

BRIEF CLINICAL REPORT

Cognitive behavioural therapy for severe fatigue following COVID-19 in adolescents: a serial single-case observational study of five consecutively referred patients

Tanja A. Kuut^{1,2}, Fabiola Müller^{1,2}, Annemarie M.J. Braamse^{1,2}, Jan Houtveen^{1,2},
Chantal P. Rovers³ and Hans Knoop^{1,2}

¹Department of Medical Psychology, Amsterdam UMC location, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands, ²Amsterdam Public Health, Amsterdam UMC location, University of Amsterdam, 1105 AZ Amsterdam, The Netherlands and ³Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboud University Medical Center, 6500 HB Nijmegen, The Netherlands

Corresponding author: Hans Knoop; Email: hans.knoop@amsterdamumc.nl

(Received 9 July 2024; revised 9 January 2025; accepted 25 February 2025)

Abstract

Background: Severe fatigue following COVID-19 is a debilitating symptom in adolescents for which no treatment exists currently.

Aims: The aim of this study was to determine the effectiveness and feasibility of cognitive behavioural therapy (CBT) for severe fatigue following COVID-19 in adolescents.

Method: A serial single-case observational design was used. Eligible patients were ≥ 12 and < 18 years old, severely fatigued and ≥ 6 months post-COVID-19. Five patients, consecutively referred by a paediatrician, were included. The primary outcome was a change in fatigue severity, assessed with the fatigue severity subscale of the Checklist Individual Strength, 12 weeks after the start of CBT, tested with a permutation distancing two-phase A-B test. Secondary outcomes were the presence of severe fatigue, difficulty concentrating and impaired physical functioning directly post-CBT as determined with questionnaires using validated cut-off scores. Also, the frequency of post-exertional malaise (PEM) and absence from school directly post-CBT determined with self-report items were evaluated.

Results: All five included patients completed CBT. Twelve weeks after starting CBT for severe post-COVID-19 fatigue, three out of five patients showed a significant reduction in fatigue severity. After CBT, all five patients were no longer severely fatigued. Also, four out of five patients were no longer physically impaired and improved regarding PEM following CBT. All five patients reported no school absence post-CBT and no difficulties concentrating.

Conclusion: This study provides a first indication for the effectiveness and feasibility of CBT among adolescents with post-COVID-19 fatigue.

Keywords: adolescents; chronic fatigue; cognitive behavioural therapy; COVID-19

Introduction

Persisting symptoms after COVID-19 for 3 months or more are referred to as a post-COVID condition or long COVID. Fatigue is among the most prevalent symptoms after COVID-19 in

© The Author(s), 2025. Published by Cambridge University Press on behalf of British Association for Behavioural and Cognitive Psychotherapies. This is an Open Access article, distributed under the terms of the Creative Commons Attribution-NonCommercial licence (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original article is properly cited. The written permission of Cambridge University Press must be obtained prior to any commercial use.

children and adolescents, with varying prevalence rates of 9.7% and 20.2%, respectively, according to two meta-analyses (Lopez-Leon *et al.*, 2022; Zheng *et al.*, 2023). While these prevalence rates are lower than in adults, severe fatigue following COVID-19 is a burdensome symptom that can lead to absence from school, interfere with children's development and therefore has potential impact on the life trajectory of the adolescent. There is currently no evidence-based intervention for severe fatigue in this population.

In adults, a beneficial effect of cognitive behavioural therapy (CBT) in reducing fatigue following COVID-19 in a subgroup of patients was demonstrated in a randomised controlled trial (RCT) (Kuut *et al.*, 2023). In chronic fatigue syndrome (ME/CFS), a syndrome with substantial overlap in symptomatology with long COVID, CBT has also been found effective in reducing severe fatigue in adults and adolescents, with adolescents benefiting most (Albers *et al.*, 2021; Kuut *et al.*, 2024).

The aim of the current study was to investigate whether CBT is also effective for adolescents with severe fatigue following COVID-19.

Method

Study design

A single-case observational design was used. This design can help to better understand for whom and under what circumstances CBT is effective. Included were five patients consecutively referred to a tertiary chronic fatigue treatment centre at the Amsterdam University Medical Center, The Netherlands.

Patients

Eligible patients were referred by a paediatrician after physical examination. They did not have somatic or psychiatric co-morbidity that could explain their fatigue. They were ≥ 12 and < 18 years old and severely fatigued, operationalised as scoring ≥ 40 on the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue) (see Supplementary material). They had a symptomatic, laboratory-confirmed SARS-CoV-2 infection. Fatigue started with the onset of symptoms of COVID-19, as reported by patients and confirmed by their paediatrician. In all patients, fatigue lasted ≥ 6 months since COVID-19 at the time of inclusion.

Measurements

Directly after the intake (pre-CBT) up to 6 weeks after completing CBT, patients completed the CIS-fatigue once per week. During CBT, they also completed daily fatigue assessments. Patients also completed questionnaires before and after CBT assessing physical functioning, difficulty concentrating, post-exertional malaise (PEM) and school absence. All assessments were completed online. Demographic characteristics, and disease- and treatment-related variables were collected from medical records. See Supplementary material for details of the measurements.

Fatigue severity was assessed with the CIS-fatigue (8 items, range 8–56); a higher score indicated more severe fatigue with a cut-off score for severe fatigue of ≥ 40 for adolescents.

Daily fatigue was assessed with one item answered on a 10-point numerical scale, i.e. 'Today I feel . . .', and the fatigue score ranged from 1 ('not tired at all') to 10 ('extremely tired').

Physical functioning was measured with the subscale physical functioning (9 items, range 0–100%) of the Child Health Questionnaire-87; a higher percentage indicated better functioning. The cut-off score for normal functioning is $\geq 85\%$.

Difficulty concentrating was assessed with the subscale concentration of the CIS (CIS-con) (5 items, range 5–35) with a cut-off score of ≥ 18 indicating difficulties concentrating.

The frequency of PEM was assessed using a 4-point Likert scale: (0) not at all; (1) a few times a month; (2) a few times a week; and (3) every day.

The frequency of school absence in the past month due to fatigue was assessed using a 4-point Likert scale: (0) not at all; (1) a few times a month; (2) once a week; and (3) several times a week.

Intervention

CBT for post-COVID-19 fatigue was originally developed for and tested in adult patients with post-COVID-19 fatigue. It is based on a cognitive behavioural model of fatigue, which assumes that COVID-19 triggers fatigue while cognitive behavioural variables contribute to its perpetuation (Hulme *et al.*, 2017). The seven perpetuating factors addressed are (1) a disrupted sleep-wake pattern; (2) unhelpful beliefs about fatigue; (3) a low or unevenly distributed activity level; (4) perceived low social support; (5) problems with psychological processing of COVID-19; (6) fears and worries regarding COVID-19; and (7) poor coping with pain. In CBT for adolescents, parents are actively involved during the treatment. The aims of the therapy take the specific developmental tasks of adolescents into account and return to full-time education is one of the treatment goals (see also Supplementary material).

Statistics

Daily and weekly assessed longitudinal data (time series) were used to evaluate a single-case change in fatigue severity. After graphical inspection for the absence of trends that could distort statistical results, changes in mean scores were tested for each patient with a permutation distancing two-phase A-B test (PDT), a non-parametric test that corrects for dependency of the observations. The A-phase is the period from the start of the assessments to the pre-defined moment an effect of the intervention was expected, i.e. with a lag from the start of CBT. As there were no data regarding this lag yet in this patient population, we hypothesised on the basis of clinical experience an effect on fatigue severity to occur 12 weeks after the start of CBT. The A-phase consists of the pre-CBT assessments until the assessment 12 weeks after start CBT. There was often a waiting period between intake and start of CBT. The B-phase consists of all assessments after the A-phase up to 6 weeks after finishing CBT. A *p*-value of less than .05 was considered statistically significant. Single-case effect sizes, based on Cohen's *d*, were computed (<1.00 small, 1.00–2.49 medium, and ≥ 2.50 large).

If no significant treatment effect was found after 12 weeks, we tested in an explorative analysis each lag between 12 and 20 weeks to explore whether a lag with a significant effect existed.

As secondary outcomes we reported whether the questionnaire scores directly post-CBT fell below the cut-off score for severe fatigue, difficulty concentrating and physical impairment. We evaluated the frequency of PEM and absence from school directly after completing CBT.

Analyses were conducted in R version 4.2.2, using the package *pdtd*.

Results

Characteristics of the patients

From November 2021 to January 2023, six consecutively referred patients were assessed for eligibility and fulfilled our inclusion criteria. One patient refused to participate in the study; five patients were included and completed treatment. One patient (case 3) stopped completing the weekly assessments because she found them too demanding. She continued CBT and completed the post-CBT questionnaires. In one patient (case 4) only 12 observations were collected, making it possible that the PDT did not have sufficient statistical power to detect changes in fatigue. Because only two patients completed the daily fatigue assessments, these results are not presented. The patients were treated by three therapists.

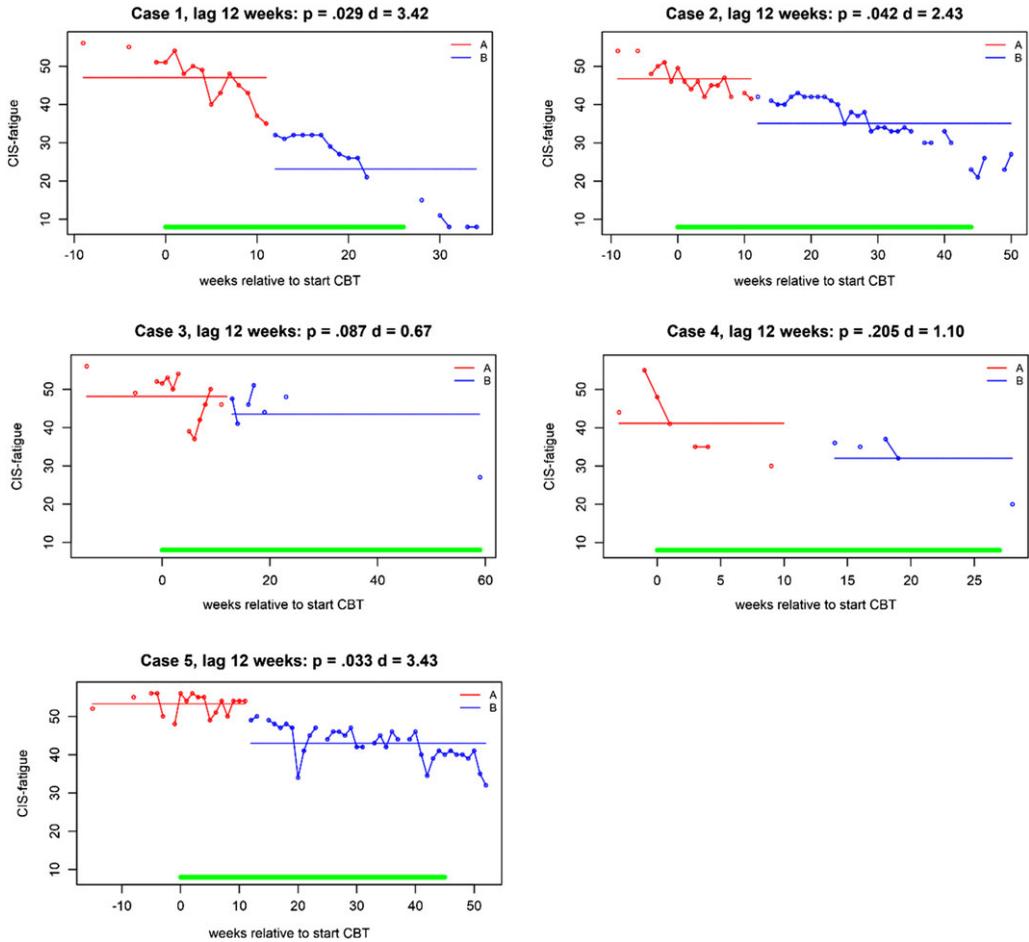


Figure 1. Results 12 weeks after starting CBT. CIS-fatigue is the Fatigue severity subscale of the Checklist Individual Strength. The green line indicates the period of CBT delivery. Cases 1, 2 and 5, show significant improvement in weekly assessed fatigue severity after 12 weeks (primary outcome). Case 3 stopped completing weekly assessments.

All five participants were female, aged 12–17 years old. They were 6–29 months post-COVID-19. They were all severely fatigued, their baseline CIS-fatigue ranged from 44 to 55. They were all physically impaired. They all reported PEM, the frequency ranged from ‘every day’ to ‘few times a week’. They all reported school absence ranging from ‘several times a week’ to ‘few times a month’. Four patients reported difficulties concentrating. The duration of CBT ranged from 27 to 55 weeks. The number of available weekly observations on the CIS-fatigue ranged from 12 to 58.

Changes in fatigue severity during CBT

With a lag of 12 weeks after the start of CBT, the PDT showed a statistically significant reduction of fatigue in three out of five patients. i.e. case 1 ($p = .029$, $d = 3.42$ (large effect)), case 2 ($p = .042$, $d = 2.43$ (medium effect)), and case 5 ($p = .033$, $d = 3.43$ (large effect)); see Fig. 1.

Exploration of lags larger than 12 weeks showed a statistically significant reduction in case 3 of fatigue 18 weeks after the start of CBT ($p = .041$, $d = 0.98$ (small effect)).

Post-CBT assessments

In all participants, the CIS-fatigue score directly post-CBT was below the cut-off score of 40 (range 8–32), indicating that all participants were no longer severely fatigued. Furthermore, in four out of five patients the physical functioning score was >85%, indicating normal physical functioning. The frequency of PEM post-CBT ranged from ‘not at all’ to ‘few times a week’, which was an improvement in four out of five patients. All patients scored below the cut-off score indicative for difficulties with concentrating. Finally, directly post-CBT, all patients reported not having been absent from school (see Table 3 in the Supplementary material).

Discussion

This study provides a first indication for the feasibility and effectiveness of CBT in adolescents with severe post-COVID-19 fatigue. Twelve weeks after starting CBT, three out of five patients showed a significant reduction in fatigue severity. After completing CBT, all five patients were no longer severely fatigued. Also, four out of five patients were no longer physically impaired and improved in the frequency of PEM. All five patients reported no school absence post-CBT and no difficulties concentrating. These results are in line with a previous RCT finding a positive effect of CBT in adults with severe post-COVID-19 fatigue and studies finding a positive effect of CBT in adolescents and adults with ME/CFS (Albers *et al.*, 2021; Kuut *et al.*, 2023; Kuut *et al.*, 2024).

Despite these improvements after CBT, three participants still reported PEM. Perhaps additional interventions are needed to address this and maybe other COVID-19-related symptoms we did not assess in our study.

This study has limitations. The lower internal validity of the observational design, coupled with the small sample size, restricts the ability to draw definitive conclusions about the effectiveness of CBT. Multiple single-case experimental design studies or RCTs are needed to confirm the effectiveness of this intervention. The PDT does not impute missing values, while we had multiple missing observations.

Strengths of this study are that patients were recruited consecutively and all patients completed CBT. The latter suggests that CBT is an acceptable and feasible intervention for at least a subgroup of adolescents with severe post-COVID-19 fatigue.

In sum, this study provides a first indication for the effectiveness and feasibility of CBT among adolescents with post-COVID-19 fatigue.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S1352465825000098>

Data availability statement. Any request to share the data of this study will be considered by the authors and will need to be approved by the ethics committee of the Amsterdam University Medical Center.

Acknowledgements. None.

Author contributions. Tanja Kuut: Conceptualization (equal), Data curation (lead), Formal analysis (equal), Investigation (equal), Methodology (equal), Project administration (equal), Visualization (equal), Writing - original draft (lead); Fabiola Müller: Project administration (equal), Supervision (equal), Writing - review & editing (equal); Annemarie Braamse: Supervision (equal), Writing - review & editing (equal); Jan Houtveen: Formal analysis (lead), Methodology (lead), Software (lead), Writing - review & editing (equal); Chantal Rovers: Funding acquisition (equal), Resources (equal), Writing - review & editing (equal); Hans Knoop: Conceptualization (equal), Funding acquisition (lead), Investigation (equal), Resources (lead), Supervision (lead), Writing - review & editing (lead).

Financial support. This work was partly supported by the Netherlands Organization for Health Research and Development (ZonMw: project number 10430012010025, research program COVID-19). The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report.

Competing interests. All authors have completed the ICMJE uniform disclosure form at <http://www.icmje.org/disclosure-of-interest/> and declare:

F.M. declared funding from NKCVC foundation.

C.R. declared grants as a payment to institution by the present study, EU Horizon 2020 Research and Innovation Framework Programme: Pandemic Preparedness and Response (PANDEM-2) and by Michael J. Fox Foundation: Hidden Sorrows of Covid-19: Impact of Stress on Parkinson's disease Progression, being a Member of the committee 'Pandemic Preparedness Plan' of the Royal Netherlands Academy of Arts and Sciences since April and a Member of the committee 'Long-term effects of COVID-19' of the Health Council of the Netherlands June 2021 to April 2022.

H.K. declared the funding of this study by the Netherlands Organization for Health Research and Development (ZonMw: project number 10430012010025, research program COVID-19), payments were made to the institution. Further, H.K. declared grants from ZonMw to conduct research into long CoVID-19 and post-lyme symptoms, from the Dutch Cancer Society, MS research and NKCVC foundation.

A.B., J.H. and T.K. declare no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical standards. This work was conducted in line with the Ethical Principles of Psychologists and Code of Conduct as set out by the American Psychological Association (2017) and in accordance with the Declaration of Helsinki. The medical ethics committee decided that the Dutch law on Medical Research Involving Human Subjects Act did not apply for this study as CBT for fatigue is part of routine clinical care if ME/CFS is diagnosed in adolescents. All included patients met the 2003 revised U.S. Centers for Disease Control and Prevention case definition of ME/CFS according to their referring paediatrician. Patients and their parents provided written informed consent. The additional assessments for the purpose of this study were considered not demanding by the ethics committee.

References

- Albers, E., Nijhof, L. N., Berkelbach van der Sprenkel, E. E., van de Putte, E. M., Nijhof, S. L., & Knoop, H. (2021). Effectiveness of internet-based cognitive behavior therapy (fatigue in teenagers on the internet) for adolescents with chronic fatigue syndrome in routine clinical care: observational study. *Journal of Medical Internet Research*, 23, e24839. <https://doi.org/10.2196/24839>
- Hulme, K., Hudson, J. L., Rojczyk, P., Little, P., & Moss-Morris, R. (2017). Biopsychosocial risk factors of persistent fatigue after acute infection: a systematic review to inform interventions. *Journal of Psychosomatic Research*, 99, 120–129. <https://doi.org/10.1016/j.jpsychores.2017.06.013>
- Kuut, T. A., Buffart, L. M., Braamse, A. M. J., Csorba, I., Bleijenberg, G., Nieuwkerk, P., Moss-Morris, R., Müller, F., & Knoop, H. (2024). Does the effect of cognitive behavior therapy for chronic fatigue syndrome (ME/CFS) vary by patient characteristics? A systematic review and individual patient data meta-analysis. *Psychological Medicine*, 54, 447–456. <https://doi.org/10.1017/S0033291723003148>
- Kuut, T. A., Müller, F., Csorba, I., Braamse, A., Aldenkamp, A., Appelman, B., Assmann-Schuilwerwe, E., Geerlings, S. E., Gibney, K. B., Kanaan, R. A. A., Mooij-Kalverda, K., Hartman, T. C. O., Pauëlsen, D., Prins, M., Slieker, K., van Vugt, M., Keijmel, S. P., Nieuwkerk, P., Rovers, C. P., & Knoop, H. (2023). Efficacy of cognitive-behavioral therapy targeting severe fatigue following coronavirus disease 2019: results of a randomized controlled trial. *Clinical Infectious Diseases*, 77, 687–695. <https://doi.org/10.1093/cid/ciad257>
- Lopez-Leon, S., Wegman-Ostrosky, T., Ayuzo Del Valle, N. C., Perelman, C., Sepulveda, R., Rebolledo, P. A., Cuapio, A., & Villapol, S. (2022). Long-COVID in children and adolescents: a systematic review and meta-analyses. *Scientific Reports*, 12, 9950. <https://doi.org/10.1038/s41598-022-13495-5>
- Zheng, Y. B., Zeng, N., Yuan, K., Tian, S. S., Yang, Y. B., Gao, N., Chen, X., Zhang, A. Y., Kondratiuk, A. L., Shi, P. P., Zhang, F., Sun, J., Yue, J. L., Lin, X., Shi, L., Lalvani, A., Shi, J., Bao, Y. P., & Lu, L. (2023). Prevalence and risk factor for long COVID in children and adolescents: a meta-analysis and systematic review. *Journal of Infection and Public Health*, 16, 660–672. <https://doi.org/10.1016/j.jiph.2023.03.005>

Cite this article: Kuut TA, Müller F, Braamse AMJ, Houtveen J, Rovers CP, and Knoop H (2025). Cognitive behavioural therapy for severe fatigue following COVID-19 in adolescents: a serial single-case observational study of five consecutively referred patients. *Behavioural and Cognitive Psychotherapy* 1–6. <https://doi.org/10.1017/S1352465825000098>