

Current tobacco smoking and risk from COVID-19: results from a population symptom app in over 2.4 million people – **ONLINE SUPPLEMENT**

Nicholas S Hopkinson^{1*}, Niccolò Rossi^{2*}, Julia S El-Sayed Moustafa², Anthony A Lavery³, Jennifer K Quint¹, Maxim B Freidin², Alessia Visconti², Benjamin Murray⁴, Marc Modat⁴, Sebastien Ourselin⁴, Kerrin Small², Richard Davies⁵, Jonathan Wolf⁵, Tim D Spector², Claire J Steves^{2#} and Mario Falchi^{2#}.

¹National Heart and Lung Institute, Imperial College London

² The Department of Twin Research & Genetic Epidemiology, King's College London

³School of Public Health, Imperial College London

⁴ School of Biomedical Engineering & Imaging Sciences, King's College London

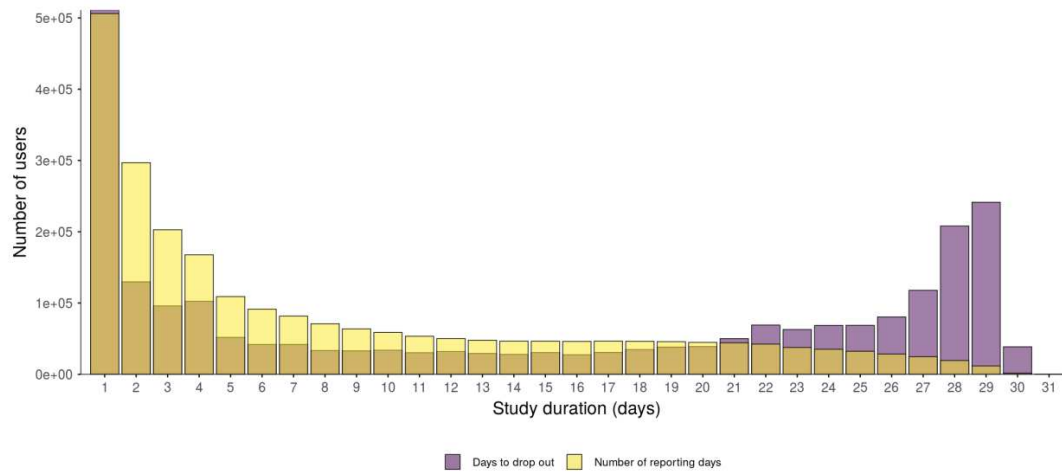
⁵Zoe Global Ltd

*Joint first author

#These authors contributed equally

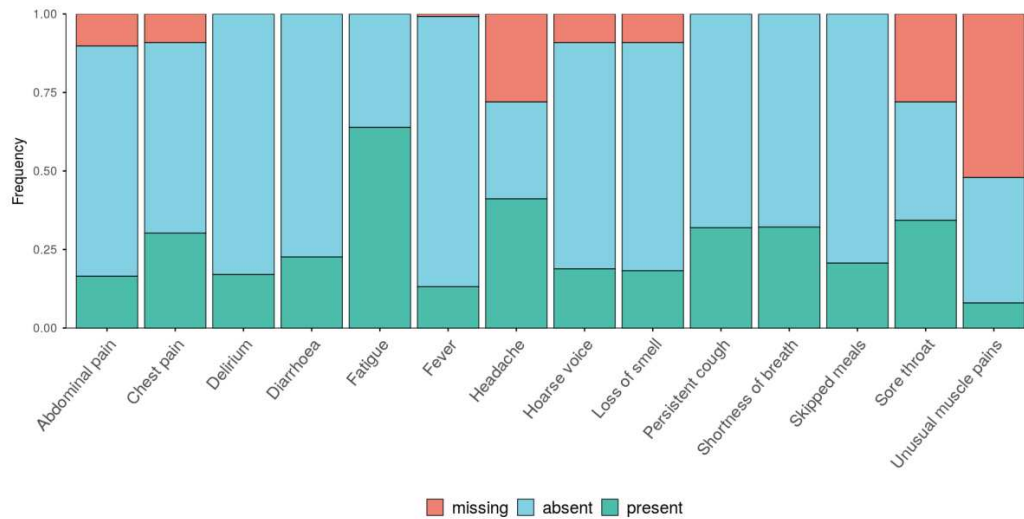
Corresponding authors Dr Nicholas S Hopkinson
Reader in Respiratory Medicine
National Heart and Lung Institute, Imperial College London
Royal Brompton Hospital Campus
Fulham Rd
London SW3 6NP
n.hopkinson@ic.ac.uk
Tel: +44 20 73407775
Fax +44 20 73497778

Dr Mario Falchi
Senior Lecturer
The Department of Twin Research & Genetic Epidemiology
King's College London
St Thomas' Campus,
Lambeth Palace Road,
London
SE1 7EH
mario.falchi@kcl.ac.uk
Tel: +44 (0) 207 188 7188 (ext. 55908)
Fax: +44 (0) 207 188 6761

Supplementary Figure E1. Distribution of per-user number of logins.

The bar plot shows the overall distribution of app users over the entire study duration up to 31 days, between 24th March 2020 and the 23rd of April 2020, according to the number of days they logged in (yellow) and the duration of engagement recorded, expressed as the number of days between first and last day of data entry (purple). The median number of login days was 5 and the median number of days between first and last data entry was 14

Supplementary Figure E2. Prevalence of symptoms among app users reporting that they were unwell.



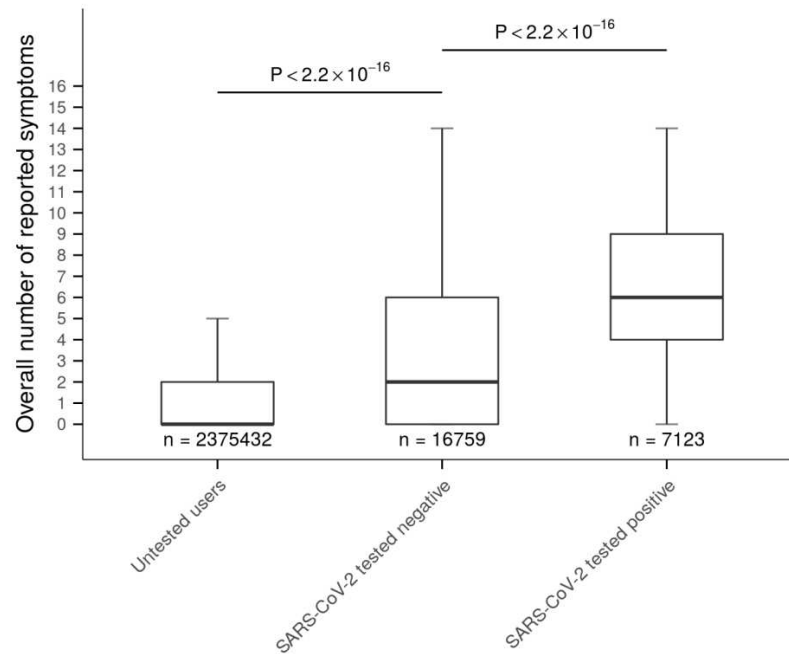
The bar plot shows, for each reported symptom, the fraction of users who reported suffering from the symptom (green) and the fraction of users for whom symptom information was not available (red). For our analyses, where possible symptoms were missing they were treated as absent.

Supplementary Table E1. Sensitivity analysis for missing smoking status. For each test group, the table reports the OR [95% CI] and p-value of the association between smoking status and individual COVID-19 symptoms, adjusted for age, sex and BMI, when subjects with missing smoking status were considered non-smokers (w/o missing) or missing smoking status was treated as such (w missing). Number of individuals (N) tested for association and of non-smokers/smokers is also reported.

	Standard Users		COVID-19 self-reported				SARS-CoV-2 Tested -				SARS-CoV-2 Tested +					
	w/o missing		w missing		w/o missing		w missing		w/o missing		w missing		w/o missing		w missing	
	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P
N	2,039,640		2,038,361		136,693		136,693		15,320		15,300		6,380		6,370	
non-smokers/smokers	1,819,505/220,135		1,818,226/220,135		117,848/18,845		117,848/18,845		13,902/1,418		13,882/1,418		5,908/472		5,898/472	
	[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]	
Abdominal pain	1.35 [1.33-1.38]	8.35x10 ⁻¹⁹⁸	1.35 [1.33-1.38]	2.47x10 ⁻¹⁹⁸	1.43 [1.37-1.50]	7.21x10 ⁻⁵⁷	1.43 [1.37-1.50]	7.21x10 ⁻⁵⁷	1.33 [1.13-1.56]	6.94x10 ⁻⁴	1.33 [1.13-1.56]	6.83x10 ⁻⁴	1.43 [1.15-1.77]	1.07x10 ⁻³	1.43 [1.15-1.77]	1.14x10 ⁻³
Chest pain	1.16 [1.14-1.18]	1.42x10 ⁻⁶³	1.16 [1.14-1.18]	7.72x10 ⁻⁶⁴	1.1 [1.06-1.14]	4.04x10 ⁻⁶	1.10 [1.06-1.14]	4.04x10 ⁻⁶	1.06 [0.92-1.23]	4.06x10 ⁻¹	1.07 [0.92-1.23]	4.02x10 ⁻¹	1.31 [1.07-1.62]	1.08x10 ⁻²	1.31 [1.07-1.62]	1.09x10 ⁻²
Delirium	1.22 [1.20-1.25]	2.12x10 ⁻⁹³	1.22 [1.2-1.25]	1.46x10 ⁻⁹³	1.26 [1.20-1.31]	1.08x10 ⁻²³	1.26 [1.20-1.31]	1.08x10 ⁻²³	1.60 [1.34-1.89]	8.09x10 ⁻⁸	1.59 [1.34-1.89]	8.34x10 ⁻⁸	1.83 [1.47-2.27]	4.38x10 ⁻⁸	1.83 [1.47-2.27]	4.70x10 ⁻⁸
Diarrhoea	1.31 [1.29-1.33]	3.94x10 ⁻²¹⁰	1.31 [1.29-1.33]	1.65x10 ⁻²¹⁰	1.28 [1.23-1.34]	5.59x10 ⁻²⁹	1.28 [1.23-1.34]	5.59x10 ⁻²⁹	1.31 [1.12-1.53]	5.55x10 ⁻⁴	1.31 [1.12-1.53]	5.88x10 ⁻⁴	1.14 [0.92-1.40]	2.34x10 ⁻¹	1.14 [0.92-1.40]	2.37x10 ⁻¹
Fatigue	1.06 [1.05-1.08]	1.75x10 ⁻¹⁵	1.06 [1.05-1.08]	1.39x10 ⁻¹⁵	0.94 [0.90-0.99]	1.40x10 ⁻²	0.94 [0.90-0.99]	1.40x10 ⁻²	1.00 [0.84-1.18]	9.55x10 ⁻¹	0.99 [0.84-1.18]	9.44x10 ⁻¹	0.78 [0.57-1.10]	1.46x10 ⁻¹	0.78 [0.57-1.10]	1.41x10 ⁻¹
Fever	1.01 [0.98-1.03]	6.37x10 ⁻¹	1.01 [0.98-1.03]	6.31x10 ⁻¹	1.01 [0.96-1.06]	8.42x10 ⁻¹	1.01 [0.96-1.06]	8.42x10 ⁻¹	0.87 [0.74-1.02]	8.79x10 ⁻²	0.87 [0.74-1.02]	8.73x10 ⁻²	0.86 [0.70-1.06]	1.54x10 ⁻¹	0.86 [0.70-1.06]	1.51x10 ⁻¹
Headache	1.10 [1.08-1.12]	1.91x10 ⁻²⁵	1.10 [1.08-1.13]	1.32x10 ⁻²⁵	1.30 [1.24-1.36]	2.77x10 ⁻²⁵	1.30 [1.24-1.36]	2.77x10 ⁻²⁵	1.03 [0.87-1.22]	7.23x10 ⁻¹	1.03 [0.87-1.22]	7.37x10 ⁻¹	1.08 [0.83-1.41]	5.89x10 ⁻¹	1.08 [0.83-1.41]	5.84x10 ⁻¹
Hoarse voice	1.06 [1.04-1.08]	8.38x10 ⁻⁸	1.06 [1.04-1.08]	7.55x10 ⁻⁸	1.06 [1.01-1.10]	1.04x10 ⁻²	1.06 [1.01-1.10]	1.04x10 ⁻²	0.95 [0.81-1.12]	5.48x10 ⁻¹	0.95 [0.81-1.12]	5.51x10 ⁻¹	1.19 [0.97-1.46]	1.02x10 ⁻¹	1.19 [0.96-1.46]	1.07x10 ⁻¹
Anosmia	1.07 [1.05-1.09]	6.98x10 ⁻¹¹	1.07 [1.05-1.09]	4.93x10 ⁻¹¹	0.88 [0.85-0.92]	4.82x10 ⁻⁹	0.88 [0.85-0.92]	4.82x10 ⁻⁹	1.18 [0.99-1.39]	5.55x10 ⁻²	1.18 [1.00-1.39]	5.33x10 ⁻²	0.93 [0.74-1.17]	5.32x10 ⁻¹	0.93 [0.75-1.17]	5.34x10 ⁻¹
Persistent cough	1.18 [1.16-1.20]	8.28x10 ⁻⁹⁰	1.18 [1.16-1.20]	5.23x10 ⁻⁹⁰	0.99 [0.95-1.03]	5.31x10 ⁻¹	0.99 [0.95-1.03]	5.31x10 ⁻¹	0.88 [0.76-1.01]	7.27x10 ⁻²	0.88 [0.76-1.01]	7.11x10 ⁻²	0.73 [0.59-0.90]	2.96x10 ⁻³	0.73 [0.59-0.90]	2.87x10 ⁻³
Shortness of breath	1.16 [1.14-1.18]	3.34x10 ⁻⁷¹	1.16 [1.14-1.18]	2.06x10 ⁻⁷¹	1.09 [1.05-1.14]	1.40x10 ⁻⁵	1.09 [1.05-1.14]	1.40x10 ⁻⁵	1.11 [0.96-1.29]	1.40x10 ⁻¹	1.11 [0.96-1.29]	1.44x10 ⁻¹	1.35 [1.09-1.68]	6.53x10 ⁻³	1.35 [1.09-1.68]	6.68x10 ⁻³
Skipped meals	1.76 [1.73-1.79]	<2.23x10 ⁻³⁰⁸	1.76 [1.73-1.79]	<2.23x10 ⁻³⁰⁸	1.52 [1.46-1.59]	4.78x10 ⁻⁸⁸	1.52 [1.46-1.59]	4.78x10 ⁻⁸⁸	1.46 [1.26-1.70]	6.92x10 ⁻⁷	1.46 [1.26-1.70]	6.27x10 ⁻⁷	1.31 [1.06-1.61]	1.15x10 ⁻²	1.31 [1.06-1.61]	1.17x10 ⁻²
Sore throat	0.93 [0.91-0.95]	2.04x10 ⁻¹⁴	0.93 [0.91-0.95]	2.29x10 ⁻¹⁴	1.17 [1.12-1.23]	2.00x10 ⁻¹¹	1.17 [1.12-1.23]	2.00x10 ⁻¹¹	0.90 [0.77-1.06]	2.12x10 ⁻¹	0.90 [0.77-1.06]	2.11x10 ⁻¹	1.32 [1.06-1.65]	1.30x10 ⁻²	1.32 [1.06-1.64]	1.37x10 ⁻²
Unusual muscle pains	1.47 [1.43-1.52]	2.41x10 ⁻¹⁵¹	1.48 [1.43-1.52]	2.61x10 ⁻¹⁵²	1.46 [1.37-1.55]	8.90x10 ⁻³⁰	1.46 [1.37-1.55]	8.90x10 ⁻³⁰	1.24 [1.02-1.50]	3.18x10 ⁻²	1.24 [1.02-1.51]	3.05x10 ⁻²	1.19 [0.94-1.51]	1.40x10 ⁻¹	1.2 [0.95-1.52]	1.34x10 ⁻¹

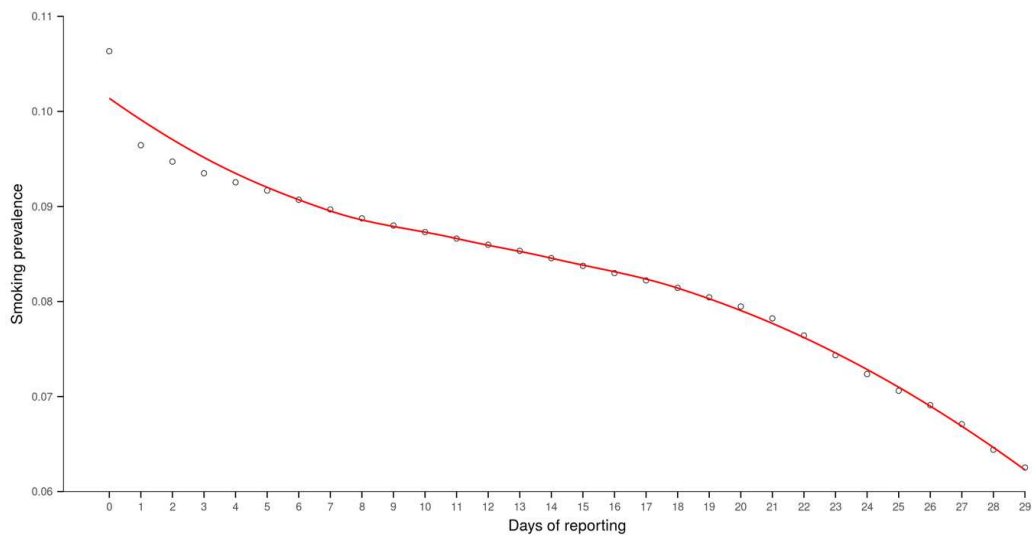
Supplementary Table E2. Sensitivity analysis for ethnicity. For each test group, the table reports the OR [95% CI] and p-value of the association between smoking status and individual COVID-19 symptoms, adjusted for age, sex and BMI, when only subjects with existing ethnicity data are tested and ethnicity is excluded (w/o ethnicity) or included (w ethnicity) as covariate in the model. Number of individuals (N) tested for association and of non-smokers/smokers is also reported.

	Standard Users				COVID-19 self-reported				SARS-CoV-2 Tested -				SARS-CoV-2 Tested +			
	N		non-smokers/smokers		N		non-smokers/smokers		N		non-smokers/smokers		N		non-smokers/smokers	
	w/o ethnicity	w ethnicity	w/o ethnicity	w ethnicity	w/o ethnicity	w ethnicity	w/o ethnicity	w ethnicity	w/o ethnicity	w ethnicity	w/o ethnicity	w ethnicity	w/o ethnicity	w ethnicity	w/o ethnicity	w ethnicity
	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P	OR	P
	[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]		[95% CI]	
Abdominal pain	1.38 [1.20-1.57]	3.63x10 ⁻⁶	1.37 [1.19-1.56]	5.43x10 ⁻⁶	1.59 [1.21-2.07]	8.01x10 ⁻⁴	1.58 [1.20-2.07]	8.82x10 ⁻⁴	1.81 [0.68-4.35]	2.03x10 ⁻¹	2.06 [0.76-5.03]	1.30x10 ⁻¹	2.22 [0.98-4.79]	4.76x10 ⁻²	2.30 [1.01-5.01]	3.98x10 ⁻²
Chest pain	1.19 [1.05-1.35]	6.97x10 ⁻³	1.19 [1.04-1.35]	8.50x10 ⁻³	1.18 [0.93-1.49]	1.64x10 ⁻¹	1.18 [0.93-1.49]	1.60x10 ⁻¹	1.14 [0.54-2.37]	7.18x10 ⁻¹	0.98 [0.44-2.11]	9.64x10 ⁻¹	0.97 [0.43-2.06]	9.37x10 ⁻¹	1.03 [0.46-2.20]	9.39x10 ⁻¹
Delirium	1.31 [1.12-1.52]	5.04x10 ⁻⁴	1.31 [1.13-1.53]	3.85x10 ⁻⁴	1.44 [1.08-1.91]	1.17x10 ⁻²	1.43 [1.07-1.90]	1.33x10 ⁻²	1.36 [0.48-3.38]	5.30x10 ⁻¹	1.56 [0.54-3.96]	3.70x10 ⁻¹	3.00 [1.34-6.49]	5.98x10 ⁻³	3.01 [1.34-6.57]	6.16x10 ⁻³
Diarrhoea	1.54 [1.35-1.75]	4.01x10 ⁻¹¹	1.54 [1.35-1.75]	5.29x10 ⁻¹¹	1.47 [1.11-1.93]	6.69x10 ⁻³	1.47 [1.11-1.93]	6.50x10 ⁻³	1.45 [0.54-3.45]	4.29x10 ⁻¹	1.64 [0.60-4.00]	3.01x10 ⁻¹	0.71 [0.25-1.72]	4.84x10 ⁻¹	0.68 [0.24-1.65]	4.22x10 ⁻¹
Fatigue	1.07 [0.97-1.19]	1.89x10 ⁻¹	1.07 [0.97-1.19]	1.96x10 ⁻¹	0.98 [0.77-1.26]	8.91x10 ⁻¹	0.98 [0.77-1.26]	8.67x10 ⁻¹	0.75 [0.34-1.75]	4.87x10 ⁻¹	0.74 [0.33-1.80]	4.88x10 ⁻¹	0.94 [0.34-3.32]	9.15x10 ⁻¹	0.95 [0.35-3.37]	9.32x10 ⁻¹
Fever	1.08 [0.91-1.28]	3.81x10 ⁻¹	1.09 [0.92-1.30]	3.10x10 ⁻¹	1.11 [0.75-1.62]	5.86x10 ⁻¹	1.13 [0.75-1.64]	5.46x10 ⁻¹	0.27 [0.04-0.96]	8.46x10 ⁻²	0.30 [0.05-1.05]	1.08x10 ⁻¹	0.94 [0.36-2.19]	8.94x10 ⁻¹	0.93 [0.35-2.18]	8.75x10 ⁻¹
Headache	1.08 [0.98-1.20]	1.28x10 ⁻¹	1.09 [0.98-1.21]	1.26x10 ⁻¹	1.30 [1.03-1.63]	2.49x10 ⁻²	1.30 [1.03-1.63]	2.48x10 ⁻²	0.92 [0.43-1.92]	8.22x10 ⁻¹	0.87 [0.40-1.89]	7.31x10 ⁻¹	1.53 [0.70-3.45]	2.93x10 ⁻¹	1.49 [0.68-3.38]	3.22x10 ⁻¹
Hoarse voice	1.05 [0.88-1.25]	5.56x10 ⁻¹	1.05 [0.88-1.25]	5.69x10 ⁻¹	0.80 [0.58-1.09]	1.73x10 ⁻¹	0.80 [0.58-1.09]	1.73x10 ⁻¹	1.16 [0.44-2.71]	7.51x10 ⁻¹	1.34 [0.50-3.19]	5.31x10 ⁻¹	1.55 [0.67-3.34]	2.79x10 ⁻¹	1.54 [0.67-3.33]	2.92x10 ⁻¹
Anosmia	1.32 [1.11-1.57]	1.87x10 ⁻³	1.34 [1.12-1.59]	1.19x10 ⁻³	0.73 [0.55-0.96]	2.57x10 ⁻²	0.73 [0.56-0.96]	2.68x10 ⁻²	1.76 [0.69-4.07]	2.05x10 ⁻¹	2.08 [0.81-4.90]	1.07x10 ⁻¹	1.39 [0.63-3.23]	4.25x10 ⁻¹	1.40 [0.64-3.28]	4.14x10 ⁻¹
Persistent cough	1.21 [1.06-1.37]	3.97x10 ⁻³	1.21 [1.07-1.37]	3.20x10 ⁻³	1.01 [0.80-1.27]	9.34x10 ⁻¹	1.02 [0.80-1.28]	8.92x10 ⁻¹	0.79 [0.37-1.65]	5.41x10 ⁻¹	0.91 [0.42-1.93]	7.99x10 ⁻¹	0.79 [0.37-1.64]	5.25x10 ⁻¹	0.81 [0.38-1.70]	5.86x10 ⁻¹
Shortness of breath	1.22 [1.07-1.38]	2.84x10 ⁻³	1.22 [1.07-1.38]	2.78x10 ⁻³	1.19 [0.95-1.50]	1.27x10 ⁻¹	1.19 [0.95-1.50]	1.29x10 ⁻¹	0.94 [0.43-1.99]	8.80x10 ⁻¹	0.75 [0.32-1.65]	4.84x10 ⁻¹	0.58 [0.27-1.23]	1.63x10 ⁻¹	0.58 [0.27-1.23]	1.65x10 ⁻¹
Skipped meals	2.29 [2.02-2.58]	1.24x10 ⁻⁴⁰	2.28 [2.02-2.58]	3.28x10 ⁻⁴⁰	2.05 [1.61-2.60]	4.39x10 ⁻⁹	2.06 [1.61-2.61]	4.17x10 ⁻⁹	0.95 [0.38-2.14]	9.07x10 ⁻¹	1.04 [0.41-2.39]	9.25x10 ⁻¹	1.54 [0.73-3.21]	2.54x10 ⁻¹	1.56 [0.73-3.27]	2.43x10 ⁻¹
Sore throat	0.91 [0.81-1.02]	9.53x10 ⁻²	0.91 [0.82-1.02]	1.07x10 ⁻¹	1.04 [0.81-1.31]	7.78x10 ⁻¹	1.03 [0.81-1.31]	7.85x10 ⁻¹	0.44 [0.18-1.00]	6.20x10 ⁻²	0.52 [0.21-1.19]	1.39x10 ⁻¹	1.97 [0.91-4.21]	7.99x10 ⁻²	1.93 [0.89-4.13]	9.15x10 ⁻²
Unusual muscle pains	1.25 [1.09-1.44]	1.44x10 ⁻³	1.27 [1.10-1.45]	9.37x10 ⁻⁴	1.67 [1.30-2.13]	5.07x10 ⁻⁵	1.68 [1.31-2.15]	3.98x10 ⁻⁵	1.34 [0.58-2.9]	4.76x10 ⁻¹	1.24 [0.52-2.78]	6.13x10 ⁻¹	0.85 [0.37-1.83]	6.79x10 ⁻¹	0.92 [0.40-1.99]	8.28x10 ⁻¹

Supplementary Figure E3. Symptom burden among tested vs untested users.

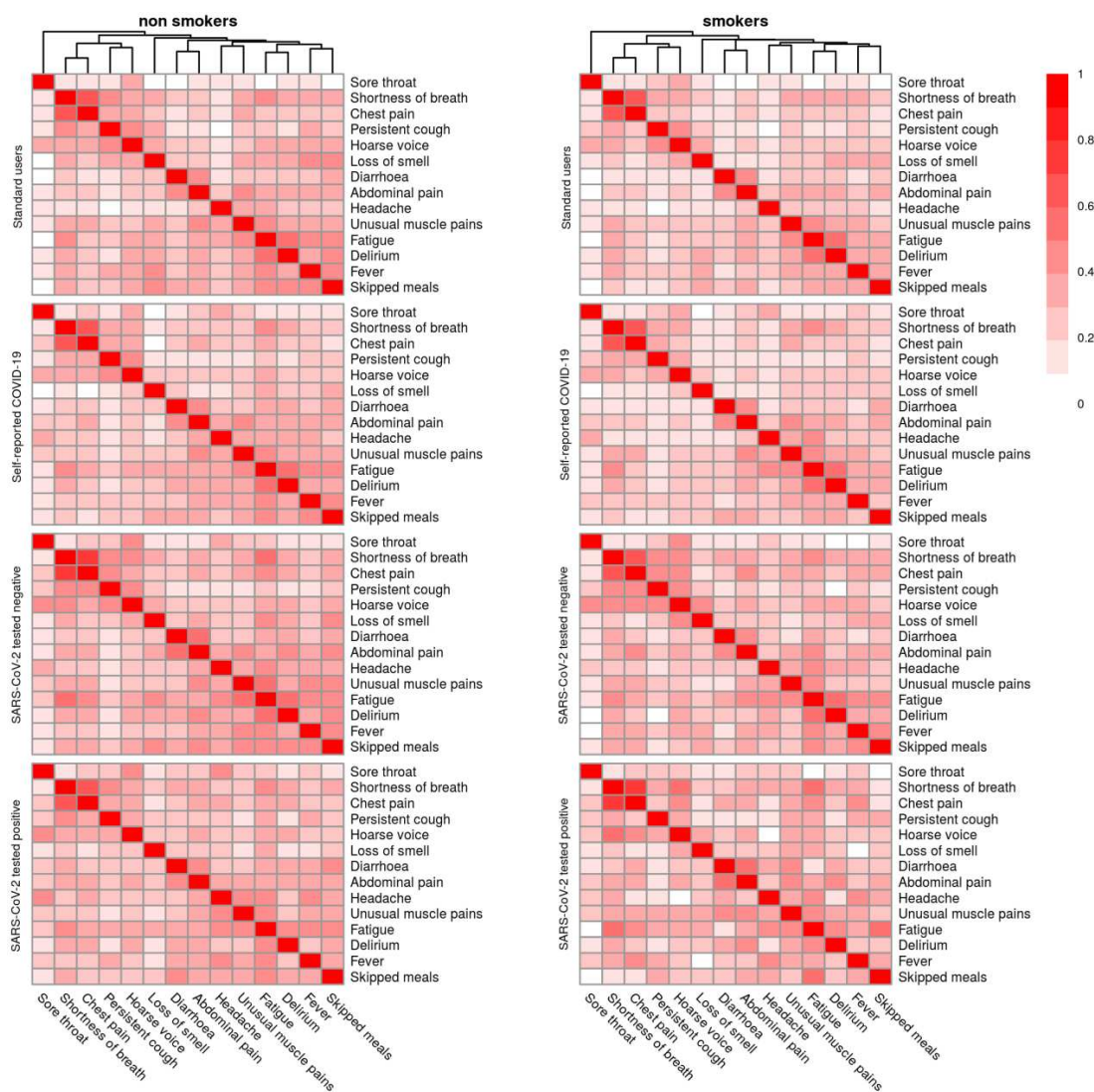
Subjects being tested for SARS-CoV-2 reported a higher symptom burden compared to untested users (Wilcoxon's test $p < 2.2 \times 10^{-16}$). Among tested users, those testing positive for SARS-CoV-2 reported a substantially higher symptom burden compared to subjects who tested negative ($p < 2.2 \times 10^{-16}$).

Supplementary Figure E4. Smokers have shorter durations of engaging with the COVID Symptom Study App.



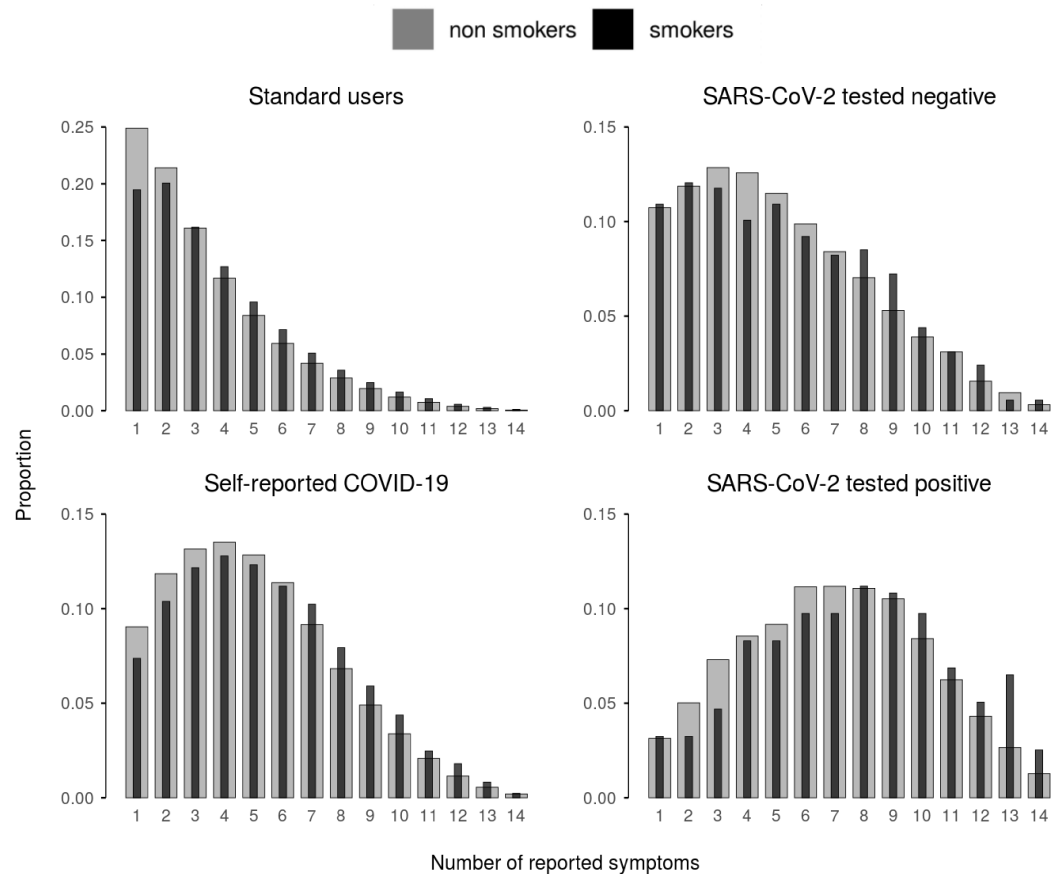
The plot shows the prevalence of smokers in the dataset who had registered before 9th April 2020, (i.e. 14 days before the April 23rd data cut off so that they could have reported for up to 14 day) as a function of time, expressed in days, between first and final time they engaged with the COVID Symptom Study App.

Supplementary Figure E5. Correlation of symptoms in smokers and non-smokers.



For each user category, the heatmaps show patterns of co-occurring COVID-19 symptoms according to smoking status. Each matrix was built based on the polychoric correlation between pairs of symptoms reported by users, and cells are coloured according to the estimated correlation coefficient (correlations close to 0 are displayed in white, while correlations close to 1 are displayed in deep red). Within each user category, smokers and non-smokers show similar pattern of co-occurring symptoms, and their symptoms co-occurrence matrices are highly correlated (lowest Mantel's test $r^2 = 0.54$; $p = 0.001$). This provides evidence that there is not a specific smoking-related pattern of symptom reporting which might be attributable to existing prior symptoms related to smoking itself rather than COVID-19.

Supplementary Figure E6. Effect of current smoking on COVID-19 symptom burden among non-healthcare workers.



For each user category, the bar plot shows the relative abundance of individuals by total number of COVID-19 symptoms reported, among non-smokers (grey) and smokers (black), after excluding healthcare workers. Current smoking was associated with increased overall COVID-19 symptom burden in all categories except the SARS-CoV-2 tested negative group.