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Systematic Reviews and Meta- and Pooled Analyses

Metal Exposure and Risk of Parkinson Disease: A Systematic Review and Meta-Analysis

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Metal exposure has been suggested as a possible environmental risk factor for Parkinson disease (PD). We searched the PubMed, EMBASE, and Cochrane databases to systematically review the literature on the relationship between metal exposure and PD risk and to examine the overall quality of each study and the exposure assessment method. A total of 83 case-control studies and 5 cohort studies published during the period 1963–July 2021 were included, of which 73 were graded as being of low or moderate overall quality. Investigators in 69 studies adopted self-reported exposure and biomonitoring after disease diagnosis for exposure assessment approaches. The meta-analyses showed that concentrations of copper and iron in serum and concentrations of zinc in either serum or plasma were lower, while concentrations of magnesium in CSF and zinc in hair were higher, among PD cases as compared with controls. Cumulative lead levels in bone were found to be associated with increased risk of PD. We did not find associations between other metals and PD. The current level of evidence for associations between metals and PD risk is limited, as biases from methodological limitations cannot be ruled out. High-quality studies assessing metal levels *before* disease onset are needed to improve our understanding of the role of metals in the etiology of PD.

meta-analysis; metals; Parkinson disease; systematic reviews

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; EA, exposure assessment; OR, odds ratio; PD, Parkinson disease; SMD, standardized mean difference.

Parkinson disease (PD) is the second most frequent neurodegenerative disease. It is characterized by movement dysfunctions including bradykinesia, muscular rigidity, rest tremor, and postural instability. The pathological features of PD are represented by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta and the Lewy body inclusions, leading to dopamine deficiency and motor defects (1). The estimated incidence of PD is 14 per 100,000 population overall, and it increases sharply to 160 per 100,000 population above the age of 65 years (2). The global burden of PD has more than doubled over the past few decades, showing faster growth than any other neurological disorder (3); this increase cannot be fully explained by the aging of the population.

Although the precise pathological mechanisms remain undetermined, current thinking is that PD arises from an interaction between genetic and environmental factors. Causative genetic mutations explain only a small proportion of PD cases, and about 90% of cases are sporadic, suggesting a significant role for environmental risk factors (2). Among these factors, heavy metal exposure is one of the concerns in PD pathogenesis. Possible mechanisms for an effect of metals in the onset and progression of PD include mitochondrial dysfunction and oxidative stress, promotion of α-synuclein aggregation and fibril formation, and activation of microglial cells and inflammation (4, 5). Human studies have shown that manganese inhalation from mining and welding fumes could induce parkinsonism (6), and dental amalgam filling restoration has been associated with an elevated risk of PD (7). Moreover, numerous studies on specific metals and PD risk have been published, but results are inconsistent. Methodological limitations may hinder drawing conclusions on the associations between metal exposure and PD risk.

We conducted a systematic review and meta-analysis aiming to evaluate the current epidemiologic evidence on associations between metal exposure and the risk of PD, with specific consideration of the quality of studies and the validity of the exposure assessment (EA) methods.

METHODS

Study search strategy

We searched the PubMed (National Library of Medicine, Bethesda, Maryland), EMBASE (Elsevier BV, Amsterdam, the Netherland), and Cochrane Library (Cochrane Collaboration, London, United Kingdom) databases through the end of July 2021. The search string consisted of a combination of Medical Subject Headings and text words (search queries are provided in Web Table 1, available at https://doi.org/10.1093/aje/kwad082). We included the terms "Parkinson's disease," "Parkinson∗," "PD," and "neurodegenerative∗" for PD, in combination with "metal" and terms for specific metals (aluminum, calcium, cadmium, chromium, copper, iron, lead, magnesium, manganese, mercury, nickel, selenium, zinc), as well as "exposure" or "exposed." We further scrutinized the reference lists of relevant reviews and meta-analyses for additional publications.

Inclusion/exclusion criteria and study selection

Eligible publications in our systematic review were selected on the basis of the following criteria: 1) original, peer-reviewed research paper; 2) human observational study with a case-control or cohort design; 3) exposure included one of the metals listed above or general metal exposure; 4) the outcome was sporadic PD; and 5) the article was written in English. Exclusion criteria were: 1) animal study; 2) review, case report or case series, editorial, letter, or conference abstract without original data; 3) repeated or overlapping publication; 4) the exposure was welding or welding fumes, not estimation of specific or general metal exposure; and 5) the outcome was parkinsonism, manganism, motor dysfunction, or neuropsychological dysfunction.

After removal of duplicate publications, all articles were screened by title and abstract to exclude records on irrelevant topics and articles based on the exclusion criteria. Full texts for the remaining articles were retrieved and assessed by one reviewer (Y.Z.). Any uncertainty was discussed with a second reviewer (S.P.). In case of multiple publications from the same study, the most complete and/or most recent paper was included. Reanalyses of data from previously published studies without updates on the association between metal exposure and PD were excluded.

Data extraction

The following information was extracted from the candidate articles: first author's surname, year of publication, country or region, study design, sample size, age and sex distribution of participants, case ascertainment and control selection, matching variables or adjustment confounders, EA method, and analysis technique for measuring metal levels. Additional information for cohort studies included the follow-up period and the number of cases who developed the outcome (PD diagnosis/mortality).

For studies with quantitative EA, data on mean metal concentrations and standard deviations for the case and control groups were collected. When the mean value and/or standard deviation was not available, alternative statistical parameters for location (median, geometric mean), variability (geometric standard deviation, standard error, interquartile range, range), and alternative statistical tests (t statistic, P value, 95% confidence interval (CI)) were considered. For studies presenting only numerical data in figures, WebPlotDigitizer (Automeris LLC, Frisco, Texas) (8) was used for digitizing the data points from the figure. For studies with dichotomous/ordinal exposure categories, the numbers in each category from each group and the crude/adjusted odds ratio (OR) or relative risk and its 95% CI were extracted.

Assessment of study quality

Study quality was assessed in terms of both study design and EA method. The Newcastle-Ottawa Scale (9) was adapted separately for case-control studies and cohort studies (Web Tables 2 and 3). Four parameters were used to evaluate methodological quality: subject selection, comparability of the groups, ascertainment of either exposure or outcome (for case-control or cohort studies, respectively), and statistical analysis. We then appraised the EA methods using an adapted version of a previously published EA rating system (10) (Web Table 4). EA methods were considered uninformative (EA score of 1) when based on self-reported exposure, which could have led to nondifferential misclassification, or registry job history/self-reported job history in industrial cohorts, which are often inaccurate and incomplete (11). Biomonitoring, environmental monitoring, and food frequency questionnaires completed after disease onset were considered not completely valid (EA score of 2) because of possible reverse causation, while bone measurements of lead, cadmium, and chromium levels after disease onset were regarded as accurate (EA score of 4) due to their slow elimination from the human body. An EA score of 3 was given to job histories from company records, a valid but not agent-specific approach. Approaches considered valid and agent-specific (EA score of 4) included a job exposure matrix, case-by-case expert assessment, and environmental monitoring or biomonitoring before disease onset. Two reviewers (Y.Z. and A.R.) independently performed the quality assessment of all selected studies. Any disagreements were discussed between the 2 reviewers, and if no consensus was reached, the disagreement was resolved by a third reviewer (S.P.).

Statistical analysis

For case-control studies assessing metals in biological matrices (except for bone), the between-group standardized mean difference (SMD) (Hedges' g) was used as the effect

measure for each study. The SMD was calculated using the mean and standard deviation on the log-transformed scale (12), due to skewed distributions and small sample sizes in many of the included studies. For case-control studies assessing dietary and occupational/environmental metal exposures, the OR for "ever/higher metal exposure" versus "never/background metal exposure" was used as the effect measure for each study. Covariate-adjusted ORs were preferred over crude ORs to reduce possible confounding. When researchers reported ORs for stratified exposure groups (e.g., for quartiles, as was done in 7 studies), the pooled OR for a single study was calculated by within-study random-effects meta-analysis of the nonreference groups (13). When the mean/standard deviation or OR/standard error was not available, it was estimated from alternative statistics according to the recommendations of the Cochrane Handbook (14). When metal levels in the same matrix or source were presented as continuous data in some studies and as categorical data in other studies, reported SMDs and ORs were mutually converted using the formula $\text{SMD} = \sqrt{3}/\pi \ \ln \ \text{OR}$ (15). All formulae are provided in the Web Appendix.

Meta-analyses were conducted for each of the different metals (aluminum, calcium, cadmium, chromium, copper, iron, lead, magnesium, manganese, mercury, nickel, selenium, zinc, and general metal exposure) from various biological matrices (bone, cerebrospinal fluid (CSF), hair, whole blood, erythrocyte, plasma, serum, urine) and sources (diet, occupation/environment) separately, provided there were at least 2 studies remaining when low-quality papers were excluded. Studies assessing plasma and serum were additionally combined because they both assessed metals in the blood. Because considerable between-study heterogeneity was anticipated, a random-effects model was used to pool effect sizes. The restricted maximum likelihood estimator (16) was used to calculate the heterogeneity variance τ^2. Knapp-Hartung adjustment (17) was applied to calculate the 95% CI around the pooled effect.

Cochran's Q test and the I^2 statistic (18) were used to assess and quantify between-study heterogeneity. A P value less than 0.05 was considered significant statistical evidence of heterogeneity. I^2 values below 25% were deemed to show a low degree of heterogeneity, values of 25%–75% a medium degree, and values above 75% a high degree (18). In an attempt to explain heterogeneity, we performed subgroup analyses for geological locations and detection methods if the original meta-analysis contained at least 10 studies. Separate estimates of τ^2 were assumed in each subgroup. To explore the robustness of meta-analyses, we calculated different influence diagnostics (difference in fits (DFFITS) value, Cook's distance, hat value, difference in betas (DFBETAS) value) of individual studies based on the leave-one-out method, omitting 1 study each time. A study was considered influential if any of the above influential measures reached the chosen cutoffs (19). The presence of publication bias was checked using a funnel plot and Egger's test (20) if the number of studies was more than 10 and then applying the trim-and-fill method (21). Analyses were performed with the *meta*, *metafor*, and *dmetar* packages in R 3.6 software (22).

RESULTS

Study selection

After removal of duplicates, a total of 4,045 papers from multiple electronic databases, as well as relevant reviews, were screened. From these, 83 case-control studies and 5 cohort studies were selected on the basis of the inclusion and exclusion criteria (Figure 1). Basic information on the candidate studies is shown in Web Table 5 for case-control studies (23–105) and in Table 1 for cohort studies (106–110). Overall, 35 (40%) of the selected studies were carried out in Europe, 21 (24%) in Asia, 22 (25%) in North America, and 10 (11%) in other parts of the world.

The numbers of case-control studies focusing on each metal in different biospecimens/sources are presented in Table 2. Many studies (n = 48; 58%) assessed more than 1 type of metal, and 24 (29%) included more than 1 biological matrix or exposure source. The metals and exposure sources varied among the 5 cohort studies (Table 1).

Quality assessment

Results of study quality assessment for all included papers are shown in Web Tables 6 and 7. For general study quality, most case-control studies (n = 66; 80%) were scaled as moderate-quality, 4 as low-quality, and 13 as high-quality (Table 3). Three cohort studies were deemed moderate-quality (108–110) and 2 high-quality (106, 107). Concerning EA methods, most case-control studies (n = 75; 90%) adopted uninformative or invalid approaches (EA scores of 1 or 2). Eight studies used more reliable methods (EA score of 4). All cohort studies assessed metal exposure before disease onset (EA score of 4).

Meta-analyses of metal levels in biological matrices

Descriptive results for metal concentrations (aluminum, calcium, cadmium, chromium, copper, iron, lead, magnesium, manganese, mercury, nickel, selenium, and zinc) in biological matrices (CSF, hair, whole blood, plasma, serum, and urine) are shown in Web Tables 8–20. The numbers of included studies and subjects and overall effects are summarized in Table 4.

The majority of meta-analyses were based on less than 5 studies, and most of them included fewer than 250 PD cases. Pooled SMDs for aluminum, calcium, chromium, manganese, mercury, nickel, and selenium did not show any statistically significant difference between PD cases and controls in any biospecimen. Statistically significant differences in effect size were observed for cadmium in blood (n = 2 studies; SMD = −0.61, 95% CI: −1.08, −0.13), copper in serum (n = 18; SMD = −0.43, 95% CI: −0.84, −0.02), iron in serum (n = 27; SMD = −0.28, 95% CI: −0.56, 0.00), zinc in plasma or serum (n = 18; SMD = −0.53, 95% CI: −0.92, −0.14), which were lower in PD cases than in controls, and for magnesium in CSF (n = 5; SMD = 0.66, 95% CI: 0.41, 0.91) and zinc in hair (n = 4; SMD = 0.52, 95% CI: 0.14, 0.90), which were higher in PD cases. Forest plots of the meta-analyses of copper, iron, and

Table 1. Overview of Cohort Studies on Metal Exposure and Parkinson Disease, 1963–2020

First Author, Year (Reference No.)	Country	Cohort/ Population	Subjects	Exposure Source and Assessment Method	Follow-up Period	Outcome	Metal	RR[a]	95% CI
Logroscino, 2008 (107)	United States	HPFS and NHS	47,406 men from HPFS; 76,947 women from NHS	Diet; food frequency questionnaire	1986–2000 for HPFS 1984–2000 for NHS	PD incidence	Iron	1.10[b,c]	0.92, 1.33
Feldman, 2011 (109)	Sweden	Swedish Twin Registry	20,225 men	Occupation; job exposure matrix	1967/1973–2009	PD incidence	Metals (nonspecified)	0.90[d]	0.40, 1.80
Palacios, 2014 (106)	United States	NHS	97,430 women	Air; environmental monitoring	1990–2008	PD incidence	Cadmium	1.01[b,e]	0.86, 1.19
							Chromium	0.90[b,e]	0.76, 1.07
							Lead	0.94[b,e]	0.80, 1.11
							Manganese	1.12[b,e]	0.95, 1.33
							Mercury	1.23[b,e]	1.05, 1.46
							Nickel	0.99[b,e]	0.85, 1.15
Brouwer, 2015 (108)	The Netherlands	NLCS	58,279 men	Occupation; job exposure matrix	1986–2003	PD mortality	Metals (nonspecified)	1.02[b,f]	0.77, 1.35
Vinceti, 2016 (110)	Italy	Residents who consumed high-selenium tap water and a less exposed comparison group	Exposed cohort: n = 2,065; unexposed cohort: n = 95,715	Drinking water; environmental monitoring	1986–2012	PD mortality	Selenium	2.47[g]	1.15, 5.28

Abbreviations: CI, confidence interval; HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; NLCS, Netherlands Cohort Study on Diet and Cancer; RR, relative risk.
[a] RR for ever/higher exposure versus never/background exposure.
[b] Calculated from RRs in nonreference exposure groups using within-study random-effects meta-analysis.
[c] Adjusted for age, smoking, total energy, caffeine, body mass index, vitamin C, vitamin E, lactose, physical activity, and Alternate Healthy Eating Index score.
[d] Adjusted for age, education, and smoking.
[e] Adjusted for age, smoking, and population density.
[f] Adjusted for smoking, nonoccupational physical activity, and body mass index.
[g] Adjusted for age and calendar year.

Table 2. Numbers of Case-Control Studies Included in a Systematic Review and Meta-Analysis of Metal Exposure and Parkinson Disease, According to Biospecimen or Source, 1963–2020

Metal	Biospecimen or Source										Total No. of Studies
	Blood	Bone	CSF	Erythrocyte	Hair	Plasma	Serum	Urine	Diet	Occupation/ Environment	
Aluminum	1	NA	4	NA	3	NA	4	1	NA	1	9
Calcium	1	NA	4	NA	3	NA	5	1	4	NA	13
Cadmium	2	NA	2	NA	1	NA	2	2	NA	2	7
Chromium	1	NA	5	NA	1	NA	6	3	NA	1	11
Copper	3	NA	11	1	3	8	19	5	3	6	45
Iron	1	NA	11	NA	4	5	28	4	6	2	46
Lead	3	2	4	NA	1	1	4	2	NA	5	17
Magnesium	1	NA	5	NA	2	NA	7	1	3	NA	14
Manganese	4	NA	8	NA	4	2	9	5	3	6	30
Mercy	4	NA	2	NA	3	NA	4	3	NA	3	12
Nickel	1	NA	3	NA	1	1	3	1	NA	2	9
Selenium	NA	NA	3	NA	1	3	7	2	2	NA	14
Zinc	3	NA	7	1	4	6	13	6	4	3	32
Metals[a]	NA	NA	NA	NA	NA	NA	NA	NA	NA	8	8
Total	8	2	15	1	7	11	41	11	8	13	83

Abbreviations: CSF, cerebrospinal fluid; NA, not available.
[a] Results were reported only for general metal exposure, not particular kinds of metal.

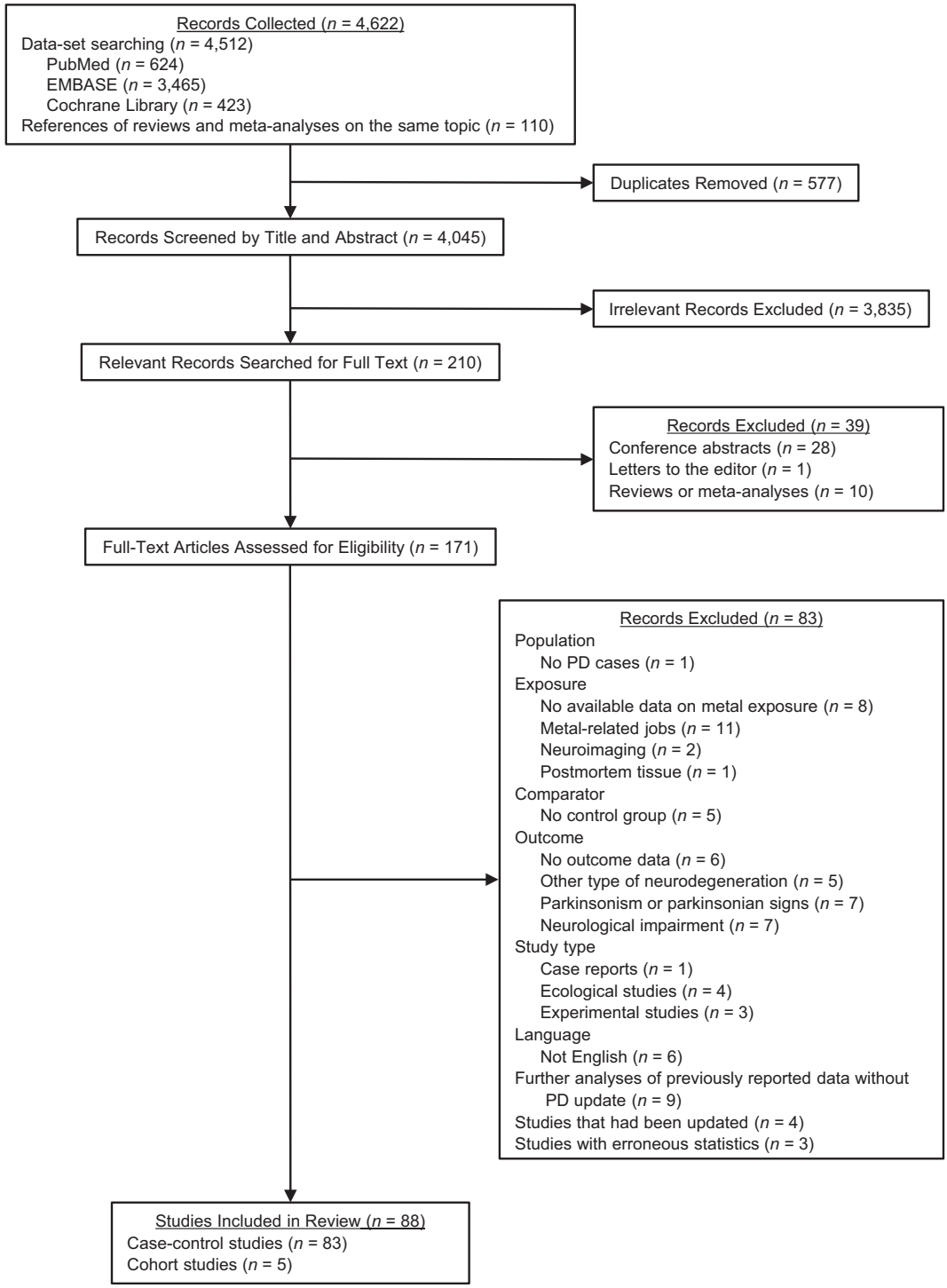

Figure 1. Selection of studies for inclusion in a systematic review and meta-analysis on associations between metal exposure and risk of Parkinson disease (PD), 1963–2020.

zinc in plasma/serum, from more than 15 studies, are shown in Figures 2–4. Forest plots of the other metal-biospecimen combinations are presented in Web Figure 1.

In the 2 included studies on bone lead levels, investigators reported an increased risk of PD for individuals with higher overall lead bone levels relative to the lowest quartile (OR = 1.34 (95% CI: 1.02, 1.76) (49) and OR = 1.32 (95% CI: 1.04, 1.66) (66)). Further, a positive exposure-response relationship was observed for tibia bone lead (*P* for trend = 0.012 (49) and *P* for trend = 0.06 (66)).

Table 3. Quality of Articles Included in a Systematic Review and Meta-Analysis of Metal Exposure and Parkinson Disease, by Exposure Assessment Method and General Study Design Quality, 1963–2020

EA Score	EA Method	No. of Studies	General Study Design Quality		
			Low	Moderate	High
	Case-Control Studies[a]				
			(*n* = 4)	(*n* = 66)	(*n* = 13)
1	Self-reported occupational/environmental exposure	6	1	3	2
2	Biomonitoring after disease onset	64	3	58	3
2	Food frequency questionnaire after disease onset	8	0	3	5
2	Environmental monitoring after disease onset	1	0	1	0
4	Biomonitoring, lead in bone	2	0	1	1
4	Job exposure matrix	4	0	2	2
4	Expert assessment	2	0	1	1
	Cohort Studies				
			(*n* = 0)	(*n* = 3)	(*n* = 2)
4	Food frequency questionnaire before disease onset	1	0	0	1
4	Job exposure matrix	2	0	2	0
4	Environmental monitoring before disease onset	2	0	1	1

Abbreviation: EA, exposure assessment.
[a] Four studies adopted 2 methods of EA.

For many meta-analyses, between-study heterogeneity was considerable (Table 4). Studies assessing copper, iron, and zinc in plasma/serum had an I^2 value greater than 90%. Subgroup analyses revealed a subtle change in effect sizes between geographic locations (Web Table 21). Significant differences were observed among the detection techniques for copper in CSF (P for subgroup = 0.014), copper in plasma/serum (P for subgroup < 0.001), iron in CSF (P for subgroup < 0.001), iron in serum (P for subgroup = 0.005), manganese in plasma/serum (P for subgroup = 0.025), and zinc in serum (P for subgroup = 0.034). Influential studies were detected in some meta-analyses, including those of iron in plasma/serum, selenium in plasma/serum, and zinc in serum (Web Table 22, Web Figure 2). Removal of these influential studies caused small deviations from both the original pooled effects and between-study heterogeneity.

Funnel plots and Egger's tests did not reveal any significant evidence of publication bias, except for studies on copper in CSF (Egger's test, $P = 0.03$) (Web Table 23, Web Figure 3). After trim-and-fill method adjustment, the pooled effect of −0.23 (95% CI: −0.49, 0.02) in the meta-analysis of iron in plasma/serum changed to 0.02 (95% CI: −0.27, 0.32).

Meta-analyses of metal exposure from diet and occupation/environment

Characteristics and effect sizes of case-control studies assessing dietary and occupational/environmental metal are shown in Web Tables 24 and 25. Case-control studies mainly focused on essential nutritional metals (calcium, copper, iron, magnesium, zinc) and did not show consistent results in meta-analyses (Table 5). An overall OR of 1.11 (95% CI: 0.70, 1.76) was estimated for manganese, indicating no significant difference in dietary manganese intake between cases and controls. In a cohort study by Logroscino et al. (107), a modest increase in PD risk was associated with dietary iron intake (highest quintile vs. lowest: relative risk = 1.30, 95% CI: 0.94, 1.80).

As for occupational/environmental metal exposure, a borderline-significant OR from combining 4 studies (OR = 1.04, 95% CI: 1.01, 1.06) was found for manganese exposure and PD risk (Table 6). Lead exposure was associated with an elevated risk (OR = 1.14), but the effect was not statistically significant (95% CI: 0.64, 2.01). The same was true for nonspecified metal exposure (OR = 1.22, 95% CI: 0.70, 2.14). The impacts of exposure to copper, iron, mercury, and zinc were inconclusive, and the 95% CIs for mercury and zinc were wide. Forest plots of all meta-analyses are shown in Web Figures 4 and 5.

Feldman et al. (109) and Brouwer et al. (108) explored the association between occupational metal exposures and PD among men in large population-based prospective cohort studies in Sweden and the Netherlands, respectively, but neither of them observed any significant association (Table 1). Palacios et al. (106) found a positive monotonic association with airborne mercury exposure and risk of PD (quartile 2: hazard ratio = 1.15 (95% CI: 0.87, 1.52); quartile 3: hazard ratio = 1.24 (95% CI: 0.93, 1.65); quartile 4: hazard ratio = 1.33 (95% CI: 0.99, 1.79)) in a cohort of female nurses, while relationships with other hazardous metals (cadmium,

Table 4. Pooled Effect Estimates for Associations Between Metal Levels in Biospecimens and Parkinson Disease, 1963–2020

Metal and Biological Matrix	No. of Studies	No. of PD Cases	No. of Controls	Pooled SMD	95% CI	I^2, %
Aluminum						
CSF	4	219	140	−0.50	−1.05, 0.04	53
Hair	3	186	243	0.92	−1.15, 3.00	94
Serum	4	464	447	−0.44	−2.53, 1.64	97
Calcium						
CSF	4	219	140	0.30	−0.10, 0.71	18
Hair	3	163	75	−0.58	−1.27, 0.11	10
Serum	5	497	546	0.80	−0.69, 2.30	99
Cadmium						
Blood	2	49	37	−0.61	−1.08, −0.13	0
CSF	2	68	33	−1.20	−12.21, 9.82	92
Serum	2	97	137	−0.88	−7.43, 5.68	84
Urine	2	49	37	−0.04	−4.21, 4.13	53
Chromium						
CSF	5	182	178	−0.40	−1.58, 0.78	92
Serum	6	440	586	0.10	−0.14, 0.34	33
Urine	3	79	64	−0.14	−0.45, 0.17	0
Copper						
Blood	2	114	42	0.42	−3.76, 4.59	64
CSF	11	418	336	0.16	−0.38, 0.70	86
Hair	3	150	56	−0.03	−0.80, 0.73	14
Plasma	7	603	746	0.27	−0.58, 1.12	97
Serum	18	1,147	1,164	−0.43	−0.84, −0.02	94
Plasma + serum	25	1,750	1,910	−0.23	−0.60, 0.14	96
Urine	4	198	127	−0.11	−1.21, 0.98	84
Iron						
CSF	11	483	312	−0.29	−0.71, 0.13	81
Hair	4	176	89	−0.13	−1.03, 0.77	78
Plasma	5	525	601	0.02	−0.86, 0.90	95
Serum	27	2,060	2,380	−0.28	−0.56, 0.00	89
Plasma + serum	32	2,585	2,981	−0.23	−0.49, 0.02	92
Urine	4	223	152	0.27	−1.34, 1.87	88
Lead						
Blood	2	49	37	0.37	−6.35, 7.09	81
CSF	4	154	133	−0.60	−2.59, 1.40	95
Serum	4	380	516	−0.13	−1.48, 1.22	91
Plasma + serum	5	530	691	0.09	−1.01, 1.19	94
Magnesium						
CSF	5	239	155	0.66	0.41, 0.91	0
Hair	2	137	42	−0.35	−1.32, 0.62	0
Serum	6	572	580	0.45	−0.19, 1.09	82

Table continues

Table 4. Continued

Metal and Biological Matrix	No. of Studies	No. of PD Cases	No. of Controls	Pooled SMD	95% CI	I^2, %
Manganese						
Blood	3	209	139	0.02	−0.83, 0.87	66
CSF	8	296	243	−0.15	−0.64, 0.34	76
Hair	4	199	257	2.70	−3.84, 9.23	99
Plasma	2	375	300	0.43	−7.02, 7.88	98
Serum	8	589	664	0.11	−0.43, 0.66	89
Plasma + serum	10	964	964	0.18	−0.29, 0.65	93
Urine	4	205	130	−0.61	−1.33, 0.11	64
Mercury						
Blood	4	182	286	−0.20	−1.69, 1.30	93
CSF	2	68	33	−1.05	−4.14, 2.04	12
Hair	3	179	273	−0.20	−1.85, 1.45	90
Serum	4	195	301	−0.66	−1.91, 0.59	90
Urine	3	103	133	−0.62	−4.55, 3.01	91
Nickel						
CSF	3	208	150	−0.81	−1.80, 0.17	46
Serum	3	130	236	0.25	−0.92, 1.42	75
Plasma + serum	4	355	361	0.75	−1.09, 2.59	98
Selenium						
CSF	3	100	106	0.71	−0.04, 1.46	28
Plasma	3	285	356	0.16	−1.15, 1.47	76
Serum	7	254	309	0.16	−0.88, 1.20	94
Plasma + serum	10	539	665	0.16	−0.52, 0.84	92
Urine	2	52	54	0.04	−0.43, 0.50	0
Zinc						
Blood	2	114	42	0.40	−7.49, 8.29	90
CSF	7	312	213	−0.06	−0.85, 0.73	83
Hair	4	176	89	0.52	0.14, 0.90	0
Plasma	5	551	522	−1.04	−2.07, −0.01	92
Serum	13	815	837	−0.33	−0.75, 0.09	85
Plasma + serum	18	1,366	1,359	−0.53	−0.92, −0.14	94
Urine	4	198	127	−0.01	−0.33, 0.30	0

Abbreviations: CI, confidence interval; CSF, cerebrospinal fluid; PD, Parkinson disease; SMD, standardized mean difference.

chromium, lead, manganese, nickel) showed little evidence of differences. Vinceti et al. (110) found that high selenium levels in drinking water were associated with excess PD mortality, with a relative risk of 2.47 (95% CI: 1.15, 5.28) as compared with the control region.

DISCUSSION

In this systematic review and meta-analysis, we assessed the current literature to summarize the evidence on the association between metal exposure and PD risk. Most case-control studies were biomonitoring studies and were of moderate quality. Overall, there were no consistent associations regarding most metals in biospecimens or from dietary, occupational, or environmental sources. Only for lead exposure was there an indication of a possible increased risk of PD, given the higher bone lead level among PD cases reported in 2 studies (49, 66). Prospective studies assessing metal exposure prior to the occurrence of the outcome were limited, and most did not find changes in risk of PD after metal exposure, except for the increased risk observed after exposure to airborne mercury and elevated PD mortality among residents consuming drinking water with high selenium concentrations in 1 single study (110).

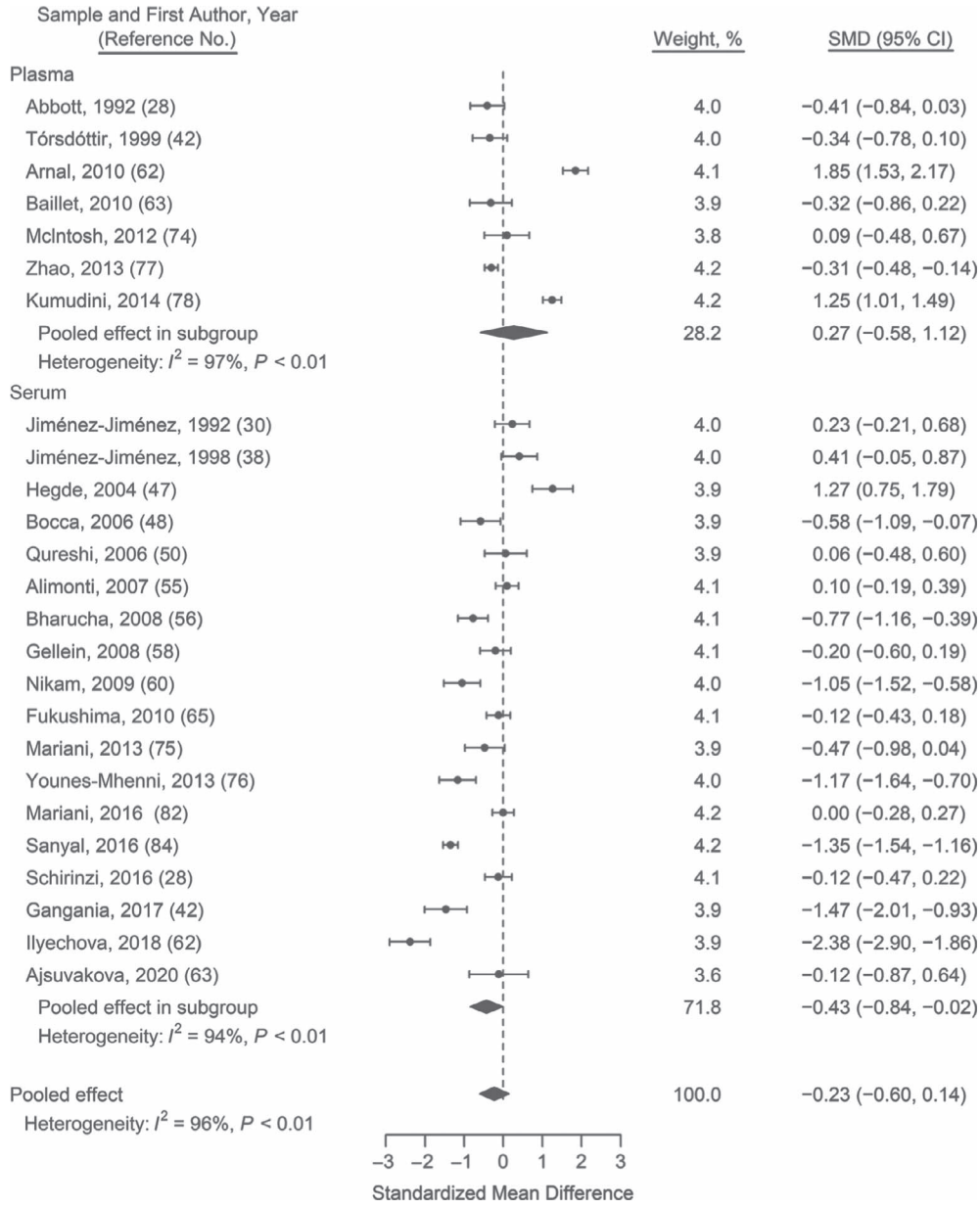

Figure 2. Forest plot for the associations of copper levels (plasma, serum, and overall) with Parkinson disease, 1992–2020. All included studies were rated as moderate-quality. The dashed line represents the referent (standardized mean difference (SMD) = 0). Bars show 95% confidence intervals (CIs).

Trace metals are responsible for a wide variety of neuronal functions, and disturbances of metal homeostasis have been implicated in the progression of PD. In mechanistic studies, excessive levels of some metals (e.g., manganese, iron, lead, mercury, aluminum, cadmium) have been shown to induce injury in dopaminergic neurons (5, 111–114), which are the cells primarily affected in PD, while magnesium is expected to act as a neuroprotective agent by inhibiting *N*-methyl-D-aspartate (NMDA) receptor activity and oxidative stress (115). However, the role of other metals (e.g., zinc, copper, selenium) remains unclear and complicated, as both beneficial and deleterious actions have been postulated in PD (116, 117).

To date, human studies on the relationship between metal exposures and the risk of PD have faced several limitations. The number of studies available for most metal-biospecimen combinations is less than 5 and the studies are based on small-scale research, often including fewer than 50 PD patients. Further, few studies on metal exposure from diet, occupation, or the environment are available to date, although they have included larger numbers of PD cases. Such data sparsity makes the pooled effects in this

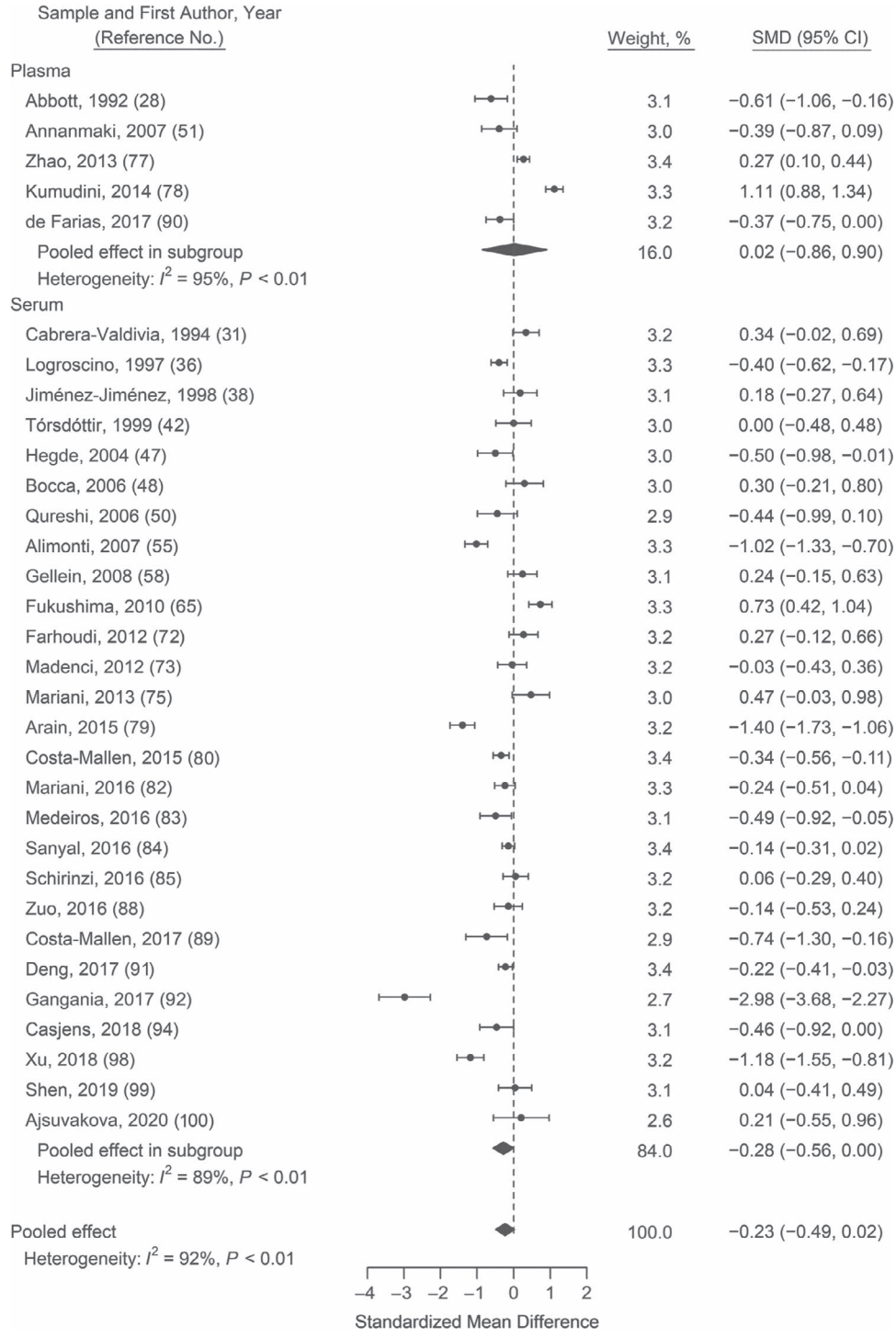

Figure 3. Forest plot for the associations of iron levels (plasma, serum, and overall) with Parkinson disease, 1992–2020. The 2017 study by Costa-Mallen et al. (89) was rated high-quality, and the rest of the studies were rated moderate-quality. The dashed line represents the referent (standardized mean difference (SMD) = 0). Bars show 95% confidence intervals (CIs).

review less accurate, because the standard random-effects meta-analysis method can lead to serious distortions in the presence of few studies and/or limited sample sizes (118). Additionally, consistently lower levels of iron and copper in serum were drawn from 18 and 27 studies, respectively, but the result became ambiguous when a few

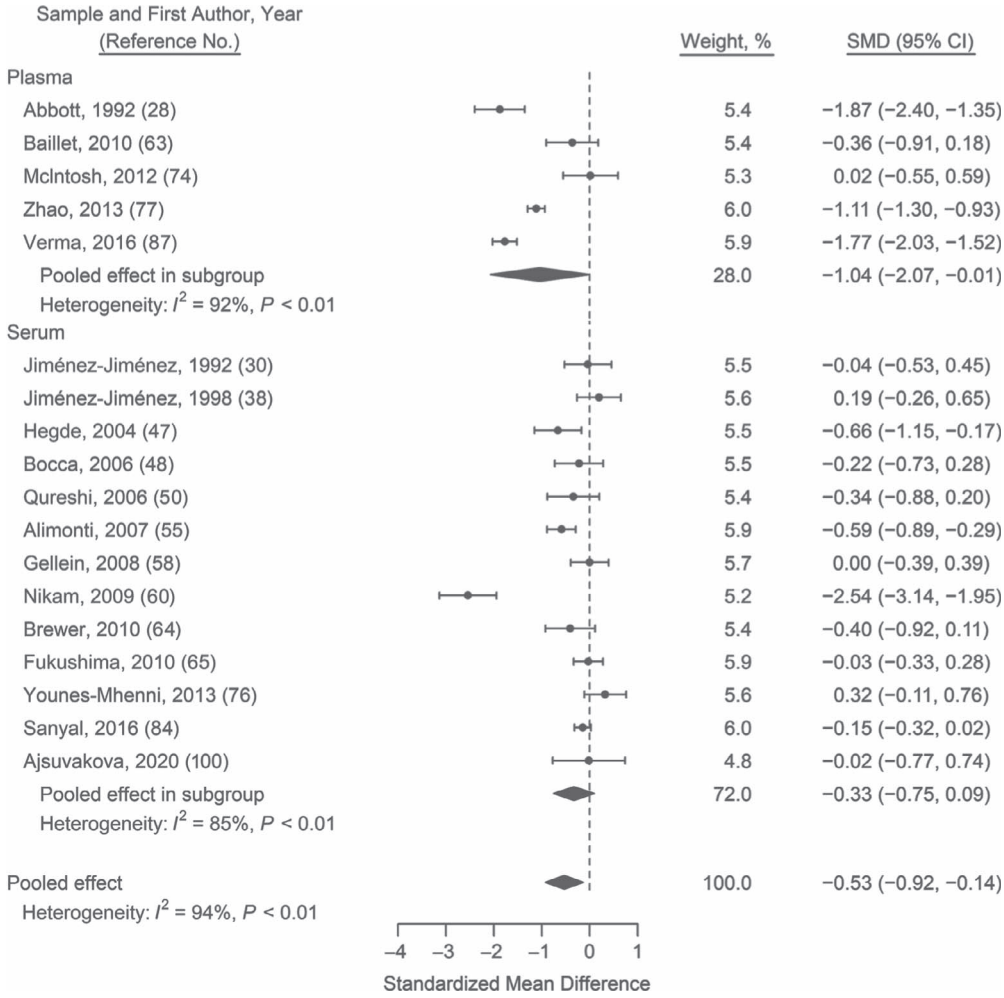

Figure 4. Forest plot for the associations of zinc levels (plasma, serum, and overall) with Parkinson disease, 1992–2020. All included studies were rated as moderate-quality. The dashed line represents the referent (standardized mean difference (SMD) = 0). Bars show 95% confidence intervals (CIs).

studies assessing metals in plasma were added, making the inverse associations of iron and copper with PD in the combined matrices undecisive. Another concern when utilizing biomonitoring studies is that circulating metal in the body is not necessarily representative of long-term exposure due to rapid elimination in biological fluids. The

Table 5. Pooled Effect Estimates for Associations Between Dietary Metal Intake and Parkinson Disease, 1963–2020

Metal	No. of Studies	No. of PD Cases	No. of Controls	Pooled OR	95% CI	I^2, %
Calcium	4	826	1,151	1.03	0.77, 1.39	64
Copper	3	700	719	0.83	0.30, 2.27	85
Iron	6	1,140	1,704	0.99	0.60, 1.61	69
Magnesium	3	700	719	0.89	0.22, 3.63	89
Manganese	3	700	719	1.11	0.70, 1.76	0
Selenium	2	122	111	1.24	0.44, 3.51	0
Zinc	4	740	748	0.85	0.42, 1.72	83

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson disease.

Table 6. Pooled Effect Estimates for Associations Between Occupational/Environmental Metal Exposure and Parkinson Disease, 1963–2020

Metal	No. of Studies	No. of PD Cases	No. of Controls	Pooled OR	95% CI	I^2, %
Copper	3	1,163	2,779	1.11	0.68, 1.80	0
Iron	2	911	2,453	1.08	0.91, 1.29	0
Lead	4	1,351	1,571	1.14	0.64, 2.01	41
Manganese	4	1,547	25,893	1.04	1.01, 1.06	0
Mercury	2	524	840	1.02	0.01, 111.70	17
Zinc	3	947	1,045	1.56	0.06, 44.07	66
Metal[a]	7	2,526	2,971	1.22	0.70, 2.14	65

Abbreviations: CI, confidence interval; OR, odds ratio; PD, Parkinson disease.
[a] Results were reported only for general metal exposure, not particular kinds of metal.

pathogenesis and progression of PD are slow; thus, chronic exposures to environmental stimuli will play a major role in the etiology of the disease.

Bone lead level, an exception in biomonitoring, is a proxy measure for distant past exposure because of the decades-long half-life of lead in bone. In 2 large-scale case-control studies assessing bone lead levels (451 PD patients and 722 controls in total), researchers consistently reported increased risk of PD in relation to cumulative lead exposure (49, 66). Further considering the relatively good quality of study design, these studies have indicated lead as a possible environmental risk factor for PD.

In our meta-analysis, PD patients had somewhat increased blood manganese levels in comparison with controls, but 95% CIs were wide and there was considerable heterogeneity across studies ($I^2 > 90\%$). Studies assessing occupational/environmental exposure, however, indicated a possible association (OR = 1.04, 95% CI: 1.01, 1.06; $I^2 = 0\%$). This limited evidence regarding manganese as risk factor for PD seemed contradictory to the well-established finding of manganese-induced parkinsonism. The reason behind the inconsistency might be different mechanisms of pathogenesis. Unlike PD, manganese-induced parkinsonism does not involve degeneration of midbrain dopamine neurons, and levodopa is not an effective treatment (119). Therefore, manganese may make differing contributions to the pathogenesis of these 2 different movement disorders.

The overall lack of consistency among studies limits drawing firm conclusions on associations. The high level of between-study heterogeneity was confirmed among the many studies evaluated, which indicates that effects might differ in certain contexts. From our subgroup analysis, metal detection methods in biomonitoring studies might have contributed to the high heterogeneity. Other relevant factors such as age distribution, sex ratio, disease severity, and disease duration may also have resulted in heterogeneity, but no sufficient data were available to address their impact. What is more, the nearly null effect of serum or plasma iron level after trim-and-fill correction indicates that the pooled effect in the meta-analysis might have been overestimated because of small-study effects.

More importantly, methodological limitations in the available studies could have resulted in serious bias and distorted the association between metal exposure and the risk of PD. First, there is possible case selection bias, as some studies identified the PD outcome through death certificates or health-care registers (41, 108–110). Register-based case ascertainment is likely to omit patients with early or mild disease, leading to results based only on more severe cases, which may not be translatable to all PD cases. Overlapping clinical features with other types of neurodegeneration and secondary parkinsonism, as well as symptom-based diagnosis, might also obscure the association with PD, since disease etiologies may be different. A second possible limitation is the selection of controls, which is often based on patients from the same hospital. Hospital controls, however, may not be representative of the source population, whereas the use of relatives as controls (31, 66, 85) may be affected by overmatching due to shared living conditions, activities, and life habits, resulting in a similar exposure status. Third, self-reported information on exposure in case-control studies can be affected by the awareness of disease status (44, 101), resulting in differential recall between cases and controls. Furthermore, PD manifestations may have changed the toxicokinetics of metals, and altered metal levels after diagnosis may erroneously be thought to play an etiological role—so-called reverse causality. Fourth, almost half of the case-control studies did not adopt matching between case and control groups. Confounding introduced by age, sex, smoking status, alcohol consumption, and comorbidity could bias effect estimates, and adjustment should be considered.

To our knowledge, this is the first meta-analysis and systematic review to have investigated the associations between metal exposures from various routes and the risk of PD. Besides consistency of results, we also considered the impact of EA and study design, which was recently recommended when applying pooled estimates to causal inference in observational studies (120). Because of inadequate study quality, high heterogeneity of reported results, and methodological limitations, the extant research on PD epidemiology is yet insufficient to establish an association between specific metal exposures and risk of the

disease. Future research on the association between metals and PD risk should aim to address the above challenges effectively to provide more reliable evidence. This further evidence will rely heavily on large prospective cohort studies, with comprehensive lifelong exposure history, a sufficient follow-up period, well-established biobanks, and careful case ascertainment.

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