

Review

# Healthy Aging in Menopause: Prevention of Cognitive Decline, Depression and Dementia through Physical Exercise

Carmen Guerrero-González <sup>1</sup>, Cristina Cueto-Ureña <sup>1</sup>, Vanesa Cantón-Habas <sup>2,3</sup>, María Jesús Ramírez-Expósito <sup>1</sup>  
and José Manuel Martínez-Martos <sup>1,\*</sup>

<sup>1</sup> Experimental and Clinical Physiopathology Research Group CTS-1039, Department of Health Sciences, School of Experimental and Health Sciences, University of Jaén, 23071 Jaén, Spain; ccueto@ujaen.es (C.C.-U.); mramirez@ujaen.es (M.J.R.-E.)

<sup>2</sup> Department of Nursing, Pharmacology and Physiotherapy, Faculty of Medicine and Nursing, University of Córdoba, Avda. Menéndez Pidal, s/n, 14004 Córdoba, Spain; n92cahav@uco.es

<sup>3</sup> Maimonides Institute of Biomedical Research of Córdoba (IMIBIC), Reina Sofía University Hospital, Avda. Menéndez Pidal, s/n, 14004 Córdoba, Spain

\* Correspondence: jmmartos@ujaen.es; Tel.: +34-953-212-600

**Abstract:** The aging of the global population is a significant and complex phenomenon with far-reaching implications for healthcare systems and society. By 2030, it is projected that the number of individuals over the age of 65 will increase by nearly 1 billion, largely due to advancements in healthcare and improvements in quality of life. Aging is a multifaceted process that encompasses a wide array of changes, spanning from the cellular level to the intricate physiological systems of the human body. At the central nervous system level, aging represents a major risk factor for conditions such as depression and cognitive impairment, which are likely linked to neuroinflammatory processes and can potentially lead to more severe dementias, including Alzheimer’s disease (AD). The higher prevalence of AD in women compared to men has led to speculation that the onset of menopause and associated phenomena, particularly the decline in estrogen levels, may play a role in the development of the disease. Furthermore, research has shown that physical exercise confers both physical and mental health benefits to older adults, with women potentially experiencing the greatest advantages. Understanding the multifaceted nature of aging and its implications for health will ensure that older adults receive the support and care essential for maintaining their health and quality of life.

**Keywords:** aging; cognitive impairment; depression; Alzheimer’s disease; menopause; neuroinflammation; physical exercise



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## 1. Introduction

Aging is the set of alterations that occur at the cellular and physiological level as a consequence of the passage of time. According to the WHO, it is more precisely defined as the “physiological process that begins at conception and causes changes in the characteristics of the species throughout the life cycle; these changes produce a limitation of the adaptability of the organism in relation to the environment. The rates of these changes in the various organs of the same individual or in different individuals are not the same” [1–3]. Population aging is increasing rapidly as health care and living standards improve, especially in developed countries, and this is a major challenge facing the world’s population in general [4–7].

One of the visible consequences of aging is the onset of cognitive decline. In this last stage of life, the brain begins to atrophy, reducing blood flow and weight. This greatly affects the functioning of the central nervous system (CNS), causing memory loss, difficulty concentrating and learning problems. This reduction in the individual’s capacity is associated with an increased risk of dementia among other phenomena affecting health, such as different types of functional limitations and disability [4,6,8–13]. In fact, a first

stage is the onset of depression, in turn associated with various risk factors. It is currently considered that between 30–50% of elderly people suffer from depression, a percentage that increases in individuals with cognitive impairment. A similar percentage increase can also be observed with other chronic degenerative diseases [14–16].

Among the pathophysiological substrates of these processes is CNS inflammation, also called neuroinflammation, which is also clearly related to cognitive impairment and aging [17]. Moreover, neuroinflammation also seems to be responsible for one of the diseases related to aging, that is, Alzheimer's disease (AD), or dementia of Alzheimer's type (DAD). This pathology is a neurodegenerative disorder characterized by the gradual and irreparable deterioration of memory and other cognitive functions, which impairs patients and their mental and social functioning, daily activities and way of life [18]. There are currently almost 50 million people with Alzheimer's disease globally, with the number expected to increase by 70% by mid-century [19–21].

A peculiar feature of AD is that it is diagnosed more frequently in women than in men (almost two-thirds of all patients are women). Although women live an average of 4.5 years longer than men and they outnumber men from the age of 85 years in most subpopulations worldwide, which could explain this difference, it is difficult to assess differences in the actual risk of AD between men and women of the same age, since studies have found contradictory results [21].

However, this difference has been linked to the onset of menopause. Menopause is the change in a woman from a reproductive to a non-reproductive state and is diagnosed 12 months after the permanent cessation of ovarian function. It should be noted that, as life expectancy increases, women live with menopause for about one-third of their lives. It is estimated that by 2030, a total of 1.2 billion women will be menopausal or postmenopausal [22–25].

In addition, one of the factors that exacerbates a number of health problems, including menopause-related problems themselves, is physical inactivity. Physical exercise has been shown to be one of the non-pharmacological interventions with the most benefits for mental and physical health in older adults and postmenopausal women [26–35]. In addition, it also has an important role in the prevention of cognitive decline because it induces functional and structural variations in the brain that provide important biological and psychological benefits [7,36–38].

The importance of considering sex as a biological variable has been recently highlighted in scientific research, particularly in the field of neuroscience [39–41]. The exclusive use of male animal models in preclinical research has led to higher rates of misdiagnosis and adverse side effects in women. The authors also note that the lack of studies that include both sexes in preclinical research is partly due to a lack of incentives [40]. Therefore, a cultural and structural shift is needed in the way research is conducted and scientific progress is evaluated to produce a more equitable, representative, and more translational body of knowledge. Thus, it is crucial to conduct preclinical and clinical studies on both sexes to ensure that research is more representative and accurate. This is especially important when it comes to studying the effects of physical exercise in older people. Physical exercise can have a positive impact on the health of older adults, including improved cardiovascular function, increased muscle strength, and reduced risk of falls [42]. However, the study also found that the benefits of physical exercise may differ between men and women, particularly postmenopausal women. Postmenopausal women are at a higher risk of developing osteoporosis, a condition that weakens bones and increases the risk of fractures [42]. Physical exercise can help prevent osteoporosis by increasing bone density, but the benefits may be more pronounced in postmenopausal women than in men [40]. Therefore, it is essential to provide more incentives for researchers to conduct preclinical and clinical studies on both sexes to ensure that scientific research is more representative and accurate, leading to better health outcomes for all.

The main objective of this work is to know the mechanisms underlying age-related cognitive decline, with a specific emphasis on neuroinflammation, its association with

depression and Alzheimer's disease (AD), and the potential factors contributing to sexual dimorphism, particularly in relation to the hormonal status of women. Additionally, we aim to evaluate the impact of physical exercise as an intervention for preventing these conditions, particularly in the context of menopausal women.

The choice to explore cognitive decline, depression, and physical exercise in the context of menopause is underpinned by their interconnectedness and significant implications for women's health. Cognitive decline is a complex process influenced by various factors, including neuroinflammation, which has been increasingly recognized as a contributing factor to age-related cognitive impairment. Furthermore, the link between neuroinflammation and its progression to depression and AD is a critical area of study, given the substantial burden of these conditions on individuals and healthcare systems.

Importantly, the hormonal transitions associated with menopause have been identified as a unique period in a woman's life that may influence cognitive function and mood regulation. The fluctuations in sex hormones, particularly estrogen, during menopause have been implicated in the increased vulnerability to neuroinflammation and the higher prevalence of depression and AD in women. Understanding the underlying mechanisms linking these factors is essential for developing targeted interventions and personalized approaches to mitigate the impact of cognitive decline and mood disorders in menopausal women.

Moreover, the consideration of physical exercise as a potential intervention is motivated by its well-documented benefits in promoting cognitive health and reducing the risk of depression and AD. In the context of menopause, this role becomes even more pertinent due to its potential to mitigate the adverse effects of hormonal changes on brain health and mood regulation. Therefore, evaluating its magnitude as a preventive measure in the context of menopausal women is integral to comprehensively addressing the multifaceted nature of cognitive aging and associated conditions.

## 2. Methodology

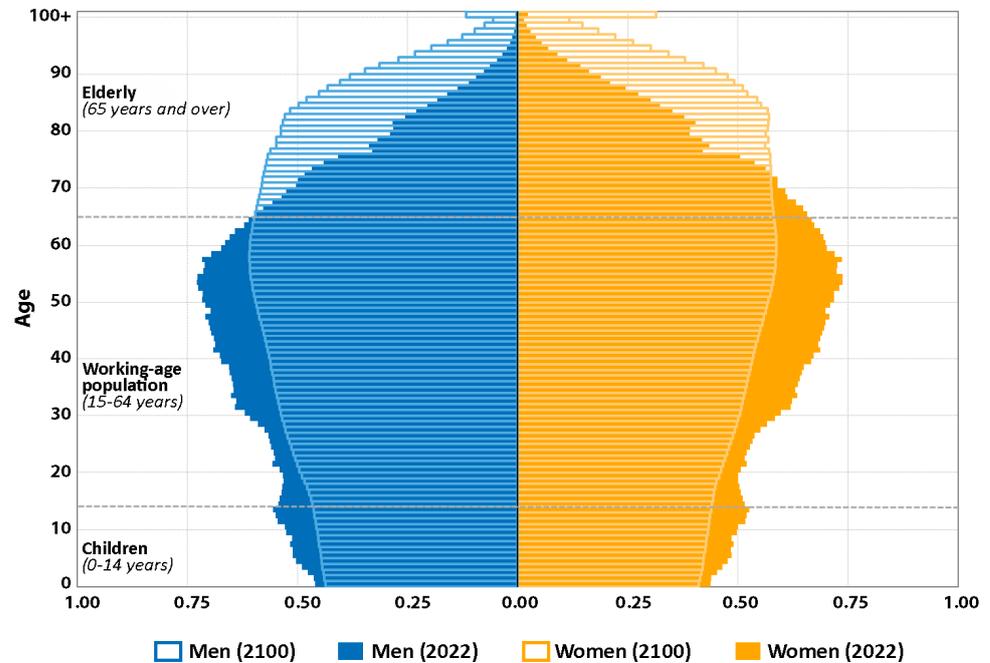
A comprehensive literature review was conducted in the English language utilizing the PUBMED, WEB OF SCIENCE, and Google Scholar databases. Various combinations of search terms, including aging, cognitive impairment, depression, Alzheimer's disease, menopause, neuroinflammation, and physical exercise, were employed. The search was restricted to articles published within the last six years. All types of scholarly articles were considered for inclusion and were assessed for relevance. Conference abstracts, book references, case reports, and content deemed irrelevant were excluded from the review process.

## 3. Aging

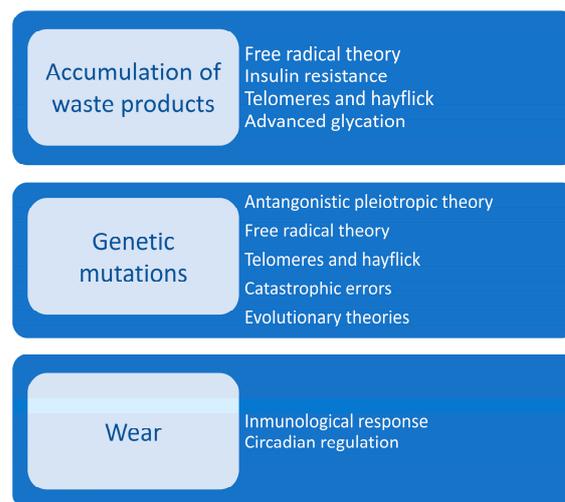
Aging is a process that takes place at different levels: physiological, morphological, cellular and molecular, but also social and psychological [35]. It is estimated that, by 2030, the number of adults over 65 years of age in the world will increase from 420 million in the year 2000 to almost 1 billion in that year. In Spain, according to data from the National Institute of Statistics (INE) in 2022, this demographic covered approximately 47 million people, of whom 19.9% were aged 65 or over. This means that around 9.3 million people are considered elderly. In addition, the aging of the population is a continuing trend, as the provision of adults over 65 is expected to continue to grow in the coming decades. According to INE projections, in 2031 it is estimated that 23.8% of the Spanish population will be over 65 years of age, and in 2066 this figure could reach 34.7% (Figure 1) [43]. As a result, old age has become the greatest risk component for the development of chronic degenerative conditions [2].

Aging is a process that has been defined as universal, intrinsic, progressive and deleterious: universal, because aging occurs in all individuals; intrinsic, because the causes that produce it are endogenous, that is, it does not depend on external factors; progressive, because it occurs gradually throughout life; and harmful, because that is the way of thinking about any harmful aging process. Moreover, this definition is supported by different theories

about how aging develops over time (Figure 2). However, the exact cause is unknown [44]. Among these different theories, the free radical theory states that free oxygen-derived radicals are responsible for age-related oxidative damage. As our antioxidant system cannot cope with all the reactive oxygen species (ROS) produced throughout cellular life, this creates an imbalance between oxidants and antioxidants [38,45–48].



**Figure 1.** Pyramid projection of world population by gender and age groups. Age is divided into three categories: children (0–14 years), working-age population (15–64 years) and elderly (65 years and over). The proportion of men (blue) and women (orange) is based on data for the year 2022 and for a projection to the year 2100. A significant increase in the proportion of elderly people is expected for the year 2100, especially among women.



**Figure 2.** Theories of aging. The diagram illustrates the three primary categories of aging theories. Each category is further subdivided into specific theories that explain the underlying mechanisms of aging processes, supporting the multifaceted nature of aging and its implications for human health and longevity.

Aging can also be divided now into two types: primary and secondary. Primary aging refers to the varieties observed in aging, those that cannot be avoided and those that are not related to diseases, that is, it focuses on the changes produced in the genetic, molecular and cellular mechanism involved in the process. Secondary aging suggests that it is due to changes produced by external phenomena that occur throughout life, such as habits and lifestyle [38,49–52]. However, it has been shown that there are multiple functional and morphological changes associated with aging that take place in the locomotor, cardiovascular, central nervous, metabolic and renal systems (Table 1). In general, the cognitive functions of individuals (attention, direction, perception, speed, memory, etc.) will change with increasing age, which will disrupt the psychological mechanisms necessary in the vital process [16,53].

**Table 1.** Functional and morphological changes associated with aging that take place at different physiological systems.

Physiological System	Functional Changes	Morphological Changes
Glucose metabolism	-Increased insulin resistance and predisposition to diabetes. -Increased production of adipokines and inflammatory factors.	-Lower $\beta$ -pancreatic cell mass. -Fatty infiltration of tissues. -Increased visceral fat.
Endocrine	-Decrease in growth hormone (GH). -Decreased sensitivity to hormones.	-Decreases cell size, weight and number of cells. -Increases fibrous content. -Decreases the number and/or affinity of receptors.
Renal	-Lower hydroxylation of vitamin D. -Lower levels of renin and aldosterone. -Reduced ability to concentrate urine.	-Thickening of glomerular basement membrane. -Sclerosis of glomerular arteries, due to the formation of atheromatous plaques at this level. -Thinning renal cortex and decreased nephrons number.
Locomotor	-Bone fragility due to loss of muscle mass. -Decrease in strength.	-Morphological changes in the bone system: osteoporosis. -Fatty infiltration of the muscle. -Loss of muscle mass.
Cardiovascular	-Increased risk of arrhythmias. -Endothelial dysfunction. -Preservation of ejection fraction. -Vascular and cardiac stiffness.	-Decreased cardiomyocytes and increased extracellular matrix. -Cardiac hypertrophy with thickening of the septum and especially of the left ventricle. -Loss of elastin fibers. -Increase of collagenous matrix in tunica media.
Central nervous system	-Reduced motor skills. -Decreased recent memory. -Slower processing speed. -Proprioceptive sensitivity is altered.	-Minimal neuronal loss, focal. -Increased cerebrospinal fluid. -Lower brain mass: decrease in volume and weight.

At the cardiovascular level, the most relevant changes associated with aging are those that occur in the vascular wall, which promote an increase in arterial pressure with physical exercise. The increase in stiffness also produces ventricular hypertrophy and a lower capacitance of the elastic arteries, leading to difficulty in ventricular emptying and aortic dilatation. From a functional point of view, there is a decrease in vascular response due to the aging of the endothelium by reducing nitric oxide (NO) synthesis and the response to soluble guanylate cyclase (an enzyme that acts as a nitric oxide receptor and is involved in peripheral vasodilatation), thus producing an imbalance between vasodilator and vasoconstrictor substances [3,54].

Focusing additionally on this alteration, it should be pointed out that it is fundamentally characterized by a progressive decrease in the bioavailability of NO and by the increased production of vasoconstrictor factors derived from cyclooxygenase (COX). Both changes are in turn related to increased production of oxygen free radicals or reactive oxygen species (such as peroxides), both of which are vasoconstrictors. However,

NO bioavailability varies according to the synthesis from its precursor, the amino acid L-arginine, by endothelial (NOSe), neuronal (NOSn) and inducible (NOSi) NO synthase isoenzymes (NOS). During aging, an increase in asymmetric NG-NG'-dimethyl-arginine (ADMA), which is a by-product of L-arginine methylation, is also observed. This functions as an endogenous inhibitor of NOSe, also producing a decrease in tetrahydrobiopterin (BH4), which is a necessary cofactor for NO synthesis. However, as a compensatory mechanism, there is an increase in NOSi expression, which is related to a pro-atheromatous phenotype and degeneration of the endothelium-dependent vasomotor response [3,54].

Thus, the important role of NO in the maintenance of neurovascular function in the CNS is evident, as it is a vasodilator and an important inhibitor of platelet aggregation. These processes also promote smooth muscle cell destruction and leukocyte adhesion, have anti-inflammatory effects, and promote angiogenesis. As a derivative of endothelial cells, NO acts as an energetic neurovascular-nerve connecting element, in addition to various regular physiological processes, such as immunological processes, vascular tone and neurotransmission processes [18,55–57].

Alterations in any of these processes can accelerate cognitive decline. Indeed, NO has also been shown to help regulate the expression and processing of  $\beta$ -amyloid precursor protein in vascular endothelium and nervous tissue, and acts as a neurovascular protective molecule during aging; however, exercise appears to be a protective factor in cognitive decline by promoting guanylate cyclase signaling and activation of phosphodiesterase isoform inhibitors, mediators of the beneficial effects of endothelial NO [18,55–57].

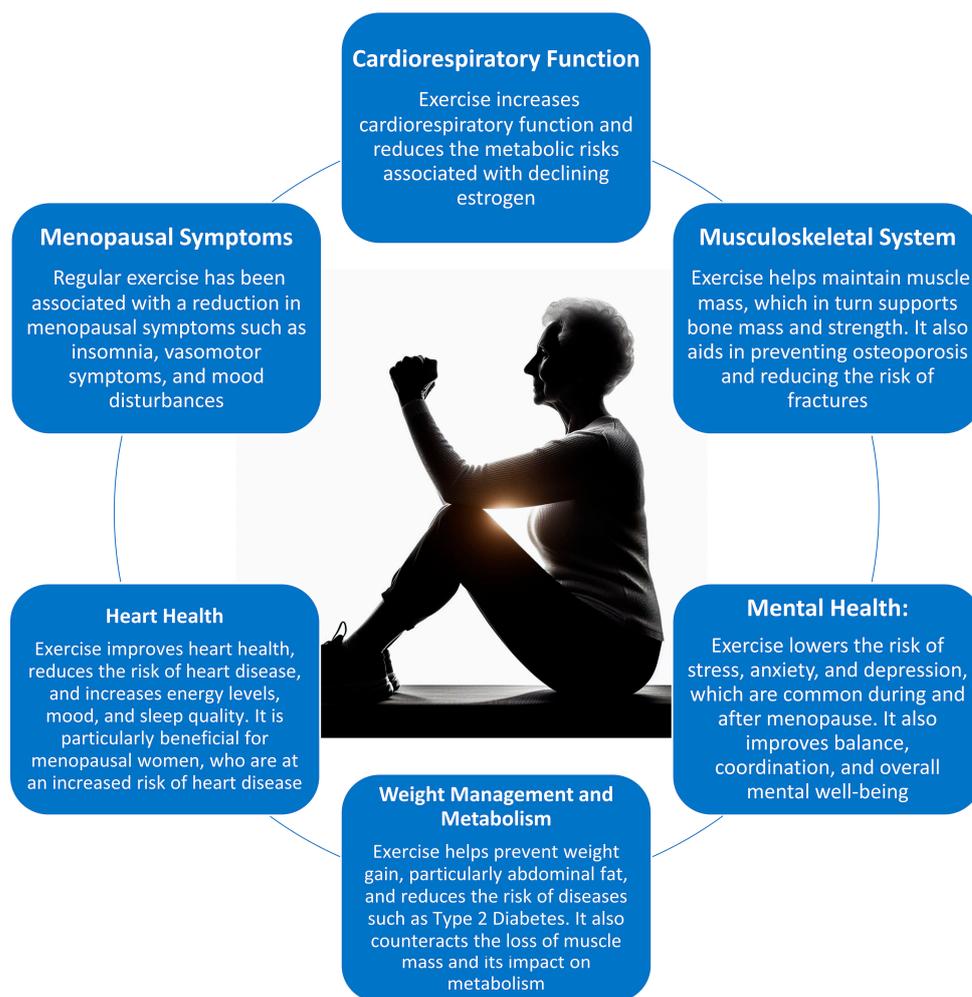
#### 4. Menopause

Menopause is the natural period that all women experience as they age. It is a complex interaction between genetic, biological and psychological factors. Produced by the decline in estrogen levels, it causes a variety of symptoms that can alter a woman's quality of life, including physical, mental and sexual health [27,58,59] (Figure 3).

This universal aging process of the female reproductive system occurs at an average age of 51 years, with a range of 40 to 58 years for 88% of women. From a clinical perspective, premenopausal women have regular menstrual cycles that have less than 7 days of variability in cycle length. Perimenopausal women have irregular menstrual cycles with variations in cycle length of more than 7 days. Menopausal women achieve this designation when they exceed 12 months without a menstrual cycle [60–63].

From the point of view of endocrine physiology, the onset of menopause is caused by a reduction in the levels of a number of hormones. One of these is hypothalamic inhibin, which, in turn, reduces the synthesis of pituitary follicle stimulating hormone (FSH), leading to a decrease in estradiol (female sex hormone) by the ovary. A decrease in estrogen levels leads to a reduction in the follicular phase, the period of time between the onset of menstruation and ovulation, which results in a shorter duration of menstrual cycles [64].

Another phenomenon that takes place in menopause is the increase of FSH in the blood, due to atresia of the ovarian follicles, reducing the production of estrogens, which are responsible for producing this hormone. This is a form of negative feedback, since the hypothalamus releases more gonadotropin (GnRH), a hormone that releases FSH and luteinizing hormone (LH). Thus, the adenohypophysis receives a signal to release more FSH, produced by the decrease in blood estrogens (especially estradiol), the major problem being a deficit of follicles for such production. Therefore, during menopause, estrone is dominant, whereas during the menstrual cycle 17- $\beta$ estradiol (E2) dominates, both estrogens. This occurs because granulosa cells cannot produce aromatase to convert testosterone to estradiol, in addition to the increased peripheral conversion of androstenedione, a steroid hormone produced by the reticular layer of the adrenal cortex, estrone (Figure 4) [64–67].



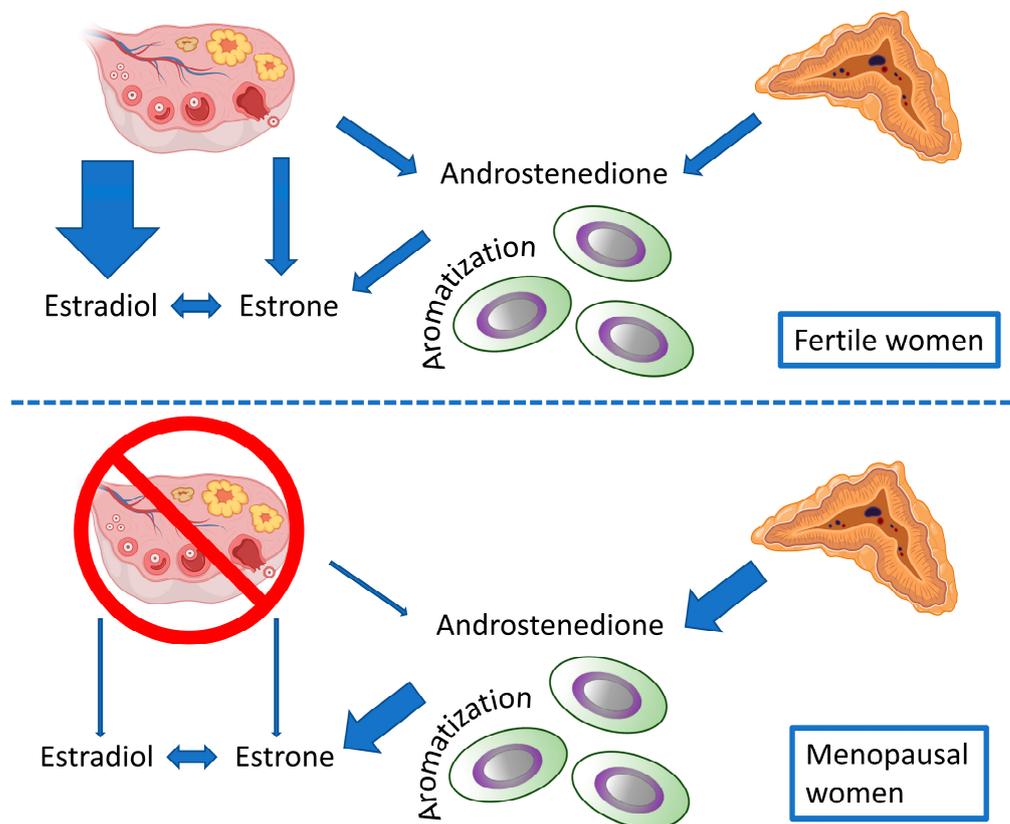
**Figure 3.** Effects of physical exercise in several physiological systems in menopausal women.

Since estrogen receptors appear in all the neuronal structures of the brain that control the multiple functions of the CNS, the lack of estrogen in menopause causes many of these functions to be altered. These receptors are located in plasma membranes, mitochondria and the nucleus of cells, and are particularly abundant in the hypothalamus, which is the main thermo-regulatory center and regulator of sleep and circadian rhythms, as well as other brain regions that are crucial for learning and memory, including the prefrontal cortex, hippocampus, amygdala and posterior cingulate cortex. Other regions also contain significant amounts of estrogen receptors [63,68–70].

Preclinical studies indicate that, during perimenopause, when brain estrogens decline, the systems required for estrogenic activation of brain glucose metabolism rates (CMR<sub>glc</sub>) and suppression of ketogenic pathways are deactivated. Following CMR<sub>glc</sub> depletion, there is induction of an adaptive starvation reaction to increase fatty acid metabolism for the generation and utilization of ketone bodies by mitochondria as an alternative fuel. Hypometabolism, reduced mitochondrial function and subsequent oxidative damage are known to promote  $\beta$ -amyloid accumulation and neuronal dysfunction [60,63,71–73].

As we have indicated above, menopause also affects psychologically due to the various postmenopausal symptoms, such as night sweats (80% of women suffer vasomotor symptoms), hot flashes (temperature dysregulation), pain, fatigue, irritability, vaginal dryness, mood swings, depression and cognitive dysfunction. Some postmenopausal symptoms may last for a long time, being associated with poor quality of life, poorer self-esteem, lower work productivity and greater use of public health resources [24,74–79]. Postmenopausal women are also characterized by greater difficulty falling asleep than younger women. Between

40% and 60% report sleeping poorly and suffering from insomnia, which means a poorer quality of life. Poor sleep quality reduces overall health and is associated with physical and psychological problems. In addition, menopausal status is associated with a high risk of mood disorders. In women with no history of depression or anxiety, perimenopausal and postmenopausal phases were associated with an increased risk of anxiety symptoms compared to premenopausal periods [26,80–86].



**Figure 4.** Hormone synthesis in fertile and menopausal women. The diagram illustrates the conversion of androstenedione to estradiol and estrone in both fertile and menopausal women, through a process called aromatization. The diagram shows that, in fertile women, the ovary is the main site of hormone production while, in menopausal women, the adipose tissue and the adrenal glands take over this role.

Another possible symptom of menopause is the appearance of sarcopenia, which is characterized by the loss of muscle mass, strength and function in older adults, and it is estimated that in postmenopausal women it appears in between 10 and 40%, one of the main causes being hypoestrogenism. In addition, these women have impaired balance related to android fat distribution and low bone mass density and loss of balance, which in turn increases the frequency of falls [30,87–90].

To assess the severity of menopausal symptoms and their impact on health-related quality of life, the Menopause Rating Scale (MRS) is used. It is a self-administered questionnaire of 11 items agglomerated into three distinct subscales: somatic (four items), psychological (four items) and urogenital (three items). The higher the scores, the greater the severity of symptoms [24,91–93].

Importantly, women who were active around menopause had lower rates of cognitive decline compared to women who were inactive at all stages of life, confirming that physical exercise may be a vital protector factor against cognitive decline and dementia [18,94].

## 5. Neuroinflammation

In recent years neuroinflammation has been recognized as an important signal of neuronal death. Inflammatory processes include injury-induced molecular, cellular and physiological responses designed to prevent and eliminate infection or repair damage. In most cases, the inflammatory process is mediated by immune cells in the periphery and CNS. This process attracts different immune cells depending on the affected tissue, such as astroglia and microglia, which act in the brain tissue. Therefore, we can define it as an activation by different factors of the brain immune response. This results in different events: activation of resident cells, such as astrocytes and microglia, production of proinflammatory mediators, entry of exogenous immune cells (dendritic cells and T lymphocytes) into the cerebral circulation and activation of the complement system, together with an upregulation of cytokine expression [17,95].

The neuroinflammation–neurodegeneration relationship is clear due to the disposition of CNS immune mediators, which induces different pathological conditions related to cognitive limitations. In addition, it is known that, during the course of aging, there is an increased susceptibility to different CNS diseases and increased neuroinflammatory mechanisms, which play a fundamental role in the production of toxins leading to neuronal dysfunction or neuronal death. However, the physiology, molecular signaling pathways and cell types involved in the relationship between cellular senescence and aging processes have not yet been elucidated, but we do know that in senescence there is a secretion of inflammatory proteins that are regulated by different transcription factors, which participate in the regulation of the immune system and are related to the inflammatory response produced by NFκB, a transcription factor of complex activation. However, astrocytes are involved in the neuroimmunology and neuroinflammatory responses of aging and neurodegeneration. This is due to their ability to secrete and respond to large amounts of proinflammatory factors, such as chemokines and immunoregulatory cytokines, to different stimuli [17,96–100].

On the other hand, microglia present several immunophenotypic states: the M1, or proinflammatory, state is characterized by the production of proinflammatory cytokines, such as interleukin (IL), IL-1β, IL-18, TNFα, and chemokines, which promote neuronal death and cognition in chronic inflammation. In the M2 or anti-inflammatory state, the opposite effect occurs, i.e., secretion of anti-inflammatory cytokines (such as T cells and macrophages) facilitating phagocytosis of cellular debris and tissue repair, along with the promotion of extracellular matrix remodeling [2,101,102].

## 6. Cognitive Impairment

Cognitive impairment is the stage that precedes dementia or other brain diseases. The number of elderly people with different types of dementia is increasing, with AD and vascular dementia being among the most prevalent [16,103]. This occurs in 1% among people aged 80–85 years and in 20% in people over 90 years; in Spain the prevalence is 18.5% [104,105]. It is also suspected that, by 2050, the number of people with dementia will increase to 131.5 million [106,107].

Risk factors associated with cognitive impairment include age, gender, family history, educational level and other factors associated with pathologies [16,53].

Impairment and dementia affect both social life and health, negatively affecting the functional and physical abilities of patients, leading to a state of moderate or severe dependence. At the physiological level, it may be associated with a loss of nerve cells and connections, decreased blood circulation in the brain, reduced production and release of neurotransmitters, and changes in the structure and functions of brain areas responsible for memory and other cognitive functions. In addition, it is closely related to aging due to the decrease in cognitive reserve that aging brings, making the brain more vulnerable to the negative effects of brain diseases and injuries. In other words, cognitive decline is the result of a combination of biological, environmental and lifestyle factors [18,108–112]. In general, studies conclude that factors such as smoking, depressive disorders, diabetes

mellitus, metabolic syndrome and APOE  $\epsilon$ 4 genotype are associated with greater cognitive decline, whereas better physical health, physical activity, Mediterranean diet and cognitive training are protective factors. However, no studies have been found that indicate that it affects women more than men or vice versa [107,113–131].

However, different stages of cognitive impairment are known. Mild cognitive impairment without dementia refers to people with persistent complaints of memory loss, but without changes in other cognitive domains. Mild cognitive impairment with suspected dementia presents with more pronounced memory impairment and changes in at least one cognitive domain, such as attention, thinking, language, etc. These changes do not affect the independence and development of the individual, nor do they interfere with work and community functioning of the person, i.e., they do not affect his or her interaction with other people but do affect the ability to solve more complex tasks. These characteristics show that cognitive impairment is age-related. On the other hand, we found studies showing that people with mild cognitive impairment are more likely to suffer AD and to have an alteration in their optimal functioning. However, when depression is associated with this type of impairment, the possibility of AD and death increases [16,132,133].

## 7. Depression

Depression is a psychological disorder that changes a person's thinking and behavior and hinders intra- and interpersonal relationships. It is common in the elderly, being considered the second cause of morbidity worldwide. Almost always, it is associated with other pathologies, making this disorder worse and significantly affecting the conditions of life, as those affected lose their sense of purpose in life and perceive their environment negatively. According to the World Health Organization (WHO), the prevalence of geriatric depression has been estimated to be between 10% and 20% of all older adults [16,134–137].

According to the DSM-5, for a person to be diagnosed with depression, they must have at least five symptoms, which requires the presence of discouragement, a disinterested mindset, and a diminished sense of accomplishment. In addition, they must have these symptoms daily or nearly every day for at least 2 weeks: (a) depressed mood most of the day; (b) marked loss of interest or pleasure in all or nearly all activities most of the day; (c) significant weight or appetite gain or loss, insomnia or lethargy; (d) psychomotor changes detected by an outside informant; (e) fatigue or low energy, feelings of inadequacy or excessive guilt; (f) difficulty in concentrating, and recurrent thoughts of death, suicidal attempts or plans. These symptoms can vary in intensity (mild or severe), making it difficult to perform daily tasks and solve problems. It can be treated without medication if it is mild, and if it is severe medication and psychotherapy are needed, as the affected person may attempt to end his or her own life. Several studies warn that depressive symptoms interfere with proper cognitive processing and that dementia is a risk factor for depressive symptoms, i.e., both factors maintain a fairly significant correlation [16,138].

Several pathophysiological hypotheses have attempted to explain the relationship between depression and cognitive deficit, the most prominent being related to alterations in microglia, nerve shrinkage, brain inflammation and the role of oxidative stress. In addition, it is believed that the location of the brain's cognitive capacities and its neuroanatomical support for memory and attention change over time, in particular the structure of the prefrontal and temporal cortex, the hippocampus and the limbic system. These same regions are also essential in the processing of emotions, so these functions are expected to be altered in affective disorders [16,139].

One of the theories that has been in force is the monoaminergic theory of depression. This explains that major depressive disorder (MDD) is due to a decrease in the concentration of neurotransmitters at the synaptic level, such as serotonin, noradrenaline and dopamine. In fact, it is the basis of current antidepressant treatment, i.e., the use of selective serotonin reuptake inhibitors (SSRIs). However, it is known that this treatment is not effective in the short term, as it takes about 2–6 weeks to reduce symptoms. This is why other factors, such as genetics, environmental stressors and psychosocial factors, are

currently being involved in a multifactorial disease. Together, they produce a maladaptive response, alterations in certain brain areas (prefrontal cortex, hippocampus, limbic system), inflammatory alterations, alterations in neuronal growth factors (brain-derived growth factor or BDNF), and in the hypothalamic–pituitary adrenal axis. Thus, in recent years, the role of glutamate and gamma aminobutyric acid (GABA) neurotransmitter systems in the pathophysiology of MDD has been recognized, since inhibition of N-methyl-D-aspartate receptors (NMDAR) or blockade of glutamate release have a beneficial effect on the damage produced by chronic stress in dendritic atrophy. However, other studies suggest that glutamate activation produces antidepressant effects [140–151].

Therefore, the most updated model is the synaptic model of chronic stress condition, where different traumas or repeated exposures to stressors produce a global brain effect of neuronal remodeling with a decrease in its capacity in certain brain areas, such as the left hippocampus and the prefrontal cortex. In addition, it also produces an alteration of glial cells, which are responsible for the regulation of glutamate neurotransmission. Although still unknown, current research proposes that trauma or stress produces an abnormality in glucocorticoid signaling, a modification in glutamate neurotransmission, along with a deficit in glial cell function and an alteration in glutamate uptake. However, it maintains elevated levels of extracellular glutamate [140,149,150,152]. Similarly, acute stress produces, at the frontal lobe level, a glutamate spike associated with a transient increase of glutamate at the extracellular level, causing an increase in glutamate levels.

Similarly, acute stress produces, at the frontal lobe level, a glutamate spike associated with a transient increase in glutamate at the extracellular level, causing a sustained increase in NMDAR receptor activation,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and synaptic strengthening, whereas, in chronic stress, there is a decrease in NMDAR, AMPAR and synaptic strength [149,153].

Recent studies have shown that acute stress can have sex-dependent effects on glutamate receptors in the brain [154,155]. Glutamate is the primary excitatory neurotransmitter in the brain and plays a crucial role in many cognitive processes, including learning and memory. The effects of acute stress have been described on glutamate receptors in male and female rats. Acute stress caused a significant increase in the expression of glutamate receptors in the prefrontal cortex of male rats, but not in female rats. The authors suggested that this sex-dependent effect may be due to differences in the regulation of glutamate receptors by sex hormones [156]. Other authors investigated the effects of acute stress on glutamate receptors in male and female mice. Their study found that acute stress caused a significant decrease in the expression of glutamate receptors in the hippocampus of male mice, but not in female mice. The authors suggested that this sex-dependent effect may be due to differences in the regulation of glutamate receptors by stress hormones [155]. Overall, these studies suggest that acute stress can have sex-dependent effects on glutamate receptors in the brain. These effects may be due to differences in the regulation of glutamate receptors by sex hormones and stress hormones.

It has also been observed that this pathology affects women more than men, with higher levels of neuroinflammatory, neurotrophic and serotonergic markers found in women, and a stronger relationship between neuroinflammatory and neurotrophic factors, together with the severity of depressive symptoms, in this sex [21,157–160].

## 8. Cognitive Decline and Alzheimer's Disease

AD is a multifactorial condition that generates major health, economic and social problems and affects more than 20 million individuals worldwide. At the histological level, it is determined by the appearance of extracellular senile plaques and intracellular neurofibrillary tangles, which lead to neuronal degeneration/death and cognitive loss. Both have been detected in different areas of the brain, with the highest proportion being observed in the cerebral cortex and hippocampus [1,2,161–164].

Alzheimer's disease can be sporadic, is associated with old age and with polymorphisms in the apolipoprotein E (APOE) gene, usually 95%, and is also related to lifestyle,

environment, etc., or is of the familial type, which is associated with mutations in the amyloid precursor protein (APP), Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) [1,2,161–164].

Some proteins have also been described that could be fundamental regulators in the development of aging and AD, one of them being KChIP3. It has different functions: it interrelates with presenilin, it is a transcriptional regulator with the capacity to recognize DRE elements (GTAC G sequence reaction element) that are present in its target genes, specifically in the promoter region and, finally, it interacts with type 1 voltage-dependent potassium channels. Furthermore, this protein is involved in the cognitive impairment associated, during AD, with neuroinflammation and aging. But the mechanism underlying KChIP3 in the brain and periphery is not yet known [2,165–167].

KChIP3 belongs to the family of neuronal calcium sensor proteins because of its four calcium binding sites. It is also known by several different names depending on its subcellular location and functions. Thus it is called calsenilin, because it interacts with presenilin, DREAM protein, because it is a transcription factor that binds to DRE (GTCA G) by silencing-off genes for neuronal activation, dendritic growth and memory consolidation, or KChIP3, by interacting with type 1-dependent potassium channels regulating somato-dendritic synapses [2,167–169].

Its protein levels are regulated by several factors, including the levels of intracellular calcium, glucose, cAMP and reactive oxygen species (ROS), its main modulator being calcium. However, its absence in the brain means less neuronal death in the hippocampus even at advanced ages, with KChIP3 being compromised in learning and recognition and spatial memory, promoting a proinflammatory environment in the hippocampus and compromising cognitive capacity in aging and AD [2,169].

Regarding the relationship between AD and APOE, it is known that this lipoprotein is responsible for cholesterol and phospholipid transport, and there are three genetic variants: APOE2, APOE3 and APOE4. APOE4 has been established as the strongest genetic risk factor for late-onset AD and dementia, while APOE2 is, to some extent, neuroprotective. APOE4 increases the risk of AD while the  $\epsilon$ 2 form decreases the risk compared to having the  $\epsilon$ 3 form [170,171]. Those with one copy of  $\epsilon$ 4 may have a threefold increased risk of AD compared to those with two copies of the  $\epsilon$ 3 form, and the risk increases up to 8–12 times higher if they have two copies of the  $\epsilon$ 4 form. In addition, people with the APOE- $\epsilon$ 4 form have been shown to have amyloidosis and dementia at an earlier age than those with  $\epsilon$ 2 or  $\epsilon$ 3. Although APOE4 is the major genetic risk factor for the development of AD, women with at least one copy of APOE- $\epsilon$ 4 often had a higher risk and more rapid cognitive decline and deterioration than male counterparts. The risk of AD and mild cognitive impairment associated with APOE4 peaks earlier in women than in men, giving a significant elevation between ages 65 and 75 for AD (4.37-fold increased risk in women compared with 3.14 in men) and between ages 55 and 70 for mild cognitive impairment (1.43 in women vs. 1.07 in men), while the risk of AD or APOE4-associated mild cognitive impairment among men peaked in the 75 to 85 age group [19,21,172–182].

Thus, in late-onset AD, the major risk factor is aging, whose prevalence among the 65-year-old population is about 10% and, with increasing age, the prevalence reaches about 32% in people older than 85 years. AD is an abnormal aging where neurons can be found in genomic instability, with DNA damage/oxidation, putative genetic alterations, telomeres, reduction and alteration of metabolic pathways and mitochondrial dysfunction. Aging glia and their activation also influence AD through oxidative stress, neuroinflammation and immune regulation [183]. Oxidative stress is a key factor in the development and progression of AD. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them. ROS can damage cellular components, such as lipids, proteins, and DNA, leading to inflammation, brain cell death, and cognitive deficits [183]. In fact, drugs with antioxidant activity may be effective in ameliorating the treatment of the disease. Several authors have found that drugs with antioxidant activity, such as vitamin E and melatonin, resveratrol and curcumin, quercetin

and luteolin or astaxanthin and alpha-lipoic acid can reduce oxidative stress and improve cognitive function in patients with cognitive decline and dementia [184].

Endocrine factors, especially sex steroid hormones, have been implicated in the onset and progression of AD, and life course changes are risk factors [185]. Age-related declines in female estrogen and male androgen, leading to loss of neuroprotective hormone action, are considered a potential risk factor for the development of AD. Also known as “trigger effects”, these are more transient effects of adult sex hormones. Sex steroid hormones, including estrogens, progestins and androgens, have multiple activating effects on the brain, regulate amyloidosis, tauopathy and gliosis, improve neuronal health, and protect against mild cognitive impairment and AD. In addition, sex hormones may act more generally to enhance brain function [19,21,182,186–191]. The renin–angiotensin system has also been involved in AD [192,193].

### 9. Physical Exercise

The performance of physical exercise promotes a series of physiological processes to adapt to the demands it generates. Thus, on the one hand, there is an increase in blood flow to supply oxygen and nutrients to the active muscles; likewise, there is an increase in heart rate and the force of contraction of the heart to pump more blood to the body, increase blood flow to the muscles and meet their metabolic needs. Increased respiration and dilation of the bronchi becomes necessary to eliminate the carbon dioxide produced by metabolism and, in parallel, supply oxygen to the body. These processes are promoted by the activation of the sympathetic autonomic nervous system, aided by the release of hormones, such as adrenaline and cortisol, that help mobilize stored energy in the body, increase the availability of glucose and fatty acids, and promote the additional metabolism necessary to provide energy to active muscles and maintain body temperature [26,30,194–197].

Exercise is included in some clinical guidelines as an adjunct to treatment of major depressive disorder. Strength training and multicomponent training are two types of exercise that have been shown to have positive effects on cognitive function in older adults. Strength training is a type of exercise that involves the use of weights or resistance to build muscle strength and endurance. Multicomponent training, on the other hand, is a type of exercise that combines different types of exercise, such as aerobic, strength, balance, and flexibility training, into a single program [198]. Several studies have investigated the effects of strength training and multicomponent training on cognitive function in older adults. For example, a recent meta-analysis [199] found that strength training was associated with significant improvements in cognitive function, particularly in the domains of attention, processing speed, and executive function. Similarly [200], it has been found that multicomponent training was associated with significant improvements in cognitive function, particularly in the domains of memory, attention, and executive function. Another study found similar results on cognitive function in older adults with mild cognitive impairment [201], with significant improvements particularly in the domains of attention and executive function.

A recent meta-analysis supports exercise as an additional lifestyle transformation that improves overall health, including a reduction in depressive symptoms [26,30,194,195]. Furthermore, it has been inversely associated with dementia risk, showing that middle-aged women had greater cognitive improvement than men. A systematic review has described a 50% reduction in the risk of AD when exercise is persistent and intense. In addition, beneficial effects of exercise on anxiety, sleep quality and general symptom perception have also been described [30,202–204].

Recently, new physical exercise programs based on physical and mental training have been proposed to prevent cognitive decline in older adults, including the Pilates method and High Intensity Functional Training (HIIFT). Pilates is a combination of strength, flexibility and balance exercises, which focuses on lumbar and pelvic stabilization, activates the deep abdominal muscles and seeks a complete mind–body connection. This exercise system is not limited to any age group; in fact, it is widely recommended for older adults due to the

lack of impact exercises. Pilates has been shown to have beneficial effects on both physical and mental health, as it promotes coordination of body movements and rhythmic breathing, in addition to the mind–body connection [7,205,206]. On a physiological level, a relationship has been established between physical exercise and an increase in hippocampal size, as well as frontal lobe stimulation, both of which are important aspects in the maintenance of cognitive function [4].

On the other hand, we talk about HIFT, which is a form of exercise that accentuates the functional movements of multiple joints, adapting to any level of physical condition and promoting greater muscle recruitment. These exercises can last from two minutes to over an hour, depending on the intensity of the exercise, as it utilizes multiple energy pathways through multimodal movements, thus being more effective in increasing strength and exercise adherence and having a positive effect, as strength training promotes the release of brain derived neuromuscular factor (BDNF). In addition, HIFT has shown improvements in metabolic and cardiorespiratory adaptations and a positive association between cognition and movement agility in the elderly, thus having a positive effect on cognitive function in older people with mild cognitive impairment [4,207–217].

However, Pilates is recommended for postmenopausal women because it improves physical and mental functioning, independence, sleep quality, reduces fatigue, as well as depression and anxiety, and is associated with a decrease in the rates of cognitive and physical deterioration [26,218]. However, the American Heart Association (AHA) and American College of Sports Medicine (ACSM) recommend a series of exercises that are divided into four areas: aerobic physical education, such as walking, swimming, dancing, or others that involve the use of large muscle groups; muscle strengthening, such as that of the abdomen, arms, legs, etc.; flexibility, improving the activities of daily living; and balance training, which improves stability, in turn reducing the risk of falls [30,219,220].

We can also talk about whole body vibration exercise (WBVE), as it has been shown to reduce arterial stiffness, improve bone mineral density and help reduce symptoms related to osteoporosis and sarcopenia in postmenopausal women [221–224].

This system is based on putting the patient in contact with a vibrating platform following appropriate parameters of frequency, amplitude, distance and maximum acceleration, producing an increase in muscle strength, including knee extensors and trunk flexion, thus improving balance, as long as it is combined with strength exercises [221–224].

It also improves bone mineral density because, when a body is subjected to vibration, it requires a greater response of bone and muscle tissues to absorb and dampen the energy produced by the vibration oscillations, thus producing osteogenic effects that oppose the alterations in bone mass that occur as we age [221–224].

Another beneficial aspect of physical exercise is that it delays arterial aging in postmenopausal women by leading to functional and structural vascular adaptations that help maintain or lower normal blood pressure. It has been observed that people who exercise regularly have less arterial stiffness than sedentary people and, when sedentary people engage in physical exercise, arterial stiffness decreases. Primary functional adaptation is associated with increased NOS enzyme activity and subsequent NO release, whereas moderate or high intensity exercise, especially interval training, produces beneficial endothelial adaptations for postmenopausal women [2,30,225].

## 10. Conclusions

Although there are different theories of aging, the exact causes of aging are not known, with the most common being in relation to an imbalance between oxidant and antioxidant species and their associated damage. In any case, neuroinflammation of the CNS is provoked, in which both microglia and astroglia intervene, generating alterations that can lead to depression and cognitive deterioration. These phenomena are aggravated in menopausal women, who already have CNS alterations due to the lack of estrogens, which affect various brain regions, some of them crucial for learning and memory, such as the hippocampus, also affected in depression and cognitive impairment. On the other

hand, physical exercise can be beneficial due to its capacity to increase the production of NO, growth factors, as well as a better regulation of the balance between oxidative and antioxidant systems. Also noteworthy is the release of hormones, such as cortisol and adrenaline, which are important for blood pressure control and stress reduction, essential in postmenopausal women.

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