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Association between virus variants, vaccination, previous infections, and post-COVID-19 risk

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ABSTRACT

Objectives: The SARS-CoV-2 Omicron variant has spread rapidly and has been the dominant variant since 2022. The course of acute infection, in a vaccinated population, with Omicron is milder compared with earlier variants. However, little is known about how the occurrence of long-term symptoms after Omicron infection compared with other variants is modulated by previous infections and/or vaccinations.
Methods: Participants of the DigiHero study provided information about their SARS-CoV-2 infections, vaccinations, and symptoms 12 or more weeks after infection (post-COVID-19 condition - PCC).
Results: Participants infected with wildtype SARS-CoV-2 had the highest PCC risk (adjusted odds ratio [aOR] 6.44, 95% confidence interval (CI): 5.49; 7.56), followed by participants infected with Alpha and Delta compared with the reference group (individuals infected with Omicron having received three or more vaccinations). Among those infected with a specific variant, the number of preceding vaccinations was not associated with a risk reduction for PCC, whereas previous infection was strongly associated with a lower PCC risk (aOR 0.14, 95% CI 0.07; 0.25).
Conclusions: While infection with Omicron is less likely to result in PCC compared with previous variants, lack of protection by vaccination suggests a substantial challenge for the healthcare system during the early endemic period. In the midterm, the protective effects of previous infections can reduce the burden of PCC.

Introduction

As of July 2023, more than 750 million confirmed cases of SARS-CoV-2 have been reported worldwide. The Omicron variant, first identified in 2021, spread rapidly across the world and soon became the dominant variant [1]. While the incidence of SARS-CoV-2 has decreased and most countries have lifted transmission prevention measures, it is still unclear how the long-term effects of COVID-19 will affect the healthcare system.

Post-COVID-19 condition (PCC), commonly referred to as Long COVID, is defined as persisting symptoms 3 or more months after the initial SARS-CoV-2 infection that cannot be explained by an alternative diagnosis [2]. Several studies have revealed that long-term physical and mental sequelae of COVID-19 can affect anyone infected with SARS-CoV-2, regardless of age and the severity of symptoms during acute infection [3,4]. Estimates of the risk of developing PCC vary greatly. While an early review reported that around 80% of patients with COVID-19, resulting from Wildtype SARS-CoV-2 developed one or more long-term symptoms [5], more

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recent findings suggest that around 10-30% of non-hospitalized cases develop PCC [6]. There is a wide range of clinical symptoms associated with PCC, with more than 60 physical and mental sequelae. The symptoms reported most often were fatigue, shortness of breath, muscle, joint and chest pain, headache, cough, loss of taste and/or smell, and diarrhea [5,7,8]. Additionally, several risk factors for PCC have been identified, including female sex, smoking, obesity, and other comorbidities [9].

Several primary studies have assessed the risk of PCC after infection with the Omicron variant, compared with previous variants [10–16]. Additionally, two systematic reviews have investigated the risk of PCC caused by different variants [17,18]. However, no study has assessed the effect of preceding infections on the risk of developing PCC in relation to the different virus variants.

Taking advantage of a large study in Germany, we compared the risk of developing PCC after infection with Wildtype, Alpha, Delta, and Omicron SARS-CoV-2, depending on previous vaccinations and/or infections. We also determined whether the time since previous vaccinations and/or infections plays a role. Furthermore, we evaluated the symptom severity and assessed the differences in the symptoms of PCC among the variants.

Methods

Study design

We used data from the population-based prospective cohort study for digital health research in Germany (DigiHero, DRKS Registration-ID: DRKS00025600). DigiHero is a general platform for health research and was initiated in the city of Halle (Saxony-Anhalt, Germany) in January 2021. In December 2021, it was extended to the federal state of Saxony-Anhalt and subsequently to seven other federal states in Germany. Participants were invited through regular mail using postal addresses from population registries; subsequent study participation was digital. After online registration, we asked participants questions regarding sociodemographic characteristics and some introductory questions on health-related topics. In the baseline questionnaire, we asked participants whether they had had a positive test/an infection with SARS-CoV-2. Those who reported an infection or infections were invited to complete a detailed questionnaire on symptoms after their infection(s) and about their vaccination history. Recruitment for the DigiHero cohort, as well as the detailed questionnaires on symptoms after infection, proceeded in multiple waves. However, we also updated information among participants who did not report any infections in the baseline questionnaire by repeatedly asking them if new infections occurred. Finally, in July 2022, we asked all participants whether they had had any infections since the last time they had been contacted. This questionnaire included the same detailed questions about symptoms after the infection as the earlier questionnaires. The final dataset includes all participants for whom information on whether they had a SARS-CoV-2 infection until June 15, 2022 was available (Figure S1).

The Ethics Committee of the Martin Luther University Halle-Wittenberg (2020-076) approved the study. All participants provided informed consent.

Questionnaires and measures

In the baseline questionnaire, we asked participants about their month of birth, sex, education, and country of birth. We categorized education based on the International Standard Classification of Education (ISCED-97) into three categories: low, medium, and high [19].

Assessment of SARS-CoV-2 infections and symptoms after infection

We classified participants as having had an infection if they reported a positive polymerase chain reaction (PCR) test, more than one positive rapid test result, or a positive rapid test result and symptoms. If a PCR confirmation test was negative, then we classified participants as false positives. We considered the date of the first positive test as the beginning of the infection. We considered each infection to be a separate event, when they were at least 90 days apart [20,21]. In the detailed questionnaire, we asked participants to rate their overall perceived course of the acute infection on a scale including “No Symptoms”, “Mild”, “Moderate, “Severe”, and “Very Severe”. We combined the last two categories (“Severe/Very Severe”). Additionally, we asked participants about their symptoms during acute infection, 4-12 weeks after infection, and $\geq$12 weeks after infection. When participants reported the presence of any symptoms, we asked them to rate the severity of 24 different symptoms frequently reported in the literature as linked to COVID-19 (Table S1) on a 6-point Likert scale from “not at all” to “very severe” and an additional option “I don’t know”. We interpreted “I don’t know” as the absence of a specific symptom. The other answers were used to calculate a mean symptom score.

Assessment of post-COVID-19 condition

We defined PCC based on the presence of any symptom in the time window $\geq$12 weeks after infection. In the analyses, we considered only the first occurrence of PCC (i.e., we censored further data of participants who developed PCC symptoms after their first infection).

Assessment of vaccinations

Participants were asked if and when they had been vaccinated against SARS-CoV-2. While participants could have been vaccinated before and after infection, we considered only vaccinations prior to an infection, which we assessed for the occurrence of PCC. The number of vaccinations an individual received preceding their infection was used for this analysis.

Classification of SARS-CoV-2 variants

We classified the SARS-CoV-2 variants based on the reported infection date, using information on the dominant variants during specific periods [22]. We categorized infections before January 1, 2021 as caused by the Wildtype variant, infections between January 1, 2021 and June 30, 2021 as caused by the Alpha variant, infections between July 1, 2021 and December 20, 2021 as caused by the Delta variant, and infections from December 21, 2021 as caused by the Omicron variant. We performed a sensitivity analysis that excluded transition periods when the dominant variant changed. We defined the transition periods as the interval 1 month before and after the above-mentioned dates.

Statistical analysis

We report frequencies and percentages for descriptive analyses of the study population and the relationship between virus variants, preceding vaccinations and/or infections, and PCC. For multivariable analyses, we used logistic regression with generalized estimating equations with an exchangeable working correlation matrix. These models allow the inclusion of multiple infections per individual while accounting for potential correlation in individual risk of PCC. Our main variables of interest were the virus variant responsible for the studied infection and the number of preceding infections and/or vaccinations. For adjustment, we used sex, age, country of birth (Germany vs other), living in a city, federal state, education, and perceived severity of the acute infection. In the initial analysis, we stratified the data by all available combinations

Table 1
Characteristics of all (infected) participants and participants with PCC.

		Overall N = 48,826	Participants with at least one infection N = 17,008	PCC[a] N = 2822
Sex	Male	20498 (42.0%)	6053 (35.6%)	734 (18.8%)
	Female	28086 (57.5%)	10898 (64.1%)	2081 (28.1%)
	Diverse	64 (0.1%)	11 (0.1%)	1 (33.3%)
	Not specified	21 (0.0%)	4 (0.0%)	1 (33.3%)
	NA	157 (0.3%)	42 (0.2%)	5 (17.9%)
Age	18-29	6116 (12.5%)	2290 (13.5%)	302 (21.1%)
	30-39	8473 (17.4%)	3570 (21.0%)	466 (19.0%)
	40-49	8174 (16.7%)	3423 (20.1%)	587 (25.2%)
	50-59	10717 (21.9%)	3809 (22.4%)	768 (29.9%)
	60-69	9264 (19.0%)	2404 (14.1%)	381 (26.1%)
	70+	5048 (10.3%)	822 (4.8%)	95 (21.2%)
	NA	1034 (2.1%)	690 (4.1%)	223 (34.7%)
Born in Germany	Yes	46926 (96.1%)	16487 (96.9%)	2747 (25.0%)
	No	1772 (3.6%)	495 (2.9%)	73 (23.2%)
	Not specified/Unknown	86 (0.2%)	19 (0.1%)	1 (6.7%)
	NA	42 (0.1%)	7 (0.0%)	1 (20.0%)
Federal State	Saxony-Anhalt	19107 (39.1%)	6505 (38.2%)	1130 (24.5%)
	Baden-Württemberg	910 (1.9%)	365 (2.1%)	36 (23.5%)
	Bavaria	5964 (12.2%)	2353 (13.8%)	276 (18.1%)
	Berlin	846 (1.7%)	284 (1.7%)	40 (26.7%)
	Brandenburg	3350 (6.9%)	978 (5.8%)	192 (26.5%)
	Hamburg	957 (2.0%)	359 (2.1%)	27 (19.1%)
	Rhineland-Palatinate	5043 (10.3%)	1248 (7.3%)	198 (23.9%)
	Saxony	11744 (24.1%)	4575 (26.8%)	869 (29.2%)
	Other	141 (0.3%)	68 (0.4%)	9 (27.3%)
	NA	764 (1.6%)	273 (1.6%)	46 (24.3%)
Living in a city with 500.000 inhabitants	No	41842 (85.7%)	14343 (84.3%)	2,524 (25.4%)
	Yes	6220 (12.7%)	2392 (14.1%)	252 (21.1%)
	NA	764 (1.6%)	273 (1.6%)	46 (24.3%)
Education level	low	2054 (4.2%)	774 (4.6%)	97 (19.8%)
	medium	14421 (29.5%)	5114 (30.1%)	1022 (28.5%)
	high	29452 (60.3%)	10246 (60.2%)	1531 (23.0%)
	NA	2899 (5.9%)	874 (5.1%)	172 (29.0%)
Vaccinations preceding the given infection	0		5049 (29.7%)	1594 (39.4%)
	1		622 (3.7%)	126 (26.2%)
	2		2586 (15.2%)	465 (22.4%)
	3		8664 (50.9%)	635 (13.5%)
	4		87 (0.5%)	2 (7.4%)
Variant of SARS-CoV-2[b]	Wildtype		1301 (7.6%)	676 (52.0%)
	Alpha		1533 (9.0%)	729 (47.6%)
	Delta		2015 (11.8%)	524 (26.9%)
	Omicron		11560 (68.0%)	893 (13.6%)
	NA		599 (3.5%)	
Course of acute infection[c]	No Symptoms		844 (5.0%)	36 (6.0%)
	Mild		8945 (52.6%)	876 (15.0%)
	Moderate		6059 (35.6%)	1420 (34.8%)
	Severe/Very Severe		921 (5.4%)	486 (65.1%)
	NA		239 (1.4%)	4 (8.3%)

NA, not available; PCC, post-COVID-19 condition.
[a] Among 11,333 participants with infection 12 or more weeks before filling the questionnaire on symptoms after infection, row percentages in relation to the number of participants in the given category;
[b] Based on time of infection and periods of dominance of specific variants;
[c] Self-assessed.

of the virus variant, the number of vaccinations, and the preceding infection. In additional analysis, we report the results for the variant individually when adjusting for the vaccination status.

In addition, we compared symptom severity among those with PCC, to assess whether the severity of PCC differed by variant. We repeated the analysis of the association between the virus variant, and the number of vaccinations and/or infections preceding the relevant infection and PCC by using a more conservative definition of PCC (at least one moderate symptom in the time window 12 or more weeks after infection).

We also analyzed how the risk reduction was associated with preceding infection or vaccination depended on time. For this analysis, we used generalized additive models (GAM) with locally estimated scatterplot smoothing (LOESS) for the time since the last vaccination and the time since the last infection, respectively. In the analysis of the time since the last vaccination, all considered participants had been vaccinated. We adjusted the model for the variables used in the generalized estimating equation model. To avoid instability of the GAM results in the area of sparse data, we excluded the longest 5% of observations for time since last vaccination.

Furthermore, we assessed the reported symptom severity for all variants in a descriptive analysis.

We report 95% confidence intervals (CIs) for all analyses. All analyses were performed in R (Version 4.2.0) [23], with the packages gam [24] and geepack [25].

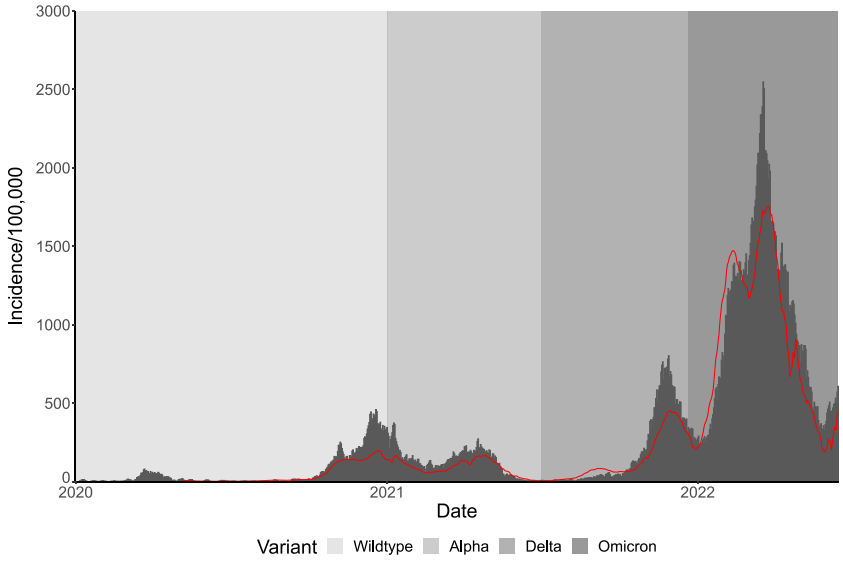

Figure 1. Daily Incidence per 100,000 people in the DigiHero Cohort from January 01, 2020 to June 15, 2022 by time. The red line indicates the reported national Incidence per 100,000 people in Germany [26].

Results

Characteristics of the participants

Overall, 48,826 individuals completed the baseline questionnaire until June 15, 2022. We classified 286 (0.6%) participants as false positive, leaving 17,008 (34.8%) participants who had had at least one SARS-CoV-2 infection. The majority of the participants were female (57.5%), born in Germany (96.1%) and had a high education status (60.3%). Women reported infections more often than men. Apart from that, there were no larger differences in the characteristics of infected compared to non-infected participants (Table 1).

Approximately 70% of infected participants had been vaccinated at the time of respective infection, and around 50% had been vaccinated three times. The proportion of vaccinated participants varied depending on the dominant variant, 0% for Wildtype, 10% for Alpha, 67% for Delta, and 89% for Omicron. The majority (68.0%) of infections occurred during Omicron dominance. Of the participants, 1350 (8.1%) reported more than one infection. However, 194 infections occurred within 90 days after their first infection and, therefore, we did not classify them as reinfections, leaving 1156 individuals with more than one infection. There were 419 reinfections in individuals who developed PCC after their first infection (in the subsequent analysis, reinfections are only considered in participants who did not develop PCC after their first infection). Only approximately 1% of infected participants were admitted to the hospital during acute infection.

Risk of post-COVID-19 condition

The incidence of SARS-CoV-2 was slightly higher in the DigiHero cohort than in the overall German population, but it generally followed the same trends over the course of the COVID-19 pandemic (Figure 1). We excluded 5755 (33.8%) of the infected individuals from further analysis, because the difference between the infection date and completing the questionnaire on symptoms was less than 12 weeks, and thus we could not classify them with respect to PCC. The median time between the infection date and completing the questionnaire on symptoms was 21 weeks (maximum = 131 weeks, mean = 33 weeks) among those considered for the analysis. Moreover, 75% completed the questionnaire between 12 and 43 weeks after infection. In total, 2822 individuals reported symptoms for the period 12 weeks after their infection, including 144 (5.1%) who did not report symptoms for the period 4-12 weeks after infection.

In unadjusted analyses, the proportion of participants reporting PCC symptoms was highest for those infected with Wildtype SARS-CoV-2, similar for Alpha, substantially lower for Delta, and lowest for Omicron (Table 2). Previous vaccinations played a minimal role, and previous infections (in individuals who did not develop PCC after their first infection) were associated with a much lower risk of PCC.

The adjusted results were similar (Figure 2 and Table S2). We observed the highest risk of PCC for unvaccinated participants infected with Wildtype SARS-CoV-2 (adjusted Odds Ratio [aOR]: 6.44, 95% CI 5.49; 7.56), followed by unvaccinated and vaccinated participants infected with the Alpha variant (aOR 5.97, 95% CI 4.00; 8.90 and aOR 5.08, 95% CI 4.28; 6.02) compared with participants infected with the Omicron variant and adjusted for sociodemographic information. Vaccination offered no meaningful protection against developing PCC in case of an infection. In contrast, there was a strong evidence that a previous infection reduced the risk of PCC (aOR 0.14, 95% CI 0.07; 0.25). The results of the sensitivity analysis, excluding periods in which variants overlapped, and the results of the analysis based only on the first infection of participants showed similar associations as the model presented in Figure 2 (Tables S3 and S4). The analysis using a more restrictive criterion of PCC resulted in very similar relative estimates, while the percentage of those classified as PCC was substantially lower (Table S5).

Among those who developed PCC, symptom severity was similar for all variants and did not differ by vaccination status or if participants had had a previous infection (Table S6).

When assessing the association between time since the last vaccination and the risk of PCC, there was an indication that risk increased with time since the last vaccination increased for the Alpha variant, whereas this association did not exist for the Delta or Omicron variant. Similarly, time since the last infection was not associated with the risk of PCC (Figure S2).

Post-COVID-19 condition symptoms by virus variant

The PCC symptom reported most often was fatigue (76.1%), followed by shortness of breath (59.6%), and cognitive impairment (59.4%). After Omicron infection, participants with PCC were less

Table 2
Proportion of Post COVID-19 condition (PCC).depending on previous infections and vaccinations

Variant	Previous Infection	Number of vaccinations	Infected	PCC	
			N	%	95% CI
Wildtype	No	0	1425	51.79	49.20; 54.38
Alpha	No	0	1269	47.20	44.46; 49.95
		1-2	140	42.14	33.96; 50.32
	Yes	0	7	0.00	0.00; 0.00
		1-2	1	0.00	0.00; 0.00
Delta	No	0	647	26.13	22.73; 29.54
		1-2	1245	27.12	24.61; 29.63
		3+	122	23.01	15.25; 30.77
	Yes	0	23	0.00	0.00; 0.00
		1-2	22	4.55	0.00; 13.25
Omicron	No	0	1093	11.36	9.03; 13.69
		1-2	1780	16.76	14.65; 18.87
		3+	8518	13.17	12.20; 14.15
	Yes	0	235	0.43	0.00; 1.29
		1-2	419	1.94	0. 61; 3.27
		3+	262	1.56	0.04; 3.08

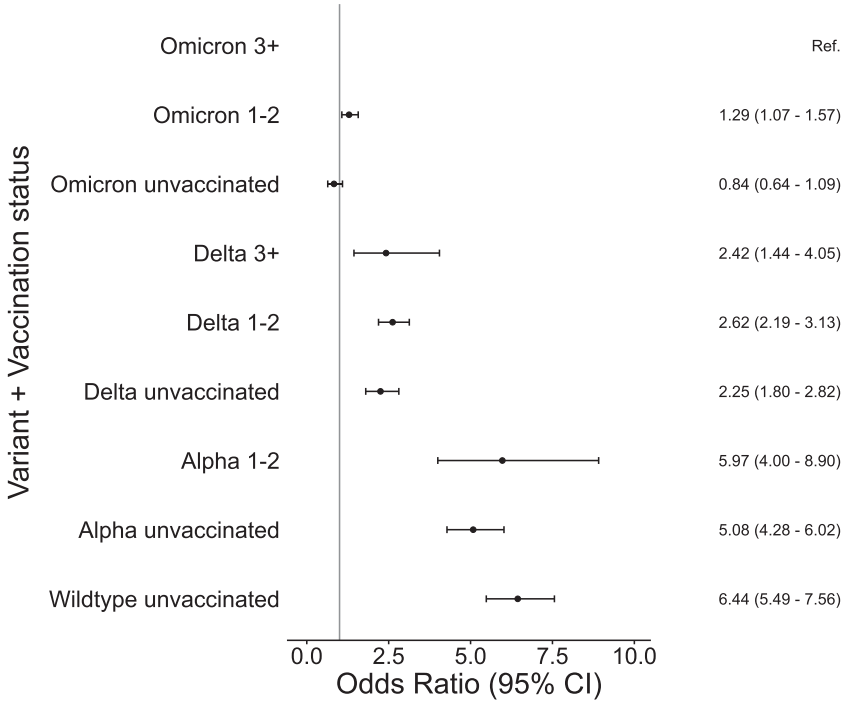

Figure 2. Association between post-COVID-19 condition and the virus variants and vaccination status (the numbers in the legend refer to number of received vaccine doses), adjusted for sex, age, country of birth, federal state, living in a big city, education, previous infection, and course of acute infection. Because multiple infection events per person are included, the odds ratios were estimated using generalized estimating equations. (N = 10,527). CI, confidence interval.

affected by smell and taste disorders (18.9%) compared with participants infected with the other variants (Figure 3). There were no other differences in the occurrence of symptoms or symptom severity across the virus variants.

Discussion

We found that participants infected with the Omicron variant had the lowest risk of developing PCC, followed by the Delta, Alpha, and Wildtype variants. The risk was substantially lower among those who had had previous infections, but it did not differ based on the vaccination status (among those who had been infected). In addition, the symptom severity in the case of developing PCC did not differ by the variant, the vaccination status, or previous infection. The symptom patterns were similar across PCC resulting from infections with various virus variants, with the exception of less frequent smell and taste disorders for the Omicron variant than for the other variants.

Our finding of a strong risk reduction for PCC in individuals infected with Omicron compared with the other variants agrees with other studies in adults [11,12,15,16] and children [27,28]. In our sample, there were relatively high proportions of participants reporting PCC symptoms compared with other studies [14,16]. This difference could be caused by the greater participation of individuals affected by PCC in our study. However, when applying a more restrictive criterion of symptoms, it resulted in a lower risk of PCC, but similar relative estimates regarding variants, which are the focus of our analyses, because the selection likely affected all groups in the same way.

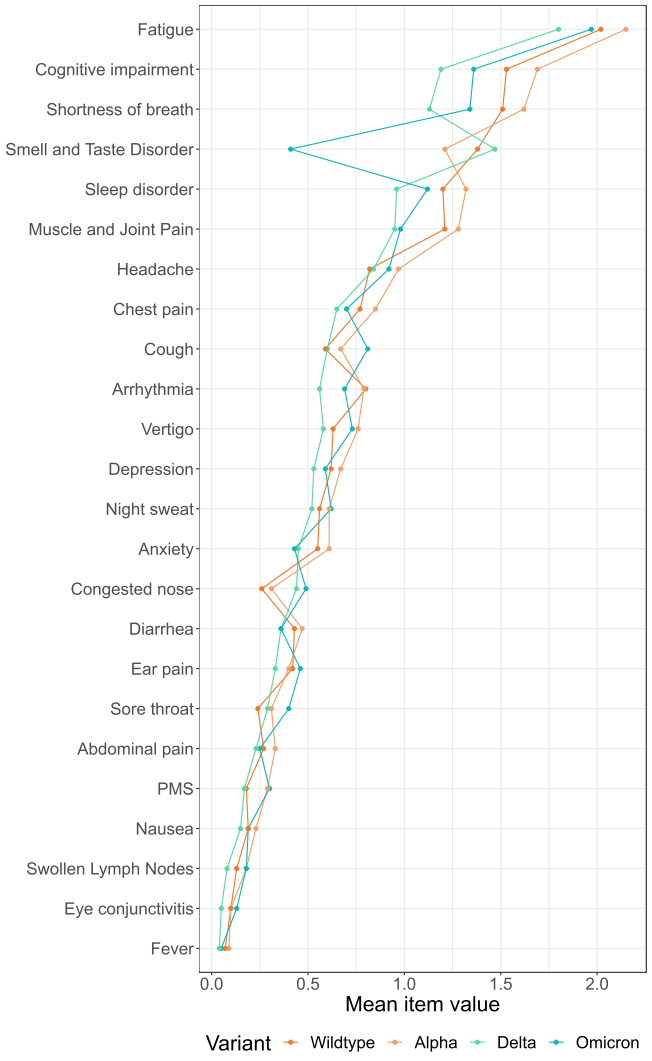

Figure 3. Symptoms reported ≥12 after infection, by variant, N = 2822.

The finding that smell disorders were less frequent in individuals infected with Omicron is consistent with a previous study that found loss of smell was less common during the acute infection [29]. Furthermore, a study in children also found that smell and taste disorders were less likely to persist if a child was infected with Omicron SARS-CoV-2 [30].

Given the large sample size of DigiHero, we were able to disentangle the differences between variants and previous infections and/or vaccinations. Previous studies addressing the question of the effects of vaccination on the risk of PCC, included in a recent review [31], that concluded that there is some evidence of a protective effect, did not assess the interaction between virus variants, vaccinations, and preceding infections. Another difficulty in comparing our data with previous studies is the different time windows to assess the occurrence of symptoms after infection. Some studies have investigated symptoms lasting for more than 4 weeks, which could more likely be affected by ongoing symptoms of an acute infection than when a later time window is considered. More important is the observation that when distinguishing between the acute outcomes and PCC symptoms, a more recent study showed no protective effects of vaccination on the main PCC symptoms [32], which is also our finding. However, we were not able to study the vaccine tailored towards the Omicron variant, so we do not know whether it has protective effects with regard to PCC. Additional research is needed to assess this effect.

As the COVID-19 pandemic progressed, repeated infections became more frequent, but information about the impact of previous infections on long-term symptoms is limited [33,34]. One study showed an increasing risk of PCC after the second and third infections compared with individuals without a preceding infection. However, researchers have not investigated the risk of PCC after a first infection compared with after a reinfection [35]. Our data suggest that the risk of PCC is decreased if individuals have had a previous infection but have not developed PCC. This risk reduction did not depend on time since previous infection. While we could assess up to 113 weeks since the previous infection (95% of the observed intervals between infections in our sample fall into this range), our data indicate that the immunological memory offering this protection does not wane. This would be a positive aspect with respect to the long-term perspective on PCC. Another potential explanation could be that individuals, who did not develop PCC after their first infection, have characteristics that lead to a lower risk of developing PCC after subsequent infections.

The strength of this study is the large population-based sample. There are also some limitations. First, participation was only online. This is typically associated with convenience sampling. However, we recruited the participants by using a population-based approach, based on postal invitations sent to the residential addresses. Second, the information we collected is based on self-reports. While many of the symptoms are individual perceptions which are self-reported, clinical examinations could provide supplemental insights. Moreover, the symptoms were reported retrospectively for several time windows after infection. The upper end of the 12 weeks or more time window was not defined; however given that 75% of participants responded between 12 and 43 weeks after their infection, this was the reference window for the majority of respondents. Nevertheless, the long time between infection and completing the survey could result in recall bias. Additionally, our definition of PCC is based on the presence of symptoms. While we conducted an additional analysis with a more restrictive requirement of at least moderate symptoms, we did not ask participants if they were negatively affected in their daily life. However, even if our definition led to a higher proportion of PCC, the comparisons across virus variants should not be affected, because we collected and analyzed the data in each subgroup in the same way. The self-reporting of infections and vaccinations could also lead to a misclassification of some individuals. In particular, we could not consider infections unknown to each participant. Additionally, we could not adjust for several known risk factors, such as the smoking status, obesity, and comorbidities [9], as this information was not available for participants of DigiHero. Furthermore, not being vaccinated could also be due to other underlying unknown factors, for which we could not adjust for. Furthermore, we could not include an adequate control group to assess whether the reported symptoms are attributable to the SARS-CoV-2 infection. Again, this applies to all variants and thus relative comparisons or time dynamics are not differentially affected. Lastly, we did not collect biosamples, and we classified the viral variants based on the time of occurrence of infections. Hence, we might have misclassified some participants. However, the sensitivity analysis, in which we excluded infections during periods of variant change, provided results similar to the main analysis.

In conclusion, while the Omicron variant was associated with a much lower risk of PCC in our study, the lack of protection by vaccination regarding the occurrence and symptom severity of PCC (in case of an infection) suggest that this condition can become a serious challenge for the health care system during the early endemic phase of SARS-CoV-2. At the same time, the strong protective effect of a preceding infection in individuals who did not have PCC after

their initial infection, suggests that in the midterm, the problem might resolve.

Declarations of competing interest

The authors have no competing interests to declare.

Data availability

The anonymized data reported in this study can be obtained from the corresponding author upon request. The dataset including individual data and an additional data dictionary will be provided. The beginning of data availability starts with the date of publication, and the authors will support any requests in the three following years. Data requests should include a proposal for the planned analyses. Decisions will be made according to data use by the use and access committee of the DigiHero study, and data transfer will require a signed data access agreement.

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Ethical approval

The Ethics Committee of the Martin Luther University Halle-Wittenberg (Registration number 2020-076) approved the study. Informed consent was obtained from all participants.

Author contributions

Sophie Diexer, Bianca Klee, Cornelia Gottschick, and Rafael Mikolajczyk developed the questionnaire. Sophie Diexer conducted the analyses, and drafted the manuscript. Mascha Binder, Thomas Frese, Matthias Girndt, Jessica I. Hoell, Irene Moor, Michael Gekle, and Rafael Mikolajczyk developed the design of the DigiHero study. All authors provided comments on the manuscript and all authors accepted the final version.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.08.019.

References

[1] World Health Organization. Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports; 2023 [accessed 02 August 2023].
[2] Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022;**22**:e102–7. doi:10.1016/S1473-3099(21)00703-9.
[3] Houben S, Bonnechère B. The impact of COVID-19 infection on cognitive function and the implication for rehabilitation: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2022;**19**:7748. doi:10.3390/IJERPH19137748.
[4] Dirican E, Bal T. COVID-19 disease severity to predict persistent symptoms: a systematic review and meta-analysis. *Prim Health Care Res Dev* 2022;**23**:e69. doi:10.1017/S1463423622000585.
[5] Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021;**11**:16144. doi:10.1038/s41598-021-95565-8.
[6] Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;**21**:133–46. doi:10.1038/s41579-022-00846-2.
[7] Michelen M, Manoharan L, Elkheir N, Cheng V, Dagens A, Hastie C, et al. Characterising long COVID: a living systematic review. *BMJ Glob Health* 2021;**6**:e005427. doi:10.1136/BMJGH-2021-005427.
[8] Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open* 2021;**4**:e2128568. doi:10.1001/JAMANETWORKOPEN.2021.28568.
[9] Subramanian A, Nirantharakumar K, Hughes S, Myles P, Williams T, Gokhale KM, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med* 2022;**28**:1706–14. doi:10.1038/s41591-022-01909-w.
[10] Fernández-de-las-Peñas C, Cancela-Cilleruelo I, Rodríguez-Jiménez J, Gómez-Mayordomo V, Pellicer-Valero OJ, Martín-Guerrero JD, et al. Associated-onset symptoms and post-COVID-19 symptoms in hospitalized COVID-19 survivors infected with wuhan, alpha or delta SARS-CoV-2 variant. *Pathogens* 2022;**11**:725. doi:10.3390/PATHOGENS11070725.
[11] Ballouz T, Menges D, Kaufmann M, Amati R, Frei A, Von Wyl V, et al. Post COVID-19 condition after Wildtype, Delta, and Omicron SARS-CoV-2 infection and prior vaccination: pooled analysis of two population-based cohorts. *PLoS One* 2023;**18**:e0281429. doi:10.1371/JOURNAL.PONE.0281429.
[12] Hernández-Aceituno A, García-Hernández A, Larumbe-Zabala E. COVID-19 long-term sequelae: omicron versus Alpha and Delta variants. *Infect Dis Now* 2023;**53**:104688. doi:10.1016/J.IDNOW.2023.104688.
[13] Magnusson K, Kristoffersen DT, Dell'Isola A, Kiadaliri A, Turkiewicz A, Runhaar J, et al. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants. *Nat Commun* 2022;**13**:7363. doi:10.1038/s41467-022-35240-2.
[14] Azzolini E, Levi R, Sarti R, Pozzi C, Mollura M, Mantovani A, et al. Association between BNT162b2 vaccination and long COVID after infections not requiring hospitalization in health care workers. *JAMA* 2022;**328**:676–8. doi:10.1001/jama.2022.11691.
[15] Morioka S, Tsuzuki S, Suzuki M, Terada M, Akashi M, Osanai Y, et al. Post COVID-19 condition of the Omicron variant of SARS-CoV-2. *J Infect Chemother* 2022;**28**:1546–51. doi:10.1016/J.JIAC.2022.08.007.
[16] Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet* 2022;**399**:2263–4. doi:10.1016/S0140-6736(22)00941-2.
[17] Du M, Ma Y, Deng J, Liu M, Liu J. Comparison of long COVID-19 caused by different SARS-CoV-2 strains: a systematic review and meta-analysis. *Int J Environ Res Public Health* 2022;**19**:16010. doi:10.3390/ijerph192316010.
[18] Fernández-de-las-Peñas C, Notarte KI, Peligro PJ, Velasco JV, Ocampo MJ, Henry BM, et al. Long-COVID symptoms in individuals infected with different SARS-CoV-2 variants of concern: a systematic review of the literature. *Viruses* 2022;**14**:2629. doi:10.3390/v14122629.
[19] Organisation for Economic Co-operation and Development. Classifying educational programmes: manual for ISCED-97 implementation in OECD countries, https://www.oecd.org/education/skills-beyond-school/1962350.pdf; 1999 [accessed 18 August 2023].
[20] European Centre for Disease Prevention and Control. Reinfection with SARS-CoV-2: implementation of a surveillance case definition within the EU/EEA, https://www.ecdc.europa.eu/sites/default/files/documents/Reinfection-with-SARSCoV2-implementation-of-a-surveillance-case-definition.pdf; 2021 [accessed 02 August 2023].
[21] Yahav D, Yelin D, Eckerle I, Eberhardt CS, Wang J, Cao B, et al. Definitions for coronavirus disease 2019 reinfection, relapse and PCR re-positivity. *Clin Microbiol Infect* 2021;**27**:315–18. doi:10.1016/j.cmi.2020.11.028.
[22] Robert Koch Institut. Wöchentlicher Lagebericht des RKI zur coronavirus-Krankheit-2019 (COVID-19), 31.03.2022, https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Situationsberichte/Wochenbericht/Wochenbericht_2022-03-31.pdf?__blob=publicationFile; 2022 [accessed 02 August 2023].
[23] R Core Team *R: A language and environment for statistical computing*; 2022.
[24] Hastie T. gam: Generalized Additive Models v1.22-2 (Version 1.22-2). 2023 (March 28). https://cran.r-project.org/web/packages/gam/index.html.
[25] Halekoh U, Højsgaard S, Yan J. The R package geepack for generalized estimating equations 2005;15:1–11. doi:10.18637/jss.v015.i02.
[26] Robert Koch Institut. 7-Tage-Inzidenz der COVID-19-Fälle nach Kreisen sowie der hospitalisierten COVID-19-Fälle nach Bundesländern, https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Daten/Inzidenz-Tabellen.html; 2023 [accessed 02 August 2023].
[27] Buonsenso D, Morello R, Mariani F, De Rose C, Mastrantoni L, Zampino G, et al. Risk of long Covid in children infected with Omicron or pre-Omicron SARS-CoV-2 variants. *Acta Paediatr* 2023;**112**:1284–6. doi:10.1111/apa.16764.
[28] Morello R, Mariani F, Mastrantoni L, De Rose C, Zampino G, Munblit D, et al. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study. *EClinicalmedicine* 2023;**59**:101961. doi:10.1016/j.eclinm.2023.101961.
[29] Menni C, Valdes AM, Polidori L, Antonelli M, Penamakuri S, Nogal A, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. *Lancet* 2022;**399**:1618–24. doi:10.1016/S0140-6736(22)00327-0.
[30] Mariani F, Morello R, Traini DO, La Rocca A, De Rose C, Valentini P, et al. Risk factors for persistent anosmia and dysgeusia in children with SARS-CoV-2 infection: a retrospective study. *Children (Basel)* 2023;**10**:597. doi:10.3390/children10030597.

[31] Notarte KI, Catahay JA, Velasco JV, Pastrana A, Ver AT, Pangilinan FC, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: a systematic review. *EClinicalmedicine* 2022;**53**:101624. doi:10.1016/j.eclinm.2022.101624.
[32] 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. doi:10.1016/J.BBI.2022.04.013.
[33] Altarawneh HN, Chemaitelly H, Hasan MR, Ayoub HH, Qassim S, AlMukdad S, et al. Protection against the omicron variant from previous SARS-CoV-2 infection. *N Engl J Med* 2022;**386**:1288–90. doi:10.1056/NEJMc2200133.
[34] Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, et al. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. *Science* 2022;**376**:eabn4947. doi:10.1126/science.abn4947.
[35] Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med* 2022;**28**:2398–405. doi:10.1038/s41591-022-02051-3.