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Temporal trajectories of long-COVID symptoms in adults with 22 months follow-up in a prospective cohort study in Norway

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ABSTRACT

Objectives: There is a lack of large studies on long-COVID symptoms with symptoms measurements before the onset of COVID-19. Therefore, long-COVID is still poorly defined.
Methods: The Norwegian COVID-19 Cohort Study is a population-based, open cohort of adult participants (aged 18-96 years) from Norway. From March 27, 2020, participants were recruited through social media, invitations, and nationwide media coverage. Fourteen somatic and cognitive symptoms were assessed at baseline and four follow-ups for up to 22 months. SARS-CoV-2 test status was obtained from a mandatory national registry or from self-report.
Results: After follow-up, 15 737 participants had a SARS-CoV-2-positive test, 67 305 had a negative test, and 37 563 were still untested. Persistent symptoms reported more frequently by positive compared with negative participants one month after infection, were memory problems (3-6 months: adjusted odds ratio (aOR) = 6.8, CI = 5.7-8.1; >18 months: aOR = 9.4, CI = 4.1-22), and concentration problems (3-6 months: aOR = 4.1, CI = 3.5-4.7; >18 months: aOR = 4.4, CI = 2.0-9.7) as well fatigue, dyspnea, anosmia and dysgeusia.
Conclusions: COVID-19 was associated with cognitive symptoms, anosmia, dysgeusia, dyspnea, and fatigue as well as worsening of overall health up to 22 months after a SARS-CoV-2 test, even when correcting for symptoms before the onset of COVID-19.

Introduction

The World Health Organization (WHO) has reported more than 775 million COVID-19 cases, including around 7.1 million deaths globally, as of May 2024 [1]. It has been estimated that more than 65 million individuals around the world suffer from post-acute sequelae of SARS-CoV-2 infection, often termed "long-COVID". [2] The definition of the phases of COVID-19 disease varies across studies [3–5]. An acute phase 0-1 month after diagnosis, followed by a post-acute phase 1-3 months, and a post-COVID-19 phase >3 months have been described [3]. The WHO's description of the time frame for long-COVID coincides with the post-COVID-19 phase [6].

Previous studies have reported a range of potential long-COVID symptoms such as anosmia and dysgeusia, fatigue, headache, muscle pain, abdominal pain, cough, dyspnea, hair loss, and cognitive symptoms [2,7–16]. However, most of these studies lacked rele-

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vant control groups, data on symptoms before COVID-19, and a long follow-up time. We initiated a large prospective cohort study in which we examined the temporal trajectories of symptoms in SARS-CoV-2-positive, -negative, and -untested participants, with a high response rate and a follow-up time of up to 22 months after the test date.

Methods

Study population

The Norwegian COVID-19 Cohort Study is a population-based, open cohort study of adult participants (aged 18-96 years) from Norway. From March 27, 2020, participants were recruited through social media, invitations, and nationwide media coverage. Participants completed a baseline questionnaire at inclusion and were invited to regular follow-up questionnaires. All participants had a Norwegian identification number and electronic access to the secure national digital governmental identification service.

Between March 27, 2020, to April 15, 2021, a total of 146 065 participants completed the baseline questionnaire (99% before June 30, 2020). Of these, 127 798 participants were untested at baseline according to the mandatory Surveillance System for Communicable Diseases (MSIS) registry and confirmed this through self-report. We excluded 7193 participants who did not complete any follow-up questionnaires.

Our final study population of 120 605 had completed a baseline questionnaire and at least one follow-up questionnaire before July 6, 2022. The response rates for the first (May 2020), second (July 2020), third (November 2020), and fourth follow-up (December 2021) questionnaires were 79.3%, 84.2%, 80.4%, and 72.1%, respectively (Supplementary eFigure 1).

In a substudy between the 3rd and 4th follow-ups (July 2021), 6279 participants (all SARS-CoV-2-positive participants, and randomly selected negative and untested participants) were invited for an extra questionnaire (89.9% responded) (Supplementary eFigure 1). To assess the impact of non-response in our overall study, a random subset of these (n = 343) received telephone reminders if unresponsive electronically, with a 97% response rate in that group.

In another add-on study, SARS-CoV-2 seroprevalence was measured on 998 blood samples from 966 unvaccinated participants from October 2020 to December 2021 (Supplementary eMethods 2).

The study was approved by the Norwegian Regional Committee for Research Ethics (REK 124170), and all participants submitted electronic informed consent forms. The study is registered in ClinicalTrials (https://clinicaltrials.gov; ID: NCT04320732). The study is reported according to the Strengthening The Reporting Of Observational Studies In Epidemiology (STROBE) guidelines for cohort studies.

Assessment of exposure

The exposure, SARS-CoV-2 status, was obtained through linkage of the participant's personal identification numbers with the MSIS registry or self-report. COVID-19 became a compulsory reportable disease to MSIS on January 31, 2020. SARS-CoV-2 tests were done by a nasopharyngeal and/or oropharyngeal swab test and detected using real-time polymerase chain reaction (rt-PCR) in any accredited Norwegian clinical microbiology laboratory. From early in January 2022, self-tests became increasingly available and PCR tests no longer mandated. SARS-CoV-2 status was therefore based on self-report in the last months of the study. Participants could change their exposure status during the study period. We considered a participant untested from inclusion until the date of a SARS-CoV-2 test (positive or negative). If the first test was negative, a participant would be considered negative until the date of a later positive test. A participant with only negative tests was considered SARS-CoV-2-negative throughout the follow-up.

Community testing for SARS-CoV-2 status was free of charge and after the initial few months of the pandemic widely available and strongly encouraged. Testing for international travel was done at private facilities and required a fee and results were reported to MSIS like all other tests. Testing criteria changed during the study period and are described in Supplementary eFigure 2. From January 24, 2022, a PCR test was no longer routinely offered after a positive self-test.

Assessment and definition of end points

Outcome measures were self-reported symptoms assessed through electronic follow-up questionnaires (Supplementary eMethods 3). Questionnaires were designed using existing knowledge about COVID-19 symptoms and the International Severe Acute Respiratory and Emerging Infection Consortium forms [17]. For each questionnaire, participants were asked to check off symptoms they had experienced in the past 3 weeks.

In the second follow-up questionnaire, a health transition question ("Compared to a year ago, or before you had COVID-19, how will you describe your health?") with a 5-point Likert scale (the variable was dichotomized in the analyses), from the 36-Item Short Form Survey was added [18]. As several participants reported memory problems in the free-text fields in the second follow-up questionnaire, questions on memory- and concentration were added to the third and fourth follow-up questionnaires and in the substudy between these questionnaires.

Statistical analyses

To investigate the temporal trajectory of symptoms after COVID-19, we examined the combined effect of SARS-CoV-2 status (untested, negative, or positive) and time since a SARS-CoV-2 test (0-1, 1-3,3-6, 6-12, 12-18 and >18 months) had on symptoms. Time since test was defined as the time since the first positive or negative test, or the time since baseline (for the untested). We included information from all questionnaires and used mixed-effect logistic regression calculating odds ratios (ORs) with 95% confidence intervals (CIs) of each symptom associated with SARS-CoV-2 status and time since test (Supplementary eMethods 4). We compared symptoms of SARS-CoV-2-positive and untested participants with SARS-CoV-2-negative participants at one fixed time point, 1-3 months after their first negative test. We also compared the symptoms of SARS-CoV-2-positive and untested participants at each time point with the SARS-CoV-2-negative participants.

Analyses were adjusted for potential confounders: age (10-year categories), gender (men, women), body mass index (BMI,<25 kg/ m^2 , ≥25kg/ m^2, missing), annual household income level (< 299 999, 300 000-599 999, 600 000-100 0000, >1 000 000 NOK, missing), smoking status (never, former, current, missing), underlying medical condition (no, yes, missing), and symptom status for each symptom at baseline (no, yes, missing) or at the first questionnaire asking about the symptom, but before the outcome symptom.

To illustrate the trajectories of symptoms before, during, and after a positive or negative test, we calculated the unadjusted moving average (with 95% CI) of symptoms prevalence for each exposure group (using the SARS-CoV-2-status at the last follow-up) over the whole study period (Supplementary eMethods 5).

We performed the following sensitivity analyses: only including participants with pre-omicron-variants, those who completed all questionnaires (not including the substudy), those who were

Table 1
Frequency distribution and mean values of covariates by SARS-CoV-2 status at fourth follow-up[a] (n = 120 605).

	SARS-CoV-2 positive[a] (n = 15 737)	SARS-CoV-2-negative (n = 67 305)	Untested[b] (n = 37 563)
Characteristics			
	Median (IQR)[c]		
Time since test (days)[d]	55 (15-106)	419 (292-501)	637 (633-669)
	Mean (SD)		
Age (years)	46 (12.1)	48 (13.3)	51 (14.7)
	n (%)		
18-29	1298 (8)	5081 (8)	3150 (8)
30-39	3956 (25)	14 331 (21)	6490 (17)
40-49	4899 (31)	17 108 (26)	7769 (21)
50-59	3429 (22)	16 164 (24)	8765 (24)
60-69	1608 (10)	10 325 (15)	7166 (19)
70+	547 (4)	4296 (6)	4223 (11)
Sex			
Men	4287 (27)	18 879 (28)	13 750 (37)
Women	11 450 (73)	48 426 (72)	23 813 (63)
Income (NOK per household and year)			
< 299 999	477 (3)	2422 (4)	1492 (4)
300 000-599 999	2181(14)	12 185 (18)	7049 (19)
600 000-1000 000	4148 (26)	19 323 (29)	9905 (26)
>1000 000	7096 (45)	27 681 (41)	11 890 (32)
Missing	1835 (12)	5692 (8)	7227 (19)
Body mass index (kg/m^2)			
<25	7603 (48)	30 902 (46)	16 924 (45)
≥25	8018 (51)	35 946 (53)	20 301 (54)
Missing	116 (1)	457 (1)	338 (1)
Smoking status			
Never	8443 (54)	35 418 (53)	18 947 (50)
Former	6109 (39)	25 651 (38)	14 344 (38)
Current	890 (5)	4913 (7)	3313 (9)
Missing	295 (2)	1323 (2)	959 (3)
Underlying medical conditions[e]			
No	11 817 (75)	47 947 (71)	25 654 (68)
Yes	3777 (24)	18 622 (28)	11 393 (31)
Missing	143 (1)	736 (1)	516 (1)

[a] The SARS-CoV-2 status of the negative participants was obtained from the Norwegian Messaging System for Reporting of Infectious Diseases (MSIS) registry. The SARS-CoV-2-positive status was obtained from the MSIS registry 58% or self-report 42%. Only one SARS-CoV-2-positive-test was included for each participant.
[b] Participants that remained untested for the whole follow-up period.
[c] Interquartile range.
[d] Time from the first SARS-CoV-2 positive test or first SARS-CoV-2 negative test to last follow up. For participants remaining untested, time from baseline to the last follow-up is shown.
[e] Chronic heart disease, high blood pressure, chronic lung disease (not asthma), asthma, diabetes, receiving immunodeficiency treatment, cancer (under treatment).

non-hospitalized participants, and finally, participants with self-reported SARS-CoV-2 status.

Analyses were performed using Stata (Stata Statistical Software, release 16 and 17, Stata Corp., College Station, TX), R (version 4.2.2), and SPSS 27 (IBM).

Patient and public involvement statement

We have involved patients in the Norwegian COVID-19 Cohort since the spring of 2020. Our focus on persisting cognitive symptoms was initiated after reports of such symptoms by a patient representative which led to the inclusion of relevant questions in the following questionnaires. We communicated with our participants through newsletters and free-text fields in the questionnaires and had regular meetings with patients and the patient organization Norwegian Covid Association.

Results

Participants and follow-up

Of 120 605 participants, 15 737 were SARS-CoV-2-positive (58% from MSIS and 42% self-report), 67 305 negative, and 37 563 untested at the end of follow-up (July 6, 2022; Supplementary eFigure 1). The follow-up time from the test date varied between the groups (710 SARS-CoV-2 positive, 35 309 negative, and 18 997 untested participants had >12 months follow-up after the test, Table 1). In total, 530 200 questionnaires were included in the analyses. Of the participants, 69% were women, 41% had a per household income/ year >1 000 000 NOK (about US$ 100 000), and the mean age was 49 years (SD= 13.7 years). SARS-CoV-2-positive participants were younger, had a higher income, a lower BMI, and fewer underlying medical conditions, and were less likely to be current smokers compared with negative and untested participants.

Symptoms among SARS-CoV-2-positive participants

The temporal trajectory of each symptom differed by SARS-CoV-2 status (Unadjusted: Figure 1 and Supplementary eFigure 3, and adjusted: Table 2, Supplementary eTables 2 and 3). When comparing SARS-CoV-2-positive participants with negative participants (1-3 months after a negative test), there were several persistent symptoms. The strongest findings in the adjusted analyses were memory problems (3-6 months: adjusted OR = 9.1, 95% CI = 7.5-10.9; 6-12 months: OR = 13.3, CI = 10.7-16.6; 12-18 months: OR = 7.8, CI = 5.7-10.8; >18 months: OR = 9.96, CI = 4.3-23.0),

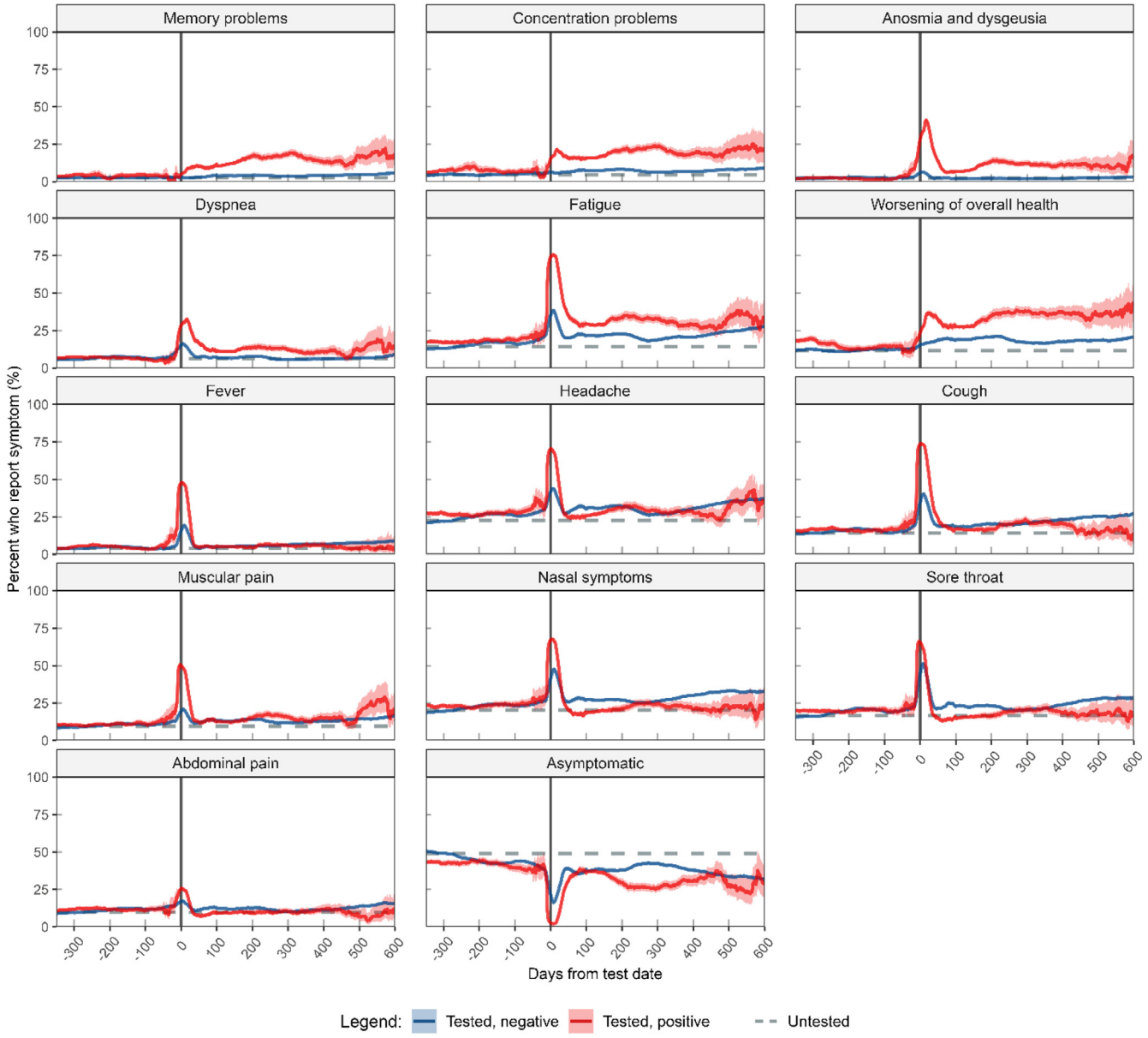

Figure 1. The frequencies (moving average and 95% confidence intervals) of symptoms reported before, during and after a positive or negative SARS-CoV-2 test. Participants are grouped by their SARS-CoV-2 status at the end of follow-up. Participants remaining untested for the complete study period (without a test date) are represented with a horizontal (flat) line representing their average (supplementary eMethods 5). The horizontal grey dashed line represents the mean response for untested study participants. The vertical line represents the day of the positive- or negative SARS-CoV-2 test. The figure is based on all completed questionnaires (N = 530 200). In each questionnaire, the presence of a symptom the past 3 weeks was reported by the participant. Note that the 95% confidence interval for the Tested, negative group falls inside the line and it is therefore not visible. In the interval -50 to 100 days, the lines represent a 21-day moving average and between <-50 and >100, the lines represent an 84-day moving average.

concentration problems (3-6 months: OR = 5.7, CI = 4.9-6.7; 6-12 months: OR = 7.5, CI = 6.1-9.1; 12-18 months: OR = 5.3, CI = 3.9-7.1; >18 months: OR = 4.9, CI = 2.1-11.1), and anosmia and dysgeusia (3-6 months: OR = 5.2, 95% CI = 4.4-6.2, 6-12 months: OR = 8.9, CI = 7.2-11;12-18 months; OR = 5.5, CI = 4.0-7.5; >18 months: OR = 5.3, CI = 2.4-2.1) (Table 2). Self-assessed worsening of overall health was also significantly higher among the SARS-CoV-2-positive participants compared to negatives, with the highest risk being at 18 months (OR = 3.7, CI = 2.0-6.8). The risk of reporting dyspnea and fatigue was higher for the positive than negative participants, but the risk attenuated over time. SARS-CoV-2 positive participants were equally or less likely to report fever, headache, cough, muscular pain, nasal symptoms, sore throat, and abdominal pain late in follow-up compared to the negative participants (Supplementary eTable 1).

Symptoms among SARS-CoV-2-negative and untested participants

Eighty percent of participants with a negative test reported at least one symptom indicating an infection in the three-week period around testing (data not shown). At later follow-up periods, SARS-CoV-2-negative participants had a higher risk of reporting symptoms compared to 1-3 months after the negative test. Memory problems (3-6 months: OR = 1.3, CI = 1.2-1.5; >18 months: OR = 2.0, CI = 1.7-2.3), fever (3-6 months: OR = 1.2, CI = 1.00-1.4; >18 months: OR = 2.1, CI = 1.8-2.3), and cough (3-6 months: OR = 1.0, CI = 0.94-1.1; >18 months: OR = 1.5, CI = 1.4-1.7) were increasingly reported over time among negative participants (Table 2 and Supplementary eTable 1). Untested participants were less likely to report all symptoms when compared to SARS-CoV-2-negative participants. We therefore conducted analyses comparing

Table 2
Odds ratio (OR) estimates and 95% confidence interval (CI) for reporting each symptom at different time-intervals after a positive or negative SARS-CoV-2 test (or inclusion for untested) with symptoms reported 1-3 months after a negative test as reference (n = 120 605).[a]

		Time since test (months)[b]											
		0-1		>1-3		>3-6		>6-12		>12-18		>18	
Symptoms	SARS-CoV-2 status	Yes: n (%)	OR (95% CI)[c]	Yes: n (%)	OR (95% CI)	Yes: n (%)	OR (95% CI)	Yes: n (%)	OR (95% CI)	Yes: n (%)	OR (95% CI)	Yes: n (%)	OR (95% CI)
Memory problems[d]	Untested	–		4 (3.6)	1.01 (0.28-3.65)	22 (2.2)	0.61 (0.36-1.04)	1502 (2.5)	0.72 (0.64-0.81)	58 (4.3)	2.6 (1.81-3.73)	441 (2.4)	1 (0.84-1.19)
	Negative	253 (2.7)	0.8 (0.66-0.96)	604 (3.4)	1 (Ref.)	720 (4.1)	1.33 (1.16-1.54)	836 (4.1)	1.54 (1.34-1.78)	1289 (4.6)	1.49 (1.32-1.69)	417 (6)	1.98 (1.68-2.34)
	Positive	395 (6.8)	3.34 (2.78-4.02)	502 (9.8)	6.18 (5.16-7.42)	481 (12)	9.05 (7.49-10.94)	339 (17.3)	13.3 (10.69-16.55)	101 (13.7)	7.83 (5.68-10.79)	13 (15.5)	9.96 (4.31-23.01)
Concentration problems[d]	Untested	–		7 (6)	0.85 (0.29-2.54)	46 (4.5)	0.71 (0.47-1.06)	2812 (4.7)	0.64 (0.58-0.71)	92 (6.8)	2.34 (1.72-3.19)	698 (3.7)	0.8 (0.69-0.92)
	Negative	586 (6)	0.95 (0.82-1.09)	1276 (7)	1 (Ref.)	1336 (7.6)	1.17 (1.04-1.3)	1490 (7.2)	1.31 (1.17-1.47)	2179 (7.5)	1.16 (1.05-1.27)	672 (9.6)	1.46 (1.27-1.68)
	Positive	1040 (17.8)	6.05 (5.23-7)	830 (16.2)	5.61 (4.81-6.54)	662 (16.6)	5.71 (4.85-6.73)	423 (21.6)	7.46 (6.11-9.1)	141 (19)	5.27 (3.93-7.06)	17 (20.2)	4.86 (2.13-11.07)
Anosmia and dysgeusia[e]	Untested	6898 (3.5)	1.01 (0.91-1.13)	495 (1.4)	0.65 (0.56-0.74)	1018 (1.3)	0.58 (0.51-0.65)	564 (1)	0.37 (0.33-0.43)	15 (1.1)	0.73 (0.42-1.28)	258 (1.4)	0.69 (0.58-0.81)
	Negative	929 (5.8)	3.27 (2.88-3.71)	575 (2.4)	1 (Ref.)	398 (2)	0.83 (0.72-0.96)	459 (2.2)	0.96 (0.83-1.11)	704 (2.4)	1.13 (0.99-1.28)	234 (3.4)	1.31 (1.09-1.57)
	Positive	2004 (33.8)	66.22 (57.75-75.93)	587 (11.4)	9.65 (8.31-11.21)	310 (7.7)	5.22 (4.38-6.22)	248 (12.6)	8.88 (7.24-10.88)	80 (10.8)	5.47 (4-7.48)	13 (15.5)	5.28 (2.44-11.43)
Dyspnoea[e]	Untested	17386 (8.7)	0.98 (0.91-1.05)	1445 (4.2)	0.58 (0.53-0.64)	2672 (3.5)	0.48 (0.44-0.51)	2152 (3.3)	0.48 (0.44-0.52)	91 (6.8)	1.62 (1.22-2.14)	664 (3.5)	0.58 (0.52-0.65)
	Negative	2212 (13.8)	3.04 (2.78-3.32)	1761 (7.2)	1 (Ref.)	1348 (6.9)	0.99 (0.9-1.08)	1380 (6.7)	0.95 (0.87-1.05)	1858 (6.4)	0.99 (0.91-1.07)	625 (9)	0.97 (0.86-1.09)
	Positive	1765 (29.7)	14.14 (12.69-15.76)	769 (14.9)	4.07 (3.6-4.6)	449 (11.1)	2.44 (2.12-2.81)	247 (12.6)	2.66 (2.2-3.21)	82 (11.1)	2.02 (1.49-2.73)	10 (11.9)	2.03 (0.9-4.59)
Fatigue[e]	Untested	34532 (17.4)	0.51 (0.49-0.54)	3779 (11)	0.47 (0.44-0.49)	8332 (10.9)	0.43 (0.41-0.45)	7667 (11.7)	0.57 (0.54-0.6)	227 (16.9)	1.43 (1.19-1.73)	1982 (10.5)	0.63 (0.59-0.68)
	Negative	5617 (35)	2.92 (2.76-3.1)	5245 (21.5)	1 (Ref.)	4306 (22)	1.08 (1.02-1.15)	4359 (21)	1.14 (1.08-1.21)	6578 (22.8)	1.23 (1.17-1.3)	1953 (28)	1.44 (1.33-1.55)
	Positive	4236 (71.4)	27.63 (25.25-30.23)	1735 (33.5)	2.86 (2.62-3.12)	1182 (29.3)	2.02 (1.83-2.23)	647 (32.9)	2.47 (2.16-2.82)	218 (29.5)	1.78 (1.44-2.2)	26 (31)	1.3 (0.72-2.36)
Self-assessed worsening of overall health[f]	Untested	27 (13.3)	0.5 (0.3-0.82)	1625 (11.9)	0.49 (0.45-0.53)	8070 (10.6)	0.42 (0.39-0.44)	8652 (13.3)	0.66 (0.62-0.69)	107 (10.7)	0.52 (0.4-0.66)	2137 (11.5)	0.55 (0.51-0.59)
	Negative	2308 (16.5)	0.84 (0.78-0.9)	4461 (18.7)	1 (Ref.)	3740 (19.4)	1.06 (1-1.13)	3811 (18.8)	1.02 (0.96-1.09)	5193 (18.1)	1 (0.95-1.06)	1432 (20.7)	1.01 (0.93-1.1)
	Positive	1717 (29.7)	2.38 (2.18-2.59)	1537 (30.6)	2.61 (2.38-2.85)	1041 (28.0)	2.32 (2.1-2.57)	618 (37.1)	3.63 (3.15-4.19)	238 (36.2)	3.44 (2.77-4.26)	30 (40.0)	3.77 (2.05-6.94)

[a] adjusted for age (10-years categories), gender (men, women) body mass index (<25 kg/ m^2, ≥25 kg/ m^2), income level per household (< 299 999, 300 000-599 999, 600 000-1000 000, >1000 000 NOK, missing), smoking status (never, former, current, missing), underlying medical condition (no, yes, missing) and symptom status at baseline (no, yes, missing).

[b] for the untested, time since baseline was used in place of time since a positive- or negative SARS-CoV-2 test.

[c] Bonferroni adjusted confidence intervals; ***Memory*** (**Untested; 0-1**:-, **>1-3**: 0.15-6.75, **>3-6**: 0.28-1.34, **>6-12**: 0.60-0.86, **>12-18**:1.53-4.43, **>18**: 0.77-1.30, **Negative: 0-1**: 0.61-1.04, **>1-3**: Ref, **>3-6**: 1.08-1.65, **>6-12**: 1.25-1.90, **>12-18**:1.24-1.79, **>18**: 1.54-2.54, **Positive: 0-1**: 2.54-4.40, **>1-3**: 4.72-8.09, **>3-6**: 6.84-11.98, **>6-12**: 9.63-18.37, **>12-18**: 4.88-12.57, **>18**: 2.89-34.3) or
concentration problems (**Untested; 0-1**: -, **>1-3**: 0.17-4.28, **>3-6**: 0.39-1.29, **>6-12**: 0.55-0.74, **>12-18**:1.48-3.70, **>18**: 0.65-0.99, **Negative: 0-1**: 0.78-1.16, **>1-3**: Ref, **>3-6**: 1.00-1.37-, **>6-12**: 1.11-1.55, **>12-18**:1.01-1.33, **>18**: 1.18-1.80, **Positive: 0-1**: 4.88-7.50, **>1-3**: 4.47-7.04, **>3-6**: 4.48-7.28, **>6-12**: 5.57-10.00, **>12-18**: 3.42-8.12, **>18**: 1.44-16.38),
anosmia and dysgeusia (**Untested; 0-1**: 0.86-1.19, **>1-3**: 0.53-0.79, **>3-6**: 0.49-0.68, **>6-12**: 0.30-0.46, **>12-18**:0.32-1.66, **>18**: 0.54-0.88, **Negative: 0-1**: 2.72-3.93, **>1-3**: Ref, **>3-6**: 0.67-1.03, **>6-12**: 0.78-1.19, **>12-18**:0.94-1.35, **>18**: 1.01-1.71, **Positive: 0-1**: 54.11-81.04, **>1-3**: 7.74-12.04, **>3-6**: 4.03-6.76, **>6-12**: 6.58-11.99, **>12-18**: 3.45-8.68, **>18**: 1.69-16.51),***dyspnoeae*** (**Untested; 0-1**: 0.89-1.08, **>1-3**: 0.50-0.67, **>3-6**: 0.43-0.53, **>6-12**: 0.43-0.54, **>12-18**:1.08-2.44, **>18**: 0.49-0.68, **Negative: 0-1**: 2.67-3.45, **>1-3**: Ref, **>3-6**: 0.87-1.13, **>6-12**: 0.83-1.09, **>12-18**:0.88-1.11, **>18**: 0.81-1.16, **Positive: 0-1**: 12.05-16.59, **>1-3**: 3.39-4.88, **>3-6**: 1.98-3.01, **>6-12**: 2.02-3.51, **>12-18**: 1.30-3.14, **>18**: 0.61-6.77),
fatigue (**Untested; 0-1**: 0.47-0.55, **>1-3**: 0.44-0.51, **>3-6**: 0.40-0.46, **>6-12**: 0.53-0.61, **>12-18**:1.08-1.89, **>18**: 0.57-0.70, **Negative: 0-1**: 2.67-3.19, **>1-3**: Ref, **>3-6**: 0.99-1.18, **>6-12**: 1.04-1.25, **>12-18**:1.14-1.33, **>18**: 1.29-1.61, **Positive: 0-1**: 24.19-31.56, **>1-3**: 2.51-3.26, **>3-6**: 1.75-2.33, **>6-12**: 2.03-3.01, **>12-18**: 1.30-2.44, **>18**: 0.54-3.14) and ***self-assessed worsening of overall health*** (**Untested; 0-1**: 0.24-1.04, **>1-3**: 0.43-0.56, **>3-6**: 0.39-0.46, **>6-12**: 0.62-0.71, **>12-18**:0.37-0.74, **>18**: 0.50-0.60, **Negative: 0-1**: 0.76-0.92, **>1-3**: Ref, **>3-6**: 0.97-1.16, **>6-12**: 0.93-1.12, **>12-18**: 0.92-1.09, **>18**: 0.89-1.15, **Positive: 0-1**: 2.10-2.69, **>1-3**: 2.29-2.97, **>3-6**: 1.99-2.71, **>6-12**: 2.94-4.48, **>12-18**: 2.50-4.72, **>18**: 1.53-9.29).

[d] n = 200 778 questionnaires, 120 605 participants. Questionnaire introduced from 3rd follow-up onward.

[e] n = 530 200 questionnaires, 120 605 participants.

[f] n = 304 958 questionnaires, 120 605 participants.

SARS-CoV-2-positive with negative participants at each time point (Supplementary eTable 2).

Sensitivity analyses

When excluding participants with SARS-CoV-2 Omicron variants (BA.1 and BA.2, n = 11 154), the results were consistent, but the ORs for memory problems, concentration problems, and anosmia and dysgeusia 3-6 months after the positive test were higher compared to when all cases were included (Supplementary eTable 3). In other sensitivity analyses, we included only those who completed all questionnaires/excluding the substudy (n = 6 279), excluded hospitalized COVID-19 participants (4%), and excluded participants with self-reported SARS-CoV-2 status (n = 6 485 SARS-CoV-2-posittive, Supplementary eTable 4), and the results remained largely unchanged.

Non-response and SARS-CoV-2 seroprevalence analyses

In the subgroup of participants contacted by telephone (n = 343), a lower proportion, reported symptoms compared with those who responded through electronic invitations. This difference was more pronounced among SARS-CoV-2-positive than among negative participants (data reported in a manuscript under submission). In the add-on SARS-CoV-2 seroprevalence study on 966 participants, three participants (0.3%) were positive but classified as negative or untested at the time of sampling (Supplementary eMethods 2).

Discussion

In this prospective cohort study, we have analyzed the temporal trajectory of 14 symptoms (13 symptoms and self-assessed worsening of overall health) before, during, and after a positive or negative SARS-CoV-2 test. When comparing SARS-CoV-2-positive participants with negative participants, persistent symptoms were memory- and concentration problems, anosmia and dysgeusia, dyspnoeae, fatigue, and self-assessed worsening of overall health. The cognitive symptoms and self-assessed worsening of overall health did not attenuate over time.

Our finding of memory- and concentration problems as long-COVID symptoms is in line with a report by the WHO [6] and several studies [7–12,16,19–21]. However, the results elaborate this association with several important findings. Firstly, the association between COVID-19 and memory- and concentration problems was very strong, and after the acute phase – as strong as the association between COVID-19 and anosmia and dysgeusia. Secondly, memory- and concentration problems increased in the 0-6 months interval after a positive SARS-CoV-2 test and persisted throughout the follow-up time up to 22 months. In contrast, the other symptoms peaked in prevalence during the acute phase and thereafter exhibited a downward trend. To our knowledge, this has not previously been reported and may indicate that the pathophysiological processes underlying the cognitive symptoms may differ from other long-COVID symptoms. The strong association and a temporal trajectory specific to cognitive symptoms warrant further research.

Several studies have examined the neuropathological effects of the SARS-CoV-2 virus and possible mechanisms associated with COVID-19 [22–25]. Brain imaging studies have reported a greater reduction of grey matter [22] and an increase of white matter lesions after COVID-19 [23], whereas an autopsy study found the virus persisting in the brains of COVID-19 patients [24]. Another study has suggested that synaptic signaling of neurons may expand after COVID-19 disease [25] and could be linked to neurodegenerative and psychiatric disorders [26,27]. An increasing number of studies have reported that many people experience long-term persistence of cognitive deficits after COVID-19 disease [20,21]. This can have profound effects on everyday functioning [28]. The fact that cognitive symptoms are persistent, and most of the population have been, or will be, infected by the SARS-CoV-2 virus, makes it crucial that further research focuses on the pathophysiology, and treatment (including whether immediate treatment upon symptom debut are effective) of these symptoms [29].

Our findings are consistent with a large recent cohort study examining cognitive trajectories in older adults [19]. They asked about history of COVID-19 in the year before each questionnaire, and a decline in cognition was observed after COVID-19 compared to pre-pandemic year. A report from the Lifelines Study analyzed 23 somatic (not cognitive) self-reported symptoms from 76 000 participants, 90-150 days after COVID-19, and had a matched non-infected control group [2]. Our findings on anosmia and dysgeusia, dyspnea, and fatigue are consistent with their findings. However, we included a control group with negative tests (80% of the participants with a negative test reported ≥1 symptoms of an infection at the time of testing), allowing us to identify symptoms specific to the SARS-CoV-2 virus compared to other infections. This could be one of the reasons why the current study did not find any association between COVID-19 and persisting fever, headache, cough, nasal symptoms, sore throat, or abdominal pain when we compared SARS-CoV-2 positive and negative participants. We observed an upward trend in symptoms associated with upper respiratory tract infections (URTI) among the SARS-CoV-2-negative participants over time. This was probably because lockdown measures were gradually relaxed throughout the pandemic.

Our findings of symptoms over a prolonged period are also consistent with findings from a large cohort study following 138 818 SARS-CoV-2-positive and 5 985 227 controls from the US Department of Veterans Affairs [30]. In that study, diagnoses were tracked up to 2 years after COVID-19, and the risk of 27 of 79 diagnoses was still elevated 2 years after COVID-19 compared to non-infected controls. Furthermore, in a cross-sectional study (EPILOC) on 50 457 SARS-CoV-2, positive participants reported that fatigue, neurocognitive impairment, dyspnoeae, anosmia, and dysgeusia persisted 6-12 months after the SARS-CoV-2 infection [31].

The current study is a large prospective cohort with a long follow-up period, and multiple follow-up questionnaires, including before disease, with a high response rate. The study included a SARS-CoV-2-negative control group, making it possible to capture differences between COVID-19 and other infections. The SARS-CoV-2 status was obtained from accredited laboratories through MSIS which covers nearly 100% of the population. Another strength is the proportion of missing data which was < 3% for most of the covariates.

Participants were asked to report symptoms experienced in the last 3 weeks in each questionnaire, and we cannot rule out recall bias. Knowledge of exposure status and media reports on long-COVID symptoms may have biased the self-reported outcome assessment leading to exaggerated ORs for known long-COVID symptoms, at least later in the follow-up period once these became common knowledge (“nocebo effect”). Since data on the symptoms were reported as a three-week symptom prevalence, participants reporting “no symptoms” could still have had symptoms at some point in time. Our coverage of long-COVID symptoms is not exhaustive, and symptoms not known to be related to acute or long-COVID early in the pandemic are not included (i.e. orthostatic intolerance, dysautonomia, palpitations, light-headedness, or post-exertional malaise). There may be testing bias in the comparison between the tested and untested participants.

We cannot rule out non-differential measurement error caused by false negative SARS-CoV-2 tests. However, in our add-on seroprevalence study, we only identified 3 out of 966 (0.3%) unac-

knowledged cases of COVID-19. In the sensitivity analysis of the substudy, we contacted a subgroup of participants by telephone and found that a lower proportion reported symptoms compared with those who responded through electronic invitations. This could have led to an overestimation of the effect of COVID-19 on symptoms in the current study. We did adjust for multiple testing (Bonferroni) in the statistical analyses. Nevertheless, the clinical relevance of the actual differences and sizes is the most essential. The generalizability of our findings is limited by our cohort composition, which has lower proportions of males, non-white ethnic groups, individuals with lower income, older individuals, and no children compared to the Norwegian population.

Because of self-testing, it is possible that we have missed more untested infections from January 2022 onwards. This could have influenced the results in the way that the untested would have reported respiratory symptoms which could have led to a smaller difference between the SARS-CoV-2-positive and this group and hence smaller effects estimates than we have observed in the current study.

Participants were classified as "positive" regardless of the number of positive tests during follow-up. In another analysis from this cohort, we investigated whether reinfections influenced the proportion of symptoms over time. We observed a higher proportion of symptoms reported after reinfections. Tested participants could first have a negative test followed by a positive test, and 0.3% of those who tested negative tested positive for SARS-CoV-2 within a week after the negative test. This could have caused a smaller difference between the groups.

We did not take the vaccination status into account in this analysis. However, we have published a paper taking the vaccination status into account [32] and we found that SARS-CoV-2 vaccines offered minor protection against long-COVID symptoms. However, fewer memory problems were reported among the vaccinated than the unvaccinated participants.

Persistent long-COVID symptoms lasting up to 22 months were memory- and concentration problems, anosmia and dysgeusia, dyspnoeae, fatigue, and self-assessed worsening of overall health. We could not establish an association between COVID-19 and persisting fever, headache, cough, nasal symptoms, sore throat, or abdominal pain suggesting that the role of previous COVID-19 infections in patients presenting with such symptoms may not be important.

Declaration of competing interest

All authors declared no potential conflicts of interest. However, Karl Trygve Kalleberg and Arne Søraas are founders and shareholders of the company Age Labs AS which develops epigenetic tests, including one for COVID-19 severity.

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Author contributions

Merete Ellingjord-Dale, Anders B. Nygaard, and Arne Søraas had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Merete Ellingjord-Dale and Anders B. Nygaard contributed equally as co-first authors.

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Critical revision of the manuscript for important intellectual content: all authors.

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Final approval of the manuscript and work: all authors.

Additional contributions

The authors would like to thank all the participants in the study.

Transparancy statement

The lead authors (MED and ABN) affirm that this manuscript is an honest, accurate, and transparent account of the trial being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned, and registered have been explained.

Data availability statement

Individual-level data from the study for the purposes outlined in the consent form can be shared with other researchers in a timely fashion. The data are regulated under the European GDPR regulative and sharing of data must be approved by the Data Protection Officer at Oslo University Hospital. Data will be made available for researchers whose proposed use of the data has been approved.

Trial registration

ClinicalTrials ID: NCT04320732.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2024.107263.

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