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Association of Self-reported COVID-19 Infection and SARS-CoV-2 Serology Test Results With Persistent Physical Symptoms Among French Adults During the COVID-19 Pandemic

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IMPORTANCE After an infection by SARS-CoV-2, many patients present with persistent physical symptoms that may impair their quality of life. Beliefs regarding the causes of these symptoms may influence their perception and promote maladaptive health behaviors.

OBJECTIVE To examine the associations of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms (eg, fatigue, breathlessness, or impaired attention) in the general population during the COVID-19 pandemic.

DESIGN, SETTING, AND PARTICIPANTS Participants in this cross-sectional analysis were 26 823 individuals from the French population-based CONSTANCES cohort, included between 2012 and 2019, who took part in the nested SAPRIS and SAPRIS-SERO surveys. Between May and November 2020, an enzyme-linked immunosorbent assay was used to detect anti–SARS-CoV-2 antibodies. Between December 2020 and January 2021, the participants reported whether they believed they had experienced COVID-19 infection and had physical symptoms during the previous 4 weeks that had persisted for at least 8 weeks. Participants who reported having an initial COVID-19 infection only after completing the serology test were excluded.

MAIN OUTCOMES AND MEASURES Logistic regressions for each persistent symptom as the outcome were computed in models including both self-reported COVID-19 infection and serology test results and adjusting for age, sex, income, and educational level.

RESULTS Of 35 852 volunteers invited to participate in the study, 26 823 (74.8%) with complete data were included in the present study (mean [SD] age, 49.4 [12.9] years; 13 731 women [51.2%]). Self-reported infection was positively associated with persistent physical symptoms, with odds ratios ranging from 1.39 (95% CI, 1.03-1.86) to 16.37 (95% CI, 10.21-26.24) except for hearing impairment (odds ratio, 1.45; 95% CI, 0.82-2.55) and sleep problems (odds ratio, 1.14; 95% CI, 0.89-1.46). A serology test result positive for SARS-COV-2 was positively associated only with persistent anosmia (odds ratio, 2.72; 95% CI, 1.66-4.46), even when restricting the analyses to participants who attributed their symptoms to COVID-19 infection. Further adjusting for self-rated health or depressive symptoms yielded similar results. There was no significant interaction between belief and serology test results.

CONCLUSIONS AND RELEVANCE The findings of this cross-sectional analysis of a large, population-based French cohort suggest that persistent physical symptoms after COVID-19 infection may be associated more with the belief in having been infected with SARS-CoV-2 than with having laboratory-confirmed COVID-19 infection. Further research in this area should consider underlying mechanisms that may not be specific to the SARS-CoV-2 virus. A medical evaluation of these patients may be needed to prevent symptoms due to another disease being erroneously attributed to "long COVID."

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Supplemental content

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Group Information: A complete list of the members of the SAPRIS-SERO study group appears in Supplement 2.

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After infection by SARS-CoV-2, both hospitalized and nonhospitalized patients have an increased risk of various persistent physical symptoms that may impair their quality of life, such as fatigue, breathlessness, or impaired attention.[1-3] Although the term "long COVID" has been coined to describe these symptoms[4] and putative mechanisms have been proposed,[3,5,6] the symptoms may not emanate from SARS-CoV-2 infection per se but instead may be ascribed to SARS-CoV-2 despite having other causes. In this study, we examined the association of self-reported COVID-19 infection and of serology test results with persistent physical symptoms. We hypothesized that the belief in having been infected with SARS-CoV-2 would be associated with persistent symptoms while controlling for actual infection.

Key Points

Question Are the belief in having had COVID-19 infection and actually having had the infection as verified by SARS-CoV-2 serology testing associated with persistent physical symptoms during the COVID-19 pandemic?

Findings In this cross-sectional analysis of 26 823 adults from the population-based French CONSTANCES cohort during the COVID-19 pandemic, self-reported COVID-19 infection was associated with most persistent physical symptoms, whereas laboratory-confirmed COVID-19 infection was associated only with anosmia. Those associations were independent from self-rated health or depressive symptoms.

Meaning Findings suggest that persistent physical symptoms after COVID-19 infection should not be automatically ascribed to SARS-CoV-2; a complete medical evaluation may be needed to prevent erroneously attributing symptoms to the virus.

Methods

The French CONSTANCES population-based cohort study[7] received ethical approval and included approximately 200 000 volunteers who were aged 18 to 69 years between 2012 and 2019 and who consented to be followed up through annual questionnaires and linked administrative databases.[8] A total of 35 852 volunteers responding to annual questionnaires through the internet were invited to take part in the nested Santé, Pratiques, Relations et Inégalités Sociales en Population Générale Pendant la Crise COVID-19 (SAPRIS) and SAPRIS-Sérologie (SERO) surveys.[9,10] Ethical approval and written or electronic informed consent were obtained from each participant before enrollment in the original cohort. The SAPRIS survey was approved by the French Institute of Health and Medical Research ethics committee, and the SAPRIS-SERO study was approved by the Sud-Mediterranée III ethics committee. Electronic informed consent was obtained from all participants for dried-blood spot testing. No one received compensation or was offered any incentive for participating in this study. The present study is a cross-sectional analysis of data from the SAPRIS and SAPRIS-SERO surveys nested in the French CONSTANCES cohort.

Serologic Testing

Between May and November 2020, self-sampling dried-blood spot kits were mailed to each participant. Each kit included material (a dried-blood spot card, lancets, and a pad), printed instructions, and an addressed, stamped, and padded envelope to be returned with the card to a centralized biobank (CEPH Biobank). Received blood spots were visually assessed, registered, punched, and stored in tubes (0.5 mL, FluidX 96-Format 2D code; Brooks Life Sciences) at −30 °C. Eluates were processed with an enzyme-linked immunosorbent assay (Euroimmun) to detect anti-SARS-CoV-2 antibodies (IgG) directed against the S1 domain of the virus spike protein. A test was considered positive for SARS-CoV-2 when the results indicated an optical density ratio of 1.1 or greater (sensitivity, 87%; specificity, 97.5%).[11] The participants received their serology test results by mail or email.

Self-reported COVID-19 Infection

Between December 2020 and January 2021, the participants answered this question from the fourth SAPRIS questionnaire: "Since March, do you think you have been infected by the coronavirus (whether or not confirmed by a physician or a test)?" Participants answered "Yes," "No," or "I don't know." At the time they answered this question, the participants were aware of their serology test results (eFigure in Supplement 1). A total of 2788 participants (7.8%) who answered "I don't know" were excluded.

The participants who answered "Yes" additionally answered this question: "When did you get the coronavirus? Between March and June; In July or August; Between September and now." Participants who indicated having been initially infected after serologic testing (n = 1312 [3.6%]) were excluded. The participants who answered "Yes" also answered this question: "Has this been confirmed? Yes, by virological or PCR test (based on nose swab; results provided after at least 24 hours); Yes, by antigenic test performed (based on nose swab; results provided within 1 hour); Yes, by serological test (based on a blood test; results provided after at least 24 hours); Yes, by rapid diagnostic test (based on blood test; results provided within 1 hour); Yes, by saliva test; Yes, by chest CT scan; Yes, by a physician (without testing); No, but I think I had it; I don't know."

Persistent Physical Symptoms

In the same questionnaire, symptoms were measured by the following question: "Since March 2020, have you had any of the following symptoms that you did not usually have before?" On the basis of the literature,[1-3] the following symptoms were explored: sleep problems, joint pain, back pain, muscular pain, sore muscles, fatigue, poor attention or concentration, skin problems, sensory symptoms (pins and needles, tingling or burning sensation), hearing impairment, constipation, stomach pain, headache, breathing difficulties, palpitations, dizziness, chest pain, cough, diarrhea, anosmia, and other symptoms.

Two additional questions were asked for each symptom: "Has this symptom been present in the past 4 weeks?" Participants answered "Yes, but not present anymore," "Yes, and still present," or "No"; "How much time did this symptom last? Or how long has it been since you have had this symptom (if it is still present)?" with possible responses ranging from "Less than a week" to "More than 8 weeks." To avoid considering symptoms that were no longer present or only transient and to limit recall bias, only participants who responded "Yes" and "More than 8 weeks" to these 2 questions were considered as having persistent symptoms. Because we aimed to compare participants who self-reported having had COVID-19 infection with those who did not, we did not distinguish between persistent symptoms that were similar to those experienced at the time of the initial episode and potentially new symptoms.

Participants who declared having any of the listed persistent symptoms also answered the following question: "Do you attribute the current symptoms to COVID-19?" and participants answered "Yes, all"; "Yes, only a few"; "No"; or "I don't know." Participants who answered "Yes, all" or "Yes, only a few" were considered to attribute their symptoms to COVID-19 infection.

Covariates

Age, sex, educational level, income, and self-rated health in 2019 were obtained from the inclusion questionnaire and the 2019 CONSTANCES questionnaire. Depressive symptoms during the pandemic were measured as part of the SAPRIS survey by using the Center for Epidemiologic Studies Depression Scale.[12]

Statistical Analysis

The crude prevalence of persistent physical symptoms was first calculated for 4 groups of participants according to both belief (ie, self-reported COVID-19 infection) and serology test results: belief negative and serology negative; belief positive and serology negative; belief negative and serology positive; and belief positive and serology positive. We used χ^2 tests to search for between-group differences. To specifically test our hypothesis, we used separate logistic regressions for each persistent symptom as the outcome computed in models including either belief (model 1), serology test result (model 2), or both (model 3), adjusting for age, sex, income, and educational level. Additional models searched for belief by serology test result interactions. In sensitivity analyses, the models were further adjusted for self-rated health or depressive symptoms. Exploratory analyses were restricted to participants attributing their persistent symptoms to COVID-19 infection. A 2-sided value of $P < .05$ was considered statistically significant. All analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Of 35 852 volunteers invited to participate in this cross-sectional analysis, a cohort of 26 823 (74.8%) with complete data were included (mean [SD] age, 49.4 [12.9] years; 13 731 women [51.2%]; and 13 092 men [48.8%]) (**Table 1**). The crude prevalence rates of persistent symptoms by belief and by serology test result categories are given in **Table 2**. Compared with participants in the CONSTANCES cohort, the participants in the present study were more likely to be older, men, more educated, have higher levels of income, and have better self-reported health (eTable 1 in Supplement 1). The prevalence of persistent physical symptoms ranged from 0.5% (146 participants with anosmia) to 10.2% (2729 participants with sleep problems). A total of 1091 participants had a serology test result positive for SARS-CoV-2, including 453 participants (41.5%) who subsequently reported having had COVID-19 infection before the serology test. A total of 914 participants reported having had COVID-19 infection before the serology test, includ-

Table 1. Characteristics of 26 823 Participants

Characteristic	No. (%) of the population
Age, mean (SD), y	49.4 (12.9)
Sex	
Female	13 731 (51.2)
Male	13 092 (48.8)
Monthly income, € (US$)	
<450 (520)	69 (0.3)
450 to <1000 (520 to <1154)	293 (1.1)
1000 to <1500 (1154 to <1730)	741 (2.8)
1500 to <2100 (1730 to < 2424)	1828 (6.9)
2100 to <2800 (2424 to <3232)	3199 (12.0)
2800 to <4200 (3232 to <4848)	8563 (32.2)
4200 or higher (4848)	11 026 (41.5)
Does not know how to answer	166 (0.6)
Does not wish to answer	685 (2.6)
Missing	253 (0.9)
Educational level	
No diploma	148 (0.6)
General education certificate, primary education certificate, school-leaving certificate	863 (3.2)
Certificate of professional competence, vocational training certificate	2518 (9.5)
Baccalaureate or equivalent diploma	3711 (14.0)
Baccalaureate plus 2 or 3 y	7392 (27.8)
Baccalaureate plus 4 y	2884 (10.8)
Baccalaureate plus 5 y and more	9012 (33.9)
Other	48 (0.2)
Missing	247 (0.9)
Self-rated health (scale from 1 to 8)[a]	
1	4135 (15.5)
2	13 353 (50.2)
3	5783 (21.7)
4	1716 (6.4)
5	813 (3.1)
6	554 (2.1)
7	204 (0.8)
8	62 (0.2)
Missing	203 (0.8)

[a] Lower scores indicated better self-rated health.

Table 2. Descriptive Statistics of Symptom Prevalence by Belief and Serology Test Result Status

Symptom	Total No.	No. (%) of participants				P value[b]
		Serology−[a]		Serology+[a]		
		Belief− (n = 25 271)	Belief+ (n = 461)	Belief− (n = 638)	Belief+ (n = 453)	
Sleep problems	2729	2580 (10.4)	49 (10.9)	55 (8.7)	45 (10.1)	.58
Joint pain	1894	1802 (7.3)	30 (6.7)	26 (4.2)	36 (8.2)	.02
Back pain	1630	1525 (6.2)	32 (7.1)	33 (5.2)	40 (9.1)	.048
Digestive tract problems[c]	909	838 (3.5)	33 (7.4)	20 (3.3)	18 (4.2)	<.001
Muscular pain, sore muscles	867	808 (3.2)	22 (4.8)	18 (2.9)	19 (4.3)	.16
Fatigue	766	625 (2.5)	57 (12.6)	22 (3.5)	62 (13.8)	<.001
Poor attention or concentration	644	555 (2.2)	34 (7.5)	17 (2.7)	38 (8.5)	<.001
Skin problems	632	598 (2.4)	17 (3.8)	6 (1.0)	11 (2.5)	.02
Other symptoms[d]	514	463 (2.0)	17 (3.8)	8 (1.3)	26 (6.0)	<.001
Sensory symptoms	492	463 (1.8)	16 (3.5)	8 (1.3)	5 (1.1)	.02
Hearing impairment	479	456 (1.8)	7 (1.5)	6 (1.0)	10 (2.2)	.33
Headache	360	323 (1.3)	13 (2.8)	8 (1.3)	16 (3.6)	<.001
Breathing difficulties	256	192 (0.8)	29 (6.4)	9 (1.4)	26 (5.8)	<.001
Palpitations	213	175 (0.7)	17 (3.7)	6 (1.0)	15 (3.4)	<.001
Dizziness	178	158 (0.6)	7 (1.5)	5 (0.8)	8 (1.8)	.002
Chest pain	174	138 (0.6)	14 (3.1)	2 (0.3)	20 (4.5)	<.001
Cough	167	144 (0.6)	10 (2.2)	2 (0.3)	11 (2.5)	<.001
Anosmia	146	75 (0.3)	20 (4.4)	7 (1.1)	44 (9.9)	<.001

[a] Serology test result negative (−) or positive (+) for SARS-CoV-2 infection.

[b] Reflects the statistical significance of between-group differences according to χ^2 tests.

[c] Digestive tract problems refer to the presence of 1 or more of the following persistent symptoms: nausea, diarrhea, constipation, and stomach pain.

[d] Other symptoms refer to additional symptoms that patients declared and are not on the symptoms list, plus symptoms with a low number of cases (<100), such as speech problems (n = 56), fever or fever sensation (n = 26), anomaly of the facial nerves (n = 16), and discomfort (n = 12).

ing 453 (49.6%) with a serology test result positive for SARS-CoV-2 (Table 2). Differences in covariates according to the serology test results, the belief in having had COVID-19 infection, and both are reported in eTables 2, 3, and 4 in Supplement 1. Whether or not the diagnosis was confirmed by a laboratory test or by a physician among the participants with a positive belief is reported in eTable 5 in Supplement 1.

Before adjustment, the belief in having had COVID-19 infection was associated with 15 of 18 categories of persistent symptoms (**Table 3**, model 1), whereas a positive serology test result was associated with 10 categories of persistent symptoms (Table 3, model 2). After mutual adjustment, positive belief was significantly associated with higher odds of having all persistent symptoms, with odds ratios (ORs) ranging from 1.39 (95% CI, 1.03-1.86) to 16.37 (95% CI, 10.21-26.24) except for hearing impairment (OR, 1.45; 95% CI, 0.82-2.55) and sleep problems (OR, 1.14; 95% CI, 0.89-1.46) (Table 3, model 3). By contrast, a positive serology test result remained positively associated only with anosmia (OR, 2.72; 95% CI, 1.66-4.46) and was negatively associated with skin problems (OR, 0.49; 95% CI, 0.29-0.85) (Table 3, model 3). There was no significant interaction between belief and serology. Adjusting for self-rated health or depressive symptoms yielded similar results except for joint pain (OR, 1.31; 95% CI, 0.97-1.77) and back pain (OR, 1.29; 95% CI, 0.97-1.72), which were no longer associated with belief when adjusting for depressive symptoms (eTable 6 in Supplement 1).

Restricting the analyses to participants with a positive belief and attributing their persistent symptoms to COVID-19 showed a positive serology test result to be associated only with anosmia (OR, 2.97; 95% CI, 1.58-5.57) (eTable 7 in Supplement 1). Similarly, confirmation of the diagnosis by a laboratory test or by a physician (vs the response, "No, but I think I had it," and excluding participants who answered "I don't know") was also associated only with anosmia (OR, 4.29; 95% CI, 1.92-9.58) (eTable 7 in Supplement 1).

Discussion

This cross-sectional analysis of data from a population-based cohort found that persistent physical symptoms 10 to 12 months after the COVID-19 pandemic first wave were associated more with the belief in having experienced COVID-19 infection than with having laboratory-confirmed SARS-CoV-2 infection.

In previous studies, the association between persistent symptoms and SARS-CoV-2 serology test results may be explained by the belief in having experienced COVID-19 infection.[13] Furthermore, most previous studies assessing "long COVID" included only patients who had COVID-19 infection, thus lacking a control group of patients who did not have the infection.[3,14] Indeed, our results showed that the persistent physical symptoms observed after COVID-19 infection were

Table 3. Associations Between Persistent Symptoms, Belief, and Serology Test Results

		Odds ratio (95% CI)[a]			
				Model 3	
Symptom	No.	Model 1 Belief	Model 2 Serology	Belief	Serology
Sleep problems	2729	1.09 (0.88-1.36)	0.96 (0.77-1.19)	1.14 (0.89-1.46)	0.91 (0.71-1.15)
Joint pain	1894	1.32 (1.01-1.71)	1.03 (0.79-1.35)	1.39 (1.03-1.86)	0.89 (0.65-1.21)
Back pain	1630	1.41 (1.10-1.80)	1.16 (0.91-1.49)	1.40 (1.05-1.85)	1.01 (0.76-1.33)
Digestive tract problems[b]	909	1.92 (1.43-2.57)	1.06 (0.73-1.50)	2.19 (1.57-3.06)	0.73 (0.49-1.08)
Muscular pain, sore muscles	867	1.79 (1.29-2.48)	1.33 (0.94-1.87)	1.78 (1.22-2.59)	1.01 (0.68-1.50)
Fatigue	766	5.20 (4.20-6.43)	2.59 (2.03-3.30)	4.90 (3.79-6.33)	1.13 (0.84-1.52)
Poor attention or concentration	644	3.63 (2.79-4.71)	2.10 (1.57-2.82)	3.42 (2.50-4.67)	1.13 (0.79-1.61)
Skin problems	632	1.36 (0.92-2.00)	0.65 (0.39-1.06)	1.79 (1.17-2.73)	0.49 (0.29-0.85)
Other symptoms[c]	514	3.07 (2.22-4.25)	1.91 (1.32-2.75)	2.93 (1.99-4.31)	1.10 (0.71-1.70)
Sensory symptoms	492	1.60 (1.02-2.51)	0.77 (0.43-1.38)	2.06 (1.25-3.40)	0.54 (0.28-1.03)
Hearing impairment	479	1.47 (0.90-2.41)	1.22 (0.73-2.03)	1.45 (0.82-2.55)	1.03 (0.57-1.84)
Headache	360	2.52 (1.71-3.73)	1.69 (1.10-2.59)	2.40 (1.52-3.80)	1.10 (0.67-1.82)
Breathing difficulties	256	8.16 (5.95-11.19)	3.60 (2.48-5.24)	7.75 (5.25-11.43)	1.11 (0.70-1.76)
Palpitations	213	5.27 (3.55-7.82)	2.61 (1.62-4.19)	5.14 (3.18-8.29)	1.05 (0.59-1.87)
Dizziness	178	3.23 (1.88-5.56)	2.37 (1.33-4.24)	2.71 (1.40-5.24)	1.42 (0.70-2.88)
Chest pain	174	7.34 (4.95-10.88)	3.70 (2.33-5.87)	6.58 (4.02-10.75)	1.25 (0.70-2.22)
Cough	167	4.67 (3.00-7.25)	2.22 (1.25-3.97)	4.85 (2.75-8.56)	0.91 (0.45-1.83)
Anosmia	146	28.66 (20.16-40.74)	15.69 (10.85-22.70)	16.37 (10.21-26.24)	2.72 (1.66-4.46)

[a] Model 1 includes belief only, controlling for age, sex, educational level, and income. Model 2 includes serology test results only, controlling for age, sex, educational level, and income. Model 3 includes both belief and serology test results, controlling for age, sex, educational level, and income. We additionally tested interactions between serology test results and belief among all of the symptoms, and none were significant.

[b] Digestive tract problems refer to the presence of 1 or more of the following persistent symptoms: nausea, diarrhea, constipation, and stomach pain.

[c] Other symptoms refer to additional symptoms that patients declared and are not on the symptom list, plus symptoms with a low number of cases (<100), such as speech problems (n = 56), fever or fever sensation (n = 26), anomaly of the facial nerves (n = 16), and discomfort (n = 12).

quite frequent in the general population. Because our study also included participants who reported not having had COVID-19 infection with either positive or negative serology test results, we were able to compare the prevalence of persistent physical symptoms according to these 2 variables. We were also able to perform analyses restricted to participants attributing their persistent symptoms to COVID-19 infection. Although our study did not assess long COVID per se because we also included participants without COVID-19 infection, these specific analyses may be more representative of the long COVID clinical issue in real-life settings[15] than the picture provided by cohorts of patients with a laboratory-confirmed or physician-documented COVID-19 infection.

Although the participants were aware of the serology results when they reported having had COVID-19 infection or not, less than half of those with a positive serology test reported having experienced the disease. Conversely, among those who reported having had the disease, approximately half had a negative serology test result, consistent with some findings in clinical settings.[15] These results, which allowed for disentangling the correlates of the serology test results from those of the belief in having had COVID-19 infection, were not unexpected. First, patients with a positive serology test result but no or only mild symptoms of COVID-19 infection may not believe that they had the disease. Because persistent symptoms may be more frequent among patients who experienced a higher number of acute COVID-19 symptoms,[16] the severity of the initial episode may partially confound the association between the belief in having experienced COVID-19 infection and persistent symptoms among participants with positive serology test results. However, this belief was associated with persistent symptoms to a similar extent among participants with negative serology test results as shown by the lack of any interaction between belief and serology. Even if this belief could be explained by the experience of a COVID-19 infection–like episode among some of these participants, these results support the idea that persistent physical symptoms attributed to COVID-19 infection may not be specific to SARS-CoV-2. Second, patients who believe that they have had COVID-19 infection may reject a negative serology test result for several reasons, including perceptions about the frequency of false-negative tests and data suggesting that a weak anti-SARS-CoV-2 antibody response could be a risk factor of long COVID.[17] Indeed, since the first definitions of long COVID, it has been proposed that the associated antibodies profile is "uncharacterized."[18] Among participants in the present study who believed that they had experienced COVID-19 infection, anosmia was the only symptom associated with the confirmation of the diagnosis by a laboratory test or a physician. In other words, those who responded, "No, but I think I had it" were 4 times less likely to have anosmia, with no differences regarding all other symptoms, further suggesting that these other symptoms were not specific to actual infection by SARS-CoV-2.

Two main mechanisms may account for our findings. First, having persistent physical symptoms may have led to the belief in having had COVID-19, especially in the context of a growing concern regarding long COVID. Although adjusting for self-rated health before the pandemic did not affect our results, another disease may underlie symptoms attributed to COVID-19 infection. Second, the belief in having had COVID-19 infection may have increased the likelihood of symptoms, either directly by affecting perception[19,20] or indirectly by prompting maladaptive health behaviors, such as physical activity reduction or dietary exclusion. These mechanisms are thought to contribute to the long-described persistence of physical symptoms after acute infections.[21]

Strengths and Limitations

In addition to a large, population-based sample, the strengths of our study included the joint examination of self-reported COVID-19 infection and serology testing results while controlling for several covariates, including self-rated health—a robust indicator of physical health—and depressive symptoms.

This study had limitations. First, selection biases limit the representativeness of our sample. Second, our study may not have investigated all of the symptoms that patients with long COVID are reporting. However, the symptoms we studied were among those that are frequently explored in studies investigating long COVID[3] and reported by patients with long COVID.[22] Third, we analyzed persistent symptoms separately; different outcomes may be tested by clustering symptoms. In addition, because our study also included participants who did not report having had COVID-19 infection, we did not distinguish between symptoms that were experienced at the time of the initial episode of COVID-19 infection and new symptoms that occurred afterward. Fourth, we cannot exclude the possibility of misclassification regarding serology test results. On the basis of the present results, we estimate the prevalence of previous SARS-CoV-2 infection to be about 4%, and with a sensitivity of 87%, we would expect 139 participants to have false-negative results, which is less than 1% of those with negative serology test results. False-negative results were thus unlikely to have much influence on the associations between persistent symptoms and serology. In addition, the lack of any interaction between belief and serology test results suggests that persistent symptoms were associated with belief to a similar extent in participants with positive and negative serology test results. This finding makes our results unlikely to be explained solely by false-negative results. Furthermore, serology test results were associated only with persistent anosmia, a hallmark of COVID-19 infection, strengthening our confidence in the serology test results. This result held true even when restricting our analyses to participants attributing their symptoms to COVID-19 infection. Fifth, participants were aware of their serology test results when they reported having had COVID-19 infection or not. This factor may have reduced our ability to disentangle the associations of the 2 measures with persistent physical symptoms.

Conclusions

The results of this cross-sectional analysis of a large, population-based French cohort suggest that physical symptoms persisting 10 to 12 months after the COVID-19 pandemic first wave may be associated more with the belief in having experienced COVID-19 infection than with actually being infected with the SARS-CoV-2 virus. Although our study cannot determine the direction of the association between belief and symptoms, our results suggest that further research regarding persistent physical symptoms after COVID-19 infection should also consider mechanisms that may not be specific to the SARS-CoV-2 virus. From a clinical perspective, patients in this situation should be offered a medical evaluation to prevent their symptoms being erroneously attributed to COVID-19 infection and to identify cognitive and behavioral mechanisms that may be targeted to relieve the symptoms.[23]

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Additional Contributions: Céline Ribet, PhD, Mireille Pellicer, MD, Laura Quintin, MSc, Stephane Le Got, MSc, all from the CONSTANCES cohort, and Céline Dorival, PhD, and Jerôme Nicol, MSc, from INSERM Institut Pierre Louis d'Epidémiologie et de Santé Publique, substantially contributed to data collection for this work.

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