References

1. Curry SR, Hecker MT, O'Hagan J, et al. Natural history of *Clostridioides difficile* colonization and infection following new acquisition of carriage in healthcare settings: a prospective cohort study. Clin Infect Dis **2023**; 77:77–83.
2. Salamonowicz M, Ociepa T, Frączkiewicz J, et al. Incidence, course, and outcome of Clostridium difficile infection in children with hematological malignancies or undergoing hematopoietic stem cell transplantation. Eur J Clin Microbiol Infect Dis **2018**; 37:1805–12.
3. Mani J, Levy S, Angelova A, et al. Epidemiological and microbiome associations of Clostridioides difficile carriage in infancy and early childhood. Gut Microbes **2023**; 15:2203969.
4. Thomas R, Wong WSW, Saadon R, et al. Gut microbial composition difference between pediatric ALL survivors and siblings. Pediatr Hematol Oncol **2020**; 37: 475–88.
5. Masetti R, Muratore E, Leardini D, et al. Gut microbiome in pediatric acute leukemia: from predisposition to cure. Blood Adv **2021**; 5:4619–29.
6. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis **2018**; 66: e1–e48.

Correspondence: S. K. Hourigan, Clinical Microbiome Unit (CMU), Laboratory of Host Immunity and Microbiome, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Building 50, Rm 5511, 50 South Dr, Bethesda, MD 20892 (Suchitra.hourigan@nih.gov).

Clinical Infectious Diseases® 2024;78(4):1076–8
Published by Oxford University Press on behalf of Infectious Diseases Society of America 2023.

https://doi.org/10.1093/cid/ciad628

Positive Effects of Cognitive-Behavioral Therapy Targeting Severe Fatigue Following COVID-19 Are Sustained Up to 1 Year After Treatment

To the Editor—Recently, our article entitled "Efficacy of Cognitive-Behavioral Therapy Targeting Severe Fatigue Following Coronavirus Disease 2019: Results of a Randomized Controlled Trial" [1] was published in *Clinical Infectious Diseases*. This study demonstrated a beneficial effect of cognitive-behavioral therapy (CBT) in reducing severe fatigue following coronavirus disease 2019 (COVID-19), as compared with care as usual. All secondary outcomes also favored CBT. Positive effects were maintained up to 6 months post-treatment [1].

In this letter, we present the 1 year follow-up outcomes of CBT for post–COVID-19 fatigue. All details on the methods used in this follow-up study are described in the published study protocol [2] and the Supplementary Appendix. In this long-term follow-up study, all 57 patients randomized to CBT were eligible. Of them, 52 participated. For ethical reasons, patients randomized to care as usual were offered CBT and could therefore no longer serve as a control.

The primary outcome was fatigue severity. Secondary outcomes were physical functioning, problems with social functioning, somatic symptom severity, problems concentrating, and proportions of patients being no longer severely fatigued, no longer severely fatigued with a reliable change, and not chronically fatigued. Additionally, for each individual patient, it was calculated whether the change in fatigue severity between 6 months and 1 year post-CBT was reliable and/or clinically significant.

All outcomes at the 4 assessment time points are presented in Table 1. Fatigue severity decreased significantly from baseline to 1 year post-CBT. Problems in social functioning, somatic symptom severity, and problems concentrating also decreased significantly from baseline to 1 year post-CBT. Physical functioning improved significantly.

Levels of fatigue severity, physical functioning, problems with social functioning, somatic symptom severity, and problems concentrating as assessed at 1 year post-CBT did not differ significantly from outcomes at 6 months post-CBT. Cohen's *d* effect sizes from baseline to 1 year post-CBT were moderate to large. Further, proportions of patients being no longer severely fatigued (with or without a reliable change) or not chronically fatigued did not differ statistically significantly between 6 months and 1 year post-CBT. These results indicate that, at the group level, there was no statistically significant further improvement or deterioration.

An analysis of data on fatigue severity at the individual level showed that between 6 months and 1 year of follow-up, 4 patients (8%) reported a reliable and clinically significant deterioration, confirming the stability of the treatment response in most patients.

Our study was the first showing that CBT can be effective in reducing severe fatigue after COVID-19. At long-term follow-up, favorable outcomes following CBT were maintained. The clinical implication of these findings is that, if a patient with severe fatigue following COVID-19 benefits from CBT, it is likely that the favorable outcomes are sustained at least up to 1 year post-treatment. We encourage the replication of these findings in a larger controlled study.

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

Disclaimer. The funders had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Data sharing. The de-identified patient dataset can be made available after publication. Any request to share the data of this study will be considered by the Trial Steering Committee and will need to be approved by the Ethics Committee of the Amsterdam UMC location University of Amsterdam. The meta-dataset is available at https://COVID19initiatives.health-ri.nl/p/Project/27866022694497984. The informed consent form is published with the protocol paper: https://doi.org/10.1186/s13063-021-05569-y.

Financial support. This long-term follow-up of the ReCOVer study was supported by the NKCV Foundation (Nederlands Kenniscentrum Chronische Vermoeidheid). The ReCOVer study was supported by the Netherlands Organization for Health Research and Development (ZonMw: project number 10430012010025, research program COVID-19).

Potential conflicts of interest. F. M. declares funding from the NKCV Foundation. C. P. R. declares grants as a payment to their institution for the present study, EU Horizon 2020 Research and Innovation Framework Programme: Pandemic Preparedness and Response (PANDEM-2); being an unpaid member of the committee "Pandemic Preparedness Plan" of the Royal Netherlands Academy of Arts and Sciences; and an unpaid member of the committee "Long-term effects of

Table 1. Analyses of the Long-term Outcomes of Cognitive-Behavioral Therapy for Post–COVID-19 Fatigue

	Estimated Mean (SE)				Baseline – 1 Year Post-CBT		Six Months Post-CBT – 1 Year Post-CBT
Outcome Measure	Baseline (n = 57)	Directly Post-CBT (n = 56)	Six Months Post-CBT (n = 54)	One Year Post-CBT (n = 52)[a]	*P*-Value Difference	Cohen's *d* Effect Size	*P*-Value Difference
Fatigue severity	47.8 (0.7)	30.9 (1.7)	31.6 (1.7)	33.2 (1.8)	<.001	1.08	.537
Physical functioning	64.7 (2.4)	81.4 (2.2)	78.4 (2.8)	79.7 (3.2)	<.001	0.60	.763
Social functioning	24.5 (1.0)	12.7 (1.3)	12.4 (1.5)	12.9 (1.7)	<.001	0.98	.815
Somatic symptoms	11.4 (0.6)	7.9 (0.7)	8.5 (0.7)	8.5 (0.7)	.002	0.52	.961
Problems concentrating	26.6 (0.7)	18.9 (1.0)	17.9 (1.1)	19.4 (1.2)	<.001	0.85	.381
No longer severely fatigued, n (%)	…	33/56 (59%)	34/54 (63%)	28/52 (54%)	…	…	.342
No longer severely fatigued with a reliable change, n (%)	…	33/56 (59%)	34/54 (63%)	28/52 (54%)	…	…	.342
Not chronically fatigued, n (%)	…	36/56 (64%)	39/54 (72%)	30/52 (58%)	…	…	.150

Abbreviations: CBT, cognitive-behavioral therapy; COVID-19, coronavirus disease 2019; SE, standard error.

[a]n = 51 for the other outcomes besides fatigue.

COVID-19" of the Health Council of the Netherlands. H. K. declares funding for this study by the Netherlands Organization for Health Research and Development (ZonMw: project number 10430012010025, research program COVID-19), with payments made to their institution. H. K. also declares grants from ZonMw to conduct research into long COVID-19 and post-Lyme symptoms, from the Dutch Cancer Society, MS Research, Pfizer, and the NKCV Foundation. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Tanja A. Kuut,[1,2] Fabiola Müller,[1,2] Irene Csorba,[1,2] Annemarie M. J. Braamse,[1,2] Pythia Nieuwkerk,[1,2,3] Chantal P. Rovers,[4] and Hans Knoop[1,2]

[1]Department of Medical Psychology, Amsterdam UMC, University of Amsterdam, 1105 AZ Amsterdam, the Netherlands; [2]Amsterdam Public Health, Amsterdam UMC, University of Amsterdam, 1105 AZ Amsterdam, the Netherlands; [3]Amsterdam Institute for Infection and Immunity, Amsterdam UMC, University of Amsterdam, 1105 AZ Amsterdam, the Netherlands; and [4]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, 6500 HB Nijmegen, the Netherlands

References

1. Kuut TA, Müller F, Csorba I, et al. Efficacy of cognitive-behavioral therapy targeting severe fatigue following coronavirus disease 2019: results of a randomized controlled trial. Clin Infect Dis **2023**; 77:687–95.
2. Kuut TA, Müller F, Aldenkamp A, et al. A randomised controlled trial testing the efficacy of Fit after COVID, a cognitive behavioural therapy targeting severe post-infectious fatigue following COVID-19 (ReCOVer): study protocol. Trials **2021**; 22:867.

Correspondence: H. Knoop, Department of Medical Psychology, J3-213, Amsterdam UMC University of Amsterdam, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands (hans.knoop@amsterdamumc.nl).

Clinical Infectious Diseases® 2024;78(4):1078–9

https://doi.org/10.1093/cid/ciad661

Tetanus Toxoid Antibody Seroprevalence in Japan

To the Editor—I read the report by Dr Bampoe and colleagues on tetanus toxin antibody seroprevalence in the United States with great interest [1]. Similar surveys are conducted in Japan every 5 years to assess the antibody seroprevalence against tetanus toxoid, based on the Immunization Act, and they consistently report prolonged antibody retention over extended periods.

According to the latest report of the National Epidemiological Surveillance for tetanus from the National Institute of Infectious Diseases, in 2018, a total of 1047 individuals in 7 prefectures, ranging from infants to those older than 70 years were surveyed: Hokkaido, Tokyo, Toyama, Fukui, Aichi, Ehime, and Kochi [2]. Tetanus toxin antibody levels were measured using a tetanus antibody measurement kit based on indirect hemagglutination (Kaneka passive agglutination [KPA]). Setting the protective threshold for tetanus onset at 0.01 IU/mL or higher, it was reported that a 93.9% antibody seroprevalence was observed among the participants under 50 years of age who were born after 1968 when tetanus immunization was introduced into the pediatric vaccination program based on the Immunization Act (Table 1).

Conversely, the antibody seroprevalence is notably low at 26.7% for participants aged 50 and older who were born before the initiation of routine vaccinations. Regarding field epidemiology, in 2018, 134 cases of tetanus were reported in Japan under the Infectious Disease Act; a total of 118 cases (88.1%) included patients in this age bracket [3]. Furthermore, a staggering 105 cases (78.4%) were from patients aged 65 and older who were born before 1953, the year the tetanus toxoid vaccine became available in Japan. Separate demographic statistics highlighted 5 cases in 2018 in which tetanus was the cause of death, reaffirming that tetanus remains a preventable infectious disease that can result in fatalities in the modern era. This is despite the fact that the infectious disease incidence trend survey under the Infectious Disease Act does not provide clarity on patient clinical outcomes [4].

Standard medical guidelines advocate for a decennial booster of a tetanus-containing vaccine. However, the adherence should also be higher. Furthermore, after the age of 11 years, the immunization program under the Immunization