Prospective Pre- and Post-COVID-19 Memory Assessment

To the Editor:

An estimated 400 million people throughout the world have been experiencing symptoms of what has been termed long-COVID. [1] Some studies have demonstrated an association between COVID-19 and persistent memory problems. [2,3] We used a validated questionnaire on self-reported memory problems [4], including pre-and post-morbid assessments, to investigate this potential association.

Of 188,137 participants in the nationwide Norwegian COVID-19 Cohort study from March 27, 2020 through April 2023, 134,373 (71%) completed ≥1 Everyday Memory Questionnaire (EMQ) and 111,992 (60%) had documented positive or negative SARS-CoV-2 tests (Figure S1)as determined from the Norwegian Surveillance System for Communicable Diseases or by self-report. The EMQ has 13-items with a maximum total range of 0-52 [4]; we report scores averaged over all items (total/13; each item is scored 0-4 (signified as A-E in the source publication) and higher scores indicates worse memory complaints. Further details are in the supplementary Appendix available at NEJM.org.

We used a linear mixed effects model to compare mean EMQ-scores in participants before and after positive (n=57,319) and negative (n=54,673) SARS-CoV-2-tests. Analyses were adjusted

for age, body mass index, sex, vaccination status, smoking, income, questionnaire number, and underlying medical conditions. (See Supplementary Appendix)

Individuals with SARS-CoV-2-positive tests were younger (48 years; standard deviation [SD],13.0) compared to those with negative tests (50 years; SD, 13.8), and most were women in both groups (Table S1). The adjusted mean EMQ-scores were numerically higher (worse) after a positive than negative test, respectively, at all time points: 0-1 month after a test, 0.66, vs 0.60; 3-6 months, 0.72 vs 0.62; 6-9 months, 0.71 vs 0.62; 9-12 months, 0.75 vs 0.63; 12-18 months, 0.82 vs 0.62; and 18-36 months, 0.82 vs 0.62 (95% confidence intervals [CI] around these point estimates of test scores at each time point are given in Table S3). The results are shown graphically in Figure 1. In contrast, test results were essentially the same before a SARS-CoV-2-test (>1 month prior to a positive, mean, 0.61 (95% CI, 0.60 to 0.62) vs the same time frame prior to a negative test, 0.60 (95% CI, 0.58 to 0.62). Among those self-reporting memory problems (answered yes to a (yes/no) question about experiencing memory problems) after a SARS-CoV-2 test, individuals who were SARS-CoV-2-positive also had numerically higher EMQ-scores than those with negative tests (Figure S2). However, both individuals with positive and negative SARS-CoV-2-tests who self-reported memory problems after a SARS-CoV-2 test (but not before the test) had higher EMQ-scores before the test compared to those reporting no memory problems. The mean EMQ-scores for the SARS-CoV-2-positive participants generally increased with days bedridden: 1-6 days, 0.79 and >13 days, 1.29 points (confidence intervals for scores at each time point are given in Table S4). Age was apparently inversely associated (Figure S3), and BMI apparently positively associated with EMQ-scores (Figure S4). Overall, women had higher EMQ-scores than men (Figure S5), consistent with several studies investigating psychiatric and neurological complications of long-COVID [5]. Limitations of the current study

include possible response bias between those who responded and those who did not and recall bias due to self-report in the EMQ-questionnaires (Supplementary Appendix, Methods).

Self-reported memory function scored on the EMQ questionnaire of self-reported symptoms was numerically worse at several time points up to 36 months following a positive SARS-CoV-2 test compared to scores following a negative SARS-CoV-2 test in a group of Norwegian participants from 2020 to 2023.

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Figure 1. Mean scores[a] and 95 % confidence intervals[b] of Everyday Memory Questionnaire (EMQ)[c] in SARS-CoV-2 positive and negative participants by months since SARS-CoV-2 test[d].

[a]Adjusted for age (<30, 30-39, 40-49, 50-59, >=60) body mass index (<25m/kg^2, 25-29.9, >=30), sex (men, women), vaccination status (no, yes), smoking status (never, former, current, vaper), income (<299 999 NOK, 300 000-599 999, 600 000-1000 000, >1000 000), questionnaire number (1,2) and underlying medical conditions (no, yes).[b]Confidence interval widths have not been adjusted for multiplicity and should not be used in place of hypothesis testing.[c]Each item is scored on a 5-point rating scale (0 to 4), based on frequency of reported difficulty. Higher scores indicate more reported difficulties.
[d]4 012 SARS-CoV-2-positives and 1 836 negatives with an EMQ-measurement from 1 month before the test up to test date were excluded to make sure we did not include participants that were already sick and experiencing symptoms, and therefore possibly yielding a higher symptom-load before the test. There were 57 319 SARS-CoV-2-positives and 54 673 negatives with a total of 153 052 questionnaires.

Months since SARS-CoV-2 test

SARS-CoV-2 negative   SARS-CoV-2 positive