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Severe Fatigue in the First Year Following SARS-CoV-2 Infection: A Prospective Cohort Study

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Background. Severe fatigue can persist for months after coronavirus disease 2019 (COVID-19) onset. This longitudinal study describes fatigue severity and its determinants up to 12 months after illness onset across the full spectrum of COVID-19 severity.

Methods. RECoVERED, a prospective cohort study in Amsterdam, the Netherlands, enrolled participants aged ≥16 years after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnosis. Fatigue was measured using the validated Short Fatigue Questionnaire (SFQ; range 4–28) at months 1, 3, 6, 9, and 12 of follow-up. Fatigue severity was modeled over time using mixed-effects linear regression. Determinants of severe fatigue (SFQ ≥18) at 6 months since illness onset (ie, persistent fatigue) were identified using logistic regression.

Results. Between May 2020 and July 2021, 303 participants completed at least 1 fatigue questionnaire. Twelve months after illness onset, 17.4% (95% CI, 6.7% to 38.3%), 21.6% (95% CI, 11.2% to 37.7%), and 44.8% (95% CI, 28.0% to 62.9%) of participants with mild, moderate, and severe/critical COVID-19 (World Health Organization definition), respectively, experienced severe fatigue. When adjusting for age and sex, having ≥3 comorbidities ($P = .007$), severe/critical COVID-19 ($P = .002$), low mood ($P < .001$), and dyspnea in the first 2 weeks of illness ($P = .001$) were associated with more severe fatigue over time. Severe/critical COVID-19 (adjusted odds ratio [aOR], 3.37; 95% CI, 1.28 to 8.93) and low mood at enrollment (aOR, 2.43; 95% CI, 1.11 to 5.29) were associated with persistent fatigue. Recovery rarely occurred beyond 6 months after illness onset, regardless of COVID-19 severity.

Conclusions. The occurrence of severe fatigue in our cohort was high, especially among those with initially severe/critical COVID-19, with little recovery beyond 6 months after illness onset. Our findings highlight an urgent need for improved understanding of persistent severe fatigue following COVID-19 to help inform prevention and intervention.

Keywords. COVID-19; fatigue; infection; persistence; predictors.

Fatigue is among the most commonly reported symptoms of postacute coronavirus disease 2019 (COVID-19) syndrome (PACS). PACS is defined by the World Health Organization (WHO) as the persistence of symptoms at 3 months after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, lasting for at least 2 months [1]. Fatigue persisting beyond 6 months after infection is frequently reported among previously hospitalized COVID-19 patients [2–5], and a growing body of evidence suggests that fatigue may also be long-lasting following mild COVID-19 [6, 7].

Persistent fatigue has been linked to other infectious diseases, including Epstein-Barr virus [8], Q-fever [9], influenza [10], and SARS-CoV-1 infection [11]. Estimates of the prevalence of fatigue following COVID-19 vary widely due to differences in the definition of fatigue, study design, and study population [4, 7, 12, 13]. Few studies have measured fatigue using instruments with validated cutoffs for severe fatigue, nor have they explored risk factors for fatigue using prospectively collected longitudinal data [14–16]. Insights into the occurrence, severity, and risk factors of persistent fatigue post-COVID-19 are crucial to understanding and mitigating the long-term consequences of infection.

In this prospective cohort study, we aimed to describe the presence of severe fatigue up to 12 months after illness onset across the full spectrum of COVID-19 severity and identify risk

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factors associated with both severity of fatigue over time and persistent severe fatigue specifically.

METHODS

Study Design and Participants

RECoVERED is a cohort study of individuals with SARS-CoV-2 infection in Amsterdam, the Netherlands. Enrollment began on May 11, 2020. Nonhospitalized participants were identified from notification data of laboratory-confirmed SARS-CoV-2 infection at the Public Health Service of Amsterdam and enrolled within 7 days of diagnosis [17]. Prospectively enrolled hospitalized participants were identified from admissions to the COVID-19 wards of the Amsterdam University Medical Centres (AUMC) and enrolled within 7 days of admission. Up to June 30, 2020, a limited number of hospitalized patients were included retrospectively within 3 months after SARS-CoV-2 diagnosis.

Eligibility criteria included laboratory confirmation of SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (RT-PCR), age 16–85 years, residing in the municipal region of Amsterdam, and adequate understanding of Dutch or English. Nursing home residents were excluded due to inability to attend follow-up appointments. For the present analyses, we included all participants with at least 1 month of follow-up and at least 1 completed fatigue questionnaire by August 1, 2021.

RECoVERED was approved by the medical ethical review board of the AUMC (NL73759.018.20). All participants provided written informed consent.

Study Procedures and Instruments

Study visits at enrollment (D0) and day 7 (D7) of follow-up took place at the participant's home or hospital ward. Subsequent visits took place at 1 of 2 study sites.

Sociodemographic and Clinical Characteristics

Medical history and sociodemographic data were collected during the first month of follow-up. Data on presence and duration of symptoms (based on the WHO Case Report Form [18]) were collected at the D0, D7, and month 1 visits through participant interview and monthly from month 2 via online questionnaires. Participants rated their anxiety and sadness on a scale from 0 (low) to 10 (high) at the D0 and D7 visits.

Physical measurements (ie, heart rate, respiratory rate [RR], oxygen saturation [SpO_2]) were measured at D0 and D7, or retrieved from hospital records for retrospectively enrolled participants.

At month 1 of follow-up, participants reported their pre-COVID occupation. Participants in paid employment were asked at month 12 whether they were on long-term leave due to COVID-19 symptoms.

Measurement of Fatigue

At months 1, 3, 6, 9, and 12 of follow-up, participants completed the Short Fatigue Questionnaire (SFQ) [19], which asks participants to rate their agreement on a 7-point scale with 4 statements regarding fatigue in the past 2 weeks [19]. The total SFQ score ranges from 4 to 28. A validated cutoff threshold of 18 defines severe fatigue [20].

Definitions

Persistent severe fatigue was defined as being severely fatigued (SFQ ≥18) 6 months after illness onset [14]. Illness onset was the first day when COVID-19 symptoms were experienced for symptomatic patients or the SARS-CoV-2 diagnosis date for asymptomatic patients. Acute COVID-19 symptoms were those reported within 14 days of illness onset. Clinical severity groups were defined based on WHO COVID-19 severity criteria [21]: mild disease as having an RR <20/min and SpO_2 >94% on room air at both D0 and D7; moderate disease as having an RR 20–30/min and/or SpO_2 90%–94% or receiving oxygen therapy at D0 or D7; severe disease as having an RR >30/min and/or SpO_2 <90% or receiving oxygen therapy at D0 or D7; critical disease as intensive care unit (ICU) admission due to COVID-19 at any point. High-risk comorbidities were those associated with severe COVID-19 [21]. Body mass index (BMI) was coded in kg/m^2 as follows: <25, underweight or normal weight; 25–30, overweight; >30, obese. Migration background was categorized as Dutch and non-Dutch based on the country of birth of the participant and their parents [22, 23]; those of non-Dutch background were further classified as originating from a high-income (HIC) or low-/middle-income country (LMIC) [24]. Highest educational level was categorized as none, primary/secondary school, vocational training, or university level. The highest reported anxiety and sadness scores at D0 and D7 (baseline) were categorized as hardly any anxiety/sadness (0 or 1), low (2–5), and high (6–10).

Statistical Analyses

Sociodemographic and clinical characteristics of participants were compared between clinical severity groups. Proportions of participants with severe fatigue and corresponding 95% CIs were calculated among survey responders at months 1, 3, 6, 9, and 12, overall and by clinical severity. The proportions of participants in paid employment on prolonged leave due to COVID-19 at month 12 were compared between those severely fatigued or not using Pearson's χ^2 test.

Fatigue severity over time was modeled using linear mixed-effects regression, including a random intercept to account for between-patient variation at baseline. Months since illness onset, age, and sex were included as fixed covariates, regardless of statistical significance. Three multivariable models were constructed: model 1 added sociodemographic and clinical characteristics; model 2 added COVID-19 clinical severity; model 3 added symptoms reported during acute infection (ie, baseline anxiety and sadness, acute fatigue, myalgia, headache, cough, dyspnea, and fever). Variables with a Wald χ^2 test P value <.20 in the multivariable model with age, sex, and months since illness

onset were included in further multivariable analyses. Each multivariable model was then generated using a backwards selection approach. Adjusted beta-coefficients (aβ) and their 95% CIs are presented, showing the mean difference in fatigue severity compared with the reference value. Changes in fatigue severity following illness onset were compared between baseline and month 6 and between month 6 and month 12 using a Wald χ^2 test obtained from a model that included age, sex, and clinical severity.

Persistent severe fatigue was modeled using logistic regression. Multivariable model construction was performed as described above. Adjusted odds ratios (aORs) and their 95% CIs are presented. Two sensitivity analyses were performed. First, we restricted our analyses to prospectively enrolled participants. Second, we redefined the outcome as having chronic fatigue (ie, fatigue present within the first month of illness and persisting up to 6 months after illness onset).

Two-sided *P* values <.05 were considered statistically significant. Statistical analyses were performed using Stata (version 15.1; StataCorp, College Station, TX, USA).

RESULTS

Study Population

Participant flow is described in Supplementary Figure 1. By August 1, 2021, 350 participants had been enrolled. Forty-seven participants did not complete a fatigue questionnaire. Consequently 303 participants were included in our analyses (Table 1). None of the participants had been vaccinated for COVID-19 before enrollment. There were no statistically significant differences in sociodemographic and clinical characteristics between participants who were excluded vs included in our analyses (Supplementary Table 1a). The proportion of missing surveys during follow-up is displayed in Supplementary Figure 2. Between those who were later lost to follow-up and those who remained in the study, the sex (50% male vs 58%; *P* = .330), number of comorbidities (*P* = .100), clinical severity (*P* = .415), and proportion of participants reporting severe fatigue in their first completed survey (65% vs 50%, respectively; *P* = .081) did not differ. However, participants who were lost to follow-up (LTFU) were on average 8 years younger than those who remained in active follow-up (β = −7.96; *P* = .003).

Severe Fatigue and Paid Employment

The occurrence of severe fatigue among participants with mild, moderate, and severe/critical disease who completed the SFQ was 39.7% (95% CI, 29.2% to 51.3%), 63.7% (95% CI, 54.0% to 72.5%), and 62.2% (95% CI, 45.7% to 76.2%) 1 month after illness onset, respectively; this decreased to 24.7% (95% CI, 16.1% to 35.8%), 42.7% (95% CI, 34.3% to 51.6%), and 45.9% (95% CI, 33.8% to 58.5%) by 3 months after illness onset (Figure 1). One year after illness onset, approximately one-fifth of those with mild or moderate disease had severe fatigue (17.4%; 95% CI, 6.7% to 38.3%; and 21.6%; 95% CI, 11.2% to 37.7%; respectively) compared with 44.8% (95% CI, 28.0% to 62.9%) of those with severe/critical disease.

Before SARS-CoV-2 infection, most study participants (193/303; 64%) had paid employment (Table 1). Of these 193, 52 (26.9%) reached their month 12 study visit and completed the questionnaire on long-term leave. Thirty-eight percent (6/16) of those with severe fatigue at month 12 were either fully or partially on long-term leave, whilst this proportion was 11% (4/36) for those without severe fatigue at month 12 (*P* < .026).

Factors Associated With Fatigue Severity Over Time

In the linear mixed-effects Model 1, participants who were female, obese, originated from LMICs, or had ≥3 comorbidities at illness onset had significantly higher mean fatigue severity scores compared with their respective reference groups, when adjusting for age and time since illness onset (Table 2; Supplementary Figure 3a). When adjusting for clinical severity in Model 2, BMI and migration background were no longer statistically significant (Supplementary Table 2), but female participants continued to have higher mean fatigue severity scores than males (aβ, 2.21; 95% CI, 0.78 to 3.64) (Table 2). Participants with moderate (aβ, 3.37; 95% CI, 1.72 to 5.03) or severe/critical disease (aβ, 4.39; 95% CI, 2.35 to 6.42) experienced significantly higher fatigue severity than those with mild disease (Table 2; Supplementary Figure 3b). In Model 3, participants with dyspnea in the acute phase (aβ, 2.47; 95% CI, 1.01 to 3.93), a high level of baseline sadness (aβ, 3.25; 95% CI, 1.40 to 4.90), severe/critical disease (aβ, 3.17; 95% CI, 1.11 to 5.22), and ≥3 comorbidities (aβ, 4.41; 95% CI, 1.64 to 7.18) had higher mean SFQ scores when adjusting for age and sex (Table 2; Supplementary Figure 3c). A statistically significant decline in fatigue severity was observed in the first 6 months after illness onset (aβ, −4.32; 95% CI, −5.29 to −3.35), but no further decrease was observed between month 6 and month 12 (*P* = .561).

Risk Factors for Persistent Severe Fatigue at 6 Months After Illness Onset

Six months after illness onset, 28.4% (95% CI, 22.4% to 35.0%) of participants were severely fatigued (Figure 1). In the logistic regression Model 1, the odds of having persistent severe fatigue were higher in those with ≥3 comorbidities compared with no comorbidities (aOR, 4.38; 95% CI, 1.40 to 13.74) (Figure 2). In Model 2, those with severe/critical COVID-19 had higher odds of developing persistent severe fatigue than those with mild disease (aOR, 3.51; 95% CI, 1.37 to 8.96). In Model 3, a high level of baseline sadness (aOR, 2.43; 95% CI, 1.11 to 5.29) and severe/critical COVID-19 (aOR, 3.37; 95% CI, 1.28 to 8.93) were independently associated with persistent severe fatigue.

Results were comparable when restricting the analyses to prospectively enrolled participants (Supplementary Table 3a).

Table 1. Sociodemographic, Clinical, and Study Characteristics of Recovered Study Participants Enrolled Between May 2020 and August 2021, Amsterdam, the Netherlands, by COVID-19 Clinical Severity

	Total	Mild COVID-19	Moderate COVID-19	Severe/Critical COVID-19	
	n = 303	n = 88	n = 136	n = 79	*P* Value
Sociodemographic features					
Sex					.21
Male	173 (57)	44 (50)	79 (58)	50 (63)	
Female	130 (43)	44 (50)	57 (42)	29 (37)	
Age, y	51.0 (36.0–62.0)	40.0 (27.5–54.5)	49.0 (34.0–60.5)	60.0 (50.0–66.0)	<.001
BMI, kg/m^2	26.1 (23.2–29.4)	24.6 (22.8–27.7)	26.2 (23.5–29.4)	27.3 (25.6–32.9)	<.001
BMI category					<.001
Normal weight[a]	124 (41)	50 (57)	56 (41)	18 (23)	
Overweight	106 (35)	24 (27)	48 (35)	34 (43)	
Obese	69 (23)	13 (15)	32 (24)	24 (30)	
Missing	4 (1)	1 (1)	0 (0)	3 (4)	
Migration background (OECD)[b]					.001
Dutch	184 (61)	63 (72)	78 (57)	43 (54)	
Non-Dutch, OECD HIC	37 (12)	12 (14)	21 (15)	4 (5)	
Non-Dutch, OECD LMIC	73 (24)	10 (11)	34 (25)	29 (37)	
Missing	9 (3)	3 (3)	3 (2)	3 (4)	
Smoking					.17
Nonsmoker	191 (63)	54 (61)	81 (60)	56 (71)	
Smoker	20 (7)	8 (9)	11 (8)	1 (1)	
Ex-smoker	87 (29)	23 (26)	43 (32)	21 (27)	
Missing	5 (2)	3 (3)	1 (1)	1 (1)	
Highest level of education					<.001
None, primary or secondary education	42 (14)	7 (8)	24 (18)	11 (14)	
Vocational training	73 (24)	9 (10)	34 (25)	30 (38)	
University education	178 (59)	69 (78)	75 (55)	34 (43)	
Missing	10 (3)	3 (3)	3 (2)	4 (5)	
Work situation before COVID-19					.025
Paid employment or self-employed	193 (64)	64 (73)	87 (64)	42 (53)	
On sick leave	15 (5)	0 (0)	6 (4)	9 (11)	
Retired	37 (12)	9 (10)	16 (12)	12 (15)	
Other[c]	50 (17)	14 (16)	23 (17)	13 (16)	
Missing	8 (3)	1 (1)	4 (3)	3 (4)	
No. of COVID-19 high-risk comorbidities[d]					<.001
0	168 (55)	63 (72)	81 (60)	24 (30)	
1	71 (23)	17 (19)	29 (21)	25 (32)	
2	38 (13)	5 (6)	17 (13)	16 (20)	
≥3	26 (9)	3 (3)	9 (7)	14 (18)	
Cardiovascular disease	81 (27)	12 (14)	33 (24)	36 (46)	<.001
Diabetes	34 (11)	5 (6)	11 (8)	18 (23)	<.001
Chronic respiratory disease	20 (7)	1 (1)	8 (6)	11 (14)	.003
Cancer	17 (6)	6 (7)	7 (5)	4 (5)	.85
Immunosuppressed	6 (2)	0 (0)	3 (2)	3 (4)	.20
Psychiatric illness	18 (6)	5 (6)	9 (7)	4 (5)	.90
Other comorbidities	64 (21)	11 (13)	34 (25)	19 (24)	.063
	Total	Mild	Moderate	Severe/Critical	*P* Value
	n = 303	n = 88	n = 136	n = 79	
Clinical features of SARS-CoV-2 infection					
Symptom status at baseline					.44
Symptomatic	302 (100)	87 (99)	136 (100)	79 (100)	
Asymptomatic	1 (0)	1 (1)	0 (0)	0 (0)	
Hospital admission	144 (48)	4 (5)	64 (47)	76 (96)	<.001
ICU admission	39 (13)	0 (0)	0 (0)	39 (49)	<.001
Days from illness onset to SARS-CoV-2 diagnosis	4 (2–10)	3 (1–8)	5 (2–11)	7 (2–11)	.078

Table 1. Continued

	Total	Mild	Moderate	Severe/Critical	*P* Value
	n = 303	n = 88	n = 136	n = 79	
Days from illness onset to hospitalization	9 (7–14)	24 (9–66)	9 (8–15)	9 (7–13)	.24
Days from illness onset to ICU admission	10 (8–12)	NA	NA	10 (8–12)	
Received oxygen therapy before or during follow-up	137 (45)	0 (0)	63 (46)	74 (95)	<.001
Physical measurements[e]					
Maximal HR, beats/min	82 (72–94)	76 (66–81)	84 (76–94)	94 (79–107)	<.001
Maximal RR, breaths/min	20 (16–24)	16 (16–16)	20 (20–24)	25 (20–32)	<.001
Lowest SpO2, %	96 (92–98)	98 (97–99)	96 (93–98)	88 (81–90)	<.001
Highest baseline sadness score[f]					<.001
0–1	125 (41)	40 (45)	44 (32)	41 (52)	
2–5	90 (30)	35 (40)	43 (32)	12 (15)	
6–10	81 (27)	13 (15)	45 (33)	23 (29)	
Missing	7 (2)	0 (0)	4 (3)	3 (4)	
Highest baseline anxiety score[f]					<.001
0–1	131 (43)	48 (55)	43 (32)	40 (51)	
2–5	86 (28)	28 (32)	47 (35)	11 (14)	
6–10	80 (26)	12 (14)	42 (31)	26 (33)	
Missing	6 (2)	0 (0)	4 (3)	2 (3)	
Acute presence of symptom[g]					
Fatigue	243 (80)	71 (81)	108 (79)	64 (81)	.95
Myalgia	156 (51)	49 (56)	76 (56)	31 (39)	.040
Cough	186 (61)	52 (59)	83 (61)	51 (65)	.76
Fever	175 (58)	46 (52)	79 (58)	50 (63)	.35
Dyspnea	173 (57)	34 (39)	83 (61)	56 (71)	<.001
Headache	157 (52)	53 (60)	79 (58)	25 (32)	<.001
Vaccinated at enrollment	0 (0)	0 (0)	0 (0)	0 (0)	NA
Vaccinated during follow-up	217 (72)	68 (78)	93 (68)	56 (72)	.28
Time from illness onset to first vaccination, d	246 (144–361)	197 (130–302)	247 (164–314)	372 (139–393)	.007
Died during follow-up	0	0	0	0	NA
			Study characteristics		
Place of recruitment					<.001
Nonhospital (public health service)	150 (50)	77 (88)	69 (51)	4 (5)	
Hospital	153 (50)	11 (13)	67 (49)	75 (95)	
Type of inclusion					<.001
Prospective	218 (72)	76 (86)	105 (77)	37 (47)	
Retrospective	85 (28)	12 (14)	31 (23)	42 (53)	
Days from illness onset to inclusion in study	12 (6–51)	6 (4–12)	12 (7–33)	40 (14–89)	<.001
Prospective inclusions only	9 (5–14)	6 (4–9)	9 (6–16)	14 (10–18)	<.001
Retrospective inclusions only	85 (73–94)	92 (66–94)	84 (74–92)	88 (73–97)	.56
Follow-up time from enrollment in study	292.0 (194.0–405.0)	292.0 (209.0–402.0)	284.5 (190.5–403.0)	319.0 (136.0–410.0)	.85
LTFU[h]	40	13	19	7	NA

Continuous variables are presented as median (IQR) and compared using the Kruskal-Wallis test; categorical and binary variables presented as No. (%) and compared using the Pearson χ^2 test (or Fisher exact test if n < 5). COVID-19 clinical severity groups defined as follows: mild as having an RR <20/min and SpO_2 on room air >94% at both day 0 and day 7; moderate disease as having an RR of 20–30/min, SpO_2 90%–94%, and/or receiving oxygen therapy at day 0 or day 7; severe disease as having an RR >30/min or SpO_2 <90% at day 0 or day 7; critical disease as requiring ICU admission.

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; HIC, high-income country; HR, heart rate; ICU, intensive care unit; IQR, interquartile range; LMIC, low- or middle-income country; LTFU, loss to follow-up; NA, not applicable; OECD, Organisation for Economic Co-operation and Development; RR, respiratory rate; SpO_2, oxygen saturation; WHO, World Health Organization.

[a]Normal BMI group includes 3 individuals with BMI between 18.0 and 18.5 kg/m^2.

[b]Migration background was based on country of birth of participant and that of their parents and included first- and second-generation migrants.

[c]Other work situation includes unemployed, receiving welfare or benefits, homemaker, student.

[d]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.

[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.

[f]Highest baseline anxiety and sadness scores defined as the highest reported level of anxiety or sadness at D0 and D7 (baseline), subjectively reported on a scale from 0 to 10.

[g]Acute presence of a symptom defined as reporting it during the first 2 weeks after overall illness onset.

[h]LTFU defined as active withdrawal from the study or 2 consecutive no-show appointments despite 3 attempts to establish contact.

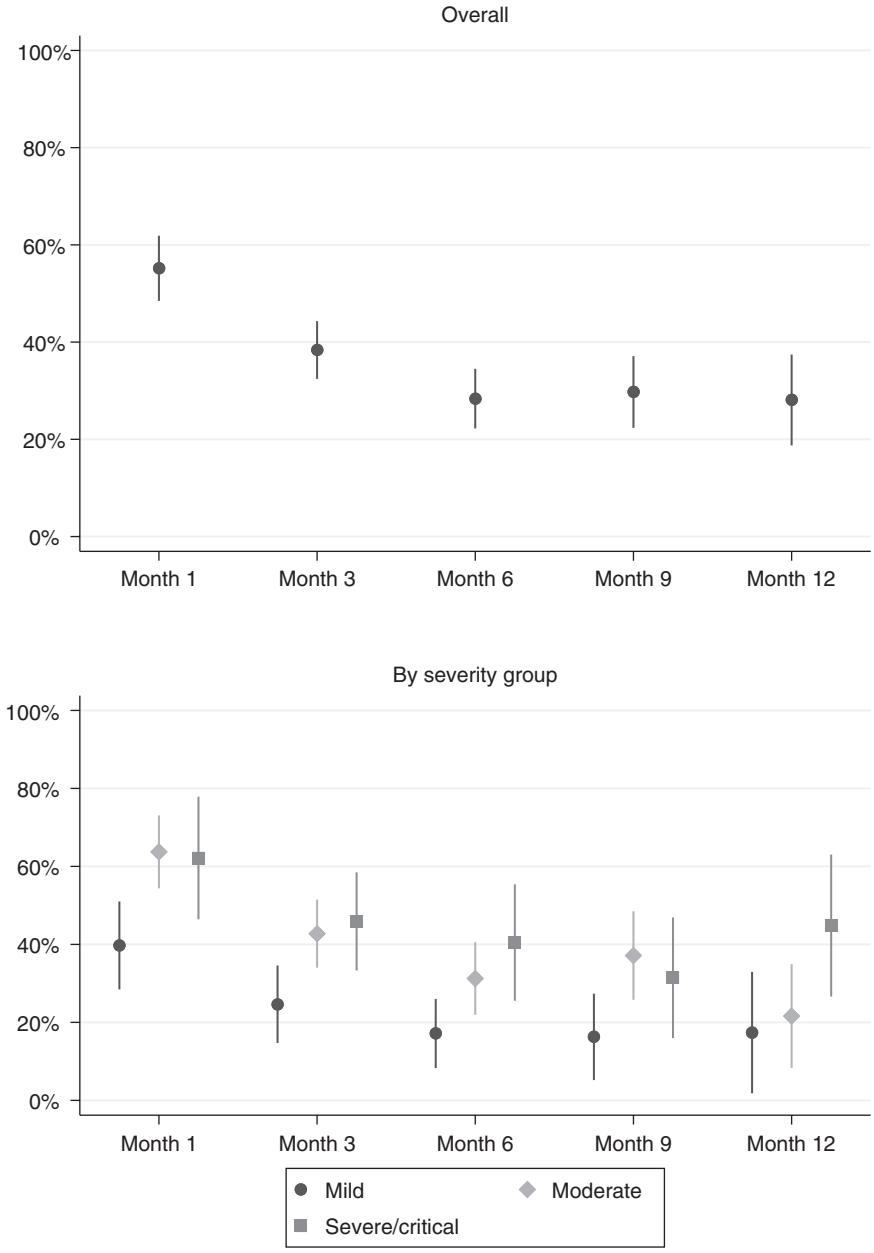

Figure 1. Central dot represents proportion with severe fatigue among those who completed each questionnaire; vertical bars are corresponding 95% CIs for that group. Total sample size differs per month due to varying survey response rates and lengths of follow-up time: Month 1: n = 212, Month 3: n = 258, Month 6: n = 208, Month 9: n = 148, Month 12: n = 89. Severe fatigue defined has a short fatigue questionnaire (SFQ) score ≥ 18.

When redefining the outcome to having chronic fatigue, the effect size of severe/critical COVID-19 became stronger (aOR, 5.18; 95% CI, 1.73 to 15.5; from aOR, 3.51; 95% CI, 1.37 to 8.96; in Model 2; aOR, 5.22; 95% CI, 1.68 to 16.2; from aOR, 3.37; 95% CI, 1.28 to 8.93; in Model 3) with minimal change in the effect size of other covariates (Supplementary Table 3b).

DISCUSSION

This is the first prospective cohort study on clinically severe fatigue (measured using a validated instrument) up to 12 months after illness onset in COVID-19 patients across the full spectrum of COVID-19 severity. The occurrence of severe fatigue in our cohort was high, particularly during the first 6 months after infection. Even after 1 year from COVID-19 disease onset, severe fatigue was reported by 17%, 22%, and 45% of participants with initially mild, moderate, and severe/critical COVID-19 illness, respectively. As these individuals were significantly more likely to take long-term leave compared with those without severe fatigue at month 12, the socio-economic consequences of persistent fatigue following COVID-19 could be substantial. Risk factors for higher fatigue severity during the first year

Table 2. Determinants of Higher Fatigue Severity Over Time (Linear Mixed-Effects Models)[a]

		Multivariable Model 1[a]		Multivariable Model 2[a]		Multivariable Model 3[a]	
	Determinant (Selected a Priori)	aβ Coef. (95% CI)	*P* Value	aβ Coef. (95% CI)	*P* Value	aβ Coef. (95% CI)	*P* Value
	Time since illness onset, mo	−0.35 (−0.45 to −0.25)	<.001	−0.35 (−0.44 to −0.25)	<.001	−0.33 (−0.42 to −0.23)	<.001
Sociodemographic and medical characteristics at illness onset	Age per 10-y increase, y	−0.12 (−0.66 to 0.43)	.590	−0.03 (−0.88 to 0.02)	.173	−0.03 (−0.08 to 0.02)	.174
	Sex		.025		.004		.057
	Male	Ref.		Ref.		Ref.	
	Female	1.90 (0.40 to 3.40)		2.21 (0.78 to 3.64)		1.48 (0.07 to 2.90)	
	BMI group		.021	n.s.	n.s.	n.s.	n.s.
	Normal weight	Ref.		n.s.	n.s.	n.s.	n.s.
	Overweight	2.09 (0.37 to 3.81)		n.s.	n.s.	n.s.	n.s.
	Obese	2.26 (0.31 to 4.20)		n.s.	n.s.	n.s.	n.s.
	No. of high-risk COVID-19 comorbidities at illness onset[b]		.002		.003		.007
	0	Ref.		Ref.		Ref.	
	1	1.41 (−0.53 to 3.35)		1.53 (−0.32 to 3.38)		0.59 (−1.24 to 2.41)	
	2	1.14 (−1.26 to 3.55)		1.16 (−1.16 to 3.49)		0.95 (−1.35 to 3.25)	
	3+	4.91 (2.02 to 7.79)		4.93 (2.12 to 7.75)		4.41 (1.64 to 7.18)	
	Migration background[c]		.008	n.s.	n.s.	n.s.	n.s.
	Dutch	Ref.		n.s.	n.s.	n.s.	n.s.
	Non-Dutch, OECD high-income	1.81 (−0.44 to 4.06)		n.s.	n.s.	n.s.	n.s.
	Non-Dutch, OECD LMIC	2.03 (0.29 to 3.76)		n.s.	n.s.	n.s.	n.s.
Clinical severity	COVID-19 Clinical severity[d]	NA	NA		<.001		.002
	Mild	NA	NA	Ref.		Ref.	
	Moderate	NA	NA	3.37 (1.72 to 5.03)		2.13 (0.48 to 3.79)	
	Severe/critical	NA	NA	4.39 (2.35 to 6.42)		3.17 (1.11 to 5.22)	
Clinical features of COVID-19	Highest baseline sadness score[e]	NA	NA	NA	NA		<.001
	0–1	NA	NA	NA	NA	Ref.	
	2–5	NA	NA	NA	NA	1.00 (−0.65 to 2.65)	
	6–10	NA	NA	NA	NA	3.15 (1.40 to 4.90)	
	Presence of acute dyspnea[f]	NA	NA	NA	NA		.001
	No	NA	NA	NA	NA	Ref.	
	Yes	NA	NA	NA	NA	2.47 (1.01 to 3.93)	

Abbreviations: COVID-19, coronavirus disease 2019; ICU, intensive care unit; NA, not applicable; n.s., not statistically significant; RR, respiratory rate; SpO_2, oxygen saturation; WHO, World Health Organization.

[a]Sequential addition of groups of covariates, described as follows: Model 1: sociodemographic and medical characteristics at illness onset. Model 2: sociodemographic and medical characteristics at illness onset + clinical severity. Model 3: sociodemographic and medical characteristics at illness onset + clinical severity + clinical features of COVID-19.

[b]COVID-related comorbidities are based on the 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.

[c]Migration background was based on country of birth of participant and that of their parents and included first- and second-generation migrants.

[d]Clinical severity groups defined as follows: mild as having an RR <20/min and SpO_2 on room air >94% at both day 0 and day 7; moderate disease as having an RR 20–30/min, SpO_2 90%–94%, and/or receiving oxygen therapy at day 0 or day 7; severe disease as having an RR >30/min or SpO_2 <90% at day 0 or day 7; critical disease as requiring ICU admission.

[e]Highest baseline sadness score defined as the highest reported level of sadness at D0 or D7, subjectively reported on a scale from 0 to 10.

[f]Acute presence of a symptom defined as reporting it during the first 2 weeks after overall illness onset.

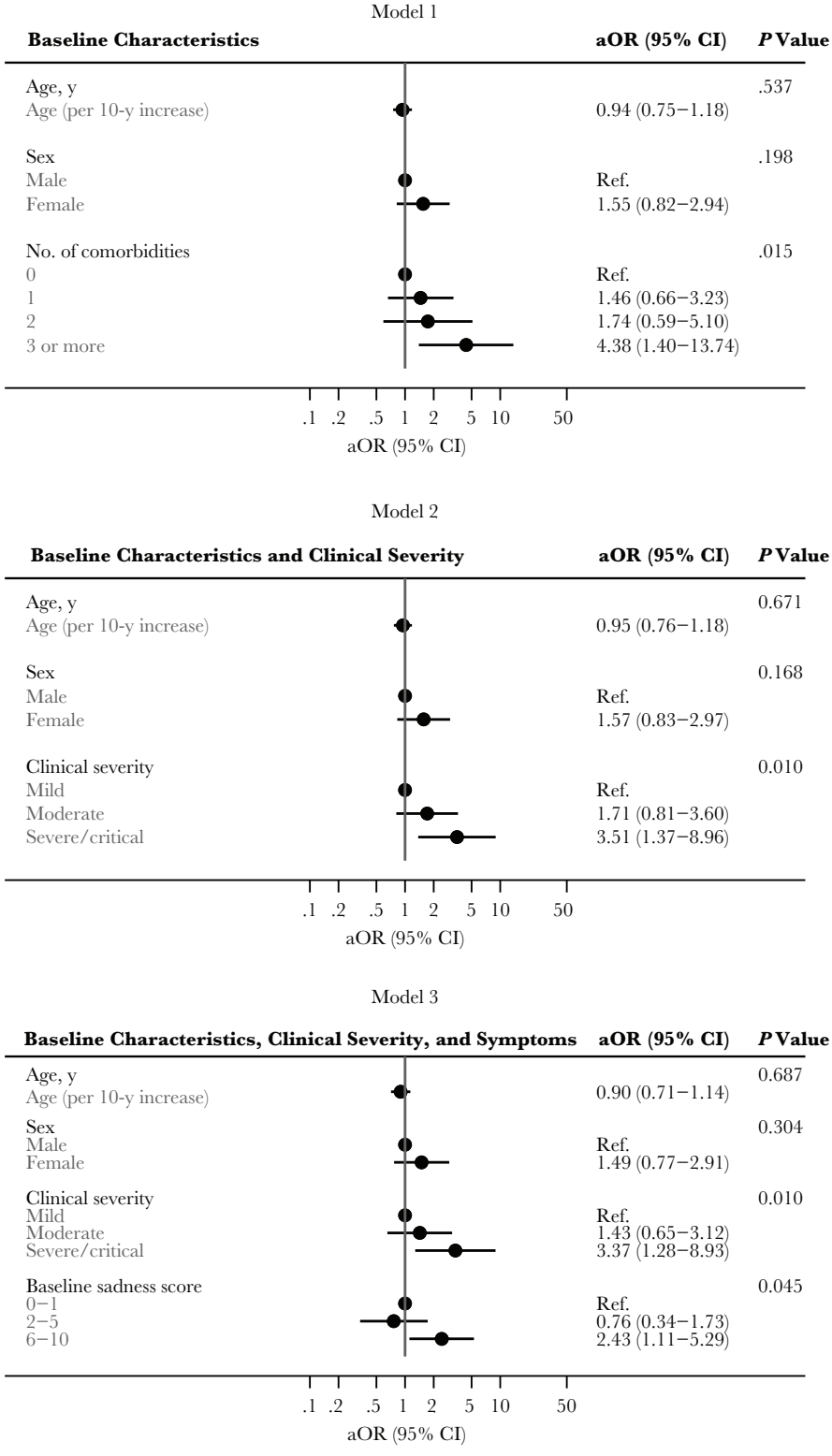

Figure 2. COVID-19 clinical severity defined as follows: mild disease as having a RR <20/min and SpO_2 >94% on room air at both D0 and D7 study visits; moderate disease as having a RR20–30/min and SpO_2 90–94% or receiving oxygen therapy at D0 and/or D7 study visits; severe disease as having a RR >30/min and SpO2 <90% or receiving oxygen therapy at D0 and/or D7 study visits; critical disease as requiring ICU admission as a result of COVID-19 at any point. Highest baseline sadness score defined as the highest reported level of sadness at D0 or D7, subjectively reported on a scale from 0 to 10. Abbreviation: aOR, adjusted odds ratio.

included having multiple comorbidities, more severe COVID-19, acute dyspnea, and a high level of baseline sadness.

Owing to its prospective longitudinal design, our study provides valuable insight into temporal changes in post-COVID-19 fatigue. The proportion of participants with severe fatigue was highest in the moderate and severe/critical groups at all time points. Although a significant decline in fatigue severity was observed between months 0 and 6 after illness onset, measurements stabilized between months 6 and 12, also for those with initially mild COVID-19, suggesting poor prognosis beyond this point. Indeed, among those with mild COVID-19, approximately one-fifth developed persistent severe fatigue. It is not evident whether this proportion differs from the general Dutch population as we lacked an appropriate comparison group [25]. However, as those with mild disease represent the largest proportion of COVID-19 patients globally, millions worldwide may be experiencing severe fatigue after COVID-19. In addition to ongoing efforts to prevent new SARS-CoV-2 infections, identifying effective interventions for persistent severe fatigue that can be readily scaled up should therefore be a research priority.

We identified several risk factors for fatigue severity following SARS-CoV-2 infection, several of which are modifiable and provide scope for risk reduction. First, having multiple comorbidities was an independent risk factor. Previous studies have also reported a relationship between comorbidities and postinfectious fatigue [25], with comorbidities probably both lying on the causal pathway and partly representing preexisting fatigue. These findings add to the multitude of reasons why prevention of noncommunicable diseases, such as cardiovascular disease and diabetes, is crucial for public health worldwide, not only during a pandemic. Dyspnea during the acute phase of infection was also independently associated with fatigue severity. Since many participants with acute dyspnea experience persistent dyspnea as part of PACS [17], the association between dyspnea and fatigue may be a direct consequence of acute respiratory distress syndrome and ongoing reduced functional capacity due to lung tissue damage [26, 27]. Underlying contributing factors including lung pathology should be a focus of future research.

Interestingly, reporting a high level of sadness was identified as an independent risk factor for fatigue severity over time. Explaining this finding is challenging, as fatigue is both a known symptom of depression and, in turn, depression can be a reaction to persistent fatigue [25]. Additionally, other symptoms of depression, such as sleep disorders and concentration problems, have been reported as long-term sequelae of COVID-19 disease [28, 29] and may be associated with severe fatigue. The association between sadness levels and fatigue severity following COVID-19 is not likely explained by preexisting clinical depression as only 18/303 (6%) of our participants reported a previous psychiatric diagnosis.

We did not explore the contribution of underlying biochemical, hormonal, or body system (eg, lung, cardiac, neurological, or psychological) abnormalities to fatigue in our study participants. To date, the pathogenesis of postinfectious fatigue is largely unknown. Several theories have been proposed, which include end-organ damage, ongoing inflammation, changes in skeletal muscle morphology and function, and neurological causes [30]. Others have also described psychological factors, such as cognitive and behavioral responses to acute illness and cultural factors [30]. Regardless of its cause, persistent severe fatigue can have serious consequences for the individual as well as impact health care usage and the economic productivity of a population [31, 32]. Unsurprisingly, the predictors of persistent severe fatigue largely matched the factors associated with fatigue severity over time. Future studies should further elucidate predictors of persistent severe fatigue post-COVID-19 to target active prevention against SARS-CoV-2 infection for those at highest risk for post-COVID-19 fatigue.

Our study has several strengths. Our prospective cohort study follows individuals from disease onset, minimizing the selection bias resulting from individuals self-referring after the onset of persistent fatigue. Furthermore, by including both hospitalized and nonhospitalized patients, we captured the entire spectrum of severity of COVID-19. Another strength is our long follow-up length and use of a validated instrument to assess fatigue [20, 33]. An important limitation of our study is that levels of fatigue pre-COVID-19, for example, due to other chronic illnesses, were unknown. In addition, due to a lack of COVID-negative controls, we cannot infer what proportion of fatigue was directly attributable to SARS-CoV-2 infection, as opposed to a result of lockdown restrictions, coined "pandemic fatigue" [34]. Another limitation is that analysis of the prevalence of, and risk factors for, severe fatigue may be influenced by differential LTFU of participants and missing survey data. The direction of bias in prevalence estimates depends on whether fatigue severity influenced the likelihood to drop out or skip surveys. When comparing the sex, number of comorbidities, clinical severity, and proportion of participants reporting severe fatigue in their earliest completed survey, no difference was found between those who were later lost to follow-up and those who remained in the study. However, those who were LTFU were generally younger than those who remained in active follow-up. Although we cannot rule out that attrition of these younger participants may have resulted in an overexaggeration of severe fatigue prevalence estimates, the lack of difference observed in other baseline variables, notably initial fatigue prevalence, suggests that this retention bias is unlikely to be substantial. Finally, within our cohort, those who did not complete the month 6 survey were more likely to be of non-Dutch than Dutch origin ($P = .005$) (Supplementary Table 1b), and therefore migrant groups were underrepresented in the persistent fatigue analysis.

The occurrence of severe fatigue in our cohort was high, particularly among participants with severe/critical COVID-19. Although a decline in fatigue severity was observed in the first 6 months after illness onset, fatigue severity subsequently stabilized, indicating poor prognosis beyond this point. Participants with severe/critical COVID-19, multiple comorbidities, and high baseline sadness levels are at increased risk of persistent severe fatigue, a condition that may have substantial socio-economic implications. Our findings highlight an urgent need for improved understanding of the causes of persistent severe fatigue following COVID-19 in order to develop effective strategies for prevention.

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Author contributions. P.N. led the Psychosocial Study Group within the RECoVERED cohort study, of which P.N., M.P., H.K., E.M.v.C., A.L., U.D., A.V., and E.W. were key members. For the present study, E.W., A.V., H.K., M.P., and P.N. conceptualized the research question and analyses. E.W., A.V., A.B., and P.N. conducted the formal analysis and data visualisation. E.W. and A.V. drafted the initial manuscript. All authors read a draft of the manuscript and provided feedback, contributed to interpretation of the data, and approved the final manuscript. E.W., A.V., and H.v.W. contributed to the data collection and curation and coordinated the RECoVERED cohort study. G.d.B., M.d.J., and M.P. led the RECOVERED study. G.d.B., M.d.J., M.P., and P.N. secured study financing and medical ethical approval.

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