[Diffuse Lung Disease Original Research]

CHEST

A Causal Atlas on Comorbidities in Idiopathic Pulmonary Fibrosis

A Bidirectional Mendelian Randomization Study

Jiahao Zhu; Dan Zhou, PhD; Jing Wang, PhD; Ye Yang, PhD; Dingwan Chen, PhD; Fan He, PhD; and Yingjun Li, PhD

BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease with a high burden of both pulmonary and extrapulmonary comorbidities.

RESEARCH QUESTION: Do these comorbidities have causal relationships with IPF?

STUDY DESIGN AND METHODS: We searched PubMed to pinpoint possible IPF-related comorbid conditions. Bidirectional Mendelian randomization (MR) was performed using summary statistics from the largest genome-wide association studies for these diseases to date in a two-sample setting. Findings were verified using multiple MR approaches under different model assumptions, replication datasets for IPF, and secondary phenotypes.

RESULTS: A total of 22 comorbidities with genetic data available were included. Bidirectional MR analyses showed convincing evidence for two comorbidities and suggestive evidence for four comorbidities. Gastroesophageal reflux disease, VTE, and hypothyroidism were associated causally with an increased risk of IPF, whereas COPD was associated causally with a decreased risk of IPF. For the reverse direction, IPF showed causal associations with a higher risk of lung cancer, but a reduced risk of hypertension. Follow-up analyses of pulmonary function parameters and BP measures supported the causal effect of COPD on IPF and the causal effect of IPF on hypertension.

INTERPRETATION: The present study suggested the causal associations between IPF and certain comorbidities from a genetic perspective. Further research is needed to understand the mechanisms of these associations.

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KEY WORDS: causality; comorbidities; idiopathic pulmonary fibrosis; Mendelian randomization

ABBREVIATIONS: GBMI = Global Biobank Meta-analysis Initiative; GERD = gastroesophageal reflux disease; GWAS = genome-wide association study; IPF = idiopathic pulmonary fibrosis; IVW = inverse-variance weighted; MR = Mendelian randomization; PRESSO = pleiotropy residual sum and outlier; SNP = single-nucleotide polymorphism

AFFILIATIONS: From the Department of Epidemiology and Health Statistics (J. Z, J. W., Y. Y., and Y. L.), School of Public Health (D. C.), Hangzhou Medical College, the School of Public Health and the Second Affiliated Hospital (D. Z.), Zhejiang University School of Medicine, the Zhejiang Provincial Center for Disease Control and Prevention (F. H.), Hangzhou, China; and the Vanderbilt Genetics Institute (D. Z.), Vanderbilt University Medical Center, Nashville, TN.

CORRESPONDENCE TO: Yingjun Li, PhD; email: 2016034036@hmc.edu.cn

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Take-home Points

Study Question: Do the observed associations between idiopathic pulmonary fibrosis (IPF) and comorbidities represent causality?

Results: Gastroesophageal reflux disease, VTE, and hypothyroidism were associated causally with an increased risk of IPF, whereas COPD was associated causally with a decreased risk of IPF. IPF showed causal associations with a higher risk of lung cancer, but a reduced risk of hypertension.

Interpretation: This Mendelian randomization study supported the causal associations between IPF and certain comorbidities from a genetic perspective. A deeper understanding of the pathways underlying these diverse associations would be worthwhile, with implications in terms of optimal prevention and treatment strategies for comorbidities.

Idiopathic pulmonary fibrosis (IPF) is a progressive and fibrotic lung disease of unknown cause that occurs primarily in older adults.[1] Although pharmacologic therapies for IPF have evolved remarkably in recent years, it remains a lethal condition with a median survival of 3 to 5 years.[2] In addition to the adverse effects directly induced by pulmonary fibrosis itself, patients with IPF frequently have a variety of comorbid conditions that lead to substantial negative outcomes, including increased mortality and poor quality of life.[3-5] Comorbid illness can be pulmonary or extrapulmonary. Common pulmonary comorbidities include pulmonary hypertension, COPD, and lung cancer, whereas nonrespiratory conditions involve coronary artery disease, gastroesophageal reflux disease (GERD), and depression.

Despite the clear observed association between IPF and comorbidities, the nature and direction of any causal relationships between IPF and these comorbidities is yet to be established.[4] It is not known whether comorbidities cause IPF or IPF contributes to comorbidities, or alternatively whether IPF and comorbidities develop independently because of shared or common causative factors such as aging, smoking, and genetic susceptibilities. Well-designed randomized controlled trials usually are the gold standard to deduce causality, but their use frequently is limited in the field of comorbidities because of practical and ethical considerations.[6] Therefore, a better approach is needed to assess the causal relationships between IPF and comorbidities, thereby understanding the disease cause, providing better care, and ultimately improving clinical outcomes among patients.

Mendelian randomization (MR) is an increasingly used approach that enables reliable causal inferences by exploiting genetic variants as instruments for the exposure.[7] MR by nature is not prone to confounding because genetic variants are assorted randomly at conception and thus are unrelated to environmental factors that usually act as confounders. Furthermore, this method can minimize reverse causation because genetic variants are fixed at birth and are unaffected by the onset and progression of disease. Bidirectional MR is an extension of basic MR in which the exposure-outcome association is investigated from both directions, providing a higher level of evidence for causality.[8] Moreover, the availability of summary statistics from large genome-wide association studies (GWASs) offers a timely opportunity to explore the causal associations between IPF and various comorbidities in a cost-effective manner.[8]

Previous MR studies have examined partial IPF-related comorbidities. Zhang et al[9] found that hypothyroidism is a causal risk factor of IPF that in turn does not affect hypothyroidism causally. Fadista et al[10] showed that IPF may have a causal role in increasing the risk of severe COVID-19, albeit with high uncertainty. A preprint suggested a causal effect of GERD on IPF, but no effect in the opposite direction.[11] However, most IPF-related comorbidities have not yet been assessed using the MR approach, especially in a unified bidirectional framework. Herein, leveraging the largest available GWAS data, we performed a systematic bidirectional MR study to dissect the causal relationships between IPF and a wide range of possible comorbidities proposed by epidemiologic studies.

Study Design and Methods

Study Design

An overview of the study design is illustrated in Figure 1. The present study consisted of four parts. First, we identified possible IPF-related comorbidities by a literature search in PubMed. Second, we investigated the bidirectional causal relationships between IPF and comorbidities for which data are available using the MR method. Third, we evaluated the credibility of findings based on the strength of associations, fitness of MR assumptions, and consistency of effect

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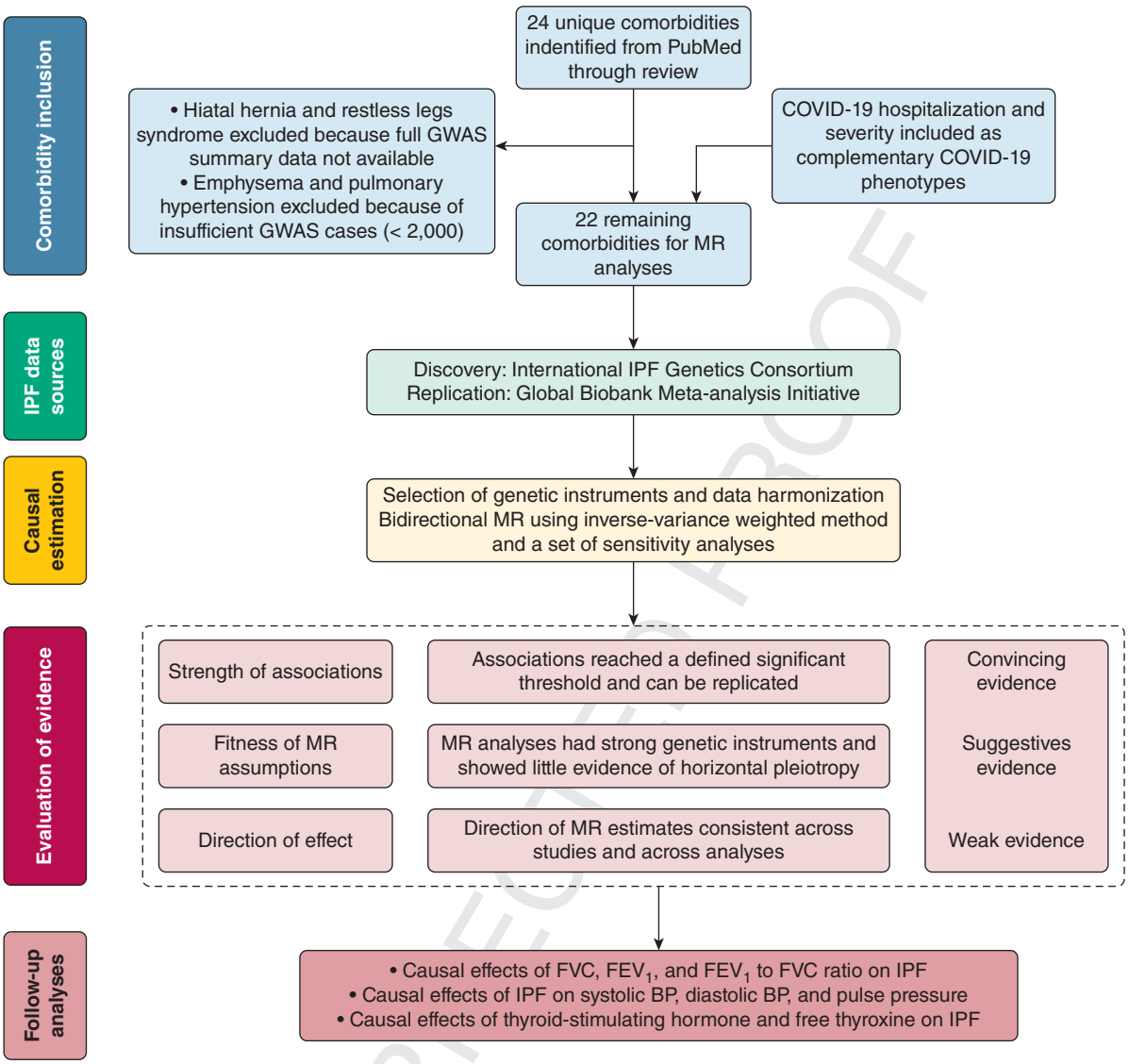

Figure 1 – *Flow diagram showing an overview of the study design. IPF = idiopathic pulmonary fibrosis; IVW = inverse-variance weighted; MR = Mendelian randomization.*

directions. Finally, follow-up analyses using secondary phenotypes were conducted to strengthen the evidence. Reporting and analytic process followed the Strengthening the Reporting of Observational Studies in Epidemiology Statement using MR guidelines.[12] This study relied only on de-identified summary statistics from published GWASs; ethical approval and informed consent were obtained in all original studies.

Selection of Comorbidities

We performed a literature search in the PubMed database to identify IPF-related comorbidities on November 1, 2022. The specific search terms and strategy are detailed in e-Table 1. Results were restricted to English language articles. The initial electronic search was supplemented by a manual review of the reference lists of all relevant articles. Studies looking into IPF either as an exposure or as an outcome were included. We identified 24 unique comorbidities in total. After searching the GWAS summary statistics through the GWAS catalog[13] and MRC-IEU OpenGWAS project,[14] four comorbidities were excluded because the full GWAS summary statistics were not available or GWAS summary statistics included fewer than 2,000 cases. For COVID-19, we tested three different phenotypes for comprehensive assessment, including COVID-19 susceptibility, hospitalization, and severity. Eventually, 22 comorbidities were included for MR analyses (Table 1).

Data Sources for IPF

The GWAS summary statistics for IPF were derived from a meta-analysis of five studies (United Kingdom, Chicago, Colorado, UUS, and Genentech Study) by the International IPF Genetics Consortium (4,125 patients and 20,464 control participants).[15] For replication, we extracted summary statistics for IPF from the Global Biobank Meta-analysis Initiative (GBMI; 6,257 patients and 947,616 control participants), which comprises nine biobanks (BioVU, Colorado Center for Personalized Medicine, Estonian Biobank, FinnGen, HUNT Study, Michigan Genomics Initiative, Mass General Brigham, UCLA Precision Health Biobank, and UK Biobank).[16] Note that both the International IPF Genetics Consortium and GBMI included

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TABLE 1] Characteristics of the GWASs on Comorbidities Used for Analyses

Comorbidity	Data Source	PubMed Identification	No. of Patients	No. of Control Participants	Data as Exposure, Outcome, or Both[a]
COPD	Sakornsakolpat et al (2019)	30804561	35,735	222,076	Exposure
	FinnGen-R5		6,915	186,723	Outcome
Lung cancer	McKay et al (2017) ILCCO and LC3	28604730	29,266	56,450	Exposure
	Wang et al (2014) ILCCO	24880342	11,348	15,861	Outcome
OSA	Strausz et al (2021)	33243845	16,761	201,194	Both
COVID-19	COVID-19 HGI-R7	32404885	122,616	2,475,240	Both
Hospitalized COVID-19	COVID-19 HGI-R7	32404885	32,519	2,062,805	Both
Very severe respiratory-confirmed COVID-19	COVID-19 HGI-R7	32404885	13,769	1,072,442	Both
Pulmonary embolism	FinnGen-R5		4,185	214,228	Both
Hypertension	FinnGen-R5		55,917	162,837	Both
Coronary artery disease	Harst et al (2018) CARDIoGRAMplusC4D	29212778	122,733	424,528	Both
Stroke	Malik et al (2018) MEGASTROKE Consortium	29531354	40,585	406,111	Both
Atrial fibrillation	Nielsen et al (2018)	30061737	60,620	970,216	Both
Heart failure	Shah et al (2020) HERMES Consortium	31919418	47,309	930,014	Both
VTE	Lindström et al (2019) INVENT Consortium	31420334	30,234	172,122	Exposure
	FinnGen-R5		9,176	209,616	Outcome
Type 2 diabetes	Mahajan et al (2022) DIAGRAM Consortium	35551307	80,154	853,816	Both
Hyperlipidemia	FinnGen-R5		4,535	197,259	Both
Hypothyroidism	FinnGen-R5		26,342	59,827	Both
Gastroesophageal reflux disease	Ong et al (2022)	34187846	129,080	473,524	Both
Major depressive disorder	Howard et al (2019) PGC	30718901	246,363	561,190	Exposure
	Howard et al (2019) PGC	30718901	170,756	329,443	Outcome
Anxiety disorders	Otowa et al (2016) PGC	26754954	7,016	14,745	Both
Osteoporosis	FinnGen-R5		3,203	209,575	Both
Fractures	Morris et al (2019)	30598549	53,184	373,611	Both
Muscle weakness	Jones et al (2021) CHARGE Consortium	33510174	48,596	207,927	Both

CARDIoGRAMplusC4D = Coronary Artery Disease Genome Wide Replication and Meta-analysis plus the Coronary Artery Disease Genetics; CHARGE = Cohorts for Heart and Aging Research in Genomic Epidemiology; DIAGRAM = Diabetes Genetics Replication and Meta-analysis; GWAS = genome-wide association study; HERMES = Heart Failure Molecular Epidemiology for Therapeutic Targets; HGI = Host Genetics Initiative; INVENT = International Network Against Venous Thrombosis; LC3 = Cancer Cohort Consortium; ILCCO = International Lung Cancer Consortium; PGC = Psychiatric Genomic Consortium.

[a]We extracted genetic instruments for comorbidities from the largest GWASs to examine the causal effect of comorbidities on idiopathic pulmonary fibrosis. For comorbidities in which the largest full summary statistics were inaccessible, we used available full summary statistics for comorbidities with relatively small sample size to assess the causal effect of idiopathic pulmonary fibrosis on comorbidities.

the UK Biobank, which means that the GBMI may not be an entirely independent dataset. Among all studies, participants were of European ancestry. Patients with IPF were diagnosed clinically using American Thoracic Society/European Respiratory Society guidelines in the International IPF Genetics Consortium and were ascertained using International Classification of Diseases codes in the GBMI.

Data Sources for Comorbidities

We retrieved the GWAS summary statistics for 22 comorbidities generated by the largest studies to date with participants of European ancestry while ensuring minimum sample overlap with IPF studies (Table 1). For some of the comorbidities, GWAS summary statistics were derived from the FinnGen, where the

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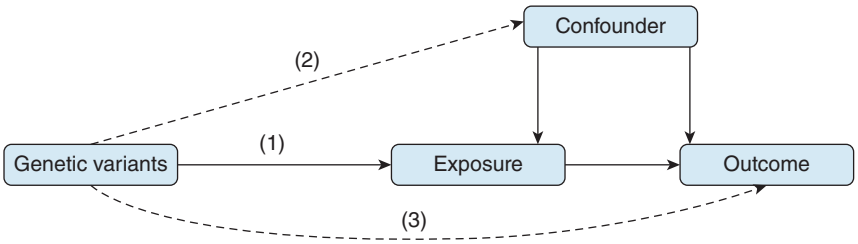

Figure 2 – *Diagram showing the Mendelian randomization model and the three key assumptions: genetic variants (1) are strongly associated with the exposure (relevance assumption), (2) are independent of confounders (independence assumption), and (3) affect the outcome through the exposure of interest only (exclusion restriction assumption, also known as the no pleiotropy).*

Finnish population has a different population structure to the central European population. The population differences may affect the power of the MR analysis. We therefore performed an additional analysis using GWAS summary statistics from the Neale laboratory analysis of the UK Biobank to test the robustness of our results.

Instrument Selection and Data Harmonization

To select genetic instruments for IPF and each studied comorbidity, genome-wide significant ($P < 5 \times 10^{-8}$) single-nucleotide polymorphisms (SNPs) were clumped by linkage disequilibrium ($r^2 < 0.001$ within 10,000-kB clumping distance) using the EUR reference panel of the 1000 Genome Project. Instrumental SNPs for the exposure absent in the outcome datasets were proxied using SNPs in high linkage disequilibrium ($r^2 > 0.8$), where possible. All SNPs were harmonized between the exposure and the outcome by alleles to ensure the alignment of effect. Characteristics of SNPs used as genetic instruments are given in e-Table 2.

Statistical Analysis

For the primary analysis, we calculated the Wald ratio for each tested SNP and combined them using the inverse-variance weighted (IVW) method to obtain the overall estimates.[17] The IVW method provides the most precise and robust estimates when three pivotal assumptions regarding instrumental variables are satisfied (Fig 2).[18] How the three MR assumptions were tested is detailed in e-Appendix 1.

All statistical analyses were performed using the TwoSampleMR,[14] MVMR,[19] and MRPRESSO[20] packages in R version 3.6.3 software (R Foundation for Statistical Computing). Statistical power for MR analyses was estimated using the mRnd webtool.[21] To address multiple testing, a conservative Bonferroni-corrected threshold ($P < 1.11 \times 10^{-3}$, because 22 comorbidities were evaluated for bidirectional analyses) was adopted. Follow-up analyses and evaluation of MR evidence are detailed in e-Appendix 2, with additional data information in e-Table 3.

Results

Instrument Statistics and Statistical Power

For the bidirectional MR analysis of the relationships between IPF and 22 comorbidities, the number of SNPs used as genetic instruments ranged from 1 (anxiety disorders) to 187 (type 2 diabetes), explaining 0.04% to 2.66% of the phenotypic variance. *F* statistics for all diseases are > 30, suggesting the good strength of genetic instruments (e-Table 4). Power calculation results are presented in e-Table 5. Generally, 84% and 64% of the tested associations have sufficient statistical power (> 80%) to detect a moderate effect (OR, ≥ 1.10 or ≤ 0.91) and a weak effect (OR, ≥ 1.05 or ≤ 0.95), respectively.

Comorbidities Showing Convincing Evidence

Among the 22 tested comorbidities, COPD and GERD were the only two that showed reliable evidence for their associations with IPF (Fig 3). Genetic liability to COPD was associated with a decreased risk of IPF (International IPF Genetics Consortium: $P = 2.45 \times 10^{-4}$, IVW method; GBMI: $P = 0.048$, IVW method), whereas genetic liability to GERD was associated with a higher risk of IPF (International IPF Genetics Consortium: $P = 8.12 \times 10^{-3}$, IVW method; GBMI: $P = 9.80 \times 10^{-4}$, IVW method). The direction is consistent across sensitivity analyses, including pleiotropy-robust methods, multivariate MR with adjustment for smoking initiation, Steiger filtering controlling for possible reverse causation, and the analysis using the UK Biobank data (e-Tables 6-9).

Comorbidities Showing Suggestive Evidence

Evidence suggestive of supporting that genetic liability to VTE (International IPF Genetics Consortium: $P = .033$, MR pleiotropy residual sum and outlier [PRESSO] method; GBMI: $P = .020$, IVW method) and hypothyroidism (International IPF Genetics Consortium: $P = .040$, MR PRESSO method; GBMI: $P = .002$, IVW method) could lead to IPF was found (Fig 3). In the reverse direction, genetic liability to IPF presented a suggestive detrimental effect on lung cancer (International IPF Genetics Consortium: $P = .034$, weighted median; GBMI: $P = 1.84 \times 10^{-7}$, IVW method) and a suggestive protect effect on hypertension (International IPF Genetics Consortium: $P = .046$, IVW method; GBMI: $P = .007$, IVW method) (Fig 4). The less significant associations observed in the International IPF Genetics Consortium than GBMI may be the results of smaller sample size. Sensitivity analyses did not change the pattern of the primary findings (e-Tables 6-9).

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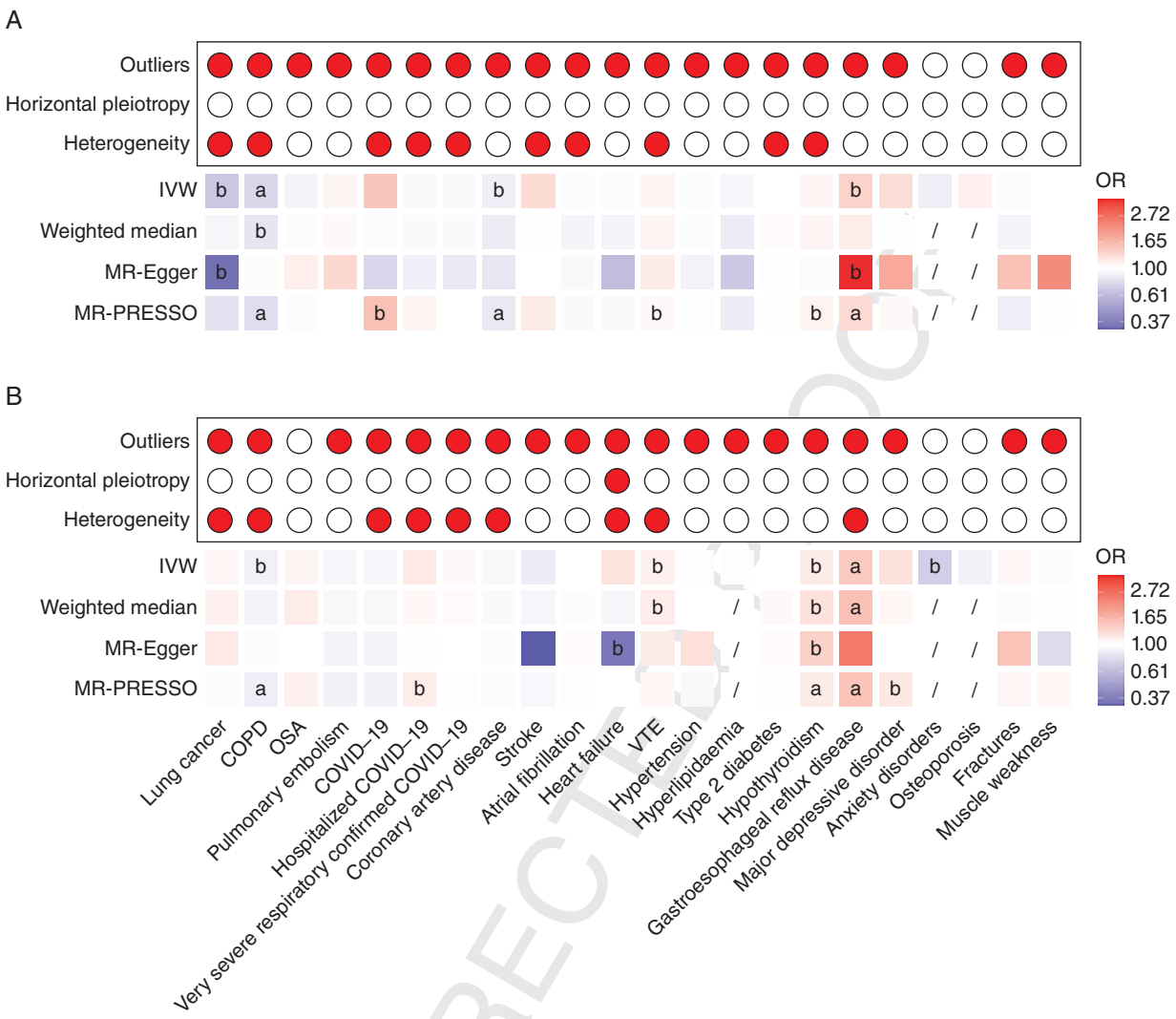

Figure 3 – *A, B, MR estimates of the associations between genetic liability to 22 comorbidities and idiopathic pulmonary fibrosis (IPF) using the summary statistics for IPF from the International IPF Genetics Consortium (A) and the Global Biobank Meta-analysis Initiative (GBMI) (B). Red dots denote the presence of outliers, horizontal pleiotropy, or heterogeneity; red boxes indicate positive associations; blue boxes indicate negative associations; and slashes mean that MR estimates of specific sensitivity analyses cannot be computed because of the insufficient number of single-nucleotide polymorphisms.* [a]*P values of MR estimates passed the Bonferroni-corrected threshold ($P < 1.1 \times 10^{-3}$).* [b]*P values of MR estimates were between the Bonferroni-corrected threshold and 0.05. IVW = inverse-variance weighted; MR = Mendelian randomization; PRESSO = pleiotropy residual sum and outlier.*

Comorbidities Showing Weak Evidence

The remaining comorbidities showed weak evidence for associations with IPF in both directions because of insufficient strength of associations, presence of horizontal pleiotropy, or inconsistency in direction of effect across analyses. We noted apparent horizontal pleiotropy in the associations of genetic liability to IPF with COVID-19 hospitalization and severe. The leave-one-out analysis and MR-PRESSO outlier test detected genetic variants at the *MUC5B* locus as extreme outliers, where the risk allele has a different protective effect compared with all other IPF-related variants (e-Figs 1, 2). The MR-PRESSO method correcting for these outliers yielded a possible effect of genetic liability to IPF on increasing the risk of both COVID-19 hospitalization (GBMI: $P = .009$, MR-PRESSO method) and severe COVID-19 (International IPF Genetics Consortium: $P = 0.001$, MR-PRESSO method).

Follow-up Analyses of Principal Findings

As shown in Figure 5, genetically predicted lower FEV_1 and FEV_1 to FVC ratio, but not FVC, were associated with a reduced risk of IPF, providing additional evidence to support the protective role of COPD in the cause of

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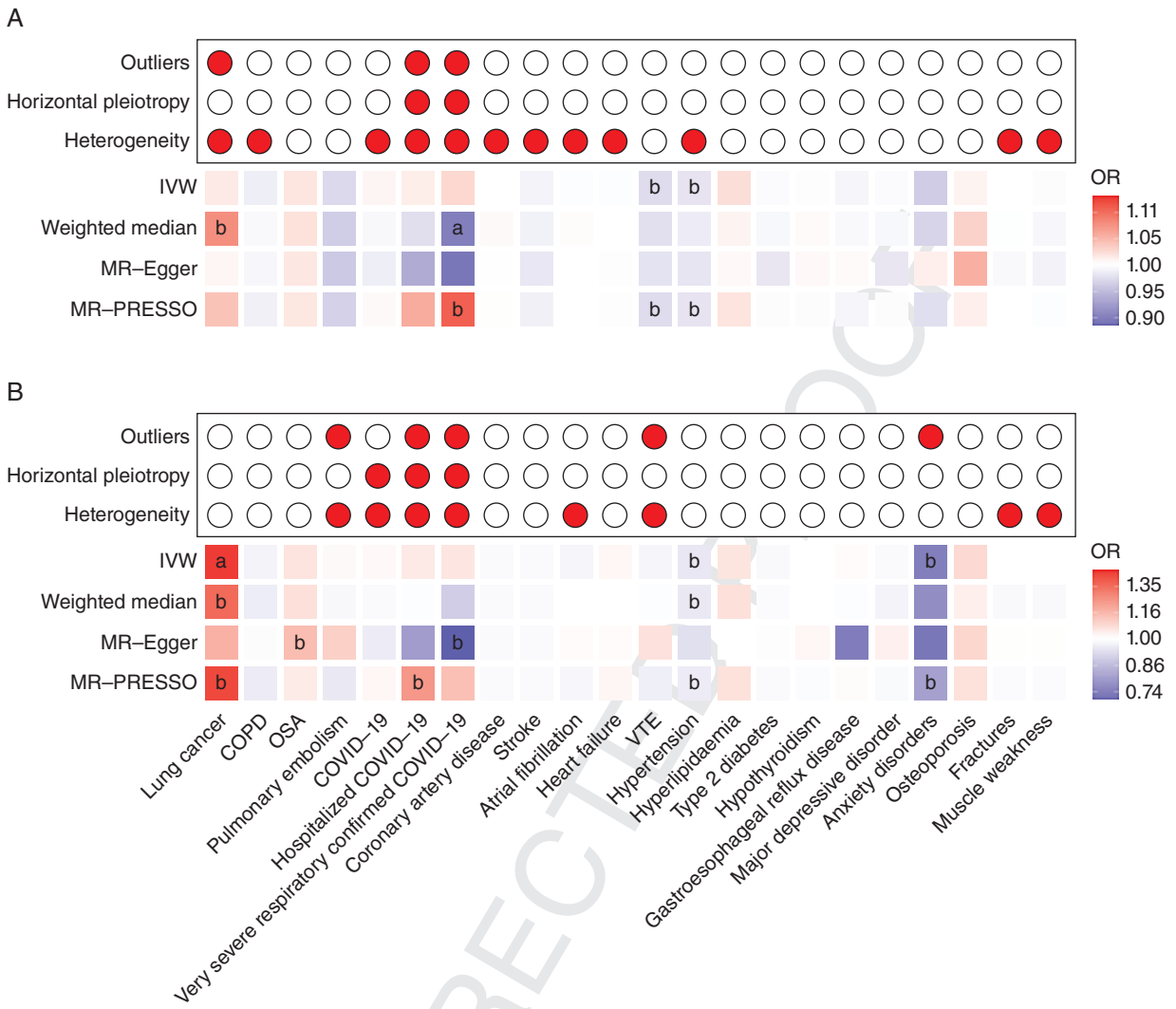

Figure 4 – *A, B, MR estimates of the associations between genetic liability to idiopathic pulmonary fibrosis (IPF) and 22 comorbidities using the summary statistics for IPF from the International IPF Genetics Consortium (A) and the Global Biobank Meta-analysis Initiative (B). Red dots denote the presence of outliers, horizontal pleiotropy, or heterogeneity; red boxes indicate positive associations; and blue boxes negative associations.* [a]*P values of MR estimates passed the Bonferroni-corrected threshold* ($P < 1.1 \times 10^{-3}$). [b]*P values of MR estimates were between the Bonferroni-corrected threshold and 0.05. IVW = inverse variance weighted; MR = Mendelian randomization; PRESSO = pleiotropy residual sum and outlier.*

IPF. Consistent with the protective effect on hypertension, our follow-up analyses showed negative associations of genetic liability to IPF with systolic BP, diastolic BP, and pulse pressure after controlling for potential outliers. Although a suggestive association between hypothyroidism and IPF was observed in the primary analysis, we detected limited evidence to support the effects of thyroid-stimulating hormone and free thyroxine (e-Table 10).

Discussion

In this MR study, we comprehensively evaluated the bidirectional causal associations between IPF and 22 comorbidities. Using multiple MR methods and large-scale genetic data from different sources, we found convincing evidence that COPD was associated causally with a lower risk of IPF, whereas GERD was associated causally with a higher risk of IPF. In addition, evidence was suggestive of favoring the causal roles of VTE and hypothyroidism in increasing IPF risk as well as the causal roles of IPF in increasing lung cancer risk, but decreasing hypertension risk. The remaining 16 considered comorbidities presented weak evidence to support a causal association with IPF in both directions. A summary of the main MR findings is presented in Figure 6.

GERD has been presumed to be an external factor predisposing patients to IPF because of its resultant

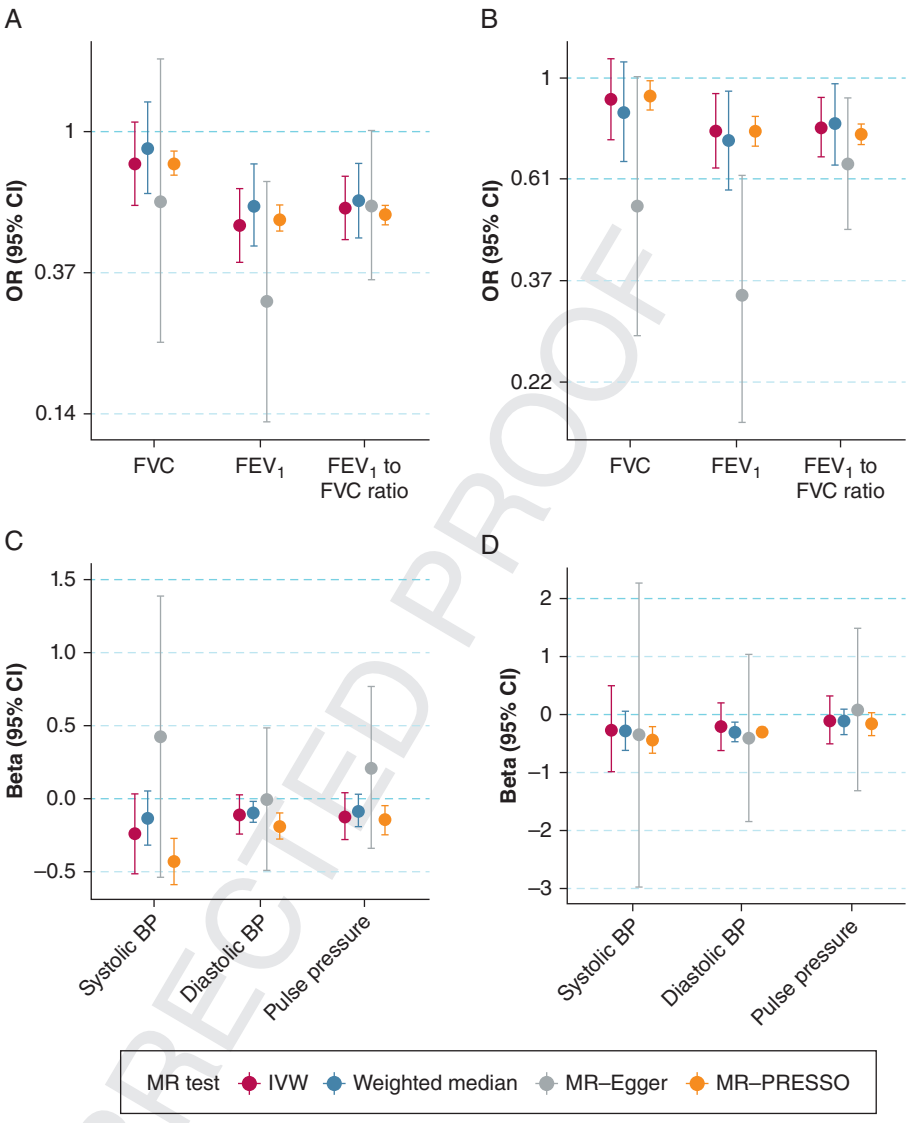

Figure 5 – *A-D, Graphs showing results of follow-up analyses. A, B, MR estimates (expressed as OR) of the associations of genetically predicted lower FVC, FEV_1, and FEV_1 to FVC ratio with idiopathic pulmonary fibrosis (IPF) using the summary statistics for IPF from the International IPF Genetics Consortium (A) and the Global Biobank Meta-analysis Initiative (GBMI) (B). C, D, MR estimates (expressed as β) of the associations of genetic liability to IPF with systolic BP, diastolic BP, and pulse pressure using the summary statistics for IPF from the International IPF Genetics Consortium (C) and the GBMI (D). IVW = inverse-variance weighted; MR = Mendelian randomization; PRESSO = pleiotropy residual sum and outlier.*

microaspiration.[3] However, whether GERD and IPF are causally related remains controversial. A systematic review confirmed a higher prevalence of GERD in patients with IPF compared with the general population, but concluded that a causal relationship cannot be demonstrated after evaluating evidence from 14 studies.[22] Similarly, a subsequent meta-analysis of 18 case-control studies indicated that the observed association between GERD and IPF is likely to be confounded by smoking.[23] The debate extended further to the role of antireflux and antacid therapy. Some studies showed that antacid treatment was associated with a slower decline in lung function and a longer survival time in IPF,[24,25] whereas two more recent meta-analyses suggested inconclusive evidence for the beneficial effects of pharmacologic GERD treatment on IPF.[26,27] Corroborating a preprint,[11] our MR study supported a causal effect of GERD on increasing IPF risk, which was unchanged in the multivariable MR analysis conditioning for smoking. This finding may have important clinical implications for renewing the interest in GERD as a potential therapeutic target for IPF.

Intriguingly, our MR study found evidence that COPD seems to confer protection against IPF, which contradicts the observational findings for the coexistence of COPD or emphysema and IPF. Follow-up analyses of lung function suggested that a decreased FEV_1 to FVC ratio resulting from a decrease in the magnitude of FEV_1 as compared with FVC accounted for the protective effect of COPD. The negative association between IPF and COPD or lung function can be explained by their distinct genetic architecture. A previous GWAS identified signals near *DSP*, *FAM13A*, *ZKSCAN1*, and

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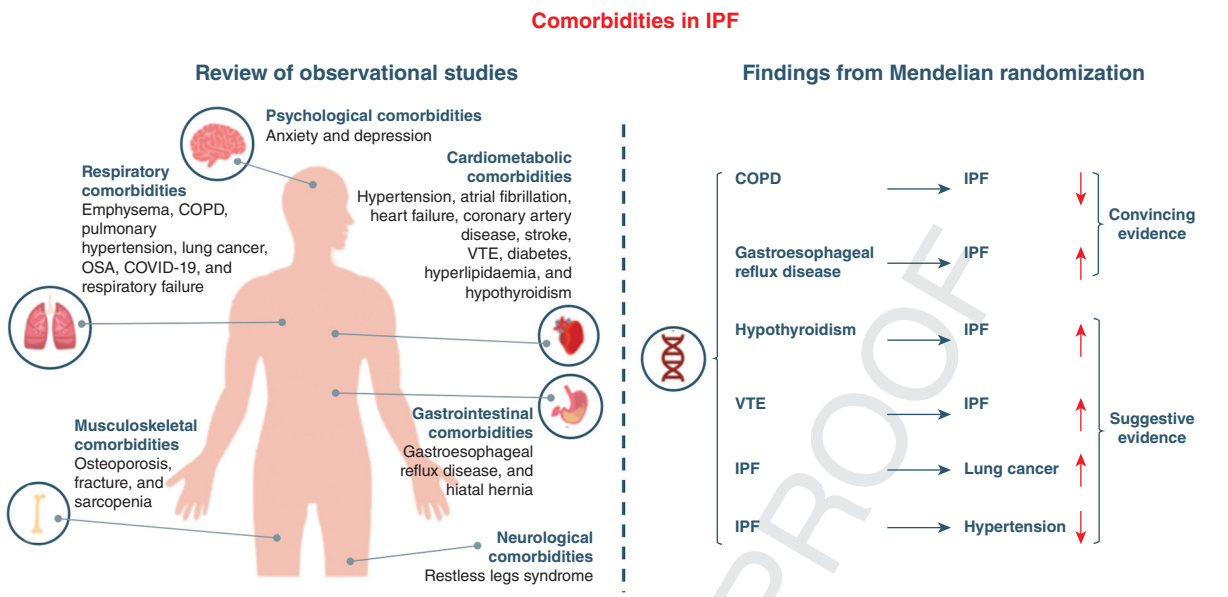

Figure 6 – *Causal atlas of comorbidities in IPF. Left-hand side refers to IPF-related comorbidities identified from observational studies. Right-hand side refers to the causal associations between IPF and six comorbidities shown in the present Mendelian randomization study. IPF = idiopathic pulmonary fibrosis.*

MAPT for both IPF and COPD, but the alleles showed apparent opposite effects (ie, the risk alleles of COPD being associated with a decreased risk of IPF).[28] Moreover, only about 3% of the identified lung function loci were reported to be associated with IPF susceptibility, pointing to more IPF-specific pathways outside of general lung health.[28] However, diagnoses of IPF (a restrictive lung disease) and COPD (an obstructive lung disease) are mutually exclusive. In practice, a substantial number of patients have overlapping emphysema and fibrosis, but would not meet UIP or IPF criteria. It is possible that the protective effect of COPD on IPF could reflect protection from an IPF disease label, rather than actual protection from lung fibrosis developing.

We also detected a protective effect of IPF on hypertension and BP phenotypes. A similar trend was observed in most other studied cardiovascular diseases. These results were opposed to those from observational studies,[29,30] but implied a potentially different genetic cause between IPF and cardiovascular diseases that needs further investigation. In contrast, VTE exhibited a positive causal association with IPF in this study. Multiple observational studies have implicated the coexistence of VTE and IPF, but the issue of which disorder comes first remains inconclusive.[31-33] Our bidirectional MR analysis suggested that VTE is more likely to be a cause, rather than a consequence, of IPF progression. The exact mechanisms by which VTE contributes to IPF are unknown, but it is plausible that thrombin, a core enzyme involved in blood coagulation, plays a role in the cause of IPF.[34]

IPF has been established as a strong risk factor for lung cancer. Previous studies have reported that patients with IPF have a sevenfold higher risk of lung cancer compared with the general population, and the annual risk of lung cancer seems to increase over time after IPF diagnosis.[35,36] Our MR study strengthened the evidence for a causal effect of IPF on lung cancer. Common pathogenic mechanisms include accumulation of carcinogens resulting from lymphatic obstruction, fibrosis-related cytokines and growth factors, and shared genetic and epigenetic alterations.[37,38]

Hypothyroidism is a recently proposed comorbidity in IPF. A case-control study and an MR study consistently revealed that hypothyroidism was associated with a higher risk of IPF, even after controlling for other comorbidities.[9,39] In this MR study, we validated the findings of hypothyroidism using two IPF datasets. However, follow-up analyses provided little evidence to support the causal effects of thyroid-stimulating hormone and free thyroxine. This result is in line with an early case-control study showing that hypothyroidism, but not thyroid-stimulating hormone itself, predict mortality in IPF.[39] We speculated that

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thyroid function-independent pathways (eg, immune dysregulation) could play a role in the association between hypothyroidism and IPF. In a gene expression analysis, polymorphisms in *CTLA-4*, *ICOS*, and *CD28* (associated with autoimmune thyroid disease and thyroid autoantibody production) predicted poor outcomes in patients with IPF.[40]

Pulmonary fibrosis has been linked to COVID-19 because of their shared risk factors such as older age, male sex, and comorbidities.[41,42] A MR study demonstrated that IPF has no causal effect on COVID-19 severity, but this association was statistically significant when removing a genetic variant at *MUC5B*,[10] which agrees with our MR results. *MUC5B* is the strongest genetic determinant of IPF.[28] However, its risk allele seems to protect against COVID-19 severity, which may be explained by the protective effect of mucin overproduction on the airways or selection bias.[43,44] Overall, a causal relationship between IPF and COVID-19 severity cannot be determined in our MR study. The remaining comorbidities also showed no reliable evidence to support their causal associations with IPF.

The most notable strength of this study is the ability of MR design to improve the causal inference, especially in the context of studying rare diseases (eg, IPF) where prospective cohort studies are always difficult to perform because of the inability to collect large samples. Another strength is the use of two large datasets for IPF, which greatly enhanced the reliability of the causal atlas on comorbidities in IPF.

Our study also has several limitations. First, estimates from MR studies may not be compatible with those from observational or interventional studies, which is even greater when testing binary exposures (eg, IPF).[45] Nevertheless, MR remains a robust method to test the causal null hypothesis. Therefore, the main purpose of this study was to investigate whether a causal relationship exists, rather than to calculate causal estimates. Second, although the largest summary statistics were collected, only a very limited number of SNPs are available as genetic instruments for some diseases (eg, anxiety disorders), which results in low statistical power. Further MR studies are warranted to validate these associations when more robust genetic instruments are available. Third, horizontal pleiotropy is a major concern for the reliability of MR results. Nonetheless, the likelihood of this bias is reduced because consistent estimates were observed across multiple MR methods, which have different assumptions. Furthermore, the MR-Egger regression test showed no clear directional pleiotropy for most tested associations. Fourth, the data for certain comorbidities were obtained from the FinnGen and UK Biobank, which are also included in the GBMI or International IPF Genetics Consortium control data, leading to potential bias because of sample overlap. Nevertheless, we believe this has little impact on the interpretation of our results because two-sample MR methods, except for MR-Egger, can be used safely when overlapping samples are from large biobanks (eg, FinnGen and UK Biobank in our study),[46] and the robust strength of our instruments (ie, *F* statistics much larger than 10) likely minimized bias from sample overlap.[47] Finally, because the study participants from GWASs were predominately of European ancestry, our results should not be generalized directly to other ethnicities.

Interpretation

The current bidirectional MR analysis supports the causal associations between IPF and certain comorbidities from a genetic perspective. A deeper understanding of the pathways underlying these diverse associations would be worthwhile, with implications in terms of optimal prevention and treatment strategies for comorbidities.

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Financial/Nonfinancial Disclosures

None declared. Q11

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Additional information: The e-Appendixes, e-Figures, and e-Tables are available online under "Supplemental Data."

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