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ORIGINAL RESEARCH

Causal Relationships Between Emotional Instability and Respiratory Diseases: A Mendelian Randomization Analysis

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Background: In the past few years, there has been a growing fascination with the connection between mental well-being and respiratory conditions. However, the causal relationship between personality traits and respiratory diseases remains largely unknown. This study aimed to investigate the link between genetically predicted emotional instability and eight respiratory conditions using a two-sample Mendelian randomization (MR) analysis.

Methods: In a GWAS dataset from the UK Biobank, SNPs linked to emotional instability were discovered among 204,412 participants of European descent. Genetic information for lung cancer, pulmonary fibrosis, pneumonia, and bronchiectasis was obtained from the European Bioinformatics Institute (EBI). While data for chronic obstructive pulmonary disease (COPD), pulmonary embolism, chronic cough, and asthma was collected from the UK BioBank. An MR study was carried out to investigate how specific single nucleotide polymorphisms (SNPs) impact the likelihood of developing the eight respiratory conditions listed. Our main approach for the initial screening was the utilization of inverse variance weighting (IVW). Multiplicity was assessed using the MR-Egger regression test, while heterogeneity was evaluated with Cochran's Q test. To ensure the reliability of the findings, a leave-one-out analysis was conducted.

Results: IVW found evidence that emotional instability had a significant causal effect on the increased risk of COPD (OR = 1.009; 95% CI = 1.001–1.017; P = 0.022), pneumonia (OR = 1.648; 95% CI = 1.036–2.622; P = 0.035), chronic cough (OR = 1.077; 95% CI = 1.013–1.145; P = 0.017) and increased risk of asthma (OR = 1.073; 95% CI = 1.026–1.123; P = 0.002) had a significant causal relationship. This association remained strong in the case of potential confounders, including smoking. Additionally, the instrumental variable weighted method in this study did not find any indication of a causal link between emotional instability and lung cancer, pulmonary embolism, pulmonary fibrosis, and bronchiectasis (all P > 0.05).

Conclusion: The research discovered a link between emotional instability and a higher likelihood of developing COPD, pneumonia, chronic cough, and asthma. This study also found that emotional instability was not causally associated with lung cancer, pulmonary embolism, pulmonary fibrosis, and bronchiectasis.

Keywords: emotional instability, respiratory diseases, Mendelian randomization

Introduction

Respiratory illnesses such as lung cancer, pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease (COPD) are significant contributors to global mortality.[1] The rising prevalence of respiratory illnesses worldwide is becoming a significant danger to human well-being, attributed to air pollution, smoking, genetic predisposition, and various other influences.[2,3] There has been a growing focus on the connection between mental well-being and respiratory conditions in recent times. Prior research has indicated that individuals with mental disorders have a higher prevalence of respiratory diseases than the general population.[4] However, few studies have examined the causal relationship between personality traits and respiratory disorders. Personality or temperament, with its genetic foundation, consistently impacts

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an individual's behavioral and biological processes from birth, unlike psychiatric disorders that typically show delayed and episodic patterns.[5] Consequently, they could potentially impact the respiratory system more significantly.[6]

Emotional instability is a condition marked by frequent and erratic shifts in an individual's emotional condition.[7] Emotional lability, defined as frequent, abrupt, and unpredictable changes in irritability, arousal/activation, and anxiety/depression, is associated with psychopathology in youth and adults and is a transdiagnostic concept.[8] This behavior is frequently displayed by individuals with psychopathic tendencies and is a prevalent characteristic seen in most people. A study conducted on 7403 private households in England revealed that 13.9% of individuals exhibited emotional instability.[9] Research has demonstrated that emotional volatility is linked to various negative health consequences.[10] Prior studies have found emotional factors that could be linked to the onset of asthma and COPD, serving as potential additional risk factors for respiratory conditions.[11,12] Due to the limitations of observational studies in addressing confounding and reverse causation bias, the causal relationship between emotional instability and respiratory disease is still uncertain.

Mendelian randomization (MR) is a state-of-the-art method for clarifying potential bias in observational studies.[13] The method effectively leverages large datasets obtained from genome-wide association studies (GWAS) to uncover causal connections between certain exposure factors and results, employing single nucleotide polymorphisms (SNPs) as instrumental variables(IV).[14] In essence, MR is akin to a randomized controlled trial in that genetic variation is randomly allocated during meiosis.[15] MR analysis helps mitigate the effects of reverse causality by utilizing genetic variation, which remains constant and is not influenced by the development or advancement of respiratory illness. Therefore, if the genetic predisposition for emotional volatility is linked to respiratory illness, this offers compelling proof to back the assertion that emotional volatility is a contributing factor to respiratory disease. As far as we know, there is no proven link between emotional instability and various respiratory illnesses through MR. Our theory is that emotional instability could be a primary factor that greatly raises the likelihood of developing respiratory diseases. In this study, we investigated the possible link between genetic predisposition to emotional instability and respiratory illnesses using publicly accessible GWAS data within an MR framework.

Method

Study Design and Data Sources

We conducted a two-sample MR analysis using GWAS pooled data to investigate the potential causal link between emotional instability and respiratory disease. All GWAS studies were restricted to unrelated individuals of European ancestry. The research involved genetic variations linked to emotional instability from the UK Biobank, which consisted of 204,412 individuals of European descent. We separately extracted genetic data from UK Biobank for COPD (1605 cases and 461,328 controls), pulmonary embolism (3823 cases and 459,110 controls), pneumonia (22,567 cases and 463,917 controls), chronic cough (15,367 cases and 97,216 controls), asthma (53,598 cases and 409,335 controls) genetic data. Genetic data were also extracted from the European Bioinformatics Institute (EBI) for lung cancer (3791 cases and 489,012 controls), pulmonary fibrosis (1566 cases and 467,560 controls), and bronchiectasis (2888 cases and 440,263 controls). Within the MR framework, we employed autonomous instrumental SNPs as IVs for exposures (such as emotional instability) to estimate and examine their causal impacts on outcomes (specifically, 8 respiratory diseases). For instrumental variables to be validly used, standard MR analyses depend on three crucial model assumptions: (i) IV has a significant association with emotional instability at the genome-wide level; (ii) IV must be unrelated to any potential confounders; and (iii) IV affects the presence of the eight respiratory disorders mentioned above solely by impacting emotional instability (Figure 1). This study was exempted by the Ethics Review Committee of Shandong University of Traditional Chinese Medicine due to the fact that the data used were publicly available and had been anonymized to ensure that individuals were not identifiable. Detailed information on the exposure and outcome variable datasets is provided in Table 1.

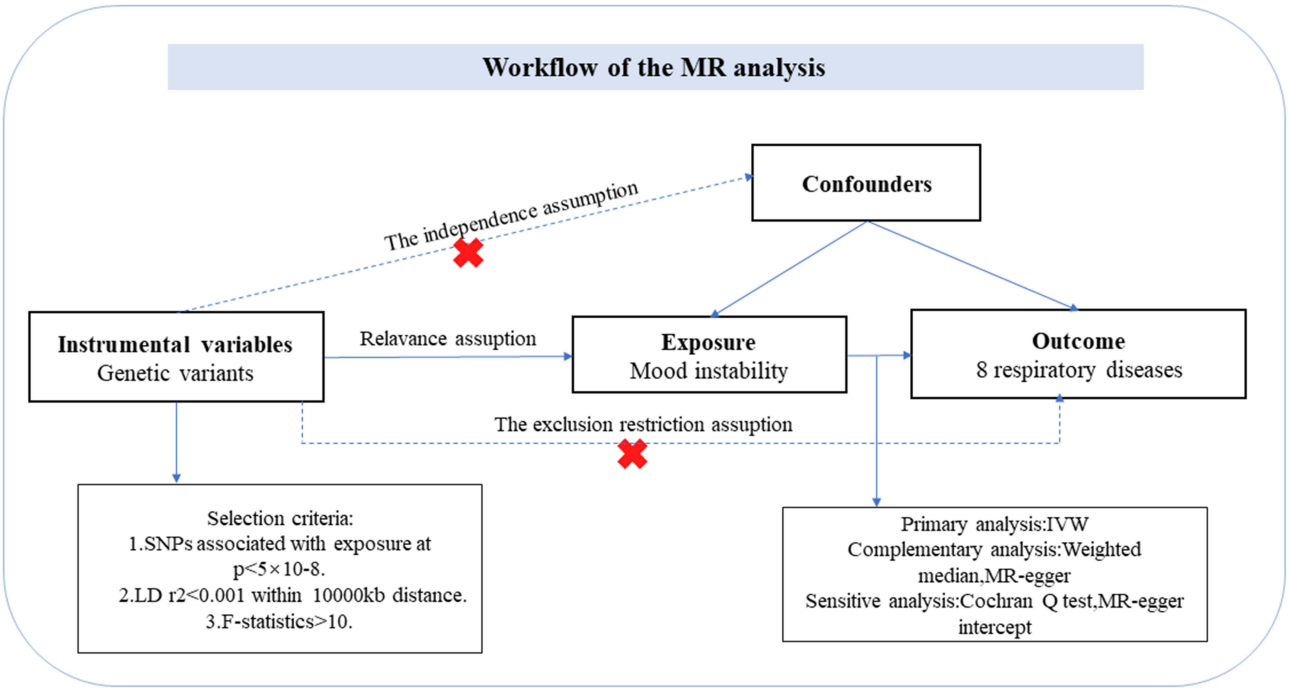

Figure 1 Study design of univariable MR to identify the causal association between mood instability and 8 respiratory diseases.

Genetic Instrumental Variables

To meet the initial hypothesis of the MR analysis that instrumental variables (IVs) are closely linked to emotional instability, we chose independent IVs with significant correlations with emotional instability at the genome-wide level ($P < 5 \times 10–8$, linkage disequilibrium < 0. 001, genetic distance = 10,000 KB).[16] Using RStudio version 4.3.2 along with the TwoSampleMR tool, we identified 62 SNPs that are strongly linked to emotional instability, as shown in Supplementary Table 1, confirming our initial hypothesis. In order to prevent any potential interference from genetic differences, we utilized the PhenoScanner database (https://www.phenoscanner.medschl.cam.ac.uk) to investigate if the IVs included were linked to any confounding factors. In this study, we excluded SNPs linked to smoking and other relevant confounders, utilizing the remaining SNPs as instrumental variables for emotional instability. Furthermore, we computed the F-statistic (F = beta^2/se^2) to prevent the impact of weak IVs on the included IVs.[17,18]

Table 1 Detailed Information of the Genome-Wide Association Study (GWAS) Used in This Study

Consortium	Exposure/Outcome	Cases	Controls	Sample Size	Population	First Author(Year)
UK Biobank	Mood swings	204,412	247,207	451,619	European	Ben Elsworth(2018)
UK Biobank	COPD	1605	461,328	462,933	European	Ben Elsworth(2018)
EBI	Lung cancer	3791	489,012	492,803	European	Sakaue S(2021)
UK Biobank	Pulmonary embolism	3823	459,110	462,933	European	Ben Elsworth(2018)
EBI	Pulmonary fibrosis	1566	467,560	469,126	European	Sakaue S(2021)
UK Biobank	Pneumonia	22,567	463,917	486,484	European	Hamilton F(2021)
UK Biobank	Cough on most days	15,367	97,216	112,583	European	Ben Elsworth(2018)
UK Biobank	Asthma	53,598	409,335	462,933	European	Ben Elsworth(2018)
EBI	Bronchiectasis	2888	440,263	443,151	European	Sakaue S(2021)

Statistical Analysis

We mainly utilized the IVW method for estimating causal effects as outlined in reference.[19] We contrasted the outcomes from the IVW technique with the results from the weighted median and MR-Egger approaches. The IVW approach yields trustworthy estimates when over half of the data is derived from valid instrumental variables. In contrast, the MR-Egger method allows all IVs to be invalid. Every method has its pros and cons. For instance, the IVW method relies on the validity of all core MR assumptions, which could lead to potential horizontal polymorphism effects and biased causal estimates. MR-Egger techniques offer impartial evaluations even in cases where the exclusion restriction assumption is breached, although their statistical strength is somewhat limited. The integration of multiple MR methods minimizes confounding and reverse causality bias and improves the accuracy of causality estimates. Thus, when the three models are consistent, they are more persuasive. In order to assess the strength of the findings, we conducted two extra sensitivity analyses: weighted mode and simple mode.[20,21] In order to prevent reverse causality, Steiger filtering was employed to examine the causality direction of each SNP on exposure and outcome and to eliminate SNPs that showed a stronger association with the outcome compared to exposure.[22] Cochran's Q-test was used to evaluate the heterogeneity of the IVW model. Cochran's Q-test of $p<0.05$ would indicate the presence of heterogeneous.[23] Despite the presence of heterogeneity, it does not automatically mean that the IVW model is invalid. The MR-Egger technique permits non-zero intercepts and is utilized to identify directed pleiotropy. Furthermore, a leave-one-out sensitivity analysis was conducted to assess if a single SNP had a significant impact on the overall estimate. Anomalies are identified and eliminated using the MR-PRESSO technique. After removing outliers, we rerun the MR analysis. The R software (version 4.3.2) was utilized for conducting all analyses, employing the software packages "MendelianRandomization", "MRPRESSO", and "TwoSampleMR" software packages.[24,25] We set the statistical significance level at 0.05.

Result

We searched for genetic variations linked to emotional volatility and identified a sum of 62 SNPs ($P < 5E-08$, $r2 < 0.001$). All of these SNPs had F-statistics exceeding the standard threshold of 10, suggesting a minor instrumental bias in our MR investigation. In the screening phase, we excluded SNPs linked to smoking and SNPs linked to their confounding factors. Detailed information on all pertinent SNPs can be found in Supplementary Tables 2–9The results of IVW analysis showed that emotional instability was associated with COPD (OR= 1.0093; 95% CI= 1.0014–1.0174; P = 0.0219), pneumonia (OR= 1.6482; 95% CI= 1.0362–2.6216; P = 0.0348), chronic cough (OR= 1.0769; 95% CI= 1.0133–1.1446; P = 0.0171) and asthma (OR= 1.0731; 95% CI= 1.02255–1.1229; P = 0.0023) were associated with increased risk. Consistent trends were also observed in the MR-Egger and weighted median models, providing additional validation for this discovery. Furthermore, in this MR study, emotional instability was associated with lung cancer (OR= 1.7406; 95% CI= 0.3611–8.3910; P = 0.4898), pulmonary embolism (OR= 1.0063; 95% CI= 0.9917–1.0211; P = 0.4017), pulmonary fibrosis (OR= 2.9066; 95% CI= 0.2443–34.5842; P = 0.3894), and bronchiectasis (OR= 0.9148; 95% CI= 0.1898–4.4086; P = 0.9116) were not causally related. Additional MR analysis findings can be found in Table 2. While

Table 2 MR Analysis Results Between Mood Instability and 8 Respiratory Diseases

Outcome	Method	OR (95% CI)	P	P value for Heterogeneity Test	P value for Pleiotropy Test
COPD					
	IVW	1.0093(1.0013–1.0174)	0.022	0.6348	
	MR-Egger	1.0056(0.9660–1.0447)	0.822	0.5732	0.8120
	Weighted median	1.0091(0.9971–1.0213)	0.138		
Lung cancer					
	IVW	1.7406(0.3611–8.3910)	0.490	0.0023	
	MR-Egger	252.12(0.2617–242,635)	0.130	0.0051	0.1601
	Weighted median	2.0019(0.3851–10.406)	0.409		

(*Continued*)

Table 2 (Continued).

Outcome	Method	OR (95% CI)	P	P value for Heterogeneity Test	P value for Pleiotropy Test
Pulmonary embolism					
	IVW	1.0063(0.9917–1.0211)	0.402	0.2626	
	MR-Egger	1.0477(0.9820–1.1177)	0.178	0.2996	0.2286
	Weighted median	1.0043(0.9838–1.0252)	0.682		
Pulmonary fibrosis					
	IVW	2.9066(0.2443–34.584)	0.398	0.5687	
	MR-Egger	10.304(8.6E-05-12,320)	0.700	0.5049	0.8306
	Weighted median	1.4617(0.0494–43.245)	0.826		
Pneumonia					
	IVW	1.6482(1.0362–2.6216)	0.035	0.1405	
	MR-Egger	5.5487(0.4484–68.662)	0.188	0.1409	0.3407
	Weighted median	1.7520(0.9394–3.2674)	0.078		
Chronic cough					
	IVW	1.0769(1.0133–1.1446)	0.017	0.1420	
	MR-Egger	0.9054(0.6639–1.2347)	0.532	0.1495	0.2683
	Weighted median	1.0607(0.9759–1.1528)	0.166		
Asthma					
	IVW	1.0731(1.0255–1.1229)	0.002	0.0014	
	MR-Egger	0.8979(0.7217–1.1171)	0.341	0.0034	0.1122
	Weighted median	1.0500(0.9967–1.1061)	0.007		
Bronchiectasis					
	IVW	0.9148(0.1898–4.4086)	0.912	0.4530	
	MR-Egger	0.2576(0.0003–178.75)	0.688	0.4043	0.6990
	Weighted median	1.4413(0.1708–12.165)	0.737		

Abbreviations: IVW, Inverse variance weighted; OR, odds ratio; 95% CI, The 95% confidence intervals.

there was diversity in MR studies involving asthma and lung cancer (Cochrane's Q-test P<0.05), indicating that some SNPs may have shown horizontal pleiotropy, the MR-Egger intercept results indicated the absence of any directed pleiotropy (Table 2). Furthermore, individual 'leave-one-out' analyses were conducted for each outcome, demonstrating the strong reliability of the positive findings (Figure 2). The balanced design of the funnel plot eliminates the potential impact of variability on our calculations during the estimation process (Figure 3). The scatterplot is shown in Figure 4.

Discussion

This study investigated the relationship between emotional instability and eight respiratory diseases using a two-sample MR framework. Utilizing an independent validation dataset and a diverse MR methodology based on different model assumptions, we rigorously tested our results to ensure the robustness and credibility of our findings. In addition, we ruled out potential reverse causation through a two-way analysis. This study fully utilizes the potential of genetic tools for MR analysis and benefits from the large sample size provided by GWAS. In our research, we discovered that individuals with emotional volatility had a higher likelihood of developing COPD, pneumonia, chronic cough, and asthma. However, it has to be mentioned that the small effect of emotional instability with COPD and chronic cough suggests a very modest increase in risk, with limited clinical significance for both diseases. No direct causal relationship was found between emotional instability and lung cancer, pulmonary embolism, pulmonary fibrosis, or bronchiectasis.

There are studies that prove that many people with chronic lung disease suffer from emotional distress. Patients with COPD often experience mood disorders, which can lead to decreased adherence to medication.[26] Furthermore, research has shown that there is a correlation between mood or anxiety disorders and increased likelihood of pneumonia complications in children attending school (OR 1.80; 95% CI 1.20–2.71) and teenagers (OR 1.63; 95% CI 1.31–2.02). Hospital stays were longer for school-age children and adolescents with mood or anxiety disorders compared to those

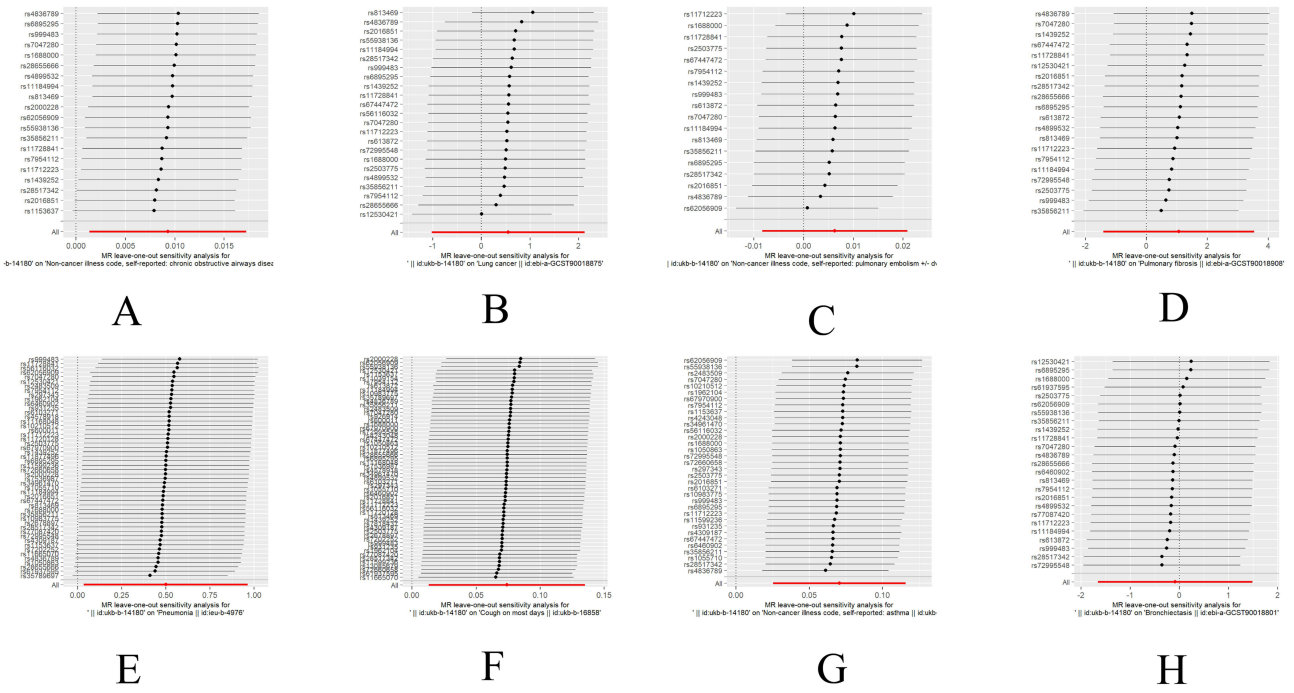

Figure 2 Forest plot for leave-one-out analysis, where each point on the left side represents the causal effect determined by IVW after removing the specific SNP.
Notes: COPD(**A**), lung cancer(**B**), pulmonary embolism (**C**), pulmonary fibrosis (**D**), pneumonia (**E**), chronic cough (**F**), asthma(**G**), bronchiectasis (**H**).
Abbreviation: IVW, inverse variance weighted method.

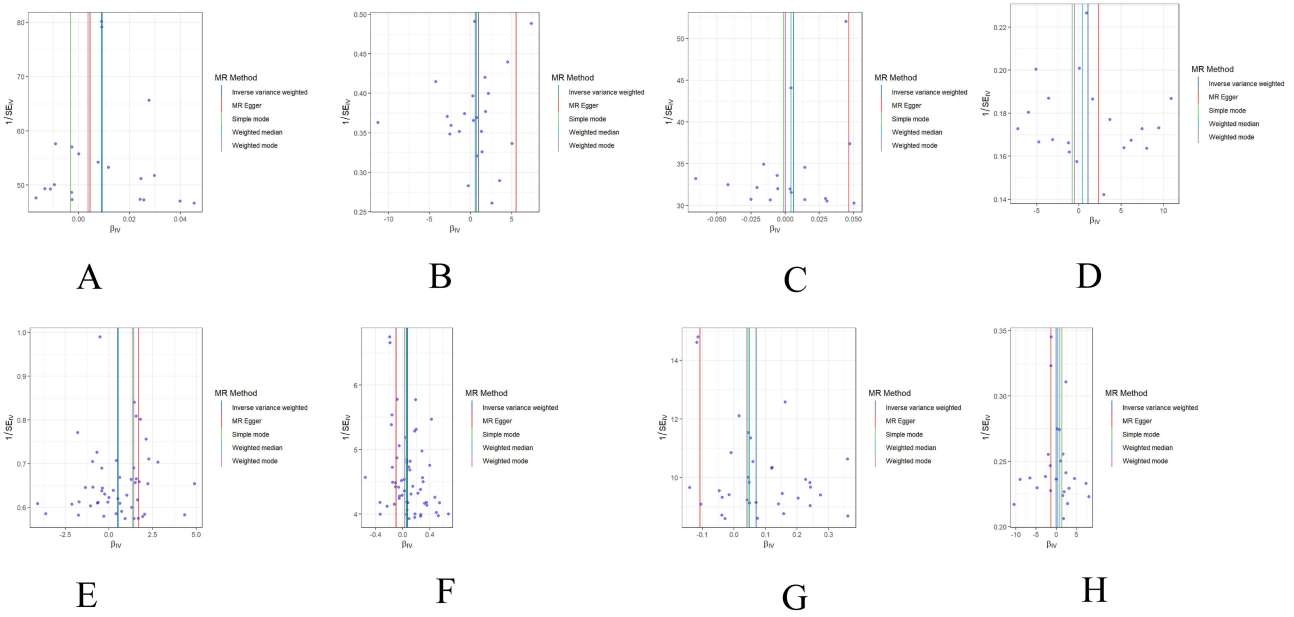

Figure 3 Funnel plot for the general heterogeneity in the impact of mood instability on the risk of 8 respiratory diseases.
Notes: COPD(**A**), lung cancer(**B**), pulmonary embolism (**C**), pulmonary fibrosis (**D**), pneumonia (**E**), chronic cough (**F**), asthma(**G**), bronchiectasis (**H**).

without, with rates of 11.2% and 13.6% respectively (p<0.001).[27] Asthma sufferers have long been known to experience psychological distress, with elevated levels of stress and negative emotions such as fear, irritability, and depression. Research indicates that the severity of asthma symptoms may have a significant impact on stress levels and perceived control in individuals with asthma.[28] Emotional stress can worsen the physical symptoms of atopic disease and potentially lead to asthma attacks.[29] In summary, the findings from these observational studies indicate that a lack of

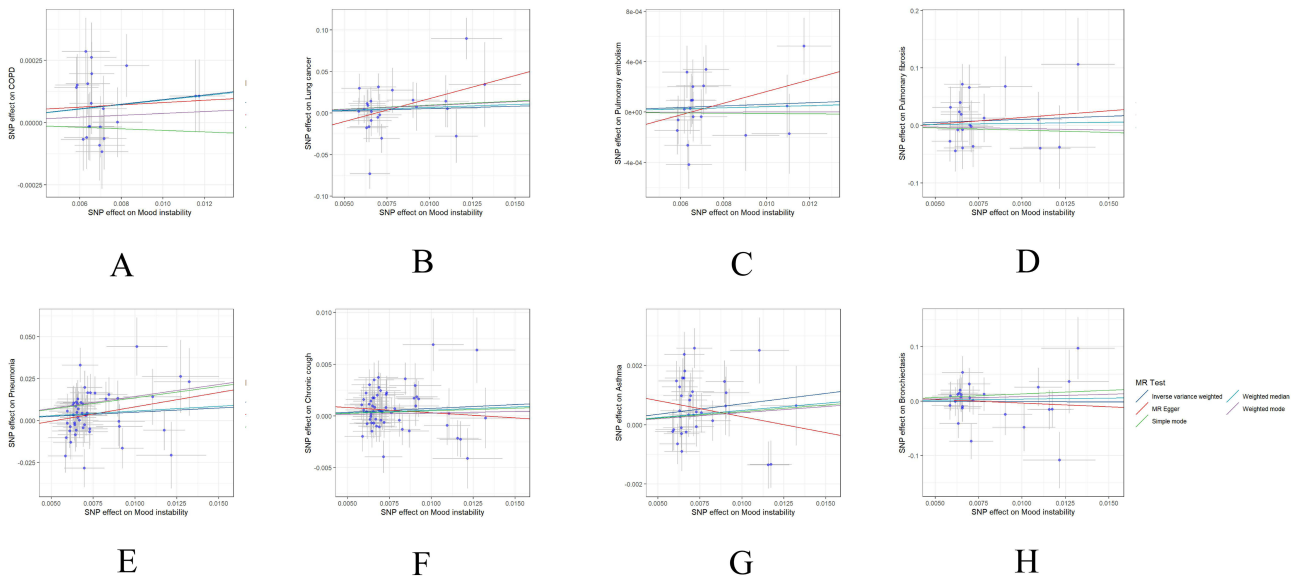

Figure 4 Scatter plot for the causal effect of mood instability on 8 respiratory diseases risk.
Notes: The extent of the cause-and-effect relationship is demonstrated by the incline of the linear graph.COPD (**A**), lung cancer(**B**), pulmonary embolism (**C**), pulmonary fibrosis (**D**), pneumonia (**E**), chronic cough (**F**), asthma(**G**), bronchiectasis (**H**).

emotional stability could potentially elevate the likelihood of developing respiratory illnesses. However, observational studies cannot completely rule out the effects of residual confounders and potential reverse causation. Like retrospective case-control studies, recall bias is a significant concern that impacts the precision of findings.[30]

This study has several significant strengths. Initially, we employed a Mendelian randomization strategy to investigate the causal link between emotional volatility and eight respiratory conditions, successfully avoiding the constraints of conventional observational research, including the risk of reverse causation and inadequate sample size. Second, with the help of a large number of sample case data, we substantially increased the credibility of our findings. Furthermore, we performed various sensitivity analyses to verify the absence of horizontal pleiotropy and heterogeneity, validated the lack of violation of the assumption of independence of instrumental variables in the analysis, and identified and removed potential outliers using the MR-PRESSO method, enhancing the strength and reliability of our results.

Although this study has many strengths, it is crucial to acknowledge the presence of certain limitations. The results primarily focus on individuals of European descent, potentially restricting their applicability to other ethnicities. Moreover, Mendelian randomization analysis was unable to ascertain the effects of clinical interventions. Hence, additional investigation is required to delve into the possible connections between emotionally volatile composition and respiratory ailments in order to enhance comprehension and treatment of these conditions in medical settings.

Conclusion

The research indicates that individuals with emotional volatility are more likely to develop COPD, pneumonia, chronic cough, and asthma. Furthermore, the results indicated that there was no causal connection between emotional instability and lung cancer, pulmonary embolism, pulmonary fibrosis, or bronchiectasis.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its Additional files.

Ethical Approval

The summary statistics for the MR study were acquired from GWAS https://www.ebi.ac.uk.All of this data is ethically approved and freely accessible.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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