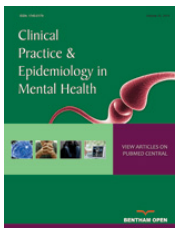

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RESEARCH ARTICLE

Moderate Exercise Improves Cognitive Function in Healthy Elderly People: Results of a Randomized Controlled Trial

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Abstract:

Background:

Physical activity in the elderly is recommended by international guidelines to protect against cognitive decline and functional impairment.

Objective:

This Randomized Controlled Trial (RCT) was set up to verify whether medium-intensity physical activity in elderly people living in the community is effective in improving cognitive performance.

Design:

RCT with parallel and balanced large groups.

Setting:

Academic university hospital and Olympic gyms.

Subjects:

People aged 65 years old and older of both genders living at home holding a medical certificate for suitability in non-competitive physical activity.

Methods:

Participants were randomized to a 12-week, 3 sessions per week moderate physical activity program or to a control condition focused on cultural and recreational activities in groups of the same size and timing as the active intervention group. The active phase integrated a mixture of aerobic and anaerobic exercises, including drills of “life movements”, strength and balance. The primary outcome was: any change in Addenbrooke's Cognitive Examination Revised (ACE-R) and its subscales.

Results:

At the end of the trial, 52 people completed the active intervention, and 53 people completed the control condition. People in the active

intervention improved on the ACE-R (ANOVA: F(1;102)=4.32, p=0.040), and also showed better performances on the memory (F(1;102)=5.40 p=0.022) and visual-space skills subscales of the ACE-R (F(1;102)=4.09 p=0.046).

Conclusion:

A moderate-intensity exercise administered for a relatively short period of 12 weeks is capable of improving cognitive performance in a sample of elderly people who live independently in their homes.

Clinical Trials Registration No: NCT03858114

Keywords: Aging, Physical activity, Quality of life, RCT, Cognition, Dementia.

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1. INTRODUCTION

Physical activity in the elderly is recommended by several national and international guidelines as a health determinant and preventive factor against cognitive decline and functional limitations [1 - 3]. Indeed, there is evidence that regular physical activity in the elderly is associated with better cognitive function [4 - 6] and may improve cognition even in people with dementia [7]; conversely, physical inactivity represents a risk factor for dementia [8]. There is also some evidence that physical activity may exert neuroprotective effects by bolstering the cardiovascular and immune and metabolic systems, which might be especially important in cardiovascularly-based degenerative conditions [8 - 12].

However, a recent systematic review has pointed out that despite the consensus on potential effectiveness, the evidence about which exercise characteristics (type, intensity, duration, and frequency) are more effective remains fragmented. This heterogeneity makes the results inconsistent [13]. Moreover, most of the studies that were included in the recent meta-analyses showed a strong imbalance in the sample size of the experimental groups (generally larger) towards the control groups (generally smaller) and a strong inhomogeneity in the methods of the control groups (with or without placebo or with different types of placebo) [13]. Overall, there is scarce evidence that exercise might decrease the incidence of cognitive impairment [13]. Nevertheless, there is some evidence, based on more permissive criteria of inclusion and outcome, that exercise may produce beneficial effects for both physical and cognitive functions in the elderly [14].

The literature on the effects of exercise or physical activity in the elderly remains controversial about the definition of practical standards about duration and type of exercises, their level of intensity, and the method and the setting of administration. Most trials focus on high-intensity exercises, which, although useful for defining the effectiveness of the intervention [15], are difficult to translate into practical use for the potential beneficiaries. Indeed, elderly people living in the community are often affected by mild pathologies such as hypertension and diabetes that limit the recourse to high-intensity training. A recent review described studies that required participants to exercise from up to 3 times a week to more than 5 times a week [13]. In everyday life, people rarely exercise more than three times a week, especially if they have mild physical ailments like many elderly people, even if they are autonomous. In the preventive field, higher power studies are needed because the outcome indicators are rare, like the new (incident) cases, and then the expected differences between groups are less marked; as a consequence, the meta-analysis coming from a large heterogeneity of trials show inconsistent findings [13, 16, 17].

There is no hard proof that a medium-intensity activity practicable by elderly people living independently in the community may be effective on the cognitive decline [13]. However, a prototype usable by the elderly in the community with evidence of being safe and effective will be the one that would have the greatest impact in contrasting the loss of autonomy and cognitive decline. The intervention on healthy elderly people still capable of autonomous life could, in fact, drastically affect the numbers of people with cognitive decline and delay the institutionalization of the elderly in protected structures for people with disabilities.

The objective of this study was to verify, through a randomized-controlled study with parallel and balanced large groups, whether a medium-intensity physical activity that can be enjoyed by elderly people living in the community, even with mild chronic diseases, is effective in improving their cognitive performance.

2. METHODS

The study is a 12 weeks Randomized Controlled Trial (RCT). The detailed protocol of the study, including the CONSORT flow diagram, has been published elsewhere [17].

2.1. Design

Participants (N=120) were assigned by randomization to either an active interventional protocol based on physical activity (N=60) or to a control intervention (N=60), with the same commitment of time and the same level of social exchange as the experimental intervention and based on group activities focused on the history of local culture and education to wellness. All participants were assessed in the pre-treatment period and at the end of the trial. The pre-treatment period consists of two-week without intervention in which participants have been assessed about physical, medical, and psychological conditions and received a large amount of information about the study in order to reach a fully disclosed informed consent

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to participate. After inclusion in the study, the participants have received a 12-week active intervention or the control intervention. Health-trained staff supervised interventions. They were both occupational therapist and staff with a degree in rehabilitation educator. Two psychologists also provided support and supervision for the patients.

Randomization was carried out at the "Centro di Psichiatria di Consultazione e Psicosomatica" of the University Hospital San Giovanni di Dio, Cagliari, after the pre-assessment of participants. Randomization was computerized and was concealed. The researchers who carried out the procedure were blind to the identities of participants. Randomization was conducted by blocks with a 1:1 rate; codes were masked.

The participants were blind about which intervention (exercise or cultural and well-being activities) was expected to be the active one. Research evaluators were blind about which intervention (active or the control) each participant was assigned. The researchers and staff involved in the administration of the activity or the control intervention were blind about the cognitive status of the participants.

2.2. Setting

The Assessment has been carried out at "Centro di Psichiatria di Consultazione e Psicosomatica" of the University Hospital San Giovanni di Dio, Cagliari, with the collaboration of the Department of Medical Science and Public Health of the University of Cagliari (Psychological and Medical Assessment). The active intervention was conducted in 4 gyms of the Italian Olympic Committee (Comitato Olimpico Nazionale Italiano – CONI) with experience in previous studies in collaboration with the same group of University of Cagliari [14]. The control intervention was delivered in 8 historical and cultural sites of the City of Cagliari with the collaboration of the Municipality of Cagliari.

2.3. Participants and Recruitment

The study sample includes people aged 65 years old and older of both genders living at home. The sample was recruited through public notices, the Italian Olympic Committee (CONI) contributed to recruitment through radio, TV, newspapers advertising. People interested in participating should have contacted a telephone number dedicated to their general practitioners. To be eligible for the trial, each participant was requested to provide a medical certificate for suitability in non-competitive physical activity.

Exclusion criteria were: BMI> 35; unsuitability for moderate physical activity due to any medical condition after medical examination; the presence of organic brain disease; to be already involved in a program of physical exercise equal or superior to the 70% of the expected level physical activity of the intervention study.

2.4. Study Tool

The cognitive performance of each participant was measured through the Italian version of Addenbrooke's Cognitive Examination Revised (ACE-R) [18]. The ACE-R is a well internationally known short cognitive test, which allows measuring the whole performance cognition and detailing it into five sub-domains (attention, memory, verbal fluency, language, visual-spatial skills) [19, 20]. The ACE-R is used to identify moderate cognitive impairment in the elderly and to discriminate cognitively normal persons from people with mild dementia [21]. Scores on the ACE-R range from 0 to 100, with higher scores indicating better cognitive function. In the Italian validation study, a score of 60 was the best cut-off to differentiate elderly with mild cognitive impairment from cognitively intact peers [18].

2.5. Interventions

Active intervention. Physical exercise activity was delivered in 3 sessions per week. Physical activity was fixed at 40-59% of the Heart Rate Reserve (HRR). HRR was monitored continuously during activity and transmitted by a telemetry system to the professionals. The individual HRR for each participant was assessed according to the Estimated Maximal Heart Rate Formula. The mean of three days of Baseline HR was registered for each participant. The intervention was delivered in three phases: 1) warm-up, which lasted 10-min, reaching 49% of HRR; 2) active phase, which lasted 45-min, reaching 60-84% HRR; 3) cool down, which lasted 10-min, reaching maximum less than 49% HRR [22]. The active phase integrated a mixture of aerobic and anaerobic exercises, including drills of "life movements", strength and balance.

2.6. Control Intervention

The control intervention consisted of cultural and education to wellness activities. People in groups of the same number of people of the groups in gyms (15-20 people) and in the same amount of time of active intervention reviewed the history of some local cultural sites of the town with the presentation of an "animator" (with a degree of educator on rehabilitation) and received wellness advice.

2.7. Ethical Iissues

The project coordinator was responsible for dealing with any adverse issues or events during the trial. Each patient at the end of the whole trial had the opportunity to receive clarification about testing and have feedback and explanation on treatment and results. No health conditions emerged during the trial that might have precluded participation in the trial. All participants were insured through a trusted insurance company (name omitted for privacy). The trial was conducted according to the Declaration of Helsinki and its revisions [23]. The Regional Committee for Medical and Health Research Ethics, region Sardinia, has approved the study with reference number PG/2018/15546 (approved on 25 October 2018). The study (Active Elderly and Health) has been registered in the ClinicalTrials.gov site with number code NCT03858114.

2.8. Statistical Analysis

All tests were two-tailed, with alpha set at $p<0.05$. Means with standard deviations were reported for continuous variables. Counts and percentages were reported for categorical variables. Continuous variables were tested with Student's t-test or ANOVA. Categorical analyses were carried out with the chi-

square, along with Yates correction, whenever necessary. As for the main outcome, the results on the ACE-R were compared in the experimental group and the control group as mean scores (± standard deviation) on the overall scale and the subscales before and after the trial (T0 and T1). Statistical analysis was conducted by means of the analysis of variance (ANOVA) for repeated measures.

3. RESULTS

At the end of the trial, after 12 weeks, 52 people (87%) completed the active intervention versus 53 people (88%) in the control group. The two samples did not differ by gender, age, or education (Table **1**).

Table 1. Characteristics of the sample at the end of the trial.

-	Active group	Control group	Statistics
	N = 52	N = 53	
Gender Men Women	23 (44%) 29 (56%)	19 (36%) 34 (64%)	χ^2=0.77, p=0.381
Age	71.8 (4.7)	72.7 (4.7)	F(1;103)=0.76, p=0.385
Years of education	14.1 (4.6)	12.7 (4.9)	F(1;103)=2.27, p=0.124

Data: counts (%) or mean (standard deviation).

The intervention group had a statistically significant improvement on the ACE-R total score, improving from 90.1 (SD= 5.5) at the baseline to 92.5 (6.0) at the end of treatment: F(1;102)=4.32, p=0.040.

People in the control group didn't show an increment of their cognitive performances in the ACE-R from baseline (89.3 [6.6]) to the end of their intervention (90.1[6.8]): F(1;104)=1.64, p=0.199.

The improvement in cognition, as measured by the ACE-R, was evident for the experimental group, especially in the memory and visual-spatial skills subdomains of the ACE-R (Table **2**).

The control group, instead, didn't improve on any of the subscales of the ACE-R (p>10 in all comparisons) (Table **2**).

4. DISCUSSION

Our study has shown that in a group of elderly people living in the community, a 12 week mild-moderate non-competitive physical activity suitable for elderly people, without excluding mild chronic pathologies such as hypertension and/or diabetes, can have positive effects on cognition. The improvement concerned the total score but also the specific subscales of memory and visual-spatial skills.

Our study was characterized by a shorter duration than most of the trials found in the literature. Indeed, among the studies of a recent systematic review that examined this parameter, 16% lasted up to 24 weeks, 46% between 25 and 52 weeks, 20% more than 53 weeks, and 16% of the studies didn't specify the duration of the trials [13]. Previous systematic reviews and meta-analyses about the effectiveness of physical exercise against cognitive decline in healthy elderly people, the most controversial results concerned short-term interventions, with some reviews concluding for efficacy [14, 24], and others for the lack of consistent evidence [13, 25]. For trials over 12 months of intervention, the data were more consistent in favor of efficacy [26].

Table 2. Differences by groups on ACE-R subscales.

-	Attention	Memory	Verbal fluency	Language	Visual-spatial skills
Active group (n=52) T0 T1 ANOVA	17.7 (2.3) 17.8 (0.4) F(1;102)=0.16 p=0.690	22.2 (3.5) 23.6 (2.9) **F(1;102)=5.40** **p=0.022**	10.4 (1.7) 10.5 (1.9) F(1;102)=0.03 p=0.866	25.1 (0.9) 25.3 (1.4) F(1;102)=0.52 p=0.473	14.6 (1.3) 15.2 (1.4) **F(1;102)=4.09** **p=0.046**
Control group (N=53) T0 T1 ANOVA	17.4 (1.1) 17.6 (0.9) F(1;104)=0.86 p=0.356	21.5 (4.1) 22.5 (4.0) F(1;104)=1.66 p=0.200	10.9 (1.8) 10.3 (3.0) F(1;104)=0.89 p=0.348	25.1 (1.2) 24.9 (2.1) F(1;104)=0.73 p=0.395	14.5 (1.6) 14.5 (1.8) F(1;104)=0.001 p=0.999

Data: mean (standard deviation); statistically significant results are in bold.

Our research has adopted a test on cognitive performance specifically created to detect early slight cognitive changes, therefore specifically suitable for this type of investigation. Most researches so far had employed, in a prevention setting and with samples of healthy people, screening tools that were not capable of identifying early and fine changes in cognitive performance [27 - 29]. The more accurate cognitive tests used in the clinic, which require very long administration times, cannot be applied in studies on large samples of healthy people without the risk of a great loss at follow-up. Indeed our study showed a low follow-up loss rate compared with other similar trials.

A past systematic review and meta-analysis found exercise was effective when provided in group sessions [30]. The present study confirmed the effectiveness of group sessions in delivering physical activity programs. However, these effects do not depend on the social dimension of the activities in a group since the involvement in a control group without physical activity did not improve cognitive performance.

Some limitations have to be taken into account. The sample size was quite large for similar studies but not large enough to allow a multivariate analysis of the outcome determinants. However, the sample was well balanced for the main known confounding factors (age, gender, educational level). Moreover, the short duration of the trial, although useful to confirm the effectiveness of a short-term intervention, implies a potential loss of statistical power for effects that require more time to be evident.

CONCLUSION

In conclusion, this study has shown that a moderate-intensity exercise administered for a relatively short period of 12 weeks is associated with the improvement of cognitive performance in a sample of elderly people who live independently at their home

The medical certification necessary to support such a non-competitive physical activity did not exclude the presence of mild chronic pathologies, among those very frequent in the elderly, such as hypertension and diabetes. This makes the results of this study relevant in terms of public health,

especially for those states, such as European countries, where life expectancy has increased. However, the proportion of older people with cognitive disabilities has also increased [31, 32]. This problem implies an immense suffering of people and families as well as high social and health costs [31]. For this reason, European Union has indicated research on active aging as a priority [33]. The possibility of the systematic use of a preventive, simple, and easily applicable intervention could positively impact these aspects.

KEY POINTS

Physical activity in the elderly is recommended to protect against cognitive decline.

Past studies varied widely in terms of type, intensity, duration, and frequency of provided physical activity.

A 12-week, 3 sessions per week moderate physical activity program improved cognition in elderly people living in the community.

These effects were not seen in a control group involved in cultural and education to wellness activities.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Regional Committee for Medical and Health Research Ethics, region Sardinia, has approved the study with reference number PG/2018/15546 (approved on 25 October 2018).

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from the participants.

AVAILABILITY OF DATA AND MATERIALS

Data will be available on ClinicalTrials.gov site with number code NCT03858114.

FUNDING

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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The authors wish to dedicate the study to the memory of Gianfranco Fara, former president of CONI Sardinia, who was an active supporter of the research and supported us in this work until his sudden death.

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