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Evaluation of an Integrated Multidisciplinary Care Model for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Open-label, Non-randomized Controlled Intervention Study

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A Prospective, Open-label, Non-randomized Controlled Intervention Study

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All authors had access to the data

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Abstract

Background

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a disabling condition with limited treatment options and inadequate healthcare structures worldwide. We assessed the effectiveness of an integrated care model specifically adapted for ME/CFS.

Methods

In this prospective, open-label, non-randomized controlled intervention study conducted at Charité Fatigue Center we enrolled patients with ME/CFS between 2022 and 2023. Participants in the intervention group received multidisciplinary specialist assessment, comprehensive clinical management, and tailored inpatient rehabilitation, while the control group received a single outpatient consultation and a medical report for their primary physician. Primary outcome was change in physical functioning, measured using the SF-36 physical functioning subscale, at 12 months. Secondary outcomes included disability, symptom severity, quality of life, handgrip strength, and steps per day.

Results

89 intervention and 93 control participants were included in the per-protocol analysis. At 12 months, no statistically significant difference in SF-36 physical functioning scores was observed between groups. Secondary outcomes also showed no substantial between-group differences. Inpatient rehabilitation was completed by all participants who initiated it. Most participants reported that rehabilitation was helpful for learning disease management strategies, and for coping better with daily life. Post-rehabilitation Bell Disability Scale scores decreased in 42/94 (45%) and increased in only 13/94 (14%) patients.

Conclusions

The integrated multidisciplinary care model was feasible and associated with high retention but did not improve physical functioning or key secondary outcomes at 12 months. Current rehabilitative and management strategies may be insufficient to alter disease trajectory, underscoring the need for more effective, disease-modifying therapeutic interventions.

Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a chronic, complex, and disabling condition characterized by profound fatigue, exertion intolerance with post-exertional malaise (PEM), cognitive impairment, sleep disturbances, autonomic dysfunction, and pain [1, 2]. ME/CFS affects a large number of patients with a worldwide pre-pandemic prevalence estimated in the range of 0·1% to 0·7% using different case definitions [3, 4]. The condition is triggered by an infection in most cases. Prevalence is expected to have risen significantly in the aftermath of the COVID-19 pandemic, as SARS-CoV-2 has become a major trigger of ME/CFS [5]. The burden on patients is substantial, with quality-of-life scores on average lower than in multiple sclerosis, cancer, or stroke [6]. Employment capacity is severely impaired; over half of patients are unable to work [7].

Despite the high disease burden, healthcare structures for ME/CFS remain inadequate. Diagnostic delays and misdiagnosis are frequent, and few physicians are familiar with the disease [8]. Specialized clinics are available at only a few centers, and treatment options remain limited to supportive and symptomatic interventions. While pacing and energy management are central [9, 10], no disease-modifying therapy has yet been identified [11]. The lack of coordinated care contributes to patient distress, fragmented treatment, and high healthcare costs [12].

Based on current expert recommendations, management of ME/CFS should be supportive and individualized, with a focus on accurate diagnosis, patient education, activity pacing, symptom-oriented treatment, and longitudinal specialist follow-up [3, 11, 13]. However, controlled evaluations of such care models are scarce, and evidence for the effectiveness of rehabilitation in ME/CFS remains weak.

To address these gaps, we conducted and evaluated an integrated, multidisciplinary care approach for patients with ME/CFS, combining specialist diagnostic assessment and

symptomatic therapy including patient education, physiotherapy, relaxation-based interventions, pharmacological treatment and, where appropriate, evaluation of potential workplace accommodations, delivered within a specialized ME/CFS outpatient clinic and an inpatient rehabilitation center. Here we report the results of our prospective controlled study assessing the feasibility and effectiveness of this intervention in improving physical functioning and other key outcome parameters.

Methods

Study design

In this prospective, single-center, two-arm, non-randomized intervention study, conducted at the Charité Fatigue Center, Germany, we recruited 238 patients with ME/CFS between January 2022 and October 2023. Participants in the intervention group received multidisciplinary specialist assessment, comprehensive clinical management, and tailored inpatient rehabilitation, while the control group received a single outpatient consultation and a medical report for their primary physician.

Participants

Eligible patients were adults aged 18 to 65 years who fulfilled the Canadian Consensus Criteria for ME/CFS [14], had a disease duration of less than five years and a Bell Disability Scale score of 30 to 70 [15]. Patients were diagnosed and recruited at the ME/CFS outpatient clinic at the Institute of Medical Immunology or the Neuroimmunology outpatient clinic. Exclusion criteria were relevant comorbidities, pre-existing chronic fatigue before ME/CFS onset, evidence of organ dysfunction, acute or chronic infections, and inability to leave the home because of disease severity. Sex and gender were self-reported by patients, ethnicity was not collected. The study was approved by the institutional ethics committee of Charité

Universitätsmedizin Berlin (EA4/179/21, date of approval: 16.09.2021). All participants provided written informed consent.

Procedures

Allocations to groups was based on pension insurance provider as rehabilitation within this study was only covered for patients insured by the German Pension Insurance DRV-Bund. Due to the nature of the intervention, blinding patients and providers was not possible. Assessments were performed by experienced study physicians and nurses. Questionnaires were self-completed by patients. Participants in the intervention group underwent a standardized multidisciplinary diagnostic assessment including evaluation of comorbidities, physical capacity, and autonomic and endothelial function. Patients received counselling on disease management and symptom-based recommendations and a written report for their primary care physician. Participants subsequently completed a five-week specialized inpatient rehabilitation program at the Bavaria clinic in Kreischa, Germany. At follow-up visits at months 3, 6, and 9 at the Charité outpatient clinic, participants received counselling on individualized disease management. Detailed procedures are provided in the appendix.

Participants in the control group attended a baseline visit, and received the same counselling as the intervention group, without the multidisciplinary diagnostic assessment, and with no specialized inpatient rehabilitation and follow-up visits.

Outcomes

The primary outcome was physical functioning (PF) at 12 months assessed with the PF subscale of the 36-item Short Form Survey (SF-36) [16, 17]. SF-36PF was completed by patients at baseline, at 3, 6, and 12 months. Secondary outcomes included fatigue, disability, health-related quality of life, autonomic symptoms, daytime sleepiness, handgrip strength, physical activity, sick leave, and health-care costs and were assessed at baseline and 12 months. Detailed methods are provided in the appendix. No artificial intelligence tools were used in data collection or analysis.

Statistical Analysis

For descriptive statistics, continuous variables (interval and ratio) are presented as mean and standard deviation (SD), while categorical variables (nominal) are reported as absolute and relative frequencies. For the primary outcome, differences at 12 months were assessed using analysis of covariance (ANCOVA) models. To account for potential confounders, all models were adjusted for baseline values of the respective outcomes, age, sex, BMI, disease duration at baseline, disease severity (Bell scale), and educational level (according to the International Standard Classification of Education. Following the Intention-to-Treat (ITT) and Per-Protocol (PP) principles, different analysis populations were defined. The primary analysis was based on all patients meeting the inclusion criteria who were allocated to the groups (**Population B**), reflecting real-world clinical effectiveness. Additionally, a stricter PP analysis was conducted including only patients who provided evaluable data for the primary outcome (**Population C**).

As sensitivity analyses, the primary outcome was further evaluated using two additional frameworks: a stricter ITT approach including all patients as originally allocated regardless of rehabilitation program initiation (**Population A**), and a broader PP approach including all patients who completed the study, irrespective of the completeness of primary outcome data (**Population P**). Figure 1 depicts these different populations. Missing outcome data in the full analysis set, which served as the basis for the ITT analysis, were imputed using Multiple Imputation by Chained Equations. To ensure convergence, m = 30 complete datasets were generated after 50 iterations. The imputation process utilized Predictive Mean Matching, stratified by treatment group. The imputation model incorporated the ANCOVA covariates as well as baseline as predictors. The goodness of fit and distributional stability of the imputed data were assessed using kernel density plots. If more than half of the data points were missing for a variable, imputation was not performed. Final estimates were obtained by pooling the results from the m imputed data sets using Rubin's rules. Health care cost and sick leave data

were not imputed. Missing values in educational levels were imputed using multinomial logistic regression incorporating all other baseline covariates as predictors.

Estimated average group differences were reported alongside their 95 % confidence intervals (CIs), corresponding two-sided p-values, and the partial eta-squared value as a standardized effect size measure. The two-sided level of significance for the primary outcome was set to α = 0·05. All other analyses were considered exploratory; p-values are reported without adjustment for multiple testing and should be interpreted with caution. The interpretation of the results of secondary outcomes is based on effect size estimates and 95% CIs. All analyses were performed using R version 4.4.2 (with packages tidyverse, mice, and emmeans).

Sample Size Estimation

Limited published data exist regarding structured specialist care for ME/CFS. The landmark study by Brown, Khorana, and Jason [9] reported significantly greater improvement in physical functioning in those patients adhering to pacing (n=17) than in those exceeding these limits (n=27) after 12 months. Owing to the heterogeneity of disease presentations, smaller effect sizes were anticipated. To detect a difference with an effect size of $d \geq 0{\cdot}387$ using a two-sample t-test (80 % power, two-sided α = 0.05), 106 patients per group are required. Accounting for an estimated 10 % dropout rate, a total of 120 patients per group were planned for this study.

Role of the funding source

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

Results

Between January 2022 and October 2023, 247 patients meeting the inclusion criteria were assessed for eligibility. Figure 1 shows patient allocation, exclusion and withdrawals as well as the study population in the CONSORT-style flow diagram. Baseline demographic and disease characteristics for populations B and C are summarized in Table 1. Baseline characteristics were comparable between the intervention and control groups.

Analyses of primary outcome: SF-36 Physical Functioning

Table 2 presents the results of SF-36PF for populations B (ITT) and C (PP) as well as for subgroups. Figure 2 shows the distribution of PF values for the control and the intervention group at baseline and at 12 months for population B (ITT). The mean SF-36PF score at baseline was 40·4 in both cohorts. At month 12, the intervention group reported lower (worse) SF-36PF than the control group. The adjusted difference of −3·9 points was not statistically significant, favored the control group slightly, and remained below the estimated minimal clinically important difference (MCID) of 10 points – a threshold consistent with ME/CFS literature [16, 18] literature. Per-protocol results (population C) were similar, with an adjusted difference of −1·9 points (95% CI: −8·2 to 4·5, p = 0·564).

Sensitivity Analyses

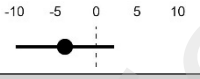
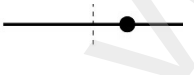
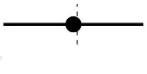
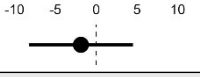
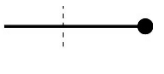
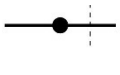
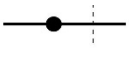
To evaluate the robustness of these findings, sensitivity analyses were performed using populations A and P. As detailed in the Appendix, supplementary Table 2B, these analyses consistently yielded negative point estimates, mirroring the primary results. Adjusted differences were −4·1 points (95% CI: −9·5 to 1·2) in population A and −3·2 points (95% CI: −9·3 to 2·9) in population P. These checks confirmed both the marginal effect in favor of the control group and the statistical uncertainty of the primary analysis, with all 95% CIs encompassing zero.

Table 1: Baseline characteristics for populations B (ITT) and C (PP).

Baseline Characteristics (population B)	**Control N = 100**	**Intervention N = 97**	**Total N = 197**
Patient Characteristics			
Age [Years], Mean (SD)	39·3 (11·1)	44·0 (9·5)	41·6 (10·5)
Body Mass Index [kg/m^2], Mean (SD)	25·0 (5·0)	25·2 (5·3)	25·1 (5·1)
Sex, N (%)			
Female	83 (83·0%)	86 (88·7%)	169 (85·8%)
Male	15 (16·1 %)	9 (10·1 %)	24 (13·2 %)
Disease Characteristics			
Bell Severity scale, Mean (SD)	36·5 (7·8)	36·8 (7·6)	36·6 (7·7)
Disease duration (months), Mean (SD)	21·1 (14·0)	17·0 (9·3)	19·1 (12·1)
Trigger, N (%)			
COVID-19	77 (78·6 %)	78 (80·4 %)	155 (79·5 %)
Epstein-Barr-Virus	5 (5·1 %)	2 (2·1 %)	7 (3·6 %)
Other respiratory tract infections [1]	9 (9·2 %)	10 (10·3 %)	19 (9·7 %)
Other infections [2]	3 (3·1 %)	2 (2·1 %)	5 (2·6 %)
No infection [3]	4 (4·1 %)	5 (5·2 %)	9 (4·6 %)
Not known, not reported	2	0	2
Baseline Characteristics (population C)	**Control N = 93**	**Intervention N = 89**	**Total N = 182**
Patient Characteristics			
Age [Years], Mean (SD)	39·3 (10·9)	44·4 (10·9)	41·8 (10·4)
Body Mass Index [kg/m^2], Mean (SD)	25·0 (4·9)	25·4 (5·5)	25·2 (5·2)
Sex, N (%)			
Female	78 (83·9 %)	80 (89·9 %)	158 (86·8 %)
Male	15 (16·1 %)	9 (10·1 %)	24 (13·2 %)
Disease Characteristics			
Bell Severity scale, Mean (SD)	36·8 (8·0)	36·5 (7·3)	36·6 (7·6)
Disease duration (months), Mean (SD)	21·1 (14·1)	16·9 (9·3)	19·0 (12·2)
Trigger, N (%)			
COVID-19	71 (78·0 %)	70 (78·7 %)	141 (77·5 %)
Epstein-Barr-Virus	5 (5·5 %)	2 (2·2 %)	7 (3·8 %)
Other respiratory tract infections [1]	8 (8·8 %)	10 (11·2 %)	18 (9·9 %)
Other infections [2]	3 (3·3 %)	2 (2·2 %)	5 (2·7 %)
No infection [3]	4 (4·4 %)	5 (5·6 %)	9 (4·9 %)
Not known, not reported	2	0	2

SD: standard deviation, N: absolute frequency. [1] pneumonia, bronchitis, sinusitis, influenza, and others. [2] meningitis, pyelonephritis, borreliosis, herpes simplex, cytomegalovirus. [3] vaccination, physical exertion.

Table 2: Descriptive and model-based estimates of primary outcome and subgroup analysis. Results are displayed for populations B (ITT) and C (PP).

Physical Function (SF-36)[score]		Control		Intervention		Adjusted Difference [a, b] [95-% Confidence Interval]
		N	Mean (SD)	N	Mean (SD)	
Population B	**Overall**					
	BL	99	40·4 (19·2)	94	40·4 (18·5)	
	M12	94	41·8 (25·9)	92	36·0 (20.6)	 -3·9 [-9·9; 2·2] η^2 = 0·008 P = 0·211
	By Sex (η^2 = 0.006)					
	Men BL	17	43·5 (19·5)	11	45·0 (17·5)	
	Men M12	15	45·3 (27·3)	9	51·1 (24·2)	 4·1 [-11·7; 20·0] P = 0·604
	Women BL	82	39·7 (19·2)	83	39·8 (18·7)	
	Women M12	79	41·1 (25·7)	83	34·4 (19·4)	 -5·2 [-11·7; 1·3] P = 0·115
	By Disease Severity (η^2 = 0.006)					
	Bell = 30 BL	51	29·5 (15·5)	44	32·7 (16·7)	
	Bell = 30 M12	46	32·5 (24·2)	43	32·2 (19·6)	 -0·5 [-9·0; 8·1] P = 0·915
	Bell ≥ 40 BL	48	51·9 (15·9)	50	47·2 (17·6)	
	Bell ≥ 40 M12	48	50·7 (24·4)	49	39·4 (21·1)	 -6·9 [-15·3; 1·4] P = 0·101
Population C	**Overall**					
	BL	93	41·6 (18·7)	89	40·0 (18·3)	
	M12	93	41·6 (25·9)	89	36·6 (20·3)	 -1·9 [-8·2; 4·5] η^2 = 0·002 P = 0·564
	By Sex (η^2 = 0.012)					
	Men BL	15	46·7 (27·3)	9	42·8 (13·9)	
	Men M12	15	45·3 (27·3)	9	51·1 (24·2)	 8·2 [-10·0; 26·3] P = 0·376
	Women BL	78	40·6 (18·7)	80	39·7 (18·7)	
	Women M12	78	40·9 (25·8)	80	35·2 (19·4)	 -3·5 [-10·5; 3·5] P = 0·329
	By Disease severity (η^2 = 0.008)					
	Bell = 30 BL	46	30·4 (14·9)	42	31·9 (15·2)	
	Bell = 30 M12	46	32·5 (24·2)	42	33·0 (19·2)	 0·4 [-9·0; 9·8] P = 0·932
	Bell ≥ 40 BL	47	52·6 (15·3)	47	47·2 (17·9)	
	Bell ≥ 40 M12	47	50·5 (24·6)	47	40·3 (20·9)	 -4·1 [-13·2; 5·0] P = 0·372

N: number of non-missing values, SD: standard deviation, BL: baseline, M12: month 12. [a] Adjusted for baseline, age, BMI, sex, disease duration, disease severity, and education (ISCED). [b] Results were pooled across m = 30 multiple imputed data sets.

Subgroup analyses

Subgroup analyses were conducted in populations B (ITT) and C (PP) to investigate potential heterogeneity of treatment effects across the primary outcome. Subgroup analyses (table 2) revealed heterogeneous intervention effects across sex and baseline severity, although results lacked statistical robustness due to wide confidence intervals. Among males, a positive intervention effect was observed, whereas females showed a marginal negative effect. When stratified by clinical severity, differences were negligible for more severely affected. Conversely, less severely affected patients (Bell score ≥ 40) exhibited a slight negative intervention. (table 2)

Analyses of secondary outcomes

Tables 3a and b summarize the results for the secondary outcomes for populations B (ITT) and C (PP). At baseline, both cohorts were comparable across most measures. At 12 months, the intervention group did not demonstrate clinically relevant advantages over the control group across physical, psychological, or health economic metrics. These findings remained consistent across populations A and P (data not shown).

Contrary to the hypothesized benefits, the intervention group reported higher levels of disability on the Bell scale. The adjusted mean difference favored the control group by -4·4 points. Handgrip strength also moderately favored the control group. No meaningful differences were observed for daily step counts or daytime sleepiness.

Fatigue and autonomic dysfunction were similar between groups at 12 months with little change from baseline. Small differences were observed in selected SF-36 domains at 12 months, with marginally lower scores in social functioning and general health in the intervention group. There was a modest improvement from month 0 to 12 in the emotional role functioning in the intervention group and in general health in both groups.

Table 3a: Descriptive and model-based estimates of secondary outcomes. Population B (ITT)

Secondary Outcomes (Pop. B)	Control (n = 93)		Intervention (n = 89)		Difference [95-% Confidence Interval]	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted [a, b]
COMPASS-31 Total Score						
Baseline	93	40·3 (14·0)	83	38·6 (15·3)		
Month 12	87	39·4 (14·4)	87	39·7 (14·8)	0·4 [-4·0; 4·7] η^2 < 0·001 P = 0·870	-1·4 [-5·1; 2·4] η^2 = 0·003 P = 0·470
Chalder Total Score						
Baseline	95	27·9 (3·5)	93	27·8 (3·0)		
Month 12	94	25·8 (4·5)	93	26·0 (4·9)	0·2 [-1·2; 1·6] η^2 < 0·001 P = 0·769	-0·2 [-1·5; 1·1] η^2 < 0·001 P = 0·796
Bell Disability Scale						
Baseline	100	36·5 (7·8)	97	36·8 (7·2)		
Month 12	95	37·9 (16·0)	94	33·0 (9·5)	-4·9 [-8·7; -1·1] η^2 = 0·034 P = 0·011	-4·4 [-8·1; -0·6] η^2 = 0·029 P = 0·022
Hand Grip Strength (Fmax in First Session)						
Baseline	100	20·7 (9·6)	97	20·4 (8·9)		
Month 12	89	20·1 (9·7)	89	16·7 (9·5)	-3·4 [-6·2; -0·6] η^2 = 0·031 P = 0·018	-2·5 [-4·6; -0·5] η^2 = 0·033 P = 0·014
Step Count						
Baseline	84	5113 (2685)	84	4643 (2463)		
Month 12	58	4421 (2697)	47	4558 (2880)	139 [-945; 1219] η^2 < 0·001 P = 0·802	149 [-648; 946] η^2 = 0·002 P = 0·711
Sick Leave[c]						
Month 3-12	25	131 (124)	21	175 (103)	44 [-26; 112] η^2 = 0·036 P = 0·209	11 [-64; 86] η^2 = 0·002 P = 0·771
Health Care Costs[c,d]						
Month 3-12	25	432 (728) 219 (123 - 361)	21	664 (922) 400 (226 - 649)	50.6 % [-16·9; 173·0] η^2 = 0·042 P = 0·172	35·1 % [-33·3; 173·8] η^2 = 0·019 P = 0·393
ESS						
Baseline	92	10·2 (5·2)	92	10·2 (5·4)		
Month 12	93	9·6 (5·5)	94	9·7 (5·7)	0·1 [-1·5; 1·7] η^2 < 0·001 P = 0·882	-0·5 [-1·6; 0·6] η^2 = 0·004 P = 0·383
PHQ-9						
Baseline	98	13·2 (4·7)	92	12·9 (4·1)		
Month 12	94	11·4 (4·9)	94	11·9 (4·3)	0·5 [-0·9; 1·8] η^2 = 0·003 P = 0·491	-0·0 [-1·1; 1·1] η^2 < 0·001 P = 0·987
EQ-5D-5L						
Baseline	99	0·46 (0·25)	89	0·48 (0·25)		
Month 12	95	0·51 (0·29)	94	0·49 (0·26)	-0·02 [-0·10; 0·05] η^2 = 0·002 P = 0·550	-0·01 [-0·09; 0·07] η^2 < 0·001 P = 0·758
SF-36 (Social Functioning)						
Baseline	97	25·5 (19·8)	96	23·6 (18·7)		
Month 12	89	32·6 (26·8)	93	22·6 (21·7)	-10·0 [-17·1; -2·9] η^2 = 0·041 P = 0·006	-6·9 [-13·7; -0·1] η^2 = 0·022 P = 0·046
SF-36 (Health Change)						
Baseline	100	25·5 (29·9)	96	20·6 (28·3)		
Month 12	94	53·2 (28·7)	93	42·5 (42·5)	-10·7 [-18·6; -2·9] η^2 = 0·038 P = 0·008	-9·1 [-17·3; -0·9] η^2 = 0·026 P = 0·031
SF-36 (Role Limitations Due to Emotional Problems)						
Baseline	99	66·0 (43·6)	95	62·5 (62·5)		
Month 12	92	69·2 (43·7)	94	75·2 (40·6)	6·0 [-6·2; 18·2] η^2 = 0·005 P = 0·335	12·1 [1·6; 22·7] η^2 = 0·028 P = 0·024

Table 3b: Descriptive and model-based estimates of secondary outcomes. Population C (PP)

Secondary Outcomes (Pop. C)	Control (n = 93)		Intervention (n = 89)		Difference [95-% Confidence Interval]	
	n	Mean (SD)	n	Mean (SD)	Unadjusted	Adjusted [a, b]
COMPASS-31 Total Score						
Baseline	86	39·3 (13·5)	77	38·1 (15·2)		
Month 12	95	39·7 (13·9)	82	38·9 (14·5)	-0·7 [-5·1; 3·6] η^2 < 0·001 P = 0·737	-0·9 [-5·0; 3·2] η^2 = 0·001 P = 0·656
Chalder Total Score						
Baseline	89	27·7 (3·5)	86	27·7 (2·9)		
Month 12	93	25·9 (4·5)	88	25·9 (4·9)	0·0 [-1·4; 1·4] η^2 < 0·001 P = 0·995	0·0 [-1·4; 1·4] η^2 < 0·001 P = 0·995
Bell Disability Scale						
Baseline	93	36·8 (8·0)	89	36·5 (7·2)		
Month 12	93	38·0 (16·1)	89	33·1 (9·5)	-4·8 [-8·7; -0·9] η^2 = 0·032 P = 0·015	-3·7 [-7·5; 0·1] η^2 = 0·011 P = 0·058
Hand Grip Strength (Fmax in First Session)						
Baseline	93	20·9 (9·8)	89	20·2 (9·0)		
Month 12	85	20·3 (9·7)	83	16·8 (9·4)	-3·4 [-6·4; -0·5] η^2 = 0·032 P = 0·021	-1·9 [-3·9; 0·1] η^2 = 0·021 P = 0·065
Step Count						
Baseline	88	5053 (2648)	91	4680 (2560)		
Month 12	62	4304 (2685)	50	4655 (2876)	352 [-693; 1396] η^2 = 0·004 P = 0·506	459 [-3186; 2268] η^2 = 0·005 P = 0·735
Sick Leave [c]						
Month 3-12	21	125 (125)	21	184 (98)	60 [-12; 130] η^2 = 0·068 P = 0·100	42 [-40; 123] η^2 = 0·032 P = 0·301
Health Care Costs [c,d]						
Month 3-12	20	471 (789) 219 (123 - 465)	21	662 (946) 378 (222 - 594)	39.5 % [-27·4; 168·0] η^2 = 0·027 P = 0·309	3.5 % [-52·3; 124·4] η^2 < 0·001 P = 0·928
ESS						
Baseline	85	9·9 (5·0)	86	10·2 (5·4)		
Month 12	91	9·6 (5·4)	89	9·5 (5·6)	-0·1 [-1·8; 1·5] η^2 < 0·001 P = 0·861	-0·7 [-1·9; 0·5] η^2 = 0·009 P = 0·221
PHQ-9						
Baseline	91	12·8 (4·3)	86	12·9 (4·2)		
Month 12	92	11·4 (4·9)	89	11·9 (4·3)	0·5 [-0·9; 1·8] η^2 = 0·002 P = 0·513	-0·1 [-1·3; 1·0] η^2 < 0·001 P = 0·806
EQ-5D-5L						
Baseline	92	0·47 (0·25)	82	0·47 (0·24)		
Month 12	93	0·51 (0·29)	89	0·49 (0·26)	-0·01 [-0·09; 0·07] η^2 < 0·001 P = 0·742	0·02 [-0·07; 0·10] η^2 = 0·001 P = 0·684
SF-36 (Social Functioning)						
Baseline	90	26·5 (19·7)	89	23·6 (18·7)		
Month 12	89	32·6 (26·8)	88	21·9 (20·6)	-10·7 [-17·8; -3·6] η^2 = 0·048 P = 0·003	-7·9 [-15·1; -0·8] η^2 = 0·029 P = 0·029
SF-36 (Health Change)						
Baseline	93	26·6 (30·6)	89	19·1 (28·0)		
Month 12	93	53·0 (28·8)	89	43·3 (25·8)	-9·7 [-17·7; -1·7] η^2 = 0·031 P = 0·018	-7·3 [-15·6; 1·0] η^2 = 0·017 P = 0·086
SF-36 (Role Limitations Due to Emotional Problems)						
Baseline	92	68·8 (42·2)	88	61·0 (44·1)		
Month 12	91	68·9 (43·8)	89	76·4 (40·0)	7·5 [-4·8; 19·9] η^2 = 0·031 P = 0·230	14·6 [3·8; 25·4] η^2 = 0·040 P = 0·009

N: number of non-missing values, SD: standard deviation.
[a] Adjusted for baseline, age, sex, BMI, disease duration, disease severity and educational level.
[b] Reported differences, partial η^2, and P-values present the pooled results from m = 30 multiple imputed datasets.
[c] Only for BKK-insured patients.
[d] In addition to the mean and standard deviation, the median and interquartile range are also shown. Reported differences, partial η^2, and P-values represent percentage changes, estimated using a log-linear regression model.

Rehabilitation experience

All 97 patients were able to complete the five-week rehabilitation program. 55/72 (76%) patients reported that rehabilitation was helpful for learning disease and symptom management strategies and 54/73 (74%) for better coping with daily life (Figure 3A). However, most patients also reported a temporary worsening either due to the travel to the rehabilitation facility or due to participation in the rehabilitation program itself. Overall, 23% of patients reported that their health improved as a result of rehabilitation. At the post-rehabilitation visit the Bell scale was lower in 45% of patients and higher in only 14% compared with baseline as shown in Figure 3B.

Adverse events

No serious adverse events attributable to the intervention were reported. Most patients reported transient symptom exacerbation during rehabilitation.

Discussion

In this prospective, open-label, non-randomized controlled intervention study, we found that a multidisciplinary integrative care model for ME/CFS, although feasible and with high retention, did not result in clinical meaningful improvements in physical functioning or the other outcome parameters at 12 months. Our findings highlight the challenges of improving outcomes in ME/CFS within currently available management strategies.

Our results add to the limited body of research on structured care models for ME/CFS. Previous studies have indicated that pacing and energy management can lead to improvement

in physical functioning and fatigue [9, 10]. In our study, pacing constituted a central recommendation for both groups, but did not result in improvements in functional ability or symptom severity. Thus, the absence of measurable improvement in either group suggests that pacing may contribute to disease stabilization, but is unlikely to be sufficient to improve clinical outcomes in the majority of patients. These findings are consistent with expert recommendations, emphasizing symptomatic therapy and disease stabilization rather than recovery as a realistic goal (2, 11, 13).

Earlier trials of behavioral and rehabilitative approaches, including cognitive behavioral therapy and graded exercise therapy, have reported modest benefits [19]. However, these findings have been strongly contested due to methodological concerns and patient reports of harm, particularly in relation to PEM [20]. Guidelines from the National Institute for Health and Care Excellence (NICE) recommend pacing and energy management as the core of care, while discouraging interventions that risk symptom exacerbation (13).

Although most patients reported that the rehabilitation helped them learning disease management strategies and cope better with the disease in daily life, only 23% reported that their condition had improved. In our study, the rehabilitation concept was specifically tailored to the needs of ME/CFS patients, an approach that is not typically implemented in standard rehabilitation programs. Given the risk of PEM which may be triggered already by travel to the rehabilitation clinic and the general exertion involved, the value of rehabilitation for patients with ME/CFS should be critically re-evaluated. Even when stratifying patients by a Bell score of 30 or greater, no meaningful difference in disease course at month 12 was observed. In particular, patients with a Bell score of 30 or below should not be required to undergo rehabilitation. This is especially relevant given that participation in a rehabilitation program is often a prerequisite for eligibility for disability pension in Germany.

The study also underscores the urgent need for disease-modifying therapies and controlled clinical trials. Growing evidence suggests that ME/CFS is underpinned by immune

dysregulation, including autoantibody-mediated mechanisms and low-level inflammation, as well as autonomic and endothelial dysfunction [21].

Strengths of our study include the relatively large sample size, the prospective and controlled design, and comprehensive assessment of clinical, functional, and patient-reported outcomes. Limitations include the open-label design, which could introduce bias, the high number of early drop-outs in the intervention group, and the restriction to patients with disease duration less than five years, which may limit generalizability. The absence of improvement across both subjective and objective outcomes suggests, however, that the open-label design is unlikely to have substantially influenced the overall findings. In addition, although patients in the intervention group were seen repeatedly at the ME/CFS clinic, three-month follow-up intervals were most likely insufficient to allow for optimized individualized symptomatic treatment. Further limitations include missing data across several outcomes and accelerometer data that were deemed to be of insufficient quality.

Conclusions

This two-arm controlled study demonstrates that an integrated multidisciplinary care model for ME/CFS, although feasible and associated with high retention, did not improve physical functioning or other outcomes over 12 months. While supportive management strategies such as pacing and symptom-oriented care may contribute to disease stabilization, they appear insufficient to achieve clinically meaningful improvement in the majority of patients. Our findings question the clinical value of current rehabilitation in ME/CFS, even when specifically adapted to the disease, particularly for severely affected patients. These findings have important implications for clinical practice and health policy, especially in settings where participation in rehabilitation is linked to social or disability benefits. Our data suggest that such requirements should be carefully reconsidered to avoid potential harm and unnecessary burden for patients. Overall, these results underscore the urgent need for mechanism-based

therapeutic approaches and well-controlled clinical trials aimed at developing disease-modifying treatments for ME/CFS.

Data sharing:

According to the protocol approved by the Ethics Committee, individual participant data cannot be shared with third parties. Protocol and statistical analysis plan may be made available upon request to the corresponding author. The data dictionary and derived data may be made available upon reasonable request to the corresponding author, subject to approval by the study investigators. Requests should be sent to the corresponding author at claudia.kedor@charite.de.

Trial registration: DRKS00026960

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Figures

Figure 1: CONSORT-style flow diagram of the study path

Figure 2: SF-36 Physical Functioning at baseline and at 12 months by group (population B)

Figure 3: Patient-reported rehabilitation experience and changes in functional status

(A) Patient-reported rehabilitation outcomes (n = 72-74). **(B)** Change in functional status assessed by the Bell Disability Scale from the pre- to post-rehabilitation visit. n = number of patients, total n=94.

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Title Page

Evaluation of an Integrated Multidisciplinary Care Model for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Open-label, Non-randomized Controlled Intervention Study

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Evaluation of an Integrated Multidisciplinary Care Model for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Open-label, Non-randomized Controlled Intervention Study

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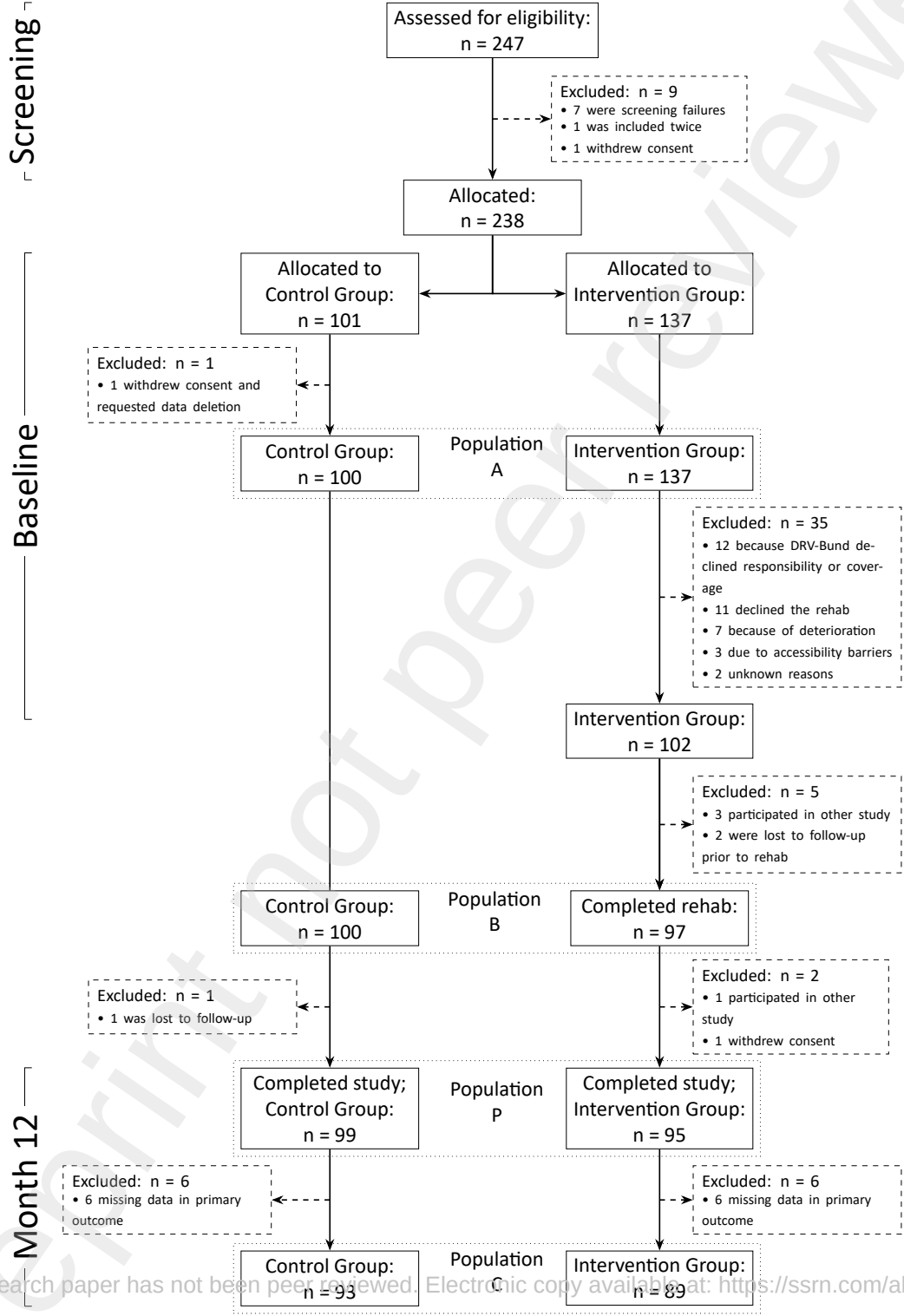
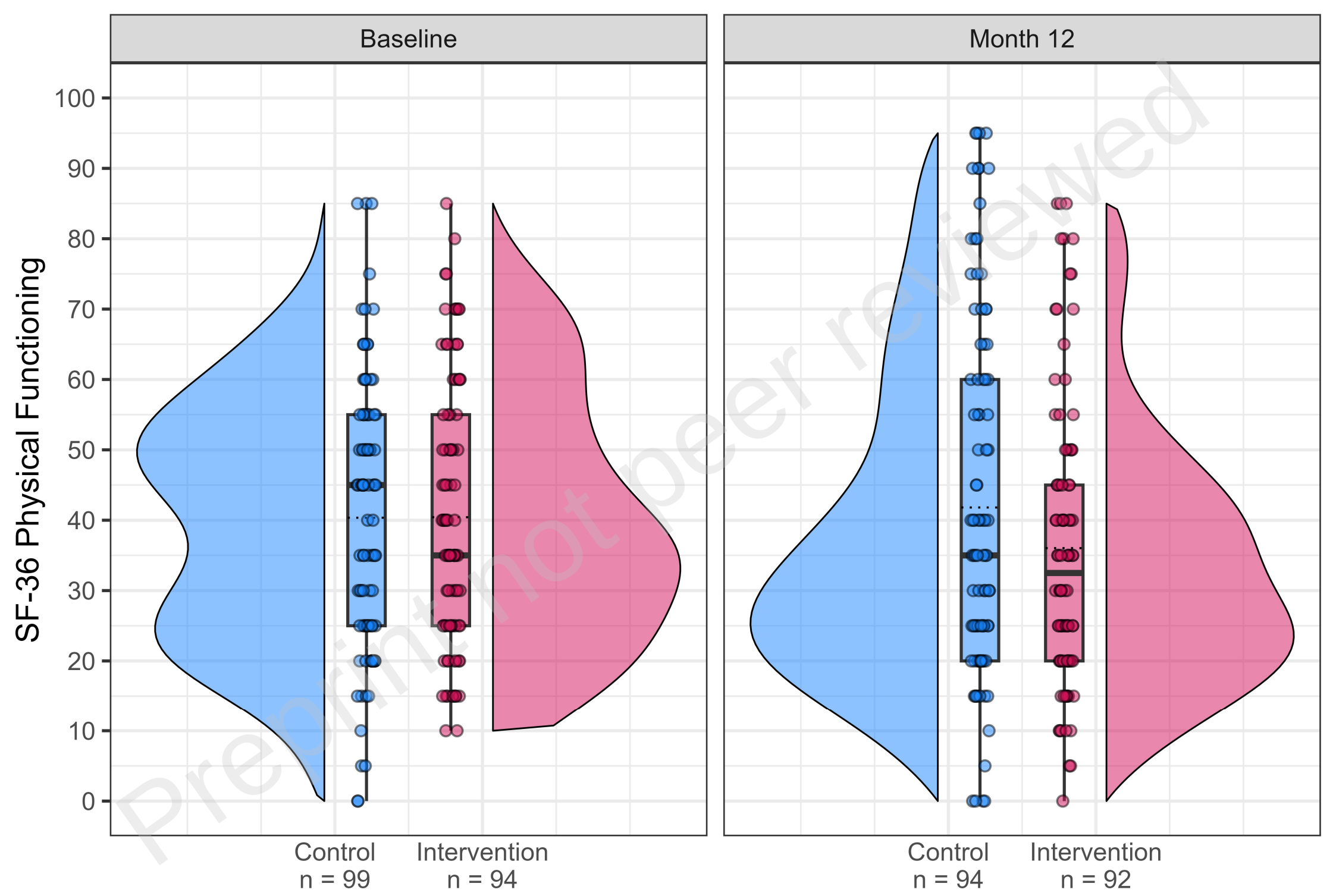
Contributors: Conceptualization: CSch, CKP, KW, PT, FP, CV, WD, NJ, TT, JMP, BW, AR, IH, ML; Methodology: CSch, CKP, KW, FP, WD, BW; Formal analysis: LM, UG, FK; Data collection: CKP, RR, EliS, KW, PT, LKi, JBS, ME, FP, CV, NJ, JMP, IH, MA, BER, CSt, AH, EleS, LKe; Data curation: AH, EleS, LKe; Writing-Original Draft: CSch, CKP, LM; Writing-Review & Editing: CSch, CK; Visualization: CSch, CKP, LM, UG, PT; Supervision: CSch, CK, KW, UG, FK; Project Administration: CSch, CKP; Funding acquisition: CSch. CKP and LM have accessed and verified the data. All authors critically reviewed the reply, contributed important intellectual content, approved the final version of the reply and accept responsibility for its submission.

All authors had access to the data





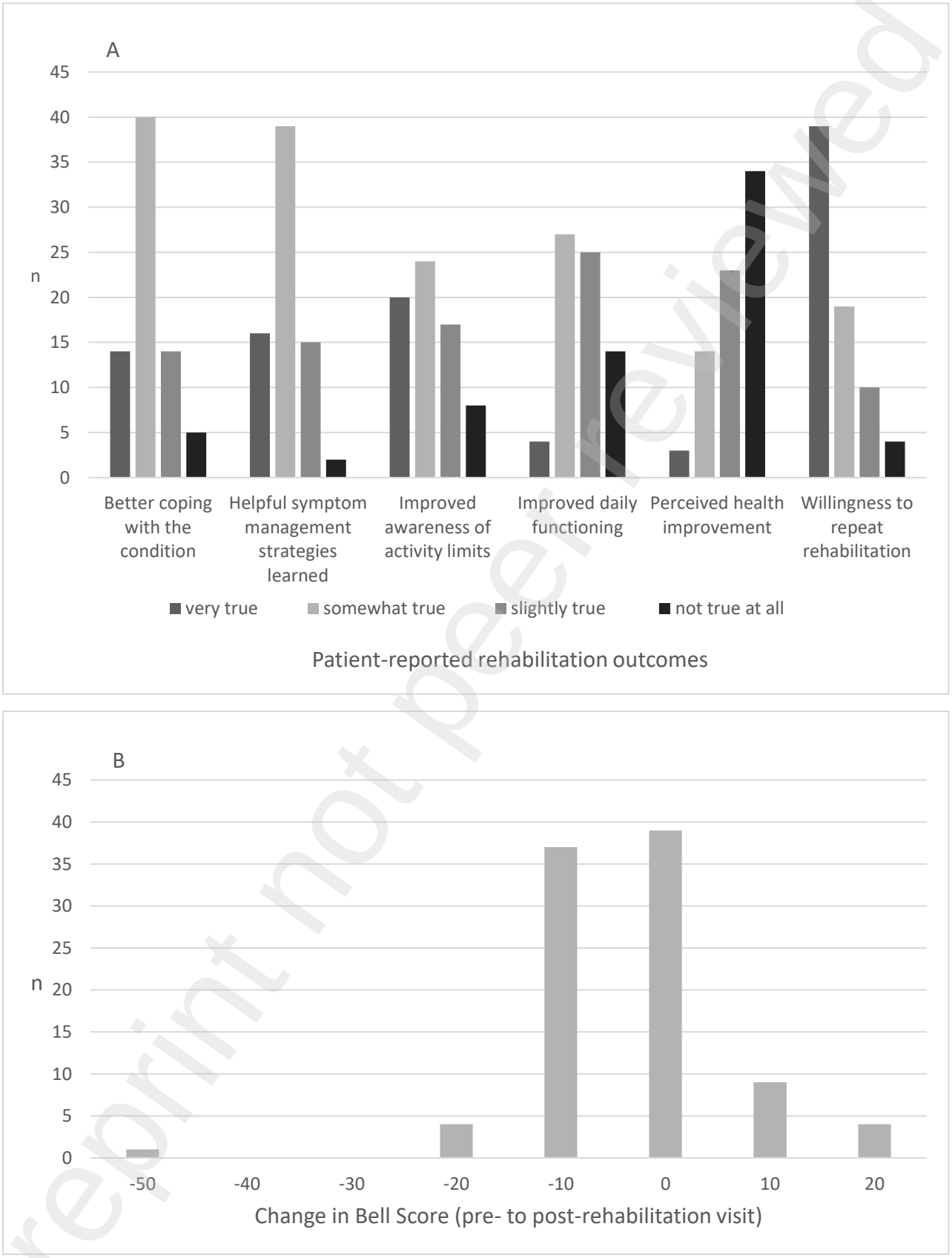


Fig. 3 Patient-reported rehabilitation experience and changes in functional status. **(A)** Patient-reported rehabilitation outcomes. **(B)** Change in functional status assessed by the Bell Disability Scale from pre- to post-rehabilitation visit. n = number of non missing values.