Research Square

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Longitudinal Pulmonary Function Progression and Risk of New-Onset Airflow Obstruction in SAD and PRISm: a Multi-Center Population-Based Cohort Study in Southwest China

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Research Article

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Abstract

Background

Small-airway dysfunction (SAD) and preserved-ratio impaired spirometry (PRISm) may precede persistent airflow obstruction, yet longitudinal data on pulmonary function progression and incident airflow obstruction in these phenotypes remain limited.

Methods

We analysed 10,692 adults from community spirometry-screening programmes in Southwest China, each with at least two quality-controlled examinations. Spirometry-defined airflow obstruction was defined as FEV1/FVC < 0.70; PRISm as FEV1/FVC ≥ 0.70 with FEV1 < 80% predicted; and SAD as FEV1/FVC ≥ 0.70 with at least two of MMEF, FEF50, and FEF75 < 65% predicted. Baseline spirometric phenotypes were categorized into five groups: normal spirometry, isolated SAD, isolated PRISm, PRISm with SAD, or airflow obstruction. Incidence rates were quantified per 1,000 person-years. Cox proportional hazards regression was used to identify risk factors associated with incident airflow obstruction, while random-intercept linear mixed-effects models were applied to characterize longitudinal FEV1 trajectories.

Results

At baseline, 5,054 participants (47.3%) had normal spirometry, 4,034 (37.7%) had isolated SAD, 24 (0.2%) had isolated PRISm, 277 (2.6%) had PRISm with SAD, and 1,303 (12.2%) had airflow obstruction. Among 9,389 participants without baseline airflow obstruction, 490 developed incident airflow obstruction during 21,804 person-years of follow-up (incidence rate: 22.5 per 1,000 person-years; cumulative risk: 5.22%). Phenotype-specific cumulative risks were 0.65% for normal spirometry, 9.77% for isolated SAD, 8.33% for isolated PRISm, and 22.02% for PRISm with SAD. Compared with normal spirometry, isolated SAD, isolated PRISm, and PRISm with SAD were all independent risk factors for incident airflow obstruction, with adjusted hazard ratios (HRs) of 12.01, 7.69, and 20.53, respectively, in the complete-case Cox model. Additional significant risk factors included male sex (adjusted HR 1.85) and current smoking (adjusted HR 1.44). The model yielded an apparent C-index of 0.843. The displayed phenotype-specific trajectories showed estimated annual FEV1 changes of -47.0 mL/year for normal spirometry, -37.0 mL/year for isolated SAD, + 3.2 mL/year for PRISm with SAD, and − 30.9 mL/year for airflow obstruction under the reference covariate profile.

Conclusions

Spirometry-defined SAD and PRISm identified heterogeneous short-term risks of incident airflow obstruction, with the highest risk in PRISm with SAD. These screening phenotypes require confirmation and should not be interpreted as clinical diagnoses in isolation.

Trial registration:

Chinese Clinical Trial Registry, ChiCTR1900024623. Registered 19 July 2019, before the first participant was enrolled.

Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition characterized by persistent airflow obstruction and substantial respiratory and systemic morbidity. China carries a large COPD burden; the nationally representative China Pulmonary Health study estimated an overall post-bronchodilator COPD prevalence of 8.6% among adults aged 20 years or older [1, 2]. COPD does not arise through a single pathway. Longitudinal studies have shown that some individuals develop COPD after accelerated decline from normal peak lung function, whereas others enter adulthood with reduced lung function and experience a more typical age-related decline [3]. This heterogeneity has increased interest in identifying “pre-COPD” states before conventional airflow obstruction is established [1].

Two spirometric patterns are especially relevant. Preserved-ratio impaired spirometry (PRISm), commonly defined by FEV1/FVC ≥ 0.70 with FEV1 < 80% predicted, is a heterogeneous phenotype associated with cardiometabolic comorbidity, transitions to and from normal or obstructive patterns, and increased mortality [4]. Small-airway dysfunction (SAD), operationalized in epidemiological studies by reduced mid-expiratory flow indices, is also common. A national Chinese study reported spirometry-defined SAD in 43.5% of adults and identified smoking, ambient particulate pollution, biomass exposure, and other factors as correlates [5]. These indices are available from routine spirometry, but they are variable, depend partly on FVC and manoeuvre quality, and should not be interpreted as a specific disease diagnosis in isolation [6, 7].

Prospective Chinese studies have linked PRISm, low peak flow, and spirometric SAD with incident COPD [8, 9]. Nevertheless, important gaps remain. There are few large, multicentre, community-based cohorts in Southwest China with repeated quality-controlled spirometry, and longitudinal phenotype transitions and FEV1 change remain insufficiently characterized. Better evidence could help community programmes distinguish individuals who need confirmatory testing and intensified prevention from those at low short-term risk.

We therefore used data from three community spirometry-screening programmes in Southwest China to (1) estimate the incidence of screening-defined fixed-ratio airflow obstruction, PRISm, and SAD; (2) quantify incident airflow obstruction across mutually exclusive baseline spirometric phenotypes; (3) identify demographic, clinical, and spirometric predictors of incident airflow obstruction; and (4)

characterize longitudinal FEV1 change. We hypothesized that baseline SAD and PRISm would be associated with a substantially higher risk of progression relative to normal spirometry.

Methods

Study design and setting

The West China Hospital of Sichuan University, in collaboration with regional medical consortia across Sichuan Province, established the Natural Population Cohort Study (NPCS), an integrative framework for investigating risk factors and pathogenesis of major chronic and endemic diseases in Southwest China [10]. This framework includes a dedicated COPD sub-cohort [11]. Since April 2020, over 40,000 participants from four sites (Mianzhu, Longquan, Pidu, and Ganzi) have been enrolled and are under active follow-up. The present study reports a longitudinal analysis of this ongoing COPD sub-cohort using repeated spirometry examinations. The manuscript was structured in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [12].

Participants

Eligible participants were permanent residents who took part in the spirometry-screening programme and had at least two examinations judged acceptable under programme quality-control procedures, together with the demographic and anthropometric information required for the planned analyses. Participants were excluded if, at the first screening, they had asthma, active tuberculosis, lung cancer, interstitial lung disease, or bronchiectasis; if spirometry was unacceptable; or if key information was missing.

The analytic cohort comprised 10,692 participants from three community screening sites (Mianzhu, Longquan and Pidu), each contributing two to four spirometry examinations. For incident airflow obstruction analysis, participants with baseline airflow obstruction were excluded; corresponding at-risk cohorts were similarly constructed for PRISm and SAD.

Spirometry and quality control

Spirometry was performed within the local screening programmes by trained and certified operators. All manoeuvres were pre-bronchodilator. Eligible participants, seated and using a disposable mouthpiece, were coached by operators to perform up to three manoeuvres with MasterScreen Pneumo spirometers (Vyaire Medical GmbH, Hoechberg, Germany). Each device was calibrated daily with a certified 3-L syringe. Acceptability criteria comprised a satisfactory start-of-test (extrapolated volume < 5% of FVC or < 150 mL), a satisfactory end-of-test (expiratory plateau ≥ 6 s), and absence of artifacts. Reproducibility required the two largest FVC and FEV_1 values to differ by ≤ 150 mL. Data were downloaded daily to the central system, and quality control was performed by expert reviewers according to American Thoracic

Society and European Respiratory Society criteria [6]. Those physically unable to complete spirometry were excluded. Tests with errors (e.g., extreme outliers, malformed numerical entries) were deemed unreliable and excluded.

Spirometric phenotypes

Screening-defined fixed-ratio airflow obstruction was defined as FEV1/FVC < 0.70. PRISm was defined as FEV1/FVC ≥ 0.70 with FEV1 < 80% predicted. SAD was defined as FEV1/FVC ≥ 0.70 with at least two of the following below 65% predicted: maximal mid-expiratory flow (MMEF, also termed FEF25–75), FEF50, and FEF75; at least two component indices had to be observed.

Five mutually exclusive baseline categories were defined: normal spirometry, isolated SAD, isolated PRISm, PRISm with SAD, and airflow obstruction. Of 301 participants meeting PRISm criteria, 24 had isolated PRISm and 277 had PRISm with SAD. The isolated SAD category contained 4,034 participants who met SAD criteria without PRISm or airflow obstruction. The five categories sum to the full cohort.

An incident screening event was the first follow-up examination meeting the relevant definition among participants free of that condition at baseline. Because post-bronchodilator testing and consecutive-visit confirmation were not uniformly available, outcomes represent newly observed spirometric phenotypes rather than adjudicated clinical diagnoses. Of 490 participants with obstruction at any follow-up, 423 were obstructed at the final visit and 67 had reverted to a non-obstructed result.

Covariates and outcomes

The primary outcome was newly observed screening-defined airflow obstruction. Secondary outcomes were incident PRISm, incident SAD, persistence of airflow obstruction at the final visit, and longitudinal change in FEV1. Candidate predictors included age, sex, BMI, smoking status, education level, mutually exclusive baseline phenotype, and baseline FEV1% predicted. Education level was treated as an ordered variable with five categories: primary school or below; junior high school; senior high school or vocational high school; college or university; and postgraduate or above.

Follow-up and person-time

The primary reconstruction followed the source convention and used total recorded follow-up from baseline to the final available examination as the event or censoring time; this reproduced 21,804 person-years among 9,389 participants at risk for obstruction. Because event times were observed only at discrete screening rounds, a sensitivity analysis instead assigned events to the first positive screening time. Baseline or exact examination dates were incomplete for a substantial subset, so event timing remains partly interval-censored.

Statistical analysis

Continuous variables were summarized as median (interquartile range) and categorical variables as number (percentage). Incidence rates were calculated as events divided by person-years and expressed per 1,000 person-years with exact Poisson 95% confidence intervals. Cumulative incidence proportions are presented with event counts and exact binomial 95% confidence intervals.

Among participants without baseline airflow obstruction, associations with newly observed airflow obstruction were estimated using Cox proportional-hazards regression with Efron handling of tied times. The complete-case model included 9,212 participants and 482 events. Covariates were age, sex, BMI, current smoking, education level, isolated SAD, isolated PRISm, PRISm with SAD, and baseline FEV1% predicted; normal spirometry was the phenotype reference. The model was $h_i(t) = h_0(t) \times \exp(\beta_{age}*age + \beta_{sex}*male + \beta_{bmi}*BMI + \beta_{smoke}*current\ smoking + \beta_{edu}*education\ level + \beta_{iSAD}*isolated\ SAD + \beta_{iPRISm}*isolated\ PRISm + \beta_{PRSAD}*PRISm\ with\ SAD + \beta_{FEV1}*FEV1\%\ predicted)$. Harrell's C-index described apparent discrimination and 100 bootstrap resamples estimated optimism. Approximate Schoenfeld residual tests screened proportional-hazards assumptions.

Longitudinal FEV1 was analysed in all eligible participants using a random-intercept linear mixed-effects model fitted by restricted maximum likelihood. Fixed effects included time, baseline age centred at 55 years, sex, BMI centred at 24 kg/m2, smoking status, education level centred at junior high school, baseline phenotype, time-by-sex, and time-by-phenotype interactions. The model was $FEV1_{ij} = \beta0 + b0_i + \beta1*time_{ij} + \beta2*male_i + \beta3*phenotype_i + \beta4*(time_{ij}*male_i) + \beta5*(time_{ij}*phenotype_i) + \beta6*age55_i + \beta7*BMI24_i + \beta8*smoking_i + \beta9*education_level_c,i + epsilon_{ij}$, where education_level_c denotes the ordered education level centred at junior high school.

Results

Cohort characteristics

The analytic cohort comprised 10,692 participants, of whom 7,796 had two examinations, 2,049 had three, and 847 had four. The median age was 55 years, and 67.3% were women. At baseline, 5,054 (47.3%) had normal spirometry, 4,034 (37.7%) had isolated SAD, 24 (0.2%) had isolated PRISm, 277 (2.6%) had PRISm with SAD, and 1,303 (12.2%) had airflow obstruction. In parallel, 4,311 participants (40.3%) met the SAD criterion irrespective of overlap with PRISm (Table 1 and Fig. 1).

Table 1
Overall characteristics and baseline spirometric phenotypes.

Characteristic	Overall value (N = 10,692)
Age, years	55.0 (49.0–61.0)
Sex	
Women	7,199 (67.3%)
Men	3,493 (32.7%)
BMI, kg/m2	24.2 (22.4–26.3)
Smoking status, n (%)	
Never smoker	8,291 (77.5%)
Former smoker	534 (5.0%)
Current smoker	1,867 (17.5%)
Education level, n (%)	
Primary school or below	2,899 (27.1%)
Junior high school	4,358 (40.8%)
Senior high school or vocational high school	2,229 (20.8%)
College or university	991 (9.3%)
Postgraduate or above	215 (2.0%)
Follow-up spirometry examinations	
Two examinations	7,796 (72.9%)
Three examinations	2,049 (19.2%)
Four examinations	847 (7.9%)
Baseline spirometric phenotypes	
Normal spirometry	5,054 (47.3%)
Isolated SAD	4,034 (37.7%)
Isolated PRISm	24 (0.2%)
PRISm with SAD	277 (2.6%)
Airflow obstruction	1,303 (12.2%)

Incidence of spirometric outcomes

During follow-up, 490 of 9,389 participants at risk had newly observed fixed-ratio obstruction over 21,804 person-years under the source time convention, corresponding to 22.5 events per 1,000 person-years (95% CI 20.5–24.6) and a cumulative risk of 5.22% (95% CI 4.78–5.69). Incident PRISm occurred in 183 of 9,088 participants over 21,166 person-years (8.7 per 1,000 person-years; 95% CI 7.4–10.0), and incident SAD occurred in 1,584 of 5,078 participants over 11,952 person-years (132.5 per 1,000 person-years; 95% CI 126.1–139.2).

For each outcome, the crude rate was highest in Mianzhu and lowest in Longquan (Table 2 and Fig. 2). Among the 490 participants with obstruction at any follow-up, 423 (86.3%) remained obstructed at the final visit and 67 (13.7%) did not. This instability, together with the biological and technical variability of mid-expiratory flows, supports reporting screening phenotypes rather than confirmed diagnoses.

Table 2
Incidence of spirometric outcomes overall, ordered as SAD, PRISm, and airflow obstruction.

Outcome	At risk	Events	Person-years	Rate /1,000 PY (95% CI)	Cumulative % (95% CI)
SAD, overall	5,078	1,584	11,952	132.5 (126.1-139.2)	31.19 (29.92–32.49)
Mianzhu	1,727	644	4,096	157.2 (145.3–169.9)	37.29
Pidu	1,602	419	3,204	130.8 (118.6–143.9)	26.15
Longquan	1,749	521	4,652	112.0 (102.6–122.0)	29.79
PRISm, overall	9,088	183	21,166	8.6 (7.4–10.0)	2.01 (1.73–2.32)
Mianzhu	3,196	103	7,484	13.8 (11.2–16.7)	3.22
Pidu	2,850	42	5,700	7.4 (5.3–10.0)	1.47
Longquan	3,042	38	7,982	4.8 (3.4–6.5)	1.25
Airflow obstruction, overall	9,389	490	21,804	22.5 (20.5–24.6)	5.22 (4.78–5.69)
Mianzhu	3,289	201	7,690	26.1 (22.6–30.0)	6.11
Pidu	2,998	149	5,996	24.9 (21.0–29.2)	4.97
Longquan	3,102	140	8,118	17.3 (14.5–20.4)	4.51

CI, confidence interval; PY, person-years.

Newly observed airflow obstruction by baseline phenotype

Risk differed substantially across baseline phenotypes. Among participants with normal spirometry, 33 of 5,054 had newly observed airflow obstruction (0.65%; 2.8 per 1,000 person-years). Among those with isolated SAD, 394 of 4,034 had the outcome (9.77%; 42.5 per 1,000 person-years). Among those with isolated PRISm, 2 of 24 had the outcome (8.33%; 41.7 per 1,000 person-years; 95% CI for cumulative risk 1.03-27.00%). Among those with PRISm with SAD, 61 of 277 had the outcome (22.02%; 103.4 per 1,000 person-years) (Table 3 and Fig. 3).

The isolated PRISm estimate was based on 24 participants and 2 events and was therefore highly imprecise. The substantially higher risk in PRISm with SAD indicates that the highest risk within PRISm was concentrated among participants who also met the SAD definition. These are unadjusted prognostic comparisons and should not be interpreted as causal effects.

Table 3
Newly observed airflow obstruction according to mutually exclusive baseline spirometric phenotype.

Baseline phenotype	At risk	Events	Cumulative incidence, % (95% CI)	Rate /1,000 PY (95% CI)
Normal spirometry	5,054	33	0.65 (0.45–0.92)	2.8 (1.9–3.9)
Isolated SAD	4,034	394	9.77 (8.87–10.72)	42.5 (38.4–47.0)
Isolated PRISm	24	2	8.33 (1.03-27.00)	41.7 (5.0-150.5)
PRISm with SAD	277	61	22.02 (17.28–27.37)	103.4 (79.1-132.8)

Markers of newly observed airflow obstruction

The multivariable Cox model included 9,212 participants with complete covariate data and 482 events. Compared with normal spirometry, adjusted HRs were 12.01 (95% CI 8.28–17.43) for isolated SAD, 7.69 (1.78–33.32) for isolated PRISm, and 20.53 (12.04–34.99) for PRISm with SAD. Male sex (1.85), current smoking (1.44), older age (1.05 per year), lower FEV1% predicted, lower BMI, and lower education level were also associated with risk (Table 4 and Fig. 4).

The apparent Harrell C-index was 0.843; the mean bootstrap optimism was 0.0025 and the 100-bootstrap optimism-corrected estimate was 0.840. The isolated PRISm estimate was imprecise because only two events occurred in this group. An approximate Schoenfeld residual screen suggested non-proportionality for education level ($P < 0.001$); its HR should therefore be interpreted as a time-averaged association pending a prespecified time-interaction sensitivity analysis.

Table 4
Univariable and multivariable Cox regression for newly observed airflow obstruction.

Variable	Univariable HR (95% CI)	P	Adjusted HR (95% CI)	P
Age, per year	1.07 (1.06–1.08)	< 0.001	1.05 (1.04–1.06)	< 0.001
Male sex	1.99 (1.66–2.38)	< 0.001	1.85 (1.48–2.33)	< 0.001
BMI, per kg/m2	0.97 (0.94-1.00)	0.077	0.95 (0.92–0.97)	< 0.001
Current smoker	1.95 (1.59–2.39)	< 0.001	1.44 (1.13–1.85)	0.004
Education level, per category increase	0.67 (0.61–0.74)	< 0.001	0.75 (0.68–0.83)	< 0.001
Isolated SAD vs normal spirometry	5.77 (4.62–7.22)	< 0.001	12.01 (8.28–17.43)	< 0.001
Isolated PRISm vs normal spirometry	2.19 (0.55–8.79)	0.268	7.69 (1.78–33.32)	0.006
PRISm with SAD vs normal spirometry	6.15 (4.69–8.05)	< 0.001	20.53 (12.04–34.99)	< 0.001
Baseline FEV1% predicted, per 1%	0.95 (0.95–0.96)	< 0.001	0.98 (0.97–0.99)	< 0.001

Longitudinal FEV1 change

The random-intercept model included 10,495 participants and 24,623 FEV1 observations. For a never-smoking woman aged 55 years with BMI 24 kg/m2, junior high school education, and normal spirometry at baseline, estimated baseline FEV1 was 2.396 L (Fig. 5A). The group-specific annual FEV1 changes were − 47.0 mL/year (95% CI -49.3 to -44.8) for normal spirometry, -37.0 mL/year (95% CI -39.4 to -34.6) for isolated SAD, + 3.2 mL/year (95% CI -6.1 to + 12.6) for PRISm with SAD, and − 30.9 mL/year (95% CI -35.5 to -26.3) for airflow obstruction. Isolated PRISm was omitted from Fig. 5B because its small sample size (n = 24) did not provide sufficiently robust support for graphical interpretation of the fitted trajectory; its coefficients remain in Table S1 in the Supplemental Materials. Figure 5B presents both model-predicted mean trajectories and group-specific annual changes with 95% CIs.

Discussion

Principal findings

In this community cohort with repeated spirometry, PRISm with SAD was associated with substantially higher risk than isolated PRISm. Cumulative risk of newly observed airflow obstruction was 0.65% with normal spirometry, 9.77% with isolated SAD, 8.33% with isolated PRISm, and 22.02% with PRISm with SAD. The isolated PRISm estimate was based on only two events and was imprecise. In the adjusted model, PRISm with SAD had the largest phenotype HR, followed by isolated SAD and isolated PRISm. Higher education level was associated with lower risk, although proportional-hazards diagnostics suggested a possible time-varying association. This graded pattern supports the pre-COPD concept that physiologic abnormalities can precede persistent airflow obstruction, while also underscoring that such markers remain probabilistic rather than diagnostic [13].

The five mutually exclusive baseline categories clarify the overlap between SAD and PRISm. The 4,034-person isolated SAD category excludes PRISm and airflow obstruction; the 301 PRISm cases divide into 24 isolated PRISm and 277 PRISm with SAD. This cross-classification preserves the full cohort denominator and shows which component drives the combined PRISm estimate.

Comparison with previous studies

The baseline burden of the SAD criterion (40.3%) is close to the 43.5% reported by the national China Pulmonary Health study [5]. The 12.2% prevalence of screening-defined fixed-ratio airflow obstruction was higher than the national post-bronchodilator COPD prevalence estimate of 8.6% [2]. Differences in age, exposure, selection into repeated screening, and pre-bronchodilator measurement may contribute.

Our findings align qualitatively with prospective Chinese evidence that spirometric SAD and PRISm identify increased risk of later obstructive spirometry [8, 9] and with multinational BOLD and UK Biobank data showing that isolated small-airways obstruction predicted later chronic airflow obstruction [14]. Direct numerical comparison is limited by differences in SAD indices, lower-limit-of-normal versus fixed-ratio definitions, and post-bronchodilator confirmation. The adjusted HR of 12.01 for isolated SAD and 20.53 for PRISm with SAD are substantially larger than estimates reported for some pre-COPD indicators. Related measurement components, threshold crossing, adjustment for baseline FEV1, shorter follow-up, and regression to the mean may contribute; these HRs indicate prognostic proximity rather than causal effects.

PRISm was heterogeneous across the mutually exclusive categories. PRISm with SAD had the highest crude absolute risk, while isolated PRISm had 2 events among 24 participants and a wide confidence interval. Similar heterogeneity was observed in the Rotterdam Study, where PRISm included transitions to normal spirometry, progression to airflow obstruction, and persistent PRISm with different lung-function and mortality profiles [15]. The small isolated PRISm group prevents a precise ranking of its risk relative to isolated SAD. Future studies should prespecify cross-classification of PRISm and SAD and ensure adequate sample size in each stratum.

FEV1 change

Model-predicted FEV1 levels and annual changes differed across baseline phenotypes. Normal spirometry, isolated SAD, and airflow obstruction showed declining group-average FEV1. Although the normal-spirometry group had the largest absolute decline, this should not be interpreted as more rapid clinical progression: the group started from a higher FEV1, and its approximate relative annual decline (-1.96%) was similar to those for isolated SAD (-1.78%) and airflow obstruction (-1.82%). PRISm with SAD had the lowest predicted baseline FEV1 and a near-flat fitted trajectory. Its small positive estimate should not be interpreted as physiological improvement; regression to the mean, baseline thresholding, measurement timing, and selective follow-up may contribute. Thus, the clinically relevant distinction among the abnormal phenotypes is their reduced baseline lung-function reserve and increased risk of newly observed airflow obstruction, rather than a consistently faster mean FEV1 decline. Isolated PRISm was not displayed because the subgroup contained only 24 participants. A random-intercept/random-slope model with flexible time functions and external validation would better characterize between-person heterogeneity if supported by the number and timing of measurements.

Clinical and public health implications

The most direct clinical implication is risk stratification, not immediate diagnosis or treatment. A participant with reduced MMEF, FEF50, or FEF75 but preserved FEV1/FVC should receive a quality review of the manoeuvre and, when clinically appropriate, repeat spirometry—ideally post-bronchodilator—rather than being labelled with COPD. Persistent abnormalities can prompt assessment of symptoms, smoking and second-hand smoke, occupational dust or fumes, biomass exposure, ambient pollution, previous respiratory infections, and comorbid disease.

Community programmes could use a staged pathway: normal spirometry with low clinical risk may remain in routine prevention; persistent isolated SAD, isolated PRISm, or PRISm with SAD may trigger closer surveillance and intensive risk-factor modification; and newly observed airflow obstruction should be confirmed and clinically evaluated according to GOLD recommendations [1]. Smoking cessation remains the highest-priority intervention. The present data do not establish that inhaled pharmacotherapy benefits asymptomatic individuals with isolated SAD, isolated PRISm, or PRISm with SAD. Consistent with this caution, the RETHINC randomized trial found no symptomatic benefit from dual long-acting bronchodilation in symptomatic tobacco-exposed people with preserved spirometry [16]. Because that trial enrolled a different population and addressed a different treatment question, it does not directly establish management for the phenotypes studied here.

Strengths and limitations

Strengths include the large sample size, three community cohorts, repeated spirometry, direct recomputation of phenotypes from raw indices, person-time incidence estimates, mutually exclusive classification of isolated PRISm and PRISm with SAD, and a formula-based random-intercept model with prespecified sex and phenotype interactions.

Several limitations require emphasis. First, this retrospective analysis included only screening participants with at least two examinations; selection into initial and repeat screening may limit

generalizability. Second, airflow obstruction was based on a fixed FEV1/FVC threshold and often pre-bronchodilator spirometry. Of 490 participants with any follow-up airflow obstruction, 67 did not have airflow obstruction at the final visit. These data can overclassify older adults, underclassify younger adults, include reversible obstruction, and capture threshold crossing. Post-bronchodilator, lower-limit-of-normal or z-score, and repeated-confirmation analyses are needed. Age-dependent lower-limit-of-normal and z-score sensitivity analyses using validated reference equations, such as the Global Lung Function Initiative 2012 equations, would quantify the effect of threshold choice [7, 17]. Finally, a random-intercept model cannot identify latent trajectory classes, and the isolated PRISm subgroup was too small for precise inference.

Conclusions

In this large community cohort, spirometry-defined isolated SAD, isolated PRISm, and PRISm with SAD identified participants with different short-term risks of newly observed airflow obstruction. PRISm with SAD had substantially higher risk than isolated PRISm, although the isolated PRISm estimate was imprecise because of the small subgroup. These screening phenotypes may help identify individuals who warrant spirometry quality review, repeat testing—preferably post-bronchodilator—risk-factor assessment, smoking cessation support when applicable, and longitudinal surveillance. The observational findings should not be used alone to assign a COPD diagnosis or initiate pharmacologic treatment. Larger samples of participants with isolated PRISm, post-bronchodilator confirmation, longer follow-up, and external validation are necessary before clinical implementation.

Abbreviations

ATS
American Thoracic Society
BMI
body mass index
CI
confidence interval
COPD
chronic obstructive pulmonary disease
ERS
European Respiratory Society
FEF50
forced expiratory flow at 50% of forced vital capacity
FEF75
forced expiratory flow at 75% of forced vital capacity
FEV1
forced expiratory volume in 1 s
FVC

forced vital capacity
GOLD
Global Initiative for Chronic Obstructive Lung Disease
HR
hazard ratio
IQR
interquartile range
MMEF
maximal mid-expiratory flow
NPCS
Natural Population Cohort Study
PRISm
preserved ratio impaired spirometry
PY
person-years
SAD
small-airway dysfunction
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of West China Hospital, Sichuan University (No. 1763). All participants provided written informed consent. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available from the corresponding authors on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Y.L and C.C conceived the longitudinal analysis, curated and analysed the data, interpreted the results, and drafted the manuscript. Y.L contributed to cohort design, data acquisition, and methodological review. R. Z and W. L supervised the study, provided resources, interpreted the findings, and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

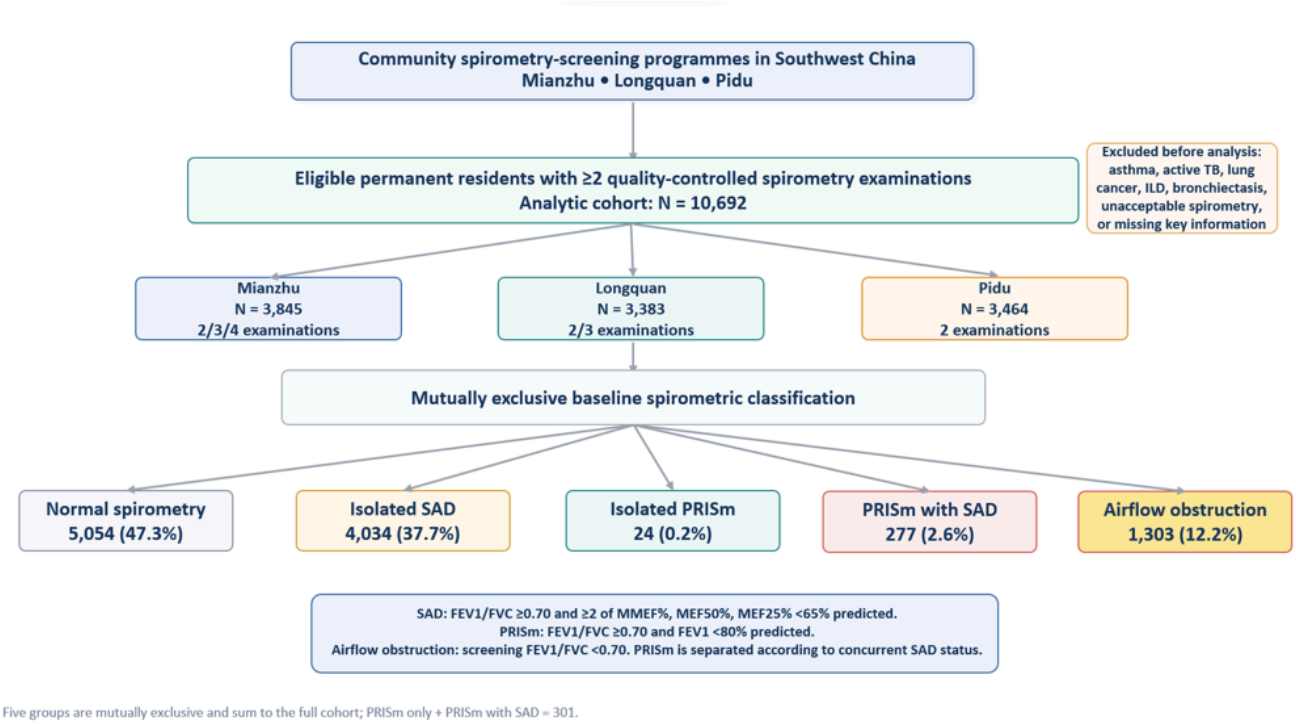


Figure 1

Analytic cohort and mutually exclusive baseline spirometric phenotypes: normal spirometry, isolated SAD, isolated PRISm, PRISm with SAD, and airflow obstruction. SAD, small-airway dysfunction; PRISm, preserved-ratio impaired spirometry.

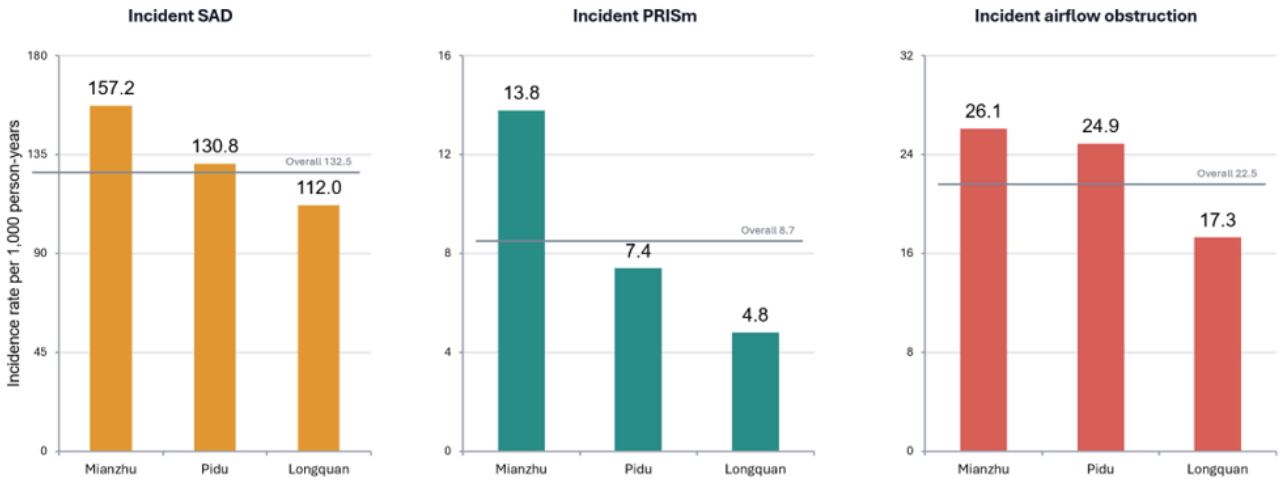


Figure 2

Incidence rates of SAD, fixed-ratio airflow obstruction, and PRISm by centre.

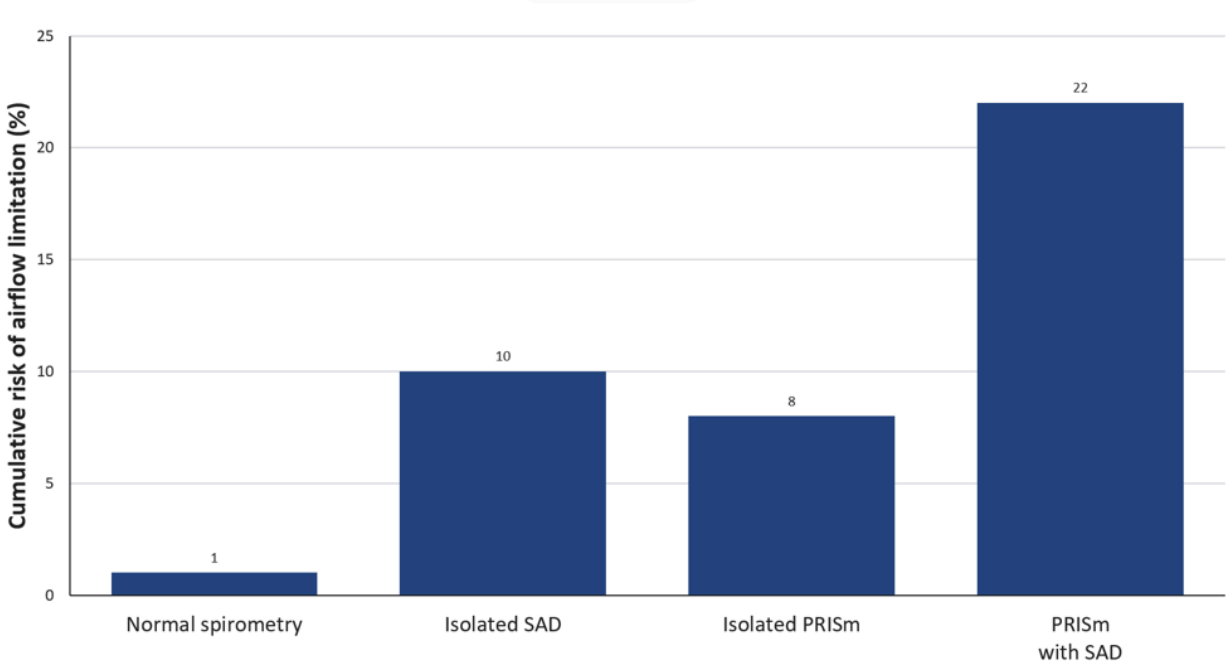
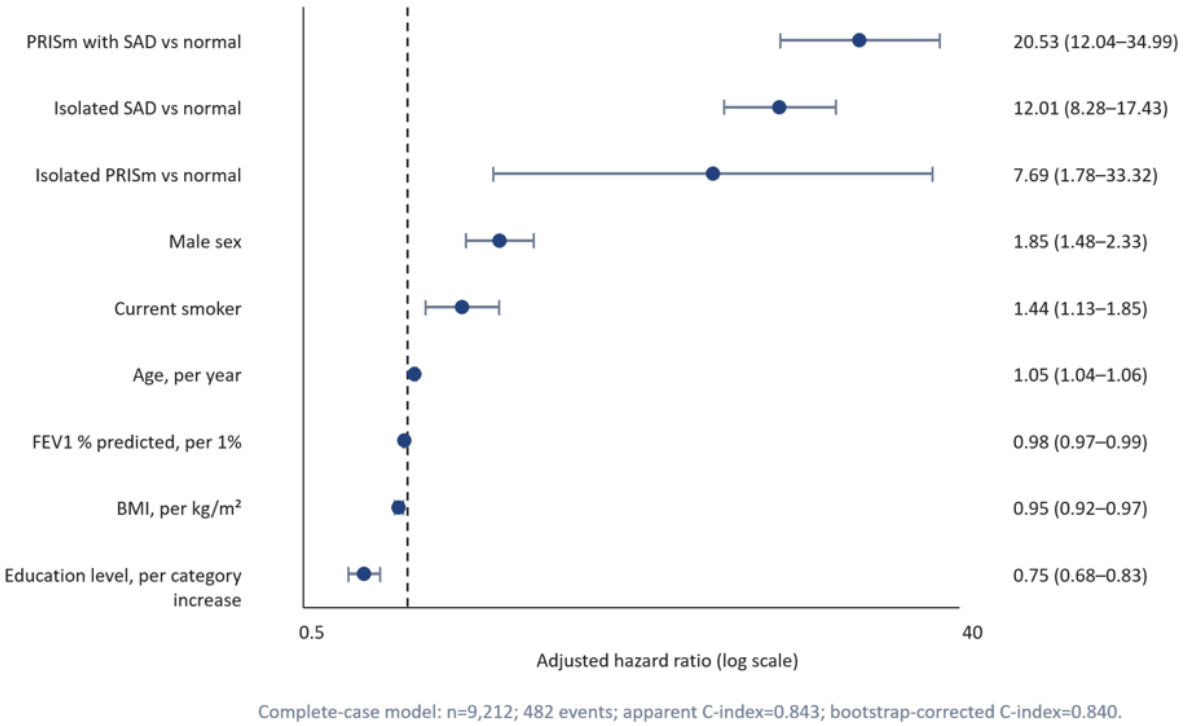


Figure 3

Cumulative risk of newly observed airflow obstruction by baseline phenotype.



Complete-case model: n=9,212; 482 events; apparent C-index=0.843; bootstrap-corrected C-index=0.840.

Figure 4

Forest plot of adjusted markers of newly observed airflow obstruction.

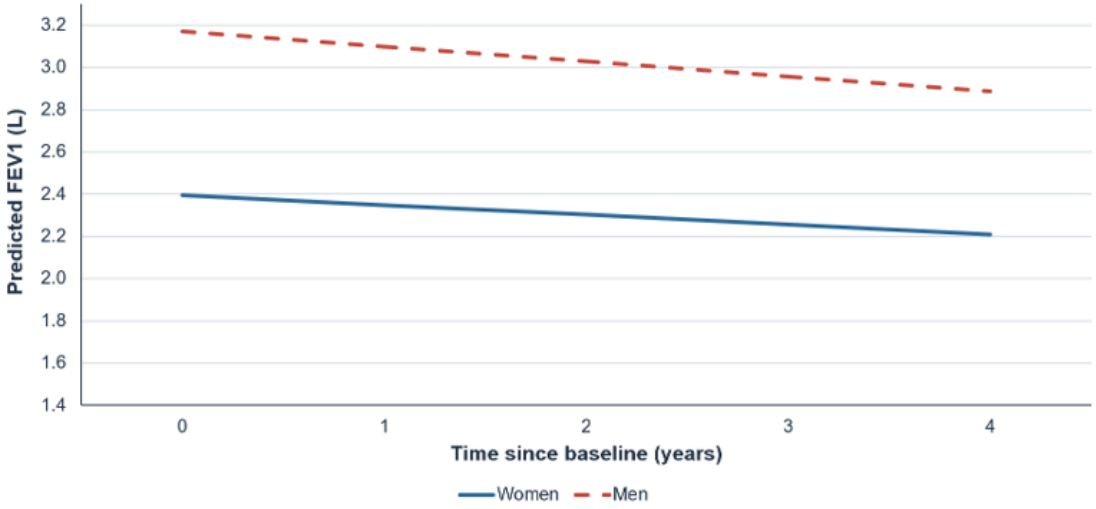


Figure 5A.

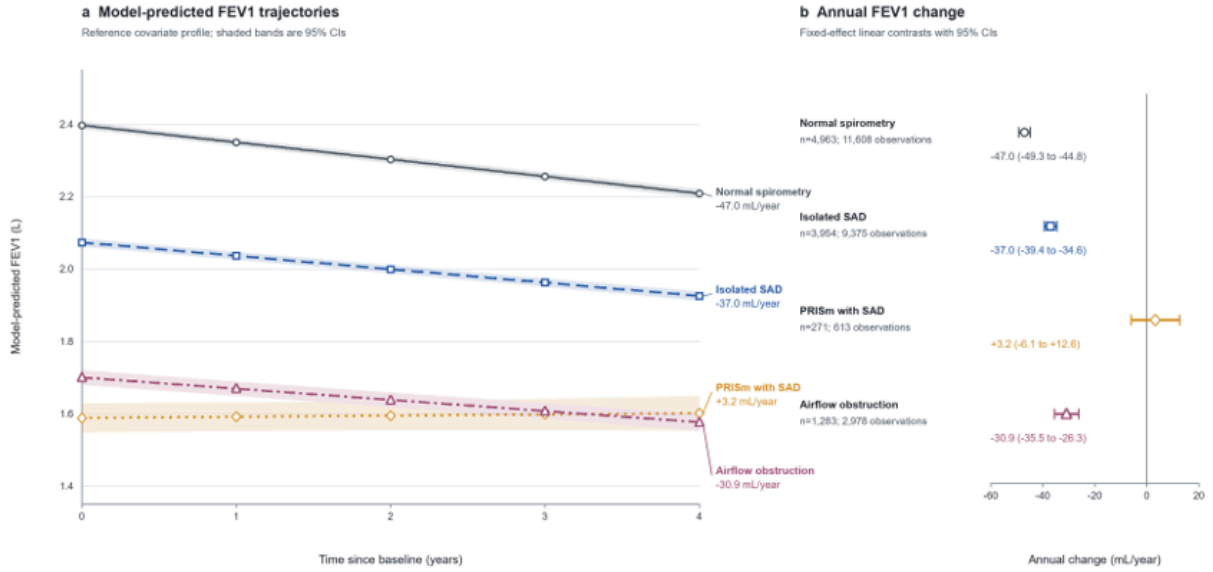


Figure 5B.

Figure 5

5A. Model-predicted FEV1 trajectories by sex among participants with normal spirometry at baseline, for a never-smoker aged 55 years with BMI 24 kg/m2 and junior high school education.

5B. Model-predicted FEV1 trajectories and annual changes for four baseline spirometric phenotypes. The left panel shows fixed-effect mean trajectories with 95% confidence bands; the right panel shows group-specific annual changes with 95% CIs calculated as linear contrasts. Predictions use the reference covariate profile (female sex, age 55 years, BMI 24 kg/m2, never-smoking status, and junior

high school education). Isolated PRISm is not displayed because its small sample size (n=24) did not support sufficiently robust graphical interpretation; its full coefficients are reported in Table S1. Curves represent model-based population means rather than individual disease courses.

Supplementary Files

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- SupplementalMaterials.docx