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Editor's Comment: Bellou and her colleagues have employed a systematic umbrella strategy review for evaluation of previously published meta-analyses and systematic reviews for the assessment of the environmental risk factors that could be potentially associated with Parkinson's disease. They describe and discuss several risk factors with potential associations. However, they also caution about many caveats in these studies that render these associations essentially unproven. They point out that more studies are needed to understand the association between environmental risk factors and Parkinson's disease.

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Review article

Environmental risk factors and Parkinson's disease: An umbrella review of meta-analyses

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ABSTRACT

Background: Parkinson's disease is a neurological disorder with complex pathogenesis implicating both environmental and genetic factors. We aimed to summarise the environmental risk factors that have been studied for potential association with Parkinson's disease, assess the presence of diverse biases, and identify the risk factors with the strongest support.

Methods: We searched PubMed from inception to September 18, 2015, to identify systematic reviews and meta-analyses of observational studies that examined associations between environmental factors and Parkinson's disease. For each meta-analysis we estimated the summary effect size by random-effects and fixed-effects models, the 95% confidence interval and the 95% prediction interval. We estimated the between-study heterogeneity expressed by I^2, evidence of small-study effects and evidence of excess significance bias.

Results: Overall, 75 unique meta-analyses on different risk factors for Parkinson's disease were examined, covering diverse biomarkers, dietary factors, drugs, medical history or comorbid diseases, exposure to toxic environmental agents and habits. 21 of 75 meta-analyses had results that were significant at $p < 0.001$ by random-effects. Evidence for an association was convincing (more than 1000 cases, $p < 10^{-6}$ by random-effects, not large heterogeneity, 95% prediction interval excluding the null value and absence of hints for small-study effects and excess significance bias) for constipation, and physical activity.

Conclusion: Many environmental factors have substantial evidence of association with Parkinson's disease, but several, perhaps most, of them may reflect reverse causation, residual confounding, information bias, sponsor conflicts or other caveats.

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; PD, Parkinson's disease; RR, risk ratio; SE, standard error; QUADAS, Quality assessment of diagnostic accuracy studies.

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease [1]. The prevalence of PD is rising steadily with age, reaching 1903 per 100,000 in those older than age 80 [2] and it is expected to impose an increasing social and economic burden on societies as population ages [1]. Approximately 630,000 people in the United States had been diagnosed with PD in 2010, with diagnosed prevalence likely to double by 2040 [3]. In the United States, the economic burden of PD exceeded $14.4 billion in 2010 (approximately $22,800 per patient) and it is projected to grow substantially over the next few decades [3].

PD risk is determined by the complex interplay and composite effects of both genetic and non-genetic risk factors [4]. Substantial progress has been made on deciphering genetic risk factors for PD [5,6]. To our knowledge, there is no previous attempt to summarize the evidence from existing meta-analyses on non-genetic risk factors for PD. We performed an umbrella review of the evidence across existing systematic reviews and meta-analyses of observational studies. Our aim is to provide an overview of the range and validity of the reported associations of diverse environmental risk factors with PD by evaluating whether there is evidence for biases in this literature. Finally we pinpoint which of the previously studied associations that have been synthesized in meta-analyses have the strongest evidence for association.

2. Methods

2.1. The concept of umbrella review

We conducted an umbrella review, a systematic collection and evaluation of multiple systematic reviews and meta-analyses performed on a specific research topic [7]. An umbrella review synthesizes the large number of existing systematic reviews and meta-analyses on risk factors rather than performing these systematic reviews from scratch. The methods of the umbrella review are standardized and follow the same principles as a previous umbrella review on risk factors for multiple sclerosis [8].

2.2. Search strategy and eligibility criteria

We systematically searched PubMed from inception to September 18, 2015 to identify systematic reviews and meta-analyses of observational studies examining associations of environmental (non-genetic) factors and biomarkers with PD. The search strategy used the keywords Parkinson* AND ("systematic review" OR meta-analysis). The full text of potentially eligible articles was scrutinized independently by two investigators (VB, LB). We excluded meta-analyses that investigated the association between genetic markers and risk for PD as these factors have been examined elsewhere [5,6]. We did not apply any language restrictions. When more than one meta-analyses on the same research question was eligible, the meta-analysis with the largest number of component studies with data on individual studies' effect sizes was retained for the main analyses.

2.3. Data extraction

Data extraction was performed independently by two investigators (VB, LB), and in case of discrepancies the final decision was that of a third investigator (EE). From each eligible article, we recorded the first author, journal, year of publication, the examined risk factors and the number of studies considered. If a quantitative synthesis was done, we also extracted the study-specific relative risk estimates (standardized mean difference, risk ratio, odds ratio, hazard ratio) along with the corresponding CI and the number of cases and controls in each study for each risk factor. Furthermore, we recorded the study design of individual studies. We noted whether the published meta-analyses applied any criteria to evaluate the quality of the included observational studies; when such an appraisal was performed, we extracted the information on this qualitative assessment. Whenever the studies used several control groups, we extracted the data considering the healthy controls as control group.

2.4. Statistical analysis

For each meta-analysis, we estimated the summary effect size and its 95% CI using both fixed-effects and random-effects models [9,10]. We also estimated the 95% prediction interval, which further accounts for between-study heterogeneity and evaluates the uncertainty for the effect that would be expected in a new study addressing that same association [11,12]. For the largest study of each meta-analysis, we estimated the SE of the effect size and we examined whether the SE was less than 0.10. In a study with SE of less than 0.10, the difference between the effect estimate and the upper or lower 95% confidence interval is less than 0.20 (i.e. this uncertainty is less than what is considered a small effect size).

In case of meta-analyses with continuous data, the effect estimate was transformed to an odds ratio with an established formula [13]. We transformed a standardized mean difference to odds ratio by multiplying the standardized mean difference by $\pi/\sqrt{3}$. Between-study heterogeneity was assessed via the I^2 metric [14]. I^2 ranges between 0% and 100% and is the ratio of between-study variance over the sum of the within- and between-study variances [15]. Values exceeding 50% or 75% are usually considered to represent large or very large heterogeneity, respectively.

We evaluated whether there was evidence for small-study effects (i.e. whether smaller studies tend to give substantially larger estimates of effect size compared to larger studies) [16] using the regression asymmetry test proposed by Egger and colleagues [17]. A p value less than 0.10 with more conservative effect in larger studies was judged to be evidence for small-study effects.

We applied the excess statistical significance test, which evaluates whether the observed (O) number of studies with nominally significant results ("positive" studies, $p < 0.05$) is larger than their expected (E) number [18]. E is calculated in each meta-analysis by the sum of the statistical power estimates for each component study. The true effect size for any meta-analysis is not known. We estimated the power of each component study using the effect size of the largest study (smallest SE) in a meta-analysis [19]. The power of each study was calculated using a non-central *t* distribution [20]. Excess statistical significance for single meta-analyses was claimed at two-sided $p < 0.10$ with $O > E$ as previously proposed [18].

For the meta-analyses on pesticides and well-water drinking, we used data from older meta-analyses [21,22], because the largest one did not adequately report the data needed to perform our analyses [23]. For the meta-analysis on diabetes mellitus, we extracted data from two different papers [24,25]. The more recently published paper [25] reported data only from case-control studies and the older one [24] included case-control and cohort studies, from which we kept cohort studies only and synthesized them with case-control studies from the recent paper [25].

Finally, we identified putative risk factors that had the strongest statistical support for association [26,27] and no signals of large heterogeneity or bias. Specifically, we used the following categories: Convincing evidence (Class I) required >1000 cases, highly significant summary associations ($p < 10^{-6}$ by random-effects), no evidence of small-study effects, no evidence of excess significance