

Association of anemia with Parkinson's disease: a systematic review with meta-analysis of epidemiological studies

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Abstract

Background: As more risk factors are identified for Parkinson's disease (PD), attention has increased toward hematological disorders, as studies have found increased eryptosis, a process characterized by increased erythrocyte apoptosis, in PD patients. We aimed to synthesize scientific evidence assessing the effect of anemia on future PD incidence.

Material and methods: A systematic review was conducted on multiple electronic databases. Any study that assessed the effect or association between presence of anemia and future PD in a longitudinal manner was considered for inclusion.

Results: Five of the 5525 articles met inclusion criteria; three retrospective cohort studies and two case-control studies. Anemia exposure definition varied among studies. Four of the five studies observed an increased risk for PD; pooled analysis showed a non-significantly increased risk for PD in the cohorts ($RR = 1.10$; 95% CI = 0.08-15.84) and case-control studies ($RR = 1.44$; 95% CI = 0.04-52.47). However, heterogeneity among studies was high ($I^2 = 97$, $p < 0.01$ and $I^2 = 85$, $p < 0.01$, respectively). **Conclusion:** There are few clinical studies on the association of anemia and PD, despite growing preclinical evidence on their connection. In this review, a tendency toward an increased risk for PD in anemic population was observed, with further research needed to reach a definite conclusion.

Keywords: Parkinson disease. Anemia. Iron. Gender. Risk factors

Asociación de la anemia con la enfermedad de Parkinson: una revisión sistemática con meta-análisis de estudios epidemiológicos

Resumen

Antecedentes: Reciente ha aumentado la atención hacia los trastornos hematológicos en pacientes con Enfermedad de Parkinson, ya que los estudios han encontrado un aumento de la eriptosis, un proceso caracterizado por un aumento de la apoptosis de los eritrocitos, en estos pacientes. Nuestro objetivo fue sintetizar la evidencia científica que evalúa el efecto de la anemia en la incidencia futura de la EP. **Material y métodos:** Se realizó una revisión sistemática en múltiples bases de datos electrónicas. Se consideró para la inclusión cualquier estudio que evaluara la asociación entre la presencia de anemia y la EP futura de forma longitudinal. **Resultados:** Cinco de los 5525 artículos cumplieron con los criterios de inclusión;

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tres estudios de cohortes retrospectivos y dos estudios de casos y controles. La definición de exposición a la anemia varió entre los estudios. Cuatro de los cinco estudios observaron un mayor riesgo de EP. El análisis combinado mostró un aumento no significativo del riesgo de EP en las cohortes (RR = 1.10; IC del 95 % = 0.08-15.84) y estudios de casos y controles (RR = 1.44; IC del 95 % = 0.04-52.47). Sin embargo, la heterogeneidad entre los estudios fue alta (I² = 97, p < 0.01 e I² = 85, p < 0.01, respectivamente). Conclusión: Existen pocos estudios clínicos sobre la asociación de anemia y EP, a pesar de la creciente evidencia preclínica sobre su conexión. En esta revisión, se observó una tendencia hacia un mayor riesgo de EP en la población anémica.

Palabras clave: Enfermedad de Parkinson. Anemia. Hierro. Género. Factores de riesgo

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease among human population¹⁻³. Characteristic symptomatology involves bradykinesia, tremor, rigidity, and common motor symptoms. With an age increasing prevalence, it affects over 1% of the population over 60 years old⁴.

Although risk factors for PD are not yet fully understood, more of them have been identified during the past decade. The importance of identifying more risk factors relies on prevention of PD and on raising focus on new mechanisms involved in its pathogenesis that could help obtain a better understanding of the disease and propose new treatment alternatives.

Among newly described risk factors, focus on the link between PD and hematologic disorders has risen, more specifically on the relation between iron deficiency anemia and future PD incidence. As PD, the prevalence of anemia increases as a function of age after the 5th decade⁵, and more than 10% of older adults suffer from this affection⁶.

Iron deposition on the substantia nigra of the brain is a hallmark of PD^{7,8}, conversely, the previous evidence has suggested that PD is associated with lower serum iron levels when compared to healthy controls^{9,10}. Studies on animals have shown dopaminergic neurodegeneration in iron deficiency states¹¹, where, on the contrary, other evidences have implied that elevated iron levels lead to reactive oxygen species (ROS) production, which produce further cellular damage and death¹². The above-mentioned statements suggest that iron dysregulation plays a role in PD pathogenesis. A study proposed linking iron excess and mitochondria to PD pathogenesis^{13,14}, as its dysfunction has long been implied in the mechanisms of the disease. This suggests that iron level balance is important for adequate brain function as iron is necessary for mitochondria biogenesis¹⁵.

In addition to the previously mentioned, a study observed erythrocytes of 30 PD patients and observed changes in their morphology, hypothesizing that the inflammatory signaling molecules involved in PD pathophysiology may affect

the hematologic system of these patients, which could be used as potential prognostic or diagnostic indicator¹⁶. It is important to remark that iron-deficiency and anemia are different events; however, the former could be a possible pathway for the relation of the latter with PD. Two clinical trials have already studied the efficacy, safety, and tolerability of erythropoietin on patients with PD^{17,18}; nevertheless, further studies are needed to corroborate these results.

Some clinical studies evaluating the association between presence of anemia and risk for further PD incidence have been published; however, results have been inconsistent, and no solid conclusion has been reached. Therefore, to further clarify this topic, we performed a systematic review to summarize the available evidence on clinical studies evaluating the relation between anemia and PD.

Material and methods

This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. A previous protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with registration number CRD42020150456.

Eligibility criteria

Prospective or retrospective cohorts and case-control studies performed on humans that directly compared the incidence of PD in anemic population (according to the World Health Organization criteria; hemoglobin [Hb] levels < 12 g/dL in women and < 13 g/dL in men¹⁹) versus non-anemic population or evaluated the association between both conditions.

Information sources

A systematic search strategy using a combination of keywords and Mesh terms regarding the population, intervention, comparison, and outcomes of interest was

developed by an experienced librarian, along with the main researchers of the study. This search was performed in MEDLINE, Scopus, EMBASE, Web of Science, and the COCHRANE Central Register for Clinical Trials (CCRCT). The time lapse considered for our search was from each database inception date until March 2020. In addition, an update was made in November 2021 (see Supplementary Material for search strategy).

Study selection

This process was conducted by four reviewers and included a title/abstract and a full-text screening phase. Before each phase, a pilot study was conducted to ensure adequate inter-rater agreement. Any disagreement that appeared in the title/abstract phase was passed on to the full-text phase, where disagreements were resolved by consensus or involvement of another reviewer. After concluding each phase, kappa index was calculated to ensure inter-rater reliability (> 0.7). Articles that were included by the reviewers in the full-text phase were included for qualitative analysis.

Data collection process

Data extraction from studies fulfilling validity criteria was conducted using a template form to standardize extraction. The data extracted were as followed: study identification data (author, year of publication, place of study conduction, and study design), population identification (baseline characteristics), and description of intervention and study outcomes (incidence rates for PD in anemic and non-anemic population, and for potential confounding variables adjusted). This process was performed by two researchers in an independent and duplicate manner, where any disagreement was resolved by intervention of a third reviewer. A final version of the data form was approved by all researchers.

Quality assessment in individual studies

Three reviewers working independently and in duplicate assessed the methodological quality of each study included in the review using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies and Case-Control Studies²⁰. This scale evaluates three domains: selection, comparability, and outcome. For our study, a maximum of eight stars was considered as maximum score for Cohort Studies, whereas a maximum of nine stars for case-control studies, indicating this greater

quality. Concerning cohort studies, the last question of the "Outcome" section with regard to the adequacy of follow-up did not apply to the included studies due to their retrospective nature.

Outcomes' measure

A qualitative synthesis is provided, where the characteristics and findings from each study are explained and summarized. Categorical data were reported as frequency and percentage, whereas numeric data as mean and standard deviation. Incidence of PD was reported for each group divided by sex and/or in total population when available. Risk of developing PD is reported in total anemic population or/and divided by sex as unadjusted hazard ratios (HR) with their respective confidence intervals (95% C.I.). HR for PD adjusted for confounders was also reported when available.

Statistical analysis

When enough data were available (more than one study reporting on the outcome), random effect meta-analysis was performed to estimate exposure's effect on PD incidence. $p < 0.10$ for the test of heterogeneity across studies and $> 50\%$ for the measure of inconsistency (I²) was considered as high heterogeneity. The primary analysis used an inverse-weighted variance random-effect meta-analysis to account for the uncertainty in the location of the mean of different effects between studies. When events were evaluated, we used a modified Mantel-Haenszel meta-analysis with Peto's method. Meta-analyses were performed using R (Version 4.0).

Results

Initially, database search identified 4153 references. Of these, 4136 studies were excluded, because they did not meet the inclusion criteria. Subsequently, 17 full-text articles were reviewed for possible eligibility and 13 were excluded for different reasons, mainly as they did not assess the intervention of interest. At the update, from March 2020 to November 2021, data search identified 1097 references, and 1093 were excluded at the abstract screening. Afterward, four full-text articles were assessed, and three of them were excluded for being duplicated. Finally, five studies met the inclusion criteria and were included in our final qualitative synthesis; three of them were retrospective cohorts; and two were case-control studies²¹⁻²⁵.

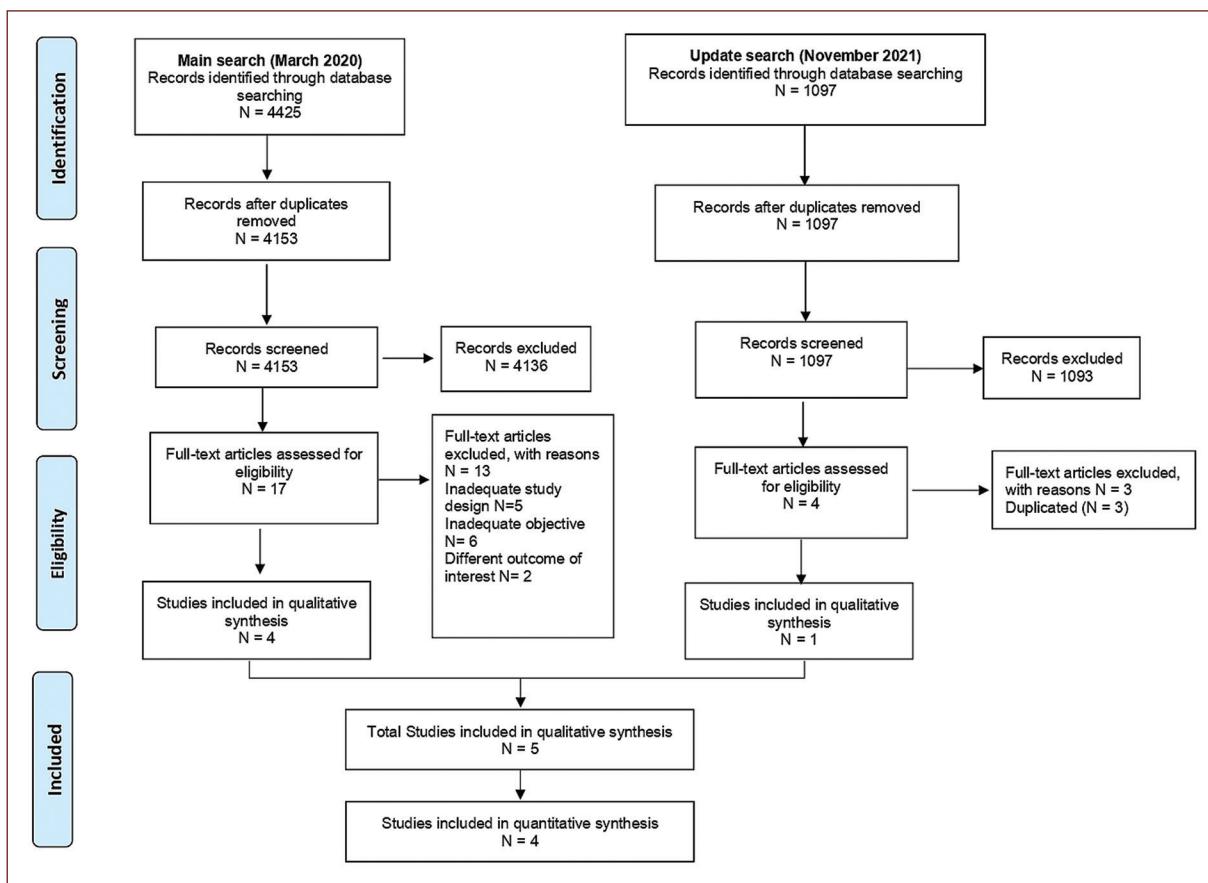


Figure 1. Flowchart of the number of identified and included studies.

The complete study selection process is depicted in Figure 1.

Study characteristics

Three retrospective cohorts were included; all of them retrieved their data from healthcare databases in Israel, Korea, and Taiwan and compared PD incidence between anemic population and a control group. Mean follow-up varied between across them, ranging from 5.0 to 8.8 years and mean age of the studied population ranged between the fifth and sixth decade. Only one cohort (Rozani et al.) had an almost balanced population based on gender (47.4% men and 52.6% female). Two case-control studies were included; both compared anemia diagnoses between a group of patients with PD and a group of matched healthy controls; one retrieved its data from a previous epidemiological project from US, while the other employed a Korean national healthcare cohort. From the five studies, two of

them reported patient comorbidities such as hypertension, diabetes mellitus, and hyperlipidemia (Table 1).

Incidence and risk of Parkinson disease

RISK FOR PD AMONG ANEMIC POPULATION

Cho et al. and Hong et al. both reported an adjusted multivariate analysis assessing PD risk among population who had a diagnosis of anemia, the former reported a decreased PD risk among this population (HR = 0.89 95% CI = 0.81-0.99), whereas contrasting results were reported on the latter (HR = 1.36 95% CI = 1.22-1.52). Rozani et al. analysis was stratified by gender; therefore, general PD risk was not reported (Table 2a). Moreover, in the case-control study performed by Savica et al., greater odds for having a diagnosis of anemia were associated with the presence of PD when compared to healthy controls (unadjusted OR = 2.00, 95% CI = 1.31-3.06). This was supported in the study by Kim et al., with an adjusted OR for the total population of 1.09, 95% CI = 1.01-1.18 (Table 2b).

Table 1. Baseline characteristics of included studies: (a) cohort studies and (b) case-control studies

A. Cohort studies									NOS score
Author, year	Country	Population number	Follow-up (years)	Age (mean, SD)	Female (n, %)	Hypertension (n, %)	Diabetes Mellitus (n, %)	Hyperlipidemia (n, %)	
Rozani et al., 2019	Israel	474,129*	8.8 ± 3.6	Male: 48.7 (9.3) Female: 47.7 (9.7)	249,181 (52.6)	NR	NR	NR	8
Cho et al., 2020	Korea	AN: 217,086 CO: 2,024,033	5.0	AN: 59.6 (9.4) CO: 57.17 (7.2)	AN: 129,962 (59.9) CO: 699,075 (34.6)	AN: 72,438 (33.4) CO: 704,394 (34.8)	AN: 25,174 (11.6) CO: 247,706 (12.3)	AN: 40,984 (18.9) CO: 468,511 (23.2)	8
Hong et al., 2016	Taiwan	AN: 86,334 CO: 86,334	6.6	AN: 56.4 (11.5) CO: 56.4 (11.5)	AN: 65,526 (75) CO: 65,526 (75)	AN: 26,018 (30.1) CO: 26,036 (30.2)	AN: 13,362 (15.5) CO: 26,037 (30.2)	AN: 17,994 (20.8) CO: 18,001 (20.9)	8
B. Case-control studies									
Author, year	Country	Population number	Age (mean, range) (years)	Female (n, %)	Median duration of enrollment (years)	NOS score			
Savica et al., 2009	United States of America	Cases: 196 Controls: 196	71 (41-97)	75 (38.3)*	38	8			
Kim et al., 2021	Korea	Cases: 5844 Controls: 23,376	NR	3094 (52.9)	13	8			

*Total population; AN: anemic population, CO: control population; NR: not reported; NOS: Newcastle-Ottawa scale.

GENDER STRATIFIED RISK FOR PD

In their unadjusted analysis, both Rozani et al. and Cho et al. found a greater risk for PD among male population with diagnosis of anemia (HR = 1.19 95% CI = 1.04-1.37; HR = 1.57 95% CI = 1.37-1.79); however, in their adjusted analysis, Cho et al. found no associated risk for PD among them (HR = 0.88 95% CI = 0.77-1.02). Rozani et al. did not report an adjusted analysis. Regarding female population with diagnosis of anemia, no higher risk of PD incidence was observed in neither of these studies (Table 2).

SUBGROUP ANALYSIS

To perform the subgroup analysis, the cohorts and case-controls studies were pooled in a separate way. In the cohort studies, the pooled relative risk of anemia and PD was 1.10; 95% CI = 0.08-15.84, and it is presented in figure 2a. On the other hand, the pooled OR

of the case-control studies was 1.44; 95% CI = 0.04-52.47 (Fig. 2b). High heterogeneity was observed among included studies.

Certainty of evidence

All studies, both cohort and case-control, were classified as high-quality studies according to Newcastle-Ottawa Quality Assessment Scale (Table 1).

Discussion

In this systematic review, we aimed to assess the currently available clinical evidence which evaluated a possible association between a diagnosis of anemia and PD. We found three retrospective cohorts that reported PD risk associated to presence of anemia and two case-control studies that reported odds of having anemia when PD was present. Among the two cohorts who reported PD risk among general population with

Table 2. Parkinson's disease incidence among included studies: (a) cohort studies and (b) Case-control studies

A. Cohort studies									
Author, year	PD incidence in male group	HR (95% CI)	aHR (95% CI)	PD incidence in female group	HR (95% CI)	aHR (95% CI)	PD incidence in total population	HR (95% CI)	aHR (95% CI)
Rozani et al., 2019	AN: 1.2% ⁰ CO: 0.6% ⁰	1.19 (1.04-1.37)	NR	AN: 0.3% ⁰ CO: 0.4% ⁰	1.02 (0.95-1.09)	NR	NR	NR	NR
Cho et al., 2020	AN: 236 (0.3%) CO: 2,258 (0.2%)	1.57 (1.37-1.79)	0.88 (0.77-1.02)	AN: 219 (0.1%) CO: 1,131 (0.1%)	1.04 (0.91-1.21)	0.91 (0.78-1.05)	AN: 455 (0.2%) CO: 3,389 (0.16%)	1.24 (1.13-1.37)	0.89 (0.81-0.99)
Hong et al., 2016	NR	NR	NR	NR	NR	NR	NR	NR	1.36 (1.22-1.52)

B. Case-control studies						
Author, year	Incidence of anemia in cases	Incidence of anemia in controls	OR total population (95% CI)	OR (95% CI) in male group	OR (95% CI) in female group	aOR total population (95% CI)
Savica et al., 2009	86 (43.9%)	54 (27.6%)	2.00 (1.31-3.06)	1.52 (0.88-2.64)	2.91 (1.47-5.77)	2.17 (1.40-3.37)* 1.74 (1.02-2.97)**
Kim et al., 2021	1090 (18.7%)	3944 (16.9%)	1.13 (1.05-1.23)	< 70 years: 1.44 (1.22-1.70) > 70 years: 1.14 (0.97-1.34)	< 70 years: 1.05 (0.92-1.21) > 70 years: 1.04 (0.90-1.20)	1.09 (1.01-1.18)***

HR: Hazard ratio, 95% CI: 95% confidence interval, aHR: adjusted Hazard ratio, NR: not reported, ⁰absolute incidence not reported.

OR: odds ratio, 95% CI: 95% confidence interval, aOR: adjusted odds ratio.

*adjusted for smoking.

**adjusted for pesticide exposure.

***adjusted for obesity, smoking, blood glucose, head trauma and alcohol exposure.

anemia diagnosis, results were contrasting. Furthermore, when analyzed by gender, unadjusted analyses revealed higher risk for PD among male anemic population; however, the only adjusted analysis, which was reported by Cho et al. did not support this finding. No higher risk for PD was observed among female anemic population. In the case-control studies, individuals with PD had higher odds of having diagnosed anemia than patients without PD diagnosis^{21,25}. Overall, the pooled relative risk observed in the included studies suggested a not significant increased risk for PD in anemic populations.

Analyzing the implications of the included studies, two cohorts and one case-control study proposed anemia to be a prodromal marker for PD. This, as it is acknowledged that this disease begins years before dopaminergic degeneration in the substantia nigra²⁶.

Thus, the presence of anemia may be originated by the inflammatory, oxidative stress changes in the prodromal stages of PD^{27,28}. Moreover, we suggest a bidirectional model, in which anemic conditions might further contribute to PD related to oxidative stress, inflammation, and iron dysregulation. Nonetheless, when considering the study by Cho et al., the authors concluded a protective effect of anemia in future PD incidence, contradicting the conclusions of the other studies. However, one important aspect that must be considered to interpret these conclusions is the definition of exposure in these included studies.

The previously mentioned is rather important as most studies define the exposure (presence of anemia) in heterogeneous ways (Table 3). Rozani et al. calculated the mean annual hemoglobin levels of each included individual, with a mean number of hemoglobin tests of

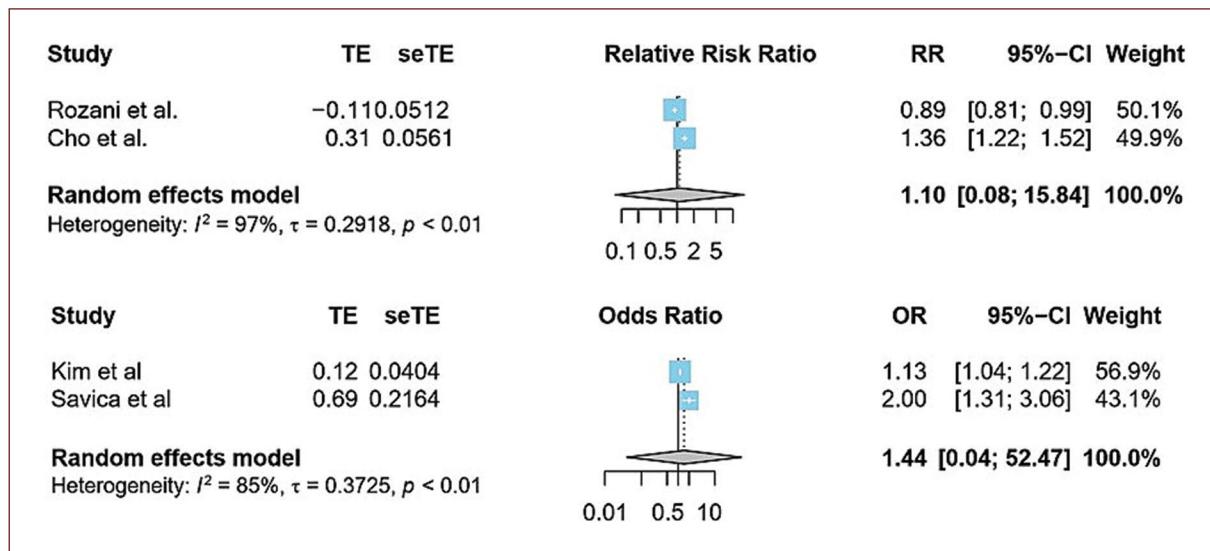


Figure 2. A: forrest plot displaying risk ratios and 95% confidence intervals of developing Parkinson's disease in anemic versus non-anemic population in cohort studies. **B:** forrest plot displaying pooled odds ratio of previous anemia exposure and Parkinson's disease risk in case-control studies.

Table 3. Definition of anemia exposure for each included study

Study	Anemia definition
Cho et al. 2020	One-time result at baseline (Hb < 13g/dL M, < 12 g/dL W)
Rozani et al. 2019	Mean annual Hb classified as anemia (Hb < 13g/dL M, <12 g/dL W)
Hong et al. 2016	At least two diagnostic claims for anemia or iron supplementary medication in a 7-year period.
Savica et al. 2009	1) A diagnosis of anemia ever mentioned in medical records or, 2) Hb < 13 g/dL M, < 12 g/dL W persisting over a 6-week period to exclude acute blood related anemia.
Kim et al. 2021	The most recent hemoglobin concentration before the diagnosis of PD (index date), Hb < 13 g/dL in M and < 12 g/dL in W

Hb: hemoglobin, M: men, W: women.

6 ± 3 per individual during the entire follow-up, where if the mean of one annual Hb measurement was below the threshold for anemia, exposure was considered positive. Moreover, Hong et al. required at least two diagnostic claims for anemia or iron supplementary therapy during a time lapse of 7 years. Savica et al. study required a diagnosis of anemia ever mentioned, or hemoglobin levels under anemic values according to the World Health Organization persisting over a 6-week

period to exclude blood loss related values. Compared to these exposure criteria, Cho et al. and Kim et al. used a one-time hemoglobin result under anemic conditions to define anemia, which raises questions on the validity of the exposure's effect on the measured outcome, as a one-time reported result might not reflect its actual effect. In this manner, the former studies, which reported an increased risk for PD incidence and used multiple hemoglobin or diagnostic claims, might reflect better the exposure's effect on the measured outcome. However, a limitation that must be highlighted in the study by Rozani et al. is the lack of adjustment for confounding variables, as the other cohort studies and case-control studies did perform. This is important as PD is influenced by various factors that have been observed in meta-analysis and observational studies such as diabetes mellitus, hypertension, pesticide exposure, and smoking²⁹⁻³².

PD clinical characteristics, progression and risk factors follow sex-specific differences³³. As an example, in this review, we found that Savica et al. reported anemia to be more associated to PD among female population, whereas lifestyle and occupational risk factors were more related to the disease in male population³⁴. As PD, anemia also has gender-dependent differences as its prevalence is higher among female population^{35,36}; nonetheless, no increased risk for PD was observed for female anemic population in neither of our included cohort studies. Whether gender-related differences are present in the

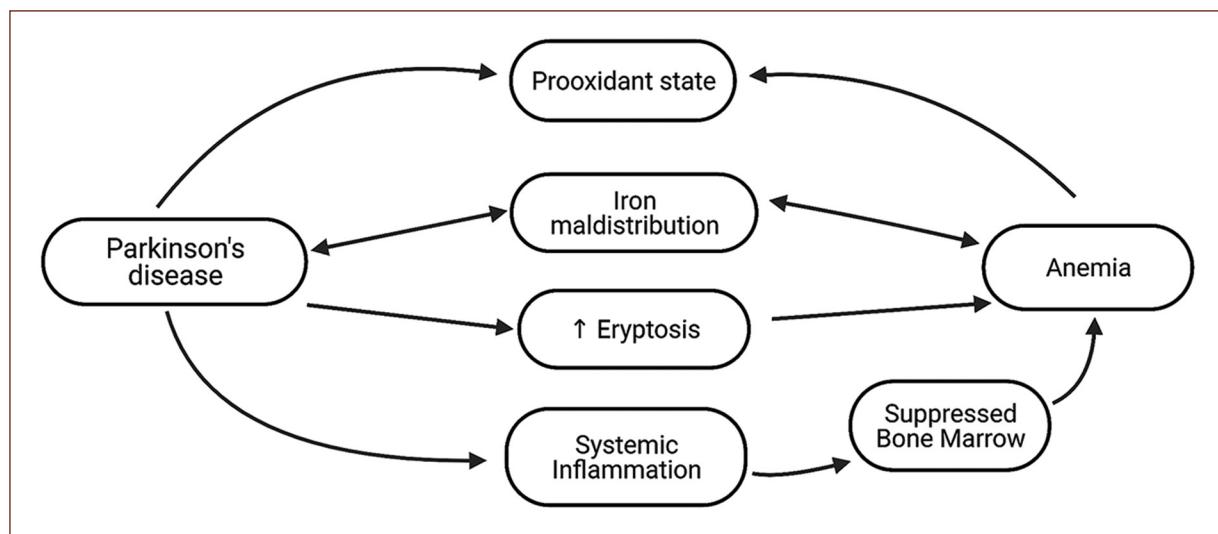


Figure 3. Diagram of the potential mechanisms in the association of anemia and Parkinson's disease.

relation of anemia and future PD incidence is a non-clarified issue to date. In this review, no conclusive evidence regarding the abovementioned was reached.

The possible pathological pathways that may explain anemia association with PD are inflammation, oxidative stress, and iron metabolism (Fig. 3). The previous evidence has assessed hemoglobin and iron levels on patients with PD, showing inconsistent results, as some studies have shown hemoglobin levels to decrease as PD progresses, but others exhibited no difference in neither hemoglobin nor iron levels compared to controls³⁷⁻³⁹. Nonetheless, as systemic inflammation has been recognized to contribute to PD pathogenesis⁴⁰, and inflammatory cytokines have been shown to suppress bone marrow and inhibit erythropoietin-induced erythrocyte maturation⁴¹, this could possibly explain the low red blood cell count and its relation with future PD.

Considering oxidative stress, some evidence has shown that red blood cells of PD patients lack superoxide dismutase, an enzyme responsible for counteracting oxidative stress, and are as a result susceptible to stress-induced damage^{42,43}. Regarding iron-deficiency anemia, a study showed that patients with this condition have a higher oxidant and a lower antioxidant activity compared to controls, which normalizes to control levels after iron treatment⁴⁴. In addition, a review described the pro-oxidant shift that occurs in anemic conditions, which is further worsened by a weakened antioxidant capacity in this environment⁴⁵. Thus, anemia might contribute to the oxidant conditions that are needed for PD pathogenesis, whereas red blood cells'

changes in PD patients might support eryptosis¹⁶, showing a hypothetical bidirectional association.

Considering the oxidant properties of iron⁴⁶ and that its deposition in the substantia nigra has been observed in PD patients⁷, its metabolism could be another element in the relationship between anemia and future PD incidence. Contrary to the hypothesis that arises when considering the oxidant properties of iron, where anemia and low serum iron levels should apparently contribute to a decreased risk for PD, evidence has shown that increased levels of serum iron were associated with a reduced risk for future PD^{9,47}. The latter could be supported considering that iron is a cofactor for the enzyme L-tyrosine hydroxylase, which is responsible for dopamine synthesis⁴⁸. Animal models of iron deficiency have shown altered dopamine metabolism and function^{49,50}, which could explain the protective effect of increase serum iron levels on PD incidence. Moreover, an iron maldistribution process could also explain the increased deposition in substantia nigra but the low serum iron levels⁵¹, which might affect erythropoiesis, exhibiting a possible link between anemia and PD incidence.

Finally, another element linking both pathologies is red cell distribution width (RDW), which is commonly increased in iron-deficiency anemia as sign of anisocytosis⁵². A study showed patients with PD have increased RDW levels compared to controls, whereas another correlated RDW to PD progression^{53,54}. The former compared hemoglobin and white blood count to controls, and no difference except RDW was shown. Although RDW has been shown to be an inflammatory marker^{55,56}, its increase

in PD patients could be related to an iron maldistribution process and could demonstrate that patients with PD experience disruption in erythrocyte cell line, possibly linking iron metabolism, and PD.

This study has some limitations. The high heterogeneity of the pooled studies limits the interpretation of the pooled analysis. Moreover, available evidence regarding our research questions was scarce and this could seriously limit our findings. Another consideration is that patients with decreases in hemoglobin values not reaching anemic WHO cutoffs might have inflammatory and iron maldistribution processes that might contribute to PD and could not be evaluated.

Conclusion

A non-significantly increased pooled risk for PD was observed in the included cohort and case-control studies. The pathophysiological mechanisms related to iron maldistribution, oxidative stress, and systemic inflammation might explain this observed tendency. Prospective studies with various hemoglobin measurements under anemic values during follow-up and control of confounding variables are needed to corroborate and further confirm the idea of anemia as prodromal marker of PD.

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None.

Conflict of interests

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

References

1. De Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol.* 2006;5:525-35.
2. Lee A, Gilbert RM. Epidemiology of Parkinson disease. *Neurol Clin.* 2016;34:955-65.
3. Nussbaum RL, Ellis CE. Alzheimer's disease and Parkinson's disease. *N Engl J Med.* 2003;348:1356-64.
4. Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *J Neural Transm (Vienna).* 2017;124:901-5.
5. Patel KV. Epidemiology of anemia in older adults. *Semin Hematol.* 2008;45:210-7.
6. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood.* 2004;104:2263-8.
7. Chen Q, Chen Y, Zhang Y, Wang F, Yu H, Zhang C, et al. Iron deposition in Parkinson's disease by quantitative susceptibility mapping. *BMC Neurosci.* 2019;20:23.
8. Mochizuki H, Yasuda T. Iron accumulation in Parkinson's disease. *J Neural Transm (Vienna).* 2012;119:1511-4.
9. Pichler I, Del Greco MF, Gögele M, Lill CM, Bertram L, Do CB, et al. Serum iron levels and the risk of Parkinson disease: a mendelian randomization study. *PLoS Med.* 2013;10:e100146.
10. Medeiros MS, Schumacher-Schuh A, Cardoso AM, Bochi GV, Baldissarelli J, Kegler A, et al. Iron and oxidative stress in Parkinson's disease: an observational study of injury biomarkers. *PLoS One.* 2016;11:e014612.
11. Yien YY, Paw BH. A role for iron deficiency in dopaminergic neurodegeneration. *Proc Natl Acad Sci U S A.* 2016;113:3417-8.
12. Martin-Bastida A, Tilley BS, Bansal S, Gentleman SM, Dexter DT, Ward RJ. Iron and inflammation: *in vivo* and post-mortem studies in Parkinson's disease. *J Neural Transm (Vienna).* 2021;128:15-25.
13. Muñoz Y, Carrasco CM, Campos JD, Aguirre P, Núñez MT. Parkinson's disease: the mitochondria-iron link. *Parkinsons Dis.* 2016;2016:7049108.
14. Mochizuki H, Choong CJ, Baba K. Parkinson's disease and iron. *J Neural Transm (Vienna).* 2020;127:181-7.
15. Gille G, Reichmann H. Iron-dependent functions of mitochondria-relation to neurodegeneration. *J Neural Transm.* 2011;118:349-59.
16. Pretorius E, Swanepoel AC, Buys AV, Vermeulen N, Duim W, Kell DB. Erytosis as a marker of Parkinson's disease. *Aging (Albany NY).* 2014;6:788-819.
17. Pedrosa I, Bringas ML, Aguiar A, Morales L, Alvarez M, Valdés PA, et al. Use of Cuban recombinant human erythropoietin in Parkinson's disease treatment. *MEDICC Rev.* 2012;14:11-7.
18. Jang W, Park J, Shin KJ, Kim JS, Kim JS, Youn J, et al. Safety and efficacy of recombinant human erythropoietin treatment of non-motor symptoms in Parkinson's disease. *J Neurol Sci.* 2014;337:47-54.
19. World Health Organization. *Nutritional anaemias : In: Tools for Effective Prevention.* Geneva: World Health Organization; 2017.
20. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality if Nonrandomized Studies in Meta-analyses; 2012. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
21. Savica R, Grossardt BR, Carlin JM, Icen M, Bower JH, Ahlskog JE, et al. Anemia or low hemoglobin levels preceding Parkinson disease: a case-control study. *Neurology.* 2009;73:1381-7.
22. Rozani V, Giladi N, Gurevich T, El-Ad B, Tsamir J, Hemo B, et al. Anemia in men and increased Parkinson's disease risk: a population-based large scale cohort study. *Park Relat Disord.* 2019;64:90-6.
23. Cho IY, Shin DW, Roh Y, Jang W, Cho JW, Lee EA, et al. Anemia and the risk of Parkinson's disease in Korean older adults: a nationwide population-based study. *Sci Rep.* 2020;10:4268.
24. Hong CT, Huang YH, Liu HY, Chiu HY, Chan L, Chien LN. Newly diagnosed anemia increases risk of parkinson's disease: a population-based cohort study. *Sci Rep.* 2016;6:29651.
25. Kim J, Oh J, Wee JH, Min CY, Yoo D, Choi H. The Association between anemia and Parkinson's disease: a nested case-control study using a national health screening cohort. *Brain Sci.* 2021;11:623.
26. Braak H, Del Tredici K, Rüb U, De Vos RA, Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging.* 2003;24:197-211.
27. Lotankar S, Prabhavalkar KS, Bhatt LK. Biomarkers for Parkinson's disease: recent advancement. *Neurosci Bull.* 2017;33:585-97.
28. Rathnayake D, Chang T, Udagama P. Selected serum cytokines and nitric oxide as potential multi-marker biosignature panels for Parkinson disease of varying durations: a case-control study. *BMC Neurol.* 2019;19:56.
29. Yue X, Li H, Yan H, Zhang P, Chang L, Li T. Risk of Parkinson disease in diabetes mellitus. *Medicine (Baltimore).* 2016;95:e3549.
30. Hou L, Li Q, Jiang L, Qiu H, Geng C, Hong JS, et al. Hypertension and diagnosis of Parkinson's disease: a meta-analysis of cohort studies. *Front Neurol.* 2018;9:162.
31. Breckenridge CB, Berry C, Chang ET, Sielken RL Jr., Mandel JS. Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis. *PLoS One.* 2016;11:e0151841.
32. Freire C, Koifman S. Pesticide exposure and Parkinson's disease: epidemiological evidence of association. *Neurotoxicology.* 2012;33:947-71.
33. Cerri S, Mus L, Blandini F. Parkinson's disease in women and men: what's the difference? *J Parkinsons Dis.* 2019;9:501-15.
34. Savica R, Grossardt BR, Bower JH, Ahlskog JE, Rocca WA. Risk factors for Parkinson's disease may differ in men and women: an exploratory study. *Horm Behav.* 2013;63:308-14.
35. Shouval R, Katz S, Nagler A, Merkel D, Ben-Zvi I, Segev S, et al. Gender disparities in the functional significance of anemia among apparently healthy adults. *Eur J Haematol.* 2017;98:435-42.

36. Shaban L, Al-Taiar A, Rahman A, Al-Sabah R, Mojiminiyi O. Anemia and its associated factors among adolescents in Kuwait. *Sci Rep.* 2020;10:5857.
37. Deng Q, Zhou X, Chen J, Pan M, Gao H, Zhou J, et al. Lower hemoglobin levels in patients with parkinson's disease are associated with disease severity and iron metabolism. *Brain Res.* 2017;1655:145-51.
38. Kasten M, Tadic V, Klein C, Rocca WA, Savica R, Ahlskog JE, et al. Anemia or low hemoglobin levels preceding parkinson disease: a case-control study. *Neurology.* 2010;74:1655-66.
39. Mariani S, Ventriglia M, Simonelli I, Donno S, Bucossi S, Vernieri F, et al. Fe and Cu do not differ in Parkinson's disease: a replication study plus meta-analysis. *Neurobiol Aging.* 2013;34:632-3.
40. Perry VH. Contribution of systemic inflammation to chronic neurodegeneration. *Acta Neuropathol.* 2010;120:277-86.
41. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. *Perfusion.* 2005;20:83-90.
42. Urakami K, Sano K, Matsushima E, Okada A, Saito H, Takahashi K, et al. Decreased superoxide dismutase activity in erythrocyte in Parkinson's disease. *Jpn Psychiatry Clin Neurosci.* 1992;46:933-6.
43. Kılıç A, Yalçın AS, Yalçın D, Taga Y, Emerk K. Increased erythrocyte susceptibility to lipid peroxidation in human Parkinson's disease. *Neurosci Lett.* 1988;87:307-10.
44. Yoo JH, Maeng HY, Sun YK, Kim YA, Park DW, Park ST, et al. Oxidative status in iron-deficiency anemia. *J Clin Lab Anal.* 2009;23:319-23.
45. Grune T, Sommerburg O, Siems WG. Oxidative stress in anemia. *Clin Nephrol.* 2000;53:S18-22.
46. Visanji NP, Collingwood JF, Finnegan ME, Tandon A, House E, Hazrati LN. Iron deficiency in parkinsonism: region-specific iron dysregulation in Parkinson's disease and multiple system atrophy. *J Parkinsons Dis.* 2013;3:523-37.
47. Miyake Y, Tanaka K, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, et al. Dietary intake of metals and risk of Parkinson's disease: a case-control study in Japan. *J Neurol Sci.* 2011;306:98-102.
48. Ramsey AJ, Hillas PJ, Fitzpatrick PF. Characterization of the active site iron in tyrosine hydroxylase. Redox states of the iron. *J Biol Chem.* 1996;271:24395-400.
49. Nelson C, Erikson K, Piñero DJ, Beard JL. *In vivo* dopamine metabolism is altered in iron-deficient anemic rats. *J Nutr.* 1997;127:2282-8.
50. Beard J, Erikson KM, Jones BC. Neonatal iron deficiency results in irreversible changes in dopamine function in rats. *J Nutr.* 2003;133:1174-9.
51. Cabantchik ZI, Munnich A, Youdim MB, Devos D. Regional siderosis: a new challenge for iron chelation therapy. *Front Pharmacol.* 2013;4:167.
52. Aslan D, Gümrük F, Gürgey A, Altay C. Importance of RDW value in differential diagnosis of hypochromic anemias. *Am J Hematol.* 2002;69:31-3.
53. Qin YH, Wei YS, Meng LQ, Chen WC. The role of red cell distribution width in patients with Parkinson's disease. *Int J Clin Exp Med.* 2016;9:6143-7.
54. Kenangil G, Ari BC, Kaya FA, Demir M, Domac FM. Red cell distribution width levels in Parkinson's disease patients. *Acta Neurol Belg.* 2020;120:1147-50.
55. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Arch Pathol Lab Med.* 2009;133:628-32.
56. Lippi G, Mattiuzzi C, Cervellin G. Learning more and spending less with neglected laboratory parameters: the paradigmatic case of red blood cell distribution width. *Acta Biomed.* 2016;87:323-8.