

## ARTICLE



# Depression and anxiety before and at the beginning of the COVID-19 pandemic and incident persistent symptoms: a prospective population-based cohort study

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Many patients affected by COVID-19 suffer from debilitating persistent symptoms whose risk factors remained poorly understood. This prospective study examined the association of depression and anxiety symptoms measured before and at the beginning of the COVID-19 pandemic with the incidence of persistent symptoms. Among 25,114 participants [mean (SD) age, 48.72 years (12.82); 51.1% women] from the SAPRIS and SAPRIS-Sérologie surveys nested in the French CONSTANCES population-based cohort, depression and anxiety symptoms were measured with the Center for Epidemiologic Studies-Depression scale and the 12-item General Health Questionnaire before the pandemic, and with the 9-item Patient Health Questionnaire and the 7-Item Generalized Anxiety Disorder scale at the beginning of the pandemic (i.e., between April 6, 2020 and May 4, 2020). Incident persistent symptoms were self-reported between December 2020 and January 2021. The following variables were also considered: gender, age, educational level, household income, smoking status, BMI, hypertension, diabetes, self-rated health, and SARS-CoV-2 infection according to serology/PCR test results. After a follow-up of seven to ten months, 2329 participants (9.3%) had been infected with SARS-CoV-2 and 4262 (17.0%) reported at least one incident persistent symptom that emerged from March 2020, regardless of SARS-CoV-2 infection. In multi-adjusted logistic regression models, participants in the highest (versus the lowest) quartile of depressive or anxiety symptom levels before or at the beginning of the pandemic were more likely to have at least one incident persistent symptom (versus none) at follow-up [OR (95%CI) ranging from 2.10 (1.89–2.32) to 3.01 (2.68–3.37)], with dose-response relationships ( $p$  for linear trend  $<0.001$ ). Overall, these associations were significantly stronger in non-infected versus infected participants, except for depressive symptoms at the beginning of the pandemic. Depressive symptoms at the beginning of the pandemic were the strongest predictor of incident persistent symptoms in both infected and non-infected participants [OR (95%CI): 2.88 (2.01–4.14) and 3.03 (2.69–3.42), respectively]. In exploratory analyses, similar associations were found for each symptom taken separately in different models. Depression and anxiety symptoms should be tested as a potential target for preventive interventions against persistent symptoms after an infection with SARS-CoV-2.

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## INTRODUCTION

Following an infection with SARS-CoV-2, a substantial proportion of patients report persistent symptoms that can impair their quality of life for months, even after a mild episode of coronavirus disease 2019 (COVID-19) [1, 2]. In clinical settings, patients suffering from this ‘Post-COVID-19 condition’, as named by the World Health Organization (WHO) [3], also frequently referred to as ‘long COVID’, present with debilitating symptoms that generally

contrast with the normality of the physical examination or daily routine tests [4–10]. From a research perspective, there is evidence that an infection with SARS-CoV-2 may be associated with long-term organ damages or physiological disturbances [7–12]. However, there is little or even no correlation between these findings and self-reported persistent symptoms [7–12], suggesting that other mechanisms could also be involved, at least for some patients [13–16].

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A recent study found that depression and anxiety symptoms measured early in the pandemic were associated with the risk of persistent symptoms in individuals with SARS-CoV-2 infection, with a dose-response relationship [17]. Strikingly, this association was stronger than those observed for established risk factors of post-COVID-19 condition, including female gender, older age, obesity, hypertension, or diabetes. These findings mimic earlier results showing that a history of psychiatric condition was an independent predictor of persistent symptoms after COVID-19 [18, 19]. To our knowledge, however, no population-based study prospectively assessed depression and anxiety symptoms before the beginning of the pandemic. Furthermore, as previous studies were restricted to patients having been infected with SARS-CoV-2, it remains unclear whether this association could also be observed among non-infected individuals. Since similar symptoms may occur in the general population, especially during the beginning of the pandemic (i.e., with high level of some stressors, as social isolation or financial issues), the underlying mechanisms may not be specific to an infection with SARS-CoV-2 virus [10, 20–22]. Such knowledge could usefully inform both preventive and therapeutic strategies.

This prospective study took advantage of the French population-based CONSTANCES cohort to examine the associations between depression and anxiety symptoms measured before and at the beginning of the COVID-19 pandemic and the incidence of persistent symptoms seven to ten months later, accounting for gender, age, educational level, household income, smoking status, body mass index (BMI), hypertension, diabetes, self-rated health, and SARS-CoV-2 infection according to serology or PCR test results. Furthermore, we examined whether these associations varied according to past infection with SARS-CoV-2.

## METHODS

### Data source

The French CONSTANCES population-based cohort study received ethical approval and included approximately 200,000 volunteers aged 18–69 years at inclusion between 2012 and 2019 and who gave informed consent to be followed-up through annual questionnaires and linked administrative databases, including the French national health insurance database [23]. Participants were selected among individuals covered by the general insurance scheme or partner health mutual societies (i.e., 85% of the French population) using a random sampling system stratified on place of residence, age, gender, occupation, and socioeconomic status. Eligible individuals were invited to participate in the study by mail. Volunteers completed a self-administered questionnaire on lifestyle and health status and attended a Health Screening Center for a comprehensive evaluation including a physical examination and laboratory tests.

From April 2020, a total of 35,852 volunteers of the CONSTANCES cohort 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 (SERO) surveys, which involved additional questionnaires and serological tests, respectively [24]. 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-Méditerranée III ethics committee. No one received compensation or was offered any incentive for participating in this study.

The present study is a longitudinal analysis of data from the CONSTANCES cohort and from the SAPRIS and SAPRIS-SERO surveys nested in the CONSTANCES cohort.

### Symptoms of depression and anxiety before the pandemic (data from the CONSTANCES cohort)

The inclusion questionnaire from 2012 to 2019 as well as the 2015 and 2018 annual questionnaires of the CONSTANCES cohort included the Center of Epidemiologic Studies-Depression Scale (CES-D) [25]. The 2016 and 2019 annual questionnaires included the 12-item version of the General Health Questionnaire (GHQ-12) [26]. In the present analyses, only the most recent available CES-D and GHQ-12 scores were considered.

### Symptoms of depression and anxiety at the beginning of the pandemic (data from the SAPRIS survey nested in the CONSTANCES cohort)

Between April 6, 2020 and May 4, 2020, depression and anxiety symptoms were measured at the same time with the 9-item Patient Health Questionnaire (PHQ-9) and the 7-item Generalized Anxiety Disorder Assessment (GAD-7) scales, respectively [27]. Since the SAPRIS survey involved three other cohorts, we could not use the same questionnaires than before the pandemic.

### Incident persistent symptoms at follow-up (data from the SAPRIS survey nested in the CONSTANCES cohort)

Between December 2020 and January 2021, incident symptoms were measured with the following question: *"Since March 2020, have you had any of the following symptoms that you did not have before?"* Based on early reports on 'post-acute sequelae of COVID-19' and 'long COVID', later confirmed in the literature [28–30], the following symptoms were explored: cough, breathing difficulties, chest pain, palpitations, back pain, muscular pain or sore muscle, headache, anomaly of the facial nerves, sensory symptoms, speech problems, nausea, diarrhea, constipation, stomach pain, anosmia, fever or fever sensation, fatigue, poor attention or concentration, dizziness, discomfort and other symptoms.

Two additional questions were asked for each 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.

### History of infection with SARS-CoV-2 at follow-up (data from the SAPRIS-SERO and SAPRIS survey nested in the CONSTANCES cohort)

Since PCR tests were not widely available during the first wave of the pandemic, the history of infection with SARS-CoV-2 at follow-up was determined through serologic testing as part of the SAPRIS-SERO survey as well as PCR testing reported in the SAPRIS survey.

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  $-30^{\circ}\text{C}$ . 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%). To reduce the risk of false-negative results, samples with indeterminate results (i.e., optical density ratio  $\geq 0.8$  and  $< 1.1$ ) were discarded.

Between December 2020 and January 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)?"* Participants answered "Yes," "No," or "I don't know." Participants had been provided with their serology test results by mail or email when answering this question from the SAPRIS survey. The participants who answered "Yes" additionally answered two questions: *"When did you get the coronavirus?"* and *"Has this been confirmed?"*

Participants who answered "Yes, by virological or PCR test" or had a positive serology test were considered as having been infected with SARS-CoV-2. Participants who reported having had a COVID-19 infection after their serology test results but without a confirmation by a PCR test were excluded from the analyses as their serology test results may not be interpretable.

### Covariates

Gender, age, educational level, household income, and smoking status were self-reported at inclusion in the CONSTANCES cohort. Self-rated health was recorded before and at the beginning of the pandemic, as it may influence both depression and anxiety symptoms and incident persistent symptoms. BMI was calculated as weight (kg)/height ( $\text{m}^2$ ) from weight and height measured in Health Screening Centers. A history of hypertension / diabetes was determined based on either 1) self-report at inclusion, 2) having a systolic blood pressure of  $> 140$  mmHg and/or

diastolic blood pressure of >90 mmHg) / fasting glucose  $\geq 7$  mmol/l on the medical examination at inclusion, or 3) a pharmacological treatment at inclusion documented in the French national health insurance database. All these data came from the CONSTANCES cohort, except self-rated health at the beginning of the pandemic, which came from the SAPRIS survey nested in the CONSTANCES cohort). Further details regarding covariates are given in Supplemental Methods 1.

### Statistical analysis

In the main analyses, participants were categorized as having either at least one incident persistent symptom (i.e., having reported one symptom or more) or none (i.e., having reported no symptom at all) at follow-up. To focus on symptoms associated with long COVID, only symptoms previously associated with either self-reported COVID-19 or positive SARS-CoV-2 serology tests in the CONSTANCES cohort were considered in the present analysis [16, 20]. Binary logistic regression models were used to compute the odds ratio (OR) and its 95%CI (confidence interval) regarding the association of having at least one incident persistent symptom at follow-up with each predictor, separately: CES-D and GHQ-12 before the pandemic; PHQ-9 and GAD-7 at the beginning of the pandemic. In the main analyses, all predictors were a priori categorized into quartiles to examine potential dose-response relationships as well as to ease the interpretation of the ORs. In sensitivity analyses, predictors were used as continuous variables, divided by their interquartile ranges (IQR) to ease the interpretation of the ORs. As expected in a population-based study, these variables were right skewed.

Models were adjusted for gender, age, educational level, household income, smoking status, BMI, hypertension, diabetes, and infection with SARS-CoV-2. Models were also adjusted for self-rated health either before the pandemic for models with CES-D and GHQ-12, or at the beginning of the pandemic for models with GAD-7 and PHQ-9.

In exploratory analyses, separate binary logistic regression models were computed for each persistent symptom with at least approximately 100 incident cases for statistical power purposes.

Finally, all the analyses were repeated in two subgroups according to the history of SARS-CoV-2 infection. To examine whether the magnitude of the associations between any measure of depression or anxiety symptoms and incident persistent symptoms would significantly vary across the two subgroups, interactions between the given measure and the history of infection with SARS-CoV-2 were systematically tested in the whole population by adding an interaction term in the models.

For the main analyses, a two-sided  $p$ -value < 0.05 was considered statistically significant. For the exploratory analyses considering each symptom separately, a two-sided  $q$ -value < 0.05 (i.e., a Bayesian posterior  $p$ -value according to a false discovery rate approach accounting for a total number of 48 tests) was considered statistically significant [31, 32]. All analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

## RESULTS

### Participants

A total of 25,114 participants with complete data on incident persistent symptoms and covariates were included [mean (SD) age, 48.72 (12.82) years; 51.1% women] (Supplementary Figure 1, Table 1).

Among these 25,114 participants, 2329 (9.3%) have been infected with SARS-CoV-2 and 4262 (17.0%) reported at least one incident persistent symptom at follow-up. Supplementary Fig. 2 show the  $N$  (%) of participants affected for each incident persistent symptom by infection status.

### Variables associated with incident persistent symptoms at follow-up

In unadjusted analyses, participants with at least one (versus no) incident persistent symptom at follow-up were more likely to be women, older, with lower educational level and household income, smokers, with obesity, poorer self-rated health, and history of SARS-CoV-2 infection (Table 1). As hypothesized, they had higher levels of depressive or anxiety symptoms before or at the beginning of the pandemic (Table 1).

### Association of symptoms of depression and anxiety before the pandemic with at least one incident persistent symptom at follow-up

In adjusted analyses, participants in the highest (versus the lowest) quartile of the CES-D score or the GHQ-12 score before the pandemic were two-fold more likely to have at least one incident persistent symptom at follow-up [OR (95%CI) 2.10 (1.89–2.32) and 2.32 (2.07–2.60) for CES-D and GHQ-12, respectively], with a gradient from the lowest to the highest quartile ( $p$  for linear trend < 0.001 for CES-D and GHQ-12) (Table 2). Incident persistent symptoms at follow-up were also associated with female gender, older age, being a current or past smoker, a higher BMI, a poorer self-rated health before the pandemic, and a history of SARS-CoV-2 infection. In sensitivity analyses using continuous measures of depression and anxiety, participants with higher CES-D and GHQ-12 scores before the pandemic were more likely to have at least one incident persistent symptom at follow-up [OR (95%CI) for one IQR increase 1.41 (1.35–1.48) and 1.37 (1.32–1.42), respectively].

### Association of symptoms of depression and anxiety at the beginning of the pandemic with at least one incident persistent symptom at follow-up

In adjusted analyses, participants in the highest (versus the lowest) quartile of the PHQ-9 score or the GAD-7 score at the beginning of the pandemic were up to three-fold more likely to have at least one incident persistent symptom at follow-up [OR (95%CI) 3.01 (2.68–3.37) and 2.25 (2.03–2.50), for PHQ-9 and GAD-7, respectively], with a gradient from the lowest to the highest quartile ( $p$  for linear trend < 0.001 for PHQ-9 and GAD-7) (Table 3). Incident persistent symptoms at follow-up were also associated with female gender, older age, being a current or past smoker, a higher BMI, a poorer self-rated health at the beginning of the pandemic, and a history of SARS-CoV-2 infection. In sensitivity analyses using continuous measures of depression and anxiety, participants with higher PHQ-9 and GAD-7 scores at the beginning of the pandemic were more likely to have at least one incident persistent symptom at follow-up [OR (95%CI) for one IQR increase 1.65 (1.57–1.72) and 1.38 (1.32–1.42), respectively].

### Association of depressive or anxiety symptoms before or at the beginning of the pandemic with each incident persistent symptom at follow-up

In adjusted analyses, participants in the highest (versus the lowest) quartile of depression or anxiety symptoms before or at the beginning of the pandemic were more likely to report each of the incident persistent symptoms with at least 100 cases at follow-up, with OR (95%CI) ranging from 1.67 (1.04–2.68) and 1.65 (1.25–2.20) for the association of depression and anxiety symptoms before the pandemic (GHQ-12) with anosmia and for the association of anxiety at the beginning of the pandemic (GAD-7) with other sensory symptoms, respectively, to 8.09 (5.75–11.38) and 15.49 (9.77–24.57) for the association of depressive symptoms at the beginning of the pandemic (PHQ-9) with fatigue and poor attention or concentration, respectively (Table 4). These associations remained significant according to a false discovery rate approach considering a total number of 48 tests.

### Subgroup analyses according to history of SARS-CoV-2 infection

Having higher levels of depressive or anxiety symptoms before the pandemic or at the beginning of the pandemic was associated with a higher risk of incident persistent symptoms at follow-up in both infected and non-infected participants (Table 5, Fig. 1). Overall, ORs were smaller in infected than non-infected individuals as shown by significant interactions between measures of depression or anxiety symptoms and SARS-CoV-2 infection in

**Table 1.** Descriptive characteristics of the sample total sample and by presence or absence of incident persistent symptoms ( $N = 25,114$ ).

Characteristic	Total population	Incident persistent symptoms at follow-up		P-value <sup>a</sup>
		None $N = 20,852$	At least one $N = 4262$	
	Mean (SD)	Mean (SD)	Mean (SD)	
Age, years	48.72 (12.82)	48.53 (12.87)	49.69 (12.52)	<0.0001
	$N$ (%)	$N$ (%)	$N$ (%)	
Gender				<0.0001
Female	12,834 (51.10)	10,401 (49.88)	2433 (57.09)	
Male	12,280 (48.90)	10,451 (50.12)	1829 (42.91)	
Monthly household income, euros				<0.0001
<1000	382 (1.52)	311 (1.49)	71 (1.67)	
1000 to <1500	753 (3.00)	600 (2.88)	153 (3.59)	
1500 to <2100	1818 (7.24)	1457 (6.99)	361 (8.47)	
2100 to <2800	3166 (12.61)	2582 (12.38)	584 (13.70)	
2800 to <4200	8401 (33.45)	7017 (33.65)	1384 (32.47)	
$\geq 4200$	10,594 (42.18)	8885 (42.61)	1709 (40.10)	
Educational level				<0.0001
No diploma or general education certificate, primary education certificate, school-leaving certificate	916 (3.65)	711 (3.41)	205 (4.81)	
Certificate of professional competence, vocational training certificate	2300 (9.16)	1869 (8.96)	431 (10.11)	
Baccalaureate or equivalent diploma	3396 (13.52)	2785 (13.36)	611 (14.34)	
Baccalaureate plus 2 or 3 years	7090 (28.23)	5896 (28.28)	1194 (28.02)	
Baccalaureate plus 4 years	2784 (11.09)	2319 (11.12)	465 (10.91)	
Baccalaureate plus 5 years and more	8628 (34.36)	7272 (34.87)	1356 (31.82)	
Smoking status				<0.0001
Never smokers	12,594 (50.15)	10,642 (51.04)	1952 (45.80)	
Past smokers	9427 (37.54)	7723 (37.04)	1704 (39.98)	
Current smokers	3093 (12.32)	2487 (11.93)	606 (14.22)	
Body mass index, kg/m <sup>2</sup>				<0.0001
<18.5	993 (3.95)	822 (3.94)	171 (4.01)	
18.5 to < 25	14,446 (57.52)	12,160 (58.32)	2286 (53.64)	
25 to < 30	7385 (29.41)	6087 (29.19)	1298 (30.46)	
$\geq 30$	2290 (9.12)	1783 (8.55)	507 (11.90)	
Hypertension				0.46
No	18,047 (71.86)	15,004 (71.95)	3043 (71.40)	
Yes	7067 (28.14)	5848 (28.05)	1219 (28.60)	
Diabetes				0.40
No	24,419 (97.23)	20,283 (97.27)	4136 (97.04)	
Yes	695 (2.77)	569 (2.73)	126 (2.96)	
CES-D score $\geq 19$ before the pandemic <sup>b</sup>				<0.0001
No	21,940 (87.36)	18,598 (89.19)	3342 (15.23)	
Yes	3174 (12.64)	2254 (10.81)	920 (28.99)	
GHQ-12 score $\geq 1$ before the pandemic <sup>c</sup>				<0.0001
No	17,475 (69.58)	15,006 (71.96)	2469 (57.93)	
Yes	7639 (30.42)	5846 (28.04)	1793 (42.07)	
Self-rated health (scale from 1 to 8) before the pandemic (missing = 15)				<0.0001
1	52 (0.21)	39 (0.19)	13 (0.31)	
2	201 (0.80)	154 (0.74)	47 (1.10)	
3	527 (2.10)	355 (1.70)	172 (4.04)	
4	745 (2.97)	496 (2.38)	249 (5.85)	



Table 1. continued

Characteristic	Total population	Incident persistent symptoms at follow-up		P-value <sup>a</sup>
		None <i>N</i> = 20,852	At least one <i>N</i> = 4262	
5	1602 (6.38)	1116 (5.35)	486 (11.42)	
6	5481 (21.84)	4302 (20.64)	1179 (27.70)	
7	12,556 (50.03)	10,785 (51.75)	1771 (41.60)	
8	3935 (15.68)	3595 (17.25)	340 (7.99)	
PHQ-9 score $\geq 10$ at the beginning of the pandemic (missing = 2912) <sup>d</sup>				<0.0001
No	20,791 (93.64)	17,658 (95.10)	3133 (86.19)	
Yes	1411 (6.36)	909 (4.90)	502 (13.81)	
GAD-7 score $\geq 10$ at the beginning of the pandemic (missing = 2948) <sup>d</sup>				<0.0001
No	20,811 (93.89)	17,599 (94.96)	3212 (88.44)	
Yes	1355 (6.11)	935 (5.04)	420 (11.56)	
Self-rated health (scale from 1 to 8) at the beginning of the pandemic (missing = 1603)				<0.0001
1	77 (0.33)	67 (0.34)	10 (0.25)	
2	224 (0.95)	165 (0.84)	59 (1.50)	
3	343 (1.46)	234 (1.20)	109 (2.77)	
4	461 (1.96)	286 (1.46)	175 (4.45)	
5	984 (4.19)	674 (3.44)	310 (7.88)	
6	3363 (14.30)	2521 (12.88)	842 (21.39)	
7	11,506 (48.94)	9708 (49.59)	1798 (45.68)	
8	6553 (27.87)	5920 (30.24)	633 (16.08)	
Infection with SARS-CoV-2				<0.0001
No	22,785 (90.73)	19,040 (91.31)	3745 (87.87)	
Yes	2329 (9.27)	1812 (8.69)	517 (12.13)	
Number of incident persistent symptoms at follow-up				NA
0	20,852 (83.03)	20,852 (100.00)	NA	
1	2605 (10.37)	NA	2605 (61.12)	
2	938 (3.73)	NA	938 (22.01)	
3	350 (1.39)	NA	350 (8.21)	
4	194 (0.77)	NA	194 (4.55)	
$\geq 5$	175 (0.70)	NA	175 (4.11)	

CES-D Center for Epidemiologic Studies-Depression scale, GAD-7 7-item General Anxiety Disorder scale, GHQ-12 12-item General Health Questionnaire, NA not applicable, PHQ-9 9-item Patient Health Questionnaire, SD Standard Deviation

<sup>a</sup>P-value for the comparison of having no incident persistent symptom with having at least one persistent symptom, using either a chi-square or a Student's *t* test.

<sup>b</sup>For descriptive purposes, a CES-D score  $\geq 19$  was used to identify participants with significant levels of depressive symptoms.

<sup>c</sup>For descriptive purposes, a GHQ-12 score  $\geq 1$  was used to identify participants with significant levels of depressive or anxiety symptoms.

<sup>d</sup>For descriptive purposes, a score  $\geq 10$  for both PHQ-9 and GAD-7 was used to identify participants with significant levels of depressive or anxiety symptoms, respectively.

the whole population (*p* for interaction <0.05), except for the PHQ-9 score (*p* for interaction >0.10). The PHQ-9 score was the strongest predictor of incident persistent symptoms in both infected and non-infected participants [OR (95%CI): 2.88 (2.01–4.14) and 3.03 (2.69–3.42), respectively].

A gradient of the ORs from the lowest to the highest quartile of depression and anxiety symptoms was observed (*p* for linear trend <0.01), except for depression and anxiety symptoms before the pandemic in infected participants. In sensitivity analyses using continuous measures of depression and anxiety, having higher levels of depressive or anxiety symptoms before the pandemic or at the beginning of the pandemic were associated with a higher risk of incident persistent symptoms at follow-up in both infected

and non-infected participants (Table 5). Overall, ORs were smaller in infected than non-infected individuals, as shown by significant interactions between measures of depression or anxiety symptoms and SARS-CoV-2 infection in the whole population (*p* for interaction <0.05) except for the PHQ-9 score (*p* for interaction >0.10). The PHQ-9 score was the strongest predictor of incident persistent symptoms in both infected and non-infected participants [OR (95%CI) for one IQR increase 1.58 (1.38–1.80) and 1.67 (1.59–1.75), respectively].

Supplementary Tables 1 and 2 display the full models for each predictor in two subgroups according to the history of SARS-CoV-2 infection. Supplementary Tables 3 and 4 provide the OR and its 95% CI for each predictor and each incident persistent symptom

**Table 2.** Association between depressive and anxiety symptoms before the pandemic and the incidence of at least one persistent symptom 7 to 10 months later; binary logistic regression.

	Adjusted OR	95% confidence limits	
<b>CES-D score before the pandemic (ref. = first quartile)</b>	<b>N = 24,971</b>		
Second quartile	<b>1.19</b>	<b>1.07</b>	<b>1.32</b>
Third quartile	<b>1.54</b>	<b>1.40</b>	<b>1.70</b>
Fourth quartile	<b>2.10</b>	<b>1.89</b>	<b>2.32</b>
Female gender	<b>1.30</b>	<b>1.21</b>	<b>1.40</b>
Age	<b>1.01</b>	<b>1.00</b>	<b>1.01</b>
Educational level	1.00	0.98	1.03
Household income	1.01	0.98	1.04
Smoking status (ref. = never smokers)			
Past smokers	<b>1.15</b>	<b>1.07</b>	<b>1.24</b>
Current smokers	<b>1.26</b>	<b>1.13</b>	<b>1.40</b>
Body mass index, kg/m <sup>2</sup> (ref. = 18.5 to < 25)			
<18.5	1.04	0.88	1.24
25 to < 30	<b>1.10</b>	<b>1.02</b>	<b>1.19</b>
≥30	<b>1.22</b>	<b>1.09</b>	<b>1.37</b>
Self-rated health before the pandemic	<b>0.78</b>	<b>0.75</b>	<b>0.80</b>
Diabetes	1.10	0.89	1.34
Hypertension	1.02	0.94	1.10
SARS-CoV-2 infection	<b>1.60</b>	<b>1.44</b>	<b>1.78</b>
<b>GHQ-12 score before the pandemic (ref. = first quartile)</b>	<b>N = 24,423</b>		
Second quartile	<b>1.34</b>	<b>1.20</b>	<b>1.50</b>
Third quartile	<b>1.55</b>	<b>1.39</b>	<b>1.73</b>
Fourth quartile	<b>2.32</b>	<b>2.07</b>	<b>2.60</b>
Female gender	<b>1.31</b>	<b>1.22</b>	<b>1.40</b>
Age	<b>1.01</b>	<b>1.01</b>	<b>1.01</b>
Educational level	1.00	0.97	1.02
Household income	0.99	0.96	1.02
Smoking status (ref. = never smokers)			
Past smokers	<b>1.15</b>	<b>1.06</b>	<b>1.24</b>
Current smokers	<b>1.26</b>	<b>1.13</b>	<b>1.40</b>
Body mass index, kg/m <sup>2</sup> (ref. = 18.5 to < 25)			
<18.5	1.06	0.89	1.27
25 to < 30	<b>1.12</b>	<b>1.03</b>	<b>1.21</b>
≥30	<b>1.25</b>	<b>1.11</b>	<b>1.40</b>
Self-rated health before the pandemic	<b>0.78</b>	<b>0.76</b>	<b>0.80</b>
Diabetes	1.10	0.90	1.36
Hypertension	1.01	0.94	1.09
SARS-CoV-2 infection	<b>1.55</b>	<b>1.39</b>	<b>1.73</b>

CES-D Center for Epidemiologic Studies-Depression scale, GHQ-12 12-item General Health Questionnaire, OR: Odds Ratio  
Results in bold are significant at  $p < 0.05$ .

with at least 100 cases at follow-up, in two subgroups according to the history of SARS-CoV-2 infection.

## DISCUSSION

This population-based prospective study aimed to examine the association between depression and anxiety symptoms before or

**Table 3.** Association between depressive and anxiety symptoms at the beginning of the pandemic and the incidence of at least one persistent symptom 7 to 10 months later; binary logistic regression.

	Adjusted OR	95% confidence limits	
<b>PHQ-9 score at the beginning of the pandemic (ref. = first quartile)</b>	<b>N = 22,140</b>		
Second quartile	<b>1.50</b>	<b>1.33</b>	<b>1.68</b>
Third quartile	<b>1.89</b>	<b>1.67</b>	<b>2.13</b>
Fourth quartile	<b>3.01</b>	<b>2.68</b>	<b>3.37</b>
Female gender	<b>1.20</b>	<b>1.11</b>	<b>1.29</b>
Age	<b>1.01</b>	<b>1.01</b>	<b>1.02</b>
Educational level	0.98	0.96	1.01
Household income	1.00	0.97	1.03
Smoking status (ref. = never smokers)			
Past smokers	<b>1.12</b>	<b>1.04</b>	<b>1.22</b>
Current smokers	<b>1.20</b>	<b>1.07</b>	<b>1.34</b>
Body mass index, kg/m <sup>2</sup> (ref. = 18.5 to < 25)			
<18.5	1.01	0.83	1.22
25 to < 30	1.06	0.98	1.16
≥30	<b>1.20</b>	<b>1.06</b>	<b>1.35</b>
Self-rated health at the beginning of the pandemic	<b>0.80</b>	<b>0.77</b>	<b>0.82</b>
Diabetes	1.09	0.88	1.36
Hypertension	1.01	0.93	1.09
SARS-CoV-2 infection	<b>1.50</b>	<b>1.33</b>	<b>1.69</b>
<b>GAD-7 score at the beginning of the pandemic (ref. = first quartile)</b>	<b>N = 22,105</b>		
Second quartile	<b>1.29</b>	<b>1.14</b>	<b>1.47</b>
Third quartile	<b>1.52</b>	<b>1.37</b>	<b>1.68</b>
Fourth quartile	<b>2.25</b>	<b>2.03</b>	<b>2.50</b>
Female gender	<b>1.23</b>	<b>1.14</b>	<b>1.33</b>
Age	<b>1.01</b>	<b>1.01</b>	<b>1.01</b>
Educational level	1.00	0.97	1.03
Household income	0.98	0.95	1.01
Smoking status (ref. = never smokers)			
Past smokers	<b>1.14</b>	<b>1.05</b>	<b>1.24</b>
Current smokers	<b>1.25</b>	<b>1.12</b>	<b>1.40</b>
Body mass index, kg/m <sup>2</sup> (ref. = 18.5 to < 25)			
<18.5	1.05	0.87	1.27
25 to < 30	<b>1.09</b>	<b>1.00</b>	<b>1.19</b>
≥30	<b>1.24</b>	<b>1.10</b>	<b>1.41</b>
Self-rated health at the beginning of the pandemic	<b>0.77</b>	<b>0.75</b>	<b>0.80</b>
Diabetes	1.09	0.88	1.36
Hypertension	1.01	0.93	1.10
SARS-CoV-2 infection	<b>1.51</b>	<b>1.34</b>	<b>1.70</b>

GAD-7 7-item General Anxiety Disorder scale, OR Odds Ratio, PHQ-9 9-item Patient Health Questionnaire  
Results in bold are significant at  $p < 0.05$ .

at the beginning of the COVID-19 pandemic and the incidence of persistent symptoms seven to ten months later. Overall, there was a dose-response relationship between depression or anxiety symptoms before or at the beginning of the pandemic and the incidence of persistent symptoms at follow-up. Effect sizes of these associations were comparable to those observed for the

**Table 4.** Association between depression and anxiety symptoms before and at the beginning of the pandemic and the incidence of persistent symptoms 7 to 10 months later; binary logistic regression models for symptoms reported by at least 100 participants.

	CES-D score before the pandemic (ref. = Q1)				Number cases/ total	GHQ-12 score before the pandemic (ref. = Q1)				Number cases/ total
	Q2	Q3	Q4			Q2	Q3	Q4		
Cough	1.48 (0.90–2.44)	<b>1.75 (1.08–2.83)</b>	<b>2.29 (1.41–3.71)</b>		170/24,789	1.37 (0.83–2.26)	1.32 (0.78–2.23)	<b>1.98 (1.18–3.33)</b>		165/24,247
Breathing difficulties	1.09 (0.75–1.59)	1.08 (0.74–1.57)	<b>1.76 (1.24–2.51)</b>		276/24,652	<b>1.12 (0.74–1.69)</b>	<b>1.32 (0.87–2.01)</b>	<b>2.25 (1.50–3.37)</b>		266/24,114
Chest pain	1.19 (0.73–1.93)	1.63 (1.04–2.55)	<b>2.08 (1.32–3.27)</b>		180/24,686	<b>1.52 (0.88–2.62)</b>	<b>1.92 (1.11–3.30)</b>	<b>3.42 (2.00–5.85)</b>		175/24,149
Palpitations	1.64 (1.02–2.64)	<b>1.85 (1.17–2.94)</b>	<b>3.27 (2.10–5.08)</b>		228/24,549	1.22 (0.75–1.98)	<b>1.71 (1.06–2.75)</b>	<b>2.64 (1.65–4.20)</b>		223/24,018
Back pain	<b>1.32 (1.12–1.56)</b>	<b>1.60 (1.36–1.87)</b>	<b>1.90 (1.62–2.23)</b>		1552/24,486	1.38 (1.16–1.64)	<b>1.60 (1.34–1.90)</b>	<b>1.91 (1.59–2.28)</b>		1514/23,961
Muscular pain, sore muscle	0.98 (0.77–1.24)	<b>1.56 (1.26–1.93)</b>	<b>1.99 (1.61–2.46)</b>		828/24,545	1.21 (0.95–1.53)	<b>1.46 (1.15–1.85)</b>	<b>2.38 (1.88–3.02)</b>		813/24,016
Headache	<b>1.54 (1.05–2.28)</b>	<b>2.22 (1.55–3.19)</b>	<b>3.21 (2.25–4.57)</b>		371/24,583	2.22 (1.41–3.51)	<b>2.76 (1.75–4.34)</b>	<b>4.79 (3.07–7.47)</b>		361/24,050
Sensory symptoms	1.06 (0.78–1.42)	<b>1.49 (1.13–1.95)</b>	<b>1.82 (1.38–2.40)</b>		475/24,680	1.48 (1.07–2.03)	<b>1.77 (1.28–2.44)</b>	<b>2.46 (1.78–3.41)</b>		455/24,145
Diarrhea	0.91 (0.51–1.61)	1.39 (0.83–2.34)	<b>2.45 (1.51–3.98)</b>		151/24,644	0.99 (0.57–1.75)	1.24 (0.71–2.17)	<b>2.16 (1.27–3.69)</b>		145/24,108
Constipation	0.96 (0.67–1.37)	1.39 (1.01–1.92)	<b>2.05 (1.50–2.80)</b>		366/24,309	1.42 (1.00–2.02)	1.40 (0.97–2.01)	<b>1.92 (1.34–2.75)</b>		358/23,786
Stomach pain	1.25 (0.87–1.79)	<b>1.56 (1.11–2.19)</b>	<b>2.41 (1.74–3.35)</b>		359/24,572	<b>1.32 (0.91–1.93)</b>	<b>1.85 (1.28–2.68)</b>	<b>2.62 (1.81–3.81)</b>		353/24,042
Anosmia	0.93 (0.57–1.51)	1.09 (0.69–1.73)	<b>2.37 (1.55–3.62)</b>		185/24,611	1.10 (0.69–1.74)	<b>1.05 (0.65–1.70)</b>	<b>1.67 (1.04–2.68)</b>		183/24,079
Fatigue	<b>1.53 (1.18–1.99)</b>	<b>2.20 (1.72–2.81)</b>	<b>3.74 (2.95–4.74)</b>		829/24,615	1.61 (1.21–2.15)	<b>2.19 (1.65–2.91)</b>	<b>4.17 (3.17–5.49)</b>		808/24,079
Poor attention or concentration	<b>1.70 (1.22–2.35)</b>	<b>2.63 (1.94–3.57)</b>	<b>5.45 (4.09–7.28)</b>		653/24,759	1.44 (1.03–2.03)	<b>2.03 (1.46–2.83)</b>	<b>5.13 (3.75–7.00)</b>		641/24,217
Dizziness	1.10 (0.65–1.85)	1.55 (0.96–2.50)	<b>2.34 (1.47–3.72)</b>		173/24,616	1.12 (0.67–1.89)	1.13 (0.66–1.94)	<b>2.84 (1.72–4.68)</b>		170/24,088
Other symptoms	1.12 (0.81–1.55)	1.18 (0.86–1.62)	<b>2.09 (1.56–2.81)</b>		403/24,822	<b>1.08 (0.77–1.49)</b>	<b>1.41 (1.02–1.95)</b>	<b>1.74 (1.25–2.42)</b>		394/24,283
	PHQ-9 score at the beginning of the pandemic (ref. = Q1)				Number cases/ total	GAD-7 score at the beginning of the pandemic (ref. = Q1)				Number cases/ total
	Q2	Q3	Q4			Q2	Q3	Q4		
Cough	1.80 (1.02–3.17)	<b>2.62 (1.47–4.65)</b>	<b>2.92 (1.67–5.10)</b>		141/21,979	1.16 (0.63–2.14)	1.47 (0.93–2.33)	<b>1.93 (1.20–3.09)</b>		138/21,950
Breathing difficulties	<b>2.32 (1.38–3.90)</b>	<b>2.75 (1.61–4.68)</b>	<b>4.35 (2.65–7.14)</b>		238/21,869	<b>1.77 (1.08–2.90)</b>	<b>1.87 (1.25–2.79)</b>	<b>2.63 (1.77–3.93)</b>		234/21,837
Chest pain	<b>2.63 (1.48–4.70)</b>	<b>2.39 (1.28–4.48)</b>	<b>3.73 (2.10–6.64)</b>		152/21,890	<b>2.07 (1.11–3.86)</b>	<b>2.69 (1.63–4.44)</b>	<b>3.15 (1.88–5.29)</b>		147/21,858
Palpitations	1.74 (1.01–3.00)	1.79 (1.01–3.20)	<b>3.74 (2.25–6.23)</b>		183/21,767	1.55 (0.84–2.86)	<b>1.85 (1.15–2.98)</b>	<b>3.65 (2.31–5.76)</b>		178/21,733
Back pain	1.18 (0.99–1.41)	<b>1.50 (1.24–1.80)</b>	<b>2.15 (1.81–2.56)</b>		1317/21,715	1.09 (0.89–1.34)	<b>1.36 (1.17–1.59)</b>	<b>1.77 (1.51–2.07)</b>		1310/21,675
Muscular pain, sore muscle	<b>1.44 (1.13–1.83)</b>	<b>1.81 (1.40–2.33)</b>	<b>2.70 (2.14–3.42)</b>		695/21,780	1.12 (0.85–1.47)	<b>1.35 (1.10–1.66)</b>	<b>1.88 (1.52–2.31)</b>		698/21,745
Headache	<b>2.31 (1.50–3.57)</b>	<b>2.32 (1.47–3.67)</b>	<b>4.64 (3.07–7.03)</b>		324/21,808	1.23 (0.79–1.92)	<b>1.48 (1.06–2.08)</b>	<b>2.59 (1.87–3.59)</b>		316/21,759
Sensory symptoms	<b>1.61 (1.19–2.19)</b>	<b>1.69 (1.21–2.37)</b>	<b>2.28 (1.68–3.10)</b>		399/21,900	1.20 (0.84–1.71)	<b>1.55 (1.18–2.02)</b>	<b>1.65 (1.25–2.20)</b>		395/21,857
Diarrhea	1.51 (0.84–2.71)	1.27 (0.65–2.47)	<b>2.74 (1.57–4.80)</b>		120/21,867	1.53 (0.84–2.80)	1.26 (0.76–2.10)	<b>2.16 (1.32–3.52)</b>		126/21,832
Constipation	1.39 (0.95–2.04)	<b>1.86 (1.26–2.75)</b>	<b>2.70 (1.88–3.88)</b>		315/21,562	1.38 (0.93–2.04)	1.30 (0.95–1.79)	<b>1.86 (1.35–2.55)</b>		314/21,524
Stomach pain	1.28 (0.88–1.86)	1.77 (0.92–2.06)	<b>2.81 (1.98–3.99)</b>		305/21,797	<b>1.63 (1.07–2.48)</b>	<b>1.81 (1.29–2.54)</b>	<b>2.64 (1.89–3.70)</b>		301/21,764
Anosmia	<b>2.35 (1.32–4.19)</b>	1.77 (0.93–3.37)	<b>3.51 (1.98–6.20)</b>		146/21,811	1.90 (1.02–3.52)	<b>2.16 (1.31–3.55)</b>	<b>3.21 (1.94–5.31)</b>		148/21,774
Fatigue	<b>2.23 (1.54–3.24)</b>	<b>3.72 (2.58–5.36)</b>	<b>8.09 (5.75–11.38)</b>		691/21,834	1.41 (1.00–1.99)	<b>2.08 (1.61–2.70)</b>	<b>4.22 (3.29–5.41)</b>		686/21,796
Poor attention or concentration	<b>2.88 (1.74–4.77)</b>	<b>6.59 (4.06–10.68)</b>	<b>15.49 (9.77–24.57)</b>		555/21,952	1.24 (0.85–1.82)	<b>1.85 (1.39–2.45)</b>	<b>4.15 (3.18–5.42)</b>		555/21,920
Dizziness	<b>1.91 (1.13–3.22)</b>	1.39 (0.76–2.55)	<b>2.66 (1.58–4.48)</b>		147/21,833	1.24 (0.68–2.25)	1.36 (0.86–2.17)	<b>2.10 (1.33–3.32)</b>		144/21,795
Other symptoms	1.25 (0.88–1.77)	<b>1.60 (1.11–2.30)</b>	<b>2.41 (1.73–3.35)</b>		341/22,013	<b>1.90 (1.31–2.74)</b>	<b>1.66 (1.22–2.27)</b>	<b>2.25 (1.64–3.08)</b>		341/21,984

CES-D Center for Epidemiologic Studies-Depression scale, GAD-7 7-item General Anxiety Disorder scale, GHQ-12 12-item General Health Questionnaire, PHQ-9 9-item Patient Health Questionnaire, Q1, Q2, Q3, and Q4: 1st, 2nd, 3rd, and 4th quartiles.

Differences in the total number of participants according to symptoms are due to slight differences of missing data for each symptom.

Other figures are odds ratios and their 95% confidence interval, adjusted for gender, age, educational level, household income, smoking status, body mass index, hypertension, diabetes, self-rated health, and SARS-CoV-2 infection.

Results in bold are significant at  $p < 0.05$  (i.e., Bayesian posterior  $p$ -value according to a false discovery rate approach accounting for a total number of 48 tests).

**Table 5.** Association between depression and anxiety symptoms before and at the beginning of the pandemic and the incidence of at least one persistent symptom 7 to 10 months later among participants with or without SARS-CoV-2 infection; binary logistic regression.

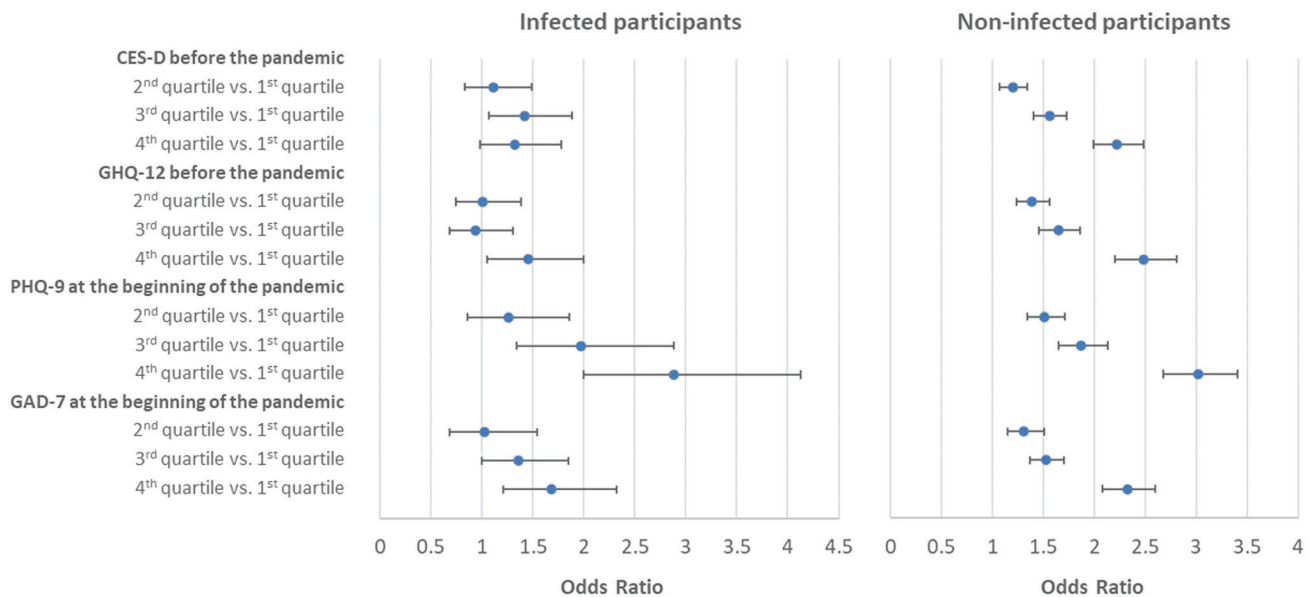
	Participants with infection			Participants without infection		
	Adjusted OR	95% confidence limits		Adjusted OR	95% confidence limits	
<b>CES-D score before the pandemic (ref. = first quartile)</b>	<b>N = 2311</b>			<b>N = 22,660</b>		
Second quartile	1.11	0.83	1.49	<b>1.20</b>	<b>1.08</b>	<b>1.34</b>
Third quartile	<b>1.43</b>	<b>1.08</b>	<b>1.89</b>	<b>1.56</b>	<b>1.40</b>	<b>1.74</b>
Fourth quartile	1.33	0.99	1.79	<b>2.23</b>	<b>2.00</b>	<b>2.48</b>
CES-D score before the pandemic as continuous variable <sup>a</sup>	<b>1.16</b>	<b>1.02</b>	<b>1.31</b>	<b>1.45</b>	<b>1.39</b>	<b>1.51</b>
<b>GHQ-12 score before the pandemic (ref. = first quartile)</b>	<b>N = 2238</b>			<b>N = 22,185</b>		
Second quartile	1.02	0.75	1.38	<b>1.40</b>	<b>1.24</b>	<b>1.57</b>
Third quartile	0.94	0.68	1.30	<b>1.65</b>	<b>1.47</b>	<b>1.86</b>
Fourth quartile	<b>1.45</b>	<b>1.05</b>	<b>2.00</b>	<b>2.49</b>	<b>2.20</b>	<b>2.81</b>
GHQ-12 score before the pandemic as a continuous variable <sup>a</sup>	<b>1.16</b>	<b>1.04</b>	<b>1.29</b>	<b>1.40</b>	<b>1.35</b>	<b>1.46</b>
<b>PHQ-9 score at the beginning of the pandemic (ref. = first quartile)</b>	<b>N = 1944</b>			<b>N = 20,196</b>		
Second quartile	1.27	0.87	1.86	<b>1.52</b>	<b>1.35</b>	<b>1.71</b>
Third quartile	<b>1.97</b>	<b>1.35</b>	<b>2.89</b>	<b>1.88</b>	<b>1.65</b>	<b>2.14</b>
Fourth quartile	<b>2.88</b>	<b>2.01</b>	<b>4.14</b>	<b>3.03</b>	<b>2.69</b>	<b>3.42</b>
PHQ-9 score at the beginning of the pandemic as a continuous variable <sup>a</sup>	<b>1.58</b>	<b>1.38</b>	<b>1.80</b>	<b>1.67</b>	<b>1.59</b>	<b>1.75</b>
<b>GAD-7 score at the beginning of the pandemic (ref. = first quartile)</b>	<b>N = 1933</b>			<b>N = 20,172</b>		
Second quartile	1.03	0.68	1.54	<b>1.32</b>	<b>1.15</b>	<b>1.51</b>
Third quartile	<b>1.37</b>	<b>1.01</b>	<b>1.86</b>	<b>1.53</b>	<b>1.38</b>	<b>1.70</b>
Fourth quartile	<b>1.68</b>	<b>1.21</b>	<b>2.33</b>	<b>2.33</b>	<b>2.09</b>	<b>2.60</b>
GAD-7 score at the beginning of the pandemic as a continuous variable <sup>a</sup>	<b>1.24</b>	<b>1.10</b>	<b>1.40</b>	<b>1.39</b>	<b>1.34</b>	<b>1.45</b>

CES-D Center for Epidemiologic Studies-Depression scale, GAD-7 7-item General Anxiety Disorder scale, GHQ-12 12-item General Health Questionnaire, OR Odds Ratio, PHQ-9 9-item Patient Health Questionnaire

OR and their 95% confidence limits are adjusted for gender, age, educational level, household income, smoking status, body mass index, hypertension, diabetes, and self-rated health.

<sup>a</sup>OR and their 95% confidence limits are given for one IQR increase of the depression or anxiety measure.

Results in bold are significant at  $p < 0.05$ .



**Fig. 1** Association of depressive or anxiety symptoms before or at the beginning of the pandemic with the incidence of at least one persistent symptom 7 to 10 months later among participants with or without SARS-CoV-2 infection. Dots and bars respectively indicate adjusted odds ratios and 95% confidence intervals for the association of depression and anxiety measures with the incidence of at least one persistent symptom 7 to 10 months later. The left and right panels display these associations among participants with and without a history of SARS-CoV-2 infection, respectively.



association between incident persistent symptoms and a history of infection with SARS-CoV-2. These associations were significant for each incident persistent symptom taken individually. Depression and anxiety symptoms were more strongly linked with incident persistent symptoms in non-infected than infected participants, except for depressive symptoms at the beginning of the pandemic, which were the strongest predictor of incident persistent symptoms in both infected and non-infected participants.

The strengths of our study include the large size and the population-based nature of the sample, as well as the prospective design. Moreover, adjusting for self-rated health, a sensitive indicator of global health, as well as for major risk factors of severe COVID-19, allowed us to partially control for the potential confounding role of symptom burden before or at the beginning of the pandemic. It is noteworthy that vaccination adherence was unlikely to mediate the associations of depressive or anxiety symptoms with incident persistent symptoms since the vaccination campaign started on December 27, 2020 in France. Finally, based on both serology test results of the SAPRIS-SERO survey and self-reported PCR test results, we were able to compare the effect sizes of these associations with those of a SARS-CoV-2 infection and to examine whether these associations were specific to post-acute symptoms of COVID-19 or could also affect non-infected individuals.

Limitations include the observational nature of the data, which prevents causal conclusions. Second, selection biases limit the representativeness of our sample. Third, self-reported questionnaires do not provide clinical diagnoses of depressive or anxiety disorders. Fourth, misclassification regarding the history of infection with SARS-CoV-2 may have occurred because of false positives and false negatives with either serology or self-reported PCR test results. Fifth, some participants may have been infected with SARS-CoV-2 before the measure of depression and anxiety symptoms at the beginning of the pandemic. Therefore, the association of depression and anxiety symptoms at the beginning of the pandemic with persistent symptoms could have been explained to some extent by the infection. However, the greater effect sizes observed in non-infected participants makes it unlikely. Sixth, symptoms reported as incident at follow-up were not assessed before the pandemic, so that some of them could have already been present at the beginning of the pandemic because of memory bias. Although self-rated health was measured both before and at the beginning of the pandemic, it may not have fully accounted for the symptom burden. This memory bias could therefore have reduced the specificity of self-reported symptoms regarding the context of the COVID-19 pandemic and SARS-CoV-2 infection. This issue could also contribute to an over-attribution of persistent symptoms to the post-COVID-19 condition in clinical settings. Moreover, adjusting for self-rated health might not have entirely captured the bi-directional association between depression and physical symptom burden, which goes beyond physical symptoms of depression and encompasses the frequent comorbidity of depression with other medical conditions. In other words, depressive symptoms might partially signal the presence of a comorbid condition and thus not be independently linked to incident persistent symptoms. Lastly, we used different measures of depression and anxiety before and at the beginning of the pandemic.

Incident persistent symptoms were quite frequent in this population with one participant out of six having at least one new persistent symptom at follow-up. Although some infected participants may not have been identified, this result is an important reminder that incident persistent symptoms may occur without any infection with SARS-CoV-2, as previously shown in the literature [10, 21, 22]. However, should such symptoms occur within three months of COVID-19 infection, affect everyday functioning, and be of otherwise unknown origin, they would

meet the definition of the 'post-COVID-19 condition' [3]. A default attribution of such symptoms to a post-COVID-19 condition among infected individuals may therefore result in clinical heterogeneity that may make it difficult to find specific biomarkers underlying this condition [15].

Our results restricted to infected participants are consistent with previous studies linking the risk of incident persistent symptoms after COVID-19 with either a history of depressive or anxiety disorder [18, 19] or measures of psychological distress at the beginning of the pandemic [17]. However, our study goes further regarding two points. First, depression and anxiety symptoms before the pandemic were measured prospectively, thus preventing memory biases to account for the associations. Second, our study provides evidence that these associations may also be observed in non-infected individuals, with even greater effect sizes. This finding suggests that the mechanisms linking depression and anxiety symptoms to the incidence of persistent symptoms may not be specific to SARS-CoV-2 infection.

Several hypotheses may account for the present results. First, some core clinical features of long COVID, such as fatigue, cognitive impairment or aberrant activation of the autonomous nervous system, are also frequent 'somatic' symptoms of depressive or anxiety disorders [33]. This overlap may partially explain why depression and anxiety symptoms were so strongly associated with fatigue and poor attention or concentration, compared to other incident persistent symptoms. Depression, however, is associated with a proneness to experience non-specific physical symptoms that go beyond those considered diagnostic criteria for major depression [34], including anosmia [35]. Second, depression and anxiety may share some risk factors with incident persistent symptoms. For instance, depression is associated with low-grade inflammation [36] or altered functioning of the autonomous nervous system [37], two putative mechanisms of long COVID [38]. However, this would not explain the association in noninfected individuals. Psychological mechanisms may also be considered [15]. For instance, uncertainty is a well-established cause of subjective distress that our brain is hardwired to reduce [39, 40]. In the context of ambiguous perceptive situations, attempts to reduce uncertainty may lead our brain to overweight top-down expectations at the expense of actual bottom-up sensory inputs, leading to nocebo effect [41–43]. Intolerance to uncertainty may thus account for both vulnerability to psychological distress, as captured by depression and anxiety symptoms, and persistent symptoms of any kind. It might partially explain why depression and anxiety symptoms have been associated with an increased risk of developing functional somatic disorders such as irritable bowel syndrome [44] or fibromyalgia [45].

Although all these mechanisms may play a role in the association between measures of depression and anxiety and the incidence of persistent symptoms in both infected and non-infected participants, their relative contribution may be smaller in infected participants, as suggested by smaller effect sizes compared to non-infected individuals. Infection-specific mechanisms unrelated to depression or anxiety may obviously be more frequent in infected participants than non-infected participants [38]. Interestingly, however, similar effect sizes were observed for depressive symptoms at the beginning of the pandemic in both infected and non-infected participants. A possible explanation is that some mechanisms specifically associated with current or recent depression, compared to those shared with anxiety or past depression, may interact with COVID-19 to trigger persistent symptoms, thus adding to mechanisms unrelated to infection. For instance, low-grade inflammation associated with depression [36] suggests a proneness to dysregulated immune function that may be triggered or amplified by an infection [38]. Likewise, poor interoceptive accuracy associated with depression [46] may reduce the relative weight of bottom-up sensory inputs compared to top-down expectations in shaping bodily sensations [41], thus

contributing to the association of depression with proneness to experience non-specific physical symptoms in the context of a potentially life-threatening experience [14].

To summarize, depression and anxiety symptoms before and at the beginning of the COVID-19 pandemic were associated with the risk of incident persistent symptoms with dose-response relationship. These associations were especially strong for depressive symptoms at the beginning of the pandemic, in both infected and non-infected individuals. Further studies should investigate potential mechanisms of these associations as they may eventually inform preventive and therapeutic strategies [47]. In addition, accounting for depression and anxiety symptoms in patients with long COVID may help to discover relevant biomarkers by reducing clinical heterogeneity between and within individuals [15].

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## AUTHOR CONTRIBUTIONS

JM and CL take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. CL designed the study; MG,

MT, GS, and MZ acquired the data; JM and CL performed statistical analysis. All authors contributed to the interpretation of data. JM and CL drafted the article; OR, EW, FC, GS, MT, CG, COV, VP, BR, BP, NH, SK, MG, MZ revised it critically for important intellectual content. All authors have read and approved the final manuscript. All authors confirm that they had full access to all the data in the study and accept responsibility to submit for publication.

## COMPETING INTERESTS

Dr Robineau reported personal fees and nonfinancial support from Gilead, ViiV Healthcare, and Merck Sharp & Dohme Corp outside the submitted work. Dr Pitron reported personal fees from Grunenthal, outside the submitted work. Dr Lemogne reported non-financial support from Nordic Pharma, outside the submitted work. No other disclosures were reported.

## ADDITIONAL INFORMATION

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