THE ROLE OF MUSCULAR STRENGTH IN THE MENTAL HEALTH OF OLDER ADULTS

EL ROL DE LA FUERZA MUSCULAR EN LA SALUD MENTAL DE ADULTOS MAYORES

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DECLARATION OF INTEREST STATEMENT

Authors from all the works presented in this International Doctoral Thesis declare that they have no conflict of interest associated with this work's research, findings, or publication.

DATA AVAILABILITY

Any additional data that support the findings of this International Doctoral Thesis are available from Darío Bellón upon reasonable request.

LIST OF ABBREVIATIONS

AGUEDA	Active Gains in brain Using Exercise During Aging
BMI	Body Mass Index
CRF	Cardiorespiratory Fitness
FDR	False Discovery Rate
HADS	Hospital Anxiety and Depression Scale
IFIS	International Fitness Scale
MEDAS	Adherence to the Mediterranean Diet
MMSE	Mini-Mental State Examination
MoCA	The Montreal Cognitive Assessment
Nm	Newtons/metres
PSS	Perceived Stress Scale
RCT	Randomized Controlled Trial
RSE	Rosenberg Self-Esteem
SD	Standard Deviation
SF-36	Short Form 36
STICS-m	Telephone Interview for Cognitive Status-Modified
SWLQ	Satisfaction with Life Questionnaire
UCLA-L	University of California, Los Angeles Loneliness
WHO	World Health Organization

ABSTRACT

Background: The global population is aging rapidly, increasing the prevalence of mental health issues such as anxiety and depression among older adults. In this context, resistance exercise has emerged as a promising strategy to improve mental health in this population.

Objectives: This international thesis examines the associations between muscular strength and mental health, including psychological ill-being and well-being, in cognitively normal older adults **(Chapter 3)**. It further evaluates the effects of a 24-week resistance exercise program on these mental health outcomes, with a focus on the moderating roles of age, sex, and baseline symptoms, as well as the mediating effects of changes in muscular strength and self-esteem **(Chapter 4)**.

Methods: A total of 90 cognitively healthy older adults participated in the AGUEDA randomized controlled trial (RCT) of a 24-weeks resistance exercise program. Muscular strength was assessed using objective (i.e., handgrip strength, biceps curl, squats, and isokinetic test) and perceived (i.e., International Fitness Scale) indicators. Self-reported questionaries assessed mental health: psychological ill-being indicators (anxiety, depression, stress, and loneliness); and psychological well-being indicators (satisfaction with life, self-esteem, and emotional well-being).

Main Findings: Cross-sectional analyses found a positive moderate association between handgrip strength and self-esteem and an inverse small association between perceived strength and depressive symptoms, as well as a positive association between elbow extension and stress. No other significant associations were observed between muscular strength and mental health outcomes in cognitively normal older adults **(Chapter 3)**. The randomized controlled trial demonstrated non-significant improvements in psychological ill-being and well-being in the whole sample. However, subgroup analyses indicated that women and younger participants experienced significant benefits, underscoring the importance of personalized exercise programs. Notably, self-esteem significantly mediated the improvement of mental health outcomes in women **(Chapter 4)**.

Conclusions: Collectively, the main findings of this international thesis underscore that both muscular strength and resistance exercise offer potential benefits for this population. While the cross-sectional study reveals positive associations between grip strength and

self-esteem, as well as other connections between perceived strength and depressive symptoms, the randomized controlled trial highlights how resistance exercise can be particularly beneficial for women and younger participants. These findings promote the use of resistance exercise as a valuable tool to improve the mental health of older adults and justify further investigations to optimize and tailor exercise interventions to individual characteristics, thereby maximizing their effectiveness.

RESUMEN

Antecedentes: La población mundial está envejeciendo rápidamente, lo que aumenta la prevalencia de problemas de salud mental como la ansiedad y la depresión entre los adultos mayores. En este contexto, el ejercicio de resistencia ha emergido como una estrategia prometedora para mejorar la salud mental en esta población.

Objetivos: Esta tesis internacional examina las asociaciones entre la fuerza muscular y la salud mental, incluido el malestar y bienestar psicológico en adultos mayores cognitivamente normales **(Capítulo 3)**. También evalúa los efectos de un programa de ejercicio de resistencia de 24 semanas sobre estos resultados de salud mental, centrándose en la moderación por edad, sexo y síntomas de base, y la mediación por cambios en la fuerza muscular y la autoestima **(Capítulo 4)**.

Métodos: Un total de 90 adultos mayores cognitivamente sanos participaron en el ensayo controlado aleatorizado (ECA) de AGUEDA. Consistió en un programa de fuerza muscular de 24 semanas. La fuerza muscular fue evaluada objetivamente (fuerza de agarre, curl de bíceps, sentadillas y pruebas isocinéticas) y percibida (Escala Internacional de Condición Física). La salud mental fue evaluada con cuestionarios validados auto-reportados, malestar psicológico: ansiedad, depresión, estrés y soledad) y bienestar psicológico: (satisfacción con la vida, autoestima y bienestar emocional).

Principales Hallazgos: Los análisis transversales encontraron una asociación positiva moderada entre la fuerza de agarre y la autoestima y una pequeña asociación inversa entre la fuerza percibida y los síntomas depresivos, así como una asociación positiva entre la extensión del codo y el estrés. No se observaron otras asociaciones significativas entre la fuerza muscular y los indicadores de salud mental en adultos mayores cognitivamente sanos **(Capítulo 3)**. El ensayo controlado aleatorizado demostró mejoras no significativas en el malestar y bienestar psicológico. Sin embargo, los análisis de subgrupos indicaron que las mujeres y los participantes más jóvenes experimentaron beneficios significativos, subrayando la importancia de los programas de ejercicio personalizados. Notablemente, la autoestima medió significativamente la mejora de los indicadores de salud mental en las mujeres **(Capítulo 4)**.

Conclusiones: En conjunto, los principales hallazgos de esta tesis internacional subrayan que tanto la fuerza muscular como el ejercicio de resistencia ofrecen beneficios potenciales para esta población. Mientras que el estudio transversal revela asociaciones positivas moderadas entre la fuerza de agarre y la autoestima, así como otras conexiones

entre la fuerza percibida y los síntomas depresivos, el ensayo controlado aleatorizado destaca cómo los programas de ejercicio de fuerza pueden ser particularmente beneficiosos para las mujeres y los participantes más jóvenes. Estos hallazgos promueven el uso del ejercicio de resistencia como una herramienta valiosa para mejorar la salud mental de los adultos mayores y justifican investigaciones adicionales para optimizar y personalizar las intervenciones de ejercicio según las características individuales, maximizando así su efectividad.

KEY CONCEPTS

Aerobic exercise: Physical activity that relies on the aerobic energy-generating process, typically involving rhythmic, repetitive movements of large muscle groups, such as walking, running, swimming, or cycling, aimed at improving cardiovascular endurance (1).

Anxiety: It is a feeling of worry, nervousness, or unease about something with an uncertain outcome. Anxiety is characterized by excessive and persistent (yet often unrealistic) worry which can inhibit one's ability to carry out activities of daily living (2)

Cardiorespiratory fitness: The ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity, often measured by maximal oxygen uptake (VO2 max) (3).

Cognitively normal individuals: Refers to individuals who do not exhibit significant cognitive impairments and perform within the expected range on standardized cognitive assessments for their age group (4).

Depression: The generic word 'depression' implies a lowering – here, a lowering of mood. Depressive diagnostic constructs include lowered mood, decreased self-esteem, and increased self-criticism; guilt about acts of commission and omission; and feelings of hopelessness and helplessness (5). As an extension, Beck's negative 'cognitive triad' emphasizes a negative view of the self (i.e. deficient, inadequate, and unworthy), the world, and the future (6).

Emotional well-being: The ability to successfully handle life's stresses and adapt to change and difficult times, encompassing the presence of positive emotions and moods, the absence of negative emotions, satisfaction with life, fulfillment, and positive functioning (7).

Exercise: A subset of physical activity that is planned, structured, and repetitive, aimed at improving or maintaining one or more components of physical fitness (8).

Loneliness: A complex and usually unpleasant emotional response to isolation or lack of companionship, which can have significant health implications (9).

Mental disorder: A clinically significant disturbance in an individual's cognition, emotional regulation, or behavior, reflecting a dysfunction in psychological, biological, or developmental processes underlying mental functioning (10).

Mental health: A state of well-being in which individuals realize their potential, can cope with normal life stresses, work productively, and contribute to their community (11).

Muscular strength: The maximum amount of force a muscle or muscle group can generate during a single contraction (12).

Objective muscular strength: Quantitative measurement of muscle strength using standardized tests and equipment, such as dynamometers, to assess the force exerted by a muscle or group of muscles (13).

Older adults: Individuals typically aged 60 years or older, often experiencing age-related physiological and cognitive changes (14)

Physical activity: Any bodily movement produced by skeletal muscles that requires energy expenditure, including activities undertaken while working, playing, carrying out household chores, traveling, and engaging in recreational pursuits (15).

Psychological ill-being: A state characterized by the presence of negative psychological conditions such as depression, chronic stress, anxiety, anger, pessimism, and dissatisfaction with one's current life (16)

Psychological well-being: A multifaceted construct encompassing the subjective experience of positive feelings and cognitive appraisals, including aspects like life purpose, emotional vitality, positive affect, life satisfaction, happiness, and optimism (7).

Resistance exercise: A form of physical activity that involves working against an external force to increase muscle strength, endurance, and size. This includes activities like weightlifting, using resistance bands, or body-weight exercises (17).

Satisfaction with life: A cognitive assessment of one's life as a whole, reflecting a judgmental process in which individuals assess the quality of their lives based on their own chosen criteria (18)

Sedentary: A lifestyle characterized by a high amount of sitting or lying down behavior, with low energy expenditure, often associated with increased health risks (19).

Self-confidence: refers to an individual's trust in their own abilities, capacities, and judgments, or belief that they can successfully face day-to-day challenges and demands (20).

Self-Concept: refers to an individual’s perception of themselves, encompassing beliefs, attitudes, and knowledge about their own attributes, abilities, and roles in various life domains (21).

Self-Efficacy: The belief in one's capabilities to organize and execute the courses of action required to manage prospective situations (22)

Self-esteem: An individual's subjective evaluation of their own worth, encompassing beliefs about oneself as well as emotional states like triumph, despair, pride, and shame (23)

Self-Worth: A person's sense of their own value or worth as a human being (24).

Stress: a state of mental or emotional strain or tension resulting from adverse or demanding circumstances." It is a natural human response that prompts us to address challenges and threats in our lives. Everyone experiences stress to some degree, and the way we respond to stress can significantly impact our overall well-being (25).

Subjective muscular strength: Refers to an individual's perceived level of muscular strength, which is often assessed through self-reported measures that capture the individual's perception of their physical capabilities, including their ability to lift, carry, or perform strength-related tasks (26).

GENERAL INTRODUCTION

Chapter 1. State of the art

1.1 Older adults

Aging is an inevitable biological process characterized by physiological, cognitive, and psychological changes that can impact an individual's overall well-being. The global population is experiencing a rapid demographic shift, with a significant increase in the proportion of older adults. According to the World Health Organization (27), by 2050, the number of people aged 60 years and older will reach 2.1 billion, nearly doubling the 2020 figures. While advances in healthcare and improved living conditions have contributed to increased life expectancy, aging is also associated with a higher prevalence of chronic diseases, cognitive decline, and mental health disorders like depression.

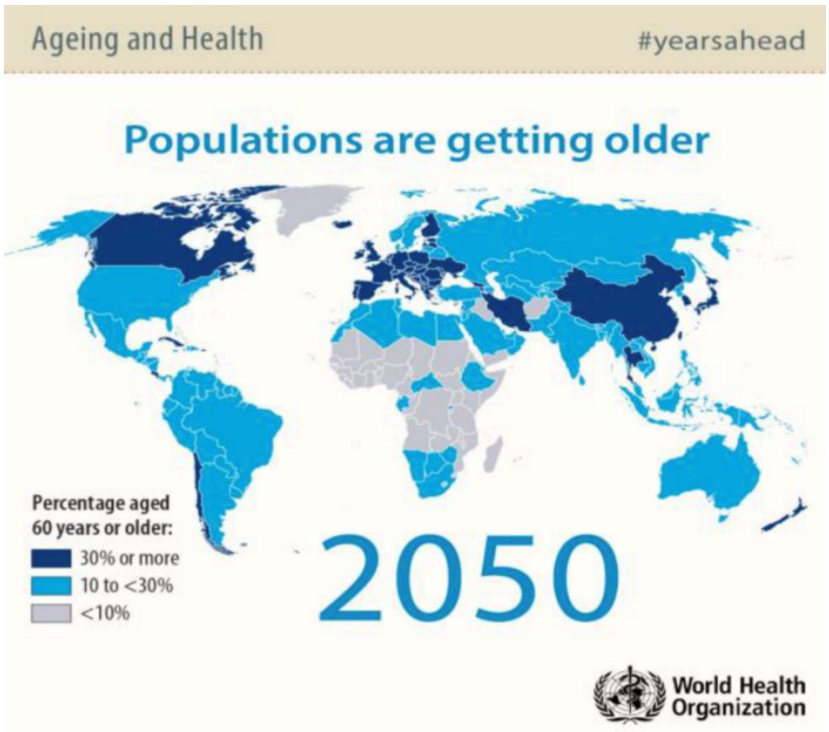

Figure 1. Percentage aged 60 years or older in the world.(28)

Cognitively normal older adults represent a crucial demographic group in aging research. Although they do not present major neurodegenerative conditions such as Alzheimer's disease or mild cognitive impairment (MCI), they remain vulnerable to cognitive and emotional changes associated with aging (29). One of the most significant

concerns in this population is mental health, given its profound impact on quality of life, independence, and long-term cognitive function (30).

1.2 Mental health

Mental health is a fundamental component of healthy aging, encompassing emotional, psychological, and social well-being. In older adults, mental health issues such as depression, anxiety, stress, loneliness, and cognitive decline are increasingly prevalent and have been associated with adverse outcomes, including functional impairment, loss of autonomy, reduced quality of life, and higher mortality rates (31,32). Depression affects between 10% and 20% of older adults, depending on diagnostic criteria and the population studied (33).

Beyond the absence of illness, mental health also includes the presence of positive psychological states, commonly referred to as psychological well-being. Key indicators of well-being include self-esteem, emotional well-being, and life satisfaction, all of which contribute to resilience, healthy aging, and a sense of purpose in later life (34). Among these, self-esteem, defined as a person's overall evaluation of their self-worth, has been identified as a crucial psychological construct, closely linked to both physical and mental health outcomes in older adults. Low self-esteem is associated with a higher risk of depression, anxiety, loneliness, and even cognitive decline (34,35).

Despite its importance, self-esteem and other psychological well-being indicators have often been overlooked in aging research, which has traditionally focused on pathology and psychological ill-being. As a result, there is a growing need to adopt a more holistic approach to mental health in older adults, one that includes both ill-being and well-being dimensions to fully capture the psychological experience of aging.

1.3 Prevention vs. treatment of mental health disorders

Although pharmacological and psychological interventions remain the primary strategies for managing mental disorders in older adults, their effectiveness is limited. Many individuals with depression or anxiety remain undiagnosed, untreated, or are non-adherent to treatment plans. Even under optimal conditions, it is estimated that only about 30% of the burden of depression and 50% of the burden of anxiety could be averted through treatment alone (36–38). These limitations highlight the importance of preventive

approaches that reduce the incidence of new cases, rather than relying exclusively on treatment.

Physical activity (PA) has emerged as a promising strategy in this context. Meta-analyses and prospective studies suggest that regular physical activity may reduce the risk of developing depression by approximately 20–30%(39,40). This is particularly relevant in cognitively normal older adults, where preventive interventions may help delay the onset of more severe psychological symptoms.

Additionally, resistance training may provide psychological benefits through mechanisms such as improved self-esteem, emotional regulation, and stress resilience, making it a potentially effective non-pharmacological intervention for mental health promotion in aging populations (41).

1.4 Potential mechanisms linking resistance exercise and mental health

While a substantial body of research has explored the relationship between PA and mental health (42,43), and some reviews have focused on the effects of resistance exercise on depression in older adults (44), there is currently no specific review addressing the broader psychological effects of resistance exercise including both psychological ill-being and well-being indicators in this population. Many of the mechanisms identified for PA, such as the release of neurotransmitters (serotonin, dopamine, norepinephrine), increased brain-derived neurotrophic factor (BDNF) levels, enhanced neurogenesis, angiogenesis, and neuroplasticity, are likely transferable to resistance exercise (45–47). Additionally, exercise-induced modulation of the hypothalamic-pituitary-adrenal (HPA) axis and reductions in systemic inflammation and oxidative stress (45) have been proposed as relevant pathways linking exercise to mental health outcomes (46,47). These mechanisms are illustrated in **Figure 2**, which adapts an existing conceptual model to reflect the potential pathways through which resistance exercise may influence mental health in older adults.

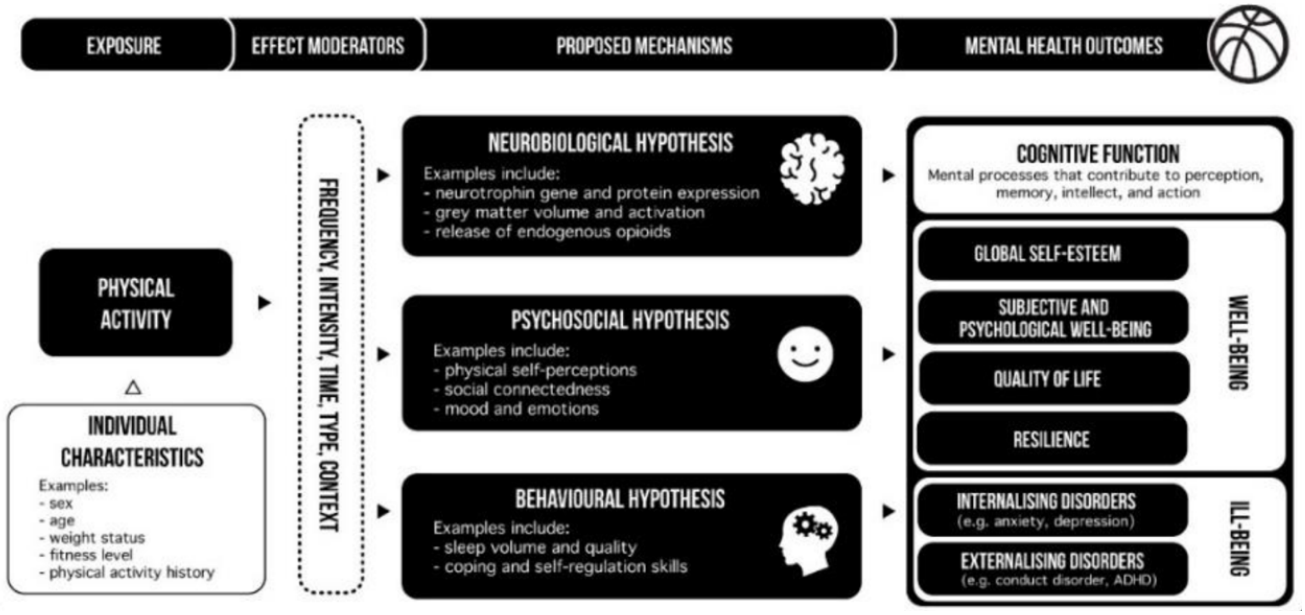

Figure 2. Adaptive version for older adults of a conceptual model for the effects of physical activity on mental health outcomes in youth. ADHD, attention-deficit/hyperactivity disorder (48)

However, resistance training may also activate unique or particularly relevant psychosocial mechanisms, beyond the general neurobiological adaptations. Notably, self-esteem has emerged as one of the most potent mediators of the mental health benefits of PA (49,50), and it could be especially significant in the context of resistance exercise. Improvements in muscular strength and functional capacity (51,52) may enhance body image, increase perceptions of autonomy and competence, and ultimately strengthen self-esteem, a critical factor for psychological well-being in later life (47,53,54).

Despite the growing evidence supporting the mental health benefits of resistance exercise (44,55), the specific pathways through which it operates, particularly regarding psychosocial mediators like self-esteem, remain underexplored. Most of the current knowledge derives from studies in youth and general PA programs (56), with a limited focus on strength training and older populations. Therefore, a clear research gap exists in investigating whether improvements in self-esteem mediate the effects of resistance exercise on mental health among older adults.

Given the aging global population and the importance of promoting psychological resilience in later life (57), further research is needed to elucidate these potential

mechanisms. In this context, we propose a conceptual framework illustrating the plausible pathways linking resistance exercise to mental health outcomes in older adults (**Figure 3**).

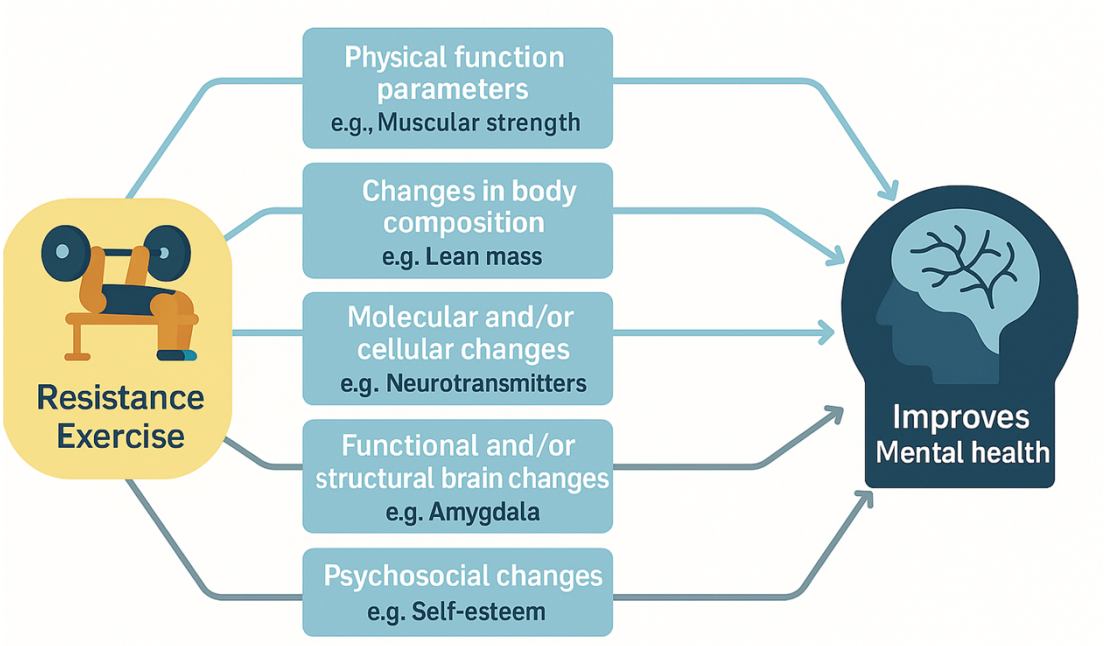

Figure 3. Possible mechanisms between resistance exercise and mental health outcomes.

1.5 Gaps and directions

Although growing evidence supports the positive effects of exercise on mental health, significant gaps remain in the literature. Most studies have primarily focused on aerobic exercise, while the potential of resistance training particularly in the context of psychological well-being remains underexplored, especially in cognitively normal older adults. Existing trials tend to prioritize clinical populations or individuals with diagnosed mental disorders, limiting our understanding of how resistance training may affect individuals who are not clinically impaired but still experience age-related psychological vulnerability (58).

Furthermore, while muscle strength has been increasingly linked to mental health outcomes, these associations have often been studied using limited strength indicators, failing to capture a comprehensive picture of the potential relevance of multiple muscular strength measures (59). Similarly, studies that include both psychological ill-being and well-being indicators remain scarce, despite growing recognition that complete mental

health includes both the absence of negative symptoms and the presence of positive psychological states (60).

Another important gap is the lack of clarity regarding the mechanisms through which resistance training influences mental health outcomes. For example, self-esteem has been identified as a key psychological mediator in the association between PA and mental health outcomes in youth populations (61). However, it remains to be elucidated whether similar mechanisms operate among older adults, particularly regarding resistance training and muscular strength improvements.

In addition, many resistance exercise programs have been designed without considering individual characteristics such as sex, age, or baseline psychological symptoms, which might moderate the effects of exercise interventions. Recent meta-analyses suggest that these factors may influence the magnitude of mental health improvements following exercise programs (62), highlighting the need for personalized interventions to maximize effectiveness (52).

AIMS AND HYPOTHESIS

Overall aim:

The present International Doctoral Thesis aims to study the role of muscular strength in the mental health of cognitively normal older adults. This overall aim is addressed in two specific aims, corresponding to two different studies.

Specific aims

Specific aim 1: to examine the associations between muscular strength (i.e., handgrip strength, biceps curl, squats, elbow-knees extension, and perceived strength) and mental health including psychological ill-being (i.e., anxiety, depression, stress, and loneliness) and well-being (i.e., satisfaction with life, self-esteem, and emotional well-being) in cognitively normal older adults (**Chapter 3**).

Specific aim 2: to evaluate the effects of a 24-week resistance exercise program on mental health outcomes, including both psychological ill-being (e.g., anxiety-depressive symptoms, stress, and loneliness) and psychological well-being (e.g., life satisfaction, self-esteem, emotional well-being). (**Chapter 4**).

Specific aim 3: to examine whether the effects of exercise on mental health outcomes are moderated by factors such as sex, age, and baseline psychological symptomatology (**Chapter 4).**

Specific aim 4: to examine whether the effects of exercise on mental health outcomes are mediated by changes in self-esteem and muscular strength. **(Chapter 4).**

Main Hypothesis:

The main hypothesis of this International Doctoral thesis is that muscular strength plays an important role in the mental health of cognitively normal older adults. Specifically, we hypothesize that:

Specific hypothesis

Specific hypothesis 1: Muscular strength is related to indicators of mental health, both in psychological distress and well-being, in cognitively normal older adults. (**Chapter 3**).
Specific hypothesis 2: The AGUEDA 24-week resistance exercise program will have positive effects on reducing psychological ill-being and increasing psychological well-being in cognitively normal older adults. (**Chapter 4)**
Specific hypothesis 3: The effects of the resistance exercise program will be moderated by factors such as sex, age, and baseline psychological symptomatology. (**Chapter 4)**
Specific hypothesis 4: The effects of the resistance exercise program will be mediated by variables such as self-esteem and muscular strength. (**Chapter 4).**

MATERIAL AND METHODS

Chapter 2. Methodological overview of the AGUEDA randomized controlled trial

2.1 Design and ethics

The AGUEDA trial is a single-center, two-arm, single-blind randomized controlled trial (RCT) designed to assess the effects of resistance exercise in cognitively normal older adults aged 65 to 80 years. A total of 90 participants were randomly assigned to either a resistance exercise group (n = 45) or a wait-list control group (n = 45). The study was conducted in Granada, Spain, across multiple research institutions, including the Sport and Health University Research Institute (iMUDS), the Mind, Brain and Behavior Research Centre (CIMCYC) at the University of Granada, and the Virgen de las Nieves University Hospital (63) . The participant flow throughout the study is illustrated in **Figure 4.**

This trial followed the ethical guidelines established by the Declaration of Helsinki and received approval from the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; approval number: #2317-N-19) on May 25, 2020. Additionally, the study was registered in ClinicalTrials.gov (Identifier: NCT05186090; Submission date: December 22, 2021). Before participation, all individuals received a detailed explanation of the study procedures and provided their written informed consent. A publicly available model consent form can be accessed on GitHub.

The AGUEDA trial had been developed following the Standard Protocol Items for Randomized Interventional Trials (SPIRIT) guidelines (64). Any significant modifications to the protocol were communicated to the trial registry and the Research Ethics Board, as per SPIRIT recommendations, and publicly updated on GitHub.

To ensure participant safety, the study was covered by a social responsibility insurance policy provided by the University of Granada, offering coverage for any necessary ancillary or post-trial care. Importantly, participants were not receiving financial compensation for their involvement in the study.

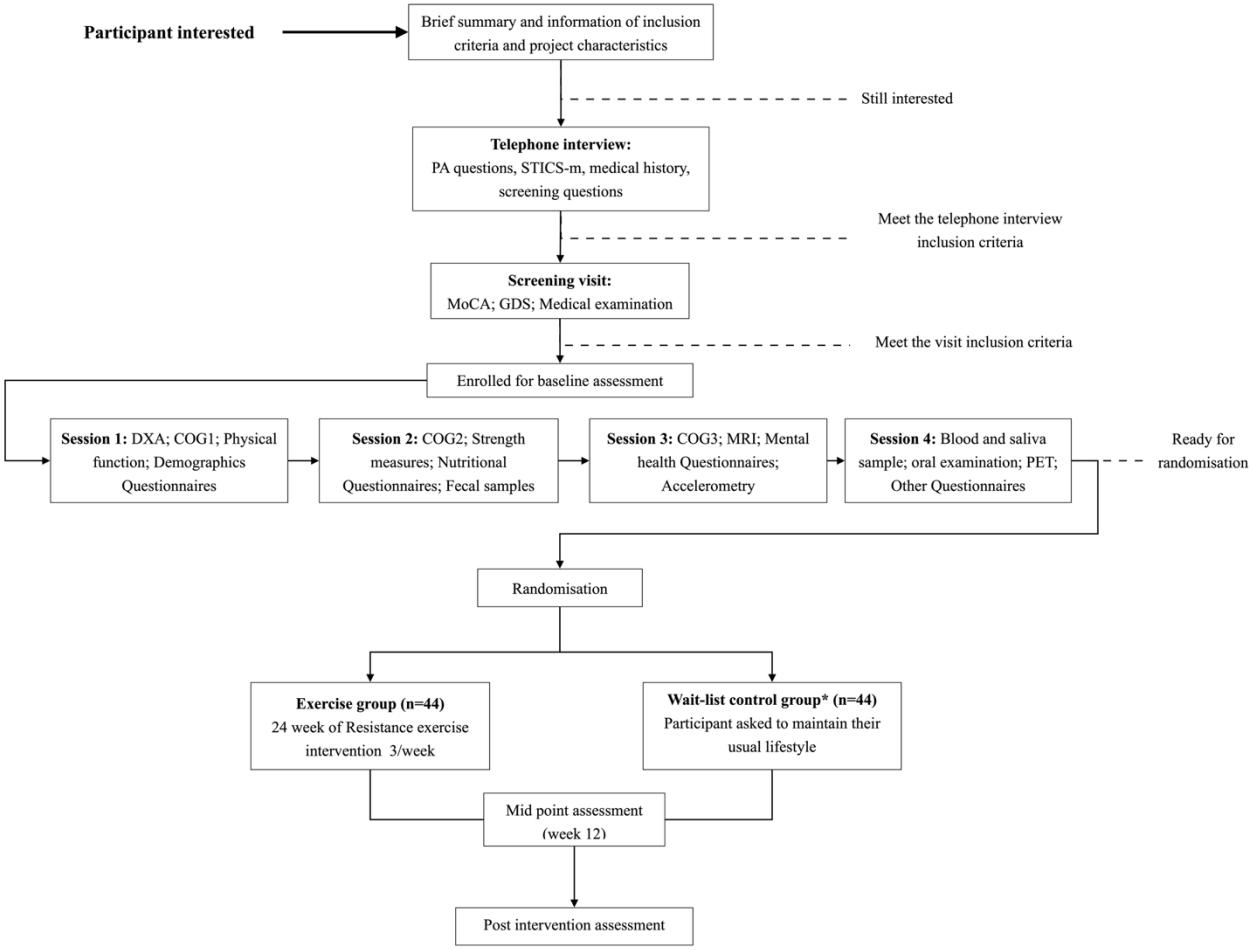

Figure 4. Visual representation of the flow in the AGUEDA trial. PA, Physical activity; STICS-m, Modified Spanish Telephone Interview of Cognitive Status; MoCA, Montreal Cognitive Assessments; GDS, Geriatric Depression Scale; DXA, dual energy X-ray absorptiometry; MMSE, Mini-Mental State Examination; MRI, Magnetic Resonance Imaging; PET, positron emission tomography. *Wait-list control group was asked to maintain its lifestyles during the 24-week period and start the exercise program after the post-intervention assessment. #Post-intervention assessment included the same outcomes as the baseline assessment. (63)

2.2 Recruitment

The recruitment process for the AGUEDA trial began in March 2021 and targets community-dwelling older adults residing in Granada (Spain) and its surrounding areas. To achieve the intended sample size, a multifaceted recruitment strategy has been implemented, combining mass mailings, social media campaigns, and word-of-mouth referrals. Additionally, advertisements in newspapers, television, radio, and online platforms have been used to enhance outreach and maximize participant enrollment.

The study aims to enroll 90 cognitively normal older adults, aged 65 to 80 years, who meet the inclusion and exclusion criteria detailed in **Table 1**. The recruitment, enrollment, and randomization processes are conducted on a rolling basis, allowing for continuous participant intake until the target sample size is reached (63).

Table 1. AGUEDA inclusion and exclusion criteria for selecting participants. (63)

Inclusion criteria	**Exclusion criteria**
- Men and women 65-80 years old.	- Ambulatory with pain or regular use of an assisted walking device
- Able to speak and read fluent Spanish.	- Medical contraindication for inclusion in an exercise program.
- Living in community during the study.	- Neurological condition (Multiple Sclerosis, Parkinson Disease, Dementia) or brain injury (traumatic or stroke).
- Reliable means of transportation.	- Current diagnosis and treatment of a DSM V Axis I or II disorder including major depression and seeing a psychologist, therapist, or psychiatrist.
- Being physically inactive: (i) not participating in any resistance exercise programs in the last 6 months, and (ii) accumulating less than 600 METs/week of moderate-vigorous physical activity.	- History of major psychiatric illness including schizophrenia, general anxiety disorder or depression (GDS-30≥15).
- Classified as cognitively healthy according to Stics-m, MoCA and MMSE.	- Current treatment for congestive heart failure, angina, uncontrolled arrhythmia, deep venous thrombosis or another cardiovascular event.
	- Myocardial infarction, coronary artery bypass grafting, angioplasty or other cardiac condition in the last year.
	- Current or previous treatment for any type of cancer.
	- Type I Diabetes or uncontrolled Type II Diabetes defined as Insulin dependent.
	- Current treatment for alcohol or substance abuse.
	- Presence of metal implants (e.g., pacemaker, stents, joint replacement) that would be MRI ineligible.
	- Claustrophobia.
	- Color blindness.
	- Diagnosis of COVID-19 with hospitalization in intensive care unit.
	- Any other consideration that interferes with the study aims and could be a risk to the participant, at the discretion of the researcher (e.g., to be participating in a different project).

DSM: Diagnostic and Statistical Manual of Mental Disorders, GDS: Geriatric Depression Scale, METs: Metabolic Equivalents, MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment.

2.3 Screening

2.3.1. Telephone screening

As part of the recruitment process, an initial telephone screening is conducted with individuals who express interest in participating in the AGUEDA trial (63). This preliminary interview serves to assess eligibility based on key criteria before scheduling an on-site evaluation.

During the call, a trained evaluator collects relevant information regarding the participant's structured exercise habits, physical activity levels, medical history, and Magnetic Resonance Imaging (MRI) compatibility. Additionally, demographic data are recorded to ensure a comprehensive assessment.

Cognitive function is evaluated using the Spanish version of the modified Telephone Interview for Cognitive Status (STICS-m) (65). To qualify for further screening, participants must obtain a score of ≥26 points on this test.

Following the interview, an initial verification of inclusion and exclusion criteria is conducted, considering the participant's medical history, physical activity levels, MRI safety considerations, and cognitive status. Only those who meet the preliminary requirements proceed to the on-site screening visit.

2.3.2. On-site screening

Prior to participant enrollment in baseline assessments, an on-site screening is conducted to ensure that individuals meet the inclusion and exclusion criteria established for the AGUEDA trial. This in-person evaluation includes a comprehensive cognitive assessment, a depression screening, and a medical examination to determine the participant's suitability for engaging in a resistance exercise program (see **Table 1**) (63).

Cognitive function is assessed using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), which are administered on separate visits. Both tests have a maximum score of 30 points and serve to confirm cognitive normality among participants. The MoCA cut-off scores are adjusted based on age and years of education for the Spanish population, following the criteria established by (66): <71 years: ≥24/30; 71–75 years: ≥22/30; >75 years: ≥21/30. For the MMSE, a score of ≥25/30 is required to qualify for participation.

In addition to cognitive screening, the Geriatric Depression Scale (GDS-30) was administered to assess depressive symptoms (67). A score of ≥15 points on the GDS-30 was considered indicative of significant depressive symptoms and results in exclusion from the study (68).

Finally, a medical examination was conducted by a physician to evaluate the participant's physical health and safety for participation in a resistance exercise program. Only individuals who meet all cognitive, psychological, and medical criteria proceed to the baseline assessments of the trial.

RESULTS AND DISCUSSION

Chapter 3. Cross-sectional study: Associations between muscular strength and mental health in cognitively normal older adults: a cross-sectional study from the AGUEDA trial.

Associations between muscular strength and mental health in cognitively normal older adults: a cross-sectional study from the AGUEDA trial.

Bellón D, Rodriguez-Ayllon M, Solis-Urra P, Fernandez-Gamez B, Olvera-Rojas M, Coca-Pulido A, Toval A, Martín-Fuentes I, Bakker EA, Sclafani A, Fernández-Ortega J, Cabanas-Sánchez V, Mora-Gonzalez J, Gómez-Río M, Lubans DR, Ortega FB, Esteban-Cornejo I. Associations between muscular strength and mental health in cognitively normal older adults: a cross-sectional study from the AGUEDA trial. Int J Clin Health Psychol. 2024 Apr-Jun;24(2):100450. doi: 10.1016/j.ijchp.2024.100450. Epub 2024 Mar 19. PMID: 38525016; PMCID: PMC10960140.

3.1 Abstract

Objective: To examine the associations between muscular strength and mental health. **Design**: We used baseline data of 91 cognitively healthy older adults (71.69± 3.91 years old, 57% women) participating in the AGUEDA randomized controlled trial. **Methods**: Muscular strength was assessed using both objective (i.e., handgrip strength, biceps curl, squats, and isokinetic test) and perceived (i.e., International Fitness Scale) indicators. Psychological ill-being indicators: anxiety, depression, stress, and loneliness; and psychological well-being indicators: satisfaction with life, self-esteem, and emotional well-being) were assessed using a set of valid and reliable self-reported questionnaires. Linear regression analyses were performed adjusting for sex, age, years of education, body mass index (BMI), alcohol, diet, and smoking (model 1), and additionally by cardiorespiratory fitness (model 2). **Results**: Elbow extension was positively associated with stress in model 1 (β = 0.252, 95% Confidence Interval [95% CI] = 0.007 to 0.497, p = 0.044), and even after further adjustment for cardiorespiratory fitness (β = 0.282, 95% CI = 0.032 to 0.532, p = 0.028). Perceived strength was negatively associated with depressive symptoms in model 1 (β = -0.271, 95% CI = (-0.491 to -0.049, p = 0.017) and model 2 reported associations tending towards significant (β = -0.220, 95% CI = -0.445 to 0.005, p = 0.055). Handgrip strength was positively associated with self-esteem in model 1 (β = 0.558, 95% CI = 0.168 to 0.949, p = 0.006) and model 2 (β = 0.546, 95% CI = 0.135 to 0.956, p = 0.010). No further associations were found among other muscular strength and mental health variables. **Conclusion**: Handgrip had a moderate association with self-esteem and there was a small association between perceived strength with depressive symptoms and elbow extension with stress. No other associations were observed between muscular strength and mental health outcomes in cognitively normal older adults.

3.2 Introduction

The World Health Organization (WHO) estimates that, by 2050, the world's population over 60 years of age will reach 2.1 billion (69). Worldwide, mental disorders affect 21% of the elderly, which contribute to other physical health problems, neurodegenerative diseases, or high morbidity (70,71) In Spain, mental disorders affect 32% of older adults, with the highest prevalence for anxiety (18%) and major depression (10%) (72). These are alarming figures, especially given the sizeable public healthcare costs that derive from them (73). Most studies in this population have focused on treating mental disorders, however, preventing the onset of the disease is essential by reducing risk factors, halting its progression, and attenuating its consequences. The first signs of mental disorders are shown as symptoms, and for this reason, it is relevant to identify modifiable risk factors (74).

Muscular strength, defined as the maximal capacity of a muscle, or group of muscles, to exert a force under a given set of conditions, is a modifiable risk factor for mortality and disease incidence (75,76). Aging results in diminished muscular strength attributed to physiological changes such as decreased voluntary activation, increased antagonist muscular co-activation, a reduced muscle mass due to sarcopenia, and the overall decline in muscular performance (77–79). Several meta-analyses showed that lower handgrip strength is associated with an increased risk of depressive symptoms in adults and older adults (74,80,81). In addition, higher levels of handgrip strength are associated with a lower incidence of depression and anxiety in adults and older people (82). There is a range of psychosocial, behavioral, and neurobiological mechanisms that may explain the link between muscular strength and mental health (50). For example, participating in physical activity (i.e., resistance training) that enhances muscular strength may provide older adults with self-confidence that leads to improved well-being. In addition, resistance training is an activity that requires focus and attention safely in executive movements. The cognitive demand of resistance training may facilitate improvements in cognition (83). Regarding neurobiological mechanisms, there is a link between muscular strength and mental health posits that increased muscular strength may elevate hormone levels, including cytokines and myokines, which play a protective role against depression through pathways such as synaptic plasticity or monoamine metabolism (84).

Although the associations between muscular strength and mental health symptoms appear mechanistically plausible, there are still several gaps in our understanding of these relationships during the aging. First, most studies have focused on examining associations between muscular strength and symptoms of depression (74,80,81) and anxiety (85). Therefore, more research is needed to understand the role of muscular strength in older adults and focus on other psychological ill-being outcomes, such as loneliness. These outcomes are particularly relevant for the mental health of older people, which are major risk factors for physical and mental illness in older adults (86,87).

Second, few studies have examined associations between muscular strength and psychological well-being outcomes in older adults (i.e., "the combination of feeling good and functioning effectively") such as satisfaction with life (85,88). Older adults with higher psychological well-being are more likely to be healthier, live longer and enjoy a better quality of life (89,90). As such, there is a need to examine associations between muscular strength and psychological ill-being as well as psychological well-being in older adults. Third, most studies have only focused on field-based muscular strength such as the handgrip test when relating it to mental health in the elderly (91). Although handgrip strength is a well-known indicator of overall muscular strength (92), it is important to contrast findings with complementary muscular strength indicators (i.e., laboratory tests and self- assessments). Some measurements may be more sensitive than others or some measurements are related to different mechanisms of action. Finally, there is a need to examine associations between individuals' perceived strength, which is understood as the self-assessment of their muscular strength, and their mental health. It is possible that self-perceptions act as a mediator of the relationship between muscular strength and mental health. It could reveal additional insights to complement the information provided by objective measures of muscular strength.

Overall, examining the associations of different muscular strength indicators using objective (i.e., field and laboratory tests) and perceived indicators (i.e., self-reports), with positive and negative indicators of mental health, will provide novel information needed for further identification of risk factors. Therefore, our study aimed to examine the associations between muscular strength (i.e., handgrip strength, biceps curl, squats, elbow-knees extension, and perceived strength) and mental health including psychological ill-being (i.e., anxiety, depression, stress, and loneliness) and well-being (i.e., satisfaction with life, self-esteem, and emotional well-being) in cognitively normal older adults.

3.3 Methods

3.3.1 Design and Ethics

Our study was carried out under the framework of the AGUEDA trial ("Active Gains in brain Using Exercise During Aging"). AGUEDA is a single-site, two-arm, single-blind randomized controlled trial (RCT). Participants were recruited by community-dwelling older adults in Granada (Spain) city and surrounding areas from March 2021 to May 2022. In particular, the present cross-sectional analyses were completed using data from the baseline assessment before randomization, from a total sample of 91 cognitively normal older adults (65-80 years).

We have previously provided a detailed description of the study's inclusion and exclusion criteria (63,93). In brief, before the enrollment of participants in the assessments, a telephone screening and an on-site screening were performed to determine whether participants met inclusion/exclusion criteria. The main inclusion criteria were to be a cognitively normal older adult between 65 to 80 years, without depressive symptoms (assessed by the Geriatric Depression Scale (68), and physically inactive.

Our study was conducted according to the Declaration of Helsinki and has been approved by the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; #2317-N-19) on May 25th, 2020. The trial was registered on Clinicaltrials.gov (ClinicalTrials.gov Identifier:; Submission date: December 22, 2021), and all participants gave written informed consent after all study details were explained to them.

3.3.2. Muscular strength

Muscular strength was assessed using both objective and perceived measures. Objective indicators for upper and lower-body muscular strength were assessed using: a handgrip test (94,95), biceps curl and squats following the Senior Fitness Test (SFT) (96), and an isokinetic test (97,98) including elbow and knee extension. Perceived strength was assessed using the International Fitness Scale (IFIS) (99).

3.3.2.1. *Handgrip Strength*

Each participant was encouraged to perform the maximal isometric force twice with each hand using a hand dynamometer (TKK 5101 Grip D, Takey, Tokyo, Japan). The subject holds the dynamometer in the hand to be tested, with the arm at right angles and the elbow by the side of the body. When ready, the subject squeezes the dynamometer with maximum isometric effort, which is maintained for about 5 seconds. No other body movement is allowed.
The maximum value of each hand was taken and averaged in kilograms (kg) as an indicator of upper-body muscular strength.

3.3.2.2 *Biceps Curl*

Participants performed bicep curl maximal repetitions in 30 seconds with the dominant arm using a dumbbell of 2.26 kg/5 lbs for women and 3.62 kg/8 lbs for men. The participant took the test twice and scored the highest. The test was carried out sitting on a chair, and the number of repetitions was used as an indicator of upper-body muscular strength.

3.3.2.3 *Squats*

Participants performed as many squats as possible in 30 seconds. The participant started by sitting on a chair and was instructed to stand up and sit back down on the chair. Participants had their hands folded across their chests to avoid helping themselves get up, and they performed the squat test twice. The participant took the test twice and scored the highest. The maximum number of repetitions was used as an indicator of lower-body muscular strength.
3.3.2.4 *Isokinetic Test*

Elbow Extension

This test was performed using the isokinetic machine (Gymnex Iso-2 dynamometer, EASYTECH S.r.l., Italy). Initially, the participant's position was as follows: back fully against the back of the seat. The non-performing handheld grip at the end. The elbow angle was approximately 130° to the horizontal. Elbow height was at the participant's chest height. In addition, before the exercise was performed, the participant received

specific instructions and started with a warm-up, which consisted of performing 10 repetitions at a slow and controlled speed. Then, the exercise consisted of extending the participant's elbow by 180º a total of five times while exerting the maximum possible force. The exercise was performed sequentially with each arm. The result was obtained from the average of the five repetitions of elbow extension in both arms, using the maximum peak force, also known as torque, and it was expressed in Newton meters (Nm).

Knee Extension

This test was performed using the same isokinetic device that was used for elbow extension. Initially, the participant's position was as follows: the knee formed an angle of approximately 90° to the horizontal. The back was fully against the back of the seat, and the hands held the grips at both ends. In addition, before the exercise was performed, the participant received specific instructions and started with a warm-up. Then, the exercise consisted of extending the participant's knee by 180 degrees a total of five times while exerting the maximum possible force. The exercise was performed sequentially with each leg. The result was obtained from the average of the five repetitions of knee extension in both legs, using the maximum peak force (Nm).

3.3.2.5. *Perceived strength*

Perceived strength was assessed using a single item from the International Fitness Scale (IFIS). Participants were asked to "rate their level of muscular strength as compared to people of the same age", with answers based on a 5-point Likert scale (very poor, poor, average, good, and very good). A higher score indicates greater perceived strength.

3.3.3. Mental health

3.3.3.1. *Psychological ill-being outcomes*

Anxiety and depressive symptoms

The Hospital Anxiety and Depression Scale (HADS) is a valid and reliable self-report questionnaire to assess anxiety and depressive symptoms in the Spanish population (100).

It consisted of 14 items with a categorized range from 0 to 3. The sum of the scores on odd-numbered questions generates a final score for anxiety, and the sum on even-numbered questions generates a final score for depression. Each direct score obtained ranges between 0 to 21, with a higher score corresponding to a higher level of anxiety or depression.

Stress

The Perceived Stress Scale (PSS) is a valid and reliable self-report tool to assess stress in adults. It consists of 14 items with a five-point scale response format. The direct score obtained ranges from 0 to 56, with a greater score indicating a higher level of perceived stress (101,102).

Loneliness

The University of California, Los Angeles Loneliness (UCLA-L) scale is a valid and reliable self-report to assess loneliness in older adults. This consists of 10 questions, with a four-point scale response format, giving a minimum of 10 and a maximum of 40 points so that an increased score corresponds to a higher level of loneliness (86,103).

3.3.3.2. Psychological well-being

Satisfaction with life

The Satisfaction with Life Questionnaire (SWLQ) is a valid and reliable self-report to assess satisfaction with life in older adults. It consisted of five questions with a five-point scale response format, with a minimum total score of 5 (low satisfaction) and a maximum of 25 (high satisfaction) (104).

Self-esteem

The Rosenberg Self-Esteem scale (RSE) is a valid and reliable self-report to assess self-esteem in adults. It consisted of 10 items with a four-point scale response format. The

total score ranged from 0 to 30, which indicates that a higher score corresponds to a higher level of self-esteem (105,106).

Emotional well-being

The SF-36 questionnaire is a valid and reliable self-report to assess emotional well-being in older adults. It consists of 5 items with a five-point scale response format, giving a minimum of 0 and a maximum of 100 points. The direct score obtained indicates that a higher score corresponds to a higher level of emotional well-being (107,108).

3.3.4. Covariates

Based on the available literature focused on mental health in older adults, we included the following covariates in our models: sex, age and years of education (109–111); diet, alcohol consumption and smoking (112,113), body mass index (BMI) and cardiorespiratory fitness (CRF) (114–116). Years of education were obtained by asking them, "*How many years of education did you complete?".* Diet quality was assessed with the adherence to the Mediterranean diet (MEDAS 14) questionnaire, using a total score ranging from 0 to 14 (117). We asked participants how often they consumed more than 5 alcoholic drinks for men and more than 4 for women in the last 12 months. Alcohol consumption was categorized into heavy (>5 drinks per week), moderate (<1 drink per month or 1-2 drinks per week), and never (never or not in the last 12 months). Participants were also asked: "Do you smoke?", and responses were categorized into current smokers, former smokers, or have never smoked. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2). Finally, cardiorespiratory fitness was assessed with the 2-km walking test (sec) (114,115), in which participants were asked to complete 2 km walking as fast as possible around a rectangular circuit.

3.3.5. Statistical analysis

The descriptive characteristics of the study sample were presented as means and standard deviation (SD) or numbers (percentages). Normal distribution was inspected with histograms and the Kolmogorov–Smirnov test. Interactions between sex and muscular strength variables were tested for psychological ill-being and psychological well-being, but no significant interactions were found. We explored Pearson´s correlation between muscular strength (exposures) measures and mental health (outcomes). The associations

between muscular strength and mental health outcomes were examined using linear regression models, adjusted for sex, age, years of education, diet, alcohol, smoking, and BMI (model 1). Finally, model 2 was additionally adjusted by cardiorespiratory fitness to examine whether cardiorespiratory fitness attenuated the association of muscular strength with mental health outcomes. We used the standardized β values and 95% CI to show the associations together with their P-value (the significance level was set at $p<0.05$). We interpreted it as an association size indicator, in which a value of 0.2 is considered a small association size, 0.5 is considered a medium association size, and 0.8 is considered a large association size. False discovery rate (FDR) (Benjamini–Hochberg method) was used to adjust for multiple comparisons (118). Correction for multiple comparisons was based on all models, one and all models two, for a total of 84 tests. The analyses were conducted in R Studio (version 4.1.1) with the *stats* and *lm.beta* packages. The database and scripts are reposited at GitHub.

3.4 Results

Descriptive characteristics are presented in **Table 2**. Ninety-one cognitively healthy older adults, 71.69 3.91 years old, participated in the study, of which 57% were women. Associations of muscular strength with psychological ill-being and psychological well-being outcomes are shown in **Figure 5** and **Figure 6,** respectively.

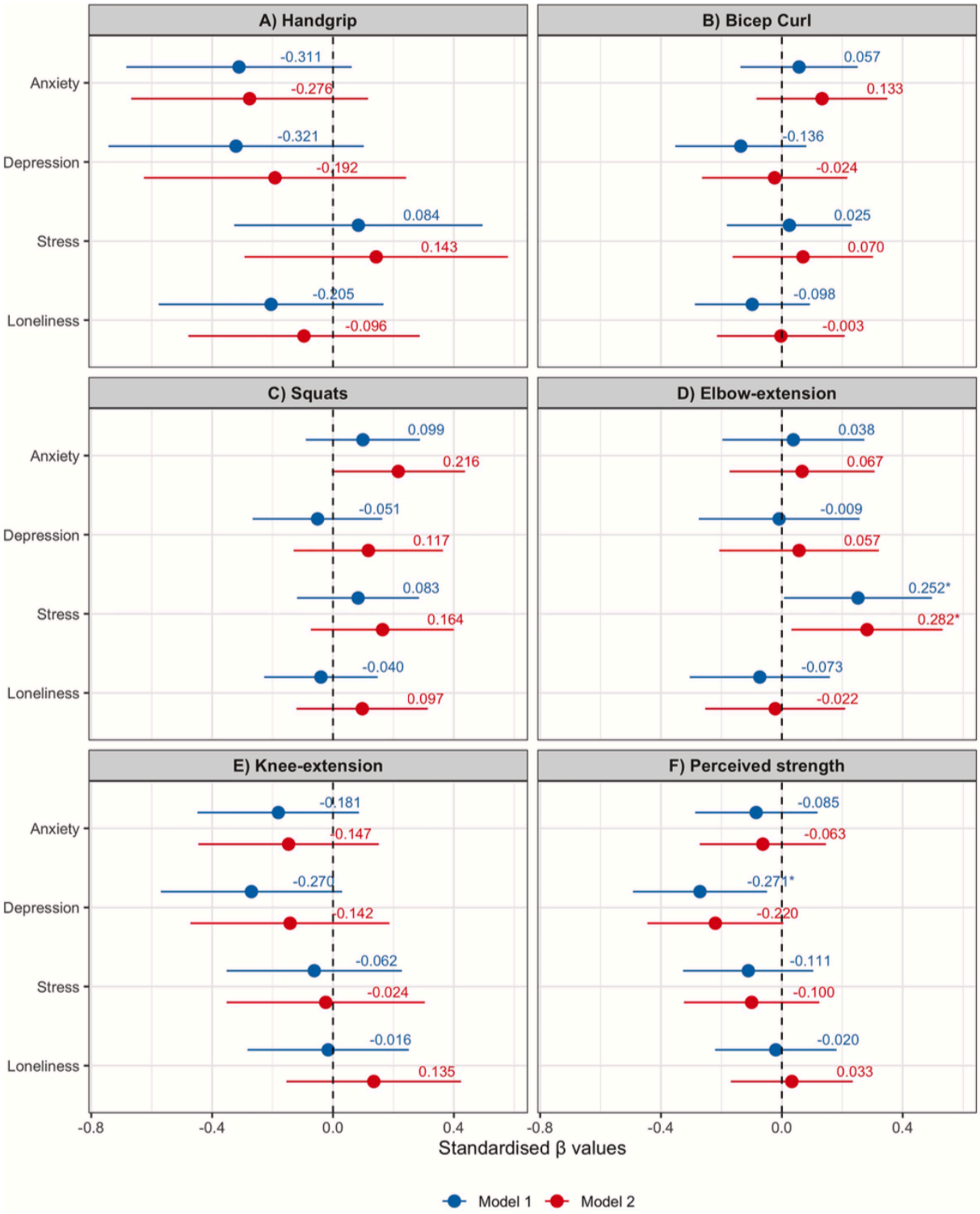

Figure 5. Associations of muscular strength with psychological ill-being in cognitively normal older adults. Model 1 was adjusted for sex, age, years of education, body mass index (BMI), diet, smoking, and alcohol, and model 2 was additionally adjusted for cardiorespiratory fitness. Values are standardized regression coefficients (β). *Denotes statistically significant.

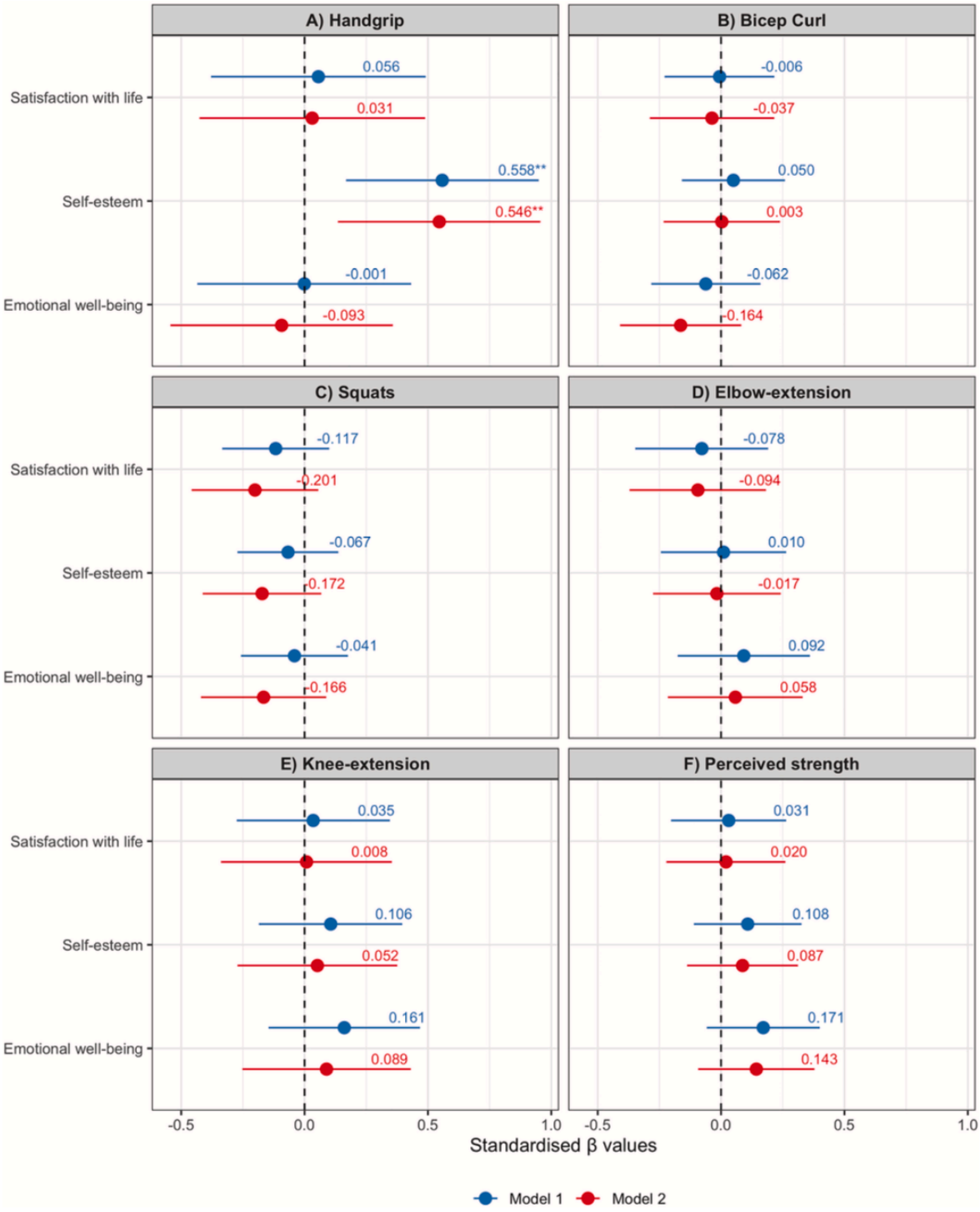

Figure 6. Associations of muscular strength with psychological well-being in cognitively normal older adults. Model 1 was adjusted for sex, age, years of education, body mass index (BMI), diet, smoking, and alcohol, and model 2 was additionally adjusted for cardiorespiratory fitness. Values are standardized regression coefficients (β). *Denotes statistically significant ($p < 0.05$).
** Denotes statistically significant ($p < 0.01$).

For psychological ill-being, elbow extension was positively associated with stress in model 1 (β = 0.252, 95% Confidence Interval [95% CI] = 0.007 to 0.497, p = 0.044), and even after further adjustment for cardiorespiratory fitness (β = 0.282, 95% CI = 0.032 to 0.532, p = 0.028). Perceived strength was inversely associated with depressive symptoms in model 1 (β = -0.271, 95% CI = (-0.491 to -0.049, p = 0.017) and model 2 reported associations tending towards significance (β = -0.220, 95% CI = -0.445 to 0.005, p = 0.055). For psychological well-being, handgrip strength was positively associated with self-esteem in model 1 (β = 0.558, 95% CI = 0.168 to 0.949, p = 0.006) and model 2 (β = 0.546, 95% CI = 0.135 to 0.956, p = 0.010). No further associations were found between other muscular strength variables and psychological ill-being (**Table 3)** or psychological well-being **(Table 4**).

Table 3. Associations of muscular strength with psychological ill-being in cognitively normal older adults.

Muscular Strength	Handgrip Strength		Biceps Curl		Squats		Knee Extension		Elbow Extension		Perceived Strength	
	β (CI)	*p*	*β (CI)*	*p*	*β(CI)*	*p*	*β(CI)*	*p*	*β(CI)*	*p*	*β(CI)*	*p*
Anxiety (HADS)												
Model 1	-0.311 (-0.684, 0.062)	0.101	0.057 (-0.137, 0.251)	0.300	0.099 (-0.090, 0.288)	0.711	-0.181 (-0.449, 0.086)	0.181	0.038 (-0.200, 0.273)	0.748	-0.085 (-0.287, 0.118)	0.408
Model 2	-0.276 (-0.668, 0.120)	0.165	0.133 (-0.084, 0.349)	0.227	0.216 (-0.004, 0.437)	0.055	-0.147 (-0.446, 0.152)	0.33	0.067 (-0.173, 0.307)	0.582	-0.063 (-0.272, 0.146)	0.552
Depression (HADS)												
Model 1	-0.321 (-0.743, 0.102)	0.135	-0.136 (-0.353, 0.081)	0.216	-0.051 (-0.266, 0.163)	0.635	-0.270 (-0.570, 0.030)	0.077	-0.009 (-0.275, 0.257)	0.945	**-0.271 (-0.491, -0.049)**	**0.017**
Model 2	-0.192 (-0.626, 0.242)	0.382	-0.024 (-0.264, 0.217)	0.844	0.017 (-0.130, 0.364)	0.409	-0.142 (-0.472, 0.187)	0.392	0.057 (-0.207, 0.321)	0.669	-0.220 (-0.445, 0.005)	0.055
Stress (PSS)												
Model 1	0.084 (-0.327, 0.495)	0.684	0.025 (-0.182, 0.231)	0.812	0.083 (-0.119, 0.285)	0.414	-0.062 (-0.352, 0.228)	0.672	**0.252 (0.007, 0.497)**	**0.044**	-0.111 (-0.327, 0.104)	0.307
Model 2	0.143 (-0.293, 0.579)	0.515	0.07 (-0.163, 0.302)	0.552	0.164 (-0.073, 0.400)	0.173	-0.024 (-0.352, 0.304)	0.885	**0.282 (0.032, 0.532)**	**0.028**	-0.100 (-0.324, 0.124)	0.376
Loneliness (UCLA-L)												
Model 1	-0.205 (-0.577, 0.1667)	0.275	-0.098 (-0.288, 0.093)	0.312	-0.04 (-0.228, 0.148)	0.672	-0.016 (-0.283, 0.251)	0.905	-0.073 (-0.305, 0.159)	0.535	-0.02 (-0.221, 0.181)	0.845
Model 2	-0.096 (-0.479, 0.287)	0.619	-0.003 (-0.215, 0.208)	0.974	0.097 (-0.121, 0.314)	0.379	0.135 (-0.154, 0.424)	0.357	-0.022 (-0.254, 0.210)	0.851	0.033 (-0.169, 0.235)	0.745

Values are standardized regression coefficients (*β)*. Model 1 was adjusted for sex, age, years of education, body mass index (BMI), diet, smoking, and alcohol, and model 2 was additionally adjusted for cardiorespiratory fitness. **HADS**: The Hospital Anxiety and Depression Scale. **PSS**: Perceived Stress Scale. **UCLA-L**: UCLA Loneliness Scale. Statistically significant values are shown in bold.

Table 4. Associations of muscular strength with psychological well-being in cognitively normal older adults.

Muscular Strength	Handgrip Strength		Biceps Curl		Squats		Knee Extension		Elbow Extension		Perceived Strength	
	β (CI)	*p*	*β (CI)*	*p*	*β(CI)*	*p*	*β(CI)*	*p*	*β(CI)*	*p*	*β(CI)*	*p*
Satisfaction with life (SWLQ)												
Model 1	0.056 (-0.379,0.491)	0.798	-0.006 (-0.229, 0.216)	0.954	-0.117 (-0.334, 0.100)	0.286	0.035 (-0.275, 0.346)	0.821	-0.078 (-0.348, 0.191)	0.566	0.031 (-0.201, 0.264)	0.794
Model 2	0.031 (-0.426, 0.489)	0.892	-0.037 (-0.289, 0.216)	0.774	-0.201 (-0.458, 0.056)	0.123	0.008 (-0.339, 0.354)	0.966	-0.094 (-0.371, 0.182)	0.500	0.020 (-0.222, 0.261)	0.871
Self-esteem (RSE)												
Model 1	**0.558 (0.168, 0.949)**	**0.006**	0.050 (-0.159, 0.259)	0.634	-0.067 (-0.272, 0.137)	0.516	0.106 (-0.185, 0.396)	0.472	0.01 (-0.244, 0.264)	0.938	0.108 (-0.109, 0.326)	0.327
Model 2	**0.546 (0.135, 0.956)**	**0.010**	0.003 (-0.233, 0.239)	0.982	-0.172 (-0.413, 0.068)	0.158	0.052 (-0.272, 0.376)	0.749	-0.017 (-0.276, 0.242)	0.897	0.087 (-0.138, 0.312)	0.443
Emotional well-being (SF-36)												
Model 1	-0.001 (-0.435, 0.432)	0.995	-0.062 (-0.283, 0.160)	0.582	-0.041 (-0.268, 0.176)	0.711	0.161 (-0.146, 0.468)	0,3	0.092 (-0.176, 0.360)	0.497	0.171 (-0.058, 0.400)	0.141
Model 2	-0.093 (-0.544, 0.358)	0.683	-0.164 (-0.410, 0.082)	0.189	-0.166 (-0.420, 0.088)	0.494	0.089 (-0.252, 0.431)	0.605	0.058 (-0.216, 0.331)	0.676	0.143 (-0.093, 0.379)	0.232

Values are standardized regression coefficients (*β)*. Model 1 was adjusted for sex, age, years of education, body mass index (BMI), diet, smoking, and alcohol, and model 2 was additionally adjusted for cardiorespiratory fitness. **RSE**: The Rosenberg Self-Esteem Scale. **SF-36:** Short Form 36 questionnaire. **SWLS**: Satisfaction With Life.

Overall, the present study found a relationship between muscular strength and mental health, highlighting a positive moderate significant association between handgrip strength and self-esteem. However, these results should be taken cautiously as all associations became non-significant when analyses were adjusted for multiple comparisons (FDR > 0.252). All the correlations between muscular strength and mental health outcomes are represented in **Figure 7.**

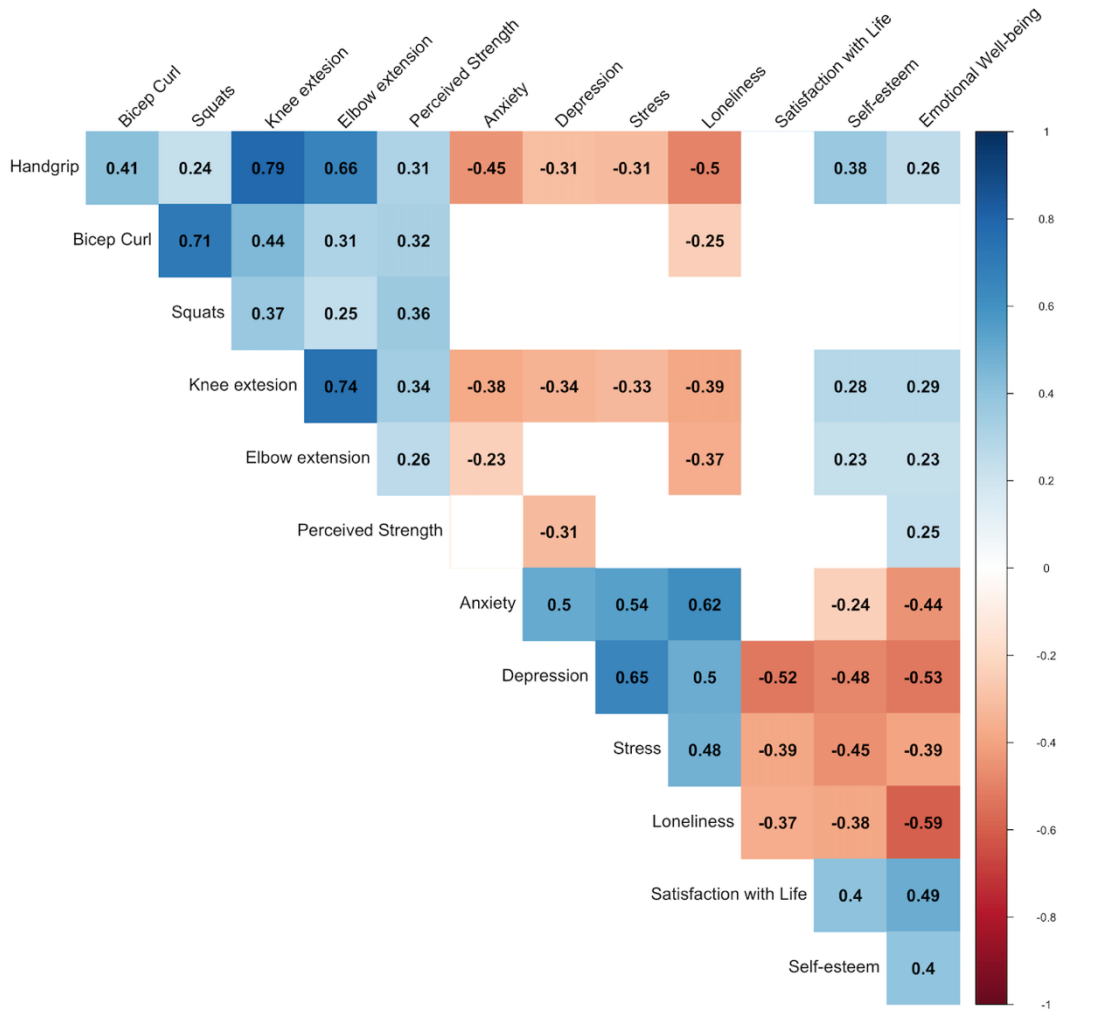

Figure 7. Correlations between muscular strength and mental health outcomes. Only significant correlations ($p<0.05$) are shown in this figure.

3.5 Discussion

This study examined the associations between different measures of muscular strength and mental health, including psychological ill-being and well-being, in a sample of cognitively normal older adults. Overall, perceived strength was associated with depressive symptoms; in contrast, we did not observe any association between any objectively measured muscular strength indicators and depressive symptoms. We found a moderate association between handgrip strength and self-esteem. Contrary to our expectations, higher elbow extension muscular strength was positively associated with stress levels. Most of these associations were independent of cardiorespiratory fitness status but became non-significant when analyses were adjusted for multiple comparisons. No other associations were observed between muscular strength and mental health outcomes in cognitively normal older adults.

We found that higher levels of perceived strength were associated with lower depressive symptoms in older adults in the first model. A possible explanation could be that experiencing a sense of strength may enhance the confidence of older individuals in maintaining their daily routines and fulfilling certain psychological needs, such as social connection and autonomy, which in turn, could protect them against the onset of depressive symptoms. In contrast, we did not observe any association between any objectively measured muscular strength indicators and depressive symptoms. It may suggest that for older people, feeling stronger could be more relevant than being stronger itself (119). However, this explanation is not in line with previous studies that observed an association between objectively measured muscular strength and depression in older people (82,120,121). Nevertheless, we only included participants without any severe mental disorder, which might explain the absence of an association between muscular strength and depressive symptoms. Therefore, future studies in clinical and non-clinical samples are warranted in older people with different mental health conditions. Lastly, no previous studies have explored the role of both objective and perceived strength in the mental health of cognitively normal older adults, which hampers the comparison of our results with current literature. However, in other populations, such as in people with fibromyalgia (122), both objective and subjective overall physical fitness was independently associated with lower psychological ill-being (i.e., negative emotions). In children and adolescents, perceived muscular strength was suggested as a mechanism that could explain the effect of physical exercise on psychological ill-being outcomes (48).

Overall, understanding the role of both objective and perceived strength in the mental health of older people might help to design more effective interventions for protecting mental health at these ages. Thus, more studies with larger sample sizes and including both muscular strength components are still needed in older people.

This study shows that handgrip strength was positively associated with self-esteem in our study sample. Previous evidence shows that muscular strength was related to other well-being variables (85,88). Even though we cannot compare these results in older adults, there are studies in children that show that greater muscular strength is related to self-esteem (123). One explanation for the relationship between muscular strength and self-esteem could be that the elderly with greater strength may have a better feeling of being fit, greater self-confidence, and positive energy associated with good health. Additionally, the elderly with greater muscular strength could have a better perception of their body image, so that they feel that they are stronger or even that their strength is aligned with aesthetic or personal ideals. Hence, self-esteem could be a mechanism through which muscular strength might improve other components of mental health. In our study, we have observed that self-esteem correlates with other components such as depression and anxiety. Therefore, future studies should test whether self-esteem is a mechanism through which strength is associated with other mental health outcomes. In the literature, self-esteem has been shown one of the most important mechanisms which mediate the associations between physical activity and psychiatric symptoms in youth (124). Consequently, it is essential to investigate whether this outcome holds for muscular strength as well.

Contrary to our expectations (i.e., higher muscular strength would be associated with lower levels of stress (125), we found that higher elbow extension muscular strength was positively associated with stress levels in older adults. This result must be interpreted carefully for several reasons. First, the overall stress levels in our population were low (i.e. “occasionally stressed” for males and “rarely or never stressed” for females) with only a limited proportion of individuals with high-stress levels, which makes our result less reliable. Second, this test based on the isokinetic device, has not been validated in older adults, so more research would be needed to confirm that this instrument measures accurately muscular strength in this population. Lastly, in this study, we assessed the relationship between muscular strength and chronic stress levels (how stressed you have felt in the last month). However, resistance training could have a greater acute effect on stress as seen with other blood markers or other myokines, which do not

remain in the blood for a long time (126,127). As our study is limited to being cross-sectional, we need intervention studies to analyze the acute and chronic effects of muscular strength on stress.

The correlation between muscular strength and other mental health variables, such as loneliness, has not been established, despite initial expectations of a potential relationship with physical activity (128,129). It is plausible that psychosocial mechanisms inherent to physical activity, such as socialization, are the factors that demonstrate an association with these mental health variables, as opposed to the mere aspect of physical fitness itself. It could be that physical activity and not muscular strength are related to them.

Together, the small-moderate magnitude of the associations identified in this study and their loss of statistical significance after adjusting for multiple comparisons might suggest a limitation in statistical power for detecting these effects. Therefore, further investigations with larger sample sizes are warranted to deepen our understanding of the relationship between muscular strength and mental health in older adults.

Our study has several limitations. Firstly, our study was a cross-sectional study, therefore, we are unable to infer causation. Secondly, the small sample size could explain the null associations found in most of the analyses. However, a positive association of handgrip with self-esteem was found. In addition, although we have controlled for potential confounding factors, there may be other variables that could interfere with these associations. On the other hand, the study has several strengths, such as a defined cognitive status on the sample, the standardization, and objective muscular strength measurements including both field and laboratory tests for the lower and upper body, the assessment of perceived strength, and the inclusion of a broad set of mental health indicators.

3.6 Conclusion

Our most robust finding suggests that handgrip muscular strength is positively associated with self-esteem in cognitively normal older adults, which in turn was correlated with most of the explored psychological well-being and ill-being outcomes. Moreover, there was a small positive association between elbow extension and stress and a negative association between perceived strength and depressive symptoms. Many of these associations remained unaffected by cardiorespiratory fitness status; nevertheless, they

lost statistical significance upon adjusting for multiple comparisons in the analyses. No other associations were observed between muscular strength and mental health outcomes in older adults. Future longitudinal studies, incorporating larger sample sizes and including both perceived and objective muscular strength indicators, remain necessary in the elderly. The findings of this research collectively provide valuable insights into considering muscular strength as a potential element in exercise interventions.

Chapter 4. Randomized clinical trial: Effects of a resistance exercise program on mental health in cognitively normal older adults. The AGUEDA Randomized Control Trial.

Bellón D, Rodriguez-Ayllon M, Solis-Urra P, … Esteban-Cornejo I. Effects of a resistance exercise program on mental health in cognitively normal older adults. The AGUEDA Project: a Randomized Control Trial. *JAMA Psychiatry.* (submitted)

4.1 Abstract

Objective: To evaluate the effects of a 24-week resistance exercise program on psychological ill-being and well-being in cognitively normal older adults, and to assess whether these effects are moderated by age, sex, and baseline mental health, and mediated by changes in muscular strength and self-esteem. **Design:** A single-center, parallel-group, 24-week randomized controlled trial conducted from March 2021 to May 2022. Ninety cognitively normal adults aged 65–80 (58% women, mean age 71.7 ± 3.9 years) without depressive symptoms at baseline. Participants were recruited through the media and underwent a two-stage screening process. Participants were randomized to a 24-week supervised resistance exercise program (3 sessions/week) or a no-intervention control group. The program used elastic bands and body weight, tailored to baseline strength and progressively adjusted. Mental health included changes in psychological ill-being (anxiety, depression, stress, loneliness) and well-being (self-esteem, life satisfaction, emotional well-being), assessed by validated self-report questionnaires at baseline and 24 weeks. **Results:** The intervention did not produce statistically significant improvements in any mental health indicator in the full sample. Trends toward reduced anxiety symptoms (z= −0.19, *P*=0.25), depressive symptoms (z= −0.35, *P*=0.08), improved self-esteem (z= 0.26, *P*=0.13), and emotional well-being (z= 0.31, *P*=0.15) were observed. Moderation analyses revealed significant benefits for self-esteem in women (*z*= 0.48, *P*=0.04) and younger (z= 0.51, *P*=0.03) and for anxiety in those with higher baseline distress (*z*= −0.54, *P*=0.03). Mediation analyses identified self-esteem as a significant mediator of mental health improvements in women. **Conclusions:** The intervention did not significantly improve mental health outcomes in the overall sample. However, subgroup analyses suggest that resistance exercise may benefit specific populations, particularly women, younger participants, and individuals with higher initial distress, with self-esteem emerging as a potential psychological mechanism.

4.2 Introduction

The global population is aging rapidly. By 2030, it is projected that over 1.4 billion individuals will be aged 60 or above, constituting nearly one-sixth of the global population. This demographic shift presents critical challenges for healthcare systems, particularly concerning mental health (130). According to the World Health Organization (WHO), approximately 14% of adults aged 60 years and older live with a mental health disorder, including depression, anxiety, and loneliness. These conditions significantly contribute to diminished quality of life, heightened mortality rates, and increased healthcare demands (131,132).

Physical activity is widely recognized as a key strategy for preventing and managing mental disorders, particularly depression(133). In older adults, physical activity is associated with significant improvements in physical and mental health, making it an effective intervention for addressing age-related challenges. However, not all types of physical activity provide the same benefits. Among them, exercise, which refers to structured and repetitive movement aimed at improving fitness, has shown stronger effects on mental health. Notably, resistance training (i.e., strength-focused exercise using resistance bands, free weights, or bodyweight exercises) plays a critical role in preserving muscle function, which is essential for maintaining independence and enhancing quality of life in older adults (134). Beyond its physical benefits, resistance training has shown potential to improve mental health by reducing symptoms of depression and anxiety, with meta-analyses providing robust evidence of its antidepressant effects in healthy older adults (135,136). Despite this, well-being indicators remain largely understudied, even though the WHO considers them essential for complete mental health (137). Consequently, the AGUEDA trial builds on this evidence by offering a novel approach: a structured, scalable 24-week resistance exercise program targeting both psychological ill-being and well-being. Although resistance training benefits mental health, its effects may not be uniform across individuals. Factors such as sex, age, and baseline mental health status may moderate the psychological effects of exercise, yet few studies have explored these interactions systematically. Recent meta-analytic evidence suggests that strength training yields greater mental health benefits in women and is particularly beneficial for younger adults (44). Additionally, individuals with higher baseline psychological distress may experience more pronounced improvements, likely due to a greater margin for change (138). Collectively,

identifying moderators is crucial for personalizing interventions, maximizing their impact, and improving adherence, particularly in populations at risk of mental health decline. Additionally, resistance training in older adults has shown small but positive effects (139–141), suggesting that uncovering key moderators and mediators could enhance these benefits.

It is believed that resistance training modestly affects certain mental health outcomes (e.g., depression), but its impact is stronger when mediated by factors, such as self-esteem an individual's overall sense of personal worth and value (23). Self-esteem is a well-established pathway linking physical activity to mental health, particularly in young populations (43,124,142). However, its role in older adults remains underexplored. In later life, resistance training might enhance self-esteem by improving muscular strength and body perception, both aesthetically and functionally. Greater strength enables everyday activities such as standing up from a chair, carrying heavy objects, or playing with grandchildren critical aspects of maintaining independence and psychological well-being. As aging often leads to muscle loss and declining strength, those improvements can be particularly meaningful.

Overall, increased muscular strength may mediate the mental health benefits of resistance training by fostering physical autonomy and self-perception. However, it remains unclear whether muscular strength itself is the primary mechanism driving improvements in self-esteem and mental health or if other factors such as social interaction or the establishment of a new routine also play a role. Addressing these gaps, the AGUEDA trial aims to provide valuable insights into how resistance training influences mental health in older adults, offering important implications for future interventions. Specifically, the main objectives of this study are to evaluate the effects of a 24-week resistance exercise program on mental health outcomes, including both psychological ill-being and psychological well-being. Additionally, the study examines whether these effects are moderated by factors such as age, sex, and baseline psychological symptomatology and mediated by changes in self-esteem.

4.3 Methods

4.3.1 Trial Design

The research was conducted within the context of the AGUEDA project (Active Gains in brain Using Exercise During Aging). This was a single-center, parallel-group, 24-week randomized controlled trial with a 1:1 allocation ratio. The research protocol was approved by the Research Ethics Board of the Andalusian Health Service (CEIM/CEI Provincial de Granada; #2317-N-19) on May 25th, 2020, and the study was conducted following the Declaration of Helsinki. Trial Registration: ClinicalTrials.gov Identifier: (NCT05186090)

Due to the nature of the intervention, blinding of participants and exercise trainers was not feasible. However, outcome assessors were blinded to group allocation to minimize bias. All participants provided written informed consent after receiving a detailed explanation of the study.

4.3.2 Participants and Recruitment

Participants were recruited via mailings, social media, and newspaper advertisements, with additional coverage on TV, radio, and online platforms. These participants were community-dwelling older adults residing in Granada, Spain, and its surrounding areas. Recruitment occurred on a rolling basis between March 2021 and May 2022. Inclusion criteria were aged 65–80 years, cognitively normal as assessed by the Montreal Cognitive Assessment (MoCA) (143), and the Spanish version of the modified Telephone Interview for Cognitive Status (STICS-m) (65). Participants were also required to be physically inactive, defined as accumulating less than 600 Metabolic Equivalent of Task (METs)/week of moderate-to-vigorous physical activity, and free from depressive symptoms (67). Additional details on the inclusion and exclusion criteria have been published elsewhere (63).

4.3.3 Resistance exercise program

Further details of the program are described in the Consensus on Exercise Reporting Template (CERT) for the AGUEDA trial (93). Participants in the 24-week resistance exercise program attended three 60-minute supervised sessions weekly at the iMUDS Sports Center. The intervention consisted of upper and lower body exercises using elastic bands with different resistance levels and body weight as the primary resistance. The program was structured into three progressive difficulty levels, allowing participants to gradually increase exercise intensity as they improved their physical performance. Sessions were tailored to participants' baseline physical capabilities, with initial assessments determining the appropriate starting level of intensity. The sessions included a 10-minute warm-up phase, a 45-minute main phase, and a 5-minute cool-down phase. The design of these sessions ensured both consistency and variety to maintain engagement. Supervision was provided by certified trainers specialized in older adults, with adherence monitored through attendance records, requiring at least 80% attendance. Flexibility in scheduling was provided to accommodate missed sessions and maintain engagement.

4.3.4 Mental health

Mental health outcomes, assessed at baseline and after 24 weeks, included indicators of psychological ill-being (anxiety-depressive symptoms, stress, and loneliness) and psychological well-being (satisfaction with life, self-esteem, and emotional well-being). Anxiety and depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS). Perceived stress was measured with the Perceived Stress Scale (PSS). Loneliness was evaluated using the UCLA Loneliness Scale. Satisfaction with life was assessed using the Satisfaction with Life Scale (SWLS). Self-esteem was measured using the Rosenberg Self-Esteem Scale (RSES). Finally, emotional well-being was assessed with the SF-36 instrument. These indicators were evaluated using validated self-reported questionnaires (100,101,103–107,144,145). Further details on the implementation and use of these questionnaires in the context of this study can be found in (59).

4.3.5 Statistical analyses

Statistical analyses were performed using R Studio version (4.1.2) with the database and analysis script reposited at GitHub. Descriptive statistics, including means, standard deviations, frequencies, and percentages, were calculated for all variables. Normality was assessed visually using histograms. The primary analysis utilized an Intention-to-Treat (ITT) approach, standardizing intervention effects as z-scores using baseline values for comparison. Cohen's d (146) was used to interpret effect sizes as small (≥0.2), moderate (≥0.5), or large (≥0.8), with statistical significance set at $p < 0.05$.

Primary Analyses

The primary analyses evaluated the effects of the intervention on mental health outcomes from baseline to 24 weeks, using constrained linear mixed-effects models with the LMMstar and lmer packages (147)

Moderation analyses were conducted to examine whether the intervention effects varied by sex (male, female), age (≤72 years, >72 years), or baseline psychological symptomatology (≤median, >median). Interaction terms for each variable were included in the models, and stratified analyses were conducted for each subgroup. The intervention effect within each subgroup was represented by the coefficient for the interaction term and its corresponding 95% confidence intervals (CIs).

Mediation analyses were performed by *lavaan* packages (148). These models included time as a categorical fixed effect, group, and group-by-time interaction, with baseline outcome scores controlled for and intercepts specified as random effects. Unequal variance across time and groups was allowed. Mediation analyses evaluated whether changes in muscular strength and self-esteem mediated the effects of the intervention on mental health outcomes. Knee extension strength was selected as the indicator of muscular strength due to its significant improvement in response to the resistance exercise program observed in the AGUEDA Project (149). Linear mixed-effects models were fitted using the lme4 package to estimate total, direct, and indirect effects. The total effect was determined by regressing each mental health outcome in the intervention group. The mediator effect was assessed by including both the intervention group and the mediator (knee extension strength or self-esteem) in the model. The mediate function from the mediation package was used to calculate direct and indirect

effects, providing formal tests of mediation. The visualization of the mediation panel modeling approach is shown in **Figure 8**.

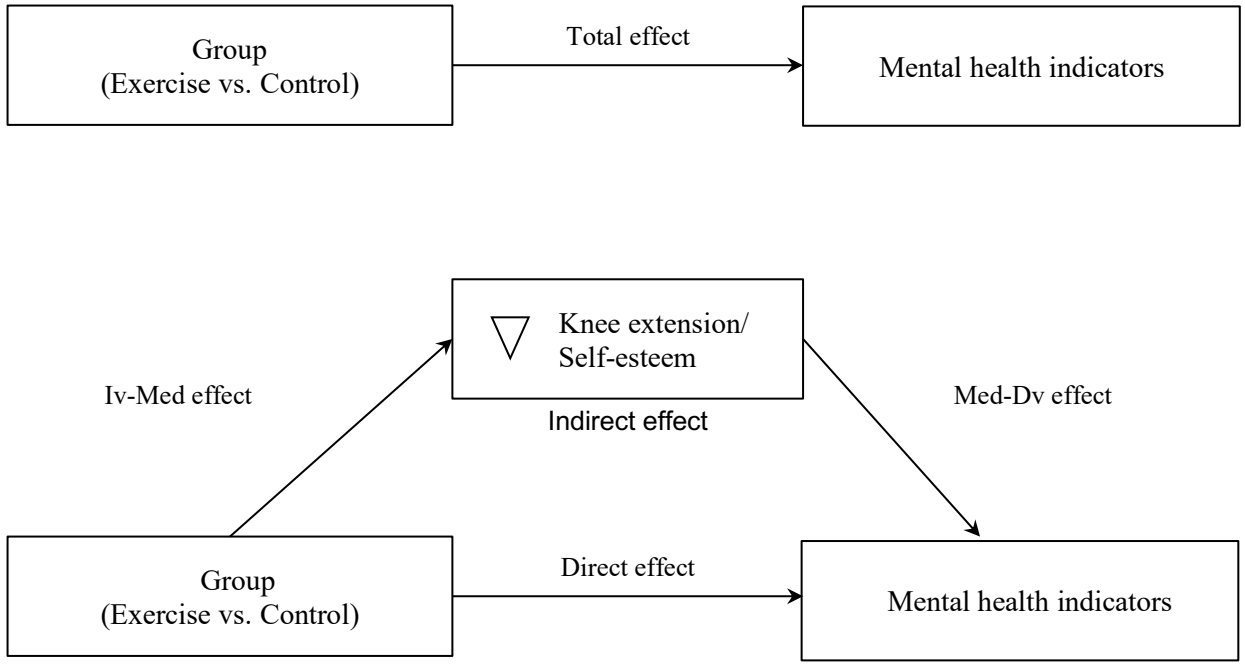

Figure 8. Visualization of the mediation panel modeling approach. Group (independent variable (Iv), Knee extension and Self-esteem (mediator = Med), and mental health indicators (dependent variable = Dv), these indicators correspond to the difference (post-pre) values. Mental health indicators = anxiety-depressive symptoms, stress, loneliness, satisfaction with life, self-esteem, and emotional well-being.

Secondary Analyses

Per-protocol analyses focused on participants with at least 80% attendance, using similar mixed-effects models as the ITT analysis.

Post-Hoc Mediation Analyses

Given the results of the moderation analyses, which suggested that women experienced greater improvements in self-esteem compared to men and based on prior evidence indicating that resistance training may differentially affect psychological outcomes by sex (44,138), additional mediation analyses were conducted exclusively in the female subsample. These analyses aimed to determine whether self-esteem served as a key psychological mechanism mediating the observed improvements in mental health outcomes among women, further exploring the role of sex-specific responses to exercise interventions.

4.4 Results

4.4.1 Sample characteristics

A flowchart of participant recruitment, randomization, and retention is shown in **Figure 9**. The baseline characteristics of the study participants are summarized in **Table 5**. Of the 90 randomized participants (58% female, mean age = 71.68 ± 3.93 years), 81 completed the trial. The intervention group included 46 participants, of whom 41 (89%) met the per-protocol criteria. On average, participants reported 11.54 years of education, and the mean BMI was 28.50 kg/m², classifying the sample as overweight.

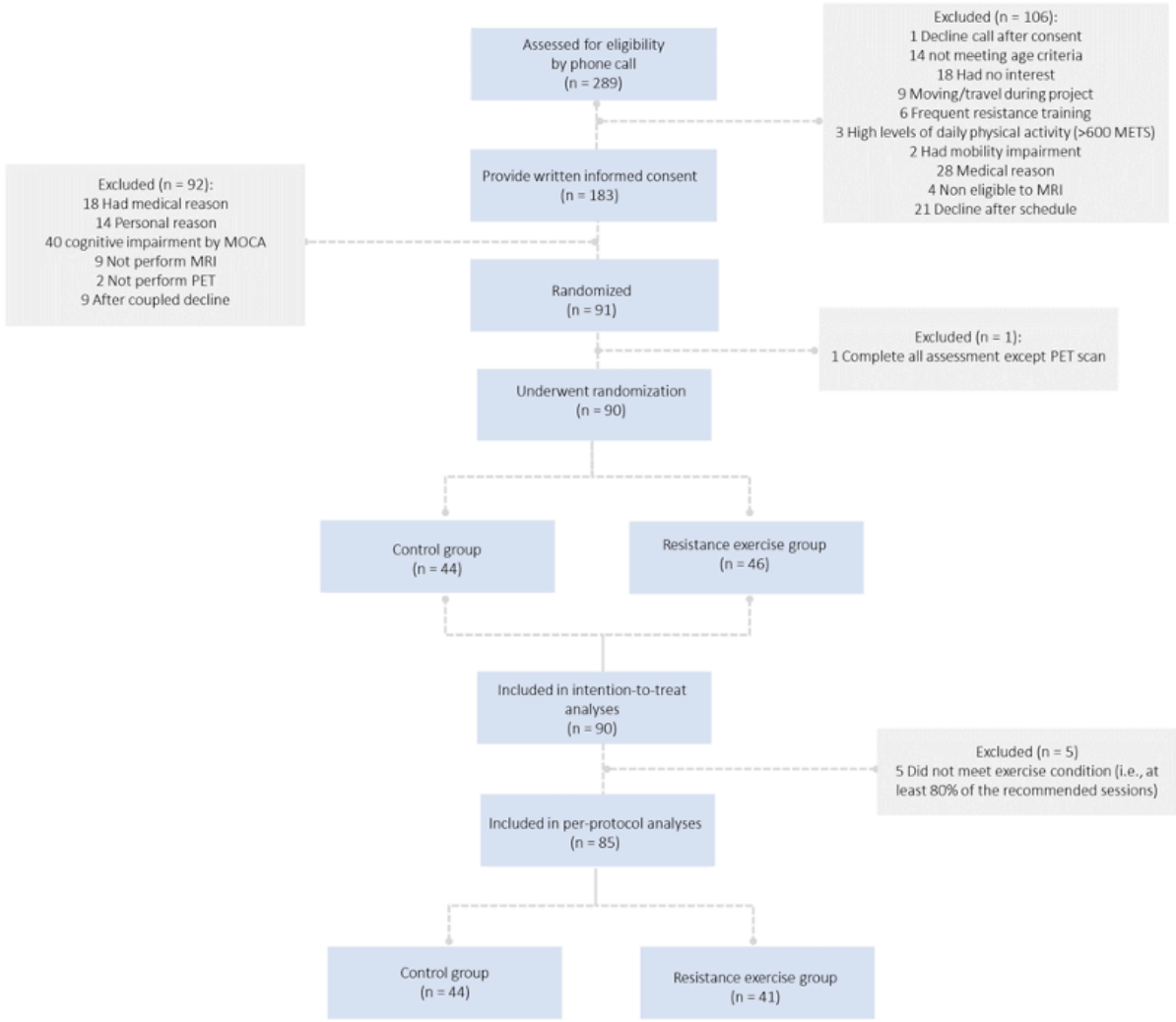

Figure 9. Flowchart of AGUEDA study.

Table 5. Descriptive characteristics of the AGUEDA participants at baseline.

	All		Exercise Group		Control Group		P value	Male		Female	P value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)		N		N	
Sex (57.8 % females)	90		46		44			38		52	
Age (years)		71.68 (3.93)		71.83 (4.15)		71.53 (3.73)	0.719	71.43 (3.69)		71.87 (4.13)	0.606
Weight (kg)		73.50 (12.86)		72.89 (13.41)		74.14 (12.39)	0.647	81.74 (10.05)		67.48 (11.31)	**<0.001**
Height (cm)		160.44 (8.98)		160.17 (8.87)		160.72 (9.18)	0.775	168.70 (7.03)		154.41 (4.10)	**<0.001**
Body Mass Index (kg/m^2)		28.50 (4.23)		28.35 (4.43)		28.67 (4.05)	0.720	28.70 (2.90)		28.36 (5.00)	0.705
Years of education (years)		11.54 (4.90)		11.17 (5.26)		11.93 (4.53)	0.467	14.00 (4.92)		9.75 (4.08)	**<0.001**
MoCa (0-30)		25.58 (2.14)		25.28 (2.21)		25.89 (2.05)	0.183	26.32 (1.93)		25.04 (2.14)	**0.005**
MMSE (0-30)		28.92 (1.06)		29.00 (0.97)		28.84 (1.16)	0.481	28.84 (0.97)		28.98 (1.13)	0.544
STICS-m (0-41)		33.91 (2.72)		33.78 (2.65)		34.05 (2.81)	0.649	34.42 (2.46)		33.54 (2.86)	0.129
GDS (0-30)		6.41 (3.84)		5.87 (3.59)		6.98 (4.04)	0.173	4.13 (3.09)		8.08 (3.48)	**<0.001**
Mental Health											
Psychological ill-being											
Anxiety symptoms (0-21)		7.27 (4.35)		7.42 (4.43)		7.11 (4.32)	0.740	4.50 (3.30)		9.33 (3.89)	**<0.001**
Depressive symptoms (0-21)		5.17 (3.45)		4.96 (3.10)		5.39 (4.83)	0.559	4.11 (3.33)		5.96 (3.36)	**0.011**
Stress (0-56)		15.31 (7.42)		14.84 (7.21)		15.80 (7.68)	0.548	12.16 (7.59)		17.67 (6.40)	**<0.001**
Loneliness (10-40)		18.14 (5.24)		17.85 (4.88)		18.45 (5.63)	0.586	14.95 (3.61)		20.48 (5.03)	**<0.001**
P*sychological well-being*											
Satisfaction with Life (5-25)		20.41 (3.73)		20.76 (3.49)		20.05 (3.96)	0.366	21.18 (3.52)		19.85 (3.81)	0.093
Self-esteem (0-30)		18.14 (3.12)		17.89 (2.49)		18.41 (3.67)	0.434	19.11 (3.35)		17.44 (2.76)	**0.012**
Emotional well-being (0-100)		55.07 (7.66)		55.65 (7.29)		54.45 (8.06)	0.461	57.47 (6.47)		53.31 (8.03)	**0.010**

Values are mean (standard deviation) or percentages; MoCa: The Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination, STICS-m: Telephone Interview for cognitive status-modified, Nm, newton-meter.

4.4.2 Primary Analyses

Effects on mental health outcomes

Changes in mental health indicators are presented in **Figure 10 and Table 6**. The 24-week resistance exercise program resulted in small improvements across various mental health indicators in cognitively normal older adults. Participants in the intervention group demonstrated reductions in psychological ill-being, with trends toward lower anxiety and depressive symptoms compared to the control group, although these differences did not reach statistical significance (z-score = -0.19, p = 0.248; z-score = -0.35, p = 0.078, respectively). Improvements in psychological well-being measures, including self-esteem and emotional well-being, were observed, but these differences were also non-significant (z-score = 0.26, p = 0.126; z-score = 0.31, p = 0.151, respectively). No significant changes were observed for stress, loneliness, or life satisfaction.

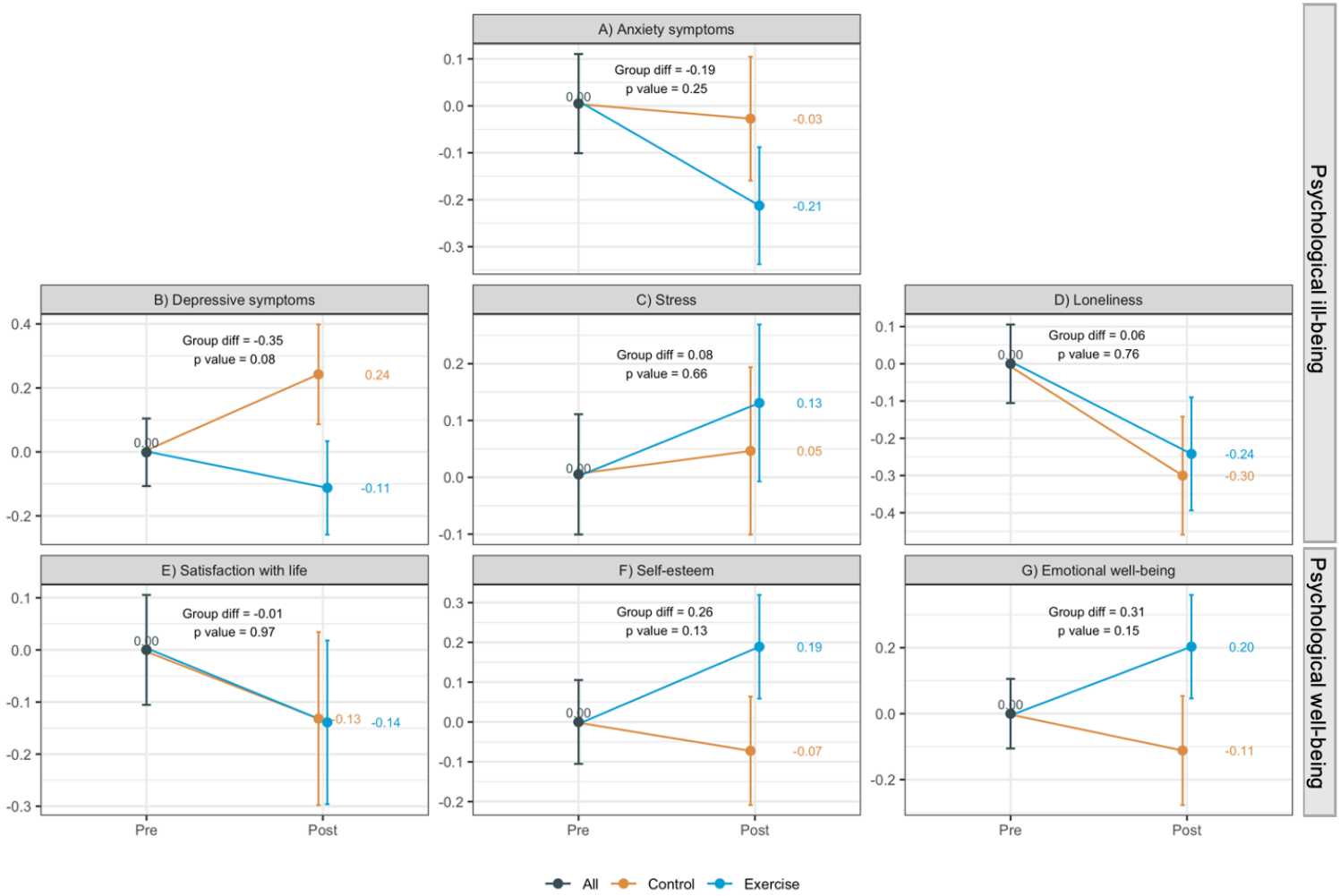

Figure 10. Intention-to-treat effect of the AGUEDA resistance exercise program on mental health indicators. Lower levels of psychological ill-being and higher levels of psychological well-being are considered better. Group diff corresponds to the difference in the change over time between the exercise and control group and its p-value (significance established at $p < 0.05$). The intervention effects were presented as z-scores of changes and error bars indicate the confidence intervals 95%.

Table 6. Intention-to-treat effect of the AGUEDA resistance exercise program on mental health indicators. Intention-to-treat basis (ITT).

	Exercise Group	Control Group	Difference between groups (Exercise *vs* Control)	
N= 90	N= 46	N=44		*P value*
Psychological ill-being				
Anxiety symptoms				
Data raw	6.34 (5.27 to 7.42)	7.15 (6.01 to 8.29)	-0.81 (-2.18 to 0.57)	
z-score	-0.21 (-0.46 to 0.03)	-0.03 (-0.29 to 0.23)	-0.19 (-0.50 to 0.13)	0.248
Depressive symptoms				
Data raw	4.78 (3.78 to 5.78)	6.01 (4.94 to 7.07)	-1.22 (-2.59 to 0.14)	
z-score	-0.11 (-0.40 to 0.18)	0.24 (-0.07 to 0.55)	-0.35 (-0.75 to 0.04)	0.078
Stress				
Data raw	16.28 (14.25 to 18.32)	15.66 (13.49 to 17.83)	0.63 (-2.17 to 3.42)	
z-score	0.13 (-0.14 to 0.41)	0.05 (-0.25 to 0.34)	0.08 (-0.29 to 0.46)	0.657
Loneliness				
Data raw	16.88 (15.30 to 18.45)	16.57 (14.92 to 18.22)	0.31 (-1.64 to 2.25)	
z-score	-0.24 (-0.54 to 0.06)	-0.30 (-0.61 to 0.01)	0.06 (-0.31 to 0.43)	0.756
Psychological well-being				
Satisfaction with life				
Data raw	19.89 (18.73 to 21.06)	19.92 (18.69 to 21.15)	-0.03 (-1.61 to 1.56)	
z-score	-0.14 (-0.45 to 0.17)	-0.13 (-0.46 to 0.20)	-0.01(-0.43 to 0.42)	0.973
Self-esteem				
Data raw	18.73 (17.93 to 19.54)	17.92 (17.07 to 18.76)	0.82 (-0.23 to 1.89)	
z-score	0.19 (-0.07 to 0.45)	-0.07 (-0.34 to 0.20)	0.26 (-0.07 to 0.61)	0.126
Emotional well-being				
Data raw	56.62 (54.24 to 59.01)	54.21 (51.69 to 56.73)	2.41 (-0.9 to 5.72)	
z-score	0.20 (-0.11 to 0.51)	-0.11 (-0.44 to 0.22)	0.31 (-0.12 to 0.75)	0.151

Lower levels of psychological ill-being and higher levels of psychological well-being are considered better. Difference between groups corresponds to the difference in the change over time between the exercise and control group and its p-value (significance established at $p< 0.05$). The intervention effects were presented as z-scores of changes and the confidence intervals 95%.

Moderation results: Interactions with baseline characteristics

Moderation analyses revealed significant interactions between intervention effects and specific baseline characteristics presented in **Figure 11** and **Tables 7, 8, and 9**. For loneliness, a significant interaction with age was observed (p for interaction = 0.037), indicating that the impact of the intervention on loneliness varied across age groups. Specifically, participants aged 72 years or younger showed greater loneliness reductions than those older than 72 years. In addition, significant improvements in self-esteem were observed in females (z-score = 0.48, p = 0.036) and in participants aged 72 years or younger (z-score = 0.51, p = 0.032). Participants with higher baseline anxiety symptoms also experienced significant reductions in anxiety symptoms (z-score = -0.54, p = 0.027). No other significant interactions were found.

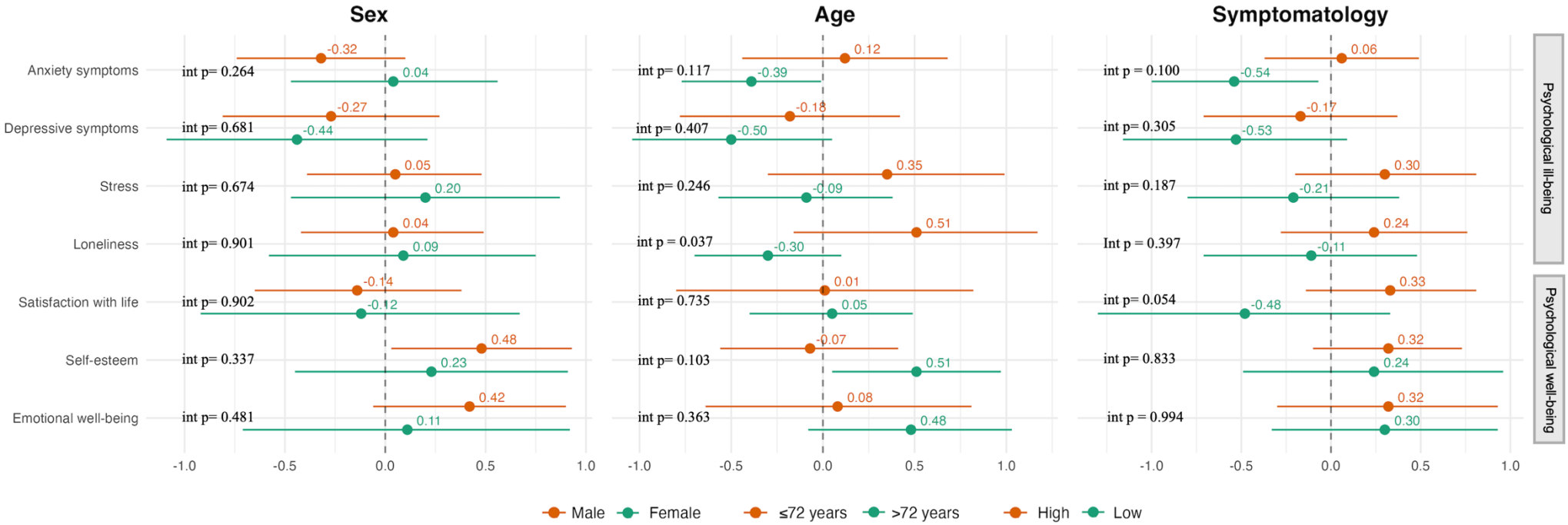

Figure 11. Intention-to-treat effects of the AGUEDA resistance exercise program on mental health indicators by sex, age, and psychological baseline symptomatology. Moderation by sex (male and female), age (≤ 72 years old and >72 years old), and symptomatology (lower and higher baseline psychological symptomatology, separated by the median). Lower levels of psychological ill-being and higher levels of psychological well-being are considered better. The intervention effects were presented as z-scores of changes, and error bars indicate the confidence intervals 95%. Significant interaction was set at $p < 0.05$ (int p = p value for interaction).

Table 7. Moderation analysis of the AGUEDA resistance exercise program on mental health indicators by sex.

	Male		Female		Male		Female		
	Exercise n=19	Control n=19	Exercise n=27	Control n=25	Differences between groups n=38	P value	Differences between groups n=52	P value	P for sex interaction
Psychological ill-being									
Anxiety symptoms									
Raw score	4.75 (3.17 to 6.33)	4.55 (2.76 to 6.35)	7.51 (6.13 to 8.88)	8.91 (7.49 to 10.32)	0.19 (-2.06 to 2.44)	0.862	-1.40 (-3.22 to 0.42)	0.128	0.264
z-score	-0.58 (-0.94 to -0.22)	-0.62 (-1.04 to -0.21)	0.05 (-0.26 to 0.37)	0.38 (0.05 to 0.70)	0.04 (-0.47 to 0.56)		-0.32 (-0.74 to 0.10)		
Depressive symptoms									
Raw score	4.03 (2.47 to 5.58)	5.55 (3.78 to 7.33)	5.38 (3.99 to 6.77)	6.32 (4.92 to 7.73)	-1.53 (-3.78 to 0.73)	0.177	-0.94 (-2.79 to 0.92)	0.313	0.681
z-score	-0.33 (-0.78 to 0.12)	0.11 (-0.40 to 0.63)	0.06 (-0.34 to 0.46)	0.33 (-0.07 to 0.74)	-0.44 (-1.09 to 0.21)		-0.27 (-0.81 to 0.27)		
Stress									
Raw score	13.29 (9.93 to 16.66)	11.84 (7.96 to 15.71)	18.56 (16.17 to 20.95)	18.21 (15.81 to 20.61)	1.46 (-3.58 to 6.44)	0.554	0.35 (-2.86 to 3.57)		
z-score	-0.27 (-0.73 to 0.18)	-0.47 (-0.99 to 0.05)	0.44 (0.12 to 0.76)	0.39 (0.07 to 0.71)	0.20 (-0.47 to 0.87)		0.05 (-0.39 to 0.48)	0.826	0.674
Loneliness									
Raw score	14.81 (12.30 to 17.32)	14.37 (11.59 to 17.14)	18.38 (16.38 to 20.37)	18.19 (16.18 to 20.20)	0.45 (-3.03 to 3.93)	0.795	0.19 (-2.18 to 2.55)	0.875	0.901
z-score	-0.64 (-1.11 to -0.16)	-0.72 (-1.25 to -0.19)	0.04 (-0.34 to 0.43)	0.01 (-0.38 to 0.39)	0.09 (-0.58 to 0.75)		0.04 (-0.42 to 0.49)		
Psychological well-being									
Satisfaction with life									
Raw score	20.40 (18.46 to 22.35)	20.86 (18.68 to 23.04)	19.14 (17.63 to 20.65)	19.65 (18.11 to 21.18)	-0.46 (-3.41 to 2.50)	0.753	-0.51 (-2.43 to 1.41)	0.597	0.902
z-score	0.00 (-0.52 to 0.52)	0.12 (-0.46 to 0.71)	-0.34 (-0.75 to 0.06)	-0.21 (-0.62 to 0.21)	-0.12 (-0.92 to 0.67)		-0.14 (-0.65 to 0.38)		
Self-esteem									
Raw score	19.56 (18.07 to 21.05)	18.83 (17.23 to 20.43)	18.45 (17.47 to 19.43)	16.95 (15.94 to 17.96)	0.73 (-1.39 to 2.85)	0.486	**1.50 (0.10 to 2.90)**	**0.036**	0.337
z-score	0.45 (-0.03 to 0.93)	0.22 (-0.29 to 0.73)	0.10 (-0.22 to 0.41)	-0.38 (-0.71 to -0.06)	0.23 (-0.45 to 0.91)		**0.48 (0.03 to 0.93)**		
Emotional well-being									
Raw score	57.89 (53.71 to 62.08)	57.08 (52.36 to 61.81)	55.64 (52.83 to 58.44)	52.41 (49.56 to 55.26)	0.81 (-5.45 to 7.08)	0.794	3.23 (-0.45 to 6.91)	0.084	0.481
z-score	0.37 (-0.18 to 0.92)	0.26 (-0.35 to 0.88)	0.07 (-0.29 to 0.44)	-0.35 (-0.72 to 0.02)	0.11 (-0.71 to 0.92)		0.42 (-0.06 to 0.90)		

The intervention effects were presented as z-scores of changes. Z-score values indicate how many standard deviations have the post-exercise program values changed with respect to the baseline mean. Lower values indicate better results in psychological ill-being and higher values indicate better results in psychological well-being.

Table 8. Moderation analysis of the AGUEDA resistance exercise program on mental health indicators by age.

	Age ≤72		Age >72		Age ≤72		Age >72		
	Exercise n=26	Control n=24	Exercise n=20	Control n=20	Differences between groups n=50		Differences between groups n=40		
						P value		P value	P for age interaction
Psychological ill-being									
Anxiety symptoms									
Raw score	5.68 (4.34 to 7.02)	7.38 (5.93 to 8.82)	7.37 (5.50 to 9.24)	6.84 (4.94 to 8.75)	-1.69 (-3.35 to -0.04)	**0.045**	0.53 (-1.90 to 2.96)	0.659	0.117
z-score	-0.36 (-0.67 to -0.05)	0.02 (-0.31 to 0.36)	0.02 (-0.41 to 0.45)	-0.01 (-0.53 to 0.34)	-0.39 (-0.77 to -0.01)		0.12 (-0.44 to 0.68)		
Depressive symptoms									
Raw score	4.40 (3.02 to 5.78)	6.11 (4.60 to 7.63)	5.25 (3.73 to 6.77)	5.88 (4.33 to 7.42)	-1.71 (-3.60 to 0.18)	0.074	-0.63 (-2.69 to 1.44)	0.541	0.407
z-score	-0.22 (-0.62 to 0.18)	0.27 (-0.17 to 0.71)	0.02 (-0.42 to 0.46)	0.20 (-0.24 to 0.65)	-0.50 (-1.04 to 0.05)		-0.18 (-0.78 to 0.42)		
Stress									
Raw score	14.49 (11.92 to 17.05)	15.18 (12.38 to 17.99)	18.84 (15.35 to 22.33)	16.28 (12.75 to 19.82)	-0.70 (-4.22 to 2.82)	0.692	2.56 (-2.26 to 7.38)	0.286	0.246
z-score	-0.11 (-0.46 to 0.23)	-0.02 (-0.40 to 0.36)	0.48 (0.00 to 0.95)	0.13 (-0.35 to 0.61)	-0.09 (-0.57 to 0.38)		0.35 (-0.30 to 0.99)		
Loneliness									
Raw score	14.95 (13.28 to 16.63)	16.52 (14.73 to 18.31)	19.59 (16.70 to 22.48)	16.93 (13.97 to 19.88)	-1.57 (-3.68 to 0.54)	0.141	2.66 (-0.83 to 6.15)	0.130	**0.037**
z-score	-0.61 (-0.93 to -0.29)	-0.31 (-0.65 to 0.03)	0.28 (-0.28 to 0.83)	-0.23 (-0.80 to 0.33)	-0.30 (-0.70 to 0.10)		0.51 (-0.16 to 1.17)		
Psychological well-being									
Satisfaction with life									
Raw score	20.15 (18.77 to 21.52)	19.97 (18.52 to 21.43)	19.73 (17.62 to 21.85)	19.70 (17.53 to 21.87)	0.17 (-1.47 to 1.82)	0.832	0.03 (-2.99 to 3.06)	0.982	0.735
z-score	-0.07 (-0.44 to 0.30)	-0.12 (-0.51 to 0.27)	-0.18 (-0.75 to 0.38)	-0.19 (-0.77 to 0.39)	0.05 (-0.40 to 0.49)		0.01 (-0.80 to 0.82)		
Self-esteem									
Raw score	19.63 (18.53 to 20.72)	18.04 (16.88 to 19.21)	17.49 (16.33 to 18.65)	17.73 (16.54 to 18.91)	1.58 (0.14 to 3.02)	**0.032**	-0.23 (-1.74 to 1.28)	0.756	0.103
z-score	0.48 (0.12 to 0.83)	-0.03 (-0.41 to 0.34)	-0.21 (-0.58 to 0.16)	-0.13 (-0.52 to 0.25)	0.51 (0.05 to 0.97)		-0.07 (-0.56 to 0.41)		
Emotional well-being									
Raw score	57.56 (54.48 to 60.64)	53.92 (50.60 to 57.23)	55.26 (51.26 to 59.25)	54.63 (50.54 to 58.72)	3.64 (-0.62 to 7.90)	0.092	0.63 (-4.91 to 6.17)	0.818	0.363
z-score	0.33 (-0.08 to 0.73)	-0.15 (-0.58 to 0.28)	0.02 (-0.50 to 0.55)	-0.06 (-0.59 to 0.48)	0.48 (-0.08 to 1.03)		0.08 (-0.64 to 0.81)		

The intervention effects were presented as z-scores of changes. Z-score values indicate how many standard deviations have the post-exercise program values changed with respect to the baseline mean. Lower values indicate better results in psychological ill-being and higher values indicate better results in psychological well-being.

Table 9. Moderation analysis of the AGUEDA resistance exercise program on mental health indicators by symptomatology.

	Lower symptomatology		Higher symptomatology		Lower symptomatology		Higher symptomatology		
	Exercise n=26	Control n=25	Exercise n=19	Control n=19	Differences between groups n= 51	P value	Differences between groups n=38	P value	P for symptoms interaction
Psychological ill-being									
Anxiety symptoms									
Raw score	4.84 (3.58 to 6.10)	4.57 (3.15 to 5.99)	8.16 (6.57 to 9.74)	10.49 (8.88 to 12.09)	0.27 (-1.61 to 2.14)	0.776	**- 2.33 (-4.37 to -0.29)**	**0.027**	0.100
z-score	-0.56 (-0.85 to -0.27)	-0.62 (-0.94 to -0.29)	0.20 (-0.16 to 0.57)	0.74 (0.37 to 1.11)	0.06 (-0.37 to 0.49)		**-0.54 (-1.00 to -0.07)**		
Depressive symptoms									
Raw score	3.97 (2.66 to 5.27)	4.55 (3.19 to 5.91)	6.10 (4.55 to 7.66)	7.95 (6.27 to 9.63)	-0.58 (-2.45 to 1.28)	0.531	-1.84 (-4.00 to 0.31)	0.091	0.305
z-score	-0.35 (-0.73 to -0.03)	-0.18 (-0.57 to 0.22)	0.27 (-0.18 to 0.72)	0.80 (0.32 to 1.29)	-0.17 (-0.71 to 0.37)		-0.53 (-1.16 to 0.09)		
Stress									
Raw score	14.34 (11.87 to 16.81)	12.08 (9.12 to 15.04)	17.87 (14.55 to 21.19)	19.42 (16.34 to 22.50)	2.26 (-1.50 to 6.02)	0.231	-1.55 (-5.90 to 2.81)	0.475	0.187
z-score	-0.13 (-0.46 to 0.20)	-0.44 (-0.84 to -0.04)	0.34 (-0.10 to 0.79)	0.55 (0.14 to 0.97)	0.30 (-0.20 to 0.81)		-0.21 (-0.80 to 0.38)		
Loneliness									
Raw score	14.50 (12.49 to 16.51)	13.24 (11.19 to 15.28)	20.05 (17.82 to 22.26)	20.64 (18.26 to 23.02)	1.26 (-1.46 to 3.99)	0.355	-0.60 (-3.70 to 2.51)	0.697	0.397
z-score	-0.70 (-1.08 to -0.31)	-0.94 (-1.33 to -0.55)	0.36 (-0.06 to 0.79)	0.48 (0.02 to 0.93)	0.24 (-0.28 to 0.76)		-0.11 (-0.71 to 0.48)		
Psychological well-being									
Satisfaction with life									
Raw score	19.16 (17.87 to 20.44)	17.92 (16.61 to 19.22)	21.20 (19.14 to 23.25)	23.00 (20.73 to 25.27)	1.24 (-0.53 to 3.01)	0.165	-1.81 (-4.85 to 1.24)	0.235	0.054
z-score	-0.34 (-0.68 to 0.01)	-0.67 (-1.02 to -0.32)	0.21 (-0.34 to 0.76)	0.70 (0.09 to 1.30)	0.33 (-0.14 to 0.81)		-0.48 (-1.30 to 0.33)		
Self-esteem									
Raw score	17.70 (16.89 to 18.51)	16.72 (15.70 to 17.74)	20.04 (18.60 to 22.20)	19.67 (18.23 to 21.10)	0.98 (-0.30 to 2.27)	0.130	0.73 (-1.53 to 2.99)	0.510	0.833
z-score	-0.14 (-0.40 to 0.12)	-0.46 (-0.79 to -0.13)	0.72 (0.15 to 1.3)	0.49 (0.03 to 0.95)	0.32 (-0.10 to 0.73)		0.24 (-0.49 to 0.96)		
Emotional well-being									
Raw score	54.43 (51.12 to 57.75)	52.01 (48.56 to 55.46)	59.51 (56.13 to 62.89)	57.22 (53.56 to 60.87)	2.42 (-2.26 to 7.11)	0.302	2.30 (-2.53 to 7.13)	0.340	0.994
z-score	-0.08 (-0.52 to 0.35)	-0.40 (-0.85 to 0.05)	0.58 (0.14 to 1.02)	0.28 (-0.20 to 0.76)	0.32 (-0.30 to 0.93)		0.30 (-0.33 to 0.93)		

The intervention effects were presented as z-scores of changes. Z-score values indicate how many standard deviations have the post-exercise program values changed with respect to the baseline mean.

Mediation Results: the mediatingrole of self-esteem

Mediation analyses, evaluating muscular strength and self-esteem as potential mediators of the intervention effects on mental health indicators, did not show significant mediation effects in the full sample (**Figures 12 and 13**). All p-values from indirect effect <0.75.

4.4.3 Secondary results

Per-protocol analyses showed results similar to those from the ITT analyses. Of the 46 participants in the intervention group, 5 did not meet the adherence criterion. The differences between the intervention and control groups remained non-significant (**Table 10**).

4.4.4 Post-Hoc mediation results

Mediation analyses in the female subsample highlighted self-esteem as a potential mediator of the intervention's effects on mental health outcomes (**Figure 14**). Specifically, self-esteem showed significant indirect effects for reductions in anxiety symptoms (indirect effect = -0.18, $p < 0.01$), depressive symptoms (indirect effect = -0.19, $p = 0.02$), and loneliness (indirect effect = -0.20, $p = 0.01$), as well as improvements in life satisfaction (indirect effect = 0.15, $p = 0.04$).

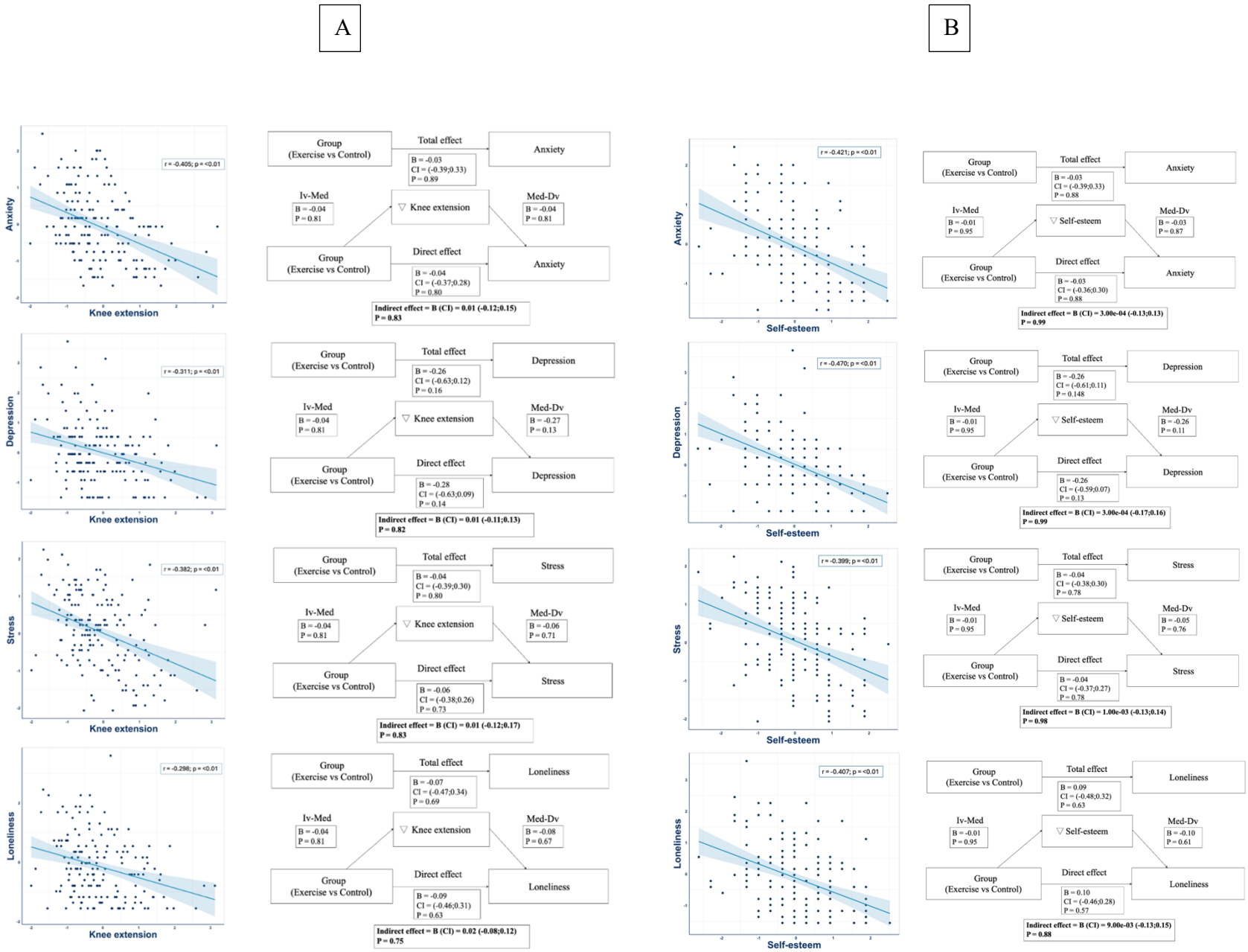

Figure 12. Muscular strength and self-esteem change and mediation models of the resistance exercise intervention effects (i.e., exercise vs. control) on psychological ill-being. Group (independent variable (Iv), Knee extension in panel A and Self-esteem in panel B (mediator = Med), and psychological ill-being indicators (dependent variable = Dv), these indicators correspond to the difference (post-pre) values. The figure shows the association between the change variables (post-pre) in indicators of psychological ill-being and knee extension-self-esteem. B = unstandardized regression coefficient; CI = Interval coefficients; P = p-value. Direct effect: The direct relationship between the independent and dependent variables without considering the mediator. Indirect effect: The effect of the independent variable on the dependent variable that is mediated through a third variable (Knee extension/Self-esteem).

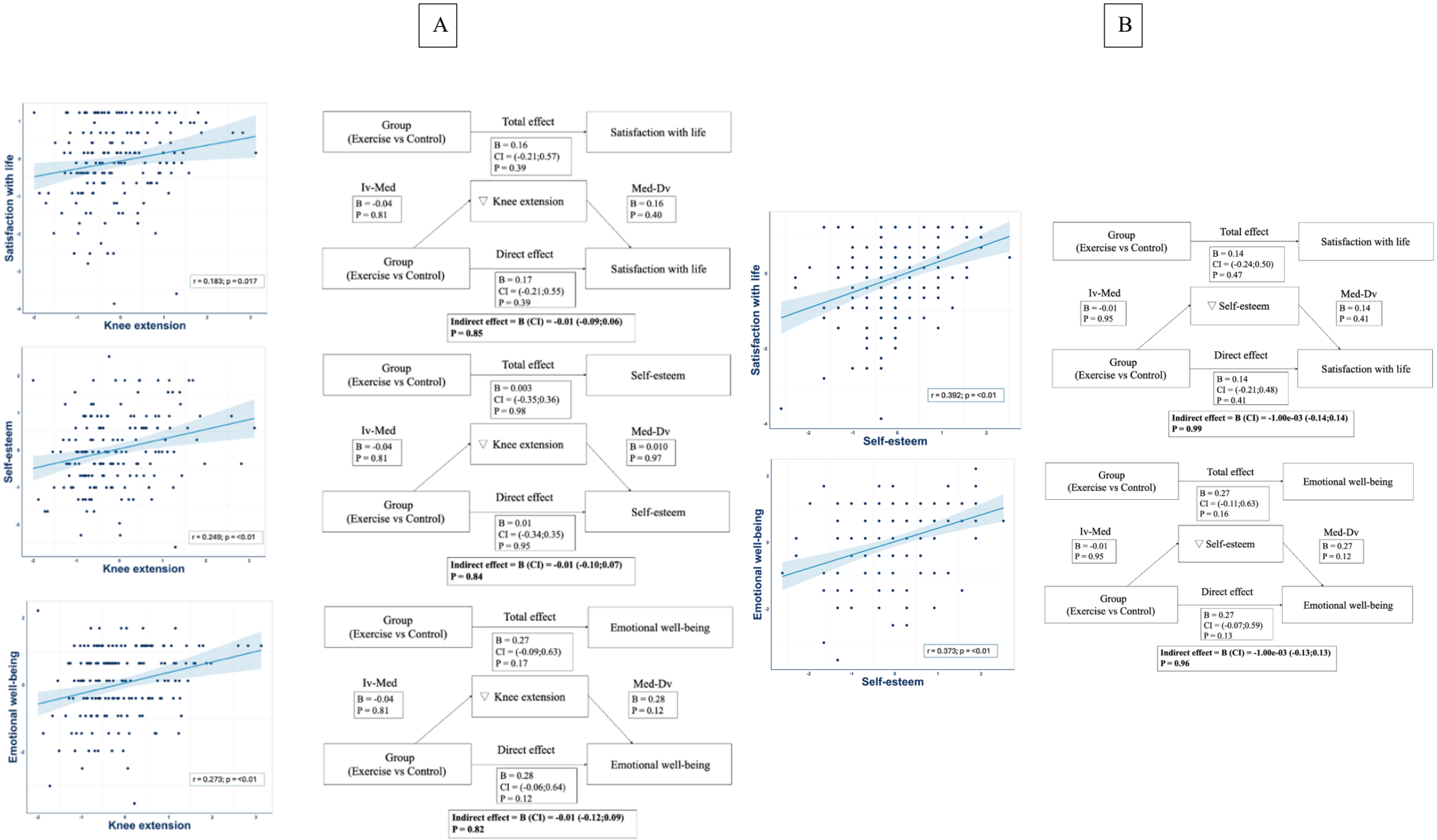

Figure 13. Muscular strength and self-esteem change and mediation models of the resistance exercise intervention effects (i.e., exercise vs. control) on psychological well-being. Group (independent variable (Iv), knee extension in panel A and self-esteem in panel B (mediator = Med), and psychological well-being indicators (dependent variable = Dv), these indicators correspond to the difference (post-pre) values. The figure shows the association between the change variables (post-pre) in indicators of psychological well-being and knee extension-self-esteem. B = unstandardized regression coefficient; CI = Interval coefficients; P = p-value. Direct effect: The direct relationship between the independent and dependent variables without considering the mediator. Indirect effect: The effect of the independent variable on the dependent variable that is mediated through a third variable (Knee extension/Self-esteem).

Table 10. Per-protocol effect of the AGUEDA resistance exercise program on mental health indicators.

	Exercise Group	Control Group	Difference between groups (Exercise *vs* Control)	
N= 85	N= 41	N=44		*P value*
Psychological ill-being				
Anxiety symptoms				
Data raw	6.29 (5.18 to 7.41)	7.09 (5.93 to 8.25)	-0.8 (-2.21 to 0.62)	0.265
z-score	-0.20 (-0.46 to 0.06)	-0.02 (-0.28 to 0.25)	-0.18 (-0.51 to 0.14)	
Depressive symptoms				
Data raw	4.89 (3.83 to 5.93)	5.97 (4.90 to 7.05)	-1.08 (-2.46 to 0.3)	0.122
z-score	-0.06 (-0.36 to 0.23)	0.24 (-0.06 to 0.55)	-0.31 (-0.69 to 0.08)	
Stress				
Data raw	16.33 (14.22 to 18.43)	15.64 (13.44 to 17.84)	0.69 (-2.16 to 3.54)	
z-score	0.14 (-0.14 to 0.42)	0.05 (-0.24 to 0.34)	0.09 (-0.29 to 0.47)	0.633
Loneliness				
Data raw	16.63 (15.02 to 18.25)	16.43 (14.77 to 18.09)	0.20 (-1.79 to 2.19)	
z-score	-0.26 (-0.57 to 0.06)	-0.29 (-0.61 to 0.03)	0.04 (-0.35 to 0.42)	0.841
Psychological well-being				
Satisfaction with life				
Data raw	19.89 (18.69 to 21.10)	19.86 (18.62 to 21.11)	0.03 (-1.59 to 1.65)	
z-score	-0.11 (-0.43 to 0.21)	-0.12 (-0.45 to 0.21)	0.01 (-0.42 to 0.44)	0.968
Self-esteem				
Data raw	18.67 (17.84 to 19.50)	17.92 (17.07 to 18.77)	0.75 (-0.31 to 1.81)	
z-score	0.16 (-0.10 to 0.43)	-0.07 (-0.35 to 0.19)	0.24 (-0.10 to 0.57)	0.161
Emotional well-being				
Data raw	56.38 (53.93 to 58.84)	54.21 (51.67 to 56.74)	2.18 (-1.19 to 5.54)	
z-score	0.17 (-0.15 to 0.49)	-0.11 (-0.44 to 0.22)	0.28 (-0.16 to 0.72)	0.201

Lower levels of psychological ill-being and higher levels of psychological well-being are considered better. Difference between groups corresponds to the difference in the change over time between the exercise and control group and its p-value (significance established at $p< 0.05$). The intervention effects were presented as z-scores of changes and the confidence intervals 95%.

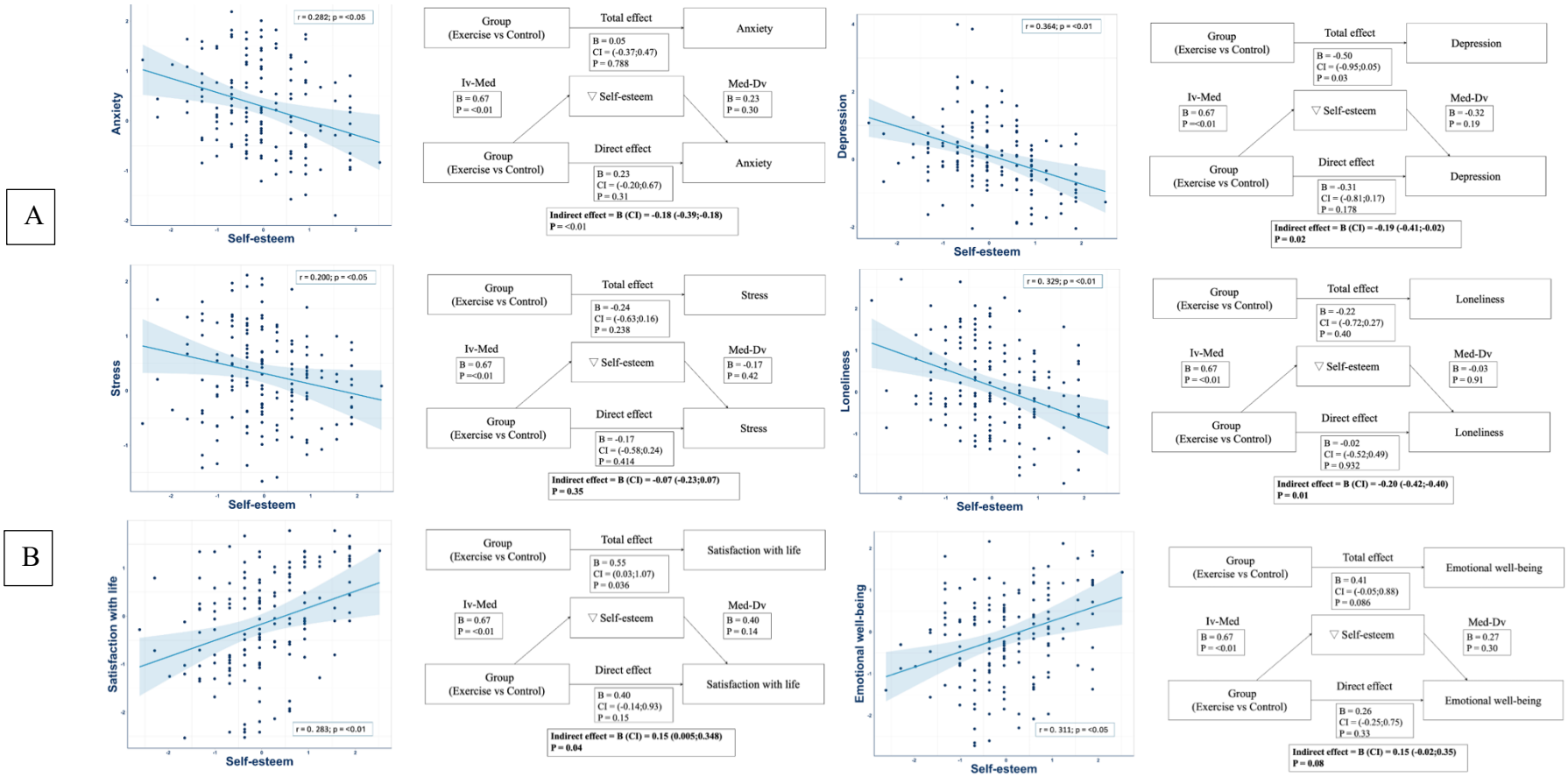

Figure 14. Self-esteem changes and mediation models of the resistance exercise intervention effects (i.e., exercise vs. control) on psychological ill being and well-being only in female. Group (independent variable (Iv), self-esteem (mediator = Med), and psychological ill-being indicators in panel A and well-being indicators in panel B (dependent variable = Dv), these indicators correspond to the difference (post-pre) values. The figure shows the association between the change variables (post-pre) in indicators of psychological ill-being and well-being and self-esteem. B = unstandardized regression coefficient; CI = Interval coefficients; P = p-value. Direct effect: The direct relationship between the independent and dependent variables without considering the mediator. Indirect effect: The effect of the independent variable on the dependent variable that is mediated through a third variable (self-esteem).

4.5 Discussion

The AGUEDA program did not demonstrate statistically significant improvements in mental health indicators among cognitively normal older adults. Despite this, observable trends were indicating potential benefits, particularly in aspects of psychological ill-being, such as reductions in anxiety and depressive symptoms. Similarly, although not reaching statistical significance, there were positive indications towards enhanced well-being, with slight improvements noted in self-esteem and emotional well-being. Notably, moderation analyses revealed significant reductions in anxiety symptoms among younger participants and those with higher baseline levels of anxiety, as well as significant increases in self-esteem in the female group and younger participants. Muscular strength did not mediate the relationship between the intervention and mental health indicators. In contrast, mediation analyses in females indicated that self-esteem significantly mediated the effects of the intervention on anxiety-depressive symptoms, loneliness, and life satisfaction. These findings emphasize the importance of tailoring interventions to individual and subgroup characteristics, highlighting age and sex as potential moderators of program effectiveness. They also underscore the potential of self-esteem as a key mechanism linking resistance exercise to mental health improvements in specific populations.

The AGUEDA program demonstrated small, non-significant reductions in anxiety and depression symptoms among cognitively normal older adults. Although resistance exercise has been shown to significantly reduce anxiety and depressive symptoms in previous studies involving older adults (58,133,140,150), the lack of statistically significant changes in our study may be attributed to several factors. Firstly, the existing literature often includes participants with more severe symptoms or diagnosed disorders, where the effects of exercise are more pronounced (151,152). In contrast, our study participants had an absence of depression at baseline, providing less room for noticeable improvement. However, consistent with the broader literature, our analyses revealed that reductions in anxiety symptoms were most evident in participants with higher baseline levels of psychological distress, suggesting that resistance exercise may be particularly beneficial for those initially experiencing greater psychological distress. Another contributing factor could be the lack of personalization in the exercise programs, which did not consider individual preferences and tastes. This lack of tailoring may have diluted

the potential effects on mental health outcomes. While anxiety and depression showed trends toward improvement, stress, and loneliness did not follow a similar trajectory. This discrepancy may be explained by the specific mechanisms through which resistance exercise exerts its effects. Resistance training may predominantly influence mood-related symptoms, such as anxiety and depression, through psychosocial mechanisms, including improvements in self-esteem, self-efficacy, and perceived competence (153).

Similarly, while no significant effects were observed for psychological well-being, small positive trends were noticed. These trends align with findings from other studies that suggest modest improvements in self-esteem and life satisfaction, particularly among older adults who engage in regular exercise, as compared to non-exercisers (154). A systematic review also emphasized that regular physical activity contributes to better quality of life and psychological well-being in older populations (155), often linked to increased self-efficacy and enhanced body image perception—key factors in improving self-esteem (156). Further research with a larger and more diverse sample is necessary to explore these preliminary findings and refine intervention strategies to maximize the mental health benefits of resistance training.

Moderation analyses demonstrated that resistance exercise had a significant positive effect on women, younger participants, and those with higher baseline levels of psychological distress. These findings suggest that tailoring exercise interventions to individual characteristics could enhance the mental health benefits of resistance exercise. In line with this, a recent meta-analysis demonstrated that strength training can significantly impact depressive symptoms, particularly in women and younger adults (44). One possible explanation for this could be that the mechanisms through which exercise affects general mental health may differ between older and younger individuals. In older adults, the benefits might primarily stem from the social interaction and the physical activity of leaving the house, which help counteract feelings of loneliness and immobility (157). In contrast, for younger individuals, the mental health benefits could be driven by other mechanisms more related to muscular strength training (e.g., the sense of feeling stronger or being perceived as more physically attractive)(44). Regarding individuals with higher baseline levels of psychological distress, our findings align with previous literature, which has shown that exercise effects on mental health are modest in healthy individuals but can be more pronounced in those with greater symptomatology

(151,152). Collectively, personalizing exercise programs based on individual characteristics and goals could further amplify the benefits of exercise on mental health.

The mediation analyses in our study highlight self-esteem as a pivotal link between resistance exercise and enhanced psychological health, particularly among females, rather than across the entire sample. Self-esteem effectively mediated reductions in anxiety, depression, and loneliness, as well as improvements in life satisfaction. These outcomes align with existing research which identifies self-esteem as a fundamental psychosocial mechanism through which physical activity benefits mental health, especially noted in youth (43). Furthermore, a recent meta-analysis has underscored the mental health advantages of physical exercise, particularly its role in diminishing depression, with significant improvements noted among female participants (44). Our findings broaden this perspective by illustrating how gains in self-esteem could indirectly alleviate psychological ill-being and bolster psychological well-being. The mechanisms underlying this mediation may involve enhanced self-efficacy and improved body image perception, both intimately connected to self-esteem. Resistance exercise contributes to a sense of achievement via tangible strength gains, reinforcing a positive self-perception and reducing negative affect (158,159). Additionally, social interactions in group-based exercise programs may further enhance self-esteem, particularly in older women, who often exhibit greater emotional engagement in social settings (158,160). An intriguing aspect of the observed-on females in self-esteem mediation could be linked to how resistance exercise helps maintain lean muscle mass, improve metabolic health, and foster a positive body image, thereby elevating self-esteem in postmenopausal women (161). These physiological changes, coupled with the psychosocial benefits of structured exercise, explain why self-esteem is a more critical mediator for women. However, research into self-esteem as a mediator in resistance exercise programs for older adults is still emerging. Our results underscore the necessity of targeting self-esteem in future exercise programs to maximize mental health benefits. Moving forward, it is crucial to investigate other biological and behavioral mechanisms to enhance the mental health effects of resistance training, aiming for a more holistic understanding of how exercise interventions can be personalized to yield the greatest benefits across diverse groups.

This study has some limitations that should be acknowledged. First, the sample size was relatively small, which may have limited the statistical power to detect

significant effects in certain outcomes. Future studies should incorporate larger samples to ensure adequate power for detecting clinically meaningful changes. Additionally, this study examines a secondary outcome within a larger project, which may have constrained the depth of analysis in certain areas. Despite these limitations, the study has several strengths. The intervention was progressive and scalable, making it feasible for implementation in community and clinical settings. Another key strength is the comprehensive assessment of mental health, including both psychological ill-being and well-being indicators, which provides a more holistic understanding of the effects of resistance training beyond anxiety and depression.

4.6 Conclusion

This randomized controlled trial provides insights into the potential benefits of resistance exercise on mental health in cognitively normal older adults. While the intervention led to small improvements in psychological ill-being and well-being, these effects were not statistically significant in the full sample. However, analyses at the subgroup level suggest that certain individuals, particularly women and younger participants, may experience greater benefits. Notably, self-esteem emerged as a potential psychological mechanism influencing mental health outcomes in women, reinforcing the role of psychosocial factors in exercise interventions. These findings highlight the importance of considering individual characteristics when designing exercise programs for older adults.

GENERAL DISCUSSION

Chapter 5. An integrative discussion of the international doctoral Thesis.

This International Doctoral Thesis has contributed to the existing knowledge with several novel findings about exercise and mental health in older adults.

The main findings of this international doctoral thesis offer a complementary and nuanced view of the role of muscular strength and resistance training in the mental health of cognitively normal older adults. Through a dual approach that includes both cross-sectional and interventional designs, this work explores the natural associations between strength and mental health, as well as the causal effects of a structured resistance training program. This combination allows for a more integrated understanding that would be limited if each study were considered separately.

The cross-sectional study revealed specific associations between different indicators of muscular strength and mental health outcomes. Notably, handgrip strength was moderately associated with self-esteem, while perceived strength was weakly associated with depressive symptoms, and elbow extension strength with stress. Although most associations were not statistically significant, these preliminary findings suggest that certain dimensions of muscular strength may be linked to specific psychological outcomes in later life (59). However, due to the cross-sectional nature of the study, no causal inferences can be drawn. It remains unclear whether greater strength improves mental health or whether individuals with better mental health are more likely to maintain physical function. This potential bidirectionality is important to consider, as mental health may also influence physical activity habits and self-perceptions of competence.

The second study, based on a 24-week randomized controlled trial, provided complementary insights into causality. Although the resistance training program did not lead to statistically significant improvements in overall mental health outcomes, consistent positive trends were observed in both psychological ill-being and well-being indicators. These results may have been influenced by the small sample size and the relatively low baseline symptom levels, which limited the capacity to detect significant changes. Nevertheless, moderation analyses revealed that certain subgroups, specifically women, younger participants, and those with higher baseline psychological distress, did experience significant improvements, particularly in self-esteem and anxiety symptoms. These findings emphasize the importance of tailoring exercise interventions to individual

characteristics, highlighting the potential of personalized approaches to enhance mental health benefits in older adults (44,162,163).

Importantly, mediation analyses indicated that self-esteem played a key role in linking resistance training to improved mental health, particularly among women. This finding is especially relevant in light of the cross-sectional results, which also identified a positive association between self-esteem and handgrip strength. Together, these findings suggest a coherent pattern across both study designs: self-esteem may not only reflect current psychological well-being but also serve as a mechanism through which resistance exercise promotes mental health. While the cross-sectional study raised hypotheses about the relevance of self-esteem, the trial provided evidence that improvements in self-esteem can mediate mental health benefits, reinforcing its central role as both an outcome and a pathway of change.

Taken together, the findings from both studies demonstrate that muscular strength and resistance training relate to mental health in cognitively normal older adults in distinct but complementary ways. The cross-sectional analysis helps identify relevant variables associated with psychological health in aging, while the interventional trial tests mechanisms and highlights differential effects across subgroups. This integration suggests that while average effects may be modest, identifying moderators and mediators is essential for designing more effective, individualized interventions(44,163). Ultimately, this thesis contributes to the growing body of evidence supporting the role of resistance exercise in promoting mental health: psychological ill-being and well-being in aging populations and underscores the need to continue refining intervention strategies that account for individual variability in psychological and physical responses, with practical implications for prevention and primary care settings (164,165).

These findings highlight the relevance of integrating resistance exercise into preventive health strategies for older adults, particularly through personalized approaches that consider psychological, demographic, and functional differences. Tailoring interventions to individual needs may enhance effectiveness and support long-term adherence in real-world settings.

Overall **limitations and strengths**

Some **limitations** of the present International Thesis need to be acknowledged:

- First, one of the two studies included in this thesis employed a cross-sectional observational design, which does not allow for causal inference between muscular strength and mental health outcomes.
- Second, the sample sizes in both studies were relatively small, particularly in the randomized controlled trial, potentially limiting the statistical power to detect significant effects, especially in subgroup and mediation analyses.
- Third, mental health outcomes in the intervention study were considered secondary endpoints, which may have affected the precision of the sample size estimation and the sensitivity of the analyses.
- Lastly, although the intervention was standardized and supervised, it was not tailored to individual preferences, which may have influenced adherence and psychological engagement with the program.

Despite these limitations, this thesis presents several notable **strengths**:

- The inclusion of a well-characterized sample of cognitively normal older adults, assessed through standardized cognitive screening tools, enhances the specificity and relevance of the findings.
- Muscular strength was comprehensively assessed using both field-based and laboratory-based standardized tests for upper and lower limbs. Additionally, the inclusion of perceived strength provided a valuable psychological dimension often overlooked in similar research.
- A broad set of mental health outcomes was evaluated, encompassing both psychological ill-being (e.g., anxiety, depression, stress, loneliness) and psychological well-being (e.g., life satisfaction, self-esteem, emotional well-being), offering a more holistic understanding of mental health in aging.
- The randomized controlled design of the second study strengthens the ability to infer causal relationships between resistance training and mental health outcomes.
- The intervention was progressive, scalable, and supervised by trained professionals, supporting its feasibility for implementation in community and clinical settings.
- Finally, the thesis explored both moderation and mediation mechanisms, providing relevant insights into for whom and how resistance training can improve mental health in older adults.

GENERAL CONCLUSIONS AND FUTURE PERSPECTIVES

Chapter 6. Conclusions of the International Doctoral Thesis and Future Perspectives.

6.1 Conclusions

General conclusion

The present International Doctoral Thesis sheds light on the importance of resistance exercise and muscular strength for older adults' mental health.

Specific conclusions

Cross-sectional study (Specific aim 1, **Chapter 3)**:

1. Muscular strength is significantly associated with mental health, encompassing both psychological well-being and ill-being in cognitively normal older adults. Particularly, handgrip is related to self-esteem, perceived strength with depressive symptoms, and elbow extension with stress.

Randomized clinical study: (Specific aims 2 to 4, **Chapter 4)**:

2. The AGUEDA 24-weeks resistance exercise did not improve significantly mental health indicators in cognitively older adults without depressive symptoms at baseline.
3. Subgroup analyses suggested that certain individuals, particularly women, younger participants and those with higher baseline psychological distress, may derive greater psychological benefits from strength training interventions.
4. Self-esteem emerged as a key psychological factor associated with mental health improvements in older women engaging in resistance training.

6.2 Future perspectives

1. **Longitudinal studies:** Future research should prioritize longitudinal designs and longer interventions to establish causal links between muscular strength and mental health outcomes in older adults, addressing the limitations of cross-sectional and short-term interventional studies.
2. **Larger and more diverse samples:** Expanding sample sizes and including more heterogeneous populations will enhance the generalizability of findings and allow for more robust subgroup analyses.
3. **Integration of perceived and objective strength measures:** Future studies should explore both perceived and objectively measured muscular strength indicators to better understand their independent and combined roles in mental health outcomes.
4. **Mechanisms underlying exercise benefits on mental health:** Future studies should explore additional mechanisms by which resistance exercise may influence mental health, including neurobiological pathways (e.g., neuroplasticity), psychosocial factors (e.g., self-esteem), and behavioral changes (e.g., improvements in lifestyle habits). Although this thesis focused on psychosocial aspects, a broader investigation into these pathways is warranted to better understand how strength exercise promotes mental health.
5. **Individualized exercise approaches:** Research should focus on identifying optimal resistance exercise protocols tailored to specific subgroups (e.g., by sex age, or psychological profile) to maximize mental health benefits. It could also be personalized based on algorithms that consider genetics, lifestyle, preferences, etc.
6. **Multidimensional assessments:** Incorporating comprehensive psychological, physiological, and social assessments will provide a more holistic understanding of the impact of resistance exercise on mental health.
7. **Real world implementation:** Future studies should also examine the feasibility and effectiveness of integrating resistance exercise into routine public health programs for older adults in primary care, considering practical barriers and facilitators to adherence and long-term engagement.

DISSEMINATION AND OPEN ACCESS

Chapter 7. Dissemination, open access, and contribution

7.1 Dissemination

This doctoral thesis has made its methodological resources publicly available on the GitHub platform to ensure transparency, promote reproducibility, and facilitate access to research data and analysis scripts. This open-access dissemination aims to foster collaboration and replicability within the scientific community.

The following materials can be accessed through the GitHub repository:

- Chapter 2 – Methodology: https://github.com/aguedaprojectugr/Protocolos_AGUEDA
- Chapter 3 – Cross-sectional Study: https://github.com/aguedaprojectugr/Muscular_strength_Mental_health
- Chapter 4 – Randomized Clinical Trial: https://github.com/aguedaprojectugr/AGUEDA-exercise-program_Mental_Health

7.2. Open Access

The intellectual property derived from this research has been carefully considered to protect novel findings while fostering their potential application in academic and practical settings. This section outlines the measures taken to secure research outputs and ensure appropriate licensing.

All protocols, scripts, and analysis plans shared in this doctoral thesis are available through open-access repositories with permissive licenses, allowing for their reuse by other researchers. This approach facilitates transparency and reproducibility and enables other scientific teams to integrate or build upon the methodological frameworks developed in this work.

- Esteban Cornejo, I., Solís Urra, P., Mora González, J. R., Molina-Hidalgo, C., Toval, A., Martín-Fuentes, I., **Bellón D**, ... & Sclafani, A. (2023). AGUEDA

(Active Gains in brain Using Exercise During Aging) trial. Bloque 1: Logística del proyecto y de los participantes: Identificador de Certificado: 2307274910461; Registro en repositorio DIGIBUG.

- Esteban Cornejo, I., Solís Urra, P., Mora González, J. R., Molina-Hidalgo, C., Fernandez Gamez, B., Coca-Pulido, A., **Bellón D**., ... & Costa Rodríguez, C. L. (2023). AGUEDA (Active Gains in brain Using Exercise During Aging) trial: Bloque 2. Pruebas cognitivas y cuestionarios. Identificador de Certificado: 2310115565140; Registro en repositorio DIGIBUG.
- Esteban Cornejo, I., Solís Urra, P., Molina-Hidalgo, C., Toval, A., Olvera-Rojas, M., Coca-Pulido, A., **Bellón D**., …, & García Rivero, Y. (2023). AGUEDA (Active Gains in brain Using Exercise During Aging) trial. Bloque 3: Pruebas de diagnóstico médico. Identificador de Certificado: 2310115565454; Registro en repositorio DIGIBUG.
- Esteban Cornejo, I., Solís Urra, P., Mora González, J. R., Molina-Hidalgo, C., **Bellón, D**., Sclafani, A., & Costa Rodríguez, C. L. (2023). AGUEDA (Active Gains in brain Using Exercise During Aging) trial. Bloque 4: Pruebas de condición-actividad física, composición corporal y antropometría. Identificador de Certificado: 2310115566567; Registro en repositorio DIGIBUG.
- Esteban Cornejo, I., Solís Urra, P., Mora González, J. R., Molina-Hidalgo, C., Martín-Fuentes, I., Fernández Gámez, B., **Bellón D**., ... & Fernández-Ortega, J. (2023). AGUEDA (Active Gains in brain Using Exercise During Aging) trial. Bloque 5: Programa de ejercicio y adherencia. Identificador de Certificado: 2310195630868; Registro en repositorio DIGIBUG.

7.3 Media, press and own contributions

The dissemination of this research extends beyond the academic community, reaching broader audiences through media and press coverage. Efforts have been made to communicate key findings through public engagement, emphasizing the relevance of the study's conclusions in the context of aging and mental health. In addition, the results from the thesis were presented in various scientific posters at international and national conferences.

Community dissemination:

- Canal UGR : "Profesionales del ibs.GRANADA, la Universidad de Granada e IBIMA Plataforma BIONAND presentan resultados de un estudio que relaciona la fuerza muscular y la salud mental en adultos mayores

- Ibs.GRANADA: “Profesionales del ibs.GRANADA, la Universidad de Granada e IBIMA Plataforma BIONAND presentan resultados de un estudio que relaciona la fuerza muscular y la salud mental en adultos mayores”.
- Europapress: “Expertos de Ibima y la Universidad de Granada presentan un estudio que relaciona la fuerza muscular y salud mental”
- La Opinión de Málaga “Demuestran que la fuerza muscular puede mejorar la salud mental de los mayores”
- Ondacero :“Por qué hacer entrenamiento de fuerza: Un studio confirma que mejora la autoestima”
- Twitter: “New Study Published from AGUEDA Trial”: Linking muscular strength & mental health in cognitively normal older adults. Vital insights for geriatrics & neuroscience”

Scientific dissemination

- **2nd International Congress "Promoting brain health through exercise across the lifespan"; Granada; 19-20 September 2024.**The effects of a resistance exercise program on mental health in cognitively normal older adults. A moderation analysis from the AGUEDA randomized controlled trial. Authors: **Darío Bellón**, María Rodriguez-Ayllon, Patricio Solis-Urra, Esmée A. Bakker, Ángel Toval, Javier Fernández-Ortega, Lucía Sánchez-Aranda, Javier Sanchez-Martinez, Jose Mora-Gonzalez, Sol Vidal-Almela, David R Lubans, Irene Esteban-Cornejo.
- **VIII Simposio EXERNET: “Ejercicio físico para la salud a lo largo de la vida” celebrado en Almería los días 20 y 21 de octubre de 2023.** Effects of a 24-week resistance exercise program on psychological well-being in cognitively normal older adults: preliminary results of The AGUEDA Randomized Control Trial. Autores: **Darío Bellón**, Maria Rodriguez Ayllon, Lucía Sánchez-Aranda, Esmée A. Bakker, Angel Toval, Patricio Solis-Urra, Irene Esteban-Cornejo.
- **Annual Alzheimer´s Association International Conference (AAIC) July 16-20, 2023, Amsterdam, Netherlands.** Effects of a 24-week resistance exercise program on psychological distress in cognitively normal older adults. Preliminary results of The AGUEDA Randomized Control Trial. Authors: **Bellón Darío**, Maria Rodriguez-Ayllon, Patricio Solis-Urra, Andrea Coca-Pulido, Jose Mora-Gonzalez, Angel Toval, Javier Fernández-Ortega, Esmée A. Bakker, Francisco B.Ortega, Irene Esteban-Cornejo.

- **27th Annual Congress of the European College of Sport Science between 30 August - 2 September 2022 in Sevilla – Spain**. Associations between muscular strength and mental health in cognitively normal older adults. A cross-sectional study from the AGUEDA trial. Authors: **Bellon, D**., Rodriguez-Ayllon, M., Mora-Gonzalez, J., Sclafani, A., Martín-Fuentes, I., Rivas-Navas, D., Cabanas-Sánchez, V.R., Lubans, D., Catena, A., Solis-Urra, P., Esteban-Cornejo, I.

- **2º Congreso de Investigación PTS febrero 9 – 11 2022. Universidad Medicina UGR. ParqueTecnológico de Ciencias de la Salud. Granada**. Capacidad cardiorrespiratoria y calidad de vida relacionada con la salud en adultos mayores cognitivamente sanos. Estudio transversal del ensayo AGUEDA. Authors: **Dario Bellon**, Patricio Solis-Urra, Jose Mora-Gonzalez, Marcos Olvera-Rojas, Beatriz Fernandez-Gamez, Angel Toval, Andrea Coca-Pulido, Alessandro Sclafani, Daniel J, Rivas-Navas, Verónica Cabanas-Sánchez, Maria Rodriguez-Ayllon, Socorro Navarrete, Francisco B.Ortega e Irene Esteban-Cornejo.

- **1st International Congress "Promoting Brain Health Through Exercise Across the Lifespan" December 9th-10th, 2021 Granada**. Associations between cardiorespiratory fitness and health-related quality of life in cognitively healthy older adults. A cross-sectional study from the AGUEDA trial. Authors: **Dario Bellon**, Patricio Solis-Urra, Jose Mora-Gonzalez, Marcos Olvera- Rojas, Beatriz Fernandez-Gamez, Angel Toval, Andrea Coca-Pulido, Alessandro Sclafani, Daniel J, Rivas-Navas, Verónica Cabanas-Sánchez, Maria Rodriguez-Ayllon, Socorro Navarrete, Francisco B.Ortega e Irene Esteban-Cornejo.

Author's Contribution to the Project

As a predoctoral researcher, I contributed substantially to multiple phases of the AGUEDA project. Although I did not participate in the original study design, I joined the team at the beginning of the recruitment phase, actively supporting the enrolment of participants. I was involved in various stages of data collection, including assessments of cognitive function, physical fitness, mental health questionnaires, MRI, PET imaging, and accelerometry. I also collaborated in the administration of self-reported questionnaires, including those evaluating mental health indicators.

Beyond data collection, I contributed to the creation and management of databases, translated questionnaires into Spanish, and helped implement the study's digital infrastructure using REDCap. I was responsible for statistical analyses aligned with the project's mental health objectives and contributed to the interpretation and

integration of findings within the broader literature. In addition, I was actively engaged in scientific writing across multiple protocols, intellectual property documentation, and manuscripts. I also played a key role in the dissemination of results through national and international conferences, media outlets, and social networks.

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ANNEXES

Mission: To advance the understanding of how exercise can enhance mental health and improve individuals' quality of life.

Vision: To contribute to the development of exercise-based interventions aimed at preventing mental health disorders and promoting a better quality of life.

3. Education

- 2021 / 2025 — International PhD in **Biomedicine**, University of Granada, Granada, Spain. Supervisors: **Irene Esteban Cornejo** and **María Rodríguez García.**
- 2020 / 2021— Master´s degree in **Physical Activity and Sport Research**, Physical Activity and Health Specialization, University of Granada, Granada, Spain.
- 2016 / 2020— Bachelor´s degree in **Physical Activity Sciences and Sport,** University of Castilla la Mancha, Toledo, Spain.

4. Publications

I am the author or co-author of 10 JCR scientific publications.

1) Bellón, J. Á., Conejo-Cerón, S., Sánchez-Calderón, A., Rodríguez-Martín, B., **Bellón, D**., Rodríguez-Sánchez, E. & Moreno-Peral, P. (2021). Effectiveness of exercise-based interventions in reducing depressive symptoms in people without clinical depression: Systematic review and meta-analysis of randomised controlled trials. *The British Journal of Psychiatry*, *219*(5), 578-587. IF (9.319, Q1, D1) DOI: 10.1192/bjp.2021.5

2) Moreno-Peral, P., Pino-Postigo, A., Conejo-Cerón, S., **Bellón, D**., Rodríguez-Martín, B., Martínez-Vizcaíno, V., & Bellón, J. Á. (2022). Effectiveness of Physical Activity in Primary Prevention of Anxiety: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *International Journal of Environmental Research and Public Health*, *19*(3), 1813. IF (3.390,Q1); DOI: https://doi.org/10.3390/ijerph19031813

3) Solis-Urra P, Costa-Rodriguez C, Molina-Hidalgo C, Fernandez-Gamez B, Olvera-Rojas M, Coca-Pulido A, **Bellón D**, Catena A, Erickson KI, Gómez-Río M, Ortega FB, Mora-Gonzalez J, Esteban-Cornejo I. Active Gains in brain Using Exercise During Aging:AGUEDA Study Protocol Clinical Trial. SPIRIT compliant. *Frontiers in Human Neuroscience*. IF (2.9, Q2). DOI: https://doi.org/10.3389/fnhum.2023.1168549

4) Fernandez-Gamez B, Olvera-Rojas M, Molina-Hidalgo C, Mora-Gonzalez J, Costa-Rodriguez C, Coca-Pulido A, **Bellón D**, Catena A, Erickson KI, Gómez-Río M, Ortega FB, Solis-Urra P, Esteban-Cornejo I. Supervised resistance training program in cognitively normal older adults: CERT-based exercise study protocol of the AGUEDA (Active Gains in brain Using Exercise During Aging) randomized controlled trial. *The journal of nutrition, health & aging*. IF (5.9, Q1). DOI: https://doi.org/10.1007/s12603-023-1982-1

5) **Darío Bellón**, María Rodriguez-Ayllon, Patricio Solis-Urra, Beatriz Fernandez-Gamez, Marcos Olvera-Rojas, Andrea Coca-Pulido, Angel Toval, Isabel Martín-Fuentes, Esmée A. Bakker, Alessandro Sclafani, Javier Fernández-Ortega, Verónica Cabanas-Sánchez, Jose Mora-Gonzalez, Manuel Gómez-Río, David R Lubans, Francisco B.

Ortega, Irene Esteban-Cornejo. Associations between muscular strength and mental health in cognitively normal older adults: a cross-sectional study from the AGUEDA trial. *International Journal of Clinical and Health Psychology* (2024) IF (5.3, Q1, D1). DOI: 10.1016/j.ijchp.2024.100450

6) Toval, A., Solis-Urra, P., Bakker, E. A., Sánchez-Aranda, L., Fernández-Ortega, J., Prieto, C., ...**Bellón, D**… & Ortega, F. B. (2024). Exercise and brain health in patients with coronary artery disease: study protocol for the HEART-BRAIN randomized controlled trial. *Frontiers in Aging Neuroscience*, *16*, 1437567. (IF 4.1, Q2) DOI: 10.3389/fnagi.2024.1437567

7) Coca-Pulido, A., Solis-Urra, P., Fernandez-Gamez, B., Olvera-Rojas, M., **Bellón, D**., Sclafani, A., ... & Esteban-Cornejo, I. (2024). Fitness, Gray Matter Volume, and Executive Function in Cognitively Normal Older Adults: Cross-Sectional Findings From the AGUEDA Trial. *Scandinavian journal of medicine & science in sports*, *34*(10), e14746. (IF 3.5, Q1). DOI: 10.1111/sms.14746

8) Gait variability is associated with gray matter volumes implicated in cognitive function: A cross-sectional analysis from the AGUEDA trial. *Innovation in Aging (under-review)*

9) Sclafani, A., Migueles, J. H., Olvera-Rojas, M., Solis-Urra, P., Fernandez-Gamez, B., Coca-Pulido, A., **Bellón, D**., ... & Esteban-Cornejo, I. (2025). Association of 24 h-movement behaviors with cerebral and hippocampal amyloid beta levels and executive function in cognitively normal older adults: a compositional data analysis from the AGUEDA trial. *Journal of Science and Medicine in Sport*.DOI: 10.1016/j.jsams.2025.04.011

9) Fernández-Gámez, B., Solis-Urra, P., Coca-Pulido, A., Molina-Hidalgo, C., Olvera-Rojas, M., Bakker, E. A., **Bellón, D**., Sclafani, A., Mora-González, J., Fernández-Ortega, J., Sánchez-Aranda, L., Martín-Fuentes, I., Toval, Á., Sanchez-Martinez, J., Wan, L., Gomez-Rio, M., Liu-Ambrose, T., Erickson, K. I., Ortega, F. B., & Esteban-Cornejo, I. (2025). Effects of a 24-week resistance exercise program on executive function in cognitively normal older adults: The AGUEDA Randomized Controlled Trial (**Preprint)**

10) Martin-Fuentes, I., Fernandez-Gamez, B., Vidal-Almela, S., Caro-Rus, A., Solis-Urra, P., Sanchez-Aranda, L., ... & Esteban-Cornejo, I. (2024). Understanding cerebral blood flow dynamics for Alzheimer's disease prevention through acute exercise (flADex): Protocol for a randomized crossover trial. *medRxiv*, 2024-12. (**Accepted**)

5. Participation in Scientific Communications and Posters at International and National Conferences

I have participated in 7 international and 3 national scientific conferences with various contributions (oral communications and posters) as both first author and co-author. Additionally, I have served as a member of the organizing committee for two international conferences. All certificates of congress contributions are available at the following Google Drive link:

Internacional congress:

1) International Meeting of Research in Physical Activity and Health. 13th and 14th December2017, Cuenca.
2) 1st International Congress “Promoting Brain Health Through Exercise Across the Lifespan” December 9th-10th, 2021 Granada.

3) 35th Annual Congress of the European Association of Nuclear Medicine – EANM'22 | October 15 - 19, 2022 | Barcelona, Spain.
4) 22º WPA World Congress of Psychiatry. 3-6 August 2022. Bangkok.
5) 27th Annual Congress of the European College of Sport Science between 30 August - 2 September 2022 in Sevilla - Spain.
6) Annual conference Alzheimer´s Association International Conference (AAIC) July 16-20, 2023, Amsterdam, Netherlands.
7) 2nd International Congress "Promoting brain health through exercise across the lifespan"; Granada; 19-20 September 2024.

Organizing Committee Member at International Conferences:

- 1st International Congress *"Promoting Brain Health Through Exercise Across the Lifespan"*, 9 y 10 de diciembre de 2021. Granada.
- 2nd International Congress *"Promoting Brain Health Through Exercise Across the Lifespan"*, 19 y 20 de septiembre de 2024. Granada.

National congress:

1. **VII EXERNET Symposium:** "Evidence-Based Prescription of Physical Exercise," held in Cuenca on October 22–23, 2021.
2. **II PTS Research Congress:** February 9–11, 2022. University of Medicine, University of Granada (UGR), Health Sciences Technology Park (PTS), Granada.
3. **VIII EXERNET Symposium:** "Physical Exercise for Health Across the Lifespan," held in Almería on October 20–21, 2023.
4. **Research Conference:** 10th Anniversary of CIMCYC (Mind, Brain and Behavior Research Center), May 11–12, 2023, Granada.

6. Participation in Research Projects

All participation certificates for research projects :

1.SmarterMove (DEP2016-79512-R); 100.000 EUR. Project funded by the Spanish Ministry of Economy and Competitiveness and the European Regional Development Fund (ERDF): *Exercise in the prevention and treatment of obesity and insulin resistance: Smart Analysis-Smart Interventions*. Principal Investigators: Francisco B. Ortega and Jonatan R. Ruiz. **Role:** Contributed to evaluations, data collection, statistical analysis, and scientific output. Specialization in: (i) physical fitness assessment through field and laboratory tests; (ii) physical activity and energy expenditure measured with accelerometers, smart bands, and laboratory methods; (iii) mental and cognitive health via questionnaires.

2.GENOBEX (B-CTS-355-UGR18); Project funded by the Spanish Ministry of Economy and Competitiveness and the ERDF: *Influence of obesity and genetic profile on cognitive and brain development in childhood: the role of physical exercise.* Principal Investigator: Francisco B. Ortega. **Role:** Contributed to evaluations, data collection, statistical analysis, and scientific

output. Specialization in: (i) physical fitness assessment; (ii) physical activity and energy expenditure monitoring; (iii) mental and cognitive health via questionnaires.

3. AGUEDA (RTI2018-095284-J-100); Project funded by the Spanish Ministry of Economy and Competitiveness and the Ministry of Science and Innovation (RYC2019-027287-I): *Active Gains in Brain Using Exercise During Aging*. Principal Investigator: Irene Esteban-Cornejo.
Role: Collaborating researcher involved in participant evaluations, data collection and analysis, literature review, and contribution to scientific publications. Specialized in physical fitness, physical activity monitoring, mental and cognitive health, and brain imaging (MRI).

4. The Hearty Brain (P20.00124**)**; Funded by the Andalusian Research, Development, and Innovation Program (PAIDI). Principal Investigator: Francisco B. Ortega.
Role: Collaborating researcher involved in study design, protocol development, participant assessments, data handling and analysis, literature review, and dissemination of scientific results. Specialized in physical fitness, physical activity, mental and cognitive health, and brain MRI markers.

5.VasculActive (PID2020-120249RB-I00); 120.000 EUR. Funded by the State Program for Scientific and Technical Research and Innovation. Principal Investigator: Francisco B. Ortega.
Role: Collaborating researcher contributing to study design, protocols, evaluations, data collection and analysis, literature review, and scientific dissemination. Specialization in physical fitness, physical activity, mental and cognitive health, and brain MRI.

6.Fladex (PID2022-137399OB-I00). Funded by the Spanish Ministry of Science and Innovation (2022 Knowledge Generation Projects). *Understanding Cerebral Blood Flow Dynamics for Alzheimer's Disease Prevention Through Exercise*. Principal Investigator: Irene Esteban-Cornejo.
Role: Collaborating researcher involved in study design, protocol writing, and participant assessments. Specialization in physical fitness, mental and cognitive health, and brain MRI.

7. Other Achievements

- Employed by the University of Granada for 22 months (673 days) under research project contracts.
- Completed a 3-month research stay at the "Population Imaging" (PopI) group within the Department of Epidemiology at Erasmus Medical Center, Rotterdam, The Netherlands, under the supervision of Meike Vernooij, a globally recognized neuroscientist.

- Served as topic coordinator for the *Frontiers* special issue: *"Physical Activity: a Promising Modifiable Behavior to Protect Brain, Cognition, and Mental Health Across the Lifespan."*
- Participated in the outreach activity *"Exercise Awakens Your Brain"* during the European Researchers' Night (30/09/22, Granada), aimed at demonstrating the effects of different types of physical exercise on cognitive performance through pre- and post-exercise tests.
- Co-Principal Investigator of a competitive research project funded by the University of Granada's 2023 Research and Transfer Plan: *"Analysis of the physiological response to fasting in children and adolescents with obesity compared to adults, and after a time-restricted eating intervention"* (€1,000).
- Guía de Práctica Clínica para el manejo de la Hipertensión Arterial en Atención Primaria. Guía de Práctica Clínica para el manejo de la Hipertensión Arterial en Atención Primaria. Ministerio de Sanidad. Servicio de Evaluación del Servicio Canario de Salud; 2024. Guías de Práctica Clínica en el SNS" (In draft).

8.Courses completed:

1. R and RStudio Course (25 hours)
2. Introduction to Programming and Data Analysis in R (20 hours)
3. Introduction to Research with Functional Magnetic Resonance Imaging (fMRI) (18 hours)
4. "Bibliographic Shortcuts" Seminar (1 hour)
5. Powerexplosive Trainer Certification (450 hours)
6. Powerexplosive Training Program (15 hours)
7. DXA Clinical Research Course (2 hours)
8. International Seminar in Physical Activity and Health Sciences (10 hours)
9. Training Activities – University of Granada (8 hours)
10. Strength Training Exercise Selection and Applied Biomechanics Course (6 hours)

9. Languages: English – Trinity College C1 Certificate.

THE ROLE OF MUSCULAR STRENGTH IN THE MENTAL HEALTH OF OLDER ADULTS

EL ROL DE LA FUERZA MUSCULAR EN LA SALUD MENTAL DE ADULTOS MAYORES

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PROGRAMA DE DOCTORADO EN BIOMEDICINA
DEPARTAMENTO DE EDUCACIÓN FÍSICA Y DEPORTIVA
FACULTAD CIENCIAD DEL DEPORTE
UNIVERSIDAD DE GRANADA

Darío Bellón Fernández

2025