

Article

The relationship between pulmonary ventilation function and bone marrow hematopoietic function: A mendelian randomization analysis

Shupeng Chen¹, Nana Tang², Yingjian Zeng^{2,*}¹ Clinical Medical School, Jiangxi University of Traditional Chinese Medicine, Nanchang 330004, China² Department of Hematology, Affiliated Hospital, Jiangxi University of Traditional Chinese Medicine, Nanchang 330006, China* **Corresponding author:** Yingjian Zeng, 13431762390@163.com

CITATION

Chen S, Tang N, Zeng Y. The relationship between pulmonary ventilation function and bone marrow hematopoietic function: A mendelian randomization analysis. *Molecular & Cellular Biomechanics*. 2024; 21(2): 274.
<https://doi.org/10.62617/mcb.v21i2.274>

ARTICLE INFO

Received: 1 August 2024
Accepted: 3 September 2024
Available online: 5 November 2024

COPYRIGHT



Copyright © 2024 by author(s).
Molecular & Cellular Biomechanics is published by Sin-Chn Scientific Press Pte. Ltd. This work is licensed under the Creative Commons Attribution (CC BY) license.
<https://creativecommons.org/licenses/by/4.0/>

Abstract: Background: In recent years, the comorbidity between respiratory and hematopoietic system diseases has emerged as a new challenge. However, the potential genetic link between the ventilatory function of the respiratory system and the hematopoietic function of the bone marrow remains unclear. In this study, we conducted a comprehensive investigation into the possible genetic connection between lung ventilatory function and bone marrow hematopoietic function. **Methods:** We selected two exposure factors, Forced Expiratory Volume in 1 second (FEV1) and Forced Vital Capacity (FVC), which represent pulmonary ventilation function, and two outcome indicators, Immature Fraction of Reticulocytes (IFR) and Reticulocyte Count (RC), which represent bone marrow hematopoiesis function, from published genome-wide association studies. Based on the three core assumptions of Mendelian randomization analysis, we extracted Single Nucleotide Polymorphism (SNPs) associated with FEV1 and FVC as instrumental variables for the exposure factors. We then conducted two-sample Mendelian randomization analyses using inverse variance weighted (IVW), weighted median, and MR-Egger regression methods. Lastly, we assessed the reliability of the testing results through MR-Egger, Cochran's Q test, and the leave-one-out test. Through these steps, we aimed to explore the causal relationship between pulmonary ventilation function and the outcome of bone marrow hematopoiesis function and evaluated the reliability of the testing results using methods such as MR-Egger, Cochran's Q test, and the leave-one-out test. **Results:** The IVW method revealed that a decrease in FEV1 is associated with an increase in IFR ($\beta = -0.072$, 95% CI: -0.131 to -0.014 , $p = 0.01$), and the results from MR-Egger regression showed a similar association ($\beta = -0.169$, 95% CI: -0.342 to -0.004 , $p = 0.05$). Furthermore, a decrease in FEV1 is associated with an increase in RC ($\beta = -0.143$, 95% CI: -0.198 to -0.087 , $p = 4.00 \times 10^{-7}$), and MR-Egger regression yielded consistent results ($\beta = -0.216$, 95% CI: -0.381 to -0.541 , $p = 1.07 \times 10^{-2}$). Similarly, a decrease in FVC is associated with an increase in IFR ($\beta = -0.073$, 95% CI: -0.116 to -0.031 , $p = 6.17 \times 10^{-4}$), and MR-Egger regression showed a similar trend ($\beta = -0.046$, 95% CI: -0.160 to -0.067 , $p = 0.42$). Additionally, a decrease in FVC is associated with an increase in RC ($\beta = -0.173$, 95% CI: -0.221 to -0.125 , $p = 2.33 \times 10^{-12}$), and MR-Egger regression yielded consistent results ($\beta = -0.142$, 95% CI: -0.272 to -0.012 , $p = 3.32 \times 10^{-2}$). The reliability tests indicated heterogeneity in the above MR analyses but no evidence of horizontal pleiotropy. Therefore, a fixed-effect model IVW was used to explore the causal relationships, which were found to be robust and reliable with no outliers or significant bias in this study. **Conclusion:** This study indicates that there is a negative causal relationship between pulmonary ventilation function and bone marrow hematopoietic function. A decrease in pulmonary ventilation function stimulates bone marrow hematopoiesis. However, further research is needed to elucidate this mechanism.

Keywords: hematopoietic cells; reticulocyte; FEV1; FVC; GWAS; mendelian randomization study

1. Introduction

In recent years, multi-system comorbidity has become a new challenge, with respiratory and hematopoietic system problems often co-occurring in clinical settings [1,2]. Increasing evidence suggests a mysterious relationship between pulmonary ventilation function and bone marrow hematopoiesis. Observational studies have shown that on the one hand, patients with myelodysplastic syndrome (MDS) have significantly impaired pulmonary ventilation function, while on the other hand, abnormal pulmonary ventilation function is also an important factor leading to increased incidence and mortality of anemia[3–5].Chronic obstructive pulmonary disease (COPD) patients are prone to anemia, and anemia is also an independent predictor of COPD mortality[6,7].In 2013, relevant basic experiments found that bone marrow-derived hematopoietic stem cells are closely related to pulmonary fibrosis[8], In 2017, Lefrançois's et al. [9] team found through basic experiments that megakaryocytes in bone marrow travel long distances to produce platelets in pulmonary tissues, suggesting a collaborative hematopoietic relationship between the lungs and bone marrow. Based on the bidirectional dialogue between the lungs and bone marrow, we raise the question: is there a causal effect between pulmonary ventilation function and bone marrow hematopoiesis function? This is an exciting study that could bring more possibilities to comorbidity research in the respiratory and hematopoietic systems.

With the rapid development in the field of genetic epidemiology, especially the increasing prevalence of Genome-Wide Association Study (GWAS) methods, opportunities have been provided for the rapid development of Mendelian randomization (MR) methods in medical research [10], MR utilizes genetic variations as instrumental variables and uses single nucleotide polymorphisms (SNPs) strongly associated with the exposure factor as instrumental variables to infer causal relationships between exposure and study outcomes through statistical models [11]. MR is also referred to as a natural randomized controlled trial (RCT), where genetic variations are applied as instrumental variables for specific risk factors to establish statistical models that explore causal associations between exposure factors and outcomes [12]. For example, genetic variations in pulmonary ventilation function that increase or decrease during gamete formation are randomly assigned to study subjects. In this regard, we designed an experiment to analyze the causal effects between SNP representing pulmonary ventilation function as an instrumental variable and the outcome indicator of bone marrow hematopoiesis function, thereby exploring the mysterious relationship between pulmonary ventilation function and bone marrow hematopoiesis function.

2. Materials and methods

2.1. MR study design

We will combine these genetic variants into a genetic tool that has stable and reliable associations with pulmonary ventilation function. Then, we will perform a regression analysis of each genetic variant in the genetic tool, including variants associated with pulmonary ventilation function and variants associated with bone

marrow hematopoiesis, to determine the overall causal effect of the exposure on the outcome.

As shown in **Figure 1**, this MR study design is similar to that of a natural experiment, and the instrumental variables must satisfy three core assumptions [13].

1) The association assumption: There must be a significant association between the single nucleotide polymorphisms and instrumental variables.

2) The independence assumption: The single nucleotide polymorphisms must be independent of potential confounding factors between the exposure and outcome.

3) The exclusion restriction assumption: The single nucleotide polymorphisms must not have any direct effect on the outcome, and can only influence causality through the exposure.

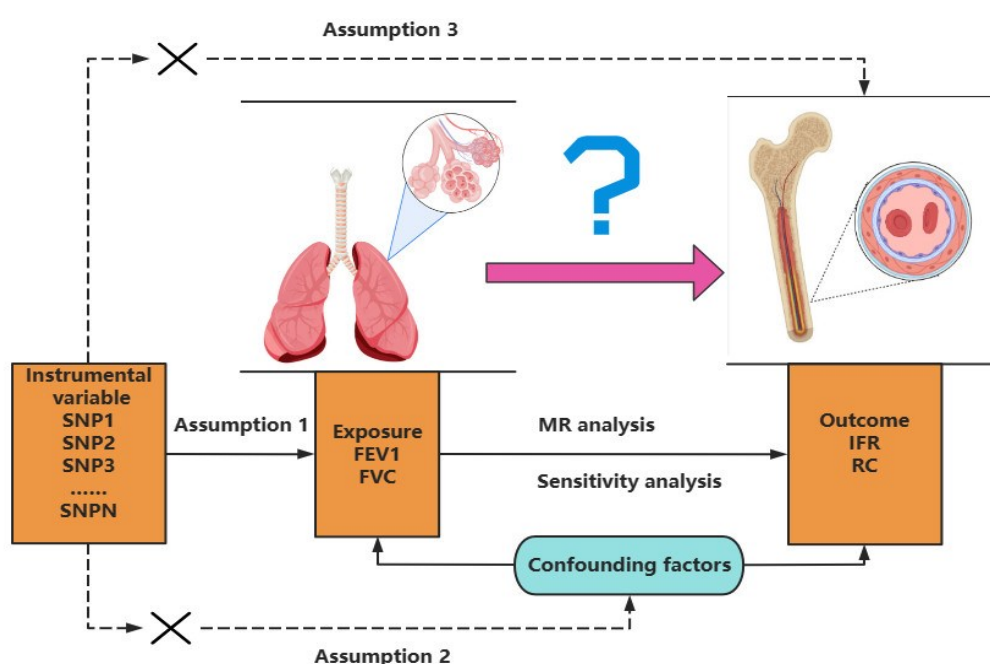


Figure 1. Conceptual framework of the causal relationship between pulmonary ventilation function and bone marrow hematopoiesis.

2.2. Data sources for MR analyses

Exposure factors include Forced Vital Capacity (FVC) and Forced Expiratory Volume in 1-second (FEV1), measured to assess their magnitude. The outcome indicators are Immature Fraction of Reticulocytes (IFR) and Reticulocyte Count (RC), reflecting bone marrow hematopoiesis. The summary information is presented in **Table 1**.

Table 1. Information on GWAS data for pulmonary ventilation function and bone marrow hematopoiesis.

Research object	GWAS ID	Sample size	Number of SNPs	Population	Sex	Year
pulmonary ventilation function	ukb-b-19657	421,986	9,851,867	European	Males and Females	2018
	ebi-a-GCST90029027	422,876	11,971,389	European	Males and Females	2018
Bone marrow hematopoietic function	ebi-a-GCST90002387	408,112	40,296,189	European	Males and Females	2020
	ebi-a-GCST90028993	520,010	11,972,425	European	Males and Females	2018

2.3. Selection of instrumental variables

Step 1: Using the whole-genome information from the European Thousand Genomes Project as a reference, we collected SNP loci that were genome-wide significant ($P < 5 \times 10^{-8}$) for FEV1 and FEVC. We set a linkage disequilibrium (LD) parameter of the r^2 threshold at 0.001 and a genetic distance of 10 MB. We selected the SNP with the minimum P -value to ensure the independence of instrumental variables and exclude the impact of LD on the results. Step 2: Data extraction and integration were performed from two databases to ensure that the exposure and outcome were associated with the same effect allele. Step 3: Potential confounding factors affecting the outcome were excluded through the use of the PhenoScanner database (<http://www.phenoscaner.medschl.cam.ac.uk>).

According to the assumptions of Mendelian randomization analysis, the instrumental variable, single nucleotide polymorphism (SNP), should be closely associated with the exposure. To assess the strength of the instrumental variable, the F -statistic for each SNP is calculated. If $F > 10$, it indicates a low likelihood of weak instrumental variable bias. F is calculated as $[(N - K - 1)/k \times [r^2/(1 - r^2)]]$, where N represents the sample size of the exposure GWAS, K is the number of SNPs, r^2 is the proportion of variance explained by the SNPs in the exposure database, and $r^2 = 2 \times (1 - \text{MAF}) \times \text{MAF} \times \beta/\text{SD}$. MAF refers to the minor allele frequency, which is equivalent to the effect allele frequency (EAF). β represents the effect size of the allele, and $\text{SD} = \text{SE} \times \sqrt{N}$, where SE (Standard error) is the standard error of β . Lastly, Mendelian randomization pleiotropy residual sum and outlier (MR-PRESSO) is used to test and calibrate the level of pleiotropy outliers.

2.4. Statistic analysis

2.4.1. Two-sample mendelian randomization analysis was conducted in this study using the TwoSampleMR package in R software (version 4.3.0)

Three commonly used MR analysis methods were employed, including the inverse-variance weighted method (IVW), MR-Egger regression, and weighted median estimator (WME). The IVW method was utilized as the primary analysis method, while the other methods served as supplementary analyses [14].

2.4.2. To further explore potential pleiotropy, a series of sensitivity analyses were conducted to assess the reliability

The Cochran Q test quantified the heterogeneity of instrumental variables, with a p -value < 0.05 indicating the presence of heterogeneity [15]. MR-Egger regression, as a weighted linear regression, assessed whether there was horizontal pleiotropy among instrumental variables by examining the intercept [16]. Additionally, a leave-one-out sensitivity test was performed to evaluate whether the causal effect was significantly influenced by individual SNPs [17]. All results are presented as β values with 95% confidence intervals (CI), and p -values < 0.05 were considered statistically significant.

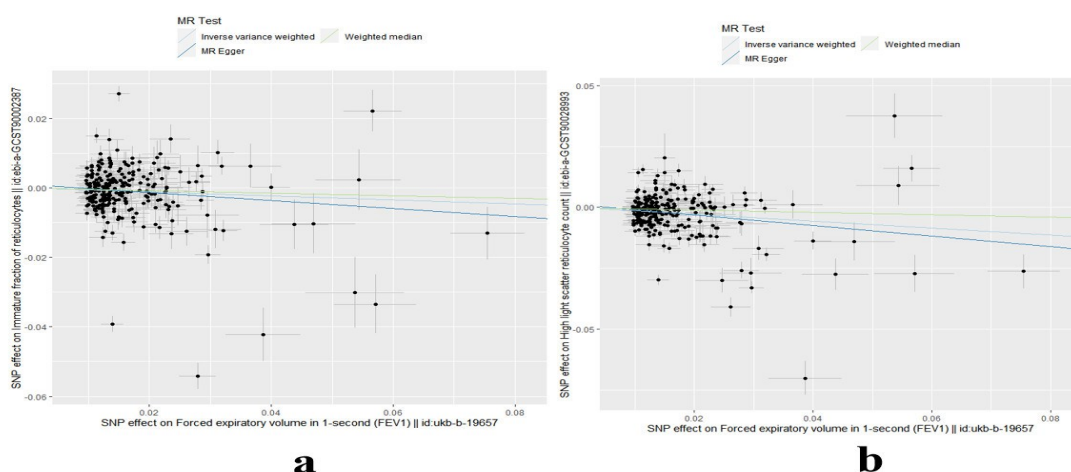
3. Results

3.1. Instrumental variable

To satisfy the three core assumptions of Mendelian randomization analysis, which include addressing linkage disequilibrium, conducting F-statistic filtering, and adjusting for heterogeneity and allele orientation, we identified 255 SNPs as instrumental variables for the analysis of FEV1 with IFR and RC, 312 SNPs for the analysis of FVC with IFR, and 301 SNPs for the analysis of FVC with RC. Detailed information on these instrumental variables can be found in the supplementary materials.

3.2. Mendelian randomization analysis

Figure 2 presents scatterplots using three MR analysis methods to depict the relationship between lung ventilation function and bone marrow hematopoietic function. **Figure 2a** suggests a negative causal relationship between FEV1 and IFR, **Figure 2b** suggests a negative causal relationship between FEV1 and RC, **Figure 2c** suggests a negative causal relationship between FVC and IFR, and **Figure 2d** suggests a negative causal relationship between FVC and RC. These findings are consistent across the three MR analysis methods. In **Table 2**, the results from the IVW method indicate that a decrease in FEV1 leads to an increase in IFR ($\beta = -0.072$, 95% CI: -0.131 to -0.014 , $p = 0.01$). The results from MR-Egger regression show a similar trend ($\beta = -0.169$, 95% CI: -0.342 to -0.004 , $p = 0.05$). It is also found that a decrease in FEV1 leads to an increase in RC ($\beta = -0.143$, 95% CI: -0.198 to -0.087 , $p = 4.00 \times 10^{-7}$), with consistent findings observed in MR-Egger regression ($\beta = -0.216$, 95% CI: -0.381 to -0.541 , $p = 1.07 \times 10^{-2}$). Moreover, a decrease in FVC leads to an increase in IFR ($\beta = -0.08$, 95% CI: -0.016 to -0.006 , $p = 0.007$), and MR-Egger regression also supports this result ($\beta = -0.046$, 95% CI: -0.160 to -0.067 , $p = 0.42$). Additionally, it is observed that a decrease in FVC leads to an increase in RC ($\beta = -0.03$, 95% CI: -0.05 to -0.01 , $p = 0.006$), with similar findings in MR-Egger regression ($\beta = -0.13$, 95% CI: -0.272 to -0.012 , $p = 0.0008$).



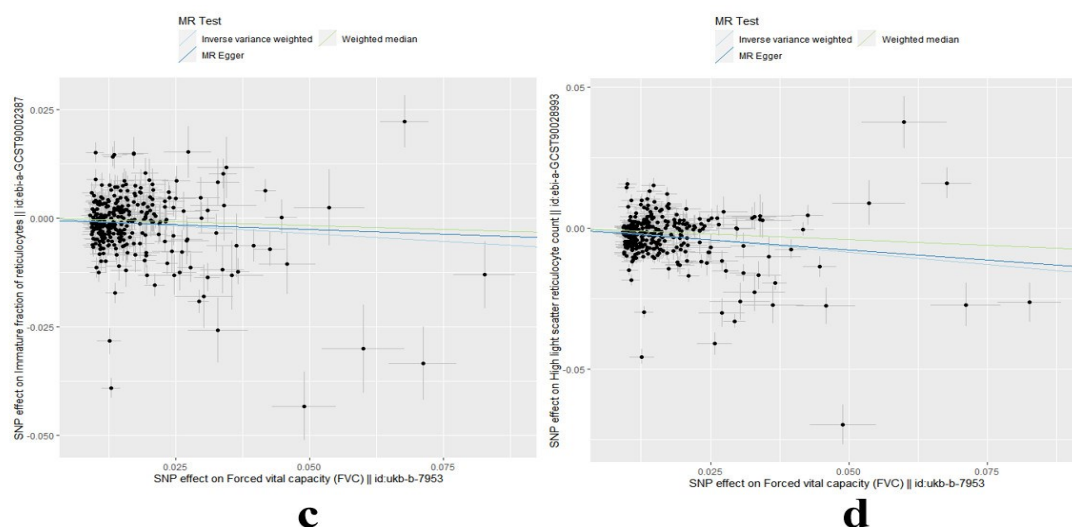


Figure 2. Scatter plots for two-sample MR analysis of lung ventilation function and bone marrow hematopoietic function.

Table 2. Two-sample MR analysis of lung ventilation function and bone marrow hematopoietic function.

Exposure	Outcome	No. of SNPs	Test used	Effect estimate (β , 95% CIs)	P-value
FEV1	IFR	255	Inverse variance weighted	-0.072(-0.131, -0.014)	0.01
			MR Egger	-0.169(-0.342,0.004)	0.05
			Weighted median	-0.043(-0.089,0.002)	0.06
FEV1	RC	255	Inverse variance weighted	-0.143(-0.198, -0.087)	4.00E-07
			MR Egger	-0.216(-0.381, -0.514)	1.07E-02
			Weighted median	-0.049(-0.087, -0.011)	1.25E-02
FVC	IFR	312	Inverse variance weighted	-0.031(-0.116, -0.031)	0.007
			MR Egger	-0.08(-0.0165, -0.006)	0.04
			Weighted median	-0.03(-0.07, -0.03)	0.004
FVC	RC	301	Inverse variance weighted	-0.03(-0.05, -0.01)	0.006
			MR Egger	-0.13(-0.272, -0.012)	0.0008
			Weighted median	-0.001(-0.02,0.012)	0.65

Note: β represents the effect value of the allele, and 95% CI represents the 95% confidence interval.

3.3. Reliability evaluation

Multiple testing: In the MR analysis of FEV1 and IFR shown in **Table 3**, the `egger_intercept` result of MR-Egger is ($P > 0.05$), and the difference between intercept and 0 is not statistically significant. In the MR analysis of FEV1 and RC, the `egger_intercept` result of MR-Egger is ($P > 0.05$), and the difference between intercept and 0 is not statistically significant. In the MR analysis of FVC and IFR, the `egger_intercept` result of MR-Egger is ($P > 0.05$), and the difference between intercept and 0 is not statistically significant. In the MR analysis of FVC and RC, the `egger_intercept` result of MR-Egger is ($P > 0.05$), and the difference between intercept and 0 is not statistically significant, indicating that there is no horizontal pleiotropy in the MR analysis of this study. At the same time, the outlier test of the SNP of the instrumental variable shows that there are no outlier values in groups a, b, c, and d, with $p > 0.05$.

Heterogeneity analysis: As shown in **Table 3**, Cochran's Q test indicated that in the analyses of FEV1 and IFR, RC, as well as FVC and IFR, RC, $p < 0.05$, indicating the presence of heterogeneity in the above MR analyses. The MR funnel plots in each group displayed a symmetrical distribution of scatter points for causal association effects, suggesting no potential bias, as shown in **Figure 3**.

Sensitivity analysis: The leave-one-out test results showed that after sequentially removing individual SNPs, the remaining SNPs' IVW analysis results were similar to the analysis results including all SNPs. No SNPs were found in the above 4 groups (a, b, c, d) that had a significant influence on the estimation of causal associations, further confirming the stability of the results (shown in supplementary materials). Therefore, the MR results of this study are reliable.

Table 3. Reliability tests of MR analysis for pulmonary ventilation function and bone marrow hematopoietic function.

NO.	Expose	Outcome	Cochran Q		MR Egger		MR-PRESSO	
			MR Egger	IVW	Q	P	Outlier	P
a	FEV1	IFR	P = 1.72E-169	P = 1.1.E-170	1.56E-03	0.25	NO	0.10
b	FEV1	RC	P = 3.12E-206	P = 3.43E-306	1.20E-03	0.36	NO	0.73
c	FVC	IFR	P = 3.49E-42	P = 9.78E-49	-0.65E-04	0.53	NO	0.37
d	FVC	RC	P = 4.91E-31	P = 2.75E-33	-0.40E-04	0.43	NO	0.42

Note: a, MR analysis of FEV1 and IFR; b, MR analysis of FEV1 and RC; c, MR analysis of FVC and IFR; d, MR analysis of FVC and RC.

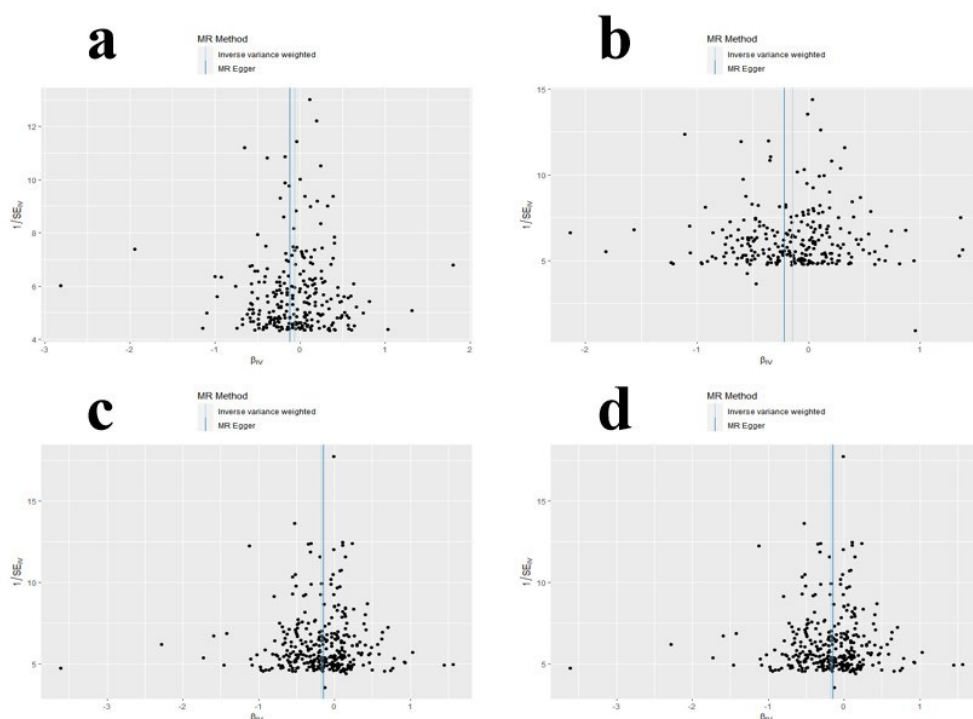


Figure 3. The funnel plot of MR analysis for pulmonary ventilation and bone marrow hematopoietic function.

Note: a, MR analysis of FEV1 and IFR; b, MR analysis of FEV1 and RC; c, MR analysis of FVC and IFR; d, MR analysis of FVC and RC.

4. Discussion

The pulmonary ventilation function represents the body's ability to exchange

gases, including the indicators of CO₂ expiration and O₂ inhalation. In cases where pulmonary ventilation function is limited, compensatory hematopoiesis increases [18]. This study utilized large-scale GWAS meta-analysis data to investigate the causal relationship between pulmonary ventilation function and bone marrow hematopoietic function using a two-sample Mendelian randomization approach. Pulmonary ventilation function was assessed using key indicators from lung function tests, with FEV1 representing the volume of forced expiratory volume in the first second, which can reflect the degree of impairment in pulmonary ventilation function. FVC, on the other hand, represents the volume of forced expiratory capacity and serves as an important indicator of lung capacity. To ensure the accuracy of the conclusions, two different stages of indicators for bone marrow hematopoietic function were selected, including immature reticulocyte count (IFR) and reticulocyte count (RC), both of which were obtained through peripheral blood testing using a hematocytometer.

The study results revealed a negative causal relationship between respiratory function and hematopoietic function. IVW method results showed that a decrease in FEV1 leads to an increase in IFR ($\beta = -0.072$, 95% CI: -0.131 to -0.014 , $p = 0.01$), and a decrease in FEV1 leads to an increase in RC ($\beta = -0.143$, 95% CI: -0.198 to -0.087 , $p = 4.00 \times 10^{-7}$). Similarly, a decrease in FVC leads to an increase in IFR ($\beta = -0.08$, 95% CI: -0.016 to -0.006 , $p = 0.007$), and a decrease in FVC leads to an increase in RC ($\beta = -0.03$, 95% CI: -0.05 to -0.01 , $p = 0.006$). The reliability tests demonstrated heterogeneity in the MR analysis, but no horizontal pleiotropy was identified. Therefore, a fixed-effect IVW model was used to explore the causal relationship, which showed no outliers and significant bias, indicating the reliability of the MR analysis in this study. It can be concluded that a decrease in pulmonary ventilation function leads to an increase in bone marrow hematopoietic function. For instance, individuals living in high-altitude areas compensate by increasing the solubility of red blood cells to obtain sufficient oxygen. Our study findings also suggest that under conditions of decreased pulmonary ventilation function, the body increases hematopoietic capacity. Through Two-sample MR analysis, this study confirms this fact by ruling out confounding factors and reverse causality.

Despite increasing attention to the dialogue between the lungs and bone marrow, the substances and pathways that connect them are still under investigation. In 2017, Lefrançois et al. [9] reported the collaboration between the lungs and bone marrow in platelet production, indicating that megakaryocytes in the bone marrow reach lung tissues through systemic circulation. Engblom et al. [19] found that in lung tumor patients without metastasis, neutrophils expressing Siglec-F in the bone marrow could be remotely activated. In 2022, Liu [20] further investigated that extracellular vesicles (EVs) from lung tissues could accumulate in the bone marrow, recruiting neutrophils from the bone marrow. Interestingly, it has been discovered that neutrophils do not die at the site of injury and require activation or editing by the lungs to selectively migrate to the bone marrow via CXCR4 [21]. Therefore, the generation and death of blood cells are closely related to the dialogue between the lungs and the bone marrow. On the one hand, some researchers propose that the connection between the lungs and bone marrow is achieved through systemic circulation. Alvar Agustí et al. hypothesize that the lungs are crucial external sensors that perceive “danger signals” from the external environment, and the bone marrow and adipose tissue are important internal

components that respond to these signals under genetic regulation. The connection between them is achieved through systemic circulation [22]. On the other hand, some researchers suggest that their connection is mediated through intestinal microbial metabolism. For example, Dang et al. [23] propose that changes in diet and the external environment can lead to alterations in the intestinal microbial structure, subsequently affecting the immune response and airway homeostasis. Additionally, microbial-derived metabolites such as short-chain fatty acids (SCFAs) further influence bone marrow hematopoietic function. It is worth noting that the dialogue between the lungs and bone marrow may also involve neural transmission pathways. For instance, bone marrow neuron damage is identified as an important factor in chemotherapy-induced bone marrow suppression [24]. Furthermore, research has shown that the activation of 5-HT (2B) receptors on bone marrow progenitor cells plays a critical role in impairing pulmonary endothelial cell function and vascular remodeling [18]. Thus, the dialogue between the lungs and bone marrow is achieved through multiple pathways.

Exploring the causal relationship between the lungs and bone marrow will better prepare us for the challenges posed by comorbidities in the respiratory and hematopoietic systems. For example, lung infections are common complications in leukemia patients. In clinical practice, when treating leukemia with concurrent infection, it is important to consider controlling the infection while also focusing on improving ventilation. Cohort studies have shown a significantly higher prevalence of iron deficiency and anemia in patients with chronic obstructive pulmonary disease (COPD) [25]. Our research also suggests that a decrease in FEV1 and FVC leads to an increase in reticulocyte count. Therefore, the treatment of COPD should alert to the hematopoietic function of the bone marrow, while also taking into account the impaired pulmonary ventilation function. This is especially crucial for patients undergoing chemotherapy. Studies have reported that patients with multiple myeloma receiving treatment with bortezomib and thalidomide have an increased risk of developing pulmonary function abnormalities [26]. Furthermore, a meta-analysis has found a negative correlation trend between asthma and non-Hodgkin lymphoma, acute lymphocytic leukemia, and acute myeloid leukemia [27,28]. Asthma attacks are closely related to immune stress in the body, and asthma exhibits a protective association with leukemia, possibly through the activation of immune surveillance against genetic mutations. However, cohort studies have also found that asthma may be a risk factor for myeloproliferative neoplasms [2]. Over the past two decades, there have been numerous controversies and challenges in the field of tumor immunology. The causal relationships between hematologic disorders and allergic diseases are subject to significant debate, as there may be confounding factors and the possibility of reverse causality [29,30].

Limitations of this study include: Although this study utilized large-scale GWAS data and strict Mendelian randomization analysis to explore the causal relationship between lung ventilation function and bone marrow hematopoietic function, caution should still be exercised in interpreting the results. This study has the following limitations: firstly, it only included individuals of European descent and may not be directly applicable to other races, countries, and regions. Therefore, further research is needed to verify whether genetic differences exist in other populations. Secondly, due to the lack of detailed clinical information, this study was unable to conduct subgroup

analysis based on age and gender, thus unable to analyze causal relationships between different subgroups. In addition, Cochran's Q-test showed heterogeneity in MR analysis, although the stability of the results was validated by leave one out analysis, this still suggests caution should be exercised when interpreting causal relationships.

5. Conclusions

In summary, there is a negative causal relationship between lung ventilation function and bone marrow hematopoietic function. It seems contradictory that patients with poor lung function in clinical practice are prone to anemia, as low oxygen conditions can stimulate bone marrow hematopoiesis, which is an objective reality. In fact, under long-term hypoxia, the body's compensatory ability will be lost. Therefore, further attention needs to be paid to the stimulating effect of lung function on bone marrow hematopoiesis in clinical practice.

The interaction between the lungs and bone marrow involves multiple mechanisms, including circulation, gut microbiota, neurotransmission, and immune pathways. These approaches deserve further research. Especially when managing comorbidities involving the respiratory and hematopoietic systems, it is crucial to adopt a holistic approach that considers these multifaceted pathways.

Supplementary materials: The supplementary materials provide detailed information on the SNPs of FEV1 and FVC instrumental variables. The results of the sensitivity analysis using the leave one method were presented, confirming the reliability of the results.

Author contributions: Conceptualization, SC and NT; methodology, SC; software, NT; validation, SC, NT and YZ; formal analysis, YZ; investigation, SC; resources, NT; data curation, SC; writing—original draft preparation, NT; writing—review and editing, SC; visualization, YZ; supervision, YZ; project administration, YZ; funding acquisition, YZ. All authors have read and agreed to the published version of the manuscript.

Acknowledgments: This work would like to thank all the authors and participants involved in the compilation and statistical analysis of the GWAS data.

Ethical approval: Not applicable.

Funding: This project was supported by the National Natural Science Foundation of China (82260914); General Project of Jiangxi Provincial Natural Science Foundation (20192BAB205100); Traditional Chinese Medicine Advantageous Disease Cultivation Project of Jiangxi Provincial Administration of Traditional Chinese Medicine (Gan Cai She Zhi [2023] No. 70); Innovation and Entrepreneurship Training Program for College Students at Jiangxi University of Traditional Chinese Medicine (202410412256).

Availability of data and materials: The data used to support the findings of this study are openly available in the UK Biobank (UKB) (<https://www.ukbiobank.ac.uk/>) and the EBI European Bioinformatics Institute <https://www.ebi.ac.uk/>).

Conflict of interest: The authors declare no conflict of interest.

References

1. Rhew K, Choi J, Kim K, et al. Increased Risk of Anemia in Patients with Asthma. *Clin Epidemiol.* 2023; 15: 31-38. doi: 10.2147/CLEP.S394717
2. Frederiksen H, Farkas DK, Horváth-Puhó E, et al. Asthma and risk of myelodysplastic syndromes: a population-based cohort study. *Br J Cancer.* 2017; 116(1): 100-102. doi: 10.1038/bjc.2016.389
3. Willen SM, Cohen R, Rodeghier M, et al. Age is a predictor of a small decrease in lungfunction in children with sickle cell anemia. *Am J Hematol.* 2018; 93(3): 408-415. doi: 10.1002/ajh.25003
4. Li XH, Luo ZQ. Research progress of endogenous bone marrow-derived mesenchymal stem cells in pulmonary fibrosis. *Sheng Li Xue Bao.* 2020; 72(5): 597-604.
5. Robalo NA, Tátá M. The impact of anaemia and iron deficiency in chronic obstructive pulmonary disease: A clinical overview. *Rev Port Pneumol (2006).* 2017;23(3):146-155. doi: 10.1016/j.rppnen.2016.12.005
6. Sangeetha T, Anand AV, Begum TN. Assessment of Inter-relationship between Anemia and COPD In Accordance with Altitude. *Open Respir Med J.* 2022; 16: e1730591170. doi: 10.2174/18743064-v16-e2206270
7. de Miguel DJM, Martín MJ, Bailón MM, et al. Impact of anemia on COPD. *Arch Bronconeumol.* 2009; 45 Suppl 4: 47-50. doi: 10.1016/S0300-2896(09)72864-9
8. Nakashima T, Liu T, Yu H, et al. Lung bone marrow-derived hematopoietic progenitor cells enhance pulmonary fibrosis. *Am J Respir Crit Care Med.* 2013; 188(8): 976-984. doi: 10.1164/rccm.201303-0479OC
9. Lefrançois E, Ortiz-Muñoz G, Caudrillier A, et al. The lung is a site of platelet biogenesis and a reservoir for haematopoietic progenitors. *Nature.* 2017; 544(7648): 105-109. doi: 10.1038/nature21706
10. Hemani G, Zheng J, Elsworth B, et al. The MR-Base platform supports systematic causal inference across the human phenome. *Elife.* 2018; 7: 1-29. doi: 10.7554/eLife.34408
11. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. *JAMA.* 2017; 318(19): 1925-1926. doi: 10.1001/jama.2017.17219
12. Sanderson E, Glymour MM, Holmes MV, et al. Mendelian randomization. *Nat Rev Methods Primers.* 2022; 2: 1-49. doi: 10.1038/s43586-021-00092-5
13. Davies NM, Holmes MV, Davey SG. Reading Mendelian randomization studies: a guide, glossary, and checklist for clinicians. *BMJ.* 2018; 362: k601. doi: 10.1136/bmj.k601
14. Cheng W, Liao Y, Mou R, et al. Inflammatory bowel disease and prostate cancer risk: a two-sample Mendelian randomization analysis. *Front Immunol.* 2023; 14: 1157313. doi: 10.3389/fimmu.2023.1157313
15. Yuan S, Kim JH, Xu P, et al. Causal association between celiac disease and inflammatory bowel disease: A two-sample bidirectional Mendelian randomization study. *Front Immunol.* 2022; 13: 1057253. doi: 10.3389/fimmu.2022.1057253
16. Mohammad NS, Nazli R, Zafar H, et al. Effects of lipid based Multiple Micronutrients Supplement on the birth outcome of underweight pre-eclamptic women: A randomized clinical trial. *Pak J Med Sci.* 2022; 38(1): 219-226. doi: 10.12669/pjms.38.1.4396
17. Verbanck M, Chen CY, Neale B, et al. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet.* 2018; 50(5): 693-698. doi: 10.1038/s41588-018-0099-7
18. Launay JM, Hervé P, Callebort J, et al. Serotonin 5-HT_{2B} receptors are required for bone marrow contribution to pulmonary arterial hypertension. *Blood.* 2012; 119(7): 1772-1780. doi: 10.1182/blood-2011-06-358374
19. Engblom C, Pflirschke C, Zilionis R, et al. Osteoblasts remotely supply lung tumors with cancer-promoting SiglecF(high) neutrophils. *Science.* 2017; 358(6367). doi: 10.1126/science.aal5081
20. Liu B, Jin Y, Yang J, et al. Extracellular vesicles from lung tissue drive bone marrow neutrophil recruitment in inflammation. *J Extracell Vesicles.* 2022; 11(5): e12223. doi: 10.1002/jev2.12223
21. Wang J, Hossain M, Thanabalasuriar A, et al. Visualizing the function and fate of neutrophils in sterile injury and repair. *Science.* 2017; 358(6359): 111-116. doi: 10.1126/science.aam9690
22. Agustí A, Barberà JA, Wouters EF, et al. Lungs, bone marrow, and adipose tissue. A network approach to the pathobiology of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2013; 188(12): 1396-1406. doi: 10.1164/rccm.201308-1404PP
23. Dang AT, Marsland BJ. Microbes, metabolites, and the gut-lung axis. *Mucosal Immunol.* 2019; 12(4): 843-850. doi:

10.1038/s41385-019-0160-6

24. Lucas D, Scheiermann C, Chow A, et al. Chemotherapy-induced bone marrow nerve injury impairs hematopoietic regeneration. *Nat Med.* 2013; 19(6): 695-703. doi: 10.1038/nm.3155
25. Pizzini A, Aichner M, Sonnweber T, et al. The Significance of iron deficiency and anemia in a real-life COPD cohort. *Int J Med Sci.* 2020; 17(14): 2232-2239. doi: 10.7150/ijms.46163
26. Bruce JT, Tran JM, Phillips G, et al. Chemotherapeutic agents increase the risk for pulmonary function test abnormalities in patients with multiple myeloma. *Clin Lymphoma Myeloma Leuk.* 2012; 12(5): 325-329. doi: 10.1016/j.clml.2012.06.002
27. Zhou MH, Yang QM. Association of asthma with the risk of acute leukemia and non-Hodgkin lymphoma. *Mol Clin Oncol.* 2015; 3(4): 859-864. doi: 10.3892/mco.2015.561
28. Sudan M, Arah OA, Olsen J, et al. Reported associations between asthma and acute lymphoblastic leukemia: insights from a hybrid simulation study. *Eur J Epidemiol.* 2016; 31(6): 593-602. doi: 10.1007/s10654-016-0126-x
29. Melbye M, Smedby KE, Lehtinen T, et al. Atopy and risk of non-Hodgkin lymphoma. *J Natl Cancer Inst.* 2007; 99(2): 158-166. doi: 10.1093/jnci/djk019
30. Turner MC, Chen Y, Krewski D, et al. An overview of the association between allergy and cancer. *Int J Cancer.* 2006; 118(12): 3124-3132. doi: 10.1002/ijc.21752