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Acute SARS-CoV-2 infection and self-reported post-acute cognitive dysfunctions from the Danish EFTER-COVID survey

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Abstract

Background The extent and burden of post-acute cognitive dysfunctions following SARS-CoV-2 infection is uncertain.

Methods 25,485 SARS-CoV-2 test-positive and 25,032 test-negative individuals were repeatedly asked to score symptoms of subjective cognitive deficits 2 to 18 months after test using the “Cognitive complaints in bipolar disorder rating assessment” (COBRA) tool. Poisson mixed-effects models were used to estimate Score Ratios (SRs) by comparing scores between test-positive and test-negative individuals.

Results At each follow-up point, test-positive individuals have low but slightly higher mean COBRA scores compared with test-negatives. For the combined 2–18 months period, COBRA scores among test-positive individuals are 11% higher than corresponding scores among test-negatives ($SR_{2-18\text{mth}} = 1.11$ (95% CI; 1.09–1.13)). Of effect modifiers explored, being hospitalized with a positive SARS-CoV-2 test particularly elevates COBRA scores ($SR_{2-18\text{mth}} = 1.38$ (95% CI; 1.24–1.54)).

Conclusion In the general population of SARS-CoV-2 infected individuals, self-reported post-acute scores of cognitive dysfunctions are low and only slightly higher than corresponding scores among test-negatives. Higher COBRA scores among hospitalized SARS-CoV-2 test positives corroborate with long-term cognitive impairment being most pronounced among those with severe SARS-CoV-2 infection.

Plain language summary

Cognitive dysfunction is a commonly studied symptom of long COVID, but the extent of this burden is difficult to ascertain. In a Danish, nation-wide survey of post-COVID conditions, we explored subjective cognitive dysfunction reported by 25,485 SARS-CoV-2 test-positive and 25,032 test-negative individuals. For the combined period 2–18 months after testing, test-positives' post-acute scores for cognitive dysfunction were only marginally higher when compared to test-negative individuals' scores. However, hospitalized test-positives had the most elevated scores, corroborating existing literature suggesting that long-term cognitive dysfunction is most pronounced among individuals who experienced severe SARS-CoV-2 infection.

According to the WHO, more than 700 million cases of SARS-CoV-2 infections have been confirmed globally (<https://covid19.who.int/>), but the actual number is estimated to be much higher¹. Although the majority of patients infected with SARS-CoV-2 recover within a few weeks, around 10–20% will experience persistent, relapsing or even new-onset symptoms also known as long-COVID or post-COVID-19 syndrome^{2,3}.

Several studies including a recent controlled human infection model study⁴ have suggested that SARS-CoV-2 test-positives are at an elevated risk of symptoms of post-acute cognitive impairment such as memory and concentration difficulties, but the exact burden of cognitive deficits following COVID-19 is still uncertain⁵. Thus, symptoms of post-acute cognitive dysfunction may affect 3% or as many as 90% of the SARS-CoV-2

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infected individuals^{6–15}. Female sex^{16–19}, lower education level^{7,10,20,21} and clinical severity of the infection^{13,20,22–24} have been found to be associated with a higher risk of post-acute cognitive deficits after SARS-CoV-2 infection, although some counterevidence exists^{17,18}. Other suggested effect modifiers are age^{7,16,21,25} and a history of neuropsychiatric disease⁷.

A considerable variability in risk estimates from previous studies can be due to the use of selected groups of study participants, often hospitalized COVID-19 patients or individuals attending long-COVID clinics, lack of appropriate control groups, or small sample sizes. In addition, many different screening tools have been used to evaluate cognitive deficits after SARS-CoV-2 infection, including objective screening tools which may not give the full picture of the person's own experienced cognitive dysfunctions²⁶.

Given the impact of cognitive dysfunction on an individual's well-being, quality of life and daily functioning, accurate estimation of the prevalence and severity of subjective cognitive deficits among all SARS-CoV-2 infected individuals—from asymptomatic to severe cases—is critically important. To assess this, we use longitudinal data from the unique Danish nationwide EFTER-COVID (“AFTER COVID”) survey exploring self-reported post-acute SARS-CoV-2 symptoms including subjective cognitive complaints in the general population up to 18 months after SARS-CoV-2 test. In the general population of SARS-CoV-2 infected individuals, we observe that self-reported post-acute scores of cognitive dysfunctions up to 18 months after test are low and only slightly higher than corresponding scores among test-negatives. However, compared to test-negatives, individuals hospitalized with a positive SARS-CoV-2 test reported higher scores.

Methods

Study cohort of SARS-CoV-2 test-positive and test-negative individuals

The study cohort is based on the EFTER-COVID survey, which was established in order to study the degree of, nature of and duration of possible post-acute symptoms and health problems among SARS-CoV-2 test-positive individuals using test-negative as a reference group²⁷. Test-positive and test-negative individuals were invited to participate using information on SARS-CoV-2 PCR test results from the national COVID-19 surveillance system at the Statens Serum Institut^{28,29}. Since 1968, the Danish Civil Registration System has assigned a unique personal ID-number (the CPR-number) to every person resident in Denmark³⁰, which is used as a personal identifier in all Danish national registers including the COVID-19 surveillance system. Invitations to participate in EFTER-COVID were sent to test-positive and test-negative individuals using E-Boks, a national digital secure two-way communication system between citizens and authorities in Denmark, via the CPR-number³¹. E-Boks usage is mandatory for all inhabitants in Denmark aged 15 years or older, unless exempted (in 2022 used by 92% of the relevant age group)²⁷. In general, all individuals who received a positive PCR-test result for the first time were invited. Test-negative individuals with no prior positive test result were density matched on test-date with a test-negative/test-positive individual ratio of 3:2 in anticipation of a lower response rate among test-negatives²⁷.

The EFTER-COVID survey

Questionnaires were sent out from August 1, 2021 and cover SARS-CoV-2 test dates from September 1, 2020 to February 21, 2023. Individuals with test dates after April 2, 2021, were randomly assigned to one of four prospective tracks focusing on physical health, mental health, cognitive deficits and fatigue, respectively²⁷. Every participant was asked to fill in a baseline questionnaire, and if they consented, they received follow-up questionnaires approximately 2, 4, 6, 9, 12 and 18 months after the test. Participants were enrolled 1 month after their test date except for a smaller fraction of participants, who received special 2- or 4-months baseline questionnaires during project start-up.

The baseline questionnaire contained questions regarding acute symptoms (symptoms in the period one week before and until four weeks after the test), and issues such as weight, height, smoking and drinking

habits, education level, employment, physical fitness, selected comorbidities, selected disease diagnoses and general health conditions²⁷. Only participants who had filled in both the baseline questionnaire and at least one follow-up questionnaire were included in the present study.

Outcome

In the present study, we used data from the EFTER-COVID track focusing on cognitive problems, which were evaluated using the “Cognitive complaints in bipolar disorder rating assessment” (COBRA) questionnaire³². In the baseline questionnaire, participants were asked about pre-existing (within the six months prior to test) cognitive function. In the follow-up questionnaires, participants rated cognitive function in relation to the past 14 days from when they responded.

COBRA is a self-reported instrument which collects cognitive complaints related to processing speed, working memory, verbal learning and memory, attention/concentration, executive function, and mental tracking³². It consists of 16 questions about cognitive difficulties in daily life scenarios e.g., “Do you find it hard to concentrate when reading a book or a news-paper?”, “Do you have the feeling that you do not finish what you begin?”³³. The COBRA questionnaire (i.e., the 16 questions) exists in several languages and are freely available through the International Society for Bipolar Disorders' website at www.isbd.org/cognitive-assessment³³. All items/questions are rated using a four-point scale, 0=never, 1=sometimes, 2=often, and 3=always. Scores are added together (0–48), and the higher the score, the more subjective complaints³². In our main analysis, we analyzed scores as count data. In a supplementary analysis, we dichotomized scores into <15 (no cognitive complaints) and ≥15 (cognitive complaints)³⁴.

Covariates and other data sources

From the Danish National Patient Register (DNPR), we obtained information on hospital contacts (outpatient, inpatient and emergency departments) for the last five years before the test date to calculate Charlson Comorbidity Index (CCI), (Supplementary table 1), pre-existing psychiatric disorders as far back as 2005 (Supplementary table 2) and severity of the SARS-CoV-2 infection, classified as non-hospitalized and hospitalized (hospitalized within 14 days after until at most 2 days prior to the positive test). Individuals who tested positive more than two days after hospital admission were censored at the date of SARS-CoV-2 test as they were considered to have acquired the infection in the hospital ($n = 32$). Healthcare workers were identified using the authorization register³⁵, vaccination status was obtained from the Danish COVID-19 vaccination register (<https://miba.ssi.dk/forskningsbetjening/ansoeg-om-data-via-forskerservice/tilgaengeligt-data>) and virus variant periods defined according to periods of predominance in Denmark (Alpha; March 15 to June 30, 2021, Delta; July 15 to November 15, 2021, Omicron; January 1, 2022 and onwards)³⁶. Individuals whose positive or negative test date fell within the transitional periods were not included in the variant stratified analysis. From the baseline questionnaire we included self-reported information on height, weight, education level and employment (Supplementary Table 3).

Statistical analysis

We used Poisson mixed effects models to estimate Score Ratios (SRs) comparing mean COBRA scores among test-positive versus those among test-negative individuals for the pre-test period (0-6 months before test) and at different time-points of follow-up, for those who had filled in the follow-up questionnaire at that specific time-point (i.e., 2-, 4-, 6-, 9-, 12-, and 18 months after test). These models took the following fixed effects into account: age group, sex, obesity (yes/no), CCI, healthcare occupation, employment status, dominant virus variant at test date, vaccination status, and education level. The individual identifier (the CPR number) was included as a random effect to account for the repeated and presumably not independent measurements of COBRA scores per individual over time (months after SARS-CoV-2 test). 95% confidence intervals (CI) were calculated using the Wald method.

Table 1 | Study cohort characteristics according to SARS-CoV-2 test status (N=50,517)

Characteristic ^a	Participants with a positive test N=25,485	Participants with a negative test (time-matched) N=25,032
Age group (years) (n, %)		
15–29	2526 (9.9)	1468 (5.9)
30–49	7055 (27.7)	4850 (19.4)
50–69	11,430 (44.8)	13,113 (52.4)
≥70	4474 (17.6)	5601 (22.4)
Age at test date (years) (median IQR)	55 (43–66)	59 (49–68)
Sex (n, %)		
Female	15,166 (59.5)	14,687 (58.7)
Male	10,319 (40.5)	10,345 (41.3)
Obesity (n, %)		
Non-obese	19,520 (76.6)	18,913 (75.6)
Obese	4148 (16.3)	4456 (17.8)
Unknown	1817 (7.1)	1663 (6.6)
Charlson Comorbidity Index (n, %)		
0	22,259 (87.3)	21,012 (83.9)
1	1902 (7.5)	2159 (8.6)
≥2	1324 (5.2)	1861 (7.4)
Healthcare occupation (n, %)		
No	23,692 (93.0)	22,769 (91.0)
Yes (frontline)	1254 (4.9)	1638 (6.5)
Yes (other)	539 (2.1)	625 (2.5)
Variant period (n, %)		
Omicron	13,199 (51.8)	10,031 (40.1)
Delta	1494 (5.9)	2915 (11.6)
Alpha	3085 (12.1)	4411 (17.6)
Transitional periods	7707 (30.2)	7675 (30.7)
Vaccinations status (n, %)		
Unvaccinated	2482 (9.7)	2678 (10.7)
Vaccinated (1 dose)	647 (2.5)	1151 (4.6)
Vaccinated (2 doses)	10,439 (41.0)	9672 (38.6)
Vaccinated (3 doses)	11,917 (46.8)	11,531 (46.1)
Employment (n, %)		
Work/study (actively)	17,233 (67.6)	15,463 (61.8)
Work/study (not temporarily)	585 (2.3)	438 (1.7)
Work/study (not able)	320 (1.3)	299 (1.2)
Pensioner	6267 (24.6)	7932 (31.7)
Unknown	1080 (4.2)	900 (3.6)
Education level (n, %)		
Higher (long)	5019 (19.7)	4112 (16.4)
Higher (medium or short)	10,934 (42.9)	11,188 (44.7)
Secondary or vocational	6481 (25.4)	6769 (27.0)
Primary	2165 (8.5)	2336 (9.3)
Unknown	886 (3.5)	627 (2.5)

^aDefinitions in supplementary table 3.

We furthermore calculated SRs for the combined 2–18 months after test by including and aggregating all COBRA scores per individual i.e., not taken time since test into consideration, while controlling for independence of the observations by including the random effect, the CPR number.

In addition, we explored factors modifying the association between infection and COBRA scores by stratifying the SRs for the combined 2–18 months of follow-up on age group, sex, obesity (yes/no), CCI, healthcare occupation (no; yes, in frontline; yes, but not in frontline), employment status, dominant virus variant at index test date, vaccination status, education level and severity of infection.

In a supplementary analysis, we used logistic mixed effects models to estimate odds ratios (ORs) with 95% CIs by comparing odds for cognitive complaints (COBRA score ≥15) vs no cognitive complaints (score <15) among test-positive with the corresponding odds among test-negative individuals. This analysis used the same fixed and random effects as the Poisson mixed effects models.

All statistical analyses were carried out using R version 4.3.0. Forest plots were generated using the R-package called forestploter³⁷.

A posteriori analysis

We repeated the main analysis only including the subgroup of individuals who had completed all the follow-up questionnaires. This was done to evaluate the impact of survey attrition whereby individuals in good cognitive health respond to fewer follow-up questionnaires than individuals who experience cognitive issues, and are thus more motivated to participate.

Ethical approval

This study was performed as a surveillance study as part of the governmental institution Statens Serum Institut’s (SSI) advisory tasks for the Danish Ministry of Health. SSI’s purpose is to monitor and fight the spread of disease in accordance with section 222 of the Danish Health Act. According to Danish law national surveillance activities conducted by SSI does not require approval from an ethics committee. It was approved by the Danish Governmental law firm and SSI’s compliance department that the study is fully compliant with all legal, ethical, and IT-security requirements and there are no further approval procedures regarding such studies.

Participation in the study was voluntary. The invitation letter to participants contained information about their rights under the Danish General Data Protection Regulation (rights to access data, rectification, deletion, restriction of processing and objection) and the type of information about them which might be processed (including registry data). Accessing and filling out the questionnaire after receiving the above information was considered informed consent to participate from the participant’s side. Participants could leave the survey at any time.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

In the cognitive track of the EFTER-COVID survey, 75,660 persons completed the baseline questionnaire and consented to receive a follow-up questionnaire. Among those, 56,051 completed at least one follow-up questionnaire (74%). After excluding test-negative individuals who reported having been tested seropositive ($n = 4564$) and individuals vaccinated within 14 days prior to the SARS-CoV-2 test thus having no full vaccine effect before test ($n = 970$), the study population consisted of 25,485 test-positive and 25,032 test-negative individuals (Supplementary fig. 1).

Association between SARS-CoV-2 infection and COBRA scores

Compared with test-negative, test-positive individuals were slightly younger, more often members of the workforce and more often tested during the Omicron-dominant period (Table 1). COBRA scores among test-positive were, apart from the pre-test period, slightly higher, but increasingly higher the longer the time of follow-up than corresponding

Fig. 1 | Adjusted Score Ratios (95% CIs) comparing COBRA scores among SARS-CoV-2 test-positive versus test-negative study participants.

Footnotes: SR=Score ratio. SRs were estimated using mixed effects Poisson regression models adjusted for age group, sex, obesity, Charlson Comorbidity Index, healthcare occupation, dominant virus variant period, vaccination status, employment status and education level.

Months since SARS-CoV-2 test	Negative n Mean (SD)	Positive n Mean (SD)	Positive/Negative SR (95% CI)
Pre-test	25032 5.58 (5.89)	25485 5.48 (5.85)	0.96 (0.94, 0.98)
2	14434 6.52 (6.01)	14540 7.25 (7.01)	1.08 (1.05, 1.10)
4	13346 6.93 (6.33)	15851 7.68 (7.06)	1.10 (1.07, 1.12)
6	12897 6.87 (6.29)	15043 7.75 (7.20)	1.11 (1.09, 1.14)
9	9829 7.02 (6.33)	12800 7.91 (7.17)	1.12 (1.09, 1.14)
12	7898 7.08 (6.31)	10482 8.02 (7.23)	1.12 (1.10, 1.15)
18	6702 7.16 (6.24)	8280 8.07 (7.20)	1.13 (1.10, 1.16)
2-18			1.11 (1.09, 1.13)

scores among test-negatives. Thus, at 18 months of follow-up, mean COBRA scores was 8.07 (Standard Deviation (SD); 7.20) among test-positive versus 7.16 (SD; 6.24) among test-negative individuals (Fig. 1, Supplementary fig. 2, Supplementary table 4). Elevated SRs were observed at each time-point during follow-up (2, 4, 6, 9, 12 and 18 months after SARS-CoV-2-test), and for the combined 2–18 month of follow-up ($SR_{2-18\text{mth}} = 1.11 (1.09-1.13)$) (Fig. 1).

Impact of possible effect modifiers on the association between SARS-CoV-2 infection and COBRA scores

In the combined period 2–18 months after testing, age, sex, obesity, period of virus variant, and educational level appeared to have the most important impact on the stratified SRs. 30–69-year-old test-positive individuals had COBRA scores higher than those among test-negative of same age, whereas no difference was observed for the youngest and oldest age groups. The SRs among females ($SR_{2-18\text{mth}} = 1.14 (1.11-1.17)$) and obese individuals ($SR_{2-18\text{mth}} = 1.17 (1.12-1.23)$) were slightly higher than the corresponding SRs among males and non-obese, respectively. The SRs among those with a higher medium/short and secondary/vocational education were higher than the corresponding SRs among individuals with higher long education. For the three virus variants explored, the SR in the alpha period stood out as the highest ($SR_{2-18\text{mth}} = 1.22 (1.13-1.31)$) (Fig. 2).

Impact of severity of the acute SARS-CoV-2 infection on the association between SARS-CoV-2 infection and COBRA scores

In the combined period 2–18 months after testing, 464 of the 25,485 SARS-CoV-2 infected participants tested positive within 14 days before to 2 days after admission to a hospital. Hospitalized test-positives had significantly higher COBRA scores compared to test-negative ($SR_{2-18\text{mth}} = 1.38 (1.24-1.54)$) (Fig. 3) and non-hospitalized test-positive individuals ($SR_{2-18\text{mth}} = (1.27 (1.14-1.42))$) (supplementary Fig. 3).

Impact of pre-existing psychiatric disorders on association between SARS-CoV-2 infection and COBRA scores in the combined period of 2–18 months after test

Overall, COBRA scores among SARS-CoV-2 infected individuals who had been diagnosed with a psychiatric disorder prior to test were slightly higher than COBRA scores among test-negative individuals with pre-existing psychiatric disorders ($SR_{2-18\text{mth}} = 1.13 (1.07-1.21)$). Elevated $SR_{2-18\text{mth}}$ were observed for test-positive individuals with depression, stress-related disorders and personality disorders but not for any of the remaining eight psychiatric disorders (Supplementary Fig. 4).

Supplementary analysis

Prior to test, 8.3% of the test-positive and test-negative individuals reported cognitive complaints (COBRA score ≥ 15). For test-positive individuals, this proportion increased to a little less than 18% at 18 months of follow-up. A similar picture was seen for test-negative individuals, although approximately 5% lower at all time-points of follow-up (Supplementary Table 4, Fig. 4). Odds of cognitive complaints (COBRA scores ≥ 15) for the combined

2–18 months of follow-up among SARS-CoV-2 test-positive were 48% higher than corresponding odds among test-negative individuals ($OR_{2-18\text{mth}} = 1.48 (1.30-1.68)$) (Fig. 4).

A posteriori analysis

2145 test-negative and 2481 test-positive individuals answered the baseline questionnaire and all of the follow-up questionnaires. SRs were compatible with those in the main analysis, but COBRA scores among test-positive were no longer statistically significantly higher than those among test-negative individuals, neither in the combined 2–18 months period of follow-up after test ($SR_{2-18\text{mth}} = 1.05 (0.98, 1.13)$), nor at any time-point of follow-up (Supplementary fig. 5).

Discussion

Compared with test-negatives, SARS-CoV-2 test-positive individuals reported between 8 to 13% higher COBRA scores at each follow-up point. SARS-CoV-2 infected were also at a higher risk of experiencing cognitive complaints (COBRA scores ≥ 15) than test negative individuals. Of possible effect modifiers, severity of infection had the highest impact on the association between SARS-CoV-2 infection and post-acute COBRA scores.

We observed that during follow-up, 15–18% of the SARS-CoV-2 infected reported cognitive complaints (COBRA scores ≥ 15). Corresponding proportions among test-negative individuals were 10–13%. Previous studies have reported that 3–6%^{14,38} up to as many as 49–66%^{8,11,13} may experience some degree of cognitive dysfunction 3–10 months after SARS-CoV-2 infection. In our study, test-positive individuals reported 11% higher COBRA scores than those among test-negative individuals, and a 1.5-fold higher risk of experiencing cognitive complaints (COBRA scores ≥ 15). In previous studies, SARS-CoV-2 infected individuals had the same risk or up to a 9-fold elevated risk of post-acute cognitive deficits, compared with control groups^{17,24,38}.

It is difficult to explain this discrepancy in the estimated burden of SARS-CoV-2 post-acute cognitive dysfunction. Apart from well-known methodological problems such as small study sizes and selection bias, different definitions of outcome may hamper the comparability between previous studies. For example, some studies registered the presence of symptoms such as brain fog or memory loss¹⁷, whereas others used different kinds of tools, to assess cognitive impairment^{7,12,18,24}, tools that may not measure the same domains of cognitive function or may not be useful for screening the general population.

We found that severity of infection further increased the risk of post-acute cognitive complaints, which is in line with many previous studies^{13,22,23}. The mechanism is unknown, but a recent study suggested that post-hospitalization COVID-19 cognitive deficits could be associated with immune-mediated brain injury³⁹. However, both a Danish¹⁸ and a German study⁷ found no impact of acute COVID-19 severity on post-acute cognitive impairment. Findings from other studies categorizing hospitalized cases into less severe and severe cases, i.e., those with respiratory problems, furthermore suggest that post-acute cognitive impairment may be associated with severity of lung affection^{8,24}.

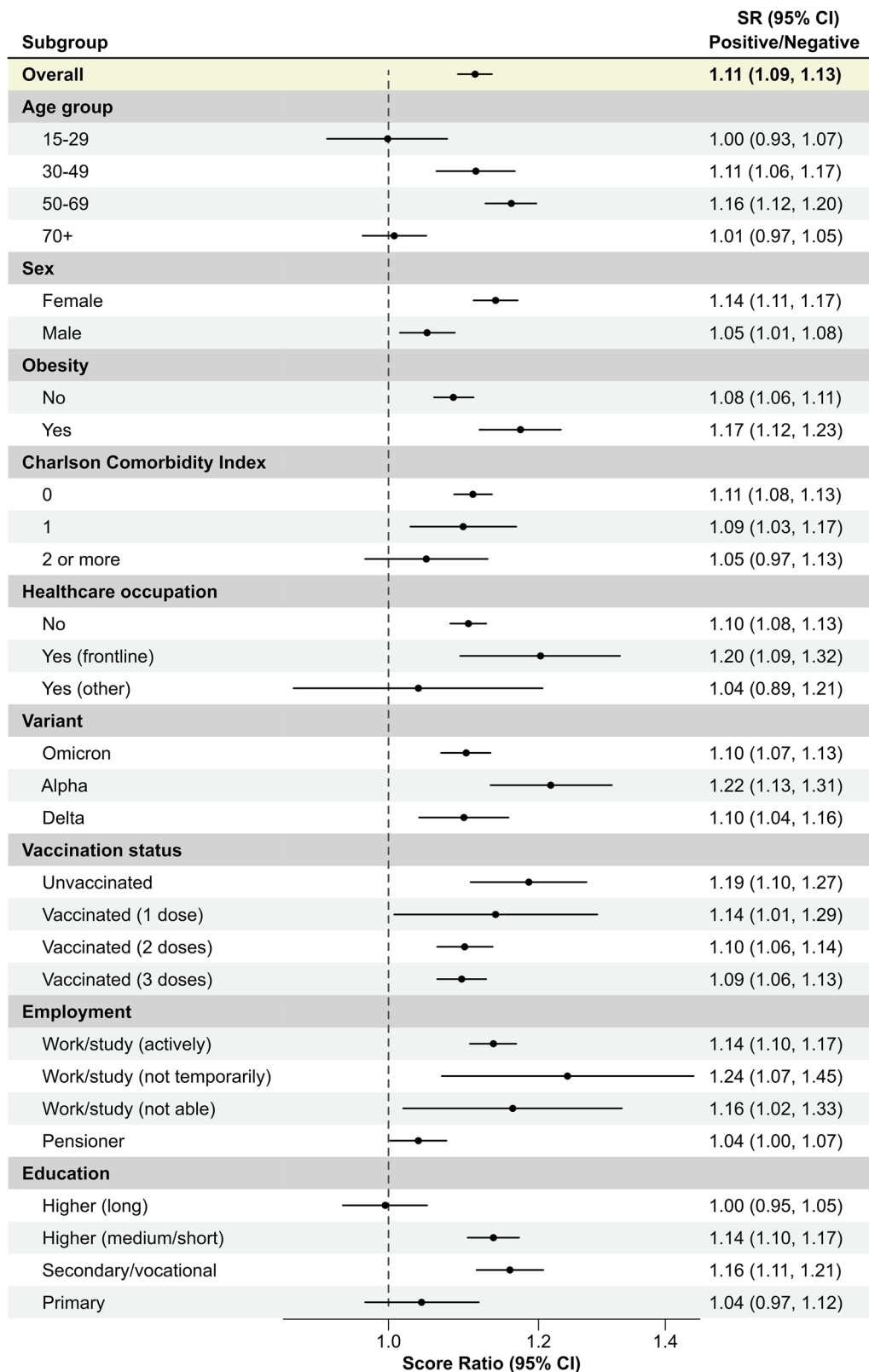


Fig. 2 | Adjusted Score Ratios (95% CIs) comparing COBRA scores among SARS-CoV-2 test-positive versus test-negative study participants in the combined period 2–18 months after testing according to possible effect modifiers. Footnotes: SR Score ratio. SRs were estimated using mixed effects Poisson regression

models. SRs for the different effect modifiers were mutually adjusted for each other. Individuals with “unknown” information was included but since they comprised small minorities of each variable subgroup, we did not show them in the plot.

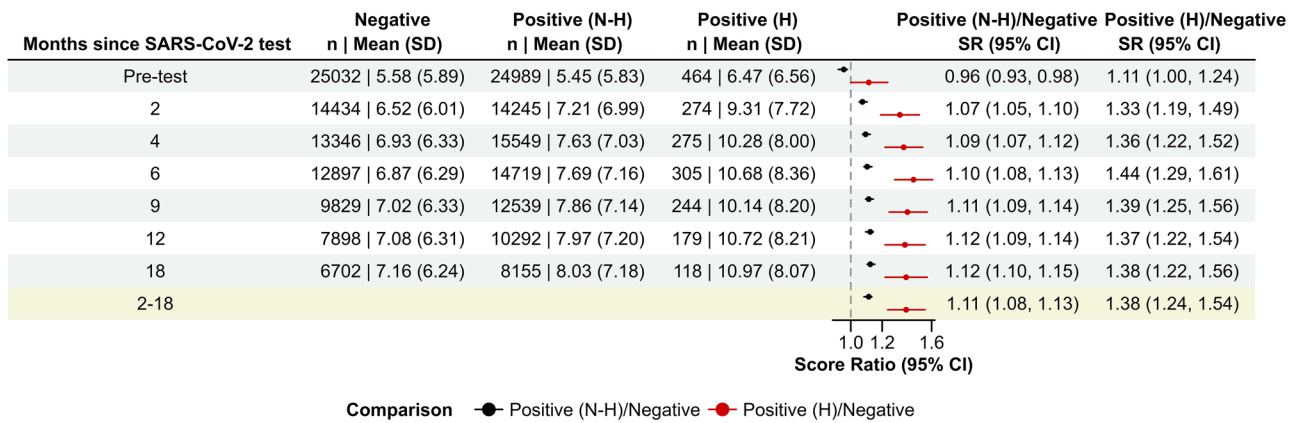
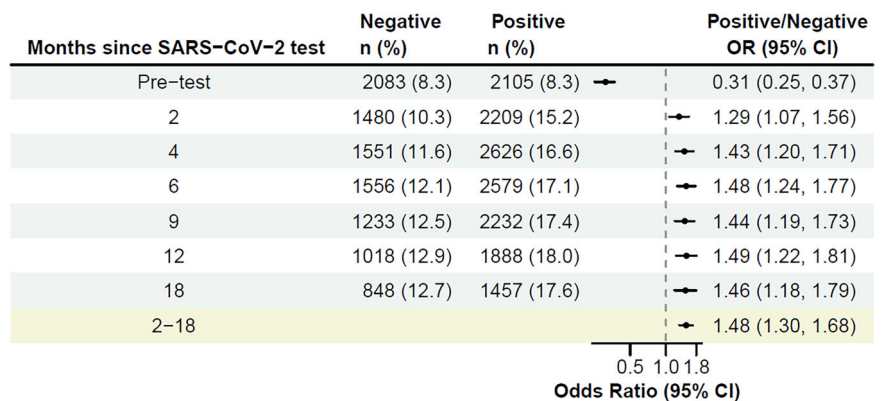


Fig. 3 | Score Ratios (95% CIs) comparing COBRA scores among hospitalized SARS-CoV-2 test-positive (H) versus test-negative study participants and non-hospitalized (N-H) test-positive versus test-negative study participants, respectively. Footnotes: SR Score ratio. (N-H) =non-hospitalized, (H) =hospitalized. SRs

were estimated using mixed effects Poisson regression models adjusted for age group, sex, obesity, Charlson Comorbidity Index, healthcare occupation, dominant virus variant period, vaccination status, employment status and education level.

Fig. 4 | Adjusted Odds Ratios (95% CIs) comparing odds of cognitive complaints (COBRA scores ≥ 15) among SARS-CoV-2 test-positive versus corresponding odds among test-negative study participants. Footnotes: ORs were estimated using mixed effects logistic regression models adjusted for age group, sex, obesity, Charlson Comorbidity Index, healthcare occupation, dominant virus variant period, vaccination status, employment status and education level.



It is important to emphasize that although SARS-CoV-2 infected individuals in the present study appeared to have higher COBRA scores than test-negative individuals, both pre-test and follow-up COBRA scores were low and appeared within the normal range compared to a Danish sample of blood donors (Miskowiak 2023, personal communication). Few studies have assessed normative COBRA scores, but in a group of 581 adult Japanese volunteers (mean age 42 years), the mean COBRA score was 8.32, and 17% had COBRA scores ≥ 15 ⁴⁰. These scores are higher than pre-test COBRA scores for test-positive (mean = 5.48) and test-negative individuals (mean = 5.58) observed in our study, close to scores for the group of test-positive individuals during follow-up, but lower than mean COBRA scores among individuals hospitalized with a positive SARS-CoV-2 test.

The EFTER-COVID survey is one of the largest and longest running studies addressing possible post-acute symptoms and health problems after SARS-CoV-2 infection²⁷. More than 2.4 million persons (40% of the Danish population) were invited to participate. The main weakness to the survey is the potential existence of bias due to the response rate of 34.5% and increased attrition with each successive follow-up questionnaire²⁷. Factors such as age, sex, educational level, chronic diseases, possible long-COVID symptoms, or lack of computer familiarity may have had an impact on the wish to participate in EFTER-COVID and the willingness to complete the several follow-up questionnaires. Thus, our results may not be replicable to certain groups of the population. In addition, although, Denmark set up one of the highest PCR mass testing capacities per capita in the world from 2020–2022²⁸, we cannot rule out that some of the test-negative individuals may have had an undocumented infection in the past or during follow-up, which could lead to differential misclassification.

We observed that the level of COBRA scores among SARS-CoV-2 infected remained higher and even increased slightly compared with COBRA scores among test-negative individuals during follow-up, which is in contrast to some of the previous studies observing improvement over time^{41,42}. However, the *a posteriori* analysis only including the small subgroup of individuals who completed all follow-up questionnaires, found that the association between SARS-CoV-2 infection and post-acute cognitive complaints in the combined 2–18 months and at each time points of follow-up were compatible with those observed in the main analysis, although no longer statistically significant. This suggests that attrition bias might only have had a minor impact on our results.

We assessed cognitive function using the subjective tool COBRA, whereas many other studies used objective tools. Subjectively experienced and objectively measured cognitive dysfunction scores may not correlate, meaning that it is not necessarily patients with a high degree of cognitive complaints who are the most impaired^{34,43}. One advantage of COBRA is that it is self-administered i.e., patients can calmly contemplate the difficulties that are important to them without being nervous in a testing situation. The use of objective neuro-cognitive tests is limited in larger epidemiological studies as they are time-consuming and costly. Furthermore, they may measure something of less importance to the patients.

Another limitation could be that COBRA was originally established to measure subjective neuro-cognition of bipolar patients³². However, COBRA has been validated in a cohort of patients with unipolar depression⁴⁴ and other studies have assessed cognitive function among healthy control groups using COBRA^{32,40,44–46} and found it as a useful tool in evaluating subjective cognitive function in the general adult population.

We decided to treat COBRA scores as a count variable and only in a supplementary analysis, we dichotomized COBRA scores. Dichotomization does have certain limitations such as loss of statistical strength, seriously underestimating the extent of variation in outcome between the groups and importantly risk of false positive results⁴⁷.

Conclusion

In the general population of SARS-CoV-2 infected individuals, self-reported post-acute scores of cognitive dysfunctions remained low and only slightly elevated. However, compared to test-negatives, individuals hospitalized with a positive SARS-CoV-2 test reported higher scores, corroborating with long-term cognitive impairment being most pronounced among those with severe SARS-CoV-2 infection.

Data availability

The datasets used in this study comprise sensitive, individual-level information from completed questionnaires and national register data. According to the Danish data protection legislation, the authors are not permitted to share this sensitive data directly upon request. However, the data are available for research purposes upon request to the Danish Health Authority (register data, email: kontakt@Sundshedsdata.dk) and Statens Serum Institut (questionnaire data, email: aii@ssi.dk), as well as within the framework of the Danish data protection legislation and any required permission from authorities. Data request processing can take an expected 3–6 months⁴⁸.

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Author contributions

NMN: Design and initiation of the EFTER-COVID survey, design of EFTER-COVID questionnaires. Written first draft of the present paper. Contributed significantly to the present paper (e.g., design of study, data interpretation, critically revision of the manuscript and approved the final version of manuscript). Agreed personally accountable for own contributions and ensure that questions related to the accuracy or integrity of any part of the present paper are appropriately investigated. PB: Design and initiation of the EFTER-COVID survey, design of EFTER-COVID questionnaires, collection of data including programming related to the EFTER-COVID. Contributed

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Competing interests

The authors declare no competing interests.

Additional information

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