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Taste loss as a distinct symptom of COVID-19: A systematic review and meta-analysis

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1 **Taste loss as a distinct symptom of COVID-19: A systematic review** 2 **and meta-analysis**

3
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13 **Abstract**

14 Chemosensory scientists have been skeptical that reports of COVID-19 taste loss are genuine, in
15 part because before COVID-19, taste loss was rare and often confused with smell loss.

16 Therefore, to establish the predicted prevalence rate of taste loss in COVID-19 patients, we
17 conducted a systematic review and meta-analysis of 376 papers published in 2020–2021, with
18 241 meeting all inclusion criteria. Additionally, we explored how methodological differences
19 (direct vs. self-report measures) may affect these estimates. We hypothesized that direct
20 prevalence measures of taste loss would be the most valid because they avoid the taste/smell
21 confusion of self-report. The meta-analysis showed that, among 138,897 COVID-19-positive
22 patients, 39.2% reported taste dysfunction (95% CI: 35.34–43.12%), and the prevalence
23 estimates were slightly but not significantly higher from studies using direct (n = 18) versus self-
24 report (n = 223) methodologies (Q = 0.57, df = 1, p = 0.45). Generally, males reported lower
25 rates of taste loss than did females and taste loss was highest in middle-aged groups. Thus, taste
26 loss is a bona fide symptom COVID-19, meriting further research into the most appropriate
27 direct methods to measure it and its underlying mechanisms.

28 **Key words:** gustatory dysfunction, taste loss, ageusia, COVID-19, coronavirus

29

30 **Introduction**

31 The novel coronavirus (COVID-19), a respiratory infection caused by severe acute
32 respiratory syndrome coronavirus-2 (SARS-CoV-2), was first identified in Wuhan, China, and
33 has since spread throughout the world. When the World Health Organization first declared this a
34 pandemic in March 2020, researchers and clinicians were not yet aware that the virus affected
35 individuals' senses of smell and taste, but these symptoms soon became apparent via patient
36 reports. As a result of COVID-19, affected people can experience chemosensory dysfunction in a
37 variety of ways, including complete loss of smell or taste (anosmia or ageusia, respectively),
38 partial loss of smell or taste (hyposmia or hypogeusia), and/or a distorted sense of smell or taste
39 (e.g., parosmia, dysgeusia). These chemosensory dysfunctions can be distressing to the affected
40 individuals and can last for extended times, with some patients experiencing resolution within a
41 few weeks to a month (Lee et al., 2020b; Gerkin et al., 2021) and others with symptoms for 6
42 months or longer (Blomberg et al., 2021).

43 Previous meta-analyses examined smell and taste loss in COVID-19 patients, but often
44 with a focus on onset and duration (Santos et al., 2021) or recovery (Boscutti et al., 2021) of
45 chemosensory symptoms. Many focused only on smell loss (Hannum et al., 2020; Pang et al.,
46 2020; Rocke et al., 2020) or general neurological symptoms (Abdullahi et al., 2020; Favas et al.,
47 2020; Mair et al., 2021; Yassin et al., 2021). Very few continued to evaluate articles published in
48 2021 and often capped reviewing articles 6-10 months after March 2020, when the pandemic
49 was declared, limiting the number of articles included (ranging from 5 to 59 articles total).
50 Therefore, we decided to conduct a more comprehensive analysis, spanning a year and a half, to
51 ensure a fuller coverage of the available research.

52 Additionally, taste loss is often neglected in research compared to smell loss, as there is a
53 common notion that taste loss is not as “real” as smell loss. Some claim taste loss is
54 indistinguishable from smell loss (Le Bon et al., 2021) or is confused with smell loss (Deems et
55 al., 1991), specifically with retronasal smell perception (Hintschich et al., 2020a). For the general
56 population, loss of taste can be difficult to distinguish from smell loss. Therefore, it may be
57 difficult to know, based on self-report measures alone, whether or not a participant truly lost
58 their sense of taste.

59 Thus, many chemosensory researchers may attribute the taste loss phenomena seen in the
60 current reports of COVID-19-positive patients to deficiencies of self-report or subjective
61 measures of taste loss. Therefore, we conducted a systematic review and meta-analysis to
62 estimate the true prevalence of taste loss in COVID-19 patients across a wide sample of studies
63 (n=241) and to evaluate effects of major methodological differences in data collection. In
64 particular, we compared overall findings on taste loss as determined by individual taste tests
65 (herein referred to as direct tests) with self-reports without direct sensory testing. We
66 hypothesized that direct methodologies would support the presence of taste loss as a distinct
67 symptom, and direct measures might even be higher than self-report despite the possible inflation
68 of self-reported taste loss which is exacerbated by smell loss.

69 Currently scientists are using both direct and self-report measures to examine
70 chemosensory dysfunction, with self-report far more common due to the pandemic restrictions,
71 e.g., sensory laboratories where direct testing is often conducted are closed. For taste, direct tests
72 include standardized and non-standardized tests that contain various sweet, salty, and sometimes
73 bitter and sour stimuli given to participants via solutions, drops, strips, or sprays (Cao et al.,
74 2021; Singer-Cornelius et al., 2021). Non-standardized direct taste measures created to study

75 COVID-19-related taste dysfunction include solution-based tests, often prepared at home by
76 participants (Vaira et al., 2020f). Self-report measures include interviews with researchers and
77 clinicians, electronic health records as well as surveys administered over the phone, online, or in
78 person.

79 To understand taste loss as a symptom of COVID-19, we conducted a large systematic
80 review and meta-analysis, examining how it has been measured (direct vs. self-report) and how
81 the measurement type can affect prevalence rates. We tested the hypothesis that direct measures
82 are at least as sensitive as self-report measures and would confirm taste loss as a distinct
83 symptom and not merely misattributed smell loss.

84 **Methods**

85 **Article Selection**

86 This systematic review and meta-analysis followed the Preferred Reporting Items for
87 Systematic Reviews and Meta-Analyses guidelines (Moher et al., 2009). Articles were selected
88 via searches on Pubmed/Medline and Google Scholar, using the keyword “COVID-19” with
89 “taste”, “smell”, and/or “olfaction”, as well as “gustatory”. Literature retrieval began on May 15,
90 2020, and concluded on June 1, 2021, resulting in 377 articles in total.

91 Initial screening of the articles included reading the titles and abstracts to assess their
92 relevance. Articles with an abstract that reported chemosensory dysfunction in COVID-19-
93 infected individuals were included in the systematic review ($n = 376$). Next, at least two authors
94 read the articles initially deemed relevant, to evaluate whether they fit the inclusion criteria:
95 reporting positive COVID-19 tests, written in the English language, and lack of population bias.
96 COVID-19 must have been confirmed via nasopharyngeal swab, reverse transcription
97 polymerase chain reaction (RT-PCR), or assessment by physician or other medical personnel.

98 The articles were then evaluated on whether they reported taste loss data specifically. In total,
99 135 articles were excluded based on such criteria as not evaluating taste loss, recruiting
100 participants with chemosensory dysfunction, not testing for COVID-19, and presenting
101 overlapping data (see Figure 1). In total, 241 articles were included in the final meta-analysis
102 (corresponding citations described in “Included Articles” section at the end of the paper).

103 **Data Extraction**

104 We extracted from each article either the number or percentage of patients with taste
105 dysfunction due to a SARS-CoV-2 infection. The prevalence of taste loss reported in each article
106 was calculated by dividing the reported number of participants with taste loss as a symptom by
107 the total number of COVID-19-positive participants. Additionally, measures of taste loss were
108 labeled as “self-report” or “direct” to identify the method used to evaluate participants. Self-
109 report measures included reported loss of taste via surveys, interviews, and electronic medical
110 health records. Most articles (n = 223) used self-report methods. Table 1 summarizes the studies
111 that used direct measures (n = 18), comprising actual taste tests administered either at home
112 (Adamczyk et al., 2020; Hintschich et al., 2020a; Petrocelli et al., 2020b; Cao et al., 2021;
113 Singer-Cornelius et al., 2021), at a testing facility (Altin et al., 2020; Bidkar et al., 2020a;
114 Mazzatenta et al., 2020; Ramteke et al., 2020; Vaira et al., 2020a; Le Bon et al., 2021; Niklassen
115 et al., 2021a; Salcan et al., 2021) or both in home and in a hospital environment (Vaira et al.,
116 2020b, 2020c, 2020d, 2020f). Vaira et al. [2020e] had an unknown testing location. Many of the
117 measures consisted of solution-based tests measuring four basic taste sensations: sweet, sour,
118 salty, and bitter.

119 Although some authors reported exclusively smell loss or taste loss, many reported on
120 both senses. Thus, it was necessary to include additional coding options for when authors
121 reported the symptoms in tandem (e.g., “loss of smell or taste”). Therefore, articles were labeled
122 as “taste only”, “smell and/or taste”, “smell and taste”, “smell or taste”, and “smell and/or taste;
123 taste only” (in the event both values were reported, the numbers were summed), depending on
124 how these symptoms were phrased in the article.

125 We also extracted demographic characteristics of each study, including the population
126 mean and/or median age, sex (expressed as percentage of males in the population), and country
127 of origin (for the geographic distribution of the study populations, see Supplementary Figure 1
128 (S1)).

129 Four authors performed the initial reading of full texts and the data extraction from the
130 studies (R.D.H., A.K.T., S.S.M., R.J.K.). Two authors confirmed this information and resolved
131 any inconsistencies (M.E.H., D.R.R.). Differences were resolved through a discussion and
132 renewed consensus on the proposed solution from all authors who read that specific article.

133 **Risk-of-Bias Assessment**

134 We used a risk-of-bias assessment from Hoy et al. (2012) to examine the articles selected
135 for the meta-analysis. The assessment contained nine questions, outlined in Supplementary
136 Materials (see Supplementary Table (S2)). Responses were scored as 1 (no) or 0 (yes), with
137 summary scores of low (0-3), moderate (4-6), and high (7-9). Two authors completed the risk-of-
138 bias assessment of each article using the checklist developed by Hoy et al. (2012), as described
139 and adapted by Tong et al. (2020) (S.S.M. and A.K.T.). One author resolved any discrepancies
140 (M.E.H.).

141 **Statistical Analysis**

142 The meta-analysis was conducted using the meta package in R (Schwarzer et al., 2019).
143 Generalized linear mixed models were used for the meta-analysis, as recommended for the
144 analysis of binary outcomes and proportions (Bakbergenuly and Kulinskaya, 2018; Schwarzer et
145 al., 2019). Heterogeneity (e.g., between study variance) was assessed using Cochran's Q , I^2 , and
146 tau squared (τ^2). We concluded there was evidence for heterogeneity when the p-value for
147 Cochran's Q was less than 0.05 and if the I^2 was greater than 50% (Higgins and Thompson,
148 2002). Tau squared (τ^2), a measure of between study variance, was estimated using the
149 maximum likelihood approach and has no associated test-statistic.

150 An overall pooled prevalence estimates were computed and reported for a random-effects
151 model with the parameters described for all 241 studies. While both fixed and random-effect
152 models were computed, excess the heterogeneity among our studies (see the Results section)
153 suggested that unmeasured effects contribute to variance in our data more than would be
154 expected from sampling error. The extreme diversity of taste loss as reported in individual
155 studies (0 to 93.4%) suggested that the random-effects model was more appropriate.

156 Subgroup analysis was performed for studied employing direct methods ($n = 18$) and
157 self-report methods ($n = 223$) to assess taste function in COVID-19-positive individuals.
158 Additionally, the average age of participants and their sex (percentage of male subjects in each
159 study) were included as covariates in univariate mixed-regression models. Subgroup analysis for
160 age was arbitrarily categorized into five groupings: adolescents (0-18 years old), young adults
161 (19-35 years old), middle-aged adults (36-50 years old), older adults (51-65 years old), and
162 elderly adults (65+ years old). Finally, studies that used direct tests were separated, and subgroup
163 analysis was performed for each type of collection methodology: solution based ($N=12$), strip
164 based ($N=5$), and other ($N=1$). For continuous variables (e.g., age), the transformed beta

165 coefficients are reported. The transformation for the generalized linear mixed models uses a logit
166 transformation for each proportion, so the models are interpreted as the $\log(\text{odds})$ or $\log(p/1 - p)$,
167 where p is equal to the prevalence for each study. Back-transformation into the prevalence
168 estimates were done for subgroup analysis (e.g., age).

169 All statistical analyses were performed using R 4.0.5 (R Core, 2021) and RStudio
170 1.4.1106 (RStudio Team, 2020). Visualization of the meta-analysis is displayed as an orchard
171 plot adapted from Nakagawa et al. (2020). The R scripts and compiled data used for this analysis
172 are available without restriction at GitHub (<https://github.com/vramirez4/COVID19-TasteLoss>).

173 **Results**

174 **Risk-of-Bias Assessment**

175 Each of the 241 articles included in this meta-analysis were reviewed for risk of bias.
176 Among these articles, none had a high risk of bias, 142 studies had a moderate risk, and 99
177 studies had a low risk (see Supplementary Table S2 for the full assessment).

178 **Prevalence of taste loss in COVID-19-positive patients**

179 Among the 241 studies, the sample sizes ranged from 11 to over 40,000 patients with
180 COVID-19. The number of cases of taste loss per study ranged from 0 to 4,668, with raw
181 prevalence estimates ranging from 0% to 93.4%. Collectively, the meta-analysis included
182 138,785 patients who tested positive for COVID-19. Of these, 32,918 patients had some form of
183 taste loss after infection with SARS-CoV-2. Heterogeneity among the prevalence estimates
184 across all studies ($n = 241$) yielded a significant Cochran's Q ($Q = 29388.75$, degrees of freedom
185 $[df] = 240$, $P < 0.001$), and an I^2 estimate of 99.2%, and τ^2 estimate of 1.5. The pooled estimate
186 for taste loss prevalence in COVID-19-positive patients following meta-analysis for the overall
187 cohort was 36.90% (95% CI: 33.27–40.69%).

188 **Effect of methodology (direct vs. self-report) on prevalence estimate**

189 We employed a subgroup analysis to determine the effect of direct versus self-report
190 approaches on taste loss prevalence (see Figure 2). Eighteen studies used direct methods to
191 assess taste loss, comprising 2,240 COVID-19 patients, with 1,092 reported cases of taste loss.
192 Per study, the prevalence of taste loss ranged from 0% to 84% among COVID-19-positive
193 patients. For studies using direct approaches, the pooled estimate of the prevalence for the
194 random-effect model was 42.0% (95% CI: 30.0-55.0%). Cochran's Q was significant (Q =
195 187.93, df = 17, P < 0.001), and an I² of 91.0% was obtained, confirming heterogeneity of the
196 data collected via direct measures. The τ^2 for the direct methodologies was 1.2.

197 A total of 223 studies used self-report methods (e.g., questionnaire, interview),
198 comprising 136,545 subjects, with 31,826 cases of taste loss. The reported prevalence of taste
199 loss ranged from 1% to 93% per study. The pooled estimate of the prevalence under the random-
200 effect models was 36.53% (95% CI: 32.8%-40.5%). Similar to the direct subgroup, Cochran's Q
201 was significant (Q = 29188.14, df = 222, P < 0.001), and the I² value was 99.2%, confirming that
202 the studies differed in prevalence across the self-report studies. The τ^2 for self-reported studies
203 was 1.5.

204 A test of heterogeneity between groups was employed using Cochran's Q, which
205 revealed that the differences between methodologies were not statistically significant (Q = 0.66,
206 df = 1, p = 0.4157) under the random-effects model. While our analysis showed that the
207 prevalence of taste loss was higher when measured directly than by self-report, there was no
208 significant effect of measurement method on the prevalence estimates of taste loss.

209 **Effect of age and sex on taste loss prevalence**

210 Additional analyses were undertaken to assess the effect of age and sex. Univariate mixed
211 models for each covariate revealed that both age and sex had significant effects on the
212 prevalence of taste loss. After categorizing each study by mean age group, we conducted the
213 meta-analysis for those 210 studies that reported the ages of the participants (see Table 2).
214 Among this subset of studied the pooled prevalence was 37.16% and demonstrated significant
215 heterogeneity with ($Q=33943.46$, $df = 209$, $p<0.001$), $I^2 = 98.9$, and $\tau^2 = 1.5$. The prevalence
216 estimates per age category ranged from 11% in studies with average ages younger than 18 years
217 to 44% in studies with average ages between 36 and 50 years. Heterogeneity in these studies was
218 high ($I^2 = 96.4-98.9\%$) both within groups ($Q = 14106.77$, $df = 205$, $p<0.0001$) and between
219 groups ($Q = 32.19$, $df = 4$, $p<0.0001$). The results demonstrated that both the youngest and oldest
220 age groups report the lowest prevalence of taste loss, while age groups between 18 and 65 years
221 had pooled estimates ranging from 32% to 44%, with the highest in the middle-age (36-50 years)
222 group. Similarly, it appeared that age accounted for some of the overall heterogeneity among
223 some groups as measured by reductions in τ^2 among studies who contained mostly adolescent
224 and elderly individuals.

225 The effects of sex were similarly examined. A univariate mixed model using percentage
226 of males in each study as a covariate found an effect of $\beta = -0.0296$ ($p < 0.001$) for each percent
227 increase. Overall, the higher the percentage of males in a study, the lower the prevalence of taste
228 loss.

229 **Effect of type of direct approach on taste loss prevalence**

230 When we compared the types of direct report test (e.g., solution-based test, taste strip-
231 based test), we found a significant difference in prevalence rates (see Table 3). We classified
232 studies into three categories: taste strip testing ($n=5$), taste solution testing ($n = 12$), and “other”

233 (n = 1) for methods that do not employ either solution or strips. Pooled prevalence for solution-
234 based tests was 54.25% (95% CI: 45.01-63.19%) and for taste strips was 24.63% (95% CI:
235 13.10-41.46%). There was reduced heterogeneity in the subgroups compared to the overall meta-
236 analysis: solution-based testing, $I^2 = 88.8\%$; and strip-based testing, $I^2 = 76.8\%$. Measurements
237 of τ^2 , were 0.3807 and 0.5991 for solution-based testing and strip-based testing respectively.
238 There was significant heterogeneity between our pooled estimates ($Q = 8.68$, $df = 2$, $p = 0.01$).
239 Together, our results demonstrate that studies using solution-based taste tests, on average, result
240 in higher prevalence of taste loss in COVID-19 patients than do studies using strips or other
241 methods.

242 **Discussion**

243 Despite the occurrence of true taste loss in a variety of diseases such as cancer (Nolden et
244 al., 2019), as well as in the general population (Rawal et al., 2016), taste loss has often been
245 confused with smell loss (Le Bon et al., 2021). However, the current coronavirus pandemic
246 suggests that in reality, taste loss is its own unique feature of the illness. The present meta-
247 analysis found an overall taste loss prevalence of 37 % among 138,897 COVID-19-positive
248 participants, which aligns with other meta-analyses of taste loss prevalence, ranging from 38%
249 (Agyeman et al., 2020) to 49% (Hajikhani et al., 2020). This high prevalence is not due to
250 confusion with smell loss because direct taste measures yield similar (or even slightly higher)
251 prevalence than self-report. Therefore self-reports of taste loss appear to be valid among people
252 with COVID-19 as they are among other groups (Jang et al., 2021).

253 The COVID-19 pandemic created an urgent need for direct taste measures suitable for the
254 pandemic research environment, e.g., home testing, and researchers were innovative, but each
255 developed their own method which makes it difficult to compare results (see Table 1). However,

256 despite the differences in methods, we can draw one general conclusion, which is that the form
257 of the tastants matters (taste solutions are better than taste strips) but this general conclusion
258 must be tentative given that the forms of delivery were not compared directly using the same
259 approach, e.g., thresholds or identification.

260 The present meta-analysis found that around 4 in every 10 COVID-19 patients experience
261 taste loss. We also found age and sex effects: females experienced higher rates of taste loss than
262 males, aligning with other meta-analyses reporting a similar effect (von Bartheld et al., 2020;
263 Amorim Dos Santos et al., 2021; Saniasiaya et al., 2021). Females may be more susceptible to
264 taste loss because they are in general are more sensitive than males and have more sensory
265 capacity to lose. Additionally, we found that COVID-19 associated taste loss peaks in middle age
266 aligning with the general consensus across other COVID-19 meta-analyses (Agyeman et al.,
267 2020; von Bartheld et al., 2020). Why the youngest and oldest groups report less taste loss than
268 do middle-age adults is not currently known.

269 Although COVID-19 has intensified awareness of taste loss and furthered chemosensory
270 research, scientists are still unsure of the biological mechanisms behind this symptom. The
271 amount of SARS-CoV-2 virus in saliva is positively related to loss of taste: the more virus, the
272 more taste loss (Huang et al., 2021; Taziki Balajelini et al., 2021), although this observation is
273 controversial (Jain et al., 2020). Taste cells may be attacked directly by the virus because studies
274 of expression patterns for ACE2, the receptor protein known to transport the SARS-CoV-2 virus
275 into cells, and for TMPRSS2, the protein essential for processing the SARS-CoV-2 spike protein,
276 showed both are expressed in the supporting cells of taste bud (Sakaguchi et al., 2020; Huang et
277 al., 2021), including taste receptor cells themselves, at least in one patient (Doyle et al., 2021).
278 There may also be direct effects on the brain that contribute to taste loss (Douaud et al., 2021).

279 **Limitations and Future Research**

280 In many of the included articles, clinicians and researchers collected self-reported taste
281 loss information in tandem with smell loss (e.g., participants responding yes to “Loss of taste and
282 smell” on a symptom screener), which can confound the results. Therefore, we explored any
283 differences in how taste loss was collected, reflecting how it was reported in the articles (e.g.,
284 “smell and taste” vs. “taste only”), and found no significant impact on the prevalence rate (see
285 Supplementary Materials S3). This result indicates that taste loss is a common and pervasive
286 symptom of COVID-19. Additionally, far more articles in this meta-analysis used self-report
287 tests (n = 223) than direct tests (n = 18). This disparity may have prevented us from capturing
288 significant differences between the two methods.

289 Nearly all of the articles included in this meta-analysis were nonspecific to different
290 tastes, instead summarizing scores across multiple stimuli (e.g., sweet and salty) and reporting
291 taste loss as a whole (though in one study participants self-reported taste-specific dysfunction:
292 salt taste loss, 29.3%; sweet taste, 25.9%; general taste, 34.5% [El Kady et al., 2021]). However,
293 specific taste sensitivities can be difficult to assess via self-report. Members of the general
294 population, untrained in chemosensory science, may have difficulties identifying whether or not
295 they truly lost a specific taste. Therefore, it is important to use direct measures to distinguish
296 dysfunctions of specific tastes.

297 There are clear opportunities for advancements of standardized direct taste tests to
298 measure taste loss. Of the 18 studies that used direct tests in general, only five used standardized
299 tests, representing just 2.06% of the 242 studies examined in this systematic review: Taste Strips
300 by Burghart Messtechnik (Hintschich et al., 2020a; Le Bon et al., 2021; Niklassen et al., 2021a;
301 Singer-Cornelius et al., 2021) and the Brief Self-Administered Waterless Empirical Taste Test

302 (SA-WETT) by Sonsonics International (Cao et al., 2021). Three other studies using direct tests
303 were examined during the systematic review but were excluded for not meeting the inclusion
304 criteria: reporting on a case study (Lee and Lee, 2020), recruiting patients with chemosensory
305 dysfunction (Le Bon et al., 2020), and not reporting the required taste loss prevalence data (Huart
306 et al., 2020). Among these three studies, Lee and Lee (2020) used a non-standardized direct test,
307 and Huart et al. (2020) and Le Bon et al. (2020) used the Taste Strips – although this represents a
308 missed opportunity to analyze more studies that used standardized tests, including these two
309 articles would have increased the rate of standardized test use among all 241 studies to just
310 2.89% (N=7).

311 As of September 2021, 220 million individuals have been infected with SARS-CoV- 2
312 virus, with large number of recovered individuals with persistent symptoms included taste loss. It
313 is well documented that disease-related or age-related or chemosensory loss have profound
314 effects on an individual’s quality of life. Unlike other disorders such as vision and hearing for
315 which preventative and screening guidelines exist (United States Preventive Services Taskforce),
316 they are not available for taste and smell disorders. The COVID-19 pandemic further highlighted
317 this existing gap, lack of standardized measures and clinical guidelines for screening, assessing,
318 and monitoring the taste system making it difficult for clinicians to track progression of disease.
319 Assessment of taste function in patients with and without confirmed COVID-19 needs to become
320 standard of practice for clinicians. This is particularly important for at least two reasons: 1)
321 having baseline measures help clinicians assess trends over time, and 2) given the
322 interrelatedness between the sense of smell and taste, objective measures of taste collected
323 during clinical assessments may help dissociate whether it is a smell or taste problem. For
324 patients who report changes in taste function during screening questionnaires, full testing with

325 standardized objective chemosensory tools should be performed. It is critical that clinicians are
326 aware that most patients with chemosensory dysfunction complain of taste alterations, therefore,
327 a closer inquiry of patient's reports regarding the specific taste quality (i.e., sweet, bitter, sour,
328 and salt, fat) affected is important to further distinguish between taste and perception of flavor.

329 **Conclusion**

330 The COVID-19 pandemic demanded an urgent response from scientists and clinicians,
331 who have been working to understand the novel virus and the symptoms it inflicts. Of the many
332 unique features of this virus, smell and taste dysfunctions are among the most prominent. Yet as
333 taste loss joined smell loss as a more prolific topic in scientific literature, many initially
334 speculated that taste loss rates were overestimated due to confusion between taste and smell in
335 self-reports. However, our meta-analysis found a prevalence rate for taste loss of 36.9% among
336 138,897 COVID-19-positive individuals (95% CI: 33.27–40.69%), supported by direct methods,
337 reflecting the validity of this distinct symptom. Dysfunction in the sense of taste was, and still is,
338 a difficult reality for millions of people affected by the virus and merits further research to fully
339 understand the mechanisms behind this phenomenon and how to properly assess and address it.
340 Among the population of 138,897 COVID-19-positive individuals included in this meta-analysis,
341 only 257 of them, across five separate studies, were assessed using standardized taste tests.
342 Future research should include the development of fast and accurate taste tests, studies that
343 measure taste and smell function separately to dissociate olfacto-gustatory interactions, as well
344 as the employment of standardized taste tests in clinical settings to examine taste dysfunction. In
345 addition, clinical trials are needed to elucidate frequency of screening and age at which to start
346 and stop screening for chemosensory disorders. Finally, more mechanistic studies to understand

347 taste and smell disorders associated with COVID-19 to aid in developing new therapeutic
348 options for patients with long-lasting impairment of their chemical senses.

349 **Included Articles**

350 In total, 241 were included in the present systematic review and meta-analysis (Gamper
351 et al., 2012; Liu et al., 2016; Adamczyk et al., 2020; Adedeji et al., 2020; Adorni et al., 2020;
352 Aggarwal et al., 2020; Al-Ani and Acharya, 2020; Altin et al., 2020; Andrews et al., 2020; Anna
353 et al., 2020; Asai et al., 2020; Bastiani et al., 2020; Beltran-Corbellini et al., 2020; Bergquist et
354 al., 2020; Biadsee et al., 2020; Bidkar et al., 2020b; Boscolo-Rizzo et al., 2020a, 2020b, 2020c,
355 2021; Boudjema et al., 2020; Brandao Neto et al., 2020; Bulgurcu et al., 2020; Calica Utku et al.,
356 2020; Carignan et al., 2020; Chary et al., 2020; Chen et al., 2020; Chiesa-Estomba et al., 2020;
357 Cho et al., 2020; Chung et al., 2020; Cocco et al., 2020; Dawson et al., 2020; Dell’Era et al.,
358 2020; De Maria et al., 2020; Durrani et al., 2020; Elimian et al., 2020; Farah Yusuf Mohamud et
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413

414 **Captions**

415 **Figure 1.** CONSORT flow diagram demonstrating the article selection process for this
416 systematic review and meta-analysis.

417

418 **Table 1.** Overview of the direct approaches to assess taste loss in participants.

419 **Figure 2.** Orchard plot following the guidelines outlined by Nakagawa et al. The point estimate
420 of the pooled prevalence (trunk) is represented by the bold blue or red dot. The confidence
421 interval of the pooled prevalence estimate (branch) is represented by the bold black line, and the
422 prediction interval (twig) is represented by the thin black line. Individual prevalence estimates
423 from each study are represented by the scattered colored points (slightly transparent circles,
424 called fruits). Each fruit is scaled by the precision of the point estimate of prevalence for each
425 study, or the inverse of the standard error.

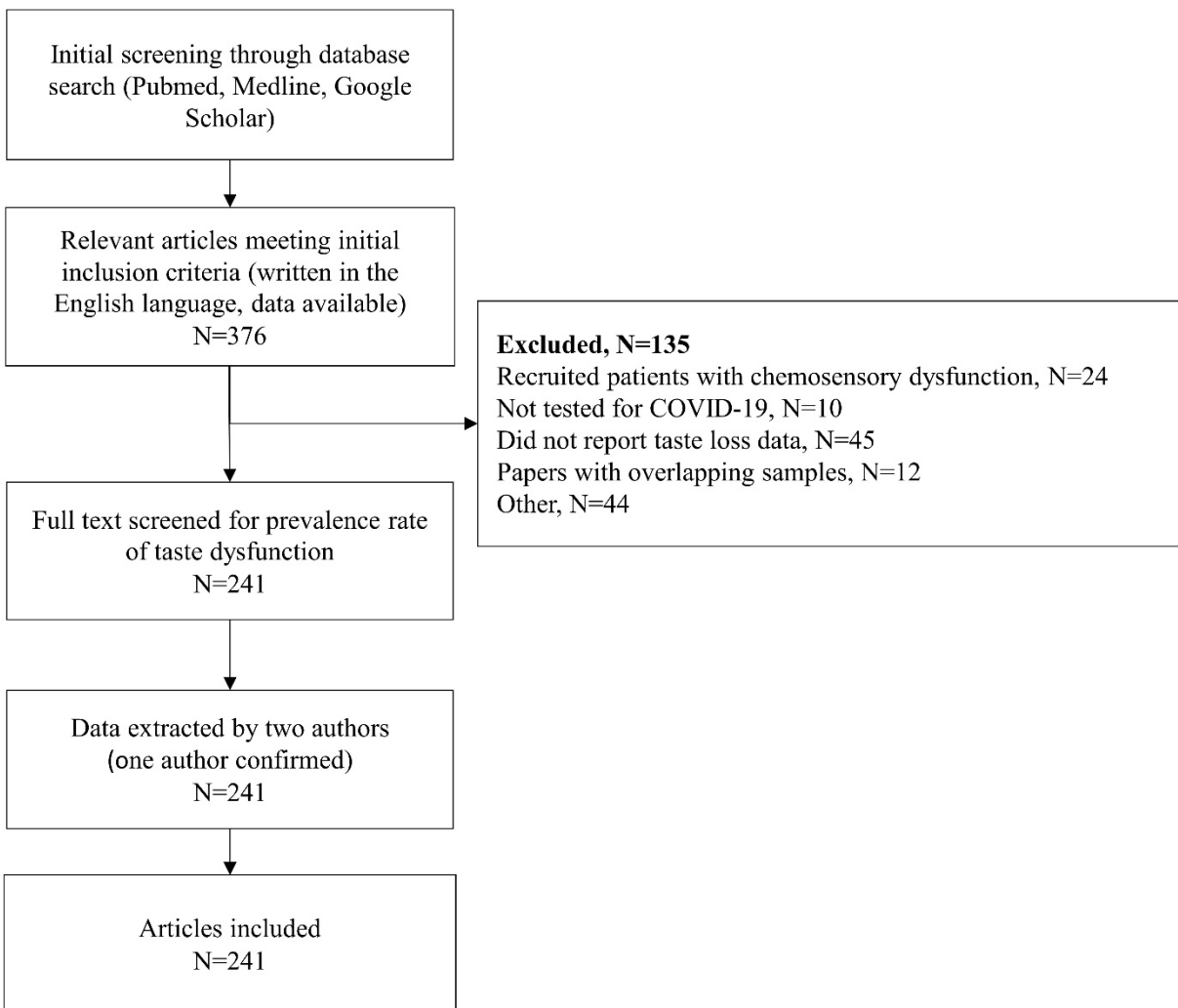
426

427 **Table 2.** Random-effect estimate of age group on COVID-19 taste loss prevalence using
428 generalized linear mixed models.

429

430 **Table 3.** Random-effect estimate of direct testing type on COVID-19 taste loss prevalence using
431 generalized linear mixed models.

432



433
434

435 **Figure 1.** CONSORT flow diagram demonstrating the article selection process for this
436 systematic review and meta-analysis.

437 **Table 1. Overview of the direct approaches to assess taste loss in participants.**

<i>Test</i>	<i>Article</i>	<i>Test Method</i>	<i>Test Objective</i>	<i>Taste Quality Measured</i>				
				<i>Salty</i>	<i>Sweet</i>	<i>Sour</i>	<i>Bitter</i>	<i>Umami</i>
Four-solution test	Vaira et al., 2020a–2020f Petrocelli et al., 2020 ^A	1 mL of each solution, plus deionized water as control, placed on the participant's tongue via cotton swab. Quarantined patients prepared their own solutions.	Identification	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Four-solution test & Taste Strips	Altin et al., 2020 Salcan et al., 2021	Participants swallowed and identified the solution. Next, paper strips dipped into each solution and placed on the participant's tongue.	Identification Duration	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Two-solution test (1)	Bidkar et al., 2020	Two drops (2 mL) of each solution placed on the participant's tongue via pipette.	Identification	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Two-solution test (2)	Mazzatenta et al., 2020	200 µl of each solution dropped onto participant's tongue.	Detection	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Taste Strips by BMG ^B	Hintschich et al., 2020 Singer-Cornelius et al., 2021 Le Bon et al., 2021 Niklassen et al., 2021 ^C	Taste strips (provided by Burghart Messtechnik GmbH) placed on the participant's tongue.	Identification and threshold concentration	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Taste sprays	Niklassen et al., 2021 ^C	Each solution sprayed onto participant's tongue.	Identification	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Tastant capsules	Adamczyk et al., 2020	Each of ten 0.33 mL gelatin capsules (one tasteless and nine with tastant) dissolved on participant's tongue.	Description	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Brief Self-Administered Waterless Empirical Taste Test (SA-WETT) ^B	Cao et al., 2021	27 disposable plastic strips that contain dried solutions of each taste (and some tasteless strips) self-placed on participant's tongue.	Identification	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
Chemosensory Test by India Protocol	Ramteke et al., 2020	Authors used coconut oil, chocolates, and flavored milk to test smell and taste function. No further details are provided.	N/A	N/A				

438 ^A These studies used a sweet solution concentration that is double what was used in the other four-solution tests.

439 ^B Validated test.

440 ^C Niklassen et al. (2021) used both Taste Strips and taste sprays with participants.

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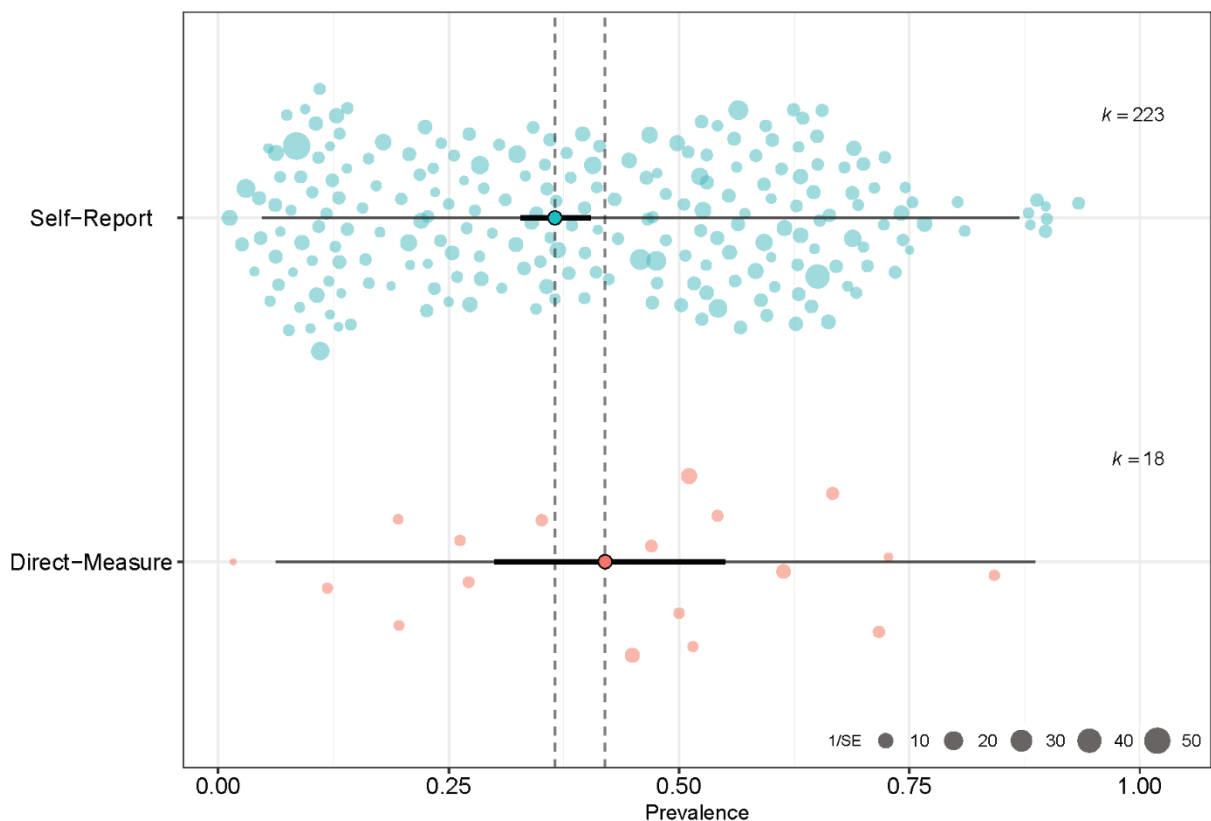
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448 **Figure 2.** Orchard plot of taste loss and COVID-19. The point estimate of the pooled prevalence
449 (trunk) is represented by the bold turquoise or pink dot. The confidence interval of the pooled
450 prevalence estimate (branch) is represented by the bold black line, and the prediction interval
451 (twig) is represented by the thin black line. Individual prevalence estimates from each study are
452 represented by the scattered colored points (slightly transparent circles). Each point is scaled by
453 the precision of the point estimate of prevalence for each study, i.e., inverse of the standard error.
454

455 **Table 2.** Random-effect estimate of age group on COVID-19 taste loss prevalence using
456 generalized linear mixed models.

457

<i>Age Category</i>	<i>k</i>	<i>Proportion</i>	<i>95%-CI</i>	<i>Q</i>	<i>I²</i>	<i>Tau²</i>
<i>Adolescent</i>	9	0.12	0.06-0.20	382.58	97.90%	0.828
<i>Young Adults</i>	20	0.32	0.1984-0.4640	1482.59	98.70%	1.961
<i>Middle Age</i>	118	0.44	0.3864-0.4954	10517.56	98.90%	1.4649
<i>Eldery</i>	8	0.18	0.0803-0.3570	193.64	96.40%	1.6031
<i>Older</i>	55	0.35	0.2882-0.4067	1522.64	96.50%	0.9307

458

459

460

461 **Table 3.** Random-effect estimate of direct testing type on COVID-19 taste loss prevalence using
462 generalized linear mixed models.

463

<i>Direct Testing Type</i>	<i>k</i>	<i>Proportion</i>	<i>95%-CI</i>	<i>Q</i>	<i>I²</i>	<i>Tau²</i>
<i>Solution</i>	11	0.5602	0.4666-0.6497	87.62	88.60%	0.3566
<i>Strip</i>	5	0.2183	0.1510-0.3048	14.45	72.30%	0.1663
<i>Other</i>	2	0.0539	0.0000-0.9868	0	0.00%	17.9895

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Initial screening through database search (Pubmed, Medline, Google Scholar)

Relevant articles meeting initial inclusion criteria (written in the English language, data available)
N=376

Full text screened for prevalence rate of taste dysfunction
N=241

Data extracted by two authors (one author confirmed)
N=241

Articles included
N=241

Excluded, N=135

Recruited patients with chemosensory dysfunction, N=24

Not tested for COVID-19, N=10

Did not report taste loss data, N=45

Papers with overlapping samples, N=12

Other, N=44

