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 common neurodegenerative disorder characterized by the loss of dopaminergic neurons and the buildup of misfolded alpha-synuclein proteins. While its exact cause remains unknown, several factors may influence its development. This review examines how factors like chronic constipation, head injuries, cholesterol and uric acid levels, pesticide exposure, smoking, NSAIDs, and caffeine intake may affect PD risk. Chronic constipation appears to be linked to a higher risk of PD, potentially serving as an early warning sign. Head injuries, especially mild-to-moderate ones, may also play a role in increasing PD risk. Surprisingly, higher levels of cholesterol seem to protect against PD, while lower levels of uric acid might increase the risk in the presence of some differences according to gender type. Exposure to certain pesticides is associated with a higher PD risk. NSAIDs, on the other hand, may or may not have a protective effect, with conflicting evidence. Interestingly, caffeine and tobacco smoking appear to lower the PD risk. 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.

Keywords: Parkinson's disease; risk factors; Review; Lewy bodies; alpha-syncuclein

Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, which is characterized by the loss of dopaminergic neurons as well as the accumulation of misfolded α-synuclein proteins, which are found in intra-cytoplasmic inclusions called Lewy bodies [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. This research aims to assess the impact of common factors, like chronic constipation, exposure to head trauma, serum cholesterol and uric acid levels, pesticide exposure, tobacco smoking, the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and 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 an obvious relationship. On the other hand, others are a little vague, as results from different studies are not consistent.

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 6790 men over 24 years, found that men who

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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 [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.

Head Injury

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 [13].

Head trauma can trigger the activation of microglial cells for up to 17 years, which means a state of chronic inflammation. [14] Furthermore, it has been observed that the cerebrospinal fluid of those who have suffered severe head trauma has significant amounts of α-synuclein [15].

Since James Parkinson's essay in 1817 [16], there has been a contentious dispute regarding the link between head injuries and the onset of neurodegenerative diseases. A case-control study of 93 twin pairs suggested that mild to moderate closed-head injuries may increase PD risk decades later [17]. A systematic review and meta-analysis study of 34 articles, which was published in 2013, also considered head trauma with concussion as a risk factor [18]. Additionally, another meta-analysis study of 15 articles published in 2023 considered traumatic brain injury as a major risk factor for developing PD [19]. However, contradictory results have also appeared in other studies [20,21].

It seems that some other factors influence the effect of head injuries on PD. For example, a retrospective cohort study was conducted on patients aged ≥55 and found that traumatic brain injury is associated with an increased risk of developing PD later in a dose-dependent manner [22]. Also, a case-control study found that the association was strongest for injuries involving concussion as well as unconsciousness [23]. Therefore, the strength of the injury plays a critical role in determining its effect on the development of PD. Additionally, a study has shown that the correlation between PD and head injury was limited to people who carried the alpha-synuclein Rep1 promoter risk allele [24], which sheds light on the importance of considering genetic factors into account. There is a need for more prospective cohort studies to more accurately understand the correlation between head trauma and the development of PD.

Cholesterol Level

In addition to being an essential structural element of cell membranes, cholesterol is a precursor to many steroid hormones, vitamin D, and bile acids. [25] 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" [26]. Sources of cholesterol include the body, mainly from your liver, as well as dietary sources including meat, eggs, poultry, and dairy products [26]. The brain is the body's organ with the highest cholesterol content [27]. Cholesterol is necessary for synapse and dendritic formation [28–29], as well as for axonal growth [30]. 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 [31]. The brain's neurodegenerative processes may be connected to the dysregulation of cholesterol metabolism [32]. Many studies have concluded that having high levels of total cholesterol, LDL cholesterol, and HDL cholesterol may protect against Parkinson's disease [33–36]. There has also been evidence linking reduced cholesterol consumption with an increased risk of developing Parkinson's disease [37]. In addition, low LDL specifically has been studied as a risk factor [38]. Finally, circulating total cholesterol has been found to be decreased

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in the prodromal stage of PD, which may in part explain its reported inverse association with PD [39].

Uric Acid Level

Uric acid is the result of the metabolic breakdown of purine nucleotides (adenine and guanine) [40]. Uric acid can act as a pro-oxidant or an antioxidant [41]. Oxidative stress plays an important role in the degeneration of dopaminergic neurons in Parkinson's disease [42]. A lower serum uric acid concentration was found in PD patients, according to a study that was done on 40 PD patients in 2007 [43]. A similar finding was observed in 161 PD patients in a study that was published in 2012 [44]. According to a meta-analysis study of 1217 patients with PD in 2013, it was found that PD patients also had a lower level of uric acid in comparison to healthy controls [45]. According to these results, can hyperuricemia be a protective factor against PD?

Hyperuricemia in gout patients is the focus of this article. There is conflicting evidence from 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 having Parkinson's disease [46]. Similar findings have also been reported by another cohort study and dose-response meta-analysis, but for both genders [47,48]. Nonetheless, a systematic review and meta-analysis study found no link between gout and Parkinson's disease in either gender [49]. Surprisingly, another systematic review and meta-analysis revealed that there were no associations in men, while a higher risk was seen in females [50].

Many variables could contribute to the disparities between males and females. For instance, male cerebral fluid has a higher percentage of uric acid than female cerebrospinal fluid [51], so females may get less protection from uric acid compared to males, as uric acid has been demonstrated to oppose the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and its active metabolite, 1-methyl-4-phenylpyridinium, which are toxins that damage the dopaminergic neurons in the brain [52]. Additionally, especially in females, uric acid may enhance the formation of reactive oxygen species, which could lead to increased oxidative stress [53]. Consequently, female patients might be more likely to be exposed to the toxic oxidative metabolites of uric acid.

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 meta-analysis that was published in 2010 [54]. Another study has suggested that ibuprofen might offer some protection [55]. Another meta-analysis of 17 studies found no evidence that NSAIDs generally decrease the incidence of Parkinson's disease [56]. 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; they have not seen a decrease in the incidence of Parkinson's disease in any of the analyses [57]. More studies are needed to emphasize their effect on Parkinson's disease.

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 [58]. Chronic low-dose pesticide exposure, however, may cause systemic problems, including delayed peripheral neuropathy [59]. 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) [60]. 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

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to a different 2018 dose-response meta-analysis of observational studies [61]. 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 [62]. 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) [63].

People are not exposed to a single substance in isolation or by pesticide application throughout their lives, which must be taken into account by scientists and authorities [64].

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 [65]. 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. Except for 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 [66]. Additionally, another study that was 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 [67]. A recent study that was published in 2023 reported the dose-response relationship between smoking and the decreased risk of PD [68].

However, smokers have a notably increased risk of dying from smoking-related malignancies, such as lung cancer [69]. Therefore, it is not advised for those with Parkinson's disease to smoke cigarettes.

Caffeine

Caffeine is a common psychoactive stimulant found in many drinks, such as coffee, tea, soda, and energy drinks [70]. Studies have demonstrated that caffeine helps with learning and memory for tasks when information is provided passively [71]. 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 [72]. Adenosine receptor antagonism, phosphodiesterase inhibition, and gamma-aminobutyric acid receptor blockage are among the several hypotheses about the pharmacodynamic effects of caffeine on the brain [73]. Additionally, it seems to influence the local release of dopamine and trigger the release of noradrenaline [74]. Through reducing the death of dopaminergic neurons, caffeine may have neuroprotective effects [75]. In the human brain, it affects striatal dopamine D2/D3 receptor availability [76]. It is significant to remember that in animal models, caffeine treatments prevented the integrity of the blood-brain barrier from being disrupted [77].

Does caffeine reduce the risk of developing Parkinson's disease? 26 studies included in the 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] [78]. A further meta-analysis study 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% CI = 0.748–0.849, $p < 0.001$) [79].

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+] [80,81], look at the table.

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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.
The 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) [80]	
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) [81]	

Conclusion

This review examines how factors like chronic constipation, head injuries, cholesterol and uric acid levels, pesticide exposure, smoking, NSAIDs, and caffeine intake may affect PD risk. Chronic constipation appears to be linked to a higher risk of PD, potentially serving as an early warning sign. Head injuries, especially mild-to-moderate ones, may also play a role in increasing PD risk. Surprisingly, higher levels of cholesterol seem to protect against PD, while lower levels of uric acid might increase the risk in the presence of some differences according to gender type. Exposure to certain pesticides is associated with a higher PD risk. NSAIDs, on the other hand, may or may not have a protective effect, with conflicting evidence. Interestingly, caffeine and tobacco smoking appear to lower the PD risk. 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.

Abbreviations

PD: Parkinson's Disease // **NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs // **HDL:** High-Density Lipoprotein // **LDL:** Low Density Lipoprotein

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