]. The Spanish Guidelines for Management of Chronic Obstructive Pulmonary Disease (GesEPOC) attempt to identify and elaborate this heterogeneity by characterizing various phenotypes in order to guide individualized diagnosis and treatment. Since its publication in 2013, the guidelines have been gradually adopted by other countries and have been continuously supported by new evidence. According to the risk stratification and clinical manifestations, the GesEPOC 2017 have incorporated some modifications to the COPD phenotypes to better reflect the differences of various COPD phenotypes observed in clinical practice.

GesEPOC defines four phenotypes: non-exacerbator (NE), frequent exacerbators with emphysema (FE-E), and frequent exacerbator with chronic bronchitis (FE-CB), and asthma-chronic obstructive pulmonary asthma overlap (ACO). The FE-CB and NE are two important phenotypes in GesEPOC.

The GesEPOC 2017 provides guidance for the diagnosis and treatment of patients with the FE-CB and NE phenotypes. Whether high-risk FE-CB patients or high-risk NE patients, initial treatment can choose the combination of long-acting β2-agonists and long-acting muscarinic antagonists. However, for high-risk patients with the FE-CB phenotype, the best treatment is guided by the individual characteristics of the patient. The optional drugs include inhaled corticosteroids, phlegm-resolving drugs, and antibiotics[4]. GesEPOC 2017 recommended long-term use of macrolide antibiotics to reduce the number of acute exacerbations in high-risk COPD patients who experienced more than three acute exacerbations in the past year.

However, these two phenotypes are not well characterized with respect to the epidemiology, risk factors, pathogenesis, clinical features, and prognosis. In terms of clinical characteristics, there is conflicting evidence of the association of these phenotypes with pulmonary function, the quantity of cigarettes smoked(pack-years), COPD Assessment Test (CAT) score, body mass index (BMI), frequency of acute exacerbations, St. George's questionnaire score (SGRQ), and complications. In a study, patients with FE-CB phenotype showed worse pulmonary function, higher CAT score, worse endurance to physical labor[5], and higher incidence of heart failure, anxiety, depression, and other complications[6]. Among all phenotypes, FE-CB was associated with more than three complications[7]. In some studies, patients with the FE-CB phenotype showed lower forced vital capacity percent predicted (FVC%pred)[8-13], forced expiratory volume in one second percent predicted (FEV_1%pred)[8-16], forced expiratory volume

in one second/ forced vital capacity (FEV_1/FVC)[9-11, 13], and forced expiratory volume in one second (FEV_1) [13, 16] as compared to those with the NE phenotype; however, other studies have revealed opposite results (FEV_1%pred[17], FEV_1/FVC[8], FEV_1[17]).

In this study, we sought to investigate the differences in pulmonary function, CAT, BMI, and the quantity of cigarettes smoked(pack-years) between COPD patients with the FE-CB phenotype and those with the NE phenotype; the objective was to better characterize the clinical features of these two phenotypes.

Research Methods

This meta-analysis was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines. The literature search and screening protocol were pre-established.

1.1 *Search Strategy*

We searched CNKI, Wan fang, Chongqing VIP, China Biology Medicine disc, PubMed, Cochrane Library, and EMBASE databases from the times of their inception to April 30, 2019. The language was restricted to English or Chinese. The following key words or combinations were used to retrieve studies: “Chronic Obstructive Pulmonary Disease” or “COPD”; merging “Non-exacerbators” or “Nonexacerbators” or “nonexacerbator” or “non-frequent exacerbators with chronic bronchitis or emphysema” or “non-exacerbator phenotype with either chronic bronchitis or emphysema” or “NE” or “NONEX” or “NE-CB/E” or “NON-AE”, merging “exacerbators with chronic bronchitis” or “frequent exacerbators with chronic bronchitis” or “frequent exacerbator phenotype with chronic bronchitis” or “exacerbator phenotype with chronic bronchitis” or “exacerbator with chronic bronchitis ”or “FE-CB”. In order to avoid omissions, the reference lists of relevant reviews and meta-analyses were manually screened.

1.2 *Inclusion and exclusion criteria*

Inclusion criteria: 1) COPD patients; 2) FE-CB phenotype and NE phenotype characteristics were reported; 3) main outcomes: pulmonary function tests including FVC, FEV_1, FVC%pred, FEV_1%pred, and FEV_1/FVC. Secondary outcomes: the quantity of cigarettes smoked(pack-years), COPD assessment Test (CAT) score, body mass index (BMI), frequency of acute exacerbations, Charlson comorbidity index, BMI, obstruction, dyspnea, exacerbations (BODEx), and modified Medical Research Council (mMRC) dyspnea scale score. Only studies that reported at least one of the main outcomes were included. 4) Clinical randomized trials, semi-randomized trials, prospective cohort studies, and retrospective case analysis.

Exclusion criteria: 1) repetitive articles; 2) plagiarized literature; 3) study design defects; 4) incomplete data or the inability to extract relevant data.

1.3 *Data extraction and quality assessment*

Two researchers (Jianjun Wu, Yingxue Zhang) independently performed literature screening and data extraction. Disagreements were determined by discussion or by a third coauthor (Hong-ri Xu). The methodological quality of the included studies was evaluated by the Cross-Sectional/Prevalence Study Quality recommendations of the American Agency for Healthcare Research and Quality (AHRQ). There are 11 items in total. If the answer was "no" or "unclear", the item was scored as "0"; if the answer was "yes", the item was scored as "1". The quality of each included study was evaluated as follows: low quality = 0-3; moderate quality = 4-7; high quality = 8-11.

1.4 *Observation indicators*

The following information was extracted: the researchers (name of authors, date of publication, language, country, type of study) and the research (sample size, average age, pulmonary function, the quantity of cigarettes smoked (pack-years), CAT score, BMI, and other variables).

1.5 *Publication bias assessment*

When more than ten studies were included in the meta-analysis, we evaluated potential publication bias by funnel plots and quantified by the Begg[18] and the Harbord [19] tests.

1.6 *Data analysis*

The statistical analyses were performed by Rev Man 5.3 software. Continuous variables were evaluated using the mean difference (MD) with 95% confidence intervals (CIs). Dichotomous variables were evaluated using the odds ratio (OR) or relative risk (RR) and 95% confidence intervals (CI). P<0.05 was considered as statistically significant. The heterogeneity was evaluated by I^2. If the heterogeneity was not significant (P>0.1 and I^2<50%), the fixed effect model was used for meta-analysis. If the heterogeneity was significant (P<0.1 and I^2>50%), the random-effects model was used for meta-analysis.

Results

2.1 *Literature Search*

A total of 372 articles were retrieved on database search. After review of titles and abstracts, 356 were eliminated for various reasons (Figure 1). Full-text of the remaining 17 articles were reviewed, after which 7 articles were excluded; therefore, 10 articles were included. Figure 1 shows a schematic illustration of the literature search and the study selection criteria.

2.2 *Basic characteristics of the included studies*

Ten studies with a combined study population of 8849 patients were included in this study[8-17]; these included 2699 patients with the FE-CB phenotype and 6150 patients with the NE phenotype. The characteristics of the included studies are summarized in Table 1.

2.3 Quality evaluation

According to the AHRQ, out of the 10 studies, no studies were evaluated as low quality, 7 were moderate quality, and 3 were high quality. The methodological quality evaluation of the included studies is shown in Table 2.

2.4 Comparison of the characteristics of COPD patients between the FE-CB and the NE phenotypes

2.4.1 FEV_1%pred

Ten studies[8-17] reported FEV_1%pred of COPD patients with the FE-CB and NE phenotypes. In nine studies[8-16], the FEV_1%pred of the FE-CB phenotype was significantly lower than that of the NE phenotype, while one other study[17] found no significant between-group difference in this respect. Owing to significant heterogeneity among the studies, the random-effects model was used for analysis. Meta-analysis showed that the FEV_1%pred of COPD patients with the FE-CB phenotype was lower than that of the NE phenotype (MD -8.50, 95% CI -11.36–-5.65, P<0.001, I^2=91%) (Figure 2). Sensitivity analysis suggested that the heterogeneity was mainly derived from the studies by Calle Rubio et al.[17], Qing et al.[16], and Koblizek et al[12]. After excluding the results of these studies, the FEV_1%pred of COPD patients with the FE-CB phenotype was still lower than that of the NE phenotype (MD -7.46, 95% CI -8.52–-6.40, P<0.001, I^2=10%).

2.4.2 FEV_1

Three studies[13, 16, 17] had reported FEV_1 of COPD patients with the FE-CB and NE phenotypes. The heterogeneity among the samples was large, and only descriptive analysis was done. In two studies[13, 16], the FEV_1 of the FE-CB phenotype was significantly lower than that of the NE phenotype, while one other study[17] found no significant between-group difference in this respect.

2.4.3 FVC%pred

Six studies[8-13] had reported the FVC%pred values of COPD patients with the FE-CB and NE phenotypes. In all six studies, the FVC%pred of patients with the FE-CB phenotype was significantly lower than that of the NE phenotype. There was no significant heterogeneity among the studies. The fixed-effect model was used for analysis. Meta-analysis showed that FVC%pred of COPD patients with the FE-CB phenotype was significantly lower than that of NE phenotype (MD -6.69, 95% CI -7.73–-5.65, P<0.001, I^2=5%) (Figure 3).

2.4.4 FEV_1/FVC

Five studies[8-11, 13] had reported FEV_1/FVC of COPD patients with the FE-CB and NE phenotypes. In three studies[10, 11, 13], the FEV_1/FVC of the FE-CB phenotype was significantly lower than that of the NE phenotype, while two studies[8, 9] found no significant between-group difference in this respect. There was no heterogeneity among the samples. The fixed-effect model was used for analysis. Meta-analysis showed that the FEV_1/FVC of FE-CB phenotype was significantly lower than that of the NE phenotype (MD -3.76, 95% CI -4.58–-2.95, P<0.001, I^2=0%) (Figure 4).

2.4.5 The quantity of cigarettes smoked (pack-years), CAT score, mMRC score, exacerbations in previous year, BMI, BODEx, Charlson comorbidity index

Secondary outcomes	included studies	MD	95% CI	P	I^2, P
the quantity of cigarettes smoked (pack-years)	Six studies	3.09	(1.60,4.58)	<0.001	41%, 0.14
CAT score	Eight studies	5.61	(4.62,6.60)	<0.001	80%, <0.001
mMRC score	Four studies	0.72	(0.63,0.82)	<0.001	57%, 0.07
Exacerbations in previous year	Four studies	2.65	(2.32,2.97)	<0.001	91%, <0.001
BMI	Seven studies	-0.14	(-0.70,0.42)	0.62	75%, <0.001
Charlson comorbidity index	Three studies	0.47	(0.37,0.58)	<0.001	0, 0.70
BODEx	Three studies	1.78	(1.28,2.28)	<0.001	91%, <0.001

CI: confidence interval; CAT: COPD assessment test; BMI: body mass index; mMRC: modified British Medical Research Council dyspnea scale; BODEx: BMI, obstruction, dyspnea, exacerbations.

Discussion

In this study, COPD patients with the FE-CB phenotype had lower FVC%, FEV_1%, and FEV_1/FVC, as compared to those with the NE phenotype. In addition, patients with the FE-CB phenotype had significantly higher CAT score, the quantity of cigarettes smoked (pack-years), number of acute exacerbations, and mMRC score.

Pulmonary function tests play an important role in the diagnosis and treatment of COPD. Airway obstruction assessed by spirometry should follow the reference values provided by the European Respiratory Society (ERS) Global Lung Initiative (GLI) [20]. In addition, pulmonary function tests should include the assessment of pulmonary hyperinflation and emphysema using whole body plethysmography and the determination of diffusion capacity. This is important because both lung hyperinflation and emphysema can occur without overt airway obstruction[20]. In clinical settings, pulmonary function tests are also widely used to evaluate the degree of airflow limitation, to monitor disease progression, and to evaluate the therapeutic response. However, the diagnostic and prognostic relevance of pulmonary function tests in the context of COPD has been constantly questioned. At present, we use FVE_1/FVC < 70% after inhalation of bronchodilator as the gold standard for diagnosis of obstructive ventilation function. However, due to considerable variability in pulmonary function itself, many authors have proposed that the lowest limit of normal and the highest limit of normal should be considered as the lowest and the highest threshold, respectively. Theoretically, these are the most scientific evaluation criteria and have been endorsed by the American Thoracic Society (ATS)/European Respiratory Society (ERS) and the American Medical Association[21]. However, a study found that basic pulmonary function of COPD patients was not related to the therapeutic response to lung rehabilitation. The degree of baseline pulmonary function was not found to predict individual improvement in dyspnea, motor performance, activities of daily living, emotional state, or disease-specific health status after lung rehabilitation. These findings suggest that baseline pulmonary function cannot be used to identify good responders to lung rehabilitation therapy; therefore, the results of

pulmonary function tests cannot be used as a criterion to recommend lung rehabilitation for COPD patients[22]. Thus, pulmonary function is not enough to capture the heterogeneity of COPD, and there are some limitations of its use to guide individual diagnosis and treatment[23]. At present, the pulmonary function characteristics of COPD patients with different phenotypes are still unclear. This study found that the pulmonary function of patients with the FE-CB phenotype is worse than that of NE phenotype, mainly with respect to FEV_1%pred, FVE_1/FVC, and FVC%pred. This may be attributable to the higher frequency of acute exacerbations in patients with the FE-CB phenotype, which results in a decline in pulmonary function. However, no positive results were found with respect to FEV_1, which may be related to the small sample size or to the large variability of FEV_1 per se. In addition, the analysis of FEV_1%pred was affected by considerable heterogeneity, which may be related to the large variability of FEV_1 per se as well as the selected samples.

Smoking is one of the major risk factors for COPD[24]. However, a considerable proportion of non-smokers (25–45%) develop COPD[25]. In addition, exposure to both maternal and own smoking was associated with lower FEV_1/FVC and higher risk of hospitalization/death from COPD than their independent associations [25]. The association between maternal smoking and COPD is influenced by the duration of smoking exposure. However, among non-smokers, there is no strong evidence that maternal smoking affects adult lung health [25]. In this study, six studies[8, 10, 13-15, 17] had reported the quantity of cigarettes smoked (pack-years). One study[13] found that the number of the quantity of cigarettes smoked (pack-years) of the FE-CB phenotype was significantly higher than that of the NE phenotype (P<0.05), while five studies[8, 10, 14, 15, 17] found no significant between-group difference in this respect. There was no heterogeneity among the samples. The fixed-effect model was used for analysis. Meta-analysis showed that the quantity of cigarettes smoked (pack-years) of the FE-CB phenotype was significantly higher than that of the NE phenotype (MD 3.09, 95% CI 1.60–4.58, P<0.001, I^2=41%).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2017 guidelines recommend the use of CAT or mMRC scale scores to assess symptoms in COPD patients[23]. The CAT questionnaire was used to assess and quantify the health-related quality of life and symptom burden of COPD patients. It consists of 8 questions with a total score of 40 points. In the mMRC dyspnea scale, the severity of dyspnea is rated on a 5-point scale (0–4). The GOLD guidelines recommend the use of CAT score 10 or MMRC score 2 as the threshold level for symptoms[23]. However, some studies have shown discrepancy between the CT and MRC scales for assessment of severity of COPD. The main reason may be that CAT also includes many aspects of quality of life, while mMRC only reflects the degree of dyspnea and does not take cognizance of other important symptoms of COPD, such as cough, sputum, chest tightness, and depression[26]. In another study, compared with other phenotypes, patients with the FE-CB phenotype had higher CAT score and lower motor ability, while patients with the NE phenotype had higher lung function index, fewer symptoms, and lower CAT score[6]. The conclusion is similar to that of the present study. In this study, eight studies[8-10, 12-15, 17] reported CAT scores. In all eight studies, the CAT score of COPD patients with the FE-CB phenotype was significantly higher than that of the NE phenotype. Meta-analysis (random-effects model) showed that CAT score of patients with the FE-CB phenotype was higher than that of patients with the NE phenotype (MD 5.61, 95% CI 4.62–6.60, P<0.001, I^2=80%). Sensitivity analysis indicated that heterogeneity was mainly derived from the studies by Calle Rubio et al.[17] and Corlateanu et al[9]. After excluding the results of these studies, CAT score of COPD patients with the FE-CB phenotype was significantly higher than that of patients with the NE phenotype (MD 5.73, 95% CI 5.32–6.14, P<0.001, I^2=38%). Four studies[12, 13, 15, 17] reported mMRC scores. In all 4 studies, the mMRC score of COPD patients with the FE-CB phenotype was significantly higher than that of the NE phenotype. Owing to significant heterogeneity between the samples, the random-effects model was used for analysis. Meta-analysis showed that the mMRC score of the FE-CB phenotype was higher than that of the NE phenotype (MD 0.72, 95% CI 0.63–0.82, P<0.001, I^2=57%). Sensitivity analysis suggested that the heterogeneity was mainly derived from the study by Miravitlles et al.[13]. After excluding the results of this study, the mMRC score of the FE-CB phenotype was still higher than that of the NE phenotype (MD 0.68, 95% CI 0.61–0.75, P<0.001, I^2=17%). We observed a consistency between the CAT and MMRC scores for evaluating the symptoms of patients with different phenotypes of COPD.

Compared with individuals with higher BMI, those with lower BMI are more likely to suffer from COPD and have lower lung function[27]. Previous studies that investigated BMI of patients with different COPD phenotypes mainly focused on the

emphysema phenotype and the bronchitis phenotype. Studies have shown that patients with emphysema phenotype have low BMI, fewer phlegm, severe dyspnea, and decreased diffusion function. The difference of BMI between the FE-CB phenotype and the NE phenotype is controversial. In this study, seven studies reported BMI. In one study[12], BMI of COPD patients with the FE-CB phenotype was significantly higher than that of the NE phenotype. One other study[17] reported the opposite relationship, while the remaining five studies[8, 10, 11, 13, 14] found no significant difference between the two phenotypes with respect to BMI. Owing to significant heterogeneity between the samples, the random-effects model was used for analysis. Meta-analysis showed that BMI of COPD patients with the FE-CB phenotype was not different from that of the NE phenotype (MD -0.14, 95% CI -0.70–0.42, P=0.62, I^2=75%). Sensitivity analysis indicated that the heterogeneity was mainly attributable to the studies by Calle Rubio et al.[17] and Koblizek et al.[12]. After excluding the results of these studies, there was no significant between-group difference with respect to BMI (MD -0.05, 95% CI -0.36–0.26, P=0.77, I^2=24%).

This study also found that compared with the NE phenotype patients, BODEx, and Charlson comorbidity index of FE-CB phenotype patients were higher; however, owing to the small sample size, further research is required to draw more definitive conclusions.

Strengths of this study

COPD is character as a heterogeneous disease [28-31]. Phenotype is helpful to recognize the heterogeneity and understand the evolution of disease [29,31]. Phenotype helps guide diagnosis and treatment [29,31]. In this study, the characteristics of patients with FE-CB and NE were studied by meta-analysis, which would help to more comprehensively describe the characteristics of FE-CB and NE of COPD and provide basis for diagnosis and treatment of COPD. This study was helpful to provide early warning and guidance for patients with FE-CB and NE phenotypes. For example, patients with poor lung function might have frequent acute exacerbations. The patients with FE-CB phenotype might be accompanied by poor lung function, and such patients might be more likely to benefit from lung rehabilitation exercise.

Limitations of this study

In this study, we compared the FEV_1%, FVC%, FEV_1/FVC, FEV_1, CAT score, BMI, mMRC score, the quantity of cigarettes smoked (pack-years), and the number of acute exacerbations between COPD patients with the FE-CB phenotype and the NE phenotype. However, we did not include several variables in the analysis such as race, sex, age, main symptoms (cough, sputum, wheeze), other smoking conditions (past smoking, current smoking, active smoking, passive smoking), complications (ischemic heart disease, heart failure, atrial fibrillation, hypertension, bronchiectasis, osteoporosis, anxiety/depression and cognitive impairment, lung cancer, severe infection, diabetes), different GOLD comprehensive assessment grades (A, B, C, D), mMRC stratification (mMRC ≥ 2, mMRC < 2), and acute aggravation stratification (frequency of aggravation). These elements need to be studied in a future study.

This study included 10 studies, 8 of which were conducted in Europe and 2 were conducted in Asia. We did not retrieve any eligible studies conducted in Africa, America, and Oceania, which is another limitation of our analysis.

In addition, some variables in this study changed with time. For example, lung function changed with the development of the disease [32]. The change of lung function might be accompanied by a series of other characteristics, such as the aggravation of wheezing symptoms, and then the increase of CAT score and MMRC score. For patients with NE phenotype, this might be a warning. If the patient's lung function continued to decline, accompanied by the increase of CAT score and MMRC score, then the patient might become a patient with FE-CB phenotype. The treatment focus and prognosis of this patient might be different. But for patients in the FE-CB phenotype, the warning effect might be smaller. If the patient's lung function continued to decline, it might be accompanied by an increase in CAT score, MMRC score, and the number of acute exacerbations. However, the patient was always in the group with FE-CB phenotype. The treatment focus and prognosis of this patient might not change. In this study, those indicators with dynamic changes had not been discussed. These elements need to be studied in a future study.

Conclusion

Compared with COPD patients with the NE phenotype, those with the FE-CB phenotype had poor pulmonary function, higher CAT score, the quantity of cigarettes smoked (pack-years), frequency of acute exacerbation, and mMRC scores.

Abbreviations

COPD	chronic obstructive pulmonary disease
FVC%pred	forced vital capacity percent predicted
FEV_1% pred	forced expiratory volume in one second percent predicted
FEV_1	forced expiratory volume in one second
FVC	forced vital capacity
FEV_1/FVC	forced expiratory volume in one second/ forced vital capacity
FE-CB	frequent exacerbator with chronic bronchitis phenotype
NE	non-exacerbator phenotype
BMI	body mass index
CAT	COPD assessment test score
mMRC	modified Medical British Research Council
BODEx	BMI, obstruction, dyspnea, exacerbations
MD	mean
CIs	confidence intervals

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication:

Not applicable.

Availability of data and material

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

JJW contributed to the conceptualization , writing-original draft preparation , writing-review and editing, supervision and visualization . HRX contributed to the writing-original draft preparation. YXZ contributed to the writing-original draft preparation.

YXL contributed to the visualization. HYY contributed to the writing-review and editing and Supervision. LDJ, CXW and MH contributed to the conceptualization. All authors have approved the final version of the work.

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Table

Table 1 Basic characteristics of the studies included in the meta-analysis

Author	Year	Country	Language	Research type	Cases (FE-CB/NE)	Gender (male) (FE-CB/NE)	Age (years) (FE-CB/NE)	Evaluation indices
Alcázar-Navarrete, B.	2016	Spain	English	Cross-sectional observation study	34/34	32/29	72±10.4 71±9.9	FEV_1%, FEV_1/FVC, FVC%, BMI, the quantity of cigarettes smoked (pack-years), CAT score
Arkhipov, V.	2017	Russia	English	Cross-sectional observation study	415/398	356/347	64.6±8.5 64.7±8.9	FEV_1%, the quantity of cigarettes smoked (pack-years), BMI, CAT score
Calle Rubio, M.	2017	Spain	English	Cross-sectional observation study	188/307	157/255	69.5±8.6 67.2±9.3	FEV_1, FEV_1%, the quantity of cigarettes smoked (pack-years), CAT, mMRC, BODEx, exacerbations in previous year, BMI
Chee-Shee Chai	2019	Malaysia	English	Cross-sectional observation study	75/54	70/50	70.7±9.2 74.1±8.1	FEV_1%, the quantity of cigarettes smoked (pack-years), CAT, mMRC, exacerbations in previous year
Corlateanu, A.	2017	Moldova	English	Cross-sectional observation study	138/175	-		FVC%, FEV_1%, FEV_1/FVC, CAT
Cosio, B. G.	2016	Spain	English	Cross-sectional observation study	99/550	85/460	69.5±8.1 67.4±9.1	FEV_1%, FVC%, FEV_1/FVC, the quantity of cigarettes smoked (pack-years), BMI, CAT, Charlson comorbidity index
Golpe, R.	2018	Spain	English	Cross-sectional observation study	194/531	167/433	72.7±8.9 68.5±9.5	FEV_1%, FVC%, FEV_1/FVC, BMI, BODEx, Charlson comorbidity index
Koblizek, V.	2017	Czech	English	Cross-sectional observation study	687/2125	494/1500	66.6±8.3 66.3±8.7	FEV_1%, FVC%, BMI, CAT, mMRC, exacerbations in previous year
Miravitlles,	2015	Germany	English	Cross-	602/1894	514/1617	69.3±9.2	FEV_1%,

M.				sectional observation study			66.6±9.7	FVC%, FEV_1, FVC, FEV_1/FVC, mMRC, exacerbations in previous year, BODEx, CAT, BMI, the quantity of cigarettes smoked (pack-years), Charlson comorbidity index
Pan Qing	2016	China	Chinese	Cross-sectional observation study	267/82	217/68	76±10.0 61±6.4	FEV_1、FEV_1%

FE-CB: frequent exacerbators with chronic bronchitis; NE: non-exacerbator; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; CAT: COPD assessment test; BMI: body mass index; mMRC: modified British Medical Research Council dyspnea scale;BODEx: BMI, obstruction, dyspnea, exacerbations; FVC%pred: forced vital capacity percent predicted; FEV_1%pred: forced expiratory volume in one second percent predicted

Figures

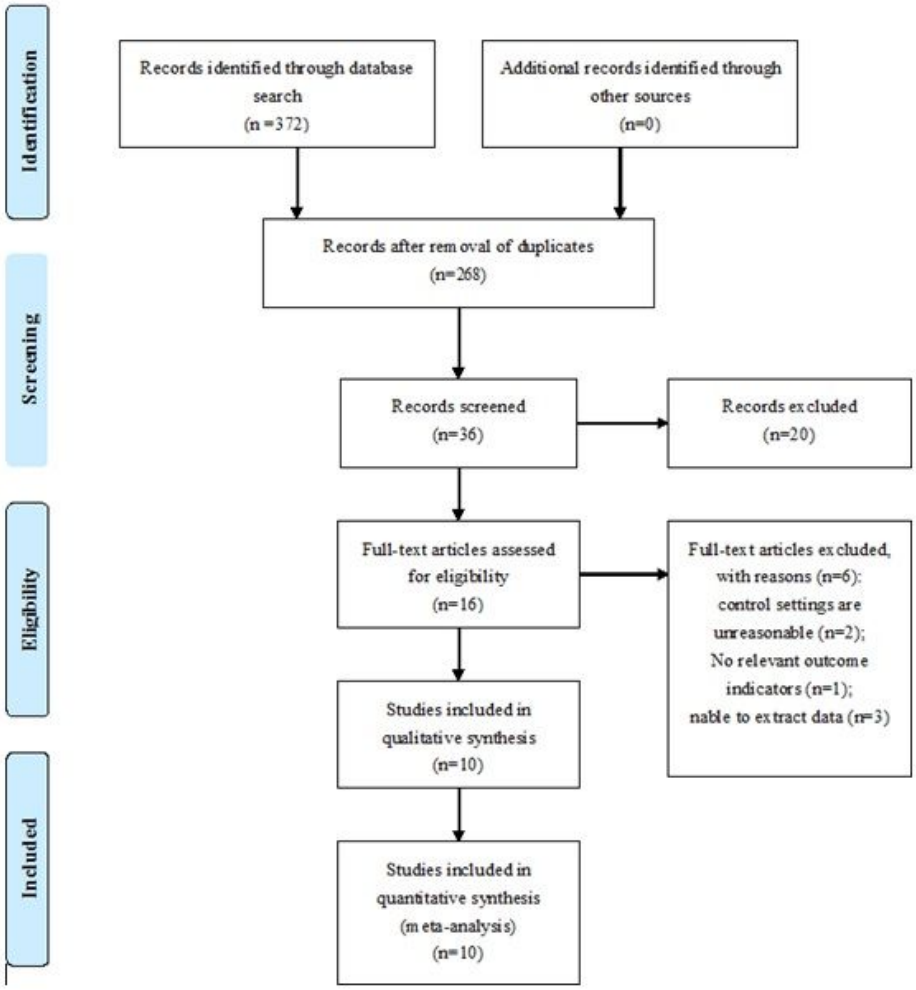

Figure 1 Schematic illustration of the study design and the study selection criteria

Figure 1

Schematic illustration of the study design and the study selection criteria

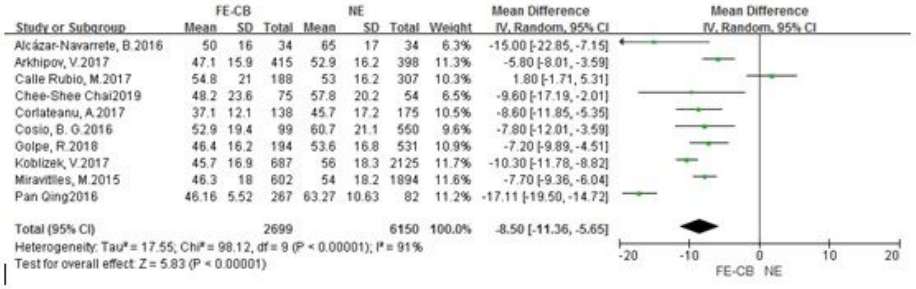

Figure 2 Difference of FEV_1%pred between the FE-CB and the NE phenotypes

Figure 2

Difference of FEV1%pred between the FE-CB and the NE phenotypes

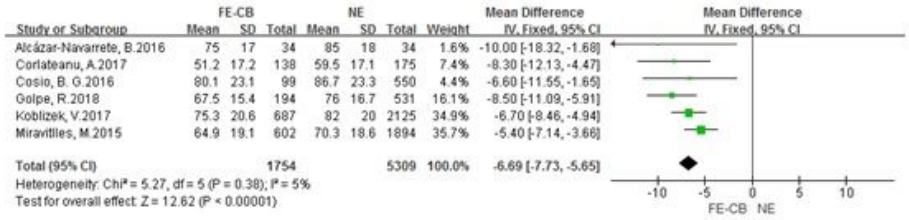

Figure 3 Difference of FVC%pred between the FE-CB and the NE phenotypes

Figure 3

Difference of FEV1 between the FE-CB and the NE phenotypes

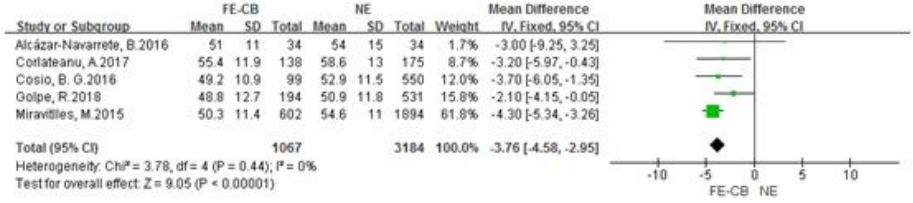

Figure 4 Difference of FEV_1/FVC between the FE-CB and the NE phenotypes

Figure 4

Difference of FVC%pred between the FE-CB and the NE phenotypes

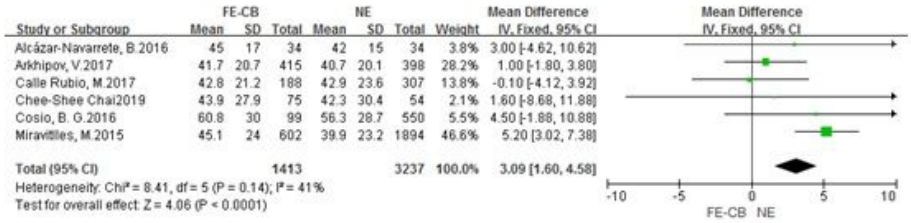

Figure 5 Difference of the quantity of cigarettes smoked (pack-years) between the FE-CB and the NE phenotypes

Figure 5

Difference of FEV1/FVC between the FE-CB and the NE phenotypes

Supplementary Files

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- FlowDiagram.pdf
- S1Text.Searchstrategies.pdf
- S1Table.Listofexcludedfulltextarticles..xlsx
- S2Table.otherindicesindifferentphenotype.xlsx