PHYSIOLOGICAL AND METABOLIC CHARACTERIZATION OF OLDER ADULTS. ESPECIAL FOCUS ON CARDIORESPIRATORY FITNESS AND ITS ROLE ON COGNITIVE FUNCTION

THE EFICCOM/INTERMAE STUDY

CARACTERIZACIÓN FISIOLÓGICA Y METABÓLICA DE PERSONAS MAYORES. ESPECIAL INTERES DE LA CAPACIDAD CARDIORRESPIRATORIA Y SU ROL EN LA FUNCIÓN COGNITIVA

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En Cádiz, a 24 de abril de 2021

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RESEARCH PROJECTS

The present Doctoral Thesis was performed as a result of the following research projects:

1. Effect of supervised physical exercise at the cerebral, cognitive and metabolomic level in older adults with mild cognitive impairment. **EFICCOM study** (Efecto del ejercicio FIsico supervisado a nivel Cerebral, COgnitivo y Metabolómico en personas mayores con deterioro cognitivo ligero. Estudio EFICCOM)
   Competitiveness (i+D+I program) of the Spanish Ministry Science and Innovation, The Government of Spain (Plan Nacional I+D+i).
   Reference: DEP2016-76123-R
   Principal investigators: Carbonell-Baeza, Ana and Jiménez-Pavón, David
   Duration: 01/01/2017 to 31/12/2020
   Funding: 120,000 €

2. Influence of a physical exercise intervention on markers associated with aging, proteomic profile and fragility. **INTERMAE study** (INfluencia de una inTervención con EjeRcicio Físico sobre Marcadores Asociados al Envejecimiento, Perfil Proteómico y Fragilidad. Estudio INTERMAE)
   Program for the financing of biomedical i+D+I and of health sciences in the province of Cadiz, Spain.
   Reference: PI-0002-2017
   Principal investigator: Jiménez-Pavón, David
   Duration: 01/01/2018 to 31/12/2021
   Funding: 492,107.54 €

The Ph-D candidate has participated in an additional project during pre-doctoral phase (data not shown in this doctoral thesis):

3. Promoting the shift sedentary Lifestyle towards active Ageing – **LifeAge Study**
   Competitiveness ERASMUS+ SPORT 2018
   Reference: 603121-EPP-1-2018-1-ES-SPO-SCP
   Cordinator: Marcos Pardo, Pablo Jorge
   Principal investigator/patner: Jiménez-Pavón, David
   Duration: 01/01/2019 to 31/12/2020
   Funding: 389,830 €

FUNDINGS AND GRANTS

The PhD candidate of the present Doctoral Thesis was funded by the Program from the promotion and impulse of research and transfer of the University of Cádiz 2016-2017, published in the Resolution of the Rector of the University of Cadiz UCA / REC01VI / 2017, of February 20, 2017, by which a public tender of pre-doctoral contracts for research staff in training (del Castellano, Personal Investigador en Formación; PIF).

The aforementioned contract was associated with the EFICCOM project.

During pre-doctoral phase, the candidate enjoyed the following grants:

1. **Research Stay** in the Research Centre in Physical Activity, Health and Leisure (CIAFEL), Faculty of Sports, University of porto, Portugal
   Reference: EST2018-100
   Responsible researcher: Mota, Jorge
   Duration: 01/05/2018 to 31/07/2018
   Funding: 1,320 €
2. **Grant to attend an international congress.** European Congress of Sport Science, Dublin, Ireland
   Reference: MV2018-199
   Duration: 04/07/2018 to 07/07/2018
   Funding: 1,000 €
3. **Grant to attend an international congress.** ESPEN CONGRESS on Clinical Nutrition & Metabolism, Madrid, Spain
   Reference: MV2018-237
   Duration: 01/09/2018 to 04/09/2018
   Funding: 500 €
4. **Grant to attend an international congress.** XII International Symposium on Strength Training Updates, Madrid, Spain
   Reference: MV2019-551
   Duration: 13/12/2019 to 14/12/2019
   Funding: 500 €
5. **Grant to attend a national course.** 1-week english language immersion course, Cuenca, Spain
   Reference: MV2018-543
   Duration: 29/10/2018 to 03/11/2018
   Funding: 358 €

6. **Grant to attend a national course.** Level I ISAK. Cineanthropometry course, Murcia, Spain
   Reference: MV2019-061
   Duration: 11/01/2019 to 13/01/2019
   Funding: 462.64 €

LIST OF ABREVIATIONS

AD, alzheimer disease

BMI, body mass index

BNT, boston naming test

CDT, clock drawing test

COWAT, controlled oral word association test

CPET, cardiopulmonary exercise test

CRF, cardiorespiratory fitness

DBP, diastolic blood pressure

DP, double product

DXA, dual energy X-ray absorptimetry

ECG, electrocardiogram

FEV1, forced expiratory volume in 1 second

FFM, fat free mass

FFMI, fat free mass index

FM, fat mass

FMI, fat mass index

FVC, forced vital capacity

GPAQ, global physical activity questionnaire

HHb, concentration of deoxyhemoglobin

HR, heart rate

HRmax, maximum heart rate

ISAK, international standards for anthropometric assessment

MAP, mean of arterial pressure

MCI, mild cognitive impairment

MET, metabolic equivalent

MMSE, mini mental scale examination

NIRS, near infrared spectroscopy

OHb, concentration of oxyhemoglobin

PEF, peak expiratory flow

RAVLT, rey auditory verbal learning test

RER, respiratory exchange ratio

RMR, resting metabolic rate

RPE, perceived exertion scale

SBP, systolic blood pressure

SEPAR, spanish society of pneumology and thoracic surgery normative

TMT, trail making test

TOI, tissue oxygen index

VCO_2, carbon dioxide production

VO_2, oxygen intake

VO_{2peak}, oxygen intake peak

WC, stroop interference

WHR, waist-hip ratio

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ABSTRACT

Advances in modern medicine from developing countries have caused an increase in overall life expectancy and consequently among the older adults population. Ageing is a multifactorial and multi-organic process characterized by decreases in physiological functions, among others, causing deterioration of the physical integrity, and increases in the incidence of health-related problems and non-communicable diseases. Dementia is one of the most common and relevant non-communicable diseases, and in fact, it is one of the main causes of dependency and disability in older adults. Scientific evidence supports that regular exercise has positive effects on ageing process and promotes brain health in older adults. There is a special interest on the relationship between physical fitness and brain health, particularly, the role of cardiorespiratory fitness (CRF) as a powerful health marker in different population groups.

Scientific literature has clearly shown an inverse association of CRF with the incidence of many chronic diseases and all-cause mortality. Therefore, to better know the factors that determine and predict CRF level is essential to develop interventions for enhancing both determinants and CRF. Since these factors have been identified in young and middle-aged adults but not clearly in older adults, additional investigation on this topic is needed.

Therefore, the main aim of this International Doctoral Thesis was to analyse the physiological, metabolic and cardiovascular determinants of CRF and to develop new and specific equations to predict CRF in older adults. Additionally, the current thesis aimed to study the associations of CRF, both objectively-measured and estimated using new equations, with cognitive function in this population.

The sample comprised of 92 people (41 females) between 65 and 75 years from the EFFICOM project (NCT03923712), recruited through the Public Health Care Centers of the province of Cadiz. Participants completed 4 measurements sessions including: i) laboratory measurements of body composition, resting cardiovascular, metabolic and spirometry parameters, and CRF by the modified Bruce incremental test; ii) field assessments of Senior Fitness Test Battery and handgrip test; iii) self-reported questionnaires and interviews on sociodemographic characteristics, activities of daily living and physical activity; and iv) a complete battery of neuropsychological tests to evaluate cognitive function.

The main findings of this thesis indicate that: i) The physiological, metabolic and cardiovascular characteristics of older adults were different between males and females

ii) body composition, resting cardiovascular and metabolic parameters, spirometry values and physical fitness performance were identified as relevant and independent determinants of CRF, iii) fifteen equations have been developed with the high prediction values for CRF of older adults. Three different complexity levels were considered; Level 1) basic variables such as body composition parameters, meeting physical activity recommendations, field tests and basal metabolic and cardiovascular parameters; Level 2) basic variables plus spirometry parameters; and Level 3) basic variables, spirometry parameters and simple cardiopulmonary exercise test (CPET) information. The best equation models proposed, from levels 1 and 2, explain 80% of the variability of CRF and, when using maximum HR and time to exhaustion from the CPET (level 3), the best model proposed reach to explain 87% of the variability of CRF, and iv) CRF, both objectively-measured and estimated, were associated with better performance on language, fluency and cognitive flexibility independently of sex, age and education level.

The findings of the present International Doctoral Thesis identify key determinants and predictors of CRF, and suggest CRF may be a protective factor against the deterioration of cognitive function associated with ageing in older adults, providing different predictive equations for CRF with low cost and high feasibility.

RESUMEN

Los avances en la medicina moderna de los países en desarrollo han provocado un aumento de la esperanza de vida en general y, en consecuencia, entre la población de personas mayores. El envejecimiento es un proceso multifactorial y multi-orgánico que se caracteriza por la disminución de las funciones fisiológicas, entre otras, provocando el deterioro de la integridad física, y el aumento de la incidencia de problemas relacionados con la salud y las enfermedades no transmisibles. La demencia es una de las enfermedades no transmisibles más comunes y relevantes, de hecho, es una de las principales causas de dependencia y discapacidad en personas mayores. La evidencia científica apoya que el ejercicio regular tiene efectos positivos en el proceso de envejecimiento y promueve la salud cerebral en personas mayores. Existe especial interés en la relación entre la condición física y la salud cerebral, en particular, el papel de la capacidad cardiorrespiratoria (CRF) como un potente marcador de salud en diferentes grupos de población.

La literatura científica ha mostrado claramente una asociación inversa de la CRF con la incidencia de muchas enfermedades crónicas y la mortalidad por todas las causas. Por lo tanto, conocer mejor los factores que determinan y predicen el nivel de CRF es esencial para desarrollar intervenciones para mejorar tanto los determinantes como la CRF. Estos factores se han identificado en adultos jóvenes de mediana edad, pero no claramente en personas mayores, por lo que son necesarias investigaciones adicionales sobre este tema.

Por lo tanto, el objetivo principal de esta Tesis Doctoral Internacional fue analizar los determinantes fisiológicos, metabólicos y cardiovasculares de la CRF y desarrollar ecuaciones nuevas y específicas para predecir la CRF en personas mayores. Además, la presente tesis pretendía estudiar las asociaciones de la CRF, tanto medida objetivamente como estimada mediante nuevas ecuaciones, con la función cognitiva en esta población.

La muestra estuvo compuesta por 92 personas (41 mujeres) de entre 65 y 75 años del proyecto EFFICOM (NCT03923712), reclutadas a través de los Centros Sanitarios Públicos de la provincia de Cádiz. Los participantes completaron 4 sesiones de mediciones que incluían: i) mediciones de laboratorio de la composición corporal, parámetros cardiovasculares, metabólicos y espirométricos en reposo, y la CRF mediante el test incremental de Bruce modificado; ii) evaluaciones de campo de la Batería Senior Fitness test y test de dinamometría manual; iii) cuestionarios autoinformados y entrevistas sobre características sociodemográficas, actividades de la vida diaria y

actividad física; y iv) una batería completa de pruebas neuropsicológicas para evaluar la función cognitiva.

Los principales resultados de esta tesis indican que: i) Las características fisiológicas, metabólicas y cardiovasculares de las personas mayores eran diferentes entre hombres y mujeres, ii) la composición corporal, los parámetros cardiovasculares y metabólicos en reposo, los valores espirométricos y el rendimiento en los test de condición física se identificaron como determinantes relevantes e independientes de la CRF, iii) Se han propuesto quince ecuaciones con altos valores de predicción la CRF en personas mayores. Se consideraron tres niveles de complejidad diferentes; Nivel 1) variables básicas como parámetros de composición corporal, cumplimiento de las recomendaciones de actividad física, pruebas de campo y parámetros metabólicos y cardiovasculares basales; Nivel 2) variables básicas más parámetros de espirometría; y Nivel 3) variables básicas, parámetros de espirometría e información simple de la prueba de esfuerzo. Los mejores modelos de ecuación propuestos, de los niveles 1 y 2, explican el 80% de la variabilidad de la CRF y, al utilizar la FC máxima y el tiempo hasta el agotamiento de la prueba de esfuerzo (nivel 3), el mejor modelo propuesto llega a explicar el 87% de la variabilidad de la CRF, y iv) la CRF, tanto medida objetivamente como estimada, se asoció con un mejor rendimiento en el lenguaje, la fluidez y la flexibilidad cognitiva, independientemente del sexo, la edad y el nivel educativo.

Los hallazgos de la presente Tesis Doctoral Internacional identifican los determinantes y predictores claves de la CRF, y sugieren que la CRF puede ser un factor de protección contra el deterioro de la función cognitiva asociado al envejecimiento en las personas mayores, proporcionando diferentes ecuaciones predictivas para la CRF con bajo coste y alta viabilidad.

INTRODUCTION

1. INTRODUCTION

1.1. Ageing process

Advances in modern medicine, improved hygiene and the implementation of antibiotics and pesticides, among others, have produced an increase in life expectancy (1). Therefore, by the end of this century, the population will increase to over 3.6 billion people worldwide (2) and, specifically in the US population aged ≥65 years is estimated to increase from 53 million in 2018 to 88 million in 2050 (3). Developing countries are experiencing the highest growth in the ageing population (4), and consequently, all countries are facing the challenge of ensuring that their health and social systems are prepared and adapted for this context (5).

Ageing is a multifactorial process influenced by both genetic and environmental factors (6,7) . This process is characterised by a decline of physiological functions, which causes an impaired physical integrity and an increase of mortality risk (6,7). Moreover, ageing is associated with a progressive loss of functional capacity and a deterioration of different physical fitness components (i.e. muscle strength, aerobic capacity or flexibility), which influence the health of older adults (8,9). In fact, all these components of physical fitness are directly related to the performance of activities of daily living and prevention and control of non-communicable diseases (8,10).

The trend of population ageing increases the incidence of health-related problems and physiological declines generating dependency, being dementia one of the most common and important non-communicable diseases and a major contributor to dependence and disability in older adults (11). This ageing process together with the increase in life expectancy worldwide have entailed a rise in dementia (12). Approximately, 50 million people live with dementia, and this number is projected to increase to 152 million by 2050 worldwide (13). For that reason, in the previous Lancet Commission 2017, dementia was defined as the greatest global challenge for health and social care in the 21st century (14). There are different types of dementia, which include vascular dementia, Lewy body dementia, frontotemporal dementia and Alzheimer´s disease (AD) (15), being AD the most common type of dementia (16) and contributing 70-80% of cases (17,18).

The World Health Organization defines AD as a neurodegenerative disease of unknown etiology characterized by progressive deterioration of memory and cognitive function (19). The main brain biomarkers of this disease are Tau and Beta-amyloid protein (13). The current recommendations emphasize the need to focus efforts and strategies in the

preclinical stage of the disease, due to greater efficacy in delaying the clinical onset of dementia (11,20). This preclinical stage is defined as mild cognitive impairment (MCI) (21). Moreover, not all cases of MCI are precursors of AD and not all are progressive, since fortunately, some cases have shown to regain a normal state of cognition (22). In particular, MCI has been defined as a cognitive decline greater than expected for age and educational level, but that does not interfere with activities of daily living (19). The concept of MCI tries to identify the intermediate cognitive deterioration that is usually, but not always, a transitory phase between the normal cognitive changes associated with ageing and those typical found in dementia (20).

Unfortunately, nowadays neither MCI, AD nor dementia have an effective treatment, therefore non-pharmacological strategies are essential to prevent disease onset (14,23,24). Lifestyle may be a fundamental element in the ageing process, thus to maintain an adequate level of physical fitness thought an active life and performing physical exercise could be considered as a real anti-ageing strategy (25,26). Literature shows that the regular physical exercise has an important effect on the ageing process, suggesting that physical exercise with adequate intensity and volume could contribute to improve the physical fitness level and obtaining a greater anti-ageing effects (6,26,27). Moreover, physical fitness may attenuate the risk of mortality among cognitively impaired individuals (28). In this line, high quality evidence supports the use of exercise programme for the promotion of brain health in older adults (29), with especial interest in the relationship between physical fitness and brain health, and specifically CRF like a powerful marker of health (30).

1.2. Cardiorespiratory fitness, the key indicator in ageing

CRF, usually assessed as peak oxygen uptake (VO_{2peak}) is a health-related component of physical fitness defined as the ability of the circulatory, respiratory, and muscular systems to supply oxygen during sustained physical activity (31), being the gold standard of exercise capacity (32).

The CRF declines during biological ageing process (33). Though, endurance trained older individuals demonstrate a greater VO_{2peak} compared to their untrained counterparts, unfortunately, an age-related decline in VO_{2peak} is still inevitable (34). Kaminsky et al. (35) in a cohort study showed that the rate of VO_{2peak} decline approximately 10% per decade. In addition, the ventilator threshold decreases with age, with a decline of 35% and 30% in males and females, respectively, during the 70' decade (36). Therefore, a lower tolerance to exercise intensity has been observed with age.

The literature has shown a considerable amount of evidence demonstrating the importance of CRF in predicting the risk of adverse health outcomes (37–39). In fact, CRF is a known important marker of health inversely associated with the incidence of many chronic diseases, all-cause mortality and even sudden cardiac dead (40,41). A number of recent studies have shown the context of survival benefit of CRF per metabolic equivalent (MET); each 1-MET increase is associated with large (10%–25%) improvements in survival (42). Moreover, there is strong scientific evidence of the association of CRF with the most relevant chronic diseases in older adults, since those with a higher level of CRF have shown a lower hypertension incidence (43), diabetes incidence (44), heart failure incidence (45), cerebrovascular accidents (46). Interestingly these associations between decreased CRF and increased of health disorders appears to be dose-dependent (47–51).

For this reason, it is essential a comprehensive interpretation of VO_2, as well as, to know to which extent other variables previously associated with CRF (32) in younger population groups such as body composition (52–55), muscle strength (56), cardiovascular (54,57,58) and spirometry parameters (59,60) are influencing the CRF in older adults.

1.2.1. Role of body composition and muscle strength on cardiorespiratory fitness

Regarding body composition, previous studies have shown that body mass index (BMI) was inversely associated with CRF in children (61), adolescents (61) and young adults (52) and a similar pattern occurred with body fat (53,55). Conversely, higher lean mass and fat free mass (FFM) have been shown to be independently associated with better CRF in children, adolescents and adults (62–64). Therefore, body composition may confound CRF measurement (65,66). To address this confounding effect of body composition it has been commonly reported the VO_{2peak} relative to body weight (67), however, Savonen et al. demonstrated that dividing VO_{2peak} by body weight introduces a bias against obese participants and distorts the achieved CRF in adults and older adults (68). Consequently, a possible alternative to avoid causing a bias in obese people could be dividing the VO_{2peak} by lean mass in adults and older adults, in fact, this procedure should be used in samples with different categories of BMI (65).

On the other hand, during ageing skeletal muscles decrease its capacity to use O_2 as a consequence of several factors (i.e. decrement of lean mass, reduced muscle capillary density, low endothelial function, and impaired muscle oxidative capacity) (25,69). , the

declines of lean mass may be affecting CRF measurement, being muscle strength, a component closely related to CRF.

The relationship between muscular strength tests and CRF is far less studied (56), although some previous studies have observed a significant positive association between muscle strength and CRF (56,70).The age-associated decline in CRF in sedentary individuals is explicable by the loss of muscle mass, which is observed with advancing age and affect the muscular strength levels (71). In older adults muscle strength may be positively associated with CRF (56), but to date few studies have examined this association in older adults (70) and the evidence is limited.

1.2.2. Role of cardiovascular parameters on cardiorespiratory fitness

In regard to the overall cardiovascular function, it has been found that a poor CRF is positively associated with elevated systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) (54,57) and an increased risk of hypertension in young (57) and older adults (43). In addition, others cardiovascular parameters as double product (DP), ratio SBP/DBP, mean of arterial pressure (MAP) and oxygen pulse should be considered due to its relevance, but few studies analysing those components in relation to VO_{2peak} in older adults have been addressed (72,73). In the case of DP, it is considered a marker of myocardial oxygen consumption (74) and showed that, when measured during exercise, DP has prognostic value among patients with a history of angina, myocardial infarction or heart failure (75,76). Similarly, oxygen pulse, calculated as the product of oxygen consumption (VO_2) per HR in resting condition and during cardiopulponary exercise test (CPET), is considered a marker related to the risk of cardiovascular events (77). Nevertheless, the potential relationships of DP, oxygen pulse, SBP/DBP ratio and MAP with CRF is unclear in older population and would be of high interest to know that, in order to better understand the physiological implications of CRF during ageing.

On the other hand, another relevant dimension of interest is the dinamic of the oxy- and deoxyhemoglobin concentrations and its relation with CRF. In this regard, one of the main parameters obtained by near-infrared spectroscopy (NIRS) is the tissue oxygenation index (TOI), from oxyhemoglobin and total hemoglobin, which provides us information about the oxygenation index of a certain body surface (78,79). This tool through an emitter issues light which is absorbed by chromophores such as oxyhemoglobin, deoxyhemoglobin or is dispersed within the tissue (78). By measuring the dispersed light returned to the receptor, the relative level of oxyhemoglobin and deoxyhemoglobin absorbed in the underlying tissue can be determined (80), reaching to

evaluate hemodynamic changes in the brain or in a certain body surface at rest or during exercise (81–85). Moreover, this instrument has the ability to accurately detect changes in oxy- and deoxyhemoglobin during a cognitive task (86,87), cerebral ischemia thresholds (88), or even changes in oxygenation produced by a specific motor task in the controlled-lateral cerebral hemisphere (86).

An advantage of NIRS over the other methods to evaluated oxygenation is that it provides direct, real-time measures of oxygenation in cortical tissue or other areas with acceptable spatial resolution and is not as sensitive to movement artifact as other measures (89). Particularly, the simultaneusly analysis of cerebral and peripherical oxygenation could provide useful information about the ability of the circulatory, respiratory, and muscular systems to supply oxygen at resting conditions and during exercise, as well as, about the oxygenation balance between central and peripherical location in different situations. Thus, TOI at resting conditions and during exercise might affect the CRF level. In fact, it has been previously reported an increased cerebral oxygen level in relation with higher levels of CRF in young and older adults (58,90,91), although more studies to analysing the relationship between TOI and CRF are needed.

1.2.3. Role of pulmonary parameters on cardiorespiratory fitness

Pulmonary function decreases with ageing and to take into account the effect of age is necessary (92,93). Ageing affects lung physiology, reducing the lung's ability to diffuse gas, reducing tidal volume compared to younger individuals, and developing a marked alveolar to arterial oxygen gradient during exercise (94,95). In addition, there is variability in the progress of the deterioration of pulmonary function, however, once the symptoms manifest themselves, the accumulated damage becomes irreversible (96). In fact, there are spirometry reference values derived from cross-sectional studies of healthy individuals of various ages (97–99). Through the measurement of pulmonary function is possible to analyse the progress of lung damage with age (96).

Pulmonary function measured through spirometry test has been found to be associated with CRF in children and adults (62–64). In fact, each additional minute during a CPET on treadmill was associated with better forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) and less decline with age in this variables in young adulthood (60). In older adults, an impaired pulmonary function could influence the risk of chronic hypoxemia, and this impaired function could affect CRF level by several pathways (100). Some studies have analysed the association between pulmonary function and CRF in older adults with lung disease. They have observed that pulmonary

function (i.e. FEV_1, FVC and FEV_1/FVC) is positively associated with CRF (101–104), but this association in older adults with healthy pulmonary function is poorly studied (105). Therefore, given that the healthy respiratory system is overbuilt with respect to requirements for oxygen uptake (105), it is of special interest to analyze the association between lung capacity and CRF in older adults free of lung disease.

Taken all together, there is a need for a detailed characterization of the physiological, metabolic and cardiovascular parameters in older adults, and to describe how this parameters interact with CRF provinding key information to understand the role of the fitness as a powerful health marker in older adults.

1.3. Prediction of cardiopulmonary fitness

Performing an incremental CPET until exhaustion is considered the gold standard method to obtain an accurate and precise measurement of CRF (106). The CPET until exhaustion entails certain physical and health risks, especially for older adults, as well as requires the use high precision and expensive equipment that hamper its implementation in large scale studies and clinical settings (32,54).

Therefore, it is important to evaluate CRF with a method that ensure safety, reliability and accuracy in older adults (107). For that reason, predict CRF level without performing a CPET until exhaustion, because of health risk or logistical reasons, would be of great interest for the research community. In this regard, previous studies have provides prediction equations of CRF in children, adults and athletes with a good prediction ratio (108,109).

Previous studies have reported non-exercise and sub-maximal exercise equations to predict CRF in older adults (110–112). In particular, Jackson et al. (111) showed in a study with over ten thousand people between 20 and 78 years that the CRF of males and females can be estimated from easily obtained health and fitness non-exercise indicators. They reported four equations by sex and six measurement more are need to calculate estimated CRF (Age, percentage of body fat or BMI, waist circumference, resting HR, smoking and physical activity level) and with these equations, the range of coefficient r^2 achieved was between 0.56 and 0.60. After that, these equations have been used with older adults to obtain CRF and this has been associated with a lower risk of hospitalizations (32), incidence of strokes (113) and mortality (114,115).

On the other hand, two previous systematic review have studied the accuracy of the different non-exercise (110) and submaximal exercise-based predictive equations of CRF

(116). Particularly, Peterman et al. (110) compared the ability of 27 distinct non-exercise prediction equations to detect changes in directly measured CRF mostly in adults and they achieved a range of coefficient r^2 between 0.34 and 0.67. They observed important variability in the accuracy between non-exercise prediction equations, in accordance with other authors (117–119).

Based on previous evidence, equations to estimate the CRF in older adults could overestimate the CRF (120) and the variability observed in the accuracy between non-exercise prediction equations (110,117–119) may have limited clinical utility (110). Therefore, predictive equations based on the availability of resources and equipment but with a good prediction rate are necessary to get a good predictor of CRF in older adults.

1.4. Cardiorespiratory fitness and cognitive function

Previously, we have mentioned that literature has shown a considerable amount of evidence demonstrating the importance of CRF in predicting the risk of adverse health outcomes (37–39) and like an important marker of health in older adults (121). Moreover, has shown a protective effect on brain function (122,123), since might be related to better cognition and reduced risk of AD (123). Literature suggests that systemic neurotrophic factors are induced by exercise and that these circulating biomolecules may cross the blood-brain barrier and be important in protecting against neurodegenerative disorders, such as dementia or AD (124).

Moreover, CRF is positively associated with cognitive function in healthy older adults and older adults with MCI, AD or dementia (125–128) and being considered an important risk factor in people with severe mental illness given its relationship to cardiovascular disease and premature mortality (129). Regarding the effect on memory, a previous review has shown that the CRF appears to be positively associated with memory function (123), also there is evidence that aerobic physical intervention which improve CRF are beneficial for cognitive function in healthy older adults, with effects observed for motor function, cognitive speed, auditory and visual attention (122). Taken all together, objectively measured CRF has shown a protective effect on cognitive function (122,123).

Additionally, several studies where CRF has been estimated through an equation reported or measured objectively reported over 50 percent reduction in risk of developing dementia among those with a high age-relative cardiorespiratory fitness compared with their counterparts unfit (130–132). Tari et al. (133) studied whether changes in estimated CRF are associated with changes in risk of incident of dementia, dementia-related mortality and longevity, and they showed estimated CRF is an independent risk

factor for incidence of dementia and dementia mortality. However, the equation they used to estimate CRF was not validated with people with cognitive impairment and only include sex, age, waist circumference, level of physical activity and resting HR (134), and not including this equation BMI, body fat or body weight, which is well know that affect CRF (72,73).

Finally, to understand the association between CRF and cognitive function are needed new studies (133). Therefore, we are especially interested in seeing the association of CRF measured objectively and obtained through equations with a complete battery of neuropsychological test in older adults. Thus, we will examine the association of CRF with key cognitive domains involved in the prevention of dementia.

AIMS

2. AIMS

General aim

The general aim of the present International Doctoral Thesis was to analyse the physiological, metabolic and cardiovascular determinants of the CRF and to develop new and specific equations to predict CRF in older adults. Additionally, the current thesis aimed to study the associations of CRF, both objectively-measured and estimated using new equations, with cognitive function in this population.

Specific aims

1) To describe the characteristics of the physiological, metabolic and cardiovascular parameters during resting and exercise conditions; and to analyses the differences between older males and females.
2) To identify the physiological, metabolic and cardiovascular determinants of CRF considering the role of sex in older adults.
3) To develop new and specific equations to predict CRF using variables with different levels of complexity and equipment requirements in older adults.
4) To analyse the associations of objectively-measured and estimated CRF levels with cognitive function in older adults.

2. OBJETIVOS

Objetivo general

El objetivo general de la presente Tesis Doctoral Internacional fue analizar los determinantes fisiológicos, metabólicos y cardiovasculares de la CRF y desarrollar ecuaciones nuevas y específicas para predecir la CRF en personas mayores. Además, la presente tesis tuvo como objetivo estudiar las asociaciones de la CRF, tanto medida objetivamente como estimada mediante ecuaciones, con la función cognitiva en esta población.

Objetivos específicos

1) Describir las características de los parámetros fisiológicos, metabólicos y cardiovasculares durante las condiciones de reposo y durante el ejercicio; y analizar las diferencias entre hombres y mujeres mayores.

2) Identificar los determinantes fisiológicos, metabólicos y cardiovasculares de la CRF considerando el rol del sexo en las personas mayores.

3) Desarrollar ecuaciones nuevas y específicas para predecir la CRF utilizando variables con diferentes niveles de complejidad y requerimientos de equipamiento en personas mayores.

4) Analizar las asociaciones de los niveles de CRF, medida objetivamente y estimada, con la función cognitiva en adultos mayores.

MATERIAL AND METHODS

3. MATERIAL AND METHODS

3.1. Design and doctoral thesis context

This doctoral thesis has been developed as part of the EFFICOM project (EFfect of supervised physIcal exercise at Cerebral, COgnitive and Metabolomic level in older adults with mild cognitive impairment. EFFICOM Study, DEP2016-76123-R, 2017-2021. The EFICCOM study is a randomized controlled trial (NCT03923712) with the main objective of analyse the effect of a 5-month supervised physical exercise intervention on brain structure, cognitive function and metabolomic level in older adults at risk of MCI. For this purpose, three phases of PRE (baseline), POST and RETEST assessment have been carried out in a pilot study (2018, n=9) and two waves (2019, n=45 and 2020, n=38) (Figure 1).

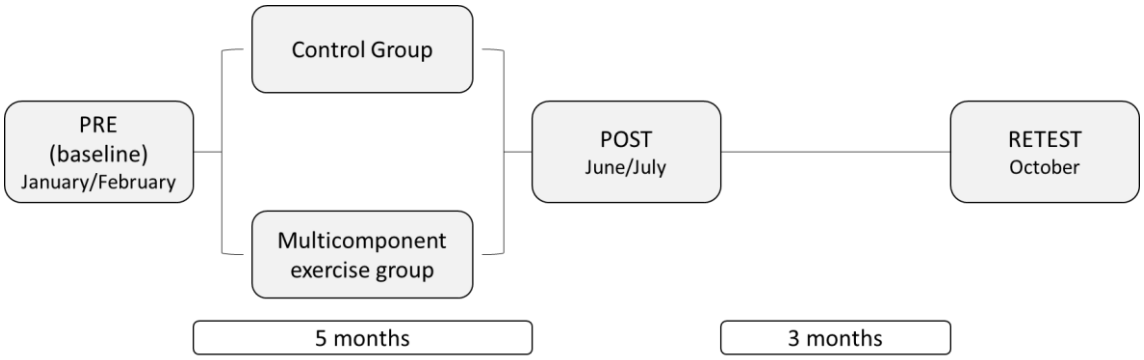

Figure 1. Design of EFFICOM study.

The current doctoral thesis is focused on the baseline data of the EFICCOM project, which were collected during January-February 2018, 2019 and 2020 with a cross-sectional design.

This project was evaluated and approved by the Ethics and Research Committee of "Hospital Universitario de Puerta del Mar", Cádiz, Spain, and conducted in accordance with the 2013 Declaration of Helsinki (135) (Appendix 1).

3.2. Participants and recruitment

Participants were recruited from 13 Public Health Care Centers of Chiclana (*La Banda, El Lugar and Los Gallos*), San Fernando (*Cayetano Roldan, Rodriguez Arias and Joaquin Pece*) and Cádiz (*Puerta Tierra, Loreto, La Paz, Mentidero, El Olivillo, La Merced and La Laguna*). In these Health Care Centers, the medical staff and researchers team members were in charge of recruiting potential candidates to participate in the project. Previously, the medical staff were instructed by the research team in a meeting and provided with a study information sheet (Appendix 2).

The inclusion and exclusion criteria are presented in table 1. The verification of compliance with these criteria was carried out in two parts. The medical staff were responsible for fulfilling the part of inclusion and exclusion medical criteria for the study (Appendix 3). The second part of the rest of inclusion and exclusion criteria were checked by members of the research team (Appendix 4) at the end of the informative meetings.

Table 1: Inclusion and exclusion criteria for the EFICCOM Study.

Inclusion criteria	Exclusion criteria
Age 65-75 years	Acute or terminal disease
Score ≥5 and ≥8 in Lawton and Brody Scale for males and females respectively	Severe depression
Do not suffer any injury avoiding participants from doing physical activity	Unstable cardiovascular disease, dementia and/or Alzheimer disease
Be able to speak and write	Medical history of ictus, epilepsy or brain cancer
Do not be involved in doing supervised physical activity greater than 20 minutes/day, 3 days/week	Medical history of head injury with loss of consciousness
Do not be participating in another research project	Severe visual problems
To want to complete the study if he/she is assigned to the control group	Alcohol and drug abuse

A total of 280 people were recruited for informative meetings about characteristics of the study, of whose, ninety-two participants (41 females) were finally included in the study after completing the entire recruitment process (Figure 2).

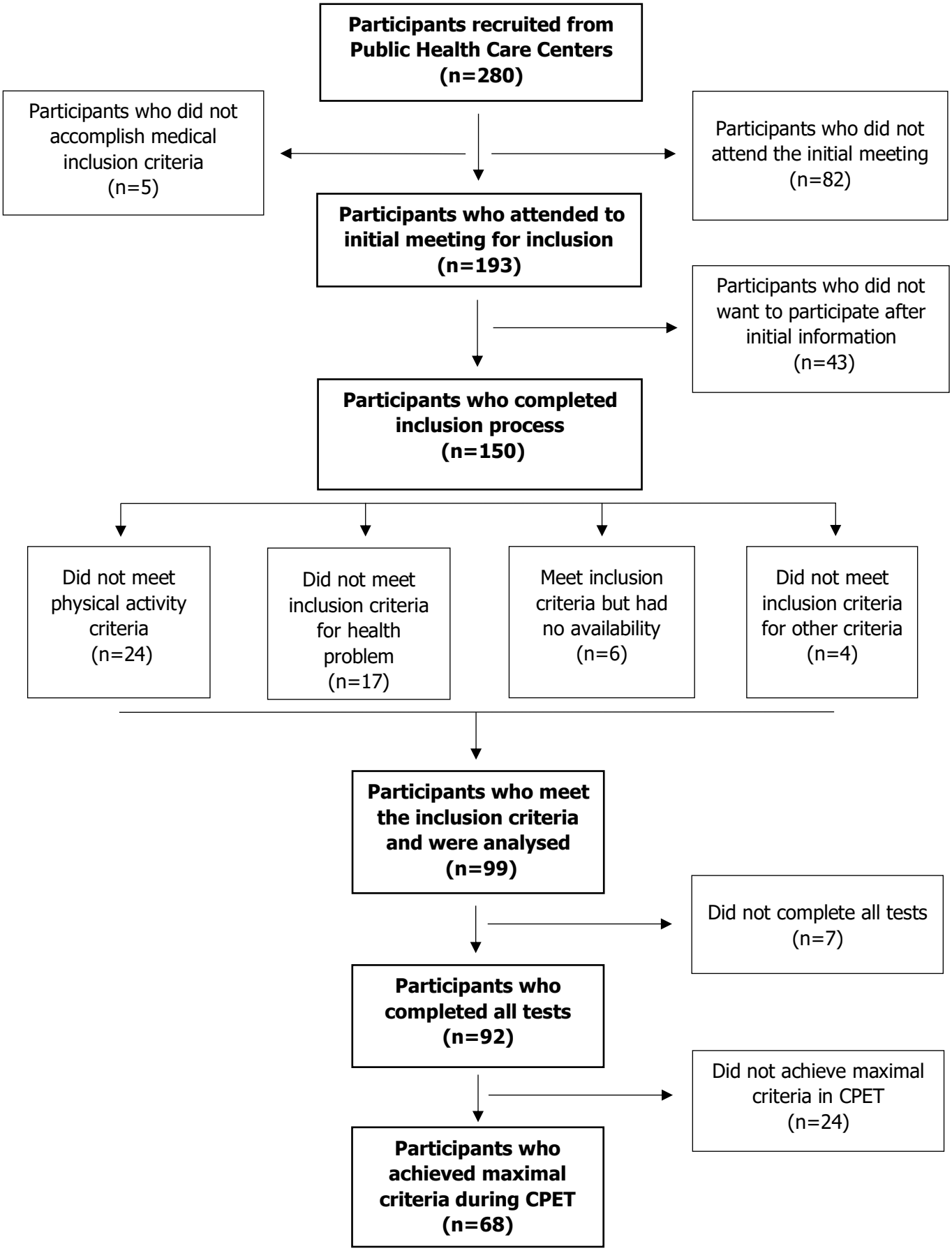

Figure 2. Baseline flow chart of the EFFICOM Study. CPET, Cardiopulmonary exercise test.

During the informative meetings, the participants were informed about the study design, the different measurements that will be carried out during the following months, and additionally, the second part of the inclusion and exclusion criteria were checked by members of the research team (Appendix 4).

When the participants were interested in getting involved, they were provided with an information sheet of the full study (Appendix 5), an informed consent (Appendix 6) and an image consent (Appendix 7) of the study. They had to return these signed documents before the first evaluation day.

3.3. Measurement procedures

The measurements of the overall project were carried out in 6 separate days during each of the 3 assessment points (PRE, POST and RETEST). In the current doctoral thesis, measurements from 4 out of 6 days at baseline were used; particularly, the laboratory test session, field test session, questionnaire session and the neuropsychological test (Figure 3).

3.3.1. Laboratory test session

The participants performed a laboratory test battery and were instructed to follow previous considerations. These standardized considerations were: To refrain 24 hours previous assessment from (i) strenuous physical exercise, (ii) alcohol intake, caffeine intake and energetic drinks and (iii) to control hydration status during the previous week. In addition, the evaluation day participants should (iv) be fasting for at least 4 hours, (v) have had adequate rest the night before and (vi) should bring comfortable clothes to walk on a treadmill (Appendix 8) (136–138). Compliance with the previous considerations was checked on the evaluation day and recorded on the laboratory information sheet (Appendix 9).

For the evaluation day, instructions were provided to each participant for their accommodation to the test to be performed and the devices will be appropriately fitted (pulsometer, electrocardiogram (ECG), gas analyser and NIRS). Moreover, temperature (22-24°C) and relative humidity (50%) of the laboratory were kept constant with an electric heating system and continuously checked using an integrated digital weather tracker (Fujitsu, Tokyo, Japan) (138,139).

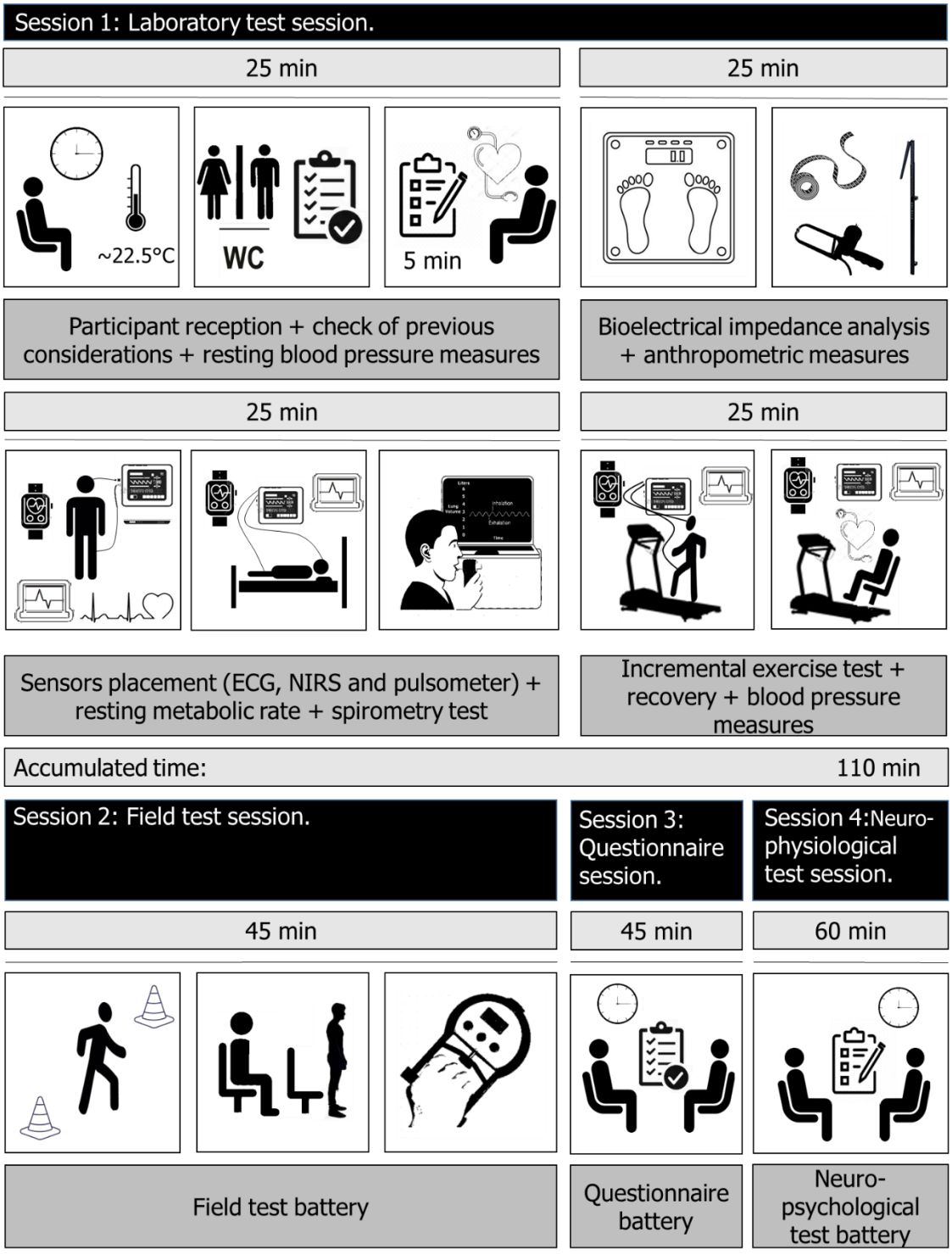

Figure 3: Summary of the doctoral thesis methodology. ECG, Electrocardiogram; NIRS, Near infrared Spectroscopy.

3.3.1.1. Blood pressure and heart rate measurements at rest

Participants were sitting in a chair and relaxed with their feet firmly on the floor. After 5 minutes basal SBP, DBP and resting HR were assessed according to the protocol of the European Society of Hypertension (140). The measurements were taken in the non-dominant arm with an Omron M3 intelligence advice (HEM-7051-E, Kyoto, Japan), previously validated (141) and the mean of three measurements, separated by one minute, was recorded.

In addition, using the previous values measured at rest (basal), several cardiovascular parameters have been calculated:

Mean arterial pressure, MAP (142):

$$MAP = SBP + (DBP \times 2) / 3$$

Systolic-Diastolic ratio, SBP/DBP ratio (143):

$$SBP/DBP\ ratio = SBP / DBP$$

Double product, DP (144):

$$DP = SBP \times HR$$

3.3.1.2. Anthropometric measurements

The participants' height was measured in standing position, heels together, looking forward, after a normal expiration and with the head on Frankfort plane using a stature-measuring instrument (SECA 225, Hamburg, Germany) (145). The mean of two measurements was recorded, except if there was higher difference than 1 cm, a third assess was performed and the mean of the two closest measurements was used in the analyses.

The waist circumference (cm) was assessed with a metallic non-extensible tape (Lufkin W606PM, Washington, United States) at the level of the thinnest part of the waist between the iliac crest and the last rib. The measurements were taken at the end of normal expiration without compressing the skin. To assess the hip circumference (cm), participants had to be in standing position, foot together, with hands on the opposite shoulder and looking forward. On the most prominent gluteal area, the hip circumference was taken horizontally; this region normally coincides with the pubic symphysis. The mean of two measurements was recorded, except if there was higher difference than

0.5 cm, a third assess was performed and the mean of the two closest measurements was used in the analysis.

To measure the thigh skinfold thicknesses a skinfold caliper (Harpenden, Bristol, United Kingdom) was used. Participants sitting on the edge of a chair without armrests extended the knee, and the skinfold of the thigh was taken at the midpoint between the groin fold and the upper edge of the patella. The mean of two measurements was recorded, except if there was higher difference than 1 cm, a third assess was performed and the mean of the two closest measurements was used in the analysis.

All the anthropometric measurement were taken in accordance with the International Standards for Anthropometric Assessment (ISAK) guidelines standard techniques (146) by an ISAK level 1 evaluator.

3.3.1.3. Bioelectrical impedance analysis

Weight (kg), fat mass (FM) (% and kg) and FFM (% and kg) were obtained using a multifrequency bioimpedance (TANITA-MC780MA) (136,137,147). Participants wore light clothing and following the previous considerations described above. They assumed a posture in accordance with the manufactures' instructions for a correct measurement (147).

The following body composition variables were calculated:

- Body mass index, BMI (148):
  BMI = weight / height^2 (kg m^{-2})
- FM Index, FMI (149,150):
  FMI = Absolute FM / height (kg m^{-2})
- FFM Index, FFMI (149,150):
  FFMI = Absolute FFM / height (kg m^{-2})
- Waist-Hip ratio, WHR (151):
  WHR = Waist circumference / hip circumference
- total energy expenditure estimated by bioimpedance.

Then, BMI was categorised as underweight (<18.5 kg m-2), normal weight (18.5-24.9 kg m-2), overweight (25-29.9 kg m-2) and obese (≥30 kg m-2) (148).

3.3.1.4. Spirometry

To perform a forced spirometry according with the Spanish Society of Pneumology and Thoracic Surgery Normative (SEPAR) (99), the test was explained to the participants, the mask was correctly adjusted to the face, thus, there were no air leaks to inspire and expire through the mouth in standing position.

Then, participants did several cycles of normal breathing to detect base line of the breath using Jaeger MasterScreen CPX® (CareFusion, San Diego, USA). The evaluator said the order to inspire as much air as possible (to achieved total lung capacity) with a pause of less than 1 second to expire the air as quickly as possible and being prolonged until it was indicated or the participants were unable to expire more air (to achieved functional residual capacity).

During the test, participants were observed and monitored to verify safety, in addition a chair was placed behind for possible dizziness.

The criteria of acceptability of the test were:

i. A quick start without oscillations.
ii. The course of the test must be continuous and without artefacts.
iii. The completion of the test does not have to show an early interruption.

FEV_1, FVC, peak expiratory flow (PEF) and FEV1/FVC values were registered and calculated according with the SEPAR normative (99). The test was performed at least twice. When the procedure was not adequate, the test was repeated after resting 2-3 minutes until at least two acceptable tests were obtained. The best measure achieved in the previous variables was used for the analysis (152,153).

3.3.1.5. Resting metabolic rate (RMR)

The VO_2, carbon dioxide production (VCO_2), respiratory exchange ratio (RER) and HR were registered at resting conditions in a supine position during 10 minutes on a bed. A mask was placed over the participant´s face to collect gas exchange. Resting indirect calorimetry was measured using a gas analyser of open circuit, Jaeger MasterScreen CPX® (CareFusion, San Diego, USA) following the criteria established to measure basal metabolism (138) and the same 24 hours considerations prior to measurement as previously required (138). Calibrations on gas analyser were performed daily before each measurement.

During test, the values of the gas analyser were recorded breath by breath and averaged every 20 and 60 seconds were registered. HR was measured continuously over the test

with Polar Team System 2 Pro (Polar Electro Oy, Kempele, Findalnd) (154) and standard 12 lead monitoring ECG.

For the analysis of studied variables, the first 2 minutes of the assessment were deleted, and a 5-minutes stable period with a coefficient of variation lower than 20% for VO_2 and VCO_2 was selected. When a 5-minutes stable period was not found, two non-consecutive periods were selected to achieve a *steady state* and improve accuracy (138). The mean value of VO_2, VCO_2, RER and HR within the selected stable period were the variables registered and total energy expenditure was calculated for each participant by an indirect equation proposed by Frayn (155). In addition, resting oxygen pulse was calculated (HR / VO_2) at resting conditions as previously reported (156,157) and was multiplied by 100 for better understanding (157,158).

3.3.1.6. Cardiopulmonary exercise test

All participants performed an incremental CPET until exhaustion on a treadmill (Lode Valiant, Groningen, Netherlands) using the modified Bruce protocol (159,160) previously used in a similar sample and designed for a geriatric population (161,162). Participants were asked if they had ever walking on a treadmill and instructed for the incremental test. If necessary, they were familiarized with the treadmill by walking slowly until the initial protocol speed was achieved. Before start, participants were instructed not to talk during the test because this is known to affect the breathing and gas exchange (162).

Participants began walking to 2.7 km/h at 0% inclination grade, every 2 minutes the speed or/and inclination were increased according the modified Bruce protocol (Table 2). At the equator of each step, the rating perceived exertion (RPE) was asked using the 10-point Borg (163). During the test, RER, VO_2 and VCO_2 consumption were measured breath-by-breath using indirect calorimetry through a gas analyser of open circuit, Jaeger MasterScreen CPX® (CareFusion, San Diego, USA) and values averaged for 5, 10, 20 and 60-second intervals. As well as, HR was measured continuously over the test with Polar Team System 2 Pro (Polar Electro Oy, Kempele, Findalnd) (154) and standard 12 lead monitoring ECG was used. In addition, all tests were supervised by at least two researchers and a medical doctor to ensure safety and, normally, incremental test finished when self-volitional exhaustion was achieved. Except in the case of the medical staff stopped the CPET if they considered that the test was clinically and/or electrically positive and there were risk to the health of the participants (~10%).

Table 2. Design of modified Bruce protocol.

Step	*Miles per hour*	*Km/h*	*% Inclination*	*Minutes*	*RPE*
1	1.7	2.7	0	2	_
2	1.7	2.7	5	4	_
3	1.7	2.7	10	6	_
4	2.1	3.4	11	8	_
5	2.5	4.0	12	10	_
6	3.0	4.8	13	12	_
7	3.4	5.5	14	14	_
8	3.8	6.1	15	18	_
9	4.2	6.8	16	20	_
10	4.6	7.4	17	22	_
11	5.0	8.0	18	24	_
Recovery					
Active	1.7	2.7	0	5	_
Passive	0	0	0	5	_

VO_{2peak} was considered as the highest observed value of oxygen consumption obtained in the last three intervals of 10 seconds. However, the stablished maximal criteria to considerate a valid incremental test were: (i) RER≥ 1.05, (ii) a levelling off of VO_2 achieved in last three intervals of 10 seconds (plateau was assessed through change over the VO_2 of these successive measurements, <2 $mL \cdot kg^{-1} \cdot min^{-1}$), (iii) subjective volitional exhaustion , (iv) HR ≥ 85% maximum HR (HR_{max}) using the formula HR_{max}= 208 – (0.7 x Age) and (v) subjective exertion, RPE≥ 7 (163–166). The CPETs meting at least three criteria were considerate maxima incremental tests. Moreover, the relative peak exercise oxygen pulse was calculated by dividing relative VO_{2peak} by the HR_{max} during exercise (156,157) and the results were multiplied by 100 for better understanding (157,158).

Active recovery was assessed when incremental CPET stopped. This phase began automatically walking at 2.7 km/h at 0% inclination grade during 5 minutes. Then, passive recovery phase was carried out during x minutes, the treadmill was stopped and a chair was placed without chair arms on the treadmill and participants seated on the chair. Blood pressure was assessed at minutes 1, 3 and 5 in these phases, as well as, VO_2, VCO_2, RER and HR were continuously registered and RPE was evaluated in the middle of each phase.

Additionally, the VO_{2peak} was also expressed in METs. One MET corresponds to an oxygen uptake of 3.5 ml/kg/min. Therefore, relative VO_{2peak} obtained during incremental test was divided by a MET.

Moreover, CRF estimated was calculated using a formula previously described (167):

✓ *Women*

Estimated CRF (METs) = 14.7873 + (age × 0.1159) – ((age^2 × 0.0017) – (BMI × 0.1534) – (WC × 0.0085) – (RHR × 0.0364) + (active × 0.5987) – (smoker × 0.2994)

✓ *Men*

Estimated CRF (METs) = 21.2870 + (age × 0.1654) – (age^2 × 0.0023) – (BMI × 0.2318) – (WC × 0.0337) – (RHR × 0.0390) + (active × 0.6351) – (smoker × 0.4263)

BMI means body mass index; WC, waist circumference; RHR, resting heart rate. Active = 1 if the participant was classified as physically active, 0 if inactive; and smoker = 1 if current smoker, 0 if not.

3.3.1.7. Near-Infrared Spectroscopy

Changes in concentration of oxyhemoglobin (OHb), deoxyhemoglobin (HHb) and TOI were measured by a near-infrared spectroscopy (NIRO-200Nx, Hamamatsu, Japan) to estimate central and peripheral oxygenation at two different locations during RMR, incremental test and active and passive recoveries (168,169). One NIRS sensor was placed on the non-dominant frontoparietal area above the supraorbital crest for estimation of central oxygenation, while another NIRS sensor for estimation of peripheral oxygenation was placed at 2/3 on the midline from the anterosuperior iliac spine to the lateral side of the patella coinciding with the muscle belly of the vastus lateralis (170,171), staying crossed with the head sensor. The skin of the head and thigh regions were cleaned with alcohol prior to placement of the NIRS sensors. The adipose tissue thickness over the point of placement on vastus lateralis was determined following a protocol previously described, since it can affect the measurement of the NIRS on the thigh (172).

Before to start recording NIRS, participants remained an initial 5 minutes period on the bed as familiarization phase with the devices placed and NIRS calibration was repeated before each test. For analysis of the studied variables, the first 2 minutes of the assessment were deleted, and the same 5 minutes stable period selected for RMR (138) was used to calculated the mean value of OHb, HHb and TOI at resting conditions.

Changes in the cerebral and peripheral oxygenation were measured during exercise and recovery periods through NIRS using the two same channel and on the same location than at resting conditions (168). OHb, HHb and TOI consumption were measured and values averaged for 5, 10, 20 and 60-second intervals (170,171,173) during incremental test, active and passive recovery periods.

3.3.2. Field test session

Participants were informed about performing the Senior Fitness Test Battery (174) and Handgrip test (175) and some previous considerations were followed (Appendix 10). All field test scores were recorded on the information sheet (Appendix 11) and several tests were selected to the analyses.

3.3.2.1. Chair stand test

The chair stand test aims to assess lower body strength. To start test, participants were sitting in a chair and at the signal of the evaluator's "GO" ("YA"), they had to stand up and sit down as fast as possible for 30 seconds with arms folded across chest. Each time they sit, their back and gluteus must be in contact with the chair. The total number of repetitions was recorded for the analyses.

3.3.2.2. 6 minutes walking test

In this test, participants had to walk around two cones 30 meters apart, during 6 minutes to evaluate cardiorespiratory fitness. An evaluator did the test with the participants to ensure a correct evaluation, and they had to go as fast as possible (without running). If necessary, the participants could stop or even sit down during the test and then return to walk. The main score obtained was the total of number meters walked in 6 minutes and the test was performance only once at the end of the evaluation session.

3.3.2.3. Handgrip test

The handgrip test aims to assess upper body strength using a digital dynamometer (TKK 5101 Grip-D, Tokyo, Japan). To start the test, participants had to maintain the standard bipedal position during entire assessment, with the elbow in complete extension and did not touch the body with the dynamometer, except the hand measured.

For a correct grip, the dynamometer was adjusted at 5.5 size to males, and for females, the optimal grip was adjusted according to the size of the hand (175). All participants did two attempts with each hand and the following variables were recorded:

- The best attempt from each hand.
- The best attempt from both hands.

- The mean of the best attempts from each hand.
- The sum of the best attempts from each hand.

The best attempt from both hands, the mean of the best attempts from each hand and the sum of the best attempts from each hand, were the variables used for the analyses.

3.3.3. Questionnaire session

3.3.3.1. Self-Maintaining and Instrumental Activitiesof Daily Living

The Self-Maintaining and Instrumental Activities of Daily Living Scale of Lawton and Brody to evaluate the dependence level was provided. The questionnaire asked about use of the telephoning, shopping, food preparation, housekeeping, laundering, use of transportation, use of medicine, and financial behaviour. The score of this questionnaire was used as exclusion criteria of the study, being necessary to achieve 5 and 8 points to be included for males and females respectively (176) (Appendix 3).

3.3.3.2. Sociodemographic questionnaire

An independent questionnaire was provided to collect information about several sociodemographic dimensions, such as marital status (i.e. single, married, widower, legally separated or divorced), economic status, educational level, medication intake, chronic diseases, family history of dementia, alcohol and tobacco consumption. (Appendix 12).

These variables were used to categorize the sample and as adjustment variables in the analyses performed.

3.3.3.3. Physical Activity Questionnaire

The Global Physical Activity Questionnaire (GPAQ) was used, which is a valid measured used as self-reported questionnaire to assess the physical activity and sedentary levels (177,178) (Appendix 13). The GPAQ questionnaire assesses physical activity behaviour in three different domains: at work (which includes paid and unpaid work, inside and outside of the home), for transport (to get to and from places), and during leisure time.

Two categorical variables were calculated and used in the analyses:

- Leisure Time Physical Activity: Participants were categorized in reaching or not at least 150 minutes a week of physical activity in their leisure time.
- Physical activity in leisure and work time: Participants were categorized in reaching or not at least 150 minutes a week of physical activity in their leisure and work time.

3.3.4. Neuropsychological test session

A complete neuropsychological test battery was proposed by a multidisciplinary research team aimed to measure cognitive function including a complete set of tests, internationally well-known and validated for older adults. The tests aimed to assess cognitive impairment, learning and verbal episodic memory, verbal and semantic fluency, visual confrontation naming, cognitive flexibility, attention, and inhibition. Total testing time range from 60 to 75 minutes. Detailed information about the constructs to be measured and tests chosen can be found below (Table 3).

Table 3: Summary neuropsychological test battery.

Domain	Neuropsychological test	Score
Screener	Mini Mental State Examination	Total Score (0-30)
Screener	Clock Drawing Test	Total Score (0-10)
Language	Boston Naming Test	Total words score (0-15)
Memory	Rey Auditory Verbal Learning Test	Total score of recognized words (0-15)
Cognitive flexibility / Alternating attention	Trail Making Test	Interference (part B – A; in seconds)
Fluency	Controlled Oral Word Association Test	Sum of total words in 1 minute with each letter (P, M and R)
Inhibition / Processing speed	Stroop Color and Word Test	Interference

3.3.4.1. Mini Mental State Examination (MMSE)

The MMSE is a valid test widely used to evaluate cognitive impairment (179,180). The MMSE was applied to measure five domains of cognitive functions: i) orientation, ii) registration, iii) attention and calculation, iv) delayed recall, and v) language and construction. The test was divided in two parts, the first one required verbal answers and the maximal punctuation is 21 while the second part assessed the skills for naming,

following different verbal and written instructions, write a spontaneous sentence and copy an interlocking pentagon, and its maximal punctuation was 9. The total punctuation summing each domain is computed ranging from 0 to 30, where the highest scores the better performance.

3.3.4.2. Clock Drawing Test (CDT)

The CDT is a valid cognitive test used to detect deterioration of the visuo-constructive and visuospatial skills (181,182). This test consisted on drawing a clock with the numbers on the circle, showing the clock hands into specific time (11:10 o'clock). They were not allowed to look at a watch or another clock for help. The total punctuation was the sum of the scores given to sphere, numbers and clock hands, ranging from 0 to 10 being the highest scores the best performance (183).

3.3.4.3. Boston Naming Test (BNT)

The BNT is a valid and widely used test for assessing visual confrontation naming (184). Particularly, the short version of the BNT containing 15-items was applied. Participants were shown line drawings of common objects one at a time and asked to name them orally, ranging from simple (high-frequency vocabulary, e.g. bed) to rare words (low-frequency vocabulary, e.g. abacus). Administration requires a spontaneous response within a 20 seconds period. If there was no response, two kinds of prompting cues (one semantic and one phonemic) were given. Total punctuation was calculating by the sum of the total correct responses at the beginning (without cues) and after the phonemic cues (the higher correct responses, the best performance).

3.3.4.4. Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT is a valid test that was applied to assess learning and verbal episodic memory (185). The test consisted of 5 verbal presentation of 15 words (list A), and the participants were asked to recall words from the initial repeated list (named as immediate recall), each attempt was followed by an immediate recall trial. Then, a distractor list (list B) with other 15 words was presented, and the participants were asked to recall these words only once. After of this distraction trial, the participants were asked to recall the initial list (list A). After 20 minutes, the participants were asked again for the list A (named as delayed recall). Finally, participants needed to answer yes/no in 75-item recognition discrimination test where the 15 initial words were included. Both recalled words and recognized were registered, however, the number of recognized words after 20 minutes was the continuous variable used for the analyses.

3.3.4.5. Trail Making Test (TMT)

The TMT is a valid and widely used test for assess executive functioning (186). The TMT consisted in two parts; A and B. The part A was based on number sequencing and assessed visual-perceptual abilities. The participants had to draw lines to link numbers from 1 to 25 in ascending order. The part B focused on number and letter switching evaluates cognitive flexibility and consisted of drawing a line to link the numbers and the letters alternatively following in ascending order (e.g. 1-A-2-B-3-C). The completion time of both parts were registered in seconds, and the interference (time record of part B – time record of part A) was the continuous variable used for analyses (the lower duration, the best performance).

3.3.4.6. Controlled Oral Word Association Test (COWAT)

The COWAT is a valid instrument designed mainly for assessing verbal and semantic fluency (187,188). This test consisted on spontaneous production of words beginning with a designated letter and a topic determined (P, M and R for the Spanish version) within a minute for each letter. The responders were not allowed to say names, numbers or words in different tenses or with the same root. For semantic fluency, they were required to say words related with the topic give, i.e., animals. Total punctuation was calculated summing all items independently for each letter (the higher is the number of words given, the best the performance). The sum of all words starting with P, M and R was the continuous variable used for this analysis.

3.3.4.7. Stroop Color and Word Test (Stroop)

The Stroop is a valid and widely applied test for examining cognitive flexibility, selective attention, and cognitive inhibition (189,190). This test was divided in three conditions:

The first condition consisted in reading names of colours printed in black ink (W).

The second condition was read the colours printed as "XXXX" (C).

The third condition consisted in doing the interference task (WC), in naming the colour of the ink instead of reading the word since words-colours were printed in an inconsistent colour ink (for instance, the word "blue" was printed in red ink).

All conditions contained 100 words, and the time was limited to 45 seconds for each condition. Total number of correct words was registered for each condition indicating that higher number of correct words, better performance.

In addition, the estimated score that each participant should obtain in WC (WC') was calculated:

WC' = (W x C) / (W + C)

Then, the score used for the analyses consisted in to calculate la interference, WC – WC'. Receiving the information on the stroop effect .

3.4. Statistical analyses

All variables were checked for normality using both graphical (normal probability plots) and statistical (Shapiro-Wilk test) procedures. When some variable did not follow a normal distribution, the most appropriate transformation was carried out; to select this transformation, the STATA command *.ladder* was used.

Descriptive statistics have been applied to characterize the physiological, metabolic and cardiovascular parameters in older males and females and these have been presented in tables as mean ± standard deviation or percentages. Sex differences were examined applying the t-test statistic for quantitative variables and Chi square statistic for qualitative variables. Then, boxplots have been created to detail the distribution of the participant's characteristics.

Multiple linear regression analyses were used to analyse the association of body composition components, resting cardiovascular parameters, RMR parameters, spirometry parameters and physical fitness field tests with absolute and relative CRF from participants achieving the maximal criteria in incremental CPET. Different adjustment models were performed; where model 1 was the unadjusted or pure model and model 2 was the adjusted model built on the base of statistical and scientific criteria. For the construction of the adjusted regression model 2, both the individual association of each potential confounder and its modifying effect (>10%) over the coefficient of the pure model were analysed. For the confounding variables included in the adjusted model 2, the interaction was verified by generating virtual dummy variables in STATA (independent * confounder). Sex and age interaction were analysed by including the interaction terms in the code of regression analyses. This allows STATA software to virtually create dummy variables (age and sex multiplied by the independent variable) to be included in the regression analyses for checking its significance. The final adjusted regression model 2 was built for each independent variable including sex, age, BMI and/or smoking status as covariates based on the results of the specific statistical verification previously described. Then, for each regression model, the normality analyses were recalculated for the residuals for the models. In addition, the collinearity of the regression models were calculated using command .*vif*, which did not show

independent variables with a coefficient > 10. The analyses were performed both for the total sample and segmented by sex.

To develop equations to predict CRF in older adults, first the *maxvar* subcommand was used to select the main predictor variables. Then, the *allset* regression command was applied to propose three new CRF prediction models using firstly basic variables: body composition, meeting physical activity recommendations (yes or no), field tests and basal parameters; secondly, spirometry parameters were added and finally, variables derived from CPET were included. These three CRF prediction models were applied to both, the total sample and only those achieving maximal criteria in CPET. This regression command from STATA selected the best prediction models including the main predictive variables of the CRF. The five best models of each condition were selected between 65,535 possible regression models automatically executed. The selection of the five best models for each condition were made based on the coefficients of Mallow's Cp, r^2, adjusted r^2, Akaike information criterion and Bayesian information criterion. Subsequently, the regression coefficients reported in the best regression models for each condition were used to develop the prediction equations for estimation of CRF.

Finally, multiple linear regression analyses were applied to analyse the association of objectively-measured and estimated CRF with cognitive function in both total sample and those achieving maximal CPET. The same procedure explained above for the models were applied for both, the pure model (Model 1) and the adjusted model (Model 2).

All analyses were performed using the STATA software for Windows version 13.0. The level of significance was set at $p < 0.05$.

RESULTS

4. RESULTS

4.1. Descriptive characteristics of the sample

The descriptive characteristics of the study participants are shown in Table 4A, while Table 4B provided the characteristics of those achieving maximal criteria during CPET. In both samples, there was no difference between males and females by age ($p>0.05$). However, significant differences for most of the anthropometric variables were found between sexes (all $p<0.05$). Although, BMI and hip circumference did not differ by sex (both $p>0.05$), neither absolute FM in those achieving maximal criteria during CPET ($p>0.05$). Moreover, there were no significant differences in resting cardiovascular parameters between sexes (all $p>0.05$). In relation to resting metabolic parameters, significant sex differences in total energy expenditure and thigh-TOI for both samples (both $p<0.05$) were found, but not for resting RER, resting oxygen pulse nor head-TOI (all $p>0.05$). Regarding spirometry parameters, males had greater FEV1, FCV and PEF than females (all $p<0.001$) in both total and maximal CPET participants, however, there was no significant differences in FEV1/FCV by sex ($p>0.05$).

In relation to physical fitness measures, males had higher values of CRF (all $p<0.001$), maximum RER ($p<0.001$), peak oxygen pulse ($p<0.001$) and physical fitness field tests (all $p<0.001$) than females in both total sample and those achieving maximal CPET. While, females had higher thigh-TOI ($p<0.001$) than males in both samples. However, no differences in FFM-relative CRF ($p>0.05$; table 4B), maximum HR ($p>0.05$) and head-TOI ($p>0.05$) by sex.

Additionally, there were significant differences for two neuropsychological tests, being males who had the best results in BNT and COWAT (both $p<0.05$). There were no significant differences in the remained neuropsychological tests (all $p>0.05$).

Table 4A. Descriptive characteristics of the overall sample by sex.

Variable	Total sample n=92	Male n=51	Female n=41	p-value
Physical characteristics				
Age (years)	68.9 ± 2.9	69.1 ± 2.9	68.7 ± 2.9	0.522
Weight (kg)	74.5 ± 13.8	80.4 ± 13.5	67.0 ± 9.9	**<0.001**
Height (cm)	161.1 ± 9.6	166.9 ± 7.4	153.7 ± 6.6	**<0.001**
Body mass index (kg m^{-2})	28.7 ± 4.5	28.9 ± 4.4	28.4 ± 4.7	0.661
Body mass index status (%) (NW/OW/Ob)[γ]	18 / 51 / 31	17 / 46 / 37	20 / 56 / 24	0.409
Fat mass (%)	31.0 ± 7.9	26.1 ± 5.8	37.3 ± 5.4	**<0.001**
Fat mass (kg)	23.3 ± 7.9	21.6 ± 8.0	25.4 ± 7.3	**0.017**
Fat Free mass (%)	69.0 ± 7.9	73.9 ± 5.8	62.7 ± 5.4	**<0.001**
Fat Free mass (kg)	51.2 ± 10.3	58.9 ± 6.9	41.6 ± 3.4	**<0.001**
Fat mass index (kg m^{-2})	9.1 ± 3.4	7.8 ± 2.8	10.8 ± 3.3	**<0.001**
Fat free mass index (kg m^{-2})	19.6 ± 2.4	21.1 ± 1.8	17.7 ± 1.7	**<0.001**
Waist circumference (cm)	99.2 ± 11.6	103.2 ± 10.7	94.2 ± 10.7	**<0.001**
Hip circumference (cm)	104.4 ± 9.3	103.3 ± 9.1	105.9 ± 9.3	0.177
Waist to hip ratio (ratio)	0.95 ± 0.08	0.99 ± 0.05	0.89 ± 0.06	**<0.001**
Resting cardiovascular parameters				
Mean blood pressure (mmHg)	98.5 ± 10.8	99.5 ± 10.1	97.2 ± 11.7	0.330
Systolic blood pressure (mmHg)	136.8 ± 18.3	138.2 ± 17.2	135.1 ± 19.6	0.419
Diastolic blood pressure (mmHg)	79.4 ± 9.1	80.2 ± 8.6	78.3 ± 9.6	0.327
Resting heart rate (bpm)	68.4 ± 10.8	68.7 ± 12.0	67.9 ± 9.1	0.738
Double product (mmHg bpm)	9336 ± 1795	9484 ± 1933	9147 ± 1605	0.372
Systolic/diastolic blood pressure (ratio)	1.73 ± 0.19	1.73 ± 0.18	1.73 ± 0.19	0.944
Resting metabolic parameters				
Total energy expenditure measured (kcal day^{-1})[a]	1648 ± 338	1827 ± 307	1425 ± 225	**<0.001**
Total energy expenditure estimated (kcal day^{-1})[b]	1511 ± 284	1707 ± 218	1261 ± 107	**<0.001**
Respiratory exchange ratio (ratio)	0.77 ± 0.06	0.78 ± 0.07	0.76 ± 0.05	0.202
Resting oxygen pulse (mL $beats^{-1}$)	5.3 ± 1.6	5.4 ± 1.5	5.3 ± 1.7	0.769
TOI, thigh (%)	76.4 ± 7.8	73.0 ± 7.3	80.9 ± 5.8	**<0.001**
TOI, head (%)	75.4 ± 6.6	74.8 ± 7.6	76.1 ± 5.2	0.355
Spirometry*				
FEV1 (L)	2.45 ± 0.60	2.70 ± 0.59	2.14 ± 0.69	**<0.001**
FCV (L)	3.66 ± 1.13	4.24 ± 1.09	2.97 ± 0.73	**<0.001**
FEV1/FCV (%)	72.1 ± 14.1	69.7 ± 15.0	75.1 ± 12.5	0.065
PEF (L s^{-1})	4.86 ± 1.80	5.50 ± 1.91	4.08 ± 1.29	**<0.001**
Physical fitness measures *Incremental cardiopulmonary exercise test*				
Absolute cardiorespiratory fitness (ml min^{-1})	1853 ± 482	2141 ± 403	1478 ± 273	**<0.001**
Relative cardiorespiratory fitness (ml kg^{-1}·min^{-1})	25.0 ± 5.2	27.1 ± 5.0	22.3 ± 4.3	**<0.001**
Relative cardiorespiratory fitness (ml kg^{-1}FFM·min^{-1})	36.1 ± 6.2	36.7 ± 6.0	35.4 ± 6.4	**<0.001**
Metabolic equivalents measured (METs)	7.1 ± 1.5	7.8 ± 7.4	6.4 ± 1.2	**<0.001**

Cardiorespiratory fitness estimated (METs)	7.9 ± 1.7	8.8 ± 1.7	7.0 ± 1.1	**<0.001**
Maximum respiratory exchange ratio (ratio)	1.10 ± 0.12	1.14 ± 0.12	1.04 ± 0.10	**<0.001**
Maximum heart rate (bpm)	139.9 ± 19.5	141.8 ± 21.5	137.6 ± 16.6	0.302
Theoretical maximum heart rate (bpm)	159.7 ± 2.1	159.7 ± 2.1	159.9 ± 2.1	0.675
Peak oxygen pulse (mL $beats^{-1}$)	17.9 ± 3.1	19.3 ± 3.1	16.2 ± 2.2	**<0.001**
TOI, thigh (%)*	65.2 ± 12.3	59.6 ± 10.9	72.6 ± 9.8	**<0.001**
TOI, head (%)*	71.1 ± 7.0	71.3 ± 7.0	70.9 ± 7.1	0.813
Physical fitness field tests				
6 minutes walking (m)	554.2 ± 83.1	582.5 ± 88.3	519.9 ± 61.6	**<0.001**
Chair stand (rep)*	11.2 ± 2.5	11.9 ± 2.7	10.2 ± 1.9	**<0.001**
Handgrip (maximum; kg)	29.1 ± 8.9	35.5 ± 6.6	21.2 ± 3.4	**<0.001**
Handgrip (mean; kg)	27.3 ± 8.6	33.2 ± 6.5	19.8 ± 3.4	**<0.001**
Handgrip (sum; kg)	55.2 ± 17.2	67.0 ± 12.9	39.9 ± 6.8	**<0.001**
Cognitive function tests				
Mini mental state examination (total score, 0-30)	27.8 ± 2.2	27.9 ± 1.8	27.6 ± 2.6	0.467
Boston naming (total score, 0-15)	10.8 ± 2.3	11.7 ± 2.0	9.8 ± 2.1	**<0.001**
Clock drawing (total score, 0-10)	7.4 ± 1.9	7.6 ± 2.0	7.2 ± 1.9	0.332
Rey auditory verbal learning (total score, 0-15)	12.5 ± 2.7	12.1 ± 3.1	13.1 ± 1.9	0.060
Trail making (s)	101.4 ± 92.3	94.7 ± 90.0	109.4 ± 95.5	0.444
COWAT (total score, words in 60s)	35.1 ± 13.4	38.3 ± 14.0	31.5 ± 11.7	**0.011**
Stroop (total score)*	4.4 ± 7.3	4.1 ± 7.6	4.8 ± 7.0	0.640

Values are presented as mean ± standard deviation or percentages. T-test and [Y]Chi square statistics was applied. Statistically significant differences between sexes are highlighted in bold. COWAT means controlled oral word association test; FEV1, forced expiratory volume in 1 second; FFM, fat free mass; FVC, forced vital capacity; NW, normalweight; METs, metabolic equivalents; Ob, obesity; OW, overweight; PEF, peak expiratory flow; TOI, tissue oxygenation index. *Subsample of 90 participants in all cases, except for TOI, 81; [a]by indirect calorimetry and [b]bioimpedance analysis.

Table 4B. Descriptive characteristics of participants achieving maximal criteria during cardiopulmonary exercise test by sex.

Variable	Total sample n=68	Male n=42	Female n=26	p-value
Physical characteristics				
Age (years)	69.0 ± 2.9	69.1 ± 3.0	68.7 ± 2.8	0.630
Weight (kg)	74.2 ± 13.5	79.4 ± 13.2	65.8 ± 9.2	**<0.001**
Height (cm)	160.9 ± 9.1	165.6 ± 7.0	153.3 ± 6.6	**<0.001**
Body mass index (kg m^{-2})	28.6 ± 4.1	29.0 ± 4.2	28.0 ± 3.9	0.369
Body mass index status (%) (NW/OW/Ob)[γ]	18 / 50 / 32	18 / 45 / 37	20 / 56 / 24	0.619
Fat mass (%)	30.4 ± 7.5	26.4 ± 5.6	36.8 ± 5.4	**<0.001**
Fat mass (kg)	22.7 ± 7.3	21.5 ± 7.6	24.6 ± 6.5	0.090
Fat Free mass (%)	69.6 ± 7.5	73.6 ± 5.6	63.2 ± 5.4	**<0.001**
Fat Free mass (kg)	51.6 ± 10.0	58.0 ± 6.7	41.2 ± 3.6	**<0.001**
Fat mass index (kg m^{-2})	8.9 ± 3.0	7.8 ± 2.7	10.5 ± 2.8	**<0.001**
Fat free mass index (kg m^{-2})	19.7 ± 2.4	21.1 ± 1.7	17.6 ± 1.5	**<0.001**
Waist circumference (cm)	99.4 ± 11.5	103.2 ± 10.5	93.3 ± 10.4	**<0.001**
Hip circumference (cm)	104.0 ± 8.5	103.5 ± 9.3	104.7 ± 7.2	0.585
Waist to hip ratio (ratio)	0.96 ± 0.08	0.99 ± 0.05	0.89 ± 0.07	**<0.001**
Resting cardiovascular parameters				
Mean blood pressure (mmHg)	98.1 ± 9.7	99.3 ± 10.2	96.1 ± 10.2	0.179
Systolic blood pressure (mmHg)	136.1 ± 16.4	137.8 ± 17.0	133.3 ± 15.4	0.274
Diastolic blood pressure (mmHg)	79.1 ± 8.6	80.1 ± 8.7	77.4 ± 8.4	0.216
Resting heart rate (bpm)	68.0 ± 10.9	67.9 ± 12.5	68.0 ± 7.8	0.983
Double product (mmHg bpm)	9227 ± 1665	9345 ± 1881	9037 ± 1252	0.462
Systolic/diastolic blood pressure (ratio)	1.73 ± 0.19	1.73 ± 0.18	1.73 ± 0.20	0.911
Resting metabolic parameters				
Total energy expenditure measured (kcal day^{-1})[a]	1635 ± 325	1791 ± 300	1389 ± 178	**<0.001**
Total energy expenditure estimated (kcal day^{-1})[b]	1516 ± 277	1683 ± 210	1246 ± 107	**<0.001**
Respiratory exchange ratio (ratio)	0.77 ± 0.07	0.78 ± 0.07	0.76 ± 0.05	0.190
Resting oxygen pulse (mL $beats^{-1}$)	5.3 ± 1.7	5.4 ± 1.7	5.1 ± 1.0	0.288
TOI, thigh (%)	76.0 ± 8.0	73.3 ± 7.7	80.6 ± 6.5	**<0.001**
TOI, head (%)	75.6 ± 7.3	74.9 ± 8.2	76.8 ± 5.6	0.294
Spirometry*				
FEV1 (L)	2.49 ± 0.62	2.74 ± 0.60	2.11 ± 0.42	**<0.001**
FCV (L)	3.79 ± 1.07	4.31 ± 0.99	2.98 ± 0.60	**<0.001**
FEV1/FCV (%)	70.6 ± 12.9	68.5 ± 13.4	73.9 ± 11.4	0.093
PEF (L s^{-1})	4.97 ± 1.85	5.66 ± 1.89	3.92 ± 1.18	**<0.001**
Physical fitness measures *Incremental cardiopulmonary exercise test*				

Absolute cardiorespiratory fitness (ml min^{-1})	1943 ± 461	2170 ± 419	1576 ± 238	**<0.001**
Relative cardiorespiratory fitness (ml $kg^{-1}·min^{-1}$)	26.3 ± 4.8	27.6 ± 5.0	24.2 ± 3.6	**0.003**
Relative cardiorespiratory fitness (ml kg^{-1}FFM$·min^{-1}$)	37.6 ± 5.6	37.4 ± 5.8	37.8 ± 5.4	0.777
Metabolic equivalents measured (METs)	7.5 ± 1.4	7.9 ± 1.4	6.9 ± 1.0	**0.003**
Cardiorespiratory fitness estimated (METs)	8.1 ± 1.6	8.8 ± 1.6	7.2 ± 0.9	**<0.001**
Maximum respiratory exchange ratio (ratio)	1.13 ± 0.11	1.16 ± 0.11	1.08 ± 0.08	**0.002**
Maximum heart rate (bpm)	144.6 ± 17.6	144.8 ± 21.2	144.3 ± 9.7	0.907
Theoretical maximum heart rate (bpm)	159.7 ± 2.0	159.6 ± 2.1	159.9 ± 1.9	0.630
Peak oxygen pulse (mL $beats^{-1}$)	18.2 ± 2.8	19.1 ± 2.7	16.8 ± 2.2	**<0.001**
TOI, thigh (%)*	64.7 ± 11.5	60.1 ± 10.6	71.8 ± 9.2	**<0.001**
TOI, head (%)*	71.1 ± 7.4	71.4 ± 7.3	70.5 ± 7.8	0.625
Physical fitness field tests				
6 minutes walking (m)	561.0 ± 88.3	583.0 ± 95.9	525.6 ± 60.8	**0.008**
Chair stand (rep)*	11.5 ± 2.3	12.1 ± 2.2	10.5 ± 1.9	**0.003**
Handgrip (maximum; kg)	30.1 ± 8.9	35.4 ± 6.8	21.5 ± 3.5	**<0.001**
Handgrip (mean; kg)	28.3 ± 8.5	33.2 ± 6.7	20.2 ± 3.4	**<0.001**
Handgrip (sum; kg)	57.2 ± 17.1	67.0 ± 13.4	40.7 ± 6.8	**<0.001**
Cognitive function tests				
Mini mental state examination (total score, 0-30)	27.7 ± 2.3	27.9 ± 1.9	27.4 ± 2.8	0.428
Boston naming (total score, 0-15)	11.0 ± 2.3	11.9 ± 2.0	9.7 ± 2.3	**<0.001**
Clock drawing (total score, 0-10)	7.3 ± 1.9	7.5 ± 1.9	7.1 ± 2.0	0.377
Rey auditory verbal learning (total score, 0-15)	12.7 ± 2.7	12.5 ± 3.0	13.0 ± 2.1	0.478
Trail making (s)	98.4 ± 91.1	89.4 ± 89.3	113.3 ± 94.0	0.303
COWAT (total score, words in 60s)	35.6 ± 13.7	39.0 ± 14.2	30.3 ± 11.2	**0.010**
Stroop (total score)*	3.6 ± 6.8	3.0 ± 7.1	4.6 ± 6.3	0.356

Values are presented as mean ± standard deviation or percentages. T-test and [Y]Chi square statistics was applied. Statistically significant differences between sexes are highlighted in bold. COWAT means controlled oral word association test; FEV1, forced expiratory volume in 1 second; FFM, fat free mass; FVC, forced vital capacity; NW, normalweight; METs, metabolic equivalents; Ob, obesity; OW, overweight; PEF, peak expiratory flow; TOI, tissue oxygenation index. *Subsample of 66 participants in all cases, except for TOI, 65; [a]by indirect calorimetry and [b]bioimpedance analysis.

Descriptive characteristics of participants regarding drug intake, chronic diseases and smoking status are shown in table 5. The highest intake was reported for anticoagulants with the 24% of the overall sample reporting anticoagulants intake, and 34% in the case of females. The two chronic diseases with the highest prevalence were Hypertension (58% of the total sample) and hypercholesterolemia (37% of the total sample). Additionally, from the total sample 49% and 13% were former and current smokers, respectively.

Table 5. Clinical and specific characteristics of the subjects according to who achieved the maximal criteria during CPET.

	Total sample			**CPET***		
	All	Male	Female	All	Male	Female
	n=92	n=51	n=41	n=68	n=42	n=26
Drug intake[a]						
Anticoagulants	22 (24)	8 (16)	14 (34)	13 (19)	8 (19)	5 (20)
Diuretics	8 (9)	5 (10)	3 (7)	6 (9)	2 (5)	4 (16)
β-Blockers	12 (13)	6 (12)	6 (15)	7 (10)	5 (12)	2 (8)
IECAs	16 (17)	7 (14)	9 (22)	10 (15)	3 (7)	7 (28)
Antidepressants	10 (11)	3 (6)	7 (17)	7 (10)	4 (9)	3 (12)
Anxiolytics	15 (16)	2 (4)	13 (32)	4 (6)	1 (2)	3 (12)
Chronic diseases[b]						
Hypertension	53 (58)	29 (57)	24 (59)	40 (59)	23 (54)	17 (68)
High cholesterol	34 (37)	18 (35)	16 (39)	22 (32)	15 (35)	7 (28)
Chronic depression	10 (11)	3 (6)	7 (17)	9 (13)	3 (7)	6 (24)
Chronic anxiety	5 (5)	1 (2)	4 (10)	5 (7)	1 (2)	4 (16)
Diabetes	17 (18)	9 (18)	8 (20)	13 (19)	7 (16)	6 (24)
Smoking						
Current	12 (13)	11 (22)	1 (2)	8 (12)	8 (19)	0 (0)
Former	45 (49)	32 (63)	13 (32)	39 (57)	29 (67)	10 (40)

Values are presented as n and (percentages). [a]Participants who are currently taking this drug permanently; [b]Participants under medical control. CPET means cardiopulmonary exercise test; IECA, Angiotensin II converting enzyme inhibitor. *Participants achieving the maximal criteria for CPET.

4.2. Distribution of the participants' characteristics

The boxplot of distribution for the physical characteristics in the total sample by sex are shown in Figure 4. The boxplots graphically shows the previously differences observed between sex in all variables except age, BMI and hip circumference.

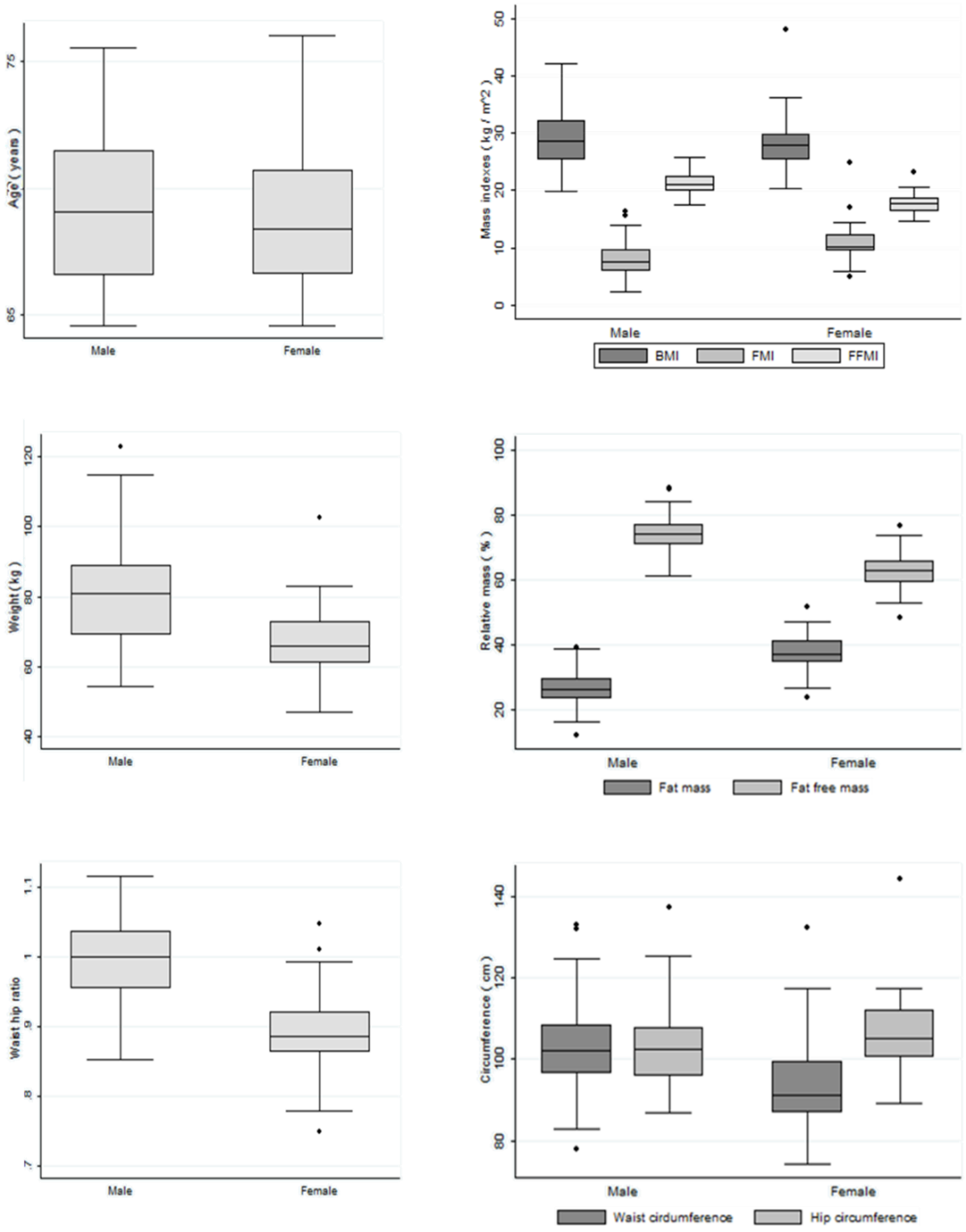

Figure 4. Distribution of physical characteristics by sex. BMI means body mass index; FFMI, fat free mass index; FMI, Fat mass index.

Similarly, boxplot of distribution for resting cardiovascular parameters by sex is described in Figure 5. Additionally, figure 6 shows the distribution of resting metabolic parameters reporting the differences in total energy expenditure and thigh-TOI by sex.

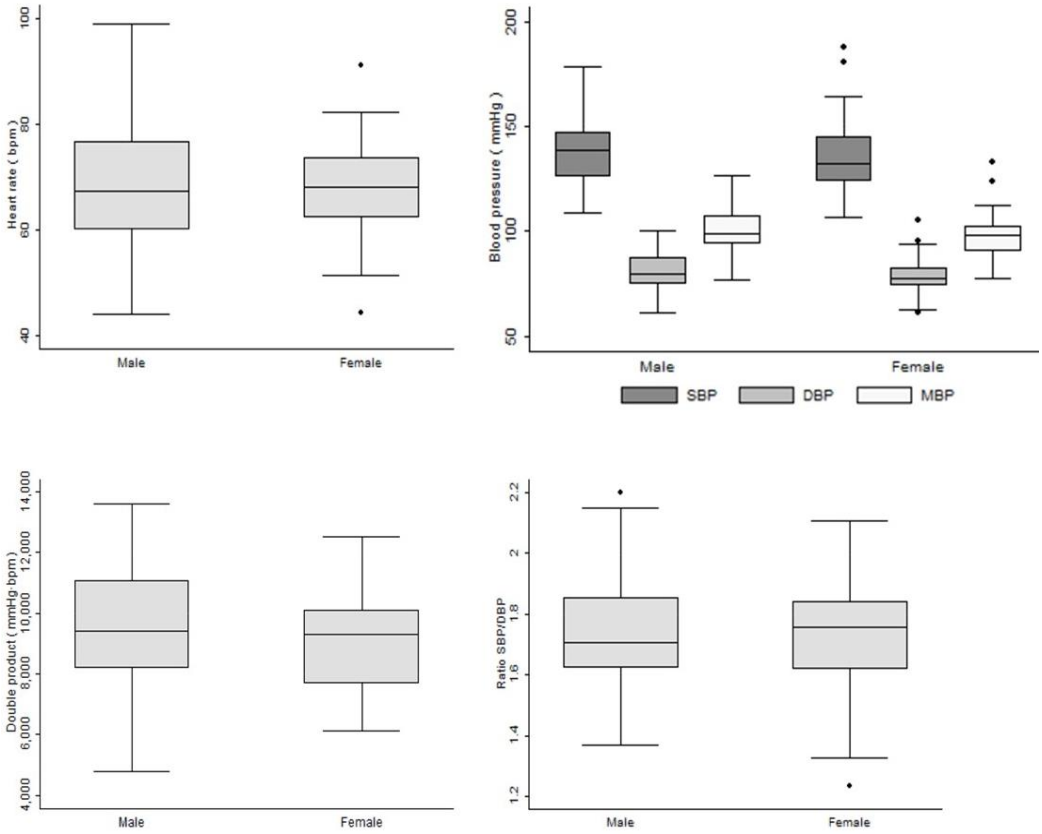

Figure 5. Distribution of resting cardiovascular parameters by sex. DBP means diastolic blood pressure; MBP, mean blood pressure; SBP, systolic blood pressure.

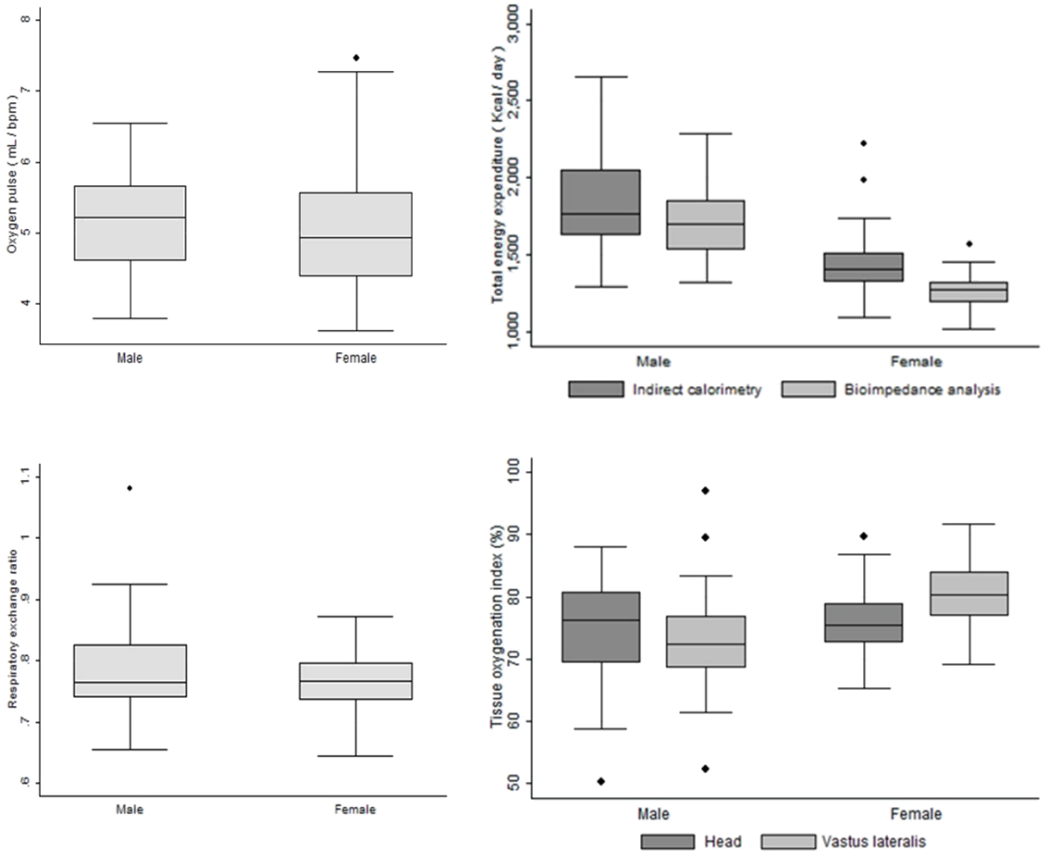

Figure 6. Distribution of resting metabolic parameters by sex.

Figure 7 shows higher values for the spirometry parameters in males than in females, except for the FEV1/FCV being higher in females.

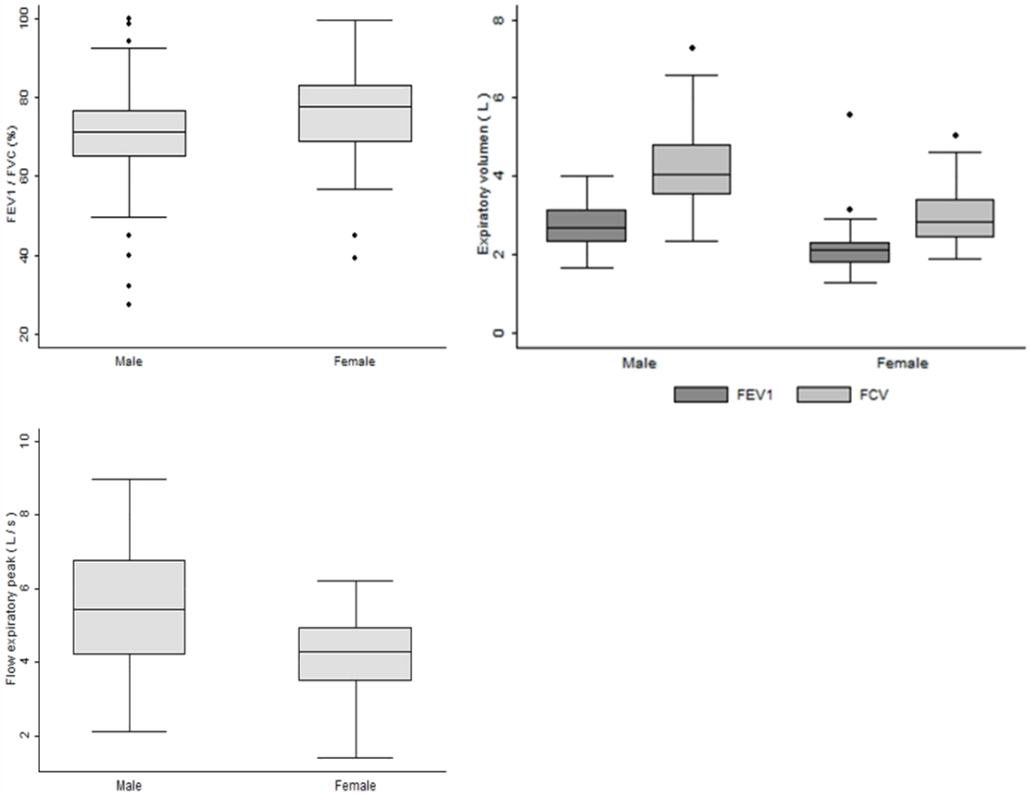

Figure 7. Distribution of spirometry parameters by sex. FEV1 means forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

Moreover, the distribution of the CRF and physical fitness field tests, together with RER, TOI and HR during incremental test are shown in Figures 8 and 9. Males had higher values in all variables than females, except to thigh TOI being higher in females.

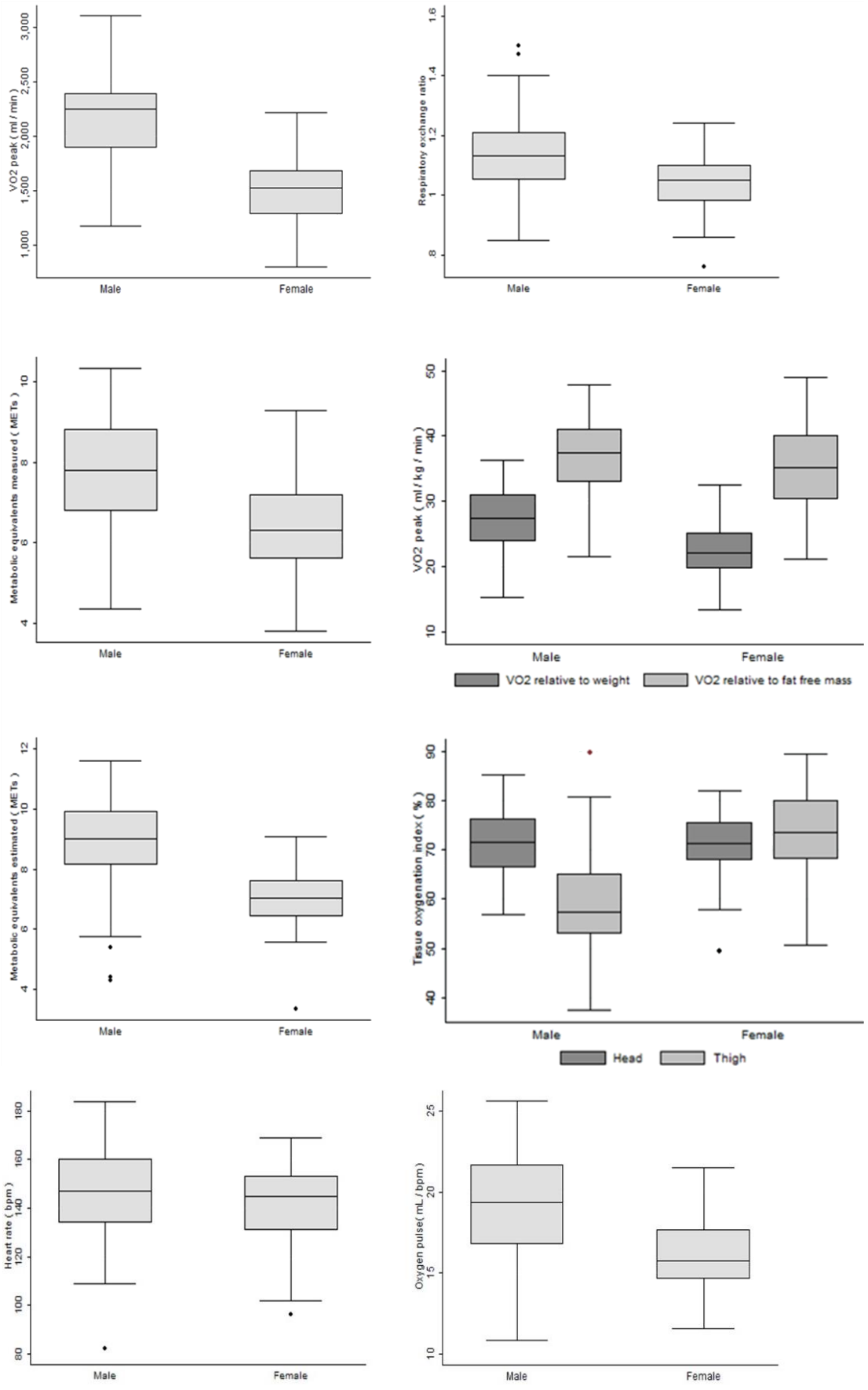

Figure 8. Distribution of maximum values achieved in the incremental cardiopulmonary test measures by sex.

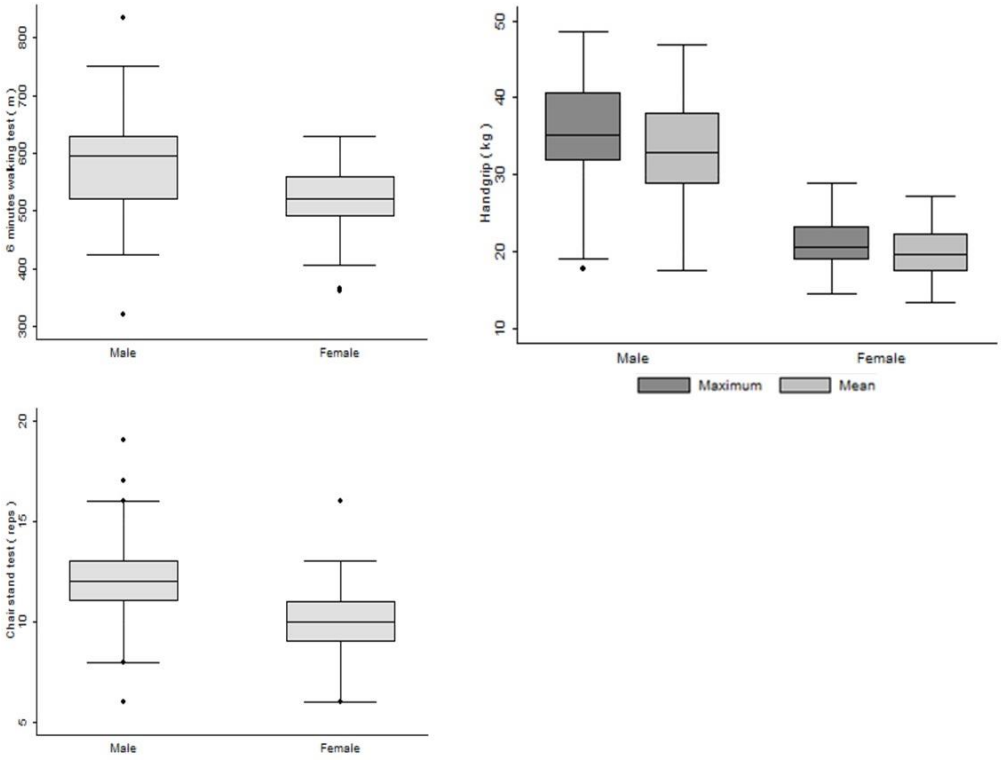

Figure 9. Distribution of physical fitness field tests by sex.

Additionally, Figure 10 shows the distribution boxplots of neuropsychological test scores by sex. A similar pattern in the distribution is found for all tests, except to BNT and COWAT where males had higher values than females.

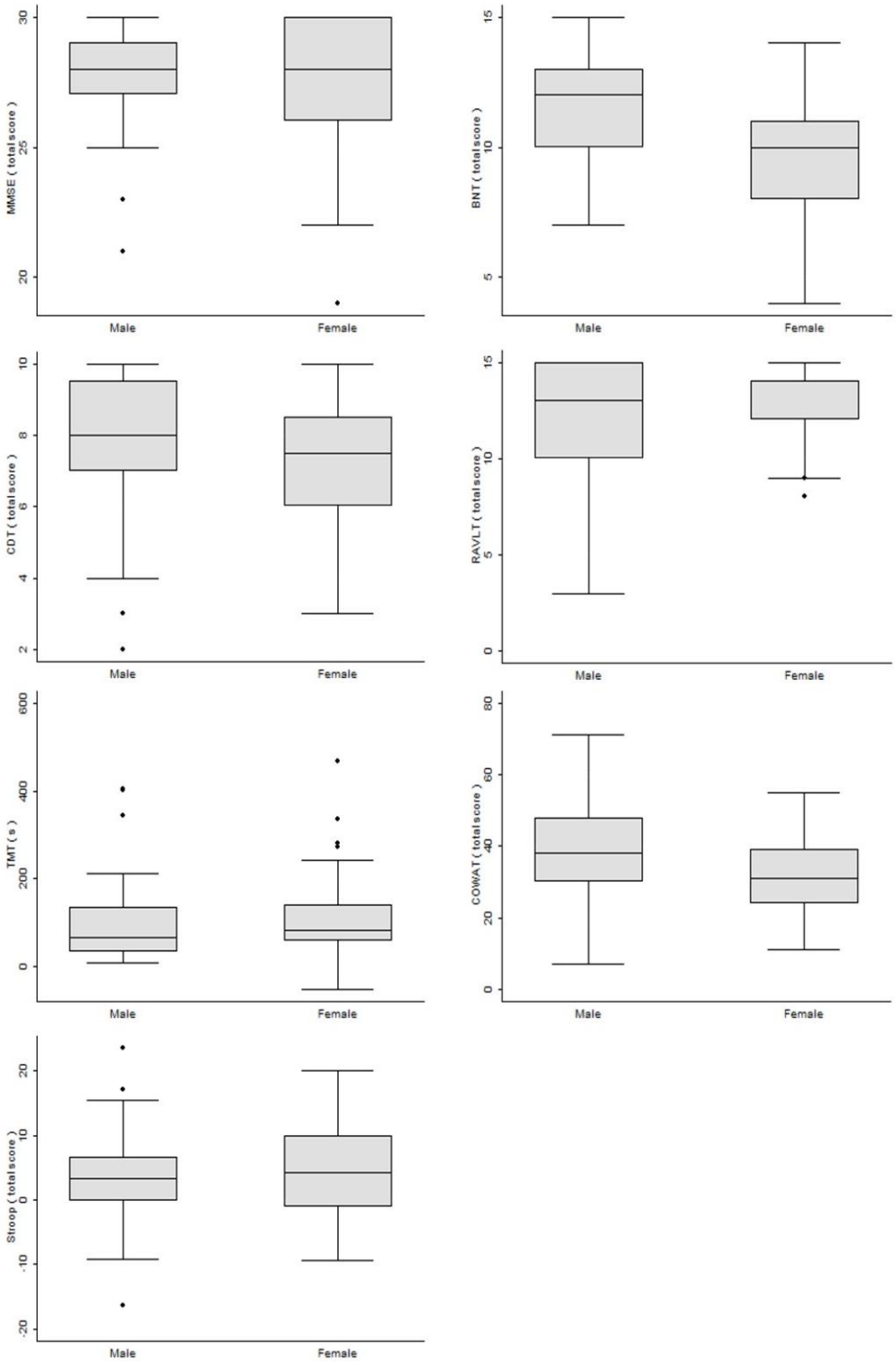

Figure 10. Boxplots of neuropsychological test scores by sex. BNT means Boston Naming Test; CDT, Clock Drawing Test; COWAT, Controlled Oral World Association; MMSE, Mini Mental State Examination; RAVLT, Rey Auditory Verbal Learning Test; TMT, Trail Making Test.

4.3. Associations of body composition components with cardiorespiratory fitness levels

Linear regression analysis indicated that there were significant associations of all body composition parameters with absolute and relative CRF level (Table 6A and Table 6B, respectively) of the sample achieving maximal criteria in CPET (all $p<0.005$), except to FMI ($p>0.05$). When the analyses were adjusted for the confounding variables (Model 2) all these associations remained (all $p<0.001$). When sample was segmented by sex, a similar trend was observed for the associations of all body composition parameters with relative CRF level in both sexes (table 6B; all $p<0.05$), except to WHR in females ($p>0.05$). Moreover, when analyses were adjusted for the confounding variables (model 2) these associations remained (all $p<0.05$). However, this trend was not observed in the associations of all body composition parameters with absolute CRF levels (table 6A; all $p>0.05$), except in males to FMI when the analyses were adjusted for the confounding variables (model 2) ($p<0.05$) and to FFMI when the analyses were unadjusted and adjusted for the confounding variables (both $p<0.05$).

4.4. Associations of resting cardiovascular parameters with cardiorespiratory fitness level

In unadjusted models, there were no significant associations of resting cardiovascular parameters with absolute or relative CRF level (Table 7A and Table 7B, respectively) in those achieving maximal criteria in CPET in the pooled sample neither segmented by sex (all $p>0.05$). However, when these associations were adjusted for confounding variables, all resting cardiovascular parameters were significantly associated with absolute and relative CRF level in the pooled sample of males and females. In general, positive associations were found of DBP, basal HR, DP with absolute and relative CRF level while negative associations were observed between MBP, SBP, SBP/DBP ratio and absolute and relative CRF. Similarly, after segmentation by sex, these associations remained in males, but only with relative CRF level in females.

Table 6A. Associations of body composition components with absolute oxygen consumption (mil/min) in maximal CPET*.

	VO2 (ml/min)											
	Total sample				Male				Female			
	B	β	95% CI	*p value*	B	β	95% CI	*p value*	B	β	95% CI	*p value*
Body Fat (%)												
Model 1	-20.2	-0.329	-34.4 ; -6.0	**0.006**	10.3	0.139	-13.2 ; 33.8	0.381	12.9	0.294	-4.8 ; 30.6	0.146
Model 2[a]	11.2	0.183	-4.6 ; 27.1	**<0.001**	NA[γ]				NA[γ]			
Fat Free Mass (%)												
Model 1	20.2	0.329	5.9 ; 34.4	**0.006**	-10.4	-0.140	-33.8 ; 13.1	0.377	-13.0	-0.295	-30.7 ; 4.7	0.087
Model 2[a]	-11.3	-0.184	-27.1 ; 4.5	**<0.001**	NA[γ]				NA[γ]			
Body Mass Index (kg/m²)												
Model 1	31.5	0.281	5.0 ; 57.9	**0.021**	28.2	0.286	-2.0 ; 58.4	0.067	15.7	0.258	-9.1 ; 40.5	0.203
Model 2[a]	23.9	0.214	3.1 ; 44.8	**<0.001**	NA[γ]				NA[γ]			
Fat Mass Index (kg FM/m²)												
Model 1	-17.0	-0.111	-54.3 ; 20.4	0.368	32.7	0.212	-15.4 ; 80.9	0.177	24.7	0.290	-9.6 ; 59.0	0.151
Model 2[b-c]	24.4	0.160	-6.1 ; 54.9	**<0.001**	27.8	0.181	-17.4 ; 73.1	**0.019**	22.0	0.259	-13.3 ; 57.3	0.264
Fat Free Mass Index (kg FFM/m²)												
Model 1	120.1	0.623	83.0 ; 157.2	**<0.001**	87.8	0.365	16.3 ; 159.3	**0.017**	21.3	0.133	-45.4 ; 88.1	0.516

Model 2[b-c]	58.9	0.305	9.2 ; 108.6	**<0.001**	73.5	0.306	4.7 ; 142.3	**0.004**	20.5	0.128	-46.3 ; 87.4	0.484
Waist Circumference (cm)												
Model 1	16.1	0.401	7.1 ; 25.2	**<0.001**	7.3	0.182	-5.3 ; 19.8	0.248	5.3	0.231	-4.1 ; 14.7	0.255
Model 2[a]	6.5	0.162	-725.1 ; -331.6	**<0.001**	NA[ɣ]				NA[ɣ]			
Waist to Hip Ratio												
Model 1	1975.1	0.339	629.9 ; 3320.4	**0.005**	-1798.5	-0.233	-1237.8 ; 1699.7	0.138	231.0	0.066	-4197.4 ; 600.5	0.748
Model 2[a]	-803.4	-0.138	-2283.7 ; 676.9	**<0.001**	NA[ɣ]				NA[ɣ]			

Statically significant values are shown in bold. B, regression coefficient; β means standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test; FM, fat mass; FFM, fat free mass; NA, analyses were not applied. Model 1, Unadjusted model; Model 2, Analyses adjusted for sex[a], sex + age[b] for total sample and age[c] for sample segmented by sex.

*Participants achieving the maximal criteria for CPET; [ɣ]Effect of cofounder variables on coefficient <10%.

Table 6B. Associations of body composition components with relative oxygen consumption (mil/kg/min) in maximal CPET*.

	VO2 (ml/kg/min)											
	Total sample				Male				Female			
	B	β	95% CI	*p value*	B	β	95% CI	*p value*	B	β	95% CI	*p value*
Body Fat (%)												
Model 1	-0.37	-0.585	-0.50 ; -0.24	**<0.001**	-0.46	-0.519	-0.70 ; -0.22	**<0.001**	-0.32	-0.486	-0.56 ; -0.08	**0.012**
Model 2[a]	-0.41	-0.643	-0.58 ; -0.24	**<0.001**	NA[γ]				NA[γ]			
Fat Free Mass (%)												
Model 1	0.37	0.584	0.24 ; 0.50	**<0.001**	0.46	0.518	0.22 ; 0.70	**<0.001**	0.32	0.485	0.08 ; 0.56	**0.012**
Model 2[a]	-0.53	0.642	0.23 ; 0.58	**<0.001**	NA[γ]				NA[γ]			
Body Mass Index (kg/m^2)												
Model 1	-0.48	-0.413	-0.74 ; -0.22	**<0.001**	-0.55	-0.471	-0.89 ; -0.22	**0.002**	-0.49	-0.535	-0.81 ; -0.16	**0.005**
Model 2[a]	-0.53	-0.457	-0.77 ; -0.29	**<0.001**	NA[γ]				NA[γ]			
Fat Mass Index (kg FM/m^2)												
Model 1	-0.92	-0.581	-1.24 ; -0.60	**<0.001**	-0.94	-0.511	-1.44 ; -0.43	**<0.001**	-0.68	-0.531	-1.13 ; -0.22	**0.005**
Model 2[b-c]	-0.84	-0.528	-1.18 ; -0.49	**<0.001**	-0.97	-0.525	-1.47 ; -0.46	**0.001**	-0.73	-0.574	-1.19 ; -0.27	**0.010**
Fat Free Mass Index (kg FFM/m^2)												
Model 1	0.04	0.022	-0.45 ; 0.53	**<0.001**	-1.00	-0.350	-1.89 ; -0.05	**0.023**	-0.97	-0.405	-1.86 ; -0.15	**0.040**

Model 2[a]	-0.99	-0.498	-1.62 ; -0.36	**<0.001**	NA[γ]					NA[γ]				
Waist circumference (cm)														
Model 1	-0.13	-0.301	-0.22 ; -0.03	**0.013**	-0.26	-0.548	-0.30 ; -0.05	**<0.001**	-0.18	-0.512	-0.39 ; -0.13	**0.008**		
Model 2[a]	-0.23	-0.550	-0.32 ; -0.14	**<0.001**	NA[γ]					NA[γ]				
Waist to Hip Ratio														
Model 1	1.60	0.027	-13.19 ; 16.39	0.830	-31.54	-0.342	-33.51 ; 9.23	**0.026**	-12.14	-0.233	-59.18 ; -3.89	0.253		
Model 2[a]	-22.02	-0.366	-39.84 ; -4.21	**<0.001**	NA[γ]					NA[γ]				

Statically significant values are shown in bold. B, regression coefficient; β means standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test; FM, fat mass; FFM, fat free mass; NA, analyses were not applied. Model 1, Unadjusted model; Model 2, Analyses adjusted for sex[a], sex + age[b] for total sample and age[c] for sample segmented by sex.
*Participants achieving the maximal criteria for CPET; [γ]Effect of cofounder variables on coefficient <10%.

Table 7A. Associations of resting cardiovascular parameters with absolute oxygen consumption (mil/min) in maximal CPET*.

	VO2 (ml/min)											
	Total sample				Male				Female			
	B	β	95% CI	*p value*	B	β	95% CI	*p value*	B	β	95% CI	*p value*
Mean blood pressure (mmHg)												
Model 1	4.568	0.096	-7.03 ; 16.17	0.435	-2.957	-0.072	-16.10 ; 10.18	0.652	5.270	0.195	-5.893 ; 16.434	0.340
Model 2	-1.671	-0.035	-10.39 ; 7.05	**<0.001**	-2.625	-0.064	-14.93 ; 9.68	**0.027**	3.162	0.117	-8.575 ; 14.898	0.454
Systolic blood pressure (mmHg)												
Model 1	-0.523	-0.019	-7.43 ; 6.39	0.880	-4.770	-0.193	-12.51 ; 2.97	0.221	0.646	0.042	-5.859 ; 7.151	0.839
Model 2	-2.306	-0.082	-7.44 ; 2.82	**<0.001**	-2.889	-0.117	-10.40 ; 4.63	**0.022**	0.117	0.008	-6.416 ; 6.649	0.511
Diastolic blood pressure (mmHg)												
Model 1	9.742	0.181	-3.24 ; 22.72	0.139	3.030	0.063	-12.37 ; 18.43	0.693	7.684	0.270	-3.867 ; 19.235	0.183
Model 2	1.037	0.019	-8.95 ; 11.03	**<0.001**	-0.144	-0.003	-14.55 ; 14.26	**0.029**	5.272	0.185	-7.233 ; 17.778	0.380
Basal heart rate (bpm)												
Model 1	10.241	0.202	-1.94 ; 22.42	0.098	7.820	0.192	-4.93 ; 20.57	0.222	8.408	0.243	-5.703 ; 22.518	0.231
Model 2	5.046	0.100	-4.11 ; 14.21	**<0.001**	4.967	0.122	-6.98 ; 16.91	**0.021**	5.787	0.168	-9.148 ; 20.722	0.398
Double product (mmHg bpm)												
Model 1	0.043	0.154	-0.02 ; 0.11	0.211	0.021	0.093	-0.05 ; 0.09	0.558	0.050	0.265	-0.027 ; 0.128	0.192
Model 2	0.017	0.061	-0.03 ; 0.07	**<0.001**	0.038	0.199	-0.05 ; 0.08	**0.027**	0.038	0.199	-0.045 ; 0.120	0.360

Systolic/diastolic blood pressure ratio														
Model 1	-422.7	-0.177	-1001 ; 155.8	0.149		-545.9	-0.243	-1243 ; 151.9	0.122		-211.8	-0.185	-687.1 ; 263.48	0.367
Model 2	-187.6	-0.078	-635.2 ; 259.8	**<0.001**		-193.8	-0.086	-904.6 ; 516.8	**0.025**		-142.4	-0.124	-632.6 ; 347.75	0.445

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test. Model 1, Unadjusted model; Model 2, analyses adjusted for sex + age + body mass index for total sample and age + body mass index for male and female. *Participants achieving the maximal criteria for CPET.

Table 7B. Associations of resting cardiovascular parameters with relative oxygen consumption (mil/kg/min) in maximal CPET*.

	VO2 (ml/kg/min)											
	Total sample				Male				Female			
	B	B	95% CI	*p value*	B	β	95% CI	*p value*	B	β	95% CI	*p value*
Mean blood pressure (mmHg)												
Model 1	-0.020	-0.042	-0.14 ; 0.10	0.736	-0.067	-0.137	-0.22 ; 0.09	0.388	-0.013	-0.032	-0.18 ; 0.16	0.877
Model 2[a]	-0.005	-0.011	-0.11 ; 0.10	**<0.001**	-0.018	-0.037	-0.16 ; 0.12	**0.009**	0.027	0.066	-0.13 ; 0.18	**0.031**
Systolic blood pressure (mmHg)												
Model 1	-0.026	-0.089	-0.10 ; 0.05	0.472	-0.049	-0.166	-0.14 ; 0.04	0.293	-0.023	-0.099	-0.12 ; 0.07	0.629
Model 2[a]	-0.021	-0.073	-0.08 ; 0.04	**<0.001**	-0.025	-0.086	-0.11 ; 0.06	**0.008**	-0.013	-0.055	-0.10 ; 0.07	**0.031**
Diastolic blood pressure (mmHg)												
Model 1	0.008	0.014	-0.13 ; 0.14	0.909	0.045	-0.078	-0.23 ; 0.14	0.624	0.017	0.041	-0.16 ; 0.20	0.842
Model 2[a]	0.029	0.052	-0.09 ; 0.15	**<0.001**	0.009	0.015	-0.16 ; 0.18	**0.009**	0.070	0.165	-0.09 ; 0.23	**0.023**
Basal heart rate (bpm)												
Model 1	0.068	0.129	-0.06 ; 0.20	0.295	0.059	0.121	-0.10 ; 0.21	0.444	0.038	0.074	-0.18 ; 0.25	0.720
Model 2[b-c]	0.091	0.173	-0.01 ; 0.20	**<0.001**	0.087	0.180	-0.05 ; 0.22	**0.004**	0.103	0.199	-0.09 ; 0.29	**0.019**
Double product (mmHg bpm)												
Model 1	0.001	0.044	0.00 ; 0.00	0.722	0.001	0.008	-0.01 ; 0.01	0.959	0.0001	0.030	-0.01 ; 0.01	0.885
Model 2[b-c]	0.001	0.152	0.00 ; 0.00	**<0.001**	0.0004	0.149	0.00 ; 0.01	**0.006**	0.0006	0.214	0.00 ; 0.01	**0.017**

Systolic/diastolic blood pressure ratio														
Model 1	-2.036	-0.082	-8.10 ; 4.02	0.505		-1.620	-0.060	-10.19 ; 6.95	0.704		-2.306	-0.135	-9.46 ; 4.85	0.512
Model 2[a]	-2.511	-0.102	-7.72 ; 2.70	**<0.001**		-1.807	-0.067	-10.03 ; 6.42	**0.009**		-3.262	-0.190	-9.49 ; 2.97	**0.019**

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test. Model 1, Unadjusted model; Model 2, analyses adjusted for sex + age + body mass index for total sample and age + body mass index for male and female.
*Participants achieving the maximal criteria for CPET.

4.5. Associations of resting metabolic parameters with cardiorespiratory fitness level

Linear regression analyses showed positive associations of total energy expenditure measured by indirect calorimetry and bioimpedance analyses with absolute CRF level (Table 8A and Table 8B respectively) in both the unadjusted and adjusted models (model 1 and model 2, respectively) (all $p<0.05$) in the pooled sample of males y females and in the segmented sample of those achieving maximal criteria in CPET. A similar pattern was observed with relative CRF level, but only in the adjusted model (model 2) (all $p<0.05$).

There were negative associations of resting RER with absolute and relative CRF (Table 8A and Table 8B respectively) only in the adjusted model (model 2) in the pooled sample and males and females in the segmented sample within those achieving maximal criteria in CPET (all $p>0.05$), except for the absolute CRF in females.

Positive associations of resting oxygen pulse with absolute CRF (Table 8A) were observed only in the adjusted model (model 2) in the pooled sample and males, whereas positive associations with relative CRF (Table 8B) were found in both the unadjusted and adjusted models (model 1 and model 2, respectively) (all $p<0.05$) in the pooled sample of males y females and in the segmented sample, except for the unadjusted model in males.

Moreover, the analyses of unadjusted models (Model 1) did not show significant associations of resting thigh and head TOI with either absolute or relative CRF (Table 8A and Table 8B, respectively) neither in the pooled nor segmented sample of those achieving maximal criteria CPET (all $p>0.05$). The only exception to the above was the positive association between thigh TOI and absolute CRF in males after segmentation. However, when the analyses were adjusted for confounding variables (Model 2), resting thigh and head TOI were positive associated with absolute and relative CRF level in the pooled sample achieving maximal criteria in CPET (all $p<0.05$). When the sample was segmented by sex the associations of thigh and head TOI with absolute CRF level remained for males in absolute and relative CRF level, but not in females to absolute CRF level (all $p>0.05$) and there were negative association of thigh and head TOI with relative CRF level (all $p<0.05$).

Table 8A. Associations of resting metabolic parameters with absolute oxygen consumption (mil/min) in maximal CPET*.

	VO2 (ml/min)											
	Total sample				Male				Female			
	B	β	95% CI	*p value*	B	B	95% CI	*p value*	B	β	95% CI	*p value*
TEE measured (kcal/day)[a]												
Model 1	0.973	0.682	0.71 ; 1.23	**<0.001**	0.663	0.470	0.26 ; 1.07	**0.002**	0.751	0.563	0.29 ; 1.22	**0.003**
Model 2	0.563	0.395	0.23 ; 0.89	**<0.001**	0.468	0.332	0.00 ; 0.94	**0.005**	0.807	0.605	0.33 ; 1.29	**0.007**
TEE estimated (kcal/day)[b]												
Model 1	1.304	0.784	1.05 ; 1.56	**<0.001**	1.231	0.617	0.73 ; 1.73	**<0.001**	1.190	0.534	0.40 ; 1.98	**0.005**
Model 2	1.400	0.842	0.85 ; 1.95	**<0.001**	1.419	0.711	0.67 ; 2.17	**<0.001**	1.475	0.662	0.39 ; 2.56	**0.026**
Respiratory exchange ratio												
Model 1	310.7	0.045	-1403.6 ; 2025.1	0.719	-416.9	-0.074	-2216.9 ; 1383.0	0.642	-371.7	-0.076	-2418.6 ; 1675.0	0.711
Model 2	-503.7	-0.072	-1849.3 ; 841.8	**<0.001**	-504.1	-0.089	-2300.5 ; 1292.1	**0.025**	-471.1	-0.097	-2583.5 ; 1641.2	0.471
Resting oxygen pulse (mL/bpm)												
Model 1	-6.375	-0.020	-84.68 ; 71.93	0.871	-29.666	-0.118	-109.74 ; 50.40	0.458	-48.83	-0.206	-146.65 ; 48.99	0.313
Model 2	2.116	0.007	-59.75 ; 63.99	**<0.001**	3.004	0.012	-74.12 ; 80.13	**0.029**	-6.457	-0.027	-139.85 ; 126.93	0.509
TOI, thigh (%)[γ]												
Model 1	-3.701	-0.064	-17.99 ; 10.59	0.607	24.425	0.448	8.87 ; 39.98	**0.003**	-6.763	-0.180	-22.66 ; 9.14	0.388
Model 2	11.752	0.203	0.16 ; 23.34	**<0.001**	17.175	0.315	0.73 ; 33.62	**0.004**	-7.335	-0.196	-25.65 ; 10.98	0.423

TOI, head (%)[ɣ]														
Model 1	5.42	0.086	-10.0 ; 20.9	0.486	12.24	0.240	-3.61 ; 28.08	0.127	5.35	0.125	-12.50 ; 23.20	0.542		
Model 2	8.20	0.130	-3.1 ; 19.5	**<0.001**	9.29	0.182	-5.57 ; 24.15	**0.014**	3.37	0.079	-14.74 ; 21.48	0.483		

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPE, cardiopulmonary exercise; TEE, total energy expenditure; TOI, tissue oxygenation index. Model 1, Unadjusted model; Model 2, analyses adjusted for sex + age + body mass index for total sample and age + body mass index for male and female.

*Participants achieving the maximal criteria for CPET; [ɣ]Subsample of 65 participants; [a]by indirect calorimetry and [b]bioimpedance analysis.

Table 8B. Associations of resting metabolic parameters with relative oxygen consumption (mil/kg/min) in maximal CPET*.

	VO2 (ml/kg/min)											
	Total sample				Male				Female			
	B	β	95% CI	*p value*	B	β	95% CI	*p value*	B	β	95% CI	*p value*
TEE measured (kcal/day)[a]												
Model 1	0.003	0.211	0.000 ; 0.007	0.087	-0.001	-0.049	-0.006 ; 0.005	0.761	0.004	0.202	0.00 ; 0.01	0.322
Model 2	0.004	0.243	0.000 ; 0.008	**<0.001**	0.002	0.146	-0.003 ; 0.008	**0.006**	0.009	0.445	0.00 ; 0.02	**0.002**
TEE estimated (kcal/day)[b]												
Model 1	0.002	0.138	-0.002 ; 0.007	0.260	-0.005	-0.197	-0.012 ; 0.003	0.211	-0.011	-0.343	-0.02 ; 0.00	0.086
Model 2	0.003	0.158	-0.005 ; 0.010	**<0.001**	0.004	0.148	-0.007 ; 0.014	**0.008**	0.001	0.035	-0.02 ; 0.02	**0.032**
Respiratory exchange ratio												
Model 1	9.740	0.135	-7.85 ; 27.33	0.273	5.705	0.085	-15.75 ; 27.16	0.594	6.227	0.086	-24.30 ; 36.76	0.678
Model 2	-6.852	-0.095	-22.53 ; 8.82	**<0.001**	-9.021	-0.134	-29.66 ; 11.62	**0.007**	-1.554	-0.021	-29.00 ; 25.89	**0.033**
Resting oxygen pulse (mL/bpm)												
Model 1	0.832	0.252	0.048 ; 1.616	**0.038**	0.488	0.162	-0.462 ; 1.437	0.305	1.613	0.455	0.28 ; 2.94	**0.019**
Model 2	0.305	0.092	-0.413 ; 1.022	**<0.001**	0.252	0.084	-0.635 ; 1.140	**0.008**	0.828	0.234	-0.86 ; 2.51	**0.021**
TOI, thigh (%)*												
Model 1	-0.040	-0.068	-0.188 ; 0.107	0.586	-0.1893	-0.339	-0.037 ; 0.365	0.108	-0.1893	-0.339	-0.415 ; 0.037	0.097
Model 2	0.129	0.217	-0.006 ; 0.265	**<0.001**	0.2389	0.368	0.054 ; 0.424	**<0.001**	-0.1100	-0.197	-0.346 ; 0.126	**0.029**

TOI, head (%)*														
Model 1	0.064	0.098	-0.095	;	0.223	0.426	0.143	0.234	-0.047	;	0.332	0.136	-0.074	-0.116	-0.34	;	0.19	0.574
Model 2	0.092	0.141	-0.040	;	0.223	**<0.001**	0.124	0.204	-0.046	;	0.295	**0.004**	-0.029	-0.046	-0.26	;	0.21	**0.032**

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPE, cardiopulmonary exercise; TEE, total energy expenditure; TOI, tissue oxygenation index. Model 1, Unadjusted model; Model 2, analyses adjusted for sex + age + body mass index for total sample and age + body mass index for male and female.
*Participants achieving the maximal criteria for CPET; [γ]Subsample of 81 participants; [a]by indirect calorimetry and [b]bioimpedance analysis.

4.6. Associations of spirometry parameters with cardiorespiratory fitness level

In general, linear regression analyses showed positive associations of spirometry parameters with absolute and relative CRF level (Table 9A and Table 9B respectively), in both adjusting models (Models 1 and 2) (all $p<0.05$) for the pooled sample of males and females of those achieving maximal criteria in CPET. The only exception to the above was to the negative association between FEV1/FVC and relative CRF in both the unadjusted and adjusted models (both $p<0.05$) (Table 9B).

When the analyses were performed by sex, there were positive associations of FEV1, FVC, FEV1/height^2 with absolute and relative CRF level and negative associations of FEV1/FVC with absolute and relative CRF level in males (all $p<0.05$). Moreover, in females there were positive associations of FEV1 with absolute and relative CRF level (all $p<0.05$) and, there were also positive associations of FEV1/FVC and PEF with relative CRF (all $p<0.05$). The positive associations of PEF and PEF/ height ^{2} observed in the in pooled sample of males and females, were not observed in either males or females, when the sample is segmented by sex.

4.7. Associations of physical fitness field tests with cardiorespiratory fitness level

Linear regression analyses showed positive associations of physical fitness field tests with absolute and relative CRF level (Table 10A and Table 10B respectively) in both adjusting models (models 1 and 2) ($p<0.05$) for the pooled sample of males and females, but also by sex in those achieving maximal criteria in CPET. The only exception to the above was to the association between chair stand test and absolute CRF level in the unadjusted model for males ($p=0.125$) and to the association between handgrip and absolute CRF level in the unadjusted model for females ($p=0.979$).

Table 9A. Associations of spirometry parameters with absolute oxygen consumption (mil/min) in maximal CPET*.

	VO2 (ml/min)													
	Total sample				Male				Female					
	B	B	95% CI	*p value*	B	B	95% CI	*p value*	B	β	95% CI	*p value*		
FEV1 (L)														
Model 1	418.59	0.555	261.90 ; 575.28	**<0.001**	240.19	0.345	25.42	454.96	**0.029**	218.56	0.383	-3.75	440.88	**0.054**
Model 2[a-d]	311.78	0.413	161.44 ; 462.12	**<0.001**	322.94	0.464	118.59	527.28	**0.002**	283.67	0.497	67.60	499.75	**0.019**
FVC (L)														
Model 1	273.57	0.628	188.93 ; 358.21	**<0.001**	184.88	0.432	58.29	311.46	**0.005**	79.47	0.201	-83.97	242.91	0.326
Model 2[b]	164.60	0.378	66.87 ; 262.32	**<0.001**	NA[γ]					NA[γ]				
FEV1/FVC (%)														
Model 1	-6.78	-0.187	-15.68 ; 2.12	0.133	-4.98	-0.159	-15.16	5.20	0.329	4.32	0.208	-4.25	12.90	0.308
Model 2[c-e]	0.12	0.003	-6.71 ; 6.95	**<0.001**	-0.80	-0.026	-10.85	9.24	**0.048**	4.14	0.199	-4.41	12.69	0.346
FEV1/Height²														
Model 1	782.18	0.313	189.71 ; 1374.7	**0.011**	324.82	0.155	-354.97	1004.6	0.340	506.91	0.307	-155.18	1169.0	0.127
Model 2[a-d]	523.34	0.209	42.33 ; 1004.4	**<0.001**	509.06	0.243	-157.96	1176.1	**0.058**	603.41	0.365	-45.94	1252.8	0.082
PEF (L/min)														
Model 1	112.84	0.447	56.40 ; 169.29	**<0.001**	45.30	0.203	-26.43	117.03	0.209	58.18	0.287	-23.48	139.84	0.154
Model 2[b]	47.86	0.189	-5.97 ; 101.69	**<0.001**	NA[γ]					NA[γ]				
PEF/Height²														

Model 1	189.54	0.261	14.73	;	364.35	**0.034**	36.36	0.059	-164.78	237.51	0.716	96.65	0.198	-104.60	297.91	0.332
Model 2[b]	51.12	0.070	-95.66	;	197.89	**<0.001**	NA[γ]					NA[γ]				

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, analyses were not applied; PEF, peak expiratory flow. Model 1, Unadjusted model; Model 2, analyses adjusted for sex[b], sex + body mass index[a] or sex + age[c] for total sample and body mass index[d] or body mass index + age[e] for male and female. *Participants achieving the maximal criteria for CPET; [γ]Effect of cofounder variables on coefficient <10%.

Table 9B. Associations of spirometry parameters with relative oxygen consumption (mil/kg/min) in maximal CPET*.

	VO2 (ml/kg/min)													
	Total sample					Male					Female				
	B	β	95% CI		*p value*	B	β	95% CI		*p value*	B	β	95% CI		*p value*
FEV1 (L)															
Model 1	3.967	0.517	2.33	5.61	**<0.001**	3.609	0.442	1.20	6.02	**0.004**	2.823	0.331	-0.57	6.21	0.099
Model 2[a]	2.499	0.326	0.70	4.30	**<0.001**	2.748	0.336	0.42	5.08	**<0.001**	1.659	0.195	-1.50	4.82	**0.012**
FVC (L)															
Model 1	2.494	0.563	1.58	3.41	**<0.001**	2.529	0.504	1.11	3.95	**<0.001**	1.861	0.315	-0.50	4.23	0.117
Model 2[b]	2.400	0.542	1.24	3.56	**<0.001**	NA[γ]					NA[γ]				
FEV1/FVC (%)															
Model 1	-0.034	-0.091	-0.13	0.06	**<0.001**	-0.011	-0.031	-0.13	0.11	0.849	0.006	0.020	-0.12	0.14	0.923
Model 2[c]	-0.029	-0.079	-0.13	0.06	**<0.001**	-0.002	-0.004	-157.9	1176.1	0.058	603.41	0.365	-45.94	1252.8	**0.082**
FEV1/Height²															
Model 1	11.554	0.455	5.91	17.20	**<0.001**	10.011	0.407	2.64	17.38	**0.009**	8.926	0.362	-0.75	18.61	**0.069**
Model 2[a]	7.411	0.292	2.14	12.68	**<0.001**	7.615	0.310	0.61	14.62	**0.001**	6.770	0.275	-1.89	15.43	**0.006**
PEF (L/min)															
Model 1	1.063	0.414	0.48	1.65	**<0.001**	0.806	0.308	-0.01	1.62	0.053	0.781	0.258	-0.45	2.01	0.053
Model 2[b]	0.801	0.312	0.15	1.45	**<0.001**	NA[γ]					NA[γ]				

PEF/Height^2															
Model 1	2.493	0.338	0.76	4.23	**0.006**	1.866	0.259	-0.42	4.15	0.106	1.752	0.241	-1.22	4.73	0.236
Model 2[b]	1.838	0.249	0.08	3.59	**<0.001**	NA[ɣ]					NA[ɣ]				

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NA, analyses were not applied; PEF, peak expiratory flow. Model 1, Unadjusted model; Model 2, analyses adjusted for sex[b], sex + body mass index[a] or sex + age[c] for total sample and body mass index[d] or body mass index + age[e] for male and female. *Participants achieving the maximal criteria for CPET; [ɣ]Effect of cofounder variables on coefficient <10%.

Table 10A. Associations of physical fitness field tests with absolute oxygen consumption (mil/min) in maximal CPET*.

	VO2 (ml/min)														
	Total sample					Male					Female				
	B	β	95% CI		*p value*	B	β	95% CI		*p value*	B	β	95% CI		*p value*
6 min walking test (m)															
Model 1	2.39	0.457	1.24	3.53	**<0.001**	1.45	0.333	0.14	2.77	**0.031**	1.64	0.418	0.14	3.14	**0.034**
Model 2[a]	1.49	0.285	0.50	2.48	**<0.001**	NA[Y]					NA[Y]				
Handrip (kg)[¥]															
Model 1	36.64	0.705	27.57	45.71	**<0.001**	32.35	0.523	15.51	49.18	**<0.001**	0.38	0.006	-28.51	29.27	0.979
Model 2[a]	27.93	0.537	14.00	41.86	**<0.001**	NA[Y]					NA[Y]				
Chair stand (rep)															
Model 1	89.16	0.432	43.02	135.31	**<0.001**	45.3	0.240	-13.13	103.74	0.125	58.2	0.462	9.94	106.39	**0.020**
Model 2[b-c]	53.49	0.259	13.92	93.06	**<0.001**	53.77	0.285	-2.64	110.18	**0.032**	57.24	0.454	9.52	104.96	**0.033**

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test; NA, analyses were not applied. Model 1, Unadjusted model; Model 2, analyses adjusted for sex[a] or sex + body mass index[b] for total sample and body mass index[c] for male and female.

*Participants achieving the maximal criteria for CPET; [¥]Best attempt; [Y]Effect of cofounder variables on coefficient <10%.

Table 10B. Associations of physical fitness field tests with relative oxygen consumption (mil/kg/min) in maximal CPET*.

	VO2 (ml/kg/min)														
	Total sample					Male					Female				
	B	β	95% CI		*p value*	B	β	95% CI		*p value*	B	β	95% CI		*p value*
6 min walking test (m)															
Model 1	0.04	0.657	0.03	0.05	**<0.001**	0.032	0.615	0.02	0.05	**<0.001**	0.036	0.613	0.02	0.06	**<0.001**
Model 2[a]	0.03	0.607	0.02	0.04	**<0.001**	NA[Y]					NA[Y]				
Handrip (kg)[¥]															
Model 1	0.13	0.459	0.07	0.19	**<0.001**	0.115	0.309	0.00	0.23	**0.046**	0.213	0.401	0.00	0.42	**0.047**
Model 2[a]	0.13	0.456	0.03	0.22	**<0.001**	NA[Y]					NA[Y]				
Chair stand (rep)															
Model 1	0.97	0.458	0.50	1.44	**<0.001**	0.804	0.358	0.13	1.47	**0.020**	0.858	0.458	0.14	1.58	**0.022**
Model 2[b]	0.74	0.347	0.30	1.17	**<0.001**	0.671	0.298	0.06	1.3	**<0.001**	0.89	0.475	0.30	1.5	**<0.001**

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test; NA, analyses were not applied. Model 1, Unadjusted model; Model 2, analyses adjusted for sex[a] or sex + body mass index[b] for total sample and body mass index[c] for male and female.

*Participants achieving the maximal criteria for CPET; [¥]Best attempt; [Y]Effect of cofounder variables on coefficient <10%.

4.8. Predictive equations for cardiorespiratory fitness

Table 11 shows the main predictors of CRF level for the total sample and for those achieving the maximal criteria in CPET. There were positive associations of the main variables measured with absolute CRF level (all $p<0.05$) and a negative association of smoking with absolute CRF level. However, meeting physical activity recommendations was not associated with absolute CRF level. These results were in line with previous results showed in Tables 6, 7, 8, 9 and 10. All these variables have been used in subsequent absolute CRF level predictive equations analyses.

Thereinafter, multivariate regression models were applied introducing into the model all the predictor variables for CRF level estimation from the formula previously described in the in section 3.3.1.6. of the present methodology (111,167). In this model, basic physical characteristics (sex and age), body composition (BMI and WC), cardiovascular (HR basal), meeting physical activity recommendations (yes or no) and smoking (yes or no) were used. The regression models showed a significant prediction model for the total sample and for those achieving maximal criteria in CPET (both $p<0.001$, $r^2=0.42$ and 0.43, respectively) (Data not shown).

Firstly, Table 12A shows the five best prediction models using basic variables in the total sample and for those achieving maximal criteria in CPET. All models were significant (all $p<0.001$) and provided higher prediction levels (all $r^2\geq0.75$ and Mallow's Cp range from 0.01 to 1.73) than previous CRF estimation models published (111). By means of the best model obtained within the present project´s sample (model 1) and employing basic variables (RMR, 6 minutes walking test and basal HR), **75% of the variability** of the absolute CRF level was explained. A similar trend was observed in the five best models obtained when the total sample for *allset* regression analyses was used instead of only those achieving maximal criteria in CPET (Table 13A) (all $p<0.001$, all $r^2=0.73$ and Mallow's Cp range from 2.05 to 3.73). We called this new formula as "Basic Equation" including only information from basic variables in resting conditions.

Secondly, when the spirometry parameters were added to the previous *allset* regression model to predict absolute CRF level in those achieving maximal criteria in CPET, the overall prediction value of the models were slightly increased (Table 12B). The best five prediction models reported significant predictions of absolute CRF level (all $p<0.001$, r^2 range from 0.76 to 0.77 and Mallow's Cp from 3.31 to 4.81). The best of those models (model 1) included RMR, 6 minutes walking test, basal HR and FEV1, explaining **77%**

of the variability of the absolute CRF level. A similar trend was observed in the five best models obtained when the total sample for *allset* regression analyses was used instead of only those achieving maximal criteria in CPET (Table 13B) (all $p<0.001$, r^2 range from 0.73 to 0.75 and Mallow's Cp from 3.72 to 5.03). We called this new formula as "Extended Equation" including information from basic variables plus spirometry parameters in resting conditions and without including CPET variables.

Finally, the variables of the CPET (HR max and time to exhaustion) were additionally added in the *allset* regression model to prediction absolute CRF level within those achieving maximal criteria in CPET (Table 12C). In the five best models obtained, the higher values of prediction were achieved (all $p<0.001$, r^2 range from 0.86 to 0.87 and Mallow's Cp from 2.50 to 4.10), being the best model (Model 1) able to explain **86% of the variability** of the absolute CRF level. A similar trend was observed in the five best models obtained when the total sample for *allset* regression analyses was used instead of only those achieving maximal criteria in CPET (Table 13C) (all $p<0.001$, all $r^2=0.86$ and Mallow's Cp from -2.29 to -0.85). We called this new formula as "Maximal Equation" including information from basic variables in resting conditions plus spirometry parameters plus variables from CPET.

The best models for each condition were calculated with the following equations reported by each model:

Estimated CRF by **"the Basic Equation":**

VO_{2peak} estimated 1 = -1309.98 + 1.83 * 6 minutes walking test (m) + 1.19 * RMR bioimpedance (kcal/day) + 6.86 * Basal HR (bpm)

Estimated CRF by **"the Extended Equation":**

VO_{2peak} estimated 2 = -1229.31 + 1.47 * 6 minutes walking test (m) + 1.11 * RMR bioimpedance (kcal/day) + 6.02 * Basal HR (bpm) + 116.95 * forced expiratory volume in 1 second (L)

Estimated CRF by **"the Maximal Equation":**

VO_{2peak} estimated 3 = -1427.30 + 1.13 * RMR bioimpedance (kcal/day) + 120.83 * forced expiratory volume in 1 second (L) + 6.67 * Maximum HR in CPET (bpm) + 32.90 * Time to exhaustion in CPET (min)

***The rest of the fifteen best equations developed are in Appendix 14.**

Table 11. Independent predictors of absolute peak oxygen consumption (mil/min).

	Total sample				CPET*			
	B	β	r^2	*p value*	B	β	r^2	*p value*
RMR (kcal/day)	0.834	0.588	0.35	**<0.001**	0.973	0.682	0.47	**<0.001**
6 min walking (m)	2.700	0.465	0.22	**<0.001**	2.385	0.457	0.21	**<0.001**
Weight (kg)	21.198	0.606	0.36	**<0.001**	22.573	0.660	0.43	**<0.001**
Waist circumference (cm)	16.259	0.393	0.15	**<0.001**	16.147	0.401	0.16	**<0.001**
HR basal (bpm)	11.050	0.207	0.04	**0.048**	10.241	0.202	0.04	0.098
Handgrip (kg)	20.050	0.711	0.51	**<0.001**	19.288	0.709	0.50	**<0.001**
Chair stand (rep)	107.63	0.492	0.24	**<0.001**	89.160	0.432	0.19	**<0.001**
FEV1 (L)	323.96	0.463	0.21	**<0.001**	418.59	0.555	0.31	**<0.001**
Smoking (yes, no)	-93.73	-0.185	0.18	**<0.001**	-94.65	-0.176	0.12	**0.039**
Meeting PA recommendations (yes, no)	235.45	0.222	0.05	0.055	162.35	0.162	0.03	0.232
HR max (bpm)	12.456	0.503	0.25	**<0.001**	12.417	0.474	0.22	**<0.001**
Time to exhaustion (min)	66.334	0.526	0.28	**<0.001**	60.691	0.455	0.21	**<0.001**

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CPET, cardiopulmonary exercise test; FEV1, forced expiratory volume in 1 second; HR, heart rate; PA, physical activity; r^2, adjusted R-squared; RMR, resting metabolic rate. *Participants achieving the maximal criteria for CPET.

Table 12A. Multivariate linear regression models predicting absolute peak oxygen consumption (mil/min) in maximal CPET* using body composition, PA recommendations, field test and basal parameters.

Coefficients	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
R^2		0.769		0.771		0.771		0.770		0.770
R^2 adjusted		0.754		0.752		0.752		0.751		0.751
Cp		0.006		1.458		1.577		1.717		1.726
AIC		737.76		739.11		739.25		739.41		739.43
BIC		745.64		748.96		749.10		749.27		749.28
p value for model		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Variables	**β**	***p value***	**β**	***p value***	**β**	***p value***	**β**	***p value***	**β**	***p value***
RMR (kcal/day)[a]	0.715	**<0.001**	0.590	**0.001**	0.710	**<0.001**	0.753	**<0.001**	0.698	**<0.001**
6 min walking (m)	0.351	**<0.001**	0.378	**<0.001**	0.330	**<0.001**	0.331	**<0.001**	0.288	**<0.001**
HR basal (bpm)	0.136	**0.036**	0.132	**0.042**	0.136	**0.038**	0.139	**0.033**	0.168	**0.019**
Weight (kg)	--	--	0.135	0.408	--	--	--	--	--	--
Chair stand (rep)	--	--	--	--	0.038	0.654	--	--	--	--
Waist circumference (cm)	--	--	--	--	--	--	-0.051	0.620	--	--
PA recommendations, (yes, non meeting)	--	--	--	--	--	--	--	--	0.052	0.461

Statically significant values are shown in bold. AIC means Akaike information criterion; BIC, Bayesian information criterion; β, standardized coefficient; Cp, Mallow's Cp; CPE, cardiopulmonary exercise; FEV1, forced expiratory volume in 1 second; HR, heart rate; PA, physical activity; RMR, resting metabolic rate. Assessed by [a]bioimpedance analysis. Model 1 includes RMR, 6 min walking and HR basal; Model 2, model 1+ weight; Model 3, model 1 + chair stand; Model 4, model 1 + waist circumference; Model 5, model 1 + PA recommendations.
*Participants achieving the maximal criteria for CPET.

Table 12B. Multivariate linear regression models predicting absolute peak oxygen consumption (mil/min) in maximal CPET* using body composition, PA recommendations, field test, basal and spirometry parameters.

Coefficients	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
R^2		0.784		0.792		0.798		0.787		0.777
R^2 adjusted		0.766		0.769		0.771		0.764		0.758
Cp		3.314		3.701		4.433		4.726		4.813
AIC		723.26		723.37		723.84		724.58		724.95
BIC		733.01		735.08		737.50		736.28		734.70
p value for model		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Variables	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**
RMR (kcal/day)[a]	0.664	**<0.001**	0.411	**0.031**	0.397	**0.037**	--	--	--	--
6 min walking (m)	0.266	**<0.001**	0.316	**<0.001**	0.294	**<0.001**	0.307	**0.001**	0.390	**<0.001**
HR basal (bpm)	0.117	0.071	0.115	0.073	0.120	0.061	0.121	0.066	0.119	0.071
Weight (kg)	--	--	0.254	0.149	0.383	0.073	0.530	**<0.001**	0.610	**<0.001**
Waist circumference (cm)	--	--	--	--	-0.14	0.277	--	--	--	--
FEV1 (L)	0.155	**0.039**	0.188	**0.017**	0.179	**0.023**	0.170	**0.003**	0.256	**0.001**
Handgrip (kg)[b]	--	--	--	--	--	--	0.226	0.087	--	--

Statically significant values are shown in bold. AIC means Akaike information criterion; BIC, Bayesian information criterion; β, standardized coefficient; Cp, Mallow's Cp; CPE, cardiopulmonary exercise; FEV1, forced expiratory volume in 1 second; HR, heart rate; RMR, resting metabolic rate. Assessed by [a]bioimpedance analysis and [b]sum of the best attempt each arm. Model 1 includes RMR, 6 min walking, HR basal and FEV1; Model 2, model 1 + weight; Model 3, model 2 + waist circumference; Model 4, 6 min walking, HR basal, weight, FEV1 and handgrip; Model 5, 6 min walking, HR basal, weight and FEV1. *Participants achieving the maximal criteria for CPET.

Table 12C. Multivariate linear regression models predicting absolute peak oxygen consumption (mil/min) in maximal CPET* using body composition, PA recommendations, field test, basal, spirometry and incremental test parameters.

Coefficients	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
R^2		0.874		0.879		0.879		0.884		0.887
R^2 adjusted		0.864		0.866		0.866		0.868		0.869
Cp		2.504		2.774		2.918		3.157		4.104
AIC		695.14		695.08		695.26		695.08		695.73
BIC		704.90		706.79		706.96		708.74		711.34
p value for model		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Variables	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**
RMR (kcal/day)[a]	0.675	**<0.001**	0.670	**<0.001**	0.476	**0.001**	0.472	**0.001**	0.411	**0.008**
HR basal (bpm)	--	--	0.036	0.508	--	--	0.035	0.513	0.078	0.171
Weight (kg)	--	--	--	--	0.201	0.123	0.200	0.126	0.250	0.076
PA recommendations (yes, non meeting)	--	--	--	--	--	--	--	--	0.070	0.192
FEV1 (L)	0.160	**0.005**	0.161	**0.005**	0.196	**0.001**	0.197	**0.001**	0.194	**0.002**
HR max (bpm)	0.247	**<0.001**	0.231	**<0.001**	0.239	**<0.001**	0.223	**<0.001**	0.206	**0.002**
Time to exhaustion (min)	0.236	**<0.001**	0.247	**<0.001**	0.267	**<0.001**	0.278	**<0.001**	0.273	**<0.001**

Statically significant values are shown in bold. AIC means Akaike information criterion; BIC, Bayesian information criterion; β, standardized coefficient; Cp, Mallow's Cp; CPE, cardiopulmonary exercise; FEV1, forced expiratory volume in 1 second; HR, heart rate; PA, physical activity; RMR, resting metabolic rate. Assessed by [a]bioimpedance analysis. Model 1 includes RMR, FEV1, HR max and time to exhaustion; Model 2, model 1 + HR basal; Model 3, model 1 + weight; Model 4, Model 3 + HR basal; Model 5, Model 4 + PA recommendations.
*Participants achieving the maximal criteria for CPET.

Table 13A. Multivariate linear regression models predicting absolute peak oxygen consumption (mil/min) in total sample using body composition, PA recommendations, field test and basal parameters.

Coefficients	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
R^2		0.743		0.750		0.745		0.745		0.744
R^2 adjusted		0.731		0.734		0.728		0.728		0.728
Cp		2.046		2.429		3.623		3.647		3.733
AIC		921.02		921.22		922.55		922.58		922.67
BIC		929.78		932.16		933.50		933.53		933.62
p value for model		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Variables	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**
RMR (kcal/day)[a]	0.664	**<0.001**	0.681	**<0.001**	0.649	**<0.001**	0.574	**<0.001**	0.636	**<0.001**
6 min walking (m)	0.340	**<0.001**	0.293	**<0.001**	0.347	**<0.001**	0.286	**<0.001**	0.309	**<0.001**
HR basal (bpm)	0.098	0.118	0.088	0.135	0.097	0.124	0.108	0.091	0.132	0.063
Chair stand (rep)	--	--	0.093	0.202	--	--	--	--	--	--
Waist circumference (cm)	--	--	--	--	0.02	0.832	--	--	--	--
Handgrip (kg)[b]	--	--	--	--	--	--	0.141	0.194	--	--
PA recommendations (yes, non meeting)	--	--	--	--	--	--	--	--	0.017	0.807

Statically significant values are shown in bold. AIC means Akaike information criterion; BIC, Bayesian information criterion; β, standardized coefficient; Cp, Mallow's Cp; CPE, cardiopulmonary exercise; FEV1, forced expiratory volume in 1 second; HR, heart rate; PA, physical activity; RMR, resting metabolic rate. Assessed by [a]bioimpedance analysis and [b]sum of the best attempt each arm. Model 1 includes RMR, 6 min walking and HR basal; Model 2, model 1+ chair stand; Model 3, model 1 + waist circumference; Model 4, model 1 + handgrip Model 5, model 1 + PA recommendations.

Table 13B. Multivariate linear regression models predicting absolute peak oxygen consumption (mil/min) in total sample using body composition, PA recommendations, field test, basal and spirometry parameters.

Coefficients	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
R^2		0.750		0.757		0.771		0.762		0.778
R^2 adjusted		0.733		0.736		0.743		0.737		0.747
Cp		3.715		4.160		4.682		4.973		5.025
AIC		908.24		908.49		908.41		909.13		908.38
BIC		919.11		921.54		925.81		924.35		927.95
p value for model		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Variables	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**
RMR (kcal/day)[a]	0.615	**<0.001**	0.645	**0.001**	0.627	**<0.001**	0.646	**<0.001**	0.642	**<0.001**
6 min walking (m)	0.281	**<0.001**	0.246	**<0.001**	0.290	**<0.001**	0.280	**<0.001**	0.251	**0.001**
HR basal (bpm)	0.094	0.133	0.082	0.168	0.056	0.386	--	--	0.056	0.379
Weight (kg)	--	--	--	--	--	--	--	--	--	--
Chair stand (rep)	--	--	0.085	0.245	--	--	--	--	0.090	0.221
FEV1 (L)	0.174	**0.009**	0.126	**0.045**	0.153	**0.018**	0.152	**0.019**	0.118	0.063
Handgrip (kg)[b]	--	--	--	--	--	--	--	--	--	--
Smoking (yes, non meeting)	--	--	--	--	0.134	**0.048**	0.153	**0.022**	0.100	0.120

Statically significant values are shown in bold. AIC means Akaike information criterion; BIC, Bayesian information criterion; β, standardized coefficient; Cp, Mallow's Cp; CPE, cardiopulmonary exercise; FEV1, forced expiratory volume in 1 second; HR, heart rate; RMR, resting metabolic rate. Assessed by [a]bioimpedance anaysis and [b]sum of the best attempt each arm. Model 1 includes RMR, 6 min walking, HR basal and FEV1; Model 2, model 1 + chair stand; Model 3, model 1 + smoking; Model 4, RMR, 6 min walking, FEV1 and smoking; Model 5, Model 3 + chair stand.

Table 13C. Multivariate linear regression models predicting absolute peak oxygen consumption (mil/min) in total sample using body composition, PA recommendations, field test, basal, spirometry and incremental test parameters.

Coefficients	**Model 1**		**Model 2**		**Model 3**		**Model 4**		**Model 5**	
R^2		0.869		0.863		0.872		0.871		0.866
R^2 adjusted		0.860		0.856		0.861		0.860		0.857
Cp		-2.294		-1.757		-1.349		-1.196		-0.855
AIC		866.15		867.21		866.84		867.03		867.90
BIC		877.02		875.90		879.88		880.08		878.77
p value for model		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**
Variables	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**	**β**	**p value**
RMR (kcal/day)[a]	0.649	**<0.001**	0.693	**<0.001**	0.678	**<0.001**	0.641	**<0.001**	0.708	**<0.001**
HR basal (bpm)	--	--	--	--	--	--	0.040	0.415	--	--
Weight (kg)	--	--	--	--	--	--	--	--	--	--
Chair stand (rep)	--	--	--	--	0.042	0.379	--	--	0.060	0.215
FEV1 (L)	0.139	**0.005**	--	--	0.106	**0.019**	0.138	**0.006**	--	--
HR max (bpm)	0.237	**<0.001**	0.229	**<0.001**	0.271	**<0.001**	0.221	**<0.001**	0.269	**<0.001**
Time to exhaustion (min)	0.295	**<0.001**	0.346	**<0.001**	0.242	**<0.001**	0.310	**<0.001**	0.274	**<0.001**

Statically significant values are shown in bold. AIC means Akaike information criterion; BIC, Bayesian information criterion; β, standardized coefficient; Cp, Mallow's Cp; CPE, cardiopulmonary exercise; FEV1, forced expiratory volume in 1 second; HR, heart rate; RMR, resting metabolic rate. Assessed by [a]bioimpedance analysis and [b]sum of the best attempt each arm. Model 1 includes RMR, FEV1, HR max and time to exhaustion; Model 2, RMR, HR max and time to exhaustion; Model 3, model 1 + chair stand; Model 4, Model 1 + HR basal; Model 5, Model 2 + chair stand.

4.9. Associations of cardiorespiratory fitness level with cognitive function

In the unadjusted linear regression analyses (model 1), both the objectively-measured and estimated CRF levels were positively associated with cognitive function by means of the BNT and COWAT neuropsychological tests in the pooled sample of males and females from those achieving maximal criteria in CPET (Table 14A) (all $p<0.05$). Moreover, after adjusting for confounder variables (model 2), these positive associations remained significant except for a negative association in the third model for estimating the CRF and BNT. Also, after adjusting for confounders appeared a negative association between CRF level (measured and estimated) and TMT test (all $p<0.05$). A similar trend was observed when the total sample was used instead of only those achieving maximal criteria in CPET (Table 14B).

When our estimated regression models were applied in the sample of those non-achieving maximal criteria in CPET (Table 14C) (n=24, 9 males), these models of the estimated absolute CRF remained the significant association with BNT (all $p<0.05$) (Data not shown).

Table 14A. Associations of absolute oxygen consumption (ml/min) and cognitive function in maximal CPET*.

	Mini Mental State Examination			Boston Naming Test			Clock Drawing Test			Rey Auditory Verbal Learning Test			Trail Making Test			Controlled Oral World Association			Stroop		
	B	β	p value	B	β	p value	B	β	p value	B	β	p value	B	β	p value	B	β	p value	B	β	p value
VO_{2peak} measured (ml/min)																					
Model 1	0.0006	0.118	0.339	0.0018	0.359	**0.003**	0.0003	0.080	0.518	-0.0007	-0.113	0.360	-0.0447	-0.227	0.067	0.0081	0.272	**0.025**	0.0001	0.006	0.962
Model 2	-0.0005	-0.011	0.081	0.0049	0.099	**<0.001**	-0.0002	-0.047	0.372	-0.0004	-0.064	0.056	-0.0437	-0.222	**<0.001**	0.0053	0.177	**<0.001**	0.0007	0.049	0.335
VO_{2peak} estimated 1 (ml/min)																					
Model 1	0.0008	0.144	0.241	0.0029	0.492	**<0.001**	0.0009	0.189	0.123	-0.0010	-0.151	0.219	-0.0435	-0.192	0.122	0.0111	0.323	**0.007**	0.0014	0.086	0.493
Model 2	0.0001	0.025	0.080	0.0018	0.305	**<0.001**	0.0005	0.100	0.359	-0.0009	-0.138	0.051	-0.0268	-0.119	**<0.001**	0.0084	0.245	**<0.001**	0.0056	0.336	0.173
VO_{2peak} estimated 2 (ml/min)																					
Model 1	0.0008	0.147	0.238	0.0028	0.490	**<0.001**	0.0007	0.160	0.200	-0.0008	-0.120	0.337	-0.0470	-0.212	0.093	0.0118	0.348	**0.004**	0.0009	0.054	0.670
Model 2	-0.0001	-0.021	0.093	0.0012	0.204	**<0.001**	-0.0002	-0.038	0.332	-0.0004	-0.065	0.088	-0.0249	-0.112	**<0.001**	0.0080	0.236	**<0.001**	0.0041	0.247	0.260
VO_{2peak} estimated 3 (ml/min)																					
Model 1	0.0006	0.116	0.354	0.0019	0.348	**0.004**	0.0005	0.114	0.362	-0.0006	-0.095	0.448	-0.0481	-0.229	0.069	0.0102	0.318	**0.009**	0.0004	0.025	0.847
Model 2	-0.0002	-0.043	0.091	-0.0003	-0.061	**<0.001**	-0.0004	-0.088	0.316	0.0001	0.011	0.091	-0.0428	-0.204	**<0.001**	0.0069	0.214	**<0.001**	0.0015	0.095	0.331

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test. Model 1, unadjusted model; Model 2, analyses adjusted for sex, age and education level. VO_{2peak} measured has been obtained by indirect calorimetry, VO_{2peak} estimated have been obtained of the best models of each condition (1, Basic Equation; 2, Extended Equation; 3, Maximal Equation).

Table 14B. Associations of absolute oxygen consumption (ml/min) and cognitive function in the total sample instead of only those achieving maximal criteria in CPET.

	Mini Mental State Examination			Boston Naming Test			Clock Drawing Test			Rey Auditory Verbal Learning Test			Trail Making Test			Controlled Oral World Association			Stroop		
	B	β	p value	B	β	p value	B	β	p value	B	β	p value	B	β	p value	B	β	p value	B	β	p value
VO_{2peak} measured (ml/min)																					
Model 1	0.2547	0.056	0.599	0.0016	0.348	**<0.001**	0.0002	0.046	0.663	-0.0007	-0.120	0.255	-0.0380	-0.196	0.064	0.0077	0.276	**0.008**	-0.0004	-0.028	0.793
Model 2	-0.0003	-0.072	0.211	0.0001	0.026	**<0.001**	-0.0006	-0.158	0.367	-0.0002	-0.030	0.061	-0.0466	-0.240	**<0.001**	0.0046	0.165	**<0.001**	0.0010	0.070	0.364
VO_{2peak} estimated 1 (ml/min)																					
Model 1	0.0005	0.104	0.322	0.0025	0.453	**<0.001**	0.0008	0.157	0.134	-0.0012	-0.191	0.069	-0.0276	-0.122	0.253	0.0087	0.266	**0.010**	0.0011	0.070	0.514
Model 2	0.0003	0.063	0.219	0.0014	0.258	**<0.001**	0.0003	0.073	0.461	-0.0010	-0.160	**0.048**	-0.0261	-0.116	**0.002**	0.0049	0.150	**<0.001**	0.0064	0.389	0.122
VO_{2peak} estimated 2 (ml/min)																					
Model 1	0.0005	0.106	0.320	0.0026	0.470	**<0.001**	0.0006	0.137	0.199	-0.0011	-0.165	0.120	-0.0346	-0.153	0.154	0.0099	0.300	**0.004**	0.0011	0.068	0.531
Model 2	-0.0001	-0.011	0.237	0.0010	0.190	**<0.001**	-0.0003	-0.066	0.470	-0.0007	-0.115	0.068	-0.0279	-0.124	**0.002**	0.0044	0.133	**<0.001**	0.0067	0.410	0.133
VO_{2peak} estimated 3 (ml/min)																					
Model 1	0.0003	0.063	0.554	0.0019	0.382	**<0.001**	0.0004	0.104	0.329	-0.0007	-0.115	0.280	-0.0434	-0.212	**0.048**	0.0092	0.308	**0.003**	0.0006	0.041	0.707
Model 2	-0.0003	-0.074	0.224	0.0001	0.018	**<0.001**	-0.0004	-0.096	0.447	0.0002	0.035	0.075	-0.0579	-0.283	**<0.001**	0.0058	0.197	**<0.001**	0.0034	0.231	0.257

Statically significant values are shown in bold. B means regression coefficient; β, standardized coefficient; CI, confidence interval; CPET, cardiopulmonary exercise test. Model 1, unadjusted model; Model 2, analyses adjusted for sex, age and education level. VO_{2peak} measured has been obtained by indirect calorimetry, VO_{2peak} estimated have been obtained of the best models of each condition (1, Basic Equation; 2, Extended Equation; 3, Maximal Equation).

DISCUSSION

5. DISCUSSION

The present Doctoral Thesis aims to analyse the physiological, metabolic and cardiovascular determinants of the CRF and to develop new specific equations to predict CRF in older adults. Additionally, this thesis aimed to study the associations of CRF, both objectively-measured and estimated using new equations, with cognitive function in this population. In general, older males showed better values in anthropometric variables, resting cardiovascular and spirometry parameters, language and fluency than older females. Similarly, during exercise older males had higher values of parameters of the CPET (including VO_{2peak}) and better performance in physical fitness tests than older females.

Moreover, those older adults with better body composition profile, cardiovascular and metabolic parameters at resting conditions, spirometry parameters and physical fitness tests showed better absolute and relative CRF levels. The findings indicated that body composition, resting cardiovascular and metabolic parameters, spirometry values and physical fitness performance were determinant factors of CRF level. Based on these results, fifteen equations of high prediction values for estimating CRF have been reported. Ours results indicate that higher objectively-measured and estimated CRF were associated with better performance on several cognitive dimensions (i.e. language, cognitive flexibility and fluency).

5.1. Physiological, metabolic and cardiovascular characteristics of the sample and differences between sexes

It is well known that males have higher weight, height, FFM, FFMI and waist circumference values than females (191–194). Our results are in line with previous studies (191–194), showing sex differences in body composition, except to BMI and hip circumference. As expected, females had higher FM and FMI values, although males have higher waist circumference values, since they tend to accumulate more abdominal fat (191,192). A biochemical mechanism that could explain these anthropometrics differences is the major level of testosterone in males (192), a hormone that plays an important role on body composition (195), particularly, by preventing the muscle mass loss with ageing and related disorders such as sarcopenia (195,196).

Among males and females from this sample, the blood pressure values observed are above the recommendations (120/80 mmHg), but slightly below the hypertension cut-off point established in 140/90 mmHg for SBP and DBP, respectively (197). However, more than half of the participants are diagnosed with hypertension, that is 57 and 59

percent of males and females, respectively. The results do not show sex differences for MAP, SBP and DBP values, which is consistent with findings previously reported by Kritz-Silverstein et al. (198). A similar trend was observed in other resting cardiovascular parameters, such as basal HR, DP and SBP/DBP ratio. This could be due to the similar prevalence of participants diagnosed with hypertension, similar age and similar BMI values.

Regarding pulmonary function, evaluated by means of spirometry test, females showed lower values in spirometry parameters than males. These findings are in agreement with reference data for spirometry across all ages (199–201) and the differences between sexes in body composition (i.e. Height and FFM) and lung size justify these results (201,202).In addition, total energy expenditure measured with both, by indirect calorimetry and bioimpedance analyses, was higher in males compared with females. These results are in accordance with previous literature (203,204) and can be explained by physical characteristics, as well as differences in the weight, height, FM or FFM (205,206).

On the other hand, CRF is considered an indicator of the oxygen transport capacity of the body, pulmonary gas exchange, peripheral circulation, muscle oxygen extraction, and migration of oxygen to mitochondria, being one of the physiological determinants for which males have higher physical fitness than females (73,207). This international thesis is focused on CRF level, therefore, the correct interpretation of its results imply to consider that one of the inclusion criteria was that participants could not be involved in supervised physical exercise programs. The CRF levels of our sample are in line with the reference standards by age and sex from the FRIEND Cohort (119), although these are below previously published reference values (117,118).

In the present thesis, the maximum HR during CPET was similar in both sexes, however, males reached higher RER values than females. These results may be explained by the greater tolerance that males could have to sports in this population and the higher background of physical activity during adulthood (208–210). However, when only participants who achieved the maximal criteria during CPET are considered, no differences in maximum HR and RER achieved between sexes are found.

The performance on physical fitness field tests showed higher CRF levels (measured by 6 minutes walking test) and muscle strength (measured by chair stand and handgrip test) in males compared to females. The mean values obtained for CRF and muscle strength tests, in both males and females, (6 minutes walking test and chair stand) are slightly below the mean values for this age group (211), however, the handgrip mean

values are in the 50th percentile by age and sex group (212). As previously explained, these results could be related to the greater capacity and size of the lung along with the higher levels of muscle mass reported in males (195,213).

Furthermore, testosterone is a critical hormone for maintaining physical function (195). According with previous studies (213,214), this could be one of the biochemical mechanisms explaining the higher RMR, muscle strength and CRF levels for males compared to females in the total sample and the pooled sample (males and females) of those achieving maximal criteria in CPET. Previous studies have also explained this differences are partially due to the highest behavioural physical activity levels generally reported in males (208–210). Moreover, a higher pulmonary capacity and lung volume is a physiological characteristic reported in males compared to females (215,216), which is directly related with CRF levels (207).

Regarding central and peripheral oxygenation, our results showed higher resting thigh-TOI in females compared to males. Unfortunately, the detailed mechanisms for the difference in SmO2 are unclear (217). Contradictory findings have been previusly published (217–219), thus, Takagi et al. (217) found that older females had higher oxygenation of the vastus lateralis than males during an incremental test, but not under resting conditions. However, other studies analysing oxygenation of the thigh in adults did not found differences between sexes (218,219). Differences in age group, body composition and methodological procedures could explain the disagreement among studies.

Our results did not found sex differences among the cognitive domains assessed, except for language and fluency, where males obtained higher scores than females. These findings are in line with previous studies, where males aged 65 or older obtained higher scores in language domain than female (220,221). Nevertheless, these differences in fluency and language have not been observed during adulthood (222). Previous studies have also showed differences on intelligence quotient and white matter between sexes, but no consensus about the mechanisms that could explains these differences has been stablished (220,221). Ucak et al. (223) described higher testosterone levels associated with better cognitive function, and therefore it could be a potential biochemical mechanism explaining the differences in cognitive performance between sexes. Unfortunately, as testosterone levels have not been assessed in this thesis, future studies should confirm this hypothesis.

5.2. Associations of physiological, metabolic, cardiovascular and pulmonary parameters with cardiorespiratory fitness

Previous studies have analysed the determinant factors of CRF in adults (20,31), but the evidence on this topic for older adults is scarce. For this reason, we have analysed the traditional parameters determining CRF level in older adults such as sex, age, body composition, cardiovascular and metabolic parameters, physical activity level, among others (72,73). Moreover, the association of less common parameters (educational level, smoking, alcohol consumption, drug intake, among others) have been verified, as well as its possible confounding effects.

5.2.1. Body composition

The prevalence of normal weight, overweight and obesity among our sample of older adults was 18, 51 and 31, respectively, according with standard thresholds for BMI (224,225). This distribution of prevalence by body weight categories should be considered when analysing the association of body composition with relative CRF level in the total sample achieving maximal criteria in CPET and/or segmented by sexes.

Findings show that males and females with better values of BMI, FM and FMI have lower relative CRF. These results are in accordance with previous studies carried out in pre-schoolers, children, adolescents, and adults (52,53,61,63,226). The effect of CRF on fat mass is well known, since CRF is one of the main predictors of fat oxidation (227). However, few studies explain the effect of body fat on CRF (61). Moreover, it has been observed that both high basal body weight and BMI were associated with lower levels of moderate to vigorous and vigorous physical activity in the future (228). This aspect is interesting since decreases in levels of physical activity over the years are accompanied by reductions on CRF (229).

In line with previous studies with children and adults (62–64) higher FFM or FFMI were associated with better relative CRF in the pooled sample of males and females of those achieving maximal criteria in CPET in unadjusted analyses. However, adjusted for age and sex, the sense of association was reversed in both cases with our sample. We have observed the same trend in the association between the FFM and absolute CRF with total sample who achieved maximal criteria in CPET and segmented by sexes.

Conversely, the opposite trend occurs with males and females with higher values of BMI, FM, FMI and waist circumference, showing better values of absolute CRF. Kongkiattikul et al. (230) analysed the relationship between obesity and respiratory functionality in children and adolescents, concluding that children who presented excess adiposity,

showed a decrease in lung functional residual capacity. This decrease in residual capacity could be explained by a decrease in the expiratory reserve volume due to the deposition of fat in the chest wall and the displacement of the diaphragm (231). The decrease in this parameter causes negative effects on the respiratory system, such as an increase in pulmonary vascular resistance and a worsening of pulmonary compliance and alveolar ventilation (232), which clearly has a negative impact on CRF (233), which may explain the higher oxygen consumption at rest in older adults with a higher level of adiposity.

Laukkanen et al. (73) analysed the determinants of CRF in adults and they observed a strong direct association between body weight and absolute CRF, and conversely, a strong inverse association between WHR and absolute CRF. Because of the lack of studies of this nature in older adults, it is difficult to directly compare our results with other studies (234). The VO_{2peak} or CRF are used interchangeably, as previously mentioned, and it explains the ability to capture oxygen from the air, which can be used by the organism, representing the integrated capacity of the pulmonary, cardiovascular and muscle systems to take up, transport and utilize oxygen (235), satisfying muscular systems to supply oxygen during sustained physical activity (40). Therefore, in studies with children and adults, it is reasonable that those with higher FFM have higher absolute and relative CRF (62–64), however, this did not occur in our sample with older adults. Thus, future studies on CRF should show the absolute values together with the strategy used for the analyses (234).

5.2.2. Resting cardiovascular parameters

Extensive scientific evidence have shown the association of CRF with resting cardiovascular parameters (57,143,198,236–240), however, the opposite effect are not clearly studied. When we have analysed the associations of resting cardiovascular parameters with CRF, we have observed significant association in all the MBP, SBP, DBP, basal HR, DP and SBP / DBP ratio with the absolute and relative CRF in the pooled sample of males y females and in the segmented sample. The only exception to the above was the non-association between resting cardiovascular parameters and the absolute CRF in females.

We have not found previous studies that analyse the association between the resting blood pressure parameters and the CRF in older adults. The negative associations that were observed of MBP, SBP, SBP/DBP ratio with absolute and relative CRF in the pooled sample of males y females and in the segmented sample in the present thesis, provided

additional benefits of resting cardiovascular parameters along with the well-known cardiovascular health benefits (54,76,240). .

Previous studies that have analysed the determinants of CRF in adults have found an inverse association between basal HR and CRF (20,31). Our results obtained with older adults are not in concordance with the results obtained from these previous studies with other age ranges. A low HR in resting conditions is a typical adaptation of physical exercise in young people, showing that a high CRF generates a decreased basal HR, for this reason, it is reasonable that those with a lower basal HR have a higher CRF (241,242). One strategies to combat the incidence of these cardiovascular accidents is the implementation of beta blockers as preventive treatment, which produces a significant decrease in HR in resting conditions (243,244), causing the same benefits as a high level of CRF. Therefore, this could affect the results of our analyses.

5.2.3. Resting metabolic rate parameters

This international doctoral thesis has included estimated RMR through bioimpedance analysis and, calculated it by indirect calorimetry in the most stable state of this period of the RMR. Moreover, RER at resting conditions was calculated in this period.

RMR represents the largest contribution to total energy expenditure (60-80%) (245) and it is relatively stable within individuals, variability between individuals is much higher (246). An important part of RMR is determined by FFM, FM and age (247), but, CRF also explains an important part of RMR (248) and people with a higher CRF level have higher RMR (249), therefore, we have considered it an important variable to analyse the association between RMR and CRF.

Our results show a positive association of RMR measured by bioimpedance and indirect calorimetry with absolute and relative CRF in the pooled sample of males y females and in the segmented sample. These results coincide with previous studies with adults where it has been observed how CRF affects RMR (248,249) and even how different training modalities can affect RMR (250).

Obviously, those with higher levels of physical activity have higher CRF (72,73). Increases in oxygen consumption after exercise are known and may partially explain the large variability on RMR (249). In addition, those who do more physical exercise have a greater amount of FFM (251), the main metabolically active tissue in our body that contributes significantly RMR (247), although it has also been observed that the association between CRF and RMR is independent of the FFM (249), despite other

physiological processes could justify this association. These physiological processes may include regulation of the sympathetic system (252,253), mitochondrial biogenesis modulated by exercise practice (254,255), endocrine activity (256) or energetic substrate (257,258).

Moreover, our results have showed negative association between RER at resting conditions and CRF. RER is defined as the ratio obtained from VCO_2 produced during our metabolism and the VO_2 intake, and in resting conditions it varies from 0.7 to 1.0, depending mainly on the metabolism of the energy substrate used by our body (259). Previous studies have shown how the practice of physical exercise affects the RER in resting conditions and even physical performance (260–262). Our results do not coincide with a previous study in which Goedecke et al. (261) have not shown association between RER at resting condition and CRF. Therefore, we consider that more studies with this objective are necessary to clarify the results, specifically in older adults.

5.2.4. Resting cerebral and peripherical oxygenation

This international doctoral thesis aimed to analyse the association of central and peripheral oxygenation at resting conditions with CRF. The results showed positive association of both TOI on the frontoparietal area and on the vastus lateralis with the absolute and relative CRF in the pooled sample of males y females and in the segmented sample. The only exception to the above was the inverse association between both central and peripheral TOI and relative CRF.

Ageing is generally accompanied by changes in brain oxygenation at resting condition, though there is considerable variability within the elderly population (79,89). In particular, literature has shown that healthy lifestyle factors, including CRF and physical exercise, which have been shown to be associated with enhanced increases in oxygenation at rest condition of the prefrontal cortex regions in young and older adults (79,263,264). Moreover, previous studies have shown the association between peripheral oxygenation and CRF during exercise (168,173,265).

Our results coincide with previous studies which analyse central oxygenation (79,263,264), with the only exception to the above, in our sample females, which have the opposite tendency. CRF has been positively associated with white matter integrity, cortical thickness, and gray matter volume of the prefrontal area in older adults (266,267), therefore, a greater oxygenation in the frontoparietal area in those older adults with a higher level of CRF could be justified. Although, on the other hand, it would be necessary to clarify the physiological mechanisms shown by the association between

TOI and CRF in older adults. Many of the previous studies comparing younger and older adults have recruited a little sample (268). Differences in the sample, methodological procedures and the unknown physiological mechanisms could explain the disagreement among studies.

Currently, there is a growing body of causal evidence with which to indicate that CRF promotes the brain health as a consequence of the positive effects of aerobic physical activity on cognition and brain function, at the molecular, cellular, systems and behavioural levels (269). Nevertheless, it is necessary to analyse the bidirectionality of this association, to observe if those people with higher central and peripheral oxygenation at rest will also have higher CRF.

5.2.5. Pulmonary function parameters

Given that lung capacity will depend on the requirements for oxygen absorption (164) and respiratory system ability is possibly reduced in the elderly compared to middle-aged and young people (95,105), it has been of special interest for us to analyse the association of spirometry parameters with the CRF in older adults free of lung disease.

Our results showed positive associations of spirometry parameters with absolute and relative CRF to total sample who achieved maximal criteria in in the pooled sample of males y females, the only exception to the above was in the analyses of associations between FEV_1/FVC and absolute CRF. When the sample was segmented by sex, there were significant positive associations of all spirometry components with absolute and relative CRF in males, except to PEF and PEF/Height^2. The only exception to the above analyses that there were significant positive association of FEV_1 with absolute and relative CRF, in addition, there were also significant association of FEV_1/FVC and PEF with relative CRF.

We findings are in accordance with previous studies where these have showed positive associations of some parameters of spirometry test (specially, FEV_1 and FVC) with CRF (60,96,101,105). Some reviews have shown the physiological mechanisms by which the respiratory system can affect CRF. Bye et al. (270) showed that impaired pulmonary capacity could affect breathing during exercise. Amann et al. (271) and Dempsey et al. (272) show how high intensity physical exercise produces increased vasoconstriction mediated by the sympathetic system, which could divert blood flow from peripheral muscles to respiratory muscles. A recent study shows positive associations of different spirometry parameters (i.e. FEV_1) with VO_{2peak}, deducing that the interactions induced

by exercise between the pulmonary and cardiovascular systems could affect the general capacity of the oxygen transport chain (101).

Moreover, previous studies have shown data for FEV_1 and PEF adjusted for height to square, $FEV_1/height^2$ and $PEF/Height^2$ respectively (273), because this has been shown in this study Cohort to be better predictor of the pulmonary function than these spirometry parameters alone (274,275). We have not found studies that analyse the association of these variables with CRF; however, our analyses show the same significant positive association of these variables with absolute and relative CRF. The only exception to the above were when we segment the sample by sex, the significance is lost for most of the analyses of $FEV_1/height^2$ and $PEF/Height^2$, not happening with the traditional spirometry parameters (i.e. FEV_1).

In addition, a powerful limitation of healthy lung function and an important habit which damages pulmonary function is smoking (276). In our study, 63% of males and 32% of females have been smokers during their lives, so it is a variable that can affect our analyses and therefore we have analysed whether this variable is a confounding variable, since scientist shows us this. However, in our statistical checks in the analysis of the association of pulmonary function with CRF, the effect of smoking on the regression coefficient is not sufficient to treat it as such (<10%), so we have not included it as covariate. This could be explained because although they have smoked during their lives, most of the participants had stopped smoking for several years. Moreover, the cut-off point established for healthy pulmonary function is in addition to 70% of the FEV1 / FVC ratio (98,99), and although the values of our sample are close to this value, not all of them exceed said cut-off point. In females, this value is higher than that males, precisely as we have mentioned previously, this could be the reason why the percentage of smokers is much lower than that of males.

On the other hand, another variable that may influence the analysis of the association of pulmonary function with CRF is the BMI, where previous studies have shown that it may have a negative confounding effect (101,277). In our case, the statistical criterion shows this, since the effect on the regression coefficient is higher than 10 and therefore we include it as a covariate in the analyses. We remember that, as we show in the descriptive table, around 80 percent of our sample is over or obese.

Smoking is the most well-known risk factor for a low pulmonary function as well as an accelerated decline (96). Also BMI is a modifiable risk factor for poor pulmonary function (278). Therefore, obviously, smoking and BMI have a significantly impact ageing-related

decline of pulmonary function, which could be affect to oxygen intake (96). Negative correlations between BMI and various spirometry parameters, including FEV1 and FVC, were reported in both cross-sectional and longitudinal studies (279,280). It should be noted that FVC seems to be more affected than FEV1, with the result that the FEV1 / FVC ratio could even increase, so the opposite effect occurs with smoking, therefore, the data The FEV_1/FVC ratio should be viewed with caution. Despite this, as we have mentioned previously, the trend of all the results of the associations of spirometry parameters with absolute and relative CRF are in agreement with those obtained in previous studies with young and older adults (60,96,101,105).

5.2.6. Field tests

Ageing decreases the capacity of skeletal muscle to consume oxygen, as consequence of several factors (i.e. decreased lean mass, reduced muscle capillary density, low endothelial function, and impaired muscle oxidative capacity), being a determinant of oxygen consumption capacity. (25,69). In fact, the declines of lean mass and muscle strength may be affecting CRF measurement (56). In addition, 6 minutes walking test is a tool that has been used to assess the functional capacity in health and geriatric older adults (32,102,286,287) and it is considered as an good alternative to CPET in older adults (286,288). Therefore, we aimed to analyse the associations of muscle strength and 6 minutes walking test with CRF.

We have measured muscle strength using handgrip and chair stand tests. Both tests are widely used to assess muscle strength in older adults (212,289,290). Our results showed a positive association of both muscle strength tests with absolute and relative CRF to total sample who achieved maximal criteria in CPET and when the sample was segmented by sex, except for females in the association between handgrip test and absolute CRF.

The relationship between muscular strength tests and CRF is far less studied (56) and we found few studies that analyses this association with older adults (70). In accordance with the finding of the present doctoral thesis, Oliveira et al. (70) showed a positive association between the quadriceps isokinetic test and CRF. Vaara et al. (56) analysed the relationships between maximal strength tests and CRF in adults, and they found a positive association between CRF with upper strength but not with lower strength.

The age-associated decline in CRF in sedentary individuals could be partially explained by the loss of muscle mass, which is observed with advancing age and affects muscular strength levels (71).

VO_{2peak} mainly determines CRF test performance (291). Previous studies with older adults have shown that VO_2 is determined by cardiac output and arteriovenous oxygen difference (292). A greater arteriovenous oxygen difference has been found to influence VO_2 improvement in older adults and appears to be determined by a higher content of type IIa fibers and increased capillarization in muscle. (292). Strength training has been associated with an increase of type IIa fibers size (293), and also with an improvement of muscle capillarization after 12 weeks (294), which could affect CRF performance. In addition, those with more muscular strength will have greater muscle mass, limiting the amount of glucose assimilated by adipose tissue to store it in the form of triglycerides, an important factor, since that body fat accumulation, and not FFM loss, contributes to the decline in maximal whole body oxygen uptake observed with ageing (295). For this reason, muscular strength affects the peripheral component that determines CRF.

On the other hand, previous studies that have shown positive associations of 6 minutes walking test with absolute and relative CRF (287,296–298), in agreement with the results reported in the present Thesis. Although the 6 minutes test is a tool that has been used to assess the functional capacity in older adults (32,102,286,287). Previous studies (299,300) in which this test has been carried out with a portable gas exchange analyser, have found that most of the elderly people exercise in a predominantly anaerobic metabolism, suggesting that their energy expenditure was close or even maximum. Therefore, we agree with previous studies about that 6 minutes walking test could be a good alternative to assess the CRF in older adults (286,288), when there are no resources to perform a CPET.

5.3. Equations to predict cardiorespiratory fitness in older adults

One of the main objectives of this doctoral thesis was to develop simple and accurate equations to estimate CRF using variables with different levels of complexity and equipment requirements. Three different complexity levels were considered; Level 1) basic variables such as body composition parameters, meeting physical activity recommendations, field tests and basal metabolic and cardiovascular parameters; Level 2) basic variables plus spirometry parameters and Level 3) basic variables, spirometry parameters and simple CPET information.

Fifteen equations (five for each level) have been reported from thousands of models' combination, selecting these with the highest prediction values of CRF in older adults.

To select the best predictor models we have been guided by the r^2 and the Mallows CP, since the first of them by itself is not a good alternative to select the best regression

model, because it does not penalize the use of predictors. If we use a greater number of predictors, r^2 will be higher, although these are not significant, however, it is easily interpretable because it explains the variability of the dependent variable when it is multiplied by one hundred. On the other hand, the Mallows CP addresses the problem of overfitting, penalizing those models that include a higher amount of predictors (294). For this reason, the combinations of both coefficients are a good tool to select the best prediction models.

For the first prediction level, we designed a regression model with non-exercise basic variables with the participants who met the maximal criteria in CPET. Our results were quite accurate to predict CRF in older adults (r^2=0.75 and Mallow's Cp range from 0.01 to 1.73). Furthermore, at the second prediction level, the precision of the models increased when spirometry parameters were considered (r^2 range from 0.76 to 0.77 and Mallow's Cp from 3.31 to 4.81). The same trend was observed at the third prediction level, when we included CPET variables in the models (r^2 range from 0.86 to 0.87 and Mallow's Cp from 2.50 to 4.10).

The precision achieved in ours regression models is higher than other studies with a larger sample size and that have included adults and older adults (110–112). Jackson et al. (111) reported four equations by sex comprised by six measurement to calculate estimated CRF (Age, body fat percentage or BMI, waist circumference, basal HR, smoking and physical activity level) and the range of coefficient r^2 achieved was between 0.56 and 0.60. Similarly, Nes et al. (134) reported two equations with similar accuracy, but they included five predictors to obtain CRF estimated (sex, age, waist circumference, basal HR and PA index). Additionally, previous studies have shown the important variability in the accuracy between the prediction equations models (110,117–119). Therefore, it is noteworthy that, we have obtained a simple equation with non-exercise variables and a higher accurate including only three variables (RMR, 6 minutes walking test and basal HR).

Performing a CPET until exhaustion entails certain physical and health risks, especially for older adults, as well as requires the use high precision and expensive equipment that hamper its implementation in large scale studies and clinical settings (32,54). So that, we have reported different equations with a good prediction rate, which conform to the availability of resources and equipment. Therefore, the prediction models developed will be able to use with non-exercise parameters, which include easily measured parameters and/or including parameters of an incremental test until exhaustion.

De souza et al. (120) compare CRF obtained during a maximal cycle ergometer cardiopulmonary exercise test with CRF estimated using sex and population specific-equations in younger (18 to 35 years), middle-aged (36 to 60 years) and older adults (> 60 years)]. The authors showed that equations provided underestimated VO_{2peak} in younger and overestimated VO_{2peak} in older adults. Some physiologic mechanism to understand these findings could be available. Previous studies have shown specific muscle fibres loss with ageing, occurring mainly in type II fibres, with an increase in type I fibres percentage, contributing to differences in mechanical efficiency observed between younger and older subjects (120). The percentage of type I fibres influences mechanical efficiency during physical activity, changes in fibre type may alter the linear relationship between workload and oxygen consumption (295). In addition, VO_2 at rest was found to be significantly lower in older adults, suggesting that the conventional value of 3.5 mL/kg/min probably overestimates their energy expenditure at rest and is not appropriate for older adults (296). Even though many CRF estimation equations include this parameter, dividing the VO_{2peak} by 3.5 and the CRF in METs is obtained (120), so this could explain the overestimation observed for CRF in older adults in the mentioned study (120).

Equations for predicting VO_{2peak} have previously been used in important studies with large samples in which they have observed that CRF have been associated with a lower risk of hospitalizations (32), incidence of strokes (113) and mortality (114,115). Consequently, the equations presented in this doctoral thesis at different levels and which are adjusted to the equipment and resources available could provide the clinical utility. Although we still do not know if with these new equations developed in this International Doctoral Thesis it will be possible to improve the reliability and overestimation of the current prediction equations of the CRF in older adults.

5.4. Associations of cardiorespiratory fitness and cognitive function in older adults

The final objective of the present doctoral thesis was to examine the association of objectively-measured and estimated CRF with key cognitive domains involved in the prevention of dementia.

Our findings showed that higher levels of measured and estimated CRF are associated with better performance on language, fluency and cognitive flexibility in older adults who achieved maximal criteria in CPET. The same trend was observed for language, fluency

and cognitive flexibility when we replicate the analyses with the entire sample, regardless of whether they achieved the maximal criteria in the CPET.

Similarly, a previous prospective cohort study support the association between higher levels of CRF and greater fluency in noninstitutionalized older adults (161). We have shown that CRF is positively associated with cognitive flexibility, in line with Verstynen et al. study (297). To further examined this relationship, the authors (297) concluded that the relationship between CRF and cognitive flexibility might be mediated by the Caudate nucleus volume. The caudate nucleus intervenes and is responsible for selecting the appropriate information in an evaluation of results, so it is involved in learning process (298), hence, it could improve cognitive flexibility. Previous studies have shown CRF are positively associated with the size of basal ganglia, subcortical region that includes the caudate nucleus (299,300). Although previous cross-sectional studies suggest that age-related caudate nucleus volume loss can be mitigated by exercise (297). Erickson et al. (301) showed that a randomized aerobic exercise intervention during one year failed to increase caudate nucleus volume.

Ours results did not find an association of CRF with the screening, memory, inhibition and processing speed. In the same line Dougherty et al. (128) did not observe a relation between CRF and memory function. However, in contrast to ours results, a recent systematic review that included 15 cross-sectional studies showed a positive association between CRF and memory function in older adults (123). The lack of agreement between this result and our findings could be explained by the different CRF and cognitive performance tests applied, and characteristics of the study sample.

The aforementioned previous studies that have analysed the relationship between CRF and cognitive function or risk of dementia have performed a CPET to obtain VO_{2peak}, however, we have not found cross-sectional studies analysing the association of estimated CRF with the cognitive domains included in this thesis, which hampers the comparison. Nevertheless, Tari et al. (133) used estimated CRF to analyse the risk of dementia, dementia-related mortality, time of onset dementia, and longevity. They concluded that changes in estimated CRF is an independent risk factor for dementia incidence and mortality, and highlighted that maintaining or improving CRF over time may be a target for reducing the risk of dementia incidence and mortality (133).

Keeping the ageing population fit for longer could have huge positive public health and economic implications (106). Pedersen et al. (302) showed the association of CRF with at least 26 chronic diseases, including dementia, which has a significant economic impact

on world gross domestic product (19). Hence, to improve CRF could potentially be a key preventive strategy to avoid complex multi-morbidity (133) and specifically, dementia like the main non-communicable disorder in older adults. Therefore, physical activity recommendations should focus on activities with intensities that are proven to be effective in enhancing CRF (106). Literature suggests that systemic neurotrophic factors are induced by exercise and that these circulating biomolecules may cross the blood-brain barrier and be important in protecting against neurodegenerative disorders, such as dementia (124). Therefore, exercise has shown a protective effect on brain function (122,123), might be related to better cognition and reduced risk of AD (123). Finally, the CRF prediction equations could be useful to detect low CRF levels early, in those at risk of dementia, as shown by Tari et al. (133).

5.6. Limitations

Findings included in the current International Doctoral Thesis have some limitations that should be taken into consideration when interpreting their results. Firstly, this study included only older adults between 65 and 75 years, the homogeneity in age limits the generalizability of these results to other ages among older adults. Moreover, the cross-sectional design does not allow us to determine causal links between independent and dependent variables.

Regarding body composition, in this doctoral thesis we have evaluated body composition using bioimpedance analyses, although the gold standard for measuring this is dual energy X-ray absorptimetry (DXA) (303). Previous studies have showed that the bioimpedance analyses may to some extent underestimate or overestimate body composition parameters (304,305), however, the reliability of bioimpedance analyses has also been shown to body composition parameters when DXA has been used as a reference method (303,305) and, because it is a time efficient method for large study samples (56).

On the other hands, to obtain total energy expenditure by indirect calorimetry, the participants did a basal metabolism for 10 minutes, however, the recommendations for a correct evaluation of this dimension advise at least between 20 and 30 minutes (138). However, the participants before starting the test, were between 5 and 10 minutes on the bed, for the analyses the first 2 minutes of the assessment were deleted, and a consecutive or non-consecutive 5-minutes stable period with a coefficient of variation lower than 20% for VO2 and VCO2 was selected.

Despite of the age, the heterogeneity in physical fitness and sedentary levels of participants, in the present thesis we performed CPET on a treadmill. Other authors in studies with a similar sample and characteristics, used a cycle ergometer to obtain CRF level (35,306), since participants could be more controlled and there are fewer risks (ie. Falls). However, one of the most common activities for all those included in this study was walking, therefore, in order to transfer this activity from its daily widow to the evaluation processes, we decided to use a treadmill to evaluate the CRF level. Moreover, regarding the protocol used for the incremental CPET, there is a lot of heterogeneity and many authors have used the balke protocol with similar samples (307–309), however, in the present study we used the modified Bruce protocol, since it seemed the most appropriate protocol to us, because it has been largely used and is designed with geriatric population (161,162).

Another limitation of this doctoral thesis is the evaluation of spirometry parameters. Normally, for the diagnosis and management of pulmonary conditions function, a specific spirometer is used (310), however, in the present study uses the Jaeger MasterScreen CPX® (CareFusion, San Diego, USA). Therefore, we always did it within the same conditions, the same mask and according to the SEPAR normative (99).

Regarding the NIRS evaluation, the channel on the vastus lateralis can reflect oxygenation only in a part of the muscle, it cannot represent tissue oxygenation in the whole muscle. Therefore, although it helps us to have a peripheral oxygenation index, to evaluate spatially heterogeneous oxygenation in muscle tissue, it would be necessary to use a multi-channel NIRS equipment (311). Moreover, a previous study reported that older adults showed lower skeletal muscle oxygenation as measured by NIRS compared to young adults (312). Ageing degenerates skeletal muscle metabolism (313), so it could be explained for this. However, in the present doctoral thesis, we do not compare adults with older adults, and the older adults included have homogeneous ages. Therefore, NIRS has been largely used with older adults at resting condition (79,264,306) and during exercise (168,173,265).

The consistency of the procedure, conditions and familiarization for the 6-minutes walking test is critical for a correct registration (314). In our case, we worked so that the procedure and the conditions were always the same, in addition to the evaluators, they were familiar with both the procedure and the instructions that they should give to the participants. However, in the present doctoral thesis, the participants did not

performed a specific familiarization with the test procedure due to logistical problems and time available of each evaluation. Despite this, the test were carried out individually and an evaluator did the test next to the participant giving the necessary indications for a correct registration of the test.

In this doctoral thesis, we have proposed fifteen equations to predict CRF level, although a limited sample size needs to be acknowledged. Other studies that propose equations to predict CRF in adults, elderly, or both (110–112,134), have a larger sample size, however, the age range for each group is much broader and the sample is more heterogeneous. For this reason, although the sample size is limited, for a given age range in a homogeneous sample, we have managed to report several equations for estimating CRF level with prediction coefficients similar or greater than previous studies (111,134).

Regarding the neuropsychological tests, due to the resources of the present study, there was no neuropsychologist linked to the study during the three waves, therefore the same researcher has not always evaluated the participants. However, the neuropsychologist was trained, familiar with the tests, and in all cases, they had previous experience in neuropsychological evaluations. In addition, in this doctoral thesis seven tests has been used, not all of them are validated in older adults, neither there is cut-off points to categorize the sample, for this reason we have used some of the continuous variables extracted from each test to describe the test battery and to analyse its associations with CRF level.

CONCLUSIONS

6. CONCLUSIONS

1) The physiological, metabolic and cardiovascular characteristics of older adults were different between males and females. Body composition, total energy expenditure, spirometry parameters and physical fitness components reported more favourable values for older males compared with females. However, the oxygenation indexes (thigh) were better for females at both resting and exercising protocols. Regarding cognitive function, males showed better performance on language and fluency than females.
2) A number of physiological, metabolic and cardiovascular parameters were identified as relevant determinants of CRF. Specifically, body composition, resting cardiovascular and metabolic parameters, spirometry values and physical fitness performance were the main dimensions providing relevant and independent determinants of CRF.
3) Fifteen equations have been developed from thousands of models' combination, selecting these with the highest prediction values for CRF of older adults. Three different complexity levels were considered; Level 1) basic variables such as body composition parameters, meeting physical activity recommendations, field tests and basal metabolic and cardiovascular parameters; Level 2) basic variables plus spirometry parameters; and Level 3) basic variables, spirometry parameters and simple CPET information. The best equation models proposed, from levels 1 and 2, explain 80% of the variability of CRF and, when using maximum HR and time to exhaustion from the CPET (level 3), the best model proposed reach to explain 87% of the variability of CRF.
4) CRF, both objectively-measured and estimated, were associated with better performance on language, fluency and cognitive flexibility independently of sex, age and education level, suggesting that CRF is a protective factor against deterioration of cognitive function associated to ageing in older adults.

6. CONCLUSIONES

1) Las características fisiológicas, metabólicas y cardiovasculares de las mayores fueron diferentes entre hombres y mujeres. La composición corporal, el gasto energético total, los parámetros espirométricos y los componentes de la condición física reportaron valores más favorables para los hombres mayores en comparación con las mujeres. Sin embargo, los índices de oxigenación (muslo) fueron mejores para las mujeres tanto en el protocolo de reposo como en el de ejercicio. En cuanto a la función cognitiva, los hombres mostraron un mejor desempeño en el lenguaje y la fluidez que las mujeres.

2) Se identificaron varios parámetros fisiológicos, metabólicos y cardiovasculares como determinantes relevantes de la CRF. Específicamente, la composición corporal, los parámetros cardiovasculares y metabólicos en reposo, los valores espirométricos y el rendimiento en los test físicos fueron las principales dimensiones que determinaron de forma relevante e independiente la CRF.

3) Se han desarrollado quince ecuaciones a partir de la combinación de miles de modelos, seleccionándolos con los valores de predicción más altos para la CRF en personas mayores. Se consideraron tres niveles de complejidad diferentes; Nivel 1) variables básicas como parámetros de composición corporal, cumplimiento de recomendaciones de actividad física, pruebas de campo y parámetros metabólicos y cardiovasculares en condiciones basales; Nivel 2) variables básicas más parámetros espirométricos; y Nivel 3) variables básicas, parámetros espirométricos e información sencilla de la prueba de esfuerzo. Los mejores modelos de ecuaciones propuestos, a partir de los niveles 1 y 2, explican el 80% de la variabilidad de la CRF y, al utilizar la FC máxima y el tiempo hasta el agotamiento de la prueba de esfuerzo (nivel 3), el mejor modelo propuesto alcanza a explicar el 87% de la variabilidad de CRF.

4) La CRF, tanto objetivamente medida como estimada, se asoció con un mejor desempeño en el lenguaje, la fluidez y la flexibilidad cognitiva independientemente del sexo, la edad y el nivel educativo, lo que sugiere que la CRF es un factor protector contra el deterioro de la función cognitiva asociado al envejecimiento en las personas mayores.

FUTURE RESEARCH DIRECTIONS

7. FUTURE RESEARCH DIRECTIONS

An important dimension involved in the prevention of dementia is the brain structure and function. Therefore, we are specially interested in to analyse the relationships of brain oxygenation, cognitive function, brain structure/function and other markers associated with ageing, since these dimensions have been evaluated in the present Doctoral Thesis has been developed within the context of the EFICCOM/INTERMAE project.

Thus, in order to establish causal relationships, we will analyse the effect of 5-month-intervention of supervised multicomponent exercise on body composition, cardiovascular and metabolic parameters at resting conditions, spirometry parameters and physical fitness components in older adults. Moreover, we will focus in analysing the effect of 5-month-intervention of supervised multicomponent exercise on the brain oxygenation, cognitive function, brain structure/function and other markers of ageing.

Additionally, we will aim to apply the CRF prediction equations developed under this International Doctoral Thesis in two epidemiological projects such as the "InLIFEAGING" currently ongoing, and the international project "LifeAge". In that projects we will analyse the association of the estimated CRF level with different dimensions health involved in the prevention of Alzheimer's disease.

Finally, an important finality for both, my research group and to myself, is the scientific dissemination and transfer of the investigation. During the predoctoral period we have participated in many innovation and transfer activities of various typologies, but betting on other options to bring our research closer to society are necessary. Therefore, different business strategies from the university (*spin off*) or from abroad (*start-ups*) will be studied in the medium and long term.

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9. APPENDICES

Appendix 1: Summary on the EFFICOM study to recruitment for medical staff

Información a dar al paciente:

Querría informarle de la posibilidad de participar en un proyecto de la Universidad de Cádiz en colaboración con el Hospital Puerta del Mar y nuestro centro de salud, dirigido a personas mayores para estudiar como el ejercicio físico puede prevenir el desarrollo de Alzheimer. Para ello, a las personas que participen se les realizará una completa evaluación médica, que incluye resonancia magnética, análisis sanguíneos, cuestionarios cognitivos y pruebas funcionales. Además, por sorteo a la mitad de los participantes se les realizará un control y seguimiento de sus hábitos de vida y la otra mitad realizará un programa de ejercicio físico de 5 meses que comenzaría después de navidad. Aun así, si a usted le tocará el grupo control, una vez terminado todo el estudio se le ofrecería el programa de ejercicio físico. Todas las medidas incluidas, así como el programa de ejercicio son gratuitas para usted, pero tienen un alto coste económico para el sistema.

Si está interesado en participar, tengo que realizarle una serie de preguntas y entregaría sus datos a los investigadores, que contactaran con usted para darle una información más detallada, y ya con esa información usted decidirá si finalmente participa o no. Sin duda, es una oportunidad única que no debería desaprovechar, ya que es difícil encontrar este tipo de oportunidades.

Nota para el personal sanitario: Le agradecemos nuevamente su valiosa colaboración, sin la cual este proyecto no podría llevarse a cabo. En caso de duda o si necesita contactar con el personal investigador, puede contactar con el número 610035133 o mediante el correo electrónico proyecto.eficcom@uca.es

Appendix 2: Inclusion and exclusion criteria EFFICOM Study: First part.

CRITERIOS DE INCLUSIÓN/EXCLUSIÓN PROYECTO EFFICOM. Parte 1.

A rellenar por el personal de atención primaria. Es necesario rellenar una hoja para cada persona a la que se le informa del estudio.

Fecha de Registro:___/___/___
Código Nuhsa del paciente:_____
Centro de atención primaria: _____
Personal de atención primaria que realiza la captación: _____
Fecha de Nacimiento:___/___/___ Edad:

Sexo:

Hombre		Mujer	

A continuación, marque con una X la opción que se corresponda:

CRITERIOS DE INCLUSIÓN	SI	NO
Entre 65 y 75 años de edad		
No presentar alguna enfermedad física que le impida realizar actividad física* * Marcar SI en el caso de NO presentar enfermedad física. En el caso de presentar enfermedad física indique cual:_____		
Capaz de comunicarse sin problemas		
Capaz de leer y entender el consentimiento informado así como el objeto del estudio		

CRITERIOS DE EXCLUSIÓN	SI	NO
Enfermedad aguda o terminal		
Diagnóstico de Alzheimer		
Historia de traumatismo craneoencefálico con pérdida de consciencia		
Historia de infarto cerebral, epilepsia, tumor cerebral		
Enfermedad cardiovascular inestable		
Fractura reciente en extremidad superior o inferior		
Abuso de alcohol y/o consumo habitual de drogas o bomba de infusión de fármacos		
Presencia de marcapasos, desfibrilador.		
Dispositivos intravasculares (stent, Coil, filtro), válvula cardíaca, clip de aneurisma, Neuroestimulador, catéter intravascular con metal o de derivación cardiovascular		

Problemas visuales o auditivos severos, implante en oído medio/interno		
No desea completar el estudio o ser asignado al grupo control		
Está participando en otro estudio de investigación que pueda influir en el presente proyecto.		

CRITERIOS DE EXCLUSIÓN PENDIENTES DE CONFIRMACIÓN	SI	NO
Implantes metálicos en la cabeza, intraocular y/o en estructuras máxilo-faciales, prótesis dental incompatibles con estudios de resonancia magnética		

CAMBIOS EN LA COGNICIÓN					
1) ¿Siente que su memoria está yendo a peor?	No 1	A veces, pero no me preocupa 2	Si, y me preocupa 3	Si y me preocupa seriamente 4	
2) ¿Cómo describiría usted su memoria actualmente?	Muy buena 1	Buena 2	Moderada 3	Mala 4	Muy mala 5
3) Comparada con hace 12 meses ¿Usted diría que su memoria ahora es mejor, la misma o peor que entonces?			Mejor 1	Misma 2	Peor 3
A RELLENAR POR EL PERSONAL INVESTIGADOR. Se considera que los participantes tienen quejas de memoria si contestan 4 o 5 en la 2 pregunta y 3 en la 3ª.			Presenta quejas	NO (0)	SI (1)

Nota: Guarde esta hoja junto con el resto en un sobre y déjelas en recepción de su centro para que pase a recogerla el equipo de investigación el viernes de cada semana.

Si el paciente cumple los criterios de inclusión (todos sí) y los de exclusión (todos no, a excepción de los criterios de exclusión pendientes de confirmación) y está dispuesto a ir a la reunión informativa o conocer telefónicamente más información al respecto, pida permiso para tomar nota de su nombre y teléfono para así poder contactar los investigadores con él/ella.

Nombre:_____-

Teléfono:_____

En caso de no estar interesado en participar (en ese caso no es obligatorio ni nombre ni teléfono), por favor, indique el motivo:

Appendix 3: Inclusion and exclusion criteria EFFICOM Study: Second part.

CRITERIOS DE INCLUSIÓN/EXCLUSIÓN. Parte 2.

A rellenar por el personal investigador.

Nombre y apellidos:

Código paciente: Fecha:

Brazo dominante:

Investigador a continuación marque con una X la opción que se corresponda, según los resultados obtenidos en las diferentes pruebas:

CRITERIOS DE INCLUSIÓN	SI (1)	NO (0)
Diagnóstico de DCL en base a los criterios de Petersen y de la Sociedad Española de Neurología;		
Puntúa ≥5 hombres/8 mujeres en la escala de actividades instrumentales de la vida diaria de Lawton y Brody;		
No realizar ejercicio físico regular >20 minutos y >3 días/semana		
Capaz de leer y entender el consentimiento informado, así como el objeto del estudio		

Índice para actividades instrumentales de la vida diaria de Lawton y Brody

1) A la hora de utilizar el teléfono, usted.	Respuesta
Utiliza el teléfono por iniciativa propia y sin ayuda.....	1
Es capaz de marcar algunos números familiares.....	1
Es capaz de contestar al teléfono, pero no de marcar.....	1
No usa el teléfono.....	0

2) En relación a las compras, usted.	
Realiza todas las compras necesarias sin ayuda.....	1
Realiza independientemente pequeñas compras.....	0
Necesita ir acompañado para realizar cualquier compra.....	0
Completamente incapaz de comprar.....	0

SOLO PARA MUJERES, SI ES HOMBRE PASAR A PREGUNTA 6

3) Respecto a las comidas, usted **(sólo mujeres)**.	
Organiza, prepara y sirve las comidas por si sólo y sin ayuda.	1
Prepara bien las comidas si se le suministran los ingrediente.....	0
Prepara, calienta y sirve la comida, pero no sigue una dieta adecuada	0
Necesita que le preparen y sirvan la comida.	0

4) Respecto a las tareas de la casa, usted **(sólo mujeres)**.	
Cuida la casa sin ayuda, con ayuda ocasional para trabajos pesados...	1
Hace tareas domésticas ligeras, como lavar platos o hacer camas.....	1
Realiza tareas ligeras sin mantener un nivel de limpieza aceptable.....	1
Necesita ayuda con todas las tareas de la casa.....	1

No participa en ninguna tarea doméstica.....	0

5) En relación con la ropa, usted **(sólo mujeres)**.

Lava toda su ropa sin ayuda.....	1
Lava o aclara pequeñas prendas.....	1
Necesita que otro se ocupe de todo el lavado.....	0

6) En relación con el dinero y los asuntos económicos, usted.

No precisa ayuda para manejar dinero y llevar sus cuentas.....	1
Necesita ayuda para ir al banco y en grandes compras.....	1
Incapaz de manejar dinero.....	0

7) Si tiene que tomar algún medicamento, usted.

No precisa ayuda para tomar la dosis a la hora correcta.....	1
La toma si se le prepara con antelación.....	0
No es capaz de responsabilizarse de su propia medicación.	0

8) A la hora de viajar, ya sea en su ciudad o para trasladarse a otras ciudades, usted.

Viaja independientemente en transporte público o conduce su coche..	1
No usa transporte público, salvo taxis.	1
Viaja en transporte público si le acompaña otra persona.....	1
Sólo viaja en taxi o automóvil con ayuda de otros.....	0
No viaja en absoluto.....	0
TOTAL (tener esta puntuación en cuenta para responder a la tabla de criterios de arriba)	

CRITERIOS DE INCLUSIÓN DE ACTIVIDAD FÍSICA	SI (1)	NO (0)
¿Realiza usted actividad física regular durante más de 20 minutos y más de 3 días a la semana? ***Nota: aunque marque si, si en el siguiente marca que no, marcar si en los criterios de inclusión.***		
¿Participa actualmente usted en un programa regular de ejercicio físico supervisado?		

CRITERIOS DE EXCLUSIÓN	SI (1)	NO (0)
Presencia de sintomatología depresiva, evaluado mediante la Geriatric Depression Scale; (puntuación igual o mayor a 5)		

Indique la respuesta que mejor describa cómo se ha sentido la última semana.

1. ¿Está satisfecho con su vida?	SI (0)	NO (1)
2. ¿Ha abandonado muchos de sus intereses y actividades?	SI (1)	NO (0)
3. ¿Siente que su vida está vacía?	SI (1)	NO (0)
4. ¿Se encuentra a menudo aburrido?	SI (1)	NO (0)
5. ¿Está de buen humor la mayor parte del tiempo?	SI (0)	NO (1)
6. ¿Teme que algo malo vaya a ocurrirle?	SI (1)	NO (0)
7. ¿Se siente feliz la mayor parte del tiempo?	SI (0)	NO (1)
8. ¿Se siente impotente con frecuencia?	SI (1)	NO (0)
9. ¿Prefiere quedarse en casa en lugar de salir y hacer otras actividades?	SI (1)	NO (0)
10. ¿Cree que tiene más problemas de memoria que la mayoría de las personas?	SI (1)	NO (0)
11. ¿Le parece maravilloso estar vivo en este momento?	SI (0)	NO (1)
12. ¿Se siente inútil tal como está ahora?	SI (1)	NO (0)
13. ¿Se siente lleno de energía?	SI (0)	NO (1)
14. ¿Siente que su situación es desesperada?	SI (1)	NO (0)
15. ¿Piensa que la mayoría de las personas están mejor que usted?	SI (1)	NO (0)
TOTAL		

CONSUMO DE MEDICAMENTOS

1) A continuación le mostramos una lista de medicamentos. Señale aquellos que haya consumido en las ÚLTIMAS <u>DOS SEMANAS</u>

	SI	NO
1.Medicinas para el catarro, gripe, garganta, bronquios	1	0
2.Medicinas para el dolor	1	0
3.Medicinas para bajar la fiebre	1	0
4.Reconstituyentes como vitaminas, minerales, tónicos	1	0
5.Laxantes	1	0
6.Antibióticos	1	0
7.Tranquilizantes, relajantes, pastillas para dormir	1	0
8.Medicamentos para la alergia	1	0
9.Medicamentos para la diarrea	1	0
10.Medicinas para el reuma	1	0
11.Medicinas para el corazón	1	0
12.Medicinas para la tensión arterial	1	0
13.Medicinas para el estómago y/o las alteraciones digestivas	1	0
14.Antidepresivos	1	0
15.Estimulantes	1	0
16.Píldoras para no quedar embarazada (sólo las mujeres)	1	0
17.Hormonas para la menopausia (sólo las mujeres)	1	0
18.Medicamentos para adelgazar	1	0
19.Medicamentos para bajar el colesterol	1	0
20.Medicamentos para la diabetes	1	0
21.Productos homeopáticos	1	0
22. Productos naturistas	1	0
23. Otros medicamentos	1	0

16.a En caso afirmativo en alguno de ellos, indique exactamente el medicamento consumido, para qué es y la dosis diaria

Medicamento	Para que es	Dosis diaria	Medicamente permanente	
			SI	**NO**
			SI	**NO**
			SI	**NO**
			SI	**NO**

ANTECEDENTES FAMILIARES

¿Tienes o has tenido algún/os familiar/es de Alzhéimer? Indicar parentesco.

Dirección exacta domicilio:

Móvil:

Disponibilidad:

Appendix 4: Information sheet of the EFICCOM Study.

HOJA DE INFORMACIÓN AL PACIENTE

TÍTULO DEL ESTUDIO: EFECTO DEL **E**JERCICIO **FI**SICO SUPERVISADO A NIVEL **C**EREBRAL, **CO**GNITIVO Y **M**ETABOLÓMICO: PROYECTO EFICCOM
INVESTIGADORES PRINCIPALES: Miguel Moya Molina, David Jiménez Pavón, Ana Carbonell Baeza.
CENTRO COORDINADOR: UNIVERSIDAD DE CÁDIZ

INTRODUCCIÓN

Se le invita a participar en un estudio que ha sido aprobado por el Comité Ético de Investigación Clínica de Cádiz.
Por favor, lea esta hoja informativa con atención. El Dr. Miguel Moya le aclarará las dudas que le puedan surgir.

PARTICIPACIÓN VOLUNTARIA

Su participación en este estudio es voluntaria y usted puede anular su decisión y retirar el consentimiento en cualquier momento sin que por ello se altere su relación con el médico ni se produzca perjuicio en su tratamiento o en la atención que usted pueda necesitar.

DESCRIPCIÓN GENERAL DEL ESTUDIO

El objetivo de nuestro proyecto es analizar el efecto de un programa de ejercicio físico de 5 meses de duración sobre la salud de personas mayores con y sin deterioro cognitivo leve.

Para ello, estudiaremos dos grupos de sujetos: un grupo realizará los ejercicios y el otro grupo no y que servirá como grupo de control. El que usted esté en uno u otro grupo se decidirá al azar.

Evaluaremos su estado general y mental, su sangre y líquido cefalorraquídeo y su cerebro tanto si usted resulta asignado al grupo del ejercicio físico como al grupo de control:

Análisis de sangre: tomaremos tres muestras de sangre: una al principio del estudio, otra después de haber terminado el programa de ejercicios y la última, tres meses después. Estas muestras se utilizarán para analizar en su sangre una serie de sustancias o moléculas que ayudarán al equipo médico a conocer el riesgo que usted tiene de padecer deterioro cognitivo leve y/o de desarrollar enfermedad de Alzheimer (incluyen análisis de ADN, antioxidantes y perfil hematológico).

Estos análisis le serán realizados en el Servicio Central de Neuroimagen de la Universidad Pablo de Olavide (Sevilla) por personal cualificado. Además, parte de esas muestras sanguíneas se enviarán a un centro especializado (Centro de Metabolómica-Madrid) donde analizarán otras sustancias pequeñas (a nivel molecular) en su sangre.

En el caso de que, una vez realizados los análisis pertinentes, existiera sobrante de las muestras (plasma sanguíneo) de alguno de los participantes serán enviadas al Biobanco del Sistema Sanitario Público de Andalucía donde serán almacenadas a -80ºC y de acuerdo con la normativa vigente y aplicable por dicho Biobanco. Si usted quiere ceder sus muestras al Biobanco, tendrá que firmar otro permiso.

El estudio del líquido cefalorraquídeo se realizará mediante una punción lumbar que es un procedimiento que consiste en la extracción de una muestra de líquido cefalorraquídeo

mediante la punción con una aguja en la columna lumbar. Usted tendrá que acostarse en posición fetal, con las piernas flexionadas. La punción se hace a nivel de la columna lumbar, entre dos vértebras, y siempre en condiciones estériles, extrayéndose una muestra de líquido cefalorraquídeo para ser analizado. El Dr. Moya será el encargado de realizar esta prueba. Usted no tendría que someterse a esta punción si no participara en el estudio.

.

Resonancia Magnética cerebral (RM): La RM cerebral es una prueba de imagen que permite ver con detalle la estructura de su cerebro. Se le realizará una RM antes del programa de ejercicios y otra al terminar el programa. Esta prueba le será realizada en el Servicio Central de Neuroimagen de la Universidad Pablo de Olavide (Sevilla) por personal cualificado, a donde se le transportará mediante la organización del proyecto. Usted no tendría que someterse a esta prueba si no participara en el estudio.

- La valoración de carácter clínico se hace en primer lugar en los centros de atención primaria por parte de los médicos de atención primaria implicados y posteriormente en el hospital Puerta del Mar para el resto de la exploración.
- El laboratorio de Fisiología del Ejercicio Físico de la Facultad de Ciencias de la Educación será el responsable de llevar a cabo la medición de sus capacidades físicas mediante sencillos test o pruebas que consistirán en caminar, sentarse y levantarse de una silla, mantener el equilibrio, etc. Estas evaluaciones estarán bajo la supervisión de Dr. David Jiménez Pavón.

El programa de ejercicio físico se llevará a cabo en el Complejo deportivo Ciudad de Cádiz perteneciente al Ayuntamiento de Cádiz y que posee una unidad específica y Servicio Sanitario-Médico Deportivo y la disponibilidad con registro oficial de un desfibrilador externo semiautomático (DESA) en la instalación deportiva municipal. Esta Unidad está bajo la responsabilidad y dirección de forma presencial del médico del deporte Dr. Francisco Luis Peral Pérez que estará presente durante todas las pruebas que se realicen en este centro.

Beneficios derivados de su participación en el estudio.

Lo más probable es que usted no obtenga ningún beneficio para su salud por participar en este estudio. En el caso de que descubriéramos algo importante, se lo comunicaremos si usted así lo desea. Esperamos que la información que obtengamos sirva para ampliar el conocimiento científico sobre el efecto del ejercicio físico supervisado en el deterioro cognitivo leve.

Incomodidades y riesgos derivados del estudio

Todas las pruebas serán realizadas y supervisadas por especialistas en el ámbito de la medicina, especialistas en ciencias de la actividad física y del deporte y psicología.
Las extracciones sanguíneas y las pruebas de resonancia magnética funcional serán realizadas en el Servicio Central de Neuroimagen de la Universidad Pablo de Olavide (Sevilla) por personal cualificado, lo cual implica ser trasladado a dicho sitio por el equipo del propio proyecto y sin ningún coste para usted.

- Las pruebas de resonancia magnética se realizarán en un escáner abierto y consistirán en varios periodos (secuencias) de 20 min entre los que podrá descansar y acomodarse. Así mismo durante la prueba dispondrá de un intercomunicador para comunicarse con sus evaluadores. Las contraindicaciones para la resonancia magnética incluyen: tener implantado un marcapasos, desfibrilador automático, clips aneurismáticos, bomba de infusión de fármacos o cualquier prótesis metálica no extraíble.
- Los riesgos derivados de la extracción de sangre son mínimos, y podrían incluir dolor leve o un pequeño morado en la zona de la extracción.
- En cuanto a los riesgos derivados de la punción lumbar, lo más común es que aparezca dolor de cabeza al disminuir la presión del líquido, y se trata con reposo en cama

y bebiendo abundantes líquidos durante las horas siguientes a la punción y analgésicos. Las infecciones (meningitis, espondilodiscitis, celulitis) son raras al realizarse en condiciones estériles. Otras complicaciones poco frecuentes son hematomas locales en el sitio de la punción, apareciendo con mayor frecuencia en pacientes con enfermedades hematológicas o tratados con fármacos anticoagulantes. Excepcionalmente se han descrito hematomas intracraneales secundarios a la hipotensión del líquido cefalorraquídeo así como la herniación transtentorial, complicación potencialmente mortal y que puede aparecer en pacientes con algunos procesos intracraneales como grandes masas, procesos que por medio de la historia clínica y las pruebas complementarias habrán sido razonablemente descartados en su caso. Muy rara vez quedan secuelas motoras o sensitivas por contacto con una raíz nerviosa. El paciente recibirá un seguimiento directo del Dr. Miguel Ángel Moya ante cualquier incidencia. Usted no tendría que someterse a esta punción si no participara en el estudio. Ya que se trata de una prueba invasiva, los investigadores han contratado una póliza de seguros en los términos establecidos por la ley.

- Las pruebas de evaluación de su capacidad física están basadas en movimientos de la vida cotidiana: marcha lenta y rápida, levantarse de una silla, etc. por lo que no suponen riesgo añadido
- Todo el programa con ejercicio físico será realizado y supervisado por especialistas en el ámbito de ciencias de la actividad y el deporte. No se prevé ningún acontecimiento adverso, más allá de los propios de la práctica de actividad física en el caso del grupo de ejercicio como pueden ser caídas tropiezos, mareos, posibles esguinces o contusiones, Aunque no podemos descartar que sucedan otros acontecimientos. En caso de que ocurriera cualquier acontecimiento que afecte a su salud será atendido por el personal médico presente en la misma. En caso de lesión originada por la propia práctica de ejercicio físico, el equipo investigador tratará dar solución inmediata, dado su carácter multidisciplinar (especialistas del ámbito de la actividad física, médicos y psicólogos), y cualquier urgencia médica será atendida de forma inmediata por el especialista médico a cargo de la unidad específica y Servicio Sanitario del complejo deportivo.
- Además, el proyecto contará con seguro de responsabilidad civil que cubrirá los potenciales daños derivados de la participación en el proyecto según las leyes españolas.

COMPENSACIÓN ECONÓMICA

Su participación en el estudio no supondrá ningún gasto para usted. Todas las pruebas serán gratuitas.

CONFIDENCIALIDAD

Sus datos serán tratados con la más absoluta confidencialidad según lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre de Protección de Datos de Carácter Personal. De acuerdo a lo que establece la legislación mencionada, usted puede ejercer los derechos de acceso, modificación, oposición y cancelación de datos, para lo cual deberá dirigirse a alguno de los investigadores responsables del estudio, Dr. David Jiménez Pavón, Dra. Ana Carbonell Baeza, Dr. Miguel A. Moya Molina y el Dr. Francisco Luis Peral Pérez. Facultad de Ciencias de la Educación. Avda República Saharaui s/n 11519 Puerto Real (Cádiz) Teléfono: 667788602.

Los datos recogidos para el estudio estarán identificados mediante un código y sólo el investigador principal/colaboradores podrán relacionar dichos datos con usted y con su historia clínica.

En el proceso de manejo y publicación de resultados del estudio, sus datos personales no serán publicados y su identidad permanecerá anónima desde el inicio.

FINANCIACIÓN

Este estudio está financiado por el Ministerio de Economía, Industria y Competitividad

RETIRADA DEL CONSENTIMIENTO

Usted puede retirar su consentimiento en cualquier momento sin tener que dar explicaciones. Si usted no desea participar más en el estudio y usted lo quiere así, todas sus muestras identificables serán destruidas para evitar la realización de un nuevo análisis.
También debe saber que puede ser excluido del estudio si los investigadores del estudio lo consideran oportuno.
Usted tiene derecho a estar informado de cualquier proyecto de nuevos análisis del material identificable retenido no previsto en este estudio. El investigador podría tener que pedirle un nuevo consentimiento que usted podría rechazar.
Antes de firmar, lea detenidamente el documento, haga todas las preguntas que considere oportunas, y si lo desea, consúltelo con todas las personas que considere necesario.
Si requiere información adicional se puede poner en contacto con nuestro personal de la Universidad de Cádiz en el correo electrónico: proyecto.efficom@uca.es

Nombre:
Firma del paciente:

Nombre:
Firma del Investigador:

Fecha:
Este documento debería ser firmado por duplicado: una copia para el participante y otra para el investigador

Appendix 5: Informed consent of the EFICCOM Study.

CONSENTIMIENTO INFORMADO POR ESCRITO

Título del estudio
Promotor:

Yo (nombre y apellidos) _____

He leído y comprendido la hoja de información que se me ha entregado.

He podido hacer preguntas sobre el estudio.

He recibido suficiente información sobre el estudio.

He hablado con:

_____

(nombre del investigador)

Comprendo que mi participación es voluntaria.

Comprendo que puedo retirarme del estudio:

1º Cuando quiera

2º Sin tener que dar explicaciones.

3º Sin que esto repercuta en mis cuidados médicos.

Presto libremente mi conformidad para participar en el estudio.

FECHA: FIRMA DEL PARTICIPANTE

Appendix 6: Image consent of the EFICCOM Study.

AUTORIZACIÓN PARA LA PUBLICACIÓN DE IMÁGENES/ VÍDEOS

El derecho a la propia imagen está reconocido al artículo 18. de la Constitución y regulado por la Ley 1/1982, de 5 de mayo, sobre el derecho al honor, a la intimidad personal y familiar y a la propia imagen y la Ley 15/1999, de 13 de diciembre, sobre la Protección de Datos de Carácter Personal, artículo 13 del Real Decreto 1720/2007, de 21 de diciembre, por el que se aprueba el Reglamento de desarrollo de la Ley Orgánica 15/1999, de 13 de diciembre, de protección de datos de carácter personal. La Ley de Protección de Datos nos obliga a disponer de su autorización para publicar tanto las imágenes como las grabaciones que realicemos en las diferentes actividades realizadas durante el desarrollo del estudio EFICCOM. Este material gráfico o grabaciones podrá ser publicado en nuestra web, redes sociales siempre que exista autorización expresa previa.

Nombre y Apellidos:

D.N.I:

Firma:

Appendix 7: Evaluation of the Ethics and Research Committee of "Hospital Universitario de Puerta del Mar", Cádiz, Spain.

Servicio Andaluz de Salud
CONSEJERÍA DE SALUD

D. ª MÓNICA SALDAÑA VALDERAS COMO SECRETARIA DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN DE CÁDIZ

HACE CONSTAR

Que en su reunión de fecha 22 de marzo de 2018 se ha revisado el estudio de investigación promovido por D. David Jiménez Pavón y D. ª Ana Carbonell Baeza titulado: Efecto del ejercicio físico supervisado a nivel cerebral, cognitivo y metabolémico en personas mayores con/sin deterioro cognitivo ligero. Hoja de Información al Paciente y Consentimiento Informado versión de 07 de marzo de 2018.

Y hace constar que el citado proyecto es viable.

Que presenta suficiente rigor metodológico.

Que la evaluación de costes económicos es correcta.

Que con respecto a su vertiente ética el proyecto cumple los requisitos necesarios de idoneidad del protocolo en relación con los objetivos del estudio.

Y que este Comité acepta que dicho estudio sea realizado en los siguientes centros por los siguientes investigador principal:

Centro	Investigador
Hospital Universitario Puerta Del Mar	D. Miguel A. Moya Molina
Complejo deportivo Ciudad de Cádiz	D. Francisco Luis Peral Pérez

Y para que así conste, firmo la presente en Cádiz a 23 de marzo de 2018

HOSPITAL UNIVERSITARIO PUERTA DEL MAR
Avenida Ana de Viya, 21 – 11009 Cadiz
Teléfono 956 00 21 00 www.hupm.com

Appendix 8: Previous considerations to laboratory test session.

CONSIDERACIONES PREVIAS PARA EL DÍA DE PRUEBAS DE LABORATORIO

Duración prevista: 2-2,5 horas.

Lugar de realización: Laboratorio de Valoración de la actividad física. Facultad de Ciencias de la Educación. Campus Universitario de Puerto Real. Cádiz.

Pruebas a realizar: Composición corporal, prueba de caminar en cinta, frecuencia cardiaca en reposo.

Consideraciones a tener en cuenta para este día y los días previos.

La semana previa a las pruebas de laboratorio los participantes deben hacer un protocolo de hidratación. Éste consiste en:

- Tomar al menos 4 vasos de agua (4 x 250 ml aprox) repartidos a lo largo del día.
- Observar el color de la primera orina en la mañana para identificar en la escala color el nivel de hidratación cada día.
- Si el nivel es 5 o superior incrementar ligeramente la ingesta de agua.

Nivel 1		Bien hidratado
Nivel 2		Hidratado
Nivel 3		Hidratado
Nivel 4		Hidratado normal o Leve deshidratación
Nivel 5		Deshidratado
Nivel 6		Deshidratado
Nivel 7		Severa deshidratación
Nivel 8		Severa deshidratación

El día previo a las pruebas de laboratorio los participantes deben:

1. **No hacer ejercicio físico vigoroso** 24 horas antes de las pruebas.
2. **No tomar bebidas estimulantes** (tipo cafeína, teína, bebidas energéticas, etc.) 24 horas antes de las pruebas.
3. **No beber alcohol** el día antes de las pruebas.
4. Hombres intentar venir con la **barba afeitada o recortada.**

El día de las pruebas de laboratorio los participantes deben:

1. **Venir en ayunas de 3-4 horas y siendo la última comida poco abundante.**
2. **Venir en ropa cómoda para hacer deporte** (ideal ropa deportiva con camiseta cómoda y pantalón corto de deporte holgado, si lo prefieren pueden llevarla en una mochila aparte). Se aconseja traer una camiseta para cambiarse después de las pruebas y no coger frio en caso de sudoración.
3. **Venir con calzado deportivo.**

Appendix 9: Information sheet of the laboratory test session.

ID:

Temperatura ambiente	
Humedad relativa	

1. Condiciones previas (5')

ITEMS	Si	No
¿Ha cumplido el protocolo de hidratación?		
Indica el nivel de hidratación		
¿Trae ropa deportiva y zapatillas cómodas?		
¿Ha realizado algún ejercicio extenuante 24 horas antes de la prueba?		
¿Ha consumido alcohol o algún tipo de estimulante tipo cafeína, teína o similar este mismo día o el día anterior?		
¿Ha descansado bien la noche anterior?		
¿Ha realizado ayuno previo de 3-4 horas antes de a prueba?		
Hora de última comida realizada		

- ✓ *El participante debe ir al baño a orinar para registrar la bioimpedancia.*
- ✓ *Cuestionario de valoración del apetito PRE (en los 3-5 minutos de reposo para TA).*

2. Tensión arterial PRE de reposo (5')

TAS	TAD	FC (Omron)

- ✓ *Quitarse la camiseta para protocolo de cámara térmica. Se necesitan 5 minutos.*

3. Talla (cm)

*Medición 3. Si existe diferencia >1cm entre las dos primeras mediciones.

4. Bioimpedancia (5' con talla)

Si	
No	

5. Termografía PRE (5')

	Si	No
Sentado. 1m		
Sentado lateral. 1m		
Pierna ANT. 3m		
Pierna POST. 3m		
De pie. 3m		
Espalda. 3m		

6. Perímetros (12' con pliegue)

Zona corporal	Medición 1	Medición 2	Medición 3*
Cintura			
Cadera			
Muslo			

*Medición 3. Si existe diferencia >0.5cm entre las dos primeras mediciones.

7. Pliegue muslo

Zona corporal	Medición 1	Medición 2	Medición 3*
Muslo			

*Medición 3. Si existe diferencia >1mm entre las dos primeras mediciones.

- ✓ Colocamos NIRS, Polar Team, ECG y mascarilla del analizador. Explicar RPE. **(Duración: 20').**

8. Variabilidad cardiaca + Metabolismo Basal (10')

RPE basal	

Frecuencia cardiaca basal (ppm):

9. Espirometría (5')

Si	
No	

Número de pulsómetro:

10. Prueba incremental VO_{2peak} (24')

FC MAX teórica/ FC MAX reserva (ppm)	/
85% FC MAX teórica /75% reserva (ppm)	/
Tiempo final del Bruce modificado: *(observar tiempo analizador de gases)	
Tiempo final recuperación activa: *(observar tiempo analizador de gases)	
Tiempo final recuperación pasiva: *(observar tiempo analizador de gases)	

Motivo de parada:

Exhaustion/Cardiology/stress/pain/fall/others: _____.

- ✓ Recuperación activa 5' (caminando) + pasiva 5' sentado en una silla.

Estadío (km/h)	**RPE**
1 (2.7)	
2 (2.7)	
3 (2.7)	
4 (3.4)	
5 (4.0)	
6 (4.8)	
7 (5.5)	
8 (6.1)	
9 (6.8)	
10 (7.4)	
11 (8.0)	
Rec. Activa (min 2.5)	
Rec. Pasiva (min 2.5)	

11. Tensión arterial POST ejercicio (5')

(minuto 1, 3 y 5 de la recuperación pasiva)

TAS	**TAD**	**FC(Omron)**

- ✓ Tras la recuperación quitar NIRS, mascarilla, polar y ECG.

12. Termografía POST (8' con apetito POST)

	Si	**No**
Sentado. 1m		
Sentado lateral. 1m		
Pierna ANT. 3m		
Pierna POST. 3m		
De pie. 3m		
Espalda. 3m		

- ✓ Cuestionario de valoración del apetito POST.

13. Tabla de eventos NIRS y HUMON:

EVENTO	**DESCRIPCIÓN**
Evento 1	
Evento 2	
Evento 3	
Evento 4	
Evento 5	
Evento 6	
Evento 7	
Evento 8	
Evento 9	

14. Observaciones:

Appendix 10: Previous considerations to field test session.

CONSIDERACIONES PREVIAS PARA EL DÍA DE PRUEBAS DE CAMPO.

Duración prevista: 1,5 horas.
Lugar de realización: Pabellón deportivo Bahía Sur de San Fernando / Complejo Deportivo Ciudad de Cádiz/Pabellón Ciudad de Chiclana
Pruebas a realizar: Test de capacidad funcional y velocidad de marcha
Consideraciones a tener en cuenta para este día. Los participantes deben: 1. **Venir en ropa cómoda para hacer deporte.** Se aconseja traer una camiseta para cambiarse después de las pruebas y no coger frio en caso de sudoración. 2. Venir con **calzado deportivo**. 3. Llevar botella de agua para hidratarse. 4. Llevar gafas, en el caso de que se utilicen.

Appendix 11: Information sheet of the field test session.

DATOS IDENTIFICATIVOS		**ID:**	**Fecha:**
Brazo dominante		Pierna dominante	

1	**CALENTAMIENTO**				
VALORACIÓN CONDICIÓN FÍSICA					
2	**Chair sit and reach** (cm)	1 intento	D:	I:	**RPE:**
		2 intento	D:	I:	
3	**Back Scratch test** (cm)	1 intento	D:	I:	**RPE:**
		2 intento	D:	I:	
	Nota: anotar si el valor es positivo + o negativo -				
	El brazo que está para arriba define si es derecho o izquierdo?				
4	**Test equilibrio bipodal ojos abiertos** (s)	1 intento	Duración:		**RPE:**
		2 intento	Duración:		
5	**Test equilibrio bipodal ojos cerrados** (s)	1 intento	Duración:		**RPE:**
		2 intento	Duración:		
6	**Test de la marcha Optogait**	Realizado	SI	NO	**RPE:**
7	**Dinamometría manual**	1 intento	D:	I:	**RPE:**
		2 intento	D:	I:	
8	**Test equilibrio unipodal ojos abiertos** (s)	1 intento	D:	I:	**RPE:**
		2 intento	D:	I:	
9	**Test equilibrio unipodal ojos cerrados** (s)	1 intento	D:	I:	**RPE:**
		2 intento	D:	I:	
10	**8 foot go test.** Tiempo (s)	1 intento:			**RPE:**
		2 intento:			
11	**Arm curl test** (30s) nº de repeticiones		D:	I:	**RPE:**
12	**Chair stand test** (30s) nº de repeticiones		Apoyo de manos		**RPE:**
			Uso de bastón		
13	**Test 6 minutos** nº vueltas completas	Vueltas			**RPE:**
		M. totales			
	Nota: Anotar distancia exacta últimos metros				

Appendix 12: Sociodemographic questionnaire

ENCUESTA SOCIOECONÓMICA, ESTADO DE SALUD, UTILIZACIÓN RECURSOS SANITARIOS Y FRAGILIDAD

Fecha: ID:

Nota para el entrevistador: si la persona duda con alguna pregunta, anote observaciones al respecto al lado de dicha pregunta. En las preguntas aparece entre paréntesis aclaraciones que no debe leer al participante. No leer a opción de NS/NC y marcar en caso necesario.

2) Indíquenos, si usted es hombre o mujer

Hombre	0
Mujer	1

3) ¿Cuál es su estado civil?

Soltero/a	1
Casado/a o con pareja	2
Viudo/a *(sin pareja)*	3
Separado/a legalmente o divorciado/a *(sin pareja)*	4
NS / NC *(No leer, intentar evitar)*	99

4) ¿Qué nivel de estudios ha completado usted?

Sin Estudios	1
Primarios: Educación Primaria, EGB	2
Formación Profesional	3
Secundarios: Bachillerato, BUP, COU	4
Universitarios	5

5) ¿En cuál de estas situaciones se encuentra usted actualmente?

Trabaja	1
Parado/desempleado	2
Jubilado/pensionista/prejubilado	3
Incapacitado para trabajar *(marcar cuando se ha prejubilado por este motivo)*	4
Se dedica a las labores del hogar *(exclusivamente)*	5
NS/NC *(No leer, intentar evitar)*	99

6) ¿Percibe alguna pensión contributiva?

Sí, por cotización propia	1
Sí, por cotización de otra persona (pensiones de viudedad)	2
Sí, por ambos tipos de cotización	3
No	4
NS / NC *(No leer, intentar evitar)*	99

***7)* ¿Ha trabajado antes?** *(referido a trabajo remunerado)*

Sí	1
No	2
NS / NC *(No leer, intentar evitar)*	99

***8)* ¿Cuál es su ocupación actual o la última ocupación desempeñada?** Anotar con MUCHO detalle la ocupación. *Nota: por ejemplo si tiene empresa, anotar nº de trabajadores a su cargo.*

9) ¿Con quién vive usted actualmente?

Solo	1
Con la familia *(pareja, hijos, nietos, abuelos)*	2
Con otras personas	3
En una institución	4
NS / NC *(No leer, intentar evitar)*	99

10) ¿Cuántas personas conviven en el hogar?

Número de personas	

11) ¿Podría decir cuál es el importe mensual aproximado de estos ingresos del hogar, SUMANDO TODAS LAS FUENTES *(ingresos de todas las personas que viven en el hogar)* **y descontando las retenciones por impuestos, cotizaciones sociales, ¿etc.?**

500 euros o menos	1
Entre 501 y 1000 euros	2
Entre 1001 y 1.500 euros	3
Entre 1.501 y 2.000 euros	4
Entre 2.001 y 2.500 euros	5
Entre 2.501 y 3.000 euros	6
Entre 3.001 y 3.500 euros	7
Entre 3.501 y 4.000 euros	8
Entre 4.001 y 5.000 euros	9
Más de 5.001 euros	10
NS/NC*(No leer, intentar evitar)*	99

12) ¿Cuántas personas, vivan o no en el hogar, dependen de los ingresos netos del hogar?

Número de personas	

13) En la actualidad y en relación con el total de ingresos netos mensuales de su hogar ¿cómo suelen llegar a fin de mes?

Con mucha dificultad	1
Con dificultad	2
Con cierta dificultad	3
Con cierta facilidad	4
Con facilidad	5
Con mucha facilidad	6
NS/NC	99

CONSUMO DE TABACO Y ALCOHOL

14) ¿Podría decirme si actualmente fuma?

Sí, fuma diariamente	1
Sí fuma, pero no diariamente	2
No fuma actualmente, pero ha fumado antes	3
No fuma, ni ha fumado nunca de manera habitual	4

En el caso de que fume a diario

35a. ¿Qué cantidad fuma usted por término medio al día?

Cigarrillos (numero/día)	1
…..	2
NS/NC	99

15) ¿Cuál de las siguientes afirmaciones se ajusta mejor, en su opinión, a su situación en relación al consumo de alcohol?

Suelo beber alcohol habitualmente.	1
Suelo beber, pero no de forma habitual.	2
Nunca he tomado alcohol, soy abstemio	3
Solía beber alcohol, pero dejé de hacerlo.	4

En el caso de que responda 1 o 2.

TIPO DE BEBIDA	DOSIS DIARIA
Cerveza	
Vino blanco	
Vino tinto	
Bebidas destiladas	

Appendix 13: The Global Physical Activity Questionnaire

Cuestionario internacional de Actividad Física			
A continuación voy a preguntarle por el tiempo que pasa realizando diferentes tipos de actividad física. Le ruego que intente contestar a las preguntas aunque no se considere una persona activa. Piense primero en el tiempo que pasa en el trabajo, que se trate de un empleo remunerado o no, de estudiar, de mantener su casa, de cosechar, de pescar, de cazar o de buscar trabajo *[inserte otros ejemplos si es necesario]*. En estas preguntas, las "actividades físicas intensas" se refieren a aquéllas que implican un esfuerzo físico importante y que causan una gran aceleración de la respiración o del ritmo cardíaco. Por otra parte, las "actividades físicas de intensidad moderada" son aquéllas que implican un esfuerzo físico moderado y causan una ligera aceleración de la respiración o del ritmo cardíaco.			
Pregunta		Respuesta	Código
En el trabajo			
49	¿Exige su trabajo una actividad física intensa que implica una aceleración importante de la respiración o del ritmo cardíaco, como [*levantar pesos, cavar o trabajos de construcción*] durante al menos 10 minutos consecutivos? *(INSERTAR EJEMPLOS Y UTILIZAR LAS CARTILLAS DE IMÁGENES)*	Sí 1 No 2 *Si No, Saltar a P 4*	P1
50	En una semana típica, ¿cuántos días realiza usted actividades físicas intensas en su trabajo?	Número de días ⌊__⌋	P2
51	En uno de esos días en los que realiza actividades físicas intensas, ¿cuánto tiempo suele dedicar a esas actividades?	Horas : minutos ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P3 (a-b)
52	¿Exige su trabajo una actividad de intensidad moderada que implica una ligera aceleración de la respiración o del ritmo cardíaco, como caminar deprisa *[o transportar pesos ligeros*] durante al menos 10 minutos consecutivos? *(INSERTAR EJEMPLOS Y UTILIZAR LAS CARTILLAS DE IMÁGENES)*	Sí 1 No 2 *Si No, Saltar a P7*	P4
53	En una semana típica, ¿cuántos días realiza usted actividades de intensidad moderada en su trabajo?	Número de días ⌊__⌋	P5
54	En uno de esos días en los que realiza actividades físicas de intensidad moderada, ¿cuánto tiempo suele dedicar a esas actividades?	Horas : minutos ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P6 (a-b)
Para desplazarse			
En las siguientes preguntas, dejaremos de lado las actividades físicas en el trabajo, de las que ya hemos tratado. Ahora me gustaría saber cómo se desplaza de un sitio a otro. Por ejemplo, cómo va al trabajo, de compras, al mercado, al lugar de culto [*insertar otros ejemplos si es necesario*]			
55	¿Camina usted o usa usted una bicicleta al menos 10 minutos consecutivos en sus desplazamientos?	Sí 1 No 2 *Si No, Saltar a P 10*	P7
56	En una semana típica, ¿cuántos días camina o va en bicicleta al menos 10 minutos consecutivos en sus desplazamientos?	Número de días ⌊__⌋	P8
57	En un día típico, ¿cuánto tiempo pasa caminando o yendo en bicicleta para desplazarse?	Horas : minutos ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P9 (a-b)
En el tiempo libre			
Las preguntas que van a continuación excluyen la actividad física en el trabajo y para desplazarse, que ya hemos mencionado. Ahora me gustaría tratar de deportes, fitness u otras actividades físicas que practica en su tiempo libre [inserte otros ejemplos si llega el caso].			
58	¿En su tiempo libre, practica usted deportes/fitness intensos que implican una aceleración importante de la respiración o del ritmo cardíaco como [*correr, jugar al fútbol*] durante al menos 10 minutos consecutivos? *(INSERTAR EJEMPLOS Y UTILIZAR LAS CARTILLAS DE IMÁGENES)*	Sí 1 No 2 *Si No, Saltar a P 13*	P10

59	En una semana típica, ¿cuántos días practica usted deportes/fitness intensos en su tiempo libre?	Número de días ⌊__⌋	P11
60	En uno de esos días en los que practica deportes/fitness intensos, ¿cuánto tiempo suele dedicar a esas actividades?	Horas : minutos ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P12 (a-b)

SECCIÓN PRINCIPAL: Actividad física (en el tiempo libre) sigue.			
Pregunta		Respuesta	Código
61	¿En su tiempo libre practica usted alguna actividad de intensidad moderada que implica una ligera aceleración de la respiración o del ritmo cardíaco, como caminar deprisa, [*ir en bicicleta, nadar, jugar al volleyball*] durante al menos 10 minutos consecutivos? *(INSERTAR EJEMPLOS Y UTILIZAR LAS CARTILLAS DE IMÁGENES)*	Sí 1 No 2 *Si No, Saltar a P16*	P13
62	En una semana típica, ¿cuántos días practica usted actividades físicas de intensidad moderada en su tiempo libre?	Número de días ⌊__⌋	P14
63	En uno de esos días en los que practica actividades físicas de intensidad moderada, ¿cuánto tiempo suele dedicar a esas actividades?	Horas : minutos ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P15 (a-b)
Comportamiento sedentario			
La siguiente pregunta se refiere al tiempo que suele pasar sentado o recostado en el trabajo, en casa, en los desplazamientos o con sus amigos. Se incluye el tiempo pasado [ante una mesa de trabajo, sentado con los amigos, viajando en autobús o en tren, jugando a las cartas o viendo la televisión], pero no se incluye el tiempo pasado durmiendo. *[INSERTAR EJEMPLOS] (UTILIZAR LAS CARTILLAS DE IMÁGENES)*			
64	¿Cuándo tiempo suele pasar sentado o recostado en un día típico?	Horas : minutos ⌊__⌋⌊__⌋ : ⌊__⌋⌊__⌋ hrs mins	P16 (a-b)

Appendix 14: Predictive equations of the cardiorespiratory fitness

Table appendix 14: Fifteen best prediction models of the cardiorespiratory fitness.

	Equations
Basic	
VO_{2peak} basic 1	-1309.98 + 1.83 * 6 minutes walking test (m) + 1.19 * RMR bioimpedance (kcal/day) + 6.86 * Basal HR (bpm)
VO_{2peak} basic 2	-1404.95 + + 1.97 * 6 minutes walking test (m) + 0.98 * RMR bioimpedance (kcal/day) + 6.66 * Basal HR (bpm) + 4.61 * weight (kg)
VO_{2peak} basic 3	-1338.86 * 1.74 * 6 minutes walking test (m) + 1.18 * RMR bioimpedance (kcal/day) + 6.89 * Basal HR (bpm) + 7.75 * chair stand test (rep)
VO_{2peak} basic 4	-1155.09 * 1.73 * 6 minutes walking test (m) + 1.25 * RMR bioimpedance (kcal/day) + 7.05 * Basal HR (bpm) – 2.06 * waist circumference (cm)
VO_{2peak} basic 5	-1373.49 * 1.70 * 6 minutes walking test (m) + 1.17 * RMR bioimpedance (kcal/day) + 9.03 * Basal HR (bpm) +51.70 * PA recommendations (1, yes meeting; 0, non meeting)
Extended	
VO_{2peak} extended 1	-1229.31 + 1.47 * 6 minutes walking test (m) + 1.11 * RMR bioimpedance (kcal/day) + 6.02 * Basal HR (bpm) + 116.95 * forced expiratory volume in 1 second (L)
VO_{2peak} extended 2	-1444.93 + 1.75 * 6 minutes walking test (m) + 0.69 * RMR bioimpedance (kcal/day) + 5.92 * Basal HR (bpm) + 141.52 * forced expiratory volume in 1 second (L) + 8.69 * weight (kg)
VO_{2peak} extended 3	-1117.47 + 1.63 * 6 minutes walking test (m) + 0.66 * RMR bioimpedance (kcal/day) + 6.21 * Basal HR (bpm) + 134.86 * forced expiratory volume in 1 second (L) -5.56 * waist circumference (cm)
VO_{2peak} extended 4	-1432.66 + 1.70 * 6 minutes walking test (m) + 6.24 * Basal HR (bpm) + 170.12 * forced expiratory volume in 1 second (L) + 18.12 * weight (kg) + 4.65 * Handgrip test (kg)
VO_{2peak} extended 5	-1683.32 + 2.15 * 6 minutes walking test (m) + 6.16 * Basal HR (bpm) + 192.85 * forced expiratory volume in 1 second (L) + 20.89 * weight (kg)

Maximal	
VO_{2peak} maximal 1	-1427.30 + 1.13 * RMR bioimpedance (kcal/day) + 120.83 * forced expiratory volume in 1 second (L) + 6.67 * Maximum HR in CPET (bpm) + 32.90 * Time to exhaustion in CPET (min)
VO_{2peak} maximal 2	-1487.16 + 1.87 * RMR bioimpedance (kcal/day) + 121.69 * forced expiratory volume in 1 second (L) + 6.23 * Maximum HR in CPET (bpm) + 34.50 * Time to exhaustion in CPET (min)
VO_{2peak} maximal 3	-1522.16 + 0.80 * RMR bioimpedance (kcal/day) + 148.00 * forced expiratory volume in 1 second (L) + 6.45 * Maximum HR in CPET (bpm) + 37.21 * Time to exhaustion in CPET (min) + 6.88 * weight (kg)
VO_{2peak} maximal 4	-1580.32 +1.83 * Basal HR (bpm) + 0.69 * RMR bioimpedance (kcal/day) + 156.18 * forced expiratory volume in 1 second (L) + 5.52 * Maximum HR in CPET (bpm) + 38.75 * Time to exhaustion in CPET (min) + 6.85 * weight (kg)
VO_{2peak} maximal 5	-1682.24 + 4.21 * Basal HR (bpm) + 0.79 * RMR bioimpedance (kcal/day) + 148.73 * forced expiratory volume in 1 second (L) + 6.02 * Maximum HR in CPET (bpm) + 38.68 * Time to exhaustion in CPET (min) + 8.60 * weight (kg) + 70.04 * PA recommendations (1, yes meeting; 0, non meeting)

CPET means cardiopulmonary exercise test; HR, heart rate; PA, physical activity; RMR, resting metabolic rate.

10. SUMMARIZED CURRICULUM VITAE

Personal information

Daniel Velázquez Díaz

Born: May the 27 of 1993. Chiclana de la Frontera, Cadiz, Spain

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Current positions

2017-2021 Predoctoral FPI fellow. Department of Physical Education, Faculty of Education Sciences, University of Cádiz, Spain.

Education

2011-2015 Bachelor's degree in Sport Sciences. University of Cadiz, Spain.

2015-2016 Master's degree in Physical Activity and Health. University of Cádiz, Spain.

2017-2021 PhD Student in Health Sciences. University of Cadiz, Spain.

Research stays

2018 CIAFEL Research Center, Faculty of Sport, University of Porto, Portugal.
Prof: Jorge Mota
Duration: 3 months

2019 Faculty of Sport Sciences, Charles University, Prague, Czech Republic.
Prof: Jiri Balas
Duration: 1 week

2020-2021 (Online) Faculty of Sport Sciences, Catholic University of Murcia, Murcia, Spain.
Prof: Pablo Jorge Marcos-Pardo
Duration: 3 months

Research Experience

- Effect of supervised physical exercise at the cerebral, cognitive and metabolomic level in older adults with mild cognitive impairment. EFICCOM study. i+D+I program of the Spanish Ministry Science and Innovation, The Government of Spain (DEP2016-76123-R). 2017-2020. 120,000 €.
- Influence of a physical exercise intervention on markers associated with aging, proteomic profile and fragility. INTERMAE study. Program for the financing of

biomedical i+D+I and of health sciences in the province of Cadiz, Spain (PI-0002-2017). 2018-2021. 492,107.54 €.

- Promoting the shift sedentary Lifestyle towards active Ageing. LifeAge Study. Competitiveness ERASMUS+ SPORT 2018 (603121-EPP-1-2018-1-ES-SPO-SCP). 2019-2020. 389,830 €
- Influence of LIFEstyle Behaviors and Cellular Hallmarks of AGING on age-related health problems associated with dementia and fragility (InLIFEAGING). i + D + I projects within the framework of the 'FEDER' Andalusia 2014-2020 operational program (sol-201800107040-tra). 2020-2021. 67.704 €.
- Evaluation of the effects of the nasal flow restriction device (feelbreath) by means of muscular oximetry and electromyography of the respiratory muscles. Southern Association of Pulmonology and Thoracic Surgery (4/2017). 2017-2018. 8915 €.
- THERAPEUTIC INSTRUMENTED BIKE WITH ADVANCED SENSORIZATION. Research transfer office contract, 'CDTI´Interconnect Program. 2017.
- Combined effects of the Mediterranean diet and physical exercise on cardiovascular disease risk factors in university Students. Funded by the University of Cádiz. 2016. 2,000 €.
- Mediating effect of physical activity, physical fitness, and nutrition on the influence of the FTO and PPARGC1A on adiposity and fat oxidation capacity during exercise: The NutAF Study. Funded by the University of Cádiz. 2016. 1,600 €.
- Diagnosis of the pattern of commuting and physical activity of students, teaching and research academic staff, and administration personnel of the University of Cádiz. 2017. Funded by the University of Cádiz. 3,400 €.

Publications

Juan Corral Pérez, Daniel Velázquez Díaz, Alejandro Pérez Bey, Adrián Montes de Oca García, Jorge R. Fernandez Santos, Francisco J. Amaro Gahete, David Jiménez Pavón, Cristina Casals, Jesús Gustavo Ponce González. Objectively measured Physical Activity and Sedentary Breaks are associated with Maximal Fat Oxidation in young adults. 2021.

Adrián Montes de Oca García, Alejandro Pérez Bey, Daniel Velázquez Díaz, Juan Corral Pérez, Edgardo Opazo Díaz, María Rebollo Ramos, Félix Gómez Gallego, Magdalena Cuenca García, Cristina Casals, Jesús G Ponce González. Influence of ACE gene I/D polymorphism on cardiometabolic risk, maximal fat oxidation, cardiorespiratory fitness, diet and physical activity in young adults. International Journal of Environmental Research and Public Health. 2021.

Francisco J. Amaro-Gahete 1, Jesús G. Ponce-González, Juan Corral-Pérez , Daniel Velázquez-Díaz , Carl J. Lavie y David Jiménez-Pavón. Efecto de una intervención de entrenamiento concurrente de 12 semanas sobre la salud cardiometabólica en hombres obesos: un estudio piloto. Frontiers in Physiology. 2021.

Pablo Jorge Marcos Pardo, Noelia Gálvez González, Gemma María Gea García, Abraham López Vivancos, Alejandro Espeso García, Francisco Javier Orquín Castrillón, Luis Manuel Martínez Aranda, Ana Carbonell Baeza, José Daniel Jiménez García, Daniel Velázquez Díaz, Cristina Cadenas Sánchez, Emanuele Isidori, Chiara Fossati, Fabio Pigozzi, Lorenzo Rum, Catherine Norton, Audrey Tierney, Ilvis Äbelkalns, Agita Klempere Sipjagina, Juris Porozovs, Heilli Hannola, Niko Niemisalo, Leo Hokka, David Jiménez Pavón, Raquel Vaquero Cristóbal. Sarcopenia, diet, physical activity and obesity in European middle-aged and older adults: the LifeAge study. Nutrients. 2020.

Pablo Jorge Marcos Pardo; Noelia González Gálvez; Raquel Vaquero Cristobal; Gema María Guea García; Abraham López Vivancos; Alejandro Espeso García; Daniel Velázquez Díaz; Ana Carbonell Baeza; David Jiménez Pavón; Juliana Brandao Pinto de Castro; Rodrigo Gomes de Souza Vale. Functional Autonomy Evaluation Levels in Middle-Aged and Older Spanish Women: On Behalf of the Healthy-Age Network. Sustainability. 2020.

Adrian Montes de Oca García; Alejandro Pérez Bey; Daniel Velázquez Díaz; Edgardo Opazo Díaz; Jorge del Rosario Fernández Santos; María Rebollo Ramos; Francisco Javier Amaro Gahete; Magdalena Cuenca García; Jesús Gustavo Ponce González. Maximal fat oxidation capacity is associated with cardiometabolic risk factors in healthy young adults. European Journal of Sport Siences. 2020.

María Rebollo Ramos; Daniel Velázquez Díaz; Juan Corral Pérez; Barany Ruiz; Alejandro Pérez Bey; Fernández Ponce; FJ García Cózar; Jesus Gustavo Ponce González; Magdalena Cuenca García. Aerobic fitness, Mediterranean diet and cardiometabolic risk factors in adults. Endocrinol Diabetes Nutr. 2019.

Book's chapters

David Jiménez Pavón; Ana Carbonell Baeza; Vanesa España Romero; Jesús Gustavo Ponce González; Alejandro Sánchez Delgado; Daniel Velázquez Díaz. El ejercicio físico como dinamizador del envejecimiento activo. The promotion of physical activity in contemporary society. Independent publisher. 2020.

Cristina Cadenas Sanchez, Alejandro Galán Mercant, Daniel Velázquez Díaz, Sonia Ortega Gómez, David Jiménez Pavón, Ana Carbonell Baeza. Physical Activity and Physical Fitness Assessment Tests in Middle-Aged and Older Adults. European Research Repository. ISBN 9791220242363. 2020.

Pablo Jorge Marcos Pardo; Raquel Vaquero Cristóbal; Noelia González Gálvez; Alejandro Espeso García; Abraham López Vivancos; Francisco Javier Orquín Castrillón; Gemma María Gea García; Luis Manuel Martínez Aranda; Daniel Velázquez Díaz; Jesús Gustavo Ponce González; Cristina Cadenas Sánchez; Ana Carbonell Baeza; David Jiménez Pavón. Multidomain LifeAge Program. European Research Repository. ISBN 9791220242363. 2020.

Other publications

Jose Daniel Jiménez García; Sonia Ortega Gómez; Daniel Velázquez Díaz, Cristina Cadenas Sánchez; Ana Carbonell Baeza; David Jiménez Pavón. Guide to action during confinement and physical activity recommended for the elderly. Covid 19. ISBN: 978-84-09-20131-0. 2020.

Awards

2017 Award for the best oral communication. Velázquez Díaz, D., Sáchez-Delgado, A.,

Pérez Bey, A., Aragón-Martín, R., Corral Pérez, J., Ponce González, J.G. Resting and maximal fat oxidation. Role of body composition and cardiorespiratory fitness in adults. Jornadas nacionales de la Sociedad andaluza de Medicina del Deporte, Sevilla, España.

2018 Velázquez-Díaz, D., Sánchez-Delgado, A., Ponce-González, JG., Carbonell-Baeza, A., Jiménez-Pavón, D. Effects of physical activity and fitness levels on brain structure and function in older people with mild cognitive impairment. EFICCOM study. 2018.Congreso Intersanitario de Andalucía, IMPULSALUD, Cadiz, Spain.

Other merits

- Lecturer in the degree of Sport Sciences. Faculty of Education Sciences, University of Cádiz. A total of 165 hours (2017-2021). Evaluation of students: 4.9 on 5.
- Lecturer in other university training courses, congresses or others. A total of 20 hours.
- Participation in 6 teaching innovation projects.
- Author and co-author of 29 congress oral communications and 13 congress poster communications (both national and international).
- Scientific committee in 1 national congress and organizing committee in 1 international congress.
- Participation in the project meeting/sport multiplier event of the Lifeage project. Universitá degli studi di Roma "Foro Italico", Rome, Italy. 18/06/2019 to 21/06/2019
- Participation in 12 research transfer activities.
- Coordinator of 7 short talks (MOVE-IT talks) and lectures in 4 of them.

PHYSIOLOGICAL AND METABOLIC CHARACTERIZATION OF OLDER ADULTS. ESPECIAL FOCUS ON CARDIORESPIRATORY FITNESS AND ITS ROLE ON COGNITIVE FUNCTION

THE EFICCOM/INTERMAE STUDY

CARACTERIZACIÓN FISIOLÓGICA Y METABÓLICA DE PERSONAS MAYORES. ESPECIAL INTERES DE LA CAPACIDAD CARDIORRESPIRATORIA Y SU ROL EN LA FUNCIÓN COGNITIVA

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2021