Prediagnostic Blood Metal Levels and the Risk of Parkinson's Disease: A Large European Prospective Cohort

Yujia Zhao, MSc,[1] Anushree Ray, MSc,[1,2] Karin Broberg, PhD,[3] Maria Kippler, PhD,[3] Christina M. Lill, MD, MSc,[4,5] Paolo Vineis, PhD,[6] Verena A. Katzke, PhD,[7] Miguel Rodriguez-Barranco, PhD,[8,9,10] María-Dolores Chirlaque, MD, MHSc, PhD,[10,11] Marcela Guevara, MD, PhD,[10,12,13] Jesús-Humberto Gómez, MD,[10,11] Johnni Hansen, PhD,[14] Salvatore Panico, MD,[15] Lefkos T. Middleton, MD, FRCP,[5] Giovanna Masala, MD,[16] Valeria Pala, ScD,[17] Ana Vinagre-Aragon, MD,[18,19] Maurizio Zibetti, MD, PhD,[20] Roel Vermeulen, PhD,[1,21] and Susan Peters, PhD[1*]

[1]*Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands* [2]*Institute for Stroke and Dementia Research, Ludwig-Maximilians-University of Munich, Munich, Germany* [3]*Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden* [4]*Institute of Epidemiology and Social Medicine, University of Münster, Münster, Germany* [5]*Ageing Epidemiology Research Unit, School of Public Health, Imperial College London, London, United Kingdom* [6]*MRC Centre for Environment and Health, School of Public Health, Imperial College London, London, United Kingdom* [7]*Division of Cancer Epidemiology, German Cancer Research Center, Heidelberg, Germany* [8]*Escuela Andaluza de Salud Pública, Granada, Spain* [9]*Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain* [10]*Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública, Madrid, Spain* [11]*Department of Epidemiology, Regional Health Council, IMIB-Arrixaca, Murcia University, Murcia, Spain* [12]*Instituto de Salud Pública y Laboral de Navarra, Pamplona, Spain* [13]*Navarra Institute for Health Research, Pamplona, Spain* [14]*Danish Cancer Institute, Danish Cancer Society, Copenhagen, Denmark* [15]*School of Medicine, Federico II University, Naples, Italy* [16]*Institute for Cancer Research, Prevention and Clinical Network, Florence, Italy* [17]*Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Milan, Italy* [18]*Movement Disorders Unit, Department of Neurology, University Hospital Donostia, San Sebastian, Spain* [19]*Neurodegenerative Diseases Area, BioDonostia Health Research Institute, San Sebastián, Spain* [20]*Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy* [21]*Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, the Netherlands*

ABSTRACT: Background: Metals have been postulated as environmental concerns in the etiology of Parkinson's disease (PD), but metal levels are typically measured after diagnosis, which might be subject to reverse causality.

Objective: The aim of this study was to investigate the association between prediagnostic blood metal levels and PD risk.

Methods: A case-control study was nested in a prospective European cohort, using erythrocyte samples collected before PD diagnosis.

Results: Most assessed metals were not associated with PD risk. Cadmium has a suggestive negative association with PD (odds ratio [95% confidence interval] for the highest quartile, 0.70 [0.42–1.17]), which diminished among never smokers. Among current smokers only, lead was associated with decreased PD risk (0.06 [0.01–0.35]), whereas arsenic showed associations toward an increased PD risk (1.85 [0.45–7.93]).

Conclusions: We observe no strong evidence to support a role of metals in the development of PD. In particular, smoking may confound the association with tobacco-derived metals. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; metals; prospective exposure assessment; cohort study

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease. Around 90% of PD cases are related to a variety of lifestyle and environmental factors.[1] Metals have been implicated in the pathogenesis of PD for many years.[2] For the general population,

***Correspondence to:** Dr. Susan Peters, Institute for Risk Assessment Sciences, Utrecht University, Nieuw Gildestein, Room 3.59, Yalelaan 2, 3584 CM Utrecht, the Netherlands; E-mail: s.peters@uu.nl

Relevant conflicts of interest/financial disclosures: Nothing to report.

Funding agencies: This work was supported by Stichting ParkinsonFonds. Y.Z. received support from the China Scholarship Council during the PhD period in Utrecht University-Institute for Risk Assessment Sciences. C.M.L. was supported by the Heisenberg program of the German Research Foundation (grant LI 2654/4-1) and by The Michael J. Fox Foundation (grant MJFF-008994).
Full financial disclosures and author roles may be found in the online version of this article.

Received: 26 May 2023; **Revised:** 14 August 2023; **Accepted:** 23 August 2023

Published online 7 September 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.29602

metal exposures usually result from contaminated food or drinking water, cigarette smoking, air pollution, dental amalgam fillings, medication, and dietary supplements.[3]

We recently evaluated the epidemiological evidence of associations between metal exposure and PD risk in a systematic review.[2] We did not observe consistent associations with PD risk for most metals in meta-analyses. Notably, the research quality was greatly limited because of retrospective exposure assessment. Metal levels in human biofluids were mostly measured after disease diagnosis, and results were therefore possibly affected by reverse causality because patients with PD tend to change smoking and diet habits when experiencing clinical manifestations.[4]

To elucidate whether metal exposures represent genuine risk factors for PD, we assessed the association between PD risk and metal levels in blood samples collected several years before PD diagnosis, in a case-control study nested in the EPIC4PD cohort, a large prospective European study.[5] Meanwhile, possible confounding of smoking was also explored for the effect of metals on PD, because smoking was reported to be inversely associated with PD risk,[6] and cigarette smoke contains various metal species.[7]

Subjects and Methods

Study Population

The EPIC4PD study is based on 220,494 subjects from the general population residing in seven countries, within the European Prospective Investigation into Cancer and Nutrition (EPIC) study.[5,8] Within EPIC4PD, 734 incident PD cases who received a diagnosis after the date of recruitment were identified through medical record linkage and neurologist validation.[5] Here, we conducted a nested case-control study within the EPIC4PD cohort, including 362 incident PD cases for whom a baseline erythrocyte sample was available in the EPIC biobank. The reliability of the diagnoses was categorized into "definite," "very likely," "probable," and "possible" (Supporting Information Data S1).[5] One control subject per case matched by age at recruitment, sex, and study center was selected using incidence density sampling.

Measurement of Metal Levels

Metal concentrations in erythrocytes were measured by inductively coupled plasma mass spectrometry. Eleven elements were assessed: arsenic, cadmium, calcium, copper, iron, lead, magnesium, manganese, mercury, selenium, and zinc. Details were described in Supporting Information Data S2.

Statistical Analysis

Metal concentrations were compared among subjects with different smoking status. Correlations between metal levels and smoking intensity, represented by the reported number of cigarettes smoked per day at baseline when blood was collected, were tested by Spearman's correlation (correlation coefficient, ρ).

Conditional logistic regression for the matched case-control sets was applied to estimate the odds ratio (OR) and 95% confidence interval (CI) of PD incidence associated with quartile categories of metal levels (based on the distribution among controls, denoted as Q1–Q4). Considering the recognized inverse association between smoking and the risk of PD,[6] smoking status at recruitment (never, former or current smoker, and unknown) was deemed as a potential confounder in the conditional analyses. Other possible confounding factors, including alcohol consumption, coffee drinking, seafood and vegetable intake, education, body mass index, and physical activity, did not modify the risk estimated (all $P > 0.1$) and were not included in the models.

We performed stratified analyses by sex and smoking status (current, non-current, and never smokers) to test possible different effects. Two sensitivity analyses were conducted to test the robustness of our findings: (1) limiting analyses to PD cases diagnosed after 8 years (median) since recruitment (timing for blood collection) to reduce possible reverse causality, and (2) limiting analyses to PD cases with definite and very likely diagnoses. All analyses were carried out in R 4.1.3.[9]

Results

For PD cases, the median period between recruitment and PD diagnosis was 7.8 years (Table S1). At baseline, 13% of the cases were smokers, compared with 16% among controls ($P = 0.69$). Cadmium levels in current smokers were about 2.5 times higher than in never smokers (Table S3), and lead in current smokers was around 1.4 times higher compared with never smokers. Furthermore, cadmium and lead levels were both positively correlated with the number of daily smoked cigarettes ($\rho = 0.50$ and 0.26, respectively).

Our analyses did not demonstrate obvious associations between assessed metals and the risk of PD (Table 1). Cadmium was indicated to be associated with a decreased risk of PD (ORs [95% CIs]: Q2, 0.59 [0.38–0.90]; Q3, 0.75 [0.48–1.15]; Q4, 0.70 [0.42–1.17]). However, the effects attenuated toward null when limited to never smokers (Fig. 1). Zinc showed a borderline positive association in the third quartile (1.54 [0.98–2.45]; $P = 0.064$), which became most pronounced among never smokers (1.81 [1.00–3.33]) (Fig. 1) and females (2.32 [1.16–4.63]) (Fig. S4).

TABLE 1 *The association between prediagnostic blood metal concentrations and the risk of Parkinson's disease*

Exposure category	PD cases, n	Control subjects, n	OR (95% CI)[a]	Smoking adjusted OR (95% CI)[b]
Arsenic				
Quartile 1	94	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	97	90	1.02 (0.66–1.57)	1.02 (0.66–1.58)
Quartile 3	76	90	0.78 (0.48–1.27)	0.78 (0.48–1.26)
Quartile 4	95	91	0.97 (0.61–1.56)	0.96 (0.60–1.55)
P for trend, linear			0.46	0.47
Cadmium				
Quartile 1	118	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	71	90	0.59 (0.39–0.91)	0.59 (0.38–0.90)
Quartile 3	90	90	0.75 (0.49–1.15)	0.75 (0.48–1.15)
Quartile 4	83	91	0.68 (0.44–1.04)	0.70 (0.42–1.17)
P for trend, linear			0.09	0.13
Calcium				
Quartile 1	80	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	82	90	1.14 (0.70–1.87)	1.14 (0.70–1.88)
Quartile 3	114	90	1.62 (0.98–2.68)	1.60 (0.97–2.66)
Quartile 4	86	91	1.20 (0.63–2.29)	1.16 (0.61–2.23)
P for trend, linear			0.32	0.37
Copper				
Quartile 1	94	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	77	90	0.85 (0.55–1.31)	0.85 (0.55–1.31)
Quartile 3	90	90	1.01 (0.62–1.64)	1.01 (0.62–1.65)
Quartile 4	101	91	1.20 (0.70–2.08)	1.20 (0.69–2.08)
P for trend, linear			0.84	0.83
Iron				
Quartile 1	97	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	82	90	0.84 (0.54–1.32)	0.84 (0.54–1.32)
Quartile 3	100	90	1.02 (0.62–1.68)	1.00 (0.60–1.65)
Quartile 4	83	91	0.82 (0.48–1.41)	0.82 (0.48–1.42)
P for trend, linear			0.64	0.62
Lead				
Quartile 1	101	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	92	90	0.90 (0.60–1.36)	0.93 (0.61–1.41)
Quartile 3	91	90	0.85 (0.56–1.31)	0.87 (0.56–1.34)
Quartile 4	78	91	0.65 (0.38–1.11)	0.68 (0.39–1.16)
P for trend, linear			0.09	0.12
Magnesium				
Quartile 1	88	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	92	90	1.06 (0.69–1.65)	1.05 (0.68–1.63)

(Continues)

TABLE 1 *Continued*

Exposure category	PD cases, n	Control subjects, n	OR (95% CI)[a]	Smoking adjusted OR (95% CI)[b]
Quartile 3	85	90	0.99 (0.63–1.57)	0.99 (0.62–1.56)
Quartile 4	97	91	1.12 (0.71–1.77)	1.12 (0.71–1.77)
P for trend, linear			0.99	0.99
Manganese				
Quartile 1	97	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	99	90	1.02 (0.68–1.53)	1.01 (0.67–1.53)
Quartile 3	79	90	0.80 (0.52–1.24)	0.80 (0.51–1.25)
Quartile 4	87	91	0.87 (0.55–1.37)	0.86 (0.55–1.36)
P for trend, linear			0.60	0.57
Mercury				
Quartile 1	95	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	82	90	0.87 (0.56–1.34)	0.88 (0.57–1.35)
Quartile 3	89	90	0.96 (0.60–1.54)	0.96 (0.60–1.54)
Quartile 4	96	91	1.10 (0.61–1.97)	1.11 (0.61–2.00)
P for trend, linear			0.95	0.98
Selenium				
Quartile 1	90	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	103	90	1.14 (0.76–1.71)	1.12 (0.75–1.68)
Quartile 3	61	90	0.70 (0.45–1.09)	0.68 (0.43–1.07)
Quartile 4	108	91	1.28 (0.79–2.05)	1.25 (0.77–2.01)
P for trend, linear			0.94	0.88
Zinc				
Quartile 1	72	91	1.00 [Ref]	1.00 [Ref]
Quartile 2	98	90	1.43 (0.92–2.21)	1.41 (0.91–2.18)
Quartile 3	103	90	1.53 (0.97–2.42)	1.54 (0.98–2.45)
Quartile 4	89	91	1.35 (0.80–2.27)	1.35 (0.80–2.28)
P for trend, linear			0.51	0.54

Abbreviations: PD, Parkinson's disease; OR, odds ratio; CI, confidence interval; Ref, reference.
[a]Conditional logistic regression for the matched case-control sets.
[b]Conditional logistic regression for the matched case-control sets, adjusted by smoking status.

No effects were observed for the remaining metals: calcium, copper, iron, magnesium, manganese, mercury, and selenium.

Exposure-response trends were not observed from linear (Table 1) or spline regression for any of the assessed metals (Fig. S2). Effect estimates from sensitivity analyses limiting to late-diagnosed cases and definite and very likely cases were similar to those of the main analyses, despite the widening of CIs due to the smaller sample size (Fig. S5).

A few metals showed associations only among current smokers (Fig. 1). Increased lead levels were found to be associated with a decreased risk of PD among current smokers (OR for highest quartile, 0.06; 95% CI: 0.01–0.35), also showing a clear linear trend ($P = 0.007$). The inverse associations persisted after further controlling for the number of cigarettes (data not shown). In contrast, a positive association was suggested between arsenic and PD risk when limited to current smokers (ORs [95% CIs]: Q2, 3.29 [0.97–12.3]; Q3, 1.81 [0.43–7.95]; Q4, 1.85 [0.45–7.93]).

Discussion

Our study is the first prospective study to investigate the role of metal levels in PD risk by assessing blood

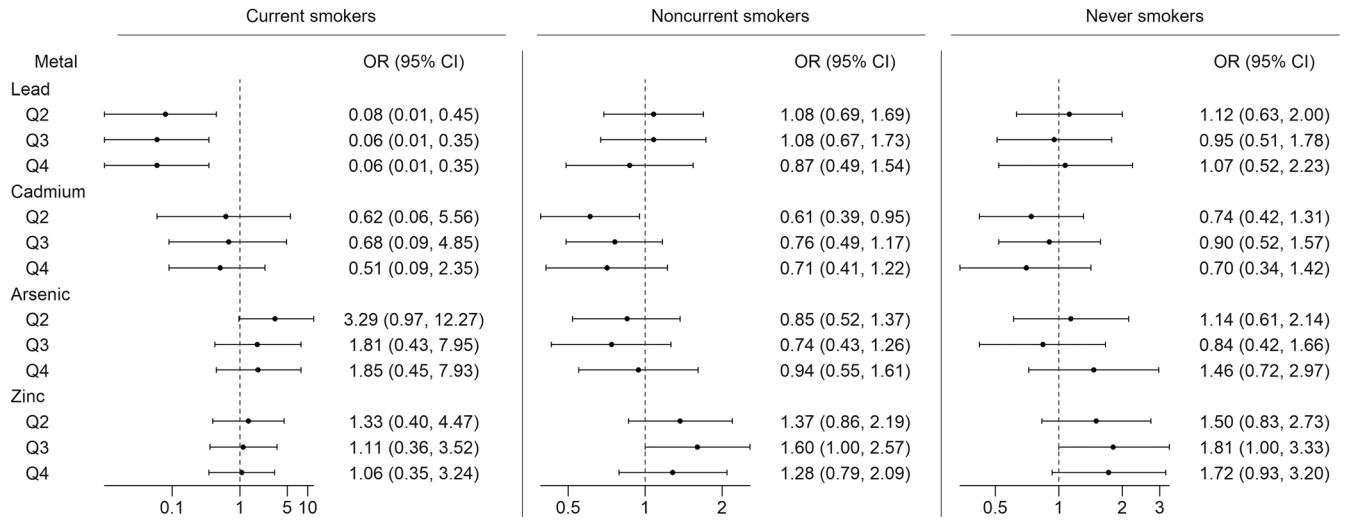

FIG. 1. The association between metal concentrations and the risk of Parkinson's disease by smoking status.

samples collected years before the clinical diagnosis. Our study did not provide robust evidence to verify the action of metals in the pathogenesis of PD.

Lead is a well-recognized toxicant primarily affecting the central nervous system.[10] Two well-designed case-control studies found bone lead, which is a biomarker for cumulative lead exposure,[11] to be associated with increased risk of PD,[12,13] indicating that long-term environmental lead exposure may be a risk factor for PD. In contrast, a strong inverse association between lead levels and PD risk was notable among current smokers in our study. A probable explanation is that lead is a surrogate measure or intermediate step of smoking in relation to PD, considering the positive correlation between lead levels and smoking intensity. This assumption is partly confirmed by our previous study on erythrocyte metal levels and the risk of amyotrophic lateral sclerosis (ALS).[14] In contrast with the observed decreased risk of PD, smoking is associated with an increased risk of ALS,[15] and a positive association between blood lead and ALS was found in current smokers.

Cadmium was also possibly subject to the influence of smoking. In terms of OR magnitude, the negative associations between cadmium and PD were stronger among current smokers than never smokers. Because cadmium source attributes to cigarette smoking more than lead,[16] it is more reasonable to speculate the participation of smoking in the relation of cadmium to PD. Future studies should aim to explore the modification effect of smoking in the relation between tobacco-derived metals and neurodegenerations and to help elucidate the etiology of the disease.

In this study, subjects with higher zinc levels showed an elevated risk of PD, especially among never smokers and females, but no clear dose-response trend was observed. In our previous meta-analyses, zinc in the blood matrix was found to be lower in patients with PD compared with control subjects, with a pooled standardized mean difference of −0.53 (95% CI: −0.92, −0.14) from 18 retrospective case-control studies.[2] The discrepancy with results in our study may be because of different biospecimens measured (blood matrix or erythrocytes) and possible reverse causality in previous studies. The precise nature and underlying mechanisms of the effect of zinc in the development of PD require further investigation.

We acknowledged some limitations in this study. First, metal levels in erythrocytes (with a life span of 120 days[17]) reflect recent exposures proximal to the time of blood sample collection. The biomonitoring at one time point could be inaccurate when metal exposures fluctuate over the lifetime. For example, unlike elevated levels in current smokers, cadmium concentrations in former smokers were similar as in never smokers (Table S3), suggesting one-time measurement cannot completely reflect past exposure. Second, blood samples were collected on average 8 years before PD diagnosis, but PD prodromal phase could occur as early as 20 years before the onset of motor symptoms.[18] Therefore, we cannot fully exclude that metal alterations were secondary to diet and smoking habit change related to PD symptoms. However, similar results were obtained when limiting analyses to those who were diagnosed more than 8 years after recruitment, indicating residual reverse causality does not appear to be substantial. Third, although a positive association for arsenic was suggestive among current smokers, it makes less sense to postulate that smoking plays a role in the impact of arsenic on PD. The arsenic levels measured in our study mostly reflected organic species (arsenobetaine) from seafood. The mechanism

of arsenic in PD development warrants further exploration. Fourth, iron levels that we measured were a crude estimation of iron status in humans. Besides iron content in erythrocytes, iron status also relies on serum-based indicators, such as ferritin, transferrin saturation, and soluble transferrin receptor.[19]

In conclusion, our study did not find strong evidence to support the risk of PD altered by metal exposures. Smoking may confound the association with lead and cadmium. To date, this is the first study to evaluate prediagnostic metal levels in blood in the development of PD, minimizing reverse causation. Further investigations are needed to gain a better understanding of the relationship between smoking, metals, and PD. Furthermore, future studies of novel biomarkers of long-term metal exposure may provide more compelling evidence of the association between metals and PD. ■

Acknowledgments: This work was supported by Stichting ParkinsonFonds. Y.Z. received support from the China Scholarship Council during the PhD period in Utrecht University-Institute for Risk Assessment Sciences. C.M.L. was supported by the Heisenberg program of the German Research Foundation (grant LI 2654/4-1) and by The Michael J. Fox Foundation (grant MJFF-008994). The national cohorts were supported by the Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Federal Ministry of Education and Research (BMBF) (Germany); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy, Compagnia di SanPaolo and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), National Institute for Public Health and the Environment (RIVM), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); Health Research Fund (FIS) – Instituto de Salud Carlos III (ISCIII), Regional Governments of Andalucía, Asturias, Basque Country, Murcia, and Navarra, the Catalan Institute of Oncology—ICO, CERCA Program/Generalitat de Catalunya for the institutional support to IDIBELL (Spain); Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (C864/A14136 to EPIC-Norfolk; C8221/A29017 to EPIC-Oxford), Medical Research Council (MR/N003284/1, MC-UU_12015/1, and MC_UU_00006/1 to EPIC-Norfolk; MR/M012190/1 to EPIC-Oxford), University of Cambridge (United Kingdom). We thank Michael Levi, Institute of Environmental Medicine, Karolinska Institutet, Sweden, for the measurement of metals in erythrocytes. The coordination of EPIC was financially supported by International Agency for Research on Cancer and also by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre. We are grateful to all the participants who have been part of the project.

Data Availability Statement

The datasets used and analyzed during the current study are not publicly available due to privacy agreements.

References

1. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. J Neural Transm (Vienna) 2017;124(8):901–905.
2. Zhao Y, Ray A, Portengen L, Vermeulen R, Peters S. Metal exposure and risk of Parkinson's disease: a systematic review and meta-analysis. Am J Epidemiol 2023;192(7):1207–1223.
3. Peters S, Visser A, Weisskopf M, Kioumourtzoglou M, Vermeulen R. Metals and neurodegeneration. Oxford Textbook of Neurological and Neuropsychiatric Epidemiology. Oxford, UK: Oxford University Press; 2020:417–424.
4. Thacker EL, O'Reilly EJ, Weisskopf MG, Chen H, Schwarzschild MA, McCullough ML, et al. Temporal relationship between cigarette smoking and risk of Parkinson disease. Neurology 2007;68(10):764–768.
5. Gallo V, Brayne C, Forsgren L, Barker RA, Petersson J, Hansson O, et al. Parkinson's disease case ascertainment in the EPIC cohort: the NeuroEPIC4PD study. Neurodegener Dis 2015; 15(6):331–338.
6. Gallo V, Vineis P, Cancellieri M, Chiodini P, Barker RA, Brayne C, et al. Exploring causality of the association between smoking and Parkinson's disease. Int J Epidemiol 2019;48(3):912–925.
7. Talhout R, Schulz T, Florek E, van Benthem J, Wester P, Opperhuizen A. Hazardous compounds in tobacco smoke. Int J Environ Res Public Health 2011;8(2):613–628.
8. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, et al. European prospective investigation into cancer and nutrition (EPIC): study populations and data collection. Public Health Nutr 2002; 5(6b):1113–1124.
9. R Core Team. R: A Language and Environment for Statistical Computing. Vienna: R Foundation for Statistical Computing; 2022.
10. Sanders T, Liu Y, Buchner V, Tchounwou PB. Neurotoxic effects and biomarkers of lead exposure: a review. Rev Environ Health 2009;24(1):15–45.
11. Barry PS, Mossman DB. Lead concentrations in human tissues. Br J Ind Med 1970;27(4):339–351.
12. Coon S, Stark A, Peterson E, Gloi A, Kortsha G, Pounds J, et al. Whole-body lifetime occupational lead exposure and risk of Parkinson's disease. Environ Health Perspect 2006;114(12):1872–1876.
13. Weisskopf MG, Weuve J, Nie H, Saint-Hilaire MH, Sudarsky L, Simon DK, et al. Association of cumulative lead exposure with Parkinson's disease. Environ Health Perspect 2010;118(11):1609–1613.
14. Peters S, Broberg K, Gallo V, Levi M, Kippler M, Vineis P, et al. Blood metal levels and amyotrophic lateral sclerosis risk: a prospective cohort. Ann Neurol 2020;89(1):125–133.
15. Wang H, O'Reilly ÉJ, Weisskopf MG, Logroscino G, McCullough ML, Thun MJ, et al. Smoking and risk of amyotrophic lateral sclerosis: a pooled analysis of 5 prospective cohorts. Arch Neurol 2011;68(2):207–213.
16. Bernhard D, Rossmann A, Wick G. Metals in cigarette smoke. IUBMB Life 2005;57(12):805–809.
17. Thiagarajan P, Parker CJ, Prchal JT. How do red blood cells die? Front Physiol 2021;12:655393.
18. Siderowf A, Lang AE. Premotor Parkinson's disease: concepts and definitions. Mov Disord 2012;27(5):608–616.
19. Pfeiffer CM, Looker AC. Laboratory methodologies for indicators of iron status: strengths, limitations, and analytical challenges. Am J Clin Nutr 2017;106(Suppl 6):1606s–1614s.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.