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Relationship Between Blood Biomarkers, Physical Fitness, Quality of Life and Cognitive Function in Older Adults with Alzheimer Disease

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September, 2021

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Dissertação defendida em Provas Públicas na Universidade Lusófona do Porto no dia 06/09/2021, perante o júri seguinte:

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Data: 06 de Setembro de 2021

September, 2021

Fernandes, M. (2021). Exploring the Relationship Between Blood Biomarkers Physical Fitness, Quality of Life and Cognitive Function in Older Adults with Alzheimer Disease. Master's degree dissertation in Exercise, Health and Well-being. Universidade Lusófona do Porto. Faculty of Psychology, Education and Sport. This dissertation was supported by the Portuguese Foundation for Science and Technology (FCT) (POCI-01–0145-FEDER-031808).

KEY WORDS: Alzheimer Disease, Physical Exercise, Fitness, Blood Biomarkers, Quality of Life.

The work presented in the context of this thesis was financially supported by the Foundation for Science and Technology (FCT) through the Research Project "Body and Brain": effects of a multicomponent exercise intervention on physical and cognitive function in elderly people with Alzheimer's (FCT) - POCI-01-0145-FEDER-031808) and by the Research Center in Physical Activity, Health and Leisure (CIAFEL) - Faculty of Sport of the University of Porto (FADEUP), Laboratory for Integrative and Translational Research in Population Health (ITR)

Agradecimentos

Uma dissertação que é muito mais do que um trabalho para a obtenção de um título, de um diploma... É o espelho de uma jornada de aprendizagem constante, pela qual fizeram parte pessoas às quais sou eternamente grato. A verdade é que não somos nada sem ninguém nem conseguimos nada sozinhos. O verdadeiro conhecimento apenas se constrói com a soma e partilha do conhecimento dos outros, sozinhos somos apenas uma parte, e por isso escrevo estas palavras a cada um de vocês que se cruzou no decorrer do meu percurso académico e o tornaram muito mais enriquecedor não só do ponto de vista académico, como também pessoal. Sem vocês esta dissertação não seria possível.

Em primeiro lugar, não poderia deixar de iniciar esta dedicatória e profundo agradecimento à minha orientadora: A professora Inês Marques Aleixo por todo o apoio atenção e dedicação no desenvolver desta dissertação, mas acima de tudo pelos preciosos ensinamentos e conhecimento transmitido ao longo do meu percurso académico... Sem dúvida para mim um modelo a seguir enquanto profissional e por quem tenho um apreço enorme!

À professora Sandra Abreu, pelo incansável suporte enquanto coordenadora do Mestrado de Exercício Saúde e Bem-Estar.

Às professoras Lucimére Bohn e Arnaldina Sampaio, pelo auxílio, apoio e disponibilidade demonstrada, para a realização desta investigação.

À Universidade Lusófona do Porto por ter sido a instituição que me acolheu, e me deu todas as ferramentas necessárias para o meu desenvolvimento profissional e pessoal, assim como tornou a concretização desta etapa possível.

Ao centro CIAFEL por colaborar no sentido de disponibilizar os recursos necessários à realização deste trabalho.

À Fundação para a Ciência e Tecnologia que tornou esta investigação possível através do financiamento de grande parte dos custos associados à sua realização.

A todos os professores que me acompanharam, me incentivaram e me fizeram crescer ao logo desta grande etapa da minha vida. Sinceramente, não conheço missão mais nobre que a vossa... A de partilhar inteligência e conhecimento em prol de preparar as novas gerações. Por isso, um enorme obrigado!

Uma palavra de apreço e agradecimento a todos os meus amigos e colegas de turma, que tornaram esta viagem muito mais enriquecedora.

Finalmente e por muito que nenhuma dedicatória seja suficiente para demonstrar todo o meu reconhecimento, admiração e amor que tenho ao meu pai Luís Fernandes e à minha mãe Ana Fernandes, resta-me dizer apenas que sou eternamente grato pelo apoio incondicional, pela educação e valores que me transmitem e pelo sólido suporte familiar que me presenteiam diariamente. Obrigado por fazerem dos meus, os vossos sonhos também!

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RESUMO

Introdução: A doença de Alzheimer (DA) é a doença neurodegenerativa mais comum, afetando milhões de pessoas. Esta doença progressiva afeta a capacidade cognitiva e funcional, levando à deterioração da qualidade de vida (QdV) do paciente e do cuidador em todos os estados da doença. No entanto, a literatura carece de informações acerca da interação e do papel de biomarcadores sanguíneos específicos assim como da saúde física e mental na QdV em indivíduos com distúrbios neurocognitivos, incluindo DA. **Objetivos:** Este estudo visa caracterizar a composição corporal, aptidão física e biomarcadores sanguíneos (perfis metabólicos, inflamatórios, neurotróficos e antioxidantes totais) de acordo com a QdV, assim como determinar a correlação entre os componentes da aptidão física e a função cognitiva em indivíduos com distúrbios neurocognitivos,. **Métodos:** Os participantes deste estudo transversal foram 34 idosos [71,4% mulheres; 74,06 ± 6,03 anos, com diagnóstico médico de distúrbio neurocognitivo (doença de Alzheimer, demência vascular ou demência a mista)] categorizados de acordo com o percentil 50 [Baixa QdV (≤30,17) ou Alta QdV (>30,17)] avaliado através do questionário QoL-AD. Foram recolhidos dados sociodemográficos, clínicos, composição corporal, antropométrica, avaliação cognitiva (Mini Exame do Estado Mental), aptidão física (Senior Fitness Test) e amostras de sangue para análise de biomarcadores. **Resultados:** Os grupos de QdV não apresentaram diferenças para idade, sexo, escolaridade, duração do diagnóstico de transtorno neurocognitivo principal e função cognitiva. O grupo com QdV alta comparado ao grupo QdV baixa apresentou melhores níveis de força na parte inferior do corpo (12,47 ± 2,81 vs. 9,59 ± 4,03 respetivamente; p = 0,021). Não foram encontradas diferenças significativas nas variáveis de composição corporal, aptidão aeróbia, agilidade ou força de membros superiores de acordo com os níveis de QdV (p> 0,05). O grupo com Alta QdV em comparação com o grupo de Baixa QdV, apresentou níveis mais elevados de IGF-1 (161,00 ± 37,82 Vs. 126,13 ± 32,42, respetivamente; p = 0,046) BDNF (31285,00 ± 4798,55 Vs,2577,00 ± 4873,46, respetivamente; p = 0,022) e z-score neurotrófico (composto de IGF-1, VEGF-1 e BDNF, 0,26 ± 0,48 Vs. -0,40 ± 0,31, respetivamente; p = 0,025). Todos os componentes da aptidão física avaliados foram significativamente correlacionados com a

função cognitiva (p <0,05). **Conclusão:** A QdV parece estar relacionada com maior aptidão física e desfechos neurotróficos. Estratégias para melhorar a QdV podem sustentar a saúde física e mental em indivíduos com distúrbios neurocognitivos. Os componentes da aptidão física parecem ser importantes para a função cognitiva e, portanto, a atividade física deve ser aconselhada para indivíduos idosos com DA.

Palavras-Chave: Doença de Alzheimer, Exercício Físico, *Fitness*, Biomarcadores Sanguíneos, Qualidade de vida.

Relationship Between Blood Biomarkers Physical Fitness, Quality of Life and Cognitive Function in Older Adults with Alzheimer Disease.

Abstract

Background: Alzheimer disease (AD) is the most common neurodegenerative disorder, affecting millions of people. This progressive disease affects cognitive and functional capacity, leading to the deterioration of both patient and caregiver quality of life (QoL) across disease states. However, there is a lack of information about disease biomarkers and physical and mental health according to QoL in individuals with major neurocognitive disorders, including AD. **Aims:** The study aims to characterize body composition, physical fitness and blood biomarkers (metabolic, inflammatory, neurotrophic profiles, and total antioxidant), according to QoL and to characterize the correlation between physical fitness and cognitive function in older people with neurocognitive disorders, particularly with AD. **Methods:** The participants of this cross-sectional study comprised 34 older adults [71.4% women; 74.06 ± 6.03 yrs, with a medical diagnosis of major neurocognitive disorder (Alzheimer disease, Vascular dementia or Mixed dementia)] were categorized according to 50th percentile [Low (≤30.17) or High (>30.17)] for quality of life (QoL) assessed using the QoL-AD scale – Questionnaire. Sociodemographic, clinical data, body composition, anthropometric, cognitive assessment (Mini Mental State Examination, MMSE), physical fitness (Senior Fitness Test) and blood samples were collected for biomarkers analysis. **Results:** QoL groups were not different for age, sex, education, duration of major neurocognitive disorder diagnose and cognitive function. High QoL group compared to low QoL have better levels of lower body strength (12.47 ± 2.81 Vs. 9.59 ± 4.03 respectively; p = 0.021). No significant differences were found in body composition, aerobic fitness, agility or upper body strength variable's according to QoL levels (p>0.05). High compared to low QoL group, showed higher levels of IGF-1 (161.00 ± 37.82 Vs. 126.13 ± 32.42, respectively p = 0.046) BDNF (31285.00 ± 4798.55 Vs.2577.00 ± 4873.46, respectively p = 0.022) and neurotrophic z-score (composite of IGF-1, VEGF-1 and BDNF, 0.26 ± 0.48 Vs. -0.40 ± 0.31, respectively; p = 0.025). Additionally, all of physical fitness components evaluated were significantly correlated with cognitive function (p<0.05). **Conclusion:** QoL seem to be related to higher physical fitness and neurotrophic outcomes. Strategies to improve QoL

might sustain physical and mental health in individuals with neurocognitive disorders. Physical fitness components seem to be important for cognitive function and therefore physical activity should be advised for older adults with AD.

Key words: Alzheimer Disease, Physical Exercise, Fitness, Blood Biomarkers, Quality of Life.

LIST OF ABBREVIATIONS

AD – Alzheimer's Disease

APP - Aβ precursor protein

AT – Aerobic Training

Aβ – Amyloid-β

BDNF - Brain-derived neurotrophic factor

BMI – Body Mass Index

CRP – C-Reative protein

HbA1c – Glycated Hemoglobin

HDL – High Density Cholesterol

IDE – Insulin degrading enzyme

IGF – Insulin growth factor

IL-6 – Interleukin 6

LDL – Low Density Cholesterol

MT – Multicomponent Training

NDD - Neurodegenerative diseases

NEP – Neprilysin

NFT – Neurofibrillary Tangles

OS – Oxidative Stress

OXPHOS - Oxidative phosphorylation

P-TAU – Tau Protein

PA – Physical Activity

QOL – Quality of Life

ROS – Reactive Oxygen Species

RT – Resistance Training

SFT – Senior Fitness Test

T2DM – Type 2 Diabetes Melitus

TNF-α - Tumor Necrosis Factor-α

VEGF - Vascular Endothelial Growth Factor

WHO – World Health Organization

1. GENERAL INTRODUCTION

The world's population is ageing at an exponential rate and thus it can be seen an increase in age-related pathologies such as Alzheimer's Disease (AD) (Castro-Caldas & Mendonca, 2005). In fact, with the worldwide increase of life expectancy, age-related neurodegenerative disorders are dramatically becoming more prevalent, representing one of the major health problems in our society. AD is the most common neurodegenerative disorder in which the nervous system progressively deteriorates. In 2015, nearly 46.8 million worldwide people developed dementia, including AD, and is expected the incidence to rise in the coming years, with an estimated number of cases of 74.7 million to occur in 2030 and 131.5 million in 2050. After the age of 65, the risk of developing dementia doubles every five years, and AD affects one in four people aged 85 and over (World Alzheimer Report, 2015). Due to its progressive degenerative nature, this syndrome contributes to physical, cognitive and social disabilities that culminate in functional dependency, usually leading to institutionalization and affecting quality of life (QoL) (Sampaio et al., 2019). Therefore, AD has devastating social consequences, and healthcare costs, making it one of the primary age-related health problems affecting worldwide (World Alzheimer Report, 2015), and major international public health organizations and national governments are calling for policies to solve and/or mitigate the global burden of dementia (World Health Organization, 2017).

The etiology of most neurodegenerative diseases, such as AD, is highly complex and multifactorial. These diseases are not only a consequence of genetic predisposition, but also a result from environmental and endogenous factors (Correia et al 2010; Migliore and Coppede, 2009). Thus, it is crucial to comprehend and to manage dementia-related risk factors, including decreased physical fitness, metabolic disorders, inflammation, obesity, increased oxidative stress (OS), and neurometabolic impairments (Marques-Aleixo, 2020). Evidences are showing that the avoidance and/or prevention of modifiable risk factors, the appropriate lifestyle and comorbidities management are associated with the mitigation of risk dementia (Baumgart et al., 2015).

Among the innumerous preventive and therapeutic strategies used to counteract dementia-associated diseases, physical exercise has been considered a promising non-pharmacological approach. Regular physical exercise during the life course of people with AD is associated with significant health benefits and it is linked with positive effects on brain function and structure (Gomez-Pinilla, et al. 2008) and fitness capacity (Nelson et al, 2004), that are fundamental to perform normal daily activities independently. Together these benefits can improve life quality perception, that are one of the major downsides of AD.

Additionally, there are also indirect mechanisms underlying this associations, by physical exercise-induced benefits on other modifiable factors (e.g. metabolic, inflammatory, lipidic, neurotrophic and oxidative factors). The present dissertation will address specific health biomarkers, body composition, physical fitness components and cognitive function according to QoL perception and examine the current literature of how they interplay into AD development and progression. Additionally, we intend to understand the relation between cognitive function and physical fitness components. A special attention will be given to the potential of physical activity, as a non-pharmacological strategy to counteract the effects of this neurodegenerative disease, as well as the potential to optimize the QoL perception of individuals with AD.

2. LITERATURE REVIEW

2.1. Aging, Loss of Cognitive Function and Dementia.

Ageing is a physiological process that involves a functional decline in all body tissues and systems, including the brain and also is the major risk factor for many noninfectious diseases, including AD (Jia, Liang, Xu, & Wang, 2019). Further, aging is associated with a decrease in health-related lifestyle patterns, such as physical activity, which can exacerbate the risk for develop a neurodegenerative disease (Whittaker et al, 2018). It is generally accepted that a decline in some aspects of cognition occurs as part of physiological ageing, including decreases in speed of processing, working memory, and executive cognitive function. Behind these functional declines, there are structural changes in the brain that correlates with these age-related cognitive impairments, including alterations in neuronal structure, loss of synapses and dysfunction of neuronal networks (Harada, Natelson Love, & Triebel, 2013).

Cognition is critical for functional independence. Although it is accepted that cognitive abilities trend to decline with age, it is important understand which cognitive alterations are expected as a part of normal aging and which might suggest the onset of a neuro-degenerative disease. In fact, several studies have reported the differences in brain physiology, morphology and neurochemistry, between physiological and pathological ageing (Irwin, 2018). For instance, it has been suggested that in normal aging there is a substantial decrease in the number of neurons, and length of dendrites, loss of dendritic spines and synapses, a decrease in the number of axons and an increase in axons with segmental demyelination, that are, at least in part, responsible for the age-related decrease in brain size and volume (Pannese, 2011). In pathological aged brain, including with AD diagnosis, morphological changes are more severe and include a progressive neuronal loss and ischemic disruption, resulting in a progressively accentuate cognitive decline and functional deficits (Cordonnier et al., 2006). Particularly associated with AD pathogenesis is an increase in the distribution and magnitude of extracellular deposition of Amyloid beta (Aβ) peptides and the intracellular deposition of neurofibrillary tangles (NFTs) which result in the morphological and functional neuronal impairments (Engelhardt, 2012).

2.2. Alzheimer's Disease

Alzheimer's disease is a neurodegenerative disorder characterized by a progressive deterioration in cognitive function, which affects memory, thought, learning, orientation, language, comprehension and judgment, as well as behavior and the ability to perform the activities of daily life (ADL). According to Reitz and Mayeux (2014), 1% to 5% of the population has a genetic background to AD, while the majority represent sporadic cases.

2.2.1. Neuropathology of Alzheimer Disease

Neuropathologically, AD is characterized by the accumulation of Aβ peptides and NFTs, which are composed of hyperphosphorylated tau (P-tau), leading to neuronal loss (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). Aβ typically begins to accumulate in the brain extracellularly around midlife (Braak & Braak, 1991). The clearance of toxic Aβ in the brain is accomplished by cells such as microglia, astrocytes, and neurons, as well as enzymes such as neprilysin (NEP) and insulin degrading enzyme (IDE) (Wang, Gu, Masters, & Wang, 2017). Although Aβ has been the major focus of AD research, it has been suggested that this amyloid pathway as a weakly correlation with the cognitive state of a patient (Hedden, Oh, Younger, & Patel, 2013; Morris, Clark, & Vissel, 2014; Murphy & Levine, 2010). Nevertheless, research indicates that Aβ may play a key role initiating the downstream of AD pathology (Holtzman, 2008; Jack et al., 2010).

Other hallmark of AD neuropathology is Tau hyperphosphorylation and subsequent formation of intracellular NFT. Microtubules are structures that mediate the transport of a variety of molecules such as nutrients and growth factors between the cell body and axon terminals in neurons. The physiological function of tau proteins is to stabilize these microtubules binding to them. Chemical alterations of tau by various kinases and phosphatases produce alterations in their biological function and interrupt its binding to the microtubules. Tau proteins separate from microtubules, clump together with other tau filaments. Lacking appropriate stabilization, the microtubules disassemble and become involved with the tau filaments, forming NFT's (H. G. Lee et al., 2005). The collapse of microtubules and tau assembly disturbing axonal transport, compromising neuronal functioning (Alonso et al, 2018).

The earliest effects of P-tau and subsequent formation of NFT are compromitted axonal transport, synaptic loss, and neuroinflammation (Ballatore, Lee, & Trojanowski, 2007). These tangles do not cause rapid neuronal degradation, once that neurons containing tangles can survive for decades (Morsch, Simon, & Coleman, 1999). Nevertheless, P-tau levels seem to correlate well with symptoms of AD and dementia (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992). Aβ oligomers also have been shown to precede tau phosphorylation, suggesting an interdependency between those hallmarks of AD (Chabrier et. Al, 2012). Additionally, abnormalities in Aβ cause an increase in the production of reactive oxygen species (ROS), leading to oxidative stress, reduced levels of superoxide dismutase and mitochondria function impairments, which in turn, contribute to an increase in hyperphosphorylation of tau and neurodegeneration (Lloret A, Fuchsberger T, Giraldo E, Viñ J, 2015).

The delay in the diagnosis and the nonexistence of a pharmacological treatment for AD, are the two of major challenges of this disease. In fact, AD is often diagnosed belatedly when cognitive symptoms emerge, and currently approved drugs only provide modest and temporary relief for AD symptoms. Today, it is well accepted that exists a temporal phase, ranging from 10 to 20 years, that precedes the symptomatic state, where many biochemical changes occur in the brain, anticipating cognitive impairment (Abate. G, 2017). Due to these constraints on AD diagnosis and treatment, its fundamental recognize this disease as not only consequence of genetic predisposition but also a result from environmental and endogenous complex factors. These factors need to be explored in order to comprehend and invest on public preventive strategies, that can mitigate AD and/or attenuate its negative effects and improve quality of life during the lifetime of people with AD.

2.2.2. Risk Factors for Alzheimer's Disease

There are indeed some non-modifiable risk factors associated with AD as genetic predisposition that have an important role on AD onset and development (Bertram & Tanzi, 2005). But there also exist a myriad of modifiable risk factors affecting AD onset and progression, including physical inactivity, enlarged time spent in sedentary behaviors, unhealthy nutrition, sleep impairments, lack of cognitive stimulation and social interaction (Alzheimer's Association, 2018; Baumgart et al., 2015; Livingston et al., 2017; C. Qiu, Kivipelto, & Von Strauss, 2009; Reitz, Brayne, & Mayeux, 2011). Importantly, many of the

aforementioned modifiable risk factors for AD are also strongly associated with other chronic diseases including hypertension, hypercholesterolemia, type 2 diabetes, obesity, among others (Qiu et al., 2009). The co-existence of many of these modifiable risk factors suggest that the development of AD may be prevented and ultimately the onset of the disease often mitigated.

2.2.2.1. Metabolic Syndrome

Metabolic syndrome is a multifactorial condition that involves dyslipidemia, obesity, hypertension and diabetes. Given the global epidemic of diabetes and obesity, metabolic syndrome has received significantly attention in recent years and it has been linked to neuro degenerative diseases, including AD (Zhou et al., 2014). In fact, literature shows that the manifestation of the components of metabolic syndrome, collectively or individually, increases the risk of AD, although the exact mechanisms are not completely understood (Juárez-Cedillo & Drier-Jonas, 2019). However, researchers have reported that this relationship can be a consequence of age-related poor health habits, including physical inactivity, sedentary lifestyle and unhealthy nutritional habits, which may mask or overpower the effect of metabolic syndrome. While the exact mechanisms are still not entirely clear, neither how the components of metabolic syndrome trigger neurodegenerative diseases and cognitive decline, it has been noted that metabolic syndrome frequently accompany AD diagnoses (Pugazhenthi S, 2017; Pal K, Mukadam N, Petersen I, Cooper C., 2018). In fact, the scientific community is currently focusing on various aspects of this association, in order to design better strategies to mitigate both unhealthy conditions.

2.2.2.2. Obesity

Obesity has become a worldwide epidemic in recent years and with this growth, attention has turned to the relation between obesity and dementia, specifically AD. Therefore, it is important to consider strategies that can control and modify obesity and overweight in order to prevent the progression of AD. In healthy conditions, adipocytes, secrete substances called adipokines, including leptin, and adiponectin (Cao. H, 2014), which regulate many important physiological functions like appetite, satiety, energy expenditure, insulin sensitivity and secretion, glucose and lipid metabolism, fat distribution, hemostasis, blood pressure, neuroendocrine regulation, and function of the immune system (Ouchi et al, 2011).

In obesity, adipocytes become bigger leading to the development of a pro-inflammatory environment, by the secretion of pro-inflammatory cytokines, as Tumor necrosis factor-alfa (TNF-α), Interleukin-6 (IL-6) and C-Reative Protein (CRP) that are linked with the development of AD and other diseases like type 2 diabetes (T2DM) (Khan & Hegde, 2020). This pro-inflammatory environment can potentially decrease nitrous oxide production and raising oxidative stress, leading to cerebral hypoperfusion (Bijland S, Mancini SJ & Salt IP, 2013). Obesity impacts dementia by limiting blood supply to the brain, which, for instance, restricts the white matter of the brain resulting in decreased neuronal connections and brain atrophy and ultimately to cognitive decline (Anjum I, 2018). In fact, the presence of obesity in young and middle ages increases the risk for AD later in life (Kivipelto et al, 2005). Finally, the underlying causes of obesity, such as a diet high in fats and sugars, influence gut microbiota and disrupt the so-called gut-brain axis, resulting in inflammation and brain atrophy that ends again in neurodegeneration (Anjum I, 2018). Given the fact that obesity is a controllable condition, this should be a focus in the prevention of AD and also reduce other risk factors for AD involved in metabolic syndrome, such as dyslipidemia, hypertension and T2DM.

2.2.2.3. Dyslipidemia

It is known that higher cholesterol levels are associated with increased risk of dementia by increasing Aβ production and accumulation, leading to the development of senile plaques. However few studies have distinguished between the effects of high or low-density lipoproteins (HDL and LDL, respectively) on AD onset and development (T. Juárez-Cedillo, 2019). It has been suggested that high levels of LDL and low levels of HDL cholesterol as early as midlife contribute to the development of AD later in life (Salomon et al, 2009). Hypercholesterolemia is also known to increase the levels of inflammatory cytokines that may increase microglial activation leading to a further inflamed state, resulting in a vicious cycle. While exact mechanisms remain elusive, it is plausible that the inflammation that accompanies dyslipidemia holds a key role in the pathogenesis of AD (Oliveira et al, 2018). In addition, elevation of serum triglycerides may be crucial for brain processes, by altering the capacity of peptides, as leptin, to cross the blood-brain barrier and thus compromising its bioavailability (Rhea, et al. 2017).

2.2.2.4. Type 2 Diabetes and Insulin Resistance

Insulin is an anabolic hormone that is secreted from pancreas to regulate blood glucose levels. Insulin maintains glucose homeostasis by regulating glucose production and release from the liver and glucose availability to the muscle and adipose tissue (Kang S, Lee Y & Lee J, 2017). Insulin resistance refers to the decreased capacity of insulin to operate on target tissues, including liver, muscle, and fat tissues. Specifically, the constrains on the stimulation of insulin receptors and consequently their ability to transmit downstream signals are seen in T2DM related conditionings (Guo S, 2014). All cell types and tissues (including the neurons and microglia cells) have insulin-signaling pathways (Medhi. B & Chakrabarty M, 2013). Insulin participates in many regulatory mechanisms in the bran like neuromodulation, neurotransmitters concentrations, neuronal differentiation, proliferation, regeneration, and inhibition of neuronal apoptosis (Russo. VC, 2005). There are several pathways related with insulin production and effectiveness, increased accumulation of advanced glycation end products, interference with accumulation of Aβ and the phosphorylation of tau as well, which can result in increased risk of AD (Tumminia. A, 2018).

Alterations in cerebral glucose metabolism, could affect the mitochondrial function, causing additional ROS production, triggering neuronal apoptosis, impacting Aβ processing and accumulation (Chornenkyy et al, 2019; Garcia-Casares et al, 2014). Finally, the increased inflammatory markers associated with insulin resistance, including IL-6, CRP and cortisol, are related with a higher risk of vascular events that can lead to cerebral damage (Singh-Manoux et al, 2014).

2.2.2.5. Hypertension

Hypertension has been identified as a risk factor for cognitive decline, and various studies have associated hypertension with dementia later in life (Knopman et al, 2011; Gottesman et al, 2014). Hypertension, by inhibiting vascular clearance of amyloids and consequently leading to Aβ accumulation, a classic indicator of AD (Serrano-Pozo, Frosch, Masliah, & Hyman, 2011). Besides, chronic hypertension can cause hypoxia and oxidative metabolism alterations, via (at least in part) changes on arterial endothelial cell lining. This in turn, triggers an inflammatory environment that ends in neuronal cell death. Hypoxia also triggers a neuropathological cycle, which involves, activation of microglia, the production

of free radicals, modifications in blood-brain barrier permeability and tau hyperphosphorylation (Iadecola. C, 2016).

2.2.2.6. Oxidative stress

Reactive oxygen species are reactive chemicals that have the capability to donate electrons to various molecules (Tangvarasittichai, 2015). In cells, under aerobic physiological conditions, ROS are produced naturally by metabolism (Cossarizza et al., 2009). Physiological levels of ROS play a vital role in maintaining cell homeostasis and the regulation of cellular antioxidant defense mechanisms. However, when ROS formation is dysregulated, oxidative stress disrupts cellular function and damages cells (Navarro-Yepes et al., 2014). Oxidative stress and cellular senescence are considered determinant mechanisms involved in the origin and progression of several organ dysfunctions and pathologies (Liguori et al, 2018)

Increased brain oxidative stress results not only in neuronal injury but also in the alteration of redox-sensitive signaling processes (Su et al, 2008). There have been suggestions that increased oxidative stress and decreased antioxidant defense system are important factors that increase the vulnerability of the brain to ageing effects. Furthermore, from a biochemical standpoint there are evidences that a decrease in the activity of essential antioxidant enzymes, such as glutathione reductase and glutathione S-transferase, that are compromitted by abnormal oxidative stress, can contribute to AD (Esposito, et al. 2006). Due to its low antioxidant capacity and higher oxygen consumption rates, brain seems to be particularly vulnerable to ROS deleterious effects, as synaptic dysfunctions, architectural mitochondrial defects and an increase in apoptotic neurons (Du, H; Guo, L & Yan, S. 2012). Unbalance ROS levels and oxidative stress impact directly and indirectly brain function and are associated with the pathogenesis and progression of many neurodegenerative disorders, such as AD.

2.2.2.7. Inflammation

Either as a driver or a consequence, inflammation plays a key role in neurodegenerative diseases. In fact, according to the amyloid hypothesis, neuroinflammation should follow amyloid deposition (Zhang & Jiang, 2015). However, evidence suggest that inflammation may be at the forefront of AD pathology and progression rather than a simple byproduct of

the neurodegenerative disease itself (Kinney et al, 2018). Microglia, as the resident immune cells in the brain, are responsible for releasing inflammatory cytokines upon binding to Aβ. Although proper microglia function protects against AD, microglial overactivation, which is often seen in AD, can result in synaptic loss and increased tau accumulation (Perry H, Nicoll A & Holmes C. 2010). The immune system dysregulation is involved earlier in AD pathology (Bettcher, & Kramer, 2013) and the pro-inflammatory environment may contribute to AD development (Wang, et al. 2015).

Some of the most prominent markers of inflammation, IL-6 and CRP levels, tend to remain low under healthy conditions but are upregulated in disease states and can subsequently promote chronic inflammation and neurodegeneration (Wang, et al. 2015). Low serum IL-6 and CRP levels are indicators of healthy aging and higher cognitive abilities, conversely, increased levels are associated with poorer cognitive performance (Darweesh, et al. 2017). Notably, as above discussed, overweight and obesity state are also significantly associated with high IL-6 and CRP levels, indicating that maintaining a healthy weight status is important from an inflammation standpoint. In this context, although is true that these immune deficits and chronic inflammation may be a natural consequence of aging, they can potentially be mitigated throughway healthy day-to-day behaviors, like healthy nutrition and exercise engagement.

2.3. Quality of Life, Physical Fitness and Alzheimer disease

2.3.1. Quality of life

Quality of Life (QoL) is a subject that has been widely studied recently across numerous fields of science. According to the WHO (2014) definition, quality of life is "individuals' perceptions of their position in life in the context of the culture and value systems in which they live in relation to their goals, expectations, standards and concerns" (WHO, 2014). QoL is a dynamic and multidimensional concept of health that must comprehend the integration of cognitive functioning, daily-life activities, social interaction, and psychological well-being. For older adults with AD, the focus of daily care must be to promote well-being and QoL for as long as life lasts (Patterson M, Whitehouse P, Edland S, et al. 2006). Consequently, QoL should be included to measure the efficacy of therapeutic non-pharmacological procedures for persons with AD, including physical exercise interventions.

Importantly, measuring QoL is challenging, especially in the case of people with dementia if they have difficulty expressing themselves and their needs.

2.3.2. Physical fitness

One of the consequences of ageing is a decrease in all components of physical fitness, including aerobic and muscular endurance, strength, dynamic agility, flexibility and body composition (Caspersen, Powell &, Christenson, 1985). Generally, people become less physically active during across the lifespan (Hesseberg K et al. 2016; Sun F, Norman IJ & While AE, 2013) and consequently, their physical fitness is negatively affected. Furthermore, older adults with AD recurrently live-in nursing homes and in other institutional settings, with lack opportunities for physical activity (Anderiesen H, et al. 2014), aggravating even more the decline of physical fitness. This have a particular importance since physical fitness components are crucial for carrying out activities of daily life (ADL) independently (Hesseberg K et al. 2016; Rikli & Jones. 2013). Forbes and collaborators (2015) concluded that older adults with dementia increased their ability to perform ADL with physical exercise interventions. Also, a meta-analysis of randomized controlled trials showed a positive association after combined physical-cognitive programs and autonomy for quotidian activities in older people with cognitive impairment or dementia (Karssemeijer A et al, 2017). Fortunately, exercise interventions for people with AD also have shown positive results in the ability to perform ADL (Rao et al, 2014).

Physical fitness has been considered one of its critical components to enhance QoL due to its importance to maintaining motor skills that are essential to performing ADL independently (Ferrucci L et al, 2004). Reinforcing this statement, the literature suggests that low QoL is associated with diminished physical and cognitive function, and both of these factors can be modified by increasing physical activity levels (Conde-Sala JL et al, 2014). So, potential benefits of physical activity and exercise could be linked with physical fitness improvements to ameliorate AD conditions, reflecting higher levels of QoL.

2.4. Physical Activity and Alzheimer Disease

Engaging in regular physical activity is important for maintaining overall wellbeing, and a robust body of evidence suggests that exercise can help mitigate cognitive decline and AD onset and progression (Baumgart et al., 2015; Carson Smith, Nielson, Woodard, Seidenberg,

& Rao, 2013; Dougherty et al., 2016; Fisher-Wellman & Bloomer, 2009; Hernández et al., 2015; Hoffmann et al., 2016; M. Stranahan, Martin, & Maudsley, 2012; C. Qiu et al., 2009; Reitz et al., 2011; Santos-Lozano et al., 2016; Taaffe et al., 2008; Tan et al., 2017). In fact, it is well consensual that physical exercise improves cognitive functions, including attention, memory, reaction time, language, visual-spatial, and executive function (Creer, Romberg, Saksida, van Praag, & Bussey, 2010; Neeper, Gomez-Pinilla, Choi, & Cotman, 1995; Nokia et al., 2016; Vina et al., 2014; Yau & Gil-Mohapel, 2014). Furthermore, physical exercise is generally associated with healthier behavior patterns in patients with neurodegenerative diseases (Marques-Aleixo et al., 2012), which can indirectly prevent or delay AD progression. Physical exercise is a relatively simple strategy, as it can easily be integrated into most people's lives and may delay AD progression and onset.

The biological mechanisms supporting the effects of physical activity on AD are still currently unclear due to the complexity of the disease. The beneficial effects of exercise seems to be related to alterations in brain structure (Åberg et al., 2009; Erickson et al., 2011; Rasberry et al., 2011), including increased hippocampal neurogenesis (Clark et al., 2011) and volume (Erickson et al., 2011; Pereira et al., 2007), increase of synaptic plasticity (Colcombe et al., 2004; Ratey & Loehr, 2011), increase of brain blood flow (Loprinzi, Herod, Cardinal, & Noakes, 2013) and the decrease of age-related atrophy in different brain areas (Colcombe et al., 2004). Additionally, physical exercise stimulates the synthesis and release of neurotrophins and growth factors (Loprinzi et al., 2013), which include brain derived neurotrophic factor (BDNF) (Eggermont, Swaab, Luiten, & Scherder, 2006), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) (Ratey & Loehr, 2011), neuromediators that seems to improve the survival and growth of neurons (K. L. Chan, Tong, & Yip, 2008; Heyn, Abreu, & Ottenbacher, 2004). Underlying these outcomes, physical activity also appears to mitigate insulin resistance, dyslipidemia, obesity, inflammation and oxidative stress, positively impacting many of the previously mentioned, modifiable risk factors for AD.

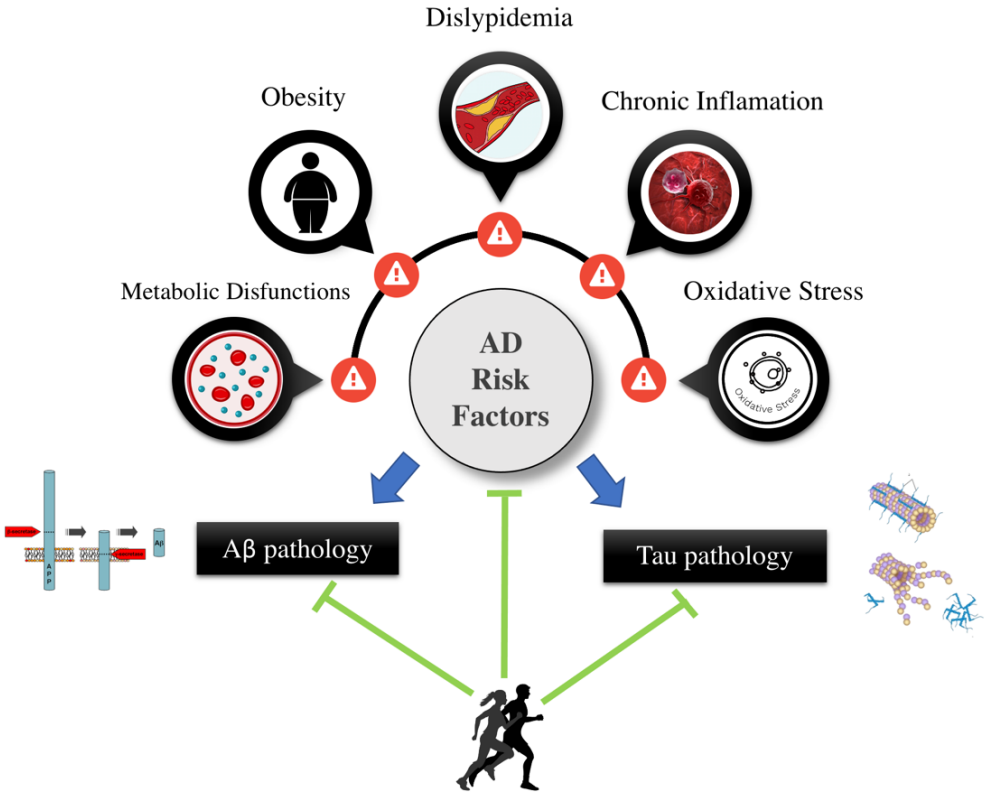

Figure 1. The preventive and therapeutic effect of exercise on the principal mechanisms of AD (AB and Tau pathologies) and other modifiable risk factors for AD development. Exercise reduces ab aggregation and Tau hyperphosphorylation as well as have the capacity to improve metabolic, lipidic and inflammatory profiles, antioxidant capacity and body composition. According to Silva et al (2019), these adaptions mediated by exercise can delay AD development and his deleterious effects.

2.4.1. Physical activity, Beta Amyloid and Tau Protein accumulation

It has been stated that physical exercise has a positive effect on this specific pathway by reduce extracellular Aβ which appears to be mediated by a change in the processing of APP (Adlard et al., 2005). Increased Aβ degradation, via alteration of APP processing can also be modulated by physical stimulation before disease onset and increases (Herring et al., 2011). Additionally, animal neuronal cell death from increased Aβ in the hippocampus decrease following 16 weeks of physical exercise program, suggesting an inhibitory potential on Aβ accumulation (Um et al., 2008). These evidences suggest that exercise represents a potential preventive and therapeutic strategy for AD, at least in part, by reducing the Aβ accumulation.

Interestingly, evidence has also suggested that physical exercise reduces the level of tau deposition by modifying the activity of tau-related kinases and phosphatases (Leem et al.,

2009; Pei et al., 1998). Leem et al (2009) demonstrated that physical training for 12 weeks in mice with tau-protein overexpression led to a significant reduction of tau phosphorylation. The results of these animal studies suggest that physical exercise might provide a positive impact in alleviate tau pathology and improve neuronal functioning in AD.

2.4.2. Physical Activity effects on Indirect Pathways for Alzheimer Disease

Although Aβ accumulation and Tau phosphorylation appears to be the main hallmarks of AD, several studies have shown that physical activity can also improve cognitive function in AD through independent mechanisms. In fact, physical exercise contracts important risk factors associated with AD by increasing neurotrophic factors such as BDNF (Erickson et al., 2012), acting against oxidative stress (Radak et al., 2007), decreasing neuroinflammation, enhancing brain vasculature and blood flow (Endres et al., 2003), increasing mitochondrial fitness (Bernardo et al., 2016), optimizing glucose uptake and insulin-related impairments (Boulé, Haddad, Kenny, Wells, & Sigal, 2001) and improving lipidic profile (Kelly, 2010).

2.4.2.1. Physical Activity and Neurotrophic Factors

Alterations in neurotrophic factors expression during the lifespan may impact the brain structure, metabolism and function, as well as the vulnerability to neurodegenerative diseases. Brain-derived neurotrophic factor (BDNF) has been considered a master regulator of neuroplasticity. This neurotrophic factor is differentially expressed across several brain tissues, serves as a mediator in neurogenesis and synaptogenesis and is able to modulate diverse biological processes such as aging via interaction with different receptors (Silhol et al., 2008). BDNF is highly expressed particularly in the hippocampus, hypothalamus and brain cortex (Tapia-Arancibia et al., 2008). This neurotrophic factor supports glutamatergic neurons in the hippocampus that promotes long-term memory storage (Zheng et al., 2012) and enhances the growth and reorganization of dendritic spines in response to alterations in neuronal activity (Phillips et al., 2014). BDNF also exerts an antioxidant effect through restoring mitochondrial electron coupling, suppressing superoxide production and upregulating antioxidant enzymes (Wu et al., 2016). Thus, considering its neuroprotective abilities, enhancing BDNF levels could ameliorate the widespread neuronal death and associated cognitive deterioration observed in AD. On the other hand, a decrease expression

of this neurotrophic factor may contribute depression, Parkinson's disease, epilepsy and AD (Tapia-Arancibia et al., 2004).

Considering the positive impact of BDNF on neuronal function, strategies that focused on the elevation of his levels, would have a vast therapeutic potential. Physical exercise is known to reduce aging-associated compromised cognition and brain function, at least in part, by intermediate organ communication, including the muscle–brain crosstalk pathways (Marques-aleixo et al, 2020). Considering the positive impact of BDNF on neuronal function, strategies that focused on the elevation of BDNF levels, would have a vast therapeutic potential (Ferris et al., 2007). Multiple animal and human studies have demonstrated a positive correlation between exercise and levels of BDNF. Overall, studies investigating the molecular mechanisms underlying the effects of exercise on cognitive enhancement strongly support a central role for BDNF in the process of neurogenesis, neuroplasticity and long-term potentiation and for the encoding of memories (Bliss & Collingridge, 1993; Sah, Peterson, Lubejko, Vivar, & Van Praag, 2017; Vivar, Peterson, & van Praag, 2016). Particularly, increased hippocampal neurogenesis and volume can be induced by physical exercise, and it has been suggested that these effects are mediated by increased BDNF levels (Blandini, Porter, & Greenamyre, 1996; Segovia, Porras, Del Arco, & Mora, 2001). Importantly, endogenous BDNF upregulation prompt by physical exercise, is considered a crucial mechanism for alleviate symptoms of AD and slow clinical progression of the disease (Marques-Aleixo et al, 2020). Additionally, it has been reported that neurotrophic factors such as BDNF and IGF-1 seem to have an important role in the reduction of amyloid deposition (Åberg, Åberg, Hedbäcker, Oscarsson, & Eriksson, 2000; Adlard, Perreau, Pop, & Cotman, 2005; Van Praag, Christie, Sejnowski, & Gage, 1999; Van Praag, Kempermann, & Gage, 1999; Zigova, Pencea, Wiegand, & Luskin, 1998)

The understanding of potential pathways that may contribute to the effects of exercise on BDNF upregulation provide an important tool for the development of preventive and therapeutic strategies for neurodegenerative diseases management.

2.4.2.2. Physical Activity, Oxidative Stress and Antioxidant Capacity

In healthy conditions, ROS formation is usually in balance with antioxidant defense, however, pathological changes can alter this balance causing free radical production that overshadow antioxidant capacity causing oxidative stress (Huang, Zhang, & Chen, 2016).

Oxidative stress may be one of the earliest event in the AD pathological cascade (Nunomura et al., 2001; Zhu, Lee, Perry, & Smith, 2007), which implies that ROS plays an important role in AD onset and development. Therefore, reducing OS may be a viable strategy to mitigate AD, for instances by enhancing antioxidant machinery in AD patients (Feng & Wang, 2012), somewhat achievable from physical exercise (Elosua et al., 2003).

During a stressful event, such as an acute bout of exercise, the increased metabolic demands initially result in free radical production (He et al., 2016). Even though, this repeatedly raise of ROS production (seen in regular exercise) can be an important signaling pathway to upregulate endogenous antioxidant systems (Elosua et al., 2003). Additionally, it has been proposed that long-term adaptations to exercise can directly diminish ROS production which in turn, helps to maintain or even decrease the accumulated oxidative damage (Radak, Chung, & Goto, 2008). In fact, the ability of regular exercise to mitigate aging-related decay, and neurodegenerative diseases seem to be partially related to the powerful improvement in the brain enzymatic antioxidant systems and downregulation of the enhanced ROS production seen in these physiopathological conditions (Radak et al, 2013). So, the efficacy of chronical forms of exercise at reverting the harmful consequences of aging, and neurodegenerative diseases seems to be partially related, to the powerful effects in antioxidant systems and downregulation of the enhanced ROS production in these physio pathological conditions.

2.4.2.3. Physical Activity and Inflammation

Physical exercise has been suggested as an feasible strategy with an anti-inflammatory effect and that can mitigate immune disorders associated AD pathology (Jankord & Jemiolo, 2004; Pedersen, Bente & Hoffman-Goetz, 2000). Acute bouts of exercise cause an immediate pro-inflammatory effect, that appears to be super compensated, with beneficial anti-inflammatory effects along with regular physical exercise engagement (Pedersen, Bente & Hoffman-Goetz, 2000). The protective effects of regular exercise may be explained by the observed decreased in pro-inflammatory environments and improved immune profiles, characterized by reduced IL-6, CRP levels, and raised IL-2 and IL-10 levels (Drela, Kozdron, & Szczypiorski, 2004; Geffken et al., 2001; Jankord & Jemiolo, 2004; Shimizu et al., 2008). In fact, IL-6 and CRP are key inflammatory markers, that tend to be elevated with aging (Franceschi & Campisi, 2014), and both markers appear to be reduced after

physical exercise engagement, which may help curb the aging-associated chronic inflammation (Colbert et al., 2004; Geffken et al., 2001; Nicklas et al., 2008). Interestingly, even slight reductions in body mass index, that for instances can be attributable to physical exercise, cause significant reductions in inflammatory markers, such as IL-6, TNF-α and CPR (Colbert et al., 2004). Physical exercise interventions seem to have benefits in attenuating pathophysiological alterations in pro-inflammatory cytokine levels commonly associated with age (Mathur & Pedersen, 2008), being also an hypothetical pathway for ameliorate AD conditions.

2.4.2.4. Physical Activity and Metabolic Profile

Metabolic processes permeate nearly all aspects of human biology, and any dysfunction has extensive effects in the whole body, including the brain, leading to neurodegenerative disease as AD (Deberardinis & Thompson, 2012). In fact, it has been suggested that metabolic disturbances can increase exponentially the risk of cognitive decline (Biessels, Staekenborg, Brunner, Brayne, & Scheltens, 2006; Cukierman, Gerstein, & Williamson, 2005; Ott et al., 1999; Paneni, Beckman, Creager, & Cosentino, 2013; Xu et al., 2015). As stated before, hyperinsulinemia, hyperglycemia, and dyslipidemia can contribute to AD pathology, and those conditions associated with chronic diseases such as T2DM have an additive effects on cognitive decline (Hassing et al., 2004; Watson & Craft, 2003).

Patients with AD frequently suffer from brain insulin resistance that leads to downregulation of insulin receptors, lower binding to insulin receptors, and impaired insulin signaling (Arnold et al., 2018; De la Monte, 2014; Qiu et al., 1998; Stanley, Macauley, & Holtzman, 2016). Also, higher levels of insulin compromise the ability of insulin degrading enzyme (IDE) to degrade Aβ, witch facilitate Aβ accumulation (Qiu et al., 1998). Hyperinsulinemia and increased insulin resistance, contributing to the development of T2DM that may also be an independent a risk factor for AD (Shanik et al., 2008).

Insulin sensitivity is improved through physical exercise and physically active individuals have higher insulin sensitivity than sedentary ones (Björntorp et al., 1972). However, the benefits of physical exercise on insulin sensitivity begin to reduce two days after exercise cessation, indicating that consistency is needed for the benefits to be maintained over time (Burstein et al., 1985). Exercise-induced increased of insulin

sensitivity could allow IDE to be available to degrade Aβ, preventing its accumulation (Kurauti et al., 2017).

Hyperglycemia may also contribute to cognitive decline and be considered a risk factor for dementia, especially in those with T2DM (Crane et al., 2013). Impaired glucose metabolism seems to occur prior to clinical symptoms and is correlated with AD clinical and pathological severity (Mosconi et al., 2009). Furthermore, mild or diabetic impairment in glucose metabolism is associated with faster cognitive decline (Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004). It has been reported that hyperglycemia produces advanced glycosylated end products, which are seen at higher levels in the brains of AD patients, causing Aβ accumulation (Vitek et al., 1994).

During a single exercise session, glucose uptake by muscles can increase, principally due to upregulation and translocation of the GLUT4 receptor (Goodyear & Kahn, 1998; Sylow, Kleinert, Richter, & Jensen, 2017). Therefore, physical exercise can improve glycemic control and prevent hyperglycemia for up to 24 hours post-exercise (Van Dijk et al., 2012). In fact, physical exercise consistently decreases blood glucose and is a well-established therapeutic option for T2DM (Boulé, Haddad, Kenny, Wells, & Sigal, 2001).

2.4.2.5. Physical Activity and Lipidic Profile

Dyslipidemia may also be involved in AD pathogenesis, although the mechanisms by which the two are related remain elusive (Reitz, 2013). Low cholesterol levels can assist in the reduction of Aβ production in hippocampal neurons and stimulates β-secretase activity (Kojro, Gimpl, Lammich, März, & Fahrenholz, 2001; Simons et al., 1998). On the other side, studies with long follow-ups beginning in midlife, tend to find a harmful effect of hypercholesterolemia and low levels of HDL for AD risk (Reitz, 2013). Exercise has demonstrated positive effects for managing lipid levels and dyslipidemia (Kelly, 2010), with these favorable effects being consistently confirmed through several meta-analyses (Halbert, Silagy, Finucane, Withers, & Hamdorf, 1999; Kodama et al., 2007). Benefits of physical exercise on lipid profiles remain for up to 15 days after cessation of exercise, denoting that also consistency is important in maintaining a long-term healthy lipid profile, particularly as physical inactivity significantly raises LDL levels (Slentz et al., 2007). Finally, exercise is

critical in managing weight and adiposity, which in turn assists in managing many off the mentioned risk factors for AD, including dyslipidemia (Grundy, 1999).

2.5. Impact of different exercise modalities on Alzheimer Disease

There is remarkably the need to identify the optimum type of PA that might prevent and revert AD pathology effects. In fact, the relationship between exercise and cognition may be dependent on the type of exercise being employed (Bamidis et al., 2014; Chapman et al., 2013; Prakash, Voss, Erickson, & Kramer, 2015). Although the vast majority of research has focused exclusively on Aerobic Training (AT) both, AT and Resistance Training (RT) have been found to enhance cognitive and brain outcomes (Cassilhas et al., 2007; Colcombe et al., 2004; Liu-Ambrose, 2010; Nagamatsu, Handy, Hsu, Voss, & Liu-Ambrose, 2012; Ten Brinke et al., 2015) with common and divergent physiological effects. The specific mechanisms that support the positive effects of AT and RT on the brain are far from fully understood, but it seems that both types of exercise reduce many of Alzheimer's risk factors. However, the mechanisms underlying the positive effects of AT and RT appears to diverge, despite common cognitive and neuroplastic outcomes. Specifically, while AT specially increase BDNF, RT preferentially increased serum brain IGF-1 (Cassilhas et al., 2012). Furthermore, hippocampal neurogenesis and volume that is seen in response to AT may not occur after RT (Nokia et al., 2016). Conversely, RT can improve regional blood flow of the brain and are associated with better memory performance (Nagamatsu et al., 2012). Taken together, the literature suggests that both AT and RT may promote brain function via divergent and common pathways. Considering these facts, the type of exercise is an important factor to consider when prescribing exercise for AD patients.

2.5.1. Aerobic Training

Aerobic training initially contributes to an increase in the levels of growth factors such as VEGF, BDNF, IGF-1, between others that act synergistic to improve memory and cognitive functions, stimulate neurogenesis, synaptogenesis, neuroplasticity, and angiogenesis (Kim, Choi, & Chung, 2016; Paillard, Rolland, & de Barreto, 2015; Radak et al., 2010). Moreover, aerobic exercise increases cerebral blood flow and the levels of endothelial nitric oxide synthase and additionally decreases the levels of ROS in brain tissues, particularly in the hippocampus (Archer, 2011; Paillard et al., 2015; Radak et al.,

2010). Aerobic exercise also increases cell survival and proliferation, upregulates Aβ clearance and decreases apoptotic cascades (Brandt, Maass, Kempermann, & Storch, 2010; Moore et al., 2016). Aerobic training is also associated with higher cortical tissue on the temporal, parietal and frontal lobes, which are the cognition key areas (S. Colcombe & Kramer, 2003) and brain activation patterns (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011).

2.5.2. Resistance training

Although an ameliorative effect of resistance exercise on any of the behavioral or biological signs of AD has not yet been reported, there is evidence that the prevalence of this disease is associated with a decline in muscle mass and muscle strength (Hurley, Hanson, & Sheaff, 2011; Ogonovszky et al., 2005). With reference to these data, it has been reported that resistance exercise may slow down the impairment of mobility and enhance balance in AD patients (Suttanon et al., 2013). In a similar way to the effect of aerobic exercise, levels of IGF-1 and BDNF have been shown to increase via resistance exercise (Lee et al., 2012; Portugal et al., 2015), which can improve cognitive functions in older adults. Considering the relationship between neurotrophic factors and neurogenesis, and the evidence about strength training effects on BDNF and IGF-1 concentrations (Ricardo C. Cassilhas et al., 2007; Coelho et al., 2012), we can deduce that strength training may be also associated with increased neurogenesis, thereby reducing aging effects and AD risk. Another factor that may explain the improvement of cognitive performance is the reduction of oxidative stress, which was observed with strength training (Parise, Brose, & Tarnopolsky, 2005). There is little evidence to indicate that strength training is a valid intervention to increase neuroprotective factor levels and thereby improve biological mechanisms associated with aging and AD. From the available information, we hypothesize that strength training practice can be an important tool to minimize muscle loss, increase neurogenesis, neuroplasticity and thereby reduce the effects of aging on the brain.

2.5.3. Multicomponent training

Several studies have suggested that exercise interventions combining various modalities, or Multicomponent Training (MT), such as combined aerobic exercise and strength training programs, may have a larger effect on cognition than aerobic or resistance training alone

(Kirk-Sanchez & McGough, 2013; S. Colcombe & Kramer, 2003; Smith et al., 2010). However, the vast majority of studies remain focused on aerobic exercise, which ignores the multimodal nature of physical exercise, including strength, flexibility and balance training. In fact a meta-analysis by Smith et al. revealed that interventions consisting of aerobic and strength training activities improved attention, processing speed, and working memory to a greater extent than aerobic exercises alone in both people who were healthy and those with mild cognitive impairment (Smith et al., 2010) and this effect likely was mediated by alterations in hippocampal volume (Erickson et al., 2011; Makizako et al., 2015). Together, these findings suggest that MT elicits compensatory mechanisms in the brains of people with neuropathologic circumstances and, in turn, improves cognitive function. Studies also have shown that MT it is an effective approach to improve functional fitness in healthy older adults (Justine, Hamid, Mohan, & Jagannathan, 2012).

However, it is likely that the mechanisms between exercise modalities will overlap, and that the substantial benefits of exercise are more strongly associated to duration, frequency, and intensity than a specific modality. Nevertheless, understanding the benefits beyond all exercise modalities is necessary to further demonstrate the categorical value of exercise as a more complete intervention.

3. AIMS OF INVESTIGATION

3.1. General Aims

The general purpose of the present dissertation is to characterize body composition, blood biomarkers and physical fitness, according to QoL and to describe the correlation between physical fitness and cognitive function in older people with neurocognitive disorders, particularly with AD.

3.2. Specific Aims

The specific aims of the present dissertation are:

a. To characterize metabolic, inflammatory, neurotrophic and antioxidant profile according to High or Low QoL groups in older people with neurocognitive disorders, particularly AD.

b. To characterize lower and upper body strength, aerobic endurance and agility / dynamic balance, according to High or Low QoL groups in older people with neurocognitive disorders, particularly AD.

c. To describe how lower and upper body strength, aerobic endurance and agility / dynamic balance correlates with cognitive function in older people with neurocognitive disorders, particularly AD.

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4. MATERIALS AND METHODS

4.1. Participants and study design

The participants of this cross-sectional study were conducted in a multi-center setting (2 hospitals, 2 community setting, and 3 daily care centers). Thirty-four older adults from both genders, aged 62–85 years, and all diagnosed by a physician with an age-related neurocognitive disorder (Alzheimer disease, vascular dementia or mixed dementia), agreed to participate in the study. The sample was restricted to older adults with the following characteristics: (age ≥ 60 years, institutionalized for more than 6 months, diagnosis with an age-related neurocognitive disorder and absence of any diagnosed or self-reported musculoskeletal or cardiovascular disorders that would contraindicate participation in physical fitness testing. During the initial screening visit, all participants, formal caregivers and institutions received a complete explanation of the purpose, risks and procedures of the study. Written informed consent was provided, and the review boards of the (Hospital Conde Ferreira, Hospital Magalhães Lemos, ULSM, FADEUP, CSPOliveira do Douro, Alzheimer Portugal e Centro Social Mario Mendes da Costa) approved all methods and procedures. This study is part of an interventional study, named 'Body and Brain' (NCT04095962), approved by was approved by the Ethical Commission of the Faculty of Sports of the University of Porto (Ref CEFADE22.2018) and was in full compliance with the Helsinki Declaration.

4.2. Measurements

All measurements were performed by the same evaluators, in the different settings. At each institution, the test was of 1-week duration. Participants or their caregivers completed body composition and anthropometric measurements (see annex 1), performed Senior Fitness Test (SFT) battery (see annex 2), Quality of Life-Alzheimer's Disease scale (QoL-AD) (see annex 3), Mini-Mental State Examination (MMSE) for cognitive assessment (see annex 5) and blood was collected for analysis, despite different institutions, all assessments were organized in the same way.

4.3. Procedures

4.3.1. Sociodemographic Questionnaire

Sociodemographic variables, including as age, gender and years of education, and medical information (comorbidities, number of medication and number of years since the diagnosis of dementia), were obtained by an anamnesis questionnaire (see annex 1) filled by participant´s caregivers. There was no specific test for the reliability or validity of this anamnesis, but the ethical committee and personal data unit of the University of Porto agreed with the format and content.

4.3.2. Body composition

Body composition was analyzed through DXA (QDR 4500/A, Hologic Explorer, Bedford, USA). Waist circumference was assessed at the midpoint between iliac crest and the bottom of the ribcage, using a spring-loaded measuring tape. Body weight, free fat mass, fat percentage and total body resistance was measured through a bioelectrical impedance analysis using a Segmental Body Composition Analyzer – BC-418 TANITA.

4.3.3. Cognitive function

The Mini-Mental State Examination (MMSE) was used for a global cognitive evaluation. The MMSE evaluates the cognitive function in a range from 0 to 30, whereby lower scores indicate greater cognitive impairment (Folstein et al., 1975; Logsdon et al., 2002). In the first part, the orientation of the participant is tested, followed by a retention test. Also, attention and calculation are checked, just as questions about language and constructive capacity (Baek, Kim, Park, & Kim, 2016). This instrument is clinically used to assess cognitive mental status, as well as to detect and follow the course of mental illness. It assesses orientation, attention, immediate and short-term recall, language and the ability to follow simple verbal and written instructions. The method is shown to have satisfactory test-retest reliability and construct validity. The validity of the MMSE was compared against a variety of gold standards that identify and measure cognitive impairment, such as DSM-III-R criteria and activities of daily living measures.

4.3.4. Physical Fitness

Physical fitness was assessed with the Senior Fitness Test (SFT), developed by Rikli and Jones (1999; 2001) which is considered a reliable instrument for assessing physical fitness in older adults (≥ 60 years of age), including those with cognitive impairment (Hesseberg et

al., 2015). Participants performed 4 tests: chair stand test (to assess lower body strength); arm curl test (to measure upper body strength); 2-minute step test (to assess aerobic endurance); and 8-foot up and go test (to assess agility and dynamic balance). Each test component of the SFT has been selected for its high content validity, criterion validity, construct validity, and reliability (Rikli and Jones, 2001). One of the major benefits of these tests is that they require very little equipment that could be easily transported and adapted to many places. Further that it is validated and translated among many countries (Wilkin D. et al, 2010), what makes the comparison with other studies that use the same methodology, easier.

4.3.5. Quality of life

The QoL-AD scale was used to measure the participant's QoL. The questionnaire includes 13 items: physical health, energy, mood, living situation, memory, family, marriage, friends, self as a whole, ability to do chores, ability to do things for fun, financial situation and QoL as a whole. The QoL-AD uses both self-report and the caregiver's reports of the participant's QoL and it is scored on a 4-point Likert scale ranging from 1 (poor) to 4 (excellent), with total scores ranging between 13 and 52 points (Longsdon et al, 2002). Categories of QoL are defined by bellow and above 50th percentile for low and high QoL respectively.

The fact that QoL-AD integrates both the patient, and his/her caregiver report results, with two times more weight for the patient self-report results in a more valid and reliable tool for measure QoL. In fact, researchers have become aware that people with dementia can give reliable self-reports of their own QoL, thereby reducing the risk of less accurate informants such as caregivers (Brod M, Stewart AL, Sands L, et al. 1999, Smith CS, Lamping DL, Banerjee S, et al. 2007, Trigg R, Jones RW, Skevington SM. 2007, Logsdon RG, Gibbons LE, McCurry SM, et al. 2002) that, depending on their personal emotions, can introduce biases in the assessment (Rosenberg PB, Mielke MM, Lyketsos CG. 2005). Another benefit is the fact that is a short and quick questionnaire to apply particularly useful in patients who have cognitive deficits. Further that it is a scale widely used by the international scientific community, being translated and valid for different languages and cultures.

4.3.6. Blood Biomarkers

Non-fasting venous blood samples were collected into serum-separating tubes (serum isolation) or tubes containing EDTA (whole blood or plasma isolation). All analysis were conducted by a commercial laboratory, according to the methods described in table 1.

Table 1. Blood Markers Samples Thecniques and Reference Values

Technique	Marker	Sample	Reference Values
High performance liquid chromatography (HPLC)	Glycated hemoglobin (HbA1c)	Whole blood	23.0 - 43.0 (4.3% - 5.9%)
Colorimetric method	Triglycerides (LPL/GK/GPO-PAP)	Serum	<150mg/dl / <1.71mmol/L
	Total cholesterol (CHOD-PAP)	Serum	< 190mg/dl / < 4.92mmol/L
	High-density lipoprotein cholesterol (HDL-C) (Catalase/CHOD-PAP)	Serum	> 45mg/dl / > 1.17mmol/L
	Antioxidante_Total	Plasma	560 - 1120 µmol/L
Friedewald formula	Low density lipoprotein-cholesterol (LDL-C)	Serum	< 116mg/dl / < 3.00 mmol/L
Enzyme Immunoassay (EIA)	Vascular endothelial growth factor (VEGF)	Plasma	< 115 ng/ml
	Brain-derived neurotrophic factor (BDNF)	Serum	6186 - 42580 pg/mL
	Interleukin 8	Whole blood	< 132 pg/mL
Chemiluminescence immunoassay (CLIA)	Insulin like growth factor 1 (IGF-1)	Serum	17 - 193 ng/mL / 2.2 - 25.1 nmol/L
	InterleukinL6	Serum	< 3.4 pg/mL
	InterleukinL10	Serum	< 9.10 pg/mL
	Tumor necrosis factor-alfa (TNF-alfa)	Serum	< 8.10 pg/mL
Immunoturbidimetric method	C-reactive protein (CRP, high-sensitivity test)	Serum	< 0.30 mg/dL

Notes: Reference values established by the laboratory Synlabs

4.4. Statistical analysis

Descriptive statistics are presented as mean ± SD or n (%). Data normality was verified using Shapiro Wilk (sample size < 30 subjects).

Characteristics of the sample were described either as means and standard deviations or absolute frequencies N (%). Participants were classified according 50th percentile (P50) for QoL and categorized as High (> 30.17) or Low (< = 30.17) QoL.

Between group comparisons were performed using independent-t testes and chi-square as appropriate. Partial correlations were used to verify if each physical fitness component is correlated with cognitive function. As stipulated in exact sciences it is suggested that r less than 0.2 indicates a very weak linear association between 0.2 and 0.39 low, between 0.4 and 0.69 moderate, between 0.7 and 0.89 high, and finally between 0.9 and 1 a very high association (Pestana & Gageiro, 2014). Significance level in all analyses was set at 0.05. SPSS version 24.0 (IBM, Chicago IL, EUA) was used in all analyses.

5. RESULTS

The 34 participants were predominantly female (71.4%) with 74.06 ± 6.03 years and had neurocognitive disorder (NCD) due to Alzheimer disease, Vascular dementia or mixed dementia and overall NPI scores 13.97 ± 7.85. Hypertension (71.9%), dyslipidemia (59.4%), minor heart condition (50.0%) and diabetes mellitus (31.3%) were the other main diagnoses besides NCD. Most of the participants are in the range overweight to obese (25.0 to 30.0 or higher). The MMSE scores showed that participants were in the moderate stage of dementia and (Table 2).

No differences between QoL groups (Low Vs High) were found for sociodemographic and body composition characteristics and cognitive function ($p > 0.05$) (Table 2).

Table 2. Between groups comparisons according to quality of life 50th Percentile

	Overall (n:34)	**Low QoL (<P50) (n:17)**	**High QoL (>P50) (n:17)**	**p value**
		Sociodemographic		
Age, yrs [Mean ± SD]	73.79 ± 5.92	74.12 ± 6.78	73.47 ± 5.10	p = 0.755
Female, n (%)	24 (70.6%)	50.0 %	50.0 %	p = 0.500
Male, n (%)	10 (29.4%)	55.6 %	44.4 %	
Education, yrs [Mean ± SD]	6.21 ± 3.88	5.65 ± 4.09	6.76 ± 3.68	p = 0.398
Duration since dementia diagnosis, yrs [Mean ± SD]	3.68 ± 2.40	4.18 ± 2.98	3.18 ± 1.55	p = 0.343
		Body composition		
BMI, kg/m^2 [Mean ± SD]	28.42 ± 4.51	28.32 ± 4.72	28.52 ± 4.43	p = 0.773
Waist circumference, cm [Mean ± SD]	91.29 ± 12.03	93.09 ± 12.14	89.49 ± 12.02	p = 0.406
Body fat, % [Mean ± SD]	34.10 ± 8.17	34.02 ± 6.92	34.16 ± 9.23	p = 0.965
Fat-free mass, kg [Mean ± SD]	43.77 ± 7.95	44.38 ± 7.66	43.30 ± 8.38	p = 0.730
		Cognitive Function		
MMSE Score [Mean ± SD]	17.03 ± 6.46	17.29 ± 7.39	16.76 ± 5.57	p = 0.815

Notes: BMI – Body Mass Index; yrs – years; sec – seconds; kg – Kilograms; cm - Centimeters

As it can be seen in figure 2, participants with high QoL score showed superior values in all physical fitness components compared with those with low QoL levels. However, only lower body strength presents a significant difference (p=0.022) comparing participants with high and low QoL levels. Upper body strength and Agility and Dynamic Balance are not statistically different between high vs low QoL groups ($p > 0.05$). Despite the difference between High vs. Low QoL groups on aerobic endurance was not statistically significant ($p > 0.05$) p-value were borderline with significance level (0.057).

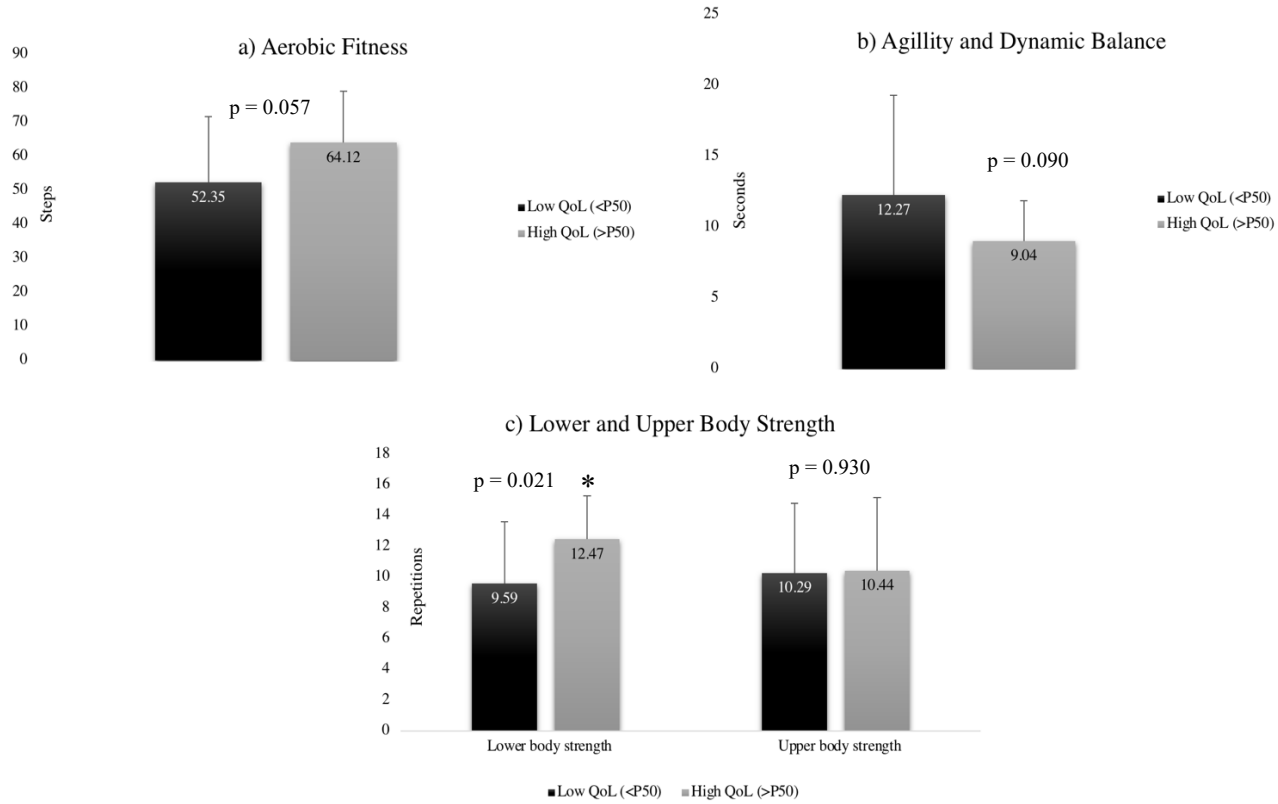

*Figure 2. Comparison of a) Aerobic Endurance, b) Agility and dynamic balance and c) Lower and upper strength between High vs Low QoL groups. *P < 0.05 - significantly different compared with Low QoL group.*

Figure 3 presents the comparison of lipidic profile blood variables between groups. Although with no statistical differences ($p > 0.05$), all biomarkers showed higher levels in high QoL group when compared with low QoL.

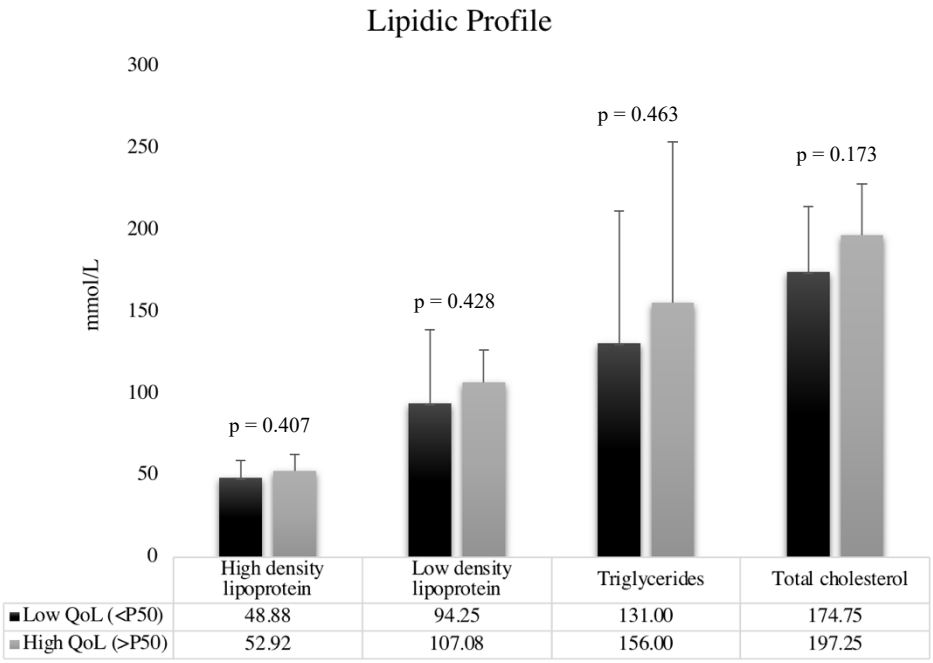

Figure 3. Comparison of lipidic blood biomarkers between High vs Low QoL groups.

Figure 4 shows that both, glycemia and glycated hemoglobin levels are superior in High QoL group, without statistical meaning ($p > 0.05$).

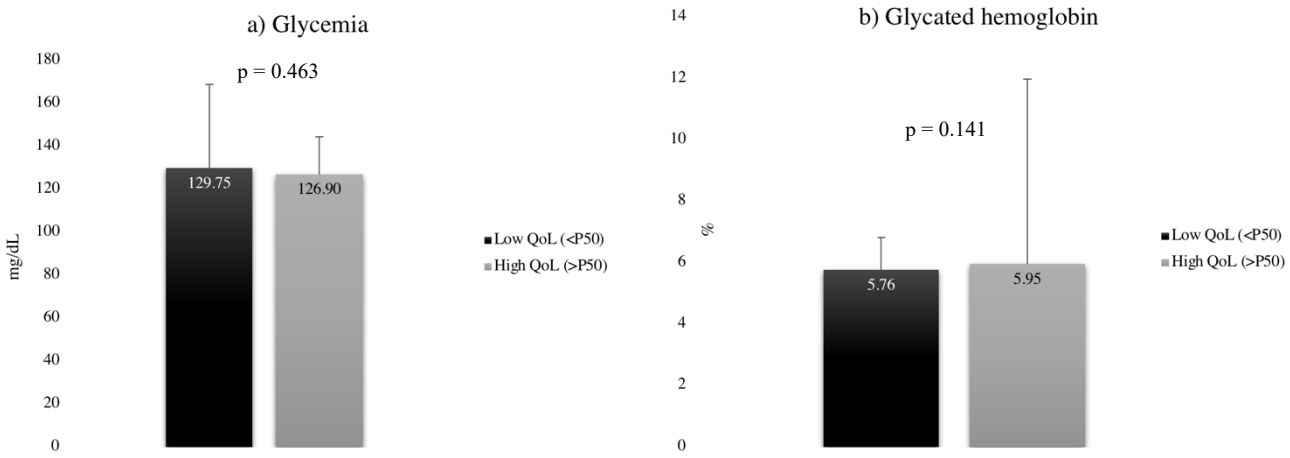

Figure 4. Comparison of a) glycemia and b) glycated hemoglobin between High vs Low QoL groups

Figure 5 displays the inflammatory profile blood variables in both groups. Although with no statistical differences ($p > 0.05$), the mean values of CPR, IL-6 and IL-8 levels are superior in High QoL when compared with Low QoL group, whereas TNF-alpha levels where superior in low QoL group.

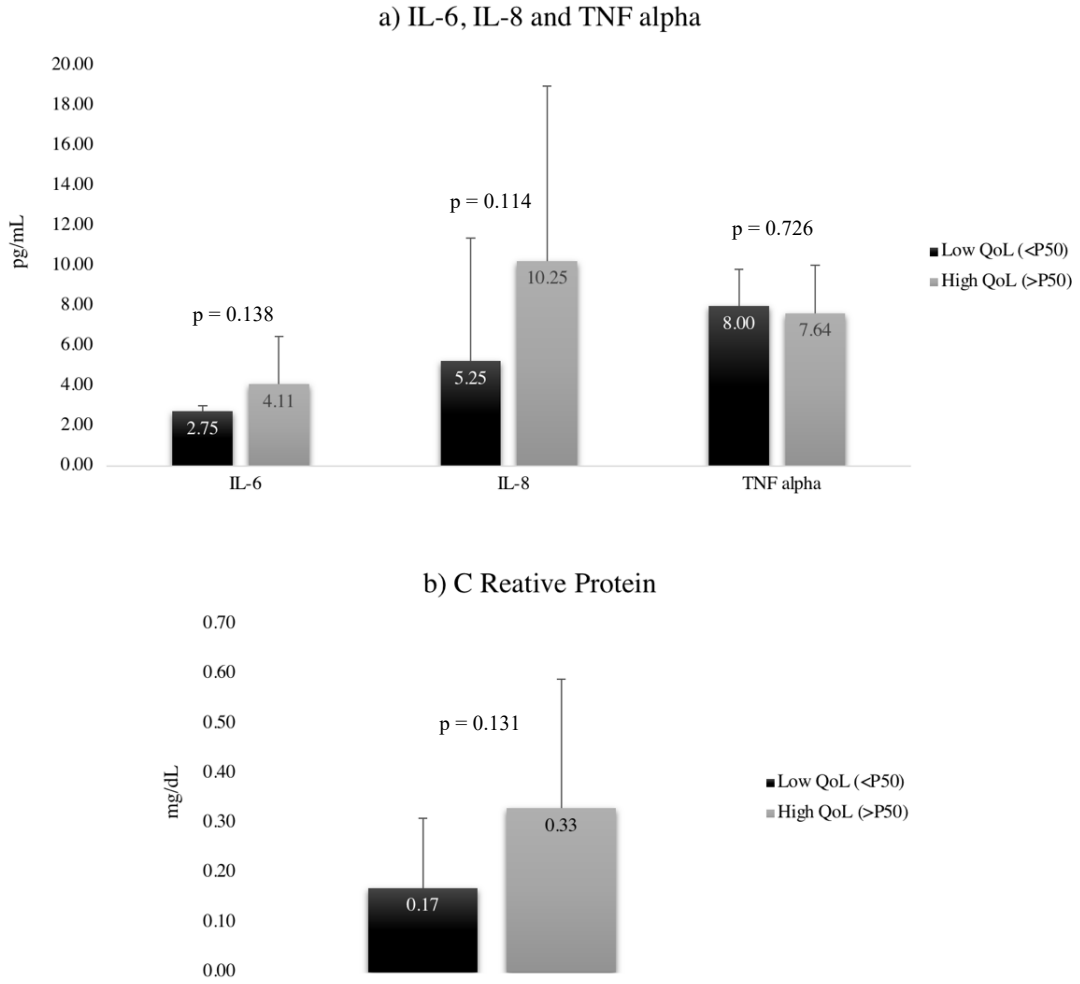

Figure 5. Comparison of a) Interleukine 6 (IL6), Interleukine 8 (IL8) and Tumor Necrosis Factor alpha (TNF-α) and b) C Reactive Protein (CRP) between High vs Low QoL groups.

Antioxidant levels presented in figure 6 also shows superior levels in High QoL group without statistically significance ($p > 0.05$).

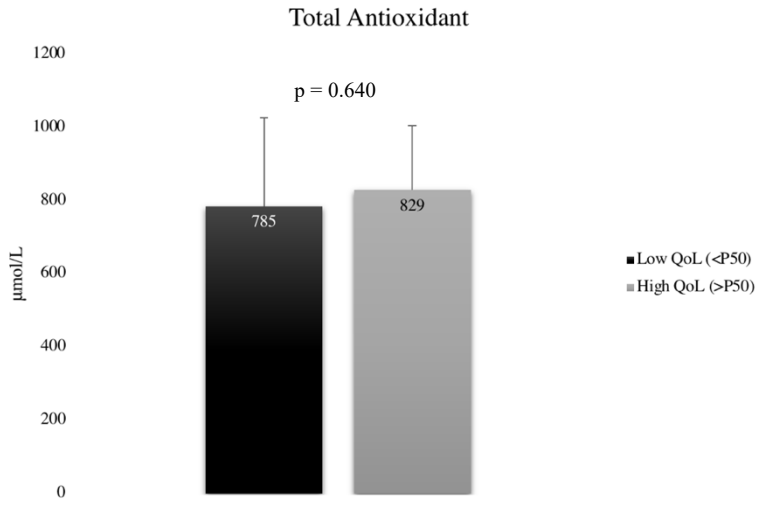

Figure 6. Comparison of Antioxidant Capacity between High vs Low QoL groups.

It is possible to see that BNDF ($p = 0.022$, figure 7a) and IGF-1 ($p = 0.047$, figure 7b) were significate superior in high QoL when compared with low QoL group. On the other hand, VEGF-1 showed to be slightly superior on high QoL group (46.13 vs 48.17 ng/mL) but the difference is not significative ($p > 0.05$).

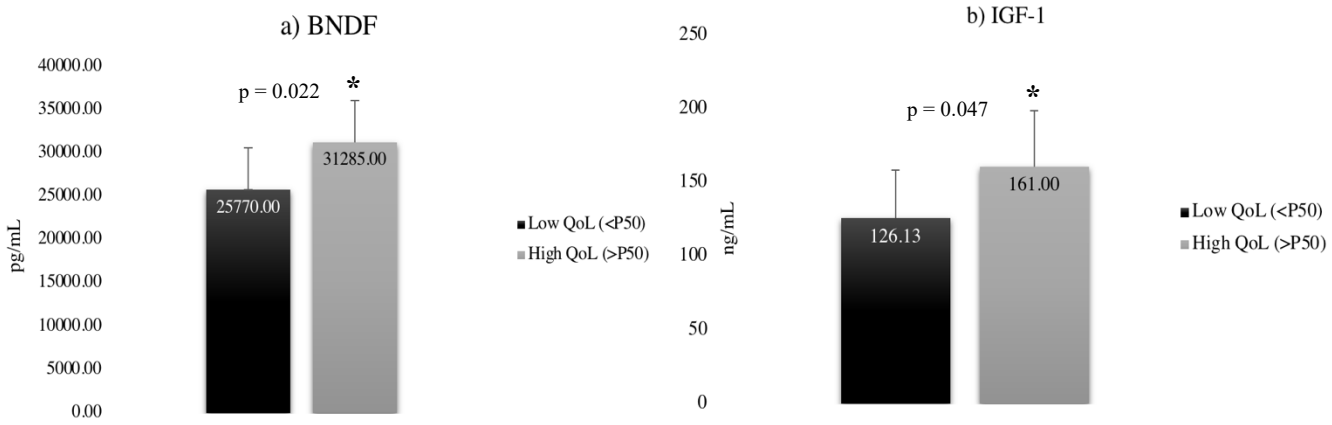

*Figure 7. Comparison of a) Brain-Derived Neurotrophic Factor (BDNF) and b) Insulin-like growth factor-1 (IGF1) between High vs Low QoL groups. *P < 0.05 - significantly different compared with Low QoL group.*

Finally figure 8 exhibit the comparison between High vs Low QoL groups on Lipidic, Metabolic, Inflammatory and Neurotrophic Z-score. Although all biomarkers z-score are superior on High QoL group compared with Low QoL, only Neurotrophic z-score presented a statistical difference (p=0.025).

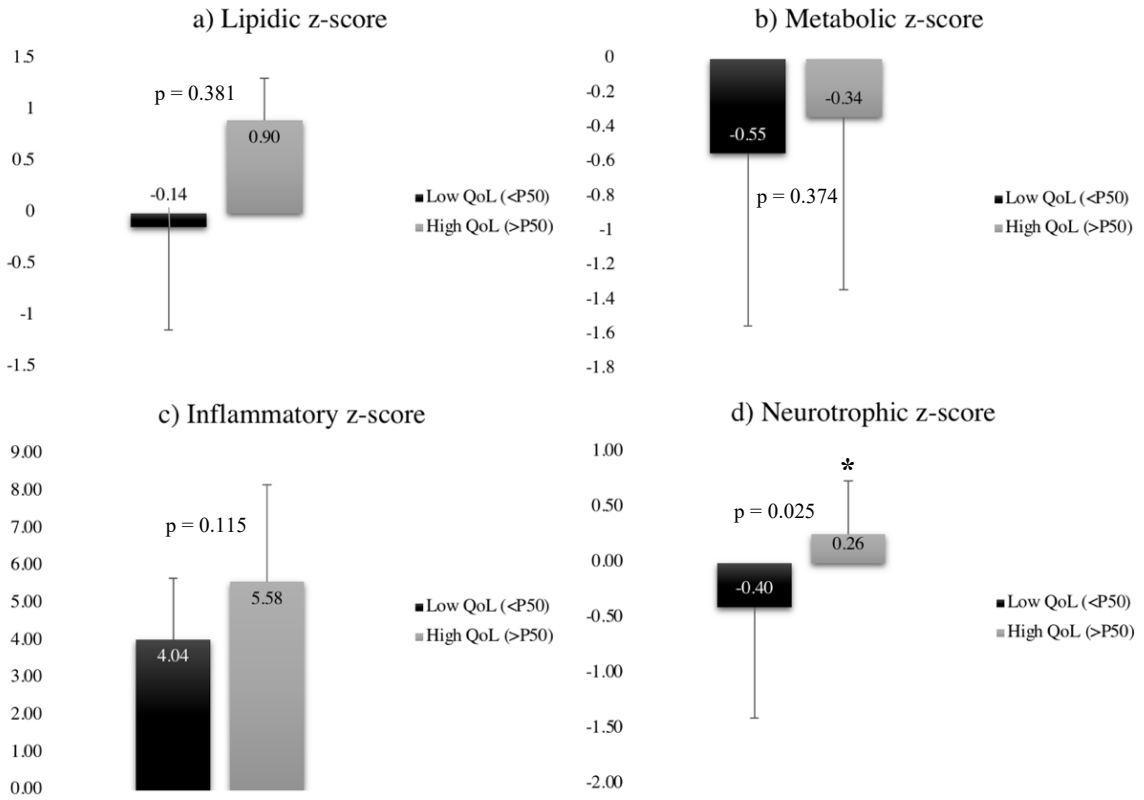

*Figure 8. Comparison of a) lipidic, b) metabolic, c) Inflammatory and c) neurotrophic Z-Scores between High vs Low QoL groups. *P < 0.05 - significantly different compared with Low QoL group.*

Correlations between physical fitness components and cognitive function is shown in Table 3 and Figure 9. It is possible to observe that the components strength and aerobic endurance show a positive and moderate correlation with cognitive performance ($p < 0.05$). Agility and dynamic balance showed a negative and low correlation with cognitive function ($p < 0.05$), meaning that less time to complete the agility/dynamic balance test is correlated with better cognition.

Table 3. Pearson Correlation between cognitive function and physical fitness components

	Variables	Upper Body Strength	Lower Body Strength	Aerobic Endurance	Agility and dynamic balance
MMSE	**Pearson Correlation**	.453*	.446**	.436**	-.343*
	Sig. (2-tailed)	.012	.008	0.01	.047

Notes: All p-values are <0.05 – Significant correlations between all fitness components and cognitive function (*)

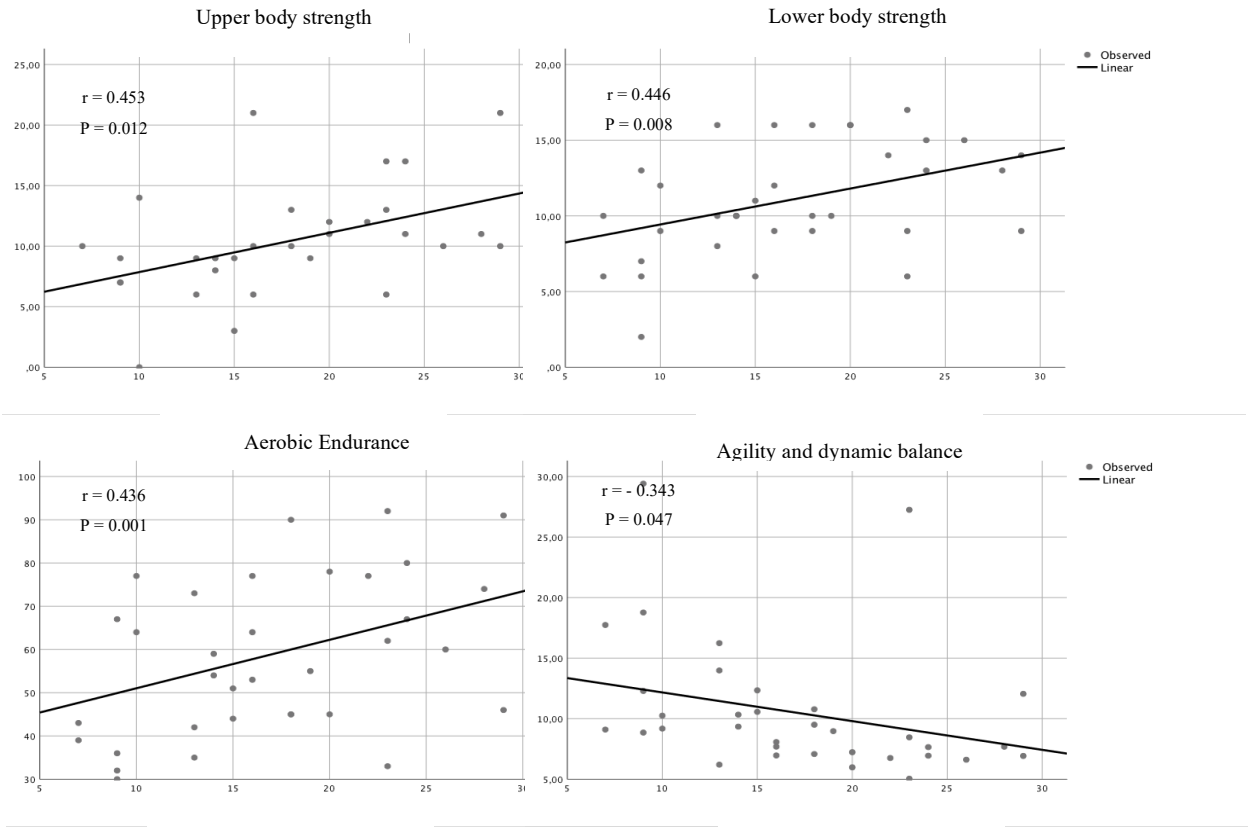

Figure 9. Linear curve estimation on the correlation between fitness components and cognitive function

6. DISCUSSION

The present dissertation is part of a broader research project (Body & Brain) funded by the Foundation for Science and Technology which aimed to analyze the effect of a physical exercise program when applied to an older adult population diagnosed with AD. Therefore, the present study intended to have a longitudinal design with a physical exercise intervention in order to evaluate the effects of exercise on health-related biomarkers, and physical fitness components, that may play a vital role in improve quality of life in older people with AD. Unfortunately, given the COVID-19 pandemic scenario that we have experienced in the last two years, it was not possible to apply the planned exercise program. Therefore, taking into account a diverse set of results collected at an early stage of the project, we tried here to understand whether the of QoL is discriminative for the expression of a distinct phenotype within the scope of AD. We stratified the participants by the 50th percentile of QoL and characterize its discriminative impact on sociodemographic parameters, body composition, physical and functional fitness and metabolic, lipidic, inflammatory, neurotrophic and antioxidant biomarkers profile. Additionally, we also analyzed hypothetical relation between physical fitness components and cognitive function in older people with AD.

Overall, our results indicated that QoL seems to be related to a higher physical fitness (lower body strength and aerobic endurance) and alterations in neurotrophic biomarkers (BNDF and IGF-1). We also found that, for the population studied, all of physical fitness components were significantly correlated with cognitive function.

QoL is a dynamic and multidimensional health concept, comprising an integration of cognitive functioning, capacity to properly perform daily life activities, to have sufficient and successful social interactions and self-perceive psychological well-being (Patterson et al., 2006). To our knowledge, this is the first study to characterize the exuberance of the perceived QoL on a vast scope of health-related markers in elderly people with AD. Concerning the sociodemographic parameters, our results showed that the QoL was not influenced by any of the analyzed factors. Thus, we can consider that the QoL groups (i.e., low *vs*. high) were not different regarding the number of years since diagnostic age, sex, education and neurocognitive disorder diagnostic.

Body composition parameters were similar regardless the QoL group, however, overall, participants were classified, according to the World Health Organization (2000), as overweight (BMI greater than or equal to 25 to 29.9) and obese (BMI greater than or equal to 30). This is interesting once there are studies showing that the risk of development of neurocognitive disorders is higher amongst obese people (Nepal et al., 2014). Moreover,

once the neurocognitive disorder is installed, the potential impairment of the ability to perform activities of daily living, with a worsening of mobility and autonomy, may negatively affect organic homeostasis, with repercussions on metabolism and energy expenditure, compromising body composition. Thus, our results seem to suggest an eventual physical activity reduction in this population, may have negative consequences from the point of view of body composition. As suggested by others (Liberman et al., 2017; Venkatraman et al., 2020; Westerterp, 2018), the regular practice of well-design physical exercise programs under a supervision by qualified professionals, along with an individualized diet, positively influences body composition, including in older adults with neurocognitive disorders.

With the eventual reduction in physical activity, alterations in physical fitness are also expected. Physical fitness is considered a critical component to improve QoL due to its importance for maintaining essential motor skills to independently perform daily life tasks (Ferrucci et al., 2004). Sampaio et al. (2020) suggested that physical fitness is important for cognition and autonomous functional capacity and that it has positive repercussions on QoL in institutionalized elderly people with dementia. Our results corroborate the literature since the participants classified as high QoL have higher levels of muscle strength in the lower limbs and a tendency (almost significant) to have a better aerobic fitness.

The incidence of ageing-induced muscle mass and strength losses seems to be associated with dementia (Tolea & Galvin, 2015). This structural and functional deterioration represents an increased risk of frailty, loss of independence and physical disability (Manty et al, 2014; Stathokostas et al, 2013). In fact, from a functional standpoint, corroborating our data that participants with higher levels of QoL have higher levels of lower body strength, studies have shown that lower body strength capacity appears to be particularly important for elderly people and their ability to maintain functional independence, once many activities of daily living with depend on this capacity (Batista et al, 2014). Also, increased strength and muscle tissue induced by resistance training can attenuate cardiovascular effort during daily activities once the load represents a lower percentage of the maximal voluntary contraction with these exercise-induced muscular adaptions (McCartney et al, 1993). Importantly, the improvement of strength and balance contributes to a lower risk of falls and, consequently, improving the autonomy and mobility of elderly people with neurocognitive disorders, fact that naturally contributes to improving the individual QoL (Vreugdenhil et al. 2012).

In our study aerobic endurance was superior on the group with higher QoL, and although the difference was not statistically significant ($p > 0.05$) p-value were borderline with significance level (0.057) and considering the reduced sample studied we can attribute some relevance to this result. In fact, aerobic endurance is the most studied component of physical fitness in older adults with dementia, being considered a predictor of cognitive performance (Jonasson et al, 2016). Positive associations between aerobic endurance with cognitive functions, and functional capacity were found in a cross-sectional study among older adults with AD (Sampaio et al, 2019). Other studies have shown that higher levels of aerobic endurance are related to improved brain health (Kramer & Colcombe, 2018; Gordon et al, 2008; Johnson et al, 2012) and cognition (Baker et al, 2010), preserving critical brain areas and reduced brain atrophy in persons with AD (Honea et al, 2009; Burns J. et al, 2008). Therefore, our results agree with the literature that reports that aerobic capacity, by improving cognition and functional capacity, is directly associated with the ability to perform activities of daily living independently and better perception on QoL (Pedroso et al, 2018).

Although not statistically significant, our results also showed a tendency ($p=0.09$) to the high QoL group to have better values of positive agility and dynamic balance. Once more, it is possible to speculate that if we had more participants in the study, the results might be significant. Older adults that have a better agility/dynamic balance also have more autonomy, better environmental interaction and more opportunities for physical practice, which could be important for maintaining their cognitive and physical capacities. In fact, evidences show that preserved cognition plays a key role in the regulation and control of mobility (Montero-Odasso et al, 2015; Ble et al, 2005; Silva et al, 2019; Soumare et al, 2009; Buchman et al, 2011), and the literature had already established the link between mobility and QoL (Fagerstrom & Borglin, 2010). Agility and dynamic balance is also inversely associated with the risk of falls (Shaw F. et al, 2003) one of the major problems that drastically increase institutionalization in older adults with and without dementia (Meuleners et al, 2016). In a study, Sampaio and collaborators (2019) found that agility and dynamic balance scores were positively associated with participants general cognition and perceptive QoL. Also, reinforcing these results Davis et al (2015) showed that agility as a predictor of health-related QoL in community-dwelling older adults.

Generally, low QoL has been associated with decreased physical and cognitive function, and both factors can be modified by increased levels of physical activity (Conde-Sala et al.,

2014). The focus on non-pharmacological interventions, including physical exercise, for AD and other neurocognitive disorders, reside at least in part, on promote a QoL for as long as life lasts. For instances, the association between physical activity on QoL in people with AD has been stablish (Ferrucci et al, 2004). Therefore, the potential benefits of physical activity and exercise may be associated with improvements in physical fitness with beneficial impact in older individuals with neurocognitive disorders (Forbes et al, 2015) and can reflect on higher levels of QoL.

Besides physical fitness deterioration, AD diagnosis have been linked with, lower levels of neurotrophins, insulin resistance, dyslipidemia, higher levels of ROS and inflammation (Qiu et al., 2009) that somehow are connected with lower cognitive functions, that compromise instrumental and basic activities of daily living and decreased QoL (Beck & Frank, 1997; Tekin et al, 2001). In fact, the pathogenesis of neurocognitive disorders, culminates with a significant decline in synaptic activity, neuronal metabolism, neurotrophic factors, as well as increased inflammation (Merlo et al., 2019). Some biomarkers of these alterations have been suggested for the diagnosis and assessment of the progression of AD and other neurocognitive disorders (Qu et al. 2021), most resort to neuroimaging techniques and still not routinely performed in a clinical context. In addition, the need to identify easily accessible blood biomarkers and thus avoid invasive, costly and/or technically challenging procedures in neurocognitive disorders diagnosis and monitoring have been reported (Qu et al., 2021).

In the present study we observed that higher levels of BNDF and IGF-1 were seen in higher QoL group. It is widely accepted that both IGF-1 and BDNF play an important role in the survival and maintenance of developing neurons and can modulate plasticity in the adult brain (Voss et al., 2013; Cotman et al., 2007). Also, it has been suggested these growth factors may protect against AD and a reduction in BNDF and IGF-I expression and signaling has been associated with AD neuropathology (Marques-Aleixo et al, 2020). Interestingly, disruptions in these neurobiological markers have been observed in stress and mood disorders, suggesting that decline of these growth factors may be key factors in the perception of QoL (Pittenger & Duman, 2008). Additionally, there is evidences that suggest a synergistic relationship between IGF-1 and BDNF signaling. For instances, blocking IGF-1 prevents the induction of BDNF expression in response to exercise and IGF-1 upregulate the levels of BDNF receptor, which in turn increases levels of BDNF signaling (McCusker et al, 2006). Physical activity has been shown to increase circulating growth factors like

BDNF and IGF-1 into the brain, (Baker et al., 2009; Adlard et al, 2004; Winter et al, 2007; Fabrigoule et al, 1995; Rasmussen, 2009). Although the exact mechanisms of how these markers can reduce AD neuropathology are not completely identified, it has been suggested that BNDF and IGF-I are vital for mediating angiogenesis and neurogenesis induced by physical activity. So, this improved neurotrophic profile may have an important role in the relationship between physical activity and AD pathology, with positive impact in cognition, depressive symptoms and mood disorders, and consequently improve QoL perception.

In our data, metabolic, lipidic, inflammatory and antioxidant markers do not show any statistical differences between high or low QoL groups. Surprisingly, total cholesterol, triglycerides, glycated hemoglobin, Interleukin 6 and C-reactive protein mean levels are above reference values in the high QoL group, reveling a clinically relevance. These results contrast with the expectation that low QoL may determine a more dependent, less autonomous condition and, perhaps, more prone to a less active and healthy lifestyle. Moreover, these results also do not corroborate many studies showing positive associations between QoL and improved lipidic (Lalonde et al, 2001), metabolic (Saboya et al, 2016) and inflammatory profiles (Nowakowski et al., 2016). There is evidence that highlighted the multifactorial and complex relationship between these biomarkers and QoL. Concerning hyperglycemia, the high intracellular glucose level on the brain, can induce oxidative stress and formation of advanced glycation end products, and both can lead to a neuronal damage (Navarro-Yepes et al., 2014; Tumminia., 2018). This increased neuronal damage, can affect the frontal and subcortical regions of the brain that regulate mood state, which can result in lower cognitive function and depressive symptoms (van Sloten & Schram, 2018). Associated with chronic inflammation, cardiovascular risk factors, including dyslipidemia and obesity appear to be either a cause and a consequence of depressive symptoms, acute psychological stress and anxiety, and can upregulate pro-inflammatory cytokine production (Kiecolt-Glaser et al., 2002), via a bidirectional pathway between the brain and immune system (Maier & Watkins, 1998). Therefore, depressed older adults have been shown to have higher levels of pro-inflammatory markers such as IL-6, CRP and TNF-α (Penninx et al., 2003). Importantly, the majority of the studies suggesting that lipidic, metabolic, inflammatory, and oxidative profile, can independently and cumulatively impair quality of life do not evaluate people with AD. Therefore, more studies accessing QoL and blood biomarkers on people with AD, are necessary to stablish a more consistent relationship between them.

The literature of the last two decades points to the existence of compensatory mechanisms in the brain that are able to protect it temporarily or permanently from neurodegenerative processes (Bobkova & Vorobyov, 2015). These transient paradoxical changes have been described in AD patients and replicated in animal and in vitro models and have been interpreted as compensatory responses to initial damage, which may explain the results found in the low QoL group towards a pro-inflammatory condition. Additionally, it is possible that other biomarkers not included in our analysis may be involved in modeling the mechanisms associated with systemic inflammation process.

It is important to emphasize that IL-6, historically seen as a pro-inflammatory molecule, is currently recognized for not only presenting pro-inflammatory but also anti-inflammatory properties. For instances, physical exercise induces an acute phase response, and plasma IL-6 concentrations increase rapidly in healthy subjects after exercise, establishing an important link between skeletal muscle contraction and exercise-related metabolic changes (Pedersen et al., 2001). In a study that included 198 individuals with AD and investigated the effect of 16 weeks of moderate to high intensity exercise, it showed that plasma IL-6 increased in the exercise group compared to the control, suggesting that the response to exercise in individuals with AD has similar effects to healthy individuals with respect to IL-6 production (Jensen et al 2019).

Finally, the present study shows that all physical fitness components assessed, including upper and lower body strength, aerobic endurance and agility/dynamic balance were correlated with better cognitive performance. Accordingly, a meta-analysis comprising 39 studies had shown that physical exercise improved cognitive function in people over 50 years, independent of the cognitive status (Northey, 2018). Also, positive effects of combined cognitive–physical interventions on global cognitive function in older adults with mild cognitive impairment or dementia were demonstrated by Karssemeijer and collaborators (2017).

Aerobic capacity is the fitness component most studied in dementia states and studies have shown that this capacity is related to better cognitive function (Baker L et al, 2010) and brain health (Kramer & Colcombe, 2018; Gordon et al, 2008; Johnson et al, 2012). As stated before, aerobic training seems to preserve critical brain areas in older adults cognitively healthy (Kramer & Colcombe, 2018) and persons with AD (Honea et al, 2009), and has the ability to prevent brain atrophy (Burns et al, 2008). Also, the upregulation of neurotrophic factors like BDNF, are associated with higher aerobic fitness levels, improving

cerebral structure and function (Churchill et al, 2002; Rasmussen et al, 2009; Seifert T et al, 2010; Wang R & Holsinger R, 2018)**.** For the reasons listed above, aerobic capacity is considered a predictor of cognitive performance (Jonasson et al, 2016; Barnes et al, 2003) and considered an efficient type of training to increase cognition in dementia states (Forbes et al, 2015).

Besides aerobic training, evidences exist that chronic strength training increases blood flow to the brain, resulting in transportation of more nutrients and oxygen **(**Cassilhas et al, 2007; Ozkaya G. et al, 2007). Casillas and collaborators also found that chronic resistance training increases IGF-1 concentrations that is involved in the upregulation of BNDF, promoting neuronal growth, and survival, and therefore improving cognitive performance (Al-Delaimy, 2009; Cotman & Berchtold, 2002).

Cross-sectional studies show that cognition plays a key role in mobility in older adults (Ble et al, 2005; Oliveira Silva et al, 2019; Soumare et al, 2009; Buchman et al, 2011; Montero-Odasso et al, 2015). The fact that agility / dynamic balance involves integrated neural systems which requires certain cognitive stimulation to execute and adapt the movement to the context demands, can explain this relationship (Rossignol S, Dubuc R, Gossard J, 2006).

As stated before, the present study intended to carry out a physical exercise intervention for older individuals with AD and other related neurocognitive disorders. Taking into account our preliminary results, showing that all physical fitness components are associated with cognition and considering the above-mentioned mechanisms that explain the relation between aerobic capacity, strength and agility/dynamic balance and the preservation of structural and functional brain activity, it is possible to speculate that the participants of the present study will benefit the most from a multicomponent exercise program.

There is a number of limitations associated with this study that must be considered when interpreting the results:

i) This is a study with a cross-sectional design, which does not allow inferring causality on the direction of the associations and results should be interpreted with caution. This means that we cannot elucidate whether physical fitness components and specific blood biomarkers evaluated improves quality of life or whether AD patients with better quality of life have more opportunities to exercise/physical activity engagement, and other health related habits that can improve fitness and neurotrophins. Additionally, we cannot affirm

that physical fitness enhances cognitive functions or if people with better cognitive performance are more likely to have better fitness capacity.

ii) The use of self-reported measures like QoL questionnaire, must be acknowledged. Although the data were collected by experienced interviewers, their interpretation may vary between informants (i.e., caregivers' appreciation), and so the findings of these reports must be cautiously interpreted.

iii) The reduced number of participants can also limit the generalizability of our findings across individuals with AD.

iv) There is an assumption in creating Z-scores that all markers involved were equally important and assigned equal weightings, which may not be valid from a physiological standpoint.

v) As biomarkers were only measured once, it is difficult to estimate how accurately they interplay with QoL, which are subjective measure that can change across certain periods of time.

vi) Lastly, this study observed the relationship between a panoply of biomarkers and QoL. However, it is plausible that other health-related biomarkers might play a role.

Future studies using longitudinal or interventional designs, and using more objective measures, should attempt to clarify the possible role of exercise on improving blood biomarkers, physical fitness, body composition, quality of life and cognitive function in older individuals with AD and other related neurocognitive disorders.

7. CONCLUSIONS

In summary, we believe that the findings of this study may contribute to a better understanding of the impact of different biomarkers and physical fitness components on cognitive function and QoL in institutionalized older adults with AD. Considering the obtained results, we can conclude that the QoL seem to be related to higher physical fitness and alterations in neurotrophic markers. Strategies to minimize the worsening of QoL can contribute to the maintenance of physical and mental health in those with neurocognitive disorders, including AD.

For years, science has proven the benefits of regular exercise. However, only in recent decades studies centered on the practice of physical exercise for individuals with neurocognitive disorders have emerged. Although not implemented for reasons already mentioned, based on the knowledge obtained through literature research and review, it seems clear that the application of physical exercise programs in this population has the potential to be considered as one of the most important non-pharmacological strategies that contribute in a preventive therapeutics perspective for the attenuation and development of the deleterious effects associated with AD.

It is well stablished that higher levels of physical exercise are related with QoL, however, the mechanisms involved remain inconclusive due, at least in part, to the multifactorial nature of perceived QoL, particularly in the context of neurocognitive disorders.

Although aerobic endurance stands out as the key component of research and exercise interventions for older individuals with AD, in our study we observed that other capacities have an equivalent importance on cognitive function and QoL. So, when planning exercise interventions is important to take into account the combination of different components of physical fitness through approaches as multicomponent training (combination of strength, aerobic, flexibility and agility/balance training). Also, it's important to consider that exercise alone, will not be sufficient to prevent AD or ameliorate is effects. Other health related factors such as diet, sleep, and cognitive stimulation will provide a multidomain approach that might amplify the benefits of exercise. Finally, it remains inconclusive the optimal duration, frequency, intensity for exercise prescription in this particular population.

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9. APPENDICES

Appendix 1 – Invitation for study, Informed Consent and Anamnesis

Convite para a participação em estudo científico

"Body and Brain" é um projeto de investigação, financiado pela Fundação para a Ciência e Tecnologia (POCI-01-0145-FEDER-031808), que tem por objetivo principal analisar os efeitos de um programa de exercício físico multicomponente em pessoas idosas com comprometimento cognitivo e demência. Este projeto é coordenado pela Professora Doutora Mª Joana Carvalho do Centro de Investigação em Atividade Física, Saúde e Lazer da Faculdade de Desporto e atual Pró-Reitora para o Desporto e Qualidade de Vida da Universidade do Porto.

Neste âmbito, convidamo-lo a colaborar neste estudo através da sua participação no programa de exercício físico que decorrerá de setembro de 2019 a junho de 2020, duas vezes por semana (duração de aproximadamente 1 h 15 min por sessão), e da sua participação na realização das seguintes avaliações:

Todas as avaliações têm caracter voluntário podendo desistir a qualquer momento.

-Questionário de Anamnese
-Avaliação da Composição Corporal pela Medida de DEXA*
-Avaliação da Força de Preensão Manual
- Avaliação da Aptidão Física e Medidas Antropométricas
-Avaliação da Intensidade das Sessões de Treino
-Avaliação do Nível de Atividade Física
-Avaliação da hidratação através da urina
-Avaliação de marcadores inflamatórios e neurotróficos (através de recolha sanguínea)
-Avaliação do Consumo de Oxigénio*
-Avaliação da Pressão e rigidez Arterial
-Avaliação da Função Cognitiva
-Avaliação do Estadio da Demência
-Avaliação da Qualidade de Vida
-Avaliação Ingestão Alimentar
-Avaliação do Risco de Queda

(se não consentir a recolha de dados de uma ou mais categorias, por favor, risque a categoria):

Garante-se a confidencialidade dos dados recolhidos e o uso exclusivo dos mesmos apenas para fins de investigação (artigos científicos, conferências, seminários, congressos, posters), assim como o anonimato dos participantes. Os dados serão conservados durante o prazo de concretização do projeto e por um período adicional necessário ao tratamento e divulgação dos dados.

Aos interessados em participar será dado um consentimento que deverá ser assinado pelo próprio, caso mantenho as suas capacidades psíquicas, e pela família. Serão considerados o Artigo 152.º e o Artigo 138.º do Código Civil que determinam a inabilitação e a interdição dos indivíduos em situação de incapacidade, e o Artigo 145.º do Código Civil que contempla a determinação de um tutor.

Muito obrigado pela sua colaboração!

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Consentimento Informado, Livre e Esclarecido para participação em investigação

- Participante

De acordo com a Declaração de Helsínquia[1] e Convenção de Oviedo[2]

Eu, abaixo-assinado e declaro que participo voluntariamente no projeto de investigação "Body and Brain" da Faculdade de Desporto da Universidade do Porto, que tem por objetivo principal analisar os efeitos de um programa de exercício físico multicomponente em pessoas idosas com comprometimento cognitivo e demência coordenado pela Professora Doutora Joana Carvalho.

Através da participação no programa de exercício físico que decorrerá de setembro de 2019 a junho de 2020, duas vezes por semana (duração de aproximadamente 1 h 15 min por sessão), e da sua participação na realização das seguintes avaliações:

-Questionário de Anamnese
-Avaliação da Composição Corporal pela Medida de DEXA*
-Avaliação da Força de Preensão Manual
- Avaliação da Aptidão Física e Medidas Antropométricas
-Avaliação da Intensidade das Sessões de Treino
-Avaliação do Nível de Atividade Física
-Avaliação da hidratação através da urina
-Avaliação de marcadores inflamatórios e neurotróficos (através de recolha sanguínea)
-Avaliação do Consumo de Oxigénio*
-Avaliação da Pressão e rigidez Arterial
-Avaliação da Função Cognitiva
-Avaliação do Estadio da Demência
-Avaliação da Qualidade de Vida
-Avaliação Ingestão Alimentar
-Avaliação do Risco de Queda

(se não consentir a recolha de dados de uma ou mais categorias, por favor, risque a categoria):

Tomei conhecimento que, de acordo com as recomendações da Declaração de Helsínquia, a informação ou explicação que me foi prestada pelo responsável desta investigação incidiu sobre os objetivos, procedimentos e implicações do referido estudo e que tais não acarretam riscos evidentes para a minha saúde, podendo eu, em qualquer momento, abandonar a pesquisa caso não me sinta satisfeito.

Data: …… /…… /……..

Assinatura do participante: _____
*Se não for o próprio, indicar o grau de parentesco.

Assinatura da pessoa responsável*: _____
* indicar o grau de parentesco.

Assinatura do investigador: _____

1 http://portal.arsnorte.min-saude.pt/portal/page/portal/ARSNorte/Comiss%C3%A3o%20de%20%C3%89tica/Ficheiros/Declaracao_Helsinquia_2008.pdf

2 http://dre.pt/pdf1sdip/2001/01/002A00/00140036.pdf

Anamnese do Idoso

Identificação Sociodemográfica

1. ID: _____

2. Idade: ____ 3. Sexo: Feminino ☐ Masculino ☐

4. Residência (distrito): _____

5. Naturalidade (distrito): _____

6. Estado Civil:

Solteiro/a ☐ Viúvo/a ☐ Separado/divorciado ☐ Casado/União de facto ☐

7. Nível de Escolaridade:

Número total de anos que frequentou a escola: _____

8. Principal profissão desempenhada na vida: _____

Diagnóstico de Demência

9. Qual é o diagnóstico e há quanto tempo recebeu o diagnóstico? _____

_____(refira se meses/anos)

10. Qual a especialidade médica do profissional que concedeu o diagnóstico?

_____

11. Qual a unidade de saúde em que é acompanhado?

_____

Mobilidade

16. Necessita ajudar para caminhar? Sempre □ Algumas Vezes □ Nunca □

16.1 Caso necessite de auxílio, qual a ajuda técnica que costuma utilizar?

Bengala □ Muleta □ Andarilho□ Outra, qual? _____

Quedas

17. Teve alguma queda?

Nos últimos 12 meses? ☐ Nos últimos 6 meses? ☐ Nenhuma queda ☐

18. Tem medo de cair? Sim ☐ Não ☐

18.1 Se sim, deixou de fazer alguma das suas atividades habituais por causa desse medo? Sim ☐ Não ☐

Sono

19. Tem dificuldade em adormecer ou fica muito tempo acordado durante a noite?

Sim ☐ Não☐ Não sei ☐

20. Tem o hábito de dormir durante o dia?

Sim ☐ Não ☐ Não sei ☐

Se sim, durante quanto tempo? _____

Participação em Atividades – Cognitivas, físicas e sociais *(por favor, informar em caso de alteração)*

Nome da Atividade	*Frequência*	*Duração*	*Há quanto tempo participa?*

Comorbilidades

21. Por favor, assinale escolha a(s) opção(ões) que melhor descreve(m) o seu estado de saúde. Caso não esteja(m) apresentada(s) alguma(s) doença(s) que lhe tenha sido diagnosticada(s), por favor, acrescente nos espaços em branco.

		SIM	**NÃO**	**OBSERVAÇÕES**
Cardiovascular	Hipertensão			
	Dislipidemia (Colesterol)			
	Enfarte Miocárdio			
	Insuficiência Cardíaca			
	Doença Vascular Periférica			
	Acidente Vascular Cerebral (AVC) ou Acidente Isquémico Transitório (AIT)			
	Outra (por favor, especifique)			
Músculo-esquelética	Osteoporose			
	Artrose			

	Artrite Reumatoide			
	Hérnias			
	Dores Lombares			
	Outra (por favor, especifique)			
Pulmonar	DPOC			
	Asma			
	Bronquite Crónica			
	Outra (por favor, especifique)			
Outras	Depressão			
	Ansiedade			
	Diabetes (por favor, especifique)			
	Cancro (por favor, especifique)			
	Tumor (por favor, especifique)			
	Patologia Gastrointestinal (por favor, especifique)			
	Patologia no Fígado (por favor, especifique)			
	Patologia Renal (por favor, especifique)			
	Patologia Tiroideia (por favor, especifique)			
	Prótese (joelho, anca, perna, etc.)			

Medicação - Idoso

Nome do Medicamento - Princípio(s) Ativo(s) e Dosagem(ns)	Propósito (Se souber)

Avaliação Aptidão Física e antropométrica

	1ª Avaliação		*2ª Avaliação*	
DATA				
AVALIADOR				
	Valor	*Obs.*	*Valor*	*Obs.*
Peso (kg) [3]				
Altura (m)				
IMC (kg/m^2)				
% Massa Gorda				
% Massa Magra				
Perímetro Cintura (cm)[4]				

Appendix 2 - Senior Fitness Test Battery

Levantar e sentar na cadeira

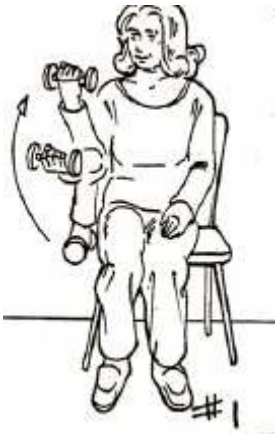
Objetivo: Avaliar a força e resistência dos membros inferiores (número de execuções em 30 segundos, sem a utilização dos membros superiores).

Instrumentos: Cronómetro, cadeira com encosto e sem braços, com altura de assento de aproximadamente 43 cm. Por questões de segurança, a cadeira deve estar encostada contra uma parede de modo a evitar que esta se mova durante a execução do teste.

Procedimento: O teste inicia-se com o participante sentado no meio da cadeira, com as costas direitas e os pés afastados à largura dos ombros e totalmente apoiados no solo. Um dos pés deve estar ligeiramente avançado em relação ao outro para ajudar a manter o equilíbrio. Os membros superiores estão cruzados ao nível dos pulsos e contra o peito. Ao sinal de "partida", o participante eleva-se até à extensão máxima (posição vertical) e regressa à posição inicial de sentado. O participante é encorajado a completar o máximo de repetições num intervalo de tempo de 30 segundos. Após uma demonstração realizada pelo avaliador, o participante testa a execução correta e, de imediato, segue-se4 a aplicação do teste.

Pontuação: A pontuação é obtida pelo número total de execuções corretas num intervalo de 30 segundos. Se o participante estiver no meio da elevação no final dos 30 segundos, deve-se contar esta como uma execução.

Flexão de antebraço



Objetivo: Avaliar a força e resistência do membro superior (número de execuções em 30 segundos).

Instrumentos: Cronómetro, cadeira com encosto e sem braços e halteres de mão (2,27 kg para mulheres e 3,36 kg para homens).

Procedimento: O participante está sentado numa cadeira, com as costas direitas, com os pés totalmente assentes no solo e com o tronco totalmente encostado. O haltere está seguro na mão dominante. O teste inicia com o antebraço em posição inferior, ao lado da cadeira, perpendicular ao solo. Ao sinal de ”partida”, o participante deve pronar gradualmente a palma da mão para cima, enquanto faz a flexão do antebraço no sentido completo do movimento; depois regressa à posição inicial de extensão do antebraço. O avaliador pode colocar os seus dedos no bicípite do executante, de modo a estabilizar a parte superior do braço e assegurar que seja realizada uma flexão completa. É importante que a parte superior do braço permaneça estática durante o teste. Após demonstração por parte do avaliador deverão ser realizadas, uma ou duas tentativas pelo participante para confirmar uma realização correta, seguindo-se a execução do teste durante 30 segundos

Pontuação: A pontuação é obtida pelo número total de flexões corretas realizadas num intervalo de 30 segundos. Se no final dos 30 segundos o antebraço estiver em meia-flexão, deve contabilizar-se como flexão total.

Up and go test

Objetivo: Avaliar a mobilidade física – velocidade, agilidade e equilíbrio dinâmico

Instrumentos: Cronómetro, fita métrica, cone e cadeira com encosta e sem braços a aproximadamente 43 cm de altura. A cadeira deve estar posicionada contra a parede de forma a garantir uma posição estática durante o teste. A cadeira deve também estar numa zona desobstruída, em frente a um cone à distância de 2,44 m (medição desde a ponta da cadeira até à parte anterior do marcador).

Procedimento: O teste é iniciado com o participante sentado na cadeira com os braços cruzados no peito e os pés totalmente assentes no solo. Ao sinal de "partida", o participante eleva-se da cadeira, caminha o mais rápido possível à volta do cone e regressa à cadeira. O participante deve ser informado que se trata de um teste "por tempo", sendo o objetivo caminhar o mais depressa possível (sem correr) à volta do cone e regressar à cadeira. O avaliador deve iniciar o tempo no cronómetro ao sinal de "partida" quer a pessoa tenha ou não iniciado movimento e pará-lo no momento exato em que a pessoa se senta. Após demonstração, o participante deve experimentar uma vez, realizando duas vezes o exercício. Deve chamar-se a atenção do participante de que o tempo é contabilizado até este estar completamente sentado na cadeira.

Pontuação: O resultado corresponde ao tempo decorrido entre o sinal de "partida" até ao momento em que o participante está sentado na cadeira. Registam-se os dois valores até ao 0,01'. O melhor resultado é utilizado para medir o desempenho.

Andar 6 minutos

Objetivo: Avaliar a resistência aeróbia percorrendo a maior distância em 6 minutos.

Instrumentos: Cronómetro, fita métrica e cones.

Montagem: O teste envolve a medição da distância máxima que pode ser caminhada durante 6 minutos ao longo do percurso de 50 m, sendo marcados segmentos de 10 m. os participantes caminham continuamente em redor do percurso marcado, durante um período de 6 minutos, tentando percorrer a máxima distância possível.

Procedimento: Para facilitar o processo de contagem de voltas ao percurso, cada participante recebe um elástico na partida sempre que uma volta é terminada. Ao sinal de "partida", os participantes são instruídos para caminhar o mais rapidamente possível (sem correrem) na distância marcada à volta dos cones. Se necessário, os participantes podem parar e descansar, sentando-se e retomando o percurso.

Pontuação: O resultado representa o número total de metros caminhados durante os 6 minutos.

Appendix 3 – QoL-AD – Versão Portuguesa

QOL – AD *versão portuguesa*

(Versão de entrevista para doente)

Aplicada por entrevistador de acordo com as instruções. Fazer um círculo à volta das respostas:				
1- Saúde Física	Fraco	Razoável	Bom	Excelente
2- Energia	Fraco	Razoável	Bom	Excelente
3- Humor/ Disposição	Fraco	Razoável	Bom	Excelente
4- Condições de vida	Fraco	Razoável	Bom	Excelente
5- Memória	Fraco	Razoável	Bom	Excelente
6- Família	Fraco	Razoável	Bom	Excelente
7- Casamento	Fraco	Razoável	Bom	Excelente
8- Amigos	Fraco	Razoável	Bom	Excelente
9- Em geral, como se sente	Fraco	Razoável	Bom	Excelente
10- Capacidade de realizar tarefas em casa	Fraco	Razoável	Bom	Excelente
11- Capacidade de fazer coisas para se divertir	Fraco	Razoável	Bom	Excelente
12- Dinheiro	Fraco	Razoável	Bom	Excelente
13- A Vida como um todo	Fraco	Razoável	Bom	Excelente

Comentários:_____
_____
_____

QOL – AD *versão portuguesa*

(Versão de questionário para familiar ou prestador de cuidados)

As questões seguintes dizem respeito à Qualidade de Vida do doente:

Quando pensa sobre a vida do doente, podemos considerar vários aspectos, alguns dos quais estão abaixo mencionados. Por favor, pense em cada um dos itens e classifique a qualidade de vida actual do doente, como ele a consideraria, em cada área usando uma de quatro palavras: **fraco, razoável, bom, excelente**. Classifique estes itens com base na vida do doente no momento presente (ou seja, nas últimas semanas). Se tiver questões acerca de qualquer item, por favor peça ajuda à pessoa que lhe forneceu este questionário.

Faça um círculo à volta das respostas:

1- Saúde Física	Fraco	Razoável	Bom	Excelente
2- Energia	Fraco	Razoável	Bom	Excelente
3- Humor/ Disposição	Fraco	Razoável	Bom	Excelente
4- Condições de vida	Fraco	Razoável	Bom	Excelente
5- Memória	Fraco	Razoável	Bom	Excelente
6- Família	Fraco	Razoável	Bom	Excelente
7- Casamento	Fraco	Razoável	Bom	Excelente
8- Amigos	Fraco	Razoável	Bom	Excelente
9- Em geral, como se sente	Fraco	Razoável	Bom	Excelente
10- Capacidade de realizar as tarefas em casa	Fraco	Razoável	Bom	Excelente
11- Capacidade de fazer coisas para se divertir	Fraco	Razoável	Bom	Excelente
12- Dinheiro	Fraco	Razoável	Bom	Excelente
13- Vida como um todo	Fraco	Razoável	Bom	Excelente

Comentários:

_____
_____
_____

Instruções para entrevistadores

A escala Qualidade de Vida-DA (QDV-DA) é administrada em formato de entrevista, a indivíduos com demência, de acordo com as instruções abaixo mencionadas.
Entregue o formulário ao participante, de modo que possa observá-lo, enquanto dá as seguintes instruções (as instruções devem ser seguidas rigorosamente e de acordo com as palavras a **negrito**):
Gostaria de lhe fazer algumas perguntas sobre a sua qualidade de vida. Por favor classifique os diferentes aspectos da sua vida, utilizando uma de quatro palavras: Fraco, Razoável, Bom, Excelente.
Aponte para cada palavra (fraco, razoável, bom e excelente) no formulário, enquanto a diz.
Quando pensa na sua vida, existem diferentes aspectos, como a sua saúde física, energia, família, dinheiro e outros. Vou-lhe pedir que classifique cada uma destas áreas. Gostaríamos de saber como se sente em relação à sua situação presente em cada área.
Se não tiver a certeza sobre o significado de alguma pergunta, pode perguntar-me. Se tiver dificuldade em classificar qualquer item, escolha o que lhe parecer melhor.
Geralmente é evidente quando a pessoa entende as perguntas. A maioria das pessoas que são capazes de comunicar e responder a perguntas simples, compreendem o sistema de medida utilizado. Se o participante responder o mesmo em todas as perguntas, ou disser algo que demonstre falta de compreensão, da escala, o entrevistador deve clarificar a pergunta. Contudo, o entrevistador não deve em circunstância alguma, sugerir uma determinada resposta. Cada uma das quatro respostas possíveis, deve ser apresentada, e o participante deve seleccionar apenas uma das quatro.
Se o participante não conseguir escolher uma resposta a um ou vários itens, tal deverá ser indicado nos comentários. Se o participante não conseguir compreender e/ou responder a dois ou mais itens, o teste poderá terminar, e tal deverá ser indicado nos comentários.
À medida que for lendo os itens abaixo mencionados, peça ao participante para fazer um círculo à volta da opção de resposta. Se o participante tiver dificuldade em fazer o círculo à volta da palavra, pode solicitar-lhe que a aponte ou que a diga, podendo o entrevistador fazer o círculo. O participante deve segurar a folha de respostas e segui-la à medida que o entrevistador for lendo cada item.

1. **Para começar, como se sente em relação à sua saúde física? Diria que é fraco, razoável, bom ou excelente? Faça um círculo à volta da palavra que pensa que melhor descreve a sua saúde física agora.**

2. **Como se sente em relação à sua energia? Acha que é fraco, razoável, bom ou excelente?** Se o participante responder que alguns dias são melhores do que outros, peça-lhe para classificar como se tem sentido a maior parte do tempo.

3. **Como tem sido o seu humor ou disposição ultimamente? Tem-se sentido bem disposto ou tem-se sentido abatido (em baixo)? Classificaria a sua disposição como fraco, razoável, bom ou excelente?**

4. **E em relação às suas condições de vida? O que pensa do local onde vive agora? Diria que é fraco, razoável, bom ou excelente?**

5. **E em relação à sua memória? Diria que é fraco, razoável, bom ou excelente?**

6. **E sobre a sua família e o seu relacionamento com os seus familiares? Descreve-a como sendo fraco, razoável, bom ou excelente?** Se o participante disser que não tem família, questione-o sobre os irmãos, as irmãs, os filhos, as sobrinhas ou sobrinhos.

7. **Como se sente em relação ao seu casamento? Como é a sua relação com (nome do cônjuge). Sente que é fraco, razoável, bom ou excelente?** Alguns participantes são solteiros, viúvos ou divorciados. Nesse caso pergunte como se sente em relação à pessoa com a qual têm a relação mais próxima, quer seja membro da família ou amigo. Se existir um cuidador familiar, pergunte-lhe sobre a sua relação com essa pessoa. Se não houver ninguém apropriado, ou o participante tiver dúvidas, pontue o item como "não resposta". Se a classificação do participante disser respeito à sua relação com alguém que não o cônjuge, registe a relação na secção de comentários.

8. **Como descreve a sua relação actual com os seus amigos? Diria que é fraco, razoável, bom ou excelente?** Se o participante responder que não tem amigos, ou que todos os seus amigos morreram, pesquise mais. **Há alguém com quem goste de conviver para além da sua família? Chamaria a essa pessoa amigo?** Se o participante continuar a afirmar que não tem amigos, pergunte: **Como se sente por não ter amigos? Fraco, razoável, bom ou excelente.**

9. **Quando pensa em si próprio em geral, como se sente? Diria fraco, razoável, bom ou excelente?**

10. **Como se sente no que diz respeito à sua capacidade para realizar tarefas em casa, ou outras coisas que precisa de fazer? Diria que é fraco, razoável, bom ou excelente?**

11. **E sobre a sua capacidade para fazer coisas para se divertir ou que lhe dão prazer? Diria que é fraco, razoável, bom ou excelente?**

12. **Como se sente em relação à sua situação actual com o dinheiro, à sua situação financeira. Diria que é fraco, razoável, bom ou excelente?** Se o participante hesitar, explique-lhe que não pretende saber qual é a situação dele (tal como a quantidade de dinheiro), mas apenas o que sente acerca disso.

13. **Como descreve a sua vida como um todo? Quando pensa na sua vida como um todo, como se sente em relação à sua vida? Diria que é fraco, razoável, bom ou excelente?**

INSTRUÇÕES PARA A PONTUAÇÃO DA QOL:

A pontuação é atribuída a cada item da seguinte forma: fraco =1; razoável =2, Bom =3, excelente =4;

A pontuação total é a soma dos 13 itens.

Para cálculo de pontuação conjunta: (2 x pontuação escala doente + pontuação escala cuidador): 3.

Appendix 4 – QoL-AD – Versão Original

Quality of Life in Alzheimer's Disease

QOL-AD

Instructions for Interviewers

The QOL-AD is administered in interview format to individuals with dementia, following the instructions below. The interview is carried out with the subject and/or an informant. The subject should be interviewed alone.

Hand the form to the participant, so that he or she may look at it as you give the following instructions (instructions should closely follow the wording given in bold type):

I want to ask you some questions about your quality of life and have you rate different aspects of your life using one of four words: poor, fair, good, or excellent.

Point to each word (poor, fair, good, and excellent) on the form as you say it.

When you think about your life, there are different aspects, like your physical health, energy, family, money, and others. I'm going to ask you to rate each of these areas. We want to find out how you feel about your current situation in each area.

If you're not sure about what a question means, you can ask me about it. If you have difficulty rating any item, just give it your best guess.

It is usually apparent whether an individual understands the questions, and most individuals who are able to communicate and respond to simple questions can understand the measure. If the participant answers all questions the same, or says something that indicates a lack of understanding, the interviewer is encouraged to clarify the question. However, under no circumstances should the interviewer suggest a specific response. Each of the four possible responses should be presented, and the participant should pick one of the four.

If a participant is unable to choose a response to a particular item or items, this should be noted in the comments. If the participant is unable to comprehend and/or respond to two or more items, the testing may be discontinued, and this should be noted in the comments.

As you read the items listed below, ask the participant to circle her/his response. If the participant has difficulty circling the word, you may ask her/him to point to the word or say the word, and you may circle it for him or her. You should let the participant hold his or her own copy of the measure, and follow along as you read each item.

1. **First of all, how do you feel about your physical health? Would you say it's poor, fair, good, or excellent? Circle whichever word you think best describes your physical health right now.**
2. **How do you feel about your energy level? Do you think it is poor, fair, good, or excellent?** If the participant says that some days are better than others, ask him or her to rate how she/he has been feeling most of the time lately.
3. **How has your mood been lately? Have your spirits been good, or have you been feeling down? Would you rate your mood as poor, fair, good, or excellent?**
4. **How about your living situation? How do you feel about the place you live now? Would you say it's poor, fair, good, or excellent?**
5. **How about your memory? Would you say it is poor, fair, good, or excellent?**
6. **How about your family and your relationship with family members? Would you describe it as poor, fair, good, or excellent?** If the respondent says they have no family, ask about brothers, sisters, children, nieces, nephews.
7. **How do you feel about your marriage? How is your relationship with (spouse's name). Do you feel it's poor, fair, good, or excellent?** Some participants will be single, widowed, or divorced. When this is the case, ask how they feel about the person with whom they have the closest relationship, whether it's a family member or friend. If there is a family caregiver, ask about their relationship with this person. It there is no one appropriate, or the participant is unsure, score the item as missing.

Quality of Life in Alzheimer's Disease cont'd

QOL-AD

8. **How would you describe your current relationship with your friends? Would you say it's poor, fair, good, or excellent?** If the respondent answers that they have no friends, or all their friends have died, probe further. **Do you have anyone you enjoy being with besides your family? Would you call that person a friend?** If the respondent still says they have no friends, ask **how do you feel about having no friends—poor, fair, good, or excellent?**
9. **How do you feel about yourself—when you think of your whole self, and all the different things about you, would you say it's poor, fair, good, or excellent?**
10. **How do you feel about your ability to do things like chores around the house or other things you need to do? Would you say it's poor, fair, good, or excellent?**
11. **How about your ability to do things for fun, that you enjoy? Would you say it's poor, fair, good, or excellent?**
12. **How do you feel about your current situation with money, your financial situation? Do you feel it's poor, fair, good, or excellent?** If the respondent hesitates, explain that you don't want to know what their situation is (as in amount of money), just how they feel about it.
13. **How would you describe your life as a whole. When you think about your life as a whole, everything together, how do you feel about your life? Would you say it's poor, fair, good, or excellent?**

Scoring instructions for QOL-AD:
Points are assigned to each item as follows: poor = 1, fair = 2, good = 3, excellent = 4.
The total score is the sum of all 13 items.

UWMC/ADPR/QOL
Aging and Dementia: Quality of Life in AD
Quality of Life: AD
(Family Version)

ID Number	Assessment Number	Interview Date	Score (for clinician's use only)
☐☐☐☐☐☐	☐☐	☐☐ ☐☐ ☐☐ Month Day Year	

Instructions: Please rate your relative's current situation, as you see it. Circle your responses.

1. Physical health	Poor	Fair	Good	Excellent	
2 Energy	Poor	Fair	Good	Excellent	
3. Mood	Poor	Fair	Good	Excellent	
4. Living situation	Poor	Fair	Good	Excellent	
5. Memory	Poor	Fair	Good	Excellent	
6. Family	Poor	Fair	Good	Excellent	
7. Marriage	Poor	Fair	Good	Excellent	
8. Friends	Poor	Fair	Good	Excellent	
9. Self as a whole	Poor	Fair	Good	Excellent	
10. Ability to do chores around the house	Poor	Fair	Good	Excellent	
11. Ability to do things for fun	Poor	Fair	Good	Excellent	
12. Money	Poor	Fair	Good	Excellent	
13. Life as a whole	Poor	Fair	Good	Excellent	

Comments:
_____
_____

Total

UWMC/ADPR/QOL
Aging and Dementia: Quality of Life in AD

Quality of Life: AD

(Participant Version)

ID Number	Assessment Number	Interview Date	Score (for clinician's use only)
☐☐☐☐☐☐	☐☐	☐☐ ☐☐ ☐☐ Month Day Year	

Instructions: Interviewer administer according to standard instructions. Circle your responses.

1. Physical health	Poor	Fair	Good	Excellent	
2 Energy	Poor	Fair	Good	Excellent	
3. Mood	Poor	Fair	Good	Excellent	
4. Living situation	Poor	Fair	Good	Excellent	
5. Memory	Poor	Fair	Good	Excellent	
6. Family	Poor	Fair	Good	Excellent	
7. Marriage	Poor	Fair	Good	Excellent	
8. Friends	Poor	Fair	Good	Excellent	
9. Self as a whole	Poor	Fair	Good	Excellent	
10. Ability to do chores around the house	Poor	Fair	Good	Excellent	
11. Ability to do things for fun	Poor	Fair	Good	Excellent	
12. Money	Poor	Fair	Good	Excellent	
13. Life as a whole	Poor	Fair	Good	Excellent	

Comments:

_____

_____

Total

Quality of Life in Alzheimer's Disease cont'd

QOL-AD

Score Summary Sheet

Informant's score of subject's QOL	☐ (maximum 52)
Subject's own QOL rating	☐ (maximum 52)

Appendix 5 – Mini Mental Score Examination - Versão Portuguesa

1 – Orientação (1 ponto por cada resposta correta)

_____ Em que ano estamos?

_____ Em que mês estamos?

_____ Em que dia do mês estamos?

_____ Em que dia da semana estamos?

_____ Em que estação do ano estamos?

_____ Em que país estamos?

_____ Em que distrito vive?

_____ Em que terra vive?

_____ Em que casa estamos?

_____ Em que andar estamos?

2 – Retenção (contar 1 ponto por cada palavra corretamente repetida)

"Vou dizer 3 palavras; queria que as repetisse, mas só depois de eu as dizer todas; procure ficar a sabê-las de cor".
_____ Pera _____ Gato _____ Bola

3 – Atenção e Cálculo (1 ponto por cada resposta correta. Se der uma resposta errada mas depois continuar a subtrair bem, consideram-se as seguintes como corretas. Parar ao fim de 5 respostas)
"Agora peço-lhe que me diga quantos são 30 menos 3 e depois ao número encontrado volta a tirar 3 e repete assim até eu lhe dizer para parar".

27 __ 24 __ 21 __ 18 __ 15 __

4 – Evocação (1 ponto por cada resposta correta)

“Veja se consegue dizer as três palavras que pedi há pouco para decorar”.

_____ Pera _____ Gato _____ Bola

5 – Linguagem (1 ponto por cada resposta correta) a) “Como se chama isto?” Mostrar os objetos: _____ Relógio _____ Lápis

b) “Repita a frase que eu lhe vou dizer: O RATO ROEU A ROLHA ____

c) “Quando eu lhe der esta folha de papel, pegue nela com a mão direita, dobre-a ao meio e ponha sobre a mesa”; dar a folha segurando com as duas mãos.
_____ Pega com a mão direita

_____ Dobra ao meio

_____ Coloca onde deve

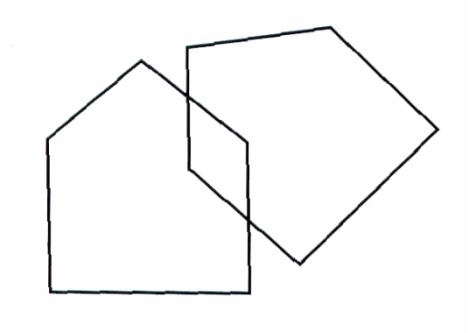
d) “Leia o que está neste cartão e faça o que lá diz”. Mostrar um cartão com a frase bem legível, “FECHE OS OLHOS”; sendo analfabeto, lê-se a frase. _____ Fechou os olhos

e) “Escreva uma frase inteira aqui”. Deve ter sujeito e verbo e fazer sentido; os erros gramaticais não prejudicam a pontuação.
Frase:_____

6. Habilidade Construtiva (1 ponto pela cópia correta)

Deve copiar um desenho. Dois pentágonos parcialmente sobrepostos; cada um deve ficar com 5 lados, dois dos quais intersetados. Não valorizar tremor ou rotação.

Cópia:



Defeito cognitivo em função do grau de escolaridade (Analfabetos ≤ 15; 1-11 anos de escolaridade ≤ 22; Mais que 11 anos de escolaridade ≤ 27).