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Symptom evolution in individuals with ongoing symptomatic COVID-19 and post-COVID-19 syndrome after SARS-CoV-2 vaccination versus influenza vaccination

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SUMMARY

Background: COVID-19 symptoms may persist beyond acute SARS-CoV-2 infection, as ongoing symptomatic COVID-19 [OSC] (symptom duration 4–12 weeks) and post-COVID syndrome [PCS] (symptom duration ≥12 weeks). Vaccination against SARS-CoV-2 decreases OSC/PCS in individuals subsequently infected with SARS-CoV-2 post-vaccination. Whether vaccination against SARS-CoV-2, or any other vaccinations (such as against influenza) affects symptoms in individuals already experiencing OSC/PCS, more than natural symptom evolution, is unknown.
Method: Using data from the ZOE COVID Symptom Study app, two comparative analyses were carried out, both in prospectively-reporting individuals with OSC/PCS: A) symptoms in individuals receiving first vaccination against SARS-CoV-2, compared with unvaccinated individuals, matched for age, sex, BMI and week of test (n=1679 in each group); B) symptoms in individuals receiving vaccination against influenza, compared with unvaccinated individuals, matched for age, sex, BMI, week of test and number of SARS-CoV-2 vaccinations (n=692 in each group). In both analyses, vaccination date (or equivalent time from start of symptoms in the unvaccinated group) was considered as the index time, and symptom evolution was measured by comparing symptoms during the second week before and second week after vaccination. Symptoms were considered by prevalence and burden over the considered periods; all results were adjusted for multiple comparisons.
Results: After first vaccination against SARS-CoV-2, many symptoms in individuals with OSC/PCS improved more rapidly than natural history resolution, including the commonly reported symptoms of fatigue ($p < 0.0001$, β=−0.9 [95% CI: −1.86; −0.67]) and myalgia ($p < 0.001$, β=−0.3 [95% CI: −0.50; −0.12]). No symptom worsened after vaccination. In contrast, there was no improvement in OSC/PCS symptoms beyond natural history resolution after vaccination against influenza.
Conclusion: In individuals with OSC/PCS, symptom resolution improved after vaccination against SARS-CoV-2 ; this was not observed, however, after other vaccinations.

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Research in Context

Evidence before this study

The PubMed database was searched for articles published from 01/12/2020 until 29/09/2022, with search criteria: "((Long COVID) OR (post-acute) OR (post-COVID) OR (ongoing-symptoms)) AND (vaccination) AND (symptoms)", yielding 320 articles. Based on abstract and the full paper screening, twelve investigated the effect of vaccination on ongoing symptomatic COVID (OSC) and/or Post-COVID-19 syndrome (PCS) symptoms. Of these, eleven showed symptom improvement after vaccination, and one showed no improvement. However, none of these studies analysed the data retrospectively and prospectively in the same study. Furthermore, no studies assessed the effect of the other vaccination (such as influenza vaccination) on ongoing symptoms after COVID-19, in comparison to SARS-CoV-2 vaccination.

Added value of this study

The association between SARS-CoV2 vaccination and symptom experience is controversial: 11 of 12 studies showed symptom improvement, while one study did not. The current study provides granular data regarding symptom change following SARS-CoV2 vaccination; and highlights differences between prospective vs. retrospective data ascertainment.

This is the largest matched cohort study investigation of the effect of SARS-CoV-2 vaccination in individuals with OSC/PCS to date, and the only study addressing this question both prospectively and retrospectively (for the retrospective analysis, please see the supplementary materials appendix A), with some individuals participating in both groups. This is also the first study to investigate the symptom course after other vaccination (influenza) in individuals with OSC/PCS.

Implications of all the available evidence

In individuals with OSC/PCS, common symptoms including fatigue and chest pain improved after SARS-CoV-2 vaccination beyond disease natural evolution. No such response was observed with vaccination against influenza. Very few individuals reported symptom worsening after vaccination. The data suggest that symptom recovery of OSC/PCS post vaccination was specific to vaccination against SARS-CoV-2 , though potential mechanisms remain to be explored.

Introduction

Acute coronavirus disease (COVID-19) caused by SARS-CoV-2 commonly presents with fever, persistent cough, anosmia or dysosmia, fatigue, headache, dyspnoea, and myalgia.[1,2] Most infected individuals recover without medical intervention within a few weeks,[3,4] although elderly individuals, males, and people with some comorbidities (including chronic respiratory disease, cancer, diabetes and cardiovascular disease) are more likely to require hospitalisation and/or die.[5,6]

Some individuals experience otherwise unexplained persistent symptoms after COVID-19, now categorised as ongoing symptomatic COVID-19 [OSC] (symptoms for 4 - 12 weeks) or the post COVID-19 syndrome [PCS] (symptoms for more than 12 weeks).[7,8] Both OSC and PCS can disrupt activities of daily living,[9–11] with dyspnoea, severe fatigue, anosmia and headaches amongst the commonest reported symptoms.[12]

The successful development of vaccines against SARS-CoV-2 infection has reduced mortality and morbidity from COVID-19, including hospitalisation, disease severity, and disease duration,[13,14] with side-effects generally mild and temporary (usually less than 7 days).[15–17] Vaccines against other infections (e.g., pneumococcal vaccine, pneumococcal polysaccharide vaccine, live influenza virus vaccine) can affect symptom experience in chronic conditions such as asthma, with mixed outcomes (improvement or worsening) after vaccination.[18,19] We hypothesised that vaccination against SARS-CoV-2 could similarly alter symptomatology in individuals with OSC/PSC.[20,21]

This study aims to investigate whether vaccination against SARS-CoV-2 affects symptomatology in individuals with OSC/PCS, and, if so, which symptoms. Furthermore, this study aims to investigate whether such effects on OSC/PSC are specific to SARS-CoV-2 vaccination or are also evident after other vaccinations, such as vaccination against influenza.

Method

The dataset was collected using the ZOE COVID Symptom Study app, a mobile application developed by ZOE Limited in collaboration with scientists and physicians at King's College London, Uppsala University, Massachusetts General Hospital and Lund University, which was launched in the UK on 24 March 2020.

Briefly, at registration, app contributors are asked to provide demographic information, including prior medical history. Subsequently they are reminded daily to log their health status, any symptoms, vaccination against SARS-CoV-2, and any testing for infection (plus result). After initial app deployment, the list of assessed symptoms was modified with an eventual list of 29 symptoms asked of all app participants after 4 November 2020. Contributors were also invited sporadically to participate in targeted surveys.

COVID-19 symptoms after vaccination against SARS-CoV-2: matched cohort study analysis using prospectively acquired symptom data

This prospective analysis used app data from all UK individuals (age ≥18 years) reporting at least one positive polymerase chain reaction (PCR) or lateral flow antigen test (LFAT) for SARS-CoV-2, who had logged symptoms regularly (defined as: at least once weekly[22]) during their illness, in whom disease duration could be estimated using previously reported methods,[19] and who experienced symptoms for at least 28 days (i.e., fulfilled OSC or PCS definition[7]). To ensure consistency in symptom reporting, only individuals whose SARS-CoV-2-related illness commenced after 4 November 2020 were included.

As shown in Fig. 1, the current study included individuals with OSC/PCS who were either a) unvaccinated over the course of their app participation, b) vaccinated after their COVID-19-related illness had resolved; or c) vaccinated during their OSC/PCS illness at least 28 days after the start of their COVID-19 related symptoms. Given UK variant prevalence at this time, individuals were assumed to have alpha variant; however, this was not formally tested.

Symptoms in individuals with OCS/PCS were considered within two-time windows: pre-vaccination (−14days to −7days before vaccination) and post-vaccination (+7days to +14days after vaccination) (shown in Supplementary Fig. S1). These time periods were chosen given: a) minimal logging frequency was at least once weekly,[22] and b) side-effects from vaccination typically resolve within one week.[17] Symptom burden was calculated as the number of days that a particular symptom was reported within a given week.

For comparison, symptoms were similarly assessed in individuals with OSC/PCS who were either a) not vaccinated over the course of their app participation; or b) vaccinated after the resolution of their COVID-19-related illness (as symptoms had resolved before vaccination, hence the effect of vaccination on symptoms was not pertinent); or c) vaccinated at a later stage in their illness (at least 6 weeks after start of illness), with symptoms experienced before vaccination considered as control data (shown in Supplementary Fig. S2). Controls were then matched to the vaccinated individuals for age, sex, body mass index (BMI) and week of test [as a proxy-control

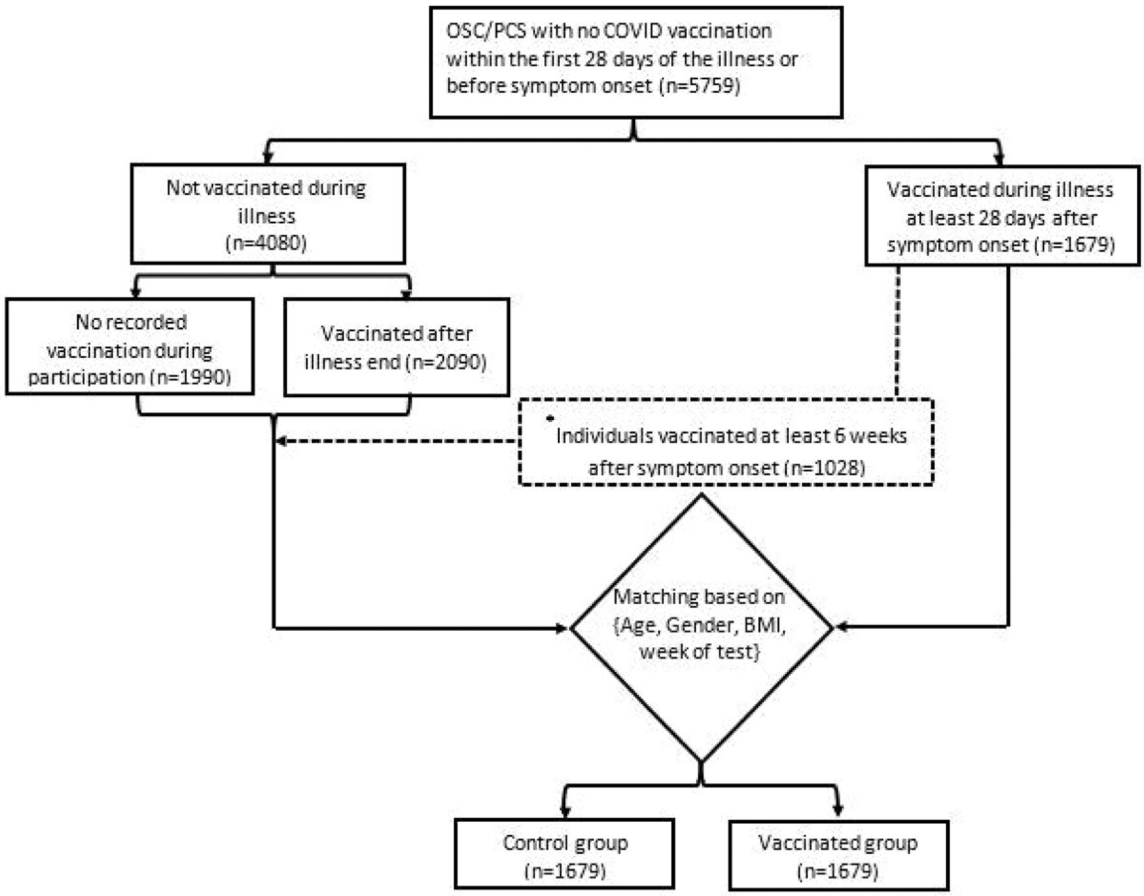

Fig. 1. Participant inclusion flowchart for matched cohort SARS-CoV-2 vaccination analysis. *Indicates individuals whose data were considered as control data until the time of vaccination against SARS-CoV-2, from which time subsequently their data formed part of the vaccinated group (see Supp. Fig S2).

for SARS-CoV-2 variant type] using the Hungarian algorithm with Euclidean distance (linear_sum_assignment function in scipy v1.9.1).

The same time periods, counted from the start of illness, were used for symptom comparisons in vaccinated vs. unvaccinated controls. For example, considering an individual vaccinated on day 28 of their illness: 28 days would be the index time, the pre-vaccination period considered 14–21 days from symptom onset (i.e., −1 to −2 weeks before vaccination date) and the post-vaccination period 35–42 days from symptom onset (i.e. +1 to +2 weeks after vaccination date). These equivalent time periods relative to symptom onset (i.e. 14–21 days and 35–42 days) would be used for symptom consideration in the matched unvaccinated individual, with 28 days from symptom onset the equivalent index date (see Supp. Fig. S1).

Symptoms were also categorised into six groups as follows: 1) Systemic/inflammatory, 2) Cardiorespiratory symptoms, 3) Upper respiratory symptoms, 4) Central neurological symptoms, 5) Immune-related/cutaneous symptoms, and 6) Abdominal symptoms based on clinical input from ELD, CJS and AH (see Supp. Table S1 for symptom groupings).

COVID-19 symptoms after vaccination against influenza: matched cohort study analysis using prospectively acquired symptom data

A similar design was used to consider the effect of influenza vaccination on symptom progression in individuals with OSC/PCS. Influenza vaccination was recorded by the individuals via Zoe app. All individuals with OSC/PCS receiving influenza vaccination at least 28 days after their symptom onset were selected for this analysis (n=692); those receiving influenza and SARS-CoV-2 vaccination simultaneously, or receiving SARS-CoV-2 vaccination between the start of their illness and their influenza vaccination date were excluded. In addition to the above-mentioned matching criteria, the number of SARS-CoV-2 vaccinations received at the time of COVID-19 disease start was also included as a matching criterion. Given UK variant prevalence at the time of the influenza vaccination campaign, individuals were likely to have the delta variant; again, this was not formally tested.

COVID-19 symptoms after SARS-CoV-2 vaccination in individuals who self-identified as OSC/PCS: retrospective analysis

As a sensitivity analysis regarding symptom reporting, data were available from 199 individuals with prospective data who had separately participated in a retrospective symptom survey (for details, please see Supplementary Materials Appendix A).

Statistical analyses

Descriptive statistics

Despite optimal matching for the SARS-CoV-2 and influenza analyses, some residual differences between groups may have remained due in particular to the vaccination roll-out strategy adopted in the UK. Differences were assessed using Wilcoxon paired test for continuous variables and chi-squared test for categorical variables.

Survival analysis

We fitted a model of recovery over time to compare symptom remission during illness between vaccinated (n=1679) and unvaccinated (n=4080) individuals, considering illness duration from symptom onset, assessed by log-rank test.

Table 1
Demographic data for vaccinated and matched control individuals, for the SARS-CoV-2 vaccination analysis.

	Vaccinated group	Control group	p-value
Number of individuals	n = 1679	n = 1679	
Sex (% females)	1181 (69.4%)	1165 (70.3%)	0.9
Age in years:(median, [IQR])	58 [51;66]	56 [49;62]	**< 0.0001**
BMI (median, [IQR])	26.7 [23.8;30.6]	26.3 [23.5;30.2]	0.1
Total illness duration days (median, [IQR])	91 [54;162]	75 [51;138]	**0.001**
Illness duration prior to vaccination in days (median, [IQR])	48 [37;70]	N/A	N/A
Comorbidities			
Cancer (%)	17 (1%)	13(0.8%)	0.5
Diabetes (%)	77 (4.6%)	52 (3.1%)	**0.03**
Lung disease (%)	234 (13.9%)	228 (13.6%)	0.8
Heart disease (%)	82 (4.8%)	53 (3.1%)	0.01
Kidney disease (%)	22 (1.3%)	14 (0.8%)	0.2
Asthma (%)	315 (18.8%)	288 (17.2%)	0.2
Vaccine brand			
AstraZeneca (%)	1115 (66.4%)	N/A	N/A
Pfizer (%)	537 (32.0%)	N/A	N/A
Moderna (%)	27 (1.6%)	N/A	N/A

BMI: body mass index; IQR: interquartile range; N/A: not applicable.
Bold results indicate significant results at p-value < 0.05.

Symptoms after vaccination against SARS-CoV-2

For each symptom, odds of reporting during the pre-vaccination period were compared between vaccinated and control groups using a conditional logistic regression model (using statsmodels version 0.14.0 in python). For those symptoms with no pre-vaccination differences between vaccinated vs. control individuals, post-vaccination presentation was assessed similarly. The false discovery rate (FDR) method was used to adjust p values for multiple testing.

Change in symptom burden (as defined above) was calculated by subtracting pre-vaccination symptom burden from post-vaccination symptom burden. Interpolation was used in case of missing log data. For each symptom, symptom burden during the pre-vaccination period was compared between the vaccinated and control group, using an ordinary least squares (OLS) regression model adjusted for age, sex, BMI, week of test and duration before vaccination. For symptoms with no difference in pre-vaccination burden between vaccinated individuals vs. controls (after adjustment for multiple comparisons), a similar analysis was performed to quantify the change in symptom burden per group.

Change in symptom burden was encoded using the standard deviation in the observed distribution for individuals experiencing the symptom in at least one of the study periods, yielding 3 categories: limited change [−1SD; 1 SD], improved < −1SD, worsened > 1 SD.

Symptoms following vaccination against influenza

Similar analyses were performed when considering the influenza vaccine analysis, the only difference being inclusion of the number of SARS-CoV-2 vaccinations received before COVID19 start as additional covariate.

Concordance analysis

To assess consistency between retrospective and prospective symptom recording, a concordance analysis was conducted of individuals whose data was included in both retrospective and prospective analyses (n=199). Only the 12 symptoms common to both reporting methods were used in this analysis.

Table 2
Symptoms (numbers, percentages) in vaccinated and control individuals, for the SARS-CoV-2 vaccination analysis, for all symptoms reported during the pre-vaccination [−14days to −7days before vaccination] and post-vaccination [+7days to +14days after vaccination] periods for SARS-CoV-2 vaccinated individuals, and equivalent periods in control individuals. Symptoms are sorted by prevalence in the pre-vaccination period. Total number of individuals in each group is 1679. AV: after vaccination; BV: before vaccination.

	Symptom reporting during pre-vaccination period or equivalent time-frame				Symptom reporting during post vaccination period or equivalent time-frame				Change = AV-BV	
Symptom	Vaccinated (SARS-COV-2)		Control		Vaccinated (SARS-COV-2)		Control		Vaccinated (SARS-COV-2)	Control
Fatigue	1492	88.8%	1447	86.1%	879	52.3%	1024	60.9%	−613	−423
Anosmia	1226	73.0%	1187	70.7%	517	30.7%	668	39.7%	−709	−519
Headache	1183	70.4%	1191	70.9%	478	28.4%	506	30.1%	−705	−685
Cough	867	51.6%	800	47.6%	177	10.5%	275	16.3%	−690	−525
Dizziness	837	49.8%	787	46.8%	229	13.6%	256	15.2%	−608	−531
Dyspnoea	730	43.4%	700	41.6%	411	24.4%	499	29.7%	−319	−201
Rhinorrhea	729	43.4%	754	44.9%	177	10.5%	251	14.9%	−552	−503
Lack of appetite	701	41.7%	646	38.4%	78	4.6%	93	5.5%	−623	−553
Myalgia	657	39.1%	629	37.4%	235	14.0%	235	14.0%	−422	−394
Brain fog	656	39.0%	647	38.5%	422	25.1%	443	26.3%	−234	−204
Sneezing	598	35.6%	635	37.8%	144	8.5%	188	11.2%	−454	−447
Low mood	576	34.3%	536	31.9%	235	14.0%	297	17.6%	−341	−239
Sore throat	552	32.8%	562	33.4%	145	8.6%	206	12.2%	−407	−356
Nausea	538	32.0%	476	28.3%	86	5.1%	92	5.4%	−452	−384
Chest pain	536	31.9%	536	31.9%	206	12.2%	293	17.4%	−330	−243
Diarrhoea	495	29.4%	460	27.4%	88	5.2%	97	5.7%	−407	−363
Ophtalmodynia	487	29.0%	488	29.0%	184	10.9%	209	12.4%	−303	−279
Rigors	479	28.5%	393	23.4%	77	4.5%	92	5.4%	−402	−301
Hoarse voice	461	27.4%	443	26.3%	103	6.1%	148	8.8%	−358	−295
Fever	451	26.8%	427	25.4%	35	2.0%	31	1.8%	−416	−396
Tinnitus	413	24.6%	407	24.2%	244	14.5%	274	16.3%	−169	−133
Abdominal pain	367	21.8%	353	21.0%	102	6.0%	126	7.5%	−265	−227
Skin burning	291	17.3%	273	16.2%	85	5.0%	86	5.1%	−206	−187
Delirium	286	17.0%	286	17.0%	89	5.3%	94	5.6%	−197	−192
Earache	265	15.7%	270	16.0%	94	5.6%	95	5.6%	−171	−175
Lymphadenopathy	259	15.4%	284	16.9%	87	5.1%	93	5.5%	−172	−191
Palpitations	233	13.8%	229	13.6%	139	8.2%	170	10.1%	−94	−59
Rash	95	5.6%	89	5.3%	23	1.3%	42	2.5%	−72	−47
Red welts	79	4.7%	61	3.6%	26	1.5%	25	1.4%	−53	−36

Table 3
Change in symptom burden between the post-vaccination [+7days after vaccination; +14days after vaccination] and the pre-vaccination period [−14days before vaccination; −7days before vaccination] in vaccinated individuals, and equivalent periods in control individuals, comparing vaccinated and control groups in the vaccinated compared to the control group, using linear regression model.

Symptoms	Beta [95%CI]	p-value	Effect size
Fatigue	**−0.9 [−1.86; −0.67]**	**< 0.0001**	−7.1
Anosmia	−0.9 [−1.25; −0.73]	0.000	−7.5
Headache	−0.2 [−0.45; 0.002]	0.05	−1.9
Cough	−0.7 [−0.94; −0.49]	0.000	−6.2
Dizziness	−0.4 [−0.65; −0.23]	0.000	−4.1
Dyspnoea	**−0.2 [−0.50; −0.07]**	**0.009**	−2.6
Rhinorrhea	−0.06 [−0.25; 0.12]	0.47	−0.7
Lack of appetite	−0.1 [−0.33; 0.05]	0.16	−1.3
Myalgia	**−0.3 [−0.50; −0.12]**	**0.001**	−3.3
Brain fog	−0.2 [−0.43; −0.001]	0.04	−1.9
Sneezing	−0.02 [−0.18; 0.14]	0.81	−0.2
Low mood	**−0.2 [−0.43; −0.07]**	**0.005**	−2.7
Sore throat	−0.04 [−0.21; 0.12]	0.61	−0.5
Nausea	−0.2 [−0.46; −0.13]	0.000	−3.5
Chest pain	**−0.2 [−0.43; −0.06]**	**0.007**	−2.6
Diarrhoea	**−0.1 [−0.33; −0.05]**	**0.006**	−2.7
Ophtalmodynia	−0.05 [−0.21; 0.11]	0.52	−0.6
Rigors	−0.05 [−0.20; 0.08]	0.44	−0.7
Hoarse voice	−0.07 [−0.24; 0.09]	0.37	−0.8
Fever	0.04 [−0.09; 0.18]	0.53	0.6
Tinnitus	**−0.2 [−0.39; −0.07]**	**0.004**	−2.8
Abdominal pain	−0.1 [−0.29; −0.01]	0.03	−2.1
Skin burning	**−0.1 [−0.28; −0.40]**	**0.006**	−2.7
Delirium	−0.03 [−0.15; 0.08]	0.54	−0.6
Earache	0.06 [−0.05; 0.19]	0.28	1.07
Lymphadenopathy	0.04 [−0.08; 0.17]	0.49	0.6
Palpitations	−0.1 [−0.27; −0.006]	0.04	−2.05
Rash	−0.06 [−0.14; 0.22]	0.14	−1.4
Red welts	−0.03 [−0.10; 0.03]	0.32	−0.9

Negative values imply improvement in the vaccinated vs. control group. Bold font indicates a significant difference between groups after false discovery rate correction (p threshold = 0.022). Symptoms are ranked by prevalence in the pre-vaccination period in subsequently vaccinated individuals.

For each symptom, the balanced accuracy (average between sensitivity and specificity) between retrospective and prospective reports was calculated for each reporting period (pre- and post-vaccination). Presence of a symptom in the pre-vaccination period for retrospective data was assumed if the answer was either (no change, increased, decreased, disappeared) and in the post-vaccination period if the answer was (no change, increased, came back, decreased). From the prospectively recorded data, change in symptom burden was again classified in three categories, using the individuals in the subsample to define the standard deviation-based categories described above.

Tools

Python programming language (version 3.9.7) was used for the analysis with the package statsmodels (version 0.14.0).

Results

COVID-19 symptoms after SARS-CoV-2 vaccination: matched cohort study analysis using prospectively acquired symptom data

Fig. 1 illustrates the participant inclusion flowchart for the SARS-CoV-2 vaccination-matched cohort study while Table 1 presents the demographic characteristics for these individuals (1679 individuals in each group). Despite matching, a significant difference in age was evident, likely due to the UK age-tiered SARS-CoV-2 vaccination delivery. Possibly related to this age difference, and/or due to UK policy directing earlier vaccination in individuals with some illnesses, some comorbidities were more prevalent in the vaccinated group also.

Table 2 presents numbers and percentages of individuals experiencing a given symptom in the pre- and post-vaccination periods for vaccinated individuals, and equivalent periods for controls.

Pre-vaccination, symptoms prevalence in both groups were similar (after correcting for age, sex, BMI, week of test and index date). Likewise, symptom burden was similar in both during the pre-vaccination (or equivalent) period for most symptoms, except for cough, dizziness, nausea and anosmia (after correction for multiple comparisons).

Post-vaccination, multiple symptoms improved in vaccinated individuals, more so than symptom evolution in unvaccinated controls. The odds of experiencing a particular symptom were reduced for thirteen symptoms (fatigue, anosmia, cough, dyspnoea, rhinorrhea, myalgia, brain fog, low mood, sore throat, chest pain, tinnitus, delirium and rash) (see Supp. Table 2). There were no symptoms, for which improvement was greater in the control group vs. the vaccinated group.

Table 3 presents the effect of vaccination on symptom burden over time. Symptom burden improved significantly more in vaccinated individuals in the post-vaccination period compared to the pre-vaccination period (compared with symptom burden for control individuals during equivalent time periods) for eight symptoms, including: fatigue, dyspnoea, myalgia, low mood, chest pain, diarrhoea, tinnitus, and skin burning (p values and effect sizes shown in Table 3). There were no symptoms for which improvement in symptom burden was greater in the control group vs. the vaccinated group.

Fig. 2 shows change in symptoms for vaccinated and control individuals. Symptom improvement was systematically more common in the vaccinated group than in the control group. Similarly, symptom worsening was less common in vaccinated (vs. control) individuals (23 of 29 symptoms), except for 6 symptoms (lack of appetite, brain fog, sneezing, tinnitus, earache and palpitations (see also Supp. Table S3).

COVID-19 symptoms after vaccination against influenza: matched cohort study analysis using prospectively-acquired symptom data

This analysis considered 692 individuals with OSC/PCS who received an influenza vaccination whilst still symptomatic after COVID-19, compared to a 1:1 matched unvaccinated control group (Table 4, see Supp. Fig. S3 for inclusion flowchart).

Table 5 presents numbers and percentages of individuals experiencing a given symptom in the pre- and post-vaccination periods after influenza vaccination, and equivalent time-frame for controls. No differences were evident, in either time period, for any symptoms (neither for prevalence nor for change in symptom burden). See also Supp. Tables S5 and S6.

Survival analysis

Table 6 shows the demographic data for individuals used in the survival analysis.

As shown in Fig. 3, symptom remission was more rapid in SARS-CoV-2-vaccinated individuals compared with controls ($p < 0.005$ by log-rank testing). ($p < 0.005$ by log-rank testing). Note that as required for recruitment into the study, both groups had symptoms present for at least 28 days after illness onset.

Concordance analysis

Table 7 presents the demographic data for the 199 vaccinated individuals contributing to both the prospective and retrospective analyses.

Symptom concordance between retrospective and prospective data appeared slightly stronger in the post-vaccination than in the

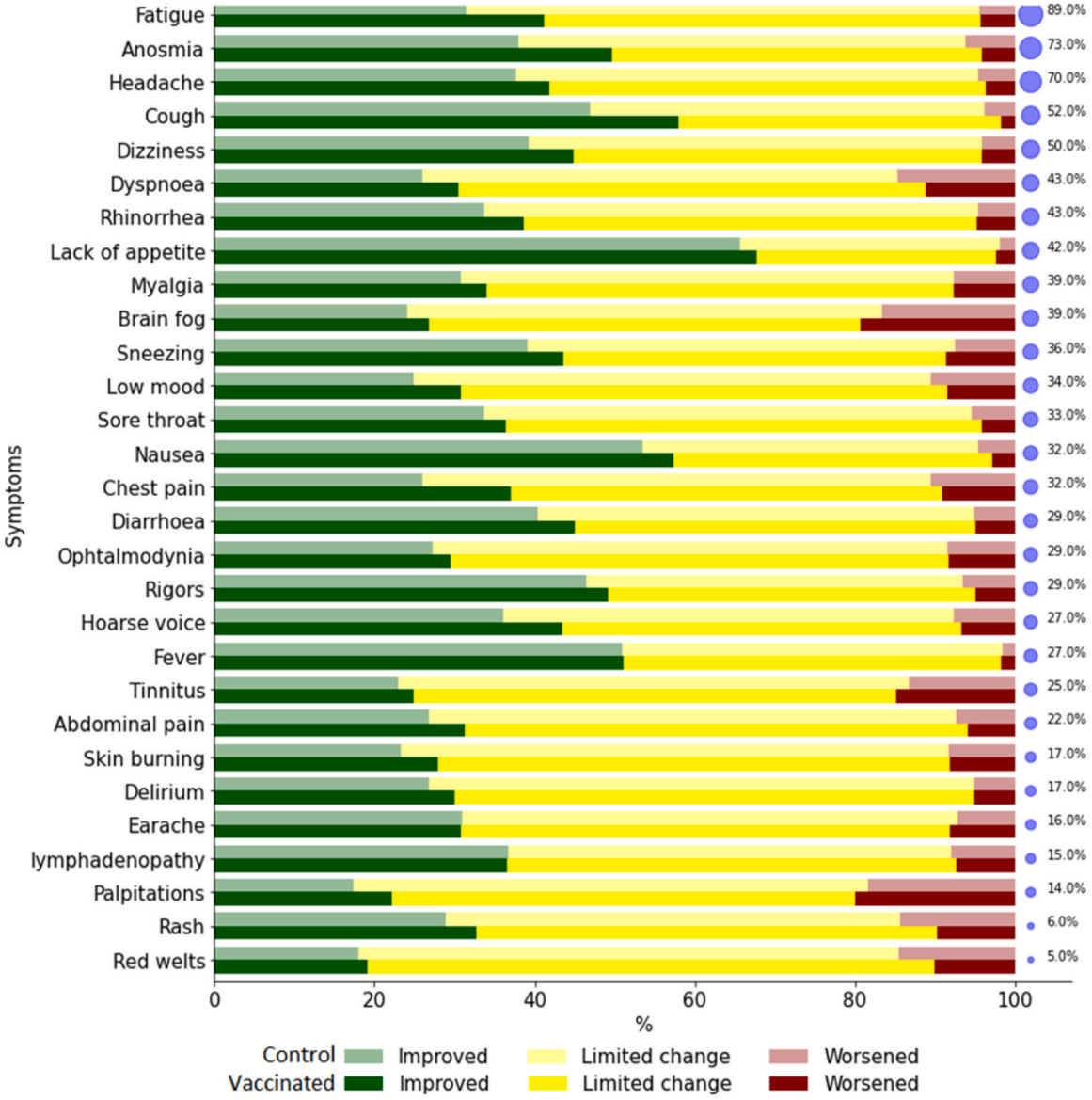

Fig. 2. Change in symptoms in vaccinated and unvaccinated individuals, comparing pre-vaccination [−14days to −7days before vaccination] and post-vaccination [+7days to +14days after vaccination] periods in vaccinated individuals, and equivalent periods in control individuals before and after vaccination in the vaccinated and matched control groups. Symptoms are ordered by decreasing prevalence in the pre-vaccination period, considered in the vaccination group. Categorisation of symptom change is based on the standard deviation in change in burden (see methods for definition).

pre-vaccination period. The balanced accuracy varied from 0.55 (myalgia) to 0.70 (anosmia) in the pre-vaccination period, whilst ranging 0.56 (sore throat) to 0.88 (hoarse voice) in the post-vaccination period (see Supp. Table S8). In the twelve symptoms common to both analyses (shown in Fig. 4), absence of change/limited change was most commonly reported for: fatigue (58.3% prospective vs 50.4% retrospective; chest pain (53.2% prospective vs 59.3% retrospective; hoarse voice (58.3% prospective vs 59.4% retrospective and sore throat (51.8% prospective vs 41.4% retrospective).

Symptoms that improved the most, in both prospective and retrospective symptom reporting, were: cough (71.3% prospective vs 51.6% retrospective), lack of appetite (77.5% prospective vs 45.2% retrospective) and diarrhoea (58.7% prospective vs 37.0% retrospective) (see Supp. Table S9 for details). In the prospective study, more individuals reported symptom improvement than those indicating symptom deterioration, across all symptoms. Similarly, in the retrospective study, more individuals reported symptom improvement than those reporting symptom duration, across all symptoms except myalgia, abdominal pain and fever. However, overall, the proportion in the "worsened" category was substantially higher in the retrospective study, compared to the same symptom in the prospective study.

Discussion

This study investigated symptom evolution in individuals with OSC/PCS, after the first dose of SARS-CoV-2 vaccination and after influenza vaccination, assessed prospectively. Vaccination against SARS-CoV-2 was associated with reduction in key COVID-19 symptoms, both in terms of odds of symptom occurrence, and symptom burden over time, more so than natural resolution of symptoms over time. In particular, symptoms commonly highlighted by people with OSC/PSC, such as fatigue and brain fog, were more likely to recover after SARS-CoV-2 vaccination than in unvaccinated individuals. In contrast, vaccination against influenza was not associated with reduction in key COVID-19 symptoms. However, we recognise that all observational designs are subject to biases (such as selection bias); and *a* priori individual expectations around SARS-CoV-2 vaccination

Table 4
Demographic characteristics of vaccinated and matched control individuals, for the influenza vaccination analysis.

	Vaccinated group	Control group	p-value
Number of individuals	n = 692	n = 692	
Sex (% females)	507 (73.2%)	497 (71.8%)	0.5
Age in years (median, [IQR])	56 [50;63]	56 [49;62]	0.2
BMI (median, [IQR])	26.1 [22.8;29.9]	26.4 [23.3;30.2]	0.2
Total duration days (median, [IQR])	98 [58;175]	79 [54;138]	**0.01**
Duration before vaccination in days (median, [IQR])	46 [35;64]	N/A	N/A
Comorbidities			
Cancer (%)	6 (1.0%)	3 (0.5%)	0.5
Diabetes (%)	24 (3.4%)	22 (3.1%)	0.8
Lung disease (%)	84 (12.1%)	114 (16.4%)	**0.02**
Heart disease (%)	27 (3.9%)	23 (3.3%)	0.6
Kidney disease (%)	12 (1.7%)	8 (1.1%)	0.4
Asthma (%)	128 (18.4%)	149 (21.5%)	0.1
Number of COVID vaccines before Influenza vaccination			
0 dose (%)	6 (1.0%)	31 (4.4)	0.3
1 dose (%)	1 (0.1%)	1 (0.1%)	0.9
2 doses (%)	675 (97.5%)	633 (91.4%)	**< 0.001**
3 doses (%)	10 (1.4%)	27 (3.9%)	**< 0.01**
Variants			
Alpha (%)	0 (0%)	3 (0.5%)	0.2
Delta (%)	692 (100%)	689 (99.5%)	0.2

BMI: body mass index; IQR: interquartile range; N/A: not applicable.
Bold results indicate significant results at p-value < 0.05.

Table 6
Demographic data for individuals in the survival analysis.

	Vaccinated group	Unvaccinated group	p-value
Number of individuals	n = 1679	n = 4080	
Sex (% females)	1181 (69.4%)	2830 (69.3%)	0.4
Age in years: (median, [IQR])	58 [51;66]	55 [47;62]	< 0.0001
BMI (median, [IQR])	26.7 [23.8;30.6]	26.1 [23.3;30.0]	< 0.0001
Vaccine brand			
AstraZeneca (%)	1115 (66.4%)	N/A	N/A
Pfizer (%)	537 (32.0%)	N/A	N/A
Moderna (%)	27 (1.6%)	N/A	N/A

Vaccination here refers to vaccination against SARS-CoV-2, specifically.

and influenza vaccination were unlikely to be the same. These potential biases necessitate cautious interpretation of our results.

Our retrospective assessment also showed symptom improvement overall, and no symptom worsening; however, these results were less impressive. This highlights the effect of recall bias in retrospective population symptom reporting. Further, evaluating symptoms retrospectively might also be affected by "memory-experience gap"[23] - individuals may only notice an improvement above a certain threshold, which may explain starker impression of condition stability in the retrospective survey. Conversely, in a prospective fashion, reporting of non-specific symptoms such as fatigue or brain fog may be more difficult. This calls for careful consideration of symptom experience data collected in PCS/OSC studies – and also highlights the value of our prospective and longitudinal cohort assessment.

Table 5
Symptoms (numbers, percentages) in vaccinated and control individuals, for the influenza vaccination analysis, for all symptoms reported during the pre-vaccination [−14days to −7days before vaccination] and post-vaccination [+7days to +14days after vaccination] periods for influenza-vaccinated individuals, and equivalent periods in control individuals.

	Symptom reporting during pre-vaccination period or equivalent time-frame				Symptom reporting during post vaccination period or equivalent time-frame				Change = AV-BV	
Symptom	Vaccinated (Influenza)		Control		Vaccinated (Influenza)		Control		Vaccinated (Influenza)	Control
Anosmia	592	53.4%	577	52.0%	371	33.4%	373	33.6%	−221	−204
Fatigue	568	51.2%	582	52.5%	313	28.2%	350	31.5%	−255	−232
Headache	446	40.2%	428	38.6%	163	14.7%	162	14.6%	−283	−266
Cough	365	32.9%	366	33.0%	94	8.4%	117	10.5%	−271	−249
Dizziness	305	27.5%	303	27.3%	96	8.6%	84	7.5%	−209	−219
Rhinorrhea	301	27.1%	296	26.7%	103	9.3%	101	9.1%	−198	−195
Brain fog	287	25.9%	276	24.9%	159	14.3%	165	14.8%	−128	−111
Hoarse voice	239	21.5%	246	22.2%	52	4.6%	61	5.5%	−187	−185
Dyspnoea	227	20.4%	235	21.2%	152	13.7%	149	13.4%	−75	−86
Sore throat	215	19.4%	220	19.8%	84	7.5%	97	8.7%	−131	−123
Sneezing	215	19.4%	210	18.9%	73	6.5%	73	6.5%	−142	−137
Ophtalmodynia	191	17.2%	184	16.6%	69	6.2%	56	5.0%	−122	−128
Tinnitus	190	17.1%	189	17.0%	94	8.4%	105	9.4%	−96	−84
Low mood	179	16.1%	195	17.6%	94	8.4%	90	8.1%	−85	−105
Lack of appetite	171	15.4%	185	16.7%	26	2.3%	36	3.2%	−145	−149
Chest pain	149	13.4%	158	14.2%	64	5.7%	60	5.4%	−85	−98
Fever	143	12.9%	152	13.7%	20	1.8%	19	1.7%	−123	−133
Myalgia	142	12.8%	144	13.0%	75	6.7%	67	6.0%	−67	−77
Nausea	128	11.5%	134	12.0%	31	2.8%	36	3.2%	−97	−98
Diarrhoea	128	11.5%	129	11.6%	32	2.8%	37	3.3%	−96	−92
Earache	123	11.1%	127	11.4%	45	4.0%	36	3.2%	−78	−91
Rigors	116	10.4%	117	10.5%	29	2.6%	25	2.2%	−87	−92
Lymphadenopathy	111	10.0%	108	9.7%	43	3.8%	41	3.7%	−68	−67
Delirium	109	9.8%	118	10.6%	34	3.0%	35	3.1%	−75	−83
Abdominal pain	101	9.1%	112	10.1%	39	3.5%	45	4.0%	−62	−67
Palpitations	79	7.1%	81	7.3%	65	5.8%	59	5.3%	−14	−22
Skin burning	68	6.1%	77	6.9%	29	2.6%	37	3.3%	−39	−40
Hair loss	29	2.6%	30	2.7%	25	2.2%	30	2.7%	−4	0
Rash	25	2.2%	20	1.8%	7	0.6%	4	0.3%	−18	−16
Red welts	19	1.7%	22	1.9%	6	0.5%	7	0.6%	−13	−15
Blisters on feet	7	0.6%	7	0.6%	6	0.5%	5	0.4%	−1	−2

Symptoms are sorted by prevalence in the pre-vaccination period. AV: after vaccination; BV: before vaccination.

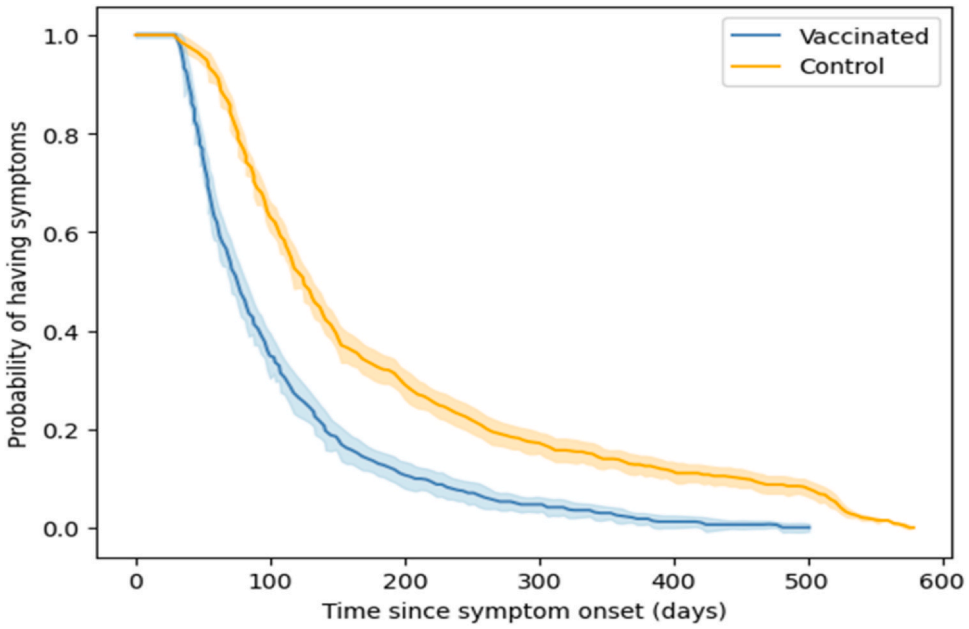

Fig. 3. Probability of ongoing symptoms in vaccinated and unvaccinated individuals with OSC/PCS.

Table 7
Demographic data for individuals included in the concordance analysis.

	Concordance analysis
Number of individuals	n=199
Sex (% females)	149 (74.8%)
Age (years; median, [IQR])	58 [53;65]
BMI (median, [IQR])	27.0 [23.8;30.0]
Duration (Days; median, [IQR])	72 [48,114]
Duration before vaccination (Days; median, [IQR])	38 [33;46]

Our prospective analysis concords with recent studies reporting improvement in fatigue, dyspnoea, and brain fog after vaccination against SARS-CoV-2.[24–28] A recent study by the UK Office for National Statistics of 28,356 vaccinated individuals, assessing the ten most reported symptoms in PCS (weakness, difficulty concentrating, headache, loss of smell, loss of taste, memory confusion, muscle ache, shortness of breath, trouble sleeping and anxiety), found the likelihood of reporting any of these symptoms decreased after vaccination (median follow-up: 141 days after first vaccination).[24] However, vaccination side effects were not excluded in this symptom assessment, as symptoms were considered from the first week after vaccination, noting that symptoms from vaccination and COVID-19 can overlap[17]; moreover, there was no control group in this study. An international study of vaccination in 812 people with OSC/PCS found all investigated symptoms (including fatigue, brain fog, and myalgia) improved after vaccination against SARS-CoV-2, except fever [26]. However, again, without a control group, differentiation between natural disease evolution and vaccination effect could not be distinguished.[26] Another small prospective study of 44 vaccinated and 22 unvaccinated individuals with OSC/PCS found a small improvement in symptoms in the vaccinated group compared to the control group; and no symptom worsening after vaccination.[27]

It is unclear how vaccination might affect symptom experience in individuals with OSC/PCS, noting that the pathophysiology underlying OSC/PSC also remains unexplained. Our data may provide important insights here, in that the absence of symptom improvement after influenza vaccination suggests a specific response to SARS-CoV-2 vaccination per se. This is further supported by recent

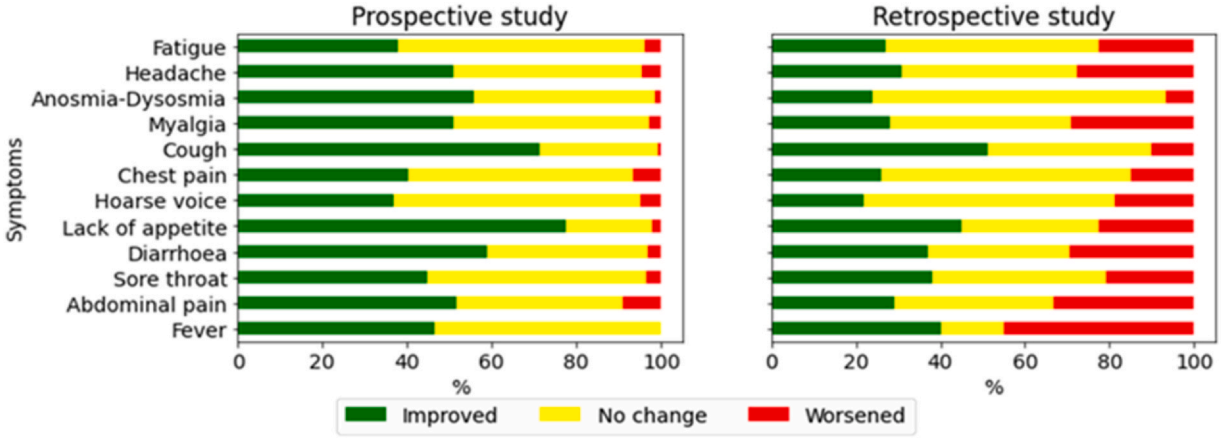

Fig. 4. Reported symptom evolution after vaccination, from 199 individuals who provided both prospective and retrospective symptom reporting. Only the 12 symptoms common to both datasets are shown. Symptoms are ordered by frequency in the retrospective data (see Supp. Table 9).

analysis on symptoms reaction after booster.[29] However, the potential of a placebo effect on symptom resolution must also be acknowledged here, noting that individuals with OSC/PCS may have quite different expectations on outcomes for influenza vs. SARS-CoV-2 vaccination; and the huge psychological effect on the community from wide-scale vaccination roll-out and relaxation of lock-down restrictions. Relevantly, a large nocebo effect was observed regarding vaccine side-effects with SARS-CoV-2 vaccination trials.[30]

The main strengths of the study include our large sample size (the largest such matched cohort study to date), granular prospective symptom recording, and matched cohort study design, allowing for characterisation of, and comparison with, natural symptom evolution. Moreover, uniquely, we were also able to compare symptom responses post-SARS-CoV-2 vaccination vs. post-influenza vaccination. Lastly, our use of a complementary data source, albeit with small numbers, enabled comparison of findings between retrospective and prospective ascertainment.

We recognise the many limitations of our study population and design, which necessarily urge caution in considering our results and their generalisability. Firstly, the app user population from which this current study's cohort was drawn was disproportionally female [69.4%]; and other differences compared to the general population included age, ethnicity, and educational background.[31] In addition, our analyses were limited to UK participants. Secondly, and critically for this particular study, individuals who chose to receive SARS-CoV-2 vaccination may differ systematically from those who did not - for example, due to differing underlying health beliefs, health status, access to healthcare, and/or socioeconomic conditions. Next, only one post-vaccination period was investigated: whilst allowing inclusion of more individuals this decision meant longer-term persistence of symptom improvement/resolution could not be assessed, noting that 22.6% of our cohort stopped logging shortly after vaccination. Further, only the first vaccination dose was considered, and we did not discriminate according to vaccine type. Next, despite matching at recruitment, there were age differences between vaccinated and control individuals, likely due to the age-tiered UK SARS-CoV-2 vaccination campaign. In addition, due to timing of vaccination campaigns against different infections, the influenza vaccination analysis relates mostly to individuals with OSC/PCS following infections with Delta variant, while the SARS-CoV-2 vaccination analysis was conducted in individuals whose illness commenced during the period of Alpha variant dominance. Furthermore, the number of individuals in the influenza vaccination analysis is smaller than the number of individuals in the SARS-CoV-2 vaccination analysis, which might decrease our power to see small effects. Moreover, we could only include individuals who kept logging to the Zoe app to record their symptoms. Mitigating this particular bias, however, we have shown previously that app participation did not differ by symptom persistence.[31] Lastly, placebo/nocebo effect may affect symptom reporting after vaccination[30] and may differ according to targeted organism, particularly in the context of a pandemic with SARS-CoV-2, thus limiting the utility of influenza vaccination data as a positive control. Whilst being transparent regarding these various limitations, we hope these methodological difficulties can be appreciated as inherent when collecting real-world data quickly, and during a pandemic.

Conclusion

This study examined symptom evolution in OSC/PCS individuals after the first vaccination against SARS-CoV-2, and after vaccination against influenza. Many symptoms commonly reported in OSC/PCS improved after SARS-CoV-2 vaccination, beyond natural disease evolution, which improvements appeared specific to vaccination against SARS-CoV-2 and not observed after vaccination against influenza. Additional work is still needed to understand better the biological mechanisms involved.

Data sharing statements

To access the data, a request should be made via the Health Data Research Innovation Gateway (https://web.www.healthdatagateway.org/dataset/fddcb382–3051-4394–8436-b92295f14259). The data collected via COVID Symptom Study app are shared with researchers through the UK National Health Service-funded Health Data Research UK and Secure Anonymised Information Linkage consortium, housed with the UK Secure Research Platform (Swansea, UK). Anonymised data can be shared with researchers for research in the public interest. Researchers need to declare their protocol and can take advantage of ExeTera software to process the database.[32]

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Author contributions

CHS designed the study with input from CJS, ELD, and AH. JCP, CH, CJS, TS and JW contributed to data acquisition design. MA, BM, JCP and CHS contributed to data curation. KR analysed the data and contributed to data visualisation with input from CHS. KR wrote the first draft of the manuscript, with subsequent input from ELD, AH, EM, CJS, and CHS. CHS supervised the study. All authors contributed to data interpretation and to critical review of the manuscript.

Declaration of Competing Interest

T.D. Spector and J.Wolf are co-founders and founder shareholders of ZOE Ltd. C.Hu and J. Capdevila Pujol are employees of ZOE Ltd. C.J. Steves and S.Ourselin have consulted for ZOE Ltd. All other authors declare no conflict of interest

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106406.

References

1. Sudre CH, Lee KA, Lochlainn MN, Varsavsky T, Murray B, Graham MS. *Symptom clusters in COVID-19: a potential clinical prediction tool from the COVID Symptom Study app. Sci Adv* 2021;**7**(12):eabd4177. https://doi.org/10.1126/sciadv.abd4177
2. Raveendran AV, Jayadevan R, Sashidharan S. *Long COVID: an overview [published correction appears in Diabetes Metab Syndr. 2022 May;16(5):102504]. Diabetes Metab Syndr* 2021;**15**(3):869–75. https://doi.org/10.1016/j.dsx.2021.04.007
3. World Health Organization (WHO). Coronavirus; 2022 [online]. Available at: ⟨https://www.who.int/health-topics/coronavirus#tab=tab_1⟩[Accessed 16 September 2022].
4. Hu B, Guo H, Zhou P, Shi ZL. *Characteristics of SARS-CoV-2 and COVID-19 [published correction appears in Nat Rev Microbiol. 2022 May;20(5):315]. Nat Rev Microbiol* 2021;**19**(3):141–54. https://doi.org/10.1038/s41579-020-00459-7
5. British Heart Foundation (BHF). What factors put you at risk from coronavirus? [online]; 2022. Available at: ⟨https://www.bhf.org.uk/informationsupport/heart-matters-magazine/news/coronavirus-and-your-health/what-makes-you-at-risk-from-coronavirus⟩ [Accessed 16 September 2022].
6. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al. *Comorbidity and its impact on patients with COVID-19. SN Compr Clin Med* 2020;**2**(8):1069–76. https://doi.org/10.1007/s42399-020-00363-4
7. National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: managing the long-term effects of COVID-19. [online]; 2022. Available at: ⟨https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-51035515742⟩ [Accessed 16 September 2022].
8. The World Health Organization (WHO). Post COVID-19 condition (Long COVID). [online]; 2021. Available at: ⟨https://www.who.int/srilanka/news/detail/16-10-2021-post-covid-19-condition⟩ [Accessed 16 September 2022].
9. Marshall M. *The lasting misery of coronavirus long-haulers. Nature* 2020;**585**(7825):339–41. https://doi.org/10.1038/d41586-020-02598-6
10. Mehandru S, Merad M. *Pathological sequelae of long-haul COVID. Nat Immunol* 2022;**23**(2):194–202. https://doi.org/10.1038/s41590-021-01104-y
11. Brown K, Yahyouche A, Haroon S, Camaradou J, Turner G. *Long COVID and self-management. Lancet* 2022;**399**(10322):355. https://doi.org/10.1016/S0140-6736(21)02798-7
12. Office for National Statistics (ONS). Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK – Office for National Statistics; 2022. Available at: ⟨https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1april2021⟩ [Accessed 16 September 2022].
13. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. *Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. Lancet Infect Dis* 2022;**22**(1):43–55. https://doi.org/10.1016/S1473-3099(21)00460-6
14. Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. *Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. Lancet* 2022;**399**(10335):1618–24. https://doi.org/10.1016/S0140-6736(22)00327-0
15. Remmel A. COVID vaccines and safety: what the research says. nature; 2022. Available at: ⟨https://doi.org/10.1038/d41586-021-00290-x⟩ [Accessed 16 September 2022].
16. Menni C, Klaser K, May A, Polidori L, Capdevila Pujol J, Louca P, et al. *Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis* 2021;**21**(7):939–49. https://doi.org/10.1016/S1473-3099(21)00224-3
17. Canas LS, Österdahl MF, Deng J, Hu C, Selvachandran S, Polidori L, et al. *Disentangling post-vaccination symptoms from early COVID-19. EClinicalMedicine* 2021;**42**:101212. https://doi.org/10.1016/j.eclinm.2021.101212
18. Lanz AM, Chartrand E, Eisenlohr CP, Lanz MJ. *Can PPSV-23 vaccine impact exacerbations of chronic cough symptoms and medication use in younger adult asthmatics? A clinical question that needs answering. Vaccines* 2022;**10**(2):219. https://doi.org/10.3390/vaccines10020219
19. Zeck R, Solliday N, Kehoe T, Berlin B. *Respiratory effects of live influenza virus vaccine: healthy older subjects and patients with chronic respiratory disease. Am Rev Respir Dis* 1976;**114**(6):1061–7. https://doi.org/10.1164/arrd.1976.114.6.1061
20. Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan F, et al. *Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: a systematic review. EClinicalMedicine* 2022;**53**:101624. https://doi.org/10.1016/j.eclinm.2022.101624
21. Gao P, Liu J, Liu M. *Effect of COVID-19 vaccines on reducing the risk of long COVID in the real world: a systematic review and meta-analysis. Int J Environ Res Public Health* 2022;**19**(19):12422. https://doi.org/10.3390/ijerph191912422
22. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. *Attributes and predictors of long COVID [published correction appears in Nat Med. 2021 Jun;27(6):1116]. Nat Med* 2021;**27**(4):626–31. https://doi.org/10.1038/s41591-021-01292-y
23. Miron-Shatz T, Stone A, Kahneman D. *Memories of yesterday's emotions: does the valence of experience affect the memory-experience gap? Emotion* 2009;**9**(6):885–91. https://doi.org/10.1037/a0017823
24. Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al. *Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study. BMJ* 2022;**377**:e069676. https://doi.org/10.1136/bmj-2021-069676
25. Belluck P. Do Vaccines Protect Against Long Covid?; 2022. The New York Times. Available at: ⟨https://www.nytimes.com/article/long-covid-vaccines.html⟩ [Accessed 16 September 2022].
26. Strain WD, Sherwood O, Banerjee A, Van der Togt V, Hishmeh L, Rossman J. *The impact of COVID vaccination on symptoms of long COVID: an international survey of people with lived experience of long COVID. Vaccines* 2022;**10**(5):652. https://doi.org/10.3390/vaccines10050652
27. Arnold DT, Milne A, Samms E, Stadon L, Maskell N, Hamilton NF. *Are vaccines safe in patients with Long COVID? A prospective observational study.* 03.11.21253225 *medRxiv*2021. https://doi.org/10.1101/2021.03.11.21253225
28. Massey D, Berrent D, Akrami A, Assaf G, Davis H, Harris K, et al. *Change in symptoms and immune response in people with post-acute sequelae of SARS-Cov-2 infection (PASC) after SARS-Cov-2 vaccination. MedRxiv* 2021.
29. Buckner CM, Kardava L, El Merhebi O, Narpala SR, Serebryannyy L, Lin CB, et al. *Interval between prior SARS-CoV-2 infection and booster vaccination impacts magnitude and quality of antibody and B cell responses.* ISSN 0092-8674 *Cell* 2022;**185**(23):4333–46. https://doi.org/10.1016/j.cell.2022.09.032
30. Haas JW, Bender FL, Ballou S, Kelley JW, Wilhelm M, Miller FG, et al. *Frequency of adverse events in the placebo arms of COVID-19 vaccine trials: a systematic review and meta-analysis [published correction appears in JAMA Netw Open. 2022 Feb 1;5(2):e221277]. JAMA Netw Open* 2022;**5**(1):e2143955. https://doi.org/10.1001/jamanetworkopen.2021.43955
31. Sudre CH, Antonelli M, Cheetham NJ, Molteni E, Canas LS, Bowyer V, et al. *Symptoms before and after COVID-19: a population and case-control study using prospective data. Eur Respir J* 2024;**64**(1):2301853. https://doi.org/10.1183/13993003.01853-2023
32. Murray B, Kerfoot E, Chen L, Deng J, Graham MS, Sudre CH, et al. *Accessible data curation and analytics for international-scale citizen science datasets. Sci Data* 2021;**8**(1):297. https://doi.org/10.1038/s41597-021-01071-x