A Narrative Review of Lifestyle Factors Associated with Parkinson's Disease Risk and Progression

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Abstract

Parkinson's disease is a complex slowly progressive neurodegenerative disorder with motor and non-motor symptoms affecting daily living. Despite effective symptomatic treatments, with various degrees of side effects, no disease-modifying therapeutic options presently exist. Symptoms progress, with an accumulating burden, reducing the quality of life and forming the impression that medications are no longer effective. Adopting positive lifestyle behaviours can empower patients, improve the quality of life, alleviate symptoms, and potentially slow disease progression. Lifestyle behaviours including nutrition, cognitive enrichment, physical activity, and stress management have beneficial effects on brain health and quality of life. While some evidence of an association of lifestyle with Parkinson's disease risk and progression exists, the sparse and often conflicting data make it difficult to provide clinical recommendations. Herein, we highlight studies showing promising associations between lifestyle and Parkinson's disease. Given the increasing

aging of populations worldwide and the prevalence of neurological disorders, further research into self-management through adoption of positive lifestyle behaviours is clearly warranted to better enable individualized care.

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder with widespread neuronal damage, clinically diagnosed by motor symptoms of bradykinesia, in combination with either resting tremor, rigidity, or postural instability [1]. These and a spectrum of non-motor symptoms, including mood and sleep disorders, cognitive decline, and fatigue, can have a significant impact on daily living and quality of life.

Current treatments primarily address the motor symptoms of PD; however, the complexity of the symptoms requires an individualized multidisciplinary approach to care. Even with optimal medical management, patients experience a deterioration of bodily function and daily activities and a decline in mobility. This can lead to increased dependence, inactivity, and social isolation, re-

Fig. 1. Lifestyle behaviours associated with Parkinson's disease. Mind-body practices, physical activity, and diet are associated with Parkinson's disease risk and symptom management. Their association with disease progression is difficult to determine, primarily due to the absence of objective and sensitive markers.

sulting in a reduced quality of life. The role of lifestyle behaviours in these outcomes has been poorly studied but may well be important, as in other neurological diseases.

Herein, current treatments for PD are outlined, the notion of how lifestyle behaviours may affect the risk of acquiring PD and the management of symptoms is introduced, and promising associations between lifestyle and PD (Fig. 1), primarily derived from randomized controlled trials (RCTs), longitudinal studies, and meta-analyses, are presented.

Current Treatments for PD

As diagnostic motor symptoms result from low levels of dopamine in the brain, most pharmaceutical treatments are aimed at either replenishing dopamine levels or mimicking its action. Levodopa is the most effective, though prolonged use at high doses may lead to dyskinesia [2, 3]. Dopamine agonists, monoamine oxidase B and catechol-*O*-methyltransferase inhibitors, and anticholinergic agents are also used for initial treatment or in combination with levodopa in advanced PD.

Surgical treatments are typically reserved for patients who suffer medication-induced dyskinesias. Most common is deep brain stimulation, which usually provides prolonged and efficient control of motor symptoms and

a reduction in dopaminergic medication but has variable effects on other symptoms which require dedicated management [4]. Ablative procedures are performed for select tremor symptoms, but they are primarily unilateral, limiting their effectiveness in a bilateral disease process [4]. Gene therapy, immunotherapy, and cell transplantation are promising future treatments; however, they remain investigational [5–7].

Non-invasive brain stimulation has therapeutic potential, with repetitive transcranial magnetic stimulation improving depression [8] and motor symptoms [9–11], and transcranial direct current stimulation improving balance, functional mobility, and executive function [12, 13]. Overall improvements, however, have been negligible with respect to functional independence and quality of life.

How Can Lifestyle Behaviours Affect PD Outcomes?

Lifestyle behaviours may play a role in neuroprotection, disease progression, and symptom management. Neuroprotection refers to protecting the structure or function of nerve cells, thereby reducing neurodegeneration. Treatments that target anti-oxidative and anti-inflammatory pathways are one area of focus, with promising dietary sources including flavonoids, caffeine, and high-purine foods that result in higher urate levels [14–16]. Epidemiological studies show consistent associations of smoking – and physical activity – with reduced risk of PD [17]. It is debatable whether nicotine is neuroprotective or whether the observation is due to the harm-avoiding personality of people who develop PD [18]. As shown in animal models, exercise is beneficial to cell regeneration, survival, and oxidative stress [19], and thus can be recommended as an approach for neuroprotection.

Disease modification refers to the ability to affect the underlying pathophysiology of the disease and have a beneficial effect on the course of the disease by stopping, slowing, or reversing progression. No study to date has shown a delay in progression of neurodegeneration in PD. This is primarily because of the difficulty in monitoring progression. Neuroimaging via ^{18}F -DOPA PET and ^{123}I -beta-CIT SPECT allows monitoring of the progressive loss of presynaptic nigrostriatal projections in PD, but these measures are expensive, variable, and unable to detect subtle changes.

Symptom management refers to the treatment of symptoms, without necessarily impacting disease progression; these processes are closely intertwined. As PD progression is currently measured by clinical assessment

of motor and non-motor symptoms and a stable medication dose, it is impossible to know with certainty whether symptom management is altering disease pathology and/or progression. Sensitive biomarkers are yet to be discovered to answer such questions.

Lifestyle Behaviours Associated with PD Outcomes

While the evidence is sparse and often conflicting, research findings suggest promising effects of mind-body practices, physical activity, and diet on health outcomes in PD.

Mind-Body Practices

Mind-body practices, including goal-oriented movement such as yoga, Tai Chi, and dance, have immediate beneficial effects on motor symptoms, postural instability, and functional mobility among individuals with mild-to-moderate PD [20]. Pilot RCTs showed that twice-weekly yoga for 8 weeks improved motor function, postural stability, functional gait, and freezing gait and reduced fall risk [21], while twice-weekly yoga for 3 months reduced bradykinesia and rigidity and increased muscle strength and power [22].

An RCT of 195 PD patients, randomized to twice-weekly sessions of Tai Chi, resistance training, or stretching, revealed that Tai Chi had beneficial effects on motor function and postural stability and reduced the incidence of falls. These effects were retained for 3 months after the intervention [23]. A systematic review and meta-analysis of the effects of Chinese medical exercise on PD, comparing medication plus either Tai Chi or other therapy, showed that the former combination led to greater improvements in motor function and balance, but not in gait or quality of life [24].

Dance also promotes significant improvements in motor symptoms and functional mobility in people with PD when compared to other types of physical activity, and in motor symptoms when compared to absence of an intervention [25]. Qigong [24, 26], therapeutic singing [27, 28], and music therapy [29] additionally have beneficial effects on motor and non-motor symptoms, as well as on quality of life. More methodologically rigorous and large-scale studies, with long-term follow-up, are needed to validate these findings.

Physical Activity

Physical activity is thought to have a neuroprotective effect, potentially through promoting the release of brain-

derived neurotrophic factor and reducing cortisol, vascular risk, and neuroinflammation [19, 30].

An inverse relation between the amount of physical activity and PD risk has been shown in both prospective and longitudinal studies [31–33]. In the National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study cohort, higher levels of moderate-to-vigorous activities at ages of 35–39 years, or in the past 10 years, were associated with a lower risk of PD ($n = 767$), with significant dose-response relationships. Individuals with consistent and frequent participation in moderate-to-vigorous activities in both periods had an approximately 40% lower risk than those who were inactive in both periods [32].

The potential benefits of physical activity to individuals with existing PD continue to be an active area of research. Participants from the National Parkinson Foundation Quality Improvement Initiative Data ($n = 3,408$), who maintained regular exercise at least 2.5 h/week or became a regular exerciser after the baseline visit, had better quality of life and functional mobility after 2 years than non-exercisers [34]. Quality-of-life improvements were greater in advanced PD than mild PD. Participants who became regular exercisers after their second visit were the same as non-exercisers 1 year later, suggesting that benefits from regular, informal, independent exercise may require more time to accumulate than short-term, supervised, research-based exercise [35–37].

Common physical activity interventions for people with PD include skill-based, aerobic, resistance, and cued training. The lack of commonality between outcome measures, training sequences, and intervention periods makes results difficult to translate into patient recommendations. Examples of skill-based exercise include yoga, dance, and Tai Chi, as described under Mind-Body Practices.

Aerobic exercise in the form of treadmill training, Nordic walking, and elliptical trainer exercise significantly improves gait and balance [38–41]; however, benefits on functional mobility and quality of life are inconsistent [40]. Individuals with poor baseline performance may benefit most, as ceiling effects may occur in highly functional participants [42], while low baseline disability may be the strongest predictor of outcomes [43].

Progressive resistance training has positive effects on muscle strength, balance, functional mobility, and quality of life that last for at least 12 weeks [40]. Few resistance training studies have assessed muscle strength improvement; therefore the correlation of resistance training to improved outcome is unclear [44], and the superiority of

resistance training over other training or usual activities remains to be determined [45].

Cued training involves using external visual, rhythmic auditory, or somatosensory cues to learn compensatory strategies to assist movement. These techniques improve gait speed, balance, and daily living activities [46, 47], but their success relies on preserved cognitive abilities and their benefits may be equal to those obtained with conventional physical therapy [48].

It is unclear whether the benefits of physical activity are long-lasting or evident in later stages of PD, and what form, frequency, and intensity of physical activity is required to see clinically significant results. While there are many exercise interventions that may modulate neuroplasticity, it is not necessarily the type of exercise that matters, but rather the parameters within the physical activity. These include task intensity and difficulty, the learning challenge to the subject, task specificity to motor circuits, and task complexity to engage the individual [49].

Diet

The main difficulties in diet studies are that dietary questionnaires are prone to recall bias, a single food does not contain a single micronutrient, and combination foods need to be considered. Additionally, most existing cohorts have a population with relatively homogeneous lifestyles and dietary patterns, collect diet information infrequently, or have relied on single dietary assessment to predict PD risk over decades. While associations of certain food components with PD risk have been identified, the evidence is conflicting and often unsupported by subsequent clinical trials. These discrepancies may be due to patient inclusion criteria, small sample sizes, and differences in quantifying food components and adjustment for confounding effects. Nevertheless, highlighted below are findings from cohort studies showing associations of dietary components with risk of PD, some of which have been used to model clinical trials to modify PD progression.

Risk-Increasing Dietary Factors

The strongest dietary association with increased risk of PD is dairy consumption, as shown in large prospective cohort studies in the USA and Europe [50–54]. Some studies report no association with total dairy intake, rather specifically with consumption of low-fat dairy products [50] and milk [53, 54]. The association is postulated to be due to the urate-lowering effects of dairy products [55]. Urate is a potent antioxidant, with high serum levels linked to lower PD risk [56] and to clinical progression

[57, 100]. Alternatively, dairy products may be contaminated with pesticides, which are associated with increased PD risk [58].

Cholesterol is essential for maintaining the structure and function of cell membranes [59]. Conflicting results are reported regarding the association of cholesterol with risk of PD. High total and low-density lipoprotein cholesterol was associated with a lower risk of PD in US populations [60, 61], Israeli men [62], and Dutch women [63]. Conversely, a significant increase in risk of PD with increasing total cholesterol was reported for Finnish subjects aged 25–44 and 45–54 years at baseline, and for never-smokers and smokers, but not for subjects aged 55 years or older [64]; a meta-analysis of 8 studies showed no association between cholesterol and PD risk [65]. The association between cholesterol and PD is yet to be elucidated.

Type 2 diabetes has been shown to be associated with increased risk of PD in European and Asian population cohorts [66–68], and in one of three US cohorts [61, 69, 70]. Methodological, self-reported diagnostic, demographic, and genetic differences may contribute to conflicting results. A national Danish hospital registry found that diagnosis of, or treatment received for, diabetes was associated with a 35% increased risk of developing PD [67]. In a US cohort, baseline diabetes was associated with a 41% higher risk of PD; the risk was higher among individuals who had had diabetes for more than 10 years at baseline [70]. It is unclear whether diabetes and PD share common pathological pathways of chronic inflammation and oxidative stress, or whether aspects of diabetes increase the risk of PD.

Risk-Reducing Dietary Factors

Of the possible PD risk-reducing dietary components, caffeine, nicotine, and antioxidants are the most examined. Caffeine may be neuroprotective through its antagonistic action on adenosine A₂ receptors in the brain. In two US cohorts, a lower PD risk was evident among individuals with high coffee or caffeine intake [71, 72], as was in individuals who do not drink coffee but whose sources of caffeine were mainly tea and cola [72]. In a Greek cohort, no association between PD risk and caffeine was observed [54]. Meta-analyses have shown that the risk of PD is 30 and 25% lower, respectively, among coffee drinkers [73] and caffeine consumers [74], suggesting that the neuroprotective mechanism is related to caffeine and not to other components of coffee.

Nicotine reduces the oxidative stress associated with progression of PD by scavenging free radicals produced

by monoamine oxidase B, which metabolizes dopamine [75]. The risk of PD is lower among tobacco smokers [73, 76, 77]. Among past smokers, those who smoked the longest number of years or quit most recently had the lowest risk of PD. The quantity of cigarettes smoked was unrelated once adjusted for time smoked, and since quitting. Amongst current smokers, the duration smoked was similar and the quantity smoked unrelated to the risk of PD [73, 76, 77]. Given that smoking duration appears to be a major determinant of risk reduction, testing of any therapeutic potential is limited. Moreover, due to the many adverse effects of smoking, it is not a recommended lifestyle behaviour. However, consumption of nicotine-containing plants of the Solanaceae family, such as peppers, tomatoes, potatoes, and eggplants, is also associated with a lower risk of PD [78]; these feature in the apparently neuroprotective Mediterranean diet [79], and their consumption could thus be encouraged.

Oxidative stress contributes to dopaminergic neuron degeneration in PD [80]. Dietary antioxidants may offset oxidative stress and cellular damage. Hundreds of substances can act as antioxidants; each has its own role and can interact with others to help the body work effectively. Uric acid, an antioxidant found in high concentrations in serum and in the brain, has been hypothesized to protect against oxidative damage and cell death in PD. High urate is associated with a reduced risk of PD [81–83], though the association in women is unclear [84]. The authors suggest that a single measurement of urate in all of these studies may not capture long-term exposure, particularly in women as urate levels may vary more due to menopause and postmenopausal hormone use [84]. While uric acid has shown to have strong antioxidant properties, the potential benefits of a urate-rich diet have to be weighed against the risk of developing gout and cardiovascular disease.

Other potentially beneficial antioxidants include polyphenolic compounds such as flavonoids present in vegetables and fruits that may reduce the risk of neurodegenerative diseases through acting on cell signalling pathways to inhibit cell death and promote cell growth and survival, and as anti-inflammatory agents [85]. High flavonoid intake was associated with a reduced risk of PD in men from the Health Professionals Follow-Up Study cohort (PD: $n = 438$), though not in women from the NHS cohort (PD: $n = 367$). The authors acknowledge that other dietary components may confound the association between flavonoids and PD risk [86]. In a pooled analysis of these two cohorts, a diet comprising high intakes of fruit, vegetables, legumes, whole grain, poultry, and fish was

associated with a reduced risk of PD [87], suggesting that an overall healthy diet is more beneficial than addition of a single dietary component.

Potential Modifiers of Disease Progression

Less is known about lifestyle associations with PD progression, primarily due to the heterogeneous nature of symptoms unique to individuals, in addition to the absence of sensitive and reliable biomarkers. Moreover, given the extensive neuronal damage at diagnosis, lifestyle behaviours after the diagnosis are more likely to impact the quality of life than dopamine levels, the latter of which may be measured via imaging techniques. PD progression is generally assessed by clinical evaluations of motor function, a stable medication dose, and surveys on quality of life and non-motor symptoms. The limitations of clinical and self-assessments as primary measures of health outcomes include composite scores of multiple outcome domains, variability in performance assessments due to assessor subjectivity and possibly medication effects, and the lack of sensitivity to detect small changes which may not be clinically relevant.

Many RCTs examining potential dietary therapies have focused on single components. Thus far, none has shown a beneficial effect on PD progression in phase III trials. In addition to limitations of study design and the focus on single compounds or interventions, it may be that components associated with risk of PD are not associated with disease progression. Though there are strong associations of smoking and caffeine with reduced risk of PD, no benefit has been observed in the treatment of symptoms of the established disease. A 50-week phase II RCT showed that 28 weeks of transdermal nicotine therapy ($n = 20$ /group) did not improve Unified Parkinson's Disease Rating Scale motor scores [88]. Similarly, a daily 400-mg dose of caffeine for 6 months ($n = 60$ /group) did not have any clinically significant effects on motor function [89].

Compounds with strong antioxidant properties, and associations with reduced risk of PD, have been trialled for their potential in slowing PD progression. In two clinical trials (PD: $n = 800$ /trial), patients with higher baseline plasma urate levels showed decreased disease progression as measured by progression to clinical disability requiring levodopa therapy [90, 91]. Trials of inosine, an antioxidant that raises urate levels, are in progress, thus far reporting its safety, tolerability, and effectiveness in raising levels of uric acid [92]. Other antioxidants have proven to be futile as potential therapies to slow PD progression. The largest studies include vitamin E, thought to have an-

tioxidant functions in cell membranes, trialled in a multi-centre placebo-controlled RCT of 800 de novo PD patients. The study demonstrated no benefit of 2,000 IU/day of vitamin E over placebo in delaying disability or the need to initiate treatment with levodopa [93]. Coenzyme Q₁₀, an antioxidant that supports mitochondrial function, showed a potential clinical benefit in a phase II trial. In the subsequent phase III RCT (PD: *n* = 600) over 16 months, neither 1,200 mg/day nor 2,400 mg/day of coenzyme Q₁₀ had a clinical benefit. The study was terminated early as the subjects in all groups required conventional treatment at similar rates [94]. Similarly, creatine, important in cellular energy production, showed a possible benefit to motor symptoms [95, 96]. In the subsequent phase III RCT (PD: *n* = 1,741), creatine failed to slow PD progression as measured by a difference in clinical decline from baseline to 5-year follow-up between the intervention and control groups. The researchers suggested that the outcome may have been related to the creatine dosage or to a change in the stage of the PD patients studied compared with the futility study [97].

Though there is a lack of evidence that a higher intake of specific antioxidants can reduce the risk of disease, a predominantly plant-based diet that includes a variety of antioxidants may potentially be beneficial. A cross-sectional study of 1,053 PD patients showed that fresh vegetables, fresh fruit, nuts and seeds, non-fried fish, olive oil, wine, coconut oil, fresh herbs, and spices were associated with a significantly reduced rate of decline across 33 common PD symptoms. Foods associated with more rapid PD progression included canned fruits and vegetables, diet and non-diet soda, fried foods, beef, ice cream, yogurt, and cheese [79]. While these findings need to be verified, minimizing exposures to these potentially disease-progressing foods may not be justified on the basis of one observational study but is in keeping with generally positive overall health benefits.

Conclusions

While studies have yet to determine precise mechanisms by which modifiable lifestyle behaviours contribute to neuronal health generally, given their known impact on chronic disease risk reduction and management, as well as on quality of life, these should be prescribed more frequently as basic skills for disease prevention and self-management.

In PD in particular, there is limited evidence that some lifestyle factors are related to a lowered risk of developing

the disease, including caffeine intake, smoking, physical activity, and some dietary factors including a diet that results in higher serum urate. There is less evidence that such factors are involved in modifying disease progression, but since protective factors appear to have additive effects in reducing the risk of PD [98], there may be a role for multimodal positive lifestyle behavioural interventions in PD disease management. However, this is an area that demands considerably more research, including lifestyle behaviours such as sleep, stress, and social and cognitive engagement, which appear to have an impact on the risk and management of other neurological disorders [99], before any clinical recommendations can be made. With an aging population, and an increased incidence of PD with age [17], it is increasingly important to better elucidate the potential contribution of lifestyle to PD health outcomes.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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