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# Proposed Longitudinal Analysis of the Modulation of the Gut Microbiome Through Diet and Exercise for the Prevention and Treatment of Parkinson's Disease

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## Abstract

Parkinson's disease is the second most prevalent neurodegenerative disease worldwide. Previous models of the disease solely focused on the effects happening in the brain, specifically the neurodegeneration of dopaminergic neurons which causes impairment in movement. Recent research has been shifting the focus to the gut microbiome since many patients with Parkinson's Disease have gastrointestinal issues that can precede the diagnosis of Parkinson's Disease by over a decade. It is unclear if Parkinson's Disease starts in the gut or if gut issues are caused by the disease. Either way, the gut microbiome influences the progression and development of the disease since gut dysbiosis is found in most patients with Parkinson's disease. This research proposal aims to address the link between the gut microbiome and Parkinson's disease and the possibility of treating and preventing the disease through dietary and lifestyle modifications, such as exercise, and a possible study design to address the link between these factors and the development of Parkinson's Disease.

## 1. Introduction

Parkinson's disease (PD) is the second most prominent neurodegenerative disease in the world, second only to Alzheimer's disease[1]. Since it is such a prevalent disease and currently there is not a cure, it should be a priority to gain a better understanding of the disease and possible underlying causes that could also create a foundation for prevention. PD is characterized by motor dysfunction, which includes tremors, impaired balance and walking, and bradykinesia[1]. However, PD is more than just the motor symptoms. It also includes cognitive, mood, sleep, and autonomic impairments that can often be even more disabling and disruptive to everyday life than the motor symptoms. Medications to treat these symptoms often are not very effective and have many side effects. As such, looking into non-pharmaceutical options is important in preserving quality of life as much as possible[2]. There is also a lot of research linking PD to the gastrointestinal (GI) tract, with evidence suggesting that GI issues could precede the diagnosis of PD by decades[3]. It could be that PD actually starts in the GI tract and could lead to PD via gut dysbiosis and inflammation[3]. If the link between PD and the GI tract is solidified with more research this could open up a lot of opportunities for treatment and prevention through lifestyle modification such as diet and exercise.

## 2. The gut microbiome and Parkinson's Disease

It was previously thought that PD occurred from the death of dopamine neurons in the motor regions of the brain resulting in impaired movement capabilities[3]. As such, current treatments focus on replacing Dopamine in the brain, providing a temporary relief from motor symptoms [4]. However, the medications used in treatment, primarily Levodopa, has notable side effects and does not address the debilitating non-motor symptoms [4]. Emerging theories

are now suggesting that PD could start outside the brain and that the motor impairments are a symptom near the end of the disease process, not the beginning [3]. The leading hypothesis is that PD is associated with impairments of the gastrointestinal (GI) tract. Up to 80% of PD patients also suffer from GI struggles, which in many cases precede the diagnosis of PD by decades [3, 5]. Constipation is especially common in PD patients, reported by 60-80% of patients[5,6]. One possible link between constipation and PD could be a decrease in gut microbiome diversity associated with constipation[5]. The link between the gut microbiome and PD is becoming more clear as patients with PD regularly display dysbiosis of the gut microbiome, commonly presenting with more pro-inflammatory bacteria than beneficial bacteria[5,7]. Gut dysbiosis is problematic for several reasons. The gut microbiota influences a number of critical functions in the body. One such critical function is maintaining the intestinal barrier[5]. When the intestinal barrier is not maintained it makes it easier for pro-inflammatory products to enter the bloodstream and cause widespread inflammation which can eventually cause damage to the blood brain barrier, possibly exacerbating neurodegeneration[5]. Dysfunction of the intestinal barrier can be found in patients just diagnosed with PD, which supports the hypothesis that PD may begin in the gut[7].

Beneficial bacteria also produce byproducts that are necessary for our health, such as short-chain fatty acids (SCFAs). When the numbers of good bacteria are decreased, the creation of those byproducts are also lost[7]. SCFAs are a fermented intestinal byproduct of beneficial bacteria that aid in the health of the GI tract including maintenance of the intestinal barrier, intestinal motility, and the immune system[6]. SCFAs may also be helpful in decreasing inflammation and promote the production of Brain Derived Neurotrophic Factor (BDNF) in the brain. BDNF is essential for neurogenesis and the survival of neurons[6]. When BDNF levels are low it can indicate increased inflammation and can exacerbate non-motor symptoms of PD, such as insulin resistance. Maintaining high levels of beneficial bacteria in the gut can prevent the disruption of BDNF signaling and decrease the severity of non-motor symptoms of PD[7].

The means by which the GI tract communicates with the brain is not yet completely understood, but one possible mode of communication could be through the Vagus nerve[6,7]. This hypothesis is supported by the finding that subjects with a severed vagus nerve have a reduced risk of developing PD[6]. However, because the gut-brain axis is a two-way communication system, causality cannot be determined, as it is possible that PD starts in the brain and then causes gut dysbiosis[7]. Although details of the connection between the gut microbiome and PD is not fully understood, there is a clear association between the gut microbiome and PD. Even if gut dysbiosis is not the root cause of PD, the microbiome still plays a crucial role in the progression of the disease[7]. Evidence for this can be seen in rodent studies demonstrating that rodents without a normal gut microbiome do not develop PD[7]. The gut microbiome also influences drug effectiveness, specifically the body's ability to use Levodopa to create Dopamine[6]. Monitoring changes in the gut microbiome may be one way to predict the development of PD and opens up a new world of possibilities for treatment. Dietary interventions and fecal transplants may be the future of PD prevention and treatment[5].

Motor symptoms of PD typically present after age 50[8]. There is a natural shift in the composition of the gut microbiome that occurs with age. Research has uncovered the importance of maintaining a healthy and diverse gut microbiome for healthy ageing[9]. When the shifts in the gut microbiome become negative, such as a loss of biodiversity and an increase in inflammation, it can put the individual at risk for developing neurodegenerative disorders, such as PD [3,9]. Promoting a healthy and balanced gut microbiome throughout the aging process can be achieved through healthy diet and exercise which can help to maintain a high level of microbiome diversity[10].

## 3. Diet and Parkinson's Disease

Diet is inextricably linked to the gut microbiome and associated dysbiosis. Diet also influences inflammation, which is often associated with PD. PD patients have elevated levels of inflammatory markers in stool samples[6]. Inflammation of the gut is problematic because it can become systemic and lead to disruption of the blood brain barrier[6]. Inflammation is thought to play a role in the development of PD and be linked to the gut microbiome because a buildup of inflammatory markers called alpha-synuclein has been found in both the brain and and the gut of patients with PD[3]. These inflammatory proteins could enter the brain possibly through the vagus nerve or through a breakdown of the blood brain barrier where they can cause the buildup of Lewy bodies, a hallmark of PD[7].

Addressing inflammation in the gut through dietary changes could be key to preventing systemic inflammation related to neurodegeneration. Inflammatory diets, such as the typical western diet, are associated with a higher risk of PD, whereas healthier diets, such as the Mediterranean diet, are associated with a decreased risk of PD[6]. There is strong evidence that following a Mediterranean diet could be especially beneficial for patients with PD[3]. However, in a study done by Hegelmaier et al, the vegetarian treatment group did see clinical improvements, an increase in the diversity of the gut microbiome, and possible antiinflammatory effects[6]. The Mediterranean diet is particularly

beneficial because it emphasizes the daily consumption of vegetables, frutis, nuts, wholegrains, and healthy fats while also limiting the consumption of (0-1 servings per week) fish, meat, and most dairy products, and discouraging against the consumption of processed foods, sugar, and red meat[11]. This combination of foods makes the Mediterranean diet both antiinflammatory and high in antioxidants[11]. While the Mediterranean diet has been shown to be beneficial to those with PD, there is limited research that supports the elimination of dairy and meat as well may be even more beneficial. The research has not found a clear connection between meat and dairy consumption and PD but there is reason to believe that consumption could lead to an increase in the risk of PD. Several studies have shown that a high consumption of dairy products is linked with an increased risk of PD[7]. Dairy is associated with an increased risk of developing PD because of the neurotoxins found in milk. In small doses the neurotoxic may not be harmful, but a steady consumption of milk over a lifetime means those neurotoxins buildup and cause damage to the brain[8]. The same neurotoxins can be found in meat, along with alphasyn nucleic proteins[7]. Meat consumption may be even more dangerous in regards to neurotoxin buildup because of the biomagnification that occurs when mass farmed animals are fed slaughterhouse by-products[8]. These findings may not be substantial enough to recommend against meat and dairy entirely but they are an important factor to note as still including them in a prescribed diet could influence the effectiveness of the diet at preventing or aiding in the treatment of PD.

The Mediterranean diet places an emphasis on high fiber consumption, healthy fats, and lots of fruits and vegetables which are the main reasons adherence to this diet is associated with a decreased risk of PD[7]. Fiber is critically important to a healthy gut microbiome because it is the main energy source of good bacteria that use fiber for energy which are the bacteria that produce SCFAs and in the typical western diet the daily intake is very low (15 g/day and less) but in the meditteranean diet the intake can be as high as over 35 g/day[7]. When fiber intake is limited, protein becomes used as the main energy source, which promotes the growth of negative bacteria that do not produce the beneficial byproducts[7]. Another important component of the Mediterranean diet is the high consumption of healthy fats, polyunsaturated fatty acids (PUFAs), especially omega 3 fatty acids. These fatty acids may be protective against developing PD and can also help to decrease depression for those with PD[7]. Omega 3s can decrease the death of dopaminergic cells, promote ideal dopamine functioning, and protect against inflammation[7]. Lastly, the high consumption of fruits and vegetables means there is a high consumption of antioxidants such as flavonoids. Another reason the Mediterranean diet is beneficial to those with PD is because of the high intake of fruits and vegetables and the associated flavonoids that have been associated with a decreased risk of PD[3,7]. Flavonoids may help to increase the production of SCFAs. Berries are one of the best sources of flavonoids and including a high consumption of berries may help prevent the development of PD by preventing the buildup of alpha synuclein proteins[8]. Peppers are also rich in flavonoids and could have more protective qualities due to their source of nicotine, which has been found to be associated with a lower risk of PD[8]. These components of the Meditteranean diet may be able to help maintain a balanced gut microbiome and decrease inflammation while being neuroprotective, which is why looking to diets such as the Mediterranean diet as a treatment plan and preventative measures for PD is important.

## 4. Exercise and Parkinson's Disease

In addition to diet, exercise also has the ability to alter the gut microbiome and thus has been found to play an important role in PD. Exercise can help to reduce the amount of time stool is in the GI tract. This is important because the longer the stool sits in the GI tracts the more opportunity there is for possible toxins to be absorbed by the body[10]. Exercise also helps to increase the biodiversity of the gut microbiome, which is good for health in general[10]. Maintaining high diversity in the gut microbiome as well as preventing GI tract dysfunction that could come about from slow transient stool time, both could offer protective benefits against the development of PD[10]. It has been found that regardless of diet, higher cardiorespiratory fitness levels are associated with a more diverse microbiome and can also help reduce inflammation, including the inflammation associated with a poor diet[10]. Physical activity and higher fitness levels have been associated with a lower risk of developing PD[12,13]. Exercise increases production of growth factors and receptors that provide a neuroprotective effect and can prevent damage to dopamine neurons[12]. People who are sedentary put themselves at greater risk for metabolic diseases and increases inflammation, both of which may increase their risk of developing PD[12].

Once PD develops, exercise has shown to be beneficial for patients with PD in decreasing the severity of both motor and non-motor symptoms. Due to the movement impairments associated with PD, the risk of falling is high, and exercise can help reduce that risk by building strength and helping to decrease the motor impairments[4]. Both aerobic and strength training have been shown to be beneficial for patients with PD, but strength training appears to be the most beneficial[13]. There are many forms of physical activity for PD and no study has found one to be more beneficial than the other. Modalities such as thai chi and dance are a good way to focus on balance and stability, while stationary

bikes are a good way to get aerobic exercise without having to worry about balance and coordination[12]. The greatest benefits may be seen from a mix of exercise formats that includes aerobic, strength, and balance training[12]. In a study conducted by Oliveira et al found that forced exercise resulted in more improvements in motor symptoms than voluntary exercise which has implications for using exercise as part of a treatment plan for patients with PD. While the impact of exercise on motor symptoms is beneficial, perhaps the greatest benefits of exercise for people with PD comes from its influence on non-motor symptoms. Non-motor symptoms of PD are often what have the greatest impact on quality of life and include autonomic dysfunction, cognitive decline, sleep disorders, and neuropsychiatric symptoms[2]. Exercise has been found to be beneficial for all of these struggles and does not come with the often debilitating side effects associated with medication. Including exercise as part of a treatment plan for PD could prevent patients from needing extra medications to treat non-motor symptoms or decrease the dosage needed to see the desired effects.

## 5. Study Design Proposal

While a lot of research has been done on how diet, the gut microbiome, inflammation, and exercise can affect PD there has not yet been a longitudinal study that looks at how these components may be associated with the development of PD in the first place. The objective for this research study is to look at how PD may start in the gut and see if certain lifestyle changes can prevent the development of PD and possibly slow the progression should PD develop. The study participants should be individuals aged 30-50 years old who are possibly at risk for developing PD due to issues of the GI tract which can include chronic constipation, inflammatory bowel disease, and crohn's disease. These patients should be selected from primary care offices. There will also be a subset of participants who do not have GI tract dysfunction. The study participants will then be randomly placed into one of four treatment groups. One group will receive a dietary intervention, one group will receive an exercise intervention, one group will receive an exercise and dietary intervention, and one group will receive treatment as usual. Each group should be given a fitbit to track their daily movement and nightly sleep and will have access to an app where they will log their daily food intake and their exercise.

The dietary intervention group will consist of people being placed on a Mediterranean diet. The purpose is to ensure that the members of this group are getting plenty of fruits and vegetables and the dietary fiber that comes with that. They will also be getting plenty of dietary fats, especially omega 3s from the oils in the diet. They should be allowed to have a limited consumption of dairy products and meat. These participants should be given access to an app to log their food intake and should be supplied with a meal box for their meals each day. The meal box item should be sourced with ingredients to supply them with their daily intake of essential fatty acids. They will also be provided with a recipe book for the mediteranean diet.

The exercise group will have two options for completing their weekly exercise. They should be provided with a YMCA membership where they can participate in PD exercises classes in person, or they can access workouts through an app. They should be required to complete 5 exercise classes a week, 2 strength/ balance training classes and 3 aerobic classes. They will log what exercises they did and when in the app.

At the beginning of the study, a stool sample should be collected from each participant to look at the diversity of the gut microbiome. Then, every 6 months another stool sample should be collected for the duration of the study . The stool samples should be examining the diversity of the gut microbiome and specifically the ratio of good to bad bacteria. If the ratio of bad bacteria is more than good bacteria, the participant should be considered to be in a state of gut dysbiosis.

Participants will also be monitored for symptoms of PD and depression yearly using the unified Parkinson’s Disease rating scale (UPDRS) and the Beck’s Depression inventory. For the first year the participants will also have a monthly check in to see how they are following their treatment plan and after that they should be followed up with every 6 months. If the participants develop PD they will continue to be followed to see how the disease progresses and the amount of levodopa they are prescribed should be recorded. Participants will also complete a questionnaire to identify other factors that could be influencing their overall wellbeing as well as the health of their gut microbiome including other health issues, medications, any traveling or change in environment, and average stress levels.

## 6. Projected Limitations

The main goal of this study design is to look at how changed in the gut microbiome can influence the development and progression of PD longitudinally. Given that this study takes place over such a long period of time, there will undoubtedly be confounding factors that influence the gut microbiome that are unable to be controlled. This can include exposure to environmental toxins, stress levels, occupation, genetic predisposition, early life development of the gut microbiome, and other pre existing health issues. Identification of these variables will aim to be addressed through questionnaires but may not be able to be controlled.

## 7. Implications

The results of this study could open new ways to screen for and prevent PD. If GI issues such as constipation, inflammatory bowel disease, and crohn's disease are found to be linked to the development of PD, screening for those diseases and possibly other GI dysfunction could become a novel way to identify individuals who have a higher risk of developing PD. Those individuals can then be given counseling on how they can modify their lifestyle, especially relating to diet and exercise habits to be preventative of PD. Information regarding how diet and exercise relates to the progression of PD can be used when establishing treatment plans and the prescription of medication to preserve quality of life as much as possible for as long as possible.

## 8. Conclusion

The gut microbiome is inextricably linked to PD. Monitoring changes in the gut microbiome could be a way to monitor the risk of PD and modulation of the gut microbiome through diet and exercise could become preventative measures and be included as part of the treatment plan for PD. This study design aims to address both aspects of the connection of the gut microbiome to PD to establish more concretely how best to modify lifestyle factors to prevent and treat PD.

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