Using a digital platform to understand the Long COVID burden in Germany

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Abstract

Background and aim: Long COVID, characterized by persistent symptoms following SARS-CoV-2 infection, has emerged as a public health concern. Prevalence estimates for Long COVID vary greatly and a wide range of symptoms have been linked to this condition. Several risk factors have been identified, including female sex, smoking, obesity, and comorbidities. Nonetheless, there is still uncertainty about the underlying causes of Long COVID. Additionally, there is no specific diagnostic tool or treatment for Long COVID.

The aim of this thesis is to understand the Long COVID burden in Germany, with a focus on determining its prevalence and investigating factors associated with the development as well as the early recovery of Long COVID.

Methods: To answer the research question, data from the DigiHero study was analyzed. DigiHero was initiated in 2021 in Halle (Saale) as an online population-based prospective cohort study. As of June 2022, 48,826 individuals have been enrolled in the study. Participants provided information about their SARS-CoV-2 infections, vaccinations, and symptoms at several time points (during acute infection, four to twelve weeks after infection, and more than twelve weeks after infection).

Results: Of all infected individuals, 45% and 25% reported at least one symptom four weeks and twelve weeks after the infection, respectively. Participants infected with Omicron SARS-CoV-2 had the lowest Long COVID risk. A previous SARS-CoV-2 infection reduced the risk of Long COVID, while vaccination against SARS-CoV-2 had no effect. The identified factors associated with persistence of symptoms were similar to the factors associated with the development of Long COVID, including female sex, older age, a more severe course of acute infection, and an infection with the Omicron variant.

Conclusion: This thesis gives an overview of the extensive burden of Long COVID in Germany using a population-based digital cohort study.

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Referat

Hintergrund und Zielsetzung: Long COVID, charakterisiert durch anhaltende Symptome nach einer SARS-CoV-2-Infektion, ist zu einem Problem für die öffentliche Gesundheit geworden. Die Schätzungen der Prävalenz von Long COVID sind sehr unterschiedlich und mehrere Symptome wurden mit dieser Krankheit in Verbindung gebracht. Verschiedene Risikofaktoren wie weibliches Geschlecht, Rauchen, Adipositas und Begleiterkrankungen wurden identifiziert. Dennoch sind die Ursachen von Long COVID nach wie vor unklar. Darüber hinaus gibt es weder ein spezifisches Diagnoseinstrument noch eine Behandlung für Long COVID. Ziel dieser Arbeit ist es, die Belastung durch Long COVID in Deutschland zu verstehen. Der Schwerpunkt liegt auf der Bestimmung der Prävalenz und der Untersuchung von Faktoren, die mit der Entwicklung und frühen Genesung von Long COVID assoziiert sind.

Methoden: Zur Beantwortung der Forschungsfrage wurden Daten der DigiHero-Studie ausgewertet, einer bevölkerungsbasierten, prospektiven Online-Kohortenstudie, die 2021 in Halle (Saale) initiiert wurde. Im Juni 2022 waren 48.826 Personen eingeschlossen. Die Teilnehmenden machten Angaben zu ihren SARS-CoV-2-Infektionen, Impfungen und Symptomen zu verschiedenen Zeitpunkten (während der akuten Infektion, vier bis zwölf Wochen nach der Infektion und mehr als zwölf Wochen nach der Infektion).

Ergebnisse: Von allen Infizierten berichteten 45% vier Wochen nach der Infektion über mindestens ein Symptom und 25% nach zwölf Wochen. Teilnehmende, die mit Omikron SARS-CoV-2 infiziert waren, hatten das geringste Risiko für Long COVID. Eine frühere Infektion mit SARS-CoV-2 reduzierte das Risiko für Long COVID, während Impfungen keinen Einfluss hatte. Die Faktoren, die mit der Persistenz der Symptome in Verbindung gebracht werden, ähneln denen, die mit der Entwicklung von Long COVID verbunden sind.

Schlussfolgerungen: Diese Arbeit gibt einen Überblick über die umfangreiche Belastung durch Long COVID in Deutschland anhand einer bevölkerungsbasierten Online-Kohortenstudie.

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List of abbreviations

COVID-19	Coronavirus disease 2019
DALY	Disability-adjusted life years
EBV	Epstein-Barr virus
ICD	International Statistical Classification of Diseases and Related Health Problems
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
NICE	National Institute for Health and Care Excellence
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization
YLD	Years lived with disability

1. Introduction and objectives

1.1. Long COVID

In December 2019 a new coronavirus emerged in China [1] that rapidly spread to other countries [2, 3]. The disease caused by the virus, termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4], was named coronavirus disease 2019 (COVID-19) on February 11, 2020 [5]. One month later, on March 11, 2020, the World Health Organization (WHO) officially declared COVID-19 a global pandemic [6]. As of May 2024 nearly 800 million cases of COVID-19 have been reported worldwide [7].

Initial reports stated that the majority of infected individuals would experience mild illness and recover within a short time [8, 9]. However, there were multiple early reports that some individuals suffered from persisting symptoms weeks after their initial recovery [10–13]. These long-term symptoms are commonly referred to as “Long COVID”. It is estimated that at least 65 million people worldwide have been affected, but the number is likely higher [14].

1.1.1. Definition of Long COVID

The term “Long COVID” was first used in May 2020 on the social media platform “X”, formerly known as “Twitter”, by Elisa Perego to describe her own persisting symptoms after her SARS-CoV-2 infection [15]. Since then, multiple terms have been used to describe this phenomenon. Other common terms include “post-acute sequelae of COVID-19”, “long-haul COVID”, “post-COVID condition”, and “post-COVID syndrome”. The WHO refers to it as “Post COVID-19 condition” [16]. It is defined as having symptoms three months after COVID-19 onset, that last for at least two months in individuals with a confirmed or probable SARS-CoV-2 infection. Furthermore, it is stated that these symptoms cannot be explained by an alternative diagnosis and that they can persist from the initial illness, but can also be new, following the initial recovery [16].

The guideline provided by the National Institute for Health and Care Excellence (NICE) in the United Kingdom proposes a differentiation between symptoms observed between four and twelve weeks after SARS-CoV-2 infection (referred to as ongoing symptomatic COVID-19) and symptoms that persist beyond twelve

weeks (referred to as post-acute COVID-19 syndrome) [17]. Additionally, they state that the term "Long COVID" includes both definitions (Figure 1). The German Guideline also describes this differentiation between Long COVID and Post-COVID syndrome [18]. Apart from these definitions, it is also important to have a standardized classification of the disease. In Germany, the German modification of the 10th edition of the International Statistical Classification of Diseases and Related Health Problems (ICD) is used for diagnostic coding. There, the code “U09.9 - Post COVID-19 condition, unspecified” has been determined to code Long COVID [19]. This ICD-10 code is only to be used to link an otherwise classified disorder with COVID-19. It should not be used in case of active COVID-19. However, no time frame is described for how long the symptoms should persist.

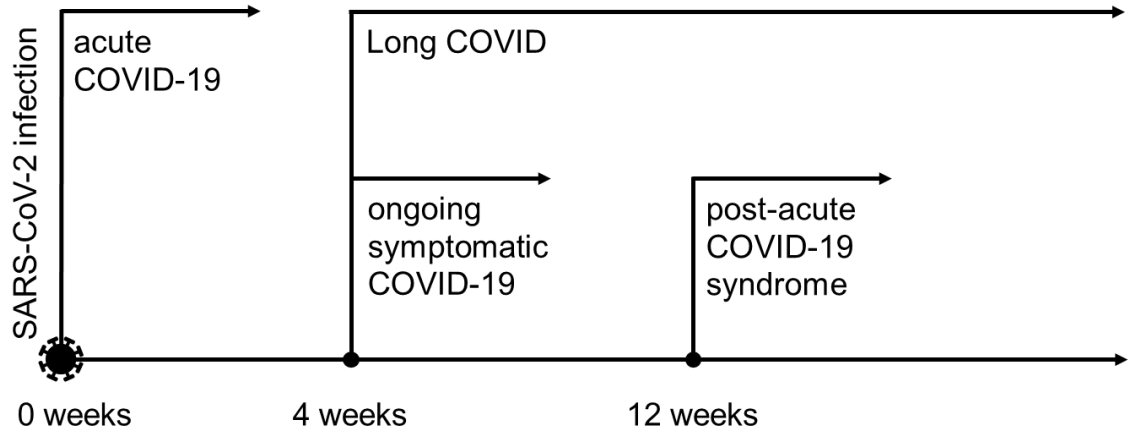

Figure 1 – Long COVID definition based on the NICE guideline [17]

The use of different terms comes with difficulties, especially since the time frames of symptoms vary between definitions. In the following, the term Long COVID will be used to describe symptoms four or more weeks after SARS-CoV-2 infection, as this term is widely used in the literature and it includes symptoms four and twelve weeks after SARS-CoV-2 infection.

1.1.2. Prevalence of Long COVID

The prevalence estimates of Long COVID vary greatly. Early reports from 2020 suggested that around 87% of infected hospitalized individuals report the persistence of at least one symptom [13]. However, differences between hospitalized and non-hospitalized patients have been reported. A meta-analysis

estimated a pooled Long COVID prevalence of 43%, with 54% in hospitalized and 34% in non-hospitalized patients [20]. Contradictory, another meta-analysis found a global prevalence of only 6.2% [21].

Estimates in Germany also vary, with one study claiming that around 50% of infected individuals still reported at least one symptom nine months after infection [22]. Furthermore, severe Long COVID occurred in 13% to 20% of participants, with estimates varying by sub-cohort [22]. Another study, that investigated long-term sick leave associated with COVID-19, found a prevalence of 5.8% [23]. However, these are early reports from 2020 and 2021. A newer study using claims data, including data until March 2022, found that approximately 14% of infected individuals had Long COVID [24].

Overall, the estimates depend on the definition of Long COVID, how it is measured, as well as the population that is investigated. Using routine healthcare generally results in lower prevalence estimates than data based on self-reports [25]. Furthermore, most studies lack a comparison group. A study from the Netherlands, that compared infected individuals with matched controls, found that in 12.6% the persistent symptoms could be attributed to COVID-19 [26]. Similar results were reported by a Scottish study that also used controls [27]. This is consistent with the reported estimates from the WHO of 10-20% [28].

1.1.3. Long COVID symptoms

More than 100 symptoms have been linked to Long COVID, affecting multiple organ systems, including respiratory, cardiovascular, gastrointestinal, endocrine and neurological systems [29].

One of the most commonly reported symptoms is fatigue. A similarity to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) has been noted [30]. ME/CFS compromises symptoms such as fatigue, pain, sleep disturbances and worsening of symptoms following minor increases in physical and/or cognitive activity. The latter is referred to as post-exertional malaise [31].

Other symptoms often reported include symptoms affecting the respiratory tract, like shortness of breath and cough. According to a meta-analysis these symptoms were found in 24% and 19% of infected individuals respectively [30]. Furthermore, cardiovascular symptoms are common in Long COVID patients with

around 15% reporting these symptoms [32]. Other symptoms include gastrointestinal symptoms such as loss of appetite, dyspepsia, and loss of taste. Up to 22% of individuals with Long COVID report these symptoms [33]. Additionally, neuropsychiatric symptoms have been linked to Long COVID [30].

As individuals suffering from Long COVID tend to report symptoms in one particular system, it is hypothesized that clusters or subgroups of Long COVID patients exist [34]. Three clusters were consistently identified: one characterized by inflammation, another by cardiorespiratory issues and the third by neurological symptoms [35].

Symptoms can persist for a long time, with one study reporting that around 50% still report symptoms three years after initial onset [36]. The time course and onset of symptoms can vary among individuals and depends on the type of symptom experienced [14]. While neurological symptoms have a delayed onset, they tend to persist longer. On the contrary, gastrointestinal and respiratory symptoms are more likely to resolve [14]. The mean symptom duration also differs between patients who have been hospitalized because of COVID-19 and non-hospitalized patients. Specifically, it was observed to be four months for non-hospitalized patients, whereas hospitalized patients experienced symptoms for an average of nine months [21].

1.1.4. Long COVID pathophysiology

The causes of Long COVID are still unknown, but multiple pathogenic pathways have been hypothesized.

1.1.4.1. Viral persistence

One of the hypotheses for the cause of Long COVID is viral persistence of SARS-CoV-2 [37]. The pathogen might be able to establish a persistent long-lasting infection. Several studies have investigated this, and SARS-CoV-2 RNA and protein have been found in various human tissues including the lung [38], brain [39], gastrointestinal tract [40], and in the plasma [41]. However, not all individuals experiencing Long COVID exhibit persistent SARS-CoV-2 RNA. A recent systematic review showed that, depending on the sample tested, the prevalence of SARS-CoV-2 RNA ranged from 5% to 59 % in patients with Long

COVID. However, it is also noted that the lack of analyzed control groups infected with SARS-CoV-2 without Long COVID limits the generalizability of the findings [42].

1.1.4.2. Reactivation of other viruses

Another explanation behind the development of Long COVID could be the reactivation of other viruses, such as the Epstein-Barr virus (EBV). This reactivation could result in the development of various symptom. A study from 2021 found a link between Long COVID and EBV reactivation [43]. Additionally a meta-analysis found that the prevalence of active herpes viruses in COVID-19 survivors ranged from 18% to 41%. However, this prevalence did not differ considerably between SARS-CoV-2 infected and non-infected individuals [44]. Furthermore, one study found no EBV DNA in individuals with Long COVID who had asymptomatic or mild SARS-CoV-2 infection [45]. Therefore, the reactivation of other viruses is likely not the sole cause of Long COVID, but could potentially influence the development of the long-term symptoms in some patients.

1.1.4.3. Autoimmunity

SARS-CoV-2 infection may trigger the production of various autoantibodies [46]. This could persist even after recovery and might also play a role in the development of Long COVID. Elevated levels of autoantibodies have been found in individuals with Long COVID [47, 48]. Contradictory, another study that investigated multiple potential pathways found that the autoantibody levels were not higher in individuals with Long COVID in comparison to matched controls, suggesting less involvement of autoantibodies in Long COVID [49].

1.1.4.4. Long-Lasting inflammation

Inflammation has been implicated in causing damage to many organ systems during the acute phase of COVID-19 and furthermore, prolonged inflammation has also been found to be an important factor contributing to the development of Long COVID [50]. For instance, a systematic review found that inflammatory biomarkers are elevated in Long COVID patients [51].

1.1.4.5. Endothelial Dysfunction

Long COVID might also be caused by endothelial dysfunction, as SARS-CoV-2 is able to penetrate the endothelial barrier. This can cause endothelitis and multi-organ injury, which could lead to long-term symptoms [52]. Multiple studies have found an association with Long COVID and endothelial dysfunction [53, 54]. In particular, it is hypothesized that endothelial dysfunction can explain the cardiovascular Long COVID symptoms [55].

1.1.4.6. Microbiome alteration

A healthy microbiome in the human body serves to protect the host's immune system by inhibiting pathogen invasion and colonization [56]. The gut microbiome may be perturbed by SARS-CoV-2 infection, which could result in Long COVID, through e.g. increased inflammation [57]. In fact, multiple studies showed that the gut microbiome was altered in Long COVID patients [58, 59].

1.1.5. Risk factors associated with Long COVID

Several studies have investigated risk factors associated with the development of Long COVID and various sociodemographic factors have been linked to Long COVID. Four different meta-analyses found that women are more at risk of developing Long COVID [60–63]. Older age was also found to be associated with long-term symptoms in observational studies [64, 65]. This association was confirmed in two meta-analyses [62, 63]. However, another meta-analysis could not support this, finding no association between old age and Long COVID [61]. Another large-scale analysis of primary care data even found that older age was associated with a lower risk of the development of Long COVID, but only non-hospitalized patients were included in this study [66]. Contradicting results have also been found in regards to ethnicity. A recent study using registry data found that ethnic minorities had a higher risk of Long COVID [67], whereas a meta-analysis associated white ethnicity with an increased risk of Long COVID [62].

Other factors have also been linked to an increased risk of Long COVID development. Obesity, smoking, and several pre-existing comorbidities are associated with the disease [61–63, 66]. Additionally, individuals who

experienced more severe acute COVID-19 are at higher risk of developing Long COVID [60, 63].

1.1.6. Diagnosis and treatment of Long COVID

Although some diagnostic tools for certain aspects of Long COVID exist, comprehensive and standardized diagnostic criteria specific to Long COVID are mostly still under development [14]. The final determination of the disease is made by a differential diagnosis. This can take a long time as numerous tests have to be performed to rule out other diseases [68]. Identification of biomarkers for the diagnosis of Long COVID is critical for improving diagnostic accuracy and managing the disease [14, 68].

Furthermore, until now, no standard treatment for Long COVID exists and interventions are often individualized based on patients' symptoms and clinical needs [69]. Treatments for specific components of Long COVID have been effective for specific patient groups. For instance, strategies for ME/CFS can also be effective for individuals with Long COVID [14]. Pharmacologic interventions may be used to manage symptoms such as pain, fatigue, dyspnea, and cognitive dysfunction. In addition, non-pharmacologic approaches such as physical therapy, occupational therapy, cognitive behavioral therapy, and pulmonary rehabilitation can be beneficial for Long COVID patients [69]. Smaller pilot studies evaluating specific treatment options exist and several trials are in progress [14]. Various guidelines have been published, including a German guideline, in which recommendations on treating and managing Long COVID are given [18].

1.2. Digital cohort studies

Cohort studies have long been a cornerstone of epidemiologic research, providing valuable insights into prevalence, risk factors, and long-term health outcomes within a defined population. However, in recent times, cohort studies have faced significant challenges, particularly with regard to participant recruitment, retention, and engagement. Traditional cohort studies often rely on time-consuming and resource-intensive recruitment methods, such as face-to-face recruitment in clinical settings or community outreach efforts, which can be inefficient and costly. Moreover, participant attrition over time is a common

issue in longitudinal studies, leading to reduced generalizability of outcomes and statistical power [70]. In addition, the COVID-19 pandemic brought its own challenges to conducting health research. As in-person interactions and gatherings were restricted, researchers had to rely on other ways of engaging participants [71]. In this context, digital research methodologies offer promising solutions to overcome the limitations of traditional cohort studies in general and especially during the COVID-19 pandemic. However, web-based studies come with their own challenges, including lower response rates compared to traditional studies and concerns regarding the reliability and validity of the data obtained [72]. Nevertheless, Ebert et al. found that while the response rate for web-based questionnaires was lower than paper-based, they were more cost-effective and had lower numbers of missing values [73]. They found that the non-responders in the groups did not differ in regard to socioeconomic variables. This might imply that the lower response rate in web-based surveys does not necessarily increase the selection bias [73]. Apart from the cost reductions, there are several other advantages to web-based studies. Generally, data quality is better since validation checks can be incorporated and the return rate is quicker than postal questionnaires [72]. Additionally, digital research methods can improve participant engagement and retention in cohort studies. A meta-analysis found that studies that used more emerging retention strategies, like keeping participants up-to-date with study news and events using study websites and social media, were associated with improved retention rates [74].

The results of this thesis are based on data from the DigiHero study, a population-based prospective cohort study with digital study participation in Germany (DRKS Registration-ID: DRKS00025600). It was initiated in Halle (Saale) in January 2021 [75]. Since then, the study was expanded and includes over 90,000 participants from 14 German federal states. A detailed description can be found elsewhere [76].

1.3. Research question

Overall, Long COVID is a burden on healthcare systems. Prevalence estimates vary greatly worldwide and in Germany. Furthermore, even four years after the start of the pandemic little is known about the causes behind it and influencing factors. As the pandemic progressed, new SARS-CoV-2 variants emerged and vaccines were developed. The dynamic nature of the pandemic and the evolving landscape of COVID-19 interventions further complicate efforts to assess the burden of Long COVID in Germany. One way to investigate this, is through cohort studies. In recent years, online studies are commonly used and they offer a unique opportunity to study diseases during a pandemic where in-person interactions are limited.

1. The present thesis investigates the prevalence of Long COVID in the study population using the population-based online cohort study DigiHero. Additionally, the effect of virus variants, previous vaccinations, and infections on Long COVID is examined. The aim is to determine whether the time since the last vaccination or infection influences the development of Long COVID and if Long COVID symptoms vary by variant.

2. To gain a more comprehensive understanding of the Long COVID burden, the early recovery of symptoms is analyzed. The focus is on individuals who recovered twelve weeks after SARS-CoV-2 infection, but initially had symptoms four weeks after infection. In addition, the aim is to identify symptom groups present four weeks after infection and study their association with early recovery of Long COVID.

2. Discussion

Of all infected individuals 5,098 (45%) reported symptoms four weeks after SARS-CoV-2 infection and 2,822 (25%) after twelve weeks. However, this varied by SARS-CoV-2 variant. Participants infected with the Omicron variant had the lowest risk of developing Long COVID, followed by the Delta, Alpha, and Wildtype variants. While the vaccination status was not associated with the development of Long COVID, a prior SARS-CoV-2 infection, in case the individual did not develop Long COVID previously, offered protection. Other factors associated with the development of Long COVID were female sex, older age, and a more severe course of acute infection. The Long COVID symptom patterns were similar across all variants, except, that individuals infected with the Omicron variant reported smell and taste disorders less frequently.

Of the 5,098 individuals that still had symptoms after four weeks, 48% have recovered twelve weeks after infection. The factors associated with symptom persistence were similar to the factors associated with development of symptoms. Fatigue, shortness of breath, and cognitive impairment were the most common symptoms in DigiHero participants with Long COVID. Four symptom groups were identified that can be described as diverse symptoms including typical Long COVID symptoms, symptoms of an acute infection, gastrointestinal symptoms, and cardiorespiratory symptoms. While the second group was positively associated with early recovery from Long COVID, the first and fourth group were both negatively associated with early recovery. The third group was not associated with early recovery.

The individual findings have been thoroughly discussed in the publications (P1, P2). Thus, the following discussion attempts to place these results within a broader context, by examining their implications within the larger framework of the Long COVID burden in Germany.

2.1. Aspects of the Long COVID burden in Germany

The burden of Long COVID encompasses various dimensions, including the prevalence, the impact on individuals, healthcare systems, and society, as well as the economic and social consequences.

Precise estimates of the prevalence of Long COVID are difficult to ascertain due to various reasons, including varying definitions, diagnostic criteria, and reporting mechanisms. In the DigiHero study, 45% and 25% of SARS-CoV-2 infected individuals reported at least one symptom four weeks and twelve weeks after the infection, respectively. This data is based on self-reports, however a discrepancy in prevalence estimates between reporting methodology has been noted. A systematic review identified that studies utilizing self-reported data tend to yield higher prevalence estimates of Long COVID compared to those using clinical coding documented within healthcare records. The pooled estimate from the review indicated a prevalence of 43.9% among studies using self-reported data and 13.6% in studies based on clinical coding [25]. While self-reported data may be influenced by recall bias and symptom perception, clinical coding might underestimate the prevalence of Long COVID due to underdiagnosis or incomplete documentation of symptoms. The systematic review additionally identified that studies defining Long COVID as having at least one symptom tended to report higher prevalence than studies that assessed a specific symptom [25]. The DigiHero study also used the definition that at least one symptom had to be present. Employing a stricter definition in DigiHero, where Long COVID was defined as having at least one moderate symptom, resulted in a decrease in the prevalence of symptoms persisting twelve weeks after SARS-CoV-2 infection from 25% to 8% (P1). These identified differences in reporting methodology may suggest that although a notable proportion of individuals infected with SARS-CoV-2 suffer from long term symptoms, fewer experience severe impairments requiring medical intervention. In the DigiHero study, it was observed that only approximately 36% of individuals experiencing symptoms four weeks after the infection visited a doctor due to their symptoms. If the criterion for defining Long COVID was based on the act of seeking medical care for these symptoms, the estimated prevalence four weeks after infection would be 16% compared to 45% (P2).

The burden of Long COVID extends beyond the prevalence of the disease. It presents several challenges for healthcare systems. First, Long COVID is associated with a substantial increase in the utilization of healthcare services [77]. In comparison to other acute respiratory infections, COVID-19 increased the use of outpatient services during the post-infection period [78]. Additionally, compared to a control group, the number of new diagnostics and new prescriptions six months after infection was higher in SARS-CoV-2 infected individuals [79]. In the six months following infection, there was an increase in the utilization of spirometry, chest computed tomography scans, and electrocardiography among individuals previously admitted to the intensive care unit with SARS-CoV-2 [80].

Second, the influx of Long COVID patients is straining healthcare resources, including healthcare facilities and staff. The COVID-19 pandemic already severely affected healthcare workers. They experienced an increased work load and little rest which can lead to the high levels of stress, anxiety and depression that were found in healthcare workers [81]. Physicians voiced difficulties in diagnosing Long COVID patients due to the lack of a comprehensive definition or guideline [82]. Additionally, they faced challenges in managing these patients overall. Individuals suffering from Long COVID, on the other hand, encounter obstacles in obtaining care [83]. Specific barriers include long waiting times and communication gaps across services. Overall, this can lead to patients being dissatisfied with the care they receive [84]. The doctor-patient relationship, however, is crucial for a positive experience of care [83, 85]. Results from the DigiHero study indicate that individuals seeking medical care are less likely to recover early from Long COVID (P2). This emphasizes the need for a prompt identification and management of Long COVID.

Finally, COVID-19 is associated with increased healthcare costs [86]. In the United States the medical costs for Long COVID per person annually are projected to be about $9000 [87]. Similarly, a study conducted in Germany identified an average cost of €3242 per Long COVID patient [86] and another study in Israel found that Long COVID was associated with a doubling of the direct medical costs compared to the costs before infection [77].

Moreover, the COVID-19 pandemic also had other economic consequences as the illness-related absences from work increased during the COVID-19 pandemic [88]. On average, illness reduced labor force participation by about seven percentage points and COVID-19 absences have reduced the labor force in the United States by approximately 500,000 people. The impact of this loss was equivalent to roughly $62 billion in forgone earnings [88]. In the United Kingdom it was estimated that 0.56% of the employed workforce may have long-term health issues and disabilities from Long COVID [89]. This could include absence from work or restrictions on the amount or type of work they can do. The estimated number of employment losses caused by Long COVID is around 3.7%. The economic impact of Long COVID also includes reduced quality of life and loss of productivity. Kerksieck et al. found that self-reported Long COVID was strongly associated with a reduction in work ability 12 months post diagnosis [90]. Among individuals that had not recovered, higher levels of health impairment were also associated with lower work ability including ability to undertake physically and intellectually demanding tasks. Combining the effect of lower productivity, higher sick leaves, lower hours, and increased unemployment or inactivity, Long COVID could have caused an output loss of 0.1-0.2% in 2021 and 0.2-0.3% in 2022 in Europe [91]. Furthermore, Long COVID had a notable effect on quality of life [92]. Particular, the health-related quality of life among these patients was found to be comparative to individuals experiencing heart failure.

Disability-adjusted life years (DALY) is a metric commonly used to quantify the burden of disease and injuries on populations. It combines the years of life lost due to premature mortality and years lived with disability (YLD) into a single measure. These measures are valuable tools for assessing the burden of Long COVID. An Australian study found that during the first Omicron wave the total YLDs for acute COVID-19 and Long COVID combined were comparable to the YLDs caused by chronic kidney disease and ischemic heart disease. Overall, the COVID-19 disease burden, including Long COVID, accounted for 2.4% of all health loss during this period [93]. Furthermore, two years after SARS-CoV-2 infection Long COVID contributed 80.4 DALYs per 1,000 persons among non-hospitalized and 642.8 DALYs per 1,000 persons among hospitalized individuals

[94] and in general COVID-19 was the leading cause of DALYs globally in 2021 [95].

2.2. The future burden of Long COVID

In May 2023 the WHO declared an end to the COVID-19 public health emergency [96] and subsequently COVID-19 entered an endemic state [97]. However, the impact of Long COVID is likely to persist even as the acute phase of the pandemic wanes. The future development of Long COVID will be influenced by several factors, including vaccination, the emergence of new variants of the virus, the potential for reinfection, and new treatment options.

The emergence of new SARS-CoV-2 variants shaped the pandemic. With each new variant, there are concerns about its transmissibility, virulence, and other potential effects. After the emergence of the Omicron variant in 2021, it quickly became the dominant variant [98]. The results from the DigiHero study suggest that the risk of developing Long COVID is lowest for individuals with the Omicron variant, followed by the Delta, Alpha, and Wildtype variants (P1). This finding is supported by other studies that also found a risk reduction in individuals infected with Omicron compared to the other variants [99–102]. Still, it is unknown how a future variant could affect the risk of Long COVID.

Concurrently, vaccinations undoubtedly changed the course of the pandemic. In the first year of COVID-19 vaccination estimations suggest that vaccinations averted almost 20 million deaths from COVID-19 [103]. Additionally, vaccinated individuals are less likely to be hospitalized and have a severe course of COVID-19 [104]. Furthermore, vaccinations can reduce the likelihood of reinfection [105]. Nevertheless, the effect of vaccinations on Long COVID is less clear. While a recent meta-analysis found an association between vaccinations administered before SARS-CoV-2 and a lower risk of Long COVID [106], the results of the DigiHero study show that this effect was not evident when the different variants were taken into account (P1). This finding is supported by a large observational study in Norway that reported similar results [107]. A possible lack of protection by vaccination regarding Long COVID symptoms could pose a challenge in the future. Nevertheless, the COVID-19 vaccination protects against infection and reduces the severity of infection, thereby also reducing the risk of Long COVID.

Still, it is likely that the protection has to be renewed annually. In Germany, the uptake of SARS-CoV-2 booster vaccination was low in the infection season in 2022/2023 [76]. Therefore, it remains to be seen how vaccinations continue to influence the burden of Long COVID. Besides the effect of vaccination before SARS-CoV-2 infection on Long COVID, the effect of vaccination after the infection has also been investigated. However, vaccination was not associated with a change in Long COVID symptoms [106].

The emergence of new variants is linked to an increased risk of reinfection with SARS-CoV-2 [108], but most reinfections tend to be mild [109]. However, there is still limited information on the risk of Long COVID following reinfection. The results from the DigiHero study show that the risk of developing Long COVID is reduced in individuals who were previously infected and did not develop Long COVID at the time (P1). Additionally, the findings suggest that this effect is not dependent on the time since previous infection. Similar findings have been reported by studies in the United Kingdom and Italy [110, 111]. This would be a positive aspect regarding the perspective of Long COVID, as there is the possibility that the burden of Long COVID will decrease as new cases of the disease become less likely. Nevertheless, the question of how reinfections influence individuals that already suffer from Long COVID remains. Peghin et al. found that reinfection was not associated with the worsening of Long COVID, but more research is needed [112].

Several medications are in use to manage the acute SARS-CoV-2 infection. Antivirals are able to inhibit virus replication and can prevent disease progression to a more severe form [113]. Research is ongoing to determine the effect of these drugs on the development of Long COVID. A recent systematic review found evidence of a potential benefit of this treatment, but it is noted that further studies are needed [114]. A general Long COVID medication could have the potential to notably impact the future burden of the disease, but as the underlying biological mechanisms of Long COVID are under investigation, it is difficult to find an effective treatment.

2.3. The applicability of an online platform to study Long COVID

Online surveys have emerged as a valuable tool for studying COVID-19 and its impact, offering several advantages over traditional research methods [115]. Particularly during the pandemic, online studies have provided researchers with the ability to reach a large and diverse population quickly and efficiently. By facilitating remote data collection, online surveys eliminate the need for in-person visits, thereby reducing logistical barriers to study participation [115]. This remote approach not only minimizes the burden on participants but also proves especially beneficial when studying Long COVID, as individuals experiencing persistent symptoms may find it challenging to visit a study center in person. On the other hand, it is also more practicable for healthy individuals, as the time needed for study participation is minimized.

Furthermore, web-based surveys are more cost-effective than paper-based surveys [73]. Moreover, online studies enable fast data collection, with shorter response times and the ability to collect data on current topics in almost real-time [116]. This advantage was demonstrated in the DigiHero study, where a survey about the mental health of participants was distributed just eight days after the Russian invasion of Ukraine in 2022 [117]. Through this rapid data collection it was possible to study the impact of significant events promptly after their occurrence, highlighting the agility and responsiveness of online research methodologies.

Despite these advantages, disparities in digital literacy, internet access, and technological resources may limit the participation of certain populations, such as older adults, individuals from rural areas, and those with low socioeconomic status [115]. Researchers must be aware of these access disparities when using an online approach to study Long COVID.

2.4. Strengths and limitations

The biggest strength of the findings is the large population-based sample. At the time of analysis, 48,826 individuals were enrolled in the DigiHero study. Additionally, the study includes mainly individuals who were not hospitalized during the acute SARS-CoV-2 infection, offering insights into the burden of Long COVID among non-hospitalized individuals. However, there are also several limitations. All the information in the DigiHero study is based on self-reports, therefore the proportion of individuals with Long COVID might be overestimated. In addition, self-reported data can lead to misclassification of infections, vaccinations, and SARS-CoV-2 variants. Some risk factors for Long COVID could not be taken into account, as this information was not available. This could limit the study ability to account for all factors influencing the development of Long COVID and lead to biased results. Moreover, the lack of an appropriate control group poses challenges in determining whether the observed persisting symptoms are unique to individuals infected with SARS-CoV-2. Without a suitable comparison group, it is difficult to ascertain whether the symptoms reported in the study population are directly attributable to SARS-CoV-2 infection or if they are prevalent in the general population regardless of infection.

Finally, a systematic limitation is that children could not be assessed, as the DigiHero study only includes individuals older than 18. Therefore, the findings of the burden of Long COVID are limited to adults. One meta-analysis found that the pooled Long COVID prevalence in children was 23% [118]. A cohort study that investigated the prevalence of both, adults and children, found that the Long COVID prevalence was lower in children [119]. The symptoms reported by children suffering from Long COVID are similar to the symptoms of adults [118]. Without inclusion of pediatric populations, our understanding of the full spectrum of the Long COVID burden in Germany remains incomplete.

In general, the previously described limitations of an online study must be taken into account when interpreting the results.

2.5. Conclusion

Overall, the burden of Long COVID is multifaceted, with implications for individuals, healthcare systems, and society as a whole. This thesis gives an overview of the Long COVID burden in Germany by using a population-based online cohort study. This is crucial for guiding public health strategies and optimizing resource allocation to address the challenges posed by Long COVID.

The prevalence of symptoms persisting twelve weeks after SARS-CoV-2 infection varies between 8% and 25%, depending on the stringency of the criteria employed. Long COVID encompass a wide range of symptoms, and often requires ongoing medical care. The increased utilization of healthcare services and higher costs are placing an additional strain on the healthcare system in Germany. Additionally, Long COVID has a notable impact on the economy due to illness-related absences, reduced quality of life, and loss of productivity.

Despite advances in understanding Long COVID, numerous uncertainties persist. The biological mechanisms underlying Long COVID are still unknown and the trajectory of the future Long COVID burden also remains uncertain. Findings from the DigiHero study suggest an association between different virus variants and Long COVID, with individuals infected with the Omicron variant having the lowest likelihood of developing Long COVID. However, the potential impact of future variants on Long COVID risk remains unclear. Encouragingly, prior infection with SARS-CoV-2, in individuals who did not experience symptoms previously, appears to offer protection against Long COVID. Furthermore, vaccinations hold promise in mitigating the Long COVID burden, although the uptake of booster doses has been limited in the 2022/23 season.

During the pandemic, online studies offered a unique opportunity to study Long COVID, leveraging their strengths in data collection and accessibility. By addressing the associated challenges, researchers can contribute valuable insights to public health research and policy development.

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4. Theses

(1) Of all SARS-CoV-2 infected individuals, 45% and 25% reported at least one symptom four weeks and twelve weeks after the infection, respectively.

(2) Approximately 50% of the individuals reporting symptoms four weeks after the infection have recovered twelve weeks after the infection.

(3) Participants infected with Wildtype SARS-CoV-2 had the highest Long COVID risk (adjusted odds ratio: 6.44, 95% confidence interval: 5.49; 7.56).

(4) A previous infection was strongly associated with a lower Long COVID risk (adjusted odds ratio: 0.14, 95% confidence interval: 0.07; 0.25), offering the possibility that the Long COVID burden will decrease in the future.

(5) Vaccination was not associated with a Long COVID risk reduction, but may provide protection through lowering the infection risk and severity of infection.

(6) The factors associated with persistence of symptoms are female sex, older age, a more severe course of acute infection, and being infected with the Omicron variant. They are similar to the factors associated with the development of Long COVID.

(7) Individuals who did not seek medical care had a higher chance of early recovery from Long COVID.

(8) Four weeks after SARS-CoV-2 infection four symptom groups were identified, that can be described as diverse symptoms including typical Long COVID symptoms, symptoms of an acute infection, gastrointestinal symptoms, and cardiorespiratory symptoms.

(9) Long COVID is a burden on the healthcare system, due to increased utilization of healthcare services and high costs. Additionally, the economy is impacted due to illness-related absences, reduced quality of life, and loss of productivity.

5. Publications

List of included publications

1. **Association between virus variants, vaccination, previous infections, and post-COVID-19 risk (P1)**

Diexer S, Klee B, Gottschick C, Xu C, Broda A, Purschke O, Binder M, Frese T, Girndt M, Hoell JI, Moor I, Gekle M, Mikolajczyk R. International Journal of Infectious Diseases 2023;136:14–21. https://doi.org/10.1016/j.ijid.2023.08.019

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2. **Insights into early recovery from Long COVID—results from the German DigiHero Cohort (P2)**

Diexer S, Klee B, Gottschick C, Broda A, Purschke O, Binder M, Gekle M, Girndt M, Hoell JI, Moor I, Sedding D, Rosendahl J, Mikolajczyk R. Scientific Reports 2024;14. https://doi.org/10.1038/s41598-024-59122-3

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Personal contribution to publications

P1: Diexer S, Klee B, Gottschick C et al. 2023

Development of the questionnaire and the research question, data cleaning, statistical analysis, reporting of results, interpretation of results, writing of the manuscript, revision of the manuscript.

P2: Diexer S, Klee B, Gottschick C et al. 2024

Development of the questionnaire and the research question, data cleaning, statistical analysis, reporting of results, interpretation of results, writing of the manuscript, revision of the manuscript.

Publication 1 (P1)

Diexer S, Klee B, Gottschick C, Xu C, Broda A, Purschke O, Binder M, Frese T, Girndt M, Hoell JI, Moor I, Gekle M, Mikolajczyk R. **Association between virus variants, vaccination, previous infections, and post-COVID-19 risk.** International Journal of Infectious Diseases 2023;136:14–21. https://doi.org/10.1016/j.ijid.2023.08.019

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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.

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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].

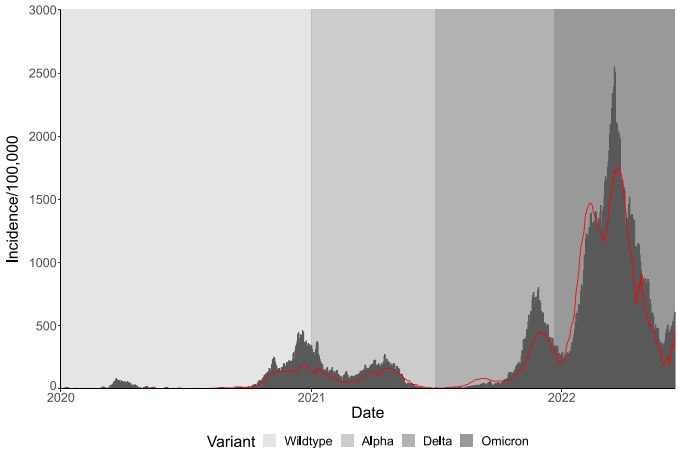

Figure 1. Daily Incidence per 100,000 people in the DigiHero Cohort from January 01, 2020 to June 15, 2022 by time. The red line indicates the reported national Incidence per 100,000 people in Germany [26].

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

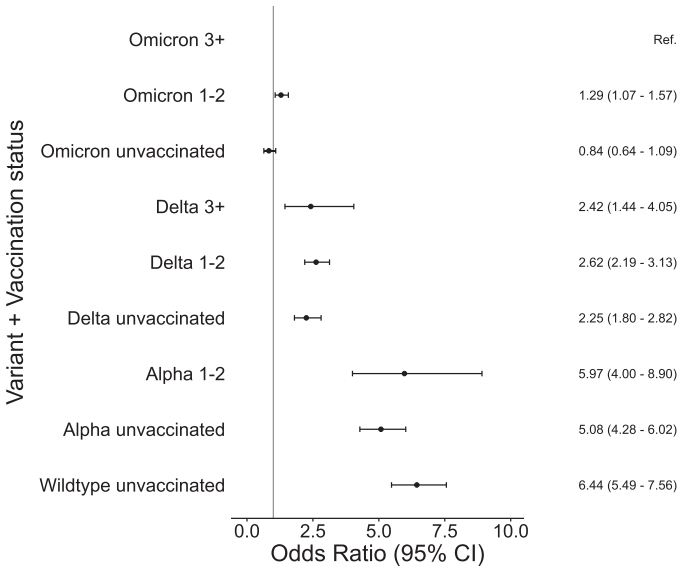

Figure 2. Association between post-COVID-19 condition and the virus variants and vaccination status (the numbers in the legend refer to number of received vaccine doses), adjusted for sex, age, country of birth, federal state, living in a big city, education, previous infection, and course of acute infection. 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.

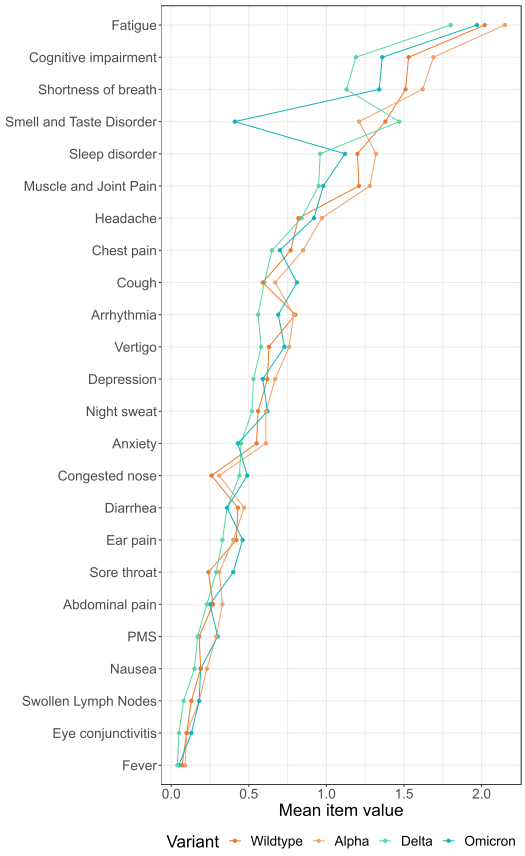

Figure 3. Symptoms reported ≥12 after infection, by variant, N = 2822.

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.

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Publication 2 (P2)

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Insights into early recovery from Long COVID—results from the German DigiHero Cohort

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65 million people worldwide are estimated to suffer from long-term symptoms after their SARS-CoV-2 infection (Long COVID). However, there is still little information about the early recovery among those who initially developed Long COVID, i.e. had symptoms 4–12 weeks after infection but no symptoms after 12 weeks. We aimed to identify associated factors with this early recovery. We used data from SARS-CoV-2-infected individuals from the DigiHero study. Participants provided information about their SARS-CoV-2 infections and symptoms at the time of infection, 4–12 weeks, and more than 12 weeks post-infection. We performed multivariable logistic regression to identify factors associated with early recovery from Long COVID and principal component analysis (PCA) to identify groups among symptoms. 5098 participants reported symptoms at 4–12 weeks after their SARS-CoV-2 infection, of which 2441 (48%) reported no symptoms after 12 weeks. Men, younger participants, individuals with mild course of acute infection, individuals infected with the Omicron variant, and individuals who did not seek medical care in the 4–12 week period after infection had a higher chance of early recovery. In the PCA, we identified four distinct symptom groups. Our results indicate differential risk of continuing symptoms among individuals who developed Long COVID. The identified risk factors are similar to those for the development of Long COVID, so people with these characteristics are at higher risk not only for developing Long COVID, but also for longer persistence of symptoms. Those who sought medical help were also more likely to have persistent symptoms.

Keywords SARS-CoV-2, Long COVID, COVID-19, Post COVID Condition

Based on conservative estimates, 65 million people worldwide suffer from long-term symptoms after their SARS-CoV-2 infection[1]. These persistent symptoms are commonly referred to as Long COVID, but there are several different terms and definitions. The World Health Organization (WHO) refers to it as "post COVID-19 condition" and defines it as symptoms persisting in individuals with a history of probable or confirmed SARS-CoV-2 infection that cannot be explained by an alternative diagnosis. For the definition to be fulfilled, these symptoms should be present three months after infection and last for at least two months[2]. The UK National Institute for Health and Care Excellence (NICE) guideline suggests a distinction between symptoms that are present between 4 and 12 weeks after infection (ongoing symptomatic COVID-19) and symptoms that persist beyond 12 weeks (post-acute COVID-19 syndrome). The term "Long COVID" is meant to include both[3].

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Long COVID comprises a wide range of symptoms. The most common symptoms include fatigue, headache, shortness of breath, muscle weakness and joint pain[4–6]. Furthermore, individuals suffering from Long COVID symptoms report worse health-related quality of life[7]. These symptoms can vary in severity and duration. Some studies have reported that symptoms persist for 24 months after infection and investigated factors associated with the recovery of symptoms[8–10]. One study showed that younger, male participants without pre-existing depression, anxiety, or cardiovascular disease were more likely to experience improvement of long-term dyspnea[11]. However, there is limited knowledge about the recovery in individuals who initially develop Long COVID symptoms and recover at an early stage.

In this study, we aimed to identify factors associated with the early recovery from Long COVID (i.e. no symptoms 12 weeks after SARS-CoV-2 infection among those who had symptoms 4–12 weeks after infection). Furthermore, we wanted to identify symptom groups present at 4–12 weeks after infection and how those are associated with early recovery.

Methods

Study design

The sample used in this study is part of the population-based prospective cohort study for digital health research in Germany (DigiHero, DRKS Registration-ID: DRKS00025600). The questionnaire and design of the study was described elsewhere[12]. In brief, DigiHero started in the city of Halle (Saxony-Anhalt, Germany) in January 2021 and was later extended to other federal states in Germany. Participants' addresses were taken from population registers and invitations were sent by post. After an online registration, participants received a baseline questionnaire with questions regarding socio-demographic characteristics. The current analysis is based on 48,826 participants, of which 17,008 reported at least one infection, recruited until June 15, 2022.

Questionnaire and measures

In the baseline questionnaire, participants were asked several sociodemographic questions, including their month of birth, sex, country of birth, and education. Education was categorized into three categories (low, medium, high) based on the International Standard Classification of Education (ISCED-97)[13]. If either the participant or one of their parents was not born in Germany, we considered this as having a migration background.

Furthermore, we repeatedly asked participants if they ever had a SARS-CoV-2 infection and those who answered "yes" were subsequently invited to a dedicated questionnaire. In the questionnaire on SARS-CoV-2 infections, we asked the participants about their infection and vaccination dates. In addition, we asked whether they had symptoms and visited a doctor at the time of infection, 4–12 weeks after infection, and 12 or more weeks after infection ("Yes" and "No"). If participants reported that they had any symptoms at the specific time windows, they were asked to rate the severity of 24 different symptoms on a 6-point Likert scale from "not at all" to "very severe" and an additional option "I don't know" (the last option was treated as a missing value in the analyzes). We categorized this into "presence of symptom" if any of the options apart from "not at all" was selected. Furthermore, participants were asked to rate their course of the acute infection ("no symptoms", "mild", "moderate, "severe", and "very severe"). The last two categories were combined ("severe/very severe"). The SARS-CoV-2 variants were classified based on the reported infection date and periods of dominance of specific variants from official surveillance in Germany[14]. We classified participants as having Long COVID if they reported having symptoms 4–12 weeks after infection. Early recovery was classified if they did not report symptoms anymore for the period 12 or more weeks after infection.

For this analysis, we considered only the first infection per participant. In addition, we only included participants for whom the difference between the date of infection and the completion of the survey was more than 12 weeks, so that they could report symptoms for this period. This definition includes 11,333 participants.

Statistical analysis

Descriptive analysis is presented using frequencies and percentages. Backward stepwise logistic regression based on the Akaike Information Criterion was used to identify possible factors associated with the early symptom recovery. The ten variables selected for inclusion in the regression analysis included the available sociodemographic factors and factors associated with the infection (sex, age, education, migration background, federal state, living in a city, self-assessed course of acute infection, virus variant combined with information on the number of previous vaccinations, whether the participant visited a doctor 4–12 weeks after infection, and an interaction term between age and sex). The variables found in the final model were used as adjustments in additional models to determine which individual symptoms present at 4–12 weeks after infection are associated with the early recovery from Long COVID.

Principal components analysis (PCA) was conducted on all symptoms for the time window 4–12 weeks after infection using the symptom scale as metric variable to identify symptom groups. To assist interpretation of the results promax rotation was used, this oblique rotation allows the factors to be intercorrelated[15]. We selected four components for the main analysis, using the scree plot (Fig. S1). To determine if a specific symptom should be included in a symptom group, a score of at least 0.40 on the primary loadings of items after rotation was used as a cutoff. The component scores were used as independent variables in a logistic regression to determine the association between the symptom groups and symptom recovery. The model was adjusted for the variables previously found to be associated with Long COVID recovery in the stepwise logistic regression.

Additionally we performed a sensitivity analysis, with a more conservative definition of Long COVID. A participant had to report at least one symptom as "moderate" to be defined as a Long COVID case and subsequently, persistence was defined only if a having long term symptoms at the time window 4–12 after infection, as well as the time window 12 weeks or more.

We report 95% confidence intervals (CI) for all analyses. All analyses were performed in R (Version 4.2.0)[16].

Ethical approval
The Ethics Committee of the Martin Luther University Halle-Wittenberg (2020-076) approved the study.

Informed consent
The study was conducted following the Helsinki Declaration and informed consent was obtained from all individual participants included in the study.

Results
Characteristics of participants
In total, 5098 (45%) of 11,333 infected individuals reported symptoms for the time window 4–12 weeks after infection, of whom 2441 (48%) reported no symptoms for the time window after 12 weeks. The majority of the analyzed sample were female, with high education, and had no migration background (Table 1). The mean age was 46 (standard deviation = 14). Around 45% of the participants were infected during the Omicron SARS-CoV-2 period. Almost 50% of the participants classified their course of acute infection as "moderate". Of the 5098 individuals, only 181 (4%) were hospitalized during acute infection.

Factors associated with Long COVID recovery
Of the ten variables tested in the stepwise regression, the variables included in the final model were sex, age, self-assessed course of acute infection, the variant and vaccination status, and if participants visited a doctor in the time window 4–12 weeks after their infection. Specifically, women were less likely to recover than men were (Odds Ratio (OR) 0.80, 95% CI 0.69; 0.93). Furthermore, participants between 50 and 69 years old were more likely to still report symptoms after 12 weeks compared to the reference category (18–29 years old, OR 0.73 and 0.75, 95% CI 0.58; 0.91 and 0.58; 0.98). Participants infected during the Omicron period, independent of vaccination status, were most likely to recover early compared to all other considered variants. In addition, participants were more likely to recover early (OR 2.32, 95% CI 2.01; 2.67) if they did not seek medical care 4–12 weeks after infection (Table 2).

In the sensitivity analysis, using a more conservative definition for Long COVID, we identified the same variables using the stepwise regression. While the overall number of participants fulfilling the more restrictive definition of Long COVID was lower, the relative estimates were similar to the estimates for the initial definition, reported in Table 2 (Table S1).

Single symptoms associated with early recovery from Long COVID
We investigated the association of the presence of symptoms at 4–12 weeks after infection with the early recovery until 12 weeks. Hereby, cough was the only symptom identified that had a positive association with early recovery of symptoms (OR 1.18, 95% CI 1.03; 1.35). There was no association with early recovery for having a sore throat, fever, or congested nose. All other symptoms were associated negatively with early recovery (Fig. 1).

Symptom groups associated with early recovery from Long COVID
We identified four distinct groups of symptoms in PCA, and four single symptoms that were not grouped (ear pain, premenstrual syndrome—PMS, swollen lymph nodes and eye conjunctivitis). The first group included diverse symptoms, described as typical symptoms associated with Long COVID like cognitive impairment and fatigue. The second group contained symptoms that could be described as symptoms of an acute infection (congested nose, sore throat, cough, and fever). The third group, termed gastrointestinal symptoms, included the symptoms abdominal pain, diarrhea, and nausea. Lastly, the fourth group was characterized by cardio-respiratory symptoms (chest pain, shortness of breath, and arrhythmia). The total variance explained by the four-factor model was 45% (Table S2).

In the logistic regression using the PCA scores, we found that symptom group 1 and 4 were negatively associated with an early recovery, while symptom group 2 was positively associated with early recovery, and symptom group 3 had no association (Table 3).

In the sensitivity analysis, with a more restrictive definition of Long COVID, the four identified groups were very similar. The symptoms headache, vertigo, and smell and taste disorder were not grouped anymore, however the estimates from the logistic regression using the PCA resulted in similar associations as the model presented in Table 3 (data not shown).

Recovery from specific symptoms
The three most commonly reported symptoms at 4–12 weeks after infection were fatigue, shortness of breath and cognitive impairment. This did not change at the time window after 12 weeks. The greatest reductions were seen in fatigue, shortness of breath and cough (Fig. 2).

Discussion
Using a large sample of individuals suffering from symptoms in the time window 4–12 weeks after SARS-CoV-2 infection, we studied factors associated with the early recovery from Long COVID. These factors included male sex, younger age, a milder self-assessed course of acute infection, being infected during SARS-CoV-2 Omicron dominance, and not seeking medical 4–12 weeks after infection. Additionally, having a cough at 4–12 weeks was positively associated with early recovery. Fatigue, shortness of breath, and cognitive impairment were the

		Overall	Not Recovered[a]	Recovered[a]
		N = 5098	N = 2657	N = 2441
Sex	Male	1432 (28.1%)	695 (26.2%)	737 (30.2%)
	Female	3655 (71.7%)	1956 (73.6%)	1699 (69.6%)
	Diverse	2 (0.0%)	1 (0.0%)	1 (0.0%)
	NA	9 (0.2%)	5 (0.2%)	4 (0.2%)
Age	18–29	597 (11.7%)	281 (10.6%)	316 (12.9%)
	30–39	1005 (19.7%)	429 (16.1%)	576 (23.6%)
	40–49	1068 (20.9%)	553 (20.8%)	515 (21.1%)
	50–59	1264 (24.8%)	734 (27.6%)	530 (21.7%)
	60–69	624 (12.2%)	360 (13.5%)	264 (10.8%)
	70 +	158 (3.1%)	89 (3.3%)	69 (2.8%)
	NA	382 (7.5%)	211 (7.9%)	171 (7.0%)
Migration Background	No	4204 (82.5%)	2168 (81.6%)	2036 (83.4%)
	Yes	854 (16.8%)	462 (17.4%)	392 (16.1%)
	Not specified/Unknown	40 (0.8%)	27 (1.0%)	13 (0.5%)
Federal State[b]	Saxony-Anhalt	2089 (41.0%)	1058 (39.8%)	1031 (42.2%)
	Baden-Württemberg	58 (1.1%)	31 (1.2%)	27 (1.1%)
	Bavaria	565 (11.1%)	257 (9.7%)	308 (12.6%)
	Berlin	69 (1.4%)	37 (1.4%)	32 (1.3%)
	Brandenburg	349 (6.8%)	184 (6.9%)	165 (6.8%)
	Hamburg	58 (1.1%)	25 (0.9%)	33 (1.4%)
	Rhineland-Palatinate	355 (7.0%)	185 (7.0%)	170 (7.0%)
	Saxony	1461 (28.7%)	831 (31.3%)	630 (25.8%)
	Other	14 (0.3%)	9 (0.3%)	5 (0.2%)
	NA	80 (1.6%)	40 (1.5%)	40 (1.6%)
Living in a city with 500.000 inhabitants	No	4521 (88.7%)	2360 (88.8%)	2161 (88.5%)
	Yes	497 (9.7%)	257 (9.7%)	240 (9.8%)
	NA	80 (1.6%)	40 (1.5%)	40 (1.6%)
Education	Low	199 (3.9%)	95 (3.6%)	104 (4.3%)
	Medium	1776 (34.8%)	967 (36.4%)	809 (33.1%)
	High	2833 (55.6%)	1437 (54.1%)	1396 (57.2%)
	NA	290 (5.7%)	158 (5.9%)	132 (5.4%)
Number of vaccinations preceding infection	0	2238 (43.9%)	1510 (56.8%)	728 (29.8%)
	1	230 (4.5%)	119 (4.5%)	111 (4.5%)
	2	967 (19.0%)	433 (16.3%)	534 (21.9%)
	3	1653 (32.4%)	593 (22.3%)	1060 (43.4%)
	4	10 (0.2%)	2 (0.1%)	8 (0.3%)
Variant of SARS-CoV-2	Wildtype	956 (18.8%)	706 (26.6%)	250 (10.2%)
	Alpha	892 (17.5%)	627 (23.6%)	265 (10.9%)
	Delta	980 (19.2%)	489 (18.4%)	491 (20.1%)
	Omicron	2270 (44.5%)	835 (31.4%)	1435 (58.8%)
Self-assessed course of acute infection	No symptoms	69 (1.4)	27 (1.0)	42 (1.7)
	Mild	1906 (37.4%)	801 (30.1%)	1105 (45.3%)
	Moderate	2479 (48.6%)	1353 (50.9%)	1126 (46.1%)
	Severe/very severe	638 (12.5%)	472 (17.8%)	166 (6.8%)
	NA	6 (0.1%)	4 (0.2%)	2 (0.1%)
Visited a doctor 4–12 weeks after infection	Yes	1828 (35.9%)	1252 (47.1%)	576 (23.6%)
	No	3237 (63.5%)	1395 (52.5%)	1842 (75.5%)
	NA	33 (0.6%)	10 (0.4%)	23 (0.9%)

Table 1. Characteristics of participants who reported SARS-CoV-2 infection and symptoms in the time window 4–12 weeks after infection. [a]Within 12 weeks after infection. [b]DigiHero did not target an equal coverage of all regions. NA, not available.

Early Recovery from Long COVID			
		OR	95% Confidence Interval
Sex	Male	Ref	
	Female	0.80	0.69; 0.93
Age	18–29	Ref	
	30–39	1.18	0.93; 1.48
	40–49	0.82	0.65; 1.03
	50–59	0.73	0.58; 0.91
	60–69	0.75	0.58; 0.98
	70 +	0.74	0.49; 1.11
Self-assessed course of acute infection	Mild	Ref	
	No Symptoms	1.13	0.64; 2.00
	Moderate	0.74	0.64; 0.85
	Severe/Very Severe	0.45	0.36; 0.57
SARS-CoV-2 variant and number of preceding vaccinations	Omicron and 3 + vaccinations	Ref	
	Omicron and 1–2 vaccinations	0.75	0.59; 0.95
	Omicron and no vaccination	0.83	0.59; 1.17
	Delta and 3 + vaccinations	0.49	0.26; 0.92
	Delta and 1–2 vaccinations	0.55	0.44; 0.67
	Delta and no vaccination	0.41	0.31; 0.54
	Alpha and 1–2 vaccinations	0.21	0.11; 0.38
	Alpha and no vaccination	0.27	0.22; 0.33
	Wildtype and no vaccinations	0.21	0.17; 0.26
Visited a doctor in the time window 4–12 weeks after infection	Yes	Ref	
	No	2.32	2.01; 2.67

Table 2. Variables associated with early recovery (during 12 weeks after infection) from Long COVID—multivariable logistic regression. $N_{All} = 4316$, $N_{Recovered} = 2084$. OR, Odds ratio; Ref, Reference category.

symptoms reported most frequently at both time windows. Furthermore, we identified four symptom groups that can be described as diverse symptoms including typical Long COVID symptoms, symptoms of an acute infection, gastrointestinal symptoms, and cardiorespiratory symptoms. The first and fourth group were both negatively associated with early recovery from Long COVID while the second group was positively associated with early recovery. This could be an indicator that there were two groups of individuals suffering from Long COVID in the initial phase. One group with symptoms, such as fatigue, that appear quickly after infection and persist later, and another group that is still dealing with lingering symptoms of an acute infection, but who will eventually recover at an early stage.

Multiple studies tried to identify Long COVID symptom clusters and patterns[17–21]. One study that looked at clusters in relation to the SARS-CoV-2 variants identified three groups of symptoms that clustered consistently across variants. These three groups included a cardiorespiratory cluster, a central neurological cluster, and a multi-organ systemic inflammatory cluster. However, overall the number of clusters differed per variant[18]. Comparable to our results one study found five clusters including gastrointestinal, airway, and cardiopulmonary clusters[19]. Another study described three clusters, where cluster one was characterized by symptoms related to pain and the other by cardiorespiratory symptoms. The third one was generally associated with less symptoms[20]. Furthermore, one study identified four distinct clusters, categorized as diverse systemic, neurocognitive, cardiorespiratory, and musculoskeletal[17]. Lastly, other research suggested three clusters where cluster 1 could be described as diverse systemic, cluster 2 included cardiorespiratory symptoms like shortness of breath, and the last one is dominated by neurological symptoms[21]. All of these studies have found a group of symptoms that include cardiorespiratory symptoms, which is similar to the symptom group 4 we identified. However, these studies used different analytic approaches to identify Long COVID symptom groups, which makes it difficult to compare the findings. Nevertheless, our findings are in line with previous studies and additionally could help in the early identification of individuals whose symptoms persist longer.

Multiple studies have identified cough as a common Long COVID symptom[4–6,21], while we found that cough was associated with an early recovery of symptoms. However, we do not see a contradiction between these studies and our findings. Almost 20% of participants with symptoms after 12 weeks still report cough as a symptom, and while cough was associated with early symptom recovery in our study, this doesn't imply universal recovery. In our analysis, cough was grouped with symptoms such as sore throat, whereas a separate group encompassed more severe respiratory symptoms like shortness of breath, which was linked to prolonged symptom persistence. This leads us to the hypothesis that distinct groups of individuals exist, with cough potentially manifesting as either a chronic symptom or a lingering remnant of acute infection.

Most previous studies focused on identifying risk factor in regards to developing Long COVID, in contrast, there is limited information on early recovery from Long COVID. One study found that male sex is associated with recovery[22], while another study found an association of recovery and COVID-19 severity[23]. This is in line

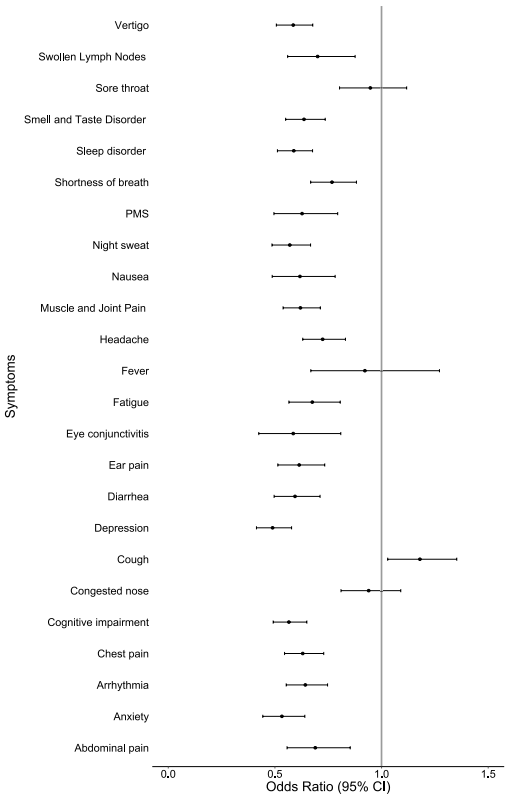

Figure 1. Association of symptoms present at 4–12 weeks after infection with early recovery from Long COVID, adjusted for sex, age, self-assessed course of acute infection, variant + vaccination status, and if a participant visited a doctor 4–12 weeks after infection.

	Recovery of Long COVID	
	aOR[a]	95% Confidence Interval
Symptom group 1[b]	0.48	0.43; 0.55
Symptom group 2[c]	1.16	1.06; 1.28
Symptom group 3[d]	1.00	0.90; 1.10
Symptom group 4[e]	0.87	0.79; 0.96

Table 3. Association of symptom groups using PCA scores in the time window 4–12 weeks with early recovery from Long COVID. [a]Adjusted for sex, age, course of acute infection, variant + vaccination status and if a participant visited a doctor 4–12 weeks after infection. [b]Symptoms included: cognitive impairment, depression, fatigue, sleep disorder, anxiety, muscle and joint pain, night sweat, smell and taste disorder, vertigo, headache. [c]Symptoms included: congested nose, sore throat, cough, fever. [d]Symptoms included: abdominal pain, diarrhea, nausea. [e]Symptoms included: chest pain, shortness of breath, arrhythmia. aOR, adjusted Odds Ratio.

with our findings. Several risk factors for Long COVID have been identified including female sex, younger age, smoking, a high Body-Mass-Index, and comorbidities[21,24], and it is likely that risk factors for Long COVID also influence the symptom recovery. However, a recent study in Germany found that men were less likely to recover from cognitive deficits[25]. This is contrary to our finding that men are more likely to recover. Future studies should investigate if individual symptom recovery differs by sex. Furthermore, several studies investigated the influence of different SARS-CoV-2 variants on Long COVID risk and showed a strong risk reduction in individuals infected

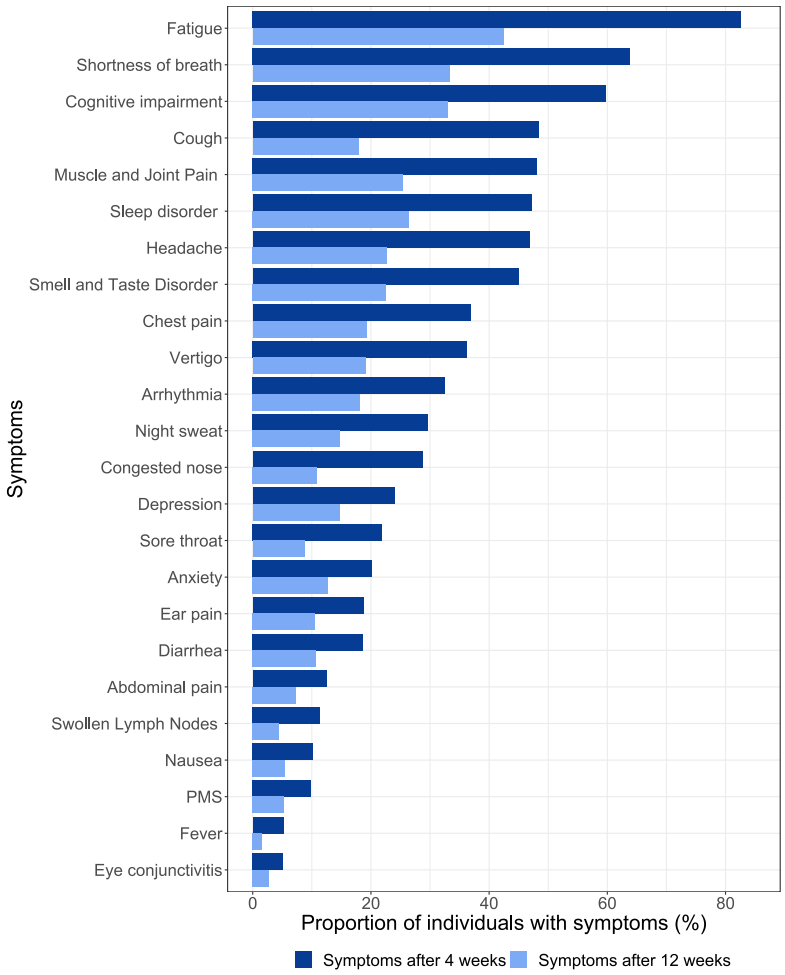

Figure 2. Proportion of individuals with symptoms 4 to 12 weeks and more than 12 weeks after infection.

with Omicron SARS-CoV-2[12,17,26–28]. These findings are consistent with our results which show that having been infected during the Omicron dominance is associated with an early recovery from Long COVID. Nevertheless, more research is needed to understand which factors influence the (early) recovery of Long COVID.

We found that individuals suffering from symptoms who visited a doctor 4–12 weeks after their SARS-CoV-2 infection were less likely to recover early. A possible explanation could be that the symptoms of individuals who do not seek medical care are less severe and these individuals will then eventually recover fully. Another explanation could be that patients are already concerned about their symptoms at an early time point and therefore want to consult a general practitioner. A study identified that the "wait-and-see approach" was a common non-pharmacological intervention of German general practitioners[29]. This approach is also recommended by the German S1 guideline "Long/ Post-COVID", in case of clinical stability of symptoms after a basic diagnosis[30]. Furthermore, a study observed the importance for patients of being believed and listened to, and at the same time that it was difficult to find a general practitioner who believed their symptoms were real[31]. Furthermore, patients participating in a German study reported that their general practitioner did not take their Long COVID symptoms seriously[32]. This could lead to an overall disappointment and mistrust. Notably, a general lack of knowledge about Long COVID was identified among healthcare professionals[33]. We believe that clinicians' understanding of Long COVID needs to be improved and that special attention should be given to individuals who seek help early. Furthermore, more research regarding Long COVID diagnosis and treatment is needed to help clinicians. Particular emphasis should be placed on the importance of early intervention for individuals

experiencing persistent symptoms following SARS-CoV-2 infection. Prompt identification and management of Long COVID can mitigate the impact on patients' quality of life and long-term health outcomes.

The strength of our study is the large sample systematically recruited from the population. In contrast to studies following patients after hospital stay due to COVID-19, our sample includes mainly participants who did not require hospital treatment. Nevertheless, there are also limitations of this study. All of the information is based on retrospective self-reports, which may introduce recall bias. This could lead to an overestimation of the proportion of people suffering from Long COVID. However, we were able to show that the results were similar for a more restrictive definition of Long COVID. Additionally, we did not use an official classification for the course of acute infection, which could bias the results. Self-reporting could also lead to misclassification of infections, vaccinations and variants. In addition, we do not have information on why participants visited a doctor and what help, if any, was received. This would provide valuable insights into the care individuals receive at an early stage and their satisfaction with that care. In addition, the results might be limited to countries, like Germany, where healthcare is widely available to everyone. As the study is set in Germany, we therefore did not consider that there might be limiting factors in receiving appropriate healthcare that could negatively affect the recovery of symptoms. Furthermore, other known risk factors of Long COVID, like smoking status and comorbidities could not be taken into account, as this information was not available for DigiHero participants yet. This could lead to biased results and especially other comorbidities could also have an impact on the symptom groups. We also could not include an adequate control group with individuals not infected with SARS-CoV-2 to identify if the symptoms are unique to infected individuals. While our study offers valuable insights into Long COVID, it's essential to interpret the findings within the context of these limitations and consider avenues for future research to address these gaps comprehensively.

In summary, we identified factors and symptoms associated with the early recovery from Long COVID. There are indications that there are distinct groups of people suffering from Long COVID, those who still report lingering symptoms of an acute infection but who will recover early and the others whose symptoms will persist longer. Having sought medical help for COVID symptoms was an indicator for a higher risk of persistence.

Data availability

The anonymized data reported in this study can be obtained from the corresponding author upon request. The dataset includes 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 access committee of the DigiHero study, and data transfer will require a signed data access agreement.

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