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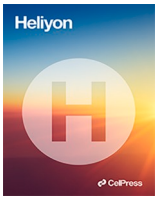

Research article

Causal relationship between serum metabolites and idiopathic pulmonary fibrosis: Insights from a two-sample Mendelian randomization study

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ABSTRACT

Background: Idiopathic pulmonary fibrosis (IPF) is an irreversible lung disease with unclear pathological mechanisms. In this study, we utilized bidirectional Mendelian randomization (MR) to analyze the relationship between serum metabolites and IPF, and conducted metabolic pathway analysis.
Aim: To determine the causal relationship between serum metabolites and IPF using MR analysis.
Methods: A two-sample MR analysis was conducted to evaluate the causal relationship between 824 serum metabolites and IPF. The inverse variance weighted (IVW) method was used to estimate the causal relationship between exposure and results. Sensitivity analysis was conducted using MR Egger, weighted median, and maximum likelihood to eliminate pleiotropy. Additionally, metabolic pathway analysis was conducted to identify potential metabolic pathways.
Results: We identified 12 serum metabolites (6 risks and 6 protective) associated with IPF from 824 metabolites. Among them, 11 were known and 1 was unknown. 1-Eicosatrienoylglycophorophospholine and 1-myristoylglycophorophospholine were bidirectional MR positive factors, with 1-myristoylglycophorophospholine being a risk factor (1.0013, 1.0097) and 1-eicosatrienoylglycophorine being a protective factor (0.9914, 0.9990). The four lipids (1-linoleoylglycerophoethanolamine*, total cholesterol in large high-density lipoprotein [HDL], cholesterol esters in very large HDL, and phospholipids in very large HDL) and one NA metabolite (degree of unsaturation) were included in the known hazardous metabolites. The known protective metabolites included three types of lipids (carnitine, 1-linoleoylglycerophoethanolamine*, and 1-eicosatrienoylglycerophophophorine), one amino acid (hypoxanthine), and two unknown metabolites (the ratio of omega-6 fatty acids to omega-3 fatty acids, and the ratio of photoshopids to total lipids ratio in chylomicrons and extremely large very low-density lipoprotein [VLDL]). Moreover, sn-Glycerol 3-phosphate and 1-Acyl-sn-glycero-3-phosphocline were found to be

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involved in the pathogenesis of IPF through metabolic pathways such as Glycerolide metabolism and Glycerophospholipid metabolism.
Conclusion: Our study identified 6 causal risks and 6 protective serum metabolites associated with IPF. Additionally, 2 metabolites were found to be involved in the pathogenesis of IPF through metabolic pathways, providing a new perspective for further understanding the metabolic pathway and the pathogenesis of IPF.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a genetically heterogeneous disease. It involves complex mechanisms and can result in progressive dyspnea and irreversible loss of lung function [1–3]. Early detection and intervention are crucial for slowing disease progression [4]. However, current methods for early detection of IPF have been limited [5]. Serum metabolites are promising biomarkers for IPF, owing to their robust monitoring capabilities, broad applicability, and accessible analysis [6,7]. Although previous studies have identified serum biomarkers for IPF, such as matrix metalloproteinase (MMP), krebs von den lungen-6 (KL-6), and chitinase-3-like protein 1 (YKL-40) [8–11], these biomarkers lack robust evidence to support their causal relationship with the onset of IPF. Moreover, potential confounding and reverse causality make it challenging to draw causal inferences for IPF solely through traditional observational studies. Therefore, it is essential to identify serum biomarkers that can be used to causally monitor or refine the risk of IPF and to further broaden the research into its mechanisms. Mendelian randomization (MR) is a method used to evaluate the causal relationship between circulating biomarkers and disease occurrence. This method employs germline genetic variations as instrumental variables to assess the role of risk factors in disease susceptibility [12]. The random distribution of genetic variation during conception in MR substantially minimizes associations with most confounding factors, thereby enhancing the research credibility of causal inference between biomarkers and disease occurrence [13]. Furthermore, the distribution of these Mendelian genetic variants typically occurs before the onset of the disease, thereby mitigating concerns related to reverse causality.

This study was aimed to effectively screen serum metabolites through the application of MR design, and identify circulating metabolites influencing the risk of IPF. Our goal was to ensure that candidate metabolites shared common genetic signals for causation with IPF and were not influenced by linkage disequilibrium (LD) in MR results. Firstly, we evaluated the serum metabolites of IPF identified through MR and colocalization analysis. Secondly, we conducted bidirectional MR analysis on the selected significant serum metabolites to differentiate between one-way MR-positive serum metabolites, indicating causal relationships that can serve as predictive markers, and bidirectional MR-positive serum metabolites related to IPF. Finally, metabolic pathway analysis was conducted to identify metabolites involved in the pathogenesis of IPF through metabolic pathways (Fig. 1). The experimental findings might contribute to a better understanding of the pathogenesis of IPF, laying a solid foundation for future exploration of potential mechanisms and therapeutic targets for IPF.

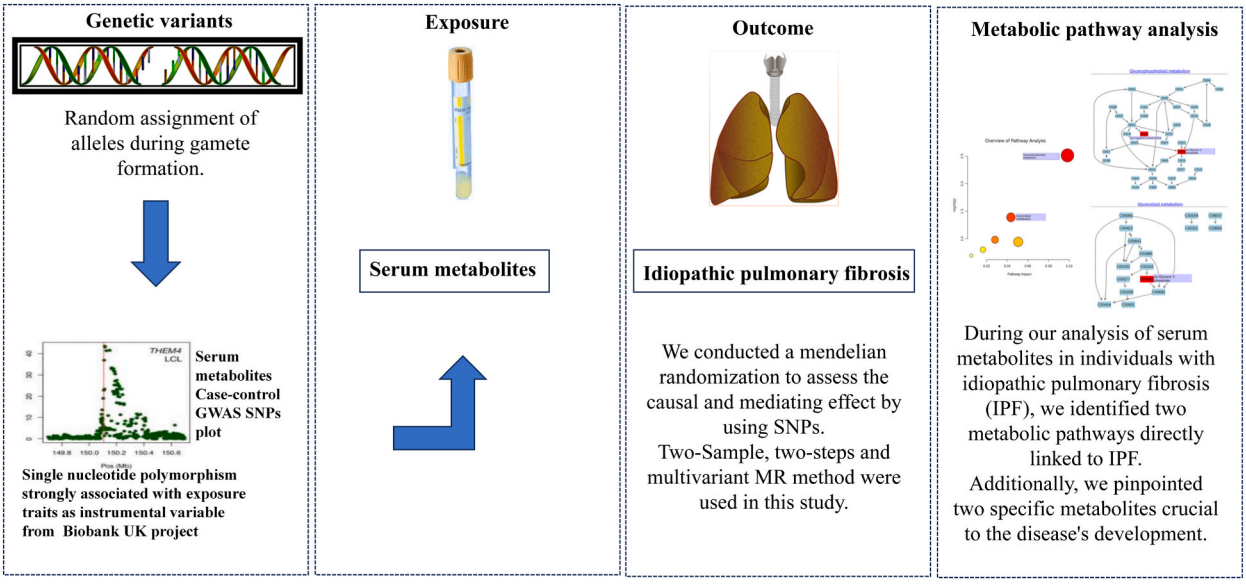

Fig. 1. Study design and workflow.

2. Methods

2.1. GWAS data source

We adopted a two-sample MR design to identify serum metabolites related to IPF using the serum metabolite databases from the extensive study conducted by Shin et al. (Table 1). This database included 486 known and 309 unknown metabolites, mainly from liver metabolism and partly from fat [14]. Among these metabolites, 177 known metabolites were categorized into 309 biological groups, such as amino acids, peptides, lipids, and more. The Genome-wide association study (GWAS) collected serum and data from over 20, 000 single nucleotide polymorphisms (SNPs) in 7,824 European adults, which were further compiled for analysis. After rigorous quality control, 486 metabolites were considered suitable for GWAS analysis. Furthermore, another study examined the characteristics of 925 metabolites, including lipids, fatty acids, amino acids, and glycolytic precursors [15]. This investigation into lipoprotein subclass-specific lipids addressed the limitations of the original GWAS data. These serum metabolite data are accessible via the Metabolomics GWAS server (https://metabolomics.helmholtz-muenchen.de/gwas/).

The SNP database for IPF was derived from Anna Duckworth's GWAS study [16], including previous GWAS and case-control studies from research and Europe, with age and sex appropriately adjusted [16]. The aggregated GWAS summary data were derived from two meta-analyses primarily covering European populations. Following quality control, a total of 16,380,413 variants were retained in the final association analysis. The original study was conducted with the informed consent of all participants, and the IPF dataset is accessible at this website: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30364-7/fulltext.

2.2. Selection of instrumental variables

To identify high-intensity instrumental variables for the analysis of the relationship between serum metabolites and IPF, we first identified serum metabolites associated with IPF based on a p-value of less than 1×10^{-5} [17,18]. We then ranked the p-values and selected the top 5 % as the threshold. Due to the relatively small sample size, we utilized the 1000 Genome Project as a reference panel for analysis, focusing on a physical distance range of 5000 kb and an r-squared value less than 0.01. Additionally, we calculated the F-statistic for each metabolite to assess the strength of the instrumental variables.

2.3. MR analysis

MR relies on three main assumptions [19]. Firstly, genetic variations must be reliably associated with the exposure of interest. With the emergence of modern large-scale GWASs, genetic variations related to the exposure can be identified in large datasets [20]. Secondly, genetic variations cannot be associated with confounding factors in the exposure-outcome relationship. Potential violation of this hypothesis may occur due to confounding by LD and/or population ancestry [21]. Finally, genetic variation should not affect the outcome unless through the exposure of interest (known as a lack of horizontal pleiotropy) [22]. Large-scale genomic association studies on serum metabolites GWASs often find a close correlation between the genetic determinants of serum metabolites and their coding genes. This close-range effect can be reduced using SNPs for MR analysis to reduce uncertainty and improve the effectiveness of the study. SNPs closely related to metabolites may directly affect gene transcription, thereby affecting the level of metabolites.

We used the inverse variance weighted (IVW) method as the primary method for estimating the causal relationship between metabolites and IPF in our MR analysis [23]. When genetic variation conforms to the hypothesis of three instrumental variables and is unaffected by pleiotropy, IVW method would yield consistent estimates of causal effects between exposure and outcomes.

Table 1
Characteristics of blood metabolites and idiopathic pulmonary fibrosis in Biobank UK project.

Exposures	Another name	No. cases	No. SNPs	Category
Carnitine	NA	7,797	2,545,563	Continuous
1-myristoylglycerophosphocholine	LysoPC(14:0/0:0)	7,812	2,545,688	Continuous
1-linoleoylglycerophosphoethanolamine*	glycerophosphoric acid	7,817	2,545,675	Continuous
1-eicosatrienoylglycerophosphocholine	LysoPC(20:2 (11Z,14Z))	7,809	2,545,640	Continuous
Total cholesterol in large HDL	NA	21,558	11,861,714	Continuous
Cholesterol esters in very large HDL	NA	19,273	11,806,428	Continuous
Phospholipids in very large HDL	NA	19,273	11,820,655	Continuous
Hypoxanthine	NA	7,287	2,545,756	Continuous
Ratio of omega-6 fatty acids to omega-3 fatty acids	NA	114,999	12,321,875	Continuous
Degree of unsaturation	NA	114,999	12,321,875	Continuous
Phospholipids to total lipids ratio in chylomicrons and extremely large VLDL	NA	111,631	12,321,875	Continuous
X-12749	NA	7,178	2,545,560	Continuous
Outcome	**No. cases (Female, %)**	**No. controls (Female, %)**	**No. SNPs**	**Category**
IPF	1,369 (NA)	435,866 (NA)	16,137,102	Binary

Met, Metabolites; IPF, Idiopathic pulmonary fibrosis; No., number of; SD, standard deviation; SNPs, single nucleotide polymorphism.

2.4. Sensitivity analysis

In addition to the IVW method, there are other MR analysis methods that can reduce bias and provide sensitivity analysis. MR Egger's analysis evaluates the heterogeneity of individual SNP estimation and detects horizontal pleiotropy effects [24]. The weighted median (WM) method combines multiple data into a single causal estimate, allowing up to half of SNPs to be invalid instruments [25]. MR pleiotropy residual sum and outlier (MR-PRESSO) global and outlier tests can calculate horizontal pleiotropy and remove outlier SNPs [26]. LD score regression (LDSC) was used to estimate the heritability and genetic correlation of GWAS traits (https://github.com/bulik/LDSC) [27] and SUPER GeNetic covariance Analyzer (SUPERGNOVA) was used to calculate the local genetic covariance of LD genome regions (https://github.com/Qlu lab/SUPERGNOVA) [28]. Finally, we conducted exclusion and single SNP analyses to determine whether a single SNP influenced the central causal relationship. Statistical analysis was performed using R-4.2.3 software (https://www.rstudio.com/) for TwoSampleMR and MR-PRESSO.

2.5. Metabolic pathway analysis

The relationship between metabolic pathways and IPF was explored using MetaboAnalyst 5.0 (https://www.metaboanalyst.ca/). Metabolites were categorized into two groups based on their causal relationships with IPF: positively correlated and negatively correlated. We used two databases, the Small Molecular Pathway Database (SMPDB) [29] and the Kyoto Encyclopedia of Genes and Genomes (KEGG) [30], for metabolite analysis.

2.6. Statistical analysis

R software (version 4.2.2) was used to perform the bioinformatics analyses. A $p < 0.05$ was considered statistically significant.

3. Results

3.1. Causal effect of serum metabolites on IPF

A total of 56,204 independent SNP components were obtained for the 824 metabolites (14, 15). Supplementary Table 1 demonstrates that SNPs related to 12 metabolic products have a causal relationship with IPF and serve as genetic tools in our study. The minimum F-value of the calculated instrumental variable was greater than 10, indicating that the instrumental variable among the 824 metabolites was robust in MR analysis.

3.2. Effect of genetically determined metabolites on IPF

As shown in Fig. 2, 12 significative metabolites were detected, and multiple MR models, including IVW, Egger, and WM, indicated a genetic causal relationship between these metabolites and IPF (Table 2). However, our findings failed to prove the role of IPF in causing the changes in serum metabolites, except for 1-eicosatrienoylglycophorophospholine and 1-myristoylglycophorophospholine (Table 3). Interestingly, these two metabolites exhibited bidirectional MR positive effects in IPF. Moreover, in addition to these two

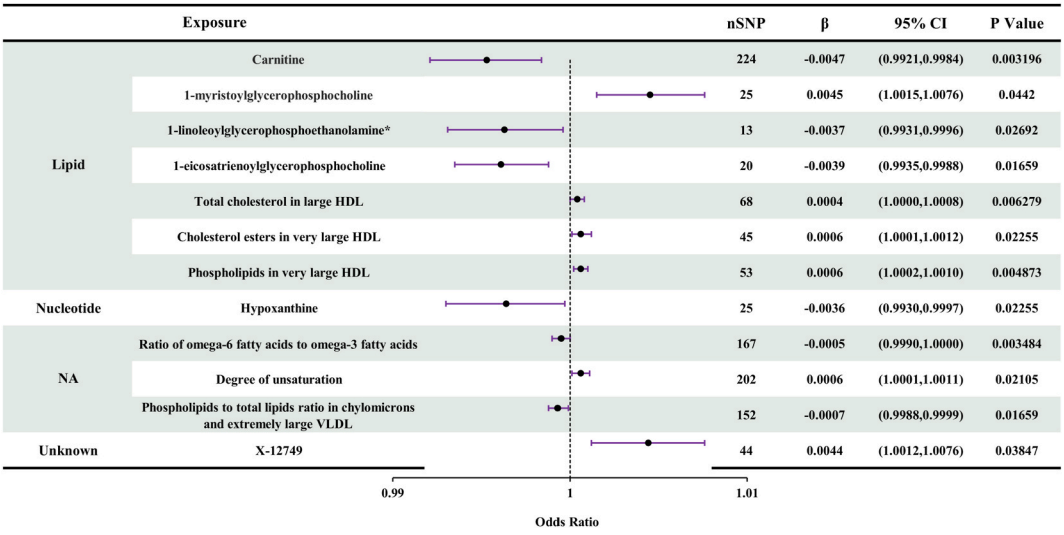

Fig. 2. Mendelian randomization results of serum metabolites and idiopathic pulmonary fibrosis (IPF) risk based on inverse variance weighted (IVW) method.

Table 2
MR Analysis between serum metabolites and IPF.

Metabolites	IVW		MR-Egger		Weighted median		Penalised weighted median		Maximum likelihood	
	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
Lipid										
Carnitine	(0.9921, 0.9984)	0.0032	(0.9862 , 1.0029)	0.2007	(0.9879 , 0.9997)	0.0391	(0.9878 , 0.9994)	0.0310	(0.9920 , 0.9985)	0.0037
1-myristoylglycerophosphocholine	(1.0015,1.0076)	0.0442	(1.0000 , 1.0102)	0.1074	(1.0013 , 1.0097)	0.0104	(1.0013 , 1.0097)	0.0105	(1.0014 , 1.0078)	0.0045
1-linoleoylglycerophosphoethanolamine*	(0.9931,0.9996)	0.0269	(0.9892 , 1.0063)	0.6086	(0.9910 , 1.0001)	0.0528	(0.9912 , 0.9998)	0.0425	(0.9930 , 0.9996)	0.0275
1-eicosatrienoylglycerophosphocholine	(0.9935,0.9988)	0.0166	(0.9865 , 1.0009)	0.1010	(0.9914 , 0.9990)	0.0125	(0.9912 , 0.9991)	0.0156	(0.9933 , 0.9988)	0.0055
Total cholesterol in large HDL	(1.0000,1.0008)	0.0063	(0.9996 , 1.0011)	0.3441	(1.0001 , 1.0015)	0.0171	(1.0003 , 1.0016)	0.0055	(1.0000 , 1.0008)	0.0345
Cholesterol esters in very large HDL	(1.0001,1.0012)	0.0226	(0.9997 , 1.0018)	0.1572	(0.9998 , 1.0012)	0.2009	(0.9997 , 1.0012)	0.2128	(1.0002 , 1.0011)	0.0102
Phospholipids in very large HDL	(1.0002,1.0010)	0.0049	(0.9995 , 1.0009)	0.5421	(1.0000 , 1.0013)	0.0526	(1.0001 , 1.0014)	0.0229	(1.0002 , 1.0010)	0.0037
Nucleotide										
Hypoxanthine	(0.9930,0.9997)	0.0226	(0.9848 , 1.0052)	0.3413	(0.9897 , 0.9992)	0.0214	(0.9897 , 0.9991)	0.0186	(0.9929 , 0.9997)	0.0329
NA										
Ratio of omega-6 fatty acids to omega-3 fatty acids	(0.9990,1.0000)	0.0035	(0.9986 , 0.9999)	0.0265	(0.9988 , 1.0001)	0.1146	(0.9988 , 1.0001)	0.1167	(0.9991 , 1.0000)	0.0347
Degree of unsaturation	(1.0001,1.0011)	0.0211	(0.9999 , 1.0013)	0.0745	(0.9999 , 1.0013)	0.1012	(0.9999 , 1.0013)	0.1107	(1.0001 , 1.0011)	0.0169
Phospholipids to total lipids ratio in chylomicrons and extremely large VLDL	(0.9988,0.9999)	0.0166	(0.9989 , 1.0006)	0.6076	(0.9984 , 1.0002)	0.1247	(0.9982 , 1.0000)	0.0568	(0.9988 , 0.9999)	0.0138
Unknown										
X-12749	(1.0012,1.0076)	0.0385	(1.0002 , 1.0125)	0.0493	(0.9998 , 1.0101)	0.0601	(0.9996 , 1.0103)	0.0698	(1.0012 , 1.0077)	0.0066

IVW: inverse variance weighted; MR-Egger: Mendelian randomization Egger; CI: confidence interval; OR: odds ratio. The significance of bold values is $p < 0.05$.

Table 3
MR analysis between IPF and blood metabolites.

Metabolites	MR Egger		Inverse variance weighted		Maximum likelihood		Weighted median		Panalised weighted median	
	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value	OR (95 % CI)	p value
Carnitine	(0.0009 , 21.4072)	0.4591	(0.4871 , 9.3182)	0.3151	(0.6503 , 7.3757)	0.2057	(0.1613 , 5.0916)	0.9111	(0.1619 , 4.8453)	0.8886
1-myristoylglycerophosphocholine	(4.4186E-09 , 308.5737)	0.3140	(0.0003 , 0.8699)	0.0426	(0.0003 , 0.9393)	0.0466	(0.0005 , 26.8073)	0.4340	(0.0005 , 26.6312)	0.4334
1-linoleoylglycerophosphoethanolamine*	(0.0762 , 1787035022.8185)	0.1552	(0.0062 , 20.7314)	0.6194	(0.0071 , 18.0203)	0.6071	(0.0317 , 2188.2664)	0.4556	(0.0374 , 1890.8798)	0.4409
1-eicosatrienoylglycerophosphocholine	(6.07045E-08 , 913.3138)	0.4315	(0.0002 , 0.4136)	0.0154	(0.0002 , 0.4052)	0.0156	(0.0002 , 6.2407)	0.2030	(0.0002 , 7.4843)	0.2186
Total cholesterol in large HDL	(0.0333 , 770.6663)	0.5300	(0.0686 , 129.5312)	0.5704	(0.0687 , 140.3244)	0.5601	(0.0209 , 1290.1503)	0.5585	(0.0185 , 1456.4117)	0.5669
Cholesterol esters in very large HDL	(0.1219 , 2955.4584)	0.2592	(0.0509 , 104.1552)	0.6683	(0.0499 , 114.8076)	0.6586	(0.1102 , 9280.1681)	0.2310	(0.0744 , 13755.9774)	0.2627
Phospholipids in very large HDL	(0.0158 , 383.7577)	0.7282	(0.0443 , 90.0988)	0.7218	(0.0436 , 97.4237)	0.7131	(0.0216 , 1692.2682)	0.5312	(0.0184 , 1970.2997)	0.5432
Hypoxanthine	(1.4904E-07 , 10690893.06581)	0.9777	(0.0060 , 87.6030)	0.8946	(0.0316 , 15.7102)	0.8253	(0.0512 , 791.0648)	0.4521	(0.1169 , 1301.0834)	0.2905
Ratio of omega-6 fatty acids to omega-3 fatty acids	(0.0020 , 38.9699)	0.6155	(0.0486 , 9.7496)	0.7826	(0.0983 , 4.5807)	0.6838	(0.0609 , 56.4408)	0.7232	(0.0674 , 52.2538)	0.7108
Degree of unsaturation	(0.0668 , 108.7245)	0.6015	(0.2587 , 13.6665)	0.5326	(0.3150 , 11.9045)	0.4756	(0.2820 , 100.9284)	0.2644	(0.2731 , 100.8459)	0.2717
Phospholipids to total lipids ratio in chylomicrons and extremely large VLDL	(0.0055 , 15.5996)	0.5479	(0.0825 , 5.8923)	0.7405	(0.1000 , 4.6975)	0.7004	(0.0013 , 0.4545)	0.0129	(0.0012 , 0.4095)	0.0106
X-12757	(0.5348 , 778297.6290)	0.1042	(0.3154 , 32.2510)	0.3258	(0.3681 , 29.9518	0.2849	(0.2974 , 86.9388)	0.2615	(0.2909 , 100.3596)	0.2578

CI: confidence interval; MR-Egger: Mendelian randomization Egger; OR: odds ratio; RSS: residual sum of squares.
The significance of bold values is $p < 0.05$.

metabolites, the other 10 serum metabolites were also significant in predicting the risk of IPF.

Out of the twelve metabolites identified, eleven were known serum metabolites, with 5 associated with an increased risk of IPF and six associated with protection against IPF. Additionally, an unknown serum metabolite was found to be associated with potential risk for IPF. Carnitine, a protective lipid serum metabolite, showed the most significant causal relationship with IPF (*P*-weighted median = 0.031, two-tailed). Among the known hazardous metabolites, there were four types of lipids (1-myristoylglycophorophosphocline, total cholesterol in large high-density lipoprotein (HDL), cholesterol esters in very large HDL, and phospholipids in very large HDL), and one unknown metabolite (degree of unsaturation). The known protective metabolites included three types of lipids (Carnitine, 1-linoleoylglycerophoethanolamine*, 1-eicosatrienoylglycerophophophorine), one amino acid (Hypoxanthine), and two NA metabolites (the ratio of omega-6 fatty acids to omega-3 fatty acids and the ratio of phospholipids to total lipids ratio in chylomicrons and extremely large very low-density lipoprotein [VLDL]). These findings were significant for a deeper understanding of the pathogenesis of IPF and might provide insights into potential treatment strategies (Supplementary Figs. 1–2).

3.3. Sensitivity analysis

In the Two-Sample Mendelian Randomization (TSMR) analysis, no evidence of heterogeneity or horizontal pleiotropy was found between 12 Metabolites and IPF, as indicated by the heterogeneity test and MR-Egger intercept test (Supplementary Table 2).

3.4. Genetic correlation

Both LDSC and SUPERGNOVA were used to estimate the genetic correlation between metabolites and IPF. LDSC calculated the global correlation, whereas SUPERGNOVA estimated local genetic correlation. Our study did not identify a significant causal correlation between metabolites and IPF using LDSC. Furthermore, we did not observe significant local genetic covariance between the 12 metabolites identified by the IVW method. These results suggest that our findings were not influenced by genetic confounding or causal SNPs.

3.5. Metabolic pathway analysis

As shown in Table 4, the two metabolic pathways binding to metabolites exhibited a positive causal relationship with IPF. The most significant metabolic pathways associated with IPF was Glycerophorid metabolism and Glycerophorid metabolism. The metabolites involved in the occurrence of IPF, named 1-Acyl-sn-glyco-3-phosphocline, sn-Glycerol 3-phosphate, and sn-Glycerol 3-phosphate, were part of the two pathways (Glycerophospholipid metabolism and Glyceroolipid metabolism).

4. Discussion

To the best of our knowledge, this is the first study to utilize a MR approach to establish the genetic causality between 12 metabolites and IPF. Our study identified components of the sn-Glycerol 3-phosphate and 1-Acyl-sn-glycero-3-phosphate metabolic pathways to be involved in the occurrence and development of IPF. The GWAS data and a two-sample MR method were used to explore the causal association between IPF and metabolites. Rigorous sensitivity analyses were conducted to eliminate confounding factors, thereby elevating the robustness and credibility of our findings.

In our bidirectional MR study, we found that Carnitine, a well-established metabolite, had remarkable protective efficacy against IPF. Carnitine is a vitamin-like biological factor that plays a crucial role in regulating fatty acid metabolism and energy utilization. Previous investigations conducted by Sonia Zambrano and her research team have shown that carnitine can upregulate PPAR-γ, thereby effectively mitigating the progression of renal fibrosis and myocardial fibrosis in rat models [31,32]. Multiple studies further substantiated Carnitine's intervention in fibrosis by ameliorating inflammation, modulating oxidative stress, and impeding the production and release of fibrosis-inducing factors [31,33–37]. Results of our MR research corroborated Carnitine's protective role in the onset and development of IPF, highlighting its potential as a predictive biomarker for assessing the occurrence and impact of IPF. This finding is of great significance in clinical practice, offering novel avenues for early prevention and therapeutic strategies in IPF and deepening our understanding of Carnitine's biological effects.

Our analysis found that 1-eicosatrienoylglycophorophospholine and 1-myristoylglycophorophospholine exhibited bidirectional MR positive effects in IPF, suggesting that these two metabolites may have potential value as biomarkers and also potentially becoming novel therapeutic targets for IPF. 1-Myristoylglycerophosphate is a lysophospholipid (LyP) and serves as a precursor to lysophosphatidic acid (LPA), a bioactive glycerophospholipid with various forms characterized by differing chain lengths and degrees of fatty acid saturation [38]. LPA is implicated in many physiological processes, including fibrosis, systemic sclerosis, cancer, inflammation,

Table 4
Important metabolic pathways in the pathogenesis of IPF.

Metabolic pathway	Metabolites involved	p value	Database
Glycerophospholipid metabolism	1-Acyl-sn-glycero-3-phosphocholine , sn-Glycerol 3-phosphate	0.0031	KEGG
Glycerolipid metabolism	sn-Glycerol 3-phosphate	0.0407	KEGG SMP

KEGG: Kyoto Encyclopedia of Genes and Genomes; SMPDB: Small Molecule Pathway Database.

atherosclerosis, obesity, asthma, and multiple sclerosis [39–44]. Besides, LPA can induce fibrotic conditions in the lung, kidney, and liver, mediated through mechanisms involving epithelial cell apoptosis, vascular permeability, and fibroblast migration and proliferation [45,46]. Our MR study underscored the clinical significance of 1-myristoylglycerophosphate by elucidating its positive association with the elevated risk of IPF.

Hypoxanthine, which belongs to the nucleotide class, is a purine metabolite that has been identified to have a causal relationship with fibrosis. Purines are pivotal in modulating the immune response during wound healing and fibrosis, serving as critical signaling hubs in scar tissue formation within fibrotic regions [39]. Our MR study reinforced the protective role of hypoxanthine in the initiation and progression of IPF, contributing to the ongoing exploration of potential drug targets for this condition. In contrast, inosine, another purine metabolite and precursor to adenosine, remains controversial regarding its involvement in the onset and development of fibrosis. Metabolic analysis using gas chromatography with mass spectrometry of lung tissue from IPF patients has shown an increase in inosine's molecular weight compared to normal lung tissue [47]. Moreover, adenosine levels have been found to be associated with the progression of IPF [48]. An alternative study suggests that inosine, acting as a potential receptor agonist in certain adenosine A3 formulations, may inhibit fibrosis by suppressing the proliferation of hepatic stellate cell-derived sodium channel regulatory factor cells [49]. Interestingly, our research did not find a direct correlation between inosine and IPF, highlighting the multifactorial nature of fibrosis development. This finding suggests new avenues for future exploration, such as investigating other metabolites and cytokines, to gain deeper insights. Despite the absence of a confirmed link between inosine and IPF as a significant metabolic product, its biological effects and functions warrant continued attention and investigation, potentially offering applications in other domains.

1-Eicosatrienoylglycerophosphocline belongs to the serum metabolite of lipids. Both eicosatrienoylglycerophosphocline (ETEPC) and epoxyicosatrienoic acid (EETs) contain eicosatrienoic acid. The biological activity of EET is closely related to the synthesis of ETEPC and its lipid metabolism pathway. ETEPC serves as a precursor for EET synthesis, which can be produced through the metabolism of ETEPC by lipoxygenase; EET, in turn, can regulate the metabolism and levels of ETEPC through different pathways. Current research has indicated that EETs have inhibitory effects on pulmonary fibrosis (50). EETs can reduce the occurrence and progression of fibrosis by inhibiting molecular signaling pathways and inflammatory responses related to IPF, reducing oxidative stress and cell apoptosis, and inhibiting the proliferation and migration of reticulocytes and pulmonary artery endothelial cells [50,51]. Our MR studies also demonstrated the preventive and inhibitory effects of 1-eicosatrienoylglycophorine on fibrosis.

The ratio of omega-6 fatty acids to omega-3 fatty acids quantifies the balance between these two types of fatty acids in the human diet. These fatty acids play crucial roles in various physiological functions in the human body, including cell membrane synthesis, cell signaling, inflammatory responses, and immune regulation [52,53]. Current research has underscored the potential of excessive omega-6 fatty acid consumption to promote fibrosis development. This propensity can be attributed to the generation of bioactive compounds like prostaglandin E2 (PGE2) by omega-6 fatty acids, which can trigger inflammation and exacerbate fibrosis progression [54,55]. Moreover, omega-6 fatty acids can influence cell growth and gene expression, potentially accelerating fibrosis progression [56,57]. In contrast, omega-3 fatty acids, also known as polyunsaturated fatty acids, play a protective role in preventing and mitigating the onset of fibrosis by suppressing inflammatory reactions [58] and enhancing antioxidant activity [59]. Our MR study suggests that the ratio of omega-6 fatty acids to omega-3 fatty acids may be a critical determinant in the development of IPF. Specifically, an elevated omega-3 to omega-6 ratio may accelerate the process of IPF, while reducing this ratio may have a preventive effect on IPF, likely due to the physiological attributes of omega-3 fatty acids. This conclusion serves as a crucial reference for developing strategies to prevent and treat IPF. Thus, increasing daily dietary intake of omega-3 fatty acids could be an effective intervention to reduce the omega-3 to omega-6 ratio, thereby preventing and managing IPF.

The degree of unsaturation refers to the number of unsaturated bonds present in blood metabolites. This metric is significant as it reflects metabolic changes resulting from various biochemical reactions, thereby serving as a biomarker for assessing metabolic disorders and susceptibility to diseases [60,61]. Previous studies have supported a connection between the number of unsaturated bonds in lipid components and other blood metabolites with fibrotic diseases [62]. Our MR research findings provided initial evidence of a potential positive correlation between the degree of unsaturation and IPF, which offered new insights into the management and prevention of IPF, and further enhanced our understanding of the regulatory role of lipid metabolism in the pathogenesis of IPF. It may also pave the way for developing novel targets for regulating lipid metabolism, ultimately improving diagnostic accuracy and treatment outcomes for IPF. These discoveries hold promise for exerting a positive and lasting impact on the treatment and prognosis of patients with IPF.

Additionally, 1-linoleoylglycerophoethanolamine* is a phospholipid molecule that plays pivotal roles in various biological processes within the human body, including cell membrane composition and signal transduction [63]. Our MR study represents a pioneering effort in elucidating the connection between 1-linoleoylglycerophoethanolamine* and IPF, and suggest that this metabolite may act as a protective factor in serum, potentially reducing the risk of IPF. However, its precise role within the pathophysiological mechanisms of IPF remains ambiguous, making 1-linoleoylglycerophoethanolamine* a compelling subject for further investigation. A recently study has identified a novel etiological mechanism involving HMGCS2-mediated lipid metabolism in alveolar type II epithelial cells (AECII), which plays a significant role in the onset and progression of pulmonary fibrosis. This finding highlights a potential new target for clinical intervention [64].

Through metabolic pathway analysis, we identified a significant correlation between IPF and the glycerophospholipid and glyceride metabolism pathways, both of which involved the metabolic processing of the glycerol scaffold. Specifically, our findings highlighted a strong association with a phosphatidylglycerol molecule known as sn-Glycerol 3-phosphate, posing an increased risk of IPF. Consequently, sn-Glycerol 3-phosphate emerges as a promising candidate for a potential diagnostic marker and therapeutic target in the context of IPF.

However, our study had several limitations. Firstly, a larger sample size and more comprehensive GWAS data are necessary for a

thorough exploration of the roles of metabolites, particularly amino acids, in IPF. Secondly, the GWAS databases used in this research were primarily composed by European populations. Therefore, caution should be exercised when generalizing these results to other racial or ethnic groups, as their applicability to these populations remains uncertain.

5. Conclusion

We identified six primary causal risk factors and six protective serum metabolites closely linked with IPF. Our research highlighted carnitine as the most significant protective element against the development of IPF. Additionally, we identified two metabolites, specifically sn-Glycerol 3-phosphate and 1-Acyl-sn-glycero-3-phosphocholine, playing pivotal roles in the pathogenesis of IPF through metabolic pathways. These metabolites were demonstrated to be crucial for the metabolic processes influencing the progression of IPF.

Ethical recognition

Due to the use of publicly available data, no separate ethical approval is required.

Consent for publication

All the authors have read and approved the final version of manuscript and give consent.

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Data availability statement

All data utilized in this study were sourced from the publicly available summary statistics of GWAS. These serum metabolite data are accessible via the Metabolomics GWAS server: https://metabolomics.helmholtz-muenchen.de/gwas/. The IPF dataset is accessible at this website:https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30364-7/fulltext.

CRediT authorship contribution statement

Qiong-Chao Zou: Writing – original draft, Software. **Jun-Pei Hu:** Writing – review & editing, Writing – original draft, Software. **Yan Cao:** Formal analysis. **Chang She:** Data curation. **Li-Hui Liang:** Writing – review & editing, Formal analysis. **Zheng-Yu Liu:** Writing – review & editing, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e36125.

Abbreviation

MR	Mendelian randomization
IPF	Idiopathic pulmonary fibrosis
HDL	High density lipoprotein
VLDL	Very Low Density Lipoprotein
GWAS	Genome-wide association study
SNP	Nucleotide polymorphism
IVW	Inverse-variance weighted method
LD	Linkage disequilibrium
SUPERGNOVA	SUPER GeNetic cOVariance Analyzer
LDSC	Linkage Disequilibrium Score Regression

MR-Egger Mendelian Randomization-Egger regression
MR-PRESSO MR pleiotropy residual sum and outlier
OR Odds ratio
SMPDB Small Molecule Pathway Database
KEGG Kyoto Encyclopedia of Genes and Genomes
LyP Lysophosphatidylcholine
LPA Lysophosphatidic Acid
ETEPC Eicosatrienoylglycerophosphocholine
EETs epoxyeicosatrienoic acid
PGE2 Prostaglandin E2

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