TITLE: Associations of Pre-pandemic Spirometry With COVID-19 Outcomes: The Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study

AUTHORS:

Pallavi Balte, MBBS, PhD[1]; Yifei Sun, PhD[2]; Nori Allen, PhD[3]; Alexander Arynchyn, PhD[4], R. Russell Bowler, MD, PhD[5]; Shelley A. Cole, PhD[6]; David Couper, PhD[7]; Ryan Demmer, PhD[8]; Margaret Doyle, PhD[9]; Mitchell Elkind, MD[10]; Robert Kaplan, PhD[11]; John Kim, MD[12]; Joyce Lee, MD[13]; Wendy Post, MD[14]; Vasan Ramachandran, MD[15]; Annie Rusk, MD[16]; David Schwartz, MD[13]; Jason G Umans, MD, PhD[17]; Sally Wenzel, MD[18]; Prescott Woodruff, MD[19]; Vanessa Xanthakis, PhD[15]; Will McKleroy, MD[20]; Suresh Garudadri, MD[20]; Victor E. Ortega, MD, PhD[16]; Elizabeth Oelsner, MD, MPH[1]

[1]Department of Medicine, Columbia University Irving Medical Center, New York, NY, USA

[2]Department of Biostatistics, Columbia University Mailman School of Public Health, New York, NY, USA

[3]Northwestern University, Chicago, IL, USA

[4]University of Alabama at Birmingham, Birmingham, AL, USA

[5]National Jewish Health, Denver, CO, USA

[6]Texas Biomedical Research Institute, San Antonio, TX, USA

[7]Biostatistics, University of North Carolina, Chapel Hill, NC, USA

[8]Mayo Clinic, Minneapolis, MN, USA

[9]University of Vermont, Burlington, VT, USA

[10]Department of Neurology, Columbia University Irving Medical Center, New York, NY, USA

[11]Albert Einstein College of Medicine, New York, NY, USA

[12]Department of Medicine, University of Virginia School of Medicine, Charlottesville, VA, USA

[13]University of Colorado Denver, Aurora, CO, USA

[14]Johns Hopkins University, Baltimore, MD, USA

[15]Boston University School of Medicine, Boston, MA, USA

[16]Pulmonary and Critical Care, Mayo Clinic, Phoenix, AZ, USA

[17]Georgetown University Medical Center, Washington, DC

[18]University of Pittsburgh, Pittsburgh, PA, USA

[19]Medicine, University of California, San Francisco, San Francisco, CA, USA

[20]Pulmonary, Critical Care, Allergy, Sleep Medicine, University of California, San Francisco, San Francisco, CA, USA

MANUSCRIPT WORD COUNT: 3371/3500

ABSTRACT WORD COUNT: 271/250

FORMATTED FOR: AJRCCM

ABSTRACT

Rationale: Increased risk of COVID-19 hospitalization and death has been reported among patients with clinical chronic obstructive pulmonary disease (COPD) and interstitial lung disease.

Objectives: To test the association of pre-pandemic lung function with COVID-19 outcomes in a US general population-based sample of adults.

Methods: Pre-pandemic lung function, including obstruction (FEV_1/FVC<0.70) and restriction (FEV_1/FVC≥0.7, FVC<80%), were defined based on the most recent spirometry exam conducted in nine prospective US general population-based cohorts. Obstruction severity was classified as mild (FEV_1 ≥80%), moderate (FEV_1 50-79%), or severe (FEV_1 <50%). Incident COVID-19 was ascertained via questionnaires, serosurvey, and medical records from 2020-2023, and classified as severe (hospitalized or fatal) or non-severe. Cause-specific hazards models were adjusted for socio-demographics, anthropometry, smoking, comorbidities, and vaccination status.

Measurements and Main Results: Among 28,887 participants (mean age, 67 years; 59% female; 46% non-Hispanic white; 31% Hispanic/Latino; 20% Black), there were 3,389 (12%) non-severe and 740 (3%) severe incident COVID-19 cases. Lower hazard of incident severe COVID-19 was associated with higher FEV_1 (HR 0.88 per SD, 95%CI:0.79-0.97) and FVC (HR 0.88 per SD, 95%CI:0.78-0.98). Greater hazard of severe COVID-19 was associated with restriction (vs normal spirometry, HR=1.42; 95%CI:1.15-1.75) and severe obstruction (HR, 2.16; 95%CI:1.32-3.54), but not mild or moderate obstruction. Similar associations were observed in participants without smoking, obesity, diabetes, hypertension, COPD, or cardiovascular disease.

Conclusions: Impaired pre-pandemic lung function, particularly restriction and severe obstruction, was associated with greater hazard of severe COVID-19 in a US population-based sample, even among otherwise healthy adults without clinical cardiovascular or lung disease. This supports enhanced COVID-19 prevention and treatment for adults with impaired lung function and warrants further mechanistic and clinical investigation.

INTRODUCTION

Coronavirus disease 19 (COVID-19) is a leading cause of hospitalization and death (1). A heightened risk of COVID-19 hospitalization and death has been observed in patients with chronic obstructive pulmonary disease (COPD) and restrictive lung disease (2-6). However, these results could be biased by the fact that a clinical diagnosis of lung disease may influence personal and clinical decisions regarding whether to present to the hospital and whether to hospitalize for COVID-19. Furthermore, treatments for chronic lung diseases—particularly immunomodulatory medications—could confound the observed associations. The lack of association between genetic determinants of lung function and COVID-19 infection (7) suggests that further investigation is needed to understand the associations of lung health and lung physiology with COVID-19 outcomes, particularly with respect to less severe or subclinical lung diseases.

To our knowledge, no large study has examined whether pre-existing lung function impairment is associated with COVID-19 outcomes in the US general population. Impaired lung function is common in the general US population, with the majority of cases remaining undetected and undiagnosed. Obstruction on spirometry, defined by a forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) ratio less than 0.70, is observed in 13.5% of adults (8, 9), compared to a prevalence of 6.4% for clinical COPD (10). The estimated prevalence of restriction on spirometry, defined by an FEV_1/FVC ratio ≥ 0.70 and FVC < 80% of predicted, is 7% to 11% (8, 9, 11, 12), compared to 0.2% for interstitial lung disease (13). Both obstruction

and restriction are associated with an increased risk of all-cause and cardiovascular mortality, independent of common risk factors such as smoking and obesity (9, 14-20).

We aimed to test if pre-pandemic lung function was associated with risk of COVID-19 in the Collaborative Cohort of Cohorts for COVID-19 Research (C4R) (21), a nationwide meta-cohort of adult participants from 14 long-standing cardiovascular, neurological, and respiratory cohort studies. We examined associations of COVID-19 severity with pre-pandemic FEV_1, FVC, and FEV_1/FVC, and their rates of decline, as well as categorical definitions of airflow obstruction and restriction. To evaluate potential confounding and selection biases, we conducted multivariable adjusted analyses and subgroup analyses limited to participants without smoking, obesity, clinical lung disease or cardiovascular disease.

METHODS

Design

C4R received funding in 2020 to perform standardized prospective data collection on COVID-19 and to harmonize pre-pandemic deep phenotyping available in 14 long-term NIH-funded cohorts. Data collection on COVID-19 was accomplished by two waves of questionnaires, a SARS-CoV-2 serosurvey, and ascertainment and adjudication of COVID-19 hospitalizations and deaths (21).

This report includes nine cohorts that conducted spirometry: Atherosclerosis Risk in Communities (ARIC) study (22), Coronary Artery Risk Development in Young Adults (CARDIA) study (23), COPD Genetic Epidemiology (COPDGene) study (24), Framingham Heart Study (FHS) (25), Hispanic Community Health Study (HCHS) (26), Jackson Heart Study (JHS) (27), the Multi-

Ethnic Study of Atherosclerosis (MESA) (28), the Strong Heart Study (SHS) (29), and Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) (30) (**Table E1**). Approval for all studies was obtained from institutional review boards at participating institutions. Participants with missing data for pre-pandemic spirometry or COVID-19 case status were excluded.

Spirometry

Prebronchodilator spirometry was performed at exams conducted from 1983-2017 using water seal, dry-rolling seal, or flow-sensing spirometers, and measures were harmonized as previously described (24, 31). Percent predicted and lower-limit-of-normal (LLN) values were calculated using the US population-based National Health and Nutrition Examination Survey (NHANES) III reference equations (32). The most recent pre-pandemic spirometry exam was used to define pre-pandemic FEV_1, FVC, and FEV_1/FVC, as well as to classify normal lung function (FEV_1/FVC>=0.70, FVC>=80%), obstruction (FEV_1/FVC<0.70), and restriction (FEV_1/FVC>=0.70, FVC<80%). Obstruction was further subclassified by severity as mild (FEV_1 ≥80% predicted), moderate (50% ≤ FEV_1 <80% predicted), or severe (FEV_1 <50% predicted) (9). Decline in FEV_1, FVC, and FEV_1/FVC ratio was calculated based on the difference from the most recent pre-pandemic exam versus the first cohort spirometry exam, divided by the years elapsed.

Incident Covid-19

C4R ascertained incident COVID-19 using two waves of standardized questionnaires administered across the entire C4R population via telephone interview, mailed pamphlet, electronic survey, and/or in-person examinations (**Table E2**). Confirmation of self-reported

cases, when possible, involved adjudication of medical records for hospitalizations and deaths linked to COVID-19, and a SARS-CoV-2 serosurvey conducted via dried blood spots. The present analysis includes all COVID-19 illnesses defined by self-report in response to a questionnaire or ascertained by active surveillance or serosurvey. Sensitivity analyses were limited to cases confirmed by self-report of a positive test, medical record review, or the C4R serosurvey.

All incident COVID-19 cases were classified as severe (hospitalized or fatal) or non-severe (all other cases). Re-infections with SARS-CoV-2 were excluded from all analyses.

Covariates

All covariates were obtained from the most recent pre-pandemic examination and were systematically harmonized. Age at enrollment in March 2020 was calculated from cohort enrollment age. Sex and educational attainment were self-reported. Race and ethnicity were self-reported according to fixed categories that differed by cohort, hence they were harmonized into a single classification of race and ethnicity (American Indian [AI], Asian, Black, Hispanic, Non-Hispanic White). Body mass index (BMI) was calculated using height and weight measured using standard methods, and obesity was classified based on CDC criteria (33). Smoking status was self-reported, with biochemical verification in a subset. Ever smoking status was defined as at least 100 lifetime cigarettes, and current smoking status as smoking within the past 30 days. Pack-years were calculated as ([cigarettes per day × years smoked]/20). Hypertension was defined by self-report, systolic blood pressure >=140, diastolic blood pressure>= 90, or use of antihypertensive medications. Diabetes was defined by self-report, fasting blood glucose>= 126 mg/dL, or the use of insulin or hypoglycemic medications. Clinical

COPD was defined based on either self-reported physician diagnosis or adjudication/administrative criteria for COPD, chronic bronchitis, or emphysema. Similarly, clinical CVD was defined by self-reported physician diagnosis or adjudication/administrative criteria for myocardial infarction, angina pectoris, or stroke. Region was defined by the three-digit zip code for the most recent residential address. COVID-19 vaccination was assessed by C4R questionnaires, and vaccination status at time of incident infection was defined by comparison of infection versus vaccination dates. Missing covariate data was assumed to be missing at random and addressed by multiple imputation (N=10 imputations).

Statistical analysis

Cumulative incidence functions for severe and non-severe COVID-19 were plotted according to pre-pandemic lung function categories. Associations with lung function were tested using cause-specific hazards models that treated incident non-severe and severe COVID-19 as mutually-exclusive (competing) risks, with days since March 1, 2020 treated as time-to-event. Models were adjusted for age at C4R baseline, sex, race and ethnicity, educational attainment, BMI, smoking status, packyears, comorbidities, vaccination status at the time of infection or time of last follow-up, and geographical region. Cohort was treated as a stratum term, which allows each cohort to have its own baseline hazard function. Because of the potential for type I error due to multiple comparisons, all sub-group analyses should be interpreted as 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.

Sensitivity analyses

To assess potential selection biases due to clinical conditions, analyses were repeated in subsets of participants without pre-pandemic clinical COPD or cardiovascular disease, as well as subsets with and without obesity and smoking history. Effect modification by all covariates was assessed by multiplicative interaction terms and in fully stratified models. Analyses were performed in participants without missing covariate data (complete cases) and limited to incident COVID-19 cases that were confirmed by testing or medical records. Analyses were also performed using the LLN for the FEV_1/FVC and FVC, rather than fixed thresholds, to define obstruction and restriction. Finally, as an alternative analytic approach to the cause-specific hazards model, we assessed associations of pre-pandemic lung function with incident severe COVID-19 using logistic models, limited to those participants with a history of COVID-19.

RESULTS

Participants

There were 28,887 participants with valid pre-pandemic lung function and incident COVID-19 data (**Table 1**, **Figure E1**). The mean (SD) age of participants in March 2020 was 67.2 (14.0) years (range: 26 to 90 years). The majority (58.7%) were women and the distribution of race and ethnicity was 45.6% non-Hispanic white, 31.3% Hispanic/Latino, 19.7% Black, 1.7% AI, and 1.6% Asian. Over a median of 17.4 months of follow up by C4R (range, 0.03-34.2 months), there were 3,389 (11.7%) incident non-severe and 740 (2.6%) severe COVID-19 cases. Compared to participants with no COVID-19 at last follow-up, or non-severe incident COVID-19, participants with incident severe COVID-19 were older, more likely to be male, and more likely to have pre-

pandemic obesity, smoking history, hypertension, diabetes, CVD, clinical asthma, and/or COPD (**Table 1**).

Pre-pandemic lung function

Lung function was measured a median of 9 years (interquartile range: 5 -11) prior to initiation of C4R enrollment in 2020. On average, pre-pandemic FEV_1 was 93.2% predicted, FVC was 95.9% predicted, and FEV_1/FVC was 0.76. Normal spirometry was most prevalent (70.1%), followed by obstruction (19.9%) and restriction (10.0%). Obstruction was mild in 9.2%, moderate in 9.0%, and severe in 1.7%.

Lung function was slightly lower in participants with incident severe versus non-severe COVID-19 and normal lung function was less common (66.8% vs 77.0%), primarily due to greater prevalence of restriction (16.1% vs 9.0%, **Table 1**). Among 16,024 individuals with at least two spirometry measurements, those with incident severe COVID-19 had a higher decline in FEV_1 (40.1 vs. 31.9 mL/year) and FVC (46.4 vs. 31.3 mL/year) compared to those with incident non-severe COVID-19 (**Table 1**).

Incident COVID-19

Higher pre-pandemic FEV_1 and FVC were associated with greater hazards of non-severe COVID-19 and lower risks of severe COVID-19 in both unadjusted and multivariable-adjusted models (**Table 2**). The FEV_1/FVC ratio was not associated in adjusted models. Greater rates of decline in FEV_1 and FVC were associated with greater hazards of severe-COVID-19 in unadjusted models, but not after adjustment (**Table 2**).

The cumulative incidence of non-severe and severe COVID-19 differed by categories of lung function impairment (**Figure 1**). The incidence of non-severe COVID-19 was lower in participants with obstruction (66.7 per 1,000 person-years), particularly in those with severe obstruction (73.5 per 1,000 person- years), than in those with restriction (86.7 per 1,000 person-years) or normal spirometry (103.3 per 1,000 person-years; **Figure 1A**). In adjusted models, restriction was associated with lower hazards of non-severe COVID-19 (aHR=0.88, 95%CI:0.78-0.99) and obstruction was not associated (aHR=0.97, 95%CI:0.87-1.09; **Table 3**).

The incidence of severe COVID-19 was highest among participants with severe obstruction (36.8 per 1,000 person- years) and restriction (34.6 per 1,000 person- years) versus those with moderate obstruction (19.1 per 1,000 person- years), mild obstruction (15.66 per 1,000 person-years), or normal spirometry (19.6 per 1,000 person- years; **Figure 1B**). Compared to normal spirometry, restriction was associated with an adjusted HR of 1.42 (95%CI:1.15-1.75) for severe COVID-19 (**Table 3**). Although obstruction was not associated overall (aHR=1.04; 95%CI:0.83-1.29), severe obstruction was associated with a greater hazard of severe COVID-19 (aHR=2.16; 95%CI:1.32-3.54, **Table 3**).

Sub-group analyses

Results were similar in analyses that excluded 5,446 participants with pre-pandemic clinical COPD or CVD (**Table E3**). Increased hazard of incident severe COVID-19 was associated with restriction (aHR=1.53; 95%CI:1.18-1.97) and severe obstruction (aHR=3.41; 95%CI:1.91-6.12). In covariate-stratified analyses, associations with incident severe COVID-19 were also consistent with the main results: higher FEV_1 and FVC were favorably associated **(Figures E5, E6)**,

restriction was adversely associated (**Figure 2**), and obstruction was not associated (**Figure E2, E4**). Multiplicative interaction terms were significant for age, sex, hypertension, and diabetes for stratified analyses for FEV_1 and FVC **(Figures E5, E6)**, but not for restriction or obstruction. Associations were also generally consistent across cohorts **(Figure E3)** and multiplicative interaction terms with cohort were non-significant. Findings suggested that associations of lung function impairment with incident severe COVID-19 were attenuated in subgroups with higher baseline risk of severe COVID-19 (e.g., age ≥80 years).

In analyses limited to participants with confirmed COVID-19 (**Table E4**), associations with severe COVID-19 were generally consistent with the main analysis. Associations remained significant for FEV_1 (aHR per SD=0.87; 95%CI:0.78-0.96), FVC (aHR per SD=0.87; 95%CI:0.78-0.97), restriction (aHR=1.45; 95%CI:1.18-1.79) and severe obstruction (aHR=2.22; 95%CI:1.36-3.64).

Sensitivity analyses

Results were consistent in complete case analysis (**Table E5**), using the LLN to define obstruction and restriction (**Table E6**), and applying logistic regression (**Table E7**).

DISCUSSION

Pre-pandemic lung function impairment was associated with increased hazard of incident severe COVID infection in a US general population-based meta-cohort of adults with prospective ascertainment of COVID-19. Restrictive physiology was consistently associated with higher risk of severe COVID-19, independent of pre-pandemic obesity and CVD. Greater risk of severe COVID-19 was also associated with severe obstruction, but not with mild or moderate

obstruction. These findings persisted in adults without clinical COPD or CVD, establishing the importance of low lung function as a risk factor for severe COVID-19 in the general population.

Our findings confirm and extend prior findings with respect to the significance of COPD as a risk factor for severe COVID-19. Our results regarding severe obstruction using a prospective cohort study design are broadly consistent with prior research that identified physician-diagnosed COPD as a risk factor for adverse COVID-19 outcomes in hospital-based, claims data, or national registry settings (2, 4, 6, 34, 35). Furthermore, we found that pre-pandemic severe obstruction remained strongly associated with severe COVID-19 in participants who did not self-report pre-pandemic COPD, which somewhat mitigates the possibility that personal or physician expectations regarding COPD risk could account for the observed association. Nonetheless, in the context of significant time intervals between pre-pandemic and pandemic data collection, we cannot exclude the possibility that participants with pre-pandemic severe obstruction were diagnosed with clinical COPD prior to COVID-19. We also did not have sufficient data on pre-pandemic or pandemic COPD medication use (e.g., inhaled corticosteroids) to account for potential confounding by these therapies, although participants without self-reported COPD or asthma were less likely to be on therapy. Of importance, our study indicates that mild or moderate obstruction—which account for most obstruction cases, including among those with clinical COPD (8, 9)—was not associated with increased risk of severe COVID-19.

We believe that our study is the first to establish that pre-pandemic restriction was associated with increased risk of severe COVID-19, including in participants without other established COVID-19 risk factors. Several studies have demonstrated an increased risk of COVID-19-related hospitalizations and deaths in individuals with interstitial lung disease (ILD) (2, 3, 36); however,

ILD typically accounts for a small proportion of spirometric restriction. Confounding by shared risk factors for restriction and severe COVID-19 was a major consideration that we investigated via adjusted and stratified models. We found that while covariate adjustment substantially attenuated associations, restriction remained strongly associated with greater hazard of severe COVID-19. Moreover, associations were similar in participants with and without obesity (37, 38) and stronger in participants without clinical CVD. Although there was no statistical evidence for effect modification, stratified analyses suggested that restriction was not associated with severe COVID-19 in participants older than 80 years, identifying as American Indian, or reporting current smoking. Of note, rates of severe COVID-19 were substantially higher in older and American Indian participants than in other groups, hence lung function may have been less influential. Prior studies have also linked current smoking to severe COVID-19 (7, 39, 40), although these may be mediated by severe obstruction, rather than restriction. The presence of a "healthy smoker" bias, wherein individuals who persist in smoking may be especially resilient, should also be considered. Of note, our findings are consistent with a Mendelian randomization study observed trends indicating an increased risk of severe COVID-19 with a higher FEV_1/FVC ratio (7), providing further assurance that our findings were robust and warrant additional investigation.

Our study showed that risk of non-severe COVID-19 also varied according to pre-pandemic lung function, which may be due to social and/or behavioral factors. Our findings suggest that participants with higher pre-pandemic lung function were more likely to be infected but, if infected, their infections were less likely to be severe. This may be explained by the fact that adults who perceived that they were at elevated risk of adverse COVID-19 outcomes—due to

clinical disease such as COPD, symptoms such as cough or dyspnea, or smoking history, all of which are associated with lower lung function—were more likely to implement and maintain risk mitigation measures such as social isolation and masking, particularly during the first two years of the pandemic, from which most of our data was collected (41-43). They were therefore less likely to be infected during the observation period, especially during the pre-vaccine era. The observation that infection probability was dependent on lung function and other covariates supports our primary analysis strategy, which assesses the incidence of both severe and non-severe COVID-19 in the entire population of interest. We also implemented an alternative approach that tested the odds of severe COVID-19 among COVID-19 cases (i.e., omitting those not infected at time of last follow-up); odds ratios were numerically larger than the hazards ratios from the main analysis, yet results were consistent.

From a clinical perspective, our results underscore the importance of enhanced COVID-19 risk mitigation for adults with lung function impairment, particularly severe obstruction and restriction. COVID-19 vaccination remains a powerful tool to reduce risks of severe COVID-19 yet rates of re-vaccination are lagging across both low and high risk groups. That being said, our study demonstrated similar associations of lung function impairment with COVID-19 outcomes among participants who were and were not vaccinated at time of COVID-19, suggesting that vaccination does not eliminate lung function-related risk; additional measures beyond vaccination may be indicated. More generally, our findings add to the growing body of literature linking obstruction and restriction to adverse health outcomes, including an elevated risk of CVD, heart failure, and all-cause mortality (9, 11, 14-17, 20). In particular, restriction

remains underdiagnosed and incompletely understood, warranting further etiologic, mechanistic, and clinical investigation.

Strengths of the current work include the use of a large, multiethnic, US population based meta-cohort of adults; pre-pandemic measurement of spirometry; systematic, prospective COVID-19 ascertainment; and consideration of multiple potential confounders. Nonetheless, this study has several limitations, in addition to those mentioned above. First, there is a possibility of COVID-19 misclassification due to use of some self-reported measures; however, sensitivity analyses limited to confirmed cases yielded consistent results. Second, the interval between the most recent pre-pandemic exam and the pandemic period may lead to exposure misclassification. Since most measurements, including lung function, are likely to deteriorate over time, earlier measures may bias our results to the null. Third, use of pre-bronchodilator spirometry may overestimate obstruction, but prebronchodilator measures exhibit high correlation with postbronchodilator measures in the general population (44, 45) and results were consistent with exclusion of participants with asthma. Fourth, the use of race and ethnicity specific NHANES prediction equations is no longer recommended. Nevertheless, due to the absence of a consensus on which reference equations to employ, we opted for NHANES equations, which were derived from the US general population similar to C4R. Fifth, the use of fixed versus lower-limit-of-normal thresholds (LLN) to define obstruction and restriction remains controversial; sensitivity analysis using LLN-defined lung function categories yielded consistent results. Sixth, pooling cohort data introduced additional sources of heterogeneity and confounding yet pre-pandemic data were systematically harmonized, prospective ascertainment of COVID-19 was conducted using a unified protocol, models were designed to

allow each cohort to have its own baseline hazard, and no evidence for effect modification by cohort was identified. Finally, the 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 bi-directional associations between lung function and COVID-19 outcomes, including post-acute sequelae, in the present era.

In conclusion, pre-pandemic lung function impairment was associated with increased hazard of incident severe COVID infection in a large, multi-ethnic, US general population-based meta-cohort of adults. Controlling for major potential confounders, and in subgroups without clinical cardiovascular or lung disease, increased hazard of severe COVID-19 was associated with restrictive physiology and severe obstruction, but not with mild or moderate obstruction. These results confirm that adults with lung function impairment merit enhanced COVID-19 risk mitigation measures and warrant additional mechanistic and clinical research to optimize COVID-19 and other health outcomes in adults with clinical and subclinical lung disease.

REFERENCES

1. Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature* 2023; 613: 130-137.
2. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, Coupland CAC, Tan PS, Clift AK, Harrison D, Gould DW, Pavord ID, Hippisley-Cox J. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *The Lancet Respiratory Medicine* 2021; 9: 909-923.
3. Fadista J, Kraven LM, Karjalainen J, Andrews SJ, Geller F, Baillie JK, Wain LV, Jenkins RG, Feenstra B. Shared genetic etiology between idiopathic pulmonary fibrosis and COVID-19 severity. *EBioMedicine* 2021; 65: 103277.
4. Gerayeli FV, Milne S, Cheung C, Li X, Yang CWT, Tam A, Choi LH, Bae A, Sin DD. COPD and the risk of poor outcomes in COVID-19: A systematic review and meta-analysis. *EClinicalMedicine* 2021; 33: 100789.
5. Sahu KK, Mishra AK, Martin K, Chastain I. COVID-19 and restrictive lung disease: A deadly combo to trip off the fine balance. *Monaldi Archives for Chest Disease* 2020; 90.
6. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584: 430-436.
7. Au Yeung SL, Li AM, He B, Kwok KO, Schooling CM. Association of smoking, lung function and COPD in COVID-19 risk: a two-step Mendelian randomization study. *Addiction* 2022; 117: 2027-2036.
8. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health and Nutrition Examination surveys from 1988-1994 to 2007-2010. *Chest* 2013; 143: 1395-1406.
9. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance-United States, 1971-2000. 2002.
10. Biener AI, Decker SL, Rohde F. Prevalence and Treatment of Chronic Obstructive Pulmonary Disease (COPD) in the United States. *JAMA* 2019; 322: 602-602.
11. Backman H, Eriksson B, Hedman L, Stridsman C, Jansson S-A, Sovijärvi A, Lindberg A, Rönmark E, Lundbäck B. Restrictive spirometric pattern in the general adult population: methods of defining the condition and consequences on prevalence. *Respiratory medicine* 2016; 120: 116-123.
12. Torén K, Schiöler L, Brisman J, Malinovschi A, Olin A-C, Bergström G, Bake B. Restrictive spirometric pattern and true pulmonary restriction in a general population sample aged 50 - 64 years. *BMC Pulmonary Medicine* 2020; 20: 55.
13. Jeganathan N, Sathananthan M. The prevalence and burden of interstitial lung diseases in the USA. *ERJ Open Research* 2022; 8: 00630-02021.

14. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. *Thorax* 2010; 65: 499-504.
15. Silvestre OM, Nadruz W, Roca GQ, Claggett B, Solomon SD, Mirabelli MC, London SJ, Loehr LR, Shah AM. Declining Lung Function and Cardiovascular Risk. *Journal of the American College of Cardiology* 2018; 72: 1109-1122.
16. Wan ES, Balte P, Schwartz JE, Bhatt SP, Cassano PA, Couper D, Daviglus ML, Dransfield MT, Gharib SA, Jacobs DR, Jr, Kalhan R, London SJ, Navas-Acien A, O'Connor GT, Sanders JL, Smith BM, White W, Yende S, Oelsner EC. Association Between Preserved Ratio Impaired Spirometry and Clinical Outcomes in US Adults. *JAMA* 2021; 326: 2287-2298.
17. Eckhardt CM, Balte PP, Barr RG, Bertoni AG, Bhatt SP, Cuttica M, Cassano PA, Chaves P, Couper D, Jacobs DR, Kalhan R, Kronmal R, Lange L, Loehr L, London SJ, O'Connor GT, Rosamond W, Sanders J, Schwartz JE, Shah A, Shah SJ, Smith L, White W, Yende S, Oelsner EC. Lung function impairment and risk of incident heart failure: the NHLBI Pooled Cohorts Study. *European Heart Journal* 2022; 43: 2196-2208.
18. Sin DD, Man SFP. Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases? *Circulation* 2003; 107: 1514-1519.
19. Sin DD, Man SFP. Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Morbidity and Mortality. *Proceedings of the American Thoracic Society* 2005; 2: 8-11.
20. Cuttica MJ, Colangelo LA, Dransfield MT, Bhatt SP, Rana JS, Jacobs DR, Thyagarajan B, Sidney S, Lewis CE, Liu K, Lloyd-Jones D, Washko G, Kalhan R. Lung Function in Young Adults and Risk of Cardiovascular Events Over 29 Years: The CARDIA Study. *Journal of the American Heart Association* 2018; 7: e010672.
21. Oelsner EC, Krishnaswamy A, Balte PP, Allen NB, Ali T, Anugu P, Andrews HF, Arora K, Asaro A, Barr RG, Bertoni AG, Bon J, Boyle R, Chang AA, Chen G, Coady S, Cole SA, Coresh J, Cornell E, Correa A, Couper D, Cushman M, Demmer RT, Elkind MSV, Folsom AR, Fretts AM, Gabriel KP, Gallo LC, Gutierrez J, Han MLK, Henderson JM, Howard VJ, Isasi CR, Jacobs Jr DR, Judd SE, Mukaz DK, Kanaya AM, Kandula NR, Kaplan RC, Kinney GL, Kucharska-Newton A, Lee JS, Lewis CE, Levine DA, Levitan EB, Levy BD, Make BJ, Malloy K, Manly JJ, Mendoza-Puccini C, Meyer KA, Min Y-IN, Moll MR, Moore WC, Mauger D, Ortega VE, Palta P, Parker MM, Phipatanakul W, Post WS, Postow L, Psaty BM, Regan EA, Ring K, Roger VL, Rotter JI, Rundek T, Sacco RL, Schembri M, Schwartz DA, Seshadri S, Shikany JM, Sims M, Hinckley Stukovsky KD, Talavera GA, Tracy RP, Umans JG, Vasan RS, Watson KE, Wenzel SE, Winters K, Woodruff PG, Xanthakis V, Zhang Y, Zhang Y, Investigators ftCR. Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study: Study Design. *American Journal of Epidemiology* 2022; 191: 1153-1173.
22. The ARIC Investigators. The atherosclerosis risk in communit (ARIC) study: design and objectives. *American journal of epidemiology* 1989; 129: 687-702.
23. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs Jr DR, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *Journal of clinical epidemiology* 1988; 41: 1105-1116.
24. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of COPD (COPDGene) study design. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2011; 7: 32-43.

25. Tsao CW, Vasan RS. Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. *International journal of epidemiology* 2015; 44: 1800-1813.
26. Sorlie PD, Avilés-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, Schneiderman N, Raij L, Talavera G, Allison M. Design and implementation of the Hispanic community health study/study of Latinos. *Annals of epidemiology* 2010; 20: 629-641.
27. Taylor H, Wilson J, Jones D, Sarpong D, Srinivasan A, Garrison R. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. vol. 15, pp: S6-4-17. Ethn Dis; 2005.
28. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, JacobsJr DR, Kronmal R, Liu K. Multi-ethnic study of atherosclerosis: objectives and design. *American journal of epidemiology* 2002; 156: 871-881.
29. Lee ET, Welty TK, Fabsitz R, Cowan LD, Le N-A, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The Strong Heart Study A study of cardiovascular disease in American Indians: design and methods. *American journal of epidemiology* 1990; 132: 1141-1155.
30. Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, Woodruff PG. Design of the subpopulations and intermediate outcomes in COPD study (SPIROMICS). *Thorax* 2013: thoraxjnl-2013-203897.
31. Oelsner EC, Balte PP, Cassano PA, Couper D, Enright PL, Folsom AR, Hankinson J, Jacobs DR, Jr., Kalhan R, Kaplan R, Kronmal R, Lange L, Loehr LR, London SJ, Navas Acien A, Newman AB, O'Connor GT, Schwartz JE, Smith LJ, Yeh F, Zhang Y, Moran AE, Mwasongwe S, White WB, Yende S, Barr RG. Harmonization of Respiratory Data From 9 US Population-Based Cohorts: The NHLBI Pooled Cohorts Study. *American Journal of Epidemiology* 2018; 187: 2265-2278.
32. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *American journal of respiratory and critical care medicine* 1999; 159: 179-187.
33. Division of Nutrition PA, and Obesity, National Center for Chronic Disease Prevention and Health Promotion. Defining Adult Overweight & Obesity. 2022. Available from: https://www.cdc.gov/obesity/basics/adult-defining.html.
34. Attaway AA, Zein J, Hatipoğlu US. SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: An analysis of Cleveland clinic's COVID-19 registry. *EClinicalMedicine* 2020; 26.
35. Parra-Bracamonte GM, Lopez-Villalobos N, Parra-Bracamonte FE. Clinical characteristics and risk factors for mortality of patients with COVID-19 in a large data set from Mexico. *Annals of epidemiology* 2020; 52: 93-98. e92.
36. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, Babu S, Barber CM, Barratt S, Bendstrup E, Bianchi S, Villegas DC, Chaudhuri N, Chua F, Coker R, Chang W, Crawshaw A, Crowley LE, Dosanjh D, Fiddler CA, Forrest IA, George PM, Gibbons MA, Groom K, Haney S, Hart SP, Heiden E, Henry M, Ho L-P, Hoyles RK, Hutchinson J, Hurley K, Jones M, Jones S, Kokosi M, Kreuter M, MacKay LS, Mahendran S, Margaritopoulos G, Molina-Molina M, Molyneaux PL, O'Brien A, O'Reilly K, Packham A, Parfrey H, Poletti V, Porter JC, Renzoni E, Rivera-Ortega P, Russell A-M, Saini G, Spencer LG, Stella GM, Stone

H, Sturney S, Thickett D, Thillai M, Wallis T, Ward K, Wells AU, West A, Wickremasinghe M, Woodhead F, Hearson G, Howard L, Baillie JK, Openshaw PJM, Semple MG, Stewart I, Jenkins RG. Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease. An International Multicenter Study. *American Journal of Respiratory and Critical Care Medicine* 2020; 202: 1656-1665.
37. Fenger RV, Gonzalez-Quintela A, Vidal C, Husemoen L-L, Skaaby T, Thuesen BH, Aadahl M, Madsen F, Linneberg A. The longitudinal relationship of changes of adiposity to changes in pulmonary function and risk of asthma in a general adult population. *BMC pulmonary medicine* 2014; 14: 1-10.
38. Jones RL, Nzekwu M-MU. The effects of body mass index on lung volumes. *Chest* 2006; 130: 827-833.
39. Clift AK, von Ende A, Tan PS, Sallis HM, Lindson N, Coupland CAC, Munafò MR, Aveyard P, Hippisley-Cox J, Hopewell JC. Smoking and COVID-19 outcomes: an observational and Mendelian randomisation study using the UK Biobank cohort. *Thorax* 2022; 77: 65-73.
40. Mahamat-Saleh Y, Fiolet T, Rebeaud ME, Mulot M, Guihur A, El Fatouhi D, Laouali N, Peiffer-Smadja N, Aune D, Severi G. Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies. *BMJ open* 2021; 11: e052777.
41. Alqahtani JS, Oyelade T, Aldhahir AM, Mendes RG, Alghamdi SM, Miravitlles M, Mandal S, Hurst JR. Reduction in hospitalised COPD exacerbations during COVID-19: A systematic review and meta-analysis. *PLOS ONE* 2021; 16: e0255659.
42. Hurst JR, Cumella A, Niklewicz CN, Philip KE, Singh V, Hopkinson NS. Acceptability of hygiene, face covering and social distancing interventions to prevent exacerbations in people living with airways diseases. *Thorax* 2021.
43. McAuley H, Hadley K, Elneima O, Brightling CE, Evans RA, Steiner MC, Greening NJ. COPD in the time of COVID-19: an analysis of acute exacerbations and reported behavioural changes in patients with COPD. *ERJ Open Research* 2021; 7: 00718-02020.
44. Kato B, Gulsvik A, Vollmer W, Janson C, Studnika M, Buist S, Burney P. Can spirometric norms be set using pre-or post-bronchodilator test results in older people? *Respiratory research* 2012; 13: 1-11.
45. Mannino DM, Diaz-Guzman E, Buist S. Pre-and post-bronchodilator lung function as predictors of mortality in the Lung Health Study. *Respiratory research* 2011; 12: 1-7.

FUNDING

The Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study is supported by National Heart, Lung, and Blood Institute (NHLBI)–Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS) grant OT2HL156812, with co-funding from the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA).

The Atherosclerosis Risk in Communities Study has been funded in whole or in part by the NHLBI, National Institutes of Health (NIH), US Department of Health and Human Services, under contracts 75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, and 75N92022D00005. Neurocognitive data are collected under grants U01 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, and 2U01HL096917 from the NHLBI, the NINDS, the NIA, and the National Institute on Deafness and Other Communication Disorders. Ancillary studies funded additional data elements. The Blood Pressure and Cognition Study is supported by the NINDS (grant R01 NS102715).

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is conducted and supported by the NHLBI in collaboration with the University of Alabama at Birmingham (contracts HHSN268201800005I and HHSN268201800007I), Northwestern University (contract HHSN268201800003I), the University of Minnesota (contract HHSN268201800006I), and the Kaiser Foundation Research Institute (contract HSN268201800004I).

The Genetic Epidemiology of COPD (COPDGene) Study was supported by awards U01 HL089897 and U01 HL089856 from the NHLBI. COPDGene is also supported by the COPD Foundation through contributions made to an industry advisory board comprised of AstraZeneca AB (Cambridge, United Kingdom), Boehringer-Ingelheim (Ingelheim am Rhein, Germany), Genentech, Inc. (South San Francisco, California), GlaxoSmithKline plc (London, United Kingdom), Novartis International AG (Basel, Switzerland), Pfizer, Inc. (New York, New York), Siemens AG (Berlin, Germany), and Sunovion Pharmaceuticals Inc. (Marlborough, Massachusetts).

The Framingham Heart Study has received support from the NHLBI (grant N01-HC-25195, contract HHSN268201500001I, and grant 75N92019D00031).

The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a collaborative study supported by contracts between the NHLBI and the University of North Carolina (contract HHSN268201300001I/N01-HC-65233), the University of Miami (contract HHSN268201300004I/N01-HC-65234), Albert Einstein College of Medicine (contract HHSN268201300002I/N01-HC-65235), the University of Illinois at Chicago (contract HHSN268201300003I/N01-HC-65236 (Northwestern University)), and San Diego State University (contract HHSN268201300005I/N01-HC-65237). The following institutes/centers/offices have contributed to the HCHS/SOL through a transfer of funds to the NHLBI: the National Institute on Minority Health and Health Disparities, the National Institute on Deafness and Other Communication Disorders, the National Institute of Dental and Craniofacial Research, the National Institute of Diabetes and Digestive and Kidney Diseases, the NINDS, and the NIH Office of Dietary Supplements.

The Jackson Heart Study is supported by and conducted in collaboration with Jackson State University (contract HHSN268201800013I), Tougaloo College (contract HHSN268201800014I), the Mississippi State Department of Health (contract HHSN268201800015I), the University of Mississippi Medical Center (contracts HHSN268201800010I, HHSN268201800011I, and HHSN268201800012I), the NHLBI, and the National Institute on Minority Health and Health Disparities.

The Multi-Ethnic Study of Atherosclerosis (MESA) and the MESA SNP Health Association Resource (SHARe) are conducted and supported by the NHLBI in collaboration with the MESA investigators. Support for MESA is

provided by grants and contracts 75N92020D00001, HHSN268201500003I, N01-HC-95159, 75N92020D00005, N01-HC-95160, 75N92020D00002, N01-HC-95161, 75N92020D00003, N01-HC-95162, 75N92020D00006, N01-HC-95163, 75N92020D00004, N01-HC-95164, 75N92020D00007, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, N01-HC-95169, R01-HL077612, R01-HL093081, R01-HL130506, R01-HL127028, R01-HL127659, R01-HL098433, R01-HL101250, and R01-HL135009 from the NHLBI; grant R01-AG058969 from the NIA; and grants UL1-TR-000040, UL1-TR-001079, and UL1-TR-001420 from the National Center for Advancing Translational Sciences. Funding for SHARe genotyping was provided by NHLBI contract N02-HL-64278. This publication was developed under Science to Achieve Results (STAR) research assistance agreements RD831697 (MESA Air) and RD-83830001 (MESA Air Next Stage), awarded by the Environmental Protection Agency. Whole genome sequencing for the Trans-Omics in Precision Medicine (TOPMed) Program was supported by the NHLBI. Whole genome sequencing for the MESA component of the TOPMed Study (Database of Genotypes and Phenotypes accession no. phs001416.v1.p1) was performed at the Broad Institute of MIT and Harvard (grant 3U54HG003067-13S1). Centralized read mapping and genotype calling, along with variant quality metrics and filtering, were provided by the TOPMed Informatics Research Center (grant 3R01HL-117626-02S1 and contract HHSN268201800002I) (Broad RNA Seq, Proteomics HHSN268201600034I, UW RNA Seq HHSN268201600032I, USC DNA Methylation HHSN268201600034I, Broad Metabolomics HHSN268201600038I). Phenotype harmonization, data management, sample-identity quality control, and general study coordination were provided by the TOPMed Data Coordinating Center (grants 3R01HL-120393 and U01HL-120393 and contract HHSN268180001I). The provision of genotyping data was supported in part by the National Center for Advancing Translational Sciences, Clinical and Translational Science Institute grant UL1TR001881, and National Institute of Diabetes and Digestive and Kidney Diseases Diabetes Research Center grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

The NHLBI Pooled Cohorts Study was supported by grants R21HL153700, K23HL130627, R21HL129924, and R21HL121457 from the NIH/NHLBI.

The Prevent Pulmonary Fibrosis cohort study was established in 2000 and has been supported by NIH awards Z01-ES101947, R01-HL095393, RC2-HL1011715, R21/33-HL120770, R01-HL097163, Z01-HL134585, UH2/3-HL123442, P01-HL092870, UG3/UH3-HL151865, and DoD W81XWH-17-1-0597.

The Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS) has been funded by contracts with the NIH/NHLBI (contracts HHSN268200900013C, HHSN268200900014C, HHSN268200900015C, HHSN268200900016C, HHSN268200900017C, HHSN268200900018C, HHSN268200900019C, and HHSN268200900020C) and grants from the NIH/NHLBI (grants U01 HL137880 and U24 HL141762) and supplemented through contributions made to the Foundation for the NIH and the COPD Foundation by AstraZeneca, MedImmune, Bayer Corporation (Whippany, New Jersey), Bellerophon Therapeutics (Warren, New Jersey), Boehringer-Ingelheim, Chiesi Farmaceutici S.p.A. (Parma, Italia), the Forest Research Institute, Inc. (Jersey City, New Jersey), GlaxoSmithKline, Grifols Therapeutics, Inc. (Research Triangle Park, North Carolina), Ikaria, Inc. (Hampton, New Jersey), Novartis, Nycomed Pharma GmbH (Zurich, Switzerland), ProterixBio, Inc. (Billerica, Massachusetts), Regeneron, Sanofi, Sunovion, Takeda Pharmaceutical Company (Tokyo, Japan), Theravance Biopharma, Inc. (South San Francisco, California), and Mylan N.V. (White Sulphur Springs, West Virginia).

The Strong Heart Study has been funded in whole or in part by the NHLBI (contracts 75N92019D00027, 75N92019D00028, 75N92019D00029, and 75N92019D00030). The Strong Heart Study was previously supported by research grants R01HL109315, R01HL109301, R01HL109284, R01HL109282, and R01HL109319

and cooperative agreements U01HL41642, U01HL41652, U01HL41654, U01HL65520, and U01HL65521. NJM was supported by U01CA260508 from the National Cancer Institute.

The views expressed in this manuscript are those of the authors and do not necessarily represent the views of the National Heart, Lung, and Blood Institute; the National Institutes of Health; or the U.S. Department of Health and Human Services.

Table 1: Baseline characteristics by COVID infection status

	No incident COVID-19	Non-severe COVID-19	Severe COVID-19	Total
Total sample, no. (%)	24758 (85.7)	3389 (11.7)	740 (2.6)	28887
Time to event or last follow up, median (IQR), months	17.9 (8.6, 20.4)	10.3 (4.9, 18.3)	8.5 (3.7, 11.5)	17.4 (7.8, 20.3)
Age, mean (SD), years	67.9 (13.8)	61.1 (13.5)	72.4 (13.4)	67.2 (14)
Age group, no. (%)				
< 65 years	10060 (40.6)	2090 (61.7)	218 (29.4)	12367 (42.8)
65-79 years	7972 (32.2)	897 (26.5)	214 (28.9)	9082 (31.4)
80+ years	6726 (27.2)	403 (11.9)	309 (41.7)	7437 (25.7)
Sex, no. (%)				
Female	14444 (58.3)	2095 (61.8)	418 (56.5)	16957 (58.7)
Male	10314 (41.7)	1294 (38.2)	322 (43.5)	11930 (41.3)
Race and ethnicity, no. (%)				
Non-Hispanic White	11760 (47.5)	1145 (33.8)	260 (35.2)	13165 (45.6)
Hispanic/Latino	7171 (29)	1659 (49)	216 (29.2)	9046 (31.3)
Black	5025 (20.3)	476 (14)	199 (26.9)	5700 (19.7)
Asian	445 (1.8)	19 (0.6)	8 (1.1)	472 (1.6)
American Indian	341 (1.4)	86 (2.5)	57 (7.7)	484 (1.7)
Other	15 (0.1)	4 (0.1)	0 (0)	19 (0.1)
BMI, mean (SD), kg/m^2	29.3 (6.1)	29.8 (6.1)	31.3 (6.8)	29.4 (6.1)
BMI category, no. (%)				
Normal (18.5-24.9)	5725 (23.1)	684 (20.2)	113 (15.3)	6522 (22.6)
Underweight (< 18.5)	222 (0.9)	19 (0.6)	3 (0.4)	244 (0.8)
Overweight (25-29.9)	9183 (37.1)	1248 (36.8)	225 (30.4)	10656 (36.9)
Obese (30+)	9628 (38.9)	1438 (42.4)	399 (53.9)	11465 (39.7)
Educational attainment, no. (%)				
Less than high school	3670 (14.8)	611 (18)	179 (24.2)	4460 (15.4)
High school	5859 (23.7)	847 (25)	205 (27.7)	6911 (23.9)
Some college	4636 (18.7)	637 (18.8)	122 (16.4)	5394 (18.7)
College or more	10594 (42.8)	1294 (38.2)	234 (31.6)	12122 (42)
Smoking status, no. (%)				
Never	11153 (45)	1845 (54.4)	324 (43.8)	13322 (46.1)
Former	9645 (39)	1105 (32.6)	301 (40.7)	11051 (38.3)
Current	3960 (16)	439 (13)	115 (15.5)	4514 (15.6)
Pack-years in ever-smokers, median (IQR)	17 (4.5, 34.2)	12.9 (2.7, 28.9)	14.4 (4, 32.3)	16.2 (4.3, 33.8)
Lung function,* mean (SD)				
% predicted FEV_1	93.1 (18)	94.3 (16.3)	92.4 (20.1)	93.2 (17.9)
% predicted FVC	95.9 (15.8)	96.7 (14.5)	94.3 (17.7)	95.9 (15.7)
FEV_1/FVC, %	75.7 (9.1)	77.5 (8.4)	76.3 (9.5)	75.9 (9.1)
Lung function category,* no. (%)				
Restriction	2465 (10)	305 (9)	119 (16.1)	2889 (10)
Obstruction	5159 (20.8)	475 (14)	127 (17.2)	5761 (19.9)
Normal	17134 (69.2)	2609 (77)	494 (66.8)	20237 (70.1)
Obstruction severity,* no. (%)				
Mild	2405 (9.7)	215 (6.3)	52 (7.0)	2672 (9.2)
Moderate	2310 (9.3)	222 (6.6)	56 (7.6)	2588 (9.0)
Severe	444 (1.8)	38 (1.1)	19 (2.6)	501 (1.7)

Decline in lung function,† mean (SD)				
Δ FEV_1, mL per year	34.5 (51.6)	31.9 (56.8)	40.1 (45.5)	34.4 (52)
Δ FVC, mL per year	34.9 (75.6)	31.3 (91.2)	46.4 (78.9)	34.9 (77.2)
Δ FEV_1/FVC, % per year	0.2 (1.1)	0.2 (1)	0.2 (1.1)	0.2 (1.1)
Comorbidities, no. (%)				
Hypertension‡	15310 (61.8)	1688 (49.8)	569 (76.9)	17567 (60.8)
Diabetes§	4865 (19.6)	666 (19.7)	257 (34.7)	5788 (20)
Asthma‖	2401 (9.7)	297 (8.8)	95 (12.8)	2792 (9.7)
COPD**	2817 (11.4)	361 (10.7)	115 (15.6)	3293 (11.4)
Cardiovascular disease††	2688 (10.9)	266 (7.8)	134 (18.1)	3088 (10.7)
COVID vaccination, ‡‡no. (%)				
Vaccinated	15013 (60.6)	977 (28.8)	62 (8.4)	16052 (55.6)
Not vaccinated	9745 (39.4)	2412 (71.2)	678 (91.6)	12835 (44.4)
Geographical region, no. (%)				
Middle Atlantic	4514 (18.2)	593 (17.5)	155 (20.9)	5262 (18.2)
Midwest	6145 (24.8)	821 (24.2)	174 (23.5)	7140 (24.7)
New England	2498 (10.1)	380 (11.2)	28 (3.7)	2906 (10.1)
South	7212 (29.1)	917 (27.1)	278 (37.6)	8407 (29.1)
Southwest	447 (1.8)	61 (1.8)	43 (5.9)	551 (1.9)
West	3942 (15.9)	617 (18.2)	62 (8.4)	4621 (16)
Cohort, no. (%)				
ARIC	4620 (18.7)	249 (7.3)	230 (31.1)	5099 (17.7)
CARDIA	2253 (9.1)	327 (9.6)	29 (3.9)	2609 (9)
COPDGene	3276 (13.2)	363 (10.7)	44 (5.9)	3683 (12.7)
FHS	2480 (10)	392 (11.6)	28 (3.8)	2900 (10)
HCHS	6654 (26.9)	1554 (45.9)	194 (26.2)	8402 (29.1)
JHS	1409 (5.7)	88 (2.6)	64 (8.6)	1561 (5.4)
MESA	2584 (10.4)	241 (7.1)	72 (9.7)	2897 (10)
SHS	292 (1.2)	80 (2.4)	57 (7.7)	429 (1.5)
SPIROMICS	1190 (4.8)	95 (2.8)	22 (3)	1307 (4.5)

Definition of abbreviations: ARIC= Atherosclerosis Risk in Communities; BMI= body mass index; CARDIA= Coronary Artery Risk Development in Young Adults; COPDGene = Chronic Obstructive Pulmonary Disease Genetic Epidemiology; FEV_1= forced expiratory volume in one second; FVC= forced vital capacity; FHS= Framingham Heart Study; HCHS= Hispanic Community Health Study; IQR= interquartile range; JHS= Jackson Heart Study; MESA= Multi-Ethnic Study of Atherosclerosis; SD= standard deviation; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study; SHS= Strong Heart Study

*Spirometry from the most recent examination available pre-pandemic were used for cross-sectional lung function measurements and lung function pattern. Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio <0.7, restriction defined as FEV_1/FVC ≥0.7 and FVC <80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted. Obstruction severity definitions: mild defined as FEV_1/FVC ratio <0.7 and FEV_1 ≥80% predicted; moderate defined as FEV_1/FVC ratio <0.7 and 50% ≤ FEV_1 <80% predicted; severe defined as 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 pre-pandemic divided by the years in between.

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

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

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

** Self-reported asthma or COPD assigned by adjudication or administrative criteria, as of March 2020

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

‡‡COVID vaccination at the time of infection of last follow-up.

Table 2: Associations of pre-pandemic FEV_1, FVC, and FEV_1/FVC, and rates of decline, with incident non-severe and severe COVID-19.

	Non-severe COVID-19		Severe COVID-19	
Pre-pandemic lung function* At risk = 28887				
Events (Cum. Inc.)	3389 (11.7)		740 (2.6)	
	Hazards ratio per SD (95% CI)	P-value	Hazards ratio per SD (95% CI)	P-value
FEV_1				
Unadjusted	1.10 (1.07, 1.14)	<.0001	0.88 (0.81, 0.95)	0.0008
Adjusted	1.07 (1.02, 1.13)	0.0057	0.88 (0.79, 0.97)	0.0132
FVC				
Unadjusted	1.08 (1.04, 1.12)	<.0001	0.89 (0.82, 0.96)	0.0017
Adjusted	1.09 (1.03, 1.15)	0.0018	0.88 (0.78, 0.98)	0.0177
FEV_1/FVC				
Unadjusted	1.09 (1.05, 1.13)	<.0001	1.00 (0.93, 1.08)	0.9698
Adjusted	0.99 (0.96, 1.04)	0.9355	1.01 (0.93, 1.1)	0.8190
Decline in lung function‡ At risk = 16024				
Events (Cum. Inc.)	1457 (9.1)		373 (2.3)	
	Hazards ratio per SD (95% CI)	P-value	Hazards ratio per SD (95% CI)	P-value
Δ FEV_1				
Unadjusted	0.97 (0.92, 1.02)	0.2637	1.11 (1.00, 1.23)	0.0504
Adjusted	0.99 (0.94, 1.05)	0.7678	1.07 (0.97, 1.18)	0.1941
Δ FVC				
Unadjusted	0.96 (0.91, 1.01)	0.1339	1.16 (1.05, 1.28)	0.0049
Adjusted	0.99 (0.95, 1.05)	0.9505	1.10 (0.99, 1.21)	0.0589
Δ FEV_1/FVC				
Unadjusted	1.00 (0.95, 1.06)	0.9797	0.97 (0.87, 1.07)	0.5381
Adjusted	0.99 (0.94, 1.05)	0.8315	0.99 (0.90, 1.09)	0.8246

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 pre-pandemic were used for cross-sectional lung function measurements.

‡Decline in FEV_1, FVC, or FEV_1/FVC ratio was calculated based on the first and last spirometry measurements available pre-pandemic divided by the years in between.

Table 3: Associations of pre-pandemic obstruction and restriction on spirometry with incident non-severe and severe COVID-19.

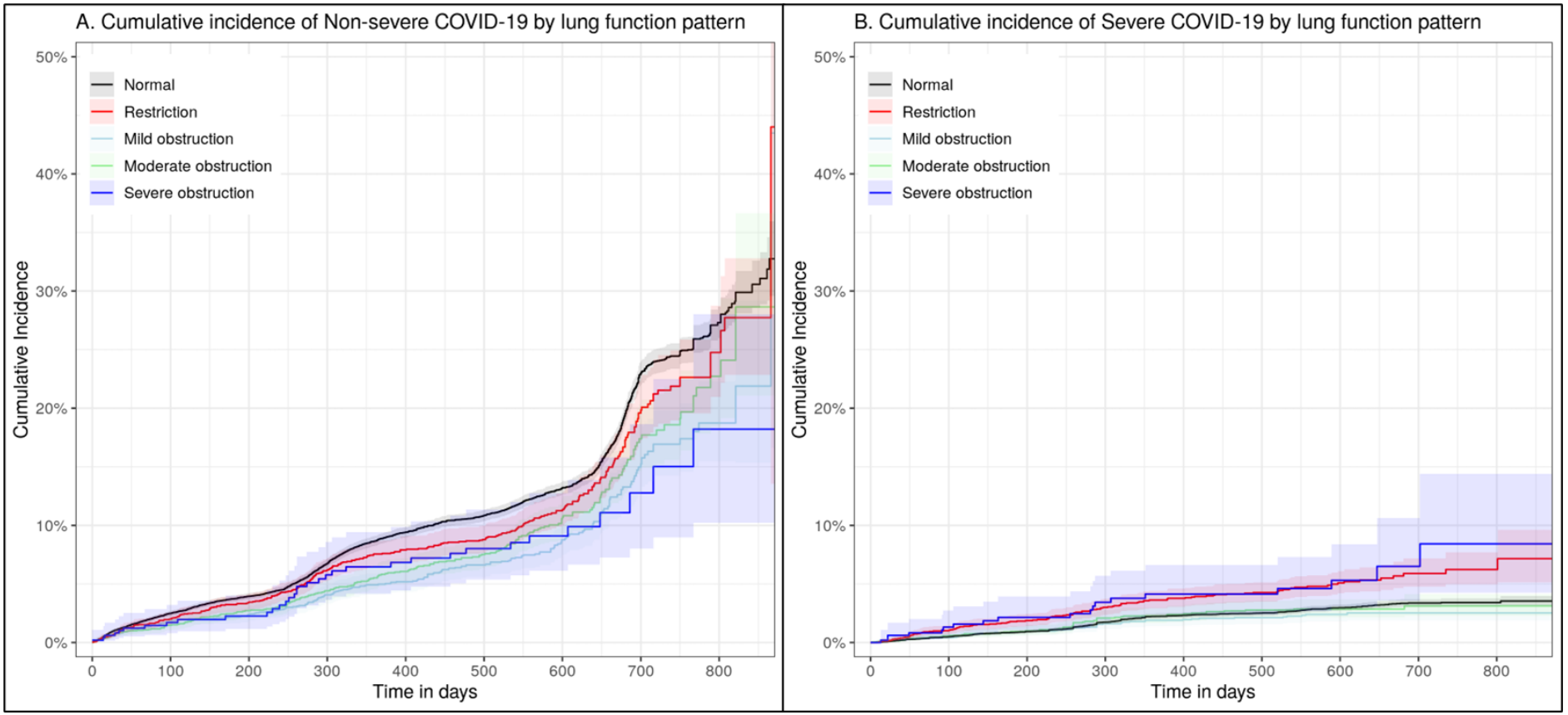
		Non-severe COVID-19			Severe COVID-19		
	At risk	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value
Normal	20237	2609 (12.9)	Referent		494 (2.4)	Referent	
Restriction	2889	298 (10.3)			119 (4.1)		
Unadjusted			0.92 (0.81, 1.03)	0.1559		1.83 (1.50, 2.24)	<.0001
Adjusted			0.88 (0.78, 0.99)	0.0419		1.42 (1.15, 1.75)	0.0011
Obstruction	5761	451 (7.8)			127 (2.2)		
Unadjusted			0.81 (0.73, 0.91)	0.0002		1.03 (0.84, 1.27)	0.7775
Adjusted			0.97 (0.87, 1.09)	0.6296		1.04 (0.83, 1.29)	0.7469
Obstruction severity							
Mild	2672	215 (8.1)			52 (2.0)		
Unadjusted			0.80 (0.69, 0.92)	0.0019		0.81 (0.60, 1.08)	0.1451
Adjusted			0.96 (0.83, 1.11)	0.5541		0.92 (0.68, 1.24)	0.5876
Moderate	2588	222 (8.6)			56 (2.2)		
Unadjusted			0.85 (0.73, 0.98)	0.0267		1.13 (0.85, 1.51)	0.3939
Adjusted			1.02 (0.88, 1.19)	0.7968		1.01 (0.75, 1.35)	0.9730
Severe	501	38 (7.9)			19 (3.8)		
Unadjusted			0.74 (0.53, 1.03)	0.0696		2.62 (1.62, 4.25)	<.0001
Adjusted			0.82 (0.58, 1.15)	0.2426		2.16 (1.32, 3.54)	0.0022

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 pre-pandemic were used for lung function pattern.

Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio <0.7, restriction defined as $FEV_1/FVC \geq 0.7$ and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted. Obstruction severity definitions: mild defined as FEV_1/FVC ratio <0.7 and $FEV_1 \geq 80\%$ predicted; moderate defined as FEV_1/FVC ratio <0.7 and $50\% \leq FEV_1 < 80\%$ predicted; severe defined as FEV_1/FVC ratio <0.7 and $FEV_1 < 50\%$ predicted.

Figure 1: Cumulative incidence of non-severe and severe COVID-19, by pre-pandemic lung function.

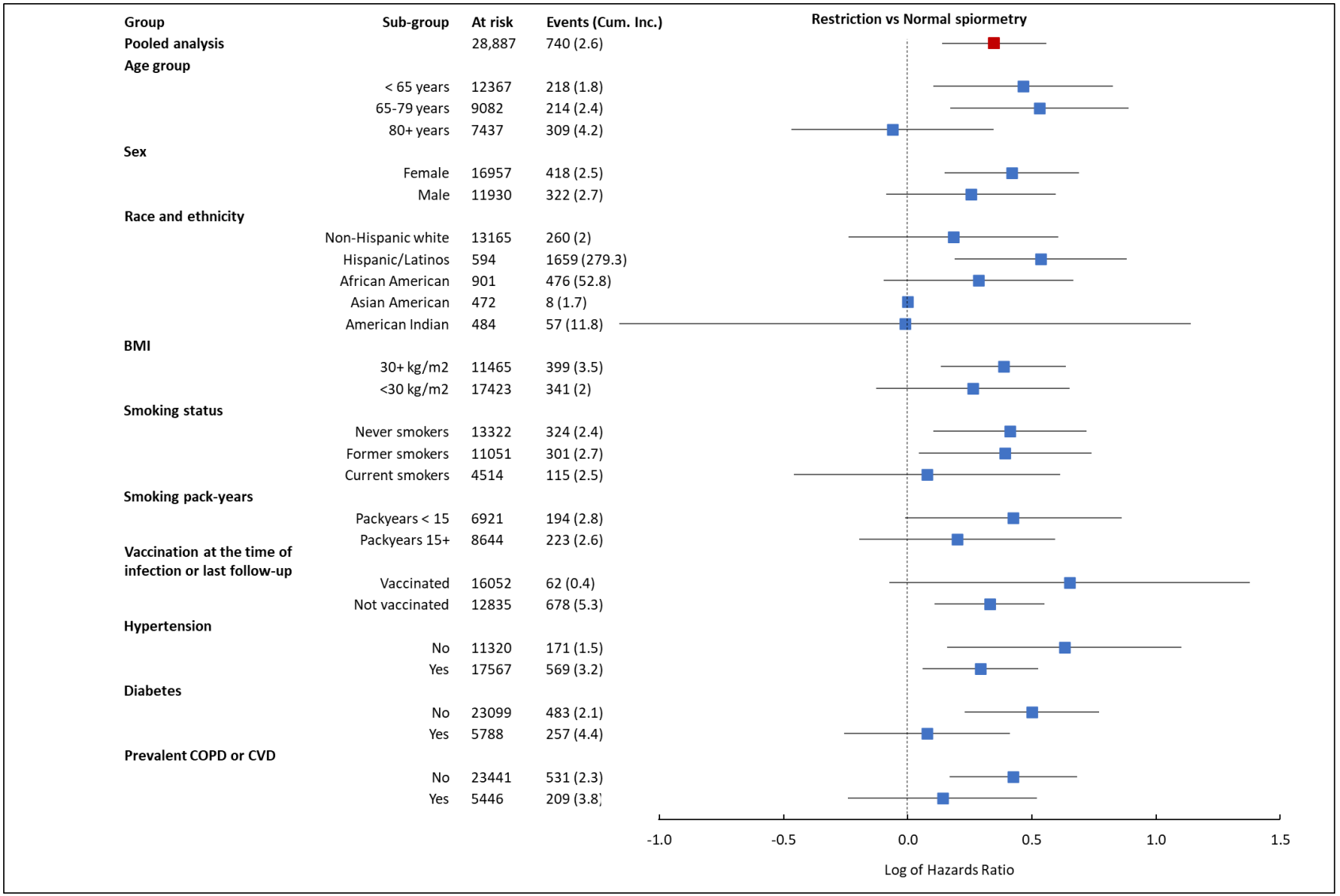


Associations of lung function with incident severe COVID infection were analyzed using Fine–Gray proportional sub-distribution hazards.

Spirometry from the most recent examination available pre-pandemic were used for cross-sectional pattern.

Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio <0.7, restriction defined as $FEV_1/FVC \geq 0.7$ and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted. Obstruction severity definitions: mild defined as FEV_1/FVC ratio <0.7 and $FEV_1 \geq 80\%$ predicted; moderate defined as FEV_1/FVC ratio <0.7 and $50\% \leq FEV_1 < 80\%$ predicted; severe defined as FEV_1/FVC ratio <0.7 and $FEV_1 < 50\%$ predicted.

Figure 2: Sub-group analyses of associations of pre-pandemic restriction versus normal spirometry with incident severe COVID-19.



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 pre-pandemic were used for lung function pattern.

Lung function pattern definitions: restriction defined as $FEV_1/FVC \geq 0.7$ and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥ 0.7 and FVC ≥80% of predicted.

SUPPLEMENTARY MATERIALS

TITLE: Associations of Pre-pandemic Spirometry With COVID-19 Outcomes: The Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study

AUTHORS:
Pallavi Balte, MBBS, PhD; Yifei Sun, PhD; Nori Allen, PhD; Alexander Arynchyn, PhD, R. Russell Bowler, MD, PhD; Shelley A. Cole, PhD; David Couper, PhD; Ryan Demmer, PhD; Margaret Doyle, PhD; Mitchell Elkind, MD; Robert Kaplan, PhD; John Kim, MD; Joyce Lee, MD; Wendy Post, MD; Vasan Ramachandran, MD; Annie Rusk, MD; David Schwartz, MD; Jason G Umans, MD, PhD; Sally Wenzel, MD; Prescott Woodruff, MD; Vanessa Xanthakis, PhD; Will McKleroy, MD; Suresh Garudadri, MD; Victor E. Ortega, MD, PhD; Elizabeth Oelsner, MD, MPH

Table E1: Study designs of cohorts included in this study

Cohort	Study design
Atherosclerosis Risk in Communities (ARIC)(22)	The ARIC study began in the mid-1980s with initial aims for its cohort component being to describe the presence of subclinical atherosclerosis (mainly via carotid ultrasound), the progression of atherosclerosis to clinical cardiovascular disease (CVD), and the association of novel risk factors with CVD. ARIC recruited its cohort of 15,792 men and women aged 45-64 in 1987-89 from four communities: Forsyth County, NC; Jackson, MS; suburban Minneapolis, MN; and Washington County, MD. The investigators used probability sampling to obtain a community wide sample, exclusively sampling African Americans in Jackson and oversampling African Americans in Forsyth County. ARIC conducted a baseline examination of cohort participants and up to seven subsequent examinations; performed annual or semi-annual telephone follow-up interviews; and throughout has identified and validated incident CVD and other outcomes, particularly cognitive decline in recent years.
Coronary Artery Risk Development in Young Adults (CARDIA)(23)	CARDIA is a study examining the development and determinants of clinical and subclinical CVD and their risk factors. It began in 1985-1986 with a cohort of 5115 Black and White men and women aged 18-30 years. The participants were selected so that there would be approximately the same number of people in subgroups of race (Black and White), gender (female and male), education (high school or less and more than high school) and age (18-24 and 25-30 years) in each of 4 field centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. These same participants were asked to participate in follow-up examinations during 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), 2010-2011 (Year 25), 2015-2016 (Year 30), and 2020-2022 (Year 35). A majority of the group has been examined at each of the follow-up examinations (91%, 86%, 81%, 79%, 74%, 72%, 72%, 71%, and 67% [despite the impact of the COVID-19 pandemic on Year 35], respectively). While the specific aims of each examination have varied, data have been collected on a variety of factors believed to be related to heart disease. These include conditions with clear links to heart disease such as blood pressure, cholesterol and other lipids, and glucose. Data have also been collected on physical measurements such as weight and body composition as well as lifestyle factors such as dietary and exercise patterns, substance use (tobacco and alcohol), behavioral and psychological variables, medical and family history, and other chemistries (e.g., insulin). In addition, subclinical atherosclerosis has been measured via echocardiography during Years 5, 10, 25, and 30, a chest CT scan during Years 15, 20, 25, and 35, an abdominal CT scan during Years 25 and 35, and carotid ultrasound during Year 20. A brain MRI was performed on a subset of participants at Years 25, 30, and 35. The CARDIA cohort, born between 1955 and 1968, has been influenced substantially by the obesity epidemic at ages younger than participants in other established NHLBI cohorts. Further investigation of the mechanisms linking obesity to derangements in cardiovascular structure and function and the etiology of clinical events promises to generate important new knowledge to inform health promotion and disease prevention efforts.
Genetic Epidemiology of COPD (COPDGene)(24)	COPDGene is a non-interventional, multicenter, longitudinal, case-control study at 21 US sites of smokers with a ≥10 pack-year history with and without COPD and healthy never smokers. The goal was to characterize disease-related phenotypes and explore associations with susceptibility genes. COPDGene research participants were extensively phenotyped with the use of comprehensive symptom and comorbidity questionnaires, spirometry, chest CT scans, and genetic and biomarker profiling. The study enrolled 10,198 participants. COPDGene has had 3 exams that include spirometry, diffusing capacity, lung CT scans and other measures; its current exam is ongoing. COPDGene examines the influence of age, sex, and race on the natural history of COPD, and the impact of comorbid conditions, chronic bronchitis, exacerbations, and asthma/COPD overlap.
Framingham Heart Study (FHS)(25)	FHS was initiated in 1948. Researchers recruited 5,209 men and women between the ages of 30 and 62 from the town of Framingham, Massachusetts, and began the first round of extensive physical examinations and lifestyle interviews that they would later analyze for common patterns related to CVD development. Since 1948, the subjects have returned to the study every two years for an examination consisting of a detailed medical history, physical examination, and laboratory tests, and in 1971, the study enrolled a second-generation

	cohort – 5,124 of the original participants' adult children and their spouses – to participate in similar examinations. The second examination of the Offspring cohort occurred eight years after the first examination, and subsequent examinations have occurred approximately every four years thereafter. In April 2002 the Study entered a new phase: the enrollment of a third generation of participants, the grandchildren of the original cohort. The first examination of the Third Generation Study was completed in July 2005 and involved 4,095 participants. Thus, the FHS has evolved into a prospective, community-based, three generation family study. In addition to research studies focused on risk factors, subclinical CVD and clinically apparent CVD, Framingham investigators have also collaborated with leading researchers from around the country and throughout the world on projects involving some of the major chronic illnesses in men and women, including dementia, osteoporosis and arthritis, nutritional deficiencies, eye diseases, hearing disorders, and chronic obstructive lung disease.
Hispanic Community Health Study/Study of Latinos (HCHS/SOL)(26)	HCHS/SOL is an ongoing population based prospective cohort study of 16,415 community dwelling Hispanic/Latino adults aged 18-74 years at baseline, recruited from four urban field centers with large populations of Hispanics/ Latinos (Bronx, NY; Chicago, IL; Miami, FL; and San Diego, CA). A two-stage area probability sample of households was selected, with stratification and over-sampling at each stage to ensure a diverse and representative sample. Participants self-identified as Hispanic/Latino and of Cuban, Dominican, Mexican, Puerto Rican, Central American, South American, or other/more than one heritage. Study participants underwent an extensive clinic exam and assessments to determine baseline risk factors (2008-2011), and annual telephone follow-up interviews for ascertainment of cardiovascular and pulmonary events. A second clinic visit was conducted in 2014-2017, and a third clinic visit is now in process (2020-2022). The overall retention rate as of December 2019 was 81.9%. The primary goals of the HCHS/SOL are to describe: (1) the prevalence and incidence of cardiovascular, pulmonary, and other major chronic conditions (2) the risk and/or protective factors associated with these conditions; and (3) the relationships between the initial sociodemographic and health profiles and future health events in the target population. The study to date has revealed a high prevalence of cardiovascular risk factors, with significant variability by Hispanic/Latino heritage and sociodemographic factors such as income and time in the United States.
Jackson Heart Study (JHS)(27)	The JHS is a community-based cohort study evaluating risk factors for cardiovascular and related diseases among adult African Americans residing in the three counties (Hinds, Madison, and Rankin) that make up the Jackson, Mississippi metropolitan area. Data and biologic materials have been collected from 5,306 participants, including a nested family cohort of 1,498 members of 264 families. The age at enrollment for the unrelated cohort was 35-84 years; the family cohort included related individuals >21 years old. Participants have provided extensive medical and psychosocial histories and had an array of physical and biochemical measurements and diagnostic procedures during a baseline examination (2000-2004) and two follow-up examinations (2005-2008 and 2009-2012). Samples for genomic DNA were collected during the first two examinations. Annual follow-up interviews and cohort surveillance of cardiovascular events and mortality are continuing, and a fourth examination is in progress.
Multi-Ethnic Study of Atherosclerosis (MESA)(28)	MESA is a study of the characteristics of subclinical CVD (disease detected non-invasively before it has produced clinical signs and symptoms) and the risk factors that predict progression to clinically overt cardiovascular disease or progression of the subclinical disease. MESA researchers study a diverse, population-based sample of 6,814 asymptomatic men and women aged 45-84. Thirty-eight percent of the recruited participants are white, 28 percent African American, 22 percent Hispanic, and 12 percent Asian, predominantly of Chinese descent. Participants were recruited from six field centers across the United States: Wake Forest University, Columbia University, Johns Hopkins University, University of Minnesota, Northwestern University and University of California – Los Angeles. Each participant received an extensive physical exam and determination of coronary calcification, ventricular mass and function, flow-mediated endothelial vasodilation, carotid intimal-medial wall thickness and presence of echogenic lucencies in the carotid artery, lower extremity vascular insufficiency, arterial wave forms, electrocardiographic (ECG) measures, standard coronary risk factors, sociodemographic factors, lifestyle factors, and psychosocial factors. Selected repetition of subclinical disease measures and risk factors at follow-up visits allows study of the progression of disease. Blood samples have been assayed for putative biochemical risk factors and stored for case-control studies. DNA has

	been extracted and lymphocytes cryopreserved (for possible immortalization) for study of candidate genes and possibly, genome-wide scanning, expression, and other genetic techniques. Participants are being followed for identification and characterization of cardiovascular disease events, including acute myocardial infarction and other forms of coronary heart disease (CHD), stroke, and congestive heart failure; for CVD interventions; and for mortality. In addition to the six Field Centers, MESA involves a Coordinating Center, a Central Laboratory, and Central Reading Centers for Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Ultrasound, and Electrocardiography (ECG). Protocol development, staff training, and pilot testing were performed in the first 18 months of the study. The first examination took place over two years, from July 2000 – July 2002. It was followed by five examination periods that were 17-20 months in length. Participants have been contacted every 9 to 12 months throughout the study to assess clinical morbidity and mortality. The MESA Lung Study enrolled 3,965 MESA participants in 2004-06 and has performed spirometry 3 times and full-lung CT scans twice, most recently in 2016-18.
Strong Heart Study (SHS)(29)	SHS was designed to respond to the recommendations from the Subcommittee on Cardiovascular and Cerebrovascular Disease of the Secretary of Health and Human Service's Task Force on Black and Minority Health that concluded that information on cardiovascular disease (CVD) in American Indians was inadequate. In its initial stages, the SHS included three components. The first was a survey to determine cardiovascular disease mortality rates from 1984 to 1994 among tribal members aged 35-74 years of age residing in the 3 study areas (the community mortality study). The second was the clinical examination of 4,500 eligible tribal members. The third component is the morbidity and mortality (M&M) surveillance of these 4,500 participants. SHS has completed three clinical examinations of the original Cohort in Phase I 1989-1991; Phase II: 1993-1995; 1998-1999, respectively. In Phases III-V, SHS expanded to include genetic epidemiologic studies and family-based genetics studies due to the importance of genetics in the occurrence of CVD. Phase VI was a surveillance of the original SHS cohort and of the SHS family study participants to better understand CVD, cancer, liver disease, and inflammation in American Indians. Phase VII is currently underway with continued surveillance beginning February 2019 for a seven-year duration. The SHS Phase VII exam serves as a platform for in-depth ancillary studies that are funded outside of the SHS contracts.
Subpopulations and Intermediate Outcome Measures in COPD Study (SPIROMICS)(30)	SPIROMICS is a multi-center, observational, longitudinal case-control study designed to guide future development of therapies for COPD by 1) providing robust criteria for sub-classifying COPD participants into groups most likely to benefit from a given therapy during a clinical trial, thereby improving the chances of successful outcome; and 2) identifying biomarkers and phenotypes that can be used as intermediate outcomes to reliably predict clinical benefit during therapeutic trials. The baseline exam included morphometric measures, spirometry, six-minute walk, an inspiratory and expiratory chest CT, and a set of standardized questionnaires. Biospecimens, including plasma, serum, DNA, urine and induced sputum, have been collected and stored. SPIROMICS has recruited 2,983 COPD cases and controls, 40-80 years old with 20+ pack-years of smoking at 12 US sites in 2010–2015.SPIROMICS has 5 follow-up exams, that include spirometry, lung CT scans, sputum induction and, in a subset, bronchoscopies; its current exam is ongoing.

Table E2: Definition of infection, infection severity, and time-to-recovery via C4R wave 1 and wave 2 questionnaires

Domain	Question	Wave 1, no. of cohorts	Wave 2, no. of cohorts
COVID-19 testing	Have you ever had any kind of test for COVID-19?	9	9
	Have you ever had a test that showed you had COVID-19? Please include all types of tests.	9	9
COVID-19 self-report	Do you think that you have had COVID-19?	9	9
	Were you tested at that time?	1 (FHS)	9
	Did a healthcare provider ever tell you that you had COVID-19?	9	9
COVID-19 hospitalization	Since March 2020, have you had an overnight stay in a hospital for any illness related to COVID-19?	9	9
	While in the hospital, did you have any of the following treatments: A breathing tube or ventilator? ICU monitoring?	4 (COPDGene, FHS, MESA, and SPIROMICS)	9
COVID-19 symptoms	When a healthcare provider told you that you had COVID-19, did you have any of the following?- Symptoms of COVID-19 (e.g., fever, cough, trouble breathing)	4 (COPDGene, FHS, MESA, and SPIROMICS)	9
	When you knew or thought that you had COVID-19 the first time, did you have any symptoms?	1 (FHS)	9

Definition of abbreviations: COPDGene = Chronic Obstructive Pulmonary Disease Genetic Epidemiology; FHS= Framingham Heart Study; MESA= Multi-Ethnic Study of Atherosclerosis; SPIROMICS = Subpopulations and Intermediate Outcome Measures in COPD Study

Table E3: Associations between lung function at the most recent pre-pandemic visit and incident non-severe and severe COVID-19, among participants without clinical COPD or CVD.

		Non-severe COVID-19			Severe COVID-19		
	At risk	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value
Lung function pattern†							
Normal	17301	2269 (13.1)	Ref.		369 (2.1)	Ref.	
Restriction	2170	242 (11.2)	0.89 (0.77, 1.02)	0.0970	79 (3.6)	1.53 (1.18, 1.97)	0.0012
Obstruction	3970	345 (8.7)	0.99 (0.88, 1.13)	0.9266	83 (2.1)	1.08 (0.83, 1.4)	0.5825
Obstruction severity							
Mild	2103	175 (8.3)	0.96 (0.82, 1.13)	0.6537	39 (1.9)	0.99 (0.70, 1.40)	0.9531
Moderate	1636	152 (9.3)	1.06 (0.89, 1.27)	0.4991	30 (1.8)	0.93 (0.63, 1.38)	0.7151
Severe	233	18 (7.7)	0.80 (0.49, 1.29)	0.3594	14 (6.0)	3.41 (1.91, 6.12)	<.0001
Lung function*							
FEV_1 per SD	23441	2855 (12.2)	1.08 (1.02, 1.14)	0.0072	531 (2.3)	0.91 (0.81, 1.03)	0.1500
FVC per SD	23441	2855 (12.2)	1.08 (1.02, 1.15)	0.0080	531 (2.3)	0.92 (0.81, 1.05)	0.2205
FEV_1/FVC per SD	23441	2855 (12.2)	1 (0.96, 1.05)	0.8662	531 (2.3)	1.01 (0.91, 1.11)	0.9009
Decline in lung function‡							
Δ FEV_1 per SD	12787	1212 (9.5)	0.98 (0.92, 1.04)	0.4466	256 (2)	1.08 (0.96, 1.22)	0.1834
Δ FVC per SD	12787	1212 (9.5)	0.99 (0.93, 1.05)	0.6337	256 (2)	1.12 (1.00, 1.26)	0.0503
Δ FEV_1/FVC per SD	12787	1212 (9.5)	0.98 (0.93, 1.05)	0.6324	256 (2)	0.97 (0.85, 1.1)	0.6418

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.

*Spirometry from the most recent examination available pre-pandemic were used for cross-sectional lung function measurements and lung function pattern.

†Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio < 0.7, restriction defined as FEV_1/FVC ≥0.7 and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted. Obstruction severity definitions: mild defined as FEV_1/FVC ratio <0.7 and FEV_1 ≥80% predicted; moderate defined as FEV_1/FVC ratio <0.7 and 50% ≤ FEV_1 <80% predicted; severe defined as 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 pre-pandemic divided by the years in between.

Table E4: Associations between lung function at the most recent pre-pandemic visit and incident non-severe and severe COVID-19, limiting to confirmed cases.

		Non-severe COVID-19			Severe COVID-19		
	At risk	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value
Lung function pattern†							
Normal	20237	2001 (9.9)	Ref.		481 (2.4)	Ref.	
Restriction	2889	232 (8)	0.93 (0.8, 1.07)	0.2914	119 (4.1)	1.45 (1.18, 1.79)	0.0005
Obstruction	5761	301 (5.2)	0.97 (0.84, 1.11)	0.6238	125 (2.2)	1.06 (0.85, 1.31)	0.6248
Obstruction severity							
Mild	2672	142 (5.3)	0.95 (0.80, 1.14)	0.5895	51 (1.9)	0.94 (0.69, 1.27)	0.6720
Moderate	2588	136 (5.3)	0.99 (0.83, 1.20)	0.9721	55 (2.1)	1.02 (0.76, 1.38)	0.8881
Severe	501	23 (4.6)	0.89 (0.58, 1.37)	0.5948	19 (3.8)	2.22 (1.36, 3.64)	0.0015
Lung function*							
FEV_1 per SD	28887	2534 (8.8)	1.07 (1.01, 1.13)	0.0305	725 (2.5)	0.87 (0.78, 0.96)	0.0076
FVC per SD	28887	2534 (8.8)	1.08 (1.02, 1.15)	0.0110	725 (2.5)	0.87 (0.78, 0.97)	0.0154
FEV_1/FVC per SD	28887	2534 (8.8)	0.99 (0.95, 1.04)	0.6700	725 (2.5)	1.08 (0.98, 1.19)	0.1291
Decline in lung function‡							
Δ FEV_1 per SD	16024	937 (5.8)	0.98 (0.91, 1.04)	0.4567	363 (2.3)	1.09 (0.99, 1.21)	0.0734
Δ FVC per SD	16024	937 (5.8)	1.01 (0.95, 1.08)	0.7494	363 (2.3)	1.01 (0.92, 1.12)	0.8159
Δ FEV_1/FVC per SD	16024	937 (5.8)	0.95 (0.89, 1.02)	0.1431	363 (2.3)	1.01 (0.92, 1.12)	0.8159

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.

*Spirometry from the most recent examination available pre-pandemic were used for cross-sectional lung function measurements and lung function pattern.

†Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio < 0.7, restriction defined as FEV_1/FVC ≥0.7 and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted. Obstruction severity definitions: mild defined as FEV_1/FVC ratio <0.7 and FEV_1 ≥80% predicted; moderate defined as FEV_1/FVC ratio <0.7 and 50% ≤ FEV_1 <80% predicted; severe defined as 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 pre-pandemic divided by the years in between.

Table E5: Associations between lung function at the most recent pre-pandemic visit and incident non-severe and severe COVID-19, among participants with complete covariate data**.**

		Non-severe COVID-19			Severe COVID-19		
	At risk	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value
Lung function pattern†							
Normal	16041	2304 (14.4)	Ref.		336 (2.1)	Ref.	
Restriction	2303	270 (11.7)	0.85 (0.74, 0.97)	0.0142	92 (4)	1.48 (1.16, 1.89)	0.0016
Obstruction	4087	365 (8.9)	0.93 (0.82, 1.05)	0.2155	75 (1.8)	0.88 (0.67, 1.16)	0.3548
Obstruction severity							
Mild	2073	175 (8.3)	0.90 (0.77, 1.07)	0.2252	31 (1.5)	0.73 (0.49, 1.08)	0.1140
Moderate	1754	169 (9.6)	0.99 (0.84, 1.17)	0.9142	37 (2.1)	0.99 (0.69, 1.41)	0.9447
Severe	260	24 (9.2)	0.67 (0.43, 1.06)	0.0859	7 (2.7)	1.30 (0.60, 2.80)	0.5062
Lung function*							
FEV_1 per SD	22431	2939 (13.1)	1.11 (1.05, 1.17)	0.0002	503 (2.2)	0.9 (0.79, 1.02)	0.1045
FVC per SD	22431	2939 (13.1)	1.11 (1.04, 1.17)	0.0007	503 (2.2)	0.86 (0.75, 0.99)	0.0339
FEV_1/FVC per SD	22431	2939 (13.1)	1.02 (0.98, 1.06)	0.3709	503 (2.2)	1.07 (0.97, 1.18)	0.1988
Decline in lung function‡							
Δ FEV_1 per SD	12040	1207 (10)	1.01 (0.95, 1.07)	0.7412	237 (2)	1.08 (0.95, 1.22)	0.2509
Δ FVC per SD	12040	1207 (10)	1 (0.94, 1.06)	0.9812	237 (2)	1.08 (0.95, 1.24)	0.2409
Δ FEV_1/FVC per SD	12040	1207 (10)	1.02 (0.96, 1.09)	0.5753	237 (2)	1.03 (0.9, 1.19)	0.6621

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.

*Spirometry from the most recent examination available pre-pandemic were used for cross-sectional lung function measurements and lung function pattern.

†Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio < 0.7, restriction defined as FEV_1/FVC ≥0.7 and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted. Obstruction severity definitions: mild defined as FEV_1/FVC ratio <0.7 and FEV_1 ≥80% predicted; moderate defined as FEV_1/FVC ratio <0.7 and 50% ≤ FEV_1 <80% predicted; severe defined as 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 pre-pandemic divided by the years in between.

Table E6: Associations between lung function pattern defined using lower-limit-of-normal at the most recent pre-pandemic visit and incident non-severe and severe COVID-19.

		Non-severe COVID-19			Severe COVID-19		
	At risk	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value	Events (Cum. Inc.)	Hazards ratio (95% CI)	P-value
Lung function pattern*							
Normal	22305	2721 (12.2)	Ref.		553 (2.5)	Ref.	
Restriction	2613	287 (11)	0.82 (0.72, 0.93)	0.0027	105 (4)	1.38 (1.11, 1.72)	0.0040
Obstruction	3969	381 (9.6)	0.95 (0.85, 1.06)	0.3770	82 (2.1)	1.09 (0.85, 1.40)	0.4944
Obstruction severity							
Mild	1458	164 (11.2)	0.92 (0.79, 1.09)	0.3362	24 (1.6)	0.91 (0.60, 1.37)	0.6412
Moderate	2039	182 (8.9)	0.99 (0.85, 1.17)	0.9922	40 (2.0)	1.00 (0.72, 1.41)	0.9842
Severe	472	35 (7.4)	0.85 (0.60, 1.20)	0.3468	18 (3.8)	2.45 (1.47, 4.06)	0.0005

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.

*Spirometry from the most recent examination available pre-pandemic were used for cross-sectional lung function measurements and lung function pattern. Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio < lower-limit-of-normal (LLN), restriction defined as FEV_1/FVC ≥LLN and FVC < LLN of predicted, and normal pattern defined as FEV_1/FVC ratio ≥LLN and FVC ≥LLN of predicted. GOLD 1: FEV_1/FVC ratio < LLN and FEV_1 ≥80% predicted; GOLD 2: FEV_1/FVC ratio < LLN and 50% ≤ FEV_1 <80% predicted; GOLD 3: FEV_1/FVC ratio < LLN and 30% ≤ FEV_1 <50% predicted; GOLD 4: FEV_1/FVC ratio < LLN and FEV_1 <30% predicted.

Table E7: Associations between lung function at the most recent pre-pandemic visit and severe COVID-19 among participants with incident COVID-19.

	At risk	Events (Cum. Inc.)	Odds ratio for severe COVID-19 vs non-severe COVID-19 (95% CI)	P-value
Lung function pattern†				
Normal	3103	494 (15.9)	Ref.	
Restriction	424	119 (28.1)	**1.92 (1.46, 2.52)**	**<.0001**
Obstruction	602	127 (21.1)	1.00 (0.5, 1.33)	0.9915
Obstruction severity				
Mild	267	52 (19.5)	0.82 (0.56, 1.21)	0.3285
Moderate	278	56 (20.1)	0.99 (0.67, 1.45)	0.9528
Severe	57	19 (33.3)	**2.75 (1.40, 5.40)**	**0.0032**
Lung function*				
FEV_1 per SD	4129	740 (17.9)	**0.81 (0.71, 0.92)**	**0.0012**
FVC per SD	4129	740 (17.9)	**0.77 (0.67, 0.89)**	**0.0003**
FEV_1/FVC per SD	4129	740 (17.9)	1.05 (0.95, 1.17)	0.3074
Decline in lung function‡				
Δ FEV_1 per SD	1830	373 (20.4)	1.14 (0.99, 1.31)	0.0754
Δ FVC per SD	1830	373 (20.4)	1.12 (0.99, 1.27)	0.0776
Δ FEV_1/FVC per SD	1830	373 (20.4)	1.00 (0.87, 1.15)	0.9672

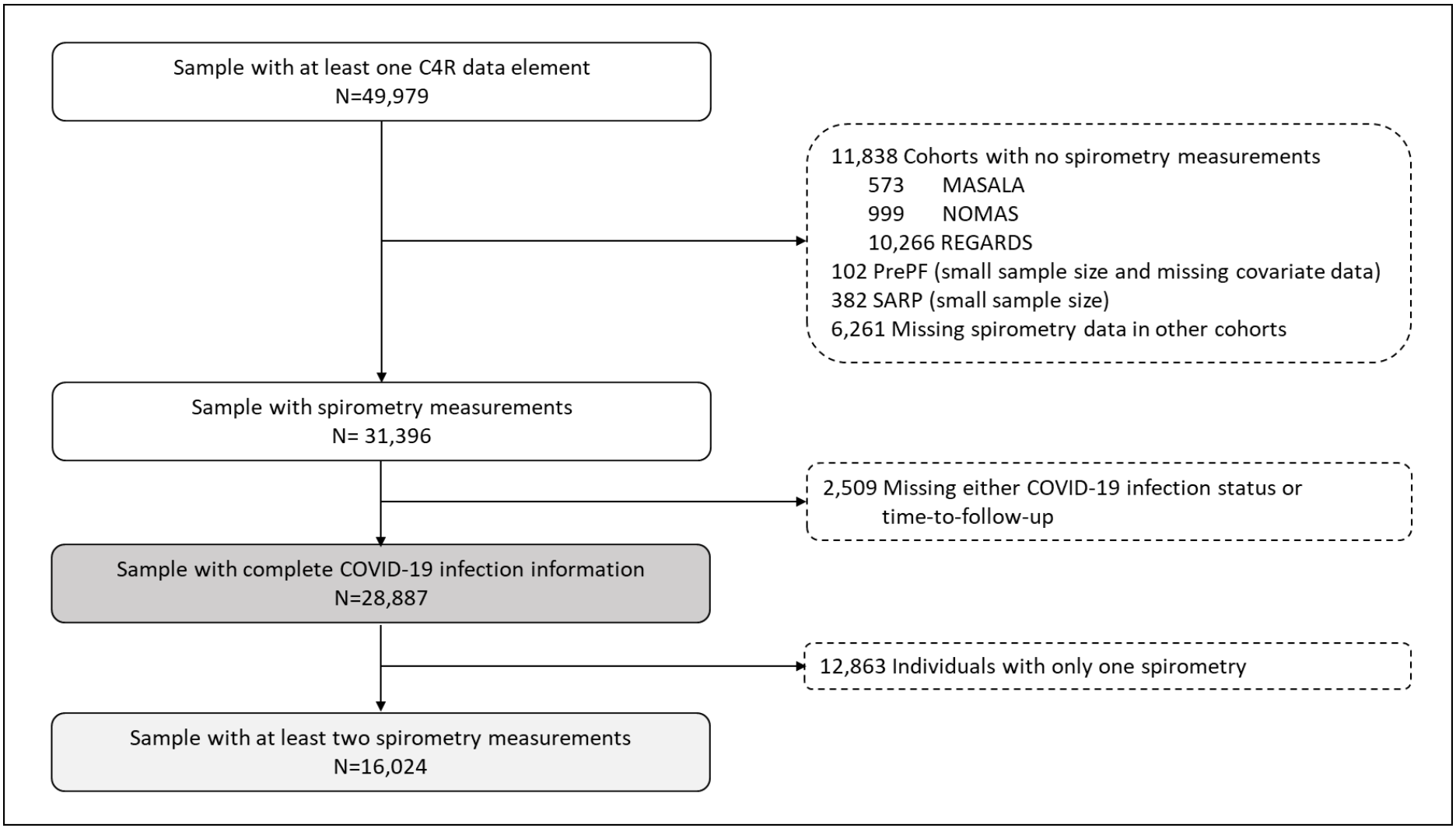
Analysis sample is restricted to individuals with non-severe or severe COVID-19. Models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID vaccination status, and geographic region; cohort was treated as a stratum variable.

*Spirometry from the most recent examination available pre-pandemic were used for cross-sectional lung function measurements and lung function pattern.

†Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio < 0.7, restriction defined as FEV_1/FVC ≥0.7 and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted. Obstruction severity definitions: mild defined as FEV_1/FVC ratio <0.7 and FEV_1 ≥80% predicted; moderate defined as FEV_1/FVC ratio <0.7 and 50% ≤ FEV_1 <80% predicted; severe defined as FEV_1/FVC ratio <0.7 and FEV_1 <50% predicted.

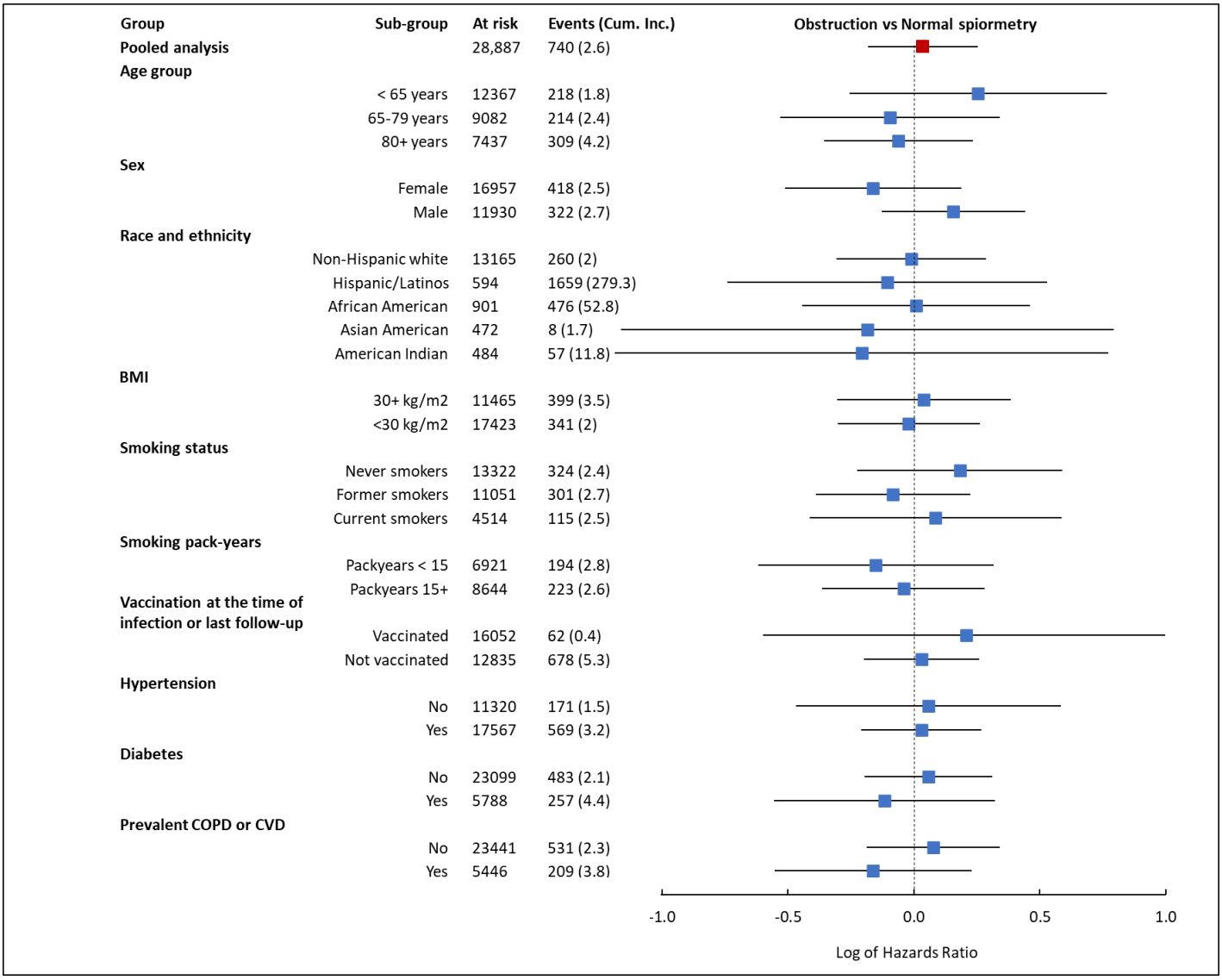
‡Decline in FEV_1, FVC, or FEV_1/FVC ratio was calculated based on the first and last spirometry measurements available pre-pandemic divided by the years in between.

Figure E1: CONSORT



Definition of abbreviations: MASALA= Mediators of Atherosclerosis in South Asians Living in America study; NOMAS= The Northern Manhattan Study; PrePF= Prevent Pulmonary Fibrosis study; REGARDS= REasons for Geographic And Racial Differences in Stroke study; SARP= Severe Asthma Research Program study

Figure E2: Sub-group analyses of associations of pre-pandemic obstruction versus normal spirometry with incident severe COVID-19.

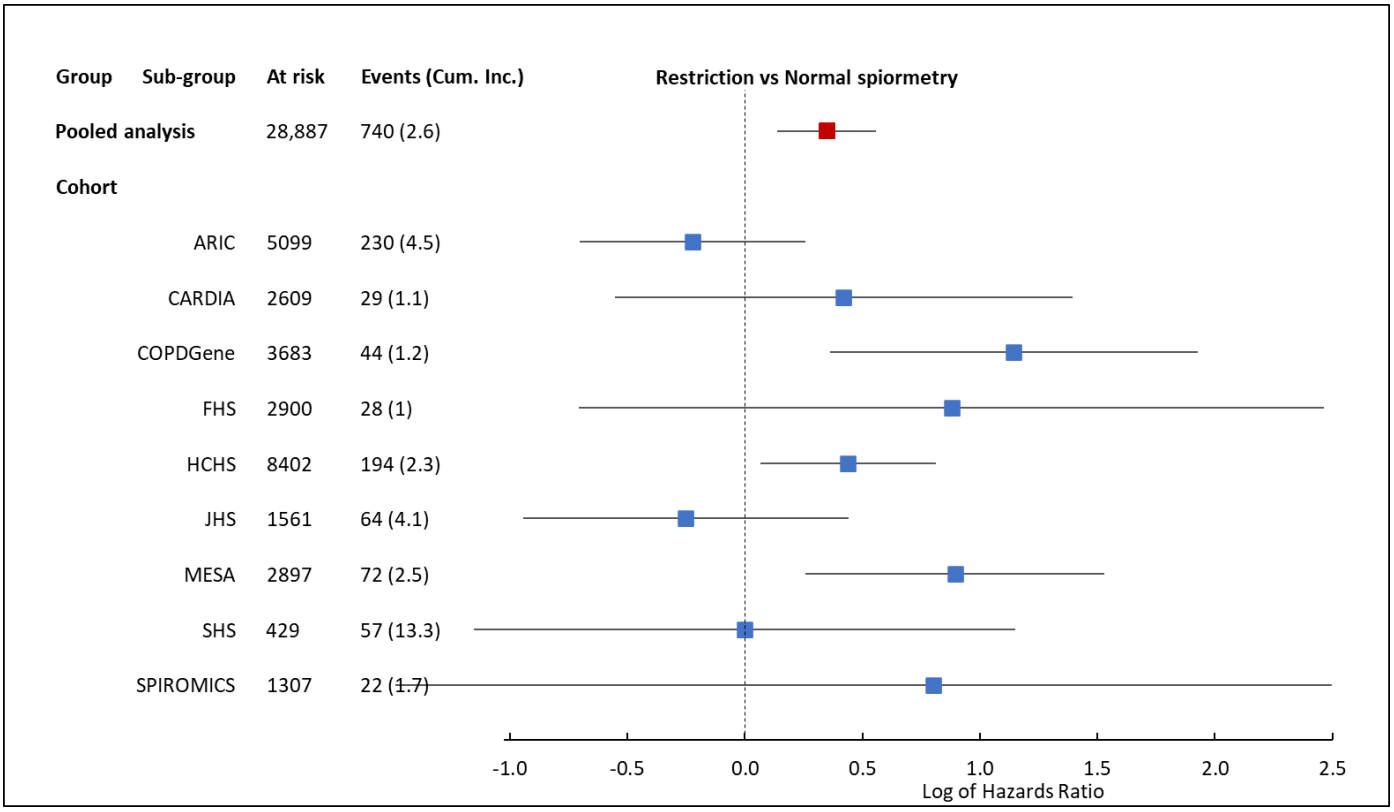


Cause-specific hazards models were used. Fully adjusted models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID vaccination status, and geographic region; cohort was treated as a stratum variable.

Spirometry from the most recent examination available pre-pandemic were used for lung function pattern.

Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio <0.7 and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted.

Figure E3. Associations of pre-pandemic restriction versus normal spirometry with incident severe COVID-19, stratified by cohort.

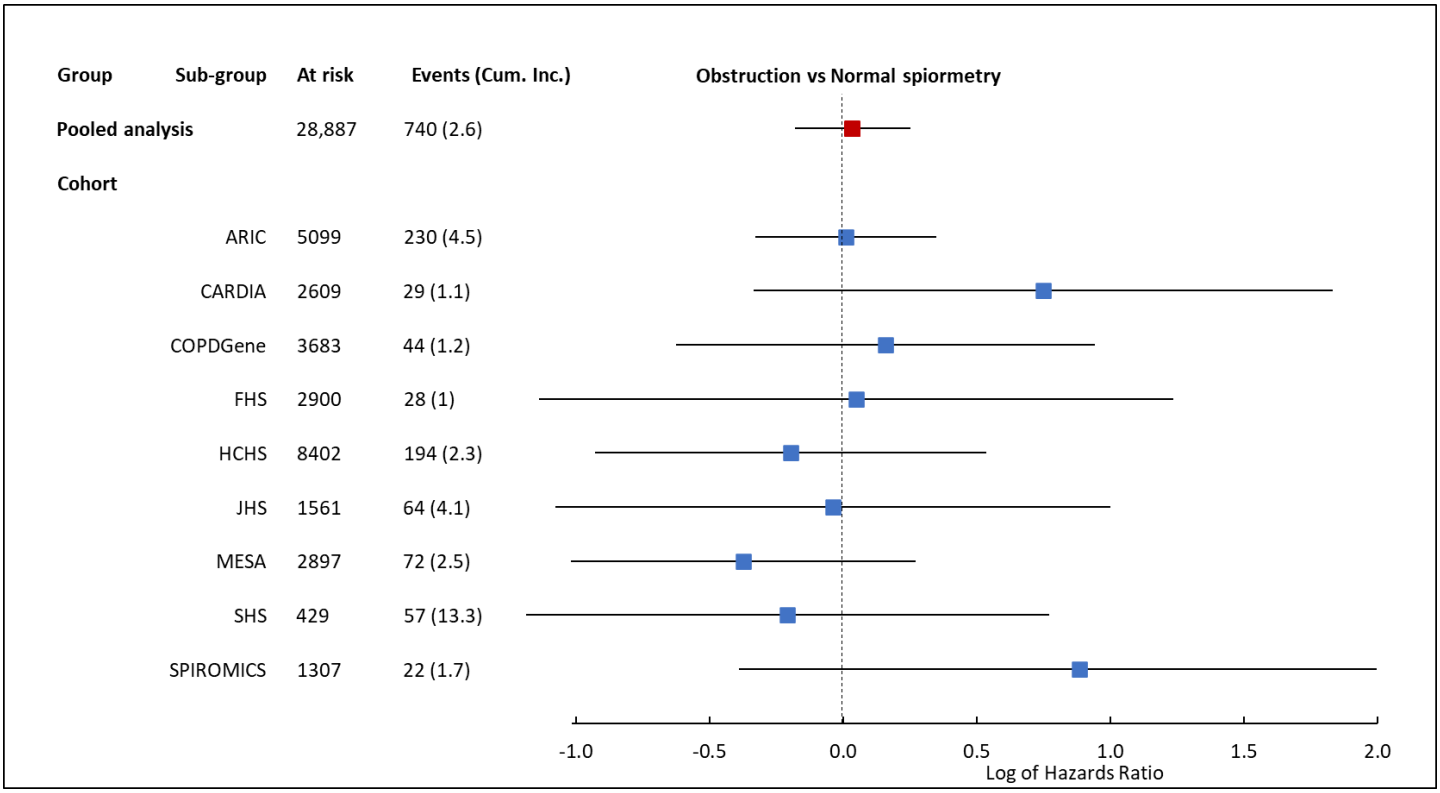


Cause-specific hazards models were used. Fully adjusted models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID vaccination status, and geographic region; cohort was treated as a stratum variable.

Spirometry from the most recent examination available pre-pandemic were used for lung function pattern.

Lung function pattern definitions: restriction defined as FEV_1/FVC ≥0.7 and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted.

Figure E4. Associations of pre-pandemic obstruction versus normal spirometry with incident severe COVID-19, stratified by cohort.

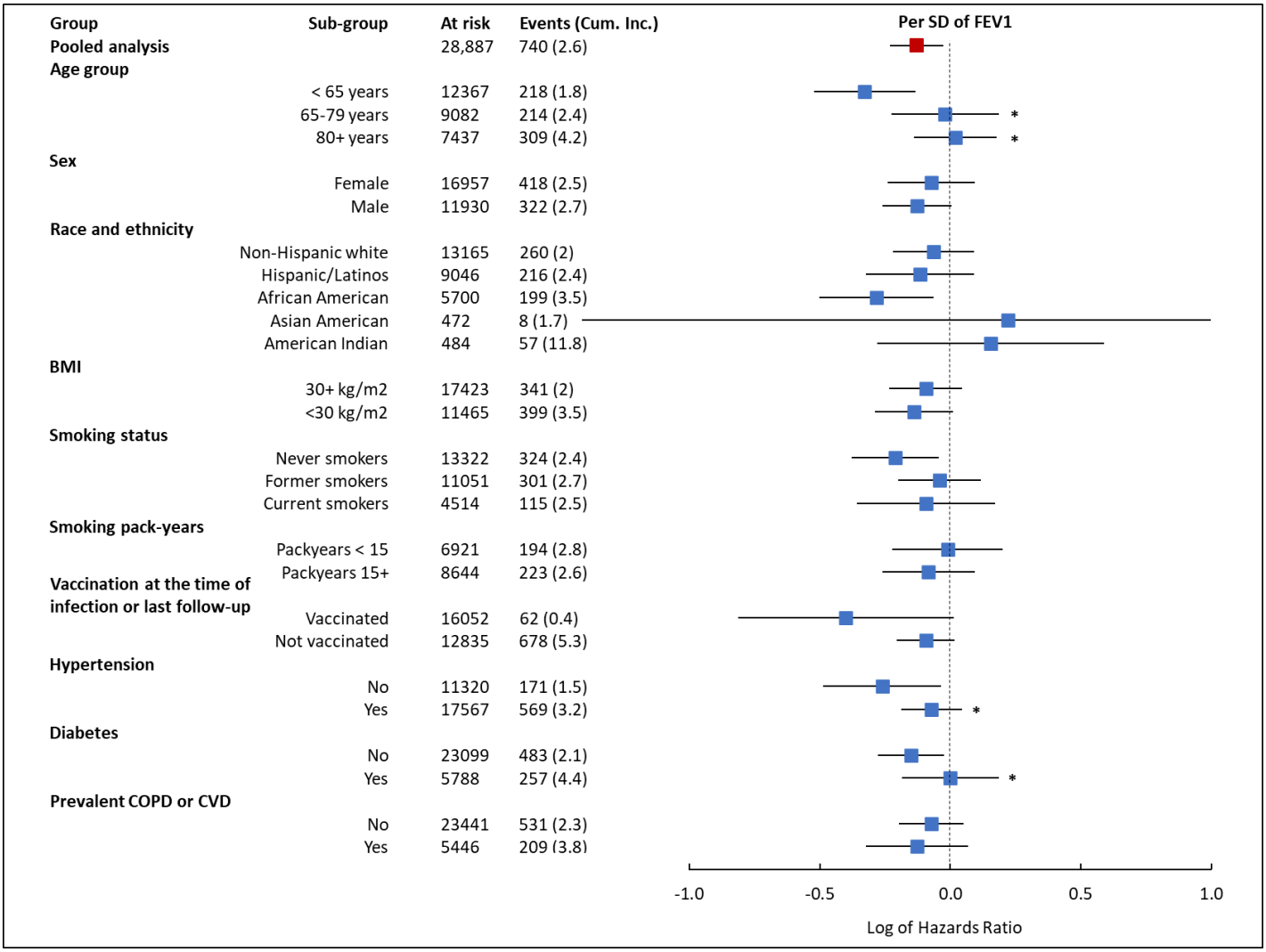


Cause-specific hazards models were used. Fully adjusted models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID vaccination status, and geographic region; cohort was treated as a stratum variable.

Spirometry from the most recent examination available pre-pandemic were used for lung function pattern.

Lung function pattern definitions: obstruction defined as FEV_1/FVC ratio <0.7 and FVC<80% of predicted, and normal pattern defined as FEV_1/FVC ratio ≥0.7 and FVC ≥80% of predicted.

Figure E5: Sub-group analyses of associations of pre-pandemic FEV_1 with incident severe COVID-19.

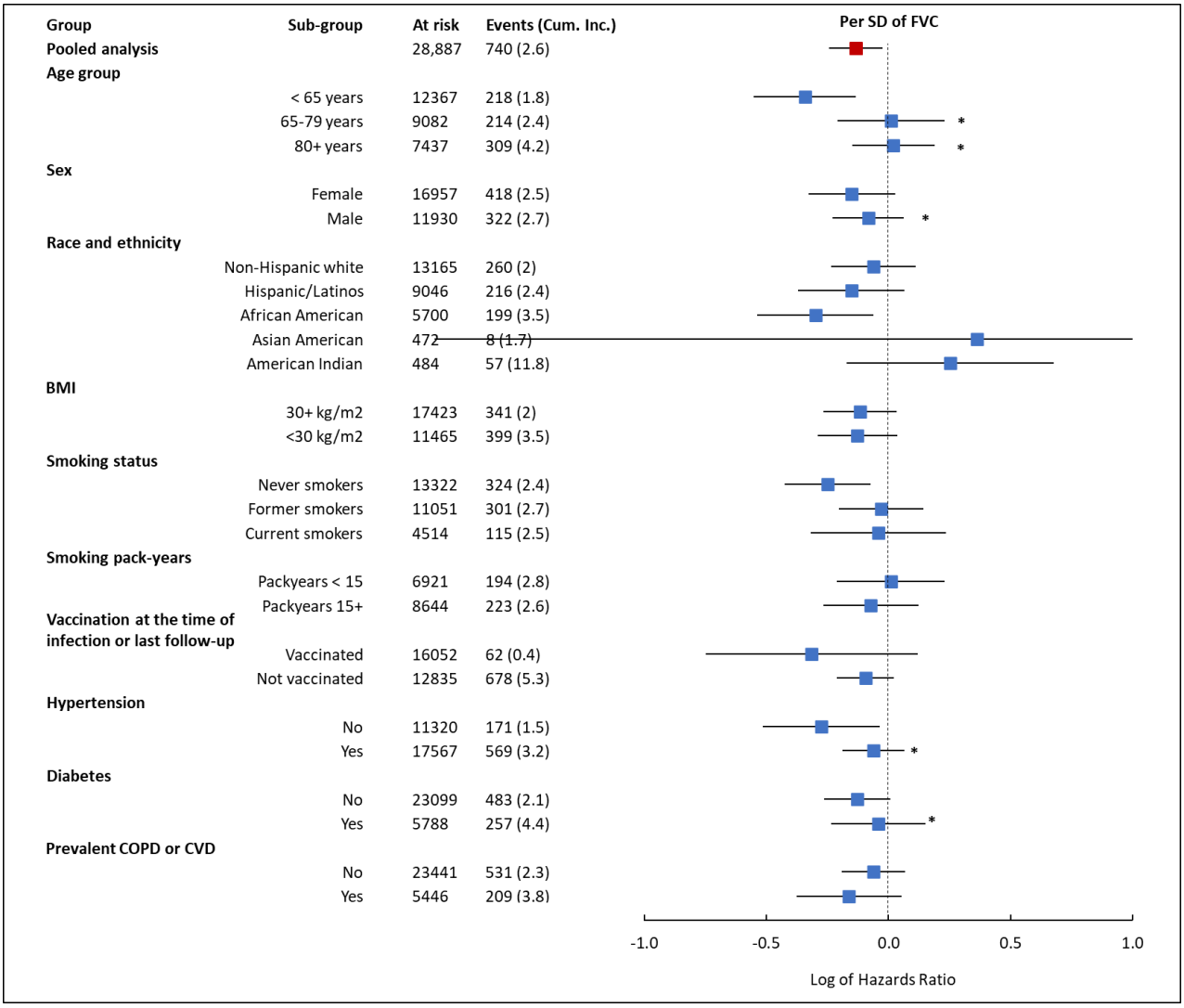


Cause-specific hazards models were used. Fully adjusted models were adjusted for age, sex, race and ethnicity, education, body mass index, smoking status, smoking pack-years, comorbidities, COVID vaccination status, and geographic region; cohort was treated as a stratum variable.

Spirometry from the most recent examination available pre-pandemic were used for cross-sectional lung function measurements.

*Significant p-value for the interaction term.

Figure E6: Sub-group analyses of associations of pre-pandemic FVC with incident severe COVID-19.



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 pre-pandemic were used for cross-sectional lung function measurements.

*Significant p-value for the interaction term.

REFERENCES

1. Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature* 2023; 613: 130-137.
2. Aveyard P, Gao M, Lindson N, Hartmann-Boyce J, Watkinson P, Young D, Coupland CAC, Tan PS, Clift AK, Harrison D, Gould DW, Pavord ID, Hippisley-Cox J. Association between pre-existing respiratory disease and its treatment, and severe COVID-19: a population cohort study. *The Lancet Respiratory Medicine* 2021; 9: 909-923.
3. Fadista J, Kraven LM, Karjalainen J, Andrews SJ, Geller F, Baillie JK, Wain LV, Jenkins RG, Feenstra B. Shared genetic etiology between idiopathic pulmonary fibrosis and COVID-19 severity. *EBioMedicine* 2021; 65: 103277.
4. Gerayeli FV, Milne S, Cheung C, Li X, Yang CWT, Tam A, Choi LH, Bae A, Sin DD. COPD and the risk of poor outcomes in COVID-19: A systematic review and meta-analysis. *EClinicalMedicine* 2021; 33: 100789.
5. Sahu KK, Mishra AK, Martin K, Chastain I. COVID-19 and restrictive lung disease: A deadly combo to trip off the fine balance. *Monaldi Archives for Chest Disease* 2020; 90.
6. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, Curtis HJ, Mehrkar A, Evans D, Inglesby P, Cockburn J, McDonald HI, MacKenna B, Tomlinson L, Douglas IJ, Rentsch CT, Mathur R, Wong AYS, Grieve R, Harrison D, Forbes H, Schultze A, Croker R, Parry J, Hester F, Harper S, Perera R, Evans SJW, Smeeth L, Goldacre B. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584: 430-436.
7. Au Yeung SL, Li AM, He B, Kwok KO, Schooling CM. Association of smoking, lung function and COPD in COVID-19 risk: a two-step Mendelian randomization study. *Addiction* 2022; 117: 2027-2036.
8. Ford ES, Mannino DM, Wheaton AG, Giles WH, Presley-Cantrell L, Croft JB. Trends in the prevalence of obstructive and restrictive lung function among adults in the United States: findings from the National Health and Nutrition Examination surveys from 1988-1994 to 2007-2010. *Chest* 2013; 143: 1395-1406.
9. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance-United States, 1971-2000. 2002.
10. Biener AI, Decker SL, Rohde F. Prevalence and Treatment of Chronic Obstructive Pulmonary Disease (COPD) in the United States. *JAMA* 2019; 322: 602-602.
11. Backman H, Eriksson B, Hedman L, Stridsman C, Jansson S-A, Sovijärvi A, Lindberg A, Rönmark E, Lundbäck B. Restrictive spirometric pattern in the general adult population: methods of defining the condition and consequences on prevalence. *Respiratory medicine* 2016; 120: 116-123.
12. Torén K, Schiöler L, Brisman J, Malinovschi A, Olin A-C, Bergström G, Bake B. Restrictive spirometric pattern and true pulmonary restriction in a general population sample aged 50 - 64 years. *BMC Pulmonary Medicine* 2020; 20: 55.
13. Jeganathan N, Sathananthan M. The prevalence and burden of interstitial lung diseases in the USA. *ERJ Open Research* 2022; 8: 00630-02021.
14. Guerra S, Sherrill DL, Venker C, Ceccato CM, Halonen M, Martinez FD. Morbidity and mortality associated with the restrictive spirometric pattern: a longitudinal study. *Thorax* 2010; 65: 499-504.
15. Silvestre OM, Nadruz W, Roca GQ, Claggett B, Solomon SD, Mirabelli MC, London SJ, Loehr LR, Shah AM. Declining Lung Function and Cardiovascular Risk. *Journal of the American College of Cardiology* 2018; 72: 1109-1122.
16. Wan ES, Balte P, Schwartz JE, Bhatt SP, Cassano PA, Couper D, Daviglus ML, Dransfield MT, Gharib SA, Jacobs DR, Jr, Kalhan R, London SJ, Navas-Acien A, O'Connor GT, Sanders JL, Smith BM, White W, Yende S, Oelsner EC. Association Between Preserved Ratio Impaired Spirometry and Clinical Outcomes in US Adults. *JAMA* 2021; 326: 2287-2298.
17. Eckhardt CM, Balte PP, Barr RG, Bertoni AG, Bhatt SP, Cuttica M, Cassano PA, Chaves P, Couper D, Jacobs DR, Kalhan R, Kronmal R, Lange L, Loehr L, London SJ, O'Connor GT, Rosamond W, Sanders J, Schwartz JE, Shah A, Shah SJ, Smith L, White W, Yende S, Oelsner EC. Lung function impairment and risk of incident heart failure: the NHLBI Pooled Cohorts Study. *European Heart Journal* 2022; 43: 2196-2208.
18. Sin DD, Man SFP. Why Are Patients With Chronic Obstructive Pulmonary Disease at Increased Risk of Cardiovascular Diseases? *Circulation* 2003; 107: 1514-1519.
19. Sin DD, Man SFP. Chronic Obstructive Pulmonary Disease as a Risk Factor for Cardiovascular Morbidity and Mortality. *Proceedings of the American Thoracic Society* 2005; 2: 8-11.
20. Cuttica MJ, Colangelo LA, Dransfield MT, Bhatt SP, Rana JS, Jacobs DR, Thyagarajan B, Sidney S, Lewis CE, Liu K, Lloyd-Jones D, Washko G, Kalhan R. Lung Function in Young Adults and Risk of Cardiovascular Events Over 29 Years: The CARDIA Study. *Journal of the American Heart Association* 2018; 7: e010672.

21. Oelsner EC, Krishnaswamy A, Balte PP, Allen NB, Ali T, Anugu P, Andrews HF, Arora K, Asaro A, Barr RG, Bertoni AG, Bon J, Boyle R, Chang AA, Chen G, Coady S, Cole SA, Coresh J, Cornell E, Correa A, Couper D, Cushman M, Demmer RT, Elkind MSV, Folsom AR, Fretts AM, Gabriel KP, Gallo LC, Gutierrez J, Han MLK, Henderson JM, Howard VJ, Isasi CR, Jacobs Jr DR, Judd SE, Mukaz DK, Kanaya AM, Kandula NR, Kaplan RC, Kinney GL, Kucharska-Newton A, Lee JS, Lewis CE, Levine DA, Levitan EB, Levy BD, Make BJ, Malloy K, Manly JJ, Mendoza-Puccini C, Meyer KA, Min Y-IN, Moll MR, Moore WC, Mauger D, Ortega VE, Palta P, Parker MM, Phipatanakul W, Post WS, Postow L, Psaty BM, Regan EA, Ring K, Roger VL, Rotter JI, Rundek T, Sacco RL, Schembri M, Schwartz DA, Seshadri S, Shikany JM, Sims M, Hinckley Stukovsky KD, Talavera GA, Tracy RP, Umans JG, Vasan RS, Watson KE, Wenzel SE, Winters K, Woodruff PG, Xanthakis V, Zhang Y, Zhang Y, Investigators ftCR. Collaborative Cohort of Cohorts for COVID-19 Research (C4R) Study: Study Design. *American Journal of Epidemiology* 2022; 191: 1153-1173.
22. The ARIC Investigators. The atherosclerosis risk in communit (ARIC) study: design and objectives. *American journal of epidemiology* 1989; 129: 687-702.
23. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs Jr DR, Liu K, Savage PJ. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *Journal of clinical epidemiology* 1988; 41: 1105-1116.
24. Regan EA, Hokanson JE, Murphy JR, Make B, Lynch DA, Beaty TH, Curran-Everett D, Silverman EK, Crapo JD. Genetic epidemiology of COPD (COPDGene) study design. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2011; 7: 32-43.
25. Tsao CW, Vasan RS. Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. *International journal of epidemiology* 2015; 44: 1800-1813.
26. Sorlie PD, Avilés-Santa LM, Wassertheil-Smoller S, Kaplan RC, Daviglus ML, Giachello AL, Schneiderman N, Raij L, Talavera G, Allison M. Design and implementation of the Hispanic community health study/study of Latinos. *Annals of epidemiology* 2010; 20: 629-641.
27. Taylor H, Wilson J, Jones D, Sarpong D, Srinivasan A, Garrison R. Toward resolution of cardiovascular health disparities in African Americans: design and methods of the Jackson Heart Study. vol. 15, pp: S6-4-17. Ethn Dis; 2005.
28. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, JacobsJr DR, Kronmal R, Liu K. Multi-ethnic study of atherosclerosis: objectives and design. *American journal of epidemiology* 2002; 156: 871-881.
29. Lee ET, Welty TK, Fabsitz R, Cowan LD, Le N-A, Oopik AJ, Cucchiara AJ, Savage PJ, Howard BV. The Strong Heart Study A study of cardiovascular disease in American Indians: design and methods. *American journal of epidemiology* 1990; 132: 1141-1155.
30. Couper D, LaVange LM, Han M, Barr RG, Bleecker E, Hoffman EA, Kanner R, Kleerup E, Martinez FJ, Woodruff PG. Design of the subpopulations and intermediate outcomes in COPD study (SPIROMICS). *Thorax* 2013: thoraxjnl-2013-203897.
31. Oelsner EC, Balte PP, Cassano PA, Couper D, Enright PL, Folsom AR, Hankinson J, Jacobs DR, Jr., Kalhan R, Kaplan R, Kronmal R, Lange L, Loehr LR, London SJ, Navas Acien A, Newman AB, O'Connor GT, Schwartz JE, Smith LJ, Yeh F, Zhang Y, Moran AE, Mwasongwe S, White WB, Yende S, Barr RG. Harmonization of Respiratory Data From 9 US Population-Based Cohorts: The NHLBI Pooled Cohorts Study. *American Journal of Epidemiology* 2018; 187: 2265-2278.
32. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *American journal of respiratory and critical care medicine* 1999; 159: 179-187.
33. Division of Nutrition PA, and Obesity, National Center for Chronic Disease Prevention and Health Promotion. Defining Adult Overweight & Obesity. 2022. Available from: https://www.cdc.gov/obesity/basics/adult-defining.html.
34. Attaway AA, Zein J, Hatipoğlu US. SARS-CoV-2 infection in the COPD population is associated with increased healthcare utilization: An analysis of Cleveland clinic's COVID-19 registry. *EClinicalMedicine* 2020; 26.
35. Parra-Bracamonte GM, Lopez-Villalobos N, Parra-Bracamonte FE. Clinical characteristics and risk factors for mortality of patients with COVID-19 in a large data set from Mexico. *Annals of epidemiology* 2020; 52: 93-98. e92.
36. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, Babu S, Barber CM, Barratt S, Bendstrup E, Bianchi S, Villegas DC, Chaudhuri N, Chua F, Coker R, Chang W, Crawshaw A, Crowley LE, Dosanjh D, Fiddler CA, Forrest IA, George PM, Gibbons MA, Groom K, Haney S, Hart SP, Heiden E, Henry M, Ho L-P, Hoyles RK, Hutchinson J, Hurley K, Jones M, Jones S, Kokosi M, Kreuter M, MacKay LS, Mahendran S, Margaritopoulos G,

Molina-Molina M, Molyneaux PL, O'Brien A, O'Reilly K, Packham A, Parfrey H, Poletti V, Porter JC, Renzoni E, Rivera-Ortega P, Russell A-M, Saini G, Spencer LG, Stella GM, Stone H, Sturney S, Thickett D, Thillai M, Wallis T, Ward K, Wells AU, West A, Wickremasinghe M, Woodhead F, Hearson G, Howard L, Baillie JK, Openshaw PJM, Semple MG, Stewart I, Jenkins RG. Outcome of Hospitalization for COVID-19 in Patients with Interstitial Lung Disease. An International Multicenter Study. *American Journal of Respiratory and Critical Care Medicine* 2020; 202: 1656-1665.

37. Fenger RV, Gonzalez-Quintela A, Vidal C, Husemoen L-L, Skaaby T, Thuesen BH, Aadahl M, Madsen F, Linneberg A. The longitudinal relationship of changes of adiposity to changes in pulmonary function and risk of asthma in a general adult population. *BMC pulmonary medicine* 2014; 14: 1-10.
38. Jones RL, Nzekwu M-MU. The effects of body mass index on lung volumes. *Chest* 2006; 130: 827-833.
39. Clift AK, von Ende A, Tan PS, Sallis HM, Lindson N, Coupland CAC, Munafò MR, Aveyard P, Hippisley-Cox J, Hopewell JC. Smoking and COVID-19 outcomes: an observational and Mendelian randomisation study using the UK Biobank cohort. *Thorax* 2022; 77: 65-73.
40. Mahamat-Saleh Y, Fiolet T, Rebeaud ME, Mulot M, Guihur A, El Fatouhi D, Laouali N, Peiffer-Smadja N, Aune D, Severi G. Diabetes, hypertension, body mass index, smoking and COVID-19-related mortality: a systematic review and meta-analysis of observational studies. *BMJ open* 2021; 11: e052777.
41. Alqahtani JS, Oyelade T, Aldhahir AM, Mendes RG, Alghamdi SM, Miravitlles M, Mandal S, Hurst JR. Reduction in hospitalised COPD exacerbations during COVID-19: A systematic review and meta-analysis. *PLOS ONE* 2021; 16: e0255659.
42. Hurst JR, Cumella A, Niklewicz CN, Philip KE, Singh V, Hopkinson NS. Acceptability of hygiene, face covering and social distancing interventions to prevent exacerbations in people living with airways diseases. *Thorax* 2021.
43. McAuley H, Hadley K, Elneima O, Brightling CE, Evans RA, Steiner MC, Greening NJ. COPD in the time of COVID-19: an analysis of acute exacerbations and reported behavioural changes in patients with COPD. *ERJ Open Research* 2021; 7: 00718-02020.
44. Kato B, Gulsvik A, Vollmer W, Janson C, Studnika M, Buist S, Burney P. Can spirometric norms be set using pre-or post-bronchodilator test results in older people? *Respiratory research* 2012; 13: 1-11.
45. Mannino DM, Diaz-Guzman E, Buist S. Pre-and post-bronchodilator lung function as predictors of mortality in the Lung Health Study. *Respiratory research* 2011; 12: 1-7.