Public University of Navarre

Department of Health Sciences

Effects of physical exercise intervention on functional and cognitive decline in geriatric hospitalized patients

ClinicalTrials.gov NCT02300896 registered on November 19, 2014

DOCTORAL THESIS

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Table of contents

Table Index

Figure Index

List of abbreviations

ACE: Acute care of the elderly
ADL: Activities of daily living
AE: Adverse event
AP: anterior-posterior
ARs: Adverse-responders
BDNF: Brain derived neurotrophic factor
BMI: Body mass index
CAM: Confusion assessment method
CBRG: Cochrane back review group
CGA: Comprehensive geriatric assessment
CI: Confidence interval
CIRS-G: Cumulative illness rating scale for geriatrics
CoV: Coefficient of variability
CONSORT: Consolidated standards of randomized clinical trials
D: Disabled
EQ-5D: EuroQol-5 dimension
ES: Effect size
EU: European Union
F: Frail
FTSST: Five times sit to stand test
GDS: Geriatric depression scale
GVT: Gait velocity test
IADL: Instrumental activities of daily living
IGF-1: Insulin-like growth factor 1
IQR: Interquartile range
IVRET: Inter individual variability in response to exercise training
HIRT: High intensity interval resistance training
MD: Mean difference
ML: medio-lateral.
MMSE: Mini mental state examination
MNA: Mini nutritional assessment
Ns: Non-responders
PA: Physical activity
PF: Pre-frail
PRISMA: Preferred reporting items for systematic reviews and meta-analysis
PW: Leg power at an intensity of 50% of 1repetition maximum
QOL: Quality of life
R: Robust
Rs: Responders
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
V: Vertical
WHO: World health organization
1RM: 1 repetition maximum

Summary
(Inglés-Español)

Summary

The current Ph.D. dissertation revolves around the effects of a physical exercise intervention on functional capacity and cognitive function in acutely hospitalized older adults. It has been suggested that acute medical illnesses and subsequent hospitalization are major events leading to disability in older people. A physical exercise intervention can be an effective therapy to reverse the functional and cognitive decline associated with acute hospitalization in very old patients. This thesis doctoral is based on 6 scientific studies that have been published or submitted for publication in scientific international journals. The first study (Chapter 1), we aimed to examine the role of different physical exercise programs (aerobic, resistance, and multicomponent training) on cognitive function in healthy older adults. The data presented in the following studies were collected in the same research project (ClinicalTrials.gov NCT02300896 registered on November 19, 2014). In the second study (Chapter 2), the main purpose was to assess the effects of a multicomponent exercise intervention on functional, cognitive function, and well-being status in very old patients admitted to the ACE unit. The third study (Chapter 3) to analyze the effects of physical exercise on functional capacity, maximal muscle strength and muscle power output during hospital stay in older adults. The fourth study (Chapter 4), we aimed to compare differences on gait characteristics and muscle performance endpoints (i.e., muscle strength and muscle power output) of older medical patients admitted to the ACE unit based on the functional status presented at admission, and to determine the mechanisms underlying the gait impairment. In the fifth study (Chapter 5), we investigated the inter-individual variability in the response to physical exercise and usual care (as indicated by functional, muscle strength and cognitive endpoints) of older adults, and the relationship between the response to the intervention with mortality at one-year post-discharge. In the last study (Chapter 6), the main purpose was to assess the effects of the multicomponent exercise training program on specific cognitive domains including executive function and verbal fluency in acutely hospitalized old patients.

Study 1 (Chapter 1)

In the first study the main purpose was to examine the role of different physical exercise programs (aerobic, resistance, and multicomponent training) on cognitive function in healthy older adults (>65 years) without known cognitive impairment. In addition, a secondary objective of the study was to clarify the discrepancies that were observed between the consistent evidence reported in animal, epidemiological and cross-sectional studies and the less consistent results observed in RCTs. The mean differences of the parameters from pre-intervention to post-intervention between groups were pooled using a random-effects model. The review was undertaken in accordance with the PRISMA statement and the method used was based on the minimum criteria established by the CBRG. Twenty-one RCTs published between 2002 and 2016 were included. Results from this review suggested that multicomponent exercise training may have the most positive effects on cognitive function in older adults. However, the small number of included studies and the large variability in study populations, study design, exercise protocols, adherence rates and outcome measures complicate the interpretation of the results and contribute to discrepancies within the exercise scientific literature.

Study 2 (Chapter 2)

The aim of the second study was to assess the effects of a multicomponent exercise intervention performed by older adults during acute hospitalization on functional capacity, cognitive function, and well-being status. Other outcomes, such as length of stay or falls, were also assessed. The control group received usual-care hospital care, which included physical rehabilitation when needed. The in-hospital intervention included individualized moderate-intensity resistance (30-60%RM), balance, and walking exercises (2 daily sessions). No adverse effects were observed with the intervention. The exercise intervention program provided significant benefits over usual care. At discharge, the exercise group showed a mean increase of 2.2 points (95%CI, 1.7, 2.6 points) on the SPPB scale and 6.9 points (95%CI, 4.4, 9.5 points) on the Barthel Index over the usual-care group. Hospitalization led to an impairment in functional capacity (mean change from baseline to discharge in the Barthel Index of −5.0 points (95%CI, −6.8 to −3.2 points) in the usual-care group, whereas the exercise intervention reversed this trend (1.9 points; 95%CI, 0.2, 3.7 points). The intervention also improved the SPPB score (2.4 points; 95%CI, 2.1, 2.7 points) vs 0.2 points; 95%CI, −0.1

to 0.5 points in control group. Significant intervention benefits were also found at the cognitive level in the MMSE test of 1.8 points (95%CI, 1.3-2.3 points) over the usual-care group. Therefore, the exercise intervention proved to be safe and effective to reverse the functional decline associated with acute hospitalization in very elderly patients.

Study 3 (Chapter 3)

In the third study we investigated the effects of an exercise intervention on functional capacity, maximal muscle strength and muscle power in very old patients admitted in the ACE unit. Changes in movement pattern in different ADLs were also assessed using an inertial sensor unit. The control group received usual- hospital care, which included physical rehabilitation when needed. The in-hospital intervention included individualized moderate-intensity resistance (30-60%RM), balance, and walking exercises (2 daily sessions). The exercise intervention program provided significant benefits over usual care. At discharge, the exercise group showed a mean increase of 1.7 points in the SPPB scale (95%CI, 0.98, 2.42) and 0.14 m·s-1 in the GVT (95%CI, 0.086, 0.194) over the usual care group. The intervention also improved the verbal (0.151 m/s; 95%CI 0.119, 0.184 vs. -0.001 m/s; 95%CI -0.025, 0.033 in the control group) and arithmetic GVT (0.115 m/s; 95%CI 0.077, 0.153 vs. -0.004 m/s; 95%CI -0.044, 0.035). Significant benefits were also observed in the intervention group in movement pattern in functional tasks and maximal muscle strength and muscle power output. These findings showed that an individualized multicomponent exercise training program improves functional capacity, maximal muscle strength, and muscle power in acutely hospitalized old patients.

Study 4 (Chapter 4)

In the fourth study we aimed to compare gait characteristics and muscle performance endpoints (i.e., maximal muscle strength and muscle power output) of hospitalized older adults based on the SPPB score (0-12 points) obtained at admission, and to determine the mechanisms underlying the gait impairment. Old patients admitted to the ACE unit were classified as disabled (SPPB 0-3 points), frail (SPPB 4-6 points), prefrail (SPPB 7-9 points) and robust (SPPB 10-12 points). The walking parameters measured at admission were related to functional status and showed significant differences among groups (disabled, frail, and prefrail groups), as well as muscle performance endpoints ($p<0.05$). In the basic model of the mediation analysis, muscle power output was found to correlate with gait variability and gait velocity (Indirect effect = -0.27 (95%CI, -0.59 to -0.05); $p<0.05$). Our results suggested that muscle power output slightly weakens the relationship between gait variability and gait velocity. In addition to maximal muscle strength and muscle power output, gait velocity and gait pattern parameters are distinguishing factors among acutely hospitalized older adults.

Study 5 (Chapter 5)

The purposes of the fifth study were to examine the response of acutely hospitalized patients to usual care and to physical exercise on functional capacity, muscle strength, and cognitive function, and to assess the relationship between the individual response of patients during hospitalization and mortality at one-year post-discharge. The intervention consisted of a multicomponent exercise training program performed during 5–7 consecutive days (2 sessions/day). The usual care group received habitual hospital care, which included physical rehabilitation when needed. Functional capacity was assessed with the SPPB and the GVT. Handgrip strength and MMSE were also measured at admission and discharge. Patients in both groups were categorized as responders (Rs), non-responders (NRs) and adverse responders (ARs) based on the individual response to each treatment during hospitalization. The prevalence of Rs was higher and the prevalence of NRs and ARs was lower in the intervention group than in the control group for functional capacity, muscle strength and cognition. The ARs for the GVT in the control group and the ARs for the SPPB in the intervention group had a significantly higher rate of mortality than the NRs and Rs in the equivalent groups ($p=0.01$ and $p=0.03$, respectively) at follow-up. In conclusion, oldest old patients performing an individualized exercise intervention presented higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function than those patients who were treated with usual care during acute hospitalization. Furthermore, an adverse response on functional capacity in older patients to physical exercise or usual care during hospitalization was associated with mortality at one-year post-discharge.

Study 6 (Chapter 6)

In the last study of the current Ph.D. dissertation we aimed to assess the effects of a multicomponent exercise intervention on cognitive function in older adults during acute hospitalization. The intervention consisted of a multicomponent exercise training program performed during 5–7 consecutive days (2 sessions/day). The usual care group received habitual hospital care, which included physical rehabilitation when needed. The intervention program provided significant benefits over usual care. At discharge, the exercise group showed a mean increase of 0.1 m/s (95% CI, 0.07, 0.13) in the verbal GVT and 0.1 m/s (95%CI, 0.08, 0.13) in the arithmetic GVT over usual care group. The intervention also improved the TMT-A score (-31.1 seconds; 95%CI, -49.5, -12.7 vs. -3.13 seconds; 95%CI, -16.3, 10.2 in the control group) and the MMSE score (2.10 points; 95%CI, 1.75, 2.46 vs. 0.27 points; 95%CI, -0.08, 0.63). Significant benefits were also observed in the exercise group for the verbal fluency test (mean 2.16 words; 95%CI, 1.56, 2.74) over usual care group. These findings suggested that an individualized multicomponent exercise training program improves cognitive function (i.e., executive function and verbal fluency domains) in very old patients during acute hospitalization.

Resumen

La actual disertación doctoral gira en torno a los efectos de una intervención de ejercicio físico en la capacidad funcional y función cognitiva en ancianos hospitalizados. Se ha sugerido que las enfermedades médicas agudas y su posterior hospitalización son eventos importantes en el desarrollo de discapacidad en las personas mayores. Una intervención de ejercicio físico puede ser una terapia efectiva para revertir el deterioro funcional y cognitivo asociado a la hospitalización en los pacientes muy mayores. Esta tesis doctoral se basa en seis estudios científicos que han sido publicados o enviados para su publicación en revistas científicas internacionales. En el primer estudio (Capítulo 1) nuestro objetivo fue examinar el papel de diferentes programas de ejercicio físico (aeróbico, fuerza y multicomponente) sobre la función cognitiva en personas mayores sanas. Los datos presentados en los siguientes estudios fueron recogidos en el mismo proyecto de investigación (ClinicalTrials.gov NCT02300896 registrado el 19 de noviembre de 2014). En el segundo estudio (Capítulo 2), el objetivo principal fue evaluar los efectos de una intervención de ejercicio físico multicomponente en la capacidad funcional, función cognitiva y estado de bienestar en pacientes muy mayores admitidos en la Unidad Geriátrica de Agudos. El tercer estudio (Capítulo 3) analiza los efectos del ejercicio físico en la capacidad funcional, fuerza muscular máxima y potencia muscular durante la estancia hospitalaria en las personas mayores. En el cuarto estudio (Capítulo 4) nuestro objetivo fue comparar diferencias en las características de la marcha y variables de rendimiento muscular (es decir, fuerza muscular máxima y potencia muscular) de los pacientes ancianos admitidos en la Unidad Geriátrica de Agudos en base al estado funcional presentado al ingreso, y determinar los mecanismos subyacentes al deterioro de la marcha. En el quinto estudio (Capítulo 5) investigamos la variabilidad inter-individual en la respuesta al ejercicio físico y a la atención habitual (indicado por variables funcionales, fuerza muscular y cognitivas) de las personas mayores, y la relación entre la respuesta a la intervención con la mortalidad al año posterior al alta hospitalaria. En el último estudio (Capítulo 6) el objetivo principal fue evaluar los efectos del programa de ejercicio físico multicomponente en dominios cognitivos específicos como la función ejecutiva y la fluencia verbal en pacientes ancianos hospitalizados.

Estudio 1 (Capítulo 1)

En el primer estudio el objetivo principal fue examinar el papel de diferentes programas de ejercicio físico (aeróbico, fuerza y multicomponente) sobre la función cognitiva en personas mayores sanas (>65 años) sin deterioro cognitivo. Además, un objetivo secundario del estudio fue clarificar las discrepancias que fueron observadas entre la evidencia consistente recogida en estudios con animales, epidemiológicos y estudios transversales con la evidencia menos consistente mostrada en los ensayos clínicos aleatorizados. Las diferencias de medias entre grupos de los parámetros pre-post intervención se agruparon mediante un modelo de efectos aleatorios. La revisión se llevó a cabo en base a la declaración PRISMA y el método utilizado fue basado en los criterios mínimos establecidos por CBRG. Se incluyeron veintiún ensayos clínicos aleatorizados publicados entre 2002 y 2016. Los resultados de esta revisión sugirieron que el entrenamiento multicomponente puede tener los efectos más positivos sobre la función cognitiva en personas mayores. Sin embargo, la pequeña cantidad de estudios incluidos y la gran variabilidad en las poblaciones de estudio, diseños de estudio, protocolos de ejercicio, tasas de adherencia y variables medidas complican la interpretación de los resultados y contribuyen a las discrepancias dentro de la literatura científica del ejercicio.

Estudio 2 (Capítulo 2)

El objetivo del segundo estudio fue evaluar los efectos de una intervención de ejercicio multicomponente realizada por ancianos durante la hospitalización en la capacidad funcional, función cognitiva y estado de bienestar. Otras variables, como la duración de la estancia y las caídas, también fueron evaluadas. El grupo control recibió la atención hospitalaria habitual, la cual incluía rehabilitación física cuando era necesario. La intervención intrahospitalaria incluía ejercicios individualizados de fuerza muscular de baja-moderada intensidad (30-60%RM), equilibrio y marcha (2 sesiones diarias). No se observaron eventos adversos con la intervención. El programa de ejercicio físico proporcionó beneficios significativos sobre la atención habitual. En el momento del alta, el grupo de ejercicio mostró un aumento promedio de 2.2 puntos (IC95%, 1.7, 2.6 puntos) en la escala SPPB y 6.9 puntos (IC95%, 4.4, 9.5 puntos) en la escala Barthel sobre el grupo de atención habitual. La hospitalización provocó un deterioro en la capacidad funcional (cambio promedio desde el ingreso hasta el alta de -5.0 puntos (IC95%, -6.8, -3.2 puntos) en la escala Barthel) en el grupo de atención habitual, mientras que la intervención de ejercicio revertió esta tendencia (1.9 puntos; IC95%, 0.2, 3.7 puntos). La intervención también mejoró la puntuación del SPPB (2.4 puntos; IC95%, 2.1, 2.7 puntos) vs. 0.2 puntos; IC95%, -0.1, 0.5 puntos en el grupo control. Además, beneficios significativos de la intervención fueron observados a nivel cognitivo de 1.8 puntos (IC95%, 1.3, 2.3 puntos) sobre el grupo de atención habitual. Por lo tanto, la intervención de ejercicio demostró ser segura y efectiva para revertir el deterioro funcional asociado a la hospitalización en pacientes ancianos.

Estudio 3 (Capítulo 3)

En el tercer estudio investigamos los efectos de una intervención de ejercicio en la capacidad funcional, fuerza muscular máxima y potencia muscular en pacientes muy mayores admitidos en la Unidad Geriátrica de Agudos. Los cambios en el patrón de movimiento en diferentes actividades de la vida diaria fueron evaluados utilizando una unidad de sensor inercial. El grupo control recibió la atención hospitalaria habitual, la cual incluía rehabilitación física cuando era necesario. La intervención intrahospitalaria incluía ejercicios individualizados de fuerza muscular de baja-moderada intensidad (30-60%RM), equilibrio y marcha (2 sesiones diarias). El programa de ejercicio físico proporcionó beneficios significativos sobre la atención habitual. En el momento del alta, el grupo de ejercicio mostró un aumento promedio de 1.7 puntos en la escala SPPB (IC95%, 0.98, 2.42) y 0.14 m/s en la prueba GVT (IC95%, 0.086, 0.194) sobre el grupo de atención habitual. La intervención también mejoró la prueba verbal (0.151 m/s; IC95%, 0.119, 0.184 vs. -0.001 m/s; IC95%, -0.025, 0.033 en el grupo control) y la prueba aritmética GVT (0.115 m/s; IC95%, 0.077, 0.153 vs. -0.004 m/s IC95%, -0.044, 0.035). Además, beneficios significativos fueron observados en el grupo intervención en el patrón de movimiento de las pruebas funcionales y en la fuerza muscular máxima y potencia muscular. Estos hallazgos mostraron que un programa de ejercicio físico multicomponente mejora la capacidad funcional, fuerza muscular máxima y potencia muscular en pacientes ancianos hospitalizados.

Estudio 4 (Capítulo 4)

En el cuarto estudio buscamos comparar las características de la marcha y variables de rendimiento muscular (es decir, fuerza muscular máxima y potencia muscular) de las personas mayores hospitalizadas en base a la puntuación de SPPB (0-12 puntos) obtenida al ingreso, y determinar los mecanismos subyacentes al deterioro de la marcha. Los pacientes ancianos admitidos en la Unidad Geriátrica de Agudos fueron clasificados como discapacitados (SPPB 0-3 puntos), frágiles (SPPB 4-6 puntos), prefrágiles (SPPB 7-9 puntos) y robustos (SPPB 10-12 puntos). Los parámetros de la marcha medidos al ingreso estaban relacionados con el estado funcional y mostraron diferencias significativas entre los grupos (discapacitados, frágiles y prefrágiles) así como las variables de rendimiento muscular ($p<0.05$). En el modelo básico del análisis de mediación se encontró que la potencia muscular se correlacionaba con la variabilidad de la marcha y la velocidad de la marcha (Efecto indirecto = -0.27 (IC95%, -0.59, -0.05); $p<0.05$). Nuestros resultados sugieren que la potencia muscular debilita ligeramente la relación entre la variabilidad de la marcha y la velocidad de la marcha. Además de la fuerza muscular máxima y la potencia muscular, la velocidad de la marcha y los parámetros del patrón de marcha son factores distintivos entre las personas mayores hospitalizadas.

Estudio 5 (Capítulo 5)

Los objetivos del quinto estudio fueron examinar la respuesta de los pacientes hospitalizados a la atención hospitalaria habitual y al ejercicio físico en la capacidad funcional, fuerza muscular y función cognitiva, y evaluar la relación entre la respuesta individual de los pacientes durante la hospitalización y la mortalidad al año posterior al alta hospitalaria. La intervención consistió en un programa de ejercicio físico multicomponente realizado durante 5-7 días consecutivos (2 sesiones/día). El grupo de atención habitual recibió la atención hospitalaria habitual, la cual incluía rehabilitación física cuando era necesario. La capacidad funcional fue evaluada con el test SPPB y la prueba GVT. La fuerza de prensión manual y el test

MMSE también fueron medidos al ingreso y al alta hospitalaria. Los pacientes en ambos grupos fueron categorizados como respondedores positivos (Rs), no-respondedores (NRs) y respondedores negativos (ARs) en base a la respuesta individual a cada tratamiento durante la hospitalización. La prevalencia de Rs fue mayor y la de NRs y ARs menor en el grupo intervención que en el grupo control para la capacidad funcional, fuerza muscular y cognición. Los ARs para la prueba GVT en el grupo control y los ARs para el test SPPB en el grupo intervención tuvieron una tasa significativamente mayor de mortalidad que los Rs y NRs en los grupos equivalentes (p=0.01 y p=0.03, respectivamente) en el seguimiento. En conclusión, los pacientes ancianos realizando una intervención de ejercicio individualizada presentaron mayor prevalencia de Rs y menor prevalencia de NRs y ARs para la capacidad funcional, fuerza muscular y función cognitiva que aquellos pacientes que fueron tratados con la atención habitual durante la hospitalización. Además, una respuesta negativa al ejercicio físico o a la atención habitual en la capacidad funcional durante la hospitalización fue asociada con mortalidad al año posterior al alta hospitalaria.

Estudio 6 (Capítulo 6)

En el último estudio de la actual disertación doctoral buscamos evaluar los efectos de una intervención de ejercicio multicomponente en la función cognitiva en personas mayores durante la hospitalización. La intervención consistió en un programa de ejercicio físico multicomponente realizado durante 5-7 días consecutivos (2 sesiones/día). El grupo de atención habitual recibió la atención hospitalaria habitual, la cual incluía rehabilitación física cuando era necesario. El programa de ejercicio físico proporcionó beneficios significativos sobre la atención habitual. En el momento del alta, el grupo de ejercicio mostró un aumento promedio de 0.1 m/s (IC95%, 0.07, 0.13) en la prueba verbal GVT y 0.1 m/s (IC95%, 0.08, 0.13) en la prueba aritmética GVT sobre el grupo de atención habitual. La intervención también mejoró la puntuación en el test TMT-A (-31.1 segundos; IC95%, -49.5, -12.7 vs. -3.13 segundos; IC95%, -16.3, 10.2 en el grupo control) y la puntuación en el test MMSE (2.10 puntos; IC95%, 1.75, 2.46 vs. 0.27 puntos; IC95%, -0.08, 0.63). Además, beneficios significativos fueron observados en el grupo de ejercicio para el test de fluencia verbal (promedio 2.16 palabras; IC95%, 1.56, 2.74) sobre el grupo de atención habitual. Estos hallazgos sugirieron que un programa de ejercicio multicomponente individualizado mejora la función cognitiva (es decir, los dominios de función ejecutiva y fluencia verbal) en pacientes muy mayores durante la hospitalización.

Declaration

I, Mikel López Sáez de Asteasu, do hereby declare that the research presented in this dissertation is based on 6 articles (Chapter 1 to 6) that have been published or submitted for publication in international peer-reviewed journals. 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 impairment associated with hospitalization in older adults. In addition, a physical exercise intervention would also improve other outcomes, such as well-being status, maximal muscle strength, and muscle power output in acutely hospitalized old patients. ClinicalTrials.gov NCT02300896 registered on November 19, 2014.

Ph.D. student involvement:

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

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Gratitude is also expressed to the Complejo Hospitalario de Navarra, especially to the Department of Geriatrics, 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

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Scholarships

The student received an Educational Grant for the Formation in Research Personnel. Public University of Navarre *May* 2016 to *May* 2019.

List of Publications

1. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, Casas-Herrero Á, Izquierdo M. Role of physical exercise on cognitive function in healthy older adults: a systematic review of randomized clinical trials. *Ageing Res Rev* 2017;37:117-134.

2. Martinez-Velilla N, Casas-Herrero Á, Zambom-Ferraresi F et al. Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial. *JAMA Intern Med* 2018;1791:28-36.

3. Sáez de Asteasu ML, Martinez-Velilla N, Zambom-Ferraresi F et al. Physical exercise improves function in acutely hospitalized old patients. SUBMITTED.

4. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, Casas-Herrero Á, Ramirez-Vélez R, Izquierdo M. Role of muscle power output as a mediator between gait variability and gait velocity in hospitalized older adults. SUBMITTED.

5. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F et al. Adverse response to exercise intervention during acute hospitalization. SUBMITTED.

6. Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F et al. A randomized clinical trial evaluating the effects of a physical exercise intervention on cognitive function in very elderly patients during acute hospitalization. SUBMITTED.

Conference papers

Oral presentation by Sáez de Asteasu ML.

September 29 to October 2/2016. FIMS 34th World Congress of Sports Medicine, Ljubljana, Slovenia.

Sáez de Asteasu ML, Martinez-Velilla N, Casas-Herrero A, Alonso-Renedo J, Izquierdo M. Multicomponent exercise program effects on functional capacity and cognition in frail hospitalized patients. *Br J Sports Med* 2016;50(1S):A9.2-A10.

Poster presentation by Sáez de Asteasu ML.

May 29 to June 2/2018. ACSM´s 65th Annual Meeting of the American College of Sports Medicine, 9th World Congress on Exercise is Medicine and World Congress on The Basic Science of Muscle Hypertrophy and Atrophy, Minneapolis, Minnesota, USA.

Sáez de Asteasu ML, Martínez-Velilla N, Casas-Herrero Á et al. Multicomponent exercise program effects on functional capacity and cognition in frail hospitalized patients. *Med Sci Sports Exerc* 2018;50(5S):239.

General background

In all EU member states, the proportion of older people has increased in last decades, because of combination of low fertility and longer life expectancy.[1] Mortality among older adults has fallen largely since the 1970s[2] in Europe, and this fall, rather than low fertility, is now the main contributor to population ageing.[3] Furthermore, projected enhancements in old age mortality imply further population ageing throughout the EU. By 2060, mean life expectancy in the EU is expected to increase by 8.5 years for men (to 84.5 years), and by 6.9 years for women (to 89.0 years)[1] and twice as many people will be aged 65 years or older as will be younger than 15 years.[4] In addition, the rise in the group of very old people (i.e., those aged 80 years or older) will be even more pronounced and is projected to triple between 2008 and 2060.[4]

A crucial point in establishment of effect of aging on health is whether increased life expectancy is associated with increased time in ill health or postponement of functional limitations and disability.[2] Life years with morbidity have been increasing together with the rise in some diseases and conditions.[2] Overall, life years in good self-perceived health have been normally rising[5] and the frequency of the most severe levels of disability seems to have decreased in Europe; however, the prevalence of older adults with less severe disability has increased.[2] Such global demographic and clinical modifications have influenced in the phenotypic manifestations of the patients and geriatric concepts as frailty, which is a clinical condition characterized by a decrease of reserves and functions across multiple physiological systems and responsible for a compromised ability to cope with stressors[6], have become more relevant in the scientific literature over the last couple of decades.[7]

Older people (aged at least 65 years according to WHO) are major users of acute hospital care in our ageing societies.[1;8-10] Patients with multiple comorbidities generally have higher risk of mortality, use of health-care resources more, and have less quality of life compared with older adults with a single disease.[11] Thus, the high risk of mortality of older people with multimorbidities makes health care complex, leads to long length of hospital stays, and increases the need of multidisciplinary care for patients both within and outside hospitals.[12]

Acute illness requiring hospitalization is frequently a sentinel event for many older adults.[13;14] A number of known physiological changes with aging, including reduces muscle strength and aerobic capacity, vasomotor instability, baroreceptors insensitivity, reduced bone density, reduced ventilation, and reduced sensory capacity.[15;16] These changes increase the susceptibility to illnesses and hospitalization and could initiate a cascade of events and complications that could finally result in a diminished quality of life and increased dependency.

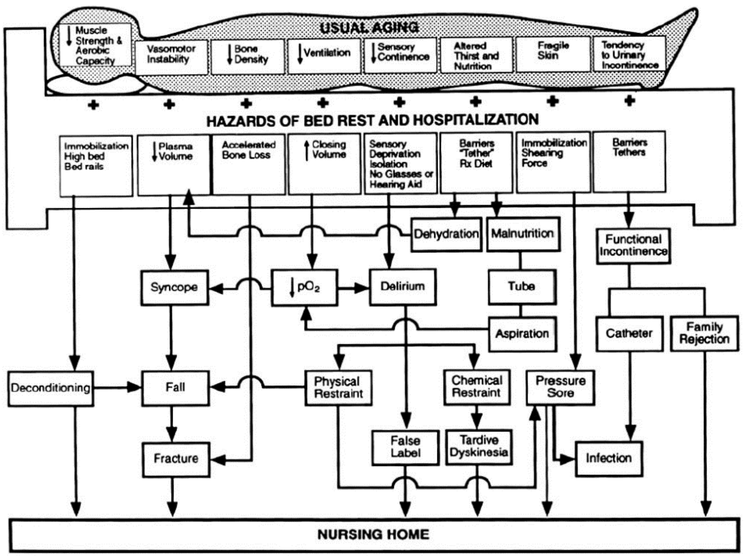

Figure 1. The cascade to dependency (Creditor et al. 1993)

The hazards of prolonged bed rest are well established some decades ago[17], and the reduction of mobility and activity levels during hospitalization has been identified as important predictors of adverse outcomes (i.e., a new institutionalization and in-hospital death) for hospitalized older adults.[18] Deconditioning, which results in a decrease of muscle mass, muscle strength, and other physiologic changes related to bed rest, has a major impact on overall weakness.[19] Functional decline –the inability to perform ADLs due to weakness, reduced muscle strength, and reduced exercise capacity- frequently occurs because of deconditioning and acute illness during hospitalization[20] and it has been identified as the leading complication of hospitalization for the elderly.[21] Loss of functional abilities from baseline was found to occur by the day 2 of hospitalization[22] and it is experienced by 30 to 60% of acutely hospitalized older adults.[23;24] In this regard, acute hospital admissions are a major contributor to disability[14] and more than half of all older adults do not recover to their preadmission functional status one year after discharge, with high rates of nursing home placement and death.[25-27] In addition, the development of new disabilities during hospital stay is associated with higher health care utilization[28], and cognitive impairment, depressive symptoms, or quality of life.[29] In acutely hospitalized patients, functional decline often precedes hospital admission, and hospitalization itself further increases the risk of worsening ADL disabilities.[30] Therefore, preadmission functional status of the older adults can also indicate risk of functional decline associated with hospitalization.

Loss of functional independence during hospitalization resulted from not only the effects of acute illness, but is also related to patient management during hospital stay.[29;31] The traditional model of hospitalized care has changed dramatically over the past century, from addressing acute self-limited pathologies toward addressing much more complex patient profiles that are characterized by frailty, disability, multimorbidity, and polypharmacy in older and chronic patients. These changes have marked the appearance of geriatric syndromes that modify patient life trajectories. Despite these changes in patient profiles, the hospital model remains stuck in the previous century model in such a way that hospitalization can perfectly manage acute diseases, but can also contribute to several risks that are clearly avoidable.[32] It is in this context that new concepts appear, such as iatrogenic nosocomial disability. A multidisciplinary working group of health professionals in 2011 defined iatrogenic disability as functional decline that results from one or more iatrogenic adverse events occurring during hospitalization, involving three components that interact and have a cumulative effect: (1) the patient's preexisting frailty, (2) the severity of the acute illness that led to the patient's admission, and (3) the hospital structure and the process of care.[33]

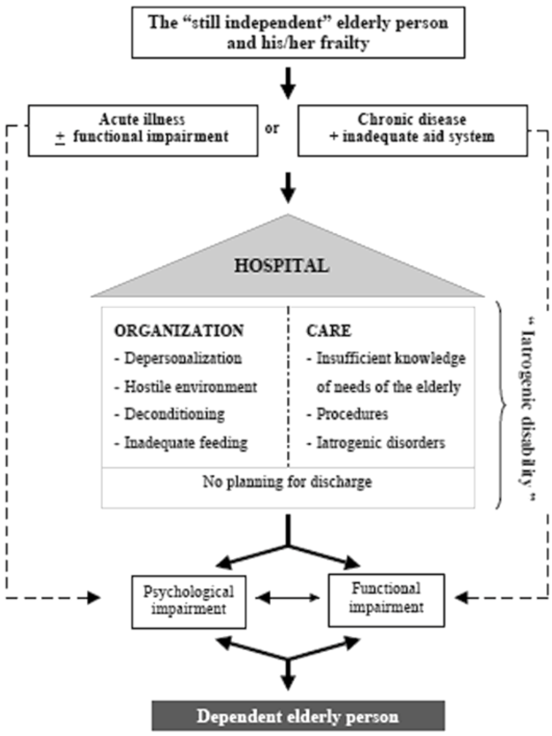

Figure 2. Factors of dependence related to the healthcare pathway (Lafont et al. 2011, adapted from Palmer 1998, Dysfunctional syndrome)

Older patients admitted to the ACE are frequently forced to prolonged bed rest and to be severely sedentary, which can lead to sarcopenia and occasionally, to chemical restraints that increase the risk of other adverse outcomes.[32] Previous studies have observed that older patients may be in bed for 83% of the hospital stay, even if they are able to walk, and the number of hours that an acutely hospitalized old patient is not lying down in bed or sitting on a chair can be approximately only 4 hours per day.[26] Functional decline during hospitalization increases the magnitude of inherent biological changes of aging process including loss of muscle mass and muscle strength (sarcopenia) and the reduction of muscle power output and aerobic capacity in older adults.[34;35] Previous studies have observed that the prevalence of sarcopenia varies between 10 to 21% in the geriatric patient[36;37] and loss of muscle function is closely related to frailty, which contribute to augment the vulnerability of the patient to the adverse events associated with hospitalization.[38] However, functional disability is only one component of iatrogenic disability. Physical or functional deficiencies are evident after the hospital stay, but recent evidence has suggested that hospitalization increases the risk of cognitive impairment and developing dementia in older adults.[39] Cognitive decline is a plausible consequence of the aging process and it is associated with an increased risk of adverse health outcomes such as functional limitations and disability.[40;41] Indeed, impairment in cognitive status was found to be associated with changes in functional status[42] and it is independently associated with other adverse health outcomes such as increased length of hospital stays, institutionalization, and mortality.[43] Additionally, hospital-related complications and inadequate hospital care have been related to the development of delirium state in acutely hospitalized older adults.[44] Delirium is defined as an acute disruption of attention and cognition, and is the most frequent complication of hospitalization in older adults (occurs in 14 to 56% of the patients).[45;46]

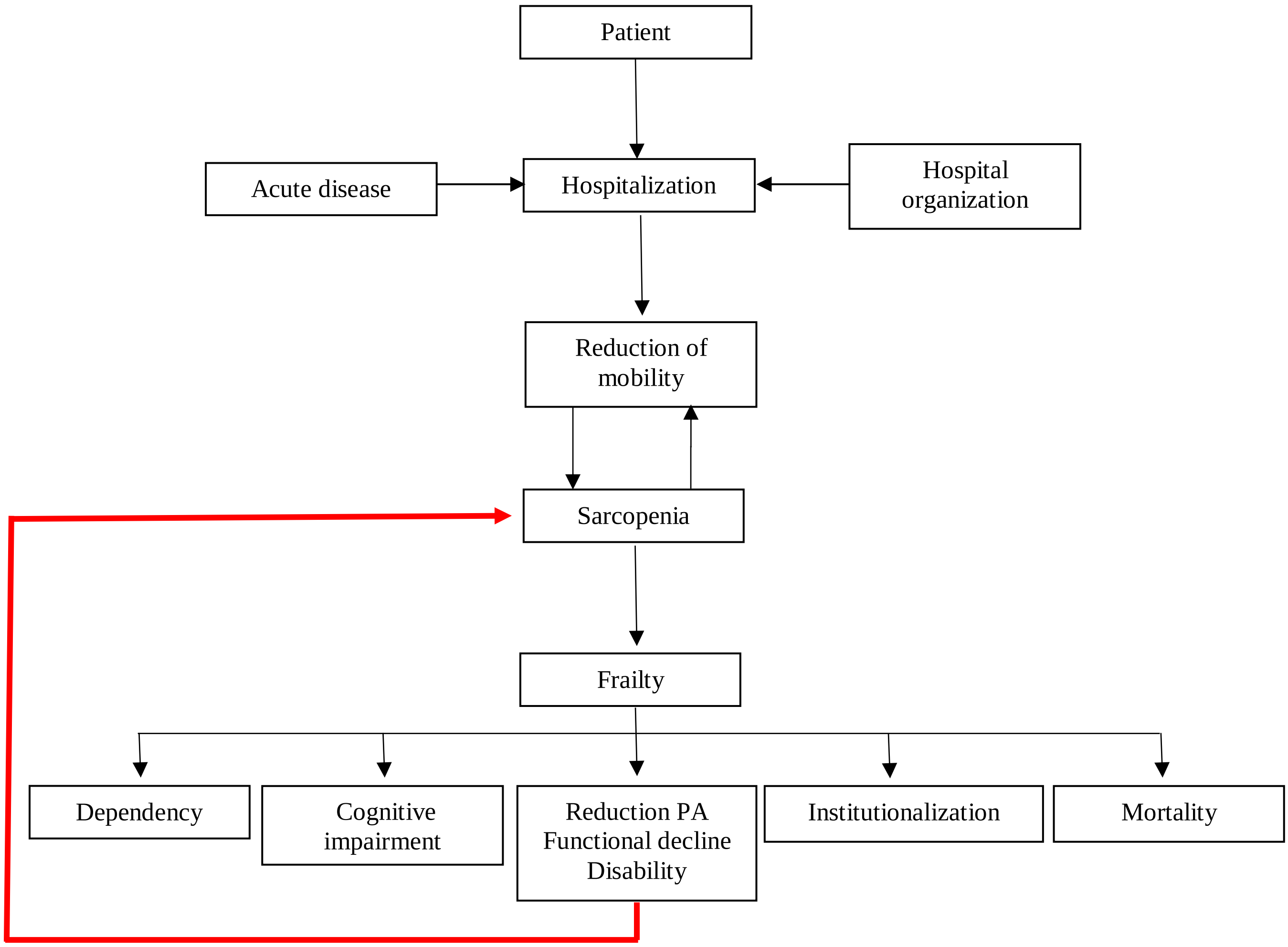

Figure 3. Adverse events associated with hospitalization (Sáez de Asteasu)

Potentially preventable iatrogenic disability has been assessed and quantified, and at least 80% of the cases were judged to be preventable.[32] Health care professionals and policy makers should prioritize this problem given the expectations of further growth of the elderly population next decades. Research evidence has supported the need for a shift from the traditional disease-focused approach in hospital ACE to one that recognizes functional status as a clinical vital sign.[32;33]

Poor health, disability, and dependency are not inevitable consequences of aging process, and functional independence is not an inevitable consequence of hospitalization in the elderly.[47;48] Thus, targeted measures that have been proved to be effective and to have potential benefits in mitigating functional and cognitive decline during hospitalization have included CGA and ACE units in tertiary hospitals.[49;50] The main aims of CGA and ACE are early identification of elder care needs to minimize the high-risk events such as falls or the onset of delirium[50], and promote a focused model of care that integrates geriatric assessment in an interdisciplinary environment.[51] As part of these measures, baseline assessments admissions have proved beneficial identifying patients at risk of functional decline during hospitalizations.[50] Although multiple screening tools are available, there is currently no gold standard for identifying older adults at risk of functional decline or measuring functional decline during hospital stay, so the predictive value of existing screening instruments and prediction models is limited.[33] Usually, preadmission and admission functional status and physical functional trajectory are measured using ADLs and IADLs scales.[52] These rating scales are based on the subjective self-report of the elderly patients, and many factors, such as cognitive impairment or dementia and delirium, can influence the total score. Additionally, assessment of functional capacity during ADLs (*i.e.*, walking or rising from a chair) is currently limited to performance time measurements, potentially missing important information about the test subtasks. In this regard, modern body-fixed sensors based on accelerometers and gyroscopes are useful tools to assess objectively functional capacity of patients in clinical practice.[53;54]

Despite the theoretical support that mobility programs have potential benefits in hospitalized patients, this approach has not been fully translated into the clinical practice and some studies have found paradoxical results including no functional improvement or even some adverse events like any other health care intervention.[55] The new alternative care models include exercise as an essential part of the conventional treatment for improving functional capacity in acutely hospitalized old patients.[56] The benefits of exercise programs are clinically, biologically and even economically confirmed[49;57], and have proved to be feasible in hospitalized patients[58], making exercise part of the therapeutic arsenal at our disposal. Previous studies have observed that simple and basic activities such as increasing their walking duration can reduce the average length of stay[59] and the incidence of chronic diseases.[60] However, recent evidence has failed to support the functional benefits of a mobility program consisting on ambulation and a behavioral strategy to encourage mobilization in this population.[61]

Exercise interventions including resistance training have been highlighted as one of the main cornerstones of prevention and treatment of sarcopenia and/or frailty.[62;63] Previous studies and systematic reviews have demonstrated that resistance training increases muscle performance outcomes (i.e., muscle mass, muscle strength and muscle power output)[64;65] and functional abilities in elderly, delaying the disability in this population.[66] With increasing age, loss of neuromuscular function results in an impaired capacity to perform ADLs and maintain an independent functioning.[67] Although there is a pronounced decrease in muscle strength, skeletal muscle power output decreases earlier and at greater rate of muscle strength with advancing age[68;69] and is a more discriminant predictor of functional capacity in older adults.[69] It is now increasingly recognized that recommendations for managing functional status should include muscle power training (explosive resistance training at low-moderate intensities (30-60% of 1RM)), principally for the lower limbs. Exercise interventions that have included muscle power training have been well tolerated, safe, and effective among frail older adults[62;68] and emerging evidence has suggested that exercise programs performed at high velocity can improve physical functioning to a greater extent than the traditional slow velocity resistance training.[69]

Multicomponent exercise programs (*i.e.*, simultaneous resistance/power training, endurance, balance, and flexibility exercises) appear to result in greater overall enhancements due to this type of intervention stimulates several components of physical health, such as strength, cardiorespiratory fitness, and balance.[70] Indeed, this training modality is the most effective to improve functional capacity in frail older adults.[70-72] A systematic review analyzed the effects of different exercise training modalities in physically frail older adults and reported that after a multicomponent training a reduction on falls incidence was observed in the 70% of the included studies; an improvement on gait velocity (54% of the studies); muscle strength gains (70% of the studies), and balance enhancements (80% of the included studies).[62]

Regarding the effects of physical exercise on cognitive function in older adults, discrepancies exist between the consistent evidence reported in epidemiological, cross-sectional, and animal studies and the less consistent results observed in RCTs. The influence of PA on brain function and structure has previously been analyzed in animal studies. Exercise training has been found to increase the levels of key neurochemicals, such as BDNF and IGF-1, which thereby improve synaptic plasticity and neuronal survival.[73;74] Many epidemiological studies have investigated the benefits of PA on cognition and showed a clear relationship between higher levels of PA and reduced risk of cognitive impairment.[75;76] On the other hand, multiple RCTs have been conducted to determine the effects of physical exercise on cognition and to identify the role of exercise training in the prevention of cognitive decline in older adults. However, clear evidence across trials has not been reported due to the large heterogeneity in the methodological aspects of the RCTs (*i.e.*, length of intervention, baseline physical performance of the participants, exercise protocol, adherence to physical exercise).[77] The increasing interest in the association between frailty and cognitive impairment in acutely hospitalized old patients[78] is driving the development of innovative interventions including exercise training for the prevention and management of both conditions.

Thus, PA as an intervention can be one of the most important components for maintaining or improving functional capacity and cognitive function in older adults. In the issue of iatrogenic nosocomial disability, it is essential to develop a multicomponent exercise program during hospitalization based on the current evidence, which should include a progressive resistance/power training, walking and balance exercises.[79;80] Multicomponent exercise programs, and especially those which include progressive resistance training, are the most effective intervention to delay disability and other adverse events.[32] Furthermore, physical exercise administration is relatively free of potential unwanted side effects caused by common medications that are prescribed in this type of patient.[81] Although physical exercise prescription is the first step, researchers have recognized the evident variability in patient response to physical exercise interventions and have sought to understand these differences.[82] Typically, "average" exercise related-benefits are reported, and there is a wide inter-individual variability in response to exercise training (IVRET), which has mainly been explored in endurance-based studies. The IVRET implies that under the same exercise conditions, some subjects, termed responders (Rs), achieve benefits after intervention, whereas others, termed non-responders (NRs; unchanged response) and adverse-responders (ARs; worsened response) do not.[82;83] In the era of precision medicine, to determine the IVRET in the magnitude of response to supervised exercise training (subject-by-training interaction) is the next step to optimize the exercise-dose for each hospitalized old patient.

This is a crucial point in time to open the possibility for a shift from the traditional-disease focused approach in hospital ACE units to one that recognizes functional capacity and cognitive function as essential components of the intrinsic capacity of older adults, and in-hospital exercises can be an effective therapy to revert the functional and cognitive decline associated with hospitalization.

Finally, this thesis describes the rational, design, methodologies and results of a RCT developed in an ACE unit in a tertiary public hospital. We hypothesized that an individualized multicomponent exercise training program would result in greater improvements on functional capacity and cognitive function compared to usual clinical care. ClinicalTrials.gov NCT02300896 registered on November 19, 2014.

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Aims and layouts of the thesis

Chapter 1

Study 1

Title: Role of physical exercise on cognitive function in healthy older adults: a systematic review of randomized clinical trials.

Research aim: To analyze the effects of different exercise training modalities, such as aerobic training, resistance training and multicomponent exercise training, on cognition in healthy older adults (>65 years) without known cognitive impairment, and to clarify the discrepancies between the consistent evidence reported in animal, epidemiological and cross-sectional studies and the less consistent results observed in RCTs.

Hypothesis: It was hypothesized that the multicomponent exercise training (due to this type of intervention stimulates several physical health components, such as strength, cardiorespiratory fitness, and balance) would have the most beneficial effects on cognitive function compared with other training modalities. The large heterogeneity in the methodological aspects of the RCTs would make it difficult to clarify the discrepancies between studies.

Chapter 2

Study 2

Title: Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial.

Research aim: To assess the effects of a multicomponent exercise intervention performed by older adults during acute hospitalization for functional capacity, cognition, well-being status and other outcomes, such as length of stay and falls.

Hypothesis: It was hypothesized that the physical exercise intervention would produce improvements on functional, cognition, and well-being status compared to usual clinical care.

Chapter 3

Study 3

Title: Physical exercise improves function in acutely hospitalized old patients.

Research aim: To analyze the effects of a multicomponent exercise training intervention on functional capacity during ADLs and muscle performance endpoints including maximal muscle strength and muscle power output of lower limbs.

Hypothesis: We hypothesized that the physical exercise intervention would improve patient´s functional capacity during ADLs, as well as maximal muscle strength and muscle power output of lower limbs.

Chapter 4

Study 4

Title: Role of muscle power output as a mediator between gait variability and gait velocity in hospitalized older adults.

Research aim: to compare gait characteristics and muscle performance endpoints including maximal muscle strength and muscle power output of very old patients admitted to an ACE unit based on functional status presented at admission, and to determine the mechanisms underlying gait impairment.

Hypothesis: It was hypothesized that acutely hospitalized older adults would present differences in gait pattern and muscle performance endpoints (i.e., maximal muscle strength and muscle power output) based on the SPPB score obtained at admission, and muscle power output would be the cornerstone of gait performance.

Chapter 5

Study 5

Title: Adverse response to exercise intervention during acute hospitalization.

Research aim: To assess the prevalence of Rs, NRs, and ARs (as indicated by functional, strength and cognitive variables) under usual care or an individualized multicomponent exercise intervention applied in an ACE unit in hospitalized old patients. We also sought to examine the relationship between the aforementioned categories of each group with mortality at one-year post-discharge, and a possible influence of the clinical differences at admission on the assessed endpoints.

Hypothesis: We hypothesized that acutely hospitalized older adults performing an individualized exercise intervention would present a higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognition compared with patients receiving usual care. In addition, ARs would have higher rates of mortality than NRs and Rs after discharge, and the functional status presented at admission would play a key role in the trajectory of patients during hospitalization and even more so at follow-up.

Chapter 6

Study 6

Title: Randomized physical exercise trial reverse cognitive impairment during acute hospitalization.

Research aim: To assess the effects of a multicomponent exercise intervention for cognitive function in older adults during acute hospitalization.

Hypothesis: It was hypothesized that multicomponent exercise intervention would maintain or even improve cognitive function compared to usual care in acutely hospitalized older adults.

Chapter 1

Role of physical exercise on cognitive function in healthy older adults: a systematic review of randomized clinical trials

1. Introduction

A plausible consequence of the aging process in older adults is cognitive decline, which is associated with an increased risk of dementia and adverse health outcomes such as functional limitations and disability[1;2], and places a substantial economic burden on health care systems and society.[3] The development of different interventions to maintain or improve cognitive function is necessary to control the epidemic of dementia and other disorders.[4] Physical activity (PA) has shown to have beneficial effects on cognition both in cognitively healthy older adults[5-7] and in older adults with cognitive impairment or dementia.[8;9]

PA has been reported to play a key role in the prevention of different disorders, such as cardiovascular disease, diabetes and some types of cancer.[10] Although evidence of the beneficial effects of PA on cognitive function has been clearly provided in the results of animal, epidemiological and cross-sectional studies, the results and conclusions of randomized controlled trials (RCTs) have been less consistent.[11]

The influence of PA on brain function and structure has previously been analyzed in animal studies. In aging animals, exercise training has been found to increase the levels of key neurochemicals, such as brain derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1), which thereby improve synaptic plasticity and neuronal survival.[12;13]

Many epidemiological studies have investigated the benefits of PA on cognition and showed a clear relationship between higher levels of PA and a reduced risk of cognitive impairment. Studies with large sample sizes and long follow up periods have shown that participants who had previously engaged in higher levels of PA were more likely to perform better on cognitive tasks when compared with subjects with previously lower PA levels.[14;15] Therefore, PA is hypothesized to have a protective effect on the cognitive decline in older adults.

Higher PA levels across different stages of life, especially during the teenage years, have been reported to be associated with a decreased likelihood of cognitive decline in later life.[16] Therefore, the results of cross-sectional studies have substantiated the evidence shown by epidemiological studies and reinforced the association between PA and better cognitive function in older adults.[6;17]

Multiple RCTs have been conducted to determine the effects of PA on cognition and to identify the role of exercise training in the prevention of cognitive decline in older adults. The influence of different exercise training protocols including aerobic exercise training, resistance training and multicomponent training that combines aerobic and strength training with other training modalities, and their relationship to cognitive outcomes have been studied; however, clear evidence across trials has not been reported. Meta-analytic reviews of RCTs have reported large variations in the magnitude of the improvements in cognitive outcomes associated with aerobic exercise training and while some meta-analyses have reported moderate cognitive gains[5;8], the cognitive benefits observed in other studies have been limited.[6;18] Reviews examining the effects of resistance training on cognitive performance have revealed similarly inconsistent results.[19;20] Although cognitive benefits have been observed in different RCTs, no consistent results have been obtained regarding significant cognitive improvements. Another interesting finding of the previously mentioned meta-analysis[5] was that studies with aerobic training interventions that also included a strength training protocol demonstrated greater benefits in terms of cognitive performance than those that only included an aerobic training component.

The presence of both inconsistent results and evidence makes it difficult to draw conclusions about the beneficial effects of exercise training on cognitive performance, especially in older adults. Updated knowledge is necessary to clarify whether PA has vital importance in promoting cognitive performance and preventing neurological disorders in older adults without known cognitive impairment who could benefit most from non-pharmacological interventions in the early stages of cognitive decline. New training modalities have been developed in recent years, such as multicomponent exercise training, that had not been included in previous systematic reviews[11] and could have beneficial effects on cognitive performance in older adults.[5;21] In our review, we aimed to update previous work[11] by analyzing the effects of different exercise training modalities, such as aerobic training, resistance training and multicomponent exercise training, on cognition in a narrower age range of healthy older adults (>65 years) without known cognitive impairment. In addition, a secondary objective of this review was to clarify the discrepancies that were observed between the consistent evidence reported in animal, epidemiological and cross-sectional studies and the less consistent results observed in RCTs.

2. Methods

2.1. Search Strategy

This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement[22] and the method used was based on the minimum criteria established by the Cochrane Back Review Group (CBRG).[23]

A systematic review was conducted to update the existing knowledge regarding the influence of PA or exercise training on cognitive outcomes in older adults, continuing the meta-analysis published by Kelly and colleagues[11] but with the addition of randomized controlled trials published from 2012 to 2016. Queries of the literature were performed using the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE (until August 30th, 2016). The search terms employed, which were the same as those used by Kelly et al.[11] in their previous review and meta-analysis, included the following: [“exercise,” “fitness,” “physical endurance,” “physical activity,” “physical training” AND “cognition,” “cognitive performance,” “cognitive decline,” “cognitive function,” “cognitive processes” AND “older adults,” “elderly,” “healthy elderly,”]. Additionally, the reference lists were examined to detect studies that were potentially eligible for inclusion. We supplemented the search using complementary databases, such as Google Scholar. Studies reported in languages other than English and Spanish were not explored.

During the inclusion period, we screened title and abstracts, and in some cases, full articles if they were of interest and when full-text screening was necessary to verify whether they met the criteria for inclusion in the review.

2.2. Selection criteria

Randomized-controlled trials (RCTs) that investigated the effects of different exercise training modalities (i.e., aerobic training, resistance training, and multicomponent exercise training) on cognition in healthy older adults (>65 years) without known cognitive impairment were selected. Parallel and crossover design trials were included. Case-reports, case-series, single- case studies, dissertations and conference proceedings were excluded.

For articles in which baseline cognitive function was measured using the Mini Mental Modified Examination (MMSE)[24], all members of the sample had to have scored ≥23 points to be included in this review. The exercise categories were chosen based on the most common exercise interventions implemented in RCTs published during the study period. At least 10 participants per training condition were required for inclusion in the review. We also excluded studies if participants had been diagnosed with any cardiovascular disease, or other significant medical, psychiatric, or neurological problems. Studies based on interventions in which participants performed specific cognitive tasks, such as cognitive training, dual-task training or exergames, were also excluded from the review, to examine the inherent effects of exercise training on cognitive function. Finally, we excluded interventions carried out in an aquatic environment.

The outcome of interest was cognitive function, which was divided into two principle domains; executive function and memory. In each domain, different sub-categories were analyzed. The executive function sub-categories were: working memory, verbal fluency, reasoning, attention and processing speed. The memory domain sub-categories were: recognition, immediate recall, delayed recall, face-name recall and paired associations. Other cognitive outcomes not included in these groups were also analyzed. Outcomes and sub-categories are detailed in Table 1.

Table 1. Lists of outcome measure and cognitive sub-categories extracted from the included studies

Executive function domain		**Memory function domain**	
Task / Outcome	**Sub-category**	**Task / Outcome**	**Sub-category**
WAIS III	Working memory	Word Learning Test	Recognition
Self-ordered pointing task	Working memory	RAVLT	Immediate recall
1-back test / 2-back test	Working memory	HVLT	Immediate recall
DSF / DSB	Working memory	LMI	Immediate recall
ROF-C	Working memory	Selective Reminding Task	Immediate recall
CBTF / CBTB	Working memory	ROF-IR	Immediate recall
Verbal digit backward / forward test	Working memory	Word Learning Test	Delayed recall
LNS	Working memory	Delayed Logical Memory	Delayed recall
Animals / vegetables / letter p / category	Verbal fluency	Memorizing face scene pairs	Paired associations
COWAT	Verbal fluency		
Stroop Word-Colour	Attention		
Covert orienting	Attention		
CCRT	Attention		
UFOV	Attention		
Go / No Go test	Attention		
WCST	Attention		
TMT A/B	Attention		
TPCN / TPCE	Attention		
Deary Liewald Reaction Time	Proc. speed		
Simple reaction time	Proc. speed		
Incompatible 8 choice reaction time	Proc. speed		
DSST	Proc. speed		
Task switching	Proc. speed		

WAIS = Wechsler Adult Intelligence Scale; DSB = Digit Span Backward; DSF = Digit Span Forward; ROF-C = Rey Osterrieth Figure Copy; CBTF = Corsis block-tapping forward; CBTB = Corsis block-tapping backward; LNS = Letter Number Sequencing; COWAT = Controlled Oral Word Association Test; CCRT = Cambridge Contextual Reading Test; UFOV = Useful Field of View; WCST = Wisconsin Card Sort Test; TMT A/B = Trail Making Test A and B; TPCN = Toulouse–Pieron Cancellations numbers; TPCE = Toulouse–Pieron Cancellations errors; DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test; = Hopkins Verbal Learning Test; LMI = Logical Memory Part I; ROF- IR = Rey Osterrieth Figure Immediate Recall.

2.3. Data extraction

Two authors (MI, NMV) independently screened the titles and abstracts of potentially eligible studies identified by the search strategy. If necessary, a third researcher (FZF) was consulted. If one abstract did not provide enough information for evaluation based on the inclusion and exclusion criteria, full articles were retrieved for a full text assessment. The following relevant data were extracted: study design, participant characteristics, methods, quality, exercise protocol description, cognitive outcomes, feasibility, and conclusions. Authors were contacted to provide missing data or to clarify if data were duplicated in multiple publications. Cognitive impairment was defined based on the description of the population or by using the MMSE scores (cut-off point of 23/30). It was assumed that the population was cognitively healthy when no specific information regarding cognitive status was reported, and in cases in which the MMSE was not performed at baseline, the reviewers contacted the authors to obtain further details about the cognitive function of the assessed population.

2.4. Assessment of risk of bias

Two independent reviewers evaluated the risk of bias among the included studies using the guidelines published in Section 8 of the Cochrane Handbook. Disagreements were resolved by consulting a third reviewer. The items selected for use in the methodological assessment of the included randomized controlled trials were: an adequate sequence generation for randomization, reported allocation concealment, a blinded assessment of outcomes, a description of losses to follow-up and exclusions, a use of intention to treat analysis and a selective reporting of study results. Each item was classified as low risk, unclear risk (specific details or description were not reported) or high risk (not fulfilling the criteria).

3. Results

3.1. Included studies

After the using the literature search strategy to identify articles published between 2012 and 2016, 42 RCTs were selected for screening out of the 1930 articles identified as potentially relevant due to assessing effects of exercise training on cognitive performance in healthy older adults. Forty-two RCTs were screened and 32 RCTs were excluded from the review because they did not meet the inclusion criteria. Therefore, 10 articles published between 2012 and 2016 were ultimately selected and included in the review. Previously, Kelly et.al[11] included 25 RCTs published between 2002 and 2012 in their review and meta-analysis, and 11 of those RCTs met the inclusion criteria for this review (Figure 1). Thus, 21 RCTs were eligible for inclusion. Overall these studies had enrolled 320 participants in aerobic exercise groups, 409 participants in resistance training groups, and 260 participants in multicomponent exercise training groups; additionally, 279 participants were enrolled in stretching/toning groups, 200 participants were enrolled in "no exercise" active control groups, and 310 participants were enrolled in "no intervention" control groups. The most common intervention was resistance training. Participants in the stretching/toning group performed stretching, range of motion exercises, toning or yoga exercises. Participants in the no exercise active control group received health education classes, guideline care, watched movies or engaged in social activities. Subjects in the no intervention groups received no contact, minimum social support or were placed on a waiting list. Characteristics of the included studies are presented in Tables 2, 3 and 4.

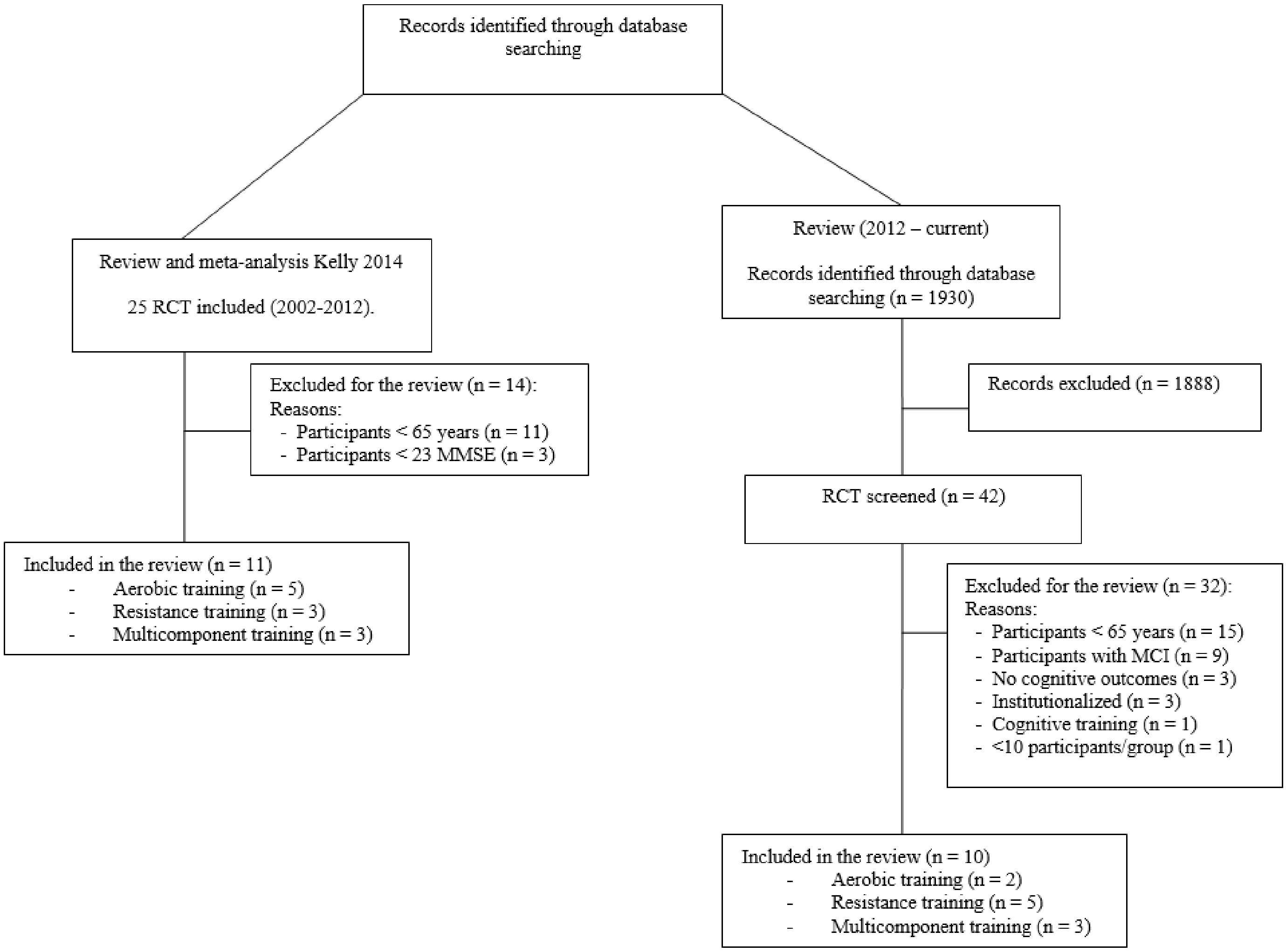

Figure 1. Flowchart showing the selection of studies for this systematic review.

Table 2. Characteristics of studies - aerobic exercise training

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Aerobic versus stretching/toning								
Oken (2006)	Three conditions: 1. Aerobic training (EG) 2. YOGA 3. Wait List Control Group (CG)	1. EG: 1 x 1h per week for 6 months at 70% of max HRR- adjusted as needed. 5 more sessions/week of aerobic training recommended at home. 2. YOGA: 1 x 1.5 h for 6 months: 30 s pose, <1 min rest. FU: PT.	135 subjects were randomized: EG n=47, YOGA n= 44 and CG n=44. Age range: 65-85. EG M^{age}: 73.6 (5.1). YOGA M^{age}: 71.5 (4.9). CG: M^{age}: 71.2 (4.4).	Delayed recall[c] (10 word list learning task) Working memory[c] (WAIS III) Attention (Stroop[c], Cov. Orient[c], CRT[c]) Divided attention (UFOV)[c] Proc. Speed[c].	10 word list learning: 0.31 WAIS III: 0. Stroop W-C: 0.09 Cov. Orient: -0.21 CRT: -0.05 UFOV: 0.03 Proc. Speed: 0.13	Attendance 69%. No AE related to the intervention.	Better adherence YOGA (78%) vs EG (69%). Training session duration less EG group (1h) vs YOGA (1.5h). Training frequency is low (1 session/week).	No significant differences between EG and CG. Lack of effect on cognitive function could be related with ceiling effect.
Smiley-Oyen (2008)	Two conditions: 1. Aerobic exercise (EG). 2. FLEX-TONE (CG): Strength, flexibility and balance.	1. EG: 3 x 1h per week for 10 months. 10 min warm up + 25-30 aerobic training + 10 min cool down. 60-70% progressed to 65-80% of max HRR. 2. CG: 3 x 50 min per week for 10 months. 10 min warm up + 25-30 min Tai Chi, flex bands, free hand weights, stability balls + 10 min cool down. FU: PT	109 subjects were randomized EG n=55 and CG n=54. Age range: 65-79. EG M^{age}: 69.86 (4.59). CG M^{age}: 70.52 (4.47).	Processing speed (simple reaction time[c], incompatible 8-choice reaction time[c], 8 choice reaction time[c]). Attention (Go/No Go[c], Stroop W-C[b], Stroop W&C[c], WCST[c]).	Simple reaction time: 0.46 Incompatible 8-choice reaction time: -0.01 8 choice reaction time: 0.48 Go/No Go: 0.26 Stroop W: -0.13 Stroop C: 0.15 Stroop W-C: -0.33 WCST: 0.12	No major AE related to the intervention.	Significant decrease in reaction time and errors in the Stroop W-C task in EG.	No significant differences between EG and CG, but significant pre-post improvements in EG.

Albinet (2010)	Two conditions: 1. Aerobic training (EG). 2. Stretching exercise control (CG).	1. EG: 3 x 1h per week for 12 weeks. 40-60% of max HRR. FU: PT.	24 subjects were randomized EG n=12 and CG n=12. Age range: 65-78. Cognitive global function: MMSE>26. EG M^{age}: 70.9 (4.9). EG MMSE: 28.5 (1.1). CG M^{age}: 70.4 (3.4). CG MMSE: 29 (0.9).	Attention[a] (WCST).	WCST: -0.66	Attendance rate of 87.6% EG and 87% CG.		Individualized-intensity AT improved executive performance vs CG.
Nagamatsu (2012)	Three conditions: 1. Resistance training (RT) 2. Aerobic training (EG) 3. Balance and toning (CG)	Single-blind. 1. 2 x 1h/session per week for 6 months. 2 sets x 6-8 rep. increasing progressively intensity training. 2. 2 x 1h/session per week. Walking 40-70/80% of max HRR. 3. 2 x 1h/session per week for 6 months. FU: PT.	86 women were randomized RT n=28, EG n=24 and CG n=27. Age range: 70-80. Cognitive global function: MMSE>24. EG M^{age}: 73.9 (3.4). EG MMSE: 27.0 (1.8). RT M^{age}: 75.6 (3.6). RT MMSE: 27.4 (1.5). CG M^{age}: 75.1 (3.6). CG MMSE: 27.1 (1.7).	Attention (Stroop C-W[c], TMT A-B[c]). Working memory[c] Associative memory (Memorizing face scene pairs[c]). Conflict resolution[c] (Everyday Problems test)	No data to calculate.	Adherence was low (not details). AE: 2 participants shortness of breath and 4 noninjuries falls.		RT significant differences vs CG, AT not. Twice weekly RT is a promising strategy to improve cognitive function. AT had not effect on cognitive function.
Ten Brinke (2015)	Three conditions: 1. Aerobic training (EG). 2. Resistance training (RT) 3. Balance and toning (CG).	1. 2 x 1h per week for 26 weeks. 40-80% of max HRR. 2. 2 x 1h per week for 26 weeks. 10 exercises. 2 sets x 6-8 rep. 7RM.	86 women were randomized EG n=30, RT n=28 and CG n=28. Age range: 70-80. Cognitive global function: MMSE>24.	Immediate recall[c] (RAVLT).	RAVLT total adquisition: -0.06 RAVLT recall interference: 0. RAVLT loss interference: -0.48 RAVLT long recall: -0.3	Attendance rate of 60% EG, 54% RT, 59% CG. AE: 1 shortness of breath RT, 2 noninjuries falls EG, 1 shortness of breath CG.	Low adherence to training session.	No significant differences were found between groups.

		3. Stretching, range of motion exercises, relaxation techniques. FU: PT.	EG M^{age}: 76.07 (3.43). EG MMSE: 27.54 (1.51). RT M^{age}: 73.75 (3.72). RT MMSE: 26.67 (2.64). CG M^{age}: 75.46 (3.93). CG MMSE: 27.17 (1.85).		RAVLT recognition: 0.19			
Aerobic versus no exercise active control								
Muscari (2010)	Two conditions: 1. Aerobic exercise in community gym (EG). 2. Educational material (CG).	1. EG: 3 x 1h per week for 12 months. At least 20 min of session 70% of max HRR. 2. CG: Counselling to increase daily PA. FU: PT.	120 subjects were randomized EG n=60 and CG=60. Age range: 65-74. Cognitive global function: MMSE>24. EG M^{age}: 68.8 (2.5). EG MMSE: 26.7. CG M^{age}: 69.6 (2.8). CG MMSE: 27.0.	Cognitive function[a] (MMSE).	No data to calculate.	No AE related to intervention.	The data analysis was limited to participants who participated at least 50% of training sessions.	AT may have a positive impact on the cognitive performance.
Legault (2011)	Four conditions: 1. Aerobic exercise and flexibility (EG). 2. Health aging (CG). 3. Cognitive training (CT). 4. Combined intervention (COM): Aerobic exercise + cognitive training.	Single blind. 1. EG: 3 x 150 min per week for 4 months. 3. 24 sessions in 4 months. Computer tasks. 4. 56 sessions in 4 months. FU: PT.	73 subjects were randomized EG n=16, CG n=17, CT n=16 and COM n=19. Age range: 70-85. Cognitive function: 3MSE score>88. CG M^{age}: 75.4. 3MSE: 94.3 EG M^{age}: 77.5. 3MSE: 94.6. CT M^{age}: 76.3. 3MSE: 95.6. COM M^{age}: 76.3. 3MSE: 94.6	Immediate recall (HVLT[c], LM1[c]). Delayed recall[c] Attention (task switching[c], TMT A-B[c]). Working memory (self ordered pointing task[c], 1-back[c], 2-back[c]). Response inhibition[c].(Eriksen flanker task)	HVLT immediate recall: -0.08 LM1: 0.29 HVLT delayed recall: 0.23 Task switching: 0.13 TMT A-B: 0.54 Self ordered pointing task: 0 1-back: -0.28 2-back: -0.54 Eriksen flanker task: -0.38	Attendance rate of 76% EG, 96% CT and 90% PACT. 1 participant present AE.	No significant outcomes reported.	No significant differences between EG and CG.

Aerobic versus no intervention

Oken (2006)	Three conditions: 1. Aerobic exercise (EG) 2. YOGA 3. Wait list Control Group (CG)	1. EG: 1 x 1h per week for 6 months at 70% of max HRR- adjusted as needed. 5 more sessions/week of aerobic training recommended at home. 2. YOGA: 1 x 1.5 h for 6 months: 30 s pose, <1 min rest. FU: PT.	135 subjects were randomized: EXER n=47, YOGA n= 44 and CG n=44. Age range: 65-85. EG M^{age}: 73.6 (5.1). YOGA M^{age}: 71.5 (4.9). CG: M^{age}: 71.2 (4.4).	Delayed recall[c] (10 word list learning task) Working memory[c] (WAIS III). Attention (Stroop[c], Cov. Orient[c], CRT[c]) Divided attention (UFOV)[c] Proc. Speed[c].	10 word list learning: 0 WAIS III: -0.06 Stroop W-C: 0.2 Cov. Orient: 0.03 CRT: 0.13 UFOV: 0.06 Proc. Speed: 0.5	Attendance 69%. No AE related to the intervention.	Better adherence YOGA (78%) vs EG (69%). Training session duration less EG group (1h) vs YOGA (1.5h). Training frequency is low (1 session/week).	No significant differences between EG and CG. Lack of effect on cognitive function could be related with ceiling effect.
Vidoni (2015)	Four conditions: 1. No intervention (CG). 2. 75WEEK 3. 150WEEK 4. 225WEEK	3-5 days x 50 min per week for 26 weeks. 75WEEK: Walking 75 min per week. 150WEEK: Walking 150 min per week. 225WEEK: Walking 225 min per week. First 4 weeks at 40-55% of max HRR. 5-18 weeks: 50-65% of max HRR. 19-26 weeks: 60-75% of max HRR. FU: PT.	101 subjects were randomized CG n=25, 75WEEK n=25, 150WEEK n=27, 225WEEK n=24. Age range: >65. Cognitive function: CDR=0. CG M^{age}: 72.5 (5.8). CG MMSE: 29.3 (0.9). 75WEEK M^{age}: 73.5 (5.9). 75WEEK MMSE: 29.2 (0.9). 150WEEK M^{age}: 72.5 (5.7). 150WEEK MMSE: 29.3 (1.2). 225WEEK M^{age}: 73.2 (5.3). 225WEEK MMSE: 29.2 (1.1).	Verbal memory (Logical Memory[c], Delayed Logical Memory[c], Selective Reminding task[c], Boston Naming test[c]). Visuospatial processing (Block Design[c], Stroop[c], DSST[c], TMT A[c]). Simple attention (DSB[c], DSF[c], Letter Number Sequencing[c]). Set Maintenance and Shifting[c] (DKEFS). Verbal fluency (animals[c], vegetables[c]) Reasoning (letter[c], word[c], matrix[c])	No data to calculate.	Adherence rate: 75WEEK 82.3%, 150WEEK 85.5%, 225WEEK 70.1%. 94 AE in total: 91% mild and 9% moderate severity.	ITT analyses, not gains in any cognitive domain. PP analyses, visuospatial processing and simple attention improved of any exercise. Better adherence and lower AE in 150WEEK vs 225WEEK.	No significant differences between EG and CG in ITT analyses. Physiologic adaptation to aerobic exercise (improvement in VO2max) is an important predictor of cognitive benefit.

EG = experimental group; CG = control group; FU = follow up; AE= Adverse Event; AT = Aerobic Training; RT = Resistance Training; PT = post training; Mage = mean age; (SD or SE) = (Standard Desviation or Standard Error); DSST = digit symbol substitution test; UFOV = Useful Field of View; HRQL = Health Related Quality of Life; WCST = Wisconsin Card Sort Test; Stroop C-W = Stroop colour – word; HVLT = Hopkins Verbal Learning Test; LMI = Logical Memory Part I; RAVLT = Rey Auditory Verbal Learning Test; CCRT = Cambridge Contextual Reading Test; WAIS = Wechsler Adult Intelligence Scale; MMSE = Mini Mental State Examination; 3MSE = Modified Mini Mental Examination; TMT= Trail Making Test; DSF = Digit Span Forward; DSB = Digit Span Backward; DKEFS: Delis Kaplan Executive function System; HRR = heart rate reserve; ITT = Intention To Treat; PP = Per protocol.

a Significantly greater improvement for training compared to control.
b Significant training effects for experimental group from baseline to PT; no significant effect for controls.
c No significant intervention difference between experimental and control groups.

Table 3. Characteristics of studies - resistance training

Ref. author (year)	**Intervention**	**Methods**	**Participants**	**Outcomes of interest**	**Effect Size (ES)**	**Feasibility/AE**	**Additional notes**	**Conclusion**
Resistance versus stretching/toning								
Cassilhas (2007)	Three conditions: 1. High intensity training group (EG) 2. Moderate training group (AC) 3. Stretching control group (CG)	1. EG: 3 x 1h/session per week for 24 weeks. 6 exercises. 2 sets x 8 rep. at 80%RM. 2. Same protocol as high intensity but 50%RM. 3. CG: 1 session per week for 24 weeks. FU: PT	62 subjects were randomized EG n=20, MG n=19 and CG n=23. Age range: 65-75. Cognitive global function: MMSE>23. EG M^{age}: 68.4 (0.67). AC M^{age}: 69.01 (1.10). CG M^{age}: 67.04 (0.54).	Immediate recall[a] (ROF-IR). Reasoning[a]. Working memory (DSF[a], DSB[c], ROF-C[c], CBTF[c], CBTB[a]). Attention (TPCN[c], TPCE[c]).	No data to calculate.	Attendance rate above 75%.	Training at moderate intensity is sufficient to obtain cognitive benefits.	EG and AC had similar improvements in cognitive tasks vs CG.
Liu Ambrose (2010)	Three conditions: 1. Twice-weekly resistance training (EG) 2. Once-weekly resistance training (RT) 3. Twice-weekly balance and tone training (CG)	Single-blind. 1. 2 x 1h/session per week for 52 weeks. 10 exercise. Progressive 7RM method. 2. Same protocol as EG but 1 session per week. 3. 2 x 1h/session per week for 52 weeks. FU: PT.	155 women were randomized EG n=52, RT n=54 and CG n=49. Age range: 65-75. Cognitive global function: MMSE>24. EG M^{age}: 69.4 (3.0). EG MMSE: 28.6 (1.5). RT M^{age}: 69.5 (2.7). RT MMSE: 28.5 (1.3). CG M^{age}: 70.0 (3.3). CG MMSE: 28.8 (1.2).	Attention (Stroop[a], TMT A-B[c]). Working memory[c] (Verbal digit backward, Verbal digit forward)	Stroop: -0.24 TMT A-B: 0.01 Verbal digit backward – Verbal digit forward: -0.15	Adherence rate of 70.3% EG, 71% RT and 62% CG. Significant differences between groups in AE; RT 29.8%, EG 10.9% and BAT 9.5%.	Cognitive performance improved by 12.6% and 10.9% in RT and EG, respectively. CG demonstrated 0.5% deterioration.	Resistance training can enhance selective function and conflict resolution..

Liu Ambrose (2012)	Three conditions: 1. Twice-weekly resistance training (EG) 2. Once weekly resistance training (RT) 3. Twice weekly balance and tone training (CG)	1. EG: 2 x 1h/session per week for 52 weeks. 10 exercise. Progressive 7RM method. 2. Same protocol as EG but 1 session per week. 3. 2 x 1h/session per week for 52 weeks FU: PT.	52 women were randomized EG n=15, RT n=20 and CG n=17. Age range: 65-75. Cognitive global function: MMSE>24. EG M^{age}: 68.9 (3.2). EG MMSE: 29.1 (0.8) RT M^{age}: 69.7 (2.8). RT MMSE: 28.6 (1.2). CG M^{age}: 69.2 (3.2). CG MMSE: 29.1 (1.1).	Conflict resolution[a] (Eriksen flanker test)	Eriksen flanker task: -0.89	Adherence rate of 79.2% EG, 75.1% RT and 71.8% CG.	EG increases cognitive performance 8.48% and CG only 1.47%.	Twice-weekly RT can positively affect functional plasticity of response inhibition processes in cortex.
Nagamatsu (2012)	Three conditions: 4. Resistance training (EG) 5. Aerobic training (AT) 6. Balance and tone training (CG)	Single-blind. 1. 2 x 1h/session per week for 6 months. 2 sets x 6-8 rep. increasing progressively intensity training. 2. 2 x 1h/session per week. Walking 40-70/80% of max HRR. 3. 2 x 1h/session per week for 6 months. FU: PT.	86 women were randomized EG n=28, AE n=24 and CG n=27. Age range: 70-80. Cognitive global function: MMSE>24. EG M^{age}: 73.9 (3.4). EG MMSE: 27.0 (1.8). RT M^{age}: 75.6 (3.6). RT MMSE: 27.4 (1.5). CG M^{age}: 75.1 (3.6). CG MMSE: 27.1 (1.7).	Attention (Stroop C-W[a], TMT A-B[c]). Working memory (Verbal Digit Backward[c], Verbal Digit Forward[c]) Associative memory[a] (Memorizing face scene pairs). Conflict resolution[c] (Everyday Problems test)	No data to calculate.	Adherence was low (not details). AE: 2 participants shortness of breath and 4 noninjuries falls.		RT significant differences vs CG, AT not. Twice weekly RT is a promising strategy to improve cognitive function. AT had not effect on cognitive function.
Forte (2013)	Two conditions: 1. Resistance training (EG)	1. 2 x 1h/session per week for 3 months. Circuit 12 strength exercises 8 rep. at	50 subjects were randomized EG n=25 and CG n=25.	Executive function[b] (Random number generation task).	Random number generation task turning point index: 0.56	Adherence rate of 86% EG and 85% CG.	Baseline cognitive global function not detailed.	RT had positive effect in executive functioning.

	2. Balance and tone training (CG)	60-80% RM. RM was calculated every 4 weeks. 2. 2 x 1h/session per week for 3 months. FU: 4 week control period and PT.	Age range: 65-75. EG M^{age} male: 69.1 (3.7). EG M^{age} female: 70.5 (3.9). CG M^{age}: 71.4 (2.9). CG M^{age} female: 69.0 (2.8).	Attention[b] (TMT A-B).	Random number generation task adjacency: 0.74 Random number generation task runs: 0.34 TMT A-B: 0.29			
Ten Brinke (2015)	Three conditions: 4. Aerobic training (AT). 5. Resistance training (EG) 6. Balance and toning (CG).	1. 2 x 1h per week for 26 weeks. 40-80% of max HRR. 2. 2 x 1h per week for 26 weeks. 10 exercises. 2 sets x 6-8 rep. 7RM. 3. Stretching, range of motion exercises, relaxation techniques. FU: PT.	86 women were randomized AT n=30, EG n=28 and CG n=28. Age range: 70-80. Cognitive global function: MMSE>24. AT Mage: 76.07 (3.43). AT MMSE: 27.54 (1.51). EG Mage: 73.75 (3.72). EG MMSE: 26.67 (2.64). CG Mage: 75.46 (3.93). CG MMSE: 27.17 (1.85).	Immediate recall[c] (RAVLT).	RAVLT total adquisition: 0.35 RAVLT recall interference: 0.13 RAVLT loss interference: -0.45 RAVLT long recall: 0.19 RAVLT recognition: -0.24	Attendance rate of 60% AT, 54% EG, 59% CG. AE: 1 shortness of breath EG, 2 noninjuries falls AT, 1 shortness of breath CG.	Low adherence.	No significant differences between EG and CG.
Best (2015)	Three conditions: 1. Twice-weekly resistance training (EG) 2. Once-weekly resistance training (RT) 3. Twice-weekly balance and tone training (CG)	Single-blind. 1. 2 x 1h/session per week for 52 weeks. 10 exercise. Progressive 7RM method. 2. Same protocol as EG but 1 session per week.	155 women were randomized EG n=52, RT n=54 and CG n=49. Age range: 65-75. Cognitive global function: MMSE>24.	Immediate recall[a] (RAVLT) Executive function[a] (Stroop C-W, TMT A-B, Verbal Digit Backward, DSST)	No data to calculate.	70% of baseline sample complete at 2 years cognitive assessments.	Secondary analysis of a previous study (Liu Ambrose et.al 2010)	EG and RT groups had long-term impact on executive function, and EG training protocol had an additional positive effect on memory domain.

		3. 2 x 1h/session per week for 52 weeks. FU: a 1-year post intervention.	EG M^{age}: 69.4 (3.0). EG MMSE: 28.6 (1.5). RT M^{age}: 69.5 (2.7). RT MMSE: 28.5 (1.3). CG M^{age}: 70.0 (3.3). CG MMSE: 28.8 (1.2).				
Resistance versus no exercise active control							
Kimura (2010)	Two conditions: 1. Resistance training (EG) 2. Health education classes.	Single-blind. 1. EG: 2 x 1.5h/session per week for 12 weeks. 3 sets x 10 rep. at 60% of 1RM. 2. 1.5h x 1 session per month for 12 weeks. FU: PT.	171 subjects were randomized EG n=86 and CG n=85. Age range: >65. Cognitive global function: MMSE>23. EG M^{age}: 73.6 (4.7). EG MMSE: 27.8 (1.8). CG M^{age}: 75.2 (6.3). CG MMSE: 27.9 (2.1).	Reaction time[c] (Task switching).	Task switching: -0.11	No AE related with the intervention.	RT had not positive impact on cognitive function.
Van de Rest (2014)	Two conditions: 1. Resistance training (EG) 2. Control group (CG)	Double-blind. 1. 2 sessions per week for 24 weeks. 6 exercises. 3-4 sets x 10-15 rep. at 50%RM and progress 3-4 sets x 8-10 rep. at 75%RM. RM was calculate at weeks 4, 8, 12, 16 and 20 of intervention. 2. No intervention.	127 subjects were randomized to EG n=62 and CG n=65. Age range: >65. Global Cognitive function: MMSE≥23. EG M^{age}: 79.2 (6.3). EG MMSE: 28 (27-29). CG M^{age}: 81.2 (7.4). CG MMSE: 28 (26-30).	Immediate recall[c] (Word Learning Test) Delayed recall[c] (Word Learning Test). Recognition[c] (Word Learning Test). Attention (Stroop W&C[c], TMT A-B[c]). Working memory (DSF[a], DSB[c]) Verbal Fluency (animals[c], letter p[c]) Reaction time[c].	Immediate recall: 0.15 Delayed recall: -0.09 Recognition: -0.13 Stroop W: 0.26 Stroop C: 0 TMT A-B: 0.02 DSF: 0.5 DSB: 0.37 Verbal fluency animals:-0.22 Verbal fluency letter p: -0.02 Reaction time: -0.22	Not described.	RT was beneficial for the cognitive domain attention.

FU: PT.

EG = experimental group; CG = control group; AC: Active control; RT = Resistance training; AT = Aerobic Training; AE= Adverse Event; FU = follow up; PT = post training; Mage = mean age; (SD or SE) = (Standard Desviation or Standard Error); MMSE:= Mini Mental State Examination; ROF- IR = Rey Osterrieth Figure Immediate Recall; DSF = Digit Span Forward; DSB = Digit Span Back; ROF- C = Rey Osterrieth Figure Copy; CBTF = Corsis block-tapping forward; CBTB = Corsis block-tapping backward; TPCN = Toulouse–Pieron Cancellations numbers; TPCE = Toulouse–Pieron Cancellations errors; DSST = Digit Symbol Substitution Test; Stroop W-C = Stroop word – colour; RAVLT = Rey Auditory Verbal Learning Test; TMT= Trail Making Test; RM: Repetition Maximum.

a Significantly greater improvement for training compared to control.
b Significant training effects for experimental group from baseline to PT; no significant effect for controls.
c No significant intervention difference between experimental and control groups

Table 4. Characteristics of studies - multicomponent exercise training

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Multicomponent versus stretching/toning								
Barnes (2013)	Four conditions: Multicomponent (Exer. Int) or Stretching (Exer. Cont.) + Computer games (Cog. Int) or educational DVDs (Cog. Cont). 1. Cog. Int/Exer. Int 2. Cog. Int/ Exer. Cont 3. Cog Cont/Exer. Int. (EG) 4. Cog. Cont/Exer. Cont. (CG)	Double-blind. EG: 3 x 1h per week for 12 weeks. 10 min warm up + 30 min aerobic training + 5 min cool down + 10 min strength training + 5 min stretching. Aerobic training: target 60-75% of max HRR. CG: Same protocol without aerobic training. FU: PT.	126 subjects were randomized. EG n=31 and CG n=32. Age range: >65. EG: M^{age}: 71.1 (5.5). EG 3MSE (0-100): 94.6 (5.6). CG: M^{age}: 73.9 (6.3). CG 3MSE: 94.8 (4.7).	Immediate recall[c] (RAVLT) Delayed recall[c] Verbal fluency (letter[c], category[c]) Proc. Speed[c] (DSST) Inhibition[c] (Eriksen Flanker Test) Visuospatial processing[c] (UFOV) Attention (TMT A-B[c], divided[c], selective[c])	No data to calculate.	Not described adherence rate. AE 9%.	ITT analysis. Results similar when dropouts excluded.	No significant differences on cognitive function between EG and CG. The study suggested that the amount of activity is more important than type of exercise.
Multicomponent versus no exercise active control								
Liu Ambrose (2008)	Two conditions: 1. Otago home based exercise program: Strength + balance + aerobic training (EG). 2. Guideline care (CG).	Single-blind. 1. EG: 3 x 30 min per week for 6 months. Strength: 5 exercises lower limbs. Progressive Intensity: 0.9-9 kg load increment as required. Aerobic training: walk 2/week for 6 months. 2. CG: Comprehensive geriatric assessment and treatment. FU: PT.	74 subjects were randomized EG n=36 and CG n=38. Age range: >70. Global cognitive function: MMSE>24. EG: M^{age}: 81.4 (6.2). EG MMSE: 28.0 (2.0). CG: M^{age}: 83.1 (6.3)- CG MMSE: 28.0 (1.6).	Attention (Stroop C-W[a], TMT B[c]). Working memory[c] (Verbal Digit Backward test).	Stroop W-C: -0.48 TMT B: -0.06 Verbal digit backward: -0.39	Adherence rate of 25% 3 days/week, 57% 2 days/week and 68% 1 day/week. AE: 2 patients low back pain because exercise.	EG group 12.8% improvement in Stroop while control had 10.2 deterioration.	Home based exercise program significantly improved executive function (attention) in EG vs CG.

Multicomponent versus no intervention

Klusmann (2010)	Three conditions: 1. Exercise training (EG): Strength + Aerobic + balance + coordination + flexibility. 2. Computer course (CC) 3. Control group (CG).	Double-blind. 1. EG: 3 x 1.5h per week for 6 months. 75 sessions in total. 2. Computer: Cognitive tasks. 3. CG: Habitual life. FU: PT.	259 subjects were randomized EG n=91, CC n=92 and CG n=76. Age range: 70-93. Global cognitive function: MMSE>26. EG: M^{age}: 73.6. EG MMSE: 28.76. CC: M^{age}: 73.6. CG MMSE: 28.8. CG: M^{age}: 73.5. CG MMSE: 28.84.	Immediate recall (story[a], word[c]). Delayed recall (story[a], word[a]). Verbal fluency[c] Attention (Stroop C-W[c], TMT A-B[a])	Immediate recall story: 0.61 Immediate recall word: 0.31 Delayed recall story: 0.67 Delayed recall word: 0.64 Verbal fluency: 0.2 Stroop C-W: 0.16 TMT A-B: -0.57	Not described.	The increase in EG in immediate and delayed story recall was approximately 26% and 40%, respectively. Performance on TMT in EG improved 10% approximately.	Similar improvements on were found in EG and CC vs CG.
Vaughan (2014)	Two conditions: 1. Exercise training (EG): Aerobic + Strength + Motor skills. 2. Control group (CG)	Single-blind. 1. EG: 2 x 1h per week for 16 weeks. 32 sessions in total. Aerobic training: Steps with music. Intensity: 3-4/10 RPE. Strength training: Upper, lower body and core muscles. 3 exercises 2 sets x 6-8 reps. Intensity: Start without load and progressive increment of 1 kg. 2. CG: Waiting list. FU: PT.	49 women were randomized EG n=25 and CG n=24. Age range: 65-75. Global cognitive function: ≥31 Telephone interview Cognitive Status (TICS). EG: M^{age}: 69.0 (3.1). EG TICS: 38.3 (4.1). CG M^{age}: 68.8 (3.5). CG TICS: 36.9 (3.0).	Inhibition[a] (COAST) Verbal fluency[a] (COWAT) Working memory[c] (LNS) Proc. Speed[c] (Deary-Liewald Reaction Time Task). Attention[a] (TMT A-B)	COAST: -0.57 COWAT: 0.38 LNS: -0.03 Proc. speed (simple reaction time): -0.2 Proc. speed (choice reaction time): 0.11 TMT A: -0.69 TMT B: -0.38	Adherence rate of 85% EG.	Significant differences in Brain Derived Neurotrophic Factor (BDNF) between EG vs CG.	Exercise training had an important role in promoting cognitive health. Neurogenesis is likely the reason whereby exercise induced improvement in cognitive functioning.

Napoli (2014)	Four conditions: 1. Exercise training (EG): Aerobic + Strength + Flexibility + Balance. 2. DIET: Diet. 3. DIETEXER: Diet + Exercise. 4. Control group (CG).	1. EG: 3 x 1.5h per week for 52 weeks. 15 min flex + 30 min aerobic + 30 min strength + 15 min balance. Aerobic training: Start 65% of max HRR and progress 70-85% of max HRR. Strength training: 9 exercises upper and lower body. Start 1-2 sets x 8-12 reps. 65%RM and progress 2-3 sets x 6-8 reps. 80%RM. FU: PT.	107 subjects were randomized EG n=26, DIET n=26, DIETEXER n=28 and CG n=27. Age range: >65. Global cognitive function: MMSE>24. EG M^{age}: 70 (4). CG M^{age}: 69 (4).	Global Cognitive function[a] (3MSE). Verbal fluency[a] (Word List Fluency Test) Attention[c] (TMT A-B)	No data to calculate.	Adherence rate of 88% EG.	EG improved 2.8 points 3MSE versus 0.1 CG. EG improved 4.1 Word Fluency test while CG had deterioration -0.8.	Multicomponent program had positive impact on verbal fluency and global cognitive function compared with CG.
Tarazona - Santabalbina (2016)	Two conditions: 1. Exercise training (EG). 2. Control group (CG).	1. EG: 5 x 65 min/session per week for 24 weeks. Intervention: aerobic + strength + coordination + balance + flexibility. Aerobic training: Start 40% of max HRR and progress to 65% of max HRR. Strength training: Elastic bands isometric + concentric + eccentric exercises upper and lower body. Start 25%RM and progress to 75%RM.	100 subjects were randomized EG n=51 and CG n=49. Age range: >70. Global Cognitive Function: MMSE>24. EG M^{age}: 79.7 (3.6). EG MMSE: 26.5 (5.3). CG M^{age}: 80.3 (3.7). CG MMSE: 27.3 (5.8).	Global Cognitive Function[a] (MMSE)	MMSE: 0.67	Adherence rate of 47.3% EG.	EG improved 9% in MMSE after the intervention.	EG improved significantly cognitive function compared with CG.

EG = experimental group; CG = control group; CC: Computer Course; DIET = Diet; DIETEXER = Diet and Exercise; FU = follow up; AE: Adverse Event; PT = post training; Mage = mean age; (SD or SE) = (Standard Desviation or Standard Error); MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; UFOV = Useful Field of View; DSST = Digit Symbol Substitution Test; Stroop C-W = Stroop colour – word; TMT= Trail Making Test; COAST = California Older Adult Stroop Test; COWAT = Controlled Oral Word Association Test; LNS = Letter Number Sequencing; 3MSE = Modified Mini Mental Examination; HRR = Hear Rate Reserve; ITT: Intention To Treat; RM: Repetition Maximum.

a Significantly greater improvement for training compared to control.
b Significant training effects for experimental group from baseline to PT; no significant effect for controls.
c No significant intervention difference between experimental and control groups.

3.2. Quality (risk of bias)

Of the included studies, 66.67% presented adequate sequence generation (14 of 21 RCT).[25-38] Only a few studies included in the review (47.62%) reported allocation concealment (10 of 21). [27-30;32-37] Of the studies 71.43% specifically reported blinded assessment of outcomes (15 of 21). [25-39] All of the RCTs included in the review described losses to follow up and exclusions (21 of 21)[25-45] and 76.19% of the studies used an intention to treat analysis (16 of 21).[25-29;31-39;41;42]. Of the studies, 90.48% were free of selective reporting of outcomes.[25-34;36-43;45] Details are described in Table 5.

Table 5. Assessment risk of bias

Articles	**1**	**2**	**3**	**4**	**5**	**6**	**Score**
Aerobic training							
Oken (2006)	Y	N	Y	Y	Y	Y	5/6
Smiley-Oyen (2008)	Y	N	Y	Y	Y	Y	5/6
Muscari (2009)	N	N	Y	Y	Y	Y	4/6
Albinet (2010)	N	N	N	Y	N	Y	2/6
Legault (2011)	N	N	U	Y	Y	Y	3/6
Ten Brinke (2015)	Y	Y	Y	Y	Y	Y	6/6
Vidoni (2015)	Y	Y	Y	Y	Y	Y	6/6
Resistance training							
Cassilhas (2007)	N	N	N	Y	Y	Y	3/6
Kimura (2010)	N	N	U	Y	N	Y	2/6
Liu Ambrose (2010)	Y	Y	Y	Y	Y	Y	6/6
Liu Ambrose (2012)	Y	Y	Y	Y	N	Y	5/6
Nagamatsu (2012)	N	N	U	N	N	U	2/6
Forte (2013)	N	N	N	Y	N	Y	2/6
Van de Rest (2014)	Y	N	Y	Y	Y	Y	5/6
Best (2015)	Y	Y	Y	Y	Y	Y	6/6
Multicomponent training							
Liu Ambrose (2008)	Y	Y	Y	Y	Y	Y	6/6
Klusmann (2010)	Y	Y	Y	Y	Y	Y	6/6
Barnes (2013)	Y	Y	Y	Y	Y	N	5/6
Vaughan (2014)	Y	Y	Y	Y	Y	Y	6/6
Napoli (2014)	Y	Y	Y	Y	Y	Y	6/6
Tarazona-Santabalbina (2016)	Y	N	Y	Y	Y	Y	5/6

Criteria items: 1. Was the randomization sequence generation adequate? 2. Was the treatment allocation concealed? 3. Was the outcome assessor blinded to the intervention? 4. Were losses to follow up and exclusions correctly described? 5. Was intention to treat analysis used for statistical analyses? 6. Are reports of the study free of suggestion of selective outcome reporting?
Unsure (U), Yes (Y), No (N).

3.3 Aerobic exercise training versus stretching/toning

Across the included studies, no significant differences were found in outcomes associated with memory domain in the aerobic exercise group compared with the stretching/toning group. [25;27;44] Significant improvements associated with aerobic exercise training in one attention task (WCST) of the 17 outcomes associated with the executive function domain were reported in four trials[25;26;40;44] and significant pre-post intervention improvement in one attention outcome (Stroop W-C) was also found in the intervention group but not in the stretching/toning group in one trial.[26] No differences between groups in other cognitive outcomes were identified.[44] None of the studies analyzed the maintenance effects of the intervention.

3.4. Aerobic exercise training versus no exercise active control/no intervention

In the three trials in which an aerobic exercise training group was compared with no active exercise or no intervention control groups, there were no significant differences identified between these groups in the 9 outcomes associated with memory function. However, members of the aerobic exercise group demonstrated significantly greater improvements in their performance on a global cognitive function assessment (MMSE) when compared with control group members in one trial.[39] Considering the outcomes associated with executive function in older adults, no significant differences in the 23 outcomes were reported between the aerobic training and control groups in three trials.[25;28;41] No differences were observed between groups in other cognitive outcomes.[28;41] No studies explored maintenance effects.

3.5. Resistance exercise training versus stretching/toning

Significantly greater improvements in three immediate recall (ROF-IR and RAVLT) and associative memory tasks (Memorizing face scene pairs) of the 4 memory domain outcomes when comparing the resistance exercise group with the stretching/toning group were reported in four trials.[27;32;42;44] For outcomes associated with the executive function domain, the resistance training groups demonstrated significantly greater improvements when compared with the control groups in nine reasoning, attention (Stroop W-C and TMT A-B), working memory (DSF, CBTB and Verbal Digit Backward) and processing speed (DSST) tasks of the 21 outcomes assessed in five RCTs[29;32;42;44;45] and significant pre-post-intervention differences were reported in the experimental group but not in the control group in one trial.[45] Conflict resolution was assessed as an additional executive function outcome in two trials; significant improvements were found in the resistance exercise group but not in the control group in one trial[30] and no between groups differences were observed in the other trial.[44] Best et al., 2015 analyzed the maintenance effects of the study conducted by Liu Ambrose and colleagues[29] one year post-intervention.

3.6. Resistance exercise training versus no exercise active control/no intervention

Between groups comparisons indicated no significant differences in the 3 outcomes associated with the memory cognitive domain assessed in one trial.[31] On the other hand, significant improvements were reported in one working memory task (DSF) of the 8 measures of executive function in two trials.[31;43] None of the included studies measured the maintenance effect of the intervention.

3.7. Multicomponent exercise training versus stretching-toning/no active exercise control

The results of the included trials revealed no significant differences between the multicomponent exercise training group and the control group in the 2 memory outcomes assessed in one trial.[35] Significant improvements were found in one attention task (Stroop W-C) of 9 outcomes related to the executive function domain in two trials.[33;35] No significant differences between groups were observed in the other cognitive outcomes in one trial.[35] Maintenance effects were not analyzed in these studies.

3.8. Multicomponent exercise training versus no intervention

In the trial in which a multicomponent training group was compared with a no intervention control group, the multicomponent group performed significantly better than did the control group on three immediate recall (story test) and delayed recall tasks (story and word test) of the 4 memory domain outcomes.[34] Significantly greater improvements were also found when comparing the multicomponent exercise training group to the no intervention group in four attention (TMT A-B), verbal fluency (COWAT and Word List Fluency Test) of 9 outcomes associated with executive function in three trials.[34;36;37] Global cognitive function (3MSE and MMSE) and other cognitive measures, such as inhibition (COAST), were analyzed in three trials, all of which reported that the multicomponent group achieved significantly better results than did the control group.[36-38] None of the four studies included follow-up assessments.

4. Discussion

The main aim of the review was to analyze the effects of aerobic exercise training, resistance training and multicomponent training on the cognitive performance of older adults without known cognitive impairment. Thirteen of the 21 RCTs that were included in this review reported significant improvements in the exercise training group in at least one cognitive outcome associated with memory domain, executive function or composite measures of cognitive function after the intervention. Despite this fact, significant differences were not found between groups for most of the cognitive outcomes. Furthermore, the great variability in RCT procedures and exercise training protocol features make it difficult to perform a specific statistical analysis, including a meta-analysis, for better understand the relationship between physical exercise training and cognitive performance.

4.1. Exercise training type

4.1.1. Aerobic training

Despite the beneficial effects observed in cognitive outcomes with aerobic exercise training in previous meta-analyses[5;8], aerobic exercise was associated with an improvement in neurocognitive functioning in older adults with and without cognitive impairment. The results obtained across individual trials in this review failed to support any consistent evidence about cognitive benefits associated with aerobic exercise training. Only one trial reported significant benefits in memory domains[44] and few studies found significant improvements in executive function after deploying an aerobic exercise training protocol.[26;40;44] Our results agreed with reviews that concluded that there is lack of consistent evidence to demonstrate the beneficial effects of aerobic exercise training on cognitive performance in older adults without known cognitive impairment.[6;18;46] Several factors could explain modest cognitive gains associated with aerobic training and the details are described below.

4.1.2. Resistance training

Some authors paid attention the effects of resistance training on cognitive performance in older adults and consistent results had not obtained. Despite this fact, some reviews provided results to suggest that cognitive improvements were associated with resistance training[19], while other reviews had not observed consistent evidence to support this hypothesis.[4;20;47] In our review, we found large variations in the magnitude of improvement in memory domain[32;42;44] with resistance exercise training and most of the trials presented significant improvements in executive function in at least one cognitive outcome.[29;30;42;44;45] Therefore, our findings suggested that moderate-high intensity and progressive resistance training could have a beneficial effect on executive function in older adults without known cognitive impairment, but more evidence based on exercise effects on executive measures was required. An emerging theory for explaining these cognitive benefits was that exercise increased production of several growth factors, such as BDNF and IGF-1.[48] Findings from animal studies[12;13] provided consistent evidence for the future study of physiologic mechanisms that caused the effect of exercise on cognitive function in older adults.[47] Future studies should also explore new stimulus of training as High Intensity Interval Resistance Training (HIRT) on cognitive function in healthy older adults. This training modality could have positive effects on cognitive performance in this population.

4.1.3. Multicomponent training

New exercise training modalities have recently been developed to optimize functional capacity and physical fitness in older adults. Multicomponent exercise training, in which aerobic and resistance training are combined with other training components such as balance and/or flexibility, is the most effective training modality to improve functional capacity in frail older adults[49-51] and to prevent disability.[52] Although the beneficial effects on physical function of this type of exercise training are well established, the evidence is less consistent regarding cognitive gains associated with multicomponent exercise training. Colcombe and Kramer[5] reported that combining aerobic and resistance training had better cognitive gains on executive tasks of attention and working memory than aerobic exercise training alone. Furthermore, a recent meta-analysis[53] observed that multicomponent exercise training should be a good strategy to improve cognitive function in younger adults (aged > 50 years), regardless the cognitive status. Our findings in this review supported this assessment, as multiple RCTs observed significant improvements on executive tasks of attention[33;34;36], verbal fluency tasks[36;37] and global cognitive function tasks[37;38] in exercise training groups compared with the control groups. The inclusion of resistance training as a component of the exercise training protocol could be the reason for cognitive gains in the intervention group in specific executive tasks, but further research is needed to determine the possible cognitive benefits of multicomponent exercise training program.

Future RCTs should also consider multidomain intervention in this population, in which exercise training is combined with other treatments, such as cognitive training and social enrichment, to optimize the cognitive performance and prevent cognitive impairment.[54] On the other hand, some studies including older adults with mild cognitive impairment but with younger age inclusion criteria (i.e. 50-55 years or older)[55;56] also showed the feasibility of exercise training in this population, as well as the relevance of physical exercise in the elderly with minimal or no cognitive impairment.

4.2. RCTs with less consistent evidence versus epidemiological and cross-sectional studies

Discrepancies between the consistent evidence reported in animal, epidemiological and cross-sectional studies contrast with the less consistent results observed in RCTs. There are several factors that could explain large variations obtained across individual trials in the magnitude of changes on cognitive performance with different exercise training modalities and, in this way, find explanations for the conflicting results observed between observational and experimental studies.

4.2.1. Baseline physical performance

Participants PA levels at baseline was a considerable factor to consider to analyze changes on cognitive performance with exercise training in older adults. A trial recruited participants who were already engaged in regular physical exercise[25] and other studies reported differences in sedentary definition. Some RCTs excluded participants if they performed more than an hour of physical exercise per week[34-37], other studies included participants with more active lifestyles than the sedentary population[38] and some RCTs used validated questionnaires to assess PA level before randomization.[28;40] Therefore, it is complicated to draw consistent conclusions considering baseline differences between studies in subject features. On the other hand, epidemiological and cross–sectional studies examined the risk of cognitive impairment based on baseline PA levels[14;15] or the relationship between PA levels in different stages of life and the likelihood of developing cognitive decline in later life.[16] These studies reported that individuals with higher levels of PA had better cognitive function[6;17] or were at a reduced risk to experience cognitive decline compared with participants who had a less active or sedentary lifestyle. Consequently, subject baseline PA differences between studies included in this review could be one of the reasons to explain large variations in the magnitude of the improvements on cognitive outcomes. Future trials would benefit from control baseline PA levels or classifying participants considering this variable to analyze the cognitive gains of exercise training.

4.2.2. Length of intervention and follow up

Differences in the intervention duration and follow-up period between studies may be one of the reasons to clarify discrepancies between the short and long-term effects of exercise training on the cognitive performance in older adults. If exercise could reverse or delay the effects of age-related cognitive decline, interventions performed over a longer time would produce more relevant alterations in cognitive gains than short-term protocols.[18] Previous longitudinal studies have shown higher PA and structured exercise were associated with more global or regional brain volumes in later life in both grey matter and white matter.[57-59] Therefore, there is consistent evidence to support the association between brain atrophy and PA[60] and brain atrophy has been associated with the change in cognitive ability in multiple studies.[61-64] However, RCTs are usually much shorter than longitudinal studies, which would make it more complicated to observe cognitive differences between groups. In our review, most of the RCTs ranged from 12 weeks to 6 months, and only one trial reported follow-up data from a previous study.[32] No consistent results were found in our review considering that similar cognitive gains were obtained in longer interventions such as one year or more[29;30;37;39] compared with shorter interventions.[36;40;45] An interesting finding is that in longer interventions while the exercise training group improved or maintained the performance of cognitive tasks, participants in the control group had deterioration after the intervention period.[29;30;37;39] New RCTs are required with longer interventions and follow-up periods to analyze the maintenance effects of exercise training on the cognitive performance in older adults and it would be interesting to complement those interventions with neuroimaging techniques to understand the changes in cognitive abilities.

4.2.3. Exercise training protocol differences and adherence

Many factors had vital importance in the intervention effect on cognitive gains, such as the efficiency of the intervention and the adherence to training sessions. The first determinant to consider was the exercise training protocol description. The great variety in exercise training protocol features may have an important influence on cognitive results heterogeneity.

Although the optimum dose of exercise training for the improvement of cognitive function has yet to be established, some RCTs included in our review failed to meet the aerobic training recommendations for older adults[65] of 150 minutes of exercise training at moderate intensity[25;27;44] or the resistance training recommendations[66] of one or more sets of 10-15 repetitions at moderate intensity with a resting interval of 2-3 minutes between sets.[27;42;44] The combination of aerobic and resistance training with other training modalities such as balance or flexibility, have positive effects on the physical fitness and the functional capacity in older adults[67-69], but there is a lack of consistent evidence to show that multicomponent training results in improved cognitive performance. On the other hand, subjects classified as "active populations" or "high-activity groups", which surpassed the recommendations mentioned above.[70;71] Well defined exercise training protocols that meet all minimum recommendations would facilitate comparisons between studies and might report better results on cognitive gains.

The lack of details in exercise training program progression during the intervention make it difficult to determine the efficiency of the intervention.[25;35;41;43;44] In our review, 7 of the 21 RCTs failed to report these exercise training program characteristics. The inclusion of this methodological information may help to understand the discrepancies on cognitive benefits between studies.

The adherence to training sessions is essential to induce adaptations associated with exercise training programs. A low-adherence rate might result in low physical activity levels in the intervention group and large variations in adherence in RCTs may contribute to inconsistent results. Our findings supported this view and in those RCTs for which the attendance rate to training sessions was less than 70%, no significant differences were found in memory and executive function outcomes between the exercise training group and the control group.[25;27;33] However, studies with an attendance rate of 85% or higher reported significant improvements in the intervention group in memory, executive function and global cognitive function tasks.[36;37;40;45]. In comparison with epidemiological studies, older adults with high levels of PA are usually engaged in regular exercise training over longer periods. Therefore, RCTs should include in the data analysis only participants who reach a minimum number of training sessions to determine the inherent effects of exercise training on cognitive performance in the data analysis.

4.3. Inconsistent results across RCTs

Other factors may explain the differences that were found in RCTs on cognitive outcomes based on the role of exercise training in older adults. First, participant inclusion criteria varied between studies. Some trials included participants who were already physically active[25], while the eligibility criteria of other studies required participants to be sedentary[35-37;41] or frail older adults.[38] Moreover, large variations were observed when the methodological quality across RCTs was analyzed. Interestingly, trials in which multicomponent training was performed had the best scores in the assessment of the risk of bias and reported the largest significant improvements on cognitive function compared with other training modalities.

4.3.1. Cognitive outcomes measurement

Regarding the cognitive outcomes that were examined, a great variety of cognitive tests were measured to analyze the effects of exercise on memory and executive function and could explain the lack of consistent evidence obtained in this review. Consequently, a consensus of the appropriate measures of cognitive function[18;20] and use computer-based tasks would be interesting to standardize and improve sensitivity of cognitive assessment. Although our findings suggested that resistance training could have an influence on prefrontal cortex and could have a positive effect on executive function, exercise training benefits on cognitive outcomes associated with episodic memory are less consistent. Therefore, further research is needed to explore physiologic and neuromuscular changes in different brain areas to understand the relationship between exercise training and memory domain.

4.4. Limitations of the review

Considering the limitations of the previous review[11], a meta-analysis was not conducted because of the great variation in methodologies between studies and because of the few RCTs that included each exercise training modality. A meta-analysis would help to understand the inherent effects of exercise training on cognitive performance in older adults but the RCTs methodological characteristics of the RCTs made it difficult to perform this analysis.

A crucial limitation of this review that made it difficult to draw consistent conclusions was the large variation in methodological aspects between RCTs. The lack of details about the exercise training protocol and the load-training progression during the intervention reduced the reproducibility of the trials and failed to show any consistent evidence.[33;41;44] The variability of exercise training features (frequency, intensity, time, type) also contributed to the explanation of inconsistent results.

The heterogeneity of the cognitive tests used to measure different cognitive domains, such as memory and executive function, was one of the principle reasons for large variations in the cognitive benefits between studies, and sometimes, discrepancies were obtained after analyzing the same domain in the same trial.[29;33;34;42;44]

Unfortunately, despite the fact that we focused on "no known cognitive impairment" and we tried to specify a "without cognitive impairment" term using the MMSE test scores at baseline (cut-off point of 23/30), some RCTs did not report baseline cognitive function scores[25;26;45] or they used another test to assess global cognitive function[35;36;41]. Therefore, a portion of subjects over the age of 65 and even more older adults over the age of 75 may have cognitive impairment but several of included studies have not done sufficient cognitive evaluation to detect a difference. Moreover, other global cognitive function test appears to be more sensitive than cut-off point greater than 23 in the MMSE test for detection of early or mild cognitive impairment.[72] Finally, high scores on the global cognitive function at baseline could also explain the lack of improvement after the intervention because participants may have already cognitively been at the ceiling.

4.5. Conclusions and future recommendations

In accordance with previous studies summarized by Colcombe and Kramer[5], results from this review suggest that multicomponent exercise training may have the most positive effects on cognitive function in older adults. However, caution should be taken regarding the training intervention period, as well as the method used to control training intensity. Furthermore, the duration of exercise training programs made it difficult to compare short-term effects of RCTs with trials performed over a longer period. Longer interventions and follow-up periods in RCTs may facilitate the comparison of results with epidemiological and cross-sectional studies. A large variability in the cognitive outcomes between included studies might be the reason for discrepancies in cognitive results. The standardization of cognitive measures, especially on executive function, would improve the comparability between RCTs. In conclusion, a standardization of the methodological aspects of RCTs is required to clarify the relationship between exercise training and cognition and to reduce discrepancies with animal, epidemiological and cross-sectional studies.

Conflict of interest

All authors have nothing to declare.

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Chapter 2

Effect of exercise intervention on functional decline in very elderly patients during acute hospitalization: a randomized clinical trial

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Chapter 3

Physical exercise improves function in acutely hospitalized old patients

1. Introduction

The functional impairment that commonly occurs in the elderly during acute hospitalization is not only caused by the disease condition that causes hospitalization.[1] Older adults, especially frail, frequently have low levels of functional reserves, which increases their vulnerability to the adverse consequences of acute hospitalization and frequently leads to an incomplete recovery of the preadmission functional status[2], new disability[3], or even continued functional decline.[4]

Health care systems are still poorly adapted to old patients with frailty, disability, multimorbidity and polypharmacy[5] with low in-hospital mobility being directly associated with functional deterioration at discharge and, even more so, at follow-up.[6;7] In this context, exercise and early rehabilitation play an essential role to prevent functional and cognitive impairment during hospitalization in the elderly.[8;9] Yet, only a few randomized controlled trials (RCT) have examined the potential benefits of exercise training for acutely hospitalized elderly patients, and the effects of in-hospital exercise intervention on objective measures of functional outcomes are uncertain.[10]

Gait is the central component of a patient´s functional ability to perform basic activities of daily living (ADLs).[11] Yet, assessment of functional capacity during ADLs (*e.g.*, the ability to rise from a chair) is currently limited to performance time measurements, potentially missing important information about the test subtasks. In this regard, modern body-fixed sensors based on accelerometers and gyroscopes allow to objectively assess functional capacity in clinical practice.[12;13]

The main aim of the present study was to analyze the effects of a multicomponent exercise training intervention on functional capacity during ADLs in older adults during stay in an Acute Care for Elderly (ACE) unit. We hypothesized that the aforementioned intervention would improve patient´s functional capacity, as well as maximal muscle strength and muscle power output of lower limbs.

2. Methods

2.1. Design

The study is a secondary analysis of a RCT (NCT02300896) performed according to the SPIRIT 2013 and the CONSORT statement for transparent reporting.[14;15] It was conducted in the ACE unit of the Department of Geriatrics in a tertiary public hospital (*Complejo Hospitalario de Navarra*, Spain). This Department has 35 beds allocated and its staff is composed of 8 geriatricians (distributed in the ACE unit, orthogeriatrics and outpatient consultations). Admissions in the ACE unit derive mainly from the Accident and Emergency Department, with heart failure, pulmonary and infectious diseases being the main causes of admissions. When the disability generated by the pathology that caused admission in the ACE unit requires long-term care, patients are usually referred to another, medium-stay hospital.

Acutely hospitalized patients who met inclusion criteria were randomly assigned to the intervention or control (usual care) group within the first 48 hours of admission. Usual care is offered to the patient by the geriatricians of our department and consists of standard physiotherapy focused on walking exercises for restoring the functionality conditioned by potentially reversible pathologies. A formal exercise prescription was not provided at study entry and patients were instructed to continue with the current activity practices through the duration of the study. The study followed the principles of the Declaration of Helsinki and was approved by the institutional Clinical Research Ethics Committee. All patients or their legal representatives provided written consent.

2.2. Participants and randomization

The participants were acute hospitalized, prefrail/frail older men and women recruited within the first 48 hours of admission to the ACU by the geriatricians. Later, a trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥75 years, Barthel Index score ≥60 points, being able to ambulate (with/without assistance), and to communicate and collaborate with the research team. Exclusion criteria included expected length of stay <6 days, very severe cognitive decline (i.e., Global Deterioration Scale score =7), terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, or extremity bone fracture in the past 3 months.

After the baseline assessment was performed, participants were randomly assigned following a 1:1 ratio, without restrictions. The randomization sequence was generated using www.randomizer.org. The assessment staff were blinded to the main study design and group allocation. Participants were explicitly informed and reminded not to discuss their randomization assignment with the assessment staff.

2.3. Intervention

The usual care group received habitual hospital care, which included physical rehabilitation when needed. The exercise training was programmed in two daily sessions (morning and evening) of 20-minutes duration during 5–7 consecutive days (including weekends) supervised by an experiences fitness specialist. Adherence to the exercise intervention program was documented in a daily register. A session was considered completed when ≥90% of the programmed exercises were successfully performed. The details of the exercise training protocol have been described previously.[16;17]

Each session was performed in a room equipped ad hoc in the geriatric acute care unit. Exercises were adapted from the multicomponent physical exercise program "Vivifrail" to prevent weakness and falls.[18] The morning sessions included individualized supervised progressive resistance, balance, and walking-training exercises. The resistance exercises were tailored to the individual's functional capacity using variable resistance training machines (Matrix, Johnson Health Tech, Ibérica, S.L.; Torrejón de Ardoz, Spain and Exercycle S.L., BHGroup; Vitoria, Spain) aiming at 2–3 sets of 8–10 repetitions with a load equivalent to 30–60% of the estimated one-repetition maximum (1-RM).[16;17] Participants performed three exercises involving mainly lower-limb muscles (squats rising from a chair, leg press and bilateral knee extension) and one involving the upper-body musculature (seated bench ('chest') press). They were instructed to perform the exercises at a high speed to optimize muscle power output, and care was taken to ensure proper exercise execution. Balance and gait retraining exercises gradually progressed in difficulty and included the following: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), altering the base of support, and weight transfer from one leg to the other. The evening session consisted of functional un-supervised exercises using light-loads (*i.e.*, 0·5–1 kg anklets and hand-grip ball), such as knee extension/flexion, hip abduction and daily walking in the corridor of the acute care unit with a duration based on the clinical physical exercise guide "Vivifrail".[18]

As soon as the clinician in charge of the patient considered that their hemodynamic situation was acceptable, and the patient could collaborate, the following endpoints were assessed and the intervention was started. Endpoints were also assessed on the day of discharge.

2.4. Endpoints

The primary endpoint was change in functional capacity during hospitalization (*i.e.*, from admission to discharge) as assessed with the Short Physical Performance Battery (SPPB) and the 6-meter Gait Velocity Test (GVT, including also the GVT under dual-task conditions). Secondary endpoints were maximal muscle strength and muscle power output during leg press exercise.

2.4.1 SPPB, 6-meter GVT and dual-task gait

The SPPB includes usual walking speed over 4 meters, a balance test, and the Five Times Sit to Stand Test (FTSST), with the sum of the three individual categorical scores yielding the final SPPB score (range points: 0 (worst)- 12 (best)).[19] For the 6-meter GVT, patients were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway. In addition to the habitual GVT, two different dual-task gait tests were performed, the arithmetic GVT (aGVT) and verbal GVT (vGVT), in which gait velocity was measured while the participants counted backward aloud from 100 down to one or named animals aloud, respectively. The results of the functional tasks were recorded using an inertial sensor unit (Xsens MTx; Xsens Technologies B.V., Enschede, The Netherlands) attached over the lumbar spine (L3) to record the acceleration data. The sampling rate of these recorded data was 100Hz.

2.4.2. Movement pattern in functional tasks

The measured gait parameters were as follows: stride regularity, gait symmetry, and gait variability. The measurements were obtained for three directions: anterior-posterior, medio-lateral and vertical.

The FTSST was divided into three different phases to assess the movement-related parameters of each sit-stand-sit cycle: impulse, sit-to-stand, and stand-to-sit. Once these three different phases were identified, we analyzed the peak of power value of the sit-to-stand phase.

2.4.3. Maximal dynamic muscle strength and muscle power output of the lower limbs

Maximal dynamic strength was measured based on the results of a one-repetition maximum (1RM) reached in bilateral leg press exercise (Exercycle S.L.; BHGroup, Vitoria, Spain) as follows. After 1RM values were determined, the participants performed ten repetitions at the maximal possible velocity at intensities of 50% of 1RM to determine the maximum power in the propulsive phase. The power output was recorded by connecting a velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain).

2.5. Statistical analysis

All analyses were performed by "intention-to-treat" approach. Between-group comparisons of continuous variables were conducted using linear mixed models. Time was treated as a categorical variable. The models included group, time, and group by time interaction as fixed effects, and participants as random effect. For each group, data are expressed as change from baseline (admission) to discharge, determined by the time coefficients (95% confidence interval (CI)) of the model. The primary conclusions about effectiveness of exercise intervention were based on between-group comparisons of change in functional capacity from baseline (beginning of the intervention) to hospital discharge, as assessed with the SPPB and the GVT (including both dual-task conditions) and determined by the time by group interaction coefficients of the model. Comparisons between groups of secondary endpoints were also performed using the same statistical method. Normality of data was checked graphically and through the Kolmogorov Smirnov test. All comparisons were two-sided, with a significance level of 0.05. MATLAB and Statistics Toolbox Release 2013b (Mathworks, Inc., Natick, MA) software was used for the data analysis and IBM-SPSS v20 software for the statistical analysis.

3. Results

The study flow diagram is shown in **Figure 1**. Baseline demographic and clinical characteristics of the participants (N = 130) are presented in **Table 1.** The median length of hospital stay was 6 days in both intervention and control groups. The number of completed morning and evening sessions per patient in the intervention group averaged 5±1 and 4±1, respectively. Mean adherence to the intervention was 98±5% for the morning sessions (*i.e.*, 286 completed sessions of 292 total possible sessions) and 83±32% for the evening sessions (197 of 237). There were no adverse events related to the intervention and no patient had to interrupt the exercise training or had their hospital stay modified because of the study protocol.

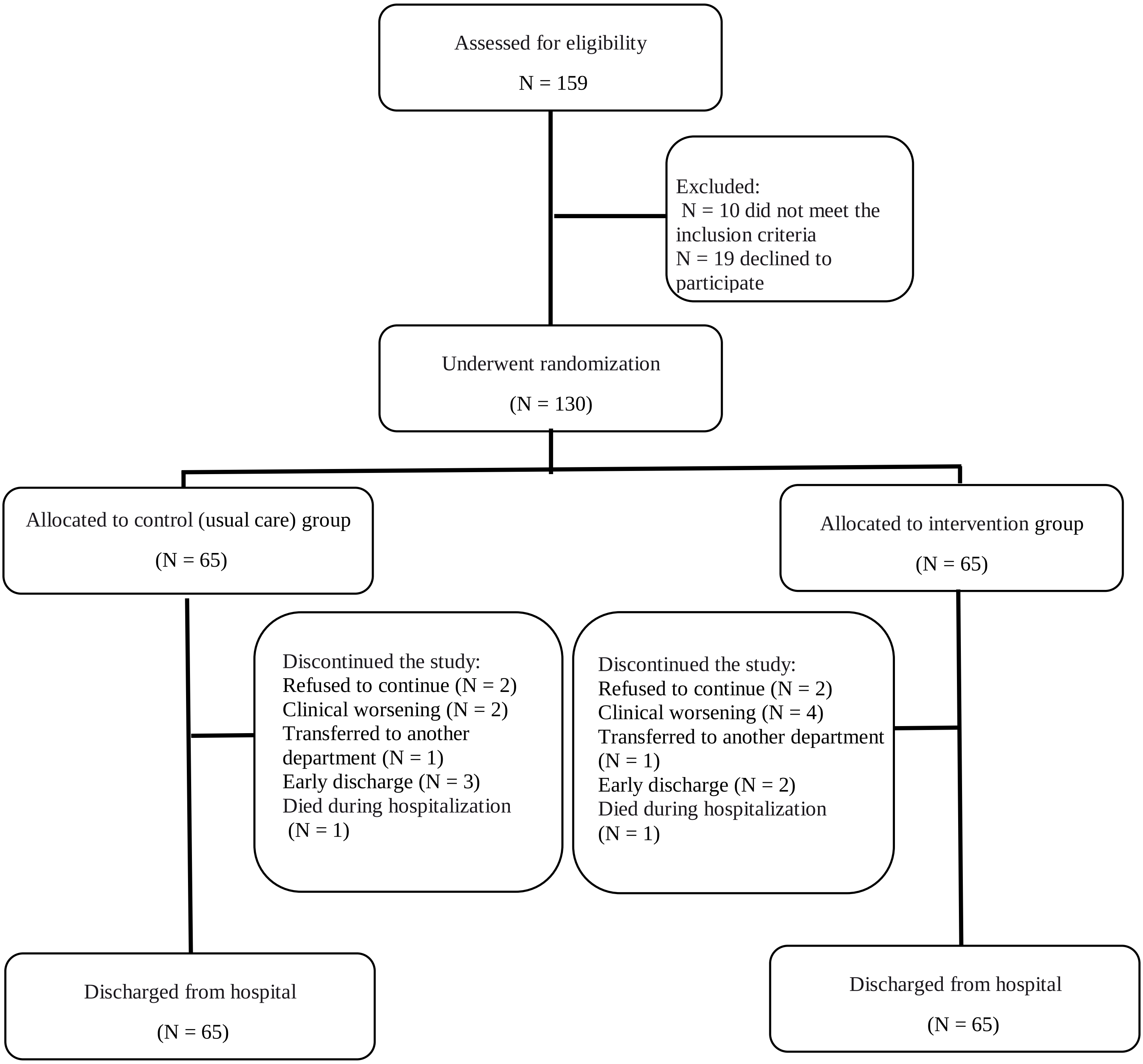

Figure 1. Study flow diagram

Table 1. Baseline characteristics of the subjects

	Control group (n=65)	**Exercise group (n=65)**
Age, years	86 ± 5	88 ± 4
Men/women	33/32	33/32
BMI, kg/m^2	27 ± 6	27 ± 4
Education, %		
< 12 years	11	21
≥ 12 years	89	79
Length of stay, median (IQR)	6 (1)	6 (0)
Barthel Index score, points	86 ± 15	86 ± 15
Falls last year, %		
0	34	26
1-2	40	42
> 2	20	26
No data available	6	6
Cognition (MMSE score), points	23 ± 4	22 ± 5
CIRS-G	13± 4	12 ± 5
Admission reason (type of disease), %		
Pulmonary	36	35
Cardiovascular	18	18
Infectious	11	15
Gastrointestinal	9	11
Neurological	5	5
Other	21	16

Data are presented as mean ± SD unless otherwise indicated. BMI, Body Mass Index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; GDS, Geriatric Depression Scale; IQR, Interquartile Range; MMSE, Mini Mental State Examination.

The primary analyses showed that the exercise intervention program provided a significant benefit over usual care. At discharge (i.e., at the primary time point), the exercise group showed a mean increase of 1.7 points in the SPPB scale (95% CI, 0.98, 2.42) over the usual care group (**Table 2** and **Figure 2**). We also found significant differences between groups in change from admission to discharge in the SPPB scale expressed as separate subtask scores (all $p<0.05$, **Table 2**). Patients in the intervention group showed improvements at discharge compared with baseline in functional capacity as measured by the GVT (including both dual-task conditions, vGVT and aGVT) whereas no such trend was found in the control group (**Table 2** and **Figure 2**). Significant differences between groups were also observed in all the secondary outcomes related to maximal muscle strength and power output (all $p<0.01$, **Table 2** and **Figure 2**).

Table 2. Results of study endpoints by group.

	Control group	Exercise group	Between-group difference (95%CI)	p value between groups
Primary endpoints				
SPPB, total score	0.30 (-0.20, 0.81)	2.00 (1.49, 2.51)	1.70 (0.98, 2.42)	<0.001
Balance score	0.17 (-0.13, 0.46)	0.71 (0.42, 1.00)	0.53 (0.12, 0.96)	0.012
Gait ability score	0.13 (-0.10, 0.36)	0.47 (0.25, 0·70)	0.34 (0.02, 0.66)	0.038
Leg strength score	0.05 (-0.22, 0.33)	0.86 (0.58, 1.13)	0.80 (0.41, 1.19)	<0.001
GVT, $m \cdot s^{-1}$	0.004 (-0.033, 0.043)	0.144 (0.106, 0.182)	0.140 (0.086, 0.194)	<0.001
Verbal GVT, $m \cdot s^{-1}$	-0.001 (-0.025, 0.033)	0.151 (0.119, 0.184)	0.152 (0.105, 0.199)	<0.001
Arithmetic GVT, $m \cdot s^{-1}$	-0.004 (-0.044, 0.035)	0.115 (0.077, 0.153)	0.120 (0.065, 0.174)	<0.001
Secondary endpoints				
Bilateral leg press 1RM, kg	-1.82 (-6.83, 3.20)	15.00 (10.92, 19.08)	16·82 (10.35, 23.29)	<0.001
PW50, watts	1.13 (-13.51, 15.78)	31.00 (20.86, 41.14)	29.87 (12.06, 47.68)	0.002

Data in each group are expressed as change from baseline (admission) to discharge (mean and 95% confidence interval). Abbreviations: GVT, gait velocity test; PW50, leg power at an intensity of 50% of 1RM test; RM, repetition maximum; SPPB, Short Physical Performance Battery.

Regarding the functional tasks analyzed by the inertial sensor unit, significant differences between groups were found for the time to complete the FTSST as well as for the peak of power during the sit-to-stand phase (all p<0.05, **Table 3**). Significant differences between groups in the walking pattern after the intervention are presented in **Table 3**. Patients in the intervention group improved gait performance in terms of gait regularity and symmetry in the GVT and dual-task at discharge compared with admission values, whereas such improvements were not observed in the control group.

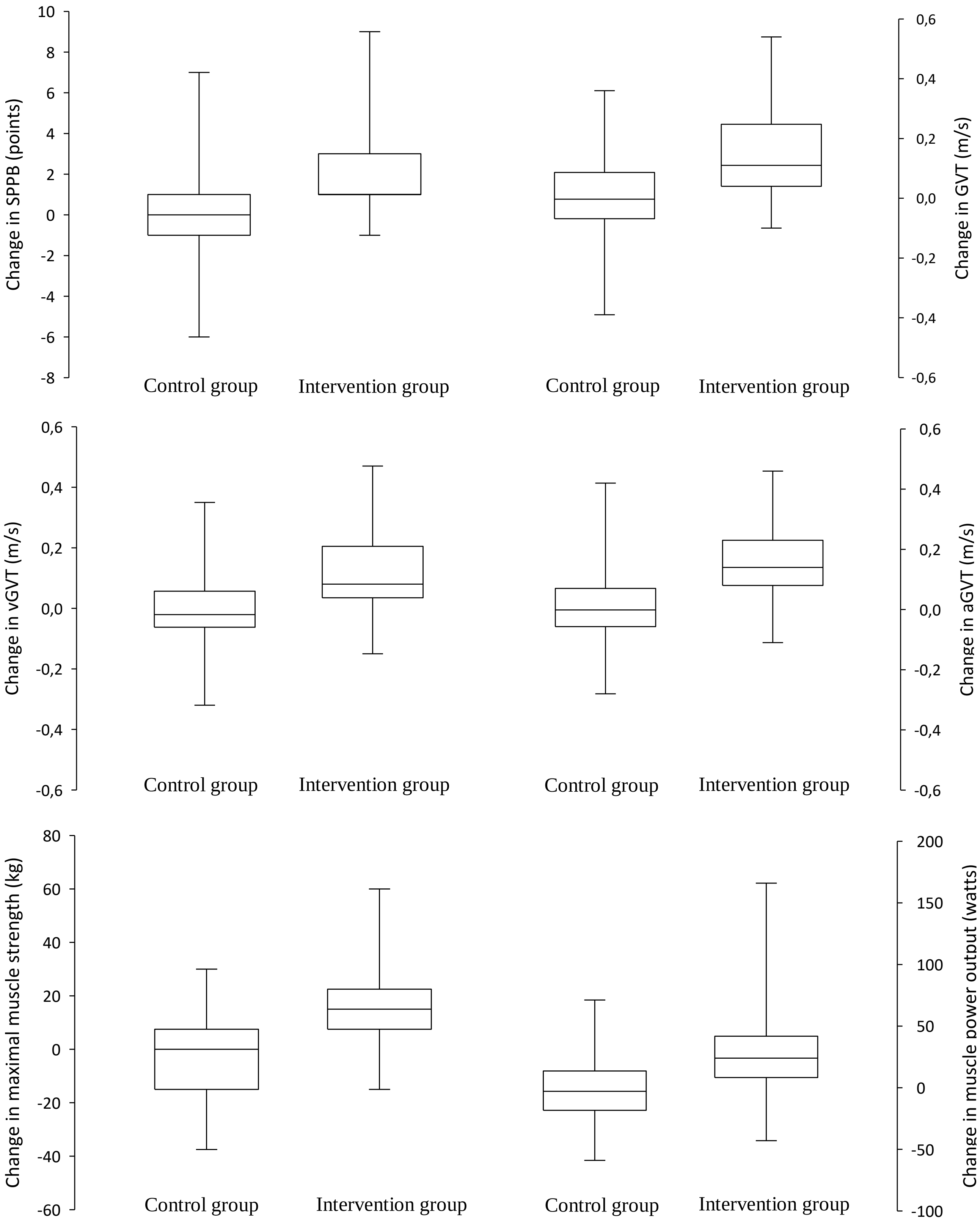

Figure 2. Box plot showing within group changes from baseline to discharge in the Short Physical Performance Battery (SPPB) test, Gait Velocity Test (GVT) including verbal (vGVT) and arithmetic (aGVT) dual-task conditions, and maximal dynamic muscle strength and muscle power output during bilateral leg press exercise

Table 3. Movement pattern in the Five Times Sit to Stand Test (FTSST) and walking tests by group

		Control group	Exercise group	Between-group differences (95%CI)	p value between groups
		FTSST			
Time, s		-2.36 (-4.90, 0.18)	-6.33 (-8.72, -3.94)	-3.97 (-7.46, -0.48)	0.029
Repetitions, n		-0.07 (-0.49, 0.35)	0.27 (-0.15, 0.69)	0.34 (-0.24, 0.94)	0.258
Sit-to-stand phase					
Peak power, W·kg		-0.12 (-0.43, 0.19)	0.39 (0.11, 0.66)	0.51 (0.09, 0.92)	0.021
		GVT			
Stride regularity	AP	0.051 (0.003, 0.099)	0.052 (0.004, 0.100)	0.001 (-0.068, 0.067)	0.986
	ML	0.056 (0.008, 0.104)	0.019 (-0.028, 0.066)	-0.037 (-0.105, 0.030)	0.282
	V	0.030 (-0.014, 0.073)	0.100 (0.056, 0.143)	0.070 (0.008, 0.131)	0.029
Symmetry	AP	-0.010 (-0.075, 0.055)	0.009 (-0.055, 0.073)	0.019 (-0.072, 0.110)	0.687
	ML	-0.038 (-0.109, 0.034)	0.012 (-0.057, 0.083)	0.049 (-0.052, 0.150)	0.340
	V	0.032 (-0.032, 0.096)	-0.087 (-0.151, -0.022)	-0.119 (-0.209, -0.028)	0.012
CoV step time		-0.031 (-0.051, -0.010)	-0.047 (-0.067, -0.026)	-0.016 (-0.045, 0.013)	0.283
		Verbal GVT			
Stride regularity	AP	0.015 (-0.041, 0.071)	0.058 (0.004, 0.112)	0.043 (-0.035, 0.122)	0.281
	ML	0.005 (-0.053, 0.062)	0.010 (-0.045, 0.065)	0.005 (-0.075, 0.085)	0.901
	V	0.053 (0.010, 0.107)	0.021 (-0.025, 0.071)	-0.032 (-0.097, 0.031)	0.392
Symmetry	AP	-0.010 (-0.079, 0.060)	-0.077 (-0.143, -0.011)	-0.067 (-0.163,0.028)	0.173
	ML	0.014 (-0.056, 0.084)	0.047 (-0.019, 0.113)	0.033 (-0.064, 0.129)	0.508
	V	-0.009 (-0.083, 0.066)	0.004 (-0.067, 0.076)	0.013 (-0.090, 0.116)	0.809
CoV step time		-0.027 (-0.053, -0.001)	-0.045 (-0.070, -0.020)	-0.018 (-0.054, 0.018)	0.320
		Arithmetic GVT			
Stride regularity	AP	0.026 (-0.029, 0.080)	0.083 (0.030,0.136)	0.058 (-0.019, 0.134)	0.143
	ML	-0.010 (-0.061, 0.041)	0.004 (-0.045, 0.054)	0.014 (-0.056, 0.085)	0.690
	V	0.023 (-0.012, 0.058)	0.078 (0.043, 0.113)	0.056 (0.006, 0.105)	0.031
Symmetry	AP	0.042 (-0.029, 0.112)	-0.094 (-0.163, -0.025)	-0.136 (-0.235, -0.037)	0.008
	ML	0.034 (-0.035, 0.105)	-0.032 (-0.101, 0.038)	-0.066 (-0.164, 0.032)	0.196
	V	0.024 (-0.052, 0.101)	-0.009 (-0.084, 0.065)	-0.034 (-0.141, 0.073)	0.541
CoV step time		-0.012 (-0.044, 0.019)	-0.033 (-0.064, -0.002)	-0.021 (-0.065, 0.023)	0.355

Data in each group are expressed as change from baseline (admission) to discharge (mean and 95% confidence interval). Abbreviations: AP, anterior-posterior; CoV, coefficient of variability; GVT, gait velocity test; FTSST, five times sit to stand test; ML, medio-lateral, V, vertical.

4. Discussion

The main findings of the present study were the enhancements achieved in the functional endpoints (i.e., SPPB, GVT and dual-task GVT), maximal strength and muscle power output in older adults admitted in an ACE after a median of only five days of multicomponent exercise training. In addition, there were improvements in movement pattern in different functional tasks in the exercise training group compared with the control group after the intervention.

Acute illness requiring hospitalization is often a sentinel event for many older adults[20] and functional decline is one of the negative short-term consequences of bed rest during hospital stay.[1] In our study, however, short-term hospitalization did not have a major impact on functional capacity in the control group. Several reasons could explain the maintenance of functional capacity in those patients. First, the poor health status of hospitalized elderly upon admission may improve with the proper management of their acute disease. Second, the length of hospital stay was lower than in other studies that have investigated the functional consequences of hospitalization in the elderly.[6] Finally, the older adults were admitted to an acute geriatric ward in which comprehensive and multidisciplinary protocols are already established and functional recovery is the main objective to prevent iatrogenic disability.[5]

Recent evidence has failed to support the functional benefits of a mobility program consisting on ambulation and a behavioral strategy to encourage mobilization in this population.[21] In agreement with previous studies, however, our results indicate that a more complete exercise training intervention including walking and other training modalities such as resistance (power) and balance training could represent an optimal treatment strategy to improve functional capacity in acutely hospitalized older adults. Indeed, it seems that multicomponent exercise training is the most effective intervention for improving overall physical outcomes in frail older adults including muscle strength and power output and for preventing disability and other adverse events associated with aging.[22;23] On the other hand, although the beneficial effects of exercise training on physical function in the general elderly population are well established, the evidence is less definitive regarding cognitive gains, at least in hospitalized old people. In our study, significant differences were observed between groups in changes at discharge compared to admission in both dual-task gait performance and movement-related parameters. The findings support that multicomponent exercise training may produce the most positive effects on cognitive function in older adults.[24;25]

Regarding the issue of functional assessment in hospitalized patients, different screening tools are available to identify older adults at risk for functional decline during hospitalization and after discharge.[26] However, there is currently no "gold standard" for measuring functional trajectory during hospitalization. In this regard, we used an innovative inertial sensor unit to analyze changes in daily functional tasks including walking and rising from a chair. Concerning the ability to stand from a seated position, patients in the intervention group improved the performance at discharge compared with admission, whereas lower values were observed in the control group. Among these parameters, peak power improvement at discharge in the intervention group is the cornerstone for counteracting the age-related functional decline.[23;27-29] This unique finding has major implications for clinical practice, first because skeletal muscle power decreases earlier and faster than muscle strength with advancing age and second because muscle power output is a more discriminant predictor of functional performance in older adults.[27-29] Functional ability, and the maintenance of autonomy and independence, is the starting point of healthy aging, a term established by the World Health Organization (WHO) in its first world report on aging and health.[30] In agreement with the WHO framework, our results indicate that multicomponent exercise training, with special emphasis on muscle power training, is the intervention of choice for maintaining function and avoiding a trajectory towards frailty/disability in acutely hospitalized older adults and exercise prescription should be considered as a front-line treatment to prevent hospital-acquired iatrogenic disability.

Our study has some limitations, including mainly the patient´s difficulty for completing all the measurements at both hospital admission and discharge. Notably, only 9% of the participants were able to achieve the full-tandem position in both assessments. Another possible limitation was that only old patients with relatively good functional capacity at preadmission (*i.e.*, Barthel Index score ≥60 points) were included in the RCT; thus, the results may not be generalizable to the entire hospitalized elderly population. Also, we did not collect functional data prior to the acute illness. However, functional status two weeks prior to admission was indirectly measured with the Barthel Index score at baseline. In turn, our study has several strengths. An innovative exercise training program of few days (i.e., 5±1 and 4±1 morning and evening sessions, respectively) was effective to reverse the functional decline associated with hospitalization in acutely hospitalized very old patients. Moreover, an inertial sensor unit was used for measuring and monitoring the functional trajectory after an innovative exercise training program. Typically, in-hospital functional status and functional trajectory are measured using subjective self-reports scales based on ADLs or instrumental ADLs.[26] From a practical standpoint, the inertial sensor unit seems to be a feasible and sensitive tool for detecting changes in functional tasks that are associated with patient´s ability to perform ADLs.

5. Conclusions and implications

An individualized multicomponent exercise training program is an effective therapy to improve functional capacity (i.e., balance, rising from a chair, GVT, dual-task performance), maximal muscle strength and power performance in very old, prefrail/frail patients during acute hospitalization. Monitoring functional capacity with latest screening tools (*i.e.*, inertial sensor units), enables to detect enhancements in movement pattern in functional tasks associated with ADL after an innovative exercise training program in hospitalized older adults. Our findings support the need for a shift from the traditional disease-focused approach in hospital ACE to one that recognizes functional capacity as a crucial vital sign during hospitalization.

Declaration of interests

All authors have nothing to declare. The authors declare non competing interest.

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Chapter 4

Role of muscle power output as a mediator between gait variability and gait velocity in hospitalized older adults

1. Introduction

Acute medical illnesses and subsequent hospitalization are crucial events leading to disability in the elderly population.[1-4] Despite the resolution of the reason for hospitalization, older medical patients are often discharged with a new major disability.[5] This loss of functional capacity is strongly associated with caregiver burden, higher resource use, institutionalization, and death.[6-9]

Functional ability, and the maintenance of autonomy and independence, is the starting point of healthy aging, a term established by the World Health Organization (WHO) in its first world report on aging and health.[10] Although functional decline has become a key outcome after hospitalization and multiple screening tools are available to identify older adults at risk of functional decline during and after hospital stays[11;12], there is currently no "gold standard" for measuring functional impairment in hospitalized older medical patients.[13]

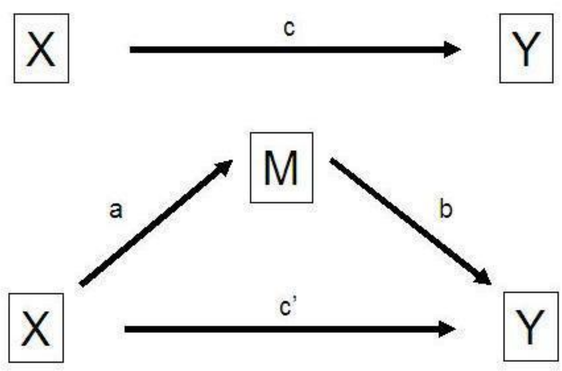
Gait is essential for performing activities of daily living (ADL).[14] Gait analysis is currently limited to performance time measurements in the clinical practice, lacking many measurable facets other than velocity.[15] With advanced age, there are increases in motor variability, especially in gait[16;17] and gait variability has been widely related to muscle system impairments.[18] Although increased gait variability is already recognized as a predictor of future falls in frail older adults[15;19], its relationship with muscle power output in hospitalized older medical patients as a confounder and therefore as a factor to be controlled in multivariable models is not yet clear. With mediation analysis, researchers might instead answer, for example, how muscle power output is related to gait variability and/or gait velocity. Recent studies have investigated the association between gait pattern and frailty syndrome[17;20], muscle mass quality[21], and cognitive impairment[22] in the elderly population. In this regard, modern body-fixed sensors based on accelerometers and gyroscopes allow for objectively assessing functional capacity in clinical practice.[23]

The purpose of this study was to compare gait characteristics and muscle performance endpoints of hospitalized older adults admitted to an acute care unit (ACU) based on functional status presented at admission, and to determine the association underlying the gait impairment. We hypothesized that acutely hospitalized older adults would present differences in gait pattern and muscle performance endpoints (i.e., maximal muscle strength and muscle power output) based on the Short Physical Performance Battery (SPPB) score obtained at admission, and muscle power output would play a key role on gait performance.

2. Methods

2.1. Theoretical model of mediation analysis

The detection of mediators is an important methodological issue in many fields, including psychology, medicine and biology. In general, outcome mediators address the mechanisms by which an effect occurs. Baron and Kenny[24] postulated several criteria for the analysis of a mediating effect: a mediator (M) that transmits the effect of a predictor variable (X) to an outcome variable (Y) in a causal sequence such that (X) causes (M) and (M) causes (Y). Summarizing, a mediating variable explain de process by which one variable causes another, using the Sobel test[25] that shows whether indirect effect are significant or not. The theoretical analyses of mediation, for example, can help researchers to move beyond answering if high levels of muscle power output lead to low levels of gait variability.



2.2. Sample population

The participants were acutely hospitalized older men and women admitted to a tertiary public hospital (*Complejo Hospitalario de Navarra*, Spain). The subjects were identified by geriatricians within the first 48 hours of admission to the ACU. A trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥75 years, Barthel index ≥60 points, being able to ambulate (with/without assistance), and to communicate and collaborate with the research team. The exclusion criteria were having very severe cognitive decline (*i.e*., global deterioration scale score ≥7 points), myocardial infarction or upper/lower extremity fracture in the past 3 months, or terminal illness. All the participants were informed about the nature and risks of the experimental procedures before obtaining their written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Navarra Clinical Research Ethics Committee, Spain (Pyto 23/2014).

2.3. Study design

This cross-sectional study was carried out to evaluate the physical performance of very old hospitalized patients based on the "*Vivifrail"* classification[26] at admission and to analyze the associations between gait variability and gait velocity with the aim of explaining gait disorders in hospitalized older medical patients. The data collection was performed from July 17, 2016, to August 30, 2017. The primary endpoints were differences in gait characteristics among groups as assessed with the 6-meter Gait Velocity Test (GVT, also including the GVT under dual-task conditions). Secondary endpoints were the maximal muscle strength of lower/upper limbs and muscle power output during leg press exercise. A mediation analysis was performed to examine the role of muscle power output between gait variability and gait velocity. The study is a subanalysis of the baseline data of a larger randomized clinical trial (RCT) with the purpose of analyzing the effects of a multicomponent exercise-training program for improving the functional capacity and cognition of acute elderly patients hospitalized for medical pathology[27] (NCT02300896).

2.4. Short Physical Performance Battery (SPPB)

The SPPB includes the usual walking speed over 4 m, a balance test, and the Five Times Sit to Stand Test (FTSST). The standing balance test required participants to maintain stances with their feet placed in side-by-side, semitandem and full-tandem positions for 10 seconds each. In the FTSST, participants had to rise five times from a chair with their arms across their chest as fast as possible. The scores assigned to the performance on each test ranged from 0 to 4 (maximum performance). Participants were categorized as "unable to perform" if they were not able to complete the test and if the physician or the participant felt that the test was unsafe. Scores of 1-4 for each task were assigned based on quartile performance for more than 5000 participants in the Established Populations for the Epidemiologic Study of the Elderly.[28] Considering the total score obtained at admission, hospitalized older adults were classified in four phenotype criteria using the classic performance-based SPPB such as: *i)* not frail if the SPPB score was 10-12 points, *ii)* prefrail if the SPPB score was 7-9 points, *iii)* frail if the SPPB score was 4-6 points, and *iv)* disabled if the SPPB score was 1-3 points.

2.5. Six-meter GVT and dual-task gait

For the 6-meter GVT, patients were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway. In addition to the habitual GVT, two different dual-task gait tests were performed, the arithmetic GVT (aGVT) and verbal GVT (vGVT), in which gait velocity was measured while participants counted backward aloud from 100 down to one or named animals aloud, respectively. The results of the functional tasks were recorded using an inertial sensor unit (Xsens MTx; Xsens Technologies B.V., Enschede, The Netherlands) attached over the lumbar spine (L3) to record the acceleration data. The MTx provides drift-free 3-dimensional (3D) orientation and kinematic data: 3-D acceleration, 3-D rate of turn (rate gyro) and 3-D earth magnetic field data. The sampling rate of these recorded data was 100Hz.

2.6. Gait pattern parameters

The measured gait parameters, which have been related to gait disorders[15;29-31] in frail older adults[21;32], were as follows: stride regularity, stride time, stride length, and the coefficient of variability of step time (CoV step time). Stride regularity was obtained from the autocorrelation sequence of the acceleration signal x.

Gait variability can be estimated by calculating the CoV step time, where t is the mean of step time across all steps and σ its standard deviation.
These measurements were obtained for three directions: anterior-posterior, medio-lateral and vertical.

2.7. Maximal dynamic muscle strength and muscle power output of the legs

Maximal dynamic strength was measured based on the results of a one-repetition maximum (1RM) reached in a bilateral leg press exercise (Exercycle S.L.; BHGroup, Vitoria, Spain) as follows. After 1RM values were determined, the participants performed ten repetitions at the maximal possible velocity at intensities of 50% of 1RM to determine the maximum power in the propulsive phase. The power output was recorded by connecting a velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain).

2.8. Maximal isometric muscle strength outcomes

Maximal isometric upper (right hand grip) and lower limb (right knee extensors and hip flexors) muscle strength were also assessed using a manual dynamometer.

2.9. Statistical analysis

Standard statistical methods were used to calculate the means and standard deviations (SD). Statistical normality was tested using both statistical (*Kolmogorov-Smirnov Test*) and graphical procedures (normal probability plots).

To investigate the differences between groups at admission based on functional status, hospitalized older adults were classified as not frail (NF), prefrail (PF), frail (F), and disabled (D). One-way analysis of variance (ANOVA) was used to assess mean differences between these categories, and pairwise *post hoc* difference were tested using the *Bonferroni* correction for multiple comparisons.

Finally, to examine whether the association between gait variability and functional capacity was mediated by muscle power output, linear regression models were fitted using the bootstrapped mediation procedures included in the PROCESS IBM-SPSS macro.[33] Data were analyzed using SPSS-IBM (Software, v.21.0 SPSS Inc., Chicago, IL, USA) and a p-value < 0.05 was considered statistically significant.

3. Results

Characteristics of the cohort are presented in **Table 1.** Overall, the patients had a mean age of 87.6 ± 4.8, and 48% were female.

The effects of functional status on gait velocity are summarized in **Figure 1**. Significant differences were found in gait velocity between the not frail and frail groups (0.76 vs. 0.47 m/s p < 0.001, respectively), not frail and disabled groups (0.76 vs. 0.29 m/s, p < 0.001), prefrail and frail groups (0.64 vs. 0.47 m/s p < 0.05), prefrail and disabled groups (0.64 vs. 0.29 m/s, p < 0.001), and frail and disabled groups (0.47 vs. 0.29 m/s, p < 0.001) in the habitual GVT. For the verbal GVT, significant differences were also observed between the not frail and frail groups (0.65 vs. 0.37 m/s p < 0.001, respectively), not frail and disabled groups (0.65 vs. 0.23 m/s, p < 0.001), prefrail and frail groups (0.52 vs. 0.37 m/s, p < 0.05), prefrail and disabled groups (0.52 vs. 0.23 m/s, p < 0.001), and frail and disabled groups (0.37 vs. 0.23 m/s, p < 0.001). Considering the arithmetic GVT, significant differences were identified between the not frail and frail groups (0.62 vs. 0.36 m/s p < 0.001, respectively), not frail and disabled groups (0.62 vs. 0.23 m/s, p < 0.001), prefrail and disabled groups (0.49 vs. 0.23 m/s, p < 0.001), and prefrail and disabled groups (0.49 vs. 0.23 m/s, p < 0.001).

Table 1. Baseline characteristics of the subjects

	Hospitalized older adults (n=130)
Age, years	87.56 ± 4.79
Men/women, n	66/64
BMI, kg/m^2	26.79 ± 5.06
Education, n (%)	
< 12 years	21 (16)
≥ 12 years	109 (84)
Barthel Index score, points	85.93 ± 15.08
SPPB, points	4.75 ± 2.66
Falls last year, n (%)	
0	39 (30)
1-2	54 (42)
> 2	29 (22)
No data available	8 (6)
MMSE score, points	22.54 ± 4.49
Shortened GDS, n (%)	
< 7 points	110 (85)
≥ 7 points	20 (15)
CIRS-G	12.83 ± 4.83
Admission reason, n (%)	
Pulmonary	46 (35)
Cardiovascular	24 (19)
Infectious	17 (13)
Gastrointestinal	13 (10)
Neurological	6 (4)
Other	24 (19)

Data are presented as mean ± standard deviation unless otherwise indicated. BMI=Body Mass Index; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; GDS=Geriatric Depression Scale; MMSE=Mini Mental State Examination; SPPB=Short Physical Performance Battery.

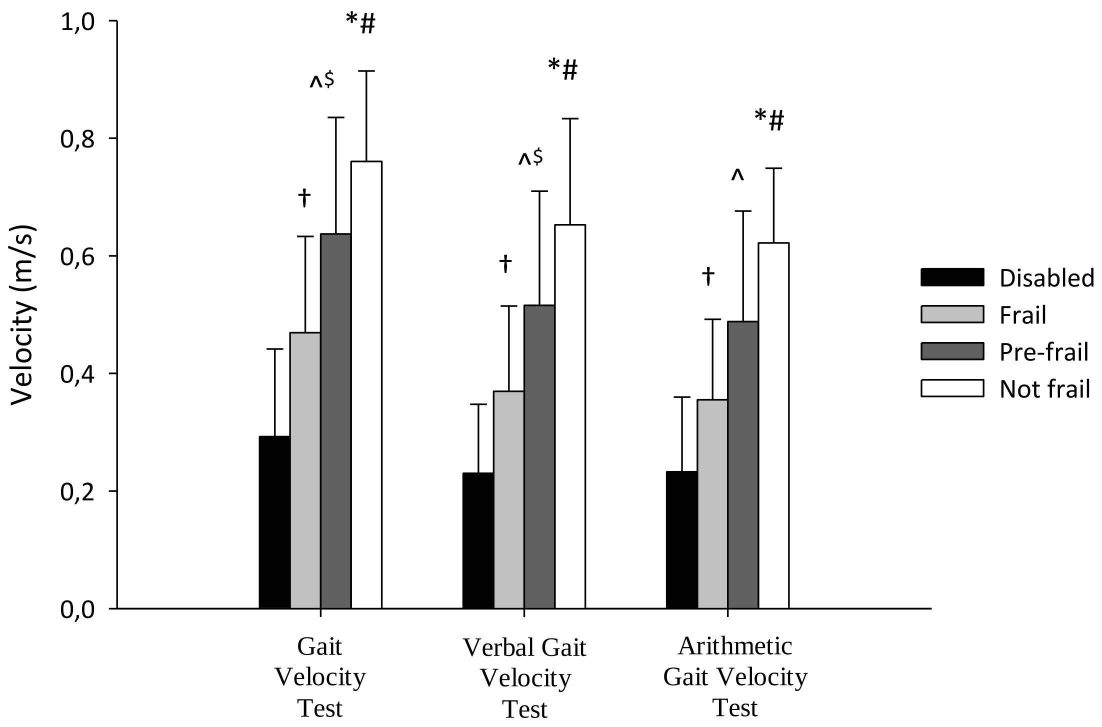


Figure 1. Results of gait velocity for the disabled, frail, pre-frail and not frail groups during the habitual Gait Velocity Test, verbal Gait Velocity Test and arithmetic Gait Velocity Test. Error bars represent standard deviations. † represents statistical significant differences ($p<0.05$) between disabled vs. frail groups. ^ represents statistical significant differences between disabled vs. pre-frail groups. * represents statistical significant differences between disabled vs. not frail groups. $ represents statistical significant differences between frail vs. pre-frail groups. # represents statistical significant differences between frail vs. not frail groups.

The significant differences between groups in terms of walking patterns in different task conditions are presented in **Table 2**. Compared with older adults with lower functional reserve, patients with better functional capacity at admission had better gait performance in terms of gait regularity, stride length and gait variability.

Regarding the muscle capacity of acutely hospitalized older adults, significant differences between groups were observed in secondary outcomes related to the maximal dynamic muscle strength and power output of the legs (all $p<0.01$, **Table 3**). Moreover, significant differences between groups were also found for the isometric knee extension and hip flexion measurements as well as for the hand grip force in this population (**Table 3**).

Table 2. Gait parameters values, and p-values between groups.

		Not frail	Pre-frail	Frail	Disabled	*Statistical significance*					
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	NF-PF	NF-F	NF-D	PF-F	PF-D	F-D
Gait Velocity Test (GVT)											
Stride regularity	AP	0.32 ± 0.11	0.41 ± 0.10	0.35 ± 0.13	0.30 ± 0.14						
	ML	0.24 ± 0.10	0.30 ± 0.14	0.33 ± 0.17	0.25 ± 0.14						
	V	0.35 ± 0.18	0.40 ± 0.14	0.26 ± 0.14	0.20 ± 0.12			*	*	*	
Stride time (s)		1.15 ± 0.19	1.35 ± 0.23	1.31 ± 0.34	1.37 ± 0.43						
Stride length (cm)		88.25 ± 17.63	81 ± 18.55	62.23 ± 22.41	42 ± 21.40		*	*	*	*	*
CoV step time		0.16 ± 0.06	0.12 ± 0.05	0.17 ± 0.09	0.20 ± 0.08					*	
Verbal Gait Velocity Test (vGVT)											
Stride regularity	AP	0.40 ± 0.19	0.34 ± 0.13	0.34 ± 0.14	0.34 ± 0.17						
	ML	0.36 ± 0.21	0.35 ± 0.17	0.34 ± 0.13	0.34 ± 0.17						
	V	0.39 ± 0.16	0.33 ± 0.16	0.23 ± 0.11	0.19 ± 0.12		*	*		*	
Stride time (s)		1.26 ± 0.34	1.43 ± 0.33	1.46 ± 0.47	1.45 ± 0.61						
Stride length (cm)		81.36 ± 25.5	76.57 ± 27.44	52.19 ± 23.40	35.69 ± 21.60		*	*	*	*	*
CoV step time		0.14 ± 0.10	0.14 ± 0.06	0.17 ± 0.08	0.19 ± 0.08						
Arithmetic Gait Velocity Test (aGVT)											
Stride regularity	AP	0.31 ± 0.14	0.32 ± 0.15	0.32 ± 0.16	0.29 ± 0.14						
	ML	0.32 ± 0.15	0.30 ± 0.14	0.31 ± 0.13	0.28 ± 0.17						
	V	0.25 ± 0.1	0.23 ± 0.11	0.20 ± 0.1	0.21 ± 0.13						
Stride time (s)		1.20 ± 0.38	1.50 ± 0.31	1.34 ± 0.42	1.43 ± 0.59						
Stride length (cm)		75 ± 25.67	70.6 ± 23.87	47.62 ± 20.42	35.37 ± 21.10		*	*	*	*	
CoV step time		0.19 ± 0.08	0.16 ± 0.06	0.19 ± 0.07	0.23 ± 0.14						

*$p<0.05$. AP=anterior-posterior; CoV=coefficient of variability; D=disabled; F=frail; ML=medio-lateral; NF= Not frail; PF=Pre-frail; SD=standard deviation; V=Vertical.
N = 118 participants completed the GVT, N = 110 for the verbal dual-task, and N = 103 for the arithmetic dual-task.

Table 3. Results of secondary endpoints of the study, and p-values between groups.

	Not frail	Pre-frail	Frail	Disabled	*Statistical significance*					
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	NF-PR	NF-F	NF-D	PF-F	PF-D	F-D
Maximal dynamic strength and power										
Bilateral leg press 1RM (kg)	95.9 ± 18.1	81.5 ± 30.6	62.4 ± 25.8	40.5 ± 23.4		*	*		*	*
PW50 (w)	239.7 ± 80.9	191.3 ± 79.1	106.7 ± 51.5	76.5 ± 50.6		*	*	*	*	
Maximal isometric strength										
Hand grip (kg)	23 ± 3.9	22.4 ± 6.3	17.9 ± 6.1	14.2 ± 5.6		*	*		*	*
Knee extension (N)	135.4 ± 34.1	113.6 ± 30	94.8 ± 34.5	94.8 ± 34.5		*	*		*	
Hip flexion (N)	131.7 ± 27.2	122.4 ± 32.8	89.5 ± 29.4	76.4 ± 23.9		*	*	*	*	

*p<0.05. D=disabled; F=frail; N=newton; NF= Not frail; PF=pre-frail; PW50=leg power at an intensity of 50% of 1RM test; RM=repetition maximum, SD=standard deviation.
N = 93 participants completed the bilateral leg press RM test, N = 85 for the power assessment.
Regarding maximal isometric force, analyses are based on N = 125 participants for the hand grip force, N = 87 for the knee extension, N= 119 for the hip flexion.

We showed **Figure 2** for mediation analysis. The effect of gait variability on functional capacity was mediated by the muscle power output of the legs. In the first regression step (equation a), gait variability was negatively related to the power output ($p \leq 0.01$). In the second step (equation c), the regression coefficient of gait variability on the dependent variable (gait velocity) showed a negative association ($p < 0.0001$). In the last regression model, the mediator variable (muscle power output) was positively associated with the dependent variable (equation b) ($p < 0.0001$). However, when power output was included in the model (equation c´), the regression coefficient remained significant, but the relationship was slightly attenuated. Using the Sobel test for mediation it was estimated 25% of the total effect of coefficient of variability of step time on gait velocity was mediated by muscle power output (indirect effect = -0.27; 95%CI, -0.59 to -0.05).

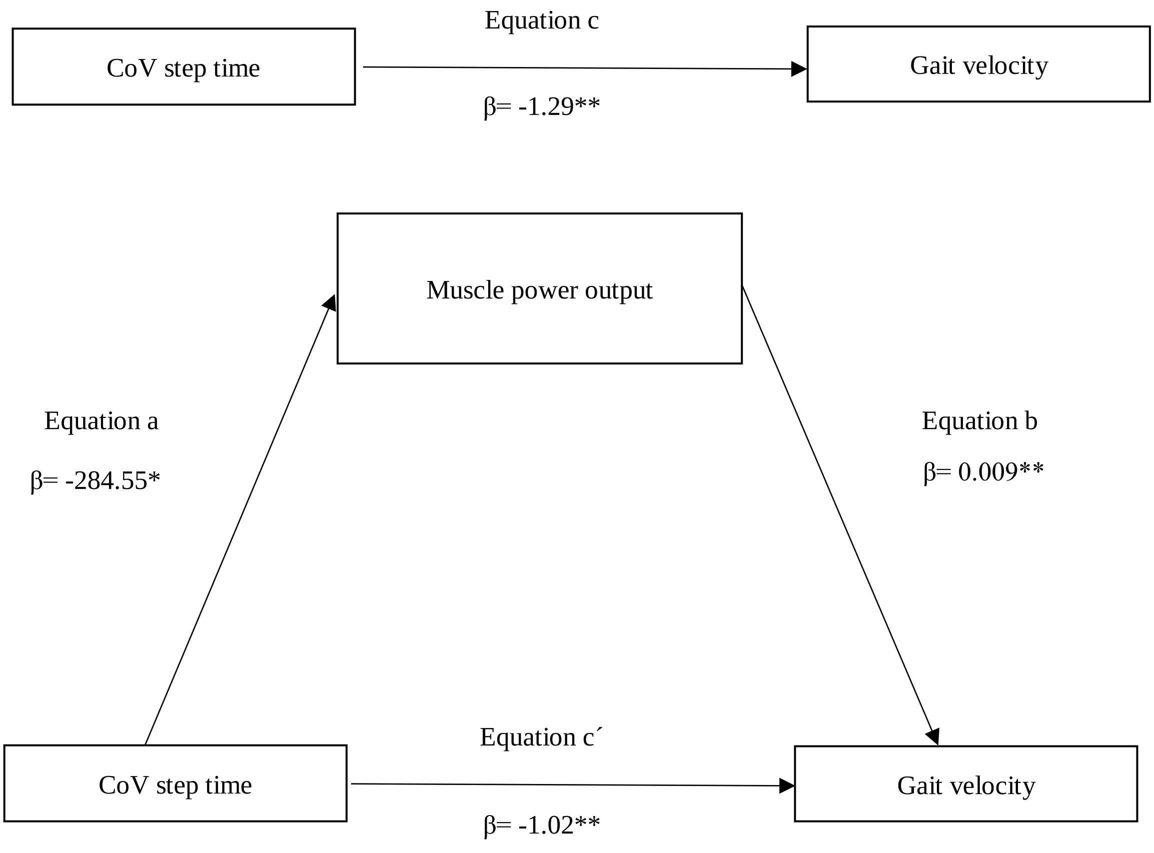


Figure 2. Muscle power output mediation models of the relationship between gait variability (coefficient of variability of step time) and gait velocity in the verbal dual-task.

4. Discussion

The main finding of the present study was the role of muscle power output as a potential mediator between gait variability and gait velocity. This result may suggest the importance of reducing gait variability and increasing power output to attenuate its negative association with functional capacity in acutely hospitalized elderly individuals. In addition, significant differences were observed between groups in the functional endpoint (*i.e.*, gait velocity) and gait pattern in different task conditions (GVT and dual-task GVT) based on the functional status presented at admission. The groups also differed significantly from one another in muscle capacity outcomes, including the maximal dynamic and isometric muscle strength of upper/lower limbs and the muscle power output of the legs. To the best of our knowledge, this is the first study to describe gait patterns using a simple automated technological tool in acutely hospitalized older adults and to compare movement-related differences between different groups based on functional status.

In older patients, acute illness requiring hospitalization is usually a sentinel event leading to loss of function in activities of daily living (ADL) and consequently, long-term disability.[34;35] According to the

Global Strategy and Action Plan on Healthy Aging currently being undertaken by WHO member states, the goal of health care systems should be to maintain a level of functional ability in older people who have, or are at high risk of, substantial losses of capacity and to ensure that this care and support is consistent.[10] In line with the WHO framework, adequate hospital care in older adults with acute medical disorders requires a comprehensive geriatric assessment (CGA) to identify those patients at highest risk of functional decline.[36] The ability to walk underlies many basic and instrumental ADL necessary for independence[14] and the appearance of difficulties in walking as a consequence of hospitalization or as a result of frailty associated progressive functional deterioration establishes a crucial point in the patient´s life / functional trajectory. In our study, gait velocity was demonstrated to be a discriminating factor among acutely hospitalized older adults, based on the functional status assessed at admission. Typically, several screening tools have been used to identify elderly patients at risk of functional decline during and after hospital admission.[11;12] However, screening instruments widely applied in clinical practice have limited predictive value.[13] The results of this study extend previous studies demonstrating that gait velocity is a quick, inexpensive, highly reproducible measure and may have particular value in identifying older patients at risk of poor health outcomes in an ACU.[37;38]

Adding an innovative tool such as an inertial sensor unit to the standard gait speed assessment is useful to understand the mechanisms underlying gait impairment in acutely hospitalized older patients. In the present study differences in step time variability were found between the prefrail and disabled groups in the habitual GVT. Our results are in agreement with previous studies, which provided empirical support that high gait variability is associated with frailty status in older adults.[15;32] A greater step time variability may represent impairment in the automatic stepping mechanism or worsening central motor control[19;39] and may lead to an increased risk of falls as a result of poor foot placement or insufficient postural stability.[40] Furthermore, gait alterations were also found in other parameters, such as stride length and stride regularity, in the habitual GVT and both dual-task conditions in those patients with less functional reserve compared with participants with better functional capacity. Stride length and cadence are the key determinants of gait velocity. The current study findings are consistent with previous research in older adults[41-43] and indicate that reduced gait velocity seems to result from a deficit in producing an appropriate stride length rather than stride frequency. A likely explanation for this fact is the differences observed between groups in terms of their lower limb maximal muscle strength and muscle power output at admission.

The quadriceps muscle is known to play a key role in the gait cycle. This muscle is mainly activated during the terminal swing phase and before the initial contact to stabilize the knee under loading and to prepare it for the weight.[44] Our results showed meaningful differences between groups in terms of leg extensor maximal dynamic and isometric muscle strength and power output values. Recently, Fragala et al.[45] observed that the muscle weakness of leg extensors was related to slow gait velocity in older adults, as well as handgrip force. In addition, differences in hip flexion maximal strength were also found at admission. Previous studies[41;46] have supported the notion that the reduction in step length, and hence gait velocity, is principally due to the limited hip extension caused by hip flexor contracture in the elderly individuals.

Several studies have suggested that muscle power output preservation is a crucial determinant for counteracting the age-related decline in functional capacity.[47-50] Our mediation analysis reveals that muscle power output mediates the relationship between gait variability and gait velocity in the verbal GVT, slightly weakening this relationship. The mechanisms whereby gait variability may negatively influence gait velocity in acutely hospitalized older adults are not clear. First, gait variability has been widely related to muscle system impairments[18] and has been considered a good marker of frailty[32] that may contribute to functional impairment in older adults. Second, the association between step time variability and muscle power has been previously described in the oldest old[21] and leg extensor peak power has been recognized as a predictor of gait velocity in frail elderly individuals.[51] From a practical standpoint, it may be suggested that exercise interventions aimed at improving muscle power (*i.e.*, muscle power training)[48] could reduce gait variability and ultimately improve gait velocity in acutely hospitalized older adults.

Our study has some limitations. First, only older adults with relatively good functional capacity at preadmission (Barthel Index score ≥ 60 points) were included in the study. Thus, these features make it difficult to generalize the results obtained to the entire hospitalized elderly population. Second, the cross-sectional nature of the study limits our ability to explore the role of muscle power in gait performance. Third, the assessment was not sensitive enough to detect differences in gait parameters and other outcomes between the not frail and prefrail groups. We did not collect functional data prior to admission. However, the functional status two weeks prior to admission was indirectly measured with the Barthel Index score at admission, but the risk of bias is likely to increase when retrospective information is recruited with this subjective self-report scale. Finally, only patients with gait pattern assessment at admission using the inertial sensor unit of the larger RCT (NCT02300896)[27] were included in the study. In turn, our study has several strengths, including the use of an inertial sensor unit for measuring functional capacity and the mediation analysis performed for understanding the role of muscle power as a potential mediator in the gait in older patients admitted to an ACU. Studies examining the dose-response relationship often incorporate multiple linear / logistic regression or covariance analysis to adjust for confounding / mediator variables; however, these statistical methods do not account for the percentage of the total explained by the potential mediators.

5. Conclusions/Relevance:

Muscle power output mediates the relationship between gait variability and gait velocity, slightly weakening this relationship. Thus, muscle power plays a key role in functional performance in acutely hospitalized older adults and its preservation is crucial for counteracting the age-related decline in functional capacity. Additionally, gait velocity and the proposed selection of walking parameters (stride regularity, stride length, CoV step time) can distinguish among acutely hospitalized older adults and can provide useful information for measuring and monitoring functional trajectory during the hospitalization.

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Conflict of interest: All authors have nothing to declare.

Author contributions: I confirm that each of the authors has read and concurs with the content in the final manuscript. The study protocol was developed by MLSA, AC, NMV and MI. Data acquisition and statistical analysis were done by MLSA, FZ, NM and MI. Finally, MLSA, FZ, AC and MI prepared the manuscript and revised it critically for intellectual content.

Sponsor´s role: None.

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Chapter 5

Adverse response to exercise intervention during acute hospitalization

1. Introduction

Adequate hospital care for older adults (≥75 years) with acute medical disorders is an important clinical issue in our ageing societies.[1-4] In this context, acute illness requiring hospitalization is a sentinel event in older adults, which can lead functional decline and frequently, long-term disability[5-7]. Loss of functional capacity is strongly associated with caregiver burden, higher resource use, institutionalization, and death.[8-11] Accordingly, this is a challenge that healthcare professionals and policy makers should prioritize given the expectations of further growth of the elderly population.[12]

Health care systems remain poorly adapted to meet the needs of old patients with frailty, disability, multimorbidity and polypharmacy,[13] and low in-hospital mobility is directly related to functional impairment at discharge and even more so at follow-up.[14;15] However, a recent randomized clinical trial (RCT) showed no significant benefit of an in-hospital mobility program and a behavioral strategy to encourage mobility in older patients´ ability to perform activities of daily living (ADL) after acute hospitalization.[16] In this context, tailored exercise interventions can play a key role in preventing functional decline and cognitive impairment in acutely hospitalized patients of advanced age (including octogenarians and nonagenarians).[12;17]

Despite the frequent reports of "average" exercise related-benefits there is, nevertheless, a wide inter-individual variability in the response to exercise training.[18] Under the same exercise conditions, some subjects, termed responders (Rs), achieve benefits after intervention, whereas others, termed non-responders (NRs; unchanged response) and adverse-responders (ARs; worsened response) do not.[19;20] To the best of our knowledge, the inter-individual analysis of exercise training effects has not been previously investigated in acutely hospitalized older adults. In addition, it remains unclear if the response influences in mortality following discharge.

The main aim of the present study was to assess the prevalence of these categories (as indicated by functional, strength and cognitive variables) under usual care or an individualized multicomponent exercise intervention applied in an Acute Care of the Elderly (ACE) unit. We also sought to examine the relationship between the aforementioned categories of each group with mortality at one-year post-discharge, and a possible influence of the clinical differences at admission on the assessed endpoints.

2. Methods

2.1. Design

The study is a secondary analysis of a RCT (NCT02300896)[12;17] conducted in the ACE unit of the Department of Geriatrics in a tertiary public hospital (*Complejo Hospitalario de Navarra*, Spain). This Department has 35 allocated beds and its staff is composed of 8 geriatricians (distributed in the ACE unit, orthogeriatrics and outpatient consultations). Admissions in the ACE unit derive mainly from the Accident and Emergency Department, with heart failure, pulmonary and infectious diseases being the main causes of admissions.

Acutely hospitalized patients who met inclusion criteria were randomly assigned to the intervention or control (usual care) group within the first 48 hours of admission. Usual care was offered to patient by the geriatricians and consists of standard physiotherapy focused on walking exercises for restoring the functionality conditioned by potentially reversible pathologies. A formal exercise prescription was not provided at study entry and patients were instructed to continue with the current activity practices through the duration of the study. The study followed the principles of the Declaration of Helsinki and was approved by the institutional Clinical Research Ethics Committee. All patients or their legal representatives provided written consent.

2.2. Participants and randomization

A trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥75 years, Barthel Index score ≥60 points, able to ambulate (with/without assistance), and to communicate and collaborate with the research team. Exclusion criteria included expected length of stay <6 days, very severe cognitive decline (i.e., Global Deterioration Scale score =7), terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, or extremity bone fracture in the past 3 months.

After the baseline assessment was performed, participants were randomly assigned following a 1:1 ratio, without restrictions (www.randomizer.org). Assessment staff were blinded to the main study design and group allocation. Participants were explicitly informed and reminded not to discuss their randomization assignment with the assessment staff.

2.3. Intervention

The usual care group received habitual hospital care, which included physical rehabilitation when needed. For the intervention group, exercise training was programmed in two daily sessions (morning and evening) of 20-minutes duration over 5–7 consecutive days (including weekends) supervised by a qualified fitness specialist. Adherence to the exercise intervention program was documented in a daily register. A session was considered completed when ≥90% of the programmed exercises were successfully performed.

Each session was performed in a room equipped ad hoc in the ACE unit. Exercises were adapted from the "Vivifrail" multicomponent physical exercise program to prevent weakness and falls.[21]. Morning sessions included individualized supervised progressive resistance, balance, and walking-training exercises. The resistance exercises were tailored to the individual's functional capacity using variable resistance training machines (Matrix, Johnson Health Tech, Ibérica, S.L.; Torrejón de Ardoz, Spain and Exercycle S.L., BHGroup; Vitoria, Spain) aiming at 2–3 sets of 8–10 repetitions with a load equivalent to 30–60% of the estimated one-repetition maximum (1RM). Participants performed three exercises involving mainly lower-limb muscles (squats rising from a chair, leg press and bilateral knee extension) and one involving the upper-body musculature (seated bench 'chest' press). They were instructed to perform the exercises at a high speed to optimize muscle power output, and care was taken to ensure proper exercise execution. Balance and gait retraining exercises gradually progressed in difficulty and included the following: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), altering the base of support, and weight transfer from one leg to the other. The evening session consisted of functional unsupervised exercises using light-loads (0·5–1 kg anklets and hand-grip ball), such as knee extension/flexion, hip abduction and daily walking in the corridor of the ACE unit with a duration based on the clinical physical exercise guide "Vivifrail".[21]

When the clinician in charge of the patient considered that the hemodynamic situation was acceptable, and the patient could collaborate, the following endpoints were assessed and the intervention was started. Endpoints were also assessed on the day of discharge.

2.4. Measures and endpoints

2.4.1. Measures of functional performance

The Short Physical Performance Battery (SPPB) and 6-meter Gait Velocity Test (GVT) were used to assess functional capacity. The SPPB includes usual walking speed over 4 meters, a balance test, and the Five Times Sit to Stand Test, with the sum of the three individual categorical scores yielding the final SPPB score (range points: 0 (worst) to 12 (best)).[22] For the GVT, the participants were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway.

2.4.2. Handgrip strength

Isometric handgrip strength was measured in the dominant hand with a handheld dynamometer (T.K.K. 5401 Grip-D, Japan). Patients were placed in a sitting position in a chair, with an elbow complete extension, and were asked to squeeze the handle as forcefully as possible for 3 seconds. After this, two valid trials followed, and the highest value was used as the data point.

2.4.3. Cognitive function

Changes in cognitive function were assessed using the Mini-Mental State Examination (MMSE)[23] (30-point questionnaire; scale of 0 (worst) to 30 (best)).

2.5. Classification of responders, non-responders and adverse responders

The inter-individual variability of the patients in the response to usual care in the control group and exercise training in the intervention group was used to categorize them as Rs, NRs or ARs using the clinical meaningful change of each variable: 1 point for the SPPB test[24], 1 kg for the handgrip test[25], 0·1 m/s for the GVT[26], and 3 points for the MMSE test.[27]

2.6. Statistical analysis

Standard statistical methods were used to calculate the mean and standard deviation (SD). Statistical normality was tested using both statistical (Kolmogorov-Smirnov test) and graphical (normal probability plots) procedures. We used Student´s t test or the Mann-Whitney U and χ^2 or Fisher test to analyze significant differences between the intervention and control groups for continuous and categorical variables at baseline, respectively. Differences in mortality at one-year post-discharge between categories in each group were assessed using the χ^2 test. One-way analysis of variance was used to test differences in functional end points (SPPB and GVT) at baseline between categories in the control and intervention group. The Bonferroni post-hoc test was applied to establish differences between categories in each group. Data were analyzed using SPSS-IBM (Software, v.21.0 SPSS Inc., Chicago, IL, USA) and a p-value < 0·05 was considered statistically significant.

3. Results

The study flow diagram is shown in **Figure 1**. No significant differences were found between groups at baseline for demographic and clinical characteristics for study endpoints (**Table 1**). A total of 370 patients were included in the analysis (209 women, 56.5%) with a mean age 87.3 (4.9) years (range 75-101 years), and 130 patients (35.1%) were nonagenarians. The median length of hospital stay was 8 days in both groups (interquartile range, 4). The mean number of intervention days for each patient was 5.3 ± 0.5 days, and most training days were consecutive (97%). The number of completed morning and evening sessions per patient averaged 5 ± 1 and 4 ± 1, respectively. Mean adherence to the intervention was 97 ± 8% for the morning sessions (i.e., 806 successfully completed sessions of 841 total possible sessions) and 85 ± 30% in the evening sessions (574 of 688). No adverse effects or falls associated with the prescribed exercises were recorded and no patient had to interrupt the intervention or had their hospital stay modified because of it.

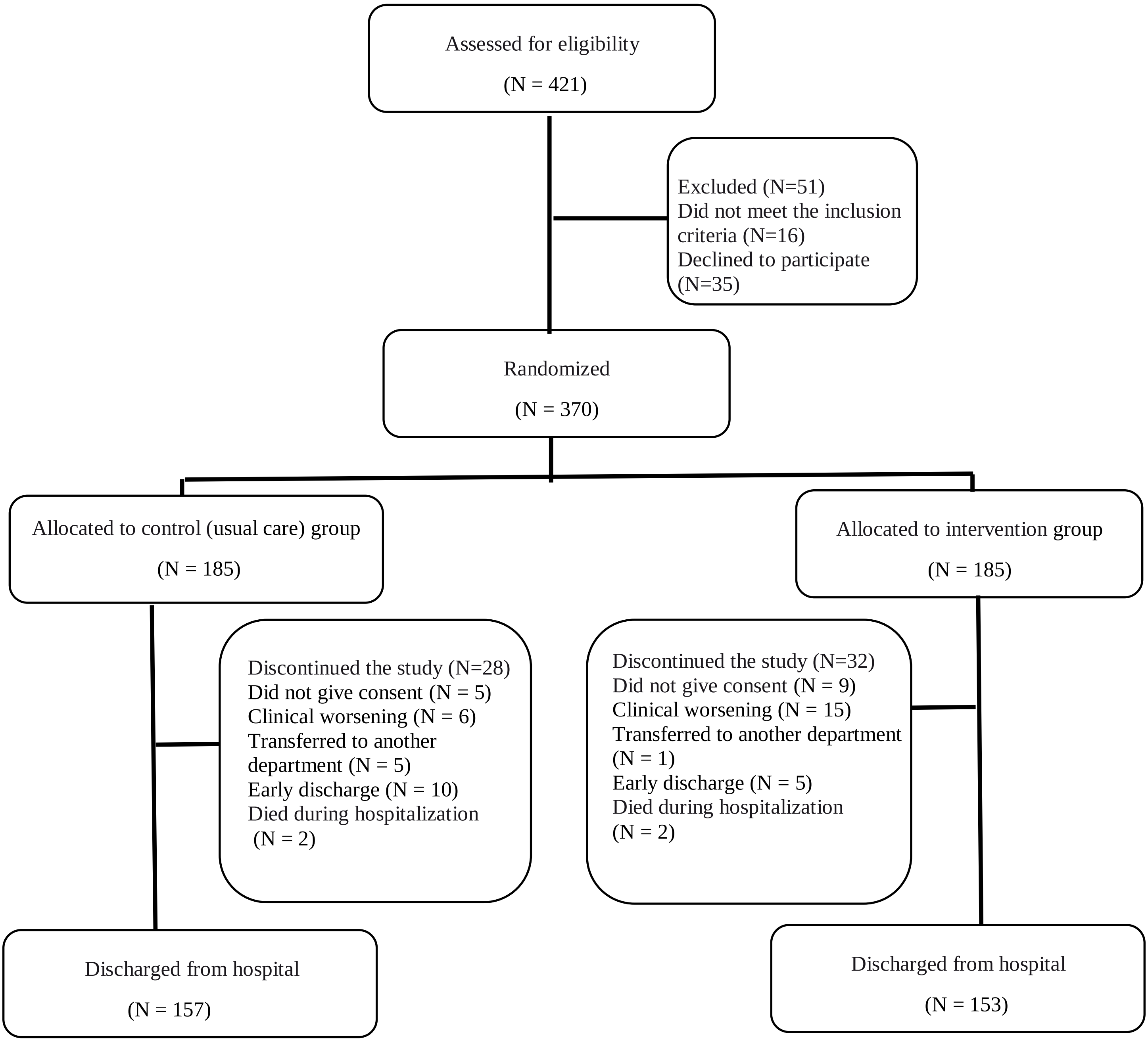


Figure 1. Study flow diagram

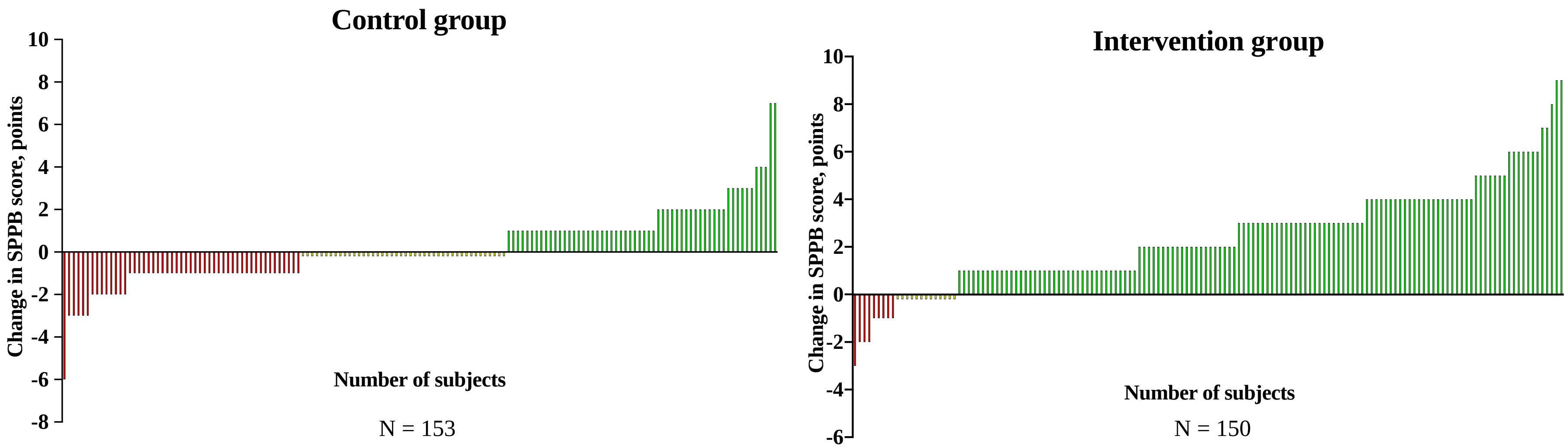
Table 1. Baseline characteristics of the participants

Variable	**Control group (n=185)**	**Intervention group (n=185)**
Demographic data		
Age, years	87.1 (5.2)	87.6 (4.6)
Women (N (%))	109 (59%)	100 (54%)
Body mass index, kg/m^2	26.9 (4.9)	27.1 (4.4)
Clinical data		
Barthel Index, score	83 (17)	84 (17)
CIRS (median, IQR), score	12 (5)	13 (5)
MNA (median, IQR), score	24 (4)	24 (4)
1RM leg press, kg	62 (31)	57 (25)
1RM chest press, kg	25 (12)	24 (11)
1RM knee extension, kg	41 (14)	39 (13)
GDS, score	3.6 (2.9)	4.0 (2.4)
QoL (EQ-VAS), score	60 (21)	58 (22)
Delirium (CAM, %)	12%	17%
Endpoint measures		
SPPB scale, score	4.7 (2.7)	4.4 (2.5)
6-meter GVT, seconds	16.1 (8.8)	16.2 (13.1)
Handgrip, kg	17 (8)	17 (6)
MMSE, score	23 (4)	22 (5)
Admission reason, (N (%))		
Cardiovascular	67 (36)	65 (35)
Infectious	33 (18)	33 (18)
Pulmonary	20 (11)	28 (15)
Gastrointestinal	17 (9)	20 (11)
Neurological	9 (5)	9 (5)
Other	39 (21)	30 (16)

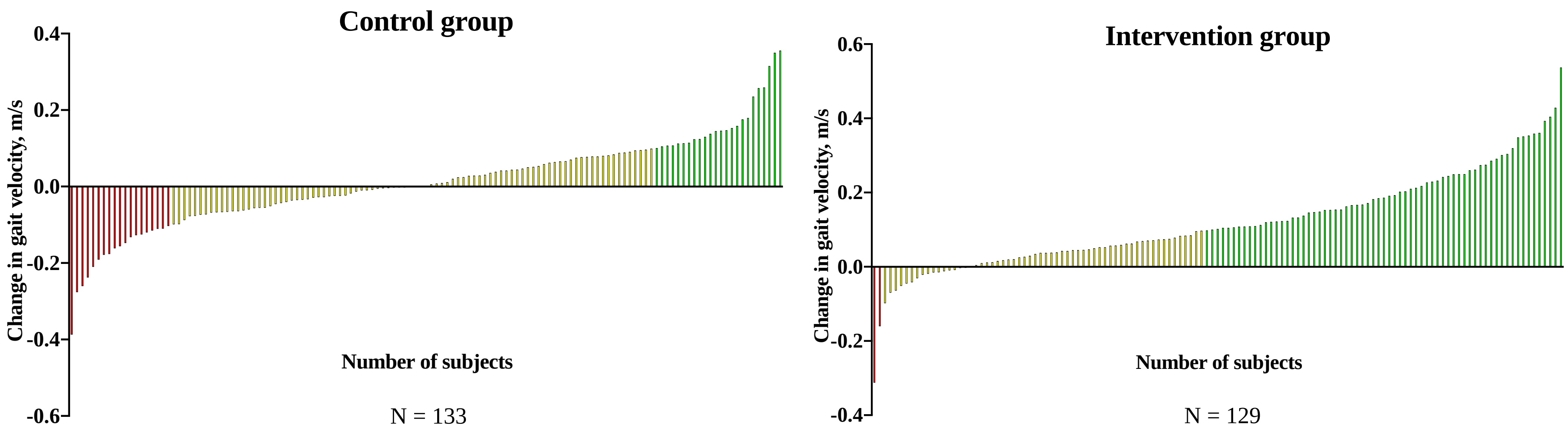
Data are mean (SD) unless otherwise stated. No statistically significant differences were found between groups (all P>0.05).
Abbreviations: 1RM, one-repetition maximum; CAM, Confussion Assessment Method; CIRS, Cumulative Illness Rating Scale; GDS, Yesavage Geriatric Depression Scale; GVT, Gait Velocity Test; IQR, interquartile range; MNA: Mini-nutritional Assessment; MMSE: Mini-Mental State Evaluation; QoL, quality of life; EQ-VAS, visual analogue scale of the EuroQol questionnaire (EQ-5D); SPPB: Short Physical Performance Battery.

The results of the prevalence of Rs, NRs, and ARs to usual care and individualized exercise training program are shown in **Figure 2**. Considering the functional endpoints, 33.3% of acutely hospitalized older adults in the control group were ARs, 28.8% were NRs, and 37.9% were Rs for the SPPB in the control group, and 6.0% were ARs, 8.7% NRs, and 85.3% Rs in the intervention group. For the GVT, 14.3% were ARs, 67.7% NRs, and 18.0% Rs in the control group and 1.6% were ARs, 47.3% NRs and 51.2% Rs in the intervention group. Regarding the handgrip strength, 42.0% were ARs, 38.0% NRs, and 20.0% Rs in the control group and 11.3% were ARs, 26.5% NRs, and 62.3% Rs in the intervention group. For the cognitive function test, 9.7% of the patients in the control group were ARs, 76.6% NRs, and 13.8% Rs whereas 1.4% were ARs, 57.1% NRs, and 41.5% Rs in the exercise training group.

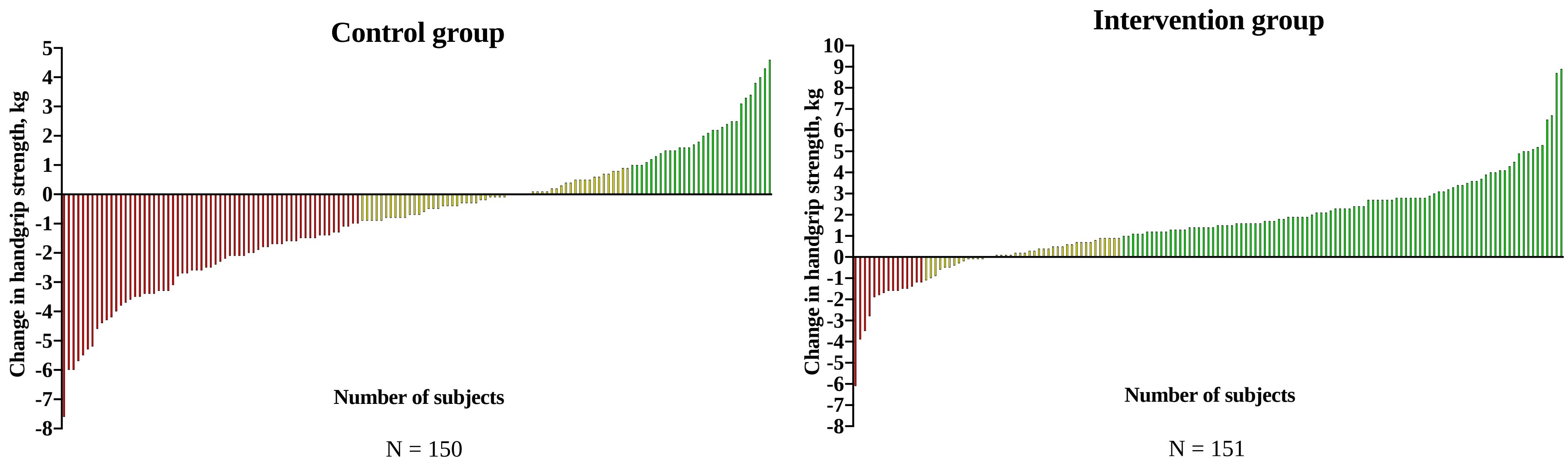
a. SPPB


Control group
Change in SPPB score, points
10
8
6
4
2
0
-2
-4
-6
-8
Number of subjects
N = 153
Intervention group
Change in SPPB score, points
10
8
6
4
2
0
-2
-4
-6
Number of subjects
N = 150

b. GVT


Control group
Change in gait velocity, m/s
0.4
0.2
0.0
-0.2
-0.4
-0.6
Number of subjects
N = 133
Intervention group
Change in gait velocity, m/s
0.6
0.4
0.2
0.0
-0.2
-0.4
Number of subjects
N = 129

c. Handgrip strength



d. MMSE

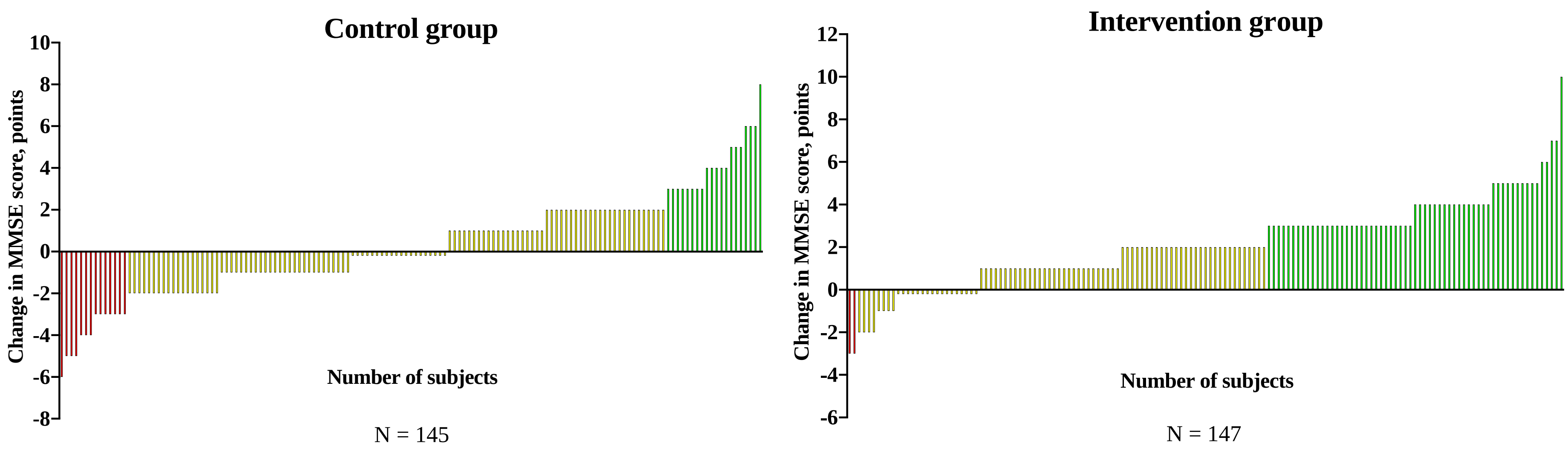
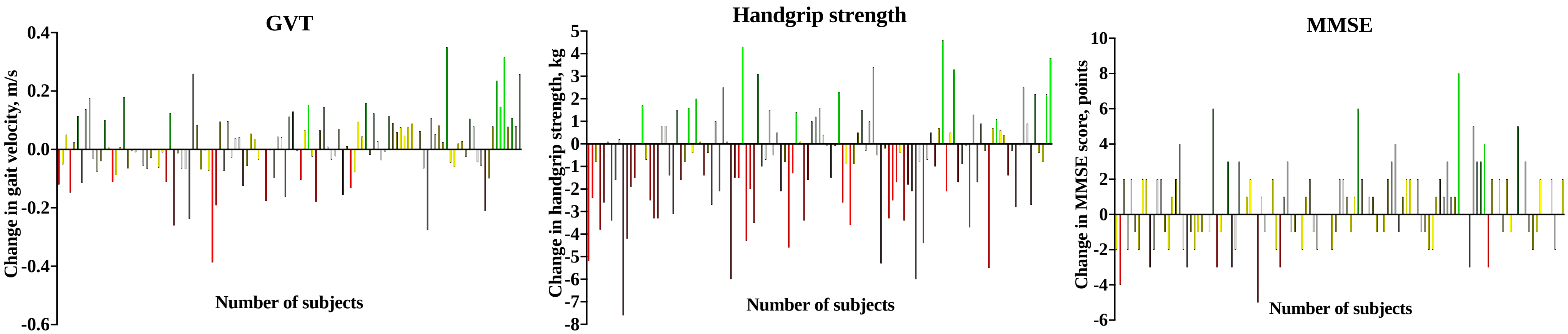


Figure 2. Responders (green line), non-responders (yellow line), and adverse responders (red line) on functional (a and b), muscle strength (c), and cognitive (d) endpoints. Abbreviations; GVT, Gait Velocity Test; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

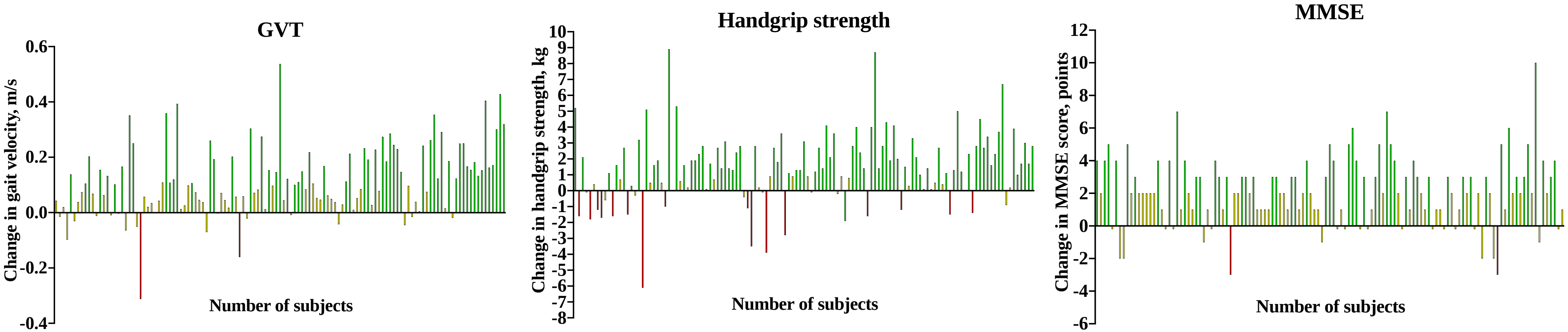
Functional, maximal strength and cognitive changes of all the patients of both groups are shown in **Figure 3** based on the response obtained for the functional endpoints (SPPB and GVT, see above **Figure 2**).

a. Control group



N = 121 N = 121 N = 121

b. Intervention group



N = 123 N = 123 N = 123

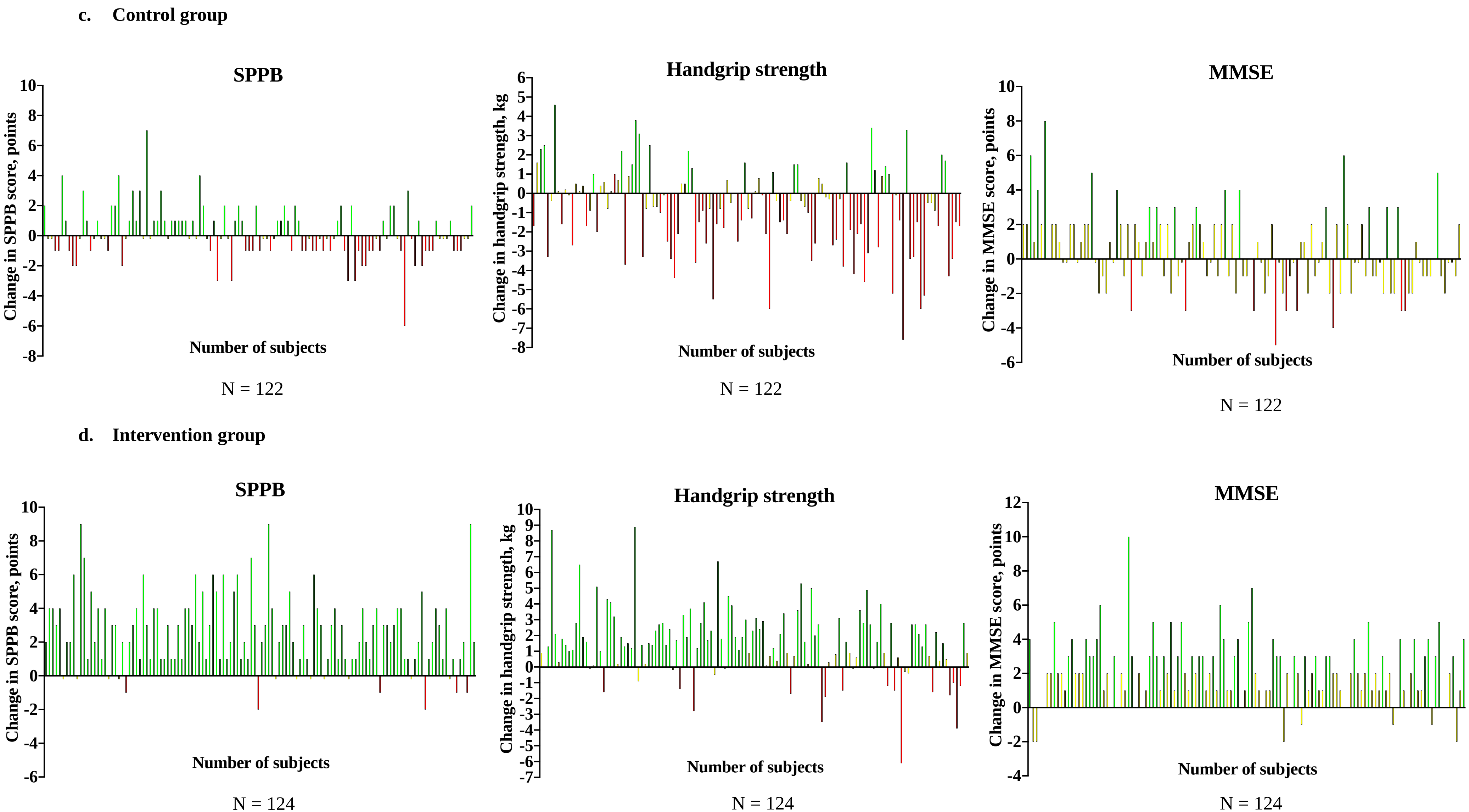


Figure 3. Changes in functional, muscle strength, and cognitive endpoints based on the SPPB response (a and b) and GVT response (c and d). Abbreviations: GVT, Gait Velocity Test; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

The secondary analysis showed that patients with an adverse response on the functional endpoints was associated with mortality at one-year post-discharge in both control and intervention groups (**Table 2**). Significant differences were found between categories for the SPPB in the intervention group (p = 0.01) and for the GVT in the control group (p = 0.03).

Table 2. Mortality rate at one-year post-discharge

End points	Control group	Intervention group
SPPB		
Adverse-responders	13 (25.5)	5 (62.5) *
Non-responders	12 (27.3)	3 (23.1)
Responders	14 (24.1)	23 (18)
GVT		
Adverse-responders	7 (36.8) *	0 (0)
Non-responders	20 (22.2)	17 (27.9)
Responders	1 (4.2)	9 (13.6)
Handgrip strength		
Adverse-responders	21 (33.3)	3 (17.6)
Non-responders	11 (19.3)	7 (17.5)
Responders	8 (26.7)	21 (22.3)
MMSE		
Adverse-responders	5 (35.7)	0 (0)
Non-responders	30 (27)	17 (20.2)
Responders	4 (20)	12 (20)

Data are presented as n (%). * $p<0.05$
Abbreviations: GVT, Gait Velocity Test; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

We also observed significant differences between categories for the SPPB score at admission in the intervention group (ARs = 3.6 ± 1.2 points, NRs = 4.4 ± 3.4 points, Rs = 4.5 ± 2.5 points; p = 0.01) and for the GVT in the control group (ARs = 0.59 ± 0.2 m/s, NRs = 0.46 ± 0.2 m/s, Rs = 0.38 ± 0.2 m/s; p < 0.01).

4. Discussion

Our study shows that acutely hospitalized older adults performing an individualized exercise intervention presented a higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function compared with patients receiving usual care. An adverse response on functional capacity in older patients treated with physical exercise or usual care during hospitalization was associated with mortality at one-year post-discharge. Moreover, the functional status presented at admission seems to play a key role in the trajectory of patients during hospital stay and even more so at follow up. To the best of our knowledge, this is the first study to analyze the inter-individual variability in the response to physical exercise and usual care in this population.

Acute illness requiring hospitalization is often a crucial event for many older adults[7] and functional decline is one of the negative short-term consequences of bed rest during hospitalization.[28] However, recent evidence has demonstrated that specific in-hospital exercises could provide significant benefits over usual care and could help to reverse the functional decline associated with acute hospitalization in older adults.[12] Although beneficial effects of exercise intervention on functional capacity are well established, frequent reports based of "average" exercise-related changes do not represent the wide individual variability in response to exercise.[18] The present inter-individual analysis study may be a first step towards to a greater precision in each individual, in-hospital treatments. We found a higher prevalence of Rs in the exercise training group compared with usual care group for both functional end points. Thus, tailored multicomponent exercise training appears to be an effective therapy for improving functional capacity in acutely hospitalized older adults. In addition, we observed a higher prevalence of Rs and a lower prevalence of NRs and ARs for handgrip strength and cognitive function in the intervention group than in the control group. We believe that these findings are important because muscle mass and neuromuscular function tend to decrease during hospital stay in older adults, with muscle strength and mass strongly associated with disability, morbidity, and cardiometabolic disease-related mortality.[29] Moreover, prolonged bed rest increases the risk of developing cognitive impairment and dementia in older adults.[30]

We also explored whether the response rate for functional capacity was accompanied by similar changes for muscle strength and cognition. Our findings indicate a considerable heterogeneity of response for handgrip strength and cognitive function after usual care or physical exercise. Therefore, response rate for functional capacity could not predict similar changes in other clinical characteristics, such as muscle strength and cognition.

Changes in functional status during hospitalization play an important role in the life trajectory of older adults after discharge. In agreement with previous studies.[8;11] our findings show that functional decline (*i.e.*, ARs for the GVT) during hospitalization is associated with a higher rate of mortality at one-year post-discharge compared with NRs and Rs. In the intervention group, those patients who experienced loss of functional capacity after the exercise training program (*i.e*., ARs for the SPPB) also showed a higher rate of mortality at follow up in comparison with other categories. Our results support the importance of measuring functional status in hospitalized older patients[11], a useful vital sign that should be assessed by hospital clinicians.[28]

Finally, functional status at admission contains crucial information about prognosis of different interventions in acutely hospitalized older people. Our data suggest that those older adults with higher gait velocity at admission had worse response to usual care and, consequently, major vulnerability to iatrogenic nosocomial disability, than those patients with less functional reserve at baseline. A greater window of worsening during hospitalization could be a possible explanation for the major functional decline. Our findings also showed differences in responses to exercise training based on the functional capacity presented at baseline. Older adults who experienced a worsened response in the intervention group had less functional reserve at admission (SPPB score <4 points) compared with NRs and Rs. It means that patients at worst functional status at admission have greater possibility to be an adverse-responder to the exercise intervention. Taken together with the above-mentioned association between adverse-responsiveness to exercise and mortality, older adults with poor scores in the SPPB at admission are also at major risk of mortality after discharge.

Overall, our study is in line with the long trajectory of research supporting the relevance of patients´ baseline function as a useful benchmark and goal for discharge and follow-up outcomes.[28]

Our study has some limitations, including patients´ difficulty in completing all the measurements at both hospital admission and discharge. Another possible limitation was that only old patients with relatively good functional capacity at preadmission (i.e., Barthel Index score ≥60 points) were included in the study; thus, the results may not be generalizable to the entire hospitalized elderly population. Also, we did not collect functional data prior to the acute illness and functional decline in acutely hospitalized older people frequently occurs before admission.[28] Our study, nevertheless, has several strengths. An innovative exercise intervention of few days (i.e., 5±1 and 4±1 morning and evening sessions, respectively) was performed with older adults in acute settings. Also, patients with multiple comorbidities and mild dementia/cognitive impairment were included in the study (routinely excluded from exercise studies). The prevalence of Rs was higher for functional capacity, muscle strength and cognitive function in the exercise training group compared with the usual care group, indicating that the physical exercise program was effective to reverse functional decline and cognitive impairment associated with hospitalization in older adults. Both functional capacity endpoints (SPPB and GVT) measured in the study for monitoring functional trajectory of patients were associated with mortality at one-year post-discharge. Finally, we identified clinical differences between categories at admission in both exercise and usual care groups.

5. Conclusions

Older medical patients performing an individualized exercise intervention showed a higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function than those patients who were treated with usual care during acute hospitalization. An adverse response on functional capacity in older medical patients to physical exercise or usual care during hospitalization was associated with mortality at one-year post-discharge. Moreover, the functional status presented at admission seems to be a cornerstone in the trajectory of patients during hospital stay and even more so at follow up. These findings support the need for a shift from the traditional disease-focused approach in hospital ACE to one that recognizes functional status as a clinical vital sign.

Declaration of interests

All authors have nothing to declare.

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Author's statement form

The study protocol was developed by MLSA, ACH, NMV and MI. Data acquisition and statistical analysis were done by MLSA, FZF, NMV and MI. Finally, MLSA, FZF, NMV, ELD, RRR and MI prepared the manuscript and revised it critically for intellectual content.

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Chapter 6

A randomized clinical trial evaluating the effects of a physical exercise intervention on cognitive function in very elderly patients during acute hospitalization

1. Introduction

The provision of inpatient acute care for frail older adults has become a crucial clinical issue in our aging societies.[1-3] Acute medical illnesses and subsequent hospitalization are major events leading to disability in older people.[4-6] In addition to functional decline, prolonged bed rest increases the risk of developing cognitive impairment and dementia in hospitalized older medical patients.[7] Indeed, cognitive impairment is highly prevalent in this patient group and is independently associated with multiple adverse outcomes including functional decline, increased length of hospital stays, institutionalization, and mortality.[8]

Many of the age-associated processes leading to frailty in older adults are also possible responsible for brain aging and consecutive cognitive decline. Accordingly, frail older people are likely to be at high risk of cognitive impairment, and *vice versa*.[9] The increasing interest in the association between frailty and cognitive impairment in hospitalized older adults[10] is driving the development of innovative interventions for the prevention and management of both conditions.

Exercise and early rehabilitation protocols applied during acute hospitalization can prevent functional decline in older patients[11] and are associated with a reduced length of stay and lower costs.[12] The exercise benefits on cognitive function are not entirely clear, but previous studies support that multicomponent exercise training seems to have the most positive effects on cognition in older adults.[13;14] To the best of our knowledge, the benefits of a multicomponent exercise intervention consisting of resistance (power), balance, and gait-retraining exercises to attenuate cognitive impairment in acutely hospitalized older adults have not been previously investigated.

The present study is in line with the long trajectory of research that has explored new possibilities to avoid dangers of prolonged bed-rest.[15] The main purpose of our study was to assess the effects of a multicomponent exercise intervention for cognitive function in older adults during acute hospitalization. Our hypothesis was that multicomponent exercise intervention would maintain or even improve cognitive function compared to usual care in these patients.

2. Methods

2.1. Design

The study is a secondary analysis of a randomized clinical trial (RCT) (NCT02300896).[11;16] It was conducted in the Acute Care of the Elderly (ACE) unit of the Department of Geriatrics in a tertiary public hospital (*Complejo Hospitalario de Navarra*, Spain). This Department has 35 allocated beds and its staff is composed of 8 geriatricians (distributed in the ACE unit, orthogeriatrics and outpatient consultations). Admissions in the ACE unit derive mainly from the Accident and Emergency Department, with heart failure, pulmonary and infectious diseases being the main causes of admissions.

Acutely hospitalized patients who met inclusion criteria were randomly assigned to the intervention or control (usual care) group within the first 48 hours of admission. Usual care is offered to patients by the geriatricians of our department and consists of standard physiotherapy focused on walking exercises for restoring the functionality conditioned by potentially reversible pathologies. A formal exercise prescription was not provided at study entry and patients were instructed to continue with the current activity practices through the duration of the study. The study followed the principles of the Declaration of Helsinki and was approved by the institutional Clinical Research Ethics Committee. All patients or their legal representatives provided written consent.

2.2. Participants and randomization

A trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥ 75 years, Barthel Index score ≥ 60 points, able to ambulate (with/without assistance), and to communicate and collaborate with the research team. Exclusion criteria included expected length of stay < 6 days, very severe cognitive decline (i.e., Global Deterioration Scale score = 7), terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, or extremity bone fracture in the past 3 months.

After the baseline assessment was performed, participants were randomly assigned following a 1:1 ratio, without restrictions (www.randomizer.org). Assessment staff was blinded to the main study design and group allocation. Participants were explicitly informed and reminded not to discuss their randomization assignment with the assessment staff.

2.3. Intervention

The usual care group received habitual hospital care, which included physical rehabilitation when needed. For the intervention group, exercise training was programmed in two daily sessions (morning and evening) of 20 minutes duration during 5–7 consecutive days (including weekends) supervised by a qualified fitness specialist. Adherence to the exercise intervention program was recorded in a daily register. A session was considered completed when ≥ 90% of the programmed exercises were successfully undertaken.

Each session was performed in a room equipped ad hoc in the ACE unit. Exercises were adapted from the "Vivifrail" multicomponent physical exercise program to prevent weakness and falls.[17] The morning sessions included individualized supervised progressive resistance, balance, and walking-training exercises. The resistance exercises were tailored to the individual's functional capacity using variable resistance training machines (Matrix, Johnson Health Tech, Ibérica, S.L.; Torrejón de Ardoz, Spain and Exercycle S.L., BHGroup; Vitoria, Spain) aiming at 2–3 sets of 8–10 repetitions with a load equivalent to 30–60% of the estimated one-repetition maximum (1RM). Participants performed three exercises involving mainly lower-limb muscles (squats rising from a chair, leg press and bilateral knee extension) and one involving the upper-body musculature (seated bench 'chest' press). They were instructed to perform the exercises at a high speed to optimize muscle power output, and care was taken to ensure proper exercise execution. Balance and gait retraining exercises gradually progressed in difficulty and included the following: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), altering the base of support, and weight transfer from one leg to the other. The evening session consisted of functional unsupervised exercises using light-loads (0.5–1 kg anklets and hand-grip ball), such as knee extension/flexion, hip abduction and daily walking in the corridor of the ACE unit with a duration based on the clinical physical exercise guide "Vivifrail".[17]

When the clinician in charge of the patient considered that the hemodynamic situation was acceptable, and the patient could collaborate, the following endpoints were assessed and the intervention was started. Endpoints were also assessed on the day of discharge.

2.4. Endpoints

2.4.1. 6-meter dual-task Gait Velocity Test (GVT)

Patients were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway. Two different dual-task gait tests were performed, the arithmetic GVT and the verbal GVT, in which gait velocity was measured while the patients counted backward aloud from 100 down to one or named animals aloud, respectively.[18] The cognitive score was measured by counting the number of animals named (verbal dual-task) or by counting the numbers that were stated (arithmetic dual-task) and the errors in each task.

2.4.2. Mini-Mental State Examination (MMSE)

The MMSE test[19] is the most utilized screening instrument of cognitive decline.[20] The instrument assesses domains of orientation, memory, attention, language, and visuospatial ability. The MMSE is scored out of 30 points, with scores ≤ 23 points indicative of likely cognitive impairment.

2.4.3. Trail Making Test Part A (TMT-A)

The TMT-A is used as an indicator of visual scanning, graphomotor speed, and executive function. The patients were asked to connect randomly arranged circles containing numbers from 1 to 25 following the number sequence, and doing it as quickly as possible.[21]

2.4.4. Verbal fluency test

The patient had to say as many words as possible starting with the letter F in one minute.[22]

2.5. Statistical analysis

Analyses were performed by "intention-to-treat" principles. Between-group comparisons of continuous variables were conducted using linear mixed models. Time was treated as a categorical variable. The models included group, time, and group by time interaction as fixed effects, and participants as random effect. For each group, data are expressed as change from baseline (admission) to discharge, determined by the time coefficients (95% confidence interval [CI]) of the model. The conclusions about effectiveness of exercise intervention were based on between-group comparisons of change in cognitive function from baseline (beginning of the intervention) to hospital discharge, as assessed with the MMSE, dual-task GVT (including both verbal and arithmetic task conditions), TMT-A and verbal fluency test, and determined by the time by group interaction coefficients of the model. Between group comparisons of errors during dual-task GVT were analyzed using Poisson mixed model because of the asymmetric distribution of the endpoint.

Using the χ^2 test for linear trend, we also compared the proportion of patients in each group showing an improvement, no change, worsening at discharge at compared with baseline on the dual-task GVT.

Normality of data was checked graphically and through the Kolmogorov Smirnov test. All comparisons were two-sided, with a significance level of 0.05. Statistical analysis was carried out using IBM-SPSS v20 software (SPSS Inc., Chicago, IL).

3. Results

The study flow diagram is shown in **Figure 1**. No significant differences were found between groups at baseline for demographic and clinical characteristics for study end points (**Table 1**). Of the 370 patients included in the analyses, 209 were women (56.5%); mean age was 87.3 (4.9) years (range 75–101 years), with 130 patients [35.1%] being nonagenarians). The median length of hospital stay was 8 days in both groups (interquartile range [IQR], 4 and 4 days, respectively). The mean number of intervention days for each patient was 5.3 ± 0.5 days, with most training days being consecutive (97%). The number of completed morning and evening sessions per patient averaged 5 ± 1 and 4 ± 1, respectively. Mean adherence to the intervention was 97 ± 8% for the morning sessions (i.e., 806 successfully completed sessions of 841 total possible sessions) and 85 ± 30% in the evening sessions (574 of 688). No adverse effects or falls associated with the prescribed exercises were recorded and no patient had to interrupt the intervention or had their hospital stay modified because of it.

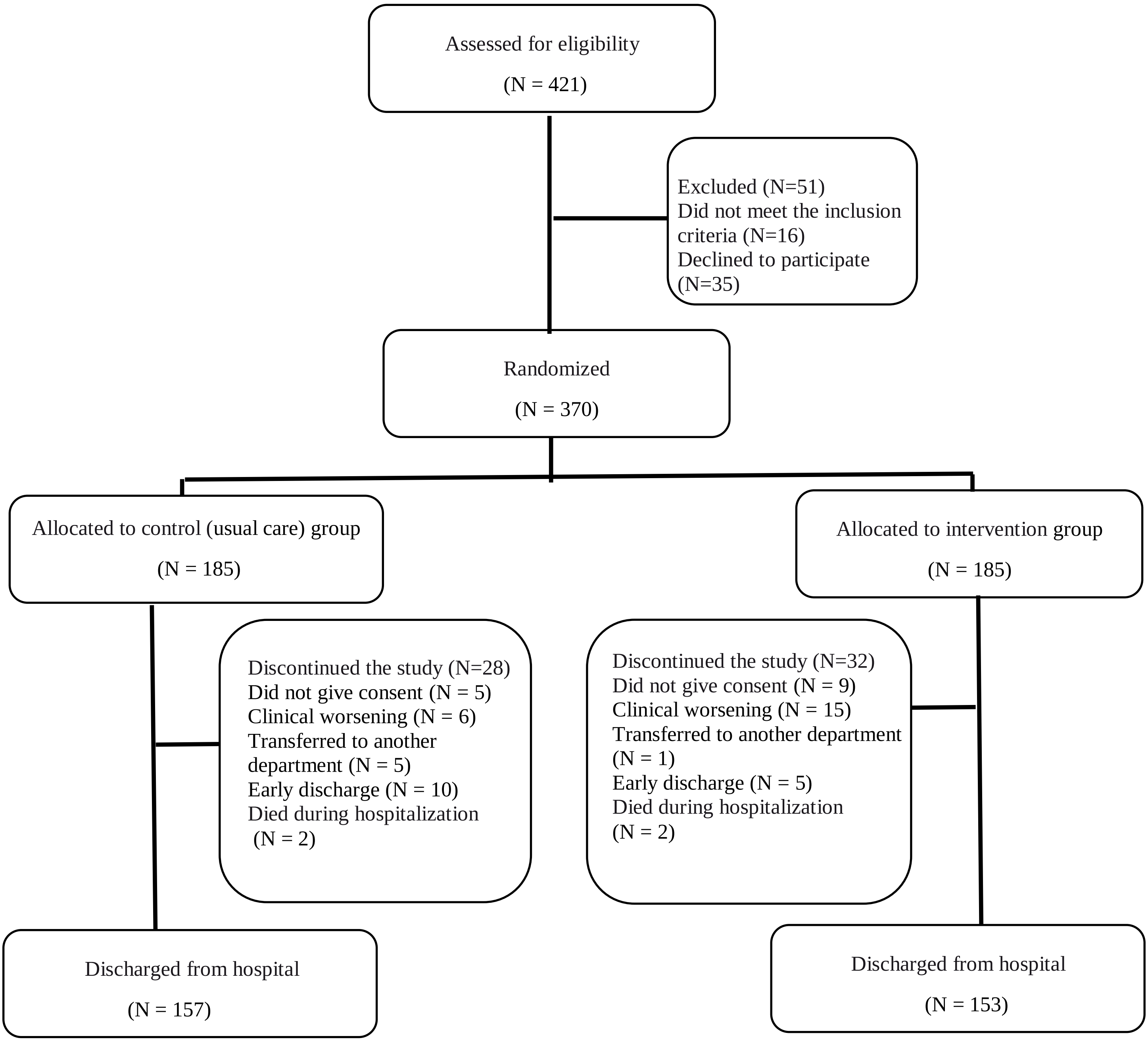

Figure 1. Study flow diagram

Table 1. Baseline characteristics of the participants.

Variable	Control group (n=185)	Intervention group (n=185)
Demographic data		
Age, years	87.1 (5.2)	87.6 (4.6)
Women, N (%)	109 (59%)	100 (54%)
Body mass index, kg/m^2	26.9 (4.9)	27.1 (4.4)
Clinical data		
Barthel Index, score	83 (17)	84 (17)
CIRS score, median (IQR)	12 (5)	13 (5)
MNA score, median (IQR)	24 (4)	24 (4)
1RM leg press, kg	62 (31)	57 (25)
1RM chest press, kg	25 (12)	24 (11)
1RM knee extension, kg	41 (14)	39 (13)
GDS, score	3.6 (2.9)	4.0 (2.4)
QoL (EQ-VAS), score	60 (21)	58 (22)
Delirium (CAM, %)	12%	17%
Endpoint measures		
Verbal GVT, m/s	0.4 (0.2)	0.4 (0.2)
Arithmetic GVT, m/s	0.4 (0.2)	0.4 (0.2)
MMSE, score	23 (4)	22 (5)
TMT-A, seconds	162.9 (97.0)	166.5 (125.4)
Verbal fluency test, score	7.2 (4.2)	6.3 (3.8)
Admission reason, N (%)		
Cardiovascular	67 (36)	65 (35)
Infectious	33 (18)	33 (18)
Pulmonary	20 (11)	28 (15)
Gastrointestinal	17 (9)	20 (11)
Neurological	9 (5)	9 (5)
Other	39 (21)	30 (16)

Data are mean (SD) unless otherwise stated. No statistically significant differences were found between groups (all P>0.05).
Abbreviations: 1RM, one-repetition maximum; CAM, Confussion Assessment Method; CIRS, Cumulative Illness Rating Scale; GDS, Yesavage Geriatric Depression Scale; GVT, Gait Velocity Test; IQR, interquartile range; MNA, Mini-nutritional Assessment; MMSE, Mini-Mental State Examination; QoL, quality of life; EQ-VAS, visual analogue scale of the EuroQol questionnaire (EQ-5D); SPPB, Short Physical Performance Battery; TMT-A, Trail Making Test Part A.

The primary analysis showed that the physical exercise provided a significant benefit over usual care. Differences between the treatment groups revealed a significant intervention effect for both dual-task GVT. The percentage distribution of patients with improvements on the verbal GVT (47.6% vs. 81.7%) or arithmetic GVT (48.7% vs. 88.5%) from admission to discharge significantly differed between the two groups, indicating a beneficial exercise intervention effect for both endpoints (all $p < 0.001$ with χ^2 test, **Figure 2A** and **2B**). At discharge, the exercise group showed an increase of 0.1 m/s (95%CI, 0.07, 0.13 m/s) on the verbal GVT and 0.1 m/s (95%CI, 0.08, 0.13 m/s) on the arithmetic GVT over the usual-care group (**Table 2**, **Figure 2C** and **2D**). Furthermore, significant differences were found between groups in the errors made during the arithmetic GVT (p < 0.001, **Table 2**).

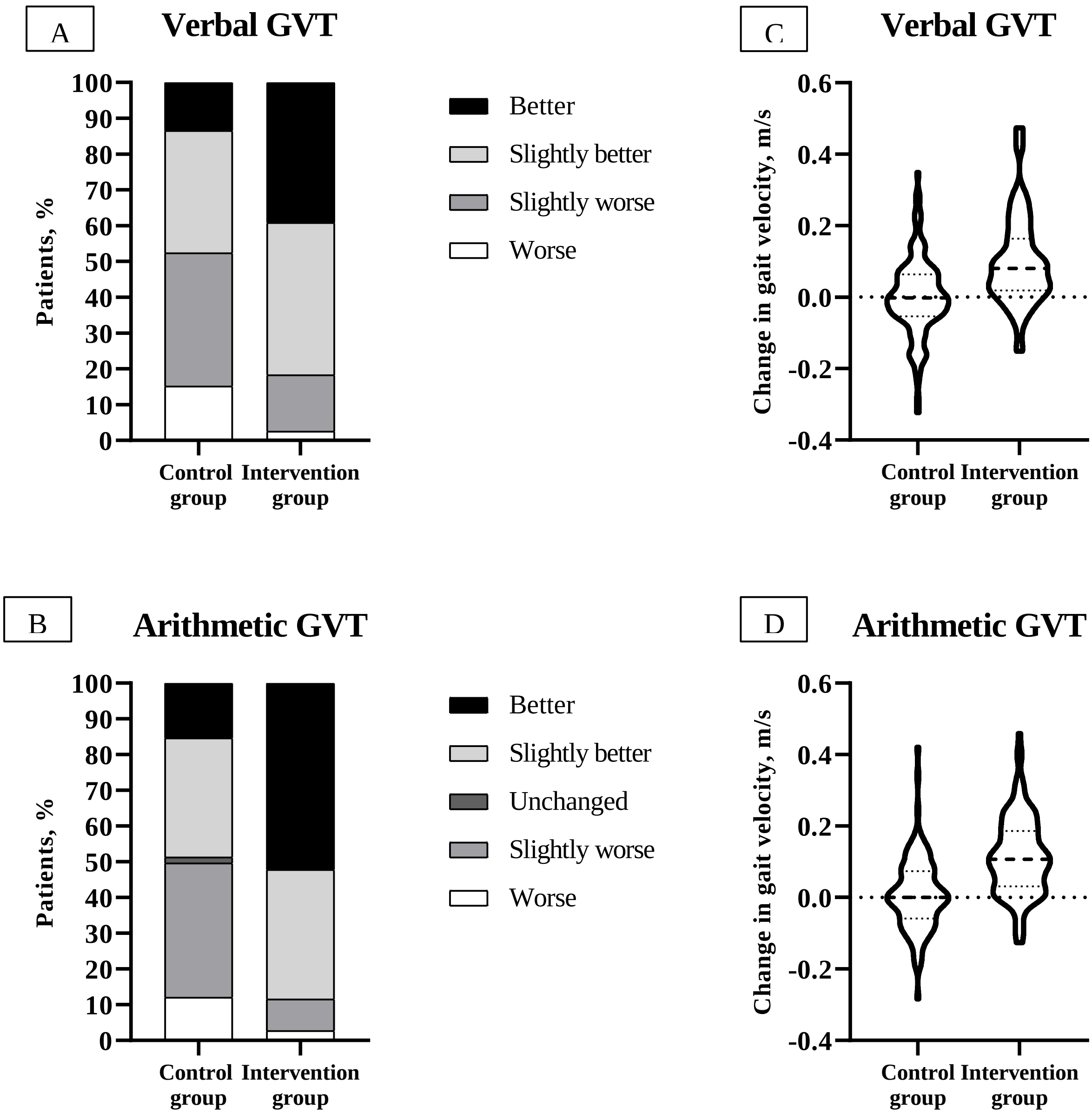

Figure 2. Changes from baseline to discharge (A and B) and within-group punctuation change distribution (C and D). Dual-task GVT changes: *better* indicates an improvement of more than 0.1 m/s, *slightly better* indicates an improvement between 0.001 and 0.1 m/s, *unchanged* indicates no difference, *slightly worse* indicates a decline between 0.001 and 0.1 m/s, *worse* indicates a decline of more than 0.1 m/s. The proportion of patients showing overall improvement and worsening in the dual-task GVT was significantly higher and lower, respectively, in the intervention than in the control group (all p < 0.001 with χ^2 test). In the violin plots, the horizontal dotted lines indicate Q1 and Q3, and the horizontal dashed line within the violin, median.

Considering the global cognitive function, the intervention group showed improvements at discharge in the MMSE test of 2.10 points (95%CI, 1.75, 2.46 points) whereas no such trend was found in the control group (0.27 points; 95%CI, -0.08, 0.63 points) (**Table 2** and **Figure 3A**).

For the executive function, the exercise group showed an improvement in the TMT-A reducing the time to complete the task by 31.1 seconds at discharge (95%CI, -49.5 to -12.7 seconds) over the control group (**Table 2** and **Figure 3B**).

Finally, acute hospitalization *per se* led to a significant impairment in patient verbal fluency ability (*i.e.*, mean change from baseline to discharge of -0.30 words (95%CI, -0.72, 0.12 words) whereas the exercise intervention improved this cognitive domain (1.85 words; 95%CI, 1.44, 2.27 words) (**Table 2** and **Figure 3C**).

Table 2. Results of study endpoints by group

Endpoints	**Control group**	**Exercise group**	**Between-group difference (95%CI)**	**p-value between groups**
Verbal GVT				
Velocity, m/s	0.002 (-0.018, 0.022)	0.10 (0.08, 0.12)	0.10 (0.07, 0.13)	<0.001
Correct answers, score	0.01 (-0.36, 0.38)	0.41 (0.04, 0.79)	0.41 (-0.12, 0.93)	0.133
Errors, score	2.03 (0.64, 7.61)	0.32 (0.016, 2.41)	0.16 (0.01, 1.65)	0.157
Arithmetic GVT				
Velocity, m/s	0.009 (-0.009, 0.029)	0.11 (0.10, 0.13)	0.10 (0.08, 0.13)	<0.001
Correct answers, score	0.12 (-0.57, 0.81)	0.18 (-0.52, 0.88)	0.06 (-0.92, 1.05)	0.901
Errors, score*	1.16 (0.92, 1.45)	0.55 (0.42, 0.69)	0.48 (0.34, 0.67)	<0.001
MMSE, score	0.27 (-0.08, 0.63)	2.10 (1.75, 2.46)	1.83 (1.32, 2.33)	<0.001
TMT-A, seconds	-3.13 (-16.3, 10.2)	-34.2 (-47.1, -21.3)	-31.1 (-49.5, -12.7)	<0.001
Verbal fluency test				
Correct answers, score	-0.30 (-0.72, 0.12)	1.85 (1.44, 2.27)	2.16 (1.56, 2.74)	<0.001
Errors, score*	1.11 (0.75, 1.63)	0.66 (0.43, 0.99)	0.58 (0.33, 1.05)	0.076

Data in each group are expressed as change from baseline (admission) to discharge (mean and 95% confidence interval). Abbreviations: GVT, gait velocity test; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test Part A.
* Poisson mixed model.

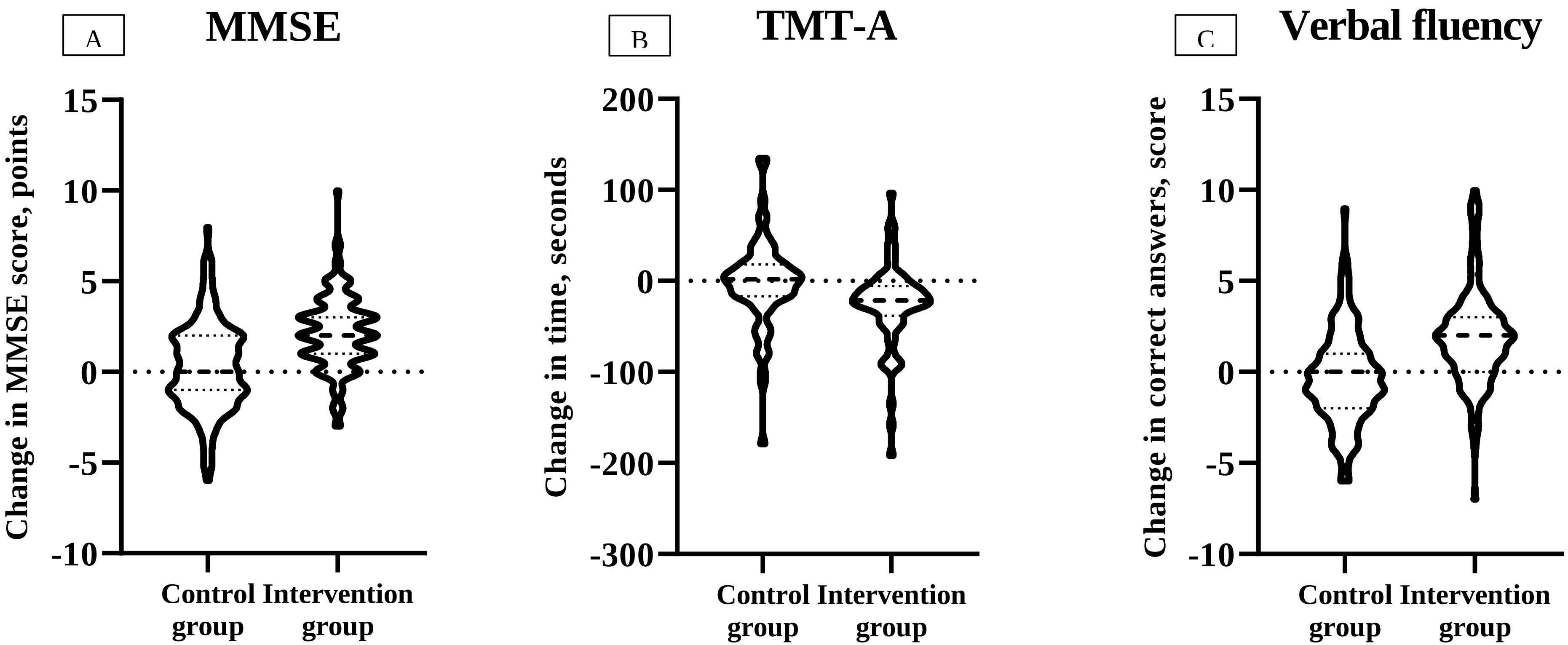

Figure 3. Changes in within-group punctuation in the Mini-Mental State Examination (MMSE) test, Trail Making Test Part A (TMT-A) and verbal fluency test. In the violin plots, the horizontal dotted lines indicate Q1 and Q3, and the horizontal dashed line within the violin, median.

4. Discussion

Our study shows that an individualized exercise intervention during a short time period (mean 5 days) provides significant benefits over usual care in acutely hospitalized older adults and can be an effective therapy to reverse the cognitive impairment usually associated with this patient group. To our knowledge, this is the first study in which a multicomponent intervention including low-intensity resistance training exercises produces enhancements on specific cognitive domains, such as executive function and verbal fluency, in hospitalized patients of advanced age.

Older patients admitted to the hospital are at risk of experiencing negative consequences following hospitalization including functional decline and frequently, long-term disability.[5;6] Research has suggested that hospitalization in older adults *per se* is associated not only with functional adverse outcomes but also with the development of cognitive decline and an increased risk of dementia.[7] Moreover, cognitively impaired older patients are at even greater risk of hazards of hospital stay as compared to patients with no cognitive decline.[23] Our findings reveal that more than one-half of the control group showed worsened gait performance in both dual-task GVT at discharge, whereas the exercise intervention reversed this trend. We also observed an improvement in the verbal fluency ability after the exercise intervention, with the opposite response found in the usual care group. Surprisingly, short-term hospitalization did not impact dramatically on some cognitive tasks, such as the MMSE and TMT-A, although significant differences were observed between groups at discharge. The poor health status of the hospitalized elderly upon admission and the comprehensive and multidisciplinary protocols already established in the ACE unit could influence the preservation of some cognitive domains.

Acute hospital admissions play a key role in the disabling process in the elderly years, and physical exercise seems to be an effective therapy to prevent nosocomial disability, which is usually linked to poor mobility during hospitalization.[24] Recent evidence has demonstrated that specific in-hospital exercises could provide significant benefits over usual care and could help to reverse the functional decline associated with acute hospitalization in older adults.[11] Although potential benefits of physical exercise on functional capacity are well established, the effects of tailored multicomponent exercise intervention on specific cognitive domains including executive function and verbal fluency are not clear in acutely hospitalized older patients. In agreement with previous studies[13;14], our findings support that multicomponent exercise training may produce the most positive effects on cognitive function in older adults. The inclusion of progressive low-intensity resistance training as a component of the exercise training protocol could be the reason for cognitive gains in the intervention group in specific executive tasks (*i.e.*, both dual-task GVT and TMT-A). An emerging theory to explain these cognitive benefits is that resistance training increases the production of several growth factors, such as brain-derived neurotrophic factor and insulin-like growth factor-1.[25] Previous evidence has suggested that gait performance is closely related to cognitive function, in particular executive function, and impaired executive function has been associated with decreased gait velocity, increased risk of falls and decreased performance on complex motor tasks in older adults.[26;27] Thus, our results indicate that, despite its short duration, an exercise training approach is effective in improving the executive function (measured by dual-task GVT) during hospitalization in very old patients.

The present study is in line with the recently published World Health Organization (WHO) Clinical Consortium of Healthy Aging, which highlights the importance of maintaining individuals´ intrinsic capacity for the preservation of autonomy and independence in essential everyday activities.[28] In accordance with the WHO framework, our findings show that multicomponent exercise training, with special emphasis on muscle power training, is the intervention of choice for avoiding a trajectory towards frailty/disability in acutely hospitalized older adults and also improves cognitive function, a key component of intrinsic capacity. Therefore, exercise prescription should be considered as front-line treatment to prevent hospital-acquired iatrogenic disability. Future RCTs should also consider the inclusion of multidomain interventions in this population, in which exercise training is combined with other treatments such as cognitive training and social enrichment, to optimize cognitive performance and prevent cognitive impairment.

Our study has some limitations, including patients´ difficulty in completing all the tasks at both hospital admission and discharge. Notably, 16% of the older patients were unable to perform the arithmetic GVT because they did not receive primary education and 47% of the participants could not complete the TMT-A because of visual impairment. Another possible limitation was that only old patients with relatively good functional capacity at preadmission (i.e., Barthel Index score ≥ 60 points) were included in the study;

thus, the results might not be generalizable to the entire hospitalized elderly population. Nevertheless, our study has several strengths. We focused on a particularly vulnerable population of advanced age (overall mean 87.3 years; range 75–101 years, with 130 patients (35.1%) being nonagenarians) to develop an innovative exercise intervention of a few days (i.e., 5 ± 1 and 4 ± 1 morning and evening sessions, respectively) in acute settings. Also, patients with multiple comorbidities (mean [SD] of 9 [6] comorbidities) and mild dementia/cognitive impairment were included in the RCT (routinely excluded from exercise studies). Considering the exercise training protocol, a daily individualized adjustment of loads was performed to optimize exercise benefits and prevent iatrogenic nosocomial disability. Finally, to minimize potential bias, the researchers were unaware of a patient test scores at admission when retesting at discharge.

5. Conclusions

An individualized, multicomponent exercise training program is an effective therapy for improving cognitive function (*i.e.*, executive function and verbal fluency domains) in very old patients during acute hospitalization. These findings support the need for a shift from the traditional (bed-rest based) hospitalization to one that recognizes the important role of maintaining functional capacity and cognitive function in older adults, key components of intrinsic capacity.

Declaration of interests

All authors have nothing to declare.

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Chapter 7

General discussion

Effects of physical exercise on cognitive function in older adults (Study 1 and Study 6)

A plausible consequence of the aging process in older adults is cognitive decline, which is associated with an increased risk of dementia and adverse health outcomes such as functional limitations and disability[1;2], and places a substantial economic burden on health care systems and society.[3] The development of different interventions to maintain or improve cognitive function is necessary to control the epidemic of dementia and other disorders.[4] PA has been reported to play a key role in the prevention of different disorders, such as cardiovascular disease, diabetes and some types of cancer.[5] Although evidence of the beneficial effects of PA on cognitive function has been clearly provided in the results of animal, epidemiological and cross-sectional studies, the results and conclusions of RCTs have been less consistent.[6] The great variability in RCT procedures and exercise training protocol features included in the review make it difficult to draw consistent conclusions for better understand the relationship between physical exercise training and cognitive performance.

First, participants PA levels at baseline was a considerable factor to consider to analyze changes on cognitive performance with exercise training in older adults. Previous cross-sectional studies analyzing the relationship between PA levels in different stages of life and the likelihood of developing cognitive decline in later life[7], reported that individuals with higher levels of PA had better cognitive function[8;9] or were at a reduced risk to experience cognitive decline compared with participants who had a less active or sedentary lifestyle. Consequently, subject baseline PA differences between studies included in the review could be one of the reasons to explain large variations in the magnitude of the improvements on cognition in different RCTs.

Second, differences in the intervention duration and follow-up period between studies may be one of the reasons to clarify discrepancies between the short and long-term effects of exercise training on the cognitive performance in older adults. If exercise could reverse or delay the effects of age-related cognitive decline, interventions performed over a longer time would produce more relevant alterations in cognitive gains than short-term protocols.[10] RCTs are usually much shorter than longitudinal studies, which would make it more complicated to produce changes in global or regional brain volumes[11-13] and to observe cognitive differences between groups.

Third, the efficiency of the intervention and the adherence to training sessions had vital importance in the intervention effect on cognitive gains. Although the optimum dose of exercise training for the improvement of cognition has yet to be established, some RCTs included in our review failed to meet the aerobic training recommendations for older adults[14] of 150 minutes of exercise training at moderate intensity or the resistance training recommendations of one or more sets of 10-15 repetitions at moderate intensity with a resting interval of 2-3 minutes between sets.[15] Therefore, RCTs should include in the data analysis only participants who reach a minimum number of training sessions to determine the inherent effects of exercise training on cognitive performance in the data analysis.

Finally, the great variety of cognitive tests were measured to analyze the effects of exercise on memory and executive function and could explain the lack of consistent evidence obtained in the review.[10;16] Although our findings suggested that resistance training could have an influence on prefrontal cortex and could have a positive effect on executive function, exercise training benefits on cognitive outcomes associated with episodic memory are less consistent. Thus, further research is needed to explore physiologic and neuromuscular changes in different brain areas to understand the relationship between exercise training and memory domain.

Regarding the effects of physical exercise intervention on cognition in acutely hospitalized old patients, our study showed that an individualized exercise intervention during a short time period (mean 5 days) provided significant benefits over usual care in acutely hospitalized older adults and could be an effective therapy to reverse the cognitive impairment usually associated with this patient group. Previous studies demonstrated that hospitalization in older adults *per se* is associated not only with functional adverse outcomes but also with the development of cognitive decline and an increased risk of dementia.[17] In agreement with previous evidence[18], our findings supported that multicomponent exercise training may produce the most positive effects on cognitive function in older adults. The inclusion of progressive low-intensity resistance training as a component of the exercise training protocol could be the reason for cognitive gains in the intervention group in specific executive tasks. An emerging theory that could explain the cognitive benefits is that resistance training increases the production of several growth factors, such as brain-derived neurotrophic factor and insulin-like growth factor-1.[19] The RCT is in line with the recently published World Health Organization (WHO) Clinical Consortium of Healthy Aging, which highlights the importance of maintaining individuals´ intrinsic capacity for the preservation of autonomy and independence in essential everyday activities[20]. A multicomponent exercise program, with special emphasis on muscle power training, is the intervention of choice for avoiding a trajectory towards frailty/disability in acutely hospitalized older adults and also improves cognitive function, a key component of intrinsic capacity.

Effects of physical exercise intervention on functional capacity in acutely hospitalized old patients (Study 2 and Study 3)

The provision of inpatient acute care for frail older adults who are at risk of adverse outcomes is becoming a major clinical issue in our aging societies[21-23]. Acute hospital admissions play an important role in the disabling process at end-life, owing to the deleterious effects of the presenting illness or injury and the hazards of hospital stay itself.[24] Regarding the latter, nosocomial disability is usually linked to poor mobility, with the most active patients showing lesser functional impairment than their less active peers[25]. Thus, preservation of functional capacity, mobility and mental capacities should be the focus of the clinical management of the elderly with disease[26], including also during acute hospitalization phases. A recent RCT showed no significant benefit of a simple in-hospital mobility program consisting of ambulation up to twice daily and a behavioral strategy to encourage mobility in older patients' ability to perform ADL after acute hospitalization.[27] However, our results showed that a more complete, multicomponent exercise intervention including low-intensity resistance training exercises performed during a very short-term period (5 days on average) provided a significant benefit over usual care and could help to reverse the functional decline associated with acute hospitalization in older adults. Acute hospitalization led to a major impairment in patients' functional ability during ADL, whereas the exercise intervention actually reversed this trend. In addition, we also observed an increase in the SPPB and GVT (including dual-task), with the opposite response found in the control group. Functional ability, and the maintenance of autonomy and independence, is the starting point of healthy aging, a term established by the WHO in its first world report on aging and health.[28] In agreement with the WHO framework, our results indicated that multicomponent exercise training, with special emphasis on muscle power training, is the intervention of choice for maintaining function and avoiding a trajectory towards frailty/disability in acutely hospitalized older adults and exercise prescription should be considered as a front-line treatment to prevent hospital-acquired iatrogenic disability.

Regarding the issue of functional assessment in in hospitalized patients, different screening tools are available to identify older adults at risk for functional decline during hospitalization and after discharge.[29] However, there is currently no "gold standard" for measuring functional trajectory during hospitalization.[30] In this regard, we used an innovative inertial sensor unit to analyze changes in daily functional tasks including walking and rising from a chair. Concerning the ability to walk and to stand from a seated position, patients in the intervention group improved the performance at discharge compared with admission, whereas lower values were observed in the control group. Thus, old patients also improved the movement pattern in different ADLs after the physical exercise intervention.

Of note, our results also showed significant intervention benefits on maximal muscle strength of upper (i.e., handgrip strength) and lower limbs, muscle power output, and QOL levels. We believe these finding are also important because there is meta-analytic evidence that muscle strength and muscle mass tend to decrease in the elderly during hospitalization (at least in electively admitted patients[31], with muscle strength/mass being associated with disability, morbidity and cardiometabolic disease-related mortality.[32] Indeed, it seems that multicomponent exercise training is the most effective intervention for improving overall physical outcomes in frail older adults including muscle strength, power output, and for preventing disability and other adverse events associated with aging.[33;34]

Mechanisms underlying gait impairment in acutely hospitalized older adults (Study 4)

Acute medical illnesses and subsequent hospitalization are crucial events leading to disability in the elderly population.[24;35;36] Despite the resolution of the reason for hospitalization, older medical patients are often discharged with a new major disability.[37] This loss of functional capacity is strongly associated with caregiver burden, higher resource use, institutionalization, and death.[38-41]

Although functional decline has become a key outcome after hospitalization and multiple screening tools are available to identify older adults at risk of functional decline during and after hospital stays[29], as we reported above, there is currently no "gold standard" for measuring functional impairment in hospitalized older medical patients.[30]

Gait is essential for performing ADLs.[42] Gait analysis is currently limited to performance time measurements in the clinical practice, lacking many measurable facets other than velocity.[43] Previous studies have investigated the association between gait pattern and frailty syndrome[44], muscle mass quality[45], and cognitive impairment in older adults.[46] We found differences in gait pattern parameters and muscle performance endpoints between old patients based on the functional status (SPPB score) presented at admission. Moreover, adding an innovative tool such as an inertial sensor unit to the standard gait speed assessment was useful to understand the mechanisms underlying gait impairment in acutely hospitalized older patients. With mediation analysis, we also observed that muscle power output plays a key role as a mediator between gait variability and gait velocity in this population. Several studies have suggested that muscle power output preservation is a crucial determinant for counteracting the age-related decline in functional capacity.[47;48]

The mechanisms whereby gait variability may negatively influence gait velocity in acutely hospitalized older adults are not clear. First, gait variability has been widely related to muscle system impairments[49] and has been considered a good marker of frailty[44] that may contribute to functional impairment in older adults. Second, the association between step time variability and muscle power has been previously described[45] in the oldest old and leg extensor peak power has been recognized as a predictor of gait velocity in frail elderly individuals.[50] From a practical standpoint, it may be suggested that exercise interventions aimed at improving muscle power (i.e., muscle power training) could reduce gait variability and ultimately improve gait velocity in acutely hospitalized older adults.

The inter-individual variability in response to physical exercise and usual care in hospitalized older adults (Study 5)

Acute illness requiring hospitalization is often a crucial event for many older adults[24] and functional decline is one of the negative short-term consequences of bed rest during hospitalization.[51] Specific in-hospital exercises could provide significant benefits over usual care and could help to reverse the functional decline associated with acute hospitalization in older adults. Although beneficial effects of exercise intervention on functional capacity are well established, frequent reports based of "average" exercise-related changes do not represent the wide individual variability in response to exercise.[52] Under the same exercise conditions, some subjects, termed responders (Rs), achieve benefits after intervention, whereas others, termed non-responders (NRs; unchanged response) and adverse-responders (ARs; worsened response) do not.[53;54] Our study showed that acutely hospitalized older adults performing an individualized exercise intervention presented a higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function compared with patients receiving usual care. We believe that these findings are important because functional capacity[51], cognitive function[17], and muscle strength[31] tend to decrease during hospitalization in elderly population.

We also explored whether the response rate for functional capacity was accompanied by similar changes for muscle strength and cognition. Our findings indicated a considerable heterogeneity of response for handgrip strength and cognitive function after usual care or physical exercise. Thus, response rate for functional capacity could not predict similar changes in other clinical characteristics, such as muscle strength and cognition.

Changes in functional status during hospitalization play an important role in the life trajectory of older adults after discharge. Our results showed that functional decline (*i.e.*, ARs for the GVT) during hospitalization is associated with a higher rate of mortality at one-year post-discharge compared with NRs and Rs. In the intervention group, those patients who experienced loss of functional capacity after the exercise training program (*i.e.*, ARs for the SPPB) also showed a higher rate of mortality at follow up in comparison with other categories. Our results support the importance of measuring functional status in hospitalized older patients[41], a useful vital sign that should be assessed by hospital clinicians.[51]

Finally, functional status at admission contains crucial information about prognosis of different interventions in acutely hospitalized older people. Our data suggested that those older adults with higher gait velocity at admission had worse response to usual care and, consequently, major vulnerability to iatrogenic nosocomial disability, than those patients with less functional reserve at baseline. A greater window of worsening during hospitalization could be a possible explanation for the major functional decline. Our findings also showed differences in responses to exercise training based on the functional capacity presented at baseline. Older adults who experienced a worsened response in the intervention group had less functional reserve at admission (SPPB score <4 points) compared with NRs and Rs. It means that patients at worst functional status at admission have greater possibility to be an adverse-responder to the exercise intervention.

This study is the first step to individualize physical exercise prescription in acutely hospitalized older adults.

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Chapter 8

Conclusions, practical applications and future perspectives

Study 1 (Chapter 1)

Conclusion 1: Multicomponent exercise training may have the most positive effects on cognitive function in older adults.

Practical application 1: This review highlights that the combination of different training modalities (endurance, resistance, balance, and flexibility) has the most positive effects on cognition in healthy older adults without known cognitive impairment.

Future perspective 1: A standardization of the methodological aspects of RCTs is required to clarify the relationship between physical exercise and cognition and to reduce discrepancies with animal, epidemiological, and cross-sectional studies. Finally, it would be interesting to determine exercise program characteristics (duration, intensity, frequency) to optimize cognitive gains in older adults.

Study 2 (Chapter 2)

Conclusion 2: An individualized multicomponent exercise program is an effective therapy to reverse functional decline associated with acute hospitalization in very elderly patients. Physical exercise also provide benefits in other endpoints, such as cognitive status and QoL**.**

Practical application 2: Physical exercise as intervention is one of the most important components in improving the functional capacity in older adults admitted in an ACE unit.

Future perspective 2: The results obtained in this study open the possibility for a shift from the traditional disease-focused approach in hospital ACE units for elders to one that recognizes functional status as a clinical vital sign that can be impaired by traditional (bed rest-based) hospitalization but effectively reversed with specific in-hospital exercises.

Study 3 (Chapter 3)

Conclusion 3: An individualized multicomponent exercise training program is an effective therapy to improve functional capacity (i.e., balance, rising from a chair, GVT, dual-task performance), maximal muscle strength and power performance in very old patients during acute hospitalization.

Practical application 3: This study highlights physical exercise as intervention to prevent functional decline and loss of muscle strength and muscle power associated with hospitalization. In addition, monitoring functional capacity with latest screening tools as inertial sensor units enables to detect enhancements in movement pattern in functional tasks associated with ADL after an innovative exercise training program in hospitalized older adults.

Future perspective 3: Our findings support the need for a shift from the traditional disease-focused approach in hospital ACE unit to one that recognizes functional capacity as a crucial vital sign during hospitalization. Moreover, the inertial sensor unit seems to be a feasible and useful tool for measuring and monitoring functional trajectory during hospitalization.

Study 4 (Chapter 4)

Conclusion 4: Muscle power output mediates the relationship between gait variability and gait velocity, slightly weakening this relationship.

Practical application 4: Muscle power output plays a key role in functional performance in acutely hospitalized older adults and its preservation is crucial for counteracting the age-related decline in functional capacity. Additionally, gait velocity and the proposed selection of walking parameters (stride regularity, stride length, CoV step time) can distinguish among acutely hospitalized older adults and can provide useful information for measuring and monitoring functional trajectory during the hospitalization.

Future perspective 4: Recommendations for managing functional status in older adults should include muscle power training (progressive resistance training interventions which emphasize high versus low muscle contraction velocity), mainly for the lower extremity muscles.

Study 5 (Chapter 5)

Conclusion 5: Oldest old patients performing an individualized exercise intervention present a higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function than those patients who are treated with usual care during acute hospitalization. An adverse response on functional capacity in older medical patients to physical exercise or usual care during hospitalization is associated with mortality at one-year post-discharge. Moreover, the functional status presented at admission seems to be a cornerstone in the trajectory of patients during hospital stay and even more so at follow up.

Practical application 5: The present inter-individual analysis study may be a first step towards to a greater precision in each individual, in-hospital treatments. A baseline functional assessment is necessary in order to prescribe an individualized physical exercise program and optimize the results of the intervention.

Future perspective 5: Our findings support the need for a shift from the traditional disease-focused approach in hospital ACE to one that recognizes functional status as a clinical vital sign. Precision exercise prescriptions can help address the substantial variability that exists in individual response to health related endpoints and tailoring of exercise programs to the individual phenotype of each hospitalized older adult.

Study 6 (Chapter 6)

Conclusion 6: An individualized, multicomponent exercise training program is an effective therapy for improving cognitive function (*i.e.*, executive function and verbal fluency domains) in very old patients during acute hospitalization.

Practical application 6: This study highlights physical exercise as intervention to prevent the cognitive impairment associated with hospitalization in older adults.

Future perspective 6: Our findings support the need for a shift from the traditional (bed-rest based) hospitalization to one that recognizes the important role of maintaining functional capacity and cognitive function in older adults, key components of intrinsic capacity. It would be interesting to combine a physical exercise intervention with cognitive training during hospitalization to reduce the incidence of delirium and improve functional capacity and cognitive function in this population.

8. Conclusiones, aplicaciones prácticas y perspectivas futuras

Estudio 1 (Capítulo 1)

Conclusión 1: El entrenamiento multicomponente parece tener los efectos más positivos sobre la función cognitiva en las personas mayores.

Aplicación práctica 1: Esta revisión destaca que la combinación de diferentes modalidades de entrenamiento (aeróbico, fuerza, equilibrio y flexibilidad) tiene los efectos más positivos sobre la cognición en las personas mayores sanas sin deterioro cognitivo conocido.

Perspectiva futura 1: Es necesaria la estandarización de los aspectos metodológicos de los ensayos clínicos aleatorizados para clarificar la relación entre ejercicio físico y cognición y reducir las discrepancias con los estudios en animales, epidemiológicos y transversales. Finalmente, sería interesante determinar las características del entrenamiento (duración, intensidad, frecuencia) para optimizar las mejoras cognitivas en las personas mayores.

Estudio 2 (Capítulo 2)

Conclusión 2: Un programa de ejercicio físico multicomponente individualizado es una terapia efectiva para revertir el deterioro funcional asociado a la hospitalización en pacientes ancianos. El ejercicio físico también proporciona beneficios en otros resultados como el estado cognitivo y la calidad de vida relacionada con la salud.

Aplicación práctica 2: El ejercicio físico como intervención es uno de los componentes más importantes para mejorar la capacidad funcional de las personas mayores admitidas en la Unidad de Agudos.

Perspectiva futura 2: Los resultados obtenidos en este estudio abren la posibilidad de un cambio del enfoque tradicional centrado en la enfermedad en la Unidad de Agudos para ancianos a uno que reconozca el estado funcional como un signo vital clínico que puede verse afectado por la hospitalización tradicional (basada en el reposo en la cama) pero que puede revertirse de forma efectiva con ejercicios específicos intrahospitalarios.

Estudio 3 (Capítulo 3)

Conclusión 3: Un programa de ejercicio físico multicomponente individualizado es una terapia efectiva para mejorar la capacidad funcional (es decir, equilibrio, levantarse de la silla, velocidad de la marcha, rendimiento en las tareas duales), fuerza muscular máxima y potencia muscular en pacientes muy mayores durante la hospitalización.

Aplicación práctica 3: Este estudio destaca el ejercicio físico como intervención para prevenir el deterioro funcional y la pérdida de fuerza muscular y potencia muscular asociada a la hospitalización. Además, monitorizar la capacidad funcional con los últimos instrumentos de detección como las unidades de sensores inerciales permite detectar mejoras en el patrón de movimiento en tareas funcionales asociadas a las actividades de la vida diaria después de un programa de ejercicio físico innovador en personas mayores hospitalizadas.

Perspectiva futura 3: Nuestros hallazgos respaldan la necesidad de un cambio enfoque tradicional centrado en la enfermedad en la Unidad de Agudos a uno que reconozca la capacidad funcional como un signo vital crucial durante la hospitalización. Además, las unidad de sensor inercial parecer ser un instrumento factible y útil para medir y monitorizar la trayectoria funcional durante la hospitalización.

Estudio 4 (Capítulo 4)

Conclusión 4: La potencia muscular media la relación entre la variabilidad de la marcha y la velocidad de la marcha, debilitando ligeramente esta relación.

Aplicación práctica 4: La potencia muscular juega un papel fundamental en el rendimiento funcional de las personas mayores hospitalizadas y su preservación es crucial para contrarrestar la disminución de la capacidad funcional relacionada con la edad. Además, la velocidad de la marcha y los parámetros seleccionados de la marcha (regularidad de zancada, longitud de zancada, coeficiente de variabilidad del tiempo de paso) pueden distinguir entre las personas mayores hospitalizadas y pueden proporcionar información útil para medir y monitorizar la trayectoria funcional durante la hospitalización.

Perspectiva futura 4: Las recomendaciones para controlar el estado funcional de las personas mayores deben incluir el entrenamiento de potencia muscular (entrenamiento de fuerza progresivo que enfatiza la velocidad de contracción alta en lugar de baja), principalmente para la musculatura de la extremidad inferior.

Estudio 5 (Capítulo 5)

Conclusión 5: Los pacientes muy mayores realizando una intervención de ejercicio físico individualizada presentan una mayor prevalencia de respondedores positivos y una menor prevalencia de no respondedores y respondedores negativos para la capacidad funcional, fuerza muscular y función cognitiva que aquellos pacientes que son tratados con la atención médica habitual durante la hospitalización. Una respuesta negativa sobre la capacidad funcional en pacientes de edad avanzada al ejercicio físico y a la atención médica habitual durante la hospitalización se asocia con la mortalidad al año después del alta. Además, el estado funcional presentado en el momento del ingreso pareces ser la piedra angular en la trayectoria de los pacientes durante la hospitalización y más aún en el seguimiento.

Aplicación práctica 5: El presente estudio de análisis interindividual puede ser un primer paso hacia una mayor precisión en cada tratamiento individual en el hospital. Es necesaria una valoración funcional inicial para prescribir un programa de ejercicio físico individualizado y optimizar los resultados de la intervención.

Perspectiva futura 5: Nuestros hallazgos respaldan la necesidad de un cambio enfoque tradicional centrado en la enfermedad en la Unidad de Agudos a uno que reconozca la capacidad funcional como un signo vital crucial durante la hospitalización. La prescripción de ejercicio físico de precisión puede ayudar a abordar la variabilidad sustancial que existe en la respuesta individual a los resultados relacionados con la salud y a la adaptación de los programas de ejercicio físico al fenotipo individual de cada persona mayor hospitalizada.

Estudio 6 (Capítulo 6)

Conclusión 6: Un programa de ejercicio físico multicomponente individualizado es una terapia efectiva para mejorar la función cognitiva (es decir, los dominios de función ejecutiva y fluencia verbal) en pacientes ancianos durante la hospitalización.

Aplicación práctica 6: Este estudio destaca el ejercicio físico como intervención para prevenir el deterioro cognitivo asociado a la hospitalización en las personas mayores.

Perspectiva futura 6: Nuestros hallazgos respaldan la necesidad de un cambio de la hospitalización tradicional (basada en el reposo en cama) a una que reconozca la importancia de mantener la capacidad funcional y la función cognitiva en las personas mayores, componentes claves de la capacidad intrínseca. Sería interesante combinar una intervención de ejercicio físico con entrenamiento cognitivo durante la hospitalización para reducir la incidencia de delirium y mejorar la capacidad funcional y la función cognitiva en esta población.

Chapter 9

Relevant papers

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Letter to the Editor

Iatrogenic Nosocomial Disability Diagnosis and Prevention

To the Editor:

The traditional model of hospitalized care has changed dramatically over the past century, from addressing acute self-limited pathologies toward addressing much more complex patient profiles that are characterized by frailty, disability, multimorbidity, and polypharmacy in older and chronic patients. These changes have marked the appearance of geriatric syndromes that modify patient life trajectories. Despite these changes in patient profiles, the hospital model remains stuck in the previous century model in such a way that hospitalization can perfectly manage acute diseases, such as pneumonia or cardiac failure, although it can also contribute to several risks that are clearly avoidable.

Hospitalization is a sentinel event and a leading cause of long-term disability, defined as disability that lasts for more than 6 months[1] and the incidence of new disability associated with hospitalization ranges from 5% to 60%.[2–4] Loss of function in activities of daily living (ADL) tasks following hospitalization increases the risk for institutionalization, regardless of preadmission ADL impairment.[5,6] One of the first studies to address this issue was the Hospital Outcomes Project for the Elderly (HOPE),[7] and it showed that at discharge, 31% of the patients had lost the ability to perform at least 1 ADL and that 40% were no longer able to carry out 3 or more ADLs. At 3 months, 19% of the surviving patients had a decline in ADLs, and 40% had a decline in Instrumental ADLs. Additionally, the development of new disabilities during hospitalization is associated with higher mortality,[8] health care utilization,[9] and cognitive impairment, depressive symptoms, or quality of life.[10] This deficiency in the clinical outcomes arises from the acute diseases themselves but is also related to patient management during the hospital stay, despite great sensitivity to this issue.[11,12]

It is in this context that several devastating concepts appear, such as iatrogenic and nosocomial disability. Iatrogenic adverse events are usually defined as any unintended injury, harm, or complication that results more from health care management rather than the underlying disease process.[13] The National Conference on Health has defined iatrogenic conditions as "any adverse condition of medical origin in the broad sense, taking into account the state of the art at a given time, and which in no way implies error, fault or negligence." Disability refers to a "limitation of function (usually of activities of daily living) or restriction of activities" (World Health Organization ICF 2001).[14] A multidisciplinary working group of health professionals addressed these issues previously in 2011, and the task force defined iatrogenic disability as functional decline that results from 1 or several iatrogenic adverse events occurring during hospitalization, involving 3 components that interact and have a cumulative effect: (1) the patient's preexisting frailty, (2) the severity of the disorder that led to the patient's admission, and (3) the hospital structure and the process of care.[15] However, since the introduction of this term, a search in PubMed for related articles found very few articles.[16]

The concept of iatrogenic adverse events in a hospital is mostly linked to nosocomial infections or other procedures, but it has not been linked to the notion of disability, although the prevalence of disability can be even worse for short- and long-term outcomes. Many older patients admitted to hospital are forced to bed and chair rest and to be severely sedentary, which can lead to sarcopenia and also occasionally, to chemical restraints that increase the risk of other unacceptable outcomes. Some studies have found that patients may be in bed for 83% of the hospitalized stay, even if they are able to walk,[17] and the number of hours that an older hospitalized patient is not bedridden or sitting in a chair can be only 4 hours per day.[18] However, functional disability is only 1 aspect of hospital iatrogenic disability. It is apparent that the functional and physical deficiencies are more evident after a hospitalization, but evidence also indicates that hospitalization increases a patient's risk of cognitive decline and developing dementia.[19]

Potentially preventable iatrogenic disability has been assessed and quantified, and at least 80% of the cases were judged to be preventable. The most common health management issues identified in patients with preventable iatrogenic disability were low mobilization (bed rest and lack of physical therapist intervention), overuse of diapers, and transurethral catheterization.[16] This problem can be addressed only by a multicomponent intervention. There are similar concerns with delirium (the cognitive side of the nosocomial iatrogenic disability), and some studies have determined a global approach to reduce its severity.[20]

Poor health, disability, and dependency are not inevitable consequences of aging. Ideally, evidence-based cognitive and functional interventions should be a routine aspect of comprehensive geriatric interventions. Physical activity as an intervention is one of the most important components in improving the functional capacity of hospitalized patients. Simple measures, such as increasing the time spent walking, have the potential to significantly decrease the incidence of chronic disease.[21] In the issue of nosocomial disability, it is essential to develop a multicomponent exercise program based on the current evidence, which should include aspects of strength, power, and balance.[22,23] Multicomponent exercise programs, and particularly those including strength training, are the most effective interventions to delay disability and other adverse events. Indeed, it has been recently reported that multicomponent exercise training, including explosive resistance training, improved neuromuscular function and functional outcomes in frail nonagenarians after long-term physical restraint,[24] as well as in frail patients with several chronic diseases.[25] Furthermore, physical exercise administration is relatively free of potential unwanted side effects caused by common medications that are prescribed in this type of patient.[25]

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Several previous consensuses have established various concepts, such as posthospital syndrome, but we must focus our attention on the whole period, not just the recovery period (secondary prevention). We should mainly focus on the period in which a primary prevention intervention can have a greater impact because the hospitalization period affects patients at high risk of iatrogenic nosocomial disability. Adding the term "nosocomial" not only allows the inclusion of the hospitalization period but also the integration and unification of the concept of iatrogenic disability when discussing research in this area. Furthermore, iatrogenic disability can occur at home, in nursing homes, and in rehabilitation units, so linking the term nosocomial to hospital-acquired iatrogenic disability focuses attention on the hospital period and the proper characteristics of this type of disability.

Although other definitions have previously been used, a search with those terms related to iatrogenic disability or posthospital discharge syndrome returns very few related articles. We consider it vital to relaunch the definition of the comprehensive concept of iatrogenic nosocomial disability to target this vulnerable population and address preventable hospital-acquired syndromes.

What does it matter if we offer the best hospital treatment or the best technology if the disability resulting from this treatment or technology leads to an overwhelming hospitalization-acquired long-term disability?

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Review

Role of physical exercise on cognitive function in healthy older adults: A systematic review of randomized clinical trials

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ABSTRACT

Cognitive impairment has a harmful effect on quality of life, is associated with functional limitations and disability in older adults. Physical activity (PA) has shown to have beneficial effects on cognition but the results and conclusions of randomized controlled trials (RCTs) are less consistent. Update of knowledge was necessary to examine the effects on cognitive function of new training modalities developed in recent years, such as multicomponent exercise training.

Therefore, the purpose of this review was to examine the role of multicomponent training versus aerobic or resistance training alone on cognition in healthy older adults (>65 years) without known cognitive impairment. The mean differences (MD) of the parameters from pre-intervention to post-intervention between groups were pooled using a random-effects model. Twenty-one RCTs published between 2002 and 2016 were included. Multicomponent exercise training may have the most positive effects on cognitive function in older adults. The small number of included studies and the large variability in study populations, study design, exercise protocols, adherence rates and outcome measures complicate the interpretation of the results and contribute to discrepancies within the exercise research literature.

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1. Introduction

A plausible consequence of the aging process in older adults is cognitive decline, which is associated with an increased risk of dementia and adverse health outcomes such as functional limitations and disability (Gill et al., 1996; Moritz et al., 1995), and places a substantial economic burden on health care systems and society (Hann and Wallace, 2004). The development of different interventions to maintain or improve cognitive function is necessary to control the epidemic of dementia and other disorders (Snowden et al., 2011). Physical activity (PA) has shown to have beneficial effects on cognition both in cognitively healthy older adults (Colcombe and Kramer, 2003; Etnier et al., 1997; van Sickle et al., 1996) and in older adults with cognitive impairment or dementia (Eggermont et al., 2006; Heyn et al., 2004).

PA has been reported to play a key role in the prevention of different disorders, such as cardiovascular disease, diabetes and some types of cancer (Katz and Pate, 2016). Although evidence of the beneficial effects of PA on cognitive function has been clearly provided in the results of animal, epidemiological and cross-sectional studies, the results and conclusions of randomized controlled trials (RCTs) have been less consistent (Kelly et al., 2014).

The influence of PA on brain function and structure has previously been analyzed in animal studies. In aging animals, exercise training has been found to increase the levels of key neurochemicals, such as brain derived neurotrophic factor (BDNF) and insulin-like growth factor 1 (IGF-1), which thereby improve synaptic plasticity and neuronal survival (Berchtold et al., 2001; Carro et al., 2001).

Many epidemiological studies have investigated the benefits of PA on cognition and showed a clear relationship between higher levels of PA and a reduced risk of cognitive impairment. Studies with large sample sizes and long follow up periods have shown that participants who had previously engaged in higher levels of PA were more likely to perform better on cognitive tasks when compared with subjects with previously lower PA levels (Sofi et al., 2011; Yaffe et al., 2001). Therefore, PA is hypothesized to have a protective effect on the cognitive decline in older adults.

Higher PA levels across different stages of life, especially during the teenage years, have been reported to be associated with a decreased likelihood of cognitive decline in later life (Middleton et al., 2010). Therefore, the results of cross-sectional studies have substantiated the evidence shown by epidemiological studies and reinforced the association between PA and better cognitive function in older adults (Dustman et al., 1994; Etnier et al., 1997).

Multiple RCTs have been conducted to determine the effects of PA on cognition and to identify the role of exercise training in the prevention of cognitive decline in older adults. The influence of different exercise training protocols including aerobic exercise training, resistance training and multicomponent training that combines aerobic and strength training with other training modalities, and their relationship to cognitive outcomes have been studied; however, clear evidence across trials has not been reported. Meta-analytic reviews of RCTs have reported large variations in the magnitude of the improvements in cognitive outcomes associated with aerobic exercise training and while some meta-analyses have reported moderate cognitive gains (Colcombe and Kramer, 2003; Heyn et al., 2004), the cognitive benefits observed in other studies have been limited (Angevaren et al., 2008; Etnier et al., 1997). Reviews examining the effects of resistance training on cognitive performance have revealed similarly inconsistent results (Chang et al., 2012; Liu-Ambrose and Donaldson, 2009). Although cognitive benefits have been observed in different RCTs, no consistent results have been obtained regarding significant cognitive improvements. Another interesting finding of the previously mentioned meta-analysis (Colcombe and Kramer, 2003) was that studies with aerobic training interventions that also included a strength training protocol demonstrated greater benefits in terms of cognitive performance than those that only included an aerobic training component.

The presence of both inconsistent results and evidence makes it difficult to draw conclusions about the beneficial effects of exercise training on cognitive performance, especially in older adults. Updated knowledge is necessary to clarify whether PA has vital importance in promoting cognitive performance and preventing neurological disorders in older adults without known cognitive impairment who could benefit most from non-pharmacological interventions in the early stages of cognitive decline. New training modalities have been developed in recent years, such as multicomponent exercise training, that had not been included in previous systematic reviews (Kelly et al., 2014) and could have beneficial effects on cognitive performance in older adults (Colcombe and Kramer, 2003; Smith et al., 2010). In our review, we aimed to update previous work (Kelly et al., 2014) by analyzing the effects of different exercise training modalities, such as aerobic training, resistance training and multicomponent exercise training, on cognition in a narrower age range of healthy older adults (>65 years) without known cognitive impairment. In addition, a secondary objective of this review was to clarify the discrepancies that were observed between the consistent evidence reported in animal, epidemiological and cross-sectional studies and the less consistent results observed in RCTs.

2. Methods

2.1. Search strategy

This study was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement (Liberati et al., 2009) and the method used was based on the minimum criteria established by the Cochrane Back Review Group (CBRG) (Furlan et al., 2009).

A systematic review was conducted to update the existing knowledge regarding the influence of PA or exercise training on cognitive outcomes in older adults, continuing the meta-analysis published by Kelly and colleagues (Kelly et al., 2014) but with the addition of randomized controlled trials published from 2012 to 2016. Queries of the literature were performed using the electronic databases Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and MEDLINE (until August 30th, 2016). The search terms employed, which were the same as those used by (Kelly et al., 2014) in their previous review and meta-analysis, included the following: [“exercise,” “fitness,” “physical endurance,” “physical activity,” “physical training” AND “cognition,” “cognitive performance,” “cognitive decline,” “cognitive function,” “cognitive processes” AND “older adults,” “elderly,” “healthy elderly,”]. Additionally, the reference lists were examined to detect studies that were potentially eligible for inclusion. We supplemented the search using complementary databases, such as Google Scholar. Studies reported in languages other than English and Spanish were not explored.

During the inclusion period, we screened title and abstracts, and in some cases, full articles if they were of interest and when full-text screening was necessary to verify whether they met the criteria for inclusion in the review.

2.2. Selection criteria

Randomized-controlled trials (RCTs) that investigated the effects of different exercise training modalities (i.e., aerobic training, resistance training, and multicomponent exercise training) on cognition in healthy older adults (>65 years) without known cognitive impairment were selected. Parallel and crossover design trials were included. Case-reports, case-series, single- case studies, dissertations and conference proceedings were excluded.

For articles in which baseline cognitive function was measured using the Mini Mental Modified Examination (MMSE) (Folstein et al., 1975), all members of the sample had to have scored $\geq$23 points to be included in this review. The exercise categories were chosen based on the most common exercise interventions implemented in RCTs published during the study period. At least 10 participants per training condition were required for inclusion in the review. We also excluded studies if participants had been diagnosed with any cardiovascular disease, or other significant medical, psychiatric, or neurological problems. Studies based on interventions in which participants performed specific cognitive tasks, such as cognitive training, dual-task training or exergames, were also excluded from the review, to examine the inherent effects of exercise training on cognitive function. Finally, we excluded interventions carried out in an aquatic environment.

The outcome of interest was cognitive function, which was divided into two principle domains; executive function and memory. In each domain, different sub-categories were analyzed. The executive function sub-categories were: working memory, verbal fluency, reasoning, attention and processing speed. The memory domain sub-categories were: recognition, immediate recall, delayed recall, face-name recall and paired associations. Other cognitive outcomes not included in these groups were also analyzed. Outcomes and sub-categories are detailed in Table 1.

2.3. Data extraction

Two authors (MI, NMV) independently screened the titles and abstracts of potentially eligible studies identified by the search strategy. If necessary, a third researcher (FZF) was consulted. If one abstract did not provide enough information for evaluation based on the inclusion and exclusion criteria, full articles were retrieved for a full text assessment. The following relevant data were extracted: study design, participant characteristics, methods, quality, exercise protocol description, cognitive outcomes, feasibility, and conclusions. Authors were contacted to provide missing data or to clarify if data were duplicated in multiple publications. Cognitive impairment was defined based on the description of the population or by using the MMSE scores (cut-off point of 23/30). It was assumed that the population was cognitively healthy when no specific information regarding cognitive status was reported, and in cases in which the MMSE was not performed at baseline, the reviewers contacted the authors to obtain further details about the cognitive function of the assessed population.

2.4. Assessment of risk of bias

Two independent reviewers evaluated the risk of bias among the included studies using the guidelines published in Section 8 of the Cochrane Handbook. Disagreements were resolved by consulting a third reviewer. The items selected for use in the methodological assessment of the included randomized controlled trials were: an adequate sequence generation for randomization, reported allocation concealment, a blinded assessment of outcomes, a description of losses to follow-up and exclusions, a use of intention to treat analysis and a selective reporting of study results. Each item was classified as low risk, unclear risk (specific details or description were not reported) or high risk (not fulfilling the criteria).

3. Results

3.1. Included studies

After the using the literature search strategy to identify articles published between 2012 and 2016, 42 RCTs were selected for screening out of the 1930 articles identified as potentially relevant due to assessing effects of exercise training on cognitive performance in healthy older adults. Forty-two RCTs were screened and 32 RCTs were excluded from the review because they did not meet the inclusion criteria. Therefore, 10 articles published between 2012 and 2016 were ultimately selected and included in the review. Previously, (Kelly et al., 2014) included 25 RCTs published between 2002 and 2012 in their review and meta-analysis, and 11 of those RCTs met the inclusion criteria for this review (Fig. 1). Thus, 21 RCTs were eligible for inclusion. Overall these studies had enrolled 320 participants in aerobic exercise groups, 409 participants in resistance training groups, and 260 participants in multicomponent exercise training groups; additionally, 279 participants were enrolled in stretching/toning groups, 200 participants were enrolled in “no exercise” active control groups, and 310 participants were enrolled in “no intervention” control groups. The most common intervention was resistance training. Participants in the stretching/toning group performed stretching, range of motion exercises, toning or yoga exercises. Participants in the no exercise active control group received health education classes, guideline care, watched movies or engaged in social activities. Subjects in the no intervention groups received no contact, minimum social support or were placed on a waiting list. Characteristics of the included studies are presented in Tables 2–4.

3.2. Quality (risk of bias)

Of the included studies, 66.67% presented adequate sequence generation (14 of 21 RCT) (Barnes et al., 2013; Best et al., 2015; Klusmann et al., 2010; Liu-Ambrose et al., 2008; Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Napoli et al., 2014; Oken et al., 2006; Smiley-Oyen et al., 2008; Tarazona-Santabalbina et al., 2016;

Table 1
Lists of outcome measure and cognitive sub-categories extracted from the included studies.

Executive function domain		Memory function domain	
Task/Outcome	Sub-category	Task/Outcome	Sub-category
WAIS III	Working memory	Word Learning Test	Recognition
Self-ordered pointing task	Working memory	RAVLT	Immediate recall
1-back test/2-back test	Working memory	HVLT	Immediate recall
DSF/DSB	Working memory	LMI	Immediate recall
ROF-C	Working memory	Selective Reminding Task	Immediate recall
CBTF/CBTB	Working memory	ROF-IR	Immediate recall
Verbal digit backward/forward test	Working memory	Word Learning Test	Delayed recall
LNS	Working memory	Delayed Logical Memory	Delayed recall
Animals/vegetables/letter p/category	Verbal fluency	Memorizing face scene pairs	Paired associations
COWAT	Verbal fluency		
Stroop Word-Colour	Attention		
Covert orienting	Attention		
CCRT	Attention		
UFOV	Attention		
Go/No Go test	Attention		
WCST	Attention		
TMT A/B	Attention		
TPCN/TPCE	Attention		
Deary Liewald Reaction Time	Proc. speed		
Simple reaction time	Proc. speed		
Incompatible 8 choice reaction time	Proc. speed		
DSST	Proc. speed		
Task switching	Proc. speed		

WAIS = Wechsler Adult Intelligence Scale; DSB = Digit Span Backward; DSF = Digit Span Forward; ROF-C = Rey Osterrieth Figure Copy; CBTF = Corsis block-tapping forward; CBTB = Corsis block-tapping backward; LNS = Letter Number Sequencing; COWAT = Controlled Oral Word Association Test; CCRT = Cambridge Contextual Reading Test; UFOV = Useful Field of View; WCST = Wisconsin Card Sort Test; TMT A/B = Trail Making Test A and B; TPCN = Toulouse–Pieron Cancellations numbers; TPCE = Toulouse–Pieron Cancellations errors; DSST = Digit Symbol Substitution Test; RAVLT = Rey Auditory Verbal Learning Test; = Hopkins Verbal Learning Test; LMI = Logical Memory Part I; ROF-IR = Rey Osterrieth Figure Immediate Recall.

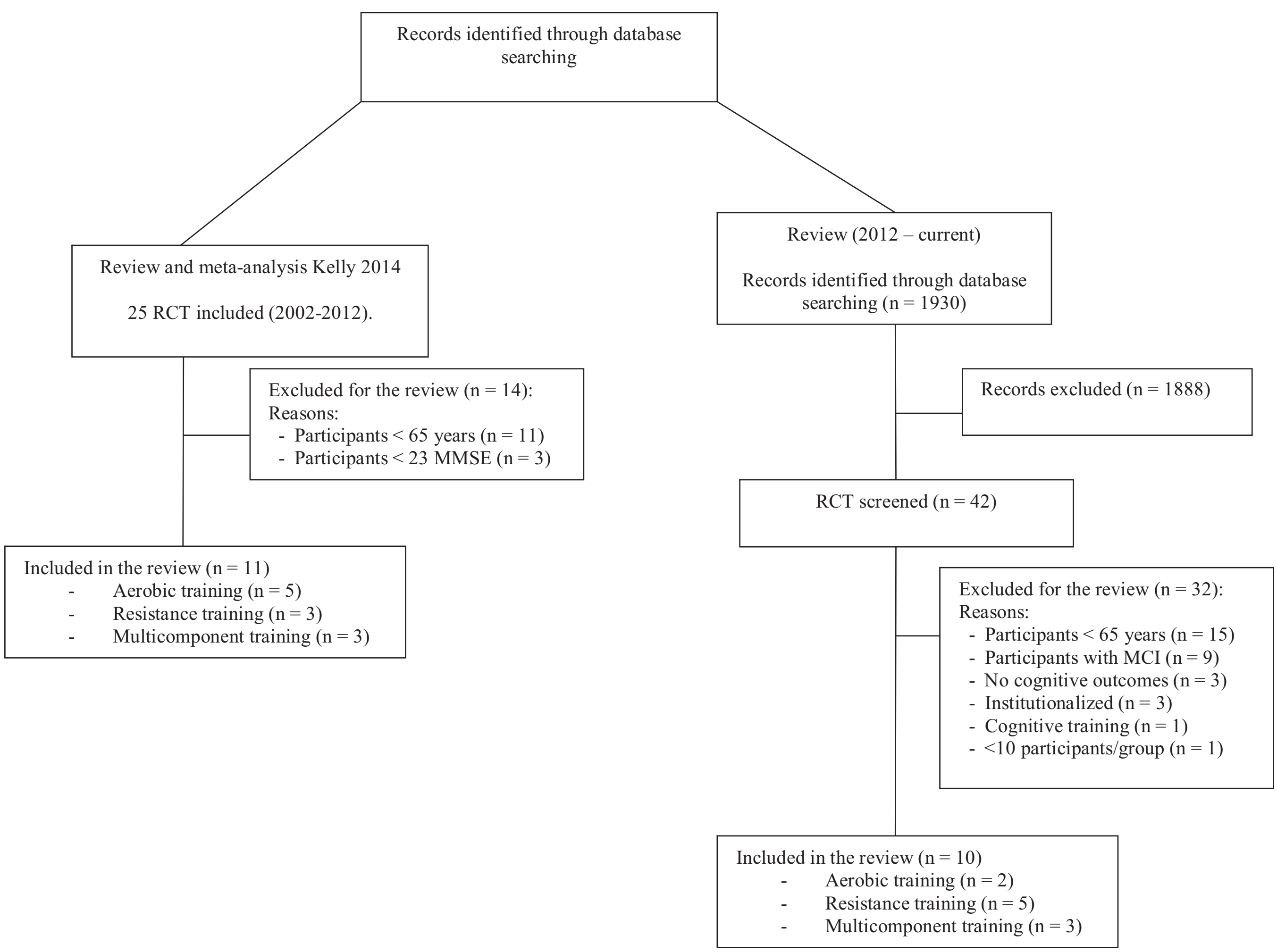

Fig. 1. Flowchart showing the selection of studies for this systematic review.

Table 2
Characteristics of studies – aerobic exercise training.

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Aerobic versus stretching/toning								
Oken (2006)	Three conditions: 1. Aerobic training (EG) 2. YOGA 3. Wait List Control Group (CG)	1. EG: 1 × 1 h per week for 6 months at 70% of max HRR-adjusted as needed. 5 more sessions/week of aerobic training recommended at home. 2. YOGA: 1 × 1.5 h for 6 months: 30 s pose,<1 min rest. FU: PT.	135 subjects were randomized: EG n = 47, YOGA n = 44 and CG n = 44. Age range: 65–85. EG M^{age}: 73.6 (5.1). YOGA M^{age}: 71.5 (4.9). CG: M^{age}: 71.2 (4.4).	Delayed recall[c] (10 word list learning task) Working memory[c] (WAIS III) Attention (Stroop[c], Cov. Orient[c], CRT[c]) Divided attention (UFOV)[c] Proc. Speed[c].	10 word list learning: 0.31 WAIS III: 0. Stroop W-C: 0.09 Cov. Orient: −0.21 CRT: −0.05 UFOV: 0.03 Proc. Speed: 0.13	Attendance 69%. No AE related to the intervention.	Better adherence YOGA (78%) vs EG (69%). Training session duration less EG group (1 h) vs YOGA (1.5 h). Training frequency is low (1 session/week).	No significant differences betweenEG and CG. Lack of effect on cognitive function could be related with ceiling effect.
Smiley-Oyen (2008)	Two conditions: 1. Aerobic exercise (EG). 2. FLEX-TONE (CG): Strength, flexibility and balance.	1. EG: 3 × 1 h per week for 10 months. 10 min warm up + 25–30 aerobic training + 10 min cool down. 60–70% progressed to 65–80% of max HRR. 2. CG: 3 × 50 min per week for 10 months. 10 min warm up + 25–30 min Tai Chi, flex bands, free hand weights, stability balls + 10 min cool down. FU: PT	109 subjects were randomized EG n = 55 and CG n = 54. Age range: 65–79. EG M^{age}: 69.86 (4.59). CG M^{age}: 70.52 (4.47).	Processing speed (simple reaction time[c], incompatible 8-choice reaction time[c], 8 choice reaction time[c]). Attention (Go/No Go[c], Stroop W-C[b], Stroop W&C[c], WCST[c]).	Simple reaction time: 0.46 Incompatible 8-choice reaction time: −0.01 8 choice reaction time: 0.48 Go/No Go: 0.26 Stroop W: −0.13 Stroop C: 0.15 Stroop W-C: −0.33 WCST: 0.12	No major AE related to the intervention.	Significant decrease in reaction time and errors in the Stroop W-C task in EG.	No significant differences between EG and CG, but significant pre-post improvements in EG.
Albinet (2010)	Two conditions: 1. Aerobic training (EG). 2. Stretching exercise control (CG).	1. EG: 3 × 1 h per week for 12 weeks. 40–60% of max HRR. FU: PT.	24 subjects were randomized EG n = 12 and CG n = 12. Age range: 65–78. Cognitive global function: MMSE >26. EG M^{age}: 70.9 (4.9). EG MMSE: 28.5 (1.1). CG M^{age}: 70.4 (3.4). CG MMSE: 29 (0.9).	Attention[a] (WCST).	WCST: −0.66	Attendance rate of 87.6% EG and 87% CG.		Individualized-intensity AT improved executive performance vs CG.
Nagamatsu (2012)	Three conditions: 1. Resistance training (RT) 2. Aerobic training (EG) 3. Balance and toning (CG)	Single-blind. 1. 2 × 1 h/session per week for 6 months. 2 sets x 6–8 rep. increasing progressively intensity training. 2. 2 × 1 h/session per week. Walking 40–70/80% of max HRR. 3. 2 × 1 h/session per week for 6 months. FU: PT.	86 women were randomized RT n = 28, EG n = 24 and CG n = 27. Age range: 70–80. Cognitive global function: MMSE >24. EG M^{age}: 73.9 (3.4). EG MMSE: 27.0 (1.8). RT M^{age}: 75.6 (3.6). RT MMSE: 27.4 (1.5). CG M^{age}: 75.1 (3.6). CG MMSE: 27.1 (1.7).	Attention (Stroop C-W[c], TMT A-B[c]). Working memory[c] Associative memory (Memorizing face scene pairs[c]). Conflict resolution[c] (Everyday Problems test)	No data to calculate.	Adherence was low (not details). AE: 2 participants shortness of breath and 4 noninjuries falls.		RT significant differences vs CG, AT not. Twice weekly RT is a promising strategy to improve cognitive function. AT had not effect on cognitive function.

Table 2 (*Continued*)

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Ten Brinke (2015)	Three conditions: 1. Aerobic training (EG). 2. Resistance training (RT) 3. Balance and toning (CG).	1. 2 × 1 h per week for 26 weeks. 40–80% of max HRR. 2. 2 × 1 h per week for 26 weeks. 10 exercises. 2 sets x 6–8 rep. 7RM. 3. Stretching, range of motion exercises, relaxation techniques. FU: PT.	86 women were randomized EG n = 30, RT n = 28 and CG n = 28. Age range: 70–80. Cognitive global function: MMSE >24. EG M^{age}: 76.07 (3.43). EG MMSE: 27.54 (1.51). RT M^{age}: 73.75 (3.72). RT MMSE: 26.67 (2.64). CG M^{age}: 75.46 (3.93). CG MMSE: 27.17 (1.85).	Immediate recall[c] (RAVLT).	RAVLT total adquisition: −0.06 RAVLT recall interference: 0. RAVLT loss interference: −0.48 RAVLT long recall: −0.3 RAVLT recognition: 0.19	Attendance rate of 60% EG, 54% RT, 59% CG. AE: 1 shortness of breath RT, 2 noninjuries falls EG, 1 shortness of breath CG.	Low adherence to training session.	No significant differences were found between groups
Aerobic versus no exercise active control								
Muscari (2010)	Two conditions: 1. Aerobic exercise in community gym (EG). 2. Educational material (CG).	1. EG: 3 × 1 h per week for 12 months. At least 20 min of session 70% of max HRR. 2. CG: Counselling to increase daily PA. FU: PT.	120 subjects were randomized EG n = 60 and CG = 60. Age range: 65–74. Cognitive global function: MMSE >24. EG M^{age}: 68.8 (2.5). EG MMSE: 26.7. CG M^{age}: 69.6 (2.8). CG MMSE: 27.0.	Cognitive function[a] (MMSE).	No data to calculate.	No AE related to intervention.	The data analysis was limited to participants who participated at least 50% of training sessions.	AT may have a positive impact on the cognitive performance.
Legault (2011)	Four conditions: 1. Aerobic exercise and flexibility (EG). 2. Health aging (CG). 3. Cognitive training (CT). 4. Combined intervention (COM): Aerobic exercise + cognitive training.	Single blind. 1. EG: 3 × 150 min per week for 4 months. 3. 24 sessions in 4 months. Computer tasks. 4. 56 sessions in 4 months. FU: PT.	73 subjects were randomized EG n = 16, CG n = 17, CT n = 16 and COM n = 19. Age range: 70–85. Cognitive function: 3MSE score >88. CG M^{age}: 75.4. 3MSE: 94.3 EG M^{age}: 77.5. 3MSE: 94.6. CT M^{age}: 76.3. 3MSE: 95.6. COM M^{age}: 76.3. 3MSE: 94.6	Immediate recall (HVLT[c], LM1[c]). Delayed recall[c] Attention (task switching[c], TMT A-B[c]). Working memory (self ordered pointing task[c], 1-back[c], 2-back[c]). Response inhibition[c]. (Eriksen flanker task)	HVLT immediate recall: −0.08 LM1: 0.29 HVLT delayed recall: 0.23 Task switching: 0.13 TMT A-B: 0.54 Self ordered pointing task: 0 1-back: −0.28 2-back: −0.54 Eriksen flanker task: −0.38	Attendance rate of 76% EG, 96% CT and 90% PACT. 1 participant present AE.	No significant outcomes reported.	No significant differences between EG and CG.

Table 2 (*Continued*)

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Aerobic versus no intervention								
Oken (2006)	Three conditions: 1. Aerobic exercise (EG) 2. YOGA 3. Wait list Control Group (CG)	1. EG: 1 × 1 h per week for 6 months at 70% of max HRR-adjusted as needed. 5 more sessions/week of aerobic training recommended at home. 2. YOGA: 1 × 1.5 h for 6 months: 30 s pose,<1 min rest. FU: PT.	135 subjects were randomized: EXER n = 47, YOGA n = 44 and CG n = 44. Age range: 65–85. EG M^{age}: 73.6 (5.1). YOGA M^{age}: 71.5 (4.9). CG: M^{age}: 71.2 (4.4).	Delayed recall[c] (10 word list learning task) Working memory[c] (WAIS III). Attention (Stroop[c], Cov. Orient[c], CRT[c]) Divided attention (UFOV)[c] Proc. Speed[c].	10 word list learning: 0 WAIS III: −0.06 Stroop W-C: 0.2 Cov. Orient: 0.03 CRT: 0.13 UFOV: 0.06 Proc. Speed: 0.5	Attendance 69%. No AE related to the intervention.	Better adherence YOGA (78%) vs EG (69%). Training session duration less EG group (1 h) vs YOGA (1.5 h). Training frequency is low (1 session/week).	No significant differences betweenEG and CG. Lack of effect on cognitive function could be related with ceiling effect.
Vidoni (2015)	Four conditions: 1. No intervention (CG). 2. 75 WEEK 3. 150 WEEK 4. 225WEEK	3–5 days x 50 min per week for 26 weeks. 75WEEK: Walking 75 min per week. 150WEEK: Walking 150 min per week. 225WEEK: Walking 225 min per week. First 4 weeks at 40–55% of max HRR. 5–18 weeks: 50–65% of max HRR. 19–26 weeks: 60–75% of max HRR. FU: PT.	101 subjects were randomized CG n = 25, 75WEEK n = 25, 150WEEK n = 27, 225WEEK n = 24. Age range: >65. Cognitive function: CDR = 0. CG M^{age}: 72.5 (5.8). CG MMSE: 29.3 (0.9). 75WEEK M^{age}: 73.5 (5.9). 75WEEK MMSE: 29.2 (0.9). 150WEEK M^{age}: 72.5 (5.7). 150WEEK MMSE: 29.3 (1.2). 225WEEK M^{age}: 73.2 (5.3). 225WEEK MMSE: 29.2 (1.1).	Verbal memory (Logical Memory[c], Delayed Logical Memory[c], Selective Reminding task[c], Boston Naming test[c]). Visuospatial processing (Block Design[c], Stroop[c], DSST[c], TMT A[c]). Simple attention (DSB[c], DSF[c], Letter Number Sequencing[c]). Set Maintenance and Shifting[c] (DKEFS). Verbal fluency (animals[c], vegetables[c]) Reasoning (letter[c], word[c], matrix[c])	No data to calculate.	Adherence rate: 75WEEK 82.3%, 150WEEK 85.5%, 225WEEK 70.1%. 94 AE in total: 91% mild and 9% moderate severity.	ITT analyses, not gains in any cognitive domain. PP analyses, visuospatial processing and simple attention improved of any exercise. Better adherence and lower AE in 150WEEK vs 225WEEK.	No significant differences between EG and CG in ITT analyses. Physiologic adaptation to aerobic exercise (improvement in VO2max) is an important predictor of cognitive benefit.

EG = experimental group; CG = control group; FU = follow up; AE = Adverse Event; AT = Aerobic Training; RT = Resistance Training; PT = post training; Mage = mean age; (SD or SE) = (Standard Desviation or Standard Error); DSST = digit symbol substitution test; UFOV = Useful Field of View; HRQL = Health Related Quality of Life; WCST = Wisconsin Card Sort Test; Stroop C-W = Stroop colour − word; HVLT = Hopkins Verbal Learning Test; LMI = Logical Memory Part I; RAVLT = Rey Auditory Verbal Learning Test; CCRT = Cambridge Contextual Reading Test; WAIS = Wechsler Adult Intelligence Scale; MMSE = Mini Mental State Examination; 3MSE = Modified Mini Mental Examination; TMT = Trail Making Test; DSF = Digit Span Forward; DSB = Digit Span Backward; DKEFS: Delis Kaplan Executive function System; HRR = heart rate reserve; ITT = Intention To Treat; PP = Per protocol.

[a] Significantly greater improvement for training compared to control.

[b] Significant training effects for experimental group from baseline to PT; no significant effect for controls.

[c] No significant intervention difference between experimental and control groups.

Table 3
Characteristics of studies – resistance training.

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Resistance versus stretching/toning								
Cassilhas (2007)	Three conditions: 1. High intensity training group (EG) 2. Moderate training group (AC) 3. Stretching control group (CG)	1. EG: 3 × 1 h/session per week for 24 weeks. 6 exercises. 2 sets x 8 rep. at 80%RM. 2. Same protocol as high intensity but 50%RM. 3. CG: 1 session per week for 24 weeks. FU: PT	62 subjects were randomized EG n = 20, MG n = 19 and CG n = 23. Age range: 65–75. Cognitive global function: MMSE >23. EG M^{age}: 68.4 (0.67). AC M^{age}: 69.01 (1.10). CG M^{age}: 67.04 (0.54).	Immediate recall[a] (ROF-IR). Reasoning[a]. Working memory (DSF[a], DSB[c], ROF-C[c], CBTF[c], CBTB[a]). Attention (TPCN[c], TPCE[c]).	No data to calculate.	Attendance rate above 75%.	Training at moderate intensity is sufficient to obtain cognitive benefits.	EG and AC had similar improvements in cognitive tasks vs CG.
Liu Ambrose (2010)	Three conditions: 1. Twice-weekly resistance training (EG) 2. Once-weekly resistance training (RT) 3. Twice-weekly balance and tone training (CG)	Single-blind. 1. 2 × 1 h/session per week for 52 weeks. 10 exercise. Progressive 7RM method. 2. Same protocol as EG but 1 session per week. 3. 2 × 1 h/session per week for 52 weeks. FU: PT.	155 women were randomized EG n = 52, RT n = 54 and CG n = 49. Age range: 65–75. Cognitive global function: MMSE >24. EG M^{age}: 69.4 (3.0). EG MMSE: 28.6 (1.5). RT M^{age}: 69.5 (2.7). RT MMSE: 28.5 (1.3). CG M^{age}: 70.0 (3.3). CG MMSE: 28.8 (1.2).	Attention (Stroop[a], TMT A-B[c]). Working memory[c] (Verbal digit backward, Verbal digit forward)	Stroop: −0.24 TMT A-B: 0.01 Verbal digit backward – Verbal digit forward: −0.15	Adherence rate of 70.3% EG, 71% RT and 62% CG. Significant differences between groups in AE; RT 29.8%, EG 10.9% and BAT 9.5%.	Cognitive performance improved by 12.6% and 10.9% in RT and EG, respectively. CG demonstrated 0.5% deterioration.	Resistance training can enhance selective function and conflict resolution.
Liu Ambrose (2012)	Three conditions: 1. Twice-weekly resistance training (EG) 2. Once weekly resistance training (RT) 3. Twice weekly balance and tone training (CG)	1. EG: 2 × 1 h/session per week for 52 weeks. 10 exercise. Progressive 7RM method. 2. Same protocol as EG but 1 session per week. 3. 2 × 1 h/session per week for 52 weeks FU: PT.	52 women were randomized EG n = 15, RT n = 20 and CG n = 17. Age range: 65–75. Cognitive global function: MMSE > 24. EG M^{age}: 68.9 (3.2). EG MMSE: 29.1 (0.8) RT M^{age}: 69.7 (2.8). RT MMSE: 28.6 (1.2). CG M^{age}: 69.2 (3.2). CG MMSE: 29.1 (1.1).	Conflict resolution[a] (Eriksen flanker test)	Eriksen flanker task: −0.89	Adherence rate of 79.2% EG, 75.1% RT and 71.8% CG.	EG increases cognitive performance 8.48% and CG only 1.47%.	Twice-weekly RT can positively affect functional plasticity of response inhibition processes in cortex.

Table 3 (*Continued*)

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Nagamatsu (2012)	Three conditions: 1. Resistance training (EG) 2. Aerobic training (AT) 3. Balance and tone training (CG)	Single-blind. 1. 2 × 1 h/session per week for 6 months. 2 sets x 6–8 rep. increasing progressively intensity training. 2. 2 × 1 h/session per week. Walking 40–70/80% of max HRR. 3. 2 × 1 h/session per week for 6 months. FU: PT.	86 women were randomized EG n = 28, AE n = 24 and CG n = 27. Age range: 70–80. Cognitive global function: MMSE >24. EG M^{age}: 73.9 (3.4). EG MMSE: 27.0 (1.8). RT M^{age}: 75.6 (3.6). RT MMSE: 27.4 (1.5). CG M^{age}: 75.1 (3.6). CG MMSE: 27.1 (1.7).	Attention (Stroop C-W[a], TMT A-B[c]). Working memory (Verbal Digit Backward[c], Verbal Digit Forward[c]) Associative memory[a] (Memorizing face scene pairs). Conflict resolution[c] (Everyday Problems test)	No data to calculate.	Adherence was low (not details). AE: 2 participants shortness of breath and 4 noninjuries falls.		RT significant differences vs CG, AT not. Twice weekly RT is a promising strategy to improve cognitive function. AT had not effect on cognitive function.
Forte (2013)	Two conditions: 1. Resistance training (EG) 2. Balance and tone training (CG)	1. 2 × 1 h/session per week for 3 months. Circuit 12 strength exercises 8 rep. at 60–80% RM. RM was calculated every 4 weeks. 2. 2 × 1 h/session per week for 3 months. FU: 4 week control period and PT.	50 subjects were randomized EG n = 25 and CG n = 25. Age range: 65–75. EG M^{age} male: 69.1 (3.7). EG M^{age} female: 70.5 (3.9). CG M^{age}: 71.4 (2.9). CG M^{age} female: 69.0 (2.8).	Executive function[b] (Random number generation task). Attention[b] (TMT A-B).	Random number generation task turning point index: 0.56 Random number generation task adjacency: 0.74 Random number generation task runs: 0.34 TMT A-B: 0.29	Adherence rate of 86% EG and 85% CG.	Baseline cognitive global function not detailed.	RT had positive effect in executive functioning.
Ten Brinke (2015)	Three conditions: 1. Aerobic training (AT). 2. Resistance training (EG) 3. Balance and toning (CG).	1. 2 × 1 h per week for 26 weeks. 40–80% of max HRR. 2. 2 × 1 h per week for 26 weeks. 10 exercises. 2 sets x 6–8 rep. 7RM. 3. Stretching, range of motion exercises, relaxation techniques. FU: PT.	86 women were randomized AT n = 30, EG n = 28 and CG n = 28. Age range: 70–80. Cognitive global function: MMSE >24. AT Mage: 76.07 (3.43). AT MMSE: 27.54 (1.51). EG Mage: 73.75 (3.72). EG MMSE: 26.67 (2.64). CG Mage: 75.46 (3.93). CG MMSE: 27.17 (1.85).	Immediate recall[c] (RAVLT).	RAVLT total adquisition: 0.35 RAVLT recall interference: 0.13 RAVLT loss interference: −0.45 RAVLT long recall: 0.19 RAVLT recognition: −0.24	Attendance rate of 60% AT, 54% EG, 59% CG. AE: 1 shortness of breath EG, 2 noninjuries falls AT, 1 shortness of breath CG.	Low adherence.	No significant differences between EG and CG.

Table 3 (*Continued*)

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Best (2015)	Three conditions: 1. Twice-weekly resistance training (EG) 2. Once-weekly resistance training (RT) 3. Twice-weekly balance and tone training (CG)	Single-blind. 1. 2 × 1 h/session per week for 52 weeks. 10 exercise. Progressive 7RM method. 2. Same protocol as EG but 1 session per week. 3. 2 × 1 h/session per week for 52 weeks. FU: a 1-year post intervention.	155 women were randomized EG n = 52, RT n = 54 and CG n = 49. Age range: 65–75. Cognitive global function: MMSE >24. EG M^{age}: 69.4 (3.0). EG MMSE: 28.6 (1.5). RT M^{age}: 69.5 (2.7). RT MMSE: 28.5 (1.3). CG M^{age}: 70.0 (3.3). CG MMSE: 28.8 (1.2).	Immediate recall[a] (RAVLT) Executive function[a] (Stroop C-W, TMT A-B, Verbal Digit Backward, DSST)	No data to calculate.	70% of baseline sample complete at 2 years cognitive assessments.	Secondary analysis of a previous study (Liu Ambrose et.al 2010)	EG and RT groups had long-term impact on executive function, and EG training protocol had an additional positive effect on memory domain.
Resistance versus no exercise active control								
Kimura (2010)	Two conditions: 1. Resistance training (EG) 2. Health education classes.	Single-blind. 1. EG: 2 × 1.5 h/session per week for 12 weeks. 3 sets x 10 rep. at 60% of 1RM. 2. 1.5 h x 1 session per month for 12 weeks. FU: PT.	171 subjects were randomized EG n = 86 and CG n = 85. Age range: >65. Cognitive global function: MMSE >23. EG M^{age}: 73.6 (4.7). EG MMSE: 27.8 (1.8). CG M^{age}: 75.2 (6.3). CG MMSE: 27.9 (2.1).	Reaction time[c] (Task switching).	Task switching: −0.11	No AE related with the intervention.		RT had not positive impact on cognitive function.
Van de Rest (2014)	Two conditions: 1. Resistance training (EG) 2. Control group (CG)	Double-blind. 1. 2 sessions per week for 24 weeks. 6 exercises. 3–4 sets x 10–15 rep. at 50%RM and progress 3–4 sets x 8–10 rep. at 75%RM. RM was calculate at weeks 4, 8, 12, 16 and 20 of intervention. 2. No intervention. FU: PT.	127 subjects were randomized to EG n = 62 and CG n = 65. Age range: >65. Global Cognitive function: MMSE ≥ 23. EG M^{age}: 79.2 (6.3). EG MMSE: 28 (27–29). CG M^{age}: 81.2 (7.4). CG MMSE: 28 (26–30).	Immediate recall[c] (Word Learning Test) Delayed recall[c] (Word Learning Test). Recognition[c] (Word Learning Test). Attention (Stroop W&C[c], TMT A-B[c]). Working memory (DSF[a], DSB[c]) Verbal Fluency (animals[c], letter p[c]) Reaction time[c].	Immediate recall: 0.15 Delayed recall: −0.09 Recognition: −0.13 Stroop W: 0.26 Stroop C: 0 TMT A-B: 0.02 DSF: 0.5 DSB: 0.37 Verbal fluency animals: −0.22 Verbal fluency letter p: −0.02 Reaction time: −0.22	Not described.		RT was beneficial for the cognitive domain attention.

EG = experimental group; CG = control group; AC: Active control; RT = Resistance training; AT = Aerobic Training; AE = Adverse Event; FU = follow up; PT = post training; Mage = mean age; (SD or SE) = (Standard Desviation or Standard Error); MMSE: = Mini Mental State Examination; ROF- IR = Rey Osterrieth Figure Immediate Recall; DSF = Digit Span Forward; DSB = Digit Span Back; ROF- C = Rey Osterrieth Figure Copy; CBTF = Corsis block-tapping forward; CBTB = Corsis block-tapping backward; TPCN = Toulouse–Pieron Cancellations numbers; TPCE = Toulouse–Pieron Cancellations errors; DSST = Digit Symbol Substitution Test; Stroop W-C = Stroop word – colour; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Test; RM: Repetition Maximum.

[a] Significantly greater improvement for training compared to control.

[b] Significant training effects for experimental group from baseline to PT; no significant effect for controls.

[c] No significant intervention difference between experimental and control groups.

Table 4
Characteristics of studies – multicomponent exercise training.

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Multicomponent versus stretching/toning								
Barnes (2013)	Four conditions: Multicomponent (Exer. Int) or Stretching (Exer. Cont.) + Computer games (Cog. Int) or educational DVDs (Cog. Cont). 1. Cog. Int/Exer. Int 2. Cog. Int/Exer. Cont 3. Cog Cont/Exer. Int. (EG) 4. Cog. Cont/Exer. Cont. (CG)	Double-blind. EG: 3 × 1 h per week for 12 weeks. 10 min warm up + 30 min aerobic training + 5 min cool down + 10 min strength training + 5 min stretching. Aerobic training: target 60–75% of max HRR. CG: Same protocol without aerobic training. FU: PT.	126 subjects were randomized. EG n = 31 and CG n = 32. Age range: >65. EG: M^{age}: 71.1 (5.5). EG 3MSE (0–100): 94.6 (5.6). CG: M^{age}: 73.9 (6.3). CG 3MSE: 94.8 (4.7).	Immediate recall[c] (RAVLT) Delayed recall[c] Verbal fluency (letter[c], category[c]) Proc. Speed[c] (DSST) Inhibition[c] (Eriksen Flanker Test) Visuospatial processing[c] (UFOV) Attention (TMT A-B[c], divided[c], selective[c])	No data to calculate.	Not described adherence rate. AE 9%.	ITT analysis. Results similar when dropouts excluded.	No significant differences on cognitive function between EG and CG. The study suggested that the amount of activity is more important than type of exercise.
Multicomponent versus no exercise active control								
Liu Ambrose (2008)	Two conditions: 1. Otago home based exercise program: Strength + balance + aerobic training (EG). 2. Guideline care (CG).	Single-blind. 1. EG: 3 × 30 min per week for 6 months. Strength: 5 exercises lower limbs. Progressive Intensity: 0.9–9 kg load increment as required. Aerobic training: walk 2/week for 6 months. 2. CG: Comprehensive geriatric assessment and treatment. FU: PT.	74 subjects were randomized EG n = 36 and CG n = 38. Age range: >70. Global cognitive function: MMSE >24. EG: M^{age}: 81.4 (6.2). EG MMSE: 28.0 (2.0). CG: M^{age}: 83.1 (6.3)- CG MMSE: 28.0 (1.6).	Attention (Stroop C-W[a], TMT B[c]). Working memory[c] (Verbal Digit Backward test).	Stroop W-C: −0.48 TMT B: −0.06 Verbal digit backward: −0.39	Adherence rate of 25% 3 days/week, 57% 2 days/week and 68% 1 day/week. AE: 2 patients low back pain because exercise.	EG group 12.8% improvement in Stroop while control had 10.2 deterioration.	Home based exercise program significantly improved executive function (attention) in EG vs CG.
Multicomponent versus no intervention								
Klusmann (2010)	Three conditions: 1. Exercise training (EG): Strength + Aerobic + balance + coordination + flexibility. 2. Computer course (CC) 3. Control group (CG).	Double-blind. 1. EG: 3 × 1.5 h per week for 6 months. 75 sessions in total. 2. Computer: Cognitive tasks. 3. CG: Habitual life. FU: PT.	259 subjects were randomized EG n = 91, CC n = 92 and CG n = 76. Age range: 70–93. Global cognitive function: MMSE >26. EG: M^{age}: 73.6. EG MMSE: 28.76. CC: M^{age}: 73.6. CG MMSE: 28.8. CG: M^{age}: 73.5. CG MMSE: 28.84.	Immediate recall (story[a], word[c]). Delayed recall (story[a], word[a]). Verbal fluency[c] Attention (Stroop C-W[c], TMT A-B[a])	Immediate recall story: 0.61 Immediate recall word: 0.31 Delayed recall story: 0.67 Delayed recall word: 0.64 Verbal fluency: 0.2 Stroop C-W: 0.16 TMT A-B: −0.57	Not described.	The increase in EG in immediate and delayed story recall was approximately 26% and 40%, respectively. Performance on TMT in EG improved 10% approximately.	Similar improvements on were found in EG and CC vs CG.

Table 4 (*Continued*)

Ref. author (year)	Intervention	Methods	Participants	Outcomes of interest	Effect Size (ES)	Feasibility/AE	Additional notes	Conclusion
Vaughan (2014)	Two conditions: 1. Exercise training (EG): Aerobic + Strength + Motor skills. 2. Control group (CG)	Single-blind. 1. EG: 2 × 1 h per week for 16 weeks. 32 sessions in total. Aerobic training: Steps with music. Intensity: 3–4/10 RPE. Strength training: Upper, lower body and core muscles. 3 exercises 2 sets x 6–8 reps. Intensity: Start without load and progressive increment of 1 kg. 2. CG: Waiting list. FU: PT.	49 women were randomized EG n = 25 and CG n = 24. Age range: 65–75. Global cognitive function: ≥31 Telephone interview Cognitive Status (TICS). EG: M^{age}: 69.0 (3.1). EG TICS: 38.3 (4.1). CG M^{age}: 68.8 (3.5). CG TICS: 36.9 (3.0).	Inhibition[a] (COAST) Verbal fluency[a] (COWAT) Working memory[c] (LNS) Proc. Speed[c] (Deary-Liewald Reaction Time Task). Attention[a] (TMT A-B)	COAST: −0.57 COWAT: 0.38 LNS: −0.03 Proc. speed (simple reaction time): −0.2 Proc. speed (choice reaction time): 0.11 TMT A: −0.69 TMT B: −0.38	Adherence rate of 85% EG.	Significant differences in Brain Derived Neurotrophic Factor (BDNF) between EG vs CG.	Exercise training had an important role in promoting cognitive health. Neurogenesis is likely the reason whereby exercise induced improvement in cognitive functioning.
Napoli (2014)	Four conditions: 1. Exercise training (EG): Aerobic + Strength + Flexibility + Balance. 2. DIET: Diet. 3. DIETEXER: Diet + Exercise. 4. Control group (CG).	1. EG: 3 × 1.5 h per week for 52 weeks. 15 min flex + 30 min aerobic + 30 min strength + 15 min balance. Aerobic training: Start 65% of max HRR and progress 70–85% of max HRR. Strength training: 9 exercises upper and lower body. Start 1–2 sets x 8–12 reps. 65%RM and progress 2–3 sets x 6–8 reps. 80%RM. FU: PT.	107 subjects were randomized EG n = 26, DIET n = 26, DIETEXER n = 28 and CG n = 27. Age range: >65. Global cognitive function: MMSE >24. EG M^{age}: 70 (4). CG M^{age}: 69 (4).	Global Cognitive function[a] (3MSE). Verbal fluency[a] (Word List Fluency Test) Attention[c] (TMT A-B)	No data to calculate.	Adherence rate of 88% EG.	EG improved 2.8 points 3MSE versus 0.1 CG. EG improved 4.1 Word Fluency test while CG had deterioration −0.8.	Multicomponent program had positive impact on verbal fluency and global cognitive function compared with CG.
Tarazona –Santabalbina (2016)	Two conditions: 1. Exercise training (EG). 2. Control group (CG).	1. EG: 5 × 65 min/session per week for 24 weeks. Intervention: aerobic + strength + coordination + balance + flexibility. Aerobic training: Start 40% of max HRR and progress to 65% of max HRR. Strength training: Elastic bands isometric + concentric + eccentric exercises upper and lower body. Start 25%RM and progress to 75%RM.	100 subjects were randomized EG n = 51 and CG n = 49. Age range:>70. Global Cognitive Function: MMSE > 24. EG M^{age}: 79.7 (3.6). EG MMSE: 26.5 (5.3). CG M^{age}: 80.3 (3.7). CG MMSE: 27.3 (5.8).	Global Cognitive Function[a] (MMSE)	MMSE: 0.67	Adherence rate of 47.3% EG.	EG improved 9% in MMSE after the intervention.	EG improved significantly cognitive function compared with CG.

EG = experimental group; CG = control group; CC: Computer Course; DIET = Diet; DIETEXER = Diet and Exercise; FU = follow up; AE: Adverse Event; PT = post training; Mage = mean age; (SD or SE) = (Standard Desviation or Standard Error); MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; UFOV = Useful Field of View; DSST = Digit Symbol Substitution Test; Stroop C-W = Stroop colour – word; TMT = Trail Making Test; COAST = California Older Adult Stroop Test; COWAT = Controlled Oral Word Association Test; LNS = Letter Number Sequencing; 3MSE = Modified Mini Mental Examination; HRR = Hear Rate Reserve; ITT: Intention To Treat; RM: Repetition Maximum.

[a] Significantly greater improvement for training compared to control.

[b] Significant training effects for experimental group from baseline to PT; no significant effect for controls.

[c] No significant intervention difference between experimental and control groups.

Table 5
Assessment risk of bias.

Articles	1	2	3	4	5	6	Score
Aerobic training							
Oken (2006)	Y	N	Y	Y	Y	Y	5/6
Smiley-Oyen (2008)	Y	N	Y	Y	Y	Y	5/6
Muscari (2009)	N	N	Y	Y	Y	Y	4/6
Albinet (2010)	N	N	N	Y	N	Y	2/6
Legault (2011)	N	N	U	Y	Y	Y	3/6
Ten Brinke (2015)	Y	Y	Y	Y	Y	Y	6/6
Vidoni (2015)	Y	Y	Y	Y	Y	Y	6/6
Resistance training							
Cassilhas (2007)	N	N	N	Y	Y	Y	3/6
Kimura (2010)	N	N	U	Y	N	Y	2/6
Liu Ambrose (2010)	Y	Y	Y	Y	Y	Y	6/6
Liu Ambrose (2012)	Y	Y	Y	Y	N	Y	5/6
Nagamatsu (2012)	N	N	U	N	N	U	2/6
Forte (2013)	N	N	N	Y	N	Y	2/6
Van de Rest (2014)	Y	N	Y	Y	Y	Y	5/6
Best (2015)	Y	Y	Y	Y	Y	Y	6/6
Multicomponent training							
Liu Ambrose (2008)	Y	Y	Y	Y	Y	Y	6/6
Klusmann (2010)	Y	Y	Y	Y	Y	Y	6/6
Barnes (2013)	Y	Y	Y	Y	Y	N	5/6
Vaughan (2014)	Y	Y	Y	Y	Y	Y	6/6
Napoli (2014)	Y	Y	Y	Y	Y	Y	6/6
Tarazona-Santabalbina (2016)	Y	N	Y	Y	Y	Y	5/6

Criteria items: 1. Was the randomization sequence generation adequate? 2. Was the treatment allocation concealed? 3. Was the outcome assessor blinded to the intervention? 4. Were losses to follow up and exclusions correctly described? 5. Was intention to treat analysis used for statistical analyses? 6. Are reports of the study free of suggestion of selective outcome reporting?
Unsure (U), Yes (Y), No (N).

ten Brinke et al., 2015; van de Rest et al., 2014; Vaughan et al., 2014; Vidoni et al., 2015). Only a few studies included in the review (47.62%) reported allocation concealment (10 of 21) (Barnes et al., 2013; Best et al., 2015; Klusmann et al., 2010; Liu-Ambrose et al., 2008; Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Napoli et al., 2014; ten Brinke et al., 2015; Vaughan et al., 2014; Vidoni et al., 2015). Of the studies 71.43% specifically reported blinded assessment of outcomes (15 of 21) (Barnes et al., 2013; Best et al., 2015; Klusmann et al., 2010; Liu-Ambrose et al., 2008; Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Muscari et al., 2010; Napoli et al., 2014; Oken et al., 2006; Smiley-Oyen et al., 2008; Tarazona-Santabalbina et al., 2016; ten Brinke et al., 2015; van de Rest et al., 2014; Vaughan et al., 2014; Vidoni et al., 2015). All of the RCTs included in the review described losses to follow up and exclusions (21 of 21) (Albinet et al., 2010; Barnes et al., 2013; Best et al., 2015; Cassilhas et al., 2007; Forte et al., 2013; Kimura et al., 2010; Klusmann et al., 2010; Legault et al., 2011; Liu-Ambrose et al., 2008; Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Muscari et al., 2010; Nagamatsu et al., 2012; Napoli et al., 2014; Oken et al., 2006; Smiley-Oyen et al., 2008; Tarazona-Santabalbina et al., 2016; ten Brinke et al., 2015; van de Rest et al., 2014; Vaughan et al., 2014; Vidoni et al., 2015) and 76.19% of the studies used an intention to treat analysis (16 of 21) (Barnes et al., 2013; Best et al., 2015; Cassilhas et al., 2007; Klusmann et al., 2010; Legault et al., 2011; Liu-Ambrose et al., 2008; Liu-Ambrose et al., 2010; Muscari et al., 2010; Napoli et al., 2014; Oken et al., 2006; Smiley-Oyen et al., 2008; Tarazona-Santabalbina et al., 2016; ten Brinke et al., 2015; van de Rest et al., 2014; Vaughan et al., 2014; Vidoni et al., 2015). Of the studies, 90.48% were free of selective reporting of outcomes (Albinet et al., 2010; Best et al., 2015; Cassilhas et al., 2007; Forte et al., 2013; Kimura et al., 2010; Klusmann et al., 2010; Legault et al., 2011; Liu-Ambrose et al., 2008; Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Muscari et al., 2010; Napoli et al., 2014; Oken et al., 2006; Smiley-Oyen et al., 2008; Tarazona-Santabalbina et al., 2016; ten Brinke et al., 2015; van de Rest et al., 2014; Vaughan et al., 2014; Vidoni et al., 2015). Details are described in Table 5.

3.3. *Aerobic exercise training versus stretching/toning*

Across the included studies, no significant differences were found in outcomes associated with memory domain in the aerobic exercise group compared with the stretching/toning group (Nagamatsu et al., 2012; Oken et al., 2006; ten Brinke et al., 2015). Significant improvements associated with aerobic exercise training in one attention task (WCST) of the 17 outcomes associated with the executive function domain were reported in four trials (Albinet et al., 2010; Nagamatsu et al., 2012; Oken et al., 2006; Smiley-Oyen et al., 2008) and significant pre-post intervention improvement in one attention outcome (Stroop W-C) was also found in the intervention group but not in the stretching/toning group in one trial (Smiley-Oyen et al., 2008). No differences between groups in other cognitive outcomes (Nagamatsu et al., 2012) were identified. None of the studies analyzed the maintenance effects of the intervention.

3.4. *Aerobic exercise training versus no exercise active control/no intervention*

In the three trials in which an aerobic exercise training group was compared with no active exercise or no intervention control groups, there were no significant differences identified between these groups in the 9 outcomes associated with memory function. However, members of the aerobic exercise group demonstrated significantly greater improvements in their performance on a global cognitive function assessment (MMSE) when compared with control group members in one trial (Muscari et al., 2010). Considering the outcomes associated with executive function in older adults, no significant differences in the 23 outcomes were reported between the aerobic training and control groups in three trials (Legault et al., 2011; Oken et al., 2006; Vidoni et al., 2015). No differences were observed between groups in other cognitive outcomes (Legault et al., 2011; Vidoni et al., 2015). No studies explored maintenance effects.

3.5. Resistance exercise training versus stretching/toning

Significantly greater improvements in three immediate recall (ROF-IR and RAVLT) and associative memory tasks (Memorizing face scene pairs) of the 4 memory domain outcomes when comparing the resistance exercise group with the stretching/toning group were reported in four trials (Best et al., 2015; Cassilhas et al., 2007; Nagamatsu et al., 2012; ten Brinke et al., 2015). For outcomes associated with the executive function domain, the resistance training groups demonstrated significantly greater improvements when compared with the control groups in nine reasoning, attention (Stroop W-C and TMT A-B), working memory (DSF, CBTB and Verbal Digit Backward) and processing speed (DSST) tasks of the 21 outcomes assessed in five RCTs (Best et al., 2015; Cassilhas et al., 2007; Forte et al., 2013; Liu-Ambrose et al., 2010; Nagamatsu et al., 2012) and significant pre-post-intervention differences were reported in the experimental group but not in the control group in one trial (Forte et al., 2013). Conflict resolution was assessed as an additional executive function outcome in two trials; significant improvements were found in the resistance exercise group but not in the control group in one trial (Liu-Ambrose et al., 2012) and no between groups differences were observed in the other trial (Nagamatsu et al., 2012). Best et al. (2015) analyzed the maintenance effects of the study conducted by Liu Ambrose and colleagues (Liu-Ambrose et al., 2010) one year post-intervention.

3.6. Resistance exercise training versus no exercise active control/no intervention

Between groups comparisons indicated no significant differences in the 3 outcomes associated with the memory cognitive domain assessed in one trial (van de Rest et al., 2014). On the other hand, significant improvements were reported in one working memory task (DSF) of the 8 measures of executive function in two trials (Kimura et al., 2010; van de Rest et al., 2014). None of the included studies measured the maintenance effect of the intervention.

3.7. Multicomponent exercise training versus stretching-toning/no active exercise control

The results of the included trials revealed no significant differences between the multicomponent exercise training group and the control group in the 2 memory outcomes assessed in one trial (Barnes et al., 2013). Significant improvements were found in one attention task (Stroop W-C) of 9 outcomes related to the executive function domain in two trials (Barnes et al., 2013; Liu-Ambrose et al., 2008). No significant differences between groups were observed in the other cognitive outcomes in one trial (Barnes et al., 2013). Maintenance effects were not analyzed in these studies.

3.8. Multicomponent exercise training versus no intervention

In the trial in which a multicomponent training group was compared with a no intervention control group, the multicomponent group performed significantly better than did the control group on three immediate recall (story test) and delayed recall tasks (story and word test) of the 4 memory domain outcomes (Klusmann et al., 2010). Significantly greater improvements were also found when comparing the multicomponent exercise training group to the no intervention group in four attention (TMT A-B), verbal fluency (COWAT and Word List Fluency Test) of 9 outcomes associated with executive function in three trials (Klusmann et al., 2010; Napoli et al., 2014; Vaughan et al., 2014). Global cognitive function (3MSE and MMSE) and other cognitive measures, such as inhibition (COAST), were analyzed in three trials, all of which reported that the multicomponent group achieved significantly better results than did the control group (Napoli et al., 2014; Tarazona-Santabalbina et al., 2016; Vaughan et al., 2014). None of the four studies included follow-up assessments.

4. Discussion

The main aim of the review was to analyze the effects of aerobic exercise training, resistance training and multicomponent training on the cognitive performance of older adults without known cognitive impairment. Thirteen of the 21 RCTs that were included in this review reported significant improvements in the exercise training group in at least one cognitive outcome associated with memory domain, executive function or composite measures of cognitive function after the intervention. Despite this fact, significant differences were not found between groups for most of the cognitive outcomes. Furthermore, the great variability in RCT procedures and exercise training protocol features make it difficult to perform a specific statistical analysis, including a meta-analysis, for better understand the relationship between physical exercise training and cognitive performance.

4.1. Exercise training type

4.1.1. Aerobic training

Despite the beneficial effects observed in cognitive outcomes with aerobic exercise training in previous meta-analyses (Colcombe and Kramer, 2003; Heyn et al., 2004), aerobic exercise was associated with an improvement in neurocognitive functioning in older adults with and without cognitive impairment. The results obtained across individual trials in this review failed to support any consistent evidence about cognitive benefits associated with aerobic exercise training. Only one trial reported significant benefits in memory domains (Nagamatsu et al., 2012) and few studies found significant improvements in executive function after deploying an aerobic exercise training protocol (Albinet et al., 2010; Nagamatsu et al., 2012; Smiley-Oyen et al., 2008). Our results agreed with reviews that concluded that there is lack of consistent evidence to demonstrate the beneficial effects of aerobic exercise training on cognitive performance in older adults without known cognitive impairment (Angevaren et al., 2008; Etnier et al., 1997; Etnier et al., 2006). Several factors could explain modest cognitive gains associated with aerobic training and the details are described below.

4.1.2. Resistance training

Some authors paid attention the effects of resistance training on cognitive performance in older adults and consistent results had not obtained. Despite this fact, some reviews provided results to suggest that cognitive improvements were associated with resistance training (Liu-Ambrose and Donaldson, 2009), while other reviews had not observed consistent evidence to support this hypothesis (Chang et al., 2012; Snowden et al., 2011; van Uffelen et al., 2008). In our review, we found large variations in the magnitude of improvement in memory domain (Best et al., 2015; Cassilhas et al., 2007; Nagamatsu et al., 2012) with resistance exercise training and most of the trials presented significant improvements in executive function in at least one cognitive outcome (Cassilhas et al., 2007; Forte et al., 2013; Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Nagamatsu et al., 2012). Therefore, our findings suggested that moderate-high intensity and progressive resistance training could have a beneficial effect on executive function in older adults without known cognitive impairment, but more evidence based on exercise effects on executive measures was required. An emerging theory for explaining these cognitive benefits was that exercise increased production of several growth factors, such as BDNF and IGF-1 (Kramer and Erickson, 2007). Findings from animal studies (Berchtold et al., 2001; Carro et al., 2001) provided consistent evidence for the future study of physiologic mechanisms that caused the effect of exercise on cognitive function in older adults (van Uffelen et al., 2008). Future studies should also explore new stimulus of training as High Intensity Interval Resistance Training (HIRT) on cognitive function in healthy older adults. This training modality could have positive effects on cognitive performance in this population.

4.1.3. Multicomponent training

New exercise training modalities have recently been developed to optimize functional capacity and physical fitness in older adults. Multicomponent exercise training, in which aerobic and resistance training are combined with other training components such as balance and/or flexibility, is the most effective training modality to improve functional capacity in frail older adults (Barnett et al., 2003; Lord et al., 2003; Villareal et al., 2011) and to prevent disability (Cadore et al., 2014). Although the beneficial effects on physical function of this type of exercise training are well established, the evidence is less consistent regarding cognitive gains associated with multicomponent exercise training. (Colcombe and Kramer, 2003) reported that combining aerobic and resistance training had better cognitive gains on executive tasks of attention and working memory than aerobic exercise training alone. Furthermore, a recent meta-analysis (Northey et al., 2017) observed that multicomponent exercise training should be a good strategy to improve cognitive function in younger adults (aged >50 years), regardless the cognitive status. Our findings in this review supported this assessment, as multiple RCTs observed significant improvements on executive tasks of attention (Klusmann et al., 2010; Liu-Ambrose et al., 2008; Vaughan et al., 2014), verbal fluency tasks (Napoli et al., 2014; Vaughan et al., 2014) and global cognitive function tasks (Napoli et al., 2014; Tarazona-Santabalbina et al., 2016) in exercise training groups compared with the control groups. The inclusion of resistance training as a component of the exercise training protocol could be the reason for cognitive gains in the intervention group in specific executive tasks, but further research is needed to determine the possible cognitive benefits of multicomponent exercise training program.

Future RCTs should also consider multidomain intervention in this population, in which exercise training is combined with other treatments, such as cognitive training and social enrichment, to optimize the cognitive performance and prevent cognitive impairment (Ngandu et al., 2015). On the other hand, some studies including older adults with mild cognitive impairment but with younger age inclusion criteria (i.e. 50–55 years or older) (Baker et al., 2010; Lautenschlager et al., 2008) also showed the feasibility of exercise training in this population, as well as the relevance of physical exercise in the elderly with minimal or no cognitive impairment.

4.2. RCTs with less consistent evidence versus epidemiological and cross-sectional studies

Discrepancies between the consistent evidence reported in animal, epidemiological and cross-sectional studies contrast with the less consistent results observed in RCTs. There are several factors that could explain large variations obtained across individual trials in the magnitude of changes on cognitive performance with different exercise training modalities and, in this way, find explanations for the conflicting results observed between observational and experimental studies.

4.2.1. Baseline physical performance

Participants PA levels at baseline was a considerable factor to consider to analyze changes on cognitive performance with exercise training in older adults. A trial recruited participants who were already engaged in regular physical exercise (Oken et al., 2006) and other studies reported differences in sedentary definition. Some RCTs excluded participants if they performed more than an hour of physical exercise per week (Barnes et al., 2013; Klusmann et al., 2010; Napoli et al., 2014; Vaughan et al., 2014), other studies included participants with more active lifestyles than the sedentary population (Tarazona-Santabalbina et al., 2016) and some RCTs used validated questionnaires to assess PA level before randomization (Albinet et al., 2010; Vidoni et al., 2015). Therefore, it is complicated to draw consistent conclusions considering baseline differences between studies in subject features. On the other hand, epidemiological and cross–sectional studies examined the risk of cognitive impairment based on baseline PA levels (Sofi et al., 2011; Yaffe et al., 2001) or the relationship between PA levels in different stages of life and the likelihood of developing cognitive decline in later life (Middleton et al., 2010). These studies reported that individuals with higher levels of PA had better cognitive function (Dustman et al., 1994; Etnier et al., 1997) or were at a reduced risk to experience cognitive decline compared with participants who had a less active or sedentary lifestyle. Consequently, subject baseline PA differences between studies included in this review could be one of the reasons to explain large variations in the magnitude of the improvements on cognitive outcomes. Future trials would benefit from control baseline PA levels or classifying participants considering this variable to analyze the cognitive gains of exercise training.

4.2.2. Length of intervention and follow up

Differences in the intervention duration and follow-up period between studies may be one of the reasons to clarify discrepancies between the short and long-term effects of exercise training on the cognitive performance in older adults. If exercise could reverse or delay the effects of age-related cognitive decline, interventions performed over a longer time would produce more relevant alterations in cognitive gains than short-term protocols (Angevaren et al., 2008). Previous longitudinal studies have shown higher PA and structured exercise were associated with more global or regional brain volumes in later life in both grey matter and white matter (Erickson et al., 2010; Gow et al., 2012; Rovio et al., 2010). Therefore, there is consistent evidence to support the association between brain atrophy and PA (Arnardottir et al., 2016) and brain atrophy has been associated with the change in cognitive ability in multiple studies (Fotenos et al., 2005; Hedden and Gabrieli, 2004; Resnick et al., 2003; Visser et al., 1999). However, RCTs are usually much shorter than longitudinal studies, which would make it more complicated to observe cognitive differences between groups. In our review, most of the RCTs ranged from 12 weeks to 6 months, and only one trial reported follow-up data from a previous study (Best et al., 2015). No consistent results were found in our review considering that similar cognitive gains were obtained in longer interventions such as one year or more (Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Muscari et al., 2010; Napoli et al., 2014) compared with shorter interventions (Albinet et al., 2010; Forte et al., 2013; Vaughan et al., 2014). An interesting finding is that in longer interventions while the exercise training group improved or maintained the performance of cognitive tasks, participants in the control group had deterioration after the intervention period (Liu-Ambrose et al., 2010; Liu-Ambrose et al., 2012; Muscari et al., 2010; Napoli et al., 2014). New RCTs are required with longer interventions and follow-up periods to analyze the maintenance effects of exercise training on the cognitive performance in older adults and it would be interesting to complement those interventions with neuroimaging techniques to understand the changes in cognitive abilities.

4.2.3. Exercise training protocol differences and adherence

Many factors had vital importance in the intervention effect on cognitive gains, such as the efficiency of the intervention and the adherence to training sessions. The first determinant to consider was the exercise training protocol description. The great variety in exercise training protocol features may have an important influence on cognitive results heterogeneity.

Although the optimum dose of exercise training for the improvement of cognitive function has yet to be established, some RCTs included in our review failed to meet the aerobic training recommendations for older adults (Haskell et al., 2007) of 150 min of exercise training at moderate intensity (Nagamatsu et al., 2012; Oken et al., 2006; ten Brinke et al., 2015) or the resistance training recommendations (Medicine, 2009) of one or more sets of 10–15 repetitions at moderate intensity with a resting interval of 2–3 min between sets (Cassilhas et al., 2007; Nagamatsu et al., 2012; ten Brinke et al., 2015). The combination of aerobic and resistance training with other training modalities such as balance or flexibility, have positive effects on the physical fitness and the functional capacity in older adults (Cadore et al., 2013; Chin et al., 2008; Daniels et al., 2008), but there is a lack of consistent evidence to show that multicomponent training results in improved cognitive performance. On the other hand, subjects classified as "active populations" or "high-activity groups", which surpassed the recommendations mentioned above (Sumic et al., 2007; Weuve et al., 2004). Well defined exercise training protocols that meet all minimum recommendations would facilitate comparisons between studies and might report better results on cognitive gains.

The lack of details in exercise training program progression during the intervention make it difficult to determine the efficiency of the intervention (Barnes et al., 2013; Kimura et al., 2010; Legault et al., 2011; Nagamatsu et al., 2012; Oken et al., 2006). In our review, 7 of the 21 RCTs failed to report these exercise training program characteristics. The inclusion of this methodological information may help to understand the discrepancies on cognitive benefits between studies.

The adherence to training sessions is essential to induce adaptations associated with exercise training programs. A low-adherence rate might result in low physical activity levels in the intervention group and large variations in adherence in RCTs may contribute to inconsistent results. Our findings supported this view and in those RCTs for which the attendance rate to training sessions was less than 70%, no significant differences were found in memory and executive function outcomes between the exercise training group and the control group (Liu-Ambrose et al., 2008; Oken et al., 2006; ten Brinke et al., 2015). However, studies with an attendance rate of 85% or higher reported significant improvements in the intervention group in memory, executive function and global cognitive function tasks (Albinet et al., 2010; Forte et al., 2013; Napoli et al., 2014; Vaughan et al., 2014). In comparison with epidemiological studies, older adults with high levels of PA are usually engaged in regular exercise training over longer periods. Therefore, RCTs should include in the data analysis only participants who reach a minimum number of training sessions to determine the inherent effects of exercise training on cognitive performance in the data analysis.

4.3. Inconsistent results across RCTs

Other factors may explain the differences that were found in RCTs on cognitive outcomes based on the role of exercise training in older adults. First, participant inclusion criteria varied between studies. Some trials included participants who were already physically active (Oken et al., 2006), while the eligibility criteria of other studies required participants to be sedentary (Barnes et al., 2013; Legault et al., 2011; Napoli et al., 2014; Vaughan et al., 2014) or frail older adults (Tarazona-Santabalbina et al., 2016). Moreover, large variations were observed when the methodological quality across RCTs was analyzed. Interestingly, trials in which multicomponent training was performed had the best scores in the assessment of the risk of bias and reported the largest significant improvements on cognitive function compared with other training modalities.

4.3.1. Cognitive outcomes measurement

Regarding the cognitive outcomes that were examined, a great variety of cognitive tests were measured to analyze the effects of exercise on memory and executive function and could explain the lack of consistent evidence obtained in this review. Consequently, a consensus of the appropriate measures of cognitive function (Angevaren et al., 2008; Chang et al., 2012) and use computer-based tasks would be interesting to standardize and improve sensitivity of cognitive assessment. Although our findings suggested that resistance training could have an influence on prefrontal cortex and could have a positive effect on executive function, exercise training benefits on cognitive outcomes associated with episodic memory are less consistent. Therefore, further research is needed to explore physiologic and neuromuscular changes in different brain areas to understand the relationship between exercise training and memory domain.

4.4. Limitations of the review

Considering the limitations of the previous review (Kelly et al., 2014), a meta-analysis was not conducted because of the great variation in methodologies between studies and because of the few RCTs that included each exercise training modality. A meta-analysis would help to understand the inherent effects of exercise training on cognitive performance in older adults but the RCTs methodological characteristics of the RCTs made it difficult to perform this analysis.

A crucial limitation of this review that made it difficult to draw consistent conclusions was the large variation in methodological aspects between RCTs. The lack of details about the exercise training protocol and the load-training progression during the intervention reduced the reproducibility of the trials and failed to show any consistent evidence (Legault et al., 2011; Liu-Ambrose et al., 2008; Nagamatsu et al., 2012). The variability of exercise training features (frequency, intensity, time, type) also contributed to the explanation of inconsistent results.

The heterogeneity of the cognitive tests used to measure different cognitive domains, such as memory and executive function, was one of the principle reasons for large variations in the cognitive benefits between studies, and sometimes, discrepancies were obtained after analyzing the same domain in the same trial (Cassilhas et al., 2007; Klusmann et al., 2010; Liu-Ambrose et al., 2008; Liu-Ambrose et al., 2010; Nagamatsu et al., 2012).

Unfortunately, despite the fact that we focused on "no known cognitive impairment" and we tried to specify a "without cognitive impairment" term using the MMSE test scores at baseline (cut-off point of 23/30), some RCTs did not report baseline cognitive function scores (Forte et al., 2013; Oken et al., 2006; Smiley-Oyen et al., 2008) or they used another test to assess global cognitive function (Barnes et al., 2013; Legault et al., 2011; Vaughan et al., 2014). Therefore, a portion of subjects over the age of 65 and even more older adults over the age of 75 may have cognitive impairment but several of included studies have not done sufficient cognitive evaluation to detect a difference. Moreover, other global cognitive function test appears to be more sensitive than cut-off point greater than 23 in the MMSE test for detection of early or mild cognitive impairment (Markwick et al., 2012). Finally, high scores on the global cognitive function at baseline could also explain the lack of improvement after the intervention because participants may have already cognitively been at the ceiling.

4.5. Conclusions and future recommendations

In accordance with previous studies summarized by (Colcombe and Kramer, 2003), results from this review suggest that multicomponent exercise training may have the most positive effects on cognitive function in older adults. However, caution should be taken regarding the training intervention period, as well as the method used to control training intensity. Furthermore, the duration of exercise training programs made it difficult to compare short-term effects of RCTs with trials performed over a longer period. Longer interventions and follow-up periods in RCTs may facilitate the comparison of results with epidemiological and cross-sectional studies. A large variability in the cognitive outcomes between included studies might be the reason for discrepancies in cognitive results. The standardization of cognitive measures, especially on executive function, would improve the comparability between RCTs. In conclusion, a standardization of the methodological aspects of RCTs is required to clarify the relationship between exercise training and cognition and to reduce discrepancies with animal, epidemiological and cross-sectional studies.

Conflict of interest

All authors have nothing to declare.

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Title: Physical exercise improves function in acutely hospitalized old patients

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Abstract: Background: Functional decline is prevalent among acutely hospitalized older patients. We aimed to evaluate the effects of an exercise intervention on functional capacity, maximal muscle strength and muscle power in very old patients admitted in an Acute Care for Elderly (ACE) unit.
Methods: In a randomized controlled trial, 130 hospitalized patients (aged ≥75 years) were allocated to an exercise intervention (n=65) or a control group (n=65). The intervention consisted of a multicomponent exercise training program performed during 5-7 consecutive days (2 sessions/day). The usual care group received habitual hospital care, which included physical rehabilitation when needed. Functional capacity, assessed with the Short Physical Performance Battery (SPPB) test and the Gait Velocity Test (GVT), were the primary endpoints. The GVT was also administered under dual-task conditions (i.e., verbal and arithmetic GVT). The functional tasks were recorded using an inertial sensor unit to determine the movement pattern. The secondary endpoints were maximal muscle strength and muscle power output.
Findings: No adverse effects were observed with the intervention. The exercise intervention program provided significant benefits over usual care. At discharge (primary time point), the exercise group showed a mean increase of 1·7 points in the SPPB scale (95%CI, 0·98, 2·42) and 0·14 m·s-1 in the GVT (95%CI, 0·086, 0·194) over the usual care group. The intervention also improved the verbal (0·151; 95%CI 0·119, 0·184 vs. -0·001; 95%CI -0·025, 0·033 in the control group) and arithmetic GVT (0·115; 95%CI 0·077, 0·153 vs. -0·004; 95%CI -0·044, 0·035). Significant benefits were also observed in the intervention group in movement pattern, as well as in muscle strength and muscle power.
Interpretation: An individualized multicomponent exercise training program improves functional capacity, maximal muscle strength, and muscle power in acutely hospitalized old patients.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:

Data will be made available on request

Editor-in-Chief
JAMDA

Dear Editor-in-Chief,

Please find enclosed our manuscript entitled *"An innovative individualized multicomponent exercise intervention improves functional capacity in acutely hospitalized older adults*", which we would like to submit for publication as an Original Article in the JAMDA.

In 1994, Fiatarone et al published an innovative study (N Eng J Med 1994;330:1769-1775) showing that high-intensity resistance exercise training is a feasible and effective means of counteracting muscle weakness and physical frailty in very elderly people. Improving or maintaining function is becoming a major target of medical care in the elderly, and it has been shown that the most effective strategy is to prevent functional decline rather than attempting to recover function once this has been lost.

In the 21st century, hospitalization is a sentinel event and a leading cause of disability in the elderly. Besides deteriorating the functional status of older adults, bedrest also increases the risk for cognitive decline and dementia. Exercise and early rehabilitation protocols applied during acute hospitalization can prevent functional and cognitive decline in older adults and are associated with a reduced length of stay and lower costs. We recently showed the benefits of a multicomponent exercise intervention consisting of resistance ('power'), balance and gait retraining exercises to reverse functional decline associated with acute hospitalization in very elderly individuals (JAMA Intern Med 2018; In press. doi:10.1001/jamainternmed.2018.4869). This current secondary study analyze the effects of a multicomponent exercise training intervention on the change in functional capacity (i.e., balance, rising from a chair, GVT, dual-task performance and muscle power) during hospitalization (i.e., from admission to discharge). Moreover, an inertial sensor unit was used for measuring and monitoring the functional trajectory after an innovative exercise training program. Typically, in-hospital functional status and functional trajectory are measured using subjective self-reports scales based on ADLs or instrumental ADLs. From a practical standpoint, we detected changes in functional tasks that are associated with patient´s ability to perform ADLs. Thi type of intervention has not yet been applied during acute hospitalization in very old (i.e. >85 years) patients. Definetively, these findings may have potential to dramatically change clinical practice and reverse functional decline in very elderly patients during acute hospitalizations or even affect mortality.

We look forward to hearing from you at your earliest convenience.

Mikel Izquierdo PhD.

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*Title Page (Containing author details)

Title page

Title: Physical exercise improves function in acutely hospitalized old patients.

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Word account: 3157

Title page

Title: Physical exercise improves function in acutely hospitalized old patients.

Summary

An individualized multicomponent exercise intervention is an effective therapy to improve functional capacity, maximal muscle strength, and muscle power in acutely hospitalized old patients.

Word account: 3157

Abstract

Objectives: To evaluate the effects of an exercise intervention on functional capacity, maximal muscle strength and muscle power in very old hospitalized patients.

Design: In a randomized controlled trial, 130 hospitalized patients were allocated to an exercise intervention (n=65) or a control group (n=65). The intervention consisted of a multicomponent exercise training program performed during 5-7 consecutive days (2 sessions/day). The usual care group received habitual hospital care, which included physical rehabilitation when needed.

Setting and participants: Acute Care for Elderly (ACE) unit. Older adults aged>75 years.

Measures: Functional capacity, assessed with the Short Physical Performance Battery (SPPB) test and the Gait Velocity Test (GVT), were the primary endpoints. The GVT was also administered under dual-task conditions (i.e., verbal and arithmetic GVT). The functional tasks were recorded using an inertial sensor unit to determine the movement pattern. The secondary endpoints were maximal muscle strength and muscle power output.

Results: The exercise intervention program provided significant benefits over usual care. At discharge (primary time point), the exercise group showed a mean increase of 1·7 points in the SPPB scale (95%CI, 0·98, 2·42) and 0·14 m·s-1 in the GVT (95%CI, 0·086, 0·194) over the usual care group. The intervention also improved the verbal (0·151; 95%CI 0·119, 0·184 vs. -0·001; 95%CI -0·025, 0·033 in the control group) and arithmetic GVT (0·115; 95%CI 0·077, 0·153 vs. -0·004; 95%CI -0·044, 0·035). Significant benefits were also observed in the intervention group in movement pattern, as well as in muscle strength and muscle power.

Conclusions and implications: An individualized multicomponent exercise training program improves functional capacity, maximal muscle strength, and muscle power in acutely hospitalized old patients. These findings support the need for a shift from the traditional disease-focused approach in hospital ACE to one that recognizes functional capacity as a crucial vital sign.

ClinicalTrials.gov Identifier: NCT02300896

Introduction

The functional impairment that commonly occurs in the elderly during acute hospitalization is not only caused by the disease condition that causes hospitalization.[1] Older adults, especially frail, frequently have low levels of functional reserves, which increases their vulnerability to the adverse consequences of acute hospitalization and frequently leads to an incomplete recovery of the preadmission functional status[2], new disability[3], or even continued functional decline.[4]

Health care systems are still poorly adapted to old patients with frailty, disability, multimorbidity and polypharmacy[5] with low in-hospital mobility being directly associated with functional deterioration at discharge and, even more so, at follow-up.[6,7] In this context, exercise and early rehabilitation play an essential role to prevent functional and cognitive impairment during hospitalization in the elderly.[8,9] Yet, only a few randomized controlled trials (RCT) have examined the potential benefits of exercise training for acutely hospitalized elderly patients, and the effects of in-hospital exercise intervention on objective measures of functional outcomes are uncertain.[10]

Gait is the central component of a patient´s functional ability to perform basic activities of daily living (ADLs).[11] Yet, assessment of functional capacity during ADLs (*e.g.*, the ability to rise from a chair) is currently limited to performance time measurements, potentially missing important information about the test subtasks. In this regard, modern body-fixed sensors based on accelerometers and gyroscopes allow to objectively assess functional capacity in clinical practice.[12,13]

The main aim of the present study was to analyze the effects of a multicomponent exercise training intervention on functional capacity during ADLs in older adults during stay in an Acute Care for Elderly (ACE) unit. We hypothesized that the aforementioned intervention would improve patient´s functional capacity, as well as maximal muscle strength and muscle power output of lower limbs.

Methods

Design

The study is a secondary analysis of a RCT (NCT02300896) performed according to the SPIRIT 2013 and the CONSORT statement for transparent reporting.[14,15] It was conducted in the ACE unit of the Department of Geriatrics in a tertiary public hospital (*Complejo Hospitalario de Navarra*, Spain). This Department has 35 beds allocated and its staff is composed of 8 geriatricians (distributed in the ACE unit, orthogeriatrics and outpatient consultations). Admissions in the ACE unit derive mainly from the Accident and Emergency Department, with heart failure, pulmonary and infectious diseases being the main causes of admissions. When the disability generated by the pathology that caused admission in the ACE unit requires long-term care, patients are usually referred to another, medium-stay hospital.

Acutely hospitalized patients who met inclusion criteria were randomly assigned to the intervention or control (usual care) group within the first 48 hours of admission. Usual care is offered to the patient by the geriatricians of our department and consists of standard physiotherapy focused on walking exercises for restoring the functionality conditioned by potentially reversible pathologies. A formal exercise prescription was not provided at study entry and patients were instructed to continue with the current activity practices through the duration of the study. The study followed the principles of the Declaration of Helsinki and was approved by the institutional Clinical Research Ethics Committee. All patients or their legal representatives provided written consent.

Participants and randomization

The participants were acute hospitalized, prefrail/frail older men and women recruited within the first 48 hours of admission to the ACU by the geriatricians. Later, a trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥75 years, Barthel Index score ≥60 points, being able to ambulate (with/without assistance), and to communicate and collaborate with the research team. Exclusion criteria included expected length of stay <6 days, very severe cognitive decline (i.e., Global Deterioration Scale score =7), terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, or extremity bone fracture in the past 3 months.

After the baseline assessment was performed, participants were randomly assigned following a 1:1 ratio, without restrictions. The randomization sequence was generated using www.randomizer.org. The assessment staff were blinded to the main study design and group allocation. Participants were explicitly informed and reminded not to discuss their randomization assignment with the assessment staff.

Intervention

The usual care group received habitual hospital care, which included physical rehabilitation when needed. The exercise training was programmed in two daily sessions (morning and evening) of 20-minutes duration during 5–7 consecutive days (including weekends) supervised by an experiences fitness specialist. Adherence to the exercise intervention program was documented in a daily register. A session was considered completed when ≥90% of the programmed exercises were successfully performed. The details of the exercise training protocol have been described previously.[16,17]

Each session was performed in a room equipped ad hoc in the geriatric acute care unit. Exercises were adapted from the multicomponent physical exercise program “Vivifrail” to prevent weakness and falls.[18] The morning sessions included individualized supervised progressive resistance, balance, and walking-training exercises. The resistance exercises were tailored to the individual’s functional capacity using variable resistance training machines (Matrix, Johnson Health Tech, Ibérica, S.L.; Torrejón de Ardoz, Spain and Exercycle S.L., BHGroup; Vitoria, Spain) aiming at 2–3 sets of 8–10 repetitions with a load equivalent to 30–60% of the estimated one-repetition maximum (1-RM).[16,17] Participants performed three exercises involving mainly lower-limb muscles (squats rising from a chair, leg press and bilateral knee extension) and one involving the upper-body musculature (seated bench (‘chest’) press). They were instructed to perform the exercises at a high speed to optimize muscle power output, and care was taken to ensure proper exercise execution. Balance and gait retraining exercises gradually progressed in difficulty and included the following: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), altering the base of support, and weight transfer from one leg to the other. The evening session consisted of functional un-supervised exercises using light-loads (*i.e.*, 0·5–1 kg anklets and hand-grip ball), such as knee extension/flexion, hip abduction and daily walking in the corridor of the acute care unit with a duration based on the clinical physical exercise guide “Vivifrail”.[18]

As soon as the clinician in charge of the patient considered that their hemodynamic situation was acceptable, and the patient could collaborate, the following endpoints were assessed and the intervention was started. Endpoints were also assessed on the day of discharge.

Endpoints

The primary endpoint was change in functional capacity during hospitalization (*i.e.*, from admission to discharge) as assessed with the Short Physical Performance Battery (SPPB) and the 6-meter Gait Velocity Test (GVT, including also the GVT under dual-task conditions). Secondary endpoints were maximal muscle strength and muscle power output during leg press exercise.

SPPB, 6-meter GVT and dual-task gait

The SPPB includes usual walking speed over 4 meters, a balance test, and the Five Times Sit to Stand Test (FTSST), with the sum of the three individual categorical scores yielding the final SPPB score (range points: 0 (worst)- 12 (best)).[19] For the 6-meter GVT, patients were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway. In addition to the habitual GVT, two different dual-task gait tests were performed, the arithmetic GVT (aGVT) and verbal GVT (vGVT), in which gait velocity was measured while the participants counted backward aloud from 100 down to one or named animals aloud, respectively. The results of the functional tasks were recorded using an inertial sensor unit (Xsens MTx; Xsens Technologies B.V., Enschede, The Netherlands) attached over the lumbar spine (L3) to record the acceleration data. The sampling rate of these recorded data was 100Hz.

Movement pattern in functional tasks

The measured gait parameters were as follows: stride regularity, gait symmetry, and gait variability. The measurements were obtained for three directions: anterior-posterior, medio-lateral and vertical.

The FTSST was divided into three different phases to assess the movement-related parameters of each sit-stand-sit cycle: impulse, sit-to-stand, and stand-to-sit. Once these three different phases were identified, we analyzed the peak of power value of the sit-to-stand phase.

Maximal dynamic muscle strength and muscle power output of the lower limbs

Maximal dynamic strength was measured based on the results of a one-repetition maximum (1RM) reached in bilateral leg press exercise (Exercycle S.L.; BHGroup, Vitoria, Spain) as follows. After 1RM values were determined, the participants performed ten repetitions at the maximal possible velocity at intensities of 50% of 1RM to determine the maximum power in the propulsive phase. The power output was recorded by connecting a velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain).

Statistical analysis

All analyses were performed by “intention-to-treat” approach. Between-group comparisons of continuous variables were conducted using linear mixed models. Time was treated as a categorical variable. The models included group, time, and group by time interaction as fixed effects, and participants as random effect. For each group, data are expressed as change from baseline (admission) to discharge, determined by the time coefficients (95% confidence interval (CI)) of the model. The primary conclusions about effectiveness of exercise intervention were based on between-group comparisons of change in functional capacity from baseline (beginning of the intervention) to hospital discharge, as assessed with the SPPB and the GVT (including both dual-task conditions) and determined by the time by group interaction coefficients of the model. Comparisons between groups of secondary endpoints were also performed using the same statistical method. Normality of data was checked graphically and through the Kolmogorov Smirnov test. All comparisons were two-sided, with a significance level of 0.05. MATLAB and Statistics Toolbox Release 2013b (Mathworks, Inc., Natick, MA) software was used for the data analysis and IBM-SPSS v20 software for the statistical analysis.

Results

The study flow diagram is shown in **Figure 1**. Baseline demographic and clinical characteristics of the participants (N = 130) are presented in **Table 1.** The median length of hospital stay was 6 days in both intervention and control groups. The number of completed morning and evening sessions per patient in the intervention group averaged 5±1 and 4±1, respectively. Mean adherence to the intervention was 98±5% for the morning sessions (*i.e*., 286 completed sessions of 292 total possible sessions) and 83±32% for the evening sessions (197 of 237). There were no adverse events related to the intervention and no patient had to interrupt the exercise training or had their hospital stay modified because of the study protocol.

The primary analyses showed that the exercise intervention program provided a significant benefit over usual care. At discharge (i.e., at the primary time point), the exercise group showed a mean increase of 1·7 points in the SPPB scale (95% CI, 0·98, 2·42) over the usual care group (**Table 2** and **Figure 2**). We also found significant differences between groups in change from admission to discharge in the SPPB scale expressed as separate subtask scores (all $p<0{\cdot}05$, **Table 2**). Patients in the intervention group showed improvements at discharge compared with baseline in functional capacity as measured by the GVT (including both dual-task conditions, vGVT and aGVT) whereas no such trend was found in the control group (**Table 2** and **Figure 2**). Significant differences between groups were also observed in all the secondary outcomes related to maximal muscle strength and power output (all $p<0{\cdot}01$, **Table 2** and **Figure 2**).

Regarding the functional tasks analyzed by the inertial sensor unit, significant differences between groups were found for the time to complete the FTSST as well as for the peak of power during the sit-to-stand phase (all p<0·05, **Table 3**). Significant differences between groups in the walking pattern after the intervention are presented in **Table 3**. Patients in the intervention group improved gait performance in terms of gait regularity and symmetry in the GVT and dual-task at discharge compared with admission values, whereas such improvements were not observed in the control group.

Discussion

The main findings of the present study were the enhancements achieved in the functional endpoints (i.e., SPPB, GVT and dual-task GVT), maximal strength and muscle power output in older adults admitted in an ACE after a median of only five days of multicomponent exercise training. In addition, there were improvements in movement pattern in different functional tasks in the exercise training group compared with the control group after the intervention.

Acute illness requiring hospitalization is often a sentinel event for many older adults[20] and functional decline is one of the negative short-term consequences of bed rest during hospital stay.[1] In our study, however, short-term hospitalization did not have a major impact on functional capacity in the control group. Several reasons could explain the maintenance of functional capacity in those patients. First, the poor health status of hospitalized elderly upon admission may improve with the proper management of their acute disease. Second, the length of hospital stay was lower than in other studies that have investigated the functional consequences of hospitalization in the elderly.[6] Finally, the older adults were admitted to an acute geriatric ward in which comprehensive and multidisciplinary protocols are already established and functional recovery is the main objective to prevent iatrogenic disability.[5]

Recent evidence has failed to support the functional benefits of a mobility program consisting on ambulation and a behavioral strategy to encourage mobilization in this population.[21] In agreement with previous studies, however, our results indicate that a more complete exercise training intervention including walking and other training modalities such as resistance (power) and balance training could represent an optimal treatment strategy to improve functional capacity in acutely hospitalized older adults. Indeed, it seems that multicomponent exercise training is the most effective intervention for improving overall physical outcomes in frail older adults including muscle strength and power output and for preventing disability and other adverse events associated with aging.[22-23] On the other hand, although the beneficial effects of exercise training on physical function in the general elderly population are well established, the evidence is less definitive regarding cognitive gains, at least in hospitalized old people. In our study, significant differences were observed between groups in changes at discharge compared to admission in both dual-task gait performance and movement-related parameters. The findings support that multicomponent exercise training may produce the most positive effects on cognitive function in older adults.[24,25]

Regarding the issue of functional assessment in hospitalized patients, different screening tools are available to identify older adults at risk for functional decline during hospitalization and after discharge.[26] However, there is currently no “gold standard” for measuring functional trajectory during hospitalization. In this regard, we used an innovative inertial sensor unit to analyze changes in daily functional tasks including walking and rising from a chair. Concerning the ability to stand from a seated position, patients in the intervention group improved the performance at discharge compared with admission, whereas lower values were observed in the control group. Among these parameters, peak power improvement at discharge in the intervention group is the cornerstone for counteracting the age-related functional decline.[23;27-29] This unique finding has major implications for clinical practice, first because skeletal muscle power decreases earlier and faster than muscle strength with advancing age and second because muscle power output is a more discriminant predictor of functional performance in older adults.[27-29] Functional ability, and the maintenance of autonomy and independence, is the starting point of healthy aging, a term established by the World Health Organization (WHO) in its first world report on aging and health.[30] In agreement with the WHO framework, our results indicate that multicomponent exercise training, with special emphasis on muscle power training, is the intervention of choice for maintaining function and avoiding a trajectory towards frailty/disability in acutely hospitalized older adults and exercise prescription should be considered as a front-line treatment to prevent hospital-acquired iatrogenic disability.

Our study has some limitations, including mainly the patient´s difficulty for completing all the measurements at both hospital admission and discharge. Notably, only 9% of the participants were able to achieve the full-tandem position in both assessments. Another possible limitation was that only old patients with relatively good functional capacity at preadmission (*i.e.*, Barthel Index score ≥60 points) were included in the RCT; thus, the results may not be generalizable to the entire hospitalized elderly population. Also, we did not collect functional data prior to the acute illness. However, functional status two weeks prior to admission was indirectly measured with the Barthel Index score at baseline. In turn, our study has several strengths. An innovative exercise training program of few days (i.e., 5±1 and 4±1 morning and evening sessions, respectively) was effective to reverse the functional decline associated with hospitalization in acutely hospitalized very old patients. Moreover, an inertial sensor unit was used for measuring and monitoring the functional trajectory after an innovative exercise training program. Typically, in-hospital functional status and functional trajectory are measured using subjective self-reports scales based on ADLs or instrumental ADLs.[26] From a practical standpoint, the inertial sensor unit seems to be a feasible and sensitive tool for detecting changes in functional tasks that are associated with patient´s ability to perform ADLs.

Conclusions and implications

An individualized multicomponent exercise training program is an effective therapy to improve functional capacity (i.e., balance, rising from a chair, GVT, dual-task performance), maximal muscle strength and power performance in very old, prefrail/frail patients during acute hospitalization. Monitoring functional capacity with latest screening tools (*i.e*., inertial sensor units), enables to detect enhancements in movement pattern in functional tasks associated with ADL after an innovative exercise training program in hospitalized older adults. Our findings support the need for a shift from the traditional disease-focused approach in hospital ACE to one that recognizes functional capacity as a crucial vital sign during hospitalization.

Declaration of interests

All authors have nothing to declare. The authors declare non competing interest.

Figure legends

Figure 1. Study flow diagram

Figure 2. Box plot showing within group changes from baseline to discharge in the Short Physical Performance Battery (SPPB) test, Gait Velocity Test (GVT) including verbal (vGVT) and arithmetic (aGVT) dual-task conditions, and maximal dynamic muscle strength and muscle power output during bilateral leg press exercise.

Table 1. Baseline characteristics of the subjects

	Control group (n=65)	Exercise group (n=65)
Age, years	86 ± 5	88 ± 4
Men/women	33/32	33/32
BMI, kg/m^2	27 ± 6	27 ± 4
Education, %		
< 12 years	11	21
≥ 12 years	89	79
Length of stay, median (IQR)	6 (1)	6 (0)
Barthel Index score, points	86 ± 15	86 ± 15
Falls last year, %		
0	34	26
1-2	40	42
> 2	20	26
No data available	6	6
Cognition (MMSE score), points	23 ± 4	22 ± 5
CIRS-G	13± 4	12 ± 5
Admission reason (type of disease), %		
Pulmonary	36	35
Cardiovascular	18	18
Infectious	11	15
Gastrointestinal	9	11
Neurological	5	5
Other	21	16

Data are presented as mean ± SD unless otherwise indicated. BMI, Body Mass Index; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; GDS, Geriatric Depression Scale; IQR, Interquartile Range; MMSE, Mini Mental State Examination.

Table 2. Results of study endpoints by group.

	Control group	Exercise group	Between-group difference (95%CI)	p value between groups
Primary endpoints				
SPPB, total score	0·30 (-0·20, 0·81)	2·00 (1·49, 2·51)	1·70 (0·98, 2·42)	<0·001
Balance score	0·17 (-0·13, 0·46)	0·71 (0·42, 1·00)	0·53 (0·12, 0·96)	0·012
Gait ability score	0·13 (-0·10, 0·36)	0·47 (0·25, 0·70)	0·34 (0·02, 0·66)	0·038
Leg strength score	0·05 (-0·22, 0·33)	0·86 (0·58, 1·13)	0·80 (0·41, 1·19)	<0·001
GVT, $m\cdot s^{-1}$	0·004 (-0·033, 0·043)	0·144 (0·106, 0·182)	0·140 (0·086, 0·194)	<0·001
Verbal GVT, $m\cdot s^{-1}$	-0·001 (-0·025, 0·033)	0·151 (0·119, 0·184)	0·152 (0·105, 0·199)	<0·001
Arithmetic GVT, $m\cdot s^{-1}$	-0·004 (-0·044, 0·035)	0·115 (0·077, 0·153)	0·120 (0·065, 0·174)	<0·001
Secondary endpoints				
Bilateral leg press 1RM, kg	-1·82 (-6·83, 3·20)	15·00 (10·92, 19·08)	16·82 (10·35, 23·29)	<0·001
PW50, watts	1·13 (-13·51, 15·78)	31·00 (20·86, 41·14)	29·87 (12·06, 47·68)	0·002

Data in each group are expressed as change from baseline (admission) to discharge (mean and 95% confidence interval). Abbreviations: GVT, gait velocity test; PW50, leg power at an intensity of 50% of 1RM test; RM, repetition maximum; SPPB, Short Physical Performance Battery.

Table 3. Movement pattern in the Five Times Sit to Stand Test (FTSST) and walking tests by group.

		Control group	Exercise group	Between-group differences (95%CI)	p value between groups
		FTSST			
Time, s		-2·36 (-4·90, 0·18)	-6·33 (-8·72, -3·94)	-3·97 (-7·46, -0·48)	0·029
Repetitions, n		-0·07 (-0·49, 0·35)	0·27 (-0·15, 0·69)	0·34 (-0·24, 0·94)	0·258
Sit-to-stand phase					
Peak power, W·kg		-0·12 (-0·43, 0·19)	0·39 (0·11, 0·66)	0·51 (0·09, 0·92)	0·021
		GVT			
Stride regularity	AP	0·051 (0·003, 0·099)	0·052 (0·004, 0·100)	0·001 (-0·068, 0·067)	0·986
	ML	0·056 (0·008, 0·104)	0·019 (-0·028, 0·066)	-0·037 (-0·105, 0·030)	0·282
	V	0·030 (-0·014, 0·073)	0·100 (0·056, 0·143)	0·070 (0·008, 0·131)	0·029
Symmetry	AP	-0·010 (-0·075, 0·055)	0·009 (-0·055, 0·073)	0·019 (-0·072, 0·110)	0·687
	ML	-0·038 (-0·109, 0·034)	0·012 (-0·057, 0·083)	0·049 (-0·052, 0·150)	0·340
	V	0·032 (-0·032, 0·096)	-0·087 (-0·151, -0·022)	-0·119 (-0·209, -0·028)	0·012
CoV step time		-0·031 (-0·051, -0·010)	-0·047 (-0·067, -0·026)	-0·016 (-0·045, 0·013)	0·283
		Verbal GVT			
Stride regularity	AP	0·015 (-0·041, 0·071)	0·058 (0·004, 0·112)	0·043 (-0·035, 0·122)	0·281
	ML	0·005 (-0·053, 0·062)	0·010 (-0·045, 0·065)	0·005 (-0·075, 0·085)	0·901
	V	0·053 (0·010, 0·107)	0·021 (-0·025, 0·071)	-0·032 (-0·097, 0·031)	0·392
Symmetry	AP	-0·010 (-0·079, 0·060)	-0·077 (-0·143, -0·011)	-0.067 (-0·163,0·028)	0·173
	ML	0·014 (-0·056, 0·084)	0·047 (-0·019, 0·113)	0·033 (-0·064, 0·129)	0·508
	V	-0·009 (-0·083, 0·066)	0·004 (-0·067, 0·076)	0·013 (-0·090, 0·116)	0·809
CoV step time		-0·027 (-0·053, -0·001)	-0·045 (-0·070, -0·020)	-0·018 (-0·054, 0·018)	0·320
		Arithmetic GVT			
Stride regularity	AP	0·026 (-0·029, 0·080)	0·083 (0·030,0·136)	0·058 (-0·019, 0·134)	0·143
	ML	-0·010 (-0·061, 0·041)	0·004 (-0·045, 0·054)	0·014 (-0·056, 0·085)	0·690
	V	0·023 (-0·012, 0·058)	0·078 (0·043, 0·113)	0·056 (0·006, 0·105)	0·031
Symmetry	AP	0·042 (-0·029, 0·112)	-0·094 (-0·163, -0·025)	-0·136 (-0·235, -0·037)	0·008

	ML	0·034 (-0·035, 0·105)	-0·032 (-03101, 0·038)	-0·066 (-0·164, 0·032)	0·196
	V	0·024 (-0·052, 0·101)	-0·009 (-0·084, 0·065)	-0·034 (-0·141, 0·073)	0·541
CoV step time		-0·012 (-0·044, 0·019)	-0·033 (-0·064, -0·002)	-0·021 (-0·065, 0·023)	0·355

Data in each group are expressed as change from baseline (admission) to discharge (mean and 95% confidence interval). Abbreviations: AP, anterior-posterior; CoV, coefficient of variability; GVT, gait velocity test; FTSST, five times sit to stand test; ML, medio-lateral, V, vertical.

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Figure 1

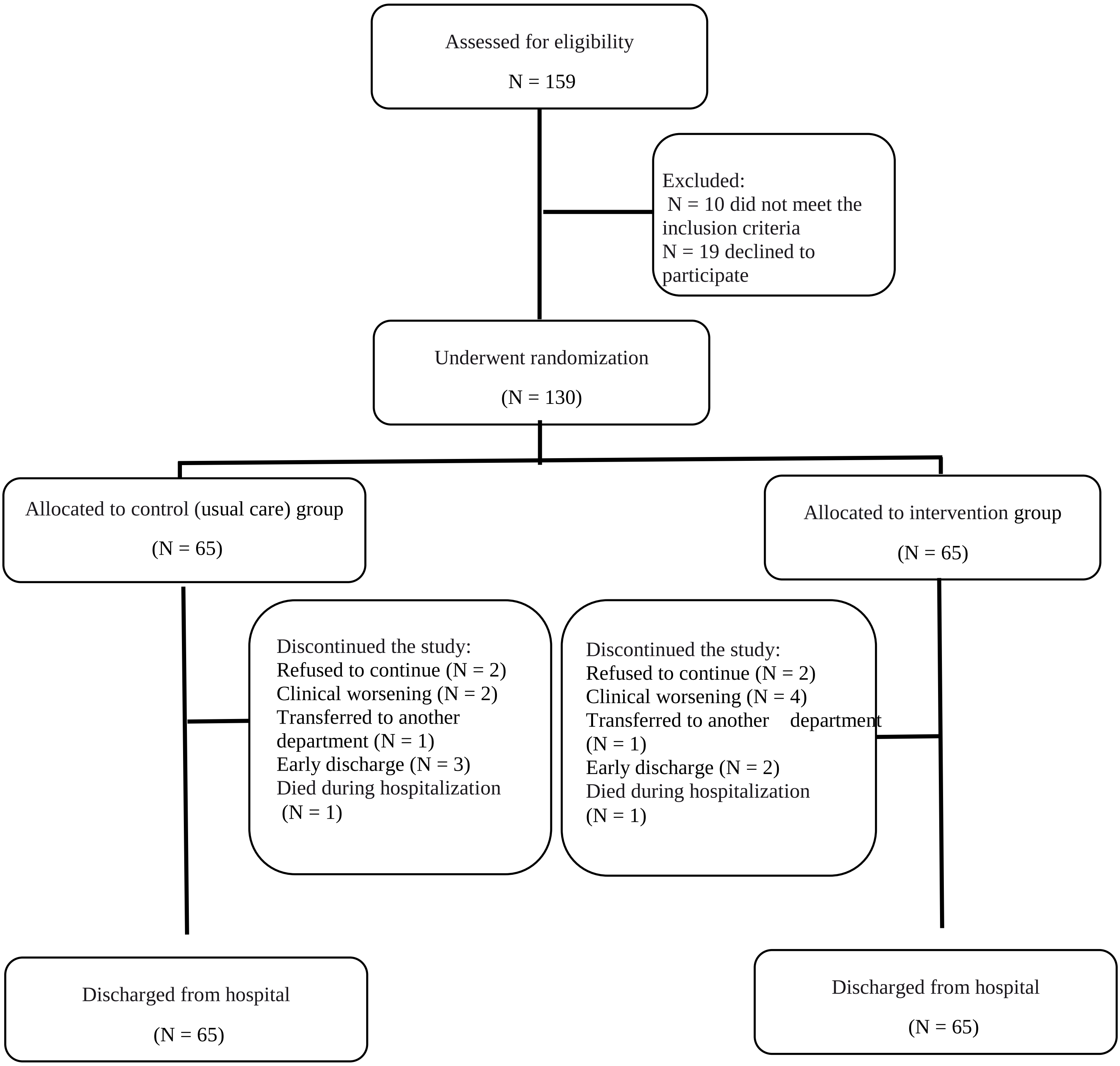

Figure 1.

Figure 2

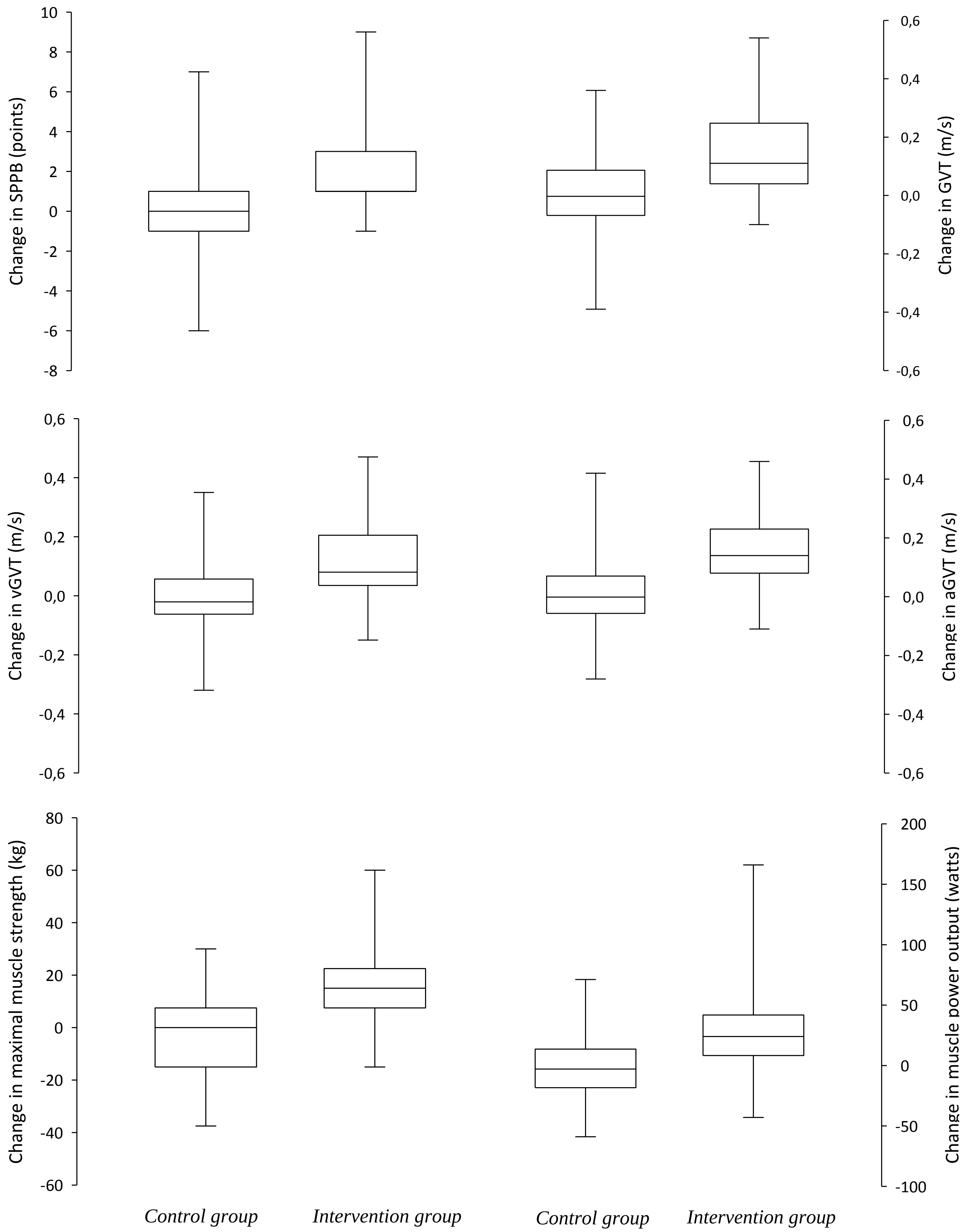

Figure 2.

Elsevier Editorial System(tm) for JAMDA
Manuscript Draft

Manuscript Number: JAMDA-D-18-00794R1

Title: Role of muscle power output as a mediator between gait variability and gait velocity in hospitalized older adults.

Article Type: Original Study

Keywords: Older adults; hospitalized; functional status; muscle power output

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Abstract: Background: Acute illness requiring hospitalization is a sentinel event leading to functional decline and frequently, long-term disability in older adults. Although functional decline has become a key outcome during and after hospitalization, there is currently no gold standard for measuring functional impairment.
Objectives: The purpose of this study was to compare gait characteristics and muscle performance endpoints of hospitalized older adults based on the Short Physical Performance Battery (SPPB) score (0-12 points) obtained at admission, and to determine the association underlying the gait impairment.
Design: A cross-sectional study.
Settings: Acute Care Unit in a tertiary public hospital in Navarra, Spain.
Participants: 130 hospitalized older adults (aged □75) were included. We created the following phenotype groups: disabled (SPPB 0-3); frail (SPPB 4-6); prefrail (SPPB 7-9); and robust (SPPB 10-12).
Measurements: The primary endpoints were differences in functional capacity between groups, assessed with the 6-meter Gait Velocity Test (GVT), verbal and arithmetic GVT, followed by gait pattern data recorded using an inertial sensor unit. Maximal muscle strength (MS) and muscle power (MP) were also measured as muscle performance endpoints. A mediation analysis was performed to understand gait disorders according to Baron and Kenny procedures.
Results: The walking parameters measured at admission were related to functional status and showed significant differences among phenotype groups (disabled, frail, and prefrail groups), as well as muscle performance endpoints (p<0.05). Finally, the indirect effect was significant (-0.27; 95%CI, -0.59 to -0.05), confirming the mediation role of MP between gait variability and gait velocity in this model.
Conclusions: MP slightly weakens the relationship between gait variability and gait velocity. In addition to MS and MP, gait velocity and gait pattern parameters are distinguishing factors among acutely hospitalized older adults.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

COVER LETTER

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Dear Editor,

We thank you for the opportunity to revise and resubmit our manuscript. Please find attached the latest version of the paper entitled "Role of muscle power output as a mediator between gait variability and gait velocity in hospitalized older adults" for consideration by JAMDA. The rebuttal letter and the changes in manuscript were approved by all the listed coauthors and meets the requirements of co-authorship. This manuscript has not been published elsewhere or are not being considered for publication elsewhere and the research reported will not be submitted for publication elsewhere until a final decision has been made as to its acceptability by the Journal.

We believe that this manuscript is appropriate for publication by JAMDA because we use a new tool for measuring and monitoring the functional capacity at admission in acutely hospitalized older adults and we perform an innovative statistical method (mediation analysis) for understanding the role of muscle power as a potential mediator between gait variability and gait velocity in this population. Studies examining the dose-response relationship often incorporate multiple linear / logistic regression or covariance analysis to adjust for confounding / mediator variables; however, these statistical methods do not account for the percentage of the total explained by the potential mediators. From a practical standpoint, we think that the findings achieved in this article open the possibility for a paradigm shift from the traditional disease-focused approach in hospital acute care units for elders to one that recognizes functional status as a clinical vital sign that can be impaired by 'traditional' (bedrest-based) hospitalization but could effectively reversed with specific in-hospital exercises, such as muscle power training.

Sincerely,

Mikel Izquierdo, PhD

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Nafarroako Unibertsitate Publikoa

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*Detailed Response to Reviewers (WITHOUT author details)

JAMDA RESPONSE TO DRIFT MANUSCRIPT: JAMDA-D-18-00794

Editor's comments:

I apologize for the delay in providing comments. The paper had gotten lost in our system (because reviewer 1 kept pending but not submitting), and so I appreciated your note the other day. The research question is complex for many non-researchers to understand, and while it is important, more care needs to be taken to provide a narrative that the naive reader will understand.

Thank you so much for considering the manuscript for publication.

Main issues involve: (a) linking the study to a theoretical model; (b) making the methods and implications clearer; and (c) explaining and justifying why this substudy is on only a minority of the original patients.

Done. Thank you.

Reviewer 2:

Thanks for your paper. I have some doubts regarding the methodology followed in your study.

Thank you very much for your positive comment. In order to clarify the methodology we wrote as follows:

"Theoretical model of mediation analysis

The detection of mediators is an important methodological issue in many fields, including psychology, medicine and biology. In general, outcome mediators address the mechanisms by which an effect occurs. Baron and Kenny[24] postulated several criteria for the analysis of a mediating effect: a mediator (M) that transmits the effect of a predictor variable (X) to an outcome variable (Y) in a causal sequence such that (X) causes (M) and (M) causes (Y). Summarizing, a mediating variable explain de process by which one variable causes another, using the Sobel test[25] that shows whether indirect effect are significant or not. The theoretical analyses of mediation, for example, can help researchers to move beyond answering if high levels of muscle power output lead to low levels of gait variability."

Abstract
Line 27: Do not start a sentence with a number.

Following the reviewer´s suggestion, we have changed this part of the abstract (page 2 line 31-32):

A total of 130 hospitalized older adults (aged ≥75) were included.

I think it is not correct to speak of robust, it would be better to say not frail. Review the rest of the text.

We completely agree with the reviewer. We have included the suggestion in the manuscript and Figure 1 (for example, page 2 line 33):

We created the following phenotype groups: disabled (SPPB 1-3); frail (SPPB 4-6); prefrail (SPPB 7-9); and not frail (SPPB 10-12).

Methods

When has the study been done?

The data collection for this study was performed from July 17, 2016, to August 30, 2017. According to the reviewer´s suggestion, we have included the interesting suggestion in the content (page 6 lines 113-114):

The data collection was performed from July 17, 2016, to August 30, 2017.

The subjects included in this study have been included in other studies?

Yes, as we mentioned in the manuscript (page 4 lines 93-96), this study is a secondary analysis of a RCT with the purpose of analyzing the effects of a multicomponent exercise-training program for improving the functional capacity and cognition of acute elderly patients hospitalized for medical pathology (NCT02300896).

Do you have the number of subjects not included? Do you have the reason for the exclusion? If you do not have this information, this should be specified as a limitation.

In this study were included all the patients that had gait pattern measurement using the inertial sensor unit at admission. Thus, this is the reason of why this substudy is on only a minority of the original patients of the RCT (NCT02300896).

Following the reviewer´s suggestion, we have added reviewer´s comment as a limitation in the manuscript (page 13 lines 297-299):

Finally, only patients with gait pattern assessment at admission using the inertial sensor unit of the larger RCT (NCT02300896) were included in the study.

Line 87: I'm not sure about the design of the study. Is it a baseline analysis or a subanalysis? From the protocol registered in Clinical Trials it turns out that the study is a RCT, and this study, if I am not mistaken, would be a subanalysis of the baseline data of 130 of the 370 included subjects.

We totally agree with the reviewer. It´s a subanalysis of the RCT. It´s a subanalysis of the baseline data of 130 of the 370 included in the RCT.

According to the reviewer´s comment, we have modified the content in the manuscript (page 6 lines 118-119):

The study is a subanalysis of the baseline data of a larger randomized clinical trial (RCT)…

Why, for this analysis, you have included only 130 of the 370 subjects who participated in the study (NCT02300896)? How have the 130 participants of the total sample been selected?

No, patients were not selected. A new endpoint was included in the RCT in July 17, 2016 (Gait pattern assessment using the inertial sensor unit). Thus, the last 130 patients recruited for the

RCT were included in this study (The RCT started in February 1, 2015). The patients of this study had the same clinical and functional characteristics of the rest of the sample size.

Line 112: Have you included subjects with SPPB of 0? Subjects with SPPB of 0 should be unable to walk. How have you assessed the ability to walk in these subjects? In the inclusion criteria available in Clinical Trials it turns out that the included subjects had to be able to walk.

We agree with the reviewer. We did not include patients with SPPB of 0 (we included those older adults with at least a score of 1 point, able to walk 4 meters). We used the Vivifrail classification for this study, and based on this classification, those older adults with an SPPB 0-3 point are categorized as disabled. However, to be able to walk was a crucial inclusion criteria. Thus, following the reviewer´s comment, we have changed the inclusion criteria of disabled group (page 2 line 29, page 5 line 111):

We created the following phenotype groups: disabled (SPPB 1-3); frail (SPPB 4-6); prefrail (SPPB 7-9); and not frail (SPPB 10-12).

….iv) disabled if the SPPB score was 1-3 points.

Line 122: How have the gait pattern parameters been measured?

According to the reviewer´s suggestion, more information was included about the inertial sensor unit and gait pattern parameters measurement (page 7 lines 144-146; page 7 lines 150-153):

The MTx provides drift-free 3-dimensional (3D) orientation and kinematic data: 3-D acceleration, 3-D rate of turn (rate gyro) and 3-D earth magnetic field data.

Stride regularity was obtained from the autocorrelation sequence of the acceleration signal x. Gait variability can be estimated by calculating the CoV step time, where t is the mean of step time across all steps and σ its standard deviation.

Results

Lines 154 to 158: Considering that walking speed is one of the parameters used to define the degree of frailty (since you have used SPPB to define frailty), it is normal to find that frail subjects have a lower walking speed than not frail subjects.

We totally agree with the reviewer. SPPB is a more complex task that include not only walking, also balance and lower limbs muscle strength with the Five Times Sit to Stand Test. A simple Gait Velocity Test can be useful for measuring functional status and for prescribing tailored interventions such as exercise training to avoid functional decline associated with hospitalization.

It is expected that subjects with lower SPPB have lower barthel. The interesting thing would have been to know if subjects with lower SPPB at admission had a worse situation at discharge. In other words, assess whether the SPPB can be a predicting factor for disability.

Thank you for your interesting idea. The reviewer´s suggestion will be include in another secondary analysis of the RCT.

Discussion

Line 258: In itself, the small number of the sample is not a limitation. This can reduce the applicability of the results.

According to the reviewer´s suggestion, we have changed the limitations of the study (page 12 line 262):

First, only older adults with relatively good functional capacity at preadmission (Barthel Index score ≥60 points) were included in the study.

Reviewer 3:

Major concerns:

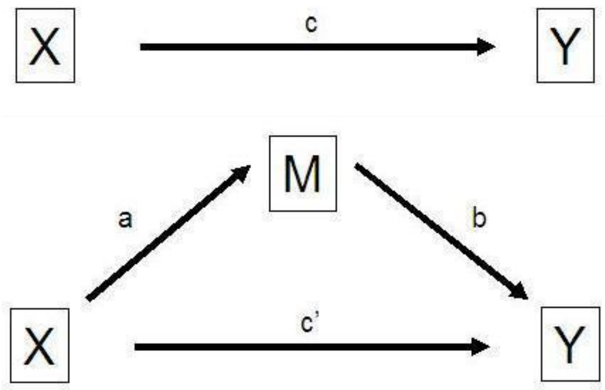
1. For most readers of JAMDA, this is basic research of potential interest but that needs more introduction. The way to do this would be, at the beginning of the methods section, to present a theoretical model that includes text and a diagram, in which you define and discuss the various measures used in the study and explain how they are hypothesized to be inter-related. This assumes, of course, that you had hypotheses that you were testing, which I believe was the case, and if so should be stated at the end of the introduction.

Following the reviewers suggestion, we have added (page 4 lines 69-71):

…its relationship with muscle power output in hospitalized older medical patients as a confounder and therefore as a factor to be controlled in multivariable models is not yet clear. With mediation analysis, researchers might instead answer, for example, how muscle power output is related to gait variability and/or gait velocity.

We also included the theoretical model to discuss how measures are inter-related (page 4-5 lines 84-93):

The detection of mediators is an important methodological issue in many fields, including psychology, medicine and biology. In general, outcome mediators address the mechanisms by which an effect occurs. Baron and Kenny postulated several criteria for the analysis of a mediating effect: a mediator (M) that transmits the effect of a predictor variable (X) to an outcome variable (Y) in a causal sequence such that (X) causes (M) and (M) causes (Y). Summarizing, a mediating variable explain de process by which one variable causes another, using the Sobel test that shows whether indirect effect are significant or not. The theoretical analyses of mediation, for example, can help researchers to move beyond answering if high levels of muscle power output lead to low levels of gait variability.



According to the reviewer´s suggestion, we have added the hypothesis at the end of the introduction (page 4 lines 79-82):

We hypothesized that acutely hospitalized older adults would present differences in gait pattern and muscle performance endpoints (i.e., maximal muscle strength and muscle power output) based on the Short Physical Performance Battery (SPPB) score obtained at admission, and muscle power output would play a key role on gait performance.

2. During hospitalization functional status often changes rapidly, even on a day to day basis. Therefore please explain how you can assume that hospitalization data will relate to baseline or post-hospitalization data.

We totally agree with the reviewer, functional status often changes rapidly during hospitalization. Previous evidence has supported the relevance of patients´ baseline function as a useful benchmark and goal for discharge and follow-up outcomes (Covinsky et. al 2003). Age is a strong independent risk factor for functional change during hospital stay, and previous studies have demonstrated that older age had a particularly deleterious effect on functional decline during hospitalization (Covinsky et. al 2003). However, considering the functional status, it could be that those older adults with higher functional reserve at admission could have worse response to hospitalization, and consequently, major vulnerability to iatrogenic nosocomial disability, than those patients with less functional capacity at baseline. A greater window of worsening during hospitalization could be a possible explanation for the major functional decline and higher loss of muscle power output and muscle strength. An individualized exercise training program would be an effective therapy to maintain or improve functional capacity during hospitalization and to avoid the hazards of prolonged bed rest.

The reviewer´s idea will be examine in a secondary analysis of the larger RCT. Thank you so much.

Covinsky KE, Palmer RM, Fortinsky RH et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. *J Am Geriatr Soc* 2003;51:451-458.

3. Figure 1 should include the full names of GVT, vGVT, and aGVT.

Done. Thank you.

4. There are two versions of the abstract. One has background, which is helpful, the other does not. Please include the background in the abstract.

Following the reviewer's suggestion, we have included the background in the abstract (page 2 lines 22-25):

Background: *Acute illness requiring hospitalization is a sentinel event leading to functional decline and frequently, long-term disability in older adults. Although functional decline has become a key outcome during and after hospitalization, there is currently no gold standard for measuring functional impairment.*

TITLE PAGE

The title: Role of muscle power output as a mediator between gait variability and gait velocity in hospitalized older adults.

Running title: MP mediator of gait features in hospitalized elderly.

Abstract

Background: Acute illness requiring hospitalization is a sentinel event leading to functional decline and frequently, long-term disability in older adults. Although functional decline has become a key outcome during and after hospitalization, there is currently no gold standard for measuring functional impairment.

Objectives: The purpose of this study was to compare gait characteristics and muscle performance endpoints of hospitalized older adults based on the Short Physical Performance Battery (SPPB) score (0-12 points) obtained at admission, and to determine the association underlying the gait impairment.

Design: A cross-sectional study.

Settings and Participants: Acute Care Unit in a tertiary public hospital in Navarra, Spain. A total of 130 hospitalized older adults (aged ≥75) were included. We created the following phenotype groups: disabled (SPPB 1-3); frail (SPPB 4-6); prefrail (SPPB 7-9); and not frail (SPPB 10-12).

Measurements: The primary endpoints were differences in functional capacity between groups, assessed with the 6-meter Gait Velocity Test (GVT), verbal and arithmetic GVT, followed by gait pattern data recorded using an inertial sensor unit. Maximal muscle strength (MS) and muscle power (MP) were also measured as muscle performance endpoints. A mediation analysis was performed to understand gait disorders according to Baron and Kenny procedures.

Results: The walking parameters measured at admission were related to functional status and showed significant differences among phenotype groups (disabled, frail, and prefrail groups), as well as muscle performance endpoints (p<0.05). Finally, the indirect effect was significant (-

0.27; 95%CI, -0.59 to -0.05), confirming the mediation role of MP between gait variability and gait velocity in this model.

Conclusions/Implications: MP slightly weakens the relationship between gait variability and gait velocity. In addition to MS and MP, gait velocity and gait pattern parameters are distinguishing factors among acutely hospitalized older adults.

Keywords: Older adults; hospitalized; functional status; muscle power output.

Introduction

Acute medical illnesses and subsequent hospitalization are crucial events leading to disability in the elderly population[1-4]. Despite the resolution of the reason for hospitalization, older medical patients are often discharged with a new major disability[5]. This loss of functional capacity is strongly associated with caregiver burden, higher resource use, institutionalization, and death[6-9].

Functional ability, and the maintenance of autonomy and independence, is the starting point of healthy aging, a term established by the World Health Organization (WHO) in its first world report on aging and health[10]. Although functional decline has become a key outcome after hospitalization and multiple screening tools are available to identify older adults at risk of functional decline during and after hospital stays[11;12], there is currently no “gold standard” for measuring functional impairment in hospitalized older medical patients[13].

Gait is essential for performing activities of daily living (ADL)[14]. Gait analysis is currently limited to performance time measurements in the clinical practice, lacking many measurable facets other than velocity[15]. With advanced age, there are increases in motor variability, especially in gait[16;17] and gait variability has been widely related to muscle system impairments[18]. Although increased gait variability is already recognized as a predictor of future falls in frail older adults[15;19], its relationship with muscle power output in hospitalized older medical patients as a confounder and therefore as a factor to be controlled in multivariable models is not yet clear. With mediation analysis, researchers might instead answer, for example, how muscle power output is related to gait variability and/or gait velocity. Recent studies have investigated the association between gait pattern and frailty syndrome[17;20], muscle mass quality[21], and cognitive impairment[22] in the elderly population. In this regard, modern body-fixed sensors based on accelerometers and gyroscopes allow for objectively assessing functional capacity in clinical practice[23].

The purpose of this study was to compare gait characteristics and muscle performance endpoints of hospitalized older adults admitted to an acute care unit (ACU) based on functional status presented at admission, and to determine the association underlying the gait impairment. We hypothesized that acutely hospitalized older adults would present differences in gait pattern and muscle performance endpoints (i.e., maximal muscle strength and muscle power output) based on the Short Physical Performance Battery (SPPB) score obtained at admission, and muscle power output would play a key role on gait performance.

Methods

Theoretical model of mediation analysis

The detection of mediators is an important methodological issue in many fields, including psychology, medicine and biology. In general, outcome mediators address the mechanisms by which an effect occurs. Baron and Kenny[24] postulated several criteria for the analysis of a mediating effect: a mediator (M) that transmits the effect of a predictor variable (X) to an outcome variable (Y) in a causal sequence such that (X) causes (M) and (M) causes (Y). Summarizing, a mediating variable explain de process by which one variable causes another, using the Sobel test[25] that shows whether indirect effect are significant or not. The theoretical analyses of mediation, for example, can help researchers to move beyond answering if high levels of muscle power output lead to low levels of gait variability.

Sample population

The participants were acutely hospitalized older men and women admitted to a tertiary public hospital (*XXXXXXXXXXXXXX*). The subjects were identified by geriatricians within the first 48 hours of admission to the ACU. A trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥75 years, Barthel index ≥60 points, being able to ambulate (with/without assistance), and to communicate and collaborate with the research team. The exclusion criteria were having very severe cognitive decline (*i.e.*, global deterioration scale score ≥7 points), myocardial infarction or upper/lower extremity fracture in the past 3 months, or terminal illness. All the participants were informed about the nature and risks of the experimental procedures before obtaining their written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Navarra Clinical Research Ethics Committee, Spain (Pyto 23/2014).

Study design

This cross-sectional study was carried out to evaluate the physical performance of very old hospitalized patients based on the "*Vivifrail*" classification[26] at admission and to analyze the associations between gait variability and gait velocity with the aim of explaining gait disorders in hospitalized older medical patients. The data collection was performed from July 17, 2016, to August 30, 2017. The primary endpoints were differences in gait characteristics among groups as assessed with the 6-meter Gait Velocity Test (GVT, also including the GVT under dual-task conditions). Secondary endpoints were the maximal muscle strength of lower/upper limbs and muscle power output during leg press exercise. A mediation analysis was performed to examine the role of muscle power output between gait variability and gait velocity. The study is a subanalysis of the baseline data of a larger randomized clinical trial (RCT) with the purpose of analyzing the effects of a multicomponent exercise-training program for improving the functional capacity and cognition of acute elderly patients hospitalized for medical pathology[27] (NCT02300896).

Short Physical Performance Battery (SPPB)

The SPPB includes the usual walking speed over 4 m, a balance test, and the Five Times Sit to Stand Test (FTSST). The standing balance test required participants to maintain stances with their feet placed in side-by-side, semitandem and full-tandem positions for 10 seconds each. In the FTSST, participants had to rise five times from a chair with their arms across their chest as fast as possible. The scores assigned to the performance on each test ranged from 0 to 4 (maximum performance). Participants were categorized as “unable to perform” if they were not able to complete the test and if the physician or the participant felt that the test was unsafe. Scores of 1-4 for each task were assigned based on quartile performance for more than 5000 participants in the Established Populations for the Epidemiologic Study of the Elderly[28]. Considering the total score obtained at admission, hospitalized older adults were classified in four phenotype criteria using the classic performance-based SPPB such as: *i)* not frail if the SPPB score was 10-12 points, *ii)* prefrail if the SPPB score was 7-9 points, *iii)* frail if the SPPB score was 4-6 points, and *iv)* disabled if the SPPB score was 1-3 points.

Six-meter GVT and dual-task gait

For the 6-meter GVT, patients were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway. In addition to the habitual GVT, two different dual-task gait tests were performed, the arithmetic GVT (aGVT) and verbal GVT (vGVT), in which gait velocity was measured while participants counted backward aloud from 100 down to one or named animals aloud, respectively. The results of the functional tasks were recorded using an inertial sensor unit (Xsens MTx; Xsens Technologies B.V., Enschede, The Netherlands) attached over the lumbar spine (L3) to record the acceleration data. The MTx provides drift-free 3-dimensional (3D) orientation and kinematic data: 3-D acceleration, 3-D rate of turn (rate gyro) and 3-D earth magnetic field data. The sampling rate of these recorded data was 100Hz.

Gait pattern parameters

The measured gait parameters, which have been related to gait disorders[15;29-31] in frail older adults[21;32], were as follows: stride regularity, stride time, stride length, and the coefficient of variability of step time (CoV step time). Stride regularity was obtained from the autocorrelation sequence of the acceleration signal *x*. Gait variability can be estimated by calculating the CoV step time, where $\bar{t}$ is the mean of step time across all steps and σ its standard deviation.

These measurements were obtained for three directions: anterior-posterior, medio-lateral and vertical.

Maximal dynamic muscle strength and muscle power output of the legs

Maximal dynamic strength was measured based on the results of a one-repetition maximum (1RM) reached in a bilateral leg press exercise (Exercycle S.L.; BHGroup, Vitoria, Spain) as follows. After 1RM values were determined, the participants performed ten repetitions at the maximal possible velocity at intensities of 50% of 1RM to determine the maximum power in the propulsive phase. The power output was recorded by connecting a velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain).

Maximal isometric muscle strength outcomes

Maximal isometric upper (right hand grip) and lower limb (right knee extensors and hip flexors) muscle strength were also assessed using a manual dynamometer.

Statistical analysis

Standard statistical methods were used to calculate the means and standard deviations (SD). Statistical normality was tested using both statistical (*Kolmogorov-Smirnov Test*) and graphical procedures (normal probability plots).

To investigate the differences between groups at admission based on functional status, hospitalized older adults were classified as not frail (NF), prefrail (PF), frail (F), and disabled (D). One-way analysis of variance (ANOVA) was used to assess mean differences between these categories, and pairwise *post hoc* difference were tested using the *Bonferroni* correction for multiple comparisons.

Finally, to examine whether the association between gait variability and functional capacity was mediated by muscle power output, linear regression models were fitted using the bootstrapped mediation procedures included in the PROCESS IBM-SPSS macro[33]. Data were analyzed using SPSS-IBM (Software, v.21.0 SPSS Inc., Chicago, IL, USA) and a p-value < 0.05 was considered statistically significant.

Results

Characteristics of the cohort are presented in **Table 1.** Overall, the patients had a mean age of 87.6 ± 4.8, and 48% were female.

The effects of functional status on gait velocity are summarized in **Figure 1**. Significant differences were found in gait velocity between the not frail and frail groups (0.76 vs. 0.47 m/s p < 0.001, respectively), not frail and disabled groups (0.76 vs. 0.29 m/s, p < 0.001), prefrail and frail groups (0.64 vs. 0.47 m/s p < 0.05), prefrail and disabled groups (0.64 vs. 0.29 m/s, p < 0.001), and frail and disabled groups (0.47 vs. 0.29 m/s, p < 0.001) in the habitual GVT. For the verbal GVT, significant differences were also observed between the not frail and frail groups (0.65 vs. 0.37 m/s p < 0.001, respectively), not frail and disabled groups (0.65 vs. 0.23 m/s, p < 0.001), prefrail and frail groups (0.52 vs. 0.37 m/s, p < 0.05), prefrail and disabled groups (0.52 vs. 0.23 m/s, p < 0.001), and frail and disabled groups (0.37 vs. 0.23 m/s, p < 0.001). Considering the arithmetic GVT, significant differences were identified between the not frail and frail groups (0.62 vs. 0.36 m/s p < 0.001, respectively), not frail and disabled groups (0.62 vs. 0.23 m/s, p < 0.001), prefrail and disabled groups (0.49 vs. 0.23 m/s, p < 0.001), and prefrail and disabled groups (0.49 vs. 0.23 m/s, p < 0.001).

The significant differences between groups in terms of walking patterns in different task conditions are presented in **Table 2**. Compared with older adults with lower functional reserve, patients with better functional capacity at admission had better gait performance in terms of gait regularity, stride length and gait variability.

Regarding the muscle capacity of acutely hospitalized older adults, significant differences between groups were observed in secondary outcomes related to the maximal dynamic muscle strength and power output of the legs (all p<0.01, **Table 3**). Moreover, significant differences between groups were also found for the isometric knee extension and hip flexion measurements as well as for the hand grip force in this population (**Table 3**).

We showed **Figure 2** for mediation analysis. The effect of gait variability on functional capacity was mediated by the muscle power output of the legs. In the first regression step (equation a), gait variability was negatively related to the power output (p ≤ 0.01). In the second step (equation c), the regression coefficient of gait variability on the dependent variable (gait velocity) showed a negative association ($p < 0.0001$). In the last regression model, the mediator variable (muscle power output) was positively associated with the dependent variable (equation b) ($p < 0.0001$). However, when power output was included in the model (equation c´), the regression coefficient remained significant, but the relationship was slightly attenuated. Using the Sobel test for mediation it was estimated 25% of the total effect of coefficient of variability of step time on gait velocity was mediated by muscle power output (indirect effect = -0.27; 95%CI, -0.59 to -0.05).

Discussion

The main finding of the present study was the role of muscle power output as a potential mediator between gait variability and gait velocity. This result may suggest the importance of reducing gait variability and increasing power output to attenuate its negative association with functional capacity in acutely hospitalized elderly individuals. In addition, significant differences were observed between groups in the functional endpoint (*i.e.*, gait velocity) and gait pattern in different task conditions (GVT and dual-task GVT) based on the functional status presented at admission. The groups also differed significantly from one another in muscle capacity outcomes, including the maximal dynamic and isometric muscle strength of upper/lower limbs and the muscle power output of the legs. To the best of our knowledge, this is the first study to describe gait patterns using a simple automated technological tool in acutely hospitalized older adults and to compare movement-related differences between different groups based on functional status.

In older patients, acute illness requiring hospitalization is usually a sentinel event leading to loss of function in activities of daily living (ADL) and consequently, long-term disability[34;35]. According to the Global Strategy and Action Plan on Healthy Aging currently being undertaken by WHO member states, the goal of health care systems should be to maintain a level of functional ability in older people who have, or are at high risk of, substantial losses of capacity and to ensure that this care and support is consistent[10]. In line with the WHO framework, adequate hospital care in older adults with acute medical disorders requires a comprehensive geriatric assessment (CGA) to identify those patients at highest risk of functional decline[36]. The ability to walk underlies many basic and instrumental ADL necessary for independence[14] and the appearance of difficulties in walking as a consequence of hospitalization or as a result of frailty associated progressive functional deterioration establishes a crucial point in the patient´s life / functional trajectory. In our study, gait velocity was demonstrated to be a discriminating factor among acutely hospitalized older adults, based on the functional status assessed at admission. Typically, several screening tools have been used to identify elderly patients at risk of functional decline during and after hospital admission[11;12]. However, screening instruments widely applied in clinical practice have limited predictive value[13]. The results of this study extend previous studies demonstrating that gait velocity is a quick, inexpensive, highly reproducible measure and may have particular value in identifying older patients at risk of poor health outcomes in an ACU[37;38].

Adding an innovative tool such as an inertial sensor unit to the standard gait speed assessment is useful to understand the mechanisms underlying gait impairment in acutely hospitalized older patients. In the present study differences in step time variability were found between the prefrail and disabled groups in the habitual GVT. Our results are in agreement with previous studies, which provided empirical support that high gait variability is associated with frailty status in older adults[15;32]. A greater step time variability may represent impairment in the automatic stepping mechanism or worsening central motor control[19;39] and may lead to an increased risk of falls as a result of poor foot placement or insufficient postural stability[40]. Furthermore, gait alterations were also found in other parameters, such as stride length and stride regularity, in the habitual GVT and both dual-task conditions in those patients with less functional reserve compared with participants with better functional capacity. Stride length and cadence are the key determinants of gait velocity. The current study findings are consistent with previous research in older adults[41-43] and indicate that reduced gait velocity seems to result from a deficit in producing an appropriate stride length rather than stride frequency. A likely explanation for this fact is the differences observed between groups in terms of their lower limb maximal muscle strength and muscle power output at admission.

The quadriceps muscle is known to play a key role in the gait cycle. This muscle is mainly activated during the terminal swing phase and before the initial contact to stabilize the knee under loading and to prepare it for the weight[44]. Our results showed meaningful differences between groups in terms of leg extensor maximal dynamic and isometric muscle strength and power output values. Recently, Fragala et al.[45] observed that the muscle weakness of leg extensors was related to slow gait velocity in older adults, as well as handgrip force. In addition, differences in hip flexion maximal strength were also found at admission. Previous studies[41;46] have supported the notion that the reduction in step length, and hence gait velocity, is principally due to the limited hip extension caused by hip flexor contracture in the elderly individuals.

Several studies have suggested that muscle power output preservation is a crucial determinant for counteracting the age-related decline in functional capacity[47-50]. Our mediation analysis reveals that muscle power output mediates the relationship between gait variability and gait velocity in the verbal GVT, slightly weakening this relationship. The mechanisms whereby gait variability may negatively influence gait velocity in acutely hospitalized older adults are not clear. First, gait variability has been widely related to muscle system impairments[18] and has been considered a good marker of frailty[32] that may contribute to functional impairment in older adults. Second, the association between step time variability and muscle power has been previously described in the oldest old[21] and leg extensor peak power has been recognized as a predictor of gait velocity in frail elderly individuals[51]. From a practical standpoint, it may be suggested that exercise interventions aimed at improving muscle power (*i.e.*, muscle power training)[48] could reduce gait variability and ultimately improve gait velocity in acutely hospitalized older adults.

Our study has some limitations. First, only older adults with relatively good functional capacity at preadmission (Barthel Index score ≥ 60 points) were included in the study. Thus, these features make it difficult to generalize the results obtained to the entire hospitalized elderly population. Second, the cross-sectional nature of the study limits our ability to explore the role of muscle power in gait performance. Third, the assessment was not sensitive enough to detect differences in gait parameters and other outcomes between the not frail and prefrail groups. We did not collect functional data prior to admission. However, the functional status two weeks prior to admission was indirectly measured with the Barthel Index score at admission, but the risk of bias is likely to increase when retrospective information is recruited with this subjective self-report scale. Finally, only patients with gait pattern assessment at admission using the inertial sensor unit of the larger RCT (NCT02300896)[27] were included in the study. In turn, our study has several strengths, including the use of an inertial sensor unit for measuring functional capacity and the mediation analysis performed for understanding the role of muscle power as a potential mediator in the gait in older patients admitted to an ACU. Studies examining the dose-response relationship often incorporate multiple linear / logistic regression or covariance analysis to adjust for confounding / mediator variables; however, these statistical methods do not account for the percentage of the total explained by the potential mediators.

Conclusions/Relevance:

Muscle power output mediates the relationship between gait variability and gait velocity, slightly weakening this relationship. Thus, muscle power plays a key role in functional performance in acutely hospitalized older adults and its preservation is crucial for counteracting the age-related decline in functional capacity. Additionally, gait velocity and the proposed selection of walking parameters (stride regularity, stride length, CoV step time) can distinguish among acutely hospitalized older adults and can provide useful information for measuring and monitoring functional trajectory during the hospitalization.

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Conflict of interest: All authors have nothing to declare.

Author contributions: I confirm that each of the authors has read and concurs with the content in the final manuscript. The study protocol was developed by MLSA, AC, NMV and MI. Data acquisition and statistical analysis were done by MLSA, FZ, NM and MI. Finally, MLSA, FZ, AC and MI prepared the manuscript and revised it critically for intellectual content.

Sponsor´s role: None.

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Table 1. Baseline characteristics of the subjects

	Hospitalized older adults (n=130)

Age, years	87.56 ± 4.79
Men/women, n	66/64
BMI, kg/m^2	26.79 ± 5.06
Education, n (%)	
< 12 years	21 (16)
≥ 12 years	109 (84)
Barthel Index score, points	85.93 ± 15.08
SPPB, points	4.75 ± 2.66
Falls last year, n (%)	
0	39 (30)
1-2	54 (42)
> 2	29 (22)
No data available	8 (6)
MMSE score, points	22.54 ± 4.49
Shortened GDS, n (%)	
< 7 points	110 (85)
≥ 7 points	20 (15)
CIRS-G	12.83 ± 4.83
Admission reason, n (%)	
Pulmonary	46 (35)
Cardiovascular	24 (19)
Infectious	17 (13)
Gastrointestinal	13 (10)
Neurological	6 (4)
Other	24 (19)

Data are presented as mean ± standard deviation unless otherwise indicated. BMI=Body Mass Index; CIRS-G=Cumulative Illness Rating Scale for Geriatrics; GDS=Geriatric Depression Scale; MMSE=Mini Mental State Examination; SPPB=Short Physical Performance Battery.

Table 2. Gait parameters values, and p-values between groups.

		Not frail	Pre-frail	Frail	Disabled	*Statistical significance*					
		Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	NF-PF	NF-F	NF-D	PF-F	PF-D	F-D
				Gait Velocity Test (GVT)							
Stride regularity	AP	0.32 ± 0.11	0.41 ± 0.10	0.35 ± 0.13	0.30 ± 0.14						
	ML	0.24 ± 0.10	0.30 ± 0.14	0.33 ± 0.17	0.25 ± 0.14						
	V	0.35 ± 0.18	0.40 ± 0.14	0.26 ± 0.14	0.20 ± 0.12			*	*	*	
Stride time (s)		1.15 ± 0.19	1.35 ± 0.23	1.31 ± 0.34	1.37 ± 0.43						
Stride length (cm)		88.25 ± 17.63	81 ± 18.55	62.23 ± 22.41	42 ± 21.40		*	*	*	*	*
CoV step time		0.16 ± 0.06	0.12 ± 0.05	0.17 ± 0.09	0.20 ± 0.08					*	
				Verbal Gait Velocity Test (vGVT)							
Stride regularity	AP	0.40 ± 0.19	0.34 ± 0.13	0.34 ± 0.14	0.34 ± 0.17						
	ML	0.36 ± 0.21	0.35 ± 0.17	0.34 ± 0.13	0.34 ± 0.17						
	V	0.39 ± 0.16	0.33 ± 0.16	0.23 ± 0.11	0.19 ± 0.12		*	*		*	
Stride time (s)		1.26 ± 0.34	1.43 ± 0.33	1.46 ± 0.47	1.45 ± 0.61						
Stride length (cm)		81.36 ± 25.5	76.57 ± 27.44	52.19 ± 23.40	35.69 ± 21.60		*	*	*	*	*
CoV step time		0.14 ± 0.10	0.14 ± 0.06	0.17 ± 0.08	0.19 ± 0.08						
				Arithmetic Gait Velocity Test (aGVT)							
Stride regularity	AP	0.31 ± 0.14	0.32 ± 0.15	0.32 ± 0.16	0.29 ± 0.14						
	ML	0.32 ± 0.15	0.30 ± 0.14	0.31 ± 0.13	0.28 ± 0.17						
	V	0.25 ± 0.1	0.23 ± 0.11	0.20 ± 0.1	0.21 ± 0.13						
Stride time (s)		1.20 ± 0.38	1.50 ± 0.31	1.34 ± 0.42	1.43 ± 0.59						
Stride length (cm)		75 ± 25.67	70.6 ± 23.87	47.62 ± 20.42	35.37 ± 21.10		*	*	*	*	
CoV step time		0.19 ± 0.08	0.16 ± 0.06	0.19 ± 0.07	0.23 ± 0.14						

*$p<0.05$. AP=anterior-posterior; CoV=coefficient of variability; D=disabled; F=frail; ML=medio-lateral; NF= Not frail; PF=Pre-frail; SD=standard deviation; V=Vertical.

N = 118 participants completed the GVT, N = 110 for the verbal dual-task, and N = 103 for the arithmetic dual-task.

Table 3. Results of secondary endpoints of the study, and p-values between groups.

	Not frail	Pre-frail	Frail	Disabled	*Statistical significance*					
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	NF-PR	NF-F	NF-D	PF-F	PF-D	F-D
			Maximal dynamic strength and power							
Bilateral leg press 1RM (kg)	95.9 ± 18.1	81.5 ± 30.6	62.4 ± 25.8	40.5 ± 23.4		*	*		*	*
PW50 (w)	239.7 ± 80.9	191.3 ± 79.1	106.7 ± 51.5	76.5 ± 50.6		*	*	*	*	
			Maximal isometric strength							
Hand grip (kg)	23 ± 3.9	22.4 ± 6.3	17.9 ± 6.1	14.2 ± 5.6		*	*		*	*
Knee extension (N)	135.4 ± 34.1	113.6 ± 30	94.8 ± 34.5	94.8 ± 34.5		*	*		*	
Hip flexion (N)	131.7 ± 27.2	122.4 ± 32.8	89.5 ± 29.4	76.4 ± 23.9		*	*	*	*	

*p<0.05. D=disabled; F=frail; N=newton; NF= Not frail; PF=pre-frail; PW50=leg power at an intensity of 50% of 1RM test; RM=repetition maximum, SD=standard deviation.
N = 93 participants completed the bilateral leg press RM test, N = 85 for the power assessment.
Regarding maximal isometric force, analyses are based on N = 125 participants for the hand grip force, N = 87 for the knee extension, N= 119 for the hip flexion.

Legends

Figure 1. Results of gait velocity for the disabled, frail, pre-frail and robust groups during the habitual Gait Velocity Test, verbal Gait Velocity Test, and arithmetic Gait Velocity Tests. Error bars represent standard deviations. † represents statistical significant differences ($p<0.05$) between disabled vs. frail groups. ^ represents statistical significant differences between disabled vs. pre-frail groups. * represents statistical significant differences between disabled vs. not frail groups. $ represents statistical significant differences between frail vs. pre-frail groups. # represents statistical significant differences between frail vs. not frail groups.

Figure 2. Muscle power output mediation models of the relationship between gait variability (coefficient of variability of step time) and gait velocity in the verbal dual-task.

Figure 1
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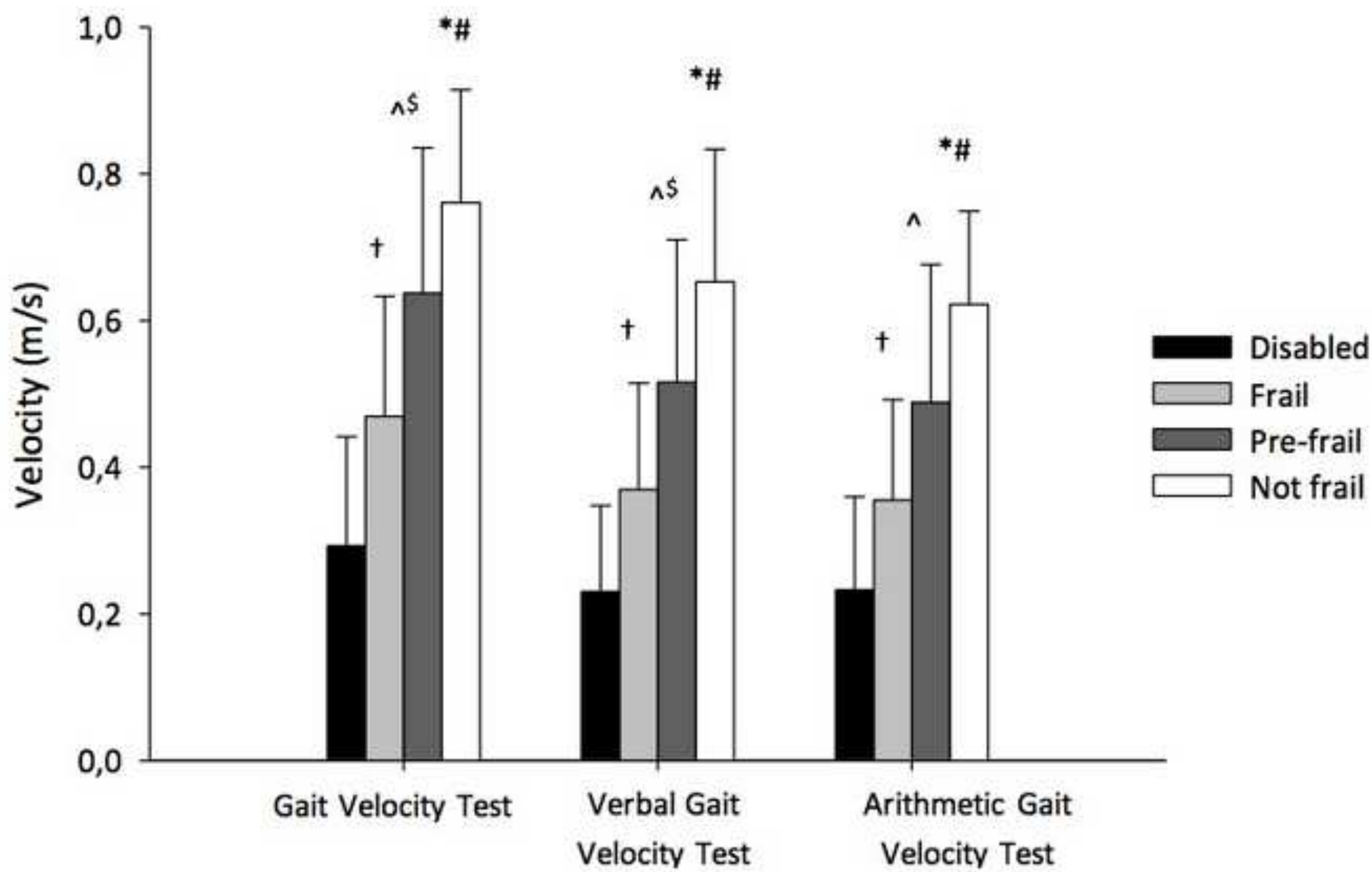

Figure 2
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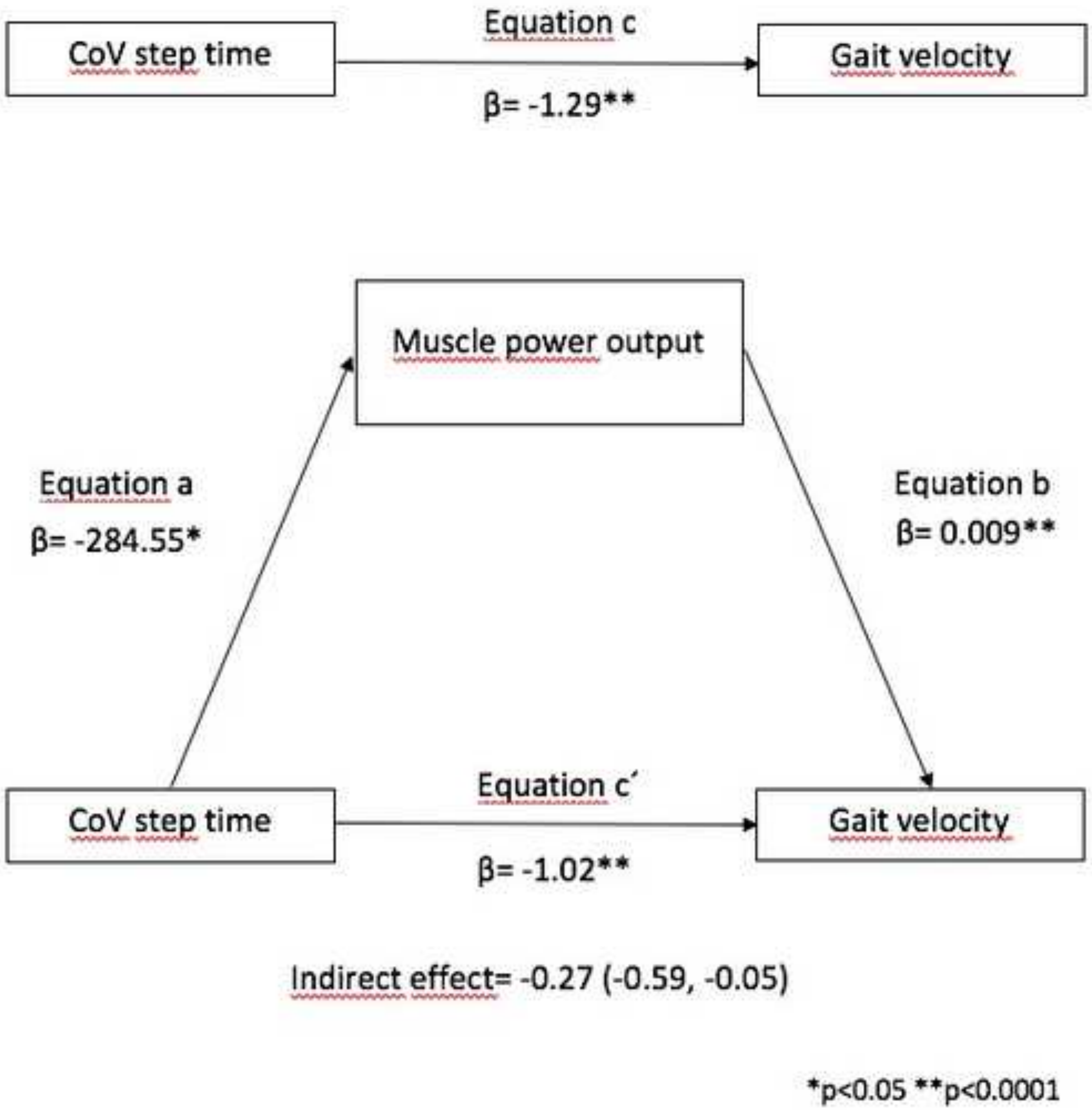

*Title Page (Containing author details)

TITLE PAGE

The title: Role of muscle power output as a mediator between gait variability and gait velocity in hospitalized older adults.

Running title: MP mediator of gait features in hospitalized elderly.

Authors: Mikel López Sáez de Asteasu, *MsC*[1,2,3], Nicolás Martínez-Velilla, *PhD, MD*[2,3,4], Fabricio Zambom-Ferraresi, *PhD*[2,3], Álvaro Casas-Herrero, *PhD, MD*[2,3,4], Robinson Ramirez-Vélez[5], Mikel Izquierdo, *PhD*[1,2,3]*.

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Main text: 2961 words.

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Impact statement: We certify that this work is novel of recent novel clinical research. We perform an innovative statistical method (mediation analysis) for understanding the role of muscle power as a potential mediator between gait variability and gait velocity in hospitalized older adults.

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Adverse Response to Exercise Intervention during Acute Hospitalization

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Abstract:	Background: Exercise protocols applied during hospitalization can prevent functional and cognitive decline in older adults. Objective: To examine the individual response of acutely hospitalized patients to usual care and to physical exercise on functional capacity, muscle strength, and cognitive function and to assess the relationship with mortality at one-year post-discharge. Design: In a single-blind randomized clinical trial, 370 hospitalized patients were allocated to an exercise intervention (n=185) or a control (n=185) group. Setting: Acute care unit in a tertiary public hospital in Navarra, Spain. Participants: Older adults aged 75 years or older. Interventions: The usual care group received habitual hospital care, which included physical rehabilitation when needed. The in-hospital intervention included individualized multicomponent exercise training program performed during 5–7 consecutive days (2 sessions/day). Main outcomes and measures: Functional capacity was assessed with the Short Physical Performance Battery (SPPB) test and the Gait Velocity Test (GVT). Handgrip strength and cognitive function were also measured at admission and discharge. Patients in both groups were categorized as responders (Rs), non-responders (NRs) and adverse responders (ARs) based on the individual response to each treatment during hospitalization. Results: The ARs for the GVT in the control group and the ARs for the SPPB in the intervention group had a significantly higher rate of mortality than the NRs and Rs in the equivalent groups (p=0.01 and p=0.03, respectively) at follow-up.

	Conclusion: An adverse response on functional capacity in older patients to physical exercise or usual care during hospitalization was associated with mortality at one-year post-discharge.

Title page

Title: Adverse response to Exercise Intervention During Acute Hospitalization

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Abstract

Background: Exercise protocols applied during hospitalization can prevent functional and cognitive decline in older adults.

Objective: To examine the individual response of acutely hospitalized patients to usual care and to physical exercise on functional capacity, muscle strength, and cognitive function and to assess the relationship with mortality at one-year post-discharge.

Design: In a single-blind randomized clinical trial, 370 hospitalized patients were allocated to an exercise intervention (n=185) or a control (n=185) group.

Setting: Acute care unit in a tertiary public hospital in Navarra, Spain.

Participants: Older adults aged 75 years or older.

Interventions: The usual care group received habitual hospital care, which included physical rehabilitation when needed. The in-hospital intervention included individualized multicomponent exercise training program performed during 5–7 consecutive days (2 sessions/day).

Main outcomes and measures: Functional capacity was assessed with the Short Physical Performance Battery (SPPB) test and the Gait Velocity Test (GVT). Handgrip strength and cognitive function were also measured at admission and discharge. Patients in both groups were categorized as responders (Rs), non-responders (NRs) and adverse responders (ARs) based on the individual response to each treatment during hospitalization.

Results: The prevalence of Rs was higher and the prevalence of NRs and ARs was lower in the intervention group than in the control group for functional capacity, muscle strength and cognition. The ARs for the GVT in the control group and the ARs for the SPPB in the intervention group had a significantly higher rate of mortality than the NRs and Rs in the equivalent groups ($p=0.01$ and $p=0.03$, respectively) at follow-up.

Conclusion: Oldest old patients performing an individualized exercise intervention presented higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function than those patients who were treated with usual care during acute hospitalization. An adverse response on functional capacity in older patients to physical exercise or usual care during hospitalization was associated with mortality at one-year post-discharge.

Trial Registration: ClinicalTrials.gov Identifier: NCT02300896

Introduction

Adequate hospital care for older adults (≥75 years) with acute medical disorders is an important clinical issue in our ageing societies.[1-4] In this context, acute illness requiring hospitalization is a sentinel event in older adults, which can lead functional decline and frequently, long-term disability[5-7]. Loss of functional capacity is strongly associated with caregiver burden, higher resource use, institutionalization, and death.[8-11] Accordingly, this is a challenge that healthcare professionals and policy makers should prioritize given the expectations of further growth of the elderly population.[12]

Health care systems remain poorly adapted to meet the needs of old patients with frailty, disability, multimorbidity and polypharmacy,[13] and low in-hospital mobility is directly related to functional impairment at discharge and even more so at follow-up.[14,15] However, a recent randomized clinical trial (RCT) showed no significant benefit of an in-hospital mobility program and a behavioral strategy to encourage mobility in older patients´ ability to perform activities of daily living (ADL) after acute hospitalization.[16] In this context, tailored exercise interventions can play a key role in preventing functional decline and cognitive impairment in acutely hospitalized patients of advanced age (including octogenarians and nonagenarians).[12,17]

Despite the frequent reports of "average" exercise related-benefits there is, nevertheless, a wide inter-individual variability in the response to exercise training.[18] Under the same exercise conditions, some subjects, termed responders (Rs), achieve benefits after intervention, whereas others, termed non-responders (NRs; unchanged response) and adverse-responders (ARs; worsened response) do not.[19,20] To the best of our knowledge, the inter-individual analysis of exercise training effects has not been previously investigated in acutely hospitalized older adults. In addition, it remains unclear if the response influences in mortality following discharge.

The main aim of the present study was to assess the prevalence of these categories (as indicated by functional, strength and cognitive variables) under usual care or an individualized multicomponent exercise intervention applied in an Acute Care of the Elderly (ACE) unit. We also sought to examine the relationship between the aforementioned categories of each group with mortality at one-year post-discharge, and a possible influence of the clinical differences at admission on the assessed endpoints.

Methods

Design

The study is a secondary analysis of a RCT (NCT02300896)[12;17] conducted in the ACE unit of the Department of Geriatrics in a tertiary public hospital (*Complejo Hospitalario de Navarra*, Spain). This Department has 35 allocated beds and its staff is composed of 8 geriatricians (distributed in the ACE unit, orthogeriatrics and outpatient consultations). Admissions in the ACE unit derive mainly from the Accident and Emergency Department, with heart failure, pulmonary and infectious diseases being the main causes of admissions.

Acutely hospitalized patients who met inclusion criteria were randomly assigned to the intervention or control (usual care) group within the first 48 hours of admission. Usual care was offered to patient by the geriatricians and consists of standard physiotherapy focused on walking exercises for restoring the functionality conditioned by potentially reversible pathologies. A formal exercise prescription was not provided at study entry and patients were instructed to continue with the current activity practices through the duration of the study. The study followed the principles of the Declaration of Helsinki and was approved by the institutional Clinical Research Ethics Committee. All patients or their legal representatives provided written consent.

Participants and randomization

A trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥75 years, Barthel Index score ≥60 points, able to ambulate (with/without assistance), and to communicate and collaborate with the research team. Exclusion criteria included expected length of stay <6 days, very severe cognitive decline (i.e., Global Deterioration Scale score =7), terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, or extremity bone fracture in the past 3 months.

After the baseline assessment was performed, participants were randomly assigned following a 1:1 ratio, without restrictions (www.randomizer.org). Assessment staff were blinded to the main study design and group allocation. Participants were explicitly informed and reminded not to discuss their randomization assignment with the assessment staff.

Intervention

The usual care group received habitual hospital care, which included physical rehabilitation when needed. For the intervention group, exercise training was programmed in two daily sessions (morning and evening) of 20-minutes duration over 5–7 consecutive days (including weekends) supervised by a qualified fitness specialist. Adherence to the exercise intervention program was documented in a daily register. A session was considered completed when ≥90% of the programmed exercises were successfully performed.

Each session was performed in a room equipped ad hoc in the ACE unit. Exercises were adapted from the "Vivifrail" multicomponent physical exercise program to prevent weakness and falls.[21]. Morning sessions included individualized supervised progressive resistance, balance, and walking-training exercises. The resistance exercises were tailored to the individual's functional capacity using variable resistance training machines (Matrix, Johnson Health Tech, Ibérica, S.L.; Torrejón de Ardoz, Spain and Exercycle S.L., BHGroup; Vitoria, Spain) aiming at 2–3 sets of 8–10 repetitions with a load equivalent to 30–60% of the estimated one-repetition maximum (1RM). Participants performed three exercises involving mainly lower-limb muscles (squats rising from a chair, leg press and bilateral knee extension) and one involving the upper-body musculature (seated bench 'chest' press). They were instructed to perform the exercises at a high speed to optimize muscle power output, and care was taken to ensure proper exercise execution. Balance and gait retraining exercises gradually progressed in difficulty and included the following: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), altering the base of support, and weight transfer from one leg to the other. The evening session consisted of functional unsupervised exercises using light-loads (0·5–1 kg anklets and hand-grip ball), such as knee extension/flexion, hip abduction and daily walking in the corridor of the ACE unit with a duration based on the clinical physical exercise guide "Vivifrail".[21]

When the clinician in charge of the patient considered that the hemodynamic situation was acceptable, and the patient could collaborate, the following endpoints were assessed and the intervention was started. Endpoints were also assessed on the day of discharge.

Measures and endpoints

Measures of functional performance

The Short Physical Performance Battery (SPPB) and 6-meter Gait Velocity Test (GVT) were used to assess functional capacity. The SPPB includes usual walking speed over 4 meters, a balance test, and the Five Times Sit to Stand Test, with the sum of the three individual categorical scores yielding the final SPPB score (range points: 0 (worst) to 12 (best)).[22] For the GVT, the participants were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway.

Handgrip strength

Isometric handgrip strength was measured in the dominant hand with a handheld dynamometer (T.K.K. 5401 Grip-D, Japan). Patients were placed in a sitting position in a chair, with an elbow complete extension, and were asked to squeeze the handle as forcefully as possible for 3 seconds. After this, two valid trials followed, and the highest value was used as the data point.

Cognitive function

Changes in cognitive function were assessed using the Mini-Mental State Examination (MMSE)[23] (30-point questionnaire; scale of 0 (worst) to 30 (best)).

Classification of responders, non-responders and adverse responders

The inter-individual variability of the patients in the response to usual care in the control group and exercise training in the intervention group was used to categorize them as Rs, NRs or ARs using the clinical meaningful change of each variable: 1 point for the SPPB test[24], 1 kg for the handgrip test[25], 0·1 m/s for the GVT[26], and 3 points for the MMSE test[27].

Statistical analysis

Standard statistical methods were used to calculate the mean and standard deviation (SD). Statistical normality was tested using both statistical (Kolmogorov-Smirnov test) and graphical (normal probability plots) procedures. We used Student´s t test or the Mann-Whitney U and χ^2 or Fisher test to analyze significant differences between the intervention and control groups for continuous and categorical variables at baseline, respectively. Differences in mortality at one-year post-discharge between categories in each group were assessed using the χ^2 test. One-way analysis of variance was used to test differences in functional end points (SPPB and GVT) at baseline between categories in the control and intervention group. The Bonferroni post-hoc test was applied to establish differences between categories in each group. Data were analyzed using SPSS-IBM (Software, v.21.0 SPSS Inc., Chicago, IL, USA) and a p-value < 0·05 was considered statistically significant.

Results

The study flow diagram is shown in **Figure 1**. No significant differences were found between groups at baseline for demographic and clinical characteristics for study end points (**Table 1**). A total of 370 patients were included in the analysis (209 women, 56·5%) with a mean age 87·3 (4·9) years (range 75-101 years), and 130 patients (35·1%) were nonagenarians. The median length of hospital stay was 8 days in both groups (interquartile range, 4). The mean number of intervention days for each patient was 5·3 ± 0·5 days, and most training days were consecutive (97%). The number of completed morning and evening sessions per patient averaged 5 ± 1 and 4 ± 1, respectively. Mean adherence to the intervention was 97 ± 8% for the morning sessions (i.e., 806 successfully completed sessions of 841 total possible sessions) and 85 ± 30% in the evening sessions (574 of 688). No adverse effects or falls associated with the prescribed exercises were recorded and no patient had to interrupt the intervention or had their hospital stay modified because of it.

The results of the prevalence of Rs, NRs, and ARs to usual care and individualized exercise training program are shown in **Figure 2**. Considering the functional end points, 33·3% of acutely hospitalized older adults in the control group were ARs, 28·8% were NRs, and 37·9% were Rs for the SPPB in the control group, and 6·0% were ARs, 8·7% NRs, and 85·3% Rs in the intervention group. For the GVT, 14·3% were ARs, 67·7% NRs, and 18·0% Rs in the control group and 1·6% were ARs, 47·3% NRs and 51·2% Rs in the intervention group. Regarding the handgrip strength, 42·0% were ARs, 38·0% NRs, and 20·0% Rs in the control group and 11·3% were ARs, 26·5% NRs, and 62·3% Rs in the intervention group. For the cognitive function test, 9·7% of the patients in the control group were ARs, 76·6% NRs, and 13·8% Rs whereas 1·4% were ARs, 57·1% NRs, and 41·5% Rs in the exercise training group.

Functional, maximal strength and cognitive changes of all the patients of both groups are shown in **Figure 3** based on the response obtained for the functional endpoints (SPPB and GVT, see above **Figure 2**).

The secondary analysis showed that patients with an adverse response on the functional endpoints was associated with mortality at one-year post-discharge in both control and intervention groups (**Table 2**). Significant differences were found between categories for the SPPB in the intervention group ($p = 0·01$) and for the GVT in the control group ($p = 0·03$).

We also observed significant differences between categories for the SPPB score at admission in the intervention group (ARs = 3·6 ± 1·2 points, NRs = 4·4 ± 3·4 points, Rs = 4·5 ± 2·5 points; $p = 0·01$) and for the GVT in the control group (ARs = 0·59 ± 0·2 m/s, NRs = 0·46 ± 0·2 m/s, Rs = 0·38 ± 0·2 m/s; $p < 0·01$).

Discussion

Our study shows that acutely hospitalized older adults performing an individualized exercise intervention presented a higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function compared with patients receiving usual care. An adverse response on functional capacity in older patients treated with physical exercise or usual care during hospitalization was associated with mortality at one-year post-discharge. Moreover, the functional status presented at admission seems to play a key role in the trajectory of patients during hospital stay and even more so at follow up. To the best of our knowledge, this is the first study to analyze the inter-individual variability in the response to physical exercise and usual care in this population.

Acute illness requiring hospitalization is often a crucial event for many older adults[7] and functional decline is one of the negative short-term consequences of bed rest during hospitalization.[28] However, recent evidence has demonstrated that specific in-hospital exercises could provide significant benefits over usual care and could help to reverse the functional decline associated with acute hospitalization in older adults.[12] Although beneficial effects of exercise intervention on functional capacity are well established, frequent reports based of "average" exercise-related changes do not represent the wide individual variability in response to exercise.[18] The present inter-individual analysis study may be a first step towards to a greater precision in each individual, in-hospital treatments. We found a higher prevalence of Rs in the exercise training group compared with usual care group for both functional end points. Thus, tailored multicomponent exercise training appears to be an effective therapy for improving functional capacity in acutely hospitalized older adults. In addition, we observed a higher prevalence of Rs and a lower prevalence of NRs and ARs for handgrip strength and cognitive function in the intervention group than in the control group. We believe that these findings are important because muscle mass and neuromuscular function tend to decrease during hospital stay in older adults, with muscle strength and mass strongly associated with disability, morbidity, and cardiometabolic disease-related mortality.[29] Moreover, prolonged bed rest increases the risk of developing cognitive impairment and dementia in older adults.[30]

We also explored whether the response rate for functional capacity was accompanied by similar changes for muscle strength and cognition. Our findings indicate a considerable heterogeneity of response for handgrip strength and cognitive function after usual care or physical exercise. Therefore, response rate for functional capacity could not predict similar changes in other clinical characteristics, such as muscle strength and cognition.

Changes in functional status during hospitalization play an important role in the life trajectory of older adults after discharge. In agreement with previous studies.[8,11] our findings show that functional decline (*i.e.*, ARs for the GVT) during hospitalization is associated with a higher rate of mortality at one-year post-discharge compared with NRs and Rs. In the intervention group, those patients who experienced loss of functional capacity after the exercise training program (*i.e.*, ARs for the SPPB) also showed a higher rate of mortality at follow up in comparison with other categories. Our results support the importance of measuring functional status in hospitalized older patients[11], a useful vital sign that should be assessed by hospital clinicians.[28]

Finally, functional status at admission contains crucial information about prognosis of different interventions in acutely hospitalized older people. Our data suggest that those older adults with higher gait velocity at admission had worse response to usual care and, consequently, major vulnerability to iatrogenic nosocomial disability, than those patients with less functional reserve at baseline. A greater window of worsening during hospitalization could be a possible explanation for the major functional decline. Our findings also showed differences in responses to exercise training based on the functional capacity presented at baseline. Older adults who experienced a worsened response in the intervention group had less functional reserve at admission (SPPB score <4 points) compared with NRs and Rs. It means that patients at worst functional status at admission have greater possibility to be an adverse-responder to the exercise intervention. Taken together with the above-mentioned association between adverse-responsiveness to exercise and mortality, older adults with poor scores in the SPPB at admission are also at major risk of mortality after discharge.

Overall, our study is in line with the long trajectory of research supporting the relevance of patients´ baseline function as a useful benchmark and goal for discharge and follow-up outcomes.[28]

Our study has some limitations, including patients´ difficulty in completing all the measurements at both hospital admission and discharge. Another possible limitation was that only old patients with relatively good functional capacity at preadmission (i.e., Barthel Index score ≥60 points) were included in the study; thus, the results may not be generalizable to the entire hospitalized elderly population. Also, we did not collect functional data prior to the acute illness and functional decline in acutely hospitalized older people frequently occurs before admission.[28]

Our study, nevertheless, has several strengths. An innovative exercise intervention of few days (i.e., 5±1 and 4±1 morning and evening sessions, respectively) was performed with older adults in acute settings. Also, patients with multiple comorbidities and mild dementia/cognitive impairment were included in the study (routinely excluded from exercise studies). The prevalence of Rs was higher for functional capacity, muscle strength and cognitive function in the exercise training group compared with the usual care group, indicating that the physical exercise program was effective to reverse functional decline and cognitive impairment associated with hospitalization in older adults. Both functional capacity endpoints (SPPB and GVT) measured in the study for monitoring functional trajectory of patients were associated with mortality at one-year post-discharge. Finally, we identified clinical differences between categories at admission in both exercise and usual care groups.

Conclusions

Oldest old patients performing an individualized exercise intervention showed a higher prevalence of Rs and a lower prevalence of NRs and ARs for functional capacity, muscle strength and cognitive function than those patients who were treated with usual care during acute hospitalization. An adverse response on functional capacity in older medical patients to physical exercise or usual care during hospitalization was associated with mortality at one-year post-discharge. Moreover, the functional status presented at admission seems to be a cornerstone in the trajectory of patients during hospital stay and even more so at follow up. These findings support the need for a shift from the traditional disease-focused approach in hospital ACE to one that recognizes functional status as a clinical vital sign.

Declaration of interests

All authors have nothing to declare.

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Authors statement form

The study protocol was developed by MLSA, ACH, NMV and MI. Data acquisition and statistical analysis were done by MLSA, FZF, NMV and MI. Finally, MLSA, FZF, NMV, ELD, RRR and MI prepared the manuscript and revised it critically for intellectual content.

Figure legends

Figure 1. Study flow diagram.

Figure 2. Responders (green line), non-responders (yellow line), and adverse responders (red line) on functional (a and b), muscle strength (c), and cognitive (d) endpoints. Abbreviations; GVT, Gait Velocity Test; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

Figure 3. Changes in functional, muscle strength, and cognitive endpoints based on the SPPB response (a and b) and GVT response (c and d). Abbreviations: GVT, Gait Velocity Test; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

Table 1. Baseline characteristics of the participants

Variable	Control group (n=185)	Intervention group (n=185)
Demographic data		
Age, years	87·1 (5·2)	87·6 (4·6)
Women (N (%))	109 (59%)	100 (54%)
Body mass index, kg/m²	26·9 (4·9)	27·1 (4·4)
Clinical data		
Barthel Index, score	83 (17)	84 (17)
CIRS (median, IQR), score	12 (5)	13 (5)
MNA (median, IQR), score	24 (4)	24 (4)
1RM leg press, kg	62 (31)	57 (25)
1RM chest press, kg	25 (12)	24 (11)
1RM knee extension, kg	41 (14)	39 (13)
GDS, score	3·6 (2·9)	4·0 (2·4)
QoL (EQ-VAS), score	60 (21)	58 (22)
Delirium (CAM, %)	12%	17%
Endpoint measures		
SPPB scale, score	4·7 (2·7)	4·4 (2·5)
6-meter GVT, seconds	16·1 (8·8)	16·2 (13·1)
Handgrip, kg	17 (8)	17 (6)
MMSE, score	23 (4)	22 (5)
Admission reason, (N (%))		
Cardiovascular	67 (36)	65 (35)
Infectious	33 (18)	33 (18)
Pulmonary	20 (11)	28 (15)
Gastrointestinal	17 (9)	20 (11)
Neurological	9 (5)	9 (5)
Other	39 (21)	30 (16)

Data are mean (SD) unless otherwise stated. No statistically significant differences were found between groups (all P>0·05).
Abbreviations: 1RM, one-repetition maximum; CAM, Confussion Assessment Method; CIRS, Cumulative Illness Rating Scale; GDS, Yesavage Geriatric Depression Scale; GVT, Gait Velocity Test; IQR, interquartile range; MNA: Mini-nutritional Assessment; MMSE: Mini-Mental State Evaluation; QoL, quality of life; EQ-VAS, visual analogue scale of the EuroQol questionnaire (EQ-5D); SPPB: Short Physical Performance Battery.

Table 2. Mortality rate at one-year post-discharge

End points	Control group	Intervention group
SPPB		
Adverse-responders	13 (25·5)	5 (62·5) *
Non-responders	12 (27·3)	3 (23·1)
Responders	14 (24·1)	23 (18)
GVT		
Adverse-responders	7 (36·8) *	0 (0)
Non-responders	20 (22·2)	17 (27·9)
Responders	1 (4·2)	9 (13·6)
Handgrip strength		
Adverse-responders	21 (33·3)	3 (17·6)
Non-responders	11 (19·3)	7 (17·5)
Responders	8 (26·7)	21 (22·3)
MMSE		
Adverse-responders	5 (35·7)	0 (0)
Non-responders	30 (27)	17 (20·2)
Responders	4 (20)	12 (20)

Data are presented as n (%). * $p<0·05$
Abbreviations: GVT, Gait Velocity Test; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery.

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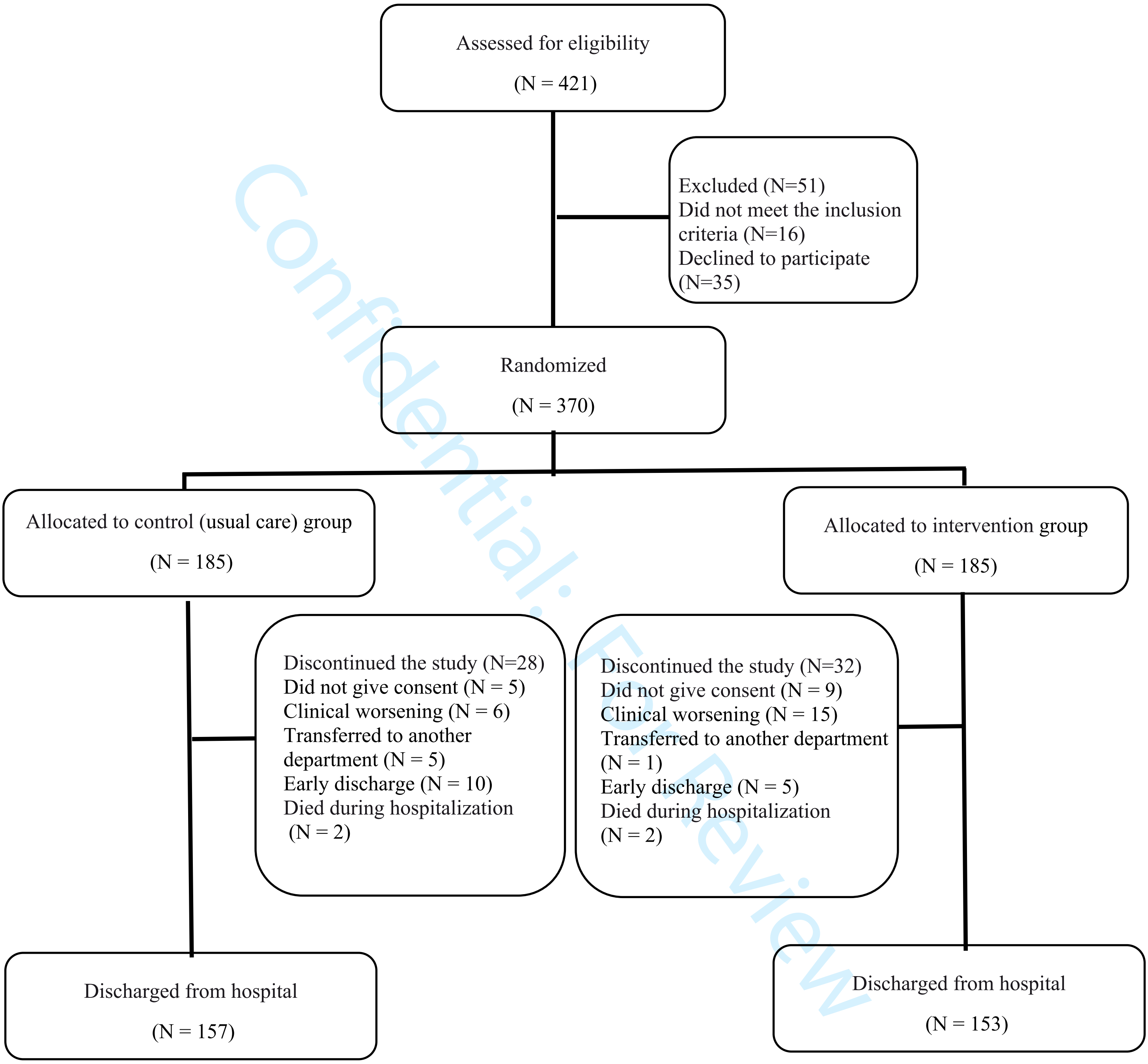
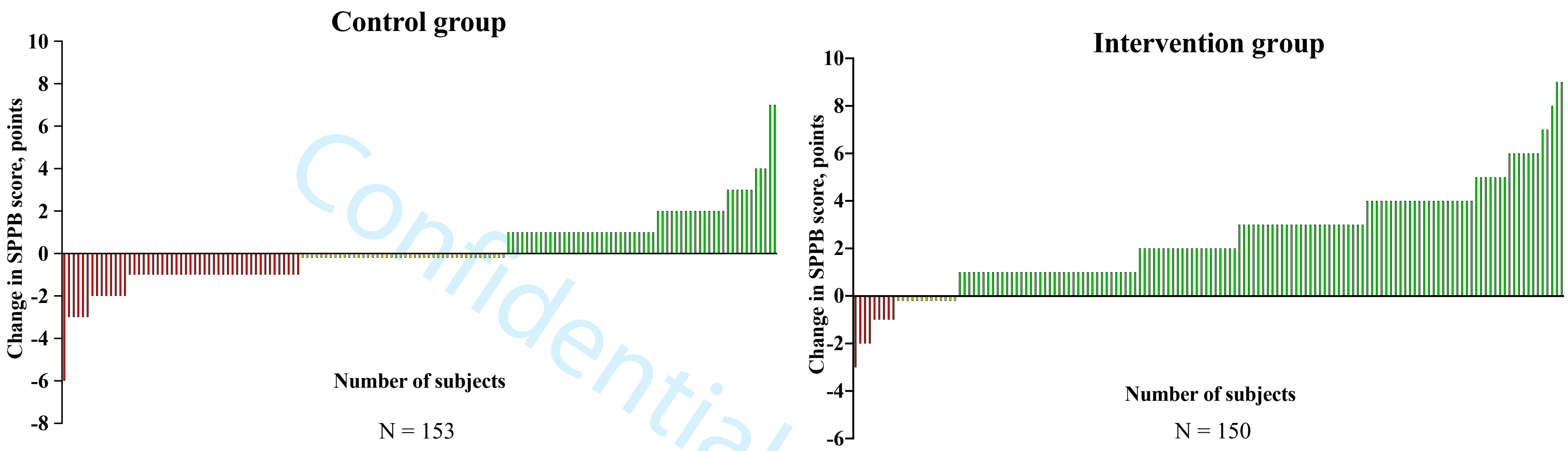
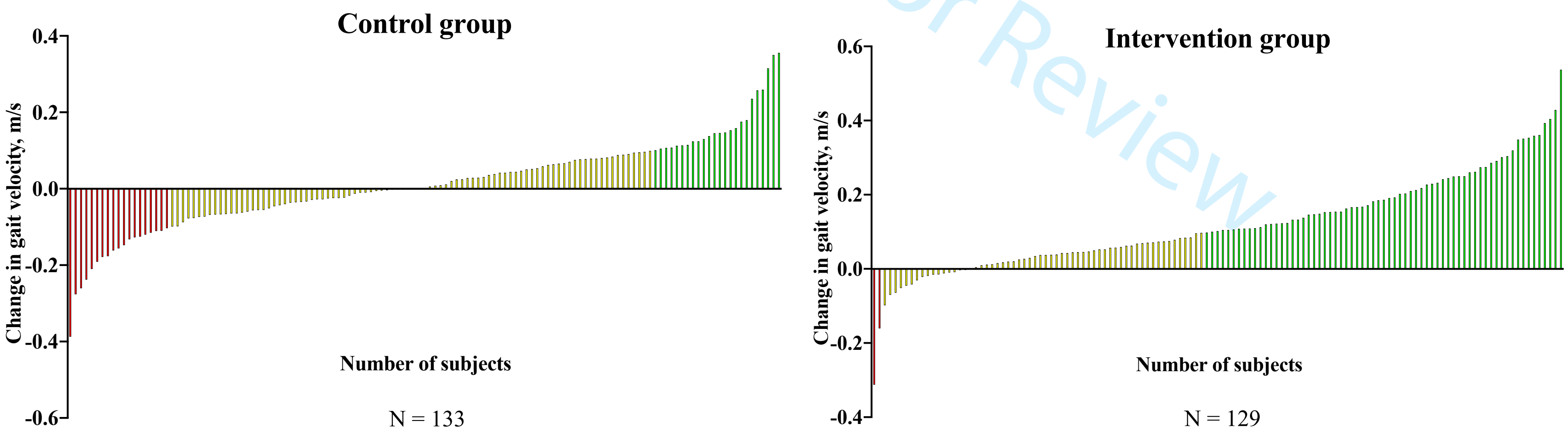

Assessed for eligibility
(N = 421)
Excluded (N=51)
Did not meet the inclusion criteria (N=16)
Declined to participate (N=35)
Randomized
(N = 370)
Allocated to control (usual care) group
(N = 185)
Allocated to intervention group
(N = 185)
Discontinued the study (N=28)
Did not give consent (N = 5)
Clinical worsening (N = 6)
Transferred to another department (N = 5)
Early discharge (N = 10)
Died during hospitalization (N = 2)
Discontinued the study (N=32)
Did not give consent (N = 9)
Clinical worsening (N = 15)
Transferred to another department (N = 1)
Early discharge (N = 5)
Died during hospitalization (N = 2)
Discharged from hospital
(N = 157)
Discharged from hospital
(N = 153)

Figure 1.

a. SPPB

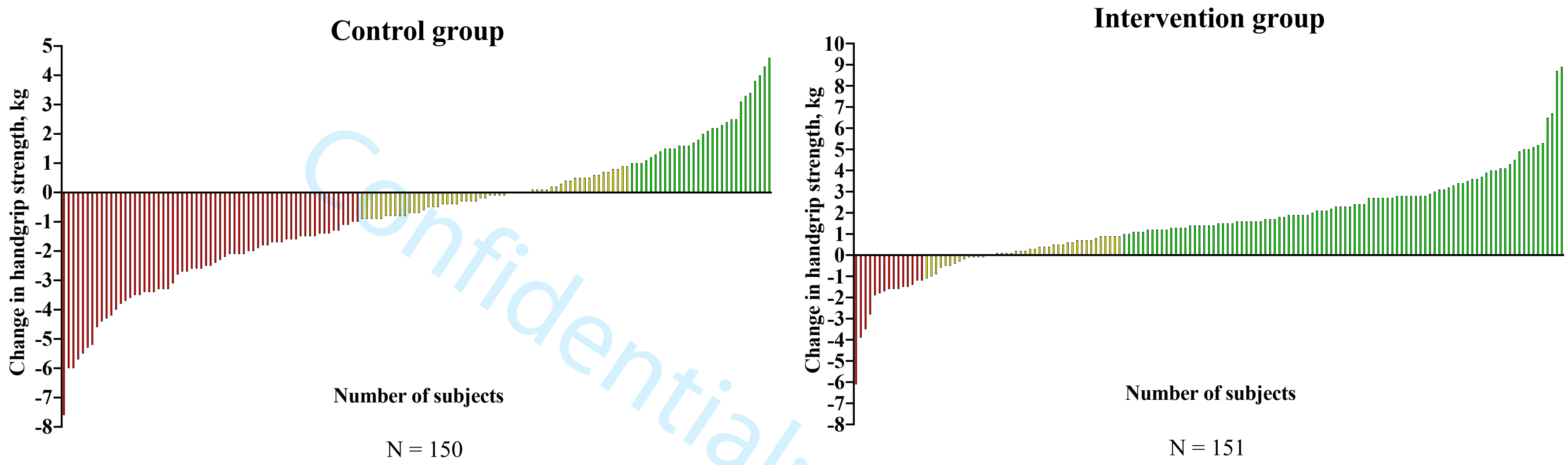

Control group
Change in SPPB score, points
10
8
6
4
2
0
-2
-4
-6
-8
Number of subjects
N = 153
Intervention group
Change in SPPB score, points
10
8
6
4
2
0
-2
-4
-6
Number of subjects
N = 150

b. GVT


Control group
Change in gait velocity, m/s
0.4
0.2
0.0
-0.2
-0.4
-0.6
Number of subjects
N = 133
Intervention group
Change in gait velocity, m/s
0.6
0.4
0.2
0.0
-0.2
-0.4
Number of subjects
N = 129

Submitted to the New England Journal of Medicine

c. Handgrip strength



d. MMSE

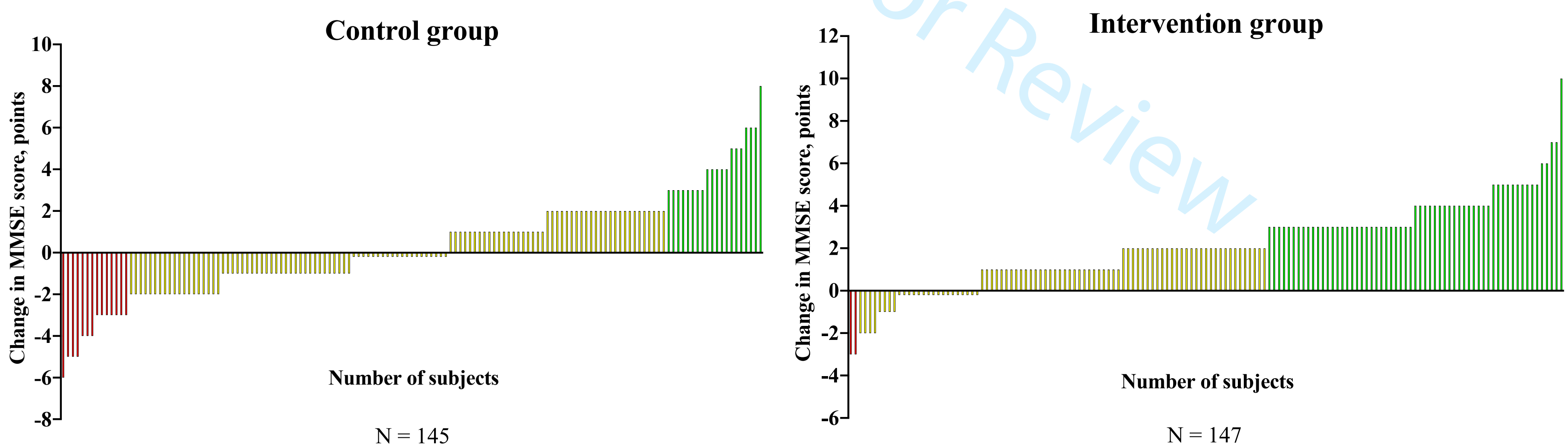
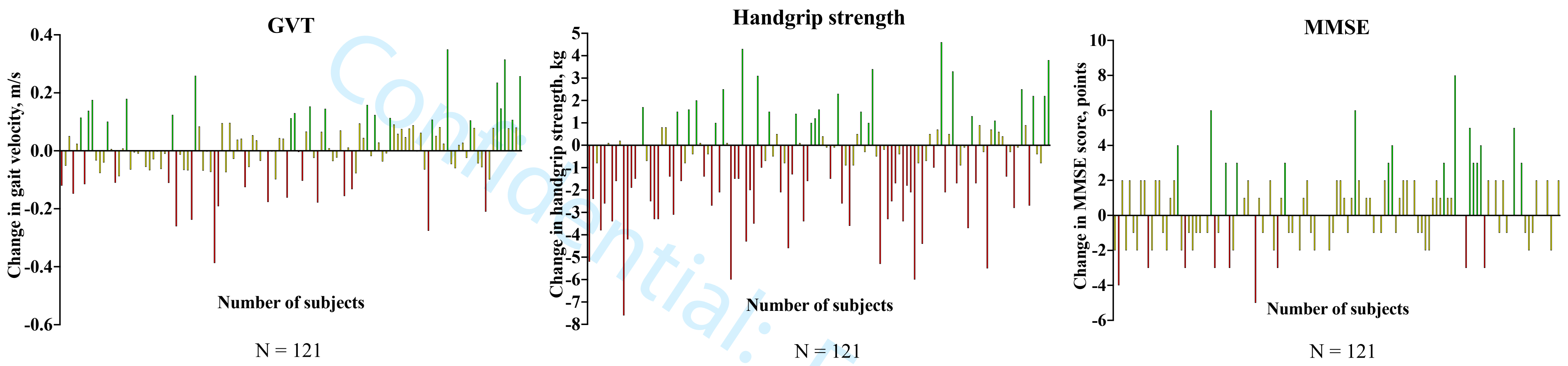
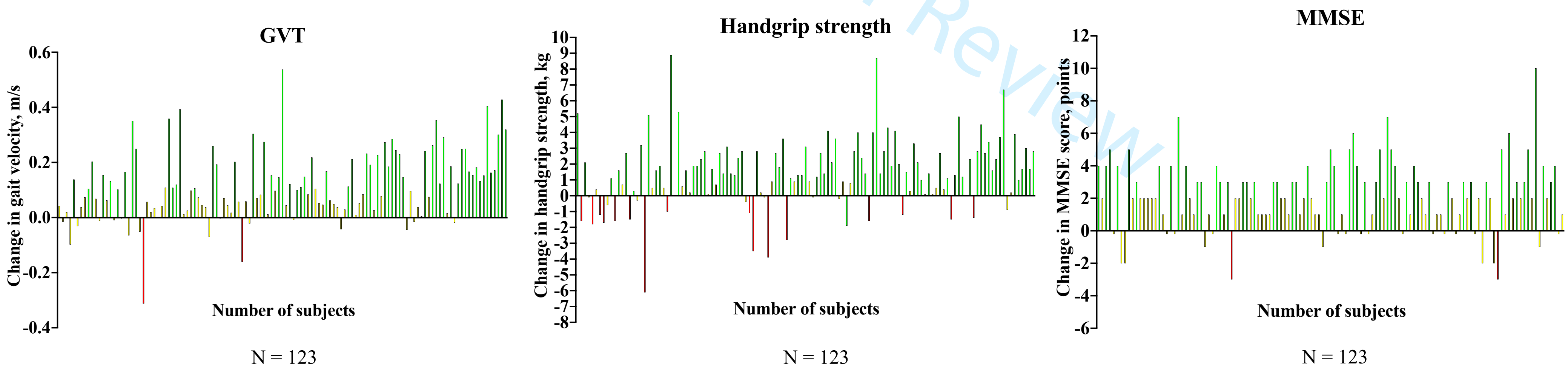


Figure 2.

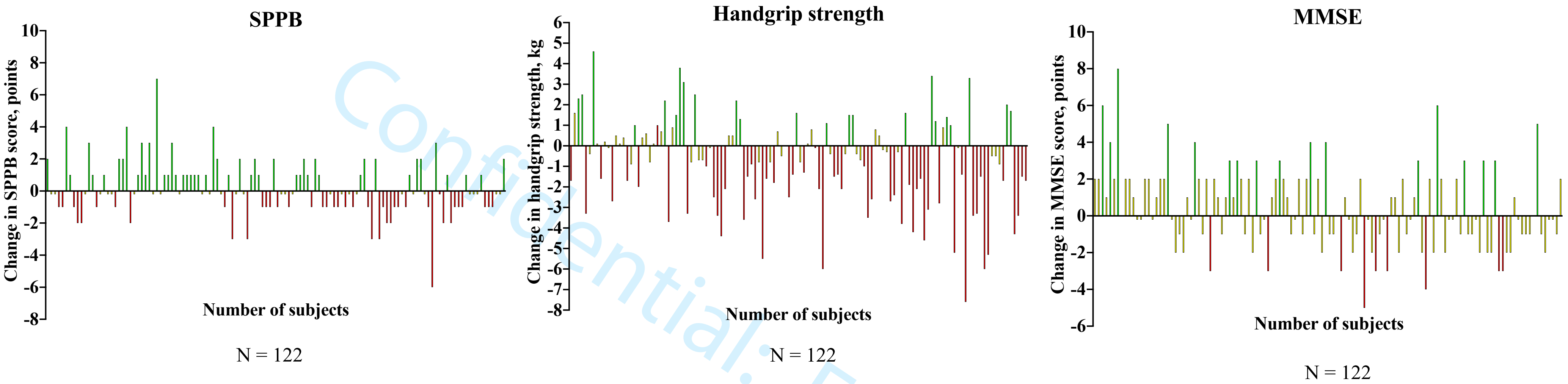
a. Control group



b. Intervention group



c. Control group



d. Intervention group

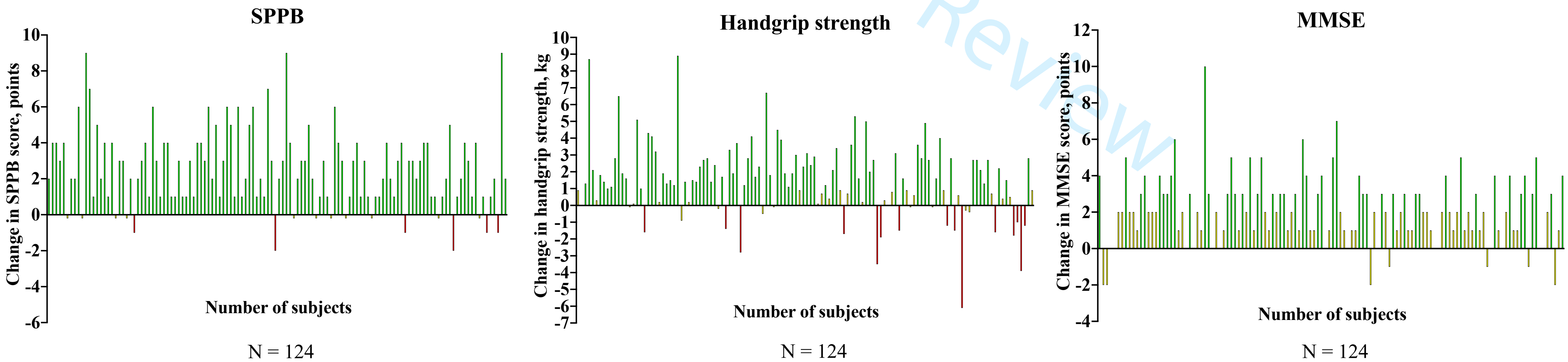


Figure 3.

PLOS Medicine

A randomized clinical trial evaluating the effects of a physical exercise intervention on cognitive function in very elderly patients during acute hospitalization

--Manuscript Draft--

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Article Type:	Research Article
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Abstract:	Background Prolonged bed rest increases the risk of developing cognitive impairment and dementia in acutely hospitalized older adults. Exercise protocols applied during acute hospitalization can prevent functional decline in older patients, but exercise benefits on specific cognitive domains have not been previously investigated. Objective We aimed to assess the effects of a multicomponent exercise intervention for cognitive function in older adults during acute hospitalization. Design In a single-blind randomized clinical trial, 370 hospitalized patients (aged ≥75 years) were allocated to an exercise intervention (n=185) or a control (n=185) group (usual care). Setting Acute Care for Elderly (ACE) unit.

Participants

Older adults aged>75 years.

Interventions

The intervention consisted of a multicomponent exercise training program performed during 5–7 consecutive days (2 sessions/day). The usual care group received habitual hospital care, which included physical rehabilitation when needed.

Main outcomes

Executive function was measured with the dual-task (i.e., verbal and arithmetic) Gait Velocity Test (GVT) and the Trail Making Test Part A (TMT-A). The Mini Mental State Examination (MMSE) test and verbal fluency ability were also assessed at admission and discharge.

Results

The intervention program provided significant benefits over usual care. At discharge, the exercise group showed a mean increase of 0.1 m/s (95% confidence interval [CI], 0.07, 0.13) in the verbal GVT and 0.1 m/s (95%CI, 0.08, 0.13) in the arithmetic GVT over usual care group. The intervention also improved the TMT-A score (-31.1 seconds; 95%CI, -49.5, -12.7 vs. -3.13 seconds; 95%CI, -16.3, 10.2 in the control group) and the MMSE score (2.10 points; 95%CI, 1.75, 2.46 vs. 0.27 points; 95%CI, -0.08, 0.63). Significant benefits were also observed in the exercise group for the verbal fluency test (mean 2.16 words; 95%CI, 1.56, 2.74) over usual care group.

Conclusions and relevance

An individualized multicomponent exercise training program improves cognitive function (i.e., executive function and verbal fluency domains) in very old patients during acute hospitalization.

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Describe where the data may be found in full sentences. If you are copying our sample text, replace any instances of XXX	The data underlying the results presented in the study are available under reasonable request.

with the appropriate details. • If the data are **held or will be held in a public repository**, include URLs, accession numbers or DOIs. If this information will only be available after acceptance, indicate this by ticking the box below. For example: *All XXX files are available from the XXX database (accession number(s) XXX, XXX.*). • If the data are all contained **within the manuscript and/or Supporting Information files**, enter the following: *All relevant data are within the manuscript and its Supporting Information files.* • If neither of these applies but you are able to provide **details of access elsewhere**, with or without limitations, please do so. For example: *Data cannot be shared publicly because of [XXX]. Data are available from the XXX Institutional Data Access / Ethics Committee (contact via XXX) for researchers who meet the criteria for access to confidential data.* *The data underlying the results presented in the study are available from (include the name of the third party and contact information or URL).* • This text is appropriate if the data are owned by a third party and authors do not have permission to share the data. * typeset	
Additional data availability information:	

Editor-in-Chief
Plos Medicine

Dear Editor-in-Chief,

Please find enclosed our manuscript entitled "*A randomized clinical trial evaluating the effects of a physical exercise intervention on cognitive function in very elderly patients during acute hospitalization*", which we would like to submit for publication as an Original Investigation in Plos Medicine

Hospitalization is a sentinel event and a leading cause of disability in the elderly. Besides deteriorating the functional status of older adults, bedrest also increases the risk for cognitive decline and dementia. Many of the age-associated processes leading to frailty in older adults are also possible responsible for brain aging and consecutive cognitive decline. Accordingly, frail older people are likely to be at high risk of cognitive impairment, and *vice versa*. The increasing interest in the association between frailty and cognitive impairment in hospitalized older adults is driving the development of innovative interventions for the prevention and management of both conditions. Exercise and early rehabilitation protocols applied during acute hospitalization can prevent functional and cognitive decline in older adults and are associated with a reduced length of stay and lower costs. We recently showed the benefits of a multicomponent exercise intervention consisting of resistance ('power'), balance and gait retraining exercises to reverse functional decline associated with acute hospitalization in very elderly individuals (JAMA Intern Med 2018; In press. doi:10.1001/jamainternmed.2018.4869).

To the best of our knowledge, the benefits of a multicomponent exercise intervention in specific cognitive domains in acutely hospitalized older adults have not been previously investigated.

We look forward to hearing from you at your earliest convenience.

Mikel Izquierdo PhD.

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Title page

A randomized clinical trial evaluating the effects of a physical exercise intervention on cognitive function in very elderly patients during acute hospitalization

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Key points

Question: Can the cognitive impairment associated with the acute hospitalization of older adults be reversed?

Findings: This randomized clinical trial including 370 hospitalized elderly patients shows that the physical exercise intervention provided benefits over usual care. At discharge, significant differences between the exercise intervention and the control groups were found in specific cognitive domains, such as executive function and verbal fluency.

Meaning: An individualized, multicomponent exercise program is an effective therapy to reverse the cognitive impairment associated with acute hospitalization in very elderly patients.

Abstract

Background: Prolonged bed rest increases the risk of developing cognitive impairment and dementia in acutely hospitalized older adults. Exercise protocols applied during acute hospitalization can prevent functional decline in older patients, but exercise benefits on specific cognitive domains have not been previously investigated.

Objective: We aimed to assess the effects of a multicomponent exercise intervention for cognitive function in older adults during acute hospitalization.

Design: In a single-blind randomized clinical trial, 370 hospitalized patients (aged ≥75 years) were allocated to an exercise intervention (n=185) or a control (n=185) group (usual care).

Setting: Acute Care for Elderly (ACE) unit.

Participants: Older adults aged>75 years.

Interventions: The intervention consisted of a multicomponent exercise training program performed during 5–7 consecutive days (2 sessions/day). The usual care group received habitual hospital care, which included physical rehabilitation when needed.

Main outcomes: Executive function was measured with the dual-task (*i.e.*, verbal and arithmetic) Gait Velocity Test (GVT) and the Trail Making Test Part A (TMT-A). The Mini Mental State Examination (MMSE) test and verbal fluency ability were also assessed at admission and discharge.

Results: The intervention program provided significant benefits over usual care. At discharge, the exercise group showed a mean increase of 0.1 m/s (95% confidence interval [CI], 0.07, 0.13) in the verbal GVT and 0.1 m/s (95%CI, 0.08, 0.13) in the arithmetic GVT over usual care group. The intervention also improved the TMT-A score (-31.1 seconds; 95%CI, -49.5, -12.7 vs. -3.13 seconds; 95%CI, -16.3, 10.2 in the control group) and the MMSE score (2.10 points; 95%CI, 1.75, 2.46 vs. 0.27 points; 95%CI, -0.08, 0.63). Significant benefits were also observed in the exercise group for the verbal fluency test (mean 2.16 words; 95%CI, 1.56, 2.74) over usual care group.

Conclusions and relevance: An individualized multicomponent exercise training program improves cognitive function (*i.e.*, executive function and verbal fluency domains) in very old patients during acute hospitalization.

Trial Registration: ClinicalTrials.gov Identifier: NCT02300896

Introduction

The provision of inpatient acute care for frail older adults has become a crucial clinical issue in our aging societies.[1-3] Acute medical illnesses and subsequent hospitalization are major events leading to disability in older people.[4-6] In addition to functional decline, prolonged bed rest increases the risk of developing cognitive impairment and dementia in hospitalized older medical patients.[7] Indeed, cognitive impairment is highly prevalent in this patient group and is independently associated with multiple adverse outcomes including functional decline, increased length of hospital stays, institutionalization, and mortality.[8]

Many of the age-associated processes leading to frailty in older adults are also possible responsible for brain aging and consecutive cognitive decline. Accordingly, frail older people are likely to be at high risk of cognitive impairment, and *vice versa*.[9] The increasing interest in the association between frailty and cognitive impairment in hospitalized older adults[10] is driving the development of innovative interventions for the prevention and management of both conditions.

Exercise and early rehabilitation protocols applied during acute hospitalization can prevent functional decline in older patients[11] and are associated with a reduced length of stay and lower costs.[12] The exercise benefits on cognitive function are not entirely clear, but previous studies support that multicomponent exercise training seems to have the most positive effects on cognition in older adults.[13,14] To the best of our knowledge, the benefits of a multicomponent exercise intervention consisting of resistance (power), balance, and gait-retraining exercises to attenuate cognitive impairment in acutely hospitalized older adults have not been previously investigated.

The present study is in line with the long trajectory of research that has explored new possibilities to avoid dangers of prolonged bed-rest.[15] The main purpose of our study was to assess the effects of a multicomponent exercise intervention for cognitive function in older adults during acute hospitalization. Our hypothesis was that multicomponent exercise intervention would maintain or even improve cognitive function compared to usual care in these patients.

Methods

Design

The study is a secondary analysis of a randomized clinical trial (RCT) (NCT02300896).[11,16] It was conducted in the Acute Care of the Elderly (ACE) unit of the Department of Geriatrics in a tertiary public hospital (*Complejo Hospitalario de Navarra*, Spain). This Department has 35 allocated beds and its staff is composed of 8 geriatricians (distributed in the ACE unit, orthogeriatrics and outpatient consultations). Admissions in the ACE unit derive mainly from the Accident and Emergency Department, with heart failure, pulmonary and infectious diseases being the main causes of admissions.

Acutely hospitalized patients who met inclusion criteria were randomly assigned to the intervention or control (usual care) group within the first 48 hours of admission. Usual care is offered to patients by the geriatricians of our department and consists of standard physiotherapy focused on walking exercises for restoring the functionality conditioned by potentially reversible pathologies. A formal exercise prescription was not provided at study entry and patients were instructed to continue with the current activity practices through the duration of the study. The study followed the principles of the Declaration of Helsinki and was approved by the institutional Clinical Research Ethics Committee. All patients or their legal representatives provided written consent.

Participants and randomization

A trained research assistant conducted a screening interview to determine whether potentially eligible patients met the following inclusion criteria: age ≥ 75 years, Barthel Index score ≥ 60 points, able to ambulate (with/without assistance), and to communicate and collaborate with the research team. Exclusion criteria included expected length of stay < 6 days, very severe cognitive decline (i.e., Global Deterioration Scale score = 7), terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, or extremity bone fracture in the past 3 months.

After the baseline assessment was performed, participants were randomly assigned following a 1:1 ratio, without restrictions (www.randomizer.org). Assessment staff was blinded to the main study design and group allocation. Participants were explicitly informed and reminded not to discuss their randomization assignment with the assessment staff.

Intervention

The usual care group received habitual hospital care, which included physical rehabilitation when needed. For the intervention group, exercise training was programmed in two daily sessions (morning and evening) of 20 minutes duration during 5–7 consecutive days (including weekends) supervised by a qualified fitness specialist. Adherence to the exercise intervention program was recorded in a daily register. A session was considered completed when ≥ 90% of the programmed exercises were successfully undertaken.

Each session was performed in a room equipped ad hoc in the ACE unit. Exercises were adapted from the "Vivifrail" multicomponent physical exercise program to prevent weakness and falls.[17] The morning sessions included individualized supervised progressive resistance, balance, and walking-training exercises. The resistance exercises were tailored to the individual's functional capacity using variable resistance training machines (Matrix, Johnson Health Tech, Ibérica, S.L.; Torrejón de Ardoz, Spain and Exercycle S.L., BHGroup; Vitoria, Spain) aiming at 2–3 sets of 8–10 repetitions with a load equivalent to 30–60% of the estimated one-repetition maximum (1RM). Participants performed three exercises involving mainly lower-limb muscles (squats rising from a chair, leg press and bilateral knee extension) and one involving the upper-body musculature (seated bench 'chest' press). They were instructed to perform the exercises at a high speed to optimize muscle power output, and care was taken to ensure proper exercise execution. Balance and gait retraining exercises gradually progressed in difficulty and included the following: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), altering the base of support, and weight transfer from one leg to the other. The evening session consisted of functional unsupervised exercises using light-loads (0.5–1 kg anklets and hand-grip ball), such as knee extension/flexion, hip abduction and daily walking in the corridor of the ACE unit with a duration based on the clinical physical exercise guide "Vivifrail".[17]

When the clinician in charge of the patient considered that the hemodynamic situation was acceptable, and the patient could collaborate, the following endpoints were assessed and the intervention was started. Endpoints were also assessed on the day of discharge.

Endpoints

6-meter dual-task Gait Velocity Test (GVT)

Patients were instructed to walk at their self-selected usual pace on a smooth, horizontal walkway. Two different dual-task gait tests were performed, the arithmetic GVT and the verbal GVT, in which gait velocity was measured while the patients counted backward aloud from 100 down to one or named animals aloud, respectively.[18] The cognitive score was measured by counting the number of animals named (verbal dual-task) or by counting the numbers that were stated (arithmetic dual-task) and the errors in each task.

Mini-Mental State Examination (MMSE)

The MMSE test[19] is the most utilized screening instrument of cognitive decline.[20] The instrument assesses domains of orientation, memory, attention, language, and visuospatial ability. The MMSE is scored out of 30 points, with scores ≤ 23 points indicative of likely cognitive impairment.

Trail Making Test Part A (TMT-A)

The TMT-A is used as an indicator of visual scanning, graphomotor speed, and executive function. The patients were asked to connect randomly arranged circles containing numbers from 1 to 25 following the number sequence, and doing it as quickly as possible.[21]

Verbal fluency test

The patient had to say as many words as possible starting with the letter F in one minute.[22]

Statistical analysis

Analyses were performed by "intention-to-treat" principles. Between-group comparisons of continuous variables were conducted using linear mixed models. Time was treated as a categorical variable. The models included group, time, and group by time interaction as fixed effects, and participants as random effect. For each group, data are expressed as change from baseline (admission) to discharge, determined by the time coefficients (95% confidence interval [CI]) of the model. The conclusions about effectiveness of exercise intervention were based on between-group comparisons of change in cognitive function from baseline (beginning of the intervention) to hospital discharge, as assessed with the MMSE, dual-task GVT (including both verbal and arithmetic task conditions), TMT-A and verbal fluency test, and determined by the time by group interaction coefficients of the model. Between group comparisons of errors during dual-task GVT were analyzed using Poisson mixed model because of the asymmetric distribution of the endpoint.

Using the χ^2 test for linear trend, we also compared the proportion of patients in each group showing an improvement, no change, worsening at discharge at compared with baseline on the dual-task GVT.

Normality of data was checked graphically and through the Kolmogorov Smirnov test. All comparisons were two-sided, with a significance level of 0.05. Statistical analysis was carried out using IBM-SPSS v20 software (SPSS Inc., Chicago, IL).

Results

The study flow diagram is shown in **Figure 1**. No significant differences were found between groups at baseline for demographic and clinical characteristics for study end points (**Table 1**). Of the 370 patients included in the analyses, 209 were women (56.5%); mean age was 87.3 (4.9) years (range 75–101 years), with 130 patients [35.1%] being nonagenarians). The median length of hospital stay was 8 days in both groups (interquartile range [IQR], 4 and 4 days, respectively). The mean number of intervention days for each patient was 5.3 ± 0.5 days, with most training days being consecutive (97%). The number of completed morning and evening sessions per patient averaged 5 ± 1 and 4 ± 1, respectively. Mean adherence to the intervention was 97 ± 8% for the morning sessions (i.e., 806 successfully completed sessions of 841 total possible sessions) and 85 ± 30% in the evening sessions (574 of 688). No adverse effects or falls associated with the prescribed exercises were recorded and no patient had to interrupt the intervention or had their hospital stay modified because of it.

The primary analysis showed that the physical exercise provided a significant benefit over usual care. Differences between the treatment groups revealed a significant intervention effect for both dual-task GVT. The percentage distribution of patients with improvements on the verbal GVT (47.6% vs. 81.7%) or arithmetic GVT (48.7% vs. 88.5%) from admission to discharge significantly differed between the two groups, indicating a beneficial exercise intervention effect for both endpoints (all $p < 0.001$ with χ^2 test, **Figure 2A** and **2B**). At discharge, the exercise group showed an increase of 0.1 m/s (95%CI, 0.07, 0.13 m/s) on the verbal GVT and 0.1 m/s (95%CI, 0.08, 0.13 m/s) on the arithmetic GVT over the usual-care group (**Table 2**, **Figure 2C** and **2D**). Furthermore, significant differences were found between groups in the errors made during the arithmetic GVT ($p < 0.001$, **Table 2**).

Considering the global cognitive function, the intervention group showed improvements at discharge in the MMSE test of 2.10 points (95%CI, 1.75, 2.46 points) whereas no such trend was found in the control group (0.27 points; 95%CI, -0.08, 0.63 points) (**Table 2** and **Figure 3A**).

For the executive function, the exercise group showed an improvement in the TMT-A reducing the time to complete the task by 31.1 seconds at discharge (95%CI, -49.5 to -12.7 seconds) over the control group (**Table 2** and **Figure 3B**).

Finally, acute hospitalization *per se* led to a significant impairment in patient verbal fluency ability (*i.e*., mean change from baseline to discharge of -0.30 words (95%CI, -0.72, 0.12 words) whereas the exercise intervention improved this cognitive domain (1.85 words; 95%CI, 1.44, 2.27 words) (**Table 2** and **Figure 3C**).

Discussion

Our study shows that an individualized exercise intervention during a short time period (mean 5 days) provides significant benefits over usual care in acutely hospitalized older adults and can be an effective therapy to reverse the cognitive impairment usually associated with this patient group. To our knowledge, this is the first study in which a multicomponent intervention including low-intensity resistance training exercises produces enhancements on specific cognitive domains, such as executive function and verbal fluency, in hospitalized patients of advanced age.

Older patients admitted to the hospital are at risk of experiencing negative consequences following hospitalization including functional decline and frequently, long-term disability.[5,6] Research has suggested that hospitalization in older adults *per se* is associated not only with functional adverse outcomes but also with the development of cognitive decline and an increased risk of dementia.[7] Moreover, cognitively impaired older patients are at even greater risk of hazards of hospital stay as compared to patients with no cognitive decline.[23] Our findings reveal that more than one-half of the control group showed worsened gait performance in both dual-task GVT at discharge, whereas the exercise intervention reversed this trend. We also observed an improvement in the verbal fluency ability after the exercise intervention, with the opposite response found in the usual care group. Surprisingly, short-term hospitalization did not impact dramatically on some cognitive tasks, such as the MMSE and TMT-A, although significant differences were observed between groups at discharge. The poor health status of the hospitalized elderly upon admission and the comprehensive and multidisciplinary protocols already established in the ACE unit could influence the preservation of some cognitive domains.

Acute hospital admissions play a key role in the disabling process in the elderly years, and physical exercise seems to be an effective therapy to prevent nosocomial disability, which is usually linked to poor mobility during hospitalization.[24] Recent evidence has demonstrated that specific in-hospital exercises could provide significant benefits over usual care and could help to reverse the functional decline associated with acute hospitalization in older adults.[11] Although potential benefits of physical exercise on functional capacity are well established, the effects of tailored multicomponent exercise intervention on specific cognitive domains including executive function and verbal fluency are not clear in acutely hospitalized older patients. In agreement with previous studies,[13,14] our findings support that multicomponent exercise training may produce the most positive effects on cognitive function in older adults. The inclusion of progressive low-intensity resistance training as a component of the exercise training protocol could be the reason for cognitive gains in the intervention group in specific executive tasks (*i.e.*, both dual-task GVT and TMT-A). An emerging theory to explain these cognitive benefits is that resistance training increases the production of several growth factors, such as brain-derived neurotrophic factor and insulin-like growth factor-1.[25] Previous evidence has suggested that gait performance is closely related to cognitive function, in particular executive function, and impaired executive function has been associated with decreased gait velocity, increased risk of falls and decreased performance on complex motor tasks in older adults.[26,27] Thus, our results indicate that, despite its short duration, an exercise training approach is effective in improving the executive function (measured by dual-task GVT) during hospitalization in very old patients.

The present study is in line with the recently published World Health Organization (WHO) Clinical Consortium of Healthy Aging, which highlights the importance of maintaining individuals´ intrinsic capacity for the preservation of autonomy and independence in essential everyday activities.[28] In accordance with the WHO framework, our findings show that multicomponent exercise training, with special emphasis on muscle power training, is the intervention of choice for avoiding a trajectory towards frailty/disability in acutely hospitalized older adults and also improves cognitive function, a key component of intrinsic capacity. Therefore, exercise prescription should be considered as front-line treatment to prevent hospital-acquired iatrogenic disability. Future RCTs should also consider the inclusion of multidomain interventions in this population, in which exercise training is combined with other treatments such as cognitive training and social enrichment, to optimize cognitive performance and prevent cognitive impairment.

Our study has some limitations, including patients´ difficulty in completing all the tasks at both hospital admission and discharge. Notably, 16% of the older patients were unable to perform the arithmetic GVT because they did not receive primary education and 47% of the participants could not complete the TMT-A because of visual impairment. Another possible limitation was that only old patients with relatively good functional capacity at preadmission (i.e., Barthel Index score ≥ 60 points) were included in the study; thus, the results might not be generalizable to the entire hospitalized elderly population. Nevertheless, our study has several strengths. We focused on a particularly vulnerable population of advanced age (overall mean 87.3 years; range 75–101 years, with 130 patients (35.1%) being nonagenarians) to develop an innovative exercise intervention of a few days (i.e., 5 ± 1 and 4 ± 1 morning and evening sessions, respectively) in acute settings. Also, patients with multiple comorbidities (mean [SD] of 9 [6] comorbidities) and mild dementia/cognitive impairment were included in the RCT (routinely excluded from exercise studies). Considering the exercise training protocol, a daily individualized adjustment of loads was performed to optimize exercise benefits and prevent iatrogenic nosocomial disability. Finally, to minimize potential bias, the researchers were unaware of a patient test scores at admission when retesting at discharge.

Conclusions

An individualized, multicomponent exercise training program is an effective therapy for improving cognitive function (*i.e.*, executive function and verbal fluency domains) in very old patients during acute hospitalization. These findings support the need for a shift from the traditional (bed-rest based) hospitalization to one that recognizes the important role of maintaining functional capacity and cognitive function in older adults, key components of intrinsic capacity.

Declaration of interests

All authors have nothing to declare.

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Figure legends

Figure 1. Study flow diagram.

Figure 2. Changes from baseline to discharge (A and B) and within-group punctuation change distribution (C and D). Dual-task GVT changes: *better* indicates an improvement of more than 0.1 m/s, *slightly better* indicates an improvement between 0.001 and 0.1 m/s, *unchanged* indicates no difference, *slightly worse* indicates a decline between 0.001 and 0.1 m/s, *worse* indicates a decline of more than 0.1 m/s. The proportion of patients showing overall improvement and worsening in the dual-task GVT was significantly higher and lower, respectively, in the intervention than in the control group (all $p < 0.001$ with χ^2 test). In the violin plots, the horizontal dotted lines indicate Q1 and Q3, and the horizontal dashed line within the violin, median.

Figure 3. Changes in within-group punctuation in the Mini-Mental State Examination (MMSE) test, Trail Making Test Part A (TMT-A) and verbal fluency test. In the violin plots, the horizontal dotted lines indicate Q1 and Q3, and the horizontal dashed line within the violin, median.

Table 1. Baseline characteristics of the participants.

Variable	Control group (n=185)	Intervention group (n=185)
Demographic data		
Age, years	87.1 (5.2)	87.6 (4.6)
Women, N (%)	109 (59%)	100 (54%)
Body mass index, kg/m^2	26.9 (4.9)	27.1 (4.4)
Clinical data		
Barthel Index, score	83 (17)	84 (17)
CIRS score, median (IQR)	12 (5)	13 (5)
MNA score, median (IQR)	24 (4)	24 (4)
1RM leg press, kg	62 (31)	57 (25)
1RM chest press, kg	25 (12)	24 (11)
1RM knee extension, kg	41 (14)	39 (13)

GDS, score	3.6 (2.9)	4.0 (2.4)
QoL (EQ-VAS), score	60 (21)	58 (22)
Delirium (CAM, %)	12%	17%
Endpoint measures		
Verbal GVT, m/s	0.4 (0.2)	0.4 (0.2)
Arithmetic GVT, m/s	0.4 (0.2)	0.4 (0.2)
MMSE, score	23 (4)	22 (5)
TMT-A, seconds	162.9 (97.0)	166.5 (125.4)
Verbal fluency test, score	7.2 (4.2)	6.3 (3.8)
Admission reason, N (%)		
Cardiovascular	67 (36)	65 (35)
Infectious	33 (18)	33 (18)
Pulmonary	20 (11)	28 (15)
Gastrointestinal	17 (9)	20 (11)
Neurological	9 (5)	9 (5)
Other	39 (21)	30 (16)

Data are mean (SD) unless otherwise stated. No statistically significant differences were found between groups (all P>0.05).
Abbreviations: 1RM, one-repetition maximum; CAM, Confussion Assessment Method; CIRS, Cumulative Illness Rating Scale; GDS, Yesavage Geriatric Depression Scale; GVT, Gait Velocity Test; IQR, interquartile range; MNA, Mini-nutritional Assessment; MMSE, Mini-Mental State Examination; QoL, quality of life; EQ-VAS, visual analogue scale of the EuroQol questionnaire (EQ-5D); SPPB, Short Physical Performance Battery; TMT-A, Trail Making Test Part A.

Table 2. Results of study endpoints by group

Endpoints	Control group	Exercise group	Between-group difference (95%CI)	p-value between groups
Verbal GVT				
Velocity, m/s	0.002 (-0.018, 0.022)	0.10 (0.08, 0.12)	0.10 (0.07, 0.13)	<0.001
Correct answers, score	0.01 (-0.36, 0.38)	0.41 (0.04, 0.79)	0.41 (-0.12, 0.93)	0.133
Errors, score	2.03 (0.64, 7.61)	0.32 (0.016, 2.41)	0.16 (0.01, 1.65)	0.157
Arithmetic GVT				
Velocity, m/s	0.009 (-0.009, 0.029)	0.11 (0.10, 0.13)	0.10 (0.08, 0.13)	<0.001
Correct answers, score	0.12 (-0.57, 0.81)	0.18 (-0.52, 0.88)	0.06 (-0.92, 1.05)	0.901
Errors, score*	1.16 (0.92, 1.45)	0.55 (0.42, 0.69)	0.48 (0.34, 0.67)	<0.001

MMSE, score	0.27 (-0.08, 0.63)	2.10 (1.75, 2.46)	1.83 (1.32, 2.33)	<0.001
TMT-A, seconds	-3.13 (-16.3, 10.2)	-34.2 (-47.1, -21.3)	-31.1 (-49.5, -12.7)	<0.001
Verbal fluency test				
Correct answers, score	-0.30 (-0.72, 0.12)	1.85 (1.44, 2.27)	2.16 (1.56, 2.74)	<0.001
Errors, score*	1.11 (0.75, 1.63)	0.66 (0.43, 0.99)	0.58 (0.33, 1.05)	0.076

Data in each group are expressed as change from baseline (admission) to discharge (mean and 95% confidence interval). Abbreviations: GVT, gait velocity test; MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test Part A.
* Poisson mixed model.

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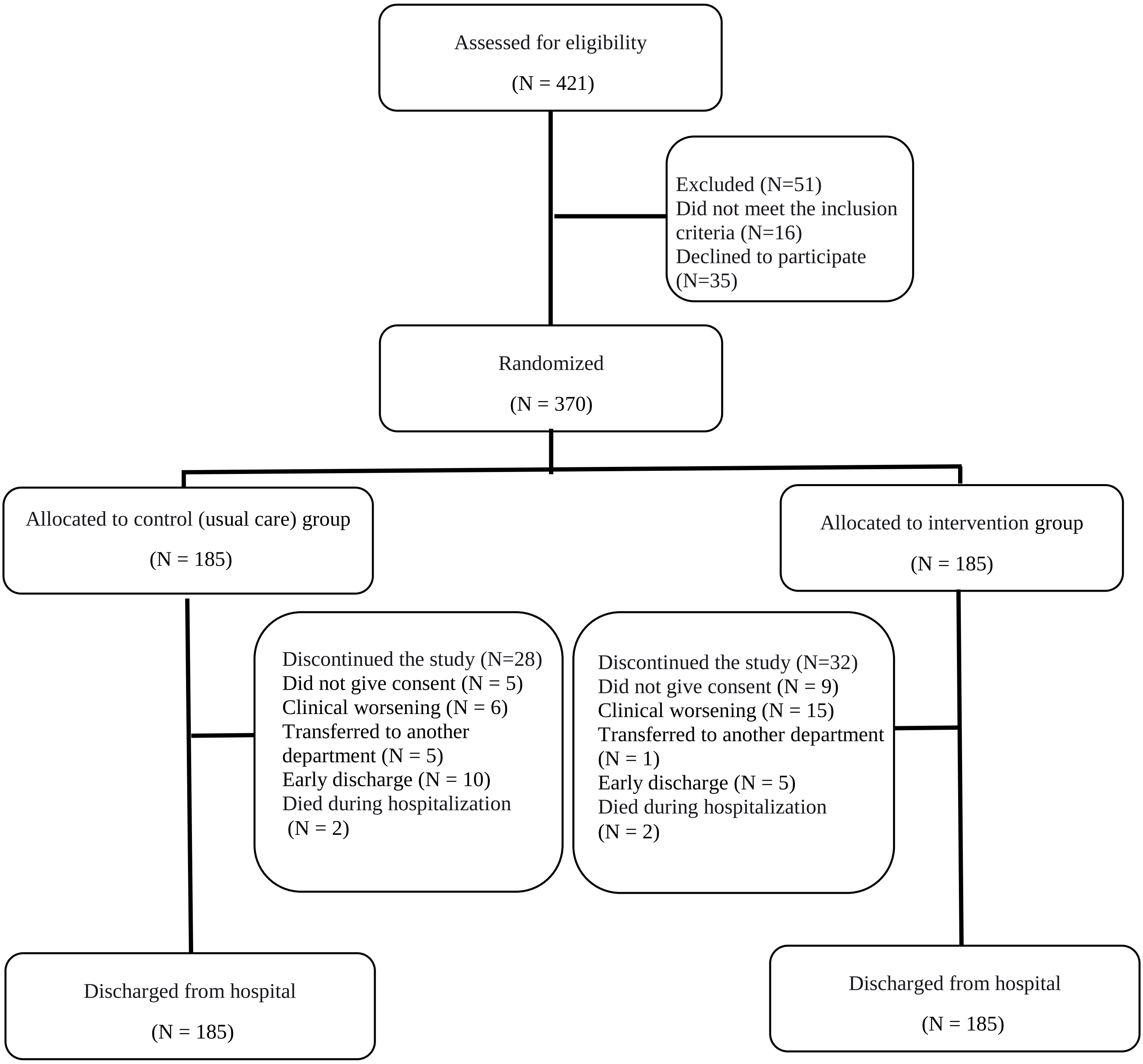
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(N = 421)
Excluded (N=51)
Did not meet the inclusion criteria (N=16)
Declined to participate (N=35)
Randomized
(N = 370)
Allocated to control (usual care) group
(N = 185)
Allocated to intervention group
(N = 185)
Discontinued the study (N=28)
Did not give consent (N = 5)
Clinical worsening (N = 6)
Transferred to another department (N = 5)
Early discharge (N = 10)
Died during hospitalization (N = 2)
Discontinued the study (N=32)
Did not give consent (N = 9)
Clinical worsening (N = 15)
Transferred to another department (N = 1)
Early discharge (N = 5)
Died during hospitalization (N = 2)
Discharged from hospital
(N = 185)
Discharged from hospital
(N = 185)

Figure 1.

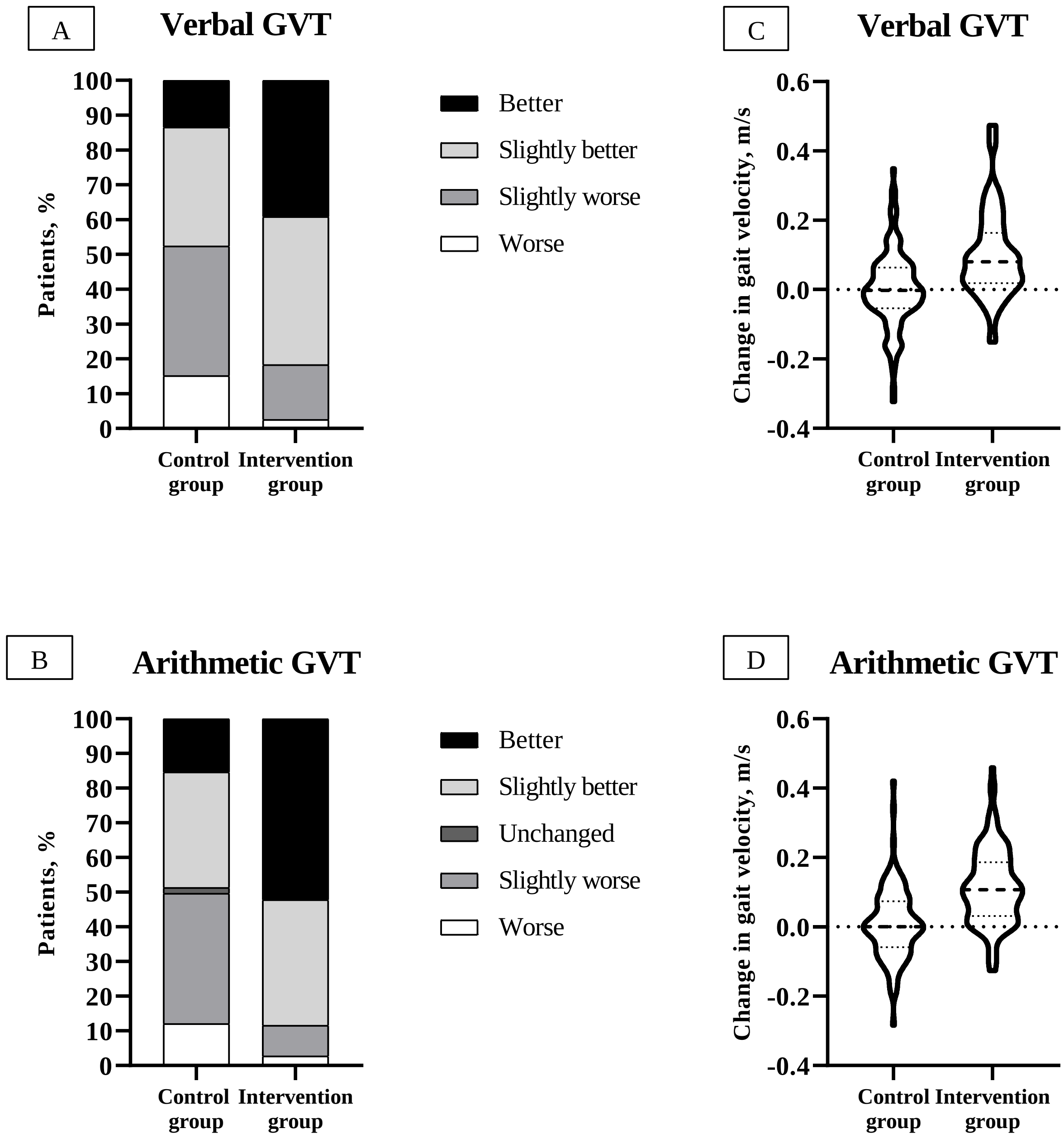
A
Verbal GVT
Patients, %
Control group
Intervention group
Better
Slightly better
Slightly worse
Worse
C
Verbal GVT
Change in gait velocity, m/s
Control group
Intervention group
B
Arithmetic GVT
Patients, %
Control group
Intervention group
Better
Slightly better
Unchanged
Slightly worse
Worse
D
Arithmetic GVT
Change in gait velocity, m/s
Control group
Intervention group

Figure 2.

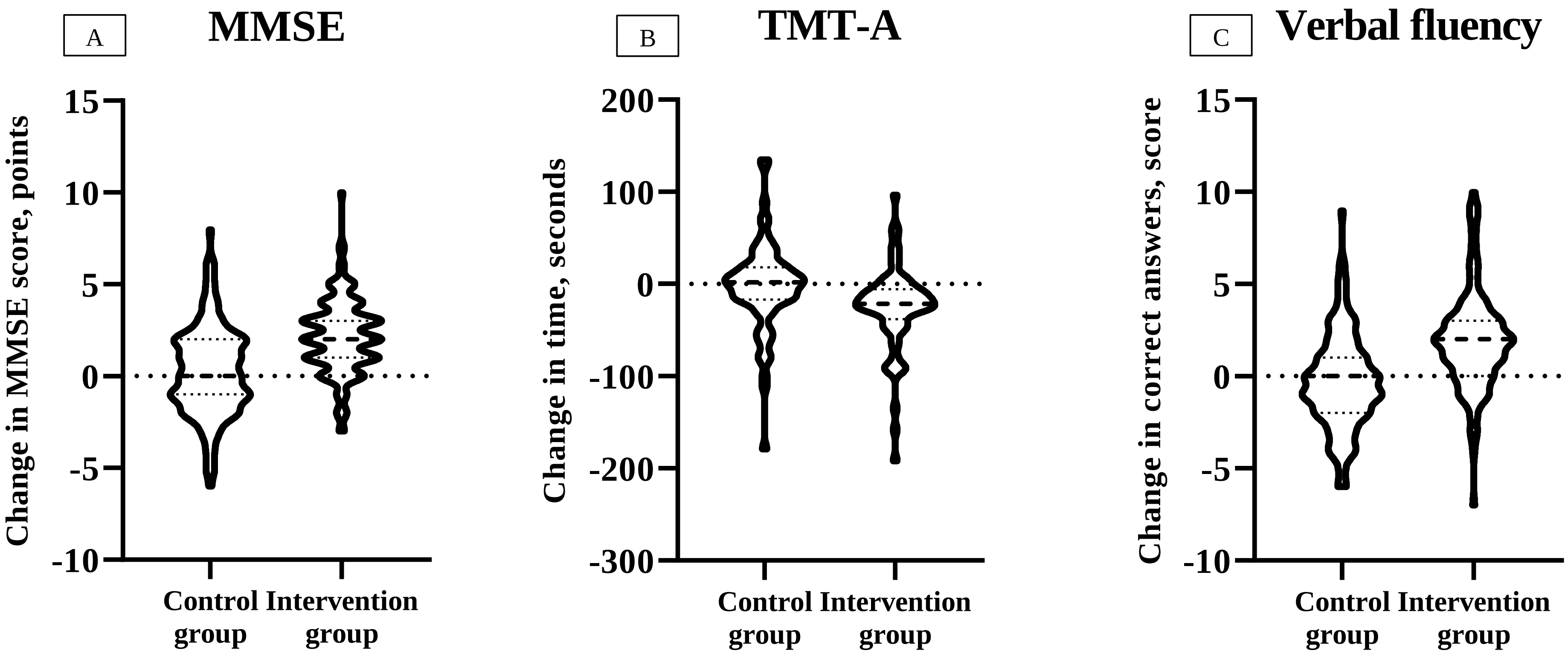
A
MMSE
Change in MMSE score, points
15
10
5
0
-5
-10
Control group
Intervention group
B
TMT-A
Change in time, seconds
200
100
0
-100
-200
-300
Control group
Intervention group
C
Verbal fluency
Change in correct answers, score
15
10
5
0
-5
-10
Control group
Intervention group

Figure 3.

protocol

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