Nutrition and Gut–Brain Pathways Impacting the Onset of Parkinson’s Disease

Damiano Terenzi 1,2,3,*, Anne-Katrin Muth 1,2 and Soyoung Q. Park 1,2,3,*

1 Department of Decision Neuroscience and Nutrition, German Institute of Human Nutrition (DIfE), Potsdam Rehbrücke, 14558 Nuthetal, Germany; anne.katrin.muth@gmail.com
2 Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Neuroscience Research Center, 10117 Berlin, Germany
3 Deutsches Zentrum für Diabetes, 85764 Muenchen-Neuherberg, Germany
* Correspondence: damianoterenzi@gmail.com (D.T.); soyoung.q.park@gmail.com (S.Q.P)

Abstract: An emerging body of literature suggests that long-term gut inflammation may be a silent driver of Parkinson’s disease (PD) pathogenesis. Importantly, specific nutritive patterns might improve gut health for PD risk reduction. Here, we review the current literature on the nutritive patterns and inflammatory markers as a predictor for early detection of PD. This knowledge might be used to foster the detection of early nutritive patterns and preclinical biomarkers to potentially alter PD development and progression.

Keywords: Parkinson’s disease; nutrition; inflammation; biomarker; prevention

1. Introduction

Parkinson’s disease (PD) is the second most common neurodegenerative disorder after Alzheimer’s disease and is now the fastest-growing neurological disease worldwide in terms of prevalence and disability [1,2]. According to the Global Burden of Disease (GBD) study, incident cases of PD in 2017 were ~1.02 million, compared with ~2.5 million in 1990 [2–4]. PD is more prevalent in men than women [5,6].

Clinically, PD is defined as a progressive movement disorder, including bradykinesia, rigidity, and rest tremor [7,8]. Furthermore, PD is often characterized by different nonmotor symptoms affecting sensory perception, cognition, mood, motivation, autonomic functions, and sleep, among others [9–13].

Pathologically, the hallmark of PD is the aggregation of misfolded α-synuclein (aSyn) protein (a neuronal protein modulating neurotransmitter release), otherwise known as Lewy bodies. Lewy bodies are a primary cause of dopaminergic loss and related motor impairments in PD [14]. In particular, the development of α-Syn pathology in dopaminergic neurons within the substantia nigra pars compacta (SNc) [14], a brain region involved in modulating motor movement, is associated with the motor deficits (e.g., tremor and bradykinesia) observed in PD [15]. A sustained inflammatory response is a key pathological feature of PD. Microglia are a class of neuroglia (neuronal support cell) situated in the central nervous system (CNS). These cells are the immune cells of the CNS and consequently play a key role in neuroinflammation [16,17]. Human and animal postmortem studies, as well as positron emission tomography (PET) studies, have shown that there is a strong microglia activation in several regions of the PD brain, including the SNc and the striatum [16–19]. A prolonged microglia activation can have detrimental effects on the brain such as the increased expression of proinflammatory cytokines (small cell proteins involved in cell signaling such as interleukin-6 (IL-6) and interferon gamma (IFN-γ)) [20]. It has been suggested that these increased levels of cytokines contribute to the degeneration of the nigrostriatal DA neurons in PD [21]. Hence, excessive or misfolded α-Syn-induced
neurotoxicity in PD may be partially mediated by altered microglia activity [20]. Astrocytes are glia cells contributing to the maintenance of brain homeostasis and neuronal metabolism. Like microglia, astrocytes respond to inflammatory stimulations and can themselves induce inflammation [22]. It has been proposed that PD may be partially due to astrocyte dysfunction [17, 23]. In particular, α-Syn aggregation in PD can trigger microglia inflammatory responses. These proinflammatory mediators released by microglia can in turn activate astrocytes, which further magnify the inflammatory responses [20].

Regarding the etiology of PD, it is likely that, for most cases, the interplay between genetic and environmental factors contributes to the causation of the disease [24, 25]. Among the environmental factors, there has been growing research interest on the relationship between the gut microbiota and PD [26–31]. The gut microbiota is the generic term referring to more than 100 trillion microbes (mostly bacteria but also viruses, fungi, and protozoa) that are present in the human gastrointestinal tract [32]. The accumulating evidence showing a bidirectional link between bacteria in the gut and neurons in the CNS (known as the “microbiota–gut–brain axis”) has resulted in an ongoing redefinition of health and disease, including neurodegenerative diseases [33, 34]. In particular, recent studies have suggested that alterations in the composition of the gut microbiota (known as gut dysbiosis) might be a potential trigger for neuroinflammation, which in turn may lead to the development of PD [35–38]. In line with this hypothesis, α-Syn aggregation may start in the gut and then be spread from the gastrointestinal tract to the midbrain via the vagus nerve, resulting in the selective death of SNc [38, 39]. Hence, alterations of the gut microbiota in PD may be used as an early biomarker of the disease [40–42]. Indeed, PD is often preceded by gastrointestinal symptoms, and gastrointestinal disorders accompany the disease [43]. Thus, testing blood and fecal biomarkers of gut inflammation and gut barrier permeability in PD might improve the accuracy of current clinical diagnostic criteria.

Investigating nutritive patterns and their association with PD is a further interesting and emerging approach [44, 45]. Increasing evidence suggests that specific nutritive patterns may influence (positively or negatively) the microbiota–gut–brain axis and, in turn, the risk of developing PD [44, 46]. These nutritive patterns include dietary macronutrients (carbohydrates, proteins, and fats) [35, 46, 47], the intake levels of omega-3 (ω3) fatty acids [48], fruits, and vegetables [45, 49], and the adherence to specific diets (e.g., Mediterranean diet or Western diet) [44, 50].

In this review, we first discuss the relationship between gut dysbiosis and PD pathogenesis [51], focusing on several possible biomarkers of inflammation. Next, we review emerging studies suggesting a link between long-term nutritive factors and diet in adulthood with subsequent risk of developing PD.

2. Long-Term Gut Inflammation: A Silent Driver of Parkinson’s Disease Pathogenesis

2.1. Current Evidence on the Gut–Brain Hypothesis of Parkinson’s Disease

The CNS and the enteric nervous system (ENS) are connected through a bidirectional network, which is known as the gut–brain axis [52] (see Figure 1). This axis is crucial in maintaining homeostasis of both CNS and ENS, and it comprises multiple pathways of communication including endocrine (through the hypothalamic–pituitary–adrenal (HPA) axis) [53], immune (cytokines) [54], and neural (through the vagus nerve) [39] pathways. Regarding the neural pathway, the vagus nerve is one of the most direct pathways linking the gut and the brain and vice versa. This nerve, being part of the parasympathetic system, is characterized by both afferent (sensory, 80% of the fibers) and efferent (motor, 20% of the fibers) fibers [39, 55]. Importantly, the gut microbiota can reach the CNS and, in turn, alter behavior through the vagus nerve. Indeed, microbiota metabolites can be detected through the afferent fibers of the vagus nerve. This gut information is in turn transferred to the CNS in order to produce a response [52, 55]. Accumulating evidence suggests that this microbiome–gut–brain axis might play a key role in the underlying pathological mechanisms of PD [35, 36, 41].
At the beginning of the 2000s, human postmortem studies led by Braak and colleagues suggested for the first time that such α-Syn pathology is not confined to the CNS and is also detectable in the ENS [56–58], which is a division of the peripheral nervous system that controls the gastrointestinal system [59]. The evidence of α-Syn pathology also in this system lent support to the theory that PD pathology could be initiated in the ENS [36] and that it could be spread from the gastrointestinal tract to the midbrain via the vagus nerve, resulting in the selective death of SNc dopamine neurons [57,60] (see Figure 1).

Growing experimental (in vitro and in vivo studies) and clinical evidence supports Braak’s hypothesis [61,62]. For example, as firstly observed by Braak and colleagues (2003), most PD patients (about 70% of patients) [63] develop gastrointestinal disorders such as constipation, dysphagia, and gastroesophageal reflux [43,56,64]. Strikingly, these gastrointestinal dysfunctions (particularly constipation and delayed gastric emptying) can be detected up to 20 years prior to PD diagnosis [37]. Furthermore, in line with Braak’s hypothesis on the role of the vagus nerve in spreading α-Syn aggregations from the gut to the brain [45], epidemiological studies have found that vagotomy can decrease PD risk [65,66]. Similar results have been found in animal models. Gastrointestinal disorders have been reported in animal models of PD at both early and advanced stages of the
disease [67–70]. Furthermore, α-Syn aggregations were observed in animal models during both early and advanced PD [61,71,72]. Strikingly, truncal vagotomy and α-Syn deficiency prevented the spread of α-Syn aggregations from the gut to the brain and associated neurodegeneration and behavioral deficits in mice models of PD [60].

Despite this experimental and clinical evidence supporting Braak’s hypothesis, it may not accurately describe the development of PD in all patients [61,73]. Thus, future longitudinal studies are needed to investigate the disease progression, particularly in preclinical and prodromal stages of PD.

2.2. Inflammatory Biomarkers of Parkinson’s Disease

In an interesting study by Scheperjans et al. (2015), the authors compared the fecal microbiomes of 72 PD patients and 72 controls. Results suggested an altered microbiota in PD participants by showing a reduction in their number of Prevotellaceae bacteria compared to controls. Strikingly, this alteration was associated with the severity of the motor symptoms [29,35]. Further findings linking gut dysbiosis and PD pathogenesis showed that PD patients may exhibit not only a decreased abundance of Prevotella but also an increased abundance of Lactobacillaceae [35,74]. These alterations may be associated with reduced levels of ghrelin, an important gut hormone involved in the survival and efficacy of dopaminergic neurons [74]. Another study showed altered fecal microbiota in PD patients compared to healthy matched controls. In particular, the study found that an abundance of Bacteroides (Gram-negative bacteria present in the gut microbiome) is associated with the severity of motor symptoms in PD [30]. Lipopolysaccharide (LPS) is a biomarker of Gram-negative bacterial infection that can cause inflammatory responses [41,75]. Interestingly, studies have found high serum LPS levels in PD patients [41,76], which can reflect altered intestinal permeability already in the early stages of the disease [76]. Furthermore, several studies on animal models of PD have shown that the administration of LPS (stereotaxic, systemic, or intranasal) can reproduce the specific motor features of PD [41,76]. Similarly, other studies on PD have used LPS-binding protein (LBP), a protein that binds to bacterial LPS, finding lower plasma LBP levels in PD patients compared to healthy controls [42,77]. Overall, these findings support the role of LPS-elicited neurotoxicity in PD [41,77].

Other possible inflammatory markers of PD are calprotectin and zonulin. The first is a marker of inflammation, while the second is a junction protein, which, if modulated by proinflammatory signals (e.g., LPS), can lead to an increase in intestinal membrane permeability [78]. Interestingly, recent findings showed that both fecal and serum levels of calprotectin and zonulin are elevated in patients with PD [78–80]. In line with this evidence, animal models of dopamine degeneration and human studies have suggested that peripheral inflammation could contribute to the etiology and evolution of PD [81,82]. A substantial number of studies have started to investigate peripheral inflammation due to the easy access to blood samples. For example, it has been shown that PD patients may show altered levels of blood proinflammatory cytokines, which are signaling molecules released by immune cells such as helper T cells (Th) and macrophages. Specifically, enhanced levels of cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), interleukin 10 (IL-10), and interleukin 8 (IL-8) have been found in PD patients when compared with healthy controls [82–84]. Similar to cytokines, chemokines (a family of small cytokines or signaling proteins) are also altered in PD. In particular, elevated levels of chemokine C–X–C motif ligand 1 (CX3CL1) have been reported in PD patients when compared with controls [82]. Furthermore, two studies have reported significant elevated levels of C–X–C motif chemokine ligand 12 (CXCL12) in PD patients [82,85].

Overall, the evidence here reported suggests (see Figure 1) that gut dysbiosis and inflammatory processes/barrier dysfunction may facilitate the mechanism underlying dopaminergic neurodegeneration in PD. As mentioned in the previous section, symptoms such as constipation can precede the motor symptoms by even more than a decade; therefore, the investigation of the biomarkers related to gut dysbiosis might be particularly relevant in preclinical models of PD. However, prospective evidence is scarce [31,78,86],...
and it is still not clear whether gut dysbiosis is a cause or an effect of the disease. Thus, future research in preclinical and prodromal cohorts and longitudinal observations are still warranted.

3. Nutritive Patterns as a Predictor of Early Detection of Parkinson’s Disease

Nutritional intake has been shown to define the healthy function of the CNS as a major lifestyle factor [47]. On the flip side, emerging studies suggest that neurodegenerative disorders such as PD may be partially due to the influence of unhealthy nutrition among other factors [44,45]. This raises the possibility of using dietary manipulations as a valuable strategy to preserve brain function and prevent neurodegeneration [45,50]. Different mechanisms may be related to the effect of nutrition on the development/progression of PD. For example, recent epidemiological findings have shown that some nutritive patterns can impact the vulnerability to oxidative stress and inflammation, which in turn may increase the risk of developing PD [35,46,87]. In contrast, other nutritive patterns may have neuroprotective effects that may decrease the risk of PD [50,88–91].

3.1. Mitochondria and Reactive Oxygen Species

Mitochondria are cell organelles that generate most of the cell’s energy through respiration and oxidative phosphorylation. The resultant energy is stored in adenosine triphosphate (ATP) molecules [92]. Thus, the mitochondria are involved in energy metabolism, stress response, and cell death [93]. Over time, mitochondrial DNA mutations and net productions of reactive oxygen species (ROS) accumulate. Specifically, ROS are a large family of oxidant molecules derived from the consumption and utilization of oxygen. Damaged mitochondria may lead to reduced ATP production and increased ROS accumulation, thereby contributing to aging [94]. Moreover, mitochondrial dysfunction plays a role in the etiology of PD [95] and might even be an early feature of the disease [96,97]. Mitochondrial dysfunction not only results in increased ROS levels and lower energy production [96] but also induces apoptosis, leading to degeneration of dopaminergic neurons [98]. In addition, other mitochondrial abnormalities are associated with PD, including mitochondrial electron transport chain impairment and changes in mitochondrial morphology and dynamics [99,100]. ROS play an important role in cellular and signaling pathways. However, excessive amounts that are not balanced by antioxidants contribute to oxidative stress [101], thereby leading to cellular degeneration [102] and cognitive decline [103]. In a recent paper, van Rensburg and colleagues (2021) proposed a toxic feedback loop that links uncurbed ROS and iron in the substantia nigra, due to aging, environmental exposure, and/or genetic predisposition [104]. Iron is needed for processes such as oxygen transportation, oxidative phosphorylation, myelin production, and neurotransmitter synthesis in the brain [105]. Accumulation of iron induces oxidative stress by generating ROS and can lead to apoptosis [106] and ferroptosis [107,108]; hence, it is implicated in PD [109]. Importantly [92,98,102], dietary intake can buffer or exacerbate the consequences of high levels of ROS [47], as further discussed in sections below.

3.2. Macronutrient Intake

Macronutrients—carbohydrates, dietary fatty acids, and proteins—impact cognitive functioning [110] and metabolic health via multiple pathways such as glucose metabolism and ROS levels associated with inflammation [47]. Such pathways are, in turn, linked with PD pathology [111–113] (see Figure 1).

Intake of specific macronutrients, as well as the diet’s macronutrient composition (i.e., the relative ratio of proteins, carbohydrates, and fatty acids), may affect several of these pathways [114–116], thereby linking dietary intake with PD risk. For instance, excessive protein intake has been shown to increase ROS in mice [117] while protein restrictions in rats reduced ROS damage in the liver [118]. Similarly, carbohydrate metabolism can impact ROS levels via glucose levels [119]. The effect of fatty acids on ROS depends on their type. For instance, high intakes of saturated fatty acids (SFAs) are proinflammatory [120],
whereas polyunsaturated fatty acids (PUFAs) reduce ROS and have anti-inflammatory properties [121,122]. Accordingly, high omega-3 PUFA intake has been associated with lower risk PD risk [48,88,90,123], as well as with lower cognitive impairment, dementia, and depression [48,124], which are often comorbid with PD [45].

There is increasing scientific evidence on the possible efficacy of PUFA supplementation in slowing the cognitive and physical decline in PD [45,48]. However, randomized, double-blind, placebo-controlled clinical trials are scarce [124–126] and involve patients with an established diagnosis of PD, meaning that the pathology has already occurred, and neurons are compromised. Thus, this may limit the efficacy of possible dietary treatment in advanced stages of PD.

3.3. Micronutrient Intake

Vitamin D serum levels are affected by both sun exposure and dietary intake (primarily from animal products and fortified foods). Inadequate vitamin D levels play a role in both chronic and neurodegenerative diseases, including PD [127], with sustained insufficiency playing a crucial role in PD pathogenesis [128]. Furthermore, vitamin D has been proposed to be a key driver of aging processes, including mitochondrial dysfunction, oxidative stress, and inflammation [129] (see Figure 1). In addition to these key processes that are affected in PD, lack of vitamin D also leads to central loss of dopaminergic neurons [127], as well as delayed gastric emptying in PD [127,130]. Two randomized controlled trials investigated the safety and efficacy of vitamin D3 supplementation in patients with PD [131,132]. The first study found that a treatment schedule of 1200 IU for 12 months was both safe and preventative of further deterioration in motor and nonmotor symptom domains using a total of 137 patients [131]. Another study investigated a supplementation schedule of 10,000 IU for 8 weeks, finding that younger participants (aged 52–66) benefitted in terms of motor symptoms, but older participants (aged 67–86) did not [132].

Other vitamins that have been studied in PD include B vitamins and antioxidant vitamins such as vitamins C, E, and A. Regarding vitamin B, studies have found that vitamin B6 is a critical cofactor for a wide range of biochemical reactions, including the synthesis of dopamine [133]. Therefore, it has been suggested that vitamin B6 may have a role in the development of PD. Accordingly, in a study by De Lau et al. (2006), vitamin B6 intake was associated with a reduced risk of developing PD. However, this result was observed only among smokers [134]. Indeed, some studies have found that smoking is associated with a reduced risk of developing PD as tobacco may regulate striatal activity through the dopaminergic system [135,136]. Thus, evidence linking vitamin B6 with the risk of developing PD should be interpreted with caution. Moreover, no associations have been found between the intake of other B vitamins such as B9 and B12 and the risk of developing PD [137]. Furthermore, studies examining the association between levels of vitamins C, E, and A and the risk of PD produced conflicting results. One study suggested that higher vitamin E intake may be associated with a reduced risk of developing PD [138]. However, no associations between the intake of vitamins C and E and incidence of PD were observed in another study [139]. Similarly, another study by Paganini and colleagues (2015) did not find associations between the intake of vitamins A and C and PD risk [140].

To sum up, according to the abovementioned studies, vitamin D may be protective against the development of PD. However, evidence regarding other vitamins intake and PD is mixed, and future studies are warranted.

3.4. Dietary Patterns

Recent epidemiological studies have suggested that diet can increase or decrease the risk of developing PD via the microbiota–gut–brain axis [44,45,50] (see Figure 1). For example, it has been shown that the Western diet is one of the greatest risk factors for PD. This diet is usually characterized by a high intake of energy-dense foods, with a high content of proteins, saturated fat, refined grains, sugar, alcohol, and salt, as well as a reduced consumption of omega-3 (ω3) fatty acids, fruits, and vegetables [49,50,141].
Several foods that are part of the Western diet (e.g., beef, ice cream, fried foods, and cheese) have been associated with PD progression [49,50]. Furthermore, high total energy intake (another characteristic of the Western diet) was positively associated with the risk of developing PD in a meta-analysis including nine clinical studies [142]. It has been proposed that Western diet gut dysbiosis and altered intestinal barrier function can induce neuroinflammation [50,143–145]. In a study on a mouse model of PD, a high-energy diet such as the Western diet led to decreased parasympathetic functioning and α-Syn accumulation in the brainstem [146]. As mentioned earlier in this review, the α-Syn accumulation is, in turn, associated with the death of dopaminergic neurons in the SNc in PD. Moreover, a typical Western high-fat diet could increase insulin resistance, which in turn could impair nigrostriatal dopamine function in a rat model of PD [147]. This finding is in line with several clinical studies reporting that motor symptoms of PD are worse in individuals with comorbid type 2 diabetes [148–150]. Overall, the findings described above suggest that several mechanisms may contribute to the effects of Western diet on PD risk including neuroinflammation and insulin resistance. Importantly, gut dysbiosis and intestinal barrier alterations induced by the Western diet can increase blood levels of LPS (see Section 2.2). Altered levels of LPS can, in turn, activate Toll-like receptors (TLRs), a family of receptors that constitute a sort of immune system against bacteria [151]. Overstimulation of this system may provoke proinflammatory reactions, as well as enteric neuroglial activation, eventually eliciting α-Syn pathology [50,151].

Unlike the Western diet, the Mediterranean diet usually consists of plant-based foods, vegetables, legumes, fruits, nuts, seeds, fish, monounsaturated fats from olive oil, and whole grains [152,153]. Interestingly, the Mediterranean diet has been associated with a reduced risk of PD [88,91,154,155]. It has been suggested that this diet may improve intestinal barrier health and normalize insulin levels via the increased release of short-chain fatty acids (SCFA) (due to the high intake of fiber-rich foods—typical of the Mediterranean diet) [50]. All these factors may reduce neuroinflammation and, thus, the risk of developing PD [50,156]. Accordingly, it has been shown that PD patients have reduced production of SCFAs when compared to matched controls [156,157]. However, future randomized clinical trials are needed to confirm the role of the Mediterranean diet in reducing the risk of PD.

The ketogenic diet (KD) is a high-fat low-carbohydrate diet that has been used as a nonpharmacologic approach to improve a range of health markers in metabolic disorders [158–161], as well as a treatment for intractable epilepsy [158,162–164]. In recent years, studies have suggested that the KD can be therapeutically useful for adjunctive therapy for PD [165]. In particular, this diet may have neuroprotective effects. The KD consists of a very high fat content with very little carbohydrate intake and normal to low protein intake. The exact ratios depend on the specific type of KD. Metabolically, KD increases ketone bodies and reduces oxidative stress brought on by excessive ROS [46]. Evidence from animal models of PD showed promise, as ketone bodies acted neuroprotectively [166] and improved motor skills [167]. Evidence in humans is limited to two studies. The first was a feasibility study in five PD patients who consumed a KD for 4 weeks [87]. All patients showed a decrease in the Unified Parkinson Disease Rating Scale (UPDRS) total scores; however, without a control group, these findings cannot be interpreted [87]. More recently, a randomized controlled trial followed 47 patients with PD that were assigned either to a 1750 kcal KD or to a low-fat diet lasting 8 weeks each. Participants in the KD diet group showed significant improvements on the nonmotor daily living experiences part of the MDS-UPDRS, as well as a nonsignificant trend for improvement on the motor examination part compared to the low-fat diet group. The authors concluded that KD shows promise complementary to L-dopa treatment [168]. Although these promising results suggest that the KD may have beneficial effects in PD, the main obstacles are the adherence to the diet and the short- and long-term effects [46]. Importantly, results from larger randomized clinical trials have not yet been reported [158], and future studies are needed.
4. Discussion and Conclusions

The current review provides an initial understanding of the role of the gut–brain axis in the development of PD. At the same time, this review offers a broader view of the systemic consideration of how nutrition may play a significant role in gut health and inflammation, with studies showing that specific nutritive patterns can increase or decrease the risk of developing PD. In particular, this review evaluates current evidence regarding the possible therapeutic utility of altering the gut microbiota through diet as a promising approach to prevent or modify PD progression.

Firstly, we discussed the increasing evidence suggesting that nonmotor symptoms such as gastrointestinal dysfunctions may precede PD diagnosis by more than a decade, lending support to Braak’s hypothesis that PD pathology may start in the gut and then spread via the vagus nerve to the brain. In particular, we reviewed and discussed evidence from epidemiological studies and animal models supporting this hypothesis. We also consider how this hypothesis may not accurately describe the development of PD in all patients. Hence, we suggest that future longitudinal studies are needed to investigate PD progression, particularly in preclinical and prodromal stages of the disease.

Secondly, we showed how the possibility that PD pathology may start in the gut is also supported by recent discoveries of close links between PD and inflammatory biomarkers. Accordingly, we discussed the current literature on these biomarkers by focusing on fecal and blood markers of gut dysbiosis in PD. More in detail, we reported that gut dysbiosis revealed by Prevotellaceae, Lactobacillaceae, Bacteroides, LPS, calprotectin, and zonulin levels emerged as some of the most consistent altered biomarkers in PD. Furthermore, peripheral inflammation has been revealed in PD by measuring the levels of blood inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6, IL-10, and IL-8) and chemokines (e.g., CX3CL1 and CXCL12). Overall, the evidence here reported suggests that gut dysbiosis and related inflammatory processes/barrier dysfunction may facilitate the mechanism underlying dopaminergic neurodegeneration in PD. We suggest that further prospective longitudinal studies could help to possibly identify alterations in these biomarkers already in the early stages of PD. Importantly, the many crucial biomarkers discussed in this review have the potential to improve the diagnosis of PD. However, the different biomarker profiles may not only vary significantly across people but could also change during the different stages of the disease. Future studies should test the accuracy of combined biomarkers for a more precise diagnosis and treatment of PD [169].

Thirdly, we summarized the evidence showing the impact of nutrition on the gut–brain axis and its possible role in the development of PD. Among different nutritive patterns, we focused on specific macro- and micronutrients, as well as on different dietary patterns, which have been recently shown to be possible modulating factors of neurodegeneration in PD.

Specifically, regarding the macronutrients, we discussed the role of carbohydrates, dietary fatty acids, and proteins and their impact on cognitive functioning and metabolic health in PD, possibly via multiple pathways such as glucose metabolism and ROS levels. In particular, we discussed the increasing scientific evidence on the possible efficacy of PUFA supplementation in slowing the cognitive and physical decline in PD. Furthermore, we summarized and discussed recent data suggesting that vitamin intake (particularly vitamin D) may be associated with the risk of developing PD.

Lastly, we revised several prospective longitudinal studies showing associations between dietary patterns and the risk of PD. Collectively, we reported that the Western diet has been associated with an increased risk of developing PD, possibly via diet-induced neuroinflammation and insulin resistance. Conversely, the Mediterranean diet (characterized by a high intake of dietary fibers) may improve intestinal barrier health and normalize insulin levels via the increased release of SCFA. All these factors may reduce neuroinflammation and, thus, the risk of developing PD. We also discussed recent human and animal evidence showing that the ketogenic diet has promise for treating PD, as ketones may have neuroprotective effects by reducing oxidative stress.
To conclude, the gut–brain axis discussed in this review is a hot topic in the study of PD. Over the past 5 years, studies testing the gut–brain hypothesis in the etiology and progress of PD have markedly expanded, and several systematic reviews and meta-analysis on this topic have been published [27,35–38,41]. However, as a future direction, much more work is needed to be able to develop new therapeutic approaches that may act on the gut microbiota composition such as probiotic or dietary therapies, as well as hopefully even preventative approaches. Regarding probiotics, these are living microbes that can have anti-inflammatory or antioxidant properties. Some recent studies have suggested that probiotics can represent a good dietary intervention for neurodegenerative diseases such as PD and Alzheimer’s disease (AD) [170–172]. Specifically, probiotics may promote an increase in anti-inflammatory factors and a decrease in proinflammatory cytokines [172,173], thereby contributing to reducing intestinal inflammation in PD [172]. However, findings from clinical trials in neurodegenerative diseases are inconsistent [170,173–176]. Additionally, evidence on the probiotic mechanisms of actions came mostly from animal studies [172,177], and future studies are needed to investigate their effects in humans [172]. In addition to the use of probiotics as a potential therapy in PD, as mentioned earlier, in this review, we highlighted areas where future research on the effect of nutritive patterns on PD is highly relevant. In particular, the role of the Mediterranean diet and the use of PUFA supplementation in PD should be further investigated as they may positively influence the onset of motor and nonmotor symptoms of the disease.

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References
1. Dorsey, E.R.; Sherer, T.; Okun, M.S.; Bloem, B.R. The Emerging Evidence of the Parkinson Pandemic. *J. Park. Dis.* 2018, 8, S3–S8. [CrossRef]
2. Feigin, V.L.; Vos, T.; Alahdab, F.; Amit, A.M.L.; Bärnighausen, T.W.; Beghi, E.; Beheshti, M.; Chavan, P.P.; Criqui, M.H.; Desai, R.; et al. Burden of Neurological Disorders Across the US From 1990–2017: A global burden of disease study. *JAMA Neurol.* 2021, 78, 165–176. [CrossRef] [PubMed]
3. James, S.L.; Abate, D.; Abate, K.H.; Abay, S.M.; Abbafati, C.; Abbasi, N.; Abbastabar, H.; Abd-Allah, F.; Abdela, J.; Abdelalim, A.; et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018, 392, 1789–1858. [CrossRef]
4. Ou, Z.; Pan, J.; Tang, S.; Duan, D.; Yu, D.; Nong, H.; Wang, Z. Global Trends in the Incidence, Prevalence, and Years Lived with Disability of Parkinson’s Disease in 204 Countries/Territories From 1990 to 2019. *Front. Public Health* 2021, 9, 776847. [CrossRef] [PubMed]
5. Miller, I.N.; Cronin-Golomb, A. Gender differences in Parkinson’s disease: Clinical characteristics and cognition. *Mov. Disord.* 2010, 25, 2695–2703. [CrossRef] [PubMed]
6. Moisan, F.; Kab, S.; Mohamed, F.; Canonico, M.; Le Guern, M.; Quintin, C.; Carcaillon, L.; Nicolau, J.; Duport, N.; Singh-Manoux, A.; et al. Parkinson disease male-to-female ratios increase with age: French nationwide study and meta-analysis. *J. Neurol. Neurosurg. Psychiatry* 2015, 87, 952–957. [CrossRef]
7. Armstrong, M.J.; Okun, M.S. Diagnosis and Treatment of Parkinson Disease: A Review. *JAMA* 2020, 323, 548–560. [CrossRef]
8. Fox, S.H.; Katzschnegler, R.; Lim, S-Y.; Barton, B.; de Bie, R.M.A.; Seppi, K.; Coelho, M.; Sampaio, C.; Movement Disorder Society Evidence-Based Medicine Committee. International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson’s disease. *Mov. Disord.* 2018, 33, 1248–1266. [CrossRef] [PubMed]
9. Chaudhuri, K.R.; Healy, D.G.; Schapira, A.H.V. Non-motor symptoms of Parkinson’s disease: Diagnosis and management. Lancet Neurol. 2006, 5, 235–245. [CrossRef]

10. Aiello, M.; Eleopra, R.; Rumiati, R.I. Body Weight and Food Intake in Parkinson’s Disease. A Review of the Association to Non-Motor Symptoms. Appetite 2015, 84, 204–211. [CrossRef]

11. Aiello, M.; Terenzi, D.; Furlanis, G.; Catalan, M.; Manganotti, P.; Eleopra, R.; Belgrado, E.; Rumiati, R.I. Deep brain stimulation of the subthalamic nucleus and the temporal discounting of primary and secondary rewards. J. Neurol. 2019, 266, 1113–1119. [CrossRef] [PubMed]

12. Terenzi, D.; Catalan, M.; Polverino, P.; Bertolotti, C.; Manganotti, P.; Rumiati, R.I.; Aiello, M. Effects of tDCS on reward responsiveness and valuation in Parkinson’s patients with impulse control disorders. J. Neurol. 2022, 269, 1557–1565. [CrossRef] [PubMed]

13. Terenzi, D.; Rumiati, R.I.; Catalan, M.; Antonutti, L.; Furlanis, G.; Garlasco, P.; Polverino, P.; Bertolotti, C.; Manganotti, P.; Aiello, M. Reward sensitivity in Parkinson’s patients with binge eating. Park. Relat. Disord. 2018, 51, 79–84. [CrossRef]

14. Meade, R.M.; Fairlie, D.P.; Mason, J.M. Alpha-synuclein structure and Parkinson’s disease—Lessons and emerging principles. Mol. Neurodegener. 2019, 14, 29. [CrossRef] [PubMed]

15. Schaeffer, E.; Kluge, A.; Böttner, M.; Zunke, F.;Arnold, P. Alpha Synuclein Connects the Gut-Brain Axis in Parkinson’s Disease Patients—A View on Clinical Aspects, Cellular Pathology and Analytical Methodology. Front. Cell Dev. Biol. 2020, 8, 573696. [CrossRef] [PubMed]

16. Sanchez-Guajardo, V.; Tentillier, N.; Romero-Ramos, M. The relation between α-synuclein and microglia in Parkinson’s disease: Recent developments. Neuroscience 2015, 302, 47–58. [CrossRef]

17. Kam, T.-I.; Hinkle, J.T.; Dawson, T.M.; Dawson, V.L. Microglia and astrocyte dysfunction in parkinson’s disease. Neurobiol. Dis. 2020, 144, 105028. [CrossRef] [PubMed]

18. Lavisse, S.; Goutal, S.; Wimberley, C.; Tonietto, M.; Bottlaender, M.; Gervais, P.; Kuhnast, B.; Peyronneau, M.-A.; Barret, O.; Lagarde, J.; et al. Increased microglial activation in patients with Parkinson disease using [18F]-DPA714 TSPO PET imaging. Park. Relat. Disord. 2020, 82, 29–36. [CrossRef]

19. Gelders, G.; Baekelantd, V.; Van Der Perren, A. Linking Neuroinflammation and Neurodegeneration in Parkinson’s Disease. J. Immunol. Res. 2018, 2018, 4784268. [CrossRef]

20. Wang, Q.; Liu, Y.; Zhou, J. Neuroinflammation in Parkinson’s disease and its potential as therapeutic target. Transl. Neurodegener. 2015, 4, 19. [CrossRef]

21. Nagatsu, T.; Mogi, M.; Ichinose, H.; Togari, A. Changes in cytokines and neurotrophins in Parkinson’s disease. J. Neurosci. 2003, 53, S16–S25. [CrossRef]

22. Linnerbauer, M.; Wheeler, M.A.; Quintana, F.J. Astrocyte Crosstalk in CNS Inflammation. Neuron 2020, 108, 608–622. [CrossRef] [PubMed]

23. Booth, H.D.; Hirst, W.D.; Wade-Martins, R. The Role of Astrocyte Dysfunction in Parkinson’s Disease Pathogenesis. Trends Neurosci. 2017, 40, 358–370. [CrossRef]

24. Pang, S.Y.Y.; Ho, P.W.L.; Liu, H.F.; Leung, C.T.; Li, L.; Chang, E.E.S.; Ramsden, D.B.; Ho, S.L. The Interplay of Aging, Genetics and Neuroinflammation and Neurodegeneration in Parkinson’s disease—Lessons and emerging principles. Mol. Neurodegener. 2019, 266, 1113–1119. [CrossRef]

25. Warner, T.T.; Schapira, A.H.V. Genetic and Environmental Factors in the Cause of Parkinson’s Disease. Adv. Res. Neurosci. 2015, 2, 277–290. [CrossRef]

26. Schaeffer, E.; Kluge, A.; Böttner, M.; Zunke, F.; Arnold, P. Alpha Synuclein Connects the Gut-Brain Axis in Parkinson’s Disease Patients—A View on Clinical Aspects, Cellular Pathology and Analytical Methodology. Front. Cell Dev. Biol. 2020, 8, 573696. [CrossRef] [PubMed]

27. Romano, S.; Savva, G.M.; Bedarf, J.R.; Charles, I.G.; Hildebrand, F.; Narbad, A. Meta-analysis of the Parkinson’s disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Park. Dis. 2021, 7, 27. [CrossRef]

28. Uyar, G.Ö.; Yildiran, H. A nutritional approach to microbiota in Parkinson’s disease. Biosci. Microbiota Food Health 2019, 38, 115–127. [CrossRef]

29. Schaper, J.; Aho, V.; Pereira, P.A.B.; Koskinen, K.; Paulin, L.; Pekkonen, E.; Haapaniemi, E.; Kaakkola, S.; Eerola-Rautio, J.; Pohja, M.; et al. Gut microbiota are related to Parkinson’s disease and clinical phenotype. Mov. Disord. 2015, 30, 350–358. [CrossRef]

30. Lin, C.-H.; Chen, C.-C.; Chiang, H.-L.; Liou, J.-M.; Chang, C.-M.; Lu, T.-P.; Chuang, E.Y.; Tai, Y.-C.; Cheng, C.; Lin, H.-Y.; et al. Altered gut microbiota and inflammatory cytokine responses in patients with Parkinson’s disease. J. Neuroinflamm. 2019, 16, 129. [CrossRef]

31. Vascellari, S.; Melis, M.; Palmas, V.; Pisano, S.; Serra, A.; Perra, D.; Santoru, M.; Oppo, V.; Cusano, R.; Uva, P.; et al. Clinical Phenotypes of Parkinson’s Disease Associate with Distinct Gut Microbiota and Metabolome Enterotypes. Biomolecules 2021, 11, 144. [CrossRef] [PubMed]

32. Matijašić, M.; Meštrović, T.; Paljetak, H.Č.; Perić, M.; Barešić, A.; Verbanac, D. Gut Microbiota beyond Bacteria-Mycobiome, Virome, Archaeome, and Eukaryotic Parasites in IBD. Int. J. Mol. Sci. 2020, 21, 2668. [CrossRef] [PubMed]

33. Mayer, E.A.; Knight, R.; Mazmanian, S.K.; Cryan, J.F.; Tillisch, K. Gut Microbes and the Brain: Paradigm Shift in Neuroscience. J. Neurosci. 2014, 34, 15490–15496. [CrossRef] [PubMed]

34. Murciano-brea, J.; Garcia-montes, M.; Geuna, S.; Herrera-rincon, C. Gut Microbiota and Neuroplasticity. Cells 2021, 10, 2084. [CrossRef] [PubMed]
35. Alfonsetti, M.; Castelli, V.; d’Angelo, M. Are We What We Eat? Impact of Diet on the Gut–Brain Axis in Parkinson’s Disease. *Nutrients* 2022, 14, 380. [CrossRef]
36. Klann, E.M.; Dissanayake, U.; Gurrala, A.; Farrer, M.; Shukla, A.W.; Ramirez-Zamora, A.; Mai, V.; Vedam-Mai, V. The Gut-Brain Axis and Its Relation to Parkinson’s Disease: A Review. *Front. Aging Neurol.* 2021, 13, 782802. [CrossRef]
37. Travaglì, R.A.; Browning, K.N.; Camilleri, M. Parkinson disease and the gut: New insights into pathogenesis and clinical relevance. *Nat. Rev. Gastroenterol. Hepatol.* 2020, 17, 673–685. [CrossRef]
38. Houser, M.C.; Tansey, M.G. The Gut-Brain Axis: Is Intestinal Inflammation a Silent Driver of Parkinson’s Disease Pathogenesis? *Npj Parkinson’s Dis.* 2017, 3, 3. [CrossRef]
39. Fülling, C.; Dinan, T.G.; Cryan, J.F. Gut Microbe to Brain Signaling: What Happens in Vagus. *Neuron* 2019, 101, 998–1002. [CrossRef]
40. Chen, S.-J.; Chi, Y.-C.; Ho, C.-H.; Yang, W.-S.; Lin, C.-H. Plasma Lipopolysaccharide-Binding Protein Reflects Risk and Progression of Parkinson’s Disease. *J. Parkinson’s Dis.* 2021, 11, 1129–1139. [CrossRef]
41. Bhattacharyya, D.; Bhunia, A. Gut-Brain axis in Parkinson’s disease etiology: The role of lipopolysaccharide. *Chem. Phys. Lipids* 2020, 235, 105029. [CrossRef] [PubMed]
42. Pal, G.D.; Shaikh, M.; Forsyth, C.B.; Ouyang, B.; Keshavarzian, A.; Shannon, K.M. Abnormal lipopolysaccharide binding protein as marker of gastrointestinal inflammation in Parkinson disease. *Front. Neurosci.* 2015, 9, 306. [CrossRef] [PubMed]
43. Lubomski, M.; Davis, R.L.; Sue, C.M. Gastrointestinal dysfunction in Parkinson’s disease. *J. Neurol.* 2020, 267, 1377–1388. [CrossRef] [PubMed]
44. Pal, G.D.; Shaikh, M.; Forsyth, C.B.; Ouyang, B.; Keshavarzian, A.; Shannon, K.M. Abnormal lipopolysaccharide binding protein as marker of gastrointestinal inflammation in Parkinson disease. *Front. Neurosci.* 2015, 9, 306. [CrossRef] [PubMed]
45. Mischley, L.K. Nutrition and Nonmotor Symptoms of Parkinson’s Disease. *Int. Rev. Neurobiol.* 2019, 134, 1143–1161. [CrossRef]
46. Włodarek, D. Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer’s Disease and Parkinson’s Disease). *Nutrients* 2019, 11, 169. [CrossRef]
47. Muth, A.-K.; Park, S.Q. The impact of dietary macronutrient intake on cognitive function and the brain. *Clin. Nutr.* 2021, 40, 3999–4010. [CrossRef]
48. Avallone, R.; Vitale, G.; Bertolotti, M. Omega-3 Fatty Acids and Neurodegenerative Diseases: New Evidence in Clinical Trials. *Int. J. Mol. Sci.* 2019, 20, 4256. [CrossRef]
49. Chu, C.-Q.; Yu, L.-L.; Chen, W.; Tian, F.-W.; Zhai, Q.-X. Dietary patterns affect Parkinson’s disease via the microbiota-gut-brain axis. *Trends Food Sci. Technol.* 2021, 116, 90–101. [CrossRef]
50. Jackson, A.; Forsyth, C.B.; Shaikh, M.; Voigt, R.M.; Engen, P.A.; Ramirez, V.; Keshavarzian, A. Diet in Parkinson’s Disease: Critical Role for the Microbiome. *Front. Neurol.* 2019, 10, 380. [CrossRef]
51. Keshavarzian, A.; Engen, P.; Bonvenga, S.; Cilia, R. The Gut Microbiome in Parkinson’s Disease: A Culprit or a Bystander? *Prog. Brain Res.* 2020, 252, 357–450. [PubMed]
52. 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, 203–209. [PubMed]
53. Stengel, A.; Taché, Y. Gut-Brain Neuroendocrine Signaling Under Conditions of Stress—Focus on Food Intake-Regulatory Mediators. *Front. Endocrinol.* 2018, 9, 498. [CrossRef] [PubMed]
54. Fung, T.C. The microbiota-immune axis as a central mediator of gut-brain communication. *Neurobiol. Dis.* 2019, 136, 104714. [CrossRef]
55. Bonaz, B.; Bazin, T.; Pellissier, S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front. Neurosci.* 2018, 12, 49. [CrossRef]
56. Braak, H.; Del Tredici, K.; Rüb, U.; de Vos, R.A.; Steur, E.N.J.; Braak, E. Staging of brain pathology related to sporadic Parkinson’s disease. *Neurobiol. Aging* 2003, 24, 197–211. [CrossRef]
57. Braak, H.; del Tredici, K. Neuropathological Staging of Brain Pathology in Sporadic Parkinson’s Disease: Separating the Wheat from the Chaff. *J. Parkinson’s Dis.* 2017, 7, S71–S85. [CrossRef]
58. Braak, H.; Ghebremedhin, E.; Rüb, U.; Bratzke, H.; Del Tredici, K. Stages in the development of Parkinson’s disease-related pathology. *Cell Tissue Res.* 2004, 318, 121–134. [CrossRef]
59. Spencer, N.J.; Hu, H. Enteric Nervous System: Sensory Transduction, Neural Circuits and Gastrointestinal Motility. *Nat. Rev. Gastroenterol. Hepatol.* 2020, 17, 338–351. [CrossRef]
60. Kim, S.; Kwon, S.-H.; Kam, T.-I.; Panicker, N.; Karuppagounder, S.S.; Lee, S.; Lee, J.H.; Kim, W.R.; Kook, M.; Foss, C.A.; et al. Transneuronal Propagation of Pathological α-Synuclein from the Gut to the Brain Models Parkinson’s Disease. *Neuron* 2019, 103, 627–641.e7. [CrossRef]
61. Riedtijk, C.D.; Perez-Pardo, P.; Garssen, J.; Van Wezel, R.J.A.; Kranevel, A.D. Exploring Braak’s Hypothesis of Parkinson’s Disease. *Front. Neurol.* 2017, 8, 37. [CrossRef] [PubMed]
62. Dagher, A.; Zeighami, Y. Testing the Protein Propagation Hypothesis of Parkinson Disease. *J. Exp. Neurol.* 2018, 12, 1179069518786715. [CrossRef] [PubMed]
63. Pfeiffer, R.F. Gastrointestinal Dysfunction in Parkinson’s Disease. *Curr. Treat. Options Neurol.* 2018, 20. [CrossRef] [PubMed]
64. Makaroff, L.; Gunn, A.; Gervasoni, C.; Richy, F. Gastrointestinal Disorders in Parkinson’s Disease: Prevalence and Health Outcomes in a US Claims Database. *J. Park. Dis.* 2011, 1, 65–74. [CrossRef] [PubMed]
65. Svensson, E.; Horváth-Puhó, E.; Thomsen, R.W.; Djurhuus, J.C.; Pedersen, L.; Borghammer, P.; Sorensen, H.T. Vagotomy and subsequent risk of Parkinson’s disease. *Ann. Neurol.* 2015, 78, 522–529. [CrossRef]

66. Liu, B.; Pedersen, N.L.; Tillander, A.; Ludvigsson, J.F.; Ekboon, A.; Svenningsson, P.; Chen, H.; Wirdefeldt, K. Vagotomy and Parkinson Disease. A Swedish Register-Based Matched-Cohort Study. *Neurology* 2017, 88, 1996–2002. [CrossRef]

67. Fleming, S.M. Behavioral and immunohistochemical effects of chronic intravenous and subcutaneous infusions of varying doses of rotenone. *Exp. Neurol.* 2004, 187, 418–429. [CrossRef]

68. Greene, J.G.; Noorian, A.R.; Srinivasan, S. Delayed gastric emptying and enteric nervous system dysfunction in the rotenone model of Parkinson’s disease. *Exp. Neurol.* 2009, 218, 154–161. [CrossRef]

69. Kuo, Y.-M.; Li, Z.; Jiao, Y.; Gaborit, N.; Pani, A.K.; Orrison, B.M.; Bruneau, B.; Giasson, B.I.; Smeyne, R.J.; Gershon, M.D.; et al. Extensive enteric nervous system abnormalities in mice transgenic for artificial chromosomes containing Parkinson disease-associated α-synuclein gene mutations precede central nervous system changes. *Hum. Mol. Genet.* 2010, 19, 1633–1650. [CrossRef]

70. Anderson, G.; Noorian, A.R.; Taylor, G.; Anitha, M.; Bernhard, D.; Srinivasan, S.; Greene, J.G. Loss of enteric dopaminergic neurons and associated changes in colon motility in an MPTP mouse model of Parkinson’s disease. *Exp. Neurol.* 2007, 207, 4–12. [CrossRef]

71. Drolet, R.E.; Cannon, J.; Montero, L.; Greenamyre, J.T. Chronic rotenone exposure reproduces Parkinson’s disease gastrointestinal neuropathology. *Neurobiol. Dis.* 2009, 36, 96–102. [CrossRef] [PubMed]

72. Wang, L.; Magen, I.; Yuan, P-Q.; Subramaniam, S.R.; Richter, F.; Chesselet, M.-F.; Taché, Y. Mice overexpressing wild-type human alpha-synuclein display alterations in colonic myenteric ganglia and defecation. *Neurogastroenterol. Motil.* 2012, 24, e425–e436. [CrossRef] [PubMed]

73. Kalaitzakis, M.E.; Graebner, M.B.; Gentleman, S.M.; Pearce, R.K.B. Evidence against a reliable staging system of alpha-synuclein pathology in Parkinson’s disease. *Neuropathol. Appl. Neurobiol.* 2009, 35, 125–126. [CrossRef] [PubMed]

74. Ye, X.; Zhu, M.; Che, X.; Wang, H.; Liang, X.-J.; Wu, C.; Xue, X.; Yang, J. Lipopolysaccharide induces neuroinflammation in microglia by activating the MTOR pathway and downregulating Vps34 to inhibit autophagosome formation. *J. Neuroinflamm.* 2020, 17, 18. [CrossRef] [PubMed]

75. Xue, X.; Zhang, S.; Cao, C.; Loh, Y.P.; Cheng, Y. Aberrations in Peripheral Inflammatory Cytokine Levels in Parkinson Disease. *Brain Behav. Immun.-Health* 2018, 25, 104–107. [CrossRef]

76. Deng, I.; Corrigan, F.; Zhai, G.; Zhou, X.-F.; Bobrovskaya, L. Lipopolysaccharide animal models of Parkinson’s disease: Recent progress and relevance to clinical disease. *Brain Behav. Immun.-Health* 2020, 4, 100060. [CrossRef] [PubMed]

77. Umamahesan, C.; Augustin, A.D.; Hayee, B.H.; Ibrahim, M.A.; Taylor, D.; Weller, C.; Charlett, A.; Dobbs, R.J.; Dobbs, S.M. Intestinal inflammation and compromised barrier function in idiopathic parkinsonism: Scenario captured by systematic review. *Neuroimmunol. Neuroinflamm.* 2021, 2020, S331–S344. [CrossRef]

78. Dumitrescu, L.; Marta, D.; Dănău, A.; Letfer, A.; Tulbă, D.; Cozma, L.; Manole, E.; Gherghiceanu, M.; Ceafalan, L.C.; Popescu, B.O. Serum and Fecal Markers of Intestinal Inflammation and Intestinal Barrier Permeability Are Elevated in Parkinson’s Disease. *Front. Neurosci.* 2021, 15, 689723. [CrossRef]

79. Schwizert, A.; Spiegel, J.; Dillmann, U.; Grundmann, D.; Bürmann, J.; Faßbender, K.; Schäfer, K.-H.; Unger, M.M. Fecal markers of intestinal inflammation and intestinal permeability are elevated in Parkinson’s disease. *Park. Relat. Disord.* 2018, 50, 104–107. [CrossRef]

80. Mulak, A.; Koszewicz, M.; Panek-Jeziora, M.; Koziorowska-Gawron, E.; Budrewicz, S. Fecal Calprotectin as a Marker of the Gut Immune System Activation Is Elevated in Parkinson’s Disease. *Front. Neurosci.* 2019, 13, 992. [CrossRef]

81. Deleidi, M.; Gasser, T. The role of inflammation in sporadic and familial Parkinson’s disease. *Cell. Mol. Life Sci.* 2013, 70, 4259–4273. [CrossRef] [PubMed]

82. Li, Y.; Yang, Y.; Zhao, A.; Luo, N.; Niu, M.; Kang, W.; Xie, A.; Lu, H.; Chen, L.; Liu, J. Parkinson’s Disease Peripheral Immune Biomarker Profile: A Multicentre, Cross-Sectional and Longitudinal Study. *J. Neuroinflamm.* 2022, 19, 116. [CrossRef] [PubMed]

83. Qin, X.-Y.; Zhang, S.-P.; Cao, C.; Loh, Y.P.; Cheng, Y. Aberrations in Peripheral Inflammatory Cytokine Levels in Parkinson Disease. *JAMA Neurol.* 2016, 73, 1316–1324. [CrossRef]

84. Reale, M.; Iarlori, C.; Thomas, A.; Gambi, D.; Perfetti, B.; Di Nicola, M.; Onofri, M. Peripheral cytokines profile in Parkinson’s disease. *Brain Behav. Immun.* 2009, 23, 55–63. [CrossRef]

85. Bagheri, V.; Khorrameladalaz, H.; Hassanshahi, G.; Moghadam-Ahmadi, A.; Vakilian, A. CXCL12 and CXCR4 in the Peripheral Blood of Patients with Parkinson’s Disease. *Neuromunomodulation* 2018, 25, 201–205. [CrossRef]

86. Stolzenberg, E.; Berry, D.; Yang, D.; Lee, E.Y.; Kroemer, A.; Kaufman, S.; Wong, G.C.; Oppenheim, J.J.; Sen, S.; Fishbein, T.; et al. A Role for Neuronal Alpha-Synuclein in Gastrointestinal Immunity. *J. Innate Immun.* 2017, 9, 456–463. [CrossRef] [PubMed]

87. Vanitallie, T.B.; Nonas, C.; Di Rocco, A.; Boyar, K.; Hyams, K.; Heymsfield, S.B. Treatment of Parkinson disease with diet-induced hyperketonemia: A feasibility study. *Nutr. Metab.* 2005, 64, 728–730. [CrossRef]

88. Gao, X.; Chen, H.; Fung, T.T.; Logroscino, G.; Schwartzchild, M.A.; Hu, F.B.; Ascherio, A. Prospective study of dietary pattern and risk of Parkinson disease. *Am. J. Clin. Nutr.* 2007, 86, 1486–1494. [PubMed]

89. Samantha, N.; Liu, Y.; Neumann, S.; Gao, X. Nicotine from cigarette smoking and diet and Parkinson disease: A review. *Transl. Neurodegener.* 2017, 6, 18. [CrossRef]

90. De Lau, L.M.L.; Bornebroek, M.; Wittteman, J.C.M.; Hofman, A.; Koudstaal, P.J.; Breteler, M.M.B. Dietary fatty acids and the risk of Parkinson disease: The Rotterdam Study. *Nutrients* 2005, 64, 2040–2045. [CrossRef]
120. Guilleminot-LeGris, O.; Muccioli, G.G. Obesity-Induced Neuroinflammation: Beyond the Hypothalamus. *Trends Neurosci.* 2017, 40, 237–253. [CrossRef]
121. Calon, F.; Cicchetti, F. Can we prevent Parkinson’s disease with n-3 polyunsaturated fatty acids? *Futur. Lipidol.* 2008, 3, 133–137. [CrossRef]
122. Da Boit, M.; Hunter, A.; Gray, S.R. Fit with good fat? The role of n-3 polyunsaturated fatty acids on exercise performance. *Metabolism* 2016, 66, 45–54. [CrossRef] [PubMed]
123. Abbott, R.D.; Ross, G.W.; White, L.R.; Sanderson, W.T.; Burchfiel, C.M.; Kashon, M.; Sharp, D.S.; Masaki, K.H.; Curb, J.D.; Petrovitch, H. Environmental, Life-Style, and Physical Precursors of Clinical Parkinson’s Disease: Recent Findings from the Honolulu-Asia Aging Study. *J. Neurol.* 2003, 250, III30–III39. [CrossRef] [PubMed]
124. da Silva, T.M.; Munhoz, R.P.; Alvarez, C.; Naliwaiko, K.; Kiss, Á.; Andreatti, R.; Ferraz, A.C. Depression in Parkinson’s disease: A double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J. Affect. Disord.* 2008, 111, 351–359. [CrossRef]
125. Pomponi, M.; Loria, G.; Salvati, S.; Di Biase, A.; Villella, C.; Righino, E.; Ciciarelli, C.; Bria, P.; La Torre, G.; et al. DHA omega-3 fatty acids and vitamin E co-supplementation on gene expression related to inflammation, insulin and lipid in patients with Parkinson’s disease: A randomized, double-blind, placebo-controlled trial. *Clin. Neurol. Neurosurg.* 2018, 176, 116–121. [CrossRef]
126. Tamtaji, O.R.; Taghizadeh, M.; Aghadavod, E.; Mafi, A.; Dadgostar, E.; Kakhaki, R.D.; Abolhassani, J.; Asemi, Z. The effects of buford, T.W. (Dis)Trust your gut: The gut microbiome in age-related inflammation, health, and disease. *Microbiome* 2017, 5, 80. [CrossRef] [PubMed]
146. Griffioen, K.J.; Rothman, S.M.; Ladenheim, B.; Wan, R.; Vranis, N.; Hutchison, E.; Okun, E.; Cadet, J.L.; Mattson, M.P. Dietary energy intake modifies brainstem autonomic dysfunction caused by mutant α-synuclein. *Neurobiol. Aging* 2012, 34, 928–935. [CrossRef] [PubMed]

147. Morris, J.; Bomhof, G.; Gores, B.; Davis, V.; Kim, J.; Lee, P.-P.; Brooks, W.; Gerhardt, G.; Geiger, P.; Stanford, J. Insulin resistance impairs nigrostriatal dopamine function. *Exp. Neurol.* 2011, 231, 171–180. [CrossRef]

148. Chohan, H.; Senkevich, K.; Patel, R.K.; McP, J.P.B.; Jacobs, B.M.; Ciga, S.B.; Gan-Or, Z.; Noyce, A.J. Type 2 Diabetes as a Determinant of Parkinson’s Disease Risk and Progression. *Mov. Disorder.* 2021, 36, 1420–1429. [CrossRef]

149. Lu, L.; Fu, D.-L.; Li, H.-Q.; Liu, A.-J.; Li, J.-H.; Zheng, G.-Q. Diabetes and Risk of Parkinson’s Disease: An Updated Meta-Analysis of Case-Control Studies. *PLoS ONE* 2014, 9, e85781. [CrossRef]

150. Maluf, F.C.; Feder, D.; Carvalho, A.A.D.S. Analysis of the Relationship between Type II Diabetes Mellitus and Parkinson’s Disease: A Systematic Review. *PARK. DIS. 2019*, 2019, 4951379. [CrossRef]

151. Caputi, V.; Giron, M.C. Microbiome-Gut-Brain Axis and Toll-Like Receptors in Parkinson’s Disease. *Int. J. Mol. Sci.* 2018, 19, 1689. [CrossRef]

152. Widmer, R.J.; Flammer, A.J.; Lerman, L.O.; Lerman, A. The Mediterranean Diet, Its Components, and Cardiovascular Disease. *Am. J. Med.* 2015, 128, 229–238. [CrossRef] [PubMed]

153. Jannasch, F.; Kröger, J.; Schulze, M.B. Dietary Patterns and Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Prospective Studies. *J. Nutr. 2017*, 147, 1174–1182. [CrossRef] [PubMed]

154. Maraki, M.I.; Yannakoulia, M.; Stamelou, M.; Stefanis, L.; Xiromerisiou, G.; Kosmidis, M.H.; Dardiotis, E.; Hadjigeorgiou, G.M.; Sakka, P.; Anastasiou, C.A.; et al. Mediterranean diet adherence is related to reduced probability of prodromal Parkinson’s disease. *Mov. Disorder.* 2019, 34, 48–57. [CrossRef] [PubMed]

155. Sääksjärvi, K.; Knk, P.; Lundqvist, A.; Mannistö, S.; Heliovaa, M.; Rissman, H.; Järvinen, R. A cohort study on diet and the risk of Parkinson’s disease: The role of food groups and diet quality. *Br. J. Nutr.* 2012, 109, 329–337. [CrossRef]

156. Silva, Y.P.; Bernardi, A.; Frozza, R.L. The Role of Short-Chain Fatty Acids from Gut Microbiota in Gut-Brain Communication. *Front. Endocrinol. 2020*, 11, 25. [CrossRef]

157. Unger, M.M.; Spiegel, J.; Dillmann, K.-U.; Grundmann, D.; Philippeit, H.; Bürmann, J.; Faßbender, K.; Schwiertz, A.; Schäfer, K.H. Short chain fatty acids and gut microbiota differ between patients with Parkinson’s disease and age-matched controls. *Parkinsonism Relat. Disord.* 2016, 32, 66–72. [CrossRef]

158. Gough, S.M.; Casella, A.; Ortega, K.J.; Hackam, A.S. Neuroprotection by the Ketogenic Diet: Evidence and Controversies. *Front. Nutr. 2021*, 8, 782657. [CrossRef]

159. Cooper, M.A.; Menta, B.W.; Perez-Sanchez, C.; Jack, M.M.; Khan, Z.W.; Ryals, J.M.; Winter, M.; Wright, D.E. A ketogenic diet reduces metabolic syndrome-induced allodynia and promotes peripheral nerve growth in mice. *Exp. Neurol.* 2018, 306, 149–157. [CrossRef]

160. Arsayd, A.; Idris, I.; Rasyid, A.A.; Usman, R.A.; Faradillah, K.R.; Latif, W.O.U.; Lubis, Z.I.; Aminuddin, A.; Yustisia, I.; Djabir, Y.Y. Long-Term Ketogenic Diet Induces Metabolic Acidosis, Anemia, and Oxidative Stress in Healthy Wistar Rats. *J. Nutr. Metab.* 2020, 2020, 3642035. [CrossRef]

161. Choi, Y.J.; Jeon, S.-M.; Shin, S. Impact of a Ketogenic Diet on Metabolic Parameters in Patients with Obesity or Overweight and with or without Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Nutrients 2020*, 12, 2005. [CrossRef] [PubMed]

162. Yang, R.; Wen, J.; Wei, W.; Chen, H.; Cao, D.; Chen, L.; Lu, X.; Hu, Y.; Huang, T.; Li, B.; et al. Improving the effects of ketogenic diet therapy in children with drug-resistant epilepsy. *Seizure 2021*, 94, 183–188. [CrossRef] [PubMed]

163. Martin-McGill, K.J.; Bresnahan, D.; Levy, R.G.; Cooper, P.N. Ketogenic Diets for Drug-Resistant Epilepsy. *Cochrane Database Syst. Rev.* 2018, 11, CD001903. [CrossRef]

164. Meira, I.D.; Romão, T.T.; Prado, H.J.P.D.; Krüger, L.T.; Pires, M.E.P.; Da Conceição, P.O. Ketogenic Diet and Epilepsy: What We Know So Far. *Front. Neurosci.* 2019, 13, 5. [CrossRef]

165. Choi, A.; Hallett, M.; Ehrlich, D. Nutritional Ketosis in Parkinson’s Disease—A Review of Remaining Questions and Insights. *Neurotherapeutics 2021*, 18, 1637–1649. [CrossRef] [PubMed]

166. Cheng, B.; Yang, X.; An, L.; Gao, B.; Liu, X.; Liu, S. Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating glutathione in a rat model of Parkinson’s disease. *Brain Res. 2009*, 1286, 25–31. [CrossRef] [PubMed]

167. Shafi, S.; Najmi, S.; Aliasgharpour, H.; Mahmoudi, J.; Sadigh-Etemad, S.; Farhoudi, M.; Baniasadi, N. The efficacy of the ketogenic diet on motor functions in Parkinson’s disease: A rat model. *Iran. J. Neurol.* 2021, 1174–1182. [PubMed]

168. Phillips, M.C.; Murtagh, D.K.; Gilbertson, L.J.; Asztely, F.J.; Lynch, C.D. Low-fat versus ketogenic diet in Parkinson’s disease: A pilot randomized controlled trial. *Mov. Disorder.* 2018, 33, 1306–1314. [CrossRef]

169. He, R.; Yan, X.; Guo, J.; Xu, Q.; Tang, B.; Sun, Q. Recent Advances in Biomarkers for Parkinson’s Disease. *Front. Aging Neurosci.* 2018, 10, 305. [CrossRef]

170. Castelli, V.; D’Angelo, M.; Quintiliani, M.; Benedetti, E.; Cifone, M.G.; Cimini, A. The Emerging Role of Probiotics in Neurodegenerative Diseases: New Hope for Parkinson’s Disease? *Neural Regen. Res.* 2021, 16, 628–634. [CrossRef]

171. Xiang, S.; Ji, J.L.; Li, S.; Cao, X.P.; Xu, W.; Tan, L.; Tan, C.C. Efficacy and Safety of Probiotics for the Treatment of Alzheimer’s Disease, Mild Cognitive Impairment, and Parkinson’s Disease: A Systematic Review and Meta-Analysis. *Front. Aging Neurosci.* 2022, 14, 730036. [CrossRef] [PubMed]
172. Tan, A.H.; Hor, J.W.; Chong, C.W.; Lim, S. Probiotics for Parkinson’s disease: Current evidence and future directions. *JGH Open* 2020, 5, 414–419. [CrossRef]

173. Klaenhammer, T.R.; Kleerebezem, M.; Kopp, M.V.; Rescigno, M. The impact of probiotics and prebiotics on the immune system. *Nat. Rev. Immunol.* 2012, 12, 728–734. [CrossRef] [PubMed]

174. Kobayashi, Y.; Sugahara, H.; Shimada, K.; Mitsuyama, E.; Kuhara, T.; Yasuoka, A.; Kondo, T.; Abe, K.; Xiao, J.-Z. Therapeutic potential of *Bifidobacterium* breve strain A1 for preventing cognitive impairment in Alzheimer’s disease. *Sci. Rep.* 2017, 7, 13510. [CrossRef]

175. Barichella, M.; Pacchetti, C.; Bolliri, C.; Cassani, E.; Iorio, L.; Pusani, C.; Pinelli, G.; Privitera, G.; Cesari, I.; Faierman, S.A.; et al. Probiotics and prebiotic fiber for constipation associated with Parkinson disease. *Neurology* 2016, 87, 1274–1280. [CrossRef] [PubMed]

176. Akbari, E.; Asemi, Z.; Daneshvar Kakhaki, R.; Bahmani, F.; Kouchaki, E.; Tamtaji, O.R.; Hamidi, G.A.; Salami, M. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer’s disease: A randomized, double-blind and controlled trial. *Front. Aging Neurosci.* 2016, 8, 256. [CrossRef] [PubMed]

177. Wang, H.; Lee, I.-S.; Braun, C.; Enck, P. Effect of Probiotics on Central Nervous System Functions in Animals and Humans: A Systematic Review. *J. Neurogastroenterol. Motil.* 2016, 22, 589–605. [CrossRef]