BMJ Open

Classification of post COVID-19 condition symptoms: a longitudinal study in the Belgian population

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To cite: Nayani S, Castanares-Zapatero D, De Pauw R, *et al*. Classification of post COVID-19 condition symptoms: a longitudinal study in the Belgian population. *BMJ Open* 2023;**13**:e072726. doi:10.1136/bmjopen-2023-072726

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-072726).

Received 17 February 2023
Accepted 18 September 2023

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ABSTRACT

Objectives Since the onset of the COVID-19 pandemic, most research has focused on its acute pathophysiology, yet some people tend to experience persisting symptoms beyond the acute phase of infection, referred to as post COVID-19 condition (PCC). However, evidence on PCC is still scarce. This study aimed to assess the distribution, classification of symptoms and associated factors of PCC in adults.

Design Longitudinal online cohort study.

Setting National study in Belgium.

Participants Participants were Belgian adults with a recent SARS-CoV-2 infection and were recruited when called up for contact tracing. A total of 3039 participants were included and completed an online questionnaire at the time of their infection and again 3 months later.

Outcome measures The baseline questionnaire assessed the initial health status of the participants and their status during the acute phase of the infection. The follow-up questionnaire assessed their PCC status 3 months after infection. A latent class analysis (LCA) was performed to assess whether there are different classes of individuals with a similar set of self-reported PCC symptoms.

Results Half of the participants reported PCC 3 months after infection (47%). The most frequent symptoms were fatigue (21%), headache (11%) and memory problems (10%). The LCA highlighted three different classes of PCC symptoms with different risk factors: (1) a combination of loss of smell and taste, (2) a combination of neurological symptoms and (3) other heterogeneous symptoms.

Conclusions With the increasing number of people who underwent COVID-19, PCC has become an important but complex public health problem due to the heterogeneity of its symptoms. The classification of symptoms performed in this study can help give insight into different aetiologies of PCC and better plan care according to the symptoms and needs of those affected.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The eligible population of this study was all adults living in Belgium and infected with SARS-CoV-2, while many studies on post COVID-19 condition (PCC) have been on people hospitalised following COVID-19 and followed after discharge.
⇒ This study used the most comprehensive list of potential PCC symptoms based on published guidelines to investigate their classification.
⇒ Although contact tracing was mandatory following laboratory-confirmed SARS-CoV-2 infection in Belgium, participation in this study was entirely at the discretion of the participant, leading to possible selection bias.
⇒ PCC symptoms are common to many other diseases and infections that affect the general population and we do not have information on the frequency of these symptoms in the general Belgian population not infected with SARS-CoV-2 (control group).

INTRODUCTION

In 2020, the world faced the appearance of a new pathogen, named the novel SARS-CoV-2.[1] To date, most of the research has focused on the acute phase of the infection but less on the consequences in the medium and long term.[2 3] Mounting evidence shows some people continue to experience symptoms beyond the acute phase of the infection with long-term consequences on their physical and mental health.[4 5] This phenomenon has been described as post COVID-19 condition (PCC).[6]

PCC was first described in 2020 by patients still experiencing symptoms months after the acute phase of the infection and calling themselves 'long haulers'.[7] There is currently no consensus on the definition of PCC and it remains poorly understood in part due to a lack of longitudinal studies.[2 8] In December 2020, the UK National Institute for Health and Care Excellence (NICE)[9] defined PCC as: 'signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis'. PCC symptoms described in some studies have included fatigue, dyspnoea, chest and joint pain, anosmia and dysgeusia, cognitive symptoms, anxiety, depression and sleeping problems.[2 10] Depending on the definition

used and terms of duration, the estimated prevalence of PCC varies widely.[11]

Studies are underway to have a better understanding of the aetiology and pathophysiology of PCC. Longitudinal cohort studies are essential to assess its distribution, patterns and risk factors. Identified risk factors of PCC include female sex,[2] a longer hospital stay in the acute phase[12] and pre-existing comorbidities.[7] Recent studies showed conflicting results for other potential risk factors. For example, some studies have found that older people were more at risk of having PCC,[13] while others found no association with age.[14] Many studies on PCC have been carried out only on hospitalised patients, with longitudinal follow-up after discharge from hospitals.[15 16] However, hospital discharge follow-up studies miss people with mild or even asymptomatic infection in the acute phase who may still develop PCC.[17] Other studies used classification analyses to identify classes of PCC symptoms and assessed whether the different classes were associated with clinical and sociodemographic characteristics of study participants.[13 18–25] Two studies[18 19] highlighted a class of neurological and mental health-related PCC symptoms (ie, brain fog, insomnia, anxiety, etc) and a class of respiratory PCC symptoms (ie, cough, shortness of breath, etc), but also found conflicting results regarding the factors associated with the different classes. For example, the first study[18] found no association between participants' age and the different classes of PCC symptoms, whereas the second study[19] found that younger people were more likely to be in the class with mental health/neurological PCC symptoms and older people were more likely to belong to the class with respiratory PCC symptoms. These two studies also present certain limitations. The first study was carried out on a fairly limited sample (n=506) of patients recruited via social network platforms and healthcare centres, which could induce important selection bias.[18] The second study was carried out on a large sample (n=486 149) but used medicoadministrative data from primary care, therefore only including patients who had been in contact with care providers.[19] Other studies have also highlighted clusters specifically linked to PCC symptoms of fatigue, hair loss, loss of smell and taste,[25] or cardiovascular manifestations.[22]

The main goals of the present cohort study are to assess the distribution and classification of PCC symptoms and the sociodemographic and clinical factors associated with adults with confirmed SARS-CoV-2 infection in the general Belgian population.

METHODS

Study design and setting

The detailed protocol of the study including the flow diagram has been published elsewhere.[26] This study was a longitudinal online cohort study. The target population was people aged 18 years and older, living in Belgium, with a recent SARS-CoV-2 infection who were invited through the contact tracing mechanism by health authorities to participate in a follow-up online questionnaire with one immediately following positive laboratory-confirmed infection, and a second follow-up 3 months after infection. Data for this study were collected between 29 April 2021 and 6 January 2022. When the study was launched, the vaccination rate in the Belgian adult population was around 6% and in January 2022, 76% of the adult population was fully vaccinated and 40% received a booster.

Study population

The follow-up of the participants was also detailed and analysed in the study protocol[26] and showed that 5% of the eligible population completed the baseline questionnaire and that the proportion of people between 46 and 65 years, women and people reporting at least one acute COVID-19 symptom was higher among cohort participants than in the eligible population, resulting in sample selection bias. This bias induces a probable overestimation of the proportion of PCC in the cohort because women and people with acute COVID-19 symptoms are groups at risk of PCC. Therefore, post-stratification weights were used and will be used for future analysis to adjust for the distribution of the eligible population (ie, all Belgian adults infected with SARS-CoV-2 during the study period, see the Statistical analyses section). In total, 81% of participants who completed the baseline questionnaire agreed to participate in the follow-up, and 62% of participants who received the follow-up questionnaire completed it.

The flow diagram of the present study is presented in figure 1. In total, 81% of participants who completed the baseline questionnaire agreed to participate in the follow-up, and 62% of participants who received the follow-up questionnaire completed it. A total of 3127 participants completed both the baseline and follow-up questionnaires. No missing values were identified for the primary outcome (ie, PCC status); however, some covariates included missing values (<2% for each variable). The percentage of missing values was calculated for each variable and the following analyses were performed using a complete case approach (n complete case=3039, n missing=88). No statistically significant difference (p=0.46) was found between the proportion of PCC in complete cases (50.4%) and in missing cases (50.3%).

Measures

The primary dichotomous outcome variable was the PCC status, that is, whether or not people self-reported at least one symptom of PCC 3 months after the infection. Although there was no consensus on the definition of PCC at the time of the development of the study protocol, the definition we have identified as the most used is that of the NICE: 'signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis'.[9] People with PCC tend to report numerous and heterogeneous symptoms[27]; therefore, a list of 30 possible symptoms was drawn up, based on published guidelines.[9 28 29] The question asked in the

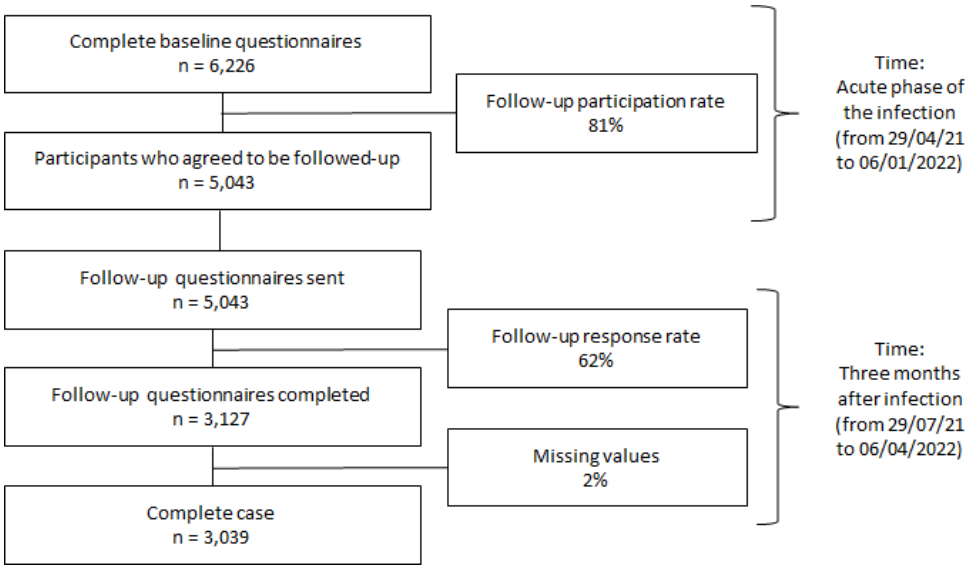

Figure 1 Flow diagram.

3-month follow-up questionnaire was: "Within the last 7 days, have you had any of these symptoms? (That you did not experience before onset of your COVID-19)'.

In addition, the following exposure variables were included in the analyses, in line with the existing literature on PCC and COVID-19[7 12 30 31]: age, sex, educational level, body mass index (BMI), COVID-19 vaccination status, medical history (ie, chronic diseases), history of mental health problem, having symptoms or not in the acute phase of the infection, having been hospitalised following the COVID-19 infection, and tobacco use and physical activity. History of mental health problem was assessed with the following question: 'In the year before the pandemic, did you have a mental health diagnosis and/or problem?'. The presence of chronic disease was assessed with the following question: 'Before your COVID-19 infection, have you had any of the following diseases or conditions?' and the following list of chronic diseases: asthma, chronic bronchitis, chronic obstructive pulmonary disease, emphysema, high blood pressure (hypertension), chronic cardiovascular disease (excluding high blood pressure), diabetes mellitus type 1 or 2, chronic neurological disorder, chronic kidney disease (including dialysis), chronic liver disease, cancer (excluding blood cancer, for example, leukaemia, lymphoma), blood cancer (eg, leukaemia, lymphoma), diseases or treatments that suppress the immune system (except HIV), having a transplantation or on the waiting list for a transplantation, other long-term illnesses (please specify). A binary indicator was then calculated to determine the presence of chronic disease. All variables were self-reported.

Statistical analyses

Post-stratification weights were used to adjust for the distribution of the eligible population (ie, all people aged 18 years and older, living in Belgium, with a recent SARS-CoV-2 infection) 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 contact tracing).

Descriptive statistics were computed for the sociodemographic and clinical characteristics of the cohort participants. A multivariable model was performed to test the association between different sociodemographic and clinical characteristics of participants and the presence of PCC 3 months after infection. The model was run only with the factors that were significantly associated ($p<0.05$) in the univariable regressions (see online supplemental table 1). We used a modified Poisson regression method to estimate the relative risk (RR) and CIs by using robust error variances.[32]

Since people with PCC tend to report numerous and heterogeneous symptoms, a latent class analysis (LCA)[33] was performed to assess whether there are different classes of individuals with a similar set of self-reported symptoms among participants with PCC. The main parameters of LCA are the conditional probabilities of the observed variables given the class (ie, the probabilities of the 30 different PCC symptoms in each class). In LCA, classes are added until the model best fits the data. In this study, 100 random sets of starting values were used. The Bayesian Information Criterion (BIC) was used to determine the optimal number of classes (ie, lower BIC value). In this study, the three-class solution had a lower BIC than the two-class or four-class solution (BIC values were 28404.47, 28158.89 and 28 381.14 for the model with two, three and four latent classes, respectively). Moreover, the three-class solution was more clinically interpretable and relevant. The two-class solution had a first small class (6% of people with PCC) of people with a significant proportion of all but three proposed PCC symptoms

(swelling, incontinence and seizures), and another large class (94%) of people with a significant proportion of symptoms of fatigue, memory problems, headaches, and loss of smell and taste. The four-class solution had similar classes as the three-class solution, and a fourth small class (2%) of people with multiple symptoms but similar to another class.

Finally, the association between participants' sociodemographic and clinical characteristics and the three classes was assessed through a multinomial logistic regression model with participants without PCC as the reference group. The model was run only with the factors that were significantly associated (p<0.05) in the univariable regressions (see online supplemental table 2). Additional descriptive statistics were performed to describe the profile of the participants in the three classes (see online supplemental table 3).

The LCA was performed in R software V.4.2.1[34] using the 'poLCA' package,[35] and other statistical analyses were performed in SAS V.9.4.

Patient and public involvement

None.

RESULTS

Table 1 describes the sociodemographic characteristics of the cohort and the proportion of people with PCC according to the different characteristics. The mean age in years of the respondents was 41.8 (SD=12.7) years and most of them were women (63.9%). More than a quarter (27.5%) of the sample had a complete primary COVID-19 vaccination and 1.9% had been hospitalised following the acute phase of the infection. Finally, the number of symptoms during the acute phase of the infection was on average 6 (IQR=3–9), and half (50.4 unweighted %, 46.6 weighted %) of the cohort had PCC (ie, reported at least one symptom related to their SARS-CoV-2 3 months later).

The final model found several factors significantly associated with the risk of having PCC 3 months after infection. Women (RR=1.26), people with obesity (RR=1.13), people with a history of chronic disease (RR=1.25) or a history of mental health problem (RR=1.18) were at risk of reporting PCC. Regarding variables related to the COVID-19 infection, people who had a least one acute COVID-19 symptom (RR=1.70) and those hospitalised following the infection (RR=1.38) were also at risk of reporting PCC. The highest proportion of PCC was found among people hospitalised following their infection (68.6%).

Table 2 presents the descriptive statistics and LCA on self-reported symptoms of PCC 3 months after infection. The results of the LCA are also shown in figure 2.

The most frequent self-reported symptoms of PCC in the cohort sample were fatigue/exhaustion (25%), headache (14%), memory problems (12%), muscle pain (11%), dyspnoea (11%) and sleeping problems (10%).

As described above, an LCA three-class solution was chosen (see the Statistical analyses section). The first class gathered 19% of the participants reporting PCC symptoms. Participants in this class had the highest probability of having a loss of smell and taste (81% and 51%, respectively). The probability of having the other symptoms for participants in class 1 was lower than in the other two classes; we have therefore labelled class 1 as 'loss of smell and taste'.

The second class was the largest and gathered 67% of the participants with PCC. The symptoms with the highest probabilities in this class were headache (51%) and memory problems (46%). These probabilities were higher than in classes 1 and 3 (see table 2 and figure 2). Fatigue-exhaustion was also common in this class (46%). We labelled this second class 'neurological symptoms'.

The third and last class was the smallest and gathered 14% of the participants with PCC. Participants in this class had a high probability of having a large number of symptoms (median=4/IQR=3–7, in comparison with the first class: median=2/IQR=1–4 and second class: median=3/IQR=2–5). The symptoms with the highest probabilities in this class were fatigue-exhaustion (89%), muscle pain (62%), dyspnoea (54%), sleeping problems (51%), headache (48%), joint pain (42%), memory problems (41%), dizziness (38%), constipation (31%) and palpitations (31%). We have chosen to label this third class 'multiple symptoms'.

The association between participants' sociodemographic and clinical characteristics and class probability is presented in table 3.

In comparison with participants without PCC symptoms, participants with a chronic disease (OR=1.86, p=0.01), with at least one acute COVID-19 symptom (OR=2.30, p=0.001), hospitalised following their infection (OR=2.26, p=0.005) and having less than 2 days of physical activity per week (OR=1.54, p=0.003) had a higher probability of being in the 'loss of smell and taste' class.

Women (OR=1.90, p=0.001), people with higher education (lower education, OR=0.70; p=0.02) and people with a history of mental health problems (OR=1.74, p=0.007) had a higher probability of being in the 'neurological symptoms' class.

Regarding the 'multiple symptoms' class, women (OR=2.73, p=0.001), people with lower education (OR=1.54, p=0.001), those who were overweight (OR=1.69, p=0.02) or obese (OR=2.12, p=0.008), with a history of chronic disease (OR=2.02, p=0.001), with at least one acute COVID-19 symptom (OR=4.69, p=0.005) and hospitalised following their infection (OR=3.79, p=0.001) were more likely to be in this class.

DISCUSSION

Interpretation of the results

This study aimed to assess the distribution and classification of PCC symptoms and the sociodemographic and

Table 1 Sociodemographic characteristics of the sample and proportion of post COVID-19 condition (PCC) and risk factors

Characteristics n (%) or mean (SD)	Whole sample (%) n=3039	PCC, weighted* %	PCC (yes) RR (95% CI) Multivariable regression model n=3039
PCC			
No	1508 (49.6)	53.4	
Yes	1531 (50.4)	46.6	
Age, years	41.8 (12.7)	/	/
Age categories			NS (not significant in univariable analysis)
18–25	376 (12.4)	47.3	
26–45	1375 (45.2)	51.1	
46–54	1050 (34.6)	42.7	
55+	238 (7.8)	43.8	
Sex			
Men	1097 (36.1)	42.5	Ref
Women	1942 (63.9)	55.8	**1.26 (1.15; 1.37)**, p<0.001
Educational status			
Secondary school diploma or below	881 (29.0)	55.1	1.07 (0.99; 1.16)
Higher education diploma	2158 (71.0)	46.3	Ref
Body mass index			
Normal (18.5–24.9)	1352 (44.5)	47.4	Ref
Overweight (25–29.9)	1023 (33.7)	50.1	1.15 (0.95; 1.15)
Obesity (≥30.0)	664 (21.8)	55.9	**1.13 (1.04; 1.22)**, p=0.02
COVID-19 vaccination status at the time of infection			NS
None	1580 (51.9)	51.3	
Partial	624 (20.6)	48.5	
Complete primary	835 (27.5)	51.4	
Chronic disease			
Yes	204 (6.7)	62.1	**1.25 (1.12; 2.39)**, p<0.001
No	2835 (93.3)	49.1	Ref
History of mental health problem			
Yes	211 (6.9)	61.7%	**1.18 (1.04; 1.32)**, p<0.001
No	2828 (93.1)	47.4%	Ref
Number of symptoms during the acute phase of infection, median (IQR)	6.0 (3.0–9.0)	/	/
At least one symptom during the acute phase of infection			
No	301 (9.9)	27.4%	Ref
Yes	2738 (90.1)	53.1%	**1.70 (1.38; 2.10)**, p<0.001
Number of PCC symptoms 3 months after infection, median (IQR)	1.0 (0.0–2.0)	/	/
Hospitalisation following COVID-19 infection			
No	2982 (98.1)	49.2	Ref
Yes	57 (1.9)	69.3	**1.38 (1.17; 1.63)**, p=0.005
Smoking habits			
Yes, everyday	256 (8.4)	59.4	1.02 (0.86; 1.12)
Yes, occasionally	209 (6.9)	54.7	1.06 (0.93; 1.19)
No	2574 (84.7)	48.3	Ref

Continued

Table 1 Continued

Characteristics n (%) or mean (SD)	Whole sample (%) n=3039	PCC, weighted* %	PCC (yes) RR (95% CI) Multivariable regression model n=3039
Sports habits, at least 2 days per week with 10 min of physical activity			
Yes	1561 (51.4)	46.2	Ref
No	1478 (48.6)	49.9	1.09 (0.98; 1.20)

*Weighted proportion of PCC in the different groups using post-stratification weights to adjust for the distribution of the eligible population in terms of age, sex and proportion having at least one acute symptom of COVID-19.
RR, relative risk.

clinical factors associated with adults with confirmed SARS-CoV-2 infection in Belgium.

We found that close to half of the participants appeared to fit the proposed case definition of PCC, that is, having at least one symptom related to a COVID-19 infection 3 months afterward. This result is consistent with those of a recent meta-analysis carried out on 33 studies on hospitalised and non-hospitalised patients with COVID-19.[13] However, having a persistent symptom does not necessarily mean that these people need care because there are different degrees of severity of PCC. Further studies should assess the care needs of people with PCC. In addition, PCC symptoms are common to many other diseases and infections in the general population and we do not have information on the frequency of these symptoms in the general Belgian population not infected with SARS-CoV-2 (control group). A previous meta-analysis on PCC also concluded that there was a lack of case–control studies or studies with a matched non-SARS-CoV-2 group.[2]

Regarding the risk factors of PCC 3 months after infection, this study found that women, people with a history of chronic diseases or mental health problems, people with obesity, those who had at least one acute COVID-19 symptom and those who were hospitalised following their COVID-19 were more likely to report PCC. These results align with the current literature regarding PCC risk factors, but some differences were observed. We confirmed a higher risk of PCC among women as in most studies.[31 36] One hypothesis to explain this result is the difference in immunity responses between males and females.[37] While women can have a more rapid immune response, they may also be more vulnerable to chronic autoimmune diseases.[38 39] Sex differences in immune response have also been reported in other viral outbreaks.[40] Other studies have also shown that having pre-existing comorbidities was a risk factor for PCC[7] as well as the severity of the acute infection (eg, being hospitalised or having more severe acute symptoms).[41]

This study also found that among the different heterogeneous symptoms of PCC, three main classes could be distinguished. This classification highlighted that the association between PCC, and certain sociodemographic and clinical characteristics of participants is complex. These classes of symptoms can be used for patient individualised care planning based on their symptoms and for specific care needs. The first class 'loss of smell and taste' was made up of individuals reporting mainly symptoms of loss of smell and taste, therefore potentially requiring olfactory and gustatory rehabilitation. This class represented one-fifth of people with PCC and included more often people with chronic disease, with at least one symptom during the acute phase of infection or being hospitalised, and doing less physical activity. While evidence shows that some patients with mild symptoms of loss of smell and taste tend to have rapid and spontaneous remission of symptoms, for other patients, intervention is needed, such as olfactory training or nasal corticosteroid therapy.[42 43] The second and largest class 'neurological symptoms', comprising 70% of people with PCC, included people with symptoms of neurological origin such as headache, memory problems and fatigue. If in need of care, they may seek primary care such as general practitioners, or specialist care such as neurologists, somnologists or psychologists. People in this class were more often women, with a higher level of education and a history of mental health problems. A meta-analysis of studies on PCC also showed that women were more likely than men to report headaches.[13] The third and smallest class (14%), 'multiple symptoms', included people with many heterogeneous symptoms, such as fatigue, muscle pain, dyspnoea, sleeping problems, headache, joint pain, memory problems, dizziness, constipation and palpitations. Given the heterogeneity of their symptoms, these individuals may require a multidisciplinary care approach, with early post-acute physical and psychological rehabilitation interventions.[44] People with a lower level of education, overweight or obesity, with a history of chronic disease, with at least one acute symptom of COVID-19 and hospitalised during the infection were more likely to be in this class. A study[18] conducted in Italy highlighted five classes of PCC symptoms. Similar to our results, this study found a class of people with neurological symptoms of PCC (ie, cognitive problems, sleep problems and tiredness), a class of people with multiple PCC symptoms, and a class of people with loss of smell and taste. In line with our findings, this study also identified that women were more likely than men to belong to the class reporting multiple symptoms of PCC.[18] Another

Table 2 Descriptive statistics and latent class analysis on self-reported symptoms of post COVID-19 condition (PCC) 3 months after infection

Self-reported symptoms of PCC 3 months after infection	Whole sample	Latent class analysis n=1531 (participants with PCC)		
		Class 1	Class 2	Class 3
		n=286 (18.7%)	n=1027 (67.1%)	n=218 (14.2%)
		'Loss of smell and taste'	'Neurological symptoms'	'Multiple symptoms'
	% (weighted %)	Probability of having the symptoms		
Fatigue-exhaustion	24.8 (20.6)	28%	46%	89%
Headache	13.7 (10.9)	13%	51%	48%
Memory problems	12.2 (10.4)	18%	46%	41%
Muscle pain	11.4 (10.1)	8%	17%	62%
Dyspnoea	10.7 (6.6)	8%	17%	54%
Sleeping problems	9.8 (8.8)	9%	16%	51%
Loss of smell	9.4 (8.5)	81%	0%	26%
Joint pain	8.0 (6.9)	4%	12%	42%
Loss of taste	6.8 (6.2)	51%	0%	27%
Dizziness	6.0 (5.0)	3%	8%	38%
Constipation	5.5 (3.9)	1%	8%	31%
Persistent cough	5.5 (4.2)	8%	10%	21%
Palpitation	5.1 (4.8)	2%	7%	31%
Problem seeing	4.5 (3.8)	3%	6%	25%
Tingling feeling	4.1 (3.1)	3%	5%	27%
Ringing in ears	4.0 (3.2)	4%	5%	23%
Chest pain	3.9 (3.4)	2%	6%	20%
Skin rashes	3.7 (2.9)	3%	6%	14%
Nausea-vomiting	3.5 (2.8)	2%	3%	27%
Loss of appetite	3.3 (2.5)	5%	0%	27%
Stomach pain	3.1 (2.4)	1%	4%	22%
Others	2.9 (2.4)	3%	7%	2%
General malaise	2.6 (2.0)	2%	2%	19%
Confusion	2.6 (1.7)	2%	3%	15%
Weight loss	2.2 (2.0)	2%	2%	15%
Problem speaking	1.8 (1.6)	1%	1%	12%
Problem swallowing	0.8 (0.2)	1%	0%	6%
Swelling-oedema	0.5 (0.1)	0%	0%	2%
Incontinence	0.3 (0.1)	0%	0%	1%
Seizures	0.06 (0.1)	0%	0%	1%

Post-stratification weights are based on the distribution of the eligible population (age, sex and having at least one acute symptom of COVID-19).

study[19] carried out in the UK highlighted three classes of symptoms, two of which were similar to the results of the present study: a class with multiple PCC symptoms and another with neurological PCC symptoms. The third class included people with respiratory PCC symptoms. As in our study, they found that women were more likely than men to belong to classes with multiple PCC symptoms and neurological symptoms. However, their results on the association between the socioeconomic position of the participants and the classes of PCC symptoms differ from our study. While the present study showed that participants from both lower and higher socioeconomic positions were more likely to belong to a specific class of symptoms, the study in the UK found that people with a

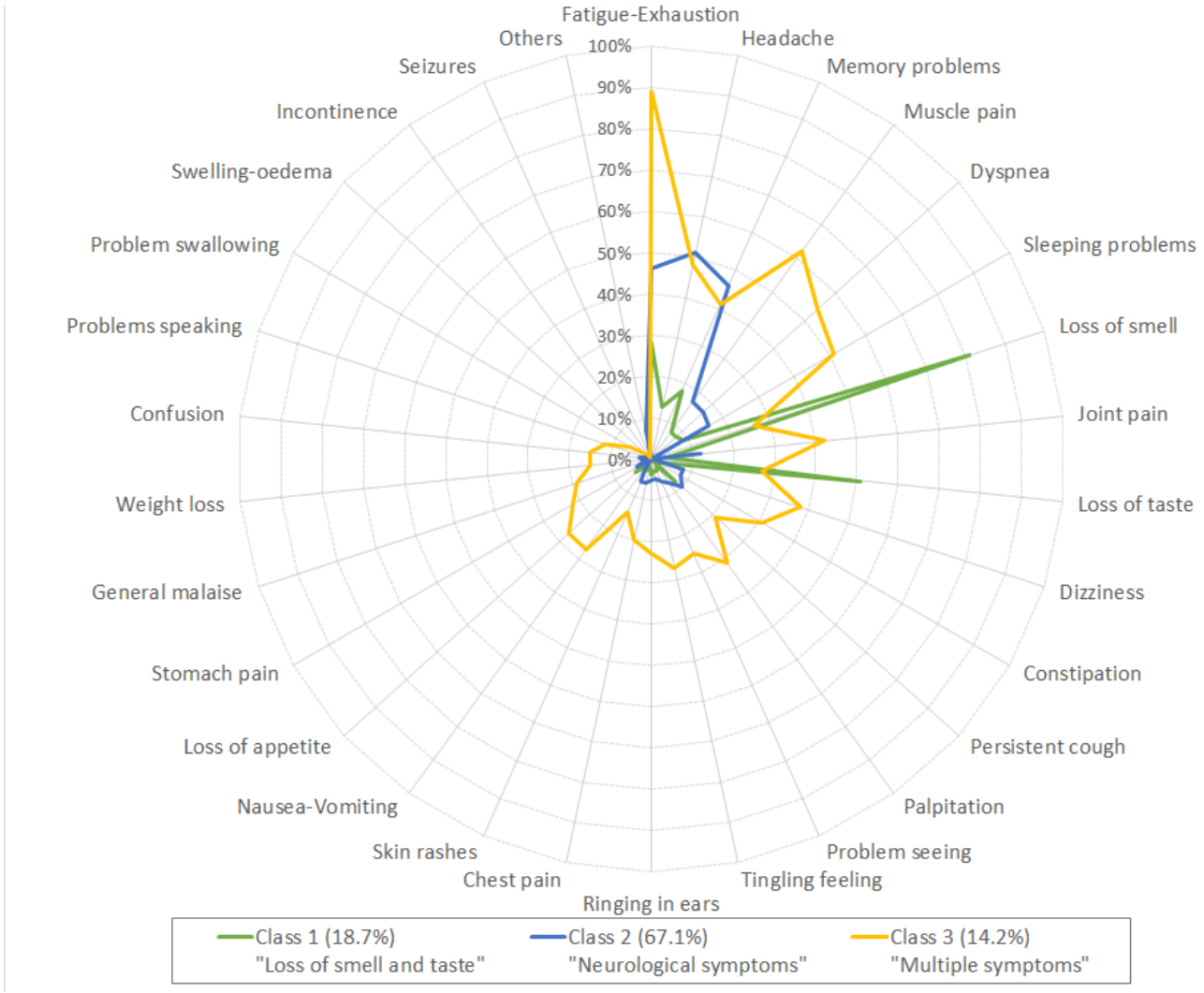

Figure 2 Three-class solution of the latent class analysis on self-reported symptoms of post COVID-19 condition (PCC) 3 months after infection (n=1531, participants with PCC).

lower socioeconomic position were more likely to belong to all classes of PCC symptoms.[19] Another study using cluster analysis found different results.[22] This study highlighted three clusters related to musculoskeletal symptoms and pain, cardiorespiratory symptoms and a cluster with people reporting fewer symptoms. Similar to our results, this study revealed that fatigue was the most frequently reported PCC symptoms.[22] Finally, a study conducted in Japan found that people with PCC can be classified into five clusters of symptoms, with results comparable with our studies for symptoms of loss of smell and taste and neurological symptoms such as fatigue, insomnia and headache.[25] The five clusters were composed of people reporting PCC symptoms of: (1) fatigue (only), (2) fatigue and some cardiorespiratory symptoms, (3) fatigue and forgetfulness, (4) hair loss, and (5) loss of smell and taste. Compared with our study, this study did not find a link between participants' BMI and the different clusters, and it found that people in the 'loss of smell and taste' cluster were less likely to have comorbidities.[25]

Amid the heterogeneity of PCC symptoms, our distinction of patterns of symptoms provides some hints that could help to unravel the underlying pathophysiology, and offer guidance for further research. Although the pathophysiology of PCC remains puzzling, some hypotheses have been put forward.[45] In our analysis, classes 'loss of smell and taste' and 'neurological symptoms' would hypothetically account for the neurotropic impairment of SARS-CoV-2, while class 'multiple symptoms' would stem from an autonomic nervous system dysfunction. Sustained neuroinflammation following initial infection has, indeed, been proposed to be involved in the onset of several PCC symptoms.[46] It can be limited to the neuroepithelium of the nasal cavity or spread to the nervous system per se.[47] On the other hand, a wide array of symptoms of dysautonomia have been reported in the aftermath of COVID-19.[48] Importantly, it should be noted that pathophysiology is presumably intertwined and the causes of symptoms are probably overlapping.

Table 3 Association between participants' sociodemographic and clinical characteristics and the three classes of PCC symptoms (n=3039, reference group=people without PCC)

Characteristics	Class 1 OR (95% CI) 'Loss of smell and taste'	Class 2 OR (95% CI) 'Neurological symptoms'	Class 3 OR (95% CI) 'Multiple symptoms'
Sex, women (ref=men)	1.41 (0.81; 2.68)	**1.90 (1.38; 2.59), p=0.001**	**2.73 (1.85; 4.03), p=0.001**
Educational status, secondary school or below (ref=higher education)	0.96 (0.79; 1.17)	**0.70 (0.52; 0.94), p=0.002**	**1.54 (1.38; 1.77), p=0.02**
BMI (ref=normal)			
Overweight	1.14 (0.93; 1.39)	1.15 (0.82; 1.58)	**1.69 (1.13; 2.52), p=0.04**
Obesity	1.26 (0.98; 1.59)	1.16 (0.79; 1.69)	**2.12 (1.37; 3.26), p=0.001**
Chronic disease, yes (ref=no)	**1.86 (1.32; 2.62), p=0.002**	1.40 (0.80; 2.43)	**2.02 (1.15; 3.54), p=0.001**
History of mental health problem, yes (ref=no)	1.19 (0.68; 2.06)	**1.74 (1.25; 2.41), p=0.006**	0.75 (0.36; 1.55)
At least one acute symptom, yes (ref=no)	**2.30 (1.63; 3.23), p=0.007**	1.41 (0.78; 1.87)	**4.69 (1.70; 8.49), p=0.003**
Hospitalisation following COVID-19 infection, yes (ref=no)	**2.26 (1.27; 4.01), p=0.002**	1.24 (0.41; 3.72)	**3.79 (1.64; 8.76), p=0.001**
Smoking habits, (ref=no)			
Yes, everyday	1.34 (0.98; 1.84)	1.18 (0.71; 1.96)	1.66 (0.97; 2.86)
Yes, occasionally	1.17 (0.81; 1.70)	1.40 (0.80; 2.45)	1.43 (0.72; 2.81)
At least 2 days per week with 10 min of physical activity (ref=yes)	**1.54 (1.15; 2.06), p=0.003**	1.14 (0.96; 1.36)	1.13 (0.80; 1.58)

BMI, body mass index; PCC, post COVID-19 condition.

Study limitations and strengths

This study has several limitations. The main limitation is the possible selection bias due to the design of the study. The study sample is drawn from a self-selected subsample of people engaging with contact tracing. Although contact tracing was obligatory following laboratory-confirmed COVID-19 infection in Belgium, participation in this survey was entirely at the discretion of the participant. As previously explained, the study protocol[26] showed that the profile of participants changed as the follow-up progressed due to loss of follow-up. The result is that the study sample does not compare perfectly with the sampling frame of the eligible population, although the weighting of the results tries to overcome this difference. However, no information was available on the proportion of PCC in the eligible population and this proportion may be underestimated (eg, people with PCC may not be in good enough condition to respond to the survey) or overestimated (eg, people without persistent symptoms may place less emphasis on completing the survey) due to the study design. Second, PCC symptoms are common to many other diseases and infections that affect the general population and we do not have information on the frequency of these symptoms in the general Belgian population not infected with COVID-19 (control group). Finally, although participants self-reported having PCC symptoms 3 months after their SARS-CoV-2 infection, we cannot assess whether these symptoms were persistent for the 3 months following infection or discontinued. Our measurement of the PCC is therefore not completely in accordance with the NICE guidelines stating that PCC is having 'signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis'.[9]

Compared with other studies on PCC, this study also has some strengths. First, most studies of PCC have been on people hospitalised following COVID-19 and followed after hospital discharge. However, PCC also affects people with mild symptoms or who were asymptomatic during the acute phase of infection.[7] In this study, the entry point is to have tested positive for COVID-19 and the eligible population was all adults living in Belgium.

CONCLUSION

Given the heterogeneity of PCC symptoms, most studies have suggested having a multidisciplinary care approach. However, our findings showed that three different classes of PCC symptoms could be distinguished with different risk factors for each class: (1) a combination of symptoms of loss of smell and taste; (2) a combination of

neurological symptoms such as headache, memory problems and fatigue; and (3) a combination of many heterogeneous symptoms. Therefore, such classification could be used to develop individualised care pathways according to the symptoms and needs of people with PCC. Future studies with longer follow-ups are needed to assess how the symptoms and their impact change over time. There is also a need for case–control studies or studies with a matched non-COVID-19 group to accurately assess PCC symptoms and their prevalence in the general population. Finally, future studies should also address PCC symptoms in children and adolescents, as well as the impact of the different SARS-CoV-2 variants on the types of PCC symptoms.

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Acknowledgements The authors would like to thank everyone who participated in the COVIMPACT Study.

Contributors PS was responsible for the research protocol design and the overall content as guarantor, the development of which was supported by SN, DC-Z, RDP, DVC, SDe, SDr, LC, BD, KDR and RC. SN led the preparation of the manuscript with support from DC-Z, RDP, DVC, SDe, SDr, LC, BD, KDR, RC and PS. All authors contributed to the present paper and critically revised and approved the final manuscript.

Funding Sciensano (Belgian Institute for Health) internal funding (award/grant no. NA).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The consent of individuals who wish to take part in the study was collected in the baseline questionnaire as well as in the follow-up questionnaire. The study was approved by the ethics committee of the Ghent University Hospital (Commissie voor Medische Ethiek; B.U.N.: B6702021000287).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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