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Post-acute symptoms 3–15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection

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ABSTRACT

Objective: We aimed to describe post-acute sequelae of SARS-CoV-2 infection (PASC) related symptoms 3–15 months after a positive test in SARS-CoV-2 unvaccinated and vaccinated participants with a breakthrough infection.

Methods: Participants of the Norwegian COVID-19 cohort, without a positive SARS-CoV-2 test, completed a questionnaire about PASC-related symptoms between November 2020 and January 2021. About a year later, a second questionnaire (which also included the Everyday Memory Questionnaire [EMQ]-13) was completed by the same participants, most still without a positive SARS-CoV-2 test, but also by unvaccinated and vaccinated participants with a positive test 3–15 months before the questionnaire. Laboratory-confirmed SARS-CoV-2 status (positive or negative swab test determined by reverse transcriptase quantitative polymerase chain reaction) at the time of completing the questionnaire was ascertained from the Mandatory Norwegian Surveillance System for Communicable Diseases.

Results: No differences were found in the self-reported PASC symptoms, dyspnea, fatigue, smell/taste changes, concentration problems, or the EMQ-13 score between unvaccinated and vaccinated participants 3–15 months after the positive test. Fewer memory problems were reported among vaccinated than unvaccinated participants.

Conclusion: SARS-CoV-2 vaccines offer minor protection against PASC symptoms, although fewer memory problems were reported among the vaccinated than the unvaccinated participants.

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Introduction

Vaccination represents the most important strategy to prevent infection, severe complications, and death caused by SARS-CoV-2 (Feikin et al., 2022). SARS-CoV-2 vaccination may also reduce the risk of post-acute sequelae of SARS-CoV-2 infection (PASC) (Antonelli et al., 2022; Azzolini et al., 2022; Kuodi et al., 2022), but conflicting results have been presented (Taquet et al., 2022). We aimed to describe self-reported PASC symptoms, including memory and concentration problems, changes in smell and taste, fa-

tigue, and dyspnea, persisting 3–15 months after a positive test in SARS-CoV-2 unvaccinated and vaccinated participants with a breakthrough infection.

Methods

Participants of the Norwegian COVID-19 cohort (started in March 2020) without a positive SARS-CoV-2 test (i.e., the untested or those with a SARS-CoV-2 negative test) by the third follow-up questionnaire (November 2020–January 2021) and who completed a fourth follow-up questionnaire a year later were included in the present study. Laboratory-confirmed SARS-CoV-2 status (positive or negative swab test determined by reverse transcriptase quantitative polymerase chain reaction) at the time of completing a questionnaire was ascertained from the Mandatory Norwegian Surveillance System for Communicable Diseases (Kjetland et al., 2020). Both the third and fourth follow-up questionnaires (as well as the two questionnaires distributed before that) had questions

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Table 1
Third follow-up questionnaire, before SARS-CoV-2 infection; study population and symptoms the last 3 weeks.

Third follow-up questionnaire	SARS-CoV-2 negative/ untested (n = 104,798)	SARS-CoV-2 positive ^a		P-value ^b
		Vaccinated (n = 360)	Unvaccinated (n = 1060)	
Characteristic				
Sex, n (%)				
Male	32,354 (30.9)	97 (26.9)	310 (29.2)	0.40
Female	72,444 (69.1)	263 (73.1)	750 (70.8)	
Age, mean (SD) years	50.9 (13.6)	48.3 (11.4)	45.7 (12.3)	<0.001
BMI, mean (SD) kg/m ²	26.2 (4.8)	25.9 (4.8)	26.3 (4.9)	0.19
Chronic disease, n (%) ^c				
No chronic disease	70,421 (69.7)	233 (66.4)	784 (76.0)	<0.001
≥1 chronic disease	30,676 (30.3)	118 (33.6)	247 (24.0)	
Symptoms, last 3 weeks				
Dyspnea, n (%)				
Yes	5720 (5.5)	25 (6.9)	57 (5.4)	0.27
No	99,078 (94.5)	335 (93.1)	1 003 (94.6)	
Fatigue, n (%)				
Yes	17,976 (17.1)	60 (16.7)	207 (19.5)	0.23
No	86,822 (82.9)	300 (83.3)	853 (80.5)	
Smell/taste changes, n (%)				
Yes	1,612 (1.5)	6 (1.7)	12 (1.1)	0.43
No	103,186 (98.5)	354 (98.3)	1 048 (98.9)	
Memory problems, n (%)				
Yes	3376 (3.2)	10 (2.8)	40 (3.8)	0.38
No	101,422 (96.8)	350 (97.2)	1 020 (96.2)	
Concentration problems, n (%)				
Yes	6360 (6.1)	23 (6.4)	83 (7.8)	0.37
No	98,438 (93.9)	337 (93.6)	977 (92.2)	

Missing information about BMI and chronic disease for 4.2% and 3.5% of the participants, respectively.

BMI; body mass index, n; number.

^a For the SARS-CoV-2 positive, third follow-up questionnaire was completed before the positive test; all were untested/negative at this point.

^b SARS-CoV-2 unvaccinated versus vaccinated participants, P-values reported from Pearson chi-square test (two-sample t-test for age and BMI).

^c One or more of the following chronic conditions: heart disease, hypertension, lung disease, asthma, diabetes mellitus, cancer, other or treated with immune suppressive medications.

about key PASC symptoms (European Observatory on Health Systems and Policies et al., 2021), including memory and concentration problems, changes in smell and taste, fatigue, and dyspnea. The fourth follow-up questionnaire also contained the Everyday Memory Questionnaire-13 (EMQ-13). SARS-CoV-2 vaccination status was self-reported, and participants were considered fully vaccinated 14 days after the second dose. In Norway, >97% of vaccine doses given have been messenger RNA vaccines. Participants with only one vaccine dose, inconclusive vaccination status, ≥2 COVID-19 diagnoses, or diagnosed with COVID-19 <3 months before the fourth follow-up questionnaire were excluded from analyses.

The main outcome was self-reported symptoms in the fourth follow-up questionnaire, comparing unvaccinated and vaccinated SARS-CoV-2 positive participants with the Pearson chi-square test (unadjusted) and logistic regression (adjusted for gender, age, body mass index (BMI), chronic disease, and days since COVID-19). Other outcomes included the mean EMQ-13 score, analyzed with a two-sample t-test (unadjusted) and linear regression (adjusted for gender, age, BMI, chronic disease, and days since COVID-19). Positive participants were also compared to what the untested/negative participants reported in the fourth follow-up questionnaire. Patient characteristics and symptoms (before any positive tests) reported in the third follow-up questionnaire were compared with chi-square and t-tests.

Results

In total, 154,050 eligible participants completed the third follow-up questionnaire, of which 116,272 also completed the fourth follow-up questionnaire. Participants with COVID-19 diagnosis <3 months ago (n = 9089), ≥2 COVID-19 diagnoses (n = 186), unconfirmed COVID-19 disease (n = 475), and/or inconclusive vaccination status (n = 660) were excluded.

Overall, 1420 participants had a positive SARS-CoV-2 test between the third and fourth follow-up questionnaires, of which

1060 were unvaccinated, and 360 were vaccinated with a breakthrough infection. In total, 104,798 were still untested/negative on the fourth follow-up questionnaire. The unvaccinated participants were younger with fewer chronic diseases than the vaccinated participants (Table 1). Overall, few participants were hospitalized due to COVID-19, but significantly more unvaccinated than vaccinated participants were hospitalized (Table 2).

In the third follow-up questionnaire, before the positive SARS-CoV-2 test, there were no differences in symptoms between unvaccinated and vaccinated participants, and only minor differences between untested/negative and participants that would become infected with SARS-CoV-2 (Table 1).

In the fourth follow-up questionnaire, 3–15 months after the positive SARS-CoV-2 test, there were no differences in symptoms or EMQ-13 scores between unvaccinated and vaccinated participants with a breakthrough infection, except for memory problems that were reported more frequently among the unvaccinated participants (Table 2). When excluding those that were hospitalized due to COVID-19, we observed that memory problems were no longer significantly different between the unvaccinated and vaccinated participants (15.8% and 12.1%, respectively; odds ratio 1.5, 95% confidence interval 0.83, 2.84). The other symptoms showed similar prevalence when excluding the hospitalized participants and for all (data not shown). Overall, significantly more symptoms were reported among positive than untested/negative participants.

Discussion

Only minor differences in PASC symptoms, persisting 3–15 months after the positive test, were observed between SARS-CoV-2 unvaccinated and vaccinated participants with a breakthrough infection. However, fewer memory problems were reported among the vaccinated than the unvaccinated participants.

SARS-CoV-2 vaccines offer efficient protection against severe disease (Feikin et al., 2022), also demonstrated by the higher num-

Table 2

Fourth follow-up questionnaire, after SARS-CoV-2 breakthrough infection; days since COVID-19, EMQ-13 score, and symptoms the last 3 weeks.

Fourth follow-up questionnaire	SARS-CoV-2 negative/ untested (n = 104,798)	SARS-CoV-2 positive ^a		P-value ^b
		Vaccinated (n = 360)	Unvaccinated (n = 1 060)	
Days since COVID-19, median (IQR)		110.0 (25.0)	293.5 (85.0)	<0.001
Hospitalized, n (%)				
Yes		4 (1.1)	64 (6.0)	<0.001
No		334 (92.8)	865 (81.6)	
EMQ-13 score, mean (95% CI) ^c	0.60 (0.59, 0.60)	0.80 (0.71, 0.88)	0.90 (0.84, 0.96)	0.69
Symptoms, last 3 weeks				
Dyspnea, n (%)				
Yes	5630 (5.4)	40 (11.1)	127 (12.0)	0.66
No	99,168 (94.6)	320 (88.9)	933 (88.0)	
OR (95% CI)		1.00	1.48 (0.77, 2.85)	0.24
Fatigue, n (%)				
Yes	19,069 (18.2)	110 (30.6)	320 (30.2)	0.90
No	85,729 (81.8)	250 (69.4)	740 (69.8)	
OR (95% CI)		1.00	0.90 (0.56, 1.43)	0.65
Smell/taste changes, n (%)				
Yes	2075 (2.0)	62 (17.2)	151 (14.3)	0.17
No	102,723 (98.0)	298 (82.8)	909 (85.8)	
OR (95% CI)		1.00	1.11 (0.62, 1.98)	0.72
Memory problems, n (%)				
Yes	3725 (3.5)	43 (11.9)	183 (17.3)	0.02
No	101,073 (96.5)	317 (88.1)	877 (82.7)	
OR (95% CI)		1.00	1.91 (1.07, 3.43)	0.03
Concentration problems, n (%)				
Yes	6141 (5.9)	63 (17.5)	231 (21.8)	0.08
No	98,657 (94.1)	297 (82.5)	829 (78.2)	
OR (95% CI)		1.00	1.23 (0.72, 2.10)	0.45

Missing information about EMQ-13 score for 4.2% of the total participants and hospitalization for 12.4% and 6.1% of the unvaccinated and vaccinated participants, respectively. CI; confidence interval; EMQ-13, Everyday Memory Questionnaire 13; IQR; interquartile range, n, number; OR, odds ratio.

^a For the SARS-CoV-2 positive, symptoms were reported 3–15 months after the positive test. The SARS-CoV-2 vaccinated had ≥ 2 vaccine doses before the positive test.

^b SARS-CoV-2 unvaccinated versus vaccinated participants, P-values reported from Pearson chi-square test and logistic regression (OR) except for days since COVID-19 (Wilcoxon rank-sum test) and EMQ-13 score (linear regression).

^c EMQ-13 using mean score in points (lower is better).

ber of hospitalized participants among the unvaccinated than the vaccinated participants in our study. We also observed that when excluding those that were hospitalized due to COVID-19, the PASC symptom memory problems were no longer significantly higher for the unvaccinated than the vaccinated participants. Nevertheless, conflicting results have been reported regarding protection against PASC in individuals with a breakthrough infection (Antonelli et al., 2022; Azzolini et al., 2022; Kuodi et al., 2022; Taquet et al., 2022). The difference between studies may be a result of temporal trends for the PASC symptoms, which can lead to under- or overestimation of the protective effect of vaccination in studies where the follow-up time for unvaccinated and vaccinated participants is not adjusted for.

The definition of PASC varies in the literature regarding time frame; it should be questioned whether symptoms are actually post-COVID-19 symptoms or part of the acute COVID-19 disease. The definition also varies regarding symptoms included, ranging from one persistent symptom to many symptoms occurring at the same time (European Observatory on Health Systems and Policies et al., 2021; Ganesh et al., 2022). In the present study, we only examined the prevalence of typical PASC symptoms beyond the three first months after a positive test and not how many symptoms or how severely participants were affected.

Strengths of our study include the design, a prospectively followed cohort with data on symptoms both before and after COVID-19, and the large group of untested/negative participants with low symptom burden at both time points, suggesting that symptoms among the positive participants were caused by the disease. Furthermore, the use of the EMQ-13 is a complement to the self-reported symptom memory problems. In addition, our study reports the medium to long-term effects of COVID-19.

Limitations include self-reported symptoms and vaccination status and uncertainty related to the small sample size (some of

the symptoms were experienced by few participants). Participants were aware of their SARS-CoV-2 status, which may have influenced the self-reporting of symptoms, in particular, the highly subjective psychological symptoms, memory, and concentration problems, but such bias would apply to both unvaccinated and vaccinated participants. Also, days since COVID-19 was significantly different between the unvaccinated and vaccinated participants, and we cannot exclude the possibility that our results are due to the domination of different SARS-CoV-2 variants in the two groups (although the logistic and linear regression analyses were adjusted for days since COVID-19).

Conclusion

We conclude that SARS-CoV-2 vaccines offer minor protection against PASC symptoms, including concentration problems, changes in smell and taste, fatigue, or dyspnea, in those with a COVID-19 breakthrough infection. However, fewer memory problems were reported among the vaccinated than the unvaccinated participants.

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Ethical approval

The study was approved by the Norwegian ethics committee (REK 124170) according to the Declaration of Helsinki and registered in ClinicalTrials (NCT04320732). All participants signed an electronic informed consent form, all data were unidentified, and results were presented as aggregated measures at the group level.

Author contributions

Concept, design, and acquisition of data: Sonja H. Brunvoll, Anders B. Nygaard, Morten W. Fagerland, and Arne Søråas. Analysis and interpretation of data: All authors. Drafting of the manuscript: Sonja H. Brunvoll, Anders B. Nygaard, and Arne Søråas. Conducted by and responsible for the statistical analyses: Sonja H. Brunvoll, Morten W. Fagerland, and Arne Søråas. Critical revision of the manuscript for important intellectual content: All authors.

The originality of content

All content in this manuscript is original.

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Declaration of competing interest

The authors have no competing interests to declare.

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References

- Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, et al. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis* 2022;22:43–55.
- Azzolini E, Levi R, Sarti R, Pozzi C, Mollura M, Mantovani A, Rescigno M. Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. *JAMA* 2022;328:676–8.
- European Observatory on Health Systems and Policies, Rajan S, Khunti K, Alwan N, Steves C, Greenhalgh T. In the Wake of the Pandemic: preparing for Long COVID 2021. World Health Organization. Regional Office for Europe.; 2021 <https://apps.who.int/iris/handle/10665/339629> accessed 15th August, 2022..
- Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet* 2022;399:924–44.
- Ganesh R, Vanichkachorn GS, Muniapalli B, Hanson SN, Abu Dabrh AM, Croghan IT, et al. Postacute sequelae of SARS-CoV-2 infection—lessons learned from a coordinated health system response. *Mayo Clin Proc Innov Qual Outcomes* 2022;6:311–19.
- Kjetland EF, Kalleberg KT, Søråas CL, Hammarström B, Myklebust TÅ, Jennum S, et al. Risk factors for community transmission of SARS-CoV-2. A cross-sectional study in 116,678 people. *medRxiv* 2020;24. December <https://www.medrxiv.org/content/10.1101/2020.12.23.20248514v1.full>. accessed 15th August, 2022.
- Kuodi P, Gorelik Y, Zayyad H, Wertheim O, Wiegler KB, Jabal KA, et al. Association between BNT162b2 vaccination and reported incidence of post-COVID-19 symptoms: cross-sectional study 2020–21, Israel. *NPJ Vaccines* 2022;7:101.
- Taquet M, Dercon Q, Harrison PJ. Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections. *Brain Behav Immun* 2022;103:154–62.