Original Article

Specific multimorbidity patterns modify the impact of an exercise intervention in older hospitalized adults

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Abstract

Background: Different multimorbidity patterns present with different prognoses, but it is unknown to what extent they may influence the effectiveness of an individualized multicomponent exercise program offered to hospitalized older adults.

Methods: This study is a secondary analysis of a randomized controlled trial conducted in the Department of Geriatric Medicine of a tertiary hospital. In addition to the standard care, an exercise-training multicomponent program was delivered to the intervention group during the acute hospitalization period. Multimorbidity patterns were determined through fuzzy c-means cluster analysis, over 38 chronic diseases. Functional, cognitive and affective outcomes were considered.

Results: Three hundred and six patients were included in the analyses (154 control; 152 intervention), with a mean age of 87.2 years, and 58.5% being female. Four patterns of multimorbidity were identified: *heart valves and prostate diseases* (26.8%); *metabolic diseases and colitis* (20.6%); *psychiatric, cardiovascular and autoimmune diseases* (16%); and an *unspecific* pattern (36.6%). The Short Physical Performance Battery (SPPB) test improved across all patterns, but the intervention was most effective for patients in the *metabolic/colitis* pattern (2.48-point difference between intervention/control groups, 95% CI 1.60-3.35). Regarding the Barthel Index and the Mini Mental State Examination (MMSE), the differences were significant for all multimorbidity patterns, except for the *psychiatric/cardio/autoimmune* pattern. Differences concerning quality of life were especially high for the p*sychiatric/cardio/autoimmune* pattern (16.9-point difference between intervention/control groups, 95% CI 4.04, 29.7).

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Conclusions: Patients in all the analyzed multimorbidity patterns improved with this tailored program, but the improvement was highest for those in the metabolic pattern. Understanding how different chronic disease combinations are associated with specific functional and cognitive responses to a multicomponent exercise intervention may allow further tailoring such interventions to older patients' clinical profile.

Key points

- Hospital associated disability is very frequent in older adults, and tailored preventive interventions are feasible.
- Not all interventions have the same effect, some patients can be non-responders or even adverse-responders.
- Specific multimorbidity patterns modified the impact of an exercise intervention in older hospitalized adults.

Background

Decreases in the fatality of most chronic conditions have led older individuals to live longer with multiple long-term conditions (i.e., multimorbidity). Multimorbidity is commonly defined as the co-occurrence of two or more chronic conditions in an individual.[1] Up to 90% of older adults 60 years and over are multimorbid,[2] and multimorbidity accounts for many of the years lived with functional decline and disability.[3] It is also related to numerous adverse outcomes such as disability, cognitive impairment, nursing home admissions, death and intense healthcare use,[3–5] and has implications beyond those generated by each of the diseases.[6]

Unplanned hospital admissions triggered by older patients' clinical complexity is one of the negative outcomes associated with multimorbidity.[7] Unplanned admissions represent over a third of all hospital admissions, lead to high care costs, create uncertainty for those responsible for planning and delivering services, and are distressing for patients and their families.[8,9] Unplanned admissions in older patients often represent sentinel episodes for accelerated health deterioration, and they often lead to iatrogenic disability and cognitive deterioration in the short and long-term following the hospitalization,[10,11] which in many cases could be prevented by means of individualized early interventions. Despite the acknowledged negative consequences of hospitalizations with the subsequent development of frailty and disability,[12–14] insufficient progress has been made on the implementation of intervention programs already during the hospitalization period. Yet, increasing evidence supports the effectiveness and feasibility of physical exercise interventions to prevent hospital-associated disability in older adults.[15–18] Multicomponent exercise programs targeting the four physical function domains (strength, balance, endurance and mobility) have been shown to be able to modify the functional and cognitive trajectories of hospitalized older adults.[19]

It is well established that tailored interventions focusing on nutrition, exercise or management of polypharmacy are effective in the maintenance of good health in old age; however, recent studies have demonstrated that certain groups of participating individuals experience no significant improvements. Such individuals are commonly termed as non- or negative responders.[20] Exercise non-response appears to be mitigated by adjustments in training volume, duration, and intensity.[21–23] It is therefore a challenge, but essential, to advance towards the personalization of exercise interventions through a better stratification and targeting of potentially eligible patients. Along these lines, the identification of negative as well as positive responders to previously evaluated interventions will be key to optimize available resources.

Patients affected by specific patterns of multimorbidity have been shown to differ in their risk of developing functional decline and disability over time[6,24] but, as far as we know, there is no study that has evaluated the influence of such patterns of chronic diseases in modulating the effectiveness of an individualized exercise program aimed at delaying or reversing functional decline in hospitalized older adults. One may hypothesize that multimorbid patients affected by cardiovascular and metabolic conditions could benefit more from this type of interventions, given the responsiveness of these diseases to aerobic exercise, endurance and weight loss. Thus, the aim of this study was to identify groups of geriatric patients characterized by their patterns of multimorbidity who could benefit most from an individual exercise intervention during hospitalization.

Methods

Study design and participants

This study is a secondary analysis of a randomized controlled trial (RCT; NCT02300896)[19] conducted in the Acute

Care Unit (ACE) of the Department of Geriatrics in a tertiary public hospital (Hospital Universitario de Navarra, Spain). This department has 40 allocated beds with a staff of eight geriatricians (distributed in the ACE unit, orthogeriatrics and outpatient consultations). Admissions to the ACE unit are mainly from the Accident and Emergency Department, with heart failure, pulmonary, and infectious diseases being the main causes of admission.

Acutely hospitalized patients who met the inclusion criteria were randomly assigned to the intervention or control (usual care) group within the first 48 hours of admission. In total, 370 participants were recruited for the original study. Details about randomization and allocation procedures and sample size considerations have been published elsewhere.[25] Inclusion criteria were age >75 years, Barthel Index score >59 points, being able to walk (with/without assistance), and being able to communicate and collaborate with the research team. Exclusion criteria included expected length of stay <6 days, very severe cognitive decline, terminal illness, uncontrolled arrhythmias, acute pulmonary embolism and myocardial infarction, and extremity bone fracture in the past three months. Out of the 370 participants, 64 with less than two chronic diseases at the initial assessment were excluded from the analyses.

Intervention

Briefly, the usual-care group received usual hospital care, which included physical rehabilitation when needed. In addition to the standard care, an exercise-training program was delivered in two daily sessions (morning and evening) of 20 minutes' duration during 5-7 consecutive days for the intervention group. The morning session included individualized progressive resistance, balance, and walking training exercises and was supervised by a physiotherapist with a background in exercise physiology (>10 years of experience). The evening session consisted of functional unsupervised exercises using light loads (0.5-1 kg anklets and handgrip 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" (http://vivifrail.com/).[26]

The study followed the principles of the Declaration of Helsinki and was approved by the Hospital Universitario de Navarra Research Ethics Committee (Pyto 23/2014). All patients or their legal representatives provided written consent.

Chronic diseases and multimorbidity assessment

Demographic, functional, cognitive and multimorbidity data were recorded during the acute hospital admission and retrospectively completed using the electronic medical records from primary care. Initially, chronic diseases were coded according to the International Classification of Diseases, 10th revision (ICD10) and later classified according to a consensus list of 60 chronic disease categories developed by Calderón-Larrañaga et al in the Swedish National study of Aging and Care in Kungsholmen (SNAC-K).[27] Each chronic disease was included as an individual binary variable. Only chronic diseases with a prevalence ≥2% in the study population were included for final analyses, i.e., 38 diseases in total.

Clinical outcomes

The main outcomes examined in this secondary analysis were functional, cognitive and affective status. More specifically, the following scales were included: the Barthel index assessing performance in activities of daily living (ranging from 0 [totally dependent] to 100 [completely independent],[28] the Short Physical Performance Battery (SPPB) that combines balance, gait velocity, and leg strength in a single score on a 0 (worst) to 12 (best) scale,[29] the handgrip strength (dominant hand),[30] the Mini-Mental State Examination (30-point questionnaire; scale from 0 [worst] to 30 [best]),[31] mood status according to the 15-item Yesavage Geriatric Depression Scale (Spanish version; scale from 0 [best] to 15 [worst]),[32] and the visual analog scale of the EuroQol–5 Dimension (EQ-5D) questionnaire for quality of life (QoL) assessment (Spanish version; scale from 0 [worst health state imaginable] to 100 [best health state imaginable]).[33]

Statistical analysis

Homogeneous groups of patients were first identified according to their commonly coexisting chronic diseases. A dimension-reduction technique on the dataset of 38 chronic diseases was applied through multiple correspondence analysis (MCA) for binary variables. This method reduced the size of the dataset while maintaining the complexity of the original data. The Karlis-Saporta-Spinaki rule was applied in order to select the appropriate number of dimensions to preserve, considering the eigenvalues of the MCA and the number of variables and individuals in the dataset. This approach accounts for the sampling variability, which can lead to the selection of dimensions that are in fact not statistically significant.[34]

Using the reduced database, multimorbidity patterns were determined through a fuzzy c-means soft clustering algorithm. The fuzzy c-means algorithm estimates c cluster centers (similar to k-means) but with fuzziness, so that individuals may belong to more than one cluster. The use of a fuzzy cluster analysis over a hard cluster analysis helps to better handle the stochastic nature of some

disease associations, the potential noise stemming from the measurement (e.g., disease assessment), and the variance due to between-individual differences.[35,36] Since clustering algorithms are unsupervised techniques, the model fitting is traditionally assessed through cost functions that depend on both the dataset and the clustering parameters, and are denoted as validation indices. In our analysis, the following indices were included (Appendix 1): Fukuyama index, Xie-Beni index, Partition coefficient index, Partition entropy index and Calinski-Harabasz index.[37] The final number of patterns was determined by combining both the analytical and clinical approaches. The consistency and clinical relevance of the final solution was evaluated in the context of previous literature as well as within the research team (2 geriatricians, 3 physiotherapists, 1 epidemiologist and 2 statisticians).

The patterns were described using three metrics: 1) the observed prevalence of a chronic disease in a specific pattern; 2) observed/expected ratios (O/E ratios) calculated by dividing the prevalence of a chronic disease in a specific pattern by the prevalence of the same chronic disease in the entire study population; 3) exclusivity determined by dividing the number of individuals with a chronic disease in a specific pattern by the number of individuals with the same chronic disease in the entire study population. A threshold of 2 for the O/E ratio was set in order for a disease to be considered overrepresented in a pattern. An exclusivity threshold of 25% was established as a complementary metric to evaluate the association of a given chronic disease with a pattern.[35,36]

The patterns were subsequently characterized by demographic and clinical variables not included in the clustering process. For these analyses, participants were forced into the pattern they were more likely to belong to. Demographic and clinical outcome data were summarized using means and standard deviations for continuous variables and frequencies and percentages for categorical variables, and were presented by multimorbidity pattern and intervention group (i.e., exercise and usual-care).

Next, we assessed whether the impact of the intervention differed across patient groups characterized by their patterns of multimorbidity. For each clinical outcome variable, pattern-stratified linear models were fitted (i.e., between-intervention group differences), with post-intervention values as the response variable, intervention group as the explanatory variable, and adjusting by sex, age and baseline outcome value. Moreover, a linear model was fitted using the whole sample (i.e., between-pattern differences), with post intervention values as the response variable, intervention group, pattern and their interaction as explanatory variables, and adjusting by sex, age and baseline outcome value.

All analyses were carried out using R version 4.1.0. The significance level was set at $\alpha=0.05$.

Results

Overall, 306 participants were included in the analyses (154 belonging to the control group and 152 to the intervention group), with a mean age of 87.2 years, and female participants conformed 58.5% of the population. Four patterns of multimorbidity were identified at baseline: *heart valves and prostate diseases* (n=82; 26.8%); *metabolic diseases and colitis* (n=63; 20.6%); *psychiatric, cardiovascular and autoimmune diseases* (n=49; 16%); and an *unspecific* pattern where none of the diseases were overrepresented (n=112; 36.6%). The baseline characteristics of study participants across multimorbidity patterns are shown in Table 1, and Figure 1 shows the observed/expected ratio and exclusivity of all included chronic diseases across the different patterns. The distribution of each multimorbidity pattern across intervention groups is described in Appendix 2.

Significant age or sex differences between the control and intervention groups for any of the multimorbidity patterns were not found (Table 1). The *heart and prostate* pattern had a lower proportion of women than the rest of patterns. Subjects in the *metabolic and colitis* pattern had a higher body mass index (BMI). Functionality was similar across all the patterns but subjects in the *metabolic and colitis* pattern and the *psychiatric, cardiovascular and autoimmune diseases* pattern had lower baseline scores in physical function (i.e., SPPB) and in basic activities of daily living (i.e., Barthel Index). Cognition was similar across all patterns and the burden of depressive symptoms (i.e., Yesavage Scale) was higher among subjects in the *metabolic and colitis* pattern and the *psychiatric, cardiovascular and autoimmune diseases* pattern. Handgrip strength was higher in patients within the *heart valves and prostate cancer* pattern and QoL was lower among subjects in the *metabolic and colitis* pattern and the *psychiatric, cardiovascular and autoimmune diseases* pattern.

Most of the outcomes improved after the intervention across the different multimorbidity patterns, although different response profiles were observed for particular multimorbidity patterns (Figure 2). Patients' physical performance (i.e., SPPB) improved in all patterns (between-intervention group difference), but the intervention was most effective for patients in the *metabolic/colitis* pattern and least effective for those in the *heart and prostate* pattern. However, between-pattern differences were not significant. Regarding basic activities of daily living (i.e., Barthel Index), between-intervention group differences were significant in all patterns except for the *psychiatric/cardio/autoimmune* pattern. The same trend was observed

Table 1. Baseline characteristics of study participants across multimorbidity patterns.

Variable	Pattern	Overall	Control group	Intervention group
Age (years, mean (SD))	Unspecific	86.8 (4.87)	86.8 (5.34)	86.9 (4.34)
	Heart/Prostate	87.6 (4.79)	87.7 (4.75)	87.5 (4.88)
	Metabolic/Colitis	86.9 (4.80)	85.9 (4.92)	87.7 (4.62)
	Psych/cardio/autoinm	87.5 (5.84)	87.6 (5.98)	87.4 (5.76)
Sex (women, n (%))	Unspecific	80 (71.4%)	43 (72.9%)	37 (69.8%)
	Heart/Prostate	26 (31.7%)	13 (35.1%)	13 (28.9%)
	Metabolic/Colitis	44 (69.8%)	20 (74.1%)	24 (66.7%)
	Psych/cardio/autoinm	29 (59.2%)	18 (58.1%)	11 (61.1%)
BMI (Kg/m^2, mean (SD))	Unspecific	26.5 (4.27)	26.7 (4.66)	26.2 (3.87)
	Heart/Prostate	26.6 (3.65)	26.9 (4-12)	26.4 (3.27)
	Metabolic/Colitis	30.4 (5.35)	30.3 (5.44)	30.4 (5.37)
	Psych/cardio/autoinm	25.4 (4.18)	24.9 (4.36)	26.0 (3.90)
# chronic diseases (median (IQR))	Unspecific	6 (2.25)	6 (3)	6 (2)
	Heart/Prostate	10 (4)	10 (5)	9 (3)
	Metabolic/Colitis	13 (5)	14 (5)	13 (3.25)
	Psych/cardio/autoinm	11 (3)	11 (3.5)	9.5 (4)
Barthel (mean (SD))	Unspecific	85.3 (16.3)	86.8 (14.9)	83.7 (17.8)
	Heart/Prostate	83.5 (16.3)	81.7 (14.7)	84.9 (17.4)
	Metabolic/Colitis	80.3 (16.4)	79.6 (16.5)	80.9 (16.5)
	Psych/cardio/autoinm	82.9 (16.0)	82.5 (17.7)	83.6 (13.2)
SPPB (mean (SD))	Unspecific	4.56 (2.91)	4.84 (2.99)	4.25 (2.82)
	Heart/Prostate	5.00 (2.67)	5.00 (2.90)	5.00 (2.51)
	Metabolic/Colitis	4.38 (2.48)	4.38 (2.62)	4.37 (2.40)
	Psych/cardio/autoinm	4.04 (2.24)	4.33 (2.44)	3.56 (1.82)
Handgrip strength (Kg, mean (SD))	Unspecific	15.7 (6.28)	15.5 (6.69)	15.9 (5.86)
	Heart/Prostate	19.1 (6.45)	18.7 (6.34)	19.5 (6.58)
	Metabolic/Colitis	16.6 (6.27)	16.3 (6.48)	16.9 (6.18)
	Psych/cardio/autoinm	15.2 (6.08)	15.3 (6.64)	15.0 (5.18)
MMSE (mean (SD))	Unspecific	22.2 (5.18)	23.6 (4.08)	20.6 (5.75)
	Heart/Prostate	23.5 (3.31)	23.7 (2.86)	23.4 (3.67)
	Metabolic/Colitis	22.1 (4.54)	22.3 (5.06)	21.9 (4.16)
	Psych/cardio/autoinm	23.1 (3.79)	22.7 (4.06)	23.8 (3.30)
Yesavage (mean (SD))	Unspecific	3.71 (2.60)	3.27 (2.83)	4.20 (2.25)
	Heart/Prostate	3.52 (2.77)	3.44 (2.99)	3.58 (2.60)
	Metabolic/Colitis	4.11 (2.68)	4.59 (3.25)	3.74 (2.09)
	Psych/cardio/autoinm	4.22 (2.73)	4.03 (2.85)	4.56 (2.55)
QoL (mean (SD))	Unspecific	61.9 (20.4)	60.7 (20.1)	63.1 (20.9)
	Heart/Prostate	61.1 (21.5)	65.2 (21.4)	57.8 (21.2)
	Metabolic/Colitis	56.3 (22.4)	59.7 (21.0)	54.3 (23.2)
	Psych/cardio/autoinm	53.0 (18.8)	50.5 (18.4)	57.4 (19.1)

Abbreviations: SD: standard deviation, IQR: interquartile range; BMI: Body mass index; SPPB: Short Performance Physical Battery; MMSE: Mini-Mental State Examination; QoL: Quality of Life.

For group comparison: Chi-square test for sex, Mann Whitney's U test for number of chronic diseases and t-test for the rest of variables.

p-values for inter-pattern comparisons: <0.001 (sex, chi-square), 0.673 (age, ANOVA), <0.001 (BMI, ANOVA), 0.439 (number of chronic diseases, Kruskal-Wallis), 0.308 (Barthel, ANOVA), 0.232 (SPPB, ANOVA), <0.001 (handgrip strength, ANOVA), 0.344 (MMSE, Kruskal-Wallis), 0.390 (Yesavage, ANOVA), 0.061 (QoL, ANOVA).

for cognition (i.e., MMSE); for this outcome variable, the pattern-intervention interaction was statistically significant (p-value=0.048). Moreover, the MMSE-specific beta-coefficients for the *metabolic/colitis* pattern and the *heart/prostate* pattern were 1.3 points (95% CI: 0.0, 2.7) and 1.1 (95% CI: -0.2, 2.3) points greater, respectively, than that for the *unspecific* pattern. Differences in depression

(i.e., Yesavage Scale) were also significant for all patterns. The *metabolic/colitis* pattern had a 1.13 (95% CI: 0.07, 2.19) point greater decrease in depressive symptoms compared to the *unspecific* pattern, although differences between patterns were not significant. With respect to the handgrip strength, the difference between intervention groups was also significant for all patterns. There was a 1.5

Figure 1. Observed/expected ratio and exclusivity of chronic diseases across multimorbidity patterns. Observed/expected (O/E) ratio calculated by dividing the prevalence of a chronic disease in a specific pattern by the prevalence of the same chronic disease in the entire study population. Exclusivity determined by dividing the number of individuals with a chronic disease in a specific pattern by the number of individuals with the same chronic disease in the entire study population.
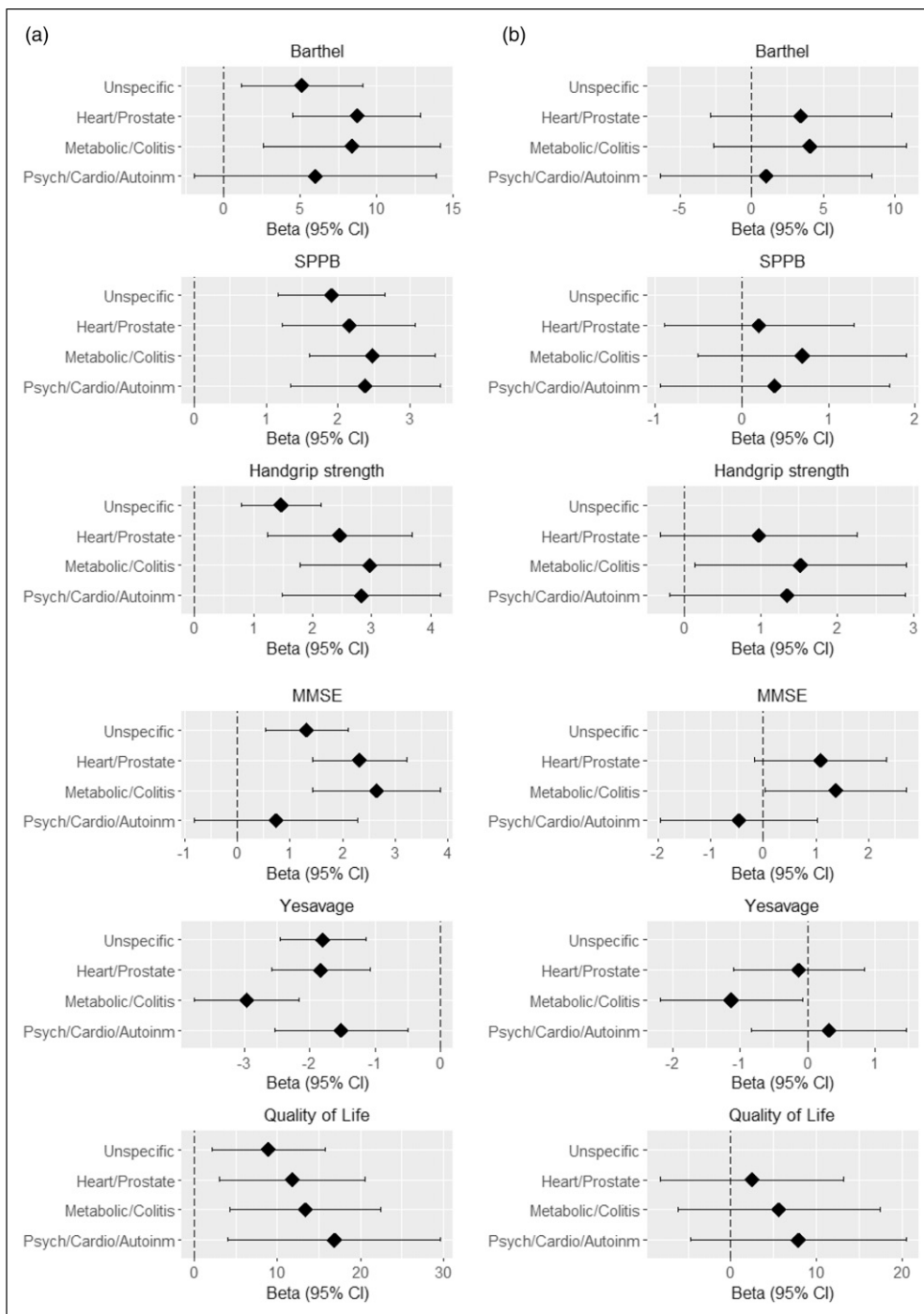
Figure 2. Effectiveness of the physical exercise intervention by multimorbidity patterns. Panel A shows pattern-stratified estimates. Panel B shows the estimates for the interaction term between intervention group and pattern (reference category: *unspecific* pattern). All models are adjusted by sex, age and baseline outcome value. Abbreviations: SPPB: Short Performance Physical Battery; MMSE: Mini-Mental State Examination; QoL: Quality of Life. Interpretation of trends in the figures: all outcomes improve to the right of the graph, except Yesavage that improves to the left. p-values of multimorbidity pattern-intervention group interactions in models included in Panel B: 0.583 (Barthel), 0.707 (SPPB), 0.108 (Handgrip strength), 0.048 (MMSE), 0.107 (Yesavage), 0.600 (QoL).

(95% CI: 0.1, 2.9) and a 1.3 (95% CI: -0.2, 2.9) point increased improvement in the *metabolic/colitis* and the *heart/prostate* patterns, respectively, compared to the *unspecific* pattern, although the pattern-intervention group interaction was not significant. Finally, the difference between intervention groups concerning QoL was significant for all patterns, and especially high for the *psychiatric/ cardio/autoimmune* pattern, but between-pattern differences were not significant.

Discussion

The findings of this study showed that the effectiveness of an individualized multicomponent exercise program in geriatric hospitalized adults varied depending on the underlying multimorbidity patterns older adults were suffering from.

There is no consistent evidence on the epidemiology of multimorbidity patterns in hospitalized elderly people. Most previous studies on multimorbidity and hospital care use have assessed multimorbidity as the mere count of chronic diseases,[2] but very few have looked at the grouping of diseases into multimorbidity patterns. In a previous systematic review, despite the methodological variability among studies, relevant similarities were seen for three groups of patterns.[38] The first one comprised a combination of cardiovascular and metabolic diseases, the second one was related with mental health problems, and the third one with musculoskeletal disorders. The few studies that have looked at multimorbidity patterns in hospitalized older people have focused mainly on subjects aged 80 years or older.[39,40] In both studies, hospitalization and mortality were better predicted by clusters of conditions rather than by the presence or absence of specific conditions. Clerencia-Sierra et al used exploratory factor analysis for the identification of multimorbidity patterns among geriatric patients attended in an acute hospital setting, and they described four different patterns: cardiovascular, induced dependency, falls and osteoarticular.[41] The reasons for the observed discrepancies between different studies may be related to the high levels of complexity and frailty of this population, as well as to the differences in the sources of information.

In our study, the patients that seemed to benefit most from the exercise program were those belonging to the *metabolic diseases and colitis* pattern, for whom we saw the biggest improvements in their functional, cognitive and affective status. This disease pattern was strongly characterized by obesity and diabetes, well-known cardiovascular risk factors likely to trigger more complex multimorbidity phenotypes. Obesity in older adults is associated with loss of functional independence and diminished well-being, as well as with an increased risk of presenting with the cardiometabolic syndrome, a combination of metabolic abnormalities predictive of cardiovascular disease and mortality.[42,43] Still, obesity does not preclude the possibility to have a preserved muscle mass in old age, and obese patients could thus optimally respond to exercise interventions, although sarcopenic obesity can be a challenge when tailoring exercise interventions. There is evidence that the combination of weight loss and exercise provides greater improvements in physical function than either intervention alone,[44] although the evidence in hospitalized older adults is more limited. Furthermore, weight loss and exercise can also improve frailty in obese older adults.[45]

Patients presenting with multimorbidity characterized by *heart valves and prostate diseases* experienced an improvement of their functional and cognitive status, but to a lower extent than those within the *metabolic* pattern, except for the Barthel Index, for which improvements were comparable. This may be explained by the fact that the Barthel Index is a composite measure of multiple basic activities of daily living, compared to the greater specificity of measures such as the SPPB or handgrip strength. Of note, the impact of the intervention on specific outcomes depends on the sensitivity and specificity of the latter to change, as well as on their potential floor and ceiling effects.

Patients with a multimorbidity pattern characterized by *psychiatric, cardiovascular and autoimmune diseases* —where sleep disorders and depression were the most prevalent conditions— improved across most of the analyzed outcomes, but to a lower degree than the rest of the multimorbidity patterns, except for QoL, for which the improvement was higher, arguably due to the high impact of non-pharmacological interventions such as those linked to exercise in this type of patients.[46,47] In older adults, neuropsychiatric diseases, alone or in association, are prevalent and major determinants of functional decline,[6] which stresses the need for a proper management of mental illness among multimorbid patients in order to increase their well-being. Indeed, the coexistence of mental health conditions as well as socioeconomic deprivation in patients with physical multimorbidity have been shown to exacerbated the risk of unplanned hospital admissions, including admissions that are potentially preventable.[48]

This study's strengths include the fact that clinical data were obtained not only through self-report, but by additionally integrating data from hospital and primary care records, physical exams, and proxies such as relatives and nursing home staff, which reduces the risk of information bias. We also performed a comprehensive geriatric assessment including functional, cognitive and affective evaluations, which enabled us to cover outcomes from multiple dimensions. Studies that incorporate multimorbidity patterns and function as coexisting and interacting modulators and/or outcomes are scarce, but the integrated assessment of both entities should remain the basis of the overall clinical decision-making process,

allowing physicians to more easily weight intervention benefits and risks, and patients to make properly informed choices.[49]

Nonetheless, there are limitations to consider. The study may have been sub-optimally powered to assess differences in the outcomes of interest by subgroups of the exposure (i.e., multimorbidity patterns), which could have veiled the statistical significance of several associations. Nevertheless, observed average differences were of potential clinical significance. Selection bias may have been introduced as all patients were hospitalized and our results can only be extrapolated to the study area population. Moreover, given the high prevalence of cognitive impairment not only among patients but often also among proxies, some information bias could have occurred. This was addressed by checking the electronic medical records of every patient. Given the complex and dynamic nature of multimorbidity in older adults, it is possible that participants' multimorbidity patterns changed after a sentinel event like a hospitalization. This limitation could have been mitigated by increasing the frequency of data collection, which would have enabled capturing day-to-day variations in symptoms and function.

The relationship between multimorbidity and exercise-induced modifications after an individualized program has not been studied previously. Understanding how different multimorbidity patterns are associated with specific functional, cognitive and affective responses may allow us to elaborate specific or tailored programs for each clinical situation, integrating clinical and functional aspects and, eventually, increasing the efficiency of healthcare systems. An enhanced understanding of the features of older multimorbid patients at high risk for developing nosocomial disability can allow public health authorities to target interventions and plan health resources accordingly, and has important implications for research and clinical management.

Conclusions

Different multimorbidity patterns differently predisposed older people admitted to an acute care ward to effectively respond to a multicomponent exercise program. Patients in all the analyzed multimorbidity patterns improved with this tailored program, but the improvement for those in the *metabolic* pattern was highest. The findings of the present study can help clinicians to better identify those patients who could benefit most from specific exercise interventions in order to prevent functional and cognitive decline during the hospitalization of older adults. At the same time, our findings highlight the need to identify more effective exercise programs for patients presenting with specific multimorbidity patterns as, for example, the pattern characterized by psychiatric, cardiovascular and autoimmune diseases.

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Appendix 1: Validation indices for the selection of the optimal number of patterns of multimorbity

Since clustering algorithms are unsupervised techniques, the model fitting is traditionally computed through cost functions that depend on both the dataset and the clustering parameters, and are denoted as validation indices. Different well-known validation indices were computed to obtain the optimal value of the fuzziness parameter m and the optimal number of clusters K. The following indices were computed and assessed: Fukuyama index, Xie-Beni index, Partition coefficient index, Partition entropy index, Calinski-Harabasz index (eRepo - Cluster validity in clustering methods. Accessed September 5, 2022. https://erepo.uef.fi/handle/123456789/109571).

The number of clusters is determined by identifying knee points (i.e. drastic changes) across the validity index values for different degrees of fuzzification m=1.1,1.2,1.4,1.5,2,4 and number of clusters K=2,..,20. Depending on the index, minimum or maximum validity index values are preferred. However, it is possible that the validity index has several local minimum or maximum points. Thus, knee point detection methods for determining the number of clusters need to rely on different indices. The decision rules for finding a knee point for each index included in our study were:

Minimum value for the Fukuyama index
Minimum value for the Xie-Beni index
Maximum value for the Partition coefficient index
Minimum value for the Partition entropy index
Maximum value for the Calinski-Harabasz index

Based on the graphs obtained for these 5 indices, m=1.1 fuzziness parameter and K=4 number of clusters were selected.
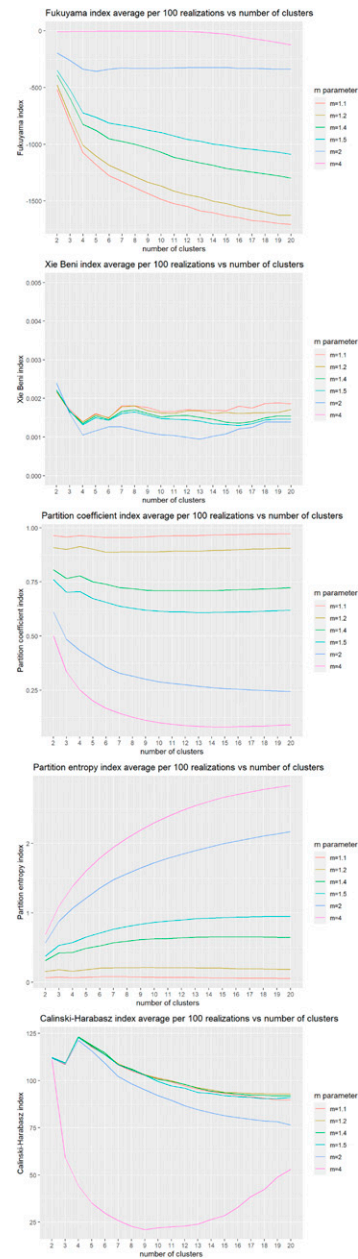
Appendix 2: Distribution of each multimorbidity pattern across intervention groups

Multimorbidity pattern	Control group	Intervention group
Unspecific	59 (62.7%)	53 (47.3%)
Heart/Prostate	37 (45.1%)	45 (54.9%)
Metabolic/Colitis	27 (42.9%)	36 (57.1%)
Psych/cardio/autoinm	31 (63.3%)	18 (36.7%)