

# Course of long COVID symptoms over time in the ComPaRe long COVID prospective e-cohort

Viet-Thi Tran (✉ [thi.tran-viet@aphp.fr](mailto:thi.tran-viet@aphp.fr))

Paris University <https://orcid.org/0000-0003-1863-6739>

Raphael Porcher

Paris University

Isabelle Pane

Assistance Publique Hôpitaux de Paris

Philippe Ravaud

Paris Descartes University

---

## Article

**Keywords:** prospective cohort, long COVID, patient-reported outcome measures, quality of life

**Posted Date:** August 3rd, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-753615/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

---

1 **Course of long COVID symptoms over time in the ComPaRe long COVID prospective e-**  
2 **cohort**

3

4 **Word count :** 1614

5 **Keywords:** prospective cohort; long COVID; patient-reported outcome measures; quality of  
6 life

7 **Abstract (142/150 words)**

8 About 10% of the people infected by the severe acute respiratory syndrome coronavirus 2 are  
9 reported to experience “long COVID,” that is, persistence of symptoms several weeks after  
10 infection. Day-by-day prevalence of long COVID symptoms was determined from responses  
11 to the Long COVID Symptom Tool by 837 patients (3075 person-months) with a confirmed  
12 infection and enrolled in the ComPaRe long COVID cohort, a prospective cohort of such  
13 patients in France. Nine months after disease onset, 88.7% patients reported persistent  
14 symptoms and 70% reported a high burden of disease. Over time, the prevalence progressively  
15 decreased for 19/53 symptoms (e.g., loss of taste/smell) and was stable for 29/53 symptoms  
16 (e.g., fatigue). For 5/53 symptoms (e.g., memory problems), prevalence increased rapidly over  
17 the first two months and then reached a plateau. These findings are important for understanding  
18 the underlying etiologies and mechanisms of long COVID.

19

## 20 **1. Background**

21 As of June 2021, about 170 million people worldwide had been infected by the severe acute  
22 respiratory syndrome coronavirus 2 (SARS-CoV-2), the pathogen responsible for coronavirus  
23 disease 2019 (COVID-19)<sup>1</sup>. According to the United Kingdom Office for National Statistics,  
24 about 10% of them will experience “long COVID” or “post-acute COVID”, that is, the  
25 persistence of symptoms such as fatigue, dyspnea, chest pain, cognitive disturbances, or  
26 arthralgia, for several weeks to months after their initial SARS-CoV-2 symptoms<sup>2</sup>. Research  
27 has mainly focused on the occurrence of specific long-term complications among hospitalized  
28 and non-hospitalized patients after a COVID-19 infection<sup>3-7</sup>. To our knowledge, only a handful  
29 of studies have investigated the specific longitudinal evolution of patients reporting persisting  
30 symptoms (i.e., with long COVID), but they have generally been small, either retrospective or  
31 limited to single centers or both<sup>8,9</sup>.

## 32 **2. Results**

33 The ComPaRe Long COVID cohort is an ongoing nationwide e-cohort of patients with long  
34 COVID in France, nested in the ComPaRe research program ([www.compare.aphp.fr](http://www.compare.aphp.fr)), an  
35 umbrella e-cohort of patients with chronic conditions<sup>10</sup>. Among the 1673 patients included in  
36 the ComPaRe long COVID cohort on the July 18, 2021, we analyzed the data from the 837  
37 patients reporting: 1) a laboratory confirmed COVID-19 infection with a positive test for  
38 SARS-CoV2 by PCR swab and/or a serologic assay; 2) symptoms persisting three weeks after  
39 onset; and 3) who enrolled in the cohort by May 1, 2021 so as to ensure at least 2 months of  
40 follow-up (**Supplementary material 1**). Their median age was 46 years, interquartile range 37  
41 to 53 with 80.1% (671/837) women. In all, 38% (321/837) reported comorbidities (7.0%,  
42 59/837 with chronic lung diseases, and 4.3%, 36/837 with high blood pressure). Median time

43 between disease onset and latest follow-up was 279 days, IQR 215 to 435 days. Among  
44 participants, 113 (13.5%) had been hospitalized during their acute disease and 24 (2.9%) had  
45 been admitted to an intensive care unit (ICU). **Supplementary material 2** summarizes the  
46 patients' characteristics.

47 Participants were followed up every 60 days with online questionnaires. At each observation  
48 point, patients were first asked if they still had symptoms related to COVID-19. Those reporting  
49 the persistence of symptoms completed the long COVID symptom tool (ST) and impact tool  
50 (IT), a pair of validated patient-reported instruments assessing respectively 53 long COVID  
51 symptoms and 6 dimensions of patients' lives that can be affected by the disease<sup>11</sup>. Those  
52 reporting that they no longer had any symptoms were asked to report the date when they first  
53 noticed the absence of symptoms (**Online Methods**). Overall, our data covered 3075 person-  
54 months, with a median follow-up since cohort enrollment of 120 days (interquartile range 60 to  
55 178 days). Retention in the cohort ranged from 84% (at 2 months) to 65% (at 6 months) and is  
56 detailed in **Supplementary material 3**.

57 Remission of symptoms (i.e., disappearance of all symptoms) was observed during follow-up  
58 for 126 patients. Its incidence since disease onset was 1.5 per 100 person-months (95%  
59 confidence interval (CI) 1.2 to 1.8). Among patients who reported remission of all of their  
60 symptoms, 21/126 (16.7%) subsequently described a relapse for at least one symptom. At 6 and  
61 9 months (180 and 270 days), the probability of symptom persistence was respectively 95.6%  
62 (95% CI 94.2% to 97.1%) and 88.7% (95% CI 86.2% to 91.2%) (**Figure 1**).

63 The day-by-day estimated prevalence of the 53 symptoms measured by the long COVID ST is  
64 presented in **Figure 2a**. First, 19 (36%) symptoms showed a progressive decrease in prevalence  
65 over time. Among them, change/loss of taste, diarrhea, change/loss of smell, congested/runny  
66 nose, cough, dizziness/malaise, difficulty sleeping, loss of appetite, and sore throat showed the

67 largest changes (>20% decrease). Second, 29 (55%) symptoms showed no specific change in  
68 prevalence over time. Among them, fatigue and brain fog/difficulty concentrating were the most  
69 prevalent; at 180 days, they affected respectively 80% and 61.8% of the study population.  
70 Finally, 5 symptoms showed a rapid increase in prevalence over the two first months and then  
71 reached a plateau. Among them, word-finding problems and hair loss changed most markedly  
72 (>20% increase) (**Supplementary material 4**). For most symptoms, evolution over time was  
73 similar in age groups. However, for 6 specific symptoms (change of taste/smell, loss of appetite,  
74 hot flushes, blurry vision and memory problems), we found important differences between  
75 patients between aged  $\leq 40$  years and older. (**Supplementary material 5**).

76 Long COVID is a relapsing-remitting disease. Thirty days after disease onset, about 50% of  
77 patients reported weekly relapses, the rest experiencing permanent or daily symptoms. Over  
78 time, relapses became less frequent, with a decrease in the proportion of patients reporting  
79 weekly relapses and a parallel increase in the proportion reporting less than weekly relapses  
80 (**Supplementary material 6**).

81 Patients' perception of the impact of the disease on their lives, measured by the long COVID  
82 IT, is shown in **Figure 2b**. In particular, we present the proportion of patients reporting an  
83 unacceptable disease state, defined as a score of the long COVID IT above the value at which  
84 >75% of patients consider that they could not cope with a similar level of symptoms lifelong<sup>11</sup>.  
85 This analysis revealed three distinct phases of the disease. In a first phase, from 21 to 50 days  
86 after disease onset, the proportion of patients reporting an unacceptable disease state quickly  
87 rose from 50% to 70%, marking the transition from an acute to a persisting subacute disease.  
88 In a second phase, lasting from 50 to 180 days, the burden of disease progressively decreased  
89 as several symptoms disappeared and the number of patients reporting an unacceptable  
90 symptom state slowly increased to 60%. Finally, from 180 to 240 days, the proportion of  
91 patients reporting an unacceptable disease state started increasing again with 70% of patients

92 considering their disease unacceptable at that time. This latter period may correspond to  
93 patients' realization that they had entered a chronic disease state.

### 94 **3. Discussion**

95 This is the first study to report the day-by-day longitudinal course of the symptoms and impact  
96 of long COVID in a large prospective cohort of patients with a laboratory confirmed infection.  
97 The incidence of symptom remission since disease onset was 1.5 per 100 person-months,  
98 consistent with the results of Nehme et al., who found that most patients with symptoms at 30-  
99 45 days still reported some at 7-9 months<sup>6</sup>. It was however lower than observations in a single-  
100 center study in Germany where 20% of patients were free from all 14 symptoms under study at  
101 12 months<sup>8</sup>. This difference may be due to selection of patients in our study, differences in  
102 disease measurements, and/or differences in follow-up.

103 The course of symptoms over time highlighted three distinct patterns that offer insight into the  
104 etiologies and mechanisms underlying long COVID. A decrease in prevalence over time for  
105 symptoms such as loss of taste or smell, coughing, or diarrhea may indicate recovery from  
106 symptoms or organ dysfunction after the acute phase. If so, our results call for reconsidering  
107 the time frames proposed by the NICE guidelines, which distinguish ongoing symptomatic  
108 COVID-19 (i.e., signs and symptoms of COVID-19 from 4 to 12 weeks) and post-COVID-19  
109 syndrome (i.e., signs and symptoms that develop during or after an infection consistent with  
110 COVID-19, continue for more than 12 weeks, and are not explained by an alternative  
111 diagnosis.<sup>12</sup> Our study showed a constant decrease in the prevalence of these symptoms lasting  
112 more than 12 weeks. The observed increase in the prevalence of symptoms such as memory  
113 problems may either indicate late onset symptoms or be an artifact due to their low prevalence  
114 in patients' ineligible for this study because they did not experience persistent symptoms.  
115 Finally, symptoms showing no change of prevalence over time can be caused by mechanisms

116 that do not change rapidly over time, such as deconditioning or post-traumatic stress disorder,  
117 or due to a mixture of recovery from acute disease and late onset symptoms appearing as a  
118 consequence of COVID-19<sup>13</sup>.

119 Our results demonstrate the substantial impact of COVID-19 and long COVID on patients'  
120 lives. In a previous report, we showed that half the patients reported impaired functioning, that  
121 is, they were no longer able to perform some activities unassisted at home or at work<sup>11</sup>. Patients'  
122 responses in this study depict the change in their perception of the disease and its symptoms  
123 over time as they realize that it is chronic rather than acute, in the specific context of a novel  
124 and previously unknown disease.

125 Strengths of this study lie in the prospective follow-up of a large population of patients with a  
126 confirmed COVID-19 infection (i.e., confirmed long COVID patients) and their regular  
127 assessment using validated patient-reported outcome measurements, developed from patients'  
128 lived experience, with excellent reproducibility (intraclass correlation coefficient 0.83, 95%  
129 confidence interval 0.80 to 0.86).

130 This study has several limitations. The voluntary nature of recruitment in the ComPaRe long  
131 COVID cohort may have selected patients who had overall more symptoms. In addition, our  
132 recruitment strategy included a social media and general media campaign that may have  
133 selected younger and better educated patients. Second, our sample included a majority of  
134 women. Although this selection bias is usual in studies relying on online surveys, its importance  
135 is difficult to assess as it has also been emphasized that women are more likely to report  
136 persisting symptoms after a COVID-19 infection<sup>3</sup>. Third, in view of the limited number of  
137 patients who were hospitalized in ICUs in our study, our results cannot be generalized to this  
138 specific population.

139 In conclusion, our study shows that most patients with long COVID have symptoms evolving  
140 in different patterns but persisting from 6 months to one year. Our results should be useful for  
141 researchers seeking the potential pathophysiological mechanisms underlying long COVID and  
142 should also help physicians to inform their patients about the potential course of their disease.

#### 143 **4. Acknowledgments**

144 XXX

#### 145 **5. Contributions**

146 XXX

#### 147 **6. Competing interests**

148 The authors declare no competing interests and no financial associations that may be relevant  
149 or seen as relevant to the submitted manuscript. The authors have no association with  
150 commercial entities that could be viewed as having an interest in the general area of the  
151 submitted manuscript.

#### 152 **7. References**

- 153 1. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Vol.  
154 2020 (World Health organization, 2020).
- 155 2. Carfi, A., Bernabei, R. & Landi, F. Persistent Symptoms in Patients After Acute  
156 COVID-19. *Jama* **324**, 603-605 (2020).
- 157 3. Huang, C., *et al.* 6-month consequences of COVID-19 in patients discharged from  
158 hospital: a cohort study. *Lancet (London, England)* **397**, 220-232 (2021).
- 159 4. Nehme, M., *et al.* COVID-19 Symptoms: Longitudinal Evolution and Persistence in  
160 Outpatient Settings. *Annals of internal medicine* (2020).
- 161 5. Ayoubkhani, D., *et al.* Post-covid syndrome in individuals admitted to hospital with  
162 covid-19: retrospective cohort study. *BMJ (Clinical research ed.)* **372**, n693 (2021).
- 163 6. Nehme, M., Braillard, O., Chappuis, F., Courvoisier, D.S. & Guessous, I. Prevalence of  
164 Symptoms More Than Seven Months After Diagnosis of Symptomatic COVID-19 in  
165 an Outpatient Setting. *Annals of internal medicine* (2021).

- 166 7. Taquet, M., Geddes, J.R., Husain, M., Luciano, S. & Harrison, P.J. 6-month  
167 neurological and psychiatric outcomes in 236 379 survivors of COVID-19: a  
168 retrospective cohort study using electronic health records. *The lancet. Psychiatry*  
169 (2021).
- 170 8. Seeßle, J., *et al.* Persistent symptoms in adult patients one year after COVID-19: a  
171 prospective cohort study. *Clinical infectious diseases : an official publication of the*  
172 *Infectious Diseases Society of America* (2021).
- 173 9. Davis, H., *et al.* Characterizing Long COVID in an International Cohort: 7 Months of  
174 Symptoms and Their Impact. *medRxiv* (2020).
- 175 10. Tran, V.T. & Ravaud, P. Collaborative open platform E-cohorts for research  
176 acceleration in trials and epidemiology. *Journal of clinical epidemiology* **124**, 139-148  
177 (2020).
- 178 11. Tran, V.T., *et al.* Development and validation of the long covid symptom and impact  
179 tools, a set of patient-reported instruments constructed from patients' lived experience.  
180 *Clinical infectious diseases : an official publication of the Infectious Diseases Society*  
181 *of America* (2021).
- 182 12. NICE. COVID-19 rapid guideline: managing the long-term effects of COVID-19.  
183 (NICE, 2020).
- 184 13. Nalbandian, A., *et al.* Post-acute COVID-19 syndrome. *Nature medicine* **27**, 601-615  
185 (2021).

186

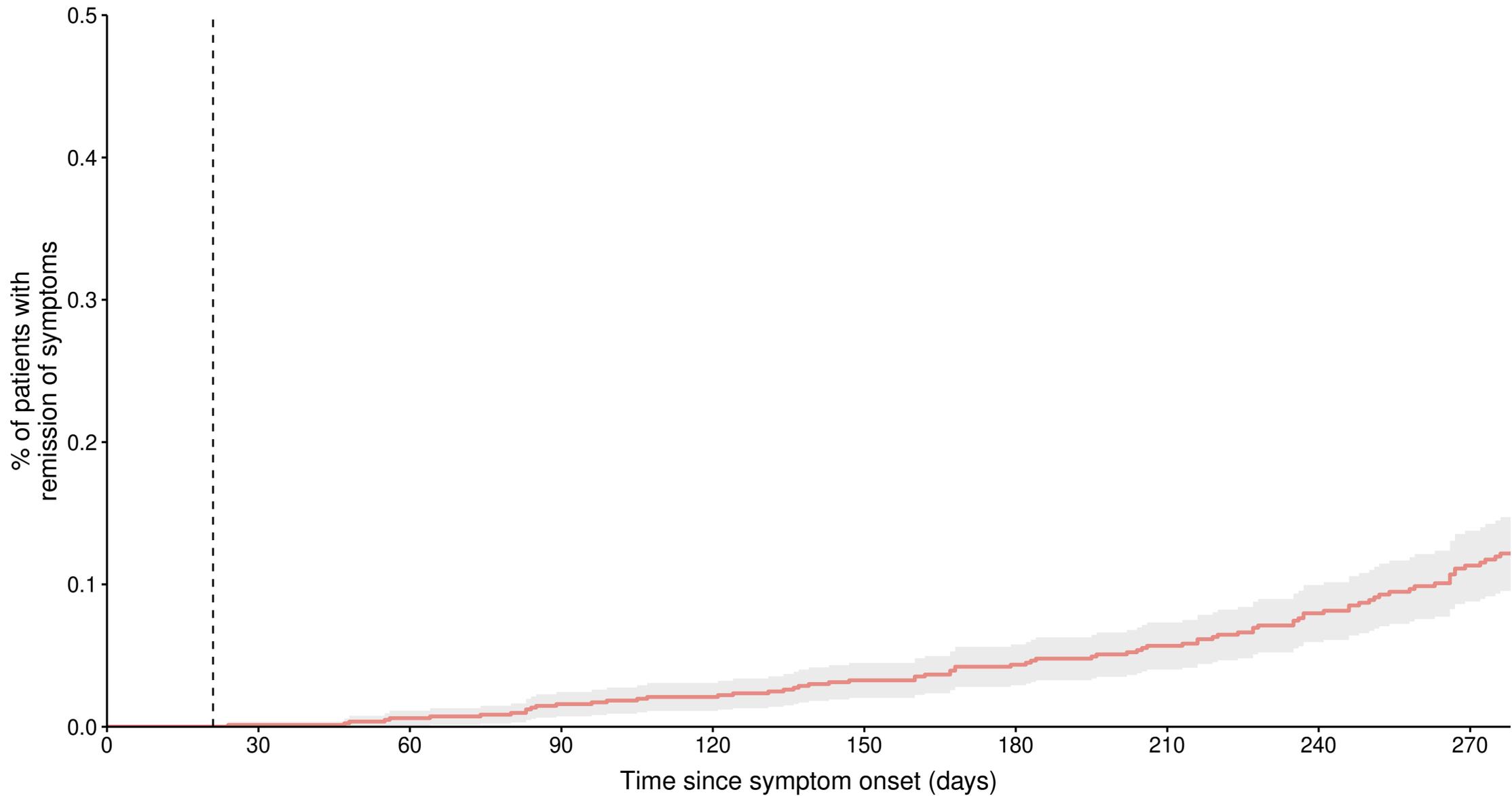
## 187 **8. Figure legends**

188 **Figure 1: Cumulative event curve for remission of long COVID symptoms.** Time of  
189 remission was defined as the first time that patients reported no longer experiencing any  
190 symptoms of long COVID. The time at risk started at disease onset and ended on July 18, 2021.  
191 Follow-up data were censored at the participants' latest observation point.

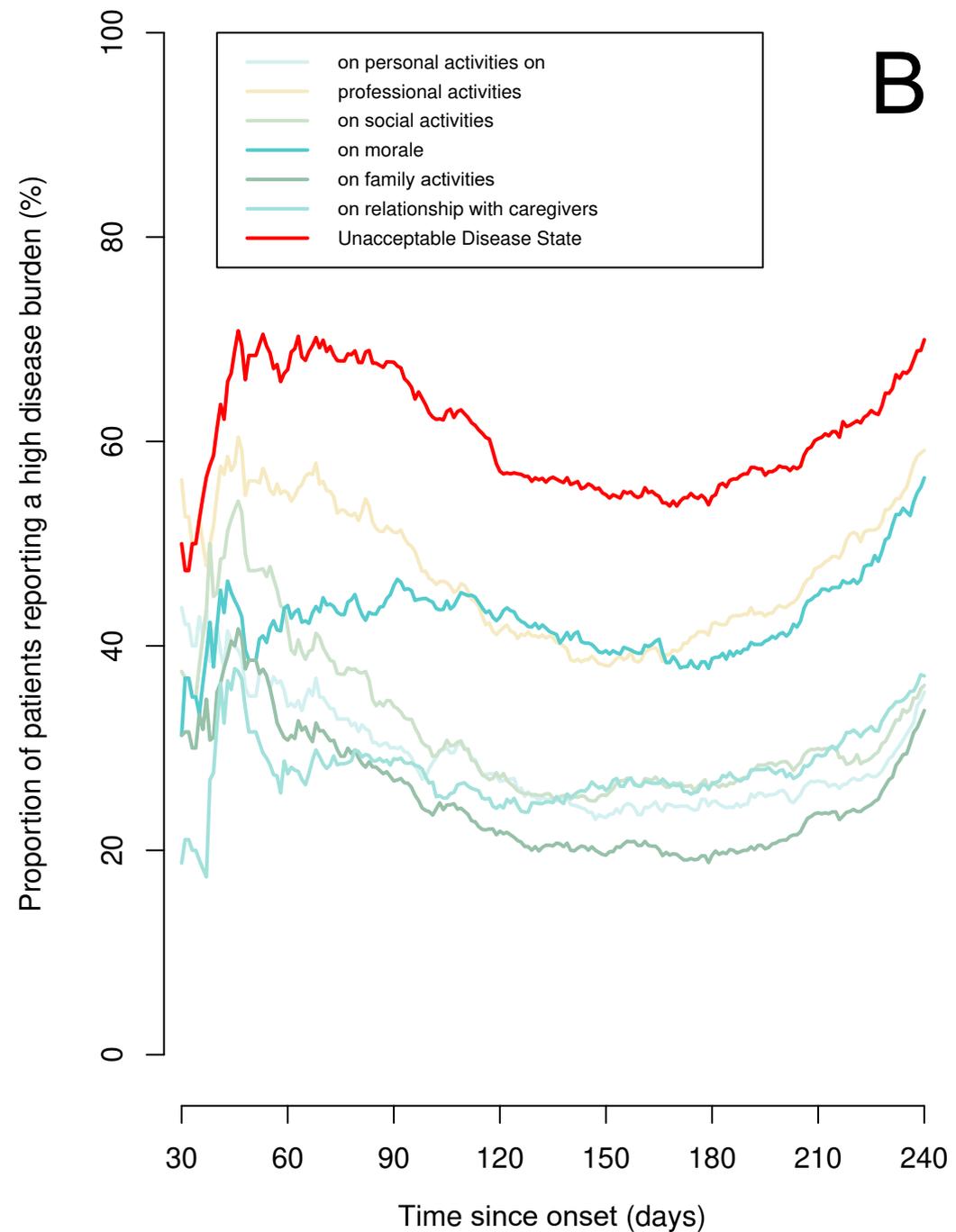
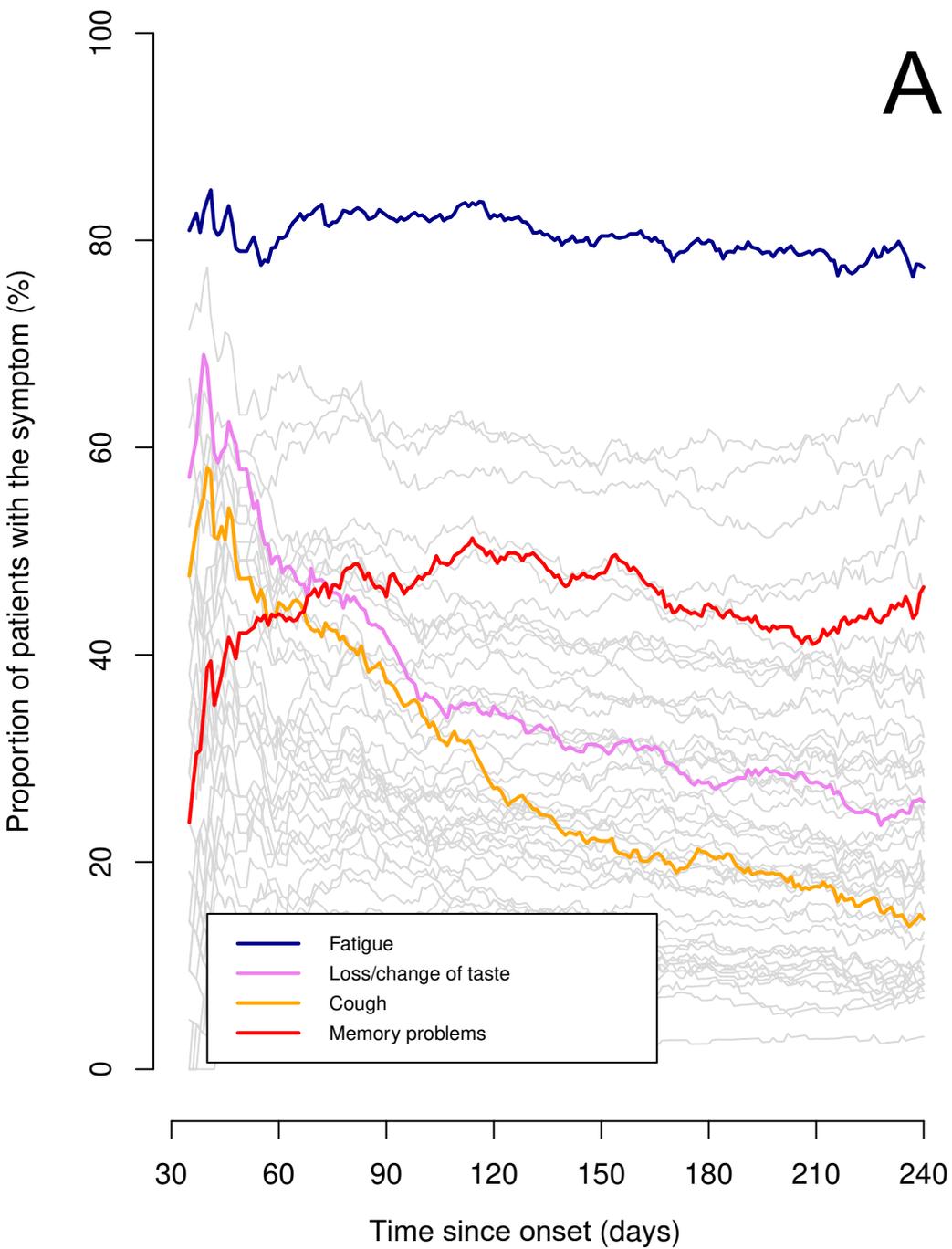
192 **Figure 2: Day-by-day trends in the prevalence of long COVID symptoms (A) and of their**  
193 **impact on patients' lives (B).** A: The figure presents the day-by-day prevalence of each of the  
194 53 symptoms of long COVID assessed by the Long COVID ST (grey lines). Examples of  
195 specific symptoms have been highlighted (colored lines). For each symptom and at each  
196 observation point, we assumed that patients could either be "experiencing" or "not  
197 experiencing" the symptom. We assumed that their state at an arbitrary time was the same as  
198 the state at their previous observation point and that their states before their first observation  
199 and after their last observation were unknown. B: The figure presents the day-by-day prevalence  
200 of the 6 domains of patients' lives that can be affected by long COVID and are assessed by the  
201 Long COVID IT. For each item of the long COVID IT and at each observation point, we  
202 modelled patients answers as either "reporting" a significant impact of long COVID in this  
203 domain" (i.e., item score >7) or "not reporting" this impact (i.e. item score <8). We assumed

204 that their state at an arbitrary time was the same as the state at their previous observation point  
205 and that their states before their first observation and after their last observation were unknown.  
206 Red line represents a similar model for the Patient Acceptable Symptomatic State (PASS) of  
207 the long COVID IT, which is the long COVID IT score below which 75% of patients find that  
208 their disease state is acceptable.

209



Number at risk      837                      817                      794                      763                      731                      678                      614                      521                      421



## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementarymaterialsNMjc.docx](#)
- [OnlineMethodsNMjc.docx](#)