Supplementary material 1: Long covid Symptom tool (ST) and Impact tool (IT)

Check the symptoms you experienced in the last 30 days:

General symptoms
- Weight loss
- Loss of appetite
- Sweats
- Fever and chills
- Hot flushes
- Fatigue
- Sleeping more
- Difficulty sleeping
- Heat/Cold intolerance
- Changing mood/impact on morale
- Body aches

Thorax
- Rib cage pain
- Chest pressure
- Sharp sudden pain, chest burns
- Tachycardia/Bradycardia/ palpitations/Arrhythmia
- Cough
- Dyspnea

Neurological
- Headache
- Tremor
- Dizziness/Malaise
- Balance disorder
- Word finding problems
- Brain fog/Difficulty concentrating
- Memory problems
- Paraesthesia (pricking, tingling, or creeping on the skin)
- Impaired/decreased tactile sensibility
- Change/loss of taste
- Change/loss of smell

Digestive
- Abdominal pain
- Nausea/Vomiting
- Diarrhea

Ear/Nose/Throat
- Sore throat/tongue/mouth/dysphagia
- Ear pain
- Clogged ears
- Tinnitus
- Congested/Runny nose

Eyes
- Dry eyes
- Blurry vision
- Photophobia/Phonophobia

Musculoskeletal
- Bone and joint pain
- Heavy legs/swelling of the legs
- Muscle aches
- Neck, back, and low back pain

Blood and lymph circulation
- Circulatory problems (including bulging veins)
- Spontaneous bruises
- Swollen lymph nodes
- High or low blood pressure

Skin and hair
- Dry/peeling skin
- Hair loss
- Skin rash
- Discoloration/swelling of hands and feet

Urinary and gynecological
- Gynecological problems
- Urinary symptoms

Assess the impact of your illness during the last 30 days…
- On your personal activities (not being able to do personal activities, driving a vehicle) *
- On your family life (feeling isolated or as a burden to others, having to ask for help, not being able to do household chores or take care of your family)
- On your professional life (having to stop working, being unable to work as well as before)
- On your social life (avoiding relationships because of the way people look at you, coping with others not taking your disease seriously, being afraid of infecting others)
- On your morale/mood (low morale, feeling that life is passing you by, fearing of the future or not recovering)
- On your relationship with caregivers (guilt, taking the illness seriously, lack of response, complexity of the care pathway)

Tran V-T, *et al. BMJMED* 2023; 2:e000229. doi: 10.1136/bmjmed-2022-000229

Supplementary material 2: Definition of treatment groups based on the observational data in the sequential emulated trials

We used data from the ComPaRe e-cohort to emulate a sequence of three trials that we subsequently pooled. The target trial and its emulated are specified below:

	Target trial	**Emulation**
Eligibility criteria	- Adult patients (age > 18 years old) - Self-reported long covid, defined as having at least one symptom among a list of 53 persisting more than three weeks past the initial infection and with at least one symptom at the time of inclusion [5] - Confirmed or suspected infection - Exclusion of patients whose date of first symptoms is <3 months before the inclusion date - Exclusion of patients with contraindication to vaccination (history of anaphylactic shock)	- Adult patients (age > 18 years old) - Self-reported long covid, defined as having at least one symptom among a list of 53 persisting more than three weeks past the initial infection and with at least one symptom at baseline [5] - Confirmed or suspected infection - Exclusion of patients whose date of first symptoms is <3 months before baseline - Exclusion of patients with a history of allergy (as a safe proxy to patients who may have had an anaphylactic reaction)
Treatment strategies	Vaccination at baseline No vaccination	Same
Treatment assignment	Random allocation to a strategy at baseline. Patients are aware of the strategy to which they have been assigned	We will classify individuals according to the strategy that their data were compatible With, at baseline. We will emulate randomization by adjusting for baseline confounders
Outcomes	Long covid ST and IT (self-reported) at 120 days	Same
Follow-up	Starts at baseline and ends 120 days after baseline	Same
Causal contrast	intention-to-treat and per-protocol effect	Observational analog per-protocol effect

For each patient, we divided his/her follow-up in the ComPaRe cohort into consecutive shorter periods defined by his/her "observation time points" (T0, T1, T2 …) during follow-up in the cohort. Therefore, for each patient, his follow-up in the cohort was divided in periods T0-T1, T1-T2, T2-T3, etc.

For each patient and for each period, we ascertained if he/she was eligible in for analyses (e.g., if the patient still had COVID-19 symptoms at the beginning of the period) and, if so, identified whether he/she received the first dose of COVID-19 vaccine during the period. For each vaccinated patient, we matched one patient who had not been vaccinated in the same period (e.g., vaccinated patients in the T1-T2 period were matched to unvaccinated patients in the T1-T2 period). Matching was based on the propensity score (probability of getting vaccinated against COVID-19 given the patient's baseline covariates. Newly vaccinated persons remained eligible for inclusion in a sequential trial, even if they had previously been selected as a control.

For vaccinated patients and their matched control, the time point defining the start of the period was considered as the patient's baseline in the emulated trial.

Each patient was followed for 120 days after his/her baseline (for example, patients whose baseline was their 1st observation point in the ComPaRe cohort were followed-up to their 3rd observation point; and patients whose baseline was the second observation point in the cohort were followed-up to their fourth observation point). Follow-up was artificially censored at the time of vaccination for unvaccinated controls.

The following figure details how baseline was defined for patients and how data were handled when observation times were missing.

Among vaccinated patients, we could not define a bassline for patients who were vaccinated before T0 (their first observation point) OR whose last observation time before receiving the vaccination was missing. These patients were excluded from the trial which baseline was the missing observation time. However, in the second case, if earlier observation periods were available before the missing time point, they were still eligible for the control group.

In the vaccination group, if the earliest observation time after receiving COVID-19 vaccination was missing, as long as they received a vaccine injection in the 60 days after baseline, we considered that they were eligible in the specific trial, and data from D60 was treated as missing.

Vaccination
Observation times
Missing observation time
December
February
April
June
August
October 2021
V0
V1 (60 days)
V2 (120 days)
For patients in the vaccination group, baseline is the latest observation time before vaccination.
Follow-up is 120 days after baseline
Controls who are vaccinated can serve as controls in periods before their vaccination
Controls who are vaccinated are censored at the date of their vaccination
V0 ?
For patients in the vaccination group, if the latest observation time before vaccination is missing, baseline cannot be defined. The patient cannot be assigned to the vaccination group (but his previous data may be used for the control group)
For patients in the vaccination group, if the observation time after vaccination is missing, the patient is included if vaccination happened in the 60 days after baseline
Patients with missing follow-up visits can be included as controls (or treatment if the aforementioned rules are verified) (missing outcome data is managed by multiple imputations with chained equations)

Supplementary material 3: Assessment of the correction of the induced time-varying selection generated by the artificial censoring of control patients who receive vaccination during their follow-up.

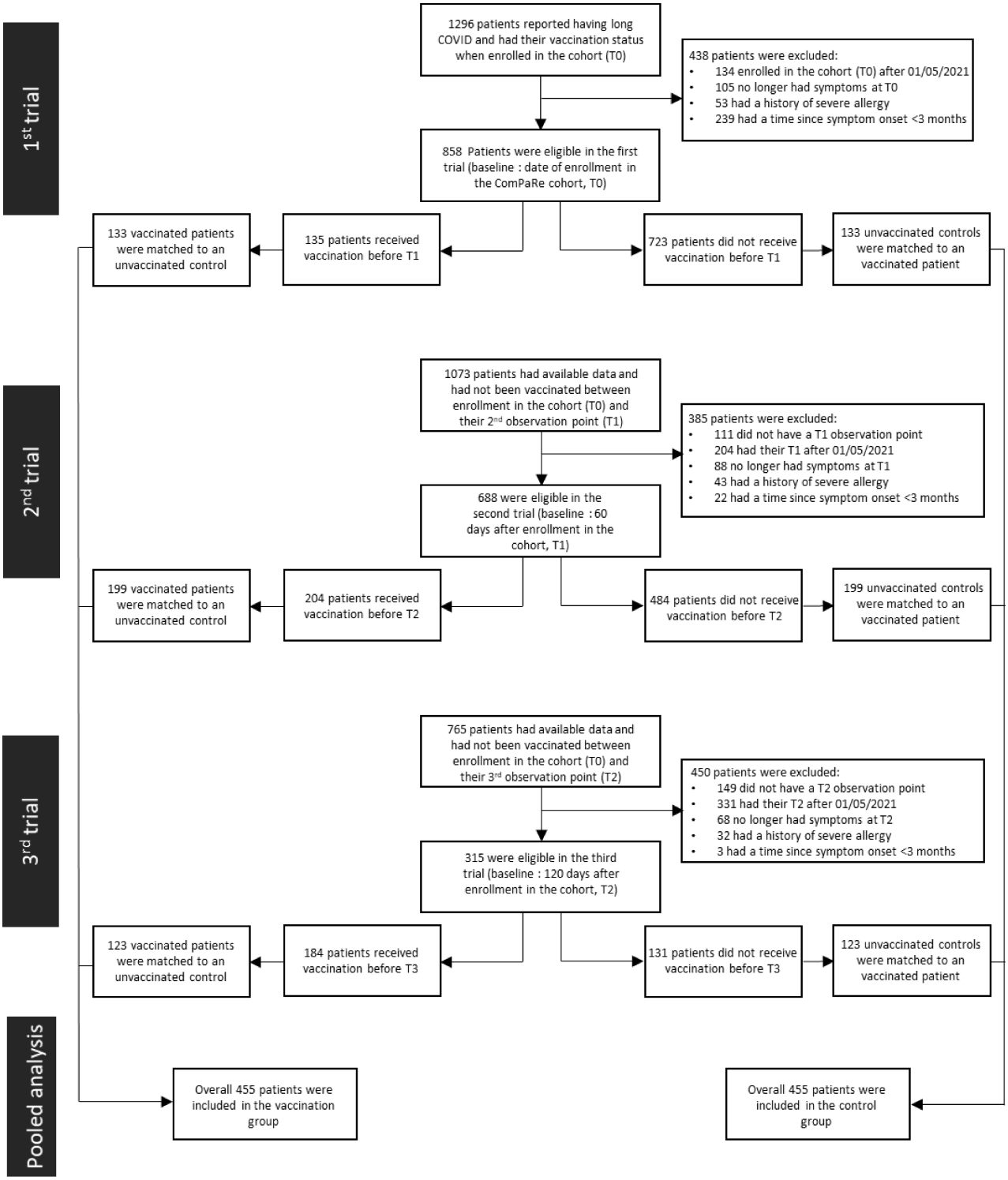
Patients in the control group were artificially censored when they received vaccination because they then deviated from the treatment strategy. To correct for the induced time-varying selection generated by the artificial censoring of patients in the unvaccinated group at the date of their first vaccine injection, we used inverse probability of censoring weighting with weights proportional to the inverse of the probability of remaining uncensored until each timepoint, given the baseline covariates. Stabilized weights were obtained by multiplying the weights by the overall probability of being uncensored at each timepoint.

To assess the correction, we 1) compared the number of patients in the two groups, over time and showed observed that it remained similar in the two groups (**Figure 1**); and 2) checked the balance between the baseline characteristics between remaining patients at risk, in the two groups at 120 days after inclusion.

Our results show that baseline characteristics were generally balanced between the two groups.
Of note, the observed differences could be associated with 1) difference in the characteristics of patients who were in remission (events); 2) bias due to loss of follow-up; or 3) bias due to the artificial censoring not corrected by the IPCW model.

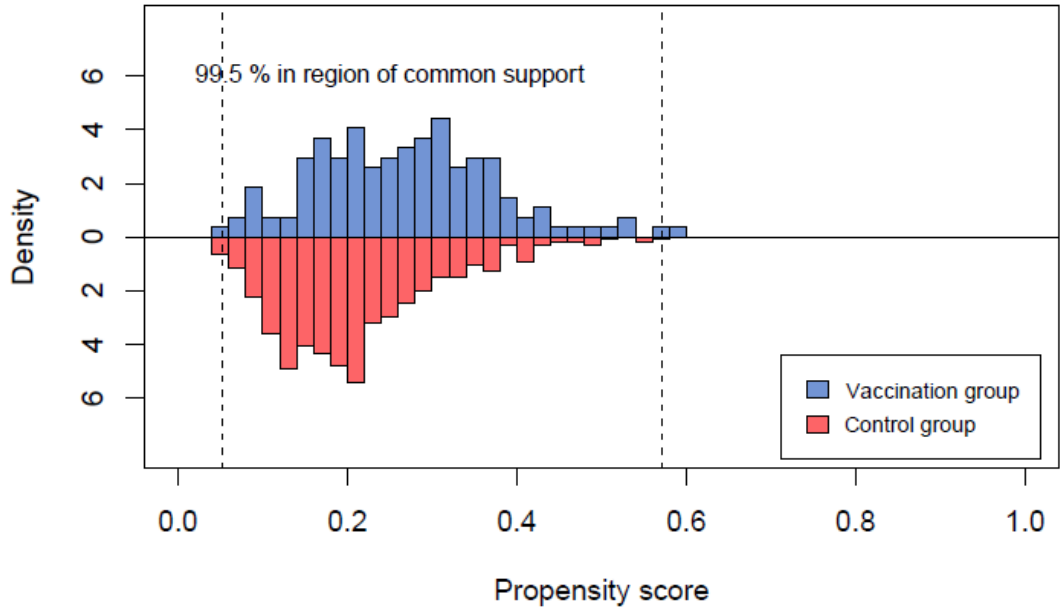
	Total (n=190)	**Treatment group (n=99)**	**Control group (n=91)**
Age – median [IQR]	46.8 [39.5 – 54.4]	48.6 [41.1 – 56.8]	45.4 [39.0 – 52.1]
Sex – number (%)	154 (80.8)	80 (80.8)	74 (80.8)
Confirmed COVID-19 infection – number (%)	122 (64.2)	69 (69.7)	53 (58.2)
Hospitalization for COVID-19 – number (%)	22 (11.7)	12 (12.1)	10 (11.3)
Number of comorbidites	1.0 [1.0 – 3.0]	1.0 [1.0 – 2.5]	1.0 [1.0 – 3.0]
Baseline ST score	13.0 [9.0 – 20.0]	14.0 [9.0 – 21.0]	12.0 [8.0 – 17.0]
Baseline IT score	28.0 [17.0 – 42.0]	29.0 [18.0 – 41.0]	26.0 [17.0 – 42.0]

Supplementary material 4: Study flow chart

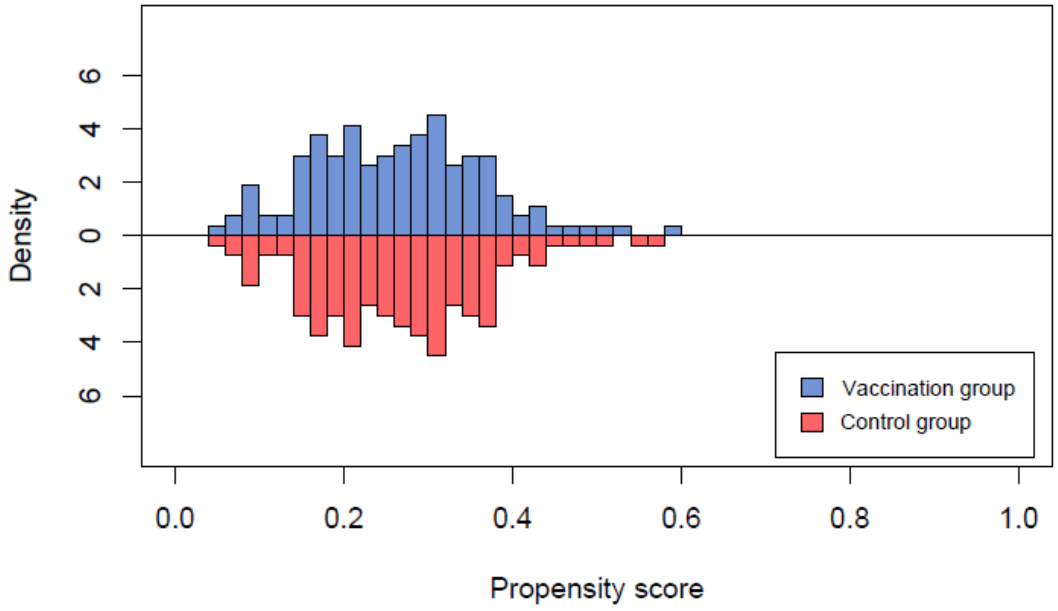


Supplementary material 5a: Propensity score development for the first trial (n=266)

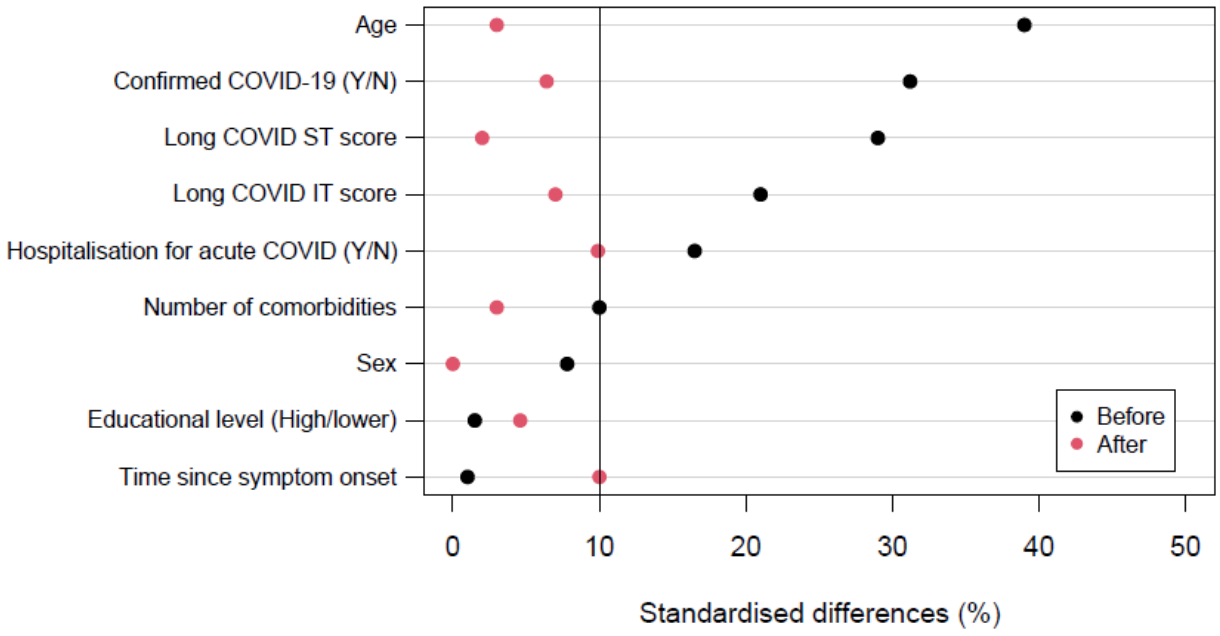
Before matching



After matching

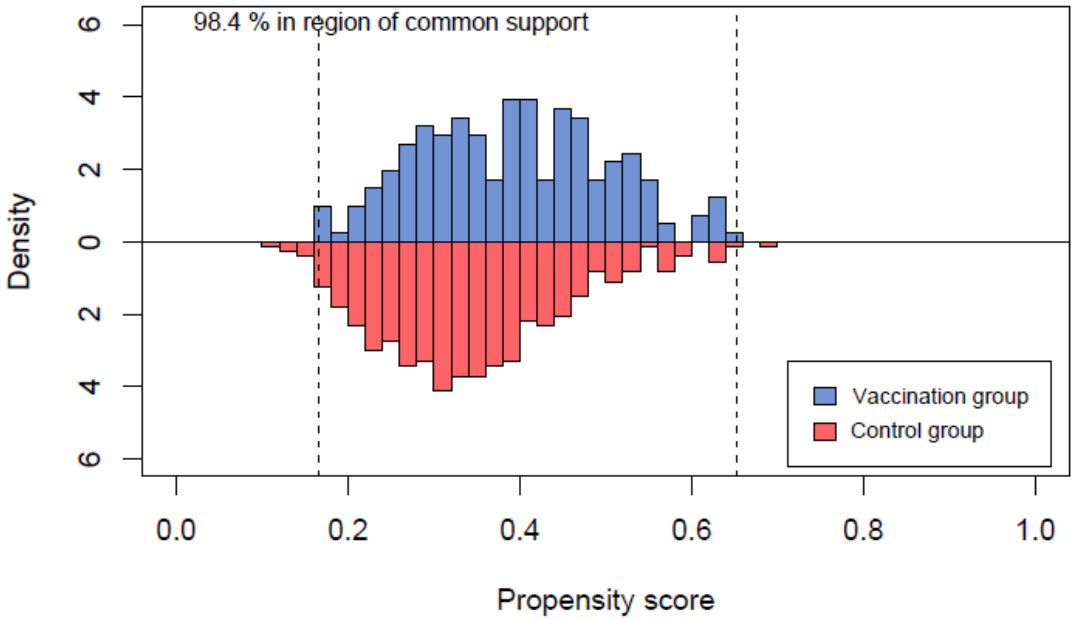


Supplementary material 5b: Standardised differences of variables used to generate the propensity score for the first trial (n=266)

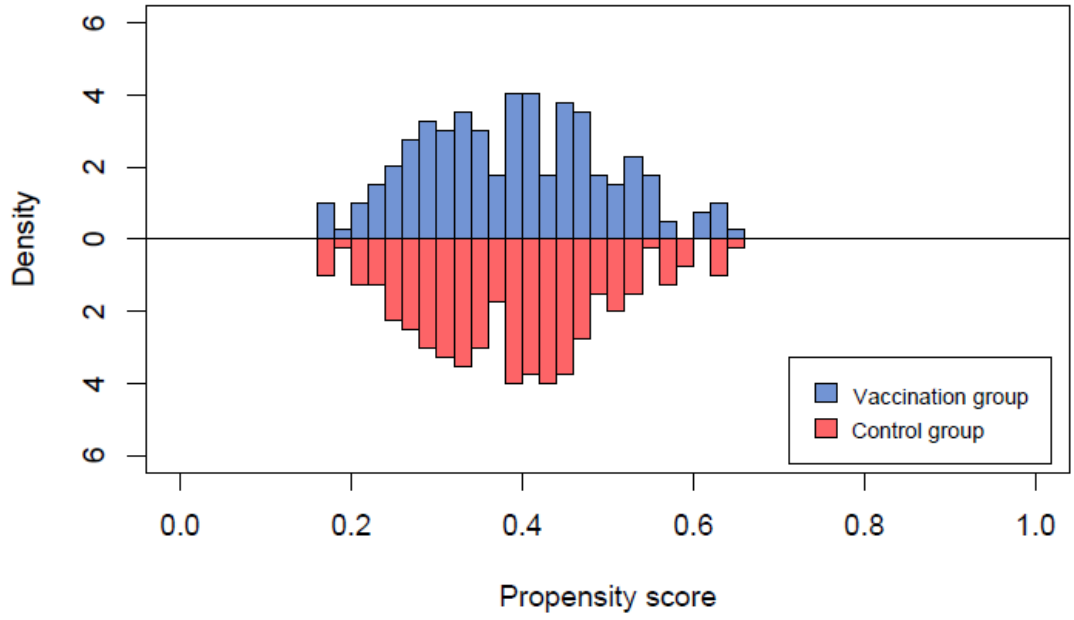


Supplementary material 6a: Propensity score development for the second trial (n=398)

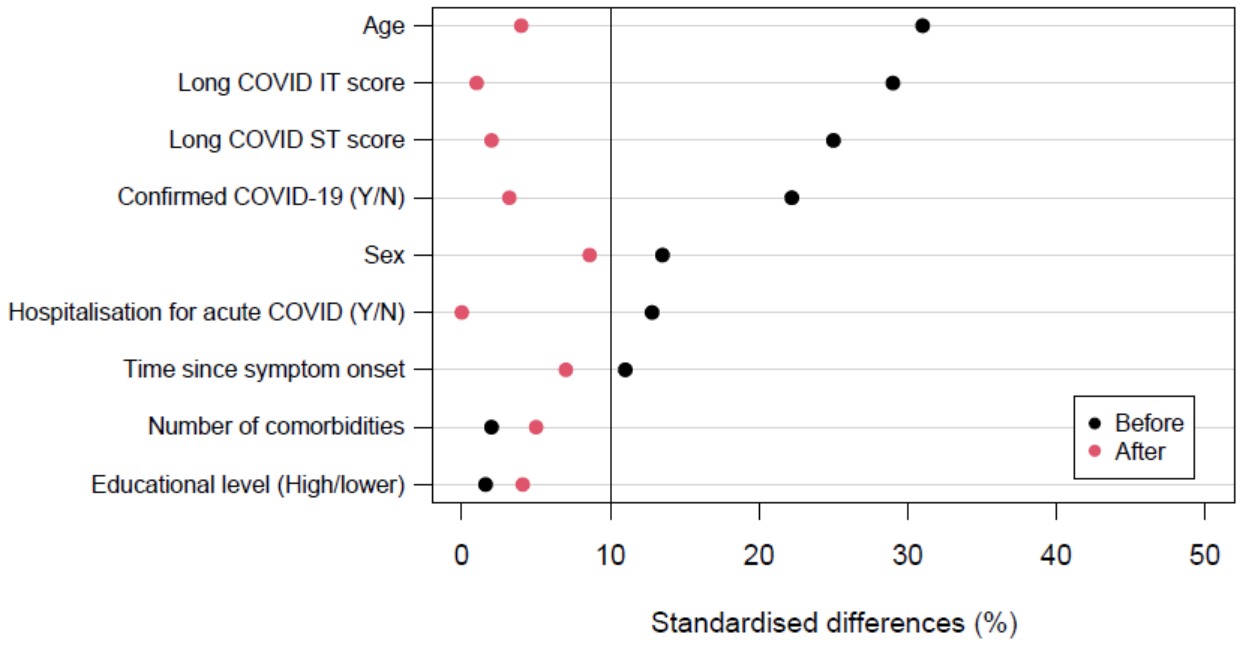
Before matching



After matching

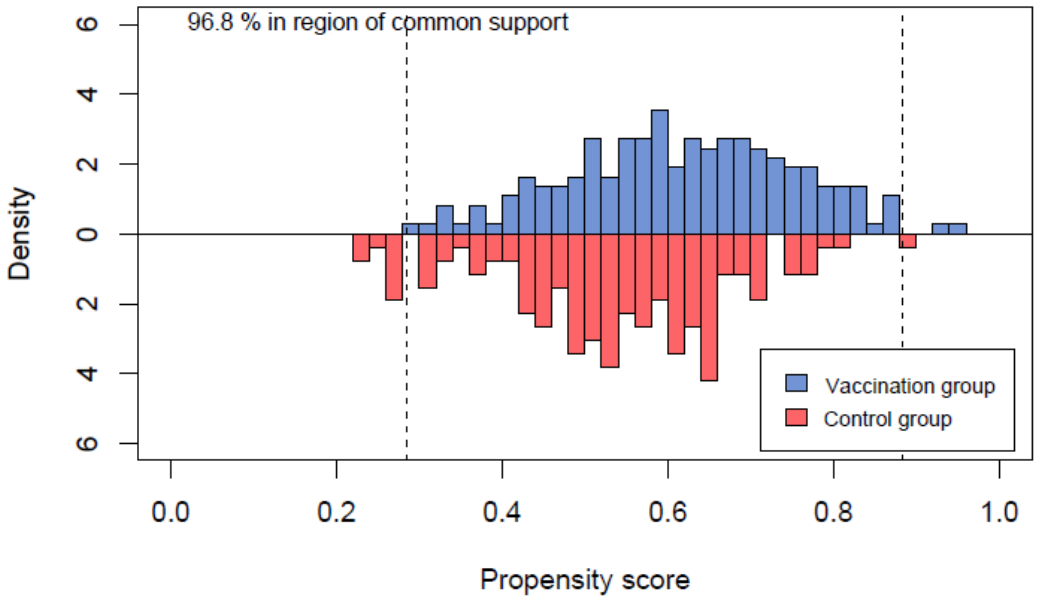


Supplementary material 6b: Standardised differences of variables used to generate the propensity score for the second trial (n=398)

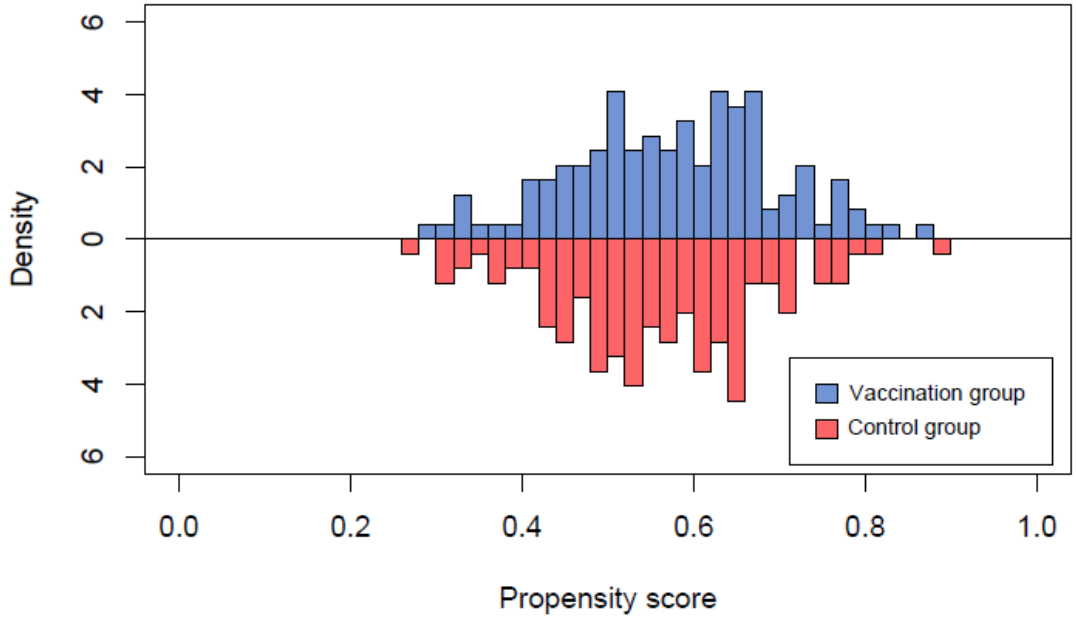


Supplementary material 7a: Propensity score development for the third trial (n=246)

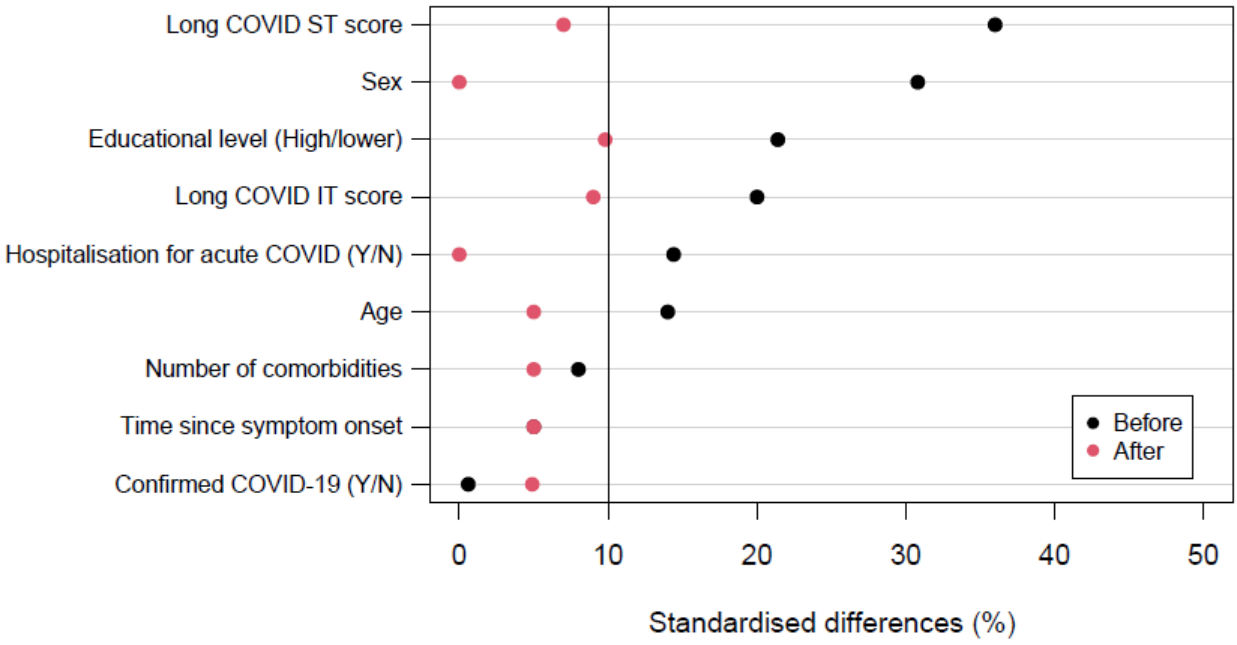
Before matching



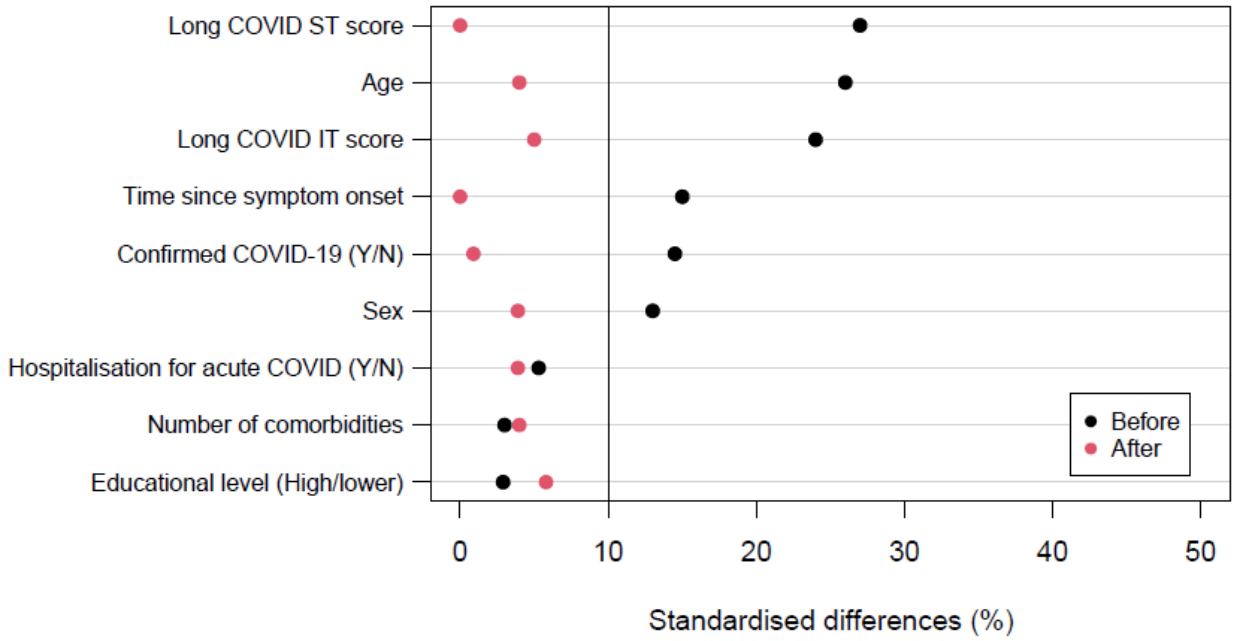
After matching



Supplementary material 7b: Standardised differences of variables used to generate the propensity score for the third trial (n=246)



Supplementary material 8: Standardised differences of variables used to generate the propensity score in the pooled analysis (n=910)



Supplementary material 9: Primary and secondary outcomes at 120 days after baseline in the subgroup of patients with confirmed COVID-19 (n=510).

[1]For 158 patients in the control group, data were censored at the date of their vaccination before 120 days; [2]Outcome data were missing for 26 (10.2 %) and 14 (5.5 %) patients in the vaccination and control group respectively. Missing outcome data were handled by multiple imputations using chained equations.

	Vaccinated patients (n=255)	**Unvaccinated controls (n=255)[1]**	**Mean difference or difference of proportion (95% CI)[2]**
Long COVID ST score at 120 days - Mean (SD)	12.0 (8.5)	13.8 (8.7)	-1.8 (-3.4 to -0.2)
Long COVID IT score at 120 days - Mean (SD)	22.7 (16.1)	26.4 (16.3)	-3.8 (-6.7 to -0.8)

Supplementary material 10a: Primary and secondary outcomes at 120 days after baseline in the subgroup of patients whose time since symptom onset was ≤ 12 months (n=582).

[1]For 176 patients in the control group, data were censored at the date of their vaccination before 120 days; [2]Outcome data were missing for 22 (7.6 %) and 22 (7.6 %) patients in the vaccination and control group respectively. Missing outcome data were handled by multiple imputations using chained equations.

	Vaccinated patients (n=291)	**Unvaccinated controls (n=291)[1]**	**Mean difference or difference of proportion (95% CI)[2]**
Long COVID ST score at 120 days - Mean (SD)	12.0 (9.1)	13.9 (9.2)	-1.9 (-3.5 to -0.3)
Long COVID IT score at 120 days - Mean (SD)	23.5 (16.3)	26.4 (16.3)	-2.9 (-5.7 to -0.1)

Supplementary material 10b: Primary and secondary outcomes at 120 days after baseline in the subgroup of patients whose time since symptom onset was > 12 months (n=294).

[1]For 58 patients in the control group, data were censored at the date of their vaccination before 120 days; [2]Outcome data were missing for 7 (4.8 %) and 11 (7.5 %) patients in the vaccination and control group respectively. Missing outcome data were handled by multiple imputations using chained equations.

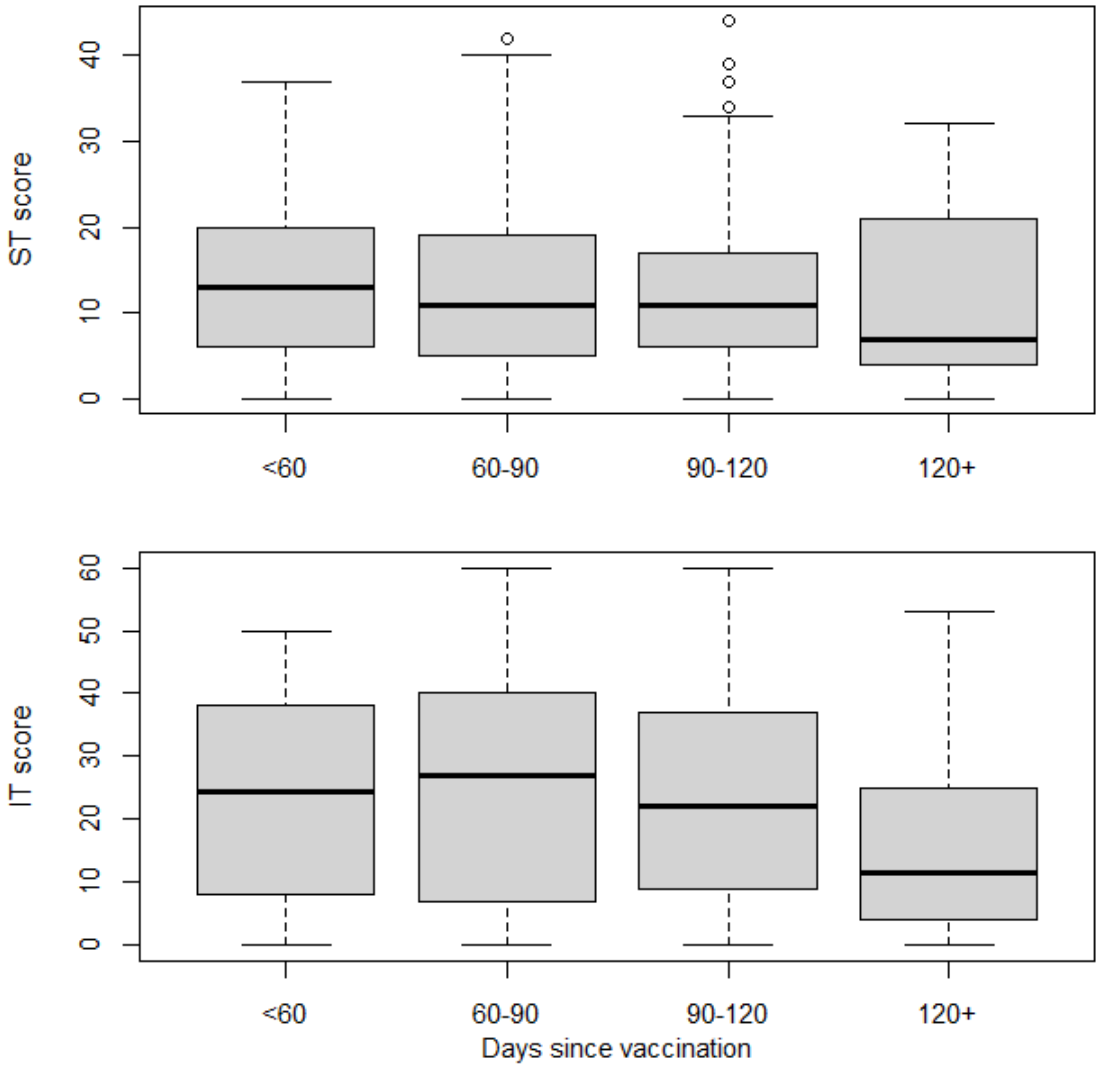
	Vaccinated patients (n=255)	**Unvaccinated controls (n=255)[1]**	**Mean difference or difference of proportion (95% CI)[2]**
Long COVID ST score at 120 days - Mean (SD)	15.3 (9.9)	17.0 (9.4)	-1.7 (-4.0 to 0.6)
Long COVID IT score at 120 days - Mean (SD)	27.8 (17.1)	30.6 (15.1)	-2.8 (-6.7 to 1.1)

Supplementary material 11: Primary and secondary outcomes at 120 days in a sensitivity analysis with the study population is limited to patients who had been included in only one of the three sequential trial (n=652).

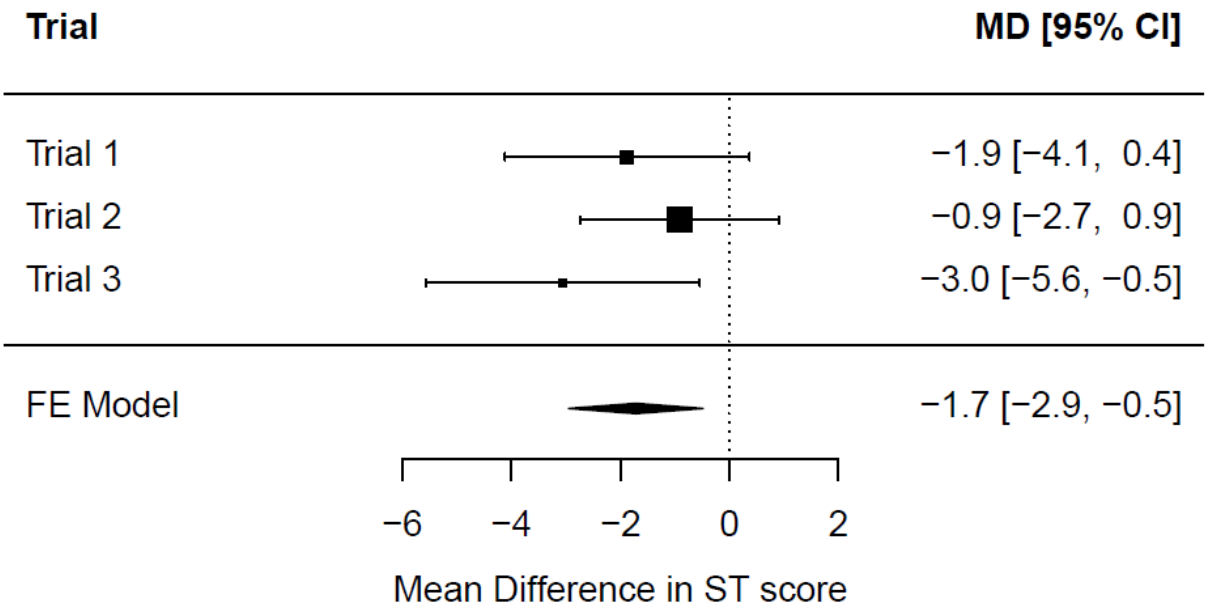
[1]For 156 patients in the control group, data were censored at the date of their vaccination before 120 days; [2] Outcome data was missing for 29 (8.9 %) and 22 (6.7 %) patients in the vaccination and control group respectively. Missing outcome data were handled by multiple imputations using chained equations.

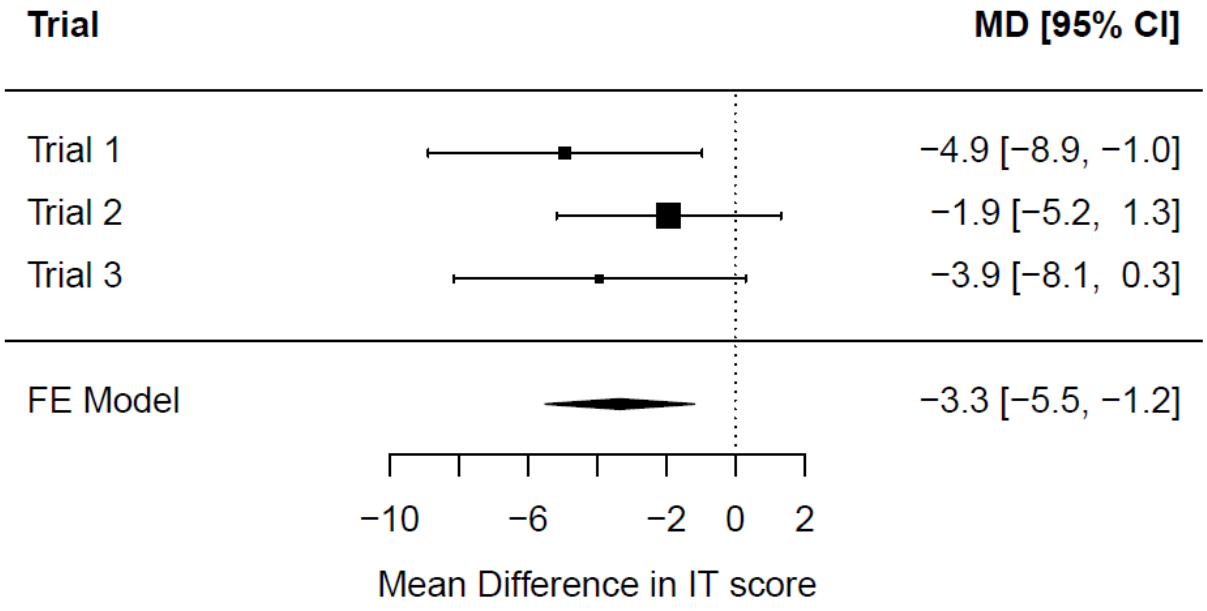
	Vaccinated patients (n=255)	**Unvaccinated controls (n=255)[1]**	**Mean difference or difference of proportion (95% CI)[2]**
Long COVID ST score at 120 days - Mean (SD)	13.2 (9.6)	14.9 (10.2)	-1.6 (-3.2 to -0.1)
Long COVID IT score at 120 days - Mean (SD)	24.1 (16.9)	27.2 (17.0)	-3.1 (-5.9 to -0.2)

Supplementary material 12: Value of the long COVID ST and IT score at 120 days after baseline, as a function of the time to vaccination, among patients who were vaccinated (n=618).



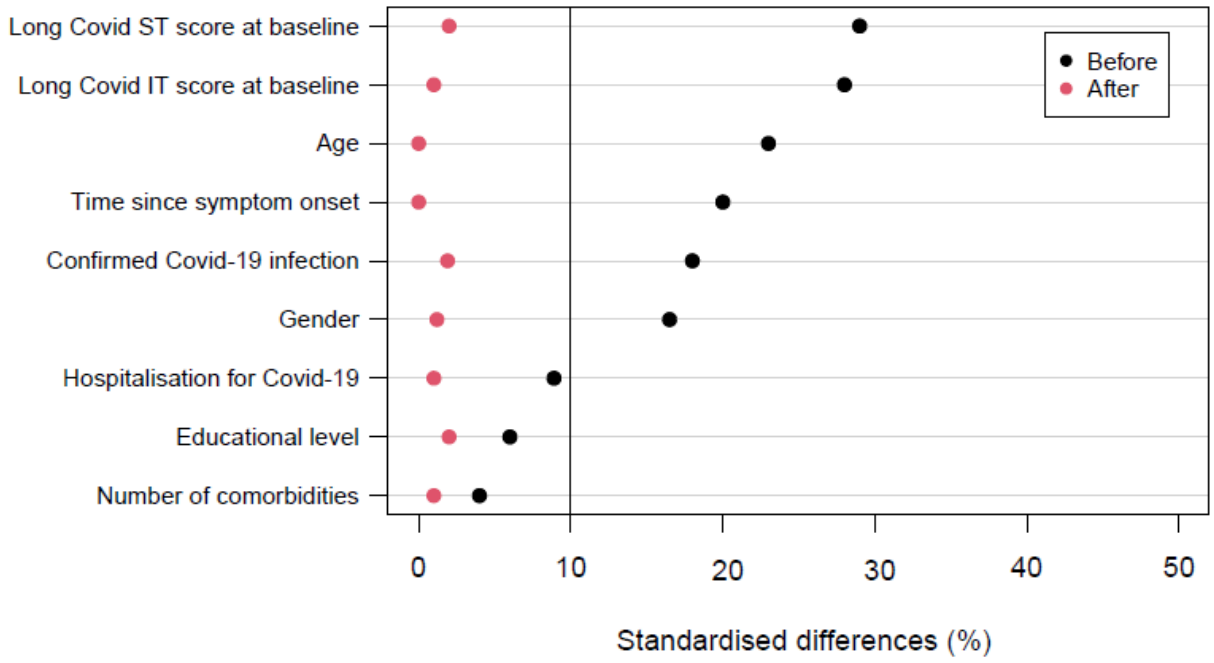
Supplementary material 13: Estimation of the treatment effect in the three trials separately and meta-analysis of these three trials.





Supplementary material 14: Primary and secondary outcomes at 120 days in a sensitivity analysis using inverse probability of treatment weighting using standardised mortality ratio weights (SMRW).

This analysis compared 523 patients who received vaccination to 1338 patients who did not receive vaccination during the same period.



	Vaccinated patients (n=523)	**Unvaccinated controls (n=1338)**	**Mean difference or difference of proportion (95% CI)**
Long COVID ST score at 120 days - Mean (SD)	12.6 (9.3)	14.1 (9.2)	-1.4 (-2.6 to -0.3)
Long COVID IT score at 120 days - Mean (SD)	23.9 (16.7)	26.6 (16.8)	-2.4 (-4.5 to -0.4)