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Less is More: COVID-19 Illness Severity Negatively Related to Smell and Taste Loss

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Abstract

Smell and taste loss as symptoms of COVID-19 have taken center stage in the study of the disease as more and more research confirmed its important role as a predictor of infection. This study builds upon the work of Yan, Faraji, Prajapati, Ostrander, & Deconde (2020b), who reported a connection between the severity of COVID-19 patients' clinical course, and the presence of anosmia and dysgeusia. The purpose was to investigate the relationship on a larger sample, discover how the two symptoms are connected to the others, and find out which symptoms tend to occur alongside with smell and taste loss. This knowledge may aid clinicians in accurately diagnosing COVID-19 and estimating a prognosis. The data used in this study was from Dutch responses to a questionnaire produced by the Global Consortium of Chemosensory Research (GCCR), which conducts an international study of changes in smell, taste, and chemesthesis in COVID-19 (https://gcchemosensr.org/). Results of analyses indicated a significantly higher reported smell loss in respondents with a mild clinical course. Nose blockage was found to have no influence on clinical course severity. Exploratory network analysis revealed thematic grouping in COVID-19 symptoms, and a disconnection of smell loss and taste loss from the rest of the symptoms. These results confirm the relationship between smell loss and illness severity outlined by Yan et al (2020b), but a proper investigation of the entire range of illness severity with robust clinical measurements is warranted to produce conclusions which might inform medical decision-making and diagnostics.

Introduction

The spread of the sudden acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes in those infected the coronavirus disease 2019 (COVID-19) was labelled a pandemic by the World Health Organization (WHO) on March 11, 2020 (Ghebreyesus, 2020). The virus has now spread to almost all countries of the world (as of April 7th, McCarthy, 2020), making it a global scientific effort to understand and deal with the disease. Understanding its etiology, function, and symptoms allows us to find effective solutions to managing COVID-19's spread, prevent unnecessary loss of life, and eventually beat the disease into remission.

COVID-19 Symptoms & Smell and Taste Loss

Until April 17th, the Centers for Disease Control and Prevention (CDC) listed the following symptoms for COVID-19: fever, cough, shortness of breath, chills, repeated shaking with chills, muscle pain, headache, sore throat (Symptoms of Coronavirus, 2020). First reports of the connection between COVID-19 and smell and taste loss appeared online about a month prior on March 20th, with Forbes and Insider reporting on anecdotal evidence from physicians (Stone, 2020; Burch, 2020), and a press release from ENT UK calling for people with anosmia and ageusia to self-isolate (ENT UK, 2020). Professional interest in these symptoms, also known as anosmia (loss of smell) and ageusia (loss of taste), grew rapidly, as the UK's Symptom Tracker team had discovered it to be more predictive of coronavirus infection than the disease's most common symptom, fever (COVID Symptom Tracker, 2020), and further research appeared, confirming their strong connection to COVID-19. On April 17th, the CDC added "new loss of taste and smell" to its list and cemented the symptoms' position.

A handful of studies have been published so far investigating smell and taste loss. Giacomelli et al. (2020) surveyed 59 COVID-19 patients in the L. Sacco Hospital in Milan, Italy, where 33.9% of respondents reported at least one taste or olfactory disorder and 18.6% both. A second study was performed in Italy with a focus on mildly symptomatic patients and took into account the onset of taste and smell disorder in relation to other symptoms. Altered smell or taste was reported by 64.4% of patients,

and while it more often appeared along with or after most symptoms, it also appeared before them in 11.9% of cases, highlighting the symptom's importance for preliminary screening and identification (Spinato et al., 2020). Lechien et al. (2020) completed a larger study in 12 European hospitals (specifically in Belgium, France, Spain, and Italy) with 417 COVID-19 patients, where the reported rate of smell and taste dysfunction was higher at 85.6% and 88% respectively. The study also found the two disorders to be significantly associated and confirmed a significantly greater frequency of the disorders in women. Another study performed in California surveyed 262 subjects, with 59 of them COVID-19-positive and 203 COVID-19-negative. In the infected sample, olfactory and gustatory impairment appeared in 68% and 71% respectively, while in the COVID-19-negative sample the impairment was only in 16% and 17% (Yan, Faraji, Prajapati, Boone & DeConde, 2020a).

A deeper look into the relation between COVID-19, smell and taste loss, and other associated factors (e.g., nasal obstruction) was performed by Parma et al. (2020), who tested a large multi-national sample ($N = 4,039$). The researchers had spread a questionnaire in 10 languages and 41 countries, which gathered quantitative, self-reported information on smell, taste, and chemesthesis (chemical stimulation in the mouth, such as feelings of burning, cold, tingling, or tickling) function during the respondents' COVID-19 infection and before. The study confirmed with extreme evidence (Bayesian analysis) that smell and taste loss were associated with COVID-19, and reported that smell and taste loss were statistically independent of nasal obstruction, meaning that the symptoms must have a different etiology. Because reported qualitative changes in smell (smell distortions and phantoms) were rare (unlike other instances of post-viral smell loss), it seems that COVID-19 mostly affects smell (and taste) function in a quantitative manner.

Illness Severity

Yan and his associates performed another study, which provided a new insight: patients who experienced anosmia or ageusia during their COVID-19 infection were ten times less likely to be hospitalized, meaning that the clinical course of their disease was milder (Yan, Faraji, Prajapati, Ostrander & Deconde, 2020b). The authors of the study speculate that a possible mechanism by which this occurs is one similar to

vaccination. The virus enters the body in a smaller dose, in a distal part of the body (i.e., distant to the lower airways, where it could lead to respiratory failure), where the host immune response is not overwhelmed and capable of dealing better with the infection. Changes in taste and smell are then signals of the virus being dealt with in a relatively safe part of the body, before it can reach more problematic areas (Yan, Faraji, Prajapati, Ostrander & Deconde, 2020b).

This proposition is rivaled by the fact that COVID-19 is neuroinvasive (Mao & Jin, 2020) and early research suggests that it affects support and stem cells in the nasal epithelium (Fitzgerald, 2020). Possible explanations are that it accesses the nervous system through the olfactory nerves in the nasal cavity (Li & Hashikawa, 2020), or not the nerves themselves, but through microvillous cells and stem cell population (Brann et al., 2020). A retrospective study found that 36.4% of analyzed patients suffering from COVID-19 had neurologic manifestations such as cerebrovascular disease, impaired consciousness, and skeletal muscle injury (Mao et al., 2020). Additionally, those patients that did show neurologic manifestations were among the more severe COVID-19 cases (Mao et al., 2020), placing this further into contrast with the findings of Yan et al.'s study (2020b).

When evaluating their own study, Yan et al. state that patients with milder cases of COVID-19 may experience more profound anosmia, but also have a greater tendency to report the condition than patients afflicted with a more severe course of the illness (2020b). Those suffering from a worse case of COVID-19 would experience lesser anosmia that would seem unimportant in contrast with the other, more pressing symptoms. The researchers conclude that "further objective olfactory testing of both outpatient and inpatient cohorts is required to clarify if quantitative differences in the severity of olfactory dysfunction correlate with differences in self-reported loss" (Yan et al., 2020b, p. 10).

Currently, it is difficult to classify symptom severity in COVID-19 patients based on existing findings about the disease. Past studies have independently classified symptom severity based on the information available in the given study, and the variables considered for symptom severity classification are not unified across studies (e.g.: Liu et al., 2020; Li et al, 2020). Furthermore, systematic reviews

investigating the differentiation of symptoms between various COVID-19 severities report statistically insignificant (Zhao et al., 2020) or inconclusive results, where findings are based on short observation periods, small sample sizes, and single geographic regions (Michelen, Jones, & Stavropoulou, 2020). Further testing of the role of smell and taste loss in COVID-19 and its association with other symptoms is warranted.

To conduct a larger study of smell and taste alterations due to COVID-19, the Global Consortium of Chemosensory Research (GCCR) unites hundreds of international chemosensory scientists, who have collaborated to develop a global multilingual survey. This master thesis makes use of the resulting dataset to test novel research questions.

Research Questions & Hypotheses

Does the appearance of smell and taste impairment in COVID-19 patients correlate with a milder clinical course of the disease? Which symptoms of COVID-19 are associated with changes in smell and taste?

In order to answer the first research question, the following hypotheses were drafted. The second research question is left without a hypothesis, due to its exploratory nature.

H1:   Respondents with a milder clinical course of their COVID-19 infection will experience greater smell loss than respondents with a more severe clinical course.

H2:   Respondents with a milder clinical course of their COVID-19 infection will experience greater taste loss than respondents with a more severe clinical course.

Method

Participants

The study uses a data sample of respondents to an online questionnaire by the GCCR on the relationship between respiratory illnesses (including COVID-19) and their effect on changes in smell and taste. Only responses in Dutch language were used. The inclusion and exclusion criteria of the study is that the respondent must have suffered from a respiratory illness in the past two weeks prior to questionnaire completion but should not have suffered from any other disease of the respiratory tract in the same past two weeks. Additionally, respondents must have filled out the optional question "Please describe the progression or order you noticed your symptoms", or "What treatment(s) or medication(s) have you received for your recent respiratory illness or diagnosis?".

The complete GCCR dataset contained a total of 41 759 responses, and the Dutch responses within this dataset accounted for 4 009 cases. Once the dataset was processed, the final count of respondents was 410. The respondents' age varied between 20 and 80, with a mean of 46.21 (SD = 13.15). The sample consisted of 333 men (81.22%), 75 women (18.29%), 1 person that chose "another not listed here", and 1 person that ticked "prefer not to say" (both 0.24%). Most respondents received their COVID-19 diagnosis after being tested by viral swab (53.41%), followed by respondent who were diagnosed based on symptoms only (40.24%), and a small portion was diagnosed using a different lab test (6.34%).

 After respondents were divided according to the severity of their clinical course (explained below), 272 (66.34%) of them were classified as mild, 94 (22.94%) had a moderate course of illness, and 44 (10.73%) had a severe course. In order to create better balanced samples, those identified with a moderate and severe course were combined into a single category, called moderate/severe, with a total of 138 cases. The new group amounted to 33.66% of the sample.

Questionnaire

The data sample was gathered using the GCCR questionnaire available on the consortium's website (https://gcchemosensr.org/). It surveyed people who have suffered from a respiratory illness (including COVID-19) in the two weeks prior to questionnaire completion. In order to obtain the dataset, the study had to be pre-registered with the GCCR (https://osf.io/yhcwt), so the questionnaire's results were not inspected prior to the completion of an analysis plan. Respondents provided demographic information, information about their respiratory illness, its symptoms, course, and treatment, and were then asked to report on their smell, taste, chemesthesis function (sensitivity to chemical irritations causing burning, cooling, or tingling sensations in the mouth), and nasal blockage before, during, and after the disease. Respondents also reported on their overall health and smoking habits.

Only certain questions from the questionnaire were used in this study. The demographic section was used in its entirety in order to describe the studied population. The following section, which asks general questions about the reported respiratory illness, was also needed for exclusion of respondents. Additionally, the question about respondents' experienced symptoms and the optional question mentioned above was used for one of the analyses. From the section about smell and taste, questions about ability to smell and taste before and during the illness were used, as well as questions about nasal blockage. No questions about chemesthesis were used, nor any questions from further sections.

The questionnaire was translated into a multitude of languages in each of the member countries, but the data sample used for this master thesis is only that of Dutch respondents to the GCCR questionnaire. The questionnaire for this language group was completed on April 21st, data collection began on the same day and is ongoing. Local members of the consortium distributed the questionnaire to respondents through social media (Twitter, Facebook), public relations offices of their universities, and public media.

Data Processing

The dataset was downloaded in its entirety from the GCCR database and processed in Microsoft Excel. The raw data was cleaned up for statistical analysis and the inclusion and exclusion criteria mentioned above were applied. First, all non-Dutch responses were deleted. Responses in demographic questions were unified (for ex. "NL" was changed to "Netherlands"), and cases which indicated no respiratory disease were removed from the dataset. Cases with any respiratory disease other than COVID-19, including cases that indicated both COVID-19 and another disease concurrently were also removed. Cases which indicated not having COVID-19 diagnosed were removed. Cases which had quit the questionnaire before answering the sections relevant for the analysis were also removed. In the section where respondents indicated how they had been diagnosed with COVID-19, the "other" responses were read through and the cases were removed when the comment indicated no COVID-19 infection or added to the corresponding category when appropriate. Cases which had incomplete or missing responses to the measures of smell and taste before and during the disease were removed, as well as cases which did not fill out either one of the optional questions: "Please describe the progression or order you noticed your symptoms" and "What treatment(s) or medication(s) have you received for your recent respiratory illness or diagnosis?". Finally, once data was plotted in using statistical software and inspected, outliers were removed.

Variables

The three variables in the first analysis were COVID-19 clinical course severity, level of smell loss as a symptom of COVID-19, and level of taste loss as a symptom of COVID-19. Clinical course severity was assessed using the questionnaire's open questions, "Please describe the progression or order you noticed your symptoms" and "What treatment(s) or medication(s) have you received for your recent respiratory illness or diagnosis?". The responses were originally planned to be read through and stratified based on ICU admittance into "mild" and "severe" categories. This information was not found in the responses, so new criteria were developed based on available data. Clinical course severity was assessed based on medication and

treatments indicated in the second question, using the following key. Respondents which answered that they used dietary supplements (i.e. vitamins, Supradyn Complex), home remedies (i.e. steam baths, ginger & curcuma tea), common nose spray (with xylometazoline or ipratropium bromide), or no medication were classified as "mild" cases. Respondents who reported using painkillers, inhalers, nose medicine, or stomach medication, including paracetamol, diclofenac, codeine, tramadol, acetylcystein, corticosteroids, noscapine, desloratadine, salmeterol, albuterol, ventolin, metoclopramide, and oral rehydration salts, were classified as "moderate". Finally, participants who indicated that they used antibiotics, such as doxycycline or amoxicillin, or reported being hospitalized were classified as "severe" cases. In a few cases (<5), when the treatment question provided insufficient information, or the symptom progression question was more telling, this first question was used to subjectively assess the severity and classify the respondent. Because the number of "moderate" and "severe" cases was relatively low compared to the number of "mild" cases, "moderate" and "severe" were combined into a single category called "non-mild". This provided more statistical power and allowed for a clearer interpretation of the results.

Changes in smell and taste perception were assessed through a set of questions from the questionnaire, which refer to participants' ability to smell and taste before and during the disease. Participants moved a slider on a visual analogue scale to the desired position, which generated a rating between 0-100, with 0 meaning "no sense of smell" or "no sense of taste", and 100 meaning "excellent sense of smell". The "before" score was subtracted from the "during" score to generate a continuous, individual-specific smell or taste loss variable.

The second analysis contained a total of 16 variables, which were the possible symptoms of COVID-19. Respondents indicated their symptoms using a question in the check-all-that-apply (CATA) format, yielding each symptom as a binary variable. The variables (symptoms) are the following: fever, dry cough, cough with mucus, difficulty breathing/shortness of breath, chest tightness, runny nose, sore throat, changes in food flavor, changes in smell, loss of appetite, headache, muscle aches, fatigue, diarrhea, abdominal pain, and nausea.

Analysis

Two analyses were performed as part of the study. The first part was a confirmatory case-control observational study which investigated the severity of the respondents' clinical course as a function of smell and taste loss. The second analysis was exploratory and investigated the relationships among the measured symptoms, with a focus on the position of the symptoms "changes in smell" and "changes in food flavor".

Shapiro-Wilk's test of normality and Fligner-Killeen's test of equality of variances was performed as assumption checks. The Fligner-Killeen test was chosen over Levene's test, because the Shapiro-Wilk test indicated a nonparametric distribution for both smell and taste. The Fligner-Killeen revealed unequal variance in smell loss scores, but not in taste loss. A Mann-Whitney test was therefore performed for taste loss scores, but since homoscedasticity is an assumption for Mann-Whitney's test, a Fligner-Pollicello test was performed for smell loss instead.

Additionally, nasal blockage was compared between the mild and non-mild groups in a logistic regression that included smell and taste loss scores, to check its relevance as a confounding variable within the model.

To check for the influence of unequal sample sizes on the results, a random selection was performed from the "mild" sample of an equal number of responses to that of the "moderate/severe" sample (138 cases). The Fligner-Killeen test was performed on the equal samples, as well as the Fligner-Pollicello test. This was performed in 20 iterations to outweigh the randomness of the selection and provide more robust findings. The results of the iterations can be found in appendix 1.

The exploratory analysis was performed by modelling the symptoms as a network using the IsingFit R package, as recommended by van Borkulo and associates (2014) for plotting binary values in a network. The resulting model was visually analyzed.

Statistical analysis was done using the JASP program for most operations (JASP Team, 2020). Operations which were not available in JASP, such as the Fligner-Killeen and Fligner-Pollicello tests, and the subsequent iterations with equal sample sizes, were performed using the R statistical package. The effect size for the Fligner-

Pollicello test was computed using the Psychometrica website (Lenhard & Lehnard, 2016).

Testing of Assumptions

Smell and taste loss scores were tested for violation of normality and inequality of variances. The Shapiro-Wilk test returned statistically significant results for all four measures (p = < .001), suggesting that the data does not follow a normal distribution. Since normality of samples was not found, Fligner-Killeen's test of equality of variances was performed over Levene's test. The test found a significant value for smell loss scores (med $\chi^2(1)$ = 12.52 ,p < .05), but not for taste loss (med $\chi^2(1)$ = 0.22, p = 0.64), suggesting that smell loss has unequal variances, while the variance of taste loss does not violate an assumption of homoscedasticity.

Table 1

Test of Normality (Shapiro-Wilk)

		W	p
Smell_loss_score	moderate/severe	0.76	< .001
	mild	0.67	< .001
taste_loss_score	moderate/severe	0.80	< .001
	mild	0.81	< .001

Note. Significant results suggest a deviation from normality.

Table 2

Test of Equality of Variances (Fligner-Killeen)

	Med Chi-squared	df	p
Smell_loss_score	12.52	1	0.00
taste_loss_score	0.21	1	0.64

Results

Hypothesis 1

Descriptive Statistics of Smell Loss Scores

A positive score on this variable means the subject's smell has improved during the illness, while a negative score means that it has deteriorated. For the entire dataset, the average smell loss score (*M* = -76.28, *SD = 32.81*) was less pronounced than the median (*Median* = -90.50), but still shows that on average, respondents suffered from a deep self-reported loss of smell due to COVID-19.

In the sample with a mild course of infection, respondents reported a high average smell loss (*M* = -79.41, *SD* = 30.58), with a median closer to a more profound loss of smell (*Median* = -92.25).

In the sample with a moderate/severe course of infection, respondents reported a high average smell loss (*M* = -70.11, *SD* = 36.14), with a median closer to a more profound loss of smell (*Median* = -83.30).

Table 3

Descriptive statistics of smell loss scores

|	Mean	Median	*SD*	Variance	Minimum	Maximum
Overall	-76.28	-90.50	32.81	1076.49	-100	30.20
Mild	-79.41	-92.25	30.58	935	-100	6
Moderate/severe	-70.11	-83.30	36.14	1306.46	-100	30.20

Test of Hypothesis

The hypothesis stated that respondents with a milder clinical course of their COVID-19 infection will experience greater smell loss than respondents with a more severe clinical course.

A Fligner–Policello test was performed to determine whether there is a statistically significant difference between the medians of smell loss scores in respondents with a mild and a moderate/severe course of COVID-19 infection. Results of the Fligner–Pollicello test indicated that there were significant differences in smell loss between people with a mild course of infection and people with a moderate/severe course of infection, ($U^* = 2.92$, $p = .003$). Smell loss score was significantly greater (had a lower negative score) for mild cases (*Median* = -92.25, *SD* = 30.58) than moderate/severe cases (*Median* = -83.30, *SD* = 36.14). Effect size was measured using the formula r = Z/√N (Rosenthal, 1994), which showed a small effect size ($r = -0.16$).

Figure 1

Mild vs moderate/severe illness course smell loss density plot
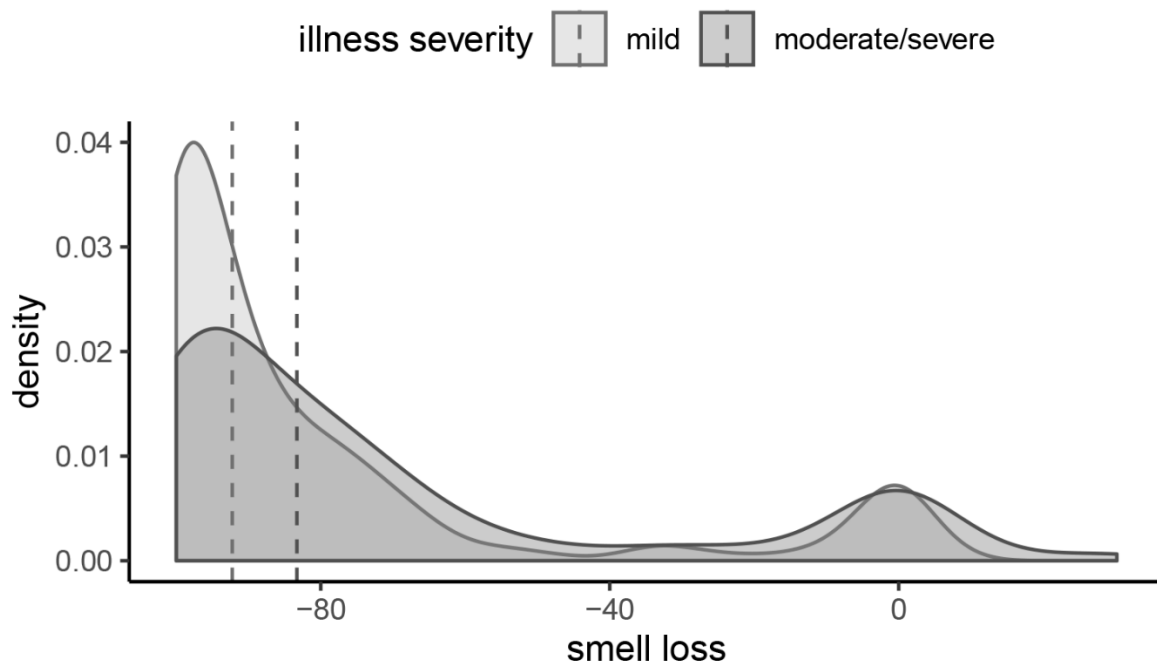
Note: dotted lines show medians of each group

Hypothesis 2

Descriptive Statistics of Taste Loss Scores

A positive score on this variable means the subject's taste has improved during the illness, while a negative score means that it has deteriorated. The central tendency of taste loss was similar to that of smell loss, with a pronounced mean taste loss score (M = -73.20, SD = 30.55). The median showed an even stronger loss of taste (*Median* = -84.70).

In the sample with a mild course of infection, respondents reported a high average smell loss (M = -73.92, SD = 30.05), with a median closer to a more profound loss of smell (*Median* = -82.50).

In the sample with a moderate/severe course of infection, respondents reported a high average smell loss (M = -71.77, SD = 31.57), with a median closer to a more profound loss of smell (*Median* = -84.15).

Table 4

Descriptive statistics of taste loss scores

|	Mean	Median	SD	Variance	Minimum	Maximum
Overall	-73.20	-84.70	30.55	933.16	-100	17.90
Mild	-73.92	-85.20	30.05	903	-100	17.90
Moderate/severe	-71.77	-84.15	31.57	996.54	-100	14.30

The hypothesis stated that respondents with a milder clinical course of their COVID-19 infection will experience greater taste loss than respondents with a more severe clinical course.

A Mann-Whitney U test was performed to determine whether there is a statistically significant difference between the medians of taste loss scores in respondents with a mild and a moderate/severe course of COVID-19 infection. Results of the Mann-Whitney U test indicated that there were no significant differences in taste loss in people with a mild course of infection and people with a severe course of infection, (U = 19902, p = .32). Effect size was measured using the rank-biserial correlation, which showed a small effect (rpb = 0.06).

Figure 2

Mild vs moderate/severe illness course taste loss density plot
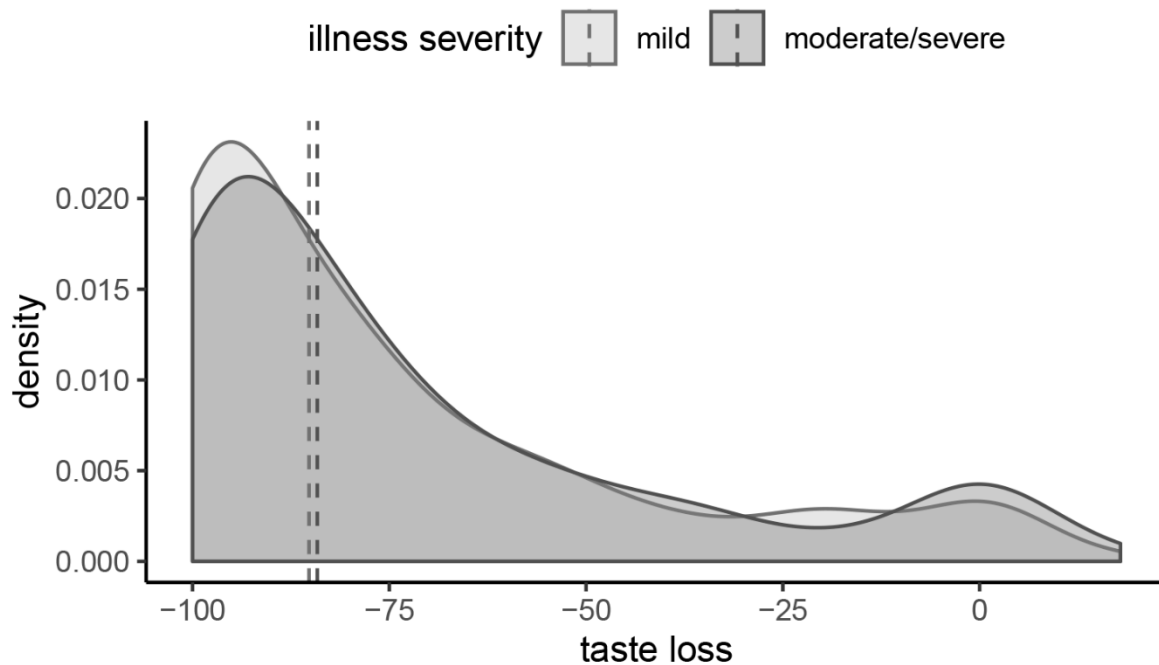
Note: dotted lines show medians of each group

Nose Blockage During Illness

   The mean nose blockage reported by the entire sample of participants was 31.13 (*SD* = 31.04), with a median of 20.55. The scores ranged across the entire scale between 0, which is a completely open nose, to 100, which is a completely blocked nose.

   The mean blockage reported by the sample with a mild course of illness was 30.16 (*SD* = 31.40), with a median of 18. The mean blockage reported by the sample with a moderate/severe course of illness was 33.04 (*SD* = 30.34), with a median of 25.05.

Table 5

Descriptive statistics of nose blockage during illness

	Mean	Median	*SD*	Variance	Minimum	Maximum
Overall	31.13	20.55	31.04	963.39	0	100
Mild	30.16	18	31.40	985.71	0	100
Moderate/severe	33.04	25.05	30.34	920.71	0	100

Nose blockage distribution plot
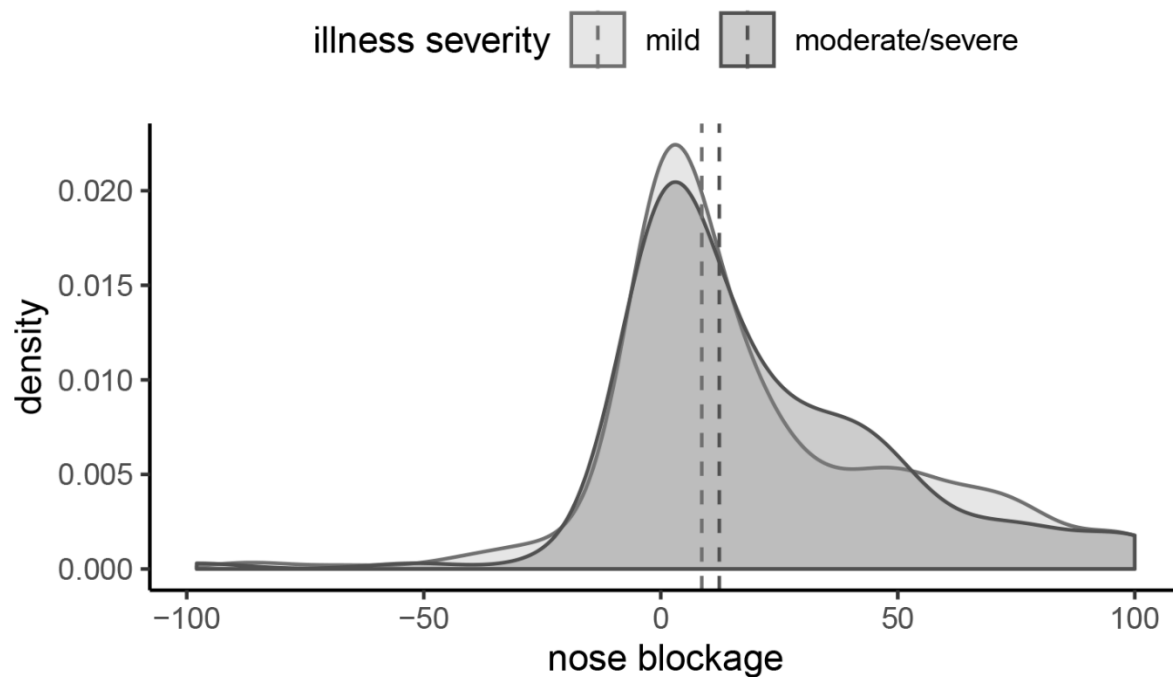
Test of Confounding Variable

A logistic regression was performed to investigate nose blockage during the illness as a confounding variable and check whether nose blockage could predict COVID-19 clinical course severity. The logistic regression model included smell loss and taste loss scores as covariates as well as nose blockage, and was statistically significant, $\chi2(407) = 52.40$, $p < .001$. Results of the binary logistic regression, however, indicated that there was no significant association between nose blockage and clinical course severity (*Wald* = 0.05, p = .83). The odds ratio of the coefficient was 1.00

Equal Sample Size Iterations

A random selection of 138 cases from the mild group was performed to check for the influence of an unequal sample size on the results of the previous tests. A Fligner-Killeen and Fligner-Pollicello test was done for smell loss and taste loss data, respectively. The procedure was repeated for 20 iterations (see Methods). The resulting data were found to provide similar results to the original sample sizes, with significant results of the Fligner-Killeen test in smell for all 20 iterations. The Fligner-Pollicello test was significant in 19 cases, and only 1 case had a *p*-value above .05 (case #16, *p* = .069). For taste loss data, both the Fligner-Killeen test and the Fligner-Pollicello test did not provide significant results for any of the iterations (appendix).
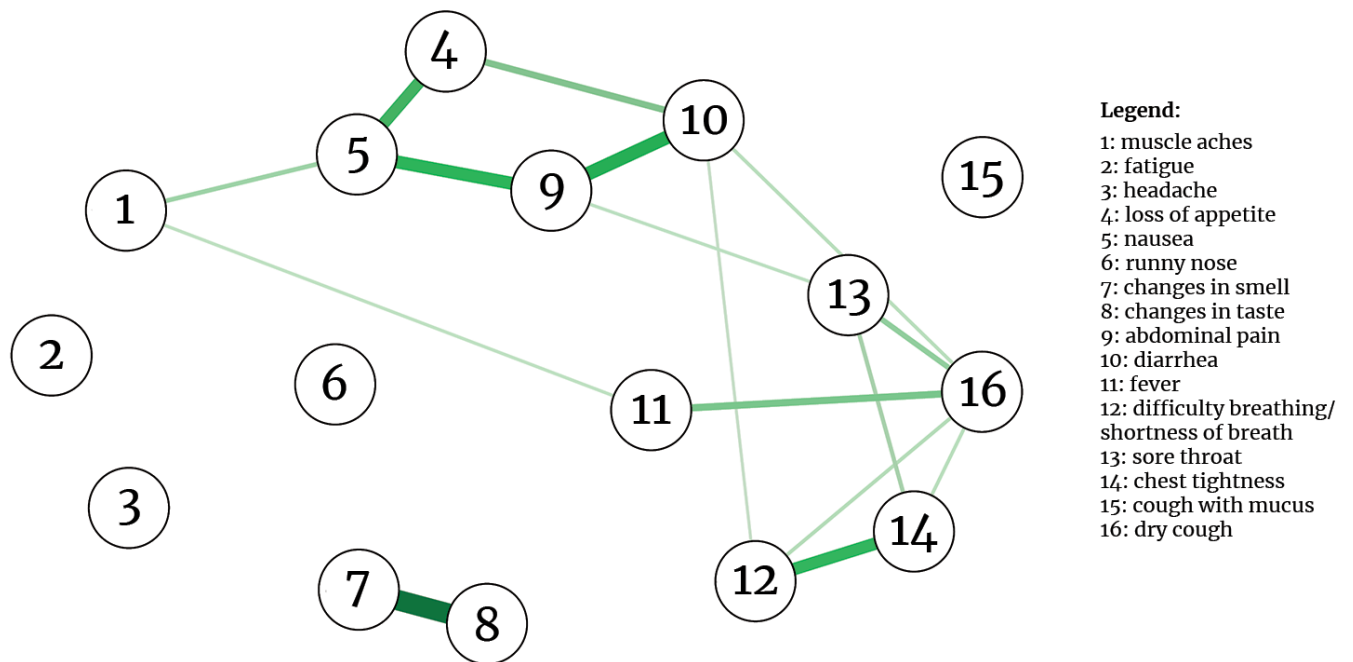
Exploratory analysis

Network

An IsingFit analysis was used to plot the symptoms of COVID-19 in a network. The IsingFit approach "combines logistic regression with model selection based on a Goodness-of-Fit measure to identify relevant relationships between variables that define connections in a network" (van Borkulo et al., 2014, p. 2).

Figure 3

Network of reported COVID-19 symptoms

Legend:
1: muscle aches
2: fatigue
3: headache
4: loss of appetite
5: nausea
6: runny nose
7: changes in smell
8: changes in taste
9: abdominal pain
10: diarrhea
11: fever
12: difficulty breathing/ shortness of breath
13: sore throat
14: chest tightness
15: cough with mucus
16: dry cough

Key Observations and Findings

The model is made up of several notable components, along with a few nodes, which are either loosely or completely disconnected from the main structure. The network features only one cluster that is larger than a triad. It is composed of four nodes: "loss of appetite", "nausea", "abdominal pain" and "diarrhea". Two more notable components appear within the interconnected space: a weakly connected open triad, consisting of "fever", "sore throat", and "dry cough", and a strong dyad composed of "difficulty breathing/shortness of breath" and "chest tightness".

"Changes in smell" and "changes in taste" are disconnected from the main structure, but form a very strongly connected dyad. "Muscle aches" are weakly connected to "nausea" and "fever", and the rest of the nodes ("fatigue", "headache", "runny nose", and "cough with mucus") are disconnected from the rest of the network completely.

Discussion

This study investigated the connection between smell and taste impairment and the clinical course severity of people infected with COVID-19, as suggested by Yan et al. (2020b). The findings of this study found a significant difference between the medians in smell loss scores of respondents suffering from a mild course of illness and those suffering from a moderate/severe course. These results suggest that there is a significant association between having a mild course of COVID-19 infection and experiencing relatively greater smell loss and having a moderate/severe course of illness and experiencing relatively lesser smell loss. There was, however, no significant difference found between the medians of taste loss in mild versus moderate/severe groups. This finding suggests that statistically, both groups have an equal chance of experiencing greater or lesser taste loss. The robustness of the findings for hypotheses 1 and 2 is supported by the fact that their results were most likely not influenced by unequal sample sizes, as this possibility was investigated with robustness checks and found to not have an effect on the results of analyses. Finally, the study also found that nose blockage was not associated with either of the illness course severity categories, which complements the findings of Parma and her colleagues (2020) that nose blockage is independent of smell and taste loss in COVID-19.

The network analysis revealed that the connectedness of symptoms "changes in smell" and "changes in taste" was not high enough to be above the threshold for a connection with any of the other symptoms, except with one another. This was not surprising, as smell and taste are closely connected, and many respondents reported these symptoms together. A notable observation is the connection between "loss of appetite", "nausea", "abdominal pain", and "diarrhea". It is logical to see these symptoms grouped, as they point to a general affliction of the digestive tract. Other significant dyads and triads of the network were similarly ontologically connected, with afflictions focused on the throat, respiratory tract, and smell and taste. Such groupings probably reflect the tendency of associated symptoms to appear together when a relevant part of the body is affected by the disease. Additionally, certain symptoms may often cause others, such as nausea causing loss of appetite, or dry

cough causing a sore throat. To address the research question of which symptoms are associated with smell and taste loss, information from the network suggests that they often occur alone. This would support the notion of smell and taste loss heralding a milder course of infection with COVID-19, given that the appearance of other symptoms is a sign of greater complications, notably the presence of respiratory problems.

A question that arises when presented with these results is the disparity in the significance of smell loss and taste loss scores. The two senses are strongly associated, as confirmed by the network analysis. Furthermore, because smell plays a key role in the creation of flavor through retronasal olfaction (smell molecules entering the mouth when food is chewed), individuals stricken with a profound anosmia are likely to experience an impairment in taste as a consequence (Giacomelli et al., 2020). Yan and associates (2020) measured both anosmia and dysgeusia in their participants, but reported almost no difference in distribution, so the analyses only focused on anosmia, where results were assumed to apply to both symptoms. This question is left to be answered and remains open to further investigation.

The study by Yan et al. (2020) reported that hospitalization for COVID-19 was significantly associated with an intact sense of smell. While the present study could not confirm this conclusion, the trend described above seems to go in this direction. There are, however, many points of difference in methodology and circumstances that need to be discussed for an objective comparison of the two studies. First, Yan et al.'s (2020) study was performed retrospectively on patients who were presenting to the UC San Diego Health System. Data gathered from these participants was drawn from their medical records, providing greater objectivity in the (albeit still self-reported) smell and taste loss results, as there was no time window between the experience and data gathering. The present study, on the other hand, may have suffered from respondent confirmation bias, as respondents may have heard about smell and taste loss being a symptom of COVID-19 and adjusted their memory of the course of the illness accordingly.

Gathering data from subjects presenting to the health system also meant unified diagnosing. All participants of Yan et al.'s study were diagnosed using

polymerase chain reaction (PCR) from swabs, while the present study included people diagnosed based on symptoms (40.24%), and other unspecified lab test (6.34%), as well as viral swab tests (53.41%). While viral swabs are not 100% percent accurate, the homogeneity in testing allows for a better estimation of how much of the sample was truly suffering from COVID-19 based on existing analyses (e.g., Deeks et al., 2020).

Finally, the biggest difficulty in comparing the results from Yan et al.'s (2020) research with the present study is in the definition and operationalization of clinical course severity. Yan et al. (2020) divided their sample based on hospital admission, which implicitly suggests that the cases in question needed specialized care and monitoring, making them more severe cases than those that were sent home. This "not-admitted" group was not stratified any further, and it is precisely in this group where the present study did most of its stratification. From the 410 responses used, 7 mentioned hospitalization. The rest of the severe cases were identified based on antibiotic use or subjective evaluation of the symptom progression question. Additionally, as the moderate and severe cases were combined into a single group, this group then included cases which would fit into both the admitted and not-admitted group. To put it simply, the Yan et al. (2020) study looked at cases at the top of the scale of clinical course severity and compared it to the rest of the scale. The present study, on the other hand, initially stratified its group into a wider range, but through the merging of groups ended up comparing cases at the bottom of the scale of clinical severity with the rest (since the mild group were people who did not use any, or very basic medication).

An additional point to consider for the comparison of the two studies is the overlap in characteristics of participants in terms of smell and taste impairment. The GCCR questionnaire called upon people who experienced changes in smell and taste to complete the questionnaire, so its respondents will be more representative of a population that did, as opposed to Yan et al.'s (2020) study, which took a general sample. Furthermore, the study did not assess degree of smell or taste loss, but only measured it as a binary yes/no option. Its results reported an association between an intact sense of smell and admittance to the hospital, but slight smell or taste loss would have been categorized as a positive finding, while the present study interpreted

slight smell or taste loss as something it expected to be associated with a more severe course of illness. Additionally, distortions of smell and taste would be interpreted by Yan et al. (2020) as smell or taste impairment, while a person that would indicate no decrease in smell or taste in the GCCR questionnaire, but would report parosmia or dysgeusia, would be considered here as having no impairment.

Despite these differences, the two studies can be reconciled if they are seen as complementing each other, rather than one building on top of the other. Yan et al.'s (2020) study covers the range of cases that could not complete the GCCR questionnaire, as they were hospitalized and by consequence incapacitated, in a coma, or even dead. The present study then takes a closer look at the group of non-admitted patients and investigates the range of smell and taste loss present within this population. The results, while having a small effect size, confirm that there is a trend of growing smell impairment as the clinical course of COVID-19 becomes more severe. Additionally, the small effect size could be explained, for one, by the stratification based on medication, which was not as robust as it should be, and for two, by the comparison of the mild group, which was very narrow, and the moderate/severe group, which was very broad.

The insights above need to be understood with reference to the fact that the present study was performed on a Dutch sample. This makes the results relevant for northwestern Europe but needs to be taken into consideration if one would like to generalize the findings to a broader population. Additionally, the categorization of illness course severity used in this study, based on used medication and treatment, is a long shot from the robustness of triage done by medical professionals, who are in physical contact with the patients, and have access to testing equipment.

Nevertheless, the above results may serve as an indicator that the connection between illness course severity in COVID-19 and smell and taste loss is worth paying attention to. The effect sizes reported here are not high enough to influence diagnostic criteria, but as is mentioned above, this research measured the difference between a very mild course of infection, and the entire range of severity that remained. Additional research, focusing on the entire range of clinical course severity, with a robust division of categories, could provide a more complete picture of the

studied relationship. Such results might be useful to clinicians dealing with COVID-19 patients, who may then better predict an appropriate response to the symptoms they encounter.

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Appendix

Results of Equal Samples Iterations

#	F–K smell med $\chi 2$	F–K smell p	F–P smell U^*	F–P smell p	F–K taste med $\chi 2$	F–K taste p	F–P taste U^*	F–P taste p
0	**12.52**	**0.000**	**2.92**	**0.004**	**0.22**	**0.641**	**17634.00**	**0.317**
1	9.35	0.002	2.95	0.003	2.54	0.111	8433.50	0.101
2	12.49	0.000	2.96	0.003	1.66	0.198	9013.50	0.444
3	7.27	0.007	2.67	0.008	0.66	0.417	8724.50	0.229
4	8.86	0.003	2.59	0.010	1.53	0.217	8433.50	0.101
5	7.02	0.008	2.40	0.016	0.64	0.424	8598.50	0.164
6	4.90	0.027	2.29	0.022	0.35	0.555	9297.00	0.735
7	6.13	0.013	2.55	0.011	0.32	0.573	8623.50	0.176
8	11.08	0.001	2.76	0.006	1.56	0.211	8664.50	0.196
9	9.25	0.002	2.64	0.008	0.92	0.338	8708.50	0.220
10	4.84	0.028	2.01	0.044	1.51	0.219	9376.50	0.827
11	8.06	0.005	2.03	0.042	0.00	0.967	9263.50	0.697
12	9.64	0.002	2.69	0.007	0.70	0.402	8610.50	0.169
13	13.42	0.000	2.91	0.004	1.00	0.316	8638.00	0.183
14	9.38	0.002	2.76	0.006	0.50	0.480	9069.00	0.495
15	14.97	0.000	2.90	0.004	0.78	0.377	8701.50	0.216
16	6.01	0.014	1.82	0.069	0.00	0.979	9145.50	0.571
17	6.51	0.011	2.32	0.020	0.11	0.736	8635.50	0.181
18	7.66	0.006	2.19	0.029	0.22	0.642	8635.50	0.784
19	8.62	0.003	2.22	0.027	0.18	0.671	9312.00	0.752
20	19.48	0.000	3.79	0.000	2.31	0.128	8114.00	0.034

Note: Iteration #0 is the original sample with unequal sizes, included for comparison.