Loss of smell and taste in combination with other symptoms is a strong predictor of COVID-19 infection

Cristina Menni, PhD[1,6*], Ana M Valdes , PhD [1,2,6], Maxim B Freidin, PhD [1], Carole H. Sudre, PhD[3], Long H. Nguyen, MD [5]; David A. Drew, PhD[5],Sajaysurya Ganesh, PhD[4], Thomas Varsavsky, Phd[3], M. Jorge Cardoso, PhD[3], , Julia S El-Sayed Moustafa, PhD[1], Alessia Visconti, PhD[1], Pirro Hysi , PhD[1], Ruth C E Bowyer, PhD[1], Massimo Mangino, PhD[1], Mario Falchi, PhD [1], Jonathan Wolf, BSc[4], Sebastien Ourselin, PhD[3], Andrew T. Chan, MD[5], Claire J Steves , PhD [1,7], Tim D Spector , MD[1,7*]

Affiliations:

[1] Department of Twin Research and Genetic Epidemiology, King's College London, Westminster Bridge Road, SE17EH London, UK

[2] Academic Rheumatology Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB, UK

[3] School of Biomedical Engineering, School of Biomedical Engineering & Imaging Sciences, King's College London, SE1 7EU London UK

[4] Zoe Global Limited, 164 Westminster Bridge Road, London SE1 7RW, UK

[5]Clinical & Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical School, 100 Cambridge Street, Boston, MA, USA

[6] equal contribution

[7] equal contribution

Corresponding authors:

tim.spector@kcl.ac.uk; cristina.menni@kcl.ac.uk

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To facilitate early detection of COVID-19 infections, we used data from 5238 users of the COVID Symptom Tracker app, who had reported an RT-PCR COVID-19 test. Loss of smell and taste was 3-fold higher (61.83%) in those testing positive than among those testing negative (19.13%); odds ratio=7.02[95%CI 6.26; 8.08]. A model combining symptoms to predict likely infection was applied to over 2 million app users and resulted in 18.79% of those presenting symptoms predicted to be COVID-19 positive.

Since the outbreak of COVID-19, an acute respiratory illness caused by the novel coronavirus SARS-CoV-2, in China in December 2019, over 1,600,000 cases have been confirmed worldwide [1]. A large proportion of the world's population is presenting with flu like symptoms, but widespread population testing is not yet available in countries, including the US[2] and the UK[3]. Thus, it is essential to identify the combination of symptoms most predictive of COVID-19 infection, to guide recommendations for self-isolation and prevent further spreading of the disease.

Case and media reports from various countries [4-6] indicate that a significant number of patients with proven COVID-19 have developed anosmia (loss of smell) and a mechanism of action for the SARS-CoV-2 viral infection causing anosmia has been postulated [7]. A growing number of reports indicate that a number of infected individuals present anosmia in the absence of other symptoms[8,9] suggesting that this symptom could be used as a more sensitive or specific screening tool to help identify potential mild cases who could be instructed to self-isolate.

Here we investigate whether loss of smell and taste is specific to COVID-19 in 2,030,563 individuals who used the *COVID Symptom Tracker*[10]*,* a mobile-phone app which collected data from both asymptomatic and symptomatic individuals that tracks in real time how the disease progresses by recording health information on a daily basis, including fever, fatigue and other symptoms. We first investigated the correlation between loss of smell and taste (anosmia) and COVID-19 in 2,043 COVID-19 positive (cases) and 3,205 COVID-19 negative (controls) who self-reported receiving a

reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2. We then identified which symptoms, besides anosmia, are most likely predicting COVID-19. Finally, we tested our predictive model in 608,385 individuals who have symptoms but have not yet been tested.

Between 24th March 2020 and 6th April 2020, 1,972,824 UK and 57,739 US individuals reported symptoms through the same app. Among those reporting in the UK, 30.6% indicated suffering from one or more potential symptoms of COVID-19. The breakdown of symptoms is presented in **Table 1**. 4,611 UK participants (1,810 cases and 2,801 controls) and 627 US participants (233 cases and 404 controls) that reported (i) having had an RT-PCR COVID-19 test, (ii) having received the outcome of the test and (iii) symptoms including loss of smell and taste were included in the analysis.

In the UK subset, 60.5% of those testing positive for COVID-19 reported loss of smell and taste compared to only 18.85% of those who tested negative resulting in significantly higher odds of having being diagnosed with COVID-19 infection (OR[95%CI]= 6.79[5.93; 7.77, P<0.0001) after adjusting for age, sex and BMI. Without adjustment, loss of smell and taste has a positive predictive value of 67.0%. We replicated this result in the US subset (OR[95%CI]= 10.35[7.03;15.23], P <0.0001) and combined the results using inverse variance fixed effect meta-analysis (OR(95%CI]=7.02[6.26; 8.08], P<0.0001).

We then reran logistic regressions adjusting for age, sex and BMI to identify other symptoms besides anosmia, associated with being infected by COVID-19 in the UK and US cohort. As shown in **Figure 1a**, all ten symptoms queried (fever, persistent cough, fatigue, shortness of breath, diarrhoea, delirium, skipped meals, abdominal pain, chest pain and hoarse voice) were positively associated in the UK cohort with testing positive for COVID-19 after adjusting for multiple testing using Benjamini-Hochberg False Discovery Rate. However, in the US, where the app was only recently launched and

only loss of smell and taste, fatigue and skipped meals were observed so far to be associated with a positive test.

We further performed stepwise logistic regression in the UK subset, by randomly dividing it into a training and test sets (ratio 80/20) to identify independent symptoms most strongly correlated to COVID-19 adjusting for age, sex and BMI. A combination of loss of smell and taste, fatigue, persistent cough and loss of appetite resulted in the best model (with the lowest Akaike information criterion AIC). We therefore generated a linear model for symptoms that included loss of smell and taste, fatigue, persistent cough and loss of appetite to get a symptoms prediction model for COVID-19:

Prediction model** = -**1.13 - (0.01 x age) + (0.51 x sex) + (1.68 x loss of smell and taste) + (0.34 x severe or significant persistent cough) + (0.77 x severe fatigue) + (0.34 x skipped meals)

where all symptoms should be coded as 1 if the person self-reports suffering from it and 0 if not. The 'sex' feature is also binary, with 1 representing males and 0 representing females.

The prediction model had a sensitivity of 0.64[0.59; 0.70], a specificity of 0.82[0.79; 0.85], and a ROC-AUC 0.78[0.76; 0.82]. Cross-validation ROC-AUC was 0.76[0.74; 0.78] and positive predictive value was 0.69[0.63; 0.74] and negative predictive value was 0.79[0.75; 0.82]. In this model, the strongest predictor was loss of smell and taste, **Figure 1b.** We also computed the ROC-AUC stratifying for sex and age-groups and found that results were similar in all groups with no significant differences between strata suggesting that our model works in the same way within different sex and age-groups. We also tested the model in the US subset and found a sensitivity of 0.71 [0.65, 0.77], a specificity of 0.78 [0.73, 0.82], a positive predictive value of 0.64 [0.58, 0.70] and a negative predictive value 0.83 [0.79, 0.87] (**Figure 1c**).

Finally, we applied the predictive model to the 608,385 UK and US individuals reporting symptoms who had not had a COVID-19 test and we find that according to our model 18.79%[14.23%;23.35%] of individuals reporting some COVID-19 symptoms are likely to be infected by the virus adding up to 114,452 individuals, or 5.6% as a proportion of the overall responders to our app.

Discussion

We report that loss of smell and taste is a strong predictor of COVID-19 in addition to the most established symptoms of a high temperature and a new, continuous cough.

COVID-19 may affect smell receptors in line with many other respiratory viruses, including previous coronaviruses thought to account for 10-15% of cases of anosmia[8].

We also identify a combination of symptoms including anosmia, fatigue, persistent cough, and loss of appetite that together can identify with high specificity and good sensitivity COVID-19 infected individuals.

Our study, although large, has some limitations. First, we used self-reported data. Second, at present, we do not know whether anosmia was acquired prior to other COVID-19 symptoms, during the illness or afterwards. This information is likely to become available as currently healthy users track symptom development over time. Third, the COVID-19 diagnosis is based on report of receipt of a test which currently is based on an RT-PCR assay with considerably less than 100% sensitivity (true positive rate)[11]. As more accurate tests become available, we have the ability to develop amore optimal model. An important caveat is that the individuals on which the model was trained are highly selected because the receipt of COVID-19 tests are not random. Testing is likely associated with the development of severe symptoms, with individual's contact with COVID-19 positive subjects, health workers, or travel in an area of particular risk. Therefore, our results may overestimate the number of expected positives. Also, volunteers using the app are a self-selected group that may not be fully representative of the general population. For example, women are

much more likely to respond than men and people over 69 and of lower socio-economic status are under-represented.

This work suggests that loss of sense of smell and taste could be implemented as part of screening for COVID-19 and should be included in the symptom list currently promoted by the World Health Organization[12]. A detailed study on the natural history of broader COVID-19 symptoms, especially according to timing and frequency, will help address these critical questions.

Online Methods

Study setting and participants

The COVID Symptom Tracker app developed by Zoe Global Limited, King's College London, and Massachusetts General Hospital, was launched in the UK on Tuesday the 24th March 2020, and in the US on 29th March 2020 and after two weeks has reached 2,030,563 users. It enables capture of self-reported information related to COVID-19 infections. On first use, the app records self-reported location, age, and core health risk factors. With continued use and notifications, participants provide daily updates on symptoms, health care visits, COVID-19 testing results, and if they are self-quarantining or seeking health care, including the level of intervention and related outcomes. Individuals without apparent symptoms are also encouraged to use the app.

Anonymised research data will be shared with third parties via the centre for Health Data Research UK (HDRUK.ac.uk). US investigators are encouraged to coordinate data requests through the COPE Consortium (www.monganinstitute.org/cope-consortium). Data updates can be found on https://covid.joinzoe.com

Ethics: The Ethics for the app has been approved by KCL ethics Committee and all users provided consent for non-commercial use. An informal consultation with TwinsUK members over email and social media prior to the app having been launched found that they were overwhelmingly supportive of the project. The US protocol was approved by the Partners Human Research Committee.

Statistical analysis

Data from the app were downloaded into a server and only records where the self-reported characteristics fell within the following ranges were utilised for further analyses: age between 16 (18 in the US) and 90; height (cm) between 110 and 220; weight (kg) between 40 and 200; BMI(kg/m^2) between 14 and 45; and temperature (in C) between 35 and 42.

Baseline characteristics are presented as the number (percentage) for categorical variables and the mean (standard deviation) for continuous variables. Multivariate logistic regression adjusting for age, sex and BMI was applied to investigate the correlation between loss of smell and taste and COVID-19 in 1,810 UK cases and 2,801 UK controls from participants of the COVID Symptom Tracker app who were also tested in the lab for COVID-19. Results were replicated in 233 US cases and 404 US controls. In this same dataset, we then performed stepwise logistic regression combining forward and backward algorithms, to identify other symptoms associated to COVID-19 independently of loss of smell and taste. We included in the model ten other symptoms (including fever, persistent cough, fatigue, shortness of breath, diarrhoea, delirium, skipped meals, abdominal pain, chest pain and hoarse voice) as well as age, sex, and BMI and chose, as the best model, the one with the lowest AIC. The sample was randomly split into the training and test sets with 80/20 ratio. The model was fit using the training set and its performance was assessed using the test set. In addition, the performance of the model has been assessed via 10-fold cross-validation in the whole sample of 4,611 individuals using the R package cvAUC[13]. We further tested the prediction model in the US subset.

For our predictive model, using the R packages pROC and epiR, we further computed the area under curve (AUC) i.e. the overall diagnostic performance of the model, the sensitivity ("positivity in disease") i.e. the proportion of subjects who have the target condition (reference standard positive) and give positive test results, and the specificity ("negativity in health") i.e. the proportion of subjects without a COVID-19 RT-PCR test that give negative model results.

Finally, we applied the predictive model to the 608,385 individuals reporting symptoms who had not had a COVID-19 test in order to estimate the percentage of individuals reporting some COVID-19 symptoms likely to be infected by the virus. The proportion of estimated infections was calculated repeatedly by sampling the dataset (with replacement) to get the 95% confidence intervals.

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Authors' contribution

Conceived and designed the experiments*:** CM, AMV, CJS, TDS; ***Analyzed the data*:** CM, MBF, CHS, SG, TV, MJC, SO, HNAMV. ***Contributed reagents/materials/analysis tools*:* TW, JC, MBF, SG, AV, JESM, PH, MM, MF, SE, DAD, ATC, LHN. ***Wrote the manuscript***: CM, AMV. ***Revised the manuscript***: all

Competing interests' declaration: TDS, AMV are consultants to Zoe Global Ltd ("Zoe"). SG and JW are employee of Zoe Global Limited. Other authors have no conflict of interest to declare.

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Table 1. Descriptive characteristics of the study population. Results are presented as (%) for dichotomous traits, as mean(SD) for continuous traits

	Tested for COVID-19				*Untested for COVID-19*	
	UK		**US**		**UK**	**US**
	COVID-19 positive	**COVID-19 negative**	**COVID-19 positive**	**COVID-19 negative**		
N	1,810	2,801	223	404	1,968,213	57,112
%Females	69.56%	75.90%	79.37%	80.20%	67.30%	74.82%
Age, yrs	40.33(12.78)	41.52(12.37)	43.09(13.58)	45.01(13.01)	42.38 (14.12)	51.07 (15.67)
BMI, kg/m²	26.38(5.72)	26.20(5.65)	26.79(6.20)	26.94(6.65)	26.21 (5.07)	27.07 (5.51)
Answered questions on symptoms	1810	2801	223	404	594,763	13,622
Loss of smell and taste	60.50%	18.55%	72.65%	21.04%	21.79%	16.21%
Fatigue	22.98%	8.57%	19.73%	16.83%	7.56%	8.39%
Shortness of breath	10.33%	5.68%	5.83%	7.67%	3.92%	4.26%
Fever	20.83%	11.78%	17.04%	16.58%	11.97%	10.57%
Persistent cough	52.49%	39.45%	43.05%	43.81%	33.95%	27.25%
Diarrhoea	19.56%	13.03%	30.94%	22.52%	19.97%	24.17%
Delirium	14.42%	8.07%	19.73%	14.85%	15.97%	17.46%
Skipped meals	34.42%	17.32%	43.50%	30.69%	20.33%	24.79%
Abdominal pain	15.41%	10.72%	15.70%	16.09%	15.52%	16.76%
Chest pain	36.19%	30.06%	36.77%	37.38%	33.09%	30.63%
Hoarse voice	25.35%	19.78%	24.22%	24.01%	20.49%	15.94%

Figure Legends

Figure 1. a. Association between symptoms and COVID-19 infection in 4611 UK and 627 US participants that were tested via RT-PCR, OR(95%CI) are reported. **b and c**. ROC-curve for prediction in the UK test and US set respectively of the risk of positive test for COVID-19 using self-reported symptoms and traits: persistent cough, fatigue, skipped meals, loss of smell, sex, age, in the COVID-19 tested subsets. AUC=area under the curve; SE=sensitivity; SP=specificity; PPV=positive predictive value; NPV= negative predictive value.