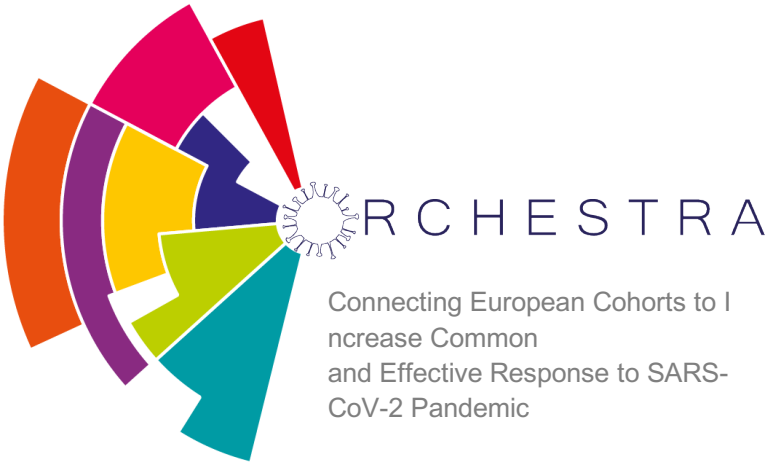

DELIVERABLE

WP2_D2.5

Final report of 6-month follow up by clinical, immunological and virological features

UNIVR

ORCHESTRA has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101016167

Project Classification

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Executive summary

Content*:* This document describes the methods of analysis and results of 2730 patients included in the ORCHESTRA WP2 prospective cohorts study who were followed for six months after the first SARS-CoV-2 positive test. The overall proportion of persisting symptoms six months after SARS-CoV-2 infection was 58%; 36% of patients reported two or more symptoms, and 20% experienced three or more symptoms. Overall, women had an increased probability of reporting symptoms at 6 months post-infection compared to men, especially in the 41-60-year-old group. Regarding the comorbidities, chronic respiratory disease and underlying medical conditions requiring chronic treatment with corticosteroids were associated with post COVID-19 sequelae. Notably, no association was observed between cardiovascular diseases and the report of symptoms at 6-month follow-up. All patients reporting neurological symptoms such as anomia and loss of memory during the acute phase were experiencing post COVID-19 sequelae at the 6-month follow-up visit. Cardiac events during the hospitalization and ICU admission were also associated with post COVID-19 sequelae. Using univariate analysis, number of symptoms in the acute phase, being a woman, complaining of dyspnea at diagnosis and ICU admission were independently associated with persistence of symptoms at month 6. We did not observe a clear association between older age and occurrence of post COVID-19 sequelae, while the probability of persistence of symptoms is higher in women compared to man. The severity of acute infection seems to have a negligible impact on the occurrence of long-lasting symptoms. A better understanding of long-lasting COVID-19 sequelae is needed to better estimate the burden of this post-acute manifestation and its determinants.

Dissemination level: *This document is still confidential; results are yet to be published.*

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Core content

Abbreviations

CINECA - Interuniversity Consortium
CINES - National IT Center for Higher Education confidence interval Cis
COVID-19 - COronaVIrus Disease 19
CRF - Clinical research form
ICU – Intensive Care Unit
INSERM - Institut National de la Santé et de la Recherche Médicale
RT-PCR - reverse transcriptase–polymerase chain reaction
SAS-Andalusian Health Service
UBA - Universidad de Buenos Aires
UMCG - University Medical Center Groningen
UNIBO - University of Bologna
UNIVR– University of Verona
WHO – World Health Organization

Introduction

The ongoing COVID-19 pandemic has created a global public health emergency that is challenging societies, health care systems and national economies worldwide [1]. Since the beginning of the pandemic, our knowledge of transmission dynamics [2], clinical presentation [3], long-term sequelae [4], and risk factors for disease progression [5-7] has been increasing steadily. COVID-19 can result in prolonged illness, even in young adults and children without underlying chronic medical conditions. In a telephone survey conducted by the Centers for Disease Control and Prevention among a random sample of 292 adults (≥18 years) who had a positive outpatient test result for SARS-CoV-2 by RT-PCR, 35% of 274 symptomatic respondents reported not having returned to their usual state of health two weeks or more later [9]. The burden of COVID-19 long-term sequelae and the exact underlying psychopathology mechanisms remain unknown.

In this report we present the results of the analysis of the incidence of the long-term sequelae in hospitalized and non-hospitalized individuals with previous SARS-CoV-2 infection, along with demographic, clinical, and determinants of persistence of symptoms after 6-month post-acute infection.

The immunological and virological features are described in details in Deliverables 6.7 and 6.9, respectively.

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Methods

Data collection

The dataset consists of the prospective cohorts involved in the WP2: UBA, UNIBO, UNIVR, SAS, INSERM (French COVID) and UMCG (COVID-HOME). The data collection for the first four cohorts was carried out using a dedicated eCRF (RedCap) hosted in CINECA. French COVID and COVID-HOME cohorts started before the ORCHESTRA project was financed, hence data from these two cohorts went through a post-data collection harmonization process under the supervision of Charité and transformation conducted by CINES in order to be included in the analysis. Data from the COVID HOME study including also household with specific timelines are separately presented.

French COVID (enrolment start: July 2020), SAS (enrolment start: May 2021), UBA (enrolment start: July 2021), UNIBO (enrolment start: June 2021) and UNIVR (enrolment start: April 2021) cohorts include hospitalized and non-hospitalized patients aged >14 years old with a laboratory confirmed SARS-CoV-2 infection. Patients are followed up at 3, 6, 12, and 18 months post-infection at an outpatient clinic setting. The enrollment can take place at any of the above mentioned time-points. Each follow up visit combines clinical and laboratory assessment, including biochemical parameters, serology and cellular immunity.

The COVID HOME study is a prospective longitudinal observational study of non-hospitalized COVID-19 patients that began in March 2020 amongst residents of the four Northern Provinces of the Netherlands. Participants of all ages were eligible for enrollment if their symptom onset <5 days, had a positive diagnostic SARS-CoV-2 RT-PCR performed <48h previously and signed a written informed consent. Household members of these positive individuals were also included in the study. Positive patients are followed weekly at home during their acute disease for at least 3 weeks post-infection, to obtain clinical data, blood samples for laboratory parameters and serological determination; and nasopharyngeal swabs. They are then followed at 3, 6, 12- and 18-months post-infection.

The features collected in WP2 at baseline include: date of symptom onset, date of positive diagnostic SARS-CoV-2 test, demographic characteristics, comorbidities, clinical presentation, treatment including oxygen supplementation, and important outcomes such as hospitalization, admission to ICU and death.

Six months post-infection features include: presence of symptoms, occurrence of new medical events, vital signs and physical examination, laboratory parameters and vaccination status (see attachment *CRF WP2 long-term sequelae,* for details).

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Data quality assessment

The established Orchestra infrastructure ensured data quality. The data are collected with the common eCRF in REDCap, harmonized according to the SNOMED-CT system, and in line with the pre-existing REDCap used by INSERM. In addition, CINECA run quality checks based on the semantic value of the variables, and reported to the cohorts to be corrected. Finally, mistakes found at the analysis step were corrected systematically by communicating with the corresponding cohorts. This analysis includes patients who completed the 6-month follow-up visit by 30th September 2021.

Data analysis

Patients reporting at least one symptom at the 6-month follow-up assessment, either persisting since the acute infection or fluctuating/relapsing, were considered as having a COVID-19 long-term sequelae. This definition of COVID-19 long-term sequelae is consistent with the recently released WHO case definition of post COVID-19 condition [10]: post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time. For the purpose of the present study, we consider any symptom listed in attachment *CRF WP2 long-term sequelae,* page 18.

The presence of any persisting, relapsing or fluctuating symptom were evaluated at 6 months according to: severity of the COVID-19 (WHO-scale, whenever available on baseline assessment), hospitalization (hospitalized vs. non-hospitalized), vaccination status, viral strains, demographic subgroups (age, sex, ethnic groups, healthcare workers, social features, living conditions), and socio-economic groups (education level, employment status). Missing data from patients were not imputed, and therefore analysis was conducted using the available data only. We report percentage of patients with at least one symptom at the 6-month follow-up assessment and chi-square values, odd ratios and corresponding p-values for subgroups. In addition, the odds ratios (ORs) and 95% confidence intervals are reported. The confidence levels were determined using standard approaches, e.g., based on the assumption of asymptotic normality. Analysis was performed in the R programming language. For the COVID HOME cohort, analysis was performed with STATA.

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Results

Results from the cohorts enrolling both hospitalized and non-hospitalized patients (French COVID (N=2265), SAS (N=15), UBA (N=7), UNIBO (N=35) and UNIVR (N=264)) and from the COVID HOME study are displayed separately according to the different purpose and design of the studies.

WP2 hospitalized and non-hospitalized prospective cohort

The WP2 prospective cohort consists of cohorts from five institutions: INSERM French COVID, SAS, UBA, UNIBO and UNIVR, accounting for a total number of 2,586 patients enrolled. Six patients were removed due to the semantic-quality check. The data included patients of all ages (**Figure 1 a**). Overall, a total of 1,281 variables were analysed. The overall proportion of persisting symptoms six months after SARS-CoV-2 infection was 58%. This rate does not differ across the cohorts, with a minor exception of UBA, which included only seven patients. Overall, 36% of patients reported two or more symptoms and 20% presented three or more symptoms at the 6-month follow-up. The number of post COVID-19 symptoms after 6-month follow-up also had a similar distribution across the cohorts (**Figure 1 b**). The analysis of the co-occurrence of symptoms during the acute phase and the 6 month follow up is shown in **Figure 1 c**. The analysis was conducted both overall and divided per single cohort. Since no major differences were found between the cohorts, the overall results are reported here. **Table 1** reports multivariate analysis of age and gender, and number of symptoms during the acute phase. **Table 2** shows univariate analysis of the association between symptoms reported during the acute phase of COVID-19, demographic features, comorbidities, medical events during hospitalization and the occurrence of post COVID-19 sequelae, defined as presence of at least one symptom at 6 months post-infection.

Demographic features and underlying medical conditions

A multivariate analysis of age and gender has been performed (**Table 1)**. The presence of symptoms at 6-month follow-up assessment had a similar distribution across all ages and was not correlated with older age (**Figure 1 a**). Overall, women had an increased probability of reporting symptoms at 6 months post-infection compared to men (OR 1.4; 95%CI 1.17-1.66; p<0.001), especially in the 41-60-year-old group (OR 1.92; 95%CI 1.41-2.63; p<0.001).
Regarding comorbidities, chronic respiratory disease and underlying medical conditions requiring chronic treatment with corticosteroids were associated with post COVID-19 sequelae. Notably, no association was observed between cardiovascular diseases and the report of symptoms at 6-month follow-up.

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Clinical presentation during acute infection and at 6 month follow up

Information on skin rash, arthralgia, wheezing, sore throat, myalgia, vomiting, altered consciousness/confusion, chest pain and/or chest tightness, headache, rhinorrhea, ageusia or dysgeusia, abdominal pain, anosmia, dyspnea, cough, fatigue and/or malaise were available for more than 70% of the cohort. In more than 60% of the patients reporting these symptoms, long-term sequelae at 6 months post-infection were detected. Cough, dyspnea and fatigue were the most common symptoms reported during the acute phase, and were associated with long term sequelae after 6 months ($p=0.02$, $p<0.001$ and $p=0.03$, respectively). Reporting 6 to 10 or 11 to 15 symptoms during the acute infection also showed an association with the occurrence of post COVID-19 sequelae at month 6 (OR 1,24; 95% CI 1.04-1,48; $p=0,02$ and OR 1,99; 95% CI 1.27-3,21; $p<0.001$, respectively). Cardiac events during the hospitalization and ICU admission were also associated with post COVID-19 sequelae ($p=0.01$ and $p<0.001$, respectively).

The analysis of the co-occurrence (**Figure 1 c**) of symptoms during the acute phase and the 6 -month follow-up shows no direct correlation. Only ~30% of patients who experienced cough in the acute phase reported this symptom also at 6 months assessment, while a high proportion of patients reported sore throat, joint pain, loss of taste and loss of smell both during the acute infection and the 6-month follow up.

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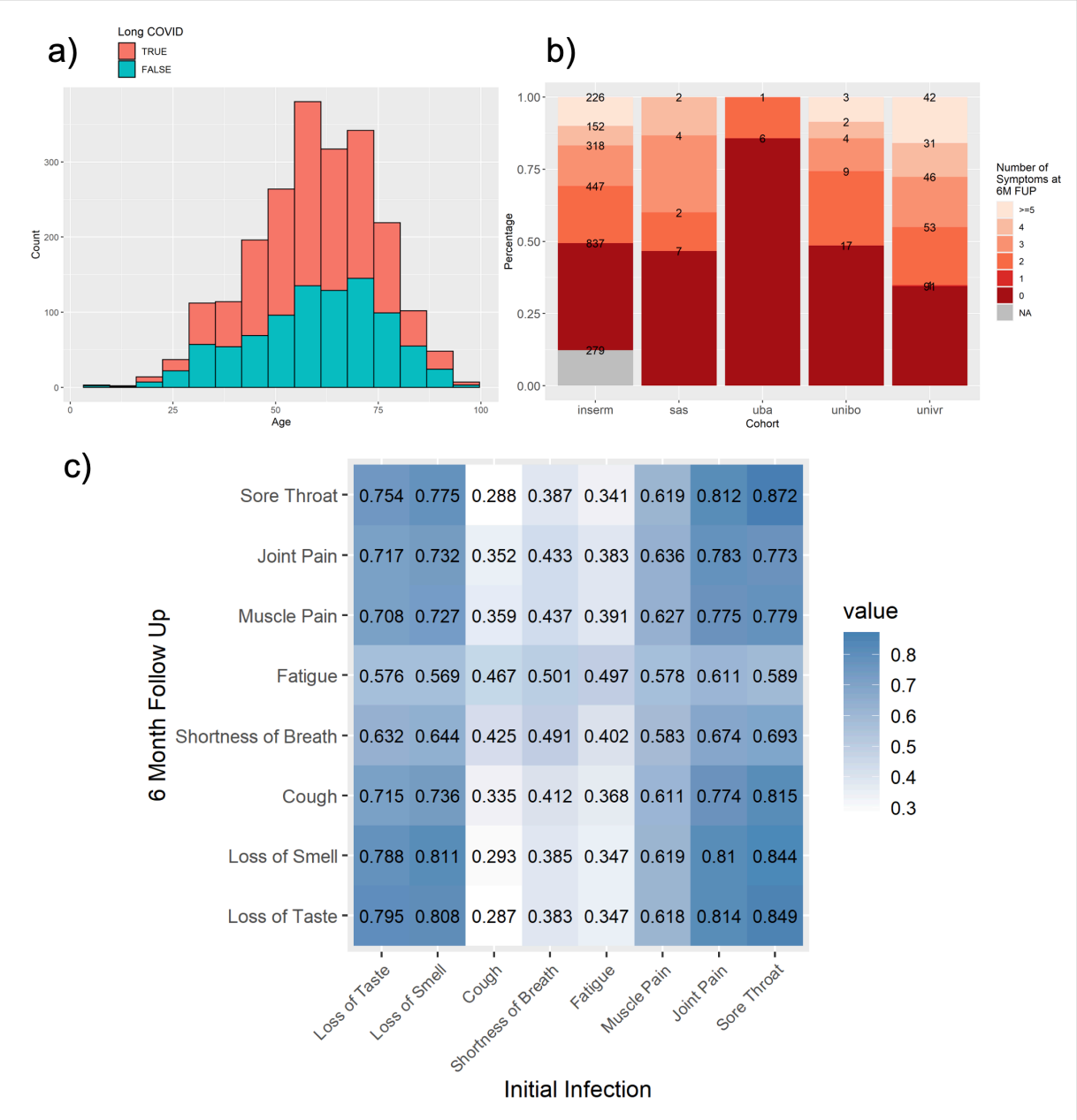

Figure 1 a) Age distribution, divided into recovered and having post-COVID sequelae series. **b)** Relative prevalence of post COVID-19 sequelae across included cohorts, disaggregated by the number of symptoms present at 6-month follow-up. **c)** Co-occurrence of the symptoms present during the acute phase of COVID infection and at the 6-month follow-up. The values in the heatmap correspond to the proportion of patients reporting each symptom both during the initial phase and at month 6 post-infection, e.g. 79,5% of patients with loss of taste during the acute phase reported the same symptom also during the 6 month follow up.

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Table 1. Analysis of age and gender, and number of symptoms during the acute phase.

Age and gender							
Variable	**N patients**	**Database portion**	**post COVID-19 sequelae**	**Odds Ratio**	**CI lower**	**CI upper**	***p*-value**
Total	2156	100.00%	58%	-	-	-	-
Male	1278	59.28%	55%	1	-	-	-
Female	878	40.72%	63%	1.4	1.17	1.66	**<0.001**
<20	16	100.00%	44%	-	-	-	-
Male	6	37.50%	-	1	-	-	-
Female	10	62.50%	40%	0.69	0.077	5.94	0.73
21 - 40	243	100.00%	47%	-	-	-	-
Male	109	44.86%	41%	1	-	-	-
Female	134	55.14%	52%	1.55	0.93	2.60	0.09
41 - 60	806	100.00%	65%	-	-	-	-
Male	495	61.41%	59%	1	-	-	-
Female	311	38.59%	74%	1.92	1.41	2.63	**<0.001**
>60	1091	100.00%	56%	-	-	-	-
Male	668	61.23%	54%	1	-	-	-
Female	423	38.77%	59%	1.23	0.96	1.57	0.11
Number of symptoms during the acute phase							
Total	2580	100.00%	58.37%	-	-	-	-
0 - 5	1583	61.36%	55.73%	1	-	-	-
6 - 10	892	34.57%	60.94%	1.24	1.04	1.48	**0.02**
11 - 15	97	3.76%	**71.58%**	1.99	1.27	3.21	**<0.001**
>16	8	0.31%	-	4.96	0.86	126.48	0.08

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Table 2 Cofounders of developing post COVID-19 sequelae at 6-month follow-up. Portion of post-COVID-19 sequelae refers to the patients for whom variable was available denoted in the Number of patients column. Green color and bold font denote significant cofounders.

Cofounder variable	Variable available		Variable positive	Portion of post-COVID-19 sequelae	X-square	*p*-value
	Number of patients	Database portion				
Symptoms in the acute phase						
Memory loss	292	11.32%	0.54%	**100.00%**	8.13	**<0.001**
Anomia	293	11.36%	0.43%	**100.00%**	6.38	**0.01**
Skin rash	2118	82.09%	1.28%	83.87%	9.22	**<0.001**
Arthralgia	2048	79.38%	12.56%	69.16%	20.97	**<0.001**
Wheezing	2118	82.09%	3.95%	66.67%	3.11	0.08
Sore throat	2031	78.72%	8.41%	64.71%	5.19	**0.02**
Myalgia	2146	83.18%	30.39%	64.53%	21.98	**<0.001**
Vomiting	2207	85.54%	12.36%	64.16%	6.05	**0.01**
Altered consciousness or confusion	2210	85.66%	5.31%	64.00%	2.19	0.14
Seizures	2168	84.03%	0.54%	63.64%	0.17	0.68
Lymphadenopathy	2077	80.50%	0.50%	63.64%	0.20	0.65
Chest pain and/or chest tightness	2172	84.19%	12.13%	63.41%	4.57	**0.03**
Headache	2140	82.95%	**22.98%**	63.24%	9.81	**<0.001**
Nasal congestion	703	27.25%	7.25%	62.36%	1.06	0.30
Lower chest wall indrawing	2067	80.12%	2.33%	62.26%	0.58	0.44
Conjunctivitis	2146	83.18%	1.82%	62.22%	0.49	0.48
Rhinorrhea	2085	80.81%	10.23%	61.85%	2.43	0.12
Ageusia or dysgeusia	1853	71.82%	15.97%	61.83%	3.31	**0.07**
Abdominal pain	2186	84.73%	8.60%	61.81%	1.87	0.17
Anosmia	1850	71.71%	14.69%	61.58%	2.73	0.10
Dyspnea	2231	86.47%	**53.18%**	61.53%	18.41	**<0.001**
Fever	712	27.60%	19.30%	60.96%	4.90	**0.03**
Diarrhea	2227	86.32%	23.80%	59.78%	1.34	0.25
Cough	2260	87.60%	**63.72%**	59.54%	5.41	**0.02**
Fatigue and/or malaise	2198	85.19%	**58.80%**	58.97%	3.79	**0.05**
Inability to walk	822	31.86%	1.74%	56.82%	0.01	0.91
Anorexia	802	31.09%	7.21%	54.29%	0.12	0.73
Syncopal episodes	296	11.47%	0.47%	50.00%	0.93	0.33
Comorbidities						
Chronic respiratory disease	2385	92.44%	10.31%	67.65%	10.02	**<0.001**
Ongoing corticosteroids	2314	89.69%	3.53%	70.73%	5.54	**0.02**
Psychiatric disorder	2577	99.88%	0.78%	70.00%	1.12	0.29
Tuberculosis	1065	41.28%	0.58%	46.67%	0.64	0.42
Cardiovascular disease	2356	91.32%	**41.78%**	58.85%	0.63	0.43
Chronic liver disease	2390	92.64%	2.52%	62.30%	0.45	0.50
Ongoing statins	1011	39.19%	4.92%	55.83%	0.13	0.71
Smoking	2107	81.67%	5.00%	58.41%	0.79	0.85
Other immunosuppressive conditions	2577	99.88%	0.50%	54.55%	0.07	0.79
Auto-inflammatory disease	2577	99.88%	2.05%	49.02%	1.89	0.17
HIV	2079	80.58%	1.47%	29.41%	10.85	**<0.001**
Events during hospitalization						
Hospital admission	2573	99.73%	**84.30%**	57.84%	1.13	0.29
ICU admission	1877	81.57%	25.68%	63.28%	10.41	**0.001**
Cardiac events	2577	99.88%	0.89%	**89.47%**	7.62	**0.01**
Embolic events	2577	99.88%	2.67%	68.42%	2.42	0.12
Gastrointestinal events	2577	99.88%	0.81%	64.71%	0.28	0.60
Renal events	2577	99.88%	7.56%	60.37%	0.28	0.60

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COVID HOME study

COVID HOME enrolled a total of 276 participants of which 12 were excluded as false positives, leaving a total of 264 individuals belonging to 101 households of which 190 (72%) were positive for SARS-CoV-2 by qRT-PCR at enrollment. At the moment of writing this report, 183 (96.3%) out of 190 positive participants have reached month 6 post-infection follow-up and of these, 144 (73.5%) have filled the 6-month questionnaire. A preliminary analysis performed with a smaller sample size showed that 43.5%, 47% and 40% of individuals reported still having at least one symptom at 3, 6- and 12-months post infection respectively. These symptoms were described as constant, recurrent or both **Figure 2**.

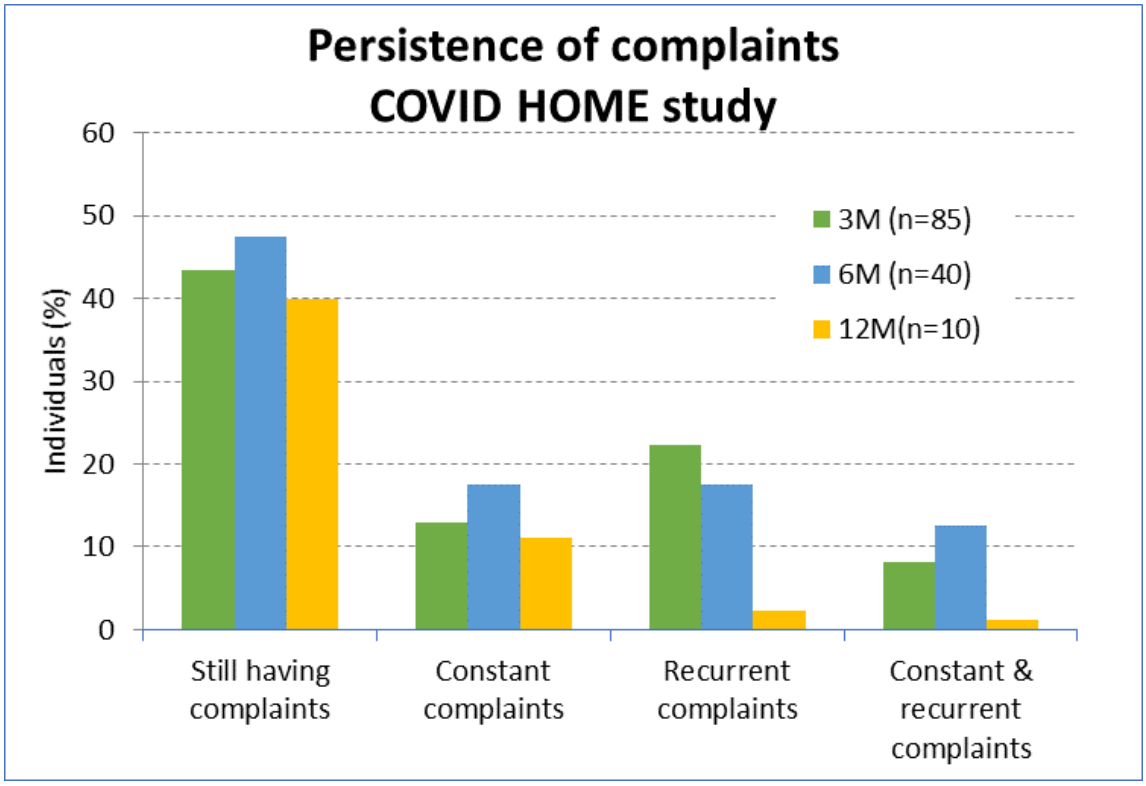

Figure 2. COVID HOME study. Percentage of individuals reporting at least one symptom at 3 (green bars), 6 (blue bars) and 12 months (yellow bars) post-infection. Patients reported these symptoms to be constant, recurrent or both and the percentage of individuals reporting these at each time point are shown.

Demographic features and underlying medical conditions

The majority of participants had no comorbidities with only 26% reporting 1 or 2 comorbidities. Univariate analysis of selected demographic and clinical factors related to having symptoms at 6 months post-infection follow up revealed no association with number of comorbidities, age nor gender, although females were more frequently affected but the association was not significant.

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Clinical presentation during acute infection and at 6-month follow up

Patients reported up to 25 different symptoms during their acute COVID-19 disease, with about 50% of them reporting 7-15 symptoms. The most frequent symptoms reported by >40% of individuals were headache (55%), dry cough (45,4%), fatigue (44%) and myalgia (40.2%) with those that lasted longer (more than 4 weeks) being fatigue, lack of smell and taste and dry cough **Table 3**.

At 6 months post-infection follow up, patients reported up to 66 different types of symptoms. The most frequent long-lasting symptom was persistent fatigue, reported by around half of the people. The other most frequent long-lasting symptoms were: mental/neurological symptoms (such as trouble concentrating, memory problems, brain fog); sleeping problems; shortness of breath; headache; lack of smell & taste; severe fatigue; palpitations; and gastrointestinal symptoms (diarrhoea, nausea, abdominal pain). Presence of symptoms at 6 months post infection were significantly associated with duration (>4 weeks) of symptoms (OR=11.9, p=0.001) and increasing number of symptoms during the acute disease.

Table 3. COVID HOME study. Symptoms reported during the acute phase of COVID-19 disease.

Clinical presentation (n=86)	N	(%)	Mean duration in days (range)
Number of symptoms reported stratified in groups in ascending order			
0	3	(3.5)	-
6	17	(19.8)	-
7-10	28	(32.6)	-
11-15	20	(23.3)	-
16-25	18	(21.0)	-
Most frequent symptoms reported and mean duration of these symptoms in days.			
Headache	48	(54.6)	4.7 (1-28)
Dry cough	39	(45.4)	**6.1 (1-32)**
Fatigue (n=87)	38	(43.9)	**8.0 (1-36)**
Myalgia	35	(40.2)	3.2 (1-21)
Rhinorrhoea (n=87)	27	(31.0)	3.6 (1-21)
Sleepiness	25	(29.1)	3.4 (1-21)
Anosmia	23	(26.7)	**7.8 (1-32)**
Sleep problems(n=78)	16	(20.5)	3.4 (1-27)
Ageusia	17	(19.8)	**6.8 (1-33)**
Dyspnea	16	(18.4)	3.1 (1-29)

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Conclusions

- A high proportion of both hospitalized and non-hospitalized individuals experience symptoms 6 months after the infection, with ICU admission being a risk factor for post-COVID19 sequelae;
- Fifty-eight percent of patients in the hospitalized/non-hospitalized WP2 prospective cohort and almost 50% of individuals in the COVID HOME non-hospitalized cohort reports long-lasting symptoms at 6-month follow-up, with a significant number of patients still following rehabilitation programs at >12 months post-infection;
- Fatigue is the most common early and long-lasting symptom of COVID-19 both in the hospitalized/non-hospitalized WP2 prospective cohort and in the COVID HOME non-hospitalized cohort;
- The hospitalized/non-hospitalized WP2 prospective cohort and in the COVID HOME non-hospitalized cohort reported a lack of clear association between older age and occurrence of post COVID-19 sequelae, while both cohorts registered a higher probability of persistence of symptoms in women compared to men.
- Even if ICU admission was found to be a risk factor for developing post COVID-19 sequelae in the hospitalized WP2 prospective cohort, the rate and characteristics of persisting symptoms do not differ with respect to COVID HOME non-hospitalized cohort, suggesting a negligible impact of the severity of acute infection on the occurrence of long-lasting symptoms

Recommendations:

- ❖ Post COVID-19 condition is still not clearly defined and does not include all symptoms identified in the WP2 ORCHESTRA cohorts. A better identification of patients at risk for long sequelae could be extremely useful for defining high risk population for early treatment, development of follow-up protocols, and assessment of COVID-19 burden.
- ❖ The partial results were presented on ECCMID conference 9 – 12 July 2021: Abstract number: 1876 **Title:** ***Long COVID and post-viral fatigue syndrome in non-hospitalised individuals: the COVID HOME study*** Tami A[1], Vincenti-Gonzalez MF[1], van der Gun BTF[1], Wold K I[1], O'Boyle S[2], Knoester M[1], Dijkstra AE[1], Veloo ACM[1], Mayaud P[2], Huckriede A[1], Niesters HGM[1], Nacul L[2,3], Friedrich AW[1] and the COVID HOME research group

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