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RESEARCH PAPER

Effects of a 12-week Vivifrail exercise program on intrinsic capacity among frail cognitively impaired community-dwelling older adults: secondary analysis of a multicentre randomised clinical trial

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Abstract

Introduction: The World Health Organisation recently defined the construct of intrinsic capacity (IC), a function-based marker of older adult's health encompassing all mental and physical capacities of the individual. Multicomponent physical exercise (MCE) is a potential intervention capable to maintain/increase IC at older age; however, evidence is scarce on the effects of MCE on IC in cognitively impaired pre-frail/frail older adults.
Methods: Secondary analyses of a randomised clinical trial. One hundred and eighty-eight older outpatients (age = 84.06 ± 4.77, 70.2% women) presenting with pre-frailty/frailty (according to Fried Criteria) and mild cognitive impairment (MCI)/mild dementia were recruited in the Geriatric clinics of three tertiary hospitals in Spain. Subjects were randomised to participate in the 12-week home-based individualised Vivifrail MCE or usual care. An IC index was created based on the *z*-score of the locomotion (Short Physical Performance Battery), cognitive (Montreal Cognitive Assessment), psychology (15-item Geriatric Depression Scale Yesavage) and vitality (handgrip strength) domains.
Results: After the 3-month intervention, linear mixed models showed significant between-group differences in the evolution of the IC composite score (β=0.48; 95% confidence interval [CI] = 0.24, 0.74; $P < 0.001$), IC Locomotion ($\beta = 0.42$; 95% CI = 0.10, 0.74; $P < 0.001$), IC Cognition ($\beta = 0.45$; 95% CI = 0.03, 0.87; $P < 0.05$) and IC Vitality domains ($\beta = 0.50$; 95% CI = 0.25, 0.74 at 3-month) favouring the MCE group.

Conclusions: The 12-week Vivifrail multicomponent exercise program is an effective strategy to enhance IC, especially in terms of locomotion, cognition and vitality IC domains in community-dwelling older adults with pre-frailty/frailty and MCI/mild dementia, compared to usual care.

Keywords: exercise, intrinsic capacity, functional ability, older adults, community-dwelling, older people

Key Points

- Experts emphasise the need to promote healthy ageing (understood as the process of developing and maintaining the functional ability that enables well-being in older age) as the central objective and focus of all health systems and policies for older populations.
- In this scope, World Health Organisation coined the term intrinsic capacity to refer to the composite of physical and mental attributes of the individual. Intrinsic capacity interacts with the environment to determine late-life functional ability.
- Despite older adults at risk of disability onset might benefit the most from intrinsic capacity promotion, evidence around potential interventions for intrinsic capacity maintenance/increase in this population group remains very scarce.
- Individualised multicomponent exercise has been suggested as a fundamental intervention for healthy ageing, but no study has evaluated the effects of exercise on global intrinsic capacity and its domains.
- Our study shows that, compared to usual care, the 12-week Vivifrail multicomponent exercise program improved the composite intrinsic capacity score of community-dwelling older adults with pre-frailty/frailty and mild cognitive impairment/mild-dementia, in particular the domains of locomotion, cognition and vitality.

Introduction

Population ageing is an ongoing worldwide occurrence, which implies the existence of a growing share of the population living with chronic diseases and functional limitations [1]. Overt expansions in the life expectancy have not been accompanied by concurrent increases in healthspan [2], with dramatic implications from the healthcare and societal perspective [3, 4]. Secondary to this demographic transition, the prevailing biomedical strategy has evolved from a disease-based one focused on increasing longevity, to a function-centred perception of older adult's health [5, 6], in which maintenance of function constitutes the priority, as a mean of guaranteeing free-of-disability late-life [7].

The World Health Organisation (WHO) recently defined healthy ageing as the process of fostering and maintaining the functional ability that enables well-being in older age [8, 9]. Under this framework, functional ability of the individual relies on the individual physical and mental capacities (intrinsic capacity [IC]) and their interactions with the environment [9]. Lately, an IC operationalisation has been proposed based on five domains (locomotion, cognitive, psychological, vitality and sensory) [10, 11], and recent research has shown that it is a measurable construct related to function-related outcomes, supporting its validity [12–14].

The concept of IC provides new opportunities for identifying proactive interventions oriented to healthy ageing promotion in those at high risk of presenting with physical/cognitive limitations [15]. Among them, frail and cognitively impaired community-dwellers might be the target of interventions oriented at prospectively increasing/maintaining IC. They represent older adults at risk of imminent disability, offering a window for intervention and halting or even reverting of the disability cascade [16, 17]. However, evidence around potential interventions for IC maintenance/increase remains scarce [18]. Multicomponent physical exercise (MCE) (comprising strength, aerobic, gait and balance and flexibility exercises), given its proven benefits on several proposed markers of individual domains of IC (locomotion [19, 20], cognitive [21], psychology [22]), has been suggested as a fundamental intervention for healthy ageing in different populations of older adults [23].

Vivifrail (www.vivifrail.com) is a MCE program tailored to the individual, designed to ease prescription of evidence-based exercise interventions in older people (https://vivifrail.com/es/inicio/) [24]. It has been included in the Integrated Care for Older People (ICOPE) guidelines developed by WHO as the treatment of choice for those at risk of mobility limitations [25]. So far, it has shown to promote benefits in terms of functional ability (single markers of physical and cognitive function) and fall risk reduction among institutionalised and community-dwelling older adults [26–29] but no study has explored the effects of the Vivifrail exercise program on IC. Especially appealing may be the potential benefits of the Vivifrail MCE program on the cognitive domain of older adults with mild cognitive impairment (MCI). Despite previous research has shown that exercise might be an effective intervention to cognition in healthy older adult populations [30], so far, its effectiveness in MCI/dementia populations is less clear [31].

This secondary analysis of a randomised clinical trial aims to explore the effects of Vivifrail individualised MCE program on IC and its operational domains among pre-frail/frail community-dwelling older adults with MCI/mild dementia, compared to usual care. Secondarily, we aimed to explore intervention effects according to baseline frailty status (pre-frailty vs. frailty) [32]. We hypothesise that the Vivifrail exercise program will promote increases on IC, specially driven by improvements in the physical and cognitive domains. Given the uncertainty around potential differential

effects of exercise across frailty levels, this aspect was explored in the present work without any *a priori* hypothesis.

Methods

Study design

This is a secondary analysis of a multicentre randomised clinical trial (NCT03657940), aiming to explore between-group differences in an IC composite score and its operational domains. The original study aimed to explore the effectiveness of Vivifrail exercise program on functional capacity of physically pre-frail/frail older individuals diagnosed with MCI/mild dementia. Detailed description of the study can be found elsewhere [33]. The study was conducted between 1 September 2017 and 31 May 2020 in the outpatient clinics of the Geriatrics Department of three tertiary hospitals in Spain (Hospital de Navarra in Pamplona, Matia Fundazioa in San Sebastian and Hospital de Getafe in Getafe). Present analyses were not planned when the original study was conceived.

Ethical disclosure

All patients provided written informed consent. No financial compensation was offered for participating in the present study. The study followed the principles of Declaration of Helsinki and was approved by the Hospital de Navarra Clinical Research Ethics Committee.

Study population

Eligibility criteria comprised: ≥75 years, Barthel Index ≥60, being able to communicate and ambulate, presenting with MCI or mild dementia according to Diagnostic and Statistical Manual of Mental Disorders (DSM) V criteria (Global Deterioration Scale [Reisberg classification] = 4 [34]), pre-frailty or frailty according to Fried's criteria and the assistance of a relative/caregiver for exercise monitoring [35]. Subjects were not included if presenting with any contraindication for physical exercising or testing (see [33] for a detailed list).

Settings and study procedures

Volunteers were recruited in the outpatient clinics of the three participating centres. Those who agreed to participate ($n = 188$) were randomised in a 1:1 ratio to an individualised home-based exercise program (Vivifrail group—VG) or usual care (Control group—GC). A simple randomisation list was generated by an independent statistician using an online instrument (www.randomizer.org) for each hospital. Outcome assessors were blinded to participants' allocation; subjects were explicitly encouraged not to disclose their group membership during the study. No double-blind strategy was possible due to the behavioural nature of the intervention.

Standard sociodemographic data (age, sex, sociodemographic characteristics and clinical data), as well as endpoints of the study, were assessed by trained staff at baseline and 1 and 3 months later.

Intervention

Subjects in the CG received usual care, including rehabilitation when needed, and were instructed to continue their activities as usual. Besides usual care, subjects randomised to the VG received a 12-week intervention based on Vivifrail, which is a home-based individualised multicomponent (thrice-a-week resistance, balance, flexibility sessions and five walking sessions per week) exercise program tailored to individual's physical function (assessed the Short Physical Performance Battery (SPPB): Level A-Disability (0–3 points), Level B-Frailty (4–6), Level C-Pre-frailty (7–9) and Level D-Robustness (10–12)) [36]. Subjects in the VG and their caregivers were instructed to follow their specific exercise protocol and progress in terms of intensity, frequency and volume according to Vivifrail guidelines [28] (see Supplementary Table 1 or visit www.vivifrail.com for a detailed description). Booklets and adherence logs were delivered and explained at the start of the interventions. Correct execution and safety were supervised by relatives and caregivers. In addition, in order to monitor adherence and performance, the research physiotherapist scheduled a face-to-face interview at week 4 as well as phone calls at weeks 2 and 8. After completion of the program, no further follow-up was performed.

Intrinsic capacity

Endpoints of present study were assessed at baseline and 1-month and 3-month follow-up visits. Different domains of IC proposed by WHO [11] were evaluated upon data availability by creating z-scores of the IC domains: (i) Locomotion was assessed by the SPPB; (ii) Cognition was evaluated by the Montreal Cognitive Assessment (MOCA), a cognitive impairment screening tool that evaluates global cognition (values ranging 0–30, lower is worse) [37]. (iii) The psychological domain was evaluated by the Yesavage 15-item Geriatric Depression Scale (GDS-15), whose values range between 0 and 15 (higher is worse) [36]. (iv) The vitality domain was evaluated by handgrip strength values (in kg) [10]. (v) Additionally, the sensory domain of IC was assessed through self-reporting of visual and hearing impairments. Specifically, a score was built based on the presence of hypoacusia (yes = 1, no = 0) and reduced visual acuity (yes = 1, no = 0), yielding a total score ranging 0–2.

A composite IC z-score was constructed as the sum of the individual z-scores of locomotion, cognition, psychology and vitality domains divided by 4 to create an IC composite score. GDS score was weighted as −1 (because greater scores indicate worse performance in this domain). The sensory domain score was not included in the composite score, given the categorical nature of the scale used for its assessment. Instead, worsening of the IC sensory domain was characterised as a one-point increase in the sensory domain score.

Table 1. Characteristics of included participants according to randomisation groups

Characteristics	Whole sample total ($n = 188$)	Control group ($n = 100$)	Vivifrail group ($n = 88$)
Women, No. (%)	120 (72.29)	60 (68.18)	60 (76.92)
Age, y	84.06 ± 4.77	83.99 ± 4.80	84.15 ± 4.76
Weight, kg	66.66 ± 10.98	66.49 ± 11.41	66.86 ± 10.54
BMI, kg/m^{2}, [a]	27.04 ± 3.97	27.02 ± 4.31	27.06 ± 3.57
Years of schooling	8.14 ± 4.47	8.15 ± 4.31	8.13 ± 4.67
Barthel Index (0–100)	91.43 ± 9.77	91.79 ± 10.23	91.13 ± 9.27
MCI, No. (%)	99 (58.93)	33 (37.50)	35 (44.30)
Dementia, No. (%)	68 (40.72)	44 (44.00)	34 (38.63)
Fried Frailty phenotype			
Pre-frailty (1–2 items), No. (%)	121 (64.36)	64 (64.00)	57 (64.77)
Frailty (>2 item), No. (%)	67 (35.64)	36 (36.00)	31 (35.23)
Polypharmacy (≥5 drugs), No. (%)	138 (75.82)	79 7 (79.80)	59 (71.08)
GDS Yesavage score (0–15)	3.62 ± 2.92	3.36 ± 2.91	3.92 ± 2.92
Gait speed, m/s	0.63 ± 0.19	0.64 ± 0.19	0.61 ± 0.18
5-STS, s	19.18 ± 13.39	18.38 ± 13.18	20.12 ± 13.64
SPPB score (0–12)	7.31 ± 2.59	7.73 ± 2.47	6.85 ± 2.66
Handgrip strength, kg	19.37 ± 7.23	19.21 ± 7.70	19.56 ± 6.69
MoCA score (0–30)	15.55 ± 5.20	15.37 ± 5.24	15.81 ± 14.30
MNA-SF score (0–14)	12.07 ± 2.09	12.06 ± 1.98	12.08 ± 2.23
IC Composite Score	0.06 ± 0.53	0.08 ± 0.55	0.04 ± 0.48

MoCA, Montreal Cognitive Assessment; BMI, body mass index. [a]Body mass index calculated as weight in kilograms divided by height in meters squared.

Statistical analysis

Descriptive statistics (mean and standard deviation and frequency and percentages were provided for continuous and categorical variables, respectively).

Mixed-effect linear models (MELMs) were used to explore the longitudinal evolution of IC domains according to randomisation group over 3 months, except for the worsening of IC sensory domain, for which logistic regression was used. In MELM, fixed terms were group allocation, time, time-by-group interaction and covariates (age, sex, educational level and baseline IC level); random terms were the participants. A random slope on time was assumed. Time was used as a categorical variable. In the logistic regression, we included the same covariates as in MELM. An intention-to-treat approach was used in analyses.

Using similar adjusted models, we investigated differences on the effectiveness of the intervention by baseline frailty levels by including a three-way interaction (group × time × frailty status) in the fixed effects, in addition to the main effects and the two-way interactions between these variables. In the case of a statistically significant interaction, analyses stratified by frailty status were run.

Statistical significance was set at an alpha value of 0.05. All analyses were performed using STATA 14.0 software (Stata Corporation, College Station, TX).

Results

Characterisation of the sample

One hundred and eighty-eight subjects were included in the present study (mean age [SD] = 84.06 ± 4.77; 70.2% [$n = 132$] women). Demographic and clinical characteristics of the sample are displayed in Table 1. Mean adherence to the intervention in the VG was 79% in the first month and 68% in the following 2 months. No adverse effects were reported by the participants nor their proxies during the follow-up.

Evolution on IC and IC domains according to randomisation group

After the 3-month intervention, we found significant differences in the evolution of the IC composite score favouring the VG ($\beta = 0.48$; 95% confidence interval [CI] = 0.24, 0.74; $P < 0.001$). Regarding the analyses on the individual IC domains, a better evolution in the IC Locomotion (both at 1- [$\beta = 0.36$; 95% CI = 0.21, 0.51; $P < 0.001$] and 3-month time-points [$\beta = 0.42$; 95% CI = 0.10, 0.; $P < 0.001$]), IC Cognition (at 1- [$\beta = 0.33$; 95% CI = 0.01, 0.65; $P < 0.05$] and 3-month time-points [$\beta = 0.45$; 95% CI = 0.03, 0.87; $P < 0.05$]) and IC Vitality domains ($\beta = 0.50$; 95% CI = 0.25, 0.74 at 3-month time-points) was displayed by the VG compared to subjects in the CG. No significant differences were found in the evolution of the IC Psychology domain between the VG and the CG. The sensory domain logistic regression analyses did not reveal differences on the risk of increasing 1 point in the IC Sensory domain score (odds ratio [OR] = 0.21; 95%CI = −0.02, 2.07). Between- and within-group effects of the intervention on endpoints are shown in Table 2.

Stratified analyses by frailty status

The time-by-group-by-frailty interaction was significant in models with IC Locomotion ($\beta = 0.48$; 95% CI = 0.10, 0.85; $P = 0.01$), IC Cognition ($\beta = 0.85$; 95% CI = 0.20, 1.51; $P = 0.01$), IC Vitality ($\beta = 0.48$; 95% CI = 0.20, 0.77; $P < 0.001$) and IC Composite score ($\beta = 0.48$;

Table 2. Mixed-effects linear models analyses for 3-month evolution from baseline in IC domains and the IC composite score according to randomisation groups

Intrinsic capacity domain	Time-point	Vivifrail group $N = 88$ β (95% CI)	Control group $N = 100$ β (95% CI)	Between-group differences β (95% CI)	*P*-value
IC Locomotion domain	1 month	0.25 (0.13, 0.39)	−0.10 (−0.23, 0.02)	0.36 (0.21, 0.51)	**<0.001**
***z*-score**	3 months	0.24 (−0.01, 0.49)	−0.18 (−0.40, 0.04)	0.42 (0.10, 0.74)	**0.01**
SPPB score	1 month	0.64 (0.29, 0.99)	−0.27 (−0.58, 0.05)	0.91 (0.52, 1.30)	**<0.001**
	3 months	0.54 (−0.12, 1.21)	−0.46 (−1.01, 0.09)	1.00 (0.18, 1.83)	**0.02**
IC Cognition domain	1 month	0.43 (0.12, 0.74)	0.10 (−0.06, 0.26)	0.33 (0.01, 0.65)	**0.05**
***z*-score**	3 months	0.39 (0.02, 0.77)	−0.06 (−0.29, 0.17)	0.45 (0.03, 0.87)	**0.03**
MoCA score	1 month	2.24 (0.61, 3.87)	0.51 (−0.31, 1.33)	1.73 (0.03, 3.43)	**0.05**
	3 months	2.04 (0.09, 3.99)	−0.31 (−1.49, 0.86)	2.35 (0.17, 4.54)	**0.03**
IC Vitality domain	1 month	0.44 (0.21, 0.68)	0.02 (−0.07, 0.12)	0.42 (0.18, 0.66)	**0.001**
***z*-score**	3 months	0.40 (0.16, 0.63)	−0.10 (−0.19, −0.01)	0.50 (0.25, 0.74)	**<0.001**
Handgrip Strength (kg)	1 month	3.22 (1.54, 4.91)	0.18 (−0.51, 0.86)	3.04 (1.33, 4.75)	**0.001**
	3 months	2.86 (1.14, 4.59)	−0.73 (−1.44, −0.01)	3.59 (1.83, 5.35)	**<0.001**
IC Psychology domain *z*-score	3 months	−0.04 (−0.40, 0.33)	−0.28 (−0.48, −0.08)	0.24 (−0.15, 0.63)	0.22
GDS Yesavage	3 months	0.11 (−0.96, 1.18)	0.82 (0.23, 1.41)	−0.71 (−1.86, 0.43)	0.22
IC Composite Score	3 months	0.29 (0.06, 0.52)	−0.10 (−0.33, −0.06)	0.48 (0.24, 0.74)	**<0.001**

Significant associations are in bold. Models were adjusted by age, sex, educational level and baseline IC level. β (95%CI), β-coefficients and 95% confidence interval; 5-STS, 5-times Sit-to-Stand Test; MoCA, Montreal Cognitive Assessment; BMI, body mass index.

95% CI = 0.06, 0.88; $P = 0.024$) as dependent variables, indicating that frailty levels might modulate the effects of the multicomponent exercise program on these domains.

Among individuals classified as pre-frail according to Fried's definition at baseline ($n = 121$ [64.36% of the whole sample], mean age = 84.09 ± 4.68, 70.75% women), subjects randomised to the VG ($n = 57$) showed significant differential prospective evolution in the IC Locomotion ($\beta = 0.29$; 95%CI = 0.02, 0.55; $P < 0.001$) and Vitality ($\beta = 0.42$; 95%CI = 0.12, 0.73; $P < 0.001$) domains compared to the CG ($n = 64$) (Figure 1 and Table 3).

When analyses were restricted to frail individuals (≥3 Fried's criteria), the VG ($n = 31$) showed significant increases in the IC Locomotion ($\beta = 0.37$; 95%CI = 0.15, 0.60 at 1-month; $\beta = 0.47$; 95%CI = 0.07, 0.87 at 3-month visit) and IC Cognitive ($\beta = 0.79$; 95%CI = 0.03, 1.55 at 3-month visit) domains. Between-group difference analyses showed significant benefits in the IC Locomotion ($\beta = 0.46$; 95%CI = 0.20, 0.72; $P < 0.001$ at 1-month visit; $\beta = 0.66$; 95%CI = 0.15, 1.17; $P < 0.001$ at 3-mont visit), IC Vitality ($\beta = 0.62$; 95%CI = 0.20, 1.05; $P < 0.001$ at 3-mont visit) and the IC Cognition domains (only at 3-month time-points: $\beta = 0.80$; 95%CI = 0.03, 1.57; $P < 0.05$) of VG compared to usual care (CG, $n = 36$). Finally, VG showed to positively impact the IC Composite score compared to CG among frail individuals (between-group difference β-coefficient = 0.83; 95%CI = 0.42, 1.25; $P < 0.001$) (Figure 1).

Discussion

The present study showed that, among community-dwelling older adults with pre-frailty/frailty and MCI/mild-dementia, a 12-week Vivifrail MCE program exerted benefits on IC composite score and its domain evolution compared to usual care. These benefits were mainly driven by improvements on the locomotion, cognitive and vitality IC domains. In addition, we showed the effects of greater magnitude among frail individuals compared to pre-frail counterparts. Our study expands evidence from the primary study from which data were used in present analyses, which showed that Vivifrail MCE was able to positively impact independent measures of physical and cognitive functions [28]. Our study shows how these benefits observed fragmentedly translate to a novel overall marker of capacities, IC, recently incorporated as functional-based indicator of older adults' health [11]. Sadly, given the distribution-based nature of our main endpoint (dimensionless IC composite score based on *z*-scores of the different domains), our results are not clinically straightforwardly interpretable in terms of effect of size. But notably, effects on the individual domains capturing cognition and mobility represent a substantial positive short-term change. In addition, if changes in the IC composite score (*z*-score = 0.5) were translated into individual domains, these would clearly pose a clinically meaningful change. Our study constitutes one of the first pieces of evidence on the effects of interventions, and specifically Vivifrail MCE, on the IC of community-dwelling individuals at risk of disability. Present analyses contribute to reinforce the role of individualised Vivifrail MCE as an effective intervention for healthy ageing promotion in older adults at risk of disability [23, 38, 39].

The concept of IC has arisen as innovative approach to older adult's health. Accordingly, there is a need to develop strategies oriented to promote healthy ageing through the maintenance or expansion of IC [40]. Nevertheless, evidence around specific interventions to improve IC are still in its infancy. Exercise has widely shown to be associated with healthier ageing phenotypes, by having been associated with a lower incidence of ageing-related chronic conditions

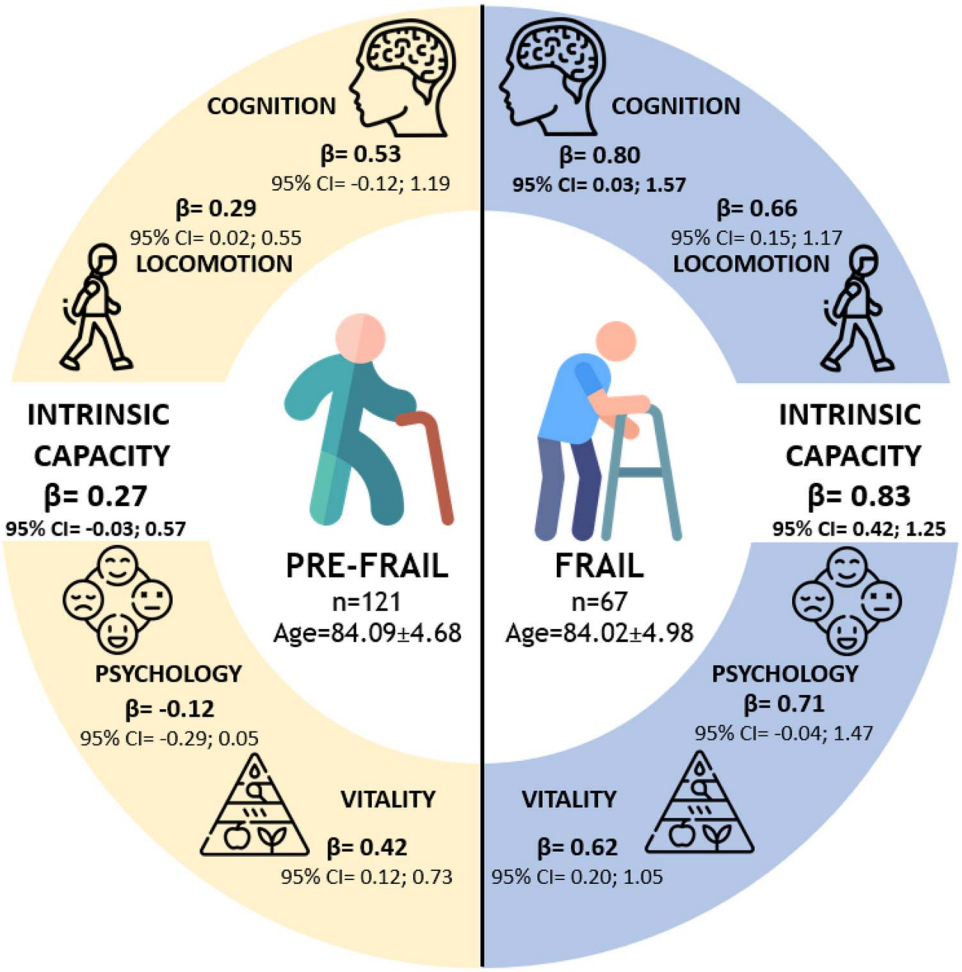

Figure 1. Between-group 3-month change in IC and its domains by randomisation group in pre-frail and frail individuals. *β*-coefficients were estimated by linear mixed models with group, time, its interaction and covariates (age, sex, educational level and baseline IC level) as fixed effects. A random slope on time was assumed. IC computed by the average of four available IC domains: IC Locomotion (average of the *z*-score of SPPB, GS and 5-STS), IC Cognition (assessed through the MoCA test), IC Vitality (evaluated through the HS) and IC Psychology (by the 15-item GDS). *β* (95%CI), *β*-coefficients and 95% confidence interval; 5-STS, 5-times Sit-to-Stand Test; MoCA, Montreal Cognitive Assessment.

[41, 42] and disability at older age [41–43]. In addition, it has been shown to positively impact individual domains of functional ability such as physical performance [32, 44], cognitive function [45, 46] and depressive symptoms [47] in different older adults' populations. Given that capacities are understood as overt expressions of integrated functioning of different physiological systems [48], exercise whole-organism benefits such as improved metabolic and cardiovascular health [49, 50], muscle mass and function [51, 52], and neurogenesis at the central nervous system [53, 54] might underlie its effectiveness in reversing frailty [55–57], reducing the risk of late-life adverse events [58, 59] and contributing to improve quality of life [60], even in the most vulnerable populations [61, 62]. Therefore, in accordance with our findings and scarcely available evidence, Vivifrail individualised MCE program might be considered an effective intervention in the development and maintenance of IC at an older age, especially for those presenting with low IC reserves [23].

MCE has been shown to be the most effective approach to improve physical performance among physically frail older adults [63–65], by combining different stimulus. Besides inducing muscle mass and function (strength and power) increases [53, 66], benefits of these programs might positively impact cognitive [28, 67, 68] and psychological domains [56]. Whereas our study contributes to the growing evidence around the role of MCE as an effective intervention to improve cognitive function among older adults [69], it failed at showing benefits on the IC psychology domain, an aspect that remains controversial in the literature [38, 70] There is a need for further research on the role of MCE effects on the psychological sphere.

So far and to our knowledge, no study has explored the effects of a structured exercise program on IC of frail/pre-frail older adults. However, one study by Huang *et al*. compared the effects of aerobic versus strength exercises on IC in a sample of Japanese older adults with memory complaints

Table 3. Within-group evolution from baseline in IC domains and the IC Composite Score by frailty status

	Pre-frail individuals ($n = 121$)			Frail individuals ($n = 67$)		
IC domain	Time-point	Vivifrail group $N = 57$ β (95% CI)[a]	Control group $N = 64$ β (95% CI)	Time-point	Vivifrail group $N = 31$ β (95% CI)[a]	Control group $N = 36$ β (95% CI)
IC Locomotion domain *z*-score	1 month	0.17 (0.01, 0.33)*	−0.08 (−0.23, 0.07)	1 month	0.37 (0.15, 0.60)	−0.20 (−0.39, −0.01)
	3 months	0.42 (0.15, 0.69)**	−0.13 (−0.35, 0.10)	3 months	0.47 (0.07, 0.87)*	−0.18 (−0.50, 0.15)
IC Cognition domain *z*-score	1 month	0.52 (−0.03, 1.08)	0.10 (−0.10, 0.31)	1 month	0.64 (−0.07, 1.35)	0.06 (−0.20, 0.33)
	3 months	0.44 (−0.17, 1.05)	−0.09 (−0.40, 0.20)	3 months	0.79 (0.03, 1.55)*	−0.01 (−0.33, 0.30)
IC Vitality domain *z*-score	1 month	0.41 (0.12, 0.70)**	0.06 (−0.05, 0.18)	1 month	0.47 (0.08, 0.86)*	−0.05 (−0.21, 0.11)
	3 months	0.38 (0.08, 0.67)*	−0.05 (−0.16, 0.07)	3 months	0.42 (0.02, 0.83)*	−0.20 (−0.38, −0.02)*
IC Psychology domain *z*-score	3 months	−0.29 (−0.72, −0.07)*	−0.17 (−0.38, 0.04)	3 months	0.21 (−0.48, 0.91)	−0.49 (−0.91, −0.09)
IC Composite Score	3 months	0.11 (−0.16, 0.38)	−0.16 (−0.33, 0.004)	3 months	0.28 (−0.09, 0.65)	−0.56 (−0.84, −0.28)

Significant associations are in bold. Models were adjusted by age, sex, educational level and baseline IC level. β (95%CI), β-coefficients and 95% confidence interval. * $P < 0.05$, ** $P < 0.01$.

($n = 415$, mean age = 72.3 ± 4.6, 47% women). They showed that both aerobic and resistance exercise were indistinctly effective in promoting IC improvements over 26 weeks compared to a health education program [71]. Interestingly, in their study, single-domain analyses revealed a differential effect of aerobic exercise (that improved IC locomotion and psychological domains), and resistance training (positively impacting IC locomotion and vitality domains), suggesting a potential maximisation of benefits when combining exercise modalities [71].

Our study further showed greater impact of exercise on the IC composite score and IC domains of frail older adults compared to pre-frail individuals. This observation is compatible with previous research [72, 73], and could be due to the lower reserves of frail individuals, for which similar exercise regimes might constitute a greater physiological insult, and therefore, lead to greater adaptations in the context of their greater trainability [74]. This fact might reinforce the need to adapt and individualise exercise prescription as proposed in Vivifrail, with the objective of optimising gains independently of the baseline frailty status/functional ability. Due to the substantial loss in statistical power in stratified analyses of present work and scarcity of studies around differential effects of exercise in frail versus pre-frail in community-dwelling older adults, this topic deserves more research.

Strengths

Our study presents several strengths, such as its novelty, its multicentre nature and the specific characteristics of included participants, oldest-old (mean age 84.06 ± 4.77) displaying IC declines, that might be the target of preventive strategies as recommended by ICOPE and are usually excluded from clinical trials. In addition, the use of a continuous composite score of IC as the outcome allowed us to monitor the trajectories of the complex construct of IC in response to exercise based on the effect on several domains. This approach allows a more nuanced and powerful analyses compared to categorical outcomes such as disability or mortality [12]. In addition, sub-group analyses allowed us to explore differential effects of the intervention based on frailty baseline levels, responding to the need of better information about how different subpopulation may respond to interventions in the era of precision medicine [75].

As limitations of the study, it should be noted that this is a secondary analysis of a study designed for exploring effects of Vivifrail multicomponent exercise program on functional capacity in frail older patients with MCI/mild dementia. Therefore, our study should be deemed as hypothesis generating—rather than hypothesis—testing. Consequently, IC operationalisation was constrained by data availability and might have slightly deviated from currently available proposed approaches [76]. Especially remarkable is the inability to include the sensory domain in the composite IC score, due to the categorical nature of the available data in this domain in the present study.

Second, the follow-up period was relatively limited. However, potential maintenance or improvement in IC in such an older and vulnerable population even in the short term might constitute a relevant functional achievement for the individual and for the whole society. Additionally, in the present study, evolution in the PA levels during the participation was not evaluated, hampering our ability to investigate to what extent such changes might have affected observed benefits. Finally, we failed at achieving the sample size proposed in the study protocol [33], given that following the coronavirus disease 2019 lockdown, recruitment had to be stopped. The latter limited the possibility of performing further exploratory sub-analyses (such as sex-stratified analysis) that might have been informative.

Conclusions

The Vivifrail MCE program has been proposed as the elective intervention for those presenting with declines in the IC locomotion domain in ICOPE by WHO [25], with potential for positively impacting cognitive, vitality and psychological domains. Our study contributes to this recommendation by demonstrating the ability of the home-based personalised Vivifrail exercise program to boost an overall marker of IC among community-dwelling older adults at risk of disability, through improvements on the physical, cognitive and vitality domain. Therefore, our study supports WHO recommendations on IC declines management. Until a consensus IC operationalisation is reached, and original data from studies primarily designed to explore the effect of interventions on IC, this might serve as a proof of concept. Further research should confirm our results in other clinical scenarios such as primary care, hospitals, nursing homes and in other older adult subpopulations.

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