Causal association between cigarette smoking and the prevalence of preserved ratio impaired spirometry (PRISm), and the progression risk factors of PRISm: A study based on Mendelian randomization and meta-analysis

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ABSTRACT

INTRODUCTION Preserved ratio impaired spirometry (PRISm) is a new and variable phenotype of spirometry impairment that was first defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2023. The identification of high-risk factors for the progression from PRISm to COPD remains insufficient at present.

METHODS Mendelian randomization (MR) analysis was conducted using genome-wide association study (GWAS) summary statistics. Genetic instruments for smoking behavior were derived from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) (n=607291), while PRISm case-control data were sourced from the UK Biobank (n=296282). The inverse-variance weighted (IVW) method served as the primary analytical approach, supplemented by heterogeneity assessment, pleiotropy evaluation, and sensitivity analyses. For the meta-analysis, PubMed, Embase, Cochrane Library, and Web of Science were systematically searched from inception to 31 December 2024, to identify relevant studies that followed up on the changes in spirometry among individuals with PRISm or studies that reported the possible factors related to the changes in spirometry among individuals with PRISm. The risk of bias and the quality of the included studies were assessed using the Newcastle–Ottawa Scale (NOS).

RESULTS The MR analysis identified 85 SNPs as genetic instruments, revealing a modest causal link between cigarette smoking and PRISm prevalence (IVW: OR=1.01–1.02, p=0.048). The meta-analysis of 14 studies (n=7336 PRISm cases) shows 20.8% (95% CI: 15.6–25.9) progress to COPD at follow-up, with no significant difference by follow-up duration (<5 vs ≥5 years). Persistent PRISm occurs in 41.5% (95% CI: 35.8–47.2), more frequently in long-term follow-up subgroups. Baseline 'chest distress/dyspnea' (OR=3.81; 95% CI: 1.47–9.84) and 'current smoking' (OR=2.18; 95% CI: 1.14–4.15) significantly predict progression, while respiratory symptoms, FEV_1/FVC ratio, TLC%, and FVC% show no association.

CONCLUSIONS Our findings suggest a modest causal link between cigarette smoking and PRISm prevalence. The progression of PRISm to COPD within 5 years is approximately 20.8%. Among individuals with PRISm at the first visit, 'chest distress or dyspnea' and 'current smoking' are potential clinical risk factors for the progression of PRISm to COPD.

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KEYWORDS

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is recognized as a heterogeneous lung condition and is characterized by a series of chronic respiratory symptoms, such as dyspnea, cough, expectoration and/or exacerbations, COPD occurs to abnormalities of the airways and/or alveoli that cause persistent, often progressive, airflow obstruction[1]. It is one of the leading causes of mortality worldwide[2]. Currently, the gold standard for the diagnosis of COPD is postbronchodilator forced expiratory volume in 1s (FEV_1)/forced vital capacity (FVC) <70%. Some individuals have chronic respiratory symptoms but do not exhibit air flow limitations. These individuals are considered to have 'pre-COPD'. Preserved ratio impaired spirometry (PRISm) is a crucial subtype of pre-COPD that is defined as the presence of a preserved FEV_1/FVC ratio (≥70%, after the use of a bronchodilator) as well as impaired spirometry (FEV_1 <80% of the reference after the use of a bronchodilator)[3].

PRISm is a new phenotype of spirometry impairment that was first defined by GOLD in 2023. PRISm increases the risks of multiple adverse outcomes, such as cardiovascular disease, heart failure, diabetes, cerebrovascular diseases, and all-cause mortality[4-6]. PRISm exhibits different clinical features and variable prognostic developments[7]. Approximately half of all individuals with PRISm have several kinds of respiratory symptoms at baseline[8]. However, these respiratory symptoms vary. Some individuals with PRISm maintain their status during follow-up for several years; several individuals exhibit a change to normal spirometry status during follow-up; and other individuals develop COPD. Tobacco smoking, a well-established pathogenic factor in respiratory diseases, has been implicated by multiple large-scale cohort studies as a critical environmental determinant in the development and progression of PRISm. Current evidence suggests smoking likely promotes PRISm pathogenesis through multiple interconnected mechanisms, including: 1) sustained inflammatory responses, 2) protease-antiprotease imbalance, 3) oxidative stress pathways; and 4) small airway remodeling processes[9-11]. However, current clinical guidelines lack consensus regarding the prediction of PRISm progression or therapeutic strategies, and there remains a notable paucity of genetic-level investigations into these clinical outcomes[12].

In this study, from the perspectives of genetics and genes, we aimed to verify the potential causal effects of smoking and PRISm within the context of a MR analysis. Additionally, through a systematic review and meta-analysis, we aimed to identify clinical risk factors for the progression of PRISm to COPD.

METHODS

Two-sample Mendelian randomization for the causal effect of smoking and the prevalence of PRISm

The causal effect of smoking and the prevalence of PRISm was verified by a two-sample Mendelian randomization (2SMR) framework utilizing summary-level data from genome-wide association studies (GWAS). The MR analysis adhered to three fundamental assumptions: 1) strong association between instrumental variables (IVs) and the exposure (F-statistic >10); 2) independence of IVs from known confounders (MR-Egger intercept test p>0.05); and 3) exclusion of horizontal pleiotropic pathways (validated through weighted median and MR-PRESSO methods)[13]. In this study, smoking status was operationalized as the exposure variable, with PRISm designated as the outcome variable. The analytical framework adhered to MR assumptions (linearity, independence, and exclusion restriction).

GWAS data selection

Genetic data for smoking status were obtained from the GWAS & Sequencing Consortium of Alcohol and Nicotine Use (GSCAN) 2019 study (n=607291 individuals of European ancestry, accession: ieu-b-4877, PMID: 30643251). PRISm genetic data were derived from the 2022 UK Biobank GWAS (n=296282, accession: ieu-b-5112), employing spirometry-defined cases (FEV_1/FVC ≥0.7 with FEV_1 <80% predicted) and controls (FEV_1/FVC ≥0.7 with FEV_1 ≥80% predicted).

IVs selection

In our PRISm analysis, we rigorously processed the summary statistics by first extracting instrumental variables (IVs) with their β coefficients and standard errors, then excluding all outcome-associated SNPs

reaching genome-wide significance ($p<5\times10^{-8}$) to satisfy the exclusion assumption, followed by harmonizing effect alleles across datasets and removing SNPs in high linkage disequilibrium (LD) ($r^2 \geq 0.001$ within 10000 kb windows) or with ambiguous strand orientation.

Software implementation of Mendelian randomization

All statistical analyses were performed using R version 4.4.3 with the TwoSampleMR package (v0.6.14), employing inverse-variance weighted (IVW) regression as the primary analytical method to estimate causal effects through weighted linear regression (weights=$1/se^2$), which provides unbiased estimates under strong instrument assumptions (mean F-statistic >10). To ensure robustness, we supplemented IVW with four additional methods: MR-Egger regression (accounting for directional pleiotropy), weighted median estimator (tolerating ≤50% invalid instruments), simple mode, and weighted mode, with all results reported as odds ratios (ORs) and 95% confidence intervals (CIs). We systematically evaluated heterogeneity using Cochran's Q statistic ($p<0.05$ threshold), assessed potential pleiotropy through MR-Egger intercept tests, and conducted leave-one-out sensitivity analyses to identify influential SNPs, following STROBE-MR guidelines for transparent causal inference reporting.

The systematic review and meta-analysis

Search strategy and eligibility criteria for meta-analysis

The PubMed, Embase, Cochrane Library, and Web of Science databases were searched from inception to 31 December 2024. The search title or abstract were matched with 'preserved ratio impaired spirometry' or 'restrictive spirometry' or 'GOLD-U' or 'GOLD-unclassified' or 'pre-COPD' or 'impaired spirometry' or 'LLN-unclassified' or 'LLN-U'. We also manually searched the references of key articles to identify any additional eligible articles. Studies were selected if they met the following inclusion criteria: 1) PRISm was diagnosed by spirometry with FEV_1/FVC ≥70% and FEV_1 <80% of reference; and 2) COPD was diagnosed by spirometry with FEV_1/FVC <70%. Duplicate reports, editorials, correspondences, conference abstracts, commentaries and case reports were excluded. Studies were independently screened by 2 investigators. Disagreements between the investigators were resolved by consensus.

Data extraction and quality assessment for meta-analysis

Two independent researchers (XZ and TC) extracted the data and evaluated the quality of the literature. Disagreements were resolved by consensus among all the investigators. The following data were extracted from each included study: first author, publishing institution, publication time, total number of individuals with PRISm at the first visit, individuals who progressed to COPD or individuals with persistent PRISm at the second visit, follow-up time, smoking history, clinical manifestation, BMI, and spirometry information at the first visit. The risk of bias and the quality of the included studies were assessed independently by two authors (TC and XD) using the Newcastle–Ottawa Scale (NOS), which was designed to assess the risk of bias in observational studies. The NOS consists of 3 sections, namely, selection, comparability, and exposure, with a maximum possible score of 9 points. A total score of 0–3 indicates poor quality, a total score of 4–6 indicates fair quality, and a total score of 7–9 indicates high quality. Discrepancies in total scores were resolved by consultation with all the investigators. The scores of the studies are shown in Supplementary file Table 1.

Statistical analysis

STATA MP17 software was used to calculate the progression rates of individuals with PRISm with corresponding 95% confidence intervals (CIs) for clinical data. Odds ratios (ORs) with 95% CIs for individuals who exhibit progressed PRISm with 'local respiratory syndrome', 'chest distress or dyspnea', 'current smoking', 'increased TLC%', 'lower FVC%', or 'low FEV_1/FVC value' were also calculated by STATA MP17. Cochran's Q test and the I^2 statistic were used to assess heterogeneity among the included studies. The results are explained as follows: when $I^2<50\%$, a fixed effects model was chosen, otherwise, a random effects model was selected. A $p<0.05$ was considered to indicate statistical significance. Publication bias was evaluated by Begg's test and Egger's test.

RESULTS

Results of the MR analysis

Causal estimates of cigarette smoking and the prevalence of PRISm

The comprehensive methodological workflow is shown in Figure 1. After quality control procedures including SNP-exposure association filtering and harmonization of effect alleles (detailed in the Supplementary file), 85 independent SNPs were retained for Mendelian randomization analysis. The primary IVW method demonstrated a positive association (OR=1.014; 95% CI: 1.000–1.103, p=0.048), suggesting a 1.4% increased risk per smoking increment. This finding was directionally consistent with weighted median estimates (OR=1.018; 95% CI: 1.000–1.104, p=0.048) and MR-Egger results (OR=1.115; 95% CI: 1.042–1.192, p=0.002), with the latter showing no evidence of directional pleiotropy (intercept p>0.05). Due to limitations in sample size and instrumental variable strength, the effect estimates (OR<1.2) should be interpreted with caution. Nevertheless, these analyses suggested a modest yet potential causal association, with comprehensive results illustrated in Table 1.

Sensitivity analysis and chart verification

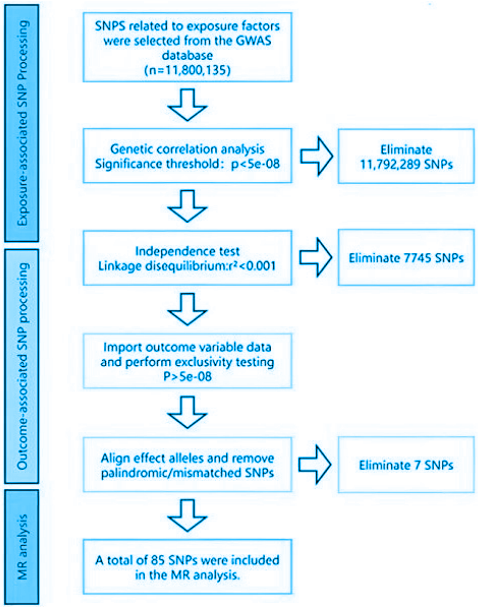
The scatter plot (Supplementary file Figure 1) demonstrated that most SNPs clustered in the first quadrant (positive effects for both exposure and outcome), corroborating the positive causal relationships identified by both IVW and MR-Egger methods. While no obvious outlier SNPs were observed, the slightly steeper slope of the MR-Egger regression line compared to IVW suggested possible pleiotropic effects. The funnel plot (Supplementary file Figure 1B) exhibited approximately symmetrical distribution of effect sizes (β) against precision (1/SE), indicating low heterogeneity among instrumental variables. Leave-one-out sensitivity analysis (Supplementary file Figure 1C) confirmed the robustness of our findings, as the confidence intervals for both IVW and MR-Egger estimates overlapped substantially after sequential exclusion of individual SNPs, demonstrating that no single SNP disproportionately drove the observed associations. In summary, this MR study provides evidence supporting smoking as a potential causal factor for increased PRISm risk, albeit with modest effect sizes.

Systematic review and meta-analysis

Characteristics of the studies and quality assessments enrolled in meta-analysis

The study selection process is illustrated in Figure

Figure 1. Flowchart of Mendelian randomization and meta-analysis. Overview of Mendelian randomization process. Following genetic correlation analysis, independence testing, and removal of palindromic/mismatched variants, a total of 85 eligible SNPs were included in the final analysis



2. Our systematic search across the 4 designated databases initially identified 415 potentially relevant publications. Following removal of 41 duplicate records, we performed title/abstract screening based on predefined eligibility criteria, which led to the exclusion of 85 records for reasons listed in Figure 2. Ultimately, 14 studies involving 7336 individuals were included in our meta-analysis and systematic review[8,12,14-25]. These studies were conducted in Asia (n=4), America (n=4), Europe (n=5), and Latin America (n=1).

Baseline demographic characteristics of the individuals enrolled in meta-analysis

The demographic characteristics and the baseline individual information of the patients included in the selected studies are listed in Table 2. Generally, the mean age of the individuals involved was 57.3 years. The study population included 46.6% males and 47.2% smokers. The follow-up duration, i.e. the time between the first visit and the second visit, ranged from 3 to 25 years. A total of 405133 subjects, including 44093 individuals with PRISm, were registered at the first visit in the 14 included studies. A total of 7336 individuals with PRISm completed the second spirometry follow-up.

Subjects with incident COPD or sustained PRISm phenotype at longitudinal follow-up

Among the individuals with PRISm at the first spirometry visit, 20.8% (95% CI: 15.6–25.9) had progressed to COPD at the second follow-up visit. Next, we divided the 14 included studies into 2 subgroups according to whether the interval between the two follow-up visits was ≥5 years. No significant differences were found between the 2 subgroups

Table 1. Core analytical results from Mendelian randomization on the association between cigarette smoking and preserved ratio impaired spirometry (PRISm)

Method	nSNP	β	SE	p	OR	95% CI
MR Egger	85	0.109	0.034	0.002	1.115	1.042–1.192
Weighted median	85	0.018	0.009	0.048	1.018	1.001–1.104
Inverse variance weighted	85	0.014	0.007	0.048	1.014	1.001–1.103
Simple mode	85	0.015	0.024	0.529	1.015	0.968–1.107
Weighted mode	85	0.027	0.021	0.205	1.028	0.986–1.107

Figure 2. PRISMA flow diagram of the meta-analysis study selection process

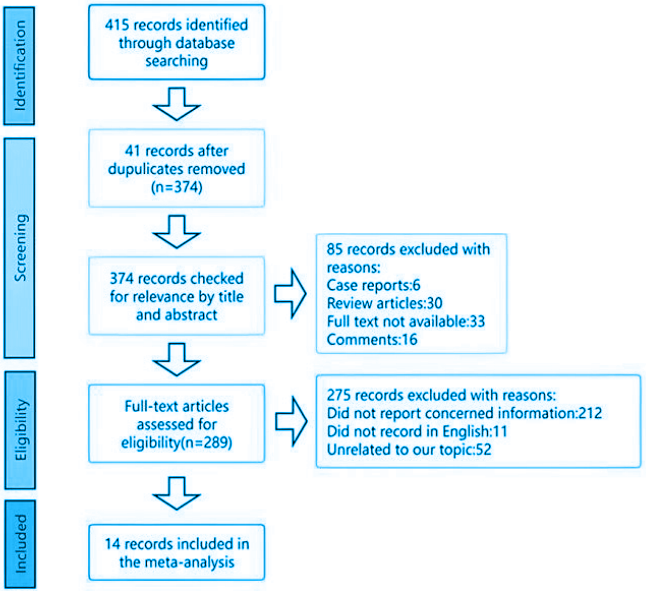
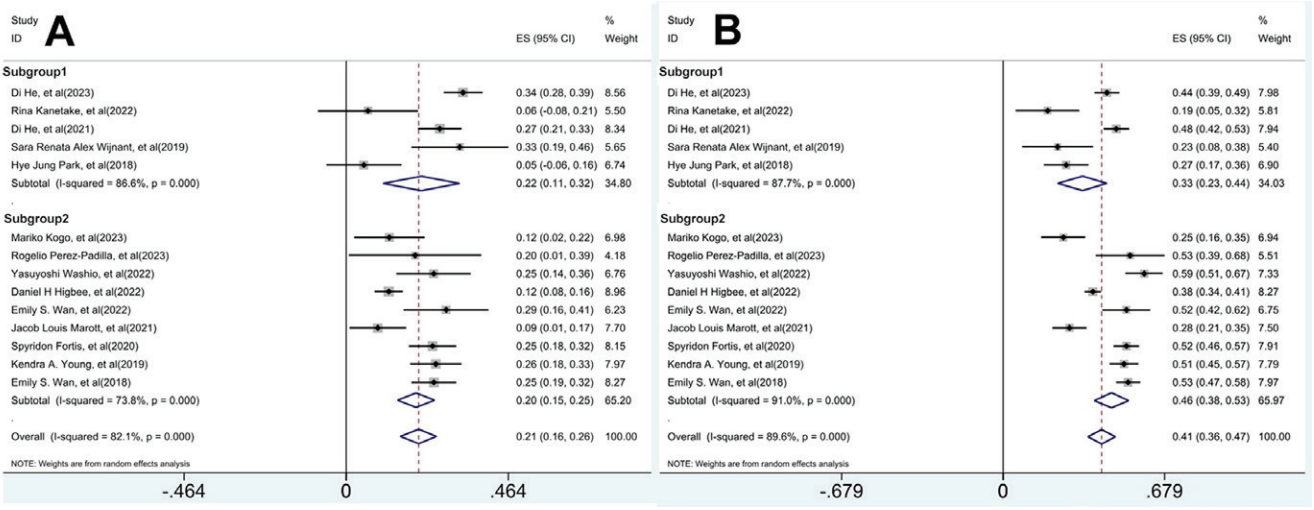


Table 2. Baseline demographic and clinical characteristics of the included studies in the systematic review and meta-analysis on the association between cigarette smoking and preserved ratio impaired spirometry (PRISm)

Study	Number of subjects	Age (years) Mean (SD)	Male n (%)	BMI Mean (SD)	Smoking history n (%)	Normal n (%)	PRISm n (%)	AFL n (%)	Follow-up duration (years)
Kogo et al.[8]	9760	53 (13.0)	3205 (32.8)	22.3 (3.5)	3412 (35.0)	8836 (90.5)	438 (4.5)	486 (5.0)	5
He at al.[16]	5901	65 (9.0)	2662 (45.1)	28.0 (4.9)	3708 (62.8)	3496 (59.2)	817 (13.8)	1588 (26.9)	4
Perez-Padilla et al.[14]	2942	57 (11.0)	1219 (41.4)	28.0 (5.0)	906 (30.8)	2294 (78.0)	146 (5.0)	502 (17.0)	5–9
Kanetake et. al.[17]	1672	56 (9.0)	976 (58.4)	23.6 (3.6)	742 (44.4)	1409 (84.3)	176 (10.5)	87 (5.2)	3
Washio et al.[18]	3032	44 (9.0)	1339 (44.2)	23.3 (3.5)	1352 (44.6)	2208 (72.8)	301 (9.9)	523 (17.2)	5
He et al.[19]	6616	66 (9.0)	3007 (45.5)	27.9 (4.8)	4204 (63.5)	3450 (52.1)	1346 (20.3)	1820 (27.5)	4
Higbee et al.[20]	350074	57 (7.0)	162627 (46.5)	27.3 (4.6)	161378 (46.1)	257643 (73.6)	36839 (10.5)	55592 (15.9)	9
Wan et al.[21]	1775	59 (8.0)	869 (49.0)	28.9 (5.7)	765 (43.1)	884 (49.8)	185 (10.4)	706 (39.8)	5
Marott et al.[12]	1084	32 (6.0)	508 (46.9)	23.1 (3.4)	707 (65.2)	857 (79.1)	227 (20.9)	NA	Approximately 25
Fortis et al.[22]	1131	57 (10.0)	518 (45.8)	31.8 (7.5)	709 (62.7)	0 (0)	1131 (100)	0 (0)	5
Young et al.[23]	2860	60 (8.0)	1496 (52.3)	NA	2860 (100.0)	NA	525 (18.4)	NA	5
Wijnant et al.[24]	5487	69 (9.0)	2418 (44.1)	27.5 (4.0)	3638 (66.3)	4185 (76.3)	387 (7.1)	915 (16.7)	4.5
Park et al.[25]	2666	57 (10.0)	2500 (93.8)	24.1 (4.0)	1418 (53.2)	1666 (62.5)	313 (11.7)	687 (25.8)	3
Wan et al.[15]	10133	60 (8.5)	5410 (53.4)	28.8 (6.0)	5365 (52.9)	4389 (43.3)	1260 (12.4)	4484 (44.3)	5

Figure 3. Forest plots depicting: A) progression of PRISm; and B) persistence of the PRISm ratio during follow-up. Subgroup 1 included the studies with a follow-up duration of <5 years. Subgroup 2 included the studies with a follow-up duration of ≥5 years



(Figure 3A). A total of 41.5% (95% CI: 35.8–47.2) of the individuals with PRISm maintained their PRISm spirometry status at the second follow-up visit. The prevalence of persistent PRISm was higher in the subgroup with a follow-up interval ≥5 years than in the subgroup with a follow-up interval of <5 years (Figure 3B).

Risk factors for the progression of PRISm

Two studies examined 'local respiratory syndrome' (such as cough and/or phlegm production), 4 studies examined 'chest distress' or 'dyspnea', and 9 studies examined 'current smoking' as potential risk factors for progression to PRISm. Among the spirometry indices possibly related to PRISm progression, 4 studies examined the 'FEV_1/FVC value', 2 studies examined the 'increased TLC%', and 3 studies examined the 'FVC%'. 'Local respiratory syndromes' (OR=0.94; 95% CI: 0.57–1.53; p=0.79), 'low FEV_1/FVC value' (termed as close to 0.7) (OR=0.95; 95% CI: 0.30–3.08; p=0.94), 'increased TLC%' (OR=0.97; 95% CI: 0.46–2.03; p=0.93) and 'lower FVC%' (termed as <80%) (OR=1.13; 95% CI: 0.42–3.01; p=0.82) were not significant predictors of PRISm progression (Supplementary file Figures 2A–2C). However, 'chest distress or dyspnea' (OR=3.81; 95% CI: 1.47–9.84; p=0.01) and 'current smoking' (OR=2.18; 95% CI: 1.14–4.15; p=0.02) were strongly associated with PRISm progression (Supplementary file Figure 2).

Publication bias

Considering that PRISm is a new spirometry impairment proposed by the GOLD 2023 guidelines, few studies have investigated this topic. Therefore, for some determinants, publication bias cannot be completely assessed. Publication bias was not detected for 'chest distress or dyspnea' (Egger's test: t=1.75, p=0.22), 'current smoking' (Egger's test: t=0.65, p=0.54), 'low FEV_1/FVC value' (Egger's test: t= -1.14, p=0.37), or 'lower FVC%' (Egger's test: t= -0.36, p=0.78).

DISCUSSION

PRISm, which was accurately defined for the first time in the GOLD 2023, presents an impaired but not fixed spirometry phenotype. Some individuals with PRISm even revert to a normal spirometry pattern during follow-up. Therefore, not all individuals with PRISm should be considered or treated as 'patients'[26]. The lack of sufficient supporting medical evidence is currently the main challenge for the treatment of individuals with PRISm. However, a large cohort study in recent years indicated that PRISm was strongly associated with several common cardiovascular comorbidities, such as myocardial infarction, coronary heart disease and heart failure, which may increase

the risk of mortality[4]. The same conclusion was drawn for stroke mortality[27]. PRISm is also reported to be associated with obstructive sleep apnea[28] and an increased risk for all-type dementia as well as Alzheimer's disease[29]. In our systematic review, all the eligible studies reported an increased risk of COPD in patients with PRISm, with an average transition ratio of 20.8% in 3–5 years. Taken together, the above evidence suggests that accurately identifying PRISm patients with a high risk of mortality and progressive spirometry impairment might be more important than simply recognizing PRISm as an independent disease.

The 14 eligible studies included in our systematic review had follow-up durations ranging from 3 to 25 years. We compared a subgroup with a longer follow-up duration (≥5 years) to a subgroup with a shorter follow-up duration (<5 years). A prolonged follow-up duration does not induce a higher rate of PRISm to COPD progression but may lead to a higher rate of persistent PRISm. Considering that PRISm is a highly heterogeneous spirometry status, we speculate that prolonging the follow-up duration may reduce the number of individuals with PRISm switching back and forth between PRISm and normal spirometry. However, the second visit time of the 14 eligible studies in our systemic review was generally 3–5 years after the first visit, so further research might be needed to determine the optimal second visit time for early recognition of these 'stable PRISm' individuals.

Contemporary epidemiological evidence consistently demonstrates that individuals with PRISm exhibit significantly higher baseline smoking prevalence compared to those with normal pulmonary function, particularly regarding current smoking status[30]. The SPIROMICS cohort analysis further substantiates the clinical consequences of smoking in this population, revealing that PRISm smokers experience a 45% increased incidence of respiratory exacerbations relative to early-stage COPD patients[31] (incidence rate ratio=1.45; 95% CI: 1.12–1.88). Notably, this smoking-PRISm association demonstrates significant demographic heterogeneity: males show nearly twofold greater susceptibility (OR=1.92) than females, likely mediated by estrogen's Nrf2-dependent antioxidant protection[32], while middle-aged adults (40–60 years) manifest the strongest correlation (OR=2.05) due to synergistic interactions between age-related lung function decline (mean FEV_1 reduction: 25 mL/year) and cumulative tobacco exposure (mean = 25.6 pack-years in affected subgroups). The aging process amplifies these pathophysiological effects, as evidenced by 15% accelerated telomere attrition in elderly smokers, reflecting compromised pulmonary repair mechanisms that exacerbate smoking-related lung function deterioration[33]. Collectively, these findings establish tobacco use as a modifiable risk factor for PRISm development, with heightened clinical relevance for male and middle-aged populations.

Currently, the underlying physiological abnormalities in PRISm remain incompletely understood. Beyond representing a potential transitional state between normal spirometry and overt airflow limitation or mild asthma, some PRISm cases exhibit isolated volume responses, biological variability, or diverse pathological conditions including restrictive disease patterns and incomplete lung emptying due to expiratory muscle weakness or chest wall stiffness[34]. Findings from the large-scale COPDGene cohort study suggest that PRISm progression to COPD predominantly manifests as an 'airway-predominant dysfunction' phenotype. However, progression from normal spirometry to COPD primarily follows a distinct 'emphysema-predominant disease' trajectory[23]. A subset of PRISm patients already demonstrate focal emphysema or reduced lung density on high-resolution computed tomography (HRCT), though these findings do not yet meet the radiographic thresholds for COPD diagnosis[35]. Smoking may contribute to these structural changes through protease-antiprotease imbalance (particularly MMP-9/TIMP-1 dysregulation), which promotes alveolar wall destruction and diminishes pulmonary elastic recoil. These pathological alterations subsequently impair both lung volume (FVC) and diffusion capacity (DLCO)[36].

To our knowledge, tobacco exposure is closely associated with small airway dysfunction (SAD). Smoking can induce chronic inflammation, fibrosis, and mucus hypersecretion in small airways (<2 mm diameter), leading to increased peripheral airway resistance[37,38]. Although the FEV_1/FVC ratio remains normal, the observed reductions in absolute FEV_1

and FVC values may reflect early-stage small airway pathology. This hypothesis is supported by the following evidence: 1) PRISm patients frequently demonstrate significantly decreased FEF25–75% (a marker of small airway function)[15]; and 2) histopathological studies reveal small airway wall thickening and goblet cell hyperplasia in smokers, even among those with preserved FEV_1/FVC ratios[31]. Data from the large-scale SPIROMICS cohort further corroborate these findings, demonstrating increased airway wall thickness and elevated total airway mucin content in symptomatic smokers with normal spirometry results. A greater airway wall thickness and a high mucus intake are independently associated with higher all-cause and respiratory mortality in individuals with PRISm[39-41]. Therefore, we believe that the underlying physiological mechanism of current smoking, as one of the major risk factors for progression from PRISm to COPD, is also associated with the actual 'SAD phenotype' caused by tobacco exposure.

In addition, systemic inflammation and pulmonary vascular abnormalities are also recognized as potential underlying mechanisms. Tobacco smoking induces low-grade systemic inflammation (elevated levels of IL-6, TNF-α, and CRP), which subsequently impairs pulmonary vascular endothelial function[42]. A subset of PRISm patients may develop mild pulmonary hypertension or microvascular rarefaction, leading to ventilation-perfusion mismatch and further deterioration of lung function[43].

Limitations

Limitations in sample size and statistical power necessitate further high-quality studies to confirm these findings for definitive clinical and public health applications.

CONCLUSIONS

This study provides preliminary genetic evidence supporting a causal relationship between smoking and PRISm while identifying current smoking status as a significant modifiable risk factor for disease progression. Future research should prioritize addressing methodological constraints identified in this work and elucidating underlying biological mechanisms to establish a more robust evidence base for clinical practice.

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CONFLICTS OF INTEREST
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ETHICAL APPROVAL AND INFORMED CONSENT
Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY
The data supporting this research can be found in the published articles and in the Supplementary file.

AUTHORS' CONTRIBUTIONS
TC and RX: research concept and design. GZ: collection and/or assembly of data. XZ, RX and GZ: data analysis and interpretation. XZ and GZ: writing of the manuscript. TC, RX and XD: critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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