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Evolution of Coronavirus Disease 2019 (COVID-19) Symptoms During the First 12 Months After Illness Onset

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Background. Few robust longitudinal data on long-term coronavirus disease 2019 (COVID-19) symptoms are available. We evaluated symptom onset, severity and recovery across the full spectrum of disease severity, up to one year after illness onset.

Methods. The RECoVERED Study is a prospective cohort study based in Amsterdam, the Netherlands. Participants aged ≥18 years were enrolled following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnosis via the local public health service and from hospitals. Standardized symptom questionnaires were completed at enrollment, 1 week and month later, and monthly thereafter. Clinical severity was defined according to World Health Organization (WHO) criteria. Kaplan-Meier methods were used to compare time from illness onset to symptom recovery, by clinical severity. We examined determinants of time to recovery using multivariable Cox proportional hazards models.

Results. Between 11 May 2020 and 1 May 2021, 342 COVID-19 patients (192 [56%] male) were enrolled, of whom 99/342 (29%) had mild, 145/342 (42%) moderate, 56/342 (16%) severe, and 42/342 (12%) critical disease. The proportion of participants who reported at least 1 persistent symptom at 12 weeks after illness onset was greater in those with severe/critical disease (86.7% [95% confidence interval {CI} = 76.5–92.7%]) compared to those with mild or moderate disease (30.7% [95% CI = 21.1–40.9%] and 63.8% [95% CI = 54.8–71.5%], respectively). At 12 months after illness onset, two-fifths of participants (40.7% [95% CI = 34.2–7.1]) continued to report ≥1 symptom. Recovery was slower in female compared to male participants (adjusted hazard ratio [aHR] 0.65 [95% CI = .47–.92]) and those with a body mass index [BMI] ≥30kg/m^2 compared to BMI <25kg/m^2 (hazard ratio [HR] 0.62 [95% CI = .39–.97]).

Conclusions. COVID-19 symptoms persisted for one year after illness onset, even in some individuals with mild disease. Female sex and obesity were the most important determinants of speed of recovery from symptoms.

Keywords. Long COVID; symptoms; recovery.

The clinical spectrum of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ranges from asymptomatic presentation to fatal illness. Although the acute symptomatology of hospitalized patients has been well documented [1–4], robust longitudinal data on the evolution of long-term symptoms across the full range of COVID-19 severity are scarce. Moreover, little is known about the risk factors that may affect recovery and provide opportunity for intervention or treatment.

Observational studies have reported that more than half of hospitalized patients [5–7] and approximately one-third of nonhospitalized patients [8] reported at least 1 ongoing symptom 4–12 months after symptom onset. In addition, online patient-led support groups [9] have provided anecdotal evidence on the impact of long-term post-COVID-19 symptoms on quality of life, daily functioning, and mental health. Indeed, post-COVID syndrome (ie, long COVID or post-acute sequelae of SARS-CoV-2 infection [PASC]) may have substantial adverse consequences for both individual quality of life and the economic productivity of society [5, 10, 11].

The RECoVERED study is a prospective cohort study of individuals with SARS-CoV-2 infection residing in the municipal region of Amsterdam, the Netherlands. We evaluated the incidence, severity, and duration of symptoms up to 12 months after illness onset in participants with mild, moderate, severe, and critical COVID-19 and examined baseline determinants of time to recovery from symptoms.

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METHODS

Study Design and Participants

The RECoVERED study is an ongoing cohort study of individuals with COVID-19 in Amsterdam, the Netherlands. The study aims to describe the immunological, clinical and psychosocial sequelae of SARS-CoV-2 infection. Enrolment began on 11 May 2020. Nonhospitalized participants were identified from notification data of laboratory-confirmed (by polymerase chain reaction [PCR] or validated antigen test [12]) SARS-CoV-2 infection at the Public Health Service of Amsterdam (PHSA). Trained study staff approached eligible patients by telephone up to 7 days after SARS-CoV-2 diagnosis. Prospectively enrolled hospitalized participants were identified from admission data and approached on the COVID-19 wards of 2 academic hospitals in Amsterdam. In hospitals, COVID-19 diagnosis was based on positive PCR and/or SARS-CoV-2-specific serology (using the WANTAI SARS-CoV-2 Ab ELISA [13]); the latter method was used as an additional diagnostic tool for cases with high clinical suspicion of COVID-19 during periods of extreme pressure on tertiary care. COVID-19 patients who had been admitted to the intensive care unit (ICU) were enrolled following step-down from ICU. A limited number of hospitalized patients were contacted after discharge up to 30 June 2020 and within 3 months following SARS-CoV-2 diagnosis in order to include participants infected during the "first wave" of COVID-19 in the Netherlands. Recruitment is ongoing; for the present analyses we included all participants with a follow-up of at least 1 month by 1 June 2021.

Eligibility criteria included prior laboratory confirmation of SARS-CoV-2 infection by PCR, validated antigen test or serology, as stated above. Further inclusion criteria were: aged 16–85 years, residing in the municipal region of Amsterdam, and adequate understanding of Dutch or English. Individuals residing in a nursing home prior to SARS-CoV-2 infection were excluded due to inability to travel independently for follow-up appointments. Individuals with mental disorders that would interfere with adherence to study procedures were also excluded.

The RECoVERED study was approved by the medical ethical review board of the Amsterdam University Medical Centre (NL73759.018.20). All participants provided written informed consent.

Study Procedures

Study visits at enrollment (D0 study visit) and day 7 (D7 study visit) took place at the participant's home (if nonhospitalized) or on the hospital ward (if hospitalized). Subsequent visits took place at 1 of 2 study sites (PHSA and Amsterdam University Medical Center [UMC] [location AMC]). All visits were performed by trained medical study staff.

At D0, D7 and D28 study visits, a symptom questionnaire on the presence, start and stop dates, and severity of 18 symptoms (based on the World Health Organization Case Report Form [14]) was completed (Supplementary Figure 2). From month 2 after enrollment onward, participants completed monthly online questionnaires on the presence of symptoms.

Heart rate, respiratory rate (RR), and oxygen saturation (SpO_2) were measured at D0 and D7 study visits, or retrieved from hospital records for retrospectively enrolled participants. Sociodemographic data and data on past medical history, COVID-19-related complications, treatment, and investigations were collected during participant interview. Self-reported data were verified with electronic medical records when available.

Definitions

COVID-19 illness onset was defined as the first day of symptoms; for asymptomatic patients, date of SARS-CoV-2 diagnosis was used. Complete recovery was defined as resolution of all COVID-19 symptoms. As per National Institute for Health and Care Excellence (NICE) guidelines [15], the acute phase of disease was defined as the first 4 weeks after illness onset, and post-COVID syndrome as symptoms persisting at least 12 weeks after illness onset.

Clinical severity groups were defined based on WHO COVID-19 disease severity criteria [16] using physical measurements from D0 and D7 study visits. Mild disease was defined as having a RR <20/minute and SpO_2>94% on room air at both D0 and D7 study visits; moderate disease as having a RR20–30/minute and SpO_2 90–94% on room air (or receiving oxygen therapy, if no off-oxygen measurement available) at either visit; severe disease as having a RR >30/minute and SpO_2<90% on room air (or receiving oxygen therapy) at either visit; critical disease as requiring ICU admission as a result of COVID-19 at any point.

Symptom severity was measured on a four-point scale, with the exception of dyspnea, measured using the six-point modified Medical Research Council (mMRC) breathlessness scale [17]. Comorbidities at illness onset were those listed by the WHO as associated with severe COVID-19 [16]: cardiovascular disease (CVD), diabetes mellitus (DM), chronic lung disease (CLD), liver disease, chronic kidney disease, immunodeficiency, cancer, cerebrovascular disease, dementia, or psychiatric illness. Obesity was excluded from the comorbidity variable because body mass index (BMI) was defined separately, categorized in kg/m^2 as: <25, underweight or normal weight; 25–30, overweight; >30, obese. Ethnicity was based on the country of birth of the study participant and their parents [18].

Loss to follow-up (LTFU) was defined as active withdrawal from the study or 2 consecutive no-show appointments despite 3 attempts to establish contact. Date of LTFU was defined as the date of last contact with the participant.

Table 1. Sociodemographic, Clinical and Study Characteristics of Participants of the RECoVERED Study, May 2020–2021 in Amsterdam, The Netherlands, by Clinical Severity Group

	Total	Mild	Moderate	Severe	Critical	*P*-value
	N = 342	N = 99	N = 145	N = 56	N = 42	
Sociodemographic and baseline characteristics						
Sex						.004
Male	192 (56%)	47 (47%)	85 (59%)	27 (48%)	33 (79%)	
Female	150 (44%)	52 (53%)	60 (41%)	29 (52%)	9 (21%)	
Age, years	51.0 (36.0–62.0)	39.0 (27.0–54.0)	49.0 (34.0–61.0)	64.0 (50.0–72.0)	56.0 (51.0–61.0)	<.001
BMI, kg/m^2	26.1 (23.2–29.7)	24.4 (22.9–27.6)	26.0 (23.1–29.5)	28.1 (25.7–34.1)	27.1 (23.9–31.0)	<.001
BMI category						<.001
Normal weight[a]	140 (41%)	54 (55%)	61 (42%)	13 (23%)	12 (29%)	
Overweight	108 (32%)	24 (24%)	49 (34%)	17 (30%)	18 (43%)	
Obese	82 (24%)	14 (14%)	34 (23%)	23 (41%)	11 (26%)	
Missing	12 (4%)	7 (7%)	1 (1%)	3 (5%)	1 (2%)	
Ethnic origin[b]						.092
Netherlands	190 (56%)	62 (63%)	81 (56%)	25 (45%)	22 (52%)	
Morocco	12 (4%)	4 (4%)	4 (3%)	2 (4%)	2 (5%)	
Asia, Middle East, Africa	32 (9%)	5 (5%)	16 (11%)	7 (13%)	4 (10%)	
South America, Caribbean	41 (12%)	4 (4%)	19 (13%)	10 (18%)	8 (19%)	
Other	25 (7%)	11 (11%)	11 (8%)	2 (4%)	1 (2%)	
Missing	42 (12%)	13 (13%)	14 (10%)	10 (18%)	5 (12%)	
Smoking						.40
Nonsmoker	199 (58%)	56 (57%)	82 (57%)	34 (61%)	27 (64%)	
Smoker	21 (6%)	8 (8%)	11 (8%)	2 (4%)	0 (0%)	
Ex-smoker	98 (29%)	23 (23%)	47 (32%)	17 (30%)	11 (26%)	
Missing	24 (7%)	12 (12%)	5 (3%)	3 (5%)	4 (10%)	
Highest level of education						<.001
None, primary or secondary education	45 (13%)	7 (7%)	24 (17%)	11 (20%)	3 (7%)	
Vocational training	73 (21%)	8 (8%)	32 (22%)	14 (25%)	19 (45%)	
University education	178 (52%)	71 (72%)	74 (51%)	19 (34%)	14 (33%)	
Missing	46 (13%)	13 (13%)	15 (10%)	12 (21%)	6 (14%)	
Number of COVID-19 high-risk comorbidities[c]						<.001
None	186 (54%)	71 (72%)	87 (60%)	12 (21%)	16 (38%)	
1	80 (23%)	19 (19%)	32 (22%)	17 (30%)	12 (29%)	
2	47 (14%)	6 (6%)	18 (12%)	17 (30%)	6 (14%)	
≥3	29 (8%)	3 (3%)	8 (6%)	10 (18%)	8 (19%)	
Cardiovascular disease	92 (27%)	13 (14%)	34 (23%)	31 (56%)	14 (33%)	<.001
Diabetes mellitus	45 (13%)	5 (5%)	11 (8%)	17 (31%)	12 (29%)	<.001
Chronic respiratory disease	25 (7%)	1 (1%)	8 (6%)	13 (24%)	3 (7%)	<.001
Cancer	17 (5%)	6 (6%)	6 (4%)	3 (6%)	2 (5%)	.89
Immunosuppression	20 (6%)	1 (1%)	8 (6%)	5 (9%)	6 (14%)	.62
Psychiatric illness	18 (5%)	5 (5%)	9 (6%)	3 (6%)	1 (2%)	.90
Other comorbidities[b]	76 (24%)	14 (16%)	39 (28%)	13 (25%)	10 (25%)	.21

Table 1. Continued

	Total	Mild	Moderate	Severe	Critical	*P*-value
	N = 342	N = 99	N = 145	N = 56	N = 42	
COVID-19 clinical characteristics						
Symptom status at baseline						.15
Symptomatic	338 (99%)	96 (97%)	145 (100%)	55 (98%)	42 (100%)	
Asymptomatic	4 (1%)	4 (4%)	0 (0%)	0 (0%)	0 (0%)	
COVID-19 hospital admission	172 (50%)	6 (6%)	72 (50%)	52 (93%)	42 (100%)	<.001
COVID-19 ICU admission	42 (12%)	0 (0%)	0 (0%)	0 (0%)	42 (100%)	
Days from illness onset to:						
SARS-CoV-2 diagnosis	5 (2–10)	3 (1–8)	5 (2–10)	7 (2–13)	7 (3–10)	.060
Hospitalization	10 (7–14)	…	9 (8–17)	11 (8–15)	8 (6–11)	…
ICU admission	10 (7–12)	…	…	…	10 (7–12)	…
Treatment received:						
Dexamethasone	60 (23%)	0 (0%)	24 (23%)	27 (64%)	9 (31%)	<.001
Remdesivir	3 (1%)	0 (0%)	0 (0%)	2 (5%)	1 (3%)	.032
Oxygen therapy	153 (46%)	0 (0%)	61 (43%)	52 (93%)	40 (98%)	<.001
Physical measurements[e]						
Maximum heart rate, beats/min	82 (72–94)	74 (66–81)	83 (74–92)	95 (84–107)	94 (80–110)	<.001
Maximum RR, breaths/min	20 (16–24)	16 (16–16)	20 (19–24)	25 (20–32)	26 (20–33)	<.001
Minimum SpO_2, %	96 (91–98)	98 (97–99)	96 (93–98)	88 (85–89)	85 (78–90)	<.001
SARS-CoV-2 serology at enrollment[d]	5 (0–17)	0 (0–3)	8 (0–18)	15 (7–20)	16 (12–19)	<.001
Ct-value at enrolment (PCR)						
Nasopharyngeal	26 (19–33)	25 (19–31)	26 (16–33)	30 (27–32)	27 (22–33)	.55
Throat	28 (0–32)	28 (22–32)	28 (0–32)	12 (0–31)	34 (32–36)	.17
Died during follow-up	2	0	1	1	0	…
Vaccinated during follow-up	205 (60%)	64 (65%)	88 (61%)	24 (43%)	29 (69%)	
Time from illness onset to vaccination, days	249 (152–365)	187 (113–300)	253 (168–320)	285 (77–399)	384 (358–393)	<.001
Study characteristics						
Place of recruitment						…
Nonhospital	161 (47%)	85 (86%)	72 (50%)	4 (7%)	0 (0%)	
Hospital	181 (53%)	14 (14%)	73 (50%)	52 (93%)	42 (100%)	
Type of inclusion						<.001
Prospective	250 (73%)	86 (87%)	114 (79%)	39 (70%)	11 (26%)	
Retrospective	92 (27%)	13 (13%)	31 (21%)	17 (30%)	31 (74%)	
Time from illness onset to enrolment in study, days	12 (6–41)	7 (4–12)	12 (6–32)	18 (11–72)	74 (20–93)	<.001
Prospective inclusions only	9 (5–14)	6 (4–9)	9 (6–16)	13 (11–17)	17 (11–20)	<.001
Retrospective inclusions only	85 (72–94)	92 (66–94)	85 (76–92)	82 (72–99)	88 (72–96)	.91
Follow-up time (from enrollment in study), days	217.5 (126.0–343.0)	204.0 (147.0–336.0)	223.0 (127.0–342.0)	171.5 (56.0–348.5)	335.5 (110.0–349.0)	.073

Table 1. Continued

	Total	Mild	Moderate	Severe	Critical	*P*-value
	N = 342	N = 99	N = 145	N = 56	N = 42	
Prospective inclusions only	190.0 (91.0–281.0)	196.5 (146.0–286.0)	216.5 (126.0–307.0)	84.0 (41.0–176.0)	85.0 (54.0–168.0)	<.001
Retrospective inclusions only	349.0 (336.0–356.0)	364.0 (341.0–379.0)	350.0 (272.0–357.0)	354.0 (349.0–356.0)	342.0 (333.0–350.0)	.074
Lost to follow-up	66	22	26	13	5	…

Continuous variables presented as median (IQR) and compared using the Kruskal-Wallis test; categorical and binary variables presented as n(%) and compared using the Pearson χ^2 test (or Fisher exact test if n <5). Clinical severity groups defined as: mild as having an RR <20/min and SpO2 on room air >94% at both D0 and D7; moderate disease as having a RR 20–30/minutes, SpO2 90–94% and/or receiving oxygen therapy at D0 or D7; severe disease as having a RR >30/minutes or SpO2 <90% at D0 or D7; critical disease as requiring ICU admission.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HR, heart rate; ICU, intensive care unit; PCR, polymerase chain reaction; PHSA, Public Health Service of Amsterdam; RR, respiratory rate; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Normal BMI group includes 3 individuals with BMI between 17.0 and 18.5 kg/m^2.

[b]Ethnic origin based on country of birth of participant and that of their parents. "Other" ethnic origin includes: Europe, Russia, Australia, Canada, United States, and New Zealand.

[c]COVID-related comorbidities are based on WHO Clinical Management Guidelines [16] and include: cardiovascular disease (including hypertension), chronic pulmonary disease (excluding asthma), renal disease, liver disease, cancer, immunosuppression (excluding HIV, including previous organ transplantation), previous psychiatric illness and dementia.

[d]SARS-CoV-2-specific antibodies were measured using the WANTAI SARS-CoV-2 Ab ELISA and a positive test result was defined according to the manufacturer's instructions.

[e]Physical measurements at D0 and D7 study visits. Oxygen saturation measured on room air if possible or retrieved from ambulance records for hospitalized participants admitted on oxygen on day of enrollment. Physical measurements not displayed for individuals with critical disease due to unreliability of measurements at admission for critically-ill patients.

Statistical analyses

Sociodemographic and clinical characteristics of participants were compared between clinical severity groups.

The incidence proportions for 18 different symptoms (based on the WHO/ISARIC Case Report Forms [CRF] [14]) at 1, 4, and 12 weeks after illness onset were calculated as the number of participants reporting each symptom since illness onset over the total number of participants in follow-up at that point and was compared by clinical severity group. Asymptomatic participants contributed to the denominator. Given the potential recall bias in reporting symptom onset, we restricted this analysis to prospectively-enrolled participants. For symptoms reported by >20% of participants at 12 weeks after symptom onset, changes in self-reported symptom severity over time during the acute phase were visualized using transition plots, stratified by clinical severity group.

The proportion of participants with ongoing symptoms (overall and for each symptom separately) were estimated using Kaplan-Meier survival curves using data from both prospectively and retrospectively enrolled participants. The at-risk period began at illness onset and continued until symptom recovery, loss to follow-up, 12 months after illness onset, date of first vaccination (to omit any effect of vaccination on time to recovery), or last study visit prior to 1 June 2021 (ie, administrative censor date), whichever occurred first. Asymptomatic participants were excluded from all symptom survival analysis.

Figure 1. Kaplan-Meier estimates of time from illness onset to complete recovery from symptoms, by clinical severity group. Clinical severity groups of severe and critically severe COVID-19 combined due to small numbers. Dashed red vertical line denotes 12 weeks (cutoff point for post-COVID syndrome, as per NICE definition); black vertical lines indicate time-points at which participants were censored. Participants who were vaccinated while still having symptoms (n = 91, median time from onset of symptoms to vaccination 249 days [IQR 142-365]) were right-censored at date of first vaccination. Curves represent the percentages of study participants recovering from symptoms during 1 year after COVID-19 illness onset. Shaded areas represent 95% CIs. The numbers of individuals at risk during each 28-day interval since illness onset are given below the graph. Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; NICE, National Institute for Health and Care Excellence.

Analysis of determinants associated with time to recovery from symptoms is described in Supplementary Methods.

A $P < .05$ was considered statistically significant. Statistical analyses were performed using Stata (StataCorp, v.15.1) and R (RStudio, v.1.2.5033).

RESULTS

Study Population

Participant enrolment and follow-up is summarized in Supplementary Figure 1. Between 11 May 2020 and 1 May 2021, 342 participants were enrolled, most (251/343;73%) prospectively. Of these 342, 99 (29%) experienced mild, 145 (42%) moderate, 56 (16%) severe and 42 (12%) critical disease (Table 1). All participants had prior confirmation of SARS-CoV-2 infection by PCR or antigen testing upon enrolment; none were enrolled solely on the basis of SARS-CoV-2-specific antibodies. Participants with severe or critical disease were older than those with mild or moderate disease ($P < .001$), had higher BMI ($P < .001$) and more frequently had a diagnosis of CVD, CLD, or DM (Table 1). Median time from illness onset to enrolment was 9 days (interquartile range [IQR] = 5–14) for prospectively enrolled and 85 days (IQR = 72–94) for retrospectively enrolled participants. Until 1 June 2021, 66 participants were lost to follow-up. Two deaths, both due to COVID-19, occurred during follow-up.

Incidence Proportions and Severity of Symptoms During the Acute Phase of Infection

Fatigue and cough were the most frequently reported symptoms overall and their incidence proportion during the acute phase did not differ between clinical severity groups (Supplementary Table 1). The incidence proportions of dyspnea, headache, and diarrhea were significantly greater in those with severe/critical disease compared to those with mild or moderate disease during the acute phase of disease, whereas the opposite was true for loss of appetite, fever, rhinorrhea, and sore throat. Transition plots showed that although most participants transitioned to a lower level of severity over time for the more persistent symptoms (fatigue, dyspnoea, loss of smell and/or taste, and myalgia), some transitioned to a higher severity level over time (Supplementary Figure 3a–3d).

Time to Recovery From Symptoms

Time to complete recovery was significantly longer in symptomatic participants with moderate and severe/critical disease than in those with mild COVID-19 (Figure 1). At least 1 ongoing symptom was reported at 12 weeks after illness onset, thus meeting NICE criteria for post-COVID syndrome, by 30.7% (95% CI = 21.1%–40.9%) of participants with mild, 63.8% (95% CI = 54.8–71.5%) with moderate and 86.7% (95%

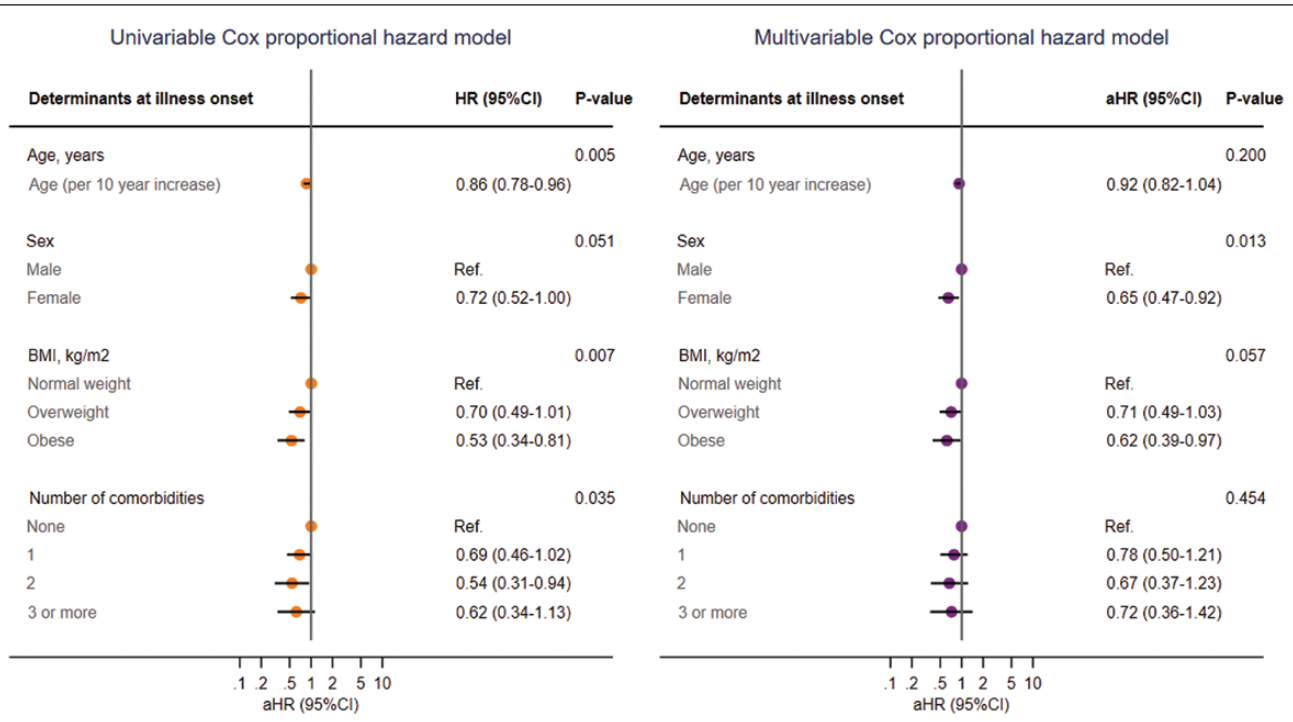

Figure 2. Unadjusted and adjusted hazard ratios of time to complete recovery for age, sex, BMI, and number of comorbidities at illness onset. Comorbidities counted are those listed by the WHO as being associated with a higher risk of developing severe or critical COVID-19 [11, excluding BMI]. BMI categorized in kg/m^2 as: <25, underweight or normal weight; 25 up to 30, overweight; >30, obese. *P*-value calculated using likelihood ratio test. Abbreviations: aHR, adjusted hazard ratio; BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; WHO, World Health Organization.

CI = 76.5–92.7%) with severe/critical disease. Among participants with mild disease, median time to complete recovery was 63 days (Figure 1), although 16.4% (95% CI = 8.5–26.5%) continued to report at least 1 ongoing symptom at twelve months after illness onset. In those with moderate disease, median time to complete recovery was 232 days (7.6 months) and 49.5% (95% CI = 39.6–58.6%) continued to report at least 1 symptom at 12 months after illness onset. More than half of those with severe/critical disease reported at least one ongoing symptom at twelve months after illness onset (52.5% [95% CI = 38.0–65.1%]). Supplementary Figure 4a–4e show Kaplan-Meier estimates for the individual 18 symptoms, by clinical severity group. Participants who were vaccinated while still having symptoms (n = 91, median time from onset of symptoms to vaccination 249 days [IQR 142–365]) were right-censored at date of first vaccination.

Determinants of Time to Recovery From Symptoms

Female participants experienced a 35% slower recovery than males (adjusted hazard ratio [aHR] 0.65 [95% CI = .47–.92]). In addition, obese participants recovered 38% more slowly than those of normal weight, when adjusting for age, sex, and comorbidities (aHR 0.62 [95% CI = .39–.97]) (Figure 2). The proportional hazards assumption was met for all covariates included in the model. When restricting the analysis to prospectively-enrolled participants, the effect of BMI was attenuated, suggesting that including retrospectively-enrolled participants, with more severe/critical disease and higher BMI, strongly influenced estimates of recovery time (Supplementary Figure 5).

In multivariable analysis of time to recovery for each of the four most persistent symptoms (Supplementary Table 2a–d), being obese at illness onset was associated with slower recovery from loss of smell and/or taste (aHR 0.51, 95% CI = .32–.82). Increased age was associated with slower recovery from dyspnoea (aHR 0.80, 95% CI = .69–.93) and myalgia (aHR 0.78, 95% CI = .68–.89). Number of comorbidities at illness onset was significantly associated with recovery from fatigue, where those with one comorbidity recovered twice as slowly as those without comorbidities (aHR 0.51, 95% CI = .34–.76). When we replaced total number of comorbidities with the presence of each of CVD, CLD, or DM in the multivariable models for each of these symptoms, no statistically significant effect on time to recovery was detected for any of these specific comorbidities.

DISCUSSION

To our knowledge, this study is one of the first to report detailed longitudinal data on the evolution of COVID-19 symptoms in a cohort of individuals with mild to critical disease up to one year after illness onset. Despite an overall improvement in severity of the most persistent COVID-19 symptoms during the acute phase of disease, approximately one-third of the mild group, nearly two-thirds of the moderate group, and more than four-fifths of patients with severe/critical disease met NICE criteria for post-COVID syndrome. Even at 1 year after illness onset, 1 in 6 of those with mild disease and approximately half of participants with moderate or severe/critical disease experienced at least 1 ongoing symptom. Female sex and obesity at illness onset were important determinants of slow recovery from symptoms.

Since the start of the COVID-19 pandemic, avoiding the immediate consequences of hospitalization and mortality has been the primary goal. As such, longer term sequelae of COVID-19 have received relatively little attention, especially among nonhospitalized patients. In our study, as many as 1 in 3 participants with mild COVID-19 still reported symptoms 12 weeks after illness onset. Indeed, the proportion of participants meeting the NICE definition of post-COVID syndrome in our cohort (60.2% overall) was comparable to other prospective cohort studies [7, 8, 19] but higher than estimates by the UK Office for National Statistics and among healthcare workers [20, 21]. Although this could be partly explained by the fact that our analysis was limited to symptomatic participants, the consequences of these proportions when extrapolated to a global level are likely to be substantial. It is therefore clear that responding to this emerging public health crisis requires urgent attention.

Although patient advocacy groups have helped in making post-COVID syndrome a research priority [22], studies to date have differed in study population, follow-up time and symptoms evaluated [15], making it difficult to synthesize all available evidence. Moreover, the symptom profiles that falls under post-COVID syndrome are diverse [23], resulting in a heterogenous patient group requiring different management strategies. A universally accepted and evidence-based definition of post-COVID syndrome is key to comparing findings across studies and settings, and to develop syndrome-specific interventions. Our study, for example, shows recovery beyond approximately 6 months after illness onset is uncommon, suggesting that individuals who remain symptomatic beyond this point may require more intensive support and care. Moreover, our findings suggest that women and obese individuals, regardless of age and the number of comorbidities at illness onset, may benefit from early intervention. In addition to the direct effect of obesity on recovery, high BMI is associated with having a lower socio-economic status and reduced access to health and care services [24], both of which may further amplify a slower recovery from symptoms. Reducing the prevalence of obesity may therefore help to reduce both acute complications [4, 25] and long-term sequelae of COVID-19.

Fatigue was the most commonly reported symptom both during the acute phase and at 12 weeks from illness onset, including among individuals with mild or moderate disease. Previous analyses have estimated that the societal impact of fatigue can be significant, due to both direct healthcare costs and indirect financial losses resulting from reduced economic productivity [26]. As those

with mild COVID-19 represent the majority of COVID-19 cases worldwide in terms of absolute numbers, developing strategies to prevent, diagnose and manage post-COVID fatigue should be given priority. Among participants with moderate and severe/critical disease, dyspnoea and myalgia additionally persisted beyond 12 weeks in a large proportion of participants. Similar results have been reported in other settings: previously-hospitalized COVID-19 patients in Wuhan, China, still had abnormal chest imaging findings and pulmonary diffusing capacity at 6 months after illness onset [5], whereas a cross-sectional study of hospitalized COVID-19 patients in the United Kingdom reported that the majority of participants reported myalgia at a median follow-up of 16 weeks after discharge from hospital [27]. In our multivariable analysis, older age was the most important determinant of slower time to recovery from both of these symptoms. Exploring the underlying mechanism as to why these symptoms persist in older patients may help identify interventions that could be beneficial in the recovery process.

This study has several strengths. Frequent symptom questionnaires collected longitudinally since illness onset allowed the natural progression of COVID-19 symptoms to be described to a level of detail not previously reported. We were able to enroll patients with mild symptoms (underrepresented in other studies) as well as those who were critically ill, so that the full spectrum of COVID-19 disease could be represented. Several limitations must be recognized. Questionnaires in languages other than English and Dutch were not offered; therefore, individuals with a migration background, who have been disproportionally affected by COVID-19, also in Amsterdam [28, 29], were underrepresented in this cohort. Furthermore, as the majority of our study participants were enrolled when wild-type SARS-CoV-2 was the dominant variant in the Netherlands, the progression of disease reported in our cohort may not be representative for patients infected with other SARS-CoV-2 variants [30]. In addition, certain symptoms that are frequently linked to post-COVID syndrome (eg, "brain fog", sleep disturbance) were not recorded. A further limitation was the effect of survival bias among retrospectively-enrolled participants (although sensitivity analysis of prospectively enrolled participants rendered comparable results). In addition, those who were in a life-threatening situation when admitted to hospital were less likely to be enrolled in the study (as demonstrated by only 2 COVID-19 deaths in our cohort and significantly older median age of nonenrolled hospitalized patients [Supplementary Figure 1]). Our study population might not be generalizable to those with extremely severe disease; however, these individuals have a high risk of death and symptom recovery is not applicable to deceased individuals. Finally, pre-COVID symptomatology was not recorded, making it difficult to accurately estimate the proportion of persistent symptoms directly attributable to post-COVID syndrome.

We demonstrated that post-COVID syndrome is common, even after mild disease. Symptoms persisted for twelve months after illness onset in one-sixth of participants with mild disease and in approximately half of participants with moderate and severe/critical disease. Female sex and obesity were the most important predictors of slow recovery, showing that creating an environment which facilitates healthy living behaviors is of utmost importance, even during a pandemic. Next steps in post-COVID syndrome research must include assessing the public health and socioeconomic impact, identifying further predictive and prognostic characteristics, and exploring the underlying biological mechanisms of disease in order to develop effective interventions.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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