



Review article

Update: Protective and risk factors for Parkinson disease

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ABSTRACT

We review the epidemiologic literature on potential protective and risk factors in Parkinson's Disease (PD). Prior research identified numerous possible protective and risk factors. Potential protective factors include tobacco abuse, physical activity, urate levels, NSAID use, calcium channel blocker use, statin use, and use of some α 1-adrenergic antagonists. Some potential protective factors could be products of reverse causation, including increased serum urate, tobacco abuse, and coffee-tea-caffeine consumption. Potential risk factors include traumatic brain injury, pesticide exposure, organic solvent exposure, lead exposure, air pollution, Type 2 Diabetes, some dairy products, cardiovascular disease, and some infections including Hepatitis C, *H. pylori*, and COVID-19. Potential non-environmental risk factors include bipolar disorder, essential tremor, bullous pemphigoid, and inflammatory bowel disease. There is an inverse relationship with PD and risk of most cancers. Though many potential protective and risk factors for PD were identified, research has not yet led to unique, rigorous prevention trials or successful disease-modifying interventions. While efforts to reduce exposure to some industrial toxicants are well justified, PD incidence might be most effectively reduced by mitigation of risks, such as Type 2 Diabetes, air pollution, traumatic brain injury, or physical inactivity, that are general public health intervention targets.

1. Introduction

Identification and evaluation of potential protective and risk factors for disease, particularly environmental risk factors, is a historically fruitful endeavor. Identification of environmental protective and risk factors can provide clues to disease pathogenesis and routes to disease prevention or mitigation. The successes of tobacco control efforts in reducing cardiovascular disease prevalence, and cancer incidence and mortality, are notable examples. There is a substantial literature focusing on potential environmental protective and risk factors in Parkinson disease (PD). Numerous recent studies expanded the range of potential protective and risk factors for PD.

This narrative review focuses on providing an updated summary of most recent studies of potential protective and risk factors for PD. We used a hybrid search approach, relying on older reviews to summarize older literature, and performing PubMed searches using terms such as "risk", "hazard", and "protection." In addition, we conducted a thorough search and screening of relevant manuscripts cited in identified articles. Through these searches, we identified greater than 400 relevant peer-

reviewed articles on different aspects of PD epidemiology. We excluded articles characterized by non-peer-reviewed sources, opinion pieces, non-English language, and low-quality studies. Those most pertinent to this aspect of PD epidemiology are discussed and cited. When reviewing epidemiological topics, we considered the scientific rigor of studies by assessing the study types, methodological quality, confounding variables, as well as internal and external validity.

We discuss potentially protective environmental factors, potentially hazardous environmental factors, some non-environmental factors, and conclude with a critical discussion of PD protective/risk factor epidemiology.

2. Potentially protective environmental factors (Table 1; Table 3)

Cigarette Smoking-Tobacco Use: A frequently reproduced finding in PD epidemiology is an association between cigarette smoking-tobacco use and reduced risk of PD with odds ratios around 0.4–0.6 (reviewed by Ascherio and Schwarzschild) [1–7]. The major interpretative

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possibilities are that tobacco products exert neuroprotective effects or that this is a case of reverse causation with a feature of PD-prone individuals reducing tobacco use risk.

Nicotine reduces neurodegeneration in toxin PD models and dietary nicotine consumption may reduce PD risk [8,9]. Other tobacco constituents may have neuroprotective effects. There is also a plausible case for reverse causation. The reinforcing effects of nicotine are mediated partly by inappropriately enhanced dopaminergic neurotransmission and PD prone individuals may have intrinsic differences in nigrostriatal dopaminergic signaling rendering them less susceptible to nicotine [10]. Consistent with this hypothesis, PD patients may find it easier to quit smoking [10,11] and second-hand smoking exposure may not reduce PD risk [12]. Twin study analyses are consistent with a neuroprotective effect [13,14], as are Mendelian randomization studies [15–18]. While not definitive, the recent NIC-PD randomized control trial showed transdermal nicotine patches did not alter PD progression of early disease [19]. The balance of the evidence favors a neuroprotective effect of tobacco, but reverse causation remains a plausible alternative.

Coffee-Tea-Caffeine: Another well-established association is a potential protective effect of coffee-tea-caffeine consumption. A comprehensive review by Chen and Schwarzschild [20] highlights the diminished PD risk associated with coffee-tea-caffeine consumption with estimated odds ratios ~0.70 [3,21–24]. Studies assessing decaffeinated products identify caffeine as the relevant actor [20]. The association between caffeine and reduced PD risk is attenuated in women. A major mediator of caffeine effects is adenosine receptor blockade [25]. Caffeine exhibits neuroprotective effects in PD models mediated by A2a subtype receptors – expressed at uniquely high levels by striatal neurons and modulating dopaminergic signal transduction – that also mediate the reinforcing effects of caffeine [20]. Adenosine receptors also influence multiple processes relevant to neuroprotection, including synaptic plasticity, synapse formation, and inflammation. It is intriguing that two apparent protective factors produce significant physiologic effects through modulation of striatal dopaminergic neurotransmission – signal transduction. This convergence increases the likelihood that the well-established risk reduction associations with tobacco and caffeine exposures are cases of reverse causation.

Physical Activity: The concept that physical activity potentially reduces PD risk is consistent with the clinical impression that PD patients pursuing regular physical exercise exhibit slower progression [26,27]. Prospective studies indicate an inverse relationship between physical activity intensity and PD risk [28–33]. Leisurely or lighter levels of exercise did not show association with PD, while moderate to strenuous physical activity is associated with an odds ratio of ~0.65. Reverse causation is a possibility, as prodromal individuals may find it harder to pursue moderate to vigorous exercise [28–31,33]. The inverse relationship between PD risk and physical activity may hold for physical activity earlier in life, perhaps decades earlier. Reduced PD risk associated with early life physical activity argues against but does not exclude reverse causation.

Urate: Several studies suggested that plasma urate levels are inversely related to PD risk [34–38]. Urate may be an intracellular antioxidant. The strongest data suggested protective effects of higher plasma urate levels in men but not in women [35–38]. The evidence supporting an inverse relationship between urate levels and PD risk includes various meta-analyses and case-control studies with a reasonable level of rigor. A meta-analysis describes an ~33 % risk reduction associated with higher serum urate [34]. Gout is a natural experiment with conflicting reports of diminished and increased PD risk associated with gout [39–43]. A Mendelian randomization study argues against serum urate as a PD protective factor [44]. The Phase III Safety of Urate Elevation in PD trial (SURE-PD3) used oral inosine to raise serum urate levels in early PD as a disease-modifying approach and was negative [45]. A recent critical review also makes a strong case for reverse causation and urate being a potential biomarker for PD progression [46].

Medications: Pharmacoepidemiologic studies suggest that some medications potentially reduce PD risk (Table 1). Non-steroidal anti-inflammatory drug (NSAID) use potentially reduces PD risk (Table 1) with meta-analyses suggesting PD risk around 0.8–0.9, though one recent meta-analysis concluded that there are no demonstrable effects of NSAIDs [47]. Other anti-inflammatory agents, including immunosuppressants, are suggested to reduce PD risk [48].

Calcium channel blockers (CCBs) may reduce PD risk (Table 1) with studies implicating the dihydropyridine (DHP) subclass of CCBs. Rigorous preclinical experiments supported a role for DHP-CCB sensitive calcium channels in dopaminergic neuron degeneration [49,50]. The CCB isradipine was trialed as a disease-modifying treatment (Safety, Tolerability and Efficacy evaluation of Dynacirc® in PD; STEADY-PD) [51] with negative results. There are concerns that the isradipine dosing schedule did not produce adequate inhibition of target DHP-CCBs and some controversy about trial outcome interpretations [52–54].

The effects of β -adrenoreceptor antagonists (beta blockers; BB) on PD risk is controversial. β 2-adrenoreceptor activation modulated α -synuclein expression in a cellular model and complementary pharmacoepidemiologic analysis suggested that β -adrenoreceptor agonist (BA) use reduced PD risk while BB use exacerbated PD risk [55]. Subsequent pharmacoepidemiologic studies return conflicting results (Table 3). Hopfner et al. suggested that an apparent protective effect of BAs could be explained by BA prescriptions in smokers [56].

Conflicting data are reported for HMG-CoA reductase inhibitors (statins) [57]. Some prospective data and meta-analyses results are consistent with prior statin use possibly reducing PD risk by ~20 % [58, 59]. In meta-analysis, this association persisted after adjustments for

Table 1
Potential protective factors.

Protective Factor	Reported Odds Ratio	Comment
Smoking-Tobacco Abuse [2,3,5,7,214]	~0.4–0.6	Highly reproducible meta-analyses showing either neuroprotective effect or reverse causation.
Coffee-Tea-Caffeine [21–23,25]	~0.7–0.75	Neuroprotective effect plausible - Possible reverse causation.
Physical Activity [28–32]	~0.65	Neuroprotective effect with strong clinical impression - Requires further study of possible mechanisms.
Serum Urate [34,215]	~0.6–0.9	Biologically plausible - Negative major clinical trial, negative mendelian randomization study.
Medications		Associations mainly based on pharmacoepidemiologic studies prone to confounders.
CCBs [216–222]	CCB~ 0.7–0.9	- Strongest support for CCBs but negative major clinical trial.
NSAIDs [47,223–229]	NSAIDs~ 0.8–0.9	
Ibuprofen [47, 223–225,227–229]	Ibuprofen 0.6–0.7	
Immunosuppressives [47,48,226]	Immunosuppressives~ 0.4–0.6	
ARBs [230]	ARBs~ 0.6	
β -agonist [55,56]	β -agonist~ 0.6–0.8	
Full truncal vagotomy [70,71]	~0.6–0.9	Controversial – Consistent with some preclinical model data - Requires further study related to potential gut α -synuclein seeding of CNS.
Hyperlipidemia		Pathogenic significance unclear - Possible prodromal markers - Require further study.
Serum cholesterol [151–156,158, 231–234]	~0.85	
LDL [151–156, 231–236]	~0.6–0.9	
Triglycerides [151–156,231–236]	~0.6–0.7	

CCB = Calcium Channel Blocker; NSAID = Non-Steroidal Anti-Inflammatory Drug; LDL – Low Density Lipoprotein.

Table 2
Potential risk factors.

Risk Factor	Reported Odds Ratio	Comment
Pesticides-Herbicides-Fungicides [6,91, 93–100,209,210]	~1.4–1.6	Significant cumulative exposure data - Supported by some preclinical model data – Strongest case for pesticides.
Solvents [87,93,103, 105–107]	~1.4	Particular concern about chlorinated hydrocarbons - Supported by some preclinical model data.
Traumatic Brain Injury [78–88,211]	~1.4–1.7	Controversial - Possible reverse causation and recall bias.
Heavy Metals Lead [95,109,111]	~1.6	Data best supports lead association amongst heavy metals.
Cardiovascular Disease Risk Factors [145,146, 148]	~1.2–1.65	Risk ratios vary with specific cardiovascular risk factor.
IBD [198,200–205]	~1.4	Requires further study to rule out surveillance bias.
<i>H. pylori</i> [162–164]	~1.5–1.9	Eradication of <i>H. pylori</i> did not affect risk - Requires further study.
Type 2 Diabetes [141–144]	~1.2–1.4	Accelerates disease progression and exacerbates clinical features.
Air Pollution [119–123]	~1.1–1.2	Mechanistically plausible – Very widespread exposures.
Hepatitis C [126,127,212, 213]	~1.2–1.5	Treatment appears to reduce risk.
Influenza infection [131, 132]	~1.5–1.7	Requires further study.
Dairy Products Milk [168–170,172,173]	~1.3–1.6	Various meta-analyses show milk as a risk – Potential confounders - Further study required.

IBD – Inflammatory Bowel Disease.

Table 3
Particularly contentious protective/risk factors.

Factor	Reported Odds Ratio	Comment
Medications		
Statins [58,59,61]	Statins~ 0.7–1.2	For Statins, negative phase II trial and possible confounding by hyperlipidemia. Conflicting results for other medications.
β-blockers [56, 237–239]	β-blockers~ 0.7–1.0	
α1-adrenergic antagonists [63, 240]	α –1 = blank	
Terazosin [240–242]	Terazosin 0.46–1.0	
Selective vagotomy [70,71]	~1.1–1.2	Controversial – Consistent with some preclinical model data - Requires further study related to potential gut α-synuclein seeding of CNS
Appendectomy [72–77]	~1.0	Controversial – Consistent with some preclinical model data - Requires further study related to potential gut α-synuclein seeding of CNS
Heavy Metals		
Copper [110,112]	~1.1–1.6	Non-lead metals have unclear associations – Manganese not likely.
Manganese [110,112, 116,117,243]	~1.1–1.2	
Hyperlipidemia HDL [151–156, 231–236]		Pathogenic significance unclear - Possible prodromal markers - Require further study.
Viral Infections [134]		Study heterogeneity, requires further study.
Dairy Products		
Cheese [168,170,171]	–	Milk established as risk but further study required for other dairy products.
Yogurt [170,171]	~0.75–1.2	
Butter [170]	~0.5–1.1	

HDL – High Density Lipoprotein.

age, sex, and smoking. A protective association was found for long-term use and for lipophilic statins, but not hydrophilic statins. Longitudinal data from the E3N cohort study of French women supports this conclusion [60]. Bykov et al. suggested that assessing statin effects on PD risk may be confounded by the effects of hyperlipidemia on PD risk (see **Potential Environmental Risk Factors: Cardiovascular Risk Factors** below) [59]. A phase II efficacy trial of simvastatin as a disease-modifying therapy is negative [61,62].

Some α1-adrenergic antagonists, terazosin (TZ) and related compounds, may reduce PD risk. The proposed mechanism is increasing glycolysis via activation of phosphoglycerate kinase 1 [63]. In preclinical models, TZ reduced or slowed neuronal loss and a pharmacoepidemiologic study suggested that TZ and related agents reduced PD incidence. These pharmacoepidemiologic findings were reproduced in some, but not all, subsequent studies (Table 3).

Vagotomy and Appendectomy: Assessments of the effects of prior vagotomy and appendectomy on PD risk were inspired by Braak’s suggestion that α-synucleinopathy begins in the gut/enteric nervous system and spreads centripetally to the CNS [64–67]. α-Synucleinopathy rodent model experiments are consistent with this hypothesis [68,69]. Results of retrospective analyses of large administrative datasets return conflicting results. Full truncal vagotomy may reduce PD risk, with reports of unchanged risk with selective vagotomy [70,71]. The impact of appendectomy on PD risk is unclear with studies suggesting increased, decreased, or no risk change after surgery [72–77].

3. Potential Environmental Risk Factors (Table 2, Table 3)

Traumatic Brain Injury (TBI): In a 2013 meta-analysis, Jafari et al. concluded that TBI was potentially associated with increased risk of PD with a risk ratio ~1.6 [78]. Marras et al. concluded that available data do not support an association between mild TBI and PD risk [79]. Reverse causation is a consideration for association between TBI and PD risk as the long prodromal phase with sub-clinical motor deficits could increase fall risk. Using the Swedish National Patient Register, Fang et al. found an association between hospitalizations for head injury and PD incidence with this association largely explained by recent head injuries [80]. Gardner et al. assessed the relationship between PD risk and TBI with a non-TBI traumatic injury control group [81]. TBI was more strongly associated with subsequent PD diagnosis than non-TBI traumatic injuries and with a dose-response relationship between TBI severity and PD risk. On the other hand, a thorough interview based case control study found no evidence of increased PD risk associated with TBI [82] and a recent nested case-control study from the Rochester Epidemiology Project (Olmsted County, Minnesota, USA) found no association between TBI occurrence, severity, or temporality, and risk of any α-synucleinopathy [83]. In a case-control study excluding injuries occurring less than 10 years prior to PD diagnosis, Taylor et al. found evidence of TBI increasing PD risk with temporal variation. Earlier injury was associated with the greatest increases in PD risk [84]. Using the USA Veteran’s Health Administration (VHA) – the Comprehensive TBI Evaluation – dataset recording TBI incurred by veterans of the US invasion and occupation of Iraq [85], Gardner et al. describe increased PD risk in service people experiencing TBI with a risk ratio of ~1.7 and a dose-response relationship. Lee et al. assessed interaction between exposure to the herbicide paraquat, TBI history, and PD risk [86]. TBI with loss of consciousness >5 min and paraquat exposure had a synergistic effect with odds ratio ~3.0.

There is considerable interest in the effects of multiple, sub-concussive brain impacts associated with contact sports. Analyses of Scots professional soccer players suggests that this type of repetitive brain trauma is associated with increased PD risk [87–89]. This result was not reproduced in a study of Swedish professional soccer players. These well-done analyses are retrospective in nature and could not take some relevant confounders into account. A cross-sectional and self-selected analysis of American football players is consistent with

repetitive head injury possibly increasing PD risk [90]. It's uncertain if these associations generalize to recreational/casual exposure.

A causal link between TBI and PD risk is biologically plausible with two primary causation models. First, TBI could result in non-specific brain injuries lowering the threshold for clinical expression of PD associated α -synucleinopathy. Second, TBI could exacerbate, or even initiate, pathologic cascades, such as neuroinflammation, underlying PD.

Pesticides-Herbicides-Fungicides: The concept that environmental toxicants contribute to PD pathogenesis came to the forefront following the discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism. MPTP has structural similarities to the herbicide paraquat, though MPTP and paraquat have different cellular toxicity mechanisms. The natural product mitochondrial complex I inhibitor rotenone, a pesticide, insecticide, and piscicide, is also used as a PD model.

A pioneering Canadian study described PD prevalence as highest in regions of Quebec with high pesticide use [91]. Several meta-analyses report the overall conclusion that pesticide-herbicide exposure is a significant risk factor for PD [4,6,92–95]. The case for pesticide exposures appears the strongest with odds ratios around 1.4–1.8. Some suggested that the association between pesticide-herbicide exposure is actually weaker because of publication bias [4], but higher quality studies return higher odds ratios [94,95]. Ritz and colleagues used unique exposure data in California and concluded pesticides, herbicides, and fungicides are significant risk factors for PD [96–98]. Their results directly implicate paraquat, as did prior work in the Agricultural Health Study [99]. With Cancer Prevention II Nutrition Cohort data, Ascherio et al. estimated an odds ratio of ~ 1.7 [100]. It is likely that pesticide-herbicide-fungicide exposure is a risk factor for PD. The case for pesticide exposure seems the strongest, and data linking paraquat exposure to PD risk is strong.

Organic Solvents: One meta-analysis described organic solvent exposure as a potentially significant risk factor with an odds ratio of ~ 1.4 [94]. The halogenated hydrocarbons trichloroethylene (TCE) and perchloroethylene are the strongest candidates. TCE is/was a widely used degreasing agent and is a widespread environmental pollutant [101,102]. Several studies implicate TCE exposure in PD, though most studies involve relatively small subject numbers [103–105]. A recent large case-control study using Finnish medical administrative and occupational data is consistent with halogenated hydrocarbon exposure as a PD risk factor [106], as is a recent cohort study of United States Marine Corps and Navy personnel with temporally remote exposures to TCE and other organic compounds [107]. In a study examining twins discordant for PD [105], exposure to TCE, and possibly other organic solvents, was associated with increased PD risk. Experimental evidence supports a connection between TCE exposure and substantia nigra degeneration [104,108]. TCE exposure upregulates Leucine-Rich Repeat Kinase 2 (LRRK2) kinase activity, a likely mechanism of neurodegeneration in LRRK2 mutant PD [108]. Dorsey et al. provide a thorough review suggesting TCE as a potential PD risk factor and highlighting the need for further studies [101].

Heavy Metals: A meta-analysis by Gunnarsson and Bodin with strict study selection criteria indicates that occupational lead exposures potentially increase PD risk with an odds ratio of ~ 1.5 [95]. This was further supported by a high-quality case-control study showing cumulative exposure to lead is associated with increased risk of PD [109]. These authors concluded that associations with other heavy metal exposures are unsubstantiated [110–113]. Manganese (Mn) exposures deserve separate discussion. Mn exposure is the cause of a complex neurologic syndrome [114,115]. Manganism was characterized as exhibiting additional clinical features distinguishing it from PD. Racette and colleagues suggested that lower-level Mn exposures produce a syndrome more resembling PD [115,116]. Positron emission tomography studies of nigrostriatal dopaminergic projections in Mn-exposed workers do not describe PD-like deficits [117]. In the only autopsy

report on Manganism from the modern era, Yamada et al. described a normal substantia nigra in the studied case [118]. It is unlikely that Mn exposure is a significant risk factor for PD.

Air Pollution: Recent studies suggest that air pollution is a risk factor for PD [119–122]. Air pollution exposures are complex due to the presence of several potentially relevant constituents. Different studies report associations with different air pollution constituents (summarized in Murata et al.; meta-analysis of Hu et al.) with the overall conclusion that air pollution is a potential PD risk factor [123,124]. The odds ratios are on the order of 1.1–1.2, but the ubiquity and chronicity of air pollution exposure places very large populations at risk. Much of best data assessing associations between air pollution and PD risk comes from high SDI nations with relatively good air pollution control. Air pollution could be a more influential risk factor in regions with worse air pollution.

Hepatitis C: Hepatitis C (HepC) is a brain penetrant flavivirus, infecting microglia [125]. HepC is a prevalent chronic infection, affecting tens of millions globally and with hundreds of thousands of new infections annually. Association between HepC infection and PD risk was identified originally in a Taiwanese dataset and subsequently replicated in studies from other nations with an odds ratio of ~ 1.35 [126,127]. Consistent with a causal relationship between HepC infection and PD risk, recent analyses suggest that curative treatment of HepC reduces PD risk [126,127].

Viral Infections: The 20th century experience with Post-Encephalitic Parkinsonism (PEP) raises the possibility that PD could be a delayed sequel of viral or other acute infections. Initiation of neurodegeneration by neurotropic viral infections or secondary to neuroinflammatory processes triggered by viral or other infections are plausible models of pathogenesis. An alternative model is infection causing acute, subclinical loss of dopaminergic nigrostriatal neurons with clinical manifestations occurring years later as the gradual, normal age-related decline in nigrostriatal dopaminergic neurons passes a threshold for manifest PD.

Donald Calne revived the concept that PD follows infection [128]. Weak cross-sectional serologic studies are consistent with associations between influenza A and HSV-1 infections and subsequent PD (reviewed by Limphaibool et al. and Olsen et al.) [129,130]. A recent retrospective case-control study using the Danish National Patient Registry addressed whether antecedent influenza infection is associated with delayed onset of PD [131]. Influenza diagnosis more than 10 years prior to PD diagnosis was associated with increased PD risk (odds ratio ~ 1.7). Different but positive results were reported recently using Finnish and British Biobank data [132]. Antecedent history of infection — pneumonia, viral hepatitis, influenza, viral infection with skin and mucosal lesions — was associated with incident PD. These associations were significant 0–1 years and 1–5 years after infection exposures. Systemic inflammation secondary to infection might accelerate disease progression of individuals in the prodromal phases of PD.

Herpes Simplex Virus 1 and 2 (HSV-1, HSV-2), and Varicella-Zoster (HVZ), are common human neurotropic viruses. Several epidemiologic studies examined the relationship between antecedent HSV/HVZ infection and risk of PD with conflicting results (discussed by Camacho-Soto et al.) [133]. Using administrative data, Camacho-Soto et al. found that diagnosis of antecedent HSV/HVZ infection or treatment with anti-herpetic agents was possibly associated with mildly reduced risk of PD (odds ratio ~ 0.9). Meta-analysis of cohort and case-control studies examining the relationship between antecedent infections and PD risk reveals considerable study heterogeneity [134].

A current question is whether COVID-19 infection increases PD risk. Zarifkar et al. examined data for approximately half the population of Denmark, focusing on outpatients with documented COVID infections [135]. Compared with controls, a history of COVID-19 increased risk for subsequent diagnoses of PD (odds ratio ~ 2.6). There was increased risk when compared to outpatients with histories of other respiratory tract infections. De Havenon et al. used a large de-identified dataset (TriNetX) to quantify incident diagnoses of several chronic neurologic disorders

(migraine, epilepsy, neuropathies, movement disorders, stroke, and dementia) in the year following in-patient hospitalization for COVID-19. Relative to a propensity matched control group hospitalized for influenza, there was reduced incidence of these diagnoses [136]. Taquet et al. aggregated several datasets and assessed the post-COVID-19 outcomes of approximately 1.2 million patients over a 2-year follow-up period [137]. There was no evidence of increased PD risk. On the other hand, Xu et al. describe increased Parkinsonism risk at 1 year post COVID-19 infection in a large US Department of Veterans Affairs dataset with an odds ratio of ~1.5 [138]. Careful, longitudinal follow-up of COVID-19 infected individuals is needed.

Type 2 Diabetes Mellitus: Whether Type 2 Diabetes Mellitus (T2DM) is a risk factor for PD was controversial with studies suggesting increased risk of PD and others suggesting diminished PD risk [139]. A possible explanation for this discrepancy is that studies suggesting reduced risk of PD were case-control studies susceptible to differential mortality effects. Recent analyses indicate that T2DM is a potential PD risk factor, a conclusion supported by Mendelian randomization data, with an odds ratio of 1.2–1.4 [139–141]. One possibility is that T2DM exacerbates the pathogenic mechanisms underlying PD. Another possibility is exacerbation of clinical features by superimposition of additional but independent T2DM-associated pathologies, lowering the threshold for clinical expression of α -synucleinopathy. This model is consistent with the observation that co-morbid T2DM is associated with more severe PD clinical features [139,140,142–144].

Cardiovascular Disease Risk Factors: Kummer et al. performed an analysis of US Medicare administrative data to address the potential role of cardiovascular disease risk factors, identifying several as possibly increasing risk of PD incidence with odds ratios in the range of 1.2–1.65 [145]. Obstructive sleep apnea had the highest risk ratio, followed by prior stroke and congestive heart failure. While limited by use of administrative data, this well-done study included both positive control and negative control analyses. White matter disease (WMD), conventionally associated with vascular injury, may be a risk factor for PD [146]. Long term follow-up of the RUN DMC (Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort) indicates that small vessel disease severity and progression increases risk of developing vascular Parkinsonism and possibly PD [147]. Cardiovascular disease risk factor load is associated with more severe PD and treatment-refractory clinical features [148]. Mediterranean-like diets, widely accepted to reduce cardiovascular disease risk, may decrease PD risk [149,150].

While inconsistent and possibly affected by sex differences, studies suggest that elevated serum cholesterol, serum low density lipoprotein (LDL) cholesterol, triglycerides, and High density lipoprotein (HDL) cholesterol levels, and levels of the HDL constituent ApoA1 are potentially associated with lower PD risk [151–156]. Park et al. suggested that metabolic syndrome might be a risk factor for PD [157]. Using data from the Health, Aging, and Body Composition study, Wang et al. found that blood cholesterol levels began to decline during the prodromal phase of PD, suggesting that some blood lipid abnormalities are prodromal markers rather than risk factors [158].

Helicobacter pylori infection: Older clinical observations suggested that PD was often preceded by peptic ulcer disease [159,160]. In United Kingdom Biobank data, Jacobs et al. found suggestive evidence that peptic ulcer disease is a possible risk factor for PD [161]. A meta-analysis concluded that *H. pylori* infection possibly increased PD risk with an odds ratio of ~1.6 [162]. Danish National Patient Registry data suggests that prescription of *H. pylori* eradication therapy and/or proton pump inhibitors greater than 5 years prior to PD diagnosis was associated with increased PD risk [163]. In the Taiwan National Insurance Research Database, *H. pylori* infected patients were more likely to develop PD (odds ratio ~2.3) [164]. Given the long prodrome of PD and the occurrence of intestinal α -synucleinopathy, reverse causation is possible explanation. Abnormalities of GI function secondary to PD could increase risk of *H. pylori* infection.

Dairy Products: Regular consumption of some dairy products may be associated with increased PD risk (odds ratio ~1.4) [165–172]. The available evidence implicates bovine milk consumption but not cheese, yogurt, or butter consumption. Vitamin D and calcium are not implicated. In a post-mortem study, Abbot et al. found that mid-life milk consumption was inversely related to substantia nigra neuronal density [173]. A recent Mendelian randomization study is consistent with higher dairy intake as a risk for PD [174]. Abbot et al. suggested milk contamination by pesticide residues as an explanation for this association. Low dairy intake might be a proxy for Mediterranean-type diets, which may lower PD risk.

4. Potential non-environmental/Emerging risk factors

Bipolar Disorder: It is well-known that depression and anxiety are non-specific prodromal features of PD. However, recent studies suggest that bipolar disorder (BD) is a potential risk factor for PD [175–180]. A meta-analysis suggests odds ratios of 3.2–3.4 [175]. BD treatments are potential confounders as some BD patients receive dopamine antagonist agents but studies adjusting for this confounder report significant PD risk odds ratios. A mainstay of BD maintenance therapy is lithium, a rare cause of drug induced Parkinsonism. It is plausible that development of Parkinsonism is a consequence of chronic lithium use. The most intriguing possibility is a connection between the underlying neurobiology of BD and PD. Major psychiatric disorders, including BD, are likely to be the result of abnormal brain development. It is plausible that abnormal brain development predisposes a subset of BD patients to nigrostriatal degeneration.

Essential Tremor: A long-standing question is whether Essential Tremor (ET) is a risk factor for PD. These are common problems and some individuals will be unlucky enough to have both disorders. There are suggestions that ET increases risk of PD [181,182]. Some studies, mainly case control studies, describe odds ratios on the order of 4–5. There are uncertainties regarding subject classification and design of these studies [181]. Longitudinal data from a prospectively followed ET subject cohort is consistent with ET as a risk factor for PD incidence [183]. This self-selected cohort, however, is relatively small and unrepresentative [184]. There are also uncertainties about potential pathogenetic links between ET and PD. The most convincing clinico-pathologic data indicates cerebellar pathologies in ET [185]. A link between ET and PD is plausible but unproven.

Bullous Pemphigoid: Forsti et al. summarized data suggesting that the autoimmune disease Bullous Pemphigoid (BP) is potentially associated with PD [186]. BP target proteins are apparently expressed in brain [187]. These studies may have multiple confounders. There are analogous reported associations with other neurologic diseases, raising the possibility of surveillance bias. This group also reported that CNS-active drugs, including dopamine antagonists, may increase risk of BP [180].

Cancer: In various retrospective and prospective case-control studies, cancer is associated with lower subsequent PD incidence, results not attributable to lower tobacco abuse or differential survival [188,189]. A reciprocal clinical impression is that cancer risk, with the exception of melanoma risk, is lower in PD. A recent comprehensive meta-analysis by Zhang et al. indicated an inverse association between PD and cancer frequency [190]. Zhang et al. also commented that individuals with cancer had a lower frequency of PD. A recent genome wide association study (GWAS) based analysis suggests genetic correlation between PD and melanoma risk (see below) as well as prostate and breast cancer risk but reduced association with ovarian cancer risk [191]. A plausible general model is that cancer predisposition is driven by processes enhancing cell proliferation with PD cell death driven by opponent processes reducing cell survival. This general concept is supported by reports that polyglutamine repeat neurodegenerative disorders may exhibit lower cancer rates [192,193].

Conversely, PD is associated with increased risk of melanoma [194, 195]. *MC1R* (melanocortin 1 receptor) gene polymorphisms are

associated with increased melanoma risk, and some may be risk factors for PD [196]. Diaz-Ortiz et al. recently described an association between *GPMB* (glycoprotein nonmetastatic melanoma protein B) polymorphisms and increased PD risk [197]. The function of this melanoma-associated protein is unknown. Diaz-Ortiz et al. presented evidence that increased *GPMB* activity alters α -synuclein intracellular trafficking in a potentially pathogenic manner.

Inflammatory Bowel Disease (IBD): A specific potential link between IBD and PD risk is the discovery that *LRRK2* polymorphisms, including some increasing *LRRK2* kinase activity, are associated with increased IBD risk [198,199]. Several studies, primarily using administrative databases, report IBD is associated with increased risk of incident PD with a meta-analysis describing a risk ratio of ~ 1.4 [198,200–203]. One study reported normalization of incident PD risk in IBD patients treated with anti-Tumor Necrosis Factor (TNF) therapy, not replicated in subsequent studies [198,204,205]. A recent Mendelian randomization study did not find any association between IBD and PD risk and another Mendelian randomization study based on polymorphisms modulating TNF activity did not find an association between these polymorphisms and PD risk [206,207]. Despite plausible mechanistic and intriguing genetic connections between IBD and PD risk, this relationship remains cloudy. One of the groups reporting increased risk of PD in IBD point to the pitfall of surveillance bias in these studies [203].

Epilepsy and Anti-Convulsants: Some data suggest that epilepsy is associated with increased risk of PD (reviewed in Belete et al.). An analysis based on United Kingdom Biobank data suggests that this association may be partially mediated by anti-convulsant exposure [208].

5. Conclusions

The extensive epidemiologic literature on protective and risk factors in PD identified many plausible associations (Tables 1–3). The best validated of these associations are the inverse relationships between tobacco abuse and coffee/tea/caffeine intake, and PD incidence. As with many epidemiologic observations, verifying causation can be challenging. Associations with several apparently protective or risk factors may be products of reverse causation. A potential example of reverse causation is the most strongly replicated protective association, the inverse relationship between tobacco abuse and PD incidence. Similar concerns about reverse causation, to varying degrees, arise for associations between PD incidence and coffee/tea/caffeine intake, TBI, serum urate levels, *H. pylori* infection, and physical exercise. These potential cases of reverse causation may identify features of the pre-clinical and prodromal phases of PD. As mentioned above, the association with TBI could result from prodromal motor impairments. Relative resistance to the reinforcing effects of nicotine or caffeine could be features of the pre-clinical phase of PD.

Another complicating factor in interpreting this literature is the possibility that risk and protective factors may have different mechanisms affecting PD incidence. There are two broad alternatives – modulation of primary pathologies driving PD pathogenesis or parallel brain injury. In the first case, the identified risk or protective factor accelerates or retards the primary process driving neurodegeneration, whether propagation of pathogenic α -Synuclein species, mitochondrial dysfunction, lysosomal dysfunction, or other primary actors in PD pathogenesis. A potential example is TCE induction of increased *LRRK2* kinase activity – a pathogenic mechanism implicated by the effects of PD-related *LRRK2* mutations. In the second case, risk or protective factors facilitate or retard accumulation of other brain pathologies that lower the threshold for clinical expression of primary pathogenic processes causing PD. Potential examples of facilitating risk factors would be cardiovascular disease risk factors, T2DM, TBI, or inflammatory processes such as HepC infection. Combined effects are also plausible. Physical activity might mitigate PD risk by reducing the likelihood and disease burden of T2DM or cardiovascular disease. Physical activity might also directly modulate primary PD pathogenesis by stimulating CNS production of relevant

neurotrophic factors.

PD-prone individuals, perhaps due to higher loading of genetic risk factors, might be particularly susceptible to facilitating risk factors during the long prodromal phase of PD. An individual in the prodromal phase experiencing a superimposed pathologic process, such as TBI or a burst of inflammation secondary to some infectious process, might experience an acceleration of their clinical disease course via either acceleration of primary pathogenic process or via parallel brain injury without any actual change in the burden of PD-specific pathologies, resulting in earlier onset of overt parkinsonism. In some cases, this might result in the emergence of PD in individuals who would otherwise die from competing causes of mortality prior to onset of parkinsonism. The scenario of superimposed brain injury during the prodromal phase of PD might be especially relevant to sequelae of COVID-19 infections. The potential role of infectious processes as hazard factors for PD suggests the possibility of something like the epidemic of post-encephalitic parkinsonism following World War I. Careful longitudinal follow-up of COVID-19 victims, particularly middle-aged to older individuals who might be in the prodromal phase of PD, is well justified. Maintaining a critical stance about potential heterogeneity of risk and protective factor mechanisms is important when considering epidemiologic associations as clues to pathogenic mechanisms.

Epidemiologic research is an important avenue for uncovering insights to pathogenesis. In PD research, pharmacoepidemiologic studies have been particularly important in suggesting clues to pathogenesis and selection of agents for disease modification clinical trials. This rational approach is certainly useful for hypothesis generation but has not yielded any successes. In the case of CCBs, epidemiologic data was complemented by excellent work in preclinical PD models. The outcome of the pivotal STEADY-PD trial was disappointing and accompanied by controversy. Results of a phase II trial of simvastatin were reported recently and are similarly negative. Analogous to the CCB experience, there is strong preclinical model work consistent with the concept that TZ might be a disease-modifying agent, but whether this agent will be successful remains to be seen. The present strategy of trialing potentially disease-modifying agents identified by pharmacoepidemiologic studies in PD populations is rational but has problematic features. As shown by the controversies accompanying interpretation of numerous trials, designing disease modifying trials for PD is challenging. A negative trial outcome is not dispositive. As frequently argued for Alzheimer disease, evaluating agents in subjects with manifest PD may be a particularly disadvantageous approach to demonstrating disease-modifying effects. Intervention trials during the prodromal phase of PD might have a better chance of identifying disease-modifying effects and providing more definitive evidence about pathogenic mechanisms.

In contrast to cardiovascular disease, cancer, and stroke, PD epidemiology research has had relatively little impact on PD prevalence or care. To date, there are no identified distinctive risk factors whose exposure reduction would likely reduce PD incidence. Indeed, the best confirmed apparently protective association, tobacco abuse, is an exposure that should be eliminated from our societies. The specific impact of the identification of several potentially modifiable risk factor associations is reduced because they point to interventions that should be pursued regardless of whether or not they impact PD incidence. Interventions in this category include encouraging reducing TBI incidence, T2DM incidence, air pollution control, and increasing HepC prevention/treatment. Successful efforts to reduce these exposures may produce significant benefits for PD incidence. The case for eliminating or reducing exposure to some industrial toxicants, such as paraquat or halogenated hydrocarbons, is strong. Given the difficulty of studying these associations, the available data supports causal relationships between these exposures and PD incidence. A significant question is the magnitude of these effects. Whether they are major contributors to PD incidence-prevalence is an open question. In a rational policy-decision analysis framework, however, we have little to lose and might have much to gain by banning paraquat, other pesticides, and reducing

halogenated hydrocarbon exposures.

For similar reasons, encouraging physical activity across the lifespan is a logical policy choice. Designing and implementing intervention studies to evaluate the potential neuroprotective capacity of physical activity in reducing PD incidence seems very challenging. Given the numerous health benefits of regular physical activity, policies to incentivize regular physical activity should be implemented regardless of any potential effects on PD incidence, but such policies may have co-benefits for PD incidence.

An obstacle to a clearer understanding of the role of potential risk and protective factors in PD is the pathologic and clinical heterogeneity of PD. As conventionally defined, PD is a broad syndrome, but more recent developments in biomarker research and genetics now allow rational fractionation of PD populations. Study of biomarker defined sub-populations may clarify the nature of PD risk and protective factors. Studies using biomarkers to define prodromal and even preclinical phases of PD might be particularly fruitful and substantial, longitudinal studies are well justified. Similarly, increased understanding of genetic factors driving PD risk provides some opportunity to fractionate PD sub-populations and to evaluate potential gene-environment interactions. Studies focused on PD sub-populations may be particularly useful in clarifying the role of risk/protective factors in PD pathogenesis. The possibility that some risk factors modify PD risk by lowering the threshold for clinical expression of primary pathogenic processes versus modulating the effects of primary pathogenic processes and potential interactions should also be evaluated.

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Nikolas Grotewold: Writing – review & editing. **Roger L. Albin:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Roger Albin reports financial support was provided by National Institute of Neurological Disorders and Stroke. Roger Albin reports financial support was provided by Parkinson's Foundation. Roger Albin reports a relationship with Ionis Pharmaceuticals Inc that includes: consulting or advisory. Roger Albin reports a relationship with IQVIA that includes: consulting or advisory. Roger Albin reports a relationship with Biogen Inc that includes: consulting or advisory. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] A. Ascherio, M.A. Schwarzschild, The epidemiology of Parkinson's disease: risk factors and prevention, *Lancet Neurol.* 15 (12) (2016) 1257–1272.
- [2] B. Ritz, A. Ascherio, H. Checkoway, K.S. Marder, L.M. Nelson, W.A. Rocca, G. W. Ross, D. Strickland, S.K. Van Den Eeden, J. Gorell, Pooled analysis of tobacco use and risk of Parkinson disease, *Arch. Neurol.* 64 (7) (2007) 990–997.
- [3] M.A. Hernan, B. Takkouche, F. Caamano-Isorna, J.J. Gestal-Otero, A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease, *Ann. Neurol.* 52 (3) (2002) 276–284.
- [4] C.B. Breckenridge, C. Berry, E.T. Chang, R.L. Sielken Jr., J.S. Mandel, Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis, *PLoS One* 11 (4) (2016) e0151841.
- [5] X. Li, W. Li, G. Liu, X. Shen, Y. Tang, Association between cigarette smoking and Parkinson's disease: a meta-analysis, *Arch. Gerontol. Geriatr.* 61 (3) (2015) 510–516.
- [6] A.J. Noyce, J.P. Bestwick, L. Silveira-Moriyama, C.H. Hawkes, G. Giovannoni, A. J. Lees, A. Schrag, Meta-analysis of early nonmotor features and risk factors for Parkinson disease, *Ann. Neurol.* 72 (6) (2012) 893–901.
- [7] B. Mappin-Kasirer, H. Pan, S. Lewington, J. Kizza, R. Gray, R. Clarke, R. Peto, Tobacco smoking and the risk of Parkinson disease: a 65-year follow-up of 30,000 male British doctors, *Neurology* 94 (20) (2020) e2132–e2138.
- [8] C. Ma, S. Molsberry, Y. Li, M. Schwarzschild, A. Ascherio, X. Gao, Dietary nicotine intake and risk of Parkinson disease: a prospective study, *Am. J. Clin. Nutr.* 112 (4) (2020) 1080–1087.
- [9] M. Quik, M. O'Neill, X.A. Perez, Nicotine neuroprotection against nigrostriatal damage: importance of the animal model, *Trends Pharmacol. Sci.* 28 (5) (2007) 229–235.
- [10] B. Ritz, P.C. Lee, C.F. Lassen, O.A. Arah, Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease, *Neurology* 83 (16) (2014) 1396–1402.
- [11] Y.H. Chuang, K.C. Paul, J.S. Sinsheimer, J.M. Bronstein, Y.M. Bordon, B. Ritz, Genetic variants in nicotinic receptors and smoking cessation in Parkinson's disease, *Parkinsonism Relat. Disorders* 62 (2019) 57–61.
- [12] N.M. Gatto, D. Deapen, Y. Bordon, S. Marshall, L. Bernstein, B. Ritz, Passive smoking and Parkinson's disease in California Teachers, *Parkinsonism Relat. Disorders* 45 (2017) 44–49.
- [13] C.M. Tanner, S.M. Goldman, D.A. Aston, R. Ottman, J. Ellenberg, R. Mayeux, J. W. Langston, Smoking and Parkinson's disease in twins, *Neurology* 58 (4) (2002) 581–588.
- [14] K. Wirdefeldt, M. Gatz, Y. Pawitan, N.L. Pedersen, Risk and protective factors for Parkinson's disease: a study in Swedish twins, *Ann. Neurol.* 57 (1) (2005) 27–33.
- [15] C. Dominguez-Baleon, J.S. Ong, C.R. Scherzer, M.E. Renteria, X. Dong, Understanding the effect of smoking and drinking behavior on Parkinson's disease risk: a Mendelian randomization study, *Sci. Rep.* 11 (1) (2021) 13980.
- [16] C. Domenighetti, P.E. Sugier, A.A.K. Sreelatha, C. Schulte, S. Grover, O. Mohamed, B. Portugal, P. May, D.R. Bobbili, M. Radivojkov-Blagojevic, P. Lichtner, A.B. Singleton, D.G. Hernandez, C. Edsall, G.D. Mellick, A. Zimprich, W. Pirker, E. Rogaeva, A.E. Lang, S. Koks, P. Taba, S. Lesage, A. Brice, J.C. Corvol, M.C. Chartier-Harlin, E. Mutez, K. Brockmann, A.B. Deuschlander, G. M. Hadjigeorgiou, E. Dardiotis, L. Stefanis, A.M. Simitsi, E.M. Valente, S. Petrucci, S. Duga, L. Straniero, A. Zecchinelli, G. Pezzoli, L. Brighina, C. Ferrarese, G. Annesi, A. Quattrone, M. Gagliardi, H. Matsuo, Y. Kawamura, N. Hattori, K. Nishioka, S.J. Chung, Y.J. Kim, P. Kolber, B.P. van de Warrenburg, B.R. Bloem, J. Aasly, M. Toft, L. Pihlstrom, L.C. Guedes, J.J. Ferreira, S. Bardin, J. Carr, E. Tolosa, M. Ezquerro, P. Pastor, M. Diez-Fairen, K. Wirdefeldt, N.L. Pedersen, C. Ran, A.C. Belin, A. Puschmann, C. Hellberg, C.E. Clarke, K.E. Morrison, M. Tan, D. Krainc, L.F. Burbulla, M.J. Farrer, R. Kruger, T. Gasser, M. Sharma, A. Elbaz, G. Comprehensive unbiased risk factor assessment for, c. Environment in Parkinson's disease, mendelian randomisation study of smoking, alcohol, and coffee drinking in relation to Parkinson's disease, *J. Parkinsons Dis.* 12 (1) (2022) 267–282.
- [17] K. Heilbron, M.P. Jensen, S. Bandres-Ciga, P. Fontanillas, C. Blauwendraat, M. A. Nalls, A.B. Singleton, G.D. Smith, P. Cannon, A.J. Noyce, T. and Me Research, Unhealthy behaviours and risk of Parkinson's disease: a mendelian randomisation study, *J. Parkinsons Dis.* 11 (4) (2021) 1981–1993.
- [18] S. Grover, C.M. Lill, M. Kasten, C. Klein, M.F. Del Greco, L.R. Konig, Risky behaviors and Parkinson disease: a mendelian randomization study, *Neurology* 93 (15) (2019) e1412–e1424.
- [19] W.H. Oertel, H.H. Muller, M.M. Unger, C. Schade-Brittinger, K. Balthasar, K. Articus, M. Brinkman, C.S. Venuto, F. Tracik, J. Eberling, K.M. Eggert, C. Kamp, K. Kiebert, J.T. Boyd, Transdermal nicotine treatment and progression of early Parkinson's disease, *NEJM Evid* 2 (9) (2023). EVID02200311.
- [20] J.F. Chen, M.A. Schwarzschild, Do caffeine and more selective adenosine A(2A) receptor antagonists protect against dopaminergic neurodegeneration in Parkinson's disease? *Parkinsonism Relat. Disorders* 80 (Suppl 1) (2020) S45–S53. Suppl 1.
- [21] L.C. Tan, W.P. Koh, J.M. Yuan, R. Wang, W.L. Au, J.H. Tan, E.K. Tan, M.C. Yu, Differential effects of black versus green tea on risk of Parkinson's disease in the Singapore Chinese Health Study, *Am. J. Epidemiol.* 167 (5) (2008) 553–560.
- [22] A. Ascherio, S.M. Zhang, M.A. Hernan, I. Kawachi, G.A. Colditz, F.E. Speizer, W. C. Willett, Prospective study of caffeine consumption and risk of Parkinson's disease in men and women, *Ann. Neurol.* 50 (1) (2001) 56–63.
- [23] H. Qi, S. Li, Dose-response meta-analysis on coffee, tea and caffeine consumption with risk of Parkinson's disease, *Geriatr. Gerontol. Int.* 14 (2) (2014) 430–439.
- [24] J. Costa, N. Lunet, C. Santos, J. Santos, A. Vaz-Carneiro, Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies, *J. Alzheimers Dis.* 20 (Suppl 1) (2010) S221–S238.
- [25] S. Ferre, Mechanisms of the psychostimulant effects of caffeine: implications for substance use disorders, *Psychopharmacology (Berl)* 233 (10) (2016) 1963–1979.
- [26] M. Schenkman, C.G. Moore, W.M. Kohrt, D.A. Hall, A. Delitto, C.L. Comella, D. A. Josbeno, C.L. Christiansen, B.D. Berman, B.M. Kluger, E.L. Melanson, S. Jain, J. A. Robichaud, C. Poon, D.M. Corcos, Effect of high-intensity treadmill exercise on motor symptoms in patients with de novo Parkinson disease: a phase 2 randomized clinical trial, *JAMA Neurol.* 75 (2) (2018) 219–226.
- [27] F.O. de Almeida, V. Santana, D.M. Corcos, C. Ugrinowitsch, C. Silva-Batista, Effects of endurance training on motor signs of Parkinson's disease: a systematic review and meta-analysis, *Sports Med.* 52 (8) (2022) 1789–1815.

- [28] I.F. Shih, C. Starhof, C.F. Lassen, J. Hansen, Z. Liew, B. Ritz, Occupational and recreational physical activity and Parkinson's disease in Denmark, *Scand. J. Work. Environ. Health* 43 (3) (2017) 210–216.
- [29] F. Yang, Y. Trolle Lagerros, R. Bellocchio, H.O. Adami, F. Fang, N.L. Pedersen, K. Wirdefeldt, Physical activity and risk of Parkinson's disease in the Swedish national march cohort, *Brain* 138 (Pt 2) (2015) 269–275.
- [30] Q. Xu, Y. Park, X. Huang, A. Hollenbeck, A. Blair, A. Schatzkin, H. Chen, Physical activities and future risk of Parkinson disease, *Neurology* 75 (4) (2010) 341–348.
- [31] E.L. Thacker, H. Chen, A.V. Patel, M.L. McCullough, E.E. Calle, M.J. Thun, M. A. Schwarzschild, A. Ascherio, Recreational physical activity and risk of Parkinson's disease, *Mov. Disord.* 23 (1) (2008) 69–74.
- [32] G. Logroscino, H.D. Sesso, R.S. Paffenbarger Jr., I.M. Lee, Physical activity and risk of Parkinson's disease: a prospective cohort study, *J. Neurol. Neurosurg. Psychiatry* 77 (12) (2006) 1318–1322.
- [33] H. Chen, S.M. Zhang, M.A. Schwarzschild, M.A. Hernan, A. Ascherio, Physical activity and the risk of Parkinson disease, *Neurology* 64 (4) (2005) 664–669.
- [34] C. Shen, Y. Guo, W. Luo, C. Lin, M. Ding, Serum urate and the risk of Parkinson's disease: results from a meta-analysis, *Can. J. Neurol. Sci.* 40 (1) (2013) 73–79.
- [35] M.G. Weisskopf, E. O'Reilly, H. Chen, M.A. Schwarzschild, A. Ascherio, Plasma urate and risk of Parkinson's disease, *Am. J. Epidemiol.* 166 (5) (2007) 561–567.
- [36] E.J. O'Reilly, X. Gao, M.G. Weisskopf, H. Chen, M.A. Schwarzschild, D. Spiegelman, A. Ascherio, Plasma urate and Parkinson's disease in women, *Am. J. Epidemiol.* 172 (6) (2010) 666–670.
- [37] X. Gao, E.J. O'Reilly, M.A. Schwarzschild, A. Ascherio, Prospective study of plasma urate and risk of Parkinson disease in men and women, *Neurology* 86 (6) (2016) 520–526.
- [38] J.W. Davis, A. Grandinetti, C.I. Waslien, G.W. Ross, L.R. White, D.M. Morens, Observations on serum uric acid levels and the risk of idiopathic Parkinson's disease, *Am. J. Epidemiol.* 144 (5) (1996) 480–484.
- [39] P. Ungprasert, N. Srivali, C. Thongprayoon, Gout is not associated with a lower risk of Parkinson's disease: a systematic review and meta-analysis, *Parkinsonism Relat. Disorders* 21 (10) (2015) 1238–1242.
- [40] J. Pakpoor, O.O. Seminog, S.V. Ramagopal, M.J. Goldacre, Clinical associations between gout and multiple sclerosis, Parkinson's disease and motor neuron disease: record-linkage studies, *BMC Neurol.* 15 (2015) 16.
- [41] J.A. Singh, J.D. Cleveland, Gout and the risk of Parkinson's disease in older adults: a study of U.S. Medicare data, *BMC Neurol.* 19 (1) (2019) 4.
- [42] M. De Vera, M.M. Rahman, J. Rankin, J. Kopec, X. Gao, H. Choi, Gout and the risk of Parkinson's disease: a cohort study, *Arthritis Rheum.* 59 (11) (2008) 1549–1554.
- [43] A. Alonso, L.A. Rodriguez, G. Logroscino, M.A. Hernan, Gout and risk of Parkinson disease: a prospective study, *Neurology* 69 (17) (2007) 1696–1700.
- [44] D.A. Kia, A.J. Noyce, J. White, D. Speed, A. Nicolas, I. collaborators, S. Burgess, D. A. Lawlor, G. Davey Smith, A. Singleton, M.A. Nalls, R. Sofat, N.W. Wood, Mendelian randomization study shows no causal relationship between circulating urate levels and Parkinson's disease, *Ann. Neurol.* 84 (2) (2018) 191–199.
- [45] S.-P.D.I. Parkinson Study Group, M.A. Schwarzschild, A. Ascherio, C. Casaceli, G. C. Curhan, R. Fitzgerald, C. Kamp, C. Lungu, E.A. Macklin, K. Marek, D. Mozaffarian, D. Oakes, A. Rudolph, I. Shoulson, A. Videnovic, B. Scott, L. Gauger, J. Aldred, M. Bixby, J. Ciccarello, S.A. Gunzler, C. Henchcliffe, M. Brodsky, K. Keith, R.A. Hauser, C. Goetz, M.S. LeDoux, V. Hinson, R. Kumar, A. J. Espay, J. Jimenez-Shahed, C. Hunter, C. Christine, A. Daley, M. Leehey, J.A. de Marcaida, J.H. Friedman, A. Hung, G. Bwala, I. Litvan, D.K. Simon, T. Simuni, C. Poon, M.C. Schiess, K. Chou, A. Park, D. Bhatti, C. Peterson, S.R. Criswell, L. Rosenthal, J. Murphy, H.A. Shill, S.H. Mehta, A. Ahmed, A.F. Deik, J.Y. Fang, N. Stover, L. Zhang, R.B. Dewey Jr., A. Gerald, J.T. Boyd, E. Houston, V. Suski, S. Mosovsky, L. Cloud, B.B. Shah, M. Saint-Hilaire, R. James, S.E. Zaubner, S. Reich, D. Shprecher, R. Pahwa, A. Langhammer, K. LaFaver, P.A. LeWitt, P. Kaminski, J. Goudreau, D. Russell, D.J. Houghton, A. Laroche, K. Thomas, M. McGraw, Z. Mari, C. Serrano, K. Blindauer, M. Rabin, R. Kurlan, J.C. Morgan, M. Soileau, M. Ainslie, I. Bodis-Wollner, R.B. Schneider, C. Waters, A.S. Ratel, C. A. Beck, P. Bolger, K.F. Callahan, G.F. Crotty, D. Klements, M. Kostrzebski, G. M. McMahon, L. Pothier, S.S. Waikar, A. Lang, T. Mestre, Effect of urate-elevating inosine on early Parkinson disease progression: the SURE-PD3 randomized clinical trial, *JAMA* 326 (10) (2021) 926–939.
- [46] F. Seifari, A.R. Dinassarapu, H.A. Jinnah, Uric acid in Parkinson's disease: what is the connection? *Mov. Disord.* 37 (11) (2022) 2173–2183.
- [47] T.N. Poly, M.M.R. Islam, H.C. Yang, Y.J. Li, Non-steroidal anti-inflammatory drugs and risk of Parkinson's disease in the elderly population: a meta-analysis, *Eur. J. Clin. Pharmacol.* 75 (1) (2019) 99–108.
- [48] B.A. Racette, A. Gross, S.M. Vouri, A. Camacho-Soto, A.W. Willis, S. Searles Nielsen, Immunosuppressants and risk of Parkinson disease, *Ann. Clin. Transl. Neurol.* 5 (7) (2018) 870–875.
- [49] D.J. Surmeier, G.M. Halliday, T. Simuni, Calcium, mitochondrial dysfunction and slowing the progression of Parkinson's disease, *Exp. Neurol.* 298 (Pt B) (2017) 202–209.
- [50] B. Ritz, S.L. Rhodes, L. Qian, E. Schernhammer, J.H. Olsen, S. Friis, L-type calcium channel blockers and Parkinson disease in Denmark, *Ann. Neurol.* 67 (5) (2010) 600–606.
- [51] S.-P.D.I.I.I.I. Parkinson Study Group, Isradipine versus placebo in early Parkinson disease: a randomized trial, *Ann. Intern. Med.* 172 (9) (2020) 591–598.
- [52] D.J. Surmeier, J.T. Nguyen, N. Lancki, C.S. Venuto, D. Oakes, T. Simuni, R. K. Wyse, Re-analysis of the STEADY-PD II trial-evidence for slowing the progression of Parkinson's disease, *Mov. Disord.* 37 (2) (2022) 334–342.
- [53] B. Maiti, J.S. Perlmutter, A clinical trial of isradipine: what went wrong? *Ann. Intern. Med.* 172 (9) (2020) 625–626.
- [54] N.J. Ortner, Voltage-gated Ca(2+) channels in dopaminergic substantia nigra neurons: therapeutic targets for neuroprotection in Parkinson's disease? *Front. Synaptic Neurosci.* 13 (2021) 636103.
- [55] S. Mittal, K. Bjornevik, D.S. Im, A. Flierl, X. Dong, J.J. Locascio, K.M. Abo, E. Long, M. Jin, B. Xu, Y.K. Xiang, J.C. Rochet, A. Engeland, P. Rizzu, P. Heutink, T. Bartels, D.J. Selkoe, B.J. Caldarone, M.A. Glicksman, V. Khurana, B. Schule, D. S. Park, T. Riise, C.R. Scherzer, beta2-Adrenoreceptor is a regulator of the alpha-synuclein gene driving risk of Parkinson's disease, *Science* 357 (6354) (2017) 891–898.
- [56] F. Hopfner, G.U. Hoglinger, G. Kuhlbaumer, A. Pottgard, M. Wod, K. Christensen, C.M. Tanner, G. Deuschl, beta-adrenoreceptors and the risk of Parkinson's disease, *Lancet Neurol.* 19 (3) (2020) 247–254.
- [57] A. Pierzchlińska, M. Drodzdzik, M. Bialecka, A possible role for HMG-CoA reductase inhibitors and its association with HMGR genetic variation in Parkinson's disease, *Int. J. Mol. Sci.* 22 (22) (2021).
- [58] C.C. Wu, M.M. Islam, A.J. Lee, C.H. Su, Y.C. Weng, C.Y. Yeh, H.H. Lee, M.C. Lin, Association between statin use and risk of Parkinson's disease: evidence from 18 observational studies comprising 3.7 million individuals, *J. Personalized Med.* 12 (5) (2022).
- [59] K. Bykov, K. Yoshida, M.G. Weisskopf, J.J. Gagne, Confounding of the association between statins and Parkinson disease: systematic review and meta-analysis, *Pharmacoepidemiol. Drug Saf.* 26 (3) (2017) 294–300.
- [60] T.T.H. Nguyen, A. Fournier, E. Courtois, F. Artaud, S. Escolano, P. Tubert-Bitter, M.C. Boutron-Ruault, I. Degaey, E. Roze, M. Canonico, I. Ahmed, A.C. M. Thiebaut, A. Elbaz, Statin use and incidence of Parkinson's disease in women from the French E3N cohort study, *Mov. Disord.* 38 (5) (2023) 854–865.
- [61] C.B. Carroll, D. Webb, K.N. Stevens, J. Vickery, V. Eyre, S. Ball, R. Wyse, M. Webber, A. Foggo, J. Zajicek, A. Whone, S. Creanor, Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): protocol for a double-blind, randomised, placebo-controlled futility study, *BMJ Open* 9 (10) (2019) e029740.
- [62] K.N. Stevens, S. Creanor, A. Jeffery, A. Whone, J. Zajicek, A. Foggo, B. Jones, R. Chapman, L. Cocking, J. Wilks, D. Webb, C. Carroll, P.S.S. Group, Evaluation of simvastatin as a disease-modifying treatment for patients with Parkinson disease: a randomized clinical trial, *JAMA Neurol.* 79 (12) (2022) 1232–1241.
- [63] R. Cai, Y. Zhang, J.E. Simmering, J.L. Schultz, Y. Li, I. Fernandez-Carasa, A. Consiglio, A. Raya, P.M. Polgreen, N.S. Narayanan, Y. Yuan, Z. Chen, W. Su, Y. Han, C. Zhao, L. Gao, X. Ji, M.J. Welsh, L. Liu, Enhancing glycolysis attenuates Parkinson's disease progression in models and clinical databases, *J. Clin. Invest.* 129 (10) (2019) 4539–4549.
- [64] H. Braak, U. Rub, W.P. Gai, K. Del Tredici, Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen, *J. Neural. Transm.* 110 (5) (2003) 517–536.
- [65] M.G. Stokholm, E.H. Danielsen, S.J. Hamilton-Dutoit, P. Borghammer, Pathological alpha-synuclein in gastrointestinal tissues from prodromal Parkinson disease patients, *Ann. Neurol.* 79 (6) (2016) 940–949.
- [66] C. Skjaerbaek, K. Knudsen, J. Horsager, P. Borghammer, Gastrointestinal dysfunction in Parkinson's disease, *J. Clin. Med.* 10 (3) (2021).
- [67] R.A. Liddle, Parkinson's disease from the gut, *Brain Res.* 1693 (Pt B) (2018) 201–206.
- [68] N. Van Den Berge, N. Ferreira, H. Gram, T.W. Mikkelsen, A.K.O. Alstrup, N. Casadei, P. Tsung-Pin, O. Riess, J.R. Nyengaard, G. Tamguney, P.H. Jensen, P. Borghammer, Evidence for bidirectional and transynaptic parasympathetic and sympathetic propagation of alpha-synuclein in rats, *Acta Neuropathol.* 138 (4) (2019) 535–551.
- [69] S. Kim, S.H. Kwon, T.I. Kam, N. Panicker, S.S. Karuppagounder, S. Lee, J.H. Lee, W.R. Kim, M. Kook, C.A. Foss, C. Shen, H. Lee, S. Kulkarni, P.J. Pasricha, G. Lee, M.G. Pomper, V.L. Dawson, T.M. Dawson, H.S. Ko, Transneuronal propagation of pathologic alpha-synuclein from the gut to the brain models Parkinson's disease, *Neuron* 103 (4) (2019) 627–641 e7.
- [70] B. Liu, F. Fang, N.L. Pedersen, A. Tillander, J.F. Ludvigsson, A. Ekblom, P. Svenningsson, H. Chen, K. Wirdefeldt, Vagotomy and Parkinson disease: a Swedish register-based matched-cohort study, *Neurology* 88 (21) (2017) 1996–2002.
- [71] E. Svensson, E. Horvath-Puho, R.W. Thomsen, J.C. Djurhuus, L. Pedersen, P. Borghammer, H.T. Sorensen, Vagotomy and subsequent risk of Parkinson's disease, *Ann. Neurol.* 78 (4) (2015) 522–529.
- [72] H.T. Lu, Q.Y. Shen, D. Xie, Q.Z. Zhao, Y.M. Xu, Lack of association between appendectomy and Parkinson's disease: a systematic review and meta-analysis, *Aging Clin. Exp. Res.* 32 (11) (2020) 2201–2209.
- [73] N. Palacios, K.C. Hughes, E. Cereda, M.A. Schwarzschild, A. Ascherio, Appendectomy and risk of Parkinson's disease in two large prospective cohorts of men and women, *Mov. Disord.* 33 (9) (2018) 1492–1496.
- [74] E. Svensson, E. Horvath-Puho, M.G. Stokholm, H.T. Sorensen, V.W. Henderson, P. Borghammer, Appendectomy and risk of Parkinson's disease: a nationwide cohort study with more than 10 years of follow-up, *Mov. Disord.* 31 (12) (2016) 1918–1922.
- [75] C. Marras, A.E. Lang, P.C. Austin, C. Lau, D.R. Urbach, Appendectomy in mid and later life and risk of Parkinson's disease: a population-based study, *Mov. Disord.* 31 (8) (2016) 1243–1247.
- [76] B. Liu, F. Fang, W. Ye, K. Wirdefeldt, Appendectomy, tonsillectomy and Parkinson's disease risk: a Swedish register-based study, *Front. Neurol.* 11 (2020) 510.
- [77] B.A. Killinger, Z. Madaj, J.W. Sikora, N. Rey, A.J. Haas, Y. Vepa, D. Lindqvist, H. Chen, P.M. Thomas, P. Brundin, L. Brundin, V. Labrie, The vermiform

- appendix impacts the risk of developing Parkinson's disease, *Sci. Transl. Med.* 10 (465) (2018).
- [78] S. Jafari, M. Etrinan, F. Aminzadeh, A. Samii, Head injury and risk of Parkinson disease: a systematic review and meta-analysis, *Mov. Disord.* 28 (9) (2013) 1222–1229.
- [79] C. Marras, C.A. Hincapie, V.L. Kristman, C. Cancelliere, S. Soklaridis, A. Li, J. Borg, J.L. af Geijerstam, J.D. Cassidy, Systematic review of the risk of Parkinson's disease after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis, *Arch. Phys. Med. Rehabil.* 95 (3 Suppl) (2014) S238–S244.
- [80] F. Fang, H. Chen, A.L. Feldman, F. Kamel, W. Ye, K. Wirdefeldt, Head injury and Parkinson's disease: a population-based study, *Mov. Disord.* 27 (13) (2012) 1632–1635.
- [81] R.C. Gardner, J.F. Burke, J. Nettiksimmons, S. Goldman, C.M. Tanner, K. Yaffe, Traumatic brain injury in later life increases risk for Parkinson disease, *Ann. Neurol.* 77 (6) (2015) 987–995.
- [82] L. Kenborg, K. Rugbjerg, P.C. Lee, L. Ravnskjaer, J. Christensen, B. Ritz, C. F. Lassen, Head injury and risk for Parkinson disease: results from a Danish case-control study, *Neurology* 84 (11) (2015) 1098–1103.
- [83] S. Hasan, M.M. Mielke, P. Turcano, J.E. Ahlskog, J.H. Bower, R. Savica, Traumatic brain injury preceding clinically diagnosed alpha-synucleinopathies: a case-control study, *Neurology* 94 (8) (2020) e764–e773.
- [84] K.M. Taylor, M.H. Saint-Hilaire, L. Sudarsky, D.K. Simon, B. Hersch, D. Sparrow, H. Hu, M.G. Weisskopf, Head injury at early ages is associated with risk of Parkinson's disease, *Parkinsonism Relat. Disorders* 23 (2016) 57–61.
- [85] R.C. Gardner, A.L. Byers, D.E. Barnes, Y. Li, J. Boscardin, K. Yaffe, Mild TBI and risk of Parkinson disease: a chronic effects of neurotrauma consortium study, *Neurology* 90 (20) (2018) e1771–e1779.
- [86] P.C. Lee, Y. Bordelon, J. Bronstein, B. Ritz, Traumatic brain injury, paraquat exposure, and their relationship to Parkinson disease, *Neurology* 79 (20) (2012) 2061–2066.
- [87] E.R. Russell, D.F. Mackay, K. Stewart, J.A. MacLean, J.P. Pell, W. Stewart, Association of field position and career length with risk of neurodegenerative disease in male former professional soccer players, *JAMA Neurol.* 78 (9) (2021) 1057–1063.
- [88] D.F. Mackay, E.R. Russell, K. Stewart, J.A. MacLean, J.P. Pell, W. Stewart, Neurodegenerative disease mortality among former professional soccer players, *N. Engl. J. Med.* 381 (19) (2019) 1801–1808.
- [89] P. Ueda, B. Pasternak, C.E. Lim, M. Neovius, M. Kader, M. Forssblad, J. F. Ludvigsson, H. Svanstrom, Neurodegenerative disease among male elite football (soccer) players in Sweden: a cohort study, *Lancet Public Health* 8 (4) (2023) e256–e265.
- [90] H.J. Bruce, Y. Tripodis, M. McClean, M. Korell, C.M. Tanner, B. Contreras, J. Gottesman, L. Kirsch, Y. Karim, B. Martin, J. Palmisano, B. Abdolmohammadi, L.C. Shih, T.D. Stein, R.A. Stern, C.H. Adler, J. Mez, C. Nowinski, A.C. McKee, M. L. Alocco, American football play and Parkinson disease among men, *JAMA Netw. Open* 6 (8) (2023) e2328644.
- [91] A. Barbeau, M. Roy, G. Bernier, G. Campanella, S. Paris, Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas, *Can. J. Neurol. Sci.* 14 (1) (1987) 36–41.
- [92] M. van der Mark, M. Brouwer, H. Kromhout, P. Nijssen, A. Huss, R. Vermeulen, Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results, *Environ. Health Perspect.* 120 (3) (2012) 340–347.
- [93] G. Pezzoli, E. Cereda, Exposure to pesticides or solvents and risk of Parkinson disease, *Neurology* 80 (22) (2013) 2035–2041.
- [94] G. Van Maele-Fabry, P. Hoet, F. Vilain, D. Lison, Occupational exposure to pesticides and Parkinson's disease: a systematic review and meta-analysis of cohort studies, *Environ. Int.* 46 (2012) 30–43.
- [95] L.G. Gunnarsson, L. Bodin, Occupational exposures and neurodegenerative diseases-A systematic literature review and meta-analyses, *Int. J. Environ. Res. Publ. Health* 16 (3) (2019).
- [96] S. Narayan, Z. Liew, J.M. Bronstein, B. Ritz, Occupational pesticide use and Parkinson's disease in the Parkinson Environment Gene (PEG) study, *Environ. Int.* 107 (2017) 266–273.
- [97] A. Wang, S. Costello, M. Cockburn, X. Zhang, J. Bronstein, B. Ritz, Parkinson's disease risk from ambient exposure to pesticides, *Eur. J. Epidemiol.* 26 (7) (2011) 547–555.
- [98] S. Costello, M. Cockburn, J. Bronstein, X. Zhang, B. Ritz, Parkinson's disease and residential exposure to maneb and paraquat from agricultural applications in the central valley of California, *Am. J. Epidemiol.* 169 (8) (2009) 919–926.
- [99] C.M. Tanner, F. Kamel, G.W. Ross, J.A. Hoppin, S.M. Goldman, M. Korell, C. Marras, G.S. Bhudhikanok, M. Kasten, A.R. Chade, K. Comyns, M.B. Richards, C. Meng, B. Priestley, H.H. Fernandez, F. Cambi, D.M. Umbach, A. Blair, D. P. Sandler, J.W. Langston, Rotenone, paraquat, and Parkinson's disease, *Environ. Health Perspect.* 119 (6) (2011) 866–872.
- [100] A. Ascherio, H. Chen, M.G. Weisskopf, E. O'Reilly, M.L. McCullough, E.E. Calle, M.A. Schwarzschild, M.J. Thun, Pesticide exposure and risk for Parkinson's disease, *Ann. Neurol.* 60 (2) (2006) 197–203.
- [101] E.R. Dorsey, M. Zafar, S.E. Lettenberger, M.E. Pawlik, D. Kinel, M. Frissen, R. B. Schneider, K. Kiebert, C.M. Tanner, B.R. De Miranda, S.M. Goldman, B. R. Bloem, Trichloroethylene: an invisible cause of Parkinson's disease? *J. Parkinsons Dis.* 13 (2) (2023) 203–218.
- [102] B.R. De Miranda, J.T. Greenamyre, Trichloroethylene, a ubiquitous environmental contaminant in the risk for Parkinson's disease, *Environ. Sci. Proc. Imp.* 22 (3) (2020) 543–554.
- [103] F.J. Bove, P.Z. Ruckart, M. Maslia, T.C. Larson, Mortality study of civilian employees exposed to contaminated drinking water at USMC Base Camp Lejeune: a retrospective cohort study, *Environ. Health* 13 (2014) 68.
- [104] D.M. Gash, K. Rutland, N.L. Hudson, P.G. Sullivan, G. Bing, W.A. Cass, J. D. Pandya, M. Liu, D.Y. Choi, R.L. Hunter, G.A. Gerhardt, C.D. Smith, J.T. Slevin, T.S. Prince, Trichloroethylene: parkinsonism and complex 1 mitochondrial neurotoxicity, *Ann. Neurol.* 63 (2) (2008) 184–192.
- [105] S.M. Goldman, P.J. Quinlan, G.W. Ross, C. Marras, C. Meng, G.S. Bhudhikanok, K. Comyns, M. Korell, A.R. Chade, M. Kasten, B. Priestley, K.L. Chou, H. H. Fernandez, F. Cambi, J.W. Langston, C.M. Tanner, Solvent exposures and Parkinson disease risk in twins, *Ann. Neurol.* 71 (6) (2012) 776–784.
- [106] S.S. Nielsen, M.N. Warden, M. Sallmen, M. Sainio, S. Uusulainen, H. Checkoway, C. Hublin, B.A. Racette, Solvent exposed occupations and risk of Parkinson disease in Finland, *Clin. Park. Relat. Disord.* 4 (2021) 100092.
- [107] S.M. Goldman, F.M. Weaver, K.T. Stroupe, L. Cao, B. Gonzalez, K. Colletta, E. G. Brown, C.M. Tanner, Risk of Parkinson disease among service members at marine Corps base camp lejeune, *JAMA Neurol.* 80 (7) (2023) 673–681.
- [108] B.R. De Miranda, S.L. Castro, E.M. Rocha, C.R. Bodle, K.E. Johnson, J. T. Greenamyre, The industrial solvent trichloroethylene induces LRRK2 kinase activity and dopaminergic neurodegeneration in a rat model of Parkinson's disease, *Neurobiol. Dis.* 153 (2021) 105312.
- [109] M.G. Weisskopf, J. Weuve, H. Nie, M.H. Saint-Hilaire, L. Sudarsky, D.K. Simon, B. Hersch, J. Schwartz, R.O. Wright, H. Hu, Association of cumulative lead exposure with Parkinson's disease, *Environ. Health Perspect.* 118 (11) (2010) 1609–1613.
- [110] J.M. Gorell, C.C. Johnson, B.A. Rybicki, E.L. Peterson, G.X. Kortsha, G.G. Brown, R.J. Richardson, Occupational exposures to metals as risk factors for Parkinson's disease, *Neurology* 48 (3) (1997) 650–658.
- [111] S. Coon, A. Stark, E. Peterson, A. Gloi, G. Kortsha, J. Pounds, D. Chettle, J. Gorell, Whole-body lifetime occupational lead exposure and risk of Parkinson's disease, *Environ. Health Perspect.* 114 (12) (2006) 1872–1876.
- [112] J.A. Firestone, J.I. Lundin, K.M. Powers, T. Smith-Weller, G.M. Franklin, P. D. Swanson, W.T. Longstreth Jr., H. Checkoway, Occupational factors and risk of Parkinson's disease: a population-based case-control study, *Am. J. Ind. Med.* 53 (3) (2010) 217–223.
- [113] A.L. Feldman, A.L. Johansson, G. Nise, M. Gatz, N.L. Pedersen, K. Wirdefeldt, Occupational exposure in parkinsonian disorders: a 43-year prospective cohort study in men, *Parkinsonism Relat. Disorders* 17 (9) (2011) 677–682.
- [114] D. Kulshreshtha, J. Ganguly, M. Jog, Manganese and movement disorders: a review, *J. Mov. Disord.* 14 (2) (2021) 93–102.
- [115] K.M. Andruska, A.B. Racette, Neuromyology of manganism, *Curr. Epidemiol. Rep.* 2 (2) (2015) 143–148.
- [116] B.A. Racette, G. Nelson, W.W. Dlamini, P. Prathibha, J.R. Turner, M. Ushe, H. Checkoway, L. Sheppard, S.S. Nielsen, Severity of parkinsonism associated with environmental manganese exposure, *Environ. Health* 20 (1) (2021) 27.
- [117] S.R. Criswell, S.S. Nielsen, M. Warden, J.S. Perlmutter, S.M. Moerlein, H.P. Flores, J. Huang, L. Sheppard, N. Seixas, H. Checkoway, B.A. Racette, [(18)F]FDOPA positron emission tomography in manganese-exposed workers, *Neurotoxicology* 64 (2018) 43–49.
- [118] M. Yamada, S. Ohno, I. Okayasu, R. Okeda, S. Hatakeyama, H. Watanabe, K. Ushio, H. Tsukagoshi, Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain, *Acta Neuropathol.* 70 (3–4) (1986) 273–278.
- [119] H. Chen, J.C. Kwong, R. Copes, K. Tu, P.J. Villeneuve, A. van Donkelaar, P. Hystad, R.V. Martin, B.J. Murray, B. Jessiman, A.S. Wilton, A. Kopp, R. T. Burnett, Living near major roads and the incidence of dementia, Parkinson's disease, and multiple sclerosis: a population-based cohort study, *Lancet* 389 (2017) 718–726, 10070.
- [120] S. Shin, R.T. Burnett, J.C. Kwong, P. Hystad, A. van Donkelaar, J.R. Brook, R. Copes, K. Tu, M.S. Goldberg, P.J. Villeneuve, R.V. Martin, B.J. Murray, A. S. Wilton, A. Kopp, H. Chen, Effects of ambient air pollution on incident Parkinson's disease in Ontario, 2001 to 2013: a population-based cohort study, *Int. J. Epidemiol.* 47 (6) (2018) 2038–2048.
- [121] P.C. Lee, L.L. Liu, Y. Sun, Y.A. Chen, C.C. Liu, C.Y. Li, H.L. Yu, B. Ritz, Traffic-related air pollution increased the risk of Parkinson's disease in Taiwan: a nationwide study, *Environ. Int.* 96 (2016) 75–81.
- [122] B. Ritz, P.C. Lee, J. Hansen, C.F. Lassen, M. Ketzel, M. Sorensen, O. Raaschou-Nielsen, Traffic-related air pollution and Parkinson's disease in Denmark: a case-control study, *Environ. Health Perspect.* 124 (3) (2016) 351–356.
- [123] C.Y. Hu, Y. Fang, F.L. Li, B. Dong, X.G. Hua, W. Jiang, H. Zhang, Y. Lyu, X. J. Zhang, Association between ambient air pollution and Parkinson's disease: systematic review and meta-analysis, *Environ. Res.* 168 (2019) 448–459.
- [124] H. Murata, L.M. Barnhill, J.M. Bronstein, Air pollution and the risk of Parkinson's disease: a review, *Mov. Disord.* 37 (5) (2022) 894–904.
- [125] J. Wilkinson, M. Radkowski, T. Laskus, Hepatitis C virus neuroinvasion: identification of infected cells, *J. Virol.* 83 (3) (2009) 1312–1319.
- [126] T.H. Su, H.C. Yang, T.C. Tseng, S.W. Chou, C.H. Lin, C.H. Liu, C.J. Liu, C.L. Chen, J.H. Kao, Antiviral therapy in patients with chronic hepatitis C is associated with a reduced risk of parkinsonism, *Mov. Disord.* 34 (12) (2019) 1882–1890.
- [127] W.Y. Lin, M.S. Lin, Y.H. Weng, T.H. Yeh, Y.S. Lin, P.Y. Fong, Y.R. Wu, C.S. Lu, R. S. Chen, Y.Z. Huang, Association of antiviral therapy with risk of Parkinson disease in patients with chronic hepatitis C virus infection, *JAMA Neurol.* 76 (9) (2019) 1019–1027.
- [128] J.K. Tsui, D.B. Calne, Y. Wang, M. Schulzer, S.A. Marion, Occupational risk factors in Parkinson's disease, *Can. J. Public Health* 90 (5) (1999) 334–337.

- [129] L.K. Olsen, E. Dowd, D.P. McKernan, A role for viral infections in Parkinson's etiology? *Neuronal Signal* 2 (2) (2018) NS20170166.
- [130] N. Limphaibool, P. Iwanowski, M.J.V. Holstad, D. Kobylarek, W. Kozubski, Infectious etiologies of parkinsonism: pathomechanisms and clinical implications, *Front. Neurol.* 10 (2019) 652.
- [131] N.M. Cocoros, E. Svensson, S.K. Szepligeti, S.V. Vestergaard, P. Szentkuti, R. W. Thomsen, P. Borghammer, H.T. Sorensen, V.W. Henderson, Long-term risk of Parkinson disease following influenza and other infections, *JAMA Neurol.* 78 (12) (2021) 1461–1470.
- [132] K.S. Levine, H.L. Leonard, C. Blauwendraat, H. Iwaki, N. Johnson, S. Bandres-Ciga, L. Ferrucci, F. Faghri, A.B. Singleton, M.A. Nalls, Virus exposure and neurodegenerative disease risk across national biobanks, *Neuron* 111 (7) (2023) 1086–1093 e2.
- [133] A. Camacho-Soto, I. Faust, B.A. Racette, D.B. Clifford, H. Checkoway, S. Searles Nielsen, Herpesvirus infections and risk of Parkinson's disease, *Neurodegener. Dis.* 20 (2–3) (2020) 97–103.
- [134] H. Wang, X. Liu, C. Tan, W. Zhou, J. Jiang, W. Peng, X. Zhou, L. Mo, L. Chen, Bacterial, viral, and fungal infection-related risk of Parkinson's disease: meta-analysis of cohort and case-control studies, *Brain Behav.* 10 (3) (2020) e01549.
- [135] P. Zarifkar, C. Peinkhofer, M.E. Benros, D. Kondziella, Frequency of neurological diseases after COVID-19, influenza A/B and bacterial pneumonia, *Front. Neurol.* 13 (2022) 904796.
- [136] A. de Havenon, B.C. Callaghan, Y. Xu, M. Connor, C.E. Hill, J. Ney, G.J. Esper, Burden of neurologic health care and incident neurologic diagnoses in the year after COVID-19 or influenza hospitalization, *Neurology* 102 (8) (2024) e209248.
- [137] M. Taquet, R. Sillett, L. Zhu, J. Mendel, I. Camplisson, Q. Dercon, P.J. Harrison, Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients, *Lancet Psychiatr.* 9 (10) (2022) 815–827.
- [138] E. Xu, Y. Xie, Z. Al-Ally, Long-term neurologic outcomes of COVID-19, *Nat. Med.* 28 (11) (2022) 2406–2415.
- [139] J.L.Y. Cheong, E. de Pablo-Fernandez, T. Foltynie, A.J. Noyce, The association between type 2 Diabetes mellitus and Parkinson's disease, *J. Parkinsons Dis.* 10 (3) (2020) 775–789.
- [140] P.W. Cullinane, E. de Pablo Fernandez, A. Konig, T.F. Outeiro, Z. Jaunmuktane, T. T. Warner, Type 2 Diabetes and Parkinson's disease: a focused review of current concepts, *Mov. Disord.* 38 (2) (2023) 162–177.
- [141] H. Chohan, K. Senkevich, R.K. Patel, J.P. Bestwick, B.M. Jacobs, S. Bandres Ciga, Z. Gan-Or, A.J. Noyce, Type 2 Diabetes as a determinant of Parkinson's disease risk and progression, *Mov. Disord.* 36 (6) (2021) 1420–1429.
- [142] D. Athauda, J. Evans, A. Wernick, G. Virdi, M.L. Choi, M. Lawton, N. Vijiaratnam, C. Girges, Y. Ben-Shlomo, K. Ismail, H. Morris, D. Grosset, T. Foltynie, S. Gandhi, The impact of type 2 Diabetes in Parkinson's disease, *Mov. Disord.* 37 (8) (2022) 1612–1623.
- [143] N.I. Bohnen, V. Kotagal, M.L. Muller, R.A. Koeppe, P.J. Scott, R.L. Albin, K. A. Frey, M. Petrou, Diabetes mellitus is independently associated with more severe cognitive impairment in Parkinson disease, *Parkinsonism Relat. Disorders* 20 (12) (2014) 1394–1398.
- [144] V. Kotagal, R.L. Albin, M.L. Muller, R.A. Koeppe, K.A. Frey, N.I. Bohnen, Diabetes is associated with postural instability and gait difficulty in Parkinson disease, *Parkinsonism Relat. Disorders* 19 (5) (2013) 522–526.
- [145] B.R. Kummer, I. Diaz, X. Wu, A.E. Aaroe, M.L. Chen, C. Iadecola, H. Kamel, B. B. Navi, Associations between cerebrovascular risk factors and Parkinson disease, *Ann. Neurol.* 86 (4) (2019) 572–581.
- [146] D.M. Kent, L.Y. Leung, E.J. Puttock, A.Y. Wang, P.H. Luetmer, D.F. Kallmes, J. Nelson, S. Fu, C. Zheng, E.M. Vickery, H. Liu, A.J. Noyce, W. Chen, Development of Parkinson disease and its relationship with incidentally discovered white matter disease and covert brain infarction in a real-world cohort, *Ann. Neurol.* 92 (4) (2022) 620–630.
- [147] M.A. Jacob, M. Cai, M. Bergkamp, S.K.L. Darweesh, L.M.Y. Gelissen, J. Marques, D.G. Norris, M. Duering, R.A.J. Esselink, A.M. Tuladhar, F.E. de Leeuw, Cerebral small vessel disease progression increases risk of incident parkinsonism, *Ann. Neurol.* 93 (6) (2023) 1130–1141.
- [148] V. Kotagal, R.L. Albin, M.L. Muller, R.A. Koeppe, K.A. Frey, N.I. Bohnen, Modifiable cardiovascular risk factors and axial motor impairments in Parkinson disease, *Neurology* 82 (17) (2014) 1514–1520.
- [149] M.I. Maraki, M. Yannakoulia, M. Stamelou, L. Stefanis, G. Xiomerisiou, M. H. Kosmidis, E. Dardiotis, G.M. Hadjigeorgiou, P. Sakka, C.A. Anastasiou, E. Simopoulou, N. Scarmeas, Mediterranean diet adherence is related to reduced probability of prodromal Parkinson's disease, *Mov. Disord.* 34 (1) (2019) 48–57.
- [150] R.N. Alcalay, Y. Gu, H. Mejia-Santana, L. Cote, K.S. Marder, N. Scarmeas, The association between Mediterranean diet adherence and Parkinson's disease, *Mov. Disord.* 27 (6) (2012) 771–774.
- [151] Y. Lv, B. Xu, X. Zhang, C. Chen, Y. Gao, N. Li, Association of serum cholesterol with Parkinson's disease in a cohort of statin-free individuals, *Brain Behav.* 12 (1) (2022) e2454.
- [152] X. Huang, A. Alonso, X. Guo, D.M. Umbach, M.L. Lichtenstein, C.M. Ballantyne, R. B. Mailman, T.H. Mosley, H. Chen, Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study, *Mov. Disord.* 30 (4) (2015) 552–559.
- [153] X. Huang, R.D. Abbott, H. Petrovitch, R.B. Mailman, G.W. Ross, Low LDL cholesterol and increased risk of Parkinson's disease: prospective results from Honolulu-Asia Aging Study, *Mov. Disord.* 23 (7) (2008) 1013–1018.
- [154] X. Huang, H. Chen, W.C. Miller, R.B. Mailman, J.L. Woodard, P.C. Chen, D. Xiang, R.W. Murrow, Y.Z. Wang, C. Poole, Lower low-density lipoprotein cholesterol levels are associated with Parkinson's disease, *Mov. Disord.* 22 (3) (2007) 377–381.
- [155] L.M. de Lau, P.J. Koudstaal, A. Hofman, M.M. Breteler, Serum cholesterol levels and the risk of Parkinson's disease, *Am. J. Epidemiol.* 164 (10) (2006) 998–1002.
- [156] X. Fu, Y. Wang, X. He, H. Li, H. Liu, X. Zhang, A systematic review and meta-analysis of serum cholesterol and triglyceride levels in patients with Parkinson's disease, *Lipids Health Dis.* 19 (1) (2020) 97.
- [157] S.H. Park, G.E. Nam, K. Han, Y. Huh, W. Kim, M.K. Lee, E.S. Koh, E.S. Kim, M. K. Kim, H.S. Kwon, S.M. Kim, K.H. Cho, Y.G. Park, Association of dynamic changes in metabolic syndrome status with the risk of Parkinson's disease: a nationwide cohort study, *J. Parkinsons Dis.* 11 (4) (2021) 1751–1759.
- [158] K. Wang, Z. Luo, C. Li, X. Huang, E.J. Shiroma, E.M. Simonsick, H. Chen, Blood cholesterol decreases as Parkinson's disease develops and progresses, *J. Parkinsons Dis.* 11 (3) (2021) 1177–1186.
- [159] R.R. Strang, The association of gastro-duodenal ulceration and Parkinson's disease, *Med. J. Aust.* 1 (23) (1965) 842–843.
- [160] R.S. Schwab, Symptomatology and medical treatment of Parkinson's disease, *Int. J. Neurol.* 2 (1961) 61–75.
- [161] B.M. Jacobs, D. Belete, J. Bestwick, C. Blauwendraat, S. Bandres-Ciga, K. Heilbron, R. Dobson, M.A. Nalls, A. Singleton, J. Hardy, G. Giovannoni, A. J. Lees, A.E. Schrag, A.J. Noyce, Parkinson's disease determinants, prediction and gene-environment interactions in the UK Biobank, *J. Neurol. Neurosurg. Psychiatry* 91 (10) (2020) 1046–1054.
- [162] X. Shen, H. Yang, Y. Wu, D. Zhang, H. Jiang, Meta-analysis: association of Helicobacter pylori infection with Parkinson's diseases, *Helicobacter* 22 (5) (2017).
- [163] H.H. Nielsen, J. Qiu, S. Friis, L. Wermuth, B. Ritz, Treatment for Helicobacter pylori infection and risk of Parkinson's disease in Denmark, *Eur. J. Neurol.* 19 (6) (2012) 864–869.
- [164] H.K. Huang, J.H. Wang, W.Y. Lei, C.L. Chen, C.Y. Chang, L.S. Liou, Helicobacter pylori infection is associated with an increased risk of Parkinson's disease: a population-based retrospective cohort study, *Parkinsonism Relat. Disorders* 47 (2018) 26–31.
- [165] S.C. Larsson, A.B. Singleton, M.A. Nalls, J.B. Richards, C. International Parkinson's Disease Genomics, No clear support for a role for vitamin D in Parkinson's disease: a Mendelian randomization study, *Mov. Disord.* 32 (8) (2017) 1249–1252.
- [166] Y. Wang, L. Gao, W. Lang, H. Li, P. Cui, N. Zhang, W. Jiang, Serum calcium levels and Parkinson's disease: a mendelian randomization study, *Front. Genet.* 11 (2020) 824.
- [167] K. Saaksjarvi, P. Knekt, A. Lundqvist, S. Mannisto, M. Heliovaara, H. Rissanen, R. Jarvinen, A cohort study on diet and the risk of Parkinson's disease: the role of food groups and diet quality, *Br. J. Nutr.* 109 (2) (2013) 329–337.
- [168] H. Chen, E. O'Reilly, M.L. McCullough, C. Rodriguez, M.A. Schwarzschild, E. E. Calle, M.J. Thun, A. Ascherio, Consumption of dairy products and risk of Parkinson's disease, *Am. J. Epidemiol.* 165 (9) (2007) 998–1006.
- [169] M. Park, G.W. Ross, H. Petrovitch, L.R. White, K.H. Masaki, J.S. Nelson, C. M. Tanner, J.D. Curb, P.L. Blanchette, R.D. Abbott, Consumption of milk and calcium in midlife and the future risk of Parkinson disease, *Neurology* 64 (6) (2005) 1047–1051.
- [170] W. Jiang, C. Ju, H. Jiang, D. Zhang, Dairy foods intake and risk of Parkinson's disease: a dose-response meta-analysis of prospective cohort studies, *Eur. J. Epidemiol.* 29 (9) (2014) 613–619.
- [171] A. Kyrozis, A. Ghika, P. Stathopoulos, D. Vassilopoulos, D. Trichopoulos, A. Trichopoulos, Dietary and lifestyle variables in relation to incidence of Parkinson's disease in Greece, *Eur. J. Epidemiol.* 28 (1) (2013) 67–77.
- [172] K.C. Hughes, X. Gao, I.Y. Kim, M. Wang, M.G. Weisskopf, M.A. Schwarzschild, A. Ascherio, Intake of dairy foods and risk of Parkinson disease, *Neurology* 89 (1) (2017) 46–52.
- [173] R.D. Abbott, G.W. Ross, H. Petrovitch, K.H. Masaki, L.J. Launer, J.S. Nelson, L. R. White, C.M. Tanner, Midlife milk consumption and substantia nigra neuron density at death, *Neurology* 86 (6) (2016) 512–519.
- [174] C. Domenighetti, P.E. Sugier, A. Ashok Kumar Sreelatha, C. Schulte, S. Grover, O. Mohamed, B. Portugal, P. May, D.R. Bobbili, M. Radivojkov-Blagojevic, P. Lichtner, A.B. Singleton, D.G. Hernandez, C. Edsall, G.D. Mellick, A. Zimprich, W. Pirker, E. Rogaeva, A.E. Lang, S. Koks, P. Taba, S. Lesage, A. Brice, J.C. Corvol, M.C. Chartier-Harlin, E. Mutez, K. Brockmann, A.B. Deuschlander, G. M. Hadjigeorgiou, E. Dardiotis, L. Stefanis, A.M. Simitsi, E.M. Valente, S. Petrucci, S. Duga, L. Straniero, A. Zecchinelli, G. Pezzoli, L. Brighina, C. Ferrarese, G. Annesi, A. Quattrone, M. Gagliardi, H. Matsuo, Y. Kawamura, N. Hattori, K. Nishioka, S.J. Chung, Y.J. Kim, P. Kolber, B.P.C. van de Warrenburg, B. R. Bloem, J. Aasly, M. Toft, L. Pihlstrom, L. Correia Guedes, J.J. Ferreira, S. Bardien, J. Carr, E. Tolosa, M. Ezquerro, P. Pastor, M. Diez-Fairen, K. Wirdefeldt, N.L. Pedersen, C. Ran, A.C. Belin, A. Puschmann, C. Hellberg, C. E. Clarke, K.E. Morrison, M. Tan, D. Krainc, L.F. Burbulla, M.J. Farrer, R. Kruger, T. Gasser, M. Sharma, A. Elbaz, G. Comprehensive, Unbiased risk factor assessment for, C. Environment in Parkinson's disease, dairy intake and Parkinson's disease: a mendelian randomization study, *Mov. Disord.* 37 (4) (2022) 857–864.
- [175] P.R. Faustino, G.S. Duarte, I. Chendo, A. Castro Caldas, S. Reimao, R. M. Fernandes, J. Vale, M. Tinazzi, K. Bhatia, J.J. Ferreira, Risk of developing Parkinson disease in bipolar disorder: a systematic review and meta-analysis, *JAMA Neurol.* 77 (2) (2020) 192–198.
- [176] R. Erro, A. Landolfi, G. D'Agostino, L. Pace, M. Picillo, M. Scarano, A. Cuocolo, S. Pappata, C. Vitale, M.T. Pellecchia, P. Monteleone, P. Barone, Bipolar disorder and Parkinson's disease: a (123I)-ioflupane dopamine transporter SPECT study, *Front. Neurol.* 12 (2021) 652375.

- [177] M.H. Huang, C.M. Cheng, K.L. Huang, J.W. Hsu, Y.M. Bai, T.P. Su, C.T. Li, S. J. Tsai, W.C. Lin, T.J. Chen, M.H. Chen, Bipolar disorder and risk of Parkinson disease: a nationwide longitudinal study, *Neurology* 92 (24) (2019) e2735–e2742.
- [178] F.M. Nilsson, L.V. Kessing, T.G. Bolwig, Increased risk of developing Parkinson's disease for patients with major affective disorder: a register study, *Acta Psychiatr. Scand.* 104 (5) (2001) 380–386.
- [179] C. Marras, N. Herrmann, H.D. Fischer, K. Fung, A. Gruneir, P.A. Rochon, S. Rej, S. Vigod, D. Seitz, K.I. Shulman, Lithium use in older adults is associated with increased prescribing of Parkinson medications, *Am. J. Geriatr. Psychiatr.* 24 (4) (2016) 301–309.
- [180] H.L. Lin, H.C. Lin, Y.H. Chen, Psychiatric diseases predated the occurrence of Parkinson disease: a retrospective cohort study, *Ann. Epidemiol.* 24 (3) (2014) 206–213.
- [181] A. Tarakad, J. Jankovic, Essential tremor and Parkinson's disease: exploring the relationship, *Tremor Other Hyperkinet. Mov. (N Y)* 8 (2018) 589.
- [182] H. LaRoia, E.D. Louis, Association between essential tremor and other neurodegenerative diseases: what is the epidemiological evidence? *Neuroepidemiology* 37 (1) (2011) 1–10.
- [183] E.D. Louis, D. Berry, A. Ghanem, S.A. Cosentino, Conversion rate of essential tremor to essential tremor Parkinson disease: data from a prospective longitudinal study, *Neurol. Clin. Pract.* 13 (3) (2023) e200162.
- [184] M. Algarni, A. Fasano, The overlap between Essential tremor and Parkinson disease, *Parkinsonism Relat. Disorders* 46 (Suppl 1) (2018) S101–S104.
- [185] E.D. Louis, P.L. Faust, Essential tremor pathology: neurodegeneration and reorganization of neuronal connections, *Nat. Rev. Neurol.* 16 (2) (2020) 69–83.
- [186] A.K. Forsti, L. Huilaja, E. Schmidt, K. Tasanen, Neurological and psychiatric associations in bullous pemphigoid-more than skin deep? *Exp. Dermatol.* 26 (12) (2017) 1228–1234.
- [187] O. Varpuloma, J. Jokelainen, A.K. Forsti, M. Turpeinen, M. Timonen, L. Huilaja, K. Tasanen, Drugs used for neurologic and psychiatric conditions increase the risk for bullous pemphigoid: a case-control study, *J. Am. Acad. Dermatol.* 81 (1) (2019) 250–253.
- [188] J.A. Driver, T. Kurth, J.E. Buring, J.M. Gaziano, G. Logroscino, Prospective case-control study of nonfatal cancer preceding the diagnosis of Parkinson's disease, *Cancer Causes Control* 18 (7) (2007) 705–711.
- [189] X. Cui, Z. Liew, J. Hansen, P.C. Lee, O.A. Arah, B. Ritz, Cancers preceding Parkinson's disease after adjustment for bias in a Danish population-based case-control study, *Neuroepidemiology* 52 (3–4) (2019) 136–143.
- [190] X. Zhang, D. Guarin, N. Mohammadzadehonorvar, X. Chen, X. Gao, Parkinson's disease and cancer: a systematic review and meta-analysis of over 17 million participants, *BMJ Open* 11 (7) (2021) e046329.
- [191] P.E. Sugier, E.A. Lucotte, C. Domenighetti, M.H. Law, M.M. Iles, K. Brown, C. Amos, J.D. McKay, R.J. Hung, M. Karimi, D. Bacq-Daia, A. Boland-Auge, R. Olaso, J.F. Deleuze, F. Lesueur, E. Ostrumova, A. Kesminiene, F. de Vathaire, P. Guenel, E. consortium, A.A.K. Sreelatha, C. Schulte, S. Grover, P. May, D. R. Bobbili, M. Radivojkov-Blagojevic, P. Lichtner, A.B. Singleton, D.G. Hernandez, C. Edsall, G.D. Mellick, A. Zimprich, W. Pirker, E. Rogaeva, A.E. Lang, S. Koks, P. Taba, S. Lesage, A. Brice, J.C. Corvol, M.C. Chartier-Harlin, E. Mutez, K. Brockmann, A.B. Deuschlander, G.M. Hadjigeorgiou, E. Dardiotis, L. Stefanis, A.M. Simitsi, E.M. Valente, S. Petrucci, A. Zecchinelli, G. Pizzoli, L. Brighina, C. Ferrarese, G. Annesi, A. Quattrone, M. Gagliardi, H. Matsuo, A. Nakayama, N. Hattori, K. Nishioka, S.J. Chung, Y.J. Kim, P. Kolber, B.P.C. van de Warrenburg, B.R. Bloem, J. Aasly, M. Toft, L. Pihlstrom, L.C. Guedes, J. J. Ferreira, S. Bardien, J. Carr, E. Tolosa, M. Ezquerro, P. Pastor, M. Diez-Fairen, K. Wirdefeldt, N. Pedersen, C. Ran, A.C. Belin, A. Puschmann, E.Y. Rodstrom, C. E. Clarke, K.E. Morrison, M. Tan, D. Krainc, L.F. Burbulla, M.J. Farrer, R. Kruger, T. Gasser, M. Sharma, G. Comprehensive Unbiased Risk Factor Assessment for, c. Environment in Parkinson's Disease, T. Truong, A. Elbaz, Investigation of shared genetic risk factors between Parkinson's disease and cancers, *Mov. Disord.* 38 (4) (2023) 604–615.
- [192] G. Coarelli, A. Diallo, M.S. Thion, D. Rinaldi, F. Calvas, O.L. Boukiza, A. Tataru, P. Charles, C. Tranchant, C. Marelli, C. Ewencyk, M. Tchikviladze, M.L. Monin, B. Carlander, M. Anheim, A. Brice, F. Mochel, S. Tezenas du Montcel, S. Humbert, A. Durr, Low cancer prevalence in polyglutamine expansion diseases, *Neurology* 88 (12) (2017) 1114–1119.
- [193] J. Ji, K. Sundquist, J. Sundquist, Cancer incidence in patients with polyglutamine diseases: a population-based study in Sweden, *Lancet Oncol.* 13 (6) (2012) 642–648.
- [194] P. Huang, X.D. Yang, S.D. Chen, Q. Xiao, The association between Parkinson's disease and melanoma: a systematic review and meta-analysis, *Transl. Neurodegener.* 4 (2015) 21.
- [195] A. Bose, G.A. Petsko, D. Eliezer, Parkinson's disease and melanoma: Co-occurrence and mechanisms, *J. Parkinsons Dis.* 8 (3) (2018) 385–398.
- [196] X. Chen, D. Feng, M.A. Schwarzschild, X. Gao, Red hair, MC1R variants, and risk for Parkinson's disease - a meta-analysis, *Ann. Clin. Transl. Neurol.* 4 (3) (2017) 212–216.
- [197] M.E. Diaz-Ortiz, Y. Seo, M. Posavi, M. Carceles Cordon, E. Clark, N. Jain, R. Charan, M.D. Gallagher, T.L. Unger, N. Amari, R.T. Skrinak, R. Davila-Rivera, E.M. Brody, N. Han, R. Zack, V.M. Van Deerlin, T.F. Tropea, K.C. Luk, E.B. Lee, D. Weintraub, A.S. Chen-Plotkin, GPNMB confers risk for Parkinson's disease through interaction with alpha-synuclein, *Science* 377 (6608) (2022) eabk0637.
- [198] I. Peter, M. Dubinsky, S. Bressman, A. Park, C. Lu, N. Chen, A. Wang, Anti-tumor Necrosis factor therapy and incidence of Parkinson disease among patients with inflammatory bowel disease, *JAMA Neurol.* 75 (8) (2018) 939–946.
- [199] K.Y. Hui, H. Fernandez-Hernandez, J. Hu, A. Schaffner, N. Pankratz, N.Y. Hsu, L. S. Chuang, S. Carni, N. Villaverde, X. Li, M. Rivas, A.P. Levine, X. Bao, P. R. Labrias, T. Haritunians, D. Ruane, K. Gettler, E. Chen, D. Li, E.R. Schiff, N. Pontikos, N. Barzilai, S.R. Brant, S. Bressman, A.S. Cheifetz, L.N. Clark, M. J. Daly, R.J. Desnick, R.H. Duerr, S. Katz, T. Lencz, R.H. Myers, H. Ostrer, L. Ozelius, H. Payami, Y. Peter, J.D. Rioux, A.W. Segal, W.K. Scott, M. S. Silverberg, J.M. Vance, I. Ubarretxena-Belandia, T. Foroud, G. Atzmon, I. Pe'er, Y. Ioannou, D.P.B. McGovern, Z. Yue, E.E. Schadt, J.H. Cho, I. Peter, Functional variants in the LRRK2 gene confer shared effects on risk for Crohn's disease and Parkinson's disease, *Sci. Transl. Med.* 10 (423) (2018).
- [200] F. Zhu, C. Li, J. Gong, W. Zhu, L. Gu, N. Li, The risk of Parkinson's disease in inflammatory bowel disease: a systematic review and meta-analysis, *Dig. Liver Dis.* 51 (1) (2019) 38–42.
- [201] Y. Zhu, M. Yuan, Y. Liu, F. Yang, W.Z. Chen, Z.Z. Xu, Z.B. Xiang, R.S. Xu, Association between inflammatory bowel diseases and Parkinson's disease: systematic review and meta-analysis, *Neural. Regen. Res.* 17 (2) (2022) 344–353.
- [202] M. Villumsen, S. Aznar, B. Pakkenberg, T. Jess, T. Brudek, Inflammatory bowel disease increases the risk of Parkinson's disease: a Danish nationwide cohort study 1977–2014, *Gut* 68 (1) (2019) 18–24.
- [203] P. Weimers, J. Halfvarson, M.C. Sachs, R. Saunders-Pullman, J.F. Ludvigsson, I. Peter, J. Burisch, O. Olen, Inflammatory bowel disease and Parkinson's disease: a nationwide Swedish cohort study, *Inflamm. Bowel Dis.* 25 (1) (2019) 111–123.
- [204] J. Pinel Rios, C.J. Madrid Navarro, M.J. Perez Navarro, M.J. Cabello Tapia, M. J. Pina Vera, V. Campos Arillo, M.R. Gomez Garcia, A. Minguez Castellanos, F. Escamilla Sevilla, Association of Parkinson's disease and treatment with aminosalicylates in inflammatory bowel disease: a cross-sectional study in a Spain drug dispensation records, *BMJ Open* 9 (6) (2019) e025574.
- [205] A. Camacho-Soto, A. Gross, S. Searles Nielsen, N. Dey, B.A. Racette, Inflammatory bowel disease and risk of Parkinson's disease in Medicare beneficiaries, *Parkinsonism Relat. Disorders* 50 (2018) 23–28.
- [206] X. Kang, A. Ploner, N.L. Pedersen, S. Bandres-Ciga, A.J. Noyce, K. Wirdefeldt, D. M. Williams, Tumor Necrosis factor inhibition and Parkinson disease: a mendelian randomization study, *Neurology* 96 (12) (2021) e1672–e1679.
- [207] R. Zeng, J. Wang, C. Zheng, R. Jiang, S. Tong, H. Wu, Z. Zhuo, Q. Yang, F. W. Leung, W. Sha, H. Chen, Lack of causal associations of inflammatory bowel disease with Parkinson's disease and other neurodegenerative disorders, *Mov. Disord.* 38 (6) (2023) 1082–1088.
- [208] D. Belete, B.M. Jacobs, C. Simonet, J.P. Bestwick, S. Waters, C.R. Marshall, R. Dobson, A.J. Noyce, Association between antiepileptic drugs and incident Parkinson disease, *JAMA Neurol.* 80 (2) (2023) 183–187.
- [209] R. Betarbet, T.B. Sherer, G. MacKenzie, M. Garcia-Osuna, A.V. Panov, J. T. Greenamyre, Chronic systemic pesticide exposure reproduces features of Parkinson's disease, *Nat. Neurosci.* 3 (12) (2000) 1301–1306.
- [210] J.M. Biernacka, S.J. Chung, S.M. Armasu, K.S. Anderson, C.M. Lill, L. Bertram, J. E. Ahlskog, L. Brighina, R. Frigerio, D.M. Maraganore, Genome-wide gene-environment interaction analysis of pesticide exposure and risk of Parkinson's disease, *Parkinsonism Relat. Disorders* 32 (2016) 25–30.
- [211] P.K. Crane, L.E. Gibbons, K. Dams-O'Connor, E. Tritschuh, J.B. Leverenz, C. D. Keene, J. Sonnen, T.J. Montine, D.A. Bennett, S. Leurgans, J.A. Schneider, E. B. Larson, Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings, *JAMA Neurol.* 73 (9) (2016) 1062–1069.
- [212] K. Wijampreecha, S. Chesdachai, V. Jaruvongvanich, P. Ungprasert, Hepatitis C virus infection and risk of Parkinson's disease: a systematic review and meta-analysis, *Eur. J. Gastroenterol. Hepatol.* 30 (1) (2018) 9–13.
- [213] L. Goldstein, H. Fogel-Grinvald, I. Steiner, Hepatitis B and C virus infection as a risk factor for Parkinson's disease in Israel-A nationwide cohort study, *J. Neurol. Sci.* 398 (2019) 138–141.
- [214] Y. Chen, X. Sun, Y. Lin, Z. Zhang, Y. Gao, L.X.Y. Wu, Non-genetic risk factors for Parkinson's disease: an overview of 46 systematic reviews, *J. Parkinsons Dis.* 11 (3) (2021) 919–935.
- [215] M. Wen, B. Zhou, Y.H. Chen, Z.L. Ma, Y. Gou, C.L. Zhang, W.F. Yu, L. Jiao, Serum uric acid levels in patients with Parkinson's disease: a meta-analysis, *PLoS One* 12 (3) (2017) e0173731.
- [216] E.D. Louis, J. Benito-Leon, F. Bermejo-Pareja, G. Neurological, Disorders in Central Spain Study, Antihypertensive agents and risk of Parkinson's disease, essential tremor and dementia: a population-based prospective study (NEDICES), *Neuroepidemiology* 33 (3) (2009) 286–292.
- [217] T.G. Ton, S.R. Heckbert, W.T. Longstreth Jr., M.A. Rossing, W.A. Kukull, G. M. Franklin, P.D. Swanson, T. Smith-Weller, H. Checkoway, Calcium channel blockers and beta-blockers in relation to Parkinson's disease, *Parkinsonism Relat. Disorders* 13 (3) (2007) 165–169.
- [218] P.J. Garcia-Ruiz, F. Javier Jimenez-Jimenez, J. Garcia de Yebenes, Calcium channel blocker-induced parkinsonism: clinical features and comparisons with Parkinson's disease, *Parkinsonism Relat. Disorders* 4 (4) (1998) 211–214.
- [219] C. Becker, S.S. Jick, C.R. Meier, Use of antihypertensives and the risk of Parkinson disease, *Neurology* 70 (16 Pt 2) (2008) 1438–1444.
- [220] Y.C. Lee, C.H. Lin, R.M. Wu, J.W. Lin, C.H. Chang, M.S. Lai, Antihypertensive agents and risk of Parkinson's disease: a nationwide cohort study, *PLoS One* 9 (6) (2014) e98961.
- [221] K. Gudala, R. Kanakula, D. Bansal, Reduced risk of Parkinson's disease in users of Calcium Channel blockers: a meta-analysis, *Int. J. Chronic. Dis.* 2015 (2015) 697404.
- [222] Y. Lang, D. Gong, Y. Fan, Calcium channel blocker use and risk of Parkinson's disease: a meta-analysis, *Pharmacoeconom. Drug Saf.* 24 (6) (2015) 559–566.

- [223] L. Ren, J. Yi, J. Yang, P. Li, X. Cheng, P. Mao, Nonsteroidal anti-inflammatory drugs use and risk of Parkinson disease: a dose-response meta-analysis, *Medicine (Baltim.)* 97 (37) (2018) e12172.
- [224] H. Chen, S.M. Zhang, M.A. Hernan, M.A. Schwarzschild, W.C. Willett, G. A. Colditz, F.E. Speizer, A. Ascherio, Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease, *Arch. Neurol.* 60 (8) (2003) 1059–1064.
- [225] J.J. Gagne, M.C. Power, Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis, *Neurology* 74 (12) (2010) 995–1002.
- [226] J. Fan, S. Searles Nielsen, I.M. Faust, B.A. Racette, Transplant and risk of Parkinson disease, *Parkinsonism Relat. Disorders* 63 (2019) 149–155.
- [227] X. Gao, H. Chen, M.A. Schwarzschild, A. Ascherio, Use of ibuprofen and risk of Parkinson disease, *Neurology* 76 (10) (2011) 863–869.
- [228] K. Rees, R. Stowe, S. Patel, N. Ives, K. Breen, C.E. Clarke, Y. Ben-Shlomo, Non-steroidal anti-inflammatory drugs as disease-modifying agents for Parkinson's disease: evidence from observational studies, *Cochrane Database Syst. Rev.* 11 (2011) CD008454.
- [229] T.G. Ton, S.R. Heckbert, W.T. Longstreth Jr., M.A. Rossing, W.A. Kukull, G. M. Franklin, P.D. Swanson, T. Smith-Weller, H. Checkoway, Nonsteroidal anti-inflammatory drugs and risk of Parkinson's disease, *Mov. Disord.* 21 (7) (2006) 964–969.
- [230] Y. Jo, S. Kim, B.S. Ye, E. Lee, Y.M. Yu, Protective effect of Renin-angiotensin system inhibitors on Parkinson's disease: a nationwide cohort study, *Front. Pharmacol.* 13 (2022) 837890.
- [231] C.U. Choe, E. Petersen, S. Lezius, B. Cheng, R. Schulz, C. Buhmann, M. Potter-Nerger, G. Daum, S. Blankenberg, C. Gerloff, E. Schwedhelm, T. Zeller, Association of lipid levels with motor and cognitive function and decline in advanced Parkinson's disease in the Mark-PD study, *Parkinsonism Relat. Disorders* 85 (2021) 5–10.
- [232] M. Zhang, H. Chen, G. Liu, X. Wang, Z. Wang, T. Feng, Y. Zhang, Lower serum triglyceride levels linked to more severe motor performance in Parkinson's disease, *Neurol. Sci.* 43 (9) (2022) 5343–5353.
- [233] J.H. Park, C.W. Lee, M.J. Nam, H. Kim, D.Y. Kwon, J.W. Yoo, K.N. Lee, K. Han, J. H. Jung, Y.G. Park, D.H. Kim, Association of high-density lipoprotein cholesterol variability and the risk of developing Parkinson disease, *Neurology* 96 (10) (2021) e1391–e1401.
- [234] C.R. Swanson, Y. Berlyand, S.X. Xie, R.N. Alcalay, L.M. Chahine, A.S. Chen-Plotkin, Plasma apolipoprotein A1 associates with age at onset and motor severity in early Parkinson's disease patients, *Mov. Disord.* 30 (12) (2015) 1648–1656.
- [235] L.M. de Lau, M.M. Breteler, Epidemiology of Parkinson's disease, *Lancet Neurol.* 5 (6) (2006) 525–535.
- [236] O. Okunoye, L. Horsfall, L. Marston, K. Walters, A. Schrag, Mortality of people with Parkinson's disease in a large UK-based cohort study: time trends and relationship to disease duration, *Mov. Disord.* 36 (12) (2021) 2811–2820.
- [237] F. Hopfner, M. Wod, G.U. Hoglinger, M. Blaabjerg, T.W. Rosler, G. Kühlenbaumer, K. Christensen, G. Deuschl, A. Pottgert, Use of beta2-adrenoreceptor agonist and antagonist drugs and risk of Parkinson disease, *Neurology* 93 (2) (2019) e135–e142.
- [238] C.L. Chen, S.Y. Wang, T.C. Chen, C.S. Chuang, Association between beta2-adrenoreceptor medications and risk of Parkinson's disease: a meta-analysis, *Medicina (Kaunas)* 57 (10) (2021).
- [239] S. Searles Nielsen, A. Gross, A. Camacho-Soto, A.W. Willis, B.A. Racette, beta2-adrenoreceptor medications and risk of Parkinson disease, *Ann. Neurol.* 84 (5) (2018) 683–693.
- [240] R. Sasane, A. Bartels, M. Field, M.I. Sierra, S. Duvvuri, D.L. Gray, S.S. Pin, J. J. Renger, D.J. Stone, Parkinson disease among patients treated for benign prostatic hyperplasia with alpha1 adrenergic receptor antagonists, *J. Clin. Invest.* 131 (11) (2021).
- [241] P. Gros, X. Wang, J. Guan, A.E. Lang, P.C. Austin, B. Welk, N.P. Visanji, C. Marras, Exposure to phosphoglycerate kinase 1 activators and incidence of Parkinson's disease, *Mov. Disord.* 36 (10) (2021) 2419–2425.
- [242] J.E. Simmering, M.J. Welsh, L. Liu, N.S. Narayanan, A. Pottgert, Association of glycolysis-enhancing alpha-1 blockers with risk of developing Parkinson disease, *JAMA Neurol.* 78 (4) (2021) 407–413.
- [243] S.R. Criswell, S.S. Nielsen, M.N. Warden, J.S. Perlmutter, S.M. Moerlein, L. Sheppard, J. Lenox-Krug, H. Checkoway, B.A. Racette, [11C] dihydrotetrabenazine positron emission tomography in manganese-exposed workers, *J. Occup. Environ. Med.* 62 (10) (2020) 788–794.