

## Review

# Parkinson's Disease and the Gut: Symptoms, Nutrition, and Microbiota

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**Abstract.** Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide, characterized by symptoms of bradykinesia, rigidity, postural instability, and tremor. Recently, there has been a growing focus on the relationship between the gut and the development of PD. Emerging to the forefront, an interesting concept has developed suggesting that the initial pathophysiological changes occur in the gastrointestinal tract before changes are seen within the brain. This review is aimed at highlighting the relationship between PD and the gastrointestinal tract, along with the supporting evidence for this. Firstly, we will focus on the gastrointestinal conditions and symptoms which commonly affects patients, including both upper and lower gastrointestinal issues. Secondly, the impact of nutrition and diet on neurological health and PD physiology, with particular emphasis on commonly consumed items including macronutrients and micronutrients. Finally, variability of the gut microbiome will also be discussed and its link with both the symptoms and signs of PD. The evidence presented in this review highly suggests that the initial pathogenesis in the gut may proceed the development of prodromal PD subtypes, and therefore building on this further could be imperative and lead to earlier diagnosis with new and improved therapeutics.

Keywords: Gut, microbiota, nutrition, Parkinson's disease

## BACKGROUND

Parkinson's disease (PD) is characterized by degeneration of the dopaminergic neurons of the substantia nigra and spread of alpha-synuclein enriched Lewy bodies (LB) to other cortical and subcortical brain areas, particularly the basal ganglia [1, 2]. The development of LB arises from an initial template formed from pathological alpha-synuclein, which instigates seeding of nearby alpha-synuclein proteins. This triggers a shift from a benign  $\alpha$ -helical structure to a toxic, insoluble  $\beta$ -pleated sheet structure protein, which aggregates to form LB [3]. These

seeds may then disseminate throughout nearby and distal neurons, leading to the development and sites of Lewy pathology (LP) [4].

The nigrostriatal pathway plays an important role in the pathophysiology of PD. The levels of dopamine decrease due to the breakdown of the substantia nigra, in particular, within an area called the pars compacta [2]. The dopaminergic changes in PD lead to the characteristic motor symptoms of PD such as muscle rigidity, bradykinesia, tremor, and postural instability [5].

However, other symptoms, such as anosmia and autonomic dysfunction are also highly common in PD [6]. Of particular importance, gut symptoms have received increased attention with new evidence suggesting that PD pathophysiology may start in the gut. This highlights an underexplored area of research and will therefore be a focus of this review.

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The gastrointestinal microbiota could play an important role in the development of PD as a link between the intestinal microbiota, neurodevelopment and neurological diseases are increasingly recognized. Neurological function is influenced by neuropeptides, neuronal hormones and many other metabolites produced within the gut, whilst the gut itself is heavily influenced by the central nervous system (CNS) [7]. The gut microbiome, made up of bacteria, fungi and archaea form a diverse community that is highly variable and unique to each individual and encompasses a number of crucial functions, including maintaining metabolic homeostasis, vitamin biosynthesis, and drug modification [8].

Gut dysbiosis, defined broadly as an alteration of the gut microbiome, has been associated with a number of inflammatory-driven diseases including inflammatory bowel disease (IBD), Alzheimer's disease (AD), and obesity [9]. Furthermore, dysbiosis is associated with the development of low-grade inflammation, increased oxidative stress, cellular degeneration, and disturbance of the blood-brain barrier [10]. Particular focus has aimed at investigating the microbiome in PD, with increasing evidence demonstrating differences in the gut microbiota composition between PD patients and healthy controls. The intestinal microbiota in PD may also be involved in the modulation of  $\alpha$ -synuclein aggregation and may further play a role in short chain fatty acid metabolism,  $\alpha$ -synuclein pathology and microglial activation [8, 11, 12] Finally, levels of certain bacterial species may influence PD symptomology [13].

This review will cover the theory and evidence behind the reasons why PD may start within the gut, the influence of nutrition on the risk of PD and how variances in gut microbiota composition may contribute to the PD origins and associated symptoms. Our evidence for this review is sourced from key papers published and cited in this field, including case-based discussions to meta-analyses.

## BRAAK AND THE GUT THEORY

The onset of sporadic PD is unknown, but the Braak hypothesis offers to explain a mechanism for this. Braak et al. proposed the dual-hit theory which suggests that sporadic PD starts in two places—the neurons of the olfactory system and the gastrointestinal tract (GIT) [14]. This review will only focus on the GIT aspect of Braak's theory and will only briefly touch upon the involvement of the olfactory network.

Braak hypothesized that a foreign pathogen, either bacterial or viral, triggers a response which leads to LP that affects the olfactory and GIT system [15]. Subsequently, neurons allow the retrograde transmission of alpha-synuclein enriched LB to the CNS from the olfactory and the vagus nerve, respectively. The transmission of alpha-synuclein pathology is believed to spread across the nervous system through a 'prion-like' fashion [16].

A fundamental aspect of Braak's theory is the movement of alpha-synuclein from the enteric nervous system (ENS) to the CNS via the vagus nerve and dorsal motor nucleus of vagus within the medulla oblongata [17]. The ENS is a network of neurons within the gut wall which works separately from the CNS [18]. The ENS consists of two plexuses, myenteric and submucosal, and has a number of different roles including regulating motility, mucosal blood flow and water transport [19]. The vagal nerve plays an important part in functions of the body, e.g., stimulating salivation, gut peristalsis, and bladder contraction [20].

Composed of six stages, disease progression is determined by the Braak staging system. Each stage represents a site of LP, starting from the ENS and ascending through the brain. Stages 1 and 2 demonstrate hindbrain pathology, whilst stages 3 and 4 involve the midbrain, where motor symptoms become recognizable. Cognitive symptoms are apparent in stages 5 and 6 as the full neocortex is affected [21].

Braak's theory dovetails with clinical evidence of gastrointestinal symptoms, including dysphagia, constipation, early satiety, bloating, and non-specific abdominal pain. The presence of LP within GIT neurons or the ENS has been reported [22–32] and LP can be seen within the ENS up to 10–20 years prior to the diagnosis of PD, suggesting gastrointestinal dysfunction may precede the first onset of motor symptoms [33]. Two independent histological studies have reported an abundance of alpha-synuclein within the vermiform appendix and have suggested that an appendectomy, may both lower the risk of developing PD and delay the age of onset [34]. A large, nested control study conducted by Liu et al also concluded that an appendectomy was associated with a lower risk of PD [35], but interestingly, a 2021 meta-analysis demonstrated no significant difference in emergence of PD between patients with and those without an appendectomy history [36]. Moreover, LP findings have also been replicated in animal models, with aggregations of alpha-synuclein found in the GIT of both early and advanced PD [37, 38].

Retrospective autopsy-based studies have shown LP in the peripheral vagal nerves [39] and this is significant as swallowing and excessive salivation difficulties are common in PD patients [40]. Interestingly, truncal vagotomy has been suggested as a protective factor in reducing the long-term risk of PD [41]. Although, such a radical procedure and its implications need to be clearly further investigated [42].

Despite the evidence suggesting that PD may start within the gut, limitations exist to this concept. For the prion hypothesis to work in the Braak staging criteria, Lewy pathology must be seen in the lower brainstem prior to the appearance of Lewy pathology in higher structures, e.g., stage 1 involves the dorsal motor nucleus of vagus in the medulla oblongata as the first site of spread within the brain. However, patients have been found to have pathology in higher structures of the brain, including severe disease in the substantia nigra (stage 3) without involvement of the lower brainstem [43]. Therefore, perhaps alternative routes of LP spread may be present in the development of PD pathology. Furthermore, alpha-synuclein is also a major histopathological hallmark of a number of different diseases such as AD, dementia with Lewy bodies, and multiple system atrophy, but these conditions do not show the same distribution of pathology according to the prion hypothesis and Braak staging system [4, 44]. The question also remains whether the gut microbiota has an impact on the genesis of alpha-synuclein within the gut.

Another key aspect is the movement of alpha-synuclein from the ENS to CNS. This mechanism has been countered by a study which suggests the transmission of pathology actually moves from the brain to the GIT founded on results displaying higher density levels of phosphorylated alpha-synuclein in the spinal cord and peripheral nerves compared with the gut [45]. Moreover, not all PD patients have shown LP within the ENS [46]. Over the course of the disease progression, younger patients had pathology associated with the Braak staging model over the course of their disease compared with elderly patients with a shorter disease whose symptoms did not correlate [47]. Consequently, this could mean the staging system may be more inclined to certain phenotypes.

Question marks also exist as to whether Lewy pathology is beneficial in neurodegenerative disease. Lewy bodies have been theorised to enclose insoluble, misfolded alpha-synuclein and help facilitate aggregates-like degradation [48, 49]. This opposes the current views that Lewy pathology is a sign of neurodegeneration.

Finally, while the degeneration of the nigrostriatal dopamine pathway is the key characterization of PD, other non-dopaminergic systems also contribute to the pathophysiology. Affected neurotransmitters in PD also include noradrenaline, serotonin, GABA, and acetylcholine [50]. Degeneration of these neurons can lead to abnormalities attributing to both motor and non-motor symptoms. Braak's theory has little reference to this and their involvement in PD may be greater than first imagined [51].

## GIT SYMPTOMS

Aside from motor irregularities, non-motor symptoms involving the GIT are common in PD. These include abnormal salivation, dysphagia, constipation, abdominal bloating, early satiety, and fecal incontinence [52]. Here we will take a closer look at the reported symptoms and its link with PD.

### *Constipation*

Constipation occurs due to delayed intestinal transit time and decreased GI motility, with effects displayed in the small and large bowels [52, 53]. Individuals with chronic constipation have a 3–11-fold increased risk of developing PD [54], and data from both prospective and retrospective studies suggests constipation becomes evident between an average of 15.6–24.0 years before diagnosis [55]. Interestingly, middle-aged men with infrequent bowel movements (<1 bowel movement/day), had a 4 times increased risk of PD diagnosis over the next 20–25-year period compared with the same population with normal bowel movements [56]. Intestinal complications arising from constipation such as sigmoid volvulus, bowel perforation, and asymptomatic megacolon may also occur [57].

### *Defactory difficulties*

Defecation difficulties are common in patients with PD, may appear early in the disease process [58]. Incoordination of the muscles of defecation such as puborectalis, abdominal muscles, and diaphragm may result in ineffective elimination [59]. A vital part of the defecation process involves both the internal and external anal sphincter muscles, with impaired relaxation of these sphincters confirmed through defecography and anorectal manometry studies [60, 61]. Consequently, as a result of defecation difficulties and fecal impaction, a complication of fecal

251 incontinence arises, and this can be hugely distressing  
252 to the patient [62].

### 253 *Inflammatory bowel disease*

254 Nationwide population-based studies have found a  
255 significantly increased risk of PD in patients suffering  
256 from IBD [63, 64]. IBD has a genetic susceptibil-  
257 ity with LRRK2, the same gene involved in sporadic  
258 PD [65]. It is known that the risk of ulcerative  
259 colitis decreases with smoking [66] and a recent  
260 meta-analysis has also shown that long-term smoking  
261 reduces the risk of PD [67]. Smoking is hypothesized  
262 to affect the gut microbiota and reduce the production  
263 of proinflammatory cytokines, thus lessening intesti-  
264 nal inflammation [68].

### 265 *Early satiety and bloating*

266 Early satiety and bloating are due to impaired gas-  
267 tric emptying with magnetic resonance imaging and  
268 electrogastrography showing gastric motility abnor-  
269 malities [69, 70]. Loss of neuronal function within the  
270 myenteric plexus and LB inclusions embodied within  
271 the vagus nerve slowing down intestinal peristalsis  
272 may cause these abnormalities [71, 72]. Gastroparesis  
273 could have implications involving absorption of  
274 L-Dopa and thus influence the degree of motor symp-  
275 toms [73], whilst small bowel dysmotility may cause  
276 abdominal bloating and predispose to small intestinal  
277 bowel overgrowth (SIBO) [74].

### 278 *Dysphagia*

279 Dysphagia develops during the disease progres-  
280 sion in over 80% of patients [75]. In one-third of  
281 patients, the issue of swallowing arises from the  
282 motor symptoms of bradykinesia and tongue motor  
283 control [76]. Furthermore, issues with swallowing  
284 reflex and esophageal sphincter contractions have  
285 been observed [77]. LB have been detected in the  
286 esophageal myenteric plexus [78] with high resolu-  
287 tion esophageal manometry studies, barium swallow  
288 studies and scintigraphy studies showing abnormali-  
289 ties with the esophageal body and lower esophageal  
290 sphincter [79–81]. LP has also been discovered in  
291 the glossopharyngeal nerve and internal superior  
292 laryngeal nerve in patients with dysphagia [82]. The  
293 complications of dysphagia are serious, including  
294 malnutrition, dehydration, and aspiration pneumonia  
[83].

### *Hypersalivation*

295 Hypersalivation and sialorrhea occurs in the later  
296 stages of the disease [84]. It is thought to occur  
297 in patients due to decreased swallowing frequency  
298 rather than increased saliva production [85] whilst  
299 other motor features, e.g., hypomimia and stooped  
300 posture, may exacerbate drooling [86]. Additionally,  
301 sialorrhea has been linked with an increased risk of  
302 respiratory infection in patients with daily drooling  
303 [87].  
304

## DIET AND NUTRITION

305 Environmental factors are thought to contribute  
306 to the pathogenesis and development of PD. Recent  
307 research suggests that certain compounds and nutri-  
308 ents may trigger the disease process whilst others may  
309 in fact be neuroprotective [88]. The composition of  
310 gut microbiota is also heavily influenced by diet with  
311 research indicating the effect of diet on neurologi-  
312 cal health is based on the gut microbiota population  
313 rather than diet-induced neuro-inflammation [89].  
314 Microbiota dysbiosis has been linked to the type and  
315 amount of consumption including dietary macronu-  
316 trients, vegetables and dietary patterns including the  
317 Mediterranean diet (MD). This aspect of the review  
318 focuses on certain dietary compounds which may play  
319 a role in PD physiology.  
320

### *Caffeine*

321 Caffeine has several health benefits including a  
322 positive influence on cardiovascular health [90]. An  
323 inverse relationship between caffeine consumption  
324 and the risk of developing PD has been reported.  
325 A variety of epidemiological studies have implied  
326 coffee consumption as a causal factor [91–93].  
327 Experimental models have suggested adenosine A2A  
328 receptors, located with D2 dopaminergic neurons  
329 within the striatum, are involved in the mode of  
330 action [94]. Caffeine may antagonize the A2A recep-  
331 tors and accordingly stimulate the D2 receptors,  
332 leading to increased motor activity and motor symp-  
333 tom improvement [95]. The cytoprotective effects of  
334 caffeine have been displayed through activation of  
335 cell signaling pathways, particularly P13K/Akt; an  
336 important pathway in downregulating neuroinflam-  
337 mation [96]. Moreover, further animal studies have  
338 shown caffeine increased the effect of L-dopa and  
339 thereby increasing dopamine levels [97].

### Tea

Tea has been implicated as a neuroprotective agent for PD [98], although some studies have contested this [99]. A 2012 meta-analysis confirmed tea drinking was protective but with no real dose-response relationship [100]; however, a 2014 meta-analysis did find a linear-dose relationship [101]. A 2019 meta-analysis confirmed tea consumption was associated with a reduced risk of PD, and in particular, people who drink more than one cup of non-black tea daily may have a reduced risk [102]. A range of natural products within tea such as polyphenols, methylxanthine, and caffeine have been linked to a number of beneficial health effects [103]. Epigallocatechin gallate (EGCG), a polyphenol, may promote neuroprotection through inhibiting the production of free radicals and pro-inflammatory markers within the brain [104]. Theanine increases dopamine levels in the brain [105] and flavonoids may help to facilitate increased brain blood flow through their anti-inflammatory effects on the circulatory system [106].

### Dairy

Dairy products, e.g., milk have been associated with a higher incidence of PD through a number of worldwide epidemiological studies [107, 108] and this association with milk is stronger than other products such as cheese and yogurts. Interestingly, a dose-response meta-analysis of prospective cohort studies determined a 17% increased PD risk for every 200 g/day increment in milk intake [109]. Moreover, it is also thought high consumption of dairy products may lead to low serum uric acid levels in individuals through the influence of casein on uric acid concentrations [110]. High serum uric acid levels may reduce the risk of PD and the duration of the disease [111–113]. Interestingly, this protective effect of uric acid has only been seen in men [88, 114].

### Fruit and vegetables

Encompassing a number of antioxidants, a diet high in fruit and vegetable consumption has been found to lower the risk of PD [115]. Recently, the MD has been increasingly explored to determine its effects on neurological health [116]. The MD is characterized by high amounts of olive oil, vegetables, fruits, fish and lower consumption of meats and animal fats. A meta-analysis demonstrated good

adherence to the MD lead to significant improvement in health status and reduced incidence of PD [117]. Nutritional modulation of ageing pathways involving brain atrophy and neuroinflammation induced by the MD may explain the lower risk in PD.

### Vitamins

Vitamin intake could be useful in the prevention of PD. A meta-analysis has detected lower levels of Vitamin B12 in PD patients compared with controls whilst supplementation of Vitamin B6 could be associated with a decreased risk of PD [118, 119]. Vitamin B6, B9, and B12 are involved in homocysteine metabolism, with high levels of homocysteine known to cause neurotoxicity [120]. It is still unclear in the context of PD, whether high levels of homocysteine are due to medications such as L-dopa or are involved at first-hand [121]. Vitamin C, abundant in the CNS, is thought to be neuroprotective but the association is controversial [122]. Intriguingly, Vitamin D indirectly influences the breakdown of dopaminergic neurons within the substantia nigra through regulation of calcium [123]. Vitamin D deficiency has been detected in patients, with supplementation improving PD motor symptoms [124, 125]. Higher dietary consumption of vitamin E, another neuroprotective agent, was also found to reduce PD risk [122, 126].

### Fats

The relationship with the consumption of dietary fats with PD risk has been widely reported, albeit with inconsistent findings. A 2019 meta-analysis expressed an association between high intake of animal fat and the risk of PD, and this depends on the subtype of fat, for instance, arachidonic acid and cholesterol may increase PD risk [127]. Interestingly, N-3 polyunsaturated fatty acids (PUFAs) may reduce PD risk [128]. Located in neuronal membranes, an abundance of PUFAs within the brain is thought to provide a neuroprotective effect [129], whilst it has been demonstrated that PUFA deficiency may lead to poor brain function [130]. The evidence that PUFA may decrease PD risk is further strengthened as  $\alpha$ -linolenic acid, a fatty acid precursor, demonstrates an inverse association with PD risk [131]. A ketogenic diet trialed in animal and clinical trials was successful in improving parkinsonism [132] with a Unified Parkinson's Disease Rating Scale (UPDRS) improvement [133]. However, this specific diet trialed

435 contained low protein which could increase the  
436 bioavailability of L-dopa [134].

### 437 *Carbohydrates*

438 Similar to dietary fats, studies evaluating the  
439 impact of carbohydrates has also been reported, with  
440 conflicting reports [135]. Carbohydrates may influ-  
441 ence dopamine production in the brain by initiating  
442 easy passage of its precursor, tyrosine, through the  
443 blood-brain barrier [136]. Additionally, an insulin  
444 surge through the consumption of high glycemic  
445 index carbohydrates may also increase dopamine pro-  
446 duction [137]. A pilot randomized controlled trial  
447 investigating the efficacy of a low-fat, high carbo-  
448 hydrate diet against a ketogenic diet demonstrated  
449 a significant improvement in both motor and non-  
450 motor symptoms, albeit a greater improvement in the  
451 ketogenic diet [138]. Nonetheless, the link between  
452 carbohydrate consumption and PD risk may not be  
453 clinically significant. For instance, a high carbohy-  
454 drate diet is known to cause an increased risk of  
455 type 2 diabetes mellitus (T2DM) [139]. Theoretically,  
456 these patients with T2DM should have a lower risk of  
457 PD due to the effect of carbohydrates on dopamine  
458 production. However, the link between T2DM and  
459 PD has been extensively investigated, with a system-  
460 atic review demonstrating inconsistent reports [140].  
461 Therefore, clinically a balanced healthy diet should  
462 always be advised in all patients as primary and sec-  
463 ondary prevention to reduce risk of other diseases,  
464 e.g., cardiovascular, metabolic. On a side note, the  
465 effect of certain anti-diabetic medications in patients  
466 with both PD and T2DM may have an important  
467 role in influencing PD symptomology. Excitingly,  
468 incretin mimetics such as exenatide may be neuropro-  
469 tective and in a double-blinded randomized control  
470 trial demonstrated a statistically significant improve-  
471 ment in the UPDRS score [141]. Possible reasons for  
472 the neuroprotective effects of incretin mimetics may  
473 include increase tyrosine levels in neurons and inhi-  
474 bition of microglial activation [142]. Research into  
475 these medications may well lead to future therapeutic  
476 treatments for patients with or without diabetes.

## 477 **THE GUT MICROBIOTA**

478 Growing evidence suggests that a relationship  
479 exists between PD and the gastrointestinal micro-  
480 biota. The GIT consists of an incredibly diverse and  
481 complex population of microorganisms, which co-  
482 exists symbiotically with the host and plays a crucial

483 rule in enhancing overall host health [143]. In early  
484 life the microbiota changes rapidly and is fundamen-  
485 tal in the development and promotion of the immune  
486 system [144]. By the age of 3 years the gut micro-  
487 biota stabilizes but remains susceptible to a large  
488 range of environment and host factors. A change  
489 in the microbial composition towards a maladaptive  
490 and pathogenic profile [145], also called dysbiosis,  
491 has been associated with a wide range of conditions  
492 including type 1 diabetes mellitus, IBD, and a range  
493 of neurodegenerative conditions such as AD, amy-  
494 trophic lateral sclerosis, and PD [146, 147].

495 A number of studies reported that patients with  
496 PD were found to have significantly reduced lev-  
497 els of bacterial diversity when compared against a  
498 healthy population [148–154]. Until 2019, 16 human  
499 case control studies have investigated the role of  
500 gut microbiota in PD, with over 100 different bac-  
501 terial taxonomic levels reported. Between healthy  
502 controls and PD patients, all 16 case-control stud-  
503 ies reported statistically significant differences [13].  
504 A recent 2021 meta-analysis by Romano et al con-  
505 firmed consistent differences between the average  
506 gut-microbiota levels between health controls and  
507 patients with PD [12].

508 The bacterial taxa highlighted in this review  
509 were chosen as previous studies including the meta-  
510 analysis by Romana et al, have shown that there  
511 is distinct variation in the gut microbiota profiles  
512 between healthy controls and PD patients. Different  
513 relative abundances of the selected taxa have been  
514 shown by other studies to be associated with PD  
515 physiology and symptomology.

516 The composition of gut bacteria has been shown to  
517 be different in patients with both early and advanced  
518 PD [154]. Intestinal microbial overgrowth is due to  
519 an increase in coliform bacteria and has been discov-  
520 ered to be a common occurrence in PD patients [155,  
521 156]. Concentrations of urinary indican, a marker for  
522 microbial dysbiosis, demonstrated a nearly two-fold  
523 increase [157, 158] which indicates that microbiota  
524 may play a part in PD pathogenesis.

### 525 *Ralstonia, Eubacterium, Enterobacteriaceae*

526 Fecal microbiota from PD patients shows higher  
527 levels of pro-inflammatory gram-negative bacteria  
528 from the *Ralstonia* genus [159]. Higher UPDRS  
529 scores in PD patients were also associated with  
530 increased levels of *Eubacterium eligens*, *Eubac-*  
531 *terium rectale*, and *Eubacterium hallii*, correspond-  
532 ing with a worse disease state [150]. Furthermore,  
533

fecal analysis has shown an increase in *Enterobacteriaceae* family bacteria which may be linked with worsening postural instability and gait disturbances [151].

### *Prevotella*

In contrast, beneficial and anti-inflammatory bacteria were reduced in feces, most notably with lower levels of prevotellaecea [160]. *Prevotella*, a gram-negative bacterium and belonging to the phylum Bacteroidetes, is important in the degradation of complex carbohydrates to produce short-chain fatty acids. Folate and thiamine are also by-products and alongside short-chain fatty acids promote a healthy microbial environment [161, 162]. Decreased levels of *Prevotella* are associated with reduced mucin proteins [163]. Mucin proteins are required to line the mucosal surfaces and maintain the epithelial barrier of the intestines. Low mucin leads to increased intestinal permeability, a sign associated with PD [164]. Additionally, *Prevotella* levels were also decreased in idiopathic rapid eye movement behavior sleep disorders (IRBD) [165]. This is intriguing as the onset of IRBD in the majority of times precedes the diagnosis of PD and in the early stages, could potentially act as a clinical biomarker [166]. *Prevotella copri*, a species of the genus *Prevotella*, was also lower in abundance in a number of different neurodegenerative conditions, e.g., multiple system atrophy and multiple sclerosis. This suggests that higher levels of *Prevotella* may play a protective role and may be a promising future therapeutic target [149, 159, 167]. However, as *Prevotella* encompasses a number of different species, it may be unreliable to generalize these findings.

### *Lactobacillus*

*Lactobacillus*, a gram-positive bacterium belonging to the Phylum *Firmicutes*, were found to also be affected in PD [12]. Higher levels of *Lactobacillus* combined with a decrease in *Prevotella* has been associated with lower concentrations and altered secretions of ghrelin [152]. Ghrelin, known as the 'hunger hormone', is released by the stomach and small intestine [168]. The relationship between ghrelin and PD is not fully understood, but ghrelin may be involved in the maintenance of the nigrostriatal dopamine pathway [163]. Increased levels of *Lactobacillus* may be caused by frequent constipation as *Lactobacillus* is association with IBS

type constipation [169]. Its potential as a probiotic treatment, particularly using the strain *Lactobacillus casei*, which has been observed to be an effective therapeutic in PD through improving stool consistency and bowel habit [170], is currently underway.

### *Blautia and Coprococcus*

A decrease in anti-inflammatory species from the *Blautia* and *Coprococcus* genus were also confirmed in fecal microbiota studies [12]. Bacterial strains belonging to these two taxa produce the short-chain fatty acid butyrate which is important in stimulating intestinal mucus and regulating tight junction proteins to maintain the epithelial lining of the colon [171]. As only small amounts of butyrate are found in natural food e.g., milk and cheese, the majority of butyrate is sourced from the gut [172]. The levels of gut butyrate may influence GIT symptoms such as constipation, with butyric acid found to increase peristaltic efficiency by improving the contraction of intestinal smooth muscle and regulating intestinal neuropathways [173]. Butyric acid may also cause reduced water secretion from the GIT, which could also contribute to constipation [174]. Perhaps supplements with sodium butyrate may be beneficial as this has been seen to improve locomotor symptoms [175].

### *Akkermansia*

Species from the *Akkermansia* genus of the *Verrucomicrobia* phylum were higher in numbers in PD patients [12]. Representing between 1–4% of gut microbiota, *Akkermansia* has been associated with conditions like obesity and diabetes and is known to help regulate mucin levels within the intestinal tract [176]. The combination of the mucous layer made from mucin and the gut microbiome is recognized as the biofilm [177]. The biofilm helps protect against intestinal injury and consequently intestinal permeability. Intestinal permeability or 'leaky gut' can generate both local and systematic inflammation. High levels of *Akkermansia* may cause intestinal permeability as the species requires mucous for energy thereby causing a breakdown of the biofilm [178].

### *Helicobacter*

*Helicobacter pylori* (*H.pylori*) infections and subsequently gastric ulcers are less common in the general population than in PD patients [179, 180]. Tan et al reported *H. pylori* in 32% of PD patients

[181], whilst several case control studies found the *H. pylori* antibody to be five times more common in PD [182]. A double-blinded randomized control trial to investigate the relationship between idiopathic PD and *H. pylori*, was shown to worsen stride length and rigidity in PD in patients with *H. pylori* and eradication of the bacteria was found to improve symptoms—*H. pylori* may impede the absorption of levodopa which leads to worsening of motor impairments [183]. Follow up studies with *H. pylori* revealed an elevated immune response, with high levels of natural killer cells and CD4 T-helper cells associated with worsening PD symptoms; this includes increased muscle rigidity and decreased free-walking speed [184]. Two proposed theories explain the pathophysiological relationship between *H. pylori* and PD. Firstly, *H. pylori* causes a neurotoxic effect by increased cholesterol glucosides, and this subsequently degrades dopaminergic neurons within the brain [185]. Secondly, poor immune control leads to *H. pylori* crossing the blood-brain barrier and this initiates apoptosis of dopaminergic neurons [186, 187].

#### *Small intestinal bacterial overgrowth*

A recent meta-analysis found a strong association between SIBO and PD, with around 50% of patients diagnosed with SIBO (188). Gastroparesis and abnormal motility of the GIT are cited as possible causes [189]. Disruption of the small bowel epithelium may lead to increased intestinal permeability, therefore making it more prone to bacteria and foreign pathogens [74]. Similar to *H. pylori*, this condition is linked to motor dysfunction and treatment with antibiotics improves symptoms. Finally, the same study also noted increased bacterial overgrowth may predispose to the poor absorption of L-Dopa [189].

However, it is important to note that these results must be taken with caution. Investigating the variances in gut microbiota is a challenging area of research, particularly because of differences in study methodologies and the inherently large variability of gut microbiota composition between participants. Boertien et al. discussed the implications of comparing and analyzing data between gut microbiome studies in PD. From variation in sample size to influence of confounding variables, many factors need to be considered when interpreting the inconsistency of study results. It is therefore difficult to establish whether taxonomic changes are related to PD

pathology. Robust methodology through standardization of research protocols and collection of confounders is important to produce data homogenization. An integrative dataset with all sequencing data should be available publicly to address these confounders, with further expansion of atypical parkinsonism and prodromal PD data required to thoroughly investigate this area [13].

Heinzel et al. recently investigated the associations between gut microbial composition, prodromal and risk markers of PD. Markers including constipation, physical activity, smoking, IRBD and subthreshold parkinsonism were associated with variances in gut composition, with findings suggesting the microbial composition of the gut may be altered in the prodromal phase. Although, it was noted that other predictive markers of prodromal PD did not show a significant link with microbial changes such as olfactory loss, positive family history of PD, orthostatic hypotension, depression, and erectile and urinary dysfunction [190].

#### CONCLUSION

In conclusion, increasing evidence suggests a strong relationship between gut microbiota and PD. The gut influence is thought to be larger than first believed, with Braak's hypothesis the most promising in explaining a GIT impact in PD pathophysiology. This theory has been supported through a range of pathological studies investigating the role of  $\alpha$ -synuclein and other neuropathological changes within the disease progression. Clinical studies have provided further supplementary evidence of GIT symptomology, dietary impact, and changes in gut microbiota levels in PD.

The variety of GIT symptoms and conditions experienced by patients may be associated with the underlying pathophysiological origins of the disease. Recognition of these symptoms in the early stages of the disease could be important indicators leading to a prompt diagnosis and improved holistic management. However, it is important to note that the gut/microbiota may not be entirely involved in the prodromal phase of all PD patients and as such a focused systemic approach should be undertaken as suggested by Heinzel et al. [190]. Furthermore, at present, limited studies have explored the role of gut symptoms in early-disease stages. By detecting GIT symptoms in the early stages, it could be possible to associate this with the initial pathophysiological changes.

Current evidence indicates that diet is important in PD development and progression. Food therapies could not only be imperative in lowering the risk of PD, but also improve symptom severity. Combined with current medication, nutritional approaches might also improve bioavailability and pharmacological effects. The majority of dietary findings in PD studies are based on either epidemiological or meta-analyses, with little information on how diet impacts on an individual level. More research in this area is needed as it may provide novel insight into the importance of nutrition on symptom severity and gut microbiota changes, which in turn could provide the basis for new treatments. The link between PUFA's and PD should be thoroughly investigated as this is still unclear. Studies have suggested PUFA's may have anti-inflammatory and neuroprotective properties, with increased consumption of PUFA's shown to reduce PD risk. However, other studies suggest PUFA's may lead to neuronal degeneration within the substantia nigra through the involvement of oxidative radical formation. With further investigation, these food compounds could easily be tailored in everyday diet to adjust the risk of PD accordingly. Moreover, the MD could also be a key step in PD research. The clear health benefits of this diet are well known, and through either a prospective cohort or case-control study, the results may impact on our everyday diet. Finally, vitamins have been thought to influence the risk of PD although the link is still debatable. Vitamins C, D, and E are theorized to be neuroprotective, and through investigating the role of multivitamins in PD, perhaps by taking a daily multivitamin tablet, the advantages may include reducing risk, improving symptomology, and with widespread multisystem benefits.

There are limitations to our review article which are needed to be taken into consideration. For the purpose of the current review, we deliberately chose a narrative review since the current research body on this topic is very limited making a systematic review less feasible. Instead, we wanted to raise the awareness of the topic and its current research findings to the wider research community. Throughout this paper we have added limitations and future directions highlighting the need for forthcoming systematic reviews. We have also used recent high-quality research where applicable, e.g., from meta-analyses and articles to ensure the content in our review is reliable and reduce bias.

As summarized in this review, the role of gut microbiota in PD is suggested to be significant. Variance in gut in the microbiome profiles of PD patients are

associated with dysbiosis which in turn is linked with gastrointestinal disease and parkinsonian features. *Lactobacillus* and *Prevotellaceae* are the two most exciting bacterial taxa which are linked with PD. In particular, the role of these species within probiotics and fecal transplantation may be a successful future treatment in PD. A study researching these specific probiotics in a prospective cohort study of PD patients would be a step in discovering the viability of these treatments. It would be also of interest if research explored the impact of nutrition on gut microbiota, particularly in members of the same household. The rationale behind recruiting cohabiting couples who live together involves similar dietary patterns and environmental microbiota. This dyadic approach has been shown to reduce the variability in background diet patterns and microbiota composition. Finally, to note, there has been little exploration into the different stages of PD and gut microbiota. Longitudinal studies in the prodromal as well as clinical phase of PD considering multi-omics, environmental and deeply phenotypic clinical data may advance our understanding of the links between microbiota and PD.

## CONFLICT OF INTEREST

Vaclav Dostal is a Consultant for Abbvie and serves on the advisory boards for Abbvie and Novartis. Michael Hornberger is a Consultant for Abbvie and serves as a non-executive director on the advisory board of the Eastern Academic Health Sciences Network. No other authors have any conflicts to report.

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