Research Article

Effects of a multimodal exercise protocol on functional outcomes, epigenetic modulation and brain-derived neurotrophic factor levels in institutionalized older adults: a quasi-experimental pilot study

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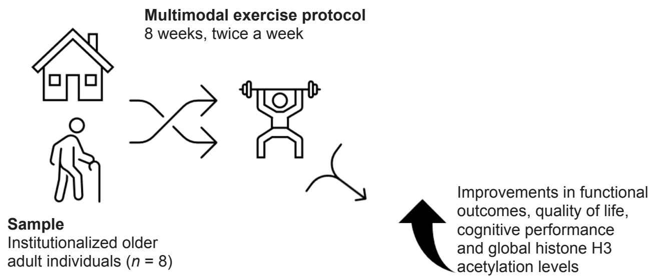
Graphical Abstract *A multimodal exercise protocol improves functional outcomes, quality of life and cognitive performance and increases global histone H3 acetylation levels*



Abstract

Epigenetic changes have been shown to be associated with both aging process and aging-related diseases. There is evidence regarding the benefits of physical activity on the functionality, cognition, and quality of life of institutionalized older adults, however, the molecular mechanisms involved are not elucidated. The purpose of this pilot study was to investigate the effects of a multimodal exercise intervention on functional outcomes, cognitive performance, quality of life (QOL), epigenetic markers and brain-derived neurotrophic factor (BDNF) levels among institutionalized older adult individuals. Participants (n = 8) without dementia who were aged 73.38 ± 11.28 years and predominantly female (87.5%) were included in this quasi-experimental pilot study. A multimodal exercise protocol (cardiovascular capacity, strength, balance/agility and flexibility, perception and cognition) consisted of twice weekly sessions (60 minutes each) over 8 weeks. Balance (Berg Scale), mobility (Timed Up and Go test), functional capacity (Six-Minute Walk test), cognitive function (Mini-Mental State Examination) and QOL (the World Health Organization Quality of Life-BREF Scale questionnaire) were evaluated before and after the intervention. Blood sample (15 mL) was also collected before and after intervention for analysis of biomarkers global histone H3 acetylation and brain-derived neurotrophic factor levels. Significant improvements were observed in cognitive function, balance, mobility, functional capacity and QOL after the intervention. In addition, a tendency toward an increase in global histone H3 acetylation levels was observed, while brain-derived neurotrophic factor level remained unchanged. This study provided evidence that an 8-week multimodal exercise protocol has a significant effect on ameliorating functional outcomes and QOL in institutionalized older adult individuals. In addition, it was also able to promote cognitive improvement, which seems to be partially related to histone hyperacetylation status. The Ethics Research Committee of Centro Universitário Metodista-IPA, Brazil approved the current study on June 6, 2019 (approval No. 3.376.078).

Key Words: aging; balance; brain-derived neurotrophic factor; cognition; epigenetics; physical exercise; quality of life; risk of falling

Chinese Library Classification No. R493; R364; R741

Introduction

In developing countries, a remarkable increase in the prevalence of older adults has been observed in the last years (Mathus-Vliegen, 2012). In fact, it is estimated that the elderly population will compose approximately 22% of the world's population by 2050 due to the increase in life expectancy (Scully, 2012). These data require attention, since the aging process is associated with a progressive loss of physiological

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and psychological functions that lead to inevitable disabilities that contribute to functional dependency and consequently lead to institutionalization (Sampaio et al., 2020).

In this sense, changes in cognitive abilities are very common, contributing to the increase in the incidence of neurodegenerative diseases (Bherer, 2015; Vedovelli et al., 2017). Emerging evidence exists that age-related cognitive deficits are related, at least in part, to decreased levels of brain-derived neurotrophic factor (BDNF) (Lommatzsch et al., 2005; Gunstad et al., 2008). BDNF is a neurotrophin known to exert a pivotal role on neuronal growth and is critical for learning-related synaptic plasticity and memory processes (Bathina and Das, 2015; Santos et al., 2016). Importantly, the levels of peripheral and central BDNF seem to be correlated (O'Bryant et al., 2011).

In addition, it was proposed that the imbalance in histone acetylation homeostasis, an important epigenetic marker, may contribute to the aged-related decline of brain functions and neurodegenerative conditions (Saha and Pahan, 2006; Lovatel et al., 2013). In this context, decreased histone H4 acetylation levels were observed in neurons from the hippocampi and cortices of old mice (Walker et al., 2013). Accordingly, Lovatel et al. (2013) showed that aged rats presented reduced levels of global histone H4 acetylation in the hippocampi in association with aversive memory impairment. On the other hand, some lines of evidence have reported that enhancements in histone acetylation levels induced a significant augment in BDNF levels (Fuchikami et al., 2010). Therefore, it is plausible to suppose that strategies that can modulate BDNF levels and histone acetylation status might be considered efficient to improve brain functions in older adult people.

Furthermore, it is known that all health-related components of physical fitness seem to be compromised in these individuals (Bherer, 2015). Specifically, significant reductions in cardiorespiratory and muscular endurance, muscular strength and flexibility and in body composition have been observed (Pisan et al., 2013). In this sense, sarcopenia is the syndrome characterized by the gradual loss of strength and muscle mass, which is highly prevalent among the older adults (Cruz-Jentoft et al., 2010; Beaudart et al., 2017).

These cognitive and functional changes can predispose the older adults to falls and fractures, which negatively affect their capability to execute activities of daily living and compromise their quality of life (QOL) (Bherer, 2015; Hsu, 2015). Contrarily, physical exercise has been highlighted as a promising non-pharmacological tool that not only prevents but also reduces age-associated deficits (Garber et al., 2011; Alfieri et al., 2012; Law et al., 2014).

Among the several available protocols, multimodal interventions that combine cognitive training and exercise have demonstrated additional effects compared to other protocols and seem to be effective in ameliorating cognitive performance and functional outcomes, such as balance, functional mobility and gait speed in healthy and sedentary older adults living in community-dwelling or institutionalized with normal cognitive status or with cognitive decline (Law et al., 2014; Both et al., 2016; Marmeleira et al., 2017; Pereira et al., 2017). In fact, some research groups have observed the effectiveness of these protocols in long-term care facilities for healthy older adults or older adults with cognitive impairment (Eggenberger et al., 2015; Marmeleira et al., 2017). The molecular mechanisms linked to these responses still need to be further investigated.

In this context, it has been demonstrated that several physical exercise programmes can improve physical/mental health and brain functions in different populations through the modulation of epigenetic markers and BDNF levels (da Silva et al., 2017; Lavratti et al., 2017; Korb et al., 2018), suggesting that this issue should be investigated in institutionalized older adults.

Then, our goal was to investigate the effect of a multimodal exercise protocol on 1) functional outcomes, such as balance, mobility and functional capacity; 2) cognitive performance; 3) QoL; and 4) the modulation of global histone H3 acetylation and BDNF levels in institutionalized older adults.

Participants and Methods

Participants

The convenience sample included institutionalized older adults living in a long-term facility in Porto Alegre City, south of Brazil. Participants did not receive any form of financial incentive to participate in the survey. Data collection took place from July to August, 2019. The study included individuals aged ≥ 60 years and with ability to walk without using an orthoses. Exclusion criteria were determined as having cognitive impairment (Mini Mental State Examination ≤ 24), using HDAC inhibitor drugs, presence of neurological diseases, orthopedic and/or musculoskeletal problems affecting gait, inability to communicate with researchers or not having medical clearance to perform physical activity (**Figure 1**).

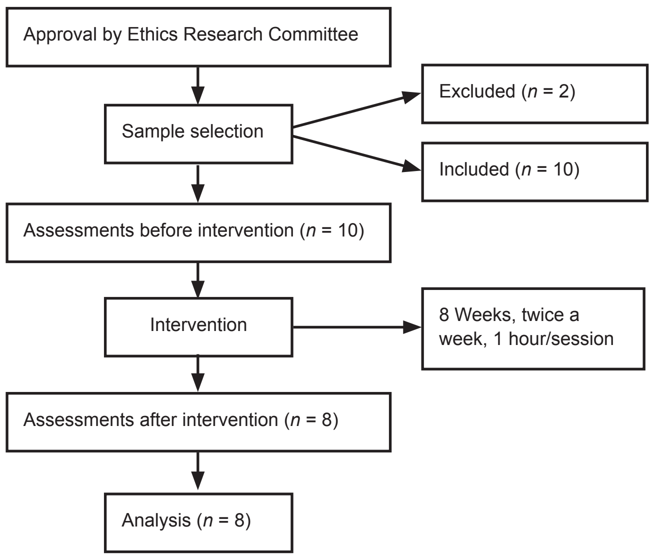

Figure 1 | Study procedures.

The Ethics Research Committee of Centro Universitário Metodista-IPA, Brazil approved the current study on June 6, 2019 (approval No. 3.376.078; **Additional file 1**) and it was also registered in the Brazilian Registry of Clinical Trials-ReBEC (registration number: RBR-2qkx69). All participants signed written informed consent before enrolment (**Additional file 2**) and all procedures were in conformity with the *Declaration of Helsinki*.

Study design

This is a quasi-experimental pilot study, and participants served as their own controls. They were submitted to a multimodal exercise protocol (in a group, during 8 weeks, twice weekly, 60 minutes each session), and during this period, they were not engaged in any other type of physical exercise programme.

The functional outcomes and cognitive performance measures were assessed before the beginning of the intervention and at the end of the intervention. To avoid learning effects, the participants were not well-known with the tests that were selected. For the biomarker measurements, participants were submitted to blood collections pre- and post-intervention.

Importantly, the exercise regimen functional tests and blood collections were performed at the same time (2 p.m.–4 p.m.). A blinded researcher to the study measured the analyses.

Physical training protocol

The multimodal protocol used in the current study was based on a previous study (Marmeleira et al., 2018). Specifically, each session was divided into the four following moments: 1) warm-up (5 minutes), with stretching and active upper/lower limb exercises; 2) exercises focused on cardiovascular capacity, strength, balance/agility and flexibility (25 minutes), which included walking, stationary gait, resistance exercises for the main upper/lower muscle groups, unipodal support with open/closed arms over the chest, anterior/lateral inclination and static stretches; 3) exercises focused on perception and cognition (such as double-task), attention, memory and processing of requested actions (25 minutes), such as walking and naming fruit/color names, completing previously established circuits, attending to requested verbal commands and memorizing motor/verbal signals; and 4) relaxation and breathing techniques (5 minutes). A schematic drawing of the protocol is shown in **Figure 2**.

Anthropometric data measurement

Body weight was assessed using a digital scale (G-Tech Glass®, Brazil). Height was measured with a maximum 3 m pocket stadiometer with 0.5 cm precision (Cescorf®, Brazil). The participant was instructed to maintain an upright vertical position, with his/her feet parallel and his/her head positioned in the Frankfurt plane.

The body mass index (BMI) was measured using the formula BMI = weight (kg)/height (m)^2, and the parameters were based on data from the World Health Organization (1995). The classification of nutritional status was based on the parameters proposed by Lipschitz (1994) for adults and the older adults.

Functional outcomes assessments

Balance

The Berg Balance Scale (BBS) (Miyamoto et al., 2004) was used to evaluate balance and risk of falls. This instrument is composed of 14 tests and dependent of the score, the risk of falls is determined: scores < 45 indicate a low to moderate risk of falls while scores < 36 are related with a 100% risk of falls.

Mobility

The Timed Up and Go (TUG) test was performed to evaluate mobility. For this, individuals begin sitting, get up from a chair, walk for 3 m, turn around, return to the chair and sit again. Periods > 20 seconds to perform the test suggest functional dependence and increased risk for falls (Viccaro et al., 2011).

Functional capacity

The Six-Minute Walk test (SMW) was used to assess functional capacity. For that, a 30-meter-long thall was needed, in which demarcations were made on the floor every 3 m. In the hall, individuals were instructed to walk for 6 minutes the longest distance that they can. According to the time was passing, the volunteer was informed. When the test ended, the volunteer should stay still and wait to have measured vital signs (Enright, 2003).

Cognitive performance analysis

The Mini-Mental State Examination (MMSE) was used to assess changes in cognitive status, being applied by the evaluator in a private environment (Folstein et al., 1975).

The questions are grouped into seven categories and score can vary from 0 to 30 points, and the cut-off point is usually adjusted for educational level, which can be 24 for people with schooling over 9 years and 17 for people with less schooling.

QOL evaluation

To assess QOL, the WHOQOL-BREF questionnaire was used (Skevington et al., 2004). The participant had privacy to answer the questionnaire alone, and when necessary, the evaluator helped. This questionnaire consists of 26 items distributed in five domains (general, physical, psychological, social relations and environment), assessing QoL and health. The score for each item ranges from 1 to 5 (Likert type), with higher values related to better QoL, with the exception of items q3 (physical pain), q4 (treatment) and q26 (negative feelings), where it occurs in the reverse.

Sample preparation

A sample of venous blood (15 mL) was collected and separated in tubes with ethylenediamine tetraacetic acid for biomarker analysis. The procedures were previously described by Bicalho et al. (1981) and Dani et al. (2020). Briefly, the peripheral blood was used to acquire the peripheral blood mononuclear cells (PBMCs) for epigenetic analysis and plasma for BDNF measurements. The samples were aliquoted and frozen at –20°C.

Measurement of global H3 histone acetylation levels

H3 histone acetylation was determined using the commercial kit (Colorimetric Detection, Cat# P-4008 EpiGentek, Madrid, Spain) as previously reported by de Oliveira et al. (2020). The Coomassie Blue Method was used to express the protein concentration of each peripheral blood mononuclear cells samples (Bradford, 1976).

Determination of BDNF levels

Plasma BDNF levels were determined as previously described by Giacomet et al. (2019). The ELISA method from the Sigma–Aldrich commercial kit (Catalog number RAB0026) was used according to the manufacturer's instructions. The sample and BDNF-specific standards were added to an ELISA microplate and incubated for 2.5 hours at room temperature. Subsequently, the solutions were discarded and the same plate was washed four times with wash buffer (PBS, Tween 20 0.01%). Afterwards, the secondary antibody bound to biotin was added and incubated for 1 hour at room temperature with gentle agitation. The plate was again washed with wash buffer and streptavidin solution was added. The plate was incubated at room temperature for 45 minutes with gentle agitation. The solution was discarded and the plate went through the washing process. Tetramethylbenzidine (TMB) was added, and the solution was incubated for 30 minutes at room temperature in the dark with gentle agitation.

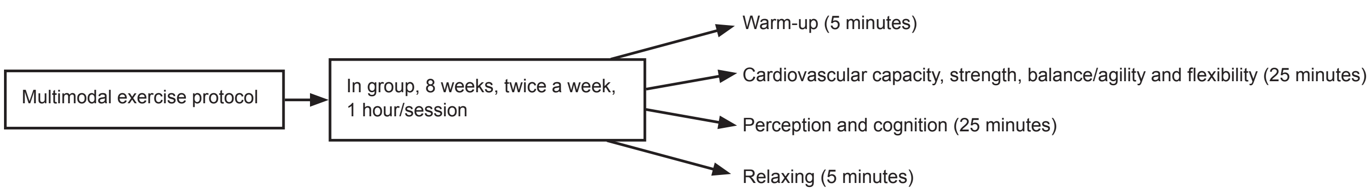

Figure 2 | Physical training protocol design.

The stop solution was added and the plate was read in a spectrophotometer at a wavelength of 450 nm. Plasma level of BDNF was expressed as ng/mL.

Statistical analysis

The normality of variables was tested with the Shapiro-Wilk test. For the pre- and post-intervention comparison, paired *t*-test was used. The SPSS 20.0 software (IBM, Armonk, NY, USA) was used for analysis and the significance level of 5% (P < 0.05) was considered.

Results

Participant characterization

Table 1 summarizes the characteristics of participants. The current study included 10 individuals; however, one individual declined to participate and one dropped out due to a stroke. As described in **Table 1**, the intervention did not alter anthropometric data, such as body mass and BMI.

Functionality, cognition and quality of life of participants

Table 1 | **Participant characteristics pre and post intervention**

	Before	After
Sex (female/male, %)	87.5/12.5	
Age (yr)	73.38±11.28	
Height (m)	1.57±0.07	
Prevalence of diseases [*n*(%)]		
Diabetes mellitus	2 (25.0)	
SAH	5 (62.5)	
Katz score [*n*(%)]		
Total independence	7 (87.5)	
Partial independence	1 (12.5)	
Body mass (kg)	69.08±13.29	70.01±13.21
BMI (kg/m^2)	27.82±4.92	28.17±4.79
Calf circumference (cm)	38.31±3.68	38.00±3.08

Data are presented as the mean ± standard deviation (numeric data) or relative frequency (categorical data). *n* = 8. BMI: Body mass index; SAH: systemic arterial hypertension.

Regarding the functional outcomes, the intervention was able to improve all variables (**Table 2**), since higher scores in the BBS (P < 0.05), SMW (P < 0.05) and TUG (P < 0.05) were observed. As described in **Table 2**, better cognitive performance (MMSE) after the intervention was also found (P < 0.05).

Table 2 | **Functional outcomes pre- and post-intervention**

	Before	After
TUG (s)	12.14±3.15	10.49±2.77*
SMW (m)	292.12±96.28	453.37±110.05*
BBS (score)	47.88±4.70	51.63±3.66*
MMSE (score)	18.25±5.06	20.50±6.02*

Data presented as the mean ± standard deviation (*n* = 8). **P* < 0.05, *vs*. pre-intervention (paired *t*-test). BBS: Berg Balance Scale; MMSE: Mini-Mental State Examination; SMW: Six-Minute Walk; TUG: Time Up and Go test.

The effect of the intervention on QOL is highlighted in **Table 3**. A significant improvement in the total score (P < 0.05) and in the domains of general health, psychological well-being and environment (P < 0.05) were observed.

Global histone H3 acetylation and BDNF levels of participants

Figure 3 illustrates the modulation of global histone H3 acetylation levels in response to the intervention, where the tendency toward an increase in global histone H3 level was found (P = 0.066). Finally, BDNF levels remained unaltered in response to the intervention (**Figure 4**).

Table 3 | **Quality of life pre-and post-intervention**

	Before	After
Total score	85.88±11.06	95.50±11.31*
General health	6.88±0.99	8.88±1.12*
Physical capacity	22.25±2.31	23.25±2.65
Psychological well-being	20.00±3.89	23.00±2.82*
Social relationships	8.63±2.82	9.25±3.80
Environment	28.13±3.68	31.00±4.78*

WHOQOL-BREF questionnaire was used to assess quality of life. Data are presented as the mean ± standard deviation (*n* = 8). **P* < 0.05, *vs*. pre-intervention (paired *t*-test). WHOQOL-BREF: The World Health Organization Quality of Life-BREF Scale.

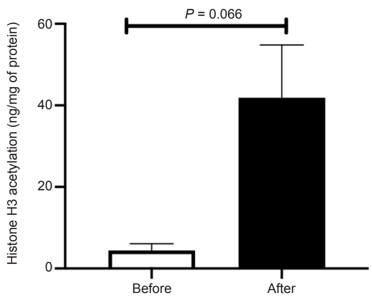

Figure 3 | **Effect of multimodal intervention on global histone H3 acetylation level in peripheral blood mononuclear cells from the institutionalized older adults.**

Data are expressed as the mean ± SD. Paired *t*-test was used to compare global histone H3 acetylation level between before and after intervention (*n* = 8).

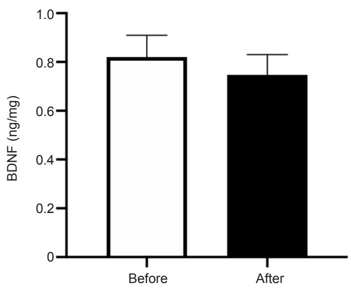

Figure 4 | **Effect of the multimodal intervention on BDNF levels in institutionalized older adults.**

Data are expressed as the mean ± SD. Paired *t*-test was used to compare BDNF level between before and after intervention (*n* = 8). BDNF: Brain-derived neurotrophic factor.

Discussion

It has been described that institutionalized older adults have sedentary habits, which can exacerbate the age-related decline in functional clinical status (Volkers et al., 2011). Therefore, strategies to attenuate this response, such as exercise interventions, might be relevant. In this sense, the current study provided evidence that an 8-week multimodal intervention induced significant improvements in physical-motor abilities and QOL in institutionalized older adults. In addition, the intervention was also able to promote better performance in cognitive function, which seems to be partially related to histone hyperacetylation status without changes in BDNF levels. Then, our data showed novel insights into the molecular mechanisms regarding the beneficial effects of multimodal exercise in this population.

Contrary to previous studies conducted with older adults submitted to physical activity protocols reporting improvements in anthropometric data (Bezerra et al., 2018; Bagheri et al., 2020; Rica et al., 2020), no alterations were found either in body mass or BMI after the intervention in the current study. Bezerra et al. (2018) observed important changes in body composition in older adult individuals submitted to an exercise protocol over 8 weeks (three times/week). Similarly, older adult women also showed altered body composition after a concurrent exercise programme over 8 weeks (three times/week). Altogether, these findings suggest that interventions with high frequency and duration can improve anthropometric variables in this population.

Deterioration of physical fitness and functional status, in general, represents high risk of frailty, physical disability and loss of independence among the older adults (Mänty et al., 2014). In agreement with other authors (Marmeleira et al., 2017), we provide evidence that it is possible to delay this tendency in response to exercise practice, since we observed better performance in mobility, functional capacity and balance in response to multimodal intervention.

It has been proposed that cognition exerts a pivotal role in the regulation and control of mobility (Montero-Odasso et al., 2015), since cognitive skills might positively impact the functional and physical abilities due to the increase in information speed velocity and decrease in the reaction time (Schaie, 2006). In fact, some researchers have also indicated a relationship between mobility and cognitive performance in institutionalized older adults (de Oliveira Silva et al., 2019). Accordingly, the intervention was able to positively impact cognitive performance in the current study, which appears to mediate, at least partially, the better functional/motor status results.

Another remarkable point to consider is the improvement in QOL observed after the intervention, a finding that is in line with growing evidence supporting the idea that functional ability and cognition are intrinsically connected with it, since QOL is related to more autonomy and better environmental interaction (Montero-Odasso et al., 2015; Ferrante et al., 2016). Furthermore, agility/dynamic balance seems to be a predictor of health-related QOL in institutionalized older adults (Davis et al., 2015).

This is an expected result, since interventions with physical exercise have shown to be beneficial in improving QOL in older adults, as well as higher levels of physical activity, which are associated with better QOL (Lok et al., 2017; Arrieta et al., 2018). In this sense, Kekäläinen et al. (2018) evaluated the effect of 9 months of resistance exercise training on QOL, using the WHOQOL-BREF questionnaire in healthy older adult individuals. The authors found significant improvements in the environment, psychological and physical domains after the intervention, corroborating our findings. Therefore, we might suggest that the enhancement in QOL observed is in response to different types of physical exercise programmes (e.g., resistance or multimodal) and that both shorter interventions, such as the protocol, used in the current study (3 months), as well as prolonged programmes, are effective in improving it.

In addition to assessing the effect of exercise on clinical outcomes, we also investigated the modulation of biomarkers to elucidate the molecular bases associated with these responses. In this context, experimental studies have revealed that increases in histone acetylation levels might be considered as the possible mechanism underlying exercise-induced memory improvement during the aging process (Lovatel et al., 2013; Cechinel et al., 2016; de Meireles et al., 2016, 2019). Besides that, PBMCs analysis has been shown to reflect epigenetic changes that can be also present in the brain (Gavin and Sharma, 2009), and the acetylation levels in PBMCs could be linked with brain injury and neurological dysfunction (Shen et al., 2014). Collectively, our results can be related to these authors, given that the intervention was able to significantly enhance global histone H3 acetylation levels in combination with the better response in cognitive performance.

To the best of our knowledge, this is the first study demonstrating the effect of exercise on epigenetic modulation in institutionalized older adults. This data is in agreement with several evidences highlighting the capacity of exercise in modulating the epigenome in different populations, which might be linked to the beneficial impact of its practice in several clinical outcomes (Dorneles et al., 2017; Lavratti et al., 2017; Korb et al., 2018).

Although increased expression of BDNF following exercise has been linked to histone hyperacetylation status (Elsner et al., 2011; Gomez Pinilla et al., 2011), as well as an exercise-mediated BDNF increase being associated with cognitive ability amelioration, no changes in this neurotrophin were found after the intervention in the current study. However, we cannot discard the involvement of epigenetic changes in regulating the expression of other genes associated with cognitive function, including Arc (activity-regulated cytoskeletal gene), zif268 (nerve growth factor inducible-A) and c-Fos, which undergo substantial changes during the aging process (de Meireles et al., 2019). Future studies should be developed to clarify this issue.

Contrary to our findings reporting the effect of an 8-week protocol, Vedovelli et al. (2017) demonstrated that a multimodal physical activity programme over 3 months was able to enhance BDNF levels in healthy older women. Besides, a multimodal physical exercise programme during 16 weeks was effective in reducing pro-inflammatory cytokines in combination with increased BDNF levels in older adult individuals with mild cognitive impairment (Nascimento et al., 2014). In this sense, higher levels of BDNF in response to long-term exercise have been previously reported (Lee et al., 2014). Collectively, these findings led us to presume that BDNF changes in response to multimodal exercise protocols in the older adults occur in a dose-dependent way, specifically demanding long-term designs to induce significant increases.

In addition, Lira et al. (2020) recently proposed that the volume of work performed by larger muscles might strictly influence BDNF levels augmentation. Then, we could infer that in the present study, the multimodal exercise protocol did not recruit the use of these muscles and therefore did not change BDNF levels.

Furthermore, it is important to consider that exercise-induced modifications in BDNF levels follow a hormetic curve (Ji et al., 2006). Specifically, it was demonstrated higher BDNF up-regulation at the beginning of exercise, which can decrease again to pre-exercise levels. In view of these considerations, it is recommended that future studies investigate the BDNF modulation in response to the proposed intervention at different time points in older adult individuals to elucidate this topic.

Finally, it is important to describe that the attendance of participants was highly considerable. Our data corroborate those obtained by Marmeleira et al. (2017), who also investigated the impact of a multimodal regimen in institutionalized older adults. In this context, it was previously reported that this kind of protocol, integrating diverse actions that target physical-motor and perceptive cognitive abilities, could increase the level of satisfaction and motivation among older adults, which might maximize the level of adherence (de Souto Barreto et al., 2016; Morley et al., 2016). In addition, it is important to note that both studies were characterized as supervised, structured and group-based interventions, supporting the idea that programmes with this profile might show successful results (Lavratti et al., 2017). In fact, regarding institutionalized older adults, physical training interventions carry out in group might be considered most appropriate, because they can contribute to reduce the social isolation usually linked to long-term care facilities (Molinari, 2002).

We believe that the preliminary findings could encourage future investigations to elucidate the precise epigenetic pathways involved in the exercise effects in institutionalized older adults. Future studies will analyse markers such as global histone H4 acetylation and DNA methylation levels as well as the expression of specific genes. The limitations of this study include short intervention time and small sample size. Furthermore, studies with a robust sample can help verify other issues within this theme including the influence of gender.

Conclusions

Our study demonstrated that an 8-week multimodal physical activity programme is an important strategy to attenuate and/or ameliorate the decline of functional status (such as functional capacity, mobility, balance) and QoL of institutionalized older adults. In addition, this intervention was able to promote cognitive improvement, which seems to be partially related to histone hyperacetylation status. Therefore, these findings reinforce the importance of encouraging and implementing multimodal physical activity programmes for this population.

Author contributions: *Study design: IF, ADB, VRE; statistical analysis: IF, CD, ADB, VRE; biomarker analysis: DP; manuscript preparation: IF, VRE; manuscript editing and review: IF, CW, WBG, LI, MW, GM, CC, JR, DP, CD and PM; data acquisition and exercise protocol intervention: IF, CW, WBG, LI, MW, GM, CC, JR. All authors approved the final version of this manuscript.*

Conflicts of interest: *The authors declare that they have no conflicts of interest.*

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Institutional review board statement: *The study was approved by the Centro Universitário Metodista-IPA committee on June 6, 2019 (approval No. 3.376.078).*

Declaration of participant consent: *The authors certify that they have obtained all appropriate participant consent forms. In the forms, the participants have given their consent for their images and other clinical information to be reported in the journal. The participants understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*

Reporting statement: *This study followed the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.*

Biostatistics statement: *The statistical methods of this study were reviewed by the biostatistician of Centro Universitário Metodista-IPA, Brasil.*

Data sharing statement: *Datasets analyzed during the current study are available from the corresponding author on reasonable request.*

Plagiarism check: *Checked twice by iThenticate.*

Peer review: *Externally peer reviewed.*

Additional files:

Additional file 1: *Ethical Approval Documentation (Portuguese).*

Additional file 2: *Model consent form (Portuguese).*

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