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Immune-inflammatory effects of the multicomponent intervention FIBROWALK in outdoor and online formats for patients with fibromyalgia

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ABSTRACT

The multicomponent intervention FIBROWALK integrates pain science education (PSE), therapeutic exercise, cognitive behavioral therapy (CBT), and mindfulness training for treating fibromyalgia (FM). This study investigated the effects of the FIBROWALK in online (FIBRO-On) and outdoor (FIBRO-Out) formats compared to treatment-as-usual (TAU) on core clinical variables along with serum immune-inflammatory biomarkers and brain-derived neurotrophic factor (BDNF). Furthermore, the predictive value of these biomarkers on clinical response to FIBROWALK was also evaluated. 120 participants were randomly divided into three groups: TAU, TAU + FIBRO-On or TAU + FIBRO-Out. Clinical and blood assessments were conducted pre-post treatment. Both FIBRO-Out and FIBRO-On showed effectiveness (vs TAU) by improving functional impairment and kinesiophobia. Individuals allocated to FIBRO-Out (vs TAU) additionally showed decreases in pain, fatigue, depressive symptoms, and serum IL-6 and IL-10 levels along with IL-6/IL-4 ratio; patients allocated to FIBRO-On only showed a less stepped increase in IL-6 compared to TAU. An exaggerated pro-inflammatory profile along with higher levels of BDNF at baseline predicted greater clinical improvements in both active treatment arms. Our results suggest that FIBROWALK −in online and outdoor formats- is effective in individuals with FM and has significant immune regulatory effects in FM patients, while immune-inflammatory pathways and BDNF levels may in part predict its clinical effectiveness.

Trial registration number NCT05377567 (clinicaltrials.gov).

1. Introduction

Fibromyalgia (FM) stands out as a highly prevalent syndrome, affecting approximately 2.7 % of the global population, with a particularly notable prevalence among women aged 40–50 years (Heidari et al. 2017; Häuser et al. 2015). The hallmark features of FM include persistent musculoskeletal pain, fatigue, and sleep disturbances, frequently intertwined with anxiety and depressive disorders

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(Lichtenstein et al. 2018). Multiple physiological factors are posited to underlie the symptomatology of FM, with the central nervous system assuming a pivotal role, contributing significantly to the manifestation and persistence of symptoms (de Tommaso et al. 2022; Sawaddiruk et al. 2017; Sluka and Clauw, 2016). Several studies have reported elevated levels of pro-inflammatory cytokines and chemokines (e.g., IL-1, IL-6, CXCL8, TNF-α) alongside reduced levels of anti-inflammatory cytokines (e.g., IL-4, IL-5, IL-10, IL-13) in individuals with FM (Bäckryd et al., 2017; Rodriguez-Pinto et al., 2014; Sluka and Clauw, 2016). These findings support the hypothesis of chronic low-grade systemic immune-inflammatory activation in FM, potentially lowering pain thresholds and contributing to peripheral nerve sensitization (Rodriguez-Pinto et al., 2014). Additionally, a systematic review and *meta*-analysis by Andrés-Rodríguez et al. (2020) highlighted mild immune alterations in individuals with FM, suggesting an imbalance between upregulated immune-inflammatory and immunoregulatory pathways, marked by elevated levels of IL-6, IL-17A, and IL-4. Both systemic and neuro-inflammation likely play a role in exacerbating FM symptoms, such as pain sensitivity, fatigue, and sleep disturbances (Andrés-Rodríguez et al., 2020). Notably, these immune aberrations are linked to dysregulation in biomarkers related to neuronal plasticity, including brain-derived neurotrophic factor (BDNF) (Deitos et al., 2015). BDNF, a neurotrophin crucial for neuroplasticity, is involved in pain modulation, nociception, and hyperalgesia, all of which are disrupted in FM (Xiong et al., 2024; Nugraha et al., 2012). Elevated BDNF levels in FM patients contribute to widespread hyperalgesia (Polli et al., 2020), and modulating BDNF through therapeutic interventions is hypothesized to reduce pain intensity (Di-Bonaventura et al., 2023).

Currently available treatments for FM are not curative and have limited efficacy (Häuser et al., 2015). Concerning pharmacological interventions, the European League Against Rheumatism (EULAR) recommends using pharmaceuticals primarily for cases involving severe pain and sleep disturbances (Häuser et al. 2015; Macfarlane et al. 2017). Non-pharmacological strategies demonstrated more ubiquitous effects than pharmacological ones, often exhibiting slightly larger effect sizes compared to pharmaceutical options (Perrot and Russell, 2014; Nüesch et al. 2013; Hong-Baik et al. 2023). These non-pharmacological approaches encompass diverse interventions such as pain science education (PSE), therapeutic physical exercise, cognitive behavioral therapy, and mindfulness training where their main goal is to alleviate symptoms and enhance the overall quality of life for individuals living with FM (Macfarlane et al. 2017). The effectiveness of multicomponent interventions combining exercise, psychological support, and education in FM treatment is well-supported (Thieme et al. 2017; Sharpe et al. 2020). These comprehensive approaches are often regarded as the optimal standard for managing the condition (De Miquel et al. 2010; Häuser et al. 2009; Macfarlane et al. 2017; Rivera et al. 2006; Thieme et al. 2017).

Non-pharmacological interventions, such as CBT, have been shown to modulate immune responses and reduce inflammation, further highlighting their clinical relevance (Andrés-Rodríguez et al. 2019; Sanada et al., 2015). A systematic review and *meta*-analysis by Shields et al. (2020) reported improvements in immune function following psychosocial interventions, with CBT and multicomponent programs showing the most significant effects on reducing pro-inflammatory biomarkers. Other studies suggest that multicomponent interventions, physical exercise, and dietary modifications may have anti-inflammatory effects, particularly on markers like IL-6 and CXCL8 (Sanada et al., 2015). Randomized controlled trials also indicate that mindfulness and compassion-based interventions can reduce FM symptoms and lower serum BDNF levels compared to active control groups (Montero-Marin et al. 2019; Sanabria-Mazo et al., 2020).

FIBROWALK is a 3-month multicomponent intervention for individuals with FM combining PSE, therapeutic physical exercise, CBT and mindfulness added to TAU, which has shown substantial improvements in functionality, pain, kinesiophobia, physical function, fatigue, anxiety, and depressive symptomatology in FM patients (Serrat et al. 2020, 2021a, 2021b, 2022a). It has demonstrated short-term clinical effectiveness compared to treatment-as-usual (TAU) in various settings, including hospitals, outdoor environments, and online platforms, although the studies conducted until now showed some methodological weaknesses (Serrat et al. 2022b). Teletherapy approaches like online FIBROWALK (FIBRO-On) are particularly promising in overcoming logistical and health barriers, potentially enhancing treatment adherence (Li et al. 2020; Schwamm et al. 2020; White et al. 2022) and were particularly useful in pandemic times (Serrat et al. 2021a). Similarly, nature-based therapeutic approaches, exemplified by outdoor FIBROWALK (FIBRO-Out), have been shown to be an effective approach in improving mental health across various clinical conditions, including chronic pain and FM (López-Pousa et al. 2015; Serrat et al. 2020; Stanhope et al. 2020). In this regard, compared to therapeutic exercise performed indoors, exercise in natural settings has been associated with greater feelings of revitalization and positive engagement, reductions in tension, confusion, anger and depressive symptomatology, and increased energy (Thompson Coon et al. 2011). In addition, there is evidence that exercising outdoors (vs. indoors) may also promote directed attention and social interactions, which may positively influence future intention to maintain an exercise routine (Rogerson et al. 2016). Furthermore, exposure to nature has been shown to positively affect immunological health, including reduced expression of pro-inflammatory cytokines and increased levels of anti-inflammatory cytokines (for a review, see Andersen et al., 2021). This suggests that adapting non-pharmacological interventions to outdoor settings may offer additional benefits in promoting immune-inflammatory normalization in patients with FM.

This trial, embedded within the On&Out study (Serrat et al. 2022b), aimed to assess the short-term effectiveness of adding the multicomponent FIBROWALK intervention, delivered in both outdoor (i.e., FIBRO-Out) and online (i.e. FIBRO-On) formats, to TAU compared to TAU alone, and to evaluate their impact on specific serum immune-inflammatory biomarkers and BDNF levels, for which there is some evidence of alteration in FM. We hypothesized that, compared to TAU, the interventions would reduce pro-inflammatory markers (IL-6, CXCL8, IL-17A, and hs-CRP) and BDNF levels, while increasing anti-inflammatory cytokines (IL-4 and IL-10), with the outdoor intervention expected to be more effective at reducing pro-inflammatory status and promoting anti-inflammatory effects. This exploratory study compares the impact of the same multicomponent program delivered in different formats, which have not been previously assessed for their effects on either biomarkers or clinical outcomes in FM. Finally, we explored the predictive capacity of baseline biomarkers to assess clinical improvement, aiming to identify potential biomarker profiles that could help predict therapeutic effectiveness and take a step toward more personalized treatment approaches.

2. Material and methods

2.1. Study design

The current study adopts a pre-post parallel-group, single-blinded randomized design, employing a computer-generated randomization list featuring three arms: 1) TAU, 2) TAU plus FIBRO-On, and 3) TAU plus FIBRO-Out. This study is embedded within a large randomized controlled trial (RCT) involving a total of 225 participants distributed across the three study arms described above, with a subsequent 6-month follow-up (Serrat et al. 2022b), received approval from the Ethics Committee of Clinical Investigation of the Hospital Universitari Vall d'Hebron (HUVH) in Barcelona, and was registered at ClinicalTrials.gov (NCT05377567). The research adhered to ethical standards outlined in the Declaration of Helsinki (current version: Fortaleza, Brazil, October 2013) and was conducted in accordance with the prescribed protocol and relevant legal requisites, including Law 14/2007, July 3, 2007, on

Biomedical Research.

2.2. Participants

A total of 120 individuals recruited from the HUVH Specialized Unit for Central Sensitivity Syndromes participated in the study. Previous RCTs of the FIBROWALK interventions demonstrated effect sizes ranging from d = 0.80 (FIBRO-On; Serrat et al. 2022b) to d = 1.83 (FIBRO-Out; Serrat et al. 2020). Based on these results, a minimum of 26 participants per condition (78 in total) with an alpha of 0.05 and a power of 0.80 was deemed necessary. Considering a 25 % dropout rate, the minimum final sample size was estimated at 33 participants per arm. However, this minimum was slightly increased to 40 per arm after reviewing previous RCTs on the effects of non-pharmacological treatments in FM on similar immune-inflammatory biomarkers (Andrés-Rodríguez et al. 2019; Montero-Marin et al. 2019).

All participants had to meet specific inclusion criteria: 1) adult females (≥18 years old), 2) diagnosis of FM according to American College of Rheumatology (ACR) 2010/2011 criteria, and 3) fluent in written and spoken Spanish. General exclusion criteria included: 1) receipt of psychological treatment within the last year or ongoing, 2) comorbid presence of severe mental disorders (e.g., schizophrenia) or other terminal clinical conditions or scheduled treatments that could disrupt study follow-up, 3) inability to consistently complete the weekly sessions/modules of the program, and 4) usual contraindications for measuring immune-inflammatory markers in blood (e.g., autoimmune diseases, recent physical trauma, cold/infection on the day of blood collection, needle phobia, pregnant or breastfeeding, and using oral or local corticosteroids, anti-cytokine biologic drugs, or oral contraceptives). Prior to randomization, written informed consent was obtained from all participants, assuring them of their voluntary participation and the option to withdraw from the study at any time.

2.3. Procedure

The study recruited participants through referrals from rheumatologists at the HUVH Specialized Unit for Central Sensitivity Syndromes and by contacting patients who had visited the Unit within the past six months. Telephone assessments by project physiotherapist identified eligible participants, who were then asked for written consent to participate in the study. Remote assessments of clinical and health services use were conducted, with a research assistant ensuring that participants understood the self-reported measures. Participants were randomly assigned to study groups following CONSORT guidelines (Schulz et al. 2010) using a computer program (1:1:1 ratio). Administrative staff communicated group assignments to participants via email. For those eligible for the biomarker substudy, a follow-up appointment was scheduled 3–5 days after the initial evaluation to collect blood samples, aiming to reach the required number of 40 subjects per arm. Fasting blood draws occurred within a specified time slot (8–10 a.m.) to minimize circadian variability. Participants were advised to avoid anti-inflammatory medications for 72 h beforehand to reduce the impact of medication on the study results. The same blood collection procedure was used after the intervention following the prespecified time interval.

The study withheld group assignment from evaluators and asked participants not to disclose their treatment. Due to its non-pharmacological nature, treatment assignment could not be blinded for participants nor therapists.

2.4. Study arms

2.4.1. TAU

While there is not a universally accepted treatment for FM, within the framework of Spanish healthcare, the TAU for FM primarily involves pharmacological interventions tailored to the individual symptom profile of each patient. Additionally, it typically includes recommendations for aerobic physical exercise adapted to each individual's limitations. Participants allocated to this treatment group were given the option to join either the FIBRO-On or FIBRO-Out programs upon completion of the trial.

2.4.2. Fibro-On

Developed from the FIBROWALK program (Serrat et al. 2020), it is designed to complement traditional treatments for FM by offering a comprehensive online intervention. It includes explanations and guidelines for practicing PSE, therapeutic physical exercise, CBT, and mindfulness, delivered through videos and slide presentations by the first author (MS), an experienced physical therapist and health psychologist. Each online session lasted 60 min, but participants were recommended to spend 120 min completing the exercises. Weekly, participants received links to the module videos via Adherence was monitored through weekly questionnaires, with direct support from the supervising therapist (MS) via mail or telephone for those who did not respond or reported problems. Initiated during confinement by COVID-19, FIBRO-On has been integrated into routine clinical practice at the Central Sensitivity Syndromes Specialized Unit of HUVH (Serrat et al. 2021a, 2022b).

2.4.3. Fibro-Out

The FIBRO-Out program is an outdoor version of the FIBROWALK program (Serrat et al. 2020) as a complementary element to TAU. It consisted of 12 weekly group sessions held in the "Parc del Cargol", a green area near HUVH in Barcelona, with 18–20 participants each. Identical to FIBRO-On, it integrates PSE, therapeutic physical exercise, CBT and mindfulness. The PSE, which is based on the "Explaining Pain" program by Butler and Moseley (2010), whose content uses examples, images and metaphors to deepen comprehension (Nijs et al. 2011). Psychological aspects are based on CBT with the aim of reshaping the understanding of pain, reducing pain catastrophizing, improving emotional regulation and sleep quality, and developing coping strategies (Moix and Kovacs, 2009). Mindfulness exercises, based on Mindfulness-Based Stress Reduction (MBSR) program (Kabat-Zinn, 2013), aim to train attention to the present experience, fostering a non-evaluative attitude.

The sessions were divided into two blocks: PSE and therapeutic exercise led by a physiotherapist (1 h duration), followed by CBT and mindfulness training conducted by a health psychologist (1 h duration). Each outdoor session began with a discussion of key issues and a review of previous concepts. Four pairs of therapists, trained in CBT and physiotherapy for FM or chronic pain, managed the groups after receiving specialized training and participating as co-therapists in a pilot program. Weekly meetings with the clinical study leader ensured consistency and addressed challenges. Treatment fidelity in the FIBRO-Out arm was monitored through assessments by independent experts, and participants were advised to continue their usual medication throughout the study.

2.5. Outcome variables

2.5.1. Study measures

- Sociodemographic questionnaire: gender, date of birth, marital status, cohabitation, educational level, and employment status.
- Clinical data: years with FM, comorbidity with other diagnosed medical/psychiatric conditions, current medication, body mass index (BMI).

2.5.2. Primary outcome measure

The *Revised Fibromyalgia Impact Questionnaire* (FIQR; Bennet et al. 2009) is a 21-item questionnaire (0–10 scale) that assesses the dimensions of physical dysfunction, the overall impact of FM and severity of the symptoms (i.e., pain, energy, stiffness, sleep quality, depression,

memory issues, anxiety, allodynia, balance problems, and increased sensitivity to noises, lights, smells, or temperatures), and is used to measure the impact of FM over the past week. This questionnaire is currently considered the "gold standard" for assessing functional impairment in individuals with FM. A total score for FIQR ranging from 0 to 100 can be obtained by adding the 3 subscales, with higher scores indicating greater FM severity. The Spanish version of the FIQR has an excellent internal consistency (α = 0.91–0.95) (Luciano et al. 2013).

2.5.3. Secondary outcome measures

Visual-analogue scale of perceived pain (VAS-Pain; Serrano-Atero et al. 2002) in which patients indicate their pain during the last week on a 10 cm line (0 = *No pain*, 10 = *Unbearable pain*).

Visual-analogue scale of perceived energy/fatigue (VAS-Fatigue; Serrano-Atero et al. 2002) in which patients indicate their fatigue during the last week on a 10 cm line (0 = *Lots of energy*, 10 = *No energy*).

The *Hospital Anxiety and Depression Scale* (HADS; Zigmond and Snaith, 1983) is used to quantify the severity of anxiety and depression symptoms. It consists of two dimensions (anxiety and depression) of 7 items each responding on a Likert scale of 4 points. Total scores of each scale (HADS-A and HADS-D) range from 0 to 21, where higher scores indicate greater symptom severity. The Spanish version of the HADS has demonstrated satisfactory internal consistency for anxiety (α = 0.83) and depression (α = 0.87) subscales in people with FM (Luciano et al. 2014).

The *Physical Function Subscale of the Short Form-36 Health Survey* (SF-36; Alonso et al. 1995) is used to measure physical function. It comprises a total of 10 items, which are answered on a Likert scale of 3 points. Total scores are transformed and can range from 0 to 100, with higher scores indicating better physical function. The Spanish version of the PF-SF-36 shows adequate internal consistency (α = 0.94).

The *Tampa Scale for Kinesiophobia* (TSK-11; Tkachuk and Harris, 2012) is a measure aimed at assessing fear of movement and comprises 11 items in a 4-point Likert scale with a total score ranging from 11 to 44, with higher scores indicating greater pain and fear of movement. The Spanish version of the TSK-11 (Gómez-Pérez et al. 2011) has an adequate internal consistency (α = 0.79).

The *FIBROWALK Fidelity Measure* (FFM; Serrat et al. unpublished manuscript) was employed to assess the extent to which therapists adhered to the FIBROWALK protocol. This tool specifically examines therapists' fidelity to the FIBROWALK principles, protocols, and prescribed methods, ensuring the therapy is delivered as intended. This measure assessed therapists' adherence to FIBROWALK principles across five areas: general organization, therapist knowledge, personal skills, therapy-related skills, and group management. Each of the 20 items was rated on a 5-point Likert scale (0 = not met, 4 = fully met), with total scores ranging from 0 to 20 with higher scores indicating greater treatment fidelity. It is recommended that at least three out of the 12 sessions are evaluated: one within the first four sessions, another in the middle four sessions, and the last one during the final four sessions.

2.6. Serum levels of immune-inflammatory markers and BDNF

Blood samples were collected in vials that were centrifuged and the resulting serum was stored frozen at −80 °C until analysis. All samples (pre and post) were analyzed in a single analytical batch to reduce inter-assay variability (approximately 15 %). Serum levels of the cytokines and chemokines IL-6, CXCL8, IL-17A, IL-4 and IL-10, in addition to hs-CRP, were assessed. For cytokine quantification, MerckMillipore Milliplex® reagents analyzed on a Luminex® platform were used. The highly sensitive Human High Sensitivity T Cell multiplex kit (catalog number: ME-HSTCMAG-28SK-05) was used. The hs-CRP was quantified by turbidimetry on a Siemens Atellica autoanalyzer. BDNF levels were assessed using an ELISA kit (reference SEA011Hu-96 T). Sample analysis was performed by the Echevarne Laboratory. Detection concentration ranges: IL-6 (0.73–10,000 pg/ml), CXCL8 (0.31–10,000 pg/ml), IL-17A (2.93–20,000 pg/ml), IL-4 (7.32–10,000 pg/ml), IL-10 (1.46–40,000 pg/ml), hs-CRP (0.1–50 mg/L), and BDNF (31.2–2,000 pg/ml). Biomarkers were assessed only at baseline and post-intervention for the following reasons: a) evidence of changes in immune-inflammatory markers and BDNF levels after non-pharmacological interventions of similar duration (Montero-Marin et al. 2019; Pérez-Aranda et al. 2019; Sanada et al. 2015); b) lower risk of sample loss (vs. assessment at 6 months); c) possibility of using baseline levels and pre-post change as a mediator of clinical changes at 6-month follow-up; and d) budgetary constraints.

2.7. Statistical analyses

Descriptive statistics were calculated for all variables and presented as means (*M*) and standard deviations (*SD*) if continuous, or as absolute numbers (*n*) and percentages (%) if categorical. Levene's test was used to evaluate the equality of variances of continuous variables and the Kolmogorov-Smirnov test was used to test the normality and distribution of the samples. In those cases where biomarker concentrations were below the detection threshold (31.4 % in IL-6, 1 % in CXCL8, 1 % in IL-17a, 16.2 % in IL-4, 38.1 % in IL-10, 1.9 % in hs-CRP and 0 % in BDNF), the detection limit value was assigned.

2.7.1. Analyses of short-term clinical effectiveness

The primary effectiveness analysis to assess the treatment effect on FM was conducted using an intention-to-treat (ITT) approach, focusing on changes in FIQR total scores (McCoy, 2017). The analysis used restricted maximum likelihood (REML) mixed-effects linear regressions, which are suitable for handling correlated repeated measures and provide more accurate variance estimates for small or unbalanced data sets (Egbewale et al. 2014). This method did not require imputation for missing data, as longitudinal mixed-model analysis can be performed without it for any type of missing data (Twisk et al. 2013).

The analysis assessed the interaction between treatment groups and time by calculating unstandardized regression coefficients (B) and 95 % confidence intervals (95 % CI) for these interactions at post-treatment. Effect sizes for between-group differences were measured using Cohen's d. Effect sizes were calculated for the mean differences of groups with unequal sample size within a pre-post-control design (Morris, 2008), applying standard cut-off points for small (0.20), medium (0.50) and large (0.80) effects. The same statistical approach was applied to the secondary clinical endpoints.

2.7.2. Analyses of changes in biomarkers

The effect of the interventions on immune-inflammatory markers and BDNF levels was assessed with REML. Cytokine/chemokine, hs-CRP, and BDNF values were natural log-transformed to normalize skewed data distributions. Additionally, to assess the balance between pro-inflammatory and anti-inflammatory responses, and to explore how this balance might influence treatment outcomes and guide strategies for restoring immune homeostasis, inflammatory balance indexes were calculated following the approach of Andres-Rodriguez et al. (2019) and Maes and Carvalho (2018). The calculated ratios included: IL6/IL4, IL6/IL10, CXCL8/IL4, CXCL8/IL10, hsCRP/IL4, hsCRP/IL10, IL-17A/IL4, and IL-17A/IL10. Since it has been reported that some medical treatments, such as antidepressants, can affect some cytokine levels (Hannestad et al. 2011), antidepressant status (0 = not taking, 1 = taking) it was also included as a covariate in the REML analyses for all clinical outcomes and biomarkers.

All analyses were conducted on an ITT basis and sensitivity analyses were also conducted in a per-protocol approach or PP (i.e. including only those participants who attended 9 or more sessions out of 12).

2.7.3. Predictive value of baseline biomarkers on the clinical response of FIBROWALK

We compared sociodemographic and clinical characteristics and

biomarker values at baseline between responders and non-responders in each of the FIBROWALK arms by computing t-tests or chi-square tests. Furthermore, we examined the predictive value of baseline immune biomarkers on the clinical effects of FIBROWALK, following the approach by Judd et al. (2001). To carry this out, change scores (calculated as post-treatment minus pre-treatment scores) for the assessed clinical measures were analyzed in relation to baseline levels of immune biomarkers and their indices using a stepwise approach. Sociodemographic and clinical variables (e.g., age, BMI, antidepressant use, ISPS, and comorbidities such as CFS, depression, and anxiety) were included in the first step of the regression analyses and baseline biomarker levels and related ratios in a second step, both steps using the stepwise method. *Negative beta values* between baseline variables and change scores should be interpreted in the sense that *higher* baseline biomarker values predict *greater* clinical improvements for all clinical measures except for the SF-36 scale, which should be interpreted inversely.

All analyses were conducted with SPSS v26.0 and the significance level was established at $\alpha = 0.05$ (two-tailed).

3. Results

The flowchart of the On&Out substudy (based on the consolidated standards of reporting trials [CONSORT] recommendations) is displayed in Fig. 1.

3.1. Demographic and baseline characteristics of the groups

A total of 120 individuals with FM ($n = 40$ per group) were included and randomized to the three treatment arms. Participants had a mean age of 55 years. About 28 % were employed, 64 % were married or in a stable relationship, 83 % were living with someone, and 78 % had at least a high school education. 47 % of the participants reported some level of disability, and 51 % had a comorbid diagnosis of chronic fatigue syndrome. Participants showed high functional impairment, with a mean FIQR score of 70 out of 100 (Table 1 and S1).

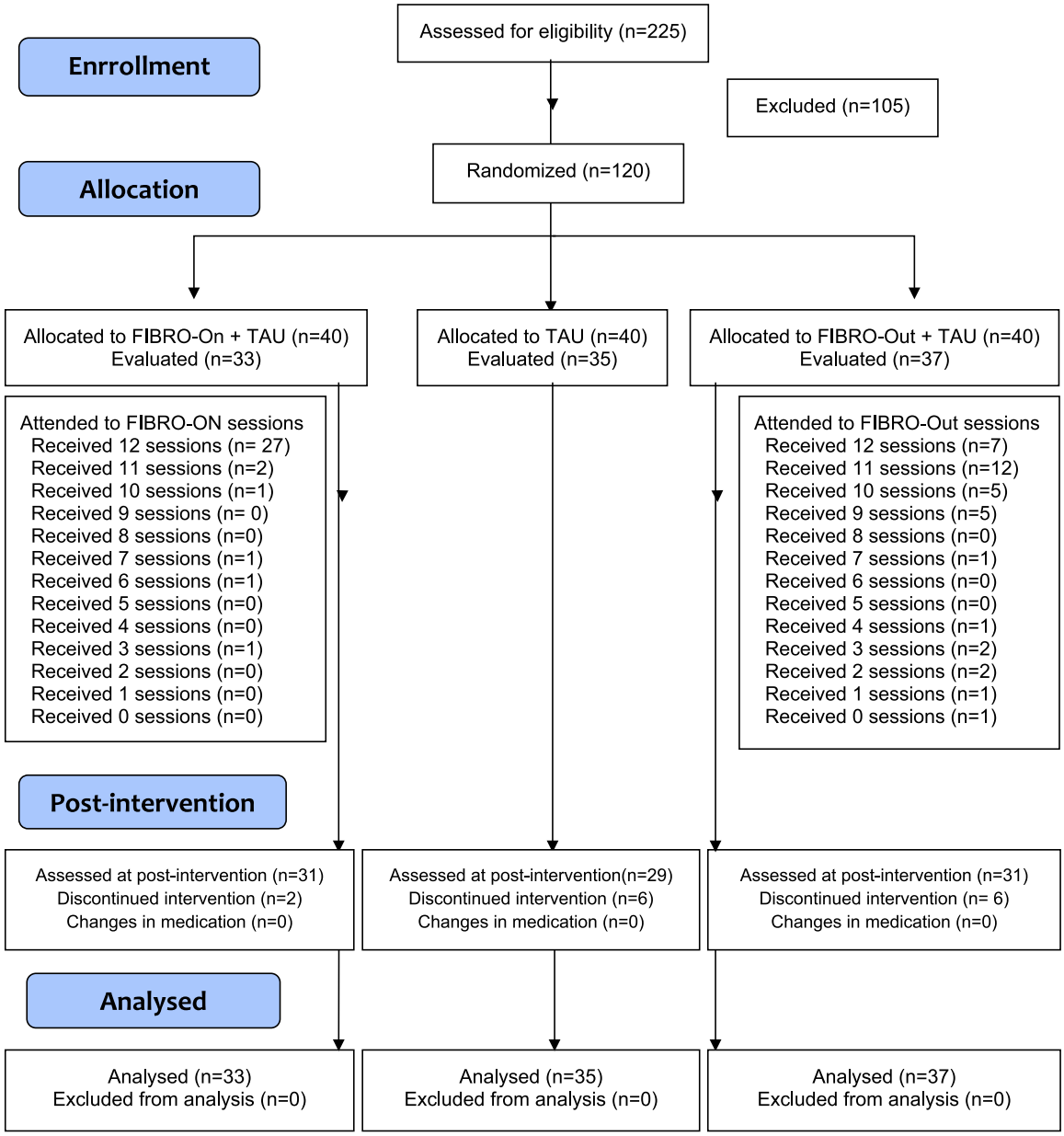

Fig. 1. Flowchart of the On&Out substudy.

Table 1
Demographic and baseline clinical characteristics by treatment groups.

	TAU	FIBRO-Out	FIBRO-On
	(*n* = 35)	(*n* = 37)	(*n* = 33)
Age (years), *M* (*SD*)	57.89 (9.71)	55.49 (10.16)	54.73 (10.33)
BMI, *M* (*SD*)	29.40 (5.57)	28.24 (5.38)	27.71 (5.69)
ISPS, *M* (*SD*)	17.86 (10.88)	10.43 (9.88)	13.15 (9.22)
With CFS, *n* (%)	18 (51.40)	17 (45.90)	19 (57.60)
Civil Status, *n* (%)			
Single	3 (8.60)	3 (8.10)	5 (15.20)
Married/Living with partner	23 (65.70)	22 (59.50)	22 (66.70)
Divorced/Separated	7 (20.00)	6 (16.20)	4 (12.20)
Widow	2 (5.70)	6 (16.20)	2 (6.10)
Not living Alone, *n* (%)	28 (80.00)	31 (83.80)	28 (84.80)
Educational Level, *n* (%)			
Without Studies	2 (5.70)	0 (0.00)	0 (0.00)
Primary Studies not completed	4 (11.40)	3 (8.10)	2 (6.10)
Primary Studies	9 (25.70)	8 (21.60)	6 (18.20)
Secondary Studies	15 (42.90)	17 (45.90)	16 (48.50)
University	4 (11.40)	8 (21.60)	7 (21.20)
Other	1 (2.90)	1 (2.70))	2 (6.10)
Employment Situation, *n* (%)			
Homemaker	4 (11.40)	3 (8.10)	3 (9.10)
Active	9 (25.70)	8 (21.60)	12 (36.40)
On leave	5 (14.30)	11 (29.70)	7 (21.20)
Unemployed with allowance	2 (5.70)	2 (5.40)	0 (0.00)
Unemployed without allowance	1 (2.90)	3 (8.10)	2 (6.10)
Retired/Pensioner	8 (22.90)	3 (8.10)	3 (9.10)
Temporary work disability	2 (5.70)	1 (2.70)	3 (9.10)
Other	4 (11.40)	6 (16.20)	3 (9.10)
Medication, *n* (%)			
Analgesics	31(88.60)	32 (86.50)	27 (81.80)
Anticonvulsants	11 (31.40)	7 (18.90)	6 (18.20)
Antidepressants	30 (85.70)	30 (81.10)	16 (48.50)
Other	29 (82.90)	29 (78.40)	25 (75.80)
Incapacity certificate, *n* (%)			
No	16 (45.70)	23 (62.20)	17 (51.50)
Less than 33 %	1 (2.90)	0 (0.00)	1 (3.00)
Between 33 % and 66 %	12 (34.30)	12 (32.40)	9 (27.30)
More than 66 %	6 (17.10)	2 (5.40)	4 (12.10)
Clinical variables, *M* (*SD*)			
FIQR (0–100)	69.24 (18.48)	71.17 (14.80)	70.63 (15.99)
VAS-Pain (0–10)	7.89 (1.92)	7.95 (1.45)	7.73 (1.61)
VAS-Fatigue (0–10)	7.26 (2.74)	7.73 (2.02)	7.91 (1.96)
HADS-Anxiety (0–21)	14.49 (4.12)	12.35 (3.87)	12.36 (5.04)
HADS-Depression (0–21)	11.97 (4.20)	12.32 (3.71)	11.58 (4.13)
SF-36 (0–100)	30.86 (23.31)	33.65 (21.49)	33.76 (21.53)
TSK-11 (11–44)	31.26 (8.63)	28.89 (7.91)	32.64 (7.70)

Note: No comparison was found to be statistically significant (p≦0.05). BMI, Body Mass Index; CFS, Chronic Fatigue Syndrome; FIBRO-On, FIBROWALK Online; FIBRO-Out, FIBROWALK Outdoor; FIQR, Revised Fibromyalgia Impact Questionnaire; HADS-A and HADS-D, Hospital Anxiety and Depression Scale; ISPS, Illness Self-Perceived Start; M, Mean; SF-36, Physical function subscale of the Short Form-36 Health Survey; TAU, treatment-as-usual; TSK-11, Tampa Scale for Kinesiophobia; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain.

3.2. Short-term effectiveness of the FIBRO-On and FIBRO-Out on clinical measures

The therapists involved in the FIBRO-Out intervention achieved an average FFM score of 18.42 out of 20 (SD = 0.55), with individual scores ranging from 17.95 to 19.46. The therapist tandems, consisting of a psychologist and a physiotherapist, across the four FIBRO-Out groups had an average FFM score of 18.75 out of 20 (SD = 0.53), with tandem averages varying between 18.07 and 19.17.

Significant between-group differences were observed in clinical variables at post-treatment (Table 2). Compared to TAU, significantly larger decreases in FIQR scores were found in the FIBRO-Out group (medium effect size) and in the FIBRO-On group (small effect size). The following secondary outcome variables showed significantly larger improvements in the FIBRO-Out group vs TAU: VAS-Pain, VAS-Fatigue and HADS-D and TSK (medium effect sizes). No significant differences between FIBRO-Out and TAU were found for the HADS-A and the SF-36. When comparing FIBRO-On and TAU, significant effects were only found in the secondary outcome variable of TSK (large effect size). No significant differences were found regarding any clinical variable when comparing both active treatment arms (all $p > 0.05$).

When replicating the analyses on PP approach we found similar treatment effects to those observed in ITT analyses (Supplementary Table S2). Unlike the ITT approach, we found that patients in the FIBRO-On group when compared to TAU presented greater reductions in VAS-Fatigue scores (medium effect size) and that the FIBRO-Out arm showed significant differences in VAS-Pain scores (medium effect size) compared to TAU.

3.3. Effects of the FIBRO-On and FIBRO-Out on serum biomarkers

Compared to TAU, the FIBRO-Out group showed greater reductions in IL-6 levels (small effect size), while the FIBRO-On group exhibited only an attenuation of the IL-6 increase over time (relative to TAU). Additionally, larger reductions in IL-10 values were observed in the FIBRO-Out group compared to TAU (small effect size). No other significant differences were found for any other immune-inflammatory biomarker nor BDNF levels (all $p > 0.05$). For more details, see Table 3.

Regarding supplementary analyses on inflammatory indexes, significant effects of FIBRO-Out were found in the IL-6/IL-4 ratio where FIBRO-Out produced a decrease in IL-6/IL-4, which is significantly different from the pattern of change seen in the TAU group, where we observed an increase in this ratio. Larger decreases in CXCL8/IL-4 ratio were also found in the FIBRO-On arm compared to FIBRO-Out (Table S3). We added as a covariable the antidepressant status and found no effect of antidepressants on our findings (Table S4 and S5).

When replicating the analyses in the PP approach, differences were found in the results from those observed in the ITT analyses (see Table S6). Participants in the FIBRO-Out group showed significantly greater decreases in IL-4 levels compared to FIBRO-On (small effect size); whereas IL-10 levels in the FIBRO-Out group (vs. TAU), showed only a trend towards statistical significance ($p = 0.051$). It was also observed that changes in the IL-6/IL-4 ratio in the FIBRO-Out group were no longer significant relative to TAU. Participants in the FIBRO-On group (vs TAU) showed significantly larger decreases in the CXCL8/IL-4 ratio (small effect size). This effect was not observed in the FIBRO-Out group. Decreases in the IL-17A/IL-4 ratio were significantly larger in the FIBRO-On group compared to FIBRO-Out (small effect size) (Table S7). No other significant differences were found for any other biomarker. Table 4 summarizes the main effects of the ITT and PP analyses, highlighting significant results and trends in clinical and biomarker outcomes.

3.4. Predictive role of immune-inflammatory biomarkers on response to treatments

While FIBRO-On and FIBRO-Out demonstrated an overall improvement in the clinical symptomatology of study participants, a considerable proportion of participants did not show a clinically relevant response to treatment. Specifically, 62.5 % of the FIBRO-On group and 60.6 % of the FIBRO-Out group failed to show a 20 % or higher reduction in the FIQR score. Subsequently, we categorized participants into responders and non-responders and conducted analyses looking for potential baseline differences between these two groups (refer to Tables S8 and S9). Notably, no statistically significant differences between responders and non-responders emerged in sociodemographic nor baseline clinical variables, session attendance, nor baseline levels in evaluated biomarkers (all $p > 0.05$).

However, regression analyses indicated that in FIBRO-Out, higher levels of BDNF before treatment predicted greater improvement in the HADS-A and TSK; higher baseline levels of hs-CRP also predicted larger improvements in the TSK (Table S10). In FIBRO-On, higher levels of IL-4

Table 2
Descriptive Statistics and Between-group Analysis for Primary and Secondary Measures (ITT Approach).

	TAU (*n* = 35)	**TAU + FIBRO-On (*n* = 33)**	**TAU + FIBRO-Out (*n* = 37)**			**TAU vs TAU + FIBRO-On**			**TAU vs TAU + FIBRO-Out**			**TAU + FIBRO-On vs TAU + FIBRO-Out**		
	Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**											
				F	***p***	***d***	***t* (*p*)**	***β* (95 % *CI*)**	***d***	***t* (*p*)**	***β* (95 % *CI*)**	***d***	***t* (*p*)**	***β* (95 % *CI*)**
Primary outcome														
FIQR (0–100) *				3.848	**0.024**									
Baseline	*n* = 35 69.24 (18.48)	*n* = 33 70.63 (15.99)	*n* = 37 71.17 (14.80)											
Post-Treatment	*n* = 34 67.57 (18.58)	*n* = 32 61.36 (18.83)	*n* = 33 61.09 (14.62)			0.43	**−2.04 (0.044)**	−7.25 (−14.32 to −0.19)	0.50	**−2.64 (0.010)**	−9.23 (−16.16 to −2.30)	0.05	−0.55 (0.580)	−1.97 (−9.01 to 5.06)
Secondary outcomes														
VAS-*Pain* (0–10) *				2.924	0.058									
Baseline	*n* = 35 7.89 (1.92)	*n* = 33 7.73 (1.61)	*n* = 37 7.95 (1.45)											
Post-Treatment	*n* = 34 7.59 (2.46)	*n* = 32 6.97 (1.86)	*n* = 33 6.58 (1.70)			0.26	−0.80 (0.426)	−0.37 (−1.28 to 0.54)	0.63	**−2.38 (0.019)**	−1.07 (−1.97 to −0.17)	0.36	−1.54 (0.126)	−0.70 (−1.61 to 0.20)
VAS-*Fatigue* (0–10) *				2.671	0.074									
Baseline	*n* = 35 7.26 (2.73)	*n* = 33 7.91 (1.95)	*n* = 37 7.73 (2.02)											
Post-Treatment	*n* = 34 7.79 (1.88)	*n* = 32 7.19 (2.00)	*n* = 33 6.97 (1.82)			0.52	−1.89 (0.061)	−1.22 (−2.49 to 0.05)	0.53	**−2.08 (0.039)**	−1.31 (−2.56 to −0.06)	0.02	−0.15 (0.880)	−0.10 (−1.36 to 1.16)
HADS-A (0–21) *				0.272	0.763									
Baseline	*n* = 35 14.49 (4.12)	*n* = 33 12.36 (5.04)	*n* = 37 12.35 (3.86)											
Post-Treatment	*n* = 34 14.03 (4.27)	*n* = 32 11.16 (5.09)	*n* = 33 11.61 (3.99)			0.16	−0.69 (0.487)	−0.57 (−2.18 to 1.04)	0.07	−0.13 (0.891)	−0.11 (−1.69 to 1.47)	−0.10	0.56 (0.574)	0.46 (−1.15 to 2.07)
HADS-D (0–21) *				4.213	**0.017**									
Baseline	*n* = 35 11.97 (4.20)	n = 33 11.58 (4.13)	*n* = 37 12.32 (3.71)											
Post-Treatment	*n* = 34 12.68 (4.82)	*n* = 32 10.71 (4.63)	*n* = 33 10.45 (4.29)			0.38	−1.63 (0.105)	−1.36 (−3.02 to 0.29)	0.65	**−2,89 (0.005)**	−2.37 (−4.00 to −0.74)	0.25	−1.20 (0.230)	−1.00 (−2.65 to 0.64)
SF-36 (0–100) *				0.522	0.595									
Baseline	*n* = 35 30.86 (23.31)	*n* = 33 33.79 (20.08)	*n* = 37 33.65 (21.49)											
Post-Treatment	*n* = 34 32.35 (23.07)	*n* = 32 38.91 (23.51)	*n* = 33 34.24 (20.70)			−0.17	0.74 (0.459)	2.95 (−4.93 to 10.84)	0.04	−0.24 (0.809)	−1.89 (−8.68 to 6.79)	0.22	−0.98 (0.327)	−3.90 (−11.76 to 3.95)
TSK-11 (11–44) *				11.123	**(<0.001)**									
Baseline	*n* = 35 31.26 (8.63)	*n* = 33 32.64 (7.70)	*n* = 37 28.89 (7.91)											

(*continued on next page*)

Table 2 (*continued*)

	TAU (n = 35) Mean (*SD*)	TAU + FIBRO-On (n = 33) Mean (*SD*)	TAU + FIBRO-Out (n = 37) Mean (*SD*)	TAU vs TAU + FIBRO-On			TAU vs TAU + FIBRO-Out			TAU + FIBRO-On vs TAU + FIBRO-Out		
Post-Treatment	n = 34 29.82 (9.43)	n = 32 24.22 (7.71)	n = 33 23.18 (6.56)	0.84	**−4.60 (< 0.001)**	−6.66 (−9.54 to −3.79)	0.51	**−3.17 (0.002)**	−4.51 (−7.33 to −1.69)	−0.34	1.49 (0.139)	2.15 (−0.71 to 5.01)

Note. The baseline level of the variable was controlled. *M* and *SD* are not adjusted. When antidepressants are taken as a covariate there is no significant difference. *The baseline level of the variable and study waves are significant covariates in the model. *CI*, confidence interval; *d*, Cohen's *d* as an effect size measure; FIBRO-On, FIBROWALK Online; FIBRO-Out, FIBROWALK Outdoor; FIQR, Revised Fibromyalgia Impact Questionnaire; HADS-A and HADS-D, Hospital Anxiety and Depression Scale; ITT, intention-to-treat; β, regression coefficients; SF-36, Physical function subscale of the Short Form-36 Health Survey; TAU, treatment-as-usual; TSK-11, Tampa Scale for Kinesiophobia; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain.

predicted lesser improvements in FIQR scores; greater levels of BDNF predicted larger improvements in the SF-36; finally, higher values in the CXCL8/IL-10 ratio predicted greater improvements in VAS-Pain and VAS-Fatigue (Supplementary Table S11).

4. Discussion

In line with previous findings on the short-term effectiveness of FIBROWALK in inpatient (Serrat et al. 2021b), outdoor (Serrat et al. 2020), and online (Serrat et al. 2021a, 2022b) settings, our study demonstrated that both FIBRO-On and FIBRO-Out effectively reduced functional impairment and kinesiophobia in FM. Additionally, we found both approaches to be equally effective in improving these core outcomes in FM, with the outdoor version of FIBROWALK exhibiting broader clinical effects compared to the online format, as it also alleviated pain, fatigue, and depressive symptoms relative to TAU, whereas the online format did not. In this regard, nature-based therapeutic approaches such as outdoor FIBROWALK (Serrat et al. 2020) have been previously shown to be useful in improving mental health in different clinical conditions (Trøstrup et al. 2019), including chronic pain conditions and FM in particular (López-Pousa et al., 2015; Serrat et al. 2020; Stanhope et al. 2020). Similarly, studies such as White et al. (2022) and Serrat et al. (2021a) have highlighted the efficacy of online therapy in chronic pain populations, including FM.

Surprisingly, despite previous findings (Serrat et al. 2020, 2021a), the FIBROWALK interventions in the present study did not significantly impact anxiety symptoms or physical function compared to TAU, with very small effect sizes observed. Several factors may explain these results, including a smaller sample size, greater variability in physical function scores, and lower comorbidity with CFS compared to prior trials. Additionally, the use of linear mixed models, which tend to yield more conservative estimates, may have also contributed to the lack of significant findings.

Regarding the effects of FIBROWALK on serum biomarkers, we observed significant reductions in both IL-6 and IL-10 levels in the FIBRO-Out group compared to TAU, indicating a potential immune-inflammatory modulation. While previous studies have reported reductions in serum levels of CXCL8 and IL-6 in individuals with FM following physical activity, multidisciplinary interventions, or dietary changes (Sanada et al., 2015), our study found a significant effect on IL-6 but not on CXCL8. IL-6 is often associated with a pro-inflammatory response, as it stimulates the immune system and the production of acute-phase proteins; however, it also plays an anti-inflammatory role by inducing cytokine antagonists and supporting neuronal regeneration (Maes et al., 2016; Raison et al., 2018). The dual nature of IL-6 becomes evident during exercise, where it is released as a myokine from contracting muscles, modulating the immune response with anti-inflammatory effects (Docherty et al., 2022; Nash et al., 2023; Hong-Baik et al., 2023). Importantly, the impact of IL-6 varies depending on the nature of the exercise: acute bouts tend to trigger short-term increases, while regular, sustained physical activity leads to long-term reductions (Docherty et al., 2022; Nash et al., 2023). In our study, the FIBRO-Out group demonstrated a decrease in IL-6, while the FIBRO-On group showed a slight increase. This difference may be explained by the higher level of supervision and support provided in the FIBRO-Out intervention, which likely encouraged greater adherence to regular home-based exercises. Consequently, this more consistent physical activity may have contributed to the observed reduction in IL-6 levels, supporting the idea that regular exercise is more effective than acute exercise in lowering IL-6 over time.

On the other hand, IL-10 plays a primarily anti-inflammatory role, suppressing pro-inflammatory cytokines, modulating the activity of various immune cells, and inhibiting antigen presentation, being key to immune balance through the Compensatory Immune Regulatory Reflex System (Maes and Carvalho, 2018). The fluctuation of anti-inflammatory cytokines, such as IL-10, in conjunction with pro-inflammatory ones (such as IL-6 in this instance), to regulate immunity (Prather et al. 2007), may also contribute to the observed reduction in IL-10 levels.

Interestingly, participants in the FIBRO-On group showed a less pronounced increase in IL-6 levels compared to those in the TAU group; these findings may suggest a buffering effect of the intervention against the natural progression toward a more pro-inflammatory status, often associated with aging (see Andrés-Rodríguez et al., 2020 where IL-6 was found to be positively correlated with age). Considering that the FIBROWALK intervention includes CBT and mindfulness training alongside therapeutic physical exercise, the effects of CBT on circulating pro-inflammatory cytokines have been studied in FM patients with studies showing significant decreases in serum IL-6 and CXCL8 levels compared to a wait-list control group (e.g., Zabihiyeganeh et al. 2019). There is also existing evidence suggesting that mindfulness-based interventions could also mitigate the inclination toward a more pro-inflammatory status in FM over time, similarly as we found in the FIBRO-On arm (Andrés-Rodríguez et al. 2019). However, in Andrés-Rodriguez et al.'s study (2019), the preventive effect primarily targeted reducing the tendency toward a decrease in IL-10 observed in the TAU group. In contrast, in our study, the focus was on IL-6, aiming to prevent its increase in the FIBROWALK arm compared to TAU.

Consistently with the main results regarding individual cytokines/chemokines, we found significant differences in pro-inflammatory/anti-inflammatory ratios between groups, with the outdoor intervention showing larger decreases in IL-6/IL-4 ratio compared to TAU suggesting a more balanced pro/anti-inflammatory status after the intervention. Interestingly, although no statistical differences were found between active arms regarding clinical variables, greater reductions in CXCL8/IL-4 ratio were found in the FIBRO-On intervention compared to FIBRO-

Table 3
Descriptive Statistics and Between-group Analysis for Biomarkers (ITT Approach).

	TAU (*n* = 35) Mean (*SD*)	TAU + FIBRO-On (*n* = 33) Mean (*SD*)	TAU + FIBRO-Out (*n* = 37) Mean (*SD*)			TAU vs TAU + FIBRO-On			TAU vs TAU + FIBRO-Out			TAU + FIBRO-On vs TAU + FIBRO-Out		
				F	*p*	*d*	*t (p)*	*β (95 % CI)*	*d*	*t (p)*	*β (95 % CI)*	*d*	*t (p)*	*β (95 % CI)*
Inflammatory markers														
IL-6 * (pg/ml)				4.673	**0.011**									
Baseline	*n* = 35 0.90 (1.21)	*n* = 33 1.06 (1.33)	*n* = 37 1.20 (1.40)											
Post-Treatment	*n* = 29 1.04 (1.10)	*n* = 31 1.10 (1.34)	*n* = 31 1.02 (1.24)			0.08	**−2,03 (0.045)**	−0.27 (−0.55 to −0.01)	0.24	**−3.00 (0.003)**	−0.40 (−0.67 to −0.13)	0.16	−0.94 (0.346)	−0.12 (−0.39 to 0.14)
CXCL8 * (pg/ml)				0.325	0.723									
Baseline	*n* = 35 2.45 (0.97)	*n* = 33 2.67 (0.72)	*n* = 37 2.76 (0.82)											
Post-Treatment	*n* = 29 2.46 (0.84)	*n* = 31 2.68 (0.74)	*n* = 31 2.81 (0.65)			0.00	−0.59 (0.557)	−0.06 (−0.27 to 0.14)	−0.04	0.17 (0.861)	0.02 (−0.18 to 0.22)	−0.05	0.77 (0.441)	0.08 (−0.12 to 0.28)
IL-17A * (pg/ml)				0.577	0.564									
Baseline	*n* = 35 4,03 (0,70)	*n* = 33 3,76 (0,82)	*n* = 37 4,04 (0,48)											
Post-Treatment	*n* = 29 4,00 (0,61)	*n* = 31 3,79 (0,85)	*n* = 31 4,08 (0,44)			−0.08	−0.21 (0.831)	−0.01 (−0.14 to 0.11)	−0.12	−1.01 (0.314)	−0.07 (−0.20 to 0.06)	−0.02	−0.80 (0.421)	−0.05 (−0.18 to 0.07)
IL-4 * (pg/ml)				2.049	0.134									
Baseline	*n* = 35 3,72 (1,23)	*n* = 33 3,60 (1,53)	*n* = 37 4,07 (1,41)											
Post-Treatment	*n* = 29 3,83 (1,30)	*n* = 31 3,76 (1,52)	*n* = 31 3,99 (1,25)			−0.04	0.58 (0.560)	0.07 (−0.17 to 0.31)	0.14	−1.37 (0.173)	−0.17 (−0.41 to 0.07)	0.16	−1.96 (0.052)	−0.24 (−0.48 to 0.00)
IL-10 * (pg/ml)				2.595	0.079									
Baseline	*n* = 35 1,56 (1,30)	*n* = 33 1,97 (1,63)	*n* = 37 2,03 (1,59)											
Post-Treatment	*n* = 29 1,75 (1,34)	*n* = 31 2,03 (1,62)	*n* = 31 1,78 (1,43)			0.09	−1.19 (0.235)	−0.23 (−0.61 to 0.15)	0.30	**−2.27 (0.025)**	−0.43 (−0.81 to −0.05)	0.19	−1,07 (0.287)	−0.20 (−0.58 to 0.17)
hs-CRP * (mg/L)				1.310	0.274									
Baseline	*n* = 35 0,69 (0,82)	*n* = 33 0,33 (1,13)	*n* = 37 0,79 (1,13)											
Post-Treatment	*n* = 29 0,73 (1,00)	*n* = 31 0,12 (1,09)	*n* = 31 0,84 (1,36)			0.25	−1.22 (0.222)	−0.23 (−0.60 to 0.14)	−0.01	0.27 (0.783)	0.05 (−0.32 to 0.42)	−0.23	1.52 (0.130)	0.28 (−0.08 to 0.65)
BDNF * (pg/ml)				0.789	0.453									
Baseline	*n* = 35 4,40 (0,60)	*n* = 33 4,23 (0,50)	*n* = 37 4,37 (0,66)											
Post-Treatment	*n* = 29 4,24 (0,45)	*n* = 31 4,29 (0,55)	*n* = 31 4,28 (0,27)			−0.39	1.18 (0.241)	0.22 (−0.15 to 0.60)	−0.11	0.20 (0.842)	0.03 (−0.33 to 0.40)	0.25	−0.99 (0.322)	−0.18 (−0.55 to 0.18)

Note. The baseline level of the variable was controlled. *M* and *SD* are not adjusted. When antidepressants are taken as a covariate there is no significant difference. *The baseline level of the variable and study waves are significant covariates in the model. BDNF, Brain-Derived Neurotrophic Factor; *CI,* confidence interval; *d*, Cohen's *d* as an effect size measure; FIBRO-On, FIBROWALK Online; FIBRO-Out, FIBROWALK Outdoor; hs-CRP, high-sensitivity C-reactive protein; ITT, intention-to-treat; TAU, treatment-as-usual; *β*, regression coefficients.

Table 4
Summary of statistically significant (or with a *tendency*) results (ITT and PP approaches).

Variable	ITT p-value; d-value	ITT Interpretation	PP p-value; d-value	PP Interpretation	Comparison
FIQR	**(F-On vs TAU) $p = 0.044$; $d = 0.43$ (F-Out vs TAU) $p = 0.010$; $d = 0.50$**	Reduction in F-On and F-Out	**(F-On vs TAU) $p = 0.014$; $d = 0.51$ (F-Out vs TAU) $p = 0.007$; $d = 0.63$**	Reduction in F-On and F-Out	Similar results in PP and ITT analyses.
VAS-*Pain*	**(F-Out vs TAU) $p = 0.019$; $d = 0.63$**	Reduction in F-Out	**(F-Out vs TAU) $p = 0.025$; $d = 0.69$**	Reduction in F-Out	Similar results in PP and ITT analyses.
VAS-*Fatigue*	*(F-On vs TAU) $p = 0.061$; $d = 0.52$* **(F-Out vs TAU) $p = 0.039$; $d = 0.53$**	F-On reduction / F-Out Reduction	**(F-On vs TAU) $p = 0.030$; $d = 0.61$** *(F-Out vs TAU) $p = 0.058$; $d = 0.52$*	Reduction in F-On / F-Out reduction	PP partially confirms ITT findings.
HADS-D	**(F-Out vs TAU) $p = 0.005$; $d = 0.65$**	Reduction in F-Out	**(F-Out vs TAU) $p = 0.005$; $d = 0.69$**	Reduction in F-Out	Similar results in PP and ITT analyses.
TSK-11	**(F-On vs TAU) $p = <0.001$; $d = 0.84$ (F-Out vs TAU) $p = 0.002$; $d = 0.51$**	Reduction in F-On and F-Out	**(F-On vs TAU) $p = <0.001$; $d = 0.87$ (F-Out vs TAU) $p = 0.001$; $d = 0.58$**	Reduction in F-On and F-Out	Similar results in PP and ITT analyses.
IL-4	*(F-On vs F-Out) $p = 0.052$; $d = 0.16$*	Increase in F-On / Reduction in F-Out	**(F-On vs F-Out) $p = 0.011$; $d = 0.36$** *(F-Out vs TAU) $p = 0.059$; $d = 0.31$*	Increase in F-On / Reduction in F-Out	PP partially confirms ITT findings.
IL-6	**(F-On vs TAU) $p = 0.045$; $d = 0.08$ (F-Out vs TAU) $p = 0.003$; $d = 0.24$**	Attenuated increase in F-On / Reduction in F-Out	**(F-On vs TAU) $p = 0.035$; $d = 0.10$ (F-Out vs TAU) $p = 0.016$; $d = 0.30$**	Attenuated increase in F-On / Reduction in F-Out	Similar results in PP and ITT analyses.
IL-10	**(F-Out vs TAU) $p = 0.025$; $d = 0.30$**	Reduction in F-Out	*(F-Out vs TAU) $p = 0.051$; $d = 0.39$*	Reduction in F-Out	PP partially confirms ITT findings.
Ratio IL-6/IL-4	**(F-Out vs TAU) $p = 0.028$; $d = -0.27$**	Reduction in F-Out	n.s.	N/A	PP does not confirm ITT findings.
Ratio CXCL8/IL-4	**(F-On vs F-Out) $p = 0.021$; $d = 0.36$**	Reduction in F-On / Increase in F-Out	**(F-On vs F-Out) $p = 0.003$; $d = 0.62$ (F-On vs TAU) $p = 0.048$; $d = -0.25$**	Reduction in F-On / Increase in F-Out	PP partially confirms ITT findings.
Ratio CXCL8/IL-10	*(F-Out vs TAU) $p = 0.091$; $d = 0.26$*	Increase in F-Out	n.s.	N/A	PP does not confirm ITT findings.
Ratio hs-CRP/IL-4	n.s.	N/A	*(F-On vs F-Out) $p = 0.091$; $d = 0.26$*	Reduction in F-On / Increase in F-Out.	PP does not confirm ITT findings.
Ratio hs-CRP/IL-10	*(F-Out vs TAU) $p = 0.078$; $d = 0.20$*	Increase in F-Out	*(F-Out vs TAU) $p = 0.073$; $d = 0.26$*	Increase in F-Out	Similar results in PP and ITT analyses.
Ratio IL-17A/IL-4	n.s.	N/A	**(F-On vs F-Out) $p = 0.048$; $d = 0.39$**	Reduction in F-On / Increase in F-Out	PP does not confirm ITT findings.

Note: Only **statistically significant effects** ($p \leq 0.05$) or showing a *tendency* towards significance ($0.05 < p \leq 0.10$) are displayed. ITT, intention-to-treat; PP, per-protocol; *d*, Cohen's *d* as an effect size measure; F-On, FIBROWALK Online; F-Out, FIBROWALK Outdoor; TAU, treatment-as-usual; FIQR, Revised Fibromyalgia Impact Questionnaire; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain; HADS-D, Hospital Anxiety and Depression Scale; TSK-11, Tampa Scale for Kinesiophobia; hs-CRP, high-sensitivity C-reactive protein.

Out.

The ITT and PP analyses revealed some divergences in the impact of FIBROWALK interventions on immune-inflammatory biomarkers and related ratios. A deactivation of the compensatory anti-inflammatory response (Maes and Carvalho, 2018) was observed in the FIBRO-Out group, particularly when compared to FIBRO-On. In the PP analyses, a significant group x time effect was found for IL-4, with increases in FIBRO-On and decreases in FIBRO-Out, suggesting decreased anti-inflammatory activity in the outdoor version of FIBROWALK. Additionally, the reduction in IL-10 levels in the FIBRO-Out group (vs TAU) observed in the ITT analyses remained marginally significant in the PP analyses. The IL-6/IL-4 ratio reduction in FIBRO-Out (vs TAU) also became non-significant, while the IL-17A/IL-4 ratio increased in FIBRO-Out (vs TAU) in the PP analyses. These findings suggest that higher adherence to the outdoor intervention, with increased exposure to natural environments and physical exercise, may be associated with a short-term adaptive inflammatory response, particularly through a reduction in compensatory anti-inflammatory activity (Maes and Carvalho, 2018; Pernambuco et al., 2013; Nash et al., 2023). In this context, the reduction in IL-4 levels could also indicate a normalization of the overactive Th2 response frequently observed in FM, where elevated IL-4 levels have been reported (Maes and Carvalho, 2018; Andrés-Rodríguez et al., 2020). Interestingly, IL-6 reductions in the FIBRO-Out group (vs TAU) were also observed in the PP analyses, supporting the normalizing effect of the intervention on the upregulated immune-inflammatory phenotype characteristic of FM (Andrés-Rodríguez et al., 2020). The simultaneous reduction in IL-6 (vs TAU) and the decrease in IL-4 levels (vs FIBRO-On) in the FIBRO-Out group may indicate a shift in immune regulation, suggesting a rebalancing of Th1/Th2 responses and normalization of immune activity in fibromyalgia. This shift could be driven by the long-term anti-inflammatory effects of regular outdoor physical activity (Andersen, Corazon and Stigsdotter, 2021; Nash et al., 2023), potentially mitigating the immune dysregulation commonly associated with chronic low-grade inflammation (Andrés-Rodríguez et al., 2020).

In contrast, FIBRO-On, despite having identical therapeutic content, showed a decrease in the IL-17A/IL-4 ratio compared to FIBRO-Out and a reduction in the CXCL8/IL-4 ratio (vs TAU and FIBRO-Out), suggesting a decrease in inflammatory activity and an increase in compensatory anti-inflammatory responses. These results point to a stronger engagement of the compensatory anti-inflammatory response system and a counterbalancing of the immune-inflammatory response system, which

could indicate that FIBRO-On's format fostered sustained anti-inflammatory effects, helping mitigate the inflammatory symptoms typically associated with FM. This may be linked to the therapeutic benefits of PSE (Shields et al., 2020), CBT (Montero-Marin et al., 2019), mindfulness (Andrés-Rodríguez et al., 2019), and regular exercise (Nash et al., 2023; Sanada et al., 2015).

These findings suggest different immune-inflammatory pathways involved in outdoor and online FIBROWALK. They contribute to an intriguing line of research exploring how contextual factors (e.g., natural environments) — beyond the therapeutic content itself — in which therapies are conducted may influence immune system functioning and interact with therapeutic components, ultimately shaping the effects of multicomponent interventions on both immune responses and clinical outcomes.

In our study, no significant changes in BDNF levels were observed in FIBROWALK interventions compared to TAU. Nevertheless, in other studies where non-multicomponent (without including physical exercise) psychological interventions (e.g., Montero-Marin et al. 2019; Sanabria-Mazo et al. 2020) were performed, reductions in BDNF were observed. Since increased levels of BDNF have been found in FM compared to healthy participants, and such increases have been associated with a chronification of pain, due to the key role of BDNF in various neuroplasticity processes (Nugraha et al. 2012), reductions reported in previous studies in FM were found to be indicative of a beneficial effect of the interventions. However, we must bear in mind that FM is a complex disease with high comorbidity with mental diseases such as depression and the specific clinical characteristics of the study sample may have a major effect on the evaluated biomarkers. In this regard, some studies have suggested that depression may be associated with *lower* BDNF levels (Cavaleri et al. 2023) and not *higher* levels as it has been reported in FM as we commented above. In this regard, one potential difference between our study and previous reports finding significant reductions in BDNF after psychotherapeutic interventions for FM (e.g., Montero-Marin et al. 2019; Sanabria-Mazo et al. 2020) may lie in the fact that our sample, recruited from a specialized treatment unit, exhibited higher levels of depressive symptoms compared to the participants in these randomized controlled trials, who were recruited from primary care settings. Therefore, the effects of a multicomponent intervention such as FIBROWALK, which includes both psychotherapeutic (which may decrease BDNF levels) and exercise approaches, may not be straightforward.

Another significant finding of our study is that −in both outdoor and online formats of the FIBROWALK- participants showing a more pro-inflammatory profile at baseline experimented larger clinical improvements after intervention. More precisely, it was found that higher pre-treatment hs-CRP values predicted improvement in kinesiophobia in the FIBRO-Out group. In the FIBRO-On group, higher levels of IL-4 predicted worsening functional impairment, while higher values of the CXCL8/IL-10 index predicted improvement in pain and fatigue. Since IL-4 is a key regulator in humoral and adaptive immunity, our results suggest that individuals with a higher basal compensatory response would have less improvement in functional impairment after FIBRO-On program. In this regard, a *meta*-analysis found elevated levels of IL-4, as well as IL-6 and IL17A, in individuals with FM compared to healthy controls, suggesting altered homeostasis with elevated immune-inflammatory and compensatory pathways (Andrés-Rodríguez et al. 2020). However, it is important to note that other studies evaluating the effects of different cognitive-behavioral therapies, also conducted in FM (e.g., Andrés-Rodríguez et al. 2019; Lasselin et al. 2016), found contrary results. In this regard, higher basal levels of CXCL8 attenuated the beneficial effect of a MBSR intervention on clinical symptomatology, including pain, energy, stiffness, or sleep quality, suggesting that basal inflammation may hinder clinical response in that sample after this specific treatment (Andrés-Rodríguez et al. 2019); similarly, higher levels of IL-6 and TNF-α before treatment were associated with lesser improvement in pain intensity (in a 0–6 scale) and psychological inflexibility (also assessed with the PIPS) following behavioral treatment (Lasselin et al. 2016). Since larger clinical improvements after interdisciplinary approaches can be particularly found in individuals with worse baseline clinical status (e.g., Worrel et al. 2001) and both IL-6 and CXCL8 have been found to positively correlate with symptom severity in FM (Andrés-Rodríguez et al. 2019), a potential explanation to our findings could be that patients with a more severe clinical profile at baseline (and also displaying greater pro-inflammatory status) would show greater improvements after multicomponent interventions. Additionally, differences between our study sample −with participants showing a more impaired clinical profile- and those from the Andrés-Rodríguez et al. (2019) and Lasselin et al. (2016) studies, may also be behind the differences in the results of regression analyses.

Finally, our study revealed intriguing insights into the predictive value of pre-treatment BDNF values. Specifically, higher baseline BDNF levels in the FIBRO-Out group were associated with larger improvements in anxiety symptoms and kinesiophobia. This suggests that elevated BDNF levels may serve as a potential biomarker for identifying individuals who are more likely to benefit from the FIBRO-Out intervention in terms of anxiety management and reducing movement-related fear. Conversely, in the FIBRO-On group, higher pre-treatment BDNF values predicted greater improvements in physical function. This finding implies that elevated BDNF levels might facilitate larger physical function improvements following the FIBRO-On program. These findings may be explained by the fact that BDNF play a crucial role in neuroplasticity and learning (Colucci-D'Amato et al. 2020) and, potentially, fostering processes both unadaptive—such as those promoting central sensitization (Nijs et al., 2015; Xiong et al. 2024)—and those adaptive—such as those related to therapeutic interventions—may be more easily promoted in those individuals with greater BDNF levels. These results underscore the potential role of BDNF as a predictive biomarker, suggesting that its levels could help tailor treatment approaches to individual patient needs, optimizing the efficacy of FIBROWALK interventions for FM.

This study has an exploratory nature and therefore there is still a need for further studies on how immune functions may play a role in the response to other multicomponent interventions in individuals with FM. Our findings should be interpreted in light of the limitations of the present study. Firstly, the sample size was rather small and, therefore, our study was somewhat underpowered. Furthermore, fifteen samples were lost post-randomization due to errors in sample processing and delayed identification of unmet inclusion criteria (e.g., autoimmune diseases, COVID-19). It was not possible to increase the number of participants to the initially proposed 40 per group due to budget limitations and because the treatment had already started when these issues were identified. Secondly, there was variability in adherence between intervention groups, with higher adherence observed in the FIBRO-On group (91 %) compared to the FIBRO-Out group (78 %). While sensitivity analyses were conducted to address the impact of attrition and non-adherence on the results, these differences may have influenced the outcomes. The FIBROWALK program includes physical therapeutic exercises that provide significant benefits for the physical and emotional health of patients with FM, alleviating symptoms of anxiety and depression and thus improving overall well-being (Serrat et al. 2020). However, the effectiveness of the program may be limited by variability in patients' levels of pain, fatigue, and functional capacity, making it difficult to customize it to meet individual needs. The outdoor program is group-based, accommodating up to 20 patients, while the online program is self-administered, which complicates its personalization. Nevertheless, participants can consult a therapist if they have questions during the program. Furthermore, it is important to consider that, in general, the risk of overexertion during aerobic and strength exercises may exacerbate pain and fatigue, negatively affecting motivation (Thieme et al. 2017; Perrot and Russell, 2014). An under-dosing or over-dosing of exercise could have affected the rate and magnitude of the observed clinical response, as well as changes in the studied biomarkers,

which could have significant implications for the study results and their clinical applicability (Serrat et al., 2021b). Future studies incorporating objective measures of effort (e.g., with Fitbit or similar devices) could help resolve this issue by providing more accurate and consistent monitoring of exercise intensity. Thirdly, the lack of blinding of participants and therapists is a common limitation in studies of non-pharmacological interventions, which may introduce bias into the reported outcomes. Additionally, there is a possibility of biased reporting of adherence to the FIBRO-On program, which could affect the interpretation of the results. Conducting the study in a specialized clinical setting may have implications for the generalizability of the findings. While it may increase the practical relevance of the results, it could also limit their applicability to other settings or populations. Furthermore, the study was constrained by budget limitations, resulting in a reduced number of biomarkers studied. Additionally, the evaluation of biomarker levels was limited to serum samples, providing only indirect insight into the effects of the interventions on the inflammatory status in FM.

5. Conclusions

This study forms part of a broader clinical trial assessing the long-term effectiveness and cost-effectiveness of FIBROWALK interventions (Serrat et al. 2022b). Our findings indicate that both online and outdoor FIBROWALK interventions not only enhance the clinical status of FM patients but also exert an impact on immune-inflammatory pathways implicated in the syndrome. Notably, baseline levels of the examined biomarkers and their indices were predictive of varying responses to the treatments assessed. Thus, integrating immune-inflammatory biomarkers and BDNF serum levels into treatment protocols may help distinguish patient profiles with differing responses to interventions. Our results underscore the importance of incorporating these biomarkers into clinical practice, paving the way for tailored treatment plans for FM individuals. Such personalized approaches hold promise for improving efficiency, cost-effectiveness, and utilization of healthcare services in FM management (Carvalho et al. 2019; Lopresti, 2017; Thase, 2014).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT to improve some sentences of the manuscript in terms of grammar and style. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

CRediT authorship contribution statement

Sònia Ferrés: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Mayte Serrat:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **William Auer:** Writing – review & editing, Visualization. **Estíbaliz Royuela-Colomer:** Writing – original draft, Data curation. **Míriam Almirall:** Writing – review & editing. **Andrea Lizama-Lefno:** Writing – review & editing. **Jo Nijs:** Writing – review & editing. **Michael Maes:** Writing – review & editing, Methodology. **Juan V. Luciano:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision. **Xavier Borràs:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation. **Albert Feliu-Soler:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JN and the Vrije Universiteit Brussel received lecturing/teaching fees from various professional associations and educational organizations. JN authored Dutch books on pain science education and pain management. The remaining authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2024.12.149.

Data availability

Data will be made available on request.

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