# Prognosis and persistence of smell and taste dysfunction in patients with covid-19: meta-analysis with parametric cure modelling of recovery curves

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Cite this as: *BMJ* 2022;378:e069503 http://dx.doi.org/10.1136/bmj-2021-069503

Accepted: 14 June 2022

## ABSTRACT

### OBJECTIVE

To clarify in patients with covid-19 the recovery rate of smell and taste, proportion with persistent dysfunction of smell and taste, and prognostic factors associated with recovery of smell and taste.

### DESIGN

Systematic review and meta-analysis.

### DATA SOURCES

PubMed, Embase, Scopus, Cochrane Library, and medRxiv from inception to 3 October 2021.

### REVIEW METHODS

Two blinded reviewers selected observational studies of adults (≥18 years) with covid-19 related dysfunction of smell or taste. Descriptive prognosis studies with time-to-event curves and prognostic association studies of any prognostic factor were included.

### DATA EXTRACTION AND SYNTHESIS

Two reviewers extracted data, evaluated study bias using QUIPS, and appraised evidence quality using GRADE, following PRISMA and MOOSE reporting guidelines. Using iterative numerical algorithms, time-to-event individual patient data (IPD) were reconstructed and pooled to retrieve distribution-free summary survival curves, with recovery rates reported at 30 day intervals for participants who remained alive. To estimate the proportion with persistent smell and taste dysfunction, cure fractions from Weibull non-mixture cure models of plateaued survival curves were logit transformed and pooled in a two stage meta-analysis. Conventional aggregate data meta-analysis was performed to explore unadjusted associations of prognostic factors with recovery.

### MAIN OUTCOME MEASURES

The primary outcomes were the proportions of patients remaining with smell or taste dysfunction. Secondary outcomes were the odds ratios of prognostic variables associated with recovery of smell and taste.

### RESULTS

18 studies (3699 patients) from 4180 records were included in reconstructed IPD meta-analyses. Risk of bias was low to moderate; conclusions remained unaltered after exclusion of four high risk studies. Evidence quality was moderate to high. Based on parametric cure modelling, persistent self-reported smell and taste dysfunction could develop in an estimated 5.6% (95% confidence interval 2.7% to 11.0%, $I^2$=70%, $\tau^2$=0.756, 95% prediction interval 0.7% to 33.5%) and 4.4% (1.2% to 14.6%, $I^2$=67%, $\tau^2$=0.684, 95% prediction interval 0.0% to 49.0%) of patients, respectively. Sensitivity analyses suggest these could be underestimates. At 30, 60, 90, and 180 days, respectively, 74.1% (95% confidence interval 64.0% to 81.3%), 85.8% (77.6% to 90.9%), 90.0% (83.3% to 94.0%), and 95.7% (89.5% to 98.3%) of patients recovered their sense of smell ($I^2$=0.0-77.2%, $\tau^2$=0.006-0.050) and 78.8% (70.5% to 84.7%), 87.7% (82.0% to 91.6%), 90.3% (83.5% to 94.3%), and 98.0% (92.2% to 95.5%) recovered their sense of taste (range of $I^2$=0.0-72.1%, $\tau^2$=0.000-0.015). Women were less likely to recover their sense of smell (odds ratio 0.52, 95% confidence interval 0.37 to 0.72, seven studies, $I^2$=20%, $\tau^2$=0.0224) and taste (0.31, 0.13 to 0.72, seven studies, $I^2$=78%, $\tau^2$=0.5121) than men, and patients with greater initial severity of dysfunction (0.48, 0.31 to 0.73, five studies, $I^2$=10%, $\tau^2$<0.001) or nasal congestion (0.42, 0.18 to 0.97, three studies, $I^2$=0%, $\tau^2$<0.001) were less likely to recover their sense of smell.

## WHAT IS ALREADY KNOWN ON THIS TOPIC

Although smell and taste abnormalities have been extensively studied for diagnostic value in covid-19, little is known about their clinical course, with inconsistent evidence on the duration of recovery based on narrative reviews

Whether covid-19 related chemosensory dysfunction is transient or permanent is unknown, and it is unclear what proportion of patients develop persistent dysfunction

The prognostic factors associated with smell and taste recovery (eg, initial severity of smell and taste dysfunction, concomitant symptoms) are not established

## WHAT THIS STUDY ADDS

Parametric cure models project that 5.6% and 4.4% of patients might develop long lasting self-reported smell and taste dysfunction post-covid-19, respectively- about 15 million and 12 million patients worldwide as of July 2022

Meta-analyses of reconstructed time-to-event individual patient data (IPD) showed that at 30, 60, 90, and 180 days, respectively, about 74%, 86%, 90%, and 96% of patients self-reported smell recovery and 79%, 88%, 90%, and 98% of patients self-reported taste recovery, among patients who remained alive at the given time

Women were less likely to recover their sense of smell and taste, and patients with greater initial severity of dysfunction and those with nasal congestion were less likely to recover their sense of smell

## CONCLUSIONS

A substantial proportion of patients with covid-19 might develop long lasting change in their sense of smell or taste. This could contribute to the growing burden of long covid.

## SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD42021283922.


### Introduction

Change in the sense of smell and taste is highly prevalent in patients with covid-19, with 40-50% of people on average reporting these symptoms globally,[1 2] and up to 98% showing olfactory dysfunction when tested objectively.[3] These chemosensory impairments are often the sole warning symptoms and the strongest predictors of SARS-CoV-2 infection.[1 4] Disturbances in these senses can include decreased (hyposmia or hypogeusia) or absent function (anosmia or ageusia),[5 6] distorted (parosmia or parageusia) or putrid sensations (cacosmia or cacogeusia),[5 6] or even hallucinations (phantosmia or phantogeusia).

Although change in sense of smell and taste has been extensively studied for diagnostic value, little is known about the clinical course of such symptoms post-covid-19, with inconsistent evidence on the duration of recovery.[7 8] In particular, it is unknown whether covid-19 related chemosensory dysfunction is transient or permanent,[8] and it is uncertain what proportion of patients develop persistent dysfunction. Furthermore, the prognostic factors associated with smell and taste recovery are unclear. While some studies have reported associations with initial severity of dysfunction, age, and sex,[9 10] not all studies are in agreement,[11 12] and the roles of viral load, concomitant symptoms, and medical history have not been well studied.

These factors raise important clinical questions relevant to patients and doctors, as persistent smell and taste dysfunction could be considered a focal neurological deficit[13] and can have an impact on quality of life and general health[14 15] long after recovery from covid-19. Affected patients are often distressed as these impairments can hinder the enjoyment of food and create hygiene problems related to body odour and bad breath.[16] Smell and taste dysfunctions might also be associated with depressive symptoms,[16] malnutrition,[17] cognitive decline,[18] and mortality.[19] In the context of covid-19, smell dysfunction has been postulated as a possible marker of accelerated neurodegenerative disease,[13] and this symptom is an important feature of long covid.

Considering the potentially serious sequelae associated with smell and taste dysfunctions, and the need for doctors to counsel patients on their anticipated recovery course, it is essential to investigate the burden of persistent symptoms and identify relevant prognostic factors. We therefore performed a systematic review and meta-analysis to bridge this knowledge gap, using recent advances in graphical digitisation and computational inference to reconstruct time-to-event individual patient data (IPD) directly from published graphs. In our main analysis, we describe the cumulative incidence of smell and taste recovery in patients with covid-19 across time. With the aid of parametric statistical cure models, we estimate the proportion of patients with persistent covid-19 related dysfunction of smell and taste. Finally, using one stage and two stage meta-analyses from reconstructed IPD and aggregate data, we identify the key prognostic factors associated with the duration and likelihood of recovery.

### Methods

This review is reported in accordance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[20 21] Supplementary table S1 includes the MOOSE checklist.

#### Search strategy

We searched five databases (PubMed, Embase, Scopus, and Cochrane Library for published studies, and medRxiv for preprints) from inception to 3 October 2021, using search terms for smell dysfunction, taste dysfunction, and covid-19 (see full search strategy in the supplementary methods). We also hand searched the bibliographies of included articles and relevant reviews but identified no additional relevant records.

#### Study selection and eligibility criteria

At least two of four authors (RH, NKWT, ESHQ, BKJT) independently selected eligible studies (based on title and abstract, followed by full text articles), extracted relevant data, and evaluated the risk of bias in a blinded manner, with conflicts resolved by a senior author (STT). We included observational studies (including control arms from interventional studies) with adult participants (≥18 years) who were infected with SARS-CoV-2 and experienced dysfunction of either smell or taste. We accepted self-reported or objective psychophysical measurements of smell or taste dysfunction, and descriptive prognosis studies that described the time to recovery of smell or taste, if time-to-event (survival) analysis was used and Kaplan-Meier or cumulative incidence curves provided. Studies that did not provide suitable curves, although potentially relevant,[22 23] were excluded as these did not permit the graphical reconstruction of IPD. For prognostic factor association studies, we included those that investigated any variable (eg, initial severity of smell or taste dysfunction, age, sex, body mass index (BMI), ethnicity) in association with the time taken or extent of recovery of smell or taste, versus patients with covid-19 with smell or taste dysfunction who did not have this variable. As we sought aggregate data, we accepted studies regardless of whether they provided survival curves. Descriptive prognosis studies that were initially excluded owing to lack of survival curves were re-evaluated for prognostic factor associations and included whenever possible (fig 1). We excluded case reports, reviews, conference abstracts, animal studies, non-English language publications, and studies that reported only combined smell and taste dysfunctions.

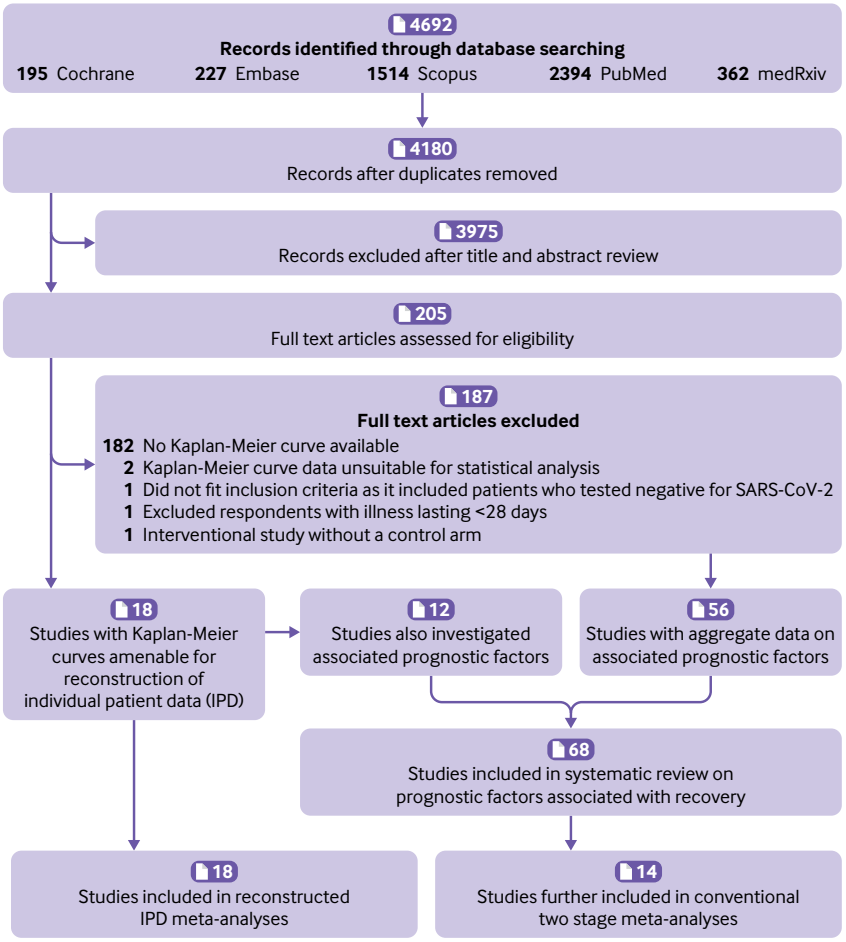


**Fig 1 | PRISMA flow diagram of study selection process. Supplementary table S2 shows the 18 studies included in reconstructed individual patient data meta-analyses, and supplementary tables S7 and S8. show the 72 studies included in conventional aggregate data systemic review (inclusive of 22 studies further used for conventional aggregate data meta-analyses)**

### Data extraction

We extracted key data (see supplementary methods) from each included article. To aid the reconstruction of IPD, we extracted step function values, timings, and number-at-risk tables from available vector and raster images of survivor or failure curves, which were processed and digitised using a semi-automated web based tool (WebPlotDigitizer, version 4.5). When necessary, we contacted authors for baseline number-at-risk data.[9]

### Risk of bias

To assess risk of bias at study level, we used the Quality In Prognosis Studies (QUIPS) tool, as recommended by the Cochrane Prognosis Methods Group.[24]

### Statistical analyses

Initially, we reconstructed time-to-event individual patient data (IPD) from digitised survivor or failure curves by solving the inverted Kaplan-Meier product limit equations using iterative numerical algorithms.[25] We evaluated the accuracy of reconstruction using published methods (see supplementary methods).[26]

In the primary analysis, we used a non-parametric two stage random effects model to retrieve a distribution-free summary survival curve.[27] This method obtains a distribution-free summary survival curve by expanding the product limit estimator of survival for aggregated survival data. As the competing event of death was not accounted for, the recovery rates reported at 30 day intervals relate to the probability of recovery for patients who remain alive before the time. The extension of DerSimonian-Laird methodology for multiple outcomes was applied to account for between study heterogeneity.[27] We retrieved $\tau^2$ values at each 15 day intervals using DerSimonian-Laird estimation. Weights were derived through inverse variance weighting.

We anticipated potential plateauing of the cumulative incidence curves, which might suggest a heterogeneous subpopulation of patients who do not recover their sense of smell or taste. Therefore, to estimate the proportion of patients with persistent smell or taste dysfunction, we fitted Weibull distributed non-mixture parametric cure models with a logistic link to explicitly model long term effects on each study's survival curves,

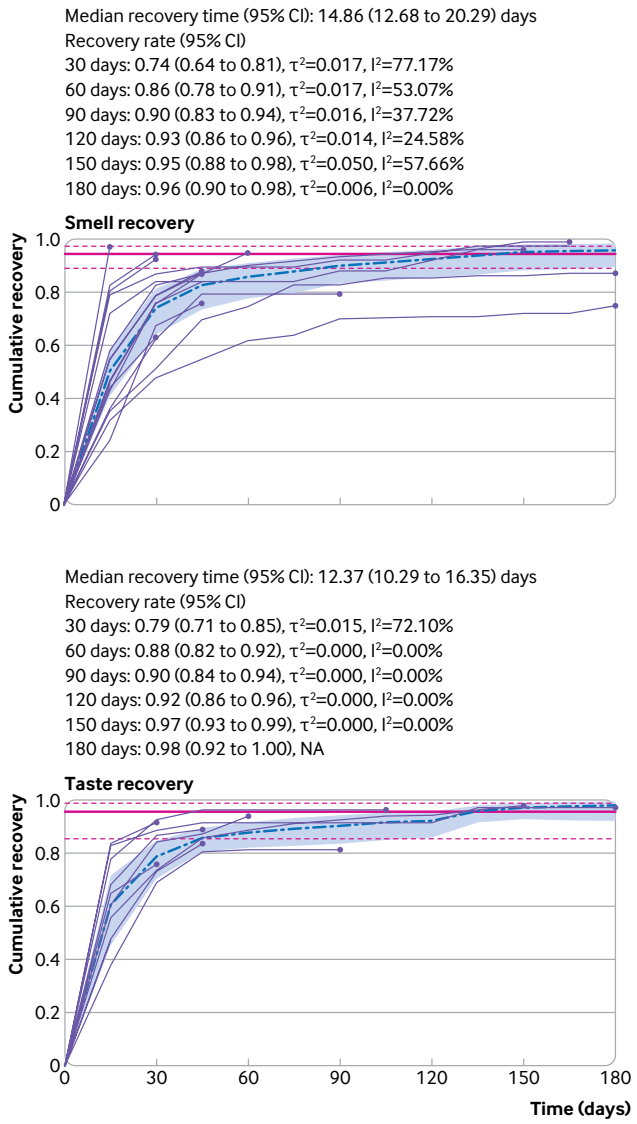


**Fig 2 | Non-parametric random effects summary survival curve from reconstructed time-to-event individual patient data for recovery of sense of smell and taste after covid-19. 1 corresponds to 100%. Blue dashed line represents the summary survival curve; purple lines represent individual studies; filled in circles represent the last follow-up time within the study; translucent blue band represents 95% confidence intervals (CIs) obtained by extension of Greenwood's formula with the delta method; solid pink and dashed pink lines represent the pooled proportion and the accompanying 95% CIs of patients with persistent dysfunction, derived from figure 3**

if plateaus were observed. The non-mixture cure model conservatively assumes that for all patients, the cure fraction may be eventually delineated, as the propensity for recovery reduces asymptotically to zero over time. Conversely, mixture cure models make the presumptive assumption that a proportion of patients, as reflected by the cure fraction, will never experience recovery, and this is independent of time. We used mixture cure models as a sensitivity analysis.

To further optimise the precision of cure models, we included only Kaplan-Meier curves with number-at-risk tables, as follow-up times of patients with censorship status were more accurately retrieved.[25] The presence of survival curve plateaus were quantitatively determined using the area-under-the-curve method, where the area-under-the-curve to median survival time >1 reflects a greater impact of long term survivors (or patients with persistent smell or taste dysfunction) on the survival curve pattern, and presence of a plateau.[28] Thereafter, logit transformed cure fractions and accompanying standard errors were pooled with generic inverse variance meta-analyses. A random effects model was utilised, with the restricted maximum likelihood estimator to estimate $\tau^2$ and the Hartung-Knapp adjustment of test statistics and confidence intervals.[29] The pooled proportion, and corresponding 95% confidence intervals and 95% prediction intervals, of patients with persistent smell or taste dysfunction were then retrieved after back transformation.

To explore the prognostic factors associated with the time to recovery, we analysed aggregate data from other studies in a conventional two stage meta-analysis. Sufficient data were available to pool the unadjusted odds ratios of various patient characteristics in association with the likelihood of persistent smell or taste dysfunction. Whenever feasible for two stage meta-analyses, we assessed between study variability with $\tau^2$ and measured the proportion of variability due to heterogeneity using the $I^2$ statistic.[30] We also assessed publication bias qualitatively through visual inspection of funnel plot asymmetry and quantitatively through Egger's bias.[31] When funnel plot asymmetry was observed, we used the trim-and-fill technique- which assumes that small study effects are due to missing studies- to impute potentially missing studies and re-estimate the pooled effect.[32] We conducted all analyses in R (version 4.0.3) following guidance from the Cochrane handbook, and considered a two sided P value <0.05 as significant (see supplementary methods).

### Certainty of evidence

We evaluated the quality of pooled evidence at the outcome level using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework,[33] modified for prognostic evidence.[34]

### Patient and public involvement

Patients and members of the public were not involved in the design and execution of the study, as this is a secondary analysis of published data. However, we plan to engage the public in the dissemination of our findings, such as, but not limited to, media coverage, social media engagement, newsletters, and public talks.

## Results

Figure 1 summarises the study selection process. From 4180 non-duplicated records, selection based on initial title and abstract yielded 205 relevant articles. After full text review, we included 18 articles for




doi: 10.1136/bmj-2021-069503 | *BMJ* 2022;378:e069503 | the bmj

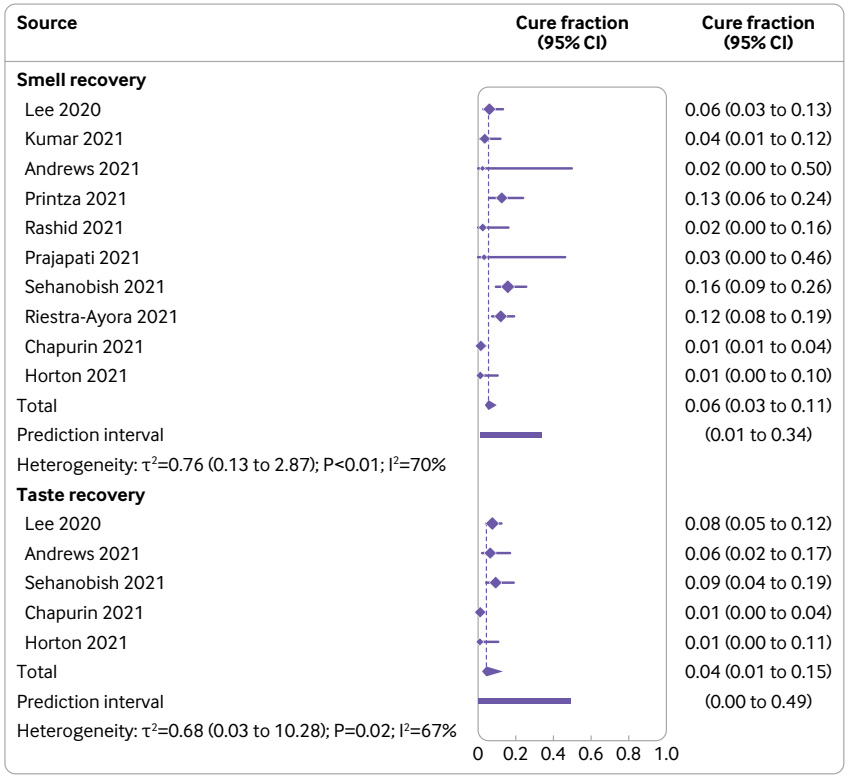


**Fig 3 | Random effects meta-analysis of Weibull non-mixture cure fraction for individual studies of persistent smell and persistent taste dysfunction after covid-19. 1 corresponds to 100%. Stretched purple diamonds are the pooled proportion with confidence intervals (CIs) for each random effects meta-analysis; symmetrical purple diamonds with horizontal lines are the study estimate with CIs, where diamond sizes reflect the relative weight apportioned to studies in the meta-analysis. The restricted maximum likelihood estimator was used to estimate τ2, and the Hartung-Knapp adjustment was applied to test statistics and CIs**

reconstructed IPD meta-analyses and 68 articles for aggregate data systematic review and meta-analyses.

### Reconstructed IPD time-to-event meta-analyses

*Study characteristics*

Of 18 studies (3699 patients) included in reconstructed IPD meta-analyses (see supplementary table S2),[9 12 35 48] all were observational, with nine retrospective and nine prospective cohorts. Four studies were conducted in the community setting and 14 studies in the hospital setting. Among these 14 studies, four involved only healthcare workers, four involved inpatients, four involved outpatients, and two involved both inpatients and outpatients. Eight studies investigated smell recovery and 10 studies separately investigated smell and taste recovery. Seventeen studies measured smell using self-report and one study used both self-report and the objective Brief Smell Identification Test. All 10 studies that investigated taste recovery used self-report. Most studies used a binary definition of recovery, although four studies of smell and three of taste provided further descriptive details on partial or complete recovery. The start point for assessment varied: 11 studies of smell and five of taste used the onset of dysfunction, two studies of smell and one of taste used a positive reverse transcriptase polymerase chain reaction (RT-PCR) SARS-CoV-2 test result, and the remaining studies used clinical diagnosis of covid-19. Assessment of smell or taste was performed once in nine studies, twice in two studies, and at regular intervals of daily to monthly in the seven remaining studies until study conclusion.

Nine studies were conducted in Europe, four in North America, and five in Asia. The mean participant age ranged from 30.0 to 55.8 years. The percentage of male participants ranged from 29.0% to 79.4%. Using QUIPS, risk of bias was high in four studies, moderate in seven studies, and low in seven studies (see supplementary table S3). Our findings remained unaltered in sensitivity analyses excluding high risk studies (see supplementary figure S1).

### Reconstructed IPD meta-analyses and cure models

Time-to-event data from 2201 and 1498 individual patients in 18 studies were available for further analysis. IPD reconstruction was of adequate quality and within acceptable error margins (see supplementary table S4 and supplementary figure S2). All except one study showed a plateau in the recovery curve within the follow-up time (see supplementary table S5).

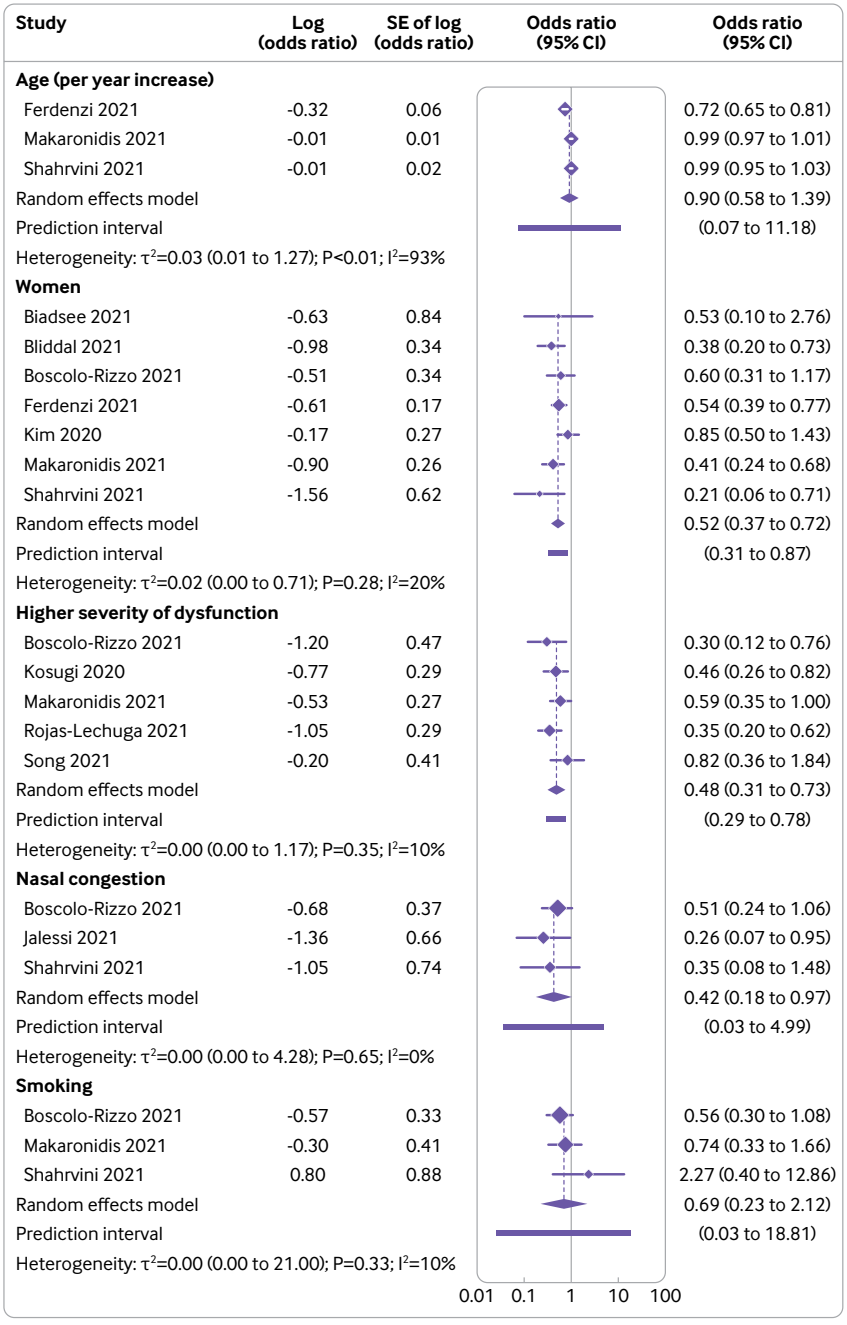


**Fig 4 | Conventional aggregate data two stage meta‐analysis of various prognostic factors in association with the odds of smell recovery. Stretched purple diamonds are the pooled proportion with confidence intervals (CIs) for each random effects meta‐analysis; symmetrical purple diamonds with horizontal lines are the study estimate with CIs, where diamond sizes reflect the relative weight apportioned to studies in the meta‐analysis. Supplementary tables S7 and S8 show these studies, with complete references. The restricted maximum likelihood estimator was used to estimate $\tau^2$, and the Hartung‐Knapp adjustment was applied to test statistics and CIs**

*Recovery of smell*

From the random effects distribution‐free summary survival curves, 74.1% (95% confidence interval 64.0% to 81.3%) of participants recovered their sense of smell at 30 days, 85.8% (77.6% to 90.9%) at 60 days, 90.0% (83.3% to 94.0%) at 90 days, and 95.7% (89.5% to 98.3%) at 180 days ($I^2$=0.0‐77.2%, $\tau^2$=0.006‐0.050), with a median recovery time of 14.9 days (95% confidence interval 12.7 to 20.3 days) (fig 2). Among four of the included studies that specified the degree of smell recovery,[10 11 41 49] between 12.8% and 30.4% of patients achieved partial recovery and 44.0% to 70.0% achieved full recovery at follow‐up.

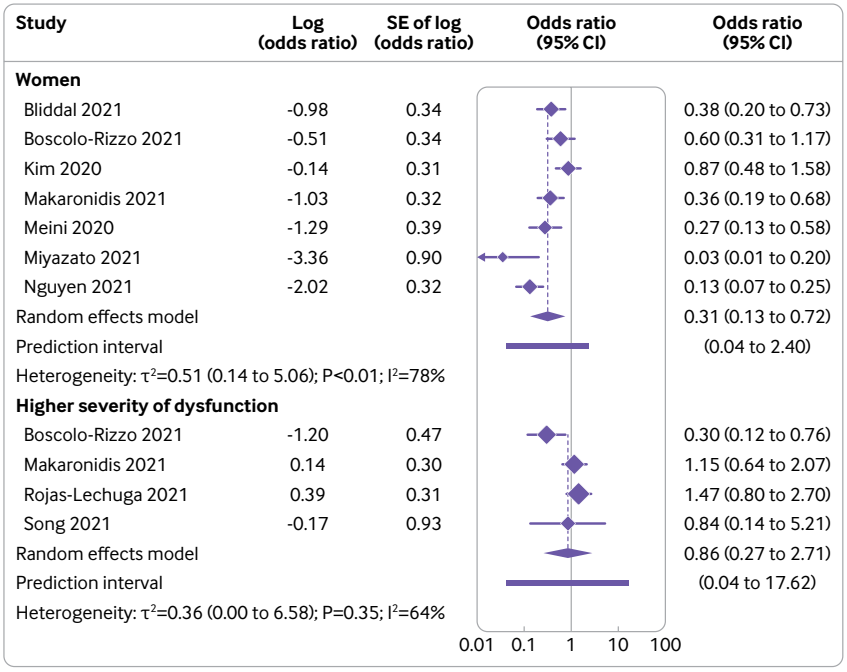


**Fig 5 | Conventional aggregate data two stage meta‐analysis of various prognostic factors in association with the odds of recovery. Stretched purple diamonds are the pooled proportion with confidence intervals (CIs) for each random effects meta‐analysis; symmetrical purple diamonds with horizontal lines are the study estimate with CIs, where diamond sizes reflect the relative weight apportioned to studies in the meta‐analysis. Supplementary tables S7 and S8 show these studies, with complete references. The restricted maximum likelihood estimator was used to estimate $\tau^2$, and the Hartung‐Knapp adjustment was applied to test statistics and CIs**

Based on meta‐analysis of logit transformed Weibull non‐mixture cure fractions, about 5.6% (95% confidence interval 2.7% to 11.0%, $I^2$=70%, $\tau^2$=0.756, prediction interval 0.7% to 33.5%) of patients might develop persistent dysfunction of smell (fig 3, see supplementary figure S3A). Funnel plot asymmetry was found (Egger's test, P=0.031) (see supplementary figure S4A), and after trim‐and‐fill adjustment for asymmetry the pooled proportion increased to 11.6% (95% confidence interval 5.2% to 23.9%), suggesting that any publication bias would have caused an underestimation of the pooled proportion of patients with persistent dysfunction. Sensitivity analysis with mixture cure models yielded a similar pooled proportion of 6.6% (95% confidence interval 3.5% to 12.0%) (see supplementary figure S5A).

*Recovery of taste*

Recovery of taste (fig 2) occurred in 78.8% (95% confidence interval 70.5% to 84.7%) of patients at 30 days, 87.7% (82.0% to 91.6%) at 60 days, 90.3% (83.5% to 94.3%) at 90 days, and 98.0% (92.2% to 95.5%) at 180 days ($I^2$=16%, $\tau^2$=0.000‐0.015), with median recovery time of 12.4 days (95% confidence interval 10.3 to 16.3 days). Among three of the included studies that specified the degree of taste recovery,[10 41 49] between 8.3% and 30.0% achieved partial recovery and 50.0% to 88.9% achieved full recovery.

Based on random effects meta‐analysis of logit transformed Weibull non‐mixture cure fractions, about 4.4% (95% confidence interval 1.2% to 14.6%, $I^2$=0.0‐72.1%, $\tau^2$=0.684, 95% prediction interval 0.2% to 49.0%) of patients might develop persistent taste dysfunction (fig 3, see supplementary figure S3B). Visual inspection of the funnel plot showed no evidence of asymmetry to suggest small study effects (see supplementary figure S4B). Sensitivity analysis with mixture cure models yielded a slightly higher pooled proportion of 8.2% (95% confidence interval 4.1% to 15.7%) (see supplementary figure S5B).

### Aggregate data systematic review and meta‐analyses

Since the reconstructed IPD meta‐analyses provided only a limited set of prognostic factors, we conducted a systematic review to investigate all prognostic factors associated with the likelihood, duration, and extent of smell and taste recovery in patients post‐covid‐19. A total of 80 prognostic factors for smell and taste recovery were reported in 68 studies, comprising 11 personal characteristics, 20 symptoms, 4 characteristics of smell or taste dysfunction, 7 characteristics of covid‐19 disease, 11 past medical conditions, 16 medical interventions or treatments, and 11 biochemical variables. These findings are summarised first by individual studies (see supplementary table S6) and then by prognostic factors (see supplementary table S7).

BMI, most symptoms (cough, fatigue, rhinorrhoea, sore throat, muscle and joint pains), and medical

comorbidities (cardiovascular disease, diabetes, sinonasal disease) appear to have little correlation with the recovery of smell and taste in covid-19. Dyspnoea and treatment with steroids were associated with smell recovery in several studies. It remains equivocal if biochemical variables can predict recovery, with few isolated studies showing the importance of immunoglobulin levels, neutrophil counts, and platelet counts. The virus variant of SARS-CoV-2 was not reported in association with smell or taste recovery.

### Aggregate data meta-analyses of prognostic factors

Sufficient data were available to perform a conventional two stage meta-analysis of reported unadjusted odds ratios of various factors in association with the likelihood of smell and taste recovery. Fourteen studies reporting 37 estimates were included in meta-analyses (fig 4 and fig 5). Female sex was strongly associated with lower likelihood of recovery of smell (odds ratio 0.52, 95% confidence interval 0.37 to 0.72, seven studies, $I^2$=20%, $\tau^2$=0.0224) and taste (0.31, 0.13 to 0.72, seven studies, $I^2$=78%, $\tau^2$=0.5121). Greater severity of smell dysfunction was associated with lower likelihood of smell recovery (0.48, 0.31 to 0.73, five studies, $I^2$=10%, $\tau^2$<0.0001) but not of taste recovery. Nasal congestion was associated with lower likelihood of smell recovery (0.42, 0.18 to 0.97, three studies, $I^2$=0%, $\tau^2$<0.001). Age (per year increase) and smoking were not associated with smell recovery.

### Quality of evidence

Using the GRADE framework (see supplementary tables S8 and S9), we judged the certainty of evidence for each outcome as high, moderate, or low quality. We found high quality evidence for the descriptive prognosis of smell and taste recovery based on our reconstructed IPD meta-analysis. The evidence for the rate of persistent dysfunction (cure fraction) and for prognostic associations were of moderate to high quality.

## Discussion

Smell and taste disorders tended to be overlooked by clinicians before the covid-19 pandemic, possibly because these senses were considered as unessential for life compared with vision and hearing.[50] As a result of the covid-19 pandemic, patients and doctors may now be aware that these are major problems that could adversely impact quality of life, personal-social functioning, mental health, general health, and safety, long after patients recover from covid-19.

In this meta-analysis of time-to-event data from 3699 patients in 18 studies, an estimated 74%, 86%, 90%, and 96% of patients self-reported smell recovery and 79%, 88%, 90%, and 98% self-reported taste recovery at 30, 60, 90, and 180 days, respectively. On the basis of parametric cure models, persistent smell or taste dysfunction might develop in about 5% of patients. Sensitivity analyses suggest this could be an underestimate. Female sex was associated with poorer recovery of both smell and taste, whereas greater initial severity of dysfunction and nasal congestion were associated with poorer smell recovery only.

### Comparison with other studies

This study used comprehensive, flexible statistical modelling to estimate the recovery curves and the proportion of patients who develop persistent smell and taste dysfunction post-covid-19. We used statistical cure models to investigate recovery from smell and taste dysfunction post-covid-19, and potentially our methods could be expanded to cover other major symptoms.

Our recovery curves are consistent with the findings of recent studies, which suggest that recovery from smell and taste dysfunction mostly occurs early in the course of covid-19.[7 51] More importantly, our cure models are consistent with other studies that explored the point prevalence of persistent dysfunction at long follow-up durations of six months to one year.[22 23 49 52] We had excluded these studies as they did not provide appropriate graphs for reconstruction of IPD for this meta-analysis. These studies reported 9.0% of patients having little or no improvement in sense of smell at six months[52]; and 7.0-8.6% still had functional anosmia or persistent to worsening smell or taste impairment at one year,[22 49] which corresponds with our cure model predictions of 3-11% of patients who develop persistent dysfunction. This provides support for the external validity of our findings and suggests that these patients are less likely to experience recovery. Nonetheless, recovery even after many years remains possible, based on previous studies of post-viral olfactory loss[53]; thus patients with covid-19 should be followed-up over the long term.

The differential recovery rates could be explained by the underlying mechanisms of smell and taste dysfunction post-covid-19. Briefly, conductive barriers can prevent odorants and tastants from reaching receptors, and sensorineural interference can block sensory receptor function or signal transmission to the brain. Sensorineural mechanisms are currently thought to be the predominant mechanism of covid-19 related smell dysfunction,[54 55] although conductive mechanisms have been implicated too.[56] SARS-CoV-2 infects and eliminates most olfactory epithelial support (sustentacular) cells that express angiotensin converting enzyme-2, which leads to olfactory neuron deciliation and necrosis.[55-57] Varying regeneration speed of support cells and sensory neurons, influenced by the degree of inflammation, could explain the delayed smell recovery. Stem cell damage and severe inflammation may also prolong smell dysfunction by slowing the regeneration of olfactory epithelial.[57] For taste dysfunction, binding of SARS-CoV-2 to angiotensin converting enzyme-2 receptors in the salivary glands could impair salivary flow, leading to "conductive" taste dysfunction.[58] Viral binding with oral mucosal cells might trigger inflammation, abnormal cell turnover, and reduced tastebud sensitivity and thus sensorineural taste dysfunction,[58 59] which may have varying regeneration speed. As these hypotheses have

not been explored in association with recovery rates, further mechanistic research is warranted among the different patient subpopulations with rapid recovery or persistent dysfunction.

Although it is unsurprising that higher initial severity of smell dysfunction may prolong recovery, it is not clear why female sex is associated with poorer recovery and is notably consistent with previous reports of post-viral smell dysfunction disproportionately affecting women.[60] One reason could be the better baseline olfaction and gustation in female participants,[61 62] which may result in greater sensitivity to changes and a larger subjective impairment. Biological explanations are also possible, as oestrogen upregulates the expression of angiotensin converting enzyme-2, and the enzyme's gene is located on the X chromosome.[63] These findings suggest that the angiotensin converting enzyme-2 receptor—the binding site of SARS-CoV-2 virus, may have higher expression in women, or may express heterodimers that alter virus binding,[64] thus potentially enhancing viral invasion in women. Furthermore, immune related X linked genes are more activated in the immune cells of women.[64] Although acute inflammation promotes olfactory epithelial regeneration, chronic inflammation is detrimental to recovery.[65 66] These factors could possibly account for the poorer observed recovery in women and should be investigated further. It is also unclear why recovery of taste occurs faster in Asian countries. One possibility is the ethnic differences between continents, which may affect smell or taste perception,[67] as well as susceptibility to SARS-CoV-2 virus.[68] Alternatively, intercontinental genetic variations in SARS-CoV-2 might influence biological mechanisms.[1 68] As many of the included studies did not specify the ethnic distribution of participants, however, further research is required to explain this phenomenon.

Our findings suggest an important burden from persistent smell and taste dysfunctions. Presently it is unknown if these sensory impairments might be associated with long term health related consequences. Smell dysfunction could predict the development of depression[69] and is potentially associated with neurodegenerative disorders, often heralding neurological and cognitive manifestations by several years.[70] Although recent studies of long covid have already reported a substantial burden of brain fog,[71] anxiety, and depression,[72] it remains uncertain if persistent smell dysfunction after covid-19 might prognosticate an increased risk of long term neurological sequelae or neurodegenerative disorders.[13] With more than 550 million people worldwide confirmed as having covid-19 as of July 2022, of whom about 50% report smell or taste dysfunction,[2] just 5.6% and 4.4% of patients with persistent smell and taste dysfunction translates to more than 15 million and 12 million patients with long term smell and taste dysfunctions, respectively. These patients may require further investigation, longitudinal follow-up, and appropriate treatment.

Finally, these findings should also be considered in the light of recent viral mutations. The omicron SARS-CoV-2 variant is associated with a less noticeable reduction in loss of smell and taste compared with the delta and alpha variants.[73] This has contributed to increasing difficulty in detecting omicron using a symptom based testing approach. In particular, one large study found that only 13-16% of patients lost their sense of smell and taste during the period when the omicron variant was dominant, compared with 44% when the delta variant dominated.[73] This may be secondary to alterations in the omicron spike protein,[74] which might result in less effective cell membrane fusion and olfactory host cell entry. Therefore, smell and taste recovery could also follow a different course after an omicron related infection. Although smell and taste dysfunction are less common with omicron, the fourfold transmissibility of omicron compared with the delta variant may still imply a net increase in the prevalence of chemosensory disorders.[75] As we found no relevant studies in our systematic search that stratified recovery according to SARS-CoV-2 variant, this remains an important area of future research.

### Strengths and limitations of this study

The strengths of this study lie in the rigorous prespecified protocol of systematic searching, bias assessment, and quality grading, following international guidelines. Only four studies had a high risk of bias; the conclusions remained unaltered after their exclusion. The use of reconstructed IPD allowed flexible and comprehensive statistical modelling of recovery curves, with little heterogeneity detected. Nonetheless, several limitations should be acknowledged. Firstly, all included studies in the reconstructed IPD meta-analyses relied on self-reported recovery of smell and taste. These senses are closely associated, and often reported as overlapping symptoms[1 76]; possibly because members of the public often use "taste" to describe flavour in food. In biology, flavour is actually a function of retronasal olfaction, whereas taste, or gustation, is the ability to differentiate between sweet, sour, salty, bitter, and umami.[77] Consequently, the prevalence of objectively assessed gustatory deficits may be lower than when self-reported.[77 78] Patient reported recovery may thus be difficult to interpret, as many cases of taste dysfunction might actually be due to impaired olfaction rather than gustation.[77] Similar limitations in subjective-objective concordance may exist, albeit to a smaller extent, when evaluating olfaction.[52] In our review, the only included study that compared objective assessments of smell with subjective assessments found that self-reported recovery (defined as 10/10 on a visual analogue scale of smell function) underestimated recovery compared with objective assessments.[44] This difference, however, disappeared when self-reported recovery was defined as 8/10 on the same scale.[44] Other studies found the opposite—that self-report overestimates recovery.[23] This might be relate to the different objective tests used, or imply true clinical variations in prevalence, or that patients are self-reporting cacosmia, phantosmia, and

parosmia, found in up to 43.1% of patients during recovery.[52] Regardless, as the primary aim of this work is to guide doctors in counselling patients with smell and taste dysfunction post-covid-19, we view self-reported outcomes as most reflective of the patient's perspective, and thus most relevant for patient counselling. Secondly, we did not find sufficient data to quantitatively analyse the completeness of recovery nor specific smell and taste dysfunction subtypes (eg, parosmia, cacosmia). These warrant further investigation, as a constant putrid odour is arguably more distressing than the inability to smell. Thirdly, half the included studies were retrospective and potentially subjected to recall bias. Therefore, our findings should be treated with caution and may be updated once further long term prospective data become available. Fourthly, as the pandemic has evolved over time, particularly with respect to vaccines, treatments, lockdowns, masks, and variants, the inherent clinical and methodological heterogeneity of the included studies might limit generalisation. Fifthly, as nearly all the included studies did not account for the competing event of death, the proportions reported in the IPD meta-analyses relate to the probability of recovery for participants who remained alive before the given time. Sixthly, the available aggregate data largely used odds ratios to measure the association; these do not account for the time varying effects shown by our reconstructed IPD meta-analyses. Further work should focus also on summarising adjusted prognostic associations, to assess added prognostic value over and above existing prognostic factors. Finally, the time based results shown in our reconstructed IPD meta-analyses are descriptive of the whole population and not necessarily of any individual patient's recovery course.

## Conclusions

In this meta-analysis with parametric cure modelling of time-to-event data from 3699 patients in 18 studies, we identified a major burden of long term self-reported smell and taste abnormalities, with about 5% of patients developing persistent dysfunction. This outcome might contribute to the growing burden of long covid. Women were less likely to recover their sense of smell and taste. Patients with higher initial severity of dysfunction and patients with nasal congestion were also less likely to recover their sense of smell. While most patients are expected to recover their sense of smell or taste within the first three months, a major subpopulation of patients might develop long lasting dysfunction. These patients require timely identification, personalised treatment, and long term follow-up for associated sequelae. Our findings are likely to be of substantial relevance to general doctors and otolaryngologists in the counselling of patients with smell and taste disorders post-covid-19.


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We thank the patients and investigators of the included primary studies for enabling this pooled analysis, Yi Xuen Chai for reviewing our manuscript, and Jun Heng Lor for his mathematical insights. CH is a co-corresponding author (claire.hopkins@gstt.nhs.uk).

**Contributors:** BKJT, RH, and JJZ contributed equally to this work. BKJT conceived the study. BKJT, RH, NKWT, ESHQ, JJZ, YHC, NWYT, and STT designed the study. RH, NKWT, ESHQ, CJWT, and BKJT collected the data. BKJT, JJZ, YHC, NKWT, and NC analysed the data; all authors contributed to data interpretation. BKJT, RH, JJZ, NKWT, ESHQ, and CJWT wrote the manuscript; all authors contributed to critical revision for important intellectual content. STT contributed to overall supervision; all authors provided approval for publication. BKJT, RH, and JJZ are the guarantors. All authors have made important intellectual contributions and have seen and approved the manuscript for submission. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

**Funding:** This study received no specific funding. BKJT is supported by the Singapore Government Public Service Commission Scholarship and SingHealth Medical Student Talent Development Award. CSvB is supported by grant GM103554 from the National Institutes of Health.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** Not required.

**Data sharing:** Additional data may be obtained from corresponding author STT (toh.song.tar@singhealth.com.sg) on reasonable request.

The manuscriptís guarantors (BKJT, RH, JJZ) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

**Dissemination to participants and related patient and public communities:** The results of the study will be published in a press release and on social media channels.

**Provenance and peer review:** Not commissioned; externally peer reviewed.



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**Supplementary information:** additional material