Taste dysfunction in Long COVID.

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Abstract

Persistent taste dysfunction is frequently reported in individuals with post-acute sequelae of infection by SARS-CoV-2 (Long COVID). The mechanisms and pathological correlates underlying this taste dysfunction are unknown. This study investigates the underlying pathology in 28 non-hospitalized subjects diagnosed with COVID-19 and who experienced taste disturbances more than 12 months after testing positive for SARS-CoV-2. To objectively establish the nature of taste deficit, we used the WETT taste test, which quantifies the subject's ability to taste each of the five taste qualities: sweet, umami, bitter, sour, and salty. We then biopsied five to eight fungiform taste papillae (FP) in 20 of the 28 subjects. The FPs were analyzed histologically for overall taste bud structure and innervation, and by quantitative PCR (qPCR) for mRNA expression of markers for different taste receptor cells. Although all subjects had reported taste dysfunction, only three showed overall taste scores below the 10th percentile for a normal population adjusted for age and sex. However, 11 of the 28 subjects exhibited total loss of one or more taste qualities. Loss of PLCβ2-dependent taste qualities (sweet, umami, bitter) was significantly more common and was correlated with reduced expression of *PLCβ2* and *Tas1R3* mRNAs. Histological analysis revealed generally preserved taste bud structure and innervation, but with occasional disorganized taste buds and abnormal, isolated PLCβ2-positive cells in the epithelium. Our findings suggest long-term taste dysfunction after COVID-19 occurs rarely -- more frequently involving PLCβ2-dependent taste qualities -- but is not due to wholesale disruption of the taste periphery.

25 **INTRODUCTION**

26 The COVID-19 pandemic has brought unprecedented attention to impairments of olfaction
27 and taste as hallmark symptoms of acute Severe Acute Respiratory Syndrome-CoronaVirus-2
28 (SARS-CoV-2) infection (Cooper *et al.* 2020; Hannum *et al.* 2023; Klein *et al.* 2021a; Klein *et*
29 *al.* 2021b). In most COVID-19-affected individuals, this dysfunction resolves within weeks but
30 can persist for months for others. Prolonged dysfunction lasting more than three months is now
31 recognized as part of post-acute COVID-19 syndrome (PACS) or Long COVID (Ely *et al.* 2024;
32 Soriano *et al.* 2022). Ongoing taste dysfunction may occur even after resolution of other
33 symptoms (Boldes *et al.* 2024; Xu *et al.* 2024) thus raising questions about the underlying
34 mechanisms. Understanding the long-term pathophysiology of taste dysfunction and, in extreme
35 cases, taste loss is crucial for patient care and the development of targeted rehabilitation strategies
36 (Lee *et al.* 2025).

37 Sensations of taste are largely mediated by lingual taste buds (TBs) situated in three types of
38 papillae: fungiform, vallate, and foliate. The fungiform papillae (FP) are concentrated on and
39 around the tip of the tongue, making them easy to biopsy. A typical human has about 200 FP with
40 0-50 taste buds (TB) in each FP (Cheng and Robinson 1991; Miller 1986; Miller 1988 ; 1989 ;
41 Miller and Reedy 1990).

42 Taste buds are complex multicellular epithelial end organs comprising between 20 and 100
43 taste cells (TCs) with approximately half being taste receptor cells (TRCs) (High and Finger
44 2025; Ogata and Ohtubo 2020; Ohtubo and Yoshii 2011; Yang *et al.* 2020). Histochemical,
45 immuno-histochemical and molecular methods allow for correlation of TRC subtypes with
46 specific taste qualities. Type II TRCs detect sweet, umami, or bitter tastes via distinct G-protein-
47 coupled receptor (GPCR) pathways involving downstream PLCβ2-dependent signaling cascades
48 (Shi *et al.* 2003; Zhang *et al.* 2003). Sweet taste is mediated via TAS1R2/R3 heterodimeric

49 receptors, and umami by TAS1R1/R3; bitter taste involves TAS2Rs, another family of taste
50 GPCRs. In contrast, Type III cells are responsible for transduction of ionic taste qualities, i.e.
51 sour and high concentrations of salt (Chang *et al.* 2010; Matsumoto *et al.* 2011) while Type I TCs
52 play a role similar to glia cells in the CNS (Bartel *et al.* 2006; Rodriguez *et al.* 2021; Wilson *et al.*
53 2025). In addition, taste buds contain a population of post-mitotic Type IV cells which mature to
54 differentiate into the other cell types. Disruption to these distinct molecular cascades or to the
55 morphological integrity of taste buds could contribute to the observed taste dysfunction in Long
56 COVID (Huang *et al.* 2021a).

57 Taste bud cells undergo continuous turnover, with new TRCs differentiating only when taste
58 fibers reach them (Farbman 1965; 1980; Farbman *et al.* 2004; Hellekant *et al.* 1987; Lee *et al.*
59 2017). Approximately 70–80% of mature TRCs form synapses with nerve fibers, highlighting the
60 importance of neural connectivity in maintaining taste function (Lee *et al.* 2017; Wilson *et al.*
61 2025; Wilson *et al.* 2022). Ongoing post-viral disruption of the nerve-TC interactions could well
62 lead to taste dysfunction.

63 SARS-CoV-2 infects cells via the ACE2 receptor and the TMPRSS2 protease, both of which
64 are expressed in oral epithelial cells, including Type II TRCs (Doyle *et al.* 2021; Yao *et al.*
65 2023). This suggests a plausible mechanism for direct viral-caused damage to the taste system.
66 Additionally, inflammatory processes, immune dysregulation, or altered saliva composition may
67 contribute to long-term taste changes following viral infection.

68 Given the clinical and biological implications of long-term taste dysfunction, this study aims
69 to investigate self-reported and objectively measured taste impairment in subjects who
70 experienced non-hospitalized COVID-19. Using a combination of psychophysical testing,
71 histological evaluation and molecular analysis -- including quantitative polymerase chain reaction
72 (qPCR) for mRNAs encoding taste cell markers and viral RNA -– this study seeks to elucidate

73 the structural and molecular changes underlying persistent taste dysfunction in Long COVID
74 subjects following COVID-19 caused by SARS-CoV-2.
75
76 **MATERIAL & METHODS**
77 ***Study design***
78 This study involved subjects aged ≥18 years who had experienced symptomatic COVID-19
79 and a confirmed SARS-CoV-2 infection verified by a positive PCR test from nasopharyngeal
80 swabs between 2020 and 2021 (inclusion criteria). All subjects had non-hospitalized COVID-19
81 and, all but one, reported long-term taste disturbances. The study population was recruited
82 between November 2021 and June 2022 from two sources at Uppsala University Hospital: the
83 COMBAT post-COVID study and the Ear, Nose and Throat (ENT) outpatient clinic.
84 From the COMBAT post-COVID cohort, 18 subjects underwent psychophysical taste
85 evaluation. Of these, 12 consented to undergo a fungiform papilla biopsy (subjects #SWE7, 8, 9,
86 12, 13, 14, 15, 18, 19, 23, 24, 26). Additionally, ten subjects were recruited from the ENT
87 outpatient clinic, eight of whom underwent biopsy (subjects #SWE17, 21, 22, 24, 25, 27, 28, 29).
88 In total, eight subjects did not undergo a biopsy.
89
90 ***Study population***
91 The COMBAT post-COVID project aimed to monitor persistent symptoms and long-term
92 consequences among non-hospitalized patients diagnosed with COVID-19. Initially, 725
93 individuals who tested positive for SARS-CoV-2 between March and December 2020 were
94 invited to complete a follow-up questionnaire 12 months after symptom onset. Of these, 401
95 subjects responded (response rate: 74%). The cohort has been described in detail elsewhere
96 (Janols *et al.* 2024; Kisiel *et al.* 2022; Kisiel *et al.* 2023a; Kisiel *et al.* 2023b; Kisiel *et al.* 2021).

97 Among the respondents, 68 individuals reported ongoing taste and/or smell disturbances. These
98 individuals were contacted by telephone and invited to participate in the current study if they
99 reported persistent taste loss and were available for in-person evaluation. Eighteen individuals
100 agreed to participate. Henceforth all individuals will be indicated as subjects.
101 Ten additional subjects attending the ENT outpatient clinic in 2021 were randomly selected
102 and invited to participate in the study if they met the same inclusion criteria. In addition, one
103 subject (#SWE17) reported no taste loss but had an active SARS-CoV-2 infection at the time of
104 sampling. Taste testing data for this subject are listed in Table 1 but are not included in the
105 statistical analysis of the cohorts reporting Long COVID taste disturbance.
106
107 **Clinical and sociodemographic variables**
108 From the COMBAT post-COVID cohort, information was documented about age, sex,
109 symptoms at COVID-19 onset, self-reported health before and one year after COVID-19, and
110 persistent symptoms one year following COVID-19. Symptoms at COVID-19 onset were also
111 retrieved from medical records from the PCR testing protocols. Additional subjects (n=11) were
112 characterized by age and sex only.
113
114 **Ethical Approval**
115 The study was approved by the institutional ethics committee of the University Hospital in
116 Uppsala (EPN number 2020-05707) and the Swedish Ethical Review Authority (EPM number
117 2021-00878) and complies with the Declaration of Helsinki for Medical Research involving
118 Human Subjects. The patients all gave written informed consent to the procedures. The
119 Combined Institutional Review Board at the University of Colorado at Anschutz approved the
120 transfer and analysis of the de-identified samples collected in Sweden. The study protocol in

121 Colorado (COMIRB number 20-1325) was determined Exempt/Non-Human Subject Research
122 and was conducted in accordance with 45 CFR 46 and institutional policies. All data were
123 pseudonymized to protect patient privacy.
124
125 **Taste evaluation**
126 As mentioned, the human sense of taste is divided into five taste qualities: sweet, umami,
127 bitter, sour and salty, (reviewed in:(Hellekant 2024; Lindemann 1996). To assess a subject's
128 ability to taste we used the quantitative and qualitative Waterless Empirical Taste Test (WETT®)
129 by Sensonics (Haddon Heights, NJ, USA). The WETT® test also measures the ability to taste
130 each taste quality with an eight-point scale from zero (no taste) to a maximum of eight (all
131 concentrations identified). The WETT® measures the ability to identify various concentrations of
132 the above five basic taste qualities with a minimum number of trials. It consists of 53 strips
133 impregnated with one tastant (a substance that produces a taste sensation) representing a specific
134 taste quality. A monomer cellulose pad (1 × 2.5 cm) is present on one side of each strip,
135 containing either: dried sucrose (sweet) (0.20, 0.10, 0.05, or 0.025 g/ml), citric acid (sour) (0.025,
136 0.05, 0.10, or 0.20 g/ml), sodium chloride (salty) (0.0313, 0.0625, 0.125, or 0.25 g/ml), caffeine
137 (bitter) (0.011, 0.022, 0.044, or 0.088 g/ml), monosodium glutamate (umami; brothy) (0.017,
138 0.034, 0.068, or 0.135 g/ml), or blank control strips, with no added chemical stimulus. The
139 subjects were instructed to place the appropriate strip on the tongue and move it along the surface
140 of the tongue for at least 5–10 seconds. The subject indicated which taste sensation was perceived
141 sött (sweet), bittert/beskt (bitter), surt (sour), buljongliknande smak/umami (umami), or salt
142 (salty), or whether no taste was sensed by verbally reporting their response to be entered on the
143 designated line of the response form. In the WETT® test sequence, the concentrations of each

144 stimulus are presented twice (eight total trials/tastant). In the first half of the test, the
145 concentrations ascend from weak to strong with the different tastants presented randomly, with
146 no tastant blanks included. In the second half of the test, the reverse presentation order is used,
147 i.e., going from strong to weak concentrations. Scores range from 53 (all correct) to 13 (no tastes
148 reported, corresponding to the number of control strips in the test). Each subject's results were
149 compared with normative values for each sex and age given in Doty et al (Doty *et al.* 2025).
150

151 **Biopsy procedures**

152 Five to eight fungiform papillae (FP) were biopsied from each subject's tongue and
153 preserved for histological and molecular analyses. Prior to biopsy, the tongue was anesthetized
154 with a Xylocaine spray (100 mg/ml Lidocaine with 10mg/spray dose), then blue or green food
155 coloring was added to enhance the tongue's fungiform papillae (FP). The tongue was held steady
156 with a gauze, and biopsies of the FP were taken with a 3-mm sterile microscissor with a curved
157 tip. The FP was cut one by one by holding down the scissor tip at the base of the chosen FP,
158 which was removed with a single cut and put in fixative for histology or RNA*later*™ (Thermo
159 Fisher Scientific Inc., Waltham, MA, USA). The biopsies for histological analysis were fixed in
160 4% buffered formaldehyde for at least four hours or overnight and then moved to phosphate-
161 buffered saline (PBS) solution. The biopsies were stored at 4°C until shipping for analyses from
162 Sweden to the United States for histopathological studies. The biopsies for RNA analysis were
163 placed in RNA*later*™ stabilization solution and stored at room temperature overnight and then
164 stored in the freezer at -18 °C initially and then at -80°C until analyses.

165 For all but two biopsy subjects, samples were taken immediately following the WETT test or
166 within two months of the WETT test as indicated in Table 1. For the other two subjects (subjects

167 SWE26 and 21), biopsies were taken four months following the WETT test. No biopsy was
168 requested for subjects SWE1-6 or SWE10 because these subjects showed relatively normal total
169 taste scores; subject SWE16 declined the biopsy procedure. For all other subjects (SWE7-9 ;
170 SWE12-15, and SWE 18-29) biopsies were obtained without regard to taste score. Subject
171 SWE17, who gave a biopsy sample, was a subject who recently tested positive for SARS-CoV-2
172 but reported no associated taste dysfunction. Histological and molecular data from this subject
173 are included in our analyses, but the taste testing data are not included in the analysis of Long
174 COVID taste testing which includes all subjects reporting taste dysfunction at the time the biopsy
175 was taken and no biopsy cohorts.
176
177 **Histology**
178 Upon receipt of fixed samples in Colorado, all specimens were cryoprotected in 20%
179 Sucrose in 0.1M phosphate buffer overnight at 4°C. Then, the tissues were cryo-sectioned (12-
180 14µm) onto Superfrost Plus microscope slides (Thermo Fisher Scientific, (Catalog# 1255015)
181 and air-dried. Slides were rinsed in 0.1M PBS pH 7.2. Antigen retrieval was performed with 10
182 mM sodium citrate buffer of pH 6.0 at 85°C for 10 minutes before incubation in blocking
183 solution (2% normal donkey serum, 1% bovine serum albumin, and 0.3% Triton in 0.1M PBS)
184 for an hour at room temperature. Slides were then incubated for four days in specific primary
185 antibodies diluted in blocking solution at 4°C including the following antisera:
186 The first two antisera were utilized in all cases, the latter two were used in some cases.
187 • Mouse anti-Tubulin β3 (clone TUJ1) at 1:1000 dilution (BioLegend, San Diego,
188 CA, USA, catalog# 801202; RRID:AB_2313773) (for total innervation),

189 • Rabbit anti-PLCβ2 (PhosphoSolutions, Denver, CO, USA, catalog# 1640-PLC;
190 RRID:AB_2801663), or guinea pig anti-PLCβ2 (PhosphoSolutions, AP8/24; RRID:
191 AB_2910247) (for identification of Type II TRCs).
192 • Goat anti-GNAT3 at 1:500 dilution (Aviva Systems Biology, San Diego, CA, USA,
193 catalog# OAEB00418; RRID:AB_10882823) (for TRCs expressing the taste-associated
194 G-protein gustducin),
195 • Rabbit anti P2X3 (Alomone, Jersusalem, Israel, catalog #APR-016, RRID
196 AB_2313760) (for labeling of taste bud-specific innervation).
197 After washing in 0.1M PBS, the slides were incubated two hours with fluorescent secondary
198 antibodies, Alexa Fluor 488 donkey anti-mouse (Invitrogen, catalog# A21202;
199 RRID:AB_141607), Alexa Fluor 568 donkey anti-rabbit (Invitrogen, catalog# A10042), Alexa
200 Fluor 647 donkey anti-goat (Invitrogen, catalog# A21447; AB_2534017), Alexa Fluor 647
201 donkey anti-guinea pig (Jackson Immuno Research Laboratories, West Grove, PA, USA,
202 catalog# 706605148; RRID: AB_2340476) or Donkey anti-Rabbit IgG (H+L) Highly Cross-
203 Adsorbed Secondary Antibody, Alexa Fluor™ 647 (ThermoFisher Catalog # A-31573;
204 AB_2536183) at 1:800 dilution each at room temperature. Lastly, the slides were washed twice
205 for 10 minutes each in 0.1M PBS and then once for 10 minutes in 0.05M PBS before coverslip
206 slides with DAPI Fluoromount-G (SouthernBiotech, Birmingham, AL, USA, catalog# 010020).
207
208 **RNA extraction**
209 The papilla tissue samples for PCR analysis were stored in RNA*later*™ at -20°C. RNA was
210 extracted with the RNeasy fibrous tissue mini kit (Qiagen, Hilden, Germany). A small piece of
211 the biopsy was taken with a pipet tip into a 1.5 ml tube containing 300 µl of RLT buffer and

212 mashed manually with a micro pestle. The pestle was rinsed when pipetting 590 µl of RNase free
213 water into the tube. The kit protocol was followed, and a DNase treatment was performed with a
214 DNA-free DNA removal kit (Invitrogen) according to their protocol. The resulting RNA
215 concentrations and quality were checked with Nanodrop 8000 (Thermo Fisher Scientific) and
216 TapeStation High Sensitivity RNA tape (Agilent, Santa Clara, CA, USA).
217
218 **Reverse transcription**
219 High-Capacity cDNA Reverse Transcriptase Kit (Applied Biosystems, Waltham, MA, USA)
220 was used to obtain cDNA from the RNA samples. 100 ng of RNA per sample, according to
221 TapeStation concentrations, was taken into the reverse transcription reaction. The kit protocol
222 was followed. The reverse transcription was performed in duplicates to obtain enough product for
223 all the qPCR runs.
224
225 **qPCR**
226 Quantitative PCR (qPCR) was performed with TaqMan (Applied Biosystems) assays for
227 *PLCβ2* (Hs01080542), *NCAM1* (Hs00941821), and *TAS1R3* (Hs01026531) as well as for two
228 reference genes *RPLP0* (Hs99999902) and *GAPDH* (Hs02758991). TaqMan Gene Expression
229 Master Mix (Applied Biosystems) was used according to its protocol, and 10 ng of cDNA was
230 added as template. All samples were run in triplicate per gene, including a negative control. One
231 gene per plate was run in the QuantStudio 5 (Applied Biosystems). Average Ct and standard
232 deviation were calculated for each gene and then normalized (Delta CT =Ct(gene of interest) –
233 Ct(reference gene)) against the reference gene *GAPDH*. The reference gene *GAPDH* gave more

234 consistent normalization than *RPLP0*, and was therefore selected as a reference for the genes of
235 interest.
236
237 **SARS-CoV-2 test**
238 A PCR test for the presence of SARS-CoV-2 virus in the tissue samples was performed in
239 triplicate, including two assays that target SARS-CoV-2 as well as negative control samples.
240 TaqMan microbe detection assay (Vi07918637) for SARS-CoV2N and TaqPath Blastopore
241 Microbial Detection Master Mix (Applied Biosystems) were used according to their protocol.
242 Positive control was TruMark Respiratory Panel 2.0 Amplification control (Applied Biosystems).
243 The qPCR was run in the QuantStudio 5 (Applied Biosystems). None of the biopsied tissue
244 samples tested showed the presence of SARS-CoV-2 virus, although one subject (#17) had an
245 active SARS-CoV-2infection as determined by a positive nasal swab test. Absence of detectable
246 SARS-CoV-2 virus in oral or salivary samples despite positive detection of virus in nasal swabs
247 is not uncommon and is described in other studies (Fernandes *et al.* 2021; Goodall *et al.* 2022).
248
249 **Statistical analysis**
250 Parametric statistical calculations were carried out by Excel (Microsoft) or with calculators
251 given at www.socscistatistics.com. Both calculators gave identical values. (Ho *et al.* 2019) For
252 comparisons (Ho *et al.* 2019)across samples, we utilized Pearson's Correlation co-efficient or
253 Fisher's Exact test for small sample sizes. For comparison of test percentile means against the
254 expected 50% percentile distribution, we employed a one-sample t-test. A criterion value of $p <$
255 0.05 was set for statistical significance in all calculations.

256 Means, standard deviations, and ranges were used to describe continuous variables such as
257 age, time from infection to testing, and taste scores. Categorical variables like sex and symptom
258 presence were summarized using counts and percentages.
259 Because taste ability varies substantially by sex and age, raw taste scores were normalized by
260 sex and age using reference data from Doty et al. (2025), which included 1,392 healthy
261 individuals. Scores for individual tastes below the 10% compared to sex and age matched
262 populations in Doty et al (2025) were considered potentially hypoguesic per the criterion set in
263 (Landis *et al.* 2009) and are highlighted in red in Table 1.
264 The binomial test or Chi-square tests (χ^2) were used to compare (categorical data) the
265 frequency of abnormal taste scores across groups. The results for Chi-square tests are reported as
266 χ^2 (degree of freedom (df), sample size) = chi-square value, p-value. Pearson's Correlation (r) was
267 used to assess linear relationships between molecular markers (qPCR results), histological
268 features, and taste scores. The results were reported as (df) sample size=correlation co-efficient,
269 p-value. (Schober *et al.* 2018).
270
271 **RESULTS**
272 *Study population*
273 All 28 subjects (24 women and 4 men) reported normal taste before the first confirmed
274 SARS-CoV-2 infection but, except for subject SWE17, altered or diminished taste thereafter .
275 The mean age at testing was 49.9 years (SD+/-1.2) and ranged between 30 and 71 years. Most
276 subjects contracted COVID-19 in early 2020. Two subjects (SWE19 & 28) experienced a second
277 infection in 2022, shortly before undergoing taste testing and biopsy. Considering only the first

infection, the time from initial SARS-CoV-2 infection to taste testing ranged from 13.5 months to 27.0 months (mean of 21.0 months).

Psychophysics:

Because taste ability varies substantially between individuals according to sex, age, and health status, we normalized all raw taste scores and overall WETT score against values given for 1,392 normal subjects (Doty *et al.* 2025). Although all subjects, except one (subject #SWE17), reported compromised taste abilities in clinical reporting, only 3 of 28 tested subjects scored below the 10th percentile in overall taste ability consistent with overall scores in a population of normal subjects (Doty *et al.* 2021) (see Table 1) and consistent with previous reports of no demonstrable long-term taste loss in broad post-covid populations following SARS-CoV-2 infection (Boscolo-Rizzo *et al.* 2023a; Sharetts *et al.* 2024). Nonetheless, 14 of the 27 of our Long Covid dysguesia subjects showed significant deficiency (10th percentile or lower) in one or more individual taste qualities (values in red shown in Table 1) which is significantly more than expected in a normal population (binomial test 24 of a total of 135 individual taste qualities; p = 0. 002). sex(Doty *et al.* 2021) One subject, who was also anosmic, (SWE29) gave no correct responses to any tastant, even at the highest concentration suggesting complete aguesia. Even subjects with a near-average total WETT score (percentiled by sex and age group) were unable to detect specific tastes, e.g. subjects SWE8 (F, age 64; WETT Score 32; 45%) and SWE9 (M, age 49; WETT Score 30; 54%) were unable to detect bitter or umami. Although individuals with a profound overall deficit also showed specific loss of one or more taste qualities (e.g. subject SWE7 [16%] showed no response to sweet, bitter or umami, but good response to sour and salty), the pattern of loss was not duplicated by other subjects (e.g. subject SWE24 [7%] with good responses to sweet, sour and salty, but total loss for bitter and umami).

302 The distribution of loss between subjects was uneven with sour standing out as the least
303 affected quality (only one score below the 10%). This may reflect the detection of "sour" being a
304 multisensory experience involving chemesthetic as well as gustatory modalities (Ohkuri *et al.*
305 2012; Yu *et al.* 2020; Zhang *et al.* 2019). In contrast, in acute COVID-19, sour taste is reported to
306 be most impacted during the acute phase of the illness (Karmous *et al.* 2023; Singer-Cornelius *et*
307 *al.* 2021).

308 More importantly, as a group, the PLCβ2-mediated taste qualities (sweet, umami, bitter)
309 showed total loss (score of 0) as well as scores below 10% significantly more than the other taste
310 qualities (sour, salty) ($X^2(1, N = 135) = 4.47, p = .03$). These findings suggest that Long Covid
311 taste disturbance may preferentially target the PLCß2-mediated taste qualities transduced by
312 Type 2 taste receptor cells.

	Subject Number	Sex	Age	Covid Date	Taste Test Date	Biopsy Date	PLC Tastes Sweet	Umami	Bitter	Sour	Salty	No Taste	WETT score	Sex/Age-corrected %
Acute Biopsy	SWE 17	F	30	Apr 2020	31/1-22	31/1-22	8	8	8	8	8	13	53	99
Post-covid No Biopsy	SWE 1	F	47	Mar 2020	19/11-21		5	3	1	5	6	12	32	42
	SWE 2	F	62	Apr 2020	19/11-21		3	0	1	8	8	11	31	36
	SWE 3	F	50	Apr 2020	24/11-21		6	0	3	7	5	12	33	45
	SWE 4	F	49	May 2020	3/12/21		0	8	6	6	7	10	37	59
	SWE 5	F	53	Nov 2020	17/1-22		8	4	8	8	7	13	48	95
	SWE 6	F	41	Nov 2020	18/1-21		7	2	4	5	4	12	34	51
	SWE 10	F	66	Nov 2020	20/1-22		8	1	8	7	5	13	42	83
	SWE 16	F	59	Apr 2020	11/2/22		5	3	6	8	7	10	39	70
Post-Covid Biopsy	SWE 7	F	68	Nov 2020	18/1-22	23/3-22	0	0	0	6	5	13	24	16
	SWE 8	F	64	Mar 2020	18/1-22	23/3-22	6	0	0	6	7	13	32	45
	SWE 9	M	49	Apr 2020	19/1-22	17/3-22	1	0	0	8	8	13	30	54
	SWE 12	F	56	Apr 2020	21/1-22	24/1-22	3	3	6	7	4	12	35	54
	SWE 13	M	45	Apr 2020	21/1-22	21/1-22	0	1	0	5	3	13	22	21
	SWE 14	F	30	Apr 2020	21/1-22	21/1-22	3	8	5	8	6	10	40	70
	SWE 15	F	53	Apr 2020	24/1-22	24/1-22	4	6	3	4	4	13	34	54
	SWE 18	F	63	June 2020	23/3-22	23/3-22	7	1	4	6	1	13	32	45
	SWE 19	F	46	May 2020 & Jan 2022	24/3-22	24/3-22	7	4	8	6	2	9	36	59
	SWE 20	F	38	Feb 2021	30/3-22	20/4-22	7	2	7	8	8	13	45	83
	SWE 21	F	71	Jan 2021	17/1-22	11/5-22	4	1	5	7	4	13	34	70
	SWE 22	F	56	Apr 2020	11/5/22	11/5-22	1	4	0	6	2	13	26	21
	SWE 23	F	49	Nov 2020	12/5/22	12/5-22	4	4	7	6	5	13	39	67
	SWE 24	M	42	June 2020	13/5-22	13/5-22	5	0	0	4	4	4	17	7
	SWE 25	F	50	Mar 2020	13/5-22	13/5-22	2	4	1	0	5	7	19	4
	SWE 26	F	24	June 2020	21/1-22	16/5-22	6	0	6	5	7	13	37	44
	SWE 27	F	52	Mar 2020	15/6-22	15/6-22	0	0	4	2	6	13	25	15
	SWE 28	F	43	Nov 2020 & Feb 2022	5/7-22	5/7-22	6	3	7	7	3	10	36	44
	SWE 29	M	30	April 2020	15/7-22	15/7-22	0	0	0	0	0	13	13	1
	Post-covid aguesia n=		27			Post-covid Cohorts ave Taste Score	4.0	2.3	3.7	5.7	4.9	11.6	32.3	46.5
	Post-covid Biopsy n=		18			scores <10%	7	3	9	1	4			
red text ≤10%						zero scores	5	9	7	2	1			

Table 1: Results from WETT testing of all subjects including basic demographic information, dates of infection, taste testing and biopsy. Columns labeled as "Sweet, Umami, Bitter, Sour, Salty and No Taste" show WETT test raw scores for each taste quality and blank "No Taste" control strips. Red numerals in columns for individual tastes indicate values below the 95% confidence interval for sex and age-matched controls based on Doty, et al 2025. The incidence of values below the 10% for all post-Covid subjects is significantly higher than expected based on a normal population ($\chi^2(1, N = 135) = 4.47$, $p < .05$). Zero values indicate that the subject was unable to identify the tastant at any concentration offered. The total number of zero values for each tastant is shown in red along the bottom row. WETT score shows the total WETT score for each subject alongside of the corresponding sex and age matched percentile ranking compared to the study population in Doty et al 2025. A perfect score is 53 (8 for each taste quality + 13 blanks). Complete ageusia would give a score of 13 (0 for all tastants and 13 for correctly identifying blank controls). PLCß2-dependent tastes are indicated by orange shading along the top and bottom rows.

313

314 **Quantitative PCR Findings**

315 RNA prepared from
316 taste papillae from all
317 biopsied subjects,
318 including SWE17, was
319 analyzed for expression
320 levels of three taste-related
321 mRNAs encoding: 1)
322 phospholipase C beta 2
323 (PLCß2) a marker of Type
324 II cells, 2)Taste receptor
325 member *TAS1R3*, coding
326 for a receptor component
327 for both sweet and umami
328 tastes and expressed in a
329 subset of Type II taste
330 cells; and 3) neural
331 adhesion molecule 1
332 (*NCAM1)*, a marker of
333 total innervation as well as

Subject #	taste test value	relative expression			Ave PLC + Tas1R3	ave sweet/ umami
		PLCb2	TAS1R3	NCAM1		
SWE 17	**53**	**1.00**	**1.00**	**1.00**	**1.00**	**8**
SWE 7	24	0.15	0.11	0.96	0.13	0
SWE 8	32	0.66	0.34	0.60	0.47	3
SWE 9	30	0.29	0.42	0.40	0.35	0.5
SWE 12	35	0.78	0.51	1.17	0.63	3
SWE 13	22	0.30	0.78	1.01	0.49	0.5
SWE 14	40	0.53	1.60	1.21	0.92	5.5
SWE 15	34	0.56	0.77	0.67	0.66	5
SWE 18	32	0.14	0.30	0.15	0.20	4
SWE 19	36	0.16	0.76	0.08	0.35	5.5
SWE 20	45	1.64	0.80	0.86	1.14	4.5
SWE 21	34	0.27	0.23	0.34	0.25	2.5
SWE 22	26	0.36	0.28	0.52	0.32	2.5
SWE 23	39	0.64	1.14	1.96	0.86	4
SWE 24	17	0.62	1.16	1.33	0.84	2.5
SWE 25	19	0.19	0.17	0.52	0.18	3
SWE 26	37	0.48	0.59	0.57	0.54	3
SWE 27	25	1.08	0.77	1.64	0.91	0
SWE 28	36	0.44	0.54	0.32	0.49	4.5
SWE 29	13	0.22	0.15	0.59	0.18	0

Table 2: Relative expression of taste-related mRNAs from qPCR of fungiform papillae. Subject SWE 17, who reported no taste disturbances, served as our comparator. Taste test values as shown in Table 1 are included for comparison. For each subject, the average of the scores for sweet and umami taste, tastes reliant on Tas1R3, are shown as well.

334 Type III TCs. All data were normalized against glyceraldehyde-3-phosphate hydrogenase
335 (*GAPDH)* mRNA, yielding Delta CT values which are expressed as a fold-change compared to
336 the values from subject SWE17 who described no taste dysfunction. These relative expression

values are given in Table 2 along with Taste Scores and computed average taste score for sweet and umami (Ave Sweet-Umami) – the Tas1R1-related taste qualities -- for comparison.

The expression levels for *PLCβ2* and *TAS1R3* mRNAs, both encoding components of the taste transduction cascade in Type II TCs, were highly correlated (r(18) = 0.64, p=0.002) as expected based on molecular features of Type II taste cells in mice. Expression of *NCAM* mRNA was not significantly correlated with either *PLCβ2* or *Tas1R3* mRNAs.

Comparing the qPCR data from all biopsy subjects to the taste scores from the same subjects shows a significant correlation of overall taste score to *PLCβ2* (r(18) = -0.51, p= 0.023) and substantial correlation with *TAS1R3* (r(18) =--0.43, p= 0.056; although not significant at p<0.05 level). This relationship is shown graphically in Fig. 1. Conversely, expression levels of *NCAM* mRNA showed no substantial correlation with taste test values (r(18) = 0.035, p>0.05)

Since both sweet and umami require the TAS1R3 receptor subunit as well as PLCß2, we compared the expression level of these mRNAs to the average of taste scores for sweet and umami for each subject. A

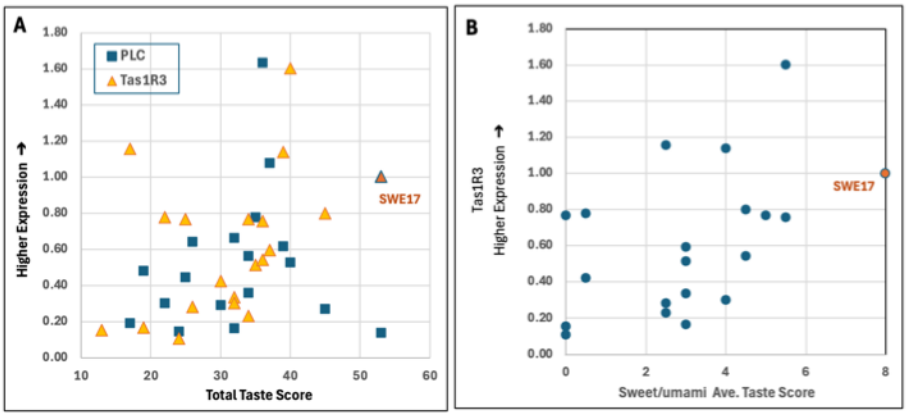

Figure 1: Correlation of relative *mRNA* expression levels with taste scores. The point indicated in orange is the data from Subject SWE17 who was used for comparison.
A) The mRNA levels for *PLCβ2* (r(18)=-.51, p= .023) and *TAS1R3*(r(18)=.43, p= .056) correlated with the overall taste score for each subject.
B) The mRNA level for *TAS1R3* correlates with the combined taste score for the related taste qualities (Sweet and brothy) (r(18)=.51, p= .02).

Alt Text: Graphs showing the correlation between Taste Score and PCR analysis of taste-related markers.

361 significant correlation exists between the average of the related taste scores for sweet and umami
362 with theDelta CT relative expression values for *TAS1R3* (r(18)= 0.45, p=0.046) and *PLCβ2*
363 (r(18)= 0.55, p=0.01). These expression levels were, however, not significantly correlated with
364 expression levels of the individual tastes: sweet or umami.
365
366 **Histological Findings**
367 Fungiform samples
368 from the subjects varied
369 between 4 and 8 papillae,
370 with a median of 7.
371 Approximately half of the
372 papillae had no
373 identifiable TBs, as
374 reported for human
375 fungiform papillae in
376 previous literature e.g.
377 (Miller 1988). Normal-
378 appearing taste buds were
379 identified in all subjects,
380 including subject 29, who
381 reported no taste
382 sensibility. While
383 relatively normal TBs
384 occur in samples of all

Subject #	taste score	# papillae	# TBs	ave tb/pap	plc/tb	plc/pap
SWE 7	24	7	42	6.0	2.4	14.3
SWE 8	32	8	42	5.3	2.0	10.5
SWE 9	30	8	10	1.3	2.0	2.5
SWE 12	35	6	30	5.0	2.1	10.3
SWE 13	22	4	6	1.5	1.8	2.7
SWE 14	41	5	61	12.2	2.9	35.4
SWE 15	34	6	13	2.2	2.6	5.7
SWE 17	53	8	25	3.1	2.7	8.5
SWE 18	32	7	7	1.0	1.8	1.8
SWE 19	36	6	8	1.3	2.0	2.7
SWE 20	45	7	41	5.9	2.0	11.7
SWE 21	34	7	28	4.0	3.3	13.2
SWE 22	26	8	32	4.0	1.8	7.2
SWE 23	39	7	17	2.4	2.3	5.6
SWE 24	17	6	22	3.7	2.0	7.3
SWE 25	19	6	2	0.3	1.5	0.5
SWE 26	37	5	22	4.4	2.4	10.6
SWE 27	25	7	32	4.6	2.8	12.8
SWE 28	26	8	17	2.1	2.5	5.3
SWE 29	13	7	27	3.9	1.9	7.3

Table 3: Counts of papillae sampled, number of taste buds and average *PLCβ2+* cells per taste bud and papilla in each case. No significant correlation was found between taste score and average number of taste buds per papilla nor of density of *PLCβ2+* cells per taste bud or papilla. The histological counts and density of *PLCβ2+* cells also did not correlate with any PCR values. # TBs, number of taste buds; ave tb/pap, average number of TBs per papilla; PLC/tb, average number of PLC+ cells per taste bud; PLC/pap, average number of PLC cells per papilla.

385 subjects (See Fig. 2), many subjects displayed disorganized TBs or unusual isolated PLCß2+
386 cells which were never observed in TBs from normal subjects (High and Finger 2025)
387 The average number of TB profiles per papilla was 3.6 (+/-2.6 s.d.). Because of the
388 significant variance in the number of TB profiles observed in a single section through a papilla,
389 we calculated the average number of TB profiles per papilla from all papillae to measure the taste
390 bud population for each subject. In addition, we counted the number of PLCß2+ taste cells
391 within each section to calculate the average proportion of PLCß2+ cells per TB. The taste score
392 for each subject was not correlated significantly with the average number of TB profiles per
393 papillae ($r(18) = 0.268$, $p = 0.25$), with the average number of PLCß2+ cells per papilla ($r(18)$ -
394 0.35, $p= 0.15$), nor with the average number of PLCß2+ cells per TB ($r(18) = 0.427$, $p = .06$). As
395 shown in Fig. 3, abnormal TBs or irregular PLCß2+ cells were especially noteworthy in 7 of our
396 19 post-covid biopsy subjects (SWE12 (Taste Score 54%), 13(21%), 22 (21%), 24 (8 %), 25
397 (4%), 28 (44%) and 29 (1%)). This incidence is significantly different (Fisher's exact test p
398 <0.03) than in tissues obtained from normal subjects where dispersed PLCß2+ cells were never
399 observed in fungiform taste buds from 12 subjects.
400
401

402

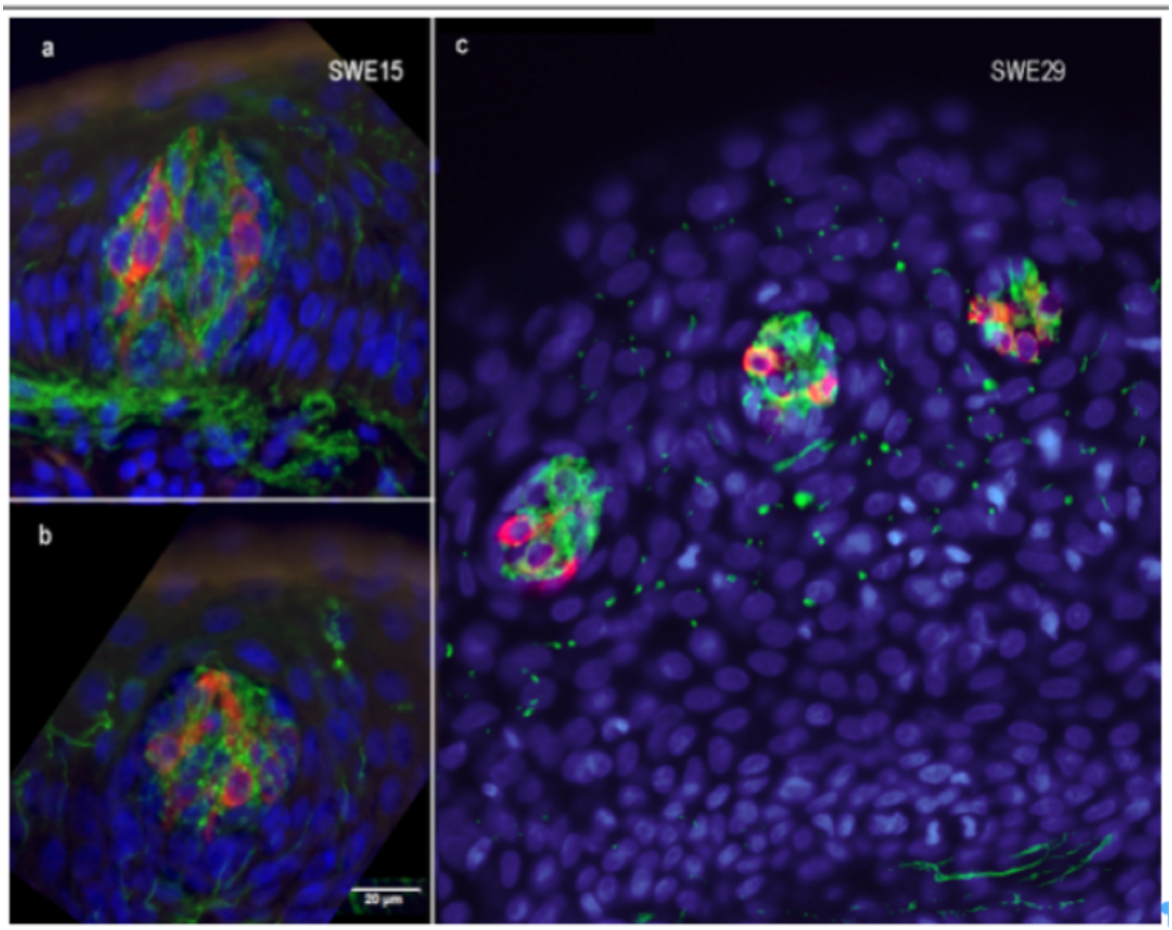

Figure 2: Appearance of normal taste buds sectioned in different planes from different subjects. Red = PLCß2 immunoreactivity showing Type II taste cells; Green = TUJ1 immunoreactivity for nerve fibers. Typical taste buds have more than one PLCß2+ cell surrounded by a dense network of TUJ1-stained nerve fibers. Green profiles outside of taste buds are extragemmal nerve fibers typical of lingual epithelium (Moayedi *et al.* 2021). **a, b.** Taste buds sectioned longitudinally appear similar in shape to garlic bulbs or onions (from Subject (SWE) 15. **c)** Taste buds sectioned perpendicular to their long axis appear circular (from subject (SWE) 29 who reported a total absence of taste perception (taste score of 13, showing no correct responses to any tastant).
Scale bar in panel (b) applies to all panels.

Alt Text: Images of 3 micrographs showing the normal appearance of taste buds in our samples. Multiple PLCß2-positive taste cells within each bud are embraced by a dense nerve plexus.

403

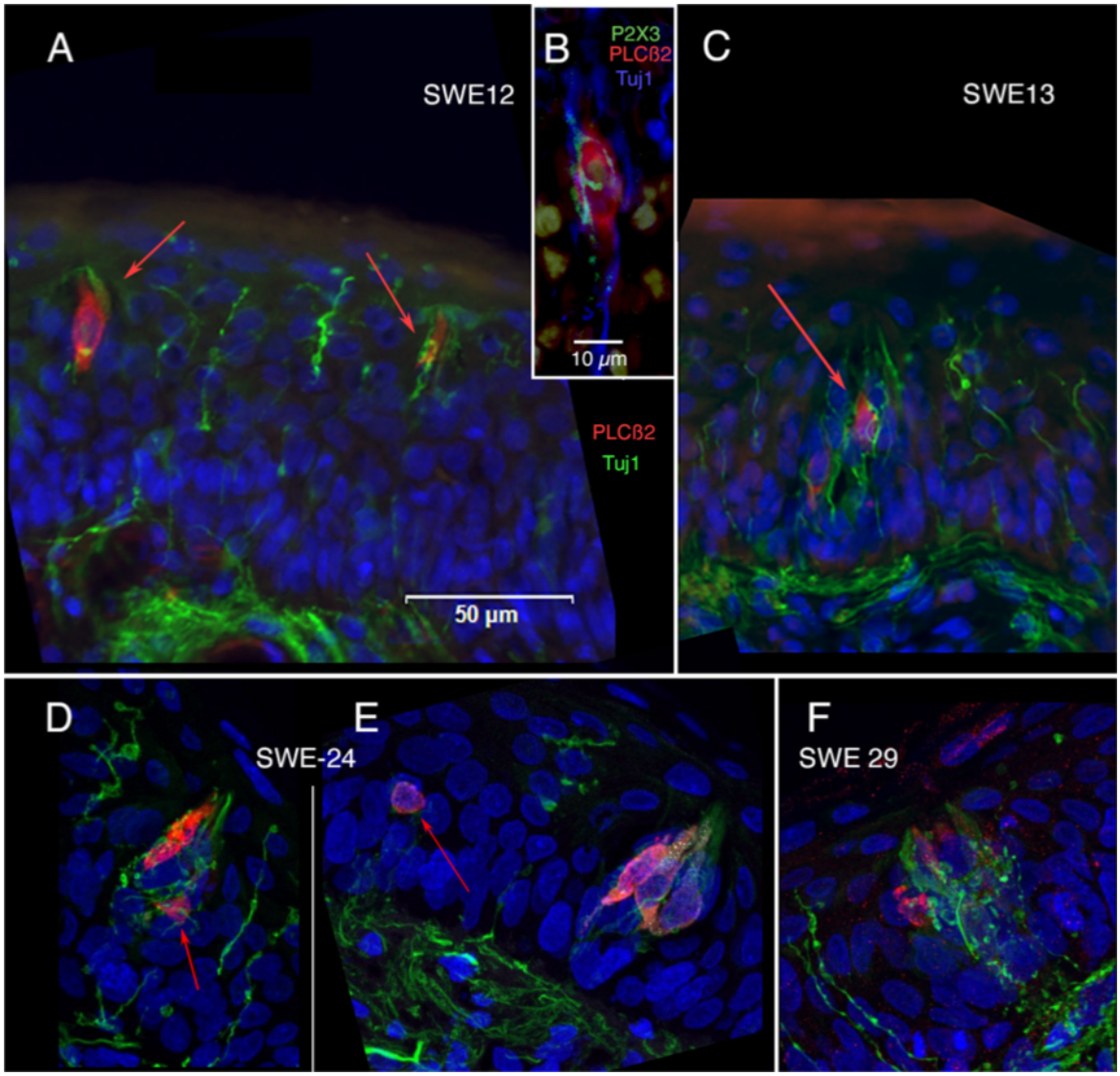

Figure 3: Examples of abnormal PLCß2+ taste-like cells from 4 cases. (A & B). Subject (SWE) 12 had a taste score of 35 (54%). (C) From subject (SWE) 13 who had a score of 22 (21%). In both cases (A & C), innervated PLCß2+ (red arrows) cells occur in relative isolation within the epithelium. Innervation of these cells (green: TUJ1) is sparse unlike innervation of taste buds (cf Fig. 2). These cells may represent very small taste buds or simply PLCß2+ cells lying outside of a taste bud structure. Panel B shows a higher magnification of one such isolated PLCß2+ cell and its innervation stained for the presence of P2X3, a neural receptor predominantly on nerve fibers that innervate taste buds. Panels D-E are from case (SWE) 24 with a taste score of 17 (4%) showing examples of aberrant PLCß2+ cells (red arrows) outside of a taste bud structure. Panel F: A disorganized taste bud from case SWE 29 who reported a total absence of taste perception (taste score of 13, showing no correct responses to any tastant). The heavy innervation is typical of taste buds, but the cellular structure revealed by PLC-staining (red) does not show typical taste bud organization.

Alt Text: Images showing abnormal isolated PLC-positive cells and abnormal taste buds within the epithelium of our subjects.

404 **DISCUSSION**

405

406 **Morbidity Changes in COVID-19 caused by SARS-CoV-2 Variants**

407 Previous studies found that the frequency of chemosensory symptoms, including taste loss,
408 varies across COVID-19 illness caused by infection of different SARS-CoV-2 variants. Early
409 variants, such as Wild type and Alpha, were more commonly associated with taste and smell loss,
410 while later emerging variants, such as Omicron, caused lower levels of taste loss (Reiter *et al.*
411 2023). Most subjects included in our study were primarily infected during the first wave of the
412 COVID-19 pandemic, and their reported taste disturbances fit well with this pattern of greater
413 taste loss early in the pandemic.

414 Published epidemiological data further illustrate this trend. Among individuals infected with
415 the Wild-type strain, 241 out of 1,141 cases (21%) reported smell and/or taste disorders. For the
416 Alpha variant, 223 out of 1265 cases (18%), for later variants such as Delta, 480 out of 1516
417 cases (32%), and for Omicron, only 317 out of 7431 cases (4%) presented with smell and/or taste
418 disorders (Ota *et al.* 2025). This supports the hypothesis that the variant-dependent tropism and
419 immune response may influence the degree and duration of taste dysfunction.

420

421 **On the role of the ACE2 receptor**

422 Relatively early in the COVID-19 pandemic, it was suggested that SARS-CoV-2 infects oral
423 tissue (Huang *et al.* 2021b). Doyle et al. (Doyle *et al.* 2021) reported that ACE2 was expressed by
424 Type II TRCs, and further demonstrated the presence of SARS-CoV-2 in Type II TRCs, which
425 mediate sweet, umami and bitter sensations, but not within the other taste cell types. This likely

426 explains why subjects in that study did not taste the “sweetness of chocolate and bitter coffee”
427 and instead reported that it “tasted like mud” .

428 Research during the COVID-19 pandemic has highlighted the potential impact of SARS-
429 CoV-2 on TBs, particularly through its interaction with ACE2 receptors (Huang *et al.* 2021a; Yao
430 *et al.* 2023). In patients experiencing taste disturbances following COVID-19 infection, SARS-
431 CoV-2 was detected in basal and suprabasal layers of fungiform papillae for extended periods. In
432 one subject, virus was detected up to 63 weeks after the initial diagnosis, coincident with
433 disrupted nerve fibers and altered taste bud cytoarchitecture (Yao *et al.* 2023).

434 Recovery of taste, and re-establishment of normal epithelial cytoarchitecture, coincided with
435 the disappearance of the virus from the taste epithelium (Yao *et al.* 2023). These findings suggest
436 that prolonged viral presence or the possibility of reinfection and the associated immune response
437 may impair the renewal and functionality of taste buds in Long COVID. In our subjects, a
438 sensitive commercial qPCR test showed that none of the tissue samples were positive for the
439 SARS-CoV-2 viral RNA suggesting that taste dysfunction may persist even after the virus is no
440 longer detectable in the peripheral taste system. This offers the potential that persistent taste
441 dysfunction in Long Covid may outlast the presence of the virus itself.

442

443 **Why loss of sweet-bitter-umami tasting ability is more frequent than the loss of other taste**
444 **qualities**

445 A previous WETT study involving 340 long-term (1-year) COVID-19 subjects and 434 non-
446 COVID controls (Sharetts *et al.* 2024) found no statistically significant differences in overall
447 taste function between groups. Similarly, a psychophysical taste-strip study (Boscolo-Rizzo *et al.*
448 2023a) of 62 post-Covid subjects who reported an altered sense of taste or smell one year after

449 infection, found no statistically significant evidence for ongoing taste loss by two years after
450 infection, although subjects still scored modestly lower than the normal population. Similarly, our
451 subjects show non-significant, slightly lower than average total taste scores (46.5%±25.1 s.d.)
452 compared to a normal population. It should be noted that our study specifically targeted subjects
453 reporting ongoing taste loss, not general chemosensory disruption, two years after COVID-19
454 infection, preventing direct comparison of our results with those surveyed from the broader
455 population surveyed in Sharetts et al. (2024) or when patients with shorter-term chemosensory
456 loss were tested (Boscolo-Rizzo *et al.* 2023b).

457 Despite the lack of measurable overall taste loss in our subjects, our psychophysical results do
458 indicate a significant disruption of taste with a tendency toward preferential impact on sweet,
459 bitter, and umami -- the PLCβ2-related taste qualities (Zhang *et al.* 2003). These taste modalities
460 all are detected by the Type II taste cells which are targeted by SARS-CoV-2 virus (Doyle *et al.*
461 2021).

462 Taste dysfunction may result from disruption of taste-related intracellular transduction cascades
463 or damage to taste buds (TBs), their receptor cells (TRCs) or the gustatory nerves. (Liman 2020;
464 Liman and Kinnamon 2021; Zhang et al. 2003; Zhao et al. 2003). The fact that the SARS-CoV-2
465 can directly infect Type II TRCs may explain why deficits in sweet, umami and bitter are more
466 frequent than for sour and salt. In our study, however, viral RNA was not detectable in taste
467 tissues and there was no evidence of wholesale destruction or abnormality in Type II, PLCβ2+,
468 taste cells. Nonetheless, in our subjects overall tasting ability correlates positively with the
469 amount of PLCβ2 and TAS1R3 mRNAs present in the tissue. Curiously, a previous study
470 (Donadoni et al. 2023) of the consequence of SARS-CoV-2 infection of taste cells in an in vitro
471 culture system showed increases in PLCβ2 expression with infection. It is unclear how the acute

472 in vitro model may relate to the long-term post-covid conditions reflected in our study.
473 Hypothetically, the long-lasting effect could be the result of an epigenetic mechanism called
474 inflammatory memory (Naik et al. 2017). This is described in several inflammatory diseases and
475 the effect is manifested as a sustained modification of the chromatin structure. This leaves open
476 the question how prior viral infection might induce long-lasting deficits in taste.

477 In the olfactory epithelium, the virus infects supporting cells, but not the olfactory receptor
478 cells (Chen *et al.* 2020). Nonetheless, the olfactory receptor cells responded to the viral infection
479 of the tissue by downregulating expression of olfactory receptors and downstream signaling
480 molecules while upregulating expression of viral response proteins (Chen *et al.* 2019; Zazhytska
481 *et al.* 2022). The transduction cascade is re-established in the receptor cells once the viral
482 infection has been cleared (Zazhytska *et al.* 2022). While a similar phenomenon may occur in
483 taste buds during viral infection, it is unlikely such a reaction would persist in the tissue after the
484 virus is cleared and all the taste cells have been replaced during the course of normal taste cell
485 turnover which requires a few months at most (Perea-Martinez *et al.* 2013). At the time of our
486 testing, up to two years after initial infection, none of the taste cells present at that time would
487 have been present at the time of viral infection.

488 Furthermore, we do note that some subjects are unable to detect non PLCβ2-dependent taste
489 qualities, i.e. sour and salty. This finding may reflect inabilities typical of a normal population but
490 might suggest that non-PLCβ2 related mechanisms may also be at work underlying taste
491 dysfunction in Long COVID. One possibility is that the infection alters the function in taste
492 nerves. Indeed, evidence exists for widespread neural dysfunction in Long COVID (Daia *et al.*
493 2021; McFarland *et al.* 2021; O'Neill *et al.* 2023; Otte *et al.* 2022; Rogn *et al.* 2024; Stepien and
494 Pastuszak 2023). If so, then some of the observed taste loss might be attributable to loss of

495 transmission in the taste nerves rather than disruption of the taste epithelium. This could explain
496 the total loss of taste perception in subject SWE29 despite the presence of normal-appearing taste
497 buds.
498
499 **Other factors that may have influenced taste during the disease process of COVID 19**
500 Recent studies (Finlay *et al.* 2022; Peluso *et al.* 2024a; Peluso *et al.* 2023) broaden the
501 perspective by suggesting that immune dysregulation and T cell dysfunction may play significant
502 roles in the long-lasting effects of COVID-19. Whole-body positron emission tomography
503 imaging with [^{18}F]F-AraG, a tracer that selectively tags activated T cells, showed that subjects
504 with Long COVID had specific tissues enriched for activated T cells compared to individuals
505 without this condition (Peluso *et al.* 2024b). All five subjects in that study showed the presence
506 of intracellular SARS-CoV-2 spike protein-encoding RNA in lamina propria tissue up to 676
507 days after initial infection with SARS-CoV-2. This offers evidence of viral persistance or of
508 multiple independent SARS-CoV-2 infections which could underlie long-term immunologic
509 perturbations for up to two years after an initial infection. Whether a similar prolonged
510 immunological response occurs in taste tissue is unknown although Yao et al (Yao *et al.* 2023)
511 report long term (>6 months) inflammatory response when virus remains in the tissue. We did
512 not, however, detect any virus by PCR in our tissue samples from patients more than one year
513 post infection. Other investigators reported an association of elevated serum concentrations of IL-
514 10 and IL-1β with persistent taste dysfunction for bitter and sweet qualities, respectively,
515 following Covid-19 (Karmous *et al.* 2023; Locatello *et al.* 2021).
516
517 **On the relation between histological changes of TB by COVID-19 and taste changes**

518 A particularly intriguing aspect of our study is that all subjects, including those with severe
519 deficits, displayed structurally intact taste buds despite the loss of taste function. However, some
520 dystrophic taste buds and isolated PLCß2-expressing cells were observed in many subjects. In
521 mice, disruption of molecular signals between nerves and taste buds can result in formation of
522 aberrant PLCß2-expressing cells outside of the taste buds themselves (Castillo *et al.* 2014). This
523 finding raises important questions about the disconnect between histological integrity and
524 functional impairment. One possible explanation is that taste bud dystrophy, rather than outright
525 loss of taste buds, may be sufficient to alter taste sensitivity by impairing cellular turnover or
526 disrupting synaptic communication with gustatory neurons (Wang *et al.* 2023). While intact taste
527 buds might suggest some functional resilience, the significant decrease in PLCß2-dependent
528 signaling suggests that molecular-level dysregulation may underlie the persistent taste
529 dysfunction. In addition, the discrepancy between PLCß2 expression and taste bud morphology,
530 especially in Subject 29 who shows complete taste loss, suggests dysfunction in peripheral nerves
531 or at higher levels of the neuraxis.
532
533 **Clinical relevance**
534 Understanding the mechanisms behind taste loss is clinically relevant, as chemosensory loss
535 negatively impacts nutritional intake, emotional well-being, and quality of life. For survival, taste
536 ability is more important than both hearing and vision. A multidisciplinary mindset is crucial for
537 appropriate diagnostics and for providing patients with appropriate treatment and underscore the
538 importance of developing targeted therapies to alleviate the burden of long-term taste dysfunction
539 in COVID-19 survivors.
540 Here we present an integrative approach combining psychophysical taste testing, RNA
541 expression analyses using markers for TRC type II and III, and histological evaluation of taste

542 tissue in subjects with Long COVID. This multidimensional analysis provides a more
543 comprehensive understanding of Long COVID taste dysfunction. While this study focuses on the
544 loss of Type II TRC, PLCß2-dependent taste qualities (sweet, umami, bitter), the loss of other
545 taste qualities in a limited number of subjects suggests that multiple mechanisms may underlie
546 the sensory loss.
547

548 **Limitations & Conclusions**

549 The study reported here is a retrospective clinical study of post-Covid patients and like other
550 case series studies has no control group although we offer a comparison to a pre-pandemic
551 dataset on gustatory phenotypes in healthy individuals (Doty *et al.* 2025). Another limitation is
552 that our study includes only a single time point measurement of taste function in a limited
553 number of subjects. This limits the statistical power of the study, but nonetheless we do find
554 highly significant correlated results even in our modest number of subjects. Furthermore, the
555 study relies on self-reported accounts of taste loss coinciding with COVID-19 onset, but baseline
556 taste function data before infection was not possible perhaps reducing the generalizability of the
557 findings.

558 Despite these apparent limitations, our study presents important new quantitative
559 psychophysical data showing significant disruption in detection of specific taste qualities in a
560 subset of subjects reporting long-term post Covid taste dysfunction. The taste qualities most
561 impacted are those detected by Type II taste cells which utilize a PLCβ2 dependent signaling
562 cascade for transduction of sweet, umami and bitter qualities. Importantly, our study also shows a
563 correlated decrease in mRNA levels for two elements of the Type II cell transduction cascade for
564 these qualities –- the first evidence for correlative changes in molecular parameters tracking
565 psychophysical taste functions. Finally, despite the well-documented recovery of post-Covid

566 taste function in most patients, our study offers quantitative evidence for prolonged disruption of

567 taste abilities in a small subset of post-Covid subjects.

568
569

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AUTHOR CONTRIBUTIONS

G. H. and T.E.F. conceived this research and along with G.L.and G.A. designed the research plan. G.H. & G.L. wrote the ethical proposal to Etikprövningsmyndigheten. H.M. provided subjects, performed the WETT tests and took the biopsies. M.A.K. provided subjects and with A.A. assisted in analysis of the subject population. T.E.F. and M.L. designed and performed the histopathology and data analysis. G.A. and T.V. designed and analyzed the quantitative PCR experiments. T.V. performed RNA extraction and quantitative PCR experiments. T.E.F. performed statistical analysis of the quantitative data and compared results to those in the Doty et al (2015) report. G.L., G.H., G.A., H.M., and T.E.F. provided funding for the project. G.H., T.E.F., G.A., and M.A.K. prepared the manuscript and all authors have discussed and revised the manuscript.

Use of AI:

This study utilized Microsoft Copilot (GPT-4) accessed through a secure university-managed Microsoft Teams environment. The tool was utilized in the process of editing and checking calculations but was not used to generate any original content. All outputs were reviewed by the lead author.

Competing interests

The authors declare no competing financial interests.

Data Availability Statement: The data underlying this article will be shared on reasonable request to the corresponding authors.

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836 SUPPLEMENTARY FIGURE
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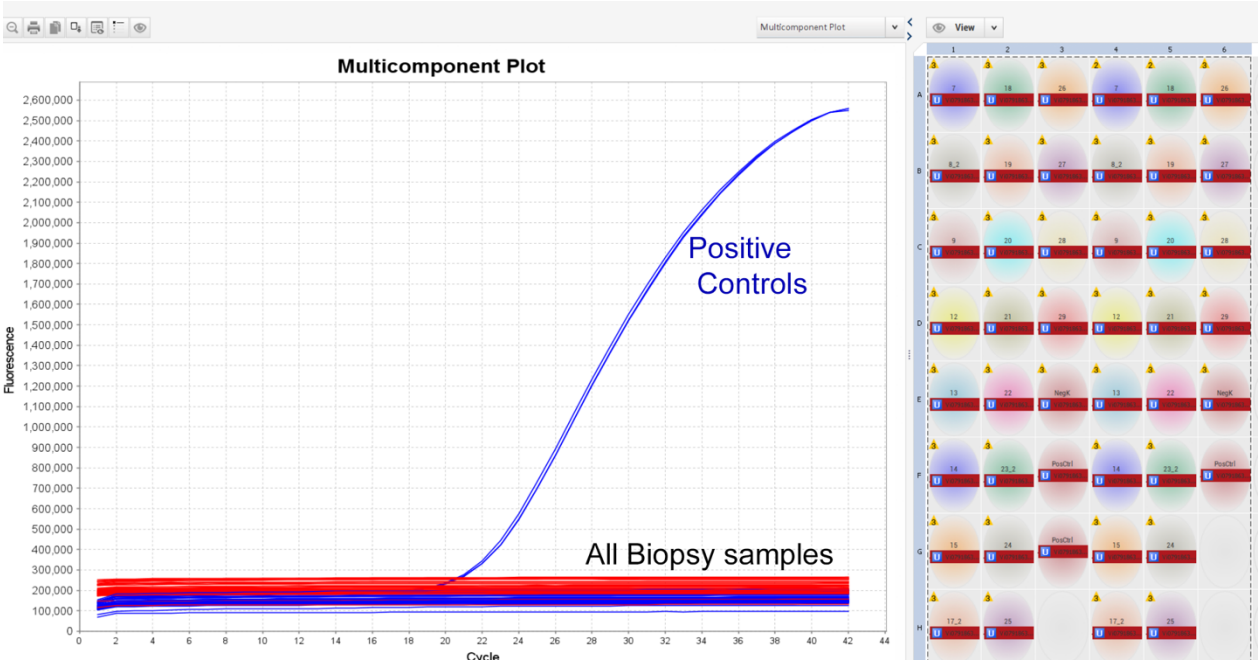

839 Supplementary Figure 1: qPCR for Covid mRNA showing positive controls. No samples from
840 any subjects show evidence of reaction for Sars-CoV2 virus.
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Supplementary Table 1: WETT taste test values shown as a percentile values as normalized to the data in Doty et al 2025.

Subject Number	Sweet	PLC Tastes Umami	Bitter	Sour	Salty
SWE 17	99	99	99	99	99
SWE 1	49	55	8	62	58
SWE 2	28	10	13	99	99
SWE 3	74	11	36	84	43
SWE 4	2	99	68	62	75
SWE 5	99	70	99	99	76
SWE 6	79	38	38	44	23
SWE 10	60	33	99	84	43
SWE 16	58	36	71	99	76
SWE 7	4	10	7	71	43
SWE 8	74	4	7	71	81
SWE 9	7	17	10	99	99
SWE 12	26	53	71	81	19
SWE 13	7	30	10	55	20
SWE 14	18	99	47	99	60
SWE 15	41	92	29	35	19
SWE 18	87	12	50	71	2
SWE 19	79	72	99	62	5
SWE 20	77	35	75	99	99
SWE 21	42	23	69	90	29
SWE 22	7	70	5	68	3
SWE 23	33	72	81	62	39
SWE 24	65	17	10	37	35
SWE 25	14	70	10	2	81
SWE 26	57	10	59	26	71
SWE 27	3	11	42	11	57
SWE 28	65	55	81	78	11
SWE 29	3	12	5	1	1
Values≤10%	**6**	**2**	**8**	**1**	**4**