National Institute for Health and Care Excellence

COVID-19 rapid guideline: managing the long-term effects of COVID-19

[K] Evidence reviews for impact of vaccines (update)

NICE guideline NG188

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Guideline version (Final)

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NICE National Institute for Health and Care Excellence

COVID-19 evidence review: Impact of vaccines (update)

Review date: August 2022

Objective

This review aims to provide a summary of the evidence relating to the effectiveness of COVID-19 vaccines against long term effects of COVID19. For completeness, the review considers evidence for vaccinations given before COVID-19 infection and after COVID-19 infection in those people experiencing long term effects.

Review question

A description of the relevant population, intervention, comparison and outcomes for this review was developed by NICE for the topic (see Appendix A for more information). The review question for this evidence review is:

What pharmacological and non-pharmacological interventions (including but not limited to vaccines, olfactory training and breathing techniques) improve the ongoing physical or mental health symptoms and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health, following acute COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

The original NICE recommendations were published in December 2020 and updated in November 2021, based on an evidence review developed by NICE, SIGN and the RCGP. Ongoing surveillance was conducted from publication to identify any new emerging evidence to be considered for inclusion in an update.

Included studies

Continual weekly surveillance searches were used to identify studies for consideration in this update (see appendix B for full details). Relevant references were screened against the protocol using their titles and abstracts and 20 full text references were obtained and assessed for relevance.

In total, 19 studies are included in this updated evidence review, 17 of which are new to this review and 2 of which were in the previous version of the evidence review.

1 study was excluded as at the time of reviewing, the pre-print had been withdrawn. Details of excluded studies are in appendix E.

A summary of the included studies is shown in Table 1 and Table 2

Table 1: Summary of included studies: Vaccination prior to initial COVID-19 infection

Study & Country	Study type	Population	Intervention	Comparator	Outcomes
New at this update Al-Aly 2022 January 2021 to October 2021 USA	Cohort	33,940 people with breakthrough COVID-19 compared to 113,474 people with COVID-19 and no vaccination (mean age 62.82 years; 88.85% male)	Completion of Ad26.COV2.S, mRNA-1273, or BNT162b2 vaccination before the date of their first positive COVID-19 test	Unvaccinated population	Risk of post-acute sequelae Risk of death
New at this update Antonelli 2021 December 2020 to July 2021 UK	Case control	4731 vaccinated adults (37% male; mean age 53 years) from the COVID Symptom Study testing positive for post-vaccination SARS-CoV-2 infection compared to 4731 unvaccinated individuals (mean age 52.6%; 37.3% male).	First and second doses COVID-19 vaccine (not specified)	Unvaccinated population	Symptoms lasting at least 28 days
New at this update Ayoubkhani 2022 Preprint Study dates not reported UK	Cohort	3090 people who were double vaccinated at the time of infection (mean age 49 years, 54.2% male) compared to 3090 people who were unvaccinated (mean age 46.7 years; 53.7% male)	At least two doses of a COVID-19 vaccine (Oxford/AstraZeneca ChAdOx1 nCoV-19 [AZD1222], Pfizer/BioNTech BNT162b2, or Moderna mRNA-1273)	Unvaccinated population	Long Covid symptoms of any severity Activity limiting symptoms

Study & Country	Study type	Population	Intervention	Comparator	Outcomes
New at this update Azzolini 2022 Letter March 2020 to April 2022 Italy	Cohort	229 healthcare workers with Long COVID with previous PCR-confirmed SARS-CoV-2 infection after vaccination compared to an unvaccinated population (mean age 44.3 years; 21.4% male).	BNT162b2 vaccine	Unvaccinated females in wave 1	Probability of Long COVID after 2 doses of vaccines Probability of Long COVID after 3 doses of vaccines
New at this update Kuodi 2022 Preprint July 2021 to Nov 2021 Israel	Cross sectional	634 people who were PCR tested for SARS-CoV-2 infection who had received a COVID-19 vaccine prior to infection compared to 317 who were unvaccinated (30% aged 19-35 years, 49% aged 36-60 years, 21% aged over 60 years; 38% male).	Mainly BNT162b2 mRNA vaccine	Unvaccinated population	Symptoms Recovery from COVID 19
New at this update Simon 2021 Preprint February 2020 to May 2021 USA	Cohort	2392 people who tested positive for COVID 19 and who had a COVID-19 vaccine prior to COVID-19 diagnosis compared to 220,460 who did not have a vaccine (mean age not reported; 40.1% male).	All vaccines approved for use (Pfizer, AstraZeneca, Moderna)	Unvaccinated population	Any symptom >1 symptom

Study & Country	Study type	Population	Intervention	Comparator	Outcomes
New at this update Tannous 2022 Preprint 3 March 2020 to 20 November 2021 USA	Cohort	332 people with breakthrough COVID-19 and Post-Acute Sequelae of SARS-CoV-2 infection (PASC) compared to 5597 with PASC who were unvaccinated (24% aged 18-39 years, 48% aged 40 to 64 years, 28% aged over 65 years; 38% male)	2-doses of mRNA vaccines or a single dose of the Ad26.COV2.S vaccine	Unvaccinated population	Likelihood of developing PASC
New at this update Taquet 2022 January 21 to August 21 USA	Cohort	18,958 individuals (mean age 57 years) with confirmed SARS-CoV-2 infection (mean age 57 years, 40% male)	COVID 19 vaccine (BNT162b2 'Pfizer/BioNTech', mRNA-1273 'Moderna', or Ad26.COV2.S 'Janssen')	Unvaccinated population	Composite of death and any long-COVID feature
New at this update Zisis 2022 21 September to 14 December 2021 USA	Cohort	25,225 people with breakthrough COVID-19 matched to a cohort of unvaccinated people with COVID-19 (mean age 55 years; 40% male).	COVID-19 vaccination unspecified	Unvaccinated population	New symptoms since COVID-19

Table 2: Summary of included studies: Vaccination after initial COVID-19 infection

Study & Country	Study type	Population	Vaccination details	Comparator	Outcomes
Arnold 2021 Dec 2020 to Feb 2021 UK	Case series	78 consecutive patients previously admitted to a single UK hospital with COVID-19 who were symptomatic at 8 months.	At least one dose of a COVID-19 vaccine [Pfizer-BioNTech (BNT162b2) or Oxford-AstraZeneca (ChAdOx1nCoV-19)]	None	Changes in symptoms Quality of life Mental wellbeing
New at this update Ayoubkhani 2021 Preprint February 2021 to September 2021 UK	Cohort	6729 people who were SARS-CoV-2 positive and reported Long Covid symptoms	First and second vaccinations of an adenovirus vector (Oxford/AstraZeneca, ChAdOx1 nCoV-19 [AZD1222]) or mRNA (Pfizer/BioNTech, BNT162b2; Moderna, mRNA-1273) COVID-19 vaccine.	None	Long COVID symptoms of any severity Activity limitation
New at this update Peghin 2022 Preprint May 2021 Italy	Cohort	479 people with previous COVID-19 infection reporting Post-COVID 19 symptoms	132 (27.6%) people vaccinated with COVID-19 vaccine within the 12 month follow up period ChAdOx1 nCoV-19 Oxford–AstraZeneca and Ad26.COV2.S	347 (72.4%) were unvaccinated	Post COVID syndrome worsening or improvement Number of post-COVID symptoms.

Study & Country	Study type	Population	Vaccination details	Comparator	Outcomes
			Janssen COVID-19 vaccine BNT162b2 Pfizer–BioNTech and mRNA-1273 Moderna		
New at this update Scherlinger 2022 August 2021 France	Cross sectional	397 adult patients with symptoms persisting over 4 weeks after confirmed or suspected COVID-19, without any identified alternative diagnosis	At the time of the study, the vaccination scheme was considered complete if the patient reported 2 doses of vaccine or 1 dose of mRNA/ChAdOx1 vaccine	None	Worsening of symptom severity Improvement of symptom severity
New at this update Simon 2021	Cohort	17,796 people vaccinated after SARs-CoV-2 infection	All vaccines approved for use (Pfizer, AstraZeneca, Moderna)	Unvaccinated population	Any symptom
Strain 2022 March 2021 to April 2021 International	Cross-sectional	812 vaccinated adults symptomatic of long term effects from pre-vaccination infection	First dose of a COVID-19 vaccination (vaccines approved for use in UK: AstraZeneca, Pfizer, Moderna)	None	Overall improvement in symptoms Overall deterioration of symptoms Overall no change in symptoms

Study & Country	Study type	Population	Vaccination details	Comparator	Outcomes
					Average improvement of symptoms
New at this update Tran 2021 Preprint November 2020 to May 2021 France	Cohort	910 adults (≥ 18 years old) with a confirmed or suspected COVID-19 infection experiencing symptoms of Long COVID	First dose of ChAdOx1 (Astra Zeneca), BNT162b2 mRNA (Pfizer-BioNTech), Ad26.COV2. S (Johnson & Johnson) or mRNA-1273 (Moderna)	Unvaccinated population	Long Covid scores Remission of all symptoms
New at this update Tsuchida 2022 April 2021 Japan	Case-series	42 people attending a Long COVID outpatient clinic	COVID-19 vaccination (not specified)	None	Post-vaccination symptoms
New at this update Wanga 2021 April 2021 USA	Cross sectional	3135 adults aged ≥18 years with long-term symptoms lasting >4 weeks since COVID-19 onset	COVID-19 vaccination (not specified)	People reporting symptoms who received a negative COVID-19 test.	Reporting that vaccine made symptoms better Reporting that vaccine did not affect symptoms at all

Study & Country	Study type	Population	Vaccination details	Comparator	Outcomes
					Reporting that vaccine made symptoms worse Reporting that symptoms were gone before receiving vaccine
New at this update Wynberg 2022 May 2020 to June 2021 Netherlands	Cohort	186 people with previous SARS-CoV-2 infection who developed PASC symptoms	Two doses (28 days apart) of the BNT162b2 mRNA (Pfizer/BioNTech) vaccine.	Unvaccinated population	Recovery from PASC
New at this update Wisnivesky 2022 August 2021 USA	Cohort	453 people with post-acute sequelae of COVID who were unvaccinated at baseline.	324 (74%) people were vaccinated between baseline and 6 month visit Pfizer, Moderna, or Johnson & Johnson	129 (26%) were not vaccinated	Post-COVID symptoms scores QoL

See appendix F for full evidence tables.

Results

Review question: What pharmacological and non-pharmacological interventions (including but not limited to vaccines, olfactory training and breathing techniques) improve ongoing physical and mental health symptoms and problems of functioning and disability following acute COVID-19?

Vaccination prior to initial COVID-19 infection

Compared to people who are unvaccinated for COVID-19, two doses plus a booster or two doses alone of COVID-19 vaccine given to people prior to SARS-CoV-2 infection may reduce the occurrence of long term effects of COVID-19 at 12 weeks or more from acute onset infection. There is less certainty around the effectiveness of a single dose of COVID-19 vaccine in reducing long term effects of COVID-19 when administered prior to SARS-CoV-2 infection.

What is the evidence informing this conclusion?

Evidence comes from 9 studies (7 cohort studies [Al-Aly 2021; Ayoubkhani 2022, Azzolini 2022, Simon 2021, Tannous 2022, Taquet 2022 and Zisis 2022], 1 case control study [Antonelli 2021] and 1 cross-sectional study [Kuodi 2022]). These studies included participants with a history of SARS-CoV-2 infection after one or two doses of a COVID-19 vaccine compared to people who were unvaccinated at the time of COVID-19 onset.

Publication status

Four studies are only available as preprints (Ayoubkhani 2022, posted to medRxiv on 24 February 2022, Kuodi 2022 posted to medRxiv on 17 January 2022, Simon 2021 posted to medRxiv on 18 November 2021 and Tannous 2022 posted to MedRxiv on 2 July 2022) and have therefore not been peer reviewed.

Summary of included studies

A cohort study (Al-Aly 2022) using the national healthcare databases of the US Department of Veterans Affairs (n=33,940 cases; n=113,474 controls; mean age 62.82 years; 88.85% male) aimed to characterise 6-month risks of incident post-acute sequelae (lasting 30 days or more from diagnosis) in people with breakthrough COVID-19 (the disease that ensues following post-vaccination breakthrough SARS-CoV-2 infection) compared to people with COVID-19 without prior history of vaccination. Main limitations included a predominantly older aged group and male sample, which is not representative of the UK population and an unspecified number of vaccine doses at the time of breakthrough infection.

Using the COVID-19 Infection survey data (CIS), a UK cohort study (Ayoubkhani 2022 preprint) aimed to investigate whether SARS-CoV-2 infection following two doses of a COVID-19 vaccine is associated with a reduction in Long Covid symptoms after 12 weeks, relative to being unvaccinated when infected (n=3,090 cases; n=3,090 controls, mean age 47.85 years; 54% male). Main limitations included not being able to have contemporaneous matching for cases and controls due to questions on Long COVID not being added to CIS until after mass vaccination began in the UK. It was also not possible to investigate participants who received a single dose of vaccine because most people had their second dose within the 12 week follow-up period. The data was also collected before the Omicron variant became widespread in the UK.

A cohort study conducted in the USA (Simon 2021 preprint) used data from patient health records to identity factors influencing the development and progression of long-COVID. They included people who tested positive for COVID-19 who had been vaccinated prior to infection compared to those who had not (n=2392 cases; n=220,460 controls; 40.1% male; mean age not reported). Main limitations included the findings being based on opportunistic availability of large volumes of data where there could be geographic, temporal and socioeconomic gaps that could influence outcomes. The analysis was conducted on data collected prior to the emergence of the delta variant in the USA.

Two other cohort studies conducted in the USA (Taquet 2022 and Zisis 2022) also used data from patient electronic health records through the TriNetX Research Network platform. Both studies included people with confirmed SARS-COV-2 infection after a COVID-19 vaccination compared to those who were unvaccinated (n=9479 vaccinated, n=9479 unvaccinated matched controls; mean age 57 years, 40% male [Taquet 2022]; n= 25,225 cases; 25,225 unvaccinated matched controls; mean age 55 years; 40% male [Zisis 2022]). Main limitations included those who had COVID-19 but were asymptomatic or were untested not being included in the dataset. The studies pre-date Omicron variant dominance and SARS-CoV-2 variant(s) unknown in the populations studied. As both studies used the same source of data, there may be overlap with the findings.

Using longitudinal data obtained from the Houston Methodist COVID-19 Surveillance and Outcomes Registry (CURATOR), a cohort study (Tannous 2022 preprint) evaluated the efficacy of COVID-19 vaccines against Post-Acute Sequelae of SARS-CoV-2 infection (PASC) in people with breakthrough SARS-CoV-2 infection compared to those with PASC who remained unvaccinated (vaccinated PASC n= 332; unvaccinated PASC n=5597; 37.8% male; 28.1% aged ≥65 years; 47.9% aged 40 to 64 years; 23.9% aged 18 to 39 years). Main limitations included data being

limited to a single healthcare system which may impact the generalisability of the findings. Details on SARS-CoV-2 variants were not reported in the study.

A cohort study conducted in Italy (Azzolini 2022; letter) followed healthcare workers with Long COVID who were required to have 3 doses of vaccine BNT162b2 and who had a documented positive result for SARS-CoV-2 between March 2020 and March 2022 (n=229; 21.4% male; mean age 44.3 years). They were compared to a reference group of females in wave 1 of the pandemic who were unvaccinated. Main limitations included that outcomes were self-reported and unclear reporting of the regression analysis. Characteristics and sample sizes of reference group of unvaccinated females in wave 1 were not reported and the regression analysis includes data where vaccines were administered at least 14 days prior to infection therefore it is unclear whether the 176 people who were unvaccinated at the time of infection were included in the analysis.

A UK case-control study (Antonelli 2021) used self- or proxy-reported data from the Zoe app to assess illness duration and symptom profile in individuals with SARS-CoV-2 infection after first or second vaccination compared to unvaccinated individuals (n=4731 case; n=4731 controls; mean age 53 years; 37% male). Main limitations included the app data sample containing disproportionately more women than men and under-represented individuals in more deprived areas and reliance on self-reporting and daily logging.

A cross-sectional study (Kuodi 2022 preprint) used an online survey to collect data from adults (n=634) and determine whether vaccination was associated with the incidence of reporting long-term symptoms after SARS-CoV-2 infection.

Outcomes

Post-acute COVID-19 symptoms

The UK cohort study (Ayoubkhani 2022) found that Long COVID symptoms of any severity and activity limited symptoms were statistically significantly reduced at 12 weeks from acute onset of COVID-19 for people who were double vaccinated prior to SARS-CoV-2 infection compared to those who were not vaccinated (Long COVID symptoms: OR 0.59 95% CI 0.5 to 0.69; n=6180; Activity limited symptoms: OR 0.59 95% CI 0.48 to 0.73).

Similar findings were shown in 3 of the cohort studies conducted in the USA (Al-Aly 2022, Simon 2021, Tannous 2022 and Zisis 2022). Al-Aly 2022 found that the risk of having post-acute sequalae was statistically significantly reduced at 6 months from acute onset of COVID-19 for people with breakthrough COVID-19 (infection after vaccination) compared to those who had infection but were not vaccinated (HR 0.85 95% CI 0.82 to 0.89; n=147,414). Tannous 2022 reported that the likelihood of

developing PASC was statistically significantly reduced in people with breakthrough COVID-19 who had received 2 doses of mRNA vaccines or a single dose of As26.COV2.S vaccine compared to those who were unvaccinated (aOR 0.58 95% CI 0.52 to 0.66; n=5929). Simon 2021 found that reporting any symptom or at least one symptom was statistically significantly reduced at 12 to 20 weeks from acute onset of COVID-19 for people who were vaccinated compared to those who were not vaccinated (Any symptom: OR 0.22 95% CI 0.2 to 0.25; n=243,040; >1 symptom: OR 0.46 95% CI 0.43 to 0.49; n=243,040). Zisis 2022 reported that vaccination prior to SARS-CoV-2 infection significantly reduced the risk of new symptoms since COVID-19 at 28 days and 90 days compared to those who were unvaccinated:

- (28 days Respiratory symptoms RR 0.70 95% CI 0.67 to 0.74; headache RR 0.56 95% CI 0.5 to 0.63; fatigue RR 0.65 95% CI 0.61 to 0.70; body ache RR 0.5 95% CI 0.42 to 0.57 and diarrhoea or constipation RR 0.60 95% CI 0.55 to 0.65)
- (90 days Respiratory symptoms RR 0.54 95% CI 0.50 to 0.57; headache RR 0.39 95% CI 0.34 to 0.45; fatigue RR 0.48 95% CI 0.43 to 0.52; body ache RR 0.34 95% CI 0.28 to 0.42 and diarrhoea or constipation RR 0.44 95% CI 0.40 to 0.49; n= 50,450).

In contrast, another cohort study from the USA, Taquet 2022 reported no difference in the outcome composite of death and any long-COVID feature for vaccinated people with COVID-19 compared to unvaccinated people (HR 1.01 95% CI 0.96 to 1.05; n= 18,958). Number of vaccination doses were not reported in Al-Aly 2022, Simon 2021, Taquet 2022 and Zisis 2022.

The UK case-control study (Antonelli 2021) found that symptoms lasting ≥ 28 days from acute onset of COVID-19 were no different for people with 1 dose of COVID-19 vaccination prior to infection compared to those who were unvaccinated (OR 1.03 95% CI 0.85 to 1.24; n=5241). However, symptoms lasting ≥ 28 days from acute onset of COVID-19 were statistically significantly reduced for people who had received 2 doses of vaccine compared to those who were unvaccinated (OR 0.51 95% CI 0.32 to 0.82; n=1074).

Similarly, the cohort study conducted in Italy on healthcare workers (Azzolini 2022) found that the probability of Long COVID with 2 or 3 vaccine doses given at least 14 days prior to infection was statistically significantly lower when compared to a reference group of unvaccinated females in wave 1 (2 vaccine doses OR 0.25 95% CI 0.07 to 0.87; 3 vaccine doses OR 0.16 95% CI 0.03 to 0.84, n= 229).

The cross-sectional study (Kuodi 2022) found no statistically significant difference for specified symptoms and recovery from COVID-19 at the time of follow-up for those people who had 1 dose of vaccine compared to those that were unvaccinated

(n=657; fatigue: RR 1.06 95% CI 0.82 to 1.36; headache: RR 1.08 95% CI 0.81 to 1.44; weakness in limbs: RR 1.04 95% CI 0.74 to 1.47; persistent muscle pain: RR 1.17 95% CI 0.77 to 1.76; loss of concentration: RR 1.24 95% CI 0.81 to 1.9; hair loss: RR 1.11 95% CI 0.74 to 1.69; sleeping problems: RR 1.35 95% CI 0.86 to 2.11; dizziness: RR 0.87 95% CI 0.54 to 1.4; persistent cough: RR 1.01 95% CI 0.59 to 1.71; shortness of breath: RR 1.08 95% CI 0.65 to 1.81; recovery from COVID-19: RR 1.02 95% CI 0.89 to 1.16;).

In contrast, Kuodi 2022 found that specified symptoms were statistically significantly improved for people with 2 doses of COVID-19 vaccination compared to those who were unvaccinated except for loss of concentration, dizziness and persistent cough and recovery from COVID-19 which remained non-statistically significant (n=611; fatigue: RR 0.36 95% CI 0.19 to 0.71; headache: RR 0.46 95% CI 0.26 to 0.83; weakness in limbs: RR 0.48 95% CI 0.2 to 0.94; persistent muscle pain: RR 0.32 95% CI 0.11 to 0.88; loss of concentration: RR 0.59 95% CI 0.17 to 2.06; hair loss: RR 0.17 95% CI 0.06 to 0.6; sleeping problems: RR 0.53 95% CI 0.18 to 1.61; dizziness: RR 0.26 95% CI 0.09 to 1.79; persistent cough: RR 0.72 95% CI 0.28 to 1.83; shortness of breath: RR 0.23 95% CI 0.07 to 0.84; recovery from COVID-19: RR 0.98 95% CI 0.8 to 1.21).

Risk of death

One cohort study (Al-Aly 2022) found that the risk of death was statistically significantly reduced for people at 6 months from acute onset of COVID-19 with breakthrough COVID-19 (infection after vaccination) compared to those who had infection but were not vaccinated (HR 0.66 95% CI 0.58 to 0.74; n=147,414). Number of vaccination doses were not reported.

Our confidence in the results

All outcomes were considered to be of very low certainty. This was due to none of the studies being randomised and therefore findings of the studies being potentially impacted by confounding variables. Whilst there may have been attempts to minimise confounding bias by adjusting for different variables, there may still be some residual bias. Some studies were also prone to selection bias due to the sources of patient data they used. For example, Al-Aly 2022 used data from the US Department of Veterans Affairs national healthcare databases which meant that the majority of the population were male and relatively older. In contrast, the data sources used in Antonelli 2021 had a predominantly white female demographic. These biases make the data less applicable to the general population. Due to the vaccine schedule, there is likely to be an imbalance in the demographics of who was vaccinated at the time of the study. For example, in the UK, older people and those at high risk were prioritised which may reflect the dominance of vaccinated older people in the studies.

Antonelli 2021 and Kuodi 2021 used self-reported data in their analyses. This type of data is prone to recall bias. As the studies were mainly retrospective and therefore not blinded, there is the risk that people may have been influenced by knowledge that they had or had not received the vaccine in terms of how they reported symptoms. The data in Antonelli 2021 also relied on daily reporting by participants. This may lead to skewed data if those with symptoms were more likely to keep reporting symptoms.

Other factors that contribute to the uncertainty relate to the directness of the evidence. All of the studies used data collected prior to the emergence of Omicron as the dominant variant and 1 study, Simon 2021 used data collected prior to the emergence of the delta variant as the predominant variant. As the effectiveness of vaccines could be impacted by different variants, this could be an important variable in the effectiveness of the vaccine to reduce the risk of developing any long term effects from subsequent SARS-CoV-2 infections. The studies also noted that effectiveness could be related to the specific vaccine used but it was not possible to analyse by vaccine given because of inconsistent data collection.

Vaccination after initial COVID-19 infection

There remains uncertainty around the effect of COVID-19 vaccination on symptoms in people experiencing long term effects of COVID-19. The findings of the evidence are mixed with some studies reporting significant improvements in symptoms but others showing no effect on symptoms and sometimes worsening of symptoms. Due to the nature of the studies and confounding variables, it is not possible to confidently attribute the observed findings in the studies to COVID-19 vaccination.

What is the evidence informing this conclusion?

Evidence comes from 11 studies (6 cohort studies [Ayoubkhani 2021, Peghin 2022, Simon 2021, Tran 2021, Wisnivesky 2022 and Wynberg 2022], 3 cross-sectional studies [Scherlinger 2022, Strain 2022 and Wanga 2021] and 2 case series [Arnold 2021 and Tsuchida 2022]).

Publication status

Three studies are only available as preprints Ayoubkhani 2021, posted to medRxiv on 9 December 2021, Simon 2021 posted to medRxiv on 18 November 2021 and Tran 2021 posted to SSRN on 29 September 2021) and have therefore not been peer reviewed.

Summary of included studies

A UK cohort study (Ayoubkahni 2021 preprint) using responses from the COVID infection survey (CIS) and linked National Immunisation Management System (NIMS) records (n=6729; mean age 45.9 years; 44.4% male) aimed to estimate associations between one or two doses of COVID-19 vaccination and long-COVID symptoms in people who had SARS-CoV-2 infection prior to vaccination. Long COVID was defined as symptoms persisting for at least 12 weeks from confirmed or suspected coronavirus infection not explained by any other health condition. Main limitations included there being no comparison group and that the study was observational so causality cannot be inferred. Long-COVID status was self-reported with no formal clinical diagnosis.

A cohort study conducted in the USA (Simon 2021 preprint) used data from patient health records to identity factors influencing the development and progression of long-COVID. Long-COVID cases were classified as those where the patient presented one or more COVID-associated symptoms between 12 and 20 weeks after the initial COVID-19 diagnosis. The study included people who tested positive for COVID-19 who had been vaccinated up to 12 weeks after SARS-COV-2 infection compared to those who had not (n=17,796 cases; n=220,460 controls; 38.7% male; mean age not reported). Main limitations included the findings being based on opportunistic availability of large volumes of data where there could be geographic, temporal and socioeconomic gaps that could influence outcomes. The analysis was conducted on data collected prior to the emergence of the delta variant in the USA.

Another cohort study conducted in Italy (Peghin 2022) used data from a single centre hospital clinical database (n=479) to evaluate vaccination on long-term symptoms of COVID-19 defined as signs and symptoms developed during or following an infection consistent with COVID-19 that continued for more than 12 weeks. The study included adults who were diagnosed with COVID-19 during the first wave. Main limitations included limited generalisability due to data coming from a single study centre and first wave COVID-19 infections only.

A cohort study conducted in France (ComPaRe long COVID; Tran 2021 preprint) included adults (n=455 vaccinated n=455 unvaccinated controls; mean age 47 years 19.5% male) with confirmed or suspected COVID-19 infection experiencing symptoms of Long COVID defined as symptoms persisting more than three weeks past the initial infection. The aim of the study was to evaluate the effect of first COVID-19 vaccine injection among patients with long COVID on the severity and impact of their symptoms. Main limitations included potential unmeasured confounders that could bias results and that the data was collected before the emergence of recent variants of concern.

Similarly, a small cohort study conducted in the Netherlands (RECoVERED; Wynberg 2022) included adults (n=36 vaccinated, n=32 unvaccinated controls; mean age 51 years; 35.5% male) with previous SARS-CoV-2 infection who developed post-acute sequalae of COVID-19 (PASC) symptoms defined as the WHO criteria as reporting at least one COVID-19 symptom that started within one month of overall illness onset and lasted beyond 3 months after illness onset. The study aimed to assess the effect of two doses of vaccine on recovery from PASC symptoms. Main limitations included the potential for residual confounding as participants were not randomised. There was no SARS-CoV-2 negative control group so it is not possible to determine whether symptoms are causally related to the infection as opposed to underlying comorbidities. All participants were infected with wild-type or Alpha SARS-CoV-2 so may not be generalisable to other variants.

A cohort study conducted in the USA (Wisnivesky 2022) included patients enrolled into an institutional Post-COVID-19 Registry at the Mount Sinai Health System (MSHS) in New York City who reported one PASC symptom and were unvaccinated at baseline (n=453; mean age 50 years; 35% male). The study aimed to assess whether vaccination was associated with resolution of or improvement in PASC symptoms at 6 month follow-up. Main limitations included being a non-randomised study so systematic differences between vaccinated and unvaccinated participants cannot be excluded. Different vaccines could be a limitation in determining effect of vaccination on changes in PASC symptoms.

An online survey among French speaking adults recruited through social media platforms (n=397; median age 44 years; 14.1% male) was used to evaluate the impact of two doses of SARS-CoV-2 vaccination on PASC burden (Scherlinger 2022). PASC symptoms were defined as symptoms persisting over 4 weeks following a confirmed or probable COVID-19, without any identified alternative diagnosis. Main limitations included recruitment from social media platforms not being representative of the general PASC population.

An international survey (Strain 2022) that was open to vaccinated adults with current or recent symptoms of long COVID (at the time of vaccination) sourced participants from Long COVID support groups (n=812; 0.4% age 20 years and under, 3.7% 21-30 years, 18.2% 31-40 years, 29.6% 41-50 years. 32.7% 51-60 years, 13% 61-70 years, 2.5% 71 years and over; 19.4% male). Main limitations included the study population being unlikely to be representative of the population as the recruitment was via social media. Participants were predominantly white and female.

Another online survey conducted in the USA (Wanga 2022) compared long-term symptom changes in people after receiving a COVID-19 vaccination in adults with and without a previous COVID-19 infection (with COVID-19 infection n=698, without

COVID-19 infection n=2437; mean age: 39.3 years vs 45.3 years). Main limitations included the study being nonprobability-based which limits its generalisability. The responses to the survey were self-reported and subject to reporting bias.

A case series conducted in the UK (Arnold 2021) included consecutive patients who had previously been admitted to a single hospital with COVID-19 who remained symptomatic at 8 months and who subsequently received a COVID-19 vaccination (n=163, median age 64 years IQR 53-73; 58% male). It aimed to describe quality of life and symptoms after vaccination. Main limitations included a small sample size and the potential for recall bias.

Another case series was conducted in a Long COVID outpatient clinic in Japan (Tsuchida 2022). The aim was to evaluate changes in symptoms after a single COVID-19 vaccination in people who presented with several sequelae symptoms after at least 2 months since the onset of acute COVID-19 (n=52, median age 40 to 50 years; 56% male). Main limitations included being a single centre with a small sample size and the potential for confounding due to some participants already receiving treatment for symptoms.

Outcomes

Changes in symptoms

Studies reported a variation in changes of symptoms following COVID-19 vaccination. The Italian cohort study (Peghin 2022) found that of people with ongoing symptoms 1 year after acute infection who had been vaccinated with at least one dose of COVID-19 vaccine, 87 (65.9%) reported that their symptoms remained unaffected or unchanged compared to 247 (71.2%) of people who were unvaccinated. 30 (22.7%) of vaccinated people reported that their symptoms had worsened compared to 55 (15.8%) of unvaccinated people. Only 15 (11%) of vaccinated people reported that their symptoms had improved compared to 45 (13%) of unvaccinated people. Similarly, a cross-sectional study conducted in the USA (Wanga 2021) found that of participants who had received a positive COVID result and subsequently had at least one dose of vaccine, 28.7% reported that the vaccine made their symptoms better, 26.4% reported that the vaccine had no effect on their symptoms at all and 16.1% reported that the vaccine made symptoms worse. A UK case series reported similar findings (Arnold 2021) in that after at least one dose of COVID vaccine, 113/159 (71.1%) of participants reported that their symptoms were unchanged, 9/159 (5.6%) reported worsening of symptoms and 31/159 (23.2%) reported improvement in their symptoms.

Similarly, a cross-sectional study conducted in France (Scherlinger 2022) found that of participants who had one or two doses of COVID vaccination, 117/380 (31%) reported worsening of symptom severity compared to 83/380 (21.8%) who reported

improvement in symptom severity. An international cross-sectional study (Strain 2022) conducted after one dose of COVID vaccine found that 470/812 (57.2%) participants reported an overall improvement in symptoms compared to 145/812 (17.9%) reporting an overall worsening of symptoms.

The cohort study conducted in the Netherlands (Wynberg 2022) reported no significant difference at 3 months for recovery from PASC for people who had received two doses of COVID vaccine 28 days apart, compared to those who remained unvaccinated (OR 1.57 95% CI 0.46 to 5.84; n = 68).

In contrast, the ComPaRe long COVID study (Tran 2021 preprint) reported that COVID vaccination significantly reduced long COVID symptoms and disease impact on patient lives after 120 days (long COVID symptom tool [ST] MD -1.8 95% CI-2.5 to -1.0; disease impact tool [IT] MD -3.3 95% CI -6.25 to -0.5; n=910). The study also reported that the rate of patients reporting complete remission of symptoms was almost doubled (remission rate HR 1.97 95% CI 1.23 to 3.15; n=910). The number of COVID vaccination doses was not reported.

Long COVID symptoms

A UK cohort study (Ayoubkhani 2021 preprint) reported that the odds of experiencing Long COVID symptoms initially decreased after first vaccination (12.8% decrease 95% CI -18.6% to -6.6%; n=6729) but this was followed by an increase per week until receiving the second dose (0.3 increase 95% CI -0.6% to 1.2%; n=6729). Second vaccination was associated with an initial decrease (8.8% decrease 95% CI -14.1% to -3.1%; n=6729) but this was followed by a decrease of 0.8% 95% CI -1.2% to -0.4% per week. Activity limitation initially decreased after first vaccination (12.3% decrease 95% CI-19.5% to -4.5%; n=4747) followed by an increase of 0.9% (-0.2% to +1.9%) per week until receiving the second dose. Second vaccination was associated with an initial 9.1% decrease (-15.6% to -2.1%; n=4747), followed by a decrease of 0.5% (-1.0% to +0.05%) per week.

The Italian cohort study (Peghin 2022) found that of people who had been vaccinated with at least one dose of COVID-19 vaccine, 73 (55.3%) reported no post-COVID symptoms compared to 180 (51.9%) who were unvaccinated. 44 (33.3%) of people who were vaccinated reported 1 or 2 post-COVID symptoms compared to 107 (30.8%) who were unvaccinated. 8 (6.1%) of people who were vaccinated reported 3 or 4 symptoms compared to 38 (11%) who were unvaccinated. 7 (5.3%) of people who were vaccinated reported 5 or more symptoms compared to 22 (6.3%) who were unvaccinated.

A cohort study conducted in the USA (Simon 2021) found that reporting any symptom was statistically significantly reduced at 12 to 20 weeks from acute onset of

COVID-19 for people who were vaccinated 0-12 weeks after COVID diagnosis compared to those who were not vaccinated (Any symptom; Vaccine 0-4 weeks after diagnosis: OR 0.38 95% CI 0.35 to 0.41; Vaccine 4-8 weeks after diagnosis: OR 0.54 95% 0.51 to 0.57; Vaccine 8-12 weeks after diagnosis: OR 0.75 95% CI 0.71 to 0.78; n=243,040). The number of COVID vaccination doses was not reported.

Another cohort study from the USA (Wisnivesky 2022) reported on Post-COVID symptom scores in 324 people who were vaccinated and compared them to 129 unvaccinated people. The study found no significant difference in any reported symptom (anosmia MD -0.02 95% CI -0.35 to 0.31; dyspnoea MD 0.05 95% CI -0.15 to 0.25; cough MD -0.17 95% CI -0.55 to 0.22; depression symptoms MD 0.02 95% -1.18 to 1.22; COVID PTSD symptoms MD 2.53 95% CI -3.06 to 8.12; non-COVID PTSD Symptoms MD -2.53 95% CI -12.11 to 7.04). There was also no significant difference reported for quality of life outcomes (QoL physical function MD -1.16 95% CI -3.35 to 1.02; QoL anxiety MD -0.29 95% CI -2.84 to 2.27; QoL depression MD -1.12 95% CI -3.8 to 1.26; QoL: fatigue MD -1.42 95% CI -4.15 to 1.32; QoL social roles MD -0.17 95% CI -3.18 to 2.83; QoL: sleep MD 1.51 95% CI -0.86 to 3.87; QoL pain MD -0.02 95% CI -2.74 to 2.7).

Our confidence in the results

All outcomes were considered to be of very low certainty. This was due to none of the studies being randomised and therefore findings of the studies being potentially impacted by confounding variables. Whilst there may have been attempts to minimise confounding bias by adjusting for different variables, there may still be some residual bias. Some studies were also prone to selection bias due to the sources of patient data they used. For example, Strain 2022 used data from social media platforms with most respondents identifying as white and female. These biases make the data less applicable to the general population. Due to the vaccine schedule, there is likely to be an imbalance in the demographics of who was vaccinated at the time of the study. For example, in the UK, older people and those at high risk were prioritised which may reflect the dominance of vaccinated older people in the studies. Other factors that can limit generalisability of the findings include where the study was conducted. For example, Peghin 2022 was carried out in a single centre which limits its generalisability. It was not always possible to determine from the studies how long participants had been experiencing the long term effects of COVID-19. This is expected to be varied as people will have had the acute COVID-19 infection at different points, prior to receiving a COVID-19 vaccine. Peghin 2022 and Wynberg 2022 only included people who had COVID-19 in the first wave of the pandemic so may not be generalisable to people who had COVID-19 in later waves, particularly when taking different variants into account.

There was also some level of inconsistency across studies in terms of diagnosing long-term effects of COVID-19. Whilst all studies were broadly using the same definition, only some studies such as Simon 2021 used electronic health record data. Other studies, particularly online surveys, relied on participants in a self-selection process, which could lead to an inconsistent population across the body of evidence.

Some studies used self-reported data in their analyses. This type of data is prone to recall bias. As the studies were mainly retrospective and therefore not blinded, there is the risk that people may have been influenced by knowledge that they had or had not received the vaccine in terms of how they reported symptoms. In addition to this, it remains uncertain whether changes in symptoms can be directly attributed to vaccination, considering the relapsing-remitting nature of symptoms reported by people experiencing long term effects of COVID-19.

Expert panel discussion

This section describes how the expert panel considered the evidence in relation to the recommendations within the guidance.

Benefits and harms

The panel reviewed published evidence and considered expert testimony (Steves 2021) on the safety and therapeutic benefit of COVID-19 vaccines in the context of long term effects of COVID-19. The panel considered that the results from the existing studies were inconclusive and agreed that there remains uncertainty for the outcomes of change in ongoing symptoms, quality of life and mental wellbeing. Considering this, the panel decided that the findings could not justify a positive recommendation for COVID-19 vaccination to treat the long term effects of COVID-19, nor a negative recommendation against this intervention in the absence of evidence of harm.

However, the panel recognised the safety and effectiveness of vaccines in preventing acute infection and the importance of the national COVID-19 vaccination programme to protect all people, particularly those who are at highest risk from serious illness or death from COVID-19 or at risk of transmitting infection. Therefore, the panel emphasised the need to encourage patients with long- term effects of COVID-19 who have not been vaccinated to have the vaccination to reduce the risk of further SARS CoV-2 infection, but to explain that it is not known if vaccines have any effect on ongoing symptomatic COVID-19 or post-COVID-19 syndrome.

In August 2022, the panel were presented with an updated evidence review on COVID-19 vaccinations and the long-term effects of COVID-19. This evidence showed that there is a likely benefit for vaccination to reduce the occurrence of long-term effects of COVID-19 in people who were vaccinated prior to SAR-CoV-2 infection. However, the evidence remained uncertain for the effects of COVID-19 vaccination on symptoms in people experiencing long-term effects of COVID-19. Considering this, the panel agreed that the current recommendation still reflects the evidence base.

Certainty of the evidence

All outcomes were considered to be of very low certainty. This was due to none of the studies being randomised and therefore findings of the studies being potentially impacted by confounding variables. Whilst there may have been attempts to minimise confounding bias by adjusting for different variables, there may still be some residual bias. Some studies were also prone to selection bias due to the sources of patient data they used. These biases make the data less applicable to the general population. Due to the vaccine schedule, there is likely to be an imbalance in the demographics of who was vaccinated at the time of the studies. For example, in the UK, older people and those at high risk were prioritised which may reflect the dominance of vaccinated older people in the studies.

Some studies used self-reported data in their analyses. This type of data is prone to recall bias. As the studies were mainly retrospective and therefore not blinded, there is the risk that people may have been influenced by knowledge that they had or had not received the vaccine in terms of how they reported symptoms. Other factors that contribute to the uncertainty relate to the directness of the evidence. All of the studies used data collected prior to the emergence of Omicron as the dominant variant. As the effectiveness of vaccines could be impacted by different variants, this could be an important variable in the effectiveness of the vaccine to reduce the risk of developing any long term effects from subsequent SARS-CoV-2 infections. The studies also noted that effectiveness could be related to the specific vaccine used but it was not possible to analyse by vaccine given because of inconsistent data collection.

There was also some level of inconsistency across studies in terms of diagnosing long-term effects of COVID-19. Whilst all studies were broadly using the same definition, only some studies used electronic health record data. Other studies, particularly online surveys, relied on participants in a self-selection process, which could lead to an inconsistent population across the body of evidence.

Values and preferences

The panel were not aware of any systematically collected data on peoples' preferences and values, but they identified critical outcomes that would be important for decision making. These included all-cause adverse effects, change in symptoms, quality of life and wellbeing. It is likely that these outcomes would also be of similar importance to patients. In addition, other outcomes including return to usual activities including work, education or leisure, are likely to be of particular importance to patients. These outcomes were not reported in studies.

The panel inferred that, in view of the lack of meaningful benefit for people with long term effects of COVID-19 and the unknown potential for harm, most would not choose vaccination as an intervention for long term effects of COVID-19 but would receive vaccination to prevent further acute infection, given the evidence for the safety and effectiveness of vaccines for their primary purpose of preventing acute COVID-19.

Equity

The panel were not aware of any evidence for vaccines use in long term effects of COVID-19 in children or pregnancy. However, because the overall recommendation is to encourage vaccination in eligible groups for preventing acute disease, it is not expected to cause inequity among any subgroups.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. However, considering the importance of the national vaccination programme and implications for patients not receiving vaccination, use of vaccines in people with long term effects would be acceptable in preventing further acute infection unless there are contraindications.

Feasibility

The panel were not aware of any systematically collected evidence about feasibility. COVID-19 vaccines are approved for use in the UK, so the recommendation supports current practice.

Appendices

Appendix A: PICO table

PICO table

RQ 7: What pharmacological and non-pharmacological interventions (including but not limited to vaccines, olfactory training and breathing techniques) improve the ongoing physical or mental health symptoms and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health, following acute COVID-19?

Criteria	Notes
Population	Adults and children who are experiencing new or ongoing symptoms: • 4-12 weeks from onset of acute COVID-19 illness • 12 weeks from onset of acute COVID-19 illness
Interventions	• Pharmacological interventions e.g. COVID-19 vaccines • Non-pharmacological interventions e.g olfactory training and breathing techniques. For treatment, management (including self-management and rehabilitation) and support
Comparators	Any or no comparator
Outcomes	• Symptom improvement (or worsening) • Mortality • Return to usual activities including work, education or leisure as defined by International classification of function • Resumption of (informal) caring arrangements

	• Quality of life and/or Wellbeing • Adverse events (relating to treatment), e.g. side effects or unintended consequences
Settings	Any

Subgroups	• Groups as defined in the EIA for example, age, sex, ethnicity, including:
	  ○ Children and young people
	• Diagnostic status of acute COVID-19 (e.g. confirmed or high clinical suspicion)
	• Treatment setting for acute COVID-19, including:
	  ○ Hospitalised for acute COVID-19
	  ○ Non-hospitalised for acute COVID-19
	  ○ Care or residential homes)
	• Health care workers

Study types	Any The following study design types for this question are preferred. Where these studies are not identified, other study designs will be considered. • Systematic reviews of RCTs and observational studies • RCTs • Prospective and retrospective observational studies
Countries	Any
Timepoints	Any
Other exclusions	• Management of acute COVID-19 (symptoms experienced for up to 4 weeks) • Management of other conditions with similar features to post-COVID-19 syndrome, for

	example post-intensive care syndrome and myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome (ME/CFS) • Management of end-organ damage, which already has defined pathways of care.

Appendix B: Literature search strategy/Data source

COVID-19 EPPI-R5 review

The search for the COVID-19 EPPI-R5 review was developed in compliance with section 8 of Appendix L of the NICE manual. EPPI-R5 is an application for systematic reviewing. Search results can be screened in EPPI-R5, and included studies are data extracted and assessed for risk of bias in the same application. The current version of Appendix L is: NICE (15 October 2020) Developing NICE guidelines: the manual. Process and methods [PMG20]. Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies.

The COVID-19 EPPI-R5 review contains papers published since 16 March 2020.

The development of the MEDLINE and Embase search strategy is detailed in the following preprint:

Levay, Paul; Finnegan, Amy (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. medRxiv 2021.06.11.21258749; doi:https://doi.org/10.1101/2021.06.11.21258749

The search is limited to those in the English language. Animal studies are removed from results. The following publication types are also excluded: MEDLINE: letter, historical article, comment, editorial, news, case reports Embase: letters, editorials, conferences, case reports.

From November 2020, the database search strategies were updated to include terms for the long-term effects of COVID-19. From August 2021, the database search strategies were updated to include terms for COVID-19 vaccines. The search results are managed in EPPI-R5. Duplicates are removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess ‘low-probability’ matches. All decisions made for the review can be accessed via the deduplication history. An automated process is used to download bioRxiv and medRxiv preprints. A daily RIS

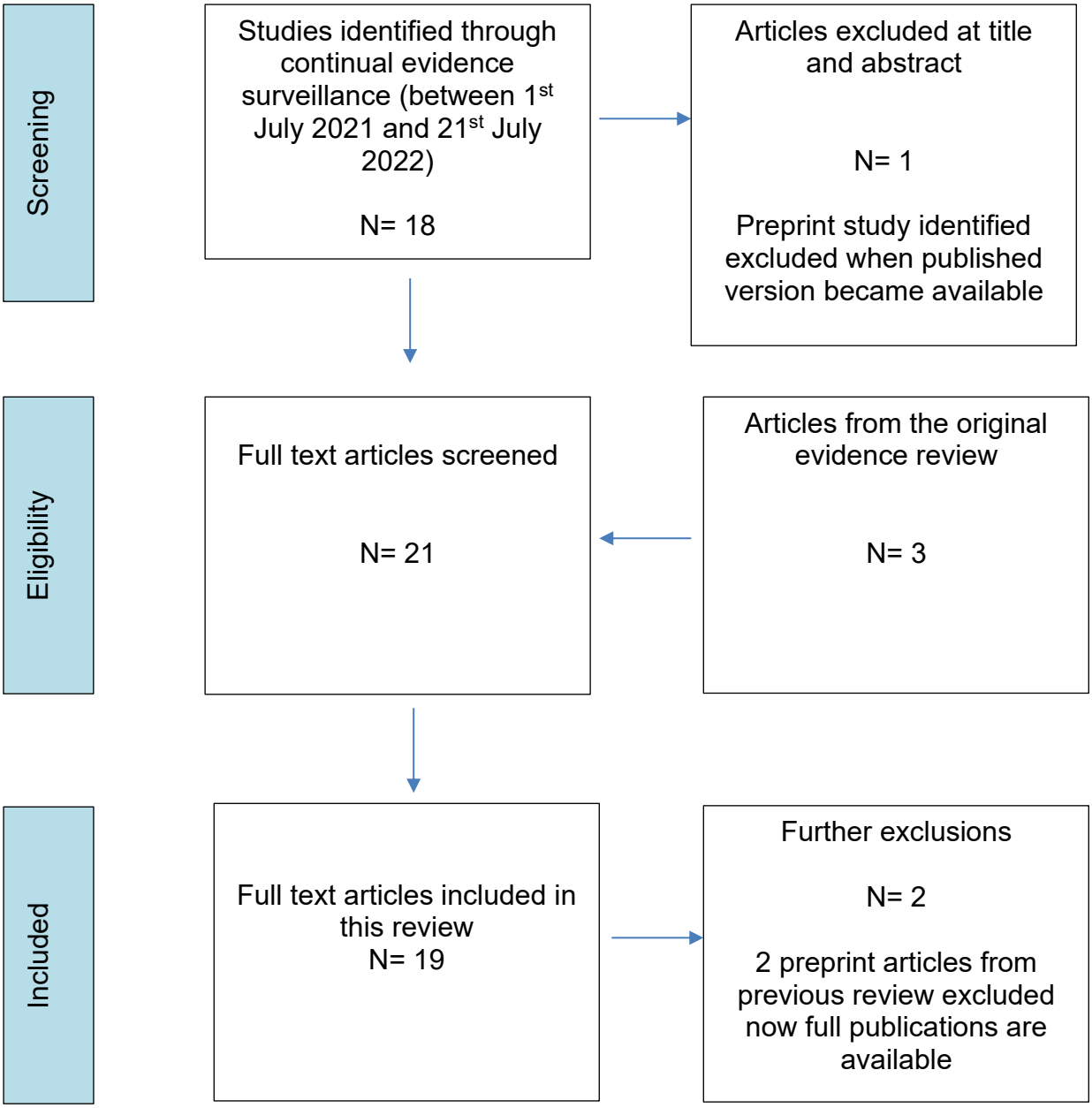
file is automatically generated from the pre-sorted COVID-19 and SARS-COV-2 collection available on the website. This RIS file is uploaded to the EPPI-R5 review weekly. Since 10 August 2021, Europe PMC and NIH COVID-19 Portfolio are also searched weekly for preprints and deduplicated in EPPI-R5. The Information Services team at NICE peer reviewed the principal database strategies according to the standard NICE checklist that was adapted from the 2015 Peer review of electronic search strategies (PRESS) checklist.

Effectiveness of COVID-19 vaccines against long term effects of COVID-19 searches

As this was review was undertaken as part of the continuous living surveillance of NICE guideline NG188, the surveillance repository* was used to identify evidence rather than running a bespoke evidence search. All records with relevance to COVID-19 vaccines and long COVID, and which were added since the update review search was conducted on 30th June 2021, were assessed for potential inclusion.

** The surveillance repository is an EPPI review that includes all search results from when surveillance searches for the COVID-19 health and social care emergency begin (March 2020) to current date.*

Appendix C: PRISMA diagram



Appendix D: Included studies

Al-Aly, Z; Bowe, B; Xie, Y (2022) Long COVID after breakthrough SARS-CoV-2 infection. Nature Medicine

Antonelli, Michela, Penfold Rose, S, Merino, Jordi et al. (2021) 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. The Lancet. Infectious diseases

Arnold, DT, Milne, A, Samms, E et al. (2021) Symptoms After COVID-19 Vaccination in Patients With Persistent Symptoms After Acute Infection: A Case Series. Annals of Internal Medicine

Ayoubkhani, Daniel, Bermingham, Charlotte, Pouwels, Koen et al. Changes in the trajectory of Long Covid symptoms following COVID-19 vaccination: community-based cohort study. medrxiv preprint

Ayoubkhani, Daniel, Bosworth, Matthew, L et al. Risk of Long Covid in people infected with SARS-CoV-2 after two doses of a COVID-19 vaccine: community-based, matched cohort study. medrxiv preprint

Azzolini, E; Levi, R; Sarti, R (2022) Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. Journal of the American Medical Association

Kuodi, Paul, Gorelik, Yanay, Zayyad, Hiba et al. Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients infected between March 2020 and November 2021. medrxiv preprint

Peghin, Maddalena, De Martino, Maria, Palese, Alvisa et al. (2022) Post-COVID-19 syndrome and humoral response association after one year in vaccinated and unvaccinated patients. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases

Scherlinger, Marc, Pijnenburg, Luc, Chatelus, Emmanuel et al. (2022) Effect of SARS-CoV-2 Vaccination on Symptoms from Post-Acute Sequelae of COVID-19: Results from the Nationwide VAXILONG Study. Vaccines 10(1): 46

Simon, Michael, A, Luginbuhl, Ryan et al. Reduced Incidence of Long-COVID Symptoms Related to Administration of COVID-19 Vaccines Both Before COVID-19 Diagnosis and Up to 12 Weeks After. medrxiv preprint

Strain W, D, Sherwood, O, Banerjee, A et al. (2022) The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID. Vaccines 10(5): 652

Tannous, Jonika, Pan, Alan, Potter, Thomas et al. (2022) Real World Evidence of Effectiveness of COVID-19 Vaccines and Anti SARS-CoV-2 Monoclonal Antibodies Against Post-Acute Sequelae of SARS-CoV-2 Infection.

Taquet, Maxime; Dercon, Quentin; Harrison Paul, J (2022) Six-month sequelae of post-vaccination SARS-CoV-2 infection: A retrospective cohort study of 10,024 breakthrough infections. Brain, behavior, and immunity 103: 154-162

Tran, Viet-Thi, Perrodeau, Elodie, Saldanha, Julia et al. (2021) Efficacy of COVID-19 Vaccination on the Symptoms of Patients With Long COVID: A Target Trial Emulation Using Data From the ComPaRe e-Cohort in France.

Tsuchida, Tomoya, Hirose, Masanori, Inoue, Yoko et al. (2022) Relationship between changes in symptoms and antibody titers after a single vaccination in patients with Long COVID. Journal of medical virology

Wanga, Valentine, Chevinsky Jennifer, R, Dimitrov Lina, V et al. (2021) Long-Term Symptoms Among Adults Tested for SARS-CoV-2 - United States, January 2020-April 2021. MMWR. Morbidity and mortality weekly report 70(36): 1235-1241

Wisnivesky, Juan, Govindarajulu, Usha, Bagiella, Emilia et al. Association of Vaccination With the Persistence of Post-COVID Symptoms.

Wynberg, Elke, Han Alvin, X, Boyd, Anders et al. (2022) The effect of SARS-CoV-2 vaccination on post-acute sequelae of COVID-19 (PASC): A prospective cohort study. Vaccine

Zisis Sokratis, N, Durieux Jared, C, Mouchati, Christian et al. (2022) The Protective Effect of Coronavirus Disease 2019 (COVID-19) Vaccination on Postacute Sequelae of COVID-19: A Multicenter Study From a Large National Health Research Network. Open forum infectious diseases 9(7): ofac228

Appendix E: Excluded studies at full text screening

Study	Reason for exclusion
Al-Aly, Ziyad; Bowe, Benjamin; Xie, Yan (2021) Long Covid after Breakthrough COVID-19: the post-acute sequelae of breakthrough COVID-19.	- Exclude - Preprint article now fully published
Antonelli, Michela, Penfold, Rose, Merino, Jordi et al. (2021) Post-vaccination SARS-CoV-2 infection: risk factors and illness profile in a prospective, observational community-based case-control study.	- Exclude - Preprint article now fully published
Strain, William David and Sherwood, Ondine and Banerjee, Amitava and van der Togt, Vicky and Hishmeh, Lyth and Rossman J (2021) The Impact of COVID Vaccination on Symptoms of Long COVID. An International Survey of People with Lived Experience of Long COVID. SSRN (Lancet pre-prints)	- Exclude - Preprint article now fully published

Appendix F: Evidence tables

Al-Aly, 2022

Bibliographic Reference	Al-Aly, Z; Bowe, B; Xie, Y; Long COVID after breakthrough SARS-CoV-2 infection; Nature Medicine; 2022

Study details

Study design	Cohort studies
Study start date	01-Jan-2021
Study end date	31-Oct-2021
Aim of the study	The authors used the national healthcare databases of the US Department of Veterans Affairs to characterize 6-month risks of incident post-acute sequelae in people with breakthrough COVID-19 who survived for at least 30 days after diagnosis
Country/ Geographical location	USA
Study setting	Cohort participants were identified from the United States Veterans Health Administration (VHA) electronic health databases. The VHA provides healthcare to discharged veterans of the US armed forces in a nationally integrated network of healthcare systems that includes more than 1,415 healthcare facilities.
Definition of long term effects used in the study	The authors prespecified a set of outcomes based on prior evidence on the post-acute sequelae of SARS-CoV-2 infection—also referred to as Long COVID. Outcomes were defined using validated definitions leveraging information from several data domains, including diagnoses, prescription medications and laboratory test results, at the time of first record of occurrence in the data. Incident post-acute sequelae were examined in a cohort with no record of the health condition in the 2 years before T0. They additionally examined outcomes of death and having at least one of post-acute sequelae that was defined at the time of the first incident prespecified post-acute sequelae in each participant. Additionally, they defined a set of outcomes where we aggregated the prespecified post-acute sequelae, where applicable, by organ system. These included cardiovascular disorders, coagulation and hematologic disorders, fatigue, gastrointestinal disorders, kidney disorders, mental health disorders, metabolic disorders, musculoskeletal disorders, neurologic disorders and pulmonary disorders. All outcomes were assessed starting from 30 days after T0.
Population description	People with breakthrough COVID-19 compared to people with COVID-19 not previously vaccinated, people without history of COVID-19 and people with seasonal influenza.,

Inclusion criteria	Participants were recruited if they had at least 1 encounter with the US Veteran Health Administration in the two years prior to cohort enrollment
Intervention/test/approach	COVID-19 vaccination. Ad26.COV2.S, mRNA-1273, or BNT162b2 vaccination before the date of their first positive COVID-19 test
Comparator (where applicable)	
Methods for population selection/allocation	To construct a group of people with breakthrough COVID-19 the authors selected, from those with a positive SARS-CoV-2 test (n = 163,024), those with a record of completion of an Ad26.COV2.S, mRNA-1273 or BNT162b2 vaccination before the date of their first positive SARS-CoV-2 test (n = 34,863). Completion of vaccination was defined following CDC guidelines at the 14th day after the second shot of the mRNA-1273 or BNT162b2 vaccination series or the 14th day after the first shot of the Ad26. COV2.S vaccination. Setting the date of first positive SARS-CoV-2 test as time zero (T0), the authors then selected those alive 30 days after T0, resulting in a cohort of 33,940 participants in the BTI group. To build the group of people with SARS-CoV-2 infection and without prior vaccination as a means of investigating the effect of prior vaccination on the risk of post-acute sequalae, the authors identified, from the 163,024 people with a first positive SARS-CoV-2 test from 1 January 2021 to 31 October 2021, 118,185 who had no record of any SARS-CoV-2 vaccination up through 30 days after first positive SARS-CoV-2 test (T0). They then selected the 113,474 who were alive 30 days after T0 to comprise the group of people with SARS-CoV-2 infection and no prior vaccination.
Methods of data analysis	The authors estimated the risk of each pre-specified post-acute sequelae associated with breakthrough COVID-19 compared to the control group. The estimated hazard ratios for each outcome and the estimated incidence rate difference (referred to as excess burden) between groups per 1,000 participants at 6 months after the start of follow-up in each group were presented. The authors examined, as positive outcome controls, the risks of the pre-specified post-acute sequelae in those with COVID-19 compared to the control group as a means of testing whether the approach would reproduce established knowledge. The application of negative outcome control may

	help detect both suspected and unsuspected sources of spurious biases. The authors therefore, tested accidental injury or poisoning and atopic dermatitis as negative outcome controls – where no prior knowledge suggests an association is expected.
Attrition/loss to follow-up	None
Source of funding	This research was funded by the United States Department of Veterans Affairs (ZAA) and two American Society of Nephrology and KidneyCure fellowship awards
Study limitations (Author)	• The breakthrough COVID-19 and COVID-19 groups only included those that had a positive test for COVID-19 and did not include those who may have had an infection with SARS-CoV-2 but were not tested; however, if present, this will bias the estimates toward the null. • Although the authors adjusted for selected covariants, they could not completely rule out residual confounding. • The authors noted that the COVID-19 global pandemic is highly dynamic, as vaccine uptake continues to increase, as vaccine schedules continue to be optimized, as treatment strategies of the acute phase of COVID-19 continue to improve, and as new variants of the virus emerge, it is likely that the epidemiology of breakthrough COVID-19 and its downstream sequelae may also change over time.
Study limitations (Reviewer)	• Patient demographics predominantly male sample and older adults. • Does not report how many doses of vaccine had been administered

Study arms

People with breakthrough COVID-19 (N = 33940)

People with SARS-CoV-2 infection and no prior history of vaccination (N = 113474)

Characteristics

Study-level characteristics

Characteristic	Study (N = 13369073)
Age Mean (SD)	62.82 (NR)

Characteristic	Study (N = 13369073)
Male No of events	n = NR ; % = 88.85
Female No of events	n = NR ; % = 11.15
White No of events	n = NR ; % = 73.4
Black No of events	n = NR ; % = 18.63

Outcomes

Post acute sequelae

Outcome	People with breakthrough COVID-19 vs People with SARS-CoV-2 infection and no prior history of vaccination, , N2 = 33940, N1 = 113474
Risk of death Hazard ratio/95% CI	0.66 (0.58 to 0.74)
Risk of post acute sequelae Hazard ratio/95% CI	0.85 (0.82 to 0.89)

Risk of death - Polarity - Lower values are better
Risk of post acute sequelae - Polarity - Lower values are better

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Risk of death

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes *((Although use of negative outcome controls helped to minimise this))*

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Unable to rule out confounding)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Yes
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Probably yes
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Probably yes
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Probably yes

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(Limited population due to source of data (US Veterans))*
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Probably yes
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Only had vaccination status information)*
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information

Section	Question	Answer
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	No information
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	No information
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Risk of post acute sequelae

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes *(Although use of negative outcome controls helped to minimise this)*
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Unable to rule out confounding)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Yes
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Probably yes
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Probably yes
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes

Section	Question	Answer
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Probably yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(Limited population due to source of data (US Veterans))*
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Probably yes
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Only had vaccination status information)*

Section	Question	Answer
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	No information
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	No information
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Antonelli, 2021

Bibliographic Reference	Antonelli, Michela; Penfold Rose, S; Merino, Jordi; Sudre Carole, H; Molteni, Erika; Berry, Sarah; Canas Liane, S; Graham Mark, S; Klaser, Kerstin; Modat, Marc; Murray, Benjamin; Kerfoot, Eric; Chen, Liyuan; Deng, Jie; Osterdahl Marc, F; Cheetham Nathan, J; Drew David, A; Nguyen Long, H; Pujol Joan, Capdevila; Hu, Christina; Selvachandran, Somesh; Polidori, Lorenzo; May, Anna; Wolf, Jonathan; Chan Andrew, T; Hammers, Alexander; Duncan Emma, L; Spector Tim, D; Ourselin, Sebastien; Steves Claire, J; 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.; The Lancet. Infectious diseases; 2021

Study details

Study design	Case–control studies
Study start date	08-Dec-2020
Study end date	04-Jul-2021
Aim of the study	1. Describe individual factors associated with SARS-CoV-2 infection at least 14 days after first vaccination 2. Assess illness duration, severity, and symptom profile in individuals with SARS-CoV-2 infection after first vaccination compared to unvaccinated individuals with SARS-CoV-2 infection.
Country/ Geographical location	UK
Study setting	Community
Inclusion criteria	Cases had received a first or second dose of a COVID-19 vaccine since Dec 8, 2020; had either a positive RT-PCR test or lateral flow antigen test (LFAT) at least 14 days after their first vaccination (but before their second; cases 1) or a positive RT-PCR test or LFAT at least 7 days after their second vaccination (cases 2); and had no positive SARS-CoV-2 test before vaccination. If more than one positive test result was reported, only the first positive test was selected. To identify risk factors for post-vaccination infection, we selected two control groups among the vaccinated (since Dec 8, 2020) UK-based adult users of the COVID Symptom Study app who had not tested positive for SARS-CoV-2 before vaccination: a control group of users reporting a negative RT-PCR test or LFAT at least 14 days after their first vaccination but before their second (controls 1) and a control group of users reporting a negative RT-PCR test or LFAT at least 7 days after their second vaccination (controls 2). Controls 1 and controls 2 were matched (1:1) with cases 1 and cases 2, respectively, by use of the date of the post-vaccination COVID-19 test, health-care worker status, and sex. If multiple negative tests were reported, the last test date was used for matching
Exclusion criteria	

Methods for population selection/allocation	Participants provided data by self- or proxy-report to a free smartphone app (Zoe Global). At registration, each participant reported baseline demographic information (e.g., age, sex, ethnicity, whether a healthcare worker) geographic location, and information on health risk factors including comorbidities, lifestyle, frailty and visits to hospital. Participants were encouraged to self-report any pre-specified symptoms daily, enabling prospective, longitudinal information on incident symptoms. Those experiencing new symptoms were invited for a SARS-CoV-2 test through local testing centres.
Methods of data analysis	In the disease profile analysis, univariate logistic regression models adjusted by age, BMI, and sex were used to assess the association of individual symptoms, overall illness duration, and disease severity (outcomes) with vaccination status (exposure). For all regression analyses, odds ratios (ORs) and 95% CIs were calculated. Analyses were not corrected for multiple testing. This study reports on vaccination with BNT162b2, ChAdOx1 nCoV-19, and mRNA-1273 only, as there were no positive cases among the few people who had received other vaccines
Source of funding	ZOE, the UK Government Department of Health and Social Care, the Wellcome Trust, the UK Engineering and Physical Sciences Research Council, UK Research and Innovation London Medical Imaging and Artificial Intelligence Centre for Value Based Healthcare, the UK National Institute for Health Research, the UK Medical Research Council, the British Heart Foundation, and the Alzheimer's Society.
Study limitations (Author)	• The app data sample contained disproportionately more women than men and under-represented individuals in more deprived areas. • It was not possible to analyse the impact of ethnicity due to the low number of participants who provided this information. • The findings might not apply at all timepoints post-vaccination, to settings with different proportions of SARS-CoV-2 variants or to countries with a different vaccine schedule. • Data were self-reported • Recording of comorbidities, test results, and vaccination status might not have been completely accurate and there might have been temporal gaps in reporting • Users of the COVID Symptom Study app are asked to log daily; therefore, if a participant reports on alternate days, the proportion of missing daily entries is 50%.

Study arms

Vaccinated UK adults from the COVID Symptom Study testing positive for post-vaccination SARS-CoV-2 infection (N = 4731)

Individuals who tested positive before 2nd dose n= 3825 Individuals who tested positive after 2nd dose n= 906

Positive unvaccinated cases who reported a positive SARS-CoV-2 test, regardless of symptoms (N = 4731)

Characteristics

Arm-level characteristics

Characteristic	Vaccinated UK adults from the COVID Symptom Study testing positive for post-vaccination SARS-CoV-2 infection (N = 4731)	Positive unvaccinated cases who reported a positive SARS-CoV-2 test, regardless of symptoms (N = 4731)
People with COVID-19 before 2nd dose: Age (years) Mean (SD)	52 (14.2)	51.5 (14.2)
People with COVID 19 after 2nd dose: Age (years) Mean (SD)	54.5 (14.3)	53.7 (13.8)
People with COVID-19 before 2nd dose: Male No of events	n = 1365 ; % = 35.7	n = 1363 ; % = 35.6
People with COVID 19 after 2nd dose: Male No of events	n = 345 ; % = 38.1	n = 353 ; % = 39
People with COVID-19 before 2nd dose: Female No of events	n = 2460 ; % = 64.3	n = 2462 ; % = 64.4
People with COVID 19 after 2nd dose: Female No of events	n = 561 ; % = 61.9	n = 553 ; % = 61

Outcomes

Symptom duration lasting more than 28 days

Outcome	Vaccinated UK adults from the COVID Symptom Study testing positive for post-vaccination SARS-CoV-2 infection, , N = NA	Positive unvaccinated cases who reported a positive SARS-CoV-2 test, regardless of symptoms, , N = NA
People with COVID-19 before 2nd dose No of events	n = 229 ; % = 9.2	n = 296 ; % = 10.7
People with COVID-19 before 2nd dose Sample size	n = 2479 ; % = NA	n = 2762 ; % = NA
People with COVID 19 after 2nd dose No of events	n = 31 ; % = 5.2	n = 55 ; % = 11.4
People with COVID 19 after 2nd dose Sample size	n = 592 ; % = NA	n = 482 ; % = NA
People with COVID-19 before 2nd dose: 18-59 years No of events	n = 124 ; % = 8.7	n = 121 ; % = 7.9
People with COVID-19 before 2nd dose: 18-59 years Sample size	n = 1430 ; % = NA	n = 1540 ; % = NA
People with COVID 19 after 2nd dose: 18-59 years No of events	n = 9 ; % = 3.1	n = 16 ; % = 7.2
People with COVID 19 after	n = 286 ; % = NA	n = 223 ; % = NA

Outcome	Vaccinated UK adults from the COVID Symptom Study testing positive for post-vaccination SARS-CoV-2 infection, , N = NA	Positive unvaccinated cases who reported a positive SARS-CoV-2 test, regardless of symptoms, , N = NA
2nd dose: 18-59 years Sample size		
People with COVID-19 before 2nd dose: at least 60 years No of events	n = 105 ; % = 10	n = 175 ; % = 14.3
People with COVID-19 before 2nd dose: at least 60 years Sample size	n = 1049 ; % = NA	n = 1222 ; % = NA
People with COVID 19 after 2nd dose: at least 60 years No of events	n = 22 ; % = 7.2	n = 39 ; % = 15.1
People with COVID 19 after 2nd dose: at least 60 years Sample size	n = 306 ; % = NA	n = 259 ; % = NA

Symptom duration lasting more than 28 days

Outcome	Vaccinated UK adults from the COVID Symptom Study testing positive for post-vaccination SARS-CoV-2 infection vs Positive unvaccinated cases who reported a positive SARS-CoV-2 test, regardless of symptoms, , N2 = NA, N1 = NA
symptoms lasting ≥28 days (1 dose of vaccine) Odds ratio/95% CI	1.03 (0.85 to 1.24)
symptoms lasting ≥28 days (1 dose of vaccine) Sample size	n1 = 2762, n2 = 2479

Outcome	Vaccinated UK adults from the COVID Symptom Study testing positive for post-vaccination SARS-CoV-2 infection vs Positive unvaccinated cases who reported a positive SARS-CoV-2 test, regardless of symptoms, , N2 = NA, N1 = NA
Age 18-59 years Odds ratio/95% CI **Age 18-59 years** Sample size	1.22 (0.94 to 1.6) n1 = 1540, n2 = 1430
Age 60+ years Odds ratio/95% CI **Age 60+ years** Sample size	0.87 (0.67 to 1.13) n1 = 1222, n2 = 1049
symptoms lasting ≥28 days (2 doses of vaccine) Odds ratio/95% CI **symptoms lasting ≥28 days (2 doses of vaccine)** Sample size	0.51 (0.32 to 0.82) n1 = 482, n2 = 292
Age 18-59 years Odds ratio/95% CI **Age 18-59 years** Sample size	0.37 (0.16 to 0.88) n1 = 223, n2 = 286
Age 60+ years Odds ratio/95% CI **Age 60+ years** Sample size	0.56 (0.31 to 0.98) n1 = 259, n2 = 306

Critical appraisal - CASP Critical appraisal checklist for case-control studies: Interventions (Case-control)

Reported symptoms lasting at least 28 days - People with COVID-19 before 2nd dose

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can’t tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No

Section	Question	Answer
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Reported symptoms lasting at least 28 days- People with COVID19 after 2nd dose

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-*

Section	Question	Answer
		economic status as indicated by the skew toward people living in less deprived areas.)
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More researc is req
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Reported symptoms lasting at least 28days-People with COVID-19 before 2nd dose: 18-59 years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes

Section	Question	Answer
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can’t tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More researc is req
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Reported symptoms lasting at least 28days- People with COVID 19 after 2nd dose:18-59 years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section

Section	Question	Answer
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More researc is req
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Reported symptoms lasting at least 28days - People with COVID-19 before 2nd dose: at least 60 years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*

Section	Question	Answer
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Unclear how vaccination status was verified).*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More researc is req
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Reported symptoms lasting at least 28 days- People with COVID19 after 2nd dose: at least 60 years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-*

Section	Question	Answer
		economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Unclear how vaccination status was verified).*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Symptoms lasting ≥ 28days (1 dose of vaccine)

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required

Section	Question	Answer
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Symptoms lasting ≥ 28days (1 dose of vaccine)-Age 18-59 years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can’t tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of	6. (b) Have the authors taken account of the	No

Section	Question	Answer
the study valid?	potential confounding factors n the design and/or in their analysis?	
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Symptoms lasting ≥ 28 days (1 dose of vaccine)-Age 60+ years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-*

Section	Question	Answer
		economic status as indicated by the skew toward people living in less deprived areas.)
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Symptoms lasting ≥ 28 days (2 doses of vaccine)

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female*

Section	Question	Answer
		and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can’t tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Symptoms lasting ≥28 days (2 doses of vaccine)-Age18-59 years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can't tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of the study valid?	6. (b) Have the authors taken account of the potential confounding factors n the design and/or in their analysis?	No
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required.

Section	Question	Answer
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Symptoms lasting ≥ 28 days (2 doses of vaccine)- Age 60+ years

Section	Question	Answer
(A) Are the results of the study valid?	1. Did the study address a clearly focused issue?	Yes
(A) Are the results of the study valid?	2. Did the authors use an appropriate method to answer their question?	Yes
(A) Are the results of the study valid?	3. Were the cases recruited in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas. Information was self-reported and therefore recording of comorbidities and test results may not be completely accurate. Symptom duration may be underestimated in both cases and controls, as some individuals only had two weeks of logging after their positive test result.)*
(A) Are the results of the study valid?	4. Were the controls selected in an acceptable way?	No *(This study used data from a large population of individuals reporting on a mobile application. This population, while large, was disproportionately female and under-represented individuals of lower socio-economic status as indicated by the skew toward people living in less deprived areas.)*
(A) Are the results of the study valid?	5. Was the exposure accurately measured to minimise bias?	Can’t tell *(Unclear how vaccination status was verified)*
(A) Are the results of the study valid?	6. (a) What confounding factors have the authors accounted for?	Age, BMI, sex, frailty, and comorbidity status but frailty and comorbidity status were not included in the reported results for duration of symptoms in older adults.
(A) Are the results of	6. (b) Have the authors taken account of the	No

Section	Question	Answer
the study valid?	potential confounding factors n the design and/or in their analysis?	
(B) What are the results?	7. What are the results of this study?	See results section
(B) What are the results?	8. How precise are the results?	Likely to be imprecise
(B) What are the results?	9. Do you believe the results?	Limitations of this study mean that the results should be considered with caution. More research is required.
(C) Will the results help locally?	10. Can the results be applied to the local population?	Can't tell *(The study sample was not representative of the whole population)*
(C) Will the results help locally?	11. Do the results of this study fit with other available evidence?	Can't tell *(Yes, to some extent but more evidence is required for full assessment)*

Arnold, 2021

Bibliographic Reference	Arnold, DT; Milne, A; Samms, E; et al; Symptoms After COVID-19 Vaccination in Patients With Persistent Symptoms After Acute Infection: A Case Series; Annals of Internal Medicine; 2021

Study details

Trial registration (if reported)	Not reported
Study start date	Dec-2020
Study end date	Feb-2021
Aim of the study	To describe quality of life and symptoms after SARS-CoV-2 vaccination in a series of patients with persistent symptoms 8 months after hospitalization with COVID-19.
Country/ Geographical location	UK
Study setting	Community (following initial hospitalisation)
Population description	Consecutive patients admitted to a single UK hospital with COVID-19. From this cohort, participants who were symptomatic at 8 months and who subsequently received the Pfizer-BioNTech (BNT162b2) or Oxford-AstraZeneca (ChAdOx1nCoV-19) vaccine between January and February 2021 were identified..

Inclusion criteria	Patients originally hospitalised with COVID-19 with a significant proportion of persistent symptoms. COVID-19 was diagnosed by PCR positive test or due to strong clinicoradiological suspicion. At least one dose of a COVID-19 vaccine
Exclusion criteria	None stated
Intervention/test/approach	At least one dose of a COVID-19 vaccine [Pfizer-BioNTech (BNT162b2) or Oxford-AstraZeneca (ChAdOx1nCoV-19)]
Comparator (where applicable)	Not applicable
Methods for population selection/allocation	The cases described here were identified from among 163 patients admitted to a single U.K. hospital with COVID-19 and prospectively recruited to an observational study with clinical follow-up at 8 months after admission (December 2020 to January 2021). Participants who were symptomatic at 8 months and who subsequently received the Pfizer-BioNTech (BNT162b2) or Oxford-AstraZeneca (ChAdOx1nCoV-19) vaccine between January and February 2021 were identified. N.B. related pre-print report states that all participants who had received at least one dose of a COVID-19 vaccine were identified via the National Immunisation Management Service (NIMS).
Methods of data analysis	Participants were telephoned approximately 1 month post vaccination (January to February 2021) with quality of life questionnaires and review of symptoms repeated, with specific questions on whether symptoms had improved, stayed the same, or worsened. Participants were only asked to confirm vaccination status after assessment, minimising bias due to perceived association between the assessment and vaccination. Participants were subsequently asked about adverse effects temporally related to the vaccine. Symptom burden was assessed via self-reported answers to a standardised review of ongoing symptoms. T-tests were used to compare 8-month quality of life and mental wellbeing metrics with the post vaccination metrics. Median number of symptoms at each time point were compared. N.B. related pre-print reports that linear models were fitted to formally test for any effect of vaccination on quality of life controlling for 8-month quality of life, age, and gender.
Attrition/loss to follow-up	Of the 78 participants who attended the 8-month follow-up, 2 could not be contacted and 32 had not yet received a vaccine. Among the remaining 44 participants who had received 1 dose of vaccine, 36 (82%) reported at least 1 persistent symptom and were included in the analysis.
Source of funding	Not reported

Study limitations (Author)	Small sample size and the inability to blind participants to their vaccination status. Also, because the U.K. national policy prioritised vaccination for older age groups and adopted a delayed second-dose approach, it was not possible to suitably match vaccinated and unvaccinated persons, and data cold only be provided for participants after their first vaccine dose.
Study limitations (Reviewer)	The cases were all hospitalised so data cannot be directly extrapolated to individuals whose initial infection did not result in hospitalisation. There was a lack of blinding and symptom recall may have been influenced by receipt of vaccination. There were 8 participants who were symptomatic at 8 months and received a vaccine but were not followed up as they did not report at least 1 persistent symptom. No explanation was given as to why these participants were excluded from the analysis. The absence of persistent symptoms in participants who were experiencing them prior to vaccination is potentially important data to record in the context of the study aim.
Other details	A related pre-print reported matching of participants with 22 controls but this data was not reported in the published case series.

Characteristics

Study-level characteristics

Characteristic	Study (N = 36)
Age Median (IQR)	64 (53 to 73)
Male Custom value	21 (58%)
Female Custom value	15 (42%)
Black, Asian or ethnic minority Custom value	5 (14%)
Body mass index Mean (SD)	31.8 (8)
Diabetes Type 1 Custom value	0 (0%)

Characteristic	Study (N = 36)
Diabetes Type 2 Custom value	4 (11%)
Heart disease Custom value	10 (28%)
Chronic lung disease Custom value	13 (36%)
Intensive care and/or non-invasive ventilation Custom value	11 (31%)
Oxygen supplementation Custom value	26 (72%)
PCR positive for SARS-CoV-2 during hospitlisation Custom value	30 (83%)
SARS-CoV-2 antibody positivity at 3 months Custom value	32 (89%)
Median SF-36 MCS score Median (IQR)	40 (29 to 51)
Median SF-36 PCS score Median (IQR)	35 (25 to 40)
Median WEMWBS score Median (IQR)	49 (42 to 54)
Median number of persistent symptoms reported Median (IQR)	4 (2 to 5)
Pfizer-BioNTech (BNT162b2) Custom value	18 (50%)
Oxford-AstraZeneca (ChAdOx1nCoV-19) Custom value	18 (50%)

Outcomes

Study timepoints

- 30 day (Participants were telephoned a median of 30 days after vaccination (IQR, 26 to 36 days) to investigate changes in symptoms and quality of life.)

Clinical status

Outcome	Study, 30 day, N = 36
Unchanged symptoms Custom value	113/159 (71.1%)
Worsened symptoms Custom value	9/159 (5.6%)
Improved symptoms Custom value	37/159 (23.2%)
Quality of life SF-36 physical and mental composite scores Custom value	NR
Pre-vaccination WEMWBS score Median (IQR)	49 (42 to 54)
Post-vaccination WEMWBS score Median (IQR)	50 (40 to 59)

Quality appraisal and risk of bias

Section	Question	Answer
Study objective	Was the hypothesis/aim/objective of the study clearly stated?	Yes
Study design	Was the study conducted prospectively?	Yes
Study design	Were the cases collected in more than one centre?	No
Study design	Were patients recruited consecutively?	Unclear
Study population	Were the characteristics of the patients included in the study described?	Yes
Study population	Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial

Section	Question	Answer
Study population	Did patients enter the study at a similar point in the disease?	Yes
Intervention and co-intervention	Was the intervention of interest clearly described?	Yes
Intervention and co-intervention	Were additional interventions (co-interventions) clearly described?	No
Outcome measure	Were relevant outcome measures established a priori?	Yes
Outcome measure	Were outcome assessors blinded to the intervention that patients received?	No
Outcome measure	Were the relevant outcomes measured using appropriate objective/subjective methods?	Partial *(Persistent symptoms were measured subjectively by self-report. It would be possible to measure some symptoms objectively. Standardised tools were used for measurement of quality of life and mental wellbeing.)*
Outcome measure	Were the relevant outcome measures made before and after the intervention?	Yes
Statistical analysis	Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear
Results and conclusions	Was follow-up long enough for important events and outcomes to occur?	No *(30 day follow up is insufficient to assess impact of vaccination on post COVID-19 syndrome. Longer term follow up is needed.)*
Results and conclusions	Were losses to follow-up reported?	Yes Unclear *(It is unclear why 8 participants were excluded from the analysis on the grounds of not reporting at least 1 persistent symptom post-vaccination)*
Results and conclusions	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No
Results and conclusions	Were the adverse events reported?	Partial *(A large proportion (26 of 36 [72%]) reported transient (<72 hours' duration) systemic effects after vaccination, including fever (44%), myalgia (22%), and headache (19%). No further adverse events were reported beyond 72 hours.)*

Section	Question	Answer
Results and conclusions	Were the conclusions of the study supported by results?	No *(Due to the limitations of the study, including small sample size, single vaccine doses and under-representation of many population groups, the conclusion was premature. However, the authors were correct in recommending that further work that includes appropriate unvaccinated controls is needed to confirm the trajectory of persistent symptoms after COVID-19 vaccination.)*
Competing interests and sources of support	Were both competing interests and sources of support for the study reported?	No
Overall Risk of Bias	Risk of Bias	High *(No control group, no blinding to intervention, risk of recall bias, selective data analysis.)*
Overall Risk of Bias	Applicability	Partially directly applicable *(The 30 day timeframe was too short to assess the longer term effects of vaccination. Analysis was undertaken after single doses only in older people with more comorbidities, hospitalised at a single centre.)* Indirectly applicable

Ayoubkhani et al.

Bibliographic Reference	Ayoubkhani, Daniel; Bermingham, Charlotte; Pouwels, Koen; B; Glickman, Myer; Nafilyan, Vahe; Zaccardi, Francesco; Khunti, Kamlesh; Alwan, Nisreen; A; Walker, Ann; Sarah; Changes in the trajectory of Long Covid symptoms following COVID-19 vaccination: community-based cohort study; medrxiv preprint

Study details

Study design	Cohort studies
Study start date	03-Feb-2021
Study end date	05-Sep-2021
Aim of the study	To estimate associations between COVID-19 vaccination and Long Covid symptoms in adults who were infected with SARS-CoV-2 prior to vaccination.
Country/ Geographical location	UK
Study setting	Random sample from the community population of the UK.

Definition of long term effects used in the study	• Long COVID defined as symptoms persisting for at least 12 weeks from confirmed or suspected coronavirus infection that could not be explained by another health condition • This definition uses self-classification of Long Covid, rather than a pre-specified symptoms list or clinical diagnosis, and thus reflects participants' perception of whether their lived experience is consistent with what they understand of the condition.
Population description	• All participants provided a nose and throat self-swab for polymerase chain reaction (PCR) testing at every follow-up visit. • At every monthly visit since 3 February 2021, all CIS participants were asked whether they would describe themselves as currently experiencing Long Covid • Participants who responded positively to the Long Covid question were further asked about the extent to which their day-to-day activities were limited as a result, and the presence of 21 individual symptoms as part of their experience of Long Covid
Intervention/test/approach	The exposures of interest were first and second vaccinations of an adenovirus vector (Oxford/AstraZeneca, ChAdOx1 nCoV-19 [AZD1222]) or mRNA (Pfizer/BioNTech, BNT162b2; Moderna, mRNA-1273) COVID-19 vaccine.
Methods for population selection/allocation	• Participants were included if they: responded to the survey question on Long Covid at least once up to 5 September 2021 (end of follow-up); received at least one COVID-19 vaccination before or during the follow-up period; and received a positive swab or blood test for SARS-CoV-2, either through the CIS or reported outside of the study, prior to vaccination. CIS participants remaining unvaccinated by 5 September 2021 were excluded because they were likely to differ from those who were vaccinated according to unmeasured characteristics (for example, personal considerations related to vaccine hesitancy). • Time of infection was the date of first positive swab or antibody test (ignoring blood tests after first vaccination), or the date when the participant first thought they had COVID-19 that was later confirmed by a positive test, whichever was earlier.
Methods of data analysis	• For participants in England, vaccination information (number of doses, dates, manufacturer) was obtained from self-reported CIS responses and linked National Immunisation Management System (NIMS) records, with NIMS being prioritised where data conflicted. Concordance between self-reported and NIMS data was previously found to be high regarding vaccination type (98%) and date (95% within ±7 days).

	Administrative records were not available for participants in Wales, Scotland, and Northern Ireland, so vaccination data for these individuals were taken from the CIS alone. • As well as time from infection and the exposure variables detailed above to modify the time trajectory of Long Covid, the authors adjusted for covariates hypothesised to be related to vaccine type and timing and the probability of experiencing Long Covid symptoms : age; sex; white or non-white ethnicity; region/country; area deprivation quintile group; health status; whether a patient-facing health or social care worker; whether hospitalised with acute COVID-19; and calendar time of infection. • Associations between exposures and outcomes were estimated using an individual-level interrupted time series approach.
Source of funding	The CIS is funded by the Department of Health and Social Care with in-kind support from the Welsh Government, the Department of Health on behalf of the Northern Ireland Government, and the Scottish Government.
Study limitations (Author)	• The observational nature of the study means that causality cannot be inferred • Placebo and side effects of vaccination may have contributed to the findings • The observed changes after vaccination could be related to the relapsing-remitting nature of symptoms experienced by many people living with Long COVID. • Long COVID status was self-reported and there is no data on formal clinical diagnosis
Results summary	**Long COVID symptoms** Long Covid symptoms of any severity were reported by 6,729 participants (23.7%) at least once during follow-up. Before vaccination, the odds of experiencing Long Covid decreased by 0.3% (-0.9% to +0.2%) per week from infection. First vaccination was associated with an initial 12.8% decrease (95% CI: -18.6% to -6.6%) in the odds, followed by an increase of 0.3% (-0.6% to +1.2%) per week until receiving the second dose. Second vaccination was associated with an initial 8.8% decrease (-14.1% to -3.1%) in the odds, followed by a decrease of 0.8% (-1.2% to -0.4%) per week **Activity limitation** Long Covid resulting in activity limitation was reported by 4,747 participants (16.7%) at least once during follow-up. First

	vaccination was associated with an initial 12.3% decrease (-19.5% to -4.5%) in the odds of activity-limiting Long Covid, followed by an increase of 0.9% (-0.2% to +1.9%) per week until receiving the second dose. Second vaccination was associated with an initial 9.1% decrease (-15.6% to -2.1%) in the odds, followed by a decrease of 0.5% (-1.0% to +0.05%) per week

Study arms

People reporting Long COVID symptoms (N = 6729)

Characteristics

Study-level characteristics

Characteristic	Study (N = 28356)
Age Mean (SD)	45.9 (13.6)
Male No of events	n = 12596 ; % = 44.4
Female No of events	n = 15760 ; % = 55.6
White No of events	n = 25141 ; % = 88.7
Non-white No of events	n = 3215 ; % = 11.3
Time since infection (days) Mean (SD)	308.9 (129)
Time since first vaccination (days) Mean (SD)	130.7 (55.9)

Outcomes

Odds of Long COVID

Outcome	People reporting Long COVID symptoms vs People reporting Long COVID symptoms, , N2 =NA , N1 =NA
Long COVID Symptoms Custom value	See results summary

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Long COVID Symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	No information

Section	Question	Answer
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	No information
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Probably yes

Section	Question	Answer
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Ayoubkhani et al.

Bibliographic Reference	Ayoubkhani, Daniel; Bosworth, Matthew; L; King, Sasha; Pouwels, Koen; B; Glickman, Myer; Nafilyan, Vahe; Zaccardi, Francesco; Khunti,

Kamlesh; Alwan, Nisreen; A; Walker, Ann; Sarah; Risk of Long Covid in people infected with SARS-CoV-2 after two doses of a COVID-19 vaccine: community-based, matched cohort study; medrxiv preprint

Study details

Study design	Cohort studies
Trial registration (if reported)	
Aim of the study	To investigate whether infection following two doses of a COVID-19 vaccine is associated with a reduction in Long Covid symptoms after 12 weeks, relative to being unvaccinated when infected.
Country/ Geographical location	UK
Study setting	Community
Definition of long term effects used in the study	Symptoms more than 4 weeks after acute COVID 19
Population description	Participants aged 18-69 years who tested positive for SARS-CoV-2, either by polymerase chain reaction test using swabs obtained at study visits (58.7% of infections) or any swab test in national testing programmes (self-reported by study participants), between 26 April 2020 and 30 November 2021.
Inclusion criteria	Double vaccinated at the time of infection
Exclusion criteria	Participants who reported suspected COVID-19 or tested positive for antibodies (in the study or elsewhere) more than two weeks before their first positive swab, reported Long Covid symptoms at any time before their first positive swab, had never responded to the survey question on Long Covid, did not have ≥12 weeks of post-infection follow-up by 30 November 2021 or were single-vaccinated when infected.
Intervention/test/approach	The exposure of interest was receipt of at least two doses of a COVID-19 vaccine (Oxford/AstraZeneca ChAdOx1 nCoV-19 [AZD1222], Pfizer/BioNTech BNT162b2, or Moderna mRNA-1273) ≥14 days before the first test-confirmed infection.
Methods for population selection/allocation	
Methods of data analysis	Vaccination status for participants in England was derived from survey data linked to National Immunisation Management System records, with the latter being prioritised where they conflicted with self-reports. Administrative data were not available for participants in Wales, Scotland, and Northern Ireland (13.6%), thus vaccination status was derived solely from self-report. Study participants were matched at time of infection to control participants who were unvaccinated when infected and

	remained so. Large imbalance after matching was identified by absolute standardized differences >10% Adjusted odds ratios (aOR) were estimated for Long Covid at ≥12 weeks using logistic regression including all covariates from the matching set, comparing participants who were double-vaccinated to those unvaccinated (reference group) when infected, using robust standard errors to account for matching
Attrition/loss to follow-up	
Source of funding	The CIS is funded by the Department of Health and Social Care with in-kind support from the Welsh Government, the Department of Health on behalf of the Northern Ireland Government, and the Scottish Government. There was no dedicated funding for this study of CIS data.
Study limitations (Author)	The question on Long Covid was not in introduced in the survey until 3 February 2021 which was after mass vaccination was began in the UK. Therefore it was not possible to match double-vaccinated and unvaccinated participants on calendar time of infection. Differences in the likelihood of developing Long Covid symptoms between exposure groups may therefore partly reflect changes in the dominant COVID-19 variant or other period effects The study data was before the Omicron variant became widespread. Unable to investigate participants who were single-vaccinated when infected because nearly all of these received their second dose within the 12-week follow-up period, confounding any relationship between one dose at infection and Long Covid symptoms.

Study arms

Double vaccinated (N = 4498)

Unvaccinated (N = 4498)

Characteristics

Arm-level characteristics

Characteristic	Double vaccinated (N = 4498)	Unvaccinated (N = 4498)
Age Mean (SD)	49 (12)	46.7 (11.2)

Characteristic	Double vaccinated (N = 4498)	Unvaccinated (N = 4498)
Male No of events	n = 1676 ; % = 54.2	n = 1659 ; % = 53.7
Female No of events	n = 1414 ; % = 45.8	n = 1431 ; % = 46.3
White No of events	n = 2837 ; % = 91.8	n = 2817 ; % = 91.2
Non-white No of events	n = 253 ; % = 8.2	n = 273 ; % = 8.8

Outcomes

Long Covid outcomes

Outcome	Double vaccinated, , N = 3090	Unvaccinated, , N = 3090
Long Covid symptoms of any severity No of events	n = 294 ; % = 9.5	n = 452 ; % = 14.6
Activity limited symptoms No of events	n = 170 ; % = 5.5	n = 268 ; % = 8.7

Long Covid outcomes

Outcome	Double vaccinated vs Unvaccinated, , N2 = 3090, N1 = 3090
Long Covid symptoms of any severity Odds ratio/95% CI	0.59 (0.5 to 0.69)
Activity limited symptoms Odds ratio/95% CI	0.59 (0.48 to 0.73)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Long Covid symptoms of any severity

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Not applicable
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably yes
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information

Section	Question	Answer
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Activity limited symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Not applicable
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable

Section	Question	Answer
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably yes
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate

Section	Question	Answer
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Long Covid symptoms of any severity-Odds Ratio

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Not applicable
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Not applicable
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
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3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
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4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
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4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably yes
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7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Activity limited symptoms-Odds Ratio

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Not applicable
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1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably yes
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Azzolini, 2022

Bibliographic Reference	Azzolini, E; Levi, R; Sarti, R; Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers; Journal of the American Medical Association; 2022

Study details

Study design	Cohort studies
Trial registration (if reported)	
Study start date	Mar-2020

Study end date	Apr-2022
Country/ Geographical location	Italy
Study setting	9 Italian Healthcare facilities
Definition of long term effects used in the study	Reporting at least 1 SARS-CoV-2–related symptom with a duration of more than 4 weeks.
Population description	The analysis was restricted to health care workers who were tested every 1 or 2 weeks with complete demographic data and a documented positive result for SARS-CoV-2 between March 2020 and March 2022.
Inclusion criteria	
Exclusion criteria	• Hospitalised individuals • Individuals with a date if infection less than 28 days before the survey
Intervention/test/approach	All health care workers were required to receive 3 doses of vaccine (BNT162b2), with the first and second doses administered in January-February 2021 and the booster dose in November-December 2021.
Comparator (where applicable)	No vaccine
Methods for population selection/allocation	Between February and April 2022, each participant completed a survey including demographics, comorbidities, a list of SARS-CoV-2–related symptoms at the time of infection and their duration, and vaccination status.
Methods of data analysis	The Clopper-Pearson method was used to calculate 95% CIs and the Mann-Whitney U test or the t test for continuous variables and the $\chi 2$-test for categorical variables to calculate P values. The significance threshold was defined as $P < .05$ (2-sided). Analyses were done in Python, version 3.8.3.
Attrition/loss to follow-up	
Source of funding	Fondazione Humanitas per la Ricerca funded this research.
Study limitations (Author)	• Self-reported outcomes
Study limitations (Reviewer)	Unclear which data was used in the regression analysis • Characteristics and sample sizes of reference group of unvaccinated females in wave 1 were not reported. • Regression analysis includes data where vaccines were administered at least 14 days prior to infection therefore it is unclear whether the 176 people who were unvaccinated at the time of infection were included in the analysis.

Study arms

Healthcare workers with Long COVID (N = 229)

Unvaccinated females in wave 1 (N = NR)

Characteristics

Study-level characteristics

Characteristic	Study (N = 229)
Age (years) Mean (SD)	44.3 (10.7)
Female No of events	n = 180 ; % = 78.6
Male No of events	n = 49 ; % = 21.4
Wave 1: February-September 2020 (wild-type variant) No of events	n = 74 ; % = 32.3
Wave 2, October 2020-July 2021 (Alpha variant) No of events	n = 108 ; % = 47.1
Wave 3, August 2021-March 2022 (Delta and Omicron variants) No of events	n = 47 ; % = 20.5

Arm-level characteristics

Characteristic	Healthcare workers with Long COVID (N = 229)	Unvaccinated females in wave 1 (N = NR)
0 vaccine doses before SARS-CoV-2 infection No of events	n = 176 ; % = 76.9	*empty data*
1 vaccine dose before SARS-CoV-2 infection No of events	n = 3 ; % = 1.31	*empty data*

Characteristic	Healthcare workers with Long COVID (N = 229)	Unvaccinated females in wave 1 (N = NR)
2 vaccine doses before SARS-CoV-2 infection No of events	n = 8 ; % = 3.5	*empty data*
3 vaccine doses before SARS-CoV-2 infection No of events	n = 42 ; % = 18.3	*empty data*
Comorbidity: Allergies No of events	n = 104 ; % = 44.5	*empty data*
Comorbidity: Heart and cardiovascular diseases No of events	n = 34 ; % = 14.8	*empty data*
Comorbidity: Obstructive lung disease (asthma/COPD/bronchiectasis) No of events	n = 28 ; % = 12.2	*empty data*
Comorbidity: Autoimmune and rheumatic diseases No of events	n = 21 ; % = 9.1	*empty data*
Comorbidity: Metabolic disease No of events	n = 18 ; % = 7.8	*empty data*
Comorbidity: Cancer No of events	n = 5 ; % = 2.1	*empty data*
Comorbidity: Pregnancy or breastfeeding No of events	n = 5 ; % = 2.7	*empty data*
Comorbidity: Anaemia/hemoglobinopathies/ coagulation disorders No of events	n = 3 ; % = 1.3	*empty data*
Comorbidity: Mental health conditions No of events	n = 3 ; % = 1.3	*empty data*
Comorbidity: IBD No of events	n = 2 ; % = 1	*empty data*

Characteristic	Healthcare workers with Long COVID (N = 229)	Unvaccinated females in wave 1 (N = NR)
Comorbidity: GERD No of events	n = 2 ; % = 1	*empty data*

Outcomes

Long COVID

Outcome	Healthcare workers with Long COVID vs Unvaccinated females in wave 1, , N2 = 229, N1 = NR
Probability of Long COVID with 2 vaccine doses (at least 14 days prior to infection) Odds ratio/95% CI	0.25 (0.07 to 0.87)
Probability of Long COVID with 3 vaccine doses (at least 14 days prior to infection) Odds ratio/95% CI	0.16 (0.03 to 0.84)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Probability of Long COVID with 2 vaccine doses (at least 14 days prior to infection)

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Probably no
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No information *(Unclear how reference group was selected)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Serious *(Unclear on how reference group was selected)*
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Probably no *(Unclear how there reference group was obtained)*
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information *(Unclear on which participants were used in the analysis)*
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably no
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate

Section	Question	Answer
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes *(Outcome was self-reported)*
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably no
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Probability of Long COVID with 3 vaccine doses (at least 14 days prior to infection)

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Probably no

Section	Question	Answer
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No information *(Unclear how reference group was selected)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Serious *(Unclear on how reference group was selected)*
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Probably no *(Unclear how there reference group was obtained)*
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Serious
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Not applicable
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information *(Unclear on which participants were used in the analysis)*
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably no
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes *(Outcome was self-reported)*
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Probably no
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Kuodi et al.

Bibliographic Reference Kuodi, Paul; Gorelik, Yanay; Zayyad, Hiba; Wertheim, Ofir; Wiegler, Karine; Beiruti; Jabal Kamal, Abu; Dror, Amiel; Nazzal, Saleh; Glikman, Daniel; Edelstein, Michael; Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients infected between March 2020 and November 2021; medrxiv preprint

Study details

Study design	Cross-sectional study
Trial registration (if reported)	
Study start date	16-Jul-2021
Study end date	18-Nov-2021
Aim of the study	To determine whether vaccination was associated with the incidence of reporting long-term symptoms post-SARS-CoV-2 infection
Country/ Geographical location	Israel
Study setting	Online survey
Population description	All individuals over the age of 18 who were tested for SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) between 15th March 2020 and 15th November 2021 in the three major government hospitals in Northern Israel, namely Ziv Medical Centre, Padeh-Poriya Medical Centre, and Galilee Medical Centre, were eligible to join the study regardless of the test result.
Inclusion criteria	
Intervention/test/approach	COVID-19 vaccination (mainly BNT162b2 mRNA vaccine)
Comparator (where applicable)	
Methods for population selection/allocation	Using available patient telephone records, individuals were invited to participate in the study between July 16th and November 18th 2021, through a Short Message Service (SMS) containing an invitation with a link to an online survey available in four commonly spoken languages in Israel: Hebrew, Arabic, Russian, and English. Two reminders to complete the survey were sent to non-responders. All individuals over the age of 18 who were tested for SARS-CoV-2 infection by reverse transcription polymerase chain reaction (RT-PCR) between 15th March 2020 and 15th November 2021 in the three major government hospitals in Northern Israel, namely Ziv Medical Centre, Padeh-Poriya Medical Centre, and Galilee Medical Centre, were eligible to join the study regardless of the test result.
Methods of data analysis	Proportions of long-term symptoms and selected health outcomes were calculated for each group with the total number of participants in each group taken as the denominator. The authors compared vaccinated and infected individuals to never infected individuals in terms of reported symptoms, also using binomial regression models
Source of funding	No specific funding was received for this study
Study limitations (Author)	• The unvaccinated and the vaccinated groups were comparable in sociodemographic characteristics

	except for age, reflecting vaccine coverage in the Israeli population. As a result, some chronic conditions present at baseline were more common in the vaccinated group. • A higher proportion of those who received two doses were asymptomatic at the time of diagnosis compared to the unvaccinated group, and those who were symptomatic at baseline reported less symptoms compared with those unvaccinated. These figures reflect the protection against symptomatic disease conferred by vaccines, which may also partly explain the lower proportion of reporting long-term symptoms among those vaccinated. • The median follow-up duration was longer in the unvaccinated group than the vaccinated individuals. This is consistent with the fact that the follow-up period started 9 months before vaccines became available in Israel. • The study relied on self-reported positive PCR results. • It is also important to note that the vaccination policy in Israel, at the time of the survey, specified that SARS-CoV-2-infected individuals were in theory only eligible for a single dose of vaccine. Therefore, individuals who received one dose also differed from those who received two doses in terms of the sequence of events: while those who received two doses will have mostly been infected after having been vaccinated, many among those who received a single dose will have been infected prior to vaccination. • The population was mainly at the mild end of the COVID-19 spectrum and the results cannot be extrapolated to patients who are severely ill in the acute phase. • Children were not included in the survey. • Symptoms were self-reported.

Study arms

Received one dose of vaccines (N = 340)

Received two doses of vaccine (N = 294)

Unvaccinated (N = 317)

Characteristics

Arm-level characteristics

Characteristic	Received one dose of vaccines (N = 340)	Received two doses of vaccine (N = 294)	Unvaccinated (N = 317)
19-35 years No of events	n = 109 ; % = 32.1	n = 59 ; % = 20.1	n = 120 ; % = 37.9
36-60 years No of events	n = 171 ; % = 50.3	n = 135 ; % = 45.9	n = 162 ; % = 51.1
≥60 years No of events	n = 60 ; % = 17.6	n = 100 ; % = 34	n = 35 ; % = 11
Male No of events	n = 96 ; % = 35.4	n = 100 ; % = 42.4	n = 87 ; % = 35.8
Female No of events	n = 175 ; % = 64.6	n = 136 ; % = 57.6	n = 156 ; % = 64.2
Jewish No of events	n = 118 ; % = 66.3	n = 97 ; % = 73.5	n = 110 ; % = 69.2
Christian/Muslim Arabs/Druze No of events	n = 60 ; % = 33.7	n = 35 ; % = 26.5	n = 49 ; % = 30.8

Outcomes

Post COVID symptoms

Outcome	Received one dose of vaccines vs Unvaccinated, , N2 = 340, N1 = 317	Received two doses of vaccine vs Unvaccinated, , N2 = 294, N1 = 317
Fatigue Sample size	n1 = 82 ; %1 = NA, n2 = 93 ; %2 = NA	n1 = 82 ; %1 = NA, n2 = 33 ; %2 = NA
Fatigue Relative risk/95% CI	1.06 (0.82 to 1.36)	0.36 (0.19 to 0.71)
Headache Sample size	n1 = 95 ; %1 = NA, n2 = 110 ; %2 = NA	n1 = 95 ; %1 = NA, n2 = 77 ; %2 = NA

Outcome	Received one dose of vaccines vs Unvaccinated, , N2 = 340, N1 = 317	Received two doses of vaccine vs Unvaccinated, , N2 = 294, N1 = 317
Headache Relative risk/95% CI	1.08 (0.81 to 1.44)	0.46 (0.26 to 0.83)
Weakness in arms and legs Sample size	n1 = 103 ; %1 = NA, n2 = 127 ; %2 = NA	n1 = 103 ; %1 = NA, n2 = 82 ; %2 = NA
Weakness in arms and legs Relative risk/95% CI	1.04 (0.74 to 1.47)	0.48 (0.2 to 0.94)
Persistent muscle pain Sample size	n1 = 86 ; %1 = NA, n2 = 106 ; %2 = NA	n1 = 86 ; %1 = NA, n2 = 80 ; %2 = NA
Persistent muscle pain Relative risk/95% CI	1.17 (0.77 to 1.76)	0.32 (0.11 to 0.88)
Loss of concentration Sample size	n1 = 55 ; %1 = NA, n2 = 59 ; %2 = NA	n1 = 55 ; %1 = NA, n2 = 48 ; %2 = NA
Loss of concentration Relative risk/95% CI	1.24 (0.81 to 1.9)	0.59 (0.17 to 2.06)
Hair loss Sample size	n1 = 36 ; %1 = NA, n2 = 43 ; %2 = NA	n1 = 36, n2 = 9 ; %2 = NA
Hair loss Relative risk/95% CI	1.11 (0.74 to 1.69)	0.17 (0.056 to 0.6)
Sleeping problems Sample size	n1 = 29 ; %1 = NA, n2 = 42 ; %2 = NA	n1 = 29, n2 = 14 ; %2 = NA
Sleeping problems	1.35 (0.86 to 2.11)	0.53 (0.18 to 1.61)

Outcome	Received one dose of vaccines vs Unvaccinated, , N2 = 340, N1 = 317	Received two doses of vaccine vs Unvaccinated, , N2 = 294, N1 = 317
Relative risk/95% CI		
Dizziness Sample size	n1 = 32 ; %1 = NA, n2 = 30 ; %2 = NA	n1 = 32 ; %1 = NA, n2 = 12 ; %2 = NA
Dizziness Relative risk/95% CI	0.87 (0.54 to 1.4)	0.26 (0.087 to 1.79)
Persistent cough Sample size	n1 = 24 ; %1 = NA, n2 = 26 ; %2 = NA	n1 = 24 ; %1 = NA, n2 = 20 ; %2 = NA
Persistent cough Relative risk/95% CI	1.01 (0.59 to 1.71)	0.72 (0.28 to 1.83)
Shortness of breath Sample size	n1 = 25 ; %1 = NA, n2 = 29 ; %2 = NA	n1 = 25 ; %1 = NA, n2 = 14 ; %2 = NA
Shortness of breath Relative risk/95% CI	1.08 (0.65 to 1.81)	0.23 (0.065 to 0.84)
Recovery from COVID-19 Sample size	n1 = 170 ; %1 = NA, n2 = 190 ; %2 = NA	n1 = 170 ; %1 = NA, n2 = 173 ; %2 = NA
Recovery from COVID-19 Relative risk/95% CI	1.02 (0.89 to 1.16)	0.98 (0.8 to 1.21)

Critical appraisal - –Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross Sectional Studies: Interventions (cross-sectional)

Fatigue

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes

Section	Question	Answer
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Headache

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Weakness in arms and legs

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

PostCOVID symptoms-Persistent muscle pain

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns

Section	Question	Answer
Overall bias and directness	Directness	Directly applicable

Loss of concentration

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Hair loss

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes

Section	Question	Answer
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Sleeping problems

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Dizziness

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear

Section	Question	Answer
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Persistent cough

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Shortness of breath

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Recovery from COVID-19

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Yes
Assessment questions	Were confounding factors identified?	Yes
Assessment questions	Were strategies to deal with confounding factors stated?	Yes
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Peghin, 2022

Bibliographic Reference	Peghin, Maddalena; De Martino, Maria; Palese, Alvisa; Gerussi, Valentina; Bontempo, Giulia; Graziano, Elena; Visintini, Erica; Elia Denise, D'; Dellai, Fabiana; Marrella, Francesco; Fabris, Martina; Curcio, Francesco; Sartor, Assunta; Isola, Miriam; Tascini, Carlo; Post-COVID-19 syndrome and humoral response association after one year in vaccinated and unvaccinated patients.; Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases; 2022

Study details

Study design	Cohort studies
Study end date	May-2021
Aim of the study	To describe the post-COVID-19 syndrome one year after the acute infection by focusing (a) on the influence of vaccination on long-term symptoms, and (b) on the role of humoral responses among survivors with natural and hybrid immunity.
Country/ Geographical location	Italy
Study setting	Databases of people cared for by an Academic Hospital in all settings
Definition of long term effects used in the study	Post-COVID-19 syndrome was defined as signs and symptoms developed during or following an infection consistent with COVID-19, continued for more than 12 weeks, and not explained by an alternative diagnosis
Population description	Adults with history of COVID-19 during the first wave
Inclusion criteria	• all adults (≥ 18 years) diagnosed with COVID-19 during the first wave (March–May 2020) and cared for by an Academic Hospital in all settings • followed up at 6 (September–November 2020) and at 12 months (March–May 2021) • willing to participate
Exclusion criteria	None reported
Intervention/test/approach	COVID-19 vaccination
Comparator (where applicable)	No vaccine
Methods for population selection/allocation	• Demographic and clinical databases were populated at the enrolment and over time. • Participants were telephone-interviewed by the same trained nurses at 6 and 12 months using a homogeneous questionnaire, pilot-tested and previously validated investigating persistent or

	emerging symptoms potentially associated with COVID-19, as expressed by patients' own words. • Signs/symptoms reported by patients were classified by four independent researchers and then matched between the first and the second interview in order to check changes, if any, over time. Therefore, patients were classified as: (a) unaffected when asymptomatic at both follow-ups; (b) unchanged when symptoms remained the same; (c) worsened when new symptoms emerged; and (d) improved, when symptoms were recovered/resolved. • At 12 months, patients were asked to communicate vaccination state (yes/no) by also reporting the date and type of vaccine received. Data collected were matched in their accuracy with electronic health records; then, patients were categorized as vaccinated if they had received the vaccine at least 2 weeks before the interview; those with combined immunity from natural SARS-CoV-2 infection and vaccination were considered to have hybrid immunity
Methods of data analysis	The Shapiro–Wilk test was used to assess whether data were normally or non-normally distributed. Categorical variables were compared using the chi-square (χ2) test or Fisher's exact test, while quantitative variables were compared using the t-test or Mann–Whitney U test, as appropriate. A univariable and multivariable logistic regression was performed to explore features associated with post-COVID-19 syndrome, estimating the odds ratio (OR) at 95% Confidence Interval
Attrition/loss to follow-up	Overall, during the first wave, 1,067 COVID-19 patients were diagnosed in our hospital. Of them, 599 attended the 6-month interview and 479 the 12-month interview
Source of funding	This research was funded by PRIN 2017 n.20178S4EK9 – "Innovative statistical methods in biomedical research on biomarkers: from their identification to their use in clinical practice".
Study limitations (Author)	• Single centre study including patients cared for in the first wave limiting its generalisability • A 20% drop-off rate between 6-12 month interviews was observed • No COVID-19 control group was included • The vaccine campaign in Italy prioritised healthcare workers and the elderly which may have introduced a gender bias. • Symptoms were self-reported and subjectivity may have affected the findings

Study arms

Vaccinated (N = 132)

Unvaccinated (N = 347)

Characteristics

Arm-level characteristics

Characteristic	Vaccinated (N = 132)	Unvaccinated (N = 347)
Age 18-40 years No of events	n = 33	n = 74 ; % = 21.3
Age 41-60 years No of events	n = 64 ; % = 48.5	n = 141 ; % = 40.6
Age >60 years No of events	n = 35 ; % = 26.5	n = 132 ; % = 38
Male No of events	n = 38 ; % = 28.8	n = 189 ; % = 54.5
Female No of events	n = 94 ; % = 71.2	n = 158 ; % = 45.5
Native Italian No of events	n = 112 ; % = 89.6	n = 310 ; % = 93.4
Native Italian Sample size	n = 125	n = 332
European No of events	n = 12 ; % = 9.6	n = 20 ; % = 6
European Sample size	n = 125	n = 332
Non-European No of events	n = 1 ; % = 0.8	n = 2 ; % = 0.6
Non-European Sample size	*empty data*	n = 332

Characteristic	Vaccinated (N = 132)	Unvaccinated (N = 347)
Hypertension No of events	n = 25 ; % = 19.5	n = 81 ; % = 23.8
Hypertension Sample size	n = 128	n = 340
Obesity No of events	n = 22 ; % = 16.7	n = 56 ; % = 16.1
Obesity Sample size	n = 132	n = 347
Diabetes No of events	n = 6 ; % = 4.6	n = 19 ; % = 5.5
Diabetes Sample size	n = 130	n = 345
Chronic respiratory disease No of events	n = 6 ; % = 4.6	n = 11 ; % = 3.2
Chronic respiratory disease Sample size	n = 130	n = 345
Cardiovascular disease No of events	n = 2 ; % = 1.5	n = 5 ; % = 1.4
Cardiovascular disease Sample size	n = 130	n = 345
Liver disease No of events	n = 2 ; % = 1.5	n = 7 ; % = 2
Liver disease Sample size	n = 130	n = 345
Psychiatric disorders No of events	n = 1 ; % = 0.8	n = 4 ; % = 1.1
Psychiatric disorders Sample size	n = 132	n = 347
Acute COVID-19 severity: Asymptomatic	n = 19 ; % = 14.4	n = 19 ; % = 5.5

Characteristic	Vaccinated (N = 132)	Unvaccinated (N = 347)
No of events		
Acute COVID-19 severity: Mild No of events	n = 86 ; % = 65.1	n = 237 ; % = 68.7
Acute COVID-19 severity: Moderate, severe and critical No of events	n = 27 ; % = 20.5	n = 89 ; % = 25.8
Acute COVID-19 management: Outpatients No of events	n = 99 ; % = 75	n = 241 ; % = 69.4
Acute COVID-19 management: Ward No of events	n = 30 ; % = 22.7	n = 88 ; % = 25.4
Acute COVID-19 management: ICU No of events	n = 3 ; % = 2.3	n = 18 ; % = 5.2

Outcomes

Post COVID symptoms

Outcome	Vaccinated, , N = 132	Unvaccinated, , N = 347
Post COVID syndrome: Unaffected and unchanged No of events	n = 87 ; % = 65.9	n = 247 ; % = 71.2
Post COVID syndrome: Worsened No of events	n = 30 ; % = 22.7	n = 55 ; % = 15.8
Post COVID syndrome: Improved No of events	n = 15	n = 45 ; % = 13
Number of post-COVID symptoms: 0 No of events	n = 73 ; % = 55.3	n = 180 ; % = 51.9
Number of post-COVID symptoms: 1 No of events	n = 27 ; % = 20.4	n = 65 ; % = 18.7
Number of post-COVID symptoms: 2 No of events	n = 17 ; % = 12.9	n = 42 ; % = 12.1

Outcome	Vaccinated, , N = 132	Unvaccinated, , N = 347
Number of post-COVID symptoms: 3 No of events	n = 7 ; % = 5.3	n = 27 ; % = 7.8
Number of post-COVID symptoms: 4 No of events	n = 1 ; % = 0.8	n = 11 ; % = 3.2
Number of post-COVID symptoms: 5 or more No of events	n = 7 ; % = 5.3	n = 22 ; % = 6.3

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Post COVID syndrome

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	Risk of bias judgement for confounding	Serious
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics	Probably no

Section	Question	Answer
	observed after the start of intervention? If N/PN to 2.1: go to 2.4	
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Number of post-COVID symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	No information
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information
1. Bias due to confounding	Risk of bias judgement for confounding	Serious
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably yes
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Scherlinger, 2022

Bibliographic Reference	Scherlinger, Marc; Pijnenburg, Luc; Chatelus, Emmanuel; Arnaud, Laurent; Sibilia, Jean; Gottenberg, Jacques-Eric; Felten, Renaud; Effect of SARS-CoV-2 Vaccination on Symptoms from Post-Acute Sequelae of COVID-19: Results from the Nationwide VAXILONG Study; Vaccines; 2022; vol. 10 (no. 1); 46

Study details

Study design	Cross-sectional study
Study start date	03-Aug-2021

Study end date	17-Aug-2021
Aim of the study	To evaluate the impact of SARS-CoV-2 vaccination on post-acute sequelae of COVID-19 (PASC) burden.
Country/ Geographical location	France
Study setting	Online survey among French speaking adults recruited through social media platforms.
Population description	Adult patients with PASC as defined by symptoms persisting over 4 weeks following a confirmed or probable COVID-19, without any identified alternative diagnosis
Inclusion criteria	Inclusion criteria were the definition of PASC by the French Haute Autorité de Santé : a reported viral illness with a probable or confirmed COVID-19 diagnosis, persistent symptoms lasting >4 weeks and the lack of an alternative diagnosis to explain the presentation. The severity of a wide set of symptoms before and after vaccination was evaluated using a previously validated symptom set . Information about the type of vaccine used or the reason for non-vaccination was evaluated. At the time of the study, the vaccination scheme was considered complete if the patient reported 2 doses of vaccine or 1 dose of mRNA/ChAdOx1 vaccine with a prior biologically confirmed infection (either RT-PCR or serology).
Intervention/test/approach	At the time of the study, the vaccination scheme was considered complete if the patient reported 2 doses of vaccine or 1 dose of mRNA/ChAdOx1 vaccine
Methods of data analysis	Quantitative data are reported as median with interquartile range (IQR 25–75) and qualitative results as a percentage. Quantitative data were compared using Student's t-test, and qualitative data using the Chi2 test. Statistical analysis was conducted using JMP Software 14.0 (SAS Institute, Cary, CA, USA). A p-value < 0.05 was considered statistically significant.
Source of funding	This research received no external funding
Study limitations (Author)	• The recruitment was conducted using social media platforms that could select a younger population or one that is not accurately representative of the general PASC population. • The aim of this study was descriptive and did not aim at comparing the safety of the SARS-CoV-2 vaccine between PASC and non-PASC individuals, explaining the lack of a control group to compare vaccination safety and reason for non-vaccination. • The limited number of included patients and the absence of information on comorbidities are also limiting factors.

Study arms

Vaccinated population (N = 397)

Characteristics

Arm-level characteristics

Characteristic	Vaccinated population (N = 397)
Age Median (IQR)	44 (37 to 50)
% Female No of events	n = 327 ; % = 85.9
Time since initial COVID-19 (days) Median (IQR)	483 (266 to 506)

Outcomes

Impact on symptoms

Outcome	Vaccinated population, , N = 380
Global worsening of symptom severity No of events	n = 117 ; % = 31
Global improvement of symptom severity No of events	n = 83 ; % = 21.8

Critical appraisal - GUT - JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies: Interventions (cross-sectional)

Global worsening of symptom severity

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear

Section	Question	Answer
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Unclear
Assessment questions	Were confounding factors identified?	Unclear
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Unclear
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Global improvement of symptom severity

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Unclear
Assessment questions	Were confounding factors identified?	Unclear
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear
Assessment questions	Was appropriate statistical analysis used?	Unclear
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Simon et al.

Bibliographic Reference	Simon, Michael; A; Luginbuhl, Ryan; Parker, Richard; Reduced Incidence of Long-COVID Symptoms Related to Administration of COVID-19 Vaccines Both Before COVID-19 Diagnosis and Up to 12 Weeks After; medrxiv preprint

Study details

Study design	Cohort studies
Trial registration (if reported)	
Study start date	Feb-2020
Study end date	May-2021
Aim of the study	As part of a federated research study with the COVID-19 Patient Recovery Alliance, Arcadia.io performed a retrospective analysis of the medical history of 240,648 COVID-19-infected persons to identity factors influencing the development and progression of long-COVID.
Country/ Geographical location	USA
Study setting	Data for this analysis were collected from Arcadia Data Research (Arcadia.io, Burlington, MA), a normalized, de-identified clinical and operational dataset containing over 150 million patient records. Data were captured directly from electronic health record (EHR) systems, practice management systems, and health care payer claims and eligibility data, and subjected to data quality analyses for compliance with quality measure, risk adjustment, utilization and finance, and care management requirements.
Definition of long term effects used in the study	Long-COVID cases were classified as those where the patient presented one or more COVID-associated symptoms between 12 and 20 weeks after the initial COVID-19 diagnosis
Intervention/test/approach	COVID vaccination All vaccines approved for use (Pfzer, AstraZeneca, Moderna)
Methods for population selection/allocation	Patients qualified for inclusion were further classified as having been diagnosed with COVID-19 during this period or not. The study cohort was further limited to patients diagnosed with COVID-19, having met either of the following requirements: (1) they were diagnosed with ICD-10 code U07.1 at any time or B97.29 prior to May 2020 in a medical encounter (i.e., the diagnosis was assessed by a provider in a face-to-face or equivalent encounter); or (2) they received a positive result from a COVID-19 nucleic acid amplification test (NAAT) or antigen test result. For patients meeting these criteria, an “index date” was set for the first incidence of COVID-19 diagnosis or positive test result. The index date needed to be at least 20 weeks prior to the cutoff date of the data extraction for the patient to be included in the sample population. Patients who died within twelve weeks of this index date were also excluded from this analysis, as any long-COVID outcomes could not be determined for those individuals.

Methods of data analysis	A logistic regression model based on a Newton Conjugate Gradient solution (Python statsmodels v0.12.2) was used to identify factors potentially influencing the persistence or onset of long-COVID symptoms.
Attrition/loss to follow-up	
Study limitations (Reviewer)	• The findings are based on opportunistic availability of large volumes of patient data and may have geographic, temporal, contractual, and socioeconomic gaps that could influence outcomes. • These findings use vaccination data recorded by payer entities or documented in EHRs by providers but do not incorporate dedicated vaccination surveillance data sources and so may have gaps in vaccination data that are presently undetectable. • It is possible, but unlikely, that some of the patients with COVID-19 were misclassified due to a false-positive test result (with no documented correction) or an inaccurate COVID-19 diagnosis. • No distinction was made between which of the three U.S. COVID-19 vaccines administered; it is possible that some of the effect described is related to a specific vaccine, and that such an effect could not be detected based on the data used here. • While interactions between the observed demographic factors have been explored, interactions between pre-existing chronic conditions have not and may introduce unforeseen effects to the findings described here. • This analysis was conducted on patient data collected prior to the emergence of the delta variant as the predominant variant circulating in the United States.

Study arms

Vaccine prior to COVID diagnosis (N = 2392)

Vaccine 0-4 weeks after COVID diagnosis (N = 3560)

Vaccine 4-8 weeks after COVID diagnosis (N = 6181)

Vaccine 8-12 weeks after COVID diagnosis (N = 8055)

No vaccine before 12 weeks (N = 220460)

Characteristics

Arm-level characteristics

Characteristic	Vaccine prior to COVID diagnosis (N = 2392)	Vaccine 0-4 weeks after COVID diagnosis (N = 3560)	Vaccine 4-8 weeks after COVID diagnosis (N = 6181)	Vaccine 8-12 weeks after COVID diagnosis (N = 8055)	No vaccine before 12 weeks (N = 220460)
Male No of events	n = 888 ; % = 37.1	n = 1358 ; % = 38.1	n = 2389 ; % = 39.7	n = 3192 ; % = 39.6	n = 88695 ; % = 40.2
Female No of events	n = 1504 ; % = 62.8	n = 2202 ; % = 61.9	n = 3792 ; % = 61.3	n = 4863 ; % = 60.4	n = 131765 ; % = 59.8
Hispanic or Latino No of events	n = 167 ; % = 6.98	n = 263 ; % = 7.39	n = 589 ; % = 9.53	n = 880 ; % = 10.9	n = 24418 ; % = 11.1
Not hispanic or latino No of events	n = 1298 ; % = 54.3	n = 1836 ; % = 51.6	n = 3147 ; % = 50.9	n = 3808 ; % = 47.3	n = 107334 ; % = 48.7

Outcomes

Long COVID

Outcome	Vaccine prior to COVID diagnosis vs No vaccine before 12 weeks, , N2 = 2392, N1 = 220460	Vaccine 0-4 weeks after COVID diagnosis vs No vaccine before 12 weeks, , N2 = 3560, N1 = 220460	Vaccine 4-8 weeks after COVID diagnosis vs No vaccine before 12 weeks, , N2 = 6181, N1 = 220460	Vaccine 8-12 weeks after COVID diagnosis vs No vaccine before 12 weeks, , N2 = 8055, N1 = 220460
Any symptom Odds ratio/95% CI	0.22 (0.2 to 0.25)	0.38 (0.35 to 0.41)	0.54 (0.51 to 0.57)	0.75 (0.71 to 0.78)

Outcome	Vaccine prior to COVID diagnosis vs No vaccine before 12 weeks, , N2 = 2392, N1 = 220460	Vaccine 0-4 weeks after COVID diagnosis vs No vaccine before 12 weeks, , N2 = 3560, N1 = 220460	Vaccine 4-8 weeks after COVID diagnosis vs No vaccine before 12 weeks, , N2 = 6181, N1 = 220460	Vaccine 8-12 weeks after COVID diagnosis vs No vaccine before 12 weeks, , N2 = 8055, N1 = 220460
>1 symptom Odds ratio/95% CI	0.11 (0.09 to 0.14)	0.19 (0.16 to 0.22)	0.32 (0.29 to 0.35)	0.46 (0.43 to 0.49)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Any symptom

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics	Probably no

Section	Question	Answer
	observed after the start of intervention? If N/PN to 2.1: go to 2.4	
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

>1 symptom

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No information
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	No information
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Strain W, 2022

Bibliographic Reference	Strain W, D; 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; vol. 10 (no. 5); 652

Study details

Study design	Cross-sectional study
Study start date	16-Mar-2021
Study end date	05-Apr-2021

Aim of the study	To determine the impact of first dose of vaccination on long term symptoms of COVID-19
Country/ Geographical location	International (survey of members across international Long COVID support groups)
Study setting	Community
Population description	Vaccinated adults symptomatic of long term effects from pre-vaccination infection
Inclusion criteria	The survey was open to those with current or recent (at the time of vaccination) symptoms of long COVID, with a diagnosis of COVID-19 based on PCR/antibody testing, symptoms and contact with a proven case or symptoms alone.
Exclusion criteria	None reported
Intervention/test/approach	First dose of a COVID-19 vaccination (vaccines approved for use in UK: AstraZeneca, Pfizer, Moderna)
Comparator (where applicable)	None reported (individual vaccines were compared to each other but this is not directly relevant to the question of safety and impact of vaccines overall for long term effects of COVID-19)
Methods for population selection/allocation	The survey was co-designed and co-implemented between researchers at the University of Exeter Medical School, University of Kent, LongCovidSOS and the ZeroCovid Alliance. Respondents were invited to participate through social media posted online by the LongCovidSOS patient advocacy group on their website and promoted on Twitter, in the international Body Politic COVID-19 Support Group and in several UK-based and international Long COVID Facebook groups (Israel, Russia, India, South Africa). An invitation to participate was also sent to the LongCovidSOS subscriber email list. Participants were encouraged to wait until a week after vaccination before completing the survey to avoid the results being unduly impacted by adverse immediate reactions to the vaccine. This produced a cross-sectional convenience non-probability sample of people with lived experience.
Methods of data analysis	For this survey, no formal power calculations were made. Baseline characteristics are presented without formal statistical analysis. When determining the correlates of each symptom, multivariate regression analysis was performed evaluating the impact of each vaccine on symptoms, adjusted for baseline symptom score, age group (to within 5 years), sex, ethnicity and duration of Long COVID symptoms. Mean and 95% CI are presented after adjustment, with a positive number representing an improvement in symptoms, whereas a negative number suggesting deterioration. Whereas the intrapersonal reproducibility of visual analogue scores is good, the interpersonal agreement is less satisfactory. Therefore, we analysed the individual percentage change in symptom

	score, rather than the absolute difference in symptom score. Sensitivity analyses were performed considering only respondents who had PCR or antibody confirmed COVID-19 infections, and a further analysis that included those with a confirmed COVD-19 contact in addition to symptoms. The measured significance of the variables of interest is reported without adjustment for multiple testing. Where presented, the significance of co-variates within the models is presented only after Bonferonni correction. Statistical significance was considered at $p<0.05$. Statistical analysis was performed using Stata SE 16.1 (Mac version: Statacorp ltd Texas).
Attrition/loss to follow-up	88 participants: 45 had pre-existing myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) but no evidence of COVID infection and a further 43 did not complete the survey in full. 812 of 900 respondents were included in the final analysis.
Source of funding	No funding was provided for this survey.
Study limitations (Author)	The observational nature of the survey limits drawing direct causal inference. The online survey recruited most participants via social media and is unlikely to be representative of the population of people with Long COVID. Most respondents identified as white (90.8%) and just over 80% were female, which in the case of the latter is a much higher proportion than that reported by the ONS6 . The age range of respondents was broader, with a good representation between the ages of 31 and 65, and a further 65 respondents over 65 but only three respondents under the age of 20. The survey asks respondents to report their current symptoms and recall their symptoms pre-vaccination, with some individuals having to remember how they were feeling several weeks beforehand, possibly resulting in recall bias. Although the numerical recall may be flawed the overall trend in symptoms is likely to be robust. Specifically, an individual may not be able to accurately recall whether their score was a 7 or 8, however they are likely to accurately remember that their symptoms have improved rather than deteriorated. The authors were not able to include a control group of unvaccinated participants, however over 80% of those who completed the survey had been suffering symptoms for more than six months and we therefore consider the probability that any recovery was spontaneous as fairly low.
Study limitations (Reviewer)	

Study arms

People with Long COVID (N = 812)

Characteristics

Study-level characteristics

Characteristic	Study (N = 812)
20 years and under No of events	n = 3 ; % = 0.4
21–30 years No of events	n = 30 ; % = 3.7
31-40 years No of events	n = 148 ; % = 18.2
41-50 years No of events	n = 240 ; % = 29.6
51–60 years No of events	n = 266 ; % = 32.7
61–70 years No of events	n = 105 ; % = 13
71 years and over No of events	n = 20 ; % = 2.5
Female No of events	n = 654 ; % = 80.6
Male No of events	n = 158 ; % = 19.4
Severity of acute COVID: No symptoms No of events	n = 9 ; % = 1.1
Severity of acute COVID: Mild symptoms No of events	n = 104 ; % = 12.8
Severity of acute COVID: Moderate symptoms No of events	n = 610 ; % = 75.2

Characteristic	Study (N = 812)
Severity of acute COVID: Short hospital stay No of events	n = 60 ; % = 7.4
Longer hospital stay with or without ITU No of events	n = 29 ; % = 3.6
Diagnosis of COVID: PCR test No of events	n = 252 ; % = 31.1
Diagnosis of COVID: Antibody test No of events	n = 91 ; % = 11.2
Diagnosis of COVID: Symptoms and contact No of events	n = 72 ; % = 8.9
Diagnosis of COVID: Symptoms alone No of events	n = 380 ; % = 46.8
Duration of long COVID: 4-12 weeks No of events	n = 44 ; % = 5.4
Duration of long COVID: 3-6 months No of events	n = 122 ; % = 15
Duration of long COVID: 6-9 months No of events	n = 65 ; % = 8
>9 months No of events	n = 581 ; % = 71.6

Outcomes

Change in symptoms

Outcome	People with Long COVID, , N = 812
Overall improvement in symptoms No of events	n = 470 ; % = 57.9
Overall improvement in symptoms: with Oxford-AstraZeneca No of events	n = NR ; % = 58

Outcome	People with Long COVID, , N = 812
Overall improvement in symptoms: with Pfizer-BioNTech No of events	n = NR ; % = 56
Overall improvement in symptoms: with Moderna No of events	n = NR ; % = 66
Overall deterioration of symptoms No of events	n = 145 ; % = 17.9
Overall deterioration in symptoms: with Oxford-AstraZeneca No of events	n = NR ; % = 19
Overall deteriortion in symptoms: with Pfizer-BioNTech No of events	n = NR ; % = 18
Overall deterioration in symptoms: with Moderna No of events	n = NR ; % = 12
Overall no change in symptoms No of events	n = 188 ; % = 23.1
Overall no change in symptoms: with Oxford-AstraZeneca No of events	n = NR ; % = 23
Overall no change in symptoms: with Pfizer-BioNTech No of events	n = NR ; % = 26
Overall no change in symptoms: with Moderna No of events	n = NR ; % = 22

Critical appraisal - GUT - JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies: Interventions (cross-sectional)

Overall improvement in symptoms

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Unclear *(Baseline characteristics were presented but some important characteristics were omitted e.g. ethnicity, BMI, frailty, comorbidity status)*
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear *(Reliance on self-reporting in survey)*
Assessment questions	Were objective, standard criteria used for measurement of the condition?	No *(The authors stated that a sensitivity analysis had been conducted on respondents with a PCR or antibody confirmed COVID-19 infection but the results of this were not reported)*
Assessment questions	Were confounding factors identified?	Unclear *(Some confounders were reported but others were omitted e.g. frailty, comorbidity status)*
Assessment questions	Were strategies to deal with confounding factors stated?	Yes *(Regression analysis was adjusted for baseline symptom score, age group (to within 5 years), sex, ethnicity and duration of Long COVID symptoms)*
Assessment questions	Were the outcomes measured in a valid and reliable way?	Unclear *(Self-reported in a survey)*
Assessment questions	Was appropriate statistical analysis used?	Unclear
Overall bias and directness	Risk of bias judgment	High *(Due to lack of control group, self-reported outcomes, incomplete reporting, potential confounding, non-validated outcome measures)*
Overall bias and directness	Directness	Directly applicable

Tannous, 2022

Bibliographic Reference	Tannous, Jonika; Pan, Alan; Potter, Thomas; Bako, Abdulaziz; Dlouhy, Katharine; Drews, Ashley; Sostman, Dirk; Vahidy, Farhaan; Real World Evidence of Effectiveness of COVID-19 Vaccines and Anti SARS-CoV-2 Monoclonal Antibodies Against Post-Acute Sequelae of SARS-CoV-2 Infection; 2022

Study details

Study design	Cohort studies
Study start date	03-Mar-2020

Study end date	20-Nov-2021
Aim of the study	To evaluate real world evidence of COVID-19 vaccines against PASC in a diverse US metropolitan population
Country/ Geographical location	USA
Study setting	
Definition of long term effects used in the study	PASC was diagnosed based on the reported new onset of constitutional (palpitations, malaise / fatigue, and headache) or systemic (sleep disorders, shortness of breath, mood / anxiety disorders, cough, and cognitive impairment) symptoms / conditions as defined by the Centers for Disease Control and Prevention (CDC)
Population description	Adult patients (≥ 18 years) with a positive PCR test result for COVID-19 and flagged those who survived beyond 28-days of their initial diagnosis. Vaccine efficacy against PASC was evaluated among breakthrough cases only, which were defined as cases with positive PCR tests after achieving complete immunization (> 14 days after 2-doses of mRNA vaccines or a single dose of the Ad26.COV2.S vaccine).
Inclusion criteria	
Intervention/test/approach	2 doses of mRNA vaccines or a single dose of As26.COV2.S vaccine
Comparator (where applicable)	No vaccine
Methods for population selection/allocation	• Data was obtained from the Houston Methodist COVID-19 Surveillance and Outcomes Registry (CURATOR) • CURATOR is an institutional review board (IRB) approved COVID-19 specific bioinformatics pipeline that captures sociodemographic, comorbidity, disease severity, hospitalization, treatment • CURATOR is a longitudinal data repository with > 90% of patients having data on retrospective pre-COVID (since March 2016) encounters, and all patients having prospective post-COVID healthcare utilization encounters across the Houston Methodist system.
Methods of data analysis	• Multivariable logistic regression models reporting odds rations and 95% CUs as likelihood estimates of PASC associated with COVID-19 vaccination status. • Models were adjusted for age (18 to 39, 40 to 64, 65+ years), sex, race, ethnicity, area deprivation index (ADI: 0 to 3, 4 to 6, 7+), Charlson Comorbidity Index (CCI: 0 to 1, 2 to 4, 5+) and COVID-19 illness severity • The findings were externally validated by utilizing the TriNetX Analytics Network, a de-identified global research network that comprises EMR data across 57 healthcare organizations from six different countries

	• All analyses were replicated and adjusted for age, sex, CCI, and severe COVID-19 • Other variables included in the primary analyses were missing for a significant proportion of the TriNetX sample
Attrition/loss to follow-up	1953/55192 (3.25%) of overall cohort were excluded due to missing or unverifiable data.
Source of funding	Not reported
Study limitations (Author)	• Data limited to a single healthcare system
Study limitations (Reviewer)	Study does not report SARS-CoV-2 variant and was conducted before the emergence of Omicron.

Study arms

Vaccinated PASC (N = 332)

Unvaccinated PASC (N = 5597)

Characteristics

Study-level characteristics

Characteristic	Study (N = 5929)
Age >= 65years Mean (SD)	1669 (28.1)
Age 40 to 64 years Mean (SD)	2842 (47.9)
Age 18 to 39 years Mean (SD)	1418 (23.9)
Female No of events	n = 3686 ; % = 62.2
White/Caucasian No of events	n = 2571 ; % = 43.4

Characteristic	Study (N = 5929)
Black/African-American No of events	n = 1399 ; % = 23.6
Asian No of events	n = 313 ; % = 5.3
Native American/Other No of events	n = 34 ; % = 0.6
Hispanic/Latino No of events	n = 1612 ; % = 27.2
COVID 19: Ambulatory Mild Disease No of events	n = 4206 ; % = 70.9
COVID-19: Hospitalised - Moderate Disease No of events	n = 1278 ; % = 21.6
COVID-19: Hospitalised - Severe Disease No of events	n = 445 ; % = 7.5

Outcomes

PASC development

Outcome	Vaccinated PASC vs Unvaccinated PASC, , N2 = 332, N1 = 5597
Likelihood of developing PASC Odds ratio/95% CI	0.58 (0.52 to 0.66)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Likelihood of developing PASC

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no

Section	Question	Answer
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Probably no
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Probably no
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Probably yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably yes *(Some participants were excluded from the study for missing data)*
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably yes *(Some participants were excluded from*

Section	Question	Answer
		the study for missing data)
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Probably yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Taquet, 2022

Bibliographic Reference	Taquet, Maxime; Dercon, Quentin; Harrison Paul, J; Six-month sequelae of post-vaccination SARS-CoV-2 infection: A retrospective cohort study of 10,024 breakthrough infections.; Brain, behavior, and immunity; 2022; vol. 103; 154-162

Study details

Study design	Retrospective cohort study
Trial registration (if reported)	
Study start date	01-Jan-2021
Study end date	31-Aug-2021
Aim of the study	This cohort study based on electronic health records compares the 6-months outcomes of SARS-CoV-2 infection among individuals who were (vs. those who were not) vaccinated against COVID-19
Country/ Geographical location	USA
Study setting	Primary care centres, hospitals and specialist units
Definition of long term effects used in the study	Long COVID features (any and each of the following): • Abdominal symptoms • Abnormal breathing • Anxiety/depression • Chest/throat pain • Cognitive symptoms • Fatigue • Headache • Myalgia • Other pain
Population description	People with confirmed SARS-COV-2 infection
Inclusion criteria	• SARS-CoV-2 infection occurred at least 14 days after recorded administration of COVID-19 vaccine approved for use in the USA • People without a COVID vaccine were required to have received the influenza vaccine to exclude people with obvious vaccine hesitancy (but not those just with hesitancy towards COVID vaccine)
Exclusion criteria	
Intervention/test/approach	COVID 19 vaccine (BNT162b2 'Pfizer/BioNTech', mRNA-1273 'Moderna', or Ad26.COV2.S 'Janssen')
Comparator (where applicable)	No COVID vaccine plus influenza vaccine
Methods for population selection/allocation	• The study used TriNetX Analytics, a federated network of linked EHRs recording anonymised data from 59 healthcare organisations (HCOs), primarily in the USA, totalling 81 million patients.

	• Using the TriNetX user interface, cohorts are created based on inclusion and exclusion criteria, matched for confounding variables, and compared for outcomes of interest over specified time periods
Methods of data analysis	• Hazard ratios (HR) with 95% confidence intervals were calculated using the Cox model and the null hypothesis of no difference between cohorts was tested using log-rank tests. • The proportional hazard assumption was tested using the generalized Schoenfeld approach. When the assumption was violated, a time-varying HR was assessed using natural cubic splines fitted to the log-cumulative hazard • The contribution of the individual outcomes of interest within the composite endpoint (with death as the other component) was reported as the number of events of interest over the total number of events
Attrition/loss to follow-up	N/A
Source of funding	Work supported by the National Institute for Health Research (NIHR) Oxford Health Biomedical Research Centre
Study limitations (Author)	• SARS-CoV-2 variant(s) unknown in the population studied. Different variants could potentially affect the protective effect of the vaccines. There is evidence that variants of concerns are over-represented in break through infections. • Study pre-dates Omicron variant emergence • There is the potential that vaccination status may affect probability to seek or receive medical attention, particularly for less severe outcomes • The study will not have included people who had SARS-CoV-2 but were untested • The study was not designed to investigate whether the association between vaccination status and outcomes of subsequent SARS-CoV-2 infection was moderated by time interval between vaccine and infection • Different vaccines could not be compared against each other • Does not account for those who had a prior SARS-CoV-2 infection • No adjustments were made for medication use at the time of infection
Results summary	

Study arms

Vaccinated (N = 9479)

Unvaccinated (N = 9479)

Characteristics

Arm-level characteristics

Characteristic	Vaccinated (N = 9479)	Unvaccinated (N = 9479)
Age Mean (SD)	56.5 (18)	57.6 (20.6)
Female No of events	n = 5676 ; % = 59.9	n = 5761 ; % = 60.8
White No of events	n = 6783 ; % = 71.6	n = 6873 ; % = 72.5
Black or African American No of events	n = 1540 ; % = 16.2	n = 1514 ; % = 16
Unknown No of events	n = 783 ; % = 8.3	n = 756 ; % = 8

Outcomes

Study timepoints

6 month

Long-COVID Outcomes

Outcome	Vaccinated vs Unvaccinated, 6 month, N2 = 9479, N1 = 9479
Composite of death and any long-COVID feature Hazard ratio/95% CI	1.01 (0.96 to 1.05)

Outcome	Vaccinated vs Unvaccinated, 6 month, N2 = 9479, N1 = 9479
Composite of death and respiratory failure Hazard ratio/95% CI	0.7 (0.63 to 0.78)
Composite of death and intubation/ventilation Hazard ratio/95% CI	0.72 (0.61 to 0.84)
Composite of death and hypoxaemia Hazard ratio/95% CI	0.72 (0.65 to 0.8)
Composite of death and seizures Hazard ratio/95% CI	0.73 (0.62 to 0.86)
Composite of death and ICU admission Hazard ratio/95% CI	0.75 (0.65 to 0.85)
Composite of death and psychotic disorder Hazard ratio/95% CI	0.75 (0.63 to 0.89)
Composite of death and hair loss Hazard ratio/95% CI	0.75 (0.64 to 0.88)
Composite of death and hypercoagulopathy or venous thromboembolism Hazard ratio/95% CI	0.81 (0.72 to 0.91)
Composite of death and oxygen requirement Hazard ratio/95% CI	0.83 (0.75 to 0.92)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Composite of death and any long-COVID feature

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to	Not applicable

Section	Question	Answer
	be related to factors that are prognostic for the outcome?	
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes

Section	Question	Answer
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate

Section	Question	Answer
Overall bias	Directness	Directly applicable

Composite of death and respiratory failure

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*

Section	Question	Answer
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome	No information

Section	Question	Answer
	measurements within the outcome domain?	
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and intubation/ventilation

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable

Section	Question	Answer
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes

Section	Question	Answer
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and hypoxaemia

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants	Not applicable

Section	Question	Answer
	and reasons for missing data similar across interventions?	
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and seizures

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and ICU admission

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from	4.3. Were important co-interventions balanced across intervention groups?	No

Section	Question	Answer
intended interventions		
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and psychotic disorder

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information

Section	Question	Answer
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and hair loss

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No

Section	Question	Answer
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques	Not applicable

Section	Question	Answer
	used that are likely to correct for the presence of selection biases?	
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low

Section	Question	Answer
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information

Section	Question	Answer
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and hypercoagulopathy or venous thromboembolism

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31,*

Section	Question	Answer
		2021, a confirmed SARS-CoV-2 infection)
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Composite of death and oxygen requirement

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Data taken from EHR)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information

Section	Question	Answer
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no *(Both the primary and control cohorts were defined as all patients who had, between January 1, 2021 and August 31, 2021, a confirmed SARS-CoV-2 infection)*
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	Not applicable
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Tran, 2021

Bibliographic Reference	Tran, Viet-Thi; Perrodeau, Elodie; Saldanha, Julia; Pane, Isabelle; Ravaud, Philippe; Efficacy of COVID-19 Vaccination on the Symptoms of Patients With Long COVID: A Target Trial Emulation Using Data From the ComPaRe e-Cohort in France; 2021

Study details

Study design	Cohort studies

Trial registration (if reported)	
Study start date	Nov-2020
Study end date	May-2021
Aim of the study	The authors used data from the ComPaRe long COVID cohort to emulate a target trial evaluating the effect of a first COVID-19 vaccine injection among patients with long COVID on the severity and impact of their symptoms.
Country/ Geographical location	France
Study setting	The ComPaRe long COVID cohort is an ongoing nationwide e-cohort of patients with long COVID, in France, nested in the ComPaRe research program (www.compare.aphp.fr), an umbrella e-cohort of patients with chronic conditions.1
Definition of long term effects used in the study	Symptoms persisting more than three weeks past the initial infection and who reported at least one symptom attributable to long COVID at baseline.
Population description	Adult patients (≥ 18 years old) with a confirmed or suspected COVID-19 infection experiencing symptoms of Long COVID
Inclusion criteria	
Intervention/test/approach	COVID vaccination
Comparator (where applicable)	
Methods for population selection/allocation	To define a vaccinated group and a matched unvaccinated control group in a population where most patients were eventually vaccinated against COVID-19, the authors used the cohort data to emulate a sequence of three trials and then pooled them. Identified all patients who met the eligibility criteria when they were enrolled in the ComPaRe long COVID cohort (i.e. their first observation point, T0). Patients who received their first COVID-19 vaccination between baseline and 60 days (second observation point T1) were classified in the vaccination group and matched at a 1:1 ratio to patients who did not receive the vaccine in the same period classified as the control group. Patients were followed up for 120 days (i.e., their third observation point, T2 and endpoint of the first trial). Unvaccinated controls who were vaccinated before T2 were censored at the date of vaccination. The authors repeated this procedure by emulating two additional trials, by considering baseline at 60 days (ie, T1) for the second trial, and T2 for the third; they applied a similar follow-up strategy (ie, follow-up until T3 and T4, respectively).

	At the baseline of each of the three trials, patients' eligibility criteria were reassessed and those who no longer met the eligibility criteria, for example because they no longer reported symptoms, were excluded from that trial. Control patients who had since received COVID-19 vaccination were eligible for inclusion in the vaccination group even though they had previously served as a control. However, a patient could only be selected once as a control and once as a vaccinated patient.
Methods of data analysis	Within each of the three trials, each vaccinated patient was matched to an unvaccinated control according to their probability of getting vaccinated against COVID-19 given their baseline covariates (ie, the propensity score). The propensity score was calculated with a multivariable logistic regression model including variables planned and prespecified before outcome analyses. Data was pooled for the vaccination and the control groups from the three trials and estimated the effect of treatment by using paired t-tests for continuous outcomes, marginal Poisson models for dichotomous outcomes, and marginal Cox proportional hazard models for time-to-event outcomes.
Attrition/loss to follow-up	There were 69 patients lost to follow-up (32 in the vaccination group and 37 in the control group), and 275 (60·4%) patients in the control group were censored at their vaccination date. The median interval between baseline and censoring was 90 days (IQR 72·5 to 105).
Source of funding	None
Study limitations (Author)	• Despite the use of robust methods and statistical techniques to draw causal inferences from observational data, treatment was not randomly assigned, and potential unmeasured confounders could bias our results. • Data did not take patients' motivation to receive COVID-19 vaccination into account, although it may be related to their perception of their long COVID symptoms and this disease's impact, as measured with the long COVID ST and IT • All patients were infected before May 1, 2021 and thus were not infected with recent variants of concern.
Study limitations (Reviewer)	

Study arms

Vaccinated (N = 455)

Unvaccinated (N = 455)

Characteristics

Arm-level characteristics

Characteristic	Vaccinated (N = 455)	Unvaccinated (N = 455)
Age Median (IQR)	47 (39 to 55)	47 (40 to 53)
Male No of events	n = 92 ; % = 20.2	n = 85 ; % = 18.7

Outcomes

Study timepoints

- 120 day

Long COVID

Outcome	Vaccinated vs Unvaccinated, 120 day, N2 = 455, N1 = 455
long COVID ST score Mean (95% CI)	-1.8 (-2.5 to -1)
Remission of all symptoms Hazard ratio/95% CI	1.97 (1.23 to 3.15)
long COVID IT score Impact of Long COVID on patient's lives Mean (95% CI)	-3.3 (-6.2 to -0.5)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

long COVID ST score

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information

Section	Question	Answer
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Remission of all symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate

Section	Question	Answer
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

long COVID IT score

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Probably no
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably yes
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	No information
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	No information
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Probably yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Probably yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Tsuchida, 2022

Bibliographic Reference	Tsuchida, Tomoya; Hirose, Masanori; Inoue, Yoko; Kunishima, Hiroyuki; Otsubo, Takehito; Matsuda, Takahide; Relationship between changes in symptoms and antibody titers after a single vaccination in patients with Long COVID.; Journal of medical virology; 2022

Study details

Trial registration (if reported)	
Study start date	Apr-2021
Aim of the study	To evaluate changes in symptoms and antibody titers after a single vaccination and assess the relationship in patients with Long COVID.
Country/ Geographical location	Japan
Study setting	Long COVID outpatient clinic
Population description	The patients presented with several sequelae symptoms (fever, malaise, dyspnoea, cough, taste abnormality, olfactory abnormality, hair loss, sore throat, joint pain, numbness of limbs, muscle pain, headache, chest pain, vomiting, diarrhoea, decreased motivation, sleeplessness, anxiety, depressed mood, forgetfulness, and skin symptoms) after >2 months since the onset of the COVID-19 diagnosed using a polymerase chain reaction test or antigen test.
Intervention/test/approach	COVID-19 vaccination
Comparator (where applicable)	
Methods for population selection/allocation	For patients who requested vaccination and provided consent to participate in this study, antibody titers were measured before vaccination and approximately 2 weeks after the single vaccination. The patients were informed about the results and their interpretation. Three self-assessments of post vaccination changes in the main sequelae symptoms were confirmed based on the patient's response as follows: unchanged, relief, and worsened. Based on the results, patients chose whether to undergo the second vaccination.
Methods of data analysis	Continuous variables were compared using the Kruskal–Wallis test. Categorical variables were compared using the $\chi 2$ test and Fisher's exact test. The ratio of antibody titers before and after the first vaccination

	was calculated. Based on subjective post vaccination symptoms, patients were divided into three groups (unchanged, relief, and worsened groups) and two groups (worsened and non worsened [unchanged + relief] groups). Antibody titers before and after the first vaccination were compared using the Mann–Whitney test and Kruskal–Wallis test. If the Kruskal–Wallis test was significant, multiple comparisons were performed using the Dunn's test. Antibody titers after the first and second vaccinations were not compared because of the small number of patients who underwent the second vaccination.
Attrition/loss to follow-up	All enrolled participants were followed up
Source of funding	Not reported
Study limitations (Author)	• Single centre study with a small sample size • Changes in sequelae symptoms could not be evaluated. • It is possible that outpatient treatment for symptoms had begun and that self-assessment of sequelae did not accurately reflect the relationship of the vaccine with the sequelae status.
Other details	
Summary of findings	• Postvaccination symptoms were relieved, worsened, and unchanged in 7 (16.7%), 9 (21.4%), and 26 (61.9%) patients, respectively. • The non worsened group had more young people than the worsened group (Kruskal–Wallis test, p = 0.02; Dunn test, unchanged group vs. relief group, p = 0.04; unchanged group vs. worsened group, p = 0.01; relief group vs. worsened group, p = 0.33). • There were 12 (29%) patients who did not receive the second vaccination.

Study arms

Unchanged (N = 26)

Relief (N = 7)

Worse (N = 9)

Characteristics

Arm-level characteristics

Characteristic	Unchanged (N = 26)	Relief (N = 7)	Worse (N = 9)
Age Median (IQR)	40 (30 to 47)	53 (29 to 58)	50 (48 to 55)
Male No of events	n = 12 ; % = 46.2	n = 3 ; % = 42.9	n = 2 ; % = 22.2
Onset before vaccination (days) Median (IQR)	196 (110 to 238)	146 (58 to 338)	173 (136 to 227)

Quality appraisal and risk of bias

Section	Question	Answer
Study objective	Was the hypothesis/aim/objective of the study clearly stated?	Yes
Study design	Was the study conducted prospectively?	Yes
Study design	Were the cases collected in more than one centre?	No
Study design	Were patients recruited consecutively?	Unclear
Study population	Were the characteristics of the patients included in the study described?	Yes
Study population	Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	No
Study population	Did patients enter the study at a similar point in the disease?	Yes
Intervention and co-intervention	Was the intervention of interest clearly described?	Yes
Intervention and co-intervention	Were additional interventions (co-interventions) clearly described?	No
Outcome measure	Were relevant outcome measures established a priori?	Yes
Outcome measure	Were outcome assessors blinded to the intervention that patients received?	No

Section	Question	Answer
Outcome measure	Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes
Outcome measure	Were the relevant outcome measures made before and after the intervention?	Unclear *(No baseline symptoms reported in the paper)*
Statistical analysis	Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
Results and conclusions	Was follow-up long enough for important events and outcomes to occur?	Unclear
Results and conclusions	Were losses to follow-up reported?	No
Results and conclusions	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No
Results and conclusions	Were the adverse events reported?	Yes
Results and conclusions	Were the conclusions of the study supported by results?	Unclear
Competing interests and sources of support	Were both competing interests and sources of support for the study reported?	No
Overall Risk of Bias	Risk of Bias	High
Overall Risk of Bias	Applicability	Directly applicable

Wanga, 2021

Bibliographic Reference	Wanga, Valentine; Chevinsky Jennifer, R; Dimitrov Lina, V; Gerdes Megan, E; Whitfield Geoffrey, P; Bonacci Robert, A; Nji Miriam A, M; Hernandez-Romieu Alfonso, C; Rogers-Brown Jessica, S; McLeod, Tim; Rushmore, Julie; Lutfy, Caitlyn; Bushman, Dena; Koumans, Emilia; Saydah, Sharon; Goodman Alyson, B; Coleman, King; Sallyann, M; Jackson Brendan, R; Cope Jennifer, R; Long-Term Symptoms Among Adults Tested for SARS-CoV-2 - United States, January 2020-April 2021.; MMWR. Morbidity and mortality weekly report; 2021; vol. 70 (no. 36); 1235-1241

Study details

Study design	Cross-sectional study
Study start date	09-Apr-2021
Study end date	23-Apr-2021
Aim of the study	To compare long-term symptom changes after receiving a COVID-19 vaccination in adults with and without a previous COVID-19 infection.

Country/ Geographical location	USA
Study setting	A nonprobability-based Internet panel survey among 6,021 noninstitutionalized U.S. adults aged ≥18 years via the Lucid platform
Population description	U.S. adults aged ≥18 years with long-term symptoms lasting >4 weeks since COVID-19 onset
Intervention/test/approach	COVID-19 vaccination
Methods for population selection/allocation	Quota sampling and statistical weighting were used to align the sample with U.S. population distributions by sex, age group, U.S. Census region, race and ethnicity, and education.
Methods of data analysis	All analyses were conducted using SAS (version 9.4; SAS Institute) and were weighted by sex, age group, region, race and ethnicity, and education.
Attrition/loss to follow-up	
Source of funding	Not reported
Study limitations (Author)	• The study used a nonprobability-based sample, which limits its generalisability • Responses were self-reported and subject to reporting bias • New symptoms occurring after the month when the first positive COVID-19 test result was received among those who received a positive test result were not assessed, and the reported symptoms could not be linked directly to SARS-CoV-2. • Differences in duration or severity of long-term symptoms could not be assessed as the survey did not ask about this. • Respondents who always received a negative test result generally had a longer period in which to report symptoms, potentially inflating prevalence of their health care use and long-term symptoms. • The study could not assess validity of SARS-CoV-2 tests, and some false-positive or false-negative test results might have resulted in misclassification of some respondents

Study arms

People who received a positive COVID result (N = 698)

People who received negative COVID result (N = 2437)

Characteristics

Arm-level characteristics

Characteristic	People who received a positive COVID result (N = 698)	People who received negative COVID result (N = 2437)
18-29 years Nominal	26.3	23.2
18-29 years Range	22.8 to 29.7	21.4 to 24.9
30–39 years Nominal	25.4	19
30–39 years Range	22 to 28.8	17.4 to 20.6
40–49 years Nominal	18.6	16.4
40–49 years Range	15.1 to 22.1	14.7 to 18.2
50–59 years Nominal	15	16.6
50–59 years Range	11.8 to 18.2	14.8 to 18.4
60-69 years Nominal	10.3	16.4
60-69 years Range	7.8 to 12.8	14.8 to 18
at least 70 years Nominal	4.4	8.4
at least 70 years Range	2.8 to 6	7.2 to 9.5
Male	51.5	48.5

Characteristic	People who received a positive COVID result (N = 698)	People who received negative COVID result (N = 2437)
Nominal		
Male Range	47.4 to 55.7	46.3 to 50.7
Female Nominal	48.5	51.5
Female Range	44.3 to 52.6	49.3 to 53.7

Outcomes

Reported vaccination effects on long-term symptoms

Outcome	People who received a positive COVID result, , N = 100	People who received negative COVID result, , N = 285
Vaccine made symptoms better Percentage %	28.7	15.7
Vaccine made symptoms better Range	18.6 to 38.7	11.3 to 20
Vaccine did not affect symptoms at all Percentage %	26.4	59.2
Vaccine did not affect symptoms at all Range	16.7 to 36	53.1 to 65.4
Vaccine made symptoms worse† Percentage %	16.1	11.2
Vaccine made symptoms worse† Range	8.4 to 23.7	6.9 to 15.4
Symptoms were gone before receiving vaccine	28.4	13.1

Outcome	People who received a positive COVID result, , N = 100	People who received negative COVID result, , N = 285
Percentage %		
Symptoms were gone before receiving vaccine Range	18.4 to 38.5	8.9 to 17.3

Critical appraisal - GUT - JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies: Interventions (cross-sectional)

Vaccine made symptoms better

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Unclear
Assessment questions	Were confounding factors identified?	Unclear
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Vaccine did not affect symptoms at all

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes

Section	Question	Answer
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Unclear
Assessment questions	Were confounding factors identified?	Unclear
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Vaccine made symptoms worse

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Unclear
Assessment questions	Were confounding factors identified?	Unclear
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Symptoms were gone before receiving vaccine

Section	Question	Answer
Assessment questions	Were the criteria for inclusion in the sample clearly defined?	Yes
Assessment questions	Were the study subjects and the setting described in detail?	Yes
Assessment questions	Was the exposure measured in a valid and reliable way?	Unclear
Assessment questions	Were objective, standard criteria used for measurement of the condition?	Unclear
Assessment questions	Were confounding factors identified?	Unclear
Assessment questions	Were strategies to deal with confounding factors stated?	Unclear
Assessment questions	Were the outcomes measured in a valid and reliable way?	Yes
Assessment questions	Was appropriate statistical analysis used?	Yes
Overall bias and directness	Risk of bias judgment	Some concerns
Overall bias and directness	Directness	Directly applicable

Wisnivesky et al.

Bibliographic Reference	Wisnivesky, Juan; Govindarajulu, Usha; Bagiella, Emilia; Goswami, Ruchir; Kale, Minal; Campbell, Kirk; Meliambro, Kristin; Chen, Zijian; Aberg, Judith; Lin, Jenny; Association of Vaccination With the Persistence of Post-COVID Symptoms

Study details

Study design	Cohort studies
Trial registration (if reported)	
Study end date	23-Aug-2021
Aim of the study	To assess whether vaccination was associated with resolution of or improvement in PASC symptoms in a prospective registry of COVID-19 patients.
Country/ Geographical location	New York City, USA
Study setting	Prospective registry established at a tertiary care health system
Definition of long term effects used in the study	Post-acute sequelae of COVID (PASC) not further defined.
Population description	Patients enrolled into an institutional Post-COVID-19 Registry at the Mount Sinai Health System (MSHS) in New York City.

Inclusion criteria	• All participants were unvaccinated at the time of the baseline interview. • ≥ 18 years of age • Laboratory documented infection with SARS-CoV-2 • Spoke English or Spanish • Received care at Mount Sinai Health System. • Reported at least one PASC symptom at baseline.
Exclusion criteria	• History of dementia
Intervention/test/approach	COVID-19 vaccination
Comparator (where applicable)	No vaccination
Methods for population selection/allocation	• Study participants were recruited between July 20, 2020, and February 26, 2021, and had completed a baseline and 6-month follow-up interview • Data regarding vaccination included vaccine type (Pfizer, Moderna, or Johnson & Johnson), date of vaccination, and number of doses received. • The authors also linked registry data to information from the electronic medical record as an additional source of vaccination status. • To ensure sufficient time for an immune response, individuals who had received at least one dose of the vaccine at least 2 weeks prior to the 6-month follow-up interview were coded as vaccinated. • Participants were categorised according to the number of doses (none, one or two) received; • COVID-19 patients that received one dose of the Johnson & Johnson vaccine were included in the two-dose group.
Methods of data analysis	• For each outcome. the mean difference from baseline to 6 months was compared between vaccinated vs unvaccinated people using a two-sample *t* test • A propensity score model was used to adjust for baseline differences (age, gender, race, ethnicity, marital status, income, smoking history, comorbidities and severity of acute COVID-19). • Linear regression model was fitted to compare change in symptom scores in vaccinated vs unvaccinated people. • Secondary analyses were conducted comparing differences in the PADC trajectory according to the number of vaccines doses received.
Attrition/loss to follow-up	• Of the 1189 COVID-19 patients recruited in the post-COVID-19 registry as of the time of these analyses, 464 have completed the 6-month interview as of August 23, 2021.

	• Of these, 11 were excluded due to missing data regarding vaccination leaving a cohort of 453 participants
Source of funding	Dr. Wisnivesky received consulting honorarium from Atea, Sanofi, PPD, and Banook and grants from Sanofi, Arnold Consulting, and Regeneron. Dr. Aberg reports grants from Atea, Emergent Biosolutions, Frontier Technologies, Gilead Sciences, Glaxo Smith Kline, Janssen, Merck, Pfizer, Regeneron, and Viiv Healthcare and consulting honorarium from Glaxo Smith Kline and Merck. The other authors report no conflicts of interest.
Study limitations (Author)	• Non-randomised study so cannot exclude systematic differences among vaccinated vs. unvaccinated patients. • Differences in vaccine type may be a limitation in determining effect of vaccination on changes in PASC symptoms • Risk of reporting bias although minimised by using objective measures • Risk of selection bias as those experiencing symptoms may have been more likely to complete the 6 month interview • Insufficient power to identify small differences in some PASC symptoms • Included people who experienced first-wave COVID so may not be generalisable to later waves or different variants of the virus.
Other details	
Results summary	

Study arms

Vaccinated (N = 324)

Non-vaccinated (N = 129)

Characteristics

Arm-level characteristics

Characteristic	Vaccinated (N = 324)	Non-vaccinated (N = 129)
Age Mean (SD)	50.1 (13.4)	49.7 (14.1)
Female No of events	n = 211 ; % = 65	n = 83 ; % = 64
White No of events	n = 200 ; % = 62	n = 73 ; % = 57
Black No of events	n = 46 ; % = 14	n = 31 ; % = 24
Asian No of events	n = 17 ; % = 5	n = 2 ; % = 2
Other No of events	n = 55 ; % = 17	n = 22 ; % = 17
Hypertension No of events	n = 102 ; % = 32	n = 44 ; % = 34
Coronary artery disease No of events	n = 15 ; % = 5	n = 3 ; % = 2
Diabetes No of events	n = 38 ; % = 12	n = 15 ; % = 12
Asthma No of events	n = 86 ; % = 27	n = 40 ; % = 31
COPD No of events	n = 11 ; % = 3	n = 4 ; % = 3
Cancer No of events	n = 41 ; % = 13	n = 11 ; % = 9
Time since COVID-19 diagnosis (days) Mean (SD)	213 (62)	172 (56)
Site of COVID care: Outpatient No of events	n = 132 ; % = 41	n = 53 ; % = 41
Site of COVID care: Emergency room	n = 97	n = 28 ; % = 22

Characteristic	Vaccinated (N = 324)	Non-vaccinated (N = 129)
No of events		
Site of COVID care: Inpatient No of events	n = 73	n = 42 ; % = 33
Site of COVID care: Intensive care unit No of events	n = 18 ; % = 6	n = 6 ; % = 5

Outcomes

Adjusted Differences in Post-Covid Symptom Scores

Outcome	Vaccinated vs Non-vaccinated, , N2 = NR, N1 = NR
Anosmia Mean (95% CI)	-0.02 (-0.35 to 0.31)
Dyspnoea Mean (95% CI)	0.05 (-0.15 to 0.25)
Cough Mean (95% CI)	-0.17 (-0.55 to 0.22)
Depression symptoms Mean (95% CI)	0.02 (-1.18 to 1.22)
Covid PTSD symptoms Mean (95% CI)	2.53 (-3.06 to 8.12)
Non-Covid PTSD symptoms Mean (95% CI)	-2.53 (-12.11 to 7.04)
QoL: Physical function Mean (95% CI)	-1.16 (-3.35 to 1.02)
QoL: Anxiety Mean (95% CI)	-0.29 (-2.84 to 2.27)
QoL: Depression Mean (95% CI)	-1.12 (-3.8 to 1.56)
QoL: Fatigue Mean (95% CI)	-1.42 (-4.15 to 1.32)

Outcome	Vaccinated vs Non-vaccinated, , N2 = NR, N1 = NR
QoL: Social roles Mean (95% CI)	-0.17 (-3.18 to 2.83)
QoL: Sleep Mean (95% CI)	1.51 (-0.86 to 3.87)
QoL: Pain Mean (95% CI)	-0.02 (-2.74 to 2.7)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Anosmia

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No

Section	Question	Answer
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate

Section	Question	Answer
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Dyspnoea

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes

Section	Question	Answer
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Cough

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate

Section	Question	Answer
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Depression symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Covid PTSD symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Non-Covid PTSD symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information

Section	Question	Answer
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

QoL: Physical function

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

QoL: Anxiety

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes

Section	Question	Answer
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

QoL: Depression

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information

Section	Question	Answer
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

QoL: Fatigue

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

QoL: Social roles

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No

Section	Question	Answer
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

QoL: Sleep

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes

Section	Question	Answer
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

QoL: Pain

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	No information
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes

Section	Question	Answer
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Probably yes
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably yes
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Moderate
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	No information
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	No information
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	No
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Yes
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	No information
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	No information
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate

Section	Question	Answer
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	Probably no
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	Probably no
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	Probably no
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Wynberg, 2022

Bibliographic Reference	Wynberg, Elke; Han Alvin, X; Boyd, Anders; van Willigen Hugo D, G; Verveen, Anouk; Lebbink, Romy; van der Straten, Karlijn; Kootstra, Neeltje; van Gils Marit, J; Russell, Colin; Leenstra, Tjalling; de Jong Menno, D; de Bree Godelieve, J; Prins, Maria; RECoVERED, Study; Group; The effect of SARS-CoV-2 vaccination on post-acute sequelae of COVID-19 (PASC): A prospective cohort study.; Vaccine; 2022

Study details

Study design	Cohort studies
Trial registration (if reported)	Included participants from the RECoVERED trial (NL73759.018.20)
Study start date	11-May-2020
Study end date	21-Jun-2021
Aim of the study	To assess the effect of vaccination on recovery from PASC symptoms.
Country/ Geographical location	Netherlands
Study setting	
Definition of long term effects used in the study	The definition of PASC was based on the WHO criteria as reporting at least one COVID-19 symptom that started within one month of overall illness onset and lasted beyond 3 months after illness onset.
Population description	186 people with previous SARS-CoV-2 infection who developed PASC symptoms
Inclusion criteria	• Non-hospitalised and enrolled within 7 days of diagnosis of acute COVID-19, followed up for 3 months

	• Hopsitalised and enrolled within 7 days of hospital admission for acute COVID-19, followed up for 3 months • PCR-confirmed SARS-CoV-2 infection • Aged 16-85 years and residing in the municipal region of Amsterdam
Exclusion criteria	• Individuals residing in a nursing home and those with mental disorders deemed likely to interfere to adherence to study procedures.
Intervention/test/approach	• Two doses (28 days apart) of the BNT162b2 mRNA (Pfizer/BioNTech) vaccine.
Comparator (where applicable)	No vaccine
Methods for population selection/allocation	Participants who had not yet been vaccinated were invited to receive 2 doses of vaccine.
Methods of data analysis	• Among participants with PASC. vaccinated and unvaccinated participants were matched according to participant age group (<45 years; 45-65 years; 65+ years), sex (male/female), BMI (obese or not) and time since illness onset (in months). • This was achieved by 1:1 exact matching the month in which a participant received their first vaccination to a participant who remained unvaccinated for at least one month following the matched time-point, using a coarsened exact matching (CEM) approach • Participants were allowed to contribute multiple periods of unvaccinated follow-up and could contribute to both vaccinated and unvaccinated time intervals, provided that symptom data were available for at least one follow-up time-point after the matched time-point • The authors modelled the mean total number of symptoms at each time-point using linear regression, which was compared between the matched vaccinated and unvaccinated individuals using Wald chi-squared tests. • Variance estimates were bootstrapped to ensure that variance was independent and identically distributed across participants. These variance estimates were used to calculate 95% confidence intervals (CIs) around the mean number of PASC symptoms at each time-point. • Logistic regression was used to compared the odds of having recovered fully from PASC by the end of the matched follow-up intervals between matched pairs of vaccinated and unvaccinated individuals.
Attrition/loss to follow-up	N/A

Source of funding	This work was supported by the Netherlands Organization for Health Research and Development (ZonMw)
Study limitations (Author)	• Residual confounding may still exist as participants were not randomised. • A large proportion of the cohort were vaccinated around 12 months after illness onset after which symptom questionnaires were no longer completed. This greatly reduced the number of participants available for matching, limiting statistical power. • Without SARS-CoV-2-negative controls, we cannot be sure to what extent the symptoms recorded were causally related to SARS-CoV-2 infection as opposed to either underlying comorbidities • All participants were infected with wild-type or Alpha SARS-CoV-2 so may not be generalisable to other variants.
Study limitations (Reviewer)	
Results summary	

Study arms

Vaccinated (N = 36)

Unvaccinated (N = 32)

Characteristics

Arm-level characteristics

Characteristic	Vaccinated (N = 36)	Unvaccinated (N = 32)
Age Median (IQR)	53.5 (34.5 to 61)	48.5 (37 to 63)
Male No of events	n = 12 ; % = 33	n = 12 ; % = 38
Female	n = 24 ; % = 67	n = 20 ; % = 63

Characteristic	Vaccinated (N = 36)	Unvaccinated (N = 32)
No of events		
Mild COVID 19 No of events	n = 11 ; % = 31	n = 3 ; % = 9
Moderate COVID 19 No of events	n = 23 ; % = 64	n = 18 ; % = 56
Severe/Critical COVID 19 No of events	n = 2 ; % = 6	n = 11 ; % = 64
0 COVID-19 high-risk comorbidities No of events	n = 19 ; % = 53	n = 19 ; % = 59
1 COVID-19 high-risk comorbidity No of events	n = 9 ; % = 25	n = 7 ; % = 22
2 COVID-19 high-risk comorbidities No of events	n = 7 ; % = 19	n = 4 ; % = 13
3 or more COVID-19 high-risk comorbidities No of events	n = 1 ; % = 3	n = 2 ; % = 6

Outcomes

Study timepoints

- 3 month

Recovery from PASC

Outcome	Vaccinated vs Unvaccinated, 3 month, N2 = 36, N1 = 32
Recovery from PASC Odds ratio/95% CI	1.57 (0.46 to 5.84)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

Recovery from PASC

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Probably no
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Participants were matched for age, sex and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably yes
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No information
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Not applicable
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(Potential residual confounding remaining)*
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	Probably no
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	No information
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Probably yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Probably yes
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	Probably no
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Probably no
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(All participants and trial personnel will have been aware of intervention status which may have influenced symptom reporting.)*
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of	No information

Section	Question	Answer
	the results, from multiple analyses of the intervention-outcome relationship?	
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Zisis Sokratis, 2022

Bibliographic Reference	Zisis Sokratis, N; Durieux Jared, C; Mouchati, Christian; Perez Jamie, A; McComsey Grace, A; The Protective Effect of Coronavirus Disease 2019 (COVID-19) Vaccination on Postacute Sequelae of COVID-19: A Multicenter Study From a Large National Health Research Network.; Open forum infectious diseases; 2022; vol. 9 (no. 7); ofac228

Study details

Study design	Cohort studies
Trial registration (if reported)	
Study start date	21-Sep-2020
Study end date	14-Dec-2021
Aim of the study	To analyse the effect of immunisation on post-acute sequalae of COVID-19
Country/ Geographical location	USA
Study setting	N/A Data sourced from electronic medical records
Definition of long term effects used in the study	PASC was defined as new, continuing, or recurrent symptoms that occur 4 or more weeks after the initial SARS-CoV-2 infection
Population description	People with confirmed COVID-19 diagnosis and a 3-month follow-up divided into vaccinated with breakthrough infection and unvaccinated
Inclusion criteria	Adult patients aged ≥18 years with SARS-CoV-2 infection (confirmed by polymerase chain reaction) who sought care in the United States from 21 September 2020 to 14 December 2021.
Exclusion criteria	None reported
Intervention/test/approach	COVID-19 vaccination
Comparator (where applicable)	No vaccination

Methods for population selection/allocation	Data was sourced from the TriNetX Research Network platform, a network of electronic medical records (EMRs) from 57 healthcare organizations currently involving .70 million patients across the United States Data collection included: patients' demographics, comorbidities, and COVID-19 vaccination, as well as symptoms and diagnoses prior to, at the time of, and after 3 months of SARS-CoV-2 infection
Methods of data analysis	• Characteristics of patients were described using mean (SD) for continuous variables and frequency and percentage for categorical variables • Differences between vaccine and no-vaccine groups were calculated using independent t test or $\chi 2$ test. • Propensity score matching (1:1) using greedy nearest-neighbour method was used to balance the 2 cohorts on age, sex, race, and comorbidities. Incidence, relative risk (RR), and attributable risk (risk difference) estimates along with 95% confidence intervals (CIs) were used as measures of risk at 28 days and 90 days following COVID-19 diagnosis.
Attrition/loss to follow-up	N/A
Source of funding	Clinical and Translational Science Collaborative of Cleveland
Study limitations (Author)	• Cannot guarantee that there hasn't been mis-recording of data in the EHRs • The true prevalence of PASC among COVID-19 patients is still unknown as many asymptomatic patients have never been tested. • Cannot rule out the possibility that immunisation status affects the probability to seek or receive medical attention, particularly for less severe outcomes. • This study is not informative on outcomes in patients infected with SARS-CoV-2 but who did not get tested nor diagnosed with COVID-19. • The vaccination rate is low and they cannot rule out that EMR documentation of vaccination may have been missed in some of the vaccinated individuals. • Another potential limitation is that capturing the location where patients were seen and the difference between healthcare utilisation among the 2 groups based on their concurrent comorbidities, which might provide another potential explanation for the post–COVID-19 outcomes, is beyond the capacity of this database.
Study limitations (Reviewer)	Study does not report number of doses of vaccine received by participants

Study arms

Vaccine + COVID-19 (N = 25225)

No Vaccine + COVID-19 (N = 25225)

Characteristics

Arm-level characteristics

Characteristic	Vaccine + COVID-19 (N = 25225)	No Vaccine + COVID-19 (N = 25225)
Age Mean (SD)	54.82 (17.77)	55.06 (17.86)
Female No of events	n = 15094 ; % = 59.84	n = 15129 ; % = 59.98
Male No of events	n = 10130 ; % = 40.16	n = 10095 ; % = 40.02
Unknown No of events	n = 10 ; % = 0.04	n = 10 ; % = 0.04
Black/African American No of events	n = 4907 ; % = 19.45	n = 4853 ; % = 19.24
White No of events	n = 17266 ; % = 68.45	n = 17381 ; % = 68.9
Asian No of events	n = 860 ; % = 3.41	n = 874 ; % = 3.47
American Indian/Alaska Native No of events	n = 159 ; % = 0.63	n = 126 ; % = 0.5
Native Hawaiian/Pacific Islander No of events	n = 41 ; % = 0.16	n = 47 ; % = 0.19
Unknown	n = 1992 ; % = 7.9	n = 1944 ; % = 7.71

Characteristic	Vaccine + COVID-19 (N = 25225)	No Vaccine + COVID-19 (N = 25225)
No of events		

Outcomes

Study timepoints

- 28 day (from COVID diagnosis)
- 90 day (from COVID diagnosis)

New conditions since COVID-19

Outcome	Vaccine + COVID-19 vs No Vaccine + COVID-19, 28 day, N2 = 25225, N1 = 25225	Vaccine + COVID-19 vs No Vaccine + COVID-19, 90 day, N2 = 25225, N1 = 25225
Hypertension Relative risk/95% CI	0.45 (0.38 to 0.54)	0.33 (0.26 to 0.42)
Diabetes mellitus Relative risk/95% CI	0.43 (0.35 to 0.54)	0.28 (0.2 to 0.38)
Thyroid disease Relative risk/95% CI	0.49 (0.33 to 0.56)	0.22 (0.15 to 0.32)
Heart disease Relative risk/95% CI	0.49 (0.43 to 0.57)	0.35 (0.29 to 0.44)
Malignant neoplasm Relative risk/95% CI	0.32 (0.25 to 0.42)	0.23 (0.17 to 0.32)
Thrombosis Relative risk/95% CI	0.42 (0.34 to 0.51)	0.27 (0.2 to 0.36)
Rheumatoid arthritis Relative risk/95% CI	0.5 (0.28 to 0.91)	0.27 (0.2 to 0.87)

Outcome	Vaccine + COVID-19 vs No Vaccine + COVID-19, 28 day, N2 = 25225, N1 = 25225	Vaccine + COVID-19 vs No Vaccine + COVID-19, 90 day, N2 = 25225, N1 = 25225
Mental disorders **Relative risk/95% CI**	**0.41 (0.35 to 0.47)**	**0.25 (0.2 to 0.31)**

New symptoms since COVID-19

Outcome	Vaccine + COVID-19 vs No Vaccine + COVID-19, 28 day, N2 = 25225, N1 = 25225	Vaccine + COVID-19 vs No Vaccine + COVID-19, 90 day, N2 = 25225, N1 = 25225
Respiratory symptoms Relative risk/95% CI	0.7 (0.67 to 0.74)	0.54 (0.5 to 0.57)
Headache Relative risk/95% CI	0.56 (0.5 to 0.63)	0.39 (0.34 to 0.45)
Fatigue Relative risk/95% CI	0.65 (0.61 to 0.7)	0.48 (0.43 to 0.52)
Body ache Relative risk/95% CI	0.5 (0.42 to 0.57)	0.34 (0.28 to 0.42)
Diarrhoea or constipation Relative risk/95% CI	0.6 (0.55 to 0.65)	0.44 (0.4 to 0.49)

Critical appraisal - ROBINS-I: Interventions (cohort studies)

New conditions since COVID-19-Hypertension

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by	Not applicable

Section	Question	Answer
	the outcome or a cause of the outcome?	
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate	No information

Section	Question	Answer
intended interventions	the effect of starting and adhering to the intervention?	
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of	No information

Section	Question	Answer
	the intervention-outcome relationship?	
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19- Diabetes mellitus

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Thyroid disease

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	No information *(Based on EHR data)*

Section	Question	Answer
	measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Heart disease

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Malignant neoplasm

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from	4.3. Were important co-interventions balanced across intervention groups?	No information

Section	Question	Answer
intended interventions		
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Thrombosis

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	No information *(Based on EHR data)*

Section	Question	Answer
	measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Rheumatoid arthritis

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Mental disorders

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from	4.3. Were important co-interventions balanced across intervention groups?	No information

Section	Question	Answer
intended interventions		
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Respiratory symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	No information *(Based on EHR data)*

Section	Question	Answer
	measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably no
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19 - Headache

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Fatigue

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from	4.3. Were important co-interventions balanced across intervention groups?	No information

Section	Question	Answer
intended interventions		
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Body ache

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	No information *(Based on EHR data)*

Section	Question	Answer
	measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Diarrhoea or constipation

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Hypertension

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Diabetes mellitus

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*

Section	Question	Answer
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Thyroid disease

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by	Not applicable

Section	Question	Answer
	the outcome or a cause of the outcome?	
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate	No information

Section	Question	Answer
intended interventions	the effect of starting and adhering to the intervention?	
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of	No information

Section	Question	Answer
	the intervention-outcome relationship?	
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Heart disease

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable

Section	Question	Answer
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Malignant neoplasm

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	No information *(Based on EHR data)*

Section	Question	Answer
	measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Thrombosis

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Rheumatoid arthritis

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from	4.3. Were important co-interventions balanced across intervention groups?	No information

Section	Question	Answer
intended interventions		
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New conditions since COVID-19-Mental disorders

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	No information *(Based on EHR data)*

Section	Question	Answer
	measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Probably no
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Respiratory symptoms

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Headache

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from	4.3. Were important co-interventions balanced across intervention groups?	No information

Section	Question	Answer
intended interventions		
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Fatigue

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for	No information *(Based on EHR data)*

Section	Question	Answer
	measured validly and reliably by the variables available in this study?	
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes

Section	Question	Answer
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable

Section	Question	Answer
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Bodyache

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes

Section	Question	Answer
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable

Section	Question	Answer
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from intended interventions	4.3. Were important co-interventions balanced across intervention groups?	No information
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information

Section	Question	Answer
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

New symptoms since COVID-19-Diarrhoea or constipation

Section	Question	Answer
1. Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Yes
1. Bias due to confounding	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	No
1. Bias due to confounding	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	Not applicable
1. Bias due to confounding	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Probably yes *(Propensity score matching (1:1) using greedy nearest-neighbor method was used to balance the 2 cohorts on age, sex, race, and comorbidities)*
1. Bias due to confounding	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	No information *(Based on EHR data)*
1. Bias due to confounding	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Probably no
1. Bias due to confounding	1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	No information
1. Bias due to confounding	1.8. If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Not applicable
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate

Section	Question	Answer
2. Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4	No
2. Bias in selection of participants into the study	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Not applicable
2. Bias in selection of participants into the study	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Not applicable
2. Bias in selection of participants into the study	2.4. Do start of follow-up and start of intervention coincide for most participants?	Probably yes
2. Bias in selection of participants into the study	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Not applicable
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Yes
3. Bias in classification of interventions	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes
3. Bias in classification of interventions	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Probably no
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Probably no
4. Bias due to deviations from intended interventions	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Not applicable
4. Bias due to deviations from	4.3. Were important co-interventions balanced across intervention groups?	No information

Section	Question	Answer
intended interventions		
4. Bias due to deviations from intended interventions	4.4. Was the intervention implemented successfully for most participants?	No information
4. Bias due to deviations from intended interventions	4.5. Did study participants adhere to the assigned intervention regimen?	Not applicable
4. Bias due to deviations from intended interventions	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	No information
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate
5. Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Yes
5. Bias due to missing data	5.2 Were participants excluded due to missing data on intervention status?	No information
5. Bias due to missing data	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Probably no
5. Bias due to missing data	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Not applicable
5. Bias due to missing data	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Not applicable
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate
6. Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Probably yes
6. Bias in measurement of outcomes	6.2 Were outcome assessors aware of the intervention received by study participants?	Yes
6. Bias in measurement of outcomes	6.3 Were the methods of outcome assessment comparable across intervention groups?	No information *(Relying on EHR data)*

Section	Question	Answer
6. Bias in measurement of outcomes	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	No information
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate
7. Bias in selection of the reported result	7.1 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple outcome measurements within the outcome domain?	No information
7. Bias in selection of the reported result	7.2 Is the reported effect estimate likely to be selected, on the basis of the results, from multiple analyses of the intervention-outcome relationship?	No information
7. Bias in selection of the reported result	7.3 Is the reported effect estimate likely to be selected, on the basis of the results, from different subgroups?	No information
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Moderate *(Reporting of outcomes is reliant ton data entered in the EHR)*
Overall bias	Risk of bias judgement	Moderate
Overall bias	Directness	Directly applicable

Appendix G: GRADE tables

COVID-19 vaccination: People with history of COVID-19 infection after vaccination

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Probability of Long COVID (double vaccinated plus booster)							
229 (1 observational study)	very serious[a]	not serious	not serious	not serious	none	Very low	Odds ratio 0.16 (CI 95% 0.03 — 0.84)
Probability of Long COVID (double vaccinated)							
229 (1 observational study)	very serious[a]	not serious	not serious	not serious	none	Very low	Odds ratio 0.25 (CI 95% 0.07 — 0.87)
Likelihood of developing PASC (double vaccinated)							
5929 (1 observational study)	serious[b]	not serious	not serious	not serious	none	Very low	Odds ratio 0.58 (CI 95% 0.52 — 0.66)
Fatigue (double vaccinated)							

Certainty assessment							Summary of findings
611 (1 observational study)	serious[c]	not serious	not serious	not serious	none	Very low	Odds ratio 0.36 (CI 95% 0.19 — 0.71)
Symptoms lasting at least 28 days (double vaccinated)							
1074 (1 observational study)	serious[d]	not serious	serious[e]	not serious	none	Very low	Odds ratio 0.51 (CI 95% 0.32 — 0.82)
Shortness of breath (double vaccinated)							
611 (1 observational study)	serious[c]	not serious	not serious	not serious	none	Very low	Odds ratio 0.23 (CI 95% 0.07 — 0.84)
Shortness of breath (single vaccinated)							
657 (1 observational study)	serious[c]	not serious	not serious	serious[f]	none	Very low	Odds ratio 1.08 (CI 95% 0.65 — 1.81)
Fatigue (single vaccinated)							
657 (1 observational study)	serious[c]	not serious	not serious	serious[f]	none	Very low	Odds ratio 1.06 (CI 95% 0.82 — 1.36)
Symptoms lasting at least 28 days (single vaccinated)							

Certainty assessment							Summary of findings
5241 (1 observational study)	serious[d]	not serious	serious[e]	serious[f]	none	Very low	Odds ratio 1.03 (CI 95% 0.85 — 1.24)
Long COVID symptoms of any severity (double vaccinated) (follow-up: 12 weeks)							
6180 (1 observational study)	not serious	not serious	serious[g]	not serious	none	Very low	Odds ratio 0.59 (CI 95% 0.50 — 0.69)
Any symptoms (unknown number of vaccination doses) (follow-up: range 12 weeks to 20 weeks)							
222852 (1 observational study)	serious[b]	not serious	not serious	not serious	none	Very low	Odds ratio 0.22 (CI 95% 0.20 — 0.25)
Risk of death (unknown number of vaccination doses) (follow-up: 6 months)							
147414 (1 observational study)	serious[b]	not serious	serious[h]	not serious	none	Very low	Hazard ratio 0.66 (CI 95% 0.58 — 0.74)
Activity limited symptoms (double vaccinated) (follow-up: range 12 weeks to 20 weeks)							
6180 (1 observational study)	not serious	not serious	serious[g]	not serious	none	Very low	Odds ratio 0.59 (CI 95% 0.48 — 0.73)
At least 1 symptom (unknown number of vaccination doses) (follow-up: 6 months)							

Certainty assessment							Summary of findings
222852 (1 observational study)	serious[b]	not serious	not serious	not serious	none	Very low	Odds ratio 0.11 (CI 95% 0.09 — 0.14)
Risk of post-acute sequelae (unknown number of vaccination doses) (follow-up: 6 months)							
147414 (1 observational study)	serious[b]	not serious	serious[h]	not serious	none	Very low	Hazard ratio 0.85 (CI 95% 0.82 — 0.89)
Respiratory symptoms (unknown number of vaccination doses) (follow-up: 28 days)							
50450 (1 observational study)	serious[i]	not serious	not serious	not serious	none	Very low	Relative risk 0.70 (CI 95% 0.67 — 0.74)
Respiratory symptoms (unknown number of vaccination doses) (follow-up: 90 days)							
50450 (1 observational study)	serious[i]	not serious	not serious	not serious	none	Very low	Relative risk 0.54 (CI 95% 0.50 — 0.57)
Fatigue (unknown number of vaccination doses) (follow-up: 28 days)							
50450 (1 observational study)	serious[i]	not serious	not serious	not serious	none	Very low	Relative risk 0.65 (CI 95% 0.61 — 0.70)
Fatigue (unknown number of vaccination doses) (follow-up: 90 days)							

Certainty assessment							Summary of findings
50450 (1 observational study)	serious[i]	not serious	not serious	not serious	none	Very low	Relative risk 0.48 (CI 95% 0.43 — 0.52)
Composite of death and any long-COVID feature (follow-up: 6 months)							
18958 (1 observational study)	serious[i]	not serious	not serious	serious[f]	none	Very low	Hazard ratio 1.01 (CI 95% 0.96 — 1.05)

CI: confidence interval

Explanations

a. Unclear how reference group was selected or who was included in the analysis
b. Risk of selection bias in addition to confounding
c. Risk of reporting bias as well as confounding
d. Self-reported outcomes that relied on individuals logging data daily
e. The app data sample contained disproportionately more women than men and under-represented individuals in more deprived areas.
f. 95% CI crosses the line of no effect
g. No contemporaneous control group
h. Older, male-dominated population not representative of the UK
i. Reporting of outcomes was reliant on data entered in electronic health records which may have been inconsistent across the network

COVID-19 vaccination after infection: Adults and children who are experiencing new or ongoing symptoms (Continuous)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
Long COVID symptoms (unknown doses of vaccine) (follow-up: 120 days; assessed with: Measured by: Long COVID symptom tool (ST))							
910 (1 observational study)	serious[a]	not serious	not serious	not serious	none	Very low	MD -1.8 95% CI -2.5 to -1
Disease impact on patient lives (unknown doses of vaccine) (follow-up: 120 days; assessed with: Measured by: Disease impact tool (IT))							
910 (1 observational study)	serious[b]	not serious	not serious	not serious	none	Very low	MD -3.3 95% CI -6.25 to -0.5
Dyspnoea symptom score (at least one dose of COVID-19 vaccine) (follow-up: 6 months)							
453 (1 observational study)	serious[b]	not serious	not serious	not serious	none	Very low	MD -0.02 95% CI -0.35 to 0.31
QoL: Fatigue symptom score (at least one dose of COVID-19 vaccine) (follow-up: 6 months)							

Certainty assessment							Summary of findings
453 (1 observational study)	serious[b]	not serious	not serious	not serious	none	Very low	MD -1.42 95% CI -4.15 to 1.32
QoL: Physical function score (at least one dose of COVID-19 vaccine) (follow-up: 6 months)							
453 (1 observational study)	serious[b]	not serious	not serious	not serious	none	Very low	MD -1.16 95% CI -3.35 to 1.02

CI: confidence interval

Explanations

a. Potential unmeasured confounders. Data did not take motivation to receive COVID 19 vaccination into account.
b. Risk of reporting bias and selection bias in addition to residual confounding

COVID-19 vaccination after infection: Adults and children who are experiencing new or ongoing symptoms (dichotomous)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Impact**
Recovery from PASC (double vaccinated) (follow-up: 3 months)							

Certainty assessment							Summary of findings
68 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	Very low	Odds ratio 1.57 (CI 95% 0.46 — 5.84)
Complete remission of symptoms (unknown doses of vaccine) (follow-up: 120 days)							
910 (1 observational study)	serious[c]	not serious	not serious	not serious	none	Very low	Hazard ratio 1.97 (CI 95% 1.23 — 3.15)
Any long COVID symptom (Vaccine 0-4 weeks after diagnosis)							
243040 (1 observational study)	serious[d]	not serious	not serious	not serious	none	Very low	Odds ratio 0.38 (CI 95% 0.35 — 0.41)
Any long COVID symptom (Vaccine 4-8 weeks after diagnosis)							
243040 (1 observational study)	serious[d]	not serious	not serious	not serious	none	Very low	Odds ratio 0.54 (CI 95% 0.51 — 0.57)
Any long COVID symptom (Vaccine 8-12 weeks after diagnosis)							
243040 (1 observational study)	serious[d]	not serious	not serious	not serious	none	Very low	Odds ratio 0.75 (CI 95% 0.71 — 0.78)

CI: confidence interval

Explanations

a. Potential for residual confounding and lack of control group

b. 95% CI crosses the line of no effect
c. Potential unmeasured confounders. Data did not take motivation to receive COVID 19 vaccination into account.
d. Risk of selection bias in addition to confounding

COVID-19 vaccination after infection: Adults and children who are experiencing new or ongoing symptoms (narrative)

Certainty assessment							Summary of findings
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Impact
At least one post-COVID symptom (at least one dose of COVID-19 vaccine)							
479 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	Very low	The Italian cohort study (Peghin 2022) found that of people who had been vaccinated 44 (33.3%) reported 1 or 2 post-COVID symptoms. 8 (6.1%) of people who were vaccinated reported 3 or 4 symptoms. 7 (5.3%) of people who were vaccinated reported 5 or more symptoms.
No post-COVID symptoms (at least one dose of COVID-19 vaccine)							
479 (1 observational study)	serious[a]	not serious	not serious	serious[b]	none	Very low	The Italian cohort study (Peghin 2022) found that 73 (55.3%) people who were vaccinated reported no post-COVID symptoms compared to 180 (51.9%) who were unvaccinated.
Worsening of post-COVID 19 symptoms (at least one dose of COVID 19 vaccine) (follow-up: 1 years)							

Certainty assessment							Summary of findings
1930 (5 observational studies)	serious[c]	serious[d]	not serious	serious[b]	none	Very low	One cohort study (Peghin 2022) found that 30 (22.7%) reported that their symptoms had worsened. In a cross-sectional study (Wanga 2021) 16.1% reported that the vaccine made symptoms worse. Another cross-sectional study found that 117/380 (31%) reported worsening of symptom severity. An international cross-sectional study found that 145/812 (17.9%) reported an overall worsening of symptoms. A case series found that 9/159 (5.6%) reported worsening of symptoms.
Improvement in post-COVID 19 symptoms (at least one dose of COVID-19 vaccine) (follow-up: 1 years)							
1930 (5 observational studies)	serious[c]	serious[d]	not serious	serious[b]	none	Very low	One cohort study (Peghin 2022) found that 15 (11%) of vaccinated people reported that their symptoms had improved. In a cross-sectional study (Wanga 2021) reported that 28.7% reported that the vaccine made their symptoms better. Another cross-sectional study found that 83/380 (21.8%) reported improvement in symptom severity. An international cross-sectional study found that 470/812 (57.2%) reported an overall improvement in symptoms. A case series found that 31/159 (23.2%) reported improvement in their symptoms.
No change in post-COVID 19 symptoms (at least one dose of COVID 19 vaccine) (follow-up: 1 years)							
738 (3 observational studies)	serious[c]	serious[d]	not serious	serious[b]	none	Very low	One cohort study (Peghin 2022) found that 87 (65.9%) reported that their symptoms remained unaffected or unchanged. In a cross-sectional study (Wanga 2021) 26.4% reported that the vaccine had no effect on their symptoms at all. A case series found that 113/159 (71.1%) of participants reported that their symptoms were unchanged
Activity limitation (single vaccinated)							

Certainty assessment							Summary of findings
4747 (1 observational study)	serious[e]	not serious	not serious	not serious	none	Very low	A UK cohort study (Ayoubkhani 2021 preprint) reported that activity limitation initially decreased after first vaccination (12.3% decrease 95% CI-19.5% to -4.5%) followed by an increase of 0.9% (-0.2% to +1.9%) per week until receiving the second dose.
Odds of experiencing long COVID symptoms (single vaccinated)							
6729 (1 observational study)	serious[e]	not serious	not serious	not serious	none	Very low	A UK cohort study (Ayoubkhani 2021 preprint) reported that the odds of experiencing Long COVID symptoms initially decreased (12.8% decrease 95% CI -18.6% to -6.6%) but this was followed by an increase per week until receiving the second dose (0.3% increase 95% CI -0.6% to 1.2%)
Odds of experiencing long COVID symptoms (double vaccinated)							
4747 (1 observational study)	serious[e]	not serious	not serious	not serious	none	Very low	A UK cohort study (Ayoubkhani 2021 preprint) reported that activity limitation initially decreased 9.1% decrease (-15.6% to -2.1%), followed by a decrease of 0.5% (-1.0% to +0.05%) per week.

Appendix H: Expert testimony

Section A: Developer to complete	
Name:	Dr Claire Steves
Role:	Expert Witness – Academic Senior Clinical Lecturer
Institution/Organisation (where applicable):	King's College London
Guideline title:	Managing the long-term effects of COVID-19: update
Guideline Committee:	Expert Advisory Panel for the update of NG188
Subject of expert testimony:	Post-vaccination SARS-CoV-2 infection: risk factors and illness profile
Evidence gaps or uncertainties:	What pharmacological and non-pharmacological interventions (including but not limited to vaccines, olfactory training and breathing techniques) improve the ongoing physical or mental health symptoms and problems of functioning and disability (as defined by the World Health Organization's International classification of functioning, disability and health) following acute COVID-19?
The specific evidence gap within this review question was whether there was any effect on the long-term effects of COVID-19 experienced by people who have SARS-CoV-2 infection after 2 doses of vaccination. These are academic in confidence findings.	
Section B: Expert to complete	
Summary testimony:	

COVID symptom study - Academic in confidence

Study details:

A prospective, observational, case-control study using data from the ZOE app. Investigating risk factors for post-vaccination injection and symptoms of post-vaccination infection. Participants age 19+.

Comparisons:

Comparing people who tested positive >14 days after 1st dose, before 2nd (n=6,030) or tested positive >7 days after second vaccine dose (n=2,370) with:

a) vaccinated individuals reporting negative test at least fourteen (first dose) or seven (second dose) days post-vaccination to identify risk factors for post-vaccination infection OR

b) unvaccinated participants reporting a positive SARS-CoV-2 test to compare illness profile pre- and post-vaccination.

People who had had COVID-19 in the past, or who had post-COVID-19 syndrome were excluded.

Analysis:

Univariate logistic regression models (adjusted for age, BMI, and sex) to analyse associations between risk factors and post-vaccination infection; and associations of individual symptoms, overall illness duration, and disease severity, with vaccination status.

Results:

Risk factors for post-vaccination infection:

- Post-vaccination infection after 1 vaccination is more likely in those who are over 60 and frail, compared with younger groups.
- Post-vaccination infection after 1 vaccination is more likely in those living in more deprived areas with a high index of multiple deprivation, compared with those living in less deprived areas.

Illness profile pre- and post-vaccination:

- The risk of hospitalisation reduced with vaccination (and especially with a second vaccination) – this was consistent across vaccine manufacturers.
- There was a lower risk of having symptoms lasting more than 28 days in those vaccinated with 2 doses compared with unvaccinated participants (no effect for single dose of vaccination).
- Symptom profile: there was a reduction in most symptoms of acute COVID-19 for those vaccinated with either 1 or 2 doses compared with unvaccinated participants, with the exception of sneezing.

Strengths and limitations:

The study had a large sample size with matched participants (to reduce effect of changing contextual factors), and prospective symptom reporting. Although

participants were volunteers, the case control design may mitigate for bias by volunteer factors.

Results were consistent even when tested in scenario of everyone being vaccinated, indicating that results may be consistent even as the proportion of people vaccinated increases.

Questions from panel members

Q: Is there longer-term follow-up data available (12+ weeks)?

A: Not yet – this will be coming in the next few months. Other studies have found similar symptom profiles (numbers of those experiencing symptoms reducing but proportions similar) between time points (4, 8 and 12 weeks), indicating that these results may be reflected in 12+ week data.

Q: Neutralising antibodies wane with time – do we know whether this potential protective effect of COVID-19 vaccines will also wane with time?

A: Data is not yet indicating a drop-off but more time is required to investigate this. There is some suggestion that antibodies are better sustained after the second dose of a vaccine than after the first dose.

Q: What are the limitations of the ZOE app data?

A: If you don't log symptoms daily for more than 28 days, you cannot be included in the analysis. Those who report for more than 28 days are included, whether they stopped logging with or without symptoms.

People who are not well enough to log on won't provide data – therefore it is possible that people with more severe symptoms are under-represented in this data. If those people are distributed differently between vaccinated and unvaccinated groups, this could result in bias. There is an indication that this might affect people who are unvaccinated more than those who are vaccinated, therefore causing these results to underestimate the benefit of the vaccine – however, this is still an assumption.

Q: This data is adjusted for age, BMI and sex. In a pre-print of earlier data covering people with a single vaccine dose only (a subset of the data presented by this testimony), additional adjustments for frailty and comorbidity made results less precise. Would that be the case with this data?

A: Data including the additional adjustments will be available in supplementary information. The direction of effect is the same with the additional adjustments – uncertain about significance.

Q: What does this data mean for older people and symptom recognition?

A: Other evidence suggests that the earliest symptoms of COVID-19 are different in older people compared with younger people – for example, loss of smell is reported less frequently in older groups. There is a reduction in symptom reporting with age (regardless of illness) which is important to note. This study shows that symptoms of acute COVID-19 are reduced in older people, as well as in younger groups.

References to other work or publications to support your testimony' (if applicable):
Antonelli, Michela; Penfold, Rose; Merino, Jordi *et al*., Post-vaccination SARS-CoV-2 infection: risk factors and illness profile in a prospective, observational community-based case-control study; 2021.
Disclosure: Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.
I confirm I have no past or present links of any kind to the Tobacco industry.
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