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Understanding the links between cardiovascular disease and Parkinson's disease

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Abstract

Studies investigating the associations between genetic or environmental factors and Parkinson's disease have uncovered a number of factors shared with cardiovascular disease, either as risk factors or manifestations of cardiovascular disease itself. Older age, male sex and possibly type 2 diabetes are examples. On the other hand, coffee consumption and physical activity are each associated with a lower risk of both Parkinson's disease and cardiovascular disease. This observation raises questions about the underlying pathophysiological links between cardiovascular disease and Parkinson's disease. There is evidence for common mechanisms in the areas of glucose metabolism, cellular stress, lipid metabolism and inflammation. On the other hand, smoking and total/LDL cholesterol appear to have opposite associations with cardiovascular disease and Parkinson's disease. Thus, it is uncertain whether or not treatment of cardiovascular risk factors will impact on the onset or progression of Parkinson's disease. The available data suggest that a nuanced approach is necessary to manage risk factors such as cholesterol levels once the associations are better understood. Ultimately, the choice of therapy may be tailored to a patient's comorbidity profile. This review presents the epidemiological evidence for both

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concordant and discordant associations between cardiovascular disease and PD, discusses the cellular and metabolic processes that may underlie these links, and explores the implications this has for patient care and future research.

Keywords

Parkinson's disease; pathogenesis; cardiovascular; risk factors

Introduction

During the search to understand the etiology of Parkinson's disease (PD), a vast array of studies has investigated the associations between genetic or environmental factors and PD. Many of the associations that have been found have links to cardiovascular (CV) disease, either as risk factors or manifestations of CV disease itself. These observations raise questions about the underlying pathophysiological links between CV disease and PD, and may have important implications for the appropriate clinical care of individuals with PD who have CV risk factors requiring treatment. Due to the limitations of observational research, definitive conclusions regarding the causal nature of associations cannot be drawn, but the epidemiological studies have occurred in parallel with substantial laboratory research that may provide clues. The aim of this viewpoint is to examine known or reported associations, and highlight potential interconnection as they relate to our current understanding of PD pathogenesis. One result of this effort may be suggestions for research that would improve our understanding of the pathophysiology of PD. In addition, it may help guide treatment for PD patients in which the competing risks of CV disease and PD need to be balanced.

Cardiovascular Risk Factors and Parkinson's disease

Important heart-brain connections are indisputable and multi-faceted.[1] Potentially shared CV risk factors have been in the forefront of dementia research for the past several decades.[2] The possibility of etiological connection is strengthened by well-designed longitudinal studies that found associations of midlife diabetes (DM), hypertension (HTN), obesity, and hypercholesterolemia with higher risk of late-life cognitive impairment and dementia.[3] Potential links between heart disease and PD also have attracted attention in recent years, but have been largely limited to studying CV comorbidities[4] and cardiac autonomic dysfunction in PD patients (e.g., orthostatic hypotension).[5] This is despite the fact that many potential risk factors that have been investigated for PD are classic CV risk factors (e.g., DM, HTN, and obesity) and the fact that common mechanistic hypotheses (e.g., oxidative stress and chronic inflammation) have been proposed for both diseases.[6] However, understanding these associations between these classic CV risk factors and PD is not straightforward, as they are often complex, sometimes controversial or even counterintuitive (Figure 1).

Factors that have concordant associations with cardiovascular risk and PD

Compared to a sedentary lifestyle, physical activities, even at modest levels, are associated with lower risks of CV diseases and stroke.[7] The inverse association with leisure-time

physical activity and PD is one of the most consistent epidemiological findings, supported by multiple longitudinal and well-designed case-control studies.[8–11] There are, however, caveats. First, the risk reduction is most consistently observed for moderate to vigorous activities.[8–11] Second, findings on early-life physical activity in relation to PD risk is much less consistent than that for late-life.[9–11] Given the long prodromal stage of PD development, reverse causality cannot be excluded. Finally, the biological mechanisms underlying exercise and a lower PD risk are largely speculative, but may involve increased neuroplasticity and brain-derived neurotrophic factors[12] and a reduction in neuroinflammation.[13,10]

Moderate coffee consumption (3–5 cups/day) is associated with lower risk of multiple CV outcomes.[14] Coffee is a complex mixture of compounds that have diverse and sometimes antagonistic roles in CV health, which may explain the likely U-shaped associations of coffee consumption and CV risk.[15] The association of coffee consumption and PD appears to be monotonically protective[16, 17] and the hypothetical mechanism has been focused on caffeine as a nonspecific adenosine A_{2A} receptor antagonist.[18]

At least for coffee consumption and physical activity, apparently disparate mechanisms appear to be involved, leaving no obvious unifying pathway or biology despite the concordant associations.

Factors that have discordant associations with cardiovascular versus PD risk

According to the Global Burden of Diseases study, approximately 25% of men and 5.4% of women worldwide are daily smokers, making cigarette smoking one of the most preventable causes of chronic diseases including CV disease.[19] The association of smoking with PD, however, is inverse and understanding its basis is complicated. Smokers have about 50% lower risk of developing PD than non-smokers.[20, 21] The relationship cannot be explained by higher mortality among smokers (i.e., the competing risk hypothesis), however, this does not necessarily imply causality. Given the prolonged and largely unknown prodromal stage of PD, alternative hypotheses such as reverse causation and confounding by personality are very difficult to exclude. Answering this causal inference question has significant public health implications. If smoking indeed reduces PD risk or delays its onset as indirectly suggested by some studies,[22, 23] the decreasing trend in smoking may further increase the burden of PD upon our ever growing aging populations.[24]

Also discordant are the relationships with serum cholesterol. Although not entirely consistent, epidemiological studies have found that higher total or LDL cholesterol is associated with lower PD risk,[25–28] and slower PD progression,[29, 30] in clear contrast to their detrimental role in CV health. The evidence is reasonably robust, including support from multiple prospective cohorts[25–27]. If future studies show causality, there will be important clinical implications for statin use in PD patients or in individuals at risk for PD.[27, 31, 32]

Cardiovascular risk factors with mixed evidence or null associations with PD risk

There is controversy about whether DM is more prevalent in patients who are later diagnosed with PD. Interestingly, most cohort studies describe a modestly increased risk of PD after a diagnosis of DM (Table 1a) whereas most case-control studies observed no

association or even a decreased risk of PD in patients with DM (Table 1b). The studies are heterogeneous regarding the demographics of the populations, the definitions of the outcome and exposure, and the time between the diagnosis of DM and the observation of PD. There have been three recent meta-analyses including cohort studies (pooled adjusted relative risk of 1.38, 95% CI 1.18–1.62),[33] case-control studies (OR 0.75, 95% CI 0.58–0.98)[34] or both types (confirming these discordant effect estimates).[35] One possible explanation for the discrepancy between the results from cohort and case-control studies could be the introduction of survival bias in the latter study design because of an increased mortality among the diabetic patients leading to an inverse relationship between DM and PD in case-control studies. A prospective cohort study observed that the risk of PD was greater in patients with a short duration of DM than in longer-standing DM patients and this was not explained by a selective mortality in those with longer DM duration.[36] In contrast, a higher risk of PD has been observed in those with DM duration >10 years in two much larger studies.[37, 38] The results of the later studies support a causal relationship between DM and PD. A large cohort study including more than 14,000 patients with PD yielded a higher risk of PD in those with young onset DM.[37] The authors explain their observation by genetic effects having more impact in the young onset DM population whereas the association of DM with PD is rather linked to lifestyle and environmental factors in the older population.

There have been fewer studies published focusing on the effect of a previous diagnosis of HTN on the risk of PD (Tables 2a and 2b) and no meta-analysis of the available data has yet been performed. In a small cohort study of 58 PD patients, no statistically significant increased risk of PD in association with prior HTN was found.[39] More recent cohort studies found a null result in 530 PD patients,[40] and a statistically significant increased risk of PD in patients with HTN only for women.[41] Additionally, ten case-control studies examined the association between HTN and subsequent risk of PD[42–51], five of them yielding a statistically significantly reduced risk of PD,[44, 45, 47–49] whereas the other five studies (with small sample sizes) showing no effect.[42, 43, 46, 50, 51] The judicious conclusion from these studies is that an effect size, if present, is small.

Many other CV risk factors have been studied in relation to PD risk, but the data are largely null or, at best, mixed. In general, epidemiological studies found limited evidence that obesity[52, 53] was associated with the risk of developing PD. More studies have examined alcohol consumption in relation to PD risk. Although a meta-analysis of earlier case-control studies suggests a weak inverse relationship,[54] recent prospective studies suggest an overall null relationship.[55, 56] One recent cohort study analyzed the risk of PD associated with a previous diagnosis of metabolic syndrome and its components[57] (Table 3). In this analysis, metabolic syndrome was associated with a statistically significant decreased risk of PD (RR 0.50, 95% CI 0.30–0.83), as was increased plasma fasting glucose (RR 0.56, 95% CI 0.32–0.98). Elevated blood pressure was not associated with a change in risk of PD (RR 1.07, 95% CI 0.55–2.07). However, the exposures were only measured at baseline of the 30 years of follow-up and the study included only 89 patients with PD. A Mediterranean dietary pattern has been associated with reduced risk of CV disease in a number of studies.[58] Preliminary evidence from cross-sectional studies suggests that this dietary pattern may also be negatively associated with PD,[59] as well as prodromal PD.[60]

The relationship between hyperhomocysteinaemia and cardiovascular risk remains unclear, with many epidemiological studies suggesting an association, while interventional trials of homocysteine lowering have thus far failed to demonstrate any advantage (for review see[61]). There is, however, considerable interest in the potential role of B12 and folic acid supplementation to enhance the methylation of homocysteine to methionine, made particularly necessary in PD due to the impact of chronic levodopa use on elevated homocysteine levels. In the setting of low B12 levels it has been proposed that homocysteine metabolism to methionine exploits betaine as a cofactor which in consequence has negative effects on acetylcholine production, and potential negative effects on cholinergic process such as gait, balance and cognition (for a recent review see[62]).

As illustrated in the tables, the studies of DM and HTN and PD are very heterogeneous in terms of sample size, definition of comorbid diseases, and definition of PD. Furthermore, exclusion criteria and the kind and number of confounding variables included in the multivariate analyses also varied. Moreover, factors such as duration of comorbid disease, medication use, and additional biases (e.g. selection bias of included individuals, recall bias in case-control studies assessing exposure via self-report etc.) may have also influenced the results. A further methodological challenge in large database studies is the possibility of diagnostic misclassification. In the context of vascular risk factors and PD, the possibility of misclassifying vascular parkinsonism as PD must be considered.

Challenges in studying cardiovascular risk factors in PD etiology.

Like PD, DM, HTN, and the metabolic syndrome are predominantly diseases of the elderly. They also have in common a rather subtle onset that can obscure the observed occurrence sequence. The common co-occurrence of multiple CV risk factors make it difficult to disentangle their relationship with PD risk. In addition, most of the classic CV risk factors involve diet and lifestyle that constantly change throughout one's lifetime, influenced by education, socioeconomics, religion, as well as overall health and the aging process. Late-onset sporadic PD, is a slowly progressive degenerative disease that takes years, if not decades, to develop before a clinical diagnosis becomes possible. Many factors may be active during this decades-long prodromal stage, affecting both the onset of PD and its progression. Furthermore, a range of nonmotor symptoms (e.g., cognitive and personality changes, hyposmia) and subtle motor signs may arise within the prodromal PD period. Although empirical data are limited, many of these symptoms and signs may potentially affect diet and lifestyle. A prospective study suggested that PD patients tend to lose weight about 2–4 years before clinical diagnosis, despite a decrease in physical activity and increase in calorie intake.[63] This exceedingly long and dynamic PD prodromal development is critically important in studying PD etiology, but to date, poorly understood. Ideally, future etiological studies of PD should account for these complexities in PD prodromal development. Longitudinal and repeated evaluation from an early age will be an important methodologic feature.

Cardiovascular comorbidity and PD

Suggestive links between CV disease and PD are not only restricted to risk factors, but also manifest CV disease. Newly diagnosed PD patients may be at a statistically significant increased risk for a subsequent myocardial infarction (MI) based on a recent study using data from the National Health Insurance database in Taiwan, which found the hazard ratio of MI in incident PD patients to be 1.67 (95% CI 1.15–2.41).[64] Studies assessing the cause of death in patients with PD have yielded inconsistent results with respect to the frequency of a diagnosis of ischemic heart disease (IHD) as the proximate cause of death in PD patients compared to the general population: an increased risk of (IHD-related) death in one earlier study using primary care data from the UK (HR 2.6, 95% CI 1.5–3.4),[65] no changed risk compared to the general population (HR 1.1, 95% CI 0.6–2.0),[66] as well as a lower proportion of IHD-related deaths in the PD population (13% vs 23% of deaths[67] and 12% vs 19% of deaths).[68] At the time of the PD diagnosis, IHD seems to be as frequent as in non-PD controls: an OR of 1.05, 95% CI 0.93–1.19 was reported from a study from the UK including 3,637 incident PD cases and the same number of PD-free controls.[69]

A previous diagnosis of stroke has been found to be more prevalent in PD patients than in non-PD controls in a smaller study from Norway (OR 5.00, 95% CI 1.44–17.35).[70] An increased risk for a first-time PD diagnosis after a stroke may in part be explained by the vascular changes and by ischemic brain damage caused by a cerebrovascular accident. One larger study from the UK showed an increased risk of ischemic stroke after the PD diagnosis (OR 1.55, 95% CI 0.98–2.46).[69]

Taken together there is evidence, albeit not definitive, that the risk of incident MI and stroke may be increased following the diagnosis of PD. These data need to be interpreted with caution because of the possibility of ascertainment bias due to increased contact with the health care system after PD diagnosis.

Contributions from the basic sciences

The pathophysiological explanation for the risk factors and comorbidities associated with CV disease and PD are presently unknown, but both chronic diseases share dysregulated pathways including inflammation and metabolism.[71–73] Pathways and their potential relationships to CV disease, PD and their risk factors are summarized in Figure 2.

Glucose, lipid and cholesterol metabolism

Hyperglycemia and insulin resistance, low-grade inflammation and overproduction of reactive oxygen species and advanced glycation end products are thought to contribute to an elevated risk of both CV disease and PD. The implications of poor glucose regulation for CV health is well known; among DM patients, CV disease is the leading cause of death. The brain consumes about 25% of the body's glucose to fuel oxidative metabolism. Hyperglycemia is particularly detrimental to nigrostriatal dopaminergic neurons that are rich in mitochondria, have high levels of iron ions that promote the production of highly reactive free hydroxyl radicals, and low levels of the antioxidant glutathione. This combination of characteristics may be a factor in the susceptibility of substantia nigra pars compacta

dopamine neurons in patients with poor regulation of glucose metabolism. Consistent with this situation is the observation that in early stage PD patients in the De Novo Parkinson Cohort, disease progression was faster in participants who had CV disease risk factors, unregulated blood glucose, high uric acid levels and inflammation.[74]

Changes in lipid metabolism also play a role in both CV disease and PD. Oxidized low-density lipoproteins (oxLDL) are a major contributor to atherosclerotic plaque formation. OxLDL increase the expression of arginase, which competes with endothelial nitric oxide for arginine, reduces nitric oxide (NO) bioavailability and promotes atherosclerosis progression.[75] Idiopathic PD patients have higher plasma oxLDL than controls, but it is not clear whether this is important in disease initiation and/or progression.[76]

Accumulation of the sphingolipid ceramide impairs insulin action, is a modulator of mitochondrial and ER stress, promotes apoptosis, and potentially links CV disease, insulin resistance, low-grade inflammation[77] and PD. In a study of participants in the prospective PREDIMED (Prevención con Dieta Mediterránea) trial, plasma ceramide concentrations were linked to non-fatal acute MI, non-fatal stroke, and CV death.[78] PD is also associated with altered sphingolipid metabolism.[79] Ceramides and sphingomyelins are altered in postmortem PD brain tissue compared to the controls.[80] Some forms of ceramide in the plasma of PD patients are higher in individuals with dementia compared to non-demented patients.[81, 82] In addition, mutations in the *SMPD1* gene that encode sphingomyelinase is correlated with an increased risk of PD.[83–88] Mutations in the *GBA* gene that encodes glucocerebrosidase, which produces ceramide from glucocerebroside, are also associated with PD.[89, 90] In the lysosome, sphingomyelinase and glucocerebrosidase hydrolyze sphingolipids to produce ceramide. Sphingomyelin can modify the expression of α-synuclein.[91] Because the degradation of overproduced or pathological forms of α-synuclein depends on sphingomyelinase, changes in ceramide abundance may play a central role in PD pathology.[92] An additional central role has been proposed for ceramide metabolism in the pathobiology of PD based on retromer dysfunction and mitochondrial defects.[93] Together, these studies suggest that an imbalance of lipids may result in mitochondrial and endolysosomal dysfunction that leads to neuronal death in PD. Activating ceramidase, an enzyme that converts ceramide to sphingosine, would reduce ceramide levels and be potentially beneficial for treating CV disease, PD, insulin resistance and inflammation.[94]

One very interesting conundrum sometimes seen in medicine is when a given intervention may have opposite effects on different disorders. The relationship of cholesterol to the heart and PD is one excellent example. It is well-established that in people with elevated cholesterol, cholesterol-lowering drugs like statins have beneficial effects on CV health.[95] As introduced above, significant literature has provided evidence that circulating cholesterol also may be related to PD, yet the interpretation of the evidence has not been straightforward. Early case-control studies found that higher plasma cholesterol was associated with lower PD prevalence[47, 96–98] and later prospective studies showed that low cholesterol predated the diagnosis of PD.[26, 27, 40, 99, 100] Moreover, higher baseline cholesterol has been linked to slower PD progression,[101] better cognitive and motor performance,[30] as well as delayed age of PD onset.[102]

Despite this trend, the observed cholesterol-PD relationship may not be causal. PD diagnosis may prime for adoption of a "healthier" lifestyle, thereby leading to lower cholesterol. Alternately, an unknown behavioral (e.g., smoking) or medical (e.g., use of statin) confounder may play a role or lower plasma cholesterol simply may reflect metabolic or non-motor changes that are associated with PD. Indeed, although one often thinks of cholesterol as being related to the CV system, the brain is the most cholesterol-rich organ in the body (accounting for ~25% of the total cholesterol). In the adult brain it is synthesized primarily by astrocytes and then transported to neurons via endocytosis and interaction with the LDL receptor (LDLR) and apolipoprotein E,[103] thus the cholesterol in brain is made mainly *de novo*,[104, 105] and there is limited exchange of cholesterol across the blood brain barrier (BBB).[106] There is, however, evidence for the uptake of LDL particles and other apolipoproteins across the BBB, possibly via the LDLR and/or LDLR-related proteins, and oxysterols also may mediate peripheral-central cholesterol communication.[107]

Another fascinating association relates to the APOE gene. The least common ε2 allele is represented in only 8% of the population, but individuals with an ε2 allele have a propensity for lower plasma LDL-cholesterol levels, whereas the ε4 is linked to higher LDL-cholesterol levels.[108] Yet while the ε2 allele is linked to a number of beneficial outcomes in terms of CV disease and lower risk of Alzheimer's disease (AD), some studies,[109, 110] but not all,[111] have associated it with higher risk of PD whereas the more common ε4 allele is associated with poorer CV disease outcomes and a significantly increased risk of AD,[112, 113] but is associated with lower PD risk.[114] There are fascinating mechanisms that may be relevant, for example, a large clinical study provided evidence that lipids and lipoproteins may affect dopamine neuron-specific signaling cascades.[115] Other studies show that cholesterol recycling may be linked to PD,[109, 110, 114] and related genes are associated with increased PD risk[116] or are affected in animal models of PD[117] or PD itself.[118]

Despite the literature linking serum/plasma total- and LDL-cholesterol to PD,[26, 27, 30, 40, 47, 96–102] the cause of the association is not known and further complicated by the compartmentalization of brain and peripheral cholesterol. An investigation of a potential causal relationship between circulating cholesterol levels and PD took into consideration age, gender, APOE polymorphisms, smoking history, statin, and several related gene single nucleotide polymorphisms. Based on propensity score methods, lower total- and LDL-cholesterol were inversely associated with PD suggesting that circulating total- and LDL-cholesterol levels may influence PD risk.[119, 120] A recent study assessed whether brain cholesterol metabolism is related to PD by quantifying fasting plasma levels of both a brain and peripheral cholesterol metabolite. The data showed that the brain-derived cholesterol metabolite was inversely linked to PD and was relatively stable over time, suggesting that the numerous associations noted above may have a mechanistic basis.[121]

There are many possible mechanisms that may be involved. Cholesterol is essential for synaptogenesis,[103] and there may be higher cholesterol turnover during the compensatory repair of injured neuronal pathways as higher levels of cholesterol metabolites are found in postmortem brain and more cholesterol catabolic metabolites in cerebrospinal fluid from PD patients.[122, 123] In addition, the *(S)*24-OH cholesterol metabolite is known to be lower in PD patients[121], is formed solely in the brain, and is reported to be a positive allosteric modulator

of the N-methyl-D-aspartate glutamate receptor.[124] Indeed, glutamate may activate the synthetic enzyme CYP46A1 allosterically, thereby increasing the production of (S)24-OH. [125] The down-regulation of CYP46A1 leads to a compensatory decrease in cholesterol synthesis and consequent decreases in geranylgeraniol, a key metabolite in synaptic plasticity.[126, 127] Cholesterol has, however, many cellular functions, and a great deal of additional research is necessary to elucidate the actual mechanisms that may be involved.

There is controversy over whether the cholesterol-PD association is actually a result of the effects of cholesterol lowering agents (specifically statins) as opposed to a biological factor related to disease etiology. Statins have been suggested to be neuroprotective for PD,[128–130] yet a prospective study in the Atherosclerosis Risk in Community (ARIC) cohort found that statin usage was associated with increased future risk of PD.[27] Most recently, an analysis of the large MarketScan national claims database in the US found that statins were positively associated with PD diagnosis.[31] Although these data suggest caution to proposing statins as being neuroprotective for PD, it did not deter the launch of a trial of simvastatin as a neuroprotective agent.[131] This and future research will hopefully settle these issues.

Inflammation

Inflammation plays a key role in the development and progression of CV disease,[132] DM,[133] and PD.[134] Chronically elevated levels of C-reactive protein (CRP) are associated with all three diseases. In CV disease, inflammation is involved initially with the recruitment of leukocytes to the arterial wall and later with the rupture of unstable plaques. CRP is most likely involved with complement activation, apoptosis, endothelial NO synthase inhibition, vascular cell activation, monocyte recruitment, lipid accumulation, thrombosis, and pro-inflammatory cytokine formation.[135] CRP may activate the mechanistic target of rapamycin (mTOR) signaling and TGF-α/Smad3 pathways, which could increase renal fibrosis and lead to DM[136, 137] and increase risk of PD.

Brain and gut inflammation play a role in the development and progression of PD. Of note is the fact that autoreactive T lymphocytes, autoantigen presentation, and microglial activation are present in PD patients. The recent identification of α-synuclein-specific T cells in PD patients suggests that PD shares similarities with autoimmune disorders.[138, 139] There is strong evidence to support the hypothesis that α-synuclein deposition in PD patients begins in the gut and travels through the vagus nerve into the central nervous system (CNS).[140] It is possible that the adaptive immune system may be primed against a-synuclein deposition in the gut. PD patients also have an increased abundance of peripheral pro-inflammatory cytokines and chemokines that act on CNS endothelial cells that form the BBB, thus increasing vascular permeability[141] and making the brain more susceptible to circulating immune cells, antibodies, and pro-inflammatory cytokines.

Next steps for research and translation to the clinic

Addressing CV risk

In the context of a neurodegenerative process like PD, patients can ill afford to have additional causes for neuronal dysfunction. Evidence indicating that PD symptom severity is

worse in the presence of microvascular disease is consistent with this idea.[142] High CV disease risk scores are associated with higher PD motor scores, and worse cognitive performance, but nevertheless PD patients with high CV risk scores are frequently not treated with statins,[143, 144] despite some evidence of their beneficial effects in this subgroup without PD.[145] As alluded to already, there is also evidence that suggest that the use of statins may increase PD risk, suggesting that this important issue should be approached cautiously.[27, 31, 119]

One theoretical approach to this would be to undertake randomized trials testing interventions using conventional CV primary prevention approaches to determine if they have an impact on the rate of development or progression of symptom severity in PD. Given the possible detrimental effects of some interventions (e.g., statins, see above, or aggressive treatment of HTN in PD patients with autonomic dysfunction) patients would have to be clearly informed of the possible risks, and close data safety monitoring employed. Personalized approaches based on CV risk score[146, 147] could be designed, although long term follow-up and large sample sizes would likely be necessary to provide a clear test of any hypothesis. Whether equipoise exists for such a trial is critically important, especially given that some trial participants would be randomized not to receive routine CV disease treatments. Arguably, rather than embarking on a logistically and ethically challenging trial, we suggest that it might instead be best to devote greater efforts to ensure PD physicians consider their patients holistically and encourage them to treat patients' CV risk along with PD symptoms.

Candidate neuroprotective therapeutics

There is considerable overlap between those agents that have been shown to be useful in addressing CV risk factors, and therapeutic candidates for neuroprotection in PD. For example, treatments for DM may be effective in reducing CV risk in DM patients,[148] and are now also the subject of interest for neuroprotective trials in PD.

A key question that arises in considering how best to design trials to assess potential benefits in PD relates to the theoretical mechanism(s) of action of these drugs. It is possible that benefits from anti-diabetic drugs in PD might simply relate to their same peripheral mechanism of action (e.g., glucose lowering) that might cause reduced α-synuclein glycation,[149, 150] and thus any beneficial effects could be extrapolated to all agents with peripheral glucose lowering actions. If so, this would have a major influence on a clinical trial design, as the intervention could be personalized in terms of both drug choice and dose, according to an individual's baseline glucose/HbA1c levels and preference regarding mode of administration and/or idiosyncratic side effects.

If any of the CV drugs have "off target" (i.e., independent of their effects on glucose, blood pressure, cholesterol, etc.) beneficial effects on PD neurodegeneration, then trials must focus on single agents and/or drug classes that may share a common mechanism(s) of "neuroprotection." The GLP-1 receptor agonists may be interesting because of their potential neuroprotective/neurorestorative properties in a range of animal models[151–154] alongside data indicating potential mechanisms through anti-inflammatory effects on microglia/astrocytic processes[154] or anti-apoptotic effects through the Akt/mTOR pathway.

[155] Whether these effects are distinct or if there is overlap between the neurodegenerative and microvascular disease processes is of clear interest but not yet known.

In a one-year phase 2 trial of 60 patients randomized to self-inject exenatide or placebo, PD patients using exenatide had smaller increase in the Movement Disorders Society Unified PD Rating Scale part 3 motor scores when assessed in the off-medication state.[156] Despite the washout design of this trial (the primary outcome was evaluated 12 weeks after cessation of exenatide), it is still unclear whether these encouraging effects represent a disease-modifying effect or a prolonged symptomatic one. To evaluate this, a larger randomized two-year multicenter trial is being organized to test the impact of exenatide or placebo for two years.

Additional trials of exenatide, liraglutide, lixisenatide and semaglutide also are being planned or already in recruiting phases, reflecting the considerable academic and commercial interest in these GLP-1 receptor agonists for PD. For all of these trials, it will be of interest to perform subgroup analyses to compare whether effect sizes are greatest according to baseline glucose/HbA1c levels, or PD risk genotypes. This may help interpret whether effects of GLP-1 receptor agonists bear any relationship to CV disease risk or act via independent cellular mechanisms.

In parallel with the interest in GLP-1 receptor agonist approaches, there has been interest in the thiazolidinedione drugs, in particular pioglitazone as a PD neuroprotective agent based on epidemiological and laboratory evidence indicating its potential benefit. Unfortunately there was no advantage seen among patients treated with Pioglitazone for 44 weeks in a double blind randomised controlled trial.[157] These results highlight the uncertainty regarding how strongly preclinical laboratory evidence predicts efficacy in people with PD, as well as questions regarding the stage of disease or duration of exposure that may be necessary for disease modifying effects to become detectable.

Similarly, simvastatin has been reported to have beneficial effects in the toxicant-based models of PD, with evidence indicating anti-inflammatory effects as well as beneficial effects on α-synuclein aggregation.[158] Although observational studies have yielded conflicting results,[32] the potential for disease-modifying effects of statins in PD progression has led to a clinical trial using double blind-trial methodology, although some have challenged whether this study is justified based on available evidence.[27, 31, 121] The PD STAT trial has also used a parallel group design comparing 80 mg of simvastatin or placebo taken daily for two years. One of the challenges of this study has been to identify sufficient numbers of patients who were not already prescribed a statin, or not likely to be prescribed a statin over the two-year period based on their CV risk score.[131]

In the design of clinical trials studying the effects of CV drugs it will be helpful to plan *a priori* subgroup analyses or design the randomization strategy to help us to understand the profiles of individuals most likely to benefit and least likely to be harmed. It is perhaps sensible to hypothesize that the CV drugs are likely to have their greatest effects in patients with high CV risks, which will presumably be additive to any effects on the neurodegenerative processes of PD. However there is also the potential for detrimental

effects (e.g., use of brain-permeable cholesterol lowering drugs in subgroups of PD patients with low preexisting cholesterol, without other CV risk), thus pre-defined subgroup analyses are likely to be helpful.

Conclusions

CV disease and PD share biological processes, particularly inflammation, insulin resistance, lipid metabolism, and oxidative stress. It is unclear, however, whether or not these processes are the consequence of shared risk factors. There are modifiable risk factors that are inversely associated with both CV disease and PD, particularly physical activity and moderate coffee consumption, but the mechanisms by which they are associated with PD are not established and research to date provides most evidence for disparate mechanisms. Nonetheless, these risk factors (or their underlying mechanisms) represent logical targets for primary or secondary prevention strategies regardless of diagnosis. Despite less clear epidemiological evidence in PD, good glycemic control and treatment of HTN are also health interventions with clear benefits for CV health that can be supported to optimize health in PD patients or individuals at risk for PD based on biological mechanisms and other benefits on brain health. CV risk factors with more obvious common mechanistic links to PD (such as DM, HTN and obesity sharing oxidative stress and inflammation as mechanisms) still are not established PD risk factors, probably indicating that their associations with PD are small in magnitude.

On the other hand there are associations, in particular with cholesterol and smoking, that have discordant relationships with PD and CVD. As with the concordant associations the mechanisms (at least with PD) are not well understood and addressing this knowledge gap should help to direct preventive therapies in a way that balances risks and benefits. It will be important to understand the degree of overlap in the disease-associated mechanisms in order to guide a nuanced approach to application depending on the individuals' combination of risk factors and established disease.

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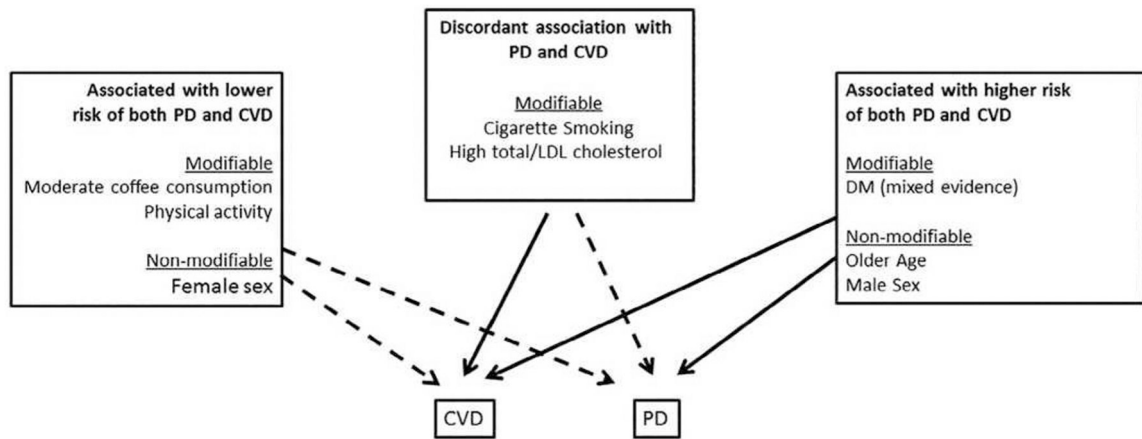
Figure 1: Associations between cardiovascular risk factors and Parkinson's disease.
Green arrows indicate inverse associations between the risk factor and disease. Red arrows indicate positive associations between the risk factor and disease. CVD=cardiovascular disease; PD = Parkinson's disease.
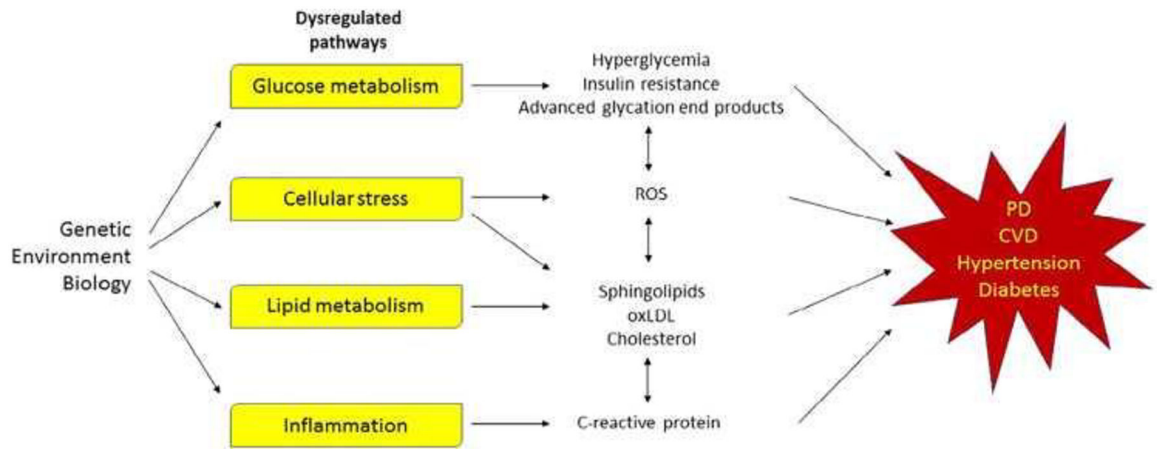
Figure 2: Pathways dysregulated in Parkinson's disease and cardiovascular disease.
Yellow boxes represented pathways that are dysregulated in both conditions. CVD = cardiovascular disease; PD = Parkinson's disease.

Table 1a:

Diabetes (Cohort studies)

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
De Pablo-Fernandez et al. 2018[37]	Hospital-based cohort of Type 2 DM patients and diabetes-free controls	UK	14'252 PD patients	**PD:** 1st hospital admission for PD Exclusion of individuals with a coded diagnosis of cerebrovascular disease, vascular/drug-induced parkinsonism, or normal pressure hydrocephalus **DM:** Hospital admission for type 2 DM	Overall: HR 1.32 (95% CI 1.29–1.35) Patients aged 25–44 y at the time of the 1st admission for DM: 3.81 (95% CI 2.84–5.11), result based on small numbers (58 PD patients) Women: 1.42 (95% CI 1.37–1.47) Men: 1.27 (95% CI 1.23–1.30)	Age, sex, year of cohort entry, region of residence, socioeconomic status	**Sensitivity analyses:** exclusion of patients with <1 yr between DM and PD: same results Limitations: Potential selection bias caused by restriction to hospitalized cases (i.e., more severe DM)
Yang et al. 2017[159]	National Health Insurance claims database Mean follow-up 7.3 y	Taiwan	1'782 PD patients	**PD:** ≥3 Dx in ambulatory care or ≥1 Dx in inpatient care **DM:** Same as for PD, Dx based on ADA criteria	Overall : HR 1.19 (95% CI 1.08–1.32) Women 1.29 (95% CI 1.12–1.49) Men : 1.12 95% CI (0.97–1.30)	Age, sex, insurance premium, residential area, occupation, CCI, schizophrenia and bipolar disorder, prescription of flunarizine, MCP or zolpidem	Exclusion of patients with <1 yr between DM and PD
Sun et al. 2012[160]	National Health Insurance claims database	Taiwan	2'422 PD patients	**PD:** Outpatient claims or hospitalization records (≥1 year after cohort entry) **DM:** Prevalent Dx plus ≥1 DM Dx during follow-up	Overall: HR 1.61 (95% CI 1.56–1.66) Women : HR 1.70 (95% CI 1.63–1.77) Men: HR 1.51 (95% CI 1.44–1.57) Men (21–40 y): HR 2.10 (95% CI 1.01–4.42) Additional adjustment for medical visits : Overall HR 1.37 (95% CI 1.32–1.41)	Age, sex, geographic area, urbanization status, medical visits, hypertension, hyperlipidemia, cardiovascular disease	Results for men (21–40 ys) based on 6 PD cases
Xu et al. 2011[38]	National Institutes of Health-AARP Diet and Health Study	USA	1'565 PD patients	**PD:** Self-reported, validated by the treating physician **DM:** Self-reported	OR 1.41 (95% CI 1.20–1.66) Only patients with DM duration at baseline ≥10 y: OR 1.75 (95% CI 1.36–2.25)	Age, sex, race, education, smoking, coffee consumption, BMI, physical activity	Sensitivity analysis: exclusion of cases with stroke, heart disease, cancer, or poor/fair health: similar results
Palacios et al. 2011[114]	Cancer Prevention Study II Nutrition Cohort Mean follow-up 6.4 y	USA	656 PD patients	**PD:** Incident, confirmed by neurologist or medical record review **DM:** Self-reported at baseline	HR 0.88 (95% CI 0.62–1.25)	Age, sex, smoking, diet, alcohol/coffee consumption, BMI, education, physical activity, pesticide exposure	**Sensitivity analyses:** exclusion of PD cases during first 5 y of follow-up: similar results
Driver et al. 2008[36]	Physicians Health Study (randomized trial) Median follow-up 23.1 y	USA	556 PD patients	**PD:** Self-reported (90% accurate according to validation study) **DM:** Self-reported (Type 2 DM)	Men: RR 1.34 (95% CI 1.01–1.77) Association significantly modified by BMI (increased risk of PD with low BMI)	Age, smoking, alcohol consumption, BMI, hypercholesterolemia, hypertension, physical activity	Increased risk with shorter DM duration –> no causal association

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
Simon et al. 2007[40]	Nurses' Health Study and Health Professionals Follow-up Study Mean Follow-up: 22.9 y/12.6 y	USA	530 PD patients	**PD:** Self-report, confirmed by treating physician (15%), neurologist (82%), or by review of medical records (3%) **DM:** Self-reported physician's Dx (validated) PD and DM status assessed at baseline and every 2 ys thereafter	With updated history of DM: RR 1.04 (95% CI 0.74–1.46) Only baseline info on DM: RR 1.12 (95% CI 0.69–1.81)	Age, sex, smoking	Patients with prevalent stroke excluded Additional adjustment for BMI, physical activity, hypertension, cholesterolemia, alcohol/ coffee consumption, diet, NSAID use yielded similar results
Hu et al. 2007[161]	Prospective study based on cross-sectional surveys in five geographic areas Mean follow-up 18 y	Finland	633 PD patients	**PD:** Data from the National Insurance Institution register, confirmed by two neurologists **DM:** Self-report, hospital discharge diagnoses **or** drug claims Assessment of covariates by questionnaires	Overall: HR 1.85 (95% CI 1.23–2.80) Men: HR 1. 08 (95% CI 1.03–3.15) Women: HR 1.93 (95% CI 1.05–3.53)	Age, study year Additional adjustments for BMI, systolic blood pressure, cholesterol, education, physical activity smoking, alcohol/coffee/tea consumption yielded similar results	Only baseline info on DM included Similar results in several sensitivity analyses
Grandinetti et al. 1994[39]	Honolulu Heart Program Follow-up: 26 ys	USA	58 PD patients	**PD:** Hospital records, death certificates, or medical records of neurologists **DM:** Self-report plus physical examination at baseline	RR 1.20 (95% CI 0.67–2.12)	Age	Main objective of the study: assessment of the impact of cigarette smoking on the risk of PD

AARP = American Association of Retired Persons; ADA = American Diabetes Association; BMI = Body mass index; CCI = Charlson Comorbidity Index; CI = Confidence interval; DM = Diabetes mellitus; Dx = Diagnosis, HR = Hazard ratio; NSAID: Non-steroidal anti-inflammatory drugs; MCP = metoclopramide; OR = Odds ratio; PD = Parkinson disease; RR = Relative risk; Rx = Prescription; UK = United Kingdom; yr/ys = year(s)

Table 1b:

Diabetes (Case-control studies)

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
Skeie et al. 2013[70]	Norwegian ParkWest Study from western and southern Norway	Norway	212 PD patients	**PD:** Incident PD cases, identified through neurology departments according to Gelb criteria[162] **DM:** Medical and drug history by self-report, referral letters, medical records from hospital and GPs, medical examination	OR 1.94 (95% CI 0.82–4.57)	Not stated	
Savica et al. 2012[43]	Records-linkage system of the Rochester Epidemiology Project All residents from Olmsted County	USA	196 PD patients	**PD:** Incident PD cases, 2 of four cardinal signs, no other cause and responsive to L-Dopa (validated approach) **DM:** Review of medical records (physician's diagnosis or use of antidiabetic drugs)	OR 0.67 (95% CI 0.31–1.48)	Age, sex, smoking, coffee consumption	No recall bias possible since diagnoses of comorbidities were documented before the onset of PD
Schernhammer et al. 2011[163]	Nationwide hospital records (Danish Hospital Register)	Denmark	1'931 PD patients	**PD:** Hospitalization or outpatient visit for PD plus 1 antiPD medication **DM:** Had to be present at least 2 ys before PD **a.** Diagnosis recorded in the Danish Hospital Register **b.** Prescription for antidiabetic medication recorded in the Danish Prescription Database	Exposure: DM diagnosis: OR 1.36 (95% CI 1.08–1.71) OR 1.50 (95% CI 1.02–2.22) women OR 1.29 (95% CI 0.97–1.72) men Onset of PD <60 y: OR 2.68 (95% CI 1.04–6.91) Exposure: antidiabetic drug use ≥2ys prior to PD diagnosis: OR 1.35 (95% CI 1.10–1.65) Onset of PD <60 y: OR 3.07 (95% CI 1.65–5.70)	Age, sex	Exclusion of PD patients with diagnosis of Alzheimer <2 y before PD and with prescription of PD inducing medication 180 days prior to PD: similar results
Miyake et al. 2010[44]	PD cases and controls recruited from hospitals in two regions	Japan	249 PD patients	**PD:** Cases included within 6 y of onset of PD, diagnosed by neurologists according to the UK PD Society Brain Bank clinical diagnostic criteria **DM:** Based on antidiabetic drug treatment (information from questionnaires)	OR 0.38 (95% CI 0.17–0.79) Women: OR 0.39 (95% CI 0.11–1.20) Men: OR 0.34 (95% CI 0.11–0.91)	Age, sex, region of residence, smoking, education, physical activity, BMI, alcohol/coffee consumption, dietary glycemic index	
D'Amelio et al. 2009[164]	Outpatients consecutively recruited at the Neurological Department	Italy	318 PD patients	**PD:** 2 of four cardinal signs, exclusion criteria: 2nd-ary causes of parkinsonism, DIP 180 days prior to PD Dx, or cognitive decline within one yr after PD Dx	OR 0.4 (95% CI 0.2–0.8)	Age, sex, BMI, smoking, alcohol/coffee consumption, years of education	

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
				DM: Self-report (questionnaire) validated by review of medical records (80% valid), plus antidiabetic drug use			
Becker et al. 2008[165]	Primary care database representative of UK population	UK	3'637 PD patients	**PD:** Dx recorded by GP plus ≥ 2 Rx for anti-PD drugs, no drugs inducing parkinsonism 6 months prior to PD Dx **DM:** Dx recorded by GP	OR 0.95 (95% CI 0.80–1.14)	Age, sex, smoking, BMI, diabetes, Asthma/COPD, ischemic heart disease, heart failure, stroke, arrhythmia, hyperlipidemia, epilepsy, affective and neurotic disorders, schizophrenia, dementia	
Scigliano et al. 2006[47]	Hospitalized patients to neurology department	Italy	178 PD patients	**PD:** Bradykinesia plus tremor, rigidity, or postural instability + good response to L–Dopa 58% with PD duration ≥ 1yr 30% 1–4ys, 12% ≥ 4ys **DM:** Patients with antidiabetic medication in medical records	OR 0.30 (95% CI 0.13–0.72)	Age, sex	Exclusion of patients with atypical parkinsonism and with DIP Control from the hospitalized population potentially more unwell than the general population
Powers et al. 2006[46]	From neurology and general practice clinics of the Group Health Cooperative HMO	USA	362 PD patients	**PD:** Incident cases, diagnosed by neurologist or GP (2 of 4 cardinal signs), no drugs causing PD within 12 months prior to PD Dx **DM:** Questionnaire + chart review	Men: OR 0.52 (95% CI 0.28–0.97) Women: OR 0.80 (95% CI 0.35–1.83)	Age, sex, ethnicity, smoking, education	
Ho et al. 1989[51]	Individuals living at homes for the elderly	HongKong	35 PD patients (not necessarily incident cases)	**PD:** Clinical examination by 3 examiners plus assessment at geriatric clinic, positive response to L–Dopa Exclusion criteria: history of cerebrovascular disease, DIP **DM:** Self-reported	OR 1.6 (95% CI 0.5–5.1)	Age, sex	Very low number of included/ exposed cases (6 patients with DM)

BMI = Body mass index; CI = Confidence interval; COPD = Chronic obstructive pulmonary disease; DIP = Drug induced parkinsonism; DM = Diabetes mellitus; Dx = Diagnosis; GP = General Practitioner; HMO = Health maintenance organization; OR = Odds ratio; PD = Parkinson disease; Rx = Prescription; UK = United Kingdom; yr/ys = year(s)

Table 2a:

Hypertension (HTN) (Cohort studies)

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
Qiu et al. 2011[41]	Seven consecutive population surveys on representative samples from 6 geographic regions Mean follow-up 18.8.ys	Finland	794 PD patients	**PD:** From National Social Insurance Institution register, Dx confirmed by 2 specialists, exclusion of patients with history of stroke at baseline **Blood pressure:** Measured at study sights according to WHO guidelines	Reference: <130/80 mmHg Women: 130–139/80–89 mmHg: HR 1.63 (95% CI 1.07–2.47) >140/90 mmHg: HR 1.62 (95% CI 1.09–2.42) Men: 130–139/80–89 mmHg: HR 0.94 (95% CI 0.64–1.39) >140/90 mmHg: HR 0.90 (95% CI 0.63–1.28)	Age, sex, study year, education, smoking, alcohol/tea/coffee consumption, BMI, physical activity, DM, cholesterol, use of antihypertensive agents	
Simon et al. 2007[40]	Nurses' Health Study and Health Professionals Follow-up Study Mean Follow-up: 22.9 y/ 12.6 y	USA	530 PD patients	**PD:** Self-report, confirmed by treating physician (15%), neurologist (82%), or by review of medical records (3%) **HTN:** Self-reported physician's Dx(validated), SBP >160 mmHg or DBP >90 mmHg or use of antihypertensive agents	RR 0.96 (95% CI 0.80–1.15)	Age, sex, smoking	
Grandinetti et al. 1994[39]	Honolulu Heart Program	58 PD patients		**PD:** Hospital records, death certificates, or medical records of neurologists **HTN:** self-report plus physical examination at baseline	RR 1.25 (95% CI 0.68–2.28)	Age	Main objective of the study: assessment of the impact of cigarette smoking on the risk of PD

BMI = Body mass index; CI = Confidence interval; DBP = Diastolic blood pressure; Dx = Diagnosis; HR = Hazard ratio; HTN Hypertension; PD = Parkinson disease; RR = Relative risk; SBP = Systolic blood pressure; WHO = World health Organization; yr/ys = year(s)

Table 2b:

Hypertension (HTN) (Case-control studies)

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
Vikdahl et al. 2015[42]	Population from a catchment area in Northern Sweden	Sweden	84 PD patients	**PD:** Incident cases, diagnosed by 2 neurologists according to UK PD Society Brain Bank clinical diagnostic criteria **HTN:** From crosslink to The Northern Sweden Health and Disease Study database, via questionnaire	HR 0.98 (95% CI 0.96–0.99)	Matching: age, sex, year of health survey, geographic area Adjustment: age, BMI, physical activity	Comorbidities were diagnosed 2–8 y before onset of motor symptoms
Savica et al. 2012[43]	All residents from Olmsted County (Records-linkage system of the Rochester Epidemiology Project)	USA	196 PD patients	**PD:** Incident PD cases, 2 of four cardinal signs, no other cause and responsive to L-Dopa (validated approach) **HTN:** Medical records (physicians' diagnosis or use of antihypertensive drugs)	OR 0.99 (95% CI 0.63–1.55)	Age, sex, smoking, coffee consumption	No difference between men and women No recall bias possible since Dx of comorbidities were documented before the onset of PD
Miyake et al. 2010[44]	PD cases and controls recruited from hospitals in two regions	Japan	249 PD patients	**PD:** Cases included within 6 y of onset of PD, diagnosed by neurologists according to the UK PD Society Brain Bank clinical diagnostic criteria **HTN:** Based on antihypertensive drug treatment (information from questionnaires)	Overall: OR 0.43 (95% CI 0.29–0.64) Women: OR 0.47 95% CI (0.28–0.78) Men: OR 0.38 (95% CI 0.19–0.72)	Age, sex, region of residence, smoking, education, physical activity, BMI, alcohol/coffee consumption, dietary glycemic index	
Becker et al. 2008[45]	Primary care database representative of UK population	UK	3'637 PD patients	**PD:** Dx recorded by GP plus ≥2 Rx for anti-PD drugs, no drugs inducing parkinsonism 6 months prior to PD Dx **HTN:** Dx recorded by GP	OR 0.83 (95% CI 0.74–0.92)	Age, sex, smoking, BMI, diabetes, Asthma/COPD, ischemic heart disease, heart failure, stroke, arrhythmia, hyperlipidemia, epilepsy, affective and neurotic disorders, schizophrenia, dementia	
Powers et al. 2006[46]	From neurology and general practice clinics of the Group Health Cooperative HMO	US	362 PD patients	**PD:** Incident cases, diagnosed by neurologist or GP (2 of 4 cardinal signs), no drugs causing PD 12 months prior to PD Dx, no other causes of parkinsonism **High blood pressure:** Questionnaire + chart review	Men: OR 0.80 (95% CI 0.55–1.17) Women: OR 1.62 (95% CI 1.00–2.62)	Age, sex, ethnicity, smoking, education	
Scigliano et al. 2006[47]	Hospitalized patients to neurology department	Italy	178 PD patients	**PD:** Bradykinesia plus tremor, rigidity, or postural instability + good response to levodopa 58% with PD duration ≤1yr 30% 1–4ys, 12% ≥4ys	OR 0.59 (95% CI 0.37–0.92)	Age, sex	Exclusion of patients with atypical parkinsonism and with DIP

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
				HTN: Patients on antihypertensive medication			Controls were drawn from the hospitalized population: potentially more unwell than the general population
Paganini-Hill et al. 2001[48]	Residents of retirement community	USA	395 PD patients (not necessarily incident cases)	**PD:** Review of hospital discharge diagnoses or death certificates or physicians' Dx mentioned in follow-up questionnaire **HTN:** History of HTN or use of antihypertensive medication (both self-reported)	Hypertension OR 0.71 (95% CI 0.56–0.89) Current use of antihypertensive medication OR 0.62 (95% CI 0.48–0.80)	Age, sex, smoking, alcohol/coffee consumption, number of children, Vitamin A/C	
McCann et al. 1998[49]	Patients recruited from hospitals, residential care centres and community groups	Australia	224 PD patients	**PD:** According to diagnostic criteria of Calne et al[166] **HTN:** self-reported	OR 0.3 (95% CI 0.18–0.42)	Age, sex, rural residency, family history of PD, stroke, ingestion of well, spring or bore water	
Semchuk et al. 1993[50]	Population-based case register of Calgary residents with neurologist-confirmed idiopathic PD	Canada	130 PD patients	**PD:** Confirmed by neurologists **HTN:** Self-reported	Cases and controls did not differ regarding history of hypertension	Age, sex	
Ho et al. 1989[51]	Individuals living at homes for the elderly	HongKong	35 PD patients (not necessarily incident cases)	**PD:** Clinical examination by 3 examiners plus assessment at geriatric clinic, positive response to L-Dopa **HTN:** Self-reported	OR 0.9 (95% CI 0.3–2.4)	Age, sex	Very low number of included/exposed cases (7 patients with hypertension)

BMI = Body mass index; CI = Confidence interval; DIP = Drug induced parkinsonism; Dx = Diagnosis, HMO = Health maintenance organization; HTN = Hypertension; OR = Odds ratio; PD = Parkinson disease; Rx = Prescription; UK = United Kingdom; yr/ys = year(s)

Table 3:

Metabolic syndrome (Cohort study)

Author (Year)	Source population	Country	Sample size	Definition of Diabetes & PD, covariates	Results	Adjusted variables	Remarks
Sääksjärvi et al. 2015[57]	Mini-Finland Health Survey (in 40 areas of Finland) Follow-up 30 y	Finland	89 PD patients	**PD:** Data from the National Insurance Institution register, based on clinical diagnostic criteria, incident cases, Dx confirmed by two neurologists **Metabolic syndrome:** 3 of the following components:[167] • BMI 25 kg/m² • SBP 130 mmHg or • DBP 85 mmHg or • antihypertensive drug treatment • Serum triglycerides 1.7 mmol/L • Serum HDL cholesterol <1.3 mmol/L (women), <1.0 mmol/L (men) • Plasma fasting glucose 5.6 mmol/L	Metabolic syndrome: RR 0.50 (95% CI 0.30–0.83) Plasma fasting glucose: <5.6 mmol/L: reference 5.6 mmol/L: RR 0.56 (95% CI 0.32–0.98) Elevated blood pressure: RR 1.07 (95% CI 0.55–2.07)	Age, sex, education, smoking, alcohol/ coffee consumption, physical activity, serum Vit D	Limitations: Lack of repeated measurements of exposure variables