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308 *Current Neuropharmacology,* **2018**, *16*, **308-326**

REVIEW ARTICLE

The Role of Physical Exercise and Omega-3 Fatty Acids in Depressive Illness in the Elderly

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ARTICLE HISTORY

Received: March 13, 2017
Revised: June 20, 2017
Accepted: July 30, 2017

DOI:
10.2174/1570159X15666170912113852

Abstract: ***Background*:** In adulthood, depression is the most common type of mental illness and will be the second leading cause of disease by 2020. Major depression dramatically affects the function of the central nervous system and degrades the quality of life, especially in old age.

Several mechanisms underlie the pathophysiology of depressive illness, since it has a multifactorial etiology. Human and animal studies have demonstrated that depression is mainly associated with imbalances in neurotransmitters and neurotrophins, hypothalamic-pituitary-adrenal axis alterations, brain volume changes, neurogenesis dysfunction, and dysregulation of inflammatory pathways. Also the gut microbiota may influence mental health outcomes.

Although depression is not a consequence of normal aging, depressive disorders are common in later life, even if often undiagnosed or mis-diagnosed in old age. When untreated, depression reduces life expectancy, worsens medical illnesses, enhances health care costs and is the primary cause of suicide among older people. To date, the underpinnings of depression in the elderly are still to be understood, and the pharmacological treatment is the most commonly used therapy.

***Objective*:** Since a sedentary lifestyle and poor eating habits have recently emerged as crucial contributors to the genesis and course of depression, in the present review, we have focused on the effects of physical activity and omega-3 fatty acids on depressive illness in the elderly.

***Results*:** A growing literature indicates that both exercise and dietary interventions can promote mental health throughout one's lifespan.

***Conclusion*:** There thus emerges the awareness that an active lifestyle and a balanced diet may constitute valid low-cost prevention strategies to counteract depressive illness in the elderly.

Keywords: Aging, depression, mood disorders, late-life depression, physical activity, exercise, diet, omega-3 fatty acids.

1. DEPRESSION IN AGING

Depression, the most common mood disorder, affects around 300 million people world-wide and is projected to become the major contributor to disease burden by 2020 [1]. Depression is going to be the major issue for public health because of both direct and indirect economic costs [2], is also comorbid to significant illnesses, and contributes to cognitive decline [3].

Major depressive disorder (MDD) is characterized by depressed mood, insomnia or hypersomnia, diminished interest or pleasure in almost all activities, significant loss or gain of weight without dieting, psychomotor agitation or retardation, fatigue, feelings of guilt, diminished ability to think or concentrate, and recurrent thoughts of death [4]. In the worst cases, depressed patients may commit suicide. MDD is the second cause of death in people from 15 to 29 years of age, with around 800.000 deaths every year [1].

DSM-5 does not have different diagnostic criteria based on age [4], in fact depression can affect people throughout their entire lifespan and it is estimated that around 1-5% of people of 65 years of age or older are depressed [5]. When depression onset occurs in 60-65 years old people or older, it can be defined as late-life depression (LLD). The late onset of MDD accounts only for half of the depressive cases [6]. Through a meta-analysis, Luppa and colleagues showed that in 75 years old patients the pooled prevalence of MDD was

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7.2% and 17.1% for depressive disorders [7]. The prevalence increases if the elders are in long-term care facilities [8].

1.1. Comorbidity

Depressive illness in the elderly increases morbidity, disability, functional decline, caregiver burden and premature mortality, and enhances health care costs [2, 6, 9]. LLD represents the major risk factor for suicide in the elderly [10].

Depression that affects people later in life is frequently associated with a cognitive decline, which often involves multiple cognitive domains, such as memory, attention, visual and verbal abilities, and finally executive functions [11-13]. These events depend on heterogeneous mechanisms and are characterized by extremely different clinical progressions. Indeed, in some cases, problems associated with cognitive malfunctions show a partial regain of function following the remission of depression (the so-called pseudodementia) [14, 15]; however, in other cases these complications lead to the classic senile dementia [16]. Furthermore, cognitive deficits can remain active even after the remission of depression. A bulk of evidence shows that depression is both a risk factor for and a prodrome of dementia [6, 17-22].

Finally, depression can share some pathophysiological characteristics with a lot of non-neurological diseases, like cardiovascular problems [23], which increase the production of proinflammatory cytokines [24] and the level of homocysteine in plasma [25]. Moreover, as cardiovascular disorders, depressive disorders are characterized by decreased glucose metabolism [26] and blood flow abnormalities [27].

1.2. Hypothesized Mechanisms of Depressive Disorders

Several hypotheses have been proposed to explain depressive illness, since it has a multifactorial etiopathogenesis linked to genetic, biological, environmental, social, and psychological factors.

During aging, starting from 40 years old, our brain loses around 5% of volume and weight each 10 years [28]. The frontal lobes are the brain structures that are more vulnerable to normal age-changes [29], but thanks to different magnetic resonance imaging (MRI) studies, we know that the whole brain goes to normal atrophy. Fjell and colleagues reported a negative correlation between cortical thickness and age, and an annual hippocampal atrophy of 0.79% to 2.0% [30]. Interestingly, there is a direct link between reduction in hippocampal size and impaired mnesic functions in aged depressed patients [31]. Neuroimaging studies have demonstrated that LLD is associated with reduced gray matter volume in frontostriatal and limbic networks (including prefrontal cortex, hippocampus, amygdala, putamen, and thalamus) [9, 32].

During the last years the role of oxidative stress and neuroinflammatory mechanisms as mediators in depressive disorders was advocated [33-35]. Indeed, a prolonged neuroinflammatory response has a negative effect on both mental and physical health [36, 37]. Depression can be considered as a "neuropsychiatric manifestation of a chronic inflammatory syndrome" also because it is associated to several autoimmune and neurodegenerative diseases, gastrointestinal dysfunctions, type 2-diabetes and also cancer, in which chronic low-grade inflammation is present [37, 38].

It has been demonstrated that patients with LLD showed a high degree of dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis activity [39]. Namely, in comparison to healthy controls depressed older adults exhibited increased levels of basal cortisol during the diurnal cycle, in particular during the evening and night hours. This might depend on several mechanisms, encompassing central nervous system and immune-endocrinological alterations and physical illnesses.

Brain-derived neurotrophic factor (BDNF), which regulates neurogenesis, neuronal survival, and neuroplasticity, is reduced in patients with depression [40]. In rodent models, the prolonged hyperactivation of the HPA axis, and the resulting prolonged exposure to glucocorticoids, may lead to a reduction in BDNF levels and therefore to a lack of adult hippocampal neurogenesis [41]. Taken together all these factors may lead to a reduction in hippocampal volume, which is associated with depression and memory decline in older adults [2].

Depressive symptoms are also linked to an imbalance in the three main monoamine neurotransmitters in the brain (*i.e*., serotonin, dopamine, and norepinephrine) [42, 43]. The different symptoms of depression are attributable to different neural systems. Dopaminergic mesolimbic system modifications are linked to anhedonia [44]. Serotonergic and noradrenergic system modifications are involved in the regulation of mood [43]. It is also known that serotonin as well as neurotrophic factors decrease during aging [45].

There is a bidirectional and reciprocal communication between the nervous system and gut microbiota [46]. The age-associated decline of the immune system accompanied by chronic low-grade inflammation [47] seems to have a close relationship with both structure and composition of the gut microbiota [48]. Since age-related neurodegenerative diseases and depression are associated with inflammation [49], it can be inferred that gut microbiota composition is influenced by age-related depression. It is interesting to note that Ogbonnaya and colleagues have discovered a correlation between gut microbiota and hippocampal neurogenesis [50]. Furthermore, a recent study by Zheng *et al*. [51] demonstrated that mice harbouring the gut microbiota from MDD patients exhibited depressive-like behaviors.

Although depression is a very common psychiatric disorder in the elderly, it is still often undiagnosed or misdiagnosed, or treated like a normal feature of aging [52]. In fact, older people tend not to complain of being depressed, being instead more prone to talk about their physical illness. By contrast, a right diagnosis could lead to the right help. To this aim non-invasive, low-cost interventions based on exercise or dietary supplements have sparked researchers' interest [53, 54]. This review focuses on the effects of exercise and omega-3 fatty acids on the pathophysiological alterations implicated in depressive illness during aging. Namely, we will examine how antidepressant properties of exercise and omega-3 fatty acids may affect brain volume, neuro-

transmission, synaptic plasticity, neuroinflammation, and gut microbiota.

2. EFFECTS OF PHYSICAL EXERCISE ON DEPRESSIVE ILLNESS IN THE ELDERLY

The leading treatments against depression for the elderly include antidepressant treatment, electroconvulsive therapy, cognitive psychological therapy, and exercise [55]. For that which concerns the most used therapy, namely the pharmacological treatment, numerous studies have demonstrated that the elderly display critical differences in respect to younger patients regarding the metabolism of the medicines [5].

Antidepressant treatments can also have relevant collateral effects, customarily targeting the cardiovascular system [56], they have extremely elevated costs [57], and they can be associated with the risk of the elderly falling [58]. Additionally, elderly patients affected by depression are frequently receiving further pharmacological treatments to fight the common pathologies tied to ageing, with the risk of generating adverse reactions due to interactions between different medicines [59]. In a recent study, it was established that 22.8% of the elderly affected by depression uses in a discontinuous manner the various pharmacological treatments, while 17.9% is forced to switch to a different curative regime because of the collateral effects of antidepressant drugs [60]. Keeping in consideration all of the inconveniences and difficulties correlated to the treatments with antidepressants, in the past years physical exercise is emerging as a possible alternate therapeutic approach applicable to patients of all ages. Undeniably, various studies have clearly shown a beneficial effect of physical activity in adults affected by depression [61]. On the other hand, data regarding the equivalent effects in older patients with depression are quite contradictory and non-definitive [62], as a consequence of the fact that physical therapies used for the higher age range are diverse within themselves, and most of the time the more beneficial ones (such as running and cycling) cannot be prescribed to older depressed patients [63]. The primary antidepressant physical therapy interventions comprise resistance training, power walking, yoga and Thai Chi [64]. As previously stated, there exists an ample variability of scientific evidence concerning the effects of physical exercise in contrasting the depressive symptoms in the elderly, starting with which exercise is being executed, the gravity of the depression, the age of the patient and from the fact that very frequently depressive symptoms diminish strongly the will to practice sports in many patients [65]. This last observation could mean that commonly, the participants in the exercise trial may not entirely represent the population of older people affected by depressive symptoms which range from more to less severe [66]. In a recent study, Underwood and colleagues have carried out a cluster-randomized controlled trial where they have analysed 891 elders (aged 65 years or older) whom lived in 78 nursing homes throughout England. In 35 of these, twice a week the inhabitants were subjected to group exercises associated with a sensitization campaign on depression for the staff, with a purpose to have them recognize depressive symptoms in elderly patients. In the other 43 nursing homes the older patients were not subjected to any physical exercise, while the staff was correspondingly trained to spot depressive symptoms in patients. At the end of the study, which lasted 12 months, no improvement whatsoever of depressive symptoms was seen in the elderly that exercised when matched to the control group; however, half of the residents of the 78 nursing homes were discovered to have symptoms steering towards depression that weren't previously diagnosed [67].

Conversely, in a systematic review conducted by Bridle [66], the authors' conclusion asserts that "for older people who are affected by clinically serious signs of depression, recommending structured exercise tailored to personal skills will decrease the severity of depression." In a further study, 138 people having more than 60 years of age with depressive symptoms have been sectioned in two groups. One group has followed for 12 months the PEARLS treatment (Program to Encourage Active Rewarding Lives for Seniors), which consists of an approach in which the elderly underwent physical and social activities, and problem solving. On the other hand, the second group followed the routine antidepressant treatment. At the end of the study it was determined that the PEARLS program had reduced by a significant amount the gravity of the depressive symptoms and had notably ameliorated the health status of the depressed patients which had taken part in it [68]. Further studies corroborated a positive role played by physical activity in the decrease of depressive symptoms in older patients. Indeed, it has been proven that the addition of a therapy based on physical exercise to the pharmacological treatment of depression is able to contribute more significant benefits in comparison to the exclusive use of medicines [69, 70], reducing the cardiovascular risks associated to antidepressant drugs [71]. From these and many other researches it can be evinced that moderate physical activity plays a largely positive role equal to, if not even more, to that exercised by the pharmacological treatment and psychotherapy. It is in fact recognized that the elderly are frequently unable to take antidepressant medications, and very often they do not have the financial resources to regularly follow the psychotherapy sessions [65], while physical activity is easy to practice consistently and has extremely low costs. In relation to this, recently the National Institute for Health and Clinical Excellence [72] has established some guidelines for the treatment of depression through physical activity. These guidelines recommend specific exercise programs supervised by an expert, three times a week (45-60 minutes) for 10-14 weeks, maintaining a low intensity for mild depressive syndromes [73].

2.1. Effects of Physical Exercise on Brain Volume and Neurotransmission Alterations Linked to Depressive Illness in the Elderly

One of the main anatomical manifestations associated with depression is represented by the decrease of hippocampal volume of about 0.3-0.4 standard deviations in depressed patients compared to healthy controls [74]. However, a number of clinical trials have recently demonstrated an enhancement of hippocampal volume following physical activity. Indeed in a study it was observed that a 6-month exercise program was able to enhance of about 2% the volume of the hippocampus in healthy elderly adults [75], and other re-

searches supported this evidence by showing a direct correlation between increase in hippocampal volumes and in aerobic exercise [76, 77]. Further information has demonstrated that the enhancement of the hippocampal volume was strictly related to improved maximal oxygen uptake, increased BDNF, and better spatial and verbal memory [75, 78]. As far as the role of physical activity in the increase in hippocampal volume of depressed patients, at present there is only one study in which patients with depression were randomly divided into two groups: a group was subjected to aerobic exercise intervention consisting of three controlled trials per week during a period of three-month, while the other group followed the control medication. The results obtained clearly indicated that physical activity was not able to increase hippocampal volume in patients suffering with mild to moderate MDD [79].

The positive action of physical exercise on the human brain, particularly in the aged human brain, is still very limited and the few data available was derived largely from animal studies [80, 81]. In many mouse and rat model research it has been demonstrated that physical exercise, more specifically voluntary or forced running, is able to finely modulate the main CNS neurotransmitters that are strictly associated with an individual's state of awareness (norepinephrine), the level of anxiety (serotonin) and the pleasure and reward system (dopamine). The antidepressant effect provided by physical activity could be explained by its specific role in modifying monoamine communication. It has been demonstrated, in animal models, that voluntary running is able to induce a significant enhancement of tryptophan in the plasma and the brain, as well as the levels of the serotonin metabolite, 5-hydroxy-indoleacetic acid (5-HIAA) [82, 83]. Another study has shown that running throughout a period of three weeks increased levels of serotonin transporters and 5-HT_{2A} receptors in sedentary males, while 4 weeks of intense exercise in well-trained athletes did not significantly modify serotonin transporters, and 5-HT_{2A} receptor density declined, proposing that the action of physical activity on serotonin neurotransmission system may be strongly associated with the intensity and duration of exercise [84]. Regarding the antidepressant effect of physical exercise in the elderly, Melancon and colleagues established tryptophan disposal to the nervous system during persistent activity in aged men; they also found that sustained exercise is able to induce a significant raise in tryptophan levels in the brain, suggesting the antidepressant action of exercise might be mediated by the increase in serotonin synthesis during the activity [85].

Other lines of evidence hypothesized that dopamine synthesis is largely enhanced in exercised animals, which also show a decrease of D2 autoreceptor-mediated inhibition of dopamine neurons. Furthermore, in the basal ganglia of physically active animals it has been observed an increase of indirect pathway inhibition mediated by the D2 receptor. [86]. A study from Dishman and colleagues linked the modification of noradrenergic transmission with exercise by showing that physical training improved the synthesis of tyrosine hydroxylase and noradrenaline levels in rodent undergone to chronic exercise [87]. However, synaptic dopamine concentrations are not altered after acute physical activity consisting of 30 minutes of highly dynamic exercise in adult volunteers [88].

2.2. Effects of Physical Exercise on Neurotrophic Factor, Neurogenesis, and Neuroinflammation Alterations Linked to Depressive Illness in the Elderly

The most powerful action of physical activity on the brain is represented by the very high increase in the levels of the neurotrophin BDNF. Indeed, it has been shown that aerobic exercise is able to increase BDNF mRNA levels in the lumbar spinal cord [89], in the cerebellum [90] and in the in neurons localized in the dentate gyrus, hilus and CA3 region of the hippocampus [90, 91]. In humans, a recent study carried out on young volunteers revealed that acute exercise was able to enhance BDNF concentrations in the serum which had not quite reverted to basal level at 30 minutes post-exercise [92], even though most of the literature proposes for a transient increase in serum BDNF during physical activity. Concerning the functional effect of an exercise-dependent increase of BDNF in the brain, many researchers suggest that it is possible to predict the risk of depression by analyzing the link between BDNF levels, hippocampal volume and the amount of physical activity. Other studies have highlighted that aerobic exercise might represent a pivotal tool for the depression treatment by enhancing BDNF level and consequently hippocampal size. Supporting this idea, two studies showed in elderly women with remitted depression [93] and in patients with panic disorders [94] a prolonged period of physical activity was able to increase the concentration of BDNF in serum.

Insulin-like growth factor-1 (IGF-1) represents another neurotrophin whose production in the serum and brain is highly stimulated during physical activity. It has been suggested that the exercise-induced enhancement of IGF-1 expression might be correlated with a mood improvement and that IGF-1 might act as a mediator of the proneurogenic action exerted by physical activity [95]. Fibroblast growth factor-2 (FGF-2), that triggers adult neural stem cell proliferation, is another mitogen protein whose hippocampal levels are highly induced after exercise [96]. Relevant interactions between IGF-1 and FGF-2 have been identified, as FGF-2 enhances IGF-1 receptors and IGF-1 binding protein [97], and IGF *in vitro* increases the action of FGF-2 on progenitor proliferation [98].

Hippocampal neurogenesis plays a pivotal role in mediating antidepressant effects of physical exercise and antidepressants [99]. Indeed, physical activity stimulates many aspects of hippocampal plasticity, including adult neurogenesis, dendritic arborization and synaptic plasticity [100]. Moreover, several studies have demonstrated that increased hippocampal neurogenesis has a positive action on depressive-like behavior in depressed animal models [101, 102]. Consequently, the ablation of hippocampal neurogenesis with x-irradiation is sufficient to arrest the effect of antidepressant treatment on depressive-like phenotypes [103]. Moreover, the infusion of the anti-mitotic Ara-c for 2 weeks not only impaired proliferation, but also ongoing hippocampal adult neurogenesis in the depressed mice-model. It has been shown that the function and structure of the hippocampus is strictly dependent on corticosteroid (CORT) levels.

Reiterated injection of CORT in rodents represents a consistent way for inducing stress and analyzing the role of stress in depressive disorders [104]. By this method a study has shown that, in a CORT-induced animal model of stress, physical activity induced BDNF levels, hippocampal adult neurogenesis and dendritic remodeling, which represented characteristic features of the beneficial effect of exercise on stress.

The adiponectin, a protein hormone secreted by peripheral mature adipocytes, has been recently demonstrated to play a pivotal role in mediating the enhancement of hippocampal neurogenesis and mitigation of depression following physical exercise. Indeed, intra-cerebroventricular overexpression of adiponectin mirrored the pro-neurogenic action of voluntary running, including the improvement of hippocampal adult neurogenesis and the proportional decline of depressive-like behavior, proposing the functional correlation between these two factors [105]. Conversely, the basal level of neurogenesis was not affected by adiponectin deficiency, while the authors observed a significant reduction of running-induced adult neurogenesis and weakened antidepressant action induced by physical activity in adiponectin deficient mice model. These data suggest that increased production of adiponectin mimics the antidepressant action of physical exercise by promoting hippocampal neurogenesis [105].

Another brain mechanism that putatively links physical activity to an improvement in depression is represented by inflammation. It has been shown that sickly behavior with symptoms consistent with depression can be produced by inflammation originating from a peripheral immune activation [106]. The main replicated inflammation-related factors in depression are represented by elevated serum and plasma levels of interleukin (IL)-6, IL-1β and tumor necrosis factor α (TNFα) [107]. Indeed, a recent study has shown that in patients with MDD there are significant differences in IL-6 levels in respect to controls [108]. Moreover, elevated IL-6 levels were also detected in the cerebrospinal fluid of depressed patients, as well as in the frontal cortex of a rat model with depressive-like behavior [109, 110]. More recently, a meta-analysis evaluating 82 studies revealed increased levels of cytokines, including IL-6, in patients suffering with MDD in comparison with healthy controls [111]. Inflammation might also indirectly affect the progression of depression by dysregulating neurotransmitter systems [112]. For instance, the tryptophan metabolism is upregulated by pro-inflammatory cytokines, giving rise to functional ligands (*e.g*. kynurenic acid and quinolinic acid) which deeply affect NMDA receptors and more generally the dopamine system [112]. A recent study showed that exercise-dependent increase of skeletal muscle kyurenine aminotransferase positively affects the kynurenine pathway, which in turn results in an improved protection against stress-induced depressive symptoms [113].

Physical activity modulates pro-inflammatory factors, providing an alteration of the number and the function of the immune system [114]. In this regard, the beneficial action of physical activity on inflammation might be partly due to the anti-inflammatory role of regular physical activity. These protective effects exerted by exercise are mediated by decreased visceral adiposity and/or enhancement of anti-inflammatory cytokines, among which the IL-1 receptor antagonist and IL-10 [115].

Importantly, the anti-inflammatory role exerted by exercise has been recently associated with improvement in the clinical manifestation of depression [116]. Indeed, 12 weeks of aerobic physical activity among 105 depressed patients produced alterations in IL-1β levels and enhancement in baseline levels of TNFα, resulting in a significant amelioration of depressive symptoms [117]. Moreover, in a recent analysis it was demonstrated that increased serum levels of IL-6, at baseline, were linearly related with large improvements of depression in a clinical course over 12 weeks of physical activity and, conversely, that higher baseline depression manifestation was linearly associated with stronger reductions in serum IL-6 levels [118]. However, at least 5 studies did not find any correlation between physical activity and changes in inflammatory markers in patients affected by depression [119].

3. EFFECTS OF OMEGA-3 FATTY ACIDS ON DEPRESSIVE ILLNESS IN THE ELDERLY

The notion that a poor diet may be a risk factor for the onset of depression has only recently emerged [120]. Among nutrients, omega-3 fatty acids are thought as "potent food-derived plasticity inducers" [121]. In fact, this family of polyunsaturated fatty acids is derived from α-linolenic acid (ALA) that cannot be synthesized by humans and thus must be obtained from the diet [122, 123]. Dietary sources of ALA include plant oils like flax, canola, soybean, perilla, chia, and walnut oils [124]. Dietary sources of the longer omega-3 fatty acids, as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), include marine algae, animals, and phytoplankton [125, 126]. Fish, squid, and krill oils are rich in EPA and DHA [123, 124].

Omega-3 fatty acids are incorporated into cell membranes, and play a role in anti-inflammatory processes and cell membrane viscosity [126]. EPA and DHA are essential for proper brain development and function from childhood to old age [123, 126]. DHA is a key component of neuronal membranes and contributes to synaptic membrane fluidity and regulation of cell signaling [126-128]. EPA and DHA are also the precursors of anti-inflammatory and pro-resolving lipid mediators, such as resolvins and protectins, considered to be beneficial in the treatment and prevention of numerous diseases [129].

The increased prevalence of depressed mood and anxiety over the last decades has been associated with an excessive consume of saturated fats and refined sugar, as well as with a raise in the ratio of omega-6 to omega-3 fatty acids [130-142]. In particular, nutritional research indicates that the "Western diet" does not provide the aged brain with an optimal supply of omega-3 fatty acids [143]. In addition, low cerebral omega-3 fatty acid levels observed during aging are linked to reduced absorption, decreased capacity of omega-3 fatty acids to cross the blood-brain barrier, and diminished facility to convert shorter chained fatty acids into longer fatty acids [144]. On the other hand, healthful ways of eating, such as Mediterranean diet or feeding "whole food" *vs*.

"processed food", have been related to an inferior risk of depression and mental illness [137, 145-149]. Some studies have demonstrated that a greater adherence to a Mediterranean-based diet (comprised of high levels of fish, fruit, vegetables, whole grains and legumes, low levels of foods with added sugars, and a low consumption of red meat) was associated with a reduced number of depressive symptoms at an older age [52, 150-154]. Anyway, the protective role of the Mediterranean diet against depression may depend on the synergic positive actions of a variety of foods with a high content of omega-3 fatty acids, such as oily fish, as well as of other dietary components, such as B vitamins [155, 156].

Up until today a growing number of animal and human studies has pointed out that low levels of omega-3 fatty acids are involved in the development of mood disorders, while omega-3 fatty acid intake is associated with reduced depressive symptomatology, even at an old age [120, 157-164]. However, results from randomized controlled trials are mixed with some meta-analyses indicating omega-3 fatty acid supplementation benefits in clinically depressed individuals, depending [165-169] or not [170, 171] on the symptom severity or EPA/DHA dosage, and other ones indicating small, non-significant effects [172, 173]. A meta-analysis of omega-3 fatty acid use for bipolar disorder showed benefits only for depressive episodes and not for manic or hypomanic episodes [174].

Overall the evidence suggesting a role of omega-3 fatty acids in preventing and alleviating depression and mood disorders during aging, even though not entirely conclusive, points to many protective mechanisms [53, 175] acting on brain volume, neurotransmission, neurotrophic factors, neurogenesis, neuroinflammation, and gut microbiota.

3.1. Effects of Omega-3 Fatty Acids on Brain Volume and Neurotransmission Alterations Linked to Depressive Illness in the Elderly

The converging evidence on the antidepressant action of omega-3 fatty acids at an old age is significant, since depressive symptoms can be linked to many aging-associated disorders, such as metabolic disorders and dementia [176, 177], and are often associated with age-related atrophy in the hippocampus and the prefrontal cortex [32, 178-180]. A few human studies indicate that omega-3 fatty acid intake may be associated with white matter integrity and greater gray matter volume (in brain areas such as orbitofrontal cortex, hippocampus, and amygdala) in parallel with a reduction in depressive symptoms during aging [181-183]. In this regard, recent interventional studies in aged mice demonstrated that omega-3 fatty acid supplementation can counteract atrophy in specific brain regions (such as prefrontal and restrosplenial cortices, and hippocampus) and increase active coping responses [184, 185]. These results fit nicely with human and animal evidence of omega-3 fatty acid-induced structural brain changes (such as the reduction in the lateral ventricular volume and the increase in the hippocampal volume) accompanying reduced depressive symptoms in adult, not aged subjects [186-189]. Further data will be available at the end of the Better Resiliency Among Veterans and non-Veterans with Omega-3's (BRAVO) study, a randomized controlled trial among individuals (aged 18-90 years) at risk for suicide that will determine if dietary supplementation with omega-3 fatty acids is able to reduce suicidal behaviors and depressive symptoms, and will further provide functional MRI data [190].

Despite the mechanisms of the antidepressant action of omega-3 fatty acids are not yet fully understood, it has been reported that their deficiency is associated with dysfunctions of serotonin, dopamine, and norepinephrine neurotransmission, which is closely involved in mood disorders [191]. For instance, animal studies have shown decreased concentrations of serotonin in the frontal cortex and lower expression of the serotonin synthesizing enzyme tryptophan hydroxylase in the midbrain as a consequence of dietary omega-3 fatty acid deficiency [192-195]. On the contrary, feeding a diet supplemented with omega-3 fatty acids increased brain and plasma concentrations of serotonin, and could reverse deficits of serotonin turnover in rodent models of depression [195-198]. Many human studies have reported associations between a decrease in serotonin and omega-3 fatty acid levels, and an increase in depressive symptoms [191]. Furthermore, the interaction between the serotonin transporter genotype and omega-3 fatty acid intake has been reported as a risk factor for post-partum depression [199].

Dopaminergic systems are also influenced by dietary omega-3 fatty acid intake. In particular, omega-3 fatty acid consumption has been positively associated with dopamine and serotonin levels in healthy human subjects [200] and rats [201, 202]. In rats being fed a diet deficient in omega-3 fatty acids, the expression of D2 dopamine receptors was decreased in the ventral striatum and in the frontal cortex, and increased in the nucleus accumbens [203, 204].

Interestingly, complex associations between omega-3 fatty acid levels or omega-6:omega-3 fatty acid balance and dopaminergic indices (such as plasma prolactin and cerebrospinal fluid homovanillic acid) have been reported in adults with MDD [205]. These findings are consistent with a model in which low omega-3 fatty acids are associated with a constitutively greater rate of dopamine breakdown and indicate that omega-3 fatty acids may influence depression pathophysiology through specific effects on the dopaminergic system.

Finally, alterations in the noradrenergic system, such as increased density of β-adrenergic receptors in the frontal cortex and alterations in α1 and α2 receptors, have also been observed in post-mortem brains of suicide completers [206-208]. Additionally, β3-adrenergic receptor agonists may exert antidepressant effects comparable to fluoxetine or imipramine for the treatment of anxiety and depressive disorders [209]. The modulating action of omega-3 fatty acids on noradrenergic neurotransmission has been relatively little investigated, so data on this issue are still controversial. In animal studies, decreased cortical, hippocampal, and striatal norepinephrine levels associated with behavioral disturbances were observed in rats fed a diet deficient in omega-3 fatty acids from birth [210]. As for human studies, EPA and DHA supplementation for 2 months reduced plasma norepinephrine concentrations in healthy young adults [211].

To our knowledge there have been no animal or human studies investigating the role of omega-3 fatty acid supplementation in modifying serotonin, dopamine, and/or norepinephrine levels to prevent depressive symptoms in aged subjects. Promising results are expected from an ongoing randomized controlled trial [9] comparing omega-3 fatty acid or sertraline (a selective serotonin re-uptake inhibitor) interventions in preventing depression in an older age cohort.

3.2. Effects of Omega-3 Fatty Acids on Neurotrophic Factor, Neurogenesis, and Neuroinflammation Alterations Linked to Depressive Illness in the Elderly

As mentioned above, BDNF has a pivotal role in the pathogenesis of depressive disorders [212]. Interestingly, dietary omega-3 fatty acid deficiency leads to reduced expression of BDNF [192, 213-215], while dietary omega-3 fatty acid supplementation results in elevated expression of BDNF [189, 198, 216-219]. However, to date no studies are available on the effects of omega-3 fatty acids on neurotrophic factor levels in the presence of depressive symptoms during aging.

Omega-3 fatty acid levels are positively associated with neurogenic and synaptogenic functions [126, 220-223]. Namely, an enhancement of hippocampal neurogenesis has been observed following the increase in brain omega-3 fatty acids [224]. Beneficial effects on hippocampal neurogenesis have also been reported in aged mice and rats supplemented with omega-3 fatty acids, and were accompanied by enhanced neuronal density, neurite outgrowth and microglial cell number, diminished neurodegeneration indices (*i.e.*, lipofuscin, caspase-3, astrogliosis levels), better cognitive functions, and more active coping skills [184, 185, 225]. Omega-3 fatty acids have demonstrated a marked neurite-promoting potential also in the sensory neurons of the dorsal root ganglia from aged rats [226]. The endocannabinoid system seems to be implicated in omega-3 fatty acid effects on adult neurogenesis, since the EPA-induced increase in the proliferation of neural stem cells has been reported to be associated with increased levels of the endocannabinoid 2-arachidonylglycerol [227].

It is well-known that omega-3 fatty acids are able to mitigate inflammation. For example, rats that consumed omega-3 fatty acid deficient diets from birth showed higher plasma levels of IL-6, C-reactive protein, and TNFα, which were reversed by subsequently feeding them with an ALA-containing diet [195]. In addition, EPA modulates the immune function by reducing membrane arachidonic acid and prostaglandin E2 synthesis [228]. Thus, another potential mechanism for the antidepressant action of omega-3 fatty acids is *via* regulation of neuroinflammation and oxidative stress [2, 37, 229, 230]. In fact, omega-3 fatty acids show inverse associations with depressive symptoms among individuals with higher oxidative stress levels [231]. Furthermore, several researches indicate that omega-3 fatty acids may exert antidepressant effects when depression is associated with inflammation [37, 232]. As for human studies, a randomized controlled trial found that EPA is able to prevent depression in hepatitis C virus patients which received interferon-α therapy [233]. Omega-3 fatty acids have been reported to attenuate both endotoxin-induced inflammation and sickness behavior in rodents and humans [234-237]. In rats, omega-3 fatty acid administration alleviated the behavioral, inflammatory, and oxidative stress consequences of the treatment with doxorubicin, a chemotherapeutic agent widely used in human malignancies whose long-term use may provoke depression [238]. Anti-inflammatory properties of omega-3 fatty acids were reported even at an old age. Namely, dietary supplementation with EPA in aged rats decreased cortical and hippocampal IL-1β, interferon-γ, and IL-4 [239-242]. Both DPA and EPA decreased age-related microglial activation and oxidative stress in aged rats [243]. An important anti-inflammatory effect of both EPA and DHA *in vitro* in peripheral blood mononuclear cells was reported in Alzheimer's disease (AD) patients [244]. Epidemiological and observational studies have demonstrated inverse correlations between omega-3 fatty acid levels and inflammatory biomarkers, such as IL-6, C-reactive protein, and TNFα, during aging [245-248]. Importantly, also telomere length, which is regulated by the exposure to proinflammatory cytokines and oxidative stress, increases with decreasing omega-6:omega-3 fatty acid ratio and increasing omega-3 fatty acid blood levels during aging [249-251].

To date, the strongest support for an anti-inflammatory effect of omega-3 fatty acids, shedding light on their antidepressant properties in the elderly, has come from a study by Kiecolt-Glaser and colleagues [252] demonstrating that the supplementation with EPA and DHA reduced serum IL-6 and TNFα levels in overweight, sedentary middle-aged and older adults, a population at high risk for depression. In a previous study [253] a higher omega-6:omega-3 fatty acid ratio in older adults was associated with elevated TNFα and IL-6 levels as depressive symptoms increased.

Finally, omega-3 fatty acids are a source of docosanoids, such as protectins and resolvins, that have anti-inflammatory properties [254-256]. Interestingly, it has been demonstrated that resolvin D1 decreases post-myocardial infarct depressive symptoms in rats [257]. Intracerebroventricular infusion of resolvin D1 and D2 produced antidepressant effects in a murine model of depression induced by lipopolysaccharide (LPS) injections [258]. Moreover, neuroprotectin D1 showed a significant role in brain cell survival and repair in aging disorders [259]. Given these promising findings, future researches on the antidepressant effects of omega-3 fatty acids *via* docosanoids in aging are expected.

4. IMPLICATIONS OF PHYSICAL EXERCISE AND OMEGA-3 FATTY ACIDS ON GUT MICROBIOTA ALTERATIONS LINKED TO DEPRESSIVE ILLNESS

As illustrated before, physical activity is able to mitigate inflammatory processes, and it has been hypothesized that one of the mechanisms through which it occurs might be through a direct effect on the modulation of gut microbiota composition [260]. However, there are few studies in this regard and most of them have been carried out in animal models. In a recent study, it has been shown that mice performing exercise display differences in 2510 taxa of bacteria in comparison with the sedentary group. More specifically exercised mice showed more abundance of the Lactobacillus order, which have been demonstrated to induce health benefits on the human body [261, 262]. Furthermore,

in a study performed by analyzing different rat strains, an increase in Lactobacillus genus was observed in obese rats after physical exercise [263]. In the unique study carried out on humans until now, Clarke and colleagues observed that a group of rugby players showed a greater diversity on microbial species - 22 phyla, 68 families and 65 genera - respect to the control group [264]. However, there is currently no evidence describing a putative correlation among physical activity, gut microbiota composition and depressive symptoms during aging.

Mood, stress, and diet can all influence the gut microbiota and promote intestinal permeability, closely linked to enhanced inflammatory responses [37, 265]. Many studies have shown a contribution of omega-3 fatty acids on anxiety and depressive-like behaviors through a modulation of the gut microbiota. For example, adult male mice subjected to social isolation and then supplemented with DHA showed reduced anxiety and depressive-like behaviors accompanied by alterations in the commensal microbiota composition [266].

Long-term supplementation of EPA and DHA could restore the disturbed gut microbiota composition and attenuate the corticosterone response to acute stress of female rats subjected to a procedure of maternal separation, considered an early-life stress, and thus a risk factor for mood disorders [267].

Neurobehavioral development is highly dependent upon the availability of omega-3 fatty acids during gestation and for the lifetime, with implications for gut microbiota composition, HPA axis activity, and inflammation. In fact, mice fed a omega-3 fatty acid deficient diet from gestation displayed depressive behaviors accompanied by dysfunctional alterations in gut microbiota composition (increased Firmicutes:Bacteroidetes ratio) and blunted systemic LPS responsiveness, while mice fed a omega-3 supplemented diet displayed enhanced behavioral abilities along with a beneficial impact on the gut microbiota (increased fecal Bifidobacterium and Lactobacillus levels) and dampened HPA axis activity [268].

Intestinal microbiota alteration (*i.e*., dysbiosis) is present in several chronic inflammatory diseases, but it has not been well studied in the elderly. Aged mice fed a high-fat diet rich in omega-6 fatty acids showed ileal bacterial overgrowth, increased body mass and infiltration of macrophages and neutrophils, while fish oil supplementation was able to restore the microbiota and reverse the intestinal inflammation [269].

Overall these studies show that omega-3 fatty acids may improve affective behaviors through their role in the regulation of gut microbiota. However, further studies are needed to elucidate the interactions among omega-3 fatty acid levels, gut microbiota composition, and depressive symptoms during aging.

5. ADDITIONAL EFFECTS OF EXERCISE AND OMEGA-3 FATTY ACIDS ON DEPRESSIVE ILLNESS IN THE ELDERLY

A growing body of evidence indicates that exercise and diet exert beneficial effects on depression [120], while less is known about their collaborative antidepressant effects [270]. Animal studies have demonstrated that DHA supplementation associated with voluntary exercise boosted the beneficial effects of each single intervention alone, by additionally enhancing spatial learning and synaptic plasticity [271, 272]. The combination of exercise and a complex dietary supplementation (containing also flax seed oil as source of omega-3 fatty acids) increased hippocampal neurogenesis and neurotrophic factors in chronically stressed mice, while these benefits were not observed if the animals were exposed to each intervention alone [273].

As for human researches, a pilot study reported that combined omega-3 fatty acids, aerobic exercise, and cognitive stimulation may prevent gray matter volume loss in frontal, parietal, and cingulate cortex in patients with mild cognitive impairment [274]. A randomized controlled trial by Schättin and de Bruin [275] is now investigating the effectiveness of exergame training (a kind of physical exercise based on video games) combined with omega-3 fatty acid supplementation in counteracting age-dependent neuronal changes in the brain. From a clinical point of view, the combined antidepressant effects of exercise and omega-3 fatty acids underpin the "Antidepressant-Lifestyle-Psychological-Social (ALPS) depression treatment model", an evidence-based integrated mental health approach including pharmaceutical medicines as well as psychological therapies, complementary medicines, nutraceuticals, and physical activity [276].

6. ROLE OF COGNITIVE AND BRAIN RESERVE IN DEPRESSION DURING AGING

One of the aspects associated to depression during elderly age is represented by the appearance of cognitive deficits as a direct consequence of the mood disorders [277-279]. However, other studies have suggested a reverse causation, *i.e*. a decrease in cognitive functions which may lead to depressive symptoms [280, 281]. The relationship between depression and cognitive activity during ageing has led some researchers to hypothesize a positive role of the Cognitive Reserve (CR) and Brain Reserve (BR) in alleviating or delaying the onset and severity of depression as well as in preventing the cognitive dysfunctions related to the depressive symptoms. The CR is related to “the capacity of the brain to resist the expression of symptoms in the face of existing neuropathology” [282]. This functional model encompasses the cognitive capacity of information processing and predicts that differences in the efficiency or flexibility of the brain network underlying task performance affects the individuals’ capability to cope with brain pathology, thus suggesting that the brain can compensate a pathological decline by using pre-existing cognitive processes [283]. On the other hand, the BR has been proposed to describe some individuals showing an improved “baseline adaptive neuroplasticity” whom are able to provide larger dynamic capacity for modifying and refining neural circuits to different stressors. In this context it has been suggested that BR, as an index of brain plasticity, may account for quantitative differences in brain resources (*i.e*., a larger brain, more neurons and synapses), explaining individual differences in task performance or in coping with neuropathologies [284]. Experiences in early life, such as

education, occupational complexity, and engagement in cognitively stimulating activity throughout life, are strictly associated to greater synaptic density and cognitive function in later life [283]. Moreover, as widely discussed above, several studies have shown that physical activity and omega-3 enriched diet are able to modulate common neuroplasticity substrates (neurotrophic signalling, neurogenesis, inflammation, stress response, and antioxidant defence) which contribute to the morphological and cognitive enhancement observed in the BR and CR [285]. These models are usually applied in the field of neuropathologies, showing particular attention in highlighting variability in the symptomatic responses of AD patients as a result of a different structure (BR) and functionality (CR) of the brain [286]. To date, research addressing the question of whether higher cognitive or BR might decrease the symptoms of depression and related psychological aspects on cognitive function during ageing remains limited, with inconstant data. In this regard, a recent study has shown that a high CR is able to mitigate the cognitive dysfunctions often produced by depression [287], while another research has highlighted how BR, characterized by educational attainment, counterbalances the depressive symptomatology in older women thereby preserving mood in late life [288].

CONCLUSION

Although much remains to be clarified about the specific molecular mechanisms through which physical activity and diet influence brain plasticity, the growing literature here summarized supports the idea that both these two non-invasive and effective interventions can promote mental health throughout the lifespan of an individual [54, 120].

Over the past centuries, the drastic change in lifestyle has produced a growing sedentariness followed by deleterious consequences on human health and social costs [289-291]. Thus, tailored interventions aimed to improve overall well-being by increasing physical activity in older adults are particularly favourable. In the same manner, the protective function of dietary omega-3 fatty acids in brain integrity during aging corroborates their efficacy against age-related mood disorder vulnerability. For these reasons, an active lifestyle and a balanced diet may constitute valid low-cost prevention strategies to counteract depressive illness in the elderly, even considering the dramatic increase in current general life expectancy.

Aging is a great challenge with regard to interventions aimed at increasing physical activity, because elderly people tend to show decreased motor skills and coordination [292]. Motivation is also important when studying interventions aimed at enhancing physical activity in the elderly [293]. Therefore, motor activities should be appealing and possibly held in company of others, so that older people can be more motivated to engage in them, and in parallel can strengthen their mental and social skills [294-296]. Future studies should also better define the antidepressant role of the different omega-3 fatty acids (*e.g.*, ALA, DHA, and EPA), also taking into account that advanced age impairs the capacity of omega-3 fatty acids to cross the blood-brain barrier and reach the brain tissues.

Finally, the consideration that depressive illness is not a homogenous disease and there is high variability among depressed patients denotes that each individual could respond differently to treatment, and thus support the use of a vast range of interventions, encompassing both exercise and nutritional factors (such as omega-3 fatty acids), especially at an old age, when subjects are more susceptible to the side effects of drugs [297, 298].

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This work was supported by Italian Ministry of Health (Grant GR-2011-02351086 to D.C.).

REFERENCES

[1] World Health Organization. *Media Center.,* http://www.who.int/mediacentre/factsheets/fs369/en/

[2] Grosso, G.; Galvano, F.; Marventano, S.; Malaguarnera, M.; Bucolo, C.; Drago, F.; Caraci, F. Omega-3 fatty acids and depression: scientific evidence and biological mechanisms. *Oxid. Med. Cell. Longev.,* **2014**, *2014*, 313570. [http://dx.doi.org/10.1155/2014/313570] [PMID: 24757497]

[3] Mackin, R.S.; Areán, P.A. Impaired financial capacity in late life depression is associated with cognitive performance on measures of executive functioning and attention. *J. Int. Neuropsychol. Soc.,* **2009**, *15*(5), 793-798. [http://dx.doi.org/10.1017/S1355617709990300] [PMID: 19635176]

[4] American Psychiatric Association. *Diagnostic and statistical manual of mental disorders.,* 5th ed. American Psychiatric Publishing: Arlington **2013**.

[5] Fiske, A.; Wetherell, J.L.; Gatz, M. Depression in older adults. *Annu. Rev. Clin. Psychol.,* **2009**, *5*, 363-389. [http://dx.doi.org/10.1146/annurev.clinpsy.032408.153621] [PMID: 19327033]

[6] Aziz, R.; Steffens, D.C. What are the causes of late-life depression? *Psychiatr. Clin. North Am.,* **2013**, *36*(4), 497-516. [http://dx.doi.org/10.1016/j.psc.2013.08.001] [PMID: 24229653]

[7] Luppa, M.; Sikorski, C.; Luck, T.; Ehreke, L.; Konnopka, A.; Wiese, B.; Weyerer, S.; König, H.H.; Riedel-Heller, S.G. Age- and gender-specific prevalence of depression in latest-life--systematic review and meta-analysis. *J. Affect. Disord.,* **2012**, *136*(3), 212-221. [http://dx.doi.org/10.1016/j.jad.2010.11.033] [PMID: 21194754]

[8] Teresi, J.; Abrams, R.; Holmes, D.; Ramirez, M.; Eimicke, J. Prevalence of depression and depression recognition in nursing homes. *Soc. Psychiatry Psychiatr. Epidemiol.,* **2001**, *36*(12), 613-620. [http://dx.doi.org/10.1007/s127-001-8202-7] [PMID: 11838834]

[9] Cockayne, N.L.; Duffy, S.L.; Bonomally, R.; English, A.; Amminger, P.G.; Mackinnon, A.; Christensen, H.M.; Naismith, S.L.; Hickie, I.B. The beyond ageing project phase 2--a double-blind, selective prevention, randomised, placebo-controlled trial of omega-3 fatty acids and sertraline in an older age cohort at risk for depression: study protocol for a randomized controlled trial. *Trials,* **2015**, *16*, 247. [http://dx.doi.org/10.1186/s13063-015-0762-6] [PMID: 26037484]

[10] Hybels, C.F.; Blazer, D.G. Epidemiology of late-life mental disorders. *Clin. Geriatr. Med.,* **2003**, *19*(4), 663-696. [http://dx.doi.org/10.1016/S0749-0690(03)00042-9] [PMID: 15024807]

[11] Butters, M.A.; Young, J.B.; Lopez, O.; Aizenstein, H.J.; Mulsant, B.H.; Reynolds, C.F., III; DeKosky, S.T.; Becker, J.T. Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin. Neurosci.,* **2008**, *10*(3), 345-357. [PMID: 18979948]

[12] Parkin, A.J. Normal age-related memory loss and its relation to frontal lobe dysfunction. In methodology of frontal and executive function, Rabbil E.D., Psychology press: Hove **1997**, pp. 177-190.

[13] Salthouse, T.A.; Hancock, H.E.; Meinz, E.J.; Hambrick, D.Z. Interrelations of age, visual acuity, and cognitive functioning. *J. Gerontol. B Psychol. Sci. Soc. Sci.,* **1996**, *51*(6), 317-330. [http://dx.doi.org/10.1093/geronb/51B.6.P317] [PMID: 8931619]

[14] Norton, S.; Matthews, F.E.; Barnes, D.E.; Yaffe, K.; Brayne, C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.,* **2014**, *13*(8), 788-794. [http://dx.doi.org/10.1016/S1474-4422(14)70136-X] [PMID: 25030513]

[15] Ritchie, K.; Carrière, I.; Ritchie, C.W.; Berr, C.; Artero, S.; Ancelin, M.L. Designing prevention programmes to reduce incidence of dementia: prospective cohort study of modifiable risk factors. *BMJ,* **2010**, *341*, c3885. [http://dx.doi.org/10.1136/bmj.c3885] [PMID: 20688841]

[16] Morimoto, S.S.; Alexopoulos, G.S. Cognitive deficits in geriatric depression: clinical correlates and implications for current and future treatment. *Psychiatr. Clin. North Am.,* **2013**, *36*(4), 517-531. [http://dx.doi.org/10.1016/j.psc.2013.08.002] [PMID: 24229654]

[17] Brailean, A.; Aartsen, M.J.; Muniz-Terrera, G.; Prince, M.; Prina, A.M.; Comijs, H.C.; Huisman, M.; Beekman, A. Longitudinal associations between late-life depression dimensions and cognitive functioning: a cross-domain latent growth curve analysis. *Psychol. Med.,* **2017**, *47*(4), 690-702. [http://dx.doi.org/10.1017/S003329171600297X] [PMID: 27834162]

[18] Byers, A.L.; Yaffe, K. Depression and risk of developing dementia. *Nat. Rev. Neurol.,* **2011**, *7*(6), 323-331. [http://dx.doi.org/10.1038/nrneurol.2011.60] [PMID: 21537355]

[19] Diniz, B.S.; Reynolds, C.F., III; Begley, A.; Dew, M.A.; Anderson, S.J.; Lotrich, F.; Erickson, K.I.; Lopez, O.; Aizenstein, H.; Sibille, E.L.; Butters, M.A. Brain-derived neurotrophic factor levels in late-life depression and comorbid mild cognitive impairment: a longitudinal study. *J. Psychiatr. Res.,* **2014**, *49*, 96-101. [http://dx.doi.org/10.1016/j.jpsychires.2013.11.004] [PMID: 24290367]

[20] Lebedeva, A.K.; Westman, E.; Borza, T.; Beyer, M.K.; Engedal, K.; Aarsland, D.; Selbaek, G.; Haberg, A.K. MRI-based classification models in prediction of mild cognitive impairment and dementia in late-life depression. *Front. Aging Neurosci.,* **2017**, *9*, 13. [http://dx.doi.org/10.3389/fnagi.2017.00013] [PMID: 28210220]

[21] Mahgoub, N.; Alexopoulos, G.S. Amyloid hypothesis: is there a role for antiamyloid treatment in late-life depression? *Am. J. Geriatr. Psychiatry,* **2016**, *24*(3), 239-247. [http://dx.doi.org/10.1016/j.jagp.2015.12.003] [PMID: 26946981]

[22] Panza, F.; Frisardi, V.; Capurso, C.; D'Introno, A.; Colacicco, A.M.; Imbimbo, B.P.; Santamato, A.; Vendemiale, G.; Seripa, D.; Pilotto, A.; Capurso, A.; Solfrizzi, V. Late-life depression, mild cognitive impairment, and dementia: possible continuum? *Am. J. Geriatr. Psychiatry,* **2010**, *18*(2), 98-116. [http://dx.doi.org/10.1097/JGP.0b013e3181b0fa13] [PMID: 20104067]

[23] Prince, M.; Patel, V.; Saxena, S.; Maj, M.; Maselko, J.; Phillips, M.R.; Rahman, A. No health without mental health. *Lancet,* **2007**, *370*(9590), 859-877. [http://dx.doi.org/10.1016/S0140-6736(07)61238-0] [PMID: 17804063]

[24] Sanchez-Villegas, A.; Martínez-González, M.A. Diet, a new target to prevent depression? *BMC Med.,* **2013**, *11*, 3. [http://dx.doi.org/10.1186/1741-7015-11-3] [PMID: 23286788]

[25] Do, D.P.; Dowd, J.B.; Ranjit, N.; House, J.S.; Kaplan, G.A. Hopelessness, depression, and early markers of endothelial dysfunction in U.S. adults. *Psychosom. Med.,* **2010**, *72*(7), 613-619. [http://dx.doi.org/10.1097/PSY.0b013e3181e2cca5] [PMID: 20498292]

[26] Ito, H.; Kawashima, R.; Awata, S.; Ono, S.; Sato, K.; Goto, R.; Koyama, M.; Sato, M.; Fukuda, H. Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. *J. Nucl. Med.,* **1996**, *37*(3), 410-414. [PMID: 8772633]

[27] Severus, W.E.; Littman, A.B.; Stoll, A.L. Omega-3 fatty acids, homocysteine, and the increased risk of cardiovascular mortality in major depressive disorder. *Harv. Rev. Psychiatry,* **2001**, *9*(6), 280-293. [http://dx.doi.org/10.1080/10673220127910] [PMID: 11600487]

[28] Peters, R. Ageing and the brain. *Postgrad. Med. J.,* **2006**, *82*(964), 84-88. [http://dx.doi.org/10.1136/pgmj.2005.036665] [PMID: 16461469]

[29] Lockhart, S.N.; DeCarli, C. Structural imaging measures of brain aging. *Neuropsychol. Rev.,* **2014**, *24*(3), 271-289. [http://dx.doi.org/10.1007/s11065-014-9268-3] [PMID: 25146995]

[30] Fjell, A.M.; Walhovd, K.B.; Fennema-Notestine, C.; McEvoy, L.K.; Hagler, D.J.; Holland, D.; Brewer, J.B.; Dale, A.M. One-year brain atrophy evident in healthy aging. *J. Neurosci.,* **2009**, *29*(48), 15223-15231. [http://dx.doi.org/10.1523/JNEUROSCI.3252-09.2009] [PMID: 19955375]

[31] Hickie, I.; Naismith, S.; Ward, P.B.; Turner, K.; Scott, E.; Mitchell, P.; Wilhelm, K.; Parker, G. Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. *Br. J. Psychiatry,* **2005**, *186*, 197-202. [http://dx.doi.org/10.1192/bjp.186.3.197] [PMID: 15738499]

[32] Vu, N.Q.; Aizenstein, H.J. Depression in the elderly: brain correlates, neuropsychological findings, and role of vascular lesion load. *Curr. Opin. Neurol.,* **2013**, *26*(6), 656-661. [http://dx.doi.org/10.1097/WCO.0000000000000028] [PMID: 24184971]

[33] Ganança, L.; Oquendo, M.A.; Tyrka, A.R.; Cisneros-Trujillo, S.; Mann, J.J.; Sublette, M.E. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology,* **2016**, *63*, 296-310. [http://dx.doi.org/10.1016/j.psyneuen.2015.10.008] [PMID: 26546783]

[34] Miller, A.H. Depression and immunity: a role for T cells? *Brain Behav. Immun.,* **2010**, *24*(1), 1-8. [http://dx.doi.org/10.1016/j.bbi.2009.09.009] [PMID: 19818725]

[35] Swardfager, W.; Rosenblat, J.D.; Benlamri, M.; McIntyre, R.S. Mapping inflammation onto mood: Inflammatory mediators of anhedonia. *Neurosci. Biobehav. Rev.,* **2016**, *64*, 148-166. [http://dx.doi.org/10.1016/j.neubiorev.2016.02.017] [PMID: 26915929]

[36] Dantzer, R.; O'Connor, J.C.; Freund, G.G.; Johnson, R.W.; Kelley, K.W. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat. Rev. Neurosci.,* **2008**, *9*(1), 46-56. [http://dx.doi.org/10.1038/nrn2297] [PMID: 18073775]

[37] Kiecolt-Glaser, J.K.; Derry, H.M.; Fagundes, C.P. Inflammation: depression fans the flames and feasts on the heat. *Am. J. Psychiatry,* **2015**, *172*(11), 1075-1091. [http://dx.doi.org/10.1176/appi.ajp.2015.15020152] [PMID: 26357876]

[38] Fehér, J.; Kovács, I.; Balacco, G.C. Role of gastrointestinal inflammations in the development and treatment of depression. *Orv. Hetil.,* **2011**, *152*(37), 1477-1485. [http://dx.doi.org/10.1556/OH.2011.29166] [PMID: 21893478]

[39] Belvederi Murri, M.; Pariante, C.; Mondelli, V.; Masotti, M.; Atti, A.R.; Mellacqua, Z.; Antonioli, M.; Ghio, L.; Menchetti, M.; Zanetidou, S.; Innamorati, M.; Amore, M. HPA axis and aging in depression: systematic review and meta-analysis. *Psychoneuroendocrinology,* **2014**, *41*, 46-62. [http://dx.doi.org/10.1016/j.psyneuen.2013.12.004] [PMID: 24495607]

[40] Masi, G.; Brovedani, P. The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression. *CNS Drugs,* **2011**, *25*(11), 913-931. [http://dx.doi.org/10.2165/11595900-000000000-00000] [PMID: 22054117]

[41] Lee, B.H.; Kim, Y.K. The roles of BDNF in the pathophysiology of major depression and in antidepressant treatment. *Psychiatry Investig.,* **2010**, *7*(4), 231-235. [http://dx.doi.org/10.4306/pi.2010.7.4.231] [PMID: 21253405]

[42] Krishnan, V.; Nestler, E.J. The molecular neurobiology of depression. *Nature,* **2008**, *455*(7215), 894-902. [http://dx.doi.org/10.1038/nature07455] [PMID: 18923511]

[43] Nutt, D.J. Relationship of neurotransmitters to the symptoms of major depressive disorder. *J. Clin. Psychiatry,* **2008**, *69*(Suppl E1), 4-7. [PMID: 18494537]

[44] Nestler, E.J.; Carlezon, W.A., Jr. The mesolimbic dopamine reward circuit in depression. *Biol. Psychiatry,* **2006**, *59*(12), 1151-1159. [http://dx.doi.org/10.1016/j.biopsych.2005.09.018] [PMID: 16566899]

[45] Mattson, M.P.; Maudsley, S.; Martin, B. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. *Trends Neurosci.,* **2004**, *27*(10), 589-594. [http://dx.doi.org/10.1016/j.tins.2004.08.001] [PMID: 15374669]

[46] Carabotti, M.; Scirocco, A.; Maselli, M.A.; Severi, C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann. Gastroenterol.,* **2015**, *28*(2), 203-209. [PMID: 25830558]

[47] Franceschi, C.; Capri, M.; Monti, D.; Giunta, S.; Olivieri, F.; Sevini, F.; Panourgia, M.P.; Invidia, L.; Celani, L.; Scurti, M.;

Cevenini, E.; Castellani, G.C.; Salvioli, S. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech. Ageing Dev.,* **2007**, *128*(1), 92-105. [http://dx.doi.org/10.1016/j.mad.2006.11.016] [PMID: 17116321]

[48] Leung, K.; Thuret, S. Gut microbiota: a modulator of brain plasticity and cognitive function in ageing. *Healthcare (Basel),* **2015**, *3*(4), 898-916. [http://dx.doi.org/10.3390/healthcare3040898] [PMID: 27417803]

[49] Brites, D.; Fernandes, A. Neuroinflammation and depression: microglia activation, extracellular microvesicles and microRNA dysregulation. *Front. Cell Neurosci.,* **2015**, *9*, 476. [http://dx.doi.org/10.3389/fncel.2015.00476] [PMID: 26733805]

[50] Ogbonnaya, E.S.; Clarke, G.; Shanahan, F.; Dinan, T.G.; Cryan, J.F.; O'Leary, O.F. Adult hippocampal neurogenesis is regulated by the microbiome. *Biol. Psychiatry,* **2015**, *78*(4), e7-e9. [http://dx.doi.org/10.1016/j.biopsych.2014.12.023] [PMID: 25700599]

[51] Zheng, P.; Zeng, B.; Zhou, C.; Liu, M.; Fang, Z.; Xu, X.; Zeng, L.; Chen, J.; Fan, S.; Du, X.; Zhang, X.; Yang, D.; Yang, Y.; Meng, H.; Li, W.; Melgiri, N.D.; Licinio, J.; Wei, H.; Xie, P. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. *Mol. Psychiatry,* **2016**, *21*(6), 786-796. [http://dx.doi.org/10.1038/mp.2016.44] [PMID: 27067014]

[52] Skarupski, K.A.; Tangney, C.C.; Li, H.; Evans, D.A.; Morris, M.C. Mediterranean diet and depressive symptoms among older adults over time. *J. Nutr. Health Aging,* **2013**, *17*(5), 441-445. [http://dx.doi.org/10.1007/s12603-012-0437-x] [PMID: 23636545]

[53] Gomez-Pinilla, F. The influences of diet and exercise on mental health through hormesis. *Ageing Res. Rev.,* **2008**, *7*(1), 49-62. [http://dx.doi.org/10.1016/j.arr.2007.04.003] [PMID: 17604236]

[54] Gomez-Pinilla, F. Collaborative effects of diet and exercise on cognitive enhancement. *Nutr. Health,* **2011**, *20*(3-4), 165-169. [http://dx.doi.org/10.1177/026010601102000401] [PMID: 22141190]

[55] Frazer, C.J.; Christensen, H.; Griffiths, K.M. Effectiveness of treatments for depression in older people. *Med. J. Aust.,* **2005**, *182*(12), 627-632. [PMID: 15963019]

[56] Vancampfort, D.; Correll, C.U.; Wampers, M.; Sienaert, P.; Mitchell, A.J.; De Herdt, A.; Probst, M.; Scheewe, T.W.; De Hert, M. Metabolic syndrome and metabolic abnormalities in patients with major depressive disorder: a meta-analysis of prevalences and moderating variables. *Psychol. Med.,* **2014**, *44*(10), 2017-2028. [http://dx.doi.org/10.1017/S0033291713002778] [PMID: 24262678]

[57] Meekums, B.; Karkou, V.; Nelson, E.A. Dance movement therapy for depression. *Cochrane Database Syst. Rev.,* **2015**, *19*(2), CD009895. [PMID: 25695871]

[58] Stubbs, B.; Stubbs, J.; Gnanaraj, S.D.; Soundy, A. Falls in older adults with major depressive disorder (MDD): a systematic review and exploratory meta-analysis of prospective studies. *Int. Psychogeriatr.,* **2016**, *28*(1), 23-29. [http://dx.doi.org/10.1017/S104161021500126X] [PMID: 26234532]

[59] Alamo, C.; López-Muñoz, F.; García-García, P.; García-Ramos, S. Risk-benefit analysis of antidepressant drug treatment in the elderly. *Psychogeriatrics,* **2014**, *14*(4), 261-268. [http://dx.doi.org/10.1111/psyg.12057] [PMID: 25495088]

[60] Mark, T.L.; Joish, V.N.; Hay, J.W.; Sheehan, D.V.; Johnston, S.S.; Cao, Z. Antidepressant use in geriatric populations: the burden of side effects and interactions and their impact on adherence and costs. *Am. J. Geriatr. Psychiatry,* **2011**, *19*(3), 211-221. [http://dx.doi.org/10.1097/JGP.0b013e3181f1803d] [PMID: 21425504]

[61] Lawlor, D.A.; Hopker, S.W. The effectiveness of exercise as an intervention in the management of depression: systematic review and meta-regression analysis of randomised controlled trials. *BMJ,* **2001**, *322*(7289), 763-767. [http://dx.doi.org/10.1136/bmj.322.7289.763] [PMID: 11282860]

[62] Sjösten, N.; Kivelä, S.L. The effects of physical exercise on depressive symptoms among the aged: a systematic review. *Int. J. Geriatr. Psychiatry,* **2006**, *21*(5), 410-418. [http://dx.doi.org/10.1002/gps.1494] [PMID: 16676285]

[63] Singh, N.A.; Stavrinos, T.M.; Scarbek, Y.; Galambos, G.; Liber, C.; Fiatarone Singh, M.A. A randomized controlled trial of high versus low intensity weight training versus general practitioner care for clinical depression in older adults. *J. Gerontol. A Biol. Sci. Med. Sci.,* **2005**, *60*(6), 768-776. [http://dx.doi.org/10.1093/gerona/60.6.768] [PMID: 15983181]

[64] Blake, H.; Mo, P.; Malik, S.; Thomas, S. How effective are physical activity interventions for alleviating depressive symptoms in older people? A systematic review. *Clin. Rehabil.,* **2009**, *23*(10), 873-887. [http://dx.doi.org/10.1177/0269215509337449] [PMID: 19675114]

[65] Rhyner, K.T.; Watts, A. Exercise and depressive symptoms in older adults: a systematic meta-analytic review. *J. Aging Phys. Act.,* **2016**, *24*(2), 234-246. [http://dx.doi.org/10.1123/japa.2015-0146] [PMID: 26372020]

[66] Bridle, C.; Spanjers, K.; Patel, S.; Atherton, N.M.; Lamb, S.E. Effect of exercise on depression severity in older people: systematic review and meta-analysis of randomised controlled trials. *Br. J. Psychiatry,* **2012**, *201*(3), 180-185. [http://dx.doi.org/10.1192/bjp.bp.111.095174] [PMID: 22945926]

[67] Underwood, M.; Lamb, S.E.; Eldridge, S.; Sheehan, B.; Slowther, A.M.; Spencer, A.; Thorogood, M.; Atherton, N.; Bremner, S.A.; Devine, A.; Diaz-Ordaz, K.; Ellard, D.R.; Potter, R.; Spanjers, K.; Taylor, S.J. Exercise for depression in elderly residents of care homes: a cluster-randomised controlled trial. *Lancet,* **2013**, *382*(9886), 41-49. [http://dx.doi.org/10.1016/S0140-6736(13)60649-2] [PMID: 23643112]

[68] Ciechanowski, P.; Wagner, E.; Schmaling, K.; Schwartz, S.; Williams, B.; Diehr, P.; Kulzer, J.; Gray, S.; Collier, C.; LoGerfo, J. Community-integrated home-based depression treatment in older adults: a randomized controlled trial. *JAMA,* **2004**, *291*(13), 1569-1577. [http://dx.doi.org/10.1001/jama.291.13.1569] [PMID: 15069044]

[69] Belvederi Murri, M.; Amore, M.; Menchetti, M.; Toni, G.; Neviani, F.; Cerri, M.; Rocchi, M.B.; Zocchi, D.; Bagnoli, L.; Tam, E.; Buffa, A.; Ferrara, S.; Neri, M.; Alexopoulos, G.S.; Zanetidou, S. Physical exercise for late-life major depression. *Br. J. Psychiatry,* **2015**, *207*(3), 235-242. [http://dx.doi.org/10.1192/bjp.bp.114.150516] [PMID: 26206864]

[70] Neviani, F.; Belvederi Murri, M.; Mussi, C.; Triolo, F.; Toni, G.; Simoncini, E.; Tripi, F.; Menchetti, M.; Ferrari, S.; Ceresini, G.; Cremonini, A.; Bertolotti, M.; Neri, G.; Squatrito, S.; Amore, M.; Zanetidou, S.; Neri, M. Physical exercise for late life depression: effects on cognition and disability. *Int. Psychogeriatr.,* **2017**, *29*(7), 1105-1112. [http://dx.doi.org/10.1017/S1041610217000576] [PMID: 28412979]

[71] Toni, G.; Belvederi Murri, M.; Piepoli, M.; Zanetidou, S.; Cabassi, A.; Squatrito, S.; Bagnoli, L.; Piras, A.; Mussi, C.; Senaldi, R.; Menchetti, M.; Zocchi, D.; Ermini, G.; Ceresini, G.; Tripi, F.; Rucci, P.; Alexopoulos, G.S.; Amore, M. Physical exercise for late-life depression: effects on heart rate variability. *Am. J. Geriatr. Psychiatry,* **2016**, *24*(11), 989-997. [http://dx.doi.org/10.1016/j.jagp.2016.08.005] [PMID: 27660194]

[72] Kendrick, T.; Peveler, R. Guidelines for the management of depression: NICE work? *Br. J. Psychiatry,* **2010**, *197*(5), 345-347. [http://dx.doi.org/10.1192/bjp.bp.109.074575] [PMID: 21037209]

[73] Catalan-Matamoros, D.; Gomez-Conesa, A.; Stubbs, B.; Vancampfort, D. Exercise improves depressive symptoms in older adults: An umbrella review of systematic reviews and meta-analyses. *Psychiatry Res.,* **2016**, *244*, 202-209. [http://dx.doi.org/10.1016/j.psychres.2016.07.028] [PMID: 27494042]

[74] Videbech, P.; Ravnkilde, B. Hippocampal volume and depression: a meta-analysis of MRI studies. *Am. J. Psychiatry,* **2004**, *161*(11), 1957-1966. [http://dx.doi.org/10.1176/appi.ajp.161.11.1957] [PMID: 15514393]

[75] Erickson, K.I.; Voss, M.W.; Prakash, R.S.; Basak, C.; Szabo, A.; Chaddock, L.; Kim, J.S.; Heo, S.; Alves, H.; White, S.M.; Wojcicki, T.R.; Mailey, E.; Vieira, V.J.; Martin, S.A.; Pence, B.D.; Woods, J.A.; McAuley, E.; Kramer, A.F. Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. USA,* **2011**, *108*(7), 3017-3022. [http://dx.doi.org/10.1073/pnas.1015950108] [PMID: 21282661]

[76] Parker, B.A.; Thompson, P.D.; Jordan, K.C.; Grimaldi, A.S.; Assaf, M.; Jagannathan, K.; Pearlson, G.D. Effect of exercise training on hippocampal volume in humans: a pilot study. *Res. Q. Exerc. Sport,* **2011**, *82*(3), 585-591. [http://dx.doi.org/10.1080/02701367.2011.10599793] [PMID: 21957719]

[77] Pereira, A.C.; Huddleston, D.E.; Brickman, A.M.; Sosunov, A.A.; Hen, R.; McKhann, G.M.; Sloan, R.; Gage, F.H.; Brown, T.R.; Small, S.A. An *in vivo* correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc. Natl. Acad. Sci. USA,* **2007**,

104(13), 5638-5643. [http://dx.doi.org/10.1073/pnas.0611721104] [PMID: 17374720]

[78] Pajonk, F.G.; Wobrock, T.; Gruber, O.; Scherk, H.; Berner, D.; Kaizl, I.; Kierer, A.; Müller, S.; Oest, M.; Meyer, T.; Backens, M.; Schneider-Axmann, T.; Thornton, A.E.; Honer, W.G.; Falkai, P. Hippocampal plasticity in response to exercise in schizophrenia. *Arch. Gen. Psychiatry,* **2010**, *67*(2), 133-143. [http://dx.doi.org/10.1001/archgenpsychiatry.2009.193] [PMID: 20124113]

[79] Krogh, J.; Rostrup, E.; Thomsen, C.; Elfving, B.; Videbech, P.; Nordentoft, M. The effect of exercise on hippocampal volume and neurotrophines in patients with major depression--a randomized clinical trial. *J. Affect. Disord.,* **2014**, *165*, 24-30. [http://dx.doi.org/10.1016/j.jad.2014.04.041] [PMID: 24882173]

[80] Deslandes, A.; Moraes, H.; Ferreira, C.; Veiga, H.; Silveira, H.; Mouta, R.; Pompeu, F.A.; Coutinho, E.S.; Laks, J. Exercise and mental health: many reasons to move. *Neuropsychobiology,* **2009**, *59*(4), 191-198. [http://dx.doi.org/10.1159/000223730] [PMID: 19521110]

[81] Dishman, R.K. The new emergence of exercise neurobiology. *Scand. J. Med. Sci. Sports,* **2006**, *16*(6), 379-380. [http://dx.doi.org/10.1111/j.1600-0838.2006.00609.x] [PMID: 17121638]

[82] Bailey, S.P.; Davis, J.M.; Ahlborn, E.N. Neuroendocrine and substrate responses to altered brain 5-HT activity during prolonged exercise to fatigue. *J. Appl. Physiol.,* **1993**, *74*(6), 3006-3012. [PMID: 8366000]

[83] Chaouloff, F.; Elghozi, J.L.; Guezennec, Y.; Laude, D. Effects of conditioned running on plasma, liver and brain tryptophan and on brain 5-hydroxytryptamine metabolism of the rat. *Br. J. Pharmacol.,* **1985**, *86*(1), 33-41. [http://dx.doi.org/10.1111/j.1476-5381.1985.tb09432.x] [PMID: 2413941]

[84] Weicker, H.; Strüder, H.K. Influence of exercise on serotonergic neuromodulation in the brain. *Amino Acids,* **2001**, *20*(1), 35-47. [http://dx.doi.org/10.1007/s007260170064] [PMID: 11310929]

[85] Melancon, M.O.; Lorrain, D.; Dionne, I.J. Exercise increases tryptophan availability to the brain in older men age 57-70 years. *Med. Sci. Sports Exerc.,* **2012**, *44*(5), 881-887. [http://dx.doi.org/10.1249/MSS.0b013e31823ede8e] [PMID: 22051569]

[86] Foley, T.E.; Fleshner, M. Neuroplasticity of dopamine circuits after exercise: implications for central fatigue. *Neuromolecular Med.,* **2008**, *10*(2), 67-80. [http://dx.doi.org/10.1007/s12017-008-8032-3] [PMID: 18274707]

[87] Dishman, R.K. Brain monoamines, exercise, and behavioral stress: animal models. *Med. Sci. Sports Exerc.,* **1997**, *29*(1), 63-74. [http://dx.doi.org/10.1097/00005768-199701000-00010] [PMID: 9000157]

[88] Wang, G.J.; Volkow, N.D.; Fowler, J.S.; Franceschi, D.; Logan, J.; Pappas, N.R.; Wong, C.T.; Netusil, N. PET studies of the effects of aerobic exercise on human striatal dopamine release. *J. Nucl. Med.,* **2000**, *41*(8), 1352-1356. [PMID: 10945526]

[89] Gómez-Pinilla, F.; Ying, Z.; Opazo, P.; Roy, R.R.; Edgerton, V.R. Differential regulation by exercise of BDNF and NT-3 in rat spinal cord and skeletal muscle. *Eur. J. Neurosci.,* **2001**, *13*(6), 1078-1084. [http://dx.doi.org/10.1046/j.0953-816x.2001.01484.x] [PMID: 11285004]

[90] Neeper, S.A.; Gómez-Pinilla, F.; Choi, J.; Cotman, C.W. Physical activity increases mRNA for brain-derived neurotrophic factor and nerve growth factor in rat brain. *Brain Res.,* **1996**, *726*(1-2), 49-56. [http://dx.doi.org/10.1016/0006-8993(96)00273-9] [PMID: 8836544]

[91] Russo-Neustadt, A.; Beard, R.C.; Cotman, C.W. Exercise, antidepressant medications, and enhanced brain derived neurotrophic factor expression. *Neuropsychopharmacology,* **1999**, *21*(5), 679-682. [http://dx.doi.org/10.1016/S0893-133X(99)00059-7] [PMID: 10516964]

[92] Griffin, E.W.; Mullally, S.; Foley, C.; Warmington, S.A.; O'Mara, S.M.; Kelly, A.M. Aerobic exercise improves hippocampal function and increases BDNF in the serum of young adult males. *Physiol. Behav.,* **2011**, *104*(5), 934-941. [http://dx.doi.org/10.1016/j.physbeh.2011.06.005] [PMID: 21722657]

[93] Laske, C.; Banschbach, S.; Stransky, E.; Bosch, S.; Straten, G.; Machann, J.; Fritsche, A.; Hipp, A.; Niess, A.; Eschweiler, G.W. Exercise-induced normalization of decreased BDNF serum concentration in elderly women with remitted major depression. *Int. J. Neuropsychopharmacol.,* **2010**, *13*(5), 595-602. [http://dx.doi.org/10.1017/S1461145709991234] [PMID: 20067661]

[94] Ströhle, A.; Stoy, M.; Graetz, B.; Scheel, M.; Wittmann, A.; Gallinat, J.; Lang, U.E.; Dimeo, F.; Hellweg, R. Acute exercise ameliorates reduced brain-derived neurotrophic factor in patients with panic disorder. *Psychoneuroendocrinology,* **2010**, *35*(3), 364-368. [http://dx.doi.org/10.1016/j.psyneuen.2009.07.013] [PMID: 19682803]

[95] Aberg, N.D.; Brywe, K.G.; Isgaard, J. Aspects of growth hormone and insulin-like growth factor-I related to neuroprotection, regeneration, and functional plasticity in the adult brain. *Sci. World J.,* **2006**, *6*, 53-80. [http://dx.doi.org/10.1100/tsw.2006.22] [PMID: 16432628]

[96] Gómez-Pinilla, F.; Dao, L.; So, V. Physical exercise induces FGF-2 and its mRNA in the hippocampus. *Brain Res.,* **1997**, *764*(1-2), 1-8. [http://dx.doi.org/10.1016/S0006-8993(97)00375-2] [PMID: 9295187]

[97] Pons, S.; Torres-Aleman, I. Basic fibroblast growth factor modulates insulin-like growth factor-I, its receptor, and its binding proteins in hypothalamic cell cultures. *Endocrinology,* **1992**, *131*(5), 2271-2278. [http://dx.doi.org/10.1210/endo.131.5.1385099] [PMID: 1385099]

[98] Aberg, M.A.; Aberg, N.D.; Palmer, T.D.; Alborn, A.M.; Carlsson-Skwirut, C.; Bang, P.; Rosengren, L.E.; Olsson, T.; Gage, F.H.; Eriksson, P.S. IGF-I has a direct proliferative effect in adult hippocampal progenitor cells. *Mol. Cell. Neurosci.,* **2003**, *24*(1), 23-40. [http://dx.doi.org/10.1016/S1044-7431(03)00082-4] [PMID: 14550766]

[99] Yau, S.Y.; Lau, B.W.; So, K.F. Adult hippocampal neurogenesis: a possible way how physical exercise counteracts stress. *Cell Transplant.,* **2011**, *20*(1), 99-111. [http://dx.doi.org/10.3727/096368910X532846] [PMID: 20887683]

[100] Eadie, B.D.; Redila, V.A.; Christie, B.R. Voluntary exercise alters the cytoarchitecture of the adult dentate gyrus by increasing cellular proliferation, dendritic complexity, and spine density. *J. Comp. Neurol.,* **2005**, *486*(1), 39-47. [http://dx.doi.org/10.1002/cne.20493] [PMID: 15834963]

[101] Bjørnebekk, A.; Mathé, A.A.; Brené, S. The antidepressant effect of running is associated with increased hippocampal cell proliferation. *Int. J. Neuropsychopharmacol.,* **2005**, *8*(3), 357-368. [http://dx.doi.org/10.1017/S1461145705005122] [PMID: 15769301]

[102] Trejo, J.L.; Llorens-Martín, M.V.; Torres-Alemán, I. The effects of exercise on spatial learning and anxiety-like behavior are mediated by an IGF-I-dependent mechanism related to hippocampal neurogenesis. *Mol. Cell. Neurosci.,* **2008**, *37*(2), 402-411. [http://dx.doi.org/10.1016/j.mcn.2007.10.016] [PMID: 18086533]

[103] Santarelli, L.; Saxe, M.; Gross, C.; Surget, A.; Battaglia, F.; Dulawa, S.; Weisstaub, N.; Lee, J.; Duman, R.; Arancio, O.; Belzung, C.; Hen, R. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science,* **2003**, *301*(5634), 805-809. [http://dx.doi.org/10.1126/science.1083328] [PMID: 12907793]

[104] Zhao, Y.; Shen, J.; Su, H.; Li, B.; Xing, D.; Du, L. Chronic corticosterone injections induce a decrease of ATP levels and sustained activation of AMP-activated protein kinase in hippocampal tissues of male mice. *Brain Res.,* **2008**, *1191*, 148-156. [http://dx.doi.org/10.1016/j.brainres.2007.11.027] [PMID: 18164281]

[105] Yau, S.Y.; Li, A.; Hoo, R.L.; Ching, Y.P.; Christie, B.R.; Lee, T.M.; Xu, A.; So, K.F. Physical exercise-induced hippocampal neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. *Proc. Natl. Acad. Sci. USA,* **2014**, *111*(44), 15810-15815. [http://dx.doi.org/10.1073/pnas.1415219111] [PMID: 25331877]

[106] Dantzer, R.; Kelley, K.W. Twenty years of research on cytokine-induced sickness behavior. *Brain Behav. Immun.,* **2007**, *21*(2), 153-160. [http://dx.doi.org/10.1016/j.bbi.2006.09.006] [PMID: 17088043]

[107] Dowlati, Y.; Herrmann, N.; Swardfager, W.; Liu, H.; Sham, L.; Reim, E.K.; Lanctôt, K.L. A meta-analysis of cytokines in major depression. *Biol. Psychiatry,* **2010**, *67*(5), 446-457. [http://dx.doi.org/10.1016/j.biopsych.2009.09.033] [PMID: 20015486]

[108] Shelton, R.C.; Falola, M.; Li, L.; Zajecka, J.; Fava, M.; Papakostas, G.I. The pro-inflammatory profile of depressed patients is (partly) related to obesity. *J. Psychiatr. Res.,* **2015**, *70*, 91-97. [http://dx.doi.org/10.1016/j.jpsychires.2015.09.001] [PMID: 26424427]

[109] Lindqvist, D.; Janelidze, S.; Hagell, P.; Erhardt, S.; Samuelsson, M.; Minthon, L.; Hansson, O.; Björkqvist, M.; Träskman-Bendz, L.; Brundin, L. Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. *Biol. Psychiatry,* **2009**, *66*(3), 287-292. [http://dx.doi.org/10.1016/

chiatry, **2009**, *66*(3), 287-292. [http://dx.doi.org/10.1016/j.biopsych.2009.01.030] [PMID: 19268915]

[110] Wei, Y.B.; Liu, J.J.; Villaescusa, J.C.; Åberg, E.; Brené, S.; Wegener, G.; Mathé, A.A.; Lavebratt, C. Elevation of Il6 is associated with disturbed let-7 biogenesis in a genetic model of depression. *Transl. Psychiatry,* **2016**, *6*, e869. [http://dx.doi.org/10.1038/tp.2016.136] [PMID: 27529677]

[111] Köhler, C.A.; Freitas, T.H.; Maes, M.; de Andrade, N.Q.; Liu, C.S.; Fernandes, B.S.; Stubbs, B.; Solmi, M.; Veronese, N.; Herrmann, N.; Raison, C.L.; Miller, B.J.; Lanctôt, K.L.; Carvalho, A.F. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatr. Scand.,* **2017**, *135*(5), 373-387. [http://dx.doi.org/10.1111/acps.12698] [PMID: 28122130]

[112] Schwarcz, R.; Bruno, J.P.; Muchowski, P.J.; Wu, H.Q. Kynurenines in the mammalian brain: when physiology meets pathology. *Nat. Rev. Neurosci.,* **2012**, *13*(7), 465-477. [http://dx.doi.org/10.1038/nrn3257] [PMID: 22678511]

[113] Agudelo, L.Z.; Femenía, T.; Orhan, F.; Porsmyr-Palmertz, M.; Goiny, M.; Martinez-Redondo, V.; Correia, J.C.; Izadi, M.; Bhat, M.; Schuppe-Koistinen, I.; Pettersson, A.T.; Ferreira, D.M.; Krook, A.; Barres, R.; Zierath, J.R.; Erhardt, S.; Lindskog, M.; Ruas, J.L. Skeletal muscle PGC-1α1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. *Cell,* **2014**, *159*(1), 33-45. [http://dx.doi.org/10.1016/j.cell.2014.07.051] [PMID: 25259918]

[114] Petersen, A.M.; Pedersen, B.K. The anti-inflammatory effect of exercise. *J. Appl. Physiol.,* **2005**, *98*(4), 1154-1162. [http://dx.doi.org/10.1152/japplphysiol.00164.2004] [PMID: 15772055]

[115] Walsh, N.P.; Gleeson, M.; Shephard, R.J.; Gleeson, M.; Woods, J.A.; Bishop, N.C.; Fleshner, M.; Green, C.; Pedersen, B.K.; Hoffman-Goetz, L.; Rogers, C.J.; Northoff, H.; Abbasi, A.; Simon, P. Position statement. Part one: Immune function and exercise. *Exerc. Immunol. Rev.,* **2011**, *17*, 6-63. [PMID: 21446352]

[116] Eyre, H.A.; Papps, E.; Baune, B.T. Treating depression and depression-like behavior with physical activity: an immune perspective. *Front. Psychiatry,* **2013**, *4*, 3. [http://dx.doi.org/10.3389/fpsyt.2013.00003] [PMID: 23382717]

[117] Rethorst, C.D.; Toups, M.S.; Greer, T.L.; Nakonezny, P.A.; Carmody, T.J.; Grannemann, B.D.; Huebinger, R.M.; Barber, R.C.; Trivedi, M.H. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. *Mol. Psychiatry,* **2013**, *18*(10), 1119-1124. [http://dx.doi.org/10.1038/mp.2012.125] [PMID: 22925832]

[118] Lavebratt, C.; Herring, M.P.; Liu, J.J.; Wei, Y.B.; Bossoli, D.; Hallgren, M.; Forsell, Y. Interleukin-6 and depressive symptom severity in response to physical exercise. *Psychiatry Res.,* **2017**, *252*, 270-276. [http://dx.doi.org/10.1016/j.psychres.2017.03.012] [PMID: 28285256]

[119] Schuch, F.B.; Deslandes, A.C.; Stubbs, B.; Gosmann, N.P.; Silva, C.T.; Fleck, M.P. Neurobiological effects of exercise on major depressive disorder: A systematic review. *Neurosci. Biobehav. Rev.,* **2016**, *61*, 1-11. [http://dx.doi.org/10.1016/j.neubiorev.2015.11.012] [PMID: 26657969]

[120] Jacka, F.N.; Berk, M. Depression, diet and exercise. *Med. J. Aust.,* **2013**, *199*(6)(Suppl.), S21-S23. [PMID: 25370279]

[121] Murphy, T.; Dias, G.P.; Thuret, S. Effects of diet on brain plasticity in animal and human studies: mind the gap. *Neural Plast.,* **2014**, *2014*, 563160. [http://dx.doi.org/10.1155/2014/563160] [PMID: 24900924]

[122] Haag, M. Essential fatty acids and the brain. *Can. J. Psychiatry,* **2003**, *48*(3), 195-203. [http://dx.doi.org/10.1177/070674370304800308] [PMID: 12728744]

[123] Ruxton, C.H.; Calder, P.C.; Reed, S.C.; Simpson, M.J. The impact of long-chain n-3 polyunsaturated fatty acids on human health. *Nutr. Res. Rev.,* **2005**, *18*(1), 113-129. [http://dx.doi.org/10.1079/NRR200497] [PMID: 19079899]

[124] Tur, J.A.; Bibiloni, M.M.; Sureda, A.; Pons, A. Dietary sources of omega 3 fatty acids: public health risks and benefits. *Br. J. Nutr.,* **2012**, *107*(Suppl. 2), S23-S52. [http://dx.doi.org/10.1017/S0007114512001456] [PMID: 22591897]

[125] Adarme-Vega, T.C.; Thomas-Hall, S.R.; Schenk, P.M. Towards sustainable sources for omega-3 fatty acids production. *Curr. Opin. Biotechnol.,* **2014**, *26*, 14-18. [http://dx.doi.org/10.1016/j.copbio.2013.08.003] [PMID: 24607804]

[126] Luchtman, D.W.; Song, C. Cognitive enhancement by omega-3 fatty acids from child-hood to old age: findings from animal and clinical studies. *Neuropharmacology,* **2013**, *64*, 550-565. [http://dx.doi.org/10.1016/j.neuropharm.2012.07.019] [PMID: 22841917]

[127] Salem, N., Jr; Litman, B.; Kim, H.Y.; Gawrisch, K. Mechanisms of action of docosahexaenoic acid in the nervous system. *Lipids,* **2001**, *36*(9), 945-959. [http://dx.doi.org/10.1007/s11745-001-0805-6] [PMID: 11724467]

[128] Spaccavento, S.; Del Prete, M.; Craca, A.; Fiore, P. Influence of nutritional status on cognitive, functional and neuropsychiatric deficits in Alzheimer's disease. *Arch. Gerontol. Geriatr.,* **2009**, *48*(3), 356-360. [http://dx.doi.org/10.1016/j.archger.2008.03.002] [PMID: 18448178]

[129] Serhan, C.N.; Chiang, N.; Van Dyke, T.E. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat. Rev. Immunol.,* **2008**, *8*(5), 349-361. [http://dx.doi.org/10.1038/nri2294] [PMID: 18437155]

[130] Aihara, Y.; Minai, J.; Aoyama, A.; Shimanouchi, S. Depressive symptoms and past lifestyle among Japanese elderly people. *Community Ment. Health J.,* **2011**, *47*(2), 186-193. [http://dx.doi.org/10.1007/s10597-010-9317-1] [PMID: 20455023]

[131] Jacka, F.N.; Kremer, P.J.; Leslie, E.R.; Berk, M.; Patton, G.C.; Toumbourou, J.W.; Williams, J.W. Associations between diet quality and depressed mood in adolescents: results from the Australian Healthy Neighbourhoods Study. *Aust. N. Z. J. Psychiatry,* **2010**, *44*(5), 435-442. [http://dx.doi.org/10.3109/00048670903571598] [PMID: 20397785]

[132] Jacka, F.N.; Pasco, J.A.; Mykletun, A.; Williams, L.J.; Hodge, A.M.; O'Reilly, S.L.; Nicholson, G.C.; Kotowicz, M.A.; Berk, M. Association of Western and traditional diets with depression and anxiety in women. *Am. J. Psychiatry,* **2010**, *167*(3), 305-311. [http://dx.doi.org/10.1176/appi.ajp.2009.09060881] [PMID: 20048020]

[133] Kant, A.K. Consumption of energy-dense, nutrient-poor foods by adult Americans: nutritional and health implications. The third National Health and Nutrition Examination Survey, 1988-1994. *Am. J. Clin. Nutr.,* **2000**, *72*(4), 929-936. [PMID: 11010933]

[134] Kessler, R.C.; Bromet, E.J. The epidemiology of depression across cultures. *Annu. Rev. Public Health,* **2013**, *34*, 119-138. [http://dx.doi.org/10.1146/annurev-publhealth-031912-114409] [PMID: 23514317]

[135] Mamplekou, E.; Bountziouka, V.; Psaltopoulou, T.; Zeimbekis, A.; Tsakoundakis, N.; Papaerakleous, N.; Gotsis, E.; Metallinos, G.; Pounis, G.; Polychronopoulos, E.; Lionis, C.; Panagiotakos, D. Urban environment, physical inactivity and unhealthy dietary habits correlate to depression among elderly living in eastern Mediterranean islands: the MEDIS (MEDiterranean ISlands Elderly) study. *J. Nutr. Health Aging,* **2010**, *14*(6), 449-455. [http://dx.doi.org/10.1007/s12603-010-0091-0] [PMID: 20617287]

[136] Nanri, A.; Kimura, Y.; Matsushita, Y.; Ohta, M.; Sato, M.; Mishima, N.; Sasaki, S.; Mizoue, T. Dietary patterns and depressive symptoms among Japanese men and women. *Eur. J. Clin. Nutr.,* **2010**, *64*(8), 832-839. [http://dx.doi.org/10.1038/ejcn.2010.86] [PMID: 20485303]

[137] Oddy, W.H.; Robinson, M.; Ambrosini, G.L.; O'Sullivan, T.A.; de Klerk, N.H.; Beilin, L.J.; Silburn, S.R.; Zubrick, S.R.; Stanley, F.J. The association between dietary patterns and mental health in early adolescence. *Prev. Med.,* **2009**, *49*(1), 39-44. [http://dx.doi.org/10.1016/j.ypmed.2009.05.009] [PMID: 19467256]

[138] Overby, N.; Høigaard, R. Diet and behavioral problems at school in Norwegian adolescents. *Food Nutr. Res.,* **2012**, *56*, 56. [http://dx.doi.org/10.3402/fnr.v56i0.17231] [PMID: 22761600]

[139] Samieri, C.; Jutand, M.A.; Féart, C.; Capuron, L.; Letenneur, L.; Barberger-Gateau, P. Dietary patterns derived by hybrid clustering method in older people: association with cognition, mood, and self-rated health. *J. Am. Diet. Assoc.,* **2008**, *108*(9), 1461-1471. [http://dx.doi.org/10.1016/j.jada.2008.06.437] [PMID: 18755318]

[140] Sobocki, P.; Jönsson, B.; Angst, J.; Rehnberg, C. Cost of depression in Europe. *J. Ment. Health Policy Econ.,* **2006**, *9*(2), 87-98. [PMID: 17007486]

[141] Stapelberg, N.J.; Neumann, D.L.; Shum, D.H.; McConnell, H.; Hamilton-Craig, I. A topographical map of the causal network of mechanisms underlying the relationship between major depressive disorder and coronary heart disease. *Aust. N. Z. J. Psychiatry,* **2011**, *45*(5), 351-369. [http://dx.doi.org/10.3109/00048674.2011.570427] [PMID: 21500954]

[142] Weng, T.T.; Hao, J.H.; Qian, Q.W.; Cao, H.; Fu, J.L.; Sun, Y.; Huang, L.; Tao, F.B. Is there any relationship between dietary patterns and depression and anxiety in Chinese adolescents? *Public Health Nutr.,* **2012**, *15*(4), 673-682. [http://dx.doi.org/10.1017/S1368980011003077] [PMID: 22115495]

[143] Woo, J. Nutritional strategies for successful aging. *Med. Clin. North Am.,* **2011**, *95*(3), 477-493, ix-x. [http://dx.doi.org/10.1016/j.mcna.2011.02.009] [PMID: 21549873]

[144] Yehuda, S. Polyunsaturated fatty acids as putative cognitive enhancers. *Med. Hypotheses,* **2012**, *79*(4), 456-461. [http://dx.doi.org/10.1016/j.mehy.2012.06.021] [PMID: 22800804]

[145] Akbaraly, T.N.; Brunner, E.J.; Ferrie, J.E.; Marmot, M.G.; Kivimaki, M.; Singh-Manoux, A. Dietary pattern and depressive symptoms in middle age. *Br. J. Psychiatry,* **2009**, *195*(5), 408-413. [http://dx.doi.org/10.1192/bjp.bp.108.058925] [PMID: 19880930]

[146] Chatzi, L.; Melaki, V.; Sarri, K.; Apostolaki, I.; Roumeliotaki, T.; Georgiou, V.; Vassilaki, M.; Koutis, A.; Bitsios, P.; Kogevinas, M. Dietary patterns during pregnancy and the risk of postpartum depression: the mother-child 'Rhea' cohort in Crete, Greece. *Public Health Nutr.,* **2011**, *14*(9), 1663-1670. [http://dx.doi.org/10.1017/S1368980010003629] [PMID: 21477412]

[147] Kuczmarski, M.F.; Cremer Sees, A.; Hotchkiss, L.; Cotugna, N.; Evans, M.K.; Zonderman, A.B. Higher healthy eating index-2005 scores associated with reduced symptoms of depression in an urban population: findings from the healthy aging in neighborhoods of diversity across the life span (HANDLS) study. *J. Am. Diet. Assoc.,* **2010**, *110*(3), 383-389. [http://dx.doi.org/10.1016/j.jada.2009.11.025] [PMID: 20184988]

[148] Park, J.Y.; You, J.S.; Chang, K.J. Dietary taurine intake, nutrients intake, dietary habits and life stress by depression in Korean female college students: a case-control study. *J. Biomed. Sci.,* **2010**, *17*(Suppl. 1), S40. [http://dx.doi.org/10.1186/1423-0127-17-S1-S40] [PMID: 20804617]

[149] Sánchez-Villegas, A.; Delgado-Rodríguez, M.; Alonso, A.; Schlatter, J.; Lahortiga, F.; Serra, M.L.; Martínez-González, M.A. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. *Arch. Gen. Psychiatry,* **2009**, *66*(10), 1090-1098. [http://dx.doi.org/10.1001/archgenpsychiatry.2009.129] [PMID: 19805699]

[150] Hernández-Galiot, A.; Goñi, I. Adherence to the Mediterranean diet pattern, cognitive status and depressive symptoms in an elderly non-institutionalized population. *Nutr. Hosp.,* **2017**, *34*(2), 338-344. [http://dx.doi.org/10.20960/nh.360] [PMID: 28421787]

[151] Hodge, A.; Almeida, O.P.; English, D.R.; Giles, G.G.; Flicker, L. Patterns of dietary intake and psychological distress in older Australians: benefits not just from a Mediterranean diet. *Int. Psychogeriatr.,* **2013**, *25*(3), 456-466. [http://dx.doi.org/10.1017/S1041610212001986] [PMID: 23199436]

[152] Rienks, J.; Dobson, A.J.; Mishra, G.D. Mediterranean dietary pattern and prevalence and incidence of depressive symptoms in mid-aged women: results from a large community-based prospective study. *Eur. J. Clin. Nutr.,* **2013**, *67*(1), 75-82. [http://dx.doi.org/10.1038/ejcn.2012.193] [PMID: 23212131]

[153] Sánchez-Villegas, A.; Henríquez-Sánchez, P.; Ruiz-Canela, M.; Lahortiga, F.; Molero, P.; Toledo, E.; Martínez-González, M.A. A longitudinal analysis of diet quality scores and the risk of incident depression in the SUN Project. *BMC Med.,* **2015**, *13*, 197. [http://dx.doi.org/10.1186/s12916-015-0428-y] [PMID: 26377327]

[154] Tyrovolas, S.; Haro, J.M.; Mariolis, A.; Piscopo, S.; Valacchi, G.; Tsakountakis, N.; Zeimbekis, A.; Tyrovola, D.; Bountziouka, V.; Gotsis, E.; Metallinos, G.; Tur, J.A.; Matalas, A.L.; Lionis, C.; Polychronopoulos, E.; Panagiotakos, D. Successful aging, dietary habits and health status of elderly individuals: a k-dimensional approach within the multi-national MEDIS study. *Exp. Gerontol.,* **2014**, *60*, 57-63. [http://dx.doi.org/10.1016/j.exger.2014.09.010] [PMID: 25240688]

[155] Araújo, J.R.; Martel, F.; Borges, N.; Araújo, J.M.; Keating, E. Folates and aging: Role in mild cognitive impairment, dementia and depression. *Ageing Res. Rev.,* **2015**, *22*, 9-19. [http://dx.doi.org/10.1016/j.arr.2015.04.005] [PMID: 25939915]

[156] Sánchez-Villegas, A.; Henríquez, P.; Bes-Rastrollo, M.; Doreste, J. Mediterranean diet and depression. *Public Health Nutr.,* **2006**, *9*(8A), 1104-1109. [http://dx.doi.org/10.1017/S1368980007668578] [PMID: 17378948]

[157] Deacon, G.; Kettle, C.; Hayes, D.; Dennis, C.; Tucci, J. Omega 3 polyunsaturated fatty acids and the treatment of depression. *Crit. Rev. Food Sci. Nutr.,* **2017**, *57*(1), 212-223. [PMID: 25830700]

[158] Giles, G.E.; Mahoney, C.R.; Kanarek, R.B. Omega-3 fatty acids influence mood in healthy and depressed individuals. *Nutr. Rev.,* **2013**, *71*(11), 727-741. [http://dx.doi.org/10.1111/nure.12066] [PMID: 24447198]

[159] Hibbeln, J.R. Seafood consumption, the DHA content of mothers' milk and prevalence rates of postpartum depression: a cross-national, ecological analysis. *J. Affect. Disord.,* **2002**, *69*(1-3), 15-29. [http://dx.doi.org/10.1016/S0165-0327(01)00374-3] [PMID: 12103448]

[160] Komori, T. The effects of phosphatidylserine and omega-3 fatty acid-containing supplement on late life depression. *Ment. Illn.,* **2015**, *7*(1), 5647. [http://dx.doi.org/10.4081/mi.2015.5647] [PMID: 26266022]

[161] Levant, B. N-3 (omega-3) polyunsaturated Fatty acids in the pathophysiology and treatment of depression: pre-clinical evidence. *CNS Neurol. Disord. Drug Targets,* **2013**, *12*(4), 450-459. [http://dx.doi.org/10.2174/18715273113120400003] [PMID: 23574159]

[162] Lin, P.Y.; Huang, S.Y.; Su, K.P. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol. Psychiatry,* **2010**, *68*(2), 140-147. [http://dx.doi.org/10.1016/j.biopsych.2010.03.018] [PMID: 20452573]

[163] Mischoulon, D. The impact of omega-3 fatty acids on depressive disorders and suicidality: can we reconcile 2 studies with seemingly contradictory results? *J. Clin. Psychiatry,* **2011**, *72*(12), 1574-1576. [http://dx.doi.org/10.4088/JCP.11com07463] [PMID: 22244020]

[164] Rondanelli, M.; Giacosa, A.; Opizzi, A.; Pelucchi, C.; La Vecchia, C.; Montorfano, G.; Negroni, M.; Berra, B.; Politi, P.; Rizzo, A.M. Long chain omega 3 polyunsaturated fatty acids supplementation in the treatment of elderly depression: effects on depressive symptoms, on phospholipids fatty acids profile and on health-related quality of life. *J. Nutr. Health Aging,* **2011**, *15*(1), 37-44. [http://dx.doi.org/10.1007/s12603-011-0011-y] [PMID: 21267525]

[165] Appleton, K.M.; Rogers, P.J.; Ness, A.R. Updated systematic review and meta-analysis of the effects of n-3 long-chain polyunsaturated fatty acids on depressed mood. *Am. J. Clin. Nutr.,* **2010**, *91*(3), 757-770. [http://dx.doi.org/10.3945/ajcn.2009.28313] [PMID: 20130098]

[166] Lin, P.Y.; Mischoulon, D.; Freeman, M.P.; Matsuoka, Y.; Hibbeln, J.; Belmaker, R.H.; Su, K.P. Are omega-3 fatty acids antidepressants or just mood-improving agents? The effect depends upon diagnosis, supplement preparation, and severity of depression. *Mol. Psychiatry,* **2012**, *17*(12), 1161-1163. [http://dx.doi.org/10.1038/mp.2012.111] [PMID: 22824812]

[167] Martins, J.G. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. *J. Am. Coll. Nutr.,* **2009**, *28*(5), 525-542. [http://dx.doi.org/10.1080/07315724.2009.10719785] [PMID: 20439549]

[168] Mocking, R.J.; Harmsen, I.; Assies, J.; Koeter, M.W.; Ruhé, H.G.; Schene, A.H. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Transl. Psychiatry,* **2016**, *6*, e756. [http://dx.doi.org/10.1038/tp.2016.29] [PMID: 26978738]

[169] Sublette, M.E.; Ellis, S.P.; Geant, A.L.; Mann, J.J. Meta-analysis of the effects of eicosapentaenoic acid (EPA) in clinical trials in depression. *J. Clin. Psychiatry,* **2011**, *72*(12), 1577-1584. [http://dx.doi.org/10.4088/JCP.10m06634] [PMID: 21939614]

[170] Grosso, G.; Pajak, A.; Marventano, S.; Castellano, S.; Galvano, F.; Bucolo, C.; Drago, F.; Caraci, F. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One,* **2014**, *9*(5), e96905. [http://dx.doi.org/10.1371/journal.pone.0096905] [PMID: 24805797]

[171] Li, F.; Liu, X.; Zhang, D. Fish consumption and risk of depression: a meta-analysis. *J. Epidemiol. Commun. Health,* **2016**, *70*(3), 299-304. [http://dx.doi.org/10.1136/jech-2015-206278] [PMID: 26359502]

[172] Appleton, K.M.; Sallis, H.M.; Perry, R.; Ness, A.R.; Churchill, R. Omega-3 fatty acids for depression in adults. *Cochrane Database Syst. Rev.,* **2015**, *11*(11), CD004692. [PMID: 26537796]

[173] Bloch, M.H.; Hannestad, J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. *Mol. Psychia-*

try, **2012**, *17*(12), 1272-1282. [http://dx.doi.org/10.1038/mp.2011.100] [PMID: 21931319]

[174] Sarris, J.; Mischoulon, D.; Schweitzer, I. Omega-3 for bipolar disorder: meta-analyses of use in mania and bipolar depression. *J. Clin. Psychiatry,* **2012**, *73*(1), 81-86. [http://dx.doi.org/10.4088/JCP.10r06710] [PMID: 21903025]

[175] Sinn, N.; Milte, C.; Howe, P.R. Oiling the brain: a review of randomized controlled trials of omega-3 fatty acids in psychopathology across the lifespan. *Nutrients,* **2010**, *2*(2), 128-170. [http://dx.doi.org/10.3390/nu2020128] [PMID: 22254013]

[176] Patel, K.; Abdool, P.S.; Rajji, T.K.; Mulsant, B.H. Pharmacotherapy of major depression in late life: what is the role of new agents? *Expert Opin. Pharmacother.,* **2017**, *18*(6), 599-609. [http://dx.doi.org/10.1080/14656566.2017.1308484] [PMID: 28317392]

[177] Snowden, M.B.; Steinman, L.E.; Bryant, L.L.; Cherrier, M.M.; Greenlund, K.J.; Leith, K.H.; Levy, C.; Logsdon, R.G.; Copeland, C.; Vogel, M.; Anderson, L.A.; Atkins, D.C.; Bell, J.F.; Fitzpatrick, A.L. Dementia and co-occurring chronic conditions: a systematic literature review to identify what is known and where are the gaps in the evidence? *Int. J. Geriatr. Psychiatry,* **2017**, *32*(4), 357-371. [http://dx.doi.org/10.1002/gps.4652] [PMID: 28146334]

[178] Erickson, K.I.; Miller, D.L.; Roecklein, K.A. The aging hippocampus: interactions between exercise, depression, and BDNF. *Neuroscientist,* **2012**, *18*(1), 82-97. [http://dx.doi.org/10.1177/1073858410397054] [PMID: 21531985]

[179] Julia, C.; Touvier, M.; Meunier, N.; Papet, I.; Galan, P.; Hercberg, S.; Kesse-Guyot, E. Intakes of PUFAs were inversely associated with plasma C-reactive protein 12 years later in a middle-aged population with vitamin E intake as an effect modifier. *J. Nutr.,* **2013**, *143*(11), 1760-1766. [http://dx.doi.org/10.3945/jn.113.180943] [PMID: 24027184]

[180] McNamara, R.K. DHA deficiency and prefrontal cortex neuropathology in recurrent affective disorders. *J. Nutr.,* **2010**, *140*(4), 864-868. [http://dx.doi.org/10.3945/jn.109.113233] [PMID: 20147466]

[181] Bos, D.J.; van Montfort, S.J.; Oranje, B.; Durston, S.; Smeets, P.A. Effects of omega-3 polyunsaturated fatty acids on human brain morphology and function: What is the evidence? *Eur. Neuropsychopharmacol.,* **2016**, *26*(3), 546-561. [http://dx.doi.org/10.1016/j.euroneuro.2015.12.031] [PMID: 26742901]

[182] McNamara, R.K.; Liu, Y.; Jandacek, R.; Rider, T.; Tso, P. The aging human orbitofrontal cortex: decreasing polyunsaturated fatty acid composition and associated increases in lipogenic gene expression and stearoyl-CoA desaturase activity. *Prostaglandins Leukot. Essent. Fatty Acids,* **2008**, *78*(4-5), 293-304. [http://dx.doi.org/10.1016/j.plefa.2008.04.001] [PMID: 18499418]

[183] Samieri, C.; Maillard, P.; Crivello, F.; Proust-Lima, C.; Peuchant, E.; Helmer, C.; Amieva, H.; Allard, M.; Dartigues, J.F.; Cunnane, S.C.; Mazoyer, B.M.; Barberger-Gateau, P. Plasma long-chain omega-3 fatty acids and atrophy of the medial temporal lobe. *Neurology,* **2012**, *79*(7), 642-650. [http://dx.doi.org/10.1212/WNL.0b013e318264e394] [PMID: 22855869]

[184] Cutuli, D.; De Bartolo, P.; Caporali, P.; Laricchiuta, D.; Foti, F.; Ronci, M.; Rossi, C.; Neri, C.; Spalletta, G.; Caltagirone, C.; Farioli-Vecchioli, S.; Petrosini, L. n-3 polyunsaturated fatty acids supplementation enhances hippocampal functionality in aged mice. *Front. Aging Neurosci.,* **2014**, *6*, 220. [http://dx.doi.org/10.3389/fnagi.2014.00220] [PMID: 25202271]

[185] Cutuli, D.; Pagani, M.; Caporali, P.; Galbusera, A.; Laricchiuta, D.; Foti, F.; Neri, C.; Spalletta, G.; Caltagirone, C.; Petrosini, L.; Gozzi, A. Effects of omega-3 fatty acid supplementation on cognitive functions and neural substrates: a voxel-based morphometry study in aged mice. *Front. Aging Neurosci.,* **2016**, *8*, 38. [http://dx.doi.org/10.3389/fnagi.2016.00038] [PMID: 26973513]

[186] Frangou, S.; Lewis, M.; Wollard, J.; Simmons, A. Preliminary *in vivo* evidence of increased N-acetyl-aspartate following eicosapentanoic acid treatment in patients with bipolar disorder. *J. Psychopharmacol. (Oxford),* **2007**, *21*(4), 435-439. [http://dx.doi.org/10.1177/0269881106067787] [PMID: 16891338]

[187] Lang, U.E.; Borgwardt, S. Molecular mechanisms of depression: perspectives on new treatment strategies. *Cell. Physiol. Biochem.,* **2013**, *31*(6), 761-777. [http://dx.doi.org/10.1159/000350094] [PMID: 23735822]

[188] Puri, B.K.; Counsell, S.J.; Hamilton, G.; Richardson, A.J.; Horrobin, D.F. Eicosapentaenoic acid in treatment-resistant depression associated with symptom remission, structural brain changes and reduced neuronal phospholipid turnover. *Int. J. Clin. Pract.,* **2001**, *55*(8), 560-563. [PMID: 11695079]

[189] Venna, V.R.; Deplanque, D.; Allet, C.; Belarbi, K.; Hamdane, M.; Bordet, R. PUFA induce antidepressant-like effects in parallel to structural and molecular changes in the hippocampus. *Psychoneuroendocrinology,* **2009**, *34*(2), 199-211. [http://dx.doi.org/10.1016/j.psyneuen.2008.08.025] [PMID: 18848400]

[190] Marriott, B.P.; Hibbeln, J.R.; Killeen, T.K.; Magruder, K.M.; Holes-Lewis, K.; Tolliver, B.K.; Turner, T.H. Design and methods for the better resiliency among veterans and non-veterans with omega-3's (BRAVO) study: A double blind, placebo-controlled trial of omega-3 fatty acid supplementation among adult individuals at risk of suicide. *Contemp. Clin. Trials,* **2016**, *47*, 325-333. [http://dx.doi.org/10.1016/j.cct.2016.02.002] [PMID: 26855120]

[191] Su, K.P. Biological mechanism of antidepressant effect of omega-3 fatty acids: how does fish oil act as a 'mind-body interface'? *Neurosignals,* **2009**, *17*(2), 144-152. [http://dx.doi.org/10.1159/000198167] [PMID: 19190401]

[192] Levant, B.; Ozias, M.K.; Davis, P.F.; Winter, M.; Russell, K.L.; Carlson, S.E.; Reed, G.A.; McCarson, K.E. Decreased brain docosahexaenoic acid content produces neurobiological effects associated with depression: Interactions with reproductive status in female rats. *Psychoneuroendocrinology,* **2008**, *33*(9), 1279-1292. [http://dx.doi.org/10.1016/j.psyneuen.2008.06.012] [PMID: 18707812]

[193] McNamara, R.K.; Hahn, C.G.; Jandacek, R.; Rider, T.; Tso, P.; Stanford, K.E.; Richtand, N.M. Selective deficits in the omega-3 fatty acid docosahexaenoic acid in the postmortem orbitofrontal cortex of patients with major depressive disorder. *Biol. Psychiatry,* **2007**, *62*(1), 17-24. [http://dx.doi.org/10.1016/j.biopsych.2006.08.026] [PMID: 17188654]

[194] McNamara, R.K.; Able, J.; Liu, Y.; Jandacek, R.; Rider, T.; Tso, P.; Lipton, J.W. Omega-3 fatty acid deficiency during perinatal development increases serotonin turnover in the prefrontal cortex and decreases midbrain tryptophan hydroxylase-2 expression in adult female rats: dissociation from estrogenic effects. *J. Psychiatr. Res.,* **2009**, *43*(6), 656-663. [http://dx.doi.org/10.1016/j.jpsychires.2008.09.011] [PMID: 18986658]

[195] McNamara, R.K.; Jandacek, R.; Rider, T.; Tso, P.; Cole-Strauss, A.; Lipton, J.W. Omega-3 fatty acid deficiency increases constitutive pro-inflammatory cytokine production in rats: relationship with central serotonin turnover. *Prostaglandins Leukot. Essent. Fatty Acids,* **2010**, *83*(4-6), 185-191. [http://dx.doi.org/10.1016/j.plefa.2010.08.004] [PMID: 20817496]

[196] Park, Y.; Moon, H.J.; Kim, S.H. N-3 polyunsaturated fatty acid consumption produces neurobiological effects associated with prevention of depression in rats after the forced swimming test. *J. Nutr. Biochem.,* **2012**, *23*(8), 924-928. [http://dx.doi.org/10.1016/j.jnutbio.2011.04.018] [PMID: 21852084]

[197] Vancassel, S.; Leman, S.; Hanonick, L.; Denis, S.; Roger, J.; Nollet, M.; Bodard, S.; Kousignian, I.; Belzung, C.; Chalon, S. n-3 polyunsaturated fatty acid supplementation reverses stress-induced modifications on brain monoamine levels in mice. *J. Lipid Res.,* **2008**, *49*(2), 340-348. [http://dx.doi.org/10.1194/jlr.M700328-JLR200] [PMID: 17991757]

[198] Vines, A.; Delattre, A.M.; Lima, M.M.; Rodrigues, L.S.; Suchecki, D.; Machado, R.B.; Tufik, S.; Pereira, S.I.; Zanata, S.M.; Ferraz, A.C. The role of 5-HT$_{1A}$ receptors in fish oil-mediated increased BDNF expression in the rat hippocampus and cortex: a possible antidepressant mechanism. *Neuropharmacology,* **2012**, *62*(1), 184-191. [http://dx.doi.org/10.1016/j.neuropharm.2011.06.017] [PMID: 21740919]

[199] Shapiro, G.D.; Fraser, W.D.; Séguin, J.R. Emerging risk factors for postpartum depression: serotonin transporter genotype and omega-3 fatty acid status. *Can. J. Psychiatry,* **2012**, *57*(11), 704-712. [http://dx.doi.org/10.1177/070674371205701108] [PMID: 23149286]

[200] Hibbeln, J.R.; Linnoila, M.; Umhau, J.C.; Rawlings, R.; George, D.T.; Salem, N., Jr. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. *Biol. Psychiatry,* **1998**, *44*(4), 235-242. [http://dx.doi.org/10.1016/S0006-3223(98)00141-3] [PMID: 9715354]

[201] Chalon, S.; Delion-Vancassel, S.; Belzung, C.; Guilloteau, D.; Leguisquet, A.M.; Besnard, J.C.; Durand, G. Dietary fish oil affects monoaminergic neurotransmission and behavior in rats. *J. Nutr.,* **1998**, *128*(12), 2512-2519. [PMID: 9868201]

[202] Chalon, S. Omega-3 fatty acids and monoamine neurotransmission. *Prostaglandins Leukot. Essent. Fatty Acids,* **2006**, *75*(4-5), 259-269. [http://dx.doi.org/10.1016/j.plefa.2006.07.005] [PMID: 16963244]

[203] Davis, P.F.; Ozias, M.K.; Carlson, S.E.; Reed, G.A.; Winter, M.K.; McCarson, K.E.; Levant, B. Dopamine receptor alterations in female rats with diet-induced decreased brain docosahexaenoic acid (DHA): interactions with reproductive status. *Nutr. Neurosci.,* **2010**, *13*(4), 161-169. [http://dx.doi.org/10.1179/147683010X12611460764282] [PMID: 20670471]

[204] Zimmer, L.; Vancassel, S.; Cantagrel, S.; Breton, P.; Delamanche, S.; Guilloteau, D.; Durand, G.; Chalon, S. The dopamine mesocorticolimbic pathway is affected by deficiency in n-3 polyunsaturated fatty acids. *Am. J. Clin. Nutr.,* **2002**, *75*(4), 662-667. [PMID: 11916751]

[205] Sublette, M.E.; Galfalvy, H.C.; Hibbeln, J.R.; Keilp, J.G.; Malone, K.M.; Oquendo, M.A.; Mann, J.J. Polyunsaturated fatty acid associations with dopaminergic indices in major depressive disorder. *Int. J. Neuropsychopharmacol.,* **2014**, *17*(3), 383-391. [http://dx.doi.org/10.1017/S1461145713001399] [PMID: 24300434]

[206] Arango, V.; Ernsberger, P.; Marzuk, P.M.; Chen, J.S.; Tierney, H.; Stanley, M.; Reis, D.J.; Mann, J.J. Autoradiographic demonstration of increased serotonin 5-HT2 and beta-adrenergic receptor binding sites in the brain of suicide victims. *Arch. Gen. Psychiatry,* **1990**, *47*(11), 1038-1047. [http://dx.doi.org/10.1001/archpsyc.1990.01810230054009] [PMID: 2173513]

[207] Biegon, A.; Israeli, M. Regionally selective increases in beta-adrenergic receptor density in the brains of suicide victims. *Brain Res.,* **1988**, *442*(1), 199-203. [http://dx.doi.org/10.1016/0006-8993(88)91453-9] [PMID: 2834015]

[208] Rivero, G.; Gabilondo, A.M.; García-Sevilla, J.A.; La Harpe, R.; Callado, L.F.; Meana, J.J. Increased α2- and β1-adrenoceptor densities in postmortem brain of subjects with depression: differential effect of antidepressant treatment. *J. Affect. Disord.,* **2014**, *167*, 343-350. [http://dx.doi.org/10.1016/j.jad.2014.06.016] [PMID: 25020269]

[209] Stemmelin, J.; Cohen, C.; Terranova, J.P.; Lopez-Grancha, M.; Pichat, P.; Bergis, O.; Decobert, M.; Santucci, V.; Françon, D.; Alonso, R.; Stahl, S.M.; Keane, P.; Avenet, P.; Scatton, B.; le Fur, G.; Griebel, G. Stimulation of the beta3-Adrenoceptor as a novel treatment strategy for anxiety and depressive disorders. *Neuropsychopharmacology,* **2008**, *33*(3), 574-587. [http://dx.doi.org/10.1038/sj.npp.1301424] [PMID: 17460614]

[210] Takeuchi, T.; Fukumoto, Y.; Harada, E. Influence of a dietary n-3 fatty acid deficiency on the cerebral catecholamine contents, EEG and learning ability in rat. *Behav. Brain Res.,* **2002**, *131*(1-2), 193-203. [http://dx.doi.org/10.1016/S0166-4328(01)00392-8] [PMID: 11844586]

[211] Hamazaki, K.; Itomura, M.; Huan, M.; Nishizawa, H.; Sawazaki, S.; Tanouchi, M.; Watanabe, S.; Hamazaki, T.; Terasawa, K.; Yazawa, K. Effect of omega-3 fatty acid-containing phospholipids on blood catecholamine concentrations in healthy volunteers: a randomized, placebo-controlled, double-blind trial. *Nutrition,* **2005**, *21*(6), 705-710. [http://dx.doi.org/10.1016/j.nut.2004.07.020] [PMID: 15925295]

[212] Jiang, H.; Chen, S.; Li, C.; Lu, N.; Yue, Y.; Yin, Y.; Zhang, Y.; Zhi, X.; Zhang, D.; Yuan, Y. The serum protein levels of the tPA-BDNF pathway are implicated in depression and antidepressant treatment. *Transl. Psychiatry,* **2017**, *7*(4), e1079. [http://dx.doi.org/10.1038/tp.2017.43] [PMID: 28375203]

[213] Bhatia, H.S.; Agrawal, R.; Sharma, S.; Huo, Y.X.; Ying, Z.; Gomez-Pinilla, F. Omega-3 fatty acid deficiency during brain maturation reduces neuronal and behavioral plasticity in adulthood. *PLoS One,* **2011**, *6*(12), e28451. [http://dx.doi.org/10.1371/journal.pone.0028451] [PMID: 22163304]

[214] DeMar, J.C., Jr; Ma, K.; Bell, J.M.; Igarashi, M.; Greenstein, D.; Rapoport, S.I. One generation of n-3 polyunsaturated fatty acid deprivation increases depression and aggression test scores in rats. *J. Lipid Res.,* **2006**, *47*(1), 172-180. [http://dx.doi.org/10.1194/jlr.M500362-JLR200] [PMID: 16210728]

[215] Rao, J.S.; Ertley, R.N.; Lee, H.J.; DeMar, J.C., Jr; Arnold, J.T.; Rapoport, S.I.; Bazinet, R.P. n-3 polyunsaturated fatty acid deprivation in rats decreases frontal cortex BDNF *via* a p38 MAPK-dependent mechanism. *Mol. Psychiatry,* **2007**, *12*(1), 36-46. [http://dx.doi.org/10.1038/sj.mp.4001888] [PMID: 16983391]

[216] Adachi, M.; Barrot, M.; Autry, A.E.; Theobald, D.; Monteggia, L.M. Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. *Biol. Psychiatry,* **2008**, *63*(7), 642-649. [http://dx.doi.org/10.1016/j.biopsych.2007.09.019] [PMID: 17981266]

[217] Blondeau, N.; Nguemeni, C.; Debruyne, D.N.; Piens, M.; Wu, X.; Pan, H.; Hu, X.; Gandin, C.; Lipsky, R.H.; Plumier, J.C.; Marini, A.M.; Heurteaux, C. Subchronic alpha-linolenic acid treatment enhances brain plasticity and exerts an antidepressant effect: a versatile potential therapy for stroke. *Neuropsychopharmacology,* **2009**, *34*(12), 2548-2559. [http://dx.doi.org/10.1038/npp.2009.84] [PMID: 19641487]

[218] Cysneiros, R.M.; Ferrari, D.; Arida, R.M.; Terra, V.C.; de Almeida, A.C.; Cavalheiro, E.A.; Scorza, F.A. Qualitative analysis of hippocampal plastic changes in rats with epilepsy supplemented with oral omega-3 fatty acids. *Epilepsy Behav.,* **2010**, *17*(1), 33-38. [http://dx.doi.org/10.1016/j.yebeh.2009.11.006] [PMID: 19969506]

[219] Wu, A.; Ying, Z.; Gomez-Pinilla, F. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. *J. Neurotrauma,* **2004**, *21*(10), 1457-1467. [http://dx.doi.org/10.1089/neu.2004.21.1457] [PMID: 15672635]

[220] Denis, I.; Potier, B.; Vancassel, S.; Heberden, C.; Lavialle, M. Omega-3 fatty acids and brain resistance to ageing and stress: body of evidence and possible mechanisms. *Ageing Res. Rev.,* **2013**, *12*(2), 579-594. [http://dx.doi.org/10.1016/j.arr.2013.01.007] [PMID: 23395782]

[221] Fedorova, I.; Salem, N., Jr. Omega-3 fatty acids and rodent behavior. *Prostaglandins Leukot. Essent. Fatty Acids,* **2006**, *75*(4-5), 271-289. [http://dx.doi.org/10.1016/j.plefa.2006.07.006] [PMID: 16973342]

[222] Hooijmans, C.R.; Pasker-de Jong, P.C.; de Vries, R.B.; Ritskes-Hoitinga, M. The effects of long-term omega-3 fatty acid supplementation on cognition and Alzheimer's pathology in animal models of Alzheimer's disease: a systematic review and meta-analysis. *J. Alzheimers Dis.,* **2012**, *28*(1), 191-209. [PMID: 22002791]

[223] Maruszak, A.; Pilarski, A.; Murphy, T.; Branch, N.; Thuret, S. Hippocampal neurogenesis in Alzheimer's disease: is there a role for dietary modulation? *J. Alzheimers Dis.,* **2014**, *38*(1), 11-38. [PMID: 23948932]

[224] He, C.; Qu, X.; Cui, L.; Wang, J.; Kang, J.X. Improved spatial learning performance of fat-1 mice is associated with enhanced neurogenesis and neuritogenesis by docosahexaenoic acid. *Proc. Natl. Acad. Sci. USA,* **2009**, *106*(27), 11370-11375. [http://dx.doi.org/10.1073/pnas.0904835106] [PMID: 19549874]

[225] Dyall, S.C.; Michael, G.J.; Michael-Titus, A.T. Omega-3 fatty acids reverse age-related decreases in nuclear receptors and increase neurogenesis in old rats. *J. Neurosci. Res.,* **2010**, *88*(10), 2091-2102. [http://dx.doi.org/10.1002/jnr.22390] [PMID: 20336774]

[226] Robson, L.G.; Dyall, S.; Sidloff, D.; Michael-Titus, A.T. Omega-3 polyunsaturated fatty acids increase the neurite outgrowth of rat sensory neurones throughout development and in aged animals. *Neurobiol. Aging,* **2010**, *31*(4), 678-687. [http://dx.doi.org/10.1016/j.neurobiolaging.2008.05.027] [PMID: 18620782]

[227] Dyall, S.C.; Mandhair, H.K.; Fincham, R.E.; Kerr, D.M.; Roche, M.; Molina-Holgado, F. Distinctive effects of eicosapentaenoic and docosahexaenoic acids in regulating neural stem cell fate are mediated *via* endocannabinoid signalling pathways. *Neuropharmacology,* **2016**, *107*, 387-395. [http://dx.doi.org/10.1016/j.neuropharm.2016.03.055] [PMID: 27044662]

[228] Farooqui, A.A.; Ong, W.Y.; Horrocks, L.A. Inhibitors of brain phospholipase A2 activity: their neuropharmacological effects and therapeutic importance for the treatment of neurologic disorders. *Pharmacol. Rev.,* **2006**, *58*(3), 591-620. [http://dx.doi.org/10.1124/pr.58.3.7] [PMID: 16968951]

[229] Dyall, S.C. Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA. *Front. Aging Neurosci.,* **2015**, *7*, 52. [http://dx.doi.org/10.3389/fnagi.2015.00052] [PMID: 25954194]

[230] Song, C.; Shieh, C.H.; Wu, Y.S.; Kalueff, A.; Gaikwad, S.; Su, K.P. The role of omega-3 polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids in the treatment of major depression and Alzheimer's disease: Acting separately or synergistically? *Prog. Lipid Res.,* **2016**, *62*, 41-54. [http://dx.doi.org/10.1016/j.plipres.2015.12.003] [PMID: 26763196]

[231] Bigornia, S.J.; Harris, W.S.; Falcón, L.M.; Ordovás, J.M.; Lai, C.Q.; Tucker, K.L. The omega-3 index is inversely associated with depressive symptoms among individuals with elevated oxidative stress biomarkers. *J. Nutr.,* **2016**, *146*(4), 758-766. [http://dx.doi.org/10.3945/jn.115.222562] [PMID: 26936135]

[232] McNamara, R.K.; Vannest, J.J.; Valentine, C.J. Role of perinatal long-chain omega-3 fatty acids in cortical circuit maturation: Mechanisms and implications for psychopathology. *World J. Psychiatry,* **2015**, *5*(1), 15-34. [http://dx.doi.org/10.5498/wjp.v5.i1.15] [PMID: 25815252]

[233] Su, K.P.; Lai, H.C.; Yang, H.T.; Su, W.P.; Peng, C.Y.; Chang, J.P.; Chang, H.C.; Pariante, C.M. Omega-3 fatty acids in the prevention of interferon-alpha-induced depression: results from a randomized, controlled trial. *Biol. Psychiatry,* **2014**, *76*(7), 559-566. [http://dx.doi.org/10.1016/j.biopsych.2014.01.008] [PMID: 24602409]

[234] Carlezon, W.A., Jr; Mague, S.D.; Parow, A.M.; Stoll, A.L.; Cohen, B.M.; Renshaw, P.F. Antidepressant-like effects of uridine and omega-3 fatty acids are potentiated by combined treatment in rats. *Biol. Psychiatry,* **2005**, *57*(4), 343-350. [http://dx.doi.org/10.1016/j.biopsych.2004.11.038] [PMID: 15705349]

[235] Pittet, Y.K.; Berger, M.M.; Pluess, T.T.; Voirol, P.; Revelly, J.P.; Tappy, L.; Chioléro, R.L. Blunting the response to endotoxin in healthy subjects: effects of various doses of intravenous fish oil. *Intensive Care Med.,* **2010**, *36*(2), 289-295. [http://dx.doi.org/10.1007/s00134-009-1689-8] [PMID: 19844694]

[236] Pluess, T.T.; Hayoz, D.; Berger, M.M.; Tappy, L.; Revelly, J.P.; Michaeli, B.; Carpentier, Y.A.; Chioléro, R.L. Intravenous fish oil blunts the physiological response to endotoxin in healthy subjects. *Intens. Care Med.,* **2007**, *33*(5), 789-797. [http://dx.doi.org/10.1007/s00134-007-0591-5] [PMID: 17377770]

[237] Song, C.; Li, X.; Leonard, B.E.; Horrobin, D.F. Effects of dietary n-3 or n-6 fatty acids on interleukin-1beta-induced anxiety, stress, and inflammatory responses in rats. *J. Lipid Res.,* **2003**, *44*(10), 1984-1991. [http://dx.doi.org/10.1194/jlr.M300217-JLR200] [PMID: 12837849]

[238] Wu, Y.Q.; Dang, R.L.; Tang, M.M.; Cai, H.L.; Li, H.D.; Liao, D.H.; He, X.; Cao, L.J.; Xue, Y.; Jiang, P. Long chain omega-3 polyunsaturated fatty acid supplementation alleviates doxorubicin-induced depressive-like behaviors and neurotoxicity in rats: involvement of oxidative stress and neuroinflammation. *Nutrients,* **2016**, *8*(4), 243. [http://dx.doi.org/10.3390/nu8040243] [PMID: 27120616]

[239] Lynch, A.M.; Loane, D.J.; Minogue, A.M.; Clarke, R.M.; Kilroy, D.; Nally, R.E.; Roche, O.J.; O'Connell, F.; Lynch, M.A. Eicosapentaenoic acid confers neuroprotection in the amyloid-beta challenged aged hippocampus. *Neurobiol. Aging,* **2007**, *28*(6), 845-855. [http://dx.doi.org/10.1016/j.neurobiolaging.2006.04.006] [PMID: 16714069]

[240] Maher, F.O.; Martin, D.S.; Lynch, M.A. Increased IL-1beta in cortex of aged rats is accompanied by downregulation of ERK and PI-3 kinase. *Neurobiol. Aging,* **2004**, *25*(6), 795-806. [http://dx.doi.org/10.1016/j.neurobiolaging.2003.08.007] [PMID: 15165704]

[241] Martin, D.S.; Spencer, P.; Horrobin, D.F.; Lynch, M.A. Long-term potentiation in aged rats is restored when the age-related decrease in polyunsaturated fatty acid concentration is reversed. *Prostaglandins Leukot. Essent. Fatty Acids,* **2002**, *67*(2-3), 121-130. [http://dx.doi.org/10.1054/plef.2002.0408] [PMID: 12324230]

[242] Minogue, A.M.; Lynch, A.M.; Loane, D.J.; Herron, C.E.; Lynch, M.A. Modulation of amyloid-beta-induced and age-associated changes in rat hippocampus by eicosapentaenoic acid. *J. Neurochem.,* **2007**, *103*(3), 914-926. [http://dx.doi.org/10.1111/j.1471-4159.2007.04848.x] [PMID: 17711425]

[243] Kelly, L.; Grehan, B.; Chiesa, A.D.; O'Mara, S.M.; Downer, E.; Sahyoun, G.; Massey, K.A.; Nicolaou, A.; Lynch, M.A. The polyunsaturated fatty acids, EPA and DPA exert a protective effect in the hippocampus of the aged rat. *Neurobiol. Aging,* **2011**, *32*(12), 2318.e1-2318.e15. [http://dx.doi.org/10.1016/j.neurobiolaging.2010.04.001] [PMID: 20570403]

[244] Serini, S.; Bizzarro, A.; Piccioni, E.; Fasano, E.; Rossi, C.; Lauria, A.; Cittadini, A.R.; Masullo, C.; Calviello, G. EPA and DHA differentially affect *in vitro* inflammatory cytokine release by peripheral blood mononuclear cells from Alzheimer's patients. *Curr. Alzheimer Res.,* **2012**, *9*(8), 913-923. [http://dx.doi.org/10.2174/156720512803251147] [PMID: 22299617]

[245] Farzaneh-Far, R.; Harris, W.S.; Garg, S.; Na, B.; Whooley, M.A. Inverse association of erythrocyte n-3 fatty acid levels with inflammatory biomarkers in patients with stable coronary artery disease: The Heart and Soul Study. *Atherosclerosis,* **2009**, *205*(2), 538-543. [http://dx.doi.org/10.1016/j.atherosclerosis.2008.12.013] [PMID: 19185299]

[246] Ferrucci, L.; Cherubini, A.; Bandinelli, S.; Bartali, B.; Corsi, A.; Lauretani, F.; Martin, A.; Andres-Lacueva, C.; Senin, U.; Guralnik, J.M. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J. Clin. Endocrinol. Metab.,* **2006**, *91*(2), 439-446. [http://dx.doi.org/10.1210/jc.2005-1303] [PMID: 16234304]

[247] Kalogeropoulos, N.; Panagiotakos, D.B.; Pitsavos, C.; Chrysohoou, C.; Rousinou, G.; Toutouza, M.; Stefanadis, C. Unsaturated fatty acids are inversely associated and n-6/n-3 ratios are positively related to inflammation and coagulation markers in plasma of apparently healthy adults. *Clin. Chim. Acta,* **2010**, *411*(7-8), 584-591. [http://dx.doi.org/10.1016/j.cca.2010.01.023] [PMID: 20097190]

[248] Ticinesi, A.; Meschi, T.; Lauretani, F.; Felis, G.; Franchi, F.; Pedrolli, C.; Barichella, M.; Benati, G.; Di Nuzzo, S.; Ceda, G.P.; Maggio, M. Nutrition and inflammation in older individuals: focus on vitamin d, n-3 polyunsaturated fatty acids and whey proteins. *Nutrients,* **2016**, *8*(4), 186. [http://dx.doi.org/10.3390/nu8040186] [PMID: 27043616]

[249] Farzaneh-Far, R.; Lin, J.; Epel, E.S.; Harris, W.S.; Blackburn, E.H.; Whooley, M.A. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA,* **2010**, *303*(3), 250-257. [http://dx.doi.org/10.1001/jama.2009.2008] [PMID: 20085953]

[250] Kiecolt-Glaser, J.K.; Epel, E.S.; Belury, M.A.; Andridge, R.; Lin, J.; Glaser, R.; Malarkey, W.B.; Hwang, B.S.; Blackburn, E. Omega-3 fatty acids, oxidative stress, and leukocyte telomere length: A randomized controlled trial. *Brain Behav. Immun.,* **2013**, *28*, 16-24. [http://dx.doi.org/10.1016/j.bbi.2012.09.004] [PMID: 23010452]

[251] O'Callaghan, N.; Parletta, N.; Milte, C.M.; Benassi-Evans, B.; Fenech, M.; Howe, P.R. Telomere shortening in elderly individuals with mild cognitive impairment may be attenuated with ω-3 fatty acid supplementation: a randomized controlled pilot study. *Nutrition,* **2014**, *30*(4), 489-491. [http://dx.doi.org/10.1016/j.nut.2013.09.013] [PMID: 24342530]

[252] Kiecolt-Glaser, J.K.; Belury, M.A.; Andridge, R.; Malarkey, W.B.; Hwang, B.S.; Glaser, R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: a randomized controlled trial. *Brain Behav. Immun.,* **2012**, *26*(6), 988-995. [http://dx.doi.org/10.1016/j.bbi.2012.05.011] [PMID: 22640930]

[253] Kiecolt-Glaser, J.K.; Belury, M.A.; Porter, K.; Beversdorf, D.Q.; Lemeshow, S.; Glaser, R. Depressive symptoms, omega-6:omega-3 fatty acids, and inflammation in older adults. *Psychosom. Med.,* **2007**, *69*(3), 217-224. [http://dx.doi.org/10.1097/PSY.0b013e3180313a45] [PMID: 17401057]

[254] Bannenberg, G.L. Resolvins: Current understanding and future potential in the control of inflammation. *Curr. Opin. Drug Discov. Devel.,* **2009**, *12*(5), 644-658. [PMID: 19736623]

[255] Farooqui, A.A.; Horrocks, L.A.; Farooqui, T. Modulation of inflammation in brain: a matter of fat. *J. Neurochem.,* **2007**, *101*(3), 577-599. [http://dx.doi.org/10.1111/j.1471-4159.2006.04371.x] [PMID: 17257165]

[256] Serhan, C.N. Novel eicosanoid and docosanoid mediators: resolvins, docosatrienes, and neuroprotectins. *Curr. Opin. Clin. Nutr. Metab. Care,* **2005**, *8*(2), 115-121. [http://dx.doi.org/10.1097/00075197-200503000-00003] [PMID: 15716788]

[257] Gilbert, K.; Bernier, J.; Godbout, R.; Rousseau, G. Resolvin D1, a metabolite of omega-3 polyunsaturated fatty acid, decreases post-myocardial infarct depression. *Mar. Drugs,* **2014**, *12*(11), 5396-5407. [http://dx.doi.org/10.3390/md12115396] [PMID: 25402828]

[258] Deyama, S.; Ishikawa, Y.; Yoshikawa, K.; Shimoda, K.; Ide, S.; Satoh, M.; Minami, M. Resolvin D1 and D2 reverse lipopolysaccharide-induced depression-like behaviors through the mTORC1 signaling pathway. *Int. J. Neuropsychopharmacol.,* **2017**, *20*(7), 575-584. [http://dx.doi.org/10.1093/ijnp/pyx023] [PMID: 28419244]

[259] Bazan, N.G.; Molina, M.F.; Gordon, W.C. Docosahexaenoic acid signalolipidomics in nutrition: significance in aging, neuroinflammation, macular degeneration, Alzheimer's, and other neurodegen-

erative diseases. *Annu. Rev. Nutr.,* **2011**, *31*, 321-351. [http://dx.doi.org/10.1146/annurev.nutr.012809.104635] [PMID: 21756134]

[260] Cerdá, B.; Pérez, M.; Pérez-Santiago, J.D.; Tornero-Aguilera, J.F.; González-Soltero, R.; Larrosa, M. Gut microbiota modification: another piece in the puzzle of the benefits of physical exercise in health? *Front. Physiol.,* **2016**, *7*, 51. [http://dx.doi.org/10.3389/fphys.2016.00051] [PMID: 26924990]

[261] Choi, J.J.; Eum, S.Y.; Rampersaud, E.; Daunert, S.; Abreu, M.T.; Toborek, M. Exercise attenuates PCB-induced changes in the mouse gut microbiome. *Environ. Health Perspect.,* **2013**, *121*(6), 725-730. [http://dx.doi.org/10.1289/ehp.1306534] [PMID: 23632211]

[262] Logan, A.C.; Venket, R.A.; Irani, D. Chronic fatigue syndrome: lactic acid bacteria may be of therapeutic value. *Med. Hypotheses,* **2003**, *60*(6), 915-923. [http://dx.doi.org/10.1016/S0306-9877(03)00096-3] [PMID: 12699726]

[263] Petriz, B.A.; Castro, A.P.; Almeida, J.A.; Gomes, C.P.; Fernandes, G.R.; Kruger, R.H.; Pereira, R.W.; Franco, O.L. Exercise induction of gut microbiota modifications in obese, non-obese and hypertensive rats. *BMC Genomics,* **2014**, *15*, 511. [http://dx.doi.org/10.1186/1471-2164-15-511] [PMID: 24952588]

[264] Clarke, S.F.; Murphy, E.F.; O'Sullivan, O.; Lucey, A.J.; Humphreys, M.; Hogan, A.; Hayes, P.; O'Reilly, M.; Jeffery, I.B.; Wood-Martin, R.; Kerins, D.M.; Quigley, E.; Ross, R.P.; O'Toole, P.W.; Molloy, M.G.; Falvey, E.; Shanahan, F.; Cotter, P.D. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut,* **2014**, *63*(12), 1913-1920. [http://dx.doi.org/10.1136/gutjnl-2013-306541] [PMID: 25021423]

[265] Vitetta, L.; Bambling, M.; Alford, H. The gastrointestinal tract microbiome, probiotics, and mood. *Inflammopharmacology,* **2014**, *22*(6), 333-339. [http://dx.doi.org/10.1007/s10787-014-0216-x] [PMID: 25266952]

[266] Davis, D.J.; Hecht, P.M.; Jasarevic, E.; Beversdorf, D.Q.; Will, M.J.; Fritsche, K.; Gillespie, C.H. Sex-specific effects of docosahexaenoic acid (DHA) on the microbiome and behavior of socially-isolated mice. *Brain Behav. Immun.,* **2017**, *59*, 38-48. [http://dx.doi.org/10.1016/j.bbi.2016.09.003] [PMID: 27621225]

[267] Pusceddu, M.M.; El Aidy, S.; Crispie, F.; O'Sullivan, O.; Cotter, P.; Stanton, C.; Kelly, P.; Cryan, J.F.; Dinan, T.G. N-3 polyunsaturated fatty acids (PUFAs) reverse the impact of early-life stress on the gut microbiota. *PLoS One,* **2015**, *10*(10), e0139721. [http://dx.doi.org/10.1371/journal.pone.0139721] [PMID: 26426902]

[268] Robertson, R.C.; Seira Oriach, C.; Murphy, K.; Moloney, G.M.; Cryan, J.F.; Dinan, T.G.; Paul Ross, R.; Stanton, C. Omega-3 polyunsaturated fatty acids critically regulate behaviour and gut microbiota development in adolescence and adulthood. *Brain Behav. Immun.,* **2017**, *59*, 21-37. [http://dx.doi.org/10.1016/j.bbi.2016.07.145] [PMID: 27423492]

[269] Ghosh, S.; Molcan, E.; DeCoffe, D.; Dai, C.; Gibson, D.L. Diets rich in n-6 PUFA induce intestinal microbial dysbiosis in aged mice. *Br. J. Nutr.,* **2013**, *110*(3), 515-523. [http://dx.doi.org/10.1017/S0007114512005326] [PMID: 23298440]

[270] Leckie, R.L.; Weinstein, A.M.; Hodzic, J.C.; Erickson, K.I. Potential moderators of physical activity on brain health. *J. Aging Res.,* **2012**, *2012*, 948981. [http://dx.doi.org/10.1155/2012/948981] [PMID: 23304508]

[271] Chytrova, G.; Ying, Z.; Gomez-Pinilla, F. Exercise contributes to the effects of DHA dietary supplementation by acting on membrane-related synaptic systems. *Brain Res.,* **2010**, *1341*, 32-40. [http://dx.doi.org/10.1016/j.brainres.2009.05.018] [PMID: 19446534]

[272] Wu, A.; Ying, Z.; Gomez-Pinilla, F. Docosahexaenoic acid dietary supplementation enhances the effects of exercise on synaptic plasticity and cognition. *Neuroscience,* **2008**, *155*(3), 751-759. [http://dx.doi.org/10.1016/j.neuroscience.2008.05.061] [PMID: 18620024]

[273] Hutton, C.P.; Déry, N.; Rosa, E.; Lemon, J.A.; Rollo, C.D.; Boreham, D.R.; Fahnestock, M.; deCatanzaro, D.; Wojtowicz, J.M.; Becker, S. Synergistic effects of diet and exercise on hippocampal function in chronically stressed mice. *Neuroscience,* **2015**, *308*, 180-193. [http://dx.doi.org/10.1016/j.neuroscience.2015.09.005] [PMID: 26358368]

[274] Köbe, T.; Witte, A.V.; Schnelle, A.; Lesemann, A.; Fabian, S.; Tesky, V.A.; Pantel, J.; Flöel, A. Combined omega-3 fatty acids, aerobic exercise and cognitive stimulation prevents decline in gray matter volume of the frontal, parietal and cingulate cortex in patients with mild cognitive impairment. *Neuroimage,* **2016**, *131*, 226-238. [http://dx.doi.org/10.1016/j.neuroimage.2015.09.050] [PMID: 26433119]

[275] Schättin, A.; de Bruin, E.D. Combining exergame training with omega-3 fatty acid supplementation: protocol for a randomized controlled study assessing the effect on neuronal structure/function in the elderly brain. *Front. Aging Neurosci.,* **2016**, *8*, 283. [http://dx.doi.org/10.3389/fnagi.2016.00283] [PMID: 27965570]

[276] Sarris, J. Clinical depression: an evidence-based integrative complementary medicine treatment model. *Altern. Ther. Health Med.,* **2011**, *17*(4), 26-37. [PMID: 22314631]

[277] Geerlings, M.I.; Schoevers, R.A.; Beekman, A.T.; Jonker, C.; Deeg, D.J.; Schmand, B.; Adèr, H.J.; Bouter, L.M.; Van Tilburg, W. Depression and risk of cognitive decline and Alzheimer's disease. Results of two prospective community-based studies in The Netherlands. *Br. J. Psychiatry,* **2000**, *176*, 568-575. [http://dx.doi.org/10.1192/bjp.176.6.568] [PMID: 10974964]

[278] van Hooren, S.A.; Valentijn, S.A.; Bosma, H.; Ponds, R.W.; van Boxtel, M.P.; Jolles, J. Relation between health status and cognitive functioning: a 6-year follow-up of the Maastricht Aging Study. *J. Gerontol. B Psychol. Sci. Soc. Sci.,* **2005**, *60*(1), 57-60. [http://dx.doi.org/10.1093/geronb/60.1.P57] [PMID: 15643040]

[279] Wilson, R.S.; Mendes De Leon, C.F.; Barnes, L.L.; Schneider, J.A.; Bienias, J.L.; Evans, D.A.; Bennett, D.A. Participation in cognitively stimulating activities and risk of incident Alzheimer disease. *JAMA,* **2002**, *287*(6), 742-748. [http://dx.doi.org/10.1001/jama.287.6.742] [PMID: 11851541]

[280] Paterniti, S.; Verdier-Taillefer, M.H.; Dufouil, C.; Alpérovitch, A. Depressive symptoms and cognitive decline in elderly people. Longitudinal study. *Br. J. Psychiatry,* **2002**, *181*, 406-410. [http://dx.doi.org/10.1192/bjp.181.5.406] [PMID: 12411266]

[281] Stewart, R. Depressive symptoms and cognitive decline--disentangling the effect of affect. *J. Neurol. Neurosurg. Psychiatry,* **2004**, *75*(1), 5. [http://dx.doi.org/10.1136/jnnp.2003.028399] [PMID: 14707296]

[282] Snowdon, D.A. Healthy aging and dementia: findings from the Nun Study. *Ann. Intern. Med.,* **2003**, *139*(5 Pt 2), 450-454. [http://dx.doi.org/10.7326/0003-4819-139-5_Part_2-200309021-00014] [PMID: 12965975]

[283] Stern, Y. Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol.,* **2012**, *11*(11), 1006-1012. [http://dx.doi.org/10.1016/S1474-4422(12)70191-6] [PMID: 23079557]

[284] Satz, P. Brain reserve capacity on symptom onset after brain injury: A formulation and review of evidence for threshold theory. *Neuropsychology,* **1993**, *7*, 273-295. [http://dx.doi.org/10.1037/0894-4105.7.3.273]

[285] Phillips, C. Lifestyle modulators of neuroplasticity: how physical activity, mental engagement, and diet promote cognitive health during aging. *Neural Plast.,* **2017**, *2017*, 3589271. [http://dx.doi.org/10.1155/2017/3589271] [PMID: 28695017]

[286] Serra, L.; Musicco, M.; Cercignani, M.; Torso, M.; Spanò, B.; Mastropasqua, C.; Giulietti, G.; Marra, C.; Bruno, G.; Koch, G.; Caltagirone, C.; Bozzali, M. Cognitive reserve and the risk for Alzheimer's disease: a longitudinal study. *Neurobiol. Aging,* **2015**, *36*(2), 592-600. [http://dx.doi.org/10.1016/j.neurobiolaging.2014.10.010] [PMID: 25433459]

[287] Opdebeeck, C.; Nelis, S.M.; Quinn, C.; Clare, L. How does cognitive reserve impact on the relationships between mood, rumination, and cognitive function in later life? *Aging Ment. Health,* **2015**, *19*(8), 705-712. [http://dx.doi.org/10.1080/13607863.2014.962005] [PMID: 25262628]

[288] Paulson, D.; Bowen, M.E.; Lichtenberg, P.A. Does brain reserve protect older women from vascular depression? *J. Gerontol. B Psychol. Sci. Soc. Sci.,* **2014**, *69*(2), 157-167. [http://dx.doi.org/10.1093/geronb/gbt007] [PMID: 23448867]

[289] Katzmarzyk, P.T. Physical activity, sedentary behavior, and health: paradigm paralysis or paradigm shift? *Diabetes,* **2010**, *59*(11), 2717-2725. [http://dx.doi.org/10.2337/db10-0822] [PMID: 20980470]

[290] Owen, N.; Healy, G.N.; Matthews, C.E.; Dunstan, D.W. Too much sitting: the population health science of sedentary behavior. *Exerc. Sport Sci. Rev.,* **2010**, *38*(3), 105-113. [http://dx.doi.org/10.1097/JES.0b013e3181e373a2] [PMID: 20577058]

[291] Raichlen, D.A.; Foster, A.D.; Gerdeman, G.L.; Seillier, A.; Giuffrida, A. Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'run-

ner's high'. *J. Exp. Biol.,* **2012**, *215*(Pt 8), 1331-1336. [http://dx.doi.org/10.1242/jeb.063677] [PMID: 22442371]

[292] Seidler, R.D.; Bernard, J.A.; Burutolu, T.B.; Fling, B.W.; Gordon, M.T.; Gwin, J.T.; Kwak, Y.; Lipps, D.B. Motor control and aging: links to age-related brain structural, functional, and biochemical effects. *Neurosci. Biobehav. Rev.,* **2010**, *34*(5), 721-733. [http://dx.doi.org/10.1016/j.neubiorev.2009.10.005] [PMID: 19850077]

[293] Teixeira, P.J.; Carraça, E.V.; Markland, D.; Silva, M.N.; Ryan, R.M. Exercise, physical activity, and self-determination theory: a systematic review. *Int. J. Behav. Nutr. Phys. Act.,* **2012**, *9*, 78. [http://dx.doi.org/10.1186/1479-5868-9-78] [PMID: 22726453]

[294] Chang, P.J.; Wray, L.; Lin, Y. Social relationships, leisure activity, and health in older adults. *Health Psychol.,* **2014**, *33*(6), 516-523. [http://dx.doi.org/10.1037/hea0000051] [PMID: 24884905]

[295] Everard, K.M.; Lach, H.W.; Fisher, E.B.; Baum, M.C. Relationship of activity and social support to the functional health of older adults. *J. Gerontol. B Psychol. Sci. Soc. Sci.,* **2000**, *55*(4), S208-S212. [http://dx.doi.org/10.1093/geronb/55.4.S208] [PMID: 11584883]

[296] Levasseur, M.; Généreux, M.; Bruneau, J.F.; Vanasse, A.; Chabot, É.; Beaulac, C.; Bédard, M.M. Importance of proximity to resources, social support, transportation and neighborhood security for mobility and social participation in older adults: results from a scoping study. *BMC Public Health,* **2015**, *15*, 503. [http://dx.doi.org/10.1186/s12889-015-1824-0] [PMID: 26002342]

[297] Alhawassi, T.M.; Krass, I.; Bajorek, B.V.; Pont, L.G. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin. Interv. Aging,* **2014**, *9*, 2079-2086. [PMID: 25489239]

[298] Alomar, M.J. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharm. J.,* **2014**, *22*(2), 83-94. [http://dx.doi.org/10.1016/j.jsps.2013.02.003] [PMID: 24648818]