

Prevalence and Reversibility of Smell Dysfunction Measured Psychophysically in a Cohort of COVID-19 patients

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Key Words: anosmia, hyposmia, COVID-19, SARS-Co-V-2, UPSIT, odor Identification, virus, olfaction

Abstract

Background: Considerable evidence suggests that smell dysfunction is common in Coronavirus Disease 2019 (COVID-19). Unfortunately, extant data on prevalence and reversibility over time are highly variable, coming mainly from self-report surveys prone to multiple biases. Thus, validated psychophysical olfactory testing is sorely needed to establish such parameters.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/alr.22680](https://doi.org/10.1111/alr.22680).

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Methods: One hundred SARS-CoV-2 positive cases were administered the 40-item University of Pennsylvania Smell Identification Test (UPSIT) in the hospital near the end of the acute phase of the disease. Eighty-two were retested 1 or 4 weeks later at home. The data were analyzed using analysis of variance and mixed-effect regression models.

Results: Initial UPSIT scores were indicative of severe microsmia, with 96% exhibiting measurable dysfunction; 18% were anosmic. The scores improved upon retest [initial and retest means (95%CI) = 21.97 (20.84,23.09) & 31.13 (30.16,32.10; $p<0.0001$)]; no patient remained anosmic. After five weeks from COVID-19 symptom onset, the test scores of 63% of the retested patients were normal. However, the mean UPSIT score at that time continued to remain below that of age- and sex-matched healthy controls ($p<0.001$). Such scores were related to time since symptom onset, sex, and age.

Conclusion: Smell loss was extremely common in the acute phase of a cohort of 100 COVID-19 patients when objectively measured. About one-third of cases continued to exhibit dysfunction after five post-symptom onset weeks. These findings have direct implications for the use of olfactory testing in identifying SARS-CoV-2 virus carriers and for counseling such patients in regards to their smell dysfunction and its reversibility.

Introduction

There is strong evidence that many persons infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience loss of smell function.¹ This has led the Centers for Disease Control (CDC) and other health organizations to recognize smell loss as a major sign of Coronavirus Disease 2019 (COVID-19), the disease caused by this virus.² Such loss has been suggested as a potential COVID-

19 biomarker.³ However, estimates of the prevalence of COVID-19-related smell dysfunction are highly variable, as are estimates of recovery of function, reflecting wide-spread reliance on self-report surveys. Such surveys are susceptible to confounding by recall bias, sampling issues, and a lack of subject awareness, the latter being common when it comes to recognizing less-than-total smell or taste loss.^{4,5} Thus, prevalence rates among such surveys range from 5%⁶ to 85%,⁷ with percentages in between (e.g., 15%,⁸ 31%,⁹ 39%,¹⁰ 41%,¹¹ 47%,¹² 50%,¹³ 65%,¹⁴, 72%¹⁵ and 74%¹⁶). Although based on fewer studies, extant information on reversibility of the smell loss comes solely from self-report surveys whose findings, like those of prevalence, are non-definitive.^{7,8,15} In most such studies, the majority of patients have reported regaining normal function within two weeks.

This study employed a well-validated and sensitive psychophysical test to estimate the prevalence, magnitude, and reversibility of the olfactory dysfunction of a cohort of COVID-19 patients. It is the first to longitudinally test smell function in such a group over the course of one to eight weeks after the onset of disease symptoms and the first to evaluate the influences of such variables as disease severity, sex, and age on the test scores. Its findings have direct implications for the use of olfactory tests in identifying SARS-CoV-2 virus carriers and for counseling patients in regards to their smell dysfunction and its likely course of return.

Methods

Study Design

The olfactory function of 100 SARS-CoV-2 positive patients, described in the next section, was tested during the late acute phase of their disease. Eighty-two of these subjects were retested a second time. The first test was performed in a tertiary referral hospital in Tehran, Iran, during the patients' inpatient recovery period. The

second test was performed, on average, either one week ($n = 35$) or four weeks ($n = 47$) later in the patients' homes. To determine whether COVID-19 had a long lasting adverse effect on smell function, the UPSIT scores of 51 patients tested 6 to 8 weeks after disease symptom onset was compared to those of 51 age- and sex-matched normal controls.

Subjects

The 100 COVID-19 patients had been admitted to Masih Daneshvari University Hospital, Tehran, Iran, between March 21, 2020, and May 3, 2020. Of these, two declined to participate in the follow-up study, three were admitted to another hospital for other symptoms or comorbidities, and 13 were not available by phone, resulting in 82 subjects who underwent retesting. The 51 healthy controls were selected from a database of 141 subjects previously tested for an earlier study at the Institute for Research in Fundamental Sciences in Tehran, as described elsewhere.³ The demographics of all patients and controls are presented in Table 1.

INSERT TABLE 1 ABOUT HERE

The patients were ready to be discharged from the hospital within 4 days; comorbidities are shown in Table 2. Inclusion criteria included (a) having either a positive chest X-ray or CT finding for COVID-19, (b) exhibiting a positive real-time reverse transcription polymerase chain reaction (rRT-PCR) of SARS-CoV-2 infection in respiratory specimens collected from nasopharyngeal wash/aspirate or nasal aspirate, and (c) being healthy enough to take the olfactory test. The rRT-PCR assays for quantitative detection of SARS-CoV-2 RNA were performed using Sansure Biotech's 2019-nCoV 30-Minute Nucleic Acid Reagent Kits (Sansure Biotech, Inc., Development Zone, Changsha, China). The specimen collection, handling, and analyses were implemented according to World Health Organization

recommendations.¹⁷ Exclusion criteria were age <18 years, pregnancy, dementia, invasive ventilation, and self-report of pre-existing chronic smell dysfunction prior to COVID-19. The clinical severity of the COVID-19 presentation was classified as mild, moderate, or severe according to the Massachusetts General Hospital COVID-19 treatment guidance algorithm.¹⁸ All subjects provided Informed consent and the study protocol was approved by the local ethics committee and the Iranian Ministry of Health (license number IR.SBMU.NRITLD.REC.1399. 013).

INSERT TABLE 2 ABOUT HERE

Olfactory Evaluation

Before psychophysical olfactory testing, the patients were asked two brief questions concerning their chemosensory perception: “Do you suffer from smell or taste problems (if yes, which one: smell, taste or both)?” If the answer to the first question was yes, the next question was: “When did your smell/taste problem start? -- Before the onset of your COVID-19 symptoms? -- With/after the onset of COVID-19 symptoms?”

A revised Persian version of the University of Pennsylvania Smell Identification Test (UPSIT; Sensonics International, Haddon Hts., NJ, USA) was used to quantitatively test olfactory function.³ This self-administered 40-odorant test is well-validated and reliable (test-retest $r=0.94$).¹⁹ In addition to providing an overall quantitative score, this forced-choice test allows for the categorization of test scores into meaningful functional categories, i.e., anosmia, severe microsmia, moderate microsmia, mild microsmia, normosmia, and malingering. The in-hospital olfactory testing was performed with the aid of a trained assistant.

Following completion of the hospital testing, each patient was provided with an UPSIT to self-administer at home. The patients were subsequently re-contacted

by telephone to confirm their willingness to perform the follow-up testing at the appropriate time for retest. If confirmed, a detailed instruction manual of the test was sent to them using WhatsApp application to remind them of the administration procedures. Patients were asked not to have any food or beverage for 15 minutes prior to taking the smell test. Each patient sent back the photo of the choices made for each of the 40 odorants via WhatsApp.

Statistical analyses

All analyses were performed using MATLAB version R2019b (The MathWorks, Inc., Natick, MA, USA). Comparisons between the initial test and retest UPSIT scores, as well as between the scores of the patients and their matched controls, were made using repeated measures analyses of variance (ANOVAs). To assess factors that impacted the COVID-19 olfactory deficit, linear mixed-effect regression models were developed. Independent variables such as age, gender, clinical symptom severity, and education were initially entered into the models. Variables that did not meaningfully contribute to a model were sequentially removed. Our use of mixed-effect regression models allowed, using maximum likelihood estimation, for the inclusion of all data, i.e., that from subjects with and without follow-up scores. The model with the lowest Akaike information criterion (AIC), which optimizes model quality by providing a trade-off between goodness of fit and model simplicity, was chosen for the final model.¹⁹

Results

The initial (Test 1) and follow-up (Test 2) UPSIT scores are shown in Figure 1, Individual trajectories are presented in Figure 2, along with a bar graph showing that the amount of UPSIT change was greater for those with a 4-week test-retest interval than those with a 1-week test-retest interval [$F(1,80) = 8.16$, $p = 0.005$, $\eta^2 = 0.09$]. Interestingly, of the 100

patients included in the study, only 28 reported experiencing a smell problem prior to the psychophysical testing.

The average Test 1 UPSIT scores were indicative of severe microsmia in the COVID-19 study group [mean (95% CIs) = 21.97 (20.84,23.09)], with 96% of the patients exhibiting measurable dysfunction; 18% were anosmic. The mean Test 2 UPSIT scores depicted in Figure 1 were higher than the Test 1 scores [$F(1,81) = 211.84$, $p < 0.0001$; $\eta^2 = 0.73$]. Despite the improvement over time, a significant number of patients continued to exhibit moderate to severe microsmia (Table 3). The proportion of subjects regaining normal smell function increased from 4% (4/100) at the first test to 61% (50/82) in the follow-up period. It is remarkable that, of the 82 patients that were retested, only 5 (6%) failed to show improvement on retest, with their scores remaining the same.

INSERT FIGURES 1 & 2 ABOUT HERE

Given reports that recovery of COVID-19-related olfactory dysfunction occurs within a month after disease onset, we compared UPSIT scores of those 51 patients who were retested after five weeks, i.e., those on the right side of the dashed vertical line of Figure 2, to those of healthy age- and sex-matched normal controls (Figure 3). Only 63% were normal, clearly indicating that smell dysfunction in many patients continues well beyond a month. The means of these two groups were significantly different (respective means (95% CIs) = 31.27 (29.97,32.57) and 34.39 (33.53,35.35; $F(1,50) = 16.44$, $p < 0.001$; $\eta^2 = 0.32$).

INSERT FIGURE 3 AND TABLE 3 ABOUT HERE

Since variables such as age, sex, and time between assessments are amalgamated in the data depicted in both Figures 1 and 2 and in the aforementioned analyses, we performed a series of linear mixed-effect regression models to identify the influences of such variables. The outcome variable was comprised of all of the UPSIT scores, i.e., both Test 1 and Test 2 scores. A number of independent variables served as fixed effects. Between

subject variability was considered a random effect. The initial regression model included age, sex, education, disease severity, and time from symptom onset. Smoking was not considered since only 4 of the 100 subjects smoked. The final model with the lowest AIC (see methods) that accounted for the most variability in UPSIT scores included time from COVID-19 symptom onset (in days), sex, and age. In this model, the time from symptom onset was positively related to the UPSIT scores [coefficient = 0.29; 95% CI = 0.24,0.34; $p < 0.0001$], as was being a woman [2.07; 95% CI = 0.21,3.94; $p = 0.02$]. Older age [mean, 95% CI = -0.16;-0.24,-0.08; $p < 0.0001$] negatively impacted the test scores. In other words, better scores occurred in women than in men, in younger than older subjects, and in those tested later with respect to the initial symptom onset. Including the intercept, this model explained over half of the UPSIT variance [25.90; 95% CI = 21.12,29.68; $p < 0.0001$] (adjusted $R^2 = 0.54$).

The proportion of patients regaining differing degrees of function over time is illustrated in Figure 4. It should be noted that all initial and follow-up scores are combined for the purpose of visualization. For the patients tested during the first two weeks after COVID-19 symptom onsets, only 6% were normosmic; most had some degree of smell dysfunction with over half exhibiting severe microsmia or anosmia. However, as time passed, these ratios changed towards improvement of function. In those tested during the third and fourth weeks, normosmia increased to 27% and anosmia and severe microsmia accounted for less than 30%. This normosmic proportion increased steadily over time so that by seven to eight weeks from the onset of symptoms, more than 60% of the patients tested had normal olfactory function and those with severe microsmia or anosmia consisted only about 17% of the group. Overall, the test scores of 86% (71/82) of the patients improved by at least one clinical category, e.g., from mild microsmia to moderate microsmia. Among those that did not so improve, four were normosmics, four had mild microsmia, and three had moderate to severe microsmia.

INSERT FIGURE 4 ABOUT HERE

Discussion

By using a sensitive 40-odorant psychophysical smell test, we found some degree of smell loss in 96% of 100 COVID-19 patients tested during the late acute phase of their disease. Anosmia, however, was not the norm. Over the course of eight post-symptom onset weeks, 61% of those retested regained normal function. However, even by six weeks the average UPSIT scores remained below those of age- and gender-matched normal controls, with a significant number of patients experiencing moderate to severe microsmia. Clearly, the time to recovery is highly variable.

Our finding that nearly all 100 COVID-19 patients tested in this study initially exhibited some degree of smell loss is remarkable, particularly in light of the fact that the initial testing of many of these patients was performed after the disease symptoms had been present for more than two weeks. This suggests that self-report surveys, whose estimates of dysfunction commonly fall below 50%, greatly underestimate the prevalence of such loss. A lack of correspondence between awareness of olfactory dysfunction and objective testing is well established in the general population⁴ and is paralleled by the present study's finding that only 28% of the COVID-19 patients were aware of their dysfunction until testing. Others have also seen significant discrepancies between self-report and psychophysical olfactory test measures.²¹⁻²³ Interestingly, the prevalence rate observed in self-report studies appears to be positively correlated with the amount of attention in the popular press paid to COVID-19's impact on the ability to smell.²⁴

The present findings also contrast with prevalences reported in the few smaller studies in which olfactory tests have been administered. Thus, using 16-item smell identification tests, Bocksberger et al.¹¹ found olfactory dysfunction in 10 of 14 (71%) COVID-19 patients and Lechien et al.²⁵ in 53 of 86 (62%) such patients. Vaira

et al.¹⁶ found deficits in 62 of 72 COVID-19 patients (86%; 2 anosmic and 60 hyposmic) using a 10-odor identification test of household objects and ethyl alcohol and n-butanol threshold tests, whereas Tsivgoulis et al.²⁶ found smell dysfunction in 17 of 22 (77%) such patients using a 3-odor smell test.

The basis for the higher initial prevalence of smell dysfunction in the present study is not clear, although several factors may be involved. First, the time of testing relative to disease onset appears to be longer in a number of studies than our mean (SD) of 14.75 (9.23) post-onset days, suggesting function may have returned in some cases.^{16,25} Second, both threshold tests and shorter odor identification tests have been shown to be less reliable and sensitive to olfactory deficits than the 40-item UPSIT,²⁷ a test which provides a more nuanced assessment of different levels of dysfunction. Third, we used 31/40 (78%) as the normative UPSIT cut-off for defining abnormality for the Persian population based upon healthy control group data obtained in Tehran. Since the 16-item test used in two of the aforementioned studies defined a smell problem as a score of 12 or below (75%), then conceivably a 3% difference in test scores would accrue. However, this difference would not completely explain our higher rate of dysfunction. Fourth, regional differences in the veracity SARS-CoV-2 and susceptibility of local populations to infection, as well as differences in subject characteristics and recruitment strategies, could be involved. For example, in accord with most COVID-19 studies,²⁸ proportionately more men (67%) were present in our sample than in the other olfactory studies in which women predominate (e.g., 30%,²⁹ 35%,⁷ 37.5%,¹⁶ 57%²⁶). Given that women generally outperform men on olfactory tests³⁰ and are more likely to volunteer for studies than men,³¹ these differences could reflect survey recruitment biases.

As clearly shown in Figure 2, the time course of return of olfactory function observed in our study varied considerably for individual patients. As we show, some of this variability relates to the sex and age of the subjects, as well as the time from the onset of COVID-19 symptoms. Our longitudinal cohort design overcame a number of limitations of self-report surveys, such as recall bias, over-representation of females, and the low awareness of smell loss observed in many individuals. Given the latter, our baseline metric for assessing change was the time of symptom onset. Although this metric has also been used in some self-report surveys,^{11,16} others have employed the time since first noticing chemosensory dysfunction,^{15,25,29} which seems questionable in light of the inaccuracy of awareness. All such studies, however, are in general agreement with ours in noting that many patients regain function over relatively brief periods of time.

Although SARS-CoV-2 viral load is significantly decreased by two weeks,³² it is not clear whether viral load, per se, meaningfully impacts smell function or, if so, at what point in time such load is associated with enough cellular damage to induce smell deficits. There is evidence of smell loss continues to be present in COVID-19 patients after rRT-PCR test findings have returned to normal.¹³ Most likely acute virus-related damage to the olfactory epithelium is the basis for the smell deficit of COVID-19, as seen in other viral infections.^{33,34} The degree of return of function likely reflects the propensity of the olfactory neuroepithelium to regenerate and the amount of prior epithelial damage from cumulative xenobiotic insults.^{35,36} The high rate of cell turnover and neurogenesis within the human olfactory neuroepithelium, as well as the presence of immune system cells critical for epithelial homeostasis, likely serve to mitigate the transport of viruses such as SARS-CoV-2 from the nasal cavity into the brain.³⁷ Animal models have found angiotensin converting enzyme 2

(ACE2) and TMPRSS2 cell surface proteins are involved in the entry of SARS-CoV-2 into both supporting (sustentacular) and progenitor (horizontal and globose basal cells) cells within the olfactory neuroepithelium, thereby disrupting epithelial regeneration. Interestingly, TMPRSS2 expression is increased with older age.³⁸ This could be a potential explanation for the negative effect of older age on the recovery of the sense of smell in the patients evaluated in this study.

The present study has both strengths and weaknesses. Among its strengths are (a) the use of a well-validated sensitive test of olfactory function that allows for determining different degrees of olfactory function, (b) testing of a reasonably sized cohort of COVID-19 patients whose clinical severity was well documented, (c) longitudinal testing of patients over a period of time ranging, in individual cases, up to eight weeks, and (d) an evaluation of the influences of multiple variables on the olfactory test scores. One limitation of the study is that no more than two time points were assessed in individual subjects. Thus, it is not known whether improvement in those with a 4-week test-retest interval might have occurred earlier than that depicted in Figure 2. Another limitation is that longitudinal testing did not go beyond eight weeks since symptom onset. Additionally, although one might argue that self-administration of a smell test is a liability, the self-administered UPSIT is very reliable and its test scores have been shown not to vary between clinic and home administrations.³⁹ The patients of our study were proficient with computers and were able to use WhatsApp to provide their home test results.

In conclusion, we found, using well-validated psychophysical testing, some measurable degree of smell dysfunction near the end of the acute recovery period in most of the COVID-19 patients. However, complete loss of function occurred in only about a quarter of such patients, with severe microsmia occurring in about a third. In

our study sample, only a minority of patients were aware of their dysfunction before testing, mirroring a phenomenon also present in the general population. Return to normal function was found in slightly over half of the patients by four weeks after symptom onset; by six weeks, this percentage rose to two-thirds. However, even by this time the average olfactory test score was significantly lower than that of healthy age- and gender-matched normal controls. Factors significantly related to the extent of smell loss included time since disease symptom onset, age, and sex. Our findings support the view that olfactory testing, when performed early in the disease, may aid in the identification of patients infected with the SARS-CoV-2 virus. Future work is needed to determine whether otherwise asymptomatic persons carrying this virus can be detected by the presence of objectively-measured smell dysfunction.

Acknowledgments

We would like to thank Mr. Iraj Fotouhi for his invaluable help in assisting patients during smell testing, Mr. Mark Potter for his comments on a draft of the paper, and Dr. Kambiz Pourrezaei for insightful discussions of the research. The study was funded by institutional funds from the Institute for Research in Fundamental Sciences.

Author Contributions

STM, and RLD had roles in the study design, data analysis, data interpretation, literature search, and writing of the manuscript. SMRH and PT had roles in recruitment, data collection, clinical management, and revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

Disclosures

RLD is a consultant to Eisai Co, Ltd, Merck Pharmaceuticals, the Michael J. Fox Foundation for Parkinson's Research, Septodont, Inc., and Johnson & Johnson. He receives royalties from Cambridge University Press, Johns Hopkins University Press, and John Wiley & Sons, Inc. He is president of, and a major shareholder in, Sonsonics International, a manufacturer and distributor of smell and taste tests, including the test used in this study. The other authors have nothing to declare.

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Table 1. Demographic characteristics of the COVID-19 and Control Subjects. See text for details.

	COVID-19 patients (Test1)	COVID-19 patients (Test 2)	6-8 week COVID-19 retest group*	Normal controls
Sample Size	100	82	51	51
Mean Age (SD; range)	45.40 (11.80; 23-76)	45.53 (11.50; 24-76)	45.54 (10.95; 25-72)	45.41 (10.90; 25-72)
Gender	67 M & 33 F	54 M & 28 F	32 M & 19 F	32 M & 19 F
Current/Never Smoker	4/96	3/79	1/50	9/42

Education	Grade school only	6%	4%	2%	0%
	Middle school	15%	14%	12%	2%
	High school	35%	39%	45%	20%
	Associate degree	4%	4%	2%	4%
	BA/BS	22%	21%	17%	27%
	MS	6%	4%	6%	33%
	MD/PhD	12%	14%	16%	14%

*These subjects were a subgroup of the 82 COVID-19 retest subjects. They were selected on the basis of having their second test 6 to 8 weeks after the onset of the disease symptoms.

Table 2. Clinical features and comorbidities of the 100 COVID-19 patients.

Clinical Features		Frequency (N = 100)
Symptoms	Fever	78%
	Cough	57%
	Shortness of breath	48%
	Headache	39%
	Myalgia	5%
	Shivering	3%
	Sweating	2%
	Gastrointestinal symptoms	3%
	Malaise	1%
	Tinnitus	1%
	Bloody sputum	1%
COVID-19 clinical severity*	Mild	58%
	Moderate	30%
	Severe	12%
Pre-test self-reports of chemosensory dysfunction	Smell loss	28%
	Taste loss	22%
	Both taste and smell loss	18%

Comorbidity	Asthma	3%
	Autoimmune disease**	5%
	Benign prostatic hyperplasia	2%
	Carcinoma***	2%
	Chronic renal failure	2%
	Congenital melanocytic nevi	1%
	Diabetes	13%
	Heart valve disease	2%
	Hyperlipidemia	2%
	Hypertension	10%
	Hypothyroidism	7%
	Sinusitis	2%

*Based on Massachusetts General Hospital COVID-19 treatment guidance for treatment algorithm.¹⁸

Autoimmune disease included Behcet's disease in combination with Crohn's disease (n = 1), multiple sclerosis (n=2), and rheumatoid arthritis (n = 2). * Prostate and cervical cancers. BA: Bachelor of Arts; BS: Bachelor of Science, MS: Master of Science; MD: Doctor of Medicine; PhD: Doctor of Philosophy

Table 3. Classification of olfactory function of the UPSIT scores of COVID-19 patients with test and retest.

UPSIT function category (score range)	Percent of patients in the initial testing (N=100)	Percent of patients in the follow-up testing (N=82)
Normosmia (31 - 40)	4%	61%
Mild microsmia (28 - 30)	13%	20%
Moderate microsmia (24 - 27)	24%	13%
Severe microsmia (17 - 23)	41%	6%
Anosmia (6 - 16)	18%	0%
Probable malingering (0 - 16)	0%	0%

Figure 1. UPSIT scores of the COVID-19 patients for the initial (Test 1) and follow-up (Test 2) periods. The distribution of the subjects' scores in each group is depicted in violin plot. The white circles indicate medians and the vertical dark lines interquartile ranges. See text for details.

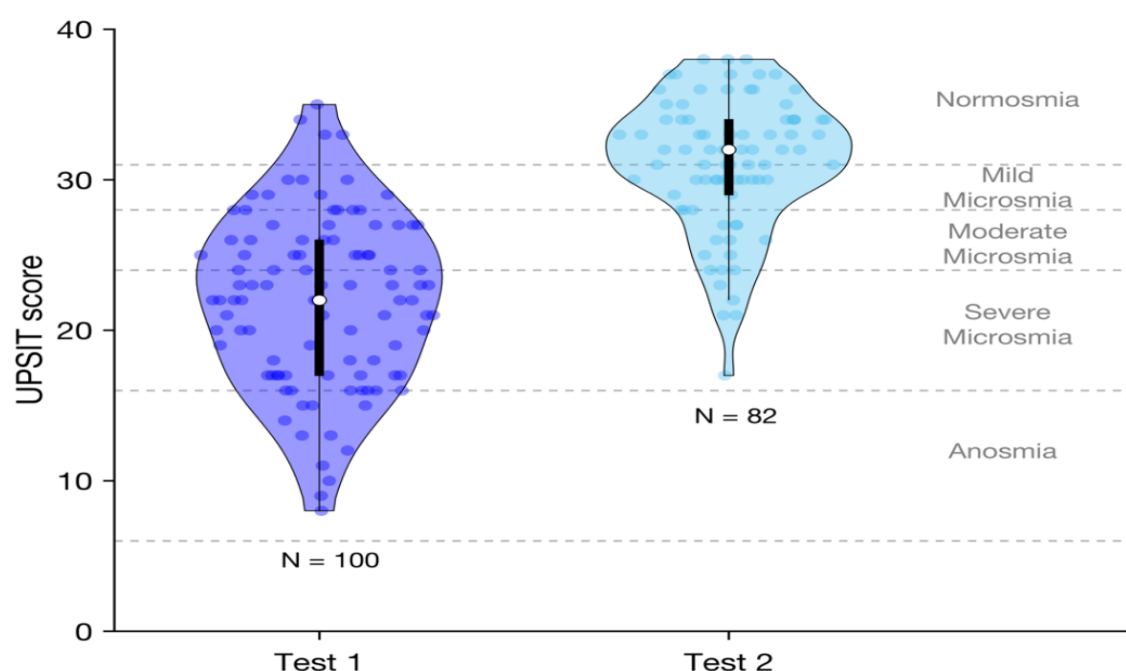


Figure 2. Test and retest UPSIT scores as a function of days from the onset of COVID-19 symptoms. The inter-test intervals were one and four weeks. Repeat test scores to the right of the vertical dashed line represent the data that were compared to those of the healthy matched controls. The inset shows the mean (95% CI) differences between the initial and retest scores for the one week and four week intervals. See text for details.

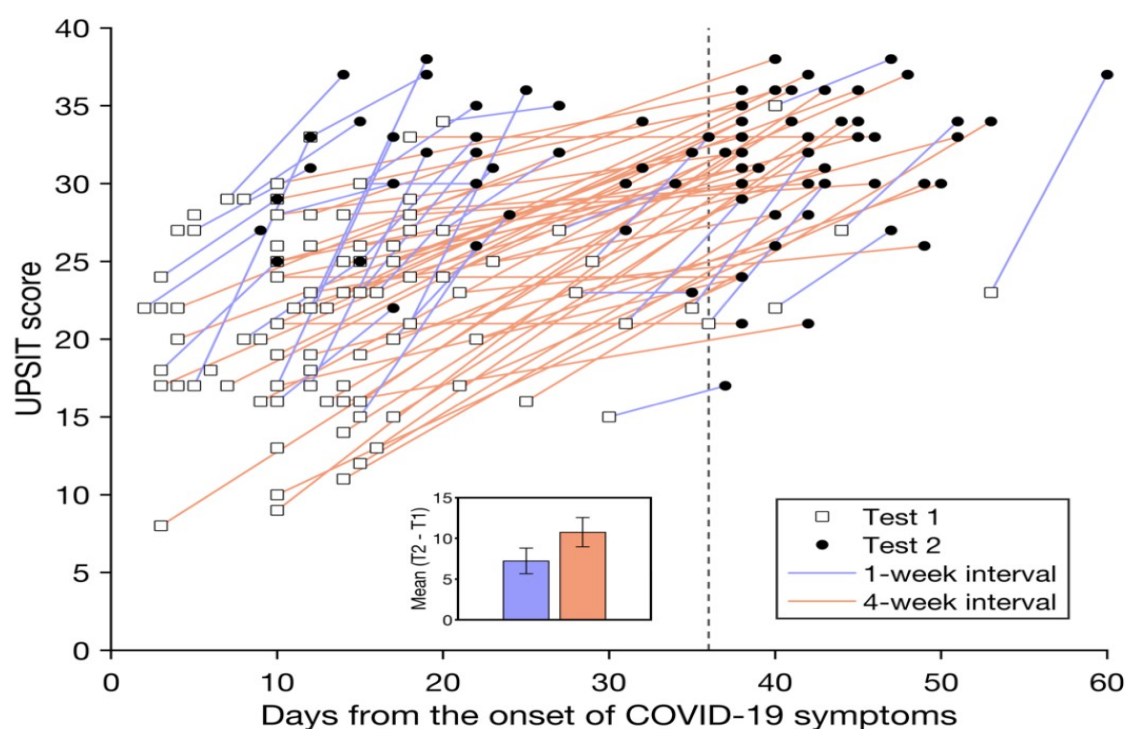


Figure 3. Comparison of UPSIT scores of patients tested 6-8 weeks after onset of initial COVID-19 symptoms (6-8 W COVID-19) to those of healthy age- and sex-matched controls. The white circles indicate medians and the vertical dark lines interquartile ranges. See text for details.

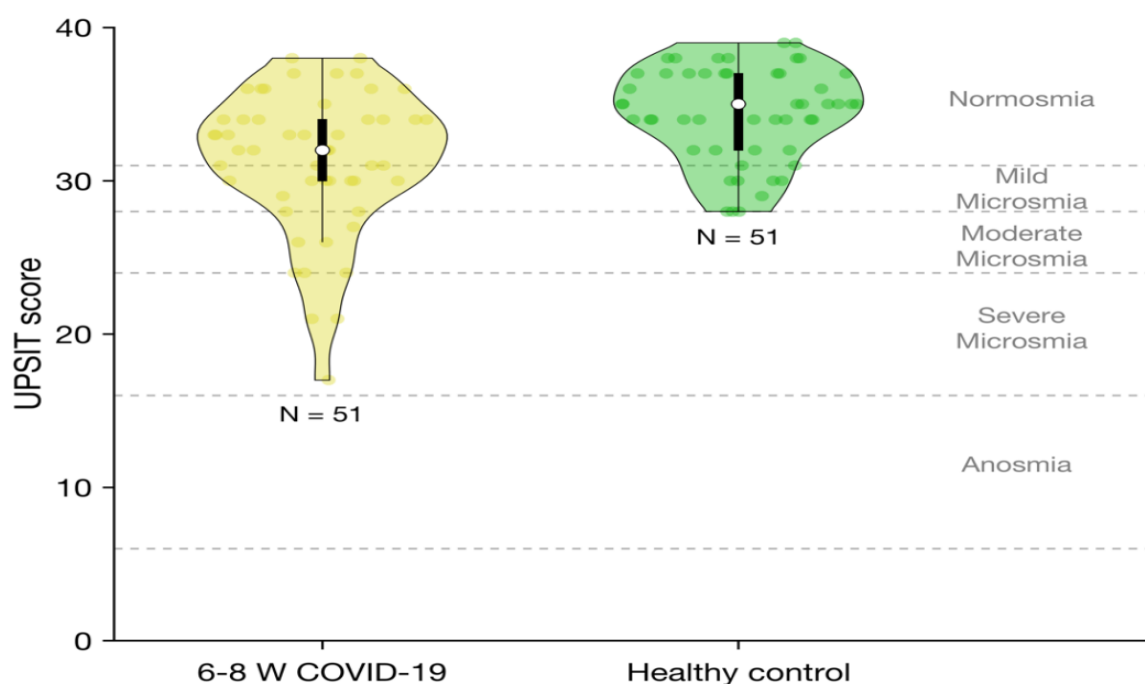


Figure 4. The proportion of patients with differing degrees of function relative to time since onset of COVID-19 symptoms. All initial and follow-up scores are combined for the purpose of visualization. See text for details.

