ORIGINAL ARTICLE

Associations of Prepandemic Lung Function and Structure with COVID-19 Outcomes

The C4R Study

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Abstract

Rationale: Increased risk of coronavirus disease (COVID-19) hospitalization and death has been reported among patients with clinical lung disease.

Objective: To test the association of objective measures of prepandemic lung function and structure with COVID-19 outcomes in U.S. adults.

Methods: Prepandemic obstruction ($FEV_1/FVC < 0.70$) and restriction ($FEV_1/FVC \geq 0.7$, $FVC < 80\%$) were defined based on the most recent spirometry exam conducted in 11 prospective U.S. general population–based cohorts. Severe obstruction was classified by $FEV_1 < 50\%$. Percentage emphysema, percentage high-attenuation areas, and interstitial lung abnormalities were defined on computed tomography in a subset. Incident COVID-19 was ascertained via questionnaires, serosurvey, and medical records from 2020 to 2023 and classified as severe (hospitalized or fatal) or nonsevere. Cause-specific hazard models were adjusted for sociodemographics, anthropometry, smoking, comorbidities, and COVID-19 vaccination status.

Measurements and Main Results: Among 29,323 participants (mean age, 67 yr), there were 748 severe incident COVID-19 cases over median follow-up of 17.3 months from March 1, 2020. Greater hazards of severe COVID-19 were associated with severe obstruction (vs. normal; adjusted hazard ratio [aHR], 2.11; 95% confidence interval [CI], 1.02–1.27), restriction (vs. normal; aHR, 1.40; 95% CI, 1.12–1.76), and percentage emphysema (highest vs. lowest quartile; aHR, 1.64; 95% CI, 1.03–2.61), but not greater high-attenuation areas or interstitial lung abnormalities. COVID-19 vaccination provided greater absolute risk reduction in these groups. Results were similar in participants without smoking, obesity, or clinical cardiopulmonary disease.

Conclusions: Prepandemic severe spirometric obstruction, spirometric restriction, and greater percentage emphysema lung on computed tomography were associated with risk of severe COVID-19. These findings support enhanced COVID-19 risk mitigation for individuals with impaired lung health and warrant further mechanistic studies on interactions of lung function, structure, and vulnerability to acute respiratory illnesses.

Keywords: COVID-19; obstructive physiology; restrictive physiology; percentage emphysema; lung function and structure

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Coronavirus disease 19 (COVID-19) was a leading cause of hospitalization and death during 2020–2023 (1). Clinical chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) have been associated with higher risk of COVID-19 hospitalization or death (hereafter, "severe COVID-19") (2–6). However, prior studies may be biased by misclassification of the exposure (e.g., definition of lung disease by self-report or administrative codes without confirmatory spirometry or imaging) or the outcome (e.g., by preferential hospitalization of patients with chronic lung disease, even for nonsevere COVID-19 illness). Furthermore, information on COVID-19 risk among those with subclinical lung disease, which is common in the general population (7–15), is lacking.

We aimed to conduct the first large U.S. general population–based study investigating the association of objective prepandemic measures of lung function and lung structure with respect to risk of severe COVID-19. We leveraged spirometry and computed tomography (CT) examinations conducted in NIH-funded cohorts with systematic prospective follow-up for COVID-19 outcomes. We tested the extent to which comorbid conditions, including smoking and cardiometabolic disease, confounded or moderated associations of lung health with COVID-19 risk. To inform clinical risk mitigation, we examined the extent to which COVID-19 vaccination reduced risk of severe COVID-19 in those with and without impaired lung health.

Methods

Study Population

The C4R (Collaborative Cohort of Cohorts for COVID-19 Research) (16) is a nationwide meta-cohort of adult participants from 14 long-standing cardiovascular, neurological, and respiratory cohorts. C4R harmonized prepandemic cohort data and conducted standardized cross-cohort prospective data collection on COVID-19, including two waves of questionnaires, a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) serosurvey, and ascertainment and adjudication of COVID-19 hospitalizations and deaths (16). This report includes 11 cohorts that conducted at least one spirometry exam during the prepandemic period; details on cohort study design are provided in Table E1 in the online supplement. Participants with missing data for prepandemic spirometry or COVID-19 case status were excluded (Figure E1).

Approval for the present work was obtained from investigators and institutional review boards at all participating institutions.

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Data sharing statement: Access to pooled C4R data is regulated by the C4R Study's publications and presentations policy, which is available on the C4R website (https://www.c4r-nih.org/). Data are made available for analyses in the C4R Analysis Commons for investigators with manuscript proposals approved by the C4R publications and cohort coordinating committees, as well as by each cohort included in a given proposal. Once harmonization and related quality control have been completed, C4R common data elements are transferred as limited data sets for public access on BioData Catalyst, in accord with cohort-specific consents and commitments.

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

At a Glance Commentary

Scientific Knowledge on the Subject: Increased risk of coronavirus disease (COVID-19) hospitalization and death has been reported among patients with clinical chronic obstructive pulmonary disease and interstitial lung disease. However, there is limited information on the extent to which objective measures of lung function and structure, including among adults without clinical lung disease, associate with COVID-19 risk.

What This Study Adds to the Field: In a U.S. population-based study of 29,323 participants with prepandemic spirometry and computed tomography, higher risk of COVID-19 hospitalization and death was observed, with severe obstructive spirometry, restrictive spirometry, and greater percentage emphysema on computed tomography; COVID-19 vaccination provided greater absolute risk reduction in these groups. Results were similar in participants without clinical lung disease and were independent of smoking status, obesity, and cardiovascular disease. These findings highlight the need for targeted COVID-19 risk mitigation for individuals with clinical and subclinical lung disease and warrant further mechanistic studies to understand how impairments of lung function and structure may increase vulnerability to acute respiratory illnesses such as COVID-19.

Spirometry

Prebronchodilator spirometry was performed at exams conducted from 1983 to 2020 using various spirometers, and measures were harmonized as previously described (17, 18). Percent predicted and lower-limit-of-normal (LLN) values were calculated using the race-neutral Global Lung Initiative 2022 reference equations (19). The most recent prepandemic spirometry exam was used to define prepandemic FEV_1, FVC, and FEV_1:FVC and to classify lung function as normal (FEV_1:FVC $\geq$ 0.70, FVC $\geq$ 80% predicted), obstructive (FEV_1:FVC $<$ 0.70), or restrictive (FEV_1:FVC $\geq$ 0.70, FVC $<$ 80% predicted) physiology. Severity of obstructive physiology was categorized as mild ($FEV_1 \geq$ 80% predicted), moderate (50% $\leq FEV_1 <$ 80% predicted), or severe ($FEV_1 <$ 50% predicted) (12). Declines in FEV_1, FVC, and FEV_1:FVC were calculated based on differences from the most recent prepandemic exam versus the first cohort spirometry exam, divided by elapsed years.

Imaging

Inspiratory lung CT scans were acquired systematically in four cohorts (COPDGene [Genetic Epidemiology of COPD], MESA [Multi-Ethnic Study of Atherosclerosis] Lung, SARP [Severe Asthma Research Program], and SPIROMICS [Subpopulations and Intermediate Outcome Measures in COPD Study]) from 2007 to 2017. Cardiac CTs, which image approximately two-thirds of the lung volume and correlate with lung CT measures (20), were available in three cohorts (ARIC [Atherosclerosis Risk in Communities], CARDIA [Coronary Artery Risk Development in Young Adults], and FHS [Framingham Heart Study]) from 2007 to 2019. Percentage emphysema was defined as the percentage of lung voxels <-950 Hounsfield units (HUs) (21), and percentage high-attenuation areas (HAAs) was defined as the percentage of lung voxels <-600 to -250 HU (22). Machine learning–based methods were used to harmonize measures (Supplementary Methods). Trained radiologists and pulmonologists assessed interstitial lung abnormalities (ILAs) from inspiratory, full-lung CT scans in four cohorts (COPDGene, FHS, MESA Lung, and SPIROMICS). ILA was defined as nondependent abnormalities, including lung distortion, honeycombing, or traction bronchiectasis ("fibrotic ILAs"), nonemphysematous cysts, and ground-glass or reticular opacities involving at least 5% of a lung zone (23). Participants with indeterminate ILA assessments were excluded from the present analysis (24, 25).

COVID-19

Incident COVID-19 was ascertained using self-reported COVID-19 infection on two waves of standardized questionnaires, review of medical records for hospitalizations and deaths whenever possible, and a SARS-CoV-2 serosurvey conducted via dried blood spots (Table E2) (26, 27). The primary outcome was incident severe COVID-19, defined as hospitalization or death due to COVID-19. The secondary outcome was nonsevere COVID-19, which was defined as nonhospitalized SARS-CoV-2 infection. Sensitivity analyses were limited to cases confirmed by self-report of a positive test, medical record review, or the C4R serosurvey (Table E3). Reinfections with SARS-CoV-2 were excluded from all analyses.

COVID-19 vaccination status was assessed by C4R questionnaires, with vaccination status at the time of incident infection determined by comparing infection and vaccination dates.

Covariates

Covariates were harmonized from the most recent prepandemic examination using standard clinical and epidemiologic criteria. Details are provided in the Supplementary Methods. Age, sex, educational attainment, race, ethnicity, income, health insurance, smoking status, and pack-years were self-reported. Body mass index (BMI) was calculated using height and weight, and obesity was classified based on CDC criteria (28). Hypertension was defined by self-report or systolic blood pressure $\geq$ 140, diastolic blood pressure $\geq$ 90, or use of antihypertensive medications. Diabetes was defined by self-report or fasting blood glucose $\geq$ 126 mg/dl, or the use of insulin or hypoglycemic medications. Cardiovascular disease was defined as a history of myocardial infarction, angina pectoris, stroke, or heart failure. Clinical COPD and asthma were defined by self-reported physician diagnoses, adjudication, or administrative criteria. Chronic kidney disease stage was classified using estimated glomerular filtration rate and albuminuria (29). Geographical region was determined by residential three-digit zip code.

Statistical Analysis

Cumulative incidence functions for severe and nonsevere COVID-19 were plotted by prepandemic lung function categories and quartiles of percentage emphysema and percentage HAA.

Associations with lung measures were tested using cause-specific hazard models that treated incident nonsevere and severe COVID-19 as mutually exclusive (competing) risks. The cause-specific hazards model was selected to address etiologic questions regarding the associations of lung physiology with COVID-19 risk (30) accounting for

time-varying vaccination status (31); subdistribution hazard models, which do not accommodate time-varying covariates, were tested in secondary analyses. More details on model selection are provided in the Supplementary Methods.

The models did not violate the proportional hazards assumption (Figure E2). Days since March 1, 2020, was treated as time to event. Cohort was treated as a stratum term, allowing each cohort to have its own baseline hazard function. Models were adjusted for age at C4R baseline, sex, race and ethnicity, educational attainment, BMI, smoking status, pack-years, comorbidities, time-varying vaccination status, and geographical region.

The magnitude of potential confounding by smoking and cardiometabolic conditions was tested by comparison of effect estimates with and without adjustment. Effect modification was tested by interaction terms and in fully stratified models.

Differences in the absolute risk reduction (ARR) provided by COVID-19 vaccination according to lung function and structure were estimated using univariable logistic regression models within lung function and structure subgroups, based on subjects with observed infections. The models included infection severity as the outcome and vaccine status at the time of infection as a covariate. ARR was defined as the difference in the probability of severe infection between vaccinated and unvaccinated individuals. Bootstrap was applied to estimate SEs and confidence intervals (CIs).

Missing covariate data were assumed to be missing at random and addressed by multiple imputations using the "mice" package in R ($N = 10$ imputations) (32). Lung structure analyses were restricted to cohorts with available imaging data, and missing lung structure biomarkers within these cohorts were imputed. Results were combined across imputed datasets using Rubin's rule (33).

Sensitivity analyses. Sensitivity analyses were performed in participants without clinical cardiopulmonary disease, without missing covariate data (complete cases), and limited to incident COVID-19 cases that were confirmed by testing or medical records. Analyses were repeated using the LLN for the FEV_1:FVC and FVC to define obstructive and restrictive physiology, using the Staging of Airflow Obstruction by Ratio classification (34), applying more stringent criteria to define "normal spirometry" (FEV_1:FVC ≥ 0.7 and FEV_1 80–90%, 90–100%, 100–110%, or $\geq$110%) (35), and by severity of restrictive pattern (12). Secondary analyses were further adjusted for time since the most recent spirometry or CT, chronic kidney disease stage, income and health insurance status, source cohort, and with coadjustment of spirometry and CT measures. Finally, we also applied a period cross-sectional approach to assess risk factors for severe COVID-19 using logistic regression, limiting the sample to participants with a history of COVID-19. This was attempted for its simplicity, acknowledging that this approach does not account for differential follow-up time.

Given the potential for type I error, all subgroup analyses should be considered exploratory. Analyses were performed using SAS Studio 9.3 and R Studio on BioData Catalyst, and two-tailed $P < 0.05$ was interpreted as statistically significant.

Results

Participants

Among 29,323 participants with valid prepandemic lung function and incident COVID-19 data (Table 1 and Figure E1), the mean (SD) age in March 2020 was 67.1 (14.1) years. Follow-up for incident infection was complete for 83.4% over the first 6 months, 72.1% over the first 12 months, and 22.4% over the first 24 months. Over a median (range) of 17.3 (0.03–34.2) months of follow up from March 1, 2020, there were 3,447 (11.8%) incident nonsevere and 748 (2.6%) severe COVID-19 cases. Compared with participants with no or nonsevere COVID-19 at last follow-up, participants with incident severe COVID-19 were older, more male predominant, and more likely to have prepandemic smoking, obesity, and/or other clinical conditions (Table 1). There was <2% missingness for all covariates except for asthma (5.3%) and vaccination status (10.8%) (Table E4).

Lung Function and Structure

Lung function was measured a median (interquartile range [IQR]) of 9 (5–11) years before C4R enrollment in March 2020. A subset of 16,362 participants had two or more spirometry measures available for analysis. Lung structure on CT was measured a median of 6.4 (IQR, 1.6–9.5) years before enrollment in 18,835 participants, of whom 10,787 had ILA measures. Baseline characteristics of participants with CT measures were similar to the full sample (Table E5).

Comparing lung function and structure measures (Table E6), 40.2% of participants with obstructive spirometry had percentage emphysema in the highest quartile, compared with 20.7% with normal spirometry and 7.1% with restrictive spirometry. Forty-nine percent of participants with restrictive spirometry had percentage HAA in the highest quartile, versus 18.8% with obstructive and 24.4% with normal spirometry. ILAs were observed in 12.2% with restrictive, 10.2% with obstructive, and 12.0% with normal spirometry ($P < 0.001$).

Associations with Incident COVID-19

The cumulative incidence of severe COVID-19 differed by categories of lung function impairment and percentage emphysema (Figures 1A and 1B). Incidence of severe COVID-19 per 1,000 person-years was highest among participants with severe obstructive (45.8) and restrictive (42.9) physiology versus those with moderate (17.9) and mild (15.3) obstructive physiology or normal spirometry (18.4).

Compared with those with nonsevere or no COVID-19 at last follow-up, participants with severe COVID-19 had lower lung function, greater prepandemic rates of decline in FEV_1 and FVC, more restriction and severe obstruction, higher percentage emphysema, and more ILAs (Table 1).

In adjusted models (Table 2), higher prepandemic FEV_1 and FVC were associated with lower hazards of severe COVID-19, and greater rates of FVC decline were associated with greater hazards of severe COVID-19. FEV_1:FVC and decline in FEV_1 and FEV_1:FVC were not associated. Compared with normal spirometry, severe obstructive physiology was associated with an adjusted hazard ratio (aHR) of 2.11 (95% CI, 1.36–3.27) for severe COVID-19 (Table 2), as was FEV_1:FVC < 0.4 (aHR, 4.11; 95% CI, 1.12–1.76; Table E7). Restrictive physiology was also associated with a greater hazard of severe COVID-19 (aHR, 1.40; 95% CI, 1.12–1.76) (Table 2).

Percentage emphysema was associated with severe COVID-19 as a continuous (aHR, 1.09 per IQR; 95% CI, 1.01–1.17) and categorical (highest vs. lowest quartile, aHR, 1.64; 95% CI, 1.03–2.61) measure

Table 1. Baseline Characteristics by Coronavirus Disease Infection Status

	No Incident COVID-19	Nonsevere COVID-19	Severe COVID-19	Total
Sample with at least one prepandemic spirometry measurement				
Total sample, *n* (%)	25,128 (85.7)	3,447 (11.8)	748 (2.6)	29,323
Time to event or last follow-up, mo, median (Q1, Q3)	17.8 (8.6, 20.4)	10.3 (4.9, 18.3)	8.5 (3.7, 11.5)	17.3 (7.7, 20.2)
Age, yr, mean (SD)	67.8 (13.9)	60.9 (13.6)	72.3 (13.4)	67.1 (14.1)
Age group, *n* (%)				
<65 yr	10,282 (40.9)	2,137 (62.0)	222 (29.6)	12,640 (43.1)
65–79 yr	8,103 (32.2)	904 (26.2)	216 (28.9)	9,223 (31.5)
⩾80 yr	6,743 (26.8)	406 (11.8)	311 (41.5)	7,459 (25.4)
Sex, *n* (%)				
Female	14,665 (58.4)	2,139 (62.1)	420 (56.1)	17,224 (58.7)
Male	10,463 (41.6)	1,308 (37.9)	328 (43.9)	12,099 (41.3)
Race and ethnicity, *n* (%)				
Non-Hispanic White	12,038 (47.9)	1,189 (34.5)	267 (35.7)	13,495 (46.0)
Hispanic/Latino	7,171 (28.5)	1,659 (48.1)	216 (28.9)	9,047 (30.9)
Black	5,084 (20.2)	486 (14.1)	200 (26.7)	5,770 (19.7)
Asian	461 (1.8)	19 (0.6)	8 (1.1)	488 (1.7)
American Indian	358 (1.4)	90 (2.6)	57 (7.6)	505 (1.7)
Other	15 (0.1)	4 (0.1)	0 (0)	19 (0.1)
BMI, kg/m^2, mean (SD)	29.3 (6.1)	29.9 (6.1)	31.3 (6.8)	29.5 (6.2)
BMI category, *n* (%)				
Normal (18.5–24.9)	5,798 (23.1)	698 (20.2)	114 (15.1)	6,609 (22.5)
Underweight (<18.5)	225 (0.9)	19 (0.6)	3 (0.4)	246 (0.8)
Overweight (25–29.9)	9,302 (37)	1,263 (36.6)	228 (30.5)	10,793 (36.8)
Obese (⩾30)	9,804 (39)	1,468 (42.6)	403 (53.9)	11,675 (39.8)
Educational attainment, *n* (%)				
Less than high school	3,708 (14.8)	614 (17.8)	180 (24.1)	4,502 (15.4)
High school	5,957 (23.7)	865 (25.1)	209 (27.9)	7,031 (24.0)
Some college	4,665 (18.6)	642 (18.6)	122 (16.2)	5,428 (18.5)
College or more	10,798 (43.0)	1,326 (38.5)	238 (31.8)	12,342 (42.2)
Smoking status, *n* (%)				
Never	11,417 (45.4)	1,894 (54.9)	329 (44.0)	13,639 (46.5)
Former	9,749 (38.8)	1,114 (32.3)	304 (40.6)	11,167 (38.1)
Current	3,963 (15.8)	439 (12.7)	115 (15.4)	4,517 (15.4)
Pack-years in ever-smokers, median (Q1, Q3)	16.8 (4.5, 34.2)	12.8 (2.7, 28.9)	14.4 (4.0, 32.4)	16.2 (4.2, 33.7)
Comorbidities, *n* (%)				
Hypertension*	15,405 (61.3)	1,703 (49.4)	574 (76.7)	17,682 (60.3)
Diabetes†	4,888 (19.5)	669 (19.4)	260 (34.7)	5,817 (19.8)
COPD‡	2,434 (9.7)	303 (8.8)	96 (12.8)	2,833 (9.7)
Asthma§	3,100 (12.3)	412 (12.0)	122 (16.4)	3,635 (12.4)
Cardiovascular disease‖	2,706 (10.8)	270 (7.8)	136 (18.2)	3,112 (10.6)
COVID-19 vaccination,¶ *n* (%)				
Vaccinated	14,741 (58.7)	1,034 (30.0)	92 (12.2)	15,866 (54.1)
Not vaccinated	10,387 (41.3)	2,413 (70.0)	656 (87.8)	13,457 (45.9)
Geographical region, *n* (%)				
Middle Atlantic	4,549 (18.1)	602 (17.5)	156 (20.8)	5,307 (18.1)
Midwest	6,258 (24.9)	835 (24.2)	177 (23.6)	7,270 (24.8)
New England	2,541 (10.1)	387 (11.2)	30 (4.0)	2,957 (10.1)
South	7,299 (29.0)	937 (27.2)	279 (37.2)	8,514 (29.0)
Southwest	462 (1.8)	62 (1.8)	44 (5.9)	568 (1.9)
West	4,019 (16.0)	625 (18.1)	63 (8.4)	4,707 (16.1)
Cohort, *n* (%)				
ARIC	4,620 (18.4)	249 (7.2)	230 (30.7)	5,099 (17.4)
CARDIA	2,253 (9)	327 (9.5)	29 (3.9)	2,609 (8.9)
COPDGene	3,276 (13)	363 (10.5)	44 (5.9)	3,683 (12.6)
FHS	2,480 (9.9)	392 (11.4)	28 (3.7)	2,900 (9.9)
HCHS	6,654 (26.5)	1,554 (45.1)	194 (25.9)	8,402 (28.7)
JHS	1,409 (5.6)	88 (2.6)	64 (8.6)	1,561 (5.3)
MESA	2,584 (10.3)	241 (7)	72 (9.6)	2,897 (9.9)
PrePF	84 (0.3)	8 (0.2)	4 (0.5)	96 (0.3)
SARP	286 (1.1)	50 (1.5)	4 (0.5)	340 (1.2)

(*Continued*)

Table 1. (*Continued*)

	No Incident COVID-19	Nonsevere COVID-19	Severe COVID-19	Total
SHS	292 (1.2)	80 (2.3)	57 (7.6)	429 (1.5)
SPIROMICS	1,190 (4.7)	95 (2.8)	22 (2.9)	1,307 (4.5)
Lung function,** mean (SD)				
% predicted FEV_1	94.3 (19)	97.3 (18.1)	91.3 (20.4)	94.6 (19)
% predicted FVC	102.7 (18.8)	104.8 (17.9)	98.6 (20.3)	102.8 (18.8)
FEV_1:FVC, %	75.6 (9.2)	77.5 (8.5)	76.3 (9.6)	75.9 (9.1)
Lung function category,** *n* (%)				
Obstructive physiology	5,268 (21.0)	493 (14.3)	129 (17.2)	5,890 (20.1)
Restrictive physiology	2,330 (9.3)	270 (7.8)	149 (19.9)	2,749 (9.4)
Normal	17,530 (69.8)	2,684 (77.9)	470 (62.8)	20,684 (70.5)
Severity of obstructive physiology,** *n* (%)				
Mild	2,547 (10.1)	236 (6.8)	54 (7.2)	2,837 (9.7)
Moderate	2,289 (9.1)	211 (6.1)	51 (6.8)	2,551 (8.7)
Severe	432 (1.7)	46 (1.3)	24 (3.2)	502 (1.7)
Sample with at least two prepandemic spirometry measurements				
Total sample, *n* (%)	14,478 (88.5)	1,507 (9.2)	377 (2.3)	16,332
Decline in lung function,†† mean (SD)				
Δ FEV_1, ml/yr	34.1 (52.4)	31.5 (56.9)	40.1 (45.5)	34 (52.7)
Δ FVC, ml/yr	34.5 (76.1)	30.7 (90.7)	46.4 (78.7)	34.5 (77.7)
Δ FEV_1:FVC, %/yr	0.2 (1.1)	0.2 (1)	0.2 (1.1)	0.2 (1.1)
Sample with lung CT measurements				
Total sample, *n* (%)	16,689 (88.6)	1,717 (9.1)	429 (2.3)	18,835
Percentage emphysema, mean (SD)	6.1 (9.9)	4.3 (8.3)	7.8 (11.2)	6.2 (10.0)
Quartiles of % emphysema, *n* (%)				
Lowest quartile	4,124 (24.7)	497 (28.9)	89 (20.7)	4,709 (25.0)
Q2	4,157 (24.9)	430 (25.0)	112 (26.1)	4,699 (25.0)
Q3	4,216 (25.3)	391 (22.8)	111 (25.9)	4,718 (25.0)
Highest quartile	4,192 (25.1)	399 (23.2)	117 (27.3)	4,708 (25.0)
Percentage HAA, mean (SD)	6.0 (4.3)	7.8 (5.4)	5.9 (4.0)	6.0 (4.3)
Quartiles of % HAA, *n* (%)				
Lowest quartile	4,237 (25.4)	387 (22.5)	83 (19.3)	4,708 (25.0)
Q2	4,209 (25.2)	416 (24.2)	85 (19.8)	4,710 (25.0)
Q3	4,159 (24.9)	425 (24.8)	123 (28.7)	4,707 (25.0)
Highest quartile	4,083 (24.5)	489 (28.5)	138 (32.2)	4,710 (25.0)
Sample with ILA measurements, *n* (%)				
Total sample	9,530 (88.4)	1,091 (10.1)	166 (1.5)	10,787
ILA	1,070 (11.2)	134 (12.3)	29 (17.5)	1,233 (11.4)
Fibrotic ILA	569 (6.0)	64 (5.9)	13 (7.8)	646 (6.0)

Definition of abbreviations: ARIC = Atherosclerosis Risk in Communities; BMI = body mass index; CARDIA = Coronary Artery Risk Development in Young Adults; COPD = chronic obstructive pulmonary disease; COPDGene = Chronic Obstructive Pulmonary Disease Genetic Epidemiology; COVID-19 = coronavirus disease; FHS = Framingham Heart Study; HAA = high-attenuation areas; HCHS = Hispanic Community Health Study; ILA = interstitial lung abnormalities; JHS = Jackson Heart Study; MESA = Multi-Ethnic Study of Atherosclerosis; PrePF = Prevent Pulmonary Fibrosis; Q1 = 25th percentile; Q2 = 50th percentile (median); Q3 = 75th percentile; SARP = Severe Asthma Research Program; SHS = Strong Heart Study; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study.

This table presents data based on the average of 10 multiply imputed datasets. Numbers may not exactly sum to totals because of rounding. Column percentages reported.

*Self-reported hypertension or systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg or use of antihypertensive medications.

†Self-reported diabetes or fasting blood sugar levels > 126 mg/dl or use of oral hypoglycemic agents or insulin.

‡Self-reported COPD assigned by adjudication or administrative criteria, as of March 2020.

§Self-reported asthma assigned by adjudication or administrative criteria, as of March 2020.

‖Self-reported or adjudicated myocardial infarction, angina pectoris, stroke, or heart failure as of March 2020.

¶COVID-19 vaccination status at the time of infection or, for those not infected, at last follow-up.

**Spirometry from the most recent examination available prepandemic was used for cross-sectional lung function measurements. Lung function category definitions: obstructive physiology = FEV_1:FVC ratio < 0.7; restrictive physiology = FEV_1:FVC ≥ 0.7 and FVC < 80% predicted; normal spirometry = FEV_1:FVC ratio ≥ 0.7 and FVC ≥ 80% predicted. Obstructive physiology severity definitions: mild = FEV_1:FVC ratio < 0.7 and FEV_1 ≥ 80% predicted; moderate = FEV_1:FVC ratio < 0.7 and 50% ≤ FEV_1 < 80% predicted; severe = FEV_1:FVC ratio < 0.7 and FEV_1 < 50% predicted.

††Decline in FEV_1, FVC, or FEV_1:FVC ratio was calculated based on the first and last spirometry measurements available prepandemic divided by the years in between.

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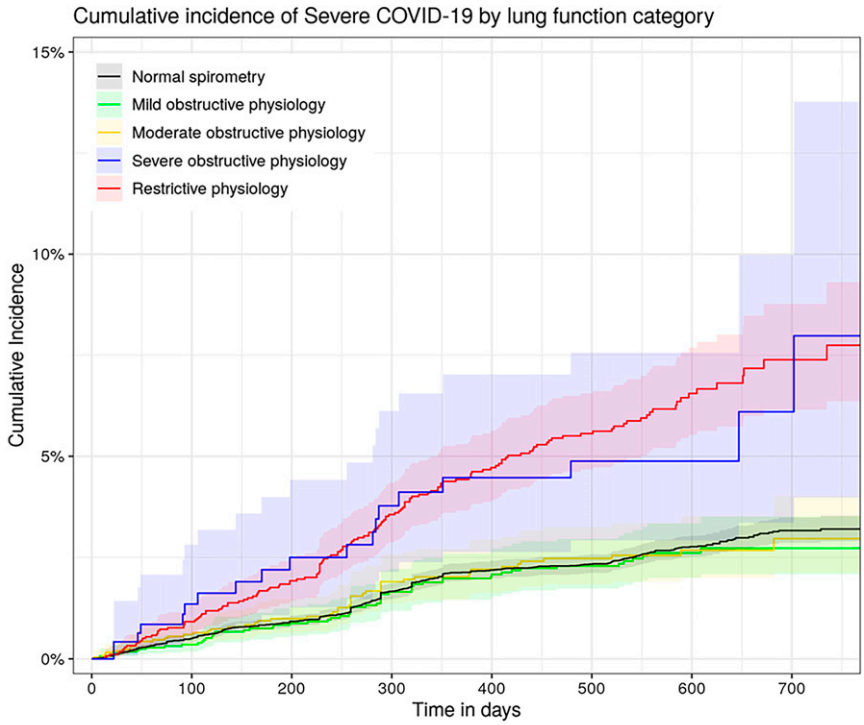
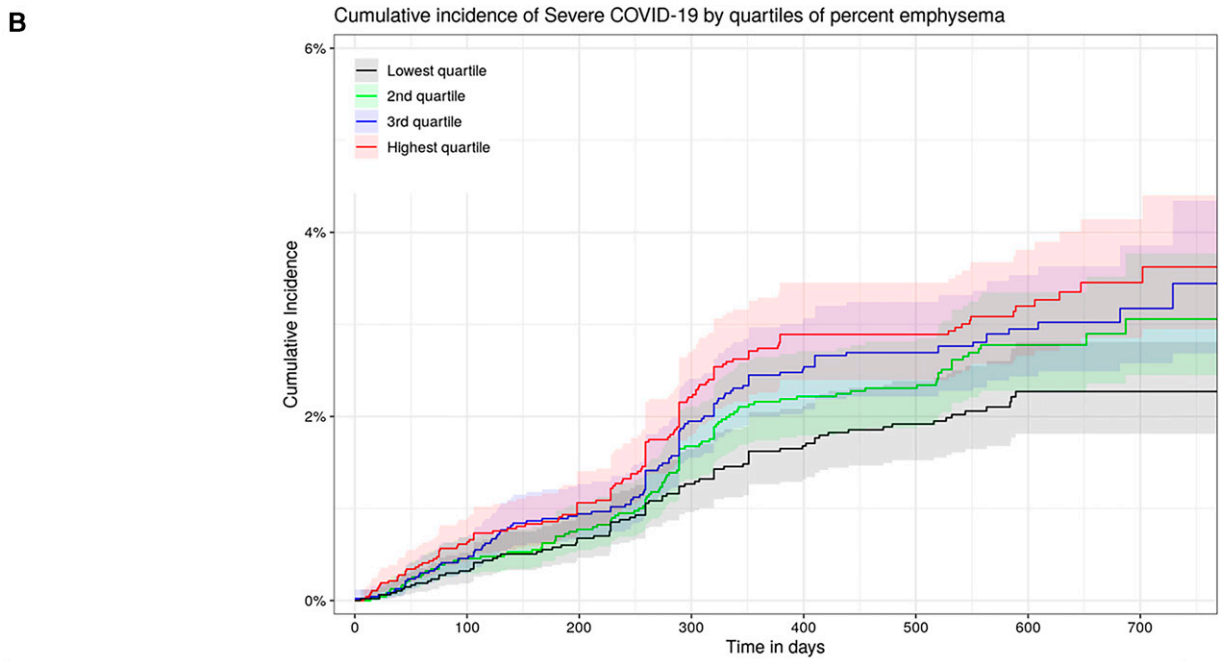


Normal spirometry	At risk	20684	19253	16122	14376	12495	11408	6234	2599
	Events	1	105	182	300	380	400	447	468
Restrictive physiology	At risk	2749	2563	2295	2061	1786	1508	771	275
	Events	0	25	50	88	113	129	142	147
Mild obstructive physiology	At risk	2837	2529	2226	2031	1827	1647	821	330
	Events	0	9	22	36	45	48	53	54
Moderate obstructive physiology	At risk	2551	2174	1807	1604	1426	1244	628	236
	Events	0	15	23	39	44	48	50	51
Severe obstructive physiology	At risk	502	406	335	288	254	212	111	43
	Events	0	7	11	18	20	22	22	23

Figure 1. (*A*) Cumulative incidence of severe coronavirus disease (COVID-19), by prepandemic lung function. Associations of lung function with incident severe COVID infection were analyzed using Fine–Gray proportional sub-distribution hazards. Spirometry from the most recent examination available prepandemic was used for cross-sectional lung function category. Lung function category definitions: obstructive physiology = FEV_1:FVC ratio < 0.7, restrictive physiology = FEV_1:FVC ≥ 0.7 and FVC $< 80\%$ of predicted, and normal spirometry = FEV_1:FVC ratio ≥ 0.7 and FVC $\geq 80\%$ of predicted. Obstructive physiology severity definitions: mild = FEV_1:FVC ratio < 0.7 and $FEV_1 \geq 80\%$ predicted; moderate = FEV_1:FVC ratio < 0.7 and $50\% \leq FEV_1 < 80\%$ predicted; severe = FEV_1:FVC ratio < 0.7 and $FEV_1 < 50\%$ predicted. (*B*) Cumulative incidence of severe COVID-19, by prepandemic percent emphysema. Associations of percent emphysema with incident severe COVID infection were analyzed using Fine–Gray proportional sub-distribution hazards. Percent emphysema measurements from the most recent examination available prepandemic were used.



Lowest quartile	At risk	4760	4328	3910	3525	3148	2821	1278	409
	Events	0	15	30	53	68	76	84	84
2nd quartile	At risk	4702	4262	3892	3579	3139	2809	1296	433
	Events	0	21	34	69	89	92	105	107
3rd quartile	At risk	4693	4219	3812	3481	3039	2739	1339	433
	Events	1	21	41	79	100	105	111	113
Highest quartile	At risk	4678	4127	3755	3440	2970	2712	1368	479
	Events	0	29	46	89	113	113	120	123

Figure 1. (*Continued*).

(Table 2). Although unadjusted models suggested an association between percentage HAA and severe COVID-19 (Table E8 and Figure E3), there was no association after adjustment (Table 2), and no associations were observed for ILAs or fibrotic ILAs (Table 2).

Regarding nonsevere COVID-19, increased hazards were observed with higher prepandemic FEV_1 and FVC and highest versus lowest quartile of percentage HAA, but there were no other significant associations with lung function category or percentage emphysema (Table E9).

Confounding and Effect Modification

Compared with a base model including only sociodemographic factors and vaccination status, the effect estimate for restrictive physiology was attenuated with additional adjustment for BMI (12.0%), diabetes (6.9%), hypertension (2.7%), and smoking history (1.6%) (Table E10). Adjustment for smoking was associated with the largest attenuation of effect estimates for severe obstructive physiology (6.2%) and percentage emphysema (0.39%) (Table E10). Adjustment of lung function for lung structure, and vice versa, did not substantially alter the main effect estimates (Table E11).

The association of restrictive physiology with severe COVID-19 was only significantly modified by smoking history, and associations were similar across strata of all covariates (Figure 2A). There was no effect modification of the association between percentage emphysema and severe COVID-19 by the covariates (P-interaction $>$ 0.05 for all) or by lung function category (P-interaction = 0.46), and the magnitude of associations remained consistent within covariate (Figure 2B) and lung function (Tables E12 and E13) strata. Additional stratified analyses are provided in the online supplement (Figures E4–E7).

Vaccination

Vaccination was associated with reduced hazard of severe COVID-19 in all strata of lung function and structure without evidence of effect modification (aHR, 0.19 to 0.50; P-interaction $>$ 0.30 for all; Table 3). However, because probabilities of severe COVID-19 were higher in those with impaired lung function or structure, the ARR associated with vaccination was lower in those with normal spirometry (ARR, 0.12) compared with restriction (ARR, 0.19; delta ARR [95% CI], 0.07 [−0.03 to 0.18]) or obstruction (ARR, 0.19; delta ARR [95% CI],

Table 2. Associations of Prepandemic Lung Function and Structure with Incident Severe Coronavirus Disease

	At Risk	Events (Cum. Inc.)	Hazard Ratio (95% CI)	*P* Value
Lung function category*				
Normal	20,684	470 (2.3)	Referent	
Obstructive physiology	5,890	129 (2.2)	0.99 (0.80–1.23)	0.97
Severity of obstructive physiology				
Mild	2,837	54 (1.9)	0.86 (0.64–1.15)	0.31
Moderate	2,551	51 (2.0)	0.95 (0.70–1.29)	0.72
Severe	502	24 (4.8)	2.11 (1.36–3.27)	<0.001
Restrictive physiology	2,749	149 (5.4)	1.40 (1.12–1.76)	0.003
Lung function				
FEV_1 per SD	29,323	748 (2.6)	0.87 (0.79–0.97)	0.01
FVC per SD	29,323	748 (2.6)	0.88 (0.79–0.98)	0.02
FEV_1:FVC per SD	29,323	748 (2.6)	0.99 (0.92–1.08)	0.98
Decline in lung function†				
Δ FEV_1 per SD	16,362	377 (2.3)	1.08 (0.98–1.19)	0.13
Δ FVC per SD	16,362	377 (2.3)	1.12 (1.02–1.24)	0.02
Δ FEV_1:FVC per SD	16,362	377 (2.3)	0.98 (0.88–1.08)	0.64
Percentage emphysema				
Percentage emphysema per IQR	18,835	429 (2.3)	1.09 (1.01–1.17)	0.02
Quartiles of percentage emphysema				
Lowest quartile	4,760	84 (1.8)	Referent	
Q2	4,704	107 (2.3)	1.34 (0.92–1.95)	0.12
Q3	4,693	114 (2.4)	1.43 (0.93–2.21)	0.10
Highest quartile	4,678	124 (2.7)	1.64 (1.03–2.61)	0.04
Percentage HAA				
Percentage HAA per IQR	18,835	429 (2.3)	1.04 (0.90–1,19)	0.60
Quartiles of percentage HAA				
Lowest quartile	4,718	67 (1.4)	Referent	
Q2	4,722	92 (1.9)	0.95 (0.61–1.50)	0.83
Q3	4,726	122 (2.6)	1.30 (0.83–2.04)	0.25
Highest quartile	4,669	148 (3.2)	1.30 (0.78–2.15)	0.30
ILA				
No	9,688	130 (1.3)	Referent	
Yes	1,099	36 (3.3)	1.47 (0.39–5.53)	0.54
Fibrotic ILA				
No	10,161	146 (1.4)	Referent	
Yes	626	20 (3.2)	1.11 (0.39–3.15)	0.84

Definition of abbreviations: CI = confidence interval; COVID-19 = coronavirus disease; Cum. Inc. = cumulative incidence; HAA = high-attenuation areas; ILA = interstitial lung abnormalities; IQR = interquartile range.

Cause-specific hazard models were used. Models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID-19 vaccination status, and geographic region; cohort was treated as a stratum variable. Spirometry from the most recent examination available prepandemic was used for cross-sectional lung function measurements. FEV_1, FVC, and FEV_1:FVC ratio were standardized to their respective means and SDs. Percentage emphysema and HAA were standardized to respective medians and IQRs.

*Lung function category definitions: obstructive physiology = FEV_1:FVC ratio < 0.7; restrictive physiology = FEV_1:FVC ≥ 0.7 and FVC $< 80\%$ predicted; normal spirometry = FEV_1:FVC ratio ≥ 0.7 and FVC $\geq 80\%$ predicted. Obstructive physiology severity definitions: mild = FEV_1:FVC ratio < 0.7 and $FEV_1 \geq 80\%$ predicted; moderate = FEV_1:FVC ratio < 0.7 and $50\% \leq FEV_1 < 80\%$ predicted; severe = FEV_1:FVC ratio < 0.7 and $FEV_1 < 50\%$ predicted.

†Decline in FEV_1, FVC, and FEV_1:FVC ratio was calculated based on the first and last spirometry measurements available prepandemic divided by the years in between.

0.08 [0.01 to 0.10]). Similarly, ARR was lower in the lowest quartile of percentage emphysema (ARR, 0.16) compared with those in the highest quartile (ARR, 0.26; delta ARR [95% CI], 0.10 [0.02–0.19]) (Table E14).

Sensitivity Analyses

Consistent results were observed in analyses that excluded participants with prepandemic clinical asthma, COPD, or cardiovascular disease (Table E15); in complete case analysis (Table E16); and limited to participants with confirmed COVID-19 (Table E17). Results were similar when using the LLN to define obstructive or restrictive physiology (Table E18), using more- and less-stringent definitions for normal spirometry (Table E19), by severity of restrictive physiology (Table E20), and with further adjustment for time since the most recent spirometry or CT measure (Table E21), chronic kidney disease (Table E22), income and health insurance (Table E23), and cohort (Table E24). Subdistribution hazards (Table E24) and logistic regression (Table E25) models yielded consistent results.

Discussion

Prepandemic lung function and structure were associated with risk of COVID-19 hospitalization or death in a large, U.S. general population–based sample of adults. Severe obstructive physiology and greater percentage emphysema on CT were

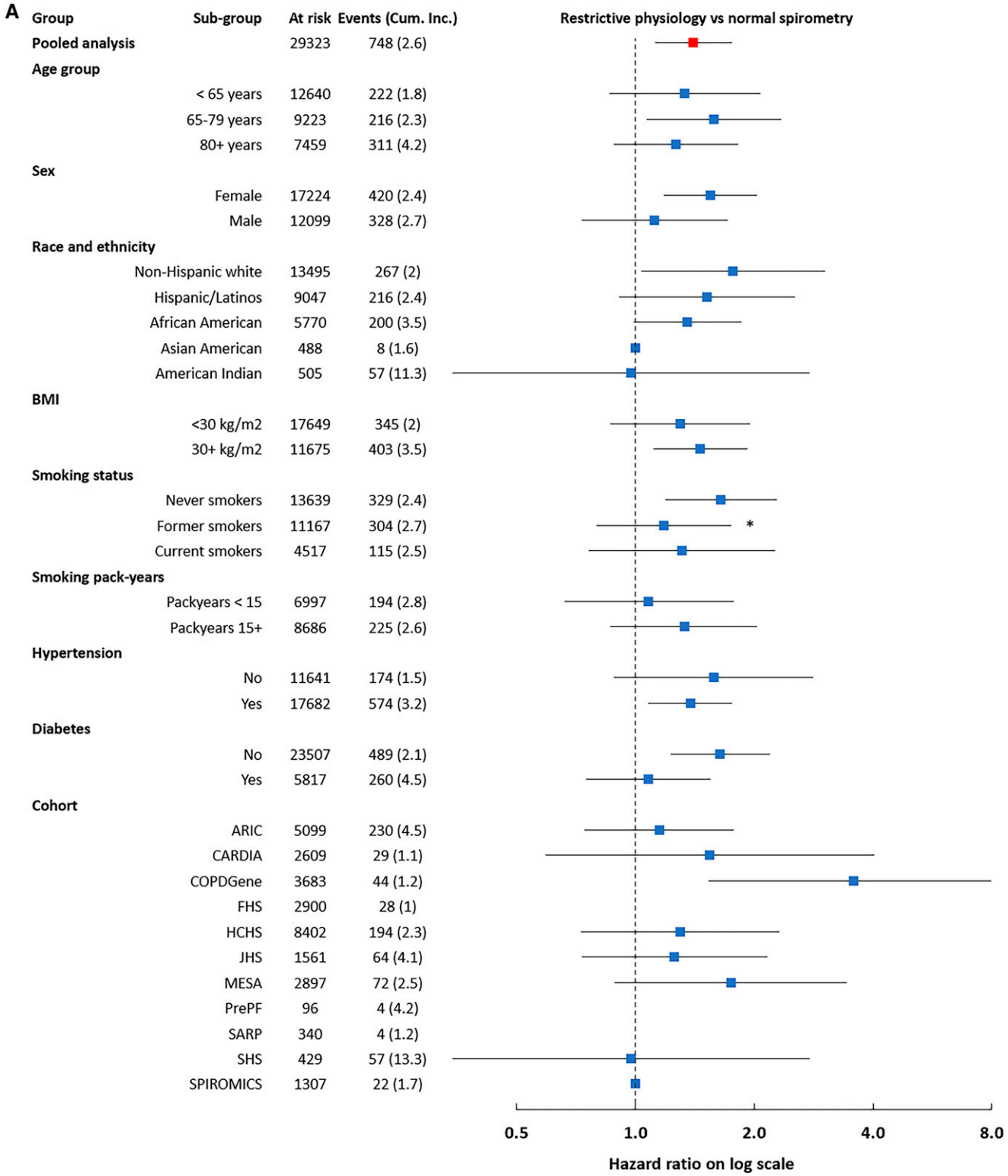


Figure 2. (*A*) Sub-group analyses of associations of prepandemic restrictive physiology versus normal spirometry with incident severe coronavirus disease (COVID-19). This figure presents data based on the average of 10 multiply imputed datasets. Numbers may not exactly sum to totals due to rounding. Cause-specific hazards models were used. Fully adjusted models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID vaccination status, and geographic region; cohort was treated as a stratum variable. Spirometry from the most recent examination available prepandemic was used for lung function category. Lung function category definitions: obstructive physiology = FEV_1:FVC ratio < 0.7, restrictive physiology = FEV_1:FVC ≥ 0.7 and FVC $< 80\%$ of predicted. *Significant *P* value for the interaction term. Cum. Inc. = cumulative incidence.

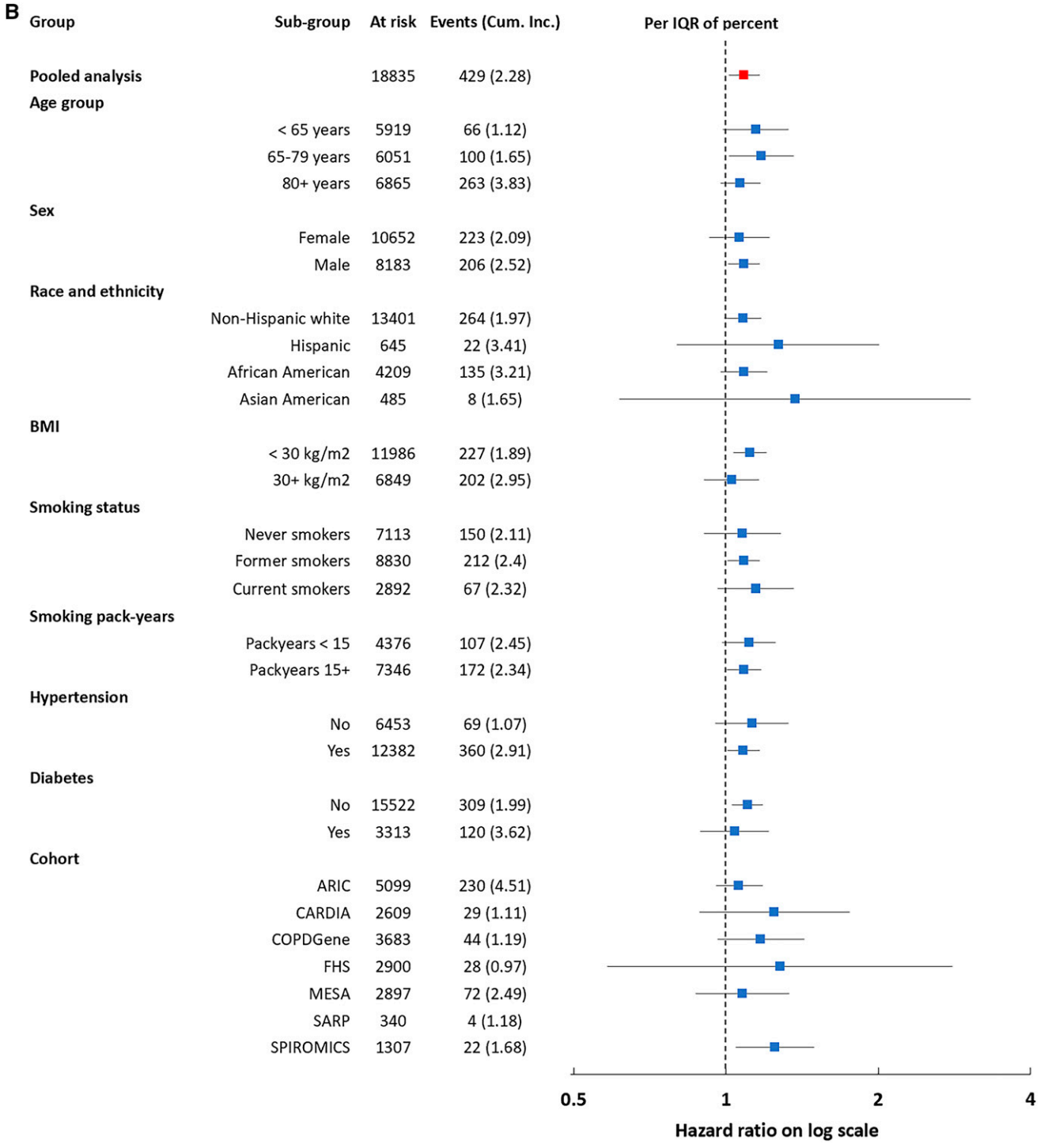


Figure 2. (*Continued*). (*B*) Sub-group analyses of associations of prepandemic percent emphysema with incident severe COVID-19. This figure presents data based on the average of 10 multiply imputed datasets. Numbers may not exactly sum to totals due to rounding. Cause-specific hazards models were used. Models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID vaccination status, and geographic region; cohort was treated as a stratum variable. Percent emphysema was standardized to its respective median and interquartile range. Cum. Inc. = cumulative incidence. BMI = body mass index; Cum. Inc. = cumulative incidence.

Table 3. Associations of Coronavirus Disease Vaccination with Severe Coronavirus Disease, Stratified by Lung Function and Structure

	Hazard Ratio (95% CI)	*P* Value	*P* Value for the Interaction between Vaccination Status and Lung Function or Structure
Lung function category*			
Normal	0.28 (0.20–0.39)	<0.0001	
Obstructive physiology	0.28 (0.15–0.53)	<0.0001	0.67
Restrictive physiology	0.50 (0.29–0.84)	<0.0001	0.73
Percentage emphysema			
Lowest quartile	0.20 (0.08–0.47)	<0.0001	
Q2	0.24 (0.12–0.50)	<0.0001	0.76
Q3	0.24 (0.12–0.50)	<0.0001	0.82
Highest quartile	0.14 (0.05–0.36)	<0.0001	0.92
Percentage HAA			
Lowest quartile	0.19 (0.08–0.48)	<0.0001	
Q2	0.13 (0.04–0.35)	<0.0001	0.62
Q3	0.19 (0.09–0.41)	<0.0001	0.51
Highest quartile	0.30 (0.18–0.53)	<0.0001	0.30
ILA binary			
No	0.25 (0.13–0.46)	<0.0001	
Yes	0.19 (0.02–1.77)	<0.001	0.98

Definition of abbreviations: CI = confidence interval; Cum. Inc. = cumulative incidence; HAA = high attenuation areas.
Cause-specific hazard models were used. Models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, and geographic region; cohort was treated as a stratum variable.
*Lung function category definitions: obstructive physiology = FEV_1:FVC ratio < 0.7; restrictive physiology = FEV_1:FVC ≥ 0.7 and FVC < 80% predicted; normal spirometry = FEV_1:FVC ratio ≥ 0.7 and FVC ≥ 80% predicted.

associated with severe COVID-19, independent of smoking history and other factors, in adults with and without clinical COPD or asthma. Restriction on spirometry was also strongly associated with severe COVID-19, independent of cardiometabolic comorbidities; however, imaging biomarkers of subclinical ILD were not associated with incident COVID-19. Our results support enhanced COVID-19 risk mitigation for adults with clinical or subclinical obstructive lung diseases or restriction on spirometry and warrant further mechanistic and clinical investigation focused on the association of lung health with susceptibility to COVID-19 and other acute respiratory infections.

Our findings for severe obstructive physiology and percentage emphysema, derived from a prospective cohort study design, align with existing literature linking physician-diagnosed COPD to adverse COVID-19 outcomes in hospital-based, claims data, or national registry settings (2, 4, 6, 36, 37). Notably, prepandemic severe obstructive physiology and percentage emphysema remained strongly linked to severe COVID-19 even in participants without reported prepandemic clinical COPD, suggesting a robust association that might have driven prior associations with self-reported or physician-based diagnoses of COPD while advancing the notation that subclinical lung disease is important for clinical prognostication. Our analysis lacked detailed data on COPD medication usage (e.g., inhaled corticosteroids), although individuals without self-reported COPD or asthma were unlikely to receive disease-specific therapies. The observed associations of obstructive physiology and percentage emphysema were independent of one another, and there was no significant effect modification on the multiplicative scale; nonetheless, associations were strongest for participants with both conditions, suggesting the potential for additive effects. Percentage emphysema appeared to have a dose–response relationship with severe COVID-19 risk in both never- and ever-smoking participants and in all age groups. These findings are consistent with prior work linking alveolar destruction with impaired antiviral response and recent work implicating interstitial macrophages, which are linked to emphysema pathogenesis, with accelerated SARS-CoV-2 replication and a hyperinflammatory response (38).

We believe that our study is the first to establish that prepandemic restrictive physiology was associated with increased risk of severe COVID-19. Restrictive physiology is a complex phenotype that can be due to ILD, intrinsic or extrinsic chest wall abnormalities, air trapping from obstructive lung disease, cardiac disease, or other extrapulmonary conditions, including adiposity. Given the null results for imaging biomarkers of subclinical ILD, the association between restriction and severe COVID-19 is unlikely to be fully explained by ILD. However, limitations in our analysis prevent us from ruling out its potential role. ILAs were relatively uncommon, even among those with restriction, and were available in only a subset of cohorts, likely leading to underpowered analyses. In addition, percentage HAA lacks specificity for ILD, introducing heterogeneity that may have biased results toward the null. Information on chest wall abnormalities was not available; however, these conditions are rare and therefore unlikely to explain the results. Stratification by degree of FEV_1:FVC impairment did not suggest that our findings for severe obstruction were due to mixed impairment, making obstruction an unlikely reason for the restrictive result. Cardiometabolic conditions, particularly obesity, were confirmed as significant, partial confounders of the association between

restrictive physiology and severe COVID-19. Nonetheless, the association of restrictive physiology persisted with adjustment for these factors and in strata of participants with and without cardiometabolic conditions, without evidence for significant effect modification. Of importance, available measures of adiposity were limited, so there may be some residual confounding by adiposity. Altogether, we were unable to identify a single etiologic factor explaining the link between spirometric restriction and COVID-19 risk, which warrants further mechanistic and clinical research.

Our study identified fewer associations with risk of nonsevere COVID-19. Participants with higher prepandemic lung function exhibited a higher likelihood of infection, yet their infections tended to be less severe. This trend may be attributed to heightened risk perception and mitigation behaviors (e.g., social distancing) among individuals with conditions associated with lower lung function, such as COPD, cough, dyspnea, or a history of smoking, particularly during the initial pandemic years when most of our data were collected (39–41). The observed dependence of infection probability on lung function and other covariates aligns with our primary analysis strategy, which evaluates the incidence of both severe and nonsevere COVID-19 across the entire population. In addition, our alternative approach, focusing on severe COVID-19 odds among COVID-19 cases (i.e., omitting those not infected at time of last follow-up), yielded numerically larger odds ratios but consistent results.

From a clinical perspective, our study highlights the importance of clinical and subclinical lung disease to COVID-19 risk and aligns with prior studies linking impaired lung function to increased susceptibility to viral respiratory infections, such as influenza and respiratory syncytial virus (42, 43). Our study also underscores the effectiveness of COVID-19 vaccination, which provided similar relative risk reduction and greater ARR in participants with impaired lung health.

Limitations

Our study has several limitations. First, there is a possibility of COVID-19 misclassification because of the use of self-reported measures; however, sensitivity analyses limited to confirmed cases yielded consistent results, and prior work in C4R has confirmed that COVID-19 illness was the cause of hospitalization in 93% of medical records adjudicated by C4R (27). Increased testing and reporting of COVID-19 infections among participants with chronic lung disease may have led to an overestimation of severe COVID-19 probabilities and vaccination-associated ARRs. Second, the interval between the latest prepandemic exam and the pandemic era might result in exposure misclassification; nonetheless, because lung function declines over time, and emphysema increases, this would bias our results toward the null, and sensitivity analyses adjusting for time since exam yielded consistent results. Third, prebronchodilator spirometry may overestimate obstruction, yet it correlates highly with post-bronchodilator measures in the general population (44, 45), and findings remained consistent after excluding participants with asthma. Fourth, partial lung coverage in cardiac scans may have led to some bias in imaging biomarkers; however, these have been previously validated on cardiac scans, and subclinical ILD has a basilar predominance, which was fully assessed. Fifth, lung structure measures, and particularly ILAs, were only available in a subset. Sixth, pooling data from multiple cohorts may have introduced heterogeneity. However, prepandemic data were systematically harmonized, COVID-19 ascertainment was prospectively conducted using a unified protocol, and models allowed each cohort to maintain its own baseline hazard, with no evidence of effect modification by source cohort. Seventh, data collection for this work was completed mainly in the pre-Omicron period; hence, generalizability to the current variants and clinical landscape is not assured. Further research is needed to evaluate bidirectional associations between lung function and COVID-19 outcomes, including postacute sequelae, in the present era. Eighth, some cohort studies recruited participants who were healthier than the average, others oversampled individuals with disease, and most recruited older adults; hence, the study is not a representative sample. However, it was broadly recruited from across the United States. Finally, the observational design provides associations but not causal inferences.

Conclusions

Prepandemic severe spirometric obstruction, spirometric restriction, and elevated emphysema on CT were associated with greater risk of severe COVID-19, independent of clinical cardiovascular or lung disease. These findings support enhanced COVID-19 risk mitigation, including COVID-19 vaccination, for individuals with impaired lung health and warrant further mechanistic studies on interactions of lung function, structure, and vulnerability to acute respiratory illnesses. ■

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