Prevalence of and Factors Associated With Post-Coronavirus Disease 2019 (COVID-19) Condition in the 12 Months After the Diagnosis of COVID-19 in Adults Followed in General Practices in Germany

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Background. Little is known about the epidemiology of post-coronavirus disease 2019 (COVID-19) condition (PCC) in primary care practices. Therefore, this study aimed to investigate the prevalence of and the factors associated with PCC in the 12 months after the diagnosis of COVID-19 in patients followed in general practices in Germany.

Methods. This retrospective cohort study included adults aged ≥18 years who were diagnosed for the first time with COVID-19 (index date) in 1 of 855 general practices in Germany between October 2020 and August 2021 (Disease Analyzer database; IQVIA). The outcome was the occurrence of PCC 91 to 365 days after the index date. Covariates included age, sex, and comorbidities documented in the 12 months before the index date. The association between covariates and PCC was assessed using a multivariable logistic regression model.

Results. We included 51,630 patients in this study (mean age, 47.1 [standard deviation, 19.8] years; 54.3% women). The prevalence of PCC was 8.3%. Age >30 years (odds ratios [ORs] ranging from 1.40 for 31–45 years to 2.10 for 46–60 years) and female sex (OR = 1.23) were positively and significantly associated with PCC compared with age 18–30 years and male sex, respectively. There was also a significant relationship of PCC with asthma (OR = 1.38), reaction to severe stress, and adjustment disorders (OR = 1.24), and somatiform disorders (OR = 1.23).

Conclusions. Post-COVID-19 condition was found in the 12 months after the diagnosis of COVID-19 in approximately 8% of adults from general practices in Germany. More data from other settings are warranted to confirm these findings.

Keywords: associated factors; Germany; post-COVID-19 condition; prevalence; retrospective cohort study.

Coronavirus disease 2019 (COVID-19) is a viral disorder caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Coronavirus disease 2019 is a systemic condition with a wide range of symptoms of pulmonary (eg, cough, dyspnea, and sputum production) and extrapulmonary nature (eg, diarrhea, abnormal heart rhythm, and headache) [2]. As of June 3, 2022, more than 528 million positive cases have been reported in the world, whereas the number of related deaths is over 6.2 million [3]. In Germany, approximately 26.5 million people have been diagnosed with COVID-19, and 139,300 have died from the disorder. Meanwhile, approximately 12 billion vaccine doses have been administered worldwide. Given the high prevalence of past history of COVID-19 in the general population, it is crucial to better understand the long-term effects of this disease on health.

A growing body of literature has shown that symptoms persist for at least several months in a substantial proportion of people affected by the SARS-CoV-2 [4–15]. For example, a study of 150 patients with noncritical COVID-19 from France revealed that 66% of them were still symptomatic 2 months after symptom onset [5]. Several factors were found to be positively associated with the persistence of symptoms, and these factors were age 40–59 years (vs <30 years) and abnormal auscultation and hospital admission at symptom onset. In another cohort, including 410 symptomatic individuals who tested positive for SARS-CoV-2 in university hospitals in Switzerland, researchers showed that the prevalence of symptoms 7 to 9 months after the diagnosis of COVID-19 was 39.0%, and that the 3 most frequent symptoms were fatigue (20.7%), loss of smell or taste (16.8%), and dyspnea (11.7%) [9]. These findings were corroborated in a systemic review...
and meta-analysis of 50 studies, because the prevalence of post-COVID-19 condition 28 days to 12 months after COVID-19 was 54% in hospitalized individuals and 34% in nonhospitalized individuals [6]. Although these studies have advanced the field, they display several limitations that need to be acknowledged. First, the majority of the previous studies had small sample sizes (ie, less than 1000 participants were included), potentially undermining the generalizability of their findings [5, 9–13, 15]. Second, data were predominantly obtained from hospital settings [4, 5, 8–12], and thus little is known about the occurrence of persistent symptoms in primary care practices, where the majority of patients with COVID-19 have been followed. Third, a substantial proportion of these studies were conducted in 2020 [4, 5, 9, 10, 12, 15], before the start of the COVID-19 vaccination campaign in late 2020 and early 2021 [16]. Because COVID-19 vaccination might, at least partially, protect against the persistence of symptoms [17], the prevalence of post-COVID-19 condition might have decreased over time since the beginning of the pandemic. Fourth, multiple definitions of persistent symptoms were considered based on different time points (eg, 2 [5], 6 [10], and 12 months [11]), and, to the best of the authors’ knowledge, none of these studies used the definition of post-COVID-19 condition provided by the World Health Organization [18], which may have facilitated the comparison of their results. Based on this definition, post-COVID-19 condition includes a wide range of symptoms (eg, abdominal pain, anxiety, and cough) frequently occurring at least 3 months after the onset of initial symptoms, usually lasting at least 2 months, and not explained by a differential diagnosis. Persistent COVID-19 symptoms do not necessarily translate into post-COVID-19 symptoms, especially if they last only a few days or weeks and if they do not have a deleterious impact on daily living. In this context, more data are urgently needed on post-COVID-19 condition in people previously diagnosed with COVID-19.

Therefore, the goal of this retrospective cohort study was to investigate the prevalence of and the factors associated with post-COVID-19 condition in the 12 months after the diagnosis of COVID-19 in patients followed in general practices in Germany between October 2020 and November 2021.

METHODS

Database
The present retrospective cohort study used data from the Disease Analyzer database (IQVIA). This database has already been described in the literature [19]. In brief, the Disease Analyzer database includes demographic, diagnosis, and prescription data obtained in general and specialized practices in Germany. Data are collected from the computer systems of these practices, anonymized, and sent to IQVIA on a regular basis. Diagnosis data are coded using the International Classification of Diseases, 10th Revision (ICD-10), whereas prescription data are coded using the Anatomical Classification of Pharmaceutical Products of the European Pharmaceutical Marketing Research Association (EphMRA). The quality of the data is assessed based on several criteria (eg, completeness of information and linkage between diagnoses and prescriptions). General and specialized practices to include in the Disease Analyzer database are selected using multiple factors such as physician’s age, specialty group, community size category, and German federal state. Finally, approximately 3% of all primary care practices in Germany are included in the database.

Study Population
This study included adults aged ≥18 years who were diagnosed for the first time with COVID-19 (ICD-10: U07.1 [COVID-19, virus identified] or U08.9 [personal history of COVID-19, unspecified]) in 1 of 855 general practices in Germany between October 2020 and August 2021. Only general practices that used the ICD-10 code U09.9 (post-COVID-19 condition, unspecified) at least once were considered for the analyses. The index date was defined as the visit date on which COVID-19 was diagnosed for the first time. Participants were followed up for a maximum of 12 months until November 2021 (end of database). Less than 25% of patients were followed up for only a few weeks, and this short follow-up is likely explained by the fact that these people fully recovered from COVID-19 and stopped consulting their general practitioner. Finally, the flow diagram of study patients is displayed in Figure 1.

Study Outcome
The outcome of the study was the occurrence of post-COVID-19 condition (ICD-10: U09.9) 91 to 365 days after the index date. Post-COVID-19 condition diagnosed in the first 90 days after the index date was not included in the analyses, because it is suggested that this disorder occurs several months after the initial diagnosis of COVID-19 [18]. For a minority of patients diagnosed with post-COVID-19 condition, symptoms were documented at diagnosis using ICD-10 codes. These symptoms were malaise and fatigue (ICD-10: R53 and G93.3), abnormalities of breathing (ICD-10: R06), disturbances of smell and taste (ICD-10: R43), and symptoms involving cognitive functions and awareness (ICD-10: R41.8).

Study Covariates
Covariates included age, sex, and comorbidities present in at least 3% of the population in the 12 months before the index date. These comorbidities included lipid metabolism disorder (ICD-10: E78), diseases of esophagus, stomach, and duodenum (ICD-10: K20-K31), thyroid gland disorders (ICD-10: E00-E07), hypertension (ICD-10: I10), depression (ICD-10: F32 and F33), osteoarthritis (ICD-10: M15-M19), reaction to
severe stress, and adjustment disorders (ICD-10: F43), and somatoform disorders (ICD-10: F45), overweight and obesity (ICD-10: E66), diabetes mellitus (ICD-10: E10-E14), chronic sinusitis (ICD-10: J32), sleep disorders (ICD-10: G47), asthma (ICD-10: J45), shoulder lesions (ICD-10: M75), chronic obstructive pulmonary disease (ICD-10: J44), vasomotor and allergic rhinitis (ICD-10: J30), heart disease (ICD-10: I20–I25, I48 and I50), spondylosis (ICD-10: M47), varicose veins (ICD-10: I83, I85, and I86), mononeuropathies (ICD-10: G56–G59), anxiety disorders (ICD-10: F41), migraine (ICD-10: G43), iron deficiency anemia (ICD-10: D50), vitamin D deficiency (ICD-10: E55), cancer (ICD-10: C00–C97), purine and pyrimidine metabolism disorder (ICD-10: E79), chronic kidney disease and kidney failure (ICD-10: N18 and N19), and nicotine dependence (ICD-10: F17).

Statistical Analyses
Demographic and clinical characteristics of study participants were described using proportions for all variables except continuous age (mean [standard deviation]). In addition, the prevalence of post-COVID-19 condition in the 12 months after the diagnosis of COVID-19 was studied in the overall sample. Because participants were not followed up for an entire year, the prevalence of post-COVID-19 condition was estimated as a cumulative incidence using the Kaplan-Meier method. Finally, the association between predefined variables (ie, age, sex, and comorbidities) and post-COVID-19 condition was studied in a multivariable logistic regression model. The results of the logistic regression analysis are displayed as odds ratios (ORs) and 95% confidence intervals (CIs). Given that the size of the study sample was large, \( P < .001 \) were considered statistically significant. All analyses were conducted with SAS 9.4.

Patient Consent Statement
The database used includes only anonymized data in compliance with the regulations of the applicable data protection laws. German law allows the use of anonymous electronic medical records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data. Because patients were only queried as aggregates and no protected health information was available for queries, no Institutional Review Board approval was required for the use of this database or the completion of this study.

RESULTS
This study included 51,630 patients diagnosed with COVID-19 in 855 general practices in Germany between October 2020 and August 2021. Mean age was 47.1 (standard deviation, 19.8) years, while 54.3% were women (Table 1). The 3 most frequent comorbidities diagnosed in the 12 months before the diagnosis of COVID-19 were lipid metabolism disorder (29.0%), diseases of esophagus, stomach and duodenum (26.5%), and thyroid gland disorders (20.9%). Mean follow-up was 188 (standard deviation, 120) days. The prevalence of post-COVID-19 condition was 8.3% in the overall sample. Post-COVID-19 symptoms were documented at diagnosis in 32.6% of patients with post-COVID-19 condition. Most frequent symptoms were malaise and fatigue (69.0%), abnormalities of breathing (21.0%), disturbances of smell and taste (6.0%), and symptoms involving cognitive functions and awareness (4.0%). The results
of the multivariable logistic regression analysis are shown in Table 2. Age >30 years (age group 18–30 years: reference; OR ranging from 1.40 [95% CI, 1.20–1.64] for the age group 31–45 years to 2.10 [95% CI, 1.81–2.45] for the age group 46–60 years) and female sex (male sex: reference; OR = 1.23 [95% CI, 1.16–1.33]) were positively and significantly associated with post-COVID-19 condition. In terms of comorbidities, there was a significant relationship of asthma (OR = 1.38 [95% CI, 1.19–1.59]), reaction to severe stress, and adjustment disorders (OR = 1.24 [95% CI, 1.10–1.41]), and somatoform disorders (OR = 1.23 [95% CI, 1.16–1.33]). The significant associations are indicated in bold.

### Table 1. Demographic and Clinical Characteristics of the Study Sample

| Variable                          | Patients With COVID-19 (n = 51,630) |
|-----------------------------------|------------------------------------|
| Age (in years)                    |                                    |
| Mean (standard deviation)         | 47.1 (19.8)                        |
| 18–30                             | 23.0                               |
| 31–45                             | 25.0                               |
| 46–60                             | 28.4                               |
| 61–70                             | 10.9                               |
| >70                               | 12.7                               |
| Sex                               |                                    |
| Female                            | 54.3                               |
| Male                              | 45.7                               |

### Table 2. Association Between Predefined Variables and Post-COVID-19 Condition in the 12 Months After the Diagnosis of COVID-19 in Patients Followed in General Practices in Germany (Multivariable Logistic Regression Model)

| Variable                          | Proportion of Individuals With Post-COVID-19 Condition (%) | Adjusted Odds Ratio (95% Confidence Interval) | P Value |
|-----------------------------------|----------------------------------------------------------|-----------------------------------------------|---------|
| Total                             | 8.3                                                      |                                               |         |
| Age (in years)                    |                                                          |                                               |         |
| 18–30                             | 5.0                                                      | Reference                                    |         |
| 31–45                             | 7.3                                                      | 1.40 (1.20–1.64)                             | <.001   |
| 46–60                             | 9.8                                                      | 2.10 (1.81–2.45)                             | <.001   |
| 61–70                             | 8.6                                                      | 1.81 (1.49–2.21)                             | <.001   |
| >70                               | 5.6                                                      | 1.54 (1.23–1.92)                             | <.001   |
| Sex                               |                                                          |                                               |         |
| Female                            | 9.1                                                      | 1.23 (1.16–1.33)                             | <.001   |
| Male                              | 7.4                                                      | Reference                                    |         |

### Abbreviations
- COVID-19: coronavirus disease 2019.
- NOTE: Data are proportion unless otherwise specified.

### Comorbidities Present in at Least 3% of Patients in the 12 Months Before the Index Date

- Lipid metabolism disorder
- Diseases of esophagus, stomach, and duodenum
- Thyroid gland disorders
- Hypertension
- Depression
- Osteoarthritis
- Reaction to severe stress, and adjustment disorders
- Somatoform disorders
- Overweight and obesity
- Diabetes mellitus
- Chronic sinusitis
- Sleep disorders
- Asthma
- Shoulder lesions
- Chronic obstructive pulmonary disease
- Vasomotor and allergic rhinitis
- Heart disease
- Spondylody
- Varicose veins
- Mononeuropathies
- Anxiety disorders
- Migraine
- Shoulder lesions
- Iron deficiency anemia
- Vitamin D deficiency
- Chronic sinusitis
- Anxiety disorders
- Mononeuropathies
- Thyroid gland disorders
- Overweight and obesity
- Varicose veins
- Heart disease
- Cancer
- Diabetes mellitus
- Hypertension
- Vasomotor and allergic rhinitis
- Spondylody
- Nicotine dependence

### Abbreviations
- COVID-19: coronavirus disease 2019.
- NOTE: Significant associations are indicated in bold. All variables listed in the table were included in the multivariable logistic regression.
disorders (OR = 1.23 [95% CI, 1.07–1.40]) with post-
COVID-19 condition.

DISCUSSION

Main Findings
This retrospective cohort study, including more than 51,600 adults with COVID-19 followed in general practices in Germany between October 2020 and November 2021, revealed that 8.3% developed post-COVID-19 condition in the 12 months after the diagnosis of COVID-19. Age >30 years, female sex, and several comorbidities (ie, asthma, reaction to severe stress, and adjustment disorders, and somatoform disorders) were positively and significantly associated with post-COVID-19 condition. To the best of our knowledge, this is one of the largest studies investigating the prevalence of post-COVID-19 condition in adults, while it is one of the first studies using data obtained in primary care practices.

Interpretation of Findings
A substantial body of literature has focused on the persistence of COVID-19 symptoms in adults previously diagnosed with COVID-19 [4–15]. One study of 968 patients diagnosed with COVID-19 in France showed that 85% of those symptomatic at 2 months had persistent symptoms at 1 year [13]. In another sample of 3135 noninstitutionalized adults being tested for SARS-CoV-2 in the United States, the prevalence of persistent symptoms (ie, symptoms lasting more than 4 weeks) was 65.9% in those with a positive test and 42.9% in those with a negative test [14]. Moreover, a study, including 47,780 individuals hospitalized for COVID-19 and 47,780 controls from the general population in the United Kingdom, found that rates of respiratory disease, cardiovascular disease, and diabetes were higher in the group with than the group without COVID-19, and this increase was particularly important in people aged <70 years and in ethnic minority groups [4]. It was observed in a fourth cohort, including 96 COVID-19 patients from Germany, that 77.1% of them had persistent symptoms 12 months after the diagnosis of COVID-19 [11]. It is important to note that the prevalence of these persistent symptoms is higher than the prevalence of post-COVID-19 condition reported in the present study. Persistent symptoms (eg, fatigue, dyspnea, and cough) do not necessarily translate into post-COVID-19 condition if these symptoms last only a few weeks or if they do not have a significant impact on activities of daily living [18]. Moreover, the majority of previous studies were conducted in hospital settings [4, 5, 8–12], and participants included in these studies may have displayed more severe initial COVID-19 symptoms than those from general practices who were included in this German study, with severe COVID-19 symptoms being a risk factor for subsequent persistent symptoms [20–22].

Age >30 years, female sex, and 3 comorbidities (ie, asthma, reaction to severe stress, and adjustment disorders, and somatoform disorders) were further found to be positively and significantly associated with post-COVID-19 condition. In terms of age, people aged >30 years were more likely to be diagnosed with post-COVID-19 condition than their counterparts aged 18–30 years, and the OR was the highest in the age group 46–60 years. There is some literature suggesting that persistent symptoms tend to be more prevalent with increasing age. For example, an analysis of data obtained in France (n = 150 patients with noncritical COVID-19) revealed that age 40–59 years was positively and significantly associated with persistent symptoms 60 days after symptom onset compared with age <30 years [5]. Another Egyptian study of 172 participants with COVID-19 predominantly treated at home showed that age was a risk factor for persistent symptoms after recovery (OR = 1.03 [95% CI, 1.01–1.05]) [23]. In a third cohort, including 807 individuals discharged from hospital after admission for COVID-19 in the United Kingdom between March 2020 and April 2021, more than 70% of the sample had not completely recovered from COVID-19 at 12 months, and there was a U-shaped association between age and the persistence of symptoms, with people aged <50 and ≥60 years being more likely to report symptoms at 12 months than their counterparts aged 50–59 years [24]. Severe COVID-19 is more frequent in older than in younger adults [25], and this could explain why old age favors the persistence of symptoms. Moreover, the duration of the clearance of SARS-CoV-2 increases with age [26, 27], and the prolonged presence of the virus may be, at least partially, involved in post-COVID-19 condition. The present study also found that women were more likely to be affected by post-COVID-19 condition than their male counterparts.

Although severe COVID-19 is less frequent in women than in men [28], this finding aligns with the literature highlighting major sex differences in the persistence of COVID-19 symptoms. In a sample of 599 patients with COVID-19 attending a hospital in Italy, female sex was significantly associated with post-COVID-19 syndrome compared with male sex (OR = 1.55; 95% CI, 1.05–2.27) [10]. Similar results were obtained in 1969 individuals hospitalized for COVID-19 in Spain: being a woman resulted in a 2.54-fold increase in the risk of reporting at least 3 post-COVID-19 symptoms (95% CI, 1.67–3.87) compared with being a man [29]. The association between sex and post-COVID-19 condition remains insufficiently understood, but there may be biological, immunological, and psychological differences between women and men that could play an important role in the sex differential incidence of post-COVID-19 condition [29]. Finally, 3 comorbidities (ie, asthma, reaction to severe stress, and adjustment disorders, and somatoform disorders) were found to be associated with post-COVID-19 condition. The relationship between asthma and post-COVID-19 condition should be interpreted with caution, because previous research has obtained opposite findings [8, 30]. That being said, patients with asthma may be more likely to be affected by
persistent symptoms of pulmonary nature such as cough and dyspnea than their counterparts without asthma. It is interesting to note that the 2 other diseases associated with post-COVID-19 condition were psychiatric disorders. Previous literature has shown that people with mental health disorders are at particular risk for deleterious COVID-19 outcomes (eg, hospitalization and mortality) [31,32]. However, little is known about the effects of prior psychiatric disorders on persistent COVID-19 symptoms. One hypothesis is that individuals with a history of mental health conditions are more likely to develop neuropsychiatric sequelae of the COVID-19 than the general population [33]. Another hypothesis is that dysregulations of the hypothalamic-pituitary-adrenal axis are frequent in people with psychiatric disorders [34], while these dysregulations may also be involved in the physiopathology of post-COVID-19 condition [35,36]. Finally, specifically, somatoform disorders are characterized by physical symptoms (eg, back pain, dizziness, and shortness of breath) without an adequate medical explanation, and inaccurate or exaggerated beliefs about such symptoms are common [37]. It is interesting to note that a study of 26 823 volunteers from France suggested that believing in having been infected with SARS-CoV-2 may be a stronger predictor of persistent physical symptoms than having a positive serology test result [38].

Public Health Implications and Directions for Future Research
Based on the results of this study, post-COVID-19 condition was diagnosed in approximately 8% of patients with COVID-19 followed in general practices in Germany. Persistent symptoms should be regularly assessed by general practitioners in individuals with a history of COVID-19. Although treatments for post-COVID-19 condition are limited, the management of this disorder should be multidisciplinary and include, for example, physical rehabilitation, management of pre-existing comorbidities, and mental health support [39]. Moreover, the status of patients for the vaccination against COVID-19 should be assessed, and, if the status is not complete, vaccine doses may be administered. It is interesting to note that the effects of COVID-19 vaccines on post-COVID-19 condition remain insufficiently understood, but some preliminary evidence suggests that being vaccinated may protect against the persistence of symptoms [17]. In terms of future research, further data are warranted to confirm or refute these findings in primary care practices in other countries. Moreover, more studies should be conducted to better characterize factors predicting post-COVID-19 condition.

Strengths and Limitations
The major strengths of this study are the large sample size and the use of data obtained in primary care. Nonetheless, this study also displays limitations that should be acknowledged. First, the diagnosis of post-COVID-19 condition exclusively relied on ICD-10 codes, and more information on symptoms would have allowed more detailed analyses. The ICD-10 code used for post-COVID-19 condition (ie, U09.9) has been implemented based on the criteria of the World Health Organization (eg, symptoms present at least 3 months after the diagnosis of COVID-19, symptoms lasting at least 2 months, and no alternative diagnosis to explain the symptoms), and it was not possible to verify how frequently these criteria were met. Second, there were no data on the severity of the SARS-CoV-2 infection, the type of SARS-CoV-2 variant, and the possible administration of vaccine doses before or after the diagnosis of COVID-19. Because these variables may be associated with post-COVID-19 condition, this lack of information may have biased the inferential analyses. Third, it is possible that some patients have been diagnosed with post-COVID-19 condition in other practices (eg, pulmonary and neuropsychiatric), and therefore the prevalence of this disorder may have been underestimated. Fourth, this was a study of retrospective nature, and more prospective studies should investigate the epidemiology of post-COVID-19 condition in the future.

CONCLUSIONS
In this study of patients from general practices in Germany, the prevalence of post-COVID-19 condition was approximately 8% in the 12 months after the diagnosis of COVID-19. Age >30 years, female sex, and several comorbidities (ie, asthma, reaction to severe stress, and adjustment disorders, and somatoform disorders) were positively and significantly associated with post-COVID-19 condition. Finally, more research is needed to corroborate or refute these settings in other countries, while future research should focus on predictors of post-COVID-19 condition.

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Potential conflicts of interest. All authors: No reported conflicts of interest.

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