2021 COPD school

# Update of the preserved ratio impaired spirometry (PRISm)

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# CONTENTS

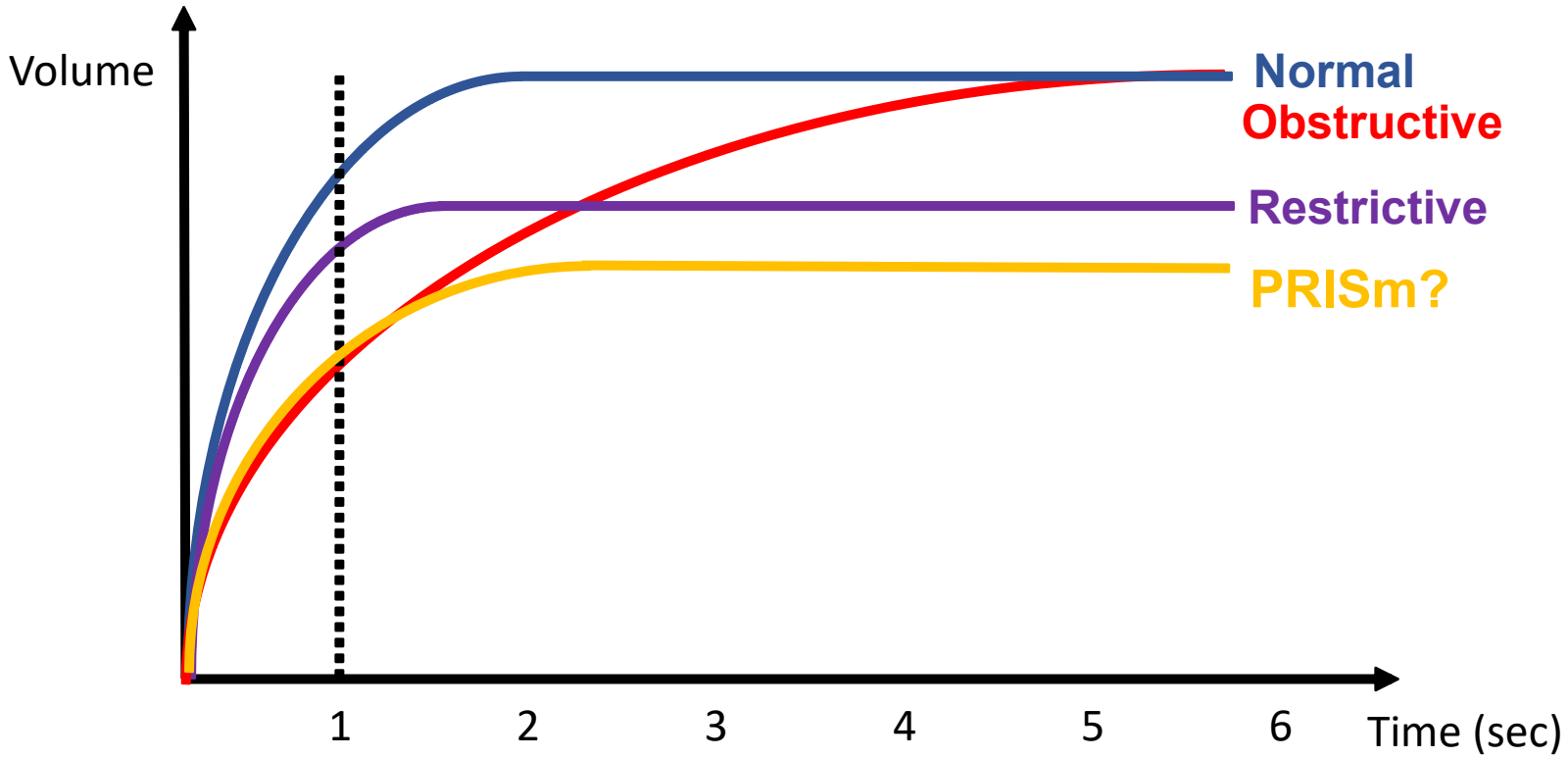
# INTRODUCTION

# PRISm (Preserved Ratio Impaired Spirometry)

- $FEV_1/FVC$ ratio > 70% → 
- Predicted $FEV_1$ < 80% → FVC < 80%?

# PRISm

- PRISm은 어디에? **Restrictive pattern?**



# PRISm = restrictive pattern?

- **FVC** predicted a reduced **TLC** with an accuracy of approximately **50%.**

**Table 4—*ATS Algorithm Predicting a Reduced TLC**

| Spirometric Restrictive Pattern | TLC Reference Values | | | |
|---|---|---|---|---|
| | Goldman and Becklake[9] | | Crapo et al[10] | |
| | Normal | Reduced | Normal | Reduced |
| FVC (n = 219) | | | | |
| Present (n = 60) | 27 | 33 | 35 | 25 |
| Absent (n = 159) | 158 | 1 | 158 | 1 |
| $FEV_6$ (n = 205) | | | | |
| Present (n = 51) | 22 | 29 | 30 | 21 |
| Absent (n = 154) | 152 | 2 | 152 | 2 |

*Data are presented as No. of patients.

Swanney et al. Chest 2004;126:1861-6

# PRISm = restrictive pattern?

- **FVC** predicted a reduced **TLC** poorly

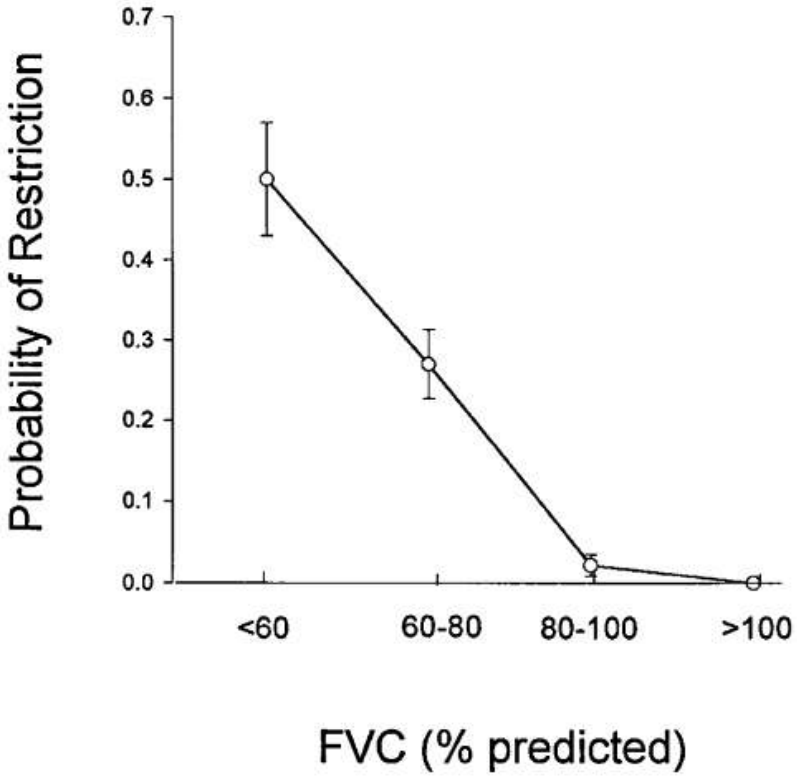



FIGURE 1. Ability of FVC percent predicted to independently predict pulmonary restriction.

*Aaron et al. Chest 2019;115:869-73*

# PRISm

- $FEV_1$/FVC ratio > 70%
- Predicted $FEV_1$ < 80%
- Predicted FVC ?

➔ Restrictive?

➔ Obstructive?

# PRISm

- GOLD-Unclassified

## [GOLD 2001 ver.]

TABLE 2. CLASSIFICATION OF COPD BY SEVERITY

| Stage | Characteristics |
|---|---|
| 0: At Risk | Normal spirometry<br>Chronic symptoms (cough, sputum production) |
| I: Mild COPD | $FEV_1/FVC < 70\%$<br>$FEV_1 \geqslant 80\%$ predicted<br>With or without chronic symptoms (cough, sputum production) |
| II: Moderate COPD | $FEV_1/FVC < 70\%$<br>$30\% \leqslant FEV_1 < 80\%$ predicted<br>(IIA: $50\% \leqslant FEV_1 < 80\%$ predicted)<br>(IIB: $30\% \leqslant FEV_1 < 50\%$ predicted)<br>With or without chronic symptoms (cough, sputum production, dyspnea) |
| III: Severe COPD | $FEV_1/FVC < 70\%$<br>$FEV_1 < 30\%$ predicted, or the presence of respiratory failure,* or clinical signs of right heart failure |

# PRISm

# STUDIES

# Clinical and Radiographic Predictors of GOLD–Unclassified Smokers in the COPDGene Study

Emily S. Wan[1], John E. Hokanson[2], James R. Murphy[3], Elizabeth A. Regan[3], Barry J. Make[3], David A. Lynch[3], James D. Crapo[3], Edwin K. Silverman[1], and the COPDGene Investigators

[1]Channing Laboratory and Pulmonary and Critical Care Division, Brigham and Women's Hospital, Boston, Massachusetts; [2]Department of Epidemiology, Colorado School of Public Health, University of Colorado Denver, Denver, Colorado; and [3]Department of Medicine, National Jewish Health, Denver, Colorado

- **COPDGene Study**

- Subjects with 10 or more pack-years of smoking

- Age between 45 and 80 years

- from 21 clinical centers throughout the United States

Prevalence of PRISm (GOLD-U): **9.1%**

*Wan et al.*
*Am J Respir Crit Care Med*
*2011;184:57-63*

# PRISm

- Characteristics of PRISm (GOLD-U)

TABLE 1. UNIVARIATE COMPARISONS BETWEEN GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE–UNCLASSIFIED SUBJECTS, SMOKING CONTROL SUBJECTS, AND SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE STAGES 2–4)

| | GOLD-U Subjects | Smoking Control Subjects | Subjects with COPD |
|---|---|---|---|
| N | 227 | 1,001 | 1,059 |
| Age, yr | 58.5 (8.7) | 57.8 (8.9) | 64.1 (8.4)* |
| Male | 48.0 | 49.2 | 51.8 |
| Non-white race | 40.5 | 32.5* | 18.8* |
| Pack-years | 43.7 (26.8) | 37.5 (20.6)* | 53.3 (26.7)* |
| Current smoking | 52.9 | 51.9 | 33.2* |
| Heart rate | 76.8 (13.1) | 74.3 (12.7)* | 77.8 (13.1) |
| BMI | 31.9 (7.2) | 28.8 (5.9)* | 28.0 (6.2)* |
| 6-min walk distance, ft | 1,251.7 (405.4) | 1,491.8 (405.2)* | 1,136.6 (429.1)* |
| Resting $O_2$ saturation | 96.3 (2.4) | 97.0 (1.8)* | 94.5 (3.6)* |
| $FEV_1$, % predicted | 70.4 (7.4) | 97.9 (12)* | 48.9 (18.1)* |
| FVC, % predicted | 71.7 (8.3) | 96.7 (12.1)* | 76.3 (17.7)* |
| % Emphysema† | 1.8 (2) | 2.7 (3.0)* | 15.5 (13.3)* |
| % Gas trapping‡ | 11.8 (8.5) | 11.7 (9.5) | 42.3 (20.3)* |
| Pi10§ | 3.8 (0.1) | 3.7 (0.1)* | 3.8 (0.1) |
| Subsegmental wall area %‖ | 65.0 (2.4) | 63.0 (2.2)* | 65.7 (2.4)* |
| TLC, % predicted | 79.4 (13) | 93.3 (15.1)* | 102.6 (16.8)* |

# PRISm

- Characteristics of PRISm (GOLD-U)

| | GOLD-U Subjects | Smoking Control Subjects | Subjects with COPD |
|---|---|---|---|
| Functional residual capacity, % predicted | 87.0 (18) | 89.9 (20.1) | 128.9 (33.4)* |
| Long-acting β-agonist, % of users | 13.7 | 3.7* | 51.7* |
| Long-acting muscarinic antagonist, % of users | 8.4 | 2.3* | 44.2* |
| Inhaled corticosteroids, % of users | 15.9 | 4.7* | 53.6* |
| Oral steroids, % of users | 2.6 | 0.4* | 6.2* |
| St. George's Respiratory Questionnaire | 27.6 (23.0) | 15.5 (17.4)* | 40.3 (21.1)* |
| MMRC | 1.4 (1.5) | 0.7 (1.1)* | 2.2 (1.4) * |
| Chronic cough | 30 | 21.6* | 38.2* |
| Chronic sputum | 22.9 | 17.9 | 35.9* |
| Chronic bronchitis | 17.6 | 13.3 | 27.3* |
| Asthma, ever | 16.7 | 10.9* | 24.1* |
| Asthma, current | 9.7 | 5.4* | 17.1* |
| Positive bronchodilator response | 13.6 | 9.5 | 36.1* |
| History of CHF | 5.3 | 0.8* | 5.1 |
| Diabetes | 22.5 | 12* | 11.9* |
| Hypertension | 48.5 | 35.5* | 47.5 |
| Stroke | 3.1 | 1.6 | 3.5 |
| TIA | 3.5 | 1.4* | 2.7 |
| Obstructive sleep apnea | 20.7 | 12* | 16.6 |

# PRISm

- Characteristics of PRISm (GOLD-U)

**TABLE 2. PREVALENCE OF RESTRICTIVE ABNORMALITIES IN GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE–UNCLASSIFIED SUBJECTS, SMOKING CONTROL SUBJECTS, AND SUBJECTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE**

| | GOLD-U Subjects | Smoking Control Subjects | Subjects with COPD |
|---|---|---|---|
| TLC,* L | 4.5 (1.1) | 5.3 (1.3)† | 6.0 (1.4)† |
| TLC, % predicted | 79.4 (13) | 93.3 (15.1)† | 102.6 (16.8)† |
| FVC < 80% predicted, % of subjects | 88.6 | 6.0† | 57.9† |
| TLC < 80% predicted, % of subjects | 56.3 | 17.8† | 9.0† |
| TLC < LLN, % of subjects | 45.5 | 13.8† | 7.2† |

*Definition of abbreviations*: COPD = chronic obstructive pulmonary disease; GOLD-U = Global Initiative for Obstructive Lung Disease–Unclassified; TLC = total lung capacity.

Data are presented as mean (SD) or percent.

* Based on chest CT measurements.

† Denotes *P* value < 0.05 when compared with GOLD-U subjects.

*Wan et al.*
*Am J Respir Crit Care Med*
*2011;184:57-63*

# PRISm

- PRISm (GOLD-U) vs. control

**TABLE 3. MULTIVARIABLE MODELS OF GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE–UNCLASSIFIED STATUS**

| | OR | 95% CI |
|---|---|---|
| GOLD-U versus Smoking Control Subjects | | |
| Clinical variables* | | |
| Resting $O_2$ saturation | 0.867 | 0.803–0.935 |
| BMI | 1.041 | 1.016–1.065 |
| History CHF | 5.016 | 1.877–13.409 |
| 6MWD (per 100 ft) | 0.890 | 0.857–0.924 |
| Clinical + radiographic variables† | | |
| Diabetes mellitus | 1.579 | 1.016–2.452 |
| Pack-years | 1.010 | 1.003–1.018 |
| Resting $O_2$ saturation | 0.882 | 0.809–0.960 |
| BMI | 1.030 | 1.004–1.057 |
| 6MWD (per 100 ft) | 0.948 | 0.905–0.993 |
| History of CHF | 3.460 | 1.107–10.817 |
| TLC,‡ L | 0.767 | 0.651–0.904 |
| Subsegmental wall area % | 1.302 | 1.202–1.409 |

*Wan et al.*
*Am J Respir Crit Care Med*
*2011;184:57-63*

# PRISm

- PRISm (GOLD-U) vs. COPD

| GOLD-U versus subjects with COPD (GOLD stages 2–4) | | |
|---|---|---|
| Clinical variables[§] | | |
| Age (per 10 yr) | 0.630 | 0.490–0.810 |
| BMI | 1.121 | 1.089–1.154 |
| Resting $O_2$ saturation | 1.244 | 1.149–1.347 |
| Bronchodilator response | 0.266 | 0.167–0.424 |
| 6MWD (per 100 ft) | 1.098 | 1.047–1.150 |
| Asthma (current) | 0.407 | 0.235–0.705 |
| Nonwhite race | 1.458 | 0.926–2.295[‖] |
| Diabetes mellitus | 2.317 | 1.427–3.761 |
| Chronic bronchitis | 0.533 | 0.339–0.838 |
| Clinical + radiographic variables[¶] | | |
| Bronchodilator response | 0.321 | 0.180–0.572 |
| Resting $O_2$ saturation | 1.159 | 1.048–1.283 |
| BMI | 1.066 | 1.028–1.105 |
| % Emphysema | 0.752 | 0.661–0.856 |
| % Gas trapping | 0.926 | 0.899–0.954 |
| TLC,[‡] L | 0.670 | 0.527–0.851 |
| Subsegmental wall area % | 0.774 | 0.693–0.865 |

*Wan et al.*
*Am J Respir Crit Care Med*
*2011;184:57-63*

# PRISm

- Obese (BMI ≥ 30 kg/m$^2$) 多 (**58.6%**)

TABLE 6. CHARACTERISTICS OF OBESE VERSUS NONOBESE GLOBAL INITIATIVE FOR OBSTRUCTIVE LUNG DISEASE–UNCLASSIFIED SUBJECTS

| | Obese | Nonobese |
|---|---|---|
| N | 133 | 94 |
| Age, yr | 58.0 (8.8) | 59.3 (8.6) |
| Sex, % male | 46.6 | 50.0 |
| Race, % African American | 39.9 | 41.5 |
| Pack-years | 44.5 (27.7) | 42.5 (25.7) |
| Current smoking (%) | 49.6 | 57.5 |
| $FEV_1$ % predicted | 70.0 (7.5) | 71.0 (7.4) |
| $FEV_1$/FVC ratio | 0.77 (0.05) | 0.76 (0.05) |
| 6MWD | 1,190.4 (412.1) | 1,338.4 (381.3)* |
| % Emphysema | 1.7 (1.7) | 1.8 (2.3) |
| % Gas trapping | 10.9 (6.2) | 13.2 (11.0) |
| Subsegmental wall area % | 65.1 (2.3) | 64.9 (2.4) |
| Pi10 | 3.82 (0.13) | 3.78 (0.11)* |
| Resting $O_2$ saturation | 95.8 (2.5) | 96.9 (1.9)* |
| MMRC | 1.7 (1.5) | 1.0 (1.3)* |
| SGRQ | 31.9 (24.2) | 21.5 (19.9)* |

*Wan et al.*
*Am J Respir Crit Care Med 2011;184:57-63*

# Study I: Summary

- PRISm are a heterogeneous group with **significant symptoms** and **functional limitation**

- PRISm have increased **BMI, reduced TLC, and diabetes**.

*Wan et al.*
*Am J Respir Crit Care Med*
*2011;184:57-63*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2011 VOL. 364 NO. 10

# Lung Volumes and Emphysema in Smokers with Interstitial Lung Abnormalities

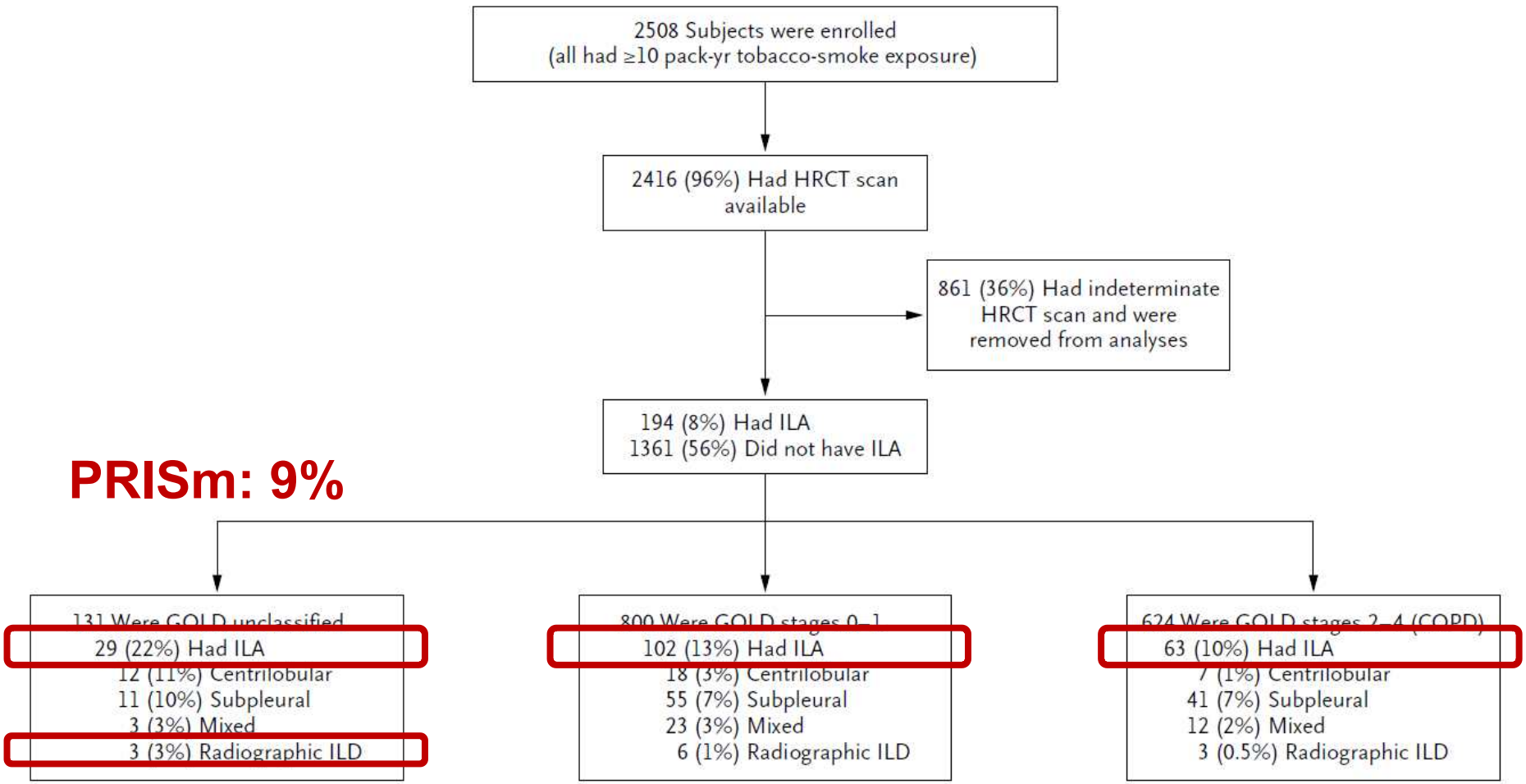
George R. Washko, M.D., M.M.Sc., Gary M. Hunninghake, M.D., M.P.H., Isis E. Fernandez, M.D., Mizuki Nishino, M.D., Yuka Okajima, M.D., Tsuneo Yamashiro, M.D., James C. Ross, M.S., Raúl San José Estépar, Ph.D., David A. Lynch, M.D., John M. Brehm, M.D., M.P.H., Katherine P. Andriole, Ph.D., Alejandro A. Diaz, M.D., Ramin Khorasani, Ph.D., Katherine D'Aco, M.S., Frank C. Sciurba, M.D., Edwin K. Silverman, M.D., Ph.D., Hiroto Hatabu, M.D., Ph.D., and Ivan O. Rosas, M.D., for the COPDGene Investigators*

- COPDGene Study
- HRCT scans

→ Interstitial lung abnormalities **(ILA): 8%**

*Washko et al. N Engl J Med 2011;364:897-906*

A

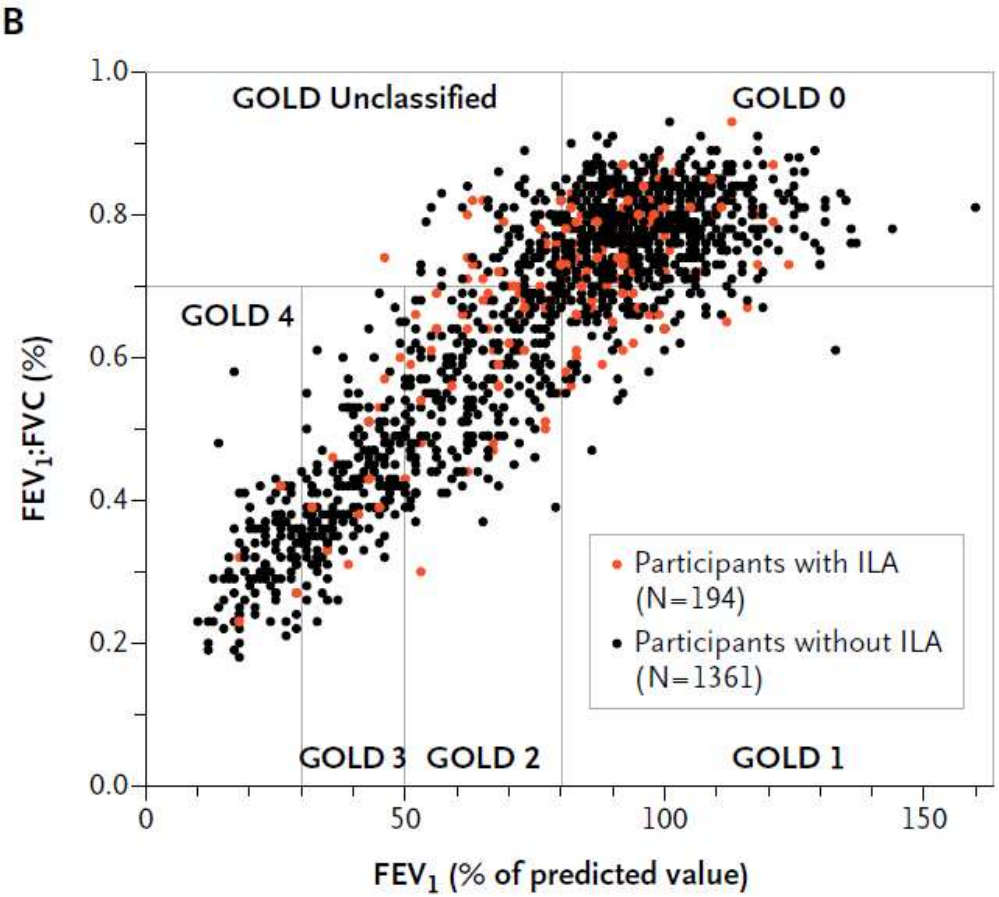



**PRISm: 9%**

*Washko et al. N Engl J Med 2011;364:897-906*

# ILA in PRISm

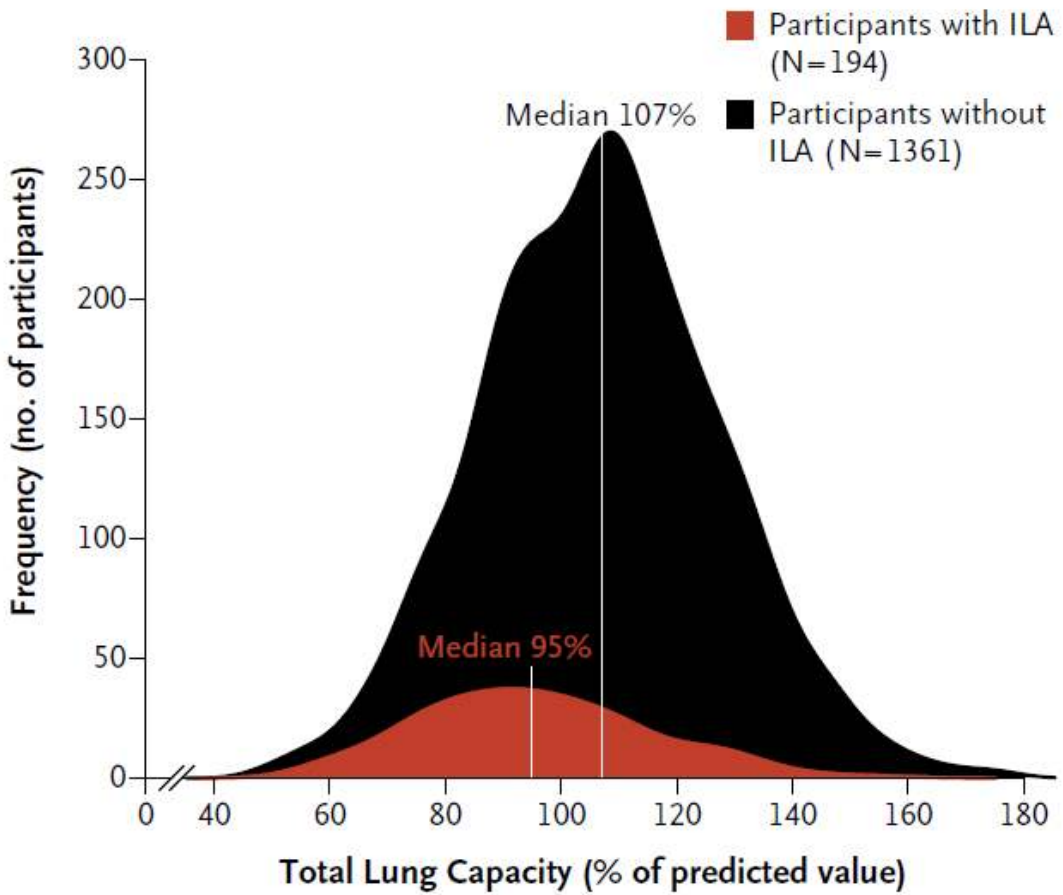
- **ILA in GOLD-U**




*Washko et al. N Engl J Med 2011;364:897-906*

# Prediction of ILA

- **TLC → ILA ??**




*Washko et al. N Engl J Med 2011;364:897-906*

# Study II: Summary

- [illegible] **do not have ILA**.

*Washko et al.*
*N Engl J Med*
*2011;364:897-906*

# Development and validation of a claims-based prediction model for COPD severity☆

Dendy Macaulay [a,*], Shawn X. Sun [b], Rachael A. Sorg [a], Sherry Y. Yan [a], Gourab De [a], Eric Q. Wu [c], Paul F. Simonelli [d]

[a] Analysis Group, Inc., New York, NY, USA
[b] Forest Research Institute, Jersey City, NJ, USA
[c] Analysis Group, Inc., Boston, MA, USA
[d] Geisinger Health System, Danville, PA, USA

- Geisinger Health System (GHS)

- Integrated health system in Pennsylvania

(3 hospitals, 40 clinics, 3 research centers – offers insurance coverage)

- [illegible]

- **GOLD-U: ratio preserved ($FEV_1$?)**

*Macaulay et al. Resp Med 2013;107:1568-77*

# PRISm (GOLD-U)

Table 2 Patient characteristics potentially associated with disease severity (demographics, comorbidities, therapies, and exacerbations).[a]

| | Observed COPD severity category | | |
|---|---|---|---|
| | GOLD-Unclassified<br>*N* = 886 | Mild/Moderate<br>*N* = 683 | Severe/Very Severe<br>*N* = 459 |
| *Demographics* | | | |
| Age on index date,[b] mean (SD) | 67.4 (12.5) | 69.9 (11.2)* | 70.0 (10.0)* |
| Male, *N* (%) | 463 (52.3%) | 447 (65.4%)* | 297 (64.7%)* |
| *Spirometry test results* | | | |
| $FEV_1$ predicted | 79.2 (18.4) | 69.0 (14.1)* | 36.2 (9.3)* |
| $FEV_1$/FVC | 78.5 (5.7) | 61.5 (6.6)* | 46.9 (11.7)* |
| *Comorbidities, N (%)* | | | |
| Respiratory related | | | |
| Respiratory infection | 223 (25.2%) | 156 (22.8%) | 136 (29.6%) |
| Respiratory distress | 366 (41.3%) | 195 (28.6%)* | 140 (30.5%)* |
| Pulmonary vascular disease | 135 (15.2%) | 74 (10.8%)* | 62 (13.5%) |
| Pulmonary fibrosis | 101 (11.4%) | 37 (5.4%)* | 18 (3.9%)* |
| Acute respiratory failure | 28 (3.2%) | 5 (0.7%)* | 23 (5.0%) |
| Asphyxia and respiratory arrest | 101 (11.4%) | 50 (7.3%)* | 80 (17.4%)* |
| Pneumonia | 94 (10.6%) | 70 (10.2%) | 75 (16.3%)* |
| Lung cancer | 53 (6.0%) | 58 (8.5%) | 32 (7.0%) |
| Thoracic malignancies | 56 (6.3%) | 60 (8.8%) | 33 (7.2%) |

*Macaulay et al. Resp Med 2013;107:1568-77*

# PRISm (GOLD-U)

Table 3 Patient characteristics potentially associated with disease severity (healthcare utilization).[a]

| | Observed COPD severity category | | |
|---|---|---|---|
| | GOLD-Unclassified<br>*N* = 886 | Mild/Moderate<br>*N* = 683 | Severe/Very Severe<br>*N* = 459 |
| Healthcare utilization | | | |
| Patients with at least one visit, *N* (%) | | | |
| Outpatient | 885 (99.9%) | 682 (99.9%) | 459 (100.0%) |
| ER | 226 (25.5%) | 138 (20.2%)* | 120 (26.1%) |
| Inpatient | 213 (24.0%) | 134 (19.6%)* | 110 (24.0%) |
| COPD-related outpatient[b] | 19 (2.1%) | 23 (3.4%) | 53 (11.5%)* |
| COPD-related ER[b] | 398 (44.9%) | 468 (68.5%)* | 392 (85.4%)* |
| COPD-related inpatient[b] | 23 (2.6%) | 25 (3.7%) | 39 (8.5%)* |
| Number of visits, mean (SD) | | | |
| Outpatient | 13.8 (9.0) | 12.3 (8.5)* | 12.0 (8.0)* |
| ER | 0.4 (0.7) | 0.3 (0.8)* | 0.4 (0.7) |
| Inpatient | 0.3 (0.7) | 0.2 (0.6)* | 0.3 (0.6) |
| COPD-related outpatient[b] | 0.8 (1.2) | 1.5 (1.7)* | 2.8 (2.4)* |
| COPD-related ER[b] | 0.0 (0.2) | 0.0 (0.3) | 0.1 (0.5)* |
| COPD-related inpatient[b] | 0.0 (0.2) | 0.0 (0.2) | 0.1 (0.4)* |

*Macaulay et al. Resp Med 2013;107:1568-77*

Table 4 Patient characteristics potentially associated with disease severity (percent of patients with medications).[a]

| | Observed COPD severity category | | |
|---|---|---|---|
| | GOLD-Unclassified $N = 886$ | Mild/Moderate $N = 683$ | Severe/Very Severe $N = 459$ |
| **Medications** | | | |
| Patients with at least one drug claim, *N* (%) | | | |
| Any of the following drugs | 355 (40.1%) | 345 (50.5%)* | 306 (66.7%)* |
| *$\beta_2$-agonists* | | | |
| Short-acting | | | |
| Levalbuterol | 4 (0.5%) | 1 (0.1%) | 9 (2.0%)* |
| Salbutamol | 147 (16.6%) | 157 (23.0%)* | 167 (36.4%)* |
| Long-acting | | | |
| Formoterol | 1 (0.1%) | 5 (0.7%) | 7 (1.5%)* |
| Arformoterol | 1 (0.1%) | 1 (0.1%) | 2 (0.4%) |
| Salmeterol | 17 (1.9%) | 24 (3.5%) | 36 (7.8%)* |
| *Anticholinergics* | | | |
| Short-acting | | | |
| Ipratropium bromide | 41 (4.6%) | 34 (5.0%) | 59 (12.9%)* |
| Long-acting | | | |
| Tiotropium | 84 (9.5%) | 135 (19.8%)* | 158 (34.4%)* |
| *Combination short-acting $\beta_2$-agonists plus anticholinergic in one inhaler* | | | |
| Salbutamol/ipratropium | 66 (7.4%) | 81 (11.9%)* | 84 (18.3%)* |
| *Methylxanthines* | | | |
| Theophylline | 0 (0.0%) | 5 (0.7%)* | 14 (3.1%)* |
| *Inhaled glucocorticosteroids* | | | |
| Beclomethasone | 0 (0.0%) | 1 (0.1%) | 1 (0.2%) |
| Budesonide | 11 (1.2%) | 12 (1.8%) | 14 (3.1%)* |
| Fluticasone propionate | 35 (4.0%) | 43 (6.3%)* | 47 (10.2%)* |
| *Combination long-acting $\beta_2$-agonists plus glucocorticosteroids in one inhaler* | | | |
| Formoterol/budesonide | 10 (1.1%) | 12 (1.8%) | 14 (3.1%)* |
| Salmeterol/fluticasone propionate | 69 (7.8%) | 101 (14.8%)* | 113 (24.6%)* |
| *Systemic glucocorticosteroids* | | | |
| Prednisone | 121 (13.7%) | 106 (15.5%) | 112 (24.4%)* |
| Methylprednisolone | 12 (1.4%) | 10 (1.5%) | 8 (1.7%) |

# Study III: Summary

- PRISm (GOLD-U)는 mild/moderate COPD와 견줄만 함 (동반질환, 의료이용 및 약물 처방 등).

*Macaulay et al. Resp Med 2013;107:1568-77*

Wan *et al. Respiratory Research* 2014, **15**:89
http://respiratory-research.com/content/15/1/89

RESPIRATORY RESEARCH

RESEARCH Open Access

# Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPDGene

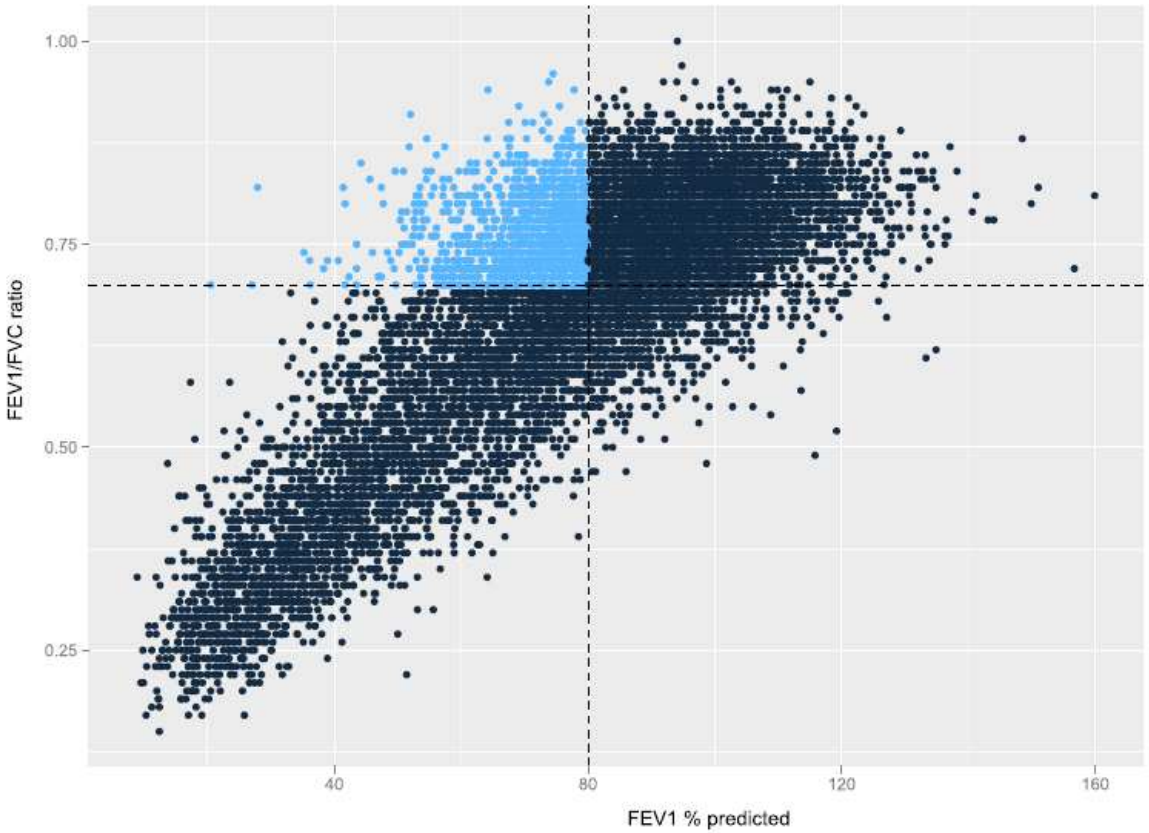
Emily S Wan[1,2*], Peter J Castaldi[1], Michael H Cho[1,2], John E Hokanson[3], Elizabeth A Regan[4], Barry J Make[4], Terri H Beaty[5], MeiLan K Han[6], Jeffrey L Curtis[7], Douglas Curran-Everett[8,9], David A Lynch[4], Dawn L DeMeo[1,2], James D Crapo[4], Edwin K Silverman[1,2] and The COPDGene Investigators

- COPDGene (n=**10,192**) ← 2011년도의 약 **4배**

*Wan et al. Resp Res 2014;15:89*

# PRISm

- Prevalence of PRISm: **12.3%**




*Wan et al. Resp Res 2014;15:89*

**Table 1 Characteristics of *P*reserved *R*atio *I*mpaired *Spiro*metry (PRISm), smoking control, and COPD subjects in COPDGene using fixed threshold criteria**

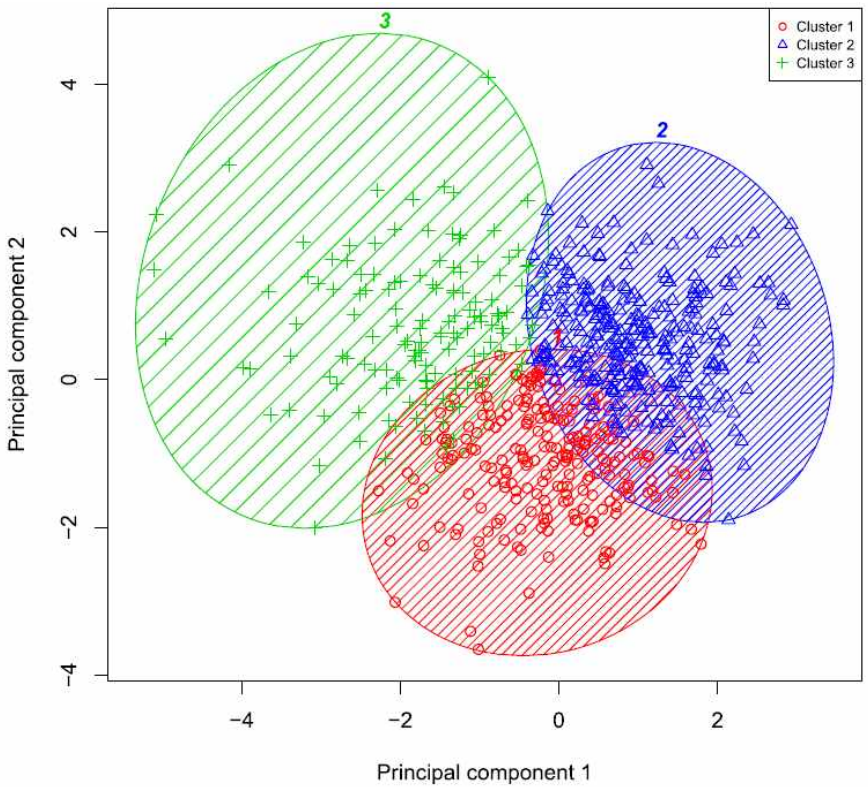
| | Control subjects | PRISm | COPD |
|---|---|---|---|
| n | 4388 | 1257 | 3690 |
| Age | 56.7 (8.4)* | 57.2 (8.2) | 63.4 (8.5)* |
| Sex (% Male) | 52.9* | 46.1 | 55.6* |
| African American | 41.2 | 43.1 | 22.7* |
| Current smoker | 59.7* | 63.8 | 40.7* |
| Pack-years | 37.2 (20.2)* | 42.7 (24.2) | 53.0 (27.5)* |
| Body Mass Index | 28.9 (5.8)* | 31.8 (7.3) | 28.1 (6.3)* |
| $FEV_1$% predicted | 97.5 (11.5)* | 70.2 (8.4) | 50.2 (18.0)* |
| FVC% predicted | 96.6 (11.9)* | 71.5 (9.1) | 76.3 (17.3)* |
| $FEV_1$/FVC | 0.79 (0.05)* | 0.77 (0.05) | 0.50 (0.13)* |
| Bronchodilator Responsiveness† | 10.0* | 13.7 | 36.6* |
| Total Lung $Capacity_{CT}$% predicted | 92.3 (14.6)* | 79.9 (13.5) | 101.5 (17.1)* |
| Segmental wall area percentage | 60.1 (2.9)* | 62.5 (3.1) | 62.9 (3.1)* |
| Percent emphysema (% $LAA\text{-}950_{insp}$) | 2.0 (2.5)* | 1.4 (2.5) | 13.0 (12.8)* |
| Percent gas trapping (% $LAA\text{-}856_{exp}$) | 11.0 (9.7) | 10.4 (9.1) | 39.2 (20.8)* |
| Pi10 | 3.65 (0.11)* | 3.73 (0.14) | 3.72 (0.14)* |
| 6 minute walk distance (feet) | 1491.5 (350.7)* | 1266.6 (366.9) | 1174.8 (397.0)* |
| MMRC‡ Dyspnea score | 0.8 (1.2)* | 1.5 (1.5) | 2.1 (1.4)* |
| Resting $O_2$ saturation | 97.1 (2.0)* | 96.5 (2.5) | 94.7 (3.6)* |
| Chronic bronchitis | 12.6* | 17.8 | 28.2* |

| | Control subjects | PRISm | COPD |
|---|---|---|---|
| Short acting beta-agonist use | 12.0* | 28.1 | 65.7* |
| Long acting beta-agonist use | 4.4* | 13.3 | 49.1* |
| Inhaled corticosteroid use | 5.5* | 16.4 | 51.2* |
| Oral corticosteroid use | 0.5* | 2 | 5.9* |
| Congestive heart failure | 1.3* | 4.6 | 5.4 |
| Coronary artery disease | 7.5* | 13.5 | 16.5* |
| Diabetes mellitus | 11.6* | 21.6 | 13.1* |
| Hypertension | 36.3* | 49.1 | 50.6 |
| Hyperlipidemia | 34.3* | 42.5 | 41.4 |
| History of blood clot | 2.8* | 5.2 | 5.7 |
| Peripheral vascular disease | 1.3* | 2.7 | 3.4 |
| History of stroke | 1.6* | 3.5 | 3.6 |
| Gastrointestinal reflux disease | 20.3* | 25.9 | 30.3* |
| History of compression fracture | 3.4* | 5.4 | 6.2 |
| Currently employed | 37.3* | 28.9 | 25.3* |
| Physician-diagnosed asthma | 11.4* | 21.1 | 24.6* |

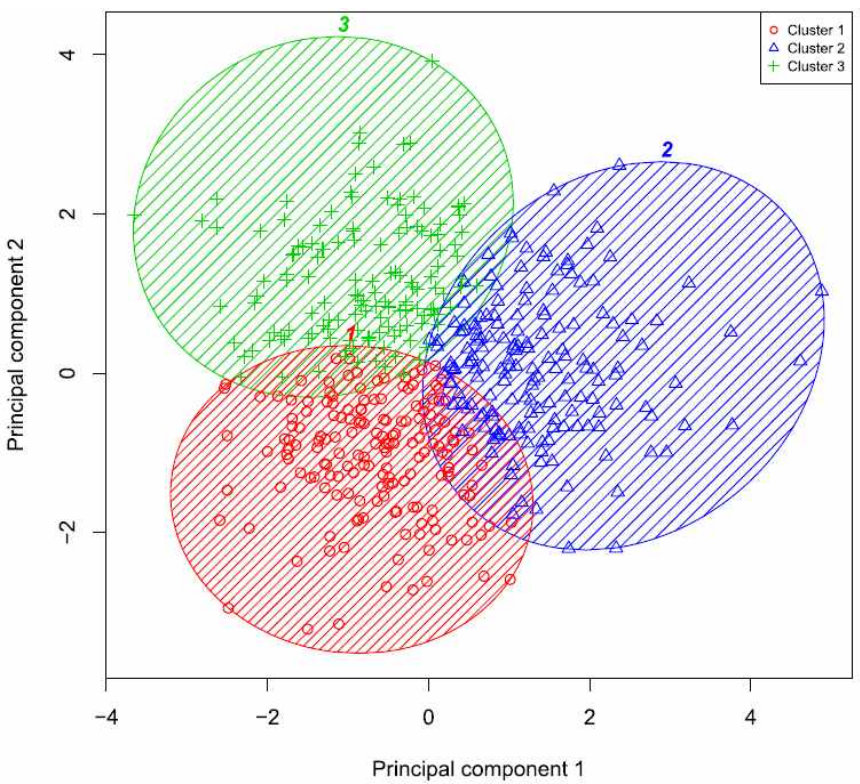
*Wan et al. Resp Res 2014;15:89*

# Clustering analysis

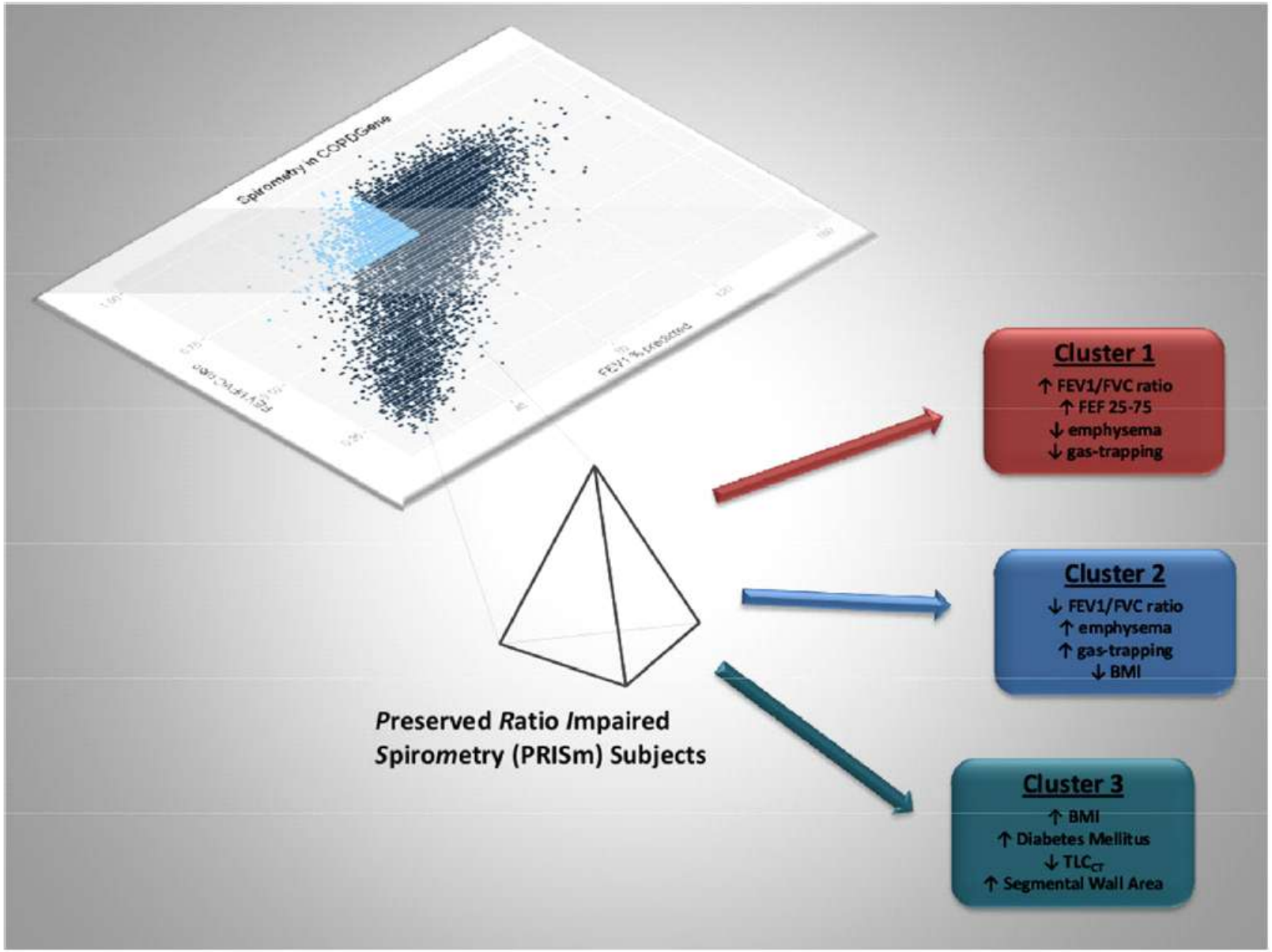
## [Non-Hispanic whites]




## [African Americans]




*Wan et al. Resp Res 2014;15:89*




多

**Figure 2** Overview of cluster analysis in subjects with Preserved Ratio Impaired Spirometry (PRISm).

**Table 3 Results of unsupervised k-means clustering in (a) non-Hispanic white and (b) African American subjects with fixed threshold-defined *P*reserved *R*atio *I*mpaired *Spiro*metry (PRISm)**

| | (a) Non-Hispanic White subjects | | | (b) African American subjects | | |
|---|---|---|---|---|---|---|
| Feature | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 1 | Cluster 2 | Cluster 3 |
| n | 227 | 291 | 137 | 171 | 167 | 142 |
| Age | 57.9 (8.2) | 62.2 (8.1) | 59.2 (9.4) | 52.9 (5.8) | 54.6 (6.1) | 52.6 (5.3) |
| Sex (% male) | 34.8 | 45.7 | 51.1 | 47.4 | 56.9 | 45.1 |
| Body Mass Index | 30.9 (6.4) | 30.4 (6.3) | 36.2 (7.1) | 32.0 (6.8) | 27.3 (6.0) | 35.7 (8.4) |
| Current smoker | 53.3 | 43.6 | 49.6 | 84.8 | 83.8 | 80.3 |
| Pack-years | 42.8 (22.6) | 46.6 (24.5) | 50.9 (29.7) | 35.6 (18.5) | 39.6 (24.0) | 38.1 (21.4) |
| $FEV_1$% predicted | 74.2 (4.3) | 73.4 (5.3) | 60.5 (7.8) | 73.3 (5.1) | 72.7 (6.2) | 62.5 (8.9) |
| $FEV_1/FVC$ | 0.80 (0.04) | 0.74 (0.03) | 0.74 (0.04) | 0.83 (0.04) | 0.74 (0.03) | 0.75 (0.03) |
| $FEF_{25-75}$ | 2.21 (0.65) | 1.58 (0.47) | 1.41 (0.47) | 2.38 (0.71) | 1.58 (0.50) | 1.42 (0.43) |
| Resting O2 saturation | 96.4(2.3) | 96.3 (2.1) | 95.2 (2.9) | 97.1 (2.2) | 97.1 (2.3) | 96.6 (2.7) |
| $TLC_{CT}^{*}$% predicted | 79.4 (9.8) | 90.4 (10.7) | 74.4 (12.7) | 71.0 (11.1) | 83.6 (12.3) | 71.6 (12.3) |
| Percent emphysema | 0.6 (0.7) | 2.6 (2.7) | 0.9 (1.1) | 0.5 (0.6) | 2.7 (4.5) | 0.8 (1.0) |
| Segmental Wall Area% | 62.0 (2.5) | 60.6 (2.3) | 64.7 (2.6) | 62.4 (2.8) | 61.9 (2.9) | 65.7 (2.5) |
| Percent Gas Trapping | 6.5 (6.0) | 13.5 (8.6) | 9.8 (7.1) | 7.2 (7.3) | 14.8 (13.5) | 9.4 (7.5) |
| Diabetes Mellitus | 18.5 | 14.4 | 36.5 | 22.8 | 15.6 | 27.5 |
| Hypertension | 36.6 | 47.4 | 56.2 | 53.8 | 51.5 | 54.2 |
| Hyperlipidemia | 45.4 | 58.8 | 59.9 | 31.0 | 24.0 | 29.6 |
| Chronic bronchitis | 16.3 | 15.8 | 32.9 | 11.1 | 19.2 | 14.8 |
| Bronchodilator Response[†] | 11.5 | 13.5 | 22.2 | 11.4 | 9.2 | 20.1 |
| MMRC[‡] | 1.154 (1.32) | 1.13 (1.29) | 1.95 (1.50) | 1.63 (1.53) | 1.57 (1.47) | 1.96 (1.53) |
| 6 minute walk distance | 1386.5 (347.1) | 1392.2 (320.4) | 1132.6 (390.2) | 1219.9 (349.4) | 1279.5 (338.1) | 1099.2 (342.1) |

# Study IV: Summary

- Normal Control < PRISm < COPD
- PRISm subjects are clinically and genetically **heterogeneous.**

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https://doi.org/10.1007/s00408-018-0162-2

COPD

# Imaging Features of Chronic Bronchitis with Preserved Ratio and Impaired Spirometry (PRISm)

Xia Wei[1,2] · Qi Ding[1] · Nan Yu[3] · Jiuyun Mi[1] · Jingting Ren[1] · Jie Li[1] · Shudi Xu[1] · Yanzhong Gao[4] · Youmin Guo[1]

Received: 24 May 2018 / Accepted: 6 September 2018 / Published online: 14 September 2018


- One institution in China (Ninth Hospital of Xi'an Affiliated Hospital of Xi'an Jiaotong University)

*Wei et al. Lung 2018;196:649-58*

Ratio < 70%
$FEV_1$ > 50%

Table 1 Comparison of demographic and PFT characteristics among the three groups

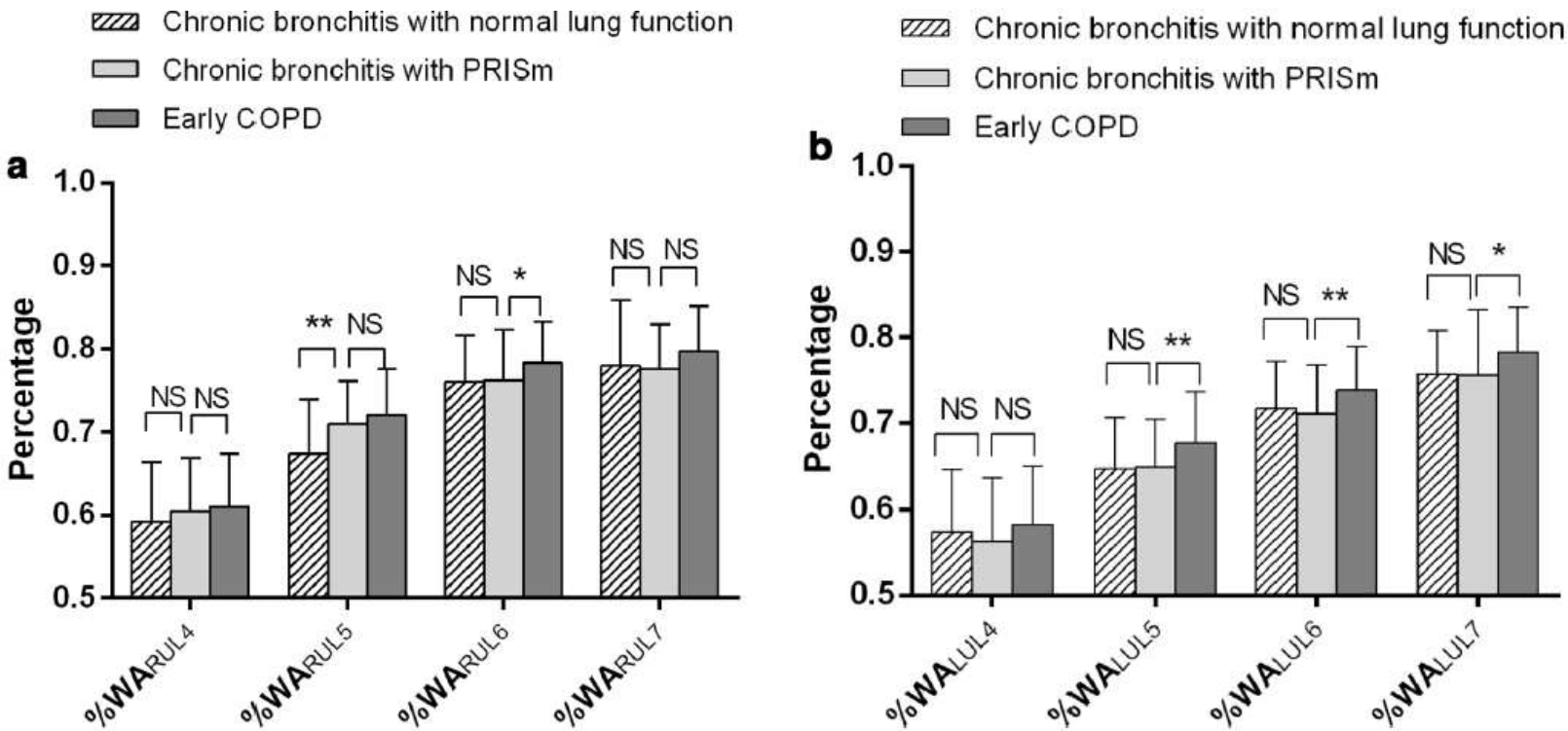
| | Chronic bronchitis with normal lung function $n=77$ | Chronic bronchitis with PRISm $n=80$ | Early COPD $n=186$ | F/$x^2$ value | *P* value |
|---|---|---|---|---|---|
| Male sex (%) | 57 (74%) | 61 (76.3%) | 160 (86%) | 6.667 | 0.036 |
| Age, years | 67.42 ± 9.72 | 70.68 ± 10.8 | 68.17 ± 10.85 | 2.166 | 0.116 |
| Current smoking (%) | 58 (75.3%) | 66 (82.5%) | 124 (66.7%) | 7.456 | 0.024 |
| Smoking pack-years | 31.86 ± 21.66 | 31.27 ± 18.18 | 41.9 ± 25.64*## | 5.084 | 0.007 |
| Hypertension (%) | 31 (40.3%) | 46 (57.5%) | 80 (43%) | 5.947 | 0.051 |
| Coronary heart disease (%) | 19 (24.7%) | 29 (36.3%) | 72 (38.7%) | 4.789 | 0.091 |
| Diabetes (%) | 10 (13%) | 12 (15%) | 19 (10.2%) | 1.318 | 0.517 |
| Comorbidities | 0.82 ± 0.91 | 1.11 ± 0.93 | 0.97 ± 0.89 | 2.077 | 0.127 |
| Exacerbations/past year | 0.45 ± 0.77 | 0.56 ± 0.94 | 0.63 ± 1.3 | 0.712 | 0.491 |
| CAT | 15.45 ± 8.82 | 16.25 ± 9.12 | 18.53 ± 8.25**# | 4.287 | 0.014 |
| mMRC | 0.96 ± 0.98 | 1.43 ± 1.13** | 1.26 ± 1.1* | 3.761 | 0.024 |
| BMI, $kg/m^2$ | 24.03 ± 2.98 | 24.02 ± 4.03 | 23.77 ± 3.53 | 0.226 | 0.797 |
| FEV1, L | 2.41 ± 0.54 | 1.64 ± 0.5*** | 1.69 ± 0.41*** | 75.983 | < 0.001 |
| FEV1%pred | 93 ± 10.71 | 63.96 ± 12.64*** | 63.95 ± 11.44 *** | 188.024 | < 0.001 |
| FVC, L | 3.03 ± 0.69 | 2.11 ± 0.67*** | 2.85 ± 0.65*### | 45.684 | < 0.001 |
| FVC%pred | 92.26 ± 11.88 | 63.82 ± 13.53*** | 84.1 ± 13.92***### | 97.93 | < 0.001 |
| FEV1/FVC% | 79.52 ± 6.54 | 78.46 ± 6.39 | 58.77 ± 7.12***### | 373.001 | < 0.001 |

**증상: PRISm ≈ early COPD**

*Wei et al. Lung 2018;196:649-58*

# Imaging features in PRISm

- The percentage of the wall area (%WA)




**%WA: PRISm ≈ NL**

*Wei et al. Lung 2018;196:649-58*

Table 3 Comparison of emphysema related parameters among the three groups

| Parameters | Chronic bronchitis with normal lung function | Chronic bronchitis with PRISm | Early COPD | *F* value | *P* value |
|---|---|---|---|---|---|
| $LC_{whole}$ | 4603.7 ± 1163.26 | 4029.17 ± 1112.22* | 5264.79 ± 1278.2**### | 20.443 | < 0.001 |
| $LC_{Right\ lung}$ | 2484.8 ± 625.29 | 2187.83 ± 623.24* | 2829.42 ± 699.43**### | 18.4 | < 0.001 |
| $LC_{Left\ lung}$ | 2118.91 ± 563.45 | 1841.34 ± 552.17* | 2415.63 ± 642.52**### | 17.617 | < 0.001 |
| $LC_{RUL}$ | 1143.54 ± 373.98 | 929.46 ± 319.53** | 1233.87 ± 399.23### | 11.292 | < 0.001 |
| $LC_{RML}$ | 304.3 ± 223.64 | 272.59 ± 183.12 | 391.98 ± 229.29*## | 6.155 | 0.003 |
| $LC_{RLL}$ | 1047.42 ± 427.64 | 1004.1 ± 380.01 | 1205.59 ± 369.52*## | 6.089 | 0.003 |
| $LC_{LUL}$ | 1209.05 ± 307.38 | 1072.56 ± 342.52 | 1330.77 ± 353.96*### | 10.31 | < 0.001 |
| $LC_{LLL}$ | 911.61 ± 334.59 | 792.16 ± 316.32 | 1112.11 ± 372.97**### | 15.915 | < 0.001 |
| $\%LAA_{whole}$ | 10.7 ± 5.34 | 9.77 ± 5.8 | 16.59 ± 8***### | 23.828 | < 0.001 |
| $\%LAA_{Right\ lung}$ | 10.48 ± 5.28 | 9.71 ± 5.88 | 16.67 ± 7.99***### | 25.474 | < 0.001 |
| $\%LAA_{Left\ lung}$ | 10.89 ± 5.53 | 9.79 ± 5.96 | 16.71 ± 8.17***### | 22.926 | < 0.001 |
| $\%LAA_{RUL}$ | 11.27 ± 5.76 | 10.51 ± 7.54 | 18.12 ± 9.39***### | 20.288 | < 0.001 |
| $\%LAA_{RML}$ | 10.68 ± 5.73 | 11.33 ± 7.36 | 18.96 ± 8.94***### | 26.041 | < 0.001 |
| $\%LAA_{RLL}$ | 8.19 ± 5.64 | 7.82 ± 5.42 | 14.54 ± 7.79***### | 24.124 | < 0.001 |
| $\%LAA_{LUL}$ | 12.46 ± 6.1 | 11.18 ± 6.83 | 18.09 ± 8.65***### | 17.816 | < 0.001 |
| $\%LAA_{LLL}$ | 7.97 ± 5.51 | 7.45 ± 5.31 | 15.14 ± 8.48***### | 27.49 | < 0.001 |

**LC:** lung capacity

**%LAA:** the extent of emphysema of CT attenuation value below -950 HU

*Wei et al. Lung 2018;196:649-58*

| Parameters | Chronic bronchitis with normal lung function | Chronic bronchitis with PRISm | Early COPD | *F* value | *P* value |
|---|---|---|---|---|---|
| $MLD_{whole}$ | −816.44 ± 39.75 | −799.96 ± 53.27 | −834.55 ± 71.93## | 6.026 | 0.003 |
| $MLD_{Right\ lung}$ | −816.55 ± 40.53 | −800.58 ± 52.06* | −840.69 ± 34.19***### | 21.176 | < 0.001 |
| $MLD_{Left\ lung}$ | −814.7 ± 41.06 | −798 ± 58.27* | −838.68 ± 35.15**### | 19.318 | < 0.001 |
| $MLD_{RUL}$ | −826.27 ± 34.75 | −810.89 ± 53.06 | −850.2 ± 32.51***### | 20.489 | < 0.001 |
| $MLD_{RML}$ | −816.33 ± 47.05 | −805.98 ± 72.41 | −851.51 ± 33.62***### | 19.964 | < 0.001 |
| $MLD_{RLL}$ | −790.34 ± 58.64 | −779.45 ± 60.17 | −820.95 ± 79.21*## | 7.18 | 0.001 |
| $MLD_{LUL}$ | −828.41 ± 34.81 | −812.98 ± 56.19 | −842.42 ± 74.89## | 3.77 | 0.025 |
| $MLD_{LLL}$ | −786.36 ± 57.05 | −768.13 ± 79.56 | −827.73 ± 42.5***### | 23.662 | < 0.001 |
| $HI_{whole}$ | 0.2 ± 0.2 | 0.15 ± 0.22 | 0.12 ± 0.25 | 2.625 | 0.075 |
| $HI_{Right\ lung}$ | 0.18 ± 0.21 | 0.16 ± 0.25 | 0.15 ± 0.27 | 0.22 | 0.803 |
| $HI_{Left\ lung}$ | 0.12 ± 0.21 | 0.09 ± 0.28 | −0.08 ± 0.29***### | 14.034 | < 0.001 |

*%LAA* the extent of emphysema of computed tomography attenuation value below −950 HU, *COPD* chronic obstructive pulmonary disease, *F value* statistical value of the ANOVA analysis, *HI* emphysema heterogeneity index, *LC* lung capacity, *MLD* mean lung density, *PRISm* preserved ratio and impaired spirometry

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared to the group of chronic bronchitis with normal lung function; #$P < 0.05$, ##$P < 0.01$, ###$P < 0.001$, compared to the group of chronic bronchitis with PRISm

**MLD:** mean lung density
**HI:** emphysema heterogeneity index

**Emphysema: PRISm ≈ NL**

*Wei et al.*
*Lung*
*2018;196:649-58*

# Study V: Summary

- In terms of **airway wall area** and **emphysema index**, PRISm were essentially **no different** than those with chronic bronchitis **without abnormal spirometry,** whereas for **symptoms**, they are more **like GOLD 1 and 2 patients.**

*Wei et al. Lung 2018;196:649-58*

Park *et al. Respiratory Research* (2018) 19:185
https://doi.org/10.1186/s12931-018-0896-7

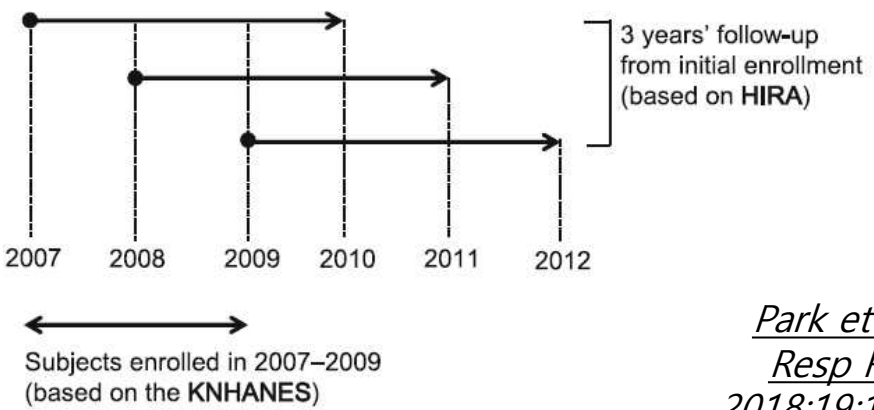
Respiratory Research

RESEARCH Open Access

# Significant predictors of medically diagnosed chronic obstructive pulmonary disease in patients with preserved ratio impaired spirometry: a 3-year cohort study

Hye Jung Park[1], Min Kwang Byun[1*], Chin Kook Rhee[2], Kyungjoo Kim[2], Hyung Jung Kim[1] and Kwang-Ha Yoo[3]

- KNHANES – matched HIRA data
- 3-year follow-up




*Park et al. Resp Res 2018;19:185*

# PRISm

- Prevalence of PRISm: **11.7%** (COPD 배제 후)

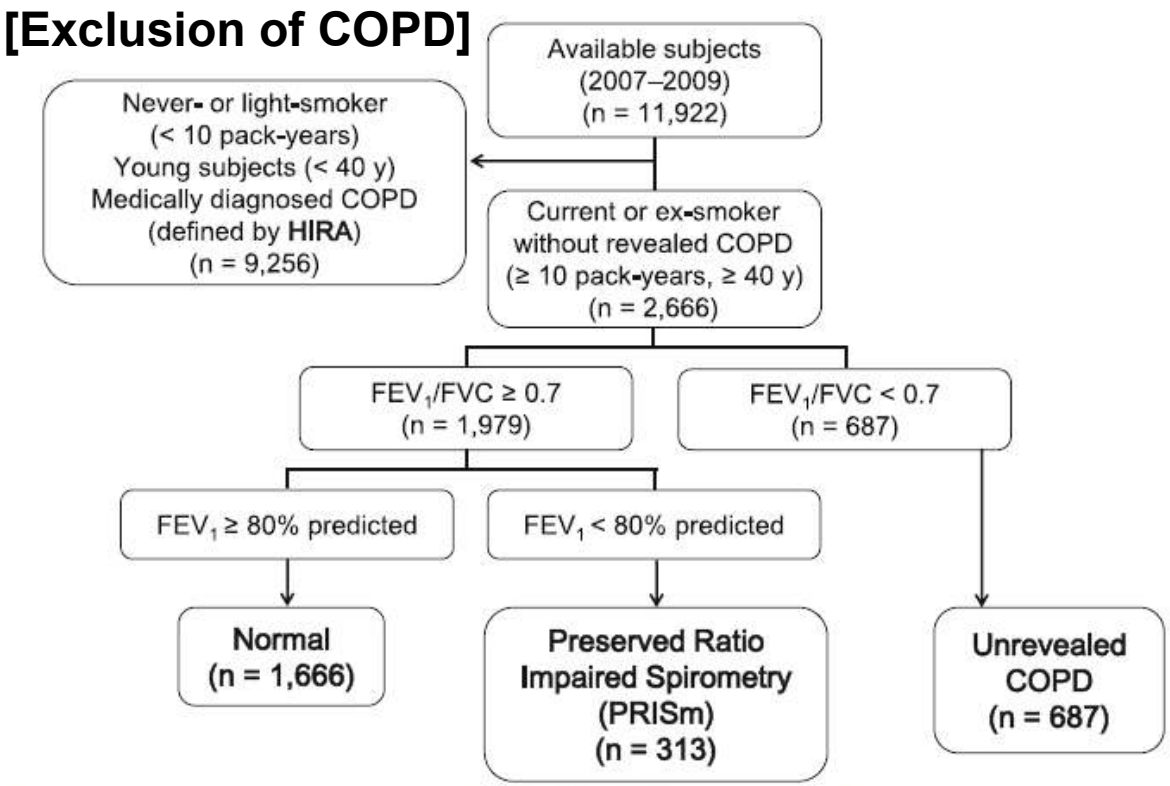



**Fig. 1** Subject selection and group assignment based on the KNHANES and HIRA data. KNHANES, Korea National Health and Nutrition Examination Survey; HIRA, Health Insurance Review & Assessment; COPD, chronic obstructive pulmonary disease; $FEV_1$, forced expiratory volume for 1 s; FVC, forced vital capacity

*Park et al. Resp Res 2018;19:185*

**Table 1** Demographics of subjects according to the group

| | Normal | PRISm | Unrevealed COPD | *P*-value | *P*-value* | *P*-value† | *P*-value‡ |
|---|---|---|---|---|---|---|---|
| Age | 54.57 ± 10.52 | 55.97 ± 10.85 | 64.48 ± 9.54 | < 0.001 | 0.083 | < 0.001 | < 0.001 |
| Male, *n* (%) | 1560 (93.6) | 286 (91.4) | 654 (95.2) | 0.063 | 0.426 | 0.432 | 0.054 |
| Height (cm) | 167.14 ± 6.94 | 166.79 ± 6.94 | 165.97 ± 6.56 | < 0.001 | 0.998 | < 0.001 | 0.236 |
| Weight (kg) | 68.29 ± 9.91 | 68.66 ± 11.6 | 63.7 ± 9.8 | < 0.001 | 0.998 | < 0.001 | < 0.001 |
| Smoking history | | | | | | | |
| Current smoking, *n* (%) | 858 (51.5) | 193 (61.7) | 367 (53.4) | 0.004 | 0.003 | 0.999 | 0.045 |
| Pack-years | 28.62 ± 17.11 | 33.20 ± 20.34 | 36.58 ± 21.14 | < 0.001 | < 0.001 | < 0.001 | 0.026 |
| Co-morbidity, *n* (%) | | | | | | | |
| Hypertension | 453 (27.2) | 91 (29.1) | 209 (30.4) | 0.269 | 0.998 | 0.336 | 0.999 |
| Hyperlipidemia | 166 (10.0) | 34 (10.9) | 47 (6.8) | 0.035 | 0.998 | 0.048 | 0.092 |
| Stroke | 48 (2.9) | 14 (4.5) | 18 (2.6) | 0.252 | 0.414 | 0.999 | 0.368 |
| Acute coronary syndrome | 17 (1.0) | 8 (2.6) | 16 (2.3) | 0.019 | 0.077 | 0.042 | 0.999 |
| Diabetes mellitus | 174 (10.4) | 63 (20.1) | 84 (12.2) | < 0.001 | < 0.001 | 0.624 | 0.003 |
| Pulmonary tuberculosis | 124 (7.4) | 21 (6.7) | 109 (15.9) | < 0.001 | 0.999 | < 0.001 | < 0.001 |
| Asthma | 20 (1.2) | 15 (4.8) | 65 (9.5) | < 0.001 | < 0.001 | < 0.001 | 0.024 |
| Lung function test | | | | | | | |
| FVC % predicted | 92.96 ± 10.02 | 72.55 ± 9.45 | 88.51 ± 15.02 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| $FEV_1$% predicted | 94.66 ± 9.14 | 72.8 ± 6.72 | 74.18 ± 16.57 | < 0.001 | < 0.001 | < 0.001 | 0.035 |
| $FEV_1$/FVC | 0.79 ± 0.05 | 0.77 ± 0.06 | 0.61 ± 0.09 | < 0.001 | < 0.001 | < 0.001 | 0.006 |
| Respiratory symptoms, *n* (%) | | | | | | | |
| Cough for more than 3 months | 1 (0.1) | 2 (0.6) | 19 (2.8) | < 0.001 | 0.047 | < 0.001 | 0.091 |
| Sputum for more than 3 months | 4 (0.2) | 2 (0.6) | 18 (2.6) | < 0.001 | 0.999 | < 0.001 | 0.104 |
| Dyspnea | 10 (0.6) | 3 (1.0) | 31 (4.5) | < 0.001 | 0.999 | < 0.001 | 0.012 |
| Wheezing | 116 (7.0) | 37 (11.8) | 154 (22.4) | < 0.001 | 0.009 | < 0.001 | < 0.001 |
| Chronic bronchitis | 4 (0.2) | 2 (0.6) | 21 (3.1) | < 0.001 | 0.717 | < 0.001 | 0.054 |
| Total | 1666 | 313 | 687 | | | | |

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**Table 2** COPD incidence, medication and hospital utilization, and cost

| | Normal | PRISm | Unrevealed COPD | *P*-value | *P*-value* | *P*-value+ | *P*-value‡ |
|---|---|---|---|---|---|---|---|
| COPD incidence (/1000PY) | 4.4 | 17.0 | 45.1 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| OPD visit, *n* (%) | 51 (3.1) | 22 (7.0) | 131 (19.1) | < 0.001 | 0.002 | < 0.001 | < 0.001 |
| No. of OPD visit | 0.10 ± 0.91 | 0.48 ± 2.96 | 1.86 ± 6.37 | < 0.001 | 0.243 | < 0.001 | < 0.001 |
| Hospitalization, *n* (%) | 79 (4.7) | 29 (9.3) | 83 (12.1) | < 0.001 | 0.004 | < 0.001 | 0.571 |
| ER visit, n (%) | 23 (1.4) | 12 (3.8) | 36 (5.2) | < 0.001 | 0.008 | < 0.001 | 0.999 |
| ICU admission, n (%) | 12 (0.7) | 6 (1.9) | 19 (2.8) | < 0.001 | 0.122 | < 0.001 | 0.999 |
| Total hospital visit, n (%) | 121 (7.3) | 41 (13.1) | 169 (24.6) | < 0.001 | 0.002 | < 0.001 | < 0.001 |
| ICS, n (%) | 4 (0.2) | 5 (1.6) | 20 (2.9) | < 0.001 | 0.003 | < 0.001 | 0.651 |
| ICS + LABA, n (%) | 2 (0.1) | 11 (3.5) | 50 (7.3) | < 0.001 | < 0.001 | < 0.001 | 0.063 |
| LAMA, n (%) | – | 4 (1.3) | 44 (6.4) | – | – | – | < 0.001 |
| SAMA, n (%) | 12 (0.7) | 12 (3.8) | 36 (5.2) | < 0.001 | < 0.001 | < 0.001 | 0.999 |
| SABA, n (%) | 14 (0.8) | 11 (3.5) | 54 (7.9) | < 0.001 | < 0.001 | < 0.001 | 0.029 |
| Systemic bronchodilator, n (%) | 28 (1.7) | 11 (3.5) | 72 (10.5) | < 0.001 | 0.094 | < 0.001 | < 0.001 |
| Methylxanthine, n (%) | 33 (2.0) | 17 (5.4) | 101 (14.7) | < 0.001 | 0.001 | < 0.001 | < 0.001 |
| Total prescribed medication, n (%) | 57 (3.4) | 26 (8.3) | 127 (18.5) | < 0.001 | < 0.001 | < 0.001 | < 0.001 |
| Hospitalization medical Cost (for 3 years) (USD) | 186.17 ± 1411.24 | 398.61 ± 1975.51 | 750.71 ± 3216.02 | < 0.001 | 0.297 | < 0.001 | 0.041 |

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**Table 6** Significant factors for COPD diagnosis in PRISm

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | *P*-value | OR | 95% CI | *P*-value |
| **Age (years)** | **1.14** | **(1.08, 1.21)** | **< 0.001** | **1.14** | **(1.05, 1.24)** | **0.002** |
| Male | | | | | | |
| Height (cm) | 0.93 | (0.87, 0.99) | 0.025 | 1.03 | (0.92, 1.16) | 0.564 |
| Weight (kg) | 0.94 | (0.9, 0.99) | 0.013 | 0.95 | (0.89, 1.02) | 0.153 |
| Smoking history | | | | | | |
| Current smoking | 0.61 | (0.22, 1.66) | 0.329 | | | |
| Pack-years | 1.01 | (0.99, 1.03) | 0.490 | | | |
| Co-morbidity | | | | | | |
| Pulmonary tuberculosis | 0.92 | (0.12, 7.35) | 0.940 | | | |
| Asthma | 8.67 | (2.41, 31.23) | 0.001 | 5.87 | (0.94, 36.56) | 0.058 |
| Lung function test | | | | | | |
| FVC % predicted | 0.93 | (0.89, 0.97) | 0.001 | 1.01 | (0.95, 1.09) | 0.694 |
| $FEV_1$% predicted | 0.95 | (0.9, 1.01) | 0.071 | | | |
| $FEV_1$/FVC | 0.001 | (0.001, 35.7) | 0.183 | | | |
| Self-reported respiratory symptoms | | | | | | |
| Cough for more than 3 months | | | | | | |
| Sputum for more than 3 months | | | | | | |
| Dyspnea | 42.29 | (3.61, 494.74) | 0.003 | 8.88 | (0.65, 121.7) | 0.102 |
| **Wheezing** | **5.15** | **(1.75, 15.14)** | **0.003** | **4.56** | **(1.08, 19.35)** | **0.040** |
| Chronic bronchitis | | | | | | |

Park et al. Resp Res 2018;19:185

# Study VI: Summary

- **KNHANES** showed that **PRISm patients are likely to develop COPD**
- **PRISm should be monitored carefully**, especially older patients and those with wheezing, regardless of lung function**.**

*Park et al. Resp Res 2018;19:185*

medicina

MDPI

Article

# Health-Related Quality of Life and Related Factors in Persons with Preserved Ratio Impaired Spirometry: Data from the Korea National Health and Nutrition Examination Surve

I Re Heo, Ho Cheol Kim and Tae Hoon Kim *

- 😐☠️☝️✌️☠️👈🩸 ☎️만 40세 이상)
- Euro Quality of Life-5D (EQ-5D)

Heo et al. Medicine 2021;57:4

# PRISm

- 1,875 had PRISm among 27,824 participants **(6.7%)**

Table 1. Baseline characteristics.

| | PRISm ($n$ = 1875) | Control ($n$ = 14,467) | $p$-Value |
|---|---|---|---|
| Age (years) | | | 0.025 * |
| 40–59 | 70.3 (1.4) | 73.4 (0.6) | |
| 60 and above | 29.7 (1.4) | 26.6 (0.6) | |
| Sex | | | <0.001 *** |
| Male | 49.4 (1.6) | 43.0 (0.5) | |
| Female | 50.6 (1.6) | 57.0 (0.5) | |
| BMI | | | <0.001 *** |
| <18.5 | 2.5 (0.5) | 1.1 (0.1) | |
| 18.5–22.9 | 27.6 (1.3) | 33.8 (0.5) | |
| 23–24.9 | 27.2 (1.4) | 27.3 (0.5) | |
| >25.0 | 42.8 (1.5) | 37.8 (0.6) | |
| Smoking habit | | | |
| Ever-smoker (>5 packs) | 44.8 (1.6) | 38.2 (0.5) | <0.001 *** |
| Current smoker | 34.2 (1.5) | 26.3 (0.5) | <0.001 *** |
| Binge-drinking | 18.0 (1.3) | 16.9 (0.4) | 0.429 |
| Regular walking exercise | 35.0 (1.5) | 39.1 (0.6) | 0.001 ** |

*Heo et al. Medicine 2021;57:4*

# PRISm

| PRISm ($n$ = 1875) | | Control ($n$ = 14,467) | $p$-Value |
|---|---|---|---|
| Hypertension | | | <0.001 *** |
| Normal | 30.3 (1.4) | 36.9 (0.6) | |
| Pre-hypertension | 25.6 (1.5) | 27.5 (0.5) | |
| Hypertension | 44.1 (1.6) | 35.6 (0.6) | |
| Diabetes mellitus | | | <0.001 *** |
| Normal | 55.9 (1.6) | 65.0 (0.5) | |
| Pre-diabetes | 27.7 (1.5) | 24.4 (0.5) | |
| Diabetes mellitus | 16.3 (1.1) | 10.6 (0.3) | |
| Hypercholesterolemia | 18.2 (1.2) | 16.7 (0.4) | 0.217 |
| Lung function tests | | | |
| FVC (L) | 2.92 (0.02) | 3.63 (0.01) | <0.001 *** |
| FVC (% of predicted) | 75.5 (0.3) | 96.1 (0.1) | <0.001 *** |
| $FEV_1$ (L) | 2.25 (0.02) | 2.89 (0.01) | <0.001 *** |
| $FEV_1$ (% of predicted) | 74.2 (0.2) | 97.1 (0.1) | <0.001 *** |
| $FEV_1$/FVC | 0.77 (0.0) | 0.80 (0.0) | <0.001 *** |
| Socioeconomic factors | | | |
| Low income | 20.3 (1.3) | 17.6 (0.5) | 0.034 * |
| No marital status | 15.3 (1.1) | 16.0 (0.4) | 0.521 |
| Low educational level | 34.6 (1.5) | 35.7 (0.7) | 0.479 |
| No economic activity | 35.6 (1.5) | 33.9 (0.6) | 0.306 |

Heo et al. Medicine 2021;57:4

# PRISm

- Poor QOL in PRISm

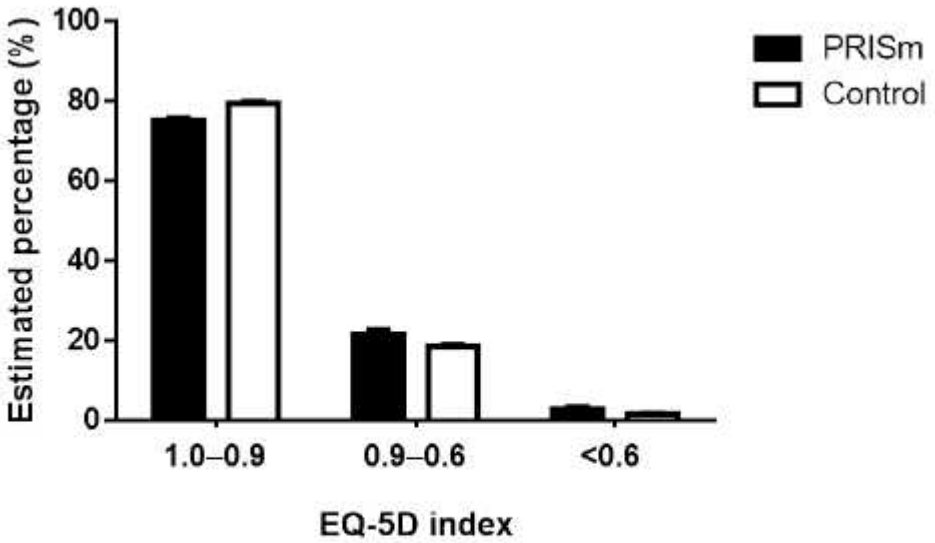


Figure 1. Distribution according to the degree of decline in health-related quality of life. Abbreviations: PRISm, preserved ratio impaired spirometry; EQ-5D, Euro Quality of Life-5D.

*Heo et al. Medicine 2021;57:4*

# PRISm

- Poor QOL in PRISm

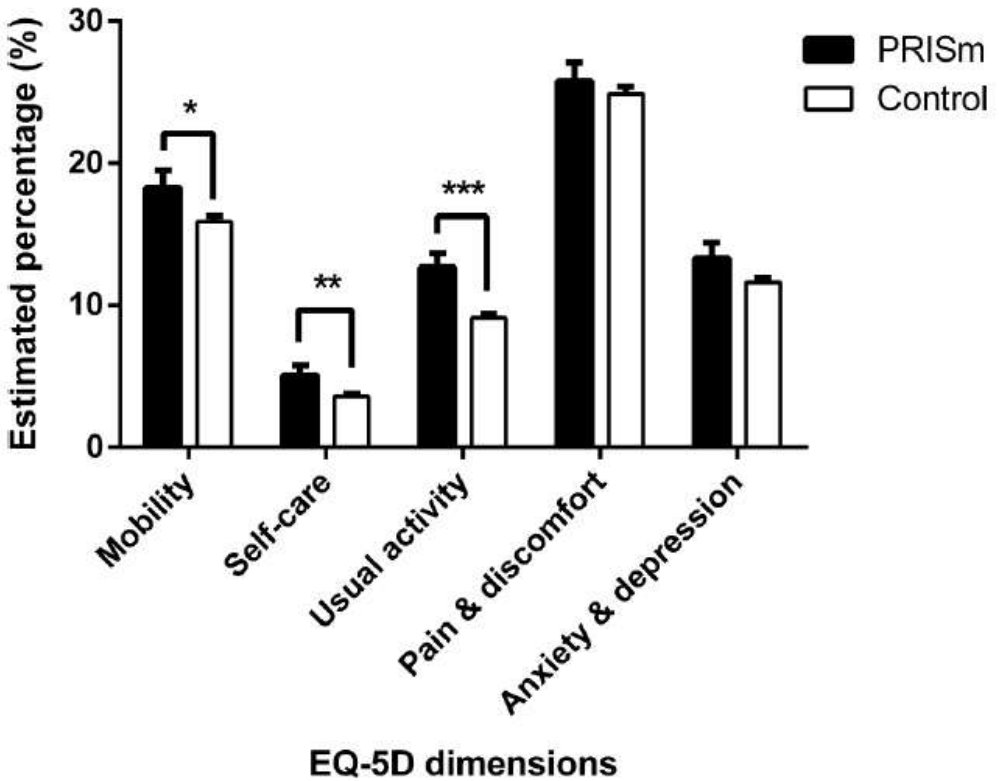


Figure 3. Dissatisfaction with health-related quality of life dimensions according to the Euro Quality of Life-5D (EQ-5D). Note: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Heo et al. Medicine 2021;57:4

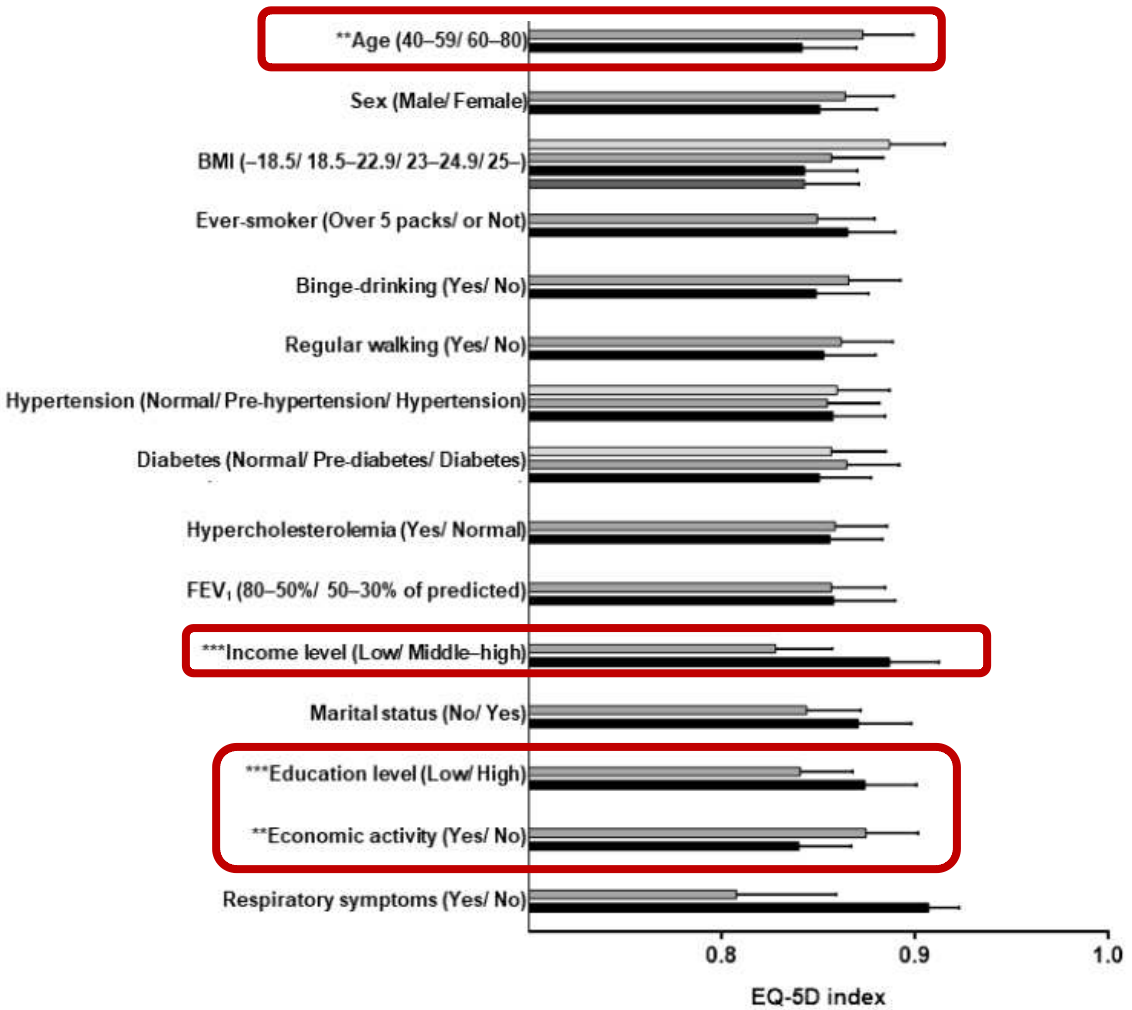


**Figure 2.** Factors influencing overall health-related quality of life in patients with preserved ratio impaired spirometry. Abbreviations: BMI, body mass index; $FEV_1$, forced expiratory volume in 1 s. Note: ** $p < 0.01$, *** $p < 0.001$.

Heo et al. Medicine 2021;57:4

# Study VII: Summary

- **KNHANES** showed that **PRISm** have **poor HR-QOL.**
- **Old age** and **low socioeconomic status** play important roles in HR-QOL deterioration in PRISm.
- **Early detection and intervention** of PRISm can be done in order to preserve patient's QOL.

*Heo et al. Medicine 2021;57:4*

ORIGINAL ARTICLE
LUNG STRUCTURE AND FUNCTION

# Trajectory and mortality of preserved ratio impaired spirometry: the Rotterdam Study

Sara Renata Alex Wijnant [1,2,3], Emmely De Roos [1,2], Maryam Kavousi[2], Bruno Hugo Stricker [2,4], Natalie Terzikhan[2], Lies Lahousse [2,3,6] and Guy G. Brusselle [1,2,5,6]

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- Rotterdam Study (population-based prospective cohort)
- 2009-2018 (9 years)

*Wijnant et al.*
*Eur Respir J*
*2020;55:1901217*

TABLE 2 Lung function values at P1 and P2 stratified by lung function category and smoking status at P2

| | Normal spirometry-P2 | PRISm-P2 | COPD GOLD 1–4-P2 | COPD GOLD 1-P2 | COPD GOLD 2–4-P2 |
|---|---|---|---|---|---|
| **Subjects n** | 970 | 83 | 550 | 355 | 195 |
| **Time between P1 and P2 years** | 4.6±0.5 | 4.7±0.43* | 4.6±0.4 | 4.6±0.4 | 4.6±0.4 |
| **$FEV_1$ % pred** | | | | | 72.1±14.8* |
| P1 | 106.2±14.7 | 82.8±12.8* | 88.8±18.2* | 97.9±12.6* | |
| P2 | 106.0±14.2 | 71.5±7.6* | 84.6±18.3* | 95.4±10.7* | 64.9±11.4* |
| **$\Delta FEV_1$ mL·year$^{-1}$** | | | | | |
| All (n=1603) | −39.1 | −76.7 | −49.2 | −45.9 | −58.6 |
| | (−65.2– −10.8) | (−109.9– −35.0)* | (−82.8– −19.1)* | (−78.6– −16.9)* | (−90.2– −23.6)* |
| Never-smoker at P2 (n=502) | −42.8 | −73.6 | −45.6 | −45.9 | −43.1 |
| | (−72.5– −13.7) | (−113.5– −41.61)* | (−76.9– −22.9) | (−80.0– −23.4) | (−75.6– −15.5) |
| Former smoker at P2 (n=1000) | −37.5 | −78.7 | −48.0 | −44.0 | −60.1 |
| | (−61.0– −8.6) | (−107.1– −28.01)* | (−82.8– −15.4)* | (−78.0– −11.2)* | (−91.9– −21.9)* |
| Current smoker at P2 (n=99) | −24.6 | −138.4 | −63.0 | −60.1 | −88.4 |
| | (−54.9– −4.9) | (−184.0– −96.1)* | (−103.1– −40.1)* | (−78.6– −40.2)* | (−132.7– −36.0)* |
| **FVC % pred** | | | | | |
| P1 | 102.4±13.8 | 80.1±11.8* | 95.7±15.5* | 102.9±12.1 | 82.6±12.1* |
| P2 | 105.3±14.3 | 72.1±8.9* | 100.7±17.2* | 109.7±12.3* | 84.4±12.0* |
| **ΔFVC mL·year$^{-1}$** | | | | | |
| All (n=1603) | −19.8 | −66.7 | −3.2 | 9.0 | −27.5 |
| | (−56.8–20.5) | (−119.4– −21.5)* | (−44.7–43.1)* | (−33.5–51.7)* | (−64.2–29.6) |
| Never-smoker at P2 (n=502) | −27.8 | −64.9 | −11.2 | −2.0 | −20.5 |
| | (−65.5–9.1) | (−124.8– −26.9)* | (−39.5–28.5)* | (−35.1–31.6)* | (−47.0–22.4) |
| Former smoker at P2 (n=100) | −17.7 | −65.7 | 0.0 | 11.9 | −27.2 |
| | (−53.6–22.8) | (−102.9– −20.6)* | (−46.3–56.9)* | (−29.7–63.2)* | (−66.5–43.2) |
| Current smoker at P2 (n=99) | 2.4 | −175.2 | −24.0 | 0.0 | −43.4 |
| | (−48.3–34.0) | (−212.4– −125.3)* | (−48.1–17.4) | (−44.1–26.0) | (−68.9–5.5)* |

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# PRISm

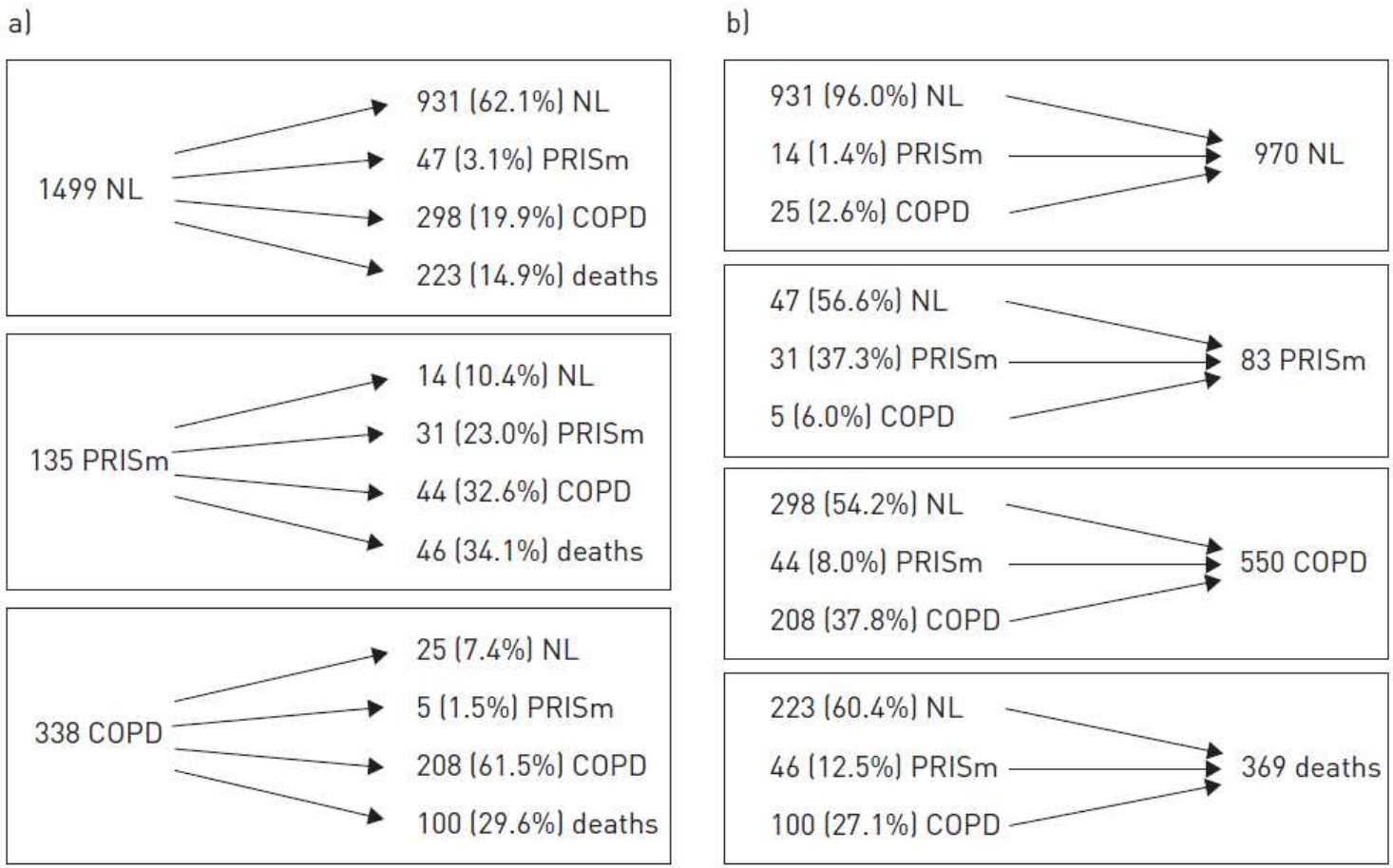


FIGURE 2 Transitions of lung function categories between a) phase 1 and b) phase 2. NL: normal spirometry; PRISm: preserved ratio impaired spirometry; COPD: chronic obstructive pulmonary disease.

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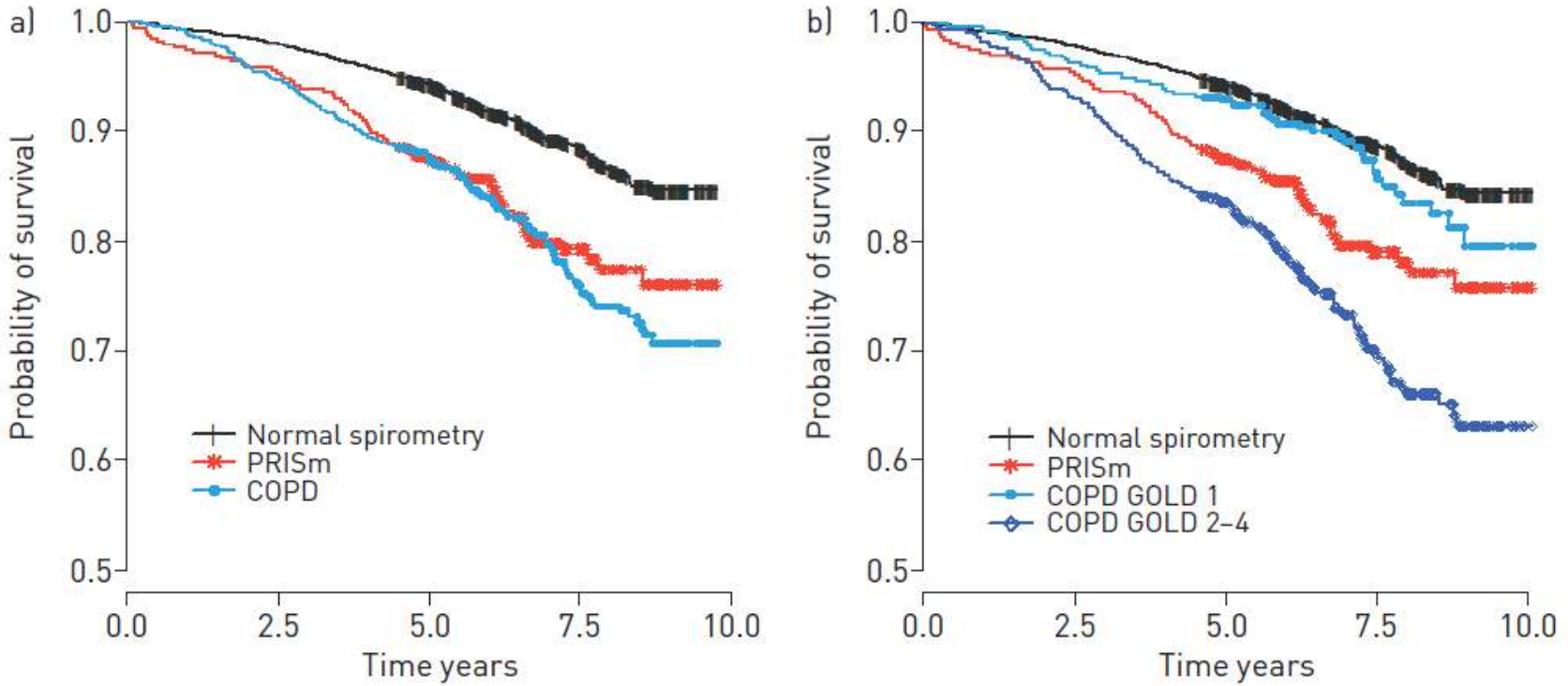


FIGURE 3 Kaplan–Meier curve of mortality for different lung function groups. PRISm: preserved ratio impaired spirometry; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

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*Eur Respir J*
*2020;55:1901217*

# Mortality

TABLE 4 Estimates of mortality stratified by lung function category at P1

| | | Number at risk | HR (95% CI)[#] | HR (95% CI)[#,¶] | HR (95% CI)[+] | HR (95% CI)[¶,+] |
|---|---|---|---|---|---|---|
| **Normal spirometry-P1** | | 4150 | Reference | Reference | Reference | Reference |
| **PRISm-P1** | | 384 | 1.6 (1.2–2.0)* | 1.6 (1.2–2.0)* | 2.7 (1.5–5.0)* | 2.6 (1.4–4.7)* |
| ***PRISm by FEV$_1$ severity*** | *FEV$_1$≥74%* | *194* | *1.3 (0.9–1.8)* | *1.4 (1.0–1.9)* | *2.6 (1.1–5.7)** | *2.5 (1.1–5.5)** |
| | *FEV$_1$<74%* | *190* | *1.9 (1.4–2.6)** | *1.7 (1.3–2.3)** | *2.8 (1.3–6.0)** | *2.6 (1.2–5.7)** |
| ***PRISm by FVC severity*** | *FVC≥73%* | *191* | *1.4 (1.0–2.1)* | *1.4 (0.9–2.0)* | *1.8 (0.7–5.1)* | *1.7 (0.6–4.8)* |
| | *FVC<73%* | *193* | *1.7 (1.2–2.3)** | *1.7 (1.3–2.3)** | *3.2 (1.6–6.4)** | *3.1 (1.6–6.1)** |
| **COPD GOLD 1-P1** | | 419 | 1.0 (0.7–1.3) | 0.7 (0.5–0.9)* | 0.5 (0.2–1.6) | 0.5 (0.1–1.5) |
| **COPD GOLD 2–4-P1** | | 493 | 1.7 (1.4–2.1)* | 1.5 (1.2–1.8)* | 1.9 (1.1–3.4)* | 1.8 (1.0–3.1)* |

*Wijnant et al. Eur Respir J 2020;55:1901217*

# Study VIII: Summary

- **PRISm** is associated with **rapid decline of lung function** and increased **mortality**

*Wijnant et al. Eur Respir J 2020;55:1901217*

SCIENTIFIC REPORTS
nature research

OPEN

# Low FVC/TLC in Preserved Ratio Impaired Spirometry (PRISm) is associated with features of and progression to obstructive lung disease

Spyridon Fortis[1,2*], Alejandro Comellas[2], Victor Kim[3], Richard Casaburi[4], John E. Hokanson[5], James D. Crapo[6], Edwin K. Silverman[7] & Emily S. Wan[7,8]

- COPDGene study
- 5-year follow-up

*Fortis et al. Sci Rep 2020;10:5169*

# Low FVC/TLC in PRISm

- Prevalence of PRISm: 1,131 of 10,199 **(11.1%)**

| FVC/TLC Quartile | High air trapping → Low air trapping | | | | P for trend |
|---|---|---|---|---|---|
| | Very Low quartile (n = 283) | Low quartile (n = 283) | High quartile (n = 282) | Very High quartile (n = 283) | |
| $FVC/TLC_{CT}$ | <0.53 | 0.53–0.59 | 0.59–0.66 | >0.66 | |
| Age, y ± SD | 62.83 ± 8.82 | 57.68 ± 7.34 | 55.70 ± 6.96) | 52.84 ± 6.27 | <0.001 |
| Female, n (%) | 186 (65.7%) | 169 (59.7%) | 143 (50.7%) | 115 (40.6%) | <0.001 |
| African American, n (%) | 86 (30.4%) | 89 (31.4%) | 126 (44.7%) | 174 (61.5%) | <0.001 |
| BMI, $Kg/m^2$ ± SD | 32.99 ± 7.42 | 32.84 ± 7.50 | 30.24 ± 6.88 | 31.05 ± 6.97 | <0.001 |
| Pack-Years ± SD | 49.46 ± 28.69 | 43.51 ± 22.51 | 39.12 ± 20.08 | 38.06 ± 22.63 | <0.001 |
| Active Smoker, n (%) | 154 (54.4%) | 162 (57.2%) | 180 (63.8%) | 213 (75.3%) | <0.001 |
| Chronic Bronchitis, n (%) | 53 (18.7%) | 54 (19.1%) | 52 (18.4%) | 42 (14.8%) | 0.23 |
| mMRC ± SD | 1.70 ± 1.47 | 1.56 ± 1.44 | 1.21 ± 1.37 | 1.44 ± 1.50 | <0.001 |
| SGRQ ± SD | 32.91 ± 22.69 | 30.06 ± 23.29 | 24.50 ± 20.54 | 29.71 ± 23.78 | <0.001 |
| Asthma, n (%) | 75 (26.5%) | 64 (22.6%) | 51 (18.1%) | 60 (21.2%) | 0.064 |
| CHF, n (%) | 21 (7.4%) | 17 (6.0%) | 5 (1.8%) | 8 (2.8%) | 0.001 |
| DM, n (%) | 75 (26.5%) | 75 (26.5%) | 44 (15.6%) | 42 (14.8%) | <0.001 |
| HTN, n (%) | 150 (53.0%) | 151 (53.4%) | 133 (47.2%) | 120 (42.4%) | 0.004 |
| CAD, n (%) | 25 (8.8%) | 32 (11.3%) | 12 (4.3%) | 10 (3.5%) | <0.001 |
| OSA, n (%) | 68 (24.0%) | 61 (21.6%) | 56 (19.9%) | 38 (13.4%) | 0.002 |
| CVA, n (%) | 15 (5.3%) | 10 (3.5%) | 7 (2.5%) | 7 (2.5%) | 0.049 |

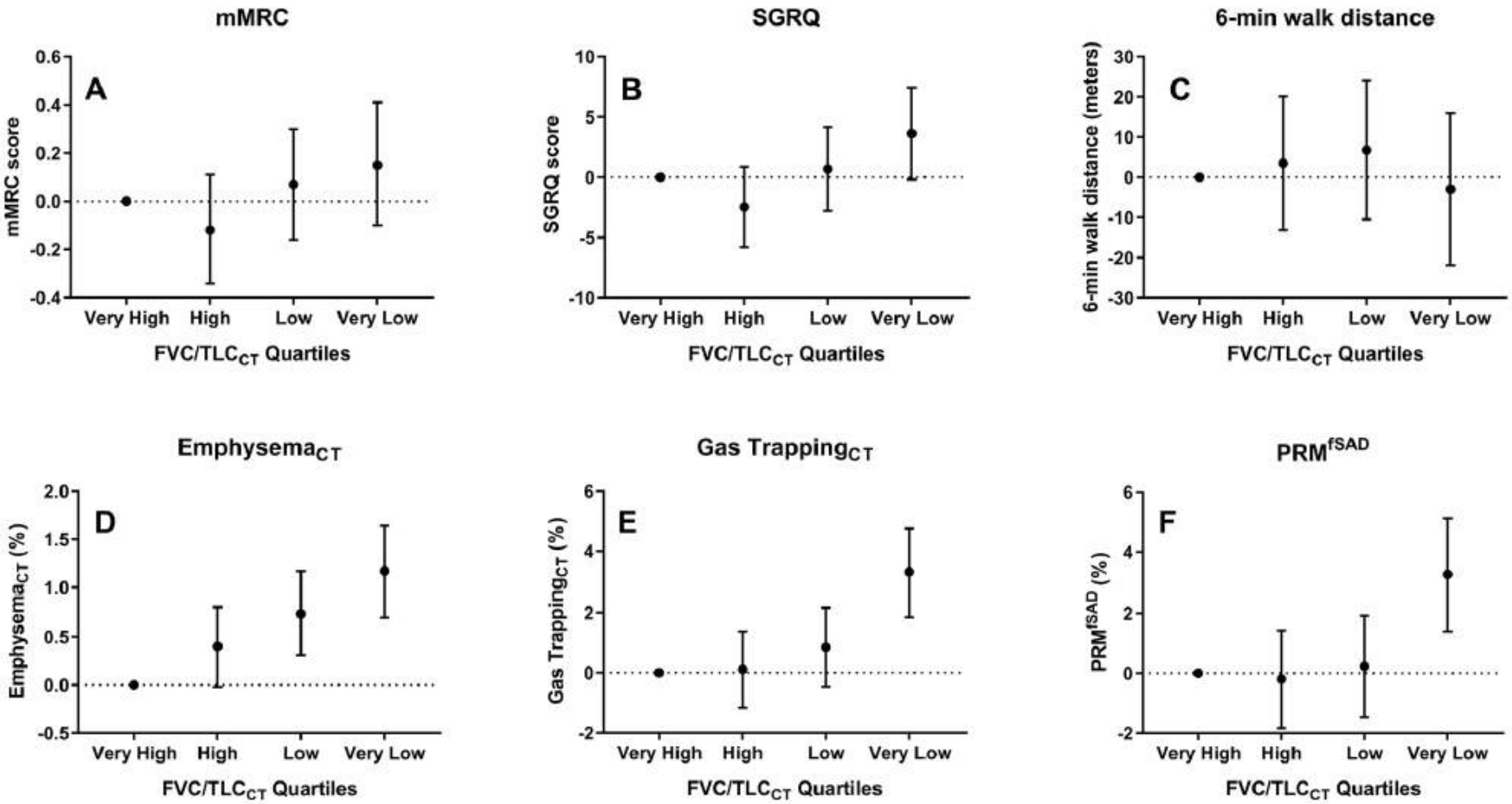
*Fortis et al. Sci Rep 2020;10:5169*

# Low FVC/TLC in PRISm

- Characteristics of PRISm

| FVC/TLC Quartile | High air trapping → Low air trapping | | | | P for trend |
|---|---|---|---|---|---|
| | Very Low quartile (n = 283) | Low quartile (n = 283) | High quartile (n = 282) | Very High quartile (n = 283) | |
| LAMA, n (%) | 33 (12.1%) | 18 (6.5%) | 18 (6.5%) | 15 (5.4%) | 0.005 |
| ICS, n (%) | 19 (7.0%) | 19 (6.8%) | 12 (4.4%) | 13 (4.6%) | 0.131 |
| LABA, n (%) | 7 (2.6%) | 1 (0.4%) | 1 (0.4%) | 4 (1.4%) | 0.2482 |
| ICS/LABA, n (%) | 59 (21.6%) | 36 (12.9%) | 22 (7.9%) | 24 (8.6%) | <0.001 |
| Post-FEV1% ± SD | 65.74 ± 9.65 | 71.33 ± 7.32 | 72.04 ± 6.54 | 73.02 ± 5.92 | <0.001 |
| Post-FVC% ± SD | 66.70 ± 10.07 | 72.47 ± 7.68 | 73.47 ± 7.58 | 75.05 ± 7.25 | <0.001 |
| BDR, n (%) | 40 (14.4%) | 41 (14.6%) | 30 (10.8%) | 47 (16.8%) | 0.71 |
| §% Emphysema ± SD | 2.02 ± 3.32 | 1.66 ± 2.92 | 1.48 ± 2.00 | 1.07 ± 1.53 | <0.001 |
| §% Gas trapping ± SD | 12.48 ± 8.64 | 9.06 ± 7.48 | 8.19 ± 6.65 | 7.50 ± 5.82 | <0.001 |
| ‡$PRM^{fSAD}$, % ± SD | 14.63 ± 9.87 | 10.60 ± 8.65 | 10.37 ± 9.24 | 10.13 ± 8.65 | <0.001 |
| §$FRC_{CT}$% ± SD | 97.25 ± 18.17 | 87.62 ± 14.63 | 80.89 ± 13.00 | 75.25 ± 12.36 | <0.001 |
| $TLC_{CT}$ % ± SD | 90.20 ± 13.58 | 85.82 ± 9.80 | 77.77 ± 9.48 | 68.96 ± 9.02 | <0.001 |
| ‡6-MWT, meters ± SD | 366.33 ± 110.24 | 394.00 ± 104.72 | 406.56 ± 114.12 | 396.23 ± 109.78 | <0.001 |

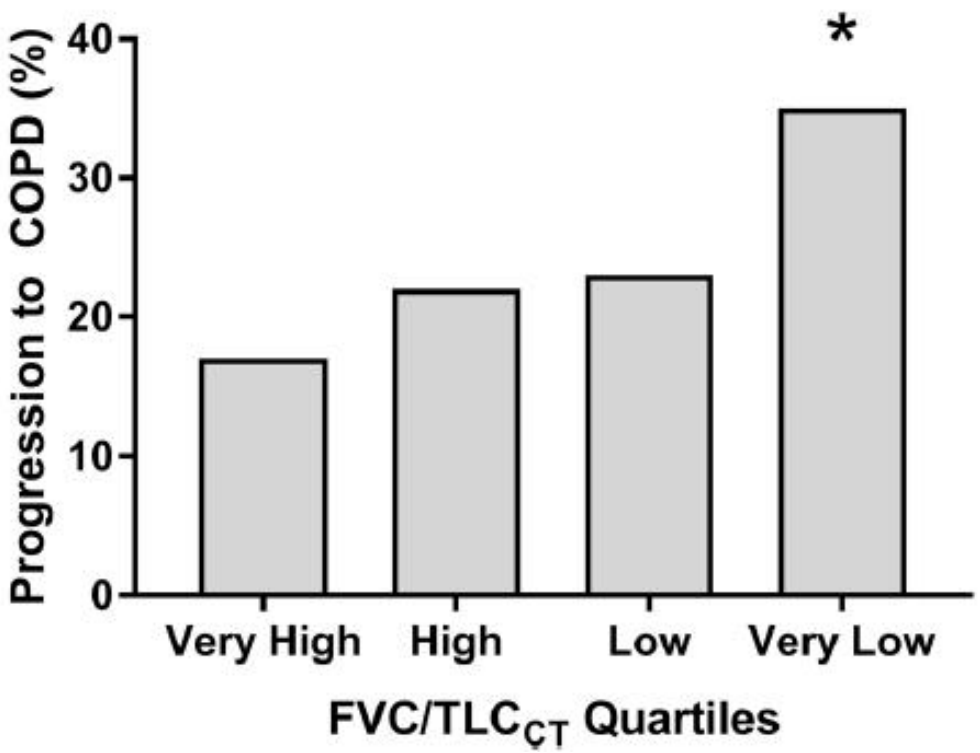
Fortis et al. Sci Rep 2020;10:5169




*Fortis et al.*
*Sci Rep*
*2020;10:5169*

# Low FVC/TLC in PRISm

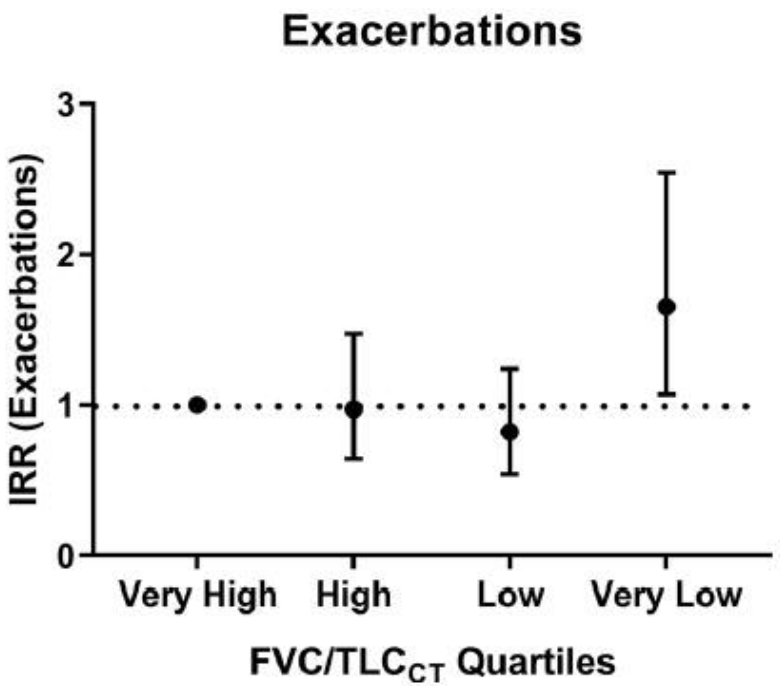
- Progression to COPD

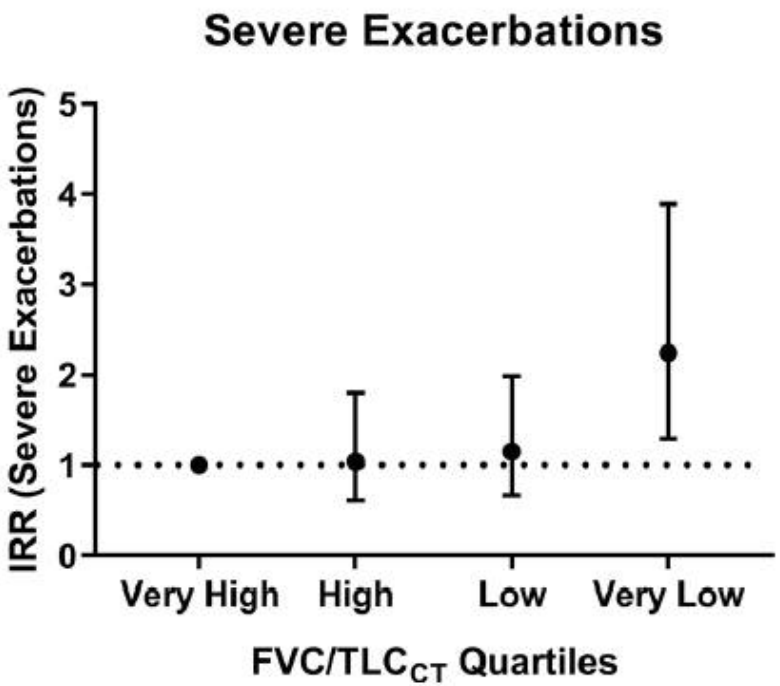



*Fortis et al. Sci Rep 2020;10:5169*

# Low FVC/TLC in PRISm

- Exacerbation risk

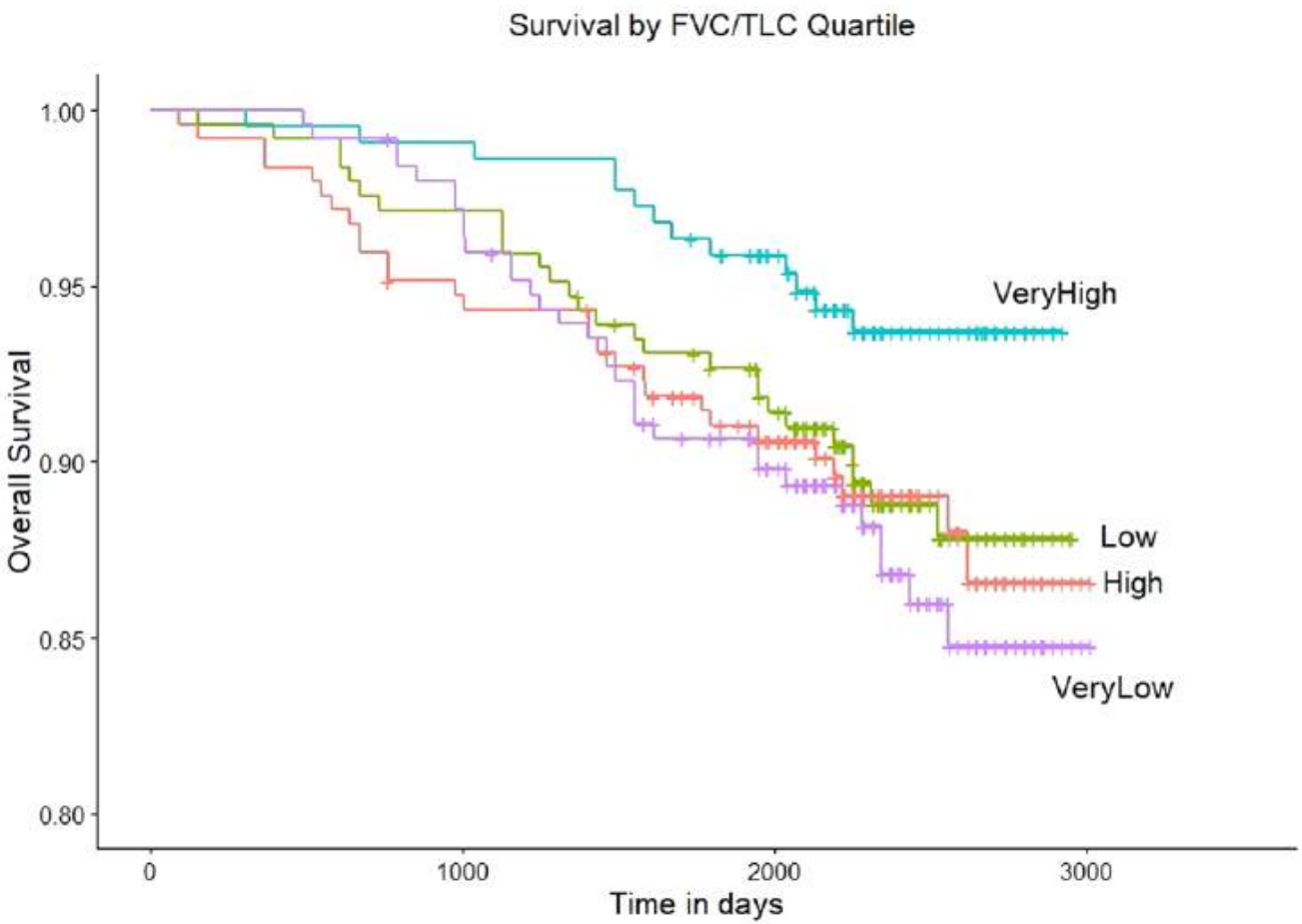



*Fortis et al. Sci Rep 2020;10:5169*

# Low FVC/TLC in PRISm

- Survival rate




*Fortis et al. Sci Rep 2020;10:5169*

# Study IX: Summary

- **Reduced FVC/TLC$_{CT}$ ratio** in PRISm is associated with increased symptoms, radiographic emphysema and gas trapping, exacerbations, and **progression to COPD.**

*Fortis et al. Sci Rep 2020;10:5169*

# SUMMARY

- **Definition of PRISm**

: FEV1/FVC ratio >70% & FEV1 < 80%

- **Characteristics of PRISm**

: Heterogeneous group

: Restrictive vs. Obstructive

: PRISm (vs. control, vs. COPD)

- **Prognosis of PRISm**

: Can progress to COPD

: Variable (biomarker?)


Thank you
With the Love of God, Free Humankind from Disease and Suffering
Severance