SMELL, TASTE AND COVID-19:

TESTING IS ESSENTIAL

Christopher H Hawkes[1] MD FRCP FAAN

1. Blizard Institute, Queen Mary University of London, 4 Newark St, London UK E1 2AT

Word count excluding references, Table and abstract 3095.

Key words: Olfaction. Taste. Covid-19. Chemosensation.

Abstract. During the Covid-19 pandemic is became clear that smell and taste (chemosensory) disturbance is very common in the early stages of disease. This article addresses: 1) why Covid-19 specifically targets the modalities of smell and possibly taste and what is the mechanism 2) what is the frequency of smell and taste loss and, 3) what is the overall prognosis. It is suggested that mouth breathers may be at particular risk of Covid-19. Symptom-based questionnaires are likely to under-estimate the prevalence of chemosensory impairment by as much as 50%. The prevalence of smell loss is so high that a person who has normal olfaction *on formal testing* is unlikely to be infected significantly with Cov-2. Furthermore, *someone without symptoms* who has an abnormal smell test could still be infected and liable to spread the disease. Brief, low cost, olfactory tests are available that would permit a high throughput in field stations and airports. A normal result might obviate the need for a nasopharyngeal swab for the Cov-2 virus

On March 20th 2020, Claire Hopkins, President of the British Rhinological Society and Nirmal Kumar, President of ENT UK [1] circulated a letter to fellow members that drew attention to the heightened incidence of isolated anosmia in their clinics. In normal circumstances they would see around one case of post-viral anosmia per month whereas in the recent past this had increased to 4 per week and remarkably all were under 40 years old. They questioned whether new onset anosmia in relatively young people might be an early warning of Covid-19 infection and emphasised the presence of similar observations from China, South Korea and Iran.

It is unusual for impairment of smell sense to be such a prominent symptom of upper respiratory viral infection. The majority of the latter are recognised in ear nose and throat (ENT) units particularly as a symptom from middle-aged or elderly in the aftermath of upper respiratory infection (URT). Most individuals who experience URT such as the common cold, accept a degree of smell impairment that results typically from a blocked nose, but what is remarkable about Covid-19 is that its occurrence is often early, of acute onset, severe and only occasionally associated with a blocked nose[2,3]. These thoughts have been given preliminary support from a study of 10 patients with proven Covid-19 infection compared to 10 people with an acute cold and 10 healthy controls[4]. Using the extended version of Sniffin' Sticks there were significant differences: those with Covid-19 infection scored lower than the acute cold group, with identification scores affected more than threshold or discrimination.

Several questions arise: why should Covid-19 specifically target chemosensation (i.e. smell and taste) and what is the mechanism? What is the frequency of smell and taste loss and what is the overall prognosis?

1. Why should Covid-19 specifically target the sense of smell and possibly taste?

Preliminary information about the likely mode of nasal invasion is just emerging. The virus, SARS-CoV-2, (shortened here to Cov-2) that causes the illness, Covid-19, infects cells through interactions between its spike protein and the ACE2 protein on target cells (Figure 1).

Figure 1. Molecular structure of the SARS-Cov-2 virus to show how the virus can attach to a pneumocyte (alveolar cell) that lines the alveoli. Reproduced with permission from David Baker, Blizard Institute, Queen Mary, University of London.

This interaction requires cleavage of the spike protein, likely by the cell surface protease, serine (TMPRSS2) and other proteases such as cathepsin B and L. It has been demonstrated that *non*-olfactory epithelial cells from the human upper airway express high levels of ACE2 and serine proteases[5] as shown in Figure 2, a finding that implies they could act as a viral reservoir.

Figure 2. Simplified model for CoV-2-induced anosmia/hyposmia in COVID-19 based on results obtained from patients and animal models. Article from Open Access journal reproduced with permission from Bilinska and Butowt[6]

According to Brann and colleagues[7] olfactory epithelial sustentacular cells, horizontal basal cells and Bowman's gland cells express the receptors required for entry of CoV-2 but there is no ACE2 expression in mature olfactory receptor neurones. In essence they propose that the anosmia of Covid-19 relates to primary infection of non-neuronal cell types and by implication, that smell loss is a consequence of local inflammation in and around the nasal neuro-epithelium. This concept has received preliminary confirmation from MRI-based studies that reveal congestion in the olfactory cleft – the area that houses olfactory neurones[8]. Although these findings are plausible it is possible, as the authors suggest, that other non-ACE2 dependent receptors may facilitate cellular entry of CoV-2. These observations are preliminary and it is still possible that CoV-2 may involve the olfactory

bulb. Indeed MRI-based studies have shown oedema of the olfactory bulb[9] (Figure 3) as well as more central changes, namely in the gyrus rectus[10] and by CT/PET, in the orbitofrontal cortex[11].

Figure 3. Transient olfactory bulb oedema as shown in coronal 3D MRI T2-weighted imaging (1.5T) during anosmia (day 7; C) compared to recovery (day 24;D). Olfactory bulb (ob; pink) displays transient volume and signal increase, olfactory cleft oedema (OC; brown), and focal left ethmoid (eth; green) sinusitis (*), and normal cranial fossa (grey line) and orbit (orb; yellow). Reproduced from Figure 1 C and D with permission from Laurendon et al[9].

There is provisional evidence that ACE2 receptors are present in the tongue (Figure 4) particularly taste buds and to lesser degree in the lingual epithelium[12,13]. Cov-2 can be isolated from saliva[14] thus there is a plausible mechanism for such infection to involved taste bud receptors. Less is known about ACE2 expression in the major taste nerves, namely the chorda tympani and glossopharyngeal nerves.

Figure 4. Bulk RNA-seq analysis of public datasets. Bar plot of ACE2 expression in normal tissues from FANTOM5 CAGE dataset, coloured by organs. Reproduced from Figure 1b with permission under Open Access from: Xu et al[14].

2. <u>What is the frequency of chemosensory loss?</u>

There have been numerous estimates worldwide, but with a few exceptions detailed below, most have been based on questionnaire surveys without objective measurement and several have not contained a control group. Samples have been varied: some are based predominantly on out-patients others reliant on in-patients with testing at varying stages of illness. The largest investigation[15,16] employed a smartphone-based app to retrieve symptomatic data on over 2 million people in UK and USA and found that in those reporting chemosensory impairment, 65% had a subsequent positive PCR for Covid-19. When this was combined with fever, cough, fatigue and loss of appetite the correlation with PCR for Cov-2 was very high. A large meta-analysis totalling 38,198 subjects[17]documentated an overall prevalence of smell impairment in Caucasians of 49% and 16.7% in Asians. Taste symptoms occurred in 51% Caucasians and 18% Asians. Other studies show wide

estimates of prevalence – up to 70%[18]with an approximately equal rate for smell or taste. Sometimes isolated impairment of smell or taste is documented as a presenting symptom. A study from San Diego based on ambulatory individuals with influenza-like symptoms, noticed that subjective report of smell impairment was associated with a 10-fold *lower* risk of hospital admission for Covid-19[19]. This finding is discussed further below

Surveys that have relied on patient reports are susceptible to multiple confounders including recall bias[20] and a tendency to over-representation of female respondents[21]. Even more importantly, less than 40% of individuals are actually aware of a proven olfactory defect[22]. For subjective awareness, the defect needs to be bilateral and of at least moderate severity. Furthermore, smell loss and taste loss are very frequently confused. Most people who complain of impaired taste have reduced olfaction[23] whereas it is unusual for someone with primary taste loss to complain of smell impairment. The mechanism of this phenomenon has not been satisfactorily explained.

Patient reports of olfactory impairment are therefore *intrinsically unreliable* and will tend to underestimate the true picture due to lack of awareness and confusion with taste. Furthermore, if taste is really affected in Covid-19 any such deficiency would inflate estimates of smell impairment where based on subjective reports. According to PubMed, at the time of writing there have been 14 articles worldwide where various *objective* olfactory measurements have been made (Table 1). Case numbers range by centre from 14-345 individuals. In nearly all instances a confirmatory polymerase chain reaction (PCR) test for Cov-2 has been undertaken. In only 9 cases was there a control group and where present the PCR test is not stated in 7 of these. Matching by age and gender was performed in just 4 instances. Subjective awareness of olfactory loss was indicated in 12 studies with a prevalence ranging from 28%-86% (mean 54%). Some authors have used non-standard olfactory measurement e.g. modified ethyl-alcohol threshold test[24] or an in-house identification test of 10 odours[25] neither containing details of control data. In one article, patients quarantined at home were instructed on how to make up their own smell and taste ingredients[26], despite the existence of readily available standardised commercial test kits for home use. The 4-odour Pocket Smell Identification Test used by one group[27] or the 3-odour Quick Smell Identification Test (Q-SIT) employed by others[28,29] are more appropriate for rapid screening in the clinic, rather than large research projects. For example, a score of 3/3 correct answers on the Q-SIT is likely to indicate normal olfaction[30] but as emphasised by the authors, a value of 2/3 could represent either hyposmia or a normal result because of wide variance. Nonetheless, a score of 3/3 would help exclude

anosmia where a low-cost, high-volume survey is required. The data from Iran[31,32] have been criticised unfairly because many of the 40 odours used in the identification kit were allegedly unfamiliar to Iranians[33]. However, the test used was in fact specifically modified to account for cultural differences[34].

It is important to be aware of the time of olfactory assessment in calculating the prevalence of Cov-2 related smell impairment, whether based on questionnaires or psychophysical tests. Clearly the closer to acute symptom onset, the more chance of an abnormal result. In four instances this information is not supplied. Where the time of testing is supplied, this ranges from 4-37 days. Taking into account the above reservations, there are just four more robust studies that have used standardised smell tests, have a control group, time of examining 14 days or less and adequate patient numbers, arbitrarily set at 45 or more [28,31,32,35]. With this reservation, it may be inferred a) that subjective awareness of smell impairment is highly variable i.e. 28%-49% b) olfactory impairment on objective testing is present in 84%-98%. c) in general, hospitalised patients who are assessed within 14 days of symptom onset have more abnormal smell tests (71%-98%). The picture for outpatients is less clear

Compared to subjective patient reports, smell measurement will therefore uncover a further 40% - 50% of proven Cov-2 infected people, indicating that the olfactory defect is near universal. In practical terms this means that *an abnormal smell test may be present in someone with no symptoms and yet be capable of spreading the virus.* Conversely, a normal standardised smell test such as the Sniffin' Sticks or UPSIT should help exclude the presence of Covid-19 and would be valuable for mass population screening.

A less clear picture is available for the sense of taste. Only 6 studies report taste measurement (Table 1) and details of a control group are not given in four of these. Just three centres[27,34,36]. implemented a standardised measurement (taste strips) and documented a normal result in a total of 40 patients from two centres[27,36] with an abnormal value from one unit[34] (5/72; 7%). The other three[25,26, 37] used in-house tests and observed abnormalities ranging from 27%-49%. No reliable conclusion can be drawn from these limited observations.

c

Table 1. Summary of articles where objective chemosensory testing was undertaken. CCCRC= Connecticut Chemosensory Clinical Research Center orthonasal olfaction test. PCR=polymerase chain reaction. ID=identification. Q-SIT= Quick Smell Identification Test. UPSIT=University of Pennsylvania Smell Identification Test. SST = Sniffin' Sticks test). TOT= time of testing. The Taste Strips Test uses four tastants at four different concentrations.

3. Prognosis.

Some subjective patient reports describe recovery of olfaction in 2-6 weeks. This finding is exemplified by one article with serial longitudinal objective assessment[32]. Return to normal was shown in nearly two thirds (61%) within 8 weeks (Figure 5). At that point, 35% still had varying degrees of impairment although complete smell loss affected just 4%. Distortion of perceived smells (cacosmia) and smell hallucinations (phantosmia) are recognised in the established and disease recovery phase[40].

The olfactory neuroepithelium has considerable capacity for regeneration, provided the stem cell layer is not damaged[41]. This process is unlikely to account for the rapid subjective recovery that in some instances appears complete in as little as 2 weeks (Figure 5). Such swift improvement is more in keeping with resolution of inflammation/oedema surrounding the nasal neuro-epithelium as shown on by MRI (Figure 3) . There are insufficient reports relating to the prevalence and recovery of taste impairment.

Figure 5. Proportion of patients with varying degrees of recovery according to COVID-19 symptom onset. All initial (n = 100) and follow-up (n = 82) scores are combined. Reproduced from Figure 4 with permission under Open Access from Moein et al[32].

Potential risk for mouth breathers. There are multiple causes of mouth breathing. It relates usually to nasal obstruction from a displaced septum, congestion, polyps and a variety of developmental abnormalities of the nasal cavity including Down's syndrome. In some it is just a bad habit. Most snorers breathe through the mouth and there is evidence that people with obstructive sleep apnoea are mouth breathers[42]. In the San Diego study of olfaction and Covid-19[19] it was speculated that milder cases of COVID-19 may present with severe anosmia and higher self-reporting, compared to the undetected or slight hyposmia associated with moderate to severe COVID-19 cases. If correct, this dichotomy may relate in part, to an individual's pattern of inspiration. Thus, habitual nose-breathers would direct airborne virus into the nasal passages where there are multiple immune-based defence functions that serve as a primary mucosal immune barrier. e.g. the nasopharynx-associated lymphoid tissue[43] (NALT) known collectively as Waldeyer's ring. A mouth-breather would therefore bypass the nasal component i.e. the adenoid and tubal tonsils and have to rely on the laryngeal and lingual tonsils. In theory, those who have had tonsillectomy or adenoidectomy might be more susceptible to subsequent viral infection although the consensus view is against this

contention[44,45]. A further defence mechanism favouring nose breathers relates to increased synthesis of sino-nasal nitric oxide (NO) which is an integral and highly conserved part of the host immune response. It acts as a first-line of defence against micro-organisms and upregulates ciliary motility. At low concentration, NO acts as a signalling molecule that promotes growth and activity of immune cells. At high concentrations it binds DNA, proteins and lipids, thereby inhibiting or killing target pathogens[46]. In support of this in the clinical setting[47], 6 human volunteers were infected with human rhinovirus (HRV-16), a non-enveloped RNA virus. Elevated nitric oxide synthase mRNA was detected in nasal turbinate scrapings from infected individuals and increased levels of exhaled NO from the nose and lower airways. Others[48] are exploring the possible benefits of inhaled nitric oxide in acute respiratory distress syndrome.

Discussion.

Smell impairment occurs in Covid-19 probably by involvement of ACE2-expressing cells (particularly the sustentacular cells) in the nasal olfactory area rather than the olfactory neurones *per se* thus resulting in a local inflammatory response in the nasal cleft, thereby impairing olfactory transduction. Involvement of the olfactory bulb and its central connections may occur in more advanced cases. The value of subjective reports is *severely limited* by low sensitivity to an established smell defect and confusion with taste impairment. Objective testing suggests that there is smell loss in nearly all patients suffering from Covid-19. In theory, a mouth breather would be more at risk of lung infection (and severe Covid-19) than a nose breather. Partial or complete smell recovery takes place in around two thirds subjects over a period of 2- 6 weeks. Hence, anosmia constitutes an important warning symptom and sign of infection by Cov-2 and has been highlighted in the UK public domain since June 2020.

Olfactory testing elevates the detection rate of a defect by about 50% i.e. from around 30-40% according to symptoms, to more than 90% where based on measurement. *The importance of smell testing as opposed to smell questioning cannot be emphasized more strongly*

The prevalence of smell symptoms and signs is so high that a person who has normal olfaction *on testing* by procedures listed below, is unlikely to be infected with Cov-2 or if so, their viral load would be low and unlikely to result in transmission to others. Where resources are limited it is suggested that a rapid screening test of olfaction could be used in field stations or airports as a substitute for or complementary to nasal and throat swabs. False positives i.e. anosmia may result from other rhinotropic viruses but these patients would require formal viral testing in any event. The risk of a false negative result is low with estimates ranging from 2%-28%. If one excludes the small

study of 41 patients that implemented a 4 odour test[27] then the false negative rate drops to 2%-16%).

The position regarding taste impairment is less clear. Subjective complaint of dysgeusia is frequent but in most instances represents confusion with olfactory loss. Objective evaluation of taste impairment is complex and reviewed elsewhere[49].

There are clearly some weaknesses in this analysis. Although 14 studies address Covid-19 and hyposmia, patient numbers are relatively small and the tests employed are varied, sometimes unorthodox. Some groups have no control group and do not state clearly the time of testing – or if so, the range in days is wide. Other investigations have been published without peer review or possibly submitted (and published) in haste, given the urgency of the current pandemic. Ethnic differences may account for some of the wide variation in results[17]. Despite this, the conclusions based primarily on the 4 most thorough investigations, show a consistent relationship between smell impairment and Covid-19 and support the main messages in this paper

The Way Forward.

The following are suggested for future Covid-19 chemosensory research

1. Smell measurement should be undertaken by centres with a proven track record of chemosensory research using internationally recognised tests
2. Large numbers of cases at varying stages of disease *and* healthy controls should be collected in the community and hospital setting. The number required should be determined from power calculations based on the number of test odours used.
3. Any of the following identification procedures would be suitable for large scale studies in walk-in centres or airports:
    - Sniffin' Sticks, 12 odour version. This may be re-used multiple times within its shelf life. Given the potential risks of transmission it would be best administered by a trained operator rather than the subjects themselves
    - B-SIT (Brief Smell Identification Test). This is a 'scratch and sniff' procedure for single use only and comprises 12 odours. It is suitable for on-site or home completion
    - NHANES-8. (US National Health and Nutrition Examination Survey). This is a low cost 8 odour version similar in principle to the B-SIT. It is under evaluation for future field use.

The above procedures could be undertaken in Covid-19 walk-in centres or airports as an inexpensive screening procedure. An initial large-scale trial would be required to assess the sensitivity of the chosen test. Based on current data, a normal result would likely avoid the need for nasal/throat swabs whereas an abnormal result would require formal virological analysis.

Acknowledgement. The author would like to acknowledge the help and advice in the preparation of this manuscript from: Professor RL Doty, Director, University of Pennsylvania Smell and Taste Center, Philadelphia, USA and Dr Glenis Scadding, Consultant Physician in Allergy and Rhinology at the Royal National Throat, Nose and Ear Hospital, London UK.

Footnote: Q-SIT (Quick Smell Identification Test), B-SIT (Brief Smell Identification Test), UPSIT (University of Pennsylvania Smell Identification Test) and the Pocket Smell Test are trademarks of Sensonics International, Haddon Heights, New Jersey, USA.

Sniffin' Sticks and Taste Strips are trademarks of Burghart Messtechnik GmbH, Wedel, Germany.

References

1. Hopkins C, Kumar N. Loss of sense of smell as marker of COVID-19 infection. The Royal College of Surgeons of England: British Rhinological Society. 2020 Mar 21.
2. Lechien JR, Chiesa-Estomba MD CM, Hans S, Barillari MD MR, Jouffe L, Saussez S. Loss of Smell and Taste in 2013 European Patients With Mild to Moderate COVID-19. Annals of Internal Medicine. 2020 May 26.
3. Beltrán-Corbellini Á, Chico-García JL, Martínez-Poles J, Rodríguez-Jorge F, Natera-Villalba E, Gómez-Corral J, et al. Acute-onset smell and taste disorders in the context of COVID-19: a pilot multicentre polymerase chain reaction based case–control study. European journal of neurology. 2020 Apr 22.
4. Huart C, Philpott C, Konstantinidis I, Altundag A, Trecca EM, Cassano M, et al. Comparison of COVID-19 and common cold chemosensory dysfunction. Rhinology. 2020 Aug 19.
5. Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune ges. Nature medicine. 2020 May;26(5):681-7.

6. Bilinska K, Butowt R. Anosmia in COVID-19: A Bumpy Road to Establishing a Cellular Mechanism. ACS Chemical Neuroscience. 2020 Jul 16;11(15):2152-5.
7. 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. 2020 Jan 1.
8. Eliezer M, Hamel AL, Houdart E, Herman P, Housset J, Jourdaine C et al. Loss of smell in COVID-19 patients: MRI data reveals a transient edema of the olfactory clefts. Neurology. 2020 Sep 11.
9. Laurendon T, Radulesco T, Mugnier J, Gérault M, Chagnaud C, El Ahmadi AA, et al. Bilateral transient olfactory bulb edema during COVID-19–related anosmia. Neurology. 2020 Aug 4;95(5):224-5.
10. Politi LS, Salsano E, Grimaldi M. Magnetic resonance imaging alteration of the brain in a patient with coronavirus disease 2019 (covid-19) and anosmia. JAMA Neurology. 2020 May 29.
11. Galougahi MK, Ghorbani J, Bakhshayeshkaram M, Naeini AS, Haseli S. Olfactory bulb magnetic resonance imaging in SARS-CoV-2-induced anosmia: the first report. Academic Radiology. 2020 Apr 11.
12. Shigemura N, Takai S, Hirose F, Yoshida R, Sanematsu K, Ninomiya Y. Expression of renin-angiotensin system components in the taste organ of mice. Nutrients. 2019 Sep;11(9):2251.
13. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. International journal of oral science. 2020a Feb 24;12(1):1-5.
14. Xu J, Li Y, Gan F, Du Y, Yao Y. Salivary glands: potential reservoirs for COVID-19 asymptomatic infection. Journal of Dental Research. 2020b Apr 9:0022034520918518.
15. Menni C, Valdes A, Freydin MB, Ganesh S, Moustafa JE, Visconti A et al. Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection. MedRxiv. 2020a Jan 1.
16. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. Nature medicine. 2020b May 11:1-4.
17. von Bartheld CS, Hagen MM, Butowt R. Prevalence of chemosensory dysfunction in COVID-19 patients: a systematic review and meta-analysis reveals significant ethnic differences. ACS chemical neuroscience. 2020 Sep 1;11(19):2944-61.

18. Tong JY, Wong A, Zhu D, Fastenberg JH, Tham T. The prevalence of olfactory and gustatory dysfunction in COVID-19 patients: a systematic review and meta-analysis. Otolaryngology–Head and Neck Surgery. 2020 May 5:0194599820926473.
19. Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. In: International Forum of Allergy & Rhinology 2020 Apr 24.
20. Coughlin, SS. Recall bias in epidemiologic studies. J Clin Epidemiol 1990; 43: 87-91.
21. Wymer W. The implications of sex differences on volunteer preferences. Voluntas: International Journal of Voluntary and Nonprofit Organizations. 2011 Dec 1;22(4):831-51.
22. Wehling E, Nordin S, Espeseth T, Reinvang I, Lundervold AJ. Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and old adults. Arch Clin Neuropsychol 2011; 26(3): 260-9
23. Deems DA, Doty RL, Settle RG, Moore-Gillon V, Shaman P, Mester AF et al. Smell and taste disorders, a study of 750 patients from the University of Pennsylvania Smell and Taste Center. Archives of otolaryngology–head & neck surgery. 1991 May 1;117(5):519-28.
24. Calvo-Henriquez C, Maldonado-Alvarado B, Chiesa-Estomba C, Rivero-Fernández I, Sanz-Rodriguez M, Villarreal IM et al. Ethyl alcohol threshold test: a fast, reliable and affordable olfactory assessment tool for COVID-19 patients. European Archives of Oto-Rhino-Laryngology. 2020 Oct;277(10):2783-92.
25. Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G, De Vito A et al. Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head & Neck. 2020a Jun;42(6):1252-8.
26. Vaira LA, Hopkins C, Salzano G, Petrocelli M, Melis A, Cucurullo M et al. Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study. Head & Neck. 2020b Jul;42(7):1560-9.
27. Hintschich CA, Wenzel JJ, Hummel T, Hankir MK, Kühnel T, Vielsmeier V et al. Psychophysical tests reveal impaired olfaction but preserved gustation in COVID-19 patients. In: International forum of allergy & rhinology 2020 Sep 1. Wiley-Blackwell.
28. Lima MA, Silva MT, Oliveira RV, Soares CN, Takano CL, Azevedo AE et al.. Smell dysfunction in COVID-19 patients: More than a yes-no question. Journal of the Neurological Sciences. 2020 Nov 15;418:117107.
29. Tsivgoulis G, Fragkou PC, Delides A, Karofylakis E, Dimopoulou D, Sfikakis PP et al. Quantitative evaluation of olfactory dysfunction in hospitalized patients with Coronavirus [2](COVID-19). Journal of Neurology. 2020 May 25:1.

30. Jackman AH, Doty RL. Utility of a three-item smell identification test in detecting olfactory dysfunction. The Laryngoscope. 2005 Dec;115(12):2209-12.
31. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. International Forum of Allergy & Rhinology 2020a; 10: 944-950, 2020
32. Moein, S.T., Hashemian, S.M., Khorram-Tousi, A., Tabarsi, P., Doty, R.L. Prevalence and reversibility of smell dysfunction measured psychophysically in a cohort of COVID-19 patients. Int Forum Allergy Rhinol. 2020b Aug 6:10.1002/alr.22680. doi: 10.1002/alr.22680. Online ahead of print. PMID: 32761796
33. Mariño-Sánchez F, Santamaría-Gadea A, de Los Santos G, Alobid I, Mullol J. Psychophysical olfactory testing in COVID-19: is smell function really impaired in nearly all patients? Int Forum Allergy Rhinol. 2020 Aug;10(8):951-952. doi: 10.1002/alr.22639. Epub 2020 Jun 25. PMID: 32497397; PMCID: PMC7300888.
34. Moein ST, Hashemian SM, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Reply to: Psychophysical olfactory testing in COVID-19: is smell function really impaired in nearly all patients?. InInternational forum of allergy & rhinology 2020c Jun 4. Wiley-Blackwell.
35. Hornuss D, Lange B, Schröter N, Rieg S, Kern WV, Wagner D. Anosmia in COVID-19 patients. Clinical Microbiology and Infection. 2020 May 22.
36. Bocksberger S, Wagner W, Hummel T, Guggemos W, Seilmaier M, Hoelscher M et al. Temporäre Hyposmie bei COVID-19-Patienten. Hno. 2020 May 28:1.
37. Altin F, Cingi C, Uzun T, Bal C. Olfactory and gustatory abnormalities in COVID-19 cases. European Archives of Oto-Rhino-Laryngology. 2020 Oct;277(10):2775-81.
38. Chung TW, Sridhar S, Zhang AJ, Chan KH, Li HL, Wong FK et al. Olfactory dysfunction in COVID-19 patients: observational cohort study and systematic review. InOpen Forum Infectious Diseases 2020 Jun 5.
39. Le Bon SD, Pisarski N, Verbeke J, Prunier L, Cavelier G, Thill MP et al. Psychophysical evaluation of chemosensory functions 5 weeks after olfactory loss due to COVID-19: a prospective cohort study on 72 patients. European Archives of Oto-Rhino-Laryngology. 2020 Aug 4:1-8.
40. Lechien JR, Cabaraux P, Chiesa-Estomba C, Khalife M, Plzak J, Hans S et al. Objective olfactory testing in patients presenting with sudden onset olfactory dysfunction as the first manifestation of confirmed COVID-19 infection. Medrxiv. 2020a Apr.
41. London B, Nabet B, Fisher AR, White B, Sammel MD, Doty RL. Predictors of prognosis in patients with olfactory disturbance. Ann Neurol 2008; 63(2): 159-66

42. Koutsourelakis I, Keliris A, Minaritzoglou A, Zakynthinos S. Nasal steroids in snorers can decrease snoring frequency: a randomized placebo-controlled crossover trial. Journal of Sleep Research. 2015 Apr;24(2):160-6.
43. Tacchi L, Musharrafieh R, Larragoite ET, Crossey K, Erhardt EB, Martin SA et al. Nasal immunity is an ancient arm of the mucosal immune system of vertebrates. Nature communications. 2014 Oct 22;5(1):1-1.
44. Bitar MA, Dowli A, Mourad M. The effect of tonsillectomy on the immune system: A systematic review and meta-analysis. International journal of pediatric otorhinolaryngology. 2015 Aug 1;79(8):1184-91
45. Altwairqi RG, Aljuaid SM, Alqahtani AS. Effect of tonsillectomy on humeral and cellular immunity: a systematic review of published studies from 2009 to 2019. European Archives of Oto-Rhino-Laryngology. 2020 Jan 1:1-7.
46. Schairer DO, Chouake JS, Nosanchuk JD, Friedman AJ. The potential of nitric oxide releasing therapies as antimicrobial agents. Virulence. 2012 May 1;3(3):271-9.
47. Sanders SP, Proud D, Permutt S, Siekierski ES, Yachechko R, Liu MC. Role of nasal nitric oxide in the resolution of experimental rhinovirus infection. Journal of allergy and clinical immunology. 2004 Apr 1;113(4):697-702.
48. Harris NS and Strickland B. Inhaled Nitric Oxide Therapy for Emergency Room COVID-19 Patients. https://rally.partners.org/study/no_cov_ed?code=ca
49. Hawkes CH, Doty RL. Smell and taste disorders. Cambridge University Press; 2018.

Conflict of interest statement

I receive an honorarium from Elsevier in respect of his Chief Editor duties for Multiple Sclerosis and Related Disorders. I receive royalties from Cambridge University Press for two books: Neurology of Olfaction by Hawkes CH and Doty RL 2009 and Smell and Taste Complaints, by Hawkes CH and Doty RL 2018. I receive royalties from Oxford University Press for Instant Neurological Diagnosis. Hawkes CH, Sethi K and Swift TJ 2019 (second edition)

Funding: none

Ethical approval. Not required

Contributions. This article is the sole work of the author

Reference and Country of Test Listed alphabetically by lead author	Type of tests	CASES Number, source, mean age/gender, Cov-2 PCR status. Time of testing	CONTROLS Number, source, mean age/gender Covid-19 PCR status. Time of testing	CASES. Number aware of smell / or taste impairment	CASES Smell test results	CONTROLS Smell test results	CASES: Taste test results
Altin [37] Turkey.	16 odour SST ID test In house taste ID of sucrose, salt, vinegar and coffee.	81 in-patients. 40 female. Mean age: 54y. All PCR positive. TOT not stated.	40 age/gender matched healthy controls. 19 female (47%). Mean age: 55y. Source not stated. All PCR negative. TOT not stated.	50/81 (62%)	Median score 6/16 Percent abnormal not stated	Median score 10/16 Percent abnormal not stated	22/81 (27%) abnormal
Bocksberger[36] Germany	12 odour SST ID test Taste Strips Test	14 in-patients for smell tests. Taste test in 10. Mean age 46y. 13 female. Cov-2 status not stated. TOT 4-23 days from symptom onset	None	26/63 (41%) complained of loss of smell or taste	10/14 (71%) abnormal Not helped by nasal decongestant	None	All 10 patients were normal
Calvo-Henriquez[24] Spain	Modified ethyl alcohol threshold test	129 in- or out-patients. Mean age 55y. 67 (52%) female. Severe cases excluded. All PCR positive. TOT not given	146 healthy hospital staff Mean age 55y. 76 female. (52%). PCR: not stated. TOT not given	Not stated	Abnormal threshold	Not supplied directly	Not done
Chung[38] Hong Kong	UPSIT and Butanol threshold test (BTT)	18 mildly infected in-patients. Mean age 28y. 11 female (61%). All PCR positive. Median TOT: 14 days.	18 students or healthcare workers. Mean age 31y. 13 (72%) female. PCR not stated. TOT not stated	12/18 (67%)	Abnormal BTT in 6/18 (33%). All 6 had abnormal UPSIT.	Not given	Not done
Hintschich[27] Germany	Pocket Smell Test (4 odours) Taste Strips Test Both self-administered	41 patients under home quarantine. All PCR positive. Median age 37y. 28 (68%) female. TOT: 3 days after positive PCR. Median of 13 days after first symptoms	30 patients. Source: not stated. Median age 33y. 22 (73%) female. All negative for IgG antibodies. TOT not stated.	25 (61%) for smell. 18 (44%) for taste	22 (54%) abnormal Where there was subjective loss of smell, abnormal in 18 (72%)	Not stated	Not significantly different from controls
Hornuss[35] Germany	12 odour SST ID test	45 in-patients. 20 female (44%). Median age 56y. All PCR positive. Mean duration of symptoms / time of testing: 10 days.	45 asymptomatic in-patients or health-care workers. Median age 54y. Gender not stated. PCR: not done. TOT not stated	Smell: 22/45 (49%)	38/45 (84%) abnormal	12/45 (27%) abnormal	Not done
Le Bon[34] Belgium	Extended SST (threshold, discrimination and Identification to 16 odours). Taste Strips Test	72 outpatients. 49 (68%) female. Mean age 38.9y. 25 PCR positive. 47 IgG antibody positive. TOT: mean of 37 days after symptom onset	None	Smell: 100% as self selected	27/72 (38%) abnormal Main effect on threshold scores. 45 normal (62%).	None	5/72 (7%) abnormal.

Lechien[40] Belgium	16- odour SST ID test	46 out-patients with 'initial sudden olfactory anosmia'. Mean age: 40.6y. 46 female (59%) PCR positive in 42/46 when tested in <12 days from symptom onset	None	Smell: 35/41 (86%) had subjective loss as reported from earlier study	35/46 (76%) abnormal overall	None	Not done
Lima[28] Brazil	QSIT. 3 odour ID test	57 Out-patients. 31 females (54%). Mean age 41.4y. All PCR positive. All but two had mild disease. Mean symptom duration: 4 days.	Total: 36. Source not stated. Mean age: 37.2y. 19 female (53%). PCR: not stated. TOT not stated	Smell: 34/57 (60%).	20/23 (87%) abnormal in those with subjective smell loss. 11/34 (32%) abnormal in those without subjective smell loss.	4/36 (11%) abnormal	Not done
Moein[31] Iran	UPSIT. 40 odour ID test Revised Persian language version	Total: 60. All in-patients. 20 female (33%). Mean age: 46y. All PCR positive. TOT: <14 days of symptom onset	60 healthy sex & age-matched controls from prior study. PCR: not stated.	Smell: 21/60 (35%)	59/60 (98%) abnormal Mean UPSIT score 21/40.	11/60 (18%) abnormal. Mean score 34/40 (normal)	Not done
Moein[32] Iran	UPSIT. 40 odour ID test Revised Persian language version	Total: 100 initial inpatients. Mean age 45y. 33 females (33%). TOT: near end of acute disease phase. After symptom onset 82 retested at 1-4 weeks. 51 retested at 6-8 weeks. All PCR positive	51 healthy age- & sex-matched to 52 COVID patients from prior study. 19 female (37%). Mean age 45.4y. PCR: not stated.	Smell: 28/100 (28%)	96/100 (96%) abnormal on initial testing. Mean UPSIT score 22/40	Not stated.	Not done
Tsivgoulis[29] Greece	Q-SIT. 3 odour ID test	Total: 22 in-patients. Mean age 55y. 10 female (45%). TOT: mean of 12 days after hospital admission. All PCR positive	22 age- & sex-matched controls taken from movement disorders clinic. PCR: not stated. TOT not stated.	Not stated	17/22 (77%) abnormal	8/22 (36%) abnormal	Not done
Vaira[25] Sardinia	CCCRC. In-house ID of 10 odours and butanol threshold. In-house taste identification for: salt, sugar, lemon & coffee solutions	Total: 72 health personnel. 25 In-patients. Others out-patients. 45 female (62%). Mean age 49y. TOT: mean 19 days from symptom onset. All PCR positive	None	Smell and/or taste symptoms in 53/72 (74%).	60/72 (83%) abnormal for composite olfactory score (threshold and discrimination)	None	Abnormal: 35/72 (49%)
Vaira[26] Italian multicentre	For quarantined patients: home self-administered and prepared odor discrimination test to 6 odour classes. Also used home self administered and prepared solutions to 4 tastants. For in-patients: CCCRC	Total 345 patients. 161 in quarantine (self evaluated at home). 184 in-patients. 199 (58%) female. Mean age 49y. TOT: mean 15 days from symptom onset. All PCR positive	None	Smell and/or taste symptoms in 256 (74%)	Overall percentages not supplied. From sequential graphs: around 70% abnormal for olfaction. 45% overall abnormal on taste test.	None	Abnormal in 190 cases (45%)

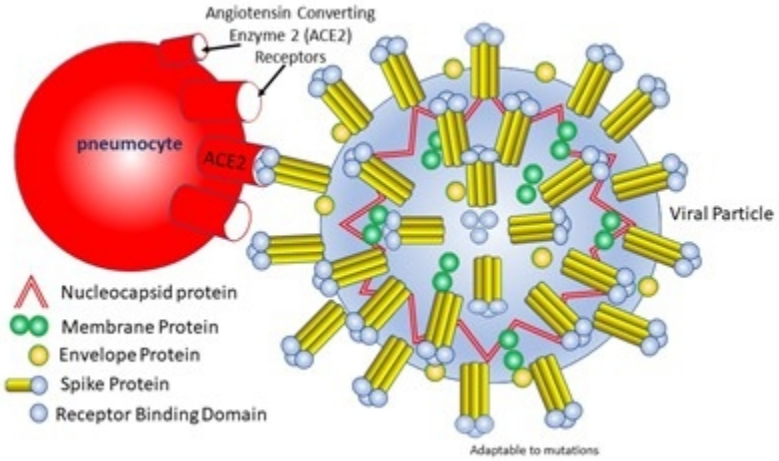

Figure 1. Molecular structure of the SARS-Cov-2 virus to show how the virus can attach to a pneumocyte (alveolar cell) that lines the alveoli. Reproduced with permission from David Baker, Blizard Institute, Queen Mary, University of London.

106x62mm (96 x 96 DPI)

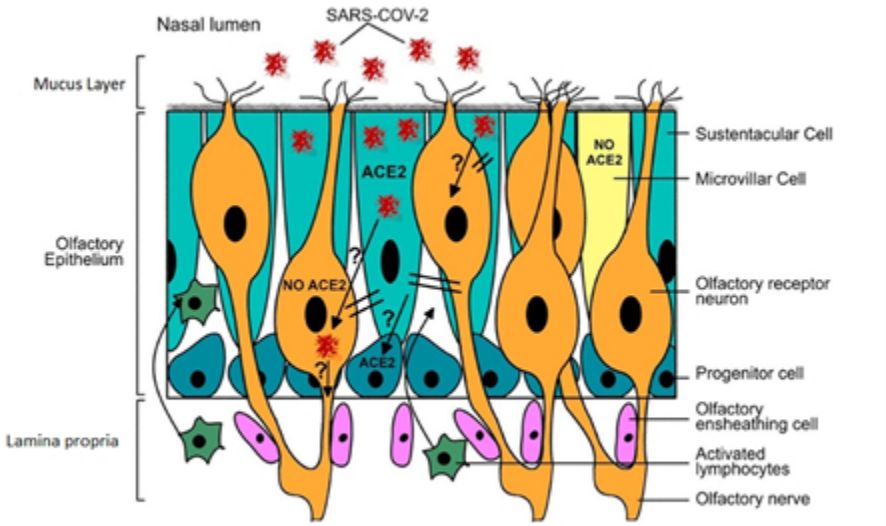

Figure 2. Simplified model for CoV-2-induced anosmia/hyposmia in COVID-19 based on results obtained from patients and animal models. Article from Open Access journal reproduced with permission from Bilinska and Butowt6

119x87mm (96 x 96 DPI)

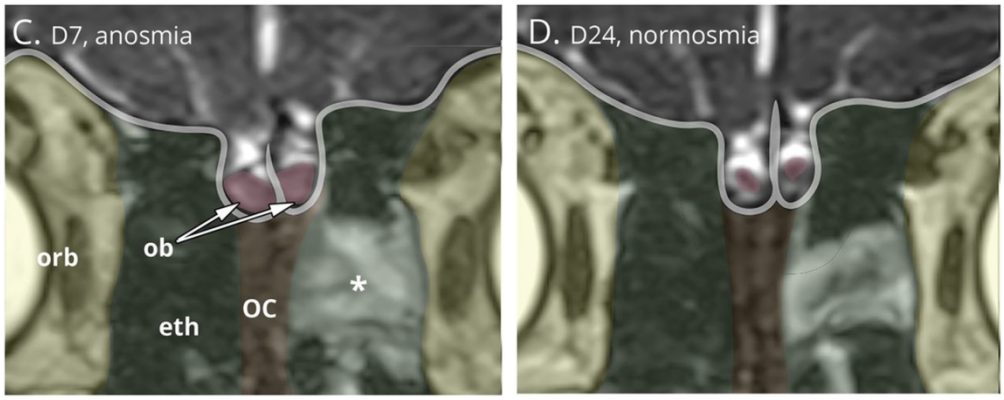

Figure 3. Transient olfactory bulb oedema as shown in coronal 3D MRI T2-weighted imaging (1.5T) during anosmia (day 7; C) compared to recovery (day 24;D). Olfactory bulb (ob; pink) displays transient volume and signal increase, olfactory cleft oedema (OC; brown), and focal left ethmoid (eth; green) sinusitis (*), and normal cranial fossa (grey line) and orbit (orb; yellow). Reproduced from Figure 1 C and D with permission from Laurendon et al9.

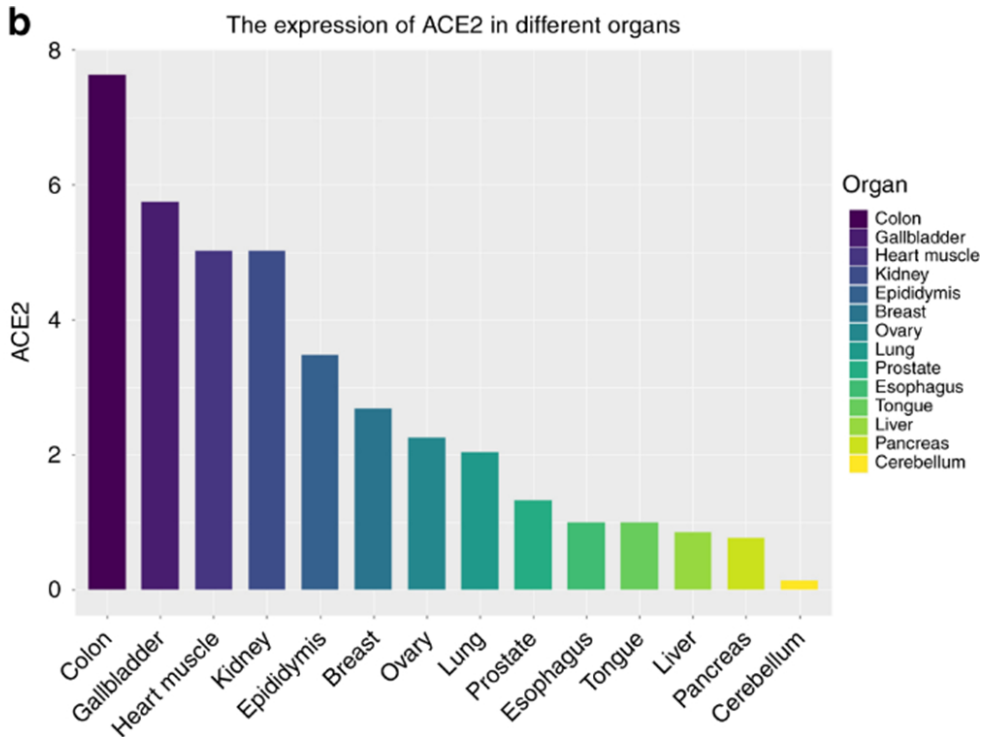

Figure 4. Bulk RNA-seq analysis of public datasets. Bar plot of ACE2 expression in normal tissues from FANTOM5 CAGE dataset, coloured by organs. Reproduced from Figure 1b with permission under Open Access from: Xu et al14.

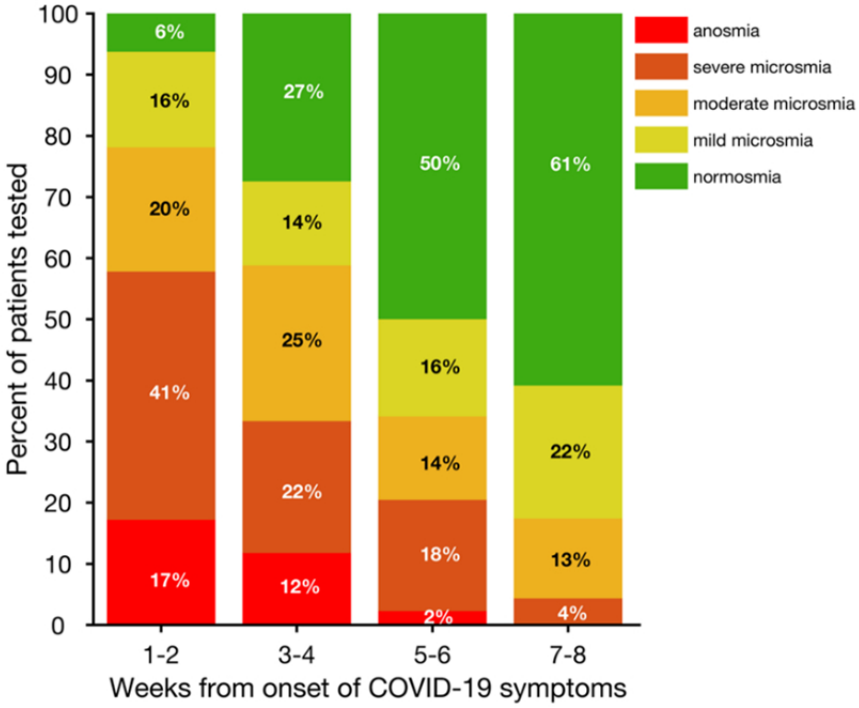

Figure 5. Proportion of patients with varying degrees of recovery according to COVID-19 symptom onset. All initial (n = 100) and follow-up (n = 82) scores are combined. Reproduced from Figure 4 with permission under Open Access from Moein et al32.