The impact of mild COVID-19 on medium-term respiratory function

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Background. There is a paucity of evidence on the impact of mild COVID-19 on the respiratory system, particularly in non-healthcare-seeking individuals.
Objectives. To investigate the effects of mild COVID-19 on respiratory function and to identify indicators of decreased lung function.
Methods. We conducted a cross-sectional study in 175 non-healthcare-seeking individuals with confirmed acute SARS-CoV-2 infection who did not require hospitalisation. Participants were divided into three groups: those who had pulmonary function tests (PFTs) within 6 months, between 6 and 12 months, and between 12 and 24 months after infection. Each participant underwent spirometry, measurement of the diffusing capacity of the lungs for carbon monoxide (DL_{CO}), a 6-minute walking distance test (6MWD) and plethysmography.
Results. The mean age of the participants was 44.3 years, and the mean body mass index (BMI) 32.7 kg/m^2. Forty-six participants had PFTs within 6 months, 64 between 6 and 12 months, and 65 between 12 and 24 months. Lower than expected DL_{CO} was the most commonly detected abnormality (57%). Spirometry anomalies were noted in 23%, 10% showing an obstructive impairment and 13% a restrictive impairment, confirmed by a total lung capacity <80%. An increased BMI was the only variable that was significantly and independently linearly associated with lower than predicted (<80%) forced vital capacity, forced expiratory volume in the 1st second, DL_{CO} and 6MWD.
Conclusion. DL_{CO} was low in a considerable proportion of non-healthcare-seeking individuals 2 years after mild COVID-19. A high BMI was found to be significantly and independently associated with lower than predicted PFT results and 6MWD.
Keywords. Body mass index, carbon monoxide, diffusion, mild COVID-19 , pulmonary function tests.

Afr J Thoracic Crit Care Med 2024;30(3):e1629. https://doi.org/10.7196/AJTCCM.2024.v30i3.1629

Study synopsis
What the study adds. We found that pulmonary function, particularly diffusing capacity, was lower than predicted in a significant proportion of non-healthcare-seeking individuals up to 2 years after mild COVID-19. A high body mass index (BMI) was found to be significantly and independently associated with decreased lung function.
Implications of the findings. There is a paucity of evidence on the medium-term effects of mild COVID-19 on the respiratory system in non-healthcare-seeking individuals. We investigated the medium-term effects of mild COVID-19 on the respiratory system, showed lower than predicted lung function, and identified one independent predictor, BMI. Even individuals classified as having 'mild' COVID-19 could have medium-term respiratory sequelae.

The World Health Organization classified COVID-19 as a pandemic on 11 March 2020.[1] Early evidence suggests that the respiratory system is the primary target of the SARS-CoV-2 virus. Severe injury to the alveolar epithelial and endothelial cells with subsequent fibroproliferation is regarded as a major underlying pathophysiological mechanism of COVID-19 , suggesting that chronic and alveolar remodelling may develop, resulting in lung fibrosis and potential long-term impairment.[2]

Mounting evidence suggests that individuals with severe COVID-19 (hospitalised during the disease) develop medium-term impaired lung function with persistent respiratory symptoms.[3] In addition, the use of corticosteroid therapy was identified to improve recovery of lung function between 6 and 12 months in some individuals with organising pneumonia.[4]

Currently, most studies focus on the effects of COVID-19 on individuals who were hospitalised during infection and/or required supplementary oxygen therapy.[3,5-8] There is a paucity of evidence on the medium-term effects of mild COVID-19 , especially in non-healthcare-seeking individuals. We therefore aimed to assess the medium-term effects of mild COVID-19 on the respiratory system and to identify predictors of lower than expected lung function.

Methods

Study design and participants

We conducted a cross-sectional study at Tygerberg Hospital, a 1 380-bed tertiary hospital in Cape Town, South Africa (SA). Hospital staff who had previously tested positive for SARS-CoV-2 on a reverse transcription polymerase chain reaction test and who had never experienced severe COVID-19 were invited to participate in the study. Data collection started on 7 May 2021 and ended on 2 September 2022. Mild COVID-19 was defined as not requiring hospitalisation or any form of supplementary oxygen during the course of the disease.[9] The date on which the specimen that tested positive was obtained was used to define day zero. Participants were stratified into three groups based on how long after SARS-CoV-2 infection pulmonary function tests (PFTs) were performed: within 6 months, between 6 and 12 months, and between 12 and 24 months.

Basic demographic and clinical data

Demographic information gathered on the day of testing included age (years), sex at birth (defined as male or female), and ethnicity (self-reported). Smoking status, defined as current smoker, non-smoker and ex-smoker (smoking cessation >6 months prior to the day of testing), was documented in all participants. Comorbidities, specifically diabetes mellitus, hypertension, chronic obstructive pulmonary disease, asthma, other respiratory diseases, active or previous tuberculosis and ischaemic heart disease, were recorded. Given that the participants were co-workers, HIV status was not documented.

Participants were asked if they had experienced any of the following symptoms during their COVID-19 disease: fever, cough, tiredness/fatigue, muscle or body aches, sore throat, nasal congestion or a runny nose, nausea or vomiting, diarrhoea, headache, loss of sense of taste or smell, difficulty breathing or shortness of breath, or chest pain.

All participants were weighed on the day of testing (wearing only light clothing), and their heights were measured up to an accuracy of 0.5 cm (no shoes). Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Pulmonary function testing

All PFTs were performed by a qualified pulmonary clinical technologist. Testing was conducted using a Jaeger MasterScreen CareFusion system V5.32.0.5 CD-Version 5.72.1.77 (Jaeger, Germany). Testing was done in accordance with the current American Thoracic Society (ATS) and European Respiratory Society guidelines,[10,11] and the Global Lung Initiative 2012 (GLI 2012) reference equations were used.[12] The GLI 2012 reference equation model is routinely adjusted for height, age and sex at birth.[12] As per SA data and guidelines, black African and mixed ethnicity was labelled as 'other', white as 'white' and Indian as 'Southeast Asian'.[13]

Routine spirometry was performed, as well as forced vital capacity (FVC), forced expiratory volume in the 1st second (FEV_1) and FEV_1/FVC ratio. The diffusing capacity of the lungs for carbon monoxide (DL_{CO}) was measured in mL/min/mmHg with a single breath-hold technique, as per the current ATS guidelines.[10,11] DL_{CO} was considered to be lower than expected when diffusion capacity was <80% of predicted. Finally, plethysmography was performed according to the current ATS guidelines.[14]

The main outcome data analysed were FVC, FEV_1 and DL_{CO}. All measurements were expressed and analysed as percentage predicted, using the GLI 2012 reference equations.[12,13] Spirometric results were categorised as normal, obstructive (with or without a reduced FVC), restrictive or mixed.[15] Where spirometry was suggestive of restriction or mixed impairment, the total lung capacity (TLC) and other parameters obtained from plethysmography were used to categorise the results. Restrictive impairment was confirmed with a TLC <80% of predicted.[14]

Six-minute walking distance

The 6-minute walking distance (6MWD) was conducted in accordance with the current ATS guidelines.[16] The test was performed on a 30 m flat indoor surface. A Nihon Covidien forehead pulse oximeter device, model number PVM-2703 (Covidien, USA), was used for recording of oxygen saturation. The 6MWD was expressed in absolute values (m).

Statistical analysis

The descriptive statistics for demographic, anthropometric, lung function and 6MWD test variables were calculated for the three COVID time groups and consisted of means, standard deviations, frequencies and percentages. The nature of the association between the lung function measurement and BMI was investigated using a non-parametric locally weighted scatterplot smoothing regression function model in each of the COVID-19 time groups. The association between lung function and the 6MWD test and BMI was evaluated using linear regression models with BMI, age, sex and smoking status as the covariates. Regression coefficients were reported with 95% confidence intervals. The 6MWD was not normally distributed, so a quantile regression model was used. Stata 17 statistical software (StataCorp, USA) was used, with a significance level of 5%. Pearson's χ^2 test and Fisher's exact test were performed to test for significant associations between the COVID-19 time groups and categorical demographic and clinical factors.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Health Research Ethics Committee of Stellenbosch University (ref. no. S21/03/004_COVID-19; project ID 21796). Informed consent was obtained from all individual participants.

Results

Baseline demographics and patient characteristics

Across the three time groups, 46, 64 and 65 participants performed PFTs and the 6MWD test. Baseline characteristics and demographics are summarised in Table 1. Most of the participants were female (*n*=140; 80%), never-smokers (*n*=140; 80%) and of mixed ethnicity (*n*=121; 69%). The mean (SD) age was 44.28 (11.40) years. A significant difference in mean BMI was observed between the time groups (p=0.023). The mean BMI was similar in the 6 - 12 months group (33.40 kg/m^2) and the 12 - 24 months group (33.71 kg/m^2), but lower in the <6 months group (30.14 kg/m^2). A total of 47% of the participants reported pre-existing comorbidities. The most common comorbidity was hypertension (33%), followed by diabetes mellitus (13%) and asthma (11%).

Headache was the most common symptom reported as having been experienced during the time of SARS-CoV-2 infection (75%), followed by tiredness/fatigue (74%), muscle or body aches (62%), sore throat (58%), loss of sense of taste or smell (57%), fever (56%) and cough (56%) (Fig. 1).

The SARS-CoV-2 variant at the time of primary infection was not known, because molecular strain typing was not routinely performed in our setting. However, 23 (13%) of the participants tested positive during a wave driven by the Alpha variant, 96 (55%) during a wave driven by the Beta variant, 38 (22%) during a wave when the Delta variant was predominantly present, and 18 (10%) when the Omicron variant was the dominant circulating strain.

Pulmonary function testing and 6-minute walking distance

The PFT results and 6MWD measurements in the population as a whole and in the different time groups are summarised in Table 2. Spirometry was normal in 35 (76%) of participants in the <6 months group and in 48 (74%) in the 12 - 24 months group, compared with 52 (82%) in the 6 - 12 months group. Spirometry was abnormal in 40 (23%) of the total study population. Obstructive impairment was consistent between the three time groups, affecting 5 (11%), 6 9%) and 6 (9%) participants, respectively. Restrictive impairment was more common in the 12 - 24 months group (*n*=11; 17%) compared with the 6 - 12 months group (*n*=6; 9%) and the <6 months group (*n*=6; 13%). Mean FVC and FEV_1 were highest in the 6 - 12 months group (94.35% and 94.12%, respectively). There was no significant difference between the three time groups for FVC (p=0.134), FEV_1 (p=0.140) or 6MWD (p=0.9081).

Of the participants, 99 had a DL_{CO} lower than predicted (Table 2). In the time groups, 59% in the <6 months group, 47% in

Table 1. Baseline characteristics and demographics of the study population as a whole and in the different COVID-19 time groups

Characteristic	Total (*N*=175), *n* (%)*	<6 months (*n*=46), *n* (%)*	6 - 12 months (*n*=64), *n* (%)*	12 - 24 months (*n*=65), *n* (%)*
Basic demographics				
Age (years), mean (SD)	44.28 (11.40)	43.02 (12.32)	45.61 (10.60)	43.86 (11.55)
Male	35 (20)	12 (26)	7 (11)	16 (25)
Female	140 (80)	34 (74)	57 (89)	49 (75)
Height (cm), mean (SD)	163.76 (8.04)	164.94 (7.95)	162.79 (8.05)	163.88 (8.08)
Weight (kg), mean (SD)	87.41 (19.63)	91.98 (19.06)	88.19 (18.32)	90.48 (20.75)
BMI (kg/m^2), mean (SD)	32.66 (7.29)	30.14 (6.50)	33.40 (7.31)	33.71 (7.51)
Population group				
Black African	23 (13)	4 (9)	8 (12)	11 (17)
White	29 (17)	11 (24)	12 (19)	6 (9)
Mixed ethnicity	121 (69)	30 (65)	44 (69)	47 (72)
Indian	2 (1)	1 (2)	0	1 (2)
Smoking status				
Active smoker	22 (13)	7 (15)	8 (13)	7 (11)
Ex-smoker	13 (7)	5 (11)	3 (5)	5 (8)
Comorbidities				
Diabetes mellitus	23 (13)	6 (13)	7 (11)	10 (15)
Hypertension	58 (33)	12 (26)	25 (39)	21 (32)
Asthma	20 (11%)	7 (15)	8 (13)	5 (8)
Tuberculosis†	10 (6)	2 (4)	4 (6)	4 (6)
Other	7 (4)	1 (2)	2 (3)	4 (6)

SD = standard deviation; BMI = body mass index.
*Except where otherwise indicated.
†Active or previous tuberculosis.

the 6 - 12 months group and 65% in the 12 - 24 months group had impairment. For DL_{CO}, we found a statistically significant difference overall (p=0.005) between the time groups, with the <6 months group having a significantly lower mean DL_{CO} compared with the other groups (p=0.003).

We observed a greater mean 6MWD in the 12 - 24 months group (486.21 m) compared with the 6 - 12 months group (475.66 m). The longest mean distance walked was observed in the <6 months group (498.54 m).

Factors associated with impaired pulmonary function

Linear regression models adjusted for BMI, age, sex and smoking status were used to determine predictors for impaired lung function and low 6MWD (Tables 3 - 6). BMI had a significant negative slope independent of time for each of FVC, FEV_1, DL_{CO} and 6MWD (p<0.001, p=0.001, p=0.007 and p<0.001, respectively). Sex had no influence on FVC, FEV_1 or 6MWD, but females had a significantly lower DL_{CO} compared with males (p=0.001). Age and smoking status were not associated with lower than predicted lung function or 6MWD.

Discussion

We found that pulmonary function, particularly DL_{CO}, was lower than predicted in a significant proportion of non-healthcare-seeking individuals with a previous history of mild COVID-19 at all time points, even 2 years after the illness. A higher BMI was found to be an independent risk factor for lower than predicted PFT results and 6MWD.

To our knowledge, this is one of the first studies to investigate the medium-term pulmonary effects of mild COVID-19. We demonstrated that the DL_{CO} was lower than predicted in almost two-thirds of the participants, and that restrictive impairment was present in almost 20% of participants 12 - 224 months after so-called 'mild' COVID-19. Of note is that these were non-healthcare-seeking individuals, and there was a statistically significant association between a higher BMI and impaired lung function.

The expiratory reserve volume and functional residual capacity are most affected by obesity, with a lesser reduction in the TLC and residual volume. Only moderate changes have been reported when investigating the effects of obesity during spirometry.[17] Mild reductions in both FVC and FEV_1 have been reported, with no significant changes in FEV_1/FVC. The most common finding on

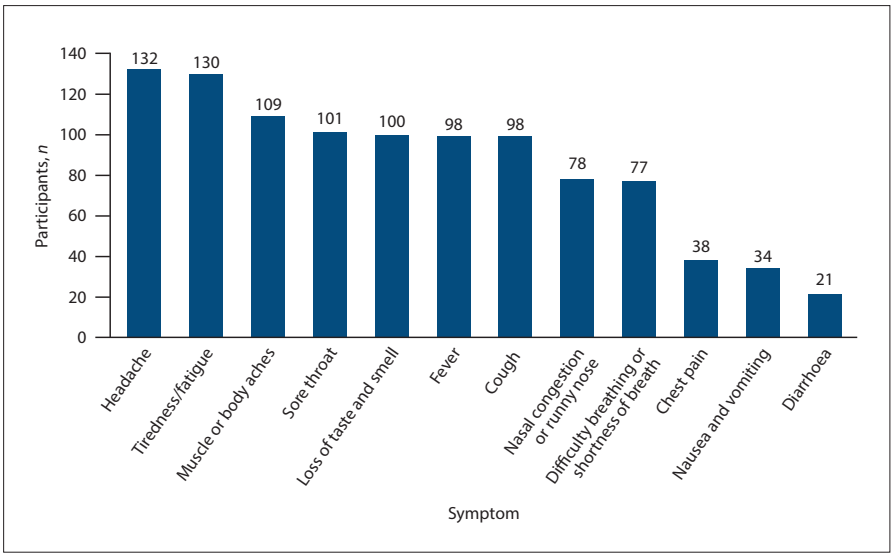

Fig. 1. Symptoms reported as having been experienced during the time of SARS-CoV-2 infection (N=175 participants).

Table 2. Pulmonary function test and 6MWD results for the study population as a whole and in the different COVID-19 time groups

Variable	Total (*N*=175), *n* (%)*	<6 months (*n*=46), *n* (%)*	6 - 12 months (*n*=64), *n* (%)*	12 - 24 months (*n*=65), *n* (%)*	*p*-value†
FVC (% predicted), mean (SD) (range)	91.58 (14.54) (54.5 - 128.2)	91.14 (13.76) (60.4 - 117)	94.35 (15.26) (62.2 - 128.2)	89.17 (14.09) (54.5 - 117.9)	0.134
FEV1 (% predicted), mean (SD) (range)	91.09 (15.31) (26.8 - 132.1)	89.35 (15.59) (26.8 - 113.7)	94.12 (14.78) (51.8 - 125.2)	89.36 (15.42) (41.7 - 132.1)	0.140
Normal spirometry	135 (77)	35 (76)	52 (82)	48 (74)	0.784
Obstructive impairment	17 (10)	5 (11)	6 (9)	6 (9)	
Restrictive impairment	23 (13)	6 (13)	6 (9)	11 (17)	
DLCO (% predicted), mean (SD) (range)	79.12 (12.56) (43.1 - 109.6)	77.22 (12.85) (43.1 - 107.9)	82.08 (12.27) (57.4 - 106.1)	77.57 (12.29) (56.5 - 109.6)	0.005
DLCO normal	76 (43)	19 (41)	34 (53)	23 (35)	0.100
DLCO mild impairment	92 (53)	24 (52)	29 (45)	39 (60)	
DLCO moderate impairment	7 (4)	3 (7)	1 (2)	3 (5)	
6MWD (m), mean (SD) (range)	487.27 (69.77) (284 - 683)	498.54 (76.77) (350 - 683)	475.66 (71.27) (284 - 628)	486.21 (64.47) (334 - 646)	0.9081

FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1st second; DLCO = diffusing capacity of the lungs for carbon monoxide; 6MWD = 6-minute walking distance.
*Except where otherwise indicated.
†Adjusted *p*-value from the linear/quantile regression models. For spirometry and DLCO impairment levels, *p*-values were obtained using the $\chi 2$ and Fisher's exact tests.

Table 3. Linear regression coefficients of modelling FVC (% predicted) on the covariates COVID-19 time groups, BMI, age, sex and smoking status

Covariate	Coefficient	*p*-value	95% CI
6 - 12 months	4.61	0.099	–0.87 - 10.09
12 - 24 months	0.16	0.954	–5.27 - 5.58
BMI	–0.56	<0.001	–0.86 - –0.26
Age	–0.06	0.550	–0.25 - 0.13
Sex female	5.04	0.069	–0.40 - 10.49
Smoking status	2.02	0.544	–4.54 - 8.58

FVC = forced vital capacity; BMI = body mass index; CI = confidence interval.

Table 4. Linear regression coefficients of modelling FEV1 (% predicted) on the covariates COVID-19 time groups, BMI, age, sex and smoking status

Covariate	Coefficient	*p*-value	95% CI
6 - 12 months	5.59	0.061	–0.26 - 11.43
12 - 24 months	1.73	0.555	–4.05 - 7.52
BMI	–0.54	<0.001	–0.86 - –0.21
Age	0.02	0.815	–0.18 - 0.23
Sex female	4.93	0.095	–0.88 - 10.75
Smoking status	–0.92	0.797	–7.92 - 6.09

FEV_1 = forced expiratory volume in 1st second; BMI = body mass index; CI = confidence interval.

Table 5. Linear regression coefficients of modelling DLCO (% predicted) on the covariates COVID-19 time groups, BMI, age, sex and smoking status

Covariate	Coefficient	*p*-value	95% CI
6 - 12 months	7.04	0.003	2.39 - 11.69
12 - 24 months	1.54	0.510	–3.07 - 6.15
BMI	–0.35	0.007	–0.61 - –0.10
Age	0.01	0.943	–0.16 - 0.17
Sex female	–8.04	0.001	–12.67 - –3.42
Smoking status	–2.77	0.327	–8.35 - 2.80

DL_{CO} = diffusing capacity of the lungs for carbon monoxide; BMI = body mass index; CI = confidence interval.

Table 6. Quantile regression coefficients of modelling 6MWD on the covariates COVID time groups, BMI, age, sex and smoking status

Covariate	Coefficient	*p*-value	95% CI
6 - 12 months	–2.77	0.862	–34.10 - 28.56
12 - 24 months	–6.75	0.669	–37.85 - 24.34
BMI	–4.13	<0.001	–5.88 - –2.38
Age	–0.47	0.399	–1.58 - 0.63
Sex female	–2.57	0.873	–34.23 - 29.08
Smoking status	–21.70	0.256	–59.27 - 15.87

6MWD = 6-minute walking distance; BMI = body mass index; CI = confidence interval.

analysis of the effect of obesity on the DL_{CO} was results within the normal range. However, there is evidence suggesting that an increased BMI tends to lead to an increase in DL_{CO}.[17]

Exercise capacity is profoundly decreased in obesity owing to mechanical factors. Some researchers have shown that despite having the same BMI, greater total body fat was observed in females compared with males. The distribution of fat differs, with males accumulating adipose tissue in the abdominal area as opposed to in the lower extremities in females, affecting physical function. Individuals with increased BMI adapt for their greater body mass by slowing down walking velocity.[18] In any type of physical activity, being overweight or obese is associated with increased physical limitations.[19,20]

Lower than predicted DL_{CO} and spirometry anomalies have been reported in individuals who had suffered from severe COVID-19.[21] Zhang *et al.*[4] found an improvement in FVC between 6 months and

1 year after infection, followed by a decline between 1 and 2 years. Furthermore, they reported a greater decline in individuals who had been moderately to severely ill compared with those who had been critically ill.

In addition, although the available data reporting on the effects of COVID-19 by means of PFTs provide insightful results, the medium- to long-term effects of COVID-19 on the pulmonary system are still poorly understood. Most of the available studies performed PFTs within 3 months after COVID-19 infection.[1,5-7,22] Furthermore, the studies only reported findings of PFTs at that specific time point. There are currently only a few studies that performed PFTs at different time intervals. Wu *et al*.[8] reported PFTs at 3 months, 6 months and 12 months after infection. Bretas *et al*.[3] reported PFTs at 45 days and 6 months after infection. Both these studies only reported findings on participants who were hospitalised during the time of infection. Wu *et al*.[8] reported PFTs up to 1 year after infection. A report on patients who had survived severe acute respiratory syndrome (SARS) caused by coronavirus infection recommended investigations beyond 1 year to further explore the morbidity of SARS patients.[23] Apart from reporting on findings in participants who were not hospitalised during the time of infection, the novelty of our study is further enhanced by providing data on PFTs beyond 1 year after infection.

The statistical association of a higher BMI with lower than expected PFT results was an unexpected but not unexplained finding. Obesity is well established as a risk factor for severe COVID-19 and for mortality from COVID-19.[24,25] Obesity now also appears to be emerging as a risk factor for post-acute sequelae of COVID-19 (PASC) or 'long COVID'.[26,27] The SARS-CoV-2 virus enters a variety of cell types, including bronchial epithelial cells and adipocytes, by binding to angiotensin-converting enzyme 2 (ACE-2) receptors.[28] In obesity there is upregulation of ACE-2 receptors, and these receptors are more abundant in obese than non-obese individuals.[29] After direct infection of the adipocyte,[30,31] there is probably viral replication with activation of the immune response driven by adipocytes. There is now also evidence of SARS-CoV-2 persistence in various anatomical tissues,[32] but it is unclear whether this persistent viral infection predisposes to PASC. Obese patients also take longer to clear SARS-CoV-2, and there is prolonged viral shedding in obesity.[29] However, persistent SARS-CoV-2 infection of adipose tissue has not as yet been demonstrated.

One of the major strengths of this study is that we invited non-healthcare-seeking individuals who had confirmed SARS-CoV-2 infections (as many of them were merely screened as part of our institution's infection prevention and control measures). We also included participants who were infected 12 - 24 months prior to enrolment.

Limitations include the fact that the participants had an overall higher than normal BMI, and there may have been recall bias as far as symptoms were concerned. Moreover, there may be some selection bias, as those with mild residual post-COVID symptoms were more likely to participate. The nature of the study precluded a formal sample size estimation, as all personnel were invited over a rather extended period of time. Moreover, we could not predefine which parameter or what degree of change would have dictated the sample size (as it was unknown at the time), which may have made it impossible to be certain of negative findings and therefore limits generalisability. The association between BMI and 6MWD may be related to obesity and deconditioning. Participants did not have baseline PFTs, and some may have had decreased values caused by other pathologies. The cross-sectional nature of our study was also a limitation, and future research should be longitudinal to measure progression/regression of pulmonary function. Furthermore, we acknowledge that the addition of a control group would have allowed us to draw better conclusions as to whether the lower than predicted lung function was mediated solely by COVID-19 or some participants had pre-existing lower function before COVID-19. However, it must be mentioned that evidence suggests that up to 50% of individuals who had COVID-19 were asymptomatic, making it challenging to add a control group.[33,34]

Conclusion

Pulmonary function, particularly DL_{CO}, was lower than predicted in a significant proportion of non-healthcare-seeking individuals at all time points, even 2 years after mild COVID-19. A high BMI was found to be associated with lower than predicted PFT results and 6MWD. Even individuals classified as having 'mild' COVID-19 could therefore have medium-term respiratory sequalae.

Declaration. BWL and CFNK are members of the editorial board. The research for this study was done in partial fulfilment of the requirements for JvH's MSc in Medical Physiology degree at Stellenbosch University.

Acknowledgements. The authors acknowledge the Pulmonary Function Laboratory at Tygerberg Hospital and all its technologists and administrative staff. Furthermore, our results shed new light on the often-hidden sacrifices that healthcare workers made for patients during the COVID-19 pandemic, at Tygerberg Hospital and worldwide. We cannot be sufficiently grateful for their commitment.

Author contributions. JvH: conception and design, administrative support, provision of study materials or patients, collection and assembly of data, manuscript writing, final approval of manuscript. HS: conception and design, administrative support, provision of study materials or patients, manuscript writing, final approval of manuscript. AP: conception and design, manuscript writing, final approval of manuscript. BWA: conception and design, manuscript writing, final approval of manuscript. UL: conception and design, manuscript writing, final approval of manuscript. CJL: conception and design, data analysis and interpretation, manuscript writing, final approval of manuscript. CFNK: conception and design, administrative support, provision of study materials or patients, manuscript writing, final approval of manuscript. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding. None.

Conflicts of interest. None. All authors completed the International Committee of Medical Journal Editors uniform disclosure form.

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Received 18 October 2023. Accepted 14 June 2024. Published 11 October 2024.