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ORIGINAL RESEARCH

Association of Chronic Obstructive Pulmonary Disease with Risk of Psychiatric Disorders: A Two-Sample Mendelian Randomization Study

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Background: Chronic obstructive pulmonary disease (COPD) is a prevalent respiratory disorder often accompanied by comorbidities. Although the past few years have witnessed significant scientific progress, the potential relationship between COPD and mental illness remains a subject of debate.

Materials and Methods: We retrieved COPD data from the genome-wide association studies (GWAS) directory and data on mental illnesses, including Alzheimer's disease, schizophrenia, panic disorder, attention deficit hyperactivity disorder (ADHD), bipolar disorder, major depressive disorder, multiple disabilities, obsessive-compulsive disorder, post-traumatic stress disorder, and schizophrenia, from the Psychiatric Genomics Consortium. A two-sample Mendelian randomization (MR) approach was applied to explore the association between COPD and mental illnesses, with subgroup analyses based on smoking history.

Results: Our two-sample MR analysis revealed no causal link between overall COPD and the development of common psychiatric disorders. Subgroup analyses based on smoking history showed no causal association between never-smokers with COPD and the occurrence of psychiatric disorders. However, ever-smokers with COPD were associated with a significantly increased risk of ADHD (OR: 2.303, 95% CI: 1.558–3.403, P = 0.001) and a modestly reduced risk of Alzheimer's disease (OR: 0.994, 95% CI: 0.988–0.999, P = 0.034).

Conclusion: COPD patients with a history of smoking face a higher risk of developing ADHD but may experience a slight reduction in the risk of Alzheimer's disease. Conversely, there was no observed causal association between COPD and psychiatric disorders among patients who never smoked.

Keywords: chronic obstructive pulmonary disease, psychiatric disorders, Mendelian randomization

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory respiratory condition characterized by symptoms like dyspnea, limited physical activity, and partially reversible airflow obstruction.[1] While smoking is widely acknowledged as the primary contributor to COPD, other factors such as genetic abnormalities, abnormal lung development, and air pollution also play a role.[2] Over the years, the global prevalence of COPD has been rising, making it the third most significant contributor to worldwide mortality and morbidity.[3] Indeed, COPD places significant financial strain on governments, healthcare systems, societies, and economies worldwide.[4]

Clinically, COPD patients often present with comorbidities such as coronary heart disease, hypertension, cognitive impairment, psychological disorders, and other ailments, suggesting that COPD should no longer be considered exclusively as a pulmonary disorder.[5] The coexistence of these chronic diseases mutually influences one another, complicating the diagnosis and treatment process and ultimately resulting in a poorer prognosis.[6] Previous studies

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have reported a higher prevalence of anxiety and depression in COPD patients compared to the general population.[7] Managing depression in patients with COPD has shown effectiveness through a diverse range of therapeutic interventions.[8] Furthermore, several studies have demonstrated an association between COPD and cognitive impairment or dementia.[9] Besides, Su et al found that COPD could independently increase the risk of bipolar disorder, especially in individuals regularly using short-acting beta-agonists (SABAs).[10]

Mendelian randomization (MR) is an approach employed to investigate causal relationships between exposures and outcomes of interest.[11] This methodology utilizes single nucleotide polymorphisms (SNPs) as unconfounded proxies for exposures, thereby mitigating issues related to residual confounding and reverse causality often encountered in conventional observational studies.[12] The MR design serves as a crucial strategy for inferring causality without relying on randomized clinical trials (RCTs), as genetic variants are randomly assorted during meiosis, simulating the principles of an RCT.[13] Given the complexity of COPD's pathogenesis and numerous confounding factors, conducting Mendelian randomization studies is essential to establish whether a causal relationship exists between COPD and psychiatric disorders at the genetic level.

Materials and Methods

In this study, all data were sourced from the Genetic Alliance's publicly accessible repository of statistical data obtained from genome-wide association studies (GWAS). All original studies received a specific ethical review and informed consent.

Study Design

Pooled data on COPD and common psychiatric disorders were collected from published GWAS. At the same time, the patients were divided into two groups according to whether they smoked. This study aimed to explore the causal relationship between COPD and the risk of psychiatric disorders using two-sample MR.

The MR Approach is predicated upon three fundamental assumptions: (1) genetic variants serving as instrumental variables (IVs) should exhibit robust associations with the risk factor under investigation; (2) the selected genetic variants should not be associated with potential confounding factors; and (3) the identified genetic variants solely influence the outcome risk through the risk factors, without involvement in alternative pathways (Figure 1).

Outcome and Exposure Data Source

COPD data were obtained from the GWAS database, and individuals were categorized into ever-smokers with COPD or never-smokers with COPD groups based on their smoking history. The GWAS Catalog database is publicly available for download at https://www.ebi.ac.uk/gwas/. Data on psychiatric disorders, including Alzheimer's disease,[14] anorexia nervosa,[15] anxiety disorder,[16] attention deficit hyperactivity disorder (ADHD),[17] bipolar disorder,[18] major depressive disorder (MDD),[19] multiple disorders,[20] obsessive-compulsive disorder (OCD),[21] post-traumatic stress disorder

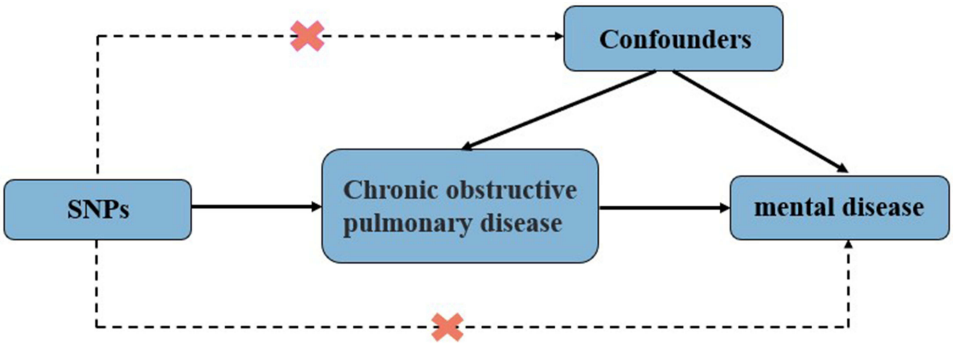

Figure 1 Overall design of Mendelian randomization analyses in the present study.

(PTSD),[22] and schizophrenia[23] were obtained from the Psychiatric Genomics Consortium (https://pgc.unc.edu/). All participants were of European ancestry. Details of the GWAS outcome are provided in Table 1.

MDD is diagnosed through questionnaires, and patients often present with pessimism, loss of interest, low mood, poor appetite, and even pessimism.[24] In adults, ADHD is often characterized by impulsivity, impatience, chatter, hyperactivity and inattention.[25]

Genetic Variants Selection Criteria

Genetic instruments for each exposure trait or disease were selected at the genome-wide significance threshold ($P < 5\times10^{8}$) from corresponding GWASs. Independent single nucleotide polymorphisms (SNPs) were defined by $R2 < 0.001$ and clump window > 10 kb, and correlated SNPs (linkage disequilibrium) with the lowest p-value were retained. Linkage disequilibrium among SNPs for each risk factor was calculated based on 1000 genomes LD reference panel (European population)[26] using the PLINK clumping approach.[27]

Statistical Analysis

Cochran's Q statistics were performed to assess the heterogeneity across individual SNPs. The random-effects inverse-variance-weighted (IVW-RE) model was used as the primary analytical method to examine the causal association.[28] The MR-Egger method was used to determine whether the instrumental SNPs have pleiotropic effects.[29] Several sensitivity analyses were conducted to explore potential pleiotropic bias. These included IVW-RE MR, MR-Egger regression, weighted median MR, funnel plots, and a leave-one-variant-out analysis for IVW-RE, wherein one variant was omitted at a time.

Results

Table 1 provides detailed information on the exposure groups and includes the results of heterogeneity and pleiotropy tests, all conducted in accordance with established academic standards.

Overall COPD

Heterogeneity was detected between COPD and some psychiatric disorders as determined by the Cochran heterogeneity test using the IVW method. Importantly, the MR-Egger method did not reveal significant horizontal pleiotropy in the association between COPD and psychiatric disorders. The IVW-RE MR analysis demonstrated no significant association between COPD and the risk of psychiatric disorders consistent with multiple MR methods, including MR Egger, weighted median, simple mode, and weighted mode. Our study did not identify any significant association between COPD and major depressive disorder (OR: 1.001, 95% CI: 0.998–1.005, P = 0.451) (Figure 2). Further verification using MR Egger, weighted median, simple mode, and weighted mode methods yielded consistent results (Supplement Table 1).

Smoking-Related COPD

Utilizing the IVW method, the Cochran heterogeneity test revealed significant heterogeneity between individuals with a smoking history and certain psychiatric disorders in the context of COPD. Interestingly, the association between COPD and psychiatric disorders did not exhibit significant horizontal pleiotropy, except for anxiety disorders. The IVW-RE MR analysis demonstrated a significant association between ever-smokers with COPD and an increased risk of ADHD (OR: 2.303, 95% CI: 1.558–3.403, P = 0.001), along with a potential protective effect against Alzheimer's disease to some extent (OR: 0.994, 95% CI: 0.988–0.999, P = 0.034) (Figure 3). However, no significant correlations were observed with other psychiatric disorders. Validation using MR Egger, weighted median, simple mode, and weighted mode methods yielded consistent results (Supplement Table 2).

Never-Smokers with COPD

After applying the IVW method, the Cochran heterogeneity test indicated significant heterogeneity between COPD individuals who never smoked and specific psychiatric disorders. The MR-Egger method did not provide significant evidence of horizontal pleiotropy in the association between COPD and psychiatric disorders. The IVW-RE MR analysis

Table 1 Details of Variance Explained by the Selected Instruments and F-Statistics for the MR Analysis Based on the Sample Size of Autoimmune Diseases

Outcome	Case	Control	Overall COPD		Smoking-Related COPD		Never-Smokers with COPD	
			P for Heterogeneity Test	P for Pleiotropy Test	P for Heterogeneity Test	P for Pleiotropy Test	P for Heterogeneity Test	P for Pleiotropy Test
Alzheimer's Disease	39,106	401,577	0.02	0.91	0.36	0.32	0.02	0.92
Anorexia nervosa	16,992	55,525	0.86	0.46	0.08	0.52	0.86	0.47
Anxiety Disorder	81,118	22,646	0.18	0.05	0.06	0.02	0.18	0.05
Attention Deficit Hyperactivity Disorder	25,895	37,148	0.01	0.09	0.01	0.82	0.01	0.09
Bipolar Disorder	9412	137,760	0.01	0.54	0.01	0.90	0.01	0.54
Major Depressive Disorder	246,363	561,190	0.49	0.54	0.59	0.70	0.49	0.54
Multiple disorders	232,964	494,162	0.01	0.50	0.01	0.50	0.01	0.50
Obsessive-compulsive disorder	2688	7037	0.01	0.58	0.01	0.97	0.01	0.58
Schizophrenia	243,649	76,755	0.01	0.07	0.01	0.99	0.01	0.07
Post Traumatic Stress Disorder	9354	25,175	0.01	0.42	0.01	0.64	0.01	0.42

Abbreviation: COPD, chronic obstructive pulmonary disease.

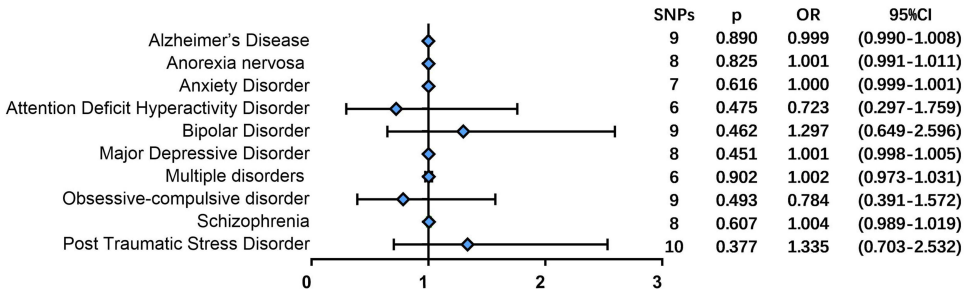

Figure 2 Mendelian randomization of overall chronic obstructive pulmonary disease and psychiatric disorders in the primary analysis.

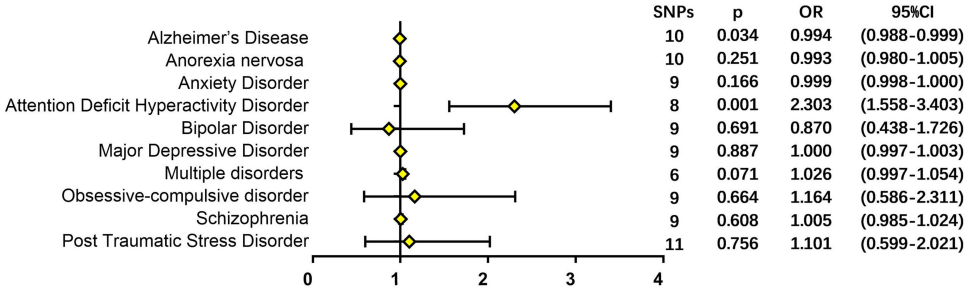

Figure 3 Mendelian randomization of ever smoking chronic obstructive pulmonary disease and psychiatric disorders in the primary analysis.

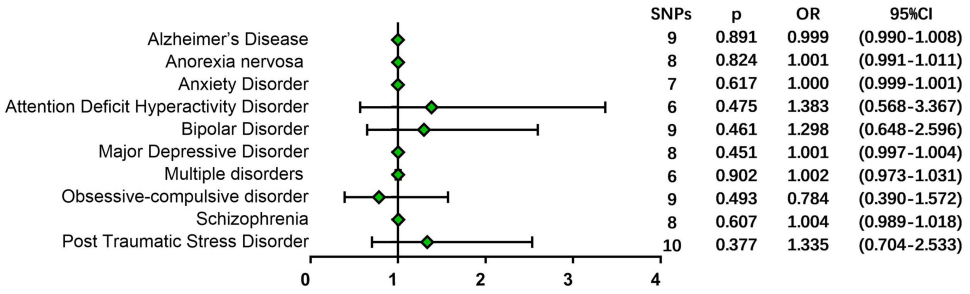

Figure 4 Mendelian randomization of never smoking chronic obstructive pulmonary disease and psychiatric disorders in the primary analysis.

indicated no significant association between never smoking COPD and psychiatric disorders (Figure 4). Validation using MR Egger, weighted median, simple mode, and weighted mode methods yielded similar findings (Supplement Table 3).

Discussion

Previous studies have explored the potential association between COPD and the occurrence of various mental disorders. However, controversy surrounds this association, prompting us to conduct a two-sample MR analysis with subgroup analysis based on smoking history. Our findings revealed that COPD patients with a smoking history exhibited a significantly elevated risk of ADHD while potentially experiencing a reduced risk of Alzheimer's disease to some extent. Conversely, we found no causal relationship between COPD patients without a smoking history and common psychiatric disorders.

Cognitive impairment is a common issue, observed in approximately 10–61% of COPD patients, with conversion rates to dementia ranging from 50% to 70% within 5 to 7 years after its onset.[30] Around 25% of individuals diagnosed with Alzheimer's disease also have COPD.[31] The association between COPD and cognitive decline is still under debate, as it remains unclear whether the decline in lung function or the shared risk factor of smoking plays a predominant role.[32] A previous MR study suggested no significant association between lung function decline in COPD patients and the development of Alzheimer's disease.[33] Smoking, as another risk factor, seems to exert a more substantial influence on the

initiation and progression of both diseases. It is widely acknowledged that tobacco smoke contains high levels of oxidants, inducing oxidative stress and affecting the normal functioning of brain tissues.[34] Cataldo et al identified smoking as a significant risk factor for the development of Alzheimer's disease.[35] However, a neuropathological analysis found no significant increase in neuroinflammatory plaques among heavy smokers with dementia compared to non-smokers.[36] Our current study suggests that individuals with COPD and a smoking history may experience a reduced susceptibility to Alzheimer's disease (OR: 0.994, 95% CI: 0.988–0.999, P = 0.034). Smoking has long been recognized as a prominent risk factor for COPD, and the most effective intervention in managing COPD is the cessation of this habit.[37] Consequently, upon diagnosis of COPD, patients should be offered smoking cessation intervention therapy.[38] Smoking may emerge as a pivotal modifiable risk factor in the pathogenesis of Alzheimer's disease.[39] Among older adults, successful quitters exhibited a significantly slower rate of cognitive decline than those who continued smoking during the subsequent 2-year period.[40] Based on the above findings, it can be inferred that quitting smoking following COPD diagnosis may confer a protective effect against the development of Alzheimer's disease in previous smokers.

The prevalence of mild cognitive impairment in patients with moderate-to-severe COPD is reported to be as high as 36%, primarily affecting executive function, memory, and attention.[41] Additionally, a cohort study by Dodd et al demonstrated that severe COPD and heavy smoking are risk factors for executive dysfunction in patients.[42] Notably, the core manifestation of ADHD is executive dysfunction, with behavioral features encompassing inattention, hyperactivity, and impulsivity.[43,44] Our study revealed a significantly elevated risk of ADHD among individuals with COPD who were former smokers compared to non-smokers. Smoking induces oxidative stress and upregulates the generation of superoxide free radicals, which play a pivotal role in the pathogenesis of COPD.[45] Therefore, quitting smoking is a crucial intervention for all patients diagnosed with COPD and has the potential to significantly enhance their prognosis.[46] At the same time, ADHD is a significant risk factor for persistent smoking, with the severity of its symptoms exhibiting a significantly positive correlation with both lifetime smoking risk and daily smoking volume.[47] Additionally, adult smokers with ADHD exhibit a higher propensity for challenges in quitting compared to individuals in the general population.[48] Therefore, the oxidative stress of smoking and the withdrawal effects of smoking cessation may be responsible for this phenomenon.

Previous studies have commonly observed that patients suffering from COPD exhibit varying degrees of anxiety symptoms, with a prevalence ranging from 6% to 33%, and in advanced COPD cases, the prevalence can exceed 25%.[49] However, the clinical manifestations of anxiety closely resemble the respiratory challenges associated with COPD, making it challenging to differentiate between the two.[50] This study's findings indicate no observed correlation between COPD and severe anxiety disorders, regardless of individuals' smoking history. It is highly conceivable that in previous studies, the symptoms of dyspnea associated with COPD were misinterpreted as manifestations of anxiety, potentially leading to false positive outcomes. Furthermore, this study solely encompassed data pertaining to major depressive disorder while excluding mild depressive disorder, resulting in a selection bias and yielding inconclusive findings. Consequently, future investigations necessitate additional GWAS data for validation.

This study represents the first attempt to investigate the causal association between COPD and psychiatric disorders using two-sample MR Analysis and GWAS-level summary data, effectively mitigating potential confounding factors and reverse causation through comprehensive aggregation of substantial genetic data. However, it is important to acknowledge the limitations of this study. Firstly, the sample population was restricted to individuals of European descent; thus, caution should be exercised when generalizing these findings to broader populations. To ensure the validity of our MR study, we selected independent SNPs that achieved genome-wide significance ($P < 5\times10^{8}$), reducing the potential impact of weak instrumental variables. Consequently, only a limited number of SNPs remained after rigorous screening. However, future GWAS studies with larger sample sizes are warranted to identify additional SNPs. Substantial heterogeneity was observed among certain SNPs, which may still introduce potential bias into the results despite employing a random-effects model.

Conclusions

In conclusion, ever-smokers with COPD have a greater risk of developing ADHD but may reduce the risk of Alzheimer's disease to some extent. No causal association with psychiatric disorders was observed in COPD patients without

a smoking history. Therefore, attention needs to be paid to preventing psychiatric disorders in COPD patients with a smoking history.

Ethics Approval and Consent to Participate

As per the regulations outlined in People's Republic of China's "Notice on the Implementation of Ethical Review Measures for Life Science and Medical Research", our study falls under the exemption criteria specified in Discussion of the regulation. Therefore, ethics approval was not required for this research, as it met the following conditions:

1. Exemption Premise: This study used only publicly available data, especially summary level data from GWAS, did not involve sensitive personal information, did not cause harm to individuals, and did not compromise their privacy.
2. Exemption Provision: Our research adheres to the exemption circumstances outlined in Discussion of the regulation: We utilized lawfully obtained publicly available data for our analysis. The data used in this study were fully anonymized, ensuring the privacy and confidentiality of individuals. Our research focuses on analyzing existing data and does not involve interventions, human biological samples, or activities related to reproductive cloning, genetic manipulation, or germ cells.

Due to the nature of our study and its compliance with the exemption criteria, we did not require explicit ethics approval. And we affirm that this research was conducted in accordance with the applicable laws, regulations, and ethical standards.

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Disclosure

The authors report no conflicts of interest in this work.

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