The epidemiology of Parkinson's disease: risk factors and prevention

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Since 2006, several longitudinal studies have assessed environmental or behavioural factors that seem to modify the risk of developing Parkinson's disease. Increased risk of Parkinson's disease has been associated with exposure to pesticides, consumption of dairy products, history of melanoma, and traumatic brain injury, whereas a reduced risk has been reported in association with smoking, caffeine consumption, higher serum urate concentrations, physical activity, and use of ibuprofen and other common medications. Randomised trials are investigating the possibility that some of the negative risk factors might be neuroprotective and thus beneficial in individuals with early Parkinson's disease, particularly with respect to smoking (nicotine), caffeine, and urate. In the future, it might be possible to identify Parkinson's disease in its prodromal phase and to promote neuroprotective interventions before the onset of motor symptoms. At this time, however, the only intervention that seems justifiable for the primary prevention of Parkinson's disease is the promotion of physical activity, which is likely to be beneficial for the prevention of several chronic diseases.

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Introduction

Major discoveries have profoundly changed our understanding of Parkinson's disease and its determinants. Whereas genetic studies[1] have revealed the heterogeneity of Parkinson's disease and provided insights into its pathogenesis and aetiology,[2] epidemiological investigations have provided robust evidence that behavioural and environmental factors have a key role in disease pathogenesis and progression. This evidence is strengthened and complemented by observations that 90% of Parkinson's disease cases have no identifiable genetic cause,[3] and that many factors associated with an altered risk of Parkinson's disease have neuroprotective or neurotoxic properties in animal models of the disease.

In this Review, we provide an update on the descriptive epidemiology of Parkinson's disease, and then focus on the epidemiological advances of the last 10 years and their implications for Parkinson's disease prevention and treatment. Studies on genetic forms of Parkinson's disease or parkinsonism other than idiopathic Parkinson's disease, and the substantial advances in the identification and characterisation of prodromal Parkinson's disease are considered beyond the scope of this Review. Where evidence exists, we mention briefly the potential underlying biological mechanism of the epidemiological findings. We describe comprehensively the longitudinal investigations of nongenetic risk factors for Parkinson's disease, and provide a critical summary of current knowledge, knowledge gaps, and implications. Because most epidemiological studies do not distinguish idiopathic Parkinson's disease from Parkinson's disease due to genetic mutations, and rely on clinical rather than pathological diagnostic criteria, from here on we refer to Parkinson's disease without further specifications, with the understanding that the conclusions, being driven by the more common clinically defined sporadic Parkinson's disease, might not apply to monogenetic forms, and might be affected by the accuracy of the clinical diagnoses, which is typically only 80–90% when compared with pathological findings.[4]

Progress over the past 10 years in understanding the risk factors for Parkinson's disease can largely be attributed to prospective longitudinal studies, which have well known advantages over case-control studies that rely on the participants' recall of past events. Recall bias is particularly important in Parkinson's disease, which has a long prodromal phase characterised by symptoms such as hyposmia, constipation, and sleep disorders that might be present up to 20 years before manifestation of the characteristic motor symptoms,[5] and are likely to affect several aspects of lifestyle, such as diet, physical activity, and medication. Further, for most case-control studies, the representativeness of the control group is uncertain. This Review, therefore, mostly relies on studies conducted within well defined cohorts of individuals without Parkinson's disease who have provided biological samples or information on the exposures of interest at time of recruitment, and were then followed prospectively for the occurrence of newly diagnosed Parkinson's disease; this category includes case-control studies nested within these cohorts (table). Validity of these investigations requires accurate information on the exposures and potential confounders and their changes over time, the duration and completeness of the follow-up and Parkinson's disease ascertainment, and the correctness of the Parkinson's disease diagnosis. Weaknesses in one or more of these aspects are common, and therefore understanding of risk factors for Parkinson's disease requires an assessment of each investigation and the exploration of potential alternative explanations of the reported findings.

The increased availability of large electronic databases has provided an additional source of epidemiological data, which are particularly useful to investigate the relation between prescription drugs and other medical events (eg, head trauma) and Parkinson's disease risk, but lack accurate information on confounders and dates

	Age at baseline	Participants*	Incident cases*	Case ascertainment	Longest follow-up*	Regularly updated exposure and confounders†
Honolulu-Asia Ageing Study (HAAS)[6]	45–68	7504 men	128	Physical exam	30 years (1968–98)	No
Health Professionals Follow-up Study (HPFS)[7]	40–75	51 500 men	438	Self-report; medical record	20 years (1986–2006)	Yes
Nurses' Health Study[8]	30–55	121 700 women	508	Self-report; medical record	30 years (1976–2008)	Yes
Cancer Prevention Study-II Nutrition (CPS-IIN)[9]	50–79	147 000 (about 45% women)	605	Self-report; medical record	13 years (1992–2005)	Yes
Rotterdam Study[10]	55+	6512 (about 60% women)	88	Physical exam	14 years (1990–2004)	No
FAME (Agricultural Health Study)[11]‡	12–92	84 739 (about 72% men)	87	Self-report; physical exam	10 years (1993–2003)	Yes
Finnish cohort[12]	25–74	51 552 (about 50% women)	633	Drug register linkage	40 years (1964–2002)	No
Finnish Mobile Clinic Health Examination Survey (FMC)[13]	40–79	4524 (about 52% women)	101	Drug register linkage (partial validation by medical record)	41 years (1966–2007)	No
National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP)[14]	50–71	309 619 (about 42% women)	1087	Self-report; medical record	11 years (1995–2006)	No
Atherosclerosis Risk in Communities (ARIC)[15]	45–64	15792 (about 57% women)	95	Mixed‡	21 years (1987–2008)	Yes
European Prospective Investigation into Cancer and Nutrition (EPIC)-Greece[16]	20–86	25 407 (85% women)	88	Self-report; phone interview	16 years (1993–2009)	No
Physician Health Study (PHS)[17]	40–84	22 007 men	616	Self-report	26 years (1982–2008)	Yes
Shanghai Women Health Study (SWHS)[18]	40–70	74 941 women	76	Physical exam	15 years (1996–2011)	Yes
Singapore Chinese Health Study (SCHS)[18]	45–74	63 257 (about 55% women)	157	Mixed; medical record	17 years (1993–2005)	No

*Numbers are approximate, as subject to changes across publications; †Answer of yes requires that all or most relevant variables were regularly updated. ‡Use of antiparkinsonian drugs, self-reported diagnosis of Parkinson's disease, or ICD code for Parkinson's disease following hospitalisation or on death certificate.

Table: **Longitudinal studies on risk factors for Parkinson's disease**

of disease onset. Date of disease onset is often equated to the date of diagnosis or first treatment for Parkinson's disease, which in some individuals can be years after symptom onset.[19] Keeping these limitations in mind, we have referred to these studies to complement the inference that could be made from prospective cohorts.

Descriptive epidemiology of Parkinson's disease

Methodological differences hinder comparisons of Parkinson's disease incidence across studies;[20,21] however, a few inferences can be made. Parkinson's disease is the second most common neurodegenerative disease (after Alzheimer's disease), with median age-standardised annual incidence rates in high-income countries of 14 per 100 000 people in the total population, and 160 per 100 000 people aged 65 years or older.[22] A perhaps more interpretable measure of disease frequency is lifetime risk, which was estimated to be 2% for men and 1·3% for women, for individuals aged 40 years in the USA, taking into account competing risks (eg, death from other causes such as cardiovascular disease or cancer).[23] Age-adjusted Parkinson's disease prevalence, which reflects both incidence and mortality, appears to be lower in Africa than in Europe and the Americas.[24–26] Incidence in Asia is similar to that in Europe and the Americas.[27,28] Data on incidence by race or ethnicity are sparse and inconsistent; in a study in New York, USA, incidence was reported to be higher in black people than in white people,[29] whereas in participants in a large health organisation in the USA, the age-adjusted and sex-adjusted incidence of Parkinson's disease was highest among Hispanic people (16·6 per 100 000 people), followed by non-Hispanic white people (13·6), Asian people (11·3) and black people (10·2).[30] In a study based on US Medicare beneficiaries, incidence was also higher in white people than in black or Asian people.[31] A 6% yearly decline in increase of Parkinson's disease was reported from 1999 to 2009 in the UK, which was attributed to the improved diagnosis of different parkinsonian syndromes, because the overall incidence of parkinsonism remained constant.[32] By contrast, both parkinsonism and Parkinson's disease were reported to decline between the 1990s and 2000–10 in Rotterdam, Netherlands,[33] and to increase from 1976 to 2005 in Minnesota, USA.[34]

The incidence of Parkinson's disease is low before the age of 50 years, but it increases rapidly with age,

peaking in most studies at around 80 years, probably because of underdiagnosis with increasing age.[35] A spurious decrease in Parkinson's disease incidence with increasing age is likely to occur because of the increasing prevalence of dementia, which when present at time of onset of motor symptoms is an exclusion criterion for the diagnosis of Parkinson's disease. The male to female (M:F) incidence ratio ranges from around 1·3 to 2·0 in most studies, but rates as low as 0·95 have been observed in Asia,[36] possibly reflecting sex differences in smoking behaviour, discussed in more detail later in this Review.

Risk factors

Dairy products

Risk of Parkinson's disease is increased among individuals with high milk and dairy consumption. In the USA, results have been reported from the Nurses' Health Study and the Health Professionals Follow-up Study (HPFS),[37] the Honolulu-Asia Ageing Study (HAAS),[6] and the Cancer Prevention Study II Nutrition (CPS-IIN).[38] In a meta-analysis of results from these cohorts, the relative risk (RR) of Parkinson's disease comparing the highest with the lowest category of dairy intake was 1·6 (p<0·0001).[38] Neither vitamin D (added to milk in the USA) nor calcium intake explained this association. A positive association for consumption of milk was found also in the Finnish Mobile Clinic (FMC) cohort,[39] and for consumption of both milk and other dairy products in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Greece cohort.[16] An updated meta-analysis including all of the above studies supported an association between high dairy intake and Parkinson's disease risk that was stronger in men than women.[40] An inverse association was reported between milk consumption and neuronal density in the substantia nigra among non-smokers in the HAAS cohort.[41] In the same study, the finding of residues of heptachlor epoxide more commonly in the brain of those who drank the most milk, as compared with those who did not drink milk, suggested that this contaminant could be causally related to Parkinson's disease risk.[41] Although the possibility that a milk contaminant underlies the association between dairy consumption and disease risk cannot be excluded, overall the findings from multiple cohorts and countries are more consistent with the increased Parkinson's disease risk being associated with the urate-lowering effects of dairy products.[42]

Pesticides

The hypothesis that exposure to pesticides and other environmental chemicals increases Parkinson's disease risk was suggested by the discovery of the neurotoxic effects of a metabolite of 1-methyl,-4-phenyl-1,2,3,6-tetra hydropyridine (MPTP), which is converted in the body to a pro-parkinsonian molecule with a structure similar to the herbicide paraquat.[43] In the HAAS cohort, Parkinson's disease risk increased with increasing duration of work in plantations (RR 1·9 for 20 or more years *vs* none, p for trend=0·006) and, albeit not-significantly, with self-reported exposure to pesticides.[44] In France, a positive association, but no dose-response, was reported between pesticide exposure—estimated through a job-exposure matrix—and Parkinson's disease risk.[45] In the CPS-IIN cohort,[46] exposure to pesticides in 1982, which was self-reported by 6% of participants, was associated with a doubling of Parkinson's disease risk after 1992; no association was found for exposure to 11 other chemicals. In the Agricultural Health Study, Parkinson's disease risk increased monotonically with increasing number of days of exposure to pesticides; the RR was 2·3 for more than 397 days versus less than 64 days of lifetime exposure (p for trend=0·009). In a prospective investigation in Finland,[47] blood concentrations of organochlorine pesticides (the only pesticides for which a single blood concentration provides a reasonable measure of long-term exposure) were not associated with Parkinson's disease risk, a result that suggests that it is other classes of pesticides that increase Parkinson's disease risk. In the Agricultural Health Study, positive associations were found between disease risk and exposure to pesticides known to affect mitochondrial complex I (including rotenone) or to cause oxidative stress (including paraquat).[48] Overall, evidence that pesticide exposure increases Parkinson's disease risk is substantial, but the risk associated with specific compounds remains uncertain.

Methamphetamine

Methamphetamine binds to the presynaptic dopamine transporter thus increasing extracellular concentrations of dopamine, and in experimental animals damages the dopaminergic neurons in the substantia nigra producing pathological changes similar to those observed in the brains of Parkinson's disease patients.[49] An association between amphetamine or methamphetamine use and Parkinson's disease risk was found in two studies based on record linkage in California (RR=2·7 based on 30 incident cases of Parkinson's disease, p=0·019)[50] and Utah (RR=2·8, based on 42 incident cases of Parkinson's disease; p<0·001).[51]

Cancer

An increased risk of Parkinson's disease among individuals with melanoma is well documented.[52] In a large Danish study[53] including over 8000 patients with Parkinson's disease, a diagnosis of melanoma was associated with a 44% increased risk of developing Parkinson's disease. Similar associations were reported in a nationwide study in Sweden.[54] Further, a markedly increased risk of melanoma has been reported among individuals with early Parkinson's disease (usually defined as Parkinson's disease within 5 years after diagnosis and with symptoms not sufficiently severe to

require dopaminergic treatment) enrolled in randomised trials.[55–57] The underlying cause of these positive associations is still uncertain. A shared risk factor for both Parkinson's disease and melanoma is hair colour (risk of both increases from black to brown, blond, and red).[58] The finding of an increased Parkinson's disease risk among individuals with family history of melanoma suggested a common genetic predisposition,[59] but associations between red hair or melanoma risk alleles and Parkinson's disease have not been substantiated,[60] and known Parkinson's disease susceptibility alleles seem unrelated to melanoma risk.[61] Further, in a Swedish nationwide study, there was no increase in melanoma risk among siblings of Parkinson's disease patients.[54] Other common risk factors or biomarkers for Parkinson's disease and melanoma include smoking (inverse),[62] caffeine (inverse),[63,64] and shorter telomeres (inverse).[65,66]

Because smokers have a markedly reduced risk of Parkinson's disease, smoking-related cancers and Parkinson's disease tend to be inversely associated.[67] Data on the relation between non-smoking-related cancers and Parkinson's disease risk are inconsistent, although a review suggested that the overall reduction in cancer risk in people with Parkinson's disease is not fully explained by smoking.[67]

Traumatic brain injury

Traumatic brain injury can cause a breakdown of the blood–brain barrier, long-lasting brain inflammation, disruption of mitochondrial function, increase in glutamate release, and α-synuclein accumulation in the brain,[68] all of which could contribute to an increased incidence of Parkinson's disease following this type of injury. However, results of several investigations[68] suggest that the risk of Parkinson's disease appears to increase soon after traumatic brain injury, but gradually decreases over time. In a Danish study of over 13 000 Parkinson's disease cases, the RR of Parkinson's disease following concussion was 6·6 (95% CI 4·4–9·9) within 3 months of the injury, 1·9 (1·3–2·8) between 4 and 12 months, 1·8 (1·4–2·2) between 1 and 4 years, 1·4 (1·1–1·7) between 5 and 9 years, and after 10 years following any type of head injury there was no significant increase in Parkinson's disease risk (RR 1·1, 95% CI 0·9–1·3).[69] In a similar study in Sweden of over 18 000 Parkinson's disease cases, the RR for Parkinson's disease was 3·34 (95% CI: 2·72–4·12) within 12 months following hospitalisation for head injury, but decreased to 1·28 (1·09–1·51) in years 1–4, 1·18 (1·00–1·40) in years 5–9, and 1·17 (0·99–1·39) after 10 years.[70] The early increase in Parkinson's disease risk in both studies is probably explained by more frequent falls and head trauma in individuals with early Parkinson's disease (reverse causation), but whether there is a long-term increase in risk of Parkinson's disease is difficult to establish. Many Parkinson's disease patients have symptoms for years before their diagnosis is recorded, as shown in a Danish study[69] where the date of the first drug prescription for Parkinson's disease often preceded the date of the first hospital contact for Parkinson's disease. Reverse causation might also explain the results of other studies with short follow-up after traumatic brain injury.[71]

Body-mass index and diabetes

No association between body-mass index (BMI) and Parkinson's disease risk has been found in most longitudinal studies,[13,16,72–78] and in a meta-analysis, the summary RR associated with a 5 kg/m² increase in BMI was 1·0 (95% CI 0·9–1·1).[79] The exception is a cohort in Finland,[74] in which being overweight (ie, BMI 27–29·9) or obese (ie, BMI ≥30) were strong risk factors for Parkinson's disease (hazard ratio [HR] 2·0 for each group compared to BMI <23). The finding of an increased Parkinson's disease risk among individuals with high triceps skinfold thickness[72] or waist-to-hip ratio[73,74] suggests that adipose distribution might be a better indicator of Parkinson's disease risk than overall body mass. In a cohort study in Finland,[80] the metabolic syndrome was associated with a 50% lower Parkinson's disease risk (RR 0·5, 95% CI 0·30–0·83); this association was mostly driven by elevated fasting plasma glucose (0·52, 0·3–0·89; p=0·02). By contrast, a significant increase in Parkinson's disease risk among individuals with type 2 diabetes has been reported in a cohort in Finland,[12] in database investigations in Denmark[81] and Taiwan,[82] in the Physician Health Study,[76] and in the NIH-AARP cohort.[83] However, no association was found between diabetes and Parkinson's disease risk in two large prospective US cohorts.[77,84] These conflicting results suggest that there is a complex relation between insulin resistance and Parkinson's disease, which is perhaps modified by other factors, such as hyperuricaemia, which is a risk factor for type 2 diabetes,[85] but inversely associated with risk of Parkinson's disease (see later in this Review). Diabetes and Parkinson's disease might have common cellular mechanisms: mitochondrial dysfunction and under-expression of the transcriptional regulator PPARγ coactivator 1α (PGC1α),[86–88] which stimulates mitochondrial biogenesis and respiration.[89] Further, Parkinson's disease risk among individuals with diabetes could be reduced by use of antidiabetic drugs such as metformin, exenatide, or dipeptidyl peptidase inhibitors.[90,91]

Blood cholesterol and hypertension

A lower risk of Parkinson's disease in participants with high blood cholesterol was found in the Rotterdam cohort (RR 0·77 per mmol/L increase, 87 incident Parkinson's disease cases)[92] and in the HAAS (RR 0·6 for 135 mg/dL *vs* 85 mg/dL, n=41; 95% CI 0·4–1·1, p for risk=0·04),[93] whereas a marked and significant increase in risk (RR 1·9 for 7 mmol/L or more *vs* less than 5 mmol/L , 95% CI 1·3–2·6; p for risk=0·002) was reported in a large cohort in Finland (n=625).[94] In the

Nurses' Health Study and HPFS (n=530 for both cohorts combined), Parkinson's disease risk decreased with increasing self-reported blood cholesterol (RR 0·86 for 50 mg/dL increase, 95% CI 0·78–0·95; p for trend=0·02), but was not associated with history of diagnosed hypercholesterolemia, hypertension, or blood pressure.[84] These discordant results suggest that there are unrecognised confounding or modifying factors that modulate the association between blood cholesterol and Parkinson's disease risk.

Alcohol

Overall, the results of longitudinal studies[95] support a modestly lower Parkinson's disease risk among drinkers as compared with non-drinkers, a result consistent with the urate-elevating effects of alcoholic beverages[96] (RR 0·86, 95% CI 0·75–1·0; p=0·05 comparing the highest and lowest categories of intake in a meta-analysis of longitudinal studies). However, in a study based on the Swedish National Inpatients Register and including over 1000 cases of Parkinson's disease, alcohol misuse (defined as hospital admission with a diagnosis of alcohol use disorder) has been associated with an increased Parkinson's disease risk (RR 1·4, 95% CI 1·3–1·5; p<0·0001).[97]

Postmenopausal hormones and reproductive factors

The higher incidence of Parkinson's disease in men than women suggests the existence of hormonal determinants of Parkinson's disease risk. Among women in the Cancer Prevention study,[98] there was a 33% (95% CI 7–67) increased risk of Parkinson's disease death (n=340) in participants who reported use of postmenopausal oestrogens compared with women who did not use these drugs. Non-significant increases in Parkinson's disease risk (ranging from 18–41%) among postmenopausal hormone users were reported among women in the Nurses' Health Study,[99] in a cohort in Denmark,[100] and in the NIH-AARP study.[101] The results of these studies suggest that use of postmenopausal hormones might be associated with an increase in Parkinson's disease risk, rather than a decreased risk that might be suggested by the difference in prevalence between men and women.[102] The association between oestrogen use and risk of Parkinson's disease might be modified by caffeine intake.[93,103,104] Overall, there is no convincing evidence of associations between Parkinson's disease risk and other reproductive factors, including age at menarche, use of oral contraceptives, pregnancy history, or type of menopause.[99–101,105]

Vitamins and other micronutrients

Total intake of antioxidant vitamins, including vitamin C and E, and carotenoids, was not associated with Parkinson's disease risk in the Nurses' Health Study and HPFS cohorts.[106] Findings from longitudinal studies mostly suggest no association between Parkinson's disease risk and folic acid and B vitamins,[107] except for an inverse relation between intake of vitamin B6 and Parkinson's disease in the Rotterdam cohort.[108] Intakes of vitamin D and calcium also seem unrelated to Parkinson's disease risk.[38] Serum 25(OH)D concentration, a marker of vitamin D status, was inversely associated with Parkinson's disease risk in a Finnish cohort.[109] Vitamin D deficiency is common in Parkinson's disease and it has been suggested that it could have prognostic value.[110] Iron accumulates in the substantia nigra in Parkinson's disease,[111] and iron overload has been proposed as a potential mechanism for Parkinson's disease pathogenesis. This hypothesis is weakened by the absence of an association between number of blood donations—which is inversely correlated with serum ferritin and total body iron—and Parkinson's disease risk.[112] In the only longitudinal study to assess iron intake, total iron intake was not associated with Parkinson's disease risk.[113] Little or no information is available on the relation between other vitamins and minerals and Parkinson's disease risk.

Fat and other macronutrients

In the HPFS and Nurses' Health Study,[114] replacement of polyunsaturated fat with saturated fat was associated with increased Parkinson's disease risk in men, but not in women (5% of energy intake; RR 1·8; 95% CI 1·10–3·03; 359 incident cases of Parkinson's disease). In the Rotterdam cohort,[115] Parkinson's disease risk decreased with increasing intakes of total fat (RR 0·69, 95% CI 0·51–0·91 for 1 SD increase) or polyunsaturated fat (0·66, 0·46–0·96), whereas in the Singapore Chinese Health study[116] Parkinson's disease risk was inversely related to intake of monounsaturated fat (0·74, 0·47–1·19 for highest to lowest quartile; p for trend=0·05), but not polyunsaturated fat (p for trend=0·66). In the HAAS,[117] intake of polyunsaturated fat was associated with lower Parkinson's disease risk, but only among never smokers (p=0·04). By contrast, a weak positive association between polyunsaturated fat intake and Parkinson's disease risk was reported in the NIH-AARP cohort (RR for highest *vs* lowest quintile 1·2, 95% CI 1·0–1·5; p=0·02).[14] Overall, there is no convincing evidence that intakes of total fat or different fatty acids or other macronutrients are related to Parkinson's disease risk.

Other factors

There are many putative risk factors for Parkinson's disease for which evidence is still sparse or inconsistent. These include early life factors such as season of birth, birthweight, parental age,[118] and several infections such as measles (inverse association),[119] infections of the CNS,[120] hepatitis C,[121] and *Helicobacter pylori*.[122] Influenza has been associated with an increased risk of parkinsonism, but not of Parkinson's disease. Manganese can cause parkinsonism,[123] but evidence on Parkinson's disease risk remains inconclusive. An increased Parkinson's disease

risk among individuals with autoimmune diseases[124] and those of higher socioeconomic status[125] has been found in registry-based studies in Sweden, and among those with rosacea in Denmark.[126] Finally, there is growing interest, but no longitudinal data, in the potential role of solvents (eg, trichloroethylene) as an adverse risk factor[127] and the gut microbiome as a modulator of Parkinson's disease risk.[128]

Protective factors

Tobacco

A low Parkinson's disease risk among tobacco smokers was reported in several prospective investigations,[129–132] and has also been reported in users of smokeless tobacco (eg, chewing tobacco).[133] Results of these investigations showed that Parkinson's disease risk decreases up to 70% with increasing duration of smoking, and increases with time since quitting in ex-smokers.[131] The strength of the association, clear dose-response, and robustness to multivariate adjustment make confounding by known risk factors for Parkinson's disease an unlikely explanation for this decrease in risk. Moreover, the inverse relation between smoking and Parkinson's disease among monozygotic twins,[134,135] makes a genetic explanation highly unlikely. Although individuals predisposed to Parkinson's disease tend to be risk-averse and low on sensation-seeking scores (consistent with a premorbid personality of Parkinson's disease), and thus less inclined to initiate or continue to smoke,[136] adjustment for a sensation-seeking score only slightly attenuated the inverse relation between smoking and Parkinson's disease, suggesting that these factors act independently.[136] Similarly, personality traits such as neuroticism and introversion do not explain the relation between smoking and Parkinson's disease risk.[137] It has been suggested that there is a decreased responsiveness to nicotine during the prodromal phase of Parkinson's disease, so that smoking cessation could be an aspect of preclinical Parkinson's disease.[138] This hypothesis, however, does not explain the lower risk of Parkinson's disease among ever smokers as compared with never smokers; because the age at first smoking is predominantly under 30 years, so the prodromal phase of Parkinson's disease would have to start in the 20s to explain this association. Alternatively, randomly occurring constitutional differences already manifest in the 20s could perhaps determine susceptibility to both nicotine addiction and low Parkinson's disease risk. There are, however, two important findings that appear to contradict the prodromal and constitutional Parkinson's disease hypotheses. First, if smoking reduced Parkinson's disease risk, a change in M:F smoking behaviour would change the M:F Parkinson's disease incidence, but no such change would be expected in the absence of a causal link. In an ecological study[139] taking advantage of the substantial changes in the M:F smoking behaviour across different countries and birth cohorts, a significant correlation (r=0·28, p=0·0002) was found between observed M:F ratio in Parkinson's disease incidence and smoking behaviour. Overall, the results suggest that smoking reduced Parkinson's disease risk by 74%.[139] Although confounding by other factors with geographical and historical trends similar to smoking cannot be excluded, these data support a causal role for smoking in the reduction of Parkinson's disease risk.

Furthermore, if the inverse association between smoking and Parkinson's disease incidence was due to a decreased responsiveness to nicotine among individuals with prodromal Parkinson's disease or constitutionally predisposed to Parkinson's disease, parental smoking behaviour would not be expected to predict Parkinson's disease risk in the offspring (unless it is postulated that the constitutional predisposition to Parkinson's disease is inherited, which is contradicted by the results of twin studies). The inverse association between parental smoking and Parkinson's disease risk thus provides indirect evidence for a protective effect of tobacco—the lower Parkinson's disease risk being explained by the higher frequency of smoking among the offspring of smokers.[140]

Although none of these arguments provides in itself unassailable proof, the evidence that tobacco use decreases Parkinson's disease risk is compelling. The potential therapeutic effect of nicotine, which is neuroprotective in some animal models of Parkinson's disease,[141] is being investigated in a randomised trial in patients with early Parkinson's disease (ie, within 18 months of diagnosis; NCT01560754), but a role of other tobacco components cannot be excluded.

Coffee and caffeine

A lower Parkinson's disease risk among coffee drinkers as compared with non-drinkers has been shown in several prospective cohorts,[142,143] and appears to be due to caffeine consumption.[144] The association is stronger and more robust in men (RR for the highest compared with the lowest category of coffee or caffeine intake ranging from 0·18 to 0·85), than in women (RR ranging from 0·39 to 1·49),[143] probably because of an interaction between caffeine and postmenopausal hormones.[144] Caffeine intake was associated with reduced Parkinson's disease risk among women not using postmenopausal hormones, but not among hormone users.[93,103,104] However, this interaction between caffeine and hormones was not substantiated by the NIH-AARP cohort.[143] Inverse associations between coffee or caffeine consumption and Parkinson's disease risk have been reported in longitudinal studies in Finland[145,146] (RR for ≥5 cups per day *vs* non-drinkers 0·40, 95% CI 0·23–0·71; p=0·005, RR for ≥10 cups per day 0·26; 95% CI 0·07–0·99, p for trend=0·18) and Singapore (RR for highest *vs* lowest quintile of caffeine intake 0·55, 95% CI 0·35–0·88; p for trend=0·002).[116] By contrast, no association between coffee consumption and Parkinson's disease risk was found in the Swedish Twins cohort, but power of that

study was limited by the fact that only about 3% of participants reported no coffee drinking.[135] Overall, evidence relating caffeine consumption to a reduced Parkinson's disease risk is robust, but uncertainty remains about possible interactions with sex hormones and the dose-response.

A neuroprotective effect of caffeine, an adenosine receptor antagonist, is well documented in experimental models of Parkinson's disease, and is probably mediated by adenosine A_{2A} receptor blockade.[147,148] This effect is stronger in male than in female mice and, as in women, there seems to be an interaction between caffeine and oestrogens in rodents.[149] Although caffeine is the most probable neuroprotective component of coffee, other constituents (eg, cafestol) might also contribute.[150,151] Low doses of caffeine have symptomatic benefits on freezing of gait,[152] and bradykinesia or rigidity.[153,154] More selective A_{2A} receptor antagonists (eg, istradefylline and tozadenant) provide symptomatic benefit in clinical trials among levodopa-treated Parkinson's disease patients.[155,156] The possibility that caffeine (a non-specific adenosine antagonist) or more selective A_{2A} receptor antagonists have neuroprotective effects has not been rigorously addressed in trials in individuals with Parkinson's disease. Considering the well established safety profile of caffeine and its probable beneficial effects in the prevention of conditions common among individuals with Parkinson's disease, such as depression,[157] its potential neuroprotective effects among individuals who are not usual caffeine consumers deserve further investigation.

Green and black tea

Parkinson's disease risk is lower among tea drinkers than non-drinkers, although this association is more apparent in individuals who are not coffee drinkers (RR 0·4, 95% CI 0·2–2·12; p for trend=0·02 for regular tea drinkers *vs* nondrinkers in the HPFS[144] and RR 0·4, 95% CI 0·2–0·8 for ≥3 cups of tea per day *vs* non-drinkers in the Finnish cohort).[145] In a cohort study in Singapore,[116] consumption of black tea was associated with a reduced risk of Parkinson's disease (RR=0·29 for the highest *vs* lowest tertile of intake, 95% CI 0·13–0·67; p for trend=0·0006), but green tea was not. Because the association persisted after adjustment for total caffeine intake, the authors concluded that components of black tea other than caffeine might contribute to reduce Parkinson's disease risk.[116] This preliminary finding—which seems to contradict early experimental studies suggesting protective effects of green tea components such as epicatechin and epigallocatechin gallate[158]—needs to be substantiated.

Urate

Urate (uric acid), the end product in the metabolism of purines such as adenosine,[159] is a potent antioxidant and is circulated within the body at high concentrations. Laboratory studies of cellular and rodent models of Parkinson's disease have provided consistent evidence that urate can protect against dopaminergic neuron degeneration,[160–163] probably via activation of the Nrf2/antioxidant response pathway.[164] Because oxidative stress is thought to play a role in the pathogenesis of Parkinson's disease, high urate concentrations would be expected to associate with a lower Parkinson's disease risk. In the HAAS cohort, an inverse trend was observed between serum urate measured at baseline and Parkinson's disease incidence in the ensuing 30 years (RR 0·6, 95% CI 0·4–1·0 for highest *vs* lowest tertiles).[165] This observation was supported by the results of the Rotterdam study[166] and in the HPFS;[167] in the HPFS cohort of 18 000 men in the HPFS cohort, Parkinson's disease risk was 55% lower among men in the highest quartile of plasma urate as compared with those in the lowest quartile.[167] Further, this inverse association was independent of age, BMI, smoking, caffeine consumption, and other aspects of lifestyle (eg, physical activity and alcohol consumption) that have been related to both Parkinson's disease and uricaemia. A 2007 meta-analysis of the available prospective data on urate and Parkinson's disease risk showed a substantially lower risk of Parkinson's disease in people who had higher plasma urate concentrations, with a 20% reduction in the pooled rate ratio of Parkinson's disease for each standard deviation (1·3 mg/dL) increase in blood urate concentration (p<0·0001).[167] Several more recent prospective cohort studies[15,168,169] have provided further evidence for serum urate as an inverse risk factor for Parkinson's disease, particularly in men.[15,170] The risk of Parkinson's disease was also reduced in people with gout, as shown in two independent prospective cohort studies,[171,172] although not in a third.[173]

In addition to serum urate concentration itself, the genetic and environmental (dietary) determinants of urate concentration have also been linked to Parkinson's disease risk, supporting the hypothesis of a causal and modifiable relation between urate concentration and Parkinson's disease. SLC2A9 is a urate transporter and variation in its gene is the strongest known genetic determinant of blood urate concentration in human beings.[174] *SLC2A9* polymorphisms predictive of higher serum urate concentrations have been associated with later age of symptom onset in Parkinson's disease.[175] Similarly, a composite genetic index of lower serum urate concentration including single nucleotide polymorphisms in *SLC2A9* and eight other urate-associated genes was significantly higher in people with Parkinson's disease than in control participants.[176] However, in a case-control study single nucleotide polymorphisms of *SLC2A9* were not associated with Parkinson's disease.[177] Complementing these so-called urate gene links to Parkinson's disease, high intake of dietary sources of urate (eg, fructose) was associated with a reduced risk of Parkinson's disease in the prospectively followed HPFS cohort (RR 0·47, 95% CI 0·30–0·74 for highest *vs* lowest quintile of a dietary urate index).[178]

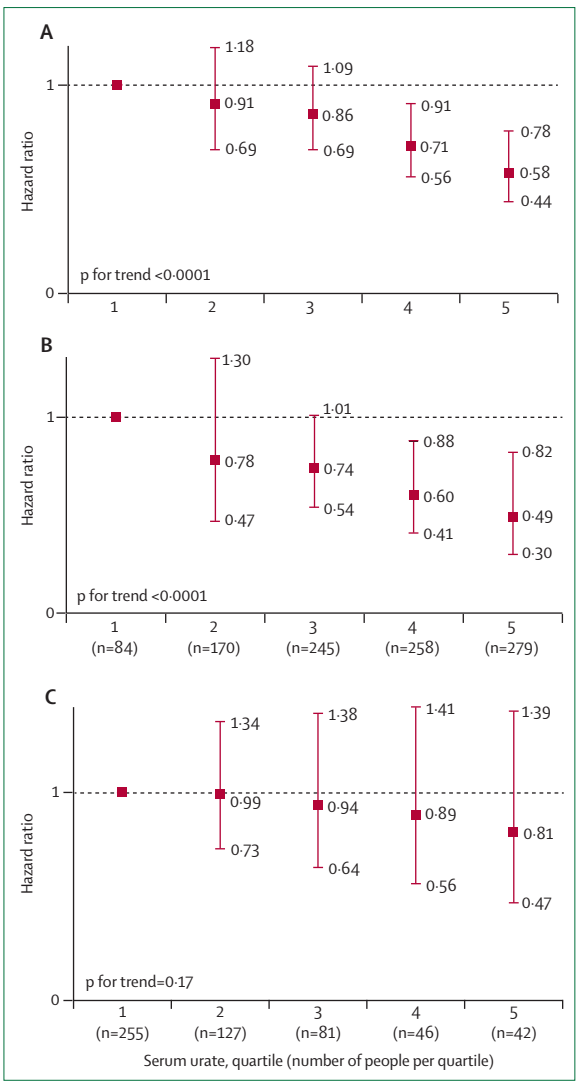

Figure 1: **Serum urate as a predictor of Parkinson's disease disability progression in the pooled PRECEPT and DATATOP cohorts**
(A) All participants. (B) Men. (C) Women. Tabulated hazard ratios of reaching the primary endpoint of disability sufficient to require dopaminergic therapy according to quintiles of serum urate. Data are presented as mean and 95% CI. p values are for trends across quintiles.

The epidemiological association with Parkinson's disease risk in healthy populations prompted the investigation of the link between urate and Parkinson's disease progression amongst participants in two long-term, rigorously managed clinical trials, known as Parkinson Research Examination of CEP-1347 Trial (PRECEPT)[179] and Deprenyl and Tocopherol Antioxidative Therapy of Parkinson's Disease (DATATOP).[180] Together these studies included over 1600 patients with early Parkinson's disease, and in both studies, the hazard ratio of reaching the primary study endpoint—ie, the development of disability sufficient to require dopaminergic therapy—declined with increasing serum urate concentration (p<0·0001 for trend in PRECEPT, and p=0·002 in DATATOP).[181,182] The similar population characteristics and design of the two studies allowed for pooled analysis and substantiation of a decreasing rate of disability progression as a function of serum urate concentrations early in Parkinson's disease (figure 1). In an analysis by sex, a more robust and progressive reduction in the hazard ratio with increasing urate concentration was found in men (p<0·0001 for trend), but this association was not shown in women (p for trend=0·17). This sex difference, however, might be because fewer women were included in these trials and urate concentrations were lower in women than in men.[179,180] A similar robust inverse association was observed between baseline urate and loss of striatal iodine-123–labelled 2-β-carboxymethoxy-3-β-(4-iodophenyl)tropane ([^{123}I]β-CIT) uptake, a marker for the presynaptic dopamine transporter, in a subset of PRECEPT participants.[181] In DATATOP, serum urate concentration was highly predictive of a slower rate of clinical decline among those participants not receiving vitamin E, but not in those receiving vitamin E (2000 IU per day), consistent with a competitive interaction between the putative protective effects of urate and vitamin E as antioxidants. Indeed, by contrast with the DATATOP results for the full cohort, among those in the lowest quintile of serum urate, vitamin E treatment appeared to significantly slow the rate of clinical progression (p<0·01), however; this was in a post-hoc secondary analysis without adjustment for multiple comparisons.[182]

A mendelian randomisation study[183] of 735 DATATOP and PRECEPT participants with available DNA addressed the causality of the link between higher serum urate concentrations and slower progression of Parkinson's disease, using a genetic variant of the urate transporter SLC2A9 as an unconfounded proxy for serum urate concentrations. Consistent with previous population-based studies, variations in *SLC2A9* were strongly associated with serum urate concentrations. The *SLC2A9* alleles associated with lower serum urate concentrations were also associated with faster clinical progression.

In a phase 2 randomised, double-blind trial,[184] inosine was generally safe, tolerable, and efficacious in raising serum and CSF urate concentrations in early Parkinson's disease. A phase 3 trial (NCT02642393) in individuals with early Parkinson's disease is now ongoing to assess whether urate elevation with inosine is a potential disease-modifying therapy for Parkinson's disease. Of note, preliminary results suggest that higher urate concentration might be beneficial in the prevention and treatment of other neurodegenerative conditions, including Alzheimer's disease,[185–187] Huntington's disease,[188] and amyotrophic lateral sclerosis.[189,190]

Physical activity

An inverse relation between amount of physical activity and Parkinson's disease risk was first prospectively reported in the Nurses' Health Study and HPFS,[191] and later substantiated in five additional longitudinal studies

(the Harvard Alumni Health Study,[192] the CPS-IIN,[193] the NIH-AARP Diet and Health Study,[194] the Finnish Mobile Clinic study,[13] and the Swedish National March Cohort[195]). The combined results of these studies show that frequent moderate or vigorous physical activity is associated with a 34% (95% CI 22–43) reduction in Parkinson's disease risk.[195] That Parkinson's disease risk in late adult life was strongly inversely associated with physical activity during high school and college (figure 2),[191] or at age 35–39 years,[194] argues against reverse causation. Although the possibility that individuals predisposed to Parkinson's disease tend to avoid strenuous physical activity in early adult life cannot be excluded, these results are consistent with a neuroprotective effect of physical activity, an interpretation supported by experimental results from animal models of Parkinson's disease.[196,197] Among the proposed mechanisms for this neuroprotective effect are an increase in serum urate, an increased released of neurotrophic factors (eg, BDNF), upregulation of PGC1α, and regulation of dopamine turnover. The potential benefits of exercise in individuals with Parkinson's disease are an area of active investigation,[198] including randomised trials.[199]

Non-steroidal anti-inflammatory drugs (NSAIDs)

Neuronal degeneration in Parkinson's disease is frequently accompanied by a substantial glial response—predominantly the activation of microglia—which could propagate neurodegeneration.[200] It seems plausible, therefore, that anti-inflammatory drugs could contribute to delay or prevent the onset of clinical Parkinson's disease by suppressing the pro-inflammatory responses of microglia. In the first prospective investigation to assess the efficacy of NSAIDs in preventing or delaying the onset of Parkinson's disease,[201] among participants in the Nurses' Health Study and HPFS cohorts, regular users of NSAIDs (defined as ≥2 times per week) had a 45% lower Parkinson's disease risk than non-users.[201] In the CPS-II cohort, a lower Parkinson's disease risk was found among users of ibuprofen, but not users of other NSAIDs (figure 3).[202] A similar result was found in an extension of the analyses in the Nurses' Health Study and HPFS cohorts.[203] In a meta-analysis including data from the above cohorts and those from the UK General Practice Research Database,[204] the Group Health Cooperative,[205] and the Rochester Project,[206] for a total of over 2700 incident Parkinson's disease cases, regular use (defined differently between studies) of ibuprofen was associated with a 27% reduction in Parkinson's disease risk ($p<0·0001$), whereas no association was found for other NSAIDs (RR 1·0; figure 3).[203,206] The results of two subsequent longitudinal studies support the absence of an association between NSAIDs use and Parkinson's disease risk,[17,207] but results specific for ibuprofen were not reported. The discordant results obtained for ibuprofen and other NSAIDs suggest that ibuprofen has specific protective properties. Among the proposed mechanisms for the protective effects of ibuprofen, most prominent is activation of PPARγ, a proposed therapeutic target for Parkinson's disease.[208–210] Ibuprofen, among several commonly used NSAIDs, is also most strongly associated with a reduced risk of Alzheimer's disease[211] and lowered amyloid β 42 concentration in animal models of Alzheimer's disease.[212] Ibuprofen therefore deserves further attention as a potential neuroprotective agent in Parkinson's disease and other neurodegenerative diseases.

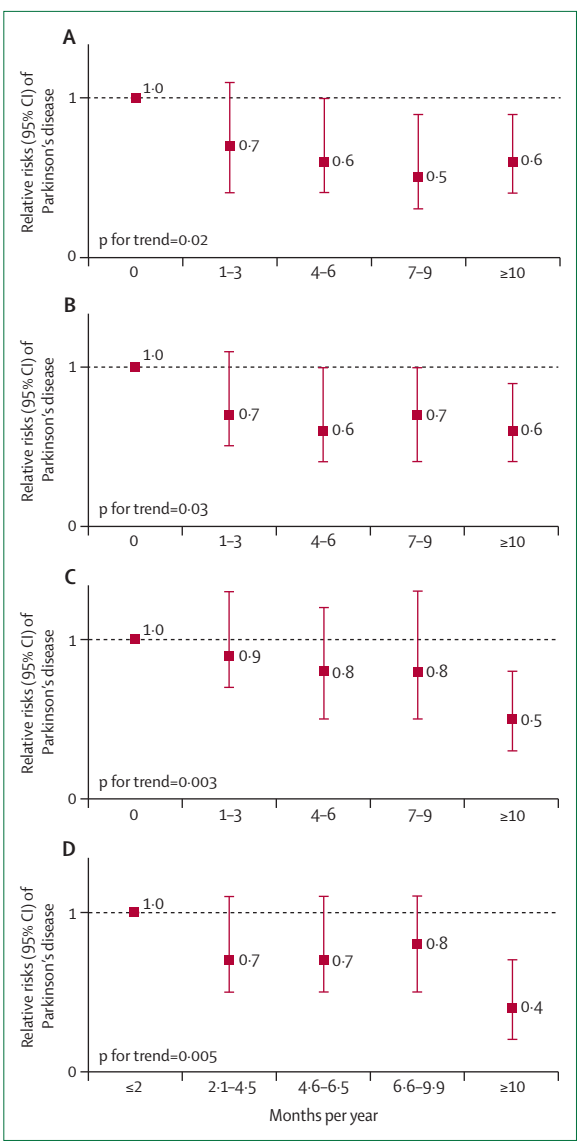

Figure 2: **Relative risk of Parkinson's disease among men in the Health Professionals Follow-up Study based on months of strenuous physical activity per year**

(A) Strenuous physical activity in high school. (B) Strenuous physical activity in college. (C) Strenuous physical activity at age 30–40 years. (D) Mean strenuous activity from high school to age 40 years. Number of incident Parkinson's disease cases=211. The distribution of men according to categories of average strenuous physical activity up to age 40 years was 19% ≤2 months per year, 21% 2·1–4·5 months per year, 18% 4·6–6·5 months per year, 25% 6·6–9·9 months per year, and 17% ≥10 months per year.

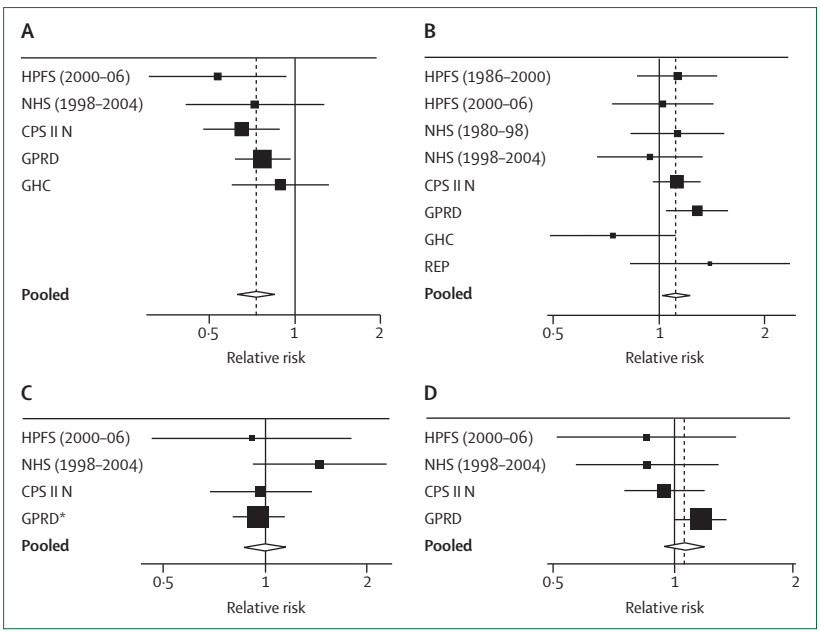

Figure 3: **Pooled relative risks of Parkinson's disease according to each type of non-steroidal anti-inflammatory drug (NSAID) or paracetamol in meta-analysis**

*In the GPRD study, RR for other NSAIDs was calculated by pooling the RR estimates for the different types of other NSAIDs (ie, diclofenac, naproxen, and others), weighted by inverse of the variance within the study. (A) Ibuprofen. (B) Aspirin. (C) Other NSAIDs. (D) Paracetamol. Squares indicate RRs from individual studies; error bars indicate 95% CIs; the unshaded diamonds indicate the pooled RR from the random-effects model and 95% CI. Pooled RR: ibuprofen, 0·73 (95% CI 0·63–0·85, p<0·0001); aspirin, 1·12 (1·01–1·23, p=0·03); other NSAIDs, 1·00 (0·86–1·16, p=1·0); paracetamol, 1·06 (0·94–1·19, p=0·37). NSAID=non-steroidal anti-inflammatory drug. RR=relative risk. CPS=Cancer Prevention Study. GPRD=General Practice Research Database. GHC=Group Health Cooperative. HPFS=Health Professionals Follow-up Study. NHS=Nurses' Health Study. REP=Rochester Epidemiology Project.

Calcium channel blockers

Although there is no convincing evidence of a relation between arterial hypertension and Parkinson's disease risk, use of dihydropyridine calcium channel blockers—commonly prescribed blood pressure lowering drugs—was associated with reduced Parkinson's disease risk (RR range 0·64–0·77) in some[213–216] but not all[217,218] studies. Because of plausible mechanisms (blockage of calcium channel-induced metabolic stress on mitochondria of the dopaminergic neurons that degenerate in Parkinson's disease)[219] and findings showing a protective effect of calcium blockers in animal models of Parkinson's disease, isradipine, a calcium blocker, is being investigated in a phase 3 trial in patients with early Parkinson's disease (NCT02168842).

Statins

Statins have potent anti-inflammatory and immune modulating effects that could be beneficial in Parkinson's disease, but they also decrease plasma concentration of coenzyme Q_{10}.[220–222] Coenzyme Q_{10}, an essential component of the mitochondrial respiratory chain and a potent antioxidant, has been hypothesised to convey protection against the development of Parkinson's disease.[223] Although high doses of coenzyme Q_{10} have not benefited patients with early Parkinson's disease,[224] reducing coenzyme Q_{10} could still have deleterious effects. The results of epidemiological studies[225–232] assessing the effect of statin use on Parkinson's disease risk have been mixed. No association was found in several studies based on prescription records, including the UK General Practice Research Database,[225] the Rotterdam cohort,[226] and studies in Canada[227] and Denmark.[228] By contrast, an inverse association specific for simvastatin was reported in a study nested within the US Veterans Affairs database (RR 0·51)[229] and an overall inverse association was found in the Nurses' Health Study and HPFS cohorts (RR 0·74),[230] a conclusion supported by a meta-analysis (RR 0·77, 95% CI 0·64–0·92; p=0·005)[231] and findings from a study in Taiwan (0·70, 0·63–0·79).[232] However, an increased risk of Parkinson's disease (RR 2·4) was reported among statin users within the Atherosclerosis Risk in Communities Study (ARIC)[233] and this apparent adverse effect was attributed to a lowering of plasma cholesterol, which was inversely related to Parkinson's disease risk in this cohort.[233] This result was based on only 56 incident cases of Parkinson's disease and should therefore be interpreted cautiously. Overall, whether use of statins or blood cholesterol concentrations are related to Parkinson's disease risk remains uncertain. The therapeutic potential of simvastatin in Parkinson's disease is being investigated in a phase 2 trial (NCT02787590).

Flavonoids

A moderate inverse association has been reported between intake of flavonoids and Parkinson's disease risk among participants in the HPFS (RR 0·60, 95% CI 0·43–0·83; p<0·001 comparing the highest *vs* the lowest quintile of intake), but not in the Nurses' Health Study.[7] This result has not been tested in other cohorts.

Dietary patterns

Among participants in the HPFS and Nurses' Health Study cohorts, a so-called prudent dietary pattern, characterised by high intakes of fruit, vegetables, and fish, was associated with a reduced risk of Parkinson's disease (RR 0·78 for the highest *vs* lowest quintile, p for trend=0·04).[234] Similar results were obtained for an alternative healthy eating index (RR 0·70, p for trend=0·01) in the same cohorts.[234] Both results need substantiation in independent studies.

A thorough investigation of the relation between diet and Parkinson's disease risk requires a comprehensive and updated assessment of diet and nutritional status of large populations. Few studies meet these requirements. In the Nurses' Health Study and HPFS, diet has been assessed with extensively validated semiquantitative food frequency questionnaires administered every 4 years; a similar approach has been followed in the CPS-IIN cohort. Other longitudinal studies on diet and Parkinson's disease risk relying on food frequency questionnaires include the HAAS, the NIH-AARP, the Finnish Mobile Clinic study,

and the EPIC Greece study, including 28 572 men and women and 88 incident Parkinson's disease cases,[16] but these studies relied on single dietary assessment to predict Parkinson's disease risk over decades. Although this approach has been effective to detect strong associations, such as for coffee in the HAAS,[142] it might be inadequate to detect more moderate associations and to adjust for confounding by multiple related nutrients. Thus, the relation between most dietary components and Parkinson's disease risk remains highly uncertain.

Implications for preventing Parkinson's disease and slowing its progression

Primary prevention of Parkinson's disease poses several challenges. Because for most ageing individuals the risk of Parkinson's disease is greatly exceeded by risk of cardiovascular disease, cancer, or Alzheimer's disease, any intervention in the general population that could have even modest adverse effects on cardiovascular disease, cancer, and Alzheimer's disease would be counterproductive. At the top of the list of interventions that are beneficial not only for Parkinson's disease prevention, but also for most other common chronic diseases, is an increase in physical activity.[235] Caffeine also has an overall favourable health profile,[236] but at least in western societies it seems likely that most individuals are already consuming a somewhat optimal amount (with the exception of individuals intolerant to caffeine for whom consumption is not an option) so that there is probably little room for improvement. If the inverse associations reported with regard to diet were to be substantiated, additional intervention could include adherence to a healthy dietary pattern and increased intake of flavonoids. Alternatively, more specific interventions could be targeted to individuals with unusually high Parkinson's disease risk (such as those with *LRRK2* mutations), or in the prodromal phase of Parkinson's disease—which can be identified by a combination of non-motor symptoms, such as constipation, rapid-eye-movement sleep behaviour disorder, and hyposmia, and imaging techniques.[237]

Epidemiological studies are useful to help establish which biological targets, among hundreds suggested by laboratory data, warrant the substantially greater investment necessary to develop trials of disease modifying therapies.[238] The ongoing trials of long-term treatment with nicotine (testing the effect of a nicotine transdermal patch delivering 7–28 mg/day on change in Unified Parkinson's Disease Rating Scale [UPDRS] score over 60 months in 160 patients with early Parkinson's disease; NCT01560754), caffeine (400 mg per day for 5 years in 119 individuals with Parkinson's disease; change in Movement Disorder Society [MDS]-UPDRS will be the primary outcome; NCT01738178), and inosine for urate elevation (NCT02642393) in patients with Parkinson's disease are examples of therapeutic interventions developed predominantly based on epidemiological data. The inosine trial is enrolling individuals with early Parkinson's disease and serum urate concentration less than 5·7 mg/dL; inosine is titrated to achieve serum urate concentration of 7–8 mg/dL, and primary outcome is the rate of change in MDS-UPDRS over a period of 24 months. If these trials are successful (ie, demonstrate a clinical benefit), nicotine, caffeine, or inosine could be proposed not only for treatment, but also for secondary prevention of Parkinson's disease.

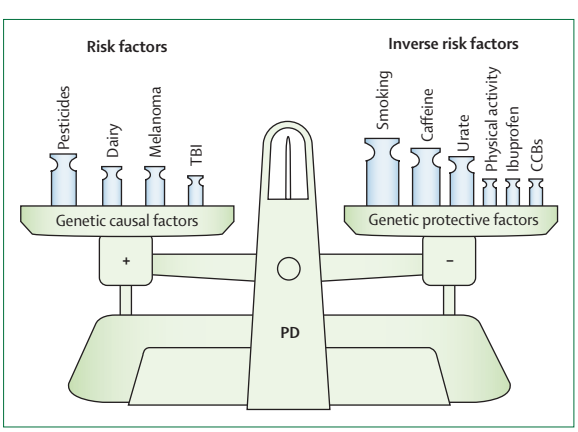

Figure 4: **The balance of genetic and environmental factors that underlie Parkinson's disease occurrence**
Larger weights have been used for those factors with stronger epidemiological evidence. We have included only factors supported by multiple prospective studies, but the presentation is not exhaustive and it is meant only for illustrative purposes. Factors included might or might not be causal. TBI=traumatic brain injury. PD=Parkinson's disease. CCBs=calcium channel blockers.

Conclusions and future directions

In the past 10 years, several longitudinal studies have identified various risk factors for Parkinson's disease (figure 4), including some that could be targeted to reduce risk of Parkinson's disease or slow its progression. Although proof of causality is incomplete due the paucity of trials in human beings, evidence is sufficiently strong to promote physical activity and, arguably, moderate doses of caffeine, for primary prevention of Parkinson's disease. The optimal treatment for individuals with Parkinson's

Search strategy and selection criteria

References for the Review were identified through searches of PubMed from May 1, 2006, to August 15, 2016, by use of the following terms: parkins*[title] AND (incidence OR prevalence OR epidemiology OR risk factor OR cohort). Bibliographies of papers were also reviewed. Only papers published in English were considered. We did not include results presented as abstracts. Studies were selected based on relevance as judged by the authors; in particular, we largely restricted our review to the results of longitudinal studies, although a few exceptions were made when needed to highlight relevant concepts and controversies.

disease should rely primarily on results of randomised trials, which are now ongoing for urate elevation, caffeine, nicotine, statins, isradipine, and physical activity. Further research should elucidate the role of other tobacco components, ibuprofen, and dietary factors in the pathogenesis and progression of Parkinson's disease. Ideally, this research should focus on individuals at high risk or in the prodromal phase of Parkinson's disease, among whom potential neuroprotective interventions are likely to have the most effect.

Contributors

The authors contributed equally to all aspects of the study.

Declaration of Interests

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