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

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

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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.

Abstract

Background: Environmental exposures underlie to a great extent the causation of Parkinson's disease. 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 April 16, 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 use of 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, 66 unique meta-analyses including primary studies of different risk factors and Parkinson's disease were examined, covering diverse biomarkers, dietary factors, drugs, medical history or comorbid diseases, exposure to toxic environmental agents and habits. 34 of 66 meta-analyses had results that were significant at p-values <0.05 and 20 at p-values <0.001 by random effects. Evidence for an association was highly suggestive (more than 1000 cases, $p<10^{-6}$ by random effects, and largest study with 95% CI excluding the null) for anxiety or depression, beta-blockers, head injury, physical activity, serum uric acid, and smoking. However, all of them had high heterogeneity and/or some hints for bias.

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.

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 1,903 per 100,000 in older than age 80[2] and 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 USA, the economic burden of PD exceeds $14.4 billion in 2010 (approximately $22,800 per patient) and it is projected to grow substantially over the next few decades.[3]

Major gene mutations cause only a small proportion of all cases and about 90% of cases are sporadic.[4] To our knowledge, there is no previous attempt to summarize the evidence from existing meta-analyses on non-genetic risk factors for Parkinson's disease. 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 with meta-analyses have the strongest evidence for association.

Methods

Search strategy and eligibility criteria

We conducted an umbrella review, a systematic collection and evaluation of multiple systematic reviews and meta-analyses performed on a specific research topic.[5] The

methods of the umbrella review are standardized and follow exactly the same principles as a previous umbrella review on risk factors for multiple sclerosis.[6] We systematically searched PubMed from inception to April 16, 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.[7] When a study included meta-analyses of both genetic and environmental risk factors, we only extracted information on the latter. Moreover, meta-analyses with an outcome related to progression of PD or severity of symptoms were excluded. We also excluded meta-analyses examining PD as a risk factor for other medical conditions. 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. We kept a record of other meta-analyses focused on the same risk factor.

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 (mean difference, risk ratio, odds ratio, hazard ratio or incident risk 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 recorded 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.

Statistical analysis

For each meta-analysis, we estimated the summary effect size and its 95% CI using both fixed-effects and random-effects models.[8,9] 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.[10,11] 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 0.1. In a study with SE of less than 0.1, the difference between the effect estimate and the upper or lower 95% confidence interval is less than 0.2 (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.[12] Between-study heterogeneity was assessed via the I^2 metric.[13] 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.[14] Values exceeding 50% or 75% are usually considered to represent large or very large heterogeneity, respectively. The 95% CI of I^2 estimates can be wide when there are few studies.[15]

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 with larger studies)[16] using the regression asymmetry test proposed by Egger and colleagues.[17] A P value less than 0.1 with more conservative effect in larger studies 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 statistically 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[21] on pesticides and well-water drinking, we used data from older meta-analyses[22,23], because the largest one did not adequately report the data needed to perform our analyses. 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. For two meta-analyses, pertaining to constipation[23] and gout[26], we were not able to assess small-study effects and to estimate the 95% prediction interval, because only 2 observational studies were available for each meta-analysis.

Finally, we identified putative risk factors that had the strongest statistical support for association[27,28] and no signals of high heterogeneity or bias. Specifically, we used the following categories: Highly convincing evidence required >1000 cases, highly statistically 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 required >1000 cases, highly statistically significant summary associations ($p<10^{-6}$ by random effects) and largest study with 95% CI excluding the null. Suggestive evidence 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. Non-significant associations were those with $p>0.05$.

Even when evidence for association is convincing or highly suggestive, this still does not prove causation. Therefore, in the Discussion, we explore systematically all putative risk factors with strong or highly suggestive 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.

Role of the funding source

There was no funding source for this study. All authors had full access to all the study data. The corresponding author had final responsibility for the decision to submit for publication.

Results

Overall, 884 articles were searched and 32 articles were eligible (figure). 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),[29–37] pesticides (n=5),[38–42] physical activity (n=2),[43,44] coffee (n=3),[35,45,46] farming (n=1)[39], aspirin (n=1),[47] bone mineral density (n=1),[48] fat intake (n=1),[49] ibuprofen (n=1),[47] tea (n=1),[45] and well water drinking (n=1)[39]. One article[50] on body mass index was excluded due to inadequate data reporting.

The 32 articles correspond to 66 unique meta-analyses, including 691 primary observational studies as a whole. The median number of studies per meta-analysis was 7 (IQR 5-11) and the median number of cases was 1405 (IQR 677-4899). The 66 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 41 meta-analyses. All eligible meta-analyses used summary-level data from published literature and none of them had access to individual participant data. In 4 papers[51–54] (7 meta-analyses) the effect size was expressed in weighted mean difference, which we transformed to standardized mean difference and then to OR. In 2 papers[55,56] (6 meta-analyses) the summary effect size was expressed in standardized mean difference, which we transformed to OR.

Thirteen articles used the Newcastle-Ottawa Scale to qualitatively assess the included primary studies. Details are presented in table 4. Another article[24] assessed the

potential existence of bias in the case ascertainment and the selection bias. An additional article[52] used the QUADAS-2 for this assessment. Taking into account the methodological assessment of the primary 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 Newcastle-Ottawa scale.

34 (51%) of 66 meta-analyses reported effects that were significant at p values less than 0.05 under the random-effects model. 20 (30%) 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 loss, gout, serum uric acid, retinal nerve fiber layer thickness, calcium channel blockers, rural living, farming, alcohol drinking and bone mineral density in lumbar spine. In seven of these (dairy products intake, welding, anxiety or depression, coffee drinking, smoking, physical activity and ibuprofen) the 95% prediction interval rule for random-effects model did not include the null. The remaining meta-analyses of risk factors had 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).

The results of the largest study were more conservative than the summary result in 34 (52%) meta-analyses (table 2). However, the largest study was typically not very large or substantially different in weight from other studies. In 21 meta-analyses, the SE of the largest study was less than 0.10 in a log OR scale (it was <0.20 in 51 meta-analyses).

38 (58%) meta-analyses had large heterogeneity estimates ($I^2 \geq 50\%$) and 19 (29%) meta-analyses had very large heterogeneity estimates ($I^2 > 75\%$). Evidence for small-

study effects was noted in 12 (18%) meta-analyses. These meta-analyses pertained to alcohol drinking, coffee drinking, energy intake, exposure to hydrocarbons, serum vitamin D, lutein intake, non-aspirin NSAIDs, organic solvents, pesticides, rural living, statins, and smoking. Assuming that the effect size in the largest study was the true effect, 35 (53%) of the 66 meta-analyses had a significant difference between the number of observed and expected positive studies (table 2).

Of the 66 meta-analyses, 15 (23%) presented a significant association at $P < 10^{-6}$. Six risk factors, which include anxiety or depression[23], beta-blockers[23], head injury[57], serum uric acid[55], physical activity[58] and smoking[23], presented highly suggestive evidence (>1000 cases, $p<10^{-6}$ and largest study 95% CI excluding the null). However, all of these six risk factors had either large or very large heterogeneity (n=3), or prediction interval including the null value (n=3) or hints for small-study effects (n=1) and/or excess significance bias (n=2).

An overall summary assessment of the strength of the evidence for association of putative risk factors with Parkinson's disease is presented in table 3.

Discussion

We provide an overview and appraisal of environmental risk factors that have been associated with Parkinson's disease. Overall, 66 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. Several putative risk factors (head injury, anxiety or depression, beta-blockers, smoking, physical activity, serum uric acid) had very low p-values ($<10^{-6}$) and an effect was

seen also in the largest study, but there was either large between-study heterogeneity and/or large uncertainty in the predictive interval and/or signals of bias.

The majority of the examined meta-analyses had large heterogeneity and some had signals of small-study effects or/and excess significance. The applied Egger test is particularly difficult to interpret when between-study heterogeneity is large. 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, mixture of differences in exposure assessment, frequency of exposed in control groups, types of exposures 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.

The observed inverse association between physical activity and PD is further supported by animal and human laboratory studies.[59,60] In animal models exposed to toxic compounds like MPTP, forced physical activity, spared nigrostriatal dopaminergic terminals and attenuated movement abnormalities.[59] In humans, physical exercise has been suggested to increase plasma urate and uric acid levels, which in turn have been associated with lower risk for Parkinson's disease.[58] 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.[61,62] Peripheral autonomic disorders in early stages of PD development may result in decreased cardiac chronotropic response during exercise and decrease

the level of physical activity. Also, for the association of physical activity with PD, we found evidence for excess significance.

Among other putative risk factors, highly statistically 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 signal. For smoking, the level of statistical significance for the association was extremely impressive ($P = 1.30 \times 10^{-37}$ by random effects), 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,[63] rather than the neuroprotective role of nicotine.[64] 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).[63,65] 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.[63]

Head trauma appeared to have a positive association with PD. According to a report by the International Collaboration on Mild Traumatic Brain Injury Prognosis,[66] the

epidemiological evidence supports that mild traumatic brain injury is not associated with PD. Reverse causality may operate here, because head injury result from imbalance which is an early sign of PD.[67,68] Likewise, 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 serotonigergic neuronal cells in the dorsal raphe nucleus.[69]

Uric acid is thought to be a predictor of clinical progression of PD.[70] In agreement to that, the meta-analysis of the two cohort studies examining the association of gout, a disease characterized by high levels of serum uric acid, with PD showed a robust protective effect, but more studies are needed to assess the reproducibility of these findings. However, the meta-analysis for serum urate, a metabolite of serum uric acid, presented a significant association supported by weak evidence. Furthermore, an association between dairy products and PD was supported by suggestive evidence. This association can be attributed to the reduction of serum uric acid levels, which was also supported by evidence from the Third National Health and Nutrition Examination Survey.[71]

Degeneration of norepinephrine neurons in the locus coeruleus and deficits in norepinephrine are common findings in PD, which could be aggravated by use of beta blockers and lead to PD. This is probably depicted in the modest harmful effect of beta-blockers.[72]

The association between pesticides and PD had a modest effect and was supported by suggestive evidence. However, there was evidence for large heterogeneity, small study effects and excess significance, leading to an inflated effect size. Furthermore, farming and rural living (proxies of exposure to pesticides) presented a significant

association with PD, but these associations were characterized by large heterogeneity and/or bias. Furthermore, organic solvents cause neurological problems and can hardly be considered specific dopaminergic toxins. The potential mechanism of action is damage of the basal ganglia. The mechanisms whereby these chemicals cause selective toxicity to these brain regions are not fully understood.[73] Epidemiological studies on these exposures include different populations (occupational exposures or not), different thresholds of duration of exposure and different method of assessment of exposure (questionnaire or interview), so it is difficult to draw a safe conclusion. The large heterogeneity on the meta-analysis on pesticides and organic solvents could not be explained by the various chemical compounds that are included in these environmental exposures. The subgroup analysis performed per chemical compound either failed to show a statistically significant effect or preserved the large statistical heterogeneity, when the effect was significant.

Two other evaluated factors, coffee and alcohol, showed impressive P values in their summary effects, suggesting a protective impact on PD. However, for both of them, the largest study showed no effect and there was evidence for small-study effects and excess significance. This suggests that the observed associations may be due to bias. However, on the basis of the protective effect of coffee in PD, adenosine receptor antagonists have been tested and there is some evidence that they improve parkinsonian symptoms in phase 2 clinical trials.[74,75] An explanation for the observed inverse association between alcohol and PD may be residual confounding, possibly by smoking or coffee.[64] Based on the Newcastle-Ottawa scale, two-thirds of the observational studies examining the association between alcohol and PD had low quality ratings. Moreover the finding that ibuprofen use, but not use of aspirin or other

NSAIDs, could be associated with lower PD risk suggests mechanisms other than a generic anti-inflammatory activity of NSAIDs.[76]

PD diagnosis is based upon clinical criteria solely and symptoms arise after damage of at least 60% of dopaminergic substantia nigra cells.[77] For that reason PD is quite often diagnosed in a stage of extensive damage, where neuroprotective agents fail to prevent any further damage.[78,79] This is why the identification of a biomarker could be a breakthrough to help slow the progression of PD, by recognizing it at an earlier, preclinical even, stage. However none of the meta-analyses on biomarkers showed unequivocal evidence for association with PD. All meta-analyses about the wide spectrum of biomarker either imaging or measured in CSF, plasma or serum, have large heterogeneity and a small sample size.

Our analysis has some caveats. Some of the caveats, pertaining to the interpretation of tests for statistical bias and the potentially effect inflation even in the largest studies, are applicable to all umbrella reviews of risk factors, as we have discussed on a previous umbrella review about risk factors for multiple sclerosis.[6] We did not appraise the quality of the individual component primary studies, because this was beyond the scope of this umbrella review. This was the aim of the original systematic reviews and meta-analyses, which should include an assessment of study quality and whether the study should be included in the quantitative calculations. Indeed, some of the systematic reviews and meta-analyses applied the Newcastle-Ottawa scale to qualitatively appraise the observational studies, indicating almost half of these primary studies were of poor quality. Also, in our analysis we assessed only associations considered by meta-analyses of observational studies. Thus, we might miss other associations with adequate evidence that have not yet been assessed through meta-analytic approaches. Recently published cohort studies investigated the

exposure to extremely low frequency magnetic fields[80], zolpidem intake[81], and the existence of end-stage renal disease[82] as risk factors for developing PD, but these factors have not been studied in a published meta-analysis and were not addressed in our analysis. Finally, while we focus on biases and other issues that may have led to false-positive associations, false-negatives cannot be excluded also, especially for associations where limited evidence from small studies is available.

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.[79,83,84] Several associations have highly suggestive evidence, and fewer, if any, are likely to be causal, rather than confounded or the result of information biases 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.

References

1 De Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. *Lancet Neurol* 2006; **5**: 525–35.

2 Pringsheim T, Jette N, Frolkis A, Steeves TDL. The prevalence of Parkinson's disease: A systematic review and meta-analysis. *Mov Disord* 2014; **29**: 1583–90.

3 Kowal SL, Dall TM, Chakrabarti R, Storm M V, Jain A. The current and projected economic burden of Parkinson's disease in the United States. *Mov Disord* 2013; **28**: 311–8.

4 Klein C, Westenberger A. Genetics of Parkinson's disease. *Cold Spring Harb Perspect Med* 2012; **2**: a008888.

5 Ioannidis JPA. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. *CMAJ* 2009; **181**: 488–93.

6 Belbasis L, Bellou V, Evangelou E, Ioannidis JPA, Tzoulaki I. Environmental risk factors and multiple sclerosis: an umbrella review of systematic reviews and meta-analyses. *Lancet Neurol* 2015; published online Feb. DOI:10.1016/S1474-4422(14)70267-4.

7 Nalls MA, Pankratz N, Lill CM, *et al.* Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet* 2014; **46**: 989–93.

8 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–88.

9 Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. *Ann Intern Med* 1997; **127**: 820–6.

10 Higgins JPT, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc* 2009; **172**: 137–59.

11 Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol* 2008; **37**: 1158–60.

12 Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Stat Med* 2000; **19**: 3127–31.

13 Cochran WG. The Combination of Estimates from Different Experiments. *Biometrics* 1954; **10**: 101.

14 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–58.

15 Ioannidis JPA, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. *BMJ* 2007; **335**: 914–6.

16 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al.* Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; **343**: d4002.

17 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; **315**: 629–34.

18 Ioannidis JPA, Trikalinos TA. An exploratory test for an excess of significant findings. *Clin Trials* 2007; **4**: 245–53.

19 Ioannidis JPA. Clarifications on the application and interpretation of the test for excess significance and its extensions. *J Math Psychol* 2013; **57**: 184–7.

20 Lubin JH, Gail MH. On power and sample size for studying features of the relative odds of disease. *Am J Epidemiol* 1990; **131**: 552–66.

21 Pezzoli G, Cereda E. Exposure to pesticides or solvents and risk of Parkinson disease. *Neurology* 2013; **80**: 2035–41.

22 Van der Mark M, Brouwer M, Kromhout H, Nijssen P, Huss A, Vermeulen R. Is pesticide use related to Parkinson disease? Some clues to heterogeneity in study results. *Environ Health Perspect* 2012; **120**: 340–7.

23 Noyce AJ, Bestwick JP, Silveira-Moriyama L, *et al.* Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol* 2012; **72**: 893–901.

24 Cereda E, Barichella M, Pedrolli C, *et al.* Diabetes and risk of Parkinson's disease: a systematic review and meta-analysis. *Diabetes Care* 2011; **34**: 2614–23.

25 Lu L, Fu D-L, Li H-Q, Liu A-J, Li J-H, Zheng G-Q. Diabetes and risk of Parkinson's disease: an updated meta-analysis of case-control studies. *PLoS One* 2014; **9**: e85781.

26 Shen C, Guo Y, Luo W, Lin C, Ding M. Serum urate and the risk of Parkinson's disease: results from a meta-analysis. *Can J Neurol Sci* 2013; **40**: 73–9.

27 Ioannidis JPA, Tarone R, McLaughlin JK. The false-positive to false-negative ratio in epidemiologic studies. *Epidemiology* 2011; **22**: 450–6.

28 Johnson VE. Revised standards for statistical evidence. *Proc Natl Acad Sci U S A* 2013; **110**: 19313–7.

29 Allam MF, Campbell MJ, Del Castillo AS, Fernández-Crehuet Navajas R. Parkinson's disease protects against smoking? *Behav Neurol* 2004; **15**: 65–71.

30 Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernández-Crehuet Navajas R. Smoking and Parkinson's disease: systematic review of prospective studies. *Mov Disord* 2004; **19**: 614–21.

31 Allam MF, del Castillo AS, Navajas RF-C. [Parkinson's disease, tobacco and age: meta analysis]. *Rev Neurol*; **36**: 510–3.

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

33 Allam MF, Serrano del Castillo A, Fernández-Crehuet Navajas R. Smoking and Parkinson's disease: explanatory hypothesis. *Int J Neurosci* 2002; **112**: 851–4.

34 Ritz B, Ascherio A, Checkoway H, *et al.* Pooled analysis of tobacco use and risk of Parkinson disease. *Arch Neurol* 2007; **64**: 990–7.

35 Hernán MA, Takkouche B, Caamaño-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol* 2002; **52**: 276–84.

36 Sugita M, Izuno T, Tatemichi M, Otahara Y. Meta-analysis for epidemiologic studies on the relationship between smoking and Parkinson's disease. *J Epidemiol* 2001; **11**: 87–94.

37 Kiyohara C, Kusuhara S. Cigarette smoking and Parkinson's disease: a meta-analysis. *Fukuoka Igaku Zasshi* 2011; **102**: 254–65.

38 Allen MT, Levy LS. Parkinson's disease and pesticide exposure--a new assessment. *Crit Rev Toxicol* 2013; **43**: 515–34.

39 Priyadarshi A, Khuder SA, Schaub EA, Priyadarshi SS. Environmental risk factors and Parkinson's disease: a metaanalysis. *Environ Res* 2001; **86**: 122–7.

40 Priyadarshi A, Khuder SA, Schaub EA, Shrivastava S. A meta-analysis of Parkinson's disease and exposure to pesticides. *Neurotoxicology* 2000; **21**: 435–40.

41 Van Maele-Fabry G, Hoet P, Vilain F, Lison D. Occupational exposure to pesticides and Parkinson's disease: a systematic review and meta-analysis of cohort studies. *Environ Int* 2012; **46**: 30–43.

42 Freire C, Koifman S. Pesticide exposure and Parkinson's disease: epidemiological evidence of association. *Neurotoxicology* 2012; **33**: 947–71.

43 Hamer M, Chida Y. Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence. *Psychol Med* 2009; **39**: 3–11.

44 Xu Q, Park Y, Huang X, *et al.* Physical activities and future risk of Parkinson disease. *Neurology* 2010; **75**: 341–8.

45 Costa J, Lunet N, Santos C, Santos J, Vaz-Carneiro A. Caffeine exposure and the risk of Parkinson's disease: a systematic review and meta-analysis of observational studies. *J Alzheimers Dis* 2010; **20 Suppl 1**: S221–38.

46 Liu R, Guo X, Park Y, *et al.* Caffeine intake, smoking, and risk of Parkinson disease in men and women. *Am J Epidemiol* 2012; **175**: 1200–7.

47 Samii A, Etminan M, Wiens MO, Jafari S. NSAID use and the risk of Parkinson's disease: systematic review and meta-analysis of observational studies. *Drugs Aging* 2009; **26**: 769–79.

48 Torsney KM, Noyce AJ, Doherty KM, Bestwick JP, Dobson R, Lees AJ. Bone health in Parkinson's disease: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2014; **85**: 1159–66.

49 Kamel F, Goldman SM, Umbach DM, *et al.* Dietary fat intake, pesticide use, and Parkinson's disease. *Parkinsonism Relat Disord* 2014; **20**: 82–7.

50 Van der Marck MA, Dicke HC, Uc EY, *et al.* Body mass index in Parkinson's disease: a meta-analysis. *Parkinsonism Relat Disord* 2012; **18**: 263–7.

51 Lv Z, Qi H, Wang L, *et al.* Vitamin D status and Parkinson's disease: a systematic review and meta-analysis. *Neurol Sci* 2014; **35**: 1723–30.

52 Gao L, Tang H, Nie K, *et al.* Cerebrospinal fluid alpha-synuclein as a biomarker for Parkinson's disease diagnosis: a systematic review and meta-analysis. *Int J Neurosci* 2014; published online Oct. DOI:10.3109/00207454.2014.961454.

53 Zhao Y, Shen L, Ji H-F. Osteoporosis risk and bone mineral density levels in patients with Parkinson's disease: a meta-analysis. *Bone* 2013; **52**: 498–505.

54 Yu J-G, Feng Y-F, Xiang Y, *et al.* Retinal nerve fiber layer thickness changes in Parkinson disease: a meta-analysis. *PLoS One* 2014; **9**: e85718.

55 Shen L, Ji H-F. Low uric acid levels in patients with Parkinson's disease: evidence from meta-analysis. *BMJ Open* 2013; **3**: e003620.

56 Mariani S, Ventriglia M, Simonelli I, *et al.* Fe and Cu do not differ in Parkinson's disease: a replication study plus meta-analysis. *Neurobiol Aging* 2013; **34**: 632–3.

57 Jafari S, Etminan M, Aminzadeh F, Samii A. Head injury and risk of Parkinson disease: a systematic review and meta-analysis. *Mov Disord* 2013; **28**: 1222–9.

58 Yang F, Trolle Lagerros Y, Bellocco R, *et al.* Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. *Brain* 2015; **138**: 269–75.

59 Tillerson JL, Caudle WM, Reverón ME, Miller GW. Exercise induces behavioral recovery and attenuates neurochemical deficits in rodent models of Parkinson's disease. *Neuroscience* 2003; **119**: 899–911.

60 Green HJ, Fraser IG. Differential effects of exercise intensity on serum uric acid concentration. *Med Sci Sports Exerc* 1988; **20**: 55–9.

61 Tanner CM, Comella CL. When brawn benefits brain: physical activity and Parkinson's disease risk. *Brain* 2015; **138**: 238–9.

62 Palma JA, Kaufmann H. Autonomic disorders predicting Parkinson's disease. *Park Relat Disord* 2014; **20**. DOI:10.1016/S1353-8020(13)70024-5.

63 Wirdefeldt K, Adami H-O, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol* 2011; **26 Suppl 1**: S1–58.

64 Van der Mark M, Nijssen PCG, Vlaanderen J, *et al.* A case-control study of the protective effect of alcohol, coffee, and cigarette consumption on Parkinson disease risk: time-since-cessation modifies the effect of tobacco smoking. *PLoS One* 2014; **9**: e95297.

65 Ritz B, Lee P-C, Lassen CF, Arah OA. Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease. *Neurology* 2014; **83**: 1396–402.

66 Marras C, Hincapié CA, Kristman VL, *et al.* Systematic review of the risk of parkinson's disease after mild traumatic brain injury: Results of the international collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil* 2014; **95**. DOI:10.1016/j.apmr.2013.08.298.

67 Gao X, Chen H, Schwarzschild MA, Logroscino G, Ascherio A. Perceived imbalance and risk of Parkinson's disease. *Mov Disord* 2008; **23**: 613–6.

68 Rugbjerg K, Ritz B, Korbo L, Martinussen N, Olsen JH. Risk of Parkinson's disease after hospital contact for head injury: population based case-control study. *BMJ* 2008; **337**: a2494.

69 Aarsland D, Påhlhagen S, Ballard CG, Ehrt U, Svenningsson P. Depression in Parkinson disease--epidemiology, mechanisms and management. *Nat Rev Neurol* 2012; **8**: 35–47.

70 Ascherio A, LeWitt PA, Xu K, *et al.* Urate as a predictor of the rate of clinical decline in Parkinson disease. *Arch Neurol* 2009; **66**: 1460–8.

71 Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum* 2005; **52**: 283–9.

72 Brichta L, Greengard P, Flajolet M. Advances in the pharmacological treatment of Parkinson's disease: targeting neurotransmitter systems. *Trends Neurosci* 2013; **36**: 543–54.

73 Lock EA, Zhang J, Checkoway H. Solvents and Parkinson disease: a systematic review of toxicological and epidemiological evidence. *Toxicol Appl Pharmacol* 2013; **266**: 345–55.

74 Hauser RA, Olanow CW, Kieburtz KD, *et al.* Tozadenant (SYN115) in patients with Parkinson's disease who have motor fluctuations on levodopa: a phase 2b, double-blind, randomised trial. *Lancet Neurol* 2014; **13**: 767–76.

75 Hauser RA, Cantillon M, Pourcher E, *et al.* Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial. *Lancet Neurol* 2011; **10**: 221–9.

76 Gao X, Chen H, Schwarzschild MA, Ascherio A. Use of ibuprofen and risk of Parkinson disease. *Neurology* 2011; **76**: 863–9.

77 Cheng H-C, Ulane CM, Burke RE. Clinical progression in Parkinson disease and the neurobiology of axons. *Ann Neurol* 2010; **67**: 715–25.

78 Lang AE. In pursuit of prodromal Parkinson's disease. *Lancet Neurol* 2015; **14**: 27–8.

79 Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol* 2015; **14**: 57–64.

80 Brouwer M, Koeman T, van den Brandt PA, *et al.* Occupational exposures and Parkinson's disease mortality in a prospective Dutch cohort. *Occup Environ Med* 2015; published online Feb. DOI:10.1136/oemed-2014-102209.

81 Huang H-C, Tsai C-H, Muo C-H, *et al.* Risk of Parkinson's disease following zolpidem use: a retrospective, population-based cohort study. *J Clin Psychiatry* 2015; **76**: e104–10.

82 Wang I-K, Lin C-L, Wu Y-Y, *et al.* Increased risk of Parkinson's disease in patients with end-stage renal disease: a retrospective cohort study. *Neuroepidemiology* 2014; **42**: 204–10.

83 Goldman SM. Environmental toxins and Parkinson's disease. *Annu Rev Pharmacol Toxicol* 2014; **54**: 141–64.

84 Berg D, Godau J, Seppi K, *et al.* The PRIPS study: screening battery for subjects at risk for Parkinson's disease. *Eur J Neurol* 2013; **20**: 102–8.

85 Zhang D, Jiang H, Xie J. Alcohol intake and risk of Parkinson's disease: a meta-analysis of observational studies. *Mov Disord* 2014; **29**: 819–22.

86 Li F-J, Ji H-F, Shen L. A meta-analysis of tea drinking and risk of Parkinson's disease. *ScientificWorldJournal* 2012; **2012**: 923464.

87 Mortimer JA, Borenstein AR, Nelson LM. Associations of welding and manganese exposure with Parkinson disease: review and meta-analysis. *Neurology* 2012; **79**: 1174–80.

88 Palin O, Herd C, Morrison KE, *et al.* Systematic review and meta-analysis of hydrocarbon exposure and the risk of Parkinson's disease. *Parkinsonism Relat Disord* 2015; **21**: 243–8.

89 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**: 362–5.

90 Jiang W, Ju C, Jiang H, Zhang D. Dairy foods intake and risk of Parkinson's disease: a dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol* 2014; **29**: 613–9.

91 Takeda A, Nyssen OP, Syed A, Jansen E, Bueno-de-Mesquita B, Gallo V. Vitamin A and carotenoids and the risk of Parkinson's disease: a systematic review and meta-analysis. *Neuroepidemiology* 2014; **42**: 25–38.

92 Wang A, Lin Y, Wu Y, Zhang D. Macronutrients intake and risk of Parkinson's disease: A meta-analysis. *Geriatr Gerontol Int* 2014; published online Aug. DOI:10.1111/ggi.12321.

93 Liu R, Gao X, Lu Y, Chen H. Meta-analysis of the relationship between Parkinson disease and melanoma. *Neurology* 2011; **76**: 2002–9.

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

95 Lang Y, Gong D, Fan Y. Calcium channel blocker use and risk of Parkinson's disease: a meta-analysis. *Pharmacoepidemiol drug Saf* 2015; **24**: 559–66.

96 Undela K, Gudala K, Malla S, Bansal D. Statin use and risk of Parkinson's disease: a meta-analysis of observational studies. *J Neurol* 2013; **260**: 158–65.

97 Wang P, Li J, Qiu S, Wen H, Du J. Hormone replacement therapy and Parkinson's disease risk in women: a meta-analysis of 14 observational studies. *Neuropsychiatr Dis Treat* 2015; **11**: 59–66.

98 Chen J, Guan Z, Wang L, Song G, Ma B, Wang Y. Meta-analysis: overweight, obesity, and Parkinson's disease. *Int J Endocrinol* 2014; **2014**: 203930.

99 Gudala K, Bansal D, Muthyala H. Role of serum cholesterol in Parkinson's disease: a meta-analysis of evidence. *J Parkinsons Dis* 2013; **3**: 363–70.

100 Sako W, Murakami N, Izumi Y, Kaji R. MRI can detect nigral volume loss in patients with Parkinson's disease: evidence from a meta-analysis. *J Parkinsons Dis* 2014; **4**: 405–11.

Figure. Flow chart of literature search for systematic reviews and meta-analyses published from inception until April 16, 2015.

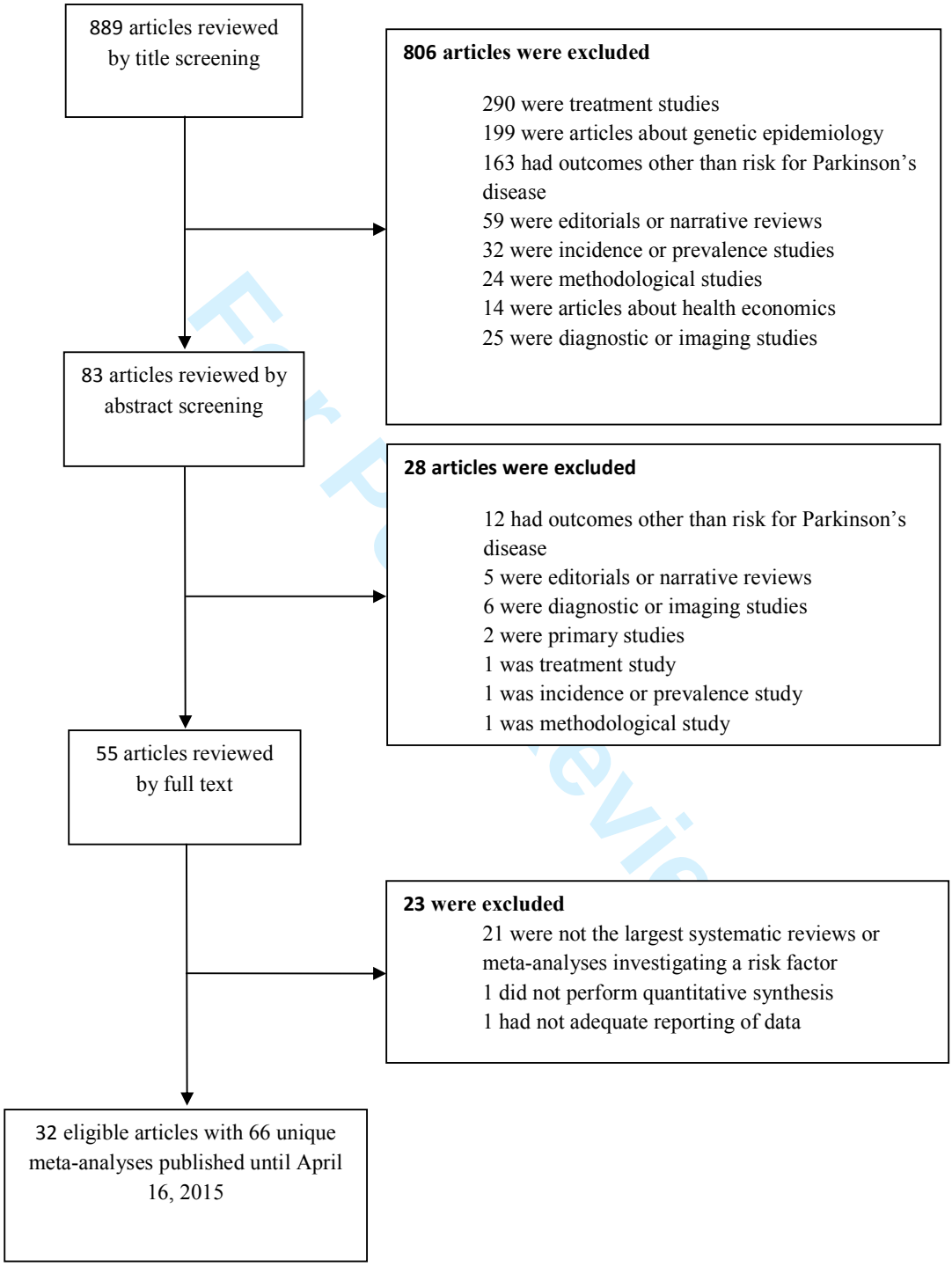

Table 1.Characteristics and quantitative synthesis of the 66 eligible meta-analyses of environmental risk factors for Parkinson's disease.

Reference	Risk factor	Level of comparison	Total number of Cases/Controls	Number of primary studies	Effect size	Random effects summary effect size (95% CI)	P random	95% PI	Fixed effects summary effect size (95% CI)	P fixed
Habits										
Zhang, 2014[85]	Alcohol intake	High intake vs. Low intake	9994/667662	33	RR	0.75 (0.66-0.85)	5.0×10^{-6}	0.44-1.25	0.79 (0.73-0.86)	4.8×10^{-9}
Noyce, 2012[23]	Coffee drinking	High intake vs. Low intake	5801/723072	19	RR	0.67 (0.58-0.76)	3.4×10^{-9}	0.45-1.00	0.72 (0.65-0.78)	1.5×10^{-13}
Noyce, 2012[23]	Smoking	Exposed vs. Non exposed	19537/1053645	67	RR	0.64 (0.60-0.69)	1.3×10^{-37}	0.45-0.92	0.67 (0.65-0.70)	5.0×10^{-77}
Li, 2012[86]	Tea drinking	High intake vs. Low intake	1418/4250	8	OR	0.86 (0.68-1.08)	0.197	0.45-1.62	0.85 (0.74-0.98)	0.025
Yang, 2015[58]	Physical activity	High activity vs. Low activity	1348/399959	5	HR	0.66 (0.57-0.78)	3.0×10^{-7}	0.55-0.80	0.66 (0.57-0.78)	3.0×10^{-7}
Exposure to toxic environmental agents										
Mortimer, 2012[87]	Manganese exposure	Exposed vs. Non exposed	1278/2762	3	RR	0.76 (0.41-1.42)	0.392	0.001-661	0.80 (0.59-1.08)	0.146
Mortimer, 2012[87]	Welding	Yes vs. No	8198/572326	9	RR	0.86 (0.80-0.92)	3.0×10^{-5}	0.79-0.94	0.86 (0.80-0.92)	3.0×10^{-5}
Palin, 2015[88]	Hydrocarbon exposure	Exposed vs. Non exposed	4483/7179	14	OR	1.36 (1.13-1.63)	0.001	0.88-2.08	1.27 (1.12-1.46)	3.6×10^{-4}
Pezzoli, 2013[21]	Farming	Exposed vs. Non exposed	9533/2303116	38	OR	1.30 (1.16- 1.46)	5.7×10^{-6}	0.86-1.98	1.29 (1.19-1.39)	6.7×10^{-10}
Pezzoli, 2013[21]	Organic solvents	Exposed vs. Non exposed	3811/163859	18	OR	1.22 (1.01-1.47)	0.036	0.72-2.08	1.12 (0.99-1.26)	0.052
van der Mark, 2012[22]	Pesticides	Exposed vs. Non exposed	7151/292210	39	OR	1.62 (1.40-1.88)	1.1×10^{-10}	0.81-3.23	1.52 (1.40-1.64)	5.9×10^{-26}
Pezzoli,	Rural living	Exposed vs.	4306/10009	31	OR	1.32 (1.18-1.48)	1.7×10^{-6}	0.84-2.10	1.01 (0.99-1.02)	0.363

2013[21]		Non exposed								
Noyce, 2012[23]	Well water drinking	Exposed vs. Non exposed	5037/8144	28	RR	1.21 (1.05-1.40)	0.011	0.66-2.21	0.99 (0.95-1.04)	0.735
Dietary factors										
Etminan, 2005[89]	Vitamin C intake	High intake vs. Low intake	1247/9214	7	OR	1.06 (0.86- 1.30)	0.602	0.64-1.74	1.00 (0.87-1.16)	0.976
Etminan, 2005[89]	Vitamin E intake	High intake vs. Low intake	936/7230	7	OR	0.81 (0.67- 0.98)	0.028	0.63-1.04	0.81 (0.67-0.98)	0.028
Jiang, 2014[90]	Dairy products intake	High intake vs. Low intake	1083/310118	7	RR	1.40 (1.20- 1.63)	2.4×10^{-5}	1.08-1.81	1.39 (1.21-1.61)	5.7×10^{-6}
Takeda, 2014[91]	Lutein intake	High intake vs. Low intake	804/124720	4	OR	1.49 (0.83- 2.68)	0.179	0.12-18.65	1.15 (0.90-1.46)	0.267
Takeda, 2014[91]	Lycopene intake	High intake vs. Low intake	678/124288	3	OR	1.03 (0.64-1.65)	0.896	0.01-174	1.02 (0.79-1.31)	0.900
Takeda, 2014[91]	Vitamin A intake	High intake vs. Low intake	624/2908	3	OR	1.09 (0.84-1.42)	0.520	0.20-5.96	1.09 (0.84-1.42)	0.520
Takeda, 2014[91]	α-carotene intake	High intake vs. Low intake	677/124268	3	OR	0.84 (0.59-1.18)	0.313	0.04-16.60	0.84 (0.64-1.11)	0.221
Takeda, 2014[91]	β-carotene intake	High intake vs. Low intake	1395/125430	6	OR	0.92 (0.70-1.20)	0.521	0.46-1.81	0.92 (0.75-1.13)	0.417
Takeda, 2014[91]	β-cryptoxanthin intake	High intake vs. Low intake	677/124268	3	OR	0.96 (0.66-1.40)	0.834	0.02-39.43	0.90 (0.69-1.16)	0.411
Wang, 2014[92]	Carbohydrate intake	High intake vs. Low intake	1482/231387	8	RR	1.24 (1.05-1.48)	0.014	1.00-1.54	1.24 (1.05-1.48)	0.014
Wang, 2014[92]	Cholesterol intake	High intake vs. Low intake	1293/168218	7	RR	0.97 (0.75-1.26)	0.833	0.46-2.07	0.91 (0.79-1.05)	0.211
Wang, 2014[92]	Energy intake	High intake vs. Low intake	1415/168643	8	RR	1.39 (1.01-1.92)	0.042	0.50-3.90	0.99 (0.95-1.03)	0.607
Wang, 2014[92]	Protein intake	High intake vs. Low intake	1570/356257	7	RR	1.13 (0.88-1.44)	0.339	0.65-1.97	1.15 (0.95-1.39)	0.151
Wang, 2014[92]	Total fat intake	High intake vs. Low intake	2516/370628	13	RR	0.88 (0.74-1.06)	0.182	0.56-1.40	0.86 (0.75-0.98)	0.024

Medical history and comorbid diseases										
Cereda, 2011[24] and Lu, 2014[25]	Diabetes mellitus	Diseased vs. Non diseased	10743/54709	6	OR	1.13 (0.73-1.76)	0.591	0.42-3.03	1.24 (0.93-1.65)	0.143
Jafari, 2013[57]	Head injury	Exposed vs. Non exposed	35799/172647	22	OR	1.55 (1.33-1.81)	2.2×10^{-8}	0.93-2.58	1.56 (1.45-1.67)	3.5×10^{-35}
Liu, 2011[93]	Melanoma	Diseased vs. Non diseased	10743/54709	6	OR	1.13 (0.73-1.76)	0.591	0.42-3.03	1.24 (0.93-1.65)	0.143
Noyce, 2012[23]	Anxiety or Depression	Diseased vs. Non diseased	16211/1639657	13	RR	1.86 (1.64-2.10)	2.6×10^{-22}	1.30-2.66	1.84 (1.78-1.91)	5.8×10^{-258}
Noyce, 2012[23]	Cancer	Diseased vs. Non diseased	9693/34173	7	RR	0.89 (0.72-1.10)	0.265	0.51-1.53	1.01 (0.94-1.09)	0.777
Noyce, 2012[23]	Constipation	Diseased vs. Non diseased	292/6890	2	RR	2.34 (1.55-3.53)	5.5×10^{-5}	NE	2.34 (1.55-3.53)	5.5×10^{-5}
Noyce, 2012[23]	Gastric ulcer	Diseased vs. Non diseased	406/661	3	RR	1.37 (0.36-5.31)	0.646	1.4×10^{-7}–1.4×10^{7}	0.81 (0.49-1.34)	0.413
Noyce, 2012[23]	Hypertension	Diseased vs. Non diseased	5993/187226	12	RR	0.75 (0.61-0.90)	0.003	0.40- 1.40	0.81 (0.75-0.87)	3.2×10^{-8}
Noyce, 2012[23]	Oophorectomy	Yes vs. No	775/122149	5	RR	0.77 (0.52-1.13)	0.180	0.23- 2.60	0.76 (0.61-0.94)	0.011
Shen, 2013[26]	Gout	Diseased vs. Non diseased	2234/72909	2	OR	0.70 (0.60-0.82)	5.1×10^{-6}	NE	0.70 (0.60-0.82)	5.1×10^{-6}
Drugs										
Gagne, 2010[94]	Aspirin	Exposed vs. Non exposed	2781/296525	6	RR	1.08 (0.93-1.27)	0.315	0.71-1.66	1.12 (1.01-1.24)	0.027
Gagne, 2010[94]	Non-aspirin NSAIDs	Exposed vs. Non exposed	3967/297453	7	RR	0.85 (0.77-0.94)	0.002	0.74-0.97	0.85 (0.77-0.94)	0.002
Gao, 2011[76]	Acetaminophen	Exposed vs. Non exposed	2086/295660	4	RR	1.09 (0.96-1.24)	0.192	0.82-1.45	1.09 (0.96-1.24)	0.192
Gao, 2011[76]	Ibuprofen use	Exposed vs. Non exposed	2170/296165	5	RR	0.73 (0.62-0.85)	6.6×10^{-5}	0.57-0.94	0.73 (0.62-0.85)	6.6×10^{-5}
Noyce, 2012[23]	Beta-blockers	Exposed vs. Non exposed	5774/13671	3	RR	1.28 (1.19-1.39)	5.0×10^{-10}	0.77-2.13	1.28 (1.19-1.39)	5.0×10^{-10}
Lang, 2015[95]	Calcium channel	Exposed vs. Non exposed	6966/2749475	5	RR	0.78 (0.67-0.90)	7.0×10^{-4}	0.55-1.11	0.76 (0.68-0.84)	1.4×10^{-7}

	blockers									
Noyce, 2012[23]	General anesthesia	Exposed vs. Non exposed	1571/3110	6	RR	1.10 (0.77-1.58)	0.601	0.35-3.51	0.93 (0.80-1.09)	0.364
Noyce, 2012[23]	Oral contraceptives	Exposed vs. Non exposed	572/121946	3	RR	0.73 (0.43-1.25)	0.250	0.002-346	0.86 (0.68-1.09)	0.215
Undela, 2013[96]	Statins	Exposed vs. Non exposed	15102/2618836	8	RR	0.77 (0.64-0.92)	0.004	0.47-1.27	0.86 (0.79-0.94)	0.001
Wang, 2014[97]	Hormone Replacement Therapy	Exposed vs. Non exposed	4035/808830	14	RR	1.00 (0.84-1.20)	0.967	0.61-1.64	1.10 (1.00-1.22)	0.064
Biomarkers										
Chen, 2014[98]	BMI	BMI≥ 30 vs. BMI< 25	1668/3882535	7	OR	0.96 (0.61-1.50)	0.854	0.20-4.62	1.15 (1.01-1.31)	0.040
Chen, 2014[98]	BMI	BMI≥ 30 vs. 25 •BMI< 30	1618/2430088	7	OR	0.83 (0.65-1.07)	0.157	0.37-1.85	0.89 (0.78-1.01)	0.061
Chen, 2014[98]	BMI	25 •BMI< 30 vs. BMI<25	2428/5058484	7	OR	1.20 (0.94-1.53)	0.148	0.53-2.69	1.28 (1.18-1.40)	1.3×10^{-8}
Gao, 2014[52]	α-synuclein in CSF	High vs. Low values	850/589	11	OR	0.29 (0.13-0.62)	0.002	0.02-5.19	0.48 (0.38-0.59)	4.9×10^{-12}
Gudala, 2013[99]	Serum cholesterol	High vs. Low values	5488/240624	8	RR	0.91 (0.71-1.15)	0.418	0.44-1.86	1.00 (0.90-1.12)	0.985
Lv, 2014[51]	Serum vitamin D	High vs. Low values	1008/4536	7	OR	0.16 (0.05-0.50)	0.002	0.003-10.09	0.40 (0.34-0.47)	9.0×10^{-29}
Mariani, 2013[56]	Copper in plasma	High vs. Low values	202/239	4	OR	1.41 (0.03-59.27)	0.856	1.7×10^{-8}–1.2×10^{8}	3.47 (2.29-5.24)	3.6×10^{-9}
Mariani, 2013[56]	Copper in CSF	High vs. Low values	215/119	5	OR	2.06 (0.57-7.44)	0.271	0.02-207.2	1.70 (1.06-2.75)	0.029
Mariani, 2013[56]	Serum copper	High vs. Low values	425/333	9	OR	1.46 (0.46-4.63)	0.519	0.02-94.65	1.47 (1.08-1.99)	0.013
Mariani, 2013[56]	Iron in CSF	High vs. Low values	215/119	5	OR	0.93 (0.35-2.45)	0.887	0.03-30.86	0.86 (0.56-1.32)	0.494
Mariani, 2013[56]	Serum iron	High vs. Low values	520/711	10	OR	0.45 (0.17-1.17)	0.102	0.01-16.71	0.41 (0.32-0.51)	2.5×10^{-14}

Sako, 2014[100]	Nigral volume loss	High vs. Low values	193/172	8	OR	0.31 (0.17-0.55)	8.3×10^{-5}	0.06-1.46	0.30 (0.20-0.44)	1.6×10^{-9}
Shen, 2013[26]	Serum urate	High vs. Low values	594/32591	6	RR	0.65 (0.43-0.97)	0.034	0.23-1.82	0.68 (0.50-0.91)	0.009
Shen, 2013[55]	Serum uric acid	High vs. Low values	1217/1276	6	OR	0.39 (0.27-0.57)	6.8×10^{-7}	0.13-1.22	0.33 (0.29-0.38)	1.1×10^{-49}
Yu, 2014[54]	RNFLT	High vs. Low values	644/604	13	OR	0.40 (0.24-0.66)	3.5×10^{-4}	0.06-2.55	0.39 (0.32-0.49)	1.7×10^{-18}
Zhao, 2013[53]	BMD in femoral neck	High vs. Low values	561/8800	8	OR	0.25 (0.09-0.66)	0.005	0.01-8.76	0.36 (0.30-0.44)	3.4×10^{-24}
Zhao, 2013[53]	BMD in hip	High vs. Low values	401/8654	6	OR	0.55 (0.38-0.80)	0.002	0.18-1.66	0.60 (0.49-0.75)	3.2×10^{-6}
Zhao, 2013[53]	BMD in lumbar spine	High vs. Low values	611/962	9	OR	0.29 (0.16-0.54)	7.8×10^{-5}	0.03-2.60	0.30 (0.25-0.37)	1.4×10^{-32}
Zhao, 2013[53]	BMD in trochanter	High vs. Low values	249/550	4	OR	0.73 (0.48-1.11)	0.146	0.16-3.34	0.75 (0.57-0.99)	0.044

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, OR: odds ratio, PI: prediction interval, RR: risk ratio, RNFLT: retinal nerve fiber layer thickness

Table 2. Bias assessment of the 66 eligible meta-analyses of environmental risk factors for Parkinson's disease.

Reference	Risk factor	Effect size	Largest study		I^2	Egger test p-value	Observed significant studies	Expected significant studies	Excess significance test p-value
			Effect size (95% CI)	SE					
Habits									
Zhang, 2014[85]	Alcohol intake	RR	1.01 (0.83-1.23)	0.100	52.3	0.060	7	1.65	2.0×10^{-5}
Noyce, 2012[23]	Coffee drinking	RR	0.85 (0.70-1.03)	0.099	42.9	0.002	8	1.66	2.6×10^{-7}
Noyce, 2012[23]	Smoking	RR	0.74 (0.67-0.82)	0.052	49.6	0.018	39	10.50	$< 1.0 \times 10^{-8}$
Li, 2012[86]	Tea drinking	OR	0.91 (0.73-1.12)	0.110	53.0	0.758	2	0.46	0.019
Yang, 2015[58]	Physical activity	HR	0.68 (0.51-0.90)	0.145	0	0.556	4	1.83	0.072
Exposure to toxic environmental agents									
Mortimer, 2012[87]	Manganese exposure	RR	0.92 (0.64-1.32)	0.185	62	0.935	1	0.19	0.053
Mortimer, 2012[87]	Welding	RR	0.85 (0.77-0.94)	0.051	0	0.221	2	1.52	0.670
Palin, 2015[88]	Hydrocarbon exposure	OR	1.06 (0.86-1.30)	0.105	28.1	0.020	5	0.75	4.5×10^{-7}
Pezzoli, 2013[21]	Farming	RR	1.32 (1.11-1.57)	0.087	37.3	0.219	10	5.18	0.022
Pezzoli, 2013[21]	Organic solvents	RR	1.06 (0.86-1.30)	0.105	43.6	0.024	3	0.96	0.032
van der Mark, 2012[22]	Pesticides	RR	1.11 (0.89-1.38)	0.112	63.7	0.057	17	2.27	$< 1.0 \times 10^{-8}$
Pezzoli, 2013[21]	Rural living	RR	1.00 (0.99-1.01)	0.005	78.6	0.001	9	1.55	$< 1.0 \times 10^{-8}$
Noyce, 2012[23]	Well water drinking	RR	1.23 (0.99-1.52)	0.107	70.6	0.005*	10	2.26	$< 1.0 \times 10^{-8}$
Dietary factors									
Etminan, 2005[89]	Vitamin C intake	OR	0.78 (0.61-1.01)	0.129	38.1	0.165	0	0.72	NP
Etminan, 2005[89]	Vitamin E intake	OR	0.69 (0.49-0.98)	0.177	0	0.264	1	0.92	0.926
Jiang, 2014[90]	Dairy products intake	RR	1.33 (1.07-1.65)	0.110	8.2	0.615	4	0.95	7.7×10^{-4}
Takeda, 2014[91]	Lutein intake	OR	0.78 (0.56-1.09)	0.170	77.8	0.096	2	0.47	0.018
Takeda, 2014[91]	Lycopene intake	OR	0.87 (0.63-1.20)	0.164	62.3	0.983	1	0.22	0.085
Takeda, 2014[91]	Vitamin A intake	OR	1.16 (0.85-1.58)	0.158	0	0.444	0	0.22	NP
Takeda, 2014[91]	α-carotene intake	OR	0.91 (0.64-1.29)	0.179	22.9	0.847	0	0.18	NP
Takeda, 2014[91]	β-carotene intake	OR	0.90 (0.63-1.29)	0.183	37.5	0.862	1	0.37	0.286
Takeda, 2014[91]	β-cryptoxanthin intake	OR	0.74 (0.53-1.03)	0.169	42.1	0.271	0	0.49	NP
Wang, 2014[92]	Carbohydrate intake	RR	1.29 (0.98-1.70)	0.141	0	0.613	1	0.91	0.917

Wang, 2014[92]	Cholesterol intake	RR	0.87 (0.69-1.10)	0.119	62.4	0.273	2	0.48	0.022
Wang, 2014[92]	Energy intake	RR	0.97 (0.93-1.02)	0.024	83.8	0.084	2	0.41	0.010
Wang, 2014[92]	Protein intake	RR	1.60 (1.10-2.20)	0.177	30.4	0.676	1	2.32	NP
Wang, 2014[92]	Total fat intake	RR	0.69 (0.52-0.91)	0.143	34.4	0.070*	2	2.52	NP
Medical history and comorbid diseases									
Cereda, 2011[24] and Lu, 2014[25]	Diabetes mellitus	OR	1.41 (1.20-1.66)	0.083	78.1	0.035*	9	6.74	0.270
Jafari, 2013[57]	Head injury	OR	1.94 (1.69-2.23)	0.071	61	0.569	10	8.58	0.533
Liu, 2011[93]	Melanoma	OR	1.44 (1.03-2.01)	0.171	24.1	0.718	1	2.77	NP
Noyce, 2012[23]	Anxiety or Depression	RR	1.79 (1.72-1.86)	0.020	67.7	0.755	10	7.3	0.132
Noyce, 2012[23]	Cancer	RR	1.04 (0.96-1.12)	0.039	50.4	0.132	1	0.43	0.364
Noyce, 2012[23]	Constipation	RR	2.18 (1.32-3.61)	0.257	0	NE	2	0.9	0.116
Noyce, 2012[23]	Gastric ulcer	RR	0.47 (0.25-0.84)	0.309	81	0.072*	2	1.04	0.243
Noyce, 2012[23]	Hypertension	RR	0.96 (0.80-1.15)	0.093	76.4	0.392	5	0.64	2.0×10^{-8}
Noyce, 2012[23]	Oophorectomy	RR	0.75 (0.56-0.99)	0.145	58.8	0.931	2	0.55	0.039
Shen, 2013[26]	Gout	RR	0.70 (0.59-0.83)	0.087	0	NE	2	1.56	0.452
Drugs									
Gagne, 2010[94]	Aspirin	RR	1.13 (0.96-1.33)	0.083	50.3	0.335	1	0.53	0.497
Gagne, 2010[94]	Non-aspirin NSAIDs	RR	0.93 (0.80-1.08)	0.077	0.1	0.034	1	0.45	0.393
Gao, 2011[76]	Acetaminophen	RR	1.16 (1.00-1.35)	0.077	0	0.058*	0	0.48	NP
Gao, 2011[76]	Ibuprofen	RR	0.77 (0.61-0.98)	0.121	0	0.588	3	1.12	0.044
Noyce, 2012[23]	Beta-blockers	RR	1.28 (1.16-1.41)	0.050	0	0.403	2	1.48	0.546
Lang, 2015[95]	Calcium channel blockers	RR	0.70 (0.61-0.81)	0.074	25.7	0.128	2	2.03	NP
Noyce, 2012[23]	General anesthesia	RR	0.74 (0.61-0.91)	0.102	74.2	0.195	2	0.92	0.223
Noyce, 2012[23]	Oral contraceptives	RR	1.02 (0.77-1.36)	0.145	71.1	0.390	1	0.15	0.025
Undela, 2013[96]	Statins	RR	0.94 (0.82-1.09)	0.073	62.9	0.015	2	0.7	0.105
Wang, 2015[97]	Hormone Replacement Therapy	RR	1.21 (1.00-1.46)	0.097	50.4	0.013*	4	1.45	0.025
Biomarkers									
Chen, 2014[98]	BMI (BMI≥ 30 vs. BMI< 25)	OR	2.34 (1.83-2.97)	0.124	90.6	0.189	2	4.94	NP
Chen, 2014[98]	BMI (BMI≥ 30 vs. 25 •BMI< 30)	OR	1.20 (0.96-1.50)	0.114	71.5	0.319	3	0.68	0.003
Chen, 2014[98]	BMI (25 •BMI< 30 vs. BMI<25)	OR	1.16 (0.99-1.37)	0.083	85.2	0.541	2	0.67	0.088

Gao, 2014[52]	α-synuclein in CSF	OR	1.17 (0.75-1.84)	0.230	91.7	0.120	7	0.60	$< 1.0 \times 10^{-8}$
Gudala, 2013[99]	Serum cholesterol	RR	1.06 (0.88-1.26)	0.092	70.3	0.234	2	0.48	0.023
Lv, 2014[51]	Serum vitamin D	OR	0.73 (0.55-0.96)	0.142	97.7	0.063	7	0.71	$< 1.0 \times 10^{-8}$
Mariani, 2013[56]	Copper in plasma	OR	85.10 (44.70-162.02)	0.329	98.7	0.272	3	3.96	NP
Mariani, 2013[56]	Copper in CSF	OR	0.91 (0.40-2.08)	0.421	83.8	0.680	2	0.25	3.8×10^{-4}
Mariani, 2013[56]	Serum copper	OR	0.66 (0.32-1.35)	0.366	92.6	0.913	4	0.63	1.0×10^{-5}
Mariani, 2013[56]	Iron in CSF	OR	0.64 (0.28-1.45)	0.421	79.8	0.487	2	0.34	3.2×10^{-3}
Mariani, 2013[56]	Serum iron	OR	0.16 (0.11-0.24)	0.204	93.6	0.615	7	5.14	0.240
Sako, 2014[100]	Nigral volume loss	OR	0.22 (0.11-0.42)	0.333	47.4	0.917	3	1.74	0.280
Shen, 2013[26]	Serum urate	RR	0.60 (0.30-1.10)	0.331	42.1	0.390	2	1.37	0.556
Shen, 2013[55]	Serum uric acid	OR	0.23 (0.19-0.29)	0.111	75.9	0.286	4	3.74	0.830
Yu, 2014[54]	RNFLT	OR	0.58 (0.35-0.95)	0.258	81	0.969	8	1.26	$< 1.0 \times 10^{-8}$
Zhao, 2013[53]	BMD in femoral neck	OR	0.47 (0.31-0.71)	0.213	95.6	0.267	5	1.81	0.007
Zhao, 2013[53]	BMD in hip	OR	0.95 (0.62-1.44)	0.213	61.8	0.192	4	0.30	$< 1.0 \times 10^{-8}$
Zhao, 2013[53]	BMD in lumbar spine	OR	0.90 (0.59-1.37)	0.217	89	0.747	6	0.48	$< 1.0 \times 10^{-8}$
Zhao, 2013[53]	BMD in trochanter	OR	0.86 (0.57-1.31)	0.213	45.6	0.733	1	0.22	0.090

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, OR: odds ratio, PI: prediction interval RR: risk ratio, RNFLT: retinal nerve fiber layer thickness

*In the annotated papers, the Egger test was statistically significant ($p<0.10$) but the largest study has larger effect size compared to the summary effect size under random effects, denoting the absence of small-study effects

Table 3. Assessment across the 66 associations of environmental risk factors with Parkinson's disease

Association does NOT imply causation. See Discussion for alternative explanations for convincing and suggestive associations.

Risk factors	Sample size (number of cases)	Estimate of heterogeneity	95% prediction interval	Small-study effect or excess significance bias	Random effects summary effect size (95% CI)	Significance threshold reached (under the random-effects model)
Associations supported by highly suggestive evidence						
Anxiety or depression[23]	>1000	Large	Excluding the null value	Neither	1.86 (1.64-2.10)	$<10^{-6}$
Beta-blockers[23]	>1000	Not large	Including the null value	Neither	1.28 (1.19-1.39)	$<10^{-6}$
Head injury[57]	>1000	Large	Including the null value	Neither	1.55 (1.33-1.81)	$<10^{-6}$
Physical activity[58]	>1000	Not large	Excluding the null value	Excess significance bias	0.66 (0.57-0.78)	$<10^{-6}$
Serum uric acid[55]	>1000	Very large	Including the null value	Neither	0.39 (0.27-0.57)	$<10^{-6}$
Smoking[23]	>1000	Not large	Excluding the null value	Both	0.64 (0.60-0.69)	$<10^{-6}$
Associations supported by suggestive evidence						
Alcohol intake[85]	>1000	Large	Including the null value	Both	0.75 (0.66-0.85)	<0.001 but $>10^{-6}$
Calcium channel blockers[95]	>1000	Not large	Including the null value	Neither	0.78 (0.67-0.90)	<0.001 but $>10^{-6}$
Coffee drinking[23]	>1000	Not large	Excluding the null value	Both	0.67 (0.58-0.76)	$<10^{-6}$
Dairy products intake[90]	>1000	Not large	Excluding the null value	Excess significance bias	1.40 (1.20-1.63)	<0.001 but $>10^{-6}$
Farming[21]	>1000	Not large	Including the null value	Excess significance bias	1.30 (1.16-1.46)	<0.001 but $>10^{-6}$
Ibuprofen[76]	>1000	Not large	Excluding the null value	Excess significance bias	0.73 (0.62-0.85)	<0.001 but $>10^{-6}$
Pesticides[22]	>1000	Large	Including the null value	Both	1.62 (1.40-1.88)	$<10^{-6}$

Rural living[21]	>1000	Very Large	Including the null value	Both	1.32 (1.18-1.48)	<0.001 but >10^{-6}
Welding[87]	>1000	Not large	Excluding the null value	Neither	0.86 (0.80-0.92)	<0.001 but >10^{-6}
Associations supported by weak evidence						
BMD in femoral neck[53]	>500 but <1000	Very large	Including the null value	Excess significance bias	0.25 (0.09-0.66)	<0.05 but >0.001
BMD in hip[53]	<500	Large	Including the null value	Excess significance bias	0.55 (0.38-0.80)	<0.05 but >0.001
BMD in lumbar spine[53]	>500 but <1000	Very large	Including the null value	Excess significance bias	0.29 (0.16-0.54)	<0.05 but >0.001
Carbohydrate intake[92]	>1000	Not large	Excluding the null value	Neither	1.24 (1.05-1.48)	<0.05 but >0.001
Energy intake[92]	>1000	Very large	Including the null value	Both	1.39 (1.01-1.92)	<0.05 but >0.001
Hydrocarbon exposure[88]	>1000	Not large	Including the null value	Both	1.36 (1.13-1.63)	<0.05 but >0.001
Hypertension[23]	>1000	Very large	Including the null value	Excess significance bias	0.75 (0.61-0.90)	<0.05 but >0.001
Nigral volume loss[100]	<500	Not large	Including the null value	Neither	0.31 (0.17-0.55)	<0.05 but >0.001
Non asprin NSAIDs[94]	>1000	Not large	Excluding the null value	Small-study effects	0.85 (0.77-0.94)	<0.05 but >0.001
Organic solvents[21]	>1000	Not large	Excluding the null value	Both	1.22 (1.01-1.47)	<0.05 but >0.001
RNFLT[54]	>500 but <1000	Very large	Including the null value	Excess significance bias	0.40 (0.24-0.66)	<0.05 but >0.001
Serum urate[26]	>500 but <1000	Not large	Including the null value	Neither	0.65 (0.43-0.97)	<0.05 but >0.001
Serum vitamin D[51]	>1000	Very large	Including the null value	Both	0.16 (0.05-0.50)	<0.05 but >0.001
Statins[96]	>1000	Large	Including the null value	Small study effects	0.77 (0.64-0.92)	<0.05 but >0.001
Vitamin E intake[89]	>500 but <1000	Not large	Including the null value	Neither	0.81 (0.67-0.98)	<0.05 but >0.001

Well water drinking[23]	>1000	Large	Including the null value	Excess significance bias	1.21 (1.05-1.40)	<0.05 but >0.001
α-synuclein in CSF[52]	>500 but <1000	Very large	Including the null value	Excess significance bias	0.29 (0.13-0.62)	<0.05 but >0.001
Associations not adequately assessed owing to small number of studies						
Constipation[23]	<500	Not large	NA	NA	2.34 (1.55-3.53)	<0.001
Gout[26]	>1000	Not large	NA	NA	0.70 (0.60-0.82)	<0.001
Not significant associations						
Acetaminophen intake[76]	>1000	Not large	Including the null value	Neither	1.09 (0.96-1.24)	>0.05
Aspirin intake[94]	>1000	Large	Including the null value	Neither	1.08 (0.93-1.27)	>0.05
BMD in trochanter[53]	<500	Not large	Including the null value	Neither	0.73 (0.48-1.11)	>0.05
BMI (BMI≥ 30 vs. BMI< 25)[98]	>1000	Very large	Including the null value	Neither	0.96 (0.61-1.50)	>0.05
BMI (BMI≥ 30 vs. 25 •BMI< 30)[98]	>1000	Large	Including the null value	Excess significance bias	0.83 (0.65-1.07)	>0.05
BMI (25 •BMI< 30 vs. BMI<25)[98]	>1000	Very large	Including the null value	Excess significance bias	1.20 (0.94-1.53)	>0.05
Cancer[23]	>1000	Large	Including the null value	Neither	0.89 (0.72-1.10)	>0.05
Cholesterol intake[92]	>1000	Large	Including the null value	Excess significance bias	0.97 (0.75-1.26)	>0.05
Copper in plasma[56]	<500	Very large	Including the null value	Neither	1.41 (0.03-59.27)	>0.05
Copper in CSF[56]	<500	Very large	Including the null value	Excess significance bias	2.06 (0.57-7.44)	>0.05
Diabetes mellitus[24,25]	>1000	Very large	Including the null value	Neither	0.91 (0.74-1.11)	>0.05
Gastric ulcer[23]	<500	Very large	Including the null value	Neither	1.37 (0.36-5.31)	>0.05
General anesthesia[23]	>1000	Large	Including the null value	Neither	1.10 (0.77-1.58)	>0.05

Hormone replacement therapy[97]	>1000	Large	Including the null value	Excess significance bias	1 (0.84-1.20)	>0.05
Iron in CSF[56]	<500	Very large	Including the null value	Excess significance bias	0.93 (0.35-2.45)	>0.05
Lutein intake[91]	>500 but <1000	Very large	Including the null value	Both	1.49 (0.83-2.68)	>0.05
Lycopene intake[91]	>500 but <1000	Large	Including the null value	Neither	1.03 (0.64-1.65)	>0.05
Manganese exposure[87]	>1000	Large	Including the null value	Neither	0.76 (0.41-1.42)	>0.05
Melanoma[93]	>1000	Not large	Including the null value	Neither	1.13 (0.73-1.76)	>0.05
Oophorectomy[23]	>500 but <1000	Large	Including the null value	Excess significance bias	0.77 (0.52-1.13)	>0.05
Oral contraceptives[23]	>500 but <1000	Large	Including the null value	Excess significance bias	0.73 (0.43-1.25)	>0.05
Protein intake[92]	>1000	Not large	Including the null value	Neither	1.13 (0.88-1.44)	>0.05
Serum cholesterol[99]	>1000	Large	Including the null value	Excess significance bias	0.91 (0.71-1.15)	>0.05
Serum copper[56]	<500	Very large	Including the null value	Excess significance bias	1.46 (0.46-4.63)	>0.05
Serum iron[56]	>500 but <1000	Very large	Including the null value	Neither	0.45 (0.17-1.17)	>0.05
Tea intake[86]	>1000	Large	Including the null value	Excess significance bias	0.86 (0.68-1.08)	>0.05
Total fat intake[92]	>1000	Not large	Including the null value	Neither	0.88 (0.74-1.06)	>0.05
Vitamin A intake[91]	>500 but <1000	Not large	Including the null value	Neither	1.09 (0.84-1.42)	>0.05
Vitamin C intake[89]	>1000	Not large	Including the null value	Neither	1.06 (0.86-1.30)	>0.05

α-carotene intake[91]	>500 but <1000	Not large	Including the null value	Neither	0.84 (0.59-1.18)	>0.05
β-carotene intake[91]	>1000	Not large	Including the null value	Neither	0.92 (0.70-1.20)	>0.05
β-cryptoxanthin intake[91]	>500 but <1000	Not large	Including the null value	Neither	0.96 (0.66-1.40)	>0.05

Table 4. Quality assessments of primary studies. 13 papers assessed the quality of the primary observational studies using the Newcastle Ottawa Scale (NOS). Two additional papers used different methods to assess the included studies (criteria set by authors in the case of Cereda 2011 and QUADAS-2 in the case of Gao 2014). The other 18 papers did not perform any quality assessment.

Reference	Risk factor	High quality (NOS score = 9)	Moderate quality (NOS score = 7 or 8)	Low quality (NOS score < 7)
Gagne, 2010[94]	Aspirin	0	6	0
	Non-aspirin NSAIDs	0	7	0
Gudala, 2013[99]	Serum cholesterol	3	1	4
Jafari, 2013[57]	Head injury	6	7	9
Lang, 2015*	Calcium channel blockers	0	5	0
Lu, 2014[25]	Diabetes mellitus	0	6	8
Lv, 2014[51]	Serum vitamin D	2	5	0
Pezzoli, 2013[21]	Farming	0	16	21
	Organic solvents	0	7	11
	Rural living	0	4	27
Shen, 2013[26] *	Serum urate	0	6	0
	Gout	0	2	0
Takeda, 2014[91]	Lutein intake	0	3	1
	Lycopene intake	0	2	1
	Vitamin A intake	0	2	1
	α-carotene intake	0	1	2
	β-carotene intake	0	3	3
	β-cryptoxanthin intake	0	1	2
Undela, 2013[96]	Statins	1	5	2
Wang, 2015[97]	Hormone replacement therapy	0	6	8
Yu, 2014[54] *	RNFLT	0	11	2
Zhang, 2014[85]	Alcohol	0	12	21

*These papers used as a threshold for moderate quality a NOS score=6