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REVIEW

Associated Factors and Pulmonary Function Outcomes of Preserved Ratio Impaired Spirometry: A Scoping Review

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Background: Preserved ratio impaired spirometry (PRISm) is a common but understudied abnormal pulmonary function state and is strongly associated with poor health outcomes. However, there is a lack of uniformity in defining the factors and pulmonary function outcomes associated with PRISm.

Objective: This scoping review aims to elucidate the associated factors and pulmonary function outcomes of PRISm, thereby enhancing healthcare professionals' understanding of PRISm and laying the groundwork for its prevention and treatment.

Methods: This scoping review follows the 5-step framework developed by Arksey and O'Malley. Literature on PRISm was systematically searched from databases including PubMed, Embase, CINAHL, the Cochrane Library, Web of Science, CNKI, and Wan Fang, spanning from inception to July 2024. Inclusion and exclusion criteria were applied to enroll relevant studies. Data were extracted, collected, summarized, and reported.

Results: A total of 38 studies were included. The analysis revealed that associated factors for PRISm encompass possible pathogenic factors (older age, female, lower education level, smoking, obesity, etc), comorbidity associations (asthma, diabetes, cardiovascular diseases, etc), and disease characteristic factors (disease burden, physical performance, radiological characteristics, etc). The pulmonary function status of the PRISm population is unstable, making progression to airflow obstruction (AFO) more likely than in the normal population. PRISm exhibits multiple subgroups (incident or stable PRISm, definite PRISm or PRISm with AFO, non-restrictive or restrictive PRISm, etc) and significant differences exist in pulmonary function outcomes among different subgroups.

Conclusion: This scoping review offers a more comprehensive understanding of PRISm. It is recommended that future research focus on a deeper investigation of the pulmonary function of PRISm, elucidating its pathophysiological characteristics, and proposing new strategies for its prevention and treatment. Furthermore, more research is needed in low-income and middle-income economies to understand PRISm comprehensively.

Keywords: preserved ratio impaired spirometry, airflow obstruction, chronic obstructive pulmonary disease, associated factors, pulmonary function outcomes, scoping review

Introduction

Preserved ratio impaired spirometry (PRISm) is a lung abnormality characterized by a normal forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio, but with a decreased FEV_1.[1,2] PRISm is a common condition with a reported incidence ranging from 7.1% to 20.3%[3] and may serve as a precursor to fixed airflow obstruction (AFO) (and hence chronic obstructive pulmonary disease (COPD)).[2,4,5] Additionally, studies have indicated that patients with PRISm at baseline showed a significantly higher risk of various comorbidities such as cardiovascular disease, diabetes,

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stroke, and all-cause mortality than those with normal spirometry.[6–10] However, since there are still several gaps in research on PRISm, the pathophysiological mechanisms of this pulmonary function phenotype are unclear currently although one study[11] found that it is related to small airway dysfunction (SAD) and reduced total lung capacity (TLC). Therefore, exploring the associated factors and pulmonary function outcomes of PRISm can help healthcare professionals (HCPs) understand the clinical characteristics of PRISm, detect and treat individuals with PRISm early, prevent or delay their progression to AFO, reduce disease burden, and improve quality of life for patients. However, given the limited research on PRISm, there is a lack of uniformity in defining the factors and pulmonary function outcomes associated with PRISm. A scoping review is a method of knowledge synthesis and evidence identification based on the concept of evidence-based practice, which can help researchers clarify the concepts and theories of a certain topic and the sources and types of evidence, summarize the research results, and identify research gaps.[12] This study serves as a scoping review focusing on the associated factors and pulmonary function outcomes of PRISm, with the goal of enhancing HCPs' understanding and providing a reference for the prevention and early treatment of PRISm.

Methods

We followed the reporting framework for scoping reviews by Arksey and O'Malley,[13] consisting of five steps: (1) identification of research questions and clarification of concepts; (2) development of a literature search plan; (3) study selection; (4) data charting; and (5) collating, summarizing, and reporting the results. Additionally, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guided our review.[12,14] The scoping review protocol was registered on Open Science Framework (https://doi.org/10.17605/OSF.IO/X9SNF).[15]

Identification of Research Questions and Clarification of Concepts

This study aimed to elucidate the factors and pulmonary function outcomes associated with PRISm. Two research questions were identified: (1) What are the associated factors for PRISm? (2) What are the pulmonary function outcomes in the PRISm population? The core concept of this study revolved around PRISm, defined by the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (GOLD) (2024 report) as individuals with preserved ratio ($FEV_1/FVC \geq 0.7$ or lower limit of normal (LLN)) but impaired spirometry ($FEV_1 < 80\%$ of reference or LLN).[2]

Development of the Literature Search Plan

Two researchers systematically searched the following databases from their inception until July 2024: PubMed, Embase, Web of Science, CINAHL, Cochrane Library, CNKI, and Wan Fang. The search employed a combination of Mesh headings and free words, and the references of the included articles were meticulously tracked and examined. The full electronic search strategy for PubMed is available in the Supplemental File.

Study Selection

To establish the inclusion criteria, we adopted the "PCC" model for this scoping review.[16] In this model, the population (P) was defined as PRISm patients, the context (C) included any setting where the PRISm population is situated (eg, medical or healthcare facility, nursing facility, community, or home), and the concept (C) encompassed factors or pulmonary function outcomes associated with PRISm. The sources of evidence included observational studies (cross-sectional, cohort, and case-control) and multivariate regression analysis, using individuals with a normal spirometry pattern as the reference group, was used in the original studies to determine the associated factors for PRISm. Exclusion criteria comprised (a) literature types such as reviews or systematic reviews, conference abstracts, policies and guidelines, research proposals, etc; (b) subject-specific (eg individuals with psychosis, HIV, lung cancer, etc); (c) publications in languages other than English or Chinese; (d) duplicate publications and those with unavailable full text. We utilized EndNote 20 software to identify and remove duplicate literature. Subsequently, the title, abstract, and content of each article were rigorously reviewed in accordance with the inclusion and exclusion criteria. A full-text screening was conducted to determine the articles' eligibility for the final review. In cases of disagreement, a third reviewer adjudicated. The search process is illustrated in Figure 1.

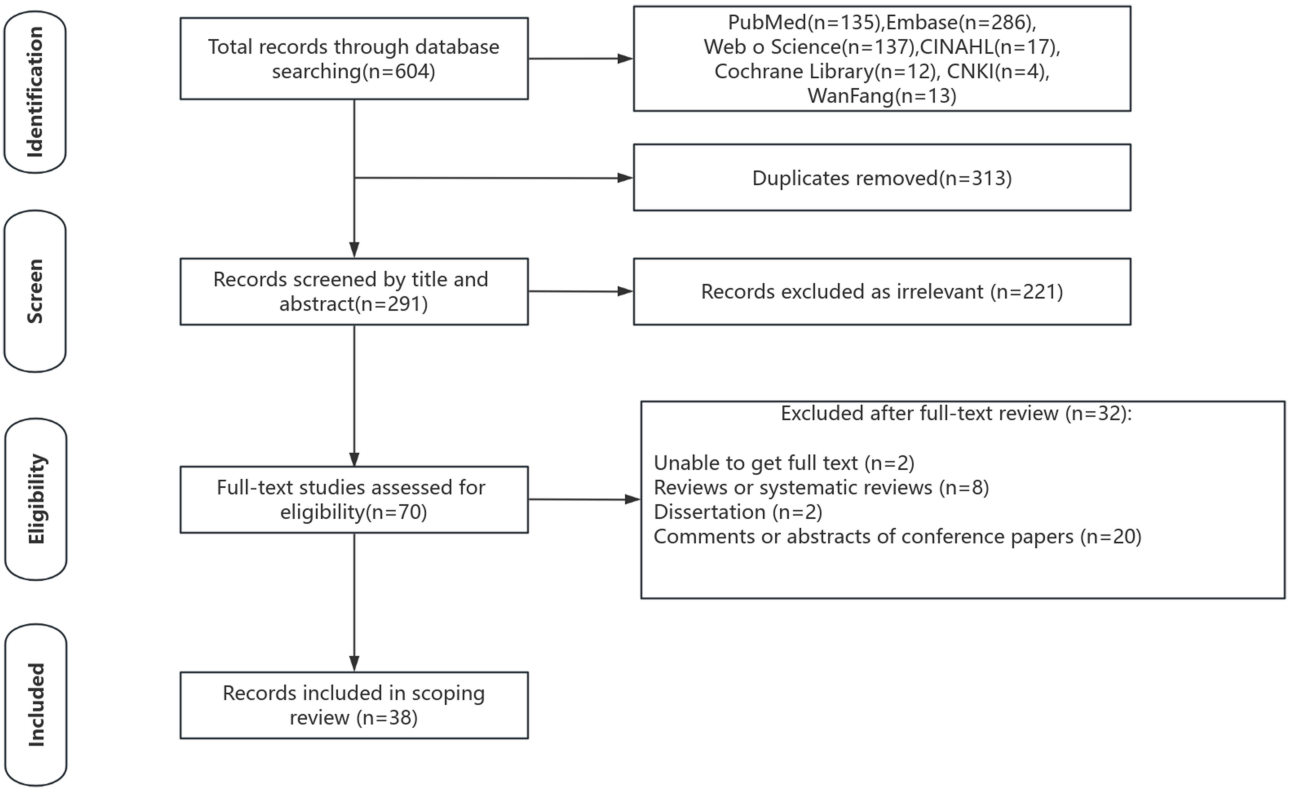

Figure 1 Flowchart for literature screening.

Charting the Data

Data extraction aimed to clearly present the basic characteristics and other relevant information from the included articles. Two researchers independently extracted all relevant data, and any discrepancies were resolved through negotiation until a consensus was reached. A third reviewer reviewed all extracted data. The extracted study characteristics included authors, country of origin, years of publication, study design, follow-up time of the study, the definition of PRISm, the prevalence of PRISm, the associated factors for PRISm, and the pulmonary function outcomes of PRISm.

Results

We identified a total of 604 pieces of literature and finally included 38, comprising 37 in English and 1 in Chinese. The articles spanned 2014–2024 with publications from high-income and upper-middle-income economies, including China (=11), the United States of America (n=9), Japan (n=6), South Korea (n=5), the Netherlands (n=3), the United Kingdom (n=1), Denmark (n=1), Spain (n=1), and Mexico (n=1). Study designs encompassed retrospective cohort studies (n=23), prospective cohort study (n=5), and cross-section study (n=10). Table 1 presents the basic characteristics of the included literature.

What are the Associated Factors for PRISm?

A total of 23[6,11,17,18,20,23–25,28,30,33,34,40–50] studies described the factors associated with PRISm, including the following aspects. Table 2 provides a summary of associated factors for PRISm.

Possible Pathogenic Factors

Sociodemographic Factors

Age,[6,17,23,24,44,50] gender,[6,17,23,34,50] race,[50] and educational background[25,42,43] may influence the occurrence of PRISm. Compared with younger patients, older patients are more prone to PRISm,[6,23,24,44,50] potentially due to bronchial wall

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Table 1 Characteristof Included Literature

Author (year)	Country	Study Design	Follow-up (years)	Age (years)	Definition of PRISm	Post-BD?	Prevalence of PRISm (baseline)	Factors Associated with PRISm	Pulmonary Function Outcomes Investigated
Choi et al (2024)[17]	South Korea	Retrospective cohort study	10	≥40	**PRISm-fixed ratio**: ① **PRISm-LLN**: ②	No	**PRISm-fixed ratio**: 10.4% **PRISm-LLN**: 11.1% (weighted estimate of average prevalence)	**PRISm-fixed ratio**: Age; BMI and fat distribution; Comorbidity associations **PRISm-LLN**: Age; BMI and fat distribution; Comorbidity associations	
Agustí et al (2024)[18]	Spain	Retrospective cohort study	3	≥12	①	Yes	14% (432/3183)	BMI and fat distribution; Disease burden	√
Yoon et al (2024)[19]	South Korea	Retrospective cohort study	5.3[a]	≥18	①	Yes	6.4% (40/623)	N/A	√
Sun et al (2024)[20]	China	Retrospective cohort study	4.3[a]	≥50	①	No	33.9% (241/711)	Laboratory indicators	
Jo et al (2024)[21]	South Korea	Prospective cohort study	12	40–69	①	No	1.4% (66/4762)	N/A	√
Zheng et al (2023)[22]	China	Prospective cohort study	8.9[a]	40–69	①	No	11.5% (37897/329954)	N/A	√
Miura et al (2023)[23]	Japan	Retrospective cohort study	5	35–65	①	No	7.5% (838/11246)	**Non-restrictive PRISm**: Smoking; Comorbidity associations **Restrictive PRISm**: Age; Sex; BMI and fat distribution	√
Tran et al (2023)[24]	USA	Retrospective cohort study	5	45–80	①	Yes	13.6% (685/5055)	Age; Smoking; Disease burden; Comorbidity associations	√
Perez-Padilla et al (2023)[25]	Mexico	Retrospective cohort study	5–9	≥40	①	Yes	5% (146/2942)	Disease burden; Educational background	√
He et al (2023)I[26]	China	Prospective cohort study	9.5[b]	≥50	①	No	13.8% (827/5901)	N/A	√
Kogo et al (2023)[27]	Japan	Retrospective cohort study	5	30–74	③	No	4.5% (438/9760)	N/A	√
Xiao et al (2022)[28]	Netherlands	Retrospective cohort study	2	≥45	①	No	6.3% (249/3941)	Comorbidity associations	
Washio et al (2022)[29]	Japan	Retrospective cohort study	5.3[b]	≥40	①	No	9.9% (301/3032)	N/A	√

Tanabe et al (2022)[30]	Japan	Retrospective cohort study	3	≥40	①	No	6.5% (706/10828)	**Definite PRISm**: BMI and fat distribution; Comorbidity associations; Laboratory indicators	√
Wan et al (2022)[31]	USA	Retrospective cohort study	10.1[a]	45–80	①	Yes	10.4% (185/1775)	N/A	√
Strand et al (2022)[32]	USA	Retrospective cohort study	10	45–80	①	Yes	14.3% (922/6413)	N/A	√
Khan et al (2022)[33]	Netherlands	Prospective cohort study	9.8[b]	≥55	①	No	2.6% (231/8766)	Laboratory indicators	
Higbee et al (2022)[34]	UK	Retrospective cohort study	9[b]	40–69	①	No	11% (38639/351874)	Gender; Smoking; BMI and fat distribution; Comorbidity associations	√
Kanetake et al (2022)[35]	Japan	Retrospective cohort study	2.9[a]	≥18	③	No	10.5% (176/1672)	N/A	√
Wan et al (2021)[6]	USA	Retrospective cohort study	11.2–29.3[b]	≥18	①	No	8.5% (4582/53701)	Age; Gender; Smoking; BMI and fat distribution; Comorbidity associations; Laboratory indicators	
He et al (2021)[36]	China	Retrospective cohort study	7.7[a]	≥50	①	No	20.3% (1346/6616)	N/A	√
Marott et al (2021)[37]	Denmark	Retrospective cohort study	42	20–40	③	No	23.9% (543/2270)	N/A	√
Wijnant et al (2020)[7]	Netherlands	Retrospective cohort study	9.8[a]	≥45	①	No	7.1% (387/5487)	N/A	√
Pompe et al (2020)[38]	USA	Retrospective cohort study	5	45–80	①	Yes	11.9% (503/4211)	N/A	√
Fortis et al (2020)[39]	USA	Prospective cohort study	5	45–80	①	Yes	12.4% (1260/10199)	N/A	√
Young et al (2019)[40]	USA	Retrospective cohort study	5	45–80	①	Yes	10.9% (1002/9234)	Comorbidity associations	√
Wan et al (2018)[41]	USA	Retrospective cohort study	5	45–80	①	Yes	12.4% (1260/10199)	BMI and fat distribution; Radiological characteristics	√
Park et al (2018)[4]	South Korea	Retrospective cohort study	3	≥40	①	No	11.7% (313/2666)	N/A	√
Sang et al (2024)[42]	China	Cross-section study	N/A	≧60	①	Yes	6.3% (141/2229)	BMI and fat distribution; Educational background; Disease burden	
Lei et al (2024)[43]	China	Cross-section study	N/A	≥20	①	Yes	4.8% (2459/50991)	Educational background; BMI and fat distribution	
Shang et al (2023)[44]	China	Cross-section study	N/A	18–80	①	No	11.4% (111/970)	Age; Smoking; Comorbidity associations	

(*Continued*)

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Table 1 (Continued).

Author (year)	Country	Study Design	Follow-up (years)	Age (years)	Definition of PRISm	Post-BD?	Prevalence of PRISm (baseline)	Factors Associated with PRISm	Pulmonary Function Outcomes Investigated
Chen et al (2023)[45]	China	Cross-section study	N/A	18–79	①	No	7% (671/9556)	Laboratory indicators	
Zhang et al (2023)[46]	China	Cross-section study	N/A	40–75	①	Yes	18.7% (221/1183)	Smoking; BMI and fat distribution; Comorbidity associations	
Zhao et al (2022)[11]	China	Cross-section study	N/A	40–80	①	Yes	8.8% (126/1439)	Comorbidity associations; Radiological characteristics	
Lu et al (2022)[47]	China	Cross-section study	N/A	≥18	①	Yes	24.8% (51/206)	Smoking; Radiological characteristics	
Kim et al (2022)[48]	South Korea	Cross-section study	N/A	≥50	①	No	8.9% (1563/17515)	BMI and fat distribution; Comorbidity associations	
Anami et al (2021)[49]	Japan	Cross-section study	N/A	≥60	①	Yes	12% (80/668)	Physical performance; Pulmonary function indicators	
Wan et al (2014)[50]	USA	Cross-section study	N/A	45–80	**PRISm-fixed ratio**: ① **PRISm-LLN**: ②	Yes	**PRISm-fixed ratio**: 12.3% (1257/10192); **PRISm-LLN**: 10.6% (1082/10192)	**PRISm-fixed ratio**: Age; Gender; Smoking; Disease burden; Physical performance; Radiological characteristics; Comorbidity associations **PRISm-LLN**: Race; Smoking; BMI and fat distribution; Disease burden; Physical performance; Radiological characteristics; Comorbidity associations	

Notes: [a]given as arithmetic mean; [b]given as median; ① $FEV_1/FVC \geq 0.7$ with $FEV_1 < 80\%$ predicted; ② $FEV_1/FVC \geq LLN$ with $FEV_1 < LLN$; ③ $FEV_1/FVC \geq LLN$ with $FEV_1 < 80\%$ predicted.

Table 2 Summary of Associated Factors for PRISm

Category	Category
Possible pathogenic factors Sociodemographic factors • Age[6,17,23,24,44,50] • Gender[6,17,23,34,50] • Educational background[25,42,43] • Race[50] BMI or fat distribution[6,17,18,23,30,34,41–43,46,48,50] Smoking[6,23,24,34,44,46,47,50] **Comorbidity associations** • Hypertension[6,17,30,44,48] • Diabetes[6,17,30,48,50] • Asthma[23,30,34,50] • Dyslipidemia[17,30,48,50] • Coronary artery disease,[6,50] • Acute bronchitis,[24] • Small airway dysfunction,[11] • Obstructive sleep apnea[46] • Nasal allergy symptoms[46] • MR-APD[40] • Congestive heart failure[6] • Ischemic heart disease[48] • Chronic renal disease[48] • Thyroid disease[48] • Peripheral vascular disease[50] • Stroke[6] • Global cognitive function[28] • Metabolic syndrome[17]	**Disease characteristic factors** Disease burden • mMRC dyspnoea scores[18,24,50] • Wheezing[18,25] • Breathlessness[18,42] • Resting oxygen saturation[50] • Missing days at work[25] • Exacerbations and hospital admissions[18] Physical performance • One-legged standing time[49] • Sit-up test times[49] • 6-minute walk distance[50] Radiological characteristics • TLC[11,41,50] • Percentage emphysema[41] • MLD[47] • PRMfSAD[47] • Lumen area[47] • Segmental bronchial wall area percentage[50] • CT-air trapping[11] Pulmonary function indicators • FVC[49] Laboratory indicators • CRP[30] • Activin A[20] • Ig A and Ig G[33] • eGFR[6] • Hb[20] • BUN[20] • Serum cadmium[45]

thickening, enlarged alveolar diameter, and reduced chest wall compliance in the lung tissue of elderly patients.[51] Additionally, prolonged exposure to other risk factors also increases the risk of PRISm with advancing age.[52] However, Choi et al[17] found that the probability of suffering from PRISm decreased with the increase of age (meanwhile, individuals with the obstructive pattern were significantly older than those with PRISm) and this finding may be related to the increasing prevalence of clinical COPD in elderly individuals.[53] Female patients are more susceptible to PRISm compared with male patients.[6,17,23,34,50] A genetics study of early-onset COPD found that females were almost two times more likely to demonstrate mild airflow limitation (FEV_1 <80% predicted) than males.[54] Nevertheless, FEV_1 is affected by age, gender, height and ethnicity, and the use of the fixed threshold may lead to false-positive diagnoses of disease in women or the elderly,[55,56] which may also explain the high incidence of PRISm in the elderly and women. A study[50] showed that African Americans were less likely to suffer from PRISm in the LLN cohort, which may reflect less accurate population-based prediction equations for or increased variability in African Americans rather than a distinct pathobiological process. Further research is needed to explore whether ethnicity is associated with PRISm. Lower education level is significantly associated with the progress from normal population to PRISm patients.[25,42,43] Education level is an important index of socioeconomic status and access to health care. Low socioeconomic status and poor access to health care are associated with environmental factors such as air pollution, smoking, malnutrition, and respiratory infections, which may limit optimal lung growth during fetal life, childhood, and adolescence and increase the risk of respiratory diseases.[57,58]

Smoking

Smoking stands out as the primary risk factor for PRISm, with a higher number of pack-years associated with an increased risk of PRISm in the population.[6,23,24,34,44,46,47,50] Smoke contains nicotine, tar, acrolein, and other harmful substances, which can damage airway epithelial cells and inhibit ciliary movement function, thereby causing small airway obstructive damage,[59] and damage to the airway mucosa due to cigarettes is significantly associated with an increased duration and number of cigarettes smoked.[60]

Body Mass Index (BMI) and Fat Distribution

The presence of PRISm relative to normal spirometry was significantly associated with an elevated BMI,[6,17,18,23,30,34,41,42,48,50] while Wan et al[6] pointed out that low BMI was also correlated with a higher risk of PRISm. Two studies[43,46] reported the association between body fat distribution and PRISm, highlighting that excessive waist-to-hip ratio was correlated with increased prevalence of PRISm. The relationship between abnormal BMI or fat distribution and PRISm can be elucidated through various mechanisms. First, the mechanical properties of the lungs and chest wall are altered significantly in obesity. Fat accumulation in the mediastinum, abdominal and thoracic cavities interferes with the normal movement of the diaphragm, which reduces the room for lung expansion, decreases vital capacity, and limits expiratory flow.[61,62] Second, in the obese state, adipokines released from adipose tissue aggravate the release of free fatty acids, and pro-inflammatory chemokines and cytokines, resulting in insulin resistance and low-grade inflammation.[58,63,64] Hyperinsulinemia due to insulin resistance has an important impact on airway hyperresponsiveness by inducing hyperresponsiveness of the parasympathetic nerves, which are crucial in controlling airway bronchoconstriction.[65] A systemic low-grade inflammatory state causes hypercontractility in airway smooth muscle cells and damages the alveolus and airway.[66] On the contrary, nutritional deficiencies and stunting reduce respiratory muscle strength and are strongly associated with decreased FEV_1.[67,68]

Comorbidity Associations

Respiratory Diseases

Respiratory diseases are closely linked to the occurrence of PRISm. Studies have indicated that patients with a history of asthma are more likely to experience PRISm.[23,30,34,50] This association may be attributed to airway obstruction and narrowing resulting from structural changes such as airway remodeling due to moderate to severe asthma.[69] In addition, asthma in childhood can lead to reduced FEV_1 and an increased risk of lung function impairment in adulthood.[70] The history of acute bronchitis,[24] small airway dysfunction,[11] the risk of obstructive sleep apnea, and nasal allergy symptoms[46] are also strongly associated with PRISm, and moderate-risk airway-predominant disease is associated with conversion from GOLD 0 to PRISm status.[40] These respiratory system-related diseases reflect that the pathological feature of PRISm may be decreased airway function. It is closely related not only to impaired lung growth, which leads to a failure to achieve maximum lung volume and maximum lung function in adulthood (small lung)[71] but also to impaired lung function due to an inflammatory response.

Other Systemic Diseases

PRISm manifests significant associations with a myriad of comorbidities, encompassing hypertension,[6,17,30,44,48] diabetes,[6,17,30,48,50] congestive heart failure,[6] coronary artery disease,[6,50] ischemic heart disease,[48] peripheral vascular disease,[50] chronic renal disease,[48] thyroid disease,[48] stroke,[6] poor global cognitive function,[28] metabolic syndrome,[17] and dyslipidemia.[17,30,48,50]

The relationship between PRISm and comorbidities is bidirectional and complicated. On the one hand, cardiovascular diseases (CVDs) cause lung congestion and limit lung capacity, thereby affecting lung function.[72] On the other hand, PRISm is associated with a lower resting oxygen saturation[50] and tissue hypoxia may result in a release of inflammatory mediators, which can damage blood vessels and increase the risk of macrovascular and microvascular complications.[73] Additionally, antihypertensive medication independent of high blood pressure has adverse effects on lung function, and the use of beta-blockers is associated with reduced FVC and FEV_1.[74] Beta-adrenergic receptors play a crucial role in the regulation of bronchomotor tone,[75] and beta-blocker medication can produce bronchoconstriction, which worsens respiratory flows and symptoms in patients with asthma.[76]

Li et al[10] observed that 121 metabolites potentially contributed to the burden of type 2 diabetes (T2D) attributable to PRISm, and glycoprotein acetyls and multiple cholesteryl components within high-density lipoprotein played key roles in mediating the association of PRISm with T2D. This suggests that the higher risk of T2D in PRISm patients is largely due to alterations in particular metabolic pathways associated with this spirometry phenotype (For example, abnormal inflammation related to the PRISm pattern may induce glucose metabolism disorders and insulin resistance). In addition, PRISm patients may be overall less active because of respiratory symptoms, which may also explain worsened glycemic control and increased risk of vascular complications.[77] Conversely, the lung is a target organ for diabetes-related damage.[78] First, oxidative stress caused by diabetes can cause lung parenchymal damage, which leads to fibrosis and structural changes. Second, prolonged hyperglycemia can lead to elevated levels of various inflammatory markers, including CRP, interleukin, and tumor necrosis factor, and cause a chronic low-grade inflammatory response in systemic and local connective tissue, which damages the pulmonary microvasculature, resulting in thickening of the pulmonary epithelial and endothelial basal lamina. Third, excessive production of advanced glycation end-products can impact lung function by exacerbating the chronic low-grade inflammatory response of the system and directly destroying connective tissue. Fourth, hyperglycemia can affect the function of respiratory muscle groups and the nerves that innervate them, leading to reduced pulmonary ventilation.[78,79]

There is a potential connection between thyroid function and lung health. Altered levels of thyroid hormones, including hypothyroidism or hyperthyroidism, may influence respiratory outcomes and lung function. Studies have shown that hypothyroidism may lead to weakened respiratory muscles and reduced lung capacity, while hyperthyroidism may result in increased airway resistance and decreased lung volume.[80,81]

The mechanisms linking PRISm to decreased cognitive function may be related to common risk factors for both, such as harmful exposures at an earlier life stage, systemic inflammation, and diabetes.[28]

Disease Characteristic Factors

Disease Burden

Compared to individuals with a normal spirometry pattern, PRISm patients exhibit significantly higher disease burdens, such as frequent wheezing[18,25] and breathlessness,[18,42] higher modified Medical Research Council (mMRC) dyspnoea scores,[18,24,50] lower resting oxygen saturation,[50] more missing days at work,[25] more frequent exacerbations[18] and hospital admissions.[18] Individuals with PRISm have not yet developed AFO, but they already suffer disease burdens similar to GOLD 1–2 (although this may be related to other potential comorbidities, such as chronic heart failure), and therefore they should be considered as "patients" requiring careful monitoring and therapeutic management.[2,18]

Physical Performance

One study[49] explored the relationship between physical performance and PRISm and found that prolonged one-legged standing time was an independent correlation factor of PRISm (52.4 ± 41.1 s vs 36.4 ± 34.1 s, $P = 0.008$), while individuals with PRISm showed a significant decrease in sit-up test times compared to individuals with normal lung capacity (6.7 ± 5.8 vs 8.7 ± 6.0, $P = 0.032$). Wan et al[50] found that the 6-minute walk distance reduced significantly for individuals with PRISm compared to normal subjects. These findings suggest that individuals with PRISm have lower core muscle endurance and overall exercise stamina but are unlikely to show reduced limb muscle strength or balance.

Radiological Characteristics

Computed tomography (CT) has become an established technique for airway morphometry and lung densitometry in patients with airway disease, which can provide a series of vital radiological parameters.[82] One scholar[47] developed a prediction model for PRISm using binary logistic regression analysis and highlighted that inspiratory mean lung density (MLD), the percent of functional small airway disease in parametric response mapping (PRM^{fSAD}), and lumen area were important predictors. Wan et al[41] indicated that decreased baseline TLC_{CT}% predicted and percentage emphysema were robust independent predictors of incident PRISm status at Phase 2 among individuals with GOLD 0 at Phase 1. Another study[50] proposed that increased percent emphysema, decreased TLC, and increased segmental bronchial wall area percentage were significant predictors of PRISm status. Zhao et al[11] found that PRISm had lower TLC, and higher

odds and more severity in CT-air trapping compared with healthy control. These chest CT imaging features can support that PRISm may be mainly characterized by small airway lesions and is associated with restrictive ventilatory impairment.

Pulmonary Function Indicators

Anami et al[49] identified an association between %FVC and PRISm, with receiver operating characteristic (ROC) analysis determining the %FVC cut-off value for predicting PRISm was 83.2% (sensitivity 0.988, specificity 0.800).

Laboratory Indicators

PRISm is closely related to elevated inflammatory markers. One study indicated that PRISm correlated with C-reactive protein (CRP) ≥0.1 mg/dL.[30] Activin A (Act A), a member of the TGFβ (transforming growth factor β) superfamily, plays a multifaceted role in inflammation, with dysregulation implicated in organ injury and mortality across various pathologies. In respiratory disorders like Asthma and COPD, plasma Act A levels were found to be elevated.[83] Sun et al[20] deciphered the association between Act A and PRISm, showing that the risk of PRISm escalated with an increase in Act A levels.

In exploring the relationship between immune molecules and PRISm, Khan et al[33] found positive correlations between immunoglobulin A (IgA) and IgG levels and the incidence of PRISm. Additionally, lower estimated glomerular filtration rate (eGFR),[6] lower hemoglobin (Hb) levels[20] and elevated blood urea nitrogen (BUN) levels[20] were also associated with an increased risk of PRISm.

Furthermore, a study[45] examining the association between heavy metal levels and PRISm found a correlation between serum cadmium levels and the risk of PRISm, with those having high serum cadmium levels (≥0.52 ug/L) having a 1.695-fold higher chance of experiencing PRISm than those with low serum cadmium levels (<0.19 ug/L). Cadmium is a globally recognized class I carcinogen and a prominent toxin commonly found in air pollution. Cadmium can lead to cell death and oxidative stress in lung epithelial cells by inducing cytotoxicity and destroying redox homeostasis, thereby inducing lung inflammation.[84]

What are the Pulmonary Function Outcomes in the PRISm Population?

A total of 23 studies[4,7,18,19,21–27,29–32,34–41] investigated the pulmonary function outcomes in individuals with PRISm, categorized into the following four perspectives:

PRISm Is Not Always a Stable Phenotype and Can Transition to Both Normal and Obstructed Spirometry Over Time

Zheng et al[22] demonstrated that, after an average follow-up of 8.9 years in the PRISm population, 64% of PRISm patients underwent transitions to different lung function types. Among these transitions, 50.4% achieved normal lung function, and 13.6% progressed to COPD. Another study[25] reported that within a 5–9 year follow-up, 46.5% of PRISm patients experienced a change in lung function category, which was a rate higher than that observed in the normal control population (12.4%) and the COPD population (30.2%). Miura et al[23] observed that more than two-thirds of PRISm patients transitioned to normal lung function or COPD after 5 years. He et al[26] reported that after a 4-month follow-up in the PRISm population, the lung function status of 22.7% of the patients returned to normal, whereas that of 33.5% changed to COPD. Wan et al[31] showed that only about half (51.9–53.9%) of the patients in the PRISm population had their lung function category remain unchanged during up to 10 years of follow-up, and ever-PRISm (if a subject had PRISm on spirometry at any visit) was a significant predictor of significant changes in patient's lung function over the follow-up period. Kanetake et al[35] pointed out that after 3 years of follow-up, 6.3% of the patients in the PRISm population progressed to COPD, whereas 34.1% returned to normal lung function. In the UK Biobank cohort,[34] only 37.7% of PRISm patients retained their PRISm status after a median follow-up of 9 years. The Rotterdam cohort study[7] revealed that a higher proportion of patients in the PRISm population (43%) transitioned to other lung function categories than those with normal lung function (23%) or COPD (8.9%), with 10.4% transitioning to normal spirometry while 32.6% progressed to COPD. In the COPDGene study,[41] the proportion of patients in the PRISm group who transitioned

to other lung function categories was 47.4%, which was significantly higher than those in the GOLD 0 (20.4%) and GOLD 1–4 (11.8%) groups. Agustí et al[18] found that during the 3-year follow-up, only about 67.7% of PRISm patients remained stable in the same initial diagnostic category over time, whereas most patients with GOLD 3–4 (89.2%) remained in the same diagnostic category. A retrospective study[19] evaluated the longitudinal changes in lung function trajectory of PRISm patients, which showed that PRISm was maintained in 40% of cases, converted to COPD in 32.5%, and converted to normal in the remaining 27.5% during an average follow-up period of 5.3 years, and classified PRISm patients into subgroups according to longitudinal changes: "persistent PRISm", "PRISm to normal", and "incident COPD". In a cohort study from South Korea,[21] significantly more status transitions in the PRISm groups were observed compared to the other groups, with 21.6% transitioning to normal status while 16.2% transitioning to pre-COPD (characterized by respiratory symptoms and structural or functional abnormalities, without obvious airflow limitation at any age) and 10.8% to COPD.

PRISm May Be a Precursor to the Development of AFO

Wan et al[41] showed that among patients with PRISm at phase 1, baseline total lung capacity (TLC)% predicted (odds ratio (OR) 1.02, 95% (confidence interval) CI 1.01–1.04, $P = 9.34\times10^{-3}$) and percentage gas trapping (OR 1.07, 95% CI 1.03–1.11, $P = 4.13\times10^{-4}$) were significant predictors of transitioning to GOLD 1–4 at phase 2. Tran et al[24] demonstrated that compared with the normal lung function group, the PRISm group was associated with a diagnosis of COPD. Perez-Padilla et al[25] identified closeness of FEV_1/FVC to 0.70 (OR 18, 95% CI 9.7–36), age (OR 1.05, 95% CI 1.03–1.08), current smoking (OR 2.0, 95% CI 1.2–3.2), and a longer forced expiratory time in the second assessment (OR 0.69, 95% CI 0.65–0.73) as the best predictors of PRISm progression to COPD. Kogo et al[27] showed that PRISm patients had a higher risk of developing airflow limitation (AFL) within 5 years than those with normal lung function, and that PRISm was an independent risk factor for COPD in patients with respiratory symptoms. Another study[29] pointed out that PRISm patients have an approximately 2.5-fold higher risk of progression to AFL than those with normal lung function, along with a higher annual rate of decline in FEV_1/FVC. Kanetake et al[35] demonstrated that a higher proportion of PRISm patients progressed to COPD (6.3%) than those with normal lung function (1.8%), establishing PRISm as an independent risk factor for the development of COPD (OR 3.75, 95% CI 1.78–7.97, P <0.001), and found that if FEV_1 was < 86% predicted (area under the curve 0.706, 95% CI 0.617–0.794), there was a risk of COPD progression by using ROC curve. A study[34] indicated that PRISm patients who are elderly, have a doctor diagnosis of asthma, and have a decrease in BMI are more likely to progress to COPD. Pompe et al[38] analyzed the inspiratory phase quantitative CT results of the COPDGene cohort, finding that the adjusted lung density of the PRISm population declined faster than that of the normal population during the 5-year follow-up period, suggesting accelerated emphysema progression in PRISm patients. Young et al[40] classified patients into 6 groups: high-risk airway-predominant disease only (APD-only), moderate-risk airway-predominant disease only (MR-APD-only), high-risk emphysema-predominant disease only (EPD-only), combined high-risk airway- and emphysema-predominant disease (combined APD-EPD), combined moderate-risk airway- and emphysema-predominant disease (combined MR-APD-EPD), and no high-risk pulmonary subtype and found that 36% of PRISm patients progressed to GOLD 2–4, with the majority concentrated in APD-only group (30.7%) and the MR-APD-only group (37.8%), while no observed conversion from PRISm to GOLD 0 or GOLD 1 in 5 years. Thus, in diseases dominated by airway lesions, PRISm serves as the transitional stage from GOLD 0 to GOLD 2–4. Park et al[4] demonstrated that the incidence of COPD was significantly higher in the PRISm population (17.0/1000 person-years) than in the normal population (4.4/1000 person-years) over a 3-year follow-up period, emphasizing that older age (OR 1.14, 95% CI 1.05–1.24, $P = 0.002$) and wheezing (OR 4.56, 95% CI 1.08–19.35, $P = 0.040$) were important predictors of PRISm progression to COPD. Jo et al[21] compared the risk of future AFO among different groups, the results showed that PRISm groups had higher risks of developing AFO at least once during the 12-year follow-up (OR 4.26, 95% CI 2.04–8.87, $P < 0.001$) and at the last visit (year 12) (OR 3.21, 95% CI 1.44–7.15, $P < 0.001$). However, after adding the presence of cardiovascular disease as a covariate, the significance was lost for the PRISm group developing AFO at the last visit (OR 3.29, 95% CI 0.87–12.44, $P = 0.079$).

PRISm Exhibits Multiple Subgroups and Significant Differences Exist in Lung Function Outcomes Among Different Subgroups

PRISm Can Be Categorized According to the Changes in Spirometry Categories During the Follow-up Period

Wan et al[41] found that during the 5-year follow-up, incident PRISm (the subjects with PRISm at phase 2 had GOLD 0 spirometry at phase 1) was independently associated with an accelerated rate of decline in FEV_1 (95% CI −59.79 to −46.34, $P = 2\times10^{-16}$), while subjects with stable PRISm (the subjects with PRISm at phase 1 and phase 2) appeared to have normal, or even subnormal, rates of lung function decline. Tanabe et al[30] reported that PRISm patients whose lung function category remained unchanged during the follow-up period (definite PRISm) or who had a record of AFL (PRISm with AFL) were more likely to progress to AFL (hazard ratio (HR) 4.65, 95% CI 1.27–30.04 and HR 28.82, 95% CI 6.99–30.05, respectively).

PRISm Can Be Categorized According to Whether There Is Restrictive Spirometry (RSP)

RSP ($FEV_1/FVC\geq0.7$ or LLN and FVC<80% predicted or LLN) is associated with increased respiratory symptoms, multiple complications such as cardiovascular disease and metabolic syndrome, and mortality due to all-cause, CVDs, diabetes, and cancer.[85–87] There is a clear overlap between PRISm and RSP,[88] and PRISm with or without RSP may have differences in pulmonary function outcomes. Miura et al[23] classified PRISm into two subgroups—non-restrictive and restrictive—based on FVC levels. Patients with non-restrictive PRISm (FVC ≥ 80% predicted), but not restrictive PRISm (FVC <80% predicted), were independently associated with the development of AFO (adjusted risk ratio 4.47; 95% CI 1.66–12.01; $P = 0.003$), potentially because non-restrictive PRISm is associated with cough, asthma, wheezing, bronchitis, pneumonia, and smoking, and its pathophysiological features may include intrapulmonary factors such as airway inflammation, bronchial hyperresponsiveness, and emphysema, which are similar to AFO, whereas restrictive PRISm is related to early life circumstances and obesity, and its pathophysiology may be associated with extrapulmonary factors.[23,87,89] He et al[36] categorized PRISm based on the decline in FEV_1 and FVC into mild ($FEV_1/FVC\geq0.7$, FEV_1 or FVC<80% predicted) and severe ($FEV_1/FVC\geq0.7$, both FEV_1 and FVC <80% predicted). Patients with severe PRISm were more likely to remain in the PRISm status or progress to GOLD 2–4 than those with mild PRISm. In patients with a restrictive ventilatory defect that coexists with obstructive lung disease, FVC may disproportionately reduce relative to TLC.[90] Fortis et al[39] obtained TLC through chest CT scans and divided the PRISm population into four groups: extremely low, low, high, and very high, according to FVC/TLC_{CT} from lowest to highest. In the very low group, 35.9% of patients progressed to COPD, which was significantly higher than that in the other three groups, indicating a relationship between FVC/TLC_{CT} decline and progression to COPD.

Factors Affecting Pulmonary Function Outcomes of PRISm

Five studies[7,29,32,37,40] reported the relationship between smoking and lung function changes in PRISm patients, all suggesting that smoking accelerates the decline of FEV_1 or FVC, increasing the risk of AFO. Strand et al[32] used linear mixed models to model changes in FEV_1 and FEV_1/FVC jointly for 5- and 10-year intervals and found that increased the square root of the wall area of a standardized airway with 10-mm internal lumen perimeter (Pi10) and functional residual capacity (FRC) were associated with losses in both FEV_1 and FEV_1/FVC for PRISm participants. Marott et al[37] highlighted that participating in physical activity contributes to the recovery of lung function and reduces the risk of progression to COPD in PRISm patients. Three studies[32,34,41] explored the correlation between BMI and lung function outcomes in PRISm patients. Wan et al[41] showed that decreasing BMI was a significant predictor of the transition to GOLD 0 in PRISm patients (OR 0.92, 95% CI 0.88–0.97, $P<0.001$). Higbee et al[34] found that change in BMI, per mg/kg^2 increase, was strongly negatively associated with PRISm changing to normal spirometry (vs persistent PRISm, relative risk ratio (RRR) 0.86, 95% CI 0.81–0.91, $P <0.0001$), while another study[32] suggested that higher BMI had a protective effect on lung function in PRISm patients. Wijnant et al[7] indicated that PRISm patients whose spirometry changed to normal during the follow-up period were more often female ($P = 0.041$), had a smaller waist circumference at baseline ($P = 0.031$), and had smoked fewer pack-years ($P = 0.098$) than other patients with PRISm. In the Copenhagen City Heart Study cohort,[37] individuals in the normal to PRISm trajectory and persistent PRISm trajectory had a higher cumulative smoking exposure, BMI, increase in BMI, high-sensitivity C-reactive protein, fibrinogen, and white blood

cell counts and reported more often dyspnea, chronic bronchitis, and low physical activity than those in the normal trajectory and PRISm to the normal trajectory during 25-year follow up, suggesting that smoking, systemic inflammation, overweight, and physical inactivity are all associated with both the development and maintenance of PRISm.

Discussion

Strengthening Early Screening for PRISm

Raising public awareness of PRISm, identifying its risk factors, and providing early screening for high-risk groups are crucial steps in slowing down the progression of the disease and reducing all-cause mortality. Currently, the diagnostic criteria for PRISm are mainly derived from pulmonary function indices, making pulmonary function tests an essential tool for PRISm screening. Medical and healthcare institutions should actively conduct pulmonary function tests for residents, particularly those exposed to risk factors and with comorbidities, to enhance PRISm screening. However, there are several aspects of pulmonary function screening for PRISm that need to be noted: firstly, it is important to ensure the quality of pulmonary function tests to avoid overdiagnosis caused by technical errors. For example, incomplete inspiration or expiration due to poor effort can also lead to low FVC and FEV_1;[56] secondly, Magner et al[91] found that there was a higher construct validity associated with the post-bronchodilator (post-BD) PRISm classification scheme compared with pre-BD, suggesting that priority should be given to post-BD spirometry. Screening questionnaires play a vital role in disease screening due to their cost-effectiveness and ease of use. Tamaki et al[92] demonstrated, through analysis of the area under the ROC curve, that the CAPTUR questionnaire (COPD assessment in primary care to identify undiagnosed respiratory disease and exacerbation risk) and COPD-SQ (COPD screening questionnaire) could potentially be effective tools for identifying PRISm patients with comorbid respiratory symptoms. This presents a new strategy for PRISm screening. Chest CT, offering more information about structural lung abnormalities and greater sensitivity than lung function tests,[2] holds promise for early PRISm screening. PRISm has unique chest CT features such as bronchial wall thickening, emphysema manifestations, and small airway dysfunction and some of them are also predictive of PRISm prognosis, which suggests that chest CT parameters may become a reference for the early identification of PRISm and the prevention of COPD in the future.

Following a Healthy Lifestyle Slows Down Lung Function Decline

PRISm signifies a transitional state for a significant proportion of patients, and the PRISm population is more likely to transition to other lung function categories than other populations. This suggests that the lung function changes in PRISm are still reversible. Although subjects transitioning from PRISm to normal spirometry may exhibit features of asthma, previous studies showed that patients who recovered from PRISm also had healthier characteristics such as less smoking, lower BMI, and more physical activity,[7,22,34,37,41] which means the risk of progressing to AFO can be mitigated by following a healthy lifestyle. In addition, the association between PRISm and comorbidities (especially metabolic syndrome) may be related to shared risk factors such as smoking, obesity, and sedentariness, indicating that a healthy lifestyle can also reduce the damage to lung function caused by complications. Smoking not only stands as the primary risk factor for PRISm but also exacerbates the deterioration of lung function in patients.[7,29,32,37,40] Hence, implementing smoking control interventions among the PRISm population is essential to promote smoking cessation, thereby reducing the damage caused by smoking to lung function. Additionally, underweight or obesity hinders the favorable transition of pulmonary function in PRISm patients.[32,34,37,41] Physical exercise has a protective effect on lung function, and higher degrees of inactivity are independent risk factors for pulmonary impairment assessed by FEV_1 <80% and non-obstructive ventilatory pattern.[93] Consequently, PRISm patients should actively engage in physical exercise, supplement nutrition appropriately, and control their weight to minimize the risk of continued deterioration of lung function.

Providing Hierarchical Management of PRISm Patients and Implementing Personalized Intervention Plans

Research has shown that PRISm is heterogeneous and exhibits multiple subgroups. Significant differences exist in clinical characteristics, disease burden, and clinical outcomes among different subgroups. Studies indicated that PRISm

with RSP not only had more respiratory symptoms, higher risks of all-cause mortality, respiratory mortality, and CVDs mortality than PRISm only,[7,36,87] but also was the subsequent progression of PRISm only.[36] As different subgroups may necessitate different interventions, it is important to identify PRISm subjects with "true restriction" in multiple dimensions including using more advanced tests than spirometry such as lung volume test, impulse oscillometry and imaging, assessing smoking history, childhood underweight, abdominal obesity, metabolic heterogeneity, and other risk factors related to restrictive ventilatory disorders.[87,94,95] For PRISm patients with severe symptoms and a poor prognosis (or with RSP), comprehensive interventions targeting risk factors such as smoking cessation, weight loss, and appropriate clinical treatment should be initiated as early as possible to decelerate disease progression and enhance the quality of life. Although the long-term risk of death in patients with mild PRISm is similar to that of the normal population,[36] they may still progress to GOLD 2–4 during the follow-up period. Therefore, this group needs regular pulmonary function tests and should adopt healthy living habits to prevent further deterioration of pulmonary function.

Limitations

Several limitations exist in this study: (i) the methodological limitations of a scoping review, especially potential selection bias, may limit our findings and conclusions; (ii) the inclusion criteria were restricted to Chinese/English language publications, potentially affecting the comprehensiveness of the conclusions; (iii) associated factors and pulmonary function outcomes were not quantified, which may be achieved through meta-analysis; (iv) the studies mainly came from high-income and upper-middle-income economies, so caution is needed when applying the findings to other countries.

Conclusions

To the best of our knowledge, to date, no literature has comprehensively consolidated research on the associated factors and pulmonary function outcomes of PRISm. This scoping review offers a more comprehensive understanding of PRISm based on an analysis of 38 primary research studies and explores the possible mechanisms. Our findings emphasize the need for focusing on high-risk populations, early identification of PRISm, and adopting specific clinical management strategies for individuals in different subgroups based on modifiable risk factors.

However, current research indicates that PRISm is a mere description of what the spirometry numbers already say. It is necessary to conduct a deeper investigation of pulmonary function (measure absolute lung volumes first) before searching for any kind of factors associated with PRISm and clarify its physiopathological mechanisms in the future. Furthermore, more research is needed in low- and middle-income economies to understand PRISm comprehensively.

Abbreviations

AFL, airflow limitation; AFO, airflow obstruction; BMI, body mass index; BD, bronchodilator; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; CVDs, cardiovascular diseases; eGFR, estimated glomerular filtration rate; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease; Hb, hemoglobin; Ig, immunoglobulin; HCPs, healthcare professionals; LLN, lower limit of normal; MLD, mean lung density; mMRC, modified Medical Research Council; MR-APD, moderate-risk airway-predominant disease; OR, odds ratio; PRISm, preserved ratio impaired spirometry; PRM^{fSAD}, the percent of functional small airway disease in parametric response mapping; RRR, relative risk ratio; RSP, restrictive spirometry; SAD, small airway dysfunction; TLC, total lung capacity; T2D, type 2 diabetes.

Ethics and Dissemination

Ethical approval was not required for this scoping review.

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Disclosure

The authors report no conflicts of interest in this work.

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