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Department of Health Sciences

Effect of a multicomponent exercise programme (VIVIFRAIL) on functional capacity in frail community elders with cognitive impairment

ClinicalTrials.gov NCT03657940. Registered on 5 September 2018.

DOCTORAL THESIS

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November 2022

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https://doi.org/10.48035/Tesis/2454/46927

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Introduction

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List of abbreviations

ADL: Activities of daily living
CI: Confidence interval
CIRS-G: Cumulative illness rating scale for geriatrics
EQ-5D: EuroQol-5 dimension (quality of life)
EQ: VAS: Visual Analog Scale of the EuroQol Questionnaire
FAQ: Functional Activities Questionnaire
GDS Yesavage: Geriatric Depression Scale of Yesavage
GDS-4: Global Deterioration Scale (Reisberg classification).
GVT: Gait Velocity Test
IDISNA: Instituto de investigación Sanitaria de Navarra.
IQR: Interquartile Range
IU: Inertial Sensor Unit
L3: Lumbar spine 3.
MCI: Mild Cognitive Impairment
MEC-Lobo: Minimental Cognitive Exam of Lobo
MICE: Multivariate Imputation via Chained Equations.
MNA: Mini Nutritional Assessment
MOCA: Montreal Cognitive Assessment
RCT: Randomized Controlled Trial.
SD: Standard deviation
SPIRIT: Standards protocol items: recommendations for interventional trials.
SPPB: Short Physical Performance Battery
TMT A: Trail Making Test Part A
US: United States.
WHO: World Health Organization.
1RM: One Repetition Maximum

Abstract

The doctoral dissertation herein focuses on the effects of multicomponent physical exercise intervention on functional capacity and cognitive functions in frail, community-dwelling older adults with cognitive impairment. Older adults suffering from these conditions are far more vulnerable to negative health-related events (i.e., premature mortality, hospitalisation, impairment in daily living activities, functional limitations and increased risk of fractures). Multicomponent physical exercise intervention (aerobic, strength, balance and mobility exercises) may be an effective therapy to improve functional and cognitive capacity in frail, community-dwelling older adults with Mild Cognitive Impairment (MCI henceforth) and mild dementia.

This doctoral thesis is based on two papers published in international scientific journals.

The aim in the first paper (paper 1) was to publish the study protocol to be followed in relation to the primary and secondary objectives, design, methodology, hypotheses and potential implications of the predicted outcomes of multicomponent physical exercise intervention compared to conventional care in frail older adults with cognitive impairment (ClinicalTrials.gov NCT03657940. Registered on 5 September, 2018).

The main study objective in the second paper (paper 2) was to assess the effects of VIVIFRAIL multicomponent physical exercise intervention on the functional capacity and cognitive status of frail, community-dwelling older adults with MCI and mild dementia.

With regard to the results of the primary objective (paper 2), it was observed that the intervention group (multicomponent physical exercise) showed an average improvement of 0.86 points in the SPPB test (95% CI 0.32, 1.41; $P < 0.01$) after the first month, and 1.40 points (95% CI 0.82, 1.98; $P < 0.001$) after a 3-month exercise period compared to the control group (conventional care). Moreover, patient distribution into the different VIVIFRAIL categories according to functional capacity (disabled, frail, pre-frail and robust) also revealed significant differences between the two groups during the intervention period ($P < 0.001$).

As for the secondary study objectives (paper 2), it was observed that multicomponent physical exercise intervention appears to have beneficial effects on cognitive functions, where the intervention group in patients suffering from MCI showed a 2.05 point improvement in the MoCA test after a 3-month exercise period (95% CI 0.80, 3.28; $p = 0.014$) while the control group reported a -0.13 point decrease in the MoCA test after a 3-month period (95% CI -1.08, 0.82, $p < 0.05$). In patients suffering from mild dementia, a difference was also observed between groups (control vs. intervention group); after a 3-month period, those who had engaged in physical exercise reported a statistically significant average improvement of 1.13 points in the MEC-Lobo test (95% CI 0.18, 2.10, $p < 0.05$). Furthermore, statistically significant differences between groups in handgrip strength were also observed in favour of the intervention group – a 1.05kg improvement (95% CI 0.05, 2.06, $p < 0.05$) –, and -1.12 point improvement on the Yesavage scale considering the mood status (95% CI 0.05, 2.06 $P < 0.05$).

Finally, regarding other secondary objectives, no statistically significant differences were observed in relation to the number of falls, hospital admissions, emergency visits, mortality and institutionalisation.

The VIVIFRAIL multicomponent physical exercise programme appears to be an effective and safe intervention in order to improve functional capacity in frail and pre-frail, community-dwelling older adults with MCI and mild dementia. In addition to improved functional capacity, the individualised multicomponent physical exercise programme also seems to have beneficial effects on cognition, muscle function and mood after a 3-month period of physical exercise intervention

Resumen

La actual disertación doctoral gira en torno a los efectos de una intervención de ejercicio físico multicomponente en la capacidad funcional y función cognitiva de las personas mayores frágiles con deterioro cognitivo a nivel comunitario. Las personas mayores con las condiciones previas son muchos más vulnerables a presentar eventos negativos relacionados con la salud (prematura mortalidad, hospitalización, deterioro de las actividades de la vida diaria, limitaciones funcionales, aumento del riesgo de fracturas y fracturas). Una intervención de ejercicio físico multicomponente (aeróbico, fuerza, equilibrio y flexibilidad) puede ser una terapia efectiva para mejorar la capacidad funcional y cognitiva en personas mayores frágiles con deterioro cognitivo leve y demencia leve que viven en la comunidad.

Esta tesis doctoral se basa en dos artículos científicos que han sido publicados en revistar científicas internacionales.

En el primer artículo (artículo 1) nuestro objetivo fue publicar el protocolo del estudio que se iba a llevar cabo con los objetivos primarios y secundarios, el diseño, la metodología, las hipotésis y las posibles implicaciones de los resultados que se esperaban encontrar según las hipótesis postuladas en relación a una intervención de ejercicio físico multicomponente en personas mayores frágiles con deterioro cognitivo comparado con cuidados convencionales (ClinicalTrials.gov NCT03657940. Registered on 5 September 2018).

En el segundo artículo (artículo 2), el objetivo principal del estudio fue evaluar los efectos de una intervención de ejercicio físico multicomponente VIVIFRAIL en la capacidad funcional y estado cognitivo de las personas mayores frágiles con deterioro cognitivo leve y demencia leve que viven en la comunidad.

En relación a los resultados del objetivo primario (artículo 2) se observó que el grupo intervención (ejercicio físico multicomponente) mostró una mejoría media de 0,86 puntos en el SPPB (95% CI 0.32, 1.41; P < 0.01) después del primer mes y 1,40 puntos (95% CI 0.82, 1.98; P < 0.001) tras los 3 meses de ejercicio en comparación con el grupo control (cuidados convencionales). Así mismo, la distribución de pacientes en las diferentes categorías del VIVIFRAIL según la capacidad funcional (discapacidad, fragilidad, prefragilidad y robustos) también presentó cambios significativos entre los dos grupos durante el periodo de intervención (P < 0.001).

En relación a los objetivos secundarios del estudio (artículo 2) se pudo observar como, la intervención de ejercicio físico multicomponente parece tener efectos beneficiosos en la función cognitiva, donde el grupo intervención en pacientes con deterioro cognitivo leve mostró una mejoría del MOCA tras los 3 meses de ejercicio de 2.05 puntos (95% CI 0.80, 3.28; P 0.014) mientras que el grupo control mostró un empeoramiento del MOCA tras los 3 meses de -0.13 puntos (95% CI -1.08, 0.82 P < 0.05). En los pacientes con demencia leve, también se observó una diferencia entre grupos (grupo control vs grupo intervención), a los 3 meses, en el que los que realizaron ejercicio físico mostraron una mejoría media estadísticamente significativa de 1.13 puntos en el MEC-lobo (95% CI 0.18, 2.10 P < 0.05). Así mismo, también se han observado diferencias estadísticamente significativas entre grupos a favor del grupo intervención en la fuerza palmar -mejoría de 1.05kg (95% CI 0.05, 2.06 P < 0.05)- y en el estado de ánimo -mejoría de -1.12. puntos en la escala Yesavage (95% CI 0.05, 2.06 P < 0.05)-.

Por último, y en relación a otros objetivos secundarios, no se han observado diferencias estadísticamente significativas en relación al número de caídas, ingresos hospitalarios, visitas a urgencias, mortalidad e institucionalización.

El programa de ejercicio físico multicomponente VIVIFRAIL parece ser una intervención efectiva y segura para mejorar la capacidad funcional en personas mayores frágiles y prefrágiles que viven en la comunidad con deterioro cognitivo leve y demencia en estadio leve. Además de la mejoría en la capacidad funcional, el programa individualizado de ejercicio físico multicomponente también parece tener efectos beneficiosos en la cognición, en la función muscular, y en el ánimo tras los 3 meses de intervención con ejercicio físico.

Declaration

I, Iván Antón Rodrigo, do hereby declare that the research presented in this dissertation is based on 2 articles (Paper 1 Paper 2) that have been published in international peer-reviewed journals (Trials 2019 https://doi.org/10.1186/s13063-019-3426-0 and Journal of Cachexia, Sarcopenia and Muscle 2022 doi:10-1002/jcsm.12925). To meet the stylistic requirements of a thesis, the formats of the papers have been adjusted accordingly throughout. These edits did not substantially change the content of the published articles. The role that I fulfilled within each of the publications is presented below.

This thesis the rationale, design, methodologies used and the results obtained in a single-blind randomized clinical trial. We hypothesized that an individualized multicomponent exercise training (progressive resistance training, balance, and walking exercises) would be an effective therapy to reverse the functional decline and cognitive status in frail community elderly people with MCI and mild dementia.

In addition, a physical exercise intervention would also improve other outcomes, such as muscle function and depression in frail community elderly people with cognitive impairment.

Ph.D. student involvement:

- Study protocol development
- Data collection.
- Data analysis and results interpretation.
- Writing of the articles included in the present thesis.

Acknowledgments

Gratitude is expressed to the professors, researchers and colleagues from the Public University of Navarre (Department of Health Sciences) for their unconditional support during the development of the research project. In addition, thanks to the Public University of Navarre as institution for the scientific support.

Gratitude is also expressed to the Hospital Universitario de Navarra, Fundación Matia and Hospital Universitario de Getafe for the technical support to conduct this thesis project.

We thank Fundacion Miguel Servet (Navarrabiomed) for its support during the implementation of the trial.

Finally, we also thank the patients and their family members who participated in the research project for their major contribution and for the confidence in the research team.

Financial Support, List of Publications and Conference Papers

Financial support

This study was part of the project entitled "Impact of a Multicomponent Exercise Program on Functional Capacity in Frail Aged Participants With Cognitive Decline (ClinicalTrials.gov NCT03657940. Registered on 5 September 2018)", which was funded by a Gobierno de Navarra project Resolution grant (426/2016, September 30th) and acknowledged with the "Beca Ortiz de Landázuri" as the best research clinical project in 2016, as well as it is funded by ISCIII (IP, professor Mikel izquierdo) and Fondos FEDER (PI17/01814)

The funder had no role in the in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

List of Publications

1. Casas-Herrero, A., Anton-Rodrigo, I., Zambom-Ferraresi, F., Sáez de Asteasu, M. L., Martinez-Velilla, N., Elexpuru-Estomba, J., ... & Izquierdo, M. (2019). Effect of a multicomponent exercise programme (VIVIFRAIL) on functional capacity in frail community elders with cognitive decline: study protocol for a randomized multicentre control trial. Trials, 20(1), 1-12.

2. Casas-Herrero, Á., de Asteasu, M. L. S., Antón-Rodrigo, I., Sánchez-Sánchez, J. L., Montero-Odasso, M., Marín-Epelde, I., ... & Izquierdo, M. (2022). Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. Journal of cachexia, sarcopenia and muscle, 13(2), 884-893.

Conference papers

Oral presentation

25-27 September 2019. Krakow. 15th International Congress of the European Geriatric Medicine Society. Eur Geriatr Med (2019) 10 (Suppl 1): S1-S326. O-76.

Itxaso Marin, **Ivan Anton,** Maria Fernanda Ramon, Juan Luis Sanchez-Sanchez, Jaione Elexpuru, Nicolas Martinez-Velilla, Mikel Izquierdo, Fabricio Zambom-Ferraresi, Mikel Lopez-Saez de Asteasu, Marta Gutierrez-Valencia, Roberto Petidier-Torregrossa, Alejandro Alvarez, Alvaro Casas-Herrero. Effect of a multicomponent exercise programme (VIVIFRAIL) on functional capacity and cognitive function in frail community elders with cognitive decline. Preliminary analysis of a multicentre randomized controlled trial.

Poster presentation

1.- October 7/9 EUGMS e-congress 2020. Covid-19: Lessons and Challenges for health care for older adults.

Fernanda Ramón-Espinoza, **Iván Antón-Rodrigo,** Itxaso Marín-Epelde, Juan Luis Sánchez-Sánchez, Abel Cedeño-Veloz, Marina Sánchez-Latorre, Chenhui Chen, Fabricio Zambon-Ferraresi, Alvaro Casas-Herrero. Effect of a Multicomponent Exercise Programme (VIVIFRAIL) on cognitive function in Frail Community Elders with Cognitive Decline: Study Protocol for a Randomized Multicentre Control Trial.

2.- 25 September 2020, Virtual Event. 21st International Conference on Falls and Postural Stability. Abstract 362.

F Ramón-Espinoza, I Marín-Epelde, **I Antón-Rodrigo**, A Cedeño-Veloz, J L Sanchez-Sanchez, M Sanchez-Latorre, C Chen, F Zambon-Ferraresi, M López Sáez de Asteasu, A Casas-Herrero. Effect of a Multicomponente exercise programme (VIVIFRAIL) on cognitive function in frail community elders with cognitive decline.

3.- May 28, 2020. Medicine & Science in sports & exercise. S476. Vol 52. Board 178.

Antonio García Hermoso, Fabricio ZAmbon-Ferraresi, Itxaso Marín-Epelde, Mikel López Sáez de Asteasu, Juan Luis Sanchez-Sanchez, María Fernanda Ramón, **Iván Antón Rodrigo**, Nicolás Martínez Velilla, Mikel Izquierdo, Robinson Ramírez-Vélez, Alvaro Casas-Herrero. Effect of a Multicomponent Exercise Program on cognitive capacity and cognitive function in Frail Community Elders With Cognitive Decline.

Introduction

The progressive ageing of the population is a reality that entails a growing proportion of the population living with chronic diseases and functional limitations (1). The proportion of people over 80 years of age is estimated to be the fastest growing age group, and is expected to increase threefold between 2015 and 2050 (2).

This demographic shift has led to the third or clinical transition in the field of healthcare, where the paradigm of single disease-based care has changed to function (3,4) and frailty-based healthcare models, resulting in a heavy burden in terms of chronic illness and geriatric syndromes in a greatly ageing population, and where maintaining functional capacity throughout the ageing process is a priority as a means to ensure a lifetime free of disability and dependency (5).

The main characteristic of the elderly from a life-cycle perspective is the loss of intrinsic capacity associated with a reduction in the functional reserve of multiple organs or systems. According to the World Health Organisation (WHO), functional capacity, considered the true core of healthcare for the elderly, comprises the health-related attributes enabling a person to be and do what is important to them. It is composed of intrinsic capacity, which is defined as the combination of all the physical and mental capacities (6) that a person possesses, the environmental characteristics affecting such capacity, and the interactions between the person and these characteristics. The WHO recently determined that intrinsic capacity is made up of five broad domains: mobility, cognition, senses, psychological capacity and vitality, each of which consists of different measurable attributes.

Healthcare professionals should thus prioritise strategies so as to prevent or reverse functional and cognitive impairment in older adults by proactively identifying interventions aimed at fostering healthy ageing, especially in those most vulnerable at the onset functional and cognitive impairment (7). In this regard, frail (8) and cognitively impaired, community-dwelling older adults could benefit from interventions to improve or maintain their functional and cognitive status as they are a population at high risk of disability and dependency (9, 10).

Physical inactivity seems to play a key role in the loss of muscle performance and functional capacity, which is thought to be a crucial factor relating to frailty (8), and is also the cause of substantial economic burden directly resulting from inactivity (11). The prevalence of frailty is high in those over 65 years of age and, depending on the screening method employed, can be as high as 7-16%, which increases with age (12). Frailty can be defined as a clinical condition where there is increased risk of individual vulnerability in terms of developing adverse events (13) such as dependency and/or mortality when exposed to stressors (14). International consensus defines physical frailty as a major "medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance and physiologic function that increases an individual's vulnerability to diminished capacity, ability and dexterity to perform basic and instrumental everyday activities and, ultimately, in terms of developing increased dependency and/or death (15,16)."

The most widely established consensus used in research is phenotypic frailty or frailty phenotype developed by Fried, which encompasses five diagnostic criteria (**Table 1**): unintentional weight loss, exhaustion, low physical activity, slowed walking speed and low grip strength, with 1 or 2 criteria classifying a person as pre-frail and 3 or more as frail (17).

Table 1. Fried Frailty Criteria. Fried et al. (17)

The frailty phenotype (FP)	
FP criteria	Measurement
Weakness	Grip strength: lowest 20% (by sex, body mass index)
Slowness	Walking time/25 feet: slowest 20% (by sex, height)
Low level of physical activity	Kcal/week: lowest 20% Males: 383 kcal/week Females: 270 Kcal/week
Exhaustion; poor endurance	"Exhaustion" (self-report)
Weight loss	>10lb lost unintentionally in prior year

The concept of phenotypic frailty is thus constructed, with its diagnostic criteria, clinical signs and symptoms, and associated adverse events identified (**Figure 1**).

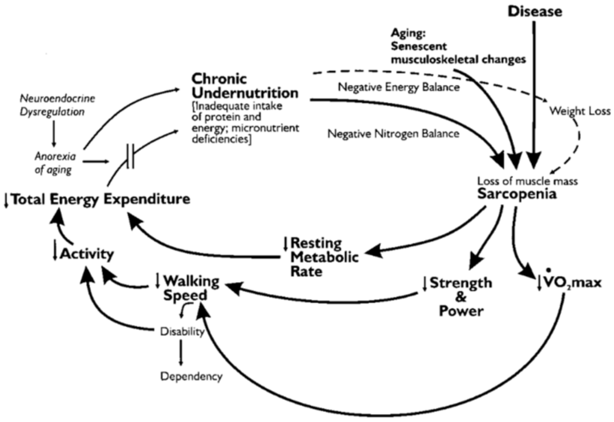

Figure 1. Cycle of frailty hypothesized as consistent with demonstrated pairwise associations and clinical signs and symptoms of frailty.

It is this individual vulnerability, along with the decline of systems and external noxae, that can cause frailty to develop into mild, moderate or severe disability, or even death (18). This whole process from robustness to frailty, disability and death is referred to as the "functional continuum" and is the main determinant of serious adverse health events, poor quality of life, the need for specialised health and social care, and resource allocation (15).

Many of the ageing-related processes leading to frailty in older adults are also most likely responsible for frailty-related cognitive impairment (19), and vice versa. Indeed, cognitive impairment is closely associated with frailty, as both conditions share common pathophysiological mechanisms and common short and long-term consequences such as a higher incidence of falls, hospitalisation, institutionalisation and death (20, 21). In this regard, the Toledo study on ageing and frailty revealed that cognitive impairment and muscle strength have a directly proportional relationship (22). Hence, this relationship indicates that dementia shares the same characteristics to be found in the frailty phenotype, such as subtle changes in gait (slowed walking speed and increased gait variability) and decreased physical activity. Neuromuscular factors that may account for diminished strength associated with ageing include: structural, physiological and functional changes affecting motor neurons, the neuromuscular junction and muscle fibres (23). Moreover, neuronal atrophy in the brain is accompanied by electrical "noise" related to decreased dopaminergic neurotransmission that impairs communication between neurons. In addition, the motor-sensory feedback that helps regulate corticospinal excitability is disrupted. Also, in the peripheral nervous system there is evidence of motor unit loss, axonal atrophy, demyelination caused by oxidative damage to proteins and lipids, and impaired electrical signal transmission across the neuromuscular junction. These findings show that globally, as we age, the ability to communicate neuronal activity to muscles is impaired (24).

One of the main risk factors leading to the development of frailty is physical inactivity (25) which, along with body changes and sedentary lifestyles, has major health-related consequences. As we age, deterioration in muscle performance and cardiorespiratory fitness results in a decrease in the ability to perform daily living activities, and thus maintain independence (26, 27).

Interventions focusing on physical activity have displayed efficacy in delaying and reversing frailty (28), and there is robust scientific evidence regarding the benefits of physical activity and exercise in the prevention and treatment of many chronic diseases such as diabetes, cardiovascular disease, hypertension, cancer, osteoporosis, depression, dementia and Parkinson's disease (29). There is also evidence that physical activity and exercise improve muscle function, mental health and quality of life, and reduce mortality (30, 31).

The potential benefits of different physical exercise interventions involving the frail population have been widely documented in the literature, reporting improvements in frailty markers such as gait, muscle strength, balance and falls (32, 33). Furthermore, physical exercise improves metabolic health by suppressing muscle atrophy, decreasing inflammatory response and protecting against bone density loss; it also helps preserve insulin sensitivity, mitochondrial activity and physical performance (34). There is now strong evidence to support that tailored physical exercise is probably the best method to improve frailty factors or markers, including functional capacity, muscle performance and state of health (35, 36). Prescribing physical activity or physical exercise in a structured way should be based on the goals for which it is intended (in primary prevention to improve frail/pre-frail patient capacity, or as treatment in the context of illness) and should be individualised, tailored and monitored as if it were any other medical treatment (36). Strategies aimed at increasing physical activity levels in the population and optimising adherence have focused on encouraging physical exercise via "lifestyle integration" by incorporating it into everyday activities. For example, going up and down stairs instead of taking the lift or sitting slowly without the use of arms are ways of incorporating aerobic, balance and strengthening exercises, respectively, into daily living activities. Current research is exploring whether the manner and techniques of prescribing physical exercise can achieve better exercise adherence compared to standard approaches by encouraging behavioural changes and targeting other clinical goals such as falls associated with older adults (37, 38).

Scientific evidence suggests that multicomponent training seems to be the most effective in improving functional capacity in frail older adults (36). Training based on multicomponent physical exercise programmes that combine muscle strength, endurance, balance and walking exercises have proven to be the most effective interventions to prevent most, if not all, of the complications and consequences of frailty syndrome (e.g. poor balance, diminished muscle strength, gait disturbances and higher incidence of falls), and their prescription is recommended in frail and pre-frail older adults (36, 39, 40). It has also been found that these improvements in functionality are a key element in maintaining independence in basic and instrumental daily living activities performed by older adults (41).

Moreover, physical exercise, specifically multicomponent exercise, may also be the cornerstone for improving cognitive functions in the frail older adults with MCI and dementia (42). The benefits of physical exercise for cognitive functions have been the subject of recent research. There is strong evidence that sedentary lifestyles may be a risk factor in the development of cognitive impairment and dementia; in both Alzheimer's (43) and vascular dementia (44). The mechanisms may be linked to reduced neurogenesis, synaptic plasticity, neurotrophic production and increased inflammation. Thus, several studies have shown how multicomponent physical exercise can improve cognition by enhancing these mechanisms (45), highlighting in particular the regulatory role of BDNF (46) in the exercise-mediated improvement of cognitive functions (47). A recent systematic review (48) noted that, despite the limitations, multicomponent physical exercise may be optimal for improvements in cognitive functions in healthy older adults, and another study revealed that a multicomponent physical exercise programme in institutionalised, frail older adults suffering from MCI and dementia produced significant improvements in functional capacity, fall risk and executive functions (49). Moreover, other authors have reported similar findings in terms of the ability to reverse frailty and obtain cognitive improvements in community-dwelling older adults without baseline cognitive impairment (41).

In relation to the concepts described above and consistent with the published scientific evidence, the VIVIFRAIL multicomponent physical exercise programme (https://vivifrail.com/es/inicio/) was developed a number of years ago, and is based on encouraging physical exercise in the older adults through individualised programmes that are specifically tailored to the person's functional capacity, with specific recommendations on the prescribed doses of exercise (intensity, amount and frequency). The VIVIFRAIL project, funded by the European Union as part of the Erasmus programme, aims to provide the knowledge required in order to prescribe physical exercise to prevent frailty and fall risk in the elderly. This programme is framed within the European Union's Strategy for Health Promotion and Quality of Life, and the World Report on Ageing and Health (4), published by the World Health Organization in 2015, which stresses the idea that health in the elderly should be quantified in terms of functional capacity (and not disease), since functions are the variable that best predicts life expectancy and quality of life, and the resources and supports needed for different populations (www.vivifrail.com). This project focuses on furthering the development of knowledge related to promoting individualised exercise that is tailored to the functional ability of older adults and the implementation of best practices, along with the development of materials that enable exercise to be prescribed as an effective way of improving the older adult health within their environment (50). To this end, different exercise programmes are presented that enable, based on assessment of the older adult's level of functional capacity according to the score obtained in the Short Physical Performance Battery (SPPB) test (**Figure 2**), an individualised multicomponent physical exercise programme to be prescribed, which includes the following training modalities:

- Muscle strength and power, both in upper and lower limbs.
- Balance and gait so as to avoid falls.
- Mobility exercises.
- Aerobic training involving cardiovascular exercises.

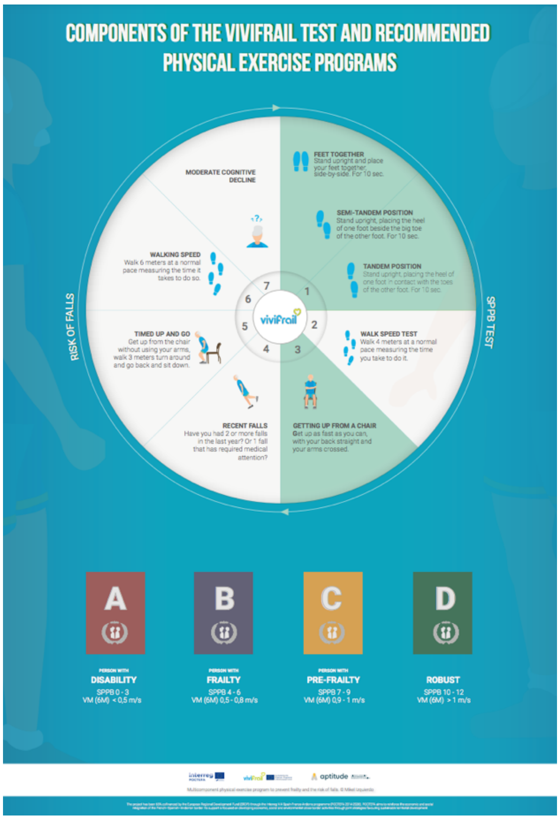

Figure 2. VIVIFRAIL test components to assess functional capacity and fall risk.

Based on the SPPB score, the following exercise programmes can be prescribed (**Figure 3**):

- Programme A (disabled): 0-3 points
- Programme B (frail): 4-6 points
- Programme C (pre-frail): 7-9 points
- Programme D (robust): 10-12 points

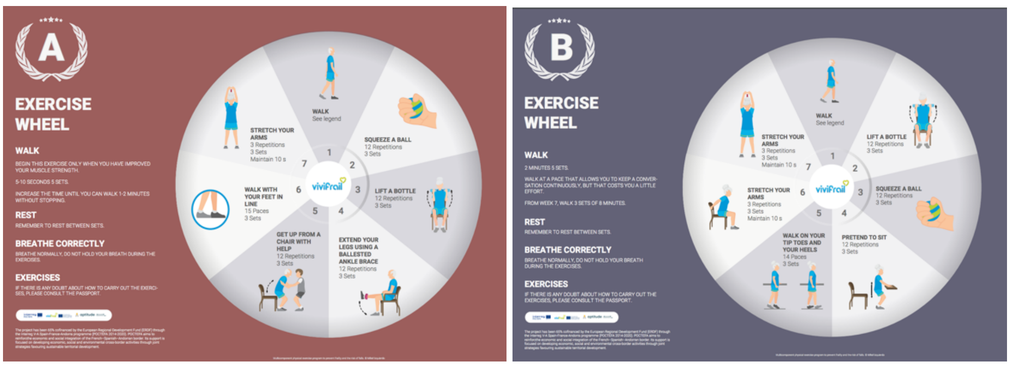

Figure 3. VIVIFRAIL multicomponent physical exercise programmes based on score obtained in the VIVIFRAIL test.

Hence, the main objective of the thesis is to examine the effects of the VIVIFRAIL multicomponent physical exercise programme on functional capacity and cognitive status in frail and pre-frail, community-dwelling older adults with MCI and mild dementia.

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Aims and layouts of the thesis

Paper 1

Title: Effect of a multicomponent exercise programme (VIVIFRAIL) on functional capacity in frail community elders with cognitive decline: study protocol for a randomized multicentre control trial.

Research aim: To examine whether an innovative multicomponent exercise programme called VIVIFRAIL has benefits for functional and cognitive status among pre-frail/frail patients with mild cognitive impairment or dementia.

Hypothesis: Frailty and cognitive impairment are two very common geriatric syndromes in elderly patients and are frequently related and overlapped. Functional decline and disability are major adverse outcomes of these conditions. Exercise is a potential intervention for both syndromes. It was hypothesized that the results of this study could contribute to understanding that an individualized multicomponent exercise programme (VIVIFRAIL) for frail elderly patients with cognitive impairment could be more effective in reducing functional and cognitive impairment than conventional care. Moreover, our study may be able to show that an innovative individualized multicomponent exercise prescription for these high-risk populations could be plausible, having at least similar therapeutic effects to other pharmacological and medical prescriptions.

Paper 2

Title: Effects of VIVIFRAIL multicomponent intervention on functional capacity: a multicenter, randomized controlled trial.

Research aim: To assess the effects of a multicomponent exercise program VIVIFRAIL on functional capacity, cognitive status and other outcomes such as muscle function, mood and falls in frail community elderly people with mild cognitive impairment and mild dementia.

Hypothesis: It was hypothesized that the multicomponent exercise intervention VIVIFRAIL would produce improvements on functional, cognition, muscle function and mood compared to usual clinical care.

Paper 1

Effect of a multicomponent exercise programme (VIVIFRAIL) on functional capacity in frail community elders with cognitive decline: study protocol for a randomized multicentre control trial.

1.- Background

The progressive ageing of the population and the challenges surrounding the care of elderly people have become an emergency for all health systems. The aged population has resulted in an increase in the activity of health and social services, and the needs of this population are completely different compared to those of similar age groups 50 years ago. Nowadays, it is time for a clinical transition in health systems, moving from disease management to a more functional perspective, around the principles of integrated, coordinated, continued and patient-centred care [1]. In this context, the World Health Organization recently stated that health-related policies should be considered from the perspective of the elderly person's functional capacity (intrinsic capacity) rather than the disease or comorbidity experienced at a single point in time [2].

Frailty is a clinical syndrome defined by vulnerability and an increased risk of the individual to develop negative health-related events as disability and/or mortality under external stressors factors [3]. The frail phenotype pays attention to five domains (nutritional status, energy, physical activity, mobility and strength), and five criteria have been stablished (one per each domain: weight loss, exhaustion, leisure-time activity, gait speed and grip strength, respectively) [4] to identify older persons at high risk of numerous adverse outcomes [5, 6]. Some cross-sectional studies show the relation between frailty, mild cognitive impairment (MCI) and dementia, but the longitudinal relation is uncertain. Probably, the relation between cognitive impairment and frailty [7] in some cases is strong and bidirectional, since they share common pathophysiological bases and the same outcomes as hospitalization, falls, fractures, disability, institutionalization and mortality. Recently, the frailty Toledo study of aging has showed that cognitive impairment and muscular strength have a direct proportional relationship [8]. Therefore, dementia shares part of the same characteristics that can be found in the frail phenotype like subtle gait impairments (slow gait velocity and increase gait variability) and poor physical activity (Fig. 1).

The regular practice of physical exercise constitutes an inexpensive and healthy way of preventing and treating several illnesses related to the cardiovascular system and a sedentary lifestyle. Physical exercise programmes have been shown to be a novel "prescription tool" to prevent or delay the appearance of disability [9], to diminish healthcare costs [10] and to delay premature mortality [11, 12]. In the context of the ageing population, the performance of physical exercise can be considered the most effective intervention to delay disability and adverse events that are usually associated with frailty and vulnerable ageing. In some studies, exercise has shown even more positive results in terms of mortality from different diseases and chronic conditions than poly-pills for cardiovascular prevention [13]. Physical exercise, as an individual intervention, is one of the most important components in improving the functional capacity of frail seniors, and muscle strengthening in particular should be at the forefront of the treatment [14].

The benefit of physical exercise in ageing and particularly in frailty has been the aim of recent research. Moreover, physical activity in the elderly is associated with a decreased risk of mortality, of common chronic illnesses (i.e. cardiovascular disease or osteoarthritis) and of institutionalization as well as with a delay in functional decline. Additionally, very recent research has shown that, despite its limitations, physical exercise is associated with a reduced risk of dementia, Alzheimer disease or mild cognitive decline [15, 16]. Nevertheless, the effect of physical exercise as a systematic, structured and repetitive type of physical activity, in the reduction of risk of cognitive decline in the elderly, is not very clear. In this context, the most beneficial type of physical exercise is called multicomponent exercise [17–20]. This type of programme combines strength, resistance (aerobic), balance and flexibility training and has been shown to result in great improvements in functional capacity, which is a key point in maintaining independence in instrumental and basic activities of daily living.

Considering the relation between frailty and cognition previously mentioned (Fig. 1), it makes sense that those interventions proved to be effective in frail elderly people could be also effective in the elderly with cognitive impairment, and vice versa. Although there are still few studies, some of them show how resistance exercise programmes during 12 weeks in older adults not only induce improvements in gait velocity but also improvements in executive functions [21] which are directly related to fall risk [22]. Additionally, recent research [23] has shown that, despite its limitations, multicomponent exercise can be one of the best approaches to improving functional capacity and executive functions and to decreasing fall risk and cognition in frail institutionalized elderly with cognitive impairment and dementia [22]. Other authors have found similar results in terms of reversing the frailty status and cognitive improvements in community-dwelling elderly without basal cognitive impairment [24].

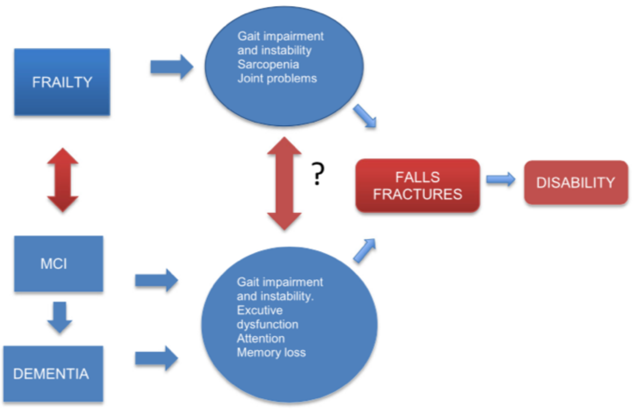

Fig. 1 Proposed relation, sharing mechanisms and similar outcomes between frailty, mild cognitive impairment (MCI) and dementia

In this context, the purpose of this study aims to examine whether an innovative multicomponent exercise programme called VIVIFRAIL [25–27] has benefits for functional and cognitive status among pre-frail/frail patients with MCI or dementia. VIVIFRAIL was developed by world experts in the field of physical exercise and frailty, and is considered an important step towards the novel era of precise prescription of physical activity [26, 27]. Recently, it has been proven safe and effective to reverse the functional decline associated with acute hospitalization in very old patients [28]. This programme is a significant step towards an individualized physical exercise programme [27] according to the functional capacity of each elderly person and includes specific recommendations on doses (intensity, volume and frequency), similar to other treatments applied to vulnerable populations, such as frail elderly individuals with cognitive complaints.

2.- Methods

2.1.- Study design and setting

This study is a multicentre randomized clinical trial to be conducted in the outpatient geriatrics clinics of three tertiary hospitals in Spain. Geriatric clinics are part of routine geriatric clinical work and normally patients come from primary care or other specialities. Patients who meet the inclusion criteria will be randomly assigned to the intervention or control group. Prior to randomization, the attending geriatrician will review the absolute and relative contraindications to participate in the exercise programme and will provide general information about the study. Patient recruitment will begin with the normal visit of the patient to the clinic assessing for inclusion criteria and obtaining informed consent. Later on, subjects will be randomly assigned (as explained in the following) to either the intervention or the control group. The researcher who decides whether the patient is assigned to the intervention or control group will not be the attending geriatrician. Patients or their relatives (if the patient has dementia) will be informed of the random inclusion in one group but will not be in- formed regarding to which group they belong. The data for both the intervention group and the control group will be obtained at three different times: at baseline and at the 1-month and 3-month follow-up. We will perform two telephone calls (15 days and 2 months after baseline) to assess adherence and reinforce the protocol applied. In addition, in order to improve the adherence of the exercise programme, participants in the intervention group will record a diary that will be reviewed during follow-up. After randomization, the research team (physiotherapist, sport science specialist and geriatrician) will together perform the baseline measurement and follow-up visits of functional, pharmacological, comorbidity and cognitive assessment, as well as of mobility and strength evaluations (Table 1). The multidisciplinary research team have well-known previous experience in functional geriatric assessment and in the prescription of exercise in frail aged participants in different clinical settings [25, 26, 28].

Table 1 Schedule for the different primary and secondary variables for the participants of the study

Measure	Screening	T1 Baseline	T2 1 month	T3 3 months
Primary outcome				
Short Physical Performance Battery (SPPB)		X	X	X
Secondary outcomes				
Barthel Index	X		X	X
Frailty according to the Fried criteria	X			
Montreal Cognitive Assessment (MOCA)—only for mild cognitive impairment	X		X	X
Categorical scale of pain		X		X
Geriatric Depression Scale of Savage (GDS)		X		X
Minimental Cognitive Exam (MEC-Lobo)		X	X	X
Gait velocity test (GVT)		X	X	X
Dual task (verbal and counting GVT)		X	X	X
Maximal isometric force of handgrip, knee extension and hip flexion		X	X	X
Isaacs Set Test		X		X
Quality of Life (EQ-5D)		X		X
Trail Making Test (TMT—Part A)		X	X	X
1RM (leg press)		X	X	X
Muscle power at 50% 1RM in leg press		X	X	X
Drugs, geriatric syndromes and psycho-behavioural symptoms		X		X
Cumulative Illness Rating Scale for Geriatrics (CIRS-G)		X		
Functional Activities Questionnaire (FAQ)		X	X	X
Mini Nutritional Assessment (MNA)		X		
Acceleration data: gait kinematic parameters (regularity, variability, cadence), Five Times Sit to Stand Test (peak power, impulse) and balance parameters (power spectrum, area)		X	X	X
Rate and risk of falls		X	X	X
Mortality		X	X	X
Admission and readmission to hospital		X	X	X
Institutionalization		X	X	X

Basic sociodemographic data of the participants will be collected in the baseline visit. All adverse events, including those related to exercise such as muscle pain, fatigue and general aches and pains, will be recorded in an "adverse events diary" during follow-up visits and telephone calls by the training and testing staff, and by self-report during the study period. The study flow diagram is shown in Fig. 2. The time at which different variables (primary and secondary) will be measured is presented in Table 1. The protocol employs relevant standard protocol items for clinical trials according to the SPIRIT 2013 statement (Additional file 1) [29] and follows the CONSORT statement [30] for transparent reporting. The trial is registered at ClinicalTrials.gov (identifier number iNCT03657940), and the status is recruitment.

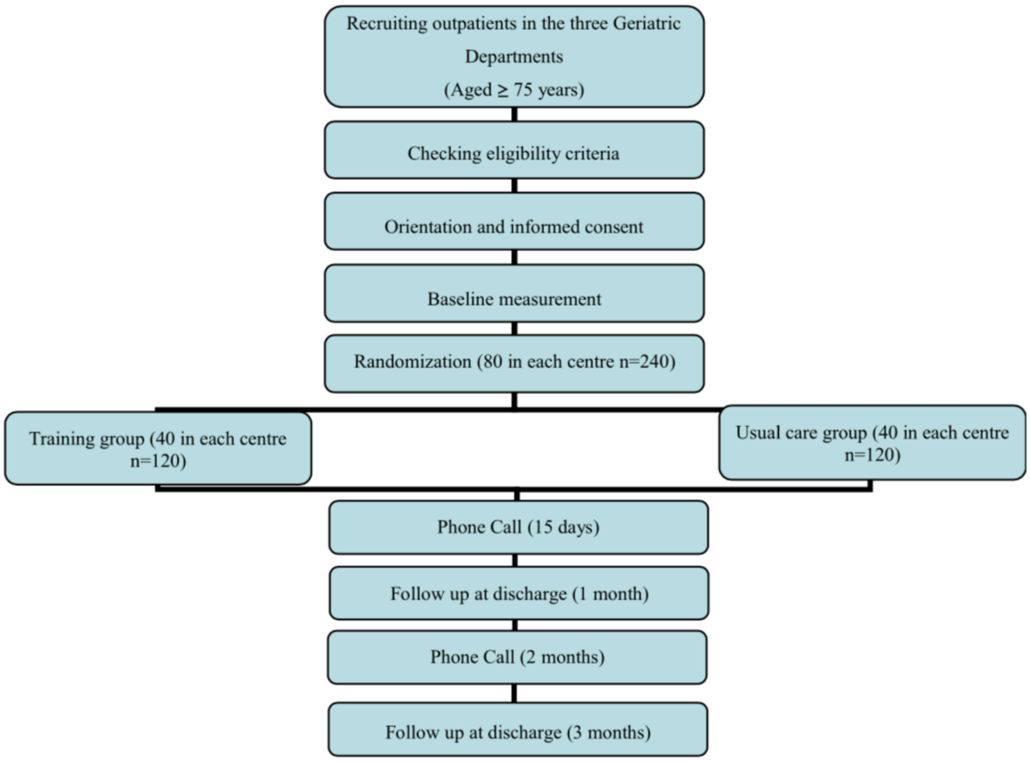

Fig. 2 Flow diagram of the study protocol

2.2.- Study participants and eligibility criteria

The study will include outpatients of the Geriatrics Department of the Complejo Hospitalario of Navarra, Matia Fundazioa in San Sebastian and the Hospital of Getafe (all three in Spain) older than 75 years of age between September 2017 and May 2019. Inclusion criteria include patients aged 75years or older being capable and willing to provide informed consent, able to communicate and ambulate with or without personal/ technical assistance, with a Barthel Index ≥ 60 and MCI or mild dementia according to DSM V criteria [31], level GDS-4 (Reisberg classification) [32], pre-frail or frail according to the Fried criteria [4] and having someone to help to supervise them when conducting the exercises.

The exclusion criteria include having any factor that precludes the performance of the physical training programme or testing procedures as determined by the attending physician. These factors, according to the VIVIFRAIL programme [26] include, but are not limited to, the following:

myocardial infarction in the past 3 months;
unstable angina pectoris;
terminal illness;
uncontrolled arrhythmia;
unstable cardiovascular disease or other unstable medical condition;
uncontrolled arterial hypertension;
recent pulmonary thromboembolism;
upper or lower extremity fracture in the past 3 months;
institutionalized or pending entry into institution; and
unwillingness to either complete the study requirements or to be randomized into the control or the intervention group.

2.3-.Randomization and blinding

Participants in the study will be randomized (www.randomizer.org) into an intervention group and a usual care group (control group) following a simple randomization procedure, in a 1:1 ratio without restriction. Participants will be explicitly informed and reminded not to discuss their randomization assignment with the assessment staff. The assessment staff will be blinded to the participants' groups as well as to the main study design and to what changes in study outcomes we expect to occur in either group.

It will not be possible to conceal the group assignment from the staff involved in the training of the intervention group. Patients (or their families) will be informed of their random inclusion in one group but will not be informed regarding to which group they belong.

2.4.- Statistics and sample size

Assuming an alpha error of $\alpha = 5\%$, a correlation tween pre and post-intervention values of the Short Physical Performance Battery (SPPB) of $\rho = 0.5$ and a standard deviation for the SPPB of $\sigma = 2.5$, the required sample size to have a power of 90% to detect a minimum difference of 1 point between groups in the post–pre SPPB score is 101 patients per group. Taking into account an expected loss of patients along the follow-up of 15%, the final sample size required is 120 per group. For the estimation, an ANCOVA method for the analysis of the differences has been considered. The research team will be focused to instruct and remind geriatricians periodically to assess inclusion and exclusion criteria in all three centres in order to reach target sample size. All of the centres have a remarkable clinical activity attending around 1000 patients every year. It is expected than 15% of these patients in every centre can be potentially eligible participants. In the unlikely case of not reaching the expected sample size, we will extend the inclusion period for a further 3 months.

The description of the sample by group will be conducted using statistics such as means and standard deviations or medians and interquartile ranges for the quantitative variables, and frequencies and percentages for the qualitative variables. For comparisons between groups at baseline, t tests or Mann–Whitney U tests will be used for continuous variables, depending on normality, which will be checked for each using the Kolmogorov–Smirnov test and normal probability plots, and the chi-square test or Fisher's test will be used for categorical variables. To determine the efficacy of the intervention in the quantitative variables, such as the SPPB, we will use ANCOVA models, using post-intervention values as dependent variables, group study as the principal effect and pre-intervention values as covariates. In the case of qualitative or categorized variables (such as whether an improvement of a given magnitude between pre and post intervention has been achieved or not), comparisons between groups will be conducted with the chi-square test or Fisher's test, and complemented with logistic regression if additional adjustment is needed. The level of statistical significance will be 0.05. Data will be analysed using an intention-to-treat approach with R and SPSS statistical packages.

We will adopt a complete case analysis as the primary analysis if the proportions of missing data are equal to or below 5% and it is implausible that certain patient groups specifically are lost to follow-up in one of the compared groups. To check the assumption that the potential impact of missing data is negligible (created by a missing complete at random or a missing not at random mechanism), best–worst and worst–best case sensitivity analyses will be used. When the proportions of missing data are above 5% and if this is supported by the previous sensitivity analysis, a missing at random mechanism will be assumed and missing values will be imputed using the R package MICE (Multivariate Imputation via Chained Equations). If the proportions of missing data are very large (more than 40%) on important variables, then trial results will be considered as hypothesis generating results.

2.5.- Data management

Completed personal data or other documents containing protected personal health information will be kept in a locked file at the principal investigator office in every centre. Data will be entered into an electronic de-identified database by authorized study team members, and checked for completeness and accuracy. Access to data with identifiers will be restricted to authorized study team members and authorities. Electronic data will be stored on a secure server regulated by the local research institute (IDISNA). Identifiable data will be destroyed 10 years after study finalization or 5 years after last publication.

2.6.- Detailed description of the intervention

Participants will be randomly assigned to the following groups.

2.6.1.- Usual care group (control)

Participants randomly assigned to the usual care group will receive normal outpatient care, including physical rehabilitation when needed.

2.6.2.- Multicomponent VIVIFRAL exercise group.

The multicomponent physical exercise programme will be the VIVIFRAIL programme which was developed in Europe (Erasmus+ programme of the European Union). The VIVIFRAIL [26, 27] multicomponent exercise intervention programme consists of resistance training, gait retraining and balance training, which appear to be the best strategy for improving gait, balance and strength, as well as reducing the rate of falls in older individuals and consequently maintaining their functional capacity during ageing [26, 27]. This type of intervention has also been proven as the most effective to delay disability, cognitive impairment and depression [33] as well as effective to reverse the functional decline associated with acute hospitalization in very old patients [28].

The VIVIFRAIL exercise programme offers a general guideline to design a multicomponent physical exercise programme for frailty and falls treatment and prevention among people aged older than 70 years [26]. The programme is personalized, depending on the older person's functional capacity level (serious limitation, moderate limitation and slight limitation as evaluated by the SPPB and a walking speed test) and the risk of falling. VIVIFRAIL works on the following components of physical fitness: arm and leg strength and power, balance and coordination to prevent falls, flexibility and cardiovascular endurance (i.e. walking).

All of the exercises outline the procedure, guidelines for starting, frequency and progression to be able to correctly monitor the instructions prescribed to the patient and improve their health [26].

To individualize the exercise programme we will assess the initial functional capacity and determine the risk of falling. Different functional capacity levels will be determined based on the scores obtained from the Short Physical Performance Battery Test (SPPB) and the 6-m gait velocity test (GVT) (see Fig. 3), with each leading to the recommendation of a certain customized multicomponent physical exercise programme (Program A, B, C1, C2 or D) (see Fig. 3). Two sub-types will be defined in order to more accurately recommend a particular cardio- vascular endurance programme for the group with slight limitation (frail/pre-frail) based on the maximum time they can walk without help. If the person can walk for 10– 30 min, they are known as C1; and if they can walk for 30–45 min, they are known as C2 [26].

This classification will be complemented according to the risk of falling, assessed by the answer to some simple questions (see Fig. 3). If a risk for falling is detected, the frequency of the exercise will be increased and some additional measures will be adopted, as depicted in the lower part of the right-hand side of Fig. 3. Finally, the participant will be assessed for potential contraindications or need of medical evaluation (left-hand side of Fig. 3) [26].

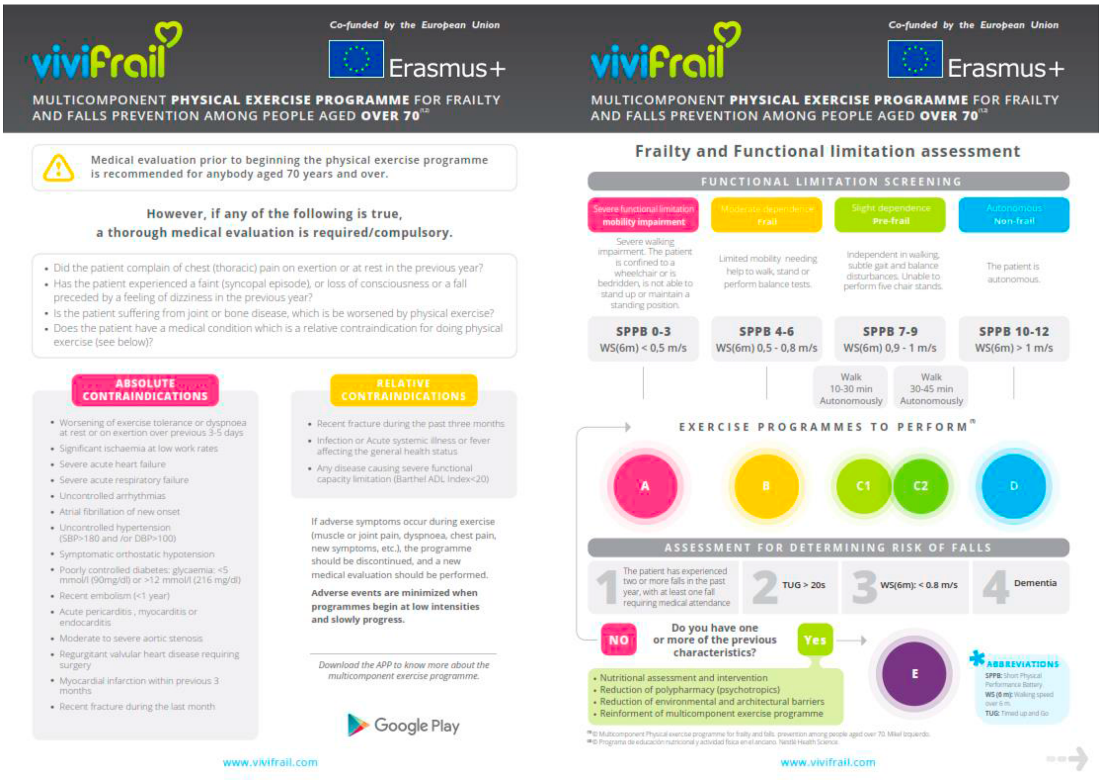

Fig. 3 Classification by allocation of the participant to a physical exercise group by the SPPB, gait speed and risk of falls. Modified from Izquierdo et al. [26]

Once the patient has been assigned to one of the six categories, a multicomponent programme taking 12 weeks will be implemented. The general characteristics of the different programmes are shown in Fig. 4.

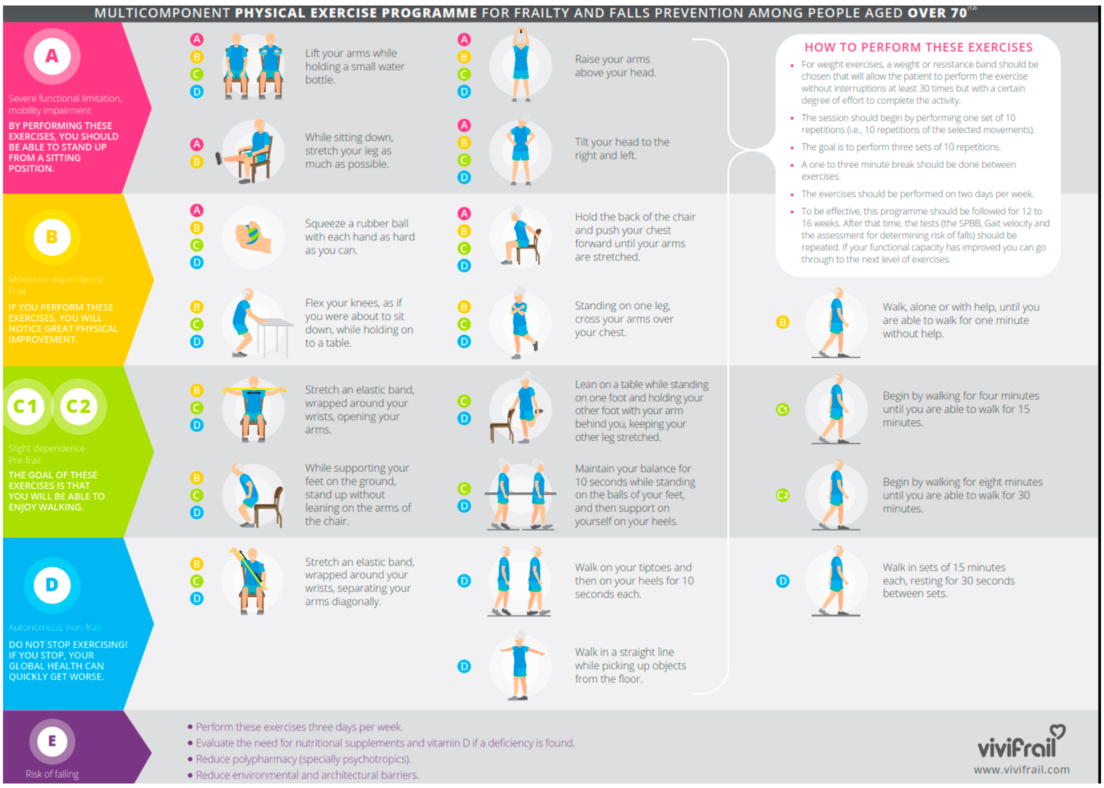

Fig. 4 Classification by allocation and examples of exercises of the participant according to a functional level group by the SPPB, gait speed and risk of falls. Modified from Izquierdo et al. [26]

Resistance training

- Sets and repetitions:
  The session should begin by performing two sets of 10 repetitions (i.e. 10 repetitions of the selected movements).
  The goal is to perform three sets of 12 repetitions.
  A 1-min to 3-min break should be taken between exercises.
  The exercises should be performed on 3 days per week.
- Intensity and progression:
  For weight exercises, a weight or resistance band should be chosen that will allow the patient to perform the exercise without interruptions at least 30 times but with a certain degree of effort to complete the activity. The first step will be to determine the exercise or weight that allows them to do the exercise properly about 30 times without stopping yet makes them feel as though they have made an effort by the end.
  To be effective, this programme should be followed for 12 weeks. After that time, the tests (the SPPB, GVT and assessment for determining risk of falls) should be repeated.
- Strength and power exercises are shown in Izquierdo et al. [26].

Cardiovascular training

- Sets and repetitions:
  When the elderly person improves their muscular strength, the cardiovascular exercise programme shall begin.
  Walk, alone or with help at usual walking pace, until you are able to walk for 1 min without help.
  For example:
  Walk 5–10 s, rest 10 s.
  Repeat five to seven times.
  +
  Walk 10–15 s, rest 20 s.
  Repeat five to seven times.
  Begin by walking for 4 min until you are able to walk for 15 min.
  Begin by walking for 8 min until you are able to walk for 30 min.
  Walk in sets of 15 min each, resting for 30 s between sets.
- Cardiovascular protocol and exercises in detail according to function are shown in Izquierdo et al. [26].

Balance training

- Sets and repetitions:
  Remain in the same position and count to 10 (progress up to 30) with each leg. Rest no less than 1 min and no more than 3 min. Repeat with each leg.
  +
  Walk one set of 10 steps. Stop and rest for 10 s without sitting. Rest no less than 1 min and no more than 3 min. Repeat.
  +
  Walk in a relaxed way and step over the obstacles. Set up five obstacles to begin. When you finish the walk, begin again. Repeat eight times.
- Intensity and progression:
  Change the position of your arms; cross your arms or make a cross shape, for example.
  Do the exercises on different surfaces; on a rug, for example.
  Close your eyes, but only if someone is near to help you.
- Balance exercises are shown in Izquierdo et al. [26].

Flexibility

- Sets and repetitions:
  Two sets of three repetitions (remain in the same position for 10 s).
- Intensity and progression:
  Stretch until you feel a bit of tension and then remain in the same position for 10–12 s.
  Stretch without creating any excessive muscular elongation or articular tension.
  Every day.
  After the muscular strength and power or cardiovascular exercises.
- Flexibility exercises are shown in Izquierdo et al. [26].

Materials will be also provided to the caregivers and the participants in the Spanish language. All of the mate- rials to be used will be properly adapted to the focused population. This exercise programme has recently launched the Vivifrail App for IOS and Android operating systems, which enables health professionals to assess the functional ability of elderly subjects and help them to prescribe a tailored multi-component physical exercise programme [26, 27] (www.vivifrail.com).

3.- Outcome measures

3.1.- Primary outcome

The primary outcome measure is the change in functional and cognitive status during the study period. The functional capacity of patients will be evaluated by the Short Physical Performance Battery (SPPB) [34], which evaluates, balance, gait ability and leg strength using a single tool. The total score ranges from 0 (worst) to 12 points (best). The SSPB test has been shown to be a valid instrument for screening frailty and predicting disability, institutionalization and mortality. A total score of less than 10 indicates frailty and a high risk of disability and falls. A 1-point change in the score has clinical relevance [35, 36].

3.2.- Secondary outcomes

Loss of handgrip in the dominant hand is a useful tool for the measurement of functional capacity. This characteristic is a strong predictor of disability, morbidity and mortality as well as one of the components of Fried's frailty phenotype [4]. Furthermore, the functional status of patients will also be assessed at recruitment with the Barthel Index [37], an international and validated tool of disability. The score ranges from 0 (severe functional dependence) to 100 (functional independence). At baseline, gait ability will be assessed using the 6-m gait velocity test (GVT). Starting and ending limits will be marked on the floor with tapelines for a total distance of 8 m. Participants will be instructed to walk at their self-selected usual pace for two attempts. The best result of both trials will be registered. The first and last metre, considered the warm-up and deceleration phases, respectively, will not be included in calculations of the gait assessment. Dual-task conditions (gait evaluation during the simultaneous performance of a cognitive task) have recently been recognized as a sensitive assessment method for interactions among cognition, gait, falls and frailty. Changes in gait parameters (i.e. gait velocity and gait variability) while performing a dual-task test (dual-task cost) may be early predictors of fall risk [38, 39] and may be useful tools for functional evaluations in frail older patients. Exercise can modify the dual-task cost and, consequently, the fall risk and functional capacity [40]. The dual-task paradigm [37] will be used in the 6- m habitual GVT. Two trials will be conducted to assess gait velocity while the patient is performing a verbal or counting task (verbal GVT and arithmetic GVT, respectively). During the verbal dual-task condition (verbal GVT), we will measure gait velocity while participants are naming animals aloud. During the arithmetic dual- task condition (arithmetic GVT), we will assess gait velocity while participants are counting backwards aloud from 100 in ones. The cognitive score will be measured by counting the number of animals named (dual-task with verbal performance) or determining how many numbers were counted backwards (dual-task with arithmetic performance). Isometric upper limb (dominant hand grip) and lower limb (right knee extensors and hip flexors) muscle strength will be measured using a manual dynamometer. Maximal dynamic strength will be assessed using the 1RM test in the bilateral leg press exercise using exercise machines (Matrix, Johnson Health Tech, Ibérica, S.L., Torrejón de Ardoz, Spain; and Exercycle S.L., BH Group, Vitoria, Spain). In the first assessment, the subjects will warm up with specific movements for the exercise test. Each subject's maximal load will be determined in no more than five attempts, with a 3-min recovery period between attempts. After the 1RM values are determined, the subjects will perform 10 repetitions at maximal velocity and at intensities of 50% of 1RM to determine the maximum power (W) and the loss of power during the 10 repetitions in the leg press exercise [41]. The power will be recorded by connecting a velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain). During all neuromuscular performance tests, strong verbal encouragement will be given to each subject to motivate them to perform each test action as optimally and rapidly as possible. Distribution of the training sessions throughout the day should minimize cumulative fatigue and help to maintain adherence. Adherence to the exercise programme will be documented in an individual daily log of the sessions. Changes in cognitive-affective status after the intervention will be measured using the Spanish validated versions of the Minimental Cognitive Exam (MEC-Lobo) [42] in the case of dementia and the MOCA [43] in the case of MCI. The Yesavage GDS [44] and Trail Making Part A [45] will be performed to assess depression and executive dysfunction. During functional tasks (such as balance, gait and rising from a chair) and cognitive evaluations (dual tasking), an inertial sensor unit (IU) will be attached over the lumbar spine (L3) to record the acceleration data in control and intervention participants [46, 47]. Primary and secondary variables are presented in Table 1.

4.- Discussion

Frailty and cognitive impairment are two very common geriatric syndromes in elderly patients and are frequently related and overlapped. Functional decline and disability are major adverse outcomes of these conditions. Exercise is a potential intervention for both syndromes. If our hypothesis is correct, the relevance of this project is that the results can contribute to understanding that the individualized multicomponent exercise programme (VIVIFRAIL) for frail elderly patients with cognitive impairment is more effective in reducing functional and cognitive impairment than conventional care. Moreover, our study may be able to show that an innovative individualized multicomponent exercise prescription for these high-risk populations is plausible, having at least similar therapeutic effects to other pharmacological and medical prescriptions.

Traditionally, health systems and policies focus attention on the management of chronic conditions as the central paradigm of care for the elderly. On the other hand, evidence coming from a geriatrics perspective in the last 30 years and international health organizations such as the World Health Organization (WHO) has emphasized the significance of maintaining functional capacity, recently renamed as intrinsic capacity, as the central objective and focus of all health systems and policies for elderly populations. Thus, this trial is in line with these objectives and recommendations. The performance of exercise programmes can improve quality of life and maintain independence in activities of daily living, and can potentially improve cognitive function and prevent adverse health outcomes (i.e. falls and fractures, hospitalizations and nursing homes admissions) in this high-risk population. In addition, the clinical impact of this trial can be significant if we help to modify and shift the traditional management of this population from an illness model to a more person-centred and functionally oriented perspective. Moreover, if our hypotheses are correct, the prescription of individualized exercise can be routinely included in the clinical practice of health professionals tending to elderly frail patients with cognitive complaints.

An important aspect of our trial is the inclusion of elderly patients with mild cognitive decline and dementia. So far, the majority of trials in aged frail participants with these conditions have been routinely excluded. The inclusion of participants with cognitive impairment in addition to frailty makes the trial novel and unique with notable external validity compared with other previous trials in assessing the effect of individualized exercise programmes on functional capacity, activities of daily living and cognitive function.

Another remarkable characteristic of our study is the utilization of an interdisciplinary team (geriatricians, nurses, physiotherapy, engineers) that manages not only the clinical aspects but also the physiotherapy and engineering kinematics. This aspect enables the translation and application of our results to different clinical practices and enables the establishment of new protocols related to the ageing process for different health professionals and for monitoring functional changes objectively.

To date, randomized clinical trials with exercise interventions in aged participants have been heterogeneous (sometimes with confusing details related to the exercise programme). An innovative aspect of our trial is the performance of a detailed and well-designed exercise intervention using the VIVIFRAIL methodology that can be easily extrapolated to other clinical settings and scenarios like community centres, day care centres, nursing homes and hospitals. If our results confirm our hypothesis, this randomized clinical trial could help to disseminate the "VIVIFRAIL exercise recipe" worldwide to frail seniors with cognitive decline.

Dissemination

We will disseminate the results of our study via presentations at international conferences and articles in peer-reviewed journals. The study will be implemented and reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines.

Future directions

In the near future, this project offers the opportunity to test and disseminate "in real life" a novel prescription exercise tool (VIVIFRAIL) in the very vulnerable population of frail elders with cognitive decline. The project will yield direct information about the effects of a specific and individualized designed exercise programme in those geriatric conditions. In the long term, we expect this trial can help to shift actual medical care from the traditional disease perspective to a more functional management. Another important expected result in our project is to generalize the prescription of exercise in this population in order to prevent disability. Finally, with the actual target of a novel era of precision medicine, our results could be a significant step forwards to move towards a "precise prescription of exercise recipe" for older patients with frailty and cognitive decline impairment.

Conflict of interest

All authors have nothing to declare.

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Paper 2

Effects of VIVIFRAIL multicomponent intervention on functional capacity: a multicentre, randomized controlled trial.

1.- Introduction

The global population is progressively aging, and lifespan is predicted to continue increasing over the next decades.[1] While substantial gains have been made in the application of precision medicine to prevent and treat aging-related health complications, frailty syndrome remains prevalent among the oldest old, reducing their ability to perform activities of daily living (ADLs) through loss of muscle function (i.e., muscle mass and muscle strength/power), ultimately leading to functional deterioration and disability.[2] Many age-related processes leading to frailty in older adults are also likely responsible for brain aging and related cognitive impairment.[3] Indeed, cognitive decline is closely associated with frailty syndrome as both diseases share several pathophysiological mechanisms and short-term and long-term consequences such as increased incidence of falls, hospitalization, institutionalization, and death.[2,4] Accordingly, healthcare professionals should prioritize strategies to prevent or reverse functional and cognitive deterioration in older populations, which may reduce visits to primary care and emergency departments, and lessen hospital resources and, ultimately, healthcare costs.

Physical inactivity seems to play a key role in the loss of muscle function and functional capacity, which in turn appears to be a crucial factor related to frailty.[5] Against this background, the potential benefits of different exercise interventions in frail individuals have been widely demonstrated in the literature, showing marked improvements in frailty hallmarks—for instance, gait ability, muscle strength, balance, and falls.[6;7] It is recognized that physical exercise improves metabolic health by suppressing muscle atrophy, blunting inflammatory responses, and protecting against loss of bone density, and it may also contribute to preserve insulin sensitivity, mitochondrial activity and physical function.[8] There is strong evidence to support that the inclusion of tailored exercise programs is probably the best method to improve the hallmarks of frailty, including functional capacity, muscle function, and health status.[9;10] In particular, multicomponent exercise programs consisting of resistance (power), balance, and gait-retraining exercises, are the most effective interventions for preventing most, if not all, of the complications of frailty syndrome (i.e., poor balance, reduced muscle strength, poor gait ability, and increased incidence of falls), and their prescription is recommendable for frail older adults, as well as for persons with prefrailty.[6,10;11] Additionally, physical exercise and specifically multicomponent exercise training, may be a cornerstone for improving physical and cognitive function in frail individuals with mild cognitive impairment (MCI) and dementia.[12] In line with this concept, we recently developed an innovative multicomponent exercise training program termed Vivifrail (http://vivifrail.com/resources/), which is based on promoting exercise in older population through individualized programs designed to prescribe tailored physical exercise.[13] In a recent study[11], the Vivifrail multicomponent tailored exercise program was very effective in the short-term (4 weeks) and prevented severe functional decline and strength loss in institutionalized older (i.e., physical frailty reversion and recovery of autonomy). Multicomponent exercise face-to-face interventions would seem advisable as an essential activity to protect older adults from severe functional decline.[14] The community-based approach is the best way forward and physical exercise is one of the main interventions with systemic effect proven to improve physical impairment related to frailty (low body mass, strength, mobility, physical activity level, energy).[15] The present multicenter study aimed to examine the effects of the Vivifrail multicomponent exercise intervention performed by frail/prefrail community-dwelling older adults with cognitive impairment and mild dementia for functional, cognition, and well-being status.

2.- Material and Methods.

2.1.- Design

The study was a multicenter, randomized clinical trial (RCT) (NCT03657940) performed according to the Spirit 2013 and the CONSORT statement for transparent reporting (Supplementary File 1).[16] It is an open label, blinded adjudication study. The study protocol has been published.[17] The multicenter RCT was conducted from September1, 2017 to May 31, 2020, in the outpatient geriatrics clinics of three tertiary hospitals in Spain (Geriatric Department of Complejo Hospitalario de Navarra, the Matia Fundazioa in San Sebastian and the Hospital of Getafe). Regarding the sample size calculations, assuming an alpha error of $\alpha = 5\%$, a correlation between pre and post-intervention values of the Short Physical Performance Battery (SPPB) of $\rho = 0.5$ and a standard deviation for the SPPB of $\sigma = 2.5$, the required sample size to have a power of 90% to detect a minimum difference of 1 point between groups in the post–pre SPPB score was 101 patients per group. Taking into account an expected loss of patients along the follow-up of 15%, the final sample size required was 120 per group for this multicenter study.[17]

The study followed the principles of Declaration of Helsinki and was approved by the Complejo Hospitalario de Navarra Clinical Research Ethics Committee. All patients or their legal representatives provided written informed consent. There was no financial compensation.

Patients who met the inclusion criteria were randomly assigned to the intervention or control (usual-care) group. Prior to randomization, the attending geriatricians reviewed the absolute and relative contraindications to participate in the intervention and provided general information about the study. Usual care was offered to the patients by the geriatricians and consisted of normal outpatient care, including physical rehabilitation when needed.

2.2.- Participants and randomization.

Potentially eligible outpatient participants were initially evaluated by the geriatricians. We focused on a particularly vulnerable population segment, but at the same time with sufficient functional and cognitive reserve to be able to complete the exercise program. A trained research assistant (AC-H, IA-R, IM-E, FR-E, RP-T) conducted the screening interview to evaluate the following inclusion criteria: age >75 years, Barthel Index score ≥60 (scale, 0 [severe functional dependence] to 100 [functional independence]), being able to communicate and ambulate (with/without assistance), MCI or mild dementia according to Diagnostic and Statistical Manual of Mental Disorders (DSM) V criteria, Global Deterioration Scale (GDS)-4 (Reisberg classification), pre-frail and frail status according to the Fried criteria[18], and having someone to help supervise the exercises. Exclusion criteria were any factor that affected physical exercise performance or testing procedures, including terminal illness, uncontrolled arrhythmias, recent myocardial infarction, unstable angina pectoris, uncontrolled arterial hypertension, unstable cardiovascular disease or other unstable medical condition, recent pulmonary thromboembolism, upper or lower extremity fracture in the past 3 months, and institutionalized older adults or pending entry into institution.

After the baseline assessment was performed, participants were randomly assigned to the intervention and control (i.e., usual-care) groups following a simple randomization procedure, in a 1:1 ratio without restrictions. The simple randomization sequence was generated by a statistician not involve in the RCT using an online system (www.randomizer.org) for the three hospitals. The assessment staff were blinded to the study design and group allocation in the course over the three months and participants (or their families) were explicitly informed and reminded not to discuss their randomized allocation with the assessment staff. Drop-out was considered only when the baseline assessment was completed.

The costs related to the intervention were fundamentally those generated by hiring one physiotherapist *ad hoc* for the project and the collaboration of other research assistants who shared the work for 5 days a week for the duration of the study. An initial investment of €8840 (US $10008) was made to buy variable resistance equipment (i.e., €7840 [US $9408] for two leg-press machines) for measuring muscle strength and approximately €1000 (US $1200) for elastic resistance bands, ankle weights, and handgrip balls.

2.3.- Intervention

Participants in the usual-care group were instructed to continue with their normal ADLs and received habitual outpatient clinical care, including medical treatments and physical rehabilitation when needed. In addition to habitual outpatient care, the intervention group received the recently developed Vivifrail multicomponent exercise program (http://vivifrail.com/resources/).[19] The Vivifrail program is a home-based exercise program focused on individualized multicomponent exercise prescription according to the functional capacity of the older adults, and consisted of resistance/power, balance, flexibility and cardiovascular endurance exercises (i.e., walking). Adherence to the program was documented in a daily register and two phone calls were performed during the intervention period to guarantee patient adherence and to address doubts and questions related to the intervention. At the end of the baseline visit, patients were familiarized with their specific exercise routine before the start of the intervention and their family members or caregivers were instructed in monitoring the exercise intervention for 30 minutes.

After the baseline assessment, patients in the intervention group were enrolled into one of the following individualized Vivifrail training programs, according to their physical functional status: Disability (0–3 points in the SPPB score), Frailty (4–6 points), Prefrailty (7–9 points), and Robust (10–12 points). A copy of their specific exercise protocol was delivered for each patient. The initial load for resistance exercises was established according to the Vivifrail exercise prescription guidelines (www.vivifrail.com/resources/) through a progressive loading protocol, adjusting the load until the patient was able to complete ~ 30 repetitions with some effort. Initial load was set at 0.5 kg (dumbbells) and gradually increased in 0.5-kg increments for upper-body exercise; lower-body leg extensions started with free weight repetitions and gradually increased in 0.5-kg increments using ankle weights to gradually increase the intensity of lower-body leg exercises based on the functional reserve of the older patients. The exercise intervention comprised a 5-day-a-week routine of multicomponent exercises (i.e., resistance, balance, and flexibility exercises 3 days per week, and walking 5 days per week) during 12 consecutive weeks (for more details see http://vivifrail.com/resources/). After the first month of exercise prescription and at the end of the 1-month follow-up visit, a new exercise training program was given to patients and caregivers according to patients´ functional status at that time.

2.4.- Endpoints

The primary endpoint was the change in functional capacity from baseline (beginning of the intervention) to 12 weeks after intervention, as assessed with the SPPB, which combines balance, gait velocity and leg strength as a single score on a 0 (worst) to 12 (best scale).[20] The meaningful clinical change is considered 1 point for the SPPB.[21]

Secondary endpoints included changes in cognitive function assessed by the Spanish validated version of the Minimental Cognitive State Examination[22] (MEC-Lobo; 0 [worst] to 35 [best] score) for older adults with dementia and the Montreal Cognitive Assessment[23] (MOCA; 0 [worst] to 30 [best] score) for those with MCI. Changes in functional status of the patients during the intervention were also measured by the Barthel Index of ADLs[24], which ranges from 0 (severe functional dependence) to 100 (functional independence). Also assessed were changes in mood-status (15-item Yesavage Geriatric Depression Scale Spanish version [GDS]; scale of 0 [best] to 15 [worst])[25], visual analog scale of the EuroQol-5 Dimension (EQ-5D)[26] questionnaire for quality of life (QoL) assessment (Spanish version of the EQ-5D; scale of 0 [worst health state imaginable] to 100 [best health state imaginable]), and handgrip strength (dominant hand).[27] Other secondary endpoints included falls, hospital admissions, visits to the emergency department, institutionalization, and mortality after 3 months of the intervention. Number of falls were based on self-report. Additionally, patients and caregivers were asked about hospital admissions, visits to the emergency department and institutionalization in the last 3 months, and these endpoints were checked from medical history. Mortality data was also collected from hospital records.

2.5.- Statistical analysis

We used the intention-to-treat approach for data analysis. Between-group comparisons of continuous variables were performed using linear mixed models for continuous variables and with ordinal mixed models for ordinal variables (i.e., patients' distribution based on the Vivifrail classification). The models included group, time, and group by time interaction as fixed effects, and participants as random effects and were adjusted for age, sex, endpoint baseline value and SPPB baseline value, all of them included as fixed effects. Cognitive endpoints (i.e., MOCA and MEC-Lobo) models were also adjusted for years of education, baseline CIRS and baseline Yesavage GDS values. Data are expressed as change from baseline (when intervention started) to 1 month and 3 months for each group, determined by the time coefficients (95% confidence interval [CI]) of the model. The primary conclusions about the effectiveness of physical exercise were focused on between-group comparisons of change in functional capacity assessed with the SPPB and determined by the time by group interaction coefficients of the model. The same strategy was used for examining the effectiveness of the intervention on secondary endpoints including cognition, muscle function and well-being status.

Comparisons of secondary endpoints indicative of adverse events were analyzed using the Mann-Whitney test for non-normally distributed quantitative data, mid-*P* value exact test for rates, and χ^2 or Fisher´s test for categorical data. Normality of data was checked graphically and through the Kolmogorov-Smirnov test. The residuals were also checked graphically, and no noticeable deviation from normality was observed. All-comparisons were two-sided, and the significance level was established at $p<0.05$. All statistical analyses were made with SPSS, version 20 (IBM Corp) and R, version 3.2.2 (R Foundation) software.

3.- Results

The study flow diagram is shown in **Figure 1.** Of the 188 patients included in the analyses, 132 were women (70.2%); the mean age was 84.1 (4.8) years (range 73-95 years). Demographic and clinical characteristics of the participants are shown in **Table 1**. The mean adherence to the exercise sessions in the intervention group was 79% in the first 4 weeks and 68% in the following 8 weeks, and 5% of the participants in the control group received physical rehabilitation. No adverse effects associated with the prescribed exercises were recorded and no patient had to stop the intervention because of it.

With regards to the primary endpoint, the physical exercise program provided a significant benefit over clinical usual-care. The exercise group showed a mean increase (over usual care) of 0.86 points in the SPPB score (95% CI 0.32, 1.41; p<0.01) after 1 month and 1.40 points (95% CI 0.82, 1.98; p<0.001) after 3 months of exercise training (**Figure 2, Table 2**). The percentage distribution of patients in different Vivifrail categories (Disability, Frailty, Prefrailty and Robust) also significantly differed between the two groups from baseline to 3 months of the intervention (p<0.001) (**Figure 3**), indicating a beneficial effect––for instance, the percentage of patients in the disability category progressively decreased in the intervention group (14.8% at baseline, 6.8% at1 month and 6.5% at 3 months), whereas no such trend was found in the control group (4.0% at baseline, 5.2% at 1 month and 11.4% at 3 months; odds ratio intervention *versus* control 0.14 [0.05, 0.45]).

Regarding the secondary endpoints, the exercise intervention also seemed to provide benefits on cognitive function. Indeed, the intervention group showed improvements in the MOCA test after 3 months of exercise intervention (2.05 points; 95%CI 0.80, 3.28), whereas no such trend was found in the control group (after 3 months -0.13 points; 95%CI -1.08, 0.82) (p<0.05) (Table 2). Similar between-group differences were found in the MEC-Lobo test for those patients with dementia (**Table 2**). We also found significant between-group differences in handgrip strength and in mood status (depression) (both p<0.05) after 3 months of intervention (**Table 2**). However, no significant between-group differences were observed for the remainder secondary endpoints, including health-related quality of life (visual analog scale of the EQ-5D), Barthel Index of functional ability in ADLs (**Table 2**), falls, hospital admissions, visits to the emergency department, and mortality (all p>0.10) (Table 3).

4.- Discussion

The present multicenter RCT adds to the growing body of evidence for the beneficial effects of physical exercise in community dwelling older adults. Our RCT shows that the Vivifrail individualized, tailored multicomponent intervention of moderate-intensity muscle strengthening, balance, flexibility and endurance exercises is safe and provides significant benefit over usual clinical care in frail older patients with MCI and dementia, as well as, contributes to prevent or reverse the functional decline that often occurs in this population. In addition to functional gains, our findings indicate that the Vivifrail exercise program promotes mood, cognitive and muscle function enhancements after 3 months of intervention compared with usual clinical care.

The protective effect of physical exercise in community dwelling older adults has been well confirmed in the literature, supporting exercise as a cornerstone for preserving functional status and muscle function in this population.[10,15,28] Contrastingly, physical inactivity is recognized to promote frailty, and physical exercise is known to maintain or improve the function of many of the physiological systems that can be altered in frailty, including muscle and heart function, endocrine function (e.g., glucose metabolism) and inflammation, and delay the onset of multiple chronic diseases.[29] Previous trials have highlighted the potential benefits of a multicomponent exercise program (resistance, endurance, flexibility and balance exercises) on the functional capacity in older populations, and for reducing the likelihood of developing disability after long-time exercise interventions (i.e., 6 months or over).[6,30;31] One of the main findings of our study is that 1 month of the intervention was sufficient for improving functional capacity in the oldest old. In addition to functional and muscle function (i.e., handgrip strength) gains, our results show that the Vivifrail exercise program has a beneficial effect on cognition in older frail/prefrail patients with MCI and mild dementia, assessed by MOCA and MEC-Lobo, respectively. The role of physical exercise on cognitive function has been widely investigated in older adults[32;33] and, specifically, multicomponent exercise training, seems to provide the best results on cognition in older patients with MCI and dementia.[6,12] Strikingly, cognitive function enhancements might mediate physical function improvements in acutely hospitalized frail elders.[34] Thus, physical activity shows promise as modifiable risk factor to reduce the risk of dementia and related neurodegenerative diseases.[35] Mechanistically, the neural and vascular adaptations induced by exercise in older adults are hypothesized to promote cognitive enhancements through stimulation of neurogenesis, angiogenesis and synaptic plasticity, and by reducing pro-inflammatory processes and cellular damage brought about by oxidative stress.[36] Moreover, the combination of different training modalities, with special emphasis on resistance training, appears to be the best strategy for preserving or improving cognitive function, but further research is warranted better understand the underlying physiological mechanisms induced by exercise in community dwelling frail older adults with MCI and dementia. Considering the mood status, patients in the exercise group also had better outcomes regarding depression than peers in the control group. The exercise program was, however, unable to influence the occurrence of falls during the intervention period. Although there is consistent evidence for exercise as an effective therapy for falls prevention in community dwelling older adults[37], our findings reveal no difference in incidence between groups. These findings should be interpreted with caution due to the short duration of the intervention period (i.e., 3 months).

The present study is in line with the previously published World Health Organization (WHO) Clinical Consortium of Healthy Aging, which stresses the importance of maintaining intrinsic capacity domains (i.e., locomotion, vitality, cognition, psychological, sensory) and specifically functional status to preserve autonomy and independence in everyday activities that enables wellbeing.[38] Our results suggest that the Vivifrail multicomponent exercise program may help to mitigate the trajectory of frailty and disability in community dwelling older adults with MCI and/or mild dementia, and seems to also provide benefits in mood, cognitive, and muscle function, which are key components of intrinsic capacity. Our data support the notion that, in accordance with the WHO framework, tailored physical exercise should be prescribed to older adults and should be considered a frontline treatment for preventing functional decline, cognitive impairment and muscle function deterioration that commonly occurs during the aging process.[14,39]

Our study has several strengths including its multicenter randomized design. Also, we focused on a particularly vulnerable segment of the older adult population, which included patients with multiple comorbidities and geriatric syndromes as MCI/mild dementia (who are frequently excluded from exercise studies). Our findings suggest that a home-based, individualized multicomponent exercise program (Vivifrail; www.vivifrail.com) has beneficial effects on many health-related outcomes, overcoming barriers often encountered with traditional exercise interventions such as material resources and transport limitations. Finally, to minimize the potential bias the assessment researchers were unaware of the study design and group allocation.

Our study has several limitations, including recruitment challenges to achieve the sample size proposed in the study protocol.[17] The "lockdown" for coronavirus disease-2019 had a negative impact on the recruitment process and made it difficult to reach the sample size initially calculated. Although a rigorous randomization procedure was carried out, significant between-group differences were obtained at baseline for functional capacity (SPPB scale) and comorbidities (CIRS score). Also, there was missing data at 1 month and 3 months post-intervention due to the characteristics of the study population (octogenarians and nonagenarians with multiple geriatric syndromes) and the coronavirus lockdown during March-June 2020. Additionally, more patients discontinued the study in the intervention group compared to the control group, which could have influenced in the results obtained. The specific features of the study population (i.e., frail or prefrail older patients according to the Fried criteria[18] with MCI or mild dementia) limits the generalizability of our results. Thus, care should be taken when extrapolating our findings to other cohorts. Lastly, the adherence to the exercise training program progressively dropped during the intervention period (79% of the total sessions were completed after 1 month of intervention, and 68% at 3 months). Our exercise adherence rate was, however, higher than in other studies that developed similar home-based exercise interventions.[40]

Our findings highlight several future directions for research. The effectiveness and safety of the Vivifrail exercise program may be examined in future RCTs with longer intervention periods (>3 months). In addition to physical exercise, further research is needed to establish consistent evidence about the effect of multidomain interventions including cognitive training on functional capacity and cognition in community dwelling older adults with cognitive impairment.

5.- Conclusions

The Vivifrail multicomponent exercise training program appears to be an effective and safe intervention for improving functional capacity in community dwelling frail/prefrail older patients with MCI or mild dementia. In fact, a 1 month of exercise intervention is sufficient to enhance physical function in this population. In addition to functional gains, the individualized multicomponent exercise program also seems to have a beneficial effect on cognition, muscle function, and mood status after 3 months of exercise intervention.

6.- Acknowledgements

This study has been funded by a Gobierno de Navarra project grant (Resolución 426/2016, del 30 de septiembre. Mikel Izquierdo is funded by a research grant PI17/01814 of the Ministerio de Economía, Industria y Competitividad (ISCIII, FEDER). We also want to thank Fundacion Miguel Servet (Navarrabiomed) for all its support during the implementation of the trial. Finally, thanks to all our patients and their families for their confidence in the research team.

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Table legends

Table 1. Baseline characteristics of the participants.

Table 2. Results of study endpoints by group at 1-month and 3-months post-intervention.

Table 3. Results of secondary endpoints indicative of adverse events for each group.

Figure legends

Figure 1. Study flow diagram.

Figure 2. Within-group SPPB score change distribution for both groups.

Figure 3. Changes in the functional categories at baseline, 1-month and 3-months after intervention according to the Vivifrail classification: Disability (SPPB score 0-3 points), Frailty (4-6 points), Prefrailty (7-9 points) and Robust (10-12 points). p-value after 1 month = 0.062. p-value after 3 months = <0.001.

Table 1. Baseline characteristics of the participants

Variable	Control group (N=100)	Intervention group (N=88)
Demographic data		
Age, years	84.0 (4.8)	84.2 (4.8)
Women, N (%)	69 (69.0%)	63 (71.6%)
Body mass index, kg/m^2	27.0 (4.3)	27.1 (3.6)
Education, N (%)		
< 12 years	80 (80.0%)	67 (76.1%)
≥ 12 years	20 (20.0%)	21 (23.9%)
Living status, N (%)		
Alone	26 (26.0)	19 (21.6)
Caregivers	12 (12.0)	9 (10.2)
Family members	60 (60.0)	58 (65.9)
Others	2 (2.0)	2 (2.3)
Clinical data		
MCI, N (%)	63 (63.0)	49 (55.7)
Mild Dementia, N (%)	37 (37.0)	38 (43.2)
Fried Criteria, N (%)		
Prefrail (1–2 points)	64 (64.0)	57 (64.8)
Frail (3–5 points)	36 (36.0)	31 (35.2)
CIRS score, median (IQR)	5.0 (5.0)	7.0 (6.0)
MNA score, median (IQR)	13.0 (3.0)	13.0 (3.0)
1RM leg press, kg	49.4 (27.2)	48.0 (24.1)
5-m GVT, s	7.8 (2.9)	8.7 (5.5)
Primary endpoint measures		
SPPB scale, score	7.7 (2.5)	6.8 (2.7)
Secondary endpoint measures		
MOCA, score	15.4 (5.2)	15.8 (5.2)
MEC Lobo, score	27.1 (4.5)	26.4 (5.3)
Barthel Index, score	91.7 (10.2)	91.1 (9.3)
Handgrip, kg	19.2 (7.7)	19.6 (6.7)
Yesavage GDS, score	3.4 (2.9)	3.9 (2.9)
QoL (EQ-VAS), score	71.4 (18.2)	70.6 (20.6)

Data are mean (SD) unless otherwise stated. Significant differences were found between groups for SPPB score and CIRS score ($p<0.05$).
Abbreviations: CIRS, Cumulative Illness Rating Scale; EQ-VAS, Visual analog scale of the EuroQol questionnaire; GVT, Gait Velocity Test; IQR, interquartile range; MNA, Mini-Nutritional Assessment; MCI, Mild Cognitive Impairment; MEC, Minimental Cognitive Exam; MOCA, Montreal Cognitive Assessment; QoL, Quality of Life; SPPB, Short Physical Performance Battery; Yesavage GDS, Yesavage Geriatric Depression Scale; 1RM, one-repetition maximum.

Table 2. Results of study endpoints by group at 1-month and 3-months post-intervention

Endpoints	Time	Control group	Exercise group	Between-group difference (95%CI)	p-value between groups
Primary Endpoint: Changes in functional capacity					
SPPB scale (points)	1 month	-0.17 (-0.54, 0.19)	0.69 (0.29, 1.09)	0.86 (0.32, 1.41)	0.002
	3 months	-0.33 (-0.70, 0.04)	1.07 (0.63, 1.51)	1.40 (0.82, 1.98)	<0.001
Secondary Endpoints: Changes in functional, cognition, muscle function and mood-status					
Barthel Index (points)	1 month	0.18 (-1.80, 2.14)	1.69 (-0.51, 3.89)	1.51 (-1.44, 4.46)	0.319
	3 months	-0.10 (-2.11, 1.99)	0.99 (-1.40, 3.39)	1.09 (-2.04, 4.21)	0.499
MOCA (points)	1 month	0.50 (-0.42, 1.42)	2.25 (1.08, 3.41)	1.75 (0.27, 3.24)	0.340
	3 months	-0.13 (-1.08, 0.82)	2.05 (0.80, 3.28)	2.17 (0.61, 3.72)	0.014
MEC-Lobo (points)	1 month	0.64 (0.03, 1.26)	0.75 (0.07, 1.43)	0.10 (-0.81, 1.02)	0.826
	3 months	-0.50 (-1.13, 0.13)	0.63 (-0.09, 1.36)	1.13 (0.18, 2.10)	0.023
Handgrip strength (kg)	1 month	0.08 (-0.54, 0.71)	0.70 (0.00, 1.40)	0.62 (-0.32, 1.56)	0.200
	3 months	-0.70 (-1.35, -0.05)	0.35 (-0.42, 1.12)	1.05 (0.05, 2.06)	0.042
Yesavage GDS (points)	3 months	0.61 (0.15, 1.07)	-0.51 (-1.04, 0.02)	-1.12 (-1.82, -0.42)	0.002
QoL (EQ-VAS) (score)	3 months	-0.71 (-4.49, 3.08)	-0.49 (-4.93, 3.96)	0.22 (-5.62, 6.06)	0.942

Data are expressed as mean (95%CI). All data were derived from linear mixed-effects model. For each group, data are expressed as change from baseline to 1-month and 3-months post-intervention, determined by the time coefficients (95%CI) of the model. Between-group differences were determined with time x group interaction.
All the endpoints were adjusted by age, sex, endpoint baseline value and SPPB baseline value. Additionally, cognitive endpoints (MOCA and MEC-Lobo) were also adjusted by Yesavage GDS, CIRS baseline value and years of education.
A total of 137 patients (78.0% of patients in the control group and 67.0% in the intervention group) at 1-month post-intervention and 118 patients (72.0% of patients in the control group and 52.3% in the intervention group) at 3-months post-intervention reached their functional and muscle function endpoints.
Cognitive data correspond to 137 patients (78.0% of patients in the control group and 67.0% in the intervention group) at 1-month post-intervention and 118 patients (71.0% of patients in the control group and 53.4% in the intervention group) at 3-months post-intervention.
Abbreviations: CIRS, Cumulative Illness Rating Scale; EQ-VAS, Visual Analog Scale of the EuroQol Questionnaire; MEC, Minimental Cognitive Exam; MOCA, MOCA, Montreal Cognitive Assessment; QoL, Quality of Life; SPPB, Short Physical Performance Battery; Yesavage GDS, Yesavage Geriatric Depression Scale

Table 3. Results of secondary endpoints indicative of adverse events for each group

Endpoints (3 months)	**Control group**	**Exercise group**	**Rate ratio (95%CI)**	**p-value between groups**
Falls rate (100 person-month)	15.4 (10.6, 21.6)	20.8 (14.2, 29.3)	1.25 (0.83, 2.21)	0.225
Hospital readmission rate (100 person-month)	3.28 (1.41, 6.46)	1.72 (0.35, 5.04)	0.53 (0.11, 1.92)	0.358
Visits to emergency department rate (100 person-month)	9.76 (6.25, 14.5)	6.32 (3.15, 11.3)	0.65 (0.31, 1.31)	0.234
Mortality, %	0	0		
Transfer, %				
Home	100	100		
Institutionalization	0	0		
Other	0	0		

Data are expressed as rate (95%CI) unless otherwise indicated.

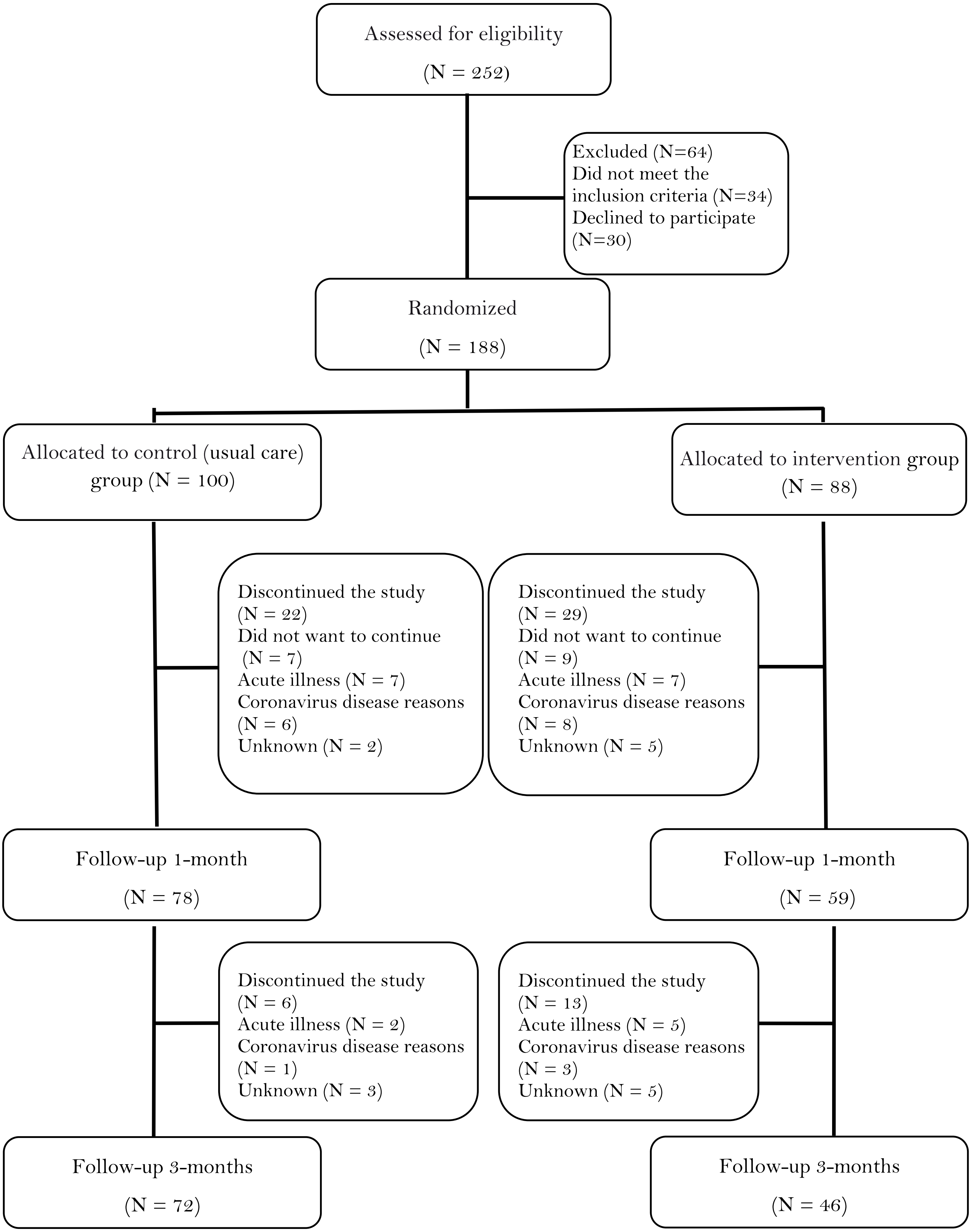

Figure 1. Study flow diagram.

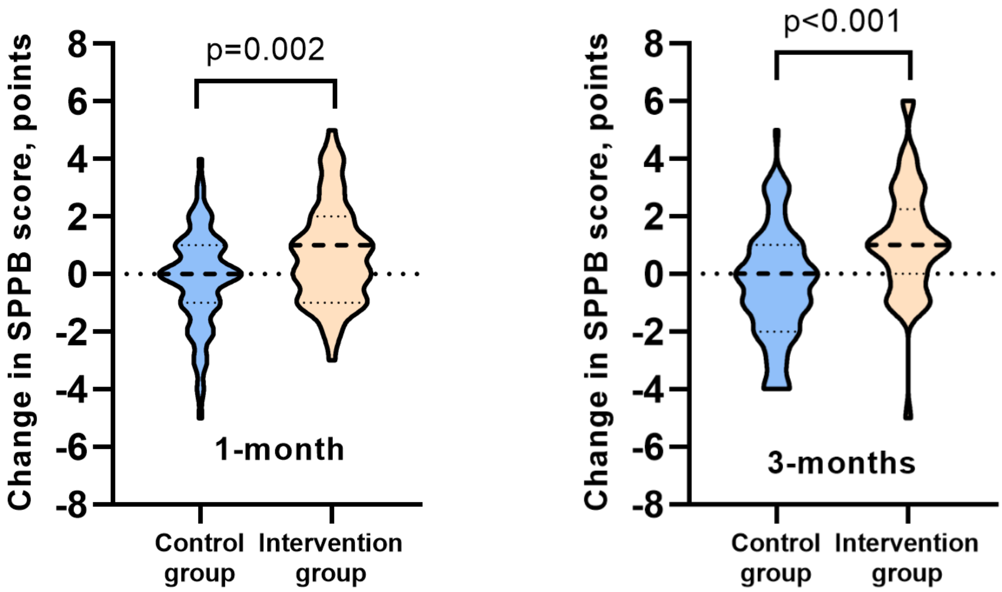

Figure 2. Within-group SPPB score change distribution for both groups.

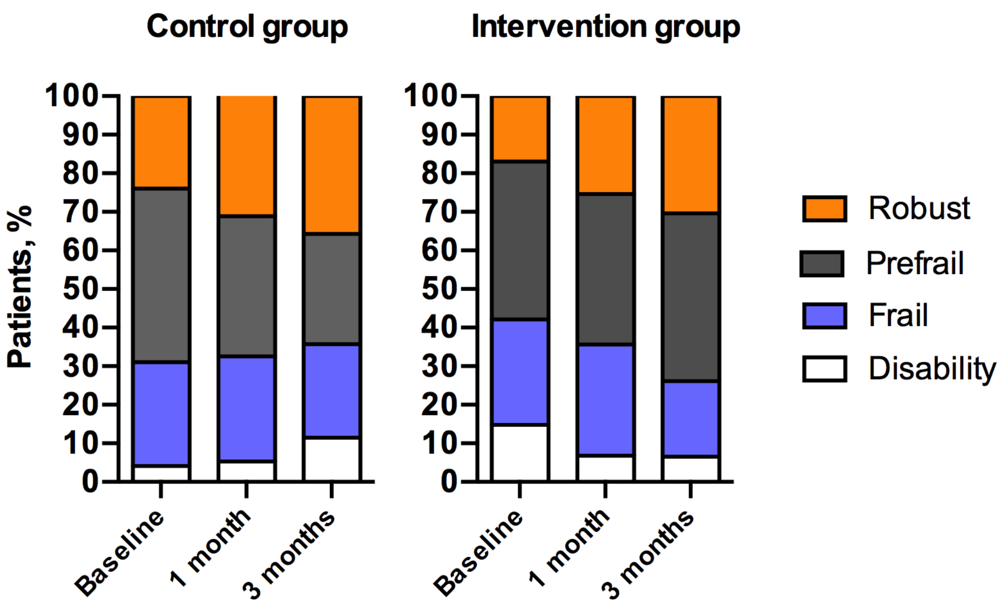

Figure 3. Changes in the functional categories at baseline, 1-month and 3-months after intervention according to the Vivifrail classification: Disability (SPPB score 0-3 points), Frailty (4-6 points), Prefrailty (7-9 points) and Robust (10-12 points). p-value after 1 month = 0.062. p-value after 3 months = <0.001.

Thesis discussion

The main objective of the thesis is to examine the effects of the VIVIFRAIL multicomponent physical exercise programme on functional capacity and cognitive status in frail and pre-frail, community-dwelling older adults with MCI and mild dementia. The VIVIFRAIL multicomponent physical exercise programme appears to be an effective and safe intervention to improve functional capacity in frail and pre-frail, community-dwelling older adults with MCI and mild dementia. In addition to improvements in functional capacity, the individualised multicomponent physical exercise programme also seems to have beneficial effects on cognition, muscle function and mood after the 3-month physical exercise intervention.

The protective effects of physical exercise in community-dwelling older adults are corroborated in the literature, underpinning exercise as a key part of preserving functional status and muscle function in this population (1,2,3). Previous studies have proven the potential effects of multicomponent physical exercise on the functional capacity of older adults, and on the probability of reducing disability after long periods of physical exercise (4). In contrast, one of the main research findings is that one month of intervention is sufficient to improve functional capacity. The unsupervised VIVIFRAIL programme therefore seems to have potentially beneficial effects on community-dwelling older adults in the very short term, despite the fact that the most clinically significant differences between the control and intervention groups were observed after a three-month period. Another recent study conducting an intervention based on the VIVIFRAIL physical exercise programme in institutionalized older adults also found significant functional improvements in SPPB, TUG, walking speed and sitting and standing exercises compared to the control group after a 4 and 24-week training period on the VIVIFRAIL programme (7). In another non-randomised clinical trial, in this case, involving frail and pre-frail, community-dwelling older adults, a 6-week multicomponent physical exercise intervention combining different training modalities such as strength exercises performed on a leg press to improve muscle power and high-intensity intervallic training for cardiovascular exercise on a treadmill, also reported significant improvements in functional capacity, which was assessed using the SPPB test, muscle strength and power, and aerobic capacity (5), in addition to reversing phenotypic frailty by 64%. Moreover, a systematic review analysing the effects of different exercise interventions for frail older adults found that multicomponent physical exercise appears to be the best strategy for improving gait, balance and strength, and, consequently, maintaining functional capacity during ageing (6).

Furthermore, the distribution of people into the 4 VIVIFRAIL categories (disability, pre-frail, frail and robust) revealed significant differences in the final distribution between the control and intervention groups, with greater improvement in terms of functionality in the intervention group on the basis of the category distribution. The results suggest that the VIVIFRAIL programme can help attenuate the trajectory of frailty and disability in frail, community-dwelling older adults suffering from MCI and/or mild dementia. This is supported by another recent study using the same VIVIFRAIL methodology, which found that frailty was reversed in 36% of institutionalised participants, thus confirming that multicomponent physical exercise is capable of attenuating or reversing frailty (7). It would be of interest for future studies to analyse the long-term cost-effectiveness of this type of physical exercise-based intervention, such as the VIVIFRAIL programme, in the healthcare system.

Moreover, the VIVIFRAIL multicomponent physical exercise programme seems to have beneficial effects on cognitive functions in frail and pre-frail older adults suffering from MCI and mild dementia, with significant differences observed between groups in the MoCA and MEC-Lobo test scores, with better results observed in the intervention group after the physical exercise programme had been implemented. The role of physical exercise in cognitive functions has been widely investigated in older adults without cognitive impairment (8, 9, 10), and multicomponent physical exercise in particular seems to yield the best results in cognition in older adults with MCI and dementia (11, 12). In a recent meta-analysis comparing the efficacy of a variety of exercise interventions involving cognitive functions in patients with MCI or dementia, it was observed that multicomponent physical exercise seems to be the most effective at maintaining and even improving executive functions in patients with MCI (13). However, only strength exercises revealed significant effects on memory in patients with MCI, and overall cognitive protection in individuals suffering from dementia (13).

At the physiological level, exercise-induced neuronal and vascular adaptations in older adults suggest that cognitive improvements may be achieved by stimulating neurogenesis, angiogenesis and synaptic plasticity, and by reducing pro-inflammatory processes and cellular damage caused by oxidative stress (14). Another study on community-dwelling older adults with MCI found that multicomponent physical exercise has positive effects on global cognitive functions, immediate memory and language (15), and a further study involving a similar population that included a multicomponent physical exercise programme for older adults with MCI found that physical exercise intervention is beneficial for improving memory and maintaining global cognitive functions (16). Thus, the combination of different exercise modalities, with particular emphasis placed on strength exercises, seems to be the best strategy for maintaining or improving cognitive functions; further research is however needed to better understand the physiological mechanisms induced by exercise in frail, community-dwelling older adults with MCI and mild dementia.

Regarding mood status, the older adults who underwent the physical exercise intervention achieved better results in terms of depressive symptomatology than their peers in the control group. Another study conducting a multicomponent physical exercise intervention for frail older adults also reported significant improvements in mood after the programme (10). Similarly, a clinical trial involving non-frail, community-dwelling older adults with MCI, which used strength and aerobic exercises, reported significant improvements in depressive symptoms in the group receiving physical exercise intervention, in addition to improvements in balance and mobility (21).

Moreover, the physical exercise programme reported significant improvements in muscle strength in favour of the intervention group compared to the control group with regard to handgrip strength. In a previously mentioned study using the same VIVIFRAIL methodology but in institutionalized older adults; despite significant functional improvements being found in many of the functional variables, no significant differences were found in handgrip muscle strength (7), in contrast to our study's findings. A further study, also mentioned earlier, involving a multicomponent exercise intervention that included strength and cardiovascular exercises for frail and pre-frail, community-dwelling older adults did report a 14% improvement in muscle strength (handgrip strength) in favour of the exercise intervention group (5). In another non-randomised study assessing the effects of a 12-week VIVIFRAIL programme on community-dwelling older adults, a significant improvement was observed in muscle strength assessed by handgrip strength (22). Similarly, a clinical trial involving institutionalised frail older adults using multicomponent physical exercise reported an improvement in muscle strength and power in upper and lower limbs (23).

Nevertheless, the exercise programme was unable to reduce the number of falls in the intervention group compared to the control group. In this regard, there is evidence that physical exercise is an effective therapy for fall prevention in community-dwelling older adults (17) and, as shown by a further systematic review, multicomponent physical exercise reduces the number of falls in frail older adults (6). Previous studies involving a multicomponent physical exercise intervention such as the New Zealand OTAGO programme (18), a programme specifically designed to prevent falls, consisting of lower limb strengthening exercises and balance exercises, have reported a reduction in the number of falls and fall-related injuries after the physical exercise programme, especially in populations over 80 years of age. Furthermore, consistent with the results obtained in this doctoral thesis, other studies observed that, after the physical exercise-based intervention (19), people aged 75-79 years did not present a significant reduction in the number of falls post-intervention. There may be several reasons for the lack of differences between groups with regard to falls. On the one hand, the main study objective was to analyse the effects of the physical exercise programme on functional capacity, and not on falls, which was ultimately a secondary study variable. On the other hand, the effects of the intervention were analysed in the short-term (1 and 3 months after intervention). An analysis of the long-term effect of the same intervention would be of interest. Moreover, the population profile in this study was highly specific, including frail and pre-frail older adults with MCI or dementia. Many studies do not consider this subject profile. In relation to this last point, it could be suggested that some forms of dementia, such as dementias with a more vascular profile and with more involvement of white matter (20), or Lewy body dementia, and with significant balance disorders, may explain why there was no decrease in the number of falls, which may be a bias to be assessed in future studies.

Similarly, no significant between-group differences were observed for other secondary endpoints like hospital admissions, visits to the emergency department and mortality. Although there is a trend of less hospital admissions and less visits to the emergency department, there are no statistically significant differences, and these could be due to sample losses during the study period and the short intervention period.

Last but not least, it is important to underline the role of the study subjects' caregivers/family members in the implementation of the physical exercise intervention. The VIVIFRAIL programme is an individualised programme whose implementation was not supervised by health professionals as in other programmes (18) and studies (4, 5, 7, 10, 11, 24). Indeed, in our particular study it was the family members and caregivers who helped the frail older adults with MCI and mild dementia to complete the exercises and who played a fundamental role in the development of and adherence to the intervention. Previous studies have compared the effects of supervised exercise programmes with unsupervised programmes. One such study is a clinical trial comparing the effects of a supervised balance and muscle power training programme for older adults with the same unsupervised programme (25), where it was observed that, after a 12-week training period, significant improvements in balance and muscle power were observed in both groups; the supervised exercise was, however, more effective. In the same context, other studies observed greater improvements in balance and muscle strength (26, 27, 28) in the supervised group compared to the unsupervised group.

One of the strengths of this study, therefore, is that the improvements in terms of functional, cognitive, affective and muscular strength results were achieved by means of an individualised, unsupervised physical exercise programme that can be performed wherever the older adult is (at a study centre, at home), thereby avoiding the obstacles often encountered in studies involving transport for the elderly to and from the intervention venue.

Finally, this study has several limitations, including recruitment challenges to achieve the sample size proposed in the study protocol (29). The “lockdown” for coronavirus disease-2019 had a negative impact on the recruitment process and made it difficult to reach the sample size initially calculated. Although a rigorous randomization procedure was carried out, significant between-group differences were obtained at baseline for functional capacity (SPPB scale) and comorbidities (CIRS score). Also, there was missing data at 1 month and 3 months post-intervention due to the characteristics of the study population (octogenarians and nonagenarians with multiple geriatric syndromes) and the coronavirus lockdown during March-June 2020. Additionally, more patients discontinued the study in the intervention group compared to the control group, which could have influenced in the results obtained. The specific features of the study population (i.e., frail or prefrail older patients according to the Fried criteria (30) with MCI or mild dementia) limits the generalizability of our results. Thus, care should be taken when extrapolating our findings to other cohorts. Lastly, the adherence to the exercise training program progressively dropped during the intervention period (79% of the total sessions were completed after 1 month of intervention, and 68% at 3 months). The exercise adherence rate was higher than in other studies that developed similar home-based exercise interventions (i.e., LIFE programme 47% of adherence (31) and New Zealand Otago trial 42% of adherence (32)).

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Conclusions

1. The VIVIFRAIL multicomponent physical exercise programme appears to be an effective and safe intervention to improve functional capacity in frail and pre-frail, community-dwelling older adults with MCI and mild dementia after a 1-month and 3-month intervention period.

2. The VIVIFRAIL multicomponent physical exercise programme appears to be an intervention that can help attenuate the trajectory of frailty and disability in frail, community-dwelling older adults with MCI and/or mild dementia after a 1-month and 3-month intervention period.

3. The VIVIFRAIL multicomponent physical exercise programme seems to have beneficial effects on cognition in frail and pre-frail, community-dwelling older adults with MCI and/or mild dementia after a 3-month intervention period.

4.- The VIVIFRAIL multicomponent physical exercise programme appears to have beneficial effects on muscle function in frail and pre-frail, community-dwelling older adults with MCI and/or mild dementia after a 3-month intervention period.

5.- The VIVIFRAIL multicomponent physical exercise programme appears to have beneficial effects on mood in frail and pre-frail, community-dwelling older adults with MCI and/or mild dementia after a 3-month intervention period.

6. Following the implementation of the VIVIFRAIL physical exercise programme, no significant differences were observed between the control and intervention groups with regard to the prevalence of falls in frail and pre-frail, community-dwelling elderly people with MCI and/or mild dementia.

7. Following the application of the VIVIFRAIL physical exercise programme, no significant differences were observed between the control and intervention groups with regard to A&E visits, hospital readmissions, institutionalisation and mortality in frail and pre-frail, community dwelling elderly people with MCI and/or mild dementia.

Practical application

Multicomponent physical exercise intervention, which includes aerobic, strength, mobility and balance exercises, is one of the most important components for improving functional capacity, in addition to having beneficial effects on cognition, muscle function and mood, in frail, community-dwelling older adults with MCI and mild dementia. Physical exercise forms part of the treatment that seeks to reverse frailty and improve physical and cognitive functions in older adults, and should be prescribed on an individualised basis.

Future prospects

The results underpin the need for a shift from the traditional disease-focused approach to an approach that acknowledges functional status as a vital clinical marker in the most vulnerable, community-dwelling older adults. In the same way that health professionals ensure the monitoring of chronic diseases, the assessment and measurement of functional capacity should also be incorporated into clinical practice so that multicomponent physical exercise tailored to functional capacity can be prescribed. It is a question of prescribing exercise, like medication, and tailoring a training plan for each individual according to their functional capacity, whilst paying particular attention to the most vulnerable, such as the frail with cognitive impairment.

Conclusiones

1. El programa de ejercicio físico multicomponente VIVIFRAIL parece ser una intervención efectiva y segura para mejorar la capacidad funcional al mes y a los 3 meses de intervención en personas mayores frágiles y prefrágiles que viven en la comunidad con deterioro cognitivo leve y demencia en estadio leve.

2. El programa de ejercicio físico multicomponente VIVIFRAIL parece ser una intervención que puede ayudar a atenuar la trayectoria de la fragilidad y la discapacidad al mes y a los 3 meses de intervención en personas mayores frágiles con DCL y/o demencia leve que viven en la comunidad.

3. El programa de ejercicio físico multicomponente VIVIFRAIL parece tener efectos beneficiosos en la cognición a los 3 meses de intervención en personas mayores frágiles y prefrágiles con DCL y/o demencia leve que viven en la comunidad.

4.- El programa de ejercicio físico multicomponente VIVIFRAIL parece tener efectos beneficiosos en la función muscular a los 3 meses de intervención en personas mayores frágiles y prefrágiles con DCL y/o demencia leve que viven en la comunidad.

5.- El programa de ejercicio físico multicomponente VIVIFRAIL parece tener efectos beneficiosos en el estado de ánimo a los 3 meses de intervención en personas mayores frágiles y prefrágiles con DCL y/o demencia leve que viven en la comunidad.

6. No se han observado diferencias significativas entre el grupo control y el grupo intervención tras la aplicación del programa de ejercicio físico VIVIFRAIL sobre la prevalencia de caídas en personas mayores frágiles y prefrágiles con DCL y/o demencia leve que viven en la comunidad.

7. No se han observado diferencias significativas entre el grupo control y el grupo intervención tras la aplicación del programa de ejercicio físico VIVIFRAIL sobre las visitas a urgencias, reingresos hospitalarios, institucionalización y mortalidad en personas mayores frágiles y prefrágiles con DCL y/o demencia leve que viven en la comunidad.

Aplicación práctica

El ejercicio físico multicomponente (aeróbico, fuerza, flexibilidad y equilibrio) es uno de los componentes más importantes para mejorar la capacidad funcional, además de tener efectos beneficiosos en la cognición, función muscular y ánimo, en personas frágiles con deterioro cognitivo leve y demencia leve que viven en la comunidad. El ejercicio físico es parte del tratamiento para tratar de revertir la fragilidad y mejorar la función física y cognitiva en personas mayores, y debe ser prescrita de forma individualizada.

Perspectiva futura

Los resultados obtenidos respaldan la necesidad de un cambio del enfoque tradicional centrado en la enfermedad a uno que reconozca el estado funcional como un signo clínico vital a nivel comunitario en las personas mayores más vulnerables. Así como los profesionales de la salud velan para el control de las enfermedades crónicas, también se debería incorporar en la práctica clínica la valoración y medición de la capacidad funcional para de esta manera poder prescribir ejercicio físico multicomponente adaptado a la capacidad funcional. Se trata de prescribir ejercicio, como un medicamento, y confeccionar un traje a medida de entrenamiento para cada persona según su funcionalidad, presentando especial atención a las personas más vulnerables como son las frágiles con deterioro cognitivo.