Lung function decline in relation to COVID-19 in the general population: a matched cohort study with pre-pandemic assessment of lung function

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Abstract: In non-hospitalized individuals, COVID-19 related decline of lung function was small but measurable and comparable to published minimal clinical important differences for FEV_1 and FVC.

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Abstract

Objective: To quantify the potential decline in dynamic lung volumes following coronavirus disease 2019 (COVID-19) in the general population.

Methods: A prospective matched cohort study of adult Copenhagen General Population Study (CGPS) participants with a pre-pandemic spirometry available. CGPS individuals with a positive SARS-CoV-2 polymerase chain reaction (PCR) test performed a repeat spirometry, a questionnaire regarding respiratory symptoms and a diffusing capacity test for carbon monoxide. A matched uninfected CGPS control sample was used, and simple regression and linear mixed effect models were computed to study lung function decline.

Results: A total of 606 were included. 92/107 (85.9%) of individuals with a positive SARS-CoV-2 PCR test experienced COVID-19 symptoms and 12 (11.2%) were hospitalized. Spirometry was performed at a median (interquartile range) of 5.6 (3.9-12.8) months after positive SARS-CoV-2 PCR test. COVID-19 was associated with an adjusted 7.3 mL (95%CI: 0.3-14.3) and 22.6 mL (95%CI: 13.1-32.0) steeper decline in annual FEV_1 and FVC or a total of 113.8 and 301.3 ml lower FEV_1 and FVC from baseline to follow up. Results were robust in analyses restricted to individuals not requiring hospitalization.

Conclusion: COVID-19 related decline of dynamic lung volumes in the general population not requiring hospitalization were small but measurable.

Keywords: ■ coronavirus disease 2019 ■ forced expiratory volume in one second ■ forced vital capacity ■ respiratory symptoms ■ severe acute respiratory syndrome coronavirus 2 ■ spirometry

Introduction

Acute viral infections of the lower respiratory tract may contribute to transient lung function decline to various degrees depending on the causative pathogen [1, 2]. Viral infections may also contribute to chronic obstructive pulmonary disease (COPD) and asthma morbidity [3, 4], and although the cause-effect relationship between viral infections and lung function may be difficult to establish, there is evidence suggesting that some viral infection episodes contribute to long-term decline in lung function [5, 6]. Specifically, evidence from severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome (MERS) patients suggests that initial impairment of lung function persists for some individuals for months to years [7, 8]. Early evidence from investigations of mid- and long-term consequences of coronavirus disease 2019 (COVID-19) suggests a reduction in forced vital capacity (FVC), diffusing capacity or transfer factor of the lung for carbon monoxide (DLCO) and total lung capacity (TLC) [9–12]. However, current studies focus primarily on hospitalized COVID-19 patients and consequences of severe disease, i.e. acute respiratory distress syndrome (ARDS) or who require mechanical ventilation, versus milder disease in these patients [9]. Moreover, an important limitation of these studies is lack of pre-COVID-19 pulmonary assessment.

Even though, COVID-19 in non-hospitalized individuals from the general population is unlikely to be associated with substantial lung injury, the scale of the pandemic, with more than 230 million infections worldwide, underlines the importance of lung function studies in this population as lower lung function, even within the normal range, is a risk factor for higher respiratory morbidity and mortality [13]. Thus, we aimed to assess longitudinal change in lung function and respiratory symptoms in individuals with COVID-19 versus unaffected individuals recruited from a general population cohort with pre-existing lung function tests available.

Materials and Methods

Study population and ethics

Participants were recruited from the Copenhagen General Population Study (CGPS), an on-going population-based cohort study initiated in November 2003 randomly recruiting individuals from the greater Copenhagen area [14, 15]. We invited and recruited individuals living in the Capital Region of Denmark to reflect the adult Danish general population. All participants completed a comprehensive questionnaire, underwent a physical health examination including spirometry, and provided blood for biochemical analyses. For the present sub-study, we included individuals who had previously performed a dynamic spirometry in the CGPS and had a positive SARS-CoV-2 test. Data on SARS-CoV-

2 real-time reverse transcription polymerase chain reaction (RT-PCR) tests was retrieved from electronic laboratory databases from the three clinical microbiology departments serving the capital region of Copenhagen. We extracted both negative and positive RT-PCR results. The majority of the CGPS participants are assumed to be serviced by these clinical microbiological departments by providing the vast majority of RT-PCR testing for both hospitalized and non-hospitalized patients. A flow diagram depicting the inclusion of CGPS participants with a positive SARS-CoV-2 RT-PCR test is presented in Figure 1. The study was approved by the Regional Ethics Committee of Copenhagen (H-KF-01-144/0; H-20072296). Written and oral consent was obtained from all participants.

Data collection and lung function

Baseline examinations were conducted between the 2nd of December 2003 and the 26th of September 2018. Follow up examinations in individuals with confirmed SARS-CoV-2 was conducted between the 15th of March 2021 and 9th of June 2021. Positive SARS-CoV-2 RT-PCR tests were identified between March 9, 2020 and January 16, 2021 with the median date being November 26, 2020. Information relating to respiratory risk factors and self-reported respiratory morbidity was obtained through identical questionnaires used at baseline and at follow-up on the same day and just prior to lung function procedures. Questionnaires were reviewed at the day of attendance by an investigator together with the participant. Smoking status was reported as current, former, and never-smoker. Cumulative tobacco consumption was assessed as pack-years, calculated as the average number of cigarettes consumed per day divided by 20 and multiplied with the number of years smoked. Dyspnea was defined by the modified Medical Research Council (mMRC) scale with a score $\geq$2 signifying more breathlessness. Sputum production was defined as productive cough for a duration of 3 months per year. A COVID-19 specific questionnaire using identical questions as well as COVID-19 specific questions were assessed in individuals with a confirmed SARS-CoV-2 RT-PCR test at follow-up on the same day as the lung function tests. Information about COVID-19 hospital admissions was retrieved from patient records.

All participants contributed with two spirometries. A portable EasyOne® Plus ultrasonic spirometer (ndd Medical, Zürich, Switzerland) was used to perform spirometry at baseline in all participants. Dynamic lung volumes, total lung capacity (TLC) and diffusing capacity of carbon monoxide (DLCO) was measured using the portable single-breath diffusing capacity device (EasyOne Pro®, ndd Medical Technologies) at follow-up in individuals with a confirmed SARS-CoV-2 using the same instructions and procedure. All spirometries were performed as described previously [16]. TLC was measured using a single breath manoeuvre by helium dilution [17]. Limitations to single-breath TLC measurement in the presence of airway obstruction were corrected for by the device using

previously published equations [18]. Predicted values for FEV_1 and FVC and the lower limit of normal (LLN) of FEV_1/FVC were calculated using the reference equations provided by the Global Lung Function Initiative (GLI) [19]. For acceptable quality for DLCO testing an inspiratory volume >85% of best vital capacity was used.

Statistics

We included CGPS participants who had baseline and follow up spirometry available as controls. For each CGPS participants with a confirmed SARS-CoV-2 test, we identified up to 5 controls with two spiromteries and matched on age at baseline and follow-up spirometries (±2.5 years at each age) and matched exactly on smoking status, ethnicity and sex and with a follow-up spirometry performed before the COVID-19 pandemic (December 2019).

Descriptive statistics included means ± standard deviation (SD) or median (interquartile range, IQR) as appropriate. Statistical significance tests included Student´s t-tests, nonparametric tests, or chi-square tests as appropriate. To investigate the rate of lung function decline in COVID-19 patients and controls, we performed repeated-measures linear mixed effects models with random case-control pair effect, random person intercept, and random age-related slope to account for baseline variability between participants. Mean yearly FEV_1 (mL) decline was the primary outcome of interest. Secondary outcome measures were mean yearly changes in FVC and FEV_1/FVC. We included fixed effects in the model that were adjusted for and which were decided *a priori.* These included age, sex, height, smoking status at baseline, pack-years of tobacco consumption at baseline and COVID-19 status. An interaction between COVID-19 status and age was included in the model to assess whether COVID-19 modifies the age-related slope of lung function decline. Different covariance structures were investigated and compared to an unstructured covariance structure using Information criteria (AIC/BIC). Overall, the independent covariance structure seemed most appropriate when evaluating across all outcomes based on AIC and parsimony. Sensitivity analyses which excluded hospitalized COVID-19 patients, and which were restricted to individuals with a lung function test performed > 180 days after a positive SARS-CoV-2 RT-PCR test. We also performed a simple linear regression with the primary outcome as change in lung function (FEV_1 and FVC measured in ml and percent predicted) while additionally adjusting for the time since baseline spirometry. A two-sided p-value of less than .05 was considered significant. Statistical analyses were conducted using R statistical software version 4.1.0 and STATA/SE 15.1 for Windows (StataCorp, College Station, Texas).

Results

Baseline characteristics of study participants

A total of 107 COVID-19 patients and 499 controls were included (Figure 1). Mean age was 57 (8.7) years and 56 (8.4) years for COVID-19 patients and controls, respectively. Participants were all caucasians and generally more likely to be female (53.3% and 53.1% in the two groups). Smoking history (8 (7.5%) and 35 (7.0%) current smokers and 54 (50.5%) and 244 (48.9%) former smokers), cumulative smoking (9.9 and 9.6 pack years), self-reported respiratory disease at baseline and dynamic lung volume measures at baseline were comparable (Table 1).

Characteristics of individuals with positive SARS-CoV-2 RT-PCR test

COVID-19 symptoms were reported by 92 (85.9%) among participants with a positive SARS-CoV-2 RT-PCR test (Table 2). The most frequently reported symptom was fatigue which was reported by 88 (82.2%). A total of 41 (38.3%) replied affirmative to the question "Did you at any time experience difficulties in breathing in relation to COVID-19", and 12 (11.2%) of those with a positive SARS-CoV-2 RT-PCR test were hospitalized. One patient (0.8%) required mechanical ventilation. Follow up examinations were performed 6.4 (2.8) and 8.4 (2.6) years after baseline examinations for COVID-19 patients and controls ($p<0.0001$), respectively. DLCO and TLC measures were only available for follow up examination of COVID-19 patients without pre-pandemic comparisons (Table 2). Both lung function measures were slightly reduced, with a mean predicted DLCO of 88.1% (17.1) and TLC of 90.15% (10.9), compared to expected values accounting for age, sex, and height, respectively.

Self-reported respiratory morbidity following COVID-19

Respiratory symptoms at baseline and follow up were compared in those with positive SARS-CoV-2 RT-PCR tests and controls (Figure 2). Symptoms at baseline were largely comparable between the two groups with dyspnea, wheezing and sputum production reported by 6.4%, 17.0%, 9.6% vs. 4.2%, 14.2%, 8.7% in individuals with positive SARS-CoV-2 RT-PCR test and controls, respectively. The only symptom which was statistically significantly different in individuals with a SARS-CoV-2 RT-PCR test was wheezing which was less frequently reported at follow-up (17.0% vs 6.7%, $p = 0.042$). Wheezing was also less frequently reported in controls at follow-up compared to baseline (14.2% vs 9.4%, $p = 0.032$).

Lung function decline following COVID-19

Distribution of FEV_1, FVC and FEV_1/FVC decline in COVID-19 cases and controls is shown in Figure 3. The annual mean decline in FEV_1 across all participants was 27.8 mL (95% CI: 30.5-24.4 mL, p < 0.001) between visits. The corresponding estimate for FVC was 21.0 mL/year (95% CI: 17.3-24.6 mL, p < 0.001). There was a faster FEV_1 decline in COVID-19 patients versus controls with mean declines of 41.8 mL/year and 23.8 mL/year, respectively; corresponding estimates for FVC were 61.9 mL/year and 16.9 mL/year. In our mixed effects model, we observed an interaction between age and COVID-19 and lung function measurements. Thus, COVID-19 patients had a faster decline of 7.3 mL/year (95% CI: 0.0-14.3 mL, p-interaction = 0.041) for FEV_1 and 22.6 mL/year (95% CI: 13.0-32.0: p-interaction < 0.0001) for FVC compared with controls in multivariable adjusted mixed effects models (Table 3), whereas the ratio decline was lower for COVID-19 patients compared to controls due to faster FVC than FEV_1 decline. As expected, male sex, increased height and less smoking were all associated with lung function.

In sensitivity analyses, restricting analysis to COVID-19 patients not requiring hospitalization, or only including COVID-19 patients with lung function tests performed 180 days after a positive SARS-CoV-2 RT-PCR test, the results were largely similar for FVC and partly for FEV_1. In the former analysis, the estimates from mixed effects models were -8.9 mL/year (n=95, 95% CI: 1.6-16.4, p-interaction < 0.0001) for FEV1 and -25.9 mL/year (n=95, 95% CI: 15.8-36.0, p-interaction < 0.0001) for FVC, while the estimates for the latter model were -2.6 mL/year (n=40, 95% CI: -8.0-13.1, p-interaction: 0.64) for FEV_1 and -21.1 mL/year (n=40, 95% CI: 8.0-34.8, p-interaction < 0.01) for FVC.

Finally, we also performed a simple linear regression model to determine change in FEV_1 and FVC while additionally adjusting for the time since baseline spirometry. We found that COVID-19 was associated with a 113.8 and 301.3 ml lower FEV_1 and FVC, respectively. This corresponded to 3.7 and 7.3 percentage point lower %-predicted.

Discussion

Using pre-pandemic lung function tests in SARS-CoV-2 positive individuals and matched controls we were able to quantify dynamic lung volume declines following asymptomatic to mild COVID-19 at mid to long-term follow up. We observed that COVID-19 was associated with an accelerated decline in FEV_1 and FVC independent of tobacco smoking. The decline was largest for FVC with a COVID-19 associated excess decline of approximately 23 mL per year during the study period, using the mixed effect model approach, or a total of 300 ml from baseline to follow up, while adjusting for follow up

time and using a simple linear regression approach. These results suggest that even mild COVID-19 may adversely affect the lungs in a sample of relatively healthy individuals from the general population.

Several studies performed after short, medium and long-term follow up have documented impairment of lung function measures to various degree depending on disease severity [20–24]. In a recent systematic review, the most important of the lung function tests affected seemed to be DLCO in that approximately 40% had abnormal levels following discharge [25]. Moreover, 15% of COVID-19 patients had evidence of restrictive abnormalities by spirometry and 7% had an obstructive pattern in this review. These findings were derived from studies performing lung function tests in discharged patients at various time-points (approximately 1-3 months) after COVID-19, and predicted measures were used to define abnormality (e.g. DLCO < 80%) without pre-disease comparisons. In our study with approximately 10% of the participants hospitalized, we found that DLCO was < 80% in 18% at follow-up. More importantly, our study enabled us to perform a pre-pandemic spirometry comparison and we were able to show a simultaneous decline of FEV_1 and FVC, a finding that was robust after excluding those individuals that were hospitalized.

Population studies have shown that lung function trajectories are characterized by steady moderate declines of FEV_1 (~31 ml/year) and FVC (~33 ml/year) from an age of approximately 30 years and onward[26]. Our results suggested that the additional COVID-19 associated lung functions decline per year were slightly lower than this (~7 and ~23 ml/year, respectively). This main outcome was presented as change in lung function over time from baseline to post-COVID using a mixed effect model approach. However, there may not be a linear rate of decline in the context of COVID-19, and a singular pulmonary insult would not have impacted the pre-COVID-19 period. Thus, we also performed a simple linear regression model with the primary outcome as change in lung function from baseline to follow-up with adjustment of time since baseline to quantify any decline specifically associated with COVID-19. These results revealed that COVID-19 was associated with a ~114 and ~300 ml lower FEV1 and FVC. The minimal clinically important difference (MCID) for FEV_1 is often cited to be 100 ml [27]The MCID for FVC is typically reported to be 2-6% [28, 29], which was also comparable to the total decline of FVC associated with COVID-19 (~7%). The effect size of COVID-19 on the additional decline per year in FEV_1 and FVC corresponded to one- and three-years pack-years of smoking, respectively.

Other viral infections may also adversely affect the lungs. For example, up to 50% of individuals with H1N1 influenza had signs of abnormal pulmonary function at one-year post discharge [30]. However, little is known about the long-term changes in pulmonary function after uncomplicated

viral infections in individuals without chronic lung diseases. Some viral infections, in particular influenza, seem to be associated with acute pulmonary function changes in non-hospitalized individuals, i.e. ~100 and ~150 ml decline of FEV_1 and FVC, respectively, three months after the infection [1, 31]. These findings may be comparable to that of uncomplicated COVID-19 but studies directly comparing these viral infections are needed to draw further conclusions.

Our findings of a simultaneous decline of FEV_1 and FVC could indicate an isolated interstitial restrictive disease process or a combined restrictive and obstructive disease process [32]. However, the mechanism of accelerated FEV_1 and FVC declines in our study cannot be fully elucidated. Pathologies in individuals with more severe disease include diffuse alveolar epithelium and capillary damage, hyaline membrane formation, alveolar septal fibrous proliferation, and pulmonary consolidation [33, 34]. The pathology in lungs of individuals with mild disease not requiring hospitalization have not been studied. It is likely that similar, but less severe findings, are present in these patients. We are not aware of existing studies that have performed chest CTs in non-hospitalized individuals with mild COVID-19, but in hospitalized patients with mild to moderate disease most patients had abnormal findings on chest CT, of which ground glass opacities was the most frequent finding [35–38].

To our knowledge only one previous study performed lung function testing in COVID-19 patients with pre-pandemic comparisons [39]. This study included 80 patients, including nearly 80% with pre-existing lung disease, from a tertiary referral healthcare institution with pre-pandemic lung function test available. Although approximately 1/3 required hospitalization, the study was not able to document significant changes in dynamic lung volumes measures at three to four months post-COVID-19. These results are somewhat in conflict with our findings. A possible explanation may be that many of the included patients had abnormal pre-pandemic lung function test values, whereby a COVID-19 associated decline could be more difficult to detect. Moreover, this study did not have a control sample for comparison and could not model the association of COVID-19 status with lung function. Although we had a pre-pandemic spirometry for comparison, it is still formally possible that the group who later developed COVID-19 were predisposed by unknown factors which would bias the results. However, as baseline lung functions were comparable in COVID-19 patients and controls, and the fact that the most COVID-19 patients did not develop severe disease, suggest absence of underlying conditions associated with an accelerated lung function decline. Thus, it is most likely that the accelerated lung function decline was directly related to SARS-CoV-2 infection, the host immune response, and/or the resolution process.

Our study has limitations. Paired lung function measures were only available for spirometries and we had no pre-pandemic DLCO or TLC tests for comparison. Moreover, although our cohort had a reasonable size to study lung function decline, we were not able to perform various sub-group analyses, e.g. analyses stratified by symptoms or smoking status. We were also unable to detect any COVID-19 related effect on respiratory symptoms and lacked more sensitive measures of self-reported respiratory morbidity. Finally, although there was almost six months of follow-up time after COVID-19, we only had two measures in time available, and we are therefore not able to provide a detailed trajectory of the decline. Thus, whether COVID-19 have induced a temporary decline in dynamic lung volumes with subsequent and late resolution, or whether these declines represent permanent changes is unknown and should be explored in future studies.

In conclusion, asymptomatic to mild COVID-19 was associated with a measurable decline in dynamic lung volumes in the general population. Future studies should perform additional follow-up and assessment of clinical consequences of mild COVID-19.

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Author contributions

AR, SA, TB, KK conceived the idea and planned the study. KI collected the data. KI, SA and AR did the statistical analysis. KI and AR wrote the draft manuscript. All authors revised the manuscript for important intellectual content. TB, BGN and KK obtained funding and provided administrative, technical, and material support. All authors contributed to subsequent writing, revisions, and approved the final version of the manuscript.

Declarations of interest

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Figure 1. Flowchart of study participants

A total of seven individuals performed an unsatisfactory spirometry with an EasyOne® spirometry (see methods and materials for further details). Controls were matched on age, sex, ethnicity and smoking status as described under methods. Definitions of abbreviations: CGPS, Copenhagen General Population Study; RT-PCR, real time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Figure 2. Self-reported respiratory morbidity in patients with COVID-19 and controls

Upper and lower three panels depict respiratory symptoms in COVID-19 patients and controls, respectively. P-values compare baseline and follow-up results in the two groups. Asterisks compare follow-up symptoms in COVID-19 patients and controls. *p = 0.06 ; **p = 0.87 ; ***p = 0.45. Definition of abbreviations: COVID-19, coronavirus disease 2019.

Figure 3. Distribution of the declines in lung function in patients with COVID-19 and controls

Shown is the distribution of observed annual decline in FEV_1, FVC and FEV_1/FVC among COVID-19 patients (upper panels) and matched controls (lower panels). The dashed lines represent mean values. Definition of abbreviations: COVID-19, coronavirus disease 2019; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity.

123 **Table 1. Baseline characteristics of study participants**

General characteristics	COVID-19 patients (n=107)	Controls (n=499)	p-value
Age (years), mean (SD)	57 (8.7)	56 (8.4)	0.166[#]
Sex (female), n (%)	57 (53.3)	265 (53.1)	1.000[#]
Ethnicity (Caucasian), n (%)	107 (100)	499 (100)	1.000[#]
BMI (kg/m^2)	26.5 (3.8)	26.0	0.256
Smoking status			0.926[#]
Never-smokers, n (%)	45 (42.1)	220 (44.1)	
Former smokers, n (%)	54 (50.5)	244 (48.9)	
Current smokers, n (%)	8 (7.5)	35 (7.0)	
Cumulative smoking (pack-years), mean (SD)	9.9 (12)	9.6 (15)	0.870
Time between baseline and follow-up examinations (years), mean (SD)	6.4 (2.8)	8.4 (2.6)	0.001
Clinical characteristics			
Self-reported asthma, n (%)*	4 (3.7)	27 (5.4)	0.83
Dyspnea, n (%)	6 (6.4)	21 (4.2)	0.52
Wheezing, n (%)	16 (17.0)	70 (14.2)	0.58
Sputum, n (%)	9 (9.57)	43 (8.65)	0.92
Dynamic lung volumes			
FEV_1 (L), mean (SD)	3.1 (0.7)	3.1 (0.8)	0.753
FEV_1 predicted (%), mean (SD)	95.0 (15.0)	95.0 (15.1)	0.97
FVC (L), mean (SD)	4.1 (0.9)	4.0 (1.0)	0.549
FVC predicted (%), mean (SD)	100.2 (13.5)	98.0 (14.8)	0.17
FEV_1/FVC, mean (SD)	0.74 (0.1)	0.76 (0.1)	0.023
FEV_1/FVC <LLN, n (%)	10 (9.3)	67 (13.4)	0.46

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125 *Asthma and COPD was defined according to an affirmative answer to the question "Do you have asthma". [#]Mathcing
126 variables. Definition of abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; COVID-19,
127 corona virus disease 2019; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; LLN, lower limit of
128 normal; mMRC, modified Medical Research Council dyspnea scale.

Table 2. COVID-19 related symptoms and DLCO of patients with confirmed SARS-CoV-2 PCR test

Any COVID-19 related symptom	
Yes, n (%)	92 (85.9)
No, n (%)	15 (14.0)
Duration of symptoms, days (SD)	12 (11.2)
Fever, n (%)	76 (71.0)
Dyspnea*, n (%)	41 (38.3)
Fatigue, n (%)	88 (82.2)
Muscle or body aches, n (%)	64 (59.8)
Sore throat, n (%)	28 (26.1)
Loss of smell or taste, n (%)	50 (46.7)
Hospital admission, n (%)	12 (11.2)
Days, median (IQR)	7 (3.7; 9.3)
Oxygen therapy, n (%)	2 (1.9)
CPAP, n (%)	3 (2.8))
Mechanical ventilation, n (%)	1 (0.9)
Days from positive SARS-CoV-2 PCR test to follow-up examinations, median (IQR)	156.0 (107.8; 359.2)
Diffusion Capacity for Carbon Monooxide test	
DLCO (mmol/min/kPa), mean (SD)	7.85 (2.1)
DLCO predicted (%), mean (SD)	88.06 (17.1)
DLCO < 80% predicted, n (%)	19 (17.7)
DLCO/V_a (mmol/kPA/L), mean (SD)	1.46 (0.4)
DLCO/$_{Va}$ predicted, mean (SD)	98 (16.1)
TLC (L), median (IQR)	5.34 (5.3; 6.4)
TLC predicted (%), mean (SD)	90.15 (10.9)

Participants were questioned about COVID-19 related symptoms on the same day and just prior to the lung function tests. Definition of abbreviations: COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; DLCO, diffusing capacity for carbon monoxide; HF, high flow; TLC, total lung capacity; Va, alveolar volume. *Individuals with a positive PCR SARS-CoV-2 test were asked: “Did you experience difficulties in breathing in relation to COVID-19”.

Table 3. Linear mixed effect model analyses for the annual change in lung function in COVID-19 patients and controls

Covariates		Change in FEV_1 (mL), FVC (mL) or FEV_1/FVC (%) per unit change in covariate	Difference in ml [95% CI]	p-value
FEV_1				
Time of follow-up	Per 1 year increment	-27.8	-30.5; - 24.4	< 0.0001
Sex	Male vs female	612.5	502.5; 722.5	< 0.0001
Height	Per 1 cm increment	34.4	28.4; 40.5	< 0.0001
Pack-years at study entry	Per 1 year increment	-9.7	-13.0; -6.3	< 0.0001
COVID-19 x time of follow up	COVID-19 vs control	-7.3	-14.3; -0.0	0.041
FVC				
Time of follow-up	Per 1 year increment	-21.0	-24.6; -17.3	< 0.0001
Sex	Male vs female	795.5	665.0; 926.0	< 0.0001
Height	Per 1 cm increment	46.3	39.1; 53.5	< 0.0001
Pack-years at study entry	Per 1 year increment	-6.4	-10.3; -2.4	< 0.01
COVID-19 x time of follow up	COVID-19 vs control	-22.6	-32.0; -13.0	< 0.001
FEV_1/FVC				
Time of follow-up	Per 1 year increment	-0.4	-0.4; -0.3	< 0.0001
Sex	Male vs female	0.5	-1.1; 2.2	0.539
Height	Per 1 cm increment	-0.5	-0.1; 0.0	0.299
Pack-years at study entry	Per 1 year increment	-0.1	-0.2; -0.1	< 0.0001
COVID-19 x time of follow up	COVID-19 vs control	0.3	0.12; 0.38	< 0.0001

Each of the three models (modelling slope of FEV_1, FVC and FEV_1/FVC) were adjusted for age, sex, height, smoking status and cumulative smoking at baseline and COVID-19 status. ":" denotes interaction. Definitions of abbreviations: COVID-19, coronavirus disease 2019; FEV1, forced expiratory volume in one second; FVC, forced vital capacity.

142 Figure 1

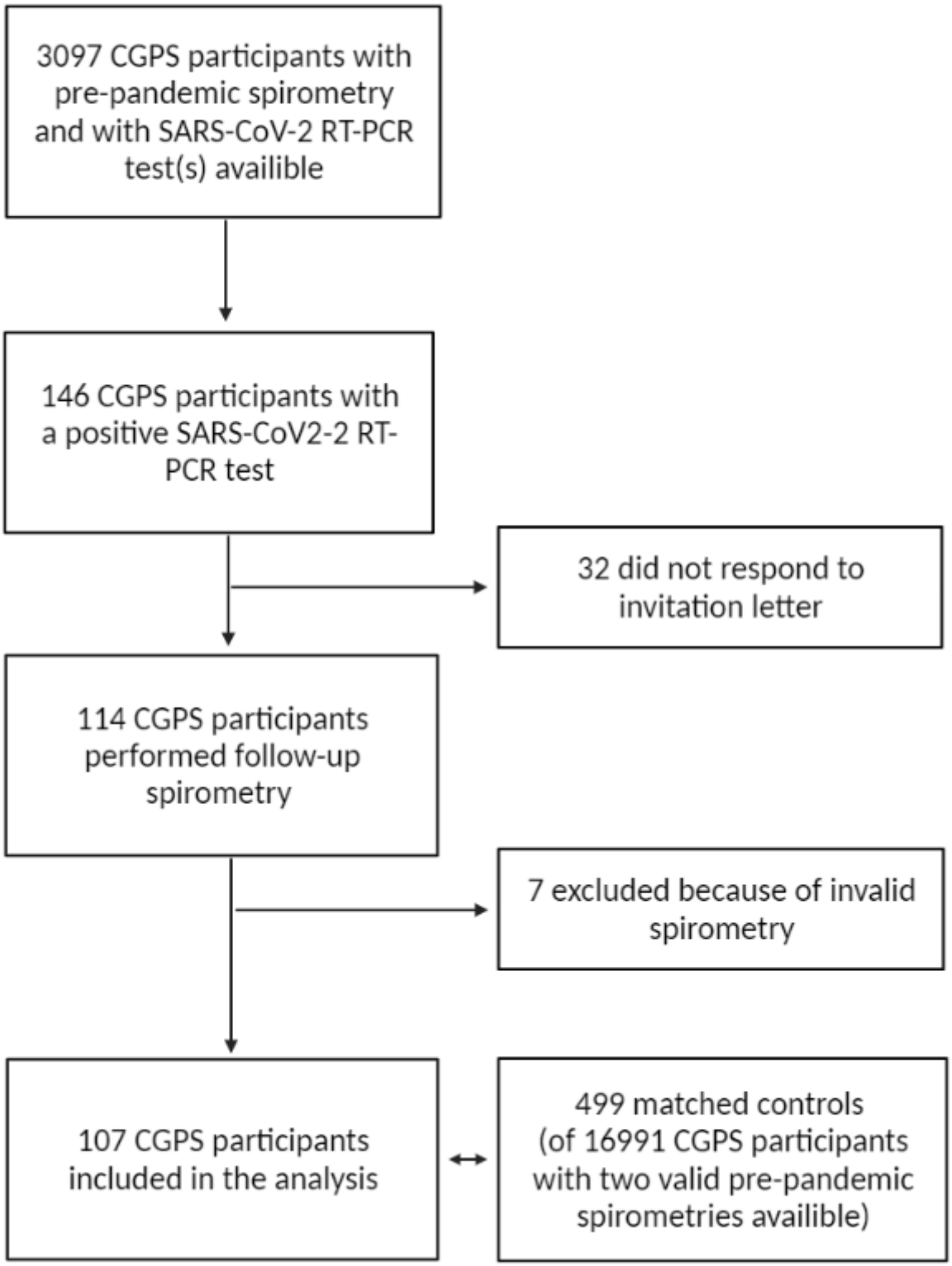

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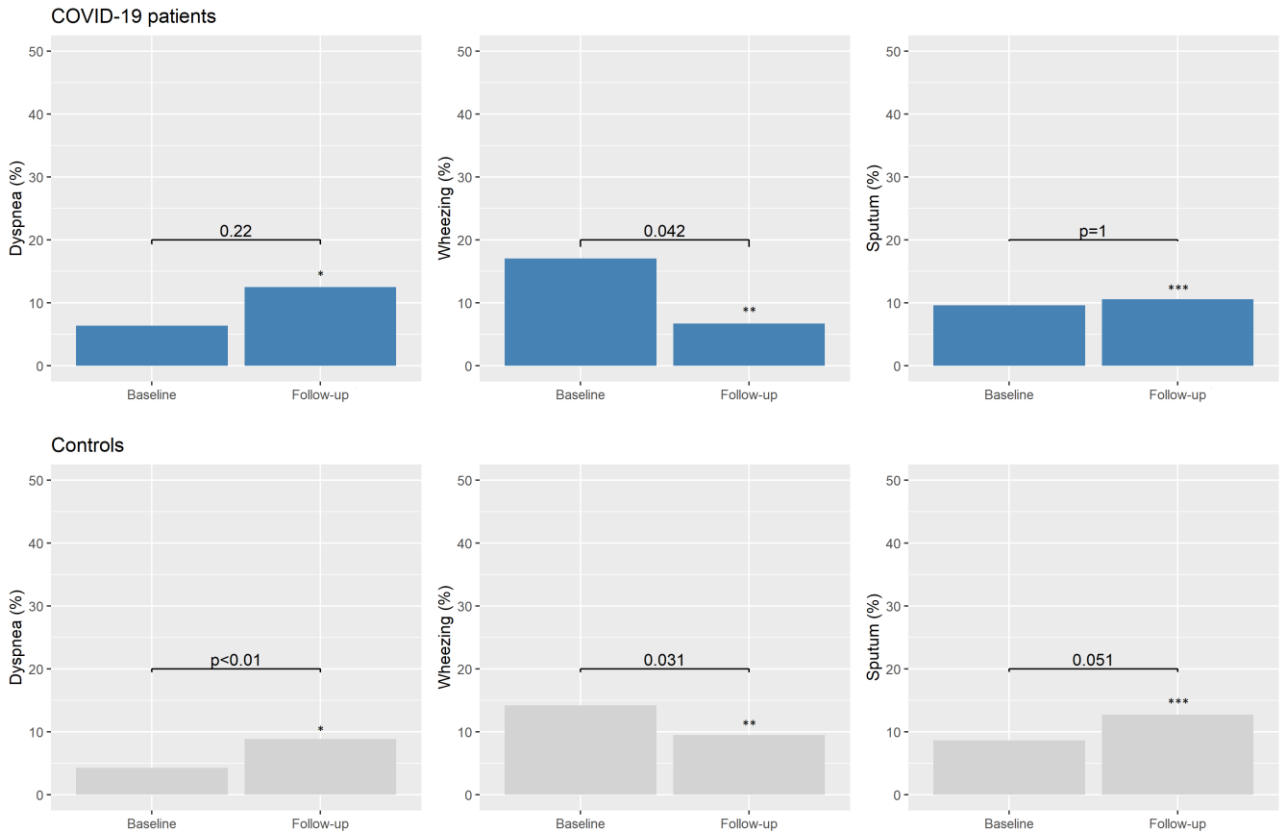
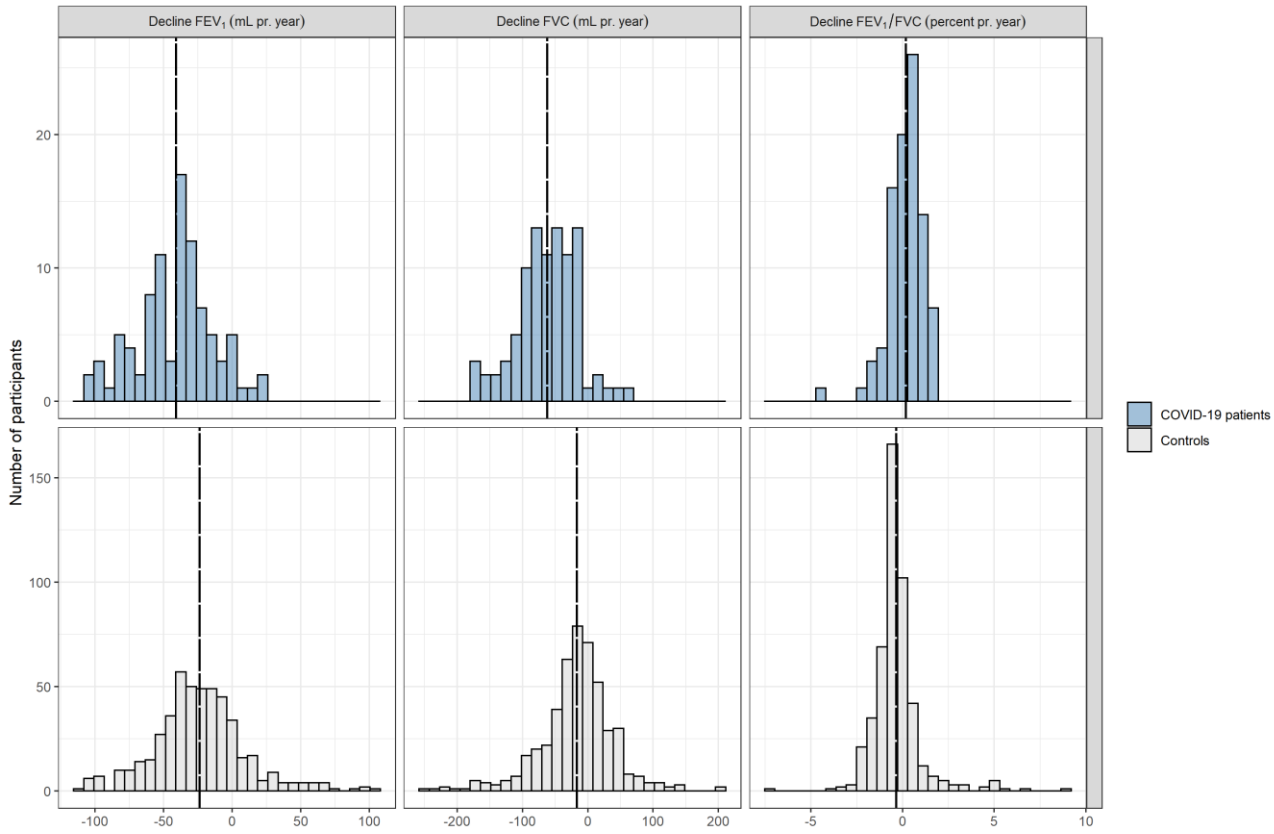
Figure 2



148 Figure 3



149