Although our knowledge on COVID-19 pathogenesis and risk factors is "work in progress" and currently mainly based on preliminary data, it is striking to us that there is currently no evidence of an increased risk of poor/fatal outcome in asthmatics and particularly in severe/uncontrolled patients. Like other respiratory viral infections, coronaviruses might exacerbate asthma symptoms, particularly in severe or uncontrolled patients but we suggest that a Th2-skewed immunity may be protective against severe COVID-19 disease, owing to the cross-regulation between allergic and interferon-mediated immune responses (Figure 2).

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CONFLICTS OF INTEREST

Dr Carli, Dr Cecchi, Prof. Parronchi and Dr Farsi have nothing to disclose. Prof. Stebbing's conflicts of interest can be found at https://www.nature.com/onc/editors and none are relevant here.

Giulia Carli[1]
Lorenzo Cecchi[1]
Justin Stebbing[2]
Paola Parronchi[3]
Alessandro Farsi[1]

[1]*SOS Allergy and Clinical Immunology, USL Toscana Centro, Prato, Italy*
[2]*Department of Surgery and Cancer, Imperial College London, London, UK*
[3]*Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy*

Correspondence
Alessandro Farsi, SOS Allergy and Clinical Immunology, USL Toscana Centro, Via Cavour 87/89, Prato, Italy.
Email: alessandro.farsi@uslcentro.toscana.it

ORCID

Giulia Carli https://orcid.org/0000-0001-6400-9205
Lorenzo Cecchi https://orcid.org/0000-0002-0658-2449
Alessandro Farsi https://orcid.org/0000-0001-6036-9094

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Telemedicine allows quantitative measuring of olfactory dysfunction in COVID-19

To the Editor,

Evidence is accumulating that olfactory dysfunction is common in COVID-19. New-onset anosmia has been considered as early marker for SARS CoV-2 infection,[1-3] but until now, all studies rely on self-evaluations of patients without objectified and quantitative measures. Moreover, no longitudinal measures of olfaction in COVID-19 are available and no data on recovery of olfaction in surviving patients. We report on the unique situation that olfaction

Ludger Klimek and Jan Hagemann contributed equally.

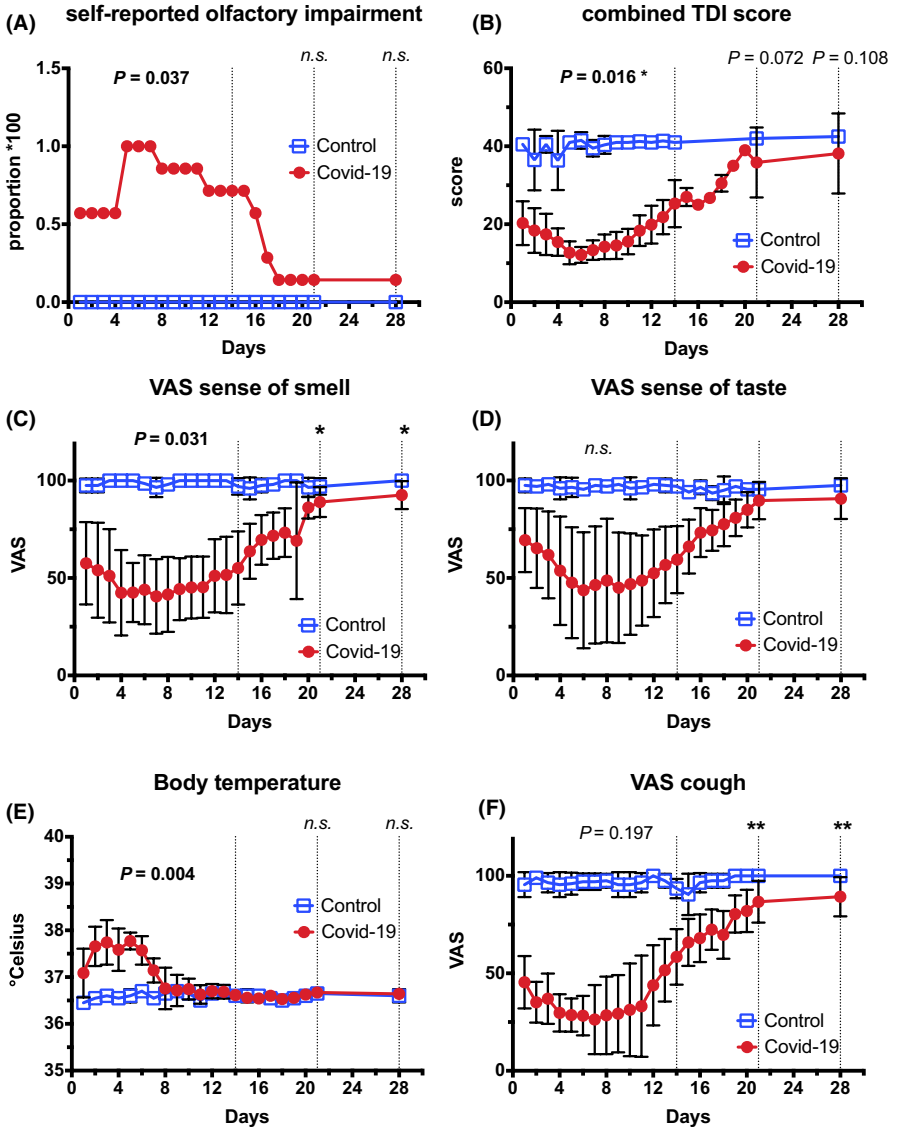

FIGURE 1 Overview of olfactory function and physiological parameters. Plotted are means of patients/controls for each day, and error bars indicate standard deviation. Significance levels are shown for days 1-14 combined and days 21, respective 28. Statistical tests were robust error variance analysis and Mann-Whitney *t* test. A *P*-value of .05 or less was considered statistically significant. n.s.: not significant. A, Olfactory impairment was assessed subjectively by yes/no question. Mean proportion is shown for each day. B, Threshold-Discrimination-Identification score (TDI). C, D, F, Visual analogue scales. E, Body temperature

could be quantitatively measured in a cohort of skiers from day 2 of infection over 4 weeks versus 2 noninfected controls in the same quarantine situation using telemedicine.

The study was performed according to the Declaration of Helsinki and approved by the regional Ethics Committee (LÄK RLP, No. 2020-14337). All participants gave written informed consent after detailed explanation of all study-related measures. COVID-19 was defined if positive to SARS-CoV-2 RNA by polymerase chain reaction (PCR) in both of 2 swabs taken from nasopharynx and throat in presence of clinical symptoms such as cough or fever. Inclusion criteria were verified SARS-CoV-2 infection or ski group member travelling together and present at time of infection leading to identical obligation to quarantine, missing other disease that may interfere with olfaction, willingness to participate, being adult (≥18 years), being intellectually and clinically able to self-perform a full Sniffin´Sticks, visual analogue scales (VAS) and questionnaires.

The cohort consisted of 9 otherwise healthy skiers (5 female, 24-32 years) who went to a 3-day holidays to Austria with 7 developing COVID-19 with mild symptoms (cough ± fever, no dyspnoea) after return. Due to a singular social event, the time of infection could be confirmed with high certainty. Over the following 4 weeks, psychophysical olfactory function tests (Sniffin´Sticks) were performed via telemedicine consultation daily from day 2 after infection during entire quarantine (14 resp. 21 days) and weekly, thereafter. After 14 days quarantine, individuals were retested again with negative PCR results in 5 out of 7, while 1 couple stayed positive and needed to prolong quarantine with negative PCR at day 21. Instructions in use of Sniffin`Sticks were given in video conferences (4 couples living together were trained and contacted together), with remote consultation every morning before breakfast, thus preventing missing any data.

Statistical analysis tested for differences in outcome parameters between patients vs. controls during the quarantine days 1 to 14 and on days 21 and 28 (Robust error variance, Mann-Whitney-*U* *t* test). Multiple regression analysis (Table S2) and Pearson/point biserial correlation were performed, and wellness-of-fit analysis

revealed good regression fit. A *P*-value of <.05 was considered statistically significant. See Appendix S1 for full data table.

Functional anosmia was measurable in all patients for 14 days in threshold, discrimination and identification (Figure 1) and differed significantly from normosmic controls ($P < .05$). Multiple independent variables for TDI score were identified in regression analysis (Table S2). Four patients self-reported smell loss, while 3 others did not notice and 1 reported anosmia without any other complaints for 6 days after infection. Self-reporting did not detect quantitatively impaired patients ($P > .05$) in the first 3 days. Olfaction recovered in 6 patients within 4 weeks ($P = .65$). Olfactory impairment occurred without symptoms of rhinitis (Table S1).

For the first time, quantitative psychophysical analyses of olfaction were performed over a full course of COVID-19 in this homogenous cohort of relatively young adults, while previous studies used self-ratings, only.[1,2,4] It is well accepted that self-ratings largely underestimate olfactory dysfunction.[5] Usually required face-to-face contact seems to cause this systematic error, while telemedicine consultations allows safe testing for patients and staff. The comprehensive impairment without nasal symptoms supports the suggestion of a neurotropic and neuro-invasive virus that is site-specific for the olfactory system using angiotensin-converting enzyme receptor-2 (ACE2) for intracellular invasion.[6]

Our data suggest (a) functional anosmia in COVID-19 is more frequent using psychophysical olfaction tests than self-evaluations, (b) telemedicine allows early detection and monitoring a full disease course, (c) smell function is largely affected, and (d) olfactory function in mildly symptomatic outpatients recovers without specific therapy in most, but not all patients within 4 weeks. Telemedicine not only can be valuable for patient monitoring of SARS-CoV-2 infection, but may be a helpful tool for ongoing COVID-19 olfaction research.

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Ludger Klimek[1,2]
Jan Hagemann[3]
Ali Alali[1]
Magdalena Spielhaupter[1]
Tilman Huppertz[3]
Karl Hörmann[4]
Sabine Stielow[5]
Laura Freudelsperger[3]
Christoph Matthias[3]

[1]*Centre for Rhinology and Allergology, Wiesbaden, Germany*
[2]*Universitätsmedizin der Johannes Gutenberg-Universität Mainz*
[3]*Department of Otorhinolaryngology, Head and Neck Surgery, University Medical Center, Mainz, Germany*
[4]*Mannheim University Hospital, Mannheim, Germany*
[5]*COVID-19 Test Center Wiesbaden, Wiesbaden, Germany*

Correspondence
Ludger Klimek, Center for Rhinology and Allergology, An den Quellen 10; D-65183 Wiesbaden, Germany.
Email: Ludger.Klimek@Allergiezentrum.org

ORCID

Jan Hagemann https://orcid.org/0000-0002-9846-7850

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.