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Investigation and Classification of Treatable Traits in Patients with Chronic Airway Diseases

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1. Introduction

1.1. Background

Chronic Obstructive Pulmonary Disease (COPD) and bronchial asthma (asthma) are common chronic airway diseases that severely impact public health. Globally, approximately 600 million people are affected. In 2015, about 3.2 million people died from COPD worldwide, and 400,000 died from asthma[1]. In China, chronic airway diseases represented by COPD and asthma have become major chronic conditions seriously endangering the health of the population. Results from the China Pulmonary Health (CPH) study, led by our team, indicate that the prevalence of COPD among people aged 20 and above in China is 8.6%[2], and the prevalence of asthma is 4.2%[3]. Chronic airway diseases impose a substantial healthcare burden. However, despite continuously rising medical costs for these diseases, key clinical outcomes have not shown corresponding improvement[4,5]， Personalized treatment tailored to different patient subtypes is crucial to addressing this dilemma.

It has been established that chronic airway diseases exhibit significant heterogeneity. Different phenotypes exist among asthma patients, such as allergic asthma, late-onset asthma, smoking-related asthma, and obesity-related asthma[6]. Similarly, COPD patients present with various phenotypes including mild stable, emphysematous type, intermediate type, multiple comorbidities, and multifactorial inflammatory type[7]. Applying traditional, uniform treatment regimens to different phenotypic patients falls short of meeting the actual needs of disease treatment and management. In clinical practice, there is a need to identify more precise treatable traits for patient classification and personalized management. Several treatable traits beneficial for the individualized management of patients with chronic airway diseases have already been identified, for example, blood eosinophil count[8] and serum allergen-specific IgE[9]， which have demonstrated clinical utility. There is a pressing need to discover and validate more clinically significant traits to provide a basis for the subsequent implementation of personalized patient management.

1.2. Rationale

Previous research has found that differences in dyspnea perception among populations with chronic airway diseases may lead to different disease outcomes. In asthma patients, approximately 26% of subjects exhibit low dyspnea perception. During follow-up, patients with low perception had higher rates of emergency department visits, hospitalizations, near-fatal asthma attacks, and mortality compared to groups with normal or high perception, suggesting that reduced dyspnea perception may predispose asthma patients to life-threatening acute episodes[10]. In COPD patients, it has also been observed that after repeated carbon dioxide breathing, patients in the frequent exacerbator group exhibited enhanced dyspnea perception, whereas those in the infrequent exacerbator group showed weakened perception. This mechanism may contribute to the difference in exacerbation frequency between the

two groups[11]. Consequently, abnormal dyspnea perception may be one of the risk factors leading to refractory chronic airway diseases, and patients with such abnormal perception might represent a novel subtype of chronic airway disease.

However, the influencing factors of dyspnea perception remain unclear. Some studies suggest potential associations with age [12]、gender[13]、airway inflammation[14]、psychological and emotional factors[15,16]among others. Nevertheless, a comprehensive description of this trait in patients with chronic airway diseases is still lacking, and we do not fully understand the distribution of dyspnea perception and its determinants in this population. This study aims to investigate the distribution and risk factors of abnormal dyspnea perception in patients with chronic airway diseases. By collecting and analyzing other relevant clinical data from these patients, we intend to construct a clinical classification of chronic airway diseases based on dyspnea perception and further identify more treatable traits. The goal is to enable more precise personalized management of patients in clinical practice[17], addressing the urgent need to reduce the frequency of disease exacerbations, disability, and mortality.

1.3. Study Objectives

This project aims to investigate the distribution of dyspnea perception within established chronic airway disease cohorts from community screenings and hospital-based populations, identify novel subtypes classified by dyspnea perception, analyze their relationships with known biomarkers and other treatable traits, and explore new treatable traits contributing to refractory chronic airway diseases. The findings will provide a foundation for subsequent implementation of personalized management strategies for patients.

2. Study Objectives

2.1. Primary and Quantitative Objectives

Primary Objectives	Quantitative Targets

● To clarify the distribution of dyspnea perception in chronic airway diseases. ● To construct novel subtypes of chronic airway diseases based on the degree of dyspnea perception and analyze their relationship with known biomarkers and other treatable traits. ● To observe the changes in dyspnea perception during follow-up and explore its relationship with outcome measures such as acute exacerbations, occurrence of comorbidities, hospitalizations, and mortality.	● Complete dyspnea perception measurements in 800 chronic airway disease subjects. ● Complete repeat dyspnea perception measurements one year after baseline in 200 subjects. ● Complete measurements of biomarkers and other treatable traits (e.g., head MRI) in 300 patients. ● Apply for 1-2 patents or software copyrights. ● Publish 2-4 Chinese and English articles; train 4 postgraduate students.

3. Methods

3.1. Source of Funding

This study is supported by the municipal fiscal science and technology funds, specifically from the Respiratory Institute's Reform and Development Project "Phenotype-based Prognosis and Individualized Diagnosis and Treatment Research for Chronic Airway Diseases."

3.2. Study Design

This is a 3-year observational study. It will involve dyspnea perception measurement, pulmonary function tests, blood sample testing, quality of life assessment, recording of acute exacerbations and comorbidities, and collection of other clinical information in 800 participants with chronic airway diseases. Additionally, 150 normal control subjects will undergo dyspnea perception measurement, pulmonary function tests, blood sample testing, and clinical information collection. Participants with good compliance will undergo regular follow-up, including brain functional magnetic resonance imaging (fMRI) examinations alongside repeated dyspnea perception measurements. The study will analyze the relationship between dyspnea perception and known biomarkers as well

as other treatable traits, aiming to identify new treatable traits underlying refractory chronic airway diseases.

3.3. Study Population:

This study will recruit approximately 800 participants with COPD or asthma and 150 normal control subjects from hospitals and the community. Participants with COPD or asthma will be aged 20-75 years, must meet the diagnostic criteria for COPD according to the 2022 GOLD guidelines or the diagnostic criteria for asthma according to the 2022 GINA guidelines, must be able to participate in the study per protocol, and must provide written informed consent before participating.

1.1.1.1. Inclusion Criteria:

Participants with COPD or asthma must meet all the following criteria:

- Age 20-75 years.
- Meet the diagnostic criteria for COPD according to the 2022 GOLD guidelines OR meet the diagnostic criteria for asthma according to the 2022 GINA guidelines.
- Agree to participate in the study and provide written informed consent.

Normal control subjects must meet all the following criteria: Age ≥20 years; no asthma symptoms and no previous diagnosis of chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease; must provide written informed consent before participation and be able to participate in the study and follow-up per protocol.

1.1.1.2. Exclusion Criteria:

Study participants must not meet any of the following criteria:

- Respiratory tract infection, acute exacerbation of COPD, or acute asthma attack within the past 3 months.
- Presence of other diseases causing substantial lung tissue destruction, such as severe bronchiectasis or tuberculosis.

- History of thoracic or abdominal surgery within the past 3 months.
- Heart rate >120 beats per minute.
- Currently undergoing anti-tuberculosis treatment.
- Presence of other severe, uncontrolled systemic diseases.
- Pregnant or lactating women.

1.1.1.3. 变量及人口学数据 Variables and Demographic Data

1.1.1.4. 暴露 Exposure

The patient's treatment regimen will be determined by their treating physician. No investigational drugs will be administered as part of this study. The study will collect information on the patient's current respiratory medication and specific concomitant medications.

1.1.1.5. Variables

- Demographic Data: Includes sex, date of birth, height, weight, living environment, education level/years of formal education; smoking history/secondhand smoke exposure history; occupational exposure history; biofuel exposure history.
- Clinical Information: Duration since diagnosis of COPD/chronic bronchitis/emphysema/asthma and age at onset; current respiratory symptoms such as shortness of breath, chest tightness, cough, wheezing, sputum production; past family history; allergy history/atopy.
- Previous Exacerbation History: Exacerbations within the 12 months prior to baseline: number of exacerbations, exacerbation severity (use of systemic corticosteroids/antibiotics/emergency department visit/hospitalization), and length of hospital stay or number of emergency department visit days.
- Comorbidities: Comorbidities present prior to the baseline visit.
- Treatments: Current medications for COPD/asthma/chronic respiratory symptoms (type/duration of use/dosage/frequency), and non-pharmacological treatments; specific concomitant medications (e.g., corticosteroids).
- Pulmonary Function Tests: Spirometry with bronchodilator test; lung volume measurements; diffusing capacity test; fractional exhaled nitric oxide (FeNO) measurement; dyspnea perception measurement.
- Blood Tests: Complete blood count, inhalant allergen screen, total IgE.
- Imaging: Chest HRCT scan (high-resolution computed tomography in inspiratory and expiratory phases).

- Health-Related Quality of Life: Assessed using the COPD Assessment Test (CAT), the Modified British Medical Research Council (mMRC) dyspnea scale, the Asthma Quality of Life Questionnaire (AQLQ), and the St. George's Respiratory Questionnaire (SGRQ).
- Dyspnea Perception Measurement.
- Brain Functional Magnetic Resonance Imaging (fMRI).

4. Data Processing

All statistical analyses will be performed using the Full Analysis Set (FAS), which includes all patients who were enrolled and met the inclusion/exclusion criteria. Missing data will be analyzed as is, without imputation.

The epidemiology and statistics working group at the Chinese Academy of Medical Sciences will perform the statistical analyses using SAS and SUDAAN software.

The analysis methods will primarily be descriptive. For continuous variables, summary statistics will include number of observations, mean, median, standard deviation, minimum, and maximum values. For categorical variables, frequencies and percentages will be calculated for each category.

Linear regression or logistic regression and multivariate analysis will be used to explore the relationship between dyspnea perception and disease outcomes.

4.1. Interim Analysis

An interim analysis will be conducted when the number of enrolled subjects reaches 400. The date when the 400th patient is enrolled will be considered the interim analysis date.

4.2. Data Management

This study will utilize an Electronic Data Capture (EDC) system for data entry via a password-protected web-based platform. Spirometry data from pulmonary function tests will be transmitted daily to the web-based data entry platform. Within a 48-hour interval, researchers will grade the quality of the pulmonary function tests (FEV1, FVC, and diffusing capacity) according to an academic grading system (A, B, C, D, or E).

The completeness and accuracy of questionnaire variables will be checked. Before data upload, the questionnaire administrator must identify and clarify any obvious errors or omissions in the questionnaires. Prior to statistical analysis, the consistency of dual-entered data will be checked, and paper questionnaires will be scanned and stored securely.

5. Study Oversight

The Project Leader will be responsible for overseeing the entire research process. Two working groups will be established, responsible for project implementation supervision and data cleaning/analysis, respectively. The leaders of these working groups will report study progress monthly to the Project Leader.

6. Collection and Reporting of Adverse Events / Adverse Drug Reactions

6.1. Definition of Adverse Events (AE)

An Adverse Event (AE) is any unfavorable medical occurrence in a patient or clinical trial subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. Therefore, an adverse event can be any unfavorable sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

The term "adverse event" encompasses both serious and non-serious adverse events.

6.2. Definition of Serious Adverse Events (SAE)

A Serious Adverse Event (SAE) is any adverse event occurring at any stage of the study (i.e., run-in period, treatment period, washout period, follow-up period) that meets one or more of the following criteria:

- Results in death
- Is life-threatening (in this context, "life-threatening" refers to the patient being at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.
- Medical judgment should be exercised in deciding whether other situations should be considered serious adverse events.

- Any suspected transmission of a pathogenic agent via a medicinal product is considered an SAE, and some countries require prompt reporting of such events.

  Any biological, viral, or infectious agent (e.g., a prion transmitting infectious spongiform encephalopathies), whether pathogenic or non-pathogenic, is considered a transmissible agent.

1.1.1.6. Definition of Adverse Drug Reactions, ADR

An Adverse Drug Reaction (ADR) is an adverse event for which a causal relationship with the drug use is suspected.

An ADR is a harmful and unintended response to a drug. Adverse reactions may arise from use within or outside the terms of the marketing authorization, including those resulting from occupational exposure.

The term "adverse drug reaction" includes both serious and non-serious adverse drug reactions.

1.1.1.7. Reporting of Adverse Events

As this is a non-interventional study, and the drugs used by participants are prescribed by the investigator according to clinical practice, adverse events will not be actively collected.

The investigator is responsible for ensuring that all personnel involved in the study are familiar with the content of this section.

7. Study Timfline

This study is anticipated to commence in the first quarter of 2023 and be completed by the fourth quarter of 2027. The study endpoint is defined as "completion of all analyses related to the study."

Study Milestone	**Estimated Date**
Protocol Approval	March 2023
Enrollment of First Participant	March 2023
Enrollment of Last Participant	December 2025
Last Visit of Last Participant	December 2027
Database Lock	December 2027
Final Study Report Completion	December 2027
Publication of Final Study Report	December 2027

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