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RESEARCH

Anxiety and depression in people with post-COVID condition: a Belgian population-based cohort study three months after SARS-CoV-2 infection

Stéphanie D'Hondt[1] · Lydia Gisle[2] · Robby De Pauw[2,3] · Dieter Van Cauteren[2] · Stefaan Demarest[2] · Sabine Drieskens[2] · Laura Cornelissen[2] · Karin De Ridder[2] · Rana Charafeddine[2] · Pierre Smith[2,4]

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Abstract

Purpose Since the onset of the COVID-19 pandemic, most research has focused on the management of the acute symptoms of the disease. Yet some people tend to experience symptoms beyond the acute phase, defined as Post-COVID-19 Condition (PCC). This study aims to assess the impact of COVID-19 and PCC on anxiety and depression.

Methods This is a prospective longitudinal cohort study among the Belgian adult population with recent SARS-CoV-2 infection for which contact tracing was initiated. A total of 3127 people were followed-up just after their infection and three months later (from April 2021 to January 2022). Anxiety and depression were assessed at the two stages using the GAD-7 (Generalized Anxiety Disorder) and the PHQ-9 (Patient Health Questionnaire).

Results Three months after infection, participants with PCC (50%) had an increased probability of having both anxiety and depressive symptoms ($p < 0.001$). The proportion with anxiety and depressive symptoms at three months were significantly higher in people with PCC (11% and 19%) compared to people without persistent COVID symptoms (3.8% and 4.2%) and to a matched sub-sample not infected with SARS-CoV-2 (6.5% and 4.3%). Having at least one acute COVID-19 symptom ($p < 0.001$), experiencing financial loss following the infection ($p < 0.001$), and different PCC symptoms were associated with anxiety and depressive symptoms worsening over time.

Conclusions This study showed that three months after a SARS-CoV-2 infection, one in two people suffer from PCC with significant consequences for their mental health. Follow-up on mental health must therefore have an important place in people suffering from PCC.

Keywords COVID-19 · Post COVID-19 condition · Anxiety · Depression

✉ Pierre Smith
pierre.smith@sciensano.be

Stéphanie D'Hondt
scdhondt@yahoo.fr

Lydia Gisle
lydia.gisle@sciensano.be

Robby De Pauw
robby.depauw@sciensano.be

Dieter Van Cauteren
dieter.vancauteren@sciensano.be

Stefaan Demarest
stefaan.demarest@sciensano.be

Sabine Drieskens
sabine.drieskens@sciensano.be

Laura Cornelissen
laura.cornelissen@sciensano.be

Karin De Ridder
karin.deridder@sciensano.be

Rana Charafeddine
rana.charafeddine@sciensano.be

[1] Faculty of Public Health, Université catholique de Louvain, Rue Juliette Wytsmanstraat 14, Brussels 1050, Belgium

[2] Department of Epidemiology and public health, Sciensano, Brussels, Belgium

[3] Department of Rehabilitation Sciences, Ghent University, Ghent, Belgium

[4] Institute of Health and Society (IRSS), Université catholique de Louvain, Brussels, Belgium

Introduction

The first cases of coronavirus disease 2019 (COVID-19) were identified in Wuhan City (China) in December 2019 and the World Health Organization (WHO) declared COVID-19 a global pandemic on March 11, 2020. In critical cases, COVID-19 symptoms escalate into an acute respiratory distress syndrome accompanied by an inflammatory cytokine response and multi-organ failure. Among patients admitted to the intensive care unit (ICU), mortality ranged from 14 to 66%, depending on patient-specific factors such as age and the presence of chronic diseases [1]. As a consequence of the rapid spread of the virus and its clinical signs, early research focused on managing the acute symptoms of the disease. However, some people continue to experience symptoms beyond the acute phase of the infection, which has drawn less immediate attention. This phenomenon is referred to as long COVID or Post-COVID-19 Condition (PCC) [2].

Currently, there is still no clear and widely accepted definition of PCC. In December 2020, the National Institute for Health and Care Excellence (NICE) proposed a definition of PCC as symptoms being reported beyond three months after onset of the disease, which cannot be explained by an alternative diagnosis [3]. A meta-analysis on 33 studies showed that PCC symptoms were present in more than 60% of people who had been infected by SARS-CoV-2 [4]. Fatigue and dyspnea (35–60%) were the most prevalent PCC symptoms, particularly 60 and ≥ 90 days after COVID-19 onset or hospitalization. Other PCC symptoms included cough (20–25%), anosmia (10–20%), ageusia (15–20%) or joint pain (15–20%). The heterogeneity of clinical manifestations of PCC highlights that it affects several systems in the body (e.g. the respiratory, gastrointestinal, muscular and neurological systems). However, there is much that remains unknown, and research on PCC is still in its infancy, in particular regarding its impact on mental health outcomes such as anxiety or depression.

Anxiety and depression are among the most prevalent mental health problems in the general population [5, 6], and are known to have a significant burden for individuals (e.g. reduced quality of life) and for society (e.g. high direct and indirect costs) [7, 8]. For example, in 2018 in Belgium, the prevalence of anxiety and depressive disorders was 11% and 9%, respectively, and they were responsible for 10% of the overall burden of disease [9]. It is therefore important to rapidly detect and treat symptoms of anxiety and depression, or even better, to prevent them. To explain the underlying mechanisms of the impact of PCC on anxiety and depression, three main hypotheses can be put forward. The first hypothesis is related to biological mechanisms, where the hyper-inflammatory cytokine storm, a prolonged pro-inflammatory response related to SARS-CoV-2 infection, provokes an atypical response of the immune system and mast cells that, in turn, induce a cascade of events affecting, among others, the central nervous systems [10, 11]. Kappelmann and colleagues suggest that this immune activation following SARS-CoV-2 infection may lead to a vicious circle of inflammation and mitochondrial dysfunction that amplifies the inflammatory process and results in long-term symptoms like fatigue, sleeping difficulties, anxiety, and depression [12]. The second hypothesis is related to the long-term consequences of the experience of the disease on mental health. In addition to the experience of the disease itself, some COVID-19 patients have been exposed to stressful events such as hospitalization, isolation and fear of death. A Chinese post-COVID-19 study found that anxiety and depression were present in approximately one-quarter of patients at 6 months follow-up after discharge from hospital [13]. Finally, the third hypothesis is related to the direct impact of PCC on mental health. A study carried out on survivors of the two previous coronavirus epidemics (SARS, MERS) revealed that people suffering from post-acute viral syndrome had mental health problems and reduced quality of life [14]. Although some studies have shown that during the acute phase of the infection, COVID-19 patients were likely to develop anxiety or depression, little is known about the prevalence and determinants of anxiety and depression several months after infection and in people with PCC.

The objectives of this longitudinal cohort study in the Belgian adult population infected with a positive SARS-CoV-2 test were (1) to assess the impact of PCC on anxiety and depression three months after the infection and (2) to identify the prognostic factors associated with a(n) (un)favourable evolution of the symptoms of anxiety and depression.

Methods

Setting

The first case of COVID-19 in Belgium was identified on February 4, 2020. Between February 2020 and January 2022 Belgium faced five waves of the COVID-19 pandemic: the first wave from March to April 2020, the second between September and December 2020, the third between March and April 2021, the fourth between October and December 2021 and the fifth between January 2022 and February 2022. This study was implemented at the end of April 2021, at the end of the third peak of the pandemic. The Belgian COVID-19 vaccination campaign started in January 2021. In April 2021 when this study was launched, the vaccination coverage in the Belgian adult population was around

6% and by January 2022, 78% of the adult population had received a primary vaccination. At the start of the study, the Alpha variant was dominant in Belgium, followed by the Delta variant from July to December 2021 and 2021 and the Omicron variant from January 2022 onwards [15].

Study design and population

The detailed protocol of this longitudinal cohort study has been published elsewhere [16]. The target population consisted of all people living in Belgium aged 18 or over with a recent SARS-CoV-2 infection confirmed by a molecular test and for who a contact tracing process was initiated between April and October 2021 via the official call centers. At the end of the contact tracing call, cases were informed about the study and asked whether they agreed to participate in the study. Access to two online questionnaires was provided to the participants: a baseline questionnaire at the time of their SARSCoV-2 infection and a follow-up questionnaire three months later. The baseline questionnaire was addressed to the incoming participants between April 29 and October 10, 2021, and the follow-up questionnaire between July 29, 2021, and January 10, 2022. In total, 3127 people completed both questionnaires. As reported in the published study protocol [16], 5% of the eligible population completed the baseline questionnaire and the follow-up participation rate was 79%. Non-response analyses revealed a higher proportion of people aged 46–65 years, of women, and of people reporting at least one acute COVID-19 symptom among cohort participants than among the non-participating eligible population, resulting in potential sample selection bias. Therefore, post-stratification weights were used to adjust the sample distribution to that of the eligible population (see statistical analysis). The survey questionnaire was developed in LimeSurvey. The study was approved by the ethics committee of the Ghent university hospital and Ghent University (Commissie voor Medische Ethiek), B.U.N.: B6702021000287.

Measures

The outcome variables were anxiety and depression and were measured at baseline and three months later using two self-administered questionnaires, namely the GAD-7 (Generalized Anxiety Disorder) to assess generalized anxiety and the PHQ-9 (Patient Health Questionnaire) to assess depressive disorders (including major depression and other forms of depressions). The GAD-7 was developed by Spitzer and colleagues [17], and validated by Kroenke and colleagues [18], for the assessment of signs and symptoms of anxiety, and their severity levels. GAD-7 consists of seven items the presence of which is reported on a four-point scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 21, assessing the frequency of anxiety symptoms over a two-week period. A validated cutoff (score ≥ 10) was used for defining a clinically significant level of anxiety symptoms [19]. The PHQ-9 scale was developed based on the DSV-IV criteria for Major Depressive Disorder, for the assessment of its signs and symptoms, and also to classify severity levels. It was validated by Spitzer and colleagues [20] and by Kroenke and colleagues [21]. It consists of nine items, arranged on a four-point frequency scale: 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). The total score ranges from 0 to 27, assessing the frequency of signs and symptoms of depression over two weeks. A validated cutoff (score ≥ 10) was used for defining a clinically significant level of depressive symptoms [22]. The validity of the two tools was evaluated in different settings, including in the general population, and both the GAD-7 and PHQ-8 showed good interval reliability (Cronbach's $\alpha = 0.86$ and 0.89, respectively) [21, 23]. To assess the change over time of anxiety and depression, a delta (Δ) score was calculated (follow-up score – baseline score) as in other studies [24–26]. These scores reflect changes over time, and range for anxiety from -21 (major improvement) to $+21$ (major deterioration) and for depression from -27 (major improvement) to $+27$ (major deterioration).

The main exposure variable was the PCC status, i.e., whether or not people have at least one symptom related to their SARS-CoV-2 infection three months afterwards. PCC was defined on the basis of the guidelines of the National Institute for Health and Care Excellence (NICE) [3] as having at least one symptom related to SARS-CoV-2 infection three months after its onset. A list of 28 potential PCC symptoms [16] was presented to participants based on most recent guidelines published at that time [2, 3, 27]. The question related to a PCC asked in the three-month follow-up questionnaire was: "Within the last seven days have you had any of these symptoms? (That you did not experience before the onset of your COVID-19 illness)".

Several socio-demographic, health and COVID-related characteristics which were likely to be associated with both anxiety and depression PCC were included in the analysis, in line with the existing literature [28–30]. It concerned age, gender, educational level, country of birth (migrant status), having had at least one COVID-19 symptom during the acute phase of the infection, having been hospitalized due to COVID-19, having had a mental health diagnosis/problem (self-declared) and / or a chronic disease before the SARS-CoV-2 infection, and having suffered a financial loss following the infection.

Data analysis

Post-stratification weights were used to adjust for the distribution of the eligible population (i.e. all people aged 18 years and older, living in Belgium, with a SARS-CoV-2 infection confirmed via a molecular test during the study period) to reduce the sampling error and potential non-response bias. The weights were calculated at the individual level based on a comparison of the distribution of the cohort sample in terms of age, sex, and proportion having at least one acute symptom of COVID-19 with the same distribution in the eligible population (data from national tracing centers).

Descriptive statistics were computed for participants' socio-demographic, health and COVID-related variables. The estimated proportion of people with anxiety and depressive symptoms is based on the dichotomized variables using the previously described validated cut-offs. The proportion of people with anxiety and depressive symptoms at the time of infection and three months later were reported for the whole sample and according to the different exposure variables. To allow a comparison with the level of anxiety and depression found in the Belgian adult population not infected with SARS-CoV-2, data from the 7th wave of the Belgian COVID-19 Health Interview Survey (September 2021) were used ($n = 17{,}347$ participants), hereafter COVHIS [31]. This survey carried out by Sciensano, the Belgian Institute of Health, was an online survey designed to assess the impact of the COVID-19 crisis on people's daily life (including mental health, measured through the GAD-7 and PHQ-9). First, a sub-sample of COVHIS participants reporting that they have not been tested positive with COVID-19 since the start of the pandemic was selected ($n = 14{,}826$). Second, based on the distribution by age, gender and level of education of this PCC study cohort, a matched sub-sample ($n = 3{,}297$) with a similar distribution was extracted from the COVHIS in order to compare the prevalence of anxiety and depression with a group with a similar socio-demographic distribution and in a similar period of time but who have not been infected with SARS-CoV-2. Then, the 95% confidence intervals (CI) were calculated in order to compare the outcomes between the two samples.

Univariable and multivariable linear regression models were built to assess the strength of the association between the different sociodemographic and clinical characteristics of participants and the evolution of their anxiety and depressive symptoms three months after their SARS-CoV-2 infection (Δ score). Finally, univariable and multivariable linear regression models were also performed to assess the strength of the association between the different symptoms of PCC (symptoms with a prevalence > 5% in the cohort sample) and the evolution of anxiety and depressive symptoms (Δ score). Only the significant factors in univariable regressions were included in the multivariable regression models to limit the number of variables in the final model (filter method). Data were analyzed using SAS® 9.4. The level of significance was set at 0.05 for all statistical tests.

Results

The sociodemographic characteristics of the cohort and proportions of anxiety and depression at the time of SARS-CoV-2 infection and three months later are presented in Table 1. In terms of sociodemographic profile of the cohort, 63% were female, 69% had a higher education level, and 87% were born in Belgium. Nearly 9 out of 10 participants had at least one acute COVID-19 symptom, 2% had been hospitalized, 28% was fully vaccinated against COVID-19, and 50% developed PCC three months after their infection. Regarding mental health, 7% declared they had a mental health problem before the COVID-19 pandemic, 11% had symptoms of depression at the time of their SARS-CoV-2 infection and 11.5% after three months. Besides, 6% presented symptoms of anxiety at the time of their infection and 8% after three months.

At the time of infection, the highest proportion of people with anxiety symptoms at the time of infection was among those having a mental health problem before the pandemic (21.7% vs. 4.2%, $p < 0.001$) and those having a chronic disease (13.1% vs. 5.0%, $p < 0.001$). Three months after infection, the proportion of anxiety symptoms was still the highest among people having a mental health problem before the pandemic (20.8% vs. 6.4%, $p < 0.001$), people having a chronic disease (14.5% vs. 7.0%, $p < 0.001$) and people aged between 18 and 24 in comparison to other age groups (12.1%, $p < 0.001$) The proportion of anxiety symptoms was also significantly higher among people with PCC (11.3% vs. 3.8%, $p < 0.001$).

Regarding depressive symptoms, the same pattern emerged: at the time of infection, the highest proportion of depressive symptoms was among people having a mental health problem before the pandemic (32.7%). The second group with the highest proportion of depressive symptoms was people having a chronic disease prior to SARS-CoV-2 infection (21.5% vs. 10.2%, $p < 0.001$). Three months after infection, the proportion of people with depressive symptoms was the highest among those having a chronic disease prior SARS-CoV-2 infection (28.2% vs. 10.0%, $p < 0.001$), people having a mental health problem before the pandemic (27.9% vs. 9.9%, $p < 0.001$) and people with PCC (18.7% vs. 4.2, $p < 0.001$).

Figure 1 presents the proportion of people with anxiety and depressive symptoms during the acute phase of

Table 1 Sociodemographic characteristics of the sample and proportions of people with anxiety and depression at the time of SARS-CoV-2 infection and at 3 months follow-up

	Whole sample ($n=3127$)	Anxiety		Depression	
		At the time of infection ($n=172$)	At 3 months follow-up ($n=232$)	At the time of infection ($n=342$)	At 3 months follow-up ($n=349$)
	n (%)	Weighted %	Weighted %	Weighted %	Weighted %
Depression					
• During infection	342 (11.1)	/	/	/	/
• At 3 months follow-up	349 (11.5)				
Anxiety					
• During infection	172 (5.6)	/	/	/	/
• At 3 months follow-up	232 (7.6)				
Age groups					
• 18–24	343 (12.1)	10.3	12.1	15.6	16.1
• 25–44	1352 (47.6)	7.0	8.5	11.7	12.0
• 45–64	1049 (36.9)	3.0	5.4	9.6	9.7
• 65+	97 (3.4)	1.1	1.1	2.1	2.2
Sex					
• Male	1159 (37.2)	2.9	4.4	7.0	7.8
• Female	1953 (62.8)	7.1	9.4	13.6	13.5
Educational level					
• Secondary or below	958 (31.2)	6.4	8.7	13.3	12.6
• Higher education	2111 (68.8)	5.2	6.8	10.1	10.7
Having PCC					
• Yes	1576 (50.4)	7.7	11.3	15.9	18.7
• No	1551 (49.6)	3.4	3.8	6.3	4.2
At least one acute COVID-19 symptom					
• Yes	2872 (91.8)	3.8	7.6	11.6	11.6
• No	255 (8.2)	5.7	6.8	5.1	10.2
Hospitalization following COVID-19					
• Yes	76 (2.5)	5.3	5.3	17.1	9.5
• No	3020 (97.5)	5.6	7.6	11.1	11.5
Mental health problem before the pandemic					
• Yes	226 (7.3)	21.7	20.8	32.7	27.9
• No	2853 (92.7)	4.2	6.4	9.4	9.9
Chronic disease prior to COVID-19					
• Yes	242 (7.8)	13.1	14.5	21.5	28.2
• No	2878 (92.2)	5.0	7.0	10.2	10.0
Financial loss following COVID-19					
• Yes	809 (26.6)	6.6	10.1	13.6	17.4
• No	2235 (73.4)	5.4	6.7	10.3	9.5

SARS-CoV-2 infection and three months later, comparing people with and without PCC after three months.

At the time of infection, 5.6% of the whole sample had anxiety symptoms. Three months after infection, this proportion was significantly higher among people with PCC (11.3%) compared to people without persisting PCC symptom (3.8%).

At the time of infection, 11.1% of the whole sample had depressive symptoms. Three months later, this proportion was higher among people with PCC (18.7%) compared to people without PCC symptom (4.2%).

In the COVHIS matched subsample of people not infected with SARS-CoV-2, the proportion of people with anxiety and depressive symptoms were 4.3% and 6.5%, not different from the present cohort at the time of infection (5.6% and 11.1% respectively) and from people without PCC symptom after three months (3.8% and 4.2% respectively), but lower compared to people with PCC (11.3% and 18.7% respectively).

Table 2 presents the factors associated with a change in anxiety and depressive symptoms between the time of SARS-CoV-2 infection and three months later.

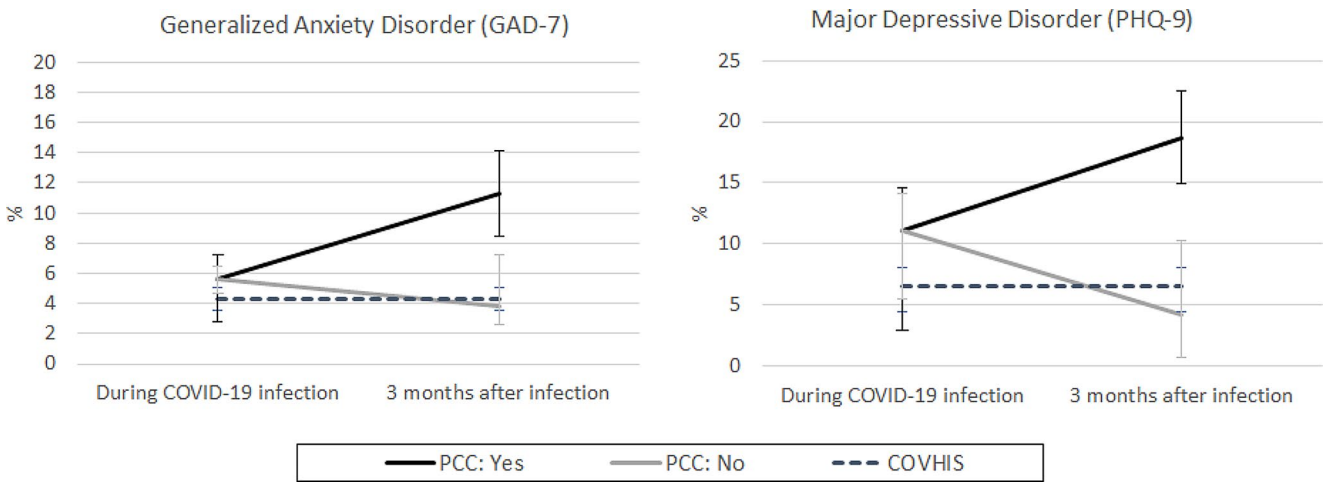

Fig. 1 Weighted proportion of people with anxiety and depressive symptoms during acute COVID-19 and 3 months later, comparing people (**i**) with PCC, (**ii**) and without PCC, and (**iii**) with a control group not infected with SARS-CoV-2 (COVHIS)

Table 2 Factors associated with a change in depressive and anxiety symptoms between the time of SARS-CoV-2 infection and 3 months later

Variables	Δ score depression from −27 (improvement) to +27 (deterioration)				Δ score anxiety from −21 (improvement) to +21 (deterioration)			
	Univariable models		Multivariable model		Univariable models		Multivariable model	
	B	95%CI	B	95%CI	B	95%CI	B	95%CI
Age groups (REF = 18–24)								
• 25–44	0.01	[-0.48;0.49]	/	/	0.01	[-0.46;0.48]	/	/
• 45–64	0.13	[-0.37;0.64]			0.19	[-0.29;0.67]		
• 65+	0.03	[-0.91;0.98]			-0.03	[-0.94;0.88]		
Sex,								
Male (REF = Female)	0.22	[-0.08;0.52]	/	/	-0.08	[-0.37;0.21]	/	/
Educational level,								
Higher education (REF = secondary school or below)	0.09	[-0.22;0.40]	/	/	-0.16	[-0.46;0.15]	/	/
Having PCC,								
Yes (REF = No)	**0.72**	**[0.44;1.01]**	**0.76**	**[0.47;1.06]**	**0.95**	**[0.67;1.23]**	**0.84**	**[0.55;1.13]**
At least one acute COVID-19 symptom,								
Yes (REF = No)	**1.07**	**[0.52;1.61]**	**1.11**	**[0.57;1.65]**	0.29	[-0.23;0.82]	/	/
Hospitalization following COVID-19,								
Yes (REF = No)	-0.33	[-1.25;0.60]	/	/	-0.15	[-1.05;0.74]	/	/
Mental health problem before the pandemic,								
Yes (REF = No)	**-1.50**	**[-2.06;-0.95]**	**-1.68**	**[-2.23;-1.13]**	-0.27	[-0.82;0.27]	/	/
Chronic disease prior to COVID-19,								
Yes (REF = No)	0.31	[-0.24;0.85]	/	/	0.11	[-0.42;0.64]	/	/
Financial loss following COVID-19,								
Yes (REF = No)	**0.67**	**[0.34;1.01]**	**0.57**	**[0.24;0.91]**	**0.39**	**[0.07;0.72]**	0.23	[-0.09;0.56]

Regarding the evolution over time of anxiety symptoms (multivariate analysis), only having PCC was significantly and positively associated ($\beta = 0.84$, $p < 0.001$), meaning that people with PCC were more likely to have an increase over time in anxiety symptoms compared to people no longer showing symptoms related to their infection three months after it.

The risk of having depressive symptoms increases significantly over time (i.e. between the time of their infection and three months later) among people with PCC ($\beta = 0.76$, $p < 0.001$) in comparison to people no longer showing symptoms related to their SARS-CoV-2 infection three months after it. People with at least one acute COVID-19 symptom were also more likely to have an increase over time in depressive symptoms compared to people without

acute symptoms; i.e. asymptomatic (β = 1.11, $p < 0.001$). The same trend was observed regarding the financial loss following COVID-19: people who suffered financial loss following their SARS-CoV-2 infection were more likely to have an increase over time in depressive symptoms (β = 0.57, $p < 0.001$) in comparison to people who didn't suffer any financial loss. Conversely, people with a mental health problem before the COVID-19 pandemic were significantly more likely to have a decrease over time in depressive symptoms (β=-1.68, $p < 0.001$) compared to people without prior mental health problems.

Table 3 presents symptoms of PCC associated with a change in anxiety and depressive symptoms between the time of SARS-CoV-2 infection and three months later.

Regarding the evolution over time of anxiety (multivariable analysis), three PCC symptoms, namely sleeping problems, dizziness (β = 0.82, $p = 0.010$), and fatigue/exhaustion (β = 0.76, $p < 0.001$), were significantly associated with an increase over time in anxiety symptoms. For depressive symptoms, fatigue/exhaustion (β = 0.99, $p < 0.001$), sleeping problems (β = 0.77, $p = 0.004$), and memory problems (β = 0.60, $p = 0.01$) were the PCC symptoms significantly associated with an increase over time.

Discussion

The objectives of this longitudinal cohort study in the Belgian adult population infected with a positive SARS-CoV-2 test were (1) to assess the impact of PCC on anxiety and depression three months after the infection and (2) to identify the prognostic factors associated with a(n) (un)favourable evolution of the symptoms of anxiety and depression.

This study found that at the time of their SARS-CoV-2 infection, the proportion of people who presented anxiety and depressive symptoms were 6% and 11% respectively, figures that are not significantly different from the matched sub-sample not infected with SARS-CoV-2 (4% and 6%). A significant increase in anxiety and depressive symptoms was observed three months after infection among people with PCC (11% and 18%) compared to people without persistent PCC symptom (4% and 4%) and to the matched sub-sample not infected with SARS-CoV-2 (4% and 6%). While several follow-up studies on people who were hospitalized following SARS-CoV-2 found an important and short-term impact on their mental health [12, 14], our results suggest that in a sample of the general population infected with SARS-CoV-2, the mental health impact is small during the acute phase of infection, but high in case of persistent symptoms at follow-up. A recent meta-analysis including 18 studies on people with PCC found a pooled prevalence for anxiety 22% (95% CI: 15–29%) and for depression of 23% (95% CI: 12–34%) [29]. Among the studies included in the meta-analysis, most were on people hospitalized following their SARS-CoV-2 infection, which might explain the higher prevalence in comparison to our study. Our study also found that 50% of the participants had PCC symptoms three months after infection and this proportion is in line with a meta-analysis on 33 studies showing that PCC symptoms were present in more than 60% of the cases three months post-infection [4]. Three months after SARS-CoV-2 infection, fatigue/exhaustion and sleeping problems were both associated with an increase in anxiety and depressive symptoms over time, dizziness was associated an increase in anxiety symptoms, and memory problems were associated with an increase in depressive symptoms. Although participants reported that these symptoms were related to their SARS-CoV-2 infection, the question of causation must be raised. Indeed, these symptoms can be linked to PCC and have a negative effect on the mental health of the

Table 3 Symptoms of PCC associated with a change in depressive and anxiety symptoms between the time of SARS-CoV-2 infection and 3 months after

Symptoms of PCC 3 months after infection (prevalence > 5%)	Whole sample, n (%)	Δ score depression from −27 (improvement) to +27 (deterioration)				Δ score anxiety from −21 (improvement) to +21 (deterioration)			
		Univariable models		Multivariable model*		Univariable models		Multivariable model*	
		B	95%CI	B	95%CI	B	95%CI	B	95%CI
Fatigue/exhaustion	775 (24.8)	**1.43**	**[1.10; 1.77]**	**0.99**	**[0.59; 1.38]**	**1.39**	**[1.04; 1.69]**	**0.76**	**[0.38; 1.14]**
Headache	430 (13.8)	**0.99**	**[0.57; 1.42]**	0.12	[-0.36; 0.60]	**1.33**	**[0.92; 1.74]**	0.46	[-0.03; 0.88]
Memory problems	383 (12.3)	**1.38**	**[0.93; 1.81]**	**0.60**	**[0.11; 1.10]**	**1.21**	**[0.78; 1.64]**	0.25	[-0.22; 0.73]
Muscle pain	357 (11.4)	**1.09**	**[0.64; 1.55]**	0.41	[-0.12; 0.95]	**1.08**	**[0.64; 1.52]**	0.06	[-0.46; 0.58]
Shortness of breath	335 (10.7)	**0.94**	**[0.47; 1.14]**	0.01	[-0.51; 0.52]	**0.77**	**[0.31; 1.22]**	-0.33	[-0.82; 0.17]
Sleeping problems	308 (9.9)	**1.49**	**[1.01; 1.98]**	**0.77**	**[0.24; 1.29]**	**2.03**	**[1.56; 2.49]**	**1.36**	**[0.84; 1.86]**
Loss of smell	294 (9.4)	0.23	[-0.27; 0.72]	/	/	0.36	[-0.13; 0.84]	/	/
Joint pain	250 (8.0)	0.65	**[0.11; 1.19]**	-0.37	[-0.98; 0.24]	**1.18**	**[0.66; 1.71]**	0.26	[-0.32; 0.85]
Loss of taste	212 (6.8)	0.38	[0.21; 0.06]	/	/	0.61	[0.07; 1.07]	/	/
Dizziness	189 (6.0)	**1.16**	**[0.55; 1.77]**	0.27	[-0.41; 0.89]	**1.69**	**[1.11; 2.28]**	**0.82**	**[0.19; 1.44]**
Palpitations	159 (5.1)	**1.09**	**[0.42; 1.75]**	0.08	[-0.62; 0.79]	**1.39**	**[0.75; 2.03]**	0.29	[-0.39; 0.97]

* Adjusted for age, gender, and educational status of the participants

participants, but it is also possible that a worsening of the mental health of the participants induces symptoms such as fatigue, sleeping problems and memory problems.

As explained previously, three main hypotheses can be put forward to explain the underlying mechanisms of the impact of PCC on mental health: (i) biological mechanisms (chronic pro-inflammatory response linked to SARS-CoV-2 and affecting, among others, the central nervous system) [10, 11], (ii) the long-term consequences of the experience of the disease (stressful events such as hospitalization, isolation and fear of death), and (iii) the direct impact of PCC on mental health. Although this study cannot conclude on one hypothesis rather than another, it can provide some lines of interpretation. The absence of a significant association between PCC symptoms such as loss of taste and smell and mental health outcomes does not support the first immunological hypothesis. Similarly, being hospitalized during the acute phase of COVID-19 was not associated with worsening symptoms of anxiety or depression, which does not support the second hypothesis. Our results therefore suggest that mental health problems in people with PCC are more related to the experience of the disease itself, and of some of the PCC symptoms described above.

To our knowledge, little evidence exists regarding other factors associated with a(n) (un)favourable evolution of anxiety and depression after SARS-CoV-2 infection. In the present study, the presence of at least one acute COVID-19 symptom was also associated with an increased risk of developing depressive symptoms. Two studies found that an increased number of COVID-related symptoms were associated with a higher risk of anxiety, depression, and post-traumatic stress disorders [32, 33]. A study on hospitalized COVID-19 patients showed that those who had an oxygen saturation $\leq 93\%$, which is an indicator of the severity of the infection, were more likely to report anxiety [34]. Experiencing financial loss following SARS-CoV-2 infection was also associated with an increase over time in anxiety and depressive symptoms. Another study in the US found that almost 40% of participants reported negative financial consequences following their COVID-19 hospitalization, 10% exhausted their savings and 6% were unable to pay for their food, heating and housing [28]. Moreover, persistent symptoms of PCC may force some people to reduce or even quit their jobs, which is another reason that can increase financial and psychological distress [28]. Indeed, during the COVID-19 pandemic, people experiencing work loss are more likely to report psychological distress, poor mental and physical health compared to those whose work was unaffected [35].

Conversely, people with a mental health condition before the pandemic were less likely to experience worsening of their depressive symptoms over time. Our main hypothesis here is that people experiencing a mental health condition prior the beginning of the pandemic already have access to mental health care or were more prone to seek help. According to Czysz et al. it is plausible that having pre-pandemic mental illness confers some protection during the pandemic [36]. In people with moderate to severe pre-pandemic depression, this may result from a ceiling effect (little room for individuals to get worse) or that disruption in employment or social routine had less impact compared to those who never experienced mental illness [36].

In terms of clinical implications, while each symptom independently can have a significant impact on mental health, people with PCC often tend to have a combination of symptoms and conditions. An important element and challenge in the care of people with PCC is therefore to provide a multidisciplinary approach, including psychological support and treatment [37]. A recent scoping review identified mental health support interventions for people with PCC, and highlighted different pharmacological and non-pharmacological interventions [38]. However, given the heterogeneity of interventions described in the literature, no "standard" treatment has been put forward, highlighting the need for more research and guidelines.

Strengths and limitations

This study has several strengths. While the vast majority of the studies are performed on hospitalized patients, this study focused on the general population infected with COVID-19 including hospitalized and non-hospitalized persons. This study also has a control group while a majority of the studies do not. Additionally, having measures of mental health outcomes at the time of infection and three months later allowed us to assess changes over time and associated factors.

This study also has several limitations. First, the online design induces a sample selection bias. As previously explained, the published study protocol [16] showed that the proportion of people between 46 and 65 years, of women, and of people reporting at least one acute COVID-19 symptom was higher among cohort participants than in the eligible population. Therefore, post-stratification weights were used to adjust this sample distribution to that of the eligible population. Second, the PCC symptoms were self-reported by participants so we cannot ensure that they are not explained by an alternative diagnosis. Indeed, PCC symptoms are common to many other diseases and infections that affect the general population (e.g. chronic fatigue, co-infection with influenza or common cold, etc.), which may result in an overestimation of PCC in our study. It is also possible that some participants were hospitalized more than three months after their initial SARS-CoV-2 infection, and that certain long-term symptoms were linked to

their hospitalization, such as post-intensive care syndrome [39]. Additionally, no information was collected on different potential confounders, such as whether participants were reinfected with SARS-CoV-2 during the follow-up period, whether a close relative was infected with SARS- CoV-2, or other events that may have negatively or positively affected their mental health during the follow-up period. Finally, the anxiety and depression measurement instruments used (the GAD-7 and the PHQ-9), have their own limitations, such as low positive predictive value [23, 40].

Conclusion

This study shows that in a sample of the general population infected with SARS-CoV-2, the mental health impact is small during the acute phase of the infection (as compared to a non-infected comparison sample), but high in case of Post COVID-19 Condition (PCC) symptoms. Half of the participants reported having PCC three months after their infection and several PCC symptoms were associated with worsening mental health over time. To support the recovery of people after a COVID-19 infection, it is essential to have a multidisciplinary approach and to offer early post-acute physical and psychological rehabilitation interventions according to PCC symptoms.

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Data availability Data are available on request to the authors.

Declarations

Ethical approval Informed consent was obtained from all subjects involved in the study. The study was approved by the ethics committee of the Ghent university hospital (Commissie voor Medische Ethiek), B.U.N.: B6702021000287.

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.
The authors declare they have no conflict of interests.

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