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Validating the pathogenic mechanism of chronic obstructive pulmonary disease induced by negative emotions via Mendelian randomization and traditional Chinese medicine theory of emotions

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ABSTRACT

Objective We employed Mendelian randomization (MR) to test the traditional Chinese medicine (TCM) theory of emotional pathogenesis concept and explore the causal relationship between negative emotions and chronic obstructive pulmonary disease (COPD).

Methods Data of negative emotions, bronchitis, emphysema, and C-reactive protein (CRP) levels were downloaded from genome-wide association study (GWAS) public database for a two-sample MR analysis. Independent single-nucleotide polymorphisms (SNPs) associated with negative emotions, bronchitis, and emphysema were selected as instrumental variables. Primary causal estimates were derived using inverse-variance weighting (IVW), supplemented by weighted median (WM), and simple mode (SM) methods. Sensitivity analyses included MR-Egger regression and MR-PRESSO to assess pleiotropy, Cochran's Q test for heterogeneity, and multivariate MR to adjust for smoking. Mediation analysis evaluated the role of inflammatory markers. Reverse MR was tested for bidirectional causality. Weak instrument bias was mitigated via F-statistic thresholds (> 10). All analyses were conducted in RStudio.

Results MR analysis identified significant causal effects of several negative emotions on COPD. Genetically, the IVW analysis of seen doctors for nerves anxiety tension or depression [OR_{IVW} = 1.006, 95% CI = (1.002, 1.010), P = 0.002], sensitivity/hurt feelings [OR_{IVW} = 1.024, 95% CI = (1.004, 1.044), P = 0.017], and irritability [OR_{IVW} = 1.019, 95% CI = (1.003, 1.035), P = 0.019 were robustly associated with increased risks of COPD. No heterogeneity was detected among the different instrumental variables (IVs) for depression (P = 0.655) and irritability (P = 0.163). MR-Egger regression intercepts for all emotional exposures were close to zero and statistically non-significant, indicating no evidence of directional pleiotropy. The horizontal pleiotropy results showed that except for worry (MR-PRESSO P = 0.006), other emotion exposures confirming no substantial pleiotropic bias. Multivariable MR demonstrated that anxiety remained independently associated with COPD after adjusting for smoking (P = 0.002), while associations with other negative emotions were attenuated post-adjustment. The mediation analysis revealed that CRP mediated 3.93% of the total effect of anxiety on COPD. However, reverse MR analysis found no evidence of reverse causality.

Conclusion This study confirmed the causal effects of negative emotions on COPD through

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MR analysis and revealed that negative emotions may trigger CRP production, which plays an essential mediating role in this relationship. This study provides a reliable modern theoretical basis for emotion theory in TCM.

1 Introduction

Chronic obstructive pulmonary disease (COPD), which encompasses chronic bronchitis and emphysema, represents a leading global cause of morbidity and mortality. This condition is primarily driven by chronic airway inflammation and oxidative stress [1-3]. While environmental factors like smoking and pollution are well-established contributors, pro-inflammatory reactions, and oxidative stress in the lungs are known to cause alveolar epithelial cell death, leading to emphysema development [4, 5]. Current COPD therapies focus on symptom management and exacerbation prevention, with no available disease-modifying treatments [6]. Emerging evidence suggests psychological stress and negative emotions may serve as potential risk modifiers [7]. A recent study revealed novel mechanisms linking pulmonary and neurological systems [8]. Their mouse depression model demonstrated that mesenchymal stem cells (MSCs) induced the release of 5-hydroxytryptamine (5-HT) in the dorsal raphe nucleus by activating vagus nerve sensory neurons innervated by pulmonary nerves. In contrast, brain-derived neurotrophic factor secreted by MSCs activate pulmonary sensory neurons via tropomyosin receptor kinase B (TrkB), and inhaled TrkB agonists showed significant therapeutic effects in male mice, revealing their potential in treating major depression. This "pulmonary vagus nerve-to-brain axis" offers a new perspective for understanding mind-body interactions. Interestingly, this modern concept resonates well with the holistic view of traditional Chinese medicine (TCM).

In TCM practice, COPD are classified under two categories: "asthma syndrome" and "cough". The TCM pathogenesis theory proposes that the onset of chronic bronchitis is inseparable from external pathogens, particularly wind and dryness, and internal emotional factors like the excess of the five minds, the combination of external and internal factors. This integrated pathogenic model exemplifies TCM's holistic philosophy, where emotional imbalances [e.g., excessive "Qiqing (七情, seven emotions)" such as anxiety or sorrow], disrupt Qi flow and organ function, potentially leading to COPD progression. Contemporary study corroborate that chronic stress activates neuroendocrine pathways (e.g., the hypothalamic-pituitary-adrenal axis), fostering systemic inflammation and immune dysregulation mechanisms overlapping with TCM's emotion-induced pathogenesis concept. However, observational data suffer from confounding and reverse causality, leaving the causal role of emotions in COPD unresolved [7].

While the Qingzhi Xueshuo (情志学说, emotion-induced pathogenesis theory) in TCM lacks robust biological evidence, its emphasis on the relationship between emotional management and health aligns with the modern medical approach to improving chronic diseases through psychological interventions, such as cognitive-behavioral therapy. This conceptual convergence suggests valuable opportunities for interdisciplinary research that integrates TCM's "emotions and viscera" theory with modern molecular biology and neuroscience approaches. Such integration could uncover deeper pathological mechanisms while providing scientific substantiation for TCM theories. However, there is currently a lack of large-scale randomized controlled trials (RCTs) confirming the important role of negative emotions in the pathogenesis and progression of this disease, primarily due to rigid inclusion and exclusion criteria, ethical constraints, limited generalizability of findings, and financial considerations. Furthermore, the concept and classification of "Qingzhi (情志, emotional activities)" in TCM present inherent complexities, compounded by the absence of unified quantitative standards, which complicate direct correlations with modern scientific parameters. To address these limitations, we employed Mendelian randomization (MR), a novel epidemiological approach that resembles the RCT designs, to elucidate the pathogenesis of emotional factors in TCM while establishing modern molecular biology basis and related possible mechanisms for classical theories.

This study aims to investigate the causal effects of negative emotions on COPD using two-sample MR. We hypothesize that genetically proxied emotional traits increase COPD risk, mediated by inflammatory pathways. By addressing methodological limitations of prior research, this investigation establishes contemporary biological correlates for TCM's emotion-viscera interaction theory and informs preventive strategies targeting psychological well-being.

2 Data and methods

2.1 Study design

MR employs instrumental variables (IVs) to establish the causal relationships between samples [9], and the IVs used in MR analysis must satisfy three assumptions: (i) relevance assumption: the single-nucleotide polymorphisms (SNPs) are strongly correlated with negative emotions;

(ii) exclusion assumption: the SNPs are not related to the occurrence of bronchitis and emphysema; and (iii) independence assumption: the SNPs are not associated with known confounders. To address our first hypothesis, we selected SNPs at a genome-wide significance threshold of $P < 5 \times 10^{-8}$ [10], ensuring robust genetic associations with negative emotions. Second, genetic variants associated with bronchitis and emphysema were excluded. Last, the independence assumption was supported by verifying that the genetic variants were not associated with negative emotions or any other underlying factors associated with bronchitis or emphysema. However, due to limited SNPs retained after stringent exclusion and the inherent challenge of objectively validating the exclusion and independence assumptions, we were unable to verify the exclusivity assumption or the independence assumption; rather, we mainly verified the causal effects of negative emotions on bronchitis and emphysema through the relevance assumption.

2.2 Data sources

The primary data for this study were derived from genome-wide association studies (GWAS) hosted in the UK Biobank (UKB, https://www.ukbiobank.ac.uk/), and the large-scale biomedical database, IEU OpenGWAS (https://gwas.mrcieu.ac.uk/). Specifically, the UKB-A-68 dataset was selected to define the phenotypes of chronic bronchitis and emphysema. Guided by the TCM theory of emotion-induced pathogenesis, we selected negative emotions as the core exposure variables. We operationalized emotional exposures according to established psychological taxonomies distinguishing internalized and externalized emotions. Internalized emotions refer to the concentrated reflection of an individual's internal psychological state, mainly as suppressing one's own emotions or introspective experiences. Examples included in this study are "miserableness" "anxiety" and "irritability". Externalized emotions are characterized by excessive behavioral reactions to external environmental stimuli, with irritability being a typical representative. Based on this taxonomy, this study screened three types of emotion exposure variable phenotypes (including internalized and externalized emotions), namely, miserable which fall into the categories of miserableness, seen doctors for nerves anxiety tension or depression, sensitivity/hurt feelings and excessive worrying after embarrassment which fall into the categories of anxiety, and irritability which falls into the categories of irritability, from the GWAS database to systematically explore their causal relationship with COPD (Table 1).

Table 1 Classification of emotions and corresponding GWAS sources

Specific emotion	Category of emotions	GWAS name	GWAS ID
Miserableness	Internalized emotions	Miserable	ebi-a-GCST90013874
		Seen doctors for nerves anxiety tension or depression	ebi-a-GCST90013959
Anxiety	Internalized emotions	Sensitivity/hurt feelings	ukb-a-48
		Worry too long after embarrassment	ukb-b-13 653
Irritability	Externalized emotions	Irritability	ukb-b-13 745

2.3 Selection of IVs

This study identified SNPs related to negative emotions as IVs from GWAS data. We performed a series of steps to select appropriate working variables to ensure they satisfied the first two basic assumptions. First, we extracted SNPs associated with negative emotions at a genome-wide significance level ($P < 5 \times 10^{-8}$). Second, to ensure the independence of genetic variables, we removed SNPs exhibiting linkage disequilibrium. If there is linkage disequilibrium, the assignment of two SNPs will appear linked, affecting the relative independence. Such a violation of MR's random assignment principle affects the research results. Therefore, in two-sample Mendelian randomization (TSMR), we eliminated SNPs that met the linkage disequilibrium criteria ($r^2 > 0.001$ within a 10 000 kb distance) [11]. Third, we queried the SNPs corresponding to their use in the database of chronic bronchitis and emphysema. For SNPs unavailable in the outcome, we identified proxy SNPs in high linkage disequilibrium (LD) with the original SNPs, using a threshold of LD $r^2 > 0.8$ [12, 13]. At the same time, we directly deleted the effect alleles and palindromic SNPs in the MR analysis.

After we initially screened out SNPs through the above steps, we tested the strength of these SNPs as IVs by calculating the total F value of the IVs. The F statistic should be greater than 10 to ensure a strong correlation between IVs and exposure and to ensure that it is not a weak IV [14].

The minor allele frequency (MAF), the effect size of SNP on exposure (β), standard deviation (SD), and the corresponding values can be found in the GWAS data. To conduct the MR statistical analysis, we used the Two-Sample MR (0.5.6) and MR-PRESSO (1.0) packages in RStudio v4.2.1 for our main data analysis [15].

2.4 MR analysis

This study used a variety of statistical methods, including inverse-variance weighting (IVW), weighted median

(WM), simple mode, heterogeneity test (Cochran's *Q* test), pleiotropy test (MR-Egger and MR-PRESSO), multivariate Mendelian randomization (MVMR), and mediation analysis. Such a comprehensive analytical approach aimed to systematically evaluate the causal relationship between negative emotions and respiratory diseases and explore the mediating role of chronic inflammatory markers. Sensitivity analysis was used to verify the robustness of the instrumental variable assumptions and results.

2.4.1 MR analysis of negative emotions and COPD The IVW method served as the primary analytical approach in this study, while supplementary methods provided corroborative evidence. The IVW analysis was predicated on the assumption that instruments influenced the outcome exclusively through the exposure of interest and not by any alternative pathway. GWAS summary statistics could validly estimate the presence and strength of causal effects between exposures and outcomes [16, 17]. In this study, we also transformed the results obtained from the IVW analysis. We took the natural logarithm of IVW to obtain the OR value to quantify exposure-outcome causal effects.

WM and simple mode methods were applied as supplementary approaches. The WM method assigned weights to SNPs based on descending Wald ratio values, enabling robust causal estimation if at least 50% of the IVs were valid [18]. The simple mode approach compared genotype/phenotype distributions between experimental and control groups to identify statistically significant differences. This method facilitated the statistical determination of between-group differences in those variables.

2.4.2 Sensitivity analysis In MR experiments, the heterogeneity test is a statistical assessment of the compatibility of IV estimates based on a single genetic variable [19]. Since the selected GWAS were drawn from multiple cohorts, there may be heterogeneity among the IVs, which would violate the assumptions. Therefore, we used the MR-Egger and IVW models to estimate heterogeneity and the Cochran's *Q* test to detect heterogeneity.

MR-Egger method can detect bias in MR study results and correct for the effects of pleiotropy, to some extent, representing the intercept of the regression model [16]. A value approximating zero ($\beta \approx 0$) supported the absence of directional pleiotropy in the regression model. In contrast, a statistically significant deviation from zero ($\beta \neq 0$, $P \leqslant 0.05$) suggested potential violations of the IV assumptions due to pleiotropic effects. A *P* value greater than 0.05 confirmed that pleiotropy did not excessively influence the IV estimates, thereby validating their suitability for causal inference.

MR-PRESSO method was applied via the following three tests. (i) Global test: this test detects whether there is horizontal pleiotropy by calculating the IVW result after each SNP is removed, calculating the sum of squares of the residuals and the IVW result, and finally adding them to obtain a value. A larger test statistic indicates more substantial evidence of horizontal pleiotropic effects. (ii) Outlier test: this test corrects horizontal pleiotropy by removing abnormal SNPs exhibiting significant deviations from the fitted causal trajectory. (iii) Distortion test: this experiment removes abnormal SNPs and compares them with the original result. A substantial discrepancy suggests that pleiotropy meaningfully distorted initial findings.

2.4.3 MVMR analysis Previous literature has established smoking as a significant risk factor for chronic bronchitis and emphysema [20]. To exclude these risk factors from biasing our previous results, we included the genetic variation of each risk factor and allergic disease in the same model and evaluated them simultaneously. Using MVMR, separate but related exposures can be assessed simultaneously by incorporating the genetic variation for each risk factor into the same model [19]. To further evaluate whether smoking has an impact on negative emotions, we separately conducted MVMR.

2.4.4 Mediation analysis To elucidate the pathological mechanisms linking negative emotions to disease development, we performed an MR mediation study. Using the following criteria for mediator selection ($r^2 = 0.001$, kb = 10 000, $P = 1 \times 10^{-6}$), we tested our hypothesis that negative emotions induce COPD through chronic inflammatory responses. Specifically, we examined the mechanism underlying the inducing of diseases via negative emotions by mediating chronic inflammatory markers such as interleukin (IL)-6 and IL-8.

3 Results

3.1 Causal associations between negative emotions and COPD

Externalized emotions are characterized by excessive reactions to external stimuli, including irritability (Table 2). For each emotional trait, the SNPs were selected based on the threshold of $P < 1 \times 10^{-8}$ and the linkage disequilibrium criteria, yielding varying numbers of SNPs. Our analysis results were mainly based on the IVW method, and the WM and simple mode methods were used for auxiliary verification. The MR analysis showed that among internalized emotions, seen doctors for nerves anxiety tension or depression [OR_{IVW} = 1.006, 95% CI = (1.002, 1.010), P = 0.002], sensitivity/hurt feelings [OR_{IVW} = 1.024, 95% CI = (1.004, 1.044), P = 0.017], as well as externalized emotion irritability [OR_{IVW} = 1.019, 95% CI = (1.003, 1.035), P = 0.019], were associated with COPD. The MR analyses revealed significant associations between multiple negative emotions and COPD risk (Figure 1).

Table 2 MR estimates of the relationship of genetically predicted negative emotions on COPD

Category	Emotion	Specific emotion	Method	nSNP	*β* value	*P* value	OR (95% CI)
Internalized emotion	Miserableness	Miserableness	Weighted median	19	0.008	0.022	1.008 (1.001, 1.015)
			Inverse variance weighted	19	0.006	0.050	1.006 (1.000, 1.012)
			Simple mode	19	0.009	0.169	1.009 (0.997, 1.022)
	Anxiety	Seen doctors for nerves anxiety tension or depression	Weighted median	23	0.005	0.078	1.005 (0.999, 1.011)
			Inverse variance weighted	23	0.006	0.002	1.006 (1.002, 1.010)
			Simple mode	23	0.013	0.051	1.013 (1.001, 1.025)
		Sensitivity/hurt feelings	Weighted median	23	0.029	0.014	1.030 (1.006, 1.054)
			Inverse variance weighted	23	0.024	0.017	1.024 (1.004, 1.044)
			Simple mode	23	0.017	0.494	1.017 (0.970, 1.067)
		Worry too long after embarrassment	Weighted median	38	– 0.006	0.592	0.994 (0.973, 1.016)
			Inverse variance weighted	38	– 0.005	0.601	0.995 (0.978, 1.013)
			Simple mode	38	– 0.014	0.575	0.986 (0.941, 1.034)
Externalized emotion	Irritability	Irritability	Weighted median	43	0.022	0.042	1.022 (1.001, 1.043)
			Inverse variance weighted	43	0.019	0.019	1.019 (1.003, 1.035)
			Simple mode	43	0.040	0.121	1.041 (0.990, 1.094)

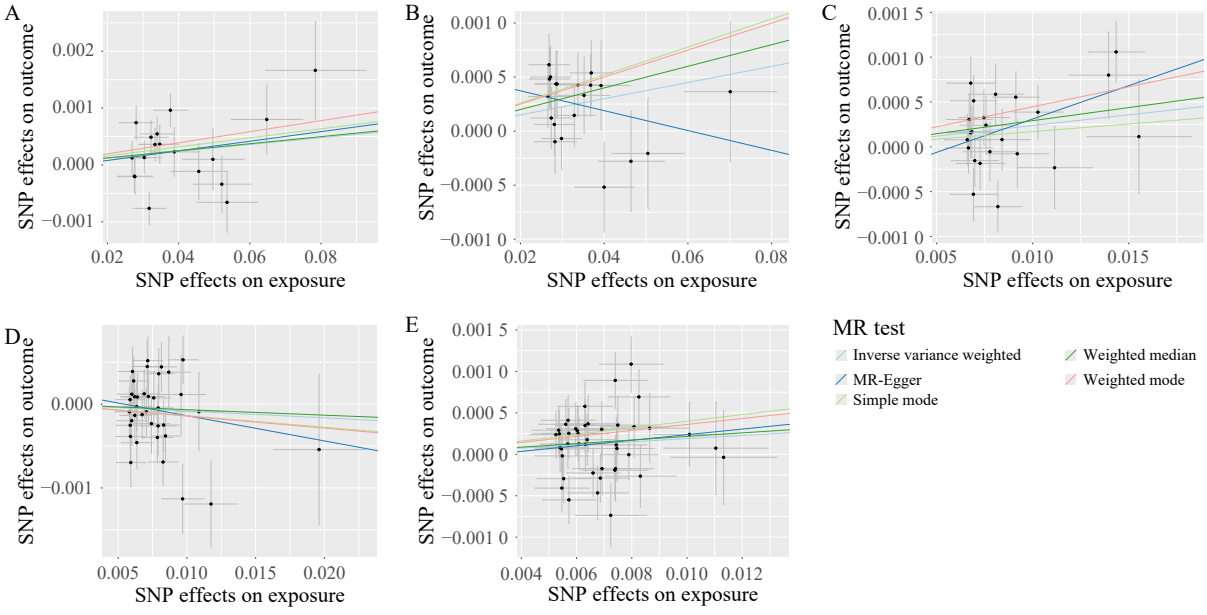

Figure 1 Scatter plots of genetic correlations of negative emotions and COPD using different MR methods

A, scatter plot of the causal effect of miserable on COPD. B, scatter plot of the causal effect of seen doctors for nerves anxiety tension or depression on COPD. C, scatter plot of the causal effect of sensitivity/hurt feelings on COPD. D, scatter plot of the causal effect of worry too long after embarrassment on COPD. E, scatter plot of the causal effect of irritability on COPD. The abscissa represents the SNP's effect estimation of exposure, while the ordinate represents the SNP's effect estimation of the outcome. Each point in the plot represents an independent genetic instrumental variable. As for the slope of the regression line, a positive slope indicates that increased exposure may result in an increased risk of outcome or an increase in the level, and a negative slope indicates that increased exposure may result in a reduced risk of outcome or a decrease in the level.

However, worry too long after embarrassment within internalized emotions showed no causal relationship with chronic bronchitis and emphysema. We also calculated *F* values to evaluate weak IVs. The *F* values in this study were all greater than 10, which indicates that there was no bias from weak IVs and the study results are reliable.

3.2 Sensitivity test and pleiotropy test

The results of the Cochran's *Q* test for heterogeneity revealed that miserable ($P = 0.006$), sensitivity/hurt feelings ($P = 0.041$), and worry too long after embarrassment ($P = 0.005$) were heterogeneous. No heterogeneity was detected among the different IVs for depression ($P = 0.655$) and

irritability (P = 0.163). MR-Egger regression intercepts for all emotional exposures were close to zero, for example, miserableness MR-Egger regression intercept = – 8.892 × 10^{-5} sensitivity/hurt feelings MR-Egger regression intercept = – 4.340 × 10^{-4}, and statistically non-significant, indicating no evidence of directional pleiotropy. The horizontal pleiotropy results showed that except for worry (MR-PRESSO P = 0.006), for other exposures, MR-PRESSO global tests yielded P > 0.05, confirming no substantial pleiotropic bias (Table 3 and Figure 2).

Table 3 MR-PRESSO results of the causal correlation between genetically predicted negative emotions on COPD

Specific emotion	Method	Cochran's Q statistic	Degree of freedom for Q test	Q test P value	P value	MR-PRESSO global test P value	MR-Egger regression intercept
Miserableness	MR-Egger	36.204	17	0.004	0.854	0.568	– 8.892 × 10^{-5}
	Inverse variance weighted	36.279	18	0.006			
Seen doctors for nerves anxiety tension or depression	MR-Egger	16.963	21	0.713	0.185	0.635	4.019 × 10^{-4}
	Inverse variance weighted	18.838	22	0.655			
Sensitivity/hurt feelings	MR-Egger	32.230	21	0.055	0.209	0.057	– 4.340 × 10^{-4}
	Inverse variance weighted	34.811	22	0.041			
Worry too long after embarrassment	MR-Egger	62.526	36	0.004	0.617	0.006	1.735 × 10^{-4}
	Inverse variance weighted	62.969	37	0.005			
Irritability	MR-Egger	50.769	41	0.141	0.749	0.553	– 9.926 × 10^{-5}
	Inverse variance weighted	50.897	42	0.163			

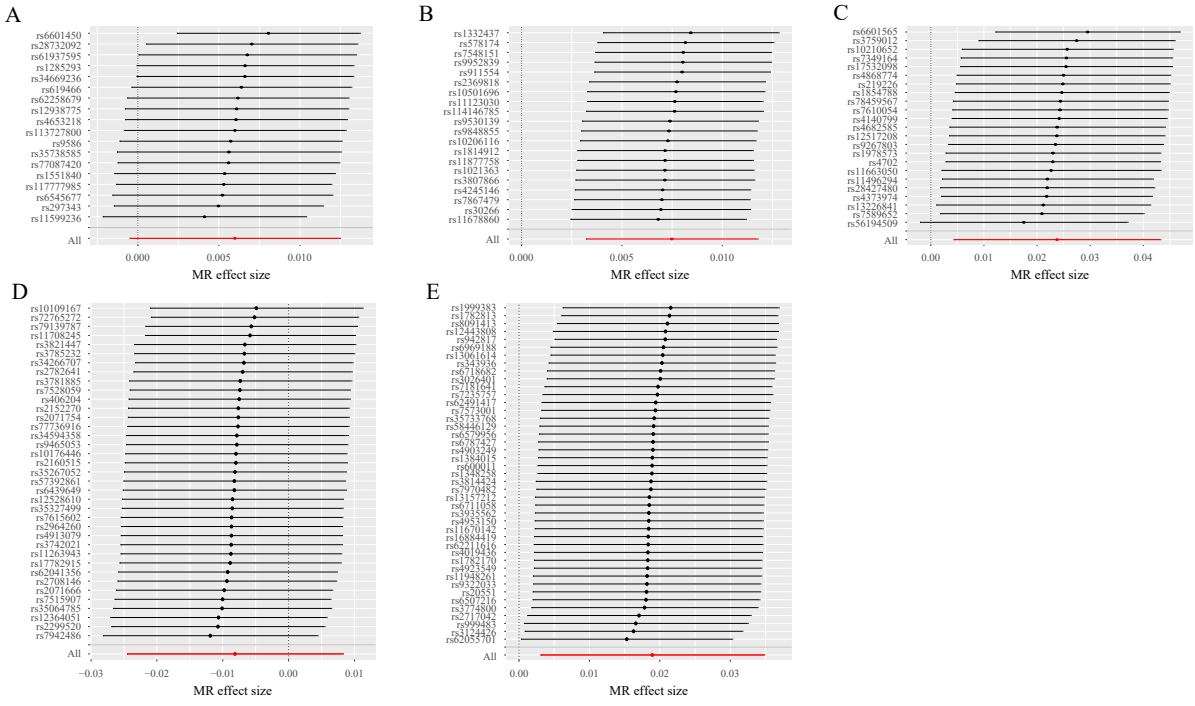

Figure 2 MR leave-one-out sensitivity analysis of the causal relationship between negative emotions and COPD

A, miserable and COPD. B, seen doctors for nerves anxiety tension or depression and COPD. C, sensitivity/hurt feelings and COPD. D, worry too long after embarrassment and COPD. E, irritability and COPD. The red lines are the analysis results of random effects IVW.

3.3 Reverse MR analysis

To examine the causal relationship between negative emotions and COPD, we also conducted a reverse analysis of the negative emotions found causally associated with COPD in the forward MR analysis. However, due to insufficient instrument availability at SNPs, we employed an expanded threshold and set P to 1× 10^{-6}. Ultimately, these analyses revealed no statistically significant reverse causal effects.

3.4 Multivariate MR analysis

This study used a multivariate Mendelian randomization model to analyze and found that the causal relationship between anxiety and COPD was independent of smoking and remained significantly associated after adjusting for smoking (P = 0.002). The initial association between miserable (P = 0.104), sensitivity/hurt feelings (P = 0.095), irritability (P = 0.206) and COPD lost statistical significance after incorporating smoking, suggesting that these associations may be confounded by smoking behavior. Although emotions such as miserable and irritability have a positive correlation with COPD, the sample size was limited to a significant level and requires larger-scale research verification analysis (Table 4).

Table 4 Multivariate MR analysis including current smoking

Exposure	Confounder	Outcome	*P* value	OR (95% CI)
Miserableness	Current smoking	COPD	0.104	1.005 (0.999, 1.011)
Seen doctors for nerves anxiety tension or depression			0.002	1.008 (1.003, 1.013)
Sensitivity/hurt feelings			0.095	1.018 (0.997, 1.040)
Irritability			0.206	1.013 (0.993, 1.033)

3.5 Mediation MR analysis

To further study how depressive mood promotes the occurrence of COPD, we performed mediation MR analysis, and we included intermediary variables related to inflammation, including IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-related activation-induced cytokines, procalcitonin, eosinophil cell count, and white blood cell count. According to MR analysis, depression promoted the development of COPD through an increase in CRP (P = 0.013). We used the IVW method to analyze the mediation of three causal effects (a, b, c'). The total effect was c' = 0.006 3, the mediating effect (ME) was a × b = 0.000 25, and the direct effect (DE) was c'– (a × b) = 0.003 8 (Table 5). These results indicated that CRP mediated the above causal associations. In summary, the mediation effect value was 0.000 24, and the mediation proportion was 0.039 32. The negative emotions (seen doctors for nerves, anxiety tension, or depression) significantly increased CRP levels (P = 0.000 57), and CRP was associated with an increased risk of COPD (P = 0.000 34). The total effect of depression on COPD was partially mediated by CRP, with a mediation effect of 0.000 24, accounting for 3.93% of the total effect. Other mediators (e.g., IL-6, IL-8, and TNF-α) were excluded from the final analysis due to non-significant associations.

Table 5 Three causal effects (a, b, c') of the mediation analysis in IVW method

Pathway	nSNP	Causal effect	*P* value
Nerves anxiety tension or depression – CRP	22	a = 0.078 0	0.000 57
CRP – COPD	303	b = 0.003 2	0.000 34
Nerves anxiety tension or depression – COPD	23	c = 0.006 3	0.001 75

a represents exposure to mediation variable causal effects, b represents mediation to outcome variable causal effects, and c represents exposure to outcome variable causal effects

4 Discussion

4.1 The relationship between negative emotion and COPD

The relationship between negative emotions, immune function, and physical diseases is increasingly recognized. Chronic negative emotions disrupt immune homeostasis by suppressing T-cell activity, impairing natural killer cell function, and skewing the Th1/Th2 balance, and altering the inflammatory microenvironment in brain regions linked to emotional regulation [7, 21, 22]. An increase in negative emotions is associated with elevated expression of pro-inflammatory genes and type I interferon (IFN) genes [21]. In COPD patients, the immune perturbations manifest as heightened systemic inflammation, evidenced by increased plasma levels of CRP, IL-6, TNF-α, and fibrinogen [23]. Notably, it has been found that 54.7% of patients with COPD exhibit symptoms of anxiety, with a higher proportion of anxiety in severe COPD patients suggesting a bidirectional relationship between psychological distress and pulmonary pathology [24].

4.2 CRP as a critical mediator linking emotions to COPD

A key finding of this study is the identification of CRP as a mediator between negative emotions (especially depression) and COPD. CRP is an acute-phase protein synthesized by the liver, and elevated levels of CRP reflect systemic inflammation, a known driver of COPD progression [25, 26]. Negative emotions, such as depression and anxiety, are known to activate the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), leading to the release of pro-inflammatory

cytokines, such as IL-6 and TNF-α [27, 28]. These cytokines stimulate the liver to produce CRP as an inflammatory marker, which can directly participate in airway inflammatory responses. Chronic elevation of CRP can exacerbate oxidative stress by activating the NF-κB pathway, disrupting the alveolar structure, and promoting the release of inflammatory mediators, ultimately driving the pathological progression of chronic bronchitis and emphysema [29]. As a marker of inflammation, the mediating effect of CRP explains how negative emotions can influence lung function through the neuroendocrine-immune axis. By excluding smoking as a confounder through multivariate models, this study confirms the robustness of adverse emotions as an independent risk factor, highlighting the potential value of psychological interventions in the primary prevention of COPD. Based on this study, it is hypothesized that negative emotions induce the elevation of CRP and influence the occurrence and development of COPD through a multi-dimensional neuro-endocrine-immune network, expanding new avenues for future treatment.

4.3 Contribution to the TCM theory of emotional pathogenesis

This study is the first to provide modern molecular biological evidence for the TCM theory of emotion-induced pathogenesis from a genetic causal perspective using Mendelian randomization. The multivariate MR analysis not only clarifies the importance of anxiety as an independent risk factor for COPD but also provides a theoretical basis for integrating psychological assessment and smoking behavior intervention in clinical practice TCM posits that excessive “seven emotions” disrupt the flow of Qi (vital energy) and visceral harmony, leading to disease. Yet, this concept has long lacked direct biological mechanistic support. Our findings demonstrate that negative emotions (e.g., anxiety and depression) drive the pathological progression of COPD by activating inflammatory responses (elevated CRP), which aligns closely with the TCM theory of “internal injury by seven emotions”. CRP, as a biomarker of systemic inflammation, can be interpreted as a modern biological manifestation of pathological products induced by “emotional disturbances” in TCM. Its mediating role elucidates the specific mechanisms within the “emotion-Qi-viscera” chain. Furthermore, the study confirms that the impact of emotions on disease is independent of traditional risk factors such as smoking, emphasizing the independent role of psychological factors in COPD pathogenesis. This aligns with the TCM concept of “internal injury by emotional factors” and provides a scientific interpretation of TCM’s holistic relationship between emotions and internal organs, highlighting the importance of emotional regulation in disease prevention and treatment. Mendelian randomization, by leveraging genetic instrumental variables to circumvent confounding biases in observational studies, establishes a methodological paradigm for causal validation of TCM theories. It bridges the holistic view of TCM with modern molecular medicine, providing a theoretical foundation and innovative directions for future integrative research, such as combining psychological interventions with anti-inflammatory therapies.

4.4 Limitations and future prospects

However, this study has certain shortcomings. When we performed reverse MR, we adjusted the screening range due to insufficient IVs. And we did not find that COPD could induce the production of negative emotions, which may reflect insufficient SNPs for analysis. In the future, it is necessary to adjust the dataset to determine whether lung diseases can induce negative emotions and to further verify the specific pathway of emotion-inflammation-organ damage by combining multi-omics data.

5 Conclusion

Our findings demonstrated that negative emotions significantly elevate COPD risk, with CRP acting as a critical mediator. Notably, multivariate MR analyses confirmed that anxiety retained its independent causal association with COPD after adjusting for smoking, underscoring the unique role of emotional factors in disease pathogenesis. These results provide robust molecular evidence supporting the TCM theory of “emotion-induced pathogenesis”, which posits that emotional imbalances disrupt Qi flow and organ harmony, leading to disease. By bridging TCM’s holistic framework with modern causal inference methods, this study highlights the translational potential of psychological interventions for COPD prevention and management.

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Competing interests

The authors declare no conflict of interest.

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基于孟德尔随机化和中医情志学说阐明不良情绪诱导慢性阻塞性肺疾病产生机制

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【摘要】目的 本研究采用孟德尔随机化（MR）方法检验中医情志病因理论，探索不良情绪与慢性阻塞性肺疾病（COPD）之间的因果关系。**方法** 从全基因组关联研究（GWAS）公共数据库下载不良情绪、支气管炎、肺气肿和C反应蛋白（CRP）水平的相关数据，开展双样本MR分析。筛选与不良情绪、支气管炎和肺气肿显著相关的独立单核苷酸多态性（SNP）作为工具变量。主要因果估计采用逆方差加权法（IVW），并辅以加权中位数（WM）法和简单模型（SM）法。敏感性分析包括MR-Egger回归和MR-PRESSO评估多重效应，Cochran's *Q*检验评估异质性，多变量MR用于调整吸烟影响；中介分析用于评估炎症标志物的作用；反向MR分析评估双向因果关系；弱工具变量偏倚通过F统计量（>10）加以控制。所有分析在RStudio中进行。**结果** MR分析发现多种不良情绪对COPD具有显著的因果效应：通过IVW分析方法，遗传层面的因神经紧张、焦虑或抑郁就诊 [OR_{IVW} = 1.006，95% CI =（1.002, 1.010），P = 0.002]，敏感/容易受伤 [OR_{IVW} = 1.024，95% CI =（1.004, 1.044），P = 0.017]，以及易怒 [OR_{IVW} = 1.019，95% CI =（1.003, 1.035），P = 0.019] 均与COPD风险升高密切相关。抑郁（P = 0.655）与易怒（P = 0.163）相关工具变量之间未检测到异质性。所有情绪暴露变量的MR-Egger回归截距均接近零且无统计学意义，提示无方向性多重效应。除忧虑（MR-PRESSO P = 0.006）外，其他情绪暴露变量未见显著水平的多重效应偏倚。多变量MR分析显示，调整吸烟因素后，焦虑仍与COPD呈独立因果关系（P = 0.002），而其他不良情绪的关联性在调整后减弱。中介分析发现CRP介导了焦虑对COPD总效应的3.93%。反向MR分析未发现反向因果关系的证据。**结论** 本研究通过MR分析证实了不良情绪与COPD的因果关系，并揭示不良情绪可能诱导CRP的产生，而CRP在此因果链中发挥重要中介作用。该发现为中医情志致病理论提供了可靠的现代理论依据。

【关键词】中医；情志致病；孟德尔随机化；逆方差加权法；慢性阻塞性肺疾病