

Age and oxygen saturation predict cognitive performance in covid- 19 survivors at least two months after discharge

George Vavougios

vavougyios.georgios@ucy.ac.cy

University of Cyprus

Dimitrios Mysiris

University of Thessaly

Vasileios Stavrou

University of Cyprus

Nico Biagi

University of Reading

Kyriaki Astara

University of Thessaly

Eleanna Pitaraki

University of Thessaly

Stylianos Boutlas

University of Thessaly

Konstantinos Turlakopoulos

University of Thessaly

Eirini Papayianni

University of Thessaly

Glykeria Tsirimona

University of Thessaly

Ilias Dimeas

University of Thessaly

Georgia Xiromerisiou

Mindful Mind

Sotirios Zarogiannis

University of Thessaly

Mohammad Zia Ul Haq Katshu

University of Nottingham

Zoe Daniil

University of Thessaly

Georgios Hadjigeorgiou

University of Cyprus

Giovanni D'Avossa

Bangor University

Konstantinos Gourgoulidis

University of Thessaly

Research Article

Keywords:

Posted Date: October 21st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10943558/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Age and oxygen saturation predict cognitive performance in covid-19 survivors at least two months after discharge

Authors: George Vavougiou¹, Dimitrios Mysiris², Vasileios Stavrou¹, Nico Biagi³, Kyriaki Astara⁴, Eleanna Pitaraki⁵, Stylianos Boutlas⁵, Konstantinos Tournakopoulos⁵, Eirini Papayianni⁵, Glykeria Tsirimonas⁵, Ilias Dimeas⁵, Georgia Xiromerisiou⁶, Sotirios Zarogiannis⁷, Mohammad Zia Ul Haq Katshu⁸, Zoe Daniil⁵, Georgios Hadjigeorgiou¹, Giovanni D'Avossa⁹, Konstantinos Gourgoulis¹

Affiliations:

1. University of Cyprus, Nicosia, Cyprus, Medical School
2. University of Thessaly, Larisa, Greece, Department of Neurology
3. University of Reading, Reading, United Kingdom, Henley Business School
4. University of Thessaly, Volos, Greece, Faculty of Medicine
5. University of Thessaly, Larisa, Greece, Department of Respiratory Medicine
6. Mindful Mind, Thessaloniki, Greece, Private Institute of Preventive Neurology and Brain Health
7. University of Thessaly, Larisa, Greece, Department of Physiology
8. University of Nottingham, Nottingham, United Kingdom, Division of Psychiatry and Applied Psychology
9. School of Human & Behavioural, Sciences, Bangor University and BCHUB NHS Trust

Corresponding Author:

George D. Vavougiou, MD, PhD

Assistant Professor of Neurology, Medical School, University of Cyprus, 75 Kallipoleos Street, P.C. 1678, Lefkosia, Cyprus. Email: vavougiou.georgios@ucy.ac.cy ; Mobile: +306936528439

Abstract

Background: COVID19 is viral illness resulting in acute respiratory syndrome. The acute disease can be followed by persistent multisystemic sequelae and in particular neuropsychiatric ones. We asked what are the risk factors and physiological markers of cognitive performance in COVID-19 survivors.

Methods: We analysed real-world clinical data from 159 COVID-19 survivors aged 40 years or older who were assessed in an outpatient clinic at least two months after discharge. The main outcome variable was the Montreal Cognitive Assessment (MoCA) total score. Predictor variables included demographics, anthropometric measures, pulmonary function, six-minute walk test measures, sit-to-stand performance and self-reported sleep quality. Exploratory factor

analysis was used to reduce the dimensionality of the predictor sets. Linear regression following multiple imputation was used to identify predictors of cognitive performance.

Results: In the initial multivariate linear regression MoCA scores were predicted by age and a composite of oxygen-saturation measurements derived from the six-minute walk test assessment. No other predictor variable was significant. In a subsequent analysis we examined the effects of age, oxygen saturation (SpO₂) and their interaction. All three predictors were significant. In particular, the effect of SpO₂ on MoCA score was modulated by age, as cognitive performance in older individuals was more susceptible to decrements in SpO₂ than younger individuals.

Conclusion: Lower oxygen saturation is associated with lower MoCA scores in older COVID-19 survivors, compared to younger adults. These findings may suggest that respiratory function is a therapeutic target for older COVID-19 survivors experiencing cognitive decline in the post-infectious period.

Main Manuscript

1. Introduction

COVID-19 is an acute, predominantly respiratory illness associated with substantial morbidity and mortality. Following the acute stage individuals can develop multisystemic sequelae sometime sufficiently severe to cause disability^{1,2}. These include fatigue, anosmia and cognitive complaints, along with dyspnoea, suggesting persistent involvement of the central nervous and pulmonary systems.^{3,4}

Acute disruption of pulmonary functions can lead to persistent cognitive impairment. Longitudinal studies of survivors of Acute Respiratory Distress Syndrome found high prevalence of decrements in psycho-motor speed, executive functions and memory up to two years after hospital discharge (Hopkins et al, 2012; Mikkelsen et al., 2012)⁵. Dycognitive phenomena also arise in other respiratory diseases such as COPD and are thought to reflect the effects of hypoxia and secondary neuroinflammation⁶.

The potential cause of post-COVID-19 persistent cognitive impairments however remains a matter of ongoing investigation⁷. One possibility is that cognitive impairments may be caused by ongoing pulmonary dysfunction.

In this study we examined a cross-sectional sample of patients who had developed persistent symptoms following an acute episode of COVID-19. We collected extensive anthropometric, physiological and physical performance measures to understand the correlates of cognitive performance and found that cognitive performance is strongly related to age and oxygen maturation. These findings have obvious if speculative implications for the aetiology and treatment of post-COVID-19 sequelae.

2. Methods

2.1 Participants

We analysed real-world data from 159 participants aged 40 years or older who were assessed in an academic outpatient clinic at least two months after hospital discharge. Participants had experienced symptomatic COVID-19 confirmed by a positive PCR test and reported persistent symptoms and impairments for at least two months following resolution of the acute illness.

Inclusion criteria were: age ≥ 40 -to- ≤ 80 years, without absolute and relative contraindications for 6-minute walk distance test⁸, body mass index ≤ 40 kg/m², daily physical strain⁹, without any form of musculoskeletal disability which could impair maximum exercise capacity¹⁰, no longer require O₂, without fever for consecutive 48-hour period, stable patients, without supplemental O₂¹¹.

The protocol was approved by the Institutional Ethics Committee of the University Hospital of Larissa (approval No. 7683/23-02-2022). All participants provided written informed consent. All study procedures involving human participants, human data and human samples were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

2.2 Data Collection

Body composition: Anthropometric characteristics such as body height (Seca 700, Hamburg, Germany), chest circumference in maximal inhalation and exhalation (Δ chest), neck circumference, and waist–hip ratio (Seca 201, Hamburg, Germany) were recorded according to previously a previously published protocol¹². For body composition assessment was used Tanita MC-980 (Arlington Heights, IL, USA)¹⁰. For each patient was calculated the body mass index and body surface area according to the equation of Mosteller¹³.

- 99 ▪ **Physical fitness tests:** i) The 6-minute walk test (6MWT) was performed according to
100 the ATS guidelines [doi:10.1164/ajrccm.166.1.at1102]. Before, at the end of 6MWT
101 and first minute of recovery were recorded blood pressure (Sphygmomanometer Mac
102 Check 501, Tokyo, Japan), arterial O₂ saturation (SpO₂) and heart rate (HR) (Nonin
103 9590 Onyx Vantage, Plymouth, MN, USA) and patients were self-assessment for
104 dyspnea and lower limbs fatigue with CR-10 Borg scale¹⁴. The SpO₂ and HR having
105 been recorded and every one minute of the test¹¹. ii) Handgrip strength test was assessed
106 with electronic dynamometer (Camry, EH 101, South El Monte, CA, USA), performing
107 one maximum isometric effort for 5 s with both hands alternately and in random order.
108 All patients reported their dominant upper limb before the trials¹¹. iii) 30s sit-to-stand
109 test was performed with a standard height (46 cm) chair without arm rests¹⁵. All patients
110 were asked to put their hands crossed on their shoulders and had to stand up and sit
111 down completely as many times as possible at self-paced (safe and comfortable) during
112 30s without using their arms as support. SpO₂ (Nonin 9590 Onyx Vantage, USA) and
113 HR (Nonin 9590 Onyx Vantage, USA) were recorded before and at the end of test.
114 Finally, was recorded the total number of completed repetitions.
- 115 ▪ **Pulmonary function test:** All patients underwent standard spirometry was recorded
116 according to ATS/ERS guidelines¹⁶ from sitting position using MasterScreen-CPX
117 pneumotachograph (VIASYS HealthCare, Germany). For each pulmonary function test,
118 three maximal flow-volume loops were obtained to determine FVC, FEV₁ and PEF.
119 Single-breath diffusing capacity for carbon monoxide (DLCO(SB)) was recorded
120 according to ATS/ERS guidelines¹⁶.
- 121 ▪ **Oxidative stress:** Blood sampling was performed 30 min before physical fitness tests,
122 and 10 mL sample was of peripheral venous blood was collected from each patient
123 having fasted the previous night¹⁷. Measurements included the determination of reactive
124 oxygen metabolites' levels (d-ROMs test) and the plasma antioxidant capacity (PAT
125 test) using the free radical analytical system, FRAS5 (Parma, Italy).
- 126 ▪ **Questionnaires and cognitive assessment:** Before physical fitness testing, participants
127 completed the Greek-language Pittsburgh Sleep Quality Index (PSQI), a previously
128 published sleep questionnaire with a Greek psychometric evaluation^{18,19}, and underwent
129 the Greek-language Montreal Cognitive Assessment (MoCA), a previously published
130 cognitive screening instrument with Greek normative and validity data^{20,21}. Neither
131 instrument was developed for this study. No separate study-specific questionnaire was
132 used; the analysis used real-world data generated during clinical assessment.

All sessions were performed in the Laboratory of Cardio-Pulmonary Testing and Pulmonary Rehabilitation of our hospital with the environmental temperature at 22.1 ± 1.3 °C and humidity $34.5 \pm 1.8\%$. The evaluation of patients was performed between 10:00 a.m. and 13:00 p.m.

2.3 Statistical analysis

The main outcome variable was the total MoCA score. The predictor set included 68 variables. In order to minimize its dimensionality, we grouped most of the variables into four sets: 1) anthropometric, 2) pulmonary functions, 3) physical performance and 4) the 6 Minutes Walking Test. An exploratory factor analysis was computed from ten imputed data sets in the following manner: from each imputed data set we obtained correlation matrices. These were normalised using an inverse hyperbolic function (Fisher, 1948), and the transformed matrices averaged. The anti-transformed average correlation matrix was factor analysed, with a maximum likelihood procedure. The number of factors was chosen by examining their eigenvalues. Retained factors included those with the largest eigenvalues at least up to the one that straddled the elbow in the scree plot. The eigenvalues of the retained factors always had a magnitude greater than 1.0.

From ten separately generated imputed data sets a multivariate linear regression was computed which included the factorised predictors as well as age, gender and the score on the PSQI. The age regressor was transformed by taking the logarithm in base 2 of the difference between 100 and the participants age in years.

3. Results

The final analysis included 159 participants aged 40 years or older. Table 1 presents their demographic and clinical characteristics and the distribution of MoCA scores.

Table 1. Patients' characteristics. Data are expressed as percent, mean $\pm$ standard deviation.

		COVID-19 survivors
Age	yrs	56.9 $\pm$ 11.0
Sex (Male/Female)	n	110 / 49
Body mass index	kg/m ²	29.0 $\pm$ 4.7
Body surface area	m ²	2.0 $\pm$ 0.4

		COVID-19 survivors
Body fat	%	33.1±13.8
Muscle mass	%	32.3±25.7
Visceral fat	score	12.7±4.5
Waist HR		0.9±0.1
6-minute walking test	m	510±120.2
30 sec Sit-to-Stand	repetitions	13.0±3.7
Handgrip strength	kg	34.4±10.9
d-ROMs	U. carr.	308.7±73.5
PAT	U. cor.	2619.9±364.9
PSQI	score	4.1±3.0
MoCA	score	24.3±3.5
Cognitively impaired	MoCA≤26	64%
	MoCA≤24	41%
FEV ₁	% of predicted	94.8±17.2
FVC	% of predicted	93.9±17.0
PEF	% of predicted	108.1±26.3
DLCO(SB)	% of predicted	77.1±17.6

Abbreviations: DLCO(SB) = single-breath diffusing capacity of the lung for CO; d-ROMs = determination of reactive oxygen metabolites' levels; FEV₁ = forced expiratory volume in 1st sec; FVC = forced vital capacity; MoCA = Montreal Cognitive Assessment questionnaire; PAT = plasma antioxidant capacity; PEF = peak expiratory flow; PSQI = Pittsburgh Sleep Quality Index questionnaire.

Table 2 reports the results of the imputed regression analysis. The only statistically significant predictors of MoCA scores were logarithmically transformed age and the composite of oxygen-saturation measurements derived from the six-minute walk test assessment.

Table 2. Predictors of MoCA scores in COVID-19 survivors.

Predictor	β	SE	df	<i>p</i> -value
Intercept	13.86	4.19	153.02	1.11·10⁻³
Log ₂ _Age	1.67	0.84	153.02	<0.05
Sex	1.40	0.87	153.02	0.11
PSQI	-0.06	0.69	153.02	0.39

Predictor	β	SE	df	<i>p</i> -value
Pulm_F1	0.05	0.17	153.02	0.79
Pulm_F2	0.17	0.18	153.02	0.36
Antr_F1	0.19	0.29	153.02	0.52
Antr_F2	-0.06	0.18	153.02	0.72
Perf_F1	0.26	0.22	153.02	0.24
Perf_F2	0.50	0.40	153.02	0.21
6MWT_F1	0.02	0.08	153.02	0.81
6MWT_F2	0.21	0.08	153.02	0.01
6MWT_F3	0.12	0.10	153.02	0.25
6MWT_F4	0.24	0.16	153.02	0.13

Abbreviations: Log₂_Age: Log 2 transformed age; “Perf” refers factors (F1-F2) derived from physical performance measures; “Antr” refers factors (F1-F2) derived from anthropometrics; refers factors (F1-F4) derived from the 6MWT; “Pulm” refers factors (F1-F2) derived from pulmonary function measures; PSQI: the Pittsburgh Sleep Quality Index.

The initial regression identified age and the oxygen-saturation composite as significant predictors of MoCA scores. The subsequent interaction analysis is reported in Table 3, and Figure 1 illustrates the relationship between age, resting oxygen saturation and MoCA scores.

Table 3. Linear regression results.

Predictor	β	SE	df	<i>p</i> -value
Intercept	8.58	3.50	163.02	$1.53 \cdot 10^{-2}$
Log ₂ _Age	1.67	0.84	163.02	$1.03 \cdot 10^{-5}$
6MWT_F2	0.21	0.08	163.02	$3.51 \cdot 10^{-3}$
Log ₂ _Age* 6MWT_F4	0.12	0.10	163.02	$5.85 \cdot 10^{-3}$

Abbreviations: β = regression coefficient; SE: standard error; df: degrees of freedom; 6MWT: 6 Minutes Walk Test.

To examine whether the predictors of MoCA exerted independent effects or rather interacted a second imputed regression was computed. The regression included three predictors, namely oxygen saturation, age and their product. All three predictors were highly significant. The figure shows a loess fit to the MoCA scores. The figure displays age and oxygen saturation measured

just before the 6MWT, while patients were at rest. The figure indicates that in younger individuals the MoCA score is unaffected by oxygen saturation. However, in older individuals the MoCA score is related to oxygen saturation measured at rest. This illustrates the nature of the interaction of age and oxygen saturation.

4. Discussion

In the present study we examined which factors predicted MoCA scores in a cross-sectional sample of a rural population of patients recovering from COVID-19 , who had presented to their local clinical services for their first follow-up post-discharge.

The sample consisted of 159 patients aged 40 years or older who had undergone an extensive clinical evaluation. This included pulmonary functions, physical performance, anthropometric and demographic variables. A first pass regression analysis indicated that age and the oxygen-saturation composite were the only significant predictors of MoCA scores. A second pass analysis suggested that the effects of these two variables on cognitive performance were not independent. Rather, cognitive performance was predicted by oxygen saturation in older patient, while middle aged individuals showed no appreciable relation between oxygen saturations and MoCA scores.

The finding that oxygen saturation modulates MoCA scores in symptomatic COVID-19 survivors is not particularly surprising given the extensive evidence that a variety of respiratory disorders which result in hypoxemia also produce cognitive decrements and are remedied by intervention to re-establish normoxia^{22,23}. Candidate mechanisms exist²⁴⁻²⁶, as well as paradigms of mechanistic, dose-response emergence of cognitive impairment in respiratory diseases^{6,27,28}. Specifically, large population-based studies have suggested that the severity of the respiratory difficulties experienced in the acute stage of the disease are monotonically related to the severity of the cognitive impairment in the recovery stage²⁹. While the correlative nature of our findings prevents conclusive statements about causality, previous evidence suggests that the effects of age on cognition of COVID-19 survivors are specific. In fact, other sequelae prevalent after COVID-19, such as fatigue, show a higher prevalence in younger rather than older survivors. Moreover, our results also suggest that hypoxemia may be the main clinical mediator of cognitive decrements in COVID-19 survivors. If so then the obvious question is why is the effect of hypoxemia strongly dependent on age? Age is known to affect human brain metabolism. In younger individuals aerobic glycolysis supplies a significant

proportion of the brain energy demands at rest and most of those stemming arising during task and stimulus evoked activity³⁰. In older individuals, basal energy demands rely more on oxidative phosphorylation instead³¹. Thus, greater dependence on oxidative metabolism may cause cerebral processes in older individuals to become less resilient to decrements in oxygen supply. Interestingly, PET studies in patients with cognitive impairment following COVID19 illness have uncovered decreases in glucose metabolism, specifically affecting those cortical regions, belonging to the Default Mode and the frontoparietal Control networks, that are most reliant on aerobic glycolysis in young healthy adults³². Another common denominator between age, hypoxia and cognitive impairment in the setting of COVID-19 is perturbations in type I interferon signalling (IFN-I). Age has been associated with proinflammatory changes in type I interferon signalling³³, a pathway we have previously shown to be common in the pathophysiology of neurodegeneration and COVID-19³⁴.

The neuropathology of COVID-19 patients has provided a strong case for potentially additive effects of age, hypoxia and immunity itself on IFN-I perturbations^{24,26,27,35}. While canonical IFN-I signalling in the brain serves homeostatic roles, unchecked activation has been shown to reliably promote neuroinflammation and independently, cognitive impairment³⁶. Within this setting, even altered bioenergetics due to age, as we've previously posited, could be affected and feed back to IFN-I signalling and persistent or aberrant immune challenge, as presented by COVID-19³⁷. This outline hypothesis however requires further mechanistic studies in order to be confirmed. Similarly, as studies on cerebral metabolism in COVID-19 survivors have not yet assessed the relative role of aerobic glycolysis and oxidative metabolism, this latter finding does not yield itself to a univocal interpretation.

What our findings confirm however, from a clinical point of view, is that an expected tripartite relationship that of age, inflammation and hypoxia, produce an expected outcome, i.e. cognitive impairment, evident in COVID-19 neuropathology³⁵. We furthermore provide a work hypothesis based on our findings and current literature, in order to inform future studies on the scope of assessments to be included, and the potential translational potential of their findings.

5. Conclusions

In this cross-sectional sample of 159 COVID-19 survivors aged 40 years or older assessed at least two months after discharge, age and an oxygen-saturation composite were associated with cognitive performance. The association between oxygen saturation and MoCA scores

was more pronounced in older participants. These findings support further investigation of respiratory function as a correlate of post-COVID cognitive impairment; the cross-sectional design does not establish causality or a treatment effect.

6. Declarations

Abbreviations

6MWT: six-minute walk test; ATS: American Thoracic Society; CNS: central nervous system; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CR-10: category-ratio 10 scale; df: degrees of freedom; DLCO(SB): single-breath diffusing capacity of the lung for carbon monoxide; d-ROMs: reactive oxygen metabolites test; ERS: European Respiratory Society; FEV1: forced expiratory volume in one second; FRAS: free radical analytical system; FVC: forced vital capacity; HIF: hypoxia-inducible factor; HR: heart rate; IFN-I: type I interferon; LOESS: locally estimated scatterplot smoothing; MoCA: Montreal Cognitive Assessment; PAT: plasma antioxidant capacity test; PCR: polymerase chain reaction; PEF: peak expiratory flow; PET: positron emission tomography; PSQI: Pittsburgh Sleep Quality Index; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SE: standard error; SpO2: peripheral oxygen saturation.

Ethics approval and consent to participate

The protocol was approved by the Institutional Ethics Committee of the University Hospital of Larissa (approval No. 7683/23-02-2022). All participants provided written informed consent. All study procedures involving human participants, human data and human samples were performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

Funding

Georgios Hadjigeorgiou and George D. Vavougiou received support from the Cyprus Academy of Sciences, Letters and Arts for the relevant clinical research and preparation of this manuscript.

Authors' contributions

GV conceived the project and wrote the first draft. NB, MZUHK, GD'A conceived the statistical analysis plan and executed it. SB, KT, ELP, EIP, GT, ID, KA, DM, GX provided data collection and curation. MZUHK, ZD, GH, GD'A, GX, SZ and KG contributed equally to the project (Team Coordination and Project Administration); VS, DM and NB contributed equally to this project (Data Collection and Analysis). All authors reviewed the manuscript. ELP denotes Eleanna Pitaraki; EIP denotes Eirini Papayianni. Both contributed to data collection and curation.

Acknowledgements

The authors acknowledge the support of the Cyprus Academy of Sciences, Letters and Arts.

7. References

1. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. Jun 2021;594(7862):259-264. doi:10.1038/s41586-021-03553-9
2. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. Jan 16 2021;397(10270):220-232. doi:10.1016/s0140-6736(20)32656-8
3. Taquet M, Geddes JR, Husain M, Luciano S, Harrison PJ. 6-month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a retrospective cohort study using electronic health records. *Lancet Psychiatry*. May 2021;8(5):416-427. doi:10.1016/s2215-0366(21)00084-5
4. Deer RR, Rock MA, Vasilevsky N, et al. Characterizing Long COVID: Deep Phenotype of a Complex Condition. *EBioMedicine*. Dec 2021;74:103722. doi:10.1016/j.ebiom.2021.103722
5. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF, Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. Feb 15 2005;171(4):340-7. doi:10.1164/rccm.200406-763OC
6. Cleutjens FA, Janssen DJ, Ponds RW, Dijkstra JB, Wouters EF. COgnitive-pulmonary disease. *Biomed Res Int*. 2014;2014:697825. doi:10.1155/2014/697825
7. de Erausquin GA, Snyder H, Brugha TS, et al. Chronic neuropsychiatric sequelae of SARS-CoV-2: Protocol and methods from the Alzheimer's Association Global Consortium. *Alzheimers Dement (N Y)*. 2022;8(1):e12348. doi:10.1002/trc2.12348

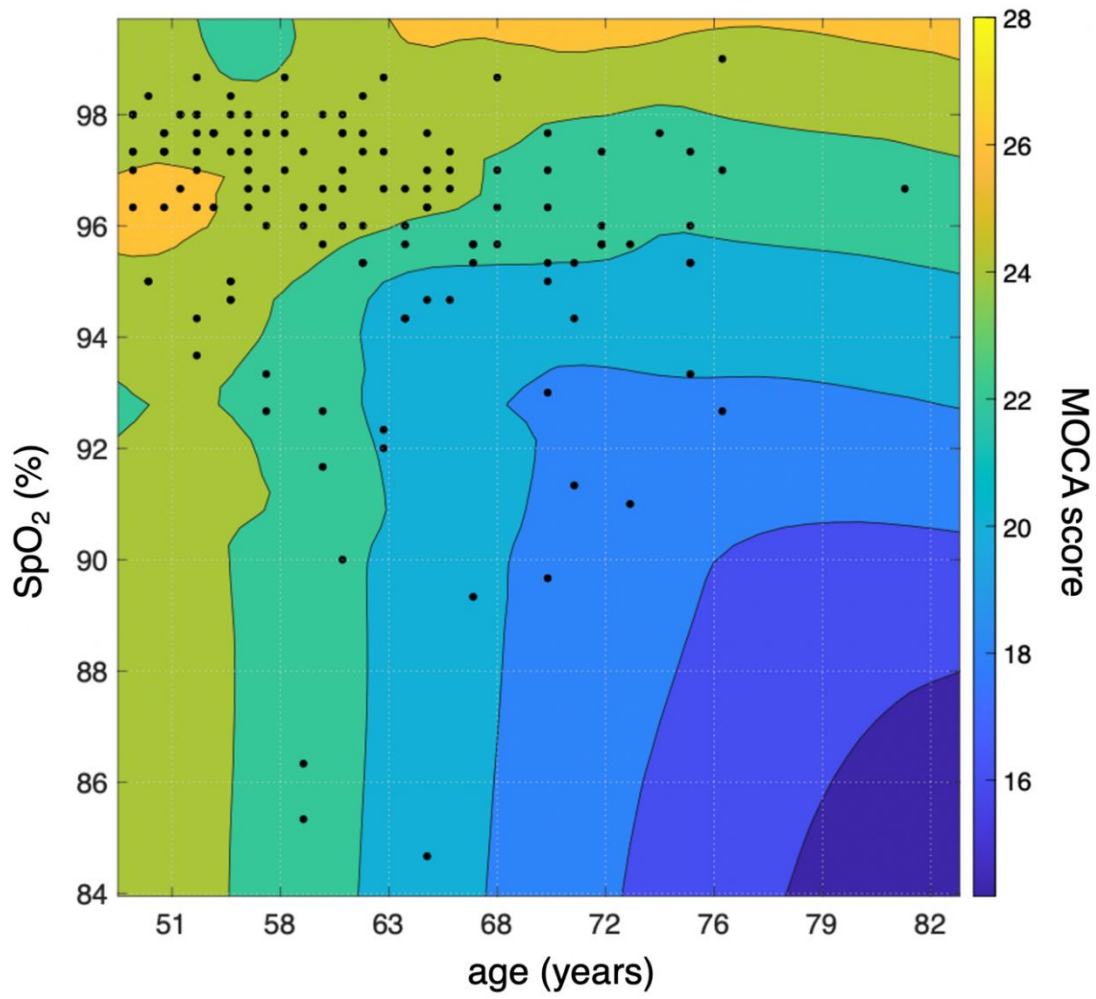
8. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*. Dec 2014;44(6):1428-46. doi:10.1183/09031936.00150314
9. Stavrou V, Bardaka F, Karetsi E, Seitanidis G, Daniil Z, Gourgoulisanis KI. The effect of physical strain on breeders patients with obstructive sleep apnea syndrome. *Respir Physiol Neurobiol*. Feb 2019;260:137-139. doi:10.1016/j.resp.2018.11.009
10. Stavrou VT, Astara K, Daniil Z, et al. The Reciprocal Association between Fitness Indicators and Sleep Quality in the Context of Recent Sport Injury. *Int J Environ Res Public Health*. Jul 3 2020;17(13)doi:10.3390/ijerph17134810
11. Stavrou VT, Vavougiou GD, Boutlas S, et al. Physical Fitness Differences, Amenable to Hypoxia-Driven and Sarcopenia Pathophysiology, between Sleep Apnea and COVID-19. *Int J Environ Res Public Health*. Jan 7 2022;19(2)doi:10.3390/ijerph19020669
12. Stavrou VT, Tourlakopoulos KN, Vavougiou GD, et al. Eight Weeks Unsupervised Pulmonary Rehabilitation in Previously Hospitalized of SARS-CoV-2 Infection. *J Pers Med*. Aug 18 2021;11(8)doi:10.3390/jpm11080806
13. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. Oct 22 1987;317(17):1098. doi:10.1056/nejm198710223171717
14. Borg E, Borg G, Larsson K, Letzter M, Sundblad BM. An index for breathlessness and leg fatigue. *Scand J Med Sci Sports*. Aug 2010;20(4):644-50. doi:10.1111/j.1600-0838.2009.00985.x
15. Reyckler G, Boucard E, Peran L, et al. One minute sit-to-stand test is an alternative to 6MWT to measure functional exercise performance in COPD patients. *Clin Respir J*. Mar 2018;12(3):1247-1256. doi:10.1111/crj.12658
16. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. Jan 2017;49(1)doi:10.1183/13993003.00016-2016
17. Stavrou VT, Vavougiou GD, Astara K, Siachpazidou DI, Papayianni E, Gourgoulisanis KI. The 6-Minute Walk Test and Anthropometric Characteristics as Assessment Tools in Patients with Obstructive Sleep Apnea Syndrome. A Preliminary Report during the Pandemic. *J Pers Med*. Jun 16 2021;11(6)doi:10.3390/jpm11060563
18. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. May 1989;28(2):193-213. doi:10.1016/0165-1781(89)90047-4
19. Kotronoulas GC, Papadopoulou CN, Papapetrou A, Patiraki E. Psychometric evaluation and feasibility of the Greek Pittsburgh Sleep Quality Index (GR-PSQI) in patients with cancer receiving chemotherapy. *Support Care Cancer*. 2011;19(11):1831-1840. doi:10.1007/s00520-010-1025-4
20. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x
21. Konstantopoulos K, Vogazianos P, Doskas T. Normative Data of the Montreal Cognitive Assessment in the Greek Population and Parkinsonian Dementia. *Arch Clin Neuropsychol*. 2016;31(3):246-253. doi:10.1093/arclin/acw002
22. Mikkelsen ME, Christie JD, Lanken PN, et al. The Adult Respiratory Distress Syndrome Cognitive Outcomes Study. *American Journal of Respiratory and Critical Care Medicine*. 2012-6-15 2012;185(12):1307-1315. doi:10.1164/rccm.201111-2025OC
23. Shieu MM, Zaheed A, Shannon C, et al. Positive Airway Pressure and Cognitive Disorders in Adults With Obstructive Sleep Apnea: A Systematic Review of the Literature. *Neurology*. 2022-05-06 2022;99(4):e334-346. doi:10.1212/WNL.0000000000200383

24. Li G, Liu J, Guo M, et al. Chronic hypoxia leads to cognitive impairment by promoting HIF-2 α -mediated ceramide catabolism and alpha-synuclein hyperphosphorylation. *Cell Death Discovery*. 2022/11/30 2022;8(1):473. doi:10.1038/s41420-022-01260-6
25. Peng T, Du SY, Son M, Diamond B. HIF-1 α is a negative regulator of interferon regulatory factors: Implications for interferon production by hypoxic monocytes. *Proc Natl Acad Sci U S A*. Jun 29 2021;118(26)doi:10.1073/pnas.2106017118
26. McDonough A, Lee RV, Noor S, et al. Ischemia/Reperfusion Induces Interferon-Stimulated Gene Expression in Microglia. *J Neurosci*. Aug 23 2017;37(34):8292-8308. doi:10.1523/jneurosci.0725-17.2017
27. Wang X, Cui L, Ji X. Cognitive impairment caused by hypoxia: from clinical evidences to molecular mechanisms. *Metab Brain Dis*. Jan 2022;37(1):51-66. doi:10.1007/s11011-021-00796-3
28. Gagnon K, Baril AA, Gagnon JF, et al. Cognitive impairment in obstructive sleep apnea. *Pathol Biol (Paris)*. Oct 2014;62(5):233-40. doi:10.1016/j.patbio.2014.05.015
29. Hampshire A, Trender W, Chamberlain SR, et al. Cognitive deficits in people who have recovered from COVID-19. *EClinicalMedicine*. 2021-09 2021;39:101044. doi:10.1016/j.eclinm.2021.101044
30. Vaishnavi SN, Vlassenko AG, Rundle MM, Snyder AZ, Mintun MA, Raichle ME. Regional aerobic glycolysis in the human brain. *Proceedings of the National Academy of Sciences*. 2010-10-12 2010;107(41):17757-17762. doi:10.1073/pnas.1010459107
31. Goyal MS, Vlassenko AG, Blazey TM, et al. Loss of Brain Aerobic Glycolysis in Normal Human Aging. *Cell Metabolism*. 2017-08-01 2017;26(2):353-360.e3. doi:10.1016/j.cmet.2017.07.010
32. Hosp JA, Dressing A, Blazhenets G, et al. Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of COVID-19. *Brain*. May 7 2021;144(4):1263-1276. doi:10.1093/brain/awab009
33. Baruch K, Deczkowska A, David E, et al. Aging. Aging-induced type I interferon response at the choroid plexus negatively affects brain function. *Science*. Oct 3 2014;346(6205):89-93. doi:10.1126/science.1252945
34. Vavougiou GD, de Erausquin GA, Snyder HM. Type I interferon signaling in SARS-CoV-2 associated neurocognitive disorder (SAND): Mapping host-virus interactions to an etiopathogenesis. *Front Neurol*. 2022;13:1063298. doi:10.3389/fneur.2022.1063298
35. Mavrikaki M, Lee JD, Solomon IH, Slack FJ. Severe COVID-19 is associated with molecular signatures of aging in the human brain. *Nature Aging*. 2022/12/01 2022;2(12):1130-1137. doi:10.1038/s43587-022-00321-w
36. Blank T, Prinz M. Type I interferon pathway in CNS homeostasis and neurological disorders. *Glia*. Sep 2017;65(9):1397-1406. doi:10.1002/glia.23154
37. Wu D, Sanin DE, Everts B, et al. Type I Interferons Induce Changes in Core Metabolism that Are Critical for Immune Function. *Immunity*. Jun 21 2016;44(6):1325-36. doi:10.1016/j.immuni.2016.06.006

8. Figure legends

Figure 1. The relationship between MoCA scores, age and resting oxygen saturation is illustrated in a contour plot. Oxygen saturation was recorded before the six-minute walk test,

403 while patients were at rest. The age axis is scaled logarithmically. MoCA scores were fitted
404 using a LOESS procedure with a linear kernel. Each point represents a participant.



405