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► To cite this version:

Olivier Robineau, Emmanuel Wiernik, Cédric Lemogne, Xavier de Lamballerie, Laetitia Ninove, et al.. Persistent symptoms after the first wave of COVID-19 in relation to SARS-CoV-2 serology and experience of acute symptoms: A nested survey in a population-based cohort. *The Lancet Regional Health - Europe*, 2022, 17, pp.100363. 10.1016/j.lanep.2022.100363 . hal-03737925

HAL Id: hal-03737925

<https://hal.science/hal-03737925>

Submitted on 30 Aug 2022

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1 Persistent symptoms after the first wave of COVID-19 in relation to SARS-CoV-2 serology and
2 experience of acute symptoms: a nested survey in a population-based cohort.

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34 Summary

35 Background

36 Many patients report persistent symptoms after COVID-19. Our aim was to determine whether
37 some of these symptoms were more associated with past SARS-CoV-2 infection compared to
38 other conditions.

39 Methods

40 This prospective survey was nested in CONSTANCES, a randomly selected French population-
41 based cohort, started in 2012. All participants being followed-up by internet completed 2
42 questionnaires during the first wave of the pandemic focusing on the acute symptoms of their
43 COVID-19-like illness. Serological tests for SARS-CoV-2 were then performed (May-Nov
44 2020). Between December 2020 and January 2021, participants completed a third questionnaire
45 about symptoms that had lasted more than 2 months. Participants were classified into four
46 groups according to both European Center for Diseases Control (ECDC) criteria for COVID-
47 19 (ECDC+ or ECDC-) and serological SARS-CoV-2 test results (Sero+ or Sero-). To compare
48 the risk of each persistent symptom among the groups, logistic regression models were adjusted
49 for age, sex, educational level, comorbidities, and the number of acute symptoms declared
50 during the first wave of the epidemic. A mediation analysis was performed to estimate the direct
51 effect of the infection on persistent symptoms and its indirect effect via the initial clinical
52 presentation.

53

54 Findings

55 The analysis was performed in 25910 participants. There was a higher risk of persistent
56 dysgeusia/anosmia, dyspnea and asthenia in the ECDC+/Sero+ group than in the ECDC+/Sero-
57 group (OR: 6.83 [4.47-10.42], 1.69 [1.07-2.6] and 1.48 [1.05-2.07], respectively). Abdominal

58 pain, sensory symptoms or sleep disorders were at lower risk in the ECDC+/Sero+ group than
59 in the ECDC+/Sero- group (0.51 [0.24-0.96], 0.40 [0.16-0.85], and 0.69 [0.49-0.95],
60 respectively). The mediation analysis revealed that the association of the serological test results
61 with each symptom was mainly mediated by ECDC symptoms (proportion mediated range
62 50%-107%).

63

64 Conclusion

65 A greater risk of persistent dysgeusia/anosmia, dyspnea and asthenia was observed in SARS-
66 CoV-2 infected people. The initial clinical presentation substantially drives the association of
67 positive serological test results with persistent symptoms.

68 Funding: French National Research Agency

69

70 **Research in context**

71 **Evidence before this study**

72 To identify existing studies on post-acute symptoms due to SARS-CoV-2 infection, we
73 searched PubMed from January, 2020 to December 20, 2021. We used the following search
74 string: (COVID-19[title/abstract] OR SARS-CoV-2[title/abstract]) AND ((long-
75 term[title/abstract] AND complications[title/abstract]) OR ((persistent[title/abstract] OR
76 persistence[title/abstract]) AND symptoms[title/abstract])) OR (long-covid [title/abstract]) OR
77 (long-hauler [title/abstract]) OR (post-covid condition [title/abstract])). We took into account
78 observational studies that described cohorts of outpatients or studies that compared persistent
79 symptoms between individuals with COVID-19 and with other conditions.

80 Most of the literature described cohorts of patients with no comparison groups. Other studies
81 comparing patients with COVID-19 and uninfected individuals were performed in populations
82 that had access to testing during the first wave of the pandemic, thus creating a selection bias.
83 These studies suggested associations between persistent symptoms and a history of COVID-
84 19, but may have been confounded by severity of the acute illness, age, sex, or comorbidities.
85 In addition, there were no studies comparing individuals from the general population who
86 received serological tests or PCR in a research context.

87 **Added value of this study**

88 This population-based cohort study included 25910 individuals divided in 4 groups defined by
89 the symptoms they presented during the first wave of the pandemic and by their serological
90 status for SARS-CoV-2 infection. All individuals received serological tests and prospectively
91 completed questionnaires. We compared the risk of presenting with several persistent
92 symptoms 7 to 8 months after the first wave of the pandemic in France. We used adjusted
93 logistic regression models to compare the risk of having each of the symptoms between the
94 groups. This showed that individuals in all groups had a similar risk of having at least one
95 symptom. However, dysgeusia/anosmia, dyspnea, and asthenia were more frequent in
96 individuals with a history of COVID-19. Some symptoms were more frequent in other groups
97 (sleep disorders, abdominal pain, sensory symptoms).

98 **Implications of all the available evidence**

99 This study shows that persistent symptoms are common in the general population, irrespective
100 of COVID-19 history. Individuals with a history of COVID-19 have however an increased risk
101 of persistent dysgeusia/anosmia, dyspnea and asthenia. Acute clinical presentation is a strong
102 determinant of these long-term symptoms. This should prompt policy makers to develop
103 holistic management strategies for patients with post-COVID-19 conditions as well as for other
104 patients with similar complaints. Promoting therapeutic and preventive strategies that reduce
105 the symptoms of the acute phase of the disease could have an effect on the post-COVID
106 symptoms.

107 Post-covid-19 condition is potentially an emerging issue in the Covid-19 pandemic. Months
108 after the acute illness caused by SARS-CoV-2 infection, clinical symptoms may persist whether
109 or not the acute phase required hospitalization.¹⁻⁴ The main persistent symptoms are asthenia,
110 pain, dyspnea, cognitive complaints, and dysgeusia/anosmia.⁵ Other symptoms such as
111 neurological or digestive complaints have also been described.⁶ The pathophysiology of these
112 persistent symptoms is poorly understood. Except for dysgeusia/anosmia, these persistent
113 symptoms are not specific to SARS-CoV-2 infection but may be related to other conditions, or
114 the consequence of changes in behavior, wellbeing, or access to care due to the pandemic. In
115 this context, characterizing the phenotypes represented by the association of these persistent
116 symptoms in persons with (versus without) SARS-CoV-2 past infection has rarely been studied.
117 Therefore, to better understand the persistent symptoms after COVID-19, it is important to
118 determine whether some of these symptoms are more specifically associated with SARS-CoV-
119 2 infection than with other conditions.⁷

120 The aim of this study using extensive data from a large population-based cohort study was to
121 compare the risk of each persistent symptom depending on serological status for SARS-CoV-2
122 and depending on the history of acute symptoms during the first pandemic wave.

123

124 Methods

125

126 *Design and participants*

127 This survey is nested in the French CONSTANCES population-based cohort⁸ which includes
128 approximately 200,000 adults aged 18 to 69 at inception. Since 2012, participants have been
129 selected from the French adult population affiliated with the National Fund for Health Insurance
130 according to a random sampling scheme stratified for age, gender, socioeconomic status and
131 region of France to be representative of the source population, and have been followed by
132 repeated yearly questionnaires and linked by administrative databases. CONSTANCES is also

133 one of the three adult cohorts that is involved in the SAPRIS-SERO ("Santé, Pratiques,
134 Relations et Inégalités Sociales en population générale pendant la crise COVID-19" - Serology)
135 survey, whose aim is to quantify the cumulative incidence of SARS-CoV-2 infection in the
136 French population using the dried blood spot (DBS) test for anti-SARS-CoV-2 antibodies.⁹ In
137 this specific COVID-19 survey, 66,848 CONSTANCES participants being followed-up by
138 internet were asked to complete two self-administered e-questionnaires between April 6, 2020,
139 and June 15, 2020. Variables included socio-demographics, comorbidities, COVID-19
140 diagnosis, and a detailed collection of 12 acute symptoms present in the participants during the
141 15 days before each questionnaire. These two questionnaires were used to classify participants
142 according to whether or not they experienced a COVID-19-like illness during the first wave of
143 the epidemic, but also to evaluate the number of acute symptoms experienced during the initial
144 episode. Between May 4, 2020, and November 30, 2020, DBS was also collected. Then,
145 between December 2020 and February 2021, a third follow-up internet questionnaire including
146 questions on clinical symptoms was completed by the participants. Overall, 35,852 participants
147 completed the first 2 questionnaires, had a serology performed and were eligible for this survey
148 on persistent symptoms.

149 Ethical approval and written or electronic informed consent were obtained from each
150 participant before enrolment in the original cohort. The SAPRIS-SERO study was approved by
151 the Sud-Méditerranée III ethics committee (approval #20.04.22.74247) and electronic informed
152 consent was obtained from all participants for DBS testing.

153

154 *Classification of participants*

155 Participants were considered "Sero+" or "Sero-" if the serological test was positive for SARS-
156 CoV-2 infection. COVID-19-like illness during the first pandemic wave was defined according
157 to the European Centre for Disease Prevention and Control (ECDC) case definition. Participants

158 were considered “ECDC+” if they reported at least one of the following symptoms that lasted
159 at least 3 days: dysgeusia/anosmia, dyspnea, fever, and cough in at least one of the two first
160 questionnaires.¹⁰ Other acute symptoms included headache, unusual asthenia, myalgia, joint
161 pain, runny nose, nausea/vomiting, diarrhea and skin problems.

162 The seropositive and seronegative status was defined by IgG results against the spike protein
163 of the virus (i.e., optical density ratio ≥ 1.1 and < 0.7 , respectively) using the (Euroimmun®,
164 Lübeck, Germany) test.⁹ In case of indeterminate results (i.e., optical density ratio ≥ 0.7 and
165 < 1.1), an in-house microneutralization assay to detect neutralizing anti-SARS-CoV-2
166 antibodies was performed. Participants with neutralizing antibody titers ≥ 40 were also
167 considered to be seropositive. Most seropositive participants were assumed to have been
168 infected during the first wave of the pandemic, between February 2020 and May 2020.

169 We selected all seropositive and seronegative participants who completed the follow-up
170 questionnaire excluding participants who reported a diagnosis of COVID-19 after the
171 serological test. There were 4 groups of participants: the ECDC+/Sero+ group defined by
172 ECDC symptoms and seropositivity to anti-SARS-CoV-2 antibodies; the ECDC+/Sero- group
173 defined by ECDC symptoms and seronegativity; the ECDC-/Sero+ group defined by the
174 absence of ECDC symptoms, seropositivity and no history of COVID-19 reported on the third
175 questionnaire; and the ECDC-/Sero- group defined by the absence of ECDC symptoms,
176 seronegativity and no history of COVID-19 reported on the third questionnaire (see
177 supplementary appendix p 1).

178

179 *Persistent symptoms*

180 To identify persistent symptoms, we used symptoms reported in the third questionnaire. The
181 list of symptoms was based on symptoms described in the literature on “post-covid-19
182 syndrome” and “long-covid”.⁶ It explored dysgeusia/anosmia, cardiothoracic symptoms

183 (cough, thoracic pain, palpitations), pains (backpain, arthralgia, myalgia, headache), digestive
184 disorders (nausea, diarrhea, constipation, abdominal pain), and others symptoms that were
185 frequently associated with long-covid (asthenia, fever, cognitive complaints, cranial nerves
186 abnormalities, sensory disorders, talk abnormalities, auditory disorders, dizziness, sleep
187 disorders, skin disorders).

188 Persistent symptoms were defined as those that began after March 2020, lasted at least two
189 months, and were still present at the time of the third questionnaire.

190

191 *Data analysis*

192 Because our goal was to compare persistent symptoms according to infection assessed by
193 SARS-CoV-2 serological status and to highlight the specific association with past infection in
194 patients with a history of acute symptoms during the first pandemic wave, the risk of presenting
195 each persistent symptom was compared between Sero+ and Sero- groups, and between
196 ECDC+/Sero+ and ECDC+/Sero- groups. Comparisons involving ECDC-/Sero+ and ECDC-
197 /Sero- are presented in the supplementary appendix (ECDC-/Sero+ VS ECDC-/Sero-;
198 ECDC+/Sero+ VS ECDC-/Sero-). Groups were compared using t-test for continuous variables
199 and Chi-square test for qualitative variables. Univariable and multivariable logistic regression
200 models were performed to estimate the strength of association (odds-ratio (OR)) between each
201 persistent symptoms (the dependent variable) and the group (independent variable).
202 Multivariable OR estimates were adjusted for sex, age, educational level, comorbidities lasting
203 more than 6 months and the number of symptoms reported during the first wave of the pandemic
204 (aOR). Indeed, persistent symptoms seem to be epidemiologically associated with the number
205 of acute symptoms in hospitalized patients and in outpatients with COVID-19.^{11,12} All tests
206 were two-sided and $P < 0.05$ was considered statistically significant.

207 We also used longitudinal data for the 10 symptoms that were collected in all questionnaires to
208 compare the persistence of each of these symptoms between Sero- and Sero+ participants.

209 We finally conducted a mediation analysis for all persistent symptoms associated with the
210 serological status in univariable analysis. In this analysis, we assumed that a part of the
211 association of the serological status on persistent symptoms was mediated by the acute
212 symptoms caused by the infection; in other words, the acute symptoms are supposed to be in
213 the causal pathway between the infection and the persistent symptoms and cannot be considered
214 as a confounding factor (figure 1).

215 Mediation analysis has been widely used in social and medical sciences.¹³⁻¹⁷ It relies on a set
216 of regression equations to model the relationships between the dependent variable, the mediator
217 and the independent variable, while allowing adjustments for confounding factors.

218 We analyzed the association of past infection (defined by the SARS-CoV-2 serology result) on
219 persistent symptoms, mediated by the initial clinical presentation, defined by ECDC status. The
220 “effect” of past infection status can thus be direct, not passing through the initial symptoms, or
221 indirect, passing through the initial clinical presentation.

222 We estimated the direct and indirect effect by calculating the following parameters:^{16,17}

- 223 - the natural direct effect (NDE), defined as the effect of a positive serology versus a
224 negative serology on the probability of persistent symptoms when the ECDC status is
225 negative. The NDE includes an interaction effect of serology with ECDC status which
226 is not mediated ;
- 227 - the natural indirect effect (NIE), defined as the effect of ECDC positive versus ECDC
228 negative on the probability of persistent symptoms when the serological status is
229 positive. The NIE includes an interaction effect of serology with ECDC status which is
230 mediated ;

- 231 - The total effect (TE) defined as the overall effect of serology on persistent symptoms,
232 which is the product of NDE and NIE, when they are calculated as adjusted OR
233 ($aOR_{TE}=aOR_{NDE} \times aOR_{NIE}$).
- 234 - The proportion of the total effect that was mediated using the formula on the risk
235 difference scale, $(100 \times aOR_{NDE} \times (aOR_{NIE} - 1) / (aOR_{TE} - 1))$
- 236 - The proportion of the effect due to interaction (see Figure 1).

237 For each persistent symptom, the estimation of direct and indirect effects was based on two
238 logistic models. A first logistic model predicted the probability of persistent symptom according
239 to serological status, ECDC status, an interaction term between these two covariates, and the
240 confounding factors. The second model predicted the probability of ECDC status according to
241 serological status and the confounding factors. Direct and indirect aOR estimates were deduced
242 from these two logistic models (formulas can be found in ref 16). All the mediation models
243 were adjusted on age, sex, and comorbidities. Confidence intervals for estimates were
244 calculated using bootstrap with 10 000 replicates.

245 Statistical analyses were performed using R software 4.0.5. Mediation analysis was performed
246 using the CAUSALMED procedure in SAS 9.4.

247

248 *Role of the funding source*

249 The sponsor of the study had no role in study design, data collection, data analysis, data
250 interpretation, or writing of the report. The corresponding author had full access to all data in
251 the study and had final responsibility for the decision to submit for publication.

252

253 **Results**

254 Overall, 29,438 of 35,852 (82%) eligible participants completed the follow-up questionnaire.
255 After excluding those whose serology was indeterminate or who reported a diagnosis of

256 COVID-19 after serology, 25,910 (72%) participants were classified into one of the four groups
257 of interest (see supplementary appendix p 1).

258 Participant characteristics according to the presence of at least one persistent symptom reported
259 through the follow-up questionnaire are summarized in Table 1. All variables were statistically
260 different between the groups declaring no persistent symptom and the group declaring at least
261 one persistent symptom. However, the most important difference was in the number of acute
262 symptoms presented during the acute phase of the epidemic (70.1% and 50.2% declared no
263 acute symptoms in the group having no persistent symptoms and in the group having at least
264 one persistent symptom, respectively). The median time between completion of the first
265 questionnaire and the third follow-up questionnaire was 242 days [IQR:238-251]. Overall, 4028
266 (15.5%) participants experienced COVID-19-like illness during the first wave and 1022 (3.9%)
267 participants had a positive SARS-CoV-2 serology. Overall, 6643 (25.6%) reported having at
268 least one persistent symptom in the follow-up questionnaire (in those participants, the median
269 number (IQR) of persistent symptoms was 1 (1-2)).

270 The association between SARS-CoV-2 serological status and each persistent symptom is
271 presented in Table 2. At least one persistent symptom was present in 318 (31.1%) and 5926
272 (24.7%) participants in the Sero+ and the Sero- groups, respectively ($P < 0.0001$).

273 Dysgeusia/anosmia, dyspnea, palpitations, asthenia, and cognitive complaints were positively
274 associated with a positive serology in multivariable adjusted models, while abdominal pain or
275 skin disorders were negatively associated. The association was strong for persistent
276 dysgeusia/anosmia (with an aOR of 8.98 (95%CI 6.03 - 13.28)), while it was weak for other
277 symptoms with aOR ranging from 1.82 (95%CI 1.20 - 2.68) for dyspnea to 0.42 (95%CI 0.21
278 - 0.74) for abdominal pain.

279 At least one persistent symptom was reported in 213/494 (43.1%) ECDC+/Sero+ participants,
280 1334/3534 (37.7%) ECDC+/Sero- participants, 105/528 (19.9%) ECDC-/Sero+ participants
281 and 4961/21,354 (23.2%), ECDC-/Sero- participants ($p < 0.0001$).

282 More than 80% of the symptoms reported during the first wave of the pandemic disappeared
283 before the follow-up questionnaire, regardless of the serological result, with the exception of
284 dysgeusia/anosmia and asthenia in the seropositive group (59/246 (24%) and 75/354 (20.3%),
285 respectively -Supplementary Appendix p 5). Dysgeusia/anosmia, asthenia and persistent
286 thoracic pain were still more frequent at the follow-up in seropositive participants than in
287 seronegative participants who experienced these symptoms during the first wave.

288 Table 3 presents the association between serological status and each persistent symptom in
289 participants who reported a COVID-19-like illness during the first wave of the pandemic
290 (ECDC+). Dysgeusia/anosmia, dyspnea, and asthenia were positively associated with a positive
291 serology while abdominal pain, sensory complaints, and sleep disorders were negatively
292 associated. The association appeared strong only with dysgeusia/anosmia (aOR= 6.83 (95%CI
293 4.47 - 10.42)).

294 Other comparisons between groups defined according to a COVID-19-like illness during the
295 first wave and serological status are presented in supplementary appendix (p 6). Of note, there
296 was no difference in any of the persistent symptoms between ECDC-/Sero+ and ECDC-/Sero-
297 participants except for palpitations which appear to be more frequent in seropositive than in
298 seronegative participants (aOR: 2.67 (95%CI 1.15, 6.22), $p = 0.02$).

299 The mediation analysis is presented on table 4 and was performed for dysgeusia/anosmia,
300 cough, dyspnea, thoracic pain, palpitations, headache, asthenia, and cognitive complaints.

301 The aOR for NDE were in the range of those found in previous analyses with an aOR of 6.87
302 (95%CI 4.72-9.70) for dysgeusia/anosmia (aOR) and lower aORs > 1 for dyspnea and asthenia.

303 All aOR for NIE were > 1 , meaning that the experience of ECDC symptoms was associated

304 with persistent symptoms in those with positive serology. The effect of positive serology on
305 each symptom was mainly mediated by ECDC symptoms (proportion mediated range 50%-
306 107%) with a high proportion of the effect due to a positive interaction between serology and
307 ECDC symptoms in all symptoms except cough.

308

309 **Discussion**

310 This population-based study quantifies the prevalence of persistent symptoms and examine
311 symptoms according to ECDC COVID-19-like illness criteria and SARS-CoV-2 serological
312 status. The results confirm the high prevalence of persistent symptoms in this population,
313 especially in participants who experienced ECDC symptoms during the first pandemic wave.
314 The mediation analysis showed that persistent symptoms associated with a seropositive status
315 are mainly driven by the acute symptoms during the first pandemic wave.

316 Some of these persistent symptoms were more frequent in participants with ECDC+/Sero+ than
317 in the other groups, independently of the number of acute symptoms. It confirmed the
318 importance of dysgeusia/anosmia, dyspnea, and asthenia in persistent symptoms.^{12,18,19} The risk
319 of having the other symptoms that have been suggested as related to “long covid “ were similar
320 or higher in ECDC+/Sero- than in ECDC+/Sero+. This suggest that these persistent symptoms
321 are common and are often not specific to the causative agent. During the first wave of the
322 epidemic in France in 2020, viruses other than SARS-CoV-2 were circulating.²⁰ Furthermore,
323 the lack of specificity of most symptoms or their combinations to the post-covid condition
324 emphasizes the importance of studying post-infectious states. Chronic post-viral fatigue (CMV,
325 EBV, HIV) is a known but poorly explained phenomenon related to a persistent inflammatory
326 state, a latent infection, a particular psychological context, or functional disorders. It has been
327 suggested that persistent symptoms are driven by the initial intensity of the disease as well as
328 other multidimensional and indirect factors.²¹ This is in line with another study based on the

329 CONSTANCES cohort which shows that, except for dysgeusia/anosmia, a self-reported
330 infection of SARS-CoV-2 was associated with persistent physical symptoms regardless of the
331 result of serological tests.²² Our results are complementary to these, by classifying individuals
332 according to their symptoms in the acute phase rather than a classification according to the
333 diagnosis, which may be affected by the beliefs of the patient and/or the doctor. Here we
334 demonstrated that some symptoms are more associated with SARS-COV-2 infection, especially
335 in case of symptomatic acute symptoms. However, it is interesting to note that the individuals
336 with asymptomatic SARS-CoV-2 infection were like ECDC-/Sero-, except for having a higher
337 risk of palpitations. These results should be considered with caution, although cardiac
338 consequences in asymptomatic or mild infections have been suggested.²³

339 Unlike in other results in the literature evaluating outpatients with covid-19, the median number
340 of persistent symptoms was low. This could be due to the population-based design of the present
341 study. Most of the studies published in the literature were performed in specific populations
342 (e.g. population with access to a PCR test during the first wave, healthcare workers) or in
343 individuals who used the healthcare system for symptoms. ^{12,19,24,25,26} This suggests that the
344 intensity and the number of acute symptoms, which are associated with persistent symptoms,
345 might have been higher in these previous studies than in the general population.^{11,12} The follow-
346 up in the present survey was also longer. Thus, certain symptoms might have disappeared over
347 time.

348 Persistent symptoms are known to be associated with the acute disease.¹² Here, we take the
349 analysis a step further by quantifying the direct impact of SARS-CoV-2 infection on symptom
350 persistence and its indirect effect, mediated by the symptoms present at the initial phase of
351 infection. Interestingly, it appears that the effect is mainly indirect for all symptoms, even for
352 those that are not included in the ECDC's definition. This strong mediation effect underlines
353 the importance of symptoms developed during the initial episode on the risk of presenting

354 persistent symptoms. In addition, the association of persistent symptoms with serology was
355 higher in case of initial ECDC symptoms except for cough. Thus, it can be speculated that all
356 interventions reducing the intensity and/or the number of symptoms of the acute phase of the
357 disease might have an impact on the incidence of post-covid persistent complaints. If this is
358 the case, the individual benefit of vaccination could be enhanced even in people at low risk of
359 severe COVID-19, as already suggested.²⁷

360 The strength of this study relies in its design, which was based on a large sample from the
361 general population followed prospectively, thus allowing comparison of different groups of
362 individuals. SARS-CoV-2 infection was evaluated by serological tests in all individuals. Data
363 were not collected through the healthcare system, making the reported symptoms more
364 representative of those perceived by the general population than in previous studies using
365 healthcare databases.^{18,26}

366 This work has certain limitations. First, symptoms were self-declared and were not evaluated
367 with specific scales. Also the declarations may have differed depending on the recent medical
368 history, especially during the pandemic where participants were more apt to believe that they
369 had had COVID-19.²² In addition, we could not separate persistent symptoms related to an
370 infection (COVID-19 or other) from those related to otherwise poor health or a change in access
371 to health care. Moreover, the possibility of serology misclassifications cannot be excluded.^{9,22}

372 However, the fact that difference in the risk of anosmia is high between ECDC+/Sero+ and
373 ECDC+/Sero- suggest that the prevalence for SARS-COV-2 infection is likely to be highest in
374 participants with both positive serology results and ECDC symptoms declared during the first
375 phase of the pandemic. Although this is one of the largest surveys on persistent symptoms after
376 Covid-19 first pandemic wave, the number of individuals with this condition remained low in
377 relation to the marked heterogeneity of the number and types of symptoms. Thus, we might
378 have been unable to detect associations between the less frequent symptoms and COVID-19.

379 We compared COVID-19 (ECDC+/Sero+) consequences to those of COVID-Like illness
380 (ECDC+/Sero-). We assumed that this latter group was heterogenous. The consequences of
381 COVID-19 need to be compared with other upper respiratory infection. A recent survey
382 compared the consequences of COVID-19 and influenza in hospitalized patients.²⁶ Although it
383 showed that the burden of COVID-19 was greater, the comparison was performed between two
384 different periods, and did not take into account the possible influence of the pandemic on other
385 factors that could affect health and the health system. Finally, some symptoms following acute
386 infection may not have been reported by participants - particularly if they appeared late after
387 the initial two questionnaires were collected. In any case, this will only reinforce the fact that
388 most of the effect of infection on persistent symptoms is mediated by the symptoms experienced
389 in the acute phase.

390

391 In conclusion, there is an increased risk of persistent anosmia/dysgeusia, dyspnea, and asthenia
392 in individuals with a history of COVID-19. Persistent symptoms are mainly driven by the acute
393 phase of the disease. Further studies are needed to determine the origin of these persistent
394 symptoms which could be associated with various pathophysiological causes that could also
395 interact, from an inappropriate inflammatory response to a persistent functional disorder.

396

397 **Authors' contributions**

398 OR and FC take responsibility for all aspects of the reliability and freedom from bias of the
399 data presented and their discussed interpretation. OR and EW accessed and verified all the data
400 . OR designed the study; EW, MG, FC, MT, GS, and MZ acquired the data; OR performed
401 statistical analysis. All authors contributed to the interpretation of data and to the design of the
402 questionnaires. OR, EW, CL and FC drafted the article. All authors have read and approved the
403 final manuscript.

404 **Declaration of interests**

405 OR reports personal fees and non-financial support from ViiV healthcare, Gilead, MSD. CL
406 reports personal fees and non-financial support from Boehringer Ingelheim, Janssen-Cilag,
407 Lundbeck and Otsuka Pharmaceutical, outside the submitted work. The other authors declare
408 that they have no competing interest.

409 **Acknowledgements**

410 We thank the SAPRIS-SERO study group for its involvement in this work (see the
411 supplementary appendix p 8 for details)

412

413 **Funding**

414 *The Constances cohort* benefits from a grant from the French National Research Agency [Grant
415 Number ANR-11-INBS-0002]: It is supported by the Caisse Nationale d'Assurance Maladie
416 (CNAM), the French Ministry of Health, the Ministry of Research, the Institut national de la
417 santé et de la recherche médicale. CONSTANCES and is also partly funded by MSD,
418 AstraZeneca, Lundbeck and L'Oreal.

419 The SAPRIS-SERO study was supported by Agence Nationale de la Recherche, #ANR-10-
420 COHO-06, Santé Publique France : N°20DMIA014-0, Fondation pour la Recherche Médicale
421 (#20RR052-00), Inserm (Institut National de la Santé et de la Recherche Médicale), #C20-26.

422 **Data availability statement**

423 Data from this study are protected by health data regulations from the French National
424 Commission on Informatics and Liberty (Commission Nationale de l'Informatique et des
425 Libertés, CNIL). Data can be made available upon reasonable request to the steering committee
426 of the CONSTANCES cohort study. While French law forbids providing free access to raw
427 data; access could be provided by the steering committee after legal verification of the use of
428 the data. The informed consent form are available in French on the CONSTANCES website.

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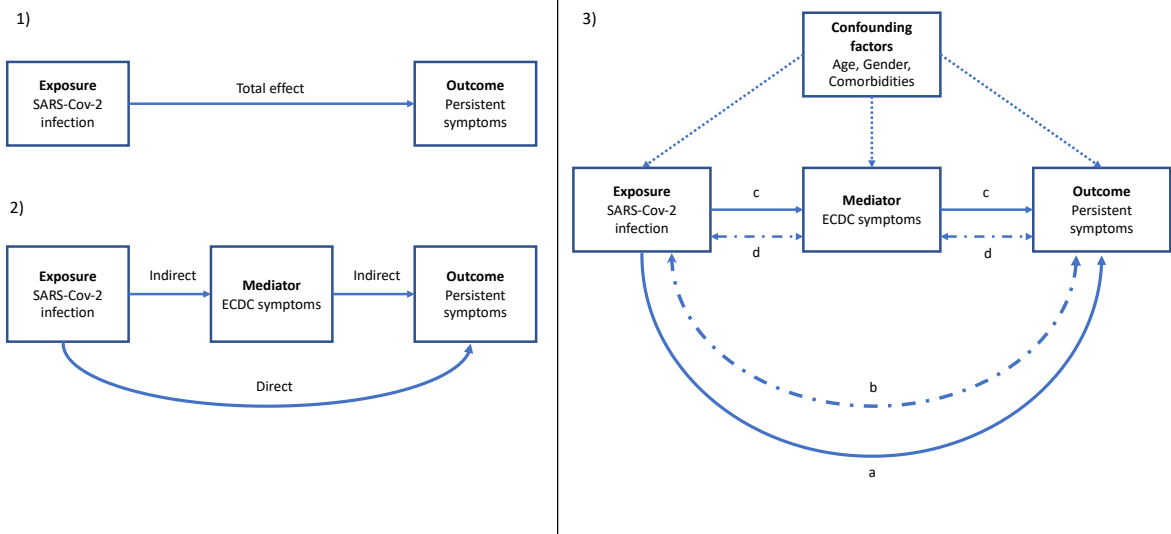
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Figure 1: Concept and design of the mediation analysis for the association of SARS-COV-2 infection with persistent symptoms. 1) Total effect model 2) Basic mediation model 3) Full mediation model used in the study.

The mediation analysis allows us to evaluate the part of the direct and indirect effect (2) in the total effect (1). The full model (3) took also into account the interaction between the exposure and the mediator (b and d) and was adjusted on confounding factors. We calculated the total effect ($TE = a + b + c + d$), the direct effect of the exposure ($a + b$: natural direct effect, NDE) and the indirect effect mediated by the ECDC symptoms ($c + d$: natural indirect effect, NIE). The proportion mediated is represented by NIE/TE . The proportion due to interaction is NDE/TE .

	All participants N=25910	At least one persistent symptom lasting more than 2 months - 12/2020-02/2021		p
		No N=19267	Yes N=6643	
Mean age (SD)	49.5 (12.9)	48.9 (13.0)	51.1 (12.2)	<0.0001
Sex (female)	13299 (51.3%)	9509 (49.4%)	3790 (57.1%)	<0.0001
Educational level				<0.0001
Other	294 (1.13%)	222 (1.2%)	72 (1.1%)	
Under high school diploma	7027 (27.1%)	5109 (26.5%)	1918 (28.9%)	
Under graduate degree	9948 (38.4%)	7326 (38.0%)	2622 (39.5%)	
Post graduate degree	8641 (33.4%)	6610 (34.3%)	2031 (30.6%)	
At least one Comorbidity**	6989 (27.2%)	4541 (23.7%)	2448 (37.3%)	<0.0001
Groups				<0.0001
ECDC-/Sero-	21354 (82.4%)	16393 (85.1%)	4961 (74.7%)	
ECDC-/Sero+	528 (2.0%)	423 (2.2%)	105 (1.6%)	
ECDC+/Sero-	3534 (13.6%)	2170 (11.3%)	1364 (20.5%)	
ECDC+/Sero+	494 (1.9%)	281 (1.5%)	213 (3.2%)	
Number of acute symptoms***				<0.0001
0	16054 (65.0%)	12919 (70.1%)	3135 (50.2%)	
1	5085 (20.6%)	3484 (18.9%)	1601 (25.7%)	
2	1926 (7.8%)	1206 (6.5%)	720 (11.5%)	
3	753 (3.1%)	427 (2.3%)	326 (5.2%)	
4 or more	863 (3.50%)	405 (2.2%)	458 (7.3%)	

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508 **Table 1: Main characteristics of participants, serological status (Sero) and experience of COVID-19-like illness during the**
509 **first wave (ECDC) according to the presentation of at least one persistent symptom in the follow-up questionnaire.**

510 Groups were compared using t-test for continuous variables and Chi-square test for qualitative variables. **Missing value:
511 n=227 (0.9%). *** missing value n=1229 (4.7%).

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	Sero- N=24888	Sero+ N=1022	OR [95% CI]	p	aOR* [95% CI]	p
Number of persistent symptoms (med [IQR])	0 [0-2]	0 [0-1]	-	-	-	-
At least one persistent symptom	5926 (24.7%)	318 (31.1%)	1.33 [1.16-1.52]	<0.0001	1.04 [0.90-1.21]	0.57
Dysgeusia/anosmia	101 (0.4%)	65 (6.4%)	16.67 [12.08-22.85]	<0.0001	8.98 [6.03-13.28]	<0.0001
Cardiothoracic complaints						
Cough	178 (0.7%)	14 (1.4%)	1.93 [1.06-3.21]	0.019	0.90 [0.46-1.64]	0.76
Dyspnea	235 (0.9%)	39 (3.8%)	4.16 [2.91-5.8]	<0.0001	1.82 [1.20-2.68]	0.004
Thoracic pain	172 (0.7%)	21 (2.1%)	3.01 [1.85-4.65]	<0.0001	1.27 [0.73-2.10]	0.38
Palpitations	195 (0.8%)	22 (2.2%)	2.79 [1.74-4.25]	<0.0001	1.40 [0.82-2.30]	0.20
Pains						
Backpain	1531 (6.2%)	63 (6.2%)	1 [0.77-1.29]	0.99	0.79 [0.59-1.04]	0.11
Arthralgia	1790 (7.2%)	65 (6.4%)	0.88 [0.67-1.12]	0.31	0.90 [0.67-1.18]	0.45
Myalgia	834 (3.4%)	40 (3.9%)	1.17 [0.84-1.6]	0.33	0.91 [0.62-1.30]	0.61
Headache	356 (1.4%)	28 (2.7%)	1.94 [1.29-2.81]	0.0008	1.01 [0.63-1.54]	0.97
Digestive complaints						
Nausea	56 (0.2%)	3 (0.3%)	1.31 [0.32-3.54]	0.65	0.68 [0.16-1.95]	0.53
Diarrhoea	155 (0.6%)	8 (0.8%)	1.26 [0.57-2.4]	0.53	0.61 [0.26-1.27]	0.22
Constipation	374 (1.5%)	16 (1.6%)	1.04 [0.6-1.67]	0.87	0.78 [0.42-1.33]	0.39
Abdominal pain	390 (1.6%)	12 (1.2%)	0.75 [0.4-1.27]	0.32	0.42 [0.21-0.74]	0.006
Other complaints						
Asthenia	694 (2.8%)	86 (8.4%)	3.2 [2.52-4.02]	<0.0001	1.43 [1.08-1.86]	0.01
Cognitive complaints	590 (2.4%)	57 (5.6%)	2.43 [1.82-3.19]	<0.0001	1.27 [0.91-1.74]	0.15
Fever	23 (0.1%)	2 (0.2%)	2.12 [0.34-7.17]	0.31	0.64 [0.09-2.72]	0.60
Cranial nerves abnormalities	16 (0.1%)	0 (0.0%)	-	-	-	-
Auditive disorders	455 (1.8%)	12 (1.2%)	0.64 [0.34-1.08]	0.13	0.66 [0.33-1.18]	0.20
Sensory disorders	491 (2.0%)	14 (1.4%)	0.69 [0.39-1.13]	0.17	0.62 [0.33-1.05]	0.10
Talk abnormalities	54 (0.2%)	4 (0.4%)	1.81 [0.55-4.42]	0.25	0.80 [0.18-2.48]	0.73
Dizziness	160 (0.6%)	13 (1.3%)	1.99 [1.07-3.38]	0.017	1.40 [0.69-2.60]	0.31
Vertigo	13 (0.1%)	0 (0.0%)	-	-	-	-
Sleep disorders	2589 (10.4%)	103 (10.1%)	0.97 [0.78-1.18]	0.74	0.83 [0.66-1.04]	0.11
Skin disorders	607 (2.4%)	17 (1.7%)	0.68 [0.4-1.06]	0.12	0.50 [0.28-0.82]	0.01

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514 **Table 2: Persistent symptoms lasting more than 2 months according to serological results.**515 *aOR were adjusted for sex, age, educational level, comorbidities lasting more than 6 months and the number of symptoms
516 declared during the first wave of the pandemic. OR odds-ratio; aOR: Adjusted odds-ratio; CI: confidence interval.

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	ECDC+/Sero-	ECDC+/Sero+	OR		aOR*	
	N=3534	N=494	[95% CI]	p	[95% CI]	p
At least one persistent symptom	1364 (38.6%)	213 (43.1%)	1.21 [1-1.46]	0.05	1.14 [0.91-1.42]	0.25
Dysgeusia/anosmia	65 (1.8%)	64 (13.0%)	7.94 [5.54-11.39]	<0.0001	6.83 [4.47-10.42]	<0.0001
Cardiothoracic complaints						
Cough	118 (3.3%)	13 (2.63%)	0.78 [0.42-1.35]	0.41	0.70 [0.33-1.31]	0.29
Dyspnea	134 (3.8%)	35 (7.1%)	1.93 [1.32-2.81]	0.0008	1.69 [1.07-2.60]	0.02
Thoracic pain	85 (2.4%)	19 (3.9%)	1.62 [0.95-2.63]	0.06	1.15 [0.61-2.06]	0.65
Palpitations	74 (2.1%)	16 (3.2%)	1.57 [0.87-2.64]	0.11	1.23 [0.63-2.26]	0.53
Pains						
Backpain	356 (10.1%)	38 (7.7%)	0.74 [0.52-1.04]	0.10	0.78 [0.52-1.15]	0.22
Arthralgia	364 (10.3%)	48 (9.7%)	0.94 [0.68-1.27]	0.69	1.02 [0.69-1.46]	0.92
Myalgia	206 (5.8%)	28 (5.7%)	0.97 [0.63-1.43]	0.89	0.82 [0.49-1.31]	0.42
Headache	119 (3.37%)	23 (4.66%)	1.40 [0.87-2.17]	0.15	1.11 [0.64-1.85]	0.69
Digestive complaints						
Nausea	17 (0.5%)	0 (0.0%)	-	-	-	-
Diarrhoea	51 (1.4%)	6 (1.2%)	0.84 [0.32-1.82]	0.68	0.61 [0.21-1.48]	0.31
Constipation	75 (2.1%)	7 (1.4%)	0.66 [0.28-1.35]	0.30	0.38 [0.11-0.99]	0.08
Abdominal pain	126 (3.6%)	11 (2.2%)	0.62 [0.31-1.10]	0.13	0.51 [0.24-0.96]	0.05
Other complaints						
Asthenia	260 (7.4%)	70 (14.2%)	2.08 [1.56-2.74]	<0.0001	1.48 [1.05-2.07]	0.02
Cognitive complaints	190 (5.4%)	45 (9.1%)	1.76 [1.24-2.45]	0.0011	1.47 [0.98-2.16]	0.06
Fever	17 (0.5%)	2 (0.4%)	0.84 [0.13-2.94]	0.82	0.68 [0.10-2.84]	0.64
Cranial nerves abnormalities	9 (0.3%)	0 (0.0%)	-	-	-	-
Sensory disorders	126 (3.6%)	7 (1.4%)	0.39 [0.16-0.78]	0.02	0.40 [0.16-0.85]	0.03
Talk abnormalities	22 (0.6%)	4 (0.8%)	1.30 [0.38-3.42]	0.63	1.00 [0.21-3.41]	>0.99
Auditive disorders	107 (3.0%)	9 (1.8%)	0.59 [0.28-1.12]	0.14	0.62 [0.25-1.32]	0.26
Dizziness	45 (1.3%)	10 (2.0%)	1.60 [0.76-3.07]	0.18	1.54 [0.65-3.35]	0.30
Vertigo	7 (0.2%)	0 (0.0%)	-	-	-	-
Sleep disorders	556 (15.7%)	56 (11.3%)	0.68 [0.51-0.91]	0.01	0.69 [0.49-0.95]	0.02
Skin disorders	136 (3.9%)	13 (2.6%)	0.68 [0.36-1.16]	0.18	0.61 [0.29-1.15]	0.15

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Table 3: Persistent symptoms lasting more than 2 months according to the presence of ECDC symptoms during the first wave of the pandemic and to the serological results.

*aOR were adjusted for sex, age, educational level, comorbidities, and the number of symptoms at the acute phase. OR odds-ratio; aOR: Adjusted odds-ratio; CI: confidence interval.

Symptoms	Total effect aOR* [95% CI]	NDE aOR* [95% CI]	NIE aOR* [95% CI]	Proportion mediated % [95% CI]	Proportion due to the interaction % [95% CI]
At least one persistent symptom	1.57 [1.34-1.83]	1.05 [0.88-1.23]	1.50 [1.34-1.69]	92 [68-131]	55 [20-85]
Dysgeusia/anosmia	21.24 [14.81-29.28]	6.87 [4.72-9.70]	3.09 [2.60-3.47]	71 [65-75]	92 [83-97]
Cough	2.22 [1.14-3.69]	0.91 [0.40-1.82]	2.45 [1.46-3.46]	107 [45-310]	-12 [-440-61]
Dyspnea	4.16 [2.83-5.83]	1.83 [2.65-2.80]	2.28 [1.70-3.02]	74 [54-93]	54 [16-77]
Palpitations	3.15 [1.82-4.85]	1.37 [0.69-2.41]	2.30 [1.50-3.38]	83 [51-127]	58 [-10-90]
Thoracic pain	2.89 [1.72-4.41]	1.95 [0.98-3.35]	1.48 [1.05-2.30]	50 [6-101]	25 [-59-80]
Headache	1.90 [1.20-2.72]	1.03 [0.57-1.67]	1.84 [1.31-2.74]	96 [48-239]	62 [-36-134]
Asthenia	3.05 [2.36-3.91]	1.62 [1.19-2.19]	1.88 [1.53-2.32]	70 [51-88]	58 [29-80]
Cognitive complaints	2.42 [1.76-3.22]	1.40 [0.94-1.99]	1.73 [1.36-2.25]	72 [45-105]	57 [14-92]

526 **Table 4: Mediation analysis. Estimates of direct and indirect effect for persistent symptoms associated with the**
527 **serological status.**

528 ECDC status is used as the mediator variable. *Estimates are adjusted for age, gender and comorbidities and interaction are
529 taken into account (reference interaction and mediated interaction). NDE: natural direct effect; NIE: natural indirect effect;
530 aOR: Adjusted odds-ratio; CI: confidence interval.
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