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RESEARCH ARTICLE

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No genetic causal association between iron status and pulmonary artery hypertension: Insights from a two-sample Mendelian randomization

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Abstract

To explore the genetic causal association between pulmonary artery hypertension (PAH) and iron status through Mendelian randomization (MR), we conducted MR analysis using publicly available genome-wide association study (GWAS) summary data. Five indicators related to iron status (serum iron, ferritin, total iron binding capacity (TIBC), soluble transferrin receptor (sTfR), and transferrin saturation) served as exposures, while PAH was the outcome. The genetic causal association between these iron status indicators and PAH was assessed using the inverse variance weighted (IVW) method. Cochran's Q statistic was employed to evaluate heterogeneity. We assessed pleiotropy using MR-Egger regression and MR-Presso test. Additionally, we validated our results using the Weighted median, Simple mode, and Weighted mode methods. Based on the IVW method, we found no causal association between iron status (serum iron, ferritin, TIBC, sTfR, and transferrin saturation) and PAH ($p_\beta > 0.05$). The Weighted median, Simple mode, and Weighted mode methods showed no potential genetic causal association ($p_\beta > 0.05$ in the three analyses). Additionally, no heterogeneity or horizontal pleiotropy was detected in any of the analyses. Our results show that there are no genetic causal association between iron status and PAH.

KEYWORDS
causal association, genetics, iron status, Mendelian randomization, pulmonary artery hypertension

Peng-Cheng Liu, Meng-Na Lv, and Yan-Yan Rong contributed equally to this study.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is defined by heightened pulmonary vascular resistance attributed to vasoconstriction, thrombosis, and structural alterations in pulmonary arterioles.[1] The resultant pressure overload on the right ventricle precipitates a cascade of events, including progressive hypertrophy and dilation, ultimately culminating in end-stage heart failure and mortality. Despite advancements in therapeutic interventions, the overall prognosis for PAH patients continues to be bleak.

In recent years, the role of iron status in PAH has garnered considerable attention. Iron availability influences pulmonary hemodynamics, modifying basal pulmonary artery pressure and the pulmonary vasoconstrictor response to hypoxia in humans.[2,3] Iron deficiency may affect up to 50% of patients with PAH.[4,5] Additionally, iron deficiency in PAH patients correlates with more severe disease manifestations, including reduced exercise capacity and poorer survival rates.[6] Guidelines from the European Respiratory Society and European Cardiac Society for managing PAH recommend considering iron replacement as part of the treatment strategy for these patients.[7] The importance of iron status in the development and progression of PAH has been emphasized.

However, findings from The Jackson Heart Study suggest that iron deficiency or low iron levels are not correlated with elevated pulmonary arterial pressure.[8] Additionally, iron supplementation trials conducted in PAH patients yielded inconclusive results in three smaller studies involving approximately 22 PAH patients each.[9–11] Notably, only two out of these three studies reported a significant increase in the 6-min walking distance among previously iron-deficient patients.[10,11] Moreover, there is insufficient evidence to definitively establish a direct link between iron status and PAH. Consequently, further investigations are warranted to explore the correlation between iron status and PAH at the genetic level.

Several factors, such as reverse causation and confounding bias, often plague observational studies, leading to a lack of high-quality randomized controlled trials (RCTs). Mendelian randomization (MR) studies, however, offer a solution to these issues. By leveraging the random allocation of genetic variants during meiosis, MR studies are less susceptible to biases inherent in observational studies. Consequently, MR has emerged as a widely utilized approach to discern causal relationships between exposures and outcomes.[12–15] In this study, we employed a two-sample MR analysis to investigate the genetic causal association between iron status (as the exposure) and PAH (as the outcome). Specifically, five serum biomarkers related to iron status (ferritin, serum iron, total iron binding capacity (TIBC), soluble transferrin receptor (sTfR), and transferrin saturation) were selected for analysis.

MATERIALS AND METHODS

Data sources

The summary statistics for PAH were obtained from the FinnGen database (gs://finngen-public-data-r9/summary_stats/finngen_R9_I9_HYPTENSPUL.gz). Serum iron, ferritin, and transferrin saturation were obtained from the NHGRI-EBI GWAS Catalog on 2/3/2024 for study GCST90012683, GCST90012653, and GCST90012756 respectively.[16] sTfR and TIBC summary statistics were downloaded from the NHGRI-EBI GWAS Catalog on 2/3/2024 for study GCST90085780 and GCST000568 respectively.[17,18] The detailed information of data sources were provided in Table 1.

Instrument selection

MR analysis is based on three critical fundamental hypotheses: (a) relevance assumption: instrumental variables robustly correlated with exposure; (b) independence assumption: instrumental variables not associated with other potential confounders; and (c) restriction assumption: instrumental variables affected outcome only through the risk factor, not directly associated with the outcome. The selection of instrumental variables SNPs followed three assumptions above. First, the statistic of SNPs at a genome-wide significance threshold of $p < 5 \times 10 - 6$. Second, the linkage disequilibrium (LD) genomes are disobeying the principles of Mendel's Second Law of heredity, not independent heredity would lead to potential bias. A 10,000 kb clumping window was used to pure the LD between SNPs, and an LD $0.001 < r2 < 0.01$ threshold was set when extracting. Furthermore, to ensure the strong effectiveness of instrumental variables, we calculated the *F*-statistic by using the following formula: $F\text{-statistic} = R2 \times (N - 2)/(1 - R2)$; $R2 = 2 \times \text{EAF} \times (1\text{-EAF}) \times \text{Beta}^2$.[19] Second, considering the difference between proxy SNPs and the original SNPs, we did not include proxy SNPs.[20,21] Finally, In the harmonization step, SNPs with a minor allele frequency (MAF) greater than 0.42 were excluded, for excluding the ambiguity of larger MAF values may confuse which allele is minor or major.[22,23] For each two-sample MR instrument selection was the same as above.

MR analysis

We conducted a two-sample MR to investigate the causal association between PAH and five molecules involved in iron status-related indicators: serum iron, ferritin, transferrin saturation, sTfR, and TIBC. The MR analysis was performed

TABLE 1 Data sources information.

Phenotypes	Consortium	Ancestry	Sample size	Website
PAH	FinnGen database	European	265,860	https://risteys.finregistry.fi/endpoints/I9_HYPTENSPUL
Serum iron	GWAS Catalog: GCST90012683	European	15,335	https://www.ebi.ac.uk/gwas/studies/GCST90012683
Ferritin	GWAS Catalog: GCST90012653	European	16,215	https://www.ebi.ac.uk/gwas/studies/GCST90012653
TAST	GWAS Catalog: GCST90012756	European	1781	https://www.ebi.ac.uk/gwas/studies/GCST90012756
sTfR	GWAS Catalog: GCST90085780	European	400	https://www.ebi.ac.uk/gwas/studies/GCST90085780
TIBC	GWAS Catalog: GCST000568	Greater Middle Eastern (Middle Eastern, North African, or Persian) individuals	6010	https://www.ebi.ac.uk/gwas/studies/GCST90013340

Abbreviation: PAH, pulmonary arterial hypertension; TSAT, transferrin saturation; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity.

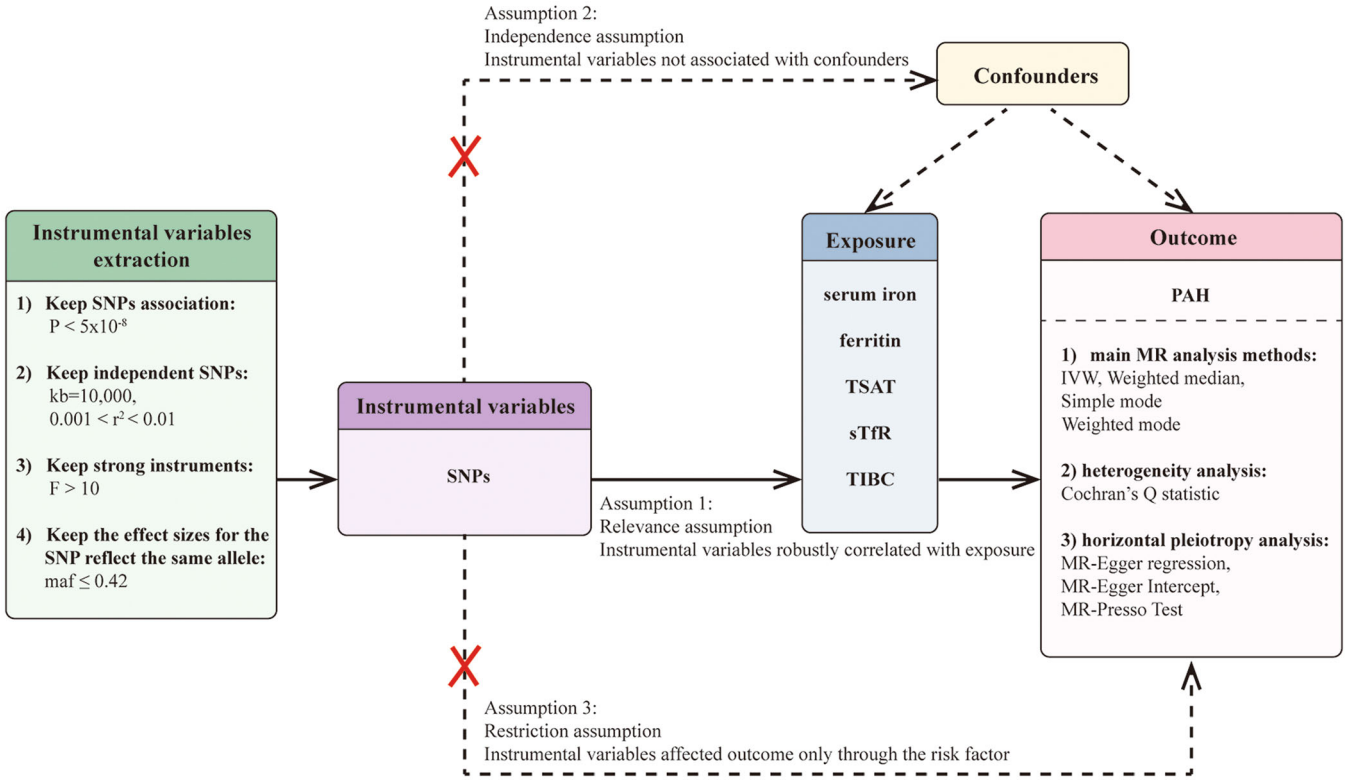

FIGURE 1 The principles and steps of MR analysis. PAH, pulmonary arterial hypertension; sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TSAT, transferrin saturation.

by the packages TwoSampleMR (version 0.5.7) and MRPRESSO (version 1.0) in R (version 4.3.1), and the analysis process was created by Adobe Illustrator (2023). To apply the sensitivity analysis to the MR analysis, we used Inverse-variance weighted (IVW), Weighted median, Simple mode, and MR Egger.[24–26] The random-effect IVW method, used as the primary analysis in two-sample MR, is a powerful method that the reciprocal of the outcome variance (the quadratic of SE) was used as a weight for fitting.

In addition, we considered the potential bias. The MR-Egger regression method was applied to evaluate the horizontal pleiotropy by the statistics of MR-Egger regression p value and MR-Egger regression intercept p value. If the MR-Egger intercept's p value surpasses 0.05, it indicates

TABLE 2 The *F*-statistic and characteristics of SNPs.

Exposure	*N*	SNP	Chromosome	effect_allele	other_allele	pval.exposure	pval.outcome	eaf.exposure	*F*_statistic
Serum iron	15,335	rs11152176	18	T	C	4.89E−06	0.664043	0.40038	19.89051841
		rs114719295	5	A	C	2.53E−07	0.228723	0.00764272	25.46610938
		rs12605411	18	C	A	1.84E−06	0.926436	0.123522	21.61166545
		rs1800562	6	A	G	1.51E−19	0.906182	0.0691881	75.31062593
		rs1852306	2	C	T	2.37E−07	0.598849	0.133486	25.39339804
		rs7843737	8	A	G	1.77E−06	0.6466	0.328674	21.68367214
		rs79195962	12	T	C	1.41E−06	0.213597	0.0253031	22.10730477
Ferritin	16,215	rs117055613	15	A	G	1.74E−07	0.79287	0.0380908	20.91107998
		rs11851875	14	C	T	3.20E−06	0.255786	0.0787005	16.60170651
		rs13094666	3	C	A	3.00E−06	0.151317	0.300794	16.721012
		rs170775	17	A	G	1.61E−06	0.525442	0.13518	17.42846024
		rs17690703	17	T	C	3.78E−08	0.940021	0.261736	22.75051468
		rs2128202	8	T	A	2.82E−06	0.143877	0.194577	16.83572372
		rs62307994	4	C	G	4.66E−06	0.377078	0.0409492	16.18480277
		rs6601515	8	C	T	2.04E−07	0.673758	0.171066	20.89605717
		rs72803737	5	G	T	3.83E−06	0.753307	0.212887	16.13517675
TSAT	1781	rs12649363	4	T	G	4.59E−06	0.610312	0.0506757	20.10910637
		rs145340711	5	G	A	4.53E−06	0.091698	0.0194695	21.18711638
		rs17412023	2	G	C	2.54E−06	0.419701	0.0263456	21.10867458
		rs61568876	18	A	G	3.35E−07	0.792563	0.222694	25.92278557
		rs662227	13	A	G	4.88E−06	0.102815	0.0691011	20.61498719
		rs76642148	1	A	G	1.42E−06	0.763656	0.0455056	22.46188649
		rs7696374	4	C	T	3.90E−06	0.211979	0.260551	21.5338065
		rs78577847	11	A	G	4.98E−06	0.534489	0.0384615	21.00141768
sTfR	400	rs294977	5	G	A	1.34E−06	0.180916	0.6531	1.335739657
		rs4814427	20	T	C	1.26E−06	0.757324	0.9414	1.475839082
		rs60642321	1	A	G	2.45E−28	0.921583	0.8082	3.398138978

TABLE 2 (Continued)

Exposure	N	SNP	Chromosome	effect_allele	other_allele	pval.exposure	pval.outcome	eaf.exposure	F_statistic
		rs639218	17	G	A	1.52E−06	0.967201	0.7187	1.168551579
		rs72741497	9	A	G	3.38E−06	0.960803	0.8757	0.654556349
TIBC	6010	rs10758126	9	G	C	4.55E−06	0.834466	0.3025	18.80427573
		rs11487175	7	G	A	4.96E−06	0.806023	0.0583	18.33855419
		rs313178	6	C	T	1.89E−06	0.0243237	0.07739	20.95355196
		rs78817088	11	T	C	3.67E−09	0.338773	0.01207	29.50941037

Abbreviations: sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TSAT, transferrin saturation.

no evidence of horizontal pleiotropy under the MR-Egger model, in accordance with the second critical fundamental hypothesis.[27] Besides, we calculated the MR-Presso Test to further identify the potential horizontal pleiotropy. Moreover, Cochran's Q statistic was conducted to investigate the heterogeneity statistics, p value > 0.05 was no presence of heterogeneity.[28] Thus, we considered the IVW analysis results were reliable. The analysis process is presented in Figure 1.

RESULTS

The selection of instrumental variables SNPs

Through rigorous instrument selection, 7 SNPs associated with serum iron, 9 SNPs associated with ferritin, 9 SNPs associated with transferrin, 5 SNPs associated with sTfR, and 4 SNPs associated with TIBC were used for forward MR analysis. The F-statistic and characteristics of SNPs are shown in Table 2.

The causal association between iron status and PAH

The summary statistics for PAH were obtained from the FinnGen database, which comprises 125 PAH cases from European ancestry. Based on IVW method, we found no causal association between iron status (serum iron, ferritin, TIBC, sTfR, and transferrin saturation) and PAH ($p_\beta > 0.05$). The Weighted median, Simple mode, and Weighted mode methods showed no potential genetic causal association ($p_\beta > 0.05$ in the three analyses) (Figure 2). Notably, considering the wide error bars in the forest plot, the study cannot rule out potential impacts within those ranges.

Heterogeneity analysis and horizontal pleiotropy analysis

The heterogeneity analysis and horizontal pleiotropy analysis of two-sample MR are shown in Figure 3. It is shown that there are potential outliers in the instrumental variables, however further MR-Presso Test showed that there were no significant outliers. In addition, the results of MR-Egger regression showed no significant horizontal pleiotropic effects for the included variant. The result of Cochran's Q statistic showed the heterogeneity was nonexistent as well.

exposure	nsnp	method	OR(95% CI)	p_value	MR_Egger_regression_p	MR_Presso_p	Intercept_p	Q_p
serum iron	7	Inverse variance weighted	0.64(0.18 to 2.29)	0.492	0.209	0.812	0.260	0.900
		Weighted median	0.85(0.16 to 4.59)	0.851				
		Simple mode	1.26(0.11 to 14.23)	0.855				
		Weighted mode	1.04(0.12 to 8.99)	0.970				
ferritin	9	Inverse variance weighted	0.75(0.21 to 2.73)	0.663	0.173	0.530	0.133	0.786
		Weighted median	0.57(0.09 to 3.60)	0.552				
		Simple mode	0.91(0.05 to 16.99)	0.951				
		Weighted mode	0.80(0.05 to 13.70)	0.879				
TSAT	9	Inverse variance weighted	0.98(0.67 to 1.44)	0.924	0.098	0.416	0.077	0.731
		Weighted median	0.87(0.53 to 1.44)	0.592				
		Simple mode	1.02(0.47 to 2.22)	0.959				
		Weighted mode	0.94(0.47 to 1.91)	0.878				
sTfR	5	Inverse variance weighted	1.36(0.04 to 10.95)	0.518	0.505	0.844	0.627	0.339
		Weighted median	0.95(0.32 to 2.81)	0.924				
		Simple mode	0.93(0.22 to 3.99)	0.927				
		Weighted mode	0.93(0.23 to 3.65)	0.919				
TIBC	4	Inverse variance weighted	1.05(1.05 to 0.41)	0.919	0.438	0.475	0.381	0.154
		Weighted median	1.29(1.29 to 0.62)	0.496				
		Simple mode	1.41(1.41 to 0.21)	0.745				
		Weighted mode	1.39(1.39 to 0.67)	0.437				

FIGURE 2 The results of IVW, Weighted median, Simple mode, and Weighted mode methods. sTfR, soluble transferrin receptor; TIBC, total iron binding capacity; TSAT, transferrin saturation.

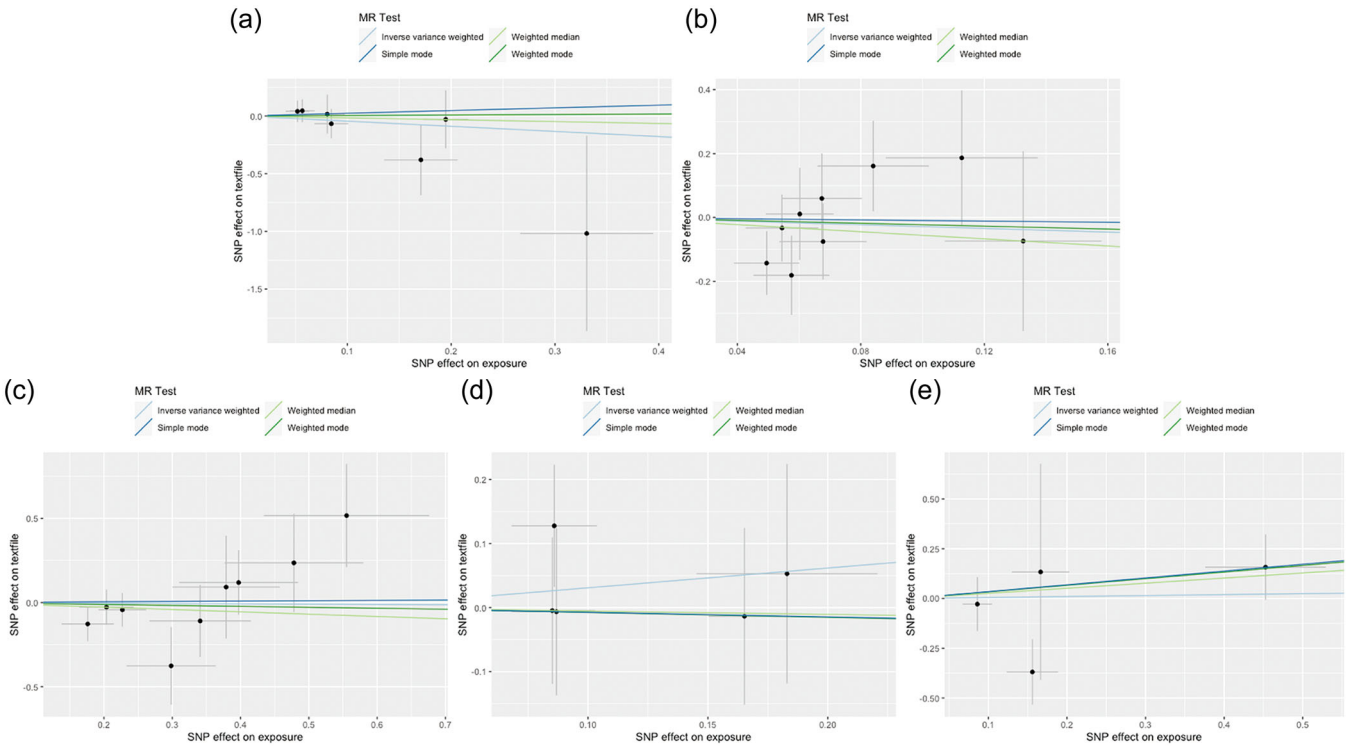

FIGURE 3 The scatter plots assessed the impact of iron status on PAH based on four MR analysis methods. (a) Outcome: PAH, Exposure: serum iron; (b) Outcome: PAH, Exposure: ferritin; (c) Outcome: PAH, Exposure: transferrin saturation; (d) Outcome: PAH, Exposure: soluble transferrin receptor; (e) Outcome: PAH, Exposure: total iron binding capacity. PAH, pulmonary arterial hypertension.

DISCUSSION

Defining iron deficiency in chronic diseases, especially those where inflammation plays a significant role, can pose challenges. Inflammation is typically associated with elevated ferritin levels and decreased serum iron and transferrin saturation. Circulating sTfR levels, however, are less influenced by inflammation. Concentrations of sTfR exceeding 28.1 nmol/L have been linked to unfavorable clinical outcomes in idiopathic PAH (IPAH) and heritable PAH (HPAH).[4] A pilot study suggested that adjunctive ferric maltol supplementation, in conjunction with targeted therapies for PAH, notably improves exercise capacity and enhances quality of life.[11] Despite the strong association between iron and PAH, no studies have yet established a genetic causal link between iron status and PAH. Investigating this genetic causal association holds significant implications for understanding the etiology, mechanisms, and treatment of PAH. This study aims to explore the causality between iron status and PAH through MR analysis. No evidence of causality between iron status and PAH was identified, suggesting that iron status lacks genetic causality with PAH. Nevertheless, other factors such as inflammation and environmental influences may potentially modulate the correlation between iron status and PAH.

An imbalance in iron status manifests as either iron overload or iron deficiency. Iron overload results in elevated levels of serum iron, ferritin, and transferrin saturation, alongside decreased levels of transferrin. Conversely, iron deficiency exhibits the opposite trend.[29] Numerous studies have indicated that iron deficiency can impact the quality of life and prognosis of patients with PAH.[4,6,9] Recent studies have revealed a high prevalence of anemia and iron deficiency in patients with PAH, which correlates with disease severity, exercise capacity, and even survival.[30] In various cohorts, the prevalence of iron deficiency, defined by reduced serum iron and transferrin saturations, has been reported to range between 28% and 50% in IPAH and up to 60% in HPAH.[5,6] Using circulating sTfR levels to determine iron deficiency, Rhodes et al. discovered that even 63% of patients with IPAH had iron deficiency without overt anemia.[4] Two human studies have provided evidence supporting the potential role of iron deficiency in the pathobiology of PAH, demonstrating that iron supplementation may attenuate hypoxic PAH, while iron depletion may exacerbate it.[3]

Notably, a previous study demonstrated that the prevalence of PAH was similar in iron-deficient and noniron-deficient subjects,[8] which was consistent with our results that found no causal association between iron status and PAH, at least at the genetic level. An interesting study by Ulrich et al. suggests that the results of iron therapy trials for PAH should be interpreted with caution. In this study, they did not observe a connection between genetically determined iron status and PAH, which was also consistent with our findings.[15] Additionally, there are lingering safety concerns regarding iron supplementation in idiopathic and heritable PAH, and its effects on pulmonary vascular resistance (PVR), cardiac function, and exercise capacity remain uncertain. An experimental study has suggested that iron-dependent oxidative stress contributes to pulmonary artery smooth muscle cell (PASMC) proliferation and may therefore be implicated in the pathogenesis of pulmonary vascular remodeling and PAH.[31]

Nevertheless, when examining the forest plot, it becomes evident that the error bars are notably wide, indicating a substantial degree of uncertainty in the data. This observation is crucial as it suggests that the study's findings may be influenced by factors not adequately captured within the current analysis. Consequently, while the study provides valuable insights, it cannot definitively rule out the potential influence of factors falling within these broad ranges. Therefore, future research endeavors should aim to address these uncertainties through additional data collection, refined methodologies, or RCTs to ensure a more comprehensive understanding of the results of this study.

Excessive iron accumulation triggers the generation of reactive oxygen species (ROS), which can inflict damage on DNA, proteins, and lipids, ultimately resulting in cell death. Additionally, iron overload can incite inflammatory reactions through the activation of the NF-kB signaling pathway.[32] Moreover, iron plays a pivotal role in the synthesis of hemoglobin and myoglobin, crucial for oxygen delivery and intracellular oxygen storage. It is worth mentioning that the regulation of iron status by hepcidin may be influenced by hypoxia and inflammation,[33] and pulmonary hypertension is intimately linked with inflammation.[34] Significantly, recent findings suggest that iron deficiency in PAH may, in part, stem from impaired dietary iron absorption, likely due to elevated levels of hepcidin. Hepcidin, a key regulatory protein in iron homeostasis, is known to inhibit dietary iron absorption and promote cellular iron storage.[35] Its regulation involves various factors, including inflammatory processes, hypoxia, erythropoietin, sTfR, and bone morphogenetic protein (BMP) signaling.[35] The latter is of particular significance in PAH, given that BMP receptor type II (BMPR2) expression is diminished in patients with IPAH, and loss-of-function mutations in BMPR2 are implicated in the majority of heritable HPAH and a notable percentage of IPAH cases.[36,37] Iron deficiency is recognized as a form of malnutrition, suggesting that

prolonged exposure to inadequate living conditions may serve as a shared risk factor for both iron status imbalance (chronic iron deficiency) and PAH. In summary, the relationship between PAH and iron status is multifaceted and influenced by numerous factors. Nonetheless, our findings indicate the absence of a genetic causal association between PAH and iron status.

In contrast to observational epidemiological investigations, MR analysis does not incur substantial measurement expenses or necessitate an extensive supply of appropriate biospecimens. Of paramount significance, MR studies mitigate confounding factors inherent in retrospective studies and circumvent issues of reverse causality commonly encountered in traditional epidemiological approaches. Consequently, MR analysis boasts high reliability and is extensively employed across various research endeavors. Although our study has excluded a causal relationship between iron status and PAH through MR analysis, it does not preclude the potential association between iron status and PAH.

We acknowledge the potential limitations of our study. First, because the human origin of TIBC is different from that of PAH, there are certain genetic differences that may lead to bias. Furthermore, the relatively weak instrumental variable strength of sTfR may potentially influence the results. Second, the PAH statistics utilized in this study are sourced exclusively from a cohort-based in Finland, potentially limiting the generalizability of the findings to broader populations. Meanwhile, the cohort studied in this research comprises a relatively small number of PAH patients, which may impact the statistical power and precision of the results obtained. Finally, the definition of PAH in this study relies on hospital ICD code data rather than assessments by expert PAH physicians. Therefore, it is crucial for future research to include more genome-wide association study (GWAS) summary statistics on PAH or conduct RCTs to further validate the findings of this study.

CONCLUSIONS

This study demonstrates that there are no genetic causal associations between iron status and PAH.

AUTHOR CONTRIBUTIONS

Peng-Cheng Liu and Rui Wu: Study design and drafting of the manuscript. Peng-Cheng Liu, Meng-Na Lv, and Yan-Yan Rong: data collection and interpretation. Meng-Na Lv and Yan-Yan Rong: data analysis. Yan-Yan Rong and Shu-Jiao Yu: modification and polishing. All authors contributed to the article and approved the submitted version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The source of the data was a publicly available database, and no human participants were involved; hence, ethical parameters are not applicable.

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