Review

Assessing the Impact of Multiple Common Factors on the Development of Parkinson's Disease: An Updated Narrative Review

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Assessing the Impact of Multiple Common Factors on the Development of Parkinson's Disease: An Updated Narrative Review

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Abstract: Parkinson's disease (PD) is a complex neurological condition characterized by bradykinesia, stiffness, tremors, and non-motor symptoms. Despite ongoing studies, the precise etiology of PD remains elusive, and treatment options are limited. This narrative review exhibits the effect of several factors, like chronic constipation, use of nonsteroidal anti-inflammatory drugs (NSAIDs), pesticide exposure, smoking, exposure to head trauma, hyperuricemia, gout, cholesterol level, use of statin medications, caffeine consumption, on the risk of developing Parkinson's disease, including up-to-date studies. Constipation emerges as a potential prodromal symptom of PD, with studies revealing a positive correlation between persistent constipation and an increased risk of developing PD. NSAIDs, present conflicting evidence regarding their role in PD prevention. Pesticide exposure, particularly long-term exposure, is associated with an elevated risk of PD, with varying outcomes for different types of pesticides. Surprisingly, cigarette smoking exhibits an inverse correlation with PD risk, suggesting a potential protective role. The relationship between repeated head trauma and PD remains uncertain, with conflicting evidence from epidemiological studies. Uric acid, known for its anti-pro-oxidant properties, shows gender-specific associations with PD risk. Cholesterol's impact on PD risk is multifaceted, with studies presenting contradictory findings. Statin medications, despite their role in managing cholesterol, yield inconclusive results regarding their association with PD risk. Caffeine consumption emerges as a potential protective factor for PD. The conflicting findings underscore the need for further studies to fully understand them. These observations are correlational, and causation remains uncertain. Individual risk factors will depend on a unique genetic and health profile.

Keywords: Parkinson's disease; risk factors; Recent studies; review; lewy bodies

Introduction:

Parkinson's disease is a neurological condition that primarily manifests as bradykinesia, or a widespread slowness of movement; stiffness or tremor at rest; excessive salivation; mood disorders; loss of smell; substantia nigra dopaminergic neuron loss; and excessive salivation are further related characteristics [1]. For the majority of patients, the precise cause of the illness is unknown [2]. Regretfully, medication treatments are unable to fully reverse the illness. The best method to manage this illness is to reduce the likelihood that it may manifest by being aware of potential risk factors and making every effort to avoid them. The aim of this research is to assess the impact of common influential factors, like chronic constipation, use of nonsteroidal anti-inflammatory drugs (NSAIDs), pesticide exposure, tobacco smoking, exposure to repeated head trauma, hyperuricemia, gout, serum cholesterol level, use of statin medications, drinking caffeine, on the risk of developing Parkinson's disease.

This narrative review is beneficial as it helps in finding brief results of updated scientific knowledge regarding the effect of these factors on the development of PD. Consequently, various distinct and interesting outcomes have been shown. Some of these factors have nearly demonstrated

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an obvious relationship. On the other hand, others have been shown to be a little vague, as results from different studies are not consistent.

1. **Chronic Constipation.**

It is believed that up to 16% of the world's population suffers from chronic constipation, a very widespread and diverse disorder defined by unsatisfactory defecation linked to infrequent stools, difficult stool passage, or both [3,4]. Over 70% of those experiencing slow-transit constipation exhibit varying degrees of autonomic neuropathy [5]. It is considered one of the most common non-motor autonomic symptoms of PD [6]. Persistent constipation has been positively correlated with an increased chance of developing Parkinson's disease, according to numerous studies. The Honolulu Asia Aging study, which evaluated the bowel habits of 7000 men over a 24-year period found that men who experienced initial constipation (less than one bowel movement per day) had a 2.7-fold increased risk of Parkinson's disease [7], a 4-fold increased risk of incident lewy body diseases [8], and a reduced neuronal density in the substantia nigra [9]. This positive link was also demonstrated by a population-based cohort study that was conducted countrywide in Taiwan in 2014 [10], as well as by a systematic review and meta-analysis study of nine observational studies that was done in 2016 [11]. Additionally, a new systematic review and meta-analysis of 3,024,193 cases of chronic constipation from 17 different studies between 1997 and 2021 was examined [12]. According to the study, patients who experienced constipation were 2.36 times more likely to develop Parkinson's disease (PD) than patients who did not. Hence, constipation may be sensitive enough to be employed as a clinical biomarker of the illness's prodromal stage.

2. **Nonsteroidal anti-inflammatory drugs (NSAIDs).**

A class of drugs known as NSAIDs is prescribed to treat fever, pain, and other inflammatory conditions. Whether NSAIDs can lower the risk of Parkinson's disease or not has been the subject of several investigations. Regular and long-term use of non-acetylsalicylic acid NSAIDs may have preventive effects, according to a 2010 meta-analysis (Gagne and Power 2010). Another study has suggested that ibuprofen might offer some protection [13]. While another meta-analysis has found no evidence that NSAIDs generally decrease the incidence of Parkinson's disease [14]. Additionally, a recent population-based retrospective study examined the frequency of Parkinson's disease among NSAID users from 2004 to 2017 using the Norwegian Prescription Database [15]. Whether NSAID exposure was considered generally or specific to diclofenac, ibuprofen, or naproxen, they have not seen a decrease in the incidence of Parkinson's disease in any of the analyses. More studies are needed to emphasize their effect on Parkinson's disease.

3. **Pesticide exposure.**

The term "pesticide" refers to any chemical compound that is used to prevent, eradicate, repel, or neutralize a pest. These substances can be employed against insects, rodents, weeds, microbes, or algae, for example [16]. Chronic low-dose pesticide exposure, however, may cause systemic problems, including delayed peripheral neuropathy [17]. When it comes to its impact on Parkinson's disease, numerous studies have examined the link between long-term pesticide exposure and PD risk. Family-based case-control research has demonstrated that people with Parkinson's disease had a considerably higher likelihood of reporting direct pesticide application than their relatives who were not afflicted (odds ratio = 1.61; 95% CI, 1.13–2.29) [18]. Five and ten years of pesticide exposure were linked to an increase in the risk of Parkinson's disease of 5% and 11%, respectively, according to a different 2018 dose-response meta-analysis of observational studies [19]. Furthermore, it has been found that pesticide exposure raises the likelihood of changes in several PD pathogenesis-related genes, including GST, PON-1, MDR1, and SNCA genes [20]. According to a systematic review and meta-analysis study, different pesticides have different associations with Parkinson's disease risk. Fumigant pesticide has the weakest association (OR = 0.87, 95% CI (0.63 to 1.21), while organophosphorus pesticide has the strongest association among other specific types of pesticides (OR = 1.89, 95% CI (1.35 to 2.64) [21].

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People are not exposed to a single substance in isolation, or by pesticide application throughout the duration of their lives, which must be taken into account by scientists and authorities [22].

4. **Tobacco smoking.**

Chronic diseases, such as cancer, diabetes, and cardiovascular and respiratory conditions, are linked to tobacco smoking. An estimated 16 million adult Americans suffer from a smoking-related illness [23]. It's surprising to learn that smoking and the chance of developing Parkinson's disease are inversely correlated. In a 2002 study, identical twin pairs were examined, one of which had Parkinson's disease and the other did not. In general, the twin without PD smoked more than the sibling with PD. With the exception of smoking, many factors often linked to a variation in PD risk were eliminated in identical twins because they share the same DNA and frequently the same environment. It was consequently suggested by the study that smoking could be a preventive factor against Parkinson's disease [24]. Additionally, another study that had been conducted between 1951 and 2016 on 30,000 male British doctors concluded that when comparing doctors who had never smoked to those who did, they showed a 40% decreased risk of Parkinson's disease in smokers [25].

What is the process by which smoking protects against Parkinson's disease? According to a recent study which has exhibited the effect of smoking on moderation the interaction between the iron content of the deep brain nuclei, considering the thalamus, red nucleus, and substantia nigra pars compacta the most affected nuclei by cigarette smoking. [26],

If smoking plays a protective role in Parkinson's disease, should physicians who treat Parkinson's patients prescribe cigarettes for them? Although smoking may protect against Parkinson's disease, there is no statistically significant correlation between smoking and PD mortality. Additionally, smokers have a notably increased risk of dying from smoking-related malignancies, such as lung cancer [27]. Therefore, it is not advised for those with Parkinson's disease to smoke cigarettes [27].

5. **Exposure to head trauma.**

These days, there is a higher prevalence of varied manufacturing and sports, which increases the risk of head trauma. In the US, there are between 1.7 and 3.8 million traumatic brain injuries reported annually, with sports and recreational activities accounting for about 10% of these cases [28].

Is there a direct correlation between PD and head trauma? Since James Parkinson's essay in 1817 [29], there has been a contentious dispute regarding the link between severe head injuries and the onset of Parkinson's illness. Numerous studies have examined head trauma as a potential risk factor for a variety of neurodegenerative illnesses [30]. Head trauma can cause neuroinflammation, as several studies have shown. This inflammation can occur directly on neuronal cells [31,32] or indirectly through the disturbance of the blood-brain barrier [32]. Furthermore, it has been observed that the cerebrospinal fluid of those who have suffered severe head trauma has significant amounts of α-syncline [33]. However, there is disagreement over epidemiological evidence; some studies have found a positive correlation between head trauma and developing Parkinson’s disease [34–37], while other studies have found none [38,39]. A different study has shown that the correlation between PD and head injury was limited to people who carried the a-synuclein Rep1 promoter risk allele [40].

The relationship between head injuries and Parkinson's disease is currently unclear, and further studies are required to fully understand the results.

6. **Hyperuricemia and gout.**

The metabolic breakdown of purine nucleotides (adenine and guanine) results in uric acid [41]. Uric acid can act as a pro-oxidant (mostly inside the cell) or an antioxidant (mainly in plasma) [42]. According to numerous studies, uric acid may have a protective function in the pathophysiology of Parkinson's disease, and might slow down the rate at which the disease progresses [43–45]. Furthermore, uric acid concentrations have been observed to be lower in Parkinson's patients than in normal individuals [48,49] which supports its existing effect in the development of PD. One possible way of this protective mechanism could be achieved by opposing the effects of 1-methyl-4-phenyl-

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1,2,3,6-tetrahydropyridine (MPTP) and its active metabolite, 1-methyl-4-phenylpyridinium (MPP+), which are toxins that damage the dopaminergic neurons in the brain [46,47].

Gout is mainly caused by chronic hyperuricemia, which ends in the deposition of monosodium urate crystals [50]. But, do gout patients have a lower risk of developing Parkinson's disease as a result of having chronic hyperuricemia? There is conflicting evidence from the several studies that have looked at the relationship between gout and the likelihood of developing Parkinson's disease, taking into consideration the gender type. Men with gout have been shown to have a decreased chance of acquiring Parkinson's disease [51]. Similar findings have been also reported by another cohort study, but for both genders [52]. Nonetheless, a 2015 systematic review and meta-analysis study found no link between gout and Parkinson's disease in either gender [53]. Surprisingly, a recent systematic review and meta-analysis in 2022 revealed that there was no link in men, while a higher risk of Parkinson's disease was seen in females [54].

Numerous variables could contribute to the disparities between males and females. For instance, male cerebral fluid has a higher percentage of uric acid than female CSF fluid [55]. Additionally, especially in females, uric acid may enhance the formation of reactive oxygen species (ROS) without changing ROS scavenging, which could lead to increased oxidative stress independent of Xanthine oxidoreductase activity [45]. Consequently, compared to male gout patients, female patients are more likely to be exposed to the toxic oxidative metabolites of uric acid and are less likely to benefit from the neuroprotective effects of uric acid in brain tissue.

7. Cholesterol.

In addition to being an essential structural element of cell membranes, cholesterol is a precursor to many steroid hormones, vitamin D, and bile acids. [56] The two primary forms of cholesterol are high-density lipoprotein (HDL), sometimes known as "good" cholesterol", and low-density lipoprotein (LDL), also known as "bad cholesterol" [57]. Your body produces the cholesterol it requires, mainly from your liver. However, dietary sources of cholesterol include meat, eggs, poultry, and dairy products [57]. The brain is the body's organ with the highest cholesterol content [58]. For synapse and dendritic formation [59,60], as well as for axonal growth [61], cholesterol is necessary. Since the intact blood-brain barrier (BBB) inhibits vertebrates from absorbing lipoproteins from the circulation, brain cholesterol is largely produced by de novo synthesis, in contrast to cholesterol seen in other peripheral organs [62]. The brain's neurodegenerative processes may be connected to dysregulation of cholesterol metabolism [63]. Because PD is becoming recognized as a systemic condition, in addition to the effect of blood cholesterol on brain cholesterol metabolisms through complicated feedback loops or pathways, the role of circulating cholesterol in PD pathogenesis cannot be ruled out [64]. High cholesterol may be associated with either risk or protective factors for Parkinson's disease. Certain research has indicated that having high levels of total cholesterol, LDL cholesterol, and HDL cholesterol may protect against Parkinson's disease [65–68]. There has also been evidence linking reduced cholesterol consumption with an increased risk of developing Parkinson's disease [69,70]. However, contrary findings have been reported by other paradoxical studies, which have shown the opposite [71,72].

There could be numerous reasons for these contradicting results. For instance, higher cholesterol may be associated with PD protective factors. For example, smoking tobacco increases total and LDL cholesterol levels [73], and it is considered a protective factor against Parkinson's disease [25]. In addition, many patients improve their physical activity after being diagnosed with dyslipidemia, which lowers their risk of Parkinson's disease, as physical activities have been found to decrease the risk of PD [74]. Additionally, changes in lifestyle that influence cholesterol levels may have resulted from neurodegenerative alterations that occurred before PD was diagnosed [68].

8. Statin medications.

Statin medications are used in the management and treatment of hypercholesteremia by inhibiting the Coenzyme A reductase and lowering total cholesterol, low-density lipoprotein (LDL), and triglyceride concentrations while increasing high-density lipoprotein (HDL) concentrations to manage cardiovascular diseases [75]. After 2013, the number of individuals who used statins

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increased by 149%, from 37 million in 2012–2013 to 92 million users in 2018–2019 [76]. A lot of debates have appeared about the role of these medications in PD. There is still no definitive agreement about their role in PD. Some studies have displayed an inverse association between the use of statin and the risk of developing PD [77–79]. While others have not shown any association [80,81]. However, an increased risk of PD from the use of statin medication has also been reported [82,83].

These results may be explained by considering the long-and short-term effects of using statin medications. How? First, statin use could unmask early PD symptoms in individuals with preclinical PD [84,85]. Therefore, it might seem that short-term statin use causes new-onset PD. Second, long-term use of statin medications helps in decreasing the risk of cardiovascular disease [86], especially arterial plaque formation, which may lead to stroke; consequently, PD risk will decrease [87].

9. **Caffeine.**

A common psychoactive stimulant found in many drinks, such as coffee, tea, soda, and energy drinks, is caffeine [88]. Studies have demonstrated that caffeine helps with learning and memory for tasks when information is provided passively [89]. Our brain's natural chemical, adenosine, is structurally identical to caffeine. Both molecules readily pass across the blood-brain barrier because they are soluble in both fat and water [90]. Adenosine receptor antagonism, phosphodiesterase inhibition, and gamma-aminobutyric acid (GABA) receptor blockage are among the several hypotheses about the pharmacodynamic effects of caffeine on the brain [91]. Additionally, it seems to influence the local release of dopamine and trigger the release of noradrenaline [92]. Through reducing the death of dopaminergic neurons, caffeine may have neuroprotective effects [93]. In the human brain, it affects striatal dopamine D2/D3 receptor availability [94]. It is significant to remember that in animal models, caffeine treatments prevented the integrity of the blood-brain barrier from being disrupted [95].

Does consuming coffee reduce the chance of developing Parkinson's disease? 26 studies were included in systematic review and meta-analysis of observational studies, which was published in 2010, found an inverse relationship between caffeine consumption and the risk of Parkinson's disease. The summary relative risk (RR) was 0.75 [95% confidence interval (95%CI): 0.68–0.82]; the heterogeneity was low to moderate (I2 = 28.8%) [96]. Further meta-analysis study was published in 2020 including 13 papers found that frequent caffeine intake was also associated with a significantly decreased risk of developing Parkinson's disease (hazard ratio = 0.797, 95% confidence interval (CI) = 0.748–0.849, $p < 0.001$) [97].

What are the mechanisms through which caffeine protects neurons in Parkinson's disease? These strategies could involve altering the gut microbiota, controlling autophagy, regulating neuroinflammation, or inhibiting voltage-gated calcium channels 1.3 [Cav 1.3Ca2+] [98,99]. Look at Table 1. Caffeine provides some protection, but it also has some possibly carcinogenic qualities and greatly raises the risk of heart disease; therefore, excessive caffeine use should be used with caution [100].

Table 1.

Suggested mechanisms	More explanation
1-Modulation of neuroinflammation.	-Caffeine reduces lipopolysaccharide (LPS)-induced microglia activation in the hippocampus. -Caffeine may control microglia-mediated neuroinflammatory responses associated with PD. -Caffeine prevents blood-brain barrier (BBB) dysregulation in a mouse model. -Caffeine attenuates α-Syn-induced microglial activation and astrogliosis in the striatum of a mouse model. -Caffeine activates signaling in the anti-oxidative pathways. -Caffeine antagonizes the adenosine a2 receptor, which controls neuroinflammation (through p38).

2-Regulating autophagy.	-Caffeine attenuates abnormal α-Syn aggregation and neurotoxicity by re-establishing autophagy activity in animal models of PD.
3-Modulating gut microbiota.	-Modulating it in many suggested complex mechanisms that end in protection from Parkinson's disease.
4-Inhibition of Voltage-gated calcium channels 1.3 [Cav 1.3 Ca2+].	-It is thought that these channels are increased in density in Parkinson's patients, and these channels generate more reactive oxygen species that lead to neurodegeneration of dopaminergic neurons.
First 3 mechanisms and their explanations have been collected from: (Ren X and Chen J-F (2020)Caffeine and Parkinson's Disease: Multiple Benefits and Emerging Mechanisms. Front. Neurosci. 14:602697. doi: 10.3389/fnins.2020.602697) [98]	
Last mechanism and its explanation have been collected from: (Roshan MHK, Tambo A, Pace NP. Potential Role of Caffeine in the Treatment of Parkinson's Disease. *Open Neurol J.* 2016;10(1):42-58. doi:10.2174/1874205x01610010042) [99]	

Conclusion:

Finally, this research has revealed a brief knowledge about the association between the risk of Parkinson's disease development and multiple factors. While certain factors may raise the risk of Parkinson's disease or have unclear effects, others seem to be protective and lower the risk of developing PD.

Constipation emerges as a potential prodromal symptom of PD, with studies revealing a positive correlation between persistent constipation and an increased risk of developing PD. NSAIDs, commonly prescribed for inflammatory conditions, present conflicting evidence regarding their role in PD prevention. Pesticide exposure, particularly long-term exposure, is associated with an elevated risk of PD, with varying outcomes for different types of pesticides. Surprisingly, cigarette smoking exhibits an inverse correlation with PD risk, suggesting a potential protective role, although the associated health risks warrant caution. The relationship between repeated head trauma and PD remains uncertain, with conflicting evidence from epidemiological studies. Uric acid, known for its anti-pro oxidant properties, shows gender-specific associations with PD risk, complicating the interpretation of results from different studies. Cholesterol's impact on PD risk is multifaceted, with studies presenting contradictory findings. Statin medications, despite their role in managing cholesterol, yield inconclusive results regarding their association with PD risk. Caffeine consumption emerges as a potential protective factor, with multiple studies suggesting a decreased risk of PD.

Overall, the importance of maintaining a healthy lifestyle to potentially reduce the risk of developing PD is very crucial. It is important to note that these findings are observational and do not establish cause-and-effect relationships. Further studies are needed to fully understand the complex interplay between these factors and PD. It's also important to remember that these are just general trends, and individual risk factors will vary depending on a person's unique genetic makeup, medical history, and overall health.

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