Meta-Analysis of Early Nonmotor Features and Risk Factors for Parkinson Disease

Alastair J. Noyce, BMedSci, MRCP,[1,2] Jonathan P. Bestwick, MSc,[3]
Laura Silveira-Moriyama, PhD, MD,[1,4] Christopher H. Hawkes, MD, FRCP,[2]
Gavin Giovannoni, PhD, FRCP,[2] Andrew J. Lees, MD, FRCP,[1] and Anette Schrag, PhD, FRCP[1]

Objective: To evaluate the association between diagnosis of Parkinson disease (PD) and risk factors or early symptoms amenable to population-based screening.
Methods: A systematic review and meta-analysis of risk factors for PD.
Results: The strongest associations with later diagnosis of PD were found for having a first-degree or any relative with PD (odds ratio [OR], 3.23; 95% confidence interval [CI], 2.65–3.93 and OR, 4.45; 95% CI, 3.39–5.83) or any relative with tremor (OR, 2.74; 95% CI, 2.10–3.57), constipation (relative risk [RR], 2.34; 95% CI, 1.55–3.53), or lack of smoking history (current vs never: RR, 0.44; 95% CI, 0.39–0.50), each at least doubling the risk of PD. Further positive significant associations were found for history of anxiety or depression, pesticide exposure, head injury, rural living, beta-blockers, farming occupation, and well-water drinking, and negative significant associations were found for coffee drinking, hypertension, nonsteroidal anti-inflammatory drugs, calcium channel blockers, and alcohol, but not for diabetes mellitus, cancer, oral contraceptive pill use, surgical menopause, hormone replacement therapy, statins, acetaminophen/paracetamol, aspirin, tea drinking, history of general anesthesia, or gastric ulcers. In the systematic review, additional associations included negative associations with raised serum urate, and single studies or studies with conflicting results.
Interpretation: The strongest risk factors associated with later PD diagnosis are having a family history of PD or tremor, a history of constipation, and lack of smoking history. Further factors also but less strongly contribute to risk of PD diagnosis or, as some premotor symptoms, require further standardized studies to demonstrate the magnitude of risk associated with them.

Idiopathic Parkinson disease (PD) has a prevalence of approximately 1% in individuals aged >65 years.[1–3] The cause is unknown, but many individual risk factors for subsequent PD have been suggested. In addition, several early nonmotor features have been identified that precede the diagnosis of PD, sometimes by several years.[4–8] In the past 10 years, there have been a small number of meta-analyses addressing risk factors for subsequent PD, including smoking, coffee consumption, pesticide exposure, and use of nonsteroidal anti-inflammatory drugs (NSAIDs).[9–21] No review has comprehensively assessed predictive risk factors for later diagnosis of PD. Here we report the largest and most comprehensive systematic review and meta-analysis to date, which uses an extensive search of observational studies to calculate effect sizes of multiple risk factors for PD.

Methods

Search Strategy

We followed PRISMA 2009 guidelines for systematic review and meta-analysis and the Cochrane Collaboration definition of both terms.[22,23] We undertook a MEDLINE database search on PubMed from 1966 until March 2011 for studies that reported factors that could be used to screen for risk of future

PD. The MeSH terms used were: Constipation OR Sleep Disorders OR Olfaction Disorders OR Smoking OR Color Vision OR Coffee OR Erectile Dysfunction OR Depression OR Anxiety OR Mood Disorders OR Hydroxymethylglutaryl-CoA Reductase Inhibitors OR Anti-Inflammatory Agents, Non-Steroidal OR Solvents OR Pesticides OR Body Mass Index OR Family OR Risk OR Risk Factors AND Parkinson Disease. We restricted our analysis to articles written in English. Reference lists of suitable retrieved articles were hand searched for any missed references, as were the reference lists of existing relevant meta-analyses identified in the original search. The final search was carried out on March 31, 2011.

Inclusion Criteria

Published studies were included if they fulfilled the following criteria: (1) assessed at least 1 risk factor or early nonmotor symptom preceding a subsequent diagnosis of PD; (2) reported original data on relative risks (RRs) or odds ratios (ORs) from cohorts representative of the general population or case–control studies with cases defined as patients diagnosed with PD; and (3) reported data that could be easily obtained in a primary care environment, that is, those factors that could be determined through questionnaires or widely available blood tests.

Exclusion Criteria

We excluded review articles, editorials, commentaries, hypothesis papers, letters that reported no new data, meta-analyses, and abstracts. We excluded studies that (1) reported on treatment and management of PD, (2) considered associations with established PD (ie, not preceding PD), (3) reported factors not easily ascertainable in the primary care setting (eg, complicated questionnaires on food frequencies, life events, physical activity, environmental, solvent or toxin exposures), (4) studied young onset PD only, (5) did not use a control group or provide adequate details of the control group (including prevalence studies), (6) used blood relatives as the control group, (7) were twin studies, (8) were genetic studies or laboratory studies not used widely, (9) reported on the same risk factor in a common study population (where >1 paper reported on the same population, we chose the larger and, where equal, the most recent report), (10) reported on a disease other than PD, or (11) reported measures other than OR/RR or an equivalent (such as proportional mortality rate and standardized hospitalization rate) or from which an OR could not be calculated. If there was disagreement between authors (A.J.N., J.P.B., A.S.), the articles were discussed in further detail until an agreement was reached.

Data Extraction

Study characteristics, a risk estimate of the main study finding, and secondary findings were extracted for all eligible studies using a standardized template. Only factors for which a significant association was reported in at least 1 study were included. We included risk factors according to binary measurements (eg, yes vs no for having a first-degree relative with PD and ever versus never for alcohol). Data that reported exposures as quar-

tiles or quintiles where the lowest exposure quartile was equal to zero were converted to binary terms. We excluded associations reported with medical conditions, drugs or toxins known to cause symptomatic Parkinsonism such as antipsychotics or carbon monoxide poisoning. We did not include studies that reported associations with dementia occurring before onset of PD, as these cases would not fulfill current criteria for PD and might include cases of dementia with Lewy bodies.[24] For cases, we used figures for PD instead of Parkinsonism. In studies that reported data for both young onset and typical age of onset PD, we excluded the young onset data where possible. If case–control studies made comparison with >1 control group, the control group most representative of the healthy general population was used. If studies did not report OR, RR, or an equivalent measure, the raw data were reviewed to determine whether ORs could be calculated. In studies that reported both crude ORs and adjusted ORs, the adjusted figures were used. After application of the above methods, no additional studies required exclusion for quality reasons, according to Newcastle Ottawa Scale guidelines.[25] Length of time that any given factor preceded onset of PD was not included in the analysis due to inconsistent reporting of these data.

Statistical Analysis

Where a factor of interest was reported by 2 or more studies in a consistent manner, these were combined in a meta-analysis; first separately for case–control and cohort studies (given that cohort studies are less subject to bias), and second for all studies together (considering odds ratios from case–control studies to be estimates of relative risks) to generate a pooled effect size and 95% confidence interval (CI) for each factor. Heterogeneity between studies was assessed using the I^2 statistic and, where statistically significant heterogeneity was found ($p < 0.05$), the random effects model was used to combine results.[26,27] Publication bias was assessed using the Egger test, and where statistically significant bias was found, the trim and fill method was used to adjust for it.[28,29] Where data were not given in a way that could be used in the meta-analysis or where only 1 significant study was identified for a given risk factor, the findings of these studies are only listed in this review. All analyses were performed using Stata version 10 (StataCorp, College Station, TX).

Results

The literature search yielded 3,856 English language articles, of which 202 were eligible for inclusion in the systematic review and 173 of these in the meta-analysis (Fig 1). The reasons for exclusion of other studies are given. Full details of studies included in the meta-analysis are provided (Supplementary Tables 1 and 2). Twenty-nine articles that could not be included in the meta-analysis, primarily due to inconsistencies in method of measurement of the studied risk factor or because only 1
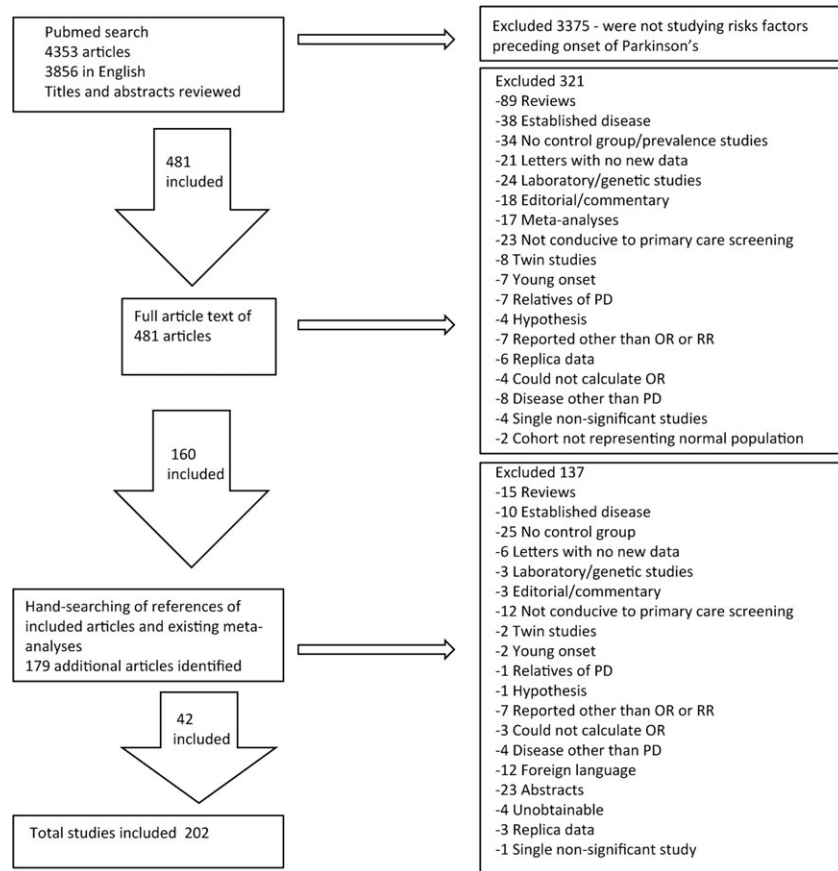
FIGURE 1: Flowchart of studies included and excluded. OR = odds ratio; PD = Parkinson disease; RR = relative risk.

study had reported a significant result on a given factor, are described and shown (Supplementary Table 3).

Summary results for positive and negative associations with PD found in the meta-analysis and those where no association was found are shown in Figures 2 to 4. Significant positive associations were found for family history of PD (including any relative and first-degree relatives only), family history of tremor, preceding constipation, prior mood disorder, exposure to pesticides (or herbicides or insecticides), previous head injury, rural living, beta-blocker use, farming/agricultural occupation, and well water drinking. Significant negative associations were found for smoking, coffee drinking, prior hypertension, use of NSAIDs, calcium channel blocker use, and alcohol consumption. No significant association was found for tea drinking; oral contraceptive pill use, preceding oophorectomy, or hormone replacement therapy; preceding diabetes mellitus, cancer, or gastric ulcer; use of statins, acetaminophen/paracetamol, or aspirin; and prior general anesthetic. In the systematic review, additional associations that were reported but could not be categorized consistently included negative associations with previously raised serum urate and conflicting results with serum cholesterol (total and various subtypes of se-

rum lipid), obesity, physical activity, any antihypertensive medication (without further subclassification), education, and various occupations. Single studies also reported negative associations with both parents having smoked and use of smokeless tobacco and positive associations with family history of any neurologic disease, hyposmia, erectile dysfunction, and excessive daytime sleepiness; complaints of stiffness, imbalance, or tremor; having a first-degree relative with melanoma; having brown, blond, and red hair versus black hair; a variety of infectious diseases; immediate-type hypersensitivity; anemia; duration of fertile life and cumulative length of pregnancies; having ≥3 children; having no children, and various occupations (see Supplementary Table 3).

Assessment of Publication Bias

According to the Egger test, there was evidence of publication bias for the factors ever smoking ($p = 0.017$), coffee drinking ($p = 0.002$), pesticides ($p < 0.001$), hormone replacement therapy ($p = 0.016$), statins ($p = 0.038$), any family history of PD ($p = 0.011$), family history of tremor ($p = 0.009$), and well water drinking ($p = 0.005$). Using the trim and fill method to account for the bias had no effect on the summary estimate for
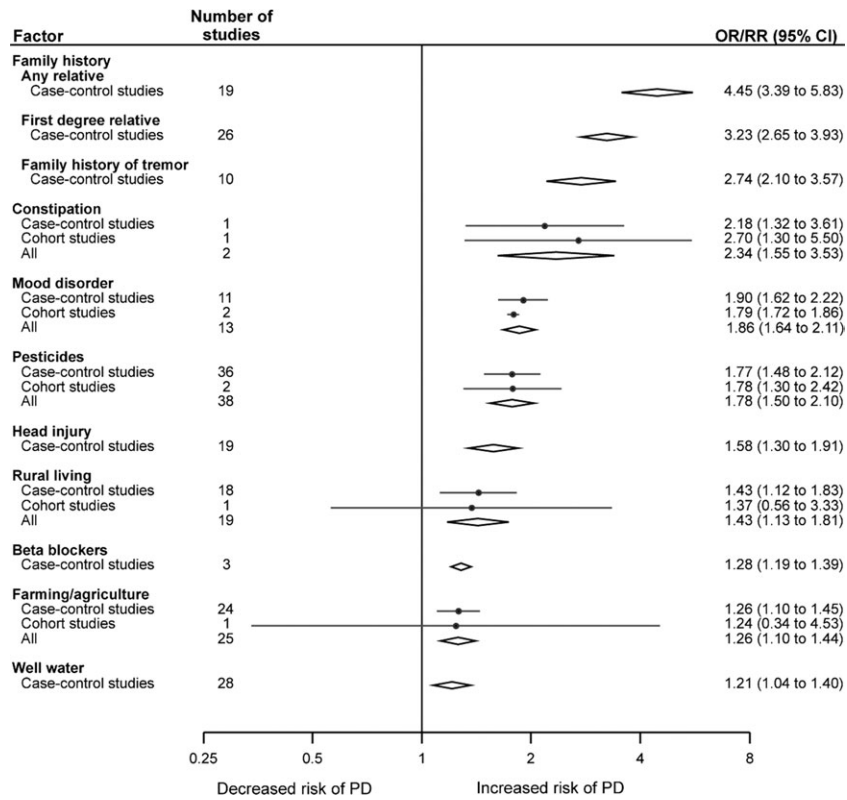
FIGURE 2: Factors included for meta-analysis that show a significant positive association with a later diagnosis of Parkinson disease (PD). CI = confidence interval; RR = relative risk; OR = odds ratio.
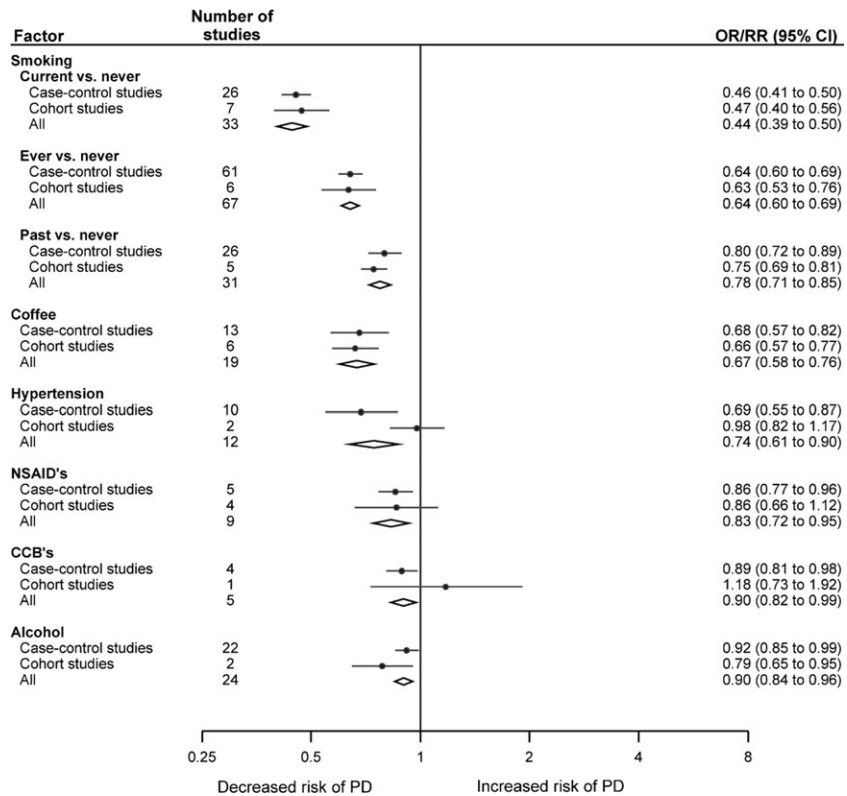

FIGURE 3: Factors included for meta-analysis that show a significant negative association with a later diagnosis of Parkinson disease (PD). CCB's = calcium channel blockers; CI = confidence interval; NSAID's = nonsteroidal anti-inflammatory drugs; PD = Parkinson disease; RR = relative risk; OR = odds ratio.
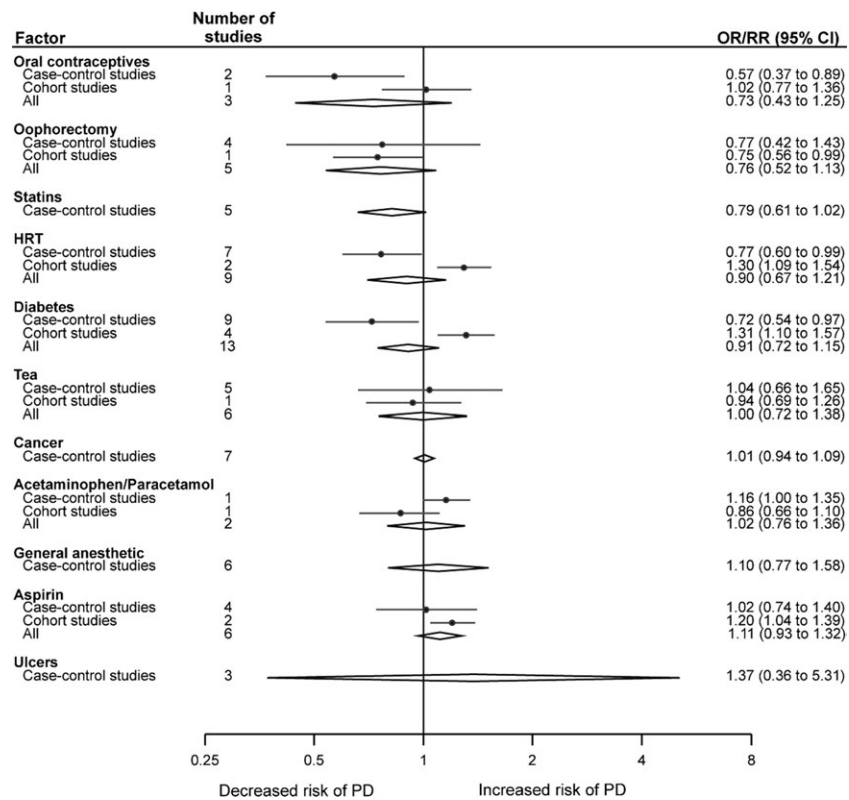
FIGURE 4: Factors included for meta-analysis that did not show a significant association with a later diagnosis of Parkinson disease. CI = confidence interval; HRT = hormone replacement therapy; RR = relative risk; OR = odds ratio.

ever smoking, coffee, hormone replacement therapy or statins, but did diminish the summary estimates for pesticides (RR from 1.78 to 1.53; 95% CI, 1.29–1.80), any family history of PD (OR from 4.45 to 3.25; 95% CI, 2.43–4.35), family history of tremor (OR from 2.74 to 2.51; 95% CI, 1.96–3.22), and well water drinking (OR from 1.21 to 1.20; 95% CI, 1.04–1.39); however, the conclusion that these are statistically significant risk factors for PD was not altered.

Discussion

This systematic review identified >40 individual risk factors of potential value for clinical screening. Identified factors include genetic and environmental risk factors, associated comorbidities, and medication exposures, as well as early nonmotor features that may represent the earliest stages of PD. Although some of these have possible pathogenic importance and others may represent early PD, they serve as markers that may help identify patients who are at high risk of a future diagnosis of PD. They also provide important information for the earlier diagnosis of PD, which is often delayed by several years.[30] Of the 30 factors that had data amenable to meta-analysis, 19 significantly altered risk of future PD and 11 did not reach significance. This information may

be used to provide the basis for primary care or population-based screening as well as improve our understanding of contribution of risk to subsequent PD for each of these factors.

Family History

Having a family member with PD was the strongest risk factor for later diagnosis of PD. Although a number of monogenic causes of PD have been identified, these account for only about 5% of PD. The excess risk in those with a family history of PD may be conveyed by multiple susceptibility loci.[31] Familial aggregation may also be explained by the effect of a shared environment, for example, concordance for not smoking and avoidance of coffee, which may influence the risk of PD, either independently or in conjunction with genetic susceptibility.

Lifestyle and Environmental Factors

A history of smoking reduces the risk of PD by about 36%, with coffee and alcohol (but not tea) consumption also reducing risk. For smoking, the effect is strongest in current smokers and weakest in past smokers (56% for current smokers and 22% for past smokers), but the association remains significant in all. The nature of this association is still poorly understood, and cannot be explained simply by selection bias and confounding.[32–36]

The risk reduction from ever versus never coffee use and ever versus never alcohol use is approximately 33% and 10%, respectively. A confounding effect of smoking, coffee, and alcohol use in combination has been noted, but other investigators suggest independence of these factors.[37,38]

Pesticide and environmental toxin exposure have been often implicated in PD causation.[13,18,19,39] Despite differences in populations studied and study design, we found an overall positive association with ever exposure to pesticides. Some suggest there may be a greater risk associated with length of exposure to pesticides, but we did not evaluate this in our analysis.[18,19] The finding that farming is also associated with subsequent PD may be in part due to increased likelihood of exposure to pesticides and other chemicals. Inconsistencies in adjustment between studies made it impossible to determine the importance of this interaction. Rural living and well water exposure were also significant positive associations. We did not include additional surrogates for pesticide or chemical exposures such as gardening, plantation work, and solvent exposures requiring more detailed exposure and lifestyle questionnaires. Other occupations that have been reported to change the risk of PD (but could not be classified consistently) included being a physician, clerk, carpenter, or cleaner or having a legal occupation (increase); production worker, driver, technician, transport/communication worker, mechanical/factory or metal worker, sales or service personnel, or engineer (reduced); or construction/extraction worker (conflicting results).

Head injury may carry increased risk of PD, particularly in those with repeated head injury and pugilist's encephalopathy.[40] In our meta-analysis, head injury with or without loss of consciousness had a significant but modest effect on the risk of subsequent diagnosis of PD.

Early Symptoms

This systematic review reaffirms the proposed early nonmotor symptoms, which may predate the diagnosis of PD by several years. Constipation and mood disorders appear to approximately double an individual's risk of subsequent PD in the meta-analysis. Both constipation and mood disorders have been suggested to correlate with brainstem involvement that, together with olfactory bulb involvement, occurs early in PD and later spreads to the substantia nigra and to the cortex.[41] This theory would also support a role for hyposmia, erectile dysfunction, and excessive daytime somnolence as early features of PD, all of which have been reported in single prospective cohort studies to be associated with significantly increased risk.[42–44] These were large, well-conducted

studies, and there is additional support for smell loss preceding PD in studies of first-degree relatives of persons with PD and idiopathic anosmia (see Hawkes[5]). However, these clinical syndromes are not routinely tested and are infrequently recorded; therefore, no case–control or further cohort studies fulfilling our criteria that allow meta-analysis are available at the present time. Rapid eye movement sleep behavior disorder (RBD) is also believed to precede PD by a number of years.[45,46] Currently, no observational studies that give ORs or RRs for this association have been reported. Further studies are required to replicate (for hyposmia, erectile dysfunction, and excessive daytime sleepiness) or delineate (for RBD) the magnitude of risk each of these conveys and to establish a comparable method of measurement for each. The association of a preceding tremor, imbalance, and stiffness with later PD (all reported in single studies) may point to early motor manifestations of the disease before a diagnosis can be made.[47,48]

Comorbidities and Medications

Hypertension was associated with reduced risk of PD, but the role of selective mortality in these individuals has not been studied. The combined analysis of studies of calcium channel blockers suggests a mild but significant overall reduction of PD risk. Beta blockers, on the other hand, were associated with increased PD risk. This could, however, potentially be explained by trials of beta blockers in those with seemingly isolated tremor. A history of diabetes mellitus did not significantly alter risk; however, further studies may be necessary, given that the case–control studies showed a statistically significant decrease in risk, whereas the cohort studies, showed a statistically significant increase in risk. Statins showed a trend of reduction in risk of subsequent PD in this meta-analysis, which may be due to a protective role through reduction of oxidative stress.[49] Hypercholesterolemia, obesity, and physical activity could not be included in the meta-analysis due to differences in assessment, and the systematic review found conflicting results.

NSAIDs are associated with risk reduction by approximately 17%. A similar finding has recently been published in a Cochrane review of NSAIDs preceding PD diagnosis.[50] There is increasing evidence that inflammation may play a role in the pathogenesis of PD, which may underlie this finding.[31,51,52] Aspirin and acetaminophen/paracetamol did not modify risk significantly. The suggestion that raised plasma urate might protect against PD may also be related to inflammatory mechanisms, because serum urate is a free radical scavenger and therefore protects against oxidative stress, which may contribute to dopaminergic neuronal loss.[53]

We did not find any association of subsequent PD with the oral contraceptive pill, surgical menopause, or hormone replacement therapy, although further studies on the latter are needed, given that case–control studies showed a statistically significant decrease in risk, whereas cohort studies showed a statistically significant increase in risk. There was no significant association of PD and preceding cancer. Although we did not include melanoma as a specific search term, a recent meta-analysis suggests a positive association of established PD with melanoma, but no association if melanoma precedes a diagnosis of PD.[54]

Helicobacter pylori infection has been suggested as a risk factor for PD in recent years, but there are no studies that specifically look at *H. pylori* and subsequent risk of PD. A surrogate marker for this could be gastric ulceration, but in our meta-analysis there was no association with prior gastric ulcer and subsequent PD diagnosis.

Factors Not Included in Analysis

Age and gender were not included in this review, as they are mainly reported in uncontrolled prevalence studies. Thus, although some of the studies included in the analysis reported risk associated with these variables, a combined risk estimate is unlikely to be representative of the full published literature on these factors. Nevertheless, the increased prevalence rate with increasing age and the higher prevalence in men are well recognized, and reporting is therefore usually stratified by age and gender.[2,55]

Limitations of the Analysis

We restricted our search to articles written in English, and therefore reports written in other languages are not included in the analysis. Due to the large number of studies used and the heterogeneity of methods and reported findings, we selected variables according to the main criterion that they can be screened for on a population basis. Therefore, risk factors and early symptoms not easily screened for would not have been included. Not all studies reported estimates of risk adjusted for confounders (eg, smoking). Where such adjustments have been made, we have included these data in the analysis.

Risk factors were dichotomized, which ignores dose effects. However, an essential feature of this analysis was to define factors that could be defined in binary terms, to allow them to be employed in combination for large-scale screening.

Statistically significant heterogeneity was found in the majority (24 of 30) of meta-analyses performed, similar to what has previously been reported.[56] In 16 of these there was moderate heterogeneity ($I^2 = 50–75\%$), and in 4 there was high heterogeneity ($I^2 > 75\%$). This is expected, because of the differences between individual studies in, for example, case ascertainment, study population characteristics, exposure measurement, and whether crude or adjusted risk estimates were reported. For this reason, the pooled estimates should be interpreted cautiously, in particular for those instances of high heterogeneity (hypertension, statin use, previous gastric ulceration, and rural living).

Conclusions

This is the first comprehensive systematic review and meta-analysis taking into account all risk factors for PD suitable for screening in primary care. This report allows comparative assessment of the evidence for, and magnitude of association for, the numerous proposed risk and early disease factors of PD, and helps to understand better their contribution to the risk of PD.

Authorship

A.J.N., J.P.B., L.S.M., and A.S. designed the study methods. A.J.N. and A.S. wrote the first draft of the manuscript. A.J.N., J.P.B., and A.S. reviewed the literature. J.P.B. undertook the statistical analysis. L.S.M., C.H.H., G.G., and A.J.L. contributed in discussions and reviewed and modified the manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity and accuracy of the data analysis.

Potential Conflicts of Interest

A.J.N.: National Institute of Health Research travel support, presentations at MDS Congresses; current grants, Parkinson's UK Innovation Grant and National Institute of Health Research Academic Clinical Fellowship. L.S.M.: Reta Lila Weston Trust, UNICAMP, Parkinsons's UK, Parkinson's Foundation; travel support, Britannia, UCB; honoraria, Britannia. C.H.H.: board membership, joint chief editor of *Multiple Sclerosis and Related Disorders*; speaking fees, Teva Lundbeck; royalties, Cambridge University Press. G.G.: consultancy fees, Merck-Serono, Biogen-Idec, Ironwood, Genentech, Teva, GSK, Sanofi-Aventis, Novartis, Roche, UCB Pharmaceuticals, Vertex, Eisai, Elan, Fiveprime, Bayer-Schering, Synthon BV, and Genyme; grants/grants pending from Biogen-Idec, Bayer-Schering, GW Pharma, Merck-Serono, Merz, Novartis,

References

1. de Lau LML, Giesbergen PCLM, de Rijk MC, et al. Incidence of parkinsonism and Parkinson disease in a general population: the Rotterdam Study. Neurology 2004;63:1240–1244.

2. Driver JA, Logroscino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. Neurology 2009;72:432–438.

3. Olanow CW, Tatton WG. Etiology and pathogenesis of Parkinson's disease. Annu Rev Neurosci 1999;22:123–144.

4. Gonera EG, van't Hof M, Berger HJ, et al. Symptoms and duration of the prodromal phase in Parkinson's disease. Mov Disord 1997; 12:871–876.

5. Hawkes CH. The prodromal phase of sporadic Parkinson's disease: does it exist and if so how long is it? Mov Disord 2008;23: 1799–1807.

6. Savica R, Rocca WA, Ahlskog JE. When does Parkinson disease start? Arch Neurol 2010;67:798–801.

7. Siderowf A, Stern MB. Premotor Parkinson's disease: clinical features, detection, and prospects for treatment. Ann Neurol 2008; 64(suppl 2):S139–S147.

8. Tolosa E, Gaig C, Santamaría J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. Neurology 2009;72(suppl 7): S12–S20.

9. Allam MF, Del Castillo AS, Navajas RF-C. Parkinson's disease, smoking and family history: meta-analysis. Eur J Neurol 2003;10: 59–62.

10. Allam MF, Campbell MJ, Del Castillo AS, Navajas RF-C. Parkinson's disease protects against smoking? Behav Neurol 2004;15:65–71.

11. Allam MF, Campbell MJ, Hofman A, et al. Smoking and Parkinson's disease: systematic review of prospective studies. Mov Disord 2004;19:614–621.

12. Bajaj A, Driver JA, Schernhammer ES. Parkinson's disease and cancer risk: a systematic review and meta-analysis. Cancer Causes Control 2010;21:697–707.

13. Brown TP, Rumsby PC, Capleton AC, et al. Pesticides and Parkinson's disease—is there a link? Environ Health Perspect 2006;114: 156–164.

14. Etminan M, Gill SS, Samii A. Intake of vitamin E, vitamin C, and carotenoids and the risk of Parkinson's disease: a meta-analysis. Lancet Neurol 2005;4:362–365.

15. Gagne JJ, Power MC. Anti-inflammatory drugs and risk of Parkinson disease: a meta-analysis. Neurology 2010;74:995–1002.

16. Hernán MA, Takkouche B, Caamano-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52:276–284.

17. Ishihara L, Brayne C. A systematic review of depression and mental illness preceding Parkinson's disease. Acta Neurol Scand 2006; 113:211–220.

18. Li AA, Mink PJ, McIntosh LJ, et al. Evaluation of epidemiologic and animal data associating pesticides with Parkinson's disease. J Occup Environ Med 2005;47:1059–1087.

19. Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. A meta-analysis of Parkinson's disease and exposure to pesticides. Neurotoxicology 2000;21:435–440.

20. Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental risk factors and Parkinson's disease: a meta-analysis. Environ Res 2001;86:122–127.

21. Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. Arch Neurol 2007;64:990–997.

22. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.

23. Green S, McDonald S. Cochrane Collaboration: more than systematic reviews? Intern Med J 2005;35:3–4.

24. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. Neurology 2005;65:1863–1872.

25. Wells G, Shea B, O'connell D. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, Canada: Ottawa Health Research Institute, 2003.

26. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–560.

27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.

28. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533–1537.

29. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–463.

30. O'Sullivan SS, Williams DR, Gallagher DA, et al. Nonmotor symptoms as presenting complaints in Parkinson's disease: a clinicopathological study. Mov Disord 2008;23:101–106.

31. International Parkinson Disease Genomics Consortium, Nalls MA, Plagnol V, Hernandez DG, et al. Imputation of sequence variants for identification of genetic risks for Parkinson's disease: a meta-analysis of genome-wide association studies. Lancet 2011;377:641–649.

32. Tanner CM, Goldman SM, Aston DA, et al. Smoking and Parkinson's disease in twins. Neurology 2002;58:581–588.

33. Wirdefeldt K, Gatz M, Pawitan Y, Pedersen NL. Risk and protective factors for Parkinson's disease: a study in Swedish twins. Ann Neurol 2005;57:27–33.

34. Quik M. Smoking, nicotine and Parkinson's disease. Trends Neurosci 2004;27:561–568.

35. Fratiglioni L, Wang HX. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res 2000;113:117–120.

36. Morens DM, Grandinetti A, Davis JW, et al. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic Parkinson disease. Am J Epidemiol 1996;144:400–404.

37. Ragonese P, Salemi G, Morgante L, et al. A case-control study on cigarette, alcohol, and coffee consumption preceding Parkinson's disease. Neuroepidemiology 2003;22:297–304.

38. Grandinetti A, Morens DM, Reed D, MacEachern D. Prospective study of cigarette smoking and the risk of developing idiopathic Parkinson's disease. Am J Epidemiol 1994;139:1129–1138.

39. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic Parkinsonism in humans due to a product of meperidine-analog synthesis. Science 1983;219:979–980.

40. Parker HL. Traumatic encephalopathy ('Punch Drunk') of professional pugilists. J Neurol Psychopathol 1934;15:20–28.

41. Braak H, Del Tredici K, Rüb U, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.

42. Ross GW, Petrovitch H, Abbott RD, et al. Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 2008;63:167–173.

43. Abbott RD, Ross GW, White LR, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology 2005;65:1442–1446.

44. Gao X, Chen H, Schwarzschild MA, et al. Erectile function and risk of Parkinson's disease. Am J Epidemiol 2007;166:1446–1450.

45. Postuma RB, Gagnon JF, Vendette M, et al. Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behavior disorder. Neurology 2009;72:1296–1300.

46. Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. Neurology 1996;46:388–393.

47. de Lau LML, Koudstaal PJ, Hofman A, Breteler MMB. Subjective complaints precede Parkinson disease: the Rotterdam study. Arch Neurol 2006;63:362–365.

48. Gao X, Chen H, Schwarzschild MA, et al. Perceived imbalance and risk of Parkinson's disease. Mov Disord 2008;23:613–616.

49. Becker C, Jick SS, Meier CR. Use of statins and the risk of Parkinson's disease: a retrospective case-control study in the UK. Drug Saf 2008;31:399–407.

50. Rees K, Stowe R, Patel S, et al. Non-steroidal anti-inflammatory drugs as disease-modifying agents for Parkinson's disease: evidence from observational studies. Cochrane Database Syst Rev 2011;(11):CD008454.

51. Hirsch EC, Hunot S. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol 2009;8:382–397.

52. Chen H, O'Reilly EJ, Schwarzschild MA, Ascherio A. Peripheral inflammatory biomarkers and risk of Parkinson's disease. Am J Epidemiol 2008;167:90–95.

53. Kutzing MK, Firestein BL. Altered uric acid levels and disease states. J Pharmacol Exp Ther 2008;324:1–7.

54. Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. Neurology 2011;76:2002–2009.

55. Wooten GF, Currie LJ, Bovbjerg VE, et al. Are men at greater risk for Parkinson's disease than women? J Neurol Neurosurg Psychiatry 2004;75:637–639.

56. van der Mark M, Brouwer M, Kromhout H, et al. Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. Environ Health Perspect 2012;120:340–347.