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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

bias, 95% prediction interval not including the null and not large heterogeneity (I^2 < 50%). Highly suggestive evidence (Class II) required >1000 cases, highly significant summary associations ($p < 10^{-6}$ by random-effects) and largest study with 95% CI excluding the null value. Suggestive evidence (Class III) required only >1000 cases and $p < 0.001$ by random-effects. All other risk factors with nominally significant summary associations ($p < 0.05$) were coined as having weak evidence (Class IV). Non-significant associations were those with $p > 0.05$.

Even when a risk factor has Class I or II evidence for association, this still does not prove causation. Therefore, for the factors with Class I or II evidence for association, we assessed the study design of component studies and we performed an additional random-effects meta-analysis based only on prospective cohort studies. In the Discussion, we systematically explored all putative risk factors with Class I or II evidence for association in terms of alternative explanations besides a causal relationship (reverse causation, residual confounding, information bias, sponsor conflicts or other caveats).

The statistical analysis and the power calculations were done with STATA version 12.0.

3. Results

Overall, 979 articles were searched and 38 articles were eligible (Fig. 1). The eligible papers were published between 2005 and 2015 (median, 2013; IQR, 2012-2014). 21 articles were excluded in full text screening, because a larger meta-analysis was available. The aforementioned 21 articles examined smoking (n = 9) [28–36], pesticides (n = 5) [37–41], physical activity (n = 2) [42,43], coffee (n = 3) [34,44,45], farming (n = 1) [38], aspirin (n = 1) [46], bone mineral density (n = 1) [47], fat intake (n = 1) [48], ibuprofen (n = 1) [46], tea (n = 1) [44], and well water drinking (n = 1) [38]. One article [49] on body mass index was excluded due to inadequate data reporting.

The 38 articles corresponded to 75 unique meta-analyses, including 755 primary observational studies as a whole. The median number of studies per meta-analysis was 7 (IQR 5-10) and the median number of cases was 1418 (IQR 707-5263). The 75 meta-analyses covered a wide range of risk factors categorized as biomarkers, dietary factors, drugs, exposure to toxic environmental agents, habits and medical history or comorbid diseases. The number of cases was greater than 1000 in 47 meta-analyses

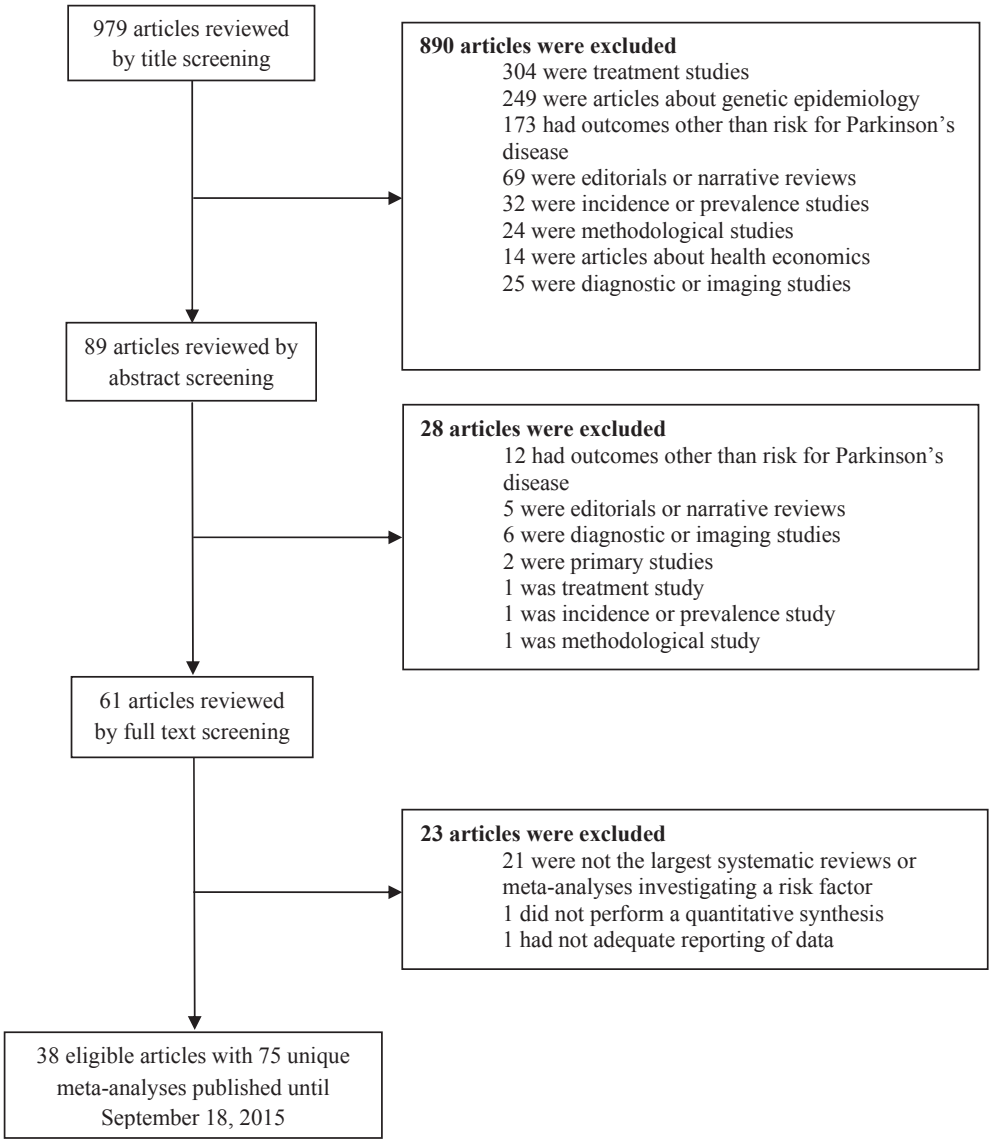

Fig. 1. Flow chart of literature search for systematic reviews and meta-analyses published from inception until September 18, 2015.

Table 1
Characteristics and quantitative synthesis of the 75 eligible meta-analyses of environmental risk factors for Parkinson's disease.

Reference	Risk factor	Number of cases	Number of primary studies	Effect size	Random-effects summary effect size (95% CI)	P random	95% PI	I^2	Small-study effects/Excess statistical significance	Class of association
Habits										
Zhang, 2014 [79]	Alcohol intake	9994	33	RR	0.75 (0.66–0.85)	5.0×10^{-6}	0.44–1.25	52.3	Yes/Yes	III
Noyce, 2012 [22]	Coffee drinking	5801	19	RR	0.67 (0.58–0.76)	3.4×10^{-9}	0.45–1.00	42.9	Yes/Yes	III
Noyce, 2012 [22]	Smoking	19,537	67	RR	0.64 (0.60–0.69)	1.3×10^{-37}	0.45–0.92	49.6	Yes/Yes	II
Shen, 2015 [80]	Outdoor work	4266	2	OR	0.72 (0.64–0.82)	5.3×10^{-7}	NE[a]	0	NE[a]/No	NS
Li, 2012 [81]	Tea drinking	1418	8	OR	0.86 (0.68–1.08)	0.197	0.45–1.62	53	No/No	NS
Yang, 2015 [52]	Physical activity	1348	5	HR	0.66 (0.57–0.78)	3.0×10^{-7}	0.55–0.80	0	No/No	I
Exposure to toxic environmental agents										
Huss, 2015 [82]	Extremely low frequency magnetic fields	43,096	11	OR	1.05 (0.98–1.13)	0.135	0.89–1.25	46.4	No/No	NS
Mortimer, 2012 [83]	Manganese exposure	1278	3	RR	0.76 (0.41–1.42)	0.392	0.001–661	62	No/No	NS
Mortimer, 2012 [83]	Welding	8198	9	RR	0.86 (0.80–0.92)	3.0×10^{-5}	0.79–0.94	0	No/No	III
Palin, 2015 [84]	Hydrocarbon exposure	4483	14	OR	1.36 (1.13–1.63)	0.001	0.88–2.08	28.1	Yes/Yes	IV
Pezzoli, 2013 [23]	Farming	9533	38	OR	1.30 (1.16–1.46)	5.7×10^{-6}	0.86–1.98	37.3	No/No	III
Pezzoli, 2013 [23]	Organic solvents	3811	18	OR	1.22 (1.01–1.47)	0.036	0.72–2.08	43.6	Yes/Yes	IV
van der Mark, 2012 [21]	Pesticides	7151	39	OR	1.62 (1.40–1.88)	1.1×10^{-10}	0.81–3.23	63.7	Yes/Yes	III
Pezzoli, 2013 [23]	Rural living	4306	31	OR	1.32 (1.18–1.48)	1.7×10^{-6}	0.84–2.10	78.6	Yes/Yes	III
Noyce, 2012 [22]	Well water drinking	5037	28	RR	1.21 (1.05–1.40)	0.011	0.66–2.21	70.6	No/Yes	IV
Dietary factors										
Etminan, 2005 [85]	Vitamin C intake	1247	7	OR	1.06 (0.86–1.30)	0.602	0.64–1.74	38.1	No/No	NS
Etminan, 2005 [85]	Vitamin E intake	936	7	OR	0.81 (0.67–0.98)	0.028	0.63–1.04	0	No/No	IV
Jiang, 2014 [86]	Dairy products intake	1083	7	RR	1.40 (1.20–1.63)	2.4×10^{-5}	1.08–1.81	8.2	No/No	III
Shen, 2015 [80]	Vitamin D supplementation	458	2	OR	0.67 (0.44–1.00)	0.052	NE[a]	0	NE[a]/Yes	NS
Shen, 2015 [87]	Folate intake	736	3	OR	1.06 (0.78–1.45)	0.714	0.14–7.97	0	No/No	NS
Shen, 2015 [87]	Vitamin B_{12} intake	736	3	OR	1.07 (0.82–1.40)	0.621	0.19–6.19	0	No/No	NS
Shen, 2015 [87]	Vitamin B_6 intake	736	3	OR	0.65 (0.37–1.16)	0.147	0.001–383	64.5	Yes/Yes	NS
Takeda, 2014 [88]	Lutein intake	804	4	OR	1.49 (0.83–2.68)	0.179	0.12–18.65	77.8	Yes/No	NS
Takeda, 2014 [88]	Lycopene intake	678	3	OR	1.03 (0.64–1.65)	0.896	0.01–174	62.3	No/No	NS
Takeda, 2014 [88]	Vitamin A intake	624	3	OR	1.09 (0.84–1.42)	0.520	0.20–5.96	0	No/No	NS
Takeda, 2014 [88]	α-Carotene intake	677	3	OR	0.84 (0.59–1.18)	0.313	0.04–16.60	22.9	No/No	NS
Takeda, 2014 [88]	β-Carotene intake	1395	6	OR	0.92 (0.70–1.20)	0.521	0.46–1.81	37.5	No/No	NS
Takeda, 2014 [88]	β-Cryptoxanthin intake	677	3	OR	0.96 (0.66–1.40)	0.834	0.02–39.43	42.1	No/No	NS
Wang, 2014 [89]	Carbohydrate intake	1482	8	RR	1.24 (1.05–1.48)	0.014	1.00–1.54	0	No/No	IV
Wang, 2014 [89]	Cholesterol intake	1293	7	RR	0.97 (0.75–1.26)	0.833	0.46–2.07	62.4	No/No	NS
Wang, 2014 [89]	Energy intake	1415	8	RR	1.39 (1.01–1.92)	0.042	0.50–3.90	83.8	Yes/Yes	IV
Wang, 2014 [89]	Protein intake	1570	7	RR	1.13 (0.88–1.44)	0.339	0.65–1.97	30.4	No/No	NS
Wang, 2014 [89]	Total fat intake	2516	13	RR	0.88 (0.74–1.06)	0.182	0.56–1.40	34.4	No/No	NS
Medical history and comorbid diseases										
Adams-Carr, 2015 [51]	Constipation	11,242	9	RR	2.30 (2.02–2.63)	3.5×10^{-35}	1.76–2.96	18.1	No/No	I
Cereda, 2011 [24] and Lu, 2014 [25]	Diabetes mellitus	10,743	6	OR	1.13 (0.73–1.76)	0.591	0.42–3.03	78.1	No/No	NS
Jafari, 2013 [53]	Head injury	35,799	22	OR	1.55 (1.33–1.81)	2.2×10^{-8}	0.93–2.58	61	No/No	II
Liu, 2011 [90]	Melanoma	10,743	6	OR	1.13 (0.73–1.76)	0.591	0.42–3.03	24.1	No/No	NS
Noyce, 2012 [22]	Anxiety or depression	16,211	13	RR	1.86 (1.64–2.10)	2.6×10^{-22}	1.30–2.66	67.7	No/No	II
Noyce, 2012 [22]	Cancer	9693	7	RR	0.89 (0.72–1.10)	0.265	0.51–1.53	50.4	No/No	NS
Noyce, 2012 [22]	Gastric ulcer	406	3	RR	1.37 (0.36–5.31)	0.646	10^{-7}–10^{7}	81	No/No	NS
Noyce, 2012 [22]	Hypertension	5993	12	RR	0.75 (0.61–0.90)	0.003	0.40–1.40	76.4	No/Yes	IV
Noyce, 2012 [22]	Oophorectomy	775	5	RR	0.77 (0.52–1.13)	0.180	0.23–2.60	58.8	No/No	NS
Ungprasert, 2015 [68]	Gout	235,301	5	RR	0.93 (0.79–1.09)	0.364	0.51–1.67	87.4	No/No	NS
Drugs										
Gagne, 2010 [91]	Aspirin	2781	6	RR	1.08 (0.93–1.27)	0.315	0.71–1.66	50.3	No/No	NS
Gagne, 2010 [91]	Non-aspirin NSAIDs	3967	7	RR	0.85 (0.77–0.94)	0.002	0.74–0.97	0.1	Yes/No	IV
Gao, 2011 [92]	Acetaminophen	2086	4	RR	1.09 (0.96–1.24)	0.192	0.82–1.45	0	No/No	NS
Gao, 2011 [92]	Ibuprofen use	2170	5	RR	0.73 (0.62–0.85)	6.6×10^{-5}	0.57–0.94	0	No/No	III
Noyce, 2012 [22]	Beta-blockers	5774	3	RR	1.28 (1.19–1.39)	5.0×10^{-10}	0.77–2.13	0	No/No	II
Lang, 2015 [93]	Calcium channel blockers	6966	5	RR	0.78 (0.67–0.90)	7.0×10^{-4}	0.55–1.11	25.7	No/No	III
Noyce, 2012 [22]	General anesthesia	1571	6	RR	1.10 (0.77–1.58)	0.601	0.35–3.51	74.2	No/No	NS
Noyce, 2012 [22]	Oral contraceptives	572	3	RR	0.73 (0.43–1.25)	0.250	0.002–346	71.1	No/Yes	NS
Undela, 2013 [94]	Statins	15,102	8	RR	0.77 (0.64–0.92)	0.004	0.47–1.27	62.9	Yes/No	IV
Wang, 2014 [95]	Hormone replacement therapy	4035	14	RR	1.00 (0.84–1.20)	0.967	0.61–1.64	50.4	No/No	NS
Biomarkers										
Chen, 2014 [96]	BMI (BMI $\geq$ 30 vs. BMI < 25)	1668	7	OR	0.96 (0.61–1.50)	0.854	0.20–4.62	90.6	No/No	NS
Chen, 2014 [96]	BMI (BMI $\geq$ 30 vs. 25 $\leq$ BMI < 30)	1618	7	OR	0.83 (0.65–1.07)	0.157	0.37–1.85	71.5	No/No	NS

Table 1 (*continued*)

Reference	Risk factor	Number of cases	Number of primary studies	Effect size	Random-effects summary effect size (95% CI)	P random	95% PI	I^2	Small-study effects/Excess statistical significance	Class of association
Chen, 2014 [96]	BMI (25 ≤ BMI < 30 vs. BMI < 25)	2428	7	OR	1.20 (0.94–1.53)	0.148	0.53–2.69	85.2	No/No	NS
Gao, 2015 [50]	α-Synuclein in CSF	850	11	OR	0.29 (0.13–0.62)	0.002	0.02–5.19	91.7	No/Yes	IV
Gudala, 2013 [97]	Serum cholesterol	5488	8	RR	0.91 (0.71–1.15)	0.418	0.44–1.86	70.3	No/No	NS
Lv, 2014 [98]	Serum vitamin D	1008	7	OR	0.16 (0.05–0.50)	0.002	0.003–10.09	97.7	Yes/Yes	IV
Mariani, 2013 [99]	Copper in plasma	202	4	OR	1.41 (0.03–59.27)	0.856	10^{-8}–10^{8}	98.7	No/No	NS
Mariani, 2013 [99]	Copper in CSF	215	5	OR	2.06 (0.57–7.44)	0.271	0.02–207	83.8	No/Yes	NS
Mariani, 2013 [99]	Serum copper	425	9	OR	1.46 (0.46–4.63)	0.519	0.02–94.65	92.6	No/Yes	NS
Mariani, 2013 [99]	Iron in CSF	215	5	OR	0.93 (0.35–2.45)	0.887	0.03–30.86	79.8	No/No	NS
Mariani, 2013 [99]	Serum iron	520	10	OR	0.45 (0.17–1.17)	0.102	0.01–16.71	93.6	No/No	NS
Sako, 2014 [100]	Nigral volume	193	8	OR	0.31 (0.17–0.55)	8.3×10^{-5}	0.06–1.46	47.4	No/No	IV
Shen, 2013 [101]	Serum urate	594	6	RR	0.65 (0.43–0.97)	0.034	0.23–1.82	42.1	No/No	IV
Shen, 2013 [54]	Serum uric acid	1217	6	OR	0.39 (0.27–0.57)	6.8×10^{-7}	0.13–1.22	75.9	No/No	II
Shen, 2015 [87]	Serum folate	735	10	OR	0.81 (0.61–1.08)	0.150	0.36–1.79	49.8	No/Yes	NS
Shen, 2015 [87]	Serum vitamin B_{12}	735	10	OR	0.50 (0.40–0.63)	4.7×10^{-9}	0.31–0.82	23.8	No/Yes	IV
Wang, 2015 [102]	BMI (per 5 kg/m^2 increase)	2706	10	RR	1.00 (0.89–1.12)	0.974	0.71–1.40	64.5	No/Yes	NS
Yu, 2014 [103]	RNFLT	644	13	OR	0.40 (0.24–0.66)	3.5×10^{-4}	0.06–2.55	81	No/Yes	IV
Zhao, 2013 [104]	BMD in femoral neck	561	8	OR	0.25 (0.09–0.66)	0.005	0.01–8.76	95.6	No/No	IV
Zhao, 2013 [104]	BMD in hip	401	6	OR	0.55 (0.38–0.80)	0.002	0.18–1.66	61.8	No/Yes	IV
Zhao, 2013 [104]	BMD in lumbar spine	611	9	OR	0.29 (0.16–0.54)	7.8×10^{-5}	0.03–2.60	89	No/Yes	IV
Zhao, 2013 [104]	BMD in trochanter	249	4	OR	0.73 (0.48–1.11)	0.146	0.16–3.34	45.6	No/No	NS

For biomarkers, the level of comparison is high values versus low values. For dietary factors, alcohol intake, coffee drinking and tea drinking the level of comparison is high intake versus low intake. For smoking, the level of comparison is ever versus never smokers. For physical activity, the level of comparison is high level versus low level. For the remaining risk factors the level of comparison is exposed versus not exposed.

BMD: bone mineral density, BMI: body mass index, CI: confidence interval, CSF: cerebrospinal fluid, HR: hazard ratio, NSAIDs: non-steroidal anti-inflammatory drugs, NE: not estimable because less than three studies were available, NS: non-significant at p = 0.05, OR: odds ratio, PI: prediction interval, RR: risk ratio, RNFLT: retinal nerve fiber layer thickness.

[a] For two meta-analyses, pertaining to outdoor work [80] and vitamin D supplementation [80], we were not able to assess small-study effects and to estimate the 95% prediction interval, because only two observational studies were available for each meta-analysis.

(Table 1, Supplementary Table 1). All eligible meta-analyses used summary-level data from published literature and none of them had access to individual participant data.

Fifteen articles used the Newcastle–Ottawa Scale to qualitatively assess the included primary studies. Details are presented in Supplementary Table 2. Another article [24] assessed the potential existence of bias in the case ascertainment and the selection bias. An additional article [50] used the QUADAS-2 for this assessment. Taking into account the methodological assessment of the observational studies performed by the eligible papers, almost half of the primary studies presented low methodological quality and were of high risk for bias, according to the Newcastle–Ottawa Scale.

35 (47%) of 75 meta-analyses reported effects that were significant at p values less than 0.05 under the random-effects model (Table 1, Supplementary Table 1). 21 (24%) were significant at p values less than 0.001 under the random-effects model: physical activity, ibuprofen, head injury, dairy products intake, welding, anxiety or depression, beta-blockers, coffee drinking, constipation, smoking, pesticides, nigral volume, serum uric acid, serum vitamin B_{12}, outdoor work, retinal nerve fiber layer thickness, calcium channel blockers, rural living, farming, alcohol drinking and bone mineral density in lumbar spine. In nine of these associations (constipation, dairy products intake, welding, anxiety or depression, coffee drinking, smoking, serum vitamin B_{12}, physical activity and ibuprofen) the 95% prediction interval rule for random-effects model did not include the null value. The remaining meta-analyses of risk factors had 95% prediction intervals that included the null value, showing that, although on average these putative risk factors are associated with PD, this might not always be the case in specific settings (Table 1, Supplementary Table 1).

The results of the largest study were more conservative than the summary result in 37 (49%) meta-analyses (Supplementary Table 3). However, the largest study was typically not very large or substantially different in weight from other studies. In 25 meta-analyses, the SE of the largest study was less than 0.10 in a log OR scale (Supplementary Table 3).

17 (23%) meta-analyses had large heterogeneity estimates ($I^2 \geq 50\%$ and $I^2 \leq 75\%$) and 16 (21%) meta-analyses had very large heterogeneity estimates ($I^2 > 75\%$) (Table 1, Supplementary Table 3). Evidence for small-study effects was noted in 13 (17%) meta-analyses (Table 1, Supplementary Table 3). These meta-analyses pertained to alcohol intake, coffee drinking, energy intake, exposure to hydrocarbons, serum vitamin D, lutein intake, non-aspirin NSAIDs, organic solvents, pesticides, rural living, vitamin B_6 intake, statins, and smoking. Assuming that the effect size in the largest study was the true effect, 23 (31%) of the 75 meta-analyses had a significant difference between the number of observed and expected positive studies (Supplementary Table 3).

Of the 75 meta-analyses, 11 (15%) presented a significant association at $p < 10^{-6}$ under random-effects model (Table 1, Supplementary Table 1). Two risk factors, pertaining to constipation [51] and physical activity [52], presented Class I evidence for association (>1000 cases, $p < 10^{-6}$, no evidence of small-study effects, no evidence of excess significance bias, 95% prediction interval not including the null and not large heterogeneity). Five risk factors, which include anxiety or depression [22], beta-blockers [22], head injury [53], serum uric acid [54], and smoking [22], presented Class II evidence for association (>1000 cases, $p < 10^{-6}$ and largest study 95% CI excluding the null). However, these five risk factors had either large or very large heterogeneity (n = 3), or 95% prediction interval including the null value (n = 3), or hints for small-study effects (n = 1) and/or excess significance bias (n = 3). An overall summary assessment of the strength of the evidence for association of putative risk factors with PD is presented in Supplementary Table 4.

Three of the seven associations (beta-blockers, head injury, serum uric acid) with Class I or II evidence did not have any

prospective cohort studies. The remaining four associations (constipation, physical activity, anxiety or depression, and smoking) remained significant at $p < 10^{-6}$ in the meta-analysis of prospective cohort studies (Table 2). For constipation and physical activity the heterogeneity was not large and the 95% prediction interval did not include the null value, while for smoking the heterogeneity was large and the 95% prediction interval included the null value. For the association of anxiety or depression, the 95% prediction interval could not be estimated, because only two prospective cohort studies were available.

4. Discussion

We provide an overview and appraisal of environmental risk factors that have been associated with PD. Overall, 75 risk factors have been studied for an association with the disease, including biomarkers, dietary factors, drugs, exposure to toxic environmental agents, habits and medical history or comorbid diseases. Two factors (constipation, physical activity) presented Class I evidence for an association with PD. Several other putative risk factors (head injury, anxiety or depression, beta-blockers, smoking, serum uric acid) had very low p-values ($<10^{-6}$) and an effect was also seen in the largest study, but there was either large between-study heterogeneity and/or large uncertainty in the 95% prediction interval and/or signals of bias.

The majority of the examined meta-analyses had large or very heterogeneity and some had signals of small-study effects or/and excess significance. The applied Egger test may give spurious signal of small-study effects when there is genuine large between-study heterogeneity [16,55]. Heterogeneity might often be a manifestation of bias in some studies of a meta-analysis, but could also emerge from genuine differences across studies. Reasons for heterogeneity include the mixture of cohort studies and case-control studies in some of the meta-analyses, differences in exposure assessment, frequency of exposed in control groups, types of exposure and source of controls and differential response rates among cases and controls in the primary studies. The reported associations with disease need to be interpreted with caution, in particular for the meta-analyses in which the heterogeneity is large, the number of studies is relatively small, the largest study is more conservative than the summary effect and small-study effects are evident.

Two associations presented Class I evidence, physical activity and constipation. Evidence from 5 prospective cohort studies supported a protective effect of physical activity for PD. Physical exercise has been suggested to increase plasma uric acid levels, which in turn have been associated with lower risk for PD [52]. However, an element of reverse causation cannot be totally excluded, since patients with pre-diagnosis of PD may exercise less because of the neurological dysfunction [56,57]. Furthermore, constipation presented a positive association with PD supported by Class I evidence with an impressively low p value (3.5×10^{-35}) [51]. The association was significant with a similar effect size in the meta-analysis of prospective cohort studies. Constipation could be an early premorbid manifestation of PD. Indeed, this reverse causation has biological plausibility and evidence from laboratory studies indicated the existence of abnormal deposits of α-synuclein within the submucosal and myenteric plexuses of the enteric nervous system [58,59]. Constipation as a symptom of dysautonomia could precede motor symptoms of PD by at least 10 and perhaps more than 20 years [60].

Among other putative risk factors, highly significant associations were seen for increased risk with head injury, anxiety or depression, and beta-blockers, and for decreased risk with smoking and uric acid levels. In all of these factors, the largest study also showed a significant association. For smoking, the level of statistical significance for the association was extremely impressive (1.3×10^{-37}), but there were strong signals for small-study effects and for excess significance. This suggests that the literature on this risk factor is probably subjected to selective reporting and other biases and the summary effects may be exaggerated. A small protective effect for smoking is nevertheless likely to exist. However, it has also been argued that much, if not all, of the association effect with smoking may be explained by various biases [61], rather than the neuroprotective role of nicotine [62]. In the meta-analysis of prospective cohort studies, although the effect remained significant, the heterogeneity was large and the 95% prediction interval included the null value. First, there may be lack of information regarding PD diagnoses in the death certificates and medical records of smokers (information bias). Second, there may be selective mortality of smokers from causes other than PD, constituting a form of selection bias due to competing risk. If smokers die earlier than non-smokers from causes unrelated to PD, smokers may be under-represented among prevalent PD patients. Third, individuals with PD may be less prone to smoke or more prone to quit (reverse causation) [61,63]. Last, smoking and PD may share common covariates (confounding) not accounted for in the primary studies. For example, genetic factors may be associated with both an increased risk of PD and a higher likelihood of abstaining from smoking [61].

Head trauma appeared to have a positive association with PD. The association may have been affected by recall bias in retrospective studies, ascertainment bias from heterogeneous measures in diagnosis of PD and definition of exposure, variable duration of follow-up and time between head injury and diagnosis of PD, and reverse causality with head injury resulting from imbalance before PD is formally diagnosed [64,65].

The association between anxiety or depression and risk for PD remained significant with a similar effect in the subgroup of prospective cohort studies. However, only 2 prospective cohort studies were available. Depression is probably best seen as a prodromal symptom of PD rather than a risk factor, because an early stage of PD is characterized by loss of serotoninergic neuronal cells in the dorsal raphe nucleus [60,66].

Serum uric acid presented Class II evidence for an association with PD and it is thought to be a predictor of clinical progression of

Table 2
Quantitative synthesis of the prospective cohort studies for the 4 associations with convincing (Class I) or highly suggestive (Class II) evidence.

References	Risk factors	Number of cases	Number of primary studies	Effect sizes	Random-effects summary effect size (95% CI)	P random	95% PI	I^2	Class of association
Adams-Carr, 2015 [51]	Constipation	2625	4	RR	2.36 (2.00–2.80)	1.4×10^{-23}	1.63–3.42	0	I
Yang, 2015 [52]	Physical activity	1348	5	HR	0.66 (0.57–0.78)	3.0×10^{-7}	0.55–0.80	0	I
Noyce, 2012 [22]	Anxiety or depression	11,687	2	RR	1.79 (1.72–1.86)	8.2×10^{-188}	NE[a]	0	II
Noyce, 2012 [22]	Smoking	2623	6	RR	0.64 (0.53–0.76)	3.4×10^{-7}	0.38–1.07	63.8	II

HR: hazard ratio, NE: not estimable because less than three studies were available, PI: prediction interval, P random: P value under random-effects meta-analysis, RR: risk ratio.
[a] Only two prospective cohort studies were available.

PD [67]. However, the between-study heterogeneity was very large and this inference is based on case-control studies. Furthermore, the meta-analysis examining the association of gout, a disease characterized by high levels of serum uric acid, with PD showed no association between PD and gout, preceding the diagnosis of PD [68].

Although beta-blockers presented Class II evidence, this inference was based only on case-control studies. Confounding or recall bias are possible alternative explanations of this association.

PD diagnosis is based upon clinical criteria solely and symptoms arise after damage of at least 60% of dopaminergic substantia nigra cells [69]. For that reason PD is often diagnosed in a stage of extensive damage, where neuroprotective agents fail to prevent any further damage [70,71]. This is why the identification of a biomarker could be a breakthrough to help slow the progression of PD, by diagnosing the disease at an earlier, preclinical even, stage. Furthermore, the discovery of credible biomarkers for diagnosis of PD could reduce the case ascertainment bias in observational studies, ensuring an accurate differential diagnosis from cases of atypical parkinsonism. However, none of the meta-analyses on biomarkers showed unequivocal evidence for association with PD. All meta-analyses about the wide spectrum of biomarkers, either imaging or measured in CSF, plasma or serum, have large heterogeneity and a small sample size.

In the present study, we have used an umbrella review approach synthesizing data from already published meta-analyses of risk factors for PD. Umbrella reviews have the advantage of building on existing meta-analyses, as opposed to performing new meta-analyses from scratch which would require far more resources with unclear advantages. However, some limitations exist. First, some of the caveats, pertaining to the interpretation of tests for statistical bias and the potential effect inflation even in the largest studies, are applicable to all umbrella reviews of risk factors, as previously discussed [8]. Second, we depended on the original meta-analyses for assessment of study quality and whether quality features should be considered in the eligibility criteria for including studies in a meta-analysis. Many systematic reviews applied the Newcastle–Ottawa Scale to qualitatively appraise the included observational studies. This scale considers the selection of study groups, the comparability of groups, and the ascertainment of exposure and outcomes [72]. Based on this scale, almost half of the primary studies were of poor quality. This scale should be interpreted with caution, because it has modest between-reviewer concordance and information on some studies may not be transparently available [72–74]. Third, our approach would miss associations that have not yet been assessed through meta-analysis. For example, recently published cohort studies have investigated zolpidem intake [75], and the existence of end-stage renal disease [76] as risk factors for developing PD, but these have not been included in any published meta-analysis. Fourth, while we focus on biases and other issues that may have led to false-positive associations, false-negatives are also possible, especially for associations where limited evidence is available. Finally, we cannot fully ensure the comprehensiveness of the literature search and there can be some subjectivity in the eligibility criteria for the included meta-analyses.

Acknowledging these caveats, our assessment maps the status of evidence on associations between environmental risk factors and risk for PD. A potential clinical implication of pinpointing the strong associations is the identification of high risk individuals for developing PD in order to run an organized screening program to detect preclinical stages of the disease. Such screening tests have already been proposed and include testing for non-motor prodromal symptoms i.e. hyposmia, constipation, depression, sleep disorders and apathy [71,77,78]. Constipation and physical activity were associated with PD, but these associations could most likely be attributed to preclinical manifestations of PD and they did not represent genuine risk factors for PD. Several other associations have highly suggestive evidence, and fewer, if any, are likely to be causal, rather than confounded or the result of information bias or reverse causality. The mechanisms of several putative risk factors are not fully understood. Data from more studies and investigation of sources of heterogeneity are needed to better understand the association between these factors and PD.

Author contributions

VB and LB had the original idea for the manuscript and all authors contributed to design the study. VB, LB performed the analyses and all authors interpreted the results. VB, LB and JPAI wrote the first draft of the manuscript. All authors critically reviewed, wrote and approved the final version.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.parkreldis.2015.12.008.

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