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Psychological burden associated with incident persistent symptoms and their evolution during the COVID-19 pandemic: a prospective population-based study

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ABSTRACT

Background Identifying factors that predict the course of persistent symptoms that occurred during the COVID-19 pandemic is a public health issue. Modifiable factors could be targeted in therapeutic interventions.

Objective This prospective study based on the population-based CONSTANCES cohort examined whether the psychological burden associated with incident persistent symptoms (ie, that first occurred from March 2020) would predict having ≥1 persistent symptom 6–10 months later.

Methods A total of 8424 participants (mean age=54.6 years (SD=12.6), 57.2% women) having ≥1 incident persistent symptom at baseline (ie, between December 2020 and February 2021) were included. The psychological burden associated with these persistent symptoms was assessed with the Somatic Symptom Disorder-B Criteria Scale (SSD-12). The outcome was having ≥1 persistent symptom at follow-up. Adjusted binary logistic regression models examined the association between the SSD-12 score and the outcome.

Findings At follow-up, 1124 participants (13.3%) still had ≥1 persistent symptom. The SSD-12 score at baseline was associated with persistent symptoms at follow-up in both participants with (OR (95% CI) for one IQR increase: 1.42 (1.09 to 1.84)) and without SARS-CoV-2 infection prior to baseline (1.39 (1.25 to 1.55)). Female gender, older age, poorer self-rated health and infection prior to baseline were also associated with persistent symptoms at follow-up.

Conclusions The psychological burden associated with persistent symptoms at baseline predicted the presence of ≥1 persistent symptom at follow-up regardless of infection prior to baseline.

Clinical implications Intervention studies should test whether reducing the psychological burden associated with persistent symptoms could improve the course of these symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Psychological factors may affect the risk of persistent symptoms after COVID-19 but their influence on the course of these symptoms is unknown.

WHAT THIS STUDY ADDS

⇒ The psychological burden associated with persistent symptoms that occurred during the first year of the pandemic predicted the presence of at least one persistent symptom 6–10 months later, regardless of SARS-CoV-2 infection.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Reducing the psychological burden associated with persistent symptoms should be tested as a therapeutic intervention.

INTRODUCTION

After an episode of coronavirus disease 2019 (COVID-19), persistent symptoms may impair the quality of life of many patients for months.[1] These persistent symptoms affect around 20% of patients 6 months after a COVID-19 episode, and 10% at 12 months, and are thus a major medical and public health issue.[2] The WHO named this situation 'post-COVID-19 condition' (also frequently referred to as 'long COVID') and defined it as follows: at least one persistent symptom occurring 3 months from the onset of COVID-19 that lasts for at least 2 months and cannot be explained by an alternative diagnosis.[3] Of note, this definition includes several non-specific symptoms (eg, fatigue, breathlessness, headaches) that could occur outside the context of COVID-19.[4–6] However, should such symptoms occur within 3 months of a SARS-CoV-2 infection, affect everyday functioning and be of otherwise unknown origin, they would meet this definition. Such default attribution to COVID-19

may thus yield important clinical heterogeneity. After infection with SARS-CoV-2, risk factors for post-COVID-19 conditions are female sex, older age, severe COVID-19 or pre-existing comorbid conditions, including anxiety and depression.[7–9] Regarding prognostic factors, slower resolution of the persistent symptoms has been associated with the number of acute symptoms of COVID-19, female sex, older age, high body mass index (BMI) or tobacco use,[2 10] but psychological factors have been relatively overlooked.[11 12]

Since depression and anxiety are risk factors of post-COVID-19 condition,[7–9] they could also influence its course. Furthermore, since many psychological factors may be modifiable by validated therapeutic interventions, they may constitute relevant therapeutic targets for the post-COVID-19 condition. For instance, the psychological burden associated with acute COVID-19 symptoms independently predicted persistent symptoms in a small sample of infected individuals.[13] However, this association awaits replication focusing on the psychological burden associated with persistent symptoms in a larger sample of infected and non-infected individuals. Indeed, the persistence of symptoms despite the remission of a disease is a long-studied issue in medicine (eg, irritable bowel syndrome complicating inflammatory bowel diseases[14] or fibromyalgia complicating inflammatory rheumatism[15]). Therefore, the prognostic factors of persistent symptoms may not be specific to the original disease. For instance, in the context of post-infectious disorders, risk factors of persistent symptoms after Lyme borreliosis are mainly similar to those of incident persistent symptoms in the general population or in individuals who had reported a tick bite without evidence for Lyme borreliosis, and mainly involve psychosocial factors.[16]

In this longitudinal study, nested in the French population-based CONSTANCES cohort, we aimed to examine whether the psychological burden associated with the persistent symptoms that occurred during the COVID-19 pandemic may predict their subsequent evolution. Since persistent symptoms may also arise in non-infected individuals,[4–6] we also aimed to examine whether this association would be observed in both infected and non-infected participants.

METHODS

The CONSTANCES cohort and SAPRIS surveys

The French population-based CONSTANCES cohort received ethical approval from the institutional review board of the National Institute of Health and Medical Research (Authorisation number 910486) and included more than 200 000 volunteers aged 18–69 years at inclusion (ie, between 2012 and 2019) who gave informed consent to be followed-up through annual questionnaires.[17]

From April 2020, a total of 63 471 CONSTANCES volunteers responding to annual questionnaires through the internet were invited to take part in the nested SAPRIS ('Santé, pratiques, relations et inégalités sociales en population générale pendant la crise COVID-19') and SAPRIS-Sérologie (SAPRIS-SERO) surveys, which concerned specifically the impact of the COVID-19 pandemic.[18]

Assessment of persistent symptoms at baseline and follow-up

At baseline, that is, between December 2020 and February 2021, persistent symptoms that first occurred from the beginning of the pandemic among participants included in the SAPRIS survey were measured by the following question: 'Since March 2020, have you had any of the following symptoms that you did not have before?'. The following symptoms were explored: cough, breathing difficulties, chest pain, palpitations, joint pain, back pain, muscular pain or sore muscle, headache, an anomaly of the facial nerves, sensory symptoms, speech problems, hearing problems, nausea or vomiting, diarrhoea, constipation, stomach pain, anosmia, fever or fever sensation, memory problems, fatigue, poor attention or concentration, dizziness, discomfort, sleep problems, skin problems and 'other symptoms'. Two additional questions were asked for each self-reported symptom: 'Has this symptom been present in the past four weeks?' and 'How much time did this symptom last? Or how long has it been since you have had this symptom (if it is still present)?' Persistent symptoms were defined by 'yes' and 'more than eight weeks' responses to these two questions.[19]

Only participants with at least one incident persistent symptom at baseline were included.

At follow-up, that is, between June and October 2021 (ie, 6–10 months after baseline), these persistent symptoms were assessed again with the same questions, except for back pain, stomach pain, constipation and discomfort.

Assessment of psychological burden associated with incident persistent symptoms at baseline

At baseline, that is, between December 2020 and February 2021, participants having reported at least one persistent symptom that first occurred from March 2020 were invited to fill the Somatic Symptoms Disorder-B Criteria Scale (SSD-12).[20] This 12-item self-reported questionnaire was designed to assess the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) somatic symptom disorder B criteria. A somatic symptom disorder is diagnosed when focused attention on physical symptoms, associated or not with a diagnosed medical condition, results in substantial distress or functional impairment. Each item is rated on a 5-point Likert scale from 0 ('never') to 4 ('very often') yielding a total score between 0 and 48. The French version of the SSD-12 had a 3-factor structure: 'Perceived impairment', 'Negative expectations' and 'Perceived severity'.[20]

SARS-CoV-2 infection prior to baseline and during follow-up

Between May and October 2020, self-sampling dried blood spot kits were mailed to each participant, with kit material and printed instructions to mail a blood spot to a centralised biobank.[18] A serology test was considered positive for SARS-CoV-2 for an optical density ratio ≥1.1 (sensitivity/specificity: 0.87/0.975). Participants with indeterminate results (ie, optical density ratio ≥0.8 and <1.1) and without declaration of an otherwise positive test were excluded.

At baseline, that is, between December 2020 and February 2021, participants answered the question: 'Since March, do you think you have been infected with the coronavirus (whether or not confirmed by a physician or a test)?'. At follow-up, that is, between July and October 2021, participants again self-reported COVID-19 infection. At both time points, those who answered 'Yes' were asked whether their infection had been confirmed.

Participants who answered 'Yes, by virological or PCR test (based on nose swab; results provided after at least 24 hours)' or 'Yes, by serological test (based on a blood test; results provided after at least 24 hours)' or had a positive serology test in the context of SAPRIS-SERO were considered as having been infected with SARS-CoV-2 prior to baseline.

Among participants without infection prior to baseline, infection during follow-up was defined by self-reporting positive PCR or (outside SAPRIS-SERO) serology test results at follow-up.

Adjustment variables

Gender, age, educational level, household income and current tobacco smoking status were self-reported at inclusion in the CONSTANCES cohort. Self-rated health was rated at baseline from 1 ('very bad') to 8 ('very good'). BMI (kg/m^2) was categorised into four categories (<18.5, 18.5–25, 25–30 and >30) from weight and height measured at inclusion.

Statistical analyses

Only participants with at least one incident persistent symptom at baseline, that is, a symptom that first occurred from March 2020, lasted at least 8 weeks, and was still present in the past 4 weeks at baseline (ie, between December 2020 and February 2021), were included.

The outcome was having at least one persistent symptom at follow-up (ie, between June and October 2021). Binary logistic regression multivariable models analysed the association between the outcome and the SSD-12 score divided by its IQR, to yield interpretable ORs and 95% CIs. This scaling allows a meaningful interpretation in that ORs compare a participant in the middle of the upper half of the predictor's distribution with a participant in the middle of the lower half. In addition to the adjustment variables, infection prior to baseline was added to the model. To determine whether the association between the SSD-12 score at baseline and persistent symptoms at follow-up depended on the infection status, the multiplicative interaction between the SSD-12 score and infection prior to baseline was tested in specific models. The analyses were repeated in the samples with and without infection prior to baseline.

In sensitivity analyses, the number of persistent symptoms at baseline was added to the model. This was done in sensitivity analyses only as this variable could act either as a confounding or a mediating factor. Indeed, should the psychological burden associated with symptoms foster their persistence, as preliminary evidence suggests,[13] the number of persistent symptoms at baseline would constitute a mediating factor (ie, a factor being involved in the pathway from the psychological burden at baseline to persistent symptoms at follow-up). In addition, among participants without infection prior to baseline, SARS-CoV-2 infection during follow-up was added as an additional adjustment variable.

In exploratory analyses, the initial multi-adjusted models were computed again with the scores of the three factors of the SSD-12 simultaneously instead of the total SSD-12 score. In addition, among participants with infection prior to baseline, exploratory analyses were also conducted for fatigue, breathing difficulties, poor attention or concentration, and anosmia, separately (ie, the presence of these symptoms at follow-up was studied among participants with these symptoms at baseline). These four symptoms were chosen as they were either highlighted as 'core' symptoms of the post-COVID-19 condition[3] or, concerning anosmia, as it was the most specific symptom of COVID-19.

The missing data were imputed following the multiple imputation method, using the multiple imputation chained equation model, with 50 imputations, assuming a missing at random hypothesis (the proportion of unavailable data is available in the online supplemental table 1). All statistical analyses were

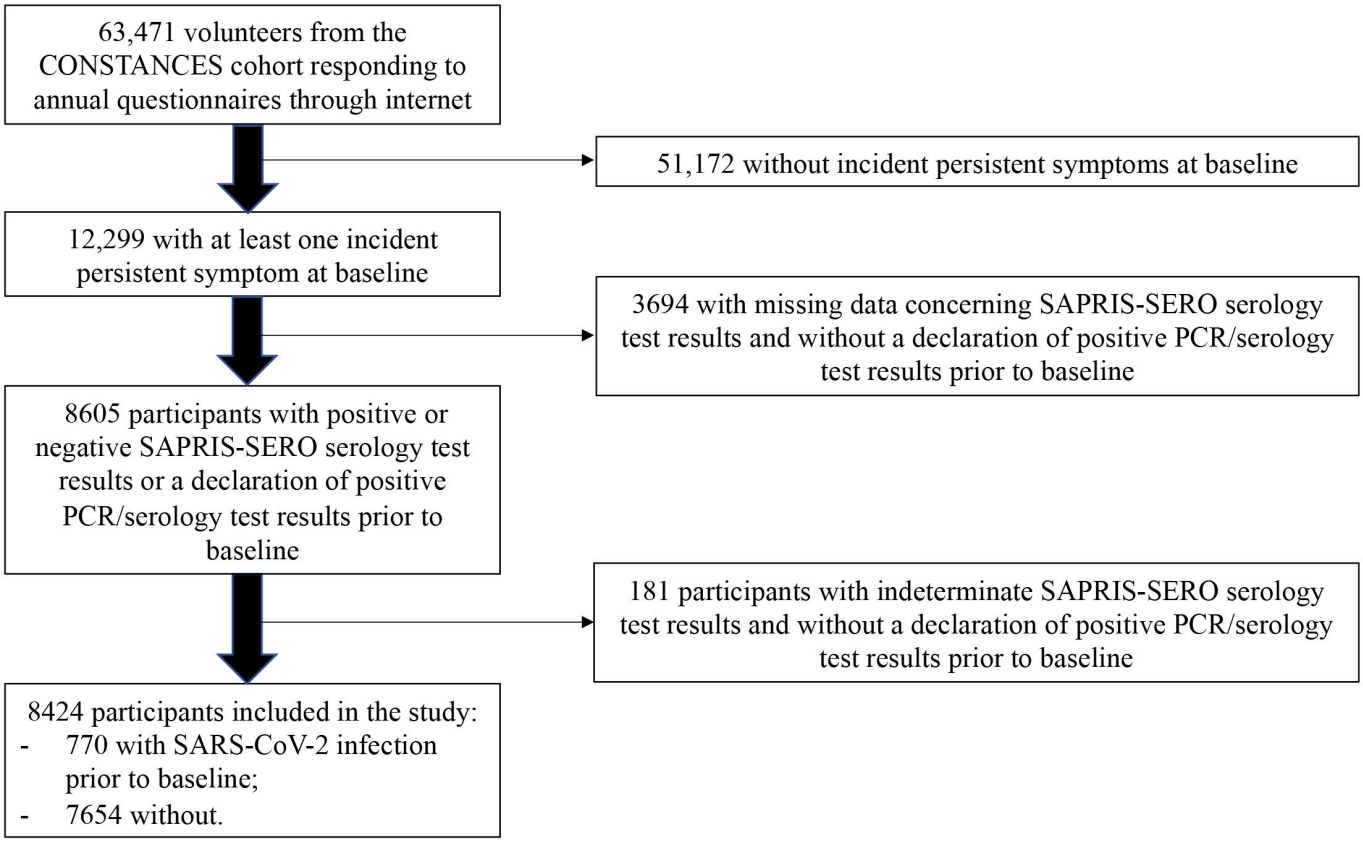

Figure 1 Flow-chart of the participants included in the study.

Table 1 Characteristics of the participants with incident persistent symptoms at baseline

	Total sample (N=8424)		SARS-CoV-2 infection prior to baseline			
			With (N=770)		Without (N=7654)	
Continuous variables	Mean	sd	Mean	sd	Mean	sd
SSD-12 total score	12.81	8.41	12.59	8.37	12.83	8.41
SSD-12 perceived severity score	3.60	3.00	3.79	2.98	3.58	3.00
SSD-12 perceived impairment score	4.60	3.85	4.51	3.86	4.61	3.85
SSD-12 negative expectations score	3.12	2.39	2.73	2.32	3.16	2.39
Number of persistent symptoms at baseline	1.96	1.52	2.18	1.86	1.94	1.48
Age (years)	54.6	12.6	48.3	12.6	55.2	12.4
Discrete variables	N	%	N	%	N	%
Female gender	4819	57.2	448	58.2	4371	57.1
Educational level *						
1	1174	14.1	68	8.9	1106	14.6
2	1184	14.2	94	12.4	1090	14.4
3	2377	28.5	224	29.4	2153	28.4
4	972	11.7	85	11.2	887	11.7
5	2630	31.5	289	38.0	2381	30.9
Monthly household income (€)						
<2100	992	12.3	85	11.4	907	12.4
2100–2800	1057	13.1	90	12.1	967	13.2
2800–4200	2627	32.6	248	33.2	2379	32.5
>4200	3379	42.0	323	43.3	3056	41.8
Smokers†	1156	13.8	95	12.7	1061	13.8
Body mass index (kg/m')						
<18.5	200	2.4	19	2.5	181	2.4
18.5–25	4605	55.5	428	56.5	4177	55.4
25–30	2544	30.6	228	30.1	2316	30.7
>30	953	11.5	83	10.9	870	11.5
Self-rated health (1: 'very bad', 8: 'very good')						
8	654	7.8	72	9.4	582	7.6
7	3814	45.6	358	46.8	3456	45.5
6	2201	26.3	186	24.3	2015	26.5
5	801	9.6	74	9.7	727	9.6
4	448	5.4	38	5.0	410	5.4
3	311	3.7	26	3.4	285	3.8
2	119	1.4	11	1.4	108	1.4
1	13	0.2	0	0.0	13	0.2
First infection during follow-up	NA	NA	NA	NA	281	3.7
At least one persistent symptom at follow-up	1122	13.3	162	21.0	960	12.5

*Educational level: 1=without diploma, without high school diploma or with certificate of vocational aptitude or vocational studies; 2=high school diploma or equivalent; 3=2 or 3 years of post-secondary education, 4=4 years of post-secondary education; 5=5 years or more of post-secondary education.
†At inclusion in the CONSTANCES cohort.
NA, not applicable; SSD-12, 12-item Somatic Symptoms Disorder-B Criteria Scale.

conducted using R software (V.4.2.3), and *mice* package for the imputation.

RESULTS

Participants

Among the 63 471 participants, 12 299 (19.4%) reported at least one incident persistent symptom that first occurred from March 2020 to baseline (ie, between December 2020 and February 2021). Among them, 8424 participants were included, including 770 with SARS-CoV-2 infection prior to baseline, and 7654 without (figure 1).

The characteristics of the participants (total sample, samples with and without infection prior to baseline) are displayed in table 1. Women were overrepresented (57.2%). Overall mean age was 54.6 years (SD: 12.6). Among participants without infection prior to baseline, 3.7% reported an infection during follow-up.

In the total sample, 1122 participants (13.3%) had at least one persistent symptom at follow-up; they were 162 (21.0%) in the sample with infection prior to baseline, and 960 (12.5%) in the sample without infection prior to baseline.

The prevalence of the different symptoms in the two samples is displayed in figure 2. Fatigue (5.6%), anosmia (5.3%), poor attention or concentration (5.2%), and sleep problems (4.0%) were the most frequent symptoms in the sample with infection prior to baseline. In the sample without infection, sleep problems (3.7%), joint pain (2.1%), and poor attention or concentration (2.1%) were the most frequent.

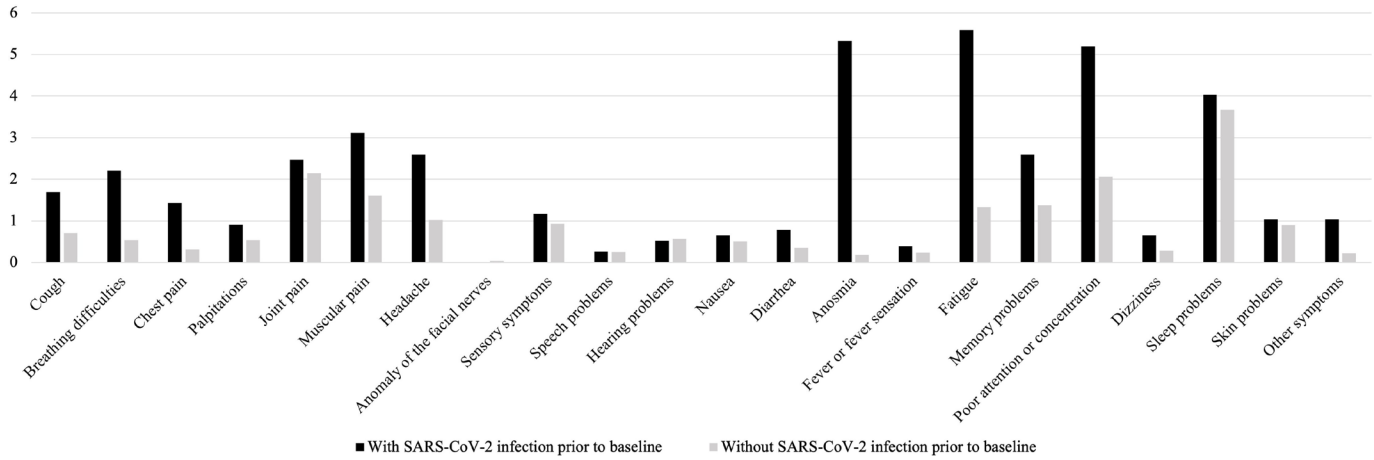

Figure 2 Barplot of the prevalence (%) of persistent symptoms at the end of the follow-up among sample with and without infection.

Unadjusted and multi-adjusted models

The details of unadjusted and multi-adjusted models are displayed in table 2.

In unadjusted analyses, the SSD-12 score (divided by its IQR) at baseline was associated with having at least one persistent symptom at follow-up in the total sample (OR (95% CI): 1.48 (1.37 to 1.60)), as well as in participants with and without infection prior to baseline (1.35 (1.08 to 1.69) and 1.57 (1.43 to 1.72), respectively). Female gender was also associated with a higher risk of persistent symptoms at follow-up, as well as SARS-CoV-2 infection prior to baseline in the total sample (1.85 (1.53 to 2.23)), older age in those with infection prior to baseline and low household income and poor self-rated health in those without. Of note, in the whole sample, the number of persistent symptoms at baseline was also associated (1.24 (1.20 to 1.28)) with the presence of at least one persistent symptom at follow-up.

In the multi-adjusted models, the SSD-12 score remained associated with persistent symptoms at follow-up in the total sample (1.36 (1.24 to 1.49)) as well as among participants with (1.42 (1.09 to 1.84)) and without SARS-CoV-2 infection prior to baseline (1.39 (1.25 to 1.55)). Female gender and older age were also associated with a higher risk of persistent symptoms at follow-up. In the total sample, SARS-CoV-2 infection prior to baseline was also associated with persistent symptoms at follow-up (2.00 (1.64 to 2.41)). In addition, in those without infection prior to baseline, higher educational level and poorer self-rated health at baseline were associated with persistent symptoms at follow-up.

There was no significant interaction between the SSD-12 score and the history of SARS-CoV-2 infection prior to baseline in the total sample (p value=0.38).

Sensitivity analyses

After further adjustment for the number of persistent symptoms at baseline, the SSD-12 score remained associated with persistent symptoms at follow-up in the total sample (1.21 (1.10 to 1.33)) and in participants without infection prior to baseline (1.23 (1.10 to 1.38)), but no longer in those with infection prior to baseline (1.29 (0.98 to 1.71)). There was still no significant interaction between the SSD-12 score and the history of infection prior to baseline in the total sample (p value=0.32). Of note, the number of persistent symptoms at baseline was associated with having at least one persistent symptom at follow-up in the total sample (1.17 (1.12 to 1.21)), as well as in both participants with (1.11 (1.01 to 1.23)) and without infection prior to baseline (1.17 (1.12 to 1.22)).

Among participants without infection prior to baseline, the adjustment for infection during follow-up did not change the association between SSD-12 at baseline and persistent symptoms at follow-up (1.39 (1.25 to 1.55)). Of note, infection during follow-up was not associated with persistent symptoms at follow-up (0.85 (0.57 to 1.23)).

Exploratory analyses

Among participants with SARS-CoV-2 infection prior to baseline, the SSD-12 score predicted the persistence of fatigue (2.10 (1.10 to 4.12)) and poor attention or concentration (4.48 (1.59 to 15.0)) at follow-up among samples of participants with these symptoms at baseline, contrary to breathing difficulties (0.88 (0.22 to 3.37)) and anosmia (1.21 (0.88 to 2.92)) (table 3).

Finally, considering the three factors of the SSD-12 simultaneously instead of the total score, the 'Perceived impairment' factor predicted persistent symptoms at follow-up in the total sample as well as in participants without infection prior to baseline (1.38 (1.22 to 1.56) and 1.34 (1.18 to 1.53), respectively), but not in those with infection prior to baseline (1.34 (0.93 to 1.93)). The 'Perceived severity' factor was not associated with persistent symptoms at follow-up (1.04 (0.94 to 1.15), 0.91 (0.62 to 1.32) and 1.04 (0.93 to 1.16) in the total sample, those with, and those without infection prior to baseline), nor was the 'Negative expectations' factor (0.97 (0.84 to 1.11), 1.19 (0.87 to 1.61) and 1.00 (0.85 to 1.16), respectively).

DISCUSSION

This prospective population-based study included 8424 participants with at least one persistent symptom that occurred during the first waves of the COVID-19 pandemic and aimed to determine whether the associated psychological burden predicted the presence of persistent symptoms 6–10 months later. Among the total sample, 13.3% of participants had at least one persistent symptom at follow-up. This rate was higher among participants with SARS-CoV-2 infection prior to baseline (21.0%) than among participants without infection prior to baseline (12.6%). Adjusting for several potential confounders including self-rated health, the psychological burden associated with persistent symptoms at baseline (ie, SSD-12 score) predicted the presence of at least one persistent symptom at follow-up in both participants with or without SARS-CoV-2 infection prior to baseline. This

Table 2 Association between baseline variables and having at least one persistent symptom at follow-up

	Unadjusted			Adjusted		
	OR	95% CI –	95% CI +	OR	95% CI –	95% CI +
Total sample of participants (N=8424)						
SSD-12 score (per IQR)	1.48***	1.37	1.60	1.36***	1.24	1.49
Female gender	1.40***	1.23	1.95	1.46***	1.28	1.68
Age (per 10 years)	1.03	0.98	1.09	1.09**	1.03	1.15
Educational level	1.00	0.96	1.05	1.04	0.99	1.09
Household income	0.98	0.92	1.04	1.00	0.94	1.08
Smokers†	0.98	0.81	1.17	1.01	0.84	1.22
Body mass index <18.5	1.19	0.79	1.74	1.08	0.71	1.60
18.5–25	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
25–30	1.10	0.95	1.26	1.13	0.98	1.31
>30	1.09	0.89	1.33	1.00	0.81	1.23
Self-rated health	0.82***	0.78	0.86	0.88***	0.84	0.93
SARS-CoV-2 infection prior to baseline	1.85***	1.53	2.23	2.00***	1.64	2.41
Participants with SARS-CoV-2 infection prior to baseline (N=770)						
SSD-12 score (per IQR)	1.35*	1.08	1.69	1.42*	1.09	1.84
Female gender	1.52*	1.06	2.20	1.55*	1.07	2.28
Age (per 10 years)	1.30***	1.13	1.49	1.33**	1.15	1.55
Educational level	0.90	0.80	1.03	0.96	0.83	1.11
Household income	1.04	0.88	1.24	1.03	0.85	1.26
Smokers†	1.12	0.67	1.83	1.24	0.72	2.09
Body mass index <18.5	1.86	0.64	4.84	2.17	0.72	5.88
18.5–25	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
25–30	1.14	0.77	1.68	1.11	0.74	1.67
>30	1.11	0.61	1.94	1.02	0.55	1.81
Self-rated health	0.91	0.80	1.04	1.03	0.88	1.22
Without SARS-CoV-2 infection prior to baseline (N=7654)						
SSD-12 score (per IQR)	1.57***	1.43	1.72	1.39***	1.25	1.55
Female gender	1.38***	1.20	1.58	1.42***	1.23	1.65
Age (per 10 years)	1.03	0.97	1.09	1.06*	1.00	1.13
Educational level	1.01	0.96	1.06	1.06*	1.00	1.12
Household income	0.92**	0.86	0.98	0.94	0.88	1.01
Smokers†	1.02	0.84	1.24	1.01	0.83	1.23
Body mass index <18.5	1.07	0.67	1.63	1.03	0.65	1.57
18.5–25	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
25–30	1.07	0.92	1.24	1.12	0.95	1.31
>30	1.08	0.87	1.34	0.98	0.78	1.23
Self-rated health	0.81***	0.78	0.85	0.88***	0.83	0.93

*p value<0.05, **p value<0.01, ***p value<0.001.
†At inclusion in CONSTANCES cohort.
ref., reference value; SSD-12, 12-item Somatic Symptoms Disorder-B Criteria Scale.

association remained significant after adjustment for the number of baseline persistent symptoms in the total sample as well as in participants without infection prior to baseline, but not in those with infection prior to baseline. However, there was no significant interaction between the SSD-12 score and the infection status at baseline, suggesting that the psychological burden

Table 3 Association between the SSD-12 score (divided by its IQR) and the persistence of post-COVID-19 condition 'core' symptoms from baseline to follow-up among participants with SARS-CoV-2 infection prior to baseline

	N (%) of participants still having the symptom at follow-up	OR	95% CI –	95% CI +
Fatigue (N=234)	29 (12.4)	2.10*	1.10	4.12
Poor attention or concentration (N=112)	20 (17.9)	4.48*	1.59	15.0
Breathing difficulties (N=97)	10 (10.3)	0.88	0.22	3.37
Anosmia (N=177)	35 (19.8)	1.21	0.88	2.92

The analyses were adjusted for gender, age, educational level, household income level, smoking status at inclusion, body mass index and self-rated health.
*P<0.05.
SSD-12, 12-item Somatic Symptoms Disorder-B Criteria Scale.

associated with persistent symptoms predicted the presence of at least one persistent symptom regardless of SARS-CoV-2 infection prior to baseline.

The present study has several strengths. The sample was fairly large and population-based, and the design was prospective. The psychological burden associated with persistent symptoms at baseline was measured with a specific scale. Moreover, participants' SARS-CoV-2 infection status at baseline was measured using different methods (serological testing and/or positive PCR/serology test results declaration). Furthermore, the adjustment for self-rated health at baseline is a major strength of our study. Indeed, self-rated health is considered as one of the best global indicators of health, as evidenced by its association with mortality, healthcare utilisation, quality of life or whole morbidity, including psychological and psychiatric morbidity. Compared with self-reporting comorbid conditions, self-rated health has the advantage of integrating the perceived severity of any comorbid condition, and not only the count of investigated conditions.

However, several significant limitations should be acknowledged. First, the sample could not be considered as representative of the general population (as participants were volunteers from the CONSTANCES cohort). Second, the date of infection prior to baseline could not be precisely determined. Concerning infection status, misclassification, especially false-positive for serology and false-negative for PCR, cannot be excluded. Moreover, most of the participants had not been infected with SARS-CoV-2 prior to baseline, so the sample of infected participants may have lacked statistical power. In addition, new infection during follow-up could not be determined in those with infection prior to baseline. Third, some participants may have filled the SSD-12 with reference to symptoms existing before the first wave of COVID-19 pandemic. Fourth, analyses were not adjusted for anxiety or depression, which have been shown to be risk factors for persistent symptoms after SARS-CoV-2 infection,[7–9] or for other comorbid conditions. However, adjustment for self-rated health may have partially accounted for comorbid conditions. To this end, self-rated health may be a better adjustment variable than any composite variable based on self-reported conditions, which would not integrate perceived severity or could miss conditions that are not listed. Fifth, the COVID-19 vaccine during the follow-up was not accounted for. Finally, this study was observational, and no causal conclusion could be drawn with the statistical methods used, especially as unmeasured confounding variables could explain the results.[21]

Two main hypotheses could explain the association between the SSD-12 score at baseline and persistent symptoms at follow-up. First, the SSD-12 score may capture the severity of persistent symptoms at baseline, which may thus confound the association between the SSD-12 score and the persistence of these symptoms at follow-up. However, this association was significant despite adjustment for self-rated health. The fact that this association did not remain significant after further adjustment for the number of persistent symptoms at baseline among subjects with infection prior to baseline might seem consistent with this hypothesis. However, the lack of significant interaction between the SSD-12 score and the infection status at baseline suggests that it might be merely due to a lack of statistical power in this smaller group, where the OR was actually higher but fell short of statistical significance.

The second main hypothesis, which should not be considered as exclusive of the first one, is that the psychological burden associated with persistent symptoms may have a detrimental effect on their evolution. The well-established association between symptoms' expectation and subsequent symptoms' perception in medicine has been observed in the context of COVID-19 symptoms as well,[13] even in non-infected participants.[22 23] Of note, this second hypothesis is consistent with the increased risk of long COVID observed after a SARS-CoV-2 infection during the first versus the second wave of the pandemic,[24] as the uncertainty associated with COVID-19 at this time may have focused the attention on bodily sensations and fostered catastrophic expectations.[25] However, contrary to this second hypothesis, the 'Negative expectations' factor at baseline was not associated with having at least one persistent symptom at follow-up, whereas only 'Perceived impairment' factor was. Further studies are needed to better understand this association as it may inform therapeutic strategies. For instance, reduced physical activity may be tested as a potential mediator of the association between perceived impairment and the persistence of symptoms.

Overall, in this prospective population-based study of participants with persistent symptoms that occurred during the COVID-19 pandemic, the associated psychological burden at baseline predicted the presence of at least one persistent symptom at follow-up, in both individuals with and without SARS-CoV-2 infection prior to baseline. Although no causal conclusions could be drawn from this observational study, further studies should test whether reducing the psychological burden associated with persistent symptoms could be effective in improving the course of these symptoms.[26] For instance, cognitive–behavioral therapy may be useful in reducing fatigue in patients with post-COVID-19 condition, as suggested by one randomised controlled trial[27] and two quasi-experimental studies.[26 28] Should these results be confirmed, further analyses would be needed to determine whether alleviating the psychological burden associated with persistent symptoms may mediate their improvement over time. Ongoing studies will also provide answers about the effectiveness of targeting negative expectations, which were not associated with persistent symptoms at follow-up in our study.[29] Importantly, such therapeutic targets may be useful in other settings than post-COVID-19 persistent symptoms, as suggested by our findings that may extend beyond the boundaries of post-infectious syndromes.

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