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Rural Residence and Chronic Obstructive Pulmonary Disease Exacerbations

Analysis of the SPIROMICS Cohort

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Abstract

Rationale: Rural residence is associated with poor outcomes in several chronic diseases. The association between rural residence and chronic obstructive pulmonary disease (COPD) exacerbations remains unclear.

Objectives: In this work, we sought to determine the independent association between rural residence and COPD-related outcomes, including COPD exacerbations, airflow obstruction, and symptom burden.

Methods: A total of 1,684 SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) participants with forced expiratory volume in 1 second/forced vital capacity < 0.70 had geocoding-defined rural-urban residence status determined ($N = 204$ rural and $N = 1{,}480$ urban). Univariate and multivariate logistic and negative binomial regressions were performed to assess the independent association between rurality and COPD outcomes, including exacerbations, lung function, and symptom burden. The primary exposure of interest was rural residence, determined by geocoding of the home address to the block level at the time of study enrollment. Additional covariates of interest included demographic and clinical characteristics, occupation, and occupational exposures. The primary outcome measures were exacerbations determined over a 1-year course after enrollment by quarterly telephone calls and at an annual research clinic visit. The odds ratio (OR) and incidence rate ratio (IRR) of exacerbations that required treatment with medications, including steroids or antibiotics (total exacerbations), and exacerbations leading to hospitalization (severe exacerbations) were determined after adjusting for relevant covariates.

Results: Rural residence was independently associated with a 70% increase in the odds of total exacerbations (OR, 1.70 [95% confidence interval (CI), 1.13–2.56]; $P = 0.012$) and a 46% higher incidence rate of total exacerbations (IRR 1.46 [95% CI, 1.02–2.10]; $P = 0.039$). There was no association between rural residence and severe exacerbations. Agricultural occupation was independently associated with increased odds and incidence of total and severe exacerbations. Inclusion of agricultural occupation in the analysis attenuated the association between rural residence and the odds and incidence rate of total exacerbations (OR, 1.52 [95% CI, 1.00–2.32]; $P = 0.05$ and IRR 1.39 [95% CI, 0.97–1.99]; $P = 0.07$). There was no difference in symptoms or airflow obstruction between rural and urban participants.

Conclusions: Rural residence is independently associated with increased odds and incidence of total, but not severe, COPD exacerbations. These associations are not fully explained by agriculture-related exposures, highlighting the need for future research into potential mechanisms of the increased risk of COPD exacerbations in the rural population.

Keywords: chronic obstructive pulmonary disease; exacerbation; rural health

Chronic obstructive pulmonary disease (COPD) is a common condition worldwide, with a prevalence estimated at 10% (1, 2). Acute exacerbations of COPD (AECOPD) are a major contributor to the morbidity and mortality of the disease (3, 4). Reduced lung function and a history of AECOPD are established risk factors for future development of AECOPD (5, 6). Persons living in rural areas of the United States face unique and important healthcare challenges. They experience higher COPD mortality rates than their urban counterparts across all regions of the United States (7), and a comparatively higher burden of chronic diseases (8–10). The potential mechanisms for poorer health outcomes in rural populations include reduced access to care, differential behavioral risk factors, and unique environmental exposures. With emergency department expenditures for COPD increasing, limited access to care among rural patients with COPD, and more AECOPD-related morbidity and mortality in the rural areas of the United States over the preceding three decades, determining the role rurality plays in AECOPD is important (11–15). The impact of rural residence on AECOPD has yet to be established in a prospective, nationwide cohort.

SPIROMICS (Subpopulations and Intermediate Outcome Measures in COPD Study) is a multicenter, observational cohort study of current and former smokers and nonsmoking control subjects with extensive physiologic, clinical, and biochemical metrics (16). SPIROMICS affords the opportunity to independently determine associations between demographic factors and COPD outcomes in a rigorous manner, including access to geocoding for patient residence and a robust assessment of environmental and work exposures. For this analysis, using home addresses obtained at the time of enrollment, urban-rural status was defined through geocoding to the block level in individuals with COPD.

We hypothesized that rural residence would be independently associated with an increased risk of total and severe COPD exacerbations. Rurality can impact COPD outcomes through several mechanisms, including environmental and occupational exposures, socioeconomic status, geographic location, smoking patterns, and access to care. This study explores how these factors impact the independent association of rural residence on 1-year COPD exacerbation outcomes.

Methods

Study Cohort

SPIROMICS is a multicenter cohort study that includes current and former smokers (>20 pack years) and nonsmoking control subjects between 40 and 80 years of age, with and without COPD (defined as postbronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC] ratio < 0.70), who were recruited from 12 clinical centers (16). The analytical cohort for this study is limited to SPIROMICS participants with spirometry-defined COPD, complete 1-year exacerbation data from the baseline visit, and rural-urban residence status determined via geocoding as described below ($N = 1{,}684$). Institutional review boards at each center approved SPIROMICS, and all participants provided written informed consent.

Data Collection

Demographic data, smoking status and history, inhaler mediation use, and AECOPD occurrence in the year before the baseline visit were obtained via self-report at enrollment. Medical comorbidities were defined via self-report of a physician's diagnosis. Respiratory symptom assessments were performed using the modified Medical Research Council (mMRC) dyspnea scale (17); body mass index, airflow obstruction, dyspnea, and exercise (BODE) index (18); and COPD assessment tool (CAT) (19). Chronic bronchitis was defined using subdomains of the St. George's Respiratory Questionnaire (20). All analyses incorporated postbronchodilator spirometry data from the baseline visit. Analyses of lung computed tomography (CT) scans were performed per protocols described previously (21), including the extent of

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A complete list of SPIROMICS Investigators may be found before the beginning of the References.

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emphysema (defined as voxels below −950 Hounsfield units) and functional small-airways disease (22, 23) evaluated on a whole-lung basis. Occupation and occupational exposures were assessed by asking the following questions: *1*) have you ever worked in a particular environment, *2*) have you ever worked in a specific occupation, and *3*) in your job, do/did you come into regular contact with any of the following specific examples of vapors, gas, dust, or fumes? A composite variable to capture any agricultural exposure was generated and defined as present with an affirmative response to any of the following questions: *1*) have you ever had a profession in agriculture, *2*) have you ever worked as a pig farmer, and *3*) have you ever been exposed to wheat, flower, grain, animal feed, or cotton dust? (24, 25).

The binary urban/rural classification was determined from the 2010 U.S. Census. The U.S. Census generally categorizes census blocks as "urban" in areas containing 500 people per square mile and at least 2,500 people total (26), or "rural" otherwise. Primary residency at the initial visit was geocoded using the ArcGIS 10.3 system (Esri), which is based primarily on parcel data. Addresses that could not be automatically geocoded (6% of the cohort) were assigned based on a Google or Bing Maps application search. Census data were obtained from the U.S. Census via the University of Washington library. The demographic variable for rurality was compiled at the block level using geocoded addresses.

Longitudinal data on AECOPD were collected by quarterly telephone calls and an annual clinic visit. Two AECOPD outcomes that occurred within the first year of study follow-up were assessed as defined previously (6, 27): *1*) exacerbations requiring treatment with medications, including oral steroids or antibiotics (total exacerbations), and *2*) exacerbations that led to an emergency department visit or hospital admission (severe exacerbations).

Statistical Methods

Chi-square tests or *t* tests (for normally distributed data) or the Kruskal-Wallis test (for skewed data) were used to identify differences in demographic and clinical factors between rural and urban participants. To determine the independent association between rural residence (exposure) and COPD exacerbations (outcomes), logistic regression and negative-binomial regression modeling approaches were employed separately. For logistic regression, exacerbations were dichotomized as either no exacerbation or any exacerbations over the first year after enrollment, with odds ratios (ORs) representing the odds of any exacerbation related to exposure variables. For negative-binomial regression models, exacerbations were modeled continuously as the number of exacerbations, with incidence rate ratios (IRRs) representing the incidence rate of an additional exacerbation related to exposure variables. For model construction, univariate models were first constructed. Covariates defined as clinically relevant from a literature review or statistically associated with outcomes of interest (threshold $P < 0.20$) were included in multivariate models. Sensitivity analyses were performed to adjust for study site, removal of previous exacerbation history from models, and addition of the agricultural occupation variable. A P value < 0.05 was used to determine statistical significance. All analyses were completed with SAS 9.4.

Results

Participant Characteristics

The total SPIROMICS cohort (N = 2,974) included 1,831 individuals with spirometry-confirmed COPD ($FEV_1/FVC < 0.7$). The analytical cohort included here comprised 1,684 participants with geocoding and exacerbation data, representing 92% of the COPD participants in SPIROMICS (*see* Figure E1 in the online supplement). There were no substantial differences in clinical or demographic characteristics between the analytical cohort and the larger cohort of COPD participants in SPIROMICS (Tables E1 and E2). Of the 1,684 SPIROMICS participants included in the analysis, 204 (12%) resided in rural areas and 1,480 (88%) resided in urban areas. More than 20% of the enrolled patients at four SPIROMICS centers (University of Alabama-Birmingham, Wake Forest University, University of Michigan at Ann Arbor, and University of Iowa at Iowa City) qualified as rural, constituting 81% of the entire rural cohort. Rural participants were more likely to be white and less likely to have an annual income below $35,000 (Table 1). There was no difference in sex, age, pack-years of smoking history, body mass index (BMI), current smoking status, or education between rural and urban residents. Nonpulmonary medical comorbidities were similar at baseline (Table E3). Rural participants were more likely to report ever being employed in synthetic-fiber manufacturing, pig farming, carpentry, agriculture, and beauty care (Table E4). Rural participants reported a higher prevalence of regular contact with wheat flour or grain dust, metal dust or fumes, cotton dust, and animal feed (Table E5).

Association between Rural Residence and COPD-related Outcomes

At the baseline visit, there was no difference in measures of postbronchodilator FEV_1 between rural and urban participants (Table 2). Postbronchodilator FVC% predicted was lower in rural participants (85.5 vs. 89.2% predicted; P = 0.01). There was no difference in the BODE index, CAT scores, mMRC, or total count of AECOPD requiring medications or severe exacerbations in the 12 months before the baseline visit between the groups. Self-report of a physician's diagnosis of asthma was less prevalent among rural participants than among urban ones (16% vs. 24%; P = 0.005), whereas self-reported diagnosis of emphysema, COPD, or chronic bronchitis did not differ between the two groups. Report of any inhaler use, short-acting bronchodilator use, or long-acting inhaler use did not differ between residence groups (Table E6). There was no difference in CT measures of emphysema or functional small-airways disease between rural and urban participants. Over the first year of follow-up, there was no difference in the rate of decline of FEV_1 between rural and urban participants (-51 ± 213 ml vs. -42 ± 213 ml; P = 0.63).

As shown in Figure 1, in the 1 year after follow-up from cohort entry, 78% of urban patients had no exacerbations, whereas 14% had one, 4% had two, and 5% had three or more AECOPD. Among the rural cohort, 66% had no exacerbations, whereas 19% had one, 10% had two, and 5% had three or more AECOPD (overall chi-square P = 0.002). For severe exacerbations, 91% of the urban participants had no severe exacerbations, 6% had one, 2% had two, and 1% had three or more severe AECOPD.

Table 1. Cohort demographic and clinical characteristics

n	Urban 1,480	Rural 204	*P* Value
Age, yr	65.3 (8.1)	65.4 (7.2)	0.89
Race			<0.001
White	1175 (79)	200 (98)	
Black	244 (16)	1 (0)	
Asian	22 (1)	0 (0)	
American Indian	7 (0)	0 (0)	
Mixed	23 (2)	3 (1)	
Missing	9 (1)	0 (0)	
Female	622 (42)	96 (47)	0.17
Body mass index, kg/m^2	27.3 (5.3)	27.5 (4.9)	0.73
Pack-years smoked	52.5 (26.6)	54.0 (23.8)	0.16
Current smoker	490 (34)	66 (33)	0.78
Education			0.12
Eighth grade or below	25 (1)	6 (3)	
Trade/business/some high school	154 (10)	24 (12)	
High school graduate	374 (25)	56 (27)	
Trade/business after high school	73 (5)	16 (8)	
Some college	444 (30)	64 (31)	
Bachelor's degree	190 (13)	21 (10)	
Post-Bachelor's education	215 (15)	17 (8)	
Declined to answer	2 (0)	0 (0)	
Total yearly income			0.005
<$15,000	255 (17)	35 (17)	
$15,000–$34,999	310 (21)	28 (14)	
$35,000–$49,999	179 (12)	38 (19)	
$50,000–$74,999	212 (14)	36 (18)	
$75,000+	260 (18)	24 (12)	
Declined to answer	250 (17)	42 (21)	

All values are mean (SD) or *n* (%) unless otherwise indicated.

In the rural cohort, 88% had no severe exacerbations, whereas 10% had one, 1% had two, and 1% had three or more severe exacerbations (overall chi-square $P = 0.37$). There was no difference in severe exacerbations between rural and urban participants who experienced an exacerbation during follow-up (34% vs. 36%; $P = 0.71$).

Association between Rural Residence and Total Exacerbations

In univariate logistic regression, several factors were associated with increased odds of total exacerbations (Table E7). These included never having graduated from high school, a reported history of asthma, lower baseline FEV_1, and a history of two or more exacerbations in the year before enrollment. Older age and male sex were associated with reduced odds of total AECOPD. In a univariate analysis, rural residence was associated with an 81% increase in the odds of total exacerbations (OR, 1.81 [95% CI, 1.32–2.47]; $P < 0.001$). A multivariate logistic regression model was generated that included age, race, sex, current smoking status, education, income, asthma history, baseline FEV_1, number of exacerbations in the year preceding enrollment, and rural status (Table 3). In this model, white race, reported history of asthma, lower baseline FEV_1, younger age, and two or more exacerbations in the year preceding enrollment were associated with significantly increased odds of total exacerbations. Rural residence was independently associated with a 70% increase in odds of total AECOPD (OR, 1.70 [95% CI, 1.34–2.56]; $P = 0.012$).

Using negative binomial regression modeling, factors associated with an increased incidence rate of total AECOPD in the univariate analysis included not graduating from high school, reduced FEV_1, two or more exacerbations in the year before enrollment, yearly income less than $50,000, and history of asthma (Table E7). Older age and male sex were associated with a lower incidence of total exacerbations. In a univariate analysis, rural residence was associated with a 46% increase in the incidence rate of total exacerbations (IRR, 1.46 [95% CI, 1.06–2.00]; $P = 0.02$). In a multivariate analysis (Table 3) incorporating the same covariates as in the logistic regression models, an increased incidence rate of total exacerbations was seen with white race, reported history of asthma, lower baseline FEV_1, younger age, and two or more exacerbations in the year before enrollment. Rural residence was independently associated with a 46% higher incidence rate of total exacerbations (IRR, 1.46 [95% CI, 1.02–2.10]; $P = 0.039$).

Association between Rural Residence and Severe Exacerbations

In univariate logistic regression, several factors were associated with severe AECOPD (Table E8). These factors included not graduating from high school, yearly income less than $50,000, lower baseline FEV_1, reported history of asthma, and having two or more exacerbations in the year before enrollment. Factors associated with lower odds of severe exacerbation included older age and white race. Rural residence was not associated with differential odds of severe exacerbation (OR, 1.38 [95% CI, 0.88–2.17]; $P = 0.16$). In multivariate logistic regression (Table 4), only a low baseline FEV_1 and not graduating from high school were associated with an increased odds of severe exacerbation. Rural residence was not associated with odds of severe exacerbation at 1-year follow-up (OR, 1.15 [95% CI, 0.63–2.11]; $P = 0.66$) in a multivariate analysis.

Using negative binomial regression modeling, factors associated with an increased incidence rate of severe exacerbations in a univariate analysis (Table E8) included not graduating from high school, annual income of less than $50,000, reported history of asthma, lower baseline FEV_1, and two or more exacerbations in the year before enrollment. Factors associated with a reduced incidence rate of severe exacerbations in univariate analysis included age and white race. Rural residence was not associated with an increased incidence rate of severe exacerbations in the univariate analysis (IRR, 1.09 [95% CI, 0.65–1.83]; $P = 0.75$). In multivariate negative binomial regression (Table 4), lower baseline FEV_1 was independently associated with a higher incidence of severe exacerbations. Rural residence was not independently associated with an increased incidence rate of severe exacerbations (IRR, 1.14 [95% CI, 0.60–2.17]; $P = 0.68$).

Table 2. Baseline pulmonary function and chronic obstructive pulmonary disease symptom characteristics

	Urban	Rural	*P* Value
FEV_1/FVC, postbronchodilator	67.4 (17.5)	68.5 (16.6)	0.40
FEV_1, postbronchodilator			
Absolute, L	1.75 (0.80)	1.70 (0.68)	0.30
% predicted	61.4 (23.4)	59.6 (20.6)	0.25
FVC, postbronchodilator			
Absolute, L	3.37 (1.08)	3.26 (0.93)	0.15
% predicted	89.2 (20.5)	85.5 (17.3)	0.005
GOLD category*			0.34
A	353 (24)	59 (29)	
B	545 (37)	70 (34)	
C	87 (6)	8 (4)	
D	486 (33)	67 (33)	
CAT score, median (IQR)	15 (12)	15 (11)	0.84
CAT score ⩾10	1,035 (73)	137 (71)	0.67
Chronic bronchitis by SGRQ	650 (46)	101 (53)	0.09
mMRC, median (IQR)	1 (1)	1 (2)	0.28
mMRC ⩾ 2	465 (32)	63 (31)	0.83
BODE index	2.08 (2.1)	1.95 (1.7)	0.23
Total COPD exacerbations in prior 12 mo			0.59
0	1,043 (72)	139 (70)	
1	213 (15)	35 (18)	
2+	184 (13)	25 (13)	
Severe COPD exacerbations in prior 12 mo			0.73
0	1,233 (84)	168 (83)	
1	158 (11)	23 (11)	
2+	69 (5)	12 (6)	
Patient-reported physician diagnosis of chronic bronchitis	374 (27)	53 (27)	0.96
Patient-reported physician diagnosis of emphysema	697 (50)	97 (49)	0.70
Patient-reported physician diagnosis of COPD	1,086 (76)	144 (72)	0.14
Patient-reported physician diagnosis of chronic bronchitis, emphysema, or COPD	1,193 (84)	158 (79)	0.091
Diagnosis of asthma	348 (25)	30 (16)	0.005
Diagnosis of asthma as a child	144 (10)	14 (7)	0.19
Diagnosis of asthma as an adult	196 (14)	15 (8)	0.018
Asthma status			0.014
Current asthma	251 (19)	19 (10)	
Past asthma	58 (4)	6 (3)	
Never asthma	1,043 (77)	160 (86)	

Definition of abbreviations: BODE = body mass index, airflow obstruction, dyspnea, exercise; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD = Global Initiative for Obstructive Lung Disease; IQR = interquartile range; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.
All values are mean (SD) or *n* (%) unless otherwise indicated.
*GOLD categorization using COPD Assessment Test criteria.

Impact of Agricultural Exposures on COPD Exacerbations and Rural Associations

Because substantial differences in occupation and occupational exposures were associated with rurality, a composite agricultural exposure variable was generated (see METHODS). The prevalence of agriculture exposure was higher in rural compared with urban participants (25% vs. 12%; $P < 0.001$). In a univariate analysis, agricultural exposure was associated with increased odds (OR, 1.60 [1.19–2.15]; $P = 0.002$) and incidence (IRR, 1.75 [1.30–2.36]; $P < 0.001$) of total exacerbations. Agriculture exposure was also associated with increased odds (OR, 1.82 [1.16–2.85]; $P = 0.009$) and incidence (IRR, 1.94 [1.30–2.89]; $P = 0.001$) of severe exacerbations. Inclusion of agricultural exposure in multivariate models demonstrated that agriculture exposure was independently associated with increased odds (OR, 2.18 [95% CI, 1.51–3.16]; $P < 0.001$) and incidence (IRR, 1.53 [95% CI, 1.11–2.11]; $P = 0.01$) of total exacerbations (Table E9). Agricultural exposure was also independently associated with increased odds (OR, 2.23 [95% CI, 1.36–3.56]; $P = 0.002$) and incidence (IRR, 2.00 [95% CI, 1.20–3.33]; $P = 0.01$) of severe exacerbations. Addition of agricultural exposure to the multivariate analysis attenuated the association between rural residence and increased odds of total exacerbations (OR, 1.52 [95% CI, 1.00–2.32]; $P = 0.05$) and the incidence rate of total exacerbations (IRR, 1.39 [95% CI, 0.97–1.99]; $P = 0.07$).

Sensitivity Analysis

The association between rural residence and total exacerbations was attenuated with inclusion of study site (OR, 1.30 [95% CI, 0.84–2.01]; $P = 0.24$; and IRR, 1.21 [95% CI, 0.84–1.76]; $P = 0.31$). Restricting analysis to the four sites with the highest rural prevalence attenuated the association between rural residence and total exacerbations (OR, 1.33 [95% CI, 0.81–2.17]; $P = 0.26$; and IRR, 1.35 [95% CI, 0.92–1.97]; $P = 0.12$). Inclusion of a metal dust/fume exposure variable did not alter the rural associations, and in these models, metal fumes were not significantly correlated with AECOPD. Inclusion of prior exacerbation history could overadjust for future exacerbations. In multivariate models excluding prior exacerbation history, rural residence remained independently associated with increased odds (OR, 1.68 [95% CI, 1.18–2.39]; $P = 0.004$) and incidence (IRR, 1.42 [95% CI, 1.03–1.95]; $P = 0.031$) of total exacerbations. Rurality remained unassociated with severe exacerbations in all sensitivity models. Smoking history measured by pack-years was not independently associated with total exacerbations ($P = 0.33$ for logistic regression and $P = 0.4$ for negative binomial model) or severe exacerbations ($P = 0.90$ for logistic regression and $P = 0.85$ for negative binomial model). Given the difference in income categories at enrollment, multivariate models incorporating income with five categories were generated. These models did not impact the associations between rural status and total exacerbations, nor was income statistically significant in these models. There was no impact of alternative income covariate modeling on the lack of a rural association with increased odds of severe exacerbations. In negative

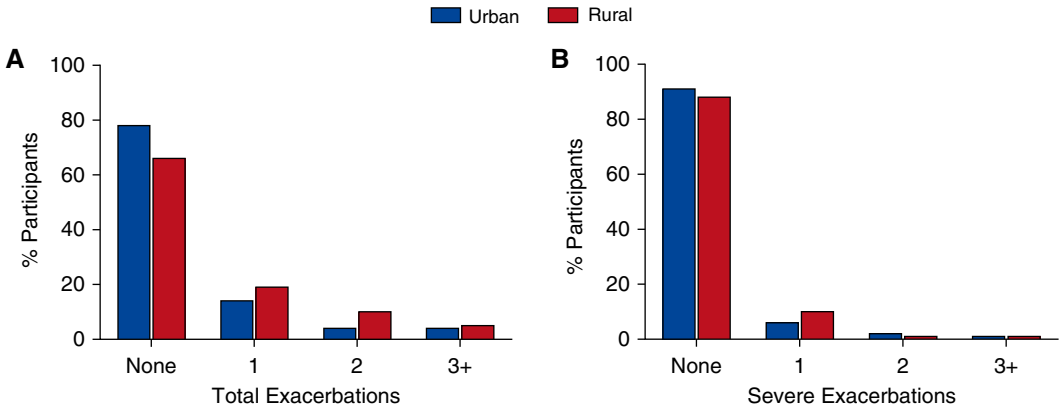

Figure 1. Percentage of urban (blue bars) and rural (red bars) SPIROMICS participants experiencing total (*A*) or severe (*B*) COPD exacerbations within the first year of study follow-up. Overall chi-square $P = 0.002$ (total) and $P = 0.37$ (severe) exacerbations. COPD = chronic obstructive pulmonary disease.

binomial modeling, only the highest income category compared with the lowest was associated with a reduced incidence of severe exacerbations (IRR, 0.33 [95% CI, 0.14–0.75]; $P = 0.008$).

Discussion

In this analysis of individuals with spirometry-confirmed COPD participating in the observational SPIROMICS cohort, we observed that rural residence was independently associated with increased odds and incidence of AECOPD requiring treatment, but not severe exacerbations requiring an emergency room visit or hospitalization. Rural residence independently conferred a 70% increase in the odds and a 46% increase in the incidence of total AECOPD. The association between rural residence and exacerbation risk persisted after we accounted for potential confounders, including smoking patterns, lung function, prior exacerbation history, and income. Rural residence was associated with agriculture-related exposures; however, the association between rural residence and exacerbation risk was not fully explained after we accounted for agriculture-related exposures.

Investigations of rural healthcare outcomes in the United States have described disparate outcomes in chronic diseases such as heart disease, stroke, and cancer (28–30). From 1980 to 2014, the rates of mortality from chronic respiratory disease have increased, as illustrated by COPD-related deaths in the rural locales of central Appalachia (15). Rural patients with COPD across the United States have more frequent hospitalizations, more severe dyspnea, worse quality of life, and access to fewer pulmonary specialists (7, 12, 13, 31–34). Rural patients in the Veterans Affairs system have been shown to have increased mortality related to acute exacerbations (14). Furthermore, patients in rural and urban hospitals experience differential outcomes (35). The adverse pulmonary outcomes seen in rural patients with COPD are due to multiple factors, including a lack of adequate diagnoses and treatments, differential access to acute and chronic care, and limited availability of pulmonary specialists (13). This study extends previous investigations by demonstrating that rural status is independently associated with more frequent COPD exacerbations requiring treatment. This finding persisted after we accounted for medication use patterns, comorbidities, and markers of socioeconomic status that are often implicated in health outcome disparities in rural populations. Although income did differ between rural and urban participants, we observed no consistent association between income and AECOPD or the impact of income on rural associations with AECOPD. Poor access to healthcare is often implicated as a cause of adverse health outcomes in chronic disease, as demonstrated by the increased rate of hospital readmissions for patients with heart failure who do not have ready access to healthcare due to rurality (36). However, the participants enrolled in SPIROMICS may have been less subject to limited access than the general rural population given their involvement in a study at an academic center. Thus, the

Table 3. Multivariate regression models* for chronic obstructive pulmonary disease total exacerbations in the first 365 days of follow-up

	Logistic Regression		Negative Binomial Regression	
	OR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Age (per 10 yr)	0.69 (0.57–0.84)	<0.001	0.74 (0.62–0.88)	0.001
White race (vs. others)	1.79 (1.19–2.68)	0.005	1.74 (1.23–2.46)	0.002
Male	1.19 (0.88–1.63)	0.27	1.06 (0.81–1.39)	0.68
Current smoking	0.77 (0.55–1.08)	0.13	0.95 (0.71–1.26)	0.71
Not graduating high school	1.32 (0.86–2.01)	0.20	1.32 (0.92–1.89)	0.13
Income < $50,000	1.03 (0.75–1.42)	0.84	1.05 (0.8–1.39)	0.71
History of asthma	1.53 (1.11–2.12)	0.011	1.49 (1.12–1.98)	0.006
Baseline FEV_1 (per 100 ml)	0.93 (0.91–0.95)	<0.001	0.93 (0.91–0.95)	<0.001
More than two exacerbations at baseline	3.03 (2.11–4.36)	<0.001	2.71 (2–3.68)	<0.001
Rural residence	1.70 (1.13–2.56)	0.012	1.46 (1.02–2.10)	0.039

Definition of abbreviations: CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; IRR = incidence rate ratio; OR = odds ratio.
*Adjusted for all covariates in the table.

Table 4. Multivariate regression models* for severe chronic obstructive pulmonary disease exacerbations in the first 365 days of follow-up

	Logistic Regression		Negative Binomial Regression	
	OR (95% CI)	*P* Value	IRR (95% CI)	*P* Value
Age (per 10 yr)	0.78 (0.60–1.02)	0.07	0.79 (0.60–1.03)	0.085
White race (vs. others)	0.85 (0.52–1.39)	0.52	0.98 (0.59–1.63)	0.93
Male	1.32 (0.86–2.02)	0.21	1.37 (0.88–2.12)	0.16
Current smoking	0.97 (0.61–1.54)	0.89	1.01 (0.64–1.61)	0.95
Not graduating high school	1.83 (1.09–3.07)	0.022	1.36 (0.78–2.38)	0.28
Income < $50,000	1.32 (0.82–2.13)	0.25	1.58 (0.98–2.55)	0.06
History of asthma	1.24 (0.79–1.94)	0.36	1.49 (0.94–2.36)	0.09
Baseline FEV_1 (per 100 ml)	0.91 (0.88–0.95)	<0.001	0.90 (0.87–0.94)	<0.001
More than two exacerbations at baseline	1.54 (0.95–2.51)	0.083	1.55 (0.93–2.58)	0.091
Rural residence	1.15 (0.63–2.11)	0.66	1.14 (0.60–2.17)	0.68

Definition of abbreviations: CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; IRR = incidence rate ratio; OR = odds ratio.
*Adjusted for all covariates in table.

estimates of association between rurality and COPD outcomes in SPIROMICS may underestimate the strength of associations in the general rural population.

Environmental exposures may explain the association between rural residence and increased AECOPD risk. Globally, exposure to biomass fuel is associated with respiratory symptoms and poor pulmonary function (37). Individuals in professions with a high risk of exposure based on job exposure matrices have been shown to have more episodes of AECOPD requiring emergency department care and hospital admission (38, 39). Agricultural work produces dusts and vapors that can cause and/or exacerbate underlying lung disease (40, 41). Agricultural workers may be exposed to ambient gasses and particles such as ammonia, pesticides, bacterial products (including peptidoglycan and endotoxin), and fungal spores, which collectively play a role in the development of COPD and respiratory symptoms (39, 40, 42). Specific farm-animal exposures may impair respiratory health. Swine farm practices over the last few decades have been associated with worsening respiratory symptoms (43, 44). Exposure to poultry and livestock has been shown to increase the risk of COPD (45) and worsen respiratory symptoms (46, 47). Higher exposure to indoor endotoxin is also associated with reduced lung function in the U.S. farming population (48). Rural populations may be exposed to an increased load of ambient endotoxin and small particulate matter that may increase respiratory symptoms in patients with COPD (49, 50). The exposure profiles of the rural participants in SPIROMICS were substantially different from those of their urban counterparts, and agricultural exposures were statistically associated with AECOPD, suggesting that these exposures may underlie some of the increased exacerbation risk. FVC was also reduced in rural participants. This reduction, which was not explained by differences in BMI, may represent early interstitial changes associated with chronic respiratory exposures.

The findings presented here confirm the results of prior studies of AECOPD risk factors, including reduced FEV_1 and previous exacerbation history (6, 51–56). Although white race was also associated with an increased exacerbation risk, the underrepresentation of other racial groups limits interpretation of these findings. Older age was associated with a reduced risk of total and severe AECOPD in this analysis. There are several potential explanations for this association: *1*) in this cohort, older individuals had fewer exacerbations in the year before enrollment and less severe airflow obstruction, and were less likely to be current smokers; *2*) younger participants may have better functional status, allowing them to work in the agricultural sector and thereby increasing their exposure profile; *3*) the older population in this study may represent a "survivor" population with overall better health; and *4*) the availability of Medicare insurance to the elderly may afford these patients better access to care and reduce the risk of exacerbations (57).

Although rural participants experienced more overall exacerbations than urban participants, severe exacerbations did not differ between these groups. There are several potential explanations for this observation. First, the factors associated with increased exacerbation rates in rural participants (i.e., agricultural exposures) may lead to milder exacerbation severity. Second, differential access to care among rural participants could lead to fewer hospital encounters, which are required to meet the criteria for severe exacerbation. Finally, this observation may be explained by the low overall prevalence of severe exacerbations in SPIROMICS, leading to insufficient power to detect this difference.

This study has several limitations. Although the reported data support the conclusion that agricultural exposures substantially contribute to pulmonary outcomes in rural participants, we are not able to fully determine the potential impact of access to healthcare on rural participants. We do not have robust data regarding health insurance at the time of recruitment or at younger ages. Because recruitment occurred primarily in urban academic medical centers, rural participants may have been required to travel to these centers for participation. We do not have data on distance from residence to recruitment center. However, participant enrollment suggests access to the recruiting medical centers. This mobility may not be reflective of a broader rural population. Alternatively, rural participants may have resided closer to urban centers, resulting in characteristics that more closely resemble urban individuals. These selection factors may result in a biased cohort of rural individuals who may not be representative of the larger U.S. rural population. Although this is supported by demographic similarities between the cohorts, agricultural and occupational profiles did differ between rural and urban participants. The impact of rural participants being more urbanized would attenuate any observed associations. In a more representative rural population, observed differences in pulmonary outcomes may be greater. Although there was no observed association between self-reported income and pulmonary outcomes, this metric may not accurately

reflect expendable income, as living wages differ across multiple U.S. geographic regions. The relatively low number of rural participants and low exacerbation rates in this cohort may limit the power to detect a true association between rural residence and severe exacerbations. Self-reported data elements (exacerbation data, comorbidities, and medication use) are susceptible to recall bias. Occupational exposures were assessed as ever-exposure, but did not include the duration of exposure or current exposure status and may not fully reflect cumulative occupational exposures. It is possible that the geographical location in the country may impact some of our observed associations. This is supported by the attenuation of our observations when we adjusted for site. However, the site variable likely encompasses many confounders relevant to the rural-COPD relationship (geographic location, exposures, and access to care), making this attenuation somewhat nonspecific. As geocoding was performed only on baseline residence, this analysis does not account for geographic migration during follow-up.

In conclusion, we have observed that rural residence is associated with an increased risk of COPD exacerbations requiring treatment. Agriculture-related exposures were more prevalent in rural populations and strongly associated with an increased risk of COPD exacerbations, but did not fully explain the association between rural residence and COPD exacerbations. Through these findings, this study advances our understanding of the impact of rural residence on COPD exacerbations and identifies areas of further investigation into the prevention of pulmonary symptoms in rural patients with COPD. These findings highlight the need for robust epidemiological cohorts to investigate within the rural COPD population factors such as access to healthcare, the impact of regional air pollution and particulate matter, the influence of longitudinal agricultural exposures, and potential biomarkers and radiographic parameters specific to rural populations. ■

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