

## High frequency of smell and taste dysfunctions in allergy health care professionals suffering from COVID-19

**Short title:** Smell & Taste dysfunction in allergists

Antolín-Amérigo D<sup>1\*</sup>, Cubero JL<sup>2\*</sup>, Colás C<sup>2</sup>, Alobid I<sup>\*\* 3</sup>, Mullol J<sup>4\*\*</sup>, Valero A<sup>5\*\*</sup>

<sup>1</sup>Allergy Department, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain.

<sup>2</sup>Allergy Department, Hospital Clínico Universitario Lozano Blesa, Instituto de Investigación Sanitaria Aragón (IIS Aragón), Zaragoza, Spain.

<sup>3</sup>Rhinology and Skull Base Unit, Department of Otorhinolaryngology, Hospital Clinic, Universidad de Barcelona. IDIBAPS, CIBERES, Barcelona, Spain.

<sup>4</sup>Rhinology Unit & Smell Clinic, Department of Otorhinolaryngology, Hospital Clinic, Universitat de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBER of Respiratory Diseases (CIBERES). Barcelona, Catalonia, Spain.

<sup>5</sup>Department of Pneumology and Allergy, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERES, Instituto de Salud Carlos III, Spain.

\*These authors contributed equally as first authors

\*\*These authors contributed equally with senior responsibilities

### Corresponding author:

Darío Antolín Amérigo

Hospital Universitario Ramón y Cajal.

M-607, km. 9, 100, 28034 Madrid

E-mail: [dario.antolin@seaic.org](mailto:dario.antolin@seaic.org)

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: 10.18176/jiaci.0670

## Abstract

**Introduction:** Since the first stages of the novel coronavirus 2019 (SARS-CoV-2) outbreak smell and/or taste dysfunction (STD), has been described from 5% to 88% in COVID-19 patients.

**Objective:** we aimed to assess STD in healthcare professionals (HCP), mainly allergists, affected with COVID-19, by means of a survey, and to evaluate the association of STD and their severity with demographic characteristics, symptoms, comorbidities, and hospital admission.

**Methods:** A 15-item questionnaire was designed including different sections as follows: demographics, diagnostic characteristics, STD patterns, medication use as well as comorbidities. The questionnaire was developed using Google forms, implemented and distributed to members of the Spanish Society of Allergology and Clinical Immunology (SEAIC) and spread via Social Media to be completed by HCP affected with COVID-19.

**Results:** HCP (n=234), 76.5%  $\leq 55$  yrs, 73.5% female, completed the survey. There was STD in up to 74.4% of the respondents, 95.6% reporting a moderate-severe impairment. Mean recovery time of taste dysfunction was  $21.6 \pm 24.0$  days in HCP  $\leq 55$  yrs and  $33.61 \pm 26.2$  days in  $> 55$  yrs ( $p=0.019$ ). Stratified analysis by severity of STD showed that more than a half of COVID-19 subjects presented severe loss of smell. An older age ( $> 55$  yrs) was associated with fever, anorexia, less headache and with a longer persistence of taste dysfunction

**Conclusion:** STD is a common symptom in COVID-19, even as a unique or preceding symptom. HCP who declared smell dysfunction (SD) were younger than those not affected with STD. Taste dysfunction (TD) may imply more systemic involvement in COVID-19-positive HCP.

**Key words:** Smell dysfunction. Hyposmia. Anosmia. Taste dysfunction. Ageusia. Hypogeusia. SARS-CoV-2. COVID-19

## Resumen

**Introducción:** Desde el inicio de la pandemia por el nuevo coronavirus (SARS-CoV-2), la afectación del sentido del olfato y del gusto se ha descrito entre el 5% y 88% de la población afectada por COVID-19.

**Objetivo:** Evaluar la alteración del gusto y del olfato en profesionales sanitarios afectados por COVID-19, en relación a parámetros de gravedad, características demográficas, síntomas, comorbilidades e ingreso hospitalario.

**Métodos:** Se diseñó un cuestionario de 15 elementos, con las siguientes secciones: demografía, características diagnósticas, patrones de alteración de olfato y del gusto, uso de medicación y efectos adversos asociados y comorbilidades. Dicho cuestionario fue difundido por las redes sociales de la Sociedad Española de Alergología e Inmunología Clínica, dirigido específicamente a profesionales sanitarios.

**Resultados:** 234 profesionales completaron la encuesta (73,5% mujeres). El 76,5% de los encuestados era  $\leq 55$  años. Hubo afectación del olfato y/o gusto en el 74,4% de los encuestados. La persistencia media de alteración del gusto fue  $21,6 \pm 24,0$  días en  $\leq 55$  años y de  $33,6 \pm 26,2$  días en  $> 55$  años ( $p=0,019$ ). Ser mayor de 55 años se asociaba estadísticamente con fiebre, anorexia, menos cefalea y mayor persistencia de afectación del gusto.

**Conclusión:** Los profesionales sanitarios que declararon haber padecido SD eran más jóvenes que los que no presentaron STD. La afectación del olfato y/o del gusto es un síntoma común entre los profesionales sanitarios con COVID-19 y puede ser patente en fases iniciales o como único síntoma en pacientes  $\leq 55$  años. La afectación del gusto puede implicar más síntomas sistémicos.

**Palabras clave:** Afectación del olfato. Hiposmia. Anosmia. Afectación del gusto. Ageusia. Hipogeusia. SARS-CoV-2. COVID-19.

## Introduction

In the past 20 years, 3 coronavirus outbreaks have occurred, the severe acute respiratory syndrome (SARS) outbreak in 2002, the Middle East Respiratory Syndrome (MERS) in 2012, and the pandemic of Coronavirus-disease-2019 (COVID-19) in 2020. In December 2019 the first human cases of COVID-19 caused by the severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2) from a potential bat origin, were identified in Wuhan (China). Since then, the COVID-19 pandemic has shown a rapid spread all over the world, affecting over 71 million people and causing over one million deaths in 191 countries (probably a larger number if infected people who did not undergo a proper diagnostic test are considered) [1–3].

In this regard, the common symptoms of COVID-19 are general malaise, fever, cough, and shortness of breath. Other symptoms include muscle and joint pain, sore throat, headache, nausea or vomiting, diarrhea, and some nasal symptoms, especially smell dysfunction (SD) and taste dysfunction (TD) [3]. Since the first stages of COVID-19 when smell and/or taste dysfunction (STD) reports were scarce, there has been a growing number of studies, with important differences among used methodology, describing a wide range of STD, from 5% to 98% in COVID-19 patients (2–5).

The perception of odor is composed of orthonasal smell due to sniffing (eg, food aroma) and retronasal smell located within the oropharynx and caused by airflow via the nasopharynx during eating or drinking. Flavor involves the combination of gustatory and olfactory perceptions, while it interacts with other sensory modalities, such as trigeminal perception, sight, and hearing [6]. The gustatory system (transmitted via the glossopharyngeal, facial and vagal nerves) only recognizes the basic tastes (sweet, sour, salty, bitter, and umami/glutamate).

Concerning SD, it affects almost 20% of the general population [7]. The main causes for persistent loss of smell are viral infections (including common cold and COVID-19), acute and chronic sinonasal inflammation, and trauma brain injury. Other causes should be investigated, including neurodegenerative diseases, brain tumors and congenital causes. There is no significant association between SD and smoking.

Interestingly, many viruses affecting the upper aerodigestive tract (e.g. rhinovirus, influenza A, parainfluenza, herpesvirus, poliovirus, rabies virus, adenovirus, Epstein-Barr virus, Japanese encephalitis virus and some coronavirus) could use the olfactory nerve as a route into the central nervous system, potentially causing SD, mostly through an inflammatory reaction of the nasal mucosa [2,8,9]. In mouse models, SARS-CoV demonstrated transneuronal penetration through the olfactory bulb [8,10]. An involvement of non-neural cells could lead to SD [8]. It remains to be elucidated if alternate receptors, different from ACE2 would be enough for SARS-CoV-2 host cell entry and may be involved to facilitate the initial infection [11].

Furthermore, up to 60% of patients with common cold or post-viral acute rhinosinusitis may have some degree of SD, this being mainly correlated with disease severity and usually transient (3-7 days) [9]. However, the pathophysiology through which SARS-CoV-2 virus affects the olfactory system is still unclear [2,3,10]. Although in the first studies from China the rate of SD did not exceed the 5%, later international studies on COVID-19 have identified SD as a frequent symptom of the novel coronavirus disease (Table 1). [2,4,28–37,16,38,39,17–19,22–24,27]

Damage to the olfactory nerve during invasion and multiplication of SARS-CoV-2 may explain anosmia observed in the early stages of COVID-19. [2,3,7] Therefore, sudden, severe, and isolated dysfunction (anosmia or ageusia) may be more frequently observed in the SARS-CoV-2 positive patients than in other respiratory viral infections [3].

Due to the lack of awareness of SD, there is often a significant delay between onset of smell loss and assessment by a healthcare professional (HCP) (up to 3 years), even though it exerts a great impairment on quality of life [2,12]

In the present study we aimed to assess the impact of smell and taste dysfunctions in HCP, mainly allergists, affected with COVID-19 by means of a survey. The main objective of the survey was to evaluate the association of STD and their severity with demographic characteristics, symptoms, comorbidities, and hospital admission (33–35).

## Methods

### 1. Study Population and design

A 15-item survey was designed including different sections as follows: demographics, diagnostic characteristics, smell and taste dysfunction patterns, symptoms, comorbidities, or medication used (Table 2). The survey was developed as a result of a collaboration between members of the Spanish ENT (SEORL) and Allergology and Clinical Immunology (SEAIC) Societies, using Google forms. It was implemented and distributed to all the SEAIC members and spread via Social Media (Twitter, LinkedIn and Facebook) to be completed by HCP, mainly allergists, who were affected with COVID-19. Data collection was performed between May 13<sup>th</sup> and June 13<sup>th</sup>, 2020. The survey incorporated relevant traits related with smell and taste functions. The study was approved by the Institutional Ethics and Clinical Research Committee of Hospital Clínic, Barcelona.

### 2. Outcomes

- **Assessment of smell and taste dysfunction.** Participants were carefully asked about the timing of the onset, duration, and the eventual recovery of the chemosensory symptoms. The survey included questions related with STD:
  - a) Smell loss score (Likert scale from 0 to 10, being 0 no smell loss and 10 total smell loss) focusing on smell and food/drink flavor.
  - b) Taste loss score (Likert scale from 0 to 10, being 0 no smell loss and 10 total smell loss). In order to avoid confusion between taste and smell/flavor, real taste perceptions (salty, sweet, bitter, and sour/acidic) were emphasized.
  - c) Two questions about the SD and TD onset (days before or after the appearance of other local or systemic COVID-19 symptoms).
  - d) Two questions about recovery time (days) of SD or TD.

Severity of SD and TD was assessed stratifying by groups (Likert scale, 0-10): mild (0-3), moderate (4-7) and severe (8-10) (see tables 2 and 3).

• **Demographics, symptoms, comorbidities, and treatment for respiratory symptoms.** Demographics on gender, age range (years), symptoms, hospital admission and associated pneumonia, and smoking habit of participants with COVID-19 were registered. COVID-19 responders were stratified according to whether they were hospitalized or not, and having pneumonia or not, as an indicator of severity and systemic involvement. Patients were also asked about their COVID-19 symptoms (fever, rhinitis, conjunctivitis, sore throat, headache, cough, dyspnea, myalgia, asthenia, anorexia, gastrointestinal, and cutaneous symptoms). COVID-19 diagnostic procedures were also recorded (clinical diagnosis, positivity to Polymerase Chain Reaction (PCR) and immunity-antibodies). The following comorbidities were also surveyed: hypertension, diabetes mellitus, obesity, chronic rhinosinusitis, allergic rhinitis, asthma and its severity, and chronic obstructive pulmonary disease. Medications used for respiratory symptoms and comorbidities were also recorded (intranasal corticosteroids, MP-AzeFlu, inhaled corticosteroids, allergen immunotherapy, and biologics) (Tables 3 and 4).

### 3. Statistical analysis

With regards the descriptive analysis, mean and standard deviation were calculated for the demographic characteristics. Moreover, median and the interquartile range to the rest of the continuous variables were calculated. The qualitative variables are expressed in absolute frequencies and percentages. The normality of the continuous variables was evaluated through the Shapiro-Wilk test with a significance level of  $p=0.01$ .

Chi-square test and Fisher's exact test were used to compare categorical variables between COVID-19 patients who suffered SD, TD or STD (SD and/or TD) compared with COVID-19 patients without SD, TD or STD symptoms respectively. Student t-test or Mann-Whitney U test were used to compare quantitative variables for 2 groups depending on whether or not the variables would follow a normal distribution, while analysis of variance (ANOVA) and Kruskal-Wallis test were used for the analysis of quantitative continuous variables for 3 or more groups. Kruskal-Wallis was also used to compare ordinal data variables (pe. severity of SD and TD). We calculated the Odds Ratio (OR) for SD, TD and STD establishing a significance level of  $p<0.05$ .

The data analysis was done using SPSS statistical software (IBM SPSS Statistics 20; Chicago, IL, USA). The graphics included in this manuscript were created in Microsoft Excel 2019 (Microsoft; Redmon, WA, USA).

## Results

- Description of the total group of participants:

Two hundred and thirty-four HCP completed the survey (Table 2), 76.5%  $\leq 55$  yrs, 172 being female (73.5%). Demographics and clinical characteristics are detailed in Tables 2-4.

- Chemosensory dysfunction: (Figures 1-2)

- Smell and Taste dysfunction: 174 HCP (74.6%) reported STD.

- Smell dysfunction: 160 HCP (68.4%) reported SD, 7.5% as a unique symptom (Figure 1A). Over 85% of participants reported severe smell impairment while the mean recovery time was 26.1 days. Moreover, HCP  $>55$  yrs showed a slightly better SD severity scale (mean  $8.49 \pm 1.29$ ) than HCP  $\leq 55$  yrs ( $9.29 \pm 2.08$ ) ( $p=0.032$ ) yet both age groups showed a great impairment. None of the older health professionals reported SD as a unique symptom or as the first symptom of COVID-19 ( $p=0.004$ ).

Over half (55.5%) of patients suffered SD with a median of 4 days after other symptoms while 30.5% being coincidental with the other symptoms. Moreover, 24.4% of the HCP suffered from persistent SD as unique symptom at the time of completion of this survey and 9.4% accompanied with other symptoms with a median of 15 days (range 2-90) (Figure 1A). Among COVID-19 subjects with sensory dysfunction, 95.6% had a loss of smell of at least moderate severity (score  $>5$ ) (Figure 1B). Moreover, the severity of the SD was higher in younger HCP ( $\leq 55$  yrs, score  $9.3 \pm 1.3$ ,  $p=0.04$ ) compared with the older group ( $>55$  yrs, score  $8.5 \pm 2.1$ ).

- Recovery time for SD. By the time of completing this survey 66.3% of the HCP have recovered from SD. In terms of recovery, SD was significantly different with regards severity of SD, being the mean time of recovery after suffering SD: mild ( $n=2$ ):  $12.5 \pm 3.5$  days; moderate ( $n=18$ ):  $7.1 \pm 3.3$  days and severe ( $n=131$ ):  $29.0 \pm 25.3$  days



( $p < 0.001$ ) (Figure 2A). Moreover, the time to recovery from SD was lower in younger patients ( $24.1 \pm 24.1$  days vs  $31.9 \pm 25.8$  days).

- Taste dysfunction: 132 HCP (56.4%) reported TD, 6.1% as a unique symptom. None of the older HCP reported TD as a unique symptom or as the first symptom of COVID-19 ( $p = 0.047$ ). From surveyed people, 6.8% of TD preceded the other COVID-19 symptoms (median 1 day). Mean persistence of TD was  $21.6 \pm 24.0$  days in physicians  $\leq 55$  yrs and  $33.6 \pm 26.2$  days in  $> 55$  yrs ( $p = 0.019$ ). Over 65% of the participants reported a severe impairment while the mean recovery time was 25.4 days. After delving into the timing of recovery in association with the severity of TD, there were no significant differences. (Figure 2B; mild TD ( $n = 8$ ): mean  $10.1 \pm 5.4$  days, moderate TD ( $n = 33$ ): mean  $22.2 \pm 22.9$  days; severe TD ( $n = 85$ ): mean  $28.4 \pm 26.8$ ;  $p = 0.108$ ). Over half (53.5%) of HCP suffered from TD with a median of 4.5 days after other symptoms and 34.1% the SD was coincidental with the rest of the symptoms. Moreover, 16.2% of the HCP suffered from persistent TD as unique symptom at the time of completion of this survey and 9.2% accompanied with other symptoms with a median of 11.5 days (range 2-95) (Figure 1A), 10.6% not being associated to SD. PCR results showed no significant correlation with TD.

- Respiratory treatments used during COVID-19 (Tables 1-3)

INCS and ICS were used by over 15% of HCP, while MP-AzeFlu, immunotherapy and biologics were used less frequently. The use of AzeFlu and immunotherapy was significantly higher in participants without TD.

## Discussion

Participants with diagnosed COVID-19 were HCP (mainly female) in which STD were observed in combination in 118 participants (67.8% of the total population surveyed). In recent reports authors mainly assess these two chemosensory dysfunctions separately. Menni et al found that 59.4% of the population included in their study was affected with SD and TD, whereas Spinato et al found a 64.4%, numbers that are slightly lower than ours.[16,17] Wee et al found that only 22.7% of the population studied suffered both SD and TD and Moein et al in Iran reported that only 17% of their population suffered both chemosensory dysfunctions.[18,19] These differences could be

explained because our population is mainly composed of HCP, mostly female, which could constitute a bias, and as it has been previously published, female affected of COVID-19 may be at higher risk to developing SD. [12,15,20,21] In a recent study published in Spain a total of 157/230 (68%) HCP described SD and 161/230 (70%) reported TD, with similar prevalence independently of age or sex. In contrast, in our sample females were significantly more affected than males in terms of STD, as it has been shown in a study using Big Data in Spain. [14,21]

There are conflicting data with regards STD and gender-predominance, as a recent meta-analysis has found no significant moderation of the prevalence of STD by sex. [22] In contrast, in a multicenter European study, females were, alike our results, significantly more affected by smell and taste dysfunctions than males. [23] Similarly in another study performed in Spain, females and younger people were predominantly affected by STD [38]. In our study, the frequencies of loss of smell (68.4%) and taste (56.4%) were higher than those reported in the early anamnestic observational studies from China, Iceland, and those recently published in Spain, [2,15,23] however lower than those from the aforementioned European multicenter study [20].

HCP participants who experienced SD were younger than those not affected with STD, as 70% of the COVID-19-positive population were  $\leq 55$  yrs, this being higher than the data reported in a recent Korean article where only a 15.3% of the total COVID-19 population showed STD, and even much higher than in other studies comprising HCP, ranging an STD from 16-40% [13]. Our data are however slightly higher than others performed in Spain, which showed a 68% of SD and 70% of TD [2,15] We hypothesize that these differences could be due to the awareness of HCP about STD and its relationship with COVID-19. In a Swedish population individuals progressing from reporting no symptoms to subsequently reporting COVID-19 symptoms reporting a large drop in olfactory performance [25] These data may suggest that measures of odor intensity, if obtained in a large and representative sample, shall be used as an indicator of SARS-CoV-2 infection in the general population.[26] Foster et al. have recently published that SD could be a prognostic factor for lower severity of COVID-19 [20] This is in line with a study from China which reported that the ratio of

hospitalized patients complaining of smell loss and taste loss was only 5.1% and 5.6%, respectively [4] Our results do not show any association in terms of SD and the severity of COVID-19. HCP who reported TD showed however a greater rate of hospital admission.

We aimed to investigate whether the age ( $\leq$  or  $>$  55 yrs) was related with the presence of SD as a unique symptom or as the first symptom of COVID-19. Interestingly, none of the older HCP reported having SD as a unique symptom or as the first symptom of COVID-19. In the same line, similar findings were obtained for TD. Our findings of SD as a unique symptom is lower in percentage than that obtained in another study performed in Spain with percentages ranging from 18.9-21.8% of patients [15] These results also contrast with another study in which STD persisted on average 11 days [14].

Our study also reflects a persistence of the SD which is on average longer than that observed in other publications [12,14,15] We presume the viral load in the clinical setting could explain this longer time to recovery. In a study which recruited HCP in Spain, most of the affected individuals recovered both smell and taste in the first 15 days and up to 26% of the HCP affected had persistent anosmia one month after the dysfunction onset [15].

In a Korean study most of the COVID-19 patients with loss of smell and/or taste recovered within 3 weeks, mimicking our results. [12] The median time to recovery was 7 days for both symptoms. A younger age, particularly the age group of 20–39 yrs, showed a tendency to be associated with a longer persistence of anosmia in the Korean study. Our results may reflect that younger individuals may suffer a longer recovery rate of the SD, but it could be biased by the fact that over 70% of the surveyed HCP were  $\leq$ 55 yrs. Similar to our results, the mean recovery time from loss/distortion of taste was similar to that from the loss of smell. [12]

Loss of smell appeared before the other COVID-19 symptoms but in lower amounts than reported in previous studies, but persisting up to 90 days. In 6.9% of the

HCP included in our study, this loss of smell preceded the other COVID-19 symptoms (median of 3 days). In a recent study comprising 417 mild-to-moderate COVID-19 patients, the SD appeared before the other symptoms in 11.8% of cases, a slightly higher proportion than in our study. In another Spanish study recently published, only 1.3% of the HCP showed SD as the unique symptom. [14]

Over a half of the surveyed HCP presented SD, TD, or combined SD/TD reporting a severity similar to previous studies [2,27] . We hypothesize that a potential greater and sustained exposure to the SARS-CoV-2 virus load inside the clinical setting along with greater quality of life impairment in HCP  $\leq 55$  yrs could explain these results. In this line, a recent meta-analysis reported a prevalence of TD ranging from 5.6% to 62.7%, being the pooled prevalence (38.2%) clearly lower than our data. The authors of the meta-analysis state that the pooled prevalence tended to decrease with increasing mean age and was slightly higher across European studies than studies from elsewhere. [22]

No significant association between SD and smoking was found. Prior non-COVID studies have found negative and positive effects of tobacco in smell dysfunction of different causes.[26] Smoking cessation seems to improve however both rated and measured smell function. Our sample has only a 4.3% of smokers, which seems to be clearly lower than in the general population. Also, our population is mainly comprised of HCP who tend to smoke to a lesser extent than the general population. Notwithstanding, a recent study including 3,900 patients with smell loss; 521 were current smokers and 316 former smokers. They concluded that patients with a history of smoking did not have a significantly lower smell function. [28] Given that our sample of smokers is quite low, the results regarding the absence of association between SD and smoking shall be taken with caution.

An older age ( $>55$  yrs) was significantly associated with fever, anorexia, but less headache, and COVID-19 positivity. These results are in line with a Big Data analysis made in Spain, in which it was shown an age-dependent increase in reported cases in both males and females, being patients  $>79$  yrs the most affected. [21] Regarding

symptoms upon diagnosis, headache, anosmia, and taste distortion were significantly more frequent in women than men in the before mentioned analysis. In our population, there was less headache reported by older patients. In a study comprising 989 individuals in Spain there was a clear association of loss of smell and taste with <60 yrs and non-hospitalized patients. [15]

Those HCP who suffered COVID-19 with pneumonia had a higher frequency of TD, which is distinctive aspect from other studies. In spite of that, there were not significant differences in smell or taste with regards sex, age range and rate of pneumonia, in line with the results of another study performed in HCP in Spain. [14]

In addition to the data reported by Villarreal et al where cough was one of the main symptoms in HCP affected from COVID-19 [14], in our study cough was significantly associated with SD and STD.

One of the limitations of the study is that a definitive diagnosis was reached in 161 out of the 234 respondents, by means of PCR and or antibodies. Since our survey aimed to assess only COVID-19 patients, we presumed that the rest of participants had a clinical diagnosis of COVID-19. In our population we could not see this association, but in the surveyed HCP of our sample, TD seemed to be a prognostic marker of COVID-19 severity. Moreover, given the recruitment period, the first stage of the survey could be biased because PCR and SARS-CoV-2 antibodies were not fully available in all centers in the midst of the SARS-CoV-2 outbreak, therefore this could constitute a limitation of the study. Another limitation of the study is that the sample could not be representative of the general population as it included HCP, but it could be representative of the specific population which is being analyzed, namely HCP, specialists in Allergology, being predominantly women. Notwithstanding this potential limitation is also a strength, as it is up to date, the first assessment of STD in allergists who have suffered from COVID-19.

In summary, smell and taste dysfunction were frequent symptoms in HCP (mainly allergists) with COVID-19, being present in 68.4% and 56.4% of our population,

respectively. Stratified analysis by the severity of STD showed that more than half of COVID-19 HCP subjects presented a severe loss of smell. Older HCP seem to suffer STD at the same time of other COVID-19 symptoms in contrast with younger HCP who showed STD as a unique or preceding symptom. The taste dysfunctions may be considered as prognostic clinical marker of COVID-19 severity since suffering from TD may imply more systemic involvement. Further studies will be needed to provide explanations for these chemosensory impairments as well as for the pathogenic mechanisms for both the loss of smell and/or taste. Finally, the assessment of STD (both SD and TD) is of significant importance in COVID-19 patients, including HCP, at any stage of the disease, and those with sudden, severe, and isolated symptom (SD and/or TD) should be isolated at home waiting for a PCR diagnostic test to be performed, when available.

#### **Funding sources**

None.

#### **Conflicts of Interest:**

Dr. Antolín Amérigo reports having received lecture fees from Mylan-MEDA Pharma, AstraZeneca, FAES Farma, Leti, GSK; advisory fees from Chiesi, Sanofi, outside the submitted work.

Dr. Carlos Colás reports having served as a consultant to Mylan and AstraZeneca; having been paid lecture fees by AstraZeneca, GSK, Mylan, MSD; grants from Roxall, from Novartis, AstraZeneca, and Sanofi.

Dr. Alobid reports personal fees from Menarini, GSK, Sanofi, Novartis, during the conduct of the study.

Dr. MULLOL reports personal fees and other from SANOFI-GENZYME & REGENERON, NOVARTIS, ALLAKOS; grants and personal fees from MYLAN-MEDA Pharma, URIACH Group; personal fees from MITSUBISHI-TANABE, MENARINI, UCB, ASTRAZENECA, GSK, MSD, outside the submitted work.

The remaining authors have no conflicts of interest to declare.

## References

1. Lee S, Persson P. Financing from family and friends. *Rev Financ Stud.* 2016;29(9):2341–86.
2. Izquierdo-Dominguez A, Rojas-Lechuga M, Mullol J, Alobid I. Olfactory dysfunction in the COVID-19 outbreak. *J Investig Allergol Clin Immunol.* 2020;30(5).
3. Mullol J, Alobid I, Mariño-Sánchez F, Izquierdo-Domínguez A, Marin C, Klimek L, et al. The Loss of Smell and Taste in the COVID-19 Outbreak: a Tale of Many Countries. *Curr Allergy Asthma Rep.* 2020 Aug;20(10):61.
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients with Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683–90.
5. Pang KW, Chee J, Subramaniam S, Ng CL. Frequency and Clinical Utility of Olfactory Dysfunction in COVID-19: a Systematic Review and Meta-analysis. *Curr Allergy Asthma Rep.* 2020 Oct;20(12):76.
6. Liu DT, Besser G, Renner B, Seyferth S, Hummel T, Mueller CA. Retronasal olfactory function in patients with smell loss but subjectively normal flavor perception. *Laryngoscope.* 2019 Aug;
7. Mullol J, Alobid I, Mariño-Sánchez F, Quintó L, de Haro J, Bernal-Sprekelsen M, et al. Furthering the understanding of olfaction, prevalence of loss of smell and risk factors: a population-based survey (OLFACAT study). *BMJ Open.* 2012;2(6).
8. Brann D, Tsukahara T, Weinreb C, Logan DW, Datta SR. Non-neural expression of SARS-CoV-2 entry genes in the olfactory epithelium suggests mechanisms underlying anosmia in COVID-19 patients. *bioRxiv [Internet].* 2020 Jan 1;2020.03.25.009084. Available from: <http://biorxiv.org/content/early/2020/03/27/2020.03.25.009084.abstract>
9. Jaume F, Quintó L, Alobid I, Mullol J. Overuse of diagnostic tools and medications in acute rhinosinusitis in Spain: A population-based study (the PROSINUS study). *BMJ Open.* 2018;8(1):1–13.
10. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the

- SARS-CoV-2 Entry Proteins, ACE2 and TMPRSS2, in Cells of the Olfactory Epithelium: Identification of Cell Types and Trends with Age. *ACS Chem Neurosci*. 2020 Jun;11(11):1555–62.
11. Hikmet F, Méar L, Edvinsson Å, Micke P, Uhlén M, Lindskog C. The protein expression profile of ACE2 in human tissues. *Mol Syst Biol*. 2020 Jul;16(7):e9610.
  12. Yan CH, Faraji F, Prajapati DP, Boone CE, DeConde AS. Association of chemosensory dysfunction and COVID-19 in patients presenting with influenza-like symptoms. *Int Forum Allergy Rhinol*. 2020 Jul;10(7):806–13.
  13. Klopfenstein T, Kadiane-Oussou NJ, Toko L, Royer P-Y, Lepiller Q, Gendrin V, et al. Features of anosmia in COVID-19. *Med Mal Infect*. 2020 Aug;50(5):436–9.
  14. Wee LE, Chan YFZ, Teo NWY, Cherng BPZ, Thien SY, Wong HM, et al. The role of self-reported olfactory and gustatory dysfunction as a screening criterion for suspected COVID-19. Vol. 277, *European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*. 2020. p. 2389–90.
  15. Lechien JR, Chiesa-Estomba CM, De Siaty DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Oto-Rhino-Laryngology [Internet]*. 2020;2(8):2251–61. Available from: <https://doi.org/10.1007/s00405-020-05965-1>
  16. Spinato G, Fabbris C, Polesel J, Cazzador D, Borsetto D, Hopkins C, et al. Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. *JAMA*. 2020 May;323(20):2089–90.
  17. Kaye R, Chang CWD, Kazahaya K, Brereton J, Denny JC 3rd. COVID-19 Anosmia Reporting Tool: Initial Findings. *Otolaryngol neck Surg Off J Am Acad Otolaryngol Neck Surg*. 2020 Jul;163(1):132–4.
  18. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol*. 2020 Aug;10(8):944–50.



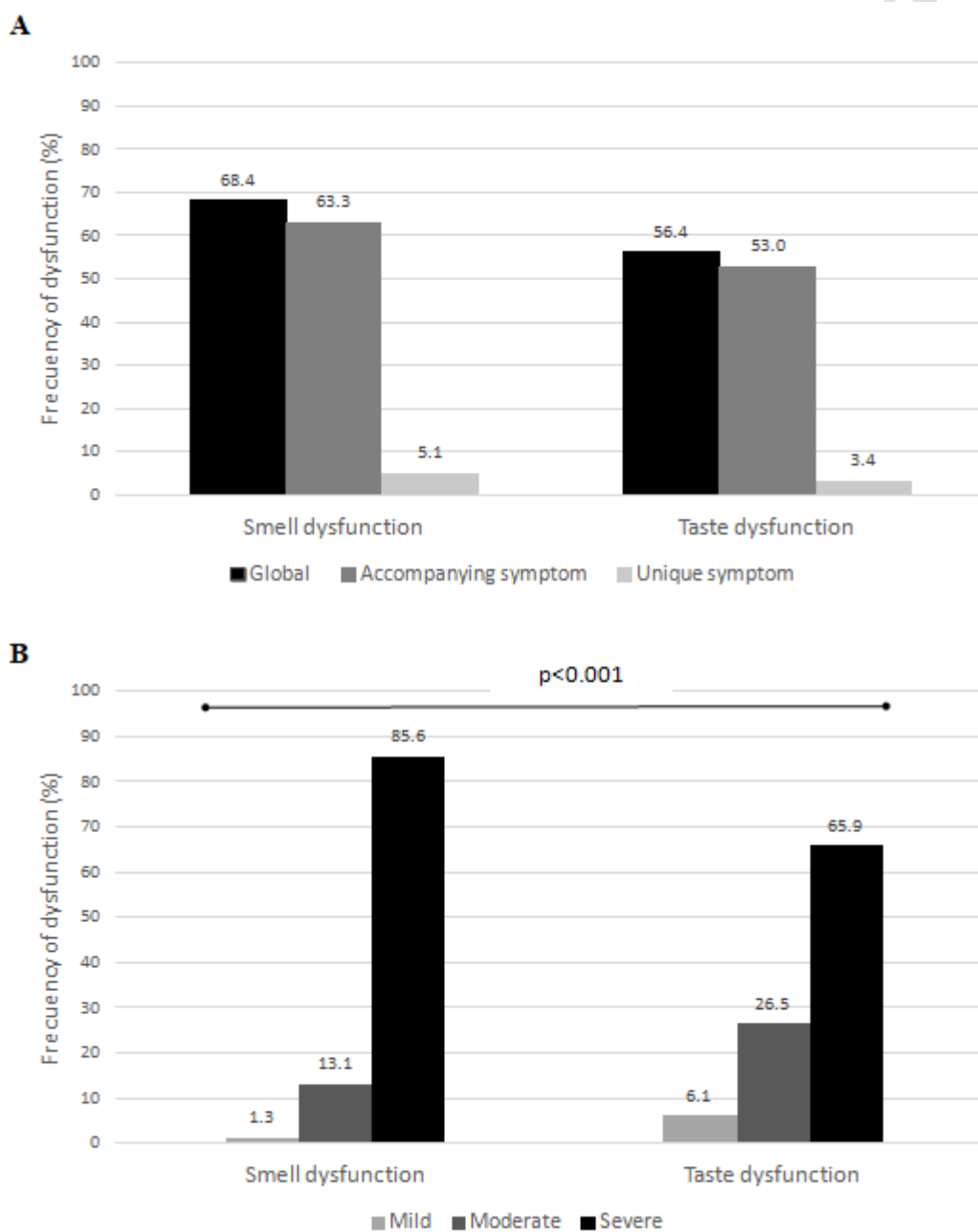
19. Lechner M, Chandrasekharan D, Jumani K, Liu J, Gane S, Lund VJ, et al. Anosmia as a presenting symptom of SARS-CoV-2 infection in healthcare workers - A systematic review of the literature, case series, and recommendations for clinical assessment and management. *Rhinology*. 2020 May;
20. Lan F-Y, Filler R, Mathew S, Buley J, Iliaki E, Bruno-Murtha LA, et al. COVID-19 symptoms predictive of healthcare workers' SARS-CoV-2 PCR results. *PLoS One* [Internet]. 2020 Jun 26;15(6):e0235460–e0235460. Available from: <https://pubmed.ncbi.nlm.nih.gov/32589687>
21. Weiss JJ, Attuquayefio TN, White EB, Li F, Herz RS, White TL, et al. Tracking Smell Loss to Identify Healthcare Workers with SARS-CoV-2 Infection. *medRxiv : the preprint server for health sciences*. 2020.
22. Agyeman AA, Chin KL, Landersdorfer CB, Liew D, Ofori-Asenso R. Smell and Taste Dysfunction in Patients With COVID-19: A Systematic Review and Meta-analysis. *Mayo Clin Proc*. 2020 Aug;95(8):1621–31.
23. Van Loon N, Verbrughe M, Cartuyvels R, Ramaekers D. Diagnosis of COVID-19 Based on Symptomatic Analysis of Hospital Healthcare Workers in Belgium: Observational Study in a Large Belgian Tertiary Care Center during Early COVID-19 Outbreak. *J Occup Environ Med*. 2020 Aug;
24. Rojas-Lechuga MJ, Izquierdo-Domínguez A, Chiesa-Estomba C, Calvo-Henríquez C, Villarreal IM, Cuesta-Chasco G, et al. Chemosensory dysfunction in COVID-19 out-patients. *Eur Arch oto-rhino-laryngology Off J Eur Fed Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology - Head Neck Surg*. 2020 Aug;1–8.
25. Bagheri SH, Asghari A, Farhadi M, Shamshiri AR, Kabir A, Kamrava SK, et al. Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak in Iran. *Med J Islam Repub Iran*. 2020;34:62.
26. Heidari F, Karimi E, Firouzifar M, Khamushian P, Ansari R, Mohammadi Ardehali M, et al. Anosmia as a prominent symptom of COVID-19 infection. *Rhinology*. 2020 Jun;58(3):302–3.
27. Menni C, Valdes AM, Freidin MB, Ganesh S, El-Sayed Moustafa JS, Visconti A, et al. Loss of smell and taste in combination with other symptoms is a strong

- predictor of COVID-19 infection. medRxiv [Internet]. 2020 Jan 1;2020.04.05.20048421. Available from: <http://medrxiv.org/content/early/2020/04/07/2020.04.05.20048421.abstract>
28. Levinson R, Elbaz M, Ben-Ami R, Shasha D, Levinson T, Choshen G, et al. Time course of anosmia and dysgeusia in patients with mild SARS-CoV-2 infection. Vol. 52, *Infectious diseases (London, England)*. England; 2020. p. 600–2.
  29. Giacomelli A, Pezzati L, Conti F, Bernacchia D, Siano M, Oreni L, et al. Self-reported Olfactory and Taste Disorders in Patients With Severe Acute Respiratory Coronavirus 2 Infection: A Cross-sectional Study. Vol. 71, *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2020. p. 889–90.
  30. Gudbjartsson DF, Helgason A, Jonsson H, Magnusson OT, Melsted P, Norddahl GL, et al. Spread of SARS-CoV-2 in the Icelandic Population. *N Engl J Med*. 2020 Jun;382(24):2302–15.
  31. Bénézit F, Le Turnier P, Declerck C, Paillé C, Revest M, Dubée V, et al. Utility of hyposmia and hypogeusia for the diagnosis of COVID-19. Vol. 20, *The Lancet. Infectious diseases*. 2020. p. 1014–5.
  32. Lee Y, Min P, Lee S, Kim SW. Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. *J Korean Med Sci*. 2020;35(18):e174.
  33. Bansal P, Bingemann TA, Greenhawt M, Mosnaim G, Nanda A, Oppenheimer J, et al. Clinician Wellness During the COVID-19 Pandemic: Extraordinary Times and Unusual Challenges for the Allergist/Immunologist. *J allergy Clin Immunol Pract*. 2020 Jun;8(6):1781-1790.e3.
  34. Villarreal IM, Morato M, Martínez-RuizCoello M, Navarro A, Garcia-Chillerón R, Ruiz Á, et al. Olfactory and taste disorders in healthcare workers with COVID-19 infection. *Eur Arch oto-rhino-laryngology Off J Eur Fed Oto-Rhino-Laryngological Soc Affil with Ger Soc Oto-Rhino-Laryngology - Head Neck Surg*. 2020 Jul;
  35. Izquierdo-Domínguez A, Rojas-Lechuga M, Chiesa-Estomba C, Calvo-Henríquez C, Ninchritz-Becerra E, Soriano-Reixach M, et al. Smell and taste dysfunctions in COVID-19 are associated with younger age in ambulatory

- settings - a multicenter cross-sectional study. *J Investig Allergol Clin Immunol* [Internet]. 2020;30(5):1–28. Available from: <http://www.jiaci.org/ahead-of-print/smell-and-taste-dysfunctions-in-covid-19-are-associated-with-younger-age-in-ambulatory-settings---a-multicenter-cross-sectional-study>
36. Foster KJ, Jauregui E, Tajudeen B, Bishehsari F, Mahdavinia M. Smell loss is a prognostic factor for lower severity of COVID-19. *Ann allergy, asthma Immunol Off Publ Am Coll Allergy, Asthma, Immunol*. 2020 Jul;
  37. Ancochea J, Izquierdo JL, Soriano JB. Evidence of gender bias in the diagnosis and management of COVID-19 patients: A Big Data analysis of Electronic Health Records. *medRxiv*. 2020 Jan;2020.07.20.20157735.
  38. Iravani B, Arshamian A, Ravia A, Mishor E, Snitz K, Shushan S, et al. Relationship between odor intensity estimates and COVID-19 prevalence prediction in a Swedish population. *Chem Senses*. 2020 May;
  39. Mariño-Sánchez F, Valls-Mateus M, Fragola C, de Los Santos G, Aguirre A, Alonso J, et al. Paediatric Barcelona Olfactory Test-6 (pBOT-6): Validation of a Combined Odour Identification and Threshold Screening Test in Healthy Spanish Children and Adolescents. *J Investig Allergol Clin Immunol*. 2019 Sep;0.
  40. Fjaeldstad AW, Ovesen T, Hummel T. The Association Between Smoking on Olfactory Dysfunction in 3,900 Patients With Olfactory Loss. *Laryngoscope*. 2020 Feb;

## **FIGURE LEGENDS**

**Figure 1.** Frequency and severity distribution of smell and taste dysfunction in the COVID-19 HCP population. **A)** Frequency of smell and taste dysfunction for both global (black bars), accompanying symptom (dark grey bars) and as unique symptom (soft grey bars). **B)** Severity of smell and taste dysfunction for either mild (soft grey bars), moderate (hard grey bars), or severe dysfunction (black bars).



**Figure 2.** Time of recovery of smell (A) and taste (B) dysfunctions in the COVID-19 HCP population for either global (black boxes) and by severity (mild, 0-3; moderate, 4-7; severe, 8-10; grey boxes). NS: not significant.

