Mini Review

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Environmental and occupational exposure to metals (manganese, mercury, iron) and Parkinson's disease in low and middle-income countries: a narrative review

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Abstract

Objectives: We designed and conducted a narrative review consistent with the PRISMA guidelines (PROSPERO registration number: CRD42018099498) to evaluate the association between environmental metals (manganese, mercury, iron) and Parkinson's Disease (PD) in low and middle-income countries (LMIC).
Methods: Data sources: A total of 19 databases were screened, and 2,048 references were gathered. Study selection: Randomized controlled trials, cluster trials, cohort studies, case-control studies, nested case-control studies, ecological studies, cross-sectional studies, case series, and case reports carried out in human adults of LMIC, in which the association between at least one of these three metals and the primary outcome were reported. Data extraction: We extracted qualitative and quantitative data. The primary outcome was PD cases, defined by clinical criteria. A qualitative analysis was conducted.
Results: Fourteen observational studies fulfilled the selection criteria. Considerable variation was observed between these studies' methodologies for the measurement of metal exposure and outcome assessment. A fraction of studies suggested an association between the exposure and primary outcome; nevertheless, these findings should be weighted and appraised on the studies' design and its implementation limitations, flaws, and implications.
Conclusions: Further research is required to confirm a potential risk of metal exposure and its relationship to PD. To our awareness, this is the first attempt to evaluate the association between environmental and occupational exposure to metals and PD in LMIC settings using the social determinants of health as a framework.

Keywords: environmental and occupational risk factors; low and middle – income countries; metallic mineral; neurodegenerative; neurotoxicity; Parkinsonism.

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Introduction

Little is known about Parkinson's Disease (PD)'s pathophysiology and etiology, even though this is the second most prevalent neurodegenerative disease worldwide [1–3]. The main finding is the progressive loss of dopaminergic neurons in the substantia nigra pars compacta in the basal ganglia and intracellular protein inclusions known as the Lewy Bodies. PD diagnosis is based on clinical criteria, and the gold standard remains the pathological assessment of post-mortem samples [1, 2]. Monogenetic PD accounts for the smallest proportion of the cases, while sporadic PD constitutes more than 80% [2–4].

Estimating PD's disease burden is a challenge, considering the lack of a confirmatory test and the

overlapping symptomatology with other movement disorders [5]. Additionally, neurological disorders' impact is highly underestimated by most of the surveys considering only mortality and not disability rates [5–8]. These challenges are even more evident in low and middle-income countries (LMIC), where the scarcity of specialized medical workforce [9–11] and weak national statistical records are prevalent [12].

Even though aging is the leading risk factor for sporadic PD development, the hypothesis of environmental factors such as toxins and atmosphere contaminants triggering genetic predisposition has been suggested [5, 13]. Controversial studies propose a relation between metal exposure and PD development.

Understanding the neurotoxic mechanism of metals is another challenge. Many of them are essential for biomolecular processes, and their levels in the organism are highly regulated and complex to measure [14, 15]. Mitochondrial alterations with the production of free radicals and reactive oxygen species (ROS) are proposed as the common mechanisms of deleterious effects in humans [15, 16]. The specific molecular target for each element is different; therefore, the exact cellular process by which metals contribute to neurodegenerative diseases is still not completely understood [16]. Neurotoxic effects of metals have a broad spectrum of behavioral, chemical, and structural manifestations. Depending on the exposure length and dose, among other factors, outcomes can vary between silent or evident symptoms [15].

Several metals have been proposed to contribute to PD development, all of them presenting inconsistent results [5]. We focused on PD associated with essential metals such as manganese (Mn) and iron (Fe) and toxic metals, like mercury (Hg), considering these three metals share toxic properties and manifest with neurological symptoms when chronic accumulation occurs [15–18]. PD cardinal symptomatology such as tremor, behavioral alterations, mood changes, and extrapyramidal symptoms have been observed in patients exposed to these metals [15–18].

Only Mn and Fe and not Hg are trace essential metals, therefore necessary to enzymatic process in the human body to survive [19–21].

Fe's main absorption route is oral, and different enzymatic processes highly regulate the uptake [22]. The principal hypothesis relating PD and Fe concerns an element's overload with secondary oxidative stress and nigrostriatal damage in CNS [22].

On the other hand, Mn's main absorption route is by inhalation and olfactory tract involvement, and it deposits principally in the globus pallidus, striatum, and cortex. The Mn's neurotoxicity mechanisms are related to ROS production, free radicals, and other pro-inflammatory substances and a defense mechanism's impairment [20, 23].

All Hg's presentations have deleterious effects in mammals, and the toxicological properties depend on its physical characteristics and presentation form [24]. Elemental Hg's primary absorption method is through inhalation, ingestion, and dermal route [24]. Accumulation and structural degeneration in the brain and kidneys have been the principal Hg toxicity chronic effects [21, 24]. The neuropathological mechanisms of Hg toxicity also concern ROS production in glial cells [24, 25].

Metal exposure in LMIC may be present through natural resources and raw material exploitation, artisanal and not artisanal mining, metal recycling activities, smelting operations, fertilizer use, and pollution [21, 25, 26]. Additionally, several sociopolitical and structural aspects prevailing in LMIC contribute to support our hypothesis that most of the environmental risk factors are clustered in specific types of occupations related to lifestyles, social status, living areas, and other intermediate social determinants of health.

Material and methods

This review was designed consistently with the PRISMA guidelines. Its protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42018099498). The research was performed following the Helsinki Declaration's tenets and was approved by an institutional review board (Charité - Universitätsmedizin, Institute of Tropical Medicine and International Health).

Studies considering environmental or occupational exposure to Mn, Hg, or Fe and the outcome of interest (PD) in adults were included. We defined LMIC following the World Bank criteria for 2020, and only studies carried out in these populations were selected. All study designs were included except systematic reviews and meta-analysis, abstracts, letters, commentaries, editorials, and conferences. No time limits were established. We used language restriction to English, Spanish, French, Italian and Portuguese articles.

We identified studies through electronic database searches between June 2018 and June 2020 (last search). We designed a search strategy based on MesH terms at the PubMed portal: "Adult"[Mesh] AND "Environmental Exposure"[Mesh] AND "Occupational Exposure"[Mesh] OR "Metals, Heavy"[Mesh]) OR "Mercury"[Mesh] OR "Manganese"[Mesh] OR "Iron"[Mesh] OR "Heavy Metal Poisoning, Nervous System"[Mesh] OR "Manganese Poisoning"[Mesh] OR "Mercury Poisoning"[Mesh] OR

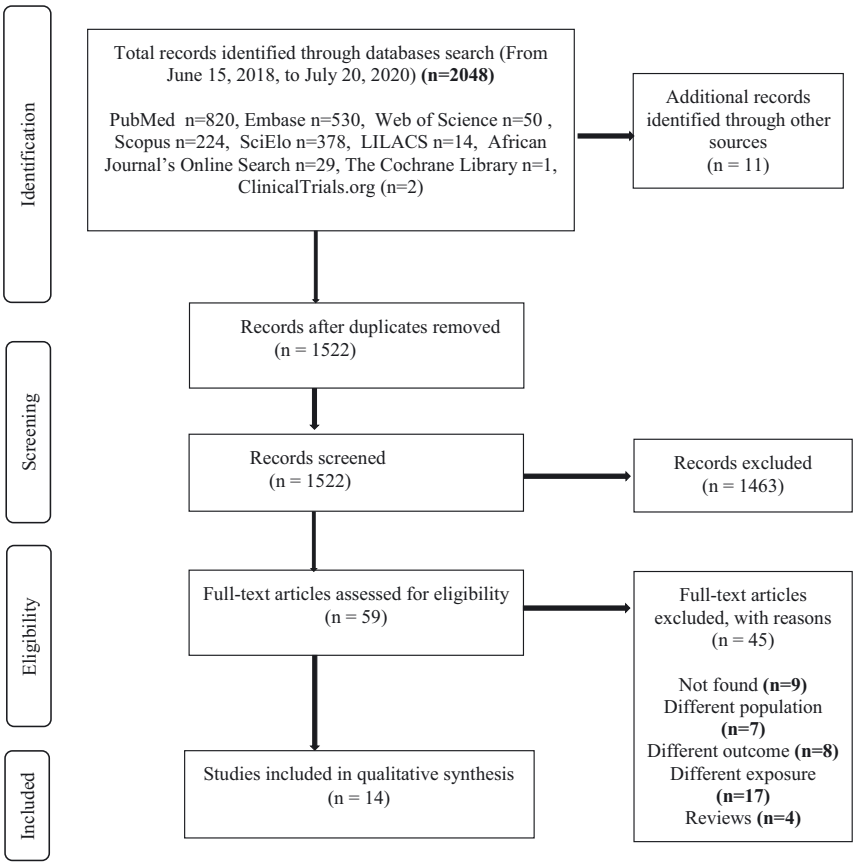

Figure 1: Study selection. PRISMA flowchart. *No results databases: Eurasia Health (2006 to present), National Databases of Indian Medical Journals (1985 to present), Bioline International (1989 to present), and MedCarib (1998 to present), The International Labour Organization databases (1993 to the present), The Latin America Journals Online database (LAMJOL) (2010 to present), The WHO Library and database (WHOLIS) and The Panamerican Health Organization database (1948 to present).

"Mercury Poisoning, Nervous System"[Mesh] AND "Parkinson Disease"[MeSH Terms] AND "Parkinsonian Disorders"[Mesh] AND "humans"[MeSH Terms]. The complete search process in all databases and the PRISMA flowchart is shown in Figure 1 [27].

One reviewer (MAGA) screened all titles and abstracts. Doubts regarding selecting a specific article were resolved in consensus with the second team member (DHB). The quantitative synthesis was not considered appropriate due to the absence of standardized dichotomous or continuous outcomes presented in the results and the study design variability.

There was no funding source for this study. The research team had all the responsibility for the decision to submit for publication.

Data extraction

One reviewer (MAGA) extracted the studies' qualitative and quantitative data. The second author (DHB) checked for accuracy, completeness and solved any doubt concerning the procedure. We contacted authors to resolve doubts or discrepancies regarding the information presented. In all articles, informed consent was obtained from individuals included in this study.

Quality evaluation

To assess the observational studies' quality and risk of bias, we adapted and used the Newcastle–Ottawa scale (NOS) checklist for case-control, cohort, and cross-sectional studies. The NOS system is based on a star (*) grading, evaluating three primary domains: (1) selection of the study groups, (2) comparability between groups, and (3) outcome assessment. A maximum of nine stars (*) is possible [28]. For case reports and case series, we adapted the Pierson Scheme to evaluate a Case Report and Case Series [29]. The research team (MAGA, DHB, NIP, HRR, DRC) judged the article's risk of bias together during the process.

Results

Characteristics of included studies

Fourteen articles were selected. All were published in English between 1989 and 2019 and consisted of non-

experimental studies. Matched case-control studies comprise the majority: eight in total [30–37]. One non-matched-case control study [38], one case report, and one case series were selected [39, 40]. Two cross-sectional studies were included [41–43], and only one longitudinal study (a population-based retrospective cohort matched study) fulfilled the criteria [44].

More than half of the finally selected references were from China; five were Taiwanese. Even though we recognized Taiwan's complex juridical and administrative situation, we decided to include the studies as part of the Chinese academic production. The other studies were run in Mongolia, India, Brazil, South Africa, and Nigeria. All countries except Nigeria, which is considered a low-income level country, are categorized as middle-income countries.

Only seven articles [31–36, 43] explicitly stated in their study the use of clinical criteria for the outcome assessment. Exposure to metals was evaluated with questionnaires and interviews (n=2) [30, 31], biomarkers and questionnaires (n=8) [32–39], environmental measurements, questionnaires and biomarkers (n=1) [41], environmental measurements, plus questionnaires (n=2) [40, 43], and national records (n=1) [44]. Biomarkers were done in plasma and blood [32–36, 39, 41], urine [32, 33, 36, 38], scalp hair [37, 38], and pubic hair [39], while environmental measurements were done in the air [35, 40, 43], water [38], and food [38] (see Tables 1 and 2).

Nine studies were conducted in hospital settings, against five community-based studies. Both rural and urban communities were considered. A total of 22,412 participants, both female and male, with baseline age, ranged from 21 to 91 years old, were studied. The retrospective cohort study length of follow-up was of 5.5 years (from 2002 to 2008). Governmental or academic sponsors funded the studies. None reported industry or private enterprises participating in the research. However, no study reached the highest quality (NOS 9/9, Pierson's scheme 10/10), more than 90% of the selection present quality levels above the average (see Tables 1 and 2).

Descriptive analysis

In 1989 Huang et al. [30] and Wang et al. [32] published a cross-sectional study followed by a case series of an outbreak of parkinsonism provoked by an unrepaired ventilation system in a ferromanganese smelter in Taiwan. 132 workers were assessed, and six cases were positive for Mn intoxication. Their symptomatology was indistinguishable from idiopathic PD. Mn concentration in blood, scalp, and pubic hair, determined by the pulse-height analyzer, reported values between 3 and 300 times the normal levels (study's reference values in blood: 7–12 ppb, scalp hair: 100–2,200 ppb, and pubic hair: 300–9,800 ppb); 75% of workers categorized as "highly exposed" were diagnosed with progressive parkinsonism, suggesting a dose-response relationship [39, 41].

Similarly, Wang et al. [31] published in 2012 a case report of Mn poisoning with PD symptomatology in 36 years women employed for 17 years in a coal mine in China. Data from the occupational hygiene investigation at the patient's workplace showed Mn concentrations in the air of 0.29 mg/m^3, almost twice the occupational limit levels established by the National Occupational Health Standards in China for 2007 of 0.15 mg/m^3. Three more cases were reported in the same setting after the centile case was found [40].

Table 1: Descriptive studies' characteristics.

Study reference and setting	Wang 1989 (Taiwan/China)	Huang 1989 (Taiwan/China)	Wang 2012 (China)	Dlamini 2019 (South Africa)
Study design	Cross-sectional	Case series	Case report	Cross-sectional
Quality score	NOS 3/9	Pierson's scheme 6/10	Pierson's scheme 6/10	NOS 5/9
Recruitment	Population-based	Population-based	Hospital-based	Population-based
Population (n)	132	6	1	187
Age (range)	34–47 years old	34–46 years old	36 years old	41.8 years old
Sex	Male	Male	Female	Male
Outcome assessment	Not specified	Not specified	Not specified	UPDRS3 score + PDQ-39[a]
Exposure assessment	Biomarkers + questionnaire: Mn in plasma	Biomarkers + questionnaire: Mn in plasma, scalp, pubic hair, and air	Mn's air concentration + questionnaire	Mn's air concentration + questionnaire

[a]The Parkinson Disease Questionnaire (PDQ-39), Unified Parkinson's Disease Rating Scale motor subsection part 3 (UPDRS3).

Table 2: Analytical studies' characteristics.

Study reference and setting	Liou 1997 (Taiwan/China)	Werneck & Alvarenga 1999 (Brazil)	Fukushima 2010 (China)	Fukushima 2011 (China)	Fukushima 2013 (China)	Komatsu 2011 (Mongolia/Japan)	Ogunrin 2013 (Nigeria)	Kumudini 2014 (India)	Hsu 2016 (Taiwan/China)	Dos Santos 2018 (Brazil)
Study design	Matched (by age and sex) case-control	Matched (by age and sex) case-control	Matched (by age and sex) case-control	Matched (by age and sex) case-control	Matched (by age and sex) case-control	Non matched case-control study	Matched (by age and sex) case-control	Matched (by age and ethnicity) case-control	Retrospective cohort	Matched (by age and sex) case-control
Quality Score	NOS 6/9	NOS 7/9	NOS 6/9	NOS 6/9	NOS 6/9	NOS 6/9	NOS 7/9	NOS 5/9	NOS 8/9	NOS 5/9
Recruitment	Hospital-based	Hospital-based	Hospital-based	Hospital-based	Hospital-based	Population-based	Hospital-based	Hospital-based	Population-based	Hospital-based
Cases expose groups (n)	120	92	82[a]	71[a]	82[a]	299	68	150	10,236	25
Controls Non-expose group (n)	240	110	82[a]	71[a]	81[a]	81	60	175	10,236	30
Age & Male/female ratio	The mean age for cases: 63.1 years old M/F: 1.1:1	Mean age for cases 70.55 years old M/F: 0.8:1	Mean age for cases: 63.9 ± 9.4 years old. M/F: 1.3:1	Mean age for cases: 63.7 ± 9.7 years old M/F: 1.3:1	Mean age for cases 63.0 ± 10.7 years. M/F: 0.84–1.41	Mean age for cases 39.7 ± 13.4 years old M/F: 0.8:1	Mean age for cases 65.7 ± 7.29 years old M/F: 2.1:1	The mean age for cases was 55.7 ± 10.6 years old M/F: 2.4:1	Mean age exposed group 64.39 ± 7.3 years old M/F: 1.5:1	Mean age for cases: 69.8 ± 14.7 years. M/F ratio: 2.25
Other variables measured	Residency (urban, rural), years of farming, drinking water source, herbicide/pesticide exposure, chemical's exposure, smoking status	Residency, drinking water source, herbicide/pesticide exposure, chemical's exposure, smoking status, head trauma, medication with parkinsonian effects use, PD's family history	Residency, herbicide/pesticide exposure, chemical's exposure, smoking status, educational background, annual income, eating habits	Residency, herbicide/pesticide exposure, chemical's exposure, smoking status, educational background, annual income, eating habits	Severity of illness	Residency	Residency, drinking water source, herbicide/pesticide exposure, chemical's exposure, smoking status, head trauma, educational background, occupation, PD's family history, PD's age at onset, previous CNS infections, chronic comorbidities	Residency, farming occupation, chemical's exposure, smoking status, head trauma, PD's family history, PD's onset, mean disease duration	Comorbidities (diabetes, hyperlipidemia, hypertension, cardiovascular disease)	Severity of illness
Outcome assessment	Not specified	UKPDSBBc[b]	UKPDSBBc	UKPDSBBc	UKPDSBBc	Not specified	UKPDSBBc	UKPDSBBc	Records (PD)	Not specified
Exposure assessment	Questionnaire	Questionnaire	Biomarkers + questionnaire: Fe, Cu, Zn, Mn in plasma	Biomarkers + questionnaire: Fe, Cu, Zn, Mn and vitamin B12, vitamin E in plasma and urine	Biomarkers + questionnaire: Fe, Cu, Zn, Mn and vitamin B12, vitamin E in plasma and urine	Biomarkers + questionnaire: Fe, Cu, Zn, Mn and vitamin B12, vitamin E in plasma and urine + cattle meat, water, and soil	Biomarkers + questionnaire: Cu, Mg, Mn, Fe, Zn in plasma	Biomarkers + questionnaire: Cu, FE, Mn, Pb in plasma	Records (amalgam filling)	Biomarkers + questionnaire: Cu, FE, Mn, Pb in hair

[a]All subjects in the three studies came from the same sample (total N: 164), [b]The New International Parkinson Disease and Movement Disorder Society Diagnostic Criteria (MDSc), The UK Parkinson's Disease Society Brain Bank Criteria (UKPDSBBc).

A recent analysis carried out in a South African manganese mine complex (South Africa is the world's top producer) determined a U-shape dose-response behavior comparing parkinsonian symptomatology against Mn cumulative exposure in years. The positive association was established up to 15 mg Mn/m^3-years of exposure. The team explains the inverse association present as the healthy worker survivor effect [43]. This phenomenon is explained as the fact that most workers who develop impairment and decide to discontinue their labor activity due to disability reasons are no longer observable in a cross-sectional study. Information regarding high levels of exposure is underestimated, and this effect will lead to a reversal association [43]. Similar findings are consistent with previous results from a US welder cohort [45].

In 1997 Liou et al. [21] explored the environmental risk factors for PD in the native Taiwanese population. Cases and controls gave information according to a structured open-ended questionnaire [30]. Werneck & Alvarenga [22] carried out a similar study in a neurologic center in Brazil. Among cases, four reported chronic exposure to Hg vapors compare to one control. The subject's occupations were technician painters, car mechanics, goldsmiths, and dentists. In both studies, the authors acknowledged confidence intervals as inaccurate and exposure's cluster as heterogeneous and did not consider the association (OR: 1.57, 95% CI: 0.002–1,416) and (OR: 5.87, 95% CI: 1.48–27.23), respectively [31].

Fukushima et al. published, between 2010 and 2013, three case-control studies [32, 33, 36] aiming to evaluate the relationship between PD and metal levels in fluids in a Chinese population. Whole blood Mn and serum Fe levels were significantly higher in the PD patients' group than controls, but only Fe urine levels were significantly higher in cases (see Tables 3 and 4). Interestingly, the mean urine Fe and Mn concentrations in both groups were higher than the upper reference limit. Cases presented relatively lower educational levels and income per year than controls. The authors suggested a chronic and unknown (drinking water, air pollution, contaminated food) exposure to these elements in the Chinese region and hypothesized an excessive Fe and Mn intake might be related to PD pathogenesis [32, 33, 36].

Komatsu et al. [29] explored a similar exposure route in a Mongolian mining setting. 299 subjects from Mongolian and 81 healthy Japanese subjects were enrolled. The researchers determined parkinsonism through questionnaires, measured scalp hair minerals, metal level in the soil, drinking water, and meat. Countryside healthy Mongolians showed higher accumulated levels of Mn and Fe compared to controls and the difference was statistically significant [38]. Once again, metal levels in Mongolian subjects were higher than the reference limit following Japanese standards (Mn's reference level: 53–248 ppb, Fe's reference level: 4,400–8,700 ppb, Hg's reference level: 1,400–5,300 ppb). The subgroup analysis showed a statistically significant difference between levels of Mn and Fe in parkinsonism patients from Mongolia compared to healthy subjects from the same context, as well as higher levels of these elements in Mongolian sheep meat compared to Japanese cattle meat (see Tables 3 and 4) [38].

On the other hand, dos Santos et al. [28] found lower scalp hair Fe levels in PD cases compared to controls from Jequié, Brazil. The research team concluded a metal dyshomeostasis might be related to the disease and proposed scalp's hair metal levels as a potential standardized biomarker [37].

To assess the possible association between rapid urbanization, air pollution, and PD, two case-control studies published between 2013 and 2014 conducted in Nigeria and India found elevated blood Fe levels in PD cases compared to controls. However, Mn levels were not statistically different between groups. In the African study, PD Fe levels were almost three times higher than the upper limit, but Mn levels of cases were under the normal range (see Tables 3 and 4) [34, 35].

Considering other exposure routes, Hsu et al. [35], in a population-based retrospective cohort study published in 2016, explored the impact of a dental amalgam filling on PD development in Taiwan. Old amalgam filling techniques involved high amounts of Hg, but their use has been controversial due to the potentially toxic effects, among them PD risk. Using coded registers from the National Health Insurance Research Database, the researchers found PD risk in the amalgam filling group significantly higher compared to the incidence in the non-exposed group even after adjusting for confounding factors such as comorbidities (HR: 1.58 95% CI: 1.12–2.2) [34]. This particular research was the only longitudinal study selected and attained the highest quality qualification based on the NOS scale (8/9*) [44].

Discussion

We conducted a narrative review aiming to evaluate the evidence of the association between metal exposure (Mn, Hg, Fe) and PD in the LMIC. Regarding the results' distribution, inconsistent findings were prevalent, and an elevated risk of biased is present. A fraction of studies

Table 3: Summary findings analytical studies: Fe and biomarkers.

Summary findings table: Fe and biomarkers							
Study reference	**Detection method**	**Reference level and measure unit**	**PD (n)**	**PD Fe levels (mean + SD)**	**Non-PD (n)**	**Non-PD Fe levels (mean + SD)**	**p-Value**
Fe in plasma							
Fukushima (2010)	AES[a]	0.45–1.45 µg/ml	82	2.00 ± 0.83 µg/ml	82	1.50 ± 0.78 µg/ml	<0.01
Fukushima (2011)	AES[a]	0.45–1.45 µg/ml	71	1.95 ± 0.85 µg/ml	71	1.44 ± 0.77 µg/ml	<0.001
Fukushima (2013)	AES[a]	0.45–1.45 µg/ml	PD + depression: 24 PD: 58	1.77 ± 0.76 µg/ml 2.10 ± 0.84 µg/ml	81	1.51 ± 0.78 µg/ml	<0.01
Ogunrin (2013)	AAS[b]	9–27 µmol/l	68	78.46 ± 23.81 µmol/l	60	17.43 ± 5.31 µmol/l	<0.0001
Kumudini (2014)	ICPMS[c]	Not specified	150	554.4 ± 123.8 ng/ml	175	421.7 ± 126.1 ng/ml	<0.02
Fe in Urine							
Fukushima (2011)	AES[a]	66–200 µg/l	71	318 ± 271 µg/l	71	218 ± 190 µg/l	0.012
Fukushima (2013)	AES[a]	66–200 µg/l	PD + depression: 19 PD: 52	0.25 ± 0.23 mg/l 0.34 ± 0.28 mg/l	70	0.22 ± 0.19 mg/l	<0.05
Fe in Scalp Hair							
Komatsu (2011)	ICPMS[c]	4.4–8.7 ppm	10 (subgroup analysis: 10 parkinsonism cases from the Mongolian countryside)	~23 ppm	214 (subgroup analysis: 214 healthy subjects from the Mongolian countryside)	~15.4 ppm	<0.01
Dos Santos (2018)	FAAS[d]	X	25	50.98 ± 44.8 µg/l	30	72.6 ± 44.8 µg/l	<0.01

[a](AES) Atomic emission spectrometry, [b](AAS) Atomic absorption spectrometry, [c](ICPMS) Inductively coupled plasma mass spectrometry, [d](FAAS) Flame atomic absorption spectrometry.

suggested an association between the metal exposure and PD's development; nevertheless, these findings should be weighed, considered, and appraised on the study's design and its implementation framework's limitations, flaws, and therefore implications.

Due to the methodological diversity of study designs and their quality rating, a pooled risk estimate useful for decision-makers was not considered appropriate [46, 47]. The studies' observational nature tends to be prone to recall, selection, and misclassification biases [5, 48]. Confounding factors were rarely measured, and together with a lack of appropriate timing and follow-up, which is associated with a high risk of reverse causality, all constitute factors that blur the results [47, 49].

We recognize the outcome's definition complexity. The absence of a specific confirmatory laboratory test for PD makes accurate diagnosis a significant obstacle [2]. Additionally, differential diagnosis, which usually demands high technology and clinical expertise, such as parkinsonism syndromes, idiopathic PD, secondary PD, PD+, Manganism, Parkinson like syndrome (a disorder which has also been related to Mn's exposure) [50], share cardinal features with PD but present slight, and sometimes, subjective, differences and therefore, achieving a consensus is a challenge, even among experts [5, 51]. Our study aims to promote all proposed risk factors' integration and highlight PD diagnosis's limitations and dynamicity.

On the other hand, environmental and biological monitoring of metals is another challenge. Due to the metal's biological disponibility, the precise assessment of its levels is complicated, and not a final recommendation is broadly accepted [52]. Technologic advances represent an improvement; nevertheless, a standardized exposure biomarker nor a validated measurement tool has been established principally due to the inter-individual variability between subjects [15, 21].

Biological samples such as whole blood, plasma, urine, and scalp hair have been proposed as non-

Table 4: Analytical studies' summary findings: Mn and biomarkers.

Summary findings table: Mn and biomarkers							
Study reference	**Detection method**	**Reference level and measure unit**	**PD (n)**	**PD Mn levels (mean + SD)**	**Non-PD (n)**	**Non-PD Mn levels (mean + SD)**	**p-Value**
Mn in plasma							
Fukushima (2010)	AAS[b]	0.8–2.5 µg/dl	82	2.60 ± 2.32 µg/dl	82	1.68 ± 0.68 µg/dl	<0.01
Fukushima (2011)	AAS[b]	0.8–2.5 mg/dl	71	2.5 ± 2.29 µg/dl	71	1.61 ± 0.69 µg/dl	<0.002
Fukushima (2013)	AAS[b]	0.75–1.41 mg/ml	PD + depression: 24 PD: 52	1.69 ± 1.02 mg/dl 2.98 ± 2.59 mg/dl[a]	81	1.68 ± 0.68 mg/dl[a]	<0.01[a]
Ogunrin (2013)	AAS[b]	9–20 µmol/l	68	15.63 ± 8.32 µmol/l	60	14.43 ± 9.21 µmol/l	0.441
Kumudini (2014)	ICPMS[c]	Not specified	150	0.098 ± 0.05 ng/ml	175	0.11 ± 0.065 ng/ml	0.56
Mn in Urine							
Fukushima (2011)	AAS[b]	<2 µg/l	71	5.42 ± 5.90 µg/l	71	7.18 ± 7.28 µg/l	0.116
Fukushima (2013)	AAS[b]	<0.2 µg/dl	PD + depression: 19 PD: 52	0.65 ± 0.68 µg/dl 0.50 ± 0.56 µg/dl	70	0.72 ± 0.73 µg/dl	>0.05
Mn in Scalp Hair							
Komatsu (2011)	ICPMS[c]	53–248 ppb	10 (subgroup analysis: 10 parkinsonism cases from the Mongolian countryside)	~4,000 ppb	214 (subgroup analysis: 214 healthy subjects from the Mongolian countryside)	~2,000 ppb	<0.01

[a](AES) Atomic emission spectrometry, [b](AAS) Atomic absorption spectrometry, [c](ICPMS) Inductively coupled plasma mass spectrometry, [d](FAAS) Flame atomic absorption spectrometry.

invasive/lesser invasive methods to assess metal intoxication [53, 54], recognizing the limitations due to lack of benchmarks cut-off values to determine chronic exposure [53].

The selected studies considered different exposure's timeframes, and therefore we have to be careful in interpreting their results. Considering the dose-response and the metal's exposure length, the clinical manifestations and neurological symptoms vary [55, 56]. The CNS is exceptionally vulnerable to toxic insults but copes with this flaw with a high capacity to maintain an adequate neuronal function until the external injury exceeds the critical point [15]. A rapid high dose metal exposure will develop acute and dramatic symptomatology, while a chronic low dose exposure may be initially subtle or even silent for then behave similarly to neurodegenerative disease [15, 21].

In seven [32–38) of the selected studies', multiple metals were measured. However, none discussed the molecular interactions among these metals and their competing relationship. Fukushima et al. [32, 33, 36] found whole blood Mn and serum Fe levels significantly higher in the PD patients group compared to controls. Contrarily to the known molecular competing relationship between Fe and Mn [53], the studies showed a possible synergic relationship between these elements.

Regarding this point, we acknowledge that coexposure to a mixture of metals can modify the nature and severity of brain function [57]. Clauss Henn et al. measured Mn and lead (Pb) blood levels as well, as they assessed the neurodevelopment of a cohort of 455 children in Mexico City. They found a significant synergism between the two metals and delayed psychomotor development for children with higher blood levels [58].

We recognize PD multifactorial genesis and the difficulties in assessing these metals' contributions as a necessary cause or even as disease modifiers for suspected cases [51]. Defining a causal link here is complicated. An example of this dilemma was made on a recent analysis by Berg and Hochstrasse discussing Fe's possible association with PD, concluding that its accumulation in the substantia nigra could be due to either neurodegenerative disease process itself or could be contributing to PD pathogenesis [59].

However, we want to highlight the review's target population and the research context. To our awareness, this is the first attempt to evaluate the association between environmental and occupational exposure to metals and PD in LMIC. LMIC's research on this topic is currently growing considering the region's demographic transition, the rapid industrialization [60], and the consequent occupational and environmental's disease rise [26, 56]. Currently, in high-income countries as well as in LMIC, the research is mainly focused on intrauterine metal exposures and early neurological manifestations. An additional research field is the role of metals' coexposure in real-world scenarios [58, 61].

Our results are consistent with current research on PD etiology, risk factors, and prevention strategies evidence-building process [17, 18, 23]. Fe, Hg, and Mn neurotoxicity are established by *in vitro* and *in vivo* experiments, but inconsistent findings remain [14, 15]. Even though Mn neurotoxicity effects and its relationship with parkinsonism was established, a recent meta-analysis sponsored by the Welding Industry Defense Group, published in 2012 by Mortimer et al. [46], established a pooled OR of 0.76 (95% CI: 0.41–1.42) for the association between PD and Mn exposure. Concerning Fe, the University of Catania published in 2017 a meta-analysis of observational studies concluding still no sufficient evidence for the association between Fe and PD, most probably due to methodological heterogeneity and reverse causality risk [18]. Although other neurological disorders related to chronic Hg intoxication, as Minamata Syndrome, are well categorized, the link between this metal and PD has been only hypothesized [62–64].

In this work, we gave a multidisciplinary perspective aligned with the Sustainable Development Goals of a health problem [65]. Recognizing the biological plausibility of the deleterious neurological effects of metal exposure and the previous studies made, we intend to propose an additive model using the social determinants of health framework to develop in future PD research. Our thesis sustains the contributing role of metal exposure plus the typical structural characteristics of LMIC populations. Susceptibility such as undernutrition, a weakened immune system, pollution, stress, and sociopolitical structural conditions as a weak labor protection system, adding to the scarce resources allocated for neurological diseases in LMIC, might constitute interrelated factors for PD development [66–68]. Adding to this fact, the Global Equity Gauge Alliance with WHO partnership declared In 2004 the mandatory need to research globalization's direct and indirect effects in LMIC and the impact on health inequities [10, 69].

Conclusion

Our final recommendation is to focus on promoting health for the next generation and vulnerable populations. Supporting this fact is the vertical *in utero* transmission route of metals, focusing on early preclinical effects of metal neurotoxicity and neuroprotection interventions in susceptible populations such as children [15, 61]. Parallel to this is the current development of more broad and dynamic PD diagnostic criteria and disease definition, such as the prodromal phase and non-motor features considerations [70].

Considering the limited data available and the heterogeneous information derived from our review, corroboration is required from further studies.

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