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ORIGINAL RESEARCH

Fatigue After Stroke Educational Recovery Program: A Prospective, Phase III, Randomized Controlled Trial

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BACKGROUND: Poststroke fatigue affects ≈50% of patients with stroke, causing significant personal, societal, and economic burden. In the FASTER (Fatigue After Stroke Educational Recovery) study, we assessed a group-based educational intervention for poststroke fatigue.

METHODS AND RESULTS: Two hundred patients with clinically significant fatigue were included and randomized to either a general stroke education control or fatigue management group (FMG) intervention and assessed at baseline, 6 weeks, and 3 months. The FMG involved weekly psychoeducation sessions over 6 weeks. Coprimary outcomes were the Fatigue Severity Scale and Multidimensional Fatigue Inventory-20 total scores. Adjusted mean total Fatigue Severity Scale scores at 6 weeks (primary end point) were nearly identical for the education control and FMG groups. The adjusted mean difference between treatment groups was −0.13 (SE, 1.4; *P*=0.92) at 6 weeks and 1.67 (SE, 1.4; *P*=0.26) at 3 months. Although there were no significant effects, Fatigue Severity Scale outcomes were in the direction of a treatment effect based on the estimated change. Adjusted mean total Multidimensional Fatigue Inventory-20 scores at 6 weeks (primary end point) were similar for the education control and FMG groups. The adjusted mean difference between treatment groups was −0.91 (SE, 1.54; *P*=0.55) at 6 weeks and −1.26 (SE, 1.8; *P*=0.49) at 3 months. Both groups had similar secondary outcomes (eg, Multidimensional Fatigue Inventory-20 subscales, sleep, pain, mood, quality of life) at 6 weeks and 3 months.

CONCLUSIONS: We found no evidence of significant group-level benefits of FMG over and above general stroke education. Educational group-based interventions for poststroke fatigue should continue to be refined and examined, including consideration of potential impacts at an individual level.

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Key Words: education ■ fatigue ■ intervention ■ stroke

Globally, poststroke fatigue (PSF) affects nearly half of all patients with stroke (pooled prevalence 47% [95% CI, 43%–50%) and may persist for years.[1] Global stroke guidelines recommend education to manage PSF.[2] Consensus-based recommendations from the third Stroke Recovery and Rehabilitation Roundtable identified psychoeducation, including but not limited to cognitive behavior therapy (CBT),[3] as one of the most promising interventions for PSF management. Psychoeducational interventions offer encouraging and sustained results in other health conditions (eg, multiple sclerosis, chronic fatigue)[4,5] that have similar experiences and consequences as stroke.[6] Furthermore, guidelines from Canada,[7] Australia, New

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RESEARCH PERSPECTIVE

What Is New?

- This prospective, phase III randomized controlled trial was the first to examine the group-level efficacy and safety of a 6-week, group-based, educational intervention for poststroke fatigue.
- Although not significant, findings showed a greater decrease in subjective physical fatigue severity in the intervention group compared with educational controls.

What Question Should Be Addressed Next?

- Further work is needed to fine-tune educational, group-based interventions for poststroke fatigue, including consideration of potential impacts at an individual level and the inclusion of written logs to capture participant's uptake of fatigue management strategies.

Nonstandard Abbreviations and Acronyms

EC	education controls
FASTER	Fatigue After Stroke Educational Recovery
FMG	fatigue management group
POSITIF	Post Stroke Intervention Trial in Fatigue
PSF	poststroke fatigue

Zealand,[8] the United Kingdom, and Ireland,[9] and the American Heart Association scientific statement[10] provide consensus-based suggestions for education, exercise, energy conservation, and sleep hygiene as means to managing PSF. Yet, there are no proven PSF management interventions.[11]

Alongside advantages of group-based interventions, including comprehensiveness, sharing goals, reinforcement of learning, and enhanced motivation/engagement,[12] we completed a pilot study of a psychoeducational fatigue management group (FMG) intervention in 16 adults at 3 to 18 months poststroke.[13] The FMG incorporated CBT elements, with a focus on education, exercise, energy conservation, sleep, and diet. Compared with a general stroke education (attention control) group, the FMG reported a greater decrease in total Fatigue Severity Scale (FSS) scores than the control group at 3 months, with a trend toward significance (P=0.08). Postintervention, all controls remained above the cutoff for fatigue, whereas 3 (33%) FMG participants had reduced FSS scores to below the cutoff. Consistent with findings in other health conditions, it was concluded that the FMG intervention offers promise as an active therapeutic agent.

We present group-level efficacy and safety findings from a randomized controlled trial of a 6-week FMG intervention compared with general stroke education controls (EC) 3 to 24 months poststroke. Based on findings of our previous pilot study and fatigue literature, we hypothesized that FMG would reduce self-reported fatigue and improve functional outcomes compared with EC.

METHODS

The authors declare that all supporting data are available within the article and its online supplementary files.

Design

FASTER (Fatigue After Stroke Educational Recovery) was an investigator-initiated, prospective, multicenter, 2-arm, phase III, individual patient randomized controlled trial (parallel group, superiority design), with blinded and predefined assessments. The trial arms were EC (control) and FMG (intervention). This article adheres to the CONSORT (Consolidated Standards of Reporting Trials) 2010 and CONSERVE-CONSORT (Consolidated Standards of Reporting Trials (CONSORT) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Extension for RCTs Revised in Extenuating Circumstances) extension checklists.[14]

Ethical Approvals

FASTER had ethical approvals (Health and Disability Ethics Committee, 13/NTB/1, and Auckland University of Technology Ethics Committee, 13/59). Written informed consent was obtained from all participants.

Recruitment

Potential participants were identified across 4 hospitals by hospital-based research nurses searching inpatient and outpatient medical records for the term fatigue, and by attending multidisciplinary team meetings. Community and primary care referrals were also invited across the 2 study regions (Waikato, Auckland) in New Zealand. To support external validity and recruitment, self-referrals and referrals from primary care health providers were also invited. Potentially eligible patients who agreed to contact when speaking with hospital-based research nurses were phoned by a trained research assistant to explain the study and screen for initial study criteria. For screening purposes,

fatigue is defined as feeling constantly weary, tired, and lacking energy or strength. Following the provision of a study information sheet and written consent, further postconsent health-related inclusion criteria were checked.

Study Criteria

Inclusion criteria were patients aged ≥18 years with clinically diagnosed stroke (computed tomography/magnetic resonance imaging confirmation of stroke pathological type) in the past 3 to 24 months, patients with clinically significant fatigue (score ≥12 on the self-report Multidimensional Fatigue Inventory [MFI-20] general subscale), patients residing in a study area, patients who can converse in English (including patients with mild expressive aphasia), and patients who gave informed consent to participate. To support recruitment, and acknowledging the reality of recurrent strokes, patients with recurrent stroke could take part. Given the study aimed to examine the impact of the intervention in a sample with PSF (not limited to physical fatigue as assessed by the FSS), and mindful of minimizing burden for potential participants, the 4-item general subscale of the MFI-20 was selected for initial screening purposes. Exclusion criteria were prestroke fatigue, significant disability, cognitive/behavioral impairments or a medical condition precluding participation, other causes of fatigue, or participation in another trial. Eligible patients with stroke were invited to nominate an informal caregiver (aged >15 years, defined as an unpaid person helping with daily activities ≥1.5 hours per week) to also take part in the trial.

Randomization

Following baseline assessment, stratified minimization randomization, using Qminum (online version of MinimPy with a documented algorithm[15]) was used by the study manager to balance groups (1:1 ratio) within each study site (Waikato, Auckland) for age (<65 years, ≥65 years), sex; disability (modified Rankin Scale: not disabled 0–1, slight/moderate disability 2–3[16]), and depression (Center for Epidemiologic Studies Depression Scale total score: no depression <16, depression ≥16[17]). The study manager advised participants of group allocation.

Blinding

Within the research team, only the study manager knew the group allocation codes, which were not disclosed until after data analyses were completed. Baseline and follow-up assessments were conducted by research assistants blinded to participant group status. Due to the nature of the intervention, participants were not blinded to group status. However, baseline assessments were performed before randomization when group allocation was unknown. Participants were aware of their group allocation at all follow-up assessments. Participants were reminded not to disclose group allocation at the start of each assessment.

Intervention: FMG Program

Participants assigned to FMG attended 6 weekly (60–90 minutes) group sessions focused on PSF management. Sessions provided an introduction to fatigue (week 1), fatigue management (week 2), sleep/relaxation (week 3), exercise and nutrition (week 4), mood (week 5), and future strategy use (week 6). Sessions aimed to explain what PSF is and why it occurs, aid understanding of personal fatigue and its relation to activity levels, identify factors that exacerbate PSF, introduce strategies to help manage PSF, and help participants in identifying the most useful strategies for them within a supportive group environment. Sessions followed traditional CBT structure of agenda setting, reviewing previous sessions and tasks, and presenting new information followed by examples from daily life, guided practice in strategy use, and group activities.

In the first FMG session, each participant received a booklet, including information to accompany each session, and a fatigue and activity diary. Material included in each session was intended to be realistic and relevant to participant needs, and this was achieved by encouraging them to generate examples from their own experience. Each session was run by a registered clinical psychologist with experience in evoking change in a patient's life in a short period of time. The brief CBT framework emphasized compensatory strategies (ie, energy conservation) given likely organic factors linked to PSF. This professionally guided process recognized the expertise of group members, validated their experiences, and enabled sharing of knowledge, reflection, and experiences. Behavior change was intended to be achieved by goal setting, planning, and trialing fatigue management strategies in the home and community. Facilitating therapists followed a manualized treatment protocol involving didactic teaching, group activities, and discussions (see Table 1 for overview of content of FMG sessions). FMG attendees completed a daily diary recording PSF frequency, duration, and self-perceived causes for personal review and reflection.

Controls: EC Program

To account for repeated measurement and spontaneous recovery effects, those in the EC group attended a single group session focused on stroke and related topics (eg, nutrition, exercise), with minimal focus on fatigue. Provision of 1 EC session rather than matching the 6 sessions of FMG was ethically advisable, because 6 sessions without an expectation of benefit was thought to be too burdensome for participants. Those is the EC group were offered written FMG materials

Table 1. Content of Fatigue Management Group Sessions

No.	Session title	Content overview
1	Overview and introduction to fatigue	Course overview, facilitated discussion of stroke experiences, define fatigue, introduction of fatigue diaries (eg, rating fatigue levels at different times of the day and in relation to activities). Homework: complete fatigue diary.
2	Fatigue management	Review fatigue diaries (eg, identifying any common patterns around experiences of fatigue), education on poststroke fatigue (eg, causes), fatigue management strategies (eg, tips for energy conservation and restoration). Homework: complete fatigue diary, try at least 2 energy conservation and restoration activities.
3	Sleep/relaxation	Review homework/diaries, including experiences using energy conservation and restoration activities, facilitated discussion of sleep patterns and sleep hygiene (eg, environment, routine, stimulation), stress education (eg, what is stress, signs of stress, who is most susceptible to stress), stress management exercises (eg, deep breathing, progressive muscle relaxation, mini relaxation and visualization exercises). Homework: complete fatigue diaries, try 2 sleep tips, complete breathing exercises every day, try visualization exercise at least once.
4	Exercise and nutrition	Review homework/diaries and use of sleep tips and stress management techniques, exercise education, and impact of activity on sleep/fatigue, nutrition/diet, and impact on fatigue. Homework: complete fatigue diary, try 1 new exercise or physical activity.
5	Mood	Review homework/diaries and use of new exercise or physical activity, relationship between mood and fatigue, 4-part cognitive behavioral model of mood and fatigue (physical-thought-mood/emotion-behavior). Homework: complete fatigue diary, note any spirals of fatigue-mood.
6	Future focus	Review homework/diaries and experiences of fatigue leading to lowered mood and strategies to break spiral, review course (eg, what was most/least helpful), and future strategy use.

following their involvement in the trial. In terms of similarities, both FMG and EC sessions were group based and run at community-based locations (ie, churches, halls, hireable rooms) by registered clinical psychologists trained in 1 of the 2 programs. Assessments were conducted face to face (usually in participants' homes) or by phone or online survey at baseline, 6 weeks, and 3 months by a research assistant. Full details of the methodology of the FASTER trial are published separately.[18] Additional advice was sought from a speech-language therapist to support the participation of those with mild aphasia in group sessions.

Mitigation Strategies

The following changes, which were planned, reviewed, and approved by the study operations team, were made once the trial had started to address processes interrupted/halted by the extenuating circumstances associated with the COVID-19 pandemic (ie, including interruptions to recruitment, in-person consent, assessment and program delivery, inconsistent timeframes such as delays in program delivery, and late assessments). From March 25, 2020 to May 13, 2020, recruitment, assessments and group sessions were halted due to COVID-19. Mitigating strategies included adding online options for program delivery, and phone and/or online options for baseline and follow-up assessments and participant consent. To mitigate impacts due to delays in groups starting, baseline primary outcome measures were readministered within 2 weeks of the start date. Mode of program delivery and assessments (eg, in person, online, phone) and time variations in baseline assessments were recorded and adjusted for ancillary outcome analyses to remove confounding effects.

Coprimary Outcomes

Prespecified coprimary outcomes were self-reported FSS and MFI-20 total scores assessed immediately after intervention (6 weeks). Although the 7-item FSS version has since been recommended as a primary outcome for studies of new PSF interventions,[3] we used the 9-item FSS to assess physical fatigue, with average scores calculated across all statements. Consistent with our previous pilot study,[13] FSS total average scores >3.9 were deemed to reflect moderate to severe fatigue.[19] The 20-item MFI-20 assesses general fatigue, physical fatigue, reduced motivation, reduced activity, and mental fatigue. MFI-20 general subscale scores ≥12 reflect moderate to severe fatigue.[20,21] Higher FSS and MFI-20 scores indicate greater fatigue.

Secondary Outcomes

Prespecified secondary outcomes were self-reported general, physical, and mental fatigue, reduced activity, and reduced motivation (MFI-20)[22]; disability (Barthel Index)[23]; sleep (Pittsburgh Sleep Quality Index[24]; Epworth Sleepiness Scale-8)[25]; pain intensity in the past 24 hours (visual analog scale [VAS])[26]; global fatigue (VAS), mood (Hospital Anxiety and Depression Scale)[27]; health-related quality of life (QoL) (Short Form-36)[28]; and for informal caregivers, self-reported Bakas Caregiving Outcomes Scale,[29] and carer QoL (Short Form-36).[30] When assessed in person, the Timed Up and Go (TUG) task,[31] capturing gait and turning movements, objectively assessed physical fatigue. The TUG was administered twice to calculate an average score, with the exception of those aged ≥65 years who took ≥12 seconds to complete the first TUG attempt (who were deemed at risk of falling).[32] Safety outcomes

included any self-reported formal admission to the hospital during trial participation and any recorded deaths. *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes and descriptions of each event were reviewed and categorized according to cause by a study stroke clinician. Stroke details (eg, type, previous stroke) were from medical records. Self-reported comorbidities were assigned a summary Elixhauser score.[33]

Study Sample

Based on pilot findings,[13] we aimed to recruit 200 participants (100 per group), providing 85% power (with 20% drop-out; 2-sided, P=0.05) to detect minimally clinically important differences of 0.60 points (SD, ±1.27)[34] in FSS and 1.70 (SD, ±3.6)[35] in MFI-20 at 3 months. Recruitment was terminated after 200 participants had been enrolled according to the sample size estimation in planning.

Statistical Analysis

Outcome Comparison

The statistical analysis plan was finalized before database lock. Descriptive profiles of study groups were examined. Adjusting for each outcome's potential confounders and prespecified clinically important covariates, between groups differences in primary and secondary outcomes were analyzed (per protocol) using repeated measures ANCOVA. Mixed model repeated measure ANOVA were used to compare between-group changes over time for each primary outcome, where patient was the random effect and variance component was the final selected covariance pattern based on Akaike's information criterion. Least square mean plots are presented for each follow-up time point for both FSS and MFI-20 outcomes.

Dose–Response Analysis

Proportional change in FSS and MFI-20 total scores at 6 weeks and 3 months compared with baseline scores were used as the response measures. The number of FMG sessions attended (0 minimum to 6 maximum) was included as the dose variable in nonparametric and parametric regression. Nonparametric models (using SAS version 9.4: Proc transreg procedure) were used to identify the degree of polynomial parameters in spline regression, and parametric models were used accordingly. Finally, quantile regressions were used as a nonparametric regression method, which regressed the median of the response on the dose variable number of FMG attendances. These analyses provided guidance in the subgroup analysis for 4 or 6 session completers (see below).

Missing Data

Missing primary outcome data were imputed using a hot-deck approximate Bayesian bootstrapping approach,[36] stratified by group, age, sex, and ethnicity assuming that participants in the same strata have the same outcome distributions. Imputed data with 100 replications were applied to the TUG due to >30% missing data.

Safety

Safety outcomes were analyzed using χ^2 test and generalized linear mixed-effects modeling.

Subgroup Analyses

Non-prespecified subgroup analyses examining dose–response relationships between total FMG sessions attended and coprimary outcomes were analyzed using nonparametric quantile regression. To provide estimates of treatment difference in 2 subgroups of participants who attended all 6 sessions and at least 4 sessions of FMG, unblinded, open label, non-prespecified, subgroup analyses of treatment effect were undertaken, using 2-way ANCOVA. Group comparisons were based on the actual treatment participants received, with 1 protocol violation of a patient swapping their randomized treatment.

Analyses were performed using SAS (version 9.4) and SPSS (version 27) software. To indicate statistical significance, α=0.05 (2-sided) was used. Familywise error controls were used to account for type I errors arising from multiple test inferences.

Data Monitoring and Trial Registration

The trial was overseen by a steering committee with support from an independent data monitoring committee. The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (unique identifier: ACTRN12619000626167).

RESULTS

Participant Baseline Characteristics

Trial participants were recruited between May 1, 2019 and July 6, 2021. Baseline assessments occurred between August 7, 2019 and July 29, 2021. FMG and EC group sessions were delivered between August 23, 2019 and March 5, 2022. Participants were followed up between October 7, 2019 and June 14, 2022. Two hundred participants (56.5% men) were recruited (Figure 1), with 100 randomized to FMG and 100 to EC. Baseline characteristics of patients with stroke and their informal caregivers were similar between the 2 groups (Table 2), except for a greater proportion of patients with stroke with skilled/unskilled occupations,

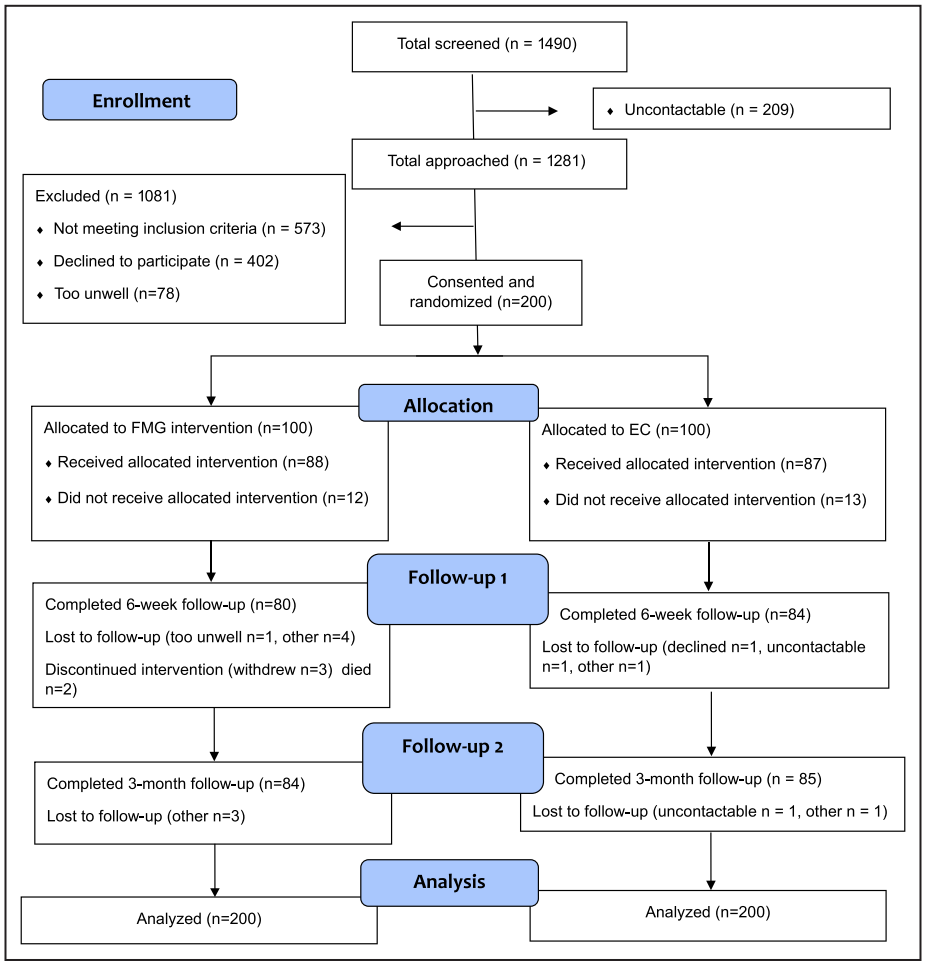

Figure 1. CONSORT 2010 flow diagram.
CONSORT indicates consolidated standards of reporting trials; EC, education controls; and FMG, fatigue management group.

and previous and recurrent stroke in the EC group than the FMG.

Primary Outcomes

Table 3 presents coprimary outcomes, including analyses using imputed data where relevant. Adjusted mean total FSS scores at 6 weeks (primary end point) were nearly identical for EC and FMG groups. The adjusted mean difference between treatment groups was −0.13 (SE, 1.4; *P*=0.92) at 6 weeks and 1.67 (SE, 1.4; *P*=0.26) at 3 months (Figure 2). There were no significant differences in the FSS total scores between 6 weeks and 3 months in the EC group, the adjusted mean difference was −0.53 (SE, 0.93 [95% CI, −2.37 to 1.31]; *P*=0.57), and there was a significant reduction in FSS total score in the FMG group, with the adjusted mean difference −2.3 (SE, 1.08 [95% CI, −4.45 to −0.15]; *P*=0.04). This *P* value was not significant (at threshold <0.025). The changes in FSS were not significant between the EC and FMG groups. Although there were no significant effects, FSS outcomes were in the direction of a treatment effect.

Adjusted mean total MFI-20 scores at 6 weeks were similar for the EC and FMG groups. The adjusted mean difference between treatment groups was −0.91 (SE, 1.54; *P*=0.55) at 6 weeks and −1.26 (SE, 1.8; *P*=0.49) at 3 months (Figure 3). There was a significant reduction in the MFI-20 total score between 6 weeks and 3 months in the EC group. The adjusted mean difference was −2.61 (SE, 1.08 [95% CI, −4.76 to −0.45]; *P*=0.018). With multiple test correction, this *P* value was not significant (at threshold <0.013), and there was a significant reduction in MFI-20 total score in the FMG group with the adjusted mean difference −2.58 (SE, 1.08 [95% CI, −4.74 to −0.42]; *P*=0.02). With multiple test correction, this *P* value was marginally significant (at threshold <0.017). The changes in MFI-20 were not significant between the EC and FMG groups.

Table 2. Baseline Characteristics of Per Protocol Analysis Population

Characteristic	EC (n=100)			FMG (n=100)		
Characteristics of patients with stroke						
Age, y, mean±SD [range]	66.0±12.3 [32–89]			64.5±12.9 [24–89]		
Sex (men)	55 (55.0)			58 (58.0)		
Ethnicity, multiple						
Māori	7 (7.0)			6 (6.0)		
Other	18 (18.0)			24 (24.0)		
New Zealand European	79 (79.0)			71 (71.0)		
Study site/region						
Waikato	27 (27.0)			24 (24.0)		
Auckland	73 (73.0)			76 (76.0)		
Case identification source						
Hospital	62 (62.0)			47 (47.0)		
General practice	6 (6.0)			5 (5.0)		
Self-referral	1 (1.0)			6 (6.0)		
Research registry	18 (18.0)			21 (21.0)		
Community stroke provider	13 (13.0)			21 (21.0)		
Clinical characteristics						
Stroke type						
Ischemic	83 (83.0)			79 (79.0)		
Intracerebral hemorrhage	13 (13.0)			16 (16.0)		
Subarachnoid hemorrhage	4 (4.0)			5 (5.0)		
Time after index stroke, mo, mean±SD [range]*	11.2±6.8 [0–24]			9.6±6.9 [0–24]		
	Median	1st quartile	3rd quartile	Median	1st quartile	3rd quartile
	10	5	17	7	4	15
Previous stroke	17 (17.0)			9 (9.0)		
Recurrent stroke since baseline	3 (3.0)			1 (1.0)		
Any comorbidities	83 (83.0)			87 (87.0)		
No. of comorbidities						
0	17 (17.0)			13 (13.0)		
1	35 (35.0)			31 (31.0)		
2	21 (21.0)			27 (27.0)		
3	27 (27.0)			29 (29.0)		
Received health care/support services in last month	23 (23.0)			35 (35.0)		
Demographic characteristic						
Living situation						
With partner	46 (46.0)			47 (47.0)		
With family/others	31 (31.0)			42 (42.0)		
Alone	23 (23.0)			11 (11.0)		
Type of accommodation						
Own, family or friend's home	76 (76.0)			76 (76.0)		
Rental home	20 (20.0)			17 (17.0)		
Other (inpatient, rest home, retirement village)	4 (4.0)			7 (7.0)		
Employment status						
Full-time (>35 h/wk)	17 (17.0)			19 (19.0)		
Part-time (≤34 h/wk)	16 (16.0)			14 (14.0)		
Retired	35 (35.0)			34 (34.0)		
Unemployed	14 (14.0)			15 (15.0)		

(*Continued*)

Table 2. Continued

Characteristic	EC (n=100)	FMG (n=100)
Other (eg, disability, homemaker, student)	18 (18.0)	18 (18.0)
Highest household SES		
Professional (ANZSCO <3)	27 (27.0)	38 (38.0)
Skilled/unskilled (ANZSCO >2)	72 (72.0)	60 (60.0)
Missing	1 (1.0)	2 (2.0)
Informal caregiver characteristic	n=38	n=43
Age at baseline, y, mean±SD [range]†	66.4±12.1 [33–84]	64.2±14.3 [34–87]
Sex (men)	12 (32.0)	24 (56.0)
Ethnicity, multiple		
Māori	2 (5.0)	1 (3.0)
Other	8 (21.0)	10 (23.0)
New Zealand European	28 (74.0)	32 (74.0)
Employment status		
Full-time (>35 h/wk)	7 (7.0)	13 (13.0)
Part-time (≤34 h/wk)	8 (8.0)	3 (3.0)
Other (eg, disability, homemaker, student)	23 (23.0)	27 (27.0)

Data are n (%) unless otherwise specified. ANZSCO indicates Australian and New Zealand Standard Classification of Occupations; EC, education controls; FMG, fatigue management group; and SES, socioeconomic status.

*EC n=86, FMG n=82 due to missing data.

†EC n=35, FMG n=40 due to missing data.

Imputation methods to manage participant attrition (EC: 16% at 6 weeks, 15% at 3 months; FMG: 20% at 6 weeks, 16% at 3 months) and maintain statistical power for the primary outcomes revealed a similar pattern of findings. The percentages of adults meeting criteria for moderate to severe fatigue for the FSS and the MFI-20 (general subscale) were similar at 6 weeks and 3 months for both groups (P>0.05) (Table S1).

Secondary Outcomes

Table 4 presents secondary outcomes, including analyses using imputed data where relevant. Adjusted mean group differences for the MFI-20 subscales (general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation), sleep, mood (anxiety and depression), health-related QoL, overall fatigue (VAS), pain (VAS), and disability were not sufficient to suggest that FMG significantly improved patient outcomes. Similarly, imputed TUG derived a median group treatment difference of 0.03 (95% CI, −0.06 to 0.12; P=0.55) at 6 weeks and 0.01 (95% CI, −0.02 to −0.05; P=0.56) at 3 months. However, a trend toward statistical significance was observed with better sleep quality in the FMG than EC group at 3 months (P=0.09).

For informal caregivers, adjusted mean group differences in health-related QoL and carer burden did not suggest the FMG program was associated with significant improvements at 6 weeks or 3 months (Table S2).

Safety

There were no significant differences in mortality rates (0, 0% vs 2, 2%) nor in the proportion of adverse events directly related to stroke (5, 5% vs 7, 7%, P=0.85) between the FMG and EC group, respectively. There were no reports of adverse events directly related to the intervention.

Subgroup Analyses

To investigate potential dose–response effects, subgroup analyses compared FSS, MFI-20, and fatigue VAS scores of participants with first-ever stroke who attended all 6 FMG sessions (Table S3) or at least 4 of the 6 FMG sessions (Table S4) with EC participants with first-ever stroke. Findings did not show a significant dose–response relationship.

DISCUSSION

We assessed the efficacy and safety of a 6-week FMG program to reduce PSF compared with an EC group. Although the FMG reported a greater decrease in the FSS than the EC group, between-group differences for the coprimary outcomes (FSS, MFI-20) were not significant. Subgroup analyses of patients with first-ever stroke who attended all 6, or at least 4, FMG sessions did not support a significant dose–response relationship. There were also no significant changes in other outcomes assessed and commonly associated with fatigue (eg, anxiety, depression, sleep, disability, pain).

Table 3. Coprimary Subjective Outcomes of Patients With Stroke: FSS-9 and MFI-20 Total Scores by Treatment Group

	EC (n=100)					FMG (n=100)					Difference at 6 wk (EC vs FMG)				Difference at 3 mo (EC vs FMG)			
	Baseline (n=100)	6 wk (n=84)		3 mo (n=85)		Baseline (n=100)	6 wk (n=80)		3 mo (n=84)									
	Mean±SD	Mean±SD	LS mean (SE)	Mean±SD	LS mean (SE)	Mean±SD	Mean±SD	LS mean (SE)	Mean±SD	LS mean (SE)	LS mean (SE)	95% CI	*P* value†	Adj *P* value‡,§	LS mean (SE)	95% CI	*P* value†	Adj *P* value‡,§
FSS	44.6±10.2	41.1±10.9	40.8 (2.2)	40.7±11.4	39.8 (2.2)	44.0±10.0	41.3±11.8	40.9 (2.1)	39.2±11.0	38.1 (2.1)	−0.13 (1.42)	−2.93 to 2.67	0.92	0.93	1.67 (1.4)	−1.09 to 4.44	0.28	0.26
MFI-20	63.2±12.8	60.7±12.9	55.9 (2.3)	58.1±13.0	55.7 (2.0)	61.8±12.5	61.0±13.0	56.9 (2.4)	59.1±14.6	57.0 (1.9)	−0.91 (1.54)	−3.95 to 2.12	0.46	0.55	−1.26 (1.80)	−4.83 to 2.31	0.33	0.49
Total MFI-20 (imputed)	61.9±15.2	60.5±12.3	60.4 (0.8)	58.2±13.0	58.2 (0.6)	60.0±11.0	60.5±13.5	60.4 (0.6)	58.4±14.7	58.3 (0.7)	−0.08 (0.9)	−1.84 to 1.69			−0.04 (0.9)	−1.73 to 1.64		

Adj indicates adjusted; EC, education controls; FMG, fatigue management group; FSS, Fatigue Severity Scale; LS, least squares; and MFI-20, Multidimensional Fatigue Inventory-20.

†*P* value is derived from 2-way ANOVA.

‡*P* value for FSS is derived from ANCOVA adjusted by (marginally) significant outcome confounders: baseline FSS measure, ethnicity (Māori/non-Māori), type of stroke, number of comorbidities, and Elixhauser Comorbidity Index.

§*P* value for MFI-20 is derived from ANCOVA adjusted by (marginally) significant outcome confounders: baseline MFI-20 total, number of previous strokes, referral center, sex, employment groups, Australian and New Zealand Standard Classification of Occupations group, and stroke type (Ischemic/Intracerebral haemorrhage/Subarachnoid haemorrhage).

Our hypothesis that the FMG program would reduce PSF and thereby improve functional outcomes compared with general stroke education alone was not supported.

The lack of evidence of significant benefit of the FMG contrasts with sustained benefits of similar approaches in other health conditions (eg, multiple sclerosis, chronic fatigue).[4,5,37] Our findings also contrast with expected mechanisms of action arising from group CBT with older adults, including the development of a shared sense of goals, facilitation and reinforcement for strategy learning and practice, enhancing motivation for sustained change, greater engagement, and broader therapeutic alliance. Thomas and colleagues found that 6 group manualized CBT sessions with 164 randomized patients with multiple sclerosis favored the intervention group compared with usual care in reducing fatigue severity 4 months postintervention (mean difference, −0.36 [95% CI, −0.63 to −0.08]; *P*=0.01), with most improvements sustained at 1 year.[37] This disparity might be explained by differences in patient populations. For example, in the first year poststroke, patients are expected to experience some spontaneous recovery. This would not be expected in progressive conditions such as multiple sclerosis and chronic fatigue. Spontaneous recovery within the stroke population may have reduced our ability to detect significant effects of the intervention as seen in different patient populations.

Furthermore, a variety of neurological deficits may present significant barriers to knowledge acquisition, participation, and education poststroke that are not observed in other populations. Individual variations in neurological deficits after stroke may render it difficult to apply a group-based approach to PSF management.[38] Previous stroke trials examining similar CBT-informed interventions delivered to individuals rather than groups[39–41] have mostly been single-armed clinical trials examining small samples (<50 participants). The multicenter POSITIF (Post Stroke Intervention Trial in Fatigue) trial examined a similar CBT-informed 6-session intervention for PSF delivered by stroke health care professionals via telephone over 12 weeks, with a booster phone call 2 to 4 weeks later.[42] Recruiting patients with stroke in the past 3 to 24 months, there were no significant adjusted mean group differences between intervention (n=39) and control (n=37) groups on the Fatigue Assessment Scale, the Generalized Anxiety Disorder-7, or Patient Health Questionnaire at 6 months. There were also no between-group differences in QoL, social participation, or return to work. Together with the current trial, evidence to date highlights the challenges of reducing PSF whether interventions are delivered to patients with stroke individually or in groups.

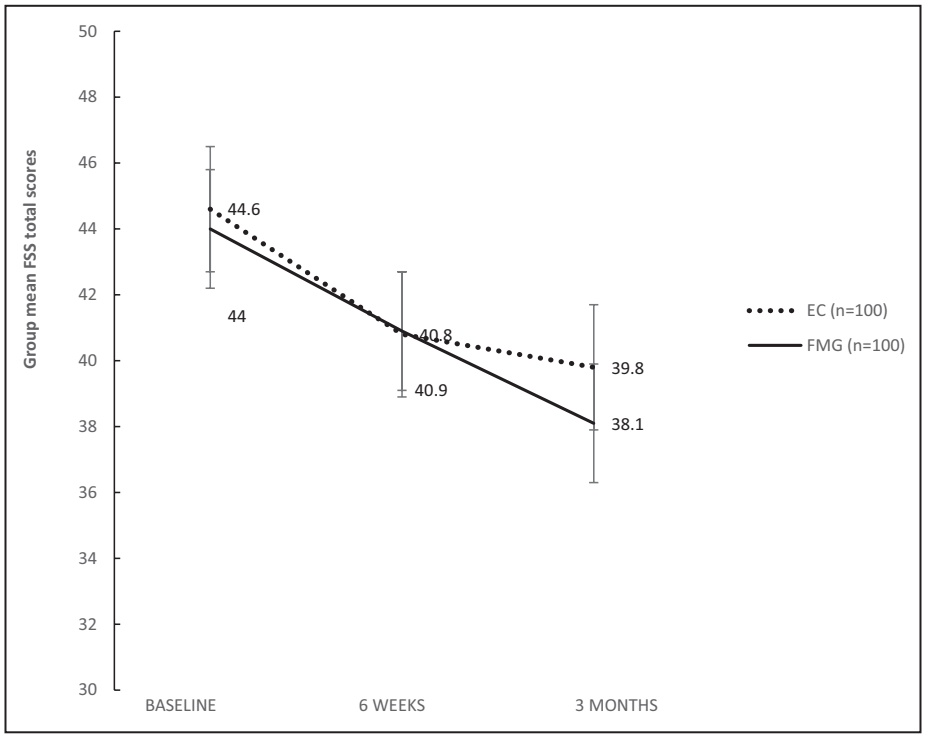

Figure 2. Least squares mean plot of FSS at 6 weeks and 3 months.
Least squares means and their standard errors are presented. EC indicates education controls; FMG, fatigue management group; and FSS, Fatigue Severity Scale.

Although not statistically significant, the pattern of findings reported in the current trial suggest there may be potential for educational, CBT-informed, group-based interventions to support some patients with stroke with PSF. Consistent with our related pilot study,[13] the FMG reported a greater decrease in

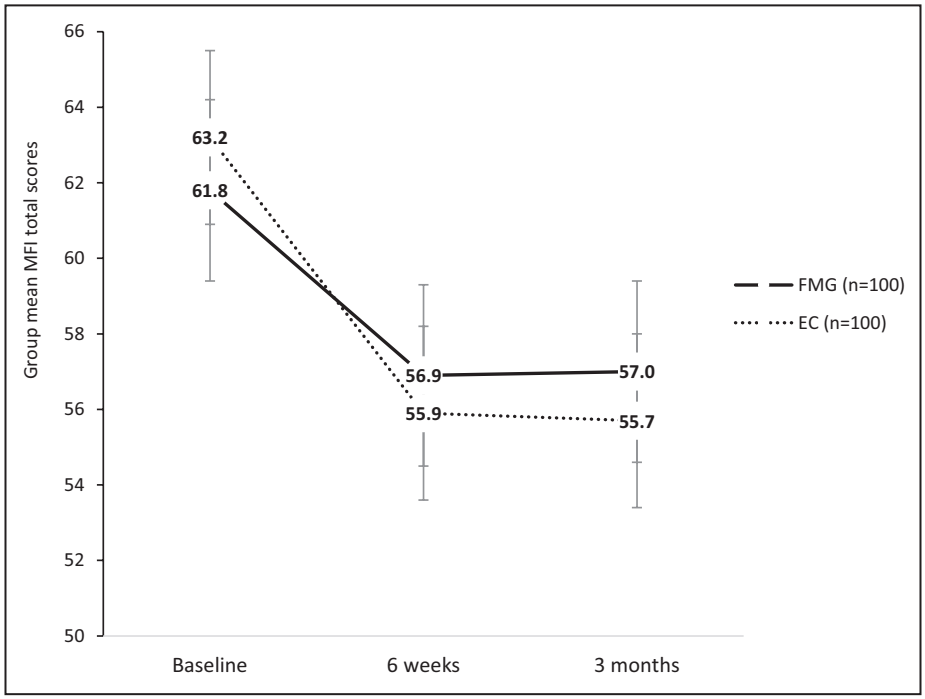

Figure 3. Least squares mean plot of MFI-20 at 6 weeks and 3 months.
Least squares means and their standard errors are presented. EC indicates education controls; FMG, fatigue management group; and MFI-20, Multidimensional Fatigue Inventory-20.

Table 4. Secondary Subjective Outcomes of Patients With Stroke: Multidimensional Fatigue, Sleep, Mood, Health-Related QoL, Fatigue VAS, Pain VAS, and Disability by Treatment Group

	EC			FMG			Difference at 6 wk (EC vs FMG)				Difference at 3 mo (EC vs FMG)			
	Baseline (n=100)	6 wk (n=84)	3 mo (n=85)	Baseline (n=100)	6 wk (n=80)	3 mo (n=84)								
Domain	Mean±SD	LS mean (SE)	LS mean (SE)	Mean±SD	LS mean (SE)	LS mean (SE)	LS mean (SE)	95% CI	*P* value†§	Adj *P* value	LS mean (SE)	95% CI	*P* value†	Adj *P* value
Multidimensional fatigue (MFI-20 subscales)														
General	14.6±3.0	12.7 (0.6)	13.3 (0.7)	14.5±2.9	14.0 (0.6)	13.8 (0.7)	−0.28	−1.10 to 0.54	0.60	0.50‡	−0.53	−1.45 to 0.39	0.14	0.26‡
Physical	13.8±3.4	12.4 (0.8)	10.3 (0.8)	13.5±3.2	12.8 (0.8)	11.1 (0.8)	−0.40	−1.40 to 0.60	0.37	0.43‡	−0.8	−1.79 to 0.19	0.42	0.11‡
Mental	11.5±4.2	10.3 (0.8)	10.0 (0.7)	11.6±4.3	11.1 (0.8)	10.6 (0.8)	−0.80	−1.79 to 0.19	0.24	0.11‡	−0.59	−1.54 to 0.37	0.54	0.22‡
Reduced activity	13.2±3.7	11.7 (0.8)	11.8 (0.8)	12.6±3.9	11.3 (0.8)	11.5 (0.8)	0.39	−0.64 to 1.42	0.62	0.45‡	0.29	−0.77 to 1.34	0.99	0.59‡
Reduced motivation	10.1±3.0	9.1 (0.6)	9.3 (0.7)	9.7±3.2	9.0 (0.6)	9.4 (0.7)	0.16	−0.61 to 0.93	0.99	0.69‡	−0.11	−1.04 to 0.81	0.63	0.81‡
Sleep														
Sleep quality (PSQI)¶	7.5±4.4	7.1 (0.4)	6.9 (0.4)	7.0±4.1	6.4 (0.4)	6.1 (0.4)	0.7 (0.5)	−0.3 to 1.6	0.16	0.18§	0.8 (0.5)	−0.1 to 1.7	0.12	0.09§
Daytime sleepiness (ESS)^	6.8±4.8	6.2 (0.6)	7.7 (0.6)	7.7±4.9	7.1 (0.5)	7.9 (0.5)	−0.7 (0.5)	−1.9 to 0.2	0.13	0.12‖	−0.2 (0.5)	−1.2 to 0.9	0.67	0.76‖
Mood (HADS)														
Anxiety	5.3±3.5	4.0 (0.5)	4.0 (0.5)	4.9±3.6	4.2 (0.5)	4.5 (0.5)	−0.2 (0.4)	−1.0 to 0.5	0.44	0.57**	−0.5 (0.4)	−1.3 to 0.3	0.12	0.26**
Depression	4.7±2.8	4.2 (0.5)	4.4 (0.5)	4.7±3.1	4.5 (0.5)	4.6 (0.5)	−0.3 (0.3)	−1.0 to 0.3	0.64	0.32††	−0.2 (0.3)	−0.9 to 0.5	0.92	0.56††
QoL (SF-36)	n=99	n=84	n=85	n=99	n=79	n=82								
Physical	45.1±1.5	48.6 (1.3)	50.8 (1.4)	45.3±1.5	49.2 (1.5)	48.3 (1.4)	−0.06 (1.9)	−4.4 to 3.2	0.95	0.89	2.5 (2.0)	−1.4 to 6.4	0.19	0.15
Mental	67.3±1.7	70.1 (1.6)	73.2 (1.5)	69.5±1.7	71.0 (1.6)	73.8 (1.5)	−0.09 (2.2)	−5.3 to 3.5	0.65	0.70	−0.5 (2.1)	−4.6 to 3.5	0.77	0.79
Fatigue VAS	4.7±2.0	5.7 (0.3)	5.8 (0.3)	4.8±2.1	5.3 (0.3)	5.5 (0.3)	0.42 (0.27)	−0.11 to 0.95	0.09	0.12‡‡	0.22 (0.32)	−0.40 to 0.85	0.43	0.48‡‡
Fatigue VAS (imputed)	4.7±2.0	5.4 (0.2)	6.0 (0.3)	4.8±2.1	4.9 (0.2)	5.6 (0.3)	0.42 (0.12)	0.39 to 0.44			0.23 (0.13)	0.21 to 0.26		
Pain VAS	20.1±2.8	21.7 (2.9)	17.9 (2.7)	23.6±2.8	25.5 (2.9)	20.9 (2.7)	−2.3 (3.9)	−10.0 to 5.3	0.37	0.55	−2.1 (3.5)	−9.0 to 4.8	0.42	0.56
Disability (n, %)							Difference (%)				Difference (%)			
BI (=20)	80±80.0	70 (83.3)	73 (85.9)	69±69.7	62 (78.5)	63 (76.8)	4.9		0.43	0.58§§	9.1		0.13	0.21§§

Adj indicates adjusted; BI, Barthel Index; EC, education controls; ESS, Epworth Sleepiness Scale-8; FMG, fatigue management group; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; LS, least squares; MFI-20, Multidimensional Fatigue Inventory-20; PSQI, Pittsburgh Sleep Quality Index; SF-36, Short Form-36; and VAS, visual analog scale.

†*P* value is derived from 2-way ANOVA.

‡*P* value for MFI-20 is derived from ANCOVA adjusted by (marginally) significant outcome confounders: baseline MFI-20 total, number of previous strokes, referral center, sex, employment groups, Australian and New Zealand Standard Classification of Occupations group, and stroke type (Ischemic/Intracerebral haemorrhage/Subarachnoid haemorrhage).

§*P* values for PSQI are derived from ANCOVA adjusted by (marginally) significant outcome confounders: patients with stroke baseline PSQI, sex, marital status (married/partnered vs single/unknown), number of previous strokes, and study site (Waikato vs Auckland).

‖*P* values for ESS are derived from ANCOVA adjusted by (marginally) significant outcome confounders: patients with stroke baseline ESS, and type of index stroke.

¶Higher PSQI indicates worse sleep quality; ^higher ESS indicate worse daily sleepiness.

#χ^2 test.

**Adjusted *P* value for Anxiety is derived from ANCOVA adjusted by (marginally) significant outcome confounders: patients with stroke baseline anxiety, age, European ethnicity, marital status (married/partnered vs single/unknown), type of accommodation (living in a self/family own home vs rental and other), living situation (living alone vs living with others), type of index stroke, and study site (Waikato vs Auckland).

††Adjusted *P* value for Depression is derived from ANCOVA adjusted by (marginally) significant outcome confounders: patients with stroke baseline depression, sex, marital status (married/partnered vs single/unknown), employment status (full-time/part-time/unemployed/other), highest household socioeconomic status, number of previous strokes, and type of index stroke.

‡‡Adjusted *P* value for Fatigue VAS is derived from ANCOVA adjusted by (marginally) significant outcome confounders: baseline fatigue VAS and type of index stroke.

§§Adjusted *P* value for BI category (=20 vs <20) is derived for logistic regression adjusted by (marginally) significant outcome confounders: baseline disability (BI), patients with stroke age and employment status, and study site (Waikato vs Auckland).

subjective physical fatigue severity than the EC group, although not significantly so. It is also important to consider the extraordinary time in which this trial took place. The COVID-19 pandemic had a significant impact on many people and had a particular impact on the delivery of the intervention. It is unclear if broader impacts of this disruption impacted upon the findings.

Future Research

Future research is needed to focus on identifying potential subgroups of patients with stroke who may benefit from educational, CBT-informed, group-based interventions. Furthermore, our FMG program offered education on factors commonly associated with PSF, such as sleep, exercise, diet, and mood. Addressing other common contributors to PSF, such as the management of pain and frequent comorbidities, may provide added benefit in future similar trials. Future trials of educational, group-based interventions for managing PSF should also consider incorporating written logs to capture participant's uptake of management strategies provided as part of the intervention (eg, participant physical activity, dietary tracking, and use of relaxation and energy conservation techniques). The use of activity and sleep monitors may also shed further light on the intervention's actual influence on lifestyle changes. Providing more structured guidance, such as specifying daily/weekly exercise routines and meditation sessions, could more effectively determine the FMG's role in mitigating fatigue symptoms. Involving patients with stroke in codesigning educational, group-based interventions for PSF may also increase the effectiveness of future efforts to address this frequent, disabling health condition.

Strengths and Limitations

FASTER has several strengths including its manualized programs to ensure consistent delivery, inclusion of multiple measures of fatigue, and stringent screening to ensure that the intervention was tested in relation to PSF and not fatigue from other sources. The trial addressed limitations of previous PSF intervention studies that have predominantly been nonrandomized clinical trials, single centered, with high risk of bias and small sample sizes (median 50).[43] Potential therapist effects were minimized by each clinical psychologist being trained in the delivery of either the EC or FMG sessions. We also achieved low participant attrition (15%) despite the COVID-19 pandemic. Although most PSF intervention studies recruit participants at 3 months after stroke to ensure that participants have continuous fatigue,[43] FASTER recruited participants up to 24 months poststroke to increase the generalizability of findings. Due to the trial coinciding with the COVID-19 pandemic, FASTER also contributes to new emerging knowledge about PSF interventions delivered online.

FASTER had some limitations, of which the most important was the reduced availability of objective measures of PSF given impacts on conducting in-person assessments due to the COVID-19 pandemic, particularly given the high-risk study population. A consequence of the pandemic was the large number of missing values for the objective TUG measure. Another limitation was the delay between baseline assessments and the start of group sessions due, in part, to COVID-19 restrictions but also due to the time required to identify enough participants in a given geographical area to create an FMG or EC group. This limitation highlights the challenges of delivering an in-person, group-based intervention, which increases as patients move from acute care to community settings for rehabilitation.[44] Although transportation was provided as a practical measure to facilitate participation, the challenges of identifying, assembling, and coordinating in-person group sessions in a timely manner over large geographical areas remained. Finally, across both study groups, most individuals included were New Zealand European. Hence, our findings may not generalize to populations with varying racial and ethnic compositions.

CONCLUSIONS

We found no evidence of significant group-level benefits of FMG over and above general stroke education within 3 to 24 months poststroke in patients with clinically significant fatigue. FASTER findings are not sufficient to change current clinical practice. Nevertheless, this study provides further insight into educational, group-based interventions for PSF that should continue to be examined to support those living with PSF, including the consideration of individual-level changes.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S4

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