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Programa de Doctorat en Psicologia de la Salut i de l'Esport

Modalitat compendi de publicacions

Universitat Autònoma de Barcelona

Bellaterra, 2025

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Certifiquem:

Que la Tesi doctoral que porta per títol "*Efectes immunoinflamatoris del programa FIBROWALK en format online o outdoor en fibromiàlgia: un assaig controlat aleatoritzat (Projecte On&Out)"* ha estat realitzada per la doctoranda Sònia Ferrés Puigdevall sota la nostra direcció i tutorització amb la finalitat d'obtenir el títol acadèmic de Doctora en Psicologia.

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Bellaterra, 2025

Fonts de finançament

Aquesta Tesi s'ha desenvolupat en el marc del projecte On&Out, finançat en part pel Ministeri de Ciència i Innovació (MICINN), Programa Estatal d'R+D+I Orientada als Reptes de la Societat (ref. PID2020-117667RA-I00), i cofinançat amb el Fons FEDER de la Unió Europea.

A totes les persones que vulguin aprendre.

“... estic convençut que la cosa més important per a un ésser humà és l'aprenentatge. Aprendre hauria de ser una experiència plaent, meravellosa».

Moshé Feldenkrais

AGRAÏMENTS

A totes les persones que m’han acompanyat durant el procés de la meva Tesi doctoral.

A les persones que m'han dirigit, Albert, Juan Vicente i Mayte.

Al meu tutor Xavier.

A tot l’equip del projecte On&Out.

Però sobretot a totes les dones participants de l’estudi.

PREFACI

Sóc fisioterapeuta des del 1995 i professora titular del grau en Fisioteràpia a les Escoles Universitàries Gimbernat des del 2000. Primer vaig cursar la diplomatura i més tard el grau, per això, el 2011 vaig haver de fer la convalidació al grau de Fisioteràpia. Posteriorment, el 2014, vaig completar el Màster en Investigació Translacional en Fisioteràpia a les Escoles Universitàries Gimbernat, amb el treball de final de màster titulat: “Influència del Mètode Feldenkrais i del Tai-txi en les migranyes relacionades amb el cicle menstrual”. Això em va permetre accedir al doctorat i continuar investigant sobre la migranya premenstrual. Però vaig descobrir que estava embarassada del meu tercer fill, i vaig saber que, de moment, aquell era el meu tercer doctorat. Quan va començar educació infantil vaig posar-me de nou en marxa, però a la meva parella li van detectar un tumor cerebral i em vaig dedicar a cuidar-lo. Per sort, tot es va solucionar, però ja va arribar la pandèmia de la Covid-19 i el confinament. De nou tocava parar.

El curs posterior a la pandèmia va ser presencial però molt exigent i amb molts reptes. Afortunadament, tot es va anar calmant i al setembre de 2021, al començar les classes amb els alumnes de primer de grau en Fisioteràpia a les Escoles Universitàries Gimbernat, vaig veure penjat al suro de la classe un full on posava: es busca professional graduat en fisioteràpia i amb màster en ciències de la salut per a sol·licitar beca predoctoral en el camp de la fibromiàlgia. Les persones interessades poden enviar en el seu CV a: Dr. Albert Feliu Soler o Dra. Mayte Serrat López. Vaig pensar que allò era una gran oportunitat i que ho havia de provar. De seguida vaig anar a parlar amb la Mayte Serrat per apuntar-me al Projecte On&Out. Vaig enviar el meu currículum amb tots els documents dels

requisits que em demanaven i em van acceptar. Vaig tenir una reunió online amb la Mayte i l'Albert en la que van animar-me molt. Tot seguit vaig anar a comprar-me unes sabates de *trekking;* darrere d'aquest equip tan potent tenia clar que havia d'anar ben calçada per seguir-los.

Finalment no em van donar la beca predoctoral perquè feia massa temps entre que havia acabat el màster i l'inici del doctorat. No passava res, la il·lusió seguia intacta. El següent pas era matricular-se i per fer-ho tranquil·lament vaig aprofitar el dilluns 11 d'octubre de 2021 que tenia pont, però no vaig poder perquè just hi havia hagut un greu atac informàtic a la Universitat Autònoma de Barcelona que l'havia deixat sense servei. Van ser dies en què tot es va paralitzar i de nou vaig aprendre a esperar i a tenir paciència. I per fi el 28 de febrer de 2022 vaig poder matricular-me i el juliol ja tenia el primer seguiment, sort que anava ben calçada i ben acompanyada pels meus directors, directora i tutor. Durant aquell període vaig col·laborar amb el grup de recerca ÀGORA en la redacció de l'article *"Effectiveness of an online multicomponent program (FATIGUEWALK) for chronic fatigue syndrome: A randomized controlled trial",* que adjunto a l'**Annex 2** com a part no fonamental de la tesi. Aquesta col·laboració em va permetre tenir eines a l'hora de redactar els dos articles que formen part de la meva tesi.

Finalment, confio que aquesta tesi pugui inspirar futurs treballs de recerca que ajudin a entendre quines conseqüències biològiques tenen les nostres intervencions per a millorar la qualitat de vida de les persones afectades per la fibromiàlgia.

PREÀMBUL

Aquesta Tesi recull la memòria del treball de recerca realitzat entre els anys 2021 i 2024. Es presenta en forma de compendi de publicacions i està formada pels següents estudis publicats en revistes internacionals indexades i amb factor d'impacte:

Estudi 1

Serrat, M., Ferrés, S., Auer, W., Almirall, M., Lluch, E., D'Amico, F., Maes, M., Lorente, S., Navarrete, J., Montero-Marín, J., Neblett, R., Nijs, J., Borràs, X., Luciano, J. V., & Feliu-Soler, A. (2022). Effectiveness, cost-utility and physiological underpinnings of the FIBROWALK multicomponent therapy in online and outdoor format in individuals with fibromyalgia: Study protocol of a randomized, controlled trial (On&Out study). *Frontiers in physiology*, *13*, 1046613. https://doi.org/10.3389/fphys.2022.1046613

Estudi 2

Ferrés, S., Serrat, M., Auer, W., Royuela-Colomer, E., Almirall, M., Lizama-Lefno, A., Nijs, J., Maes, M., Luciano, J. V., Borràs, X., & Feliu-Soler, A. (2025). Immune-inflammatory effects of the multicomponent intervention FIBROWALK in outdoor and online formats for patients with fibromyalgia. *Brain, behavior, and immunity*, *125*, 184-197 https://doi.org/10.1016/j.bbi.2024.12.149

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ABREVIATURES

AAPT	de l'anglès, *ACTTION-American Pain Society Pain Taxonomy*
ACR	de l'anglès, *American College of Rheumatology*
ACSM	de l'anglès, *American College of Sports Medicine*
ACT	*Teràpia d'Acceptació i Compromís*
AINEs	*Antiinflamatoris No Esteroïdals*
ANAs	de l'anglès*, Antinuclear Antibodies*
APA	de l'anglès, *American Psychological Association*
BDNF	de l'anglès*, Brain-Derived Neurotrophic Factor*
CIRS	de l'anglès*, Compensatory Immune-Regulatory Reflex System*
CXCL	*Quimiocina*
ECD	*Educació en Ciència del Dolor*
EULAR	de l'anglès*, European League Against Rheumatism*
FIQR	de l'anglès*, Fibromyalgia Impact Questionnaire-Revised*
FM	*Fibromiàlgia*
HADS	de l'anglès*, Hospital Anxiety and Depression Scale*
Hs-CRP	*High-Sensitivity C-Reactive Protein*
HUVH	*Hospital Universitari Vall d'Hebron*
IBS	de l'anglès, *Irritable Bowel Syndrome*
IMC	*Índex de Massa Corporal*
IL	*Interleucina*
IRS	de l'anglès *Immune-Inflammatory Response System*
ISPS	*Índex de Sensibilitat Central*

ITT	de l'anglès *Intention-to-Treat*
MBSR	de l'anglès*, Mindfulness-Based Stress Reduction*
NICE	de l'anglès, *National Institute for Health and Care Excellence*
OMS	*Organització Mundial de la Salut*
PP	de l'anglès, *Per-Protocol*
PSS	de l'anglès*, Perceived Stress Scale*
RCT	de l'anglès*, Randomized Controlled Trial*
RF	de l'anglès*, Rheumatoid Factor*
SER	*Sociedad Española de Reumatología*
SF-36	de l'anglès*, Short-Form 36 Health Survey*
SFC	*Síndrome de Fatiga Crònica*
SMD	de l'anglès, *Standardized Mean Difference*
SNC	*Sistema Nerviós Central*
SSS	de l'anglès*, Symptom Severity Scale*
SPIRIT	de l'anglès*, Standard Protocol Items: Recommendations for Interventional Trials*
TCC	*Teràpia Cognitivoconductual*
TLRs	de l'anglès*, Toll-like Receptors*
TNF-α	de l'anglès, *Tumor Necrosis Factor Alpha*
TH	*Tractament Habitual*
TSK	de l'anglès*, Tampa Scale of Kinesiophobia*
VAS-Fatigue	de l'anglès, *Visual-analogue scale of perceived pain*
VAS-Pain	de l'anglès, *Visual-analogue scale of perceived energy/fatigue*
WPI	de l'anglès*, Widespread Pain Index*
WCPT	de l'anglès*, World Confederation for Physical Therapy*

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RESUM-ABSTRACT

RESUM

Introducció

La fibromiàlgia (FM), una condició crònica i complexa que té un gran impacte en la qualitat de vida de les persones afectades. Els tractaments multicomponent s'han proposat com el gold standard, però la complexitat de la FM posa de manifest la necessitat de desenvolupar noves estratègies terapèutiques que millorin tant els símptomes clínics com el benestar emocional dels pacients. Així mateix, és fonamental investigar si aquestes intervencions poden contribuir a la regulació dels nivells alterats de biomarcadors associats a aquesta condició mèdica, així com analitzar el valor predictiu d'aquests biomarcadors en la resposta clínica. Aquesta tesi explora la intervenció FIBROWALK, tant en versions *online* com *outdoor*, a través d'un assaig controlat aleatoritzat per a estudiar els seus efectes clínics i immunoinflamatoris a curt termini en persones amb FM. Els resultats d'aquesta investigació poden obrir noves portes en la comprensió dels mecanismes immunoinflamatoris implicats en aquesta condició crònica complexa i en la identificació de predictors de resposta clínica que permetin una personalització més efectiva de les intervencions terapèutiques.

Objectius

Aquesta tesi doctoral, estructurada com a compendi de publicacions, té com a objectiu principal avaluar l'efectivitat a curt termini de la teràpia multicomponent FIBROWALK, en format *online* i *outdoor*, dissenyada per a persones amb FM, dins del protocol de l'estudi On&Out. El primer estudi presenta

el protocol On&Out que estableix el marc teòric i metodològic en el que es planteja el segon i principal article de la tesi per a l'anàlisi de la intervenció, mentre que el segon s'enfoca en els efectes a curt termini de la teràpia, l'impacte sobre les variables immunoinflamatòries i el factor neurotròfic derivat del cervell (BDNF) i la capacitat predictiva d'aquests biomarcadors en relació amb la resposta terapèutica. Mitjançant aquest enfocament integral, la tesi pretén aprofundir en l'efectivitat de FIBROWALK en el tractament de la FM i la seva correlació amb els marcadors biològics, permetent entendre els canvis biològics vinculats a les teràpies multicomponent avaluades i aportant noves perspectives per a la personalització de les estratègies terapèutiques i el desenvolupament de tractaments més efectius.

Els objectius específics són:

- Presentar de manera detallada el disseny, els components i la metodologia del protocol de l'estudi On&Out, incloent-hi els fonaments teòrics i pràctics que en justifiquen la implementació, establint així la base necessària per avaluar els resultats en estudis posteriors **(Estudi 1)**.
- Avaluar l'efectivitat clínica a curt termini de la intervenció multicomponent FIBROWALK, en formats *online* i *outdoor* en comparació amb el tractament habitual (TH) **(Estudi 2)**.
- Avaluar l'impacte de la intervenció FIBROWALK sobre els nivells de biomarcadors immunoinflamatoris i el BDNF en sèrum, en persones amb FM **(Estudi 2)**.

- Explorar el valor predictiu dels biomarcadors immunoinflamatoris i del BDNF sobre la resposta clínica de les persones amb FM a la intervenció FIBROWALK **(Estudi 2)**.

Mètodes

Estudi 1. Aquest article del protocol de l'estudi On&Out va proporcionar les bases metodològiques per al desenvolupament del segon estudi empíric. En aquest protocol d'assaig controlat aleatoritzat, es van exposar els objectius, la metodologia de les intervencions en formats *online* i *outdoor* del FIBROWALK, així com les mesures avaluatives utilitzades. Aquest primer estudi va permetre descriure de forma detallada la metodologia de l'assaig clínic On&Out seguint la guia SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) (**Annex 3**).

L'estudi On&Out tenia per objectiu avaluar l'efectivitat, l'eficiència i els fonaments fisiològics del tractament multicomponent FIBROWALK, que integra educació en ciència del dolor (ECD), exercici terapèutic, teràpia cognitivoconductual (TCC) i entrenament en mindfulness, en dos contextos diferents: *online* (FIBRO-On) o *outdoor* (FIBRO-Out). Totes dues intervencions havien demostrat en estudis previs ser efectives a curt termini, però no existia cap estudi que n'avalués l'efectivitat comparativa. Per primera vegada, aquest estudi també va avaluar el cost-utilitat (amb un horitzó temporal de 6 mesos) i els efectes sobre els biomarcadors immunoinflamatoris i els nivells de BDNF de les dues intervencions, en comparació amb el TH. Els participants van ser 225 persones amb FM reclutades a l'Hospital Universitari Vall d'Hebron (Barcelona, Espanya), assignades aleatòriament a un dels tres grups d'estudi: TH vs. TH + FIBRO-On

vs. TH + FIBRO-Out. Es va realitzar una avaluació exhaustiva per recollir l'impacte funcional, el dolor, la fatiga, els símptomes depressius i d'ansietat, l'estrès percebut, la sensibilització central, la funció física, la qualitat del son, la disfunció cognitiva percebuda, la kinesiofòbia, la catastrofització del dolor, la inflexibilitat psicològica en el dolor i el coneixement del dolor abans de la intervenció, a les 6 setmanes, després de la intervenció (12 setmanes) i en el seguiment als 6 mesos. Els canvis en els biomarcadors immunoinflamatoris [IL-6, CXCL8, IL-17A, IL-4, IL-10 i proteïna C-reactiva d'alta sensibilitat (hs-CRP)] i el BDNF van ser avaluats en 40 participants de cada braç de tractament (n total = 120) abans i després del tractament. La qualitat de vida i els costos directes i indirectes van ser avaluats en el moment inicial i en el seguiment als 6 mesos. Es van calcular models de regressió lineal d'efectes mixtos, models de mediació i una avaluació econòmica completa aplicant tècniques de bootstrapping, corbes d'acceptabilitat i anàlisi de sensibilitat.

Aquest estudi va establir la base per a l'anàlisi dels biomarcadors i el seu paper en la resposta terapèutica, fet que va permetre aprofundir en els mecanismes subjacents en l'**Estudi 2**, el qual es va centrar en l'impacte de les intervencions sobre el nivell de biomarcadors en sèrum i la seva utilitat predictiva.

Estudi 2. Aquest segon estudi va analitzar els efectes de la intervenció multicomponent FIBROWALK en formats *online* i *outdoor* en comparació amb el TH sobre variables clíniques, biomarcadors immunoinflamatoris serològics i el BDNF. Per a això, es van dividir aleatòriament 120 participants diagnosticats amb FM en tres grups: TH, TH+FIBRO-On i TH+FIBRO-Out, realitzant avaluacions

clíniques i de sang abans i després del tractament. També es va analitzar el valor predictiu d'aquests biomarcadors en la resposta clínica al FIBROWALK.

Per a l'anàlisi d'efectivitat clínica a curt termini, es va adoptar una aproximació d'intenció de tractar (ITT) per avaluar els canvis en les puntuacions totals del Qüestionari d'Impacte de la FM (FIQR), utilitzant models lineals mixtos.

Pel que fa als marcadors immunoinflamatoris i als nivells de BDNF, es van utilitzar també models lineals mixtos per avaluar l'impacte de les intervencions. Es van aplicar transformacions logarítmiques als valors de citocines, quimiocines, hs-CRP i BDNF per corregir les distribucions asimètriques de les dades, i es van calcular índexs indicatius de l'equilibri inflamatori, integrant marcadors proinflamatoris i antiinflamatoris. A més, el consum d'antidepressius es va incloure com a covariant en l'anàlisi per ajustar els resultats segons aquest factor potencialment confusor.

Finalment, es van realitzar anàlisis de regressió per explorar el valor predictiu dels biomarcadors en la resposta clínica a FIBROWALK. I també una anàlisi que va comparar els participants que van respondre al tractament amb aquells que no ho van fer, examinant la influència dels nivells basals dels biomarcadors immunoinflamatoris en els efectes clínics observats.

Resultats

Estudi 1. Els resultats esperats d'aquest estudi van incloure:

1. El desenvolupament i la descripció detallada del marc teòric de l'estudi On&Out així com també del seu protocol, incloent-hi la descripció de les teràpies multicomponent FIBRO-On i FIBRO-Out, la selecció dels

participants, el disseny, els components i el procediment del programa, amb l'objectiu d'establir els fonaments teòrics i pràctics per a la seva implementació i servir com a base per avaluar la intervenció en futurs estudis.

2. La selecció i definició dels biomarcadors d'interès, com ara IL-6, CXCL8, IL-17A, IL-4, IL-10, hs-CRP i el BDNF. Aquests biomarcadors havien de ser determinants per comprendre els mecanismes subjacents de la resposta terapèutica i preparar el terreny per a la seva anàlisi en l'**Estudi 2.**

Aquest estudi va proporcionar una base essencial per aprofundir en l'impacte clínic i en els mecanismes immunoinflamatoris en l'**Estudi 2**, a més de contribuir a una comprensió més àmplia de la resposta terapèutica en persones amb FM.

Estudi 2. Els resultats d'aquest segon estudi van indicar que tant FIBRO-Out com FIBRO-On van mostrar ser efectives (vs TH) en millorar l'impacte funcional i la kinesiofòbia. Les persones assignades a FIBRO-Out (vs TH) també van mostrar reduccions en el dolor, la fatiga, els símptomes depressius i els nivells serològics d'IL-6 i IL-10 juntament amb la proporció IL-6/IL-4; les persones amb FM assignades a FIBRO-On només van mostrar un lleuger increment en IL-6 comparat amb TH. Un perfil més proinflamatori, juntament amb nivells més alts de BDNF en l'avaluació basal, van predir millores clíniques més grans en ambdós grups de tractament actiu. Els nostres resultats van suggerir que FIBROWALK, tant en format *online* com *outdoor*, va ser eficaç en persones amb FM i va tenir efectes significatius en la regulació immune en persones amb FM, mentre que les

vies immunoinflamatòries i els nivells de BDNF van poder predir, en part, l'efectivitat clínica d'ambdues intervencions.

Conclusions

Tant FIBRO-On com FIBRO-Out van ser capaços de millorar l'impacte funcional i reduir la kinesiofòbia en comparació amb TH. A més, FIBRO-Out va mostrar una disminució significativa de dolor, fatiga, símptomes depressius i els nivells de IL-6 i IL-10, així com una reducció en la relació IL-6/IL-4. En canvi, FIBRO-On només va presentar un augment menys pronunciat de IL-6 en comparació amb TH. D'altra banda, es va observar que un perfil inicial proinflamatori combinat amb alts nivells de BDNF va predir una millor resposta clínica en ambdós formats d'intervenció. Els resultats van mostrar l'efectivitat de FIBRO-On i FIBRO-Out per millorar els símptomes i modular biomarcadors en persones amb FM, tot i que es va suggerir millorar la personalització de la intervenció *online* i incorporar més biomarcadors rellevants.

Tant el protocol com els resultats empírics podrien contribuir a avançar el coneixement sobre la FM i obrir noves línies d'investigació per a la millora de les intervencions terapèutiques en aquest camp.

ABSTRACT

Introduction

Fibromyalgia (FM) is a chronic and complex condition that has a significant impact on the quality of life of affected individuals. Multicomponent treatments have been proposed as the gold standard, but the complexity of FM highlights the need to develop new therapeutic strategies that improve both clinical symptoms and patients' emotional well-being. Furthermore, it is essential to investigate whether these interventions can contribute to the regulation of altered biomarker levels associated with this medical condition, as well as to analyze the predictive value of these biomarkers in clinical response. This thesis explores the FIBROWALK intervention, in both its *online* and *outdoor* versions, through a randomized controlled trial to study its short-term clinical and immunoinflammatory effects in individuals with FM. The findings of this research may open new avenues in understanding the immunoinflammatory mechanisms involved in this complex chronic condition and in identifying clinical response predictors that enable more effective personalization of therapeutic interventions.

Objectives

This doctoral thesis, structured as a compendium of publications, aims to evaluate the short-term effectiveness of the multicomponent therapy FIBROWALK, in both *online* and *outdoor* formats, designed for individuals with FM, within the framework of the On&Out study protocol. The first study presents the On&Out protocol, which establishes the theoretical and methodological framework for the

second and main article of the thesis, focused on analyzing the intervention. The second study examines the short-term effects of the therapy, its impact on immunoinflammatory variables and brain-derived neurotrophic factor (BDNF), as well as the predictive capacity of these biomarkers in relation to therapeutic response. Through this comprehensive approach, the thesis seeks to deepen the understanding of FIBROWALK's effectiveness in FM treatment and its correlation with biological markers, providing insight into the biological changes associated with multicomponent therapies. Ultimately, this research contributes new perspectives for the personalization of therapeutic strategies and the development of more effective treatments.

The specific objectives are:

- To present in detail the design, components, and methodology of the On&Out study protocol, including the theoretical and practical foundations that justify its implementation, thereby establishing the necessary basis for evaluating the results in future studies **(Study 1).**
- To evaluate the short-term clinical effectiveness of the multicomponent FIBROWALK intervention, in both *online* and *outdoor* formats, compared to treatment as usual (TAU) **(Study 2).**
- To evaluate the impact of the FIBROWALK intervention on serum levels of immunoinflammatory biomarkers and BDNF in individuals with FM **(Study 2).**

- To explore the predictive value of immunoinflammatory biomarkers and BDNF on the clinical response of individuals with FM to the FIBROWALK intervention **(Study 2).**

Methods

Study 1. This article from the On&Out study protocol provided the methodological foundations for the development of the second empirical study. In this randomized controlled trial protocol, the objectives, methodology of the *online* and *outdoor* FIBROWALK interventions, and the evaluation measures used were outlined. This first study allowed for a detailed description of the On&Out clinical trial methodology following the SPIRIT guidelines (Standard Protocol Items: Recommendations for Interventional Trials) (**Annex 3**).

The On&Out study aimed to evaluate the effectiveness, efficiency, and physiological underpinnings of the multicomponent FIBROWALK treatment, which integrates pain science education (PSE), therapeutic exercise, cognitive-behavioral therapy (CBT), and mindfulness training, in two different contexts: *online* (FIBRO-On) or *outdoor* (FIBRO-Out). Both interventions had previously shown short-term effectiveness in prior studies, but no study had evaluated their comparative effectiveness. For the first time, this study also assessed the cost-effectiveness (with a 6-month time horizon) and the effects on immunoinflammatory biomarkers and BDNF levels of both interventions, compared to TAU. The participants were 225 individuals with FM recruited at the Vall d'Hebron University Hospital (Barcelona, Spain), randomly assigned to one of three study groups: TAU vs. TAU + FIBRO-On vs. TAU + FIBRO-Out. A

comprehensive assessment was conducted to collect data on functional impact, pain, fatigue, depressive and anxiety symptoms, perceived stress, central sensitization, physical function, sleep quality, perceived cognitive dysfunction, kinesiophobia, pain catastrophizing, psychological inflexibility in pain, and pain knowledge before the intervention, at 6 weeks, after the intervention (12 weeks), and at the 6-month follow-up. Changes in immunoinflammatory biomarkers [IL-6, CXCL8, IL-17A, IL-4, IL-10, and high-sensitivity C-reactive protein (hs-CRP)] and BDNF were assessed in 40 participants from each treatment group (total n = 120) before and after the treatment. Quality of life and direct and indirect costs were evaluated at baseline and at the 6-month follow-up. Linear mixed-effects regression models, mediation models, and a comprehensive economic evaluation were performed using bootstrapping techniques, acceptability curves, and sensitivity analysis.

This study laid the groundwork for the analysis of biomarkers and their role in therapeutic response, allowing for a deeper understanding of the underlying mechanisms in **Study 2**, which focused on the impact of the interventions on serum biomarker levels and their predictive utility.

Study 2. This second study analyzed the effects of the multicomponent FIBROWALK intervention in both *online* and *outdoor* formats, compared to TAU, on clinical variables, serological immunoinflammatory biomarkers, and BDNF levels. For this purpose, 120 participants diagnosed with FM were randomly divided into three groups: TAU, TAU+FIBRO-On, and TAU+FIBRO-Out, with clinical and blood assessments conducted before and after treatment. The

predictive value of these biomarkers on the clinical response to FIBROWALK was also analyzed.

For the analysis of short-term clinical effectiveness, an intention-to-treat (ITT) approach was adopted to assess changes in the total scores of the FM Impact Questionnaire (FIQR), using mixed linear models.

Regarding immunoinflammatory markers and BDNF levels, mixed linear models were also used to evaluate the impact of the interventions. Logarithmic transformations were applied to cytokine, chemokine, hs-CRP, and BDNF values to correct for the skewed distributions of the data, and indices of inflammatory balance were calculated, integrating pro-inflammatory and anti-inflammatory markers. Additionally, antidepressant use was included as a covariate in the analysis to adjust the results for this potentially confounding factor.

Finally, regression analyses were conducted to explore the predictive value of the biomarkers on the clinical response to FIBROWALK. An analysis was also performed comparing participants who responded to treatment with those who did not, examining the influence of baseline levels of immunoinflammatory biomarkers on the observed clinical effects.

Results

Study 1. The expected results of this study included:

1. The development and detailed description of the theoretical framework of the On&Out study, as well as its protocol, including the description of the multicomponent therapies FIBRO-On and FIBRO-Out, the selection of participants, the design, components, and procedure of the program, with

the aim of establishing the theoretical and practical foundations for its implementation and serving as a basis for evaluating the intervention in future studies.

2. The selection and definition of biomarkers of interest, such as IL-6, CXCL8, IL-17A, IL-4, IL-10, hs-CRP, and BDNF. These biomarkers were to be key in understanding the underlying mechanisms of the therapeutic response and preparing the groundwork for their analysis in **Study 2**.

This study provided an essential foundation for further investigating the clinical impact and immunoinflammatory mechanisms in **Study 2**, as well as contributing to a broader understanding of the therapeutic response in individuals with FM.

Study 2. The results of this second study indicated that both FIBRO-Out and FIBRO-On were effective (vs TAU) in improving functional impact and kinesiophobia. Individuals assigned to FIBRO-Out (vs TAU) also showed reductions in pain, fatigue, depressive symptoms, and serum levels of IL-6 and IL-10, along with the IL-6/IL-4 ratio; individuals with FM assigned to FIBRO-On showed only a slight increase in IL-6 compared to TAU. A more proinflammatory profile, along with higher levels of BDNF at baseline, predicted greater clinical improvements in both active treatment groups. Our results suggested that FIBROWALK, both in online and outdoor formats, was effective in individuals with FM and had significant effects on immune regulation in people with FM, while immunoinflammatory pathways and BDNF levels may have partly predicted the clinical effectiveness of both interventions.

Conclusions

Both FIBRO-On and FIBRO-Out were able to improve functional impact and reduce kinesiophobia compared to TAU. Furthermore, FIBRO-Out showed a significant reduction in pain, fatigue, depressive symptoms, and levels of IL-6 and IL-10, as well as a decrease in the IL-6/IL-4 ratio. In contrast, FIBRO-On only showed a less pronounced increase in IL-6 compared to TAU. On the other hand, an initial proinflammatory profile combined with high levels of BDNF was found to predict a better clinical response in both intervention formats. The results demonstrated the effectiveness of FIBRO-On and FIBRO-Out in improving symptoms and modulating biomarkers in individuals with FM, although it was suggested that the online intervention could benefit from improved personalization and the inclusion of more relevant biomarkers.

Both the protocol and empirical results could contribute to advancing knowledge on FM and open new lines of research for the improvement of therapeutic interventions in this field.

CAPÍTOL 1.

Introducció

1. La fibromiàlgia

La La fibromiàlgia (FM) és una condició crònica i complexa, de naturalesa multifactorial i sistèmica, que afecta diversos sistemes del cos i compromet significativament la qualitat de vida de les persones que la pateixen. Es caracteritza per la presència de dolor generalitzat i persistent, acompanyat de múltiples símptomes com la fatiga, la rigidesa matutina, les alteracions del son o les disfuncions cognitives, entre molts altres. Aquests problemes cognitius, coneguts en anglès amb el terme *fibrofog*, inclouen dèficits de la memòria a curt termini, alentiment del processament cognitiu, dificultats de concentració i memòria i afectacions en la capacitat de planificació i presa de decisions. Estudis recents suggereixen que aquestes alteracions estan associades a disfuncions en la neurotransmissió dopaminèrgica i glutamatèrgica (Lichtenstein et al. 2018). Una reducció de l'activitat dopaminèrgica pot afectar la regulació del dolor i l'estat d'ànim, mentre que una hiperactivitat glutamatèrgica pot provocar sensibilització central i augmentar la percepció del dolor. La interacció entre aquests sistemes pot amplificar els símptomes, afectant tant el dolor com les funcions cognitives i emocionals (Dizner-Golab et al. 2023).

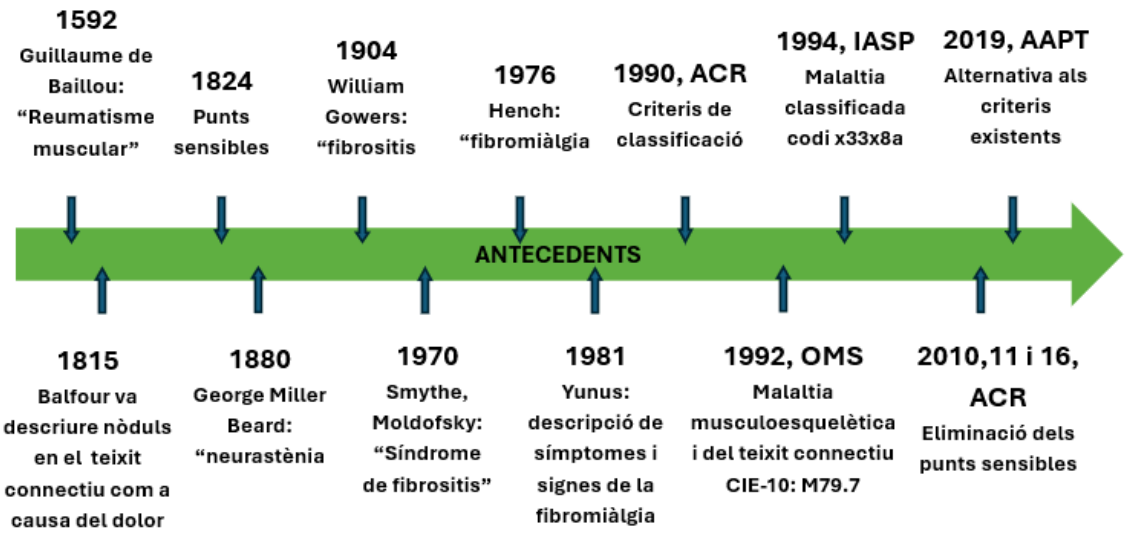
Les persones amb FM poden experimentar també una major sensibilitat a diversos estímuls ambientals, com la llum, el soroll i les variacions de temperatura. Aquesta hipersensibilitat es vincula amb una disfunció del sistema nerviós autonòmic, que pot manifestar-se mitjançant símptomes com marejos, hipotensió ortostàtica, sudoració excessiva i intolerància al fred i la calor. A més, la FM es relaciona amb una elevada prevalença d'alteracions emocionals, com l'ansietat i la depressió, que no sempre constitueixen desencadenants de la FM,

sinó una conseqüència derivada de la seva cronicitat i impacte funcional. En aquest sentit, s'han documentat alteracions en la regulació de neurotransmissors com la serotonina, la noradrenalina i la dopamina, les quals influeixen tant en la percepció del dolor com en l'estat d'ànim. A més, es considera que l'estrès crònic i els nivells elevats de cortisol poden contribuir a la perpetuació dels símptomes (Häuser et al. 2015; Thieme et al. 2017).

Un altre aspecte rellevant de la FM és la seva associació amb una sèrie de comorbiditats, que poden complicar-ne tant el diagnòstic com el tractament. Entre les condicions més comunes associades a la FM es troben la síndrome de fatiga crònica (SFC), els trastorns de l'estat d'ànim, els trastorns del son i la síndrome de l'intestí irritable (IBS). Així mateix, moltes persones amb FM presenten altres trastorns de dolor crònic, com l'artritis reumatoide, l'osteoartritis o el dolor pelvià crònic, així com trastorns de la conducta alimentària i afeccions dermatològiques. També s'han identificat trastorns neurològics com la migranya i altres tipus de cefalees, a més de diverses malalties autoimmunes, incloent-hi el lupus eritematós sistèmic i la malaltia de Sjögren, que es presenten amb una major freqüència en persones amb FM (Dizner-Golab et al. 2023).

La complexitat de la FM i la seva interacció amb altres condicions fa que el diagnòstic i la seva comprensió global resultin especialment desafiants per als professionals de la salut. Malgrat que en els darrers segles ha estat definida i descrita de diverses formes, actualment es reconeix com una entitat clínica diferenciada (veure **Figura 1**). No obstant això, la seva etiologia encara no està clarament definida, probablement a causa de la seva naturalesa multifactorial i la interacció de diferents mecanismes fisiopatològics (Lichtenstein et al. 2018).

Figura 1. *La concepció i definició de la Fibromiàlgia al llarg de la història*



Font: Adaptada de Crofford (2017)

1.1. Simptomatologia i criteris diagnòstics

La simptomatologia i els criteris diagnòstics de la FM són aspectes fonamentals per a la identificació i el maneig adequat d'aquesta condició mèdica. Algunes de les característiques rellevants de la simptomatologia i els criteris diagnòstics de la FM inclouen:

Simptomatologia:

- Dolor crònic generalitzat: El dolor és un símptoma predominant en la FM i es caracteritza per ser crònic, generalitzat i sovint descrit com a dolor muscular profund.
- Fatiga: La fatiga és un símptoma comú en les persones amb FM i pot ser tant física com mental.
- Trastorns del son: Moltes persones amb FM experimenten dificultats per conciliar el son o mantenir-lo, així com trastorns del son com l'apnea del son.

- Dificultats cognitives: Problemes com la dificultat per concentrar-se, la lentitud cognitiva i la pèrdua de memòria poden ser presents en persones amb FM.

- Sensibilitat sensorial: Algunes persones amb FM poden experimentar una sensibilitat augmentada a estímuls com la llum, els sorolls, els olors o el fred.

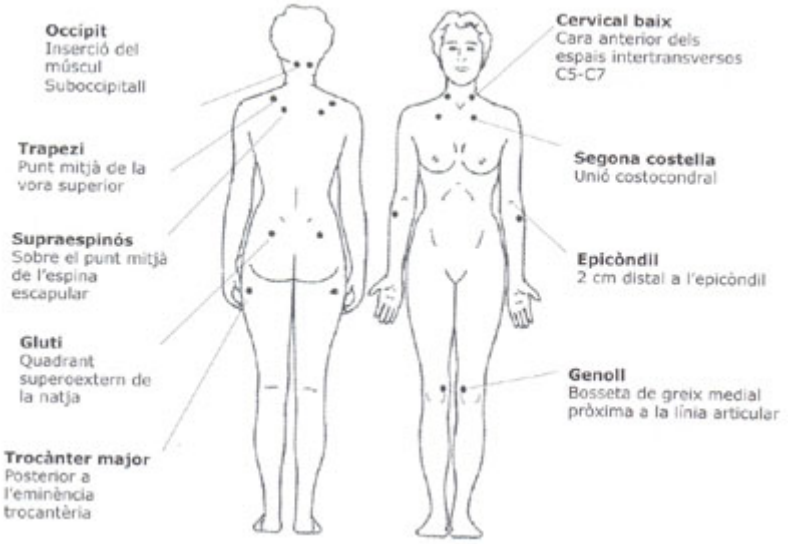
Criteris diagnòstics:

Els criteris diagnòstics de la FM han evolucionat al llarg del temps per millorar la precisió i la consistència en el diagnòstic de la FM. Els criteris de classificació de l'*American College of Rheumatology* (ACR 1990) definien la FM per la presència dels dos criteris següents:

- Història de dolor crònic generalitzat de més de 3 mesos de durada que afecta com a mínim, tres dels quatre quadrants del cos (hemicós dret i esquerre per sobre i per sota de la cintura). A més, es refereix dolor en l'esquelet axial (columna cervical, dorsal, lumbar i paret toràcica anterior).
- Dolor a la pressió en 11 o més dels 18 punts triats (9 punts parells) com es mostra a la **Figura 2**:
    1. Insercions occipitals dels músculs suboccipitals.
    2. Projecció cervical anterior dels espais intertransversos C5-C7.
    3. Punt mig del vora superior del trapezi.
    4. Origen del supraespinós.
    5. Segona unió condroesternal.
    6. 2 cm distalment de l'epicòndil.
    7. Quadrant superior extern de la natja.
    8. Cara posterior del trocànter major.
    9. Coixí adipós de la cara interna del genoll.

Per a la palpació digital, s'ha d'aplicar una força de 4 Kg (l'ungla del dit de l'explorador es torna blanca). L'exploració d'un punt sensible es considera positiva si la persona amb FM refereix que la maniobra li resulta dolorosa (Wolfe et al. 1990).

Figura 2. *Punts sensibles de la Fibromiàlgia (ACR, 1990)*



Font: Camps et al. (2002; adaptat de Wolfe et al. 1990)

Els punts sensibles de la FM són àrees del cos que presenten una sensibilitat extrema al tacte. Es descriuen sovint com doloroses, adolorides o semblants a una contusió. Aquests punts no són visibles a simple vista, i la seva ubicació pot variar d'una persona a una altra. Tot i això, hi ha algunes zones on aquests punts es manifesten amb més freqüència en persones amb FM.

Els punts sensibles es divideixen en dos tipus:

- Punts sensibles actius: Són els més dolorosos i sensibles al tacte.

- Punts sensibles latents: Són menys dolorosos, però poden causar dolor si es pressionen.

La presència de punts sensibles és una de les característiques clàssiques que els professionals sanitaris consideren per diagnosticar la FM. No obstant això, cal tenir en compte que no totes les persones amb FM presenten punts sensibles, i que altres afeccions també poden provocar dolor en aquestes zones.

L'any 2010, l'ACR va publicar un conjunt preliminar de criteris per al diagnòstic de la FM. Aquests criteris van suposar un canvi significatiu respecte als anteriors de 1990, que es basaven en un examen de punts sensibles. Els criteris del 2010/2011 van introduir un nou enfocament basat en dos components principals (**Figura 3**):

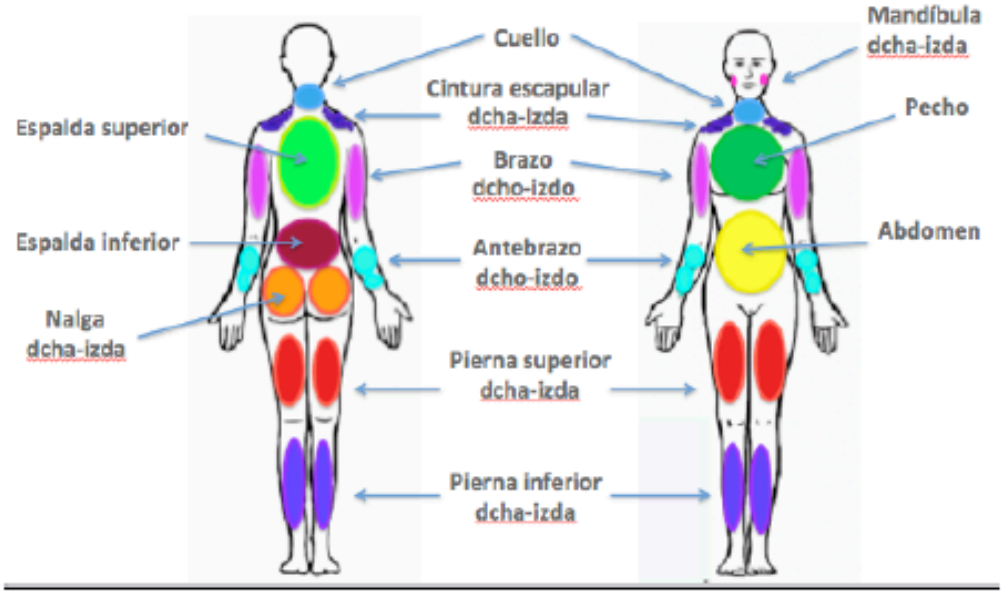
- *Widespread Pain Index* (WPI): Aquest índex comptabilitza el nombre de regions corporals on la persona amb FM experimenta dolor. Es basa en un mapa corporal que divideix el cos en 19 regions. Cada regió on el pacient informa dolor compta com un punt, i la puntuació total pot oscil·lar entre 0 i 19. Un WPI més elevat indica una major disseminació del dolor, un criteri diagnòstic fonamental en la FM.
- *Symptom Severity Scale* (SSS): És una escala complementària al WPI que avalua la gravetat de diversos símptomes associats a la FM: fatiga, son no reparador, manifestacions cognitives i símptomes somàtics. A cadascun dels símptomes se li assigna una puntuació de 0 (absent) a 3 (sever), d'acord amb la gravetat (en el cas dels tres primers) o la quantitat (en el cas dels símptomes somàtics). La puntuació total de la SSS oscil·la entre 0 i 12.

Figura 3. *Ítems de les escales WPI y SSS segons els criteris diagnòstics de la FM del 2010 de l'ACR.*

Nuevos Criterios Diagnósticos Fibromialgia
(ACR 2010)

1. . IDG/WPI ≥ 7 y SS ≥ 5 ó
IDG/WPI 3-6 y SS ≥ 9
2. Síntomas mantenidos con similar nivel los últimos 3 meses.
3. No haya otra causa que explique el dolor.

Índice de Dolor Generalizado, IDG/Widespread Pain Index , WPI
IDG = 0-19



Señale el número de áreas en las que ha tenido dolor en la **última semana**.

	Cintura escapular izda		Nalga dcha		Pecho (tórax)
	Cintura escapular dcha		Pierna superior izda		Abdomen
	Brazo superior izdo		Pierna superior dcha		Cuello
	Brazo superior dcho		Pierna inferior izda		Espalda superior
	Brazo inferior izdo		Pierna inferior dcha		Espalda inferior
	Brazo inferior dcho		Mandíbula izda		
	Nalga izda		Mandíbula dcha		

Índice Severidad de Síntomas /Symptom Severity Score
SS-1= 0-9

Indique el nivel de severidad de los siguientes síntomas durante la **última semana**.

0	Ningún problema
1	De leve a moderado, generalmente intermitente
2	De moderado a considerable, frecuente y de intensidad moderada
3	Severo, persistente, generalizado, con interferencia en las actividades diarias

Fatiga	**0**	**1**	**2**	**3**
Sueño no reparador	**0**	**1**	**2**	**3**
Trastornos cognitivos	**0**	**1**	**2**	**3**

Índice Severidad de Síntomas /Symptom Severity Score
SS-2 = 0-3

Señale cuáles de los siguientes síntomas **padece habitualmente:**
Sin síntomas = **0**; Entre 1 y 10 síntomas, puntúa **1**; De 11 a 24 síntomas, puntúa **2**; 25 o más, puntúa **3**

	Dolor muscular		Dolor en la parte alta del abdomen		Convulsiones
	Picores		Fatiga/cansancio extremo		Ojo seco
	Visión borrosa		S. Intestino irritable		Sequedad bucal
	Urticaria		Problemas para pensar o de memoria		Pérdida de apetito
	Vómitos		Dolor/ calambres en el abdomen		Erupciones, sarpullido
	Dolor de cabeza		Respiración entrecortada		Sensibilidad al sol
	Dolor torácico		Pitidos al respirar, sibilancias		Trastornos auditivos
	Ansiedad		Fenómeno de Raynaud		Entumecimiento, hormigueo
	Mareos		Debilidad muscular		Caída de cabello
	Insomnio		Zumbidos en los oídos		Micción frecuente
	Depresión		Moratones frecuentes (hematomas)		Micción dolorosa
	Estreñimiento		Acidez de estómago		Espasmos vesicales
	Diarrea		Aftas orales (úlceras)		Fiebre
	Náuseas		Pérdida o cambios en el gusto		

IDG/WPI = _____

SS1 = _____ SS2 = _____ SS = _____

Font: Wolfe et al. (2010)

Un metge podia diagnosticar FM si una persona presentava:

- Dolor generalitzat en almenys 4 de les 5 regions corporals durant almenys 3 mesos.
- Símptomes que assolien un determinat nivell de gravetat en l'escala SSS. Els valors requerits per establir el diagnòstic eren SSS ≥ 5 si el WPI era ≥ 7 o SSS ≥ 9 si el WPI es trobava entre 3 i 6.

Els criteris del 2010/2011 van representar un avenç important en el diagnòstic de la FM per diversos motius:

- Eren més objectius i fàcils d'utilitzar que l'examen de punts sensibles.
- Permetien el diagnòstic en persones amb FM que no presentaven els punts sensibles típics.
- Feien possible estudiar la FM en entorns d'investigació.

No obstant això, els criteris del 2010/2011 no estaven exempts de limitacions. Per exemple, no incloïen criteris específics per al diagnòstic de la FM en nens o adolescents. A més, l'escala SSS era subjectiva i podia estar influenciada per factors aliens a la FM.

L'any 2016, l'ACR va publicar criteris de diagnòstic revisats per a la FM que abordaven algunes d'aquestes limitacions. Els criteris revisats encara utilitzen el WPI, però van substituir l'escala SSS per una nova escala que avalua l'impacte de la FM en la vida diària del pacient. En l'actualitat, el diagnòstic es basa en aquests criteris revisats (Wolfe et al. 2016).

Per diagnosticar FM, el metge tindrà en compte:

- Presència de dolor generalitzat: Ha de ser present durant almenys 3 mesos en almenys 4 de les 5 regions següents:
    - Esquena superior esquerra
    - Superior dreta
    - Inferior esquerra
    - Inferior dreta
    - Zona general del coll, espatlles i mandíbula
- Gravetat dels símptomes: A més del dolor generalitzat, s'avalua la intensitat d'altres símptomes habituals de la FM, com ara:
    - Fatiga
    - Problemes per dormir (insomni)
    - Dificultats cognitives (problemes de memòria, concentració, boira mental)
    - Depressió
    - Malestar general

Els criteris preliminars de l'ACR del 2010 i les seves revisions posteriors del 2016 han establert paràmetres per a la diagnosi de la FM, incloent la presència de dolor generalitzat i punts dolorosos específics (Wolfe et al. 2016). Tot i que els criteris de 2016 són àmpliament utilitzats, no hi ha un consens internacional absolut sobre quin conjunt de criteris és el més adequat per al diagnòstic de la FM. Alguns metges continuen utilitzant els criteris de 1990 o 2010, depenent de la seva formació i experiència clínica. A més, la variabilitat en la presentació clínica de la FM i la manca de biomarcadors específics dificulten l'establiment d'un estàndard diagnòstic universalment acceptat. Per tant, tot i que els criteris de 2016 han estat proposats per millorar la precisió diagnòstica, la seva adopció no

és uniforme a nivell mundial, i el diagnòstic de la FM continua sent un tema de debat dins de la comunitat mèdica.

Els criteris actuals de l'*ACR/ACTTION-APS Pain Taxonomy* (AAPT) per a la classificació de la FM es basen en una avaluació multidimensional que té en compte la complexitat dels símptomes. Els elements clau per al diagnòstic són:

- Dolor generalitzat: Un dels elements principals per al diagnòstic és la presència de dolor generalitzat que ha de durar almenys 3 mesos i afectar diverses zones del cos, com extremitats, regió cervical, tòrax i esquena baixa.
- Punts dolorosos: S'ha adaptat a una metodologia més àmplia que inclou fins a 9 àrees doloroses, ajudant a quantificar la sensibilitat del pacient.
- Símptomes associats: A més del dolor, els criteris ACR/AAPT reconeixen altres símptomes com la fatiga persistent, trastorns del son, sensibilitat a la pressió i dificultats cognitives (fibrofog).
- Enfocament multidimensional: Els criteris AAPT consideren no només el dolor, sinó també l'afectació funcional, l'impacte emocional del dolor i el nivell de fatiga.

Aquests criteris proporcionen una base clara per al diagnòstic i tractament personalitzat, millorant la qualitat de vida dels pacients (Dizner-Golab et al. 2023) (**Taula 1**).

En resum, la FM és una condició mèdica complexa amb una presentació clínica diversa que requereix una avaluació detallada de la simptomatologia i el compliment dels criteris diagnòstics establerts per garantir un diagnòstic precís i un maneig adequat de les persones afectades.

Taula 1. *Criteris de classificació ACR/AAPT per a la fibromiàlgia.*

Evolució dels criteris ACR
Criteris de classificació de l'ACR de 1990 Dolor generalitzat experimentat com a dolor en els quatre quadrants (tant al costat esquerre com al dret del cos, per sobre i per sota de la cintura); més dolor esquelètic axial (dolor a la columna cervical o al tòrax anterior o a la columna toràcica o a la part baixa de l'esquena) Punts sensibles ≥ 11 de 18 Dolor generalitzat i almenys 11 punts sensibles durant almenys 3 mesos
Criteris diagnòstics preliminars de l'ACR de 2010 WPI: un recompte de 0–19 de les regions del cos reportades com a doloroses pel pacient durant la setmana passada No s'utilitzen punts sensibles SSS: gravetat de tres símptomes (fatiga, despertar sense sentir-se refrescat, símptomes cognitius) més símptomes somàtics en general (en una escala de 0–12) WPI ≥ 7 i SSS ≥ 5, o WPI 3–6 i SSS ≥ 9 Símptomes presents a un nivell similar durant almenys 3 mesos El pacient no té un trastorn que expliqui el dolor d'una altra manera
Modificacions de l'ACR de 2011 dels criteris diagnòstics preliminars de l'ACR (dissenyats per a estudis epidemiològics i clínics, i no per a diagnòstic clínic) WPI: un recompte de 0–19 de les regions del cos reportades com a doloroses pel pacient durant la setmana passada Diversos símptomes inclosos en l'SSS, una puntuació de la suma de la gravetat de tres símptomes (fatiga, despertar sense sentir-se refrescat, símptomes cognitius) més la suma del nombre dels següents símptomes ocorreguts durant els 6 mesos anteriors: mals de cap, dolor o rampes a l'abdomen inferior i depressió (en una escala de 0–12) WPI ≥ 7 i SSS ≥ 5, o WPI 3–6 i SSS ≥ 9 Símptomes presents a un nivell similar durant almenys 3 mesos

Revisions de 2016 dels criteris diagnòstics de fibromiàlgia de l'ACR de 2010/2011 Dolor generalitzat definit com a dolor en almenys 4 de les 5 regions (regió superior esquerra, regió superior dreta, regió inferior esquerra, regió inferior dreta i regió axial) El dolor a la mandíbula, al tòrax i a l'abdomen no es considera part de la definició de dolor generalitzat WPI: un recompte de 0–19 de les regions del cos reportades com a doloroses pel pacient durant la setmana passada Diversos símptomes inclosos en l'SSS, una puntuació de la suma de la gravetat de tres símptomes (fatiga, despertar sense sentir-se refrescat, símptomes cognitius) més la suma del nombre dels següents símptomes ocorreguts durant els 6 mesos anteriors: mals de cap, dolor o rampes a l'abdomen inferior i depressió WPI ≥ 7 i SSS ≥ 5, o WPI 4–6 i SSS ≥ 9 La presència de dolor generalitzat Símptomes presents a un nivell similar durant almenys 3 mesos Un diagnòstic de fibromiàlgia és vàlid independentment d'altres diagnòstics i no exclou la presència d'altres malalties
Criteris diagnòstics bàsics de l'AAPT per a la fibromiàlgia (ACTTION American Pain Society Pain Taxonomy) 2018
Ús de MSP (dolor *multisite*): un recompte de 0–9 del nombre de llocs del cos reportats com a dolorosos (els llocs consistents en el cap, braç dret, braç esquerre, tòrax, abdomen, part superior de l'esquena i columna vertebral, part baixa de l'esquena i columna vertebral —incloent les natges—, cama esquerra i cama dreta) Problemes de son moderats a severs o fatiga moderada a severa MSP ≥ 6 Problemes de son moderats a severs o fatiga Símptomes presents durant almenys 3 mesos

Nota: ACR, American College of Rheumatology; ACTTION, Analgesic, Anesthetic, and Addiction Clinical Trial Translations Innovations; APPT, ACTTION-APS Pain Taxonomy, Opportunities and Networks, APS – American Pain Society; FSS, Fibromyalgia Severity, Score; MSP, multisite pain; SSS, Symptom Severity Score; WPI, Widespread Pain Index.

Font: Traduïda de Dizner-Golab et al. (2023)

Així doncs, el diagnòstic de la FM es basa principalment en criteris positius establerts per l'ACR, com ara la presència de dolor crònic generalitzat durant més de 3 mesos que afecta tant la part superior com inferior del cos, així com ambdós costats, i la sensibilitat en punts específics a la pressió. Tanmateix, en la pràctica clínica, el metge realitzarà una exploració física completa i, si es presenten signes d'alarma o símptomes atípics, podrà sol·licitar proves complementàries, com ara anàlisis de sang, per descartar altres malalties que puguin causar dolor i fatiga similars. No hi ha una prova única per diagnosticar la FM. El diagnòstic es basa en l'avaluació dels símptomes i l'exploració física detallada (Dizner-Golab et al. 2023).

1.2. Epidemiologia

La FM afecta aproximadament entre el 2% i el 5% de la població mundial (Ruschak et al. 2021). Es presenta predominantment en dones de 40 a 50 anys, que constitueixen entre el 80% i el 96% dels casos (Cabo-Meseguer et al. 2017; Wolfe et al. 2010). Una revisió sistemàtica (Heidari, 2017) a nivell mundial sobre la FM en homes i dones va revelar que la prevalença és aproximadament d'un 3,98% en dones i d'un 2,40% en homes. Degut al nombre reduït d'homes diagnosticats, la recerca s'ha enfocat principalment en les dones, deixant de banda l'estudi en els homes. Les disparitats en la prevalença i diagnòstic de la FM entre homes i dones es deuen a l'estigma social que la considera una condició mèdica femenina i a les normes culturals occidentals que fan que els homes tendeixin menys a buscar atenció per dolor crònic, dificultant el diagnòstic precís (Ruschak et al. 2023). Segons l'estudi EPISER 2016 (Seoane-Mato et al. 2019), a Espanya la prevalença global és del 2,4% de la població, amb una taxa de

diagnòstic més alta en dones. Segons l'informe de 2023 sobre l'epidemiologia de les malalties de sensibilització central a Catalunya, s'estima que la prevalença de la FM a Catalunya és del 3,08%. La distribució de la FM és àmplia i afecta diferents grups de població en tot el món. És important tenir en compte que la freqüència de la FM pot variar segons els criteris de diagnòstic utilitzats, les característiques de la població estudiada i altres factors com les comorbiditats. En les últimes dècades, s'ha produït un augment en la consciència i el coneixement sobre la FM, la qual cosa pot influir en una major detecció i diagnòstic de la FM en diferents poblacions. S'han identificat diversos factors de risc associats amb la FM, com ara el sexe femení, l'edat avançada, altres condicions mèdiques com la diabetis mellitus i la malaltia de l'intestí irritable, i factors psicosocials com l'estrès i la depressió (Heidari, 2017).

L'estudi EPISER 2016 subratlla la importància de reconèixer la FM com un problema de salut pública significatiu i la necessitat de programes de prevenció, diagnòstic precoç i tractament efectiu per millorar la qualitat de vida de les persones amb FM. També es destaca la necessitat de formació contínua per als professionals de la salut en la gestió d'aquesta condició mèdica, així com el desenvolupament de polítiques sanitàries que abordin les necessitats específiques d'aquestes persones amb FM.

1.3. Etiopatogènesi

La FM és considerada una condició de sensibilització central. Aquesta condició mèdica es caracteritza per una sensibilitat augmentada al dolor, que és atribuïda a un mal funcionament dels mecanismes de processament del dolor del sistema nerviós central. Això pot resultar en una resposta emocional i física

desproporcionada a estímuls que normalment serien considerats no dolorosos. Aquesta sensibilització central és una característica principal de la FM i ajuda a explicar els símptomes com el dolor generalitzat i la fatiga que presenten les persones amb FM (Lichtenstein el al. 2018). La causa exacta de la FM continua sent desconeguda però se sap que és multifactorial, el que significa que cap factor desencadenant per si sol pot causar la FM (Dizner-Golab et al. 2023). La FM no és degenerativa ni empitjora amb l'edat i la millora dels símptomes i la qualitat de vida depenen de factors molt diversos. La neurociència desmunta la creença que el dolor i símptomes en la FM és psicològic, inventat o somatitzat. S'han proposat diversos factors com a contribuents a la seva etiologia, incloent la susceptibilitat genètica, factors ambientals, neuromodulació, neuroinflamació i autoimmunitat. Aquests elements actuen de manera conjunta per crear un entorn propici per al desenvolupament de la FM (Dizner-Golab et al. 2023). Se suggereix que diversos factors fisiològics contribueixen a la simptomatologia de la FM, amb el sistema nerviós central assumint un paper determinant, contribuint significativament a la manifestació i persistència de símptomes (de Tommaso et al. 2022; Sawaddiruk et al. 2017; Sluka i Clauw, 2016). En aquest sentit, s'han descrit els següents factors etiopatogènics, com es mostra a la **Figura 4**:

1. Susceptibilitat genètica: Segons D'Agnelli et al. (2019), diversos estudis apunten a un component genètic en la FM, amb evidències de mecanismes genètics en estudis de gens relacionats amb el dolor, perfils de metilació de l'ADN, perfils de mRNA i modificacions hipotètiques d'histones. A més, han identificat l'associació de diversos gens amb la FM, com el gen del transportador de serotonina (SLC64A4), el gen del canal vanil·loide de potencial transitori 2 (TRPV2), el gen del factor de transcripció de la mielina 1 i el gen de la neurexina 3

(NRXN3). Aquestes troballes suggereixen que les variants genètiques en aquests gens podrien influir en la susceptibilitat d'una persona a desenvolupar FM.

Algunes d'aquestes variants genètiques estan associades amb gens implicats en la regulació del dolor, com ara el gen COMT (catecol-O-metiltransferasa), que està implicat en la degradació de neurotransmissors com la dopamina, la noradrenalina i l'adrenalina, els quals tenen un paper important en la percepció del dolor. Altres gens com el gen SCN9A, que codifica canals de sodi implicats en la transmissió dels senyals de dolor, també s'han relacionat amb la FM (Ruschak et al. 2023).

2. Factors ambientals: S'han suggerit diversos desencadenants com ara infeccions, estrès emocional i traumatismes físics com a possibles factors que contribueixen al desenvolupament de la FM, segons diferents estudis (Bazzichi et al.2024; Rodriguez-Pintó et al. 2014; Tan et al.2019).

- Infeccions: Algunes infeccions virals o bacterianes s'han associat amb l'aparició de la FM, ja que poden desencadenar una resposta immune anormal que contribueix a la inflamació i al dolor crònic (Rodriguez-Pintó et al. 2014).
- Estrès emocional: Els esdeveniments estressants, com ara situacions traumàtiques o estrès crònic, poden exercir un paper en el desenvolupament de la FM, ja que poden afectar els sistemes nerviós i immune (Häuser et al. 2015; Tan et al.2019).
- Traumatismes físics: Les lesions físiques, com ara accidents automobilístics o lesions esportives, poden ser un factor desencadenant de la FM en algunes persones (Bazzichi et al.2024; Häuser et al. 2015).

- Esdeveniments catastròfics: Situacions de desastres naturals, conflictes armats o altres esdeveniments catastròfics poden generar un estrès extrem que pot contribuir al desenvolupament de la FM (Clauw, 2014)..
- Estil de vida: Factors com la manca d'exercici físic, una dieta inadequada, el consum de tabac, d'alcohol o altres substàncies, així com la manca de son adequada, poden influir en la simptomatologia de la FM (Dizner-Golab et al. 2023).
- Exposició a toxines ambientals: L'exposició a substàncies tòxiques presents en l'ambient, com ara productes químics o agents contaminants, poden tenir un impacte en la salut i contribuir al desenvolupament de la FM (Talotta et al. 2017).

3. Neuromodulació: Els canvis en la modulació del sistema nerviós s'han postulat com a factors en la patogènesi de la FM. Estudis amb neuroimatge, mètodes electrofisiològics i biòpsies de pell mostren una implicació dels sistemes nerviós central i perifèric. La causa principal sembla ser una disfunció central en el processament dels senyals de dolor, però també hi ha factors perifèrics, com la neuropatia de petites fibres, que tenen un paper significatiu. La neuropatia de petites fibres és comuna en persones amb FM i pot desencadenar la FM o ser una conseqüència de la hiperactivitat del sistema nerviós central (de Tommaso et al. 2022; Grayston et al. 2019).

4. Neuroinflamació: Els processos neuroinflamatoris també s'han considerat en la patogènesi de la FM. Les citocines proinflamatòries, com el factor de necrosi tumoral alfa (TNF-α), la interleucina-6 (IL-6) i la interleucina-8 (IL-8), poden contribuir a l'activació nociceptiva en la FM (Rodriguez-Pintó et al. 2014). Les citocines antiinflamatòries, com la interleucina-10 (IL-10), també poden estar

implicades en la fisiopatologia de la FM. Les quimiocines, com l'eotaxina, també s'han associat amb la signatura de la FM, indicant el conjunt d'aquestes dades un possible paper de la neuroinflamació en aquesta condició mèdica (Gerdle et al. 2024).

També l'activació de elements transposables que són seqüències d'ADN que tenen la capacitat de moure's o transposar-se dins del genoma s'han relacionat amb la FM. Alguns estudis han trobat una sobreexpressió d'elements transposables en cèl·lules immunes de persones amb FM, suggerint que les alteracions immunes podrien influir en la FM. Els elements transposables, que constitueixen el 45% del genoma humà, tenen rols importants en la regulació gènica i la patogènesi de malalties. La desregulació d'aquests elements, incloent seqüències retrovirals, podria desencadenar símptomes de FM com el dolor crònic i la fatiga (D'Agnelli et al.2019; Ovejero et al. 2020; Qiu et al. 2021).

5. Autoimmunitat: Algunes hipòtesis proposen l'autoimmunitat com a factor en el desenvolupament de la FM. L'activació immune persistent amb inflamació prolongada pot contribuir a la cronicitat del dolor i a la transformació del dolor agut en dolor crònic, com es veu en la nociplàstia. La interacció entre els sistemes immune i nerviós pot generar processos que contribueixen a les alteracions en la percepció del dolor i en les modificacions neuromorfològiques associades amb la FM. S'ha observat una signatura immune específica en persones amb FM, incloent citocines proinflamatòries i antiinflamatòries, que poden reflectir una resposta immune disfuncional en la FM. En l'estudi de O'Mahony et al. (2021), s'ha comprovat que les persones amb FM presenten un perfil immune distintiu que inclou citocines proinflamatòries i antiinflamatòries. Concretament, els nivells de TNF-α es van trobar significativament elevats amb una diferència estàndard

mitjana (SMD) de 0.36, IL-6 amb SMD de 0.15, IL-8 amb SMD de 0.26 i IL-10 amb SMD de 0.61. A més, l'eotaxina també va mostrar nivells elevats de manera consistent en persones amb FM. Aquesta combinació de citocines pot reflectir una resposta immune disfuncional en la FM, ja que la presència simultània de citocines proinflamatòries i antiinflamatòries suggereix un intent del sistema immunitari d'ajustar-se davant d'un estat inflamatori persistent. Aquesta observació coincideix amb els resultats de diversos estudis, com el de Giorgi et al. (2023), que assenyalen l'augment de citocines proinflamatòries com un factor essencial en el mecanisme de sensibilització del dolor en la FM. El fet que aquestes alteracions en la resposta immune puguin ser exacerbades per processos autoimmunes obre la possibilitat d'una relació entre la FM i altres malalties autoimmunes, com l'artritis reumatoide. Així, la identificació de citocines com TNF-α, IL-6 i altres biomarcadors immunològics podria proporcionar indicadors útils per al diagnòstic i seguiment de la FM, ajudant a determinar la gravetat d'aquesta condició mèdica i la resposta al tractament. D'altra banda, el rol de la microbiota intestinal, destacat també en altres estudis (València et al. 2022), segueix emergint com una peça fonamental en la patogènia de la FM. Les alteracions en la composició del microbioma podrien influir en la resposta immune i, per tant, en la simptomatologia de les persones amb FM. Això ofereix noves vies potencials per al tractament de la FM, destacant la importància d'explorar la salut intestinal com a factor determinant en la gestió d'aquesta condició mèdica. Per tant, com indica O'Mahony et al. (2021), és fonamental continuar la recerca en aquest camp per desxifrar els mecanismes subjacents de la FM i la seva connexió amb desordres autoimmunes. A través d'un major coneixement dels processos

immunològics implicats, es podrien desenvolupar noves teràpies més eficaces i específiques per a les persones amb FM.

Figura 4. *Resum de potencials factors etiopatogènics de la fibromiàlgia*

Font: Elaboració pròpia.

2. Estat immunoinflamatori en la fibromiàlgia

Diversos estudis han suggerit que la disfunció del sistema immune, tant de la immunitat innata com de la immunitat adaptativa, pot tenir un paper decisiu en el seu desenvolupament (Andrés-Rodríguez et al. 2020; Bäckryd et al. 2017; Rodriguez-Pinto et al. 2014; Sluka & Clauw, 2016). En particular, la recerca ha destacat alteracions en les citocines i quimiocines que regulen la resposta immune, la qual cosa suggeriria una desregulació immunitària que pot contribuir als símptomes característics de la FM.

Immunitat innata:

El sistema immune innat constitueix la primera línia de defensa del cos contra agents patògens i s'activa mitjançant respostes generals de tipus inflamatòries. Diversos estudis han demostrat que alteracions en el sistema immune innat poden ser implicades en la fisiopatologia de la FM, amb evidències d'una activació excessiva de citocines proinflamatòries que podrien provocar inflamació crònica de baix grau i sensibilització al dolor.

- Citocines proinflamatòries: En persones amb FM, s'han observat nivells elevats de citocines proinflamatòries, com la Interleucina-6 (IL-6), el Factor de Necrosi Tumoral alfa (TNF-α) i la Interleucina-1 beta (IL-1β), que són essencials en la resposta immune innata. Aquestes citocines es produeixen durant processos inflamatoris o infecciosos, però en la FM poden estar crònicament elevades, contribuint a la inflamació persistent i a la sensibilització al dolor (Clauw, 2014; Kosek et al. 2015).

- Activació de la microglia: El sistema nerviós central (SNC) també pot estar implicat en la patogènia de la FM. Les microglies, cèl·lules immunes del SNC, poden activar-se en resposta a una inflamació crònica, alliberant substàncies proinflamatòries que amplifiquen els senyals de dolor al cervell i a la medul·la espinal. Aquest fenomen, conegut com a sensibilització central, explicaria la hipersensibilitat al dolor observada en la FM (Albrecht et al. 2019; Bäckryd et al. 2017).
- Receptors tipus toll (TLRs): Els TLRs són receptors implicats en la detecció de patògens i en l'activació de la resposta immune. En la FM, s'ha suggerit que una alteració en la via de senyalització dels TLRs pot conduir a una resposta immune desregulada, amb un augment de la inflamació crònica i la fatiga, que són símptomes típics del trastorn (Kosek et al. 2015).

Immunitat adaptativa:

El sistema immune adaptatiu és més específic i es basa en la resposta de dos tipus de limfòcits: les cèl·lules T i les cèl·lules B, les quals estan implicades en la defensa contra patògens específics i en la producció d'anticossos. Tot i que la investigació en aquest àmbit és menys abundant, diversos estudis suggereixen que la desregulació de les respostes immunes adaptatives podria contribuir a la patogènia de la FM.

- Desregulació de les cèl·lules T: Les cèl·lules T, implicades en la resposta immune adaptativa, poden presentar alteracions en la seva activitat en la FM. Es pot observar un desajust entre les cèl·lules Th1, que són proinflamatòries, i les cèl·lules Th2, que tenen un efecte antiinflamatori.

Aquest desequilibri podria provocar una inflamació crònica i contribuir a la desregulació immune (Banfi et al. 2020).

- Autoimmunitat: Algunes investigacions suggereixen una possible connexió entre la FM i certes malalties autoimmunitàries, ja que s'han observat nivells elevats d'autoanticossos (com ara, anticossos antinuclears (ANAs) i factor reumatoide (RF)) en persones amb FM. No obstant això, la relació entre la FM i l'autoimmunitat continua sent un tema controvertit i necessita més investigació (Lichtenstein et al. 2018; Ryabkova et al. 2023).
- Disfunció de les cèl·lules B: Les cèl·lules B, responsables de la producció d'anticossos, poden jugar un paper en la FM. La producció anòmala d'anticossos pot contribuir a una inflamació crònica i a un mal funcionament del sistema immune, tot i que aquest mecanisme encara està en fase d'investigació (Maes & Carvalho, 2018).

Marcadors immunoinflamatoris:

Diversos marcadors immunoinflamatoris s'han identificat en persones amb FM, incloent-hi l'hs-CRP, que en alguns casos presenta nivells elevats en persones amb FM. Aquesta proteïna és un indicador d'inflamació sistèmica, tot i que els resultats sobre la seva relació amb la FM són diversos (Maes & Carvalho, 2018). Un augment dels nivells d'hs-CRP pot estar associat amb la sensibilitat al dolor i altres símptomes característics de la FM.

Una metaanàlisi d'Andrés-Rodríguez et al. (2020) va trobar alteracions lleus en la signatura immune de persones amb FM, amb un desequilibri entre les citocines proinflamatòries com la IL-6 i la IL-17 i les citocines antiinflamatòries com la IL-4. Aquest desequilibri pot contribuir a la inflamació sistèmica i a la

neuroinflamació, factors implicats en l'aparició i l'agreujament de la sensibilitat al dolor, la fatiga i els trastorns del son.

Model IRS/CIRS:

Els fenotips IRS (Sistema de Resposta Immunoinflamatòria) i CIRS (Sistema Reflex Immunoregulador Compensatori) ofereixen una perspectiva innovadora sobre el paper del sistema immune en la FM. Els fenotips IRS es caracteritzen per una activació excessiva de la resposta immunoinflamatòria, amb nivells elevats de citocines proinflamatòries, mentre que els fenotips CIRS impliquen mecanismes reguladors que intenten mitigar l'activació immune (Andrés-Rodríguez et al. 2019). La comprensió d'aquest model pot obrir noves vies per al tractament personalitzat de la FM, modulant les respostes immunes i afavorint una resolució de la inflamació (**Annex 4**).

Com a conclusió podem dir que a FM presenta una complexa alteració immunoinflamatòria que afecta tant la immunitat innata com l'adaptativa. Les evidències apunten a una desregulació de les citocines i altres biomarcadors immunoinflamatoris (**Taula 2**), la qual cosa provoca inflamació crònica i sensibilització central al dolor. Tot i que els mecanismes exactes encara no es coneixen completament, aquests factors podrien contribuir de manera significativa a la patofisiologia de la FM. A més, el model IRS/CIRS ofereix una nova línia d'investigació per comprendre millor les alteracions immunològiques associades a la FM i per desenvolupar teràpies més específiques i personalitzades (Clauw, 2014). Segons Maes i Carvalho (2018), activar el CIRS mitjançant teràpies multidimensionals orientades a resoldre les inflamacions podria representar una

via prometedora per al tractament de la FM, ja que ajudaria a reduir l'activació de l'IRS i els seus símptomes associats.

Taula 2. *Biomarcadors implicats en la fisiopatologia de la fibromiàlgia.*

Biomarcador	Tipus	Implicació en FM	Referència
IL-6, TNF-α, IL-1β	Proinflamatòries	Inflamació crònica, dolor i fatiga	Kosek et al. 2015; Clauw, 2014
IL-17	Proinflamatòria	Neuroinflamació i fatiga	Andrés-Rodríguez et al. 2020
IL-4, IL-10	Antiinflamatòries	Reduïdes → Inflamació persistent	Maes & Carvalho, 2018
hs-CRP	Indicador inflamatori	Elevada → Associada a dolor i fatiga	Maes & Carvalho, 2018
TLRs	Regulador immune	Possible desregulació → Inflamació crònica	Kosek et al. 2015
Microglies	Immunitat SNC	Sensibilització central i dolor	Bäckryd et al. 2017; Albrecht et al. 2019)
Autoanticossos (ANAs, RF)	Autoimmunitat	Presència en algunes persones amb FM	Lichtenstein et al. 2018

Nota: FM, Fibromiàlgia; IL, Interleucina; TNF-α, Tumor Necrosis Factor Alpha; hs-CRP, high-sensitivity C-reactive protein; TLRs, Toll-like Receptors; SNC, Sistema Nerviós Central; ANAs, Antinuclear Antibodies ; RF, Rheumatoid Factor.

Font: Elaboració pròpia.

3. Nivells de BDNF en la fibromiàlgia

En el marc de la recerca sobre la FM, s'ha dedicat una atenció creixent als biomarcadors relacionats amb la plasticitat neuronal com a possibles factors per entendre la complexitat del trastorn. Un dels més destacats és el BDNF, que juga un paper fonamental en diversos processos fisiològics i patològics. Aquesta neurotrofina multifuncional s'ha vinculat amb mecanismes de neuroplasticitat implicats en la modulació del dolor, un dels símptomes centrals de la FM, així com en altres fenòmens com la transducció, la nocicepció i la hiperalgèsia, tots ells alterats en la FM (Nugraha et al. 2012).

Les anomalies perifèriques detectades en persones amb FM s'han associat a alteracions en els nivells de BDNF, que és considerat un biomarcador principal del dolor neuropàtic (Deitos et al. 2015). Aquesta neurotrofina no només participa en mecanismes centrals de plasticitat neuronal, sinó que també s'ha plantejat com una possible diana terapèutica. Evidències recents suggereixen que la modulació dels nivells de BDNF mitjançant intervencions terapèutiques podria contribuir a una disminució en la intensitat del dolor i, potencialment, a una millora en altres símptomes de la FM (Di-Bonaventura et al. 2023). En un estudi de Hass et al. (2010), es va observar que els nivells plasmàtics de BDNF eren significativament més alts en persones amb FM en comparació amb un grup de control sa. Aquests nivells elevats podrien estar implicats en la fisiopatologia de la FM, ja que el BDNF està relacionat amb la supervivència neuronal i la modulació del dolor. No obstant això, no es va trobar una correlació significativa entre els nivells de BDNF i el dolor o la depressió, fet que suggereix que podrien estar implicats altres mecanismes patològics. Així, els nivells elevats de BDNF podrien representar una

resposta compensatòria al dolor crònic, tot i que es requereix més investigació per entendre el seu rol i les possibles aplicacions terapèutiques (**Taula 3**).

Taula 3. *Implicacions del BDNF en la fibromiàlgia*

BDNF	Implicacions en la FM
Funció principal	Participa en la neuroplasticitat, modulant processos com la transducció, nocicepció i hiperalgèsia, implicats en el dolor (Nugraha et al. 2012).
Relació amb la FM	Alteracions en els nivells de BDNF associades a dolor crònic, neuroplasticitat i sensibilització central al dolor (Deitos et al. 2015).
Mecanismes involucrats	Influència en la supervivència neuronal i la modulació del dolor, tot i que els mecanismes exactes necessiten més investigació.
Evidència clínica	Nivells elevats de BDNF en persones amb FM, però sense correlació significativa amb dolor o depressió (Hass et al. 2010).
Funció compensatòria	Els nivells elevats de BDNF podrien representar una resposta compensatòria al dolor crònic.
Aplicacions terapèutiques	La modulació dels nivells de BDNF es considera una estratègia potencial per al tractament personalitzat del dolor (Di-Bonaventura et al. 2023).
Investigacions recents	Estudis suggereixen que el BDNF podria ser un biomarcador del dolor neuropàtic i una diana terapèutica en la FM (Di-Bonaventura et al. 2023).
Perspectives futures	Necessitat d'investigar més sobre el paper del BDNF en la fisiopatologia de la FM i el seu potencial com a diana terapèutica.

Nota: FM, Fibromiàlgia; BDNF, Brain-Derived Neurotrophic Factor.

Font: Elaboració pròpia.

Les troballes subratllen la necessitat d'explorar més a fons el paper del BDNF en la FM, tot i que la seva utilització com a biomarcador d'aquesta patologia segueix sense estar definida. Els resultats dels estudis disponibles són inconsistents pel que fa a la seva regulació, la qual cosa suggereix que els nivells elevats de BDNF podrien ser més una resposta compensatòria al dolor crònic que no un mecanisme patogènic directe. Així, cal dur a terme més investigacions per determinar amb exactitud el seu potencial com a objectiu terapèutic i la seva aplicació en estratègies de tractament personalitzades, obrint noves vies per a la recerca i la gestió d'aquest trastorn complex.

4. Abordatge terapèutic de la fibromiàlgia

L'atenció a les persones amb FM es considera insuficient en diversos aspectes, com la qualitat del diagnòstic, el tractament multidisciplinari i la formació dels professionals de la salut (Dizner-Golab et al. 2023). Tot i que hi ha un augment en la disponibilitat de fàrmacs, tècniques d'intervenció, dispositius i tecnologies per a la gestió del dolor, així com unitats especialitzades en el dolor, el dolor persistent associat a la FM segueix augmentant, cosa que contribueix a un increment de la seva prevalença en la població (Marques et al. 2017). Encara que s'han realitzat nombrosos estudis, cap ha proporcionat un tractament curatiu per a la FM. Els tractaments actuals se centren a millorar els símptomes (dolor, trastorns del son, alteracions psicològiques) i a augmentar la funcionalitat i l'activitat, basant-se en l'evidència, encara que no són curatius.

Segons l'ACR, l'exercici, com ara el ioga, el taitxí i l'activitat aeròbica de baix impacte, és un dels tractaments més efectius per a la FM (ACR, 2019). Aquestes activitats ajuden a millorar la flexibilitat i la força muscular, a més de

reduir l'ansietat i la depressió, que sovint acompanyen aquesta condició (Haugmark et al. 2019; Malfliet et al. 2017; Nüesch et al. 2013). L'acupuntura, la quiropràctica i el massatge emergeixen com a modalitats terapèutiques complementàries potencialment útils en la mitigació dels símptomes associats a la FM. La investigació científica ha explorat àmpliament l'efectivitat d'aquestes intervencions, evidenciant la seva capacitat per a la reducció del dolor i la millora de la qualitat de vida en individus afectats per aquesta condició. Diversos estudis han mostrat que l'acupuntura pot ser eficaç per reduir el dolor i millorar la funcionalitat (Martin et al. 2006; Zhang et al. 2019). Pel que fa al massatge, diversos assaigs clínics han demostrat que és efectiu per reduir el dolor i la fatiga, així com per millorar l'estat d'ànim i la qualitat del son (Li et al. 2014; Ughreja et al. 2021). D'altra banda, l'evidència sobre l'efectivitat de la quiropràctica en el tractament de la FM és limitada i en debat, amb alguns estudis suggerint possibles efectes positius, però amb resultats poc concloents (Ernst, 2009).

Les guies terapèutiques més reconegudes per al tractament de la FM, com les de l'ACR (2019), l' *European League Against Rheumatism (*EULAR) (Macfarlane et al. 2017) i la *Sociedad Española de Reumatología* (SER, 2020), proporcionen un enfocament basat en l'evidència científica per al maneig de la FM. Tot i que coincideixen en diversos aspectes principals, també presenten algunes diferències en la seva aproximació terapèutica. Totes les guies adopten un enfocament multimodal, amb algunes diferències en les seves prioritats. L'ACR (2019) recomana un enfocament combinat, incloent tant tractaments farmacològics com estratègies no farmacològiques. Aquests inclouen l'ús de medicaments com la duloxetina, antidepressius tricíclics i anticonvulsius, així com la TCC per al maneig de la fatiga, el dolor i l'ansietat. EULAR (Macfarlane et al.

2017) destaca les estratègies no farmacològiques, prioritzant l'exercici físic i la psicoteràpia, mentre que la SER (2020) també emfatitza la importància de l'educació de la persona amb FM, el maneig de la fatiga i la promoció de l'activitat física. La fatiga és un símptoma significatiu en la FM, i pel seu maneig totes les guies promouen un enfocament multimodal que inclogui exercici i intervenció psicològica. L'ACR (2019) combina exercici, TCC i medicaments per gestionar la fatiga, mentre que EULAR (Macfarlane et al. 2017) se centra en l'activitat física i la psicoteràpia. La SER (2020) fa especial èmfasi en tècniques per millorar la qualitat del son i controlar la fatiga mitjançant l'exercici físic moderat.

En resum, les tres guies clíniques presenten algunes discrepàncies, especialment pel que fa a l'ús de medicaments i l'enfocament de l'exercici. Les guies ACR (2019) i EULAR (Macfarlane et al. 2017) posen més èmfasi en els medicaments, mentre que la SER (2020) fa un enfocament més conservador, prioritzant les estratègies no farmacològiques. Tot i aquestes diferències, el tractament multimodal, individualitzat i enfocat en l'exercici físic, la psicoteràpia i la gestió de l'estrès és comú a totes les guies.

Segons l'ACR (2019), un estil de vida saludable, que combini medicaments amb una activitat física regular, és fonamental per millorar la qualitat de vida de les persones amb FM. A més, les recomanacions d'EULAR (Macfarlane et al. 2017) subratllen la importància de l'exercici i la TCC, amb un enfocament centrat en la persona amb FM i un tractament individualitzat. Finalment, la SER (2020) també aposta per un tractament holístic que combini medicaments i teràpies no farmacològiques, amb un pla de tractament personalitzat basat en les necessitats de cada persona amb FM.

4.1. Tractaments farmacològics

Fins a l'actualitat, els tractaments farmacològics disponibles per a la FM són principalment simptomàtics i no presenten un efecte curatiu clar. A més, la seva efectivitat clínica és limitada i pot variar segons la persona amb FM (Häuser et al. 2015). Pel que fa a les intervencions farmacològiques, l'EULAR (Macfarlane et al. 2017) recomana l'ús de medicaments principalment en casos de dolor intens i alteracions del son (Häuser et al. 2015; Macfarlane et al. 2017). No obstant això, l'EULAR (Macfarlane et al. 2017) desaconsella l'ús generalitzat d'aquests fàrmacs, limitant-ne la indicació a situacions específiques depenent de la simptomatologia de cada persona amb FM. D'altra banda, l'ACR (2019) aconsella tres medicaments aprovats per la *Food and Drug Administration* (FDA) per al tractament de la FM: la duloxetina (Cymbalta) i el milnacipran (Savella), que modulen les substàncies químiques cerebrals per disminuir el dolor generalitzat, i la pregabalina (Lyrica), que bloqueja les cèl·lules nervioses hiperactives implicades en la percepció del dolor. A més, també es poden utilitzar medicaments de primera generació, com l'amitriptilina (Elavil), la ciclobenzaprina (Flexeril) i altres antidepressius. Tanmateix, l'ús d'opioides i de medicaments per al son, com el zolpidem (Ambien), no està recomanat per al tractament dels símptomes associats a la FM. Pel que fa als tractaments farmacològics, SER (2020) segueix les recomanacions generals d'altres guies internacionals, com les de l'ACR (2019) i l'EULAR (Macfarlane et al. 2017), tot i que adverteix sobre la limitació de l'ús de fàrmacs a aquelles persones amb símptomes més greus. Els antidepressius, com la duloxetina, i els anticonvulsius, com la pregabalina, són recomanats per al tractament del dolor i la fatiga associada a la FM. No obstant

això, es fa especial èmfasi en l'ús selectiu dels antiinflamatoris no esteroïdals (AINEs), ja que la seva efectivitat a llarg termini en la FM no ha quedat completament demostrada.

En línia amb aquestes recomanacions, les tres guies coincideixen en la importància de controlar els símptomes mitjançant medicaments, tot i que les recomanacions específiques poden variar. L'ACR (2019) recomana la duloxetina, els antidepressius tricíclics i els anticonvulsius com a tractaments de primera línia per al maneig del dolor crònic i la fatiga associada a la FM. L'EULAR (Macfarlane et al. 2017) comparteix aquesta visió, però també inclou els AINEs, tot i que recomana el seu ús de manera selectiva i durant períodes curts. Per la seva banda, la SER (2020) coincideix en gran mesura amb aquestes recomanacions, però adverteix que els AINEs no han demostrat una efectivitat consistent a llarg termini per al tractament de la FM.

En resum, tot i que les guies coincideixen en els principis generals per a l'abordatge farmacològic de la FM, la selecció i durada del tractament farmacològic s'ha de personalitzar segons les necessitats específiques de cada persona amb FM i la severitat dels seus símptomes. Per últim, és important ressaltar que diversos grups de recerca estan tractan de demostrar l'efectivitat de nous medicaments (com per exemple, la naltrexona a dosis baixes o la psilocibina) per aliviar la sintomatologia i millorar l'estat funcional de les persones amb FM amb menys efectes adversos que la pregabalina, la duloxetina i el milnacipran (Bornemann et al. 2024; Colomer-Carbonell et al. 2022).

4.2. Tractaments no-farmacològics

Les estratègies no farmacològiques han demostrat tenir efectes més amplis en la reducció dels símptomes, en la millora de la qualitat de vida i la capacitat funcional de les persones amb FM, en comparació amb les farmacològiques, sovint exhibint mides d'efecte lleugerament més grans en comparació amb les opcions farmacèutiques (Hong-Baik et al. 2023; Nüesch et al. 2013; Perrot et al. 2014). Aquestes aproximacions no farmacològiques engloben diverses intervencions com l'ECD, l'exercici terapèutic, la TCC i la formació en la consciència plena (mindfulness), on el seu objectiu principal és reduir els símptomes i millorar la qualitat de vida global de les persones amb FM (Macfarlane et al. 2017).

És cert que l'efectivitat de les teràpies no farmacològiques pot variar de manera significativa d'una persona a una altra, ja que cada persona amb FM té una resposta individual a diferents tipus de tractaments. Això es deu a diversos factors, com la variabilitat en la intensitat dels símptomes, les comorbiditats, les preferències personals i les circumstàncies socials i psicològiques de cada individu (Häuser et al. 2015; Macfarlane et al. 2017). Aquesta variabilitat subratlla la importància de l'enfocament individualitzat i la decisió compartida en la selecció de les teràpies no farmacològiques. En aquest context, la decisió compartida es refereix a un procés en el qual la persona amb FM i el professional de la salut treballen conjuntament per determinar el tractament més adequat per a la persona amb FM, tenint en compte les seves preferències, valors, experiències anteriors i resposta a tractaments previs (Stacey et al. 2017). Les decisions compartides són fonamentals per garantir que la persona amb FM se senti empoderada i

involucrada en el seu propi pla de tractament. Aquest enfocament també pot millorar l'adhesió al tractament, ja que la persona amb FM pot estar més disposada a seguir les recomanacions que s'han elaborat conjuntament (Légaré et al. 2014; Stacey et al.2017).

4.2.1. Educació en ciència del dolor

L'ECD, és una intervenció que té com a objectiu canviar la percepció del dolor en persones amb trastorns crònics, com la FM. Aquesta intervenció busca reconceptualitzar el dolor, ajudant a les persones a comprendre els mecanismes subjacents a les seves experiències doloroses. L'ECD es basa en models teòrics consolidats, entre els quals destaca l'obra "Explaining Pain" de Butler i Moseley (2010), els quals expliquen com el cervell percep i interpreta els senyals de dolor. Mitjançant l'ús de metàfores, exemples visuals i explicacions clares, l'ECD facilita la comprensió dels processos biològics i cognitius que modulen la percepció del dolor, permetent a les persones tenir una visió més equilibrada i menys temuda del dolor (Nijs et al. 2011).

L'ECD ha demostrat ser efectiva per modificar creences errònies sobre el dolor, reduir la catastrofització i millorar la funcionalitat en persones amb FM. Tanmateix, és essencial recordar que la FM és una condició mèdica multifactorial i sistèmica que inclou una varietat de símptomes com fatiga extrema, trastorns del son, disfunció cognitiva, hipersensibilitat sensorial i alteracions autonòmiques (Nijs et al. 2011). L'ECD se centra principalment en la reconceptualització del dolor, però no aborda altres aspectes fonamentals de la FM, com la fatiga o els dèficits cognitius. Per tant, no es pot considerar que l'ECD, per si sola, sigui suficient per millorar tota la simptomatologia de la FM, ja que només treballa els mecanismes

de percepció i modulació del dolor (Moseley & Butler, 2015). En conseqüència, esdevé imprescindible un abordatge integral que combini diverses estratègies terapèutiques per a la gestió de la complexitat de la FM.

La percepció del dolor no es limita només a la presència d'un dany físic objectiu, sinó que també depèn de factors contextuals com les creences personals, l'ambient social i l'estat emocional. El cervell no respon únicament a un dany real, sinó que genera una resposta de dolor en funció de com interpreta els senyals percebuts. Així, si el cervell interpreta una amenaça, activa la resposta protectora del dolor, però aquesta resposta pot ser exagerada o errònia, sobretot en situacions on els senyals de dolor no estan correlacionats amb un dany real (Butler & Moseley, 2010). Aquest fet és especialment rellevant en persones amb FM, ja que la percepció del dolor pot ser intensificada per creences catastròfiques o per l'ansietat sobre el dolor. En aquest context, l'ECD juga un paper fonamental en canviar aquestes creences errònies, ajudant a les persones amb FM a entendre que el dolor no sempre és una indicació d'un dany físic real i que els comportaments com l'evitació o la sobreprotecció poden augmentar la intensitat del dolor (Moseley & Butler, 2015). Així, l'ECD no només proporciona informació sobre el dolor des d'una perspectiva biològica, sinó que també permet que les persones amb FM reconeguin com les seves emocions, creences i l'entorn poden amplificar la seva experiència dolorosa (Nijs et al. 2011).

Quant a l'efectivitat de l'ECD, diversos estudis han mostrat que aquesta intervenció pot ser eficaç per reduir aspectes com l'impacte funcional, la catastrofització del dolor, els comportaments d'evitació i la inactivitat física en persones amb FM (Malfliet et al. 2017). Tanmateix, els beneficis de l'ECD són més notables quan aquesta es combina amb altres teràpies complementàries, com

l'exercici físic o tècniques de regulació emocional. Aquest enfocament integrat permet abordar les diferents dimensions del dolor, incloent-hi l'aspecte cognitiu, emocional i físic (Moseley, 2003; Malfliet et al. 2017). L'ECD pot ser efectiva per canviar la forma en què una persona percep el dolor, però per aconseguir una millora duradora, és necessari un enfocament que integri altres intervencions, com la rehabilitació física, per optimitzar la condició física, i l'abordatge dels factors emocionals com l'ansietat i la depressió, que exerceixen un paper crucial en la cronicitat del dolor (Moseley, 2003).

Pel que fa a la durabilitat dels efectes de l'ECD, és important destacar que, tot i que els canvis en la percepció del dolor poden ser notables a curt termini, aquests efectes poden ser limitats a llarg termini si no es complementen amb altres estratègies. En aquest sentit, l'estudi de Barrenengoa-Cuadra et al. (2020) va avaluar l'efectivitat d'una intervenció grupal basada en ECD en pacients amb FM en atenció primària, mitjançant cinc sessions setmanals i una sessió de recordatori un mes després. Es van abordar els mecanismes neurobiològics del dolor, analitzant el seu impacte amb qüestionaris específics, i els resultats van mostrar una millora significativa en la reducció del dolor i l'impacte funcional de la malaltia, amb efectes sostinguts durant almenys 12 mesos. Així, tot i que l'ECD pot generar beneficis importants, per mantenir-los a llarg termini pot ser necessari complementar-la amb altres estratègies terapèutiques. També és fonamental que les persones amb dolor rebin seguiment continuat per reforçar les noves creences apreses i assegurar-se que segueixin aplicant-les en la seva vida quotidiana. Per garantir la durabilitat dels efectes, l'ECD ha de formar part d'un pla de tractament integral que inclogui altres estratègies com la psicoteràpia, la meditació o l'entrenament en habilitats de regulació emocional, per garantir que les persones

no només comprenguin el dolor, sinó que també aprenguin a gestionar-lo de manera eficaç i sostenible a llarg termini (Malfliet et al. 2017; Nijs et al. 2011).

En conclusió, l'ECD és una eina molt útil per a la modificació de la percepció del dolor, especialment quan s'utilitza en combinació amb altres teràpies integrades. El coneixement dels mecanismes del dolor i la comprensió de com els factors emocionals i contextuals influeixen en la seva intensitat poden millorar significativament la qualitat de vida de les persones amb FM. Tot i això, per a una millora sostenible a llarg plaç, és necessari un enfocament integrat que combini l'educació sobre el dolor amb altres intervencions terapèutiques que abordin els aspectes físics, emocionals i cognitius de l'experiència del dolor (Malfliet et al. 2017; Moseley & Butler, 2015).

4.2.2. Exercici terapèutic

La World Confederation for Physical Therapy (WCPT) defineix l'exercici terapèutic com: "Un conjunt d'exercicis específicament dissenyats i prescrits per un fisioterapeuta amb l'objectiu de millorar la funcionalitat i la mobilitat, reduir el dolor, i prevenir la progressió de condicions patològiques o la recurrència de lesions. Aquest tipus d'exercici es personalitza segons les necessitats individuals del pacient i es fonamenta en una avaluació detallada del seu estat físic i funcional." Segons la WCPT, l'enfocament metodològic es basa en la ciència de la fisioteràpia i en l'evidència clínica per garantir l'efectivitat i la seguretat de les intervencions, requereix una avaluació contínua del progrés del pacient i ajustos regulars del programa d'exercici per adaptar-se als canvis en l'estat de salut i en els objectius terapèutics. Sovint forma part d'un pla de tractament més ampli que pot incloure altres formes de teràpia, medicació i suport educatiu o psicològic.

L'Organització Mundial de la Salut (OMS) proporciona recomanacions generals sobre l'exercici físic i l'activitat física que són aplicables a diverses condicions de salut, incloent la FM. L'ACR (2019), el NICE (National Institute for Health and Care Excellence) i l'ACSM (American College of Sports Medicine) proporcionen guies específiques basades en l'evidència per a l'exercici físic, dirigides als professionals de la salut per a l'abordatge de la FM.

Tant l'ACR (2019), l'EULAR (Macfarlane et al. 2017) com la SER (2020) coincideixen en recomanar l'exercici aeròbic i de força com a part del tractament. L'ACR (2019) recomana l'exercici regular, amb especial atenció a l'exercici aeròbic i l'entrenament de força per millorar la força muscular i reduir el dolor. EULAR (Macfarlane et al. 2017) destaca la natació i caminar com a activitats beneficioses, mentre que la SER (2020) posa èmfasi en exercicis de força adaptats a les capacitats individuals de cada persona amb FM.

Tot i que la FM no està associada amb lesions físiques cerebrals detectables, l'exercici físic continua sent una intervenció crucial. No obstant això, no es pot recomanar l'exercici a una persona que experimenta dolor intens sense proporcionar una guia adequada. És essencial que les persones rebin instruccions detallades sobre la manera correcta de realitzar l'exercici, garantint així que es maximitzin els beneficis i es minimitzin els riscos. L'exercici ha de ser progressiu i individualitzat, adaptat a la tolerància i condicions de cada persona amb FM, per evitar el malestar post-esforç que podria reduir l'adherència al programa.

L'exercici és una estratègia no farmacològica important per reduir els símptomes de la FM, millorant la qualitat de vida de les persones amb FM (Couto et al. 2022; Denche-Zamorano et al. 2023; Zhang et al. 2022). Tot i que inicialment pot causar una certa incomoditat, a llarg termini ajuda a reduir el dolor mitjançant

la millora de la circulació sanguínia, l'alliberament d'endorfines i la disminució de la sensibilitat al dolor. Tanmateix, la seva efectivitat pot variar segons la intensitat, la freqüència i la tipologia de l'exercici practicat.

És crucial adaptar el programa d'exercici a les capacitats i limitacions individuals de les persones amb FM, amb la guia d'un professional de la salut o fisioterapeuta. Els programes efectius inclouen educació sobre el dolor i estratègies psicològiques, com la reestructuració cognitiva, per ajudar les persones a comprendre millor la seva resposta al dolor i reduir la kinesiòfobia. Aquest enfocament combinat permet millorar l'adherència al tractament i optimitzar els beneficis a llarg termini.

Les guies clíniques concorden que l'exercici terapèutic hauria de ser un component principal en el tractament de la FM, ja que s'ha demostrat efectiu en la reducció dels símptomes, incloent el dolor, i en la millora de la funció física i la qualitat de vida (Bernardy et al. 2018; Sosa-Reina et al. 2017; Zhang et al. 2022). Les evidències també suggereixen que l'exercici pot tenir un paper rellevant en la modulació de marcadors neuroinflamatoris i neuroplàstics. Per exemple, s'ha observat que l'exercici aeròbic pot augmentar els nivells de BDNF, afavorint la plasticitat neuronal i millorant la percepció del dolor (Di-Bonaventura et al. 2023). No obstant això, el seu impacte en la inflamació varia segons la intensitat i la freqüència de l'activitat física, per la qual cosa cal evitar afirmacions categòriques sobre la seva efectivitat universal en aquest aspecte.

A més, l'exercici físic ha demostrat ser beneficiós en la millora de la salut mental, reduint els símptomes de depressió i ansietat mitjançant la modulació temporal dels nivells de serotonina, noradrenalina, BDNF i diversos marcadors immunoinflamatoris com TNF-α, IL-6 i IL-10 (Ross et al. 2023; Singh et al. 2023).

Aquests efectes poden contribuir indirectament a una millor percepció del dolor i a una major adherència als programes terapèutics.

Les evidències recents confirmen que l'activitat física és un pilar fonamental en la gestió terapèutica de la FM, destacant especialment caminar com una de les opcions més efectives i ben tolerades per les persones amb FM (Majdoub et al. 2023). No obstant això, la seva aplicació ha de ser individualitzada i progressiva, combinada amb educació i suport psicològic per maximitzar els seus beneficis i evitar riscos associats al malestar post-esforç.

4.2.3. Teràpia cognitivoconductual

La TCC aplicada a la FM, segons l'American Psychological Association (APA), es defineix com un enfocament psicoterapèutic dissenyat per ajudar les persones amb FM a manejar el dolor crònic i els altres símptomes associats a aquesta condició, com l'ansietat i la depressió.

Les bases principals són:

1. Afrontament del dolor i dels símptomes: La TCC ajuda les persones amb FM a entendre com els pensaments i les creences sobre el dolor poden influir en la percepció i l'experiència del dolor. Les persones amb FM aprenen tècniques per gestionar i reduir el dolor i altres símptomes associats, com la fatiga i les alteracions del son. L'efectivitat de la TCC depèn de la individualització del tractament, ja que no és igual de beneficiosa per a totes les persones amb FM. L'impacte pot variar segons la severitat dels símptomes, la predisposició al canvi i la seva integració amb altres intervencions.

2. Modificació de pensaments disfuncionals: Es treballa en identificar i desafiar pensaments disfuncionals o catastrofistes sobre la condició, que poden

exacerbar el malestar emocional i físic. La teràpia ajuda les persones amb FM a substituir aquests pensaments per creences més adaptatives i realistes.

3. Estratègies de relaxació i maneig de l'estrès: La TCC inclou tècniques de relaxació i gestió de l'estrès per ajudar a reduir la tensió muscular i la resposta d'estrès, que poden contribuir al dolor i a la fatiga.

4. Tècniques de resolució de problemes i establiment d'objectius: La teràpia ajuda les persones amb FM a desenvolupar habilitats per afrontar problemes relacionats amb la FM i establir objectius realistes per millorar la seva funció diària i qualitat de vida.

5. Millora de la qualitat del son: La TCC aborda les alteracions del son associades amb la FM, ajudant les persones amb FM a establir hàbits de son saludables i a superar els problemes de son.

6. Educació sobre la condició: La TCC proporciona informació sobre la FM i com la condició afecta el cos i la ment, ajudant les persones amb FM a comprendre millor la seva situació i a desenvolupar estratègies efectives per afrontar-la.

La TCC és considerada una intervenció eficaç per a la FM perquè aborda tant els aspectes físics com els psicològics de la condició, ajudant les persones amb FM a millorar el seu benestar general i a gestionar els símptomes de manera més efectiva (Macfarlane et al. 2017; Bernardy et al. 2018). No obstant això, la TCC no pot abordar per si sola tots els aspectes de la FM, ja que no actua directament sobre els mecanismes fisiològics subjacents de la FM, com la neuroinflamació o la disfunció autonòmica.

És important que la teràpia sigui personalitzada i adaptada a les necessitats i circumstàncies de cada persona amb FM. La TCC és més efectiva

quan es combina amb altres intervencions com l'ECD, el mindfulness i l'exercici adaptat, ja que aquests elements reforcen l'abordatge conductual i ajuden a evitar la kinesiofòbia. És recomanable que la TCC sigui realitzada per professionals de la psicologia especialitzats en el maneig de les persones amb dolor crònic.

Pel que fa a la intervenció psicològica i gestió de l'estrès, l'ACR (2019) fa especial èmfasi en la TCC per millorar l'afrontament de les persones amb FM i reduir l'estrès i l'ansietat. EULAR (2017) també recomana TCC i tècniques de relaxació com la meditació, mentre que la SER (2020) subratlla la importància de millorar la qualitat del son i evitar la sobrecàrrega emocional. A més, es considera la Teràpia d'Acceptació i Compromís (ACT) com una opció més que prometedora en el tractament de la FM, especialment per a persones amb alta sensibilitat al dolor i dificultats per regular les emocions. En aquest sentit, l'estudi de Luciano et al. (2014) va comparar l'efectivitat de l'ACT en grup amb la medicació recomanada per a la FM, trobant que aquesta teràpia pot ser una alternativa terapèutica beneficiosa per a aquestes persones amb FM. A més, la revisió sistemàtica i metanàlisi d'Eastwood i Godfrey (2024) confirma l'efectivitat de l'ACT en la millora de variables clíniques fonamentals, com la funcionalitat, l'ansietat, la depressió, el dolor i la fatiga, demostrant el seu potencial en el tractament de la FM.

Les guies clíniques, basades en una àmplia revisió de l'evidència científica, coincideixen àmpliament en què la TCC i l'exercici físic terapèutic han de ser els principals components del tractament de la FM, tal com es reflecteix en estudis com els de Bernardy et al. (2018) que van demostrar que la TCC pot reduir els nivells de dolor, disminuir la fatiga i millorar la salut mental dels pacients. i Sosa-Reina et al. (2017) que van investigar com les intervencions d'exercici

podrien millorar els símptomes de la FM, incloent la reducció del dolor, la fatiga i l'impacte sobre la qualitat de vida dels pacients.

4.2.4. Teràpies basades en *mindfulness*

El mindfulness es pot definir com "la consciència que sorgeix de prestar atenció, a propòsit, en el moment present, sense jutjar" (Kabat-Zinn, 1982). En promoure l'acceptació i la millora de l'autoregulació emocional, les intervencions basades en mindfulness poden ser adequades per a la gestió dels esdeveniments d'angoixa en persones amb FM. La majoria dels estudis que han investigat l'efectivitat d'aquestes intervencions en aquesta població han utilitzat programes de Reducció de l'Estrès Basada en la Consciència Plena (MBSR), i cada vegada hi ha més evidència que pot ser una aproximació eficaç i rendible per millorar la qualitat de vida, l'impacte funcional, l'ansietat, la depressió i altres símptomes en persones amb FM (Haugmark et al. 2019; Leça & Tavares, 2022; Meng et al. 2024; Pérez-Aranda et al. 2019).

El tractament basat en mindfulness, com la MBSR, combina tècniques de meditació, ioga suau i altres pràctiques de consciència plena, i s'ha observat que pot contribuir a la millora de la qualitat de vida, la funcionalitat i la percepció dels símptomes en persones amb FM. Tot i que alguns estudis han suggerit que pot influir en vies immunoinflamatòries, aquests efectes poden ser una resposta secundària a la reducció de l'estrès més que un mecanisme directe del mindfulness. Per exemple, s'ha proposat que podria ajudar a mantenir nivells estables de citocines antiinflamatòries com la IL-10, però cal més recerca per establir clarament aquesta relació (Andrés-Rodríguez et al. 2019).

És important destacar que la resposta al mindfulness pot ser variable i depèn de factors individuals com la predisposició personal, la pràctica continuada i la combinació amb altres estratègies terapèutiques. A més, els programes de mindfulness poden incloure tècniques psicològiques addicionals, fet que dificulta aïllar els efectes específics del mindfulness respecte a altres components del tractament. Per exemple, en els resultats de l'estudi del programa MAIR (Mindfulness Plus Amygdala and Insula Retraining) en persones amb FM, que incorpora pràctiques de MBSR juntament amb tècniques com la respiració i la programació neurolingüística, es va observar una millora en l'estat funcional i beneficis en variables cognitives i emocionals. Aquests efectes es van mantenir o fins i tot van millorar en un seguiment de tres mesos després de la intervenció. Tanmateix, no es van observar canvis significatius en marcadors inflamatoris com TNF-α, IL-6, IL-10 i hs-CRP, tot i que es van registrar reduccions en els nivells de BDNF (Sanabria-Mazo et al. 2020).

4.2.5. Intervencions multicomponent

Les intervencions multicomponent per a la FM han estat definides i promogudes per grups d'experts i organitzacions de salut (Häuser et al. 2009; Macfarlane et al. 2017). L'AAPT és el grup de treball internacional que ha establert criteris diagnòstics i un marc multidimensional per a la FM (Dizner-Golab et al. 2023). Les intervencions multicomponent en la FM combinen diverses modalitats de tractament per abordar els múltiples aspectes d'aquesta condició complexa, essent essencials per gestionar els símptomes i millorar la qualitat de vida de les persones amb FM (Thieme et al. 2017). Aquestes estratègies inclouen l'educació de les persones amb FM, proporcionant informació sobre la FM per reduir

l'ansietat i empoderar-les (Sharpe et al. 2020). Es promou també l'exercici físic regular, amb activitats aeròbiques, entrenament de força i flexibilitat, per millorar la força muscular i disminuir el dolor (De Miquel et al. 2010). La TCC ajuda a modificar pensaments negatius i comportaments que contribueixen al dolor i l'ansietat (Rivera et al. 2006). Les tècniques de relaxació, com la meditació, la respiració profunda i el ioga, són útils per reduir l'estrès (Macfarlane et al. 2017). Les intervencions farmacològiques, com els analgèsics, antidepressius i anticonvulsius, s'utilitzen per controlar el dolor i millorar el son (Häuser et al. 2009). El suport social, a través de la participació en grups de suport, facilita la compartició d'experiències i la reducció de l'aïllament (Thieme et al. 2017). Les teràpies complementàries, com l'acupuntura i la fisioteràpia, poden ajudar a gestionar els símptomes en alguns casos, però no hi ha evidència concloent que siguin essencials per a totes les persones amb FM (Sharpe et al. 2020). Encara que aquestes estratègies són l'estàndard òptim, factors com la gravetat dels símptomes, l'adherència al tractament i la presència de comorbiditats poden influir en l'efectivitat del tractament. És fonamental adoptar un enfocament personalitzat per maximitzar els beneficis en cada cas. La gestió del son implica estratègies per millorar la higiene del son i establir rutines regulars. A més, es promou una nutrició equilibrada i un estil de vida saludable per reduir l'estrès i evitar factors desencadenants (Dizner-Golab et al. 2023). Aquest enfocament integrat, amb la col·laboració entre professionals de la salut, permet dissenyar un pla de tractament personalitzat i efectiu per abordar la FM des de múltiples perspectives (Dizner-Golab et al. 2023).

L'efectivitat de les intervencions multicomponent que combinen exercici, suport psicològic i educació en el tractament de la FM està ben suportada

empíricament (Sharpe et al. 2020; Thieme et al. 2017). Aquestes aproximacions comprehensives sovint són considerades com l'estàndard òptim per a la gestió de la condició (De Miquel et al. 2010; Häuser et al. 2009; Macfarlane et al. 2017; Rivera et al. 2006; Thieme et al. 2017). Tanmateix, l'efectivitat d'aquestes intervencions és més gran quan es mantenen al llarg del temps. És essencial garantir un seguiment clínic adequat i un suport continuat per assegurar una millora sostinguda en les persones amb FM. La persona ha de rebre formació i seguiment el temps necessari, ja que, si disposa d'eines per gestionar els factors que incrementen i perpetuen el seu dolor i altres símptomes, se sent empoderada per assumir un paper actiu en el seu tractament i benestar.

4.2.6. Intervenció multicomponent FIBROWALK

FIBROWALK és una intervenció multicomponent de 3 mesos per a persones amb FM que combina ECD, exercici terapèutic, TCC i entrenament en mindfulness afegit al TH, la qual ha demostrat millores substancials en funcionalitat, dolor, kinesiofòbia, funció física, fatiga, ansietat i simptomatologia depressiva en persones amb FM (Serrat et al. 2020, 2021a, 2021b, 2022a). Ha demostrat una efectivitat clínica a curt termini comparada amb el TH en diversos entorns, incloent hospitals, entorns exteriors i plataformes online, tot i que els estudis realitzats fins ara han mostrat algunes debilitats metodològiques, com la mida de la mostra reduïda i la manca de seguiment a llarg termini. Aquestes limitacions podrien millorar-se en futures investigacions mitjançant l'ampliació de les mostres i la implementació de seguiments postintervenció més llargs. No obstant això, les modalitats de teleteràpia com FIBROWALK *online* (FIBRO-On) són particularment prometedores per superar barreres logístiques i de salut,

millorant potencialment l'adherència al tractament (Li et al. 2020; Schwamm et al. 2020; White et al. 2022) i van ser particularment útils en temps de pandèmia (Serrat et al. 2021a). De manera similar, les aproximacions terapèutiques basades en la natura, exemplificades per FIBROWALK *outdoor* (FIBRO-Out), han demostrat ser una aproximació efectiva per millorar la salut mental en diverses condicions clíniques, incloent el dolor crònic i la FM (López-Pousa et al. 2015; Serrat et al. 2020; Stanhope et al. 2020). En aquest sentit, en comparació amb l'exercici terapèutic realitzat en interiors, l'exercici en entorns naturals s'associa amb majors sentiments de revitalització i compromís positiu, reduccions en la tensió, la confusió, la ràbia i la simptomatologia depressiva, i un augment de l'energia (Thompson Coon et al. 2011). A més, hi ha evidència que fer exercici outdoor (enfront de fer-ho a l'interior) també pot promoure l'atenció dirigida i les interaccions socials, el que pot influir positivament en la intenció futura de mantenir una rutina d'exercici (Rogerson et al. 2016).

És important matisar que no totes les persones amb FM responen igual a la intervenció. S'ha observat que aquelles amb un perfil proinflamatori pronunciat tendeixen a experimentar més millores, especialment en la kinesiofòbia, mentre que altres marcadors inflamatoris podrien influir en la resposta clínica..

5. Efectes d'intervencions no farmacològiques en biomarcadors immunoinflamatoris i BDNF en fibromiàlgia.

Una revisió sistemàtica d'estudis longitudinals sobre la FM destaca els efectes positius dels programes multicomponent, l'exercici físic i la modificació de la dieta sobre els marcadors inflamatoris (com ara la IL-6 i el CXCL8), suggerint els efectes antiinflamatoris potencials d'aquestes intervencions no

farmacològiques (Sanada et al. 2015). No obstant això, la reducció de la inflamació amb aquestes intervencions pot dependre del perfil clínic de cada persona.

D'altra banda, en l'anàlisi de l'impacte de les intervencions psicosocials, especialment la psicoteràpia i la psicoeducació, en la funció immune d'adults amb diverses condicions de salut, una revisió sistemàtica i metaanàlisi exhaustiva (Shields et al. 2020) va evidenciar millores significatives en la funció immune, incloent-hi una reducció dels nivells de biomarcadors proinflamatoris. Segons aquesta revisió, les intervencions psicosocials, amb especial èmfasi en la teràpia TCC i els programes multicomponents, es van associar amb una disminució dels nivells de biomarcadors proinflamatoris, com la IL-6 i la hs-CRP. Aquestes troballes suggereixen que les intervencions psicosocials poden contribuir a la modulació de la inflamació sistèmica i a la millora de la salut immune en adults amb diverses patologies. No obstant això, la variabilitat en els resultats observats entre diferents estudis pot estar influenciada per diferències metodològiques, fet que subratlla la necessitat d'investigacions addicionals per consolidar aquests efectes. Respecte als efectes d'intervencions no farmacològiques en BDNF en persones amb FM, un assaig controlat aleatori pilot (Sanabria-Mazo et al. 2020) va mostrar que la combinació de consciència plena combinada amb un programa de “reentrenament de l'amígdala i l'ínsula” com a adjuvant al TH sembla ser efectiva en la reducció dels símptomes de la FM i dels nivells en sèrum de BDNF en comparació amb un grup de control actiu. Sanada et al. (2015) indiquen que, tot i que les intervencions no farmacològiques, com l'exercici i altres teràpies, han demostrat una reducció en determinats marcadors inflamatoris, els resultats referents al BDNF i altres neuropeptids en el context de la FM són inconsistents i

no permeten extreure conclusions definitives. Això suggereix que, malgrat el possible paper del BDNF en la FM i en les seves intervencions terapèutiques, no hi ha un consens sobre la relació exacta entre BDNF i FM. La insuficiència d'estudis consistents fa necessari aprofundir en la recerca per establir una relació clara entre les intervencions no farmacològiques i les variacions en els nivells de BDNF en aquesta població.

Els estudis actuals proporcionen la següent evidència sobre l'impacte dels components específics de la intervenció multicomponent FIBROWALK en biomarcadors immunoinflamatoris i BDNF:

ECD: L'ECD té un paper rellevant en l'empoderament de les persones amb FM en la seva comprensió del dolor, fet que pot contribuir a una reducció de l'estrès emocional i a una normalització de la resposta immunitària, amb un possible impacte en nivells de citocines proinflamatòries com la IL-6. A més, una millor gestió del dolor pot afavorir l'activació de vies neurològiques implicades en la producció de BDNF, aspecte que podria contribuir a una millora en l'estat emocional i funcional de les persones amb FM (Shields et al. 2020).

Exercici terapèutic: L'activitat física ha estat associada a una normalització de certs biomarcadors inflamatoris, com la IL-6 i la IL-10, la qual cosa suggereix la seva capacitat per modular la inflamació. No obstant això, la resposta inflamatòria pot variar en funció del perfil clínic de cada persona amb FM. A més, l'exercici regular podria afavorir un augment dels nivells de BDNF, la qual cosa estaria relacionada amb una millor salut neuronal i funció cognitiva, aspectes que sovint es veuen alterats en la FM (Sanada et al. 2015).

TCC: Tot i que no sempre es presenten dades concretes sobre biomarcadors, la TCC ha estat àmpliament associada a la reducció de l'ansietat i

el dolor, amb un possible efecte sobre la inflamació sistèmica i els nivells de BDNF mitjançant la millora de l'estat emocional i la reducció de l'estrès (Montero-Marin et al. 2019). Cal tenir en compte que les diferències metodològiques entre estudis poden influir en la variabilitat dels resultats.

Mindfulness: Les tècniques de mindfulness han estat associades a una reducció de l'estrès emocional, la qual cosa es podria traduir en una disminució de citocines inflamatòries com la IL-6 i la IL-10. Així mateix, aquesta pràctica s'ha relacionat amb increments en els nivells de BDNF, un factor important per a la salut neuronal i la plasticitat cognitiva (Andrés-Rodríguez et al. 2019). No obstant això, la manca d'homogeneïtat en les metodologies emprades en els estudis disponibles suggereix la necessitat de recerca addicional per confirmar aquests efectes.

En definitiva, les intervencions no farmacològiques constitueixen una via prometedora per a la millora de la salut de les persones amb FM, tant des d'una perspectiva immunoinflamatòria com neurobiològica. No obstant això, la variabilitat en els resultats i les limitacions metodològiques dels estudis actuals justifiquen la necessitat de recerca addicional per optimitzar l'efectivitat i la personalització d'aquestes estratègies terapèutiques.

CAPÍTOL 2.

Objectius i Hipòtesis

Objectius i Hipòtesis

Els objectius d'aquesta tesi doctoral són els següents:

- Descriure el protocol general del projecte On&Out dins del qual s'enmarca el subestudi de biomarcadors del que és objecte aquesta tesi doctoral **(Estudi 1).**
- Comparar l'efectivitat clínica a curt termini de la intervenció multicomponent FIBROWALK, en formats *online* i *outdoor*, amb el TH en persones amb FM FM **(Estudi 2).**
- Avaluar els efectes de les diferents intervencions FIBROWALK en els nivells sèrics de citocines pro i antiinflamatòries (IL-6, CXCL8, IL-17A, IL-4, IL-10), hs-CRP i BDNF **(Estudi 2).**
- Avaluar el valor predictiu d'aquests biomarcadors sobre la resposta clínica a la intervenció FIBROWALK, per identificar possibles indicadors de millora en la salut de les persones amb FM subratllant la relació entre les variables biològiques i els resultats clínics **(Estudi 2).**

A continuació s'exposen les hipòtesis:

- Es planteja que els participants que segueixin el programa FIBRO-On i FIBRO-Out experimentaran una canvi significatiu en la puntuació obtinguda en les variables clíniques estudiades (deteriorament funcional, dolor, fatiga, símptomes depressius i d'ansietat, funció física, kinesiòfobia) en comparació amb els que segueixin el TH **(Estudi 2).**
- S'espera que els grups FIBRO-On i FIBRO-Out tindran reduccions més grans en els nivells en sèrum de les citocines proinflamatòries (IL-6,

CXCL8, IL-17A), el marcador inflamatori hs-CRP i els nivells de BDNF i un augment/estabilització en les citocines antiinflamatòries (IL-4, IL-10) **(Estudi 2).**

- És probable que els nivells basals dels biomarcadors estudiats (IL-6, CXCL8, IL-17A, IL-4, IL-10, hs-CRP i BDNF) siguin un factor predictiu significatiu de la magnitud de la resposta clínica a la intervenció FIBROWALK, suggerint que certes característiques biològiques podrien influir en l'efectivitat del tractament en persones amb FM **(Estudi 2).**

CAPÍTOL 3.

Estudis

Estudi 1

Serrat, M., Ferrés, S., Auer, W., Almirall, M., Lluch, E., D'Amico, F., Maes, M., Lorente, S., Navarrete, J., Montero-Marín, J., Neblett, R., Nijs, J., Borràs, X., Luciano, J. V., & Feliu-Soler, A. (2022). Effectiveness, cost-utility and physiological underpinnings of the FIBROWALK multicomponent therapy in online and outdoor format in individuals with fibromyalgia: Study protocol of a randomized, controlled trial (On&Out study). *Frontiers in physiology*, *13*, 1046613. https://doi.org/10.3389/fphys.2022.1046613

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 10 November 2022
DOI 10.3389/fphys.2022.1046613

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Exercise Physiology,
a section of the journal
Frontiers in Physiology

RECEIVED 16 September 2022
ACCEPTED 20 October 2022
PUBLISHED 10 November 2022

CITATION
Serrat M, Ferrés S, Auer W, Almirall M, Lluch E, D'Amico F, Maes M, Lorente S, Navarrete J, Montero-Marín J, Neblett R, Nijs J, Borràs X, Luciano JV and Feliu-Soler A (2022), Effectiveness, cost-utility and physiological underpinnings of the FIBROWALK multicomponent therapy in online and outdoor format in individuals with fibromyalgia: Study protocol of a randomized, controlled trial (On&Out study).
Front. Physiol. 13:1046613.
doi: 10.3389/fphys.2022.1046613

Effectiveness, cost-utility and physiological underpinnings of the FIBROWALK multicomponent therapy in online and outdoor format in individuals with fibromyalgia: Study protocol of a randomized, controlled trial (On&Out study)

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Introduction: The On&Out study is aimed at assessing the effectiveness, cost-utility and physiological underpinnings of the FIBROWALK multicomponent intervention conducted in two different settings: online (FIBRO-On) or outdoors (FIBRO-Out). Both interventions have proved to be efficacious in the short-term but there is no study assessing their comparative effectiveness nor their long-term effects. For the first time, this study will also evaluate the cost-utility (6-month time-horizon) and the effects on immune-inflammatory biomarkers and Brain-Derived Neurotrophic Factor (BDNF) levels of both

interventions. The objectives of this 6-month, randomized, controlled trial (RCT) are 1) to examine the effectiveness and cost-utility of adding FIBRO-On or FIBRO-Out to Treatment-As-Usual (TAU) for individuals with fibromyalgia (FM); 2) to identify pre–post differences in blood biomarker levels in the three study arms and 3) to analyze the role of process variables as mediators of 6-month follow-up clinical outcomes.

Methods and analysis: Participants will be 225 individuals with FM recruited at Vall d'Hebron University Hospital (Barcelona, Spain), randomly allocated to one of the three study arms: TAU vs. TAU + FIBRO-On vs. TAU + FIBRO-Out. A comprehensive assessment to collect functional impairment, pain, fatigue, depressive and anxiety symptoms, perceived stress, central sensitization, physical function, sleep quality, perceived cognitive dysfunction, kinesiophobia, pain catastrophizing, psychological inflexibility in pain and pain knowledge will be conducted pre-intervention, at 6 weeks, post-intervention (12 weeks), and at 6-month follow-up. Changes in immune-inflammatory biomarkers [i.e., IL-6, CXCL8, IL-17A, IL-4, IL-10, and high-sensitivity C-reactive protein (hs-CRP)] and Brain-Derived Neurotrophic Factor will be evaluated in 40 participants in each treatment arm (total n = 120) at pre- and post-treatment. Quality of life and direct and indirect costs will be evaluated at baseline and at 6-month follow-up. Linear mixed-effects regression models using restricted maximum likelihood, mediational models and a full economic evaluation applying bootstrapping techniques, acceptability curves and sensitivity analyses will be computed.

Ethics and dissemination: This study has been approved by the Ethics Committee of the Vall d'Hebron Institute of Research. The results will be actively disseminated through peer-reviewed journals, conference presentations, social media and various community engagement activities. Trial registration number NCT05377567 (clinicaltrials.gov).

KEYWORDS

fibromyalgia, online, outdoor, pain neuroscience education, effectiveness, cost-utility, cytokines, BDNF

1 Introduction

Fibromyalgia (FM) is a highly prevalent syndrome (2.7% worldwide, 2.5% in Europe and 2.4% in Spain) (Queiroz, 2013) which mainly affects women, around 40–50 years of age (Häuser et al., 2015). FM is characterized by the presence of chronic widespread musculoskeletal pain, fatigue and sleep problems (Häuser et al., 2015) and, very often, it is also accompanied by anxiety (13%–63.8%) and depressive disorders (20%–80%) (Fietta et al., 2007). Remarkably, FM is the chronic pain condition with the highest rate of unemployment, sick leave, disability claims and absenteeism (Leadley et al., 2012) and 23%–66% of individuals with this syndrome are forced to leave work due to its aftermaths (Assefi et al., 2003; Gerdle et al., 2008). Furthermore, individuals with FM are usually considered "hyper-frequent users" of health services with 6% of adult patients attending primary care and 10%–20% attending rheumatology services having a diagnosis of FM (Gerdle et al., 2008; Häuser et al., 2015). Regarding this latter point, FM is the medical condition presenting higher costs, with direct costs (i.e., medication, visits to healthcare professionals, medical tests, emergency room visits and hospital admissions) being up to three times higher than the observed in other chronic pain conditions and similar sociodemographic characteristics (Berger et al., 2007; Leadley et al., 2012; Wylezinski et al., 2019).

1.1 Recommended treatments for FM and the emergence of online and outdoors therapeutic approaches

Up to date, the available treatments for FM are not curative and their clinical efficacy is generally rather low (Häuser et al., 2015). In relation to pharmacological treatments, the European League Against Rheumatism (EULAR) recommends reserving pharmacological treatment only for those cases with severe pain and for sleep disturbances (Häuser et al., 2015; Macfarlane et al., 2017). In line with this, non-pharmacological strategies appear to

promote broader clinical effects and show slightly larger effect sizes compared to pharmacological treatments (Nüesch et al., 2013, Perrot et al., 2014). Non-pharmacological strategies include interventions such as pain education, cognitive behavioral therapy (CBT), mindfulness, therapeutic physical exercise, among others, which aim primarily at alleviating symptoms and improving patients' quality of life (Macfarlane et al., 2017). More specifically, Pain Neuroscience Education (PNE) (Van Oosterwijck et al., 2013; Nijs et al., 2014; Amer-Cuenca et al., 2020) is aimed at changing patients' pain beliefs, emphasizing how overprotective behaviors can accentuate pain experience (Moseley and Butler, 2015). PNE has been found to be effective for reducing pain disability, catastrophizing, avoidance behaviors and physical inactivity in patients with FM (Malfliet et al., 2017). Concurrently, there is high agreement among clinical guidelines that CBT and therapeutic physical exercise should constitute the main therapeutic elements when treating FM (Jones et al., 2006; Bernardy et al., 2010; Sosa-Reina et al., 2017; Bernardy et al., 2018); furthermore, combining both interventions has been shown to be particularly effective (Witek-Janusek et al., 2008; Black et al., 2013). There is also mounting evidence that mindfulness training can be an efficacious and cost-effective approach for improving quality of life, functional impairment, anxiety, depression, and other symptoms in patients with FM (Haugmark et al., 2019; Pérez-Aranda et al., 2019).

Mounting empirical evidence suggests that multicomponent approaches integrating at least therapeutic physical exercise and a psychological/educational intervention can be effective in individuals with FM (e.g., Van Wilgen et al., 2007; Castel et al., 2013; Thieme et al., 2017) and some authors propose that these multicomponent interventions should be the "gold standard" in FM (Rivera et al., 2006; Häuser et al., 2008; De Miquel et al., 2010; Macfarlane et al., 2017; Thieme et al., 2017). In this regard, a metanalysis exploring the efficacy of different pharmacological and non-pharmacological therapies on fibromyalgia symptoms (Papadopoulou et al., 2016) suggested that multidisciplinary treatments would be the most beneficial ones among non-pharmacological interventions for treating FM, since statistically significant improvements were found in all FM symptoms comprising OMERACT-10 response criteria (i.e., pain, sleep, function, fatigue, anxiety, depression, cognition). Furthermore, four recent RCTs published after the aforementioned metanalysis, provided additional evidence on the short-term efficacy (i.e., post-intervention) of a 3-month multicomponent intervention for FM (i.e., the FIBROWALK program) comprising CBT, mindfulness training, therapeutic physical exercise and PNE (Serrat et al., 2020; Serrat et al., 2021a; Serrat et al., 2021b; Serrat et al., 2022b). Interestingly, the FIBROWALK program showed to be clinically efficacious when tested in hospital, outdoors and also in online settings compared to Treatment-As-Usual (TAU) alone and provided clinically relevant improvements in functionality, pain, kinesiophobia, physical function, fatigue, and anxiety and depressive symptomatology (Serrat et al., 2020; Serrat et al., 2021a; Serrat et al., 2021b; Serrat et al., 2022b).

The COVID-19 pandemic has enforced the emergence of new therapeutic approaches alternative to face-to-face treatment since mobility restrictions and infection risk have generally limited this classical format of therapy. In this regard, there is a growing body of evidence on the efficacy of alternative forms of therapy such as online (Schwamm et al., 2020; Weiling et al., 2020; Serrat et al., 2021a; White et al., 2022) and outdoor (Buckley et al., 2018; Stanhope et al., 2020) formats in chronic pain populations including FM.

Beyond pandemics, teletherapy approaches such as online FIBROWALK (Serrat et al., 2021a) are highly promising when compared to traditional face-to-face when dealing with specific logistic barriers such as time, travel or access difficulties in rural areas, or health barriers such as patients' fatigue, among other symptoms which may interfere with treatment adherence. Online programs which are highly scalable and accessible per definition may also help in decongest healthcare services (which are particularly overstretched worldwide since the COVID-19 pandemic), significantly reduce healthcare staff costs, and help increase widespread access to evidence-based treatment for FM (Assefi et al., 2003; Friedman et al., 2012; Moman et al., 2019). In this regard, in a recent systematic review on the efficacy of online psychological interventions for people with chronic health conditions, online treatments were found to be efficacious for improving depressive symptomatology and distress in people with FM, supporting the usefulness of these low cost, easily accessible, and highly scalable therapeutic approaches for treating this syndrome (White et al., 2020). Furthermore, an important aspect when implementing treatments, especially for chronic conditions, is to promote self-management and online interventions may facilitate this aspect (Leadley et al., 2012). Simultaneously, nature-based therapeutic approaches such as the outdoor FIBROWALK (Serrat et al., 2020) have shown to be useful in improving mental health in different clinical conditions (Trøstrup et al., 2019), including chronic pain and FM (López-Pousa et al., 2015; Serrat et al., 2020; Stanhope et al., 2020). In this sense, it is interesting that therapeutic programs conducted outdoors have been shown to be effective in improving mental health, pain and general health, and it is suggested that exposure to the natural environment (both in urban green areas and in nature) may produce additive positive effects at both affective (positive and negative emotions and stress) and cognitive (attention, memory, motivation, *etc.*) levels thus enhancing the beneficial effects of the program (Buckley et al., 2018). In this regard, when compared to therapeutic exercise conducted indoors, exercising in natural settings was 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). Furthermore, there is evidence that exercising

outdoors (vs. indoors) may also promote directed attention and social interactions, which may positively influence future intention of maintaining an exercise routine (Rogerson et al., 2016). Regarding the possible effects of the intervention format of the FIBROWALK intervention was found to be beneficial in hospital, outdoors and virtual settings at short term with apparently larger effect sizes in the outdoor format when compared to indoor hospital or online settings (Serrat et al., 2020; Serrat et al., 2021a; Serrat et al., 2021b; Serrat et al., 2022b). However, no clinical trial with a parallel design has yet been conducted to evaluate potential differences in the short- and the long-term efficacy between these different formats or in therapeutic adherence. The present study aims to address this important knowledge gap.

Although recommended, there is a striking lack of empirical evidence regarding the cost-effectiveness of multicomponent interventions for FM, including FIBROWALK. Bearing in mind that costs are of crucial relevance for policy-makers, who usually consider as first-choice treatment those therapeutic approaches with the lowest associated cost per quality-adjusted life-year (QALY), economic evaluations of multicomponent interventions in FM should be performed to ensure (if cost-effective) their implementation in healthcare systems.

1.2 Immune-inflammatory status and BDNF levels in individuals with FM

There are several potential physiological factors which have been proposed underpinning the FM symptomatology. In this regard, the central nervous system (CNS) seems to have a leading role (Häuser et al., 2015), involving altered function in pain neural pathways (Sluka and Clauw, 2016; Sawaddiruk et al., 2017). At the same time, there is evidence suggesting an imbalance between pro- and anti-inflammatory cytokine levels at both the peripheral and central levels in individuals with FM contributing to a chronic state of low-grade inflammation (Rodriguez-Pintó et al., 2014; Bäckryd et al., 2017; Albrecht et al., 2019; Andrés-Rodríguez et al., 2019). This proinflammatory state may be a key contributor to impaired pain processing as could lead to the sensitization of peripheral nerves and to central sensitization (Rodriguez-Pintó et al., 2014; Littlejohn, 2015), possibly through activation of glial cells (Nijs et al., 2017).

A recent meta-analysis concluded that patients with FM may present increased levels of blood IL-6, IL-4 and IL-17A compared to healthy controls (Andrés-Rodríguez et al., 2020). Coherently, increased levels in other markers indicative of an inflammatory state [e.g., high-sensitivity C-reactive protein (hs-CRP)] were also reported (Andrés-Rodríguez et al., 2020). Some of these proinflammatory cytokines (e.g., IL-6) are known to facilitate sensitization of peripheral nerves to nociceptive stimuli and to increase the activity of the hypothalamic-pituitary-adrenal axis, as well as prostaglandin and substance P synthesis, thereby reducing the pain threshold (Zhou et al., 2016). On the other hand, at a central level, pro-inflammatory cytokines along with other inflammatory-related by-products are known to alter the synthesis, reuptake and release of different neurotransmitters in the CNS (e.g., serotonin, noradrenaline, dopamine, glutamate. These neurotransmitters are involved in both pain perception and the regulation of diverse affective, cognitive and motivational processes, contributing to the neuroplastic changes observed in FM, abnormal pain experience and to other FM symptoms, such as fatigue, sleep disturbances, cognitive impairment, and affective problems (Miller et al., 2013; Rodriguez-Pintó et al., 2014; Andrés-Rodríguez et al., 2020).

Several studies have suggested that FM and other central sensitivity syndromes present not only with chronic low-grade inflammation but also with abnormalities in biomarkers related to neuronal plasticity, such as BDNF (Deitos et al., 2015). The BDNF is a multifunctional neurotrophin with numerous functions in the brain (Jensen et al., 2012; Cagnie et al., 2014), including a driving force behind (maladaptive) neuroplasticity and central sensitization (Nijs et al., 2015), and it is believed to be specifically associated with the occurrence and/or progression of mnemonic symptoms associated with a variety of conditions characterized by cognitive impairment (Napadow et al., 2012). BDNF is known to play a key role in a variety of neuroplasticity processes, including pain modulation, pain transduction, nociception, and hyperalgesia (Nugraha et al., 2012), all of which are known to be altered in FM. In this regard, plasma levels of BDNF have also been found to be augmented in individuals with FM (Haas et al., 2010; Polli et al., 2020) and DNA methylation in exon nine appears to be driving the higher BDNF protein levels in patients with FM (Polli et al., 2020); however, we have to bear in mind that associations between BDNF levels and patients' clinical complaints have not been found always consistent (Zanette et al., 2014; Jha and Trivedi, 2018) and that some studies have found no differences between FM patients and healthy controls on BDNF levels (Ranzolin et al., 2016). Furthermore, there are reciprocal associations between BDNF and immune-inflammatory pathways, which may explain the involvement of BDNF in the immune pathophysiology of mood disorders (Perrot and Russell, 2014), with BDNF acting as a conserved regulatory process that protects against the detrimental effects of immune activation including neurotoxicity (Mehterov et al., 2022).

Some of these biomarkers may also influence treatment response in individuals with chronic pain conditions including FM. Related to this, higher pretreatment levels of IL-6 and TNF-α have been found to be associated with lesser improvements in pain intensity and other patient-reported outcomes after cognitive behavioral interventions administered in individuals with chronic pain (Lasselin et al., 2016). Furthermore, higher baseline levels of CXCL8 were also found to attenuate clinical

benefits (i.e., in pain, fatigue, stiffness and quality of sleep) after an 8-week standardized mindfulness program in patients with FM (Andrés-Rodríguez et al., 2019).

1.3 Effects of non-pharmacological interventions on immune-inflammatory markers and BDNF in individuals with FM

In a systematic review of longitudinal studies in FM, multicomponent programs, physical exercise and dietary modification were found to have effects on inflammatory markers in FM patients (Sanada et al., 2015). In this regard, reductions in levels of the pro-inflammatory cytokines IL-6 and CXCL8 were observed in FM patients following these interventions, suggesting a potential anti-inflammatory effect. Similarly, in a recent study (Andrés-Rodríguez et al., 2019) evaluating the effects of mindfulness training on immune-inflammatory markers, it was also reported that levels of the anti-inflammatory cytokine IL-10 remained higher in patients assigned to mindfulness than those allocated to the TAU arm. In another study assessing the effects of an 8-week compassion-based intervention (i.e., Attachment-Based Compassion Therapy, ABCT) for FM, a global anti-inflammatory effect along with reductions in BDNF levels in individuals with FM when compared to an active control condition (i.e., relaxation training) were also reported (Montero-Marin et al., 2019). These changes in BDNF levels were significantly related and followed by ameliorations in FM functional impairment, showing significant indirect effects, which means that reductions in BDNF might function as a crucial treatment mediator. In this study, baseline BDNF levels were similar to those obtained in a previous study with patients suffering from central sensitivity syndromes with persistent somatic or visceral nociception in which, after treatment, these levels normalized, approaching to those observed in pain-free individuals (Deitos et al., 2015). Regarding the effects of psychosocial interventions (mainly psychotherapy and psychoeducation) on immune function in adults with different health conditions, in an extensive systematic review and meta-analysis (Shields et al., 2020), many different improvements in immune function (including levels of pro-inflammatory biomarkers) were robustly reported. Interestingly, these effects were more remarkable after the application of CBT and multicomponent programs. Importantly, there are no available studies assessing the effects of multicomponent interventions such as FIBROWALK in physiological markers in fibromyalgia aimed at understanding physiological mechanisms underpinning its efficacy.

The objectives of the On&Out study are 1) to examine the effectiveness and cost-utility of adding the FIBROWALK intervention in online or in outdoors format to TAU in the management of patients with FM for improving functional impairment (primary outcome) and pain, fatigue, depressive and anxiety symptoms, perceived stress, central sensitization, physical function, sleep quality and perceived cognitive dysfunction (secondary outcomes); 2) to identify pre–post differences in levels of different physiological variables (i.e., immune-inflammatory markers and BDNF levels) and correlate these changes with those observed at self-report measures and 3) evaluate the role of psychological process variables considered to be potential mediators of the interventions from a theoretical point of view (i.e., kinesiophobia, pain catastrophizing, psychological inflexibility in pain and pain knowledge) and the evaluated physiological variables as mediators of long-term clinical improvements. For the sake of personalized treatment in FM, the design of the present study will allow us to explore whether certain patient profiles or baseline psychobiological characteristics may help predict the short- and long-term clinical response to the specific evaluated treatments.

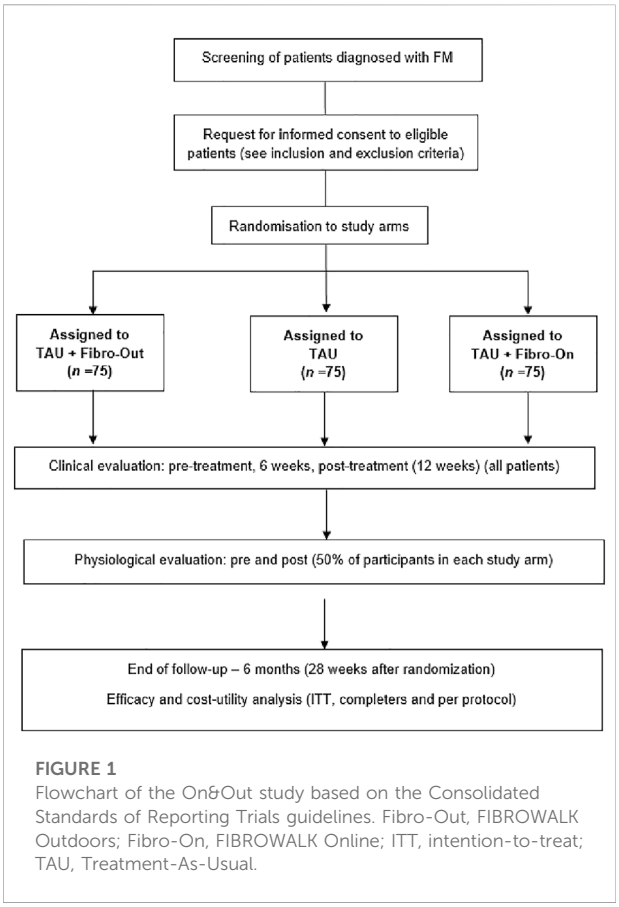

FIGURE 1
Flowchart of the On&Out study based on the Consolidated Standards of Reporting Trials guidelines. Fibro-Out, FIBROWALK Outdoors; Fibro-On, FIBROWALK Online; ITT, intention-to-treat; TAU, Treatment-As-Usual.

2 Materials and methods

2.1 Trial design

This RCT protocol was developed following the Standard Protocol Items: Recommendations for Interventional Trials

(SPIRIT) (Chan et al., 2013) and was recorded in the ClinicalTrials.gov trial register in May 2022 (NCT05377567). We designed a 6-month, parallel group, randomized (using a computer-generated randomization list), single-blind, controlled trial (RCT) with three treatment arms. The effectiveness of the FIBROWALK program (i.e., multicomponent program based on therapeutic exercise, PNE, CBT, and mindfulness training) in FIBRO-On (online) and in FIBRO-Out (outdoors) formats adjuvant to TAU, compared to TAU alone in patients with FM recruited from the Central Sensitivity Syndromes Specialized Unit from the HUVH, will be evaluated. The Consolidated Standards of Reporting Trials 2010 (CONSORT) (Schulz et al., 2010) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (Husereau et al., 2013) will be followed. The expected flowchart of participants in the study is displayed in Figure 1.

2.2 Recruitment strategy

Potential participants are individuals with FM diagnosis (ACR 2010/2011 criteria) made by a rheumatologist and seeking health services currently or in the last year at the Central Sensitivity Syndromes Specialized Unit at HUVH.

2.3 Sample size calculation

Two-hundred and twenty-five individuals who meet the selection criteria for the study will be recruited. The estimated sample size needed is n = 63 participants per condition considering a moderate effect size (Cohen's d = 0.5) for the difference between the active arms at post-intervention compared to the control group for the primary variable (i.e., FIQR score) with an alpha = 0.05 and 1-b power = 0.80. With an expected dropout rate of 20%–25%, the final sample size is estimated at 75 individuals per arm. The effect size used for the sample size calculation corresponds to the average effect size for multicomponent interventions in FM vs. control group (Nüesch et al., 2013). Previous RCTs evaluating the FIBROWALK intervention indicated effect sizes between d = 0.4 (Serrat et al., 2021a) and d = 1.83 (Serrat et al., 2020). Using as a reference previous studies of the group evaluating the effect of different non-pharmacological treatments in FM patients on blood values of immuno-inflammatory markers (Andrés-Rodríguez et al., 2019; Montero-Marin et al., 2020), it is estimated that a sample size of 40 subjects per arm will be sufficient to be able to detect changes in the evaluated variables.

2.4 Eligibility criteria

All participants will meet the following general inclusion criteria: 1. Individuals between 18 and 65 years of age. 2. Diagnosis of FM according to the ACR 2010/2011 criteria. 3. Understanding written and spoken Spanish. The general exclusion criteria will be: 1. Psychological treatment received within the last year or current. 2. Comorbid presence of severe mental disorder (e.g., schizophrenia) or other terminal clinical conditions or scheduled treatments that may interrupt study follow-up. 3. Inability to complete the weekly sessions/modules of the program on a regular basis.

For the biomarkers substudy, usual contraindications for measuring blood immune-inflammatory markers will be taken into account to establish the following additional inclusion/exclusion criteria for the biomarkers substudy: only participants of female sex, with no autoimmune-type disease, no recent physical trauma, not being vaccinated during the last week, no symptoms suggestive of cold/infection on the day of blood collection, no needle phobia, not pregnant or breastfeeding, not using oral or local corticosteroids or any anti-cytokine biologic drugs or oral contraceptives will be included in the biomarkers substudy.

2.5 Procedure and randomization

The recruitment of participants will be carried out in two ways: 1) consecutive recruitment from consultation by the rheumatologists of the HUVH Central Sensitivity Syndromes Specialized Unit and 2) by screening a list of patients (with contact telephone number) corresponding to patients who contacted the Unit during the last 6 months. The clinicians involved in the project (i.e., MA and MS) will proceed to carry out the telephone screening and those who meet the selection criteria of the study will be invited to participate. After obtaining written informed consent, the instrument battery -including clinical and economic measures-described below will be administered (online assessment). Two research assistants will coordinate the study assessments to ensure an adequate understanding of all administered self-reported measures. Random assignment of participants to study arms will be executed after baseline assessments as recommended by the CONSORT guidelines (Schulz et al., 2010). Once written consent and baseline assessment have been completed, study participants will be given a unique personal code and randomized using randomization software (1:1:1 ratio). The computer-generated randomization will apply a permuted block design to ensure that the groups are balanced taking biomarkers substudy eligibility criteria (No=Not meeting criteria for biomarkers substudy; Yes = Meeting criteria) into account. The randomization list will be stored in an encrypted file on a password-protected computer in the clinical trials supervisor's office to assure concealment of allocation. Participants will be informed of their group allocation by the administrative personnel, who will send a notification *via* email.

Patients who meet the selection criteria for the biomarkers substudy will be rescheduled 3–5 days after the first assessment to obtain blood samples (up to the required N of 40 subjects per arm). Fasting blood extractions will be performed in a pre-set time window (8a.m.–10a.m.) to reduce circadian variability in the levels of the biomarkers evaluated. In order to limit the effects of medication on the study variables, patients will be asked to refrain from taking any occasional anti-inflammatory drugs in the 72 h prior to blood sampling.

The research assistants, who will be blinded to randomization, will coordinate the three subsequent clinical assessments: at 6 weeks, at post-intervention and at 6 months after the baseline assessment (follow-up). The same procedure as in baseline will be followed for the collection of biological samples at post-intervention, respecting the pre-set time interval.

The study will be organized in two consecutive periods with six study groups (i.e., 2 TAU, 2 FIBRO-Out, 2 FIBRO-On) conducted in parallel in each period. All the groups will include 18–20 participants (i.e., FIBRO-On, FIBRO-Out, TAU), so the N = 75 is expected to be reached at the end of the study.

2.6 Interventions

2.6.1 TAU

Although there is no *gold standard* treatment for FM, in the Spanish healthcare context, the TAU for FM is mainly pharmacological and is adjusted to the symptomatologic profile of each patient. It is usually also accompanied by guidelines for aerobic physical exercise adapted to the individual's limitations. Participants assigned to this treatment arm will be offered to participate in the FIBRO-On or FIBRO-Out program (whichever is their choice) at the end of the study.

2.6.2 FIBRO-On

This program is also based in the FIBROWALK program (Serrat et al., 2020) and is virtually identical to the FIBRO-Out program described below. The FIBRO-On program will also be administered as an adjuvant intervention to TAU. All contents of the FIBROWALK (explanations and guidelines for the practice of the components of PNE, physical exercise, CBT and mindfulness) will be explained by means of videos together with slide presentations. The contents in the videos will be taught by the first author (MS) who is both a physiotherapist with more than 17 years of experience and a health psychologist with more than 8 years of experience. Furthermore, MS was the creator of the FIBROWALK program. Although the virtual sessions are 60 min long, a general recommendation is to expend 120 min to perform all the exercises indicated in each specific video. Every week, links to the videos of the corresponding module will be sent by email so that patients can access them whenever possible during the week. To limit problems of access to the videos by patients with little technological experience, a highly-accessible and user-friendly platform will be used (e.g. Youtube). To verify that participants adhered to FIBRO-On program, participants will be asked to complete a brief weekly questionnaire (5–10 items) asking for very basic concepts explained in the videos (e.g., "Please, provide a short example of a catastrophic thought"). Participants who do not answer the weekly questionnaire or those informing of any issue interfering with the adherence to treatment protocol (e.g., not being able to do the homework, watching the videos, answering the questionnaire, *etc.*) will be contacted (*via* SMS and/or telephone calls) by the therapist in charge (MS) and some guidance will be facilitated. If necessary, individuals who were unable to view or answer the questionnaire in a specific week could request an extension of the date. There was no therapeutic interaction with the participants, but participants were invited to contact the therapist by email if they experienced any problems. The FIBRO-On program was created during the COVID-19 lockdown and since then, it has been successfully applied at the Central Sensitivity Syndromes Specialized Unit from the HUVH (Serrat et al., 2021a; Serrat et al., 2022b). See Tables 1, 2 for more details.

2.6.3 FIBRO-Out

The FIBRO-Out program includes the implementation of the 12-session FIBROWALK multicomponent program (Serrat et al., 2020) in an outdoor environment as an add-on to TAU. It will be conducted weekly and in group format (18–20 participants/group) and it will be carried out in a green area in an urban environment (i.e., "Parc del Cargol") located in the neighborhood of the HUVH (Barcelona). FIBROWALK includes components of PNE, CBT, mindfulness training and therapeutic exercise. PNE aims to reconceptualize pain and is included in all sessions of the program. This is an educational program that teaches pain patients the difference between harm and pain, how the pain program is activated when actual or potential harm is appraised by the brain that seeks to generate an active protective response and how this assessment can be erroneous depending on different contextual factors. It is based on the "Explaining Pain" program by Butler and Moseley (2010). Examples, images and metaphors are used to facilitate the understanding of the educational content of the program (Nijs et al., 2011). Multi-component physical exercises such as stretching, balance training, posture correction, limb extension and low-impact walking (i.e., Nordic walking) are performed with a moderate training load. Exercises are individualized, establishing a baseline of minimum performance and guiding progression throughout the 12-week program. Following the recommendations of the *American College of Sports Medicine* (Pescatello et al., 2014), each therapeutic physical exercise session is structured in three parts: warm-up, main exercise and cool-down. At the beginning of each session, an interval of approximately 15 min is set aside to discuss the most important aspects of the task between sessions, as well as

TABLE 1 Outline of the FIBROWALK program (with FIBRO-Out and FIBRO-On specifications).

Educational and psychological contents in the FIBROWALK program
• Pain Neuroscience Education (PNE) • Cognitive Behavioral Therapy (CBT) • Mindfulness training (MT)
Physical therapeutic exercises in the FIBROWALK program
• Warm-up: activation and mobility exercises • Therapeutic exercises: moderate aerobic-cardiovascular and muscle strengthening exercises combined with some balance and coordination exercises performed in a playful manner with cognitive and emotional targets (multitask works) where the level of difficulty and dedication time gradually increases • Cooling-down: flexibility and relaxation exercises
Homework
• Moderate intensity walking is recommended from the first session in a progressive pattern: 1st month - once per week, 2 nd month - twice per week, 3rd month - three times per week • Exercises based on PNE, CBT and MT contents are also proposed every week (e.g., identifying danger signals, modifying sleep habits, challenging negative automatic thoughts, doing a 10-min body scan meditation) • Double tasks: combining TE with CBT by fostering different cognitive/affective regulation skills throughout exercise (e.g., identifying external and internal stimuli which may promote positive affect during the exercise, discovering automatic thoughts during the exercise and uncovering patterns between thoughts with negative emotions, pain experience and fatigue; diminishing catastrophic thinking; recognizing the achievements, improving self-efficacy)
Contents in each session#
Session 1: PNE (1.2) + CBT (1) + MT (1) Session 2: PNE (3.4) + CBT (2) + MT (2) Session 3: PNE (5.6) + CBT (3) + MT (3) Session 4: PNE (7.8) + CBT (4) + MT (4) Session 5: PNE (9.10) + CBT (5) + MT (5) Session 6: PNE (11) + CBT (6) + MT (6) Session 7: PNE (12) + CBT (7.8) + MT (7.8) Session 8: PNE (13) + CBT (9) + MT (9) Session 9: PNE (14) + CBT (10) + MT (10) Session 10: Family Session (PNE 1–16) Session 11: PNE (15) + CBT (11) + MT (11) Session 12: PNE (16) + CBT (12) + MT (12)
Overall structure of the sessions for the FIBRO-Out and FIBRO-On versions of the FIBROWALK program
FIBRO-Out program (face-to-face sessions)
• Review Phase (15′): Brief review of contents of the previous session • Educational and psychological contents and Physical therapeutic exercises (1h 40′) • Homework explanation (5′)
FIBRO-On program (online videos)
• Review Phase (2′): Brief review of contents of the previous session • Educational and psychological contents and Physical therapeutic exercises (55′) • Homework explanation (3′) Handouts and specific practices are facilitated in each video session and, although the FIBRO-On videos' duration is of 60 min each, the recommendation is to expend 120 min to do all the exercises proposed

Note: Both versions of the FIBROWALK (i.e., FIBRO-Out and FIBRO-On) are equivalent regarding contents and distribution of them across sessions. #The numbers between brackets correspond to specific contents of the program explained on Table 2. PNE , pain neuroscience education; CBT , cognitive behavioral therapy; TE , therapeutic exercise; MT , mindfulness training.

TABLE 2 Contents of the FIBROWALK program (i.e., Pain Neuroscience Education, Therapeutic Exercise, Cognitive Behavioral Therapy, and Mindfulness Training).

Pain neuroscience education (PNE)
1. Disassembling beliefs
2. Danger signals: modulation and modification
3. Concept of pain, fatigue, and pain system
4. Concept of central nervous system and central sensitization. The role of the brain
5. Acute vs. chronic pain: The purpose of acute pain and how it originates in the nervous central system
6. Pain vs. damage
7. Pain neuromatrix theory and representation of the virtual body
8. Nociception, nociceptors, action potential, peripheral sensitization, and synapses
9. Ascending and descending inhibitory pathways, spinal cord
10. Relationship with attention, perception, pain cognitions, and pain behaviors
11. Allodynia and hyperalgesia, hypersensitivity of the nervous central system
12. Pain memory, pain perception, and autoimmune evaluation error
13. Relationship with stress. Etiology
14. Neuroplasticity and how the pain becomes chronic
15. Relationship with emotions
16. Re-education, gradual activity, and therapeutic exercise
Therapeutic Exercise (TE)
1. Essential and necessary movement
2. Set a basal minimum of activity
3. Individualized gradual program
4. Small increases, patterns
5. Activities contingent on the task, not over time
6. Involvement in the tasks of daily life
7. Lifestyle change: cognitive coping strategies
8. Double tasks: focused on the following cognitive/affective targets: positive affect, negative affect, self-efficacy, catastrophic thinking, pain and fatigue
Cognitive Behavioral Therapy (CBT)
1. Relaxation and breathing
2. Modulating factors of pain
3. Catastrophizing and fear of movement (fear avoidance model)
4. Painful experiences: confrontation (fear avoidance model)
5. Vital values and setting goals
6. Organization of time
7. Sleep patterns
8. Sexual issues
9. Handling of attention
10. Cognitive restructuring
11. Emotional regulation tasks focused on identifying and promoting a more adaptive use of the following cognitive/affective regulation skills: self-blame, acceptance, rumination, focus on the positive, focus on plans, positive reassessment, put in perspective, catastrophizing, blaming others
12. Troubleshooting
Mindfulness Training (MT)
1. An Introduction to Body Scanning
2. Elementary Awareness

(Continued on following page)

TABLE 2 (*Continued*) Contents of the FIBROWALK program (i.e., Pain Neuroscience Education, Therapeutic Exercise, Cognitive Behavioral Therapy, and Mindfulness Training).

3. Sitting Practice and introduction to Yoga
4. Mindfulness and the brain
5. Mindfulness and communication: guilt, empathy, and conflict management
6. Responding vs. reacting
7. Dig deeper into personal practice
8. Mindfulness and Compassion: Strength vs. Cooperation
9. Stress Management
10. Thoughts Management
11. Management of difficult emotions or feelings
12. Dig deeper into personal practice

Note: More details on the interventions and program-associated materials and clinical guidelines (Serrat et al., 2022b) can be accessed through a reasonable request to the corresponding author.

to review the concepts already explained in the previous treatment sessions. The psychological approach in the FIBROWALK program is based on CBT and aims to promote cognitive changes (e.g., reduce catastrophizing about pain), improve emotional regulation, increase sleep quality, enhance problem-solving strategies and facilitate the establishment of life values and goals (Moix and Kovacs, 2009). Mindfulness exercises are also performed with the aim of training attention to present experience and fostering a non-evaluative attitude towards that experience (Kabat-Zinn, 2013). Mindfulness exercises are based on the Mindfulness-Based Stress Reduction (MBSR) program (Kabat-Zinn, 2013), for which evidence of efficacy and cost-effectiveness in FM patients has been demonstrated (Pérez-Aranda et al., 2019). CBT and mindfulness training help patients to become aware of their own thoughts, emotions and behaviors so that, once identified, they can be regulated or managed facilitating the same situation (e.g., pain) to be experienced in a more flexible and fulfilling way, with less associated suffering. Consistent with PNE, directing attention to the present (rather than to future concerns or past losses or threats) may provide the appropriate safety setting to reduce the perception of alarm or danger associated with pain and allow for successful re-education of the pain program (Moseley G. L., 2003; Moseley L., 2003; Moseley et al., 2015). The framework of motivational interviewing (Nijs et al., 2020) and the cognitive-behavioral model of fear avoidance (Vlaeyen et al., 1995) are part of the theoretical background of CBT in the FIBROWALK program. The intervention is carried out by encouraging social interactions, supported by *role-playing* techniques to promote understanding of content and enhance adherence to treatment. In order to promote an adequate motivational state for the performance of all the exercises and practices in the FIBROWALK program, individualized modifications will be proposed following the trans-theoretical model of stages of change (Prochaska, 2008). For a summary of the contents of the FIBROWALK program, see Tables 1, 2.

In RCTs of non-pharmacological treatments, it is recommended that more than one therapist deliver each treatment to create a more realistic and generalizable impression of effectiveness (Ost, 2014). FIBRO-Out intervention will be conducted by six different therapists (i.e., three health psychologists and three physiotherapists) with experience in the field of chronic pain and FM. Psychotherapists and physiotherapists will work in pairs in each study group, leading psychotherapeutic or physiotherapeutic FIBROWALK components. The physiotherapist in charge of the group will conduct the first block of each session of the program (PNE + therapeutic exercise; 1 h duration) and the psychologist will conduct the second block (CBT + mindfulness; 1 h duration). Four different pairs of therapists will be generated to lead the four FIBRO-Out groups (18–20 participants per group) that will be carried out for this study. The outdoor FIBROWALK program has already been the subject of a previous investigation by the group (Serrat et al., 2020) and very high levels of adherence were observed, with 90% of patients attending 10 or more sessions out of 12.

2.7 Treatment fidelity evaluation of the FIBRO-Out arm

All therapists involved in this treatment arm will have prior experience in CBT or physiotherapy applied to individuals with FM or chronic pain and will receive an 8-h face-to-face training prior to starting the RCT with the aim of standardization. The six therapists

TABLE 3 Summary of the assessments in the RCT.

	Baseline	6 weeks	Post-intervention (12 weeks)	Follow-up (6 months)
Sociodemographic and clinical characteristics of the sample				
Sociodemographic data	X			
Clinical data	X			
Primary outcome measure				
FIQR	X	X	X	X
Secondary outcome measures				
VAS Pain	X	X	X	X
VAS Fatigue	X	X	X	X
HADS	X	X	X	X
PSS	X	X	X	X
PF-SF-36	X	X	X	X
B-PSQI	X	X	X	X
MISCI	X	X	X	X
CSI	X	X	X	X
PGIC/PSIC			X	
Process measures				
PCS	X	X	X	X
TSK-11	X	X	X	X
PIPS	X	X	X	X
R–NPQ	X	X	X	X
Cost-utility measures				
CSRI	X			X
EQ-5D	X			X
Other self-reported measures				
CEQ	X		X	
Perceived adverse effects of the interventions		X	X	
Fidelity evaluation (adherence of the therapists to the FIBROWALK guidelines)			X	
physiological markers				
Immune-inflammatory markers	X		X	
BDNF	X		X	

Note: BDNF, Brain-Derived Neutrophic Factor; B-PSQI, brief version of the pittsburgh sleep quality index; CEQ, Credibility/Expectancy Questionnaire; CSI, central sensitization inventory, short form; CSRI, client service receipt inventory; HADS, hamilton anxiety depression scale; MISCI, multidimensional inventory of subjective cognitive impairment; PCS, Pain Catastrophizing Scale; PF-SF-36, Physical Function from the Short Form-36 Health Survey; PGIC/PSIC, Patient Global Impression of Change/Pain Specific Impression of Change; PIPS , psychological inflexibility in pain scale; PSS, perceived stress scale; R-NPQ, revised neurophysiology of pain questionnaire; TSK, tampa scale for kinesiophobia; VAS, Visual-analogue scale.

in the FIBRO-Out program will be trained by fulfilling the FIBRO-On program (which includes all the same components as the outdoor format) and participating as co-therapists in a brief FIBRO-Out program (i.e., 4 sessions, 2 h each) for people with FM with the close face-to-face supervision of the clinical manager of the study (MS). All program-related doubts raised in each training session will be shared within the therapist group and solved by MS. Furthermore, every week during the intervention, meetings will be held between the therapists and MS to allow them to discuss any difficulties experienced and find ways to overcome them. To allow quality control of the provided treatment, the training of the therapists will be based on the FIBROWALK manual and guidelines (Serrat et al., 2021a; Serrat et al., 2021b; Serrat, 2022a) and the therapists will be evaluated for treatment fidelity for independent experts at the end of their intervention. This program manual will be used for training, supervision of the therapists and also for monitoring the program's quality and performance. To monitor treatment fidelity within the FIBRO-Out arm, research assistants will audio-tape all treatment sessions and two independent experts in the program will rate adherence to each component of the FIBRO-Out. A random sample of tapes, stratified by therapist and therapy session will be rated using the instruments described below. Treatment fidelity will be assessed with a measure of fidelity criteria based on the guidelines for the FIBROWALK intervention, which will be generated by MS before the start of the interventions. The results of the evaluation of the therapist's adherence to the program will not only allow

monitoring of the program's quality but also allow providing detailed feedback to the therapists about their performance.

All study participants will be asked to continue taking the same medication regimen for the duration of the study period (6 months).

2.8 Study measures

Assessment of outcome and process measures will be carried out at baseline, 6 weeks after starting treatment, at post-intervention (12 weeks) and at 6-month follow-up after starting the trial (follow-up. Cost-utility assessment will be conducted at baseline and at the follow-up and biomarkers evaluation at baseline and post-intervention. The research assistants in charge of the evaluations will be extensively trained by researchers (MS, AF-S), who have broad experience in applying the study measures.

The following domains will be assessed (see Table 3 for a summary of assessments):

- Socio-demographic questionnaire: gender, date of birth, marital status, cohabitation, educational level and employment status.
- Clinical data: date of FM diagnosis, years with a FM diagnosis, comorbidity with other diagnosed medical/psychiatric conditions, type and dosage of current medication, weight and height.

2.8.1 Primary clinical outcome

The *Revised Fibromyalgia Impact Questionnaire* (FIQR; Luciano et al., 2013) is a 21-item questionnaire (0–10 scale) which assesses the dimensions of physical dysfunction, overall impact of FM and severity of the symptoms (i.e., pain, energy, stiffness, sleep quality, depression, memory issues, anxiety, pain to the touch, 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 patients with FM. A total score for FIQR ranging from 0–100 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).

2.8.2 Secondary clinical 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).

- *Hospital Anxiety and Depression Scale* (HADS; Luciano et al., 2014a). HADS 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 inpatients with FM (Luciano et al., 2014b).

- The *Perceived Stress Scale*, short form (PSS; Herrero and Meneses, 2006) is a 4-item scale used to evaluate the degree to which respondents appraise situations as stressful in the last month with responses scored on a Likert scale between 0 = "never" and 4 = "very often," and with total scores ranging from 0 to 16 for the short 4-item version of the scale. Higher scores indicate greater perceived stress. The Spanish version of the 4-item version of the PSS shows acceptable internal consistency (Cronbach's α = 0.77).

- The *physical function subscale of the Short Form-36 Health Survey* (PF-SF-36; Alonso et al., 1995) is used to measure physical function. This dimension comprises a total of 10 items, which are answered on a Likert scale of 3 points. Total scores on each scale 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).

- *Brief version of the Pittsburgh Sleep Quality Index* (B-PSQI; Sancho-Domingo et al., 2021). The PSQI is the most widely used questionnaire in research and clinical practice to assess sleep quality. The B-PSQI is a brief version of this measure including six questions about sleep quality. The Spanish version of the B-PSQI shows adequate internal consistency (α = 0.79).

- The *Multidimensional Inventory of Subjective Cognitive Impairment* (MISCI; Feliu-Soler et al., 2018) is a 10-item scale with a 5-point Likert scale (from 1 "Not at all/Never" to 5 "Very much/Always") for assessing perceived cognitive dysfunction in FM during last week. It includes the cognitive domains: mental clarity, memory, attention/concentration, executive functioning, and language. The MISCI was developed through classical test theory and item response theory from cognitive functioning item banks that were developed as part of the Patient Reported Outcomes Measurement Information System (PROMIS). The Spanish version of the MISCI shows excellent internal reliability (α = 0.91).

- The *Central Sensitization Inventory, short form* (CSI; Nishigami et al., 2018) is the brief form of the CSI (Cuesta-Vargas et al., 2016), and consists of two parts: part A includes nine items scored from 0 to 4, with higher total scores reflecting increased central sensitization symptoms; part B (which is not scored) determines whether one or more specific disorders of central sensitization related to pathophysiology (i.e., restless legs syndrome, chronic fatigue syndrome, FM, temporomandibular joint disorder, migraine or tension headaches, irritable bowel syndrome, multiple chemical sensitivities, neck injury, anxiety or

panic attacks, and depression) have been diagnosed before. Adequate internal consistency for the CSI-9 has been also reported (Cronbach's alpha = 0.80).

2.8.3 Cost-utility measures

- *Client Service Receipt Inventory* (CSRI; Vázquez-Barquero et al., 1997). The CSRI is a questionnaire for economic evaluation. The version used in this study is designed to retrospectively collect data on the use of health and social services during the previous 6 months.

- EuroQoL-5D-5L (EQ-5D-5L; Badia et al., 1999). The EQ-5D-5L is an instrument for assessing health-related quality of life. It consists of two parts: the first part assesses the individual's difficulties in relation to mobility, self-care, pain/discomfort and anxiety/depression; and the second part assesses the patient's current perceived health status on an analogue-visual scale from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine").

2.8.4. Process measures

- *Pain Catastrophizing Scale* (PCS; García-Campayo et al., 2008). The PCS is used to evaluate catastrophic thoughts associated with pain. It consists of three dimensions (e.g., rumination, magnification, and helplessness) with 13 items in total, which are answered on a Likert scale of 5 points. Total scores on each scale range from 0 to 52, with higher scores indicating more catastrophic thoughts. The Spanish version of the PCS shows adequate internal consistency ($\alpha = 0.79$).

- *Psychological Inflexibility in Pain Scale* (PIPS; Wicksell et al., 2008). The PIPS is a 12-item scale that assesses psychological inflexibility in pain patients, and includes two factors: avoidance and cognitive fusion with pain. The items consist of different statements that are considered to be related to chronic pain, psychological inflexibility, suffering and disability (coherent with the ACT theory). All the items are rated on a 7-point Likert scale that ranges from "1 = never true" to "7 = always true", with higher scores indicating more psychological inflexibility. The Spanish version of the PIPS (Rodero et al., 2013) shows adequate internal consistency ($\alpha = 0.90$).

- *Tampa Scale for Kinesiophobia* (TSK; Gómez-Pérez et al., 2011). The TSK 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 has an adequate internal consistency ($\alpha = 0.79$).

- The *Revised Neurophysiology of Pain Questionnaire* (R-NPQ; Torres-Lacomba et al., 2021). The R-NPQ consists of 13 statements (True/False/I do not know) about pain neurophysiology and has been extensively used to assess pain biology knowledge. The R-NPQ score ranges from 0 to 13 (sum of all correct items), and can be also expressed as a rate of correctly answered items. Excellent internal consistency for the R-NPQ has been reported in Spanish samples ($\alpha = 0.87–0.92$).

2.9 Other self-reported measures

- The *Patient Global Impression of Change (PGIC)* and the *Pain Specific Impression of Change* (PSIC) (Scott and McCracken, 2015) are measures to assess, respectively, self-perceived meaningful clinical change (on a 7-point Likert scale, from 1 = "Much better" to 7 = "Much worse") in general or in the following specific domains: physical and social functioning, work-related activities, mood, and pain.

- Adapted version of Credibility/Expectancy Questionnaire (CEQ; Devilly and Borkovec, 2000). It is a 6-item questionnaire widely used to assess treatment expectancy as well as the credibility of the FIBRO-On and FIBRO-Out interventions. The first part of the CEQ comprises three items focused on therapy credibility (i.e., the extent to which the treatment appears a)logical and b) useful, and c) the confidence with which the treatment's patient would recommend this one to a friend with the same health condition); and three more items evaluating expectations (i.e., the extent to which the patient thinks an improvement will happen as a consequence of the treatment; the extent to which the patient really feels that the intervention will reduce him/her symptoms, and the extent to which the patient really feels a symptom improvement will occur). After finishing the treatment, the patient's opinion regarding the treatment received will be also gathered by using the second part of the CEQ which includes the same questions as in the first part of the CEQ but in past tense. The CEQ showed overall adequate internal consistency ($\alpha = 0.84–0.85$) in a previous study in a similar clinical sample (Pérez-Aranda et al., 2019).

- An *ad hoc* item (i.e., *Have you experienced, during the course of the treatment, any unwanted symptom that you think might be directly or indirectly associated with the intervention?*) to check for the presence of adverse effects (e.g., headaches, dizziness, sleep problems, *etc.*) associated with the evaluated interventions. This measure has been used in a previous study (Pérez-Aranda et al., 2019) and will be administered both at 6-week and post-intervention assessments.

- Patients' adherence evaluation to the FIBRO-On and FIBRO-Out programs. An *ad hoc* instrument (i.e., personal practice log) for the weekly recording of home practice will be developed to determine level of adherence to psychotherapeutic and therapeutic exercise recommended homework.

2.10 Physiological markers

Blood samples will be collected in vials which will be centrifuged and the resulting serum will be stored frozen at -80°C until analysis. All samples (pre and post) will be analyzed in a single analytical batch in order to reduce inter-assay variability (approximately 15%). Serum levels of the cytokines IL-6, CXCL8, IL-4, IL-10, IL-17A and hs-CRP will be assessed. For the quantification of cytokines, Milliplex® reagents from

MerckMillipore analyzed on a Luminex® platform will be used. The highly sensitive Human High Sensitivity T Cell multiplex kit will be used (catalogue number: HSTCMAG28SPMX11). The hs-CRP will be quantified by turbidimetry on a Siemens Atellica autoanalyzer. BDNF levels will be evaluated using an ELISA kit (reference SEA011Hu-96T). Sample analysis will be performed by the Echevarne Laboratory. Detection concentration ranges: IL-6 (0.64–10,000 pg/ml), CXCL8 (0.64–10,000 pg/ml), IL-4 (0.64–10,000 pg/ml), IL-10 (2.6–40,000 pg/ml), IL-17A (1.3–20,000 pg/ml), hs-CRP (0.1–50 mg/L), and BDNF (31.2–2,000 pg/ml). Biomarkers will be assessed only at baseline and post-intervention because of the following reasons: a) evidence of changes in immune-inflammatory markers and BDNF levels after non-pharmacological interventions with a similar duration (Sanada et al., 2015; Montero-Marín et al., 2019; Pérez-Aranda et al., 2019); b) lower risk of sample loss (vs. assessing at 6 months); c) possibility to use pre-post change as a mediator of clinical changes at 6 months follow-up; and d) budget constraints.

2.11 Statistical analyses

SPSS v26.0, STATA v16.0 and Mplus v7.4 will be used for the statistical analyses. Descriptive statistics will be calculated for all variables and presented as means and standard deviations if continuous, or as absolute numbers and percentages (%) if categorical. The Levene test will be used to assess the equality of variances of continuous variables and Kolmogorov–Smirnov to test sample normality and distribution. One-way ANOVAs (with post hoc Tukey's HSD or Games-Howell tests) for continuous values and $\chi 2$ tests with continuity corrections for categorical values will be computed on all baseline measures and socio-demographic variables to examine between-group differences at baseline.

2.11.1 Analysis of clinical effectiveness

The primary effectiveness analysis will be conducted on an intention-to-treat (ITT) basis with the FIQR total score as a primary clinical endpoint (McCoy, 2017) and by linear mixed-effects regressions with restricted maximum likelihood (REML). REML accounts for the correlation between repeated measures for each individual and produces less biased estimates of variance parameters when using small sample sizes or unbalanced data (Egbewale et al., 2014). No imputation of missing data will be conducted, since it has been reported that multiple imputation is not necessary for all types of missing data (missing completely at random, missing at random, and missing not at random) before computing longitudinal mixed model analysis (Twisk et al., 2013). Unstandardized regression coefficients (B) and 95% confidence intervals (95% CIs) will be computed for the 'group x time' interaction between groups at 6-week, post-treatment and 6-month follow-up assessments. Cohen's d will be calculated for each pairwise comparison, using the pooled baseline SD to weight the differences in the pre–post mean values and to correct for the population estimate (Morris, 2008). The rule of thumb for effect size interpretation will be the classical cutoffs for Cohen's d of 0.20 = small, 0.50 = medium, and 0.80 = large. All secondary clinical endpoints will be analyzed using the same statistical procedure. Benjamini–Hochberg correction for multiple comparisons will be applied to control for false rate discovery (Glickman et al., 2014). All the analyses will be replicated using a "completers" approach including all participants who finished the study, and a per-protocol approach, taking into account only those patients who attended at least 75% of the sessions (9 out of 12).

In addition, to assess clinical significance of the improvement on the primary outcome (FIQR), all the participants will be allocated into the categories of "responder" and "non-responder" by using the criteria of presenting at least a 20% reduction in the pre–post FIQR total score or not, respectively (Bennett et al., 2009). This classification will be used to compute the number needed to treat (NNT) for each treatment when compared to the others. The NNT refers to the estimated number of patients who need to be treated with a new proposed treatment (i.e., rather than the control comparison treatment) for one additional patient to benefit. A 95% CI for each NNT will be calculated. This index allows findings from RCTs to be more meaningful to clinicians. Furthermore, in order to explore potential predictors of treatment response in each intervention arm, t-tests and $\chi 2$-tests will also be performed to assess potential baseline differences in sociodemographic, clinical and physiological variables between responders vs. non-responders within the FIBRO-Out and FIBRO-On arms. Finally, baseline differences between participants who completed all study assessments and those who did not will also be evaluated (with *t* and $\chi 2$-tests) to detect any potential attrition bias.

The differences between FIBRO-On and FIBRO-Out on perceived clinical improvement (assessed with PGIC and PSIC) and on treatment expectation/opinion (i.e., with the CEQ) will be computed using χ^2 tests and Student's *t* tests, respectively.

2.11.2 Mediation analyses

We will compute pre–post change scores for all process measures in the study and pre–follow-up change scores for primary and secondary outcomes. Bivariate Pearson correlations will be calculated between the pre–post change scores for the process variables and the pre–follow-up change scores for the clinical endpoints to detect statistically significant relationships. The direct and indirect associations between the treatment condition (i.e., FIBRO-On vs. TAU, FIBRO-Out vs. TAU, or FIBRO-On vs. FIBRO-Out, as independent variable), process variables (mediators), and primary and secondary outcomes (dependent variables) will be computed by using path analyses. With this statistical

approach, we are considering temporality into account, which increases the prospect of establishing conclusions about causality. Simple and multiple mediation (simultaneously testing multiple variables as mediators) models will be computed.

Similarly, for obtaining more detail about psychological mechanisms fostered during intervention and its role in the observed effect at post-intervention, mediation analyses will also be conducted by using change scores of process measures between baseline and 6-week assessment and change scores for clinical measures between baseline and post-intervention assessments. The direct paths between treatment condition and clinical outcomes and the indirect effect path through the mediation variables will be tested in all the models. Regression coefficients (B) of bias-corrected bootstrapped indirect effects will be calculated as well as their SEs and 95% CIs (Lockhart et al., 2011). Parameters of indirect effects are considered statistically significant when the 95% CI did not include 0. Participants with missing data will be excluded for this analysis.

2.11.3 Cost-utility analysis

The economic evaluation will be reported according to the Consolidated Health Economic Evaluation Reporting Standards statement (Husereau et al., 2013) and the Good Research Practices for Cost-Effectiveness Analysis Alongside Clinical Trials (Ramsey et al., 2015). The approach we will follow is estimating costs from the healthcare and the government perspectives, taking the previous 6 months as the time frame. Catalonia has full governance of health and social care and, as in every other Spanish region, healthcare is universal and publicly financed. The government perspective includes both direct healthcare costs assumed by the Catalan government (excluding out-of-pocket costs and costs associated with private insurance) and indirect costs related to productivity losses assumed by the Spanish government. The healthcare perspective includes only direct healthcare costs. Costs will be estimated for the 6 months before starting the intervention (at baseline assessment) and for the 6 months before the follow-up assessment.

Direct costs will be calculated as the sum of medication costs and health service use (primary, specialized and emergency care consultations, hospital admissions) and cost of staff to run the interventions. The cost of medication will be calculated by determining the price per milligram during the study according to the Vademecum International (Red Book), and including VAT. Total medication costs will be computed by multiplying the price per milligram by the daily dose in milligrams and the number of days receiving the specified treatment. The unit costs of medical tests and health services will be obtained from the SOIKOS health database (http://www.oblikue.com/bddcostes/). Indirect costs (lost productivity) will be computed according to the human capital approach, by multiplying the minimum daily wage in Spain in 2022 by the number of days on sick leave reported by each participant. Unit costs will be reported in Euros (€).

The utilities represent the rating of the patients' quality of life on a scale from 0 ("as bad as death") to 1 ("perfect health"). For the cost-utility analysis, the ratio between the cost of each intervention and its consequences in terms of QALYs will be calculated. QALYs will be computed using Spanish EQ-5D tariffs. Following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) core recommendations for cost-effectiveness analyses alongside RCTs (Ramsey et al., 2015), we will calculate the incremental cost-utility ratios (ICUR) for each pairwise comparison (TAU vs. FIBRO-On, TAU vs. FIBRO-Out, FIBRO-On vs. FIBRO-Out), defined as the difference in mean costs divided by the difference in mean QALYs. Given that the duration of the study is 6 months, neither costs nor outcomes are subject to discounting. QALYs at 6 months after the start of the interventions will be approximated by calculating the area under the curve.

Cost-effectiveness analyses will be performed using the Zellner's seemingly unrelated regression (SUR) model (Greene, 2003) with the STATA's *sureg* command. Using the SUR method for cost-effectiveness purposes implies the use of a bivariate system of regressions that includes both costs and outcomes (with the latter being either QALYs or EurQol-5D-5L VAS, depending on the model considered) as the dependent variables of the two separate equations, which will be estimated jointly. The regressions of costs and outcomes are therefore part of two regressions on treatment allocation (i.e., whether they are assigned to TAU, FIBRO-Out, or FIBRO-On) plus an additional set of control variables (measured at baseline) if necessary: age, gender, marital status, education level, employment status, baseline costs, or baseline outcome, depending on the equation considered.

Estimates of incremental cost and of incremental effect values using the SUR method described above will be derived with 1,000 bootstrap replications in order to address a possible skewness in the distribution of the dependent variables (Briggs et al., 1997). We also will construct acceptability curves to represent the probability of the intervention being cost-effective, given a varying threshold for the willingness to pay for each QALY gained in each intervention compared to the others. The robustness of the cost-utility results will also be tested in different case scenarios; more precisely, we will use ITT approach as the primary analysis, imputing missing values for those variables missing at 6-month follow-up by using multiple imputation methods with the chained equations approach (Royston and White, 2015). Additional scenarios (sensitivity analysis) will be also conducted repeating the same statistical analyses in a complete case analysis, including only those participants with complete

assessments at baseline and at 6-month follow-up, and in a per-protocol analysis including only those participants who attended at least 75% of the sessions (9 out of 12). STATA 16.0 statistical software will be used for cost-utility analyses.

2.11.4 Analysis of changes in biomarkers

The effect of interventions on immune-inflammatory markers and BDNF levels will be evaluated also with REML. In those cases where cytokine concentrations are under detection level of the test, the detection limit value will be assigned. Cytokines, hs-CRP and BDNF values will be subjected to a natural logarithmic transformation to normalize the significantly skewed data distributions. In order to comprehensively integrate pro-inflammatory with anti-inflammatory markers, indexes indicative of inflammatory balance will be calculated (e.g., IL-6/IL-10, CXCL8/IL-10 and hs-CRP/IL-10) in a similar way to previous studies (Andrés-Rodríguez et al., 2019). Since some pharmacological treatments such as antidepressants are reported to potentially affect some cytokine levels (Hannestad et al., 2011), differences in such levels between patients taking vs. not taking these drugs will be also evaluated. In case of any statistically significant effect, antidepressant status ("taking" = 1, "not taking" = 0) will also be included as a co-variable in the REML analyses for each specific biomarker.

2.12 Ethical issues of the project

Written informed consent will be obtained from all participants prior to randomization. Participants will be provided with a general overview of the aims and characteristics of the study and the interventions before signing the informed consent. They will also be assured that they will be participating voluntarily and can withdraw at any time from the study with the guarantee that they will continue to receive the most appropriate medical treatment prescribed by their general practitioner. The study will be conducted in compliance with the Declaration of Helsinki (version in force; currently Fortaleza, Brazil, October 2013). The study will be conducted in accordance with the protocol and with the relevant legal requirements: Law 14/2007 of July 3, on Biomedical Research. The VHIR Research Committee Board evaluated and approved the study protocol in May 2022 [PR (AG)99/2022]. All patient data will be treated as confidential and only the research team will be allowed to access it after recodification of name and personal identity number (so no individual can be directly identified). Only the principal investigator (AF-S) and the clinician coordinator of the study (MS) will have access to the code key which will be stored separately in a safe place in accordance with Spanish legislation. All data will be computer processed and stored. Blood samples will be stored encrypted, and will not be directly traceable back to individuals. Blood samples will be used only in ways to which the participants consented and may only be made available to a new research project after Ethical Research Committee approval and participants provide a new agreement. Furthermore, the participants have the right to request, without explanation, that their samples be destroyed or made completely anonymous.

2.13 Blinding

Randomization and group allocation will be completely masked for the study assessors and study participants will be asked not to communicate with the assessor about the treatment received. The study participants will be provided with a summary of evidence of the FIBROWALK program which constitute the basis for FIBRO-On and FIBRO-Out programs. As it is usual in non-pharmacological trials, neither participants nor the therapists can be blinded to treatment allocation. The therapists in the FIBRO-On and FIBRO-Out arms will not be involved in any assessment task of the study.

2.14 Forecast execution dates

Initial recruitment of patients: September 2022.
Finalization of patient recruitment: January 2023.
Finalization of patient monitoring period: July 2023.
Publication of results: December 2023.

3 Discussion

The On&Out study will evaluate the effectiveness, cost-utility and the physiological effects of adding the FIBROWALK program in Online (i.e., FIBRO-On) or in Outdoor format (i.e., FIBRO-Out) to TAU. In order to determine the mechanisms of action of these interventions, we will also evaluate potential process measures of these interventions, as well as physiological markers with evidence of alteration in FM and that are likely modifiable by non-pharmacological interventions. Three previous studies evidenced the short-term efficacy (i.e., post-intervention) compared to TAU of both the FIBRO-On (Serrat et al., 2021a; Serrat et al., 2022b) and FIBRO-Out programs (Serrat et al., 2020); however, the present RCT will evaluate for the first time if these clinical effects are maintained at 6-month follow-up along with the aforementioned analyses on cost-utility, mediation and physiological markers.

The fact that FIBROWALK's tested interventions are in online format (FIBRO-On) or in group format (FIBRO-Out) can make them more cost-effective, and therefore of interest for

health managers. Additionally, both formats can be considered "safe" in epidemiological terms (compared to face-to-face indoor classical interventions) as they do not imply in closed spaces shared with other people where exists a higher risk for contagion (e.g., Bazant and Bush, 2021). Furthermore, particularly for the FIBRO-On intervention, these therapies can also be followed under strict social distancing measures and even in lockdown circumstances. If the results of this RCT are strong enough in terms of efficacy and cost-utility, FIBRO-Out and/or FIBRO-On could be considered for their inclusion in the public healthcare Spanish system to treat individuals suffering from FM. Additionally, this RCT may also pave the way for further RCTs testing the efficacy of these interventions in other chronic diseases cursing with central sensitization (e.g., irritable bowel syndrome, chronic headache, temporomandibular disorder, pelvic pain syndromes), along with other emerging conditions such as persistent post-COVID syndrome which may display overlapped symptoms with FM (Haider et al., 2022).

The On&Out study will also evaluate the effect of the FIBROWALK multicomponent programs on immuno-inflammatory markers and BDNF levels that seem to be altered in FM and/or play a role in the effectiveness of non-pharmacological treatments (Rodriguez-Pintó et al., 2014; Andrés-Rodríguez et al., 2019; Montero-Marin et al., 2019). It should also be noted that, to date, the effect of any multicomponent program on such biomarkers in FM has not been evaluated by means of a RCT design. Furthermore, the evaluation of changes in these biomarkers and their association with clinical change will further deepen the understanding of the role of the immune system and neuroprotective agents in FM and related disorders cursing with central sensitization. Associated with this substudy of the project, it should be noted that the inclusion of biomarkers may also make it possible to determine different patient profiles (based on their psychobiological characteristics) which could be predictive of a greater or lesser response to the treatments under study. This aspect is fully connected with the emerging field of personalized treatments and can contribute to optimizing the use of healthcare services while also enhancing the efficacy and cost-effectiveness of the interventions evaluated (Thase, 2014; Lopresti, 2017; Carvalho et al., 2019).

This study has some strengths that should be highlighted. The inclusion of a relatively large sample and of a comprehensive set of measures will allow us to compare the short term (pre-post) and long-term (6 months) effectiveness of two different formats of the FIBROWALK multicomponent program on core FM outcomes and psychological process measures. Furthermore, the identification of cost-effective interventions is a priority for the national health system, especially for highly prevalent conditions such as FM. This study will evaluate for the first time the cost-effectiveness of two formats (which can be particularly useful in the pandemic and post-pandemic era) of a multicomponent intervention for FM. In this sense, it is necessary to introduce new practices in the provision of healthcare services to improve efficiency in the use of resources. In this regard, boosting treatments aimed at changing lifestyles and patterns of cognition and behavior (as it is aimed in FIBROWALK) constitutes a strategy of financial sustainability as, in the long-term, it will allow an extension of the culture of health understood holistically and, therefore, a decrease in the burden of disease on society as a whole. Our study will also explore immune-inflammatory and neuroprotective pathways behind the efficacy of the evaluated treatments, and will combine clinical and process measures which may lead to a better characterization of the syndrome, to new therapeutic interventions, and to a better prediction of treatment response in order to better determine what works for whom in the field of personalized medicine. Finally, it is also worth mentioning that the present RCT will involve six therapists (three psychologists and three physiotherapists) in delivering the FIBRO-Out intervention; doing so (instead of only one therapist delivering the therapy) can provide more realistic and generalizable results (Ost, 2014) which can be useful for the future implementation of these interventions in healthcare systems.

There are also some potential limitations that should also be recognized in this RCT. One of the main risks of this project may be dropouts and non-adherence, which are expected to be higher than in previous studies that only evaluated the short-term efficacy of the interventions (Serrat et al., 2020; Serrat et al., 2021a; Serrat et al., 2021b; Serrat et al., 2022b). In this regard, since previous studies showed very high adherence to the programs (over 90%; Serrat et al., 2020; Serrat et al., 2022b), a dramatically high dropout in the present study is not expected; however, to limit the effect of these dropouts and lack of adherence in our results, we will conduct several sensitivity analyses (ITT, completers, per protocol analysis). We also have to note the lack of blinding of participants and therapists, which is a typical bias in any RCT including non-pharmacological treatments. Although a weekly questionnaire will be administered to check the adherence to FIBRO-On program (i.e., watching the videos), there is a risk that some participants in the FIBRO-On group do not watch the videos and inform differently. It is also relevant to highlight that this RCT will be carried out in a specialized unit of tertiary referral hospital in the context of clinical practice. Related to this, stricter inclusion/exclusion criteria could not be established due to pressures in daily clinical practice (i.e., most patients will be admitted). At the same time, this latter point may have a positive aspect by increasing the external validity of the study and so the generalization of the results into the "real" clinical practice.

Up to date, there is no study assessing the cost-effectiveness of multicomponent approaches for FM neither evaluating the long-term effectiveness of such type of interventions in online or outdoor formats. If one or both treatments evaluated in this present RCT

(i.e., FIBRO-On and/or FIBRO-Out) shows to be effective and cost-effective they should be included as part of the standard of care for treating FM. Furthermore, since both interventions are, per definition, conducted out of the hospital settings, they could also be safely administered in the context of future pandemics, and (in the particular case of the FIBRO-On program) in circumstances of low accessibility to effective treatments for FM (e.g., in remote areas), highly congested healthcare services and/or low availability of clinical resources. The On&Out project is also aimed at determining psychophysiological patient profiles which can be useful for identifying potential treatment beneficiaries (i.e., treatment responders) beforehand which may in turn improve healthcare resources allocation. Last but not least, the present study may also help us in deepening our knowledge on which psychological and physiological mechanisms underpin the clinical effects of non-pharmacological interventions in FM, further contributing to the potential detection of novel therapeutic targets.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Vall d'Hebron Institute of Reseach.

Author contributions

Conceptualization, MS, AF-S; Methodology, MS, SF, MA, JL, XB, and AF-S; Resources, MS, MA, and AF-S; Writing—original draft preparation, MS, SF, WA, MA, and AF-S; Writing—review and editing, MS, SF, WA, MA, XB, FD, SL, EL, MM, JN, JM-M, RN, JL, and AF-S; Visualization, MS, SF, WA, MA, JL, and AF-S; Supervision, MS, MA, JL, and AF-S; Project administration, MS, MA, and AF-S; Funding administration, MS, MA, AF-S. All authors have read and agreed to the published version of the manuscript.

Funding

The project has been funded in part by the Spanish Ministry for Science and Innovation (MCIN) State R + D + I Program Oriented to the Challenges of Society (ref. PID 2020-117667RA-I00) and co-financed with European Union ERDF funds. The last author (AF-S) acknowledges the funding from the Serra Húnter program (Generalitat de Catalunya; reference number UAB-LE-8015). JM-M has a "Miguel Servet" contract from the ISCIII (CP21/00080). JN has a research contract awarded by the ISCIII (ICI20/00080).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ferrés, S., Serrat, M., Auer, W., Royuela-Colomer, E., Almirall, M., Lizama-Lefno, A., Nijs, J., Maes, M., Luciano, J. V., Borràs, X., & Feliu-Soler, A. (2025). Immune-inflammatory effects of the multicomponent intervention FIBROWALK in outdoor and online formats for patients with fibromyalgia. Brain, behavior, and immunity, 125, 184-197 https://doi.org/10.1016/j.bbi.2024.12.149

Brain, Behavior, and Immunity 125 (2025) 184–197

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Full length article

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

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ARTICLE INFO

Keywords:
Fibromyalgia
Multicomponent Intervention
FIBROWALK
Online
Outdoor
Cytokines
Brain-derived neurotrophic factor

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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https://doi.org/10.1016/j.bbi.2024.12.149
Received 11 June 2024; Received in revised form 10 December 2024; Accepted 21 December 2024
Available online 30 December 2024

(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).

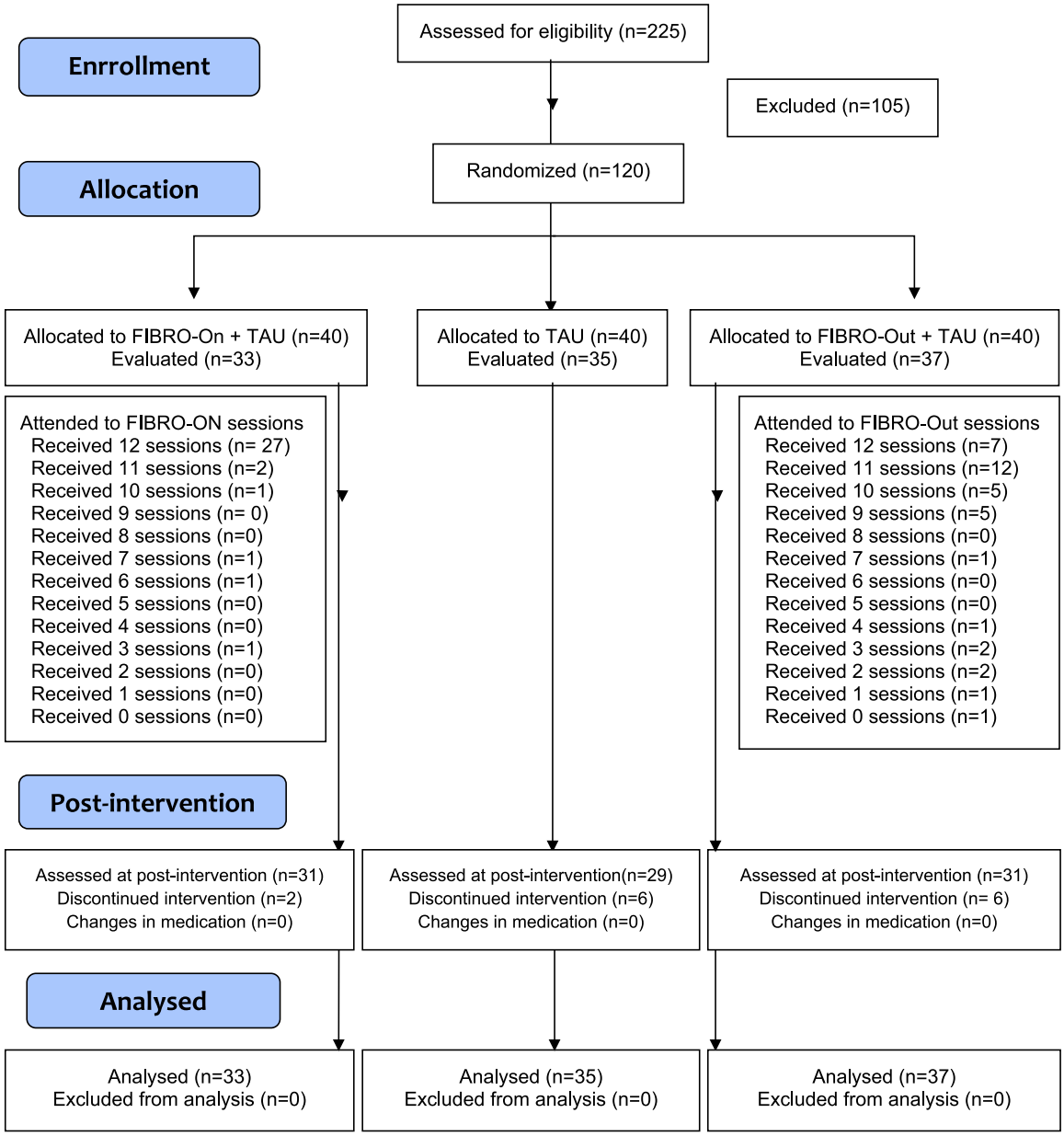

Fig. 1. Flowchart of the On&Out substudy.

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 ($p \leqq 0.05$). 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 ($n = 35$) 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)*
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.

Funding

The project has been funded in part by the Spanish Ministry for Science and Innovation (MCIN) State R + D + I Program Oriented to the Challenges of Society-MCIN/AEI/10.13039/501100011033- (ref. PID 2020-117667RA-I00) and co-financed with European Union ERDF funds. The authors are grateful to the CIBER of Epidemiology and Public Health (CIBERESP; CB06/02/0046 & CB22/02/00052) for their support. The funding sources had no influence on the design of the study, data collection and analysis, or the writing of the manuscript.

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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CAPÍTOL 4.

Discussió

1. Efectivitat a curt termini del programa FIBROWALK *online* i *outdoor* en fibromiàlgia

En el marc d'aquesta tesi doctoral, la publicació prèvia del protocol va assegurar la transparència, la replicabilitat i la qualitat de la recerca realitzada en el marc de l'estudi On&Out. La difusió del protocol en el primer article va establir una guia clara per a l'execució de l'estudi empíric del segon article, garantint que els mètodes fossin ben definits, clars i sotmesos a la revisió de la comunitat científica abans de la recollida de dades.

A més, el "Codi de bones pràctiques en la recerca" de la Universitat Autònoma de Barcelona (2020) subratlla la importància d'una planificació detallada que inclogui la definició clara dels objectius i les metodologies, elements essencials per garantir la qualitat i la transparència en qualsevol estudi. En aquest context, el protocol de l'estudi va ser registrat i publicat en la base de dades ClinicalTrials.gov, garantint la seva transparència i la disponibilitat per a una revisió independent. A més, el disseny i la metodologia de l'estudi han seguit les directrius establertes per SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials), assegurant que tots els elements essencials fossin clarament especificats i accessibles des de l'inici.

Seguint els resultats d'estudis previs que avaluaven l'efectivitat a curt termini de FIBROWALK en entorns hospitalaris (Serrat et al. 2021b), *outdoor* (Serrat et al. 2020), i *online* (Serrat et al. 2021a, 2022a) en comparació al TH, el nostre estudi (el primer on comparar directament dos dels formats del FIBROWALK) va demostrar que tant la intervenció FIBRO-On com la FIBRO-Out van reduir de manera efectiva l'impacte funcional i la kinesiofòbia en persones amb FM (vs TH), i ambdues estratègies van mostrar una efectivitat a curt termini

similar. Tanmateix, en la mostra de l'estudi de biomarcadors, la versió *outdoor* de FIBROWALK va mostrar efectes clínics més amplis en comparació amb el format *online*, ja que també va ser capaç de reduir el dolor, la fatiga i els símptomes depressius en relació amb el TH, mentre que en el grup *online* no va presentar aquests beneficis (**Taula 1**).

Taula 1. *Resum dels resultats de les anàlisis d'efectivitat a curt termini de les intervencions FIBROWALK*

Variable principal: FIQR	● FIBRO-Out superior a TH (p=0.010; d=0.50) ● FIBRO-On superior a TH (p=0.044; d=0.43) ● FIBRO-Out y FIBRO-On millores similars
Variables secundàries: VAS-Pain, VAS-Fatigue, HADS-A i D, SF-36 i TSK-11	● FIBRO-Out superior a TH en: - **VAS-Pain** (p=0.019; d=0.63), - **VAS-Fatigue** (p=0.039; d=0.53) - **HADS-D** (p=0.005; d=0.65) - **TSK-11** (p=0.002; d=0.51) ● FIBRO-On superior a TH en: - **TSK-11** (p < 0.001; d=0.84) ● Sense canvis significatius en: - **HADS-A** - **SF-36**

Nota: No s'ha trobat cap comparació entre les branques FIBROWALK que fos estadísticament significativa (totes p≦0,05). d: d de Cohen com a mesura de la mida de l'efecte; FIBRO-On, FIBROWALK *Online*; FIBRO-Out, FIBROWALK *Outdoor*;TH, tractament habitual; FIQR, Revised Fibromyalgia Impact Questionnaire; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain; HADS-A and HADS-D, Hospital Anxiety and Depression Scale; SF-36, Physical function subscale of the Short Form-36 Health Survey; TSK-11, Tampa Scale for Kinesiophobia.

Font: Elaboració pròpia.

Ja que l'estudi de biomarcadors compte amb una mostra reduïda (n=120) respecte a l'estudi principal d'On&Out d'efectivitat i cost-utilitat (n=225) i amb criteris d'inclusió/exclusió més estrictes (veure Estudi 1), serà necessari analitzar si aquests efectes es mantenen i també esbrinar si apareixen diferències entre branques en l'avaluació de seguiment a 6 mesos .

Els efectes clínics observats en el programa FIBRO-Out (vs TH), en comparació amb FIBRO-On (vs TH), es van poder atribuir a diversos factors que influïen en la dinàmica de la intervenció i en l'entorn on es va dur a terme. D'una banda, FIBRO-Out es va realitzar a l'aire lliure, un fet que podria haver afavorit un millor estat d'ànim i una sensació de benestar general entre els participants. L'exposició a la natura i el suport social derivat de la interacció entre els membres del grup podrien haver millorat la motivació i afavorit la cohesió grupal (Thompson et al. 2011), contribuint així a una major adherència al programa i, en conseqüència, a resultats clínics més positius. La variabilitat d'instructors en el grup FIBRO-Out segurament també hauria jugat un paper rellevant, ja que podria haver ofert diferents enfocaments i estils d'ensenyament, permetent una millor adaptació a les preferències i necessitats individuals dels participants, fet que podria haver resultat en una experiència d'aprenentatge més rica i personalitzada, afavorint així la consecució d'efectes clínics més amplis. En conclusió, tot i que el grup *outdoor* (vs TH) semblaria tenir associats beneficis en més dominis en comparació amb el grup *online* (vs TH), no es van observar diferències significatives entre els dos grups en cap variable clínica. Aquestes activitats enriquides van ser més efectives en la reducció dels símptomes clínics, ja que van proporcionar una experiència d'intervenció més immersiva i variada, millorant tant la salut física com emocional dels participants.

Diversos estudis han demostrat l'eficàcia dels enfocaments terapèutics basats en la natura per a la millora de la salut mental en diferents condicions clíniques (Trøstrup et al. 2019), incloent-hi les condicions de dolor crònic i, en particular, la FM. En aquest sentit, la teràpia FIBROWALK *outdoor* (Serrat et al., 2020) ha evidenciat beneficis significatius en aquesta població. L'estudi de Lopez-Pousa et al. (2015) va avaluar una intervenció amb 30 pacients amb FM, distribuïts aleatòriament en dos grups: un que realitzava caminades en un bosc madur i un altre en un bosc jove. La intervenció consistia en caminades aeròbiques de 1,25 km combinades amb teràpia de boscos (*shinrin-yoku*), i es va avaluar l'impacte en el dolor, l'ansietat i la qualitat del son mitjançant instruments com el FIQR i l'*Inventory State-Trait Anxiety* (STAI). Els resultats van mostrar millores en el dolor, la qualitat del son i la relaxació, especialment en el grup que caminava en el bosc madur. No obstant això, no es van observar canvis significatius en els nivells d'ansietat. D'altra banda, l'estudi de Serrat et al. (2020) va adaptar la teràpia FIBROWALK incorporant l'exposició a la natura i va avaluar una intervenció multicomponent, denominada NAT-FM (*Teràpia d'Activitats a la Natura per a Persones amb FM*). Aquesta intervenció incloïa ECD, exercici terapèutic, TCC, mindfulness i activitats en entorns naturals. Els resultats van evidenciar millores significatives en dolor, fatiga, ansietat, autoestima i funcionament físic. A més, es va observar una reducció en la kinesiofòbia i en els pensaments catastròfics, i la intervenció va mostrar una major eficàcia en comparació amb el TH. En la mateixa línia, Stanhope et al. (2020) van dur a terme una intervenció basada en l'exposició a espais verds, aplicada a persones amb dolor crònic amb l'objectiu de reduir la seva càrrega simptomàtica. Aquesta intervenció combinava teràpies a l'aire lliure, exercici en entorns naturals i

l'exposició a elements com la llum solar i els sons naturals. Els resultats van indicar una reducció de l'estrès, una millora de la salut mental i una possible disminució del dolor.

Paral·lelament, diversos estudis han ressaltat l'efectivitat de les teràpies *online* per al tractament del dolor crònic, incloent-hi la FM. En una revisió sistemàtica i metaanàlisi d'assaigs controlats aleatoritzats, White et al. (2022) van analitzar els programes digitals per al dolor crònic, principalment basats en la TCC. Aquestes intervencions consistien en l'accés a mòduls estructurats, programes interactius i, en alguns casos, suport de professionals com psicòlegs o estudiants de psicologia, que proporcionaven feedback i acompanyament. Els components terapèutics més freqüents incloïen la TCC, exercicis de relaxació, mindfulness i estratègies per a la gestió del dolor. Els resultats van mostrar millores en el dolor i en la qualitat de vida, tot i que l'adherència va variar, amb només un 30% dels estudis en què el 70% dels participants van completar el programa. En resposta a la necessitat d'adaptació durant la pandèmia de la COVID-19, Serrat et al. (2021) es va desenvolupar una versió virtual de la teràpia FIBROWALK dirigida a persones diagnosticades de FM. Aquesta intervenció, amb una durada de 12 setmanes, incloïa vídeos setmanals amb continguts sobre exercici aeròbic, ECD, TCC i mindfulness, així com un seguiment periòdic per fomentar l'adherència. Els resultats van mostrar millores estadísticament significatives en dolor, funcionalitat i salut mental. No obstant això, es va observar una taxa d'absentisme superior a la del format presencial, possiblement relacionada amb la variabilitat en la competència tecnològica dels participants i les circumstàncies excepcionals derivades de la pandèmia. Aquest estudi confirma l'eficàcia i viabilitat de les intervencions virtuals com una alternativa viable per al

tractament de la FM en contextos de restriccions sanitàries o dificultats d'accés a teràpies presencials.

Sorprenentment, malgrat l'evidència prèvia segons la qual el FIBROWALK generaria millores en ansietat i funció física percebuda (Serrat et al.2020), cap de les intervencions FIBROWALK provades en l'estudi present va impactar significativament cap d'aquests dominis en comparació amb el TH. En l'estudi de Serrat et al. (2020) que avaluava l'efectivitat a curt termini del FIBROWALK en persones amb FM a l'aire lliure, es van observar canvis en els nivells d'ansietat i en la funció física en les persones amb FM que van rebre el tractament TH + NAT-FM. Es van registrar efectes significatius sobre l'ansietat, amb una mida d'efecte gran tant a les 6 setmanes (d = 0,99) com després del tractament (d = 1,59). En relació amb la funció física, es va trobar una reducció significativa del dolor autoinformat, amb efectes moderats a les 6 setmanes (d = 0,53) i efectes grans després del tractament (d = 1,59). En l'estudi Serrat et al. (2021a), on es va avaluar l'efectivitat del programa multicomponent FIBROWALK aplicat en un entorn virtual per a persones amb FM, es van identificar efectes significatius del tractament ($p < 0,05$) per a l'ansietat i la funció física, amb petites mides d'efecte (d = 0,23) per a l'ansietat i mides d'efecte mitjanes (d = 0,48) per a la funció física.

En l'estudi present, i en contrast amb les expectatives, els canvis observats es van associar a mides d'efecte molt petites: (d = 0,16) per al grup FIBRO-On i (d = 0,07) per al grup FIBRO-Out en comparació amb TH per a l'ansietat, i (d = -0,17) per al grup FIBRO-On i (d = 0,04) per al grup FIBRO-Out en comparació amb TH per a la funció física. Tot i que es van observar reduccions respecte TH en aquestes mesures, l'impacte d'aquestes millores no va ser estadísticament significatiu.

S'hipotetitza que diversos factors podrien explicar la manca d'un impacte significatiu de les intervencions FIBROWALK sobre l'ansietat i la funció física en comparació amb el TH. D'una banda, el disseny de la intervenció i la complexitat inherent de la FM podrien haver influït en la variabilitat dels resultats, ja que aquesta condició es caracteritza per una simptomatologia multifactorial i fluctuacions en l'estat clínic. D'altra banda, les diferències en les característiques de la mostra també podrien haver exercit un paper determinant, ja que la heterogeneïtat dels participants (per exemple, nivell de gravetat de la FM, historial de tractaments previs o diferències en la capacitat d'adherència) podria haver generat respostes desiguals a la intervenció. Pel que fa específicament al grup *outdoor*, un aspecte rellevant és que, en aquest cas, la intervenció va ser conduïda per múltiples terapeutes, en contrast amb estudis anteriors en què només un terapeuta –la creadora de la teràpia– aplicava el programa. Aquesta variació en la implementació podria haver afectat la coherència i l'impacte de la intervenció, dificultant l'obtenció de resultats tan favorables com en estudis previs. En canvi, en el grup *online*, no hi hauria hagut diferències en la implementació que justifiquessin una menor eficàcia en comparació amb recerques anteriors. A més, les qüestions relacionades amb la mesura dels símptomes podrien haver influït en els resultats, ja que les eines utilitzades per avaluar l'ansietat i la funció física podrien no haver estat prou sensibles per captar canvis subtils en aquests dominis o podrien haver estat afectades per la variabilitat individual dels participants. Finalment, la naturalesa mateixa de les intervencions, tant en format *outdoor* com *online*, podria haver tingut un impacte diferencial sobre els símptomes objecte d'avaluació, ja que determinats components terapèutics podrien influir més en alguns aspectes de la FM que en altres.

Els efectes de la intervenció FIBROWALK sobre els biomarcadors sèrics van mostrar una modulació significativa de les citocines implicades en la resposta inflamatòria (**Taula 2**).

Taula 2. *Resum dels efectes de les intervencions sobre els biomarcadors*

Nivells de biomarcadors: IL-6, CXCL8 IL-17A hs-CRP IL-4 IL-10 BDNF	● FIBRO-Out superior a TH en: - **IL-6** (p=0.003; d= 0.24) - **IL-10** (p=0.025; d=0.30) ● FIBRO-On superior a TH en: - **IL-6** (p=0.045; d=0.08) ● Sense canvis significatius en: - **CXCL-8** - **IL-17A,** - **hs-CRP,** - **IL-4** - **BDNF**
Nivells d'índexs d'inflamació: IL-6/IL-4 IL-6/IL-10 CXCL8/IL-4 CXCL8/ IL-10 hs-CRP/IL-4 hs-CRP/IL-10 IL-17A/IL-4 IL-17A/IL-10	● FIBRO-Out superior a TH en: - **IL-6/IL-4** (p=0.028; d= -0.27) ● FIBRO-On superior a FIBRO-Out en: - **CXCL8/IL-4** (p=0.021; d=0.36)

Nota: No s'ha trobat cap comparació que sigui estadísticament significativa (p≦0,05). d: d de Cohen com a mesura de la mida de l'efecte; FIBRO-On, FIBROWALK *Online*; FIBRO-Out, FIBROWALK *Outdoor*;TH, tractament habitual; IL, Interleucina; hs-CRP, high-sensitivity C-reactive protein; BDNF, Brain-Derived Neurotrophic Factor.

Font: Elaboració pròpia.

En particular, en la nostra mostra a curt termini, es va observar una disminució significativa dels nivells d'IL-6 i IL-10 en el grup FIBRO-Out en comparació amb el TH, suggerint un efecte immunomodulador atribuïble a la intervenció. D'una banda, la disminució observada en els nivells d'IL-6 en el grup FIBRO-Out podria reflectir una reducció de l'estat proinflamatori crònic característic de la FM, en línia amb els estudis que assenyalen una disminució de citocines proinflamatòries després d'intervencions basades en exercici físic i abordatges multidisciplinaris (Sanada et al. 2015). Aquesta reducció podria contribuir a una menor activació del sistema immunitari i, en conseqüència, a una disminució dels símptomes relacionats amb la inflamació, com el dolor i la fatiga. D'altra banda, segons els resultats de Ringleb et al. (2023), l'exercici físic també pot estimular la producció transitoria d'IL-6 pels músculs esquelètics, la qual cosa afavoreix la síntesi d'IL-10 i altres citocines antiinflamatòries, com la IL-1ra. Això suggereix que la disminució d'IL-6 observada podria no implicar únicament una reducció de la inflamació, sinó també una menor activació d'aquests mecanismes compensatoris antiinflamatoris, fet que explicaria la reducció paral·lela d'IL-10 en el nostre estudi. A més, cal considerar que la IL-6 també participa en processos de neuroregeneració i modulació de la resposta immune (Maes et al. 2016; Raison et al. 2018). Per tant, és possible que la seva modulació mitjançant l'activitat física en el context del programa FIBROWALK hagi contribuït a processos de recuperació muscular i neuronal, encara que aquests efectes podrien no haver-se reflectit immediatament en millores clíniques evidents en tots els paràmetres avaluats. En conjunt, aquests factors suggereixen que la reducció d'IL-6 i IL-10 observada en la nostra mostra no es pot interpretar únicament com una disminució de la inflamació, sinó que respon probablement a una modulació

complexa del sistema immunològic i neuroinflamatori en pacients amb FM sotmesos a la intervenció FIBROWALK.

La IL-10, és una citocina amb una seva funció fonamentalment antiinflamatòria, regulant l'activitat de diverses cèl·lules immunitàries i modulant a la baixa la producció citocines proinflamatòries. Aquesta citocina té un paper essencial per mantenir l'equilibri immunitari a través del CIRS (Maes & Carvalho, 2018). Inesperadament, en el nostre estudi, hem observat una disminució en els nivells d'IL-10 en el grup FIBRO-Out en comparació amb el grup TH. És probable que la reducció observada en els nivells d'IL-10 respongui a un mecanisme de regulació associat a la disminució d'IL-6 o d'altres citocines proinflamatòries, atès que aquestes molècules actuen de manera interdependent en la modulació de la resposta immune. En aquest sentit, la IL-10 exerceix una funció antiinflamatòria compensatòria, sovint estimulada per l'increment de citocines proinflamatòries com la IL-6. Per tant, la reducció simultània d'ambdues interleucines podria reflectir una normalització de la resposta inflamatòria sistèmica en els participants sotmesos a la intervenció, més que no pas un efecte negatiu sobre els mecanismes antiinflamatoris. Aquest equilibri en la regulació de citocines suggereix que la intervenció FIBROWALK podria haver contribuït a una modulació més estable de la inflamació crònica característica de la FM. De fet, la metaanàlisi realitzada per Andrés-Rodríguez et al. (2019) va evidenciar un desajustament en la relació entre l'IRS i el CIRS, amb un augment d'IL-6, IL-4 i IL-17A i una disminució d'IL-10 en persones amb FM. suggerint que aquest desequilibri immunitari podria jugar un paper rellevant en la patofisiologia de la FM. Cal destacar, però, que les dades de la nostra recerca es van recollir de forma longitudinal, amb mesures pre i post intervenció, mentre que la metaanàlisi

realitzada per Andrés-Rodríguez et al. (2019) es va basar en dades obtingudes de manera transversal, analitzant el desajustament en la relació entre l'IRS i el CIRS en persones amb FM. Per tant, tot i que els nostres resultats longitudinals mostren una reducció dels nivells d'IL-6 i IL-10, aquest ajustament podria reflectir un intent de restablir l'equilibri immunitari en persones amb FM, de manera que els nostres resultats es podrien considerar una manifestació d'un procés compensatori dins d'un sistema immunitari dinàmic.

Pel que fa a la comparació entre el grup FIBRO-On i el TH es va observar un augment pre-post menys pronunciat en els nivells d'IL-6 en comparació amb el grup TH (que va presentar increments més notables). Aquesta troballa suggeriria un potencial efecte protector de la intervenció davant el perfil proinflamatori que tendiria a intensificar-se amb el temps, fenòmen que ja va ser descrit per Andrés-Rodríguez et al. (2020), qui van identificar una correlació positiva entre els nivells d'IL-6 i l'edat. Tot i que no es van identificar diferències significatives entre les branques del FIBROWALK pel que fa a la seva capacitat per induir canvis en els biomarcadors estudiats, sí que es va observar un efecte en la ràtio CXCL8/IL4, la qual indica el balanç pro/antiinflamatori. Cal destacar que el grup FIBRO-On va presentar una reducció més pronunciada en la ràtio CXCL8/IL-4 mentre que el grup FIBRO-Out va presentar un lleuger increment, suggerint que la intervenció en entorns naturals podria haver tingut un impacte diferencial en la regulació de les citocines. Aquestes troballes subratllen la necessitat d'una anàlisi longitudinal més àmplia per comprendre de manera més profunda la dinàmica inflamatòria en la FM. També suggereixen la importància d'incloure mesures repetides en futurs estudis per poder monitoritzar millor les variacions de les citocines al llarg del temps. A més, l'ús de mètodes menys invasius, com la recollida de mostres de

saliva (Rai et al. 2021), podria proporcionar una visió més precisa de l'evolució de la resposta inflamatòria en la FM.

Pel que fa als nivells de BDNF, no es van detectar canvis significatius en els nivells de BDNF dels participants de les intervencions FIBROWALK en comparació amb el TH. No obstant això, altres investigacions que han aplicat intervencions psicològiques però sense incorporar exercici físic (e.g. Montero-Marín et al. 2019; Sanabria-Mazo et al. 2020) han mostrat *reduccions* en aquest marcador. D'altra, existeix també una àmplia evidència que suggereix que l'exercici físic pot incrementar els nivells de BDNF (Nugraha et al. 2012; Ribeiro et al. 2021), de manera que els efectes d'una intervenció multicomponent com la FIBROWALK, que combina tant enfocaments psicoterapèutics (i.e. que podrien reduir els nivells de BDNF) com d'exercici, podrien no ser tan clars. Així, en el cas del programa multicomponent FIBROWALK podria haver-se donat certa "anul·lació" de l'efecte de la teràpia sobre aquest biomarcador donat l'efecte antagònic que potencialment podrien tenir els seus diferents components sobre la producció de BDNF. Com que els nivells de BDNF en la FM són més alts en comparació amb persones sanes (Haas et al. 2010; Montero-Marín et al. 2019), i aquests augments s'han relacionat amb la cronificació del dolor a causa del paper fonamental del BDNF en diversos processos de neuroplasticitat (Nugraha et al. 2012), les reduccions observades en estudis anteriors en la FM podrien indicar un efecte positiu de les intervencions. Els nivells de BDNF en la FM són més alts en comparació amb les persones sanes, fet que ha estat relacionat amb la cronicitat del dolor. Aquest augment dels nivells de BDNF pot jugar un paper fonamental en diversos processos de neuroplasticitat, incloent la sensibilització central, un mecanisme en què el sistema nerviós es torna més sensible als estímuls

dolorosos (Nugraha et al. 2012). Si una intervenció és capaç de reduir els nivells elevats de BDNF, podria ajudar a mitigar la sensibilització central i, per tant, contribuir a una millora en la percepció del dolor. Aquest tipus de modulació de la neuroplasticitat podria ser un mecanisme important a través del qual les teràpies basades en mindfulness, exercici físic o altres tractaments d'intervenció actuen de manera beneficiosa sobre la cronicitat del dolor en la FM (Di-Bonaventura et al. 2023). Així, la reducció de BDNF no només podria reflectir un canvi biològic cap a un perfil més saludable, sinó també una indicació d'una recuperació o modulació de la sensibilització central associada amb el dolor crònic (Xiong et al. 2024).

Cal tenir present que la FM és una condició crònica i complexa amb alta comorbiditat amb trastorns mentals com la depressió. En aquest context, alguns estudis han suggerit que la depressió pot estar relacionada amb nivells més *baixos* de BDNF (Cavaleri et al. 2023), contràriament als nivells més alts reportats en la FM, com hem mencionat anteriorment. Així, una possible diferència entre el nostre estudi i informes previs que han trobat reduccions significatives en els nivells de BDNF després d'intervencions psicoterapèutiques per a la FM (Montero-Marín et al. 2019; Sanabria-Mazo et al. 2020) podria ser que la nostra mostra, obtinguda d'una unitat de tractament especialitzada, presentava nivells més elevats de símptomes depressius (mitjanes de la mostra total: HADS-A: 13.06 i HADS-D:11.96) en comparació amb els participants d'un assaig clínic controlat aleatoritzat de Sanabria-Mazo et al. (2020) (mitjanes de la mostra total: HADS-A: 11.85 i HADS-D: 8.89), els quals provenien de serveis d'atenció primària. És important destacar que els valors basals de BDNF no són directament comparables amb els reportats en altres estudis, atès que en el present treball s'han emprat tests bioquímics amb una sensibilitat superior.

Aquesta major sensibilitat podria haver donat lloc a una disminució dels nivells basals de BDNF, fet que hauria dificultat la capacitat de la intervenció FIBROWALK per reduir-los encara més.

Cal tenir en compte que les anàlisis realitzades es basen en l'efecte de les intervencions sobre els nivells de marcadors en sèrum, no permeten una avaluació directa del possible efecte antiinflamatori a nivell del SNC. Aquesta limitació respon a la dificultat d'accés al líquid cefalorraquidi, per tant, els resultats obtinguts reflecteixen únicament un efecte indirecte (Bäckryd et al. 2017).

Totes les anàlisis anteriors es van realitzar seguint un enfocament d'intenció de tractament (ITT). Tanmateix, també es van dur a terme un anàlisis de sensibilitat seguint un enfocament per protocol (PP), incloent només els participants que van assistir al 75% de les sessions del FIBROWALK (a 9 o més sessions de les 12 programades). L'enfocament ITT permet avaluar l'efecte de l'assignació a una intervenció, mentre que l'anàlisi PP investiga l'efecte de rebre la intervenció assignada en una dosi òptima. Un dels principals resultats de l'anàlisi va ser l'augment de la ràtio IL-17A/IL-4 observat en el grup FIBRO-Out, en comparació amb el grup FIBRO-On, suggerint un desplaçament cap a un estat proinflamatori en el grup que va realitzar l'activitat a l'aire lliure. Aquest canvi podria reflectir una activació inflamatòria inicial, que, tot i ser proinflamatòria, podria ser beneficiosa per mobilitzar mecanismes de reparació i adaptació immunològica (Miossec & Kolls, 2012). Concretament, l'augment de la IL-17A, associada a la inflamació crònica, juntament amb una possible disminució de la IL-4, una citocina antiinflamatòria, suggereixen una resposta immune activa induïda per l'activitat física moderada, l'exposició a entorns naturals i l'interacció social, factors que poden estimular la producció d'IL-17A (Slavich & Irwin, 2014).

En canvi, el grup FIBRO-On va mostrar una reducció de la ràtio IL-17A/IL-4 en l'anàlisi PP, indicant que la modalitat *online* va tendir a reduir la inflamació en les persones amb FM adherides estrictament al tractament, potser per l'absència d'exposició a l'entorn natural i l'exercici exterior. Aquesta diferència podria reflectir una resposta inflamatòria adaptativa, on el sistema immune ajusta la seva activitat davant de factors externs, com l'exercici físic i l'exposició a la natura, per mantenir l'homeòstasi i promoure la salut (Maes & Carvalho, 2018). Aquesta modulació immunitària, en què es redueix l'activació proinflamatòria i es millora la regulació antiinflamatòria, podria ser crucial per a la gestió del dolor crònic en la FM. Diversos estudis han demostrat que l'activitat física en entorns naturals pot influir positivament en la regulació immunitària, amb efectes com la reducció de la inflamació sistèmica i la potenciació de la funció antiinflamatòria (Gleeson et al. 2011; Zhang et al. 2022). Aquests efectes beneficiosos poden ser atribuïts a múltiples mecanismes interrelacionats. L'exercici a l'aire lliure no només contribueix a millorar la salut física a través de la creació de condicions antiinflamatòries, sino que també incrementa la producció de citocines antiinflamatòries, com la IL-10, que modula la resposta immune i inhibeix la inflamació excessiva (Zhang et al. 2022). A més, l'activitat física regular ajuda a controlar el pes corporal i la composició corporal, factors que són determinants en la inflamació sistèmica, atès que el teixit adipós visceral està associat amb l'alliberament de mediadors proinflamatoris. Així, és fonamental considerar no només la quantitat i la intensitat de l'activitat física, sinó també el context en què aquesta es realitza (Gleeson et al. 2011). Així, els nostres resultats suggereixen que l'exposició a entorns naturals i l'activitat física adaptada del FIBRO-Out podria afavorir una reestructuració adaptativa de les respostes inflamatòries, creant un

entorn biològic més favorable per al control del dolor crònic i la simptomatologia associada a la FM.

Al fer l'anàlisi de sensibilitat PP es van identificar efectes significatius de les intervencions en altres biomarcadors. Tot i que es va notar una tendència cap a la significació en la modulació d'IL-4 en l'ITT, l'anàlisi PP va revelar una diferència significativa entre FIBRO-On i FIBRO-Out. Això suggereix que els efectes antiinflamatoris de la intervenció FIBRO-On sobre els nivells d'IL-4 serien més pronunciats en aquelles persones més adherents al programa. Per altra banda, els nivells d'IL-4 es reduirien lleugerament en els participants més adherents del grup FIBRO-Out, fet que podria indicar una modulació parcialment proinflamatòria en aquest grup *outdoor.* En les anàlisis ITT i PP, la reducció d'IL-6 va ser significativa (vs TH) en el braç FIBRO-Out, mentre que en el braç FIBRO-On es va observar una atenuació en l'increment, però no una reducció, confirmant el potencial de l'enfocament *outdoor* per reduir aquest element principal en la inflamació sistèmica. Pel que fa a la citocina IL-10, les reduccions observades van ser significatives en l'anàlisi ITT per al grup FIBRO-Out, mentre que en l'anàlisi PP la significació va ser marginal (p=0,051). Aquesta discrepància suggereix que la disminució d'IL-10 podria ser un efecte general del programa FIBRO-Out, independent del grau d'adherència al tractament. Tot i que la reducció d'IL-10 implica una disminució d'un mediador immunitari amb funcions antiinflamatòries, això no implicaria necessàriament que es doni un efecte proinflamatori global en el grup *outdoor*. No obstant això, diverses evidències apunten cap a una certa tendència a una resposta proinflamatòria en el grup FIBRO-Out, malgrat la reducció en IL-6 i la disminució de la ràtio IL-6/IL-4. Aquesta hipòtesi es veu reforçada per l'increment observat en les ràtios IL-17/IL-4 i CXCL8/IL-4, així com

per les reduccions en IL-4 i IL-10. És rellevant considerar que la IL-6 pot tenir també un paper antiinflamatori en determinats contextos (Andrés-Rodríguez et al. 2020; Bäckryd et al. 2017; Maes & Carvalho, 2018; Prather et al.2007), això suggereix que, tot i la disminució de la IL-6, la resposta global podria estar més inclinada cap a un perfil proinflamatori que no pas antiinflamatori. Aquest fet no implica necessàriament una conseqüència negativa, ja que la resposta inflamatòria pot estar vinculada a l'exercici físic realitzat pels individus del grup FIBRO-Out, que probablement van dur a terme una activitat d'intensitat superior en comparació amb els del grup FIBRO-On. L'evidència científica actual suggereix que la inflamació no sempre és perjudicial per a la recuperació postexercici. De fet, cada cop hi ha més consens en el fet que una resposta inflamatòria ben regulada és fonamental per a la reparació i regeneració muscular. Així, tot i que històricament s'ha considerat que la inflamació podia ser un factor negatiu en la recuperació de l'exercici, estudis recents indiquen que una resposta inflamatòria controlada juga un paper clau en la regeneració dels teixits musculars (Peake et al. 2017). Per tant, els resultats observats en el grup FIBRO-Out podrien ser interpretats com una adaptació fisiològica beneficiosa en resposta a l'exercici realitzat. És possible que altres mecanismes o citocines compensin aquesta disminució, mantenint l'equilibri de la resposta immune. La reducció d'IL-6 observada en el grup FIBRO-Out podria estar associada de manera paral·lela a la reducció de IL-10, ja que aquestes dues citocines estan relacionades entre si en el context de la resposta immune. Aquestes dues citocines tenen una interacció creuada, és a dir, el nivell d'una pot influir en el de l'altra. Així, la reducció simultània d'IL-6 i IL-10 podria reflectir un canvi en l'equilibri de la resposta

immune cap a una situació més equilibrada o modulada, amb un efecte més controlat sobre la inflamació (Andrés-Rodríguez et al. 2020).

A més, la mida de l'efecte va ser més gran en l'anàlisi PP en comparació amb l'ITT (d=0,39 vs. d=0,30), la qual cosa podria indicar que l'estudi no tenia prou potència estadística (degut a una N reduïda) per detectar un canvi estadísticament significatiu en la reducció de la IL-10 en els participants que van seguir estrictament el protocol.

Finalment, la ràtio IL-6/IL-4 va mostrar una reducció significativa en FIBRO-Out en ITT, però no va ser significativa en PP. Aquesta diferència suggereix que la reducció de la inflamació pot ser més evident en la població general de tractament, però no necessàriament més forta entre les persones amb FM adherents. Això podria implicar que fins i tot les persones amb FM que no compleixen completament el programa encara podrien experimentar una modulació de perfil de les respostes inflamatòries després del tractament. Aquesta falta de significació també podria dependre de la manca de suficient poder estadístic relacionat amb la mida limitada de la mostra (de fet, les mides d'efecte per a aquesta diferència en les anàlisis ITT i PP eren equivalents d= 0.27). Es necessiten més assaigs amb major potència estadística per confirmar si algunes tendències identificades en les ràtios CXCL8/IL-10, hsCRP/IL-4 i hsCRP/IL-10, que indiquen un efecte proinflamatori a curt termini de FIBRO-Out, poden ser confirmades o no. En resum, les diferències observades entre els enfocaments ITT i PP (**Taula 3**) suggereixen que l'adherència al tractament tindria un paper important en els efectes immunoinflamatoris vinculats al FIBROWALK, amb una modulació immunoinflamatòria més pronunciada en les persones que complirien millor el protocol, especialment en el grup *outdoor*.

Taula 3. *Taula resum comparativa dels resultats estadísticament significatius segons ITT i PP*

Variable	ITT (p; d)	PP (p; d)	Comparació
FIQR (F-On vs TH)	0.044; 0.43 (↓)	0.010; 0.50 (↓)	Similars en ambdós enfocaments.
VAS-Pain (F-Out vs TH)	0.019; 0.63 (↓)	0.025; 0.69 (↓)	Similars en ambdós enfocaments.
VAS-Fatigue (F-On vs TH)	0.061; 0.52 (tendència)	0.030; 0.61 (↓)	PP confirma parcialment ITT.
HADS-D (F-Out vs TH)	0.005; 0.65 (↓)	0.005; 0.69 (↓)	Similars en ambdós enfocaments.
TSK-11 (F-On vs TH)	<0.001; 0.84 (↓)	<0.001; 0.87 (↓)	Similars en ambdós enfocaments.
IL-4 (F-On vs F-Out)	0.052; 0.16 (↑F-On / ↓F-Out)	0.011; 0.36 (↑F-On / ↓F-Out)	Similars en ambdós enfocaments.
IL-6 (F-Out vs TH)	0.003; 0.24 (↓)	0.016; 0.30 (↓)	Similars en ambdós enfocaments.
IL-10 (F-Out vs TH)	0.025; 0.30 (↓)	0.051; 0.39 (↓)	PP confirma parcialment ITT.

Ràtio IL-6/IL-4 (F-Out vs TH)	0.028; -0.27 (↓)	No significatiu	ITT mostra reducció, PP no confirma.
Ràtio CXCL8/IL-4 (F-On vs F-Out)	0.021; 0.36 (↓F-On / ↑F-Out)	0.003; 0.62 (↓F-On / ↑F-Out)	Similars en ambdós enfocaments.
Ràtio CXCL8/IL-10 (F-Out vs TH)	0.091; 0.26 (↑)	No significatiu	PP no confirma ITT.
Ràtio hs-CRP/IL-4 (F-On vs F-Out)	No significatiu	0.091; 0.26 (↓F-On / ↑F-Out)	PP no confirma ITT.
Ràtio hs-CRP/IL-10 (F-Out vs TH)	0.078; 0.20 (↑)	0.073; 0.26 (↑)	Similars en ambdós enfocaments.
Ràtio IL-17A/IL-4 (F-On vs F-Out)	No significatiu	0.048; 0.39 (↓F-On / ↑F-Out)	PP no confirma ITT.

Nota: només es mostren efectes estadísticament significatius ($p \leq 0,05$) o que mostren una tendència a la significació ($0,05 < p \leq 0,10$). ITT, intenció de tractar; PP, per protocol; d , d de Cohen com a mesura de la mida de l'efecte; ↑: Augment / ↓: ReduccióF-On, FIBROWALK Online; F-Out, FIBROWALK Exterior; TAU, tractament habitual; FIQR, Qüestionari d'impacte de la fibromiàlgia revisat; VAS-Fatiga, escala visual-analògica d'energia/fatiga percebuda; VAS-Pain, escala visual-analògica del dolor percebut; HADS-D, Escala d'ansietat i depressió hospitalària; TSK-11, Escala de Tampa per a Kinesiofòbia; hs-CRP, proteïna C reactiva d'alta sensibilitat.

Font: Elaboració pròpia.

Malgrat les tècniques d'anàlisi bioquímic tenien una sensibilitat més elevada que altres estudis de referència (Montero-Marin et al. 2019), un altre factor que podria haver influït en els resultats és el percentatge de casos amb valors per sota del llindar de detecció de la prova bioquímica utilitzada per valorar els nivells sèrics dels biomarcadors avaluats. Aquesta limitació metodològica podria haver dificultat la identificació precisa dels canvis en els nivells de citocines després de la intervenció, especialment en les citocines IL-10 (38,1%) i IL-6 (31,4%), que presentaven un percentatge més elevat de casos amb valors per sota del llindar de detecció. També es van observar percentatges menors en IL-4 (16,2%) i hs-CRP (1,9%), mentre que CXCL8: 1%, IL-17A: 1% i BDNF: 0% van mostrar valors mínims o inexistents per sota d'aquest llindar. Aquesta limitació metodològica podria haver dificultat la identificació precisa dels canvis en els nivells de citocines després de la intervenció, especialment en les citocines IL-6, IL-4 i IL-10, que presentarien un percentatge més elevat de casos amb valors per sota del llindar de detecció. Per aquest motiu, futurs estudis haurien de considerar l'ús de tècniques d'anàlisi bioquímica més sensibles i/o l'aplicació de procediments que permetin incrementar temporalment els nivells d'aquestes molècules, com per exemple, la seva inducció controlada en cèl·lules immunitàries (Rai et al. 2021).

En aquest sentit, les metodologies òmiques, i en particular els estudis transcriptòmics, poden aportar informació rellevant sobre els mecanismes moleculars implicats en la FM (Maes et al. 2016). Aquests estudis analitzen els nivells d'expressió gènica a través de l'ARN missatger (mRNA), cosa que permet identificar canvis en les vies de senyalització associades a la regulació de citocines pro i antiinflamatòries (Sanada et al. 2015), oferint així una perspectiva més completa de la resposta biològica a les intervencions terapèutiques.

2. Valor predictiu de les variables inmunoinflamatòries en fibromiàlgia

Diferents estudis han demostrat que les alteracions en els nivells de citocines, com IL-6, IL-10 i la relació entre marcadors proinflamatoris i antiinflamatoris, poden influir significativament en l'estat clínic de les persones amb FM (Andrés-Rodríguez et al. 2019; Sanada et al. 2015). En l'estudi d'Andrés-Rodríguez et al. (2019), es va observar que els nivells de citocines immunoinflamatòries poden actuar com a predictors de la resposta al MBSR en persones amb FM. En particular, es va identificar una associació entre nivells elevats de CXCL8 i una menor millora clínica, així com una relació entre ràtios elevades de citocines proinflamatòries en relació amb IL-10 i una resposta terapèutica menys favorable. Aquests resultats van suggerir que aquests biomarcadors podrien contribuir a la personalització de les intervencions terapèutiques, permetent una millor monitorització i ajust del tractament segons les necessitats individuals. En l'estudi pilot de Lasselin et al. (2016), es va aportar evidència sobre el valor predictiu de les variables immunoinflamatòries en el dolor crònic, indicant que l'estat inflamatori basal va poder influir en l'eficàcia del tractament conductual per al dolor. Es va observar que nivells elevats de TNF-α i IL-6 abans del tractament es van associar amb una menor millora en la intensitat del dolor, la inflexibilitat psicològica i la qualitat de vida relacionada amb la salut mental. En canvi, els pacients amb nivells baixos d'aquestes citocines proinflamatòries van mostrar millores més significatives. Aquests resultats van suggerir que la inflamació de baix grau podia actuar com un moderador de la resposta terapèutica, explicant en part la variabilitat en l'eficàcia dels tractaments per al dolor crònic.

En el context de la intervenció FIBROWALK, els resultats obtinguts indiquen que els nivells basals d'aquests biomarcadors no només serien indicatius de l'estat inflamatori dels participants, sinó que també podrien ser útils per predir la seva resposta clínica a la intervenció. Això reforça la rellevància del tractament de precisió (Carvalho et al. 2019), ja que la identificació d'aquests marcadors podria facilitar la personalització de les estratègies terapèutiques, optimitzant-ne l'eficàcia segons les característiques individuals de cada pacient. A més, investigacions anteriors han proposat que la integració de biomarcadors immunoinflamatoris en protocols de tractament podria permetre una personalització dels plans de tractament, millorant així l'eficiència dels serveis sanitaris. En concret, Carvalho et al. (2019) i Lopresti (2017) subratllen la importància de considerar factors immunoinflamatoris a l'hora de considerar determinats tractaments per a la FM. Estudis com el de Montero-Marin et al. (2019) també recolzen la idea que l'avaluació dels biomarcadors immunoinflamatoris pot proporcionar una comprensió més profunda sobre les respostes a tractaments no farmacològics com FIBROWALK, fet que pot ajudar a identificar perfils de persones amb FM que respondran millor a determinades intervencions com per exemple les diferents modalitats del FIBROWALK.

Aquesta evidència destaca la rellevància de continuar investigant la interacció entre els biomarcadors immunoinflamatoris i les intervencions terapèutiques per desenvolupar estratègies adaptades a les necessitats específiques de les persones amb FM.

Tant en el format *outdoor* com *online* del FIBROWALK, els participants amb un perfil basal proinflamatori més pronunciat van experimentar millores clíniques més destacades després de la intervenció (**Taula 4**).

Taula 4. *Anàlisi de predicció de canvis clínics a partir dels nivells basals de biomarcadors sèrics*

Grup FIBRO-Out	● Nivells elevats abans del tractament de **BDNF** millora en: - **HADS-A** (R2=0.142; β=-0.376; t=-2.261; p=0.031) ● Nivells elevats abans del tractament de **hs-CRP y BDNF** millora en: - **TSK-11** (R2=0.274; β=-0.360,-0.348; t=-2.304, -2.224; p=0.028, 0.034, respectivament)
Grup FIBRO-On	● Nivells elevats abans del tractament de **IL-4** empitjorament en: - **FIQR** (R2=0.141; β=0.376; t=2.219; p=0.034) ● Nivells elevats abans del tractament de l'índex **CXCL8/IL-10** millora en: - **VAS-Pain** (R2=0.194; β=-0.440; t=-2.687; p=0.012) - **VAS-Fatigue** (R2=0.127; β=-0.356; t=-2.085 p=0.046) ● Nivells elevats abans del tractament de **BDNF** millora en: - **SF-36** (R2=0.156; β=0.395; t=2.353; p=0.025)

Nota: No s'ha trobat cap comparació que sigui estadísticament significativa (p≦0,05). R^2, coeficient de determinació; □, coeficient estandaritzat de la regressió; t, de la prova t; FIBRO-On, FIBROWALK *Online*; FIBRO-Out, FIBROWALK *Outdoor*; FIQR, Revised Fibromyalgia Impact Questionnaire; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain.HADS-A and HADS-D, Hospital Anxiety and Depression Scale; SF-36, Physical function subscale of the Short Form-36 Health Survey; TSK-11, Tampa Scale for Kinesiophobia; IL, Interleucina; hs-CRP, high-sensitivity C-reactive protein; BDNF, Brain-Derived Neurotrophic Factor.

Font: Elaboració pròpia.

Concretament, en el grup FIBRO-Out es va observar que valors més elevats d'hs-CRP abans del tractament estaven associats amb una millora en la kinesiofòbia. Pel que fa al grup FIBRO-On, nivells més alts d'IL-4 es van relacionar amb menors millores en l'impacte funcional, mentre que nivells més alts de l'índex CXCL8/IL-10 es van correlacionar amb millores en el dolor i la fatiga. Atès que la IL-4 és un regulador important de la immunitat humoral i adaptativa, els resultats suggereixen que aquells participants amb un CIRS basal més alt podrien experimentar menys millores en l'impacte funcional després del programa FIBRO-On. Així, els nivells elevats d'IL-4 poden representar un estat immune que no seria adequat per facilitar la resposta terapèutica efectiva al tractament. En aquest sentit, la relació observada entre una pitjor evolució de l'impacte funcional i la resposta immunitària podria indicar que aquesta no ajuda a una recuperació clínica adequada després del tractament, tal com apunten altres estudis (Häuser et al. 2015). Les persones amb FM i nivells alts d'IL-4 podrien tenir menys millores en l'impacte funcional, ja que una resposta immune més elevada podria dificultar l'eficàcia de les teràpies convencionals, així com de l'exercici i la mindfulness inclosos en el programa FIBRO-On. És important tenir en compte que, en lloc de la resposta immunitària, podria ser una altra variable, com el nivell d'activitat física de base, qui realment predigui la resposta clínica. Les persones amb un nivell més alt d'activitat física podrien tenir una percepció més positiva de la intervenció i implicar-se més en la teràpia. Aquesta variable també podria estar relacionada amb els nivells de citoquines basals, ja que l'exercici pot augmentar la inflamació. Per tant, cal mantenir la prudència quan parlem d'associacions, reconeixent que aquestes poden ser indirectes i influïdes per altres factors, en lloc de ser directament causals. Això suggereix que les persones amb FM podrien necessitar

una estratègia terapèutica adaptada a les seves característiques immunològiques per aconseguir millores més significatives. De manera similar, la metaanàlisi realitzada per Andrés-Rodríguez et al. (2020) va mostrar que els nivells d'IL-4, IL-6 i IL-17A eren significativament més alts en persones amb FM en comparació amb controls sans. Això suggereix una alteració de l'homeòstasi immunològica, implicant tant vies immunoinflamatòries com també compensatòries augmentades. En particular, l'estudi assenyala que l'augment d'aquests citocines podria ser un reflex de la resposta immune alterada en individus amb FM. Tanmateix, cal destacar que altres estudis que han avaluat els efectes de teràpies cognitivoconductuals o basades en mindfulness per a la FM, com els d'Andrés-Rodríguez et al. (2019) i Lasselin et al. (2016), han obtingut resultats contraris. Aquests treballs suggereixen que nivells basals indicatius d'un estat més proinflamatori s'associen, de fet, a una menor millora de les variables clíniques després de la intervenció. En aquest sentit, s'ha identificat que nivells basals més alts de CXCL8 reduïen l'efecte positiu d'una intervenció en MBSR sobre la simptomatologia clínica, incloent dolor, energia, rigidesa i qualitat del son, suggerint que la inflamació basal podria limitar la resposta clínica després d'aquest tractament específic (Andrés-Rodríguez et al. 2019). De manera similar, nivells més alts d'IL-6 i TNF-α abans del tractament es van trobar associats a una menor millora en la intensitat del dolor i la inflexibilitat psicològica en participants que rebien tractament conductual per al dolor (Lasselin et al. 2016). Si bé és cert que les diferències entre les mostres de l'estudi de Lasselin et al. (2016) i les del nostre no són menors i tenen implicacions rellevants a l'hora d'interpretar els resultats, cal destacar que la nostra intervenció, a diferència de les esmentades, inclou exercici físic. Aquest component podria ser un element clau per explicar els

resultats tan diferents obtinguts en el nostre estudi, ja que, tot i que altres investigacions han inclòs part dels components del FIBROWALK (com mindfulness i teràpia cognitivoconductual), no han integrat l'exercici físic de manera tan destacada. Això podria contribuir a una millora més significativa de les variables clíniques en el nostre cas. D'altra banda, la mostra de Lasselin et al. (2016) es va centrar en el dolor crònic de diversa etiologia, mentre que la nostra es va dirigir a una població específica amb FM. Aquesta distinció pot explicar variacions en la resposta a les intervencions aplicades, ja que la FM presenta característiques patofisiològiques particulars. Tot plegat posa de manifest la importància d'adaptar les intervencions a les característiques particulars de cada població clínica i la necessitat de considerar aquests aspectes en futurs estudis.

Atès que les millores clíniques més significatives després d'enfocaments multicomponent sovint es produeixen en individus amb un estat clínic inicial més greu (Worrel et al., 2001), i que la IL-6 i la CXCL8 han mostrat una correlació positiva amb la gravetat dels símptomes de FM (Andrés-Rodríguez et al., 2019), una possible explicació d'aquests resultats és que les persones amb un perfil clínic més sever abans de la intervenció, juntament amb un estat proinflamatori més pronunciat (**Annex 5**), podrien experimentar millores més grans després d'intervencions multicomponent. Segons Worrel et al. (2001), aquells amb un estat inicial més greu poden mostrar millores més notables, probablement degut a la seva major necessitat de millora i la seva capacitat d'adaptació al tractament. Aquesta adaptabilitat podria fer que percebin la intervenció com a més efectiva, ja que el contrast entre l'estat inicial i les millores obtingudes és més pronunciat, generant una resposta positiva més gran. A més, la correlació positiva entre citocines proinflamatòries com la IL-6 i el CXCL8 amb la gravetat dels símptomes,

com indica l'estudi d'Andrés-Rodríguez et al. (2019), suggereix que un estat proinflamatori més marcat podria influir no només en la intensitat del dolor, sinó també en la capacitat de resposta als tractaments. Una explicació d'aquesta dinàmica podria ser que els pacients amb un perfil clínic més greu tenen una necessitat més alta de millora, la qual cosa podria fer que qualsevol intervenció que redueixi l'estat proinflamatori i millori el benestar general sigui percebuda com a més eficaç. Així, es podria generar un efecte de "reacció al canvi", on les millores es fan més evidents en aquells amb un estat clínic més desafavorit. Això coincideix amb l'argument que les teràpies que aborden tant els aspectes físics com emocionals del dolor crònic poden ser especialment efectives en pacients amb un estat de salut més greu.

En el procés de les anàlisis de regressió, es van introduir diverses variables clíniques (edat, IMB, ús d'antidepressius, índex de sensibilitat central (ISPS) i comorbiditats, com la SFC, la depressió i l'ansietat) com a primer pas mitjançant un mètode *stepwise*. No obstant això, aquestes variables van ser excloses del model final per la seva falta de capacitat predictiva. A més, les diferències entre la mostra del segon estudi, amb participants amb un perfil clínic més deteriorat, comorbiditats, tractament farmacològic o anys de FM, i els participants dels estudis d'Andrés-Rodríguez et al. (2019) i Lasselin et al. (2016) podrien explicar les divergències en els resultats de les anàlisis de regressió.

Finalment, aquest segon estudi ha aportat descobertes rellevants sobre el valor predictiu dels nivells de BDNF abans de l'inici del tractament. En particular, nivells més elevats de BDNF en el grup FIBRO-Out es van associar amb millores significatives en els símptomes d'ansietat i en la kinesiofòbia. Aquests resultats suggereixen que BDNF podria actuar com un biomarcador predictiu per identificar

aquells individus amb una major probabilitat de respondre favorablement a la intervenció FIBRO-Out, especialment en la gestió de l'ansietat i la reducció de la por al moviment. Tanmateix, cal considerar que en persones amb una inflamació sistèmica elevada o amb una major sensibilització central, un augment de BDNF podria no ser beneficiós i fins i tot agreujar alguns símptomes. D'altra banda, en el grup FIBRO-On, nivells més alts de BDNF abans del tractament es van associar amb millores més destacades en la funció física, fet que indica un possible paper modulador d'aquest factor en la capacitat de resposta a la intervenció. El paper essencial del BDNF en la neuroplasticitat i l'aprenentatge (Colucci-D'Amato et al. 2020) podria explicar aquesta observació. El BDNF podria modular tant processos no adaptatius, com els que contribueixen a la sensibilització central (Xiong et al. 2024), com processos adaptatius, relacionats amb intervencions terapèutiques. En aquest sentit, les intervencions podrien ser més eficaces en individus amb nivells més alts de BDNF. En aquest sentit, la neuroplasticitat relacionada amb l'augment de BDNF podria ser un dels mecanismes responsables de l'intensificació i cronificació del dolor en la FM. La sensibilització central implica una modificació en la manera en què el cervell processa les senyals doloroses, de manera que petites o normals percepcions de dolor poden ser amplificades, contribuint a la percepció persistent i exagerada del dolor (Xiong et al. 2024). Aquestes troballes ressalten el potencial del BDNF com a biomarcador predictiu, suggerint que els seus nivells podrien ajudar a personalitzar els enfocaments de tractament per a cada persona amb FM, millorant l'efectivitat de les intervencions FIBROWALK per a la FM.

La personalització dels tractaments en funció del perfil immunològic de les persones amb FM podria millorar significativament l'efectivitat terapèutica i reduir

els efectes adversos associats als tractaments estàndard. Els resultats obtinguts suggereixen que una estratificació dels persones amb FM segons les seves respostes immunitàries permetria adaptar els tractaments a les característiques individuals de cada persona amb FM. Així, la identificació de biomarcadors predictius de resposta clínica als tractaments utilitzats, com les citocines IL-4, TNF-α i IL-6, podria ajudar a preveure quines persones amb FM respondran millor a determinades teràpies, optimitzant l'elecció dels tractaments i minimitzant l'exposició a aquells que podrien ser ineficaços o perjudicials. A l'àmbit clínic, aquesta personalització permetria ajustar protocols terapèutics, incloent-hi l'ús de teràpies farmacològiques, exercici físic, psicoteràpia ot teràpies multicomponent com el FIBROWALK , així com la introducció de noves estratègies, com les immunoteràpies dirigides. En definitiva, aquesta aproximació obre el camí cap a una medicina més individualitzada, millorant l'efectivitat del tractament i permetent una assignació més eficient de recursos sanitaris.

3. Limitacions i fortaleses

Aquesta tesi doctoral presenta un disseny metodològic sòlid, iniciant-se amb un estudi de protocol que proporciona una guia detallada per garantir que la recerca posterior es dugui a terme de manera organitzada i consistent, facilitant així la seva replicabilitat i fiabilitat. El segon estudi, és el primer en examinar l'impacte del programa multicomponent FIBROWALK en formats *online* i *outdoor* sobre la simptomatologia clínica, els marcadors immunoinflamatoris en sèrum i els nivells de BDNF, així com el valor predictiu de les vies immunoinflamatòries basals en la resposta clínica a la intervenció.

Malgrat aquestes fortaleses i el fet que l'estudi ha seguit un alt rigor metodològic, tal com s'evidencia a **l'Annex 6**, és important tenir en compte diverses limitacions que poden condicionar la interpretació i l'aplicabilitat dels resultats. En primer lloc, la mida de la mostra era relativament petita, la qual cosa ha limitat el poder estadístic de l'estudi. En segon lloc, es van observar diferències en l'adherència entre els grups d'intervenció, amb una taxa d'adherència més elevada en el grup FIBRO-On (91%) en comparació amb el grup FIBRO-Out (78%). Tot i que es van realitzar anàlisis de sensibilitat per avaluar l'impacte d'aquestes diferències, la diferent taxa d'adherència podria haver influït en els resultats obtinguts. Seria interessant comparar aquestes taxes d'adhesió amb altres estudis similars per contextualitzar-ne la rellevància i millorar futures estratègies de retenció de participants.

Un altre aspecte metodològic a tenir en compte és la manca d'emmascarament dels participants en l'estudi, fet que podria haver introduït un biaix en la interpretació dels resultats. Tot i que la naturalesa de les intervencions impedeix un emmascarament total, ja que és inevitable que els participants coneguin si reben una teràpia activa o formen part del grup de TH, es van implementar diverses estratègies per minimitzar aquest efecte. En particular, es va comptar amb avaluadors independents per a la recollida de dades i es van incloure mesures objectives, com biomarcadors, per reduir la subjectivitat en l'avaluació dels resultats. També cal destacar que l'avaluació dels nivells de biomarcadors es va basar exclusivament en mostres de sèrum, oferint només una visió parcial dels efectes de les intervencions sobre l'estat inflamatori global en la FM. A més, el panell de marcadors estudiat es va veure condicionat per restriccions pressupostàries, limitant el nombre de marcadors analitzats i excloent

altres mètodes, com l'anàlisi cel·lular, saliva o líquid cefalorraquidi, que podrien proporcionar una perspectiva més completa dels processos biològics subjacents. En futurs estudis, seria recomanable ampliar aquest enfocament per aprofundir en la comprensió dels mecanismes implicats en la resposta a la intervenció.

Pel que fa a l'aplicabilitat dels resultats, l'entorn de l'estudi, realitzat en una unitat especialitzada, podria limitar la seva transferibilitat a altres nivells assistencials. La replicació de l'estudi en atenció primària o altres contextos sanitaris és necessària per validar-ne la seva generalització. A més existeixen dades preliminars que apunten a la viabilitat econòmica de les intervencions en formats *online* i *outdoor*, la qual cosa podria facilitar la seva integració en el sistema sanitari públic. No obstant això, es requereixen anàlisis més exhaustives per establir-ne la relació cost-efectivitat i valorar-ne la implementació a llarg termini. En aquest sentit, l'estudi On&Out inclou tant l'avaluació de l'efectivitat d'aquestes intervencions en una mostra més àmplia i en un període prolongat com l'anàlisi de cost-efectivitat. Els resultats obtinguts permetran determinar amb més precisió la idoneïtat dels diferents formats del programa FIBROWALK per a la seva incorporació en el sistema públic de salut.

En resum, malgrat les limitacions esmentades, aquesta tesi aporta dades valuoses sobre l'efectivitat a curt termini del format online i outdoor de la teràpia multicomponent FiBROWALK en el maneig de la FM així com el seu efecte en marcadors immune-inflamatoris amb evidència d'alteració en FM. Tot i els resultats prometedors, és imprescindible continuar investigant mitjançant estudis metodològicament més rigorosos, amb mostres més extenses i seguiments a mig i llarg termini per validar la consistència i el manteniment de les millores clíniques observades. Aquests futurs estudis han de tenir en compte aspectes metodològics

fonamentals, com la replicabilitat en diferents entorns assistencials, per tal de millorar la robustesa de les conclusions i la seva aplicabilitat en el sistema sanitari públic.

CAPÍTOL 5.

Conclusions

Considerant els objectius i les hipòtesis formulades, les conclusions d'aquesta tesi doctoral són les següents:

1. Mitjançant un article de protocol es va presentar de manera detallada el disseny, els components i la metodologia del protocol de l'estudi On&Out, tant en format *online* (FIBRO-On) com *outdoor* (FIBRO-Out), incloent-hi els fonaments teòrics i pràctics que en justifiquen el seu estudi i potencial implementació en el nostre sistema sanitari, establint així la base necessària per avaluar els efectes de la intervenció sobre les variables clíniques i biomarcadors estudiats en la present tesi (**Estudi 1**)**.**

2. Les intervencions FIBROWALK, tant en el seu format *online* com *outdoor*, han demostrat ser efectives per a millorar la simptomatologia de persones amb FM en comparació amb el TH. Ambdues modalitats del tractament FIBROWALK van contribuir a una reducció rellevant de l'impacte funcional i de la kinesiofòbia, afavorint una millora en el desenvolupament de les activitats quotidianes dels participants. Cal destacar que la intervenció FIBRO-Out, en la present mostra,va mostrar beneficis addicionals, amb reduccions també en dolor, fatiga i simptomatologia depressiva en comparació al TH (**Estudi 2**).

3. Les intervencions també van produir efectesen part dels biomarcadors immunoinflamatoris estudiats i ràtios associades. El grup FIBRO-Out, en comparació amb el TH, va mostrar disminucions en els nivells sèrics d'IL-6, mentre que el grup FIBRO-On va mostrar un augment menys pronunciat d'aquest biomarcador en comparació amb el TH. A més, el grup FIBRO-Out va presentar una reducció significativa tant en els nivells d'IL-10

com en l'índex IL-6/IL-4 en comparació amb el TH. Paral·lelament, el grup FIBRO-On va mostrar una disminució de l'índex CXCL8/IL-4 en comparació amb el grup FIBRO-Out.(**Estudi 2**).

4. Els nivells basals de determinats biomarcadors van associar-se amb la resposta clínica observada després de les intervencions FIBROWALK. En el grup FIBRO-Out, nivells elevats de BDNF van predir millores més destacades en ansietat i kinesiofòbia, mentre que nivells més alts d'hs-CRP van associar-se amb millors respostes en kinesiofòbia. En el grup FIBRO-On, nivells elevats d'IL-4 es van relacionar amb una menor millora en l'impacte funcional, mentre que nivells més alts de BDNF es van associar amb millores més remarcables en la funció física. Finalment, es va observar que una ràtio més elevada de CXCL8/IL-10 s'associaria amb majors millores en dolor i fatiga (**Estudi 2**).

5. Els resultats obtinguts subratllen la potencial utilitat d'incorporar la determinació de biomarcadors immunoinflamatoris i nivells de BDNF en sèrum en la pràctica clínica, ja que podrien contribuir a la personalització dels plans de tractament, optimitzant així l'efectivitat i eficiència de les intervencions terapèutiques existents en persones amb FM (**Estudi 2**).

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Annex 1

Material suplementari electrònic dels estudis publicats

Estudi 2

Ferrés, S., Serrat, M., Auer, W., Royuela-Colomer, E., Almirall, M., Lizama-Lefno, A., Nijs, J., Maes, M., Luciano, J. V., Borràs, X., & Feliu-Soler, A. (2024). Immune-inflammatory effects of the multicomponent intervention FIBROWALK in outdoor and online formats for patients with fibromyalgia. *Brain, behavior, and immunity*, *125*, 184-197 https://doi.org/10.1016/j.bbi.2024.12.149

Supplementary material

Table S1. Demographic and Baseline Clinical Characteristics by Treatment Groups (per protocol approach).

	TAU (*n* = 35)	**FIBRO-Out (*n* = 29)**	**FIBRO-On (*n* = 30)**
Age (years), *M* (*SD*)	57.89 (9.71)	55.55 (9.61)	54.03 (10.30)
BMI, *M* (*SD*)	29.40 (5.57)	28.14 (5.20)	27.70 (5.97)
ISPS, *M* (*SD*)	17.86 (10.88)	11.03 (10.65)	13.30 (8.93)
With CFS, *n* (%)	18 (51.40)	15 (51.70)	18 (60.00)
Civil Status, *n* (%)			
Single	3 (8.60)	2 (6.9)	4 (13.30)
Married/Living with partner	23 (65.70)	17 (58.60)	20 (66.70)
Separated/ Divorced	7 (20.00)	5 (17.02)	4 (13.03)
Widowed	2 (5.70)	5 (17.20)	2 (6.70)
Not living Alone, *n* (%)	28 (80.00)	25 (86.20)	25 (83.30)
Educational Level, *n* (%)			
Without Studies	2 (5.70)	0 (0.00)	0 (0.00)
Primary Studies not completed	4 (11.40)	1 (3.40)	2 (6.70)
Primary Studies	9 (25.70)	5 (17.20)	4 (13.30)
Secondary Studies	15 (42.90)	14 (48.30)	15 (50.00)
University	4 (11.40)	8 (27.60)	7 (23.30)
Other	1 (2.90)	1 (3.40))	2 (6.70)
Employment Situation, *n* (%)			
Homemaker	4 (11.40)	2 (6.90)	2 (6.70)
Active	9 (25.70)	5 (17.20)	11 (36.70)
On leave	5 (14.30)	11 (37.90)	7 (23.30)
Unemployed with allowance	2 (5.70)	2 (6.90)	0 (0.00)
Unemployed without allowance	1 (2.90)	3 (10.30)	2 (6.70)
Retired/Pensioner	8 (22.90)	1 (3.40)	2 (6.70)
Temporary work disability	2 (5.70)	1 (3.40)	3 (10.00)
Other	4 (11.40)	4 (13.80)	3 (10.00)
Medication, *n* (%)			
Analgesics	31(88.60)	27 (93.10)	24 (80.00)
Anticonvulsants	11 (31.40)	6 (20.70)	6 (20.00)
Antidepressants	30 (85.70)	25 (86.20)	15 (50.00)
Other	29 (82.90)	24 (82.80)	23 (76.70)
Incapacity certificate, *n* (%)			
No	16 (45.70)	17 (58.60)	14 (46.70)
Less than 33%	1 (2.90)	0 (0.00)	1 (3.30)
Between 33% and 66%	12 (34.30)	10 (34.50)	9 (30.00)
More than 66%	6 (17.10)	2 (6.90)	4 (13.30)
Clinical variables, *M* (*SD*)			
FIQR (0-100)	69.24 (18.48)	72.10 (11.85)	70.54 (16.65)
VAS-Pain (0-10)	7.89 (1.92)	7.97 (1.38)	7.63 (1.65)
VAS-Fatigue (0-10)	7.26 (2.74)	7.76 (2.01)	8.00 (1.82)
HADS-Anxiety (0-21)	14.49 (4.12)	12.45 (3.79)	11.97 (5.12)
HADS-Depression (0-21)	11.97 (4.20)	12.45 (3.26)	11.57 (4.30)
SF-36 (0-100)	30.86 (23.31)	31.55 (18.76)	34.33 (20.67)
TSK-11 (11-44)	31.26 (8.63)	29.00 (8.31)	31.87 (7.59)

Note: No comparison was found to be statistically significant ($p \leqq 0.05$). 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.

Table S2. Descriptive Statistics and Between-group Analysis for Primary and Secondary Measures (PP Approach).

	TAU (*n* = 35) Mean (*SD*)	**TAU + FIBRO-On (*n* = 30)** Mean (*SD*)	**TAU + FIBRO-Out (*n* = 29)** 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)***
Primary outcome														
FIQR (0-100) *				4.809	**0.010**									
Baseline	*n* =35 69.24 (18.48)	*n*=30 70.54 (16.65)	*n*=29 72.11 (11.85)											
Post-Treatment	*n*=34 67.57 (18.58)	*n*=30 59.74 (18.30)	*n*=29 60.23 (14.60)			0.51	**-2.50 (0.014)**	-9.00 (-16.14 to -1.86)	0.63	**-2.78 (0.007)**	-10.08 (-17.29 to -2.87)	0.07	-0.28 (0.774)	-1.08 (-8.53 to 6.38)
Secondary outcomes														
VAS-*Pain* (0-10) *				2.619	0.078									
Baseline	*n*=35 7.89 (1.92)	*n*=30 7.63 (1.65)	*n*=29 7.97 (1.38)											
Post-Treatment	*n*=34 7.59 (2.46)	*n*=30 6.87 (1.87)	*n*=29 6.48 (1.77)			0.25	-0.83 (0.408)	-0.41 (-1.38 to 0.56)	0.69	**-2.28 (0.025)**	-1.12 (-2.10 to -0.14)	0.47	-1.40 (0.164)	-0.72 (-1.73 to 0.30)
VAS-*Fatigue* (0-10) *				2.953	0.057									
Baseline	*n*=35 7.26 (2.73)	*n*=30 8.00 (1.82)	*n*=29 7.76 (2.01)											

Post-Treatment	*n*=34 7.79 (1.88)	*n*=30 7.07 (2.02)	*n*=29 7.00 (1.83)			0.61	**-2.21** **(0.030)**	-1.45 (-2.76 to -0.143)	0.52	-1.92 (0.058)	-1.27 (-2.59 to -0.04)	0.09	0.26 (0.800)	0.17 (-1.19 to 1.54)
HADS-A (0-21) *				0.275	0.760									
Baseline	*n*=35 14.49 (4.12)	*n*=30 11.97 (5.12)	*n*=29 12.44 (3.79)											
Post-Treatment	*n*=34 14.03 (4.27)	*n*=30 10.83 (5.03)	*n*=29 11.44 (4.15)			0.15	-0.70 (0.485)	-0.59 (-2.25 to 1.08)	0.13	-0.54 (0.592)	-0.46 (-2.14 to 1.23)	-0.03	0.15 (0.879)	0.13 (-1.60 to 1.87)
HADS-D (0-21) *				4.254	**0.017**									
Baseline	*n*=35 11.97 (4.20)	n=30 11.57 (4.30)	*n*=29 12.45 (3.26)											
Post-Treatment	*n*=34 12.68 (4.82)	*n*=30 10.50 (4.52)	*n*=29 10.52 (4.20)			0.41	-1.87 (0.064)	-1.62 (-3.33 to 0.10)	0.69	**-2,848** **(0.005)**	-2.48 (-4.21 to -0.75)	0.22	-0.96 (0.339)	-8.86 (-2.65 to 0.92)
SF-36 (0-100) *				0.669	0.515									
Baseline	*n*=35 30.86 (23.31)	*n*=30 34.33 (20.67)	*n*=29 31.55 (18.76)											
Post-Treatment	*n*=34 32.35 (23.07)	*n*=30 40.33 (23.60)	*n*=29 33.28 (20.76)			-0.20	1.02 (0.312)	4.18 (-4.00 to 12.35)	0.04	-0.23 (0.981)	-0.97 (-8.34 to 8.15)	0.26	-1.00 (0.322)	-4.28 (-12.80 to 4.25)
TSK-11 (11-44) *				12.666	**(<0.001)**									
Baseline	*n*=35 31.26 (8.63)	*n*=30 31.87 (7.59)	*n*=29 29.00 (8.31)											
Post-Treatment	*n*=34 29.82 (9.43)	*n*=30 23.23 (6.89)	*n*=29 22.62 (6.57)			0.87	**-4.89** **(< 0.001)**	-7.17 (-10.08 to -4.25)	0.58	**-3.32** **(0.001)**	-4.91 (-7.85 to -1.97)	-0.28	1.47 (0.144)	2.25 (-0.79 to 5.29)

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.

Table S3. Descriptive Statistics and Between-group Analysis for Biomarkers Ratios (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)***
Inflammation indexes														
IL-6/IL-4 *				2.525	0.085									
Baseline	*n*=35 0,20 (0,33)	*n*=33 0,23 (0,27)	*n*=37 0,25 (0,26)											
Post-Treatment	*n*=29 0,25 (0,32)	*n*=31 0,25 (0,30)	*n*=31 0,22 (0,23)			-0.10	-1.37 (0.174)	-0.07 (-0.18 to 0.03)	-0.27	**-2.23 (0.028)**	-0.12 (-0.22 to -0.01)	-0.19	-0.85 (0.398)	-0.04 (-0.15 to 0.06)
IL-6/IL-10*				0.221	0.802									
Baseline	*n*=35 0,60 (2,03)	*n*=33 0,73 (1,64)	*n*=37 0,53 (1,00)											
Post-Treatment	*n*=29 0,64 (1,15)	*n*=31 0,64 (1,31)	*n*=31 0,63 (0,86)			-0.07	-0.64 (0.526)	0.23 (-0.93 to 0.48)	0.04	-0.15 (0.878)	-0.05 (-0.74 to 0.64)	0.14	0.49 (0.623)	0.17 (-0.52 to 0.86)
CXCL8/ IL-4*				2.985	0.055									
Baseline	*n*=35 0,72 (0,36)	*n*=33 0,82 (0,27)	*n*=37 0,71 (0,17)											

Post-Treatment	*n*=29 0,72 (0,35)	*n*=31 0,77 (0,22)	*n*=31 0,74 (0,18)			-0.16	-1.79 (0.076)	-0.07 (-0.15 to 0.01)	0.11	0.52 (0.606)	0.02 (-0,06 to 0.10)	0.36	**2.34** **(0.021)**	0.09 (0.01 to 0.17)
CXCL8/ IL-10*				1.472	0.234									
Baseline	*n*=35 3,63 (3,18)	*n*=33 3,21 (2,69)	*n*=37 2,84 (2,59)											
Post-Treatment	*n*=29 2,95 (2,58)	*n*=31 3,01 (2,64)	*n*=31 2,94 (2,31)			0.16	1.04 (0.302)	0.54 (-0.50 to 1.58)	0.26	1.71 (0.091)	0.88 (-0.14 to 1.91)	0.11	0.65 (0.514)	0.34 (-0.69 to 1.36)
hs-CRP/IL-4*				0.979	0.379									
Baseline	*n*=35 0,21 (0,27)	*n*=33 0,12 (0,38)	*n*=37 0,19 (0,30)											
Post-Treatment	*n*=29 0,22 (0,38)	*n*=31 0,06 (0,35)	*n*=31 0,21 (0,42)			-0.21	-0.95 (0.343)	-0.62 (-0.19 to 0.07)	0.04	0.40 (0.693)	0.03 (-0.10 to 0.15)	0.23	1.37 (0.175)	0.09 (-0.03 to 0.21)
hs-CRP/IL-10*				1.773	0.175									
Baseline	*n*=35 0,73 (1,21)	*n*=33 0,52 (2,26)	*n*=37 0,61 (1,69)											
Post-Treatment	*n*=29 0,58 (1,16)	*n*=31 0,32 (2,27)	*n*=31 0,76 (1,97)			-0.03	0.37 (0.710)	0.10 (-0.45 to 0.66)	0.20	1.78 (0.078)	0.49 (-0,06 to 1.03)	0.18	1.41 (0.163)	0.38 (-0.16 to 0.93)
IL-17A/IL-4*				1.238	0.294									
Baseline	*n*=35 1,19 (0,41)	*n*=33 1,17 (0,42)	*n*=37 1,10 (0,37)											
Post-Treatment	*n*=29 1,17 (0,45)	*n*=31 1,11 (0,38)	*n*=31 1,11 (0,35)			-0.10	-1.46 (0.149)	-0.08 (-0.19 to 0.03)	0.08	-0.22 (0.823)	-0.01 (-0.12 to 0.10)	0.18	1.25 (0.213)	0.07 (-0.04 to 0.18)

IL-17A/IL-10*				0.488	0.615								
Baseline	*n*=35 5,55 (4,29)	*n*=33 4,82 (4,55)	*n*=37 4,44 (4,06)										
Post-Treatment	*n*=29 4,97 (4,19)	*n*=31 4,43 (4,13)	*n*=31 4,52 (3,69)		0.04	0.23 (0.820)	0.18 (-0.35 to 1.70)	0.16	0.94 (0.348)	0.72 (-0.79 to 2.22)	0.11	0.71 (0.477)	0.54 (-0.96 to 2.04)

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 S4. Descriptive Statistics and Between-group Analysis for Primary and Secondary Measures with the Covariate Antidepressants (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)***
Primary outcome														
FIQR (0-100) *				3.813	**0.025**									
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	**-2.03 (0.045)**	-7.23 (-14.30 to -0.17)	0.50	**-2.62 (0.010)**	-9.19 (-16.12 to -2,26)	0.05	-0.55 (0.583)	-1.97 (-8,99 to 5,087)
Secondary outcomes														
VAS-*Pain* (0-10) *				2.901	0.059									
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	-0.79 (0.429)	-0.36 (-1.27 to 0.54)	0.63	**-2.36 (0.020)**	-1.06 (-1.96 to -0.17)	0.36	-1.53 (0.12)	-0.70 (-1.61 to 0.20)

VAS-*Fatigue* (0-10) *				2.648	0.076									
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	-1.88 (0.062)	-1.21 (-2.48 to 0.06)	0.53	**-2.07 (0.040)**	-1.30 (-2.55 to -0.06)	0.02	-0.14 (0.884)	-0.09 (-1.36 to 1,17)
HADS-A (0-21) *				0.270	0.764									
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 (0.490)	-0.56 (-2.18 to 1,05)	0.07	-0.12 (0.899)	-0.1 (-1.68 to 1,48)	-0.10	0.57 (0.570)	0.46 (-1,14 to 2,07)
HADS-D (0-21) *				4.225	**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 (0.104)	-1.37 (-3,02 to 0.28)	0.65	**-2.89 (0.005)**	-2.37 (-4.00 to -0.75)	0.25	-1.21 (0.229)	-1.01 (-2,66 to 0.64)
SF-36 (0-100) *				0.525	0.593									
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	0.73 (0.462)	2.93 (-4.95 to 10,82)	0.04	-0.25 (0.801)	-0.98 (-8,72 to 6.75)	0.22	-0.99 (0.325)	-3.92 (-11.78 to 3.93)
TSK-11 (11-44) *				11,129	**(< 0.001)**									

Baseline	n=35 31.26 (8.63)	n=33 32.64 (7.70)	n=37 28.89 (7.91)										
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	**-3.18** **(0.002)**	-4.52 (-7.34 to -1,70)	-0.34	1.48 (0.140)	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.

Table S5. Descriptive Statistics and Between-group Analysis for Biomarkers with the Covariate Antidepressants (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)				4.637	**0.012**									
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	**-2.01** **(0.047)**	-0.27 (-0.54 to -0.00)	0.24	**-2,99** **(0.003)**	-0.4 (-0.67 to -0.13)	0.16	-0.95 (0.343)	-0.13 (-0.39 to 0.13)
CXCL8 * (pg/ml)				0.317	0.729									
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)			<0.01	-0.57 **(**0.567)	-0.06 (-0.27 to 0.14)	-0.04	0.18 (0.854)	0.02 (-0.18 to 0.22)	-0.05	0.767 (0.445)	0.08 (-0.12 to 0.28)
IL-17A * (pg/ml)				0.574	0.565									
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	-0.20 (0.842)	-0.01 (-0.14 to 0.12)	-0.12	-1.00 (0.317)	-0.07 (-0.20 to 0.06)	-0.02	-0.81 (0.417)	-0.05 (-0.18 to 0.07)
IL-4 * (pg/ml)				2.063	0.132									
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	0.61 (0.538)	0.07 (-0.17 to 0.32)	0.14	-1.35 (0.179)	-0.16 (-0.40 to 0.07)	0.16	-1.981 (0.050)	-0.24 (-0.48 to 0.00)
IL-10 * (pg/ml)				2.583	0.080									
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)			0.087	-1.18 (0.238)	-0.23 (-0.61 to 0.15)	0.30	-2.27 (0.025)	-0.43 (-0.81 to -0.05)	0.19	-1.07 (0.286)	-0.20 (-0.58 to 0.17)
hs-CRP * (mg/L)				1.232	0.296									
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	-1.16 (0.246)	-0.22 (-0.59 to 0.15)	-0.01	0.301 (0.764)	0.05 (-0.31 to 0.42)	-0.23	1.492 (0.139)	0.55 (-0.09 to 0.64)
BDNF * (pg/ml)				0.764	0.468									
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	1.14 (0.255)	0.22 (-0.15 to 0.59)	-0.11	0.17 (0.862)	0.03 (-0.33 to 0.39)	0.25	-0.98 0.326	-0.18 (-0.55 to 0.18)

Inflammation indexes														
IL-6/IL-4 *				2.489	0.088									
Baseline	*n*=35 0,20 (0,33)	*n*=33 0,23 (0,27)	*n*=37 0,25 (0,26)											
Post-Treatment	*n*=29 0,25 (0,32)	*n*=31 0,25 (0,30)	*n*=31 0,22 (0,23)			-0.10	-1.34 (0.183)	-0.07 (-0.17 to 0.03)	-0.27	**-2.22 (0.029)**	-0.11 (-0,22 to -0.01)	-0.19	-0.86 (0.392)	-0.04 (-0.15 to 0.06)
IL-6/IL-10*				0.213	0.809									
Baseline	*n*=35 0,60 (2,03)	*n*=33 0,73 (1,64)	*n*=37 0,53 (1,00)											
Post-Treatment	*n*=29 0,64 (1,15)	*n*=31 0,64 (1,31)	*n*=31 0,63 (0,86)			-0.07	-0.62 (0.535)	-0.22 (-0.92 to 0.48)	0.04	-0.15 (0.884)	-0.05 (-0.74 to 0.64)	0.14	0.49 (0.629)	0.17 (-0.52 to 0.86)
CXCL8/ IL-4*				3.016	0.053									
Baseline	*n*=35 0,72 (0,36)	*n*=30 0,85 (0,27)	*n*=29 0,68 (0,16)											
Post-Treatment	*n*=29 0,72 (0,35)	*n*=30 0,77 (0,23)	*n*=26 0,74 (0,20)			-0.25	-1.81 (0.073)	-0.07 (-0.15 to 0.01)	0.21	0.50 (0.615)	-0.02 (-0,06 to 0.10)	0.62	**2.35 (0.021)**	0.09 (0.01 to 0.17)
CXCL8/ IL-10*				1.458	0.237									
Baseline	*n*=35 3,63 (3,18)	*n*=30 3,41 (2,73)	*n*=29 2,85 (2,69)											
Post-Treatment	*n*=29 2,95 (2,58)	*n*=30 3,07 (2,66)	*n*=26 2,90 (2,24)			0.11	1.02 (0.308)	0.54 (-0.50 to 1.58)	0.24	1.70 (0.093)	0.88 (-0.15 to 1.90)	0.14	0.660 (0.511)	0.34 (-0.68 to 1.37)
hs-CRP/IL-4*				0.947	0.391									

Baseline	*n*=35 0,21 (0,27)	*n*=30 0,13 (0,39)	*n*=29 0,16 (0,31)											
Post-Treatment	*n*=29 0,22 (0,38)	*n*=30 0,06 (0,35)	*n*=26 0,21 (0,46)			-0.24	-0.92 (0.362)	-0.06 (-0.19 to 0.07)	0.14	0.42 (0.678)	0.03 (-0.10 to 0.15)	0.34	1.35 (0.180)	0.09 (-0.04 to 0.21)
hs-CRP/IL-10*				1.778	0.174									
Baseline	*n*=35 0,73 (1,21)	*n*=30 0,55 (2,37)	*n*=29 0,47 (1,80)											
Post-Treatment	*n*=29 0,58 (1,16)	*n*=30 0,34 (2,30)	*n*=26 0,72 (2,12)			-0.03	0.40 (0.693)	0.11 (-0.44 to 0.66)	0.26	1.79 (0.077)	0.49 (-0.05 to 1.04)	0.22	1.39 (0.167)	0.38 (-0.16 to 0.92)
IL-17A/IL-4*				1.270	0.285									
Baseline	*n*=35 1,19 (0,41)	*n*=30 1,20 (0,43)	*n*=29 1,06 (0,33)											
Post-Treatment	*n*=29 1,17 (0,45)	*n*=30 1,12 (0,38)	*n*=26 1,13 (0,35)			-0.14	-1.48 (0.142)	-0.08 (-0.19 to 0.03)	0.24	-0.24 (0.810)	-0.01 (-0.12 to 0.10)	0.39	1.26 (0.210)	0.07 (-0.04 to 0.18)
IL-17A/IL-10*				0.487	0.616									
Baseline	*n*=35 5,55 (4,29)	*n*=30 5,10 (4,67)	*n*=29 4,36 (4,10)											
Post-Treatment	*n*=29 4,97 (4,19)	*n*=30 4,55 (4,15)	*n*=26 4,43 (3,42)			0.01	0.23 (0.819)	0.18 (-1.35 to 1.70)	0.15	0.94 (0.348)	0.72 (-0.79 to 2.22)	0.14	0.71 (0.478)	0.54 (-0.96 to 2.04)

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 S6. Descriptive Statistics and Between-group Analysis for Biomarkers (PP Approach).

	TAU (*n* = 35) Mean (*SD*)	**TAU + FIBRO-On (*n* = 30) Mean (*SD*)**	**TAU + FIBRO-Out (*n* = 29) 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)				3.636	**0.030**									
Baseline	*n*=35 0.90 (1.21)	*n*=30 1.02 (1.34)	*n*=29 1.17 (1.36)											
Post-Treatment	*n*=29 1.04 (1.10)	*n*=30 1.03 (1.31)	*n*=26 0.92 (1.15)			0.10	**-2.14 (0.035)**	-0.30 (-0.57 to -0.02)	0.30	**-2.46 (0.016)**	-0.35 (-0.63 to -0.07)	0.19	-0.37 (0.716)	-0.05 (-0.34 to 0.23)
CXCL8 * (pg/ml)				0.806	0.450									
Baseline	*n*=35 2.45 (0.97)	*n*=30 2.69 (0.74)	*n*=29 2.76 (0.67)											
Post-Treatment	*n*=29 2.46 (0.84)	*n*=30 2.64 (0.73)	*n*=26 2.77 (0.55)			0.07	-0.80 (0.422)	-0.09 (-0.30 to 0.13)	0.00	0.48 (0.630)	0.05 (-0.16 to 0.27)	-0.08	1.25 (0.214)	0.14 (-0.08 to 0.36)
IL-17A * (pg/ml)				0.983	0.378									
Baseline	*n*=35 4,03 (0.70)	*n*=30 3,74 (0.86)	*n*=29 4,10 (0.46)											
Post-Treatment	*n*=29	*n*=30	*n*=26			-0.10	-0.14	-0.01	-0.02	-1.29	-0.08	0.10	-1.15	-0.08

	4,00 (0.61)	3,79 (0.87)	4,08 (0.41)				(0.887)	(-0.14 to 0.12)		(0.201)	(-0.22 to 0.05)		(0.252)	(-0.21 to 0.05)
IL-4 * (pg/ml)				2.578	**0.032**									
Baseline	*n*=35 3.72 (1.23)	*n*=30 3.47 (1.54)	*n*=29 4.21 (1.28)											
Post-Treatment	*n*=29 3.83 (1.30)	*n*=30 3,71 (1.51)	*n*=26 3,93 (1.12)			-0.09	0.74 (0.459)	0.09 (-0.15 to 0.33)	0.31	-1.91 (0.059)	-0.24 (-0.49 to 0.01)	0.36	**-2,60 (0.011)**	-0.33 (-0.58 to -0.07)
IL-10 * (pg/ml)				2.001	0.141									
Baseline	*n*=35 1,56 (1.30)	*n*=30 1.90 (1.67)	*n*=29 2.03 (1.52)											
Post-Treatment	*n*=29 1,75 (1.34)	*n*=30 1.97 (1.61)	*n*=26 1.67 (1.26)			0.08	-1.19 (0.236)	-0.24 (-0.65 to 0.16)	0.39	-1.98 (0.051)	-0.41 (-0.83 to -0.001)	0.27	-0,80 (0.423)	-0.17 (-0.59 to 0.25)
hs-CRP * (mg/L)				1.760	0.178									
Baseline	*n*=35 0,69 (0.82)	*n*=30 0,34 (1.17)	*n*=29 0,72 (1.21)											
Post-Treatment	*n*=29 0.73 (1.00)	*n*=30 0.12 (1.11)	*n*=26 0.80 (1.48)			0.26	-1.16 (0.251)	-0.23 (-0.61 to 0.16)	-0.04	0.74 (0.463)	0.15 (-0.25 to 0.55)	-0.25	1.85 (0.067)	0.37 (-0.03 to 0.77)
BDNF * (pg/ml)				1.016	0.366									
Baseline	*n*=35 4,40 (0.60)	*n*=30 4,23 (0.51)	*n*=29 4,42 (0.71)											
Post-Treatment	*n*=29 4,24 (0.45)	*n*=30 4,30 (0.54)	*n*=26 4,27 (0.29)			-0.41	1.26 (0.212)	0.25 (-0.14 to 0.64)	-0.02	0.01 (0.995)	0.00 (-0.40 to 0.40)	0.35	-1.21 (0.228)	-0.25 (-0.65 to 0.16)

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 S7. Descriptive Statistics and Between-group Analysis for Biomarkers Ratios (PP Approach).

	TAU (*n* = 35) Mean (*SD*)	**TAU + FIBRO-On (*n* = 30) Mean (*SD*)**	**TAU + FIBRO-Out (*n* = 29) 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)***
Inflammation indexes														
IL-6/IL-4 *				1.593	0.209									
Baseline	*n*=35 0,20 (0,33)	*n*=30 0,22 (0,27)	*n*=29 0,23 (0,25)											
Post-Treatment	*n*=29 0,25 (0,32)	*n*=30 0,24 (0,30)	*n*=26 0,20 (0,24)			-0.10	-1.41 (0.162)	0.08 (-0.18 to 0.03)	-0.27	-1.63 (0.106)	0.09 (-0.20 to 0.02)	-0.19	-0.25 (0.801)	-0.01 (-0.13 to 0.10)
IL-6/IL-10*				0.205	0.815									
Baseline	*n*=35 0,60 (2,03)	*n*=30 0,77 (1,71)	*n*=29 0,53 (1,01)											
Post-Treatment	*n*=29 0,64 (1,15)	*n*=30 0,64 (1,33)	*n*=26 0,47 (0,62)			-0.09	-0.63 (0.532)	-0.23 (-0.98 to 0.51)	-0.06	-0.41 (0.648)	-0.16 (-0.91 to 0.60)	0.05	0.20 (0.840)	0.08 (-0.69 to 0.85)
CXCL8/ IL-4*				4.967	**0.009**									
Baseline	*n*=35 0,72 (0,36)	*n*=30 0,85 (0,27)	*n*=29 0,68 (0,16)											
Post-Treatment	*n*=29 0,72 (0,35)	*n*=30 0,77 (0,23)	*n*=26 0,74 (0,20)			-0.25	**-2.01 (0.048)**	-0.08 (-0.16 to < 0.01)	0.21	1.19 (0.238)	0.05 (-0,03 to 0.13)	0.62	**3.11 (0.003)**	0.13 (0.05 to 0.22)
CXCL8/ IL-10*				0.916	0.404									
Baseline	*n*=35 3,63 (3,18)	*n*=30 3,41 (2,73)	*n*=29 2,85 (2,69)											
Post-Treatment	*n*=29 2,95 (2,58)	*n*=30 3,07 (2,66)	*n*=26 2,90 (2,24)			0.11	0.93 (0.355)	0.51 (-0.58 to 1.59)	0.24	1.31 (0.195)	0.73 (-0.38 to 1.83)	0.14	0.39 (0.698)	0.22 (-0.90 to 1.34)

hs-CRP/IL-4*				1.396	0.253									
Baseline	*n*=35 0,21 (0,27)	*n*=30 0,13 (0,39)	*n*=29 0,16 (0,31)											
Post-Treatment	*n*=29 0,22 (0,38)	*n*=30 0,06 (0,35)	*n*=26 0,21 (0,46)			-0.24	-0.92 (0.358)	-0.06 (-0.20 to 0.07)	0.14	0.79 (0.433)	0.05 (-0,08 to 0.19)	0.34	1.67 (0.099)	0.12 (-0.02 to 0.25)
hs-CRP/IL-10*				1.824	0.167									
Baseline	*n*=35 0,73 (1,21)	*n*=30 0,55 (2,37)	*n*=29 0,47 (1,80)											
Post-Treatment	*n*=29 0,58 (1,16)	*n*=30 0,34 (2,30)	*n*=26 0,72 (2,12)			-0.03	0.34 (0.736)	0.10 (-0.48 to 0.68)	0.26	1.82 (0.073)	0.54 (-0,05 to 1.14)	0.22	1.47 (0.146)	0.44 (-0.16 to 1.05)
IL-17A/IL-4*				2.299	0.106									
Baseline	*n*=35 1,19 (0,41)	*n*=30 1,20 (0,43)	*n*=29 1,06 (0,33)											
Post-Treatment	*n*=29 1,17 (0,45)	*n*=30 1,12 (0,38)	*n*=26 1,13 (0,35)			-0.14	-1.66 (0.101)	-0.09 (-0.19 to 0.02)	0.24	0.42 (0.679)	0.02 (-0,08 to 0.13)	0.39	**2.01 (0.048)**	0.11 (<0.01 to 0.22)
IL-17A/IL-10*				0.166	0.848									
Baseline	*n*=35 5,55 (4,29)	*n*=30 5,10 (4,67)	*n*=29 4,36 (4,10)											
Post-Treatment	*n*=29 4,97 (4,19)	*n*=30 4,55 (4,15)	*n*=26 4,43 (3,42)			0.01	0.18 (0.859)	0.14 (-1.45 to 1.73)	0.15	0.57 (0.572)	0.46 (-1.16 to 2.09)	0.14	0.39 (0.700)	0.32 (-1.33 to 1.97)

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 S8. Baseline Differences between Responders and Non-Responders in the FIBRO-Out Group.

	Responders (*n* = 13)	**Non-responders (*n* = 20)**
Age (years), *M* (*SD*)	57.69 (12.04)	53.45 (7.08)
BMI, *M* (*SD*)	28.97(4.54)	27.72 (6.04)
ISPS, *M* (*SD*)	13.85 (10.38)	9.10 (10.08)
With CFS, *n* (%)	5 (38.50)	11 (55.00)
Civil Status, *n* (%)		
Single	1 (7.70)	1 (5.00)
Married/Living with partner	9 (69.20)	11 (55.00)
Divorced/Separated	1 (7,70)	5 (25.00)
Widow	2 (15.40)	3 (15.00)
Not living Alone, *n* (%)	11 (84.60)	16 (80.00)
Educational Level, *n* (%)		
Without Studies	0 (0.00)	0 (0.00)
Primary Studies not completed	0 (0.00)	1 (5.00)
Primary Studies	2 (15.40)	5 (25.00)
Secondary Studies	8 (61.50)	8 (40.00)
University	3 (23.10)	5 (25.00)
Other	0 (0.00)	1 (5.00)
Employment Situation, *n* (%)		
Homemaker	1 (7.70)	1 (5.00)
Active	2 (15.40)	6 (30.00)
On leave	2 (15.40)	9 (45.00)
Unemployed with allowance	2 (15.40)	0 (0.00)
Unemployed without allowance	1 (7.70)	2 (10.00)
Retired/Pensioner	1 (7.70)	0 (0.00)
Temporary work disability	1 (7.70)	0 (0.00)
Other	3 (23.10)	2 (10.00)
Medication, *n* (%)		
Analgesics	13 (100.00)	17 (85.00)
Anticonvulsants	3 (23.10)	3 (15.00)
Antidepressants	12 (92.30)	16 (80.00)
Other	10 (77.00)	17 (85.00)
Incapacity certificate, *n* (%)		
No	8 (61.50)	12 (60.00)
Less than 33%	0 (0.00)	0 (0.00)
Between 33% and 66%	3 (23.10)	8 (40.00)
More than 66%	2 (15.40)	0 (0.00)
Clinical variables, *M* (*SD*)		
FIQR	73.18 (10.24)	71.74 (15.58)
VAS-Pain	8.08 (0.95)	8.00 (1.59)
VAS-Fatigue	8.15 (1.07)	7.60 (2.44)
HADS-Anxiety	12.31 (4.48)	12.20 (3.75)
HADS-Depression	12.69 (3.38)	12.00 (4.18)
PSS	9,46 (3.02)	9.30 (2.62)
SF-36	36.92 (20.67)	31.00 (20.04)
TSK-11	26.92 (9.68)	30.70 (6.77)
Inflammatory biomarkers, *M* (*SD*)		
IL-6	1.49 (1.55)	1,15 (1,36)
CXCL8	2.89 (0.82)	2.78 (0.88)
IL-17A	72.50 (43.74)	58.43 (23.52)

IL-4	4.59 (1.51)	3.98 (1.30)
IL-10	2.33 (1.84)	2.02 (1.45)
hs-CRP	3.81 (4.63)	4.01 (3.79)
BDNF	113.89 (78,63)	96.35 (78.27)
Ratio IL-6/IL-4	0.26 (0.24)	0.26 (0.28)
Ratio IL-6/IL-10	0.75 (0.94)	0.43 (0.97)
Ratio CXCL8/IL-4	0.66 (0.17)	0.72 (0.15)
Ratio CXCL8/ IL-10	2.64 (2.53)	2.66 (2.66)
Ratio hs-CRP/IL-4	0.15 (0.24)	0.19 (0.34)
Ratio hs-CRP/IL-10	0.23 (1.69)	0.62 (1.71)
Ratio IL17-A/IL-4	1.01 (0.38)	1.10 (0.35)
Ratio IL-17A/IL-10	4.21 (4.26)	3.96 (3.83)

Note: No comparison was found to be statistically significant ($p \leqq 0.05$). BDNF, Brain-Derived Neurotrophic Factor; BMI: Body Mass Index; CFS: Chronic Fatigue Syndrome; FIQR, Revised Fibromyalgia Impact Questionnaire; HADS-A and HADS-D, Hospital Anxiety and Depression Scale; hs-CRP, high-sensitivity C-reactive protein; ISPS: Illness Self-Perceived Start; SF-36, Physical function subscale of the Short Form-36 Health Survey; TSK-11, Tampa Scale for Kinesiophobia; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain. Untransformed values of specific biomarkers are shown.

Table S9. Baseline Differences Between Responders and Non-Responders in the FIBRO-On Group.

	Responders (*n* = 12)	**Non-responders (*n* = 20)**
Age (years), *M* (*SD*)	56.17 (8,77)	53.15 (10.98)
BMI, *M* (*SD*)	29.10 (7.71)	26.86 (4.24)
ISPS, *M* (*SD*)	14.83 (10.28)	11.40 (8.09)
With CFS, *n* (%)	8 (66.7)	11 (55.00)
Civil Status, *n* (%)		
Single	0 (0.00)	5 (25.00)
Married/Living with partner	9 (75.00)	12 (60.00)
Divorced/Separated	3 (25.00)	1 (5.00)
Widow	0 (0.00)	2 (10.00)
Not living Alone, *n* (%)	11 (91.70)	16 (80.00)
Educational Level, *n* (%)		
Without Studies	0 (0.00)	0 (0.00)
Primary Studies not completed	2 (16.70)	0 (0.00)
Primary Studies	3 (25.00)	2 (10.00)
Secondary Studies	3 (25.00)	13 (65.00)
University	4 (33.30)	3 (15.00)
Other	0 (0.00)	2 (10.00)
Employment Situation, *n* (%)		
Homemaker	1 (8.30)	2 (10.00)
Active	3 (25.00)	9 (45.00)
On leave	3 (25.00)	4 (20.00)
Unemployed with allowance	0 (0.00)	0 (0.00)
Unemployed without allowance	0 (0.00)	2 (10.00)
Retired/Pensioner	2 (16.70)	0 (0.00)
Temporary work disability	1 (8.30)	2 (10.00)
Other	2 (16.70)	1 (5.00)
Medication, *n* (%)		
Analgesics	10 (83.30)	16 (80.00)
Anticonvulsants	2 (16.70)	4 (20.00)
Antidepressants	8 (66.70))	8 (40.00)
Other	10 (83.30)	14 (70.00)
Incapacity certificate, *n* (%)		
No	5 (41.70)	11 (55.00)
Less than 33%	1 (8.30)	0 (0.00)
Between 33% and 66%	3 (25.00)	6 (30.00)
More than 66%	3 (25.00)	1 (5.00)
Clinical variables, *M* (*SD*)		
FIQR	70.83 (16.63)	70.08 (16.33)
VAS-Pain	7.67 (1.83)	7.70 (1,53)
VAS-Fatigue	7.42 (2.35)	8.15 (1.73)
HADS-Anxiety	12.58 (5.16)	12.05 (5.16)
HADS-Depression	11.00 (3.74)	11.85 (4.50)
PSS	7.67 (2.27)	8.90 (3.51)
SF-36	32.92 (21.89)	35.00 (19.74)
TSK-11	33.42 (7.35)	31.60 (7.76)
Inflammatory biomarkers, *M* (*SD*)		
IL-6	0.86 (0.97)	1.25 (1.52)
CXCL8	2.63 (0.57)	2.72 (0.82)

IL-17A	43.79 (37.00)	67.45 (67.24)
IL-4	3.08 (1.27)	3.89 (1.66)
IL-10	1.94 (1.47)	2.03 (1.79)
hs-CRP	1.85 (2.11)	2.73 (2.99)
BDNF	90.06 (51.79)	69.92 (37.00)
Ratio IL-6/IL-4	0.24 (0.23)	0.24 (0.29)
Ratio IL-6/IL-10	0.50 (1.04)	0.91 (1.95)
Ratio CXCL8/IL-4	0.93 (0.29)	0.77 (0.25)
Ratio CXCL8/ IL-10	3.20 (2.84)	3.29 (2.72)
Ratio hs-CRP/IL-4	0.08 (0.44)	0.13 (0.36)
Ratio hs-CRP/IL-10	0.36 (2.53)	0.60 (2.21)
Ratio IL17-A/IL-4	1.21 (0.44)	1.15 (0.44)
Ratio IL-17A/IL-10	4.13 (4.24)	5.29 (4.88)

Note: **No comparison was found to be statistically significant (p≦0.05).** BDNF, Brain-Derived Neurotrophic Factor; BMI: Body Mass Index; CFS: Chronic Fatigue Syndrome; FIQR, Revised Fibromyalgia Impact Questionnaire; HADS-A and HADS-D, Hospital Anxiety and Depression Scale; hs-CRP, high-sensitivity C-reactive protein; ISPS: Illness Self-Perceived Start; SF-36, Physical function subscale of the Short Form-36 Health Survey; TSK-11, Tampa Scale for Kinesiophobia; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain. Untransformed values of specific biomarkers are shown.

Table S10. Stepwise Regression Analysis of Clinical Change Using Inflammatory Pathways and Related Indexes as Predictors in the FIBRO-Out Group.

Dependent variable	Independent variable	R^2	*β*	t	*p*
Change HADS-A	BDNF	0.142	-0.376	-2.261	0.031
Change TSK-11		0.274			
	hs-CRP		-0.360	-2.304	0.028
	BDNF		-0.348	-2.224	0.034

Note: Reported R^2 is unadjusted. None of the other clinical changes evaluated were found to be significantly predicted by inflammatory markers and/or indexes. BDNF, Brain-Derived Neurotrophic Factor; HADS-D, Hospital Anxiety and Depression Scale; hs-CRP, high-sensitivity C-reactive protein; TSK-11, Tampa Scale for Kinesiophobia.

Table S11. Stepwise Regression Analysis of Clinical Change Using Inflammatory Pathways and Related Indexes as Predictors in the FIBRO-On Group.

Dependent variable	**Independent variable**	**R^2**	***β***	**t**	***p***
Change FIQR	IL-4	0,141	0.376	2.219	0.034
Change VAS-*Pain*	Ratio CXCL8/ IL-10	0.194	-0.440	-2.687	0.012
Change VAS-*Fatigue*	Ratio CXCL8/ IL-10	0.127	-0.356	-2.085	0.046
Change SF-36	BDNF	0.156	0.395	2.353	0.025

Note: Reported R^2 is unadjusted. None of the other clinical changes evaluated were found to be significantly predicted by inflammatory markers and/or indexes. BDNF, Brain-Derived Neurotrophic Factor; FIQR, Revised Fibromyalgia Impact Questionnaire; SF-36, Physical function subscale of the Short Form-36 Health Survey; VAS-Fatigue, Visual-analogue scale of perceived energy/fatigue; VAS-Pain, Visual-analogue scale of perceived pain.

Annex 2

Estudi de la part no fonamental de la tesi doctoral

Estudi 1

Serrat, M., Navarrete, J., Ferrés, S., Auer, W., Sanmartín-Sentañes, R., Nieto, R., Neblett, R., Borràs, X., Luciano, J. V., & Feliu-Soler, A. (2023). Effectiveness of an online multicomponent program (FATIGUEWALK) for chronic fatigue syndrome: A randomized controlled trial. *Health Psychol*. Published online December 21, 2023. doi:10.1037/hea0001346. Advance online publication. https://doi.org/10.1037/hea0001346

Health Psychology

ISSN: 0278-6133

2024, Vol. 43, No. 4, 310–322
https://doi.org/10.1037/hea0001346

Effectiveness of an Online Multicomponent Program (FATIGUEWALK) for Chronic Fatigue Syndrome: A Randomized Controlled Trial

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Objective: This study aimed to evaluate the effectiveness of an online multicomponent intervention called FATIGUEWALK (FaW) compared to treatment as usual (TAU) in patients with chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). ***Method:*** FaW included pain neuroscience education, therapeutic exercise, cognitive restructuring, and mindfulness training. A total of 428 patients with CFS/ME were randomized into two study arms: online FaW plus TAU versus TAU alone. A single-blinded randomized controlled trial was conducted. Validated patient-reported outcome measures of fatigue, pain, anxiety, depression, and physical function were collected at baseline and posttreatment, following the FaW intervention, which lasted 12 weeks. ***Results:*** Statistically significant improvements (with small-to-moderate effect sizes) were observed in online FaW versus TAU alone with respect to multidimensional aspects of fatigue (Cohen's *d* ranging from 0.25 to 0.73) and most secondary outcomes (pain and fatigue intensity, depressive and anxious symptomatology, functional impairment, kinesiophobia, physical functioning). The absolute risk reduction in FaW versus TAU was 19%, 95% confidence interval (CI) [12.19, 25.80] with number needed to treat = 6, 95% CI [3.9, 8.2]. Overall, similar clinical improvements were observed in sensitivity analyses including a subgroup of patients without comorbidity with fibromyalgia ($n = 70$). ***Conclusions:*** This is the first study to assess the short-term effectiveness of an online multicomponent intervention added to TAU, compared to TAU alone, for the management of CFS/ME. Further trials, including active control groups with an equivalent treatment dose, and assessing the long-term effectiveness of the online FaW, are warranted.

Public Significance Statement
The FATIGUEWALK (FaW) program is a video-based multicomponent treatment for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). This trial strongly suggests that FaW is an effective treatment for improving fatigue and psychological and physical comorbid impairment in CFS/ME patients, both with and without fibromyalgia. This study highlights the importance of online and multicomponent interventions for CFS/ME treatment.

This article was published Online First December 21, 2023.
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The authors have no known conflicts of interest to disclose. This study has not received specific funding. Jaime Navarrete has a research contract from the Institute of Health Carlos III (ISCIII; ICI20/00080). Albert Feliu-Soler has a Serra Hunter grant award (UAB-LE-8015). The authors are grateful to the CIBER of Epidemiology and Public Health (CIBERESP CB22/02/00052; ISCIII) for its support. ClinicalTrials.gov, Identifier: NCT04593225.

Mayte Serrat and Jaime Navarrete are joint first coauthorship. Juan V. Luciano and Albert Feliu-Soler are joint senior coauthorship. Mayte Serrat contributed equally to funding acquisition, resources, software, supervision, validation, and visualization. Mayte Serrat and Albert Feliu-Soler contributed equally to conceptualization, investigation, methodology, and project administration. Mayte Serrat, Jaime Navarrete, and Albert Feliu-Soler contributed equally to formal analysis and data curation. Mayte Serrat and Jaime Navarrete contributed equally to writing–original draft. Mayte Serrat, Jaime Navarrete, Sònia Ferrés, William Auer, Ramon Sanmartín-Sentañes, Rubén Nieto, Randy Neblett, Xavier Borràs, Juan V. Luciano, and Albert Feliu-Soler contributed equally to writing–review and editing.

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Keywords: chronic fatigue syndrome, therapeutic exercise, cognitive behavioral therapy, mindfulness, randomized controlled trial

Supplemental materials: https://doi.org/10.1037/hea0001346.supp

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a complex syndrome characterized by unexplained and persistent fatigue that lasts at least 6 months, accompanied by a constellation of symptoms related to cognitive, immune system, and autonomic nervous system dysfunction (Brurberg et al., 2014; Cortes-Rivera et al., 2019). CFS/ME can cause a wide range of symptom severity and functional impairment, leaving some people able to work while others are confined to home or bed. In fact, the most severely ill individuals may require total care (Montoya et al., 2021). Overall, it is estimated to affect up to 1% of the population (Lim & Son, 2020; Sotzny et al., 2018).

Treatment options are limited, which represents a significant unmet medical need (Toogood et al., 2021). Current therapeutic approaches in CFS/ME are generally pharmacological (e.g., antidepressants), nonpharmacological (e.g., cognitive behavioral therapy—CBT), or a combination of both approaches (Noor et al., 2021). Due to the lack of a curative drug, many patients are frequently referred to nonpharmacological therapies, which, in various ways, aim to help patients manage their symptoms (Mengshoel et al., 2020). In fact, randomized controlled trials (RCTs) studying the effectiveness of nonpharmacological interventions for CFS/ME patients have become a trend in the last decade (Kim et al., 2020). Nonpharmacological interventions such as pain neuroscience education (PNE; Amer-Cuenca et al., 2020; Louw et al., 2016), therapeutic exercise (Larun et al., 2021), CBT (White et al., 2011), and mindfulness training (Greeson & Chin, 2019; Lakhan & Schofield, 2013; Pauzano-Slamm, 2004; Surawy et al., 1999), have shown promising evidence in reducing CFS/ME severity. However, no single therapeutic approach supported by a RCT has shown to be definitely effective, with coherence and reproducibility, for CFS/ME management (Kim et al., 2020). Indeed, methodological reviews have criticized the scientific rigor of previous RCTs regarding the effectiveness of CBT and therapeutic exercise for CFS/ME (e.g., Ahmed et al., 2020, Kim et al., 2020).

More recent treatment recommendations include a holistic, patient-centered approach that integrates a variety of techniques to address physical, mental, and social well-being (Noor et al., 2021). Multicomponent nonpharmacological treatments are increasingly being studied and implemented for patients with chronic conditions (e.g., Geraghty et al., 2021). For instance, the intervention FIBROWALK is a multicomponent treatment that was originally designed for treatment of fibromyalgia (FM; Serrat et al., 2020). It includes PNE, therapeutic exercise, self-management patient education, CBT techniques, and mindfulness training. FIBROWALK has been shown to be effective in reducing symptoms of impairment, depression, and anxiety and improving physical functioning in FM patients compared to treatment as usual (TAU; Serrat et al., 2020, 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021). Recently, a video-based version of the FIBROWALK program was adapted into a home-based format during the Spanish COVID-19 lockdown and tested in two RCTs (Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021). Results showed that it was effective (with small-to-large effect sizes) for improving patient-reported functional impairment and other relevant FM-related symptoms (Serrat et al., 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021).

Overall, efficacious online interventions have several advantages over face-to-face interventions, such as lower cost, convenience, and potentially higher availability for patients with limited mobility (Andersson, 2018; Andersson & Titov, 2014). In addition, current evidence suggests that the use of telerehabilitation in CFS/ME patients is as effective as conventional in-person therapy for motor, cortical, and mood disorders (Janse et al., 2019; Worm-Smeitink et al., 2019). Given the high comorbidity (>80%) between FM and CFS/ME diagnoses (Serrat et al., 2020; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021; Sotzny et al., 2018) and the fact that all therapeutic components of FIBROWALK have separately shown some evidence of efficacy in CFS/ME treatment, it would seem reasonable to expect that the FIBROWALK program could also be an effective therapeutic approach for the management of core CFS/ME symptoms.

The present RCT aimed to evaluate the short-term effectiveness of the online video-based FIBROWALK program, renamed FATIGUEWALK (FaW) for the present study, in people with CFS/ME and to compare it to TAU only. It was expected that the FaW arm would obtain greater improvements in multidimensional fatigue (primary outcome), pain, anxiety and depressive symptoms, overall functional impairment, kinesiophobia, and physical functioning when compared to TAU alone (Hypothesis 1 [H1]). Moreover, given the high comorbidity between CFS/ME and FM diagnoses that has been previously found (Serrat et al., 2020, 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021) and the fact that this virtual multicomponent intervention was determined to be effective in mixed samples of individuals with FM and CFS/ME (Serrat et al., 2022), a sensitivity analysis assessing the effects of the intervention in those participants having only CFS/ME, and not FM, was conducted to verify that the beneficial clinical effects of the intervention were not solely related to improvements in FM symptoms. It was expected that FaW would be effective in significantly improving the aforementioned symptoms in this subsample (Hypothesis 2 [H2]). Finally, an exploratory analysis was performed to determine for whom FaW worked better, by classifying participants into responders and nonresponders and assessing between-group differences at baseline in sociodemographic and clinical variables between these subgroups. On the latter point, no hypothesis was envisaged because it was the first time that the FaW was tested in this population.

Method

Study Design

We conducted a single-blinded RCT. Data were collected at baseline (pretest) and at the end of the 12-week intervention (posttest). All procedures were conducted in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and subsequent updates. The FaW

study protocol was approved by the Clinical Research Ethics Committee of Vall d'Hebron Hospital (code: PR(AG)249/2020) and registered at ClinicalTrials.gov (identifier: NCT04593225). This study was performed in accordance with the guidelines issued by the consolidated standards of reporting trials (Schulz et al., 2010).

Sample Size

The required sample size was estimated to be $n = 105$ participants per study arm, considering a moderate effect size ($f = 0.25$) according to a previous meta-analysis (Marques et al., 2015) for the between-group differences at posttreatment for the primary outcome (i.e., Multidimensional Fatigue Inventory [MFI] total score) with an $\alpha = .05$ and power $1 - b = 0.95$. Expecting an attrition of at least 20% and a low presence of patients with only CFS/ME diagnosis (less than 20%; Serrat et al., 2020; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021; Sotzny et al., 2018), this number was nearly doubled.

Participants

Of the 460 potentially eligible patients from the Central Sensitivity Syndromes Specialized Unit (CSSSU; Vall d'Hebron Hospital, Barcelona, Spain), 32 were not available to participate due to various personal reasons. The initial study sample consisted of 428 patients with a diagnosis of CFS/ME. They were randomized into the two study arms, with 212 (FaW group; 66.51% women; mean age of 51.79 ± 9.28) and 216 (TAU group; 62.44% women; mean age of 52.26 ± 8.69) individuals per arm (see Figure 1). All participants were Spaniards and their race was classified as white in all cases. Baseline sociodemographic characteristics are shown in Table 1.

Inclusion criteria were: (a) diagnosis of CFS/ME according to Carruthers et al. (2011) criteria, verified by an internal medicine doctor of the CSSSU; (b) being 18 years old or older, (c) being able to understand Spanish, and (d) having completed the written informed consent. The exclusion criteria were: (a) suffering from severe mental illnesses (e.g., psychotic disorders) or terminal illnesses (e.g., advanced cancer) or (b) being unavailable to follow the program, such as having scheduled surgical interventions.

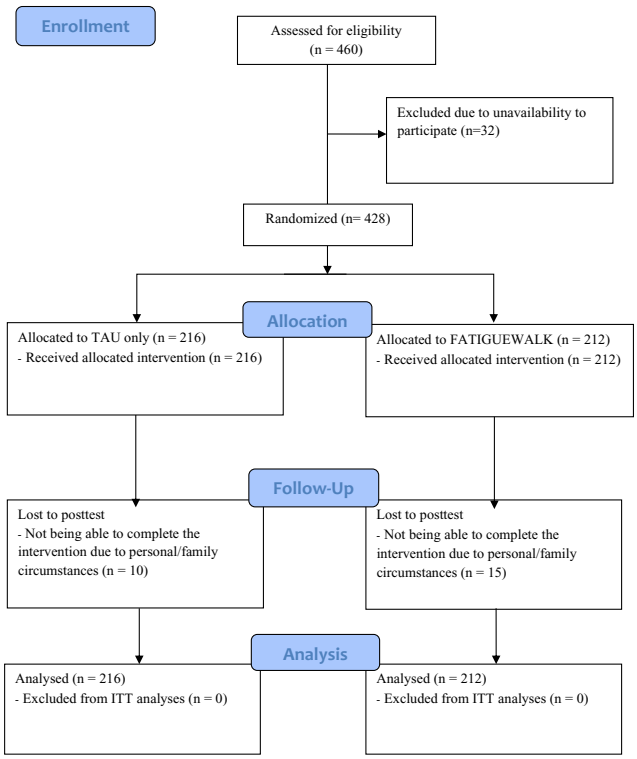
Procedure

Participant recruitment took place at the CSSSU located at Vall d'Hebron Hospital in Barcelona, Spain. The CSSSU is a clinic unit actively engaged in applied health research, focusing on both clinical and translational aspects. The unit specializes in the management of patients with FM and CFS/ME, receiving referrals from Primary Care services in the surrounding areas of Vall d'Hebron Hospital. Recruitment was performed in three waves, from September 2020 to July 2021.

The clinical professional in charge of the intervention was author Mayte Serrat, who has formation as a physiotherapist and health psychologist, with extensive experience (>20 years) treating patients with this type of conditions. MS verified the selection criteria for the whole pool of patients in the Unit, conducted an initial screening interview, and provided an overview of the study. Patients had previously been diagnosed of CFS/ME by a medical doctor (specialist in internal medicine). Written informed consent was obtained from all participants prior to the initial screening. Participants were informed of their right to withdraw from the study at any time, with the guarantee that they could continue to receive their usual treatment if they wished to do so. Those subjects who agreed to participate in the study completed a demographic questionnaire and a baseline test battery of standardized patient-reported outcome measures. Following testing, they were assigned to a list of alphanumeric codes, and randomized using the SPSS Version 26 statistical package (Kaysville, Utah, United States) to the FaW group or the control group. This process was carried out by means of numbered envelopes containing paper sheets with information on participant allocation. The envelopes were prepared by a CSSSU nurse. Neither the participants nor the clinician conducting the program (author Mayte Serrat) could be blinded within the study format. However, author Mayte Serrat was not involved in any stage of the patient assessment process and the researcher responsible for the outcome measures was unaware of the treatment allocation. All patients were assessed again with the same test battery of validated patient-reported outcome measures through an online survey after those subjects in the FaW treatment arm completed all 12-weeks of the FaW program.

Figure 1

CONSORT Flow Chart of Participants in the FaW Trial



Note. CONSORT = consolidated standards of reporting trials; FaW = FATIGUEWALK. See the online article for the color version of this figure.

Treatment Arms

Participants assigned to the FaW group underwent the online video-based FIBROWALK program—renamed here as FaW—following the usual curriculum (Serrat et al., 2022). It includes PNE (Sessions 1–10), therapeutic exercise (Sessions 2–9), self-management patient education (Sessions 2–9; 11–12), CBT techniques (Sessions 8–9; 11–12), and mindfulness training (Sessions 2–9; 11–12). The

Table 1
Baseline Demographic and Clinical Characteristics by Treatment Group

Variables	FaW ($n = 212$)	TAU ($n = 216$)	t/χ^2	p
Sociodemographic and clinical characteristics				
Age (years) $M \pm SD$	51.79 ± 9.28	52.26 ± 8.69	−0.53	.595
Women, n (%)	141 (66.51)	133 (62.44)	0.77	.381
BMI (kg/m^2) $M \pm SD$	27.05 ± 5.98	27.25 ± 5.99	−0.35	.726
ISPS (years) $M \pm SD$	16.59 ± 10.65	14.31 ± 9.63	2.33	**.020**
Civil status, n (%)			2.38	.497
Single	40 (18.87)	35 (16.20)		
Stable partner	120 (56.60)	116 (53.70)		
Divorced	43 (20.28)	57 (26.39)		
Widow	9 (4.25)	8 (3.71)		
Living alone, n (%)	16 (7.55)	12 (5.56)	2.90	.234
Education level, n (%)			6.14	.408
No schooling	2 (0.94)	6 (2.78)		
Primary studies not completed	10 (4.72)	15 (6.94)		
Primary studies	59 (27.83)	66 (30.56)		
Secondary studies	89 (41.98)	88 (40.74)		
University studies	49 (23.11)	36 (16.67)		
Other	3 (1.42)	5 (2.32)		
Disability certificate, n (%)			6.88	.230
No	63 (29.72)	74 (34.26)		
0%–33%	14 (6.60)	8 (3.70)		
33%–66%	111 (52.36)	108 (50.00)		
+66%	24 (11.32)	26 (12.26)		
FM comorbid, n (%)	174 (82.08)	181 (83.80)	0.22	.636
Outcome measures, M (SD)				
Primary measure				
MFI-total score	81.15 (11.87)	83.08 (11.38)	−1.72	.086
Secondary measures				
MFI-general	18.33 (2.15)	18.43 (2.37)	−0.46	.646
MFI-physical	17.14 (2.63)	17.51 (2.24)	−1.58	.115
MFI-reduced activity	15.21 (4.29)	15.96 (3.91)	−1.89	.059
MFI-reduced motivation	14.38 (3.66)	14.87 (3.66)	−1.39	.164
MFI-mental	16.09 (3.50)	16.31 (3.43)	−0.64	.520
Fatigue VAS	7.47 (2.43)	7.82 (2.26)	−1.53	.126
Pain VAS	7.56 (1.85)	7.70 (2.00)	−0.74	.459
HADS-A	12.50 (4.48)	13.50 (4.34)	−2.36	**.019**
HADS-D	11.92 (4.57)	12.28 (4.64)	−0.80	.422
HADS-total	24.42 (8.10)	25.79 (8.17)	−1.73	.084
FIQR	71.57 (17.01)	73.28 (16.67)	−1.05	.293
TKS	29.55 (7.75)	30.32 (7.29)	−1.06	.289
SF-PF	37.45 (20.22)	33.63 (20.30)	1.95	.052

Note. Statistically significant effects appear in bold ($p \leq .05$). FaW = FATIGUEWALK; TAU = treatment as usual; BMI = body mass index; FM = fibromyalgia; FIQR = Revised Fibromyalgia Impact Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISPS = illness self-perceived start; MFI = multidimensional fatigue inventory; SF-PF = physical functioning component of the 36-Item short form health survey; TSK = Tampa Scale for Kinesiophobia; VAS = Visual Analogue Scale.

therapeutic exercise prescribed in this program is characterized by low intensity, and the intensity is gradually increased very gently from session to session. This approach was taken to specifically address and prevent postexercise discomfort/malaise. A link to a 60-min video (hosted on a private YouTube channel) was emailed once a week for the next 11 weeks (total time of the FaW: 12 weeks). Each video provided detailed guidelines about (a) the neuroscience of pain (explanations based on Butler & Moseley, 2013); (b) how to perform different aerobic exercises at home (such as walking down the hallway at home); (c) mindfulness practice (based on Mindfulness-Based Stress Reduction program; Kabat-Zinn, 2013); and (d) CBT basics (psychoeducation about psychological processes and cognitive restructuring). For more details on the contents of the intervention, see the study by Serrat et al. (2022). Renaming the FIBROWALK program to FaW occurred at the beginning of the research. With this, we wanted to quickly identify the name of the intervention with the main diagnosis (and symptoms) of participants in the present study.

As aforementioned, it was an online video-based intervention, allowing participants to engage with the program remotely from their homes. Participants were instructed to watch the videos, and were asked to self-report their adherence to the prescribed exercises/practices for each session. Concretely, each week a short questionnaire (5–10 items) with yes/no questions was sent by email to check whether participants had watched the videos and performed the homework exercises (i.e., mindfulness practice, breathing exercises, relaxation training, therapeutic physical training). This information was not

systematically registered, but the CSSSU staff monitored the visualization of the content to identify participants who lagged behind. In the questionnaires, subjects were asked to review very basic concepts explained in each video (e.g., "Please provide a brief example of a catastrophic thought"). These weekly checks were used for early detection of possible adherence problems (e.g., not watching the videos, not doing the exercises) as well as possible dropouts. The therapist (Mayte Serrat) contacted patients via short message service and/or phone calls who did not respond to the questionnaire or reported problems related to the program or the study (e.g., not being able to do the homework, watch the videos, answer the questionnaires, etc.) and provided solutions to improve adherence. If necessary, patients who could not watch or answer the questionnaire within a specific week could request an extension date (e.g., watch/answer within 3–5 days). Participants could also contact the therapist (by email) at any time if any other problems related to the treatment or the study arose.

TAU included administration of medications tailored to each patient's symptom profile, complementary advice on aerobic exercise adapted to the patients' physical abilities, and basic health education about their pathology provided at baseline. Those patients assigned to the TAU arm had the opportunity to receive the FaW intervention once the study was completed.

No drug prescriptions were changed for any participant during the 12 weeks of the study. Rescue tablets of paracetamol (acetaminophen) 1 g (maximum 1 tablet/8 hr) were allowed only in case of acute worsening of symptoms.

Study Measures

Sociodemographic and Clinical Characteristics

An ad hoc questionnaire of sociodemographic and clinical information was used to collect the following patient data: age, gender, body mass index, illness self-perceived start (ISPS; in years), marital status, educational level, living arrangements (alone/accompanied), and certificate of disability obtained (indicating degree of disability).

Primary Measure

The MFI-20 (Smets et al., 1995) was used to measure the treatment effectiveness of the FaW. The MFI-20 is a 20-item self-report questionnaire designed to measure fatigue in five subscales (four items each): general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. All items are rated on a 5-point Likert scale and subscale scores can be calculated as the sum of their specific items (score range from 4 to 20). According to a recent study of its psychometric properties (Hinz et al., 2020), a total fatigue score can be also calculated as the sum of subscale scores (ranging scores from 20 to 100). Higher scores indicate a higher level of fatigue. The total score of the MFI-20 was used as the main clinical endpoint of this trial. The Spanish validated version (Munguía-Izquierdo et al., 2012) of the scale was used in the present study, which showed adequate internal consistency of the MFI subscales ($\alpha = .52$—MFI-Physical fatigue- and $\alpha = .82$—MFI-Reduced activity) and the total scale ($\alpha = .90$).

Secondary Measures

The Visual Analog Scales for pain (i.e., "intensity of perceived pain during last week, from 0 = "no pain" to 10 = "unbearable pain") and fatigue (i.e., "level of perceived energy during last week, from 0 = "lots of energy" to 10 = "no energy") from the Spanish validated version of the Revised Fibromyalgia Impact Questionnaire (FIQR; Luciano et al., 2013) were used to assess pain and fatigue intensity, respectively.

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to measure depressive and anxious symptomatology. It is divided into two dimensions (HADS-Anxiety [HADS-A] and HADS-Depression [HADS-D]). Each dimension is divided into seven items in a 4-point Likert scale response format. HADS-A and HADS-D subscale scores range from 0 to 21, with higher scores indicating greater symptom severity. The Spanish validated version was used (Terol et al., 2007), which showed adequate internal consistency in our sample: HADS-A ($\alpha = .86$), HADS-D ($\alpha = .87$), and total scale ($\alpha = .91$).

The FIQR (Bennett et al., 2009) is a 21-item questionnaire that measures perceived level of functional impairment related to FM during the last 7 days. Items are on a 0–10 numerical scale. The FIQR is divided into three dimensions: physical dysfunction (ranging from 0 to 30), overall impact (score ranges from 0 to 20), and intensity of symptoms (ranging from 0 to 50). A total score (from 0 to 100) can be calculated to provide a general endpoint for functional status in FM, with higher scores indicating greater functional impairment. The Spanish validated version was used in the present study (Luciano et al., 2013), which showed excellent internal consistency ($\alpha = .93$).

The Tampa Scale for Kinesiophobia (TSK; Miller et al., 1991) includes 11 items on a 4-point Likert-type scale (range 0–11). Total scores of the TSK can range from 11 to 44 points, where higher scores indicate greater fear of pain, movement, and reinjury. The Spanish validated version was used in the present study (Gómez-Pérez et al., 2011), which showed an adequate internal consistency in our sample ($\alpha = .87$).

The Short Form Health Survey—Physical Functioning subscale (SF-PF; Ware & Sherbourne, 1992) was used to measure physical functioning. This subscale consists of 10 items, with a 3-point Likert-type response format. Total scores range from 0 to 100, where higher scores indicate better physical functioning. The Spanish version (Alonso et al., 1995) was used, which showed an adequate internal consistency ($\alpha = .86$).

Data Analyses

Data analyses were computed with SPSS Version 26. Descriptive statistics were calculated for all variables and presented as means and standard deviations for continuous data or absolute numbers and percentages (%) for categorical data. Levene's test was used to assess equality of variances of continuous variables and Kolmogorov–Smirnov to test for normality and sampling distribution with no major violations noted. Student's t tests and χ^2 tests were used to examine any possible baseline differences between FaW and the TAU group and between participants who provided pre/post data and participants who did not provide pre/post data.

We used analysis of covariance (ANCOVA), including baseline values as covariates, to examine differences between FaW versus TAU alone after treatment on MFI scores and on each of the secondary outcomes. ANCOVA has been shown to have greater power to detect change than analysis of variance in randomized study designs (Van Breukelen, 2006). This analysis was conducted to examine between-group differences using both the full sample and the subsample of participants with CFS/ME but not FM. Analyses were

performed with all randomized participants and imputing missing values (i.e., an intention-to-treat approach) and additionally, including only those participants with complete data (i.e., a complete-case approach). The last observation carried forward method was used to impute missing data values despite its apparent drawbacks (Lachin, 2016) because the attrition rate was low ($n < 15$). In order to reduce the Type I error, we applied the Benjamini–Hochberg method, which controls the false discovery rate using sequential modified Bonferroni correction for multiple comparisons (Glickman et al., 2014).

As measures of effect sizes, partial eta squared, Cohen's *d*, the absolute risk reduction, and the number needed to treat (NNT) were calculated. The usual rule of thumb of $\eta_p^2 = .01$, small; 0.06, moderate; and 0.14, large was used to interpret the observed effect sizes associated to the group variable in the ANCOVAs (Cohen, 1988). In addition, we also calculated the effect size (Cohen's *d*) using the pooled initial *SD* to measure differences in the initial and subsequent mean values and to correct for the estimated population (Morris, 2008; $d = 0.20$, small effect size; 0.50, moderate; and 0.80, large). When determining the absolute risk reduction and NNT, the Jacobson and Truax method (1991) was used to calculate the clinically significant change (CSC; method C) criterium for the MFI-20, which established a cut-off point to classify participants into responders versus nonresponders. Participants were considered responders if their posttreatment MFI-20 total scores were below 65, meaning that they moved to a nonclinical level of fatigue. This value was the result of the Jacobson and Truax formula (1991): *SD* (normative data) × Pretest mean (FaW participants) + pretest *SD* (FaW participants) × Pretest mean (normative data))/(*SD* (normative data) + pretest *SD* (FaW participants). Normative data from the general population ($M = 44.3$; $SD = 14.1$; Hinz et al., 2013, 2020) were used for this calculus. An online calculator was used to compute the absolute risk reduction and NNT (https://www.graphpad.com/quickcalcs/NNT1.cfm). Finally, *t* tests and χ^2 tests were performed to assess baseline differences between responders and nonresponders to know for whom the FaW worked better.

Results

Treatment Adherence and Baseline Clinical Characteristics

All participants in the FaW group self-reported watching all the videos corresponding each of the 12 sessions and adhering to at-home practice. Baseline clinical characteristics are shown in Table 1. No differences were found between groups in posttreatment retention rate (FaW: 92.90%; TAU: 95.40%; $\chi^2 = 1.16$, $p = .309$). No differences were found between patients with data completed at posttreatment (FaW, $n = 197$; TAU, $n = 206$) and participants lost at posttreatment assessment (FaW, $n = 15$; TAU, $n = 10$) for any baseline variable (all $p > .05$).

As shown in Table 1, there were no statistically significant differences in patient-reported outcome measures between the two treatment groups (with imputed values), except for ISPS scores ($p = .020$) and HADS-A scores ($p = .019$). These between-group differences were controlled in further analyses, introducing ISPS and HADS-A baseline scores as covariables in the ANCOVAs. In parallel, three differences in questionnaire scores were found between the two treatment groups at baseline when assessing only the complete-case data set: illness self-perceive start ($p = .024$), HADS-A ($p = .039$), and SF-PF ($p = .026$). Therefore, the same covariable methodology as above was applied to further ANCOVA analyses in the complete-case data set.

Between-Group Differences in Primary and Secondary Outcomes

Table 2 shows means and *SD*s of the patient-reported outcome measures at baseline and at posttreatment (with imputed values) in the TAU and FaW groups (full sample). Statistically significant improvements ($p < .001$) were found for the primary outcome (with a moderate effect size; $\eta_p^2 = .11$) and all the secondary outcomes, with effect sizes ranging from small-to-very large (i.e., $\eta_p^2 = .02$–$.30$). Similar results were found in the complete-case data set (see Table S1 in the online supplemental materials for more details).

Table 3 shows means and *SD*s of the patient-reported outcome measures at baseline and at posttreatment (with imputed values) in the TAU only and FaW intervention groups when only CFS/ME patients without FM comorbidity were included. A post hoc power analysis was conducted to determine whether the present study was adequately powered with this subsample. Results indicated that the current study had 70.02% power for ANCOVA. Statistically significant effects with a medium effect size ($\eta_p^2 = .08$) for the primary outcome of multidimensional fatigue and most of the secondary outcomes (with moderate-to-very large effect sizes; from $\eta_p^2 = .06$ to .30) were found. Regarding the ANCOVAs with the complete-case data set of participants without FM comorbidity, similar results were found (see Table S2 in the online supplemental materials for more details).

Absolute Risk Reduction and Number Needed to Treat

From the FaW group, 55 (26%) were considered responders (MFI-20 total score < 65) and 157 (74%) nonresponders. Regarding baseline sociodemographics, as shown in Table S3 in the online supplemental materials, there were no statistically significant differences between responders and nonresponders. However, there were statistically significant differences between these groups in all clinical characteristics at baseline, showing that nonresponders reported more severe pretreatment symptomatology than responders. The absolute risk reduction in FaW versus TAU alone was 19% (95% confidence interval [CI: 12.19, 25.80]) with NNT = 6 (95% CI [3.9, 8.2]), meaning that six patients would need to be treated with FaW for one of them to become a responder, who would not have done so in the TAU alone group.

Discussion

This RCT aimed to assess the effectiveness of the FIBROWALK program (termed FaW for the present study) for CFS/ME patients, to target symptoms of fatigue, pain, anxiety, depression, kinesiophobia, and overall functional impairment. In brief, CFS/ME participants with and without comorbid FM, reported a significant decrease in all clinical symptoms measured at baseline compared to those who only received TAU. Thus, H1 was supported. Similarly, when examining the outcomes of CFS/ME participants without comorbid FM, the results showed that this subsample experienced a significant decrease in all clinical symptoms too, except for some specific aspects related to fatigue (intensity of

Table 2

Descriptive Statistics and Between-Group Differences for Primary and Secondary Outcomes From an ITT Approach (Imputation of Missing Values With LOCF Method)

Variable	FaW ($n = 212$)	TAU ($n = 216$)	FaW versus TAU			
	M (*SD*)	*M* (*SD*)	*F*	*p*	η_p^2	*d*
MFI-total			51.47	**<.001**	.11	0.56
Baseline	81.15 (11.87)	83.08 (11.38)				
Posttreatment	74.01 (15.16)	82.92 (11.10)				
MFI-general fatigue			40.78	**<.001**	.09	0.66
Baseline	18.33 (2.14)	18.43 (2.37)				
Posttreatment	16.91 (3.13)	18.50 (1.91)				
MFI-physical fatigue			56.26	**<.001**	.12	0.73
Baseline	17.14 (2.63)	17.51 (2.24)				
Posttreatment	15.30 (3.40)	17.46 (2.40)				
MFI-reduced activity			14.96	**<.001**	.03	0.27
Baseline	15.21 (4.29)	15.96 (3.91)				
Posttreatment	13.91 (4.47)	15.76 (4.11)				
MFI-reduced motivation			37.65	**<.001**	.08	0.47
Baseline	14.38 (3.66)	14.87 (3.66)				
Posttreatment	12.70 (4.10)	14.94 (3.64)				
MFI-mental fatigue			9.04	**.003**	.02	0.25
Baseline	16.09 (3.50)	16.31 (3.43)				
Posttreatment	15.18 (3.82)	16.26 (3.28)				
VAS-fatigue			23.71	**<.001**	.05	0.34
Baseline	7.47 (2.43)	7.82 (2.26)				
Posttreatment	6.65 (2.31)	7.80 (2.15)				
VAS-pain			44.63	**<.001**	.10	0.56
Baseline	7.56 (1.85)	7.70 (1.99)				
Posttreatment	6.59 (2.28)	7.80 (1.93)				
HADS-A			30.33	**<.001**	.07	0.31
Baseline	12.50 (4.48)	13.50 (4.34)				
Posttreatment	11.09 (4.56)	13.45 (4.20)				
HADS-D			47.37	**<.001**	.10	0.47
Baseline	11.92 (4.58)	12.28 (4.64)				
Posttreatment	10.19 (4.75)	12.74 (4.61)				
HADS-total			50.32	**<.001**	.11	0.43
Baseline	24.42 (8.10)	25.79 (8.17)				
Posttreatment	21.28 (8.48)	26.19 (7.96)				
FIQR			88.14	**<.001**	.17	0.72
Baseline	71.57 (17.01)	73.28 (16.67)				
Posttreatment	61.54 (20.13)	75.35 (15.17)				
TSK			177.78	**<.001**	.30	0.97
Baseline	29.55 (7.75)	30.32 (7.29)				
Posttreatment	22.56 (6.96)	30.63 (7.34)				
SF-PF			20.47	**<.001**	.05	0.28
Baseline	37.45 (20.22)	33.63 (20.30)				
Posttreatment	42.92 (21.35)	33.50 (19.87)				

Note. Statistically significant effects are shown in bold ($p \leq .05$). Unadjusted means are shown. All analyses were controlled by years since illness emerged ($p = .020$) and baseline HADS-A ($p = .019$). When the Benjamini–Hochberg correction was applied to correct for multiple comparisons, all significant effects remained significant. ITT = intention-to-treat; LOCF = last observation carried forward; FaW = FATIGUEWALK; TAU = treatment as usual; FIQR = Revised Fibromyalgia Impact Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISPS = illness self-perceived start; MFI = multidimensional fatigue inventory; SF-PF = physical functioning component of the 36-item short form health survey; TSK = Tampa Scale for Kinesiophobia; VAS = Visual Analogue Scale.

fatigue, difficulties in concentrating, reduced motivation, reduced activity). Therefore, H2 was partially supported. Finally, it was also found that clinical responders to the FaW intervention reported milder clinical symptom severity than nonresponders at baseline.

Though multiple previous studies have demonstrated the effectiveness of FIBROWALK for management of FM symptoms (Serrat et al., 2020, 2022; Serrat, Coll-Omaña, et al., 2021; Serrat, Sanabria-Mazo, et al., 2021), measures of fatigue had not been previously assessed. In the present study, a significant reduction in the level of fatigue (i.e., MFI total scores), our main outcome, was measured in the total sample of participants in the FaW arm, with a moderate effect size. In addition, a significant reduction in fatigue was measured in the subsample of CFS/ME participants without comorbid FM, also with a moderate effect size. This core symptom of CFS/ME is often a distressing phenomenon that can impair patients' lives, personally, socially, and professionally (Norheim et al., 2011). As reported in previous studies, other nonpharmacological interventions (mainly CBT, therapeutic exercise, and self-care), either online or in-person, have shown promising results in reducing reported levels of fatigue with small-to-moderate effect sizes

Table 3

Descriptive Statistics and Between-Group Analyses for Primary and Secondary Outcomes From an ITT Approach (With Imputation of Missing Data) for Those Participants Who Did Not Have a Comorbid FM Diagnosis

Variable	FaW ($n = 38$)	TAU ($n = 35$)	FaW versus TAU			
	M (*SD*)	*M* (*SD*)	*F*	*p*	η_p^2	*d*
MFI-total			6.25	**.015**	.08	0.45
Baseline	79.82 (13.06)	77.97 (12.42)				
Posttreatment	75.37 (14.21)	79.31 (11.61)				
MFI-general fatigue			9.01	**.004**	.11	0.77
Baseline	18.55 (2.32)	17.74 (3.02)				
Posttreatment	17.39 (2.71)	18.66 (2.11)				
MFI-physical fatigue			7.82	**.007**	.10	0.58
Baseline	17.34 (2.70)	17.20 (2.37)				
Posttreatment	15.87 (3.35)	17.23 (2.41)				
MFI-reduced activity			1.38	.244	.02	0.26
Baseline	15.42 (4.33)	14.46 (4.14)				
Posttreatment	14.74 (4.41)	14.91 (3.90)				
MFI-reduced motivation			3.84	.054	.05	0.31
Baseline	13.66 (4.56)	13.23 (3.74)				
Posttreatment	12.42 (4.46)	13.31 (3.86)				
MFI-mental fatigue			0.00	.948	.00	0.06
Baseline	14.84 (3.90)	15.34 (3.77)				
Posttreatment	14.94 (3.77)	15.20 (3.17)				
VAS-fatigue			3.45	.067	.05	0.25
Baseline	6.82 (2.90)	7.14 (2.44)				
Posttreatment	6.74 (2.45)	7.74 (2.13)				
VAS-pain			4.72	**.033**	.06	0.38
Baseline	6.08 (2.57)	6.06 (2.89)				
Posttreatment	5.50 (2.67)	6.54 (2.93)				
HADS-A			10.64	**.002**	.13	0.41
Baseline	10.24 (4.97)	11.69 (4.92)				
Posttreatment	9.26 (4.99)	12.77 (4.44)				
HADS-D			6.60	**.012**	.09	0.37
Baseline	10.16 (5.23)	9.80 (4.78)				
Posttreatment	9.13 (5.46)	10.63 (4.17)				
HADS-Total			10.71	**.002**	.13	0.42
Baseline	20.39 (9.33)	21.49 (9.25)				
Posttreatment	18.39 (9.43)	23.40 (8.13)				
FIQR			20.53	**<.001**	.23	0.72
Baseline	57.81 (20.57)	59.44 (17.29)				
Posttreatment	52.65 (20.58)	68.22 (19.25)				
TSK			29.74	**<.001**	.30	1.10
Baseline	27.79 (8.13)	27.03 (6.82)				
Posttreatment	22.05 (7.69)	29.63 (8.00)				
SF-PF			5.19	**.030**	.07	0.41
Baseline	44.21 (22.53)	46.86 (21.46)				
Posttreatment	46.97 (21.13)	40.57 (21.72)				

Note. Statistically significant effects are shown in bold ($p \leq .05$). Unadjusted means are shown. Since no between-group differences for any variable were found at baseline, no covariates were added. When the Benjamini–Hochberg correction was applied to correct for multiple comparisons, all significant effects remained significant. ITT = intention-to-treat; FM = fibromyalgia; FaW = FATIGUEWALK; TAU = treatment as usual; FIQR = Revised Fibromyalgia Impact Questionnaire; HADS = Hospital Anxiety and Depression Scale; ISPS = illness self-perceived start; MFI = multidimensional fatigue inventory; sf-pf = physical functioning component of the 36-item short form health survey; TSK = Tampa Scale for Kinesiophobia; VAS = Visual Analogue Scale.

(Kim et al., 2020). Thus, the between-group differences in fatigue levels found in the present study are comparable to those reported in RCTs of the most studied nonpharmacological interventions for CFS/ME. This finding reinforces the recommendation to implement multicomponent nonpharmacological treatments for these patients, as indicated in recent clinical guidelines (Noor et al., 2021), and to consider remote delivery of these treatments.

In addition to the primary outcome of fatigue, the FaW intervention in the total sample (including subjects with comorbid FM) resulted in a reduction of all the secondary outcome domains of fatigue, perceived intensity of fatigue and pain, depressive and anxious symptomatology, kinesiophobia, and perceived functional impairment (related to FM symptoms), as well as an improvement in perceived physical functioning, with small-to-large effect sizes. These are promising results, since a 2008 Cochrane review of CBT in CFS/ME adults expressed doubts about its ability to manage CFS/ME symptoms beyond fatigue, such as depression/anxiety and physical functioning, either at posttreatment or at follow-up periods (Price et al., 2021). Hence, the integration of a

diverse range of techniques is likely to have a significant impact in improving both the physical and mental quality of life of these patients. That is to say, these symptom improvements reported in the present study might be due to the effect of FaW components other than CBT (therapeutic exercise, mindfulness training, and/or PNE). For example, another Cochrane review and meta-analysis on effectiveness of therapeutic exercise in treating CFS/ME concluded that it was effective for improving self-reported fatigue severity and physical functioning at posttreatment, with a slightly greater benefit for patients with comorbid depression (Edmonds et al., 2004). Moreover, although scarce, studies about mindfulness training for CFS/ME adults have shown promising effectiveness on fatigue severity, mental functioning, and anxiety/depression (Rimes & Wingrove, 2013; Surawy et al., 1999).

When analyzing data of CFS/ME participants without comorbid FM (i.e., 17% of the total sample), the results were overall similar to the total sample, with some exceptions. There were small differences in the effect sizes of pain intensity (in favor of the mixed sample) and physical functioning (in favor of the CFS/ME subsample). In addition, there was a lack of statistical significance in the reduction of fatigue intensity (according to the single-item measure) and concentration difficulties and improvements in motivation to start and perform activities (specific domains of the MFI-20). It could be argued that the participants with comorbid FM had a more severe clinical manifestation than those without it, as shown in previous studies (Ickmans et al., 2015; Meeus et al., 2016), which in turn, reduced the scope for improving. Another possible explanation is that the subsample of participants without comorbid FM was significantly smaller than the full sample, thus increasing the risk of a Type II error. Further RCTs on the effectiveness of FaW on this population should shed light on these aspects in the future. However, the present findings provide support for the implementation of our multicomponent program in individuals with CFS/ME, both with and without comorbid FM, with the anticipation of significant improvement in the key symptoms associated with the syndrome. Initially, it was deemed appropriate that our multicomponent program was tailored to address the symptoms experienced by CFS/ME patients, both with and without comorbid FM, due to the considerable comorbidity observed between these syndromes. Notably, a substantial proportion of CFS/ME patients experience pain, including recurrent headaches (Castro-Marrero et al., 2017). Furthermore, the content of the PNE module already encompasses strategies for managing fatigue (Serrat et al., 2022). This overlap might have ensured that the FIBROWALK intervention remained customized to effectively address the specific symptoms encountered by CFS/ME patients, regardless of the presence of comorbid FM.

Although pain is a prevalent symptom in individuals with CFS/ME, previous studies have not often focused on assessment of pain symptoms and specific management treatment approaches in this patient population (Ascough et al., 2020). In this vein, the present results are remarkably important, as they support the effectiveness of our online multicomponent approach to help reduce pain intensity. Similarly, studies investigating the prevalence of mental disorders in individuals with CFS/ME have consistently reported clinically significant rates of anxiety and depression within this population. Research findings indicate a significantly higher incidence of mood and anxiety disorders among individuals with CFS/ME compared to those without functional somatic syndromes. Furthermore, the prevalence of these mental problems tends to be higher in CFS/ME compared to FM and irritable bowel syndrome (Daniels et al., 2017; Janssens et al., 2015; Leong et al., 2022). In this line, the present sample showed in average a moderate level of anxiety and depression. As previously mentioned, CFS/ME symptomatology can cause substantial functional impairment in different areas of life (e.g., social and working life). A variable directly related to functional impairment is kinesiophobia, or fear of movement. Pain-neurophysiology education has been identified as a mechanism of positive change in kinesiophobia severity for individuals with CFS/ME (Malfliet et al., 2017). The results of the present study support that assertion, as demonstrated by a significant decrease in patient-reported kinesiophobia in the FaW treatment group.

Overall, similar results were found in the last RCT with FM patients on the effectiveness of FIBROWALK, which assessed all the same patient-reported variables as the present study, except for fatigue (Serrat et al., 2022). However, Cohen's *d* effect sizes were considerably larger in the FIBROWALK study compared to the present study, including pain intensity (0.76 vs. 0.56), anxiety levels (0.51 vs. 0.31), depression level (0.63 vs. 0.47), overall functional impairment (0.80 vs. 0.72), kinesiophobia (1.48 vs. 0.97), and physical functioning (0.83 vs. 0.28). Both studies included a relatively large percentage of comorbid subjects with both FM and CFS/ME diagnoses (between 80% and 90% of participants). They were about equal in sociodemographic and outcome variables at baseline, and sample sizes were large enough to discard problems related to statistical power. It is possible that the different recruitment waves used to gather the subject cohorts in the FIBROWALK and FaW studies may have created some confounding variables (i.e., chronobiological influences). Subject recruitment in the FIBROWALK study was performed in two waves, from September 2020 to January 2021 (Serrat et al., 2022). Subject recruitment in the present FaW study was performed in three waves, from September 2020 to July 2021.

As mentioned above, overall fatigue levels in the FaW cohort in the present study improved significantly, and a subgroup reported posttreatment fatigue levels within healthy proportions (responders, 26% of the total sample). This result is in line with a previous RCT study, in which internet-based CBT was found to be effective in recovering around 40% of participants in an RCT involving adults with CFS/ME (Janse et al., 2018). Moreover, compared to the responders in the present study, the nonresponders reported significantly higher baseline severity levels in all the clinical characteristics measured. It seems that some of the nonresponders may have improved in treatment, but since they had a higher level of symptomology to overcome, fewer were able to achieve fatigue levels within normal parameters. Similarly, the previous FIBROWALK study showed that FM individuals classified as nonresponders reported more anxiety and depressive symptoms and worse physical functioning prior to treatment compared to responders (Serrat et al., 2022). Perhaps a higher dosage of treatment (e.g., longer treatment program) may have resulted in a more improved treatment response for some of the nonresponders in both of these studies. It should be noted that differences in sociodemographic variables were not found in either the FIBROWALK RCT or the present one. Another explanation from machine learning studies is that the spectrum of chronic fatigue could actually comprise different diagnostic categories, depending on the severity of the disease, and each category might benefit from different types of intervention (Maes et al., 2012).

Furthermore, the NNT was adequate, being within the standard range (from 4 to 6) for interventions for chronic conditions

(Citrome & Ketter, 2013). This result suggests that FaW can be preferred to the usual treatment that CFS/ME patients receive here in Spain because of the greater likelihood of benefit. Concretely, a therapeutic advantage can be expected for every six patients, which can be considered a significant benefit, especially taking into account the usual overloading of medical facilities.

Finally, FaW showed a relatively low attrition rate (around 7%), even lower than FIBROWALK in the last trial (around 10%; Serrat et al., 2022), thus supporting the feasibility of this online intervention. Other online interventions in patients with chronic pain have shown an attrition rate ranging between 4% and 54% (Buhrman et al., 2016). The low attrition rate of participants in the present study could have been due to the superior ability of the online format for engaging participants who were not able to attend in-person sessions, in part due to the impairment of their fatigue. Other possible reasons are the emphasis at the beginning of the study about the importance of actively participating in the intervention, the weekly questionnaires, regular check-ups with a therapist to verify patient follow-through, the high flexibility of the online format, and the convenience sampling procedure applied, since recruitment was performed in the hospital where the research team was integrated. Besides that, the research team is strongly of the view that the following key aspects played a vital role in the effective implementation of the FaW program. First, the program benefitted from the involvement of a multidisciplinary team comprising rheumatologists, psychologists, and physiotherapists. In this regard, it is important to note that the FIBROWALK program was designed to be implemented by a psychologist and by a physiotherapist. Second, a strong emphasis was placed on fostering active engagement with the program's content and encouraging regular practice. This emphasis was established early in the intervention and reinforced through timely reminders when needed. Lastly, continuous monitoring of participant progress enabled prompt communication and support for individuals who failed to report adherence and at-home practices. All these factors, putatively contributed to the program's success in delivering positive outcomes.

Several limitations of this study need to be acknowledged, including the absence of an active control group and the lack of long-term assessment, which further RCTs should overcome. It is also important to highlight that this clinical trial was conducted in a specialized unit of a tertiary referral hospital in the context of clinical practice. In relation to the latter, strict selection criteria could not be established due to pressures in daily clinical practice (i.e., most patients were admitted), and, in particular, patients who applied for a certificate of incapacity were also included in this RCT. Furthermore, for ethical reasons, and because a pretest–posttest control-group design was implemented, the inclusion of follow-up assessments would have delayed the opportunity for the TAU group to undergo the FaW program. In response to the challenges posed by the COVID-19 pandemic to this population, the research team prioritized the prompt delivery of the intervention. However, it is important to note that follow-ups are crucial for evaluating the long-term effectiveness of treatments in real-world clinical practices. Therefore, these should be considered and assessed in additional RCTs. Besides, the patients included in the study had a long duration of illness and were recruited from the hospital to which the research team belonged, so the sample cannot be representative of the entire CFS/ME population. Moreover, the subsample without FM was not enough (power < 0.80) to ensure a low risk of Type II error, so reducing our ability to detect existing differences between groups. Additionally, the study did not examine the potential impact of adherence on treatment outcomes. It is recommended that future studies systematically record this information through reports of time spent per screen and number of therapist contacts for example. It would be valuable to understand the relationships between therapist contact frequency, adherence, and outcomes. Thus, further RCTs evaluating the effects of online FaW should include larger samples from multiple centers and also include complementary objective outcomes, such as aerobic fitness and other clinician-assessed measures.

Resumen

Objetivo: Este estudio tuvo como objetivo evaluar la efectividad de una intervención multicomponente en línea llamada FATIGUEWALK (FaW) en comparación con el tratamiento habitual (TAU, por sus siglas en inglés) en pacientes con síndrome de fatiga crónica/encefalomielitis miálgica (CFS/ME, por sus siglas en inglés). ***Método:*** FaW incluyó educación en neurociencia del dolor, ejercicio terapéutico, reestructuración cognitiva y entrenamiento de atención plena. Un total de 428 pacientes con CFS/ME fueron asignados aleatoriamente a dos grupos de estudio: FaW en línea más TAU versus TAU solo. Se llevó a cabo un estudio controlado aleatorio (ECA) simple ciego. Se recopilaron medidas de resultado validadas informadas por los pacientes de fatiga, dolor, ansiedad, depresión y función física al inicio y después del tratamiento, después de la intervención FaW, que duró 12 semanas. ***Resultados:*** Se observaron mejoras estadísticamente significativas (con tamaños de efecto pequeños a moderados) en FaW en línea versus TAU solo con respecto a los aspectos multidimensionales de la fatiga (la d de Cohen oscila entre 0.25 y 0.73) y la mayoría de los resultados secundarios (intensidad de dolor y la fatiga, depresión y ansiedad sintomatológica, deterioro funcional, kinesiofobia, funcionamiento físico). La reducción del riesgo absoluto en FaW versus TAU fue del 19% (IC del 95% = [12.19, 25.80]) con número necesario a tratar (NNT) = 6 (IC del 95% = 3.9–8.2). En general, se observaron mejoras clínicas similares en los análisis de sensibilidad que incluyeron un subgrupo de pacientes sin comorbilidad con fibromialgia ($n = 70$). ***Conclusiones:*** Este es el primer estudio que evalúa la efectividad a corto plazo de una intervención multicomponente en línea agregada a TAU, en comparación con TAU sola, para el tratamiento del CFS/ME. Se justifican ensayos adicionales, que incluyan grupos de control activo con una dosis de tratamiento equivalente y que evalúen la eficacia a largo plazo del FaW en línea.

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Received April 6, 2023
Revision received September 5, 2023
Accepted September 16, 2023 ■

Annex 3

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier
Funding	4	Sources and types of financial, material, and other support
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors
	5b	Name and contact information for the trial sponsor
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention
	6b	Explanation for choice of comparators
Objectives	7	Specific objectives or hypotheses
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
	31b	Authorship eligibility guidelines and any intended use of professional writers
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

Annex 4

Diferències entre el Sistema de Resposta Immunoinflamatòria (IRS) i el Sistema Reflex Immunoregulador Compensatori (CIRS)

Taula 1. *Resum de les diferències entre IRS i CIRS*

Característica	IRS (Sistema de Resposta Immunoinflamatòria)	CIRS (Sistema Reflex Immunoregulador Compensatori)
Definició	Sistema activat per una agressió (infecció, dany tissular, estrès) que desencadena una resposta inflamatòria.	Sistema regulador que modula la resposta immune per evitar una inflamació excessiva i restaurar l'equilibri immune.
Funció principal	Provocar una resposta inflamatòria activa per defensar l'organisme d'agressions externes o interns.	Regulació de la resposta immune per contrarestar la inflamació excessiva i evitar danys inflamatòries crònics.
Tipus de resposta	Proinflamatòria, activa per combatre infeccions o lesions.	Antiinflamatòria, per equilibrar la resposta immune i prevenir la inflamació crònica.
Citoquines implicades	TNF-α, IL-1β, IL-6 (promouen la inflamació).	IL-10, TGF-β (ajuden a reduir la inflamació i modulen la resposta immune).
Impacte en l'organisme	Pot causar danys tissulars si la resposta inflamatoria és desregulada o excessiva.	Protegeix contra la inflamació crònica, però si és excessiu pot augmentar la vulnerabilitat a infeccions.
Context clínic	Sepsis, malalties autoimmunes, trastorns inflamatòries crònics.	Trastorns com la depressió, trastorn bipolar i altres condicions associades a disfunció immune.
Efectes a llarg termini	Pot generar malalties crònics inflamatòries, trastorns cardiovasculars, i neurodegeneratius.	Pot contribuir a trastorns psiquiàtrics (com la depressió) si el sistema immune no es regula adequadament.

Nota: TNF-α, Tumor Necrosis Factor Alpha; IL, Interleucina; TLRs, Toll-like Receptors.

Font: Elaboració pròpia.

Annex 5

Resultats anàlisi correlacional basal entre variables clíniques i biomarcadors

Taula 1. *Correlacions entre biomarcadors inflamatoris i variables clíniques*

Variables correlacionades	Coeficient de Pearson (r)	Valor p
Marcadors inflamatoris		
IL-6 basal - IL-10 basal	0.738	<0.001
IL-6 basal - CXCL8 basal	0.561	<0.001
IL-6 basal - hs-CRP basal	0.367	<0.001
CXCL8 basal - hs-CRP basal	0.303	0.001
IL-17a basal - IL-6 basal	0.364	<0.001
Variables clíniques		
hs-CRP basal - Fatiga	-0.170	0.041
IL-6 basal – Funció Física	-0.194	0.024
IL-6 basal - Dolor	-0.158	0.054
Desregulació immunitària		
Ràtio IL-6/IL-4 basal - IL-6 basal	0.882	<0.001
Ràtio IL-6/IL-10 basal - IL-17A basal	0.498	<0.001
Ràtio IL-6/IL-10 basal - CXCL8 basal	0.190	0.026

Nota: Valors de p <0.05 considerats estadísticament significatius. IL, Interleucina; hs-CRP, high-sensitivity C-reactive protein.

Font: Elaboració pròpia.

Les correlacions observades en els marcadors inflamatoris suggereixen una connexió entre un perfil clínic més greu abans de la intervenció i un estat proinflamatori elevat. Aquesta hipòtesi es fonamenta en diversos punts que es poden justificar mitjançant les següents evidències:

1. Correlacions entre marcadors inflamatoris:

Les correlacions significatives entre els nivells basals de diversos marcadors inflamatoris com IL-6, IL-10, CXCL8, IL-17A i hs-CRP apunten a la presència d'un estat proinflamatori altament significatiu en les persones amb FM amb un perfil clínic més greu. Els valors obtinguts, com les correlacions entre IL-6 basal i IL-10 basal ($r = 0.738$, $p < 0.001$) o entre IL-6 basal i CXCL8 basal ($r = 0.561$, $p < 0.001$), indiquen una resposta immunitària exacerbada. Aquestes dades donen suport a la hipòtesi que un major grau d'inflamació està estretament vinculat a una severitat clínica més pronunciada.

2. Relació amb variables clíniques:

Els resultats també mostren una relació entre els nivells d'hs-CRP i paràmetres clínics com el dolor i la fatiga. Tot i que la correlació entre hs-CRP i dolor no és significativa, la correlació negativa entre hs-CRP basal i energia ($r = -0.170$, $p = 0.041$) suggereix que les persones amb FM amb nivells elevats d'hs-CRP tenen major probabilitat de mostrar fatiga o baixos nivells d'energia, un signe habitual en casos d'inflamació crònica. Així mateix, la correlació negativa entre IL-6 basal i la funció física ($r = -0.194$, $p = 0.024$) reforça la idea que un estat inflamatori sostingut pot comprometre la qualitat de vida, impactant directament el benestar de les persones amb FM.

3. Indicadors de desregulació immunitària:

Les ràtios IL-6/IL-10 i IL-6/IL-4 mostren correlacions significatives amb marcadors inflamatoris, com la relació entre la ràtio IL-6/IL-4 basal i IL-6 basal ($r = 0.882$, $p < 0.001$) o entre IL-6/IL-10 basal i IL-17A basal ($r = 0.498$, $p < 0.001$). Aquests valors indiquen una desregulació en la resposta immunitària, caracteritzada per

un desequilibri entre els marcadors proinflamatoris i antiinflamatoris. Aquesta alteració contribueix a l'establiment d'un estat inflamatori crònic, que podria ser determinant en l'evolució del quadre clínic.

Aquests resultats recolzen la hipòtesi que les persones amb FM amb un perfil clínic més greu abans de la intervenció també presenten un estat proinflamatori més pronunciat. La correlació entre els biomarcadors inflamatoris i l'impacte en variables clíniques com el dolor i la funció física subratlla la necessitat de considerar el component inflamatori com un factor essencial en la gestió clínica de les persones amb FM. Així, les dades obtingudes suggereixen la necessitat d'una avaluació detallada de la inflamació com a marcador predictor de la severitat clínica, especialment en el context previ a les intervencions terapèutiques.

Annex 6

Avaluació de la qualitat metodològica de l'estudi 2

Supplementary material: Assessment of the methodological quality of the study 2

Methodological quality of the study	**8/9**
Study sample ≥ 50 participants (1= Yes, 0 = No)	**1, *page* 3**
Did the study control results for potential confounders (e.g. age, BMI, gender, race)? (1= Yes, 0 = No)	**1, *page* 3**
Where participants with FM and HCs age-and-gender matched? (1= Yes, 0 = No)	**0**
Was the time of sample collection specified (e.g. morning vs. evening)? (1= Yes, 0 = No)	**1, *page* 4**
Were participants with FM free of medication affecting inflammatory markers during sample collection (i.e. anti-cytokine, antidepressants, corticoids, and immunosuppressors)? (1= Yes, 0 = No)	**1, *page* 3**
Reporting of either the manufacturer of the test or its parameters (detection limit and coefficient of variation) (1= Yes, 0 = No)	**1, *page* 4**
Reporting how data under detection limit was handled (1= Yes, 0 = No)	**1, *page* 4**
Reporting % of the sample under detection limit (1= Yes, 0 = No)	**1, *page* 4**
Reporting blood fraction (serum, plasma, culture supernatant or whole blood) (1= Yes, 0 = No)	**1, *page* 4**
Cytokine moderators confounders red points	**0**
3 red points for comorbid illnesses such as autoimmune disorders & other immune disorders (if not adjusted statistically): should be excluded.	**0**
2 red points for comorbidity with MDD / BD (or adjusted)	**0**
2 red points when groups were not matched for age (or adjusted)	**0**
2 red points for sex not matched (or adjusted)	**0**
2 red points for medication use as for example anti-cytokine, antidepressants, corticoids, and immunosuppressors (or adjusted)	**0**
1 for BMI (nor matched or adjusted)	**0**
1 for smoking (nor matched or adjusted)	**0**
1 red point for use of oral contraceptives or NSAIDs (if not controlled statistically)	**0**
0.5 for race in countries such as US, Brazil (not China or Japan)	**0**
0.5 for seasonality	**0**