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Current Alzheimer Research, **Year,** *Volume, Page Enation*

REVIEW ARTICLE

Modifiable Risk Factors for Dementia: The Role of Gut Microbiota

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ARTICLE HISTORY

Received:
Revised:
Accepted:

DOI:

Abstract: Dementia is a syndrome resulting from chronic or progressive brain disease. Around 40% of worldwide dementia can be prevented or delayed by modifying 12 risk factors: low educational attainment in early life, mid-life hypertension, mid-life obesity, hearing loss, traumatic brain injury, excessive alcohol consumption, smoking, depression, physical inactivity, social isolation, diabetes mellitus, and air pollution. There is growing evidence that gastrointestinal tract microbiota may significantly contribute to dementia pathogenesis. In particular, gut dysbiosis can trigger metabolic diseases and the progression of low-grade systemic inflammation, being involved in much of the major modifiable risk factors. In this review, we focus on studies that have evaluated the association between modifiable risk factors for dementia and the role of gut microbiota. We also suggest clinical implications for researchers in dementia-gut microbiota related fields.

Keywords: dementia, risk factor, gut microbiota, dysbiosis, lifestyle, prevention

1. INTRODUCTION

Dementia is a syndrome resulting from chronic or progressive brain disease. It is characterized by impairment of multiple higher cortical functions, including memory, thinking, comprehension, calculation, learning ability, language and judgment. Cognitive impairments are usually accompanied or preceded by impaired emotional control, social behavior or motivation [1]. The pathophysiology of dementia is still not understood completely, but structural and chemical changes are systematically observed in the brain, resulting in neuronal loss and atrophy of brain volume [2]. There are different conditions that can cause dementia syndrome. The most common is Alzheimer's disease (AD) with 60% of total cases, vascular dementia (VaD), mixed dementia, dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD). In fact, there are many other causes, such as other degenerative diseases (e.g. Creutzfeldt-Jakob Disease (CJD), human immunodeficiency virus (HIV) and various toxic and metabolic disorders) [3]. Similarly, dementia occurs in a substantial number of patients with Parkinson's disease (PD), with a point prevalence approaching 30% [4].

During the last few years, epidemiological studies refer an exponential increase in the number of people with dementia, thus becoming an alarming global health problem and the fifth leading cause of death worldwide [5]. In fact, there are currently about 50 million people with dementia, and it is estimated that by 2050, this number will rise to 152 million [6]. The increase in life expectancy leads to an increase in the existence of chronic diseases in the population, being very likely the onset of dementia at older ages. Specifically, the prevalence of dementia is 5% in people over 65 years of age, but increases dramatically to 20-40% in people over 85 years of age [7]. However, recent evidence suggests that the prevalence of dementia is decreasing in high-income countries, possibly due to educational, socioeconomic, health and lifestyle changes [8].

The medical and social care required by patients with dementia causes a large economic impact, with the consequent overload and detriment to the health and quality of life of caregivers [9]. Currently, the drugs available for the treatment of dementia have small effect sizes and do not alter disease progression. In fact, there is also no evidence of a pharmacological intervention for the prevention of dementia [10]. However, epidemiological research provides evidence in addressing modifiable risk or protective factors to prevent or delay the onset of dementia [8].

Recently, the Lancet review of evidence [8] has proposed a dementia risk model, which reflects how lifestyle factors throughout life contribute to dementia risk. The Lancet commission concludes that 40% of dementia cases can be prevented by modifying 12 risk factors: low educational attainment in early life, mid-life hypertension, mid-life obesity, hearing loss (HL), traumatic brain injury

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(TBI), excessive alcohol consumption, smoking, depression, physical inactivity, social isolation, diabetes mellitus, and air pollution. There is substantial evidence from observational studies and randomized trials on these modifiable risk factors, although some factors of older age (e.g. depression) have potentially a two-way impact and might be involved in the prodrome of dementia as well [11].

Given the complex, multifactorial and heterogeneous nature of dementias in general, preventive interventions require a simultaneous targeting of modifiable risk factors and different mechanisms at the same time [12]. For this reason, research on dementia prevention can elucidate the factors involved in its pathogenesis and, consequently, optimize preventive treatment more effectively.

The human gastrointestinal (GI) tract is one of the largest communication pathways (250-400m^2) connecting the human internal environment with environmental factors. An estimated average of 60 tons of food passes through the GI tract over the lifetime, resulting in continuous exposure to environmental microorganisms which may threaten intestinal integrity [13]. For thousands of years, the complex of bacteria, archaea and eukaryotes which colonize the GI tract are called "gut microbiota" and have been evolving alongside the host to establish a complex and mutually beneficial relationship [14]. The estimated number of microorganisms inhabiting the GI is 10^{14}, which is about 10 times the number of human cells and more than 100 times the amount of genomic content than the human genome [15]. The importance of the gut-brain axis in maintaining homeostasis has long been appreciated. However, the gut microbiota appears recently to be one of the key regulators of gut-brain function and has led to the assessment of a distinct microbiota-gut-brain axis [16]. This axis is receiving growing attention in research fields which investigate the biological and physiological basis of psychiatric, neurodevelopmental and neurodegenerative disorders [17].

The gut microbiota and the brain interact with each other through several pathways: the immune system, the tryptophan metabolism, the vagus nerve and the enteric nervous system (ENS), which involves microbial metabolites such as short-chain fatty acids (SCFAs), branched-chain amino acids and peptidoglycan acids [18]. In particular, bacterial strains such as Escherichia, Lactobacillus, Saccharomyces and Bacillus can synthesize gamma-aminobutyric acid (GABA), 5-hydroxytryptamine, dopamine, butyrate, histamine or serotonin, and can pass through the mucous layer of the intestine, entering the bloodstream [19] and modulate brain activity [20]. There are many factors affecting the composition of the gut microbiota, such as infections [16], drug use [21], diet [22] or environmental stressors [23]. The intestinal microbiota provides numerous benefits to the host, however, it is possible that these mechanisms can be disrupted as a consequence of an altered microbial composition, known as dysbiosis. Recent works involve the gut microbiota in the pathogenesis of dementia, as it triggers metabolic diseases and the progression of low-grade systemic inflammation [17]. This mechanism can damage the blood-brain barrier (BBB), promote neuroinflammation, neural injury and result in neurodegeneration [24].

Current research about prevention of cognitive decline related to aging and neurodegenerative diseases focuses on lifestyle factors and cognitive reserve. Given the complex, multifactorial and heterogeneous nature of dementias in general and the difficulty of applying treatments that simultaneously address several modifiable risk factors for dementia at the same time, it is possible that the microbiota may be the cornerstone that allows us to more effectively access the treatment and prevention of a greater number of modifiable risk factors for dementia, as the vast majority of them are related to our lifestyle, physical exercise and social activities [25]. Neurodegenerative disorders generally manifest in advanced age, when the gut microbiota composition has been influenced by various factors. Effective interventions in diet, medications, biochemical exposures, psychological condition, pre-existing disease and lifestyle could substantially decrease the new incidence of dementia [26].

Due to the rapid growth of the aging population, the treatment strategy in dementia is shifting towards earlier stage interventions and disease prevention. For this reason, identifying modifiable risk factors, understanding how they contribute to the pathogenesis of dementia and the role of the gut microbiota, could be key to raise new aspects of prevention and intervention. The main objective of this review is to provide an updated summary of the existing evidence related to the various potentially modifiable risk factors for AD, PD, DLB and FTD and the role of the gut microbiota in them.

2. METHOD

To identify relevant literature in the field, four electronic databases were used: Web of Science, Scopus, PubMED and APA PsycNET in which studies from 1900 to January 2021 were examined. The selection of potential studies has given priority to prospective randomized trials, large meta-analyses and systematic reviews on modifiable risk factors for AD, PD, DLB and FTD and their relationship with the gut microbiota.

More specifically, the search was refined with the terms "modifiable" AND "risk" AND "factors" AND "Alzheimer's disease" OR "Parkinson's

disease". Similarly, due to lack of data, we searched with the terms "risk" AND "factors" AND "dementia with Lewy bodies" OR "frontotemporal dementia". For its part, we also searched with the terms "dementia" AND "gut microbiota" OR "dysbiosis".

Inclusion and exclusion criteria. The inclusion criteria for this study were (1) studies written in English, (2) peer-reviewed studies, and (3) reports issued by governments or global health care organizations. Exclusion criteria were (1) non-English languages, (2) non-peer-reviewed studies, (3) duplicate studies, (4) conference papers or proceedings, (5) studies that did not use standard measurement tools, and, finally, (6) studies without methodology or clearly explained findings.

3. RESULTS

3.1. Modifiable risk factors for Alzheimer's disease

AD is a complex and multifactorial disease given the plurality of interconnected genetic and environmental factors. More specifically, one third of AD cases can be attributed to potentially modifiable risk factors [27]. It is characterized by a progressive deterioration of cognitive functions, possibly related to a significant reduction in brain volume [28]. Currently, the exact mechanisms underlying the pathogenesis of AD still remain unclear. Apart from the global reduction of brain volume, studies refer to the involvement of extracellular plaque deposition of amyloid-beta (Aβ) protein and intraneuronal neurofibrillary tangles of the tau protein in the progression of the disease [29].

3.1.1 Metabolic Alzheimer's disease risk factors

Several metabolic diseases increase the risk of developing AD. These include diabetes, hypertension and obesity.

Diabetes mellitus

Diabetes mellitus is a metabolic disorder characterized by insulin resistance or insulin deficiency. During diabetes, oscillations in plasma osmotic pressure and oxidative stress levels can trigger cognitive changes in the brain. More specifically, the imbalance between oxidants and antioxidants triggers neurodegeneration through the excessive deposition of Aβ peptides and the subsequent release of free radicals, leading to dementia [30]. In a recent systematic review, Li, Cesari [31] report that current evidence indicates that the relationship between diabetes and cognitive impairment in AD patients is still uncertain.

Hypertension

Hypertension is a common human condition, defined by a sustained elevation of systolic blood pressure above 140 mmHg or diastolic blood pressure above 90 mmHg and it has been linked to the neuropathology of AD [32]. In fact, the literature reports that it doubles the risk of AD in old age relative to other vascular risk factors [33]. Although the mechanism of action of cognitive impairment in people with hypertension is not entirely clear, studies suggest that it acts by causing cerebral vascular injury, increasing cerebral blood permeability, facilitating amyloid angiopathy, worsening synaptic and neuronal loss caused by Aβ/tau pathology and hindering Aβ clearance [34].

Obesity

Obesity is defined as the accumulation of abnormal or excessive fat that is associated with increased health risk [35]. Previous studies, meta-analyses and extensive clinical evidence show that midlife obesity is a risk factor for AD [34, 36-39]. It is plausible that the actions of leptin and adiponectin, the two most common adipokines secreted by adipose tissue, may cause cognitive dysfunction and increased risk of AD [40]. In fact, the release of adipokines, such as leptin and other cytokines, causes chronic inflammation which can extend to the brain, causing a decrease in white matter and leading to a deterioration of neuronal connections [41].

3.1.2 Lifestyle Alzheimer's disease risk factors

There is growing evidence that certain lifestyle factors are involved in the development of AD. Many of these are potentially modifiable and include low educational attainment, alcohol consumption, smoking and physical activity.

Educational attainment

Higher educational level is associated with greater brain reserve [42]. Brain reserve is defined as the reserve capacity related to the very structure of the telencephalon, i.e. quantitative in nature, related to the neural substrate and linked to cognitive reserve, as the latter refers to functional rather than just structural enhancement [43]. Brain reserve is known to enhance an individual's resilience to prevent or delay the prodrome of dementia [42]. Studies support Stern's hypothesis, that education mitigates dementia risk through cognitive reserve, rather than directly affecting the pathogenesis of AD [44].

Alcohol consumption

Heavy alcohol consumption is related to structural brain changes, cognitive impairment, and increased risk of dementia [45]. It is also associated with faster cognitive decline in AD patients, suggesting that it may accelerate its progression [46]. Possibly, contributes to the observed cognitive

impairment in dementia through additional pathways to neurodegenerative processes or may contribute at several pathophysiological points of AD through neuroinflammation [47].

Smoking

Smoking is a risk factor for AD and other neurodegenerative disorders. In a study by Wallin, Sholts [48] five aromatic hydrocarbons and *four* metal ions present in cigarette smoke were proven to affect the Aβ40 peptide aggregation process, which suggests a higher prevalence of AD among smokers. Indeed, it appears that the poor cerebral blood supply characteristic of smokers enhances the synthesis of Aβ, further decreasing blood flow to the brain [49]. Possibly, this vicious circle is one of the key factors affecting AD, as the decreased blood supply to the brain induces increased production of Aβ [50], decrease in intraneuronal Aβ clearance [51], inhibition of endothelial function (involved in the pathogenesis of AD) and results to impaired brain function [52]. Another study by Durazzo, Korecka [53] reports that older people who are cognitively well or have probable AD and actively smoke are associated with higher oxidative stress, which appears to be related to a smaller hippocampal volume characteristic of AD [53].

Physical inactivity

Physical activity is associated with a reduced risk of developing AD [54]. In particular, physical exercise is associated with a lower risk of AD due to trophic factors that have clear effects on improving neuroplasticity and cognitive and behavioral function. Indeed, exercise is known to synchronously modify cerebrovascular function and glial cells to enhance neuroplasticity. However, a systematic review of Brasure, Desai [55] concluded that the effectiveness of physical activity interventions (exclusively) for preventing cognitive decline is insufficient. It seems that studies have not been long enough to demonstrate the real long-term impact of a physically active lifestyle.

3.1.3 Psychological condition Alzheimer's disease risk factors

Several psychological factors, such as personality traits and affective states like depression and psychological stress have been related to AD.

Depression

Depression is the most common mental health condition in the general population. It is characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-esteem, sleep or appetite disturbances, feelings of tiredness and lack of concentration and is associated with increased risk of dementia, VaD and AD [56, 57]. Studies report that inflammatory changes occur in both depression and AD (e.g., elevated CRP, TNFα) mediated by cytokines and glucocorticoids (GC), as both may have pro-inflammatory actions on brain [58]. However, other studies refer that depression is an early symptom of the neurodegenerative process of AD, advocating an overlap between neuropathological events causing cognitive deficits and those causing depressive symptoms in dementia [59].

Stress

Psychological stress occurs when an individual perceives that environmental demands exceed his or her ability to adapt. There is increasing evidence linking high levels of perceived stress with an increased risk of developing AD [60]. It appears that hippocampus, one of the main areas of the brain damaged during progression of AD, is also one of the first regions to be targeted by stress hormones, including cortisol, sympathetic and parasympathetic neurotransmitters, and cytokines [61]. Acute stress along with spikes in GC can enhance cognitive processes, but chronic stress coupled with sustained elevated GC levels is related to reduced hippocampal function and volume, leading to cognitive deficits [62]. The hippocampus is also involved in the closure of the stress response triggered by the hypothalamic-pituitary-adrenal axis. Consequently, the damage and atrophy of the hippocampus disrupts the feedback mechanism, resulting in a sustained hypothalamic-pituitary-adrenal response and eventually in an exacerbated neuroinflammatory environment [63].

3.1.4 Neurotoxic agents Alzheimer's disease risk factors

In particular, several work has focused on the role of neurotoxic agents such as air pollutants and their relation with dementia and AD specifically.

Air pollution

A recent meta-analysis concludes that exposure to air pollution may exacerbate the development of AD [64]. In particular, there is in vivo evidence that particulate matter (PM (2.5)) exposure can alter β-amyloid precursor protein processing [65], suggesting at least some specificity in AD disease progression, although to what extent is unknown. Further studies are required to explore whether the changes triggered by PM exposure are directly caused by changes in APP processing and other AD-specific pathways, or whether inflammation and oxidative stress are the main causes.

3.1.5 Other Alzheimer's disease risk factors

Hormones

The risk of developing AD is strongly influenced by gender. In fact, almost two-thirds of Americans with AD have been estimated to be women [66]. While woman lifespan may partly explain the difference in prevalence, researchers have started to investigate the role of gender specific traits and sex-dependent hormones in AD [67]. A decrease in sex hormone levels around menopause has been linked to an increased risk of AD [68]. Hormone Therapy (HT) imply the administration of estrogens and there have been observed neuroprotective effects in experimental animals [69]. However, clinical trials on postmenopausal HT use have been unsuccessful [70]. A pilot study found that sodium benzoate, an indirect NMDAR enhancer, benefited cognitive function only in women with behavioral and psychological symptoms in late-phase dementia [71]. Further research is needed in order to understand more precisely the role of sex differences, sex hormones, gender, and psychosocial factors that impact cognitive functioning, particularly with regard to AD risk.

Hearing loss

Studies link HL to increased chance of developing AD in older adults [72]. However, the mechanisms and causal relationship of this association are still unknown. One plausible explanation is that HL leads to cognitive impairment, since there would be less cognitive stimulation. It seems that the use of auditory function tests, could additionally provide us with an early and non-invasive biomarker to detect AD [73]. However, a recent study refers that self-reported HL is associated with reduced speed and flexibility, but not with accelerated decline in any domain studied, contrary to previous findings [74].

Traumatic brain injury

TBI is defined as altered brain function or other evidence of brain pathology caused by an external force. The severity of TBI can be classified into 3 levels: mild, moderate and severe. TBI causes brain swelling, axonal injury and hypoxia, alters BBB function and increases inflammatory responses, oxidative stress, neurodegeneration and leads to cognitive impairment. Epidemiological studies show that 30% of patients who die of TBI have Aβ plaques [75]. For this reason, TBI may act as an important epigenetic risk factor in AD. Studies report that this relationship is likely due to the fact that certain AD-related genes are expressed during TBI and contribute to disease progression [76]. Chronic inflammation is a potential common denominator in both TBI and AD. TBI induces a generalized neuroinflammatory response that can promote recovery if controlled for a defined period of time. However, excessive or chronic neuroinflammation is associated with progressive changes, including atrophy, neuronal loss, and axonal degeneration [77]. Contrary to these findings, recent studies and meta-analyses refer that there is no association between TBI and AD neuropathology [78] and the existence of methodological problems in most studies [79].

3.2 Modifiable risk factors for Parkinson's disease

PD is the second most common neurodegenerative disorder after AD. It is clinically characterized by parkinsonism (resting tremor, bradykinesia, rigidity, and postural instability), the accumulation and aggregation of alpha-synuclein (α-syn) in the substantia nigra of the central nervous system (CNS) and other neural structures [80]. In 26 years, the prevalence of PD has increased from 2.5 million to 6.1 million worldwide. Environmental and behavioral factors seem to play a very important role in the pathogenesis of PD, as studies show that 90% of PD cases have no genetic cause to identify [81].

3.2.1 Metabolic Parkinson's disease risk factors

Metabolic syndrome was associated with a 50% lower risk of developing PD. It is likely that this association is largely due to a high fasting plasma glucose concentration [82].

Diabetes mellitus

However, different studies report a significant increased risk of PD in people with type 2 diabetes (T2D) [83-85]. Of note, no association between diabetes and PD risk was found in two large prospective cohort studies in the US [86, 87]. There appear to be very different and contradictory findings, leading us to consider the existence of a complex relationship between insulin resistance and PD, which may be altered by other factors, such as hyperuricemia, which is a risk factor for T2D, but inversely associated with the risk of PD [88].

Cholesterol

Elevated blood cholesterol is linked to lower risk of PD [89]. In particular, self-reported blood cholesterol is linked to a decreased risk of PD, but was not associated with a history of hypercholesterolemia, hypertension, or diagnosed arterial problems [87]. However, a significant increased risk of PD due to blood cholesterol has been found in other studies [90]. These discordant results suggest that unknown or modifying factors may modulate the association between blood cholesterol and the risk of PD.

Body mass index

No association has been found between body mass index (BMI) and risk of PD in most longitudinal studies or in recent meta-analyses [91-

94]. However, Hu, Jousilahti [95] reported that a high BMI is an important risk factor for PD.

3.2.2 Lifestyle Parkinson's disease risk factors

Epidemiological studies suggest that lifestyle-related factors like consumption of milk and dairy products and alcohol intake may be important for the development of PD.

Dairy products

Several studies report an increased risk of PD in individuals with a high intake of milk and dairy products [93]. Similarly, a recent meta-analysis supported an association between high dairy consumption and PD risk, which was stronger in men than in women [96]. It is possible the presence of a contaminant in milk to explain the links of milk consumption to an increased risk of PD, but in general, most studies agree that the increased risk of PD is associated with the consumption of urate reducing dairy products [97]. However, it is unclear whether specific dairy foods or nutrients present in dairy products are responsible for this association and whether the associations are present among women and men or only among men.

Alcohol consumption

Alcohol consumption is associated with a lower risk of PD [98]. This finding is consistent with the urate-elevating effects of alcoholic beverages [99]. However, in a study based on the Swedish national hospitalization registry with more than 1,000 patients with PD, alcohol abuse was found to be associated with an increased risk of the disease [100]. Studies on alcohol consumption and its relationship with PD reflect mixed results and are still inconclusive.

Methamphetamine

Methamphetamine (METH) is a highly addictive and frequently abused illicit drug. Regular use of METH is associated with a number of serious medical, cognitive, and psychosocial problems, occurring not only during abuse but also in a chronically. Two studies report a positive association between amphetamine or METH use and an increased risk of PD [101, 102]. It is possible that this relationship occurs because METH binds to the presynaptic dopamine transporter, increasing extracellular dopamine concentrations and, in experimental animals, ultimately damaging dopaminergic neurons in the substantia nigra and causing pathological alterations similar to those observed in the brains of PD patients [103].

3.2.3 Occupational exposure Parkinson's disease risk factors

There is evidence from observational studies for a role of a number of environmental exposures like pesticides and other environmental chemicals in modulating the risk of PD.

Pesticides

Pesticide residues are a serious and persistent environmental problem because a large group of pesticides has been detected in food, water and soil. The evidence associating paraquat, rotenone and organochlorines with PD seems strong; however, organophosphates, pyrethroids and polychlorinated biphenyls require further study [104].

Solvents

There is growing interest, but no longitudinal data, for the potential role of solvents (e.g., Trichloroethylene) as an adverse PD risk factor [105].

3.2.4 Other Parkinson's disease risk factors

Cancer

People with melanoma have an increased risk of developing PD [106]. Studies by Olsen, Friis [107] and Wirdefeldt, Weibull [108] report that a diagnosis of melanoma is associated with a 44% increased risk of PD. However, smokers have a significantly reduced risk of PD [109]. For this reason, smoking-related cancers would not be associated with an increased risk of PD [110].

Traumatic brain injury

TBI can cause a breakdown of the BBB, long-term brain inflammation, altered mitochondrial function, increased glutamate release, and increased accumulation of α-syn in the brain, all of which may contribute to an increased risk of PD once such a chronic injury has been sustained [111]. However, the results of several investigations such as Marras, Hincapie [112] suggest that PD risk appears to increase soon after TBI, but gradually decreases over time. Further studies investigating the role of α-syn as a potential prognostic biomarker of PD after TBI and its causality are required.

Hormones

The fact that there is a higher incidence of PD in men than in women has suggested that it is possible that certain hormones increase the risk of PD. In women who reported postmenopausal estrogen use in the Cancer Prevention Study [113] had a 33% higher risk of death from PD compared with women who did not use these drugs. The results of these studies report that postmenopausal hormone use may be associated with an increased risk of PD, rather than a difference between men and women [114].

3.3 Modifiable risk factors for dementia with Lewy bodies

DLB is characterized by the presence of Lewy bodies in neocortical and paralimbic areas, and AD-type lesions. DLB is a heterogeneous disorder with variable clinical and pathological features, typically presenting dementia, visual hallucinations, parkinsonism and fluctuations in cognition and attention associated with the presence of Lewy bodies in a more widespread pattern than that generally observed in the brain nuclei of patients with PD. DLB is the second most common cause of dementia and accounts for 10% to 15% of all cases. DLB and PD are due to the accumulation of pathogenic α-syn in the brain and are characterized by heterogeneous motor and non-motor symptoms, including cognitive impairment. For this reason, they comprise different points along a continuum, belonging to the clinical spectrum of Lewy body disorders [115]. However, DLB patients may show pathological heterogeneity, especially due to the presence of concomitant AD pathology with β-amyloid plaques and neurofibrillary tangles [116].

It appears, that subjects with DLB are more likely to have a history of anxiety, depression and stroke [117]. Similarly, metabolic risk factors such as hypertension, diabetes and hyperlipidemia have been found [118].

3.4 Modifiable risk factors for frontotemporal dementia

Frontotemporal dementia (FTD) is the most common form of primary degenerative dementia after AD, affecting middle-aged people and accounts for up to 20% of presenile dementia cases [119]. There is equal incidence in men and women [120]. The average duration of the disease is 8 years, with a range of 2 to 20 years. Currently, FTD encompasses clinical disorders that include changes in behavior, language, executive control, and motor symptoms. The FTD spectrum consists of: behavioral variant FTD (bvFTD) and primary progressive primary aphasia (PPA), which includes the non-fluent/agrammatic (naPPA), semantic (svPPA) and logopenic PPA (lvPPA) variants. Similarly to AD, FTD is characterized by the pathological accumulation of hyperphosphorylated tau protein (P-tau), in the form of intracellular helical pairs filaments (PHFs) or neurofibrillary tangles (NFTs), within neurons and glia of affected brain regions, leading to cell death [121].

A small retrospective case-control study by Rosso, Landweer [122] and more recent studies such as Rasmussen, Stordal [123] or Kalkonde, Jawaid [124], arbitrate an increased risk of FTD if one has had TBI. While it may be a memory bias, the frontal lobe is known to be especially vulnerable even in mild TBI. Thyroid disease has also been associated with a 2.5-fold increased risk of FTD (95% CI, 0.9 to 7.9) [122]. Cardiovascular factors do not appear to act as risk factors for FTD [124, 125]. However, the study by Golimstok, Campora [125] found that diabetes mellitus was associated as an independent risk factor for FTD.

The study by Adani, Filippini [126] reports that most of the investigated exposures, such as occupational exposure to aluminum, pesticides, dyes, paints, gold thinners, were associated with an increased risk of FTD, as well as prolonged use of selenium-containing dietary supplements. These results suggest a role of environmental and behavioral risk factors, such as some chemical exposures and professional sports (at risk for FTD) in the etiology of FTD. However, given the paucity of existing studies, future studies are needed to confirm these observations.

4. GUT MICROBIOTA AND DEMENTIA

Changes in the composition of the gut microbiota can cause alterations in intestinal barrier function and intestinal permeability, affecting GI epithelial cells and the immune system, and also the ENS [127]. Bidirectional interactions of the brain-gut-microbiota axis modulate proinflammatory and anti-inflammatory responses [128]. In particular, dementia is associated with changes in gut microbiota composition and increased biomarkers of intestinal permeability and inflammation [129]. Being a bidirectional axis, elevated levels of stress in the CNS could affect gut physiology and alter the composition of the gut microbiota [130].

Emerging studies implicate the gut microbiota with the development of AD specifically [131]. It is still not well understood what triggers the formation of Aβ plaques, but recent studies suggest that the gut microbiota certainly plays an important role in the process via microbiome-derived amyloids and lipopolysaccharide (LPS), triggering age-related inflammatory and AD-type neurodegeneration [132]. The fecal microbiota profile in patients with AD appears to have reduced microbial diversity, lower abundance of Firmicutes and Bifidobacterium and higher abundance of Bacteroidetes [133].

In addition, memory and learning impairment implies dysfunctional glutamate neurotransmission (the agonist of the N-methyl-d-aspartate receptor and the principal excitatory neurotransmitter in the brain) [134]. Gut microbiota can affect glutamate metabolism and influence the glutamate NMDAR and cognitive functions in AD [135].

Regarding to PD and DLB, studies suggest that changes in the gut microbiota associated with intestinal inflammation may contribute to the initiation of α-syn misfolding [136], that triggers neurodegeneration both disorders [137, 138]. There

is a growing body of evidence confirming that alterations in the gut microbiota precede or occur during the course of PD [139]. Hopfner, Kunstner [140] in line with previous studies [137, 138], found a significant increase of Lactobacillus in patients with PD, suggesting that the composition of the gut microbiota might have a predictive value.

Next, the specific evidence for each risk factor for dementia and its relationship with gut microbiota is shown.

4.1 Gut microbiota and metabolic dementia risk factors

Diabetes mellitus

Gut microbiota has been linked to diabetes and its pathogenesis [141]. Studies, point to changes in the composition or function of the gut microbiota in patients with T2D, where dysbiosis depends mainly on a depletion of butyrate-producing bacteria, along with an enrichment of opportunistic pathogens [142]. Indeed, studies such as that of Dumas, Barton [143], suggest that the gut microbiota may also play an active role in the development of complex metabolic abnormalities, such as susceptibility to insulin resistance and fatty liver disease. Similarly, studies with mice on a high-fat diet revealed that both insulin sensitivity and cholesterol metabolism are metabolic targets influenced by the gut microbiota [144]. In this regard, it is noteworthy that changes in metabolites produced by the gut microbiota may be associated with the development of T2D and insulin resistance. Furthermore, these studies are in agreement with the concept that a decrease in microbial diversity is associated with increased insulin resistance, inflammation and adiposity. However, the exact composition and metabolic activity of the gut microbial community contributing to the onset of diabetes is unknown.

Hypertension

Recent studies suggest that the gut microbiota is involved in the regulation of hypertension and its pathogenesis through dysbiosis [145], due to the secretion of a variety of bioactive metabolites of microbial origin [146] such as, for example, SCFA [147]. SCFA exerts regulatory effects on hypertension by activating transmembrane G protein-coupled receptors and inhibiting histone acetylation [148].

Obesity

It is possible that neuroinflammation could be triggered by an imbalance in the gut microbiota due to the consumption of diets rich in fats and sugars [149] which could lead to an alteration in the "gut-brain axis", potentially leading to cognitive dysfunctions. Over the years, studies have shown how the gut microbiota influences body weight control [150]. Changes in gut microbiota composition that explain the development of obesity are related to increased calorie extraction and absorption, reduced secretion of anorexigenic hormones (GLP-1, PYY and leptin) and satiety, increased fat storage in adipose tissue and damage to the intestinal barrier, contributing with lipopolysaccharide translocation and in inflammation [150, 151]. However, the bacteria involved in this process have not yet been determined [151]. There are many factors that influence the composition of the gut microbiota, making it difficult to control in studies. Advances in microbiota science and analytical techniques may be useful in determining specifically the role that each type of bacteria plays in human metabolism and its relationship to the disease-health process [152].

4.2 Gut microbiota and lifestyle dementia risk factors

Smoking

The effects of smoking on the composition and diversity of the gut microbiota have been demonstrated in several prospective controlled and observational clinical studies in humans [153] and in animals [154]. In fact, cigarettes themselves are the direct cause of exposure of specific bacteria in the gut, leading to changes in the composition of the microbiota [155]. However, the exact cause-effect relationship between smoking and changes in the GI microbiome still needs further exploration, with high-throughput methodologies and controlled studies defining the role of microbiome modulation in immune response and systemic activation of proinflammatory pathways.

Physical inactivity

Studies report changes in gut microbiota composition in exercising versus sedentary mice [156]. In the only human study so far comparing athletes versus healthy controls, Clarke, Murphy [157] observed that the athletic group had a higher diversity of microbial species. However, no single effect of exercise on gut microbiota diversity could be determined, considering the high impact of diet on gut microbiota [157]. The role of these factors and the degree to which they might change the gut microbiota requires further research.

Alcohol consumption

Alcohol abuse facilitates intestinal bacterial overgrowth [158]. Specifically, heavy alcohol consumption promotes malabsorption in the small intestine and the disruption of bacterial colony balance, altering the metabolism of the intestinal microbiota [159]. In fact, alcohol-induced dysbiosis, alongside other problems, may increase individuals' susceptibility to AD [160]. However, additional studies are needed to elucidate the real causality between observed changes in the background of alcohol abuse and liver morbidities, as well as to determine the underlying mechanisms by which gut microbiota alterations ultimately affect AD.

Stress

Several studies suggest that psychosocial stressors may alter the composition of the enteric microbiota in a manner that correlates with changes in the presence of cytosines [130, 161]. New emerging research has provided support for the idea that psychosocial stressors may play a role in dysbiosis. In rats, early-life stressors result in disturbances on the microbiota that persist into adulthood [162]. Stressors experienced in adulthood appear to similarly alter the composition of the microbiota [161]. In particular, Lactobacillus species have been administered to rats to prevent stress factor-induced depletion of lactobacilli [163]. In primate models, exposure to early stressors is associated with a decrease in fecal bifidobacteria and lactobacilli [163]. In summary, studies suggest that psychosocial stressors are involved in dysbiosis. However, research in this area has been largely limited to animal models and human studies are needed. In fact, only one human study has been conducted, finding a reduction in lactobacillus concentrations in university students during exams [164].

Dairy products

Most of the health impacts of consuming dairy products may be related to their nutritional and/or caloric composition. In addition, it is possible that dairy products may also influence health outcomes through the gut microbiota. Animal studies, suggest that components of milk and dairy derivatives may generate changes in the composition of the gut microbiota [165]. However, there are few human studies demonstrating the impacts of certain dairy products on the gut microbiota (e.g. yogurt or acidified milk) [165] and, in general, they point to a modulation of the microbiota in favor of the host [166].

METH

METH administration has been shown to cause intestinal dysbiosis in rats [167] and has been linked to the gut-brain axis. It appears, that increased permeability in the BBB after using METH, allows gut-derived components to reach the brain [168]. Increases in gut permeability may be due to the inhibition of GI motility observed in METH users [169]. In the gut, dopamine and noradrenaline released by METH act on ENS receptors, resulting in decreased intestinal contractility, decreased intestinal smooth muscle tone and altering the migratory motor complex [170-172]. The release of neurotransmitters triggered by METH can also lead to the generation of oxidative stress molecules, including reactive oxygen species (ROS) and reactive nitrogen species (RNS) that can cause damage and death of enteric neurons and subsequent dysfunction of the GI system.

4.3 Gut microbiota and occupational exposure dementia risk factors

Air pollution

Exposure to air pollution has been associated with numerous intestinal diseases, such as appendicitis [173], inflammatory bowel disease (IBD) [174], and colorectal cancer [175]. Recent findings generally support that air pollution-induced intestinal pathologies are highly correlated with changes in the composition of the intestinal gut microbiota, particularly microbes which play an important role in the maintenance of intestinal integrity. In addition to the composition of gut microbiota, its diversity also takes an active role in the development of diseases. For example, recent studies have shown an association between air pollutants and the risk of T2D mediated in part by a reduced diversity of gut microbiota [176]. While studies report that exposure to PM2.5 increases the diversity of the gut microbiota [177], in most cases previously reviewed, it seems that it tends to reduce it [160]. This reduction in the diversity of the intestinal bacterial ecosystem, has been associated with intestinal diseases. For example, the diversity of the gut microbiota of patients with IBD appears to be lower in comparison to healthy controls, partly due to atmospheric pollution's effects on gut inflammation [178].

Pesticides

An increasing number of studies have demonstrated that gut microbiota can be disrupted and altered by several types of environmental pollutants [179], including some pesticides, suggesting that gut microbiota plays a role in pesticide-induced toxicity in non-target organisms [180].

Solvents

There is growing interest, but no longitudinal data, for the potential role of the gut microbiome as a risk modulator of PD through solvents exposure [181].

4.4 Gut microbiota and other dementia risk factors

TBI

TBI, inflammation, and AD. Indeed, significant changes in gut microbiota composition at the genus and species level in injured mice induce gut dysbiosis following TBI [182]. It appears that the systemic inflammatory response resulting from gut dysbiosis exerts an influence on vulnerable microglia after brain injury, further exacerbating neuroinflammation, and predisposing or accelerating the onset and progression of AD [183]. However, further studies are needed to determine whether TBI-induced alterations in the gut microbiota are direct or indirectly mediated through changes in nutrition.

Cancer

In general, studies refer three ways in which microbes and microbiota contribute to carcinogenesis by increasing or decreasing a host's risk: by altering the balance of host cell proliferation and death [184-186] by guiding the immune system function [187] or by influencing the metabolism of factors produced by the host, ingested food and pharmaceuticals [188].

Depression

In the last decade, considerable evidence has established that microglia-mediated inflammation is an important component of both AD and major depression [189]. It appears that elevated levels of proinflammatory cytokines and a shift in tryptophan use toward the microglial quinurenine pathway could be causative factors in both disorders [190]. Links between gut microbiota and depression have been reported in several studies on inflammatory states and gut barrier health [191]. Gut dysbiosis promotion of inflammation can have a role in multiple pathways into the CNS involved in the onset of depression. Increased inflammatory cytokines [192] lead to repercussions in the brain, which include the bypass of tryptophan from serotonin synthesis to the quinurenine pathway [193] and excitotoxic and neurotoxic effects [194]. However, sample sizes are small and no consensus has emerged on which bacterial taxa are most relevant to depression and it remains unclear whether depression is a prodromal symptom or a risk factor for AD.

5. DISCUSSION (Table 1)

This review examined studies that explored modifiable risk factors for dementia and the role of gut microbiota. After a full text review, the papers indicate that AD, PD, DLB and FTD have a different profile of modifiable risk factors for dementia. As reviewed above, most modifiable risk factors for dementia have been associated with alterations in the composition of the gut microbiota. More specifically, when gut dysbiosis occurs as a consequence of exposure to environmental factors such as antibiotic use, dietary changes, smoking, alcohol consumption, air pollution or TBI,

Table 1. Gut dysbiosis and modifiable risk factors for dementia

	Dementia risk factors	AD	PD	DLB	FTD	Gut dysbiosis link
Metabolic risk factors	Diabetes	Related [195-197]	Related [83-85]	Related [118]	Related [125]	Related [198]
	Hypertension	Related [32]	Related only in women [199]	Related [118]	Not related [125]	Related [145]
	Obesity	Related [34, 36-39]	Not related [91-94]	No data found	Related [200]	Related [201]
	Smoking	Related [48]	Inverse relationship [202]	Not related [117]	Not related [200]	Related [203]
Lifestyle risk factors	Less education	Related [204]	Related [205]	Not related [117]	Related [206]	Not related
	Alcohol intake	Related [47]	Inverse relationship [98]	Inverse relationship [207]	Not related [122] or inverse relationship [208], remains unclear	Related [209]
	Physical inactivity	Related [54]	Related [210]	Not enough data [211]	No data found	Related to obesity [212], hypertension or diabetes [213]
	Social isolation	Related [214]	No data found	No data found	No data found	Related to diet [212] or T2D [215].
Occupational exposure risk factors	Air pollution	Related [216, 217]	Limited evidence [207]	No data found	No data found	Related [218]
Other risk factors	Depression	Related [56]	Risk factor or a prodromal symptom, remains unclear [219]	Related [83]	Related [220]	Related to diet and physical inactivity [221].
	TBI	Related [222]	Related [223]	Not related [224]	Related [123]	Related [225]
	Hearing loss	Related [72, 226]	No data found	No data found	No data found	Related to social isolation or depression [227]

AD: Alzheimer's Disease. PD: Parkinson's Disease. DLB: Dementia with Lewy Bodies. FTD: Frontotemporal dementia. T2D: Type 2 diabetes. TBI: Traumatic brain injury.

colonization by intrinsic pathogens can disrupt the gut-brain axis, triggering host inflammatory responses and pathogen-mediated diseases such as dementia-related health conditions like diabetes, hypertension and obesity. This relationship is relevant since it emphasizes the active role of the gut microbiota in each modifiable risk factor for dementia. Furthermore, during aging, the composition of gut microbiota has been altered by a plurality of environmental factors, this would explain that aspects related to cognitive impairment and dementia are likely to appear [228].

The main factor contributing to gut microbiota diversity is diet [229]. Studies suggest that dietary changes may account for as much as 57% of the variations in the microbiota compared to genetic variations in the host (12%) [230]. Several studies demonstrate a close connection between diet and microbiota, indicating that variability in the composition of different diets will directly affect the gut microbiota [231]. Modulation of the gut microbiota represents a very interesting and promising field of research for the development of new preventive or curative strategies for dementia. In particular, new strategies for the treatment of dementia and related diseases by modulating the microbiota have been proposed (e.g., with the use of probiotics or other dietary interventions) or the use of pharmacological inhibitors/activators that directly target gut microbiota enzymes [232]. Probiotics are non-pathogenic microorganisms that are used as food ingredients to benefit host health and have been hypothesized as a promising treatment for dementia [233], with most experimental studies focusing on AD. These studies have shown improved oxidative stress, reduced cognitive impairment and reduced insulin resistance in rats [234-237]. Given that the gut microbiota has a plurality of links to modifiable dementia risk factors through metabolic and inflammatory pathways, interventions aimed at correcting the composition of the gut microbiota and focused on preventing dysbiosis could be an area of scientific interest, with the goal of slowing the widespread growth of dementia and other metabolic diseases more effectively.

However, in a systematic review and a meta-analysis by Kruger, Hillesheim [238] conclude that the current evidence on the use of probiotics and synbiotics for people with dementia is insufficient and requires further research. So far, the evidence supporting the potential relationship between gut microbiota and dementia relies on preclinical or cross-sectional studies in humans [24]. Some limitations in translating basic research results to humans are related to host-specific interactions with microbiota. To improve and enhance dementia research, large-scale epidemiological studies which investigate the highly complex interactions among microbiota, diet, modifiable risk factors for dementia, and aging should be conducted.

6. CONCLUSION

There is growing evidence of the contribution of the gut microbiota in dementia pathogenesis. Gut dysbiosis can lead to increased permeability of the intestinal barrier, triggering metabolic diseases and the progression of low-grade systemic inflammation. This mechanism can damage the blood brain barrier, promote neuroinflammation, neural injury and result in neurodegeneration. Bacteria or their products can move from the gastrointestinal tract to the central nervous system, especially in the elderly, when the composition of the gut microbiota is affected by many factors, such as diet, disease state and medications, so it is involved in much of the major modifiable risk factors implicated in the onset of dementia. It is possible that the gut microbiota is the cornerstone that allows us to access the treatment and prevention of a greater number of modifiable risk factors more effectively for dementia simultaneously.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This research was supported by the Spanish Ministry of Economy and Competitivity through Grant ID2019-103888RB-I00.

CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ACKNOWLEDGEMENTS

Declared None

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