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Study Design

The ExCITE-BA Trial: Effects of physical activity plus behavioral activation on preserving cognitive function in elderly patients with mild cognitive impairment - protocol for a randomized, controlled, phase II, parallel, single-blinded, superiority trial

Enrico Stefano Suriano[1], Jolanta Golec[2], Bassel Almarie[3], Marta P. Wiącek[4], Erica R. R. Sady[5], Dauris Rosario[6], Andrés Felipe Herrera Ortiz[7–8], Alejandra Pedrero[9], Marcia Harumy Yoshikawa[10], Rodrigo Sacchi de Freitas-Santos[11–12], Abeir Alimam[13], Jordan Bistafa Liu[14], Basma Mohamed[15], Adriana do Nascimento Martins[16], Julián Orlando Casallas Barrera[17], Rebeca Andrea Mora Matus[18]

[1]Santa Casa de São Paulo Medical School. São Paulo, Brazil; [2]Harvard T. H. Chan School of Public Health. Massachusetts, USA; [3]Department of Surgery, Cantonal Hospital of St. Gallen. St. Gallen, Switzerland; [4]First Department of Ophthalmology, Pomeranian Medical University. Szczecin, Poland; [5]Research Institute, Hospital do Coração. São Paulo, Brazil; [6]Pontificia Universidad Católica Madre y Maestra, Facultad Ciencias de La Salud, Escuela de Medicina. Santiago de los Caballeros, República Dominicana; [7]Radiology, Fundación Santa Fe de Bogotá. Bogotá, Colombia; [8]Universidad El Bosque. Bogotá, Colombia; [9]Servicio de Medicina Física y Rehabilitación, Clínica Alemana de Santiago. Santiago, Chile; [10]University of São Paulo. São Paulo, Brazil; [11]Hospital Sírio-Libanês. São Paulo, Brazil; [12]Hospital Oswaldo Cruz. São Paulo, Brazil; [13]Infectious Diseases Division, Internal Medicine Department, Hamad Medical Corporation. Doha, Qatar; [14]Faculdade de Medicina de Marília. Marília, Brazil; [15]Department of Anesthesiology, College of Medicine, University of Florida. Gainesville, USA; [16]Núcleo de Pesquisa e Ensino da Rede São Camilo. São Paulo, Brazil; [17]Department of Intensive Care, Fundación Clínica Shaio. Bogotá, Colombia; [18]Medical Oncology, Oncology Medical Manager Pfizer Central America & Caribbean

**Correspondence: Enrico Stefano Suriano. enrico.suriano-2021@ppcr.org; Tel.: +55 11 98474-6464*

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ABSTRACT:

Introduction: World population has an increased risk of developing basic neurological deterioration and mild cognitive impairment (MCI). Currently, there is no cure or disease-modifying drug for MCI. Thus, non-pharmacological interventions such as physical activity (PA) and behavioral activation (BA) arise as potential treatment options. This study will assess if a program of combined PA and BA (PABA) reduces disease progression in patients over 60 years old with MCI.

Methods: This is a randomized, controlled, phase II, parallel, single-blinded, multicenter, superiority trial with two groups. In total, 184 patients will be randomized at a 1:1 ratio and stratified by age, center, and level of education via permuted block sizes to receive: 1) a combination of moderate-to-high intensity PABA or 2) sham intervention (low-intensity PA) plus psychological support (active control). The primary outcome will be a change in cognitive function assessed by Montreal Cognitive Assessment (MoCA) from baseline to 12 months. Secondary outcomes include changes in MoCA at 3, 6, and 9 months. Furthermore, at 0, 3, 6, 9, and 12 months, subjects will be tested with the Barthel Index, Short-Form 12 Health Survey (SF-12), and Geriatric Depression Scale (GDS-15).

Conclusion: The study aims to refine treatment options for MCI and uncover directions for different therapeutic approaches. This will be the first randomized clinical trial to establish the efficacy of PABA compared to active control in the progression of MCI. This study could optimize MCI treatment and help alleviate patients, families, and the healthcare system.

Keywords: Cognitive Impairment, Exercise, Physical Activity, Behavioral Activation, Study Protocol, Study Design

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Introduction

The number of individuals at advanced ages is increasing globally. Patients older than 65 have a greater risk of developing basic neurological deterioration, memory loss, and functionality-related disorders such as mild cognitive impairment (MCI) (Stanton, 2011). MCI was first defined in 1988 as an early stage of cognitive decline in individuals who maintain the ability to independently perform most activities of daily living (Reisberg et al., 1988) (Tangalos & Petersen, 2018). Symptoms related to MCI include memory loss, language problems, lower attention, problem-solving difficulties, and difficulties with planning or completing complex tasks (Petersen, 2016). Roughly 5-17% of patients with MCI progress to dementia annually (Jongsiriyanyong & Limpawattana, 2018), leading to further functional deficits, demanding assistance with at least one activity of daily living, and increasing costs and the likelihood of hospitalization (Horr et al., 2015).

Currently, there is no cure or disease-modifying drug for MCI. Thus, nonpharmaceutical interventions, such as physical activity (PA) and behavioral activation (BA), present potential treatment options (Horr et al., 2015). The beneficial effects of PA on cognition have been documented in several previous studies (Okumiya et al., 1996) (Satoh et al., 1995), although the results are inconsistent. Observational and experimental studies have suggested that exercise may be protective against Alzheimer's disease and dementia; however, there is not enough evidence regarding exercise's effect on patients with MCI (Karssemeijer et al., 2017). On the other hand, BA is a psychological intervention that has shown certain benefits for preventing cognitive decline (Rovner, 2018). BA focuses on how someone's environment shapes their actions and mental status by promoting a systematic approach to stimulate certain behaviors, increasing pleasure and meaning, replacing unhelpful behaviors, and improving relationships with positive emotional and mental states (Hopko et al., 2015). However, as promising as these approaches may be, no previous studies have evaluated the effects of PA and BA (PABA) on slowing disease progression in MCI (Tangalos & Petersen, 2018) (Jongsiriyanyong & Limpawattana, 2018). Therefore, this study will assess the combination of PABA as multimodal therapy for 12 months, seeking to reduce disease progression in elderly retired/unemployed patients aged over 60 years old with MCI when compared to active controls.

Materials and Methods

Trial Design

The ExCITE-BA trial will be a randomized, controlled, phase II, parallel, single-blinded, multicenter (general hospitals, universities, and community-based clinics specializing in senior health and/or geriatric care), superiority trial with two groups. In total, 184 patients will be randomized at a 1:1 ratio and stratified by age, center, and level of education via permuted block sizes to receive: 1) a combination of moderate-to-high intensity PABA or 2) sham intervention (low-intensity PA) plus psychological support (active control). The primary outcome will be a change in cognitive function assessed by Montreal Cognitive Assessment (MoCA) from baseline to 12 months. Secondary outcomes include changes in MoCA and other tests such as Barthel Index, Short-Form 12 Health Survey (SF-12), and Geriatric Depression Scale (GDS-15). This study's methodology will comply with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Randomization

Participants will be assigned to either group according to a 1:1 ratio. They will be stratified by age, center, and level of education via permuted block sizes (4 to 6 subjects per block) with randomly-generated treatment allocation via the http://www.randomization.com website, which is an IWRS (interactive web randomization system). Hired professionals from outside the trial will perform this process, and there will

be no disclosure of randomization assignments or block sizes to principal investigators, outcome assessors, or data analysts. To reduce predictability of the random allocation sequence, details of blocking will be provided to those hired professionals in a separate document and kept unavailable to professionals from inside the trial. All patients who consent to participate and fulfill the inclusion criteria will be randomized. Randomization will be requested by the staff member responsible for recruitment in each center.

Blinding

Outcome assessors and data analysts will be blinded. They will not be informed about the randomization sequence or group allocation. Patients will be asked not to reveal details of their interventions to outcome assessors. If participants experience the side effects of PA (such as muscle soreness), unblinded clinicians will be able to address these effects without unblinding outcome assessors or data analysts. In case of bone fractures or other potential health-threatening side effects of PA, discontinuation of the trial will be immediately implemented.

Participants

Patients over 60 years old, retired or unemployed, who live in their own homes (not at nursing homes) and are diagnosed with MCI (MoCA score between 18 and 25) will be included. Exclusion criteria will be: living in assisted-care facilities, using medications that may frequently alter cognitive function (risk higher than 20%, as listed in the medication's product label) and/or performing more than 150 minutes of moderate-intensity or 75 minutes of vigorous aerobic exercise, as recommended by the WHO for the elderly population (World Health Organization [WHO], 2010). Patients with an acute or chronic psychiatric disorder, primary or secondary brain tumors, recent cerebrovascular events (within the last 12 months), recent head trauma (within the last 12 months), or any comorbidities limiting their ability to engage in PA will be excluded. There will be no specific eligibility criteria for study centers.

Recruitment Strategy

Enrollment will rely on convenience sampling at general hospitals, universities, and community-based clinics specializing in senior health and/or geriatric care. Participants will be recruited through clinical services at the internal, family, and geriatric medicine services in local hospitals and in senior and nursing homes. Those who meet the inclusion criteria will be referred to the study research coordinator for informed consent and eligibility assessment. Eligible subjects will be invited to participate in the study. Potential subjects will be identified by the staff coordinator or one of the investigators at each site. Potential participants and their primary care partners will be contacted for an explanation of the project. Informed consent may be obtained by investigators or program coordinators. The diagnosis of MCI should not prevent patients from providing informed consent. However, all care partners will also provide consent.

The recruitment strategy will include: flyers in public institutes (senior houses and geriatric clinics), advertising through social media (Facebook and Instagram), searching in clinical trial registration sites, and direct contact via telephone (obtained from medical records).

Adherence

In order to improve and monitor adherence to the protocol, research teams will be trained to achieve an ethical but supportive relationship with participants. They will provide a flexible schedule for outcome assessment, timely reminders on the next PA and outcome assessment sessions. They will also compensate participants and caregivers for their time and effort (free meals, parking, and childcare), involve family members (by inviting them to join the BA intervention), and provide a heart rate monitor to encourage participants and control adherence (Bravata et al., 2007). Additionally, to assess participants' compliance with the PA program, a 1-month run-in phase will be performed before the actual study begins to identify which individuals are likely to drop out.

Timeline

The schedule for conducting the study, including timelines for key study milestones, is presented in **Figure 1**. This timeline will be a living document and will be updated throughout the project. The critical study milestones for data collection are set at 3, 6, 9, and 12 months. The planned time for recruitment is from 12 to 15 months. Data analysis is expected to take up to 1 month.

Interventions

Each recruitment center will have a coordinator responsible for distributing participants to their respective study arms. The intervention group will receive a combination of moderate-to-high intensity PA and BA, while the active control group will receive the

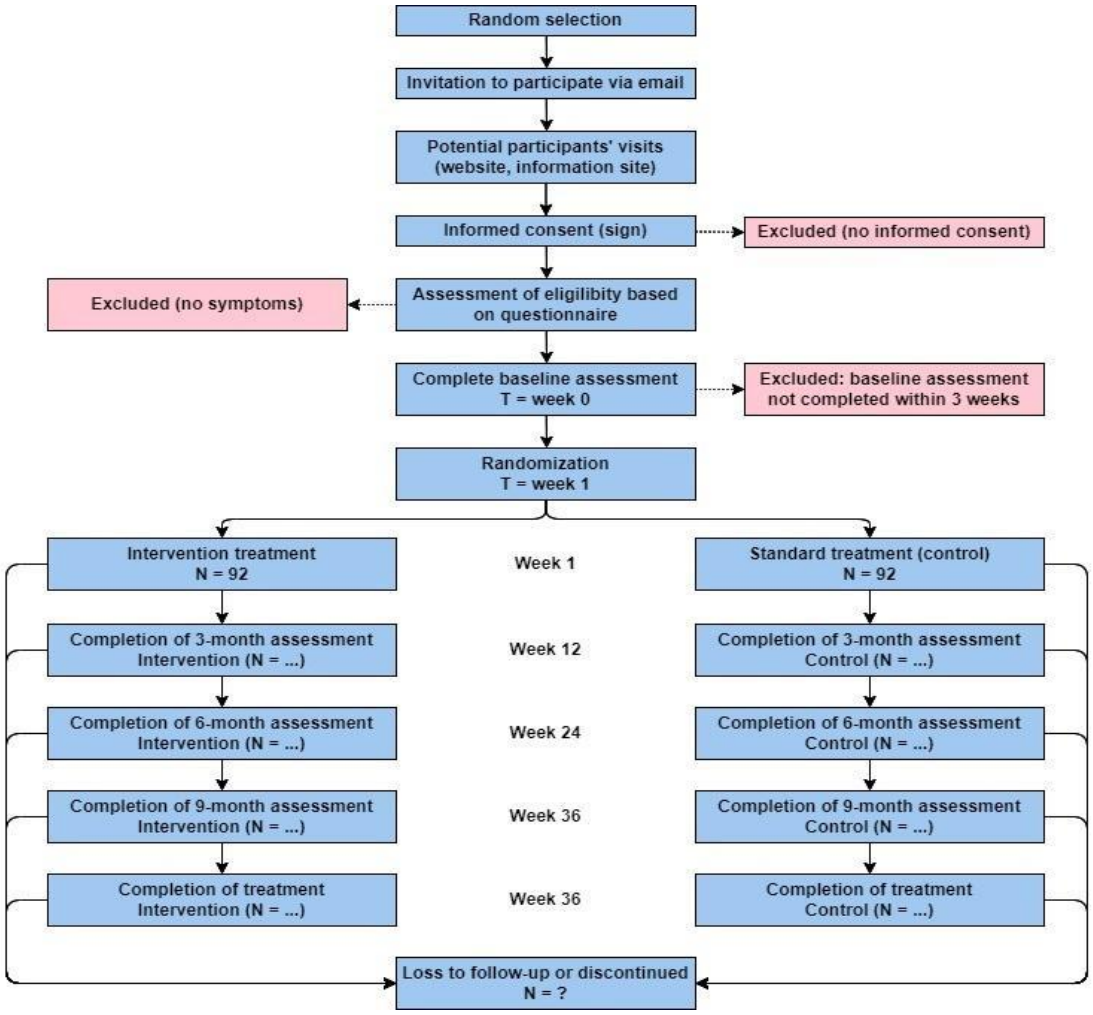

Figure 1. study timeline.

sham intervention (low-intensity PA) in addition to psychological support via daily reporting of feelings and thoughts in a diary and through regular meetings with the psychologists.

The PA program will include a minimum of 3 sessions per week, 45 minutes each, for both groups, in a gymnasium or social club. The total duration of the study will be 12 months. The intervention will be delivered through instructors who received the specific training in an instruction video to ensure a standardized intervention for all participants in all sites. Instructors will also assess adherence weekly for the first three months, then every two weeks after that. The instructors will adjust the intensity of the exercises based on the participants' physical capacity. Low-intensity exercises, including yoga or stretching, will be considered for the control group. Moderate-to-high intensity exercises (classified as Borg 11-16 and or reaching 50-85% of maximum expected heart rate) will be designed for the intervention group. Any activities exceeding these limits will not be recommended. Participants will have the option to receive pre-recorded online video training sessions if they miss their classes.

The intervention group receiving the psychological intervention and BA will be supervised in person or online (by participants' preference) by a clinician weekly in the first three months, then every two weeks after that. The sessions will emphasize behaviors that focus on 1) increasing engagement in adaptive activities usually associated with the experience of pleasure, 2) decreasing engagement in activities usually associated with negative feelings, and 3) solving problems that limit access to reward or maintain/increase aversive control. Both arms will receive a personal diary in which all sessions must be registered. The control group will receive non-structured and non-directive counseling and psychological support addressing personal difficulties and discussing long-term planning (in topics such as aging, memory loss, illness, disability, social isolation, drive, safety, and financial advice,

advice for behavioral and neuropsychiatric symptoms, etc.). The main BA domains are shown in Appendix A.

In case of discontinuation, the reason will be documented in the electronic Case Report Form (eCRF). If a subject discontinues the study intervention early, it will remain in the study and undergo the scheduled assessments (unless they withdraw from the trial). If a patient receiving sham intervention is unwilling or unable to continue the scheduled study assessments, the site personnel will attempt to collect as much follow-up information as possible.

Outcomes

The primary outcome will be a change in cognitive function assessed by MoCA from baseline to 12 months. MoCA (Nasreddine et al., 2005) is a reliable brief screening instrument for characterizing global cognitive function and screening for dementia and MCI, with a sensitivity of around 90%, and more sensitive than the Mini-Mental Status Exam (MMSE) in detecting MCI in the general population.

Secondary outcomes will include a change in cognitive function at 3, 6, and 9 months, also assessed via MoCA. Furthermore, the following tests will be performed at all five milestones (0, 3, 6, 9, and 12 months): Barthel Index, SF-12, and GDS-15. These are health-related tools that evaluate, respectively, elderly subjects' daily-life functioning, quality of life, and depressive symptoms (which may be impaired by MCI progression).

Data Management

Data will be collected using electronic data capture software (REDCap). All investigators will be responsible for completing and maintaining accurate eCFRs. The R Project for statistical analysis will be used (version R-4.1.1 for Windows [32/64 bit]).

After 33% of patients' enrollment, an interim analysis will be conducted to evaluate safety data. An adjustment for type I errors will be performed using the O'Brien-Fleming approach. The analysis will be conducted by an external Data Monitor Committee (DMC) and selected members of an Internal Assessment Committee. The DMC will be a group of five independent members, including investigators and professionals from the centers conducting the trial. DMC members will include a statistician and a clinical specialist. Information that may unblind the study during the analyses will be reported to study sites or blinded personnel once the study has been finished and unblinding is consolidated. Study sites will receive information about interim analysis results only if the investigators need to know to preserve participants' safety. There is no real or perceived direct or indirect conflict of interest related to any sponsor, grants, or honoraria.

Sample Size Calculation

No previous articles comparing PABA in patients with MCI against active controls using MoCA were reported. Thus, our sample size calculation will be based on similar trials' detected effect sizes and corresponding Cohen's d values.

Previous studies compared cognitive training or PA against SoC using other scales, showing Cohen's d values ranging from 0.80 (large effect size) to 0.45 (small-to-moderate effect size) (Peng et al., 2019) (Lee et al., 2016). With that in mind and acting conservatively, we will power this study to detect a Cohen's d of 0.5 (small-to-moderate effect size). Our calculations estimated that a Cohen's d of 0.5 is compatible with a between-group mean difference in MoCA at 12 months of 1.19 (20 points in the control group and 21.19 points in the experimental group) (Peng et al., 2019). Such expected effect size is below the clinical relevance threshold of 1.73 points (Krishnan et al., 2017). Thus, this trial will be powered up to detect all clinically relevant changes in the primary outcome.

MoCA standard deviation values were 2.2 in the experimental group and 2.57 in the control group (Peng et al., 2019). Considering that the primary outcome will be measured at 12 months via a two-sided unpaired Student's t-test with an alpha value of 0.05, a power of 80%, an allocation rate of 1:1, and an expected dropout rate of 25% (plus 5% for the interim analysis), the final sample size will be 184 (92 per arm).

Statistical Analysis

The primary outcome will be analyzed with an unpaired Student's t-test. Data variance will be determined, and then either a t-test with equal variance or a t-test with unequal variance will be applied. Based on previous literature, a normal distribution of data is expected. However, if non-normality is demonstrated, a Mann-Whitney test will be used instead. All secondary analyses will be performed via linear mixed regression, adjusting for covariates such as time, ethnicity, smoking, drinking habits, the intensity of PA performed before the trial, minutes of exercise per week before the trial, exercise sessions attended, and baseline MoCA.

In all cases, normality will be assessed via graphical distribution of data, analysis of skewness and kurtosis, and Kolmogorov–Smirnov tests. A p-value under 0.05 will be considered significant for all tests. All calculations will be performed in Stata version 17.0 (Stata Corp., College Station, TX, USA).

Missing Data

An intention-to-treat (ITT) approach will be used to preserve randomization. Secondarily, a per-protocol (PP) analysis will also be provided (considering a minimum adherence to the intervention of 80%, which translates to 9 months and three weeks of intervention). If missing data behaves as missing-at-random, which is expected, it will be handled with adjustment for baseline characteristics via multiple imputations. If it behaves as missing-not-at-random, maximum likelihood techniques will be applied. In all cases, sensitivity analyses (such as last-observation-carried-forward methods) will be performed to assess if the results remain robust (Haukoos & Newgard, 2007).

Discussion

This protocol will compare PABA against active control in slowing the progression of MCI in retired/unemployed patients aged over 60 years. This is an urgent matter worldwide, with the rising number of individuals in advanced ages developing progressive decline in functionality and requiring assistance in activities of daily living, which causes excessive direct and indirect expenses and reduced quality of life.

Previous studies compared PA programs against standard of care in preventing or slowing the progression of MCI but showed modest results (Jeong et al., 2021) (Bisbe et al., 2020) (Park et al., 2019) (Peng et al., 2019) (Lamb et al., 2018). On the other hand, meta-analyses on MCI found global cognitive improvement in the group that performed aerobic exercise (Law et al., 2019) (Song et al., 2018). Another study suggests that exercises of medium duration (45-60min) and moderate or vigorous intensity were significantly better at improving cognition, but not low intensity or short- and long-duration (Northey et al., 2018). Resistance training alone (Xiuang et al., 2021) might also be beneficial and likely brings additional benefits if added to aerobic training (multicomponent training) (Northey et al., 2018).

To date, this will be the first protocol for a superiority randomized clinical trial proposing a mixed intervention (PABA) for patients with MCI.

Most studies on MCI evaluate patients aged over 65 years, which matches the WHO criteria for the elderly in developed countries (Bisbe et al., 2020) (Jeong et al., 2021) (Peng et al., 2019). However, in developing countries, the same criteria consider the elderly to be those over 60 years old (World Health Organization, 2001). Since studies on MCI are generally performed in high-income countries (with larger elderly populations), it is hard to translate their results to the reality of low-income countries as the population between 60 and 65 years was not studied in these trials. Therefore, to increase the results' generalizability, this study will adopt the 60-year threshold.

One limitation of this study could be the lack of double-blinding. Even though participants will be randomized in a blinded fashion, the informed consent form (with the description of the design) could unblind them. Instructors and clinicians involved in the adjustments of the interventions cannot be blinded due to the nature of their roles. The interventions will be designed to keep the similarity among both arms regarding interventions' frequency, duration, and length, but not PA intensity nor psychological technique. However, all outcome assessors and analysts will be blinded throughout the trial.

PABA adds challenges to its measurement and compliance, as some heterogeneity on the individual basis is expected between participants. Individuals will most likely be in different initial physical, psychological, and neurological conditions. To maintain as much homogeneity in interventions as possible, subjects will follow the pre-specified description for PA. They will also receive a heart rate monitor to certify that at least 15 minutes of aerobic exercise are performed per training, based on the estimated HR for age (Target Heart Rates Chart | American Heart Association, n.d.; Target Heart Rate and Estimated Maximum Heart Rate | Physical Activity | CDC, n.d.). Also, performing the sessions in a designated space related to the trial, with activities kept guided by a qualified instructor, is expected to provide homogeneity and it could provide the desired generalizability of results. Online activities will be an acceptable option to maintain adherence, as long as they are provided by the gymnasium or social club assigned to the subject and the pre-specified PA program is followed.

Regarding adherence, previous studies with similar designs showed rates of up to 75% (Linardon et al., 2018) (Fernandez et al., 2015). To increase adherence further, many strategies will be employed (see the "Adherence" section).

Although Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) and MMSE are more commonly used than MoCA to assess the primary outcome in trials on MCI and/or dementia, the choice for MoCA is supported by a few facts: (1) ADAS-Cog is less suited for mild or asymptomatic cognitive deficits, (2) MoCA is more sensitive than MMSE in detecting MCI (90% against 18%) (Nasreddine et al., 2005), and (3) MoCA is shorter and more easily comprehensible than the other tests.

Finally, since the statistical analysis of our secondary outcomes will rely on mixed linear regression,

we will avoid multiple comparisons. Therefore, adjustments for the alpha value will not be necessary.

MCI is a disease with a high impact on quality of life, presenting a growing burden for society and individuals. Due to the lack of an effective MCI treatment, it is fundamental to understand the relationship between current treatment options in order to achieve the maximum therapeutic effect possible. A negative result in this trial would indicate that our mixed intervention might not be the most promising approach, which in turn may lead future studies to investigate different treatment combinations. In the long run, research of this kind has the potential to optimize MCI treatment and help alleviate patients' burdens. With this study, we aim to refine treatment options for MCI patients and uncover directions for further therapeutic approaches.

Conflicts of Interest: The authors declare no conflict of interest.

References

Bisbe, M., Fuente-Vidal, A., López, E., Moreno, M., Naya, M., de Benetti, C., Milà, R., Bruna, O., Boada, M., & Alegret, M. (2020). Comparative Cognitive Effects of Choreographed Exercise and Multimodal Physical Therapy in Older Adults with Amnestic Mild Cognitive Impairment: Randomized Clinical Trial. Journal of Alzheimer's Disease, 73(2), 769–783. https://doi.org/10.3233/JAD-190552

Bravata, D. M., Smith-Spangler, C., Sundaram, V., Gienger, A. L., Lin, N., Lewis, R., Stave, C. D., Olkin, I. & Sirard, J. R (2007). Using pedometers to increase physical activity and improve health: a systematic review. JAMA, 298(19), 2296-304. doi: 10.1001/jama.298.19.2296

Fernandez, E., Salem, D., Swift, J. K., & Ramtahal, N. (2015). Meta-analysis of dropout from cognitive behavioral therapy: Magnitude, timing, and moderators. Journal of consulting and clinical psychology, 83(6), 1108–1122. https://doi.org/10.1037/ccp0000044

Haukoos, J. S., & Newgard, C. D. (2007). Advanced Statistics: Missing Data in Clinical Research-Part 1: An Introduction and Conceptual Framework. Academic Emergency Medicine, 14(7), 662–668. https://doi.org/10.1111/j.1553-2712.2007.tb01855.x

Hopko, D. R., Cannity, K., McIndoo, C. C., File, A. A., Ryba, M. M., Clark, C. G., & Bell, J. L. (2015). Behavior therapy for depressed breast cancer patients: predictors of treatment outcome. Journal of consulting and clinical psychology, 83(1), 225–231. https://doi.org/10.1037/a0037704

Horr, T., Messinger-Rapport, B., & Pillai, J. A. (2015). Systematic review of strengths and limitations of randomized controlled trials for non-pharmacological interventions in mild cognitive impairment: focus on Alzheimer's disease. The Journal of Nutrition, Health & Aging, 19(2), 141–153. https://doi.org/10.1007/s12603-014-0565-6

Jeong, M.-K., Park, K.-W., Ryu, J.-K., Kim, G.-M., Jung, H.-H., & Park, H. (2021). Multicomponent Intervention Program on Habitual Physical Activity Parameters and Cognitive Function in Patients with Mild Cognitive Impairment: A Randomized Controlled Trial. International Journal of Environmental Research and Public Health, 18(12). https://doi.org/10.3390/ijerph18126240

Jongsiriyanyong, S., & Limpawattana, P. (2018). Mild Cognitive Impairment in Clinical Practice: A Review Article. American journal of Alzheimer's disease and other dementias, 33(8), 500–507. https://doi.org/10.1177/1533317518791401

Karssemeijer, E., Aaronson, J. A., Bossers, W. J., Smits, T., Olde Rikkert, M., & Kessels, R. (2017). Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis. Ageing research reviews, 40, 75–83. https://doi.org/10.1016/j.arr.2017.09.003

Krishnan, K., Rossetti, H., Hynan, L. S., et al. (2017). Changes in Montreal Cognitive Assessment Scores Over Time. Assessment. 24(6):772-777. doi:10.1177/1073191116654217

Lamb, S. E., Sheehan, B., Atherton, N., Nichols, V., Collins, H., Mistry, D., Dosanjh, S., Slowther, A. M., Khan, I., Petrou, S., Lall, R., & DAPA Trial Investigators. (2018). Dementia And Physical Activity (DAPA) trial of moderate to high intensity exercise training for people with dementia: randomised controlled trial. BMJ (Clinical Research Ed.), 361, k1675. https://doi.org/10.1136/bmj.k1675

Law, C. K., Lam, F. M., Chung, R. C., & Pang, M. Y. (2020). Physical exercise attenuates cognitive decline and reduces behavioural problems in people with mild cognitive impairment and dementia: a systematic review. Journal of Physiotherapy, 66(1), 9–18. https://doi.org/10.1016/j.jphys.2019.11.014

Lee, Y.-Y., Wu, C.-Y., Teng, C.-H., Hsu, W.-C., Chang, K.-C., & Chen, P. (2016). Evolving methods to combine cognitive and physical training for individuals with mild cognitive impairment: study protocol for a randomized controlled study. Trials, 17(1), 526. https://doi.org/10.1186/s13063-016-1650-4

Linardon, J., Hindle, A., & Brennan, L. (2018). Dropout from cognitive-behavioral therapy for eating disorders: A meta-analysis of randomized, controlled trials. The International journal of eating disorders, 51(5), 381–391. https://doi.org/10.1002/eat.22850

Mild Cognitive Impairment: Symptoms, Causes, Treatments & Tests. (n.d.). Cleveland Clinic. Published on March 18, 2019. Retrieved on November 13, 2021 from https://my.clevelandclinic.org/health/diseases/17990-mild-cognitive-impairment

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive

Assessment, MoCA: a brief screening tool for mild cognitive impairment. Journal of the American Geriatrics Society, 53(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: a systematic review with meta-analysis. British Journal of Sports Medicine, 52(3), 154–160. https://doi.org/10.1136/bjsports-2016-096587

Okumiya, K., Matsubayashi, K., Wada, T., Kimura, S., Doi, Y., & Ozawa, T. (1996). Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age. Journal of the American Geriatrics Society, 44(5), 569–572. https://doi.org/10.1111/j.1532-5415.1996.tb01444.x

Park, H., Park, J. H., Na, H. R., Hiroyuki, S., Kim, G. M., Jung, M. K., Kim, W. K., & Park, K. W. (2019). Combined Intervention of Physical Activity, Aerobic Exercise, and Cognitive Exercise Intervention to Prevent Cognitive Decline for Patients with Mild Cognitive Impairment: A Randomized Controlled Clinical Study. Journal of Clinical Medicine, 8(7). https://doi.org/10.3390/jcm8070940

Peng, Z., Jiang, H., Wang, X., Huang, K., Zuo, Y., Wu, X., Abdullah, A. S., & Yang, L. (2019). The Efficacy of Cognitive Training for Elderly Chinese Individuals with Mild Cognitive Impairment. BioMed Research International, 2019, 4347281. https://doi.org/10.1155/2019/4347281

Petersen R. C. (2016). Mild Cognitive Impairment. Continuum (Minneapolis, Minn.), 22(2 Dementia), 404–418. https://doi.org/10.1212/CON.0000000000000313

Reisberg, B., & Ferris, S. H. (1988). Brief Cognitive Rating Scale (BCRS). Psychopharmacology bulletin, 24(4), 629–636.

Rovner, B. W., Casten, R. J., Hegel, M. T., & Leiby, B. (2018). Preventing Cognitive Decline in Black Individuals With Mild Cognitive Impairment: A Randomized Clinical Trial. JAMA neurology, 75(12), 1487–1493. https://doi.org/10.1001/jamaneurol.2018.2513

Satoh, T., Sakurai, I., Miyagi, K., & Hohshaku, Y. (1995). Walking exercise and improved neuropsychological functioning in elderly patients with cardiac disease. Journal of internal medicine, 238(5), 423–428. https://doi.org/10.1111/j.1365-2796.1995.tb01219.x

Song, D., Yu, D., Li, P., & Lei, Y. (2018). The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: A systematic review and meta-analysis. International Journal of Nursing Studies, 79, 155–164. https://doi.org/10.1016/j.ijnurstu.2018.01.002

Stanton B. R. (2011). The neurology of old age. Clinical medicine (London, England), 11(1), 54–56. https://doi.org/10.7861/clinmedicine.11-1-54

Tangalos, E. G., & Petersen, R. C. (2018). Mild Cognitive Impairment in Geriatrics. Clinics in geriatric medicine, 34(4), 563–589. https://doi.org/10.1016/j.cger.2018.06.005

Target Heart Rates Chart | American Heart Association. (n.d.). Retrieved August 18, 2021, from https://www.heart.org/en/healthy-living/fitness/fitness-basics/target-heart-rates

Target Heart Rate and Estimated Maximum Heart Rate | Physical Activity | CDC. (n.d.). Target Heart Rates Chart. Retrieved August 16, 2021, from https://www.cdc.gov/physicalactivity/basics/measuring/heartrate.htm

World Health Organization. (2001). Men, ageing and health : achieving health across the life span.

World Health Organization (WHO). (2010). Global Recommendations on Physical Activity for Health (p. 49). World Health Organization.

Yesavage, J. A. (1986). The use of self-rating depression scales in the elderly. In L. W. Poon, T. Crook, K. L. Davis, C. Eisdorfer, B. J. Gurland, A. W. Kaszniak, & L. W. Thompson (Eds.), Handbook for clinical memory assessment of older adults (pp. 213–217). American Psychological Association. https://doi.org/10.1037/10057-017