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## A COMPREHENSIVE OVERVIEW OF PRISm: FROM SPIROMETRIC PATTERN TO CLINICAL OUTCOMES AND PSYCHOSOCIAL IMPACT

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**Introduction.** Preserved Ratio Impaired Spirometry (PRISm) is a spirometric phenotype characterized by reduced forced expiratory volume in the presence of a preserved FEV<sub>1</sub>/FVC ratio. It is increasingly recognized as a clinically meaningful condition rather than a benign or transitional state. Individuals with PRISm frequently experience respiratory symptoms, impaired functional capacity, and reduced quality of life, and are at increased risk of cardiovascular disease and mortality compared with those with normal lung function.

**Objective.** This narrative review synthesizes current evidence on the epidemiology, pathophysiology, and clinical consequences of PRISm, with particular emphasis on its association with cardiometabolic diseases and mental health outcomes.

**Methods.** A comprehensive search of PubMed, Web of Science, and Scopus was conducted to identify publications related to PRISm and its association with mental health outcomes up to December 2025, using predefined keywords and Boolean combinations. Eligible cohort, cross-sectional, case-control studies, systematic reviews, and meta-analyses were screened, and a total of 68 full-text articles meeting the inclusion criteria were analyzed.

**Results.** Current evidence indicates that the pathophysiology of PRISm is multifactorial, involving small-airway dysfunction, reduced lung volumes, systemic inflammation, skeletal muscle impairment, and metabolic abnormalities such as obesity and insulin resistance. Environmental and occupational exposures further contribute to the risk and progression of PRISm. An expanding body of research links PRISm with depression and anxiety, which increase symptom burden, healthcare utilization, and may independently worsen prognosis.

**Conclusion.** PRISm is a clinically significant and heterogeneous phenotype associated with adverse respiratory, cardiometabolic, and psychosocial outcomes. Despite its growing recognition, it remains underdiagnosed and insufficiently addressed in current clinical frameworks. A multidimensional approach integrating respiratory, metabolic, and mental health assessment is essential, and further research is needed to develop standardized diagnostic criteria and targeted interventions.

**Keywords:** Preserved Ratio Impaired Spirometry (PRISm), lung function impairment, chronic obstructive pulmonary disease, cardiometabolic risk, depression, anxiety, epidemiology, risk factors, clinical outcomes

## КОМПЛЕКСНЫЙ ОБЗОР PRISm: ОТ СПИРОМЕТРИЧЕСКОГО ПАТТЕРНА К КЛИНИЧЕСКИМ И ПСИХОСОЦИАЛЬНЫМ ИСХОДАМ

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**Введение.** Preserved Ratio Impaired Spirometry (PRISm) - это спирометрический фенотип, характеризующийся снижением объема форсированного выдоха при сохраненном соотношении FEV<sub>1</sub>/FVC. В настоящее время он все чаще рассматривается как клинически значимое состояние, а не как доброкачественное или переходное. У пациентов с PRISm часто наблюдаются респираторные симптомы, снижение функциональной способности и ухудшение качества жизни, а также повышенный риск сердечно-сосудистых заболеваний и общей смертности по сравнению с лицами с нормальной функцией легких.

**Цель.** Настоящий обзор обобщает современные данные об эпидемиологии, патофизиологии и клинических последствиях PRISm с особым акцентом на его связь с кардиометаболическими заболеваниями и психическим здоровьем.

**Материалы и методы.** Был проведен комплексный поиск публикаций в базах данных PubMed, Web of Science и Scopus до декабря 2025 года с использованием заранее определенных ключевых слов и логических операторов. В анализ были включены когортные, поперечные и случай-контроль исследования, а также систематические обзоры и метаанализы. Всего было отобрано 68 полнотекстовых статей, соответствующих критериям включения.

**Результаты.** Современные данные свидетельствуют о многофакторной природе PRISm, включающей дисфункцию мелких дыхательных путей, снижение легочных объемов, системное воспаление, нарушение функции скелетных мышц и метаболические нарушения, такие как ожирение и инсулинорезистентность. Экологические и профессиональные воздействия также вносят вклад в развитие и прогрессирование PRISm.

Растущее число исследований указывает на связь PRISm с депрессией и тревожными расстройствами, которые усиливают симптоматическую нагрузку, увеличивают потребление медицинских ресурсов и могут независимо ухудшать прогноз.

**Заключение.** PRISm представляет собой клинически значимый и гетерогенный фенотип, ассоциированный с неблагоприятными респираторными, кардиометаболическими и психосоциальными исходами. Несмотря на возрастающее признание его значимости, PRISm остается недостаточно диагностируемым и слабо представленным в современных клинических подходах. Необходим мультидисциплинарный подход, включающий оценку респираторного, метаболического и психического состояния. Дальнейшие исследования должны быть направлены на стандартизацию диагностических критериев и разработку целевых терапевтических стратегий.

**Ключевые слова:** Preserved Ratio Impaired Spirometry (PRISm); нарушение функции легких; хроническая обструктивная болезнь легких; кардиометаболический риск; депрессия; тревога; эпидемиология; факторы риска; клинические исходы

### PRISm-ТІҢ КЕШЕНДІ ШОЛУЫ: СПИРОМЕТРИЯЛЫҚ ҮЛГІДЕН КЛИНИКАЛЫҚ ЖӘНЕ ПСИХОӘЛЕУМЕТТІК НӘТИЖЕЛЕРГЕ ДЕЙІН

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**Кіріспе.** Preserved Ratio Impaired Spirometry (PRISm) - бұл FEV<sub>1</sub>/FVC қатынасы сақталған жағдайда форсирленген экспирация көлемінің (FEV<sub>1</sub>) төмендеуімен сипатталатын спирометриялық фенотип. Соңғы жылдары ол бұрынғыдай қауіпсіз немесе өтпелі күй ретінде емес, клиникалық тұрғыдан маңызды жағдай ретінде қарастырылуда. PRISm бар науқастарда жиі респираторлық симптомдар, функционалдық қабілеттің төмендеуі және өмір сапасының нашарлауы байқалады, сондай-ақ қалыпты өкпе функциясы бар адамдармен салыстырғанда жүрек-қан тамыр аурулары мен жалпы өлім-жітім қаупі жоғары болады.

**Зерттеу мақсаты.** PRISm-нің эпидемиологиясы, патофизиологиясы және клиникалық салдары туралы заманауи деректерді жинақтау, әсіресе оның кардиометаболикалық аурулармен және психикалық денсаулық көрсеткіштерімен байланысына ерекше назар аудару.

**Материалдар мен әдістер.** 2025 жылдың желтоқсанына дейін PubMed, Web of Science және Scopus халықаралық деректер базаларында PRISm және оның психикалық денсаулық көрсеткіштерімен байланысына қатысты жарияланымдарға кешенді іздеу жүргізілді. Алдын ала анықталған кілт сөздер мен логикалық операторлар қолданылды. Когорттық, көлденең, «жағдай-бақылау» зерттеулері, сондай-ақ жүйелі шолулар мен мета-талдаулар іріктелді. Іріктеу критерийлеріне сәйкес келетін 68 толық мәтінді мақала талдауға енгізілді.

**Нәтижелер.** Қазіргі деректер PRISm патофизиологиясының көпфакторлы екенін көрсетеді, оған ұсақ тыныс жолдарының дисфункциясы, өкпе көлемдерінің төмендеуі, жүйелік қабыну, қаңқа бұлшықеттерінің бұзылысы және семіздік пен инсулинге төзімділік сияқты метаболикалық өзгерістер жатады. Сонымен қатар, экологиялық және кәсіби факторлар PRISm-нің дамуы мен үдеуіне ықпал етеді. Зерттеулердің көбеюі PRISm-нің депрессия және үрей бұзылыстарымен байланысты екенін көрсетеді, бұл симптомдық жүктемені арттырып, медициналық қызметтерді пайдалануды көбейтеді және болжамды нашарлатуы мүмкін.

**Қорытынды.** PRISm — қолайсыз респираторлық, кардиометаболикалық және психоәлеуметтік нәтижелермен байланысты клиникалық маңызды және гетерогенді фенотип. Оның клиникалық маңыздылығының артуына қарамастан, PRISm жеткіліксіз диагностикаланады және қазіргі клиникалық тәжірибеде жеткілікті түрде ескерілмейді. Респираторлық, метаболикалық және психикалық денсаулықты кешенді бағалауды қамтитын мультидисциплинарлық тәсіл қажет. Болашақ зерттеулер диагностикалық критерийлерді стандарттауға және нысаналы терапиялық араласуларды әзірлеуге бағытталуы тиіс.

**Түйін сөздер:** Preserved Ratio Impaired Spirometry (PRISm), өкпе функциясының бұзылысы, өкпенің созылмалы обструктивті ауруы, кардиометаболикалық қауіп, депрессия, үрей, эпидемиология, қауіп факторлары, клиникалық нәтижелер.

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#### Introduction

Preserved Ratio Impaired Spirometry (PRISm) is a spirometric phenotype defined by a reduced forced expiratory volume in one second (FEV<sub>1</sub> < 80% predicted) in the presence of a preserved FEV<sub>1</sub>/forced vital capacity (FVC) ratio (≥ 0.70) (1). This intermediate spirometric pattern does not correspond to classical obstructive or restrictive ventilatory disorders, which has historically contributed to its under-recognition and frequent misclassification. Rather than

representing a single disease entity, PRISm reflects a heterogeneous functional pattern encompassing individuals with impaired ventilatory capacity who do not meet standard spirometric criteria for airflow obstruction (2).

Epidemiological studies indicate that PRISm represents a substantial and heterogeneous population burden. Early population-based analyses estimated a prevalence of approximately 5% in the general adult population and up to 10% among individuals with a smoking history (3). More recent studies report a broader prevalence range from 3% to 20%, reflecting differences in population characteristics, diagnostic thresholds, and study design (4,5). Although recognition of PRISm as a distinct spirometric phenotype has increased over the past decade, existing literature remains fragmented and lacks conceptual integration.

Accumulating evidence suggests that PRISm is associated with clinically significant symptoms and adverse health outcomes, challenging earlier assumptions that it represents a benign or transitional state. Individuals with PRISm frequently report respiratory symptoms, reduced exercise capacity, and impaired health-related quality of life (6). Moreover, PRISm has been consistently linked to an increased risk of cardiovascular disease and all-cause mortality (7), underscoring its clinical relevance beyond spirometric abnormalities.

The pathophysiological mechanisms underlying PRISm are incompletely understood and likely multifactorial. Proposed mechanisms include small-airway dysfunction, reduced lung volumes, systemic inflammation, impaired lung development, and metabolic dysregulation, particularly obesity and insulin resistance (8). In addition, endothelial dysfunction and systemic inflammatory pathways may contribute to increased cardiovascular risk (9). The heterogeneity of these mechanisms suggests that PRISm represents a spectrum of pathophysiological processes rather than a single unified condition.

An emerging but insufficiently explored aspect of PRISm is its association with mental health. Recent studies indicate that individuals with PRISm may experience higher rates of depression and anxiety compared with those with normal lung function, even in the absence of overt airflow obstruction (10). Mental health comorbidities may exacerbate symptom burden, reduce treatment adherence, and increase healthcare utilization, thereby adversely affecting long-term outcomes. However, current evidence on psychosocial outcomes in PRISm remains limited, inconsistent, and often derived from studies not specifically designed to investigate this phenotype (11).

Despite growing recognition of its clinical significance, PRISm remains inadequately addressed in current diagnostic and management frameworks. There is no consensus regarding screening strategies, classification, or treatment approaches, and existing respiratory guidelines rarely provide specific recommendations for this phenotype. This gap contributes to variability in clinical recognition and management.

Importantly, while previous reviews have primarily focused on the epidemiological and cardiopulmonary aspects of PRISm, an integrated analysis incorporating cardiometabolic and psychosocial dimensions remains lacking.

Accordingly, the aim of this review is to provide a comprehensive synthesis of current evidence on the epidemiology, pathophysiology, and clinical outcomes of PRISm, with a particular emphasis on mental health, including depression and anxiety. By integrating data across respiratory, cardiometabolic, and psychosocial domains, this review seeks to identify key knowledge gaps and outline priorities for future research and clinical practice.

### Materials and methods

This review was conducted using a structured approach to identify and synthesize relevant literature on Preserved Ratio Impaired Spirometry (PRISm) and its association with mental health outcomes. A comprehensive literature search was performed in the electronic databases PubMed, Web of Science, and Scopus, including studies published up to December 2025. The search strategy was based on the following keywords and their combinations: ("PRISm" OR "preserved ratio impaired spirometry") AND ("depression" OR "anxiety" OR "mental health" OR "psychological distress") AND ("clinical outcomes" OR "mortality" OR "quality of life"), using Boolean operators (AND, OR) to refine the search.

Eligible studies included observational designs (cohort, cross-sectional, and case-control studies), as well as systematic reviews and meta-analyses conducted in adult populations, provided that PRISm was defined using spirometric criteria and mental health outcomes such as depression, anxiety, or psychological distress were assessed. Studies were excluded if they were case reports, case series, editorials, expert opinions, or conference abstracts, as well as those lacking clear diagnostic criteria for PRISm or presenting duplicate data.

All identified records were independently screened based on titles, keywords, and abstracts to determine potential eligibility. Full-text articles were subsequently reviewed according to predefined inclusion and exclusion criteria. Data extracted from each study included the author and year of publication, country, study design, sample size, diagnostic criteria for PRISm, type of mental health outcomes assessed, and key findings.

A qualitative synthesis of the included studies was performed, with a focus on identifying consistent patterns, discrepancies, and gaps in the current evidence base. A total of 68 full-text studies meeting all inclusion criteria were included in the final analysis. This review was not registered in PROSPERO.

A summary of the key studies included in this review is presented in Table 1.

**Table 1** - Summary of key studies included in the review

Author (Year)	Country / Dataset	Study Design	Population	Main Outcome	Key Findings
Stubbe et al. (2025)	Europe	Review	Adults	Epidemiology	PRISm is a heterogeneous and prevalent phenotype
Robertson et al. (2025)	Global	Systematic review & meta-analysis	52 studies	Prevalence	Global prevalence ~12%, higher in LMICs
Higbee et al. (2022)	UK Biobank	Cohort	>300,000 adults	Prevalence, mortality	PRISm ~11%, associated with multimorbidity and mortality
Wan et al. (2018)	COPDGene	Longitudinal cohort	~10,000 adults	Trajectories	PRISm transitions to COPD and increased mortality
Wijnant et al. (2020)	Netherlands	Cohort	General population	Mortality	PRISm associated with higher mortality risk
Wan et al. (2021)	USA	Cohort	Adults	Clinical outcomes	Increased adverse outcomes
Choi et al. (2024)	Korea	Cross-sectional	Nationwide sample	Prevalence trends	Increasing PRISm prevalence over time
Siddharthan et al. (2024)	LMIC	Cross-sectional	Multinational	Epidemiology	Higher burden in low- and middle-income countries
Schwartz et al. (2021)	USA	Observational	Spirometry database	Prevalence	PRISm common in clinical datasets
Miura et al. (2023)	Japan	Cross-sectional	Adults	Phenotypes	PRISm includes restrictive-like subtypes
Xu et al. (2025)	Global	Scoping review	Adults	Risk factors	Identified multiple determinants of PRISm
Phillips et al. (2024)	Canada (CanCOLD)	Cohort	Adults	Physiology	Dyspnea and reduced exercise capacity
Heo et al. (2020)	Korea	Cross-sectional	Adults	Quality of life	Reduced HRQoL in PRISm
Lin et al. (2025)	China	Cohort	Adults	Symptoms, mortality	Symptoms linked to mortality
Huang et al. (2024)	Global	Review	Adults	Comorbidities	PRISm linked to metabolic and radiographic changes
Zhao et al. (2022)	China	Cross-sectional	Adults	Lung function	Small airway dysfunction and reduced TLC
Zhang et al. (2025)	China	MR + meta-analysis	Adults	Smoking	Smoking causally associated with PRISm
Kim et al. (2022)	Korea	Cross-sectional	Adults	Comorbidities	High burden of metabolic comorbidities
Cestelli et al. (2025)	Europe	Cohort	Adults	Risk & mortality	PRISm associated with increased morbidity and mortality
Li et al. (2025)	USA (NHANES)	Cross-sectional	Adults	Cardiovascular disease	PRISm linked to CVD subtypes
Yang et al. (2024)	UK Biobank	Cohort	>300,000 adults	Depression, anxiety	Increased risk of depression and anxiety
Hu et al. (2024)	China	Cohort	~280,000 adults	Depression	Reduced lung function associated with depression
Zhang et al. (2023)	China	Cross-sectional	Adults	Sleep apnea	PRISm associated with OSA
Wang et al. (2025)	Global	Meta-analysis	Multiple studies	Comorbidities	PRISm linked to multimorbidity
Yang et al. (2023)	Global	Meta-analysis	Multiple studies	Mortality	Increased all-cause mortality

## Epidemiology and risk factors

### 1.1. Global prevalence

Preserved ratio impaired spirometry (PRISm) is increasingly recognized as a common yet heterogeneous spirometric phenotype affecting a substantial proportion of the adult population worldwide. Recent meta-analytic evidence suggests that the global prevalence of PRISm is approximately 12%, although estimates vary widely across studies. Notably, prevalence appears higher in low- and middle-income countries (approximately 19%) compared with high-income regions (around 11%), highlighting a substantial and uneven global burden (12).

However, reported prevalence estimates demonstrate considerable heterogeneity, ranging from 3% to 20% across populations (4,5). This variability cannot be explained solely by true epidemiological differences and is likely driven by methodological inconsistencies, including differences in spirometric definitions, reference equations, and study design. In particular, the use of fixed FEV<sub>1</sub>/FVC thresholds versus lower-limit-of-normal criteria substantially influences classification, potentially leading to both over- and underestimation of PRISm prevalence.

Large population-based cohorts, including the UK Biobank and COPDGene, consistently confirm that PRISm represents a sizable and clinically relevant subgroup rather than a transient or incidental finding (14,15). Nevertheless, even within these well-characterized cohorts, prevalence estimates differ markedly depending on age distribution, comorbidity burden, and body composition. For example, general population studies typically report prevalence around 11%, whereas clinical or comorbidity-enriched cohorts may report substantially higher estimates (up to 24–27% or more) (16). Importantly, the conceptualization of PRISm remains inconsistent across studies. It has been variably described as a restrictive-like pattern, an obesity-related mechanical phenomenon, or a transitional state preceding airflow obstruction (17,18). These divergent interpretations contribute to inconsistencies in classification and complicate cross-study comparisons.

Taken together, current evidence suggests that PRISm represents a substantial global health burden; however, its true prevalence remains uncertain due to methodological heterogeneity and lack of standardized diagnostic criteria. This highlights the need for harmonization of spirometric definitions and improved epidemiological surveillance, particularly in underrepresented populations.

### 1.2. Demographic and lifestyle factors (age, sex, smoking, obesity)

Epidemiological data consistently identify older age as a major determinant of PRISm. Both cross-sectional and longitudinal studies demonstrate increasing prevalence with advancing age, as well as a higher likelihood of adverse lung function trajectories and mortality among older individuals with PRISm (16,19–21). However, it remains unclear whether PRISm reflects accelerated lung aging, impaired lung development, or a combination of both, indicating an important unresolved question in the field.

Associations with sex are less consistent and appear context-dependent. While several studies report higher prevalence among women (21,22), others demonstrate stronger associations in men after adjustment for smoking and body composition (16). These discrepancies likely reflect differences in exposure patterns, hormonal influences, and body fat distribution, but also highlight a lack of adequately stratified analyses. Importantly, emerging evidence suggests that the clinical impact of PRISm—including cardiometabolic burden and mental health outcomes—may differ by sex (23), although this area remains insufficiently explored.

Tobacco exposure is a well-established risk factor for PRISm, with both current and former smoking associated with increased prevalence across multiple cohorts (24). Mechanistically, smoking contributes to small airway inflammation, impaired lung growth, and structural lung damage (25,26). Longitudinal data further indicate that smoking increases the likelihood of progression from PRISm to COPD (24). However, not all individuals with PRISm have a smoking history, suggesting that additional non-smoking-related mechanisms play a substantial role.

Among modifiable risk factors, obesity emerges as one of the most consistently associated determinants of PRISm (27,28). Elevated BMI and central adiposity are strongly linked to PRISm prevalence. While mechanical restriction of lung expansion is an important contributor, obesity-related systemic inflammation, metabolic dysregulation, and altered respiratory mechanics likely play equally important roles (29). Notably, PRISm in obese individuals often lacks classical features of restrictive lung disease on imaging, supporting the concept of PRISm as a complex metabolic–respiratory phenotype rather than a purely restrictive condition.

Socioeconomic status represents an additional and often underappreciated determinant. Lower educational attainment and socioeconomic disadvantage have been associated with higher PRISm prevalence independent of smoking and obesity (30). These findings suggest that PRISm is not solely a biological phenomenon but also reflects broader social and environmental inequalities, including differences in healthcare access, occupational exposures, and living conditions.

Overall, PRISm appears to arise from a complex interplay between aging, behavioral exposures, metabolic health, and social determinants. However, the relative contribution of these factors and their interactions remain insufficiently quantified, representing a key gap in current knowledge.

### **1.3. Environmental and occupational exposures**

There is increasing evidence that environmental and occupational exposures play a significant role in the development of abnormal spirometric patterns, including PRISm (31). Ambient air pollution—particularly fine particulate matter, nitrogen oxides, and ozone—has been consistently associated with accelerated declines in lung function, including both FEV<sub>1</sub> and FVC, in large cohort studies (32).

Longitudinal analyses suggest that chronic exposure to air pollution contributes not only to reduced lung volumes but also to an increased likelihood of developing spirometric patterns consistent with PRISm

(19). Furthermore, recent evidence indicates that such exposures may influence disease trajectories, including progression from PRISm to COPD, particularly in individuals with coexisting risk factors such as smoking or metabolic dysfunction (27). However, causality remains difficult to establish due to residual confounding and variability in exposure assessment across studies.

Indoor air pollution remains a critical but underrepresented factor, especially in low- and middle-income countries, where biomass fuel exposure is common (33). Chronic exposure to household air pollution has been linked to impaired lung development, persistent inflammation, and reduced lung volumes, potentially contributing to the higher PRISm prevalence observed in these regions.

Occupational exposures constitute another important determinant. Workers exposed to dust, fumes, and industrial pollutants demonstrate persistent reductions in lung function, including patterns compatible with PRISm (34,35). However, occupational data are often limited by inadequate exposure characterization and lack of longitudinal follow-up.

Importantly, environmental and occupational factors likely interact with individual susceptibility, including smoking status, obesity, and socioeconomic disadvantage (36). These synergistic effects may amplify inflammatory and oxidative stress pathways, contributing to the development and persistence of PRISm.

Overall, current evidence supports a multifactorial model in which environmental and occupational exposures play a substantial but incompletely quantified role in PRISm. Future research should focus on improving exposure assessment, clarifying causal relationships, and identifying high-risk populations for targeted prevention strategies.

## **2. Pathophysiology of PRISm**

PRISm does not represent a single disease entity but rather a heterogeneous physiological pattern arising from multiple interacting pulmonary, systemic, and metabolic mechanisms.

**2.1. Structural and functional lung alterations**

Physiological and imaging studies suggest that PRISm encompasses at least two major sub-phenotypes. The first is a low lung volume phenotype, characterized by proportional reductions in FEV<sub>1</sub> and FVC with decreased total lung capacity, consistent with restrictive or pseudo-restrictive mechanics (37). This phenotype is often associated with extrapulmonary factors such as obesity, reduced chest wall compliance, or respiratory muscle dysfunction.

The second is a small-airway dysfunction phenotype, characterized by peripheral airway abnormalities leading to airflow limitation in distal airways, gas trapping, and altered resistance patterns despite a preserved FEV<sub>1</sub>/FVC ratio (38). This phenotype may represent an early stage of obstructive lung

disease and is increasingly detectable using advanced techniques such as impulse oscillometry and imaging.

Imaging studies further demonstrate airway wall thickening, subtle parenchymal abnormalities, reduced elastic recoil, and gas trapping in individuals with PRISm (24). However, the relative contribution of structural versus functional abnormalities remains unclear, and findings vary across studies.

Importantly, these mechanisms are not mutually exclusive. In many individuals, PRISm likely reflects overlapping processes, including obesity-related mechanical restriction and early airway disease (39). This heterogeneity may explain the wide variability in clinical presentation and disease trajectories, ranging from normalization of lung function to progression toward COPD or restrictive lung disease.

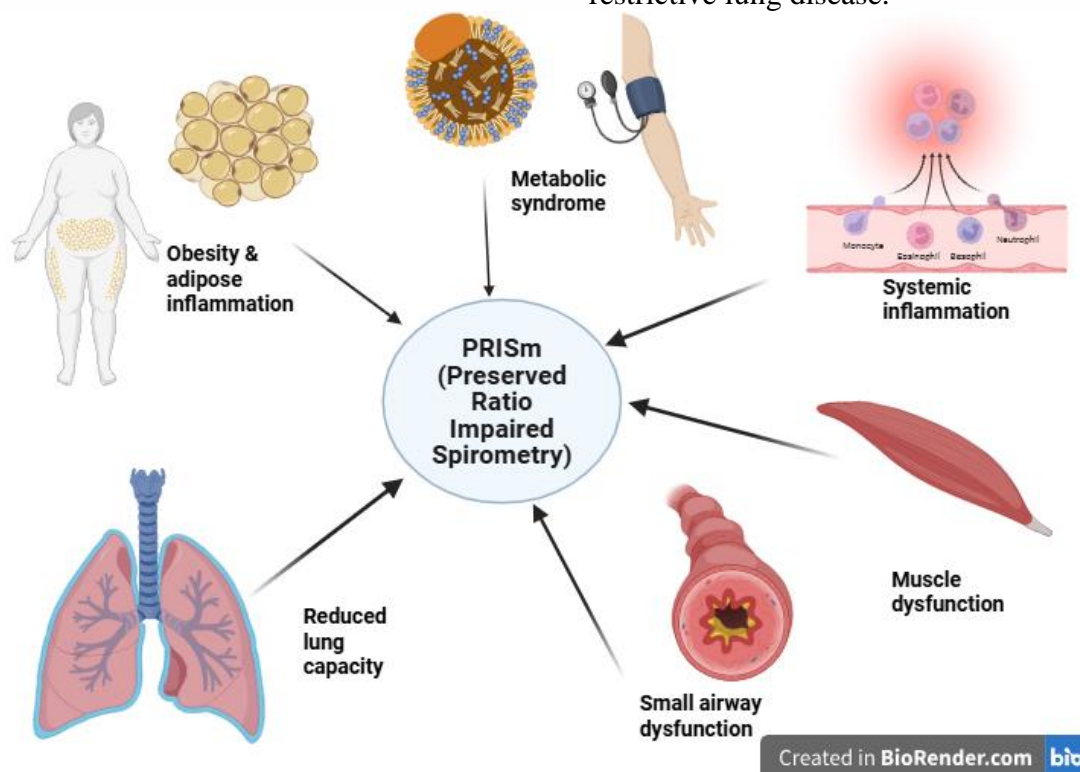


Figure 1 - Conceptual model of biological mechanisms underlying PRISm

**2.2. Role of systemic inflammation and muscle dysfunction**

Accumulating evidence suggests that PRISm is associated with a state of chronic low-grade systemic inflammation, which may represent a key mechanistic link between impaired lung function and adverse cardiometabolic outcomes (27). Large population-based

cohorts consistently demonstrate elevated circulating levels of inflammatory biomarkers—including C-reactive protein (CRP), interleukin-6 (IL-6), fibrinogen, and tumor necrosis factor- $\alpha$ -related mediators—in individuals with PRISm compared with those with normal spirometry (40). These findings support the concept that PRISm

reflects a broader systemic inflammatory phenotype rather than an isolated pulmonary abnormality.

Recent proteomic and biomarker studies further expand this framework by identifying enrichment of pathways related to innate immune activation, endothelial dysfunction, and acute-phase responses in PRISm populations (41). However, the directionality of this association remains uncertain. It is unclear whether systemic inflammation primarily drives lung function impairment or represents a downstream consequence of underlying metabolic and environmental exposures.

Mechanistically, inflammatory mediators may directly contribute to pulmonary dysfunction by promoting airway remodeling, altering smooth muscle tone, and impairing alveolar repair processes (42). In parallel, systemic inflammation exerts extrapulmonary effects, including endothelial dysfunction and microvascular impairment, which may contribute to the increased cardiovascular risk observed in PRISm (43). In addition, cytokine-mediated catabolism may affect respiratory muscles, leading to reduced diaphragmatic strength and ventilatory efficiency.

Importantly, longitudinal evidence suggests that elevated inflammatory markers are associated with accelerated lung function decline and an increased likelihood of transition from PRISm to obstructive phenotypes. These observations raise the possibility that inflammation may act not only as a marker but also as a driver of disease progression. Nevertheless, causal inference remains limited due to the observational nature of most available studies.

Skeletal muscle dysfunction represents an increasingly recognized extrapulmonary component of PRISm and contributes significantly to reduced exercise capacity and symptom burden (45). Individuals with PRISm consistently demonstrate poorer physical performance compared with those with normal lung function, even after adjustment for key confounders (46). However, data on muscle structure and function in PRISm remain limited and are

largely extrapolated from related respiratory conditions.

Several mechanisms may underlie skeletal muscle impairment in PRISm. Chronic systemic inflammation promotes muscle protein degradation and inhibits regeneration through cytokine-mediated pathways involving IL-6, CRP, and TNF- $\alpha$  (47). Additionally, oxidative stress, mitochondrial dysfunction, and reduced capillary density may impair muscle oxidative capacity and fatigue resistance (48). These processes likely interact with physical inactivity and comorbid conditions, although their relative contributions remain poorly defined.

Overall, current evidence supports a model in which systemic inflammation and skeletal muscle dysfunction contribute to both pulmonary and extrapulmonary manifestations of PRISm. However, mechanistic pathways remain incompletely understood, and further studies integrating imaging, molecular profiling, and functional assessments are needed to clarify causal relationships.

### **2.3. Metabolic syndrome and obesity**

Obesity, particularly central adiposity, is one of the most consistently identified and biologically plausible determinants of the PRISm phenotype. Excess adipose tissue imposes mechanical constraints on the respiratory system by reducing chest wall compliance and diaphragmatic excursion, leading to decreases in functional residual capacity (FRC), expiratory reserve volume (ERV), and forced vital capacity (FVC) (39). This mechanical effect can produce a pseudo-restrictive spirometric pattern that fulfills PRISm criteria even in the absence of intrinsic lung disease.

However, mechanical factors alone are insufficient to explain the association between obesity and PRISm. Increasing evidence suggests that metabolic and inflammatory pathways play a critical role. Adipose tissue functions as an active endocrine organ, releasing pro-inflammatory cytokines, adipokines, and mediators of insulin resistance that contribute to systemic inflammation, endothelial dysfunction, and altered muscle metabolism (49). These processes may impair ventilation–perfusion

matching, promote airway remodeling, and accelerate lung function decline.

Epidemiological studies consistently demonstrate that individuals with obesity and metabolic syndrome have a significantly higher likelihood of PRISm compared with lean individuals, even after adjustment for major confounders (50). Notably, central adiposity appears to be a stronger predictor than overall BMI, highlighting the importance of visceral fat as a key mediator of pulmonary impairment.

Despite strong associations, the causal relationship between obesity and PRISm remains complex. In some individuals, PRISm may represent a reversible mechanical consequence of excess weight, while in others it may reflect a more persistent metabolic–inflammatory phenotype associated with long-term cardiometabolic risk. This heterogeneity underscores the need to distinguish between mechanistic subtypes of PRISm in both research and clinical practice. Collectively, available evidence supports the concept that PRISm frequently develops within the context of a broader cardiometabolic disease spectrum. The interplay between obesity, systemic inflammation, and lung function impairment suggests the existence of a metabolic–pulmonary axis, which has important implications for risk stratification and integrated management strategies. However, longitudinal and interventional data remain limited, and further research is required to determine whether targeting metabolic dysfunction can modify PRISm trajectories.

### **3. Clinical Presentation and symptom profile**

#### **3.1. Respiratory symptoms (dyspnea, cough, exercise intolerance)**

Although PRISm does not meet spirometric criteria for airflow obstruction, affected individuals frequently experience clinically significant respiratory symptoms. Dyspnea on exertion is the most commonly reported complaint and often represents the primary trigger for clinical evaluation (51). However, the mechanisms underlying dyspnea appear to vary across PRISm subtypes. In individuals with a low-lung-volume phenotype, reduced total lung capacity and diminished inspiratory

reserve contribute to early ventilatory limitation (52), whereas those with small-airway dysfunction may experience dynamic air trapping and increased work of breathing during exertion.

Chronic cough, with or without sputum production, is also more prevalent in PRISm populations than in individuals with normal spirometry (51). While this symptom is frequently associated with smoking-related airway inflammation, its presence in non-smokers suggests additional mechanisms, including subclinical airway disease, gastroesophageal reflux, and obesity-related mechanical factors (53). This heterogeneity underscores that symptom expression in PRISm cannot be attributed to a single pathophysiological pathway.

Importantly, symptom severity in PRISm correlates poorly with FEV<sub>1</sub>, indicating that spirometry alone underestimates functional impairment in this phenotype. This dissociation highlights a key limitation of traditional spirometric assessment and supports the need for multidimensional evaluation.

Clinical presentation often overlaps with both obstructive and restrictive lung disease, contributing to frequent misclassification and delayed recognition. As a result, many individuals may not receive appropriate diagnostic workup or symptom-directed management. Consistent with this, PRISm has been associated with increased healthcare utilization, including higher rates of outpatient visits and hospital admissions due to respiratory complaints (54).

Overall, respiratory symptoms represent a central component of PRISm-related disease burden and provide important clinical cues that extend beyond spirometric classification.

#### **3.2. Extra-pulmonary manifestations and comorbidities**

PRISm is increasingly recognized as a systemic clinical phenotype rather than an isolated pulmonary abnormality. Epidemiological data consistently demonstrate a high burden of extra-pulmonary comorbidities, reflecting shared inflammatory, metabolic, and vascular pathways (55).

### 3.2.1. Cardiovascular disease

Cardiovascular disease (CVD) is one of the most consistently reported and clinically significant comorbidities in PRISm (56). Large population-based cohorts, including UK Biobank and COPDGene, show that individuals with PRISm have a higher prevalence of coronary artery disease, stroke, heart failure, and hypertension compared with those with normal spirometry (14,57). Moreover, PRISm is associated with increased incidence of cardiovascular events and mortality.

Meta-analytic evidence indicates that the risk of cardiovascular mortality in PRISm is comparable to, or in some cases exceeds, that observed in mild to moderate obstructive lung disease (58). However, whether PRISm independently contributes to cardiovascular risk or primarily reflects underlying cardiometabolic burden remains a subject of ongoing debate.

Proposed mechanisms include systemic inflammation, endothelial dysfunction, autonomic imbalance, and shared metabolic pathways. These findings support the interpretation of PRISm as a marker of systemic vascular vulnerability rather than a purely respiratory condition.

### 3.2.2. Metabolic syndrome and diabetes

Metabolic syndrome is highly prevalent among individuals with PRISm and appears to represent a core component of its clinical phenotype. Large national datasets demonstrate increased rates of insulin resistance, type 2 diabetes, dyslipidemia, and metabolic syndrome in PRISm populations (59).

The relationship between metabolic dysfunction and PRISm is likely bidirectional. Metabolic abnormalities may impair lung mechanics and promote systemic inflammation, while reduced physical activity and functional limitation may exacerbate metabolic risk. Hyperglycemia and insulin resistance have been associated with accelerated declines in lung function, and diabetes has emerged as an independent predictor of mortality in PRISm (18).

Despite strong associations, interventional data are lacking, and it remains unclear whether targeting metabolic risk factors can

modify PRISm trajectories. This represents an important area for future research.

### 3.2.3. Sleep-related breathing disorders

Sleep-related breathing disorders, particularly obstructive sleep apnea (OSA), are increasingly recognized in PRISm populations (60). Shared risk factors, including obesity and altered respiratory mechanics, likely contribute to this overlap.

Observational studies report higher prevalence of daytime sleepiness, poor sleep quality, and diagnosed sleep apnea among individuals with PRISm compared with those with normal lung function (61). However, data remain limited, and most studies lack objective sleep measurements, restricting interpretation.

Sleep fragmentation and nocturnal hypoxia may exacerbate systemic inflammation, cardiometabolic risk, and neurocognitive dysfunction, potentially contributing to the broader disease burden in PRISm. Given these associations, screening for sleep disorders may be warranted in high-risk individuals.

## 4. Psychosocial and Mental Health Impact

### 4.1. Depression in patients with PRISm

Depression is the most extensively studied mental health outcome in PRISm. Large population-based analyses, including UK Biobank data, demonstrate that PRISm is associated with a significantly increased risk of incident depression compared with normal spirometry, even after adjustment for major confounders (10). Although effect sizes are moderate, their consistency across studies supports a meaningful and reproducible association.

Importantly, PRISm may also modify the clinical course of depression. Evidence suggests that individuals with both PRISm and baseline depressive symptoms have a higher risk of adverse outcomes, including increased mortality, indicating a potential interaction between pulmonary dysfunction and psychiatric vulnerability.

The mechanisms underlying this association are likely multifactorial. Functional limitation, exertional dyspnea, and reduced physical activity are strong predictors of depressive symptoms in PRISm populations (3). Biological pathways—including systemic

inflammation, hypothalamic–pituitary–adrenal axis dysregulation, insulin resistance, and vascular dysfunction—may further contribute to this relationship.

However, current evidence remains limited by the predominance of observational designs and potential residual confounding. In addition, many studies are not specifically designed to assess psychiatric outcomes in PRISm, which may lead to underestimation or misclassification of mental health burden.

Notably, the magnitude of depression risk in PRISm approaches that reported in established chronic respiratory diseases (approximately 20–35%) (62), underscoring its clinical relevance and the need for routine psychological assessment.

#### **4.2. Anxiety and psychological distress**

Anxiety and psychological distress are also more prevalent among individuals with PRISm. Population-based studies indicate higher rates of anxiety diagnoses and increased symptom burden compared with individuals with normal lung function, independent of major confounders (10,63).

Clinically, anxiety in PRISm is often characterized by heightened perception of breathlessness, fear of exertion, and autonomic symptoms resembling panic episodes (64). This may lead to activity avoidance, physical deconditioning, and progressive functional decline, establishing a self-reinforcing cycle in which psychological and physical factors interact.

An additional contributing factor may be diagnostic uncertainty. Because PRISm is not consistently recognized as a distinct clinical entity, patients may experience uncertainty or dissatisfaction with medical explanations for their symptoms (65). This may contribute to increased healthcare utilization and reduced confidence in treatment.

Despite these observations, the relationship between anxiety and PRISm remains insufficiently characterized. Most studies rely on screening tools rather than clinical diagnoses, and longitudinal data are scarce.

From a clinical perspective, anxiety has important implications for treatment adherence, participation in rehabilitation, and physical activity levels—all of which influence long-term outcomes (66,67).

Furthermore, psychological distress may contribute to excess mortality through behavioral and physiological pathways, including autonomic dysregulation and systemic inflammation (68).

Taken together, these findings highlight that mental health is an integral component of PRISm rather than a secondary consequence. Routine screening for depression and anxiety should therefore be considered as part of comprehensive clinical assessment.

#### **Limitations**

This review has several limitations that should be considered when interpreting the findings. First, although a structured search strategy was applied, this study does not represent a fully systematic review, and therefore selection bias cannot be completely excluded. In addition, the review was not registered in PROSPERO, which may limit transparency and reproducibility.

Second, the available evidence on PRISm remains heterogeneous in terms of study design, population characteristics, and diagnostic definitions. Variability in spirometric criteria, including the use of fixed FEV<sub>1</sub>/FVC thresholds versus lower-limit-of-normal approaches, complicates cross-study comparisons and may influence prevalence estimates and reported associations.

Third, most of the included studies are observational in nature, limiting the ability to establish causal relationships. Associations between PRISm and clinical outcomes—particularly cardiometabolic and mental health conditions—may be affected by residual confounding, including smoking, obesity, and socioeconomic factors.

Fourth, data on psychosocial outcomes in PRISm are relatively limited and often derived from secondary analyses of large cohorts rather than studies specifically designed to investigate mental health in this population. As a result, depression and anxiety may be underdiagnosed or inconsistently measured across studies.

Fifth, potential publication bias should be considered, as studies reporting significant associations may be more likely to be published than those with null findings.

Finally, the lack of longitudinal and interventional studies limits understanding of

disease trajectories and the effectiveness of potential therapeutic strategies. Further prospective research is needed to clarify causal pathways and identify modifiable targets for intervention.

### Conclusion

PRISm represents a prevalent, clinically significant, and heterogeneous spirometric phenotype that extends beyond a simple functional abnormality and reflects a complex interaction between pulmonary, cardiometabolic, and systemic processes. Accumulating evidence indicates that PRISm is associated with persistent respiratory symptoms, reduced functional capacity, a high burden of comorbidities, and increased risk of cardiovascular and all-cause mortality. Importantly, this review highlights that PRISm is not only a respiratory phenotype but also a condition with substantial psychosocial implications. Depression and anxiety are consistently associated with PRISm and contribute to symptom burden, impaired quality of life, reduced physical activity, and increased healthcare utilization. However, psychosocial outcomes remain insufficiently studied and are often underrecognized in both research and clinical practice.

From a clinical perspective, recognition of PRISm as a distinct and clinically relevant

phenotype is essential for improving early detection, risk stratification, and patient management. Given that PRISm does not conform to traditional diagnostic frameworks, it is frequently underdiagnosed, leading to missed opportunities for intervention. A multidimensional approach that incorporates respiratory, cardiometabolic, and mental health assessment is therefore warranted.

Future research should focus on standardizing diagnostic criteria, identifying biologically and clinically meaningful PRISm subtypes, and clarifying longitudinal disease trajectories. In addition, interventional studies are needed to determine whether targeting modifiable factors—such as obesity, systemic inflammation, and physical inactivity—can alter disease progression and improve outcomes. Particular attention should be given to the role of mental health interventions, which remain largely unexplored in this population.

Overall, advancing the understanding of PRISm requires an integrated and multidisciplinary framework that moves beyond spirometric classification toward a more comprehensive model of respiratory and systemic health.

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