

# Elevated circulating magnesium levels in patients with Parkinson's disease: a meta-analysis

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**Background:** The association between circulating magnesium (Mg) and Parkinson's disease (PD) remains ambiguous and controversial. Thus, a meta-analysis was conducted to evaluate the circulating Mg levels in PD patients and to clarify whether high circulating Mg levels should be considered as a potential risk factor for PD.

**Methods:** In this study, 17 case-control published studies were selected in our meta-analysis by searching the electronic databases of Web of Science, PubMed, and China National Knowledge Infrastructure (CNKI) before June 1, 2018. Overall, 848 PD cases and 784 healthy controls (HC), 1,023 PD cases and 911 HC, and 180 PD cases and 144 HC met the inclusion criteria for this study Mg levels in serum, peripheral blood, and cerebrospinal fluid (CSF), respectively. Standardized mean difference (SMD) in random-effects model and 95% CI were used to assess the correlation strength through the comparison of the two groups.

**Results:** Meta-analysis showed that the serum Mg levels in PD cases were significantly higher than those in HC individuals (SMD=1.09, 95% CI=0.52, 1.66). Furthermore, this result was further confirmed by the combined analysis of serum and whole blood studies together (SMD=0.64, 95% CI=0.10, 1.19). In addition, the higher CSF Mg levels in patients of PD were observed in comparison with normal range (SMD=0.55, 95% CI=0.21, 0.88). However, this data did not further discuss and analyze because of the smaller sample size of CSF studies.

**Conclusion:** Our findings supported the notion that the increase of circulating Mg levels appears in the patients with PD.

**Keywords:** magnesium, serum, peripheral blood, CSF, Parkinson's disease, meta-analysis

## Introduction

Parkinson's disease (PD), the second most frequent neurodegenerative disorder of aging, is characterized by the dopamine reduction in striatal and progressive and selective loss of dopaminergic neurons in substantia nigra caused by unknown etiopathogenesis.<sup>1,2</sup> It affects typical motor function including muscle rigidity, abnormal posture, bradykinesia, resting tremor, and other cognitive impairments, not only affecting the life quality of patients but also increasing the society burden.<sup>3</sup> As we know, PD is a multifactorial disorder, many risk factors, including lifestyle, environmental factors, and micronutrients disturbances are involved in the occurrence and development of PD.<sup>4,5</sup> Compelling evidences suggest that genetic mutations in *α-synuclein*, *Parkin*, *PINK*, *LRRK2*, and other genes are also key factors to induce the PD, accounting for almost 10% of PD cases.<sup>6-8</sup> In addition, the rest of PD patients caused by unexplained reason are usually rare and sporadic.

Metal homeostasis plays an important role in biological processes involved in signal transduction, cell respiration, metalloproteinase activity, and other physiological processes because of their ability to accept or donate electrons.<sup>9,10</sup> However, the imbalance of

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metal homeostasis in brain, such as zinc, copper, manganese, or iron, also had potentially dangers for the onset and progression of neurodegenerative diseases, including PD.<sup>11,12</sup> For instance, metals could catalyze the formation of reactive oxygen species, which caused oxidative stress leading to the death of dopaminergic neurons.<sup>13</sup> In addition, metals even at low concentrations also could readily foster the oligomerization and aggregation of  $\alpha$ -synuclein associated with the pathophysiology of PD.<sup>14,15</sup> Therefore, it is meaningful to understand the relation with metal homeostasis and PD for developing an effective preventive targeting strategy for PD.

Magnesium (Mg) is the most abundant divalent cation in human cells.<sup>16</sup> In central nervous system (CNS), as a cofactor for various key enzymes, Mg is considered indispensable for a wide variety of neural functions, including energy production, neuromuscular conduction, and neurotransmitter release.<sup>17,18</sup> Disturbances in Mg homeostasis have been implicated in a broad spectrum of neurodegenerative disorders of aging, including PD and Alzheimer's disease.<sup>19,20</sup> Numerous studies pointed out the possible role of Mg levels in patients with PD, but the conclusions were ambiguous and inconsistent. Several studies have shown that systemic Mg levels were reduced in PD patients compared with healthy controls (HC).<sup>21–23</sup> In contrast, other articles reported a considerably higher Mg levels in PD patients.<sup>24–27</sup> Also, a few studies probably tended no statistical difference in Mg levels between PD patients and healthy populations.<sup>28,29</sup>

Thus, we conducted the meta-analysis to comprehensively assess the serum, peripheral blood, and cerebrospinal fluid (CSF) levels of Mg variations in patients with PD compared with healthy cases and to provide additional insights into the maintenance for a healthy nutritional status and the prevention of PD.

## Methods

### Search strategy

This meta-analysis fulfilled the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and the Cochrane Collaboration definition of both terms.<sup>30,31</sup> We primarily searched relevant literature from Web of Science, PubMed, and China National Knowledge Infrastructure (CNKI) before June 1, 2018. The subject terms included a combination of key words, such as “magnesium” and “Parkinson's disease”, “Parkinson”, “serum”, “blood”, “plasma”, “CSF”, “metals”, or “trace element” without any language limits. Also, other potentially missing relevant studies were further supplemented by handsearching the references of included articles.

### Inclusion criteria

Eligible publication for inclusion in the current meta-analysis simultaneously followed the following criteria: 1) case-control study design; 2) human study with PD and HC groups; and 3) studies with sample size and Mg concentration in serum, blood, or CSF in cases and controls. Exclusion criteria are as follows: 1) abstract, letter, review, editorials, or case reports; 2) repeated data; 3) animal studies; 4) studies without numerical data of Mg concentration; and 5) studies without Mg concentration for HC.

### Data extraction

Both authors (XJ and D-F Z) independently completed the data extraction from text, tables, and figures. Data information includes first author, publication year, country, Mg concentration, case number, mean age, sample source, percentage of female, analysis method, duration of PD, and other study characteristics. If available, Mg concentration were expressed with mean  $\pm$  SD, otherwise, estimated data from the median and range. All underlying units of Mg concentration varied with different studies were converted to mg/L.

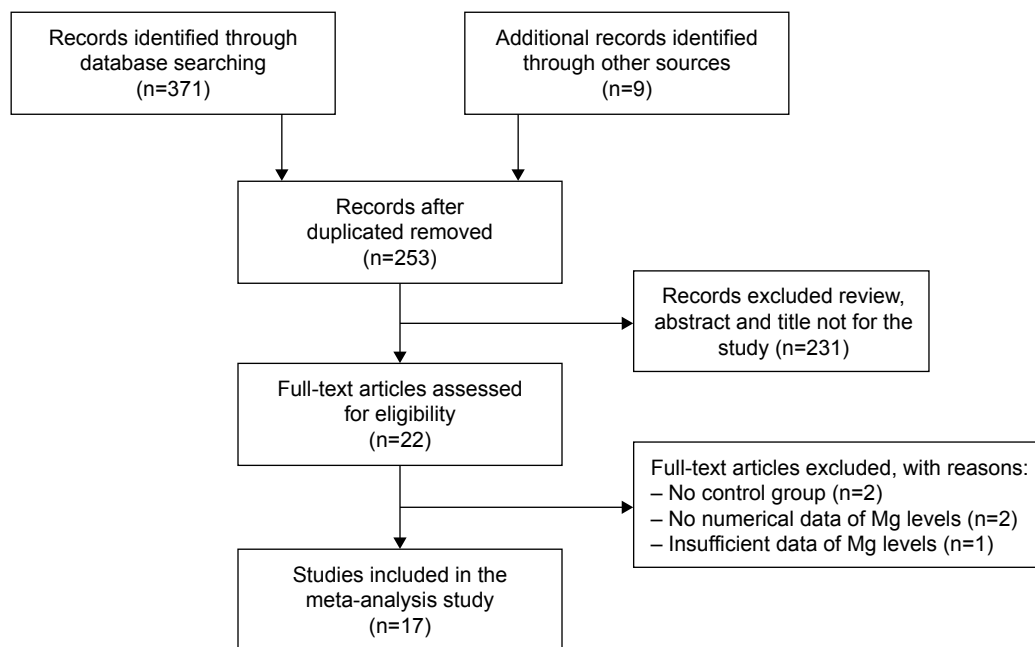
### Statistical analyses

The standardized mean difference (SMD) and 95% CI were invoked as the strength of the association between Mg concentrations and PD risk. The value of  $I^2$  was used to estimate the proportion of total variation attributable across study, with values  $>75\%$  indicative of significant heterogeneity between studies.<sup>32</sup> The random-effects model was selected if  $I^2$  value  $>50\%$ , otherwise, the fixed-effects model was adopted.<sup>33</sup> Subgroup analyses stratified by the locations and analytic methods were conducted to clarify the possible sources of between-study heterogeneity. Meta-regression analysis was employed to investigate the potentially important covariates that might affect between-study heterogeneity.<sup>34</sup> Sensitivity analysis was used to examine whether the pooled SMD was markedly influenced by the significant difference of individual studies.<sup>35</sup> Egger's test was used to assess publication bias comparing the effect sizes with their standard error.<sup>36</sup> Cumulative meta-analysis was established to evaluate the temporal effect. All statistical analyses were performed using STATA 12.0 (StataCorp LP, College Station, TX, USA). Two-tailed  $P$ -value  $<0.05$  was considered as statistically significant.

## Results

### Characteristics of eligible studies

A total of 380 potential articles matched the inclusion after preliminary search from the Web of Science, PubMed, CNKI,



**Figure 1** Meta-analysis flow diagram of the study search strategy.

and other relevant databases. After further screening, 17 final epidemiological studies were finally enrolled in current study (a total of 1,203 PD cases and 1,055 HC). The strategy of study search was provided in Figure 1.

The sample sizes of PD patients ranged from 19 to 250. The average age of PD cases ranged from 57.6 to 65.7 years old. The percentage of female patients ranged from 7.7% to 55.0%. Methods of Mg concentration analysis consisted of the atomic absorption spectrometry, inductively coupled plasma-atomic emission spectrometry, inductively coupled plasma-mass spectrometry (ICP-MS), inductively coupled plasma optical emission spectrometry (ICP-OES), and colorimetry. The geographic populations were European, American, Asian, and African, respectively. The detailed characteristics were summarized in Table 1.

### Meta-analysis of serum Mg levels between PD patients and HC subjects

The overall data from 12 articles compared the serum Mg levels between PD patients and HC subjects in a random-effects model because significant heterogeneity ( $I^2=95.6%$ ,  $P=0.000$ ) was discovered across these studies. The pooled sample size encompassed a total of 1,632 subjects including 848 PD cases and 784 HC subjects. The results demonstrated that serum Mg levels in PD patients were significantly higher than those in HC subjects (SMD =1.09, 95% CI =0.52, 1.66; Figure 2). Subgroup analysis accounting for location

disclosed that the Mg levels increased in PD patients in Asian populations (SMD =2.22, 95% CI =0.82, 3.63;  $P$  for  $Z=0.002$ ) and African populations (SMD =1.18, 95% CI =0.80, 1.55;  $P$  for  $Z=0.000$ ). In addition, the subgroup analysis stratified by analysis methods showed that a similar pattern in ICP-MS/ICP-AES (SMD =1.55, 95% CI =0.54, 2.57;  $P$  for  $Z=0.003$ ). However, neither the location nor the analysis method contributed to the source of heterogeneity (Table 2).

Meta-regression found that the duration, average age, and gender of PD patients had no influences on between-study heterogeneity (Table 3). Sensitivity analysis showed that Ahmed and Santosh's study has an excessive influence on the outcome;<sup>53</sup> however, after the exclusion of this study, the statistical significance of the combined SMD was not unduly changed, indicating the robustness of the results. Cumulative meta-analysis revealed that no temporal effect affected the overall analysis results. Moreover, Egger's test detected no publication bias in all included studies ( $P=0.054$ ) and visual observation of the funnel plot also revealed symmetrical approximately.

### Meta-analysis of peripheral blood Mg levels between PD patients and HC subjects

We further constructed a combined analysis of Mg serum and blood levels to evaluate Mg levels in peripheral blood. Fourteen articles were collected with a pooled sample size

**Table 1** Characteristics of the included studies in this meta-analysis (arranged by publication time)

First author	Year	Country	Analysis method	Sample size		Magnesium concentration (mg/L)		Age (years)		Gender (% female)		Duration of disease
				PD	HC	PD	HC	PD	HC	PD	HC	PD
<b>Serum</b>												
Schwab RS <sup>28</sup>	1964	USA	Colorimetry	75	34	20.9±2.8	20.7±1.9	NR	NR	NR	NR	NR
Luo PY <sup>50</sup>	1987	China	AAS	30	20	35.6±3.5	34.1±34.3	61.5±8.4	NR	30.0	NR	NR
Forte G <sup>24</sup>	2004	Italy	ICP-AES	26	13	19.2±1.8*	17.5±1.3	64.9±10.8	63.8±13.7	7.7	53.8	4.8±3.8
Hegde ML <sup>51</sup>	2004	India	ICP-AES	52	25	25.5±2.2	21.9±2.2	58.2±4.7	55.4±6.4	46.2	48.0	4.8±2.5
Forte G <sup>25</sup>	2005	Italy	ICP-AES	71	44	19.0±3.3*	17.2±1.8	65.5±9.4	51.9±4.0	25.4	25.0	4.6±4.5
Sanjay Pande MB <sup>52</sup>	2005	India	ICP-AES	50	25	25.5±2.2	21.8±2.2	NR	NR	NR	NR	NR
Bocca B <sup>26</sup>	2006	Italy	ICP-AES	91	18	31.7±4.7*	26.5±4.8	65.5±9.7	63.3±13.8	29.7	44.4	4.6±4.1
Alimonti A <sup>23</sup>	2007	Italy	ICP-AES	71	124	17.4±1.9	18.9±3.2	65.5±9.4	44.8±12.7	25.4	34.7	4.6±4.5
Gellein K <sup>22</sup>	2008	Norway	ICP-MS	19	99	20.7±2.5	21.4±3.0	61.9±9.5	NR	52.6	51.5	7.7±2.3
Ahmed SS <sup>53</sup>	2010	India	ICP-AES	45	42	20.1±0.4*	17.5±0.2	57.6±9.1	55.6±3.3	42.2	40.5	NR
Ogunrin AO <sup>54</sup>	2013	Nigeria	AAS	68	60	41.3±15.8*	25.0±11.2	65.7±7.3	61.5±8.3	32.4	36.7	NR
Sanyal J <sup>29</sup>	2016	India	AAS	250	280	20.4±1.2*	19.9±1.5	57.9±12.1	56.4±9.7	35.2	34.6	4.9±3.0
<b>Blood</b>												
Barbeau A <sup>21</sup>	1963	USA	Colorimetry	28	20	15.8±2.2	22.5±4.9	NR	NR	NR	NR	NR
Forte G <sup>24</sup>	2004	Italy	ICP-AES	26	13	27.9±7.0*	24.0±2.4	64.9±10.8	63.8±13.7	7.7	53.8	4.8±3.8
Forte G <sup>25</sup>	2005	Italy	ICP-AES	71	44	31.4±4.7	40.2±5.0	65.5±9.4	51.9±4.0	25.4	25.0	4.6±4.5
Feng J <sup>55</sup>	2012	China	AAS	50	50	46.2±6.8	46.4±8.5	62.7±14.1	61.4±11.8	40.0	40.0	NR
<b>CSF</b>												
Forte G <sup>24</sup>	2004	Italy	ICP-AES	26	13	20.9±2.0	21.2±3.2	64.9±10.8	63.8±13.7	7.7	53.8	4.8±3.8
Alimonti A <sup>56</sup>	2007	Italy	ICP-AES	42	20	23.7±4.3	21.9±3.5	64.5±10.7	66.2±14.7	14.3	15.0	4.9±4.3
Hozumi I <sup>57</sup>	2011	Japan	ICP-MS	20	15	31.6±3.6	29.6±6.5	NR	NR	55.0	60.0	NR
Sanyal J <sup>29</sup>	2016	India	AAS	50	60	25.3±3.4*	22.7±2.4	58.7±12.4	60.1±10.4	32.0	30.0	3.8±2.3
Maass F <sup>27</sup>	2018	Germany	ICP-OES	36	42	22.0±1.3*	21.0±1.2	67.0±11.0	65.5±13.1	50.0	42.9	5.0±5.5

**Notes:** *P*-value <0.05 was considered as statistical significance, mean ± SD. \**P*<0.05.

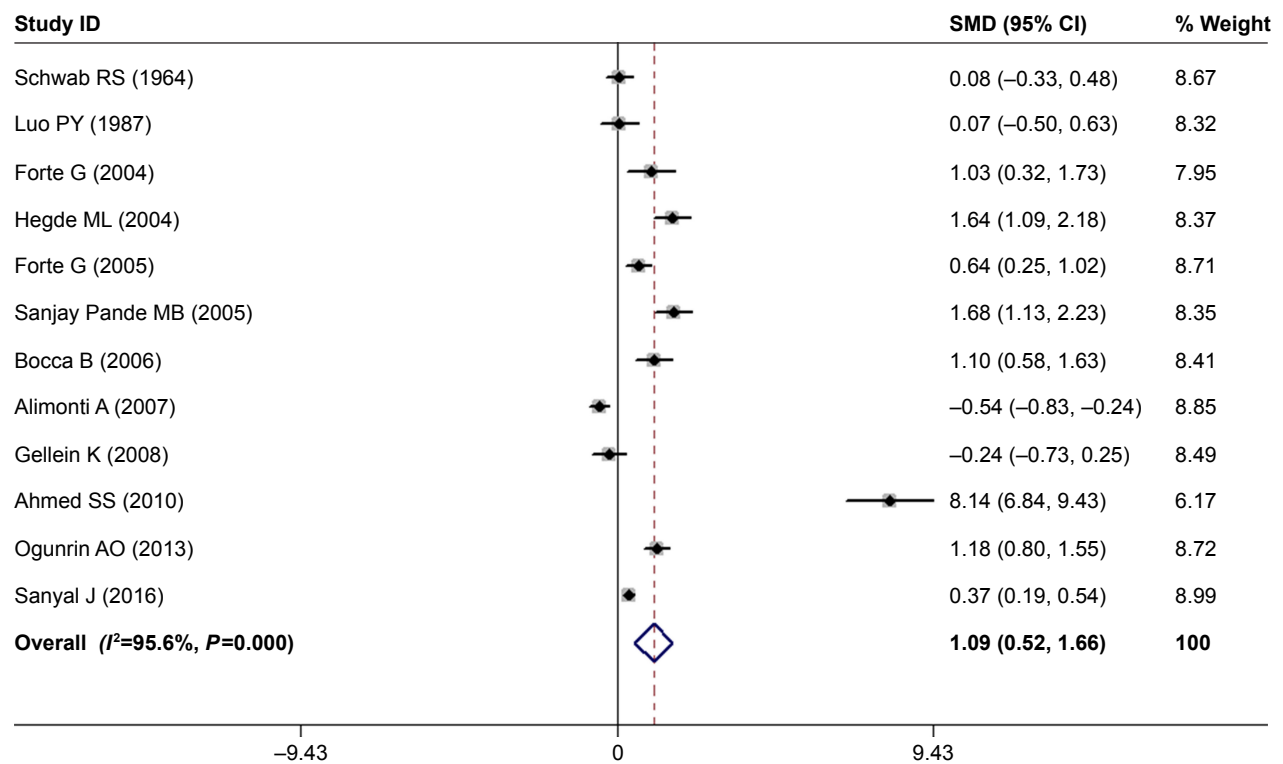
**Abbreviations:** AAS, atomic absorption spectrometry; CSF, cerebrospinal fluid; HC, healthy control; ICP-AES, inductively coupled plasma-atomic emission spectrometer; ICP-MS, inductively coupled plasma-mass spectrometry; ICP-OES, inductively coupled plasma optical emission spectrometry; NR, not reported; PD, Parkinson's disease.

of 1,934 subjects consisting of 1,023 cases and 911 controls (Table 1). Meta-analysis results showed that the peripheral blood Mg levels of PD patients had a significant rising trend in random-effects model (SMD=0.64, 95% CI=0.10, 1.19; Figure 3). However, significant heterogeneity was found among these studies ( $I^2=96.2\%$ ,  $P=0.000$ ). In addition, results of subgroup analysis stratified by locations showed that compared with HC subjects, the pooled SMD was 1.78 (95% CI=0.70, 2.86;  $P$  for  $Z=0.001$ ) for Asian populations, and 1.18 (95% CI=0.80, 1.55;  $P$  for  $Z=0.000$ ) for African populations. In addition, in stratified analysis by HC subjects matched by analysis methods, the pooled SMD was 1.13 (95% CI=0.17, 2.09;  $P$  for  $Z=0.021$ ). However, the problem of high heterogeneity was not solved by the location or analysis method (Table 4).

Furthermore, meta-regression analyses with the covariates of duration, average age, and gender of PD patients showed that no above-mentioned covariates conferred significant impact on heterogeneity (Table 5). Sensitivity analyses indicated that none of these studies significantly reverse the result. Cumulative meta-analysis showed no temporal effect affected on the overall results. Finally, no publication bias was observed in our study, according to the Egger's tests ( $P=0.324$ ).

## Meta-analysis of CSF Mg levels between PD patients and HC subjects

Currently, the research literature on CSF Mg levels in patients with PD is relatively less. Finally, only five articles were searched with less pooled population encompassing



**Figure 2** Forest plot of serum Mg levels between PD patients and HC subjects.

**Notes:** The horizontal lines represent 95% CI. The sizes of the shaded squares are proportional to study weight. Weights are from random-effects analysis.

**Abbreviations:** HC, healthy control; PD, Parkinson's disease; SMD, standardized mean difference.

324 subjects composed of 180 PD cases and 144 HC subjects (Table 1). Our investigation found that PD patients had higher Mg levels in CSF in comparison with HC subjects using a random-effects model (SMD =0.55, 95% CI =0.21, 0.88; Figure 4) with moderate heterogeneity among these studies ( $I^2=50.4%$ ,  $P=0.089$ ). Limited by fewer number of studies, no further in-depth analysis was carried out.

## Discussion

To date, available literature on circulating Mg levels in PD etiology remains controversial. Thus, we aimed the previous literature comparing Mg concentrations in serum, peripheral blood, and CSF between PD patients and HC individuals to uncover their differences in PD. As we know, this is the first meta-analysis to quantify and report the association of

**Table 2** The subgroup analysis of studies reporting serum Mg levels in PD

Subgroup	No of studies	SMD (95% CI)	Test of SMD =0		Heterogeneity	
			Z	P for Z	$I^2$ (%)	P for $I^2$
All studies	12	1.09 (0.52, 1.66)	3.76	0.000	95.6	0.000
<b>Location</b>						
Asia	5	2.22 (0.82, 3.63)	3.10	0.002	97.6	0.000
Europe	5	0.37 (-0.32, 1.06)	1.06	0.289	91.6	0.000
America	1	0.08 (-0.33, 0.48)	0.38	0.705	-	-
Africa	1	1.18 (0.80, 1.55)	6.13	0.000	-	-
<b>Analysis method</b>						
ICP-MS/ICP-AES	8	1.55 (0.54, 2.57)	2.99	0.003	97.0	0.000
AAS	3	0.55 (-0.04, 1.14)	1.84	0.066	88.2	0.000
Colorimetry	1	0.08 (-0.33, 0.48)	0.38	0.705	-	-

**Abbreviations:** AAS, atomic absorption spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectrometer; ICP-MS, inductively coupled plasma-mass spectrometry; PD, Parkinson's disease; SMD, standardized mean difference.



**Table 3** The meta-regression of studies reporting serum Mg levels in PD

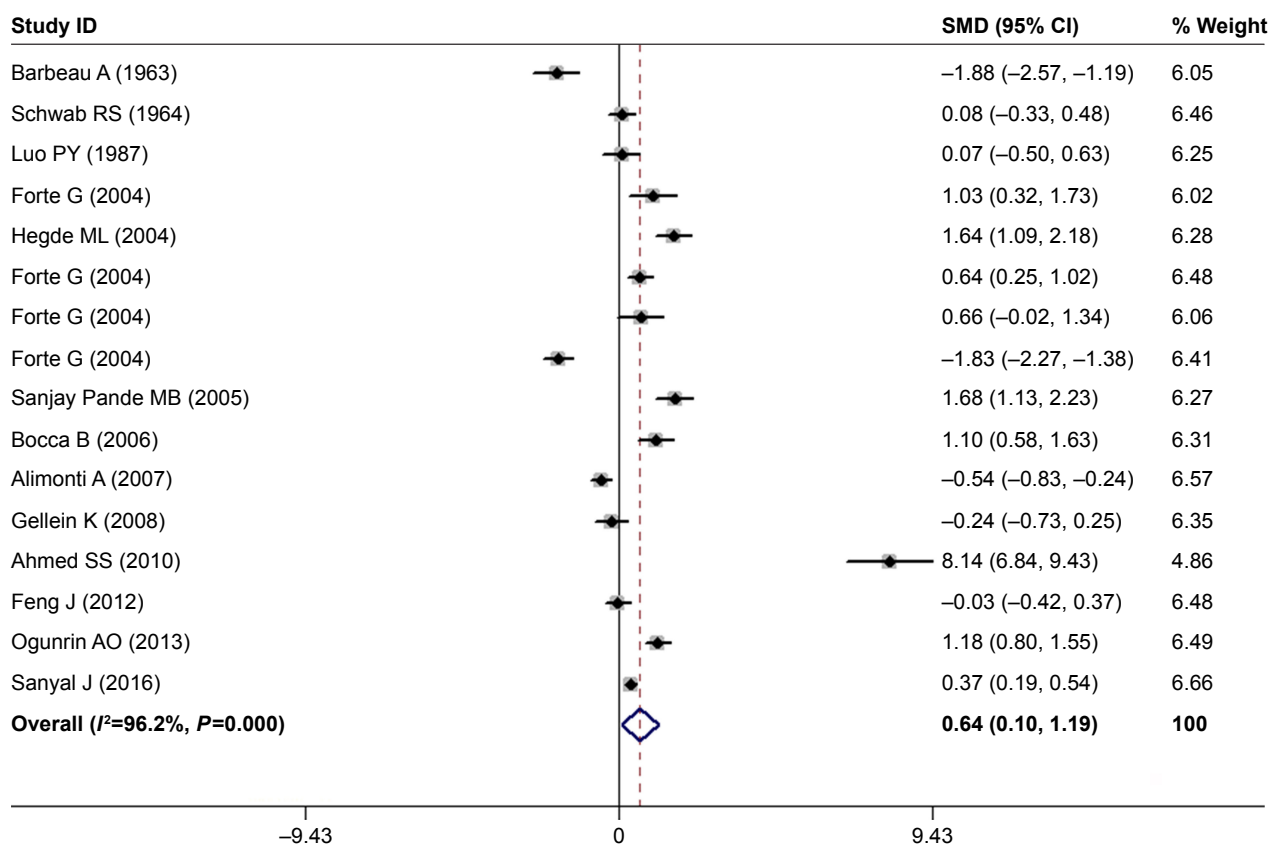
Covariates	Coefficients	95% CI	Std. Err.	P-value	Adj I <sup>2</sup> (%)
Duration (years)-PD	-0.28	-1.00, 0.43	0.28	0.357	-0.84
Mean age (years)-PD	-0.33	-0.83, 0.17	0.22	0.168	12.6
Female (%) -PD	0.04	-0.11, 0.20	2.31	0.530	-7.9

**Abbreviations:** PD, Parkinson's disease; Std. Err., standard error.

circulating Mg levels with PD. Herein, we found that PD patients had a higher serum Mg levels than the HC subjects (SMD =1.09, 95% CI =0.52, 1.66). Furthermore, this result accorded with the combination of its serum and blood levels analysis (SMD =0.64, 95% CI =0.10, 1.19). The random-effects model was applied because of the existence of significant heterogeneity ( $I^2 > 50%$ ) among the studies. Next, we investigated the sources of heterogeneity by means of subgroup analyses and meta-regression analysis. However, above-mentioned covariates had no significant contribution to the between-study heterogeneity. The study of Ahmed and Santosh has shown a highly heterogeneous result.<sup>53</sup> However, excluding the study, the recalculated values of  $I^2$  in above two meta-analyses were attenuated to 91.4% and 94.4%, respectively, the significant heterogeneity still existed.

This result indicated that the study of Ahmed and Santosh was not the main reason related to significant heterogeneity. A sensitivity analysis demonstrated the effect of leaving-out any individual study on the overall effect estimate each time was minimal, indicating that our findings were relatively certain and stable. The cumulative meta-analysis results were steady, suggesting the analytical instruments used for measuring serum Mg have become more advanced and precise in the later years. Our study suggested that the patients with PD had a tendency toward elevated circulating Mg levels, despite the high heterogeneity among studies.

Mg homeostasis is regulated mainly by Mg transporter proteins, which are located on the plasma membrane, such as TRPM6, 7 (intake) and SLC41A1 (efflux).<sup>37,38</sup> Under normal conditions, extracellular Mg ions are actively transported



**Figure 3** Forest plot of peripheral blood Mg levels between PD patients and HC subjects.

**Notes:** The horizontal lines represent 95% CI. The sizes of the shaded squares are proportional to study weight. Weights are from random-effects analysis.

**Abbreviations:** HC, healthy control; PD, Parkinson's disease; SMD, standardized mean difference.

**Table 4** The subgroup analysis of studies reporting peripheral blood Mg levels in PD

Subgroup	No of studies	SMD (95% CI)	Test of SMD =0		Heterogeneity	
			Z	P for Z	I <sup>2</sup> (%)	P for I <sup>2</sup>
All studies	16	0.64 (0.10, 1.19)	2.32	0.020	96.2	0.000
<b>Location</b>						
Asia	6	1.78 (0.70, 2.86)	3.25	0.001	97.2	0.000
Europe	8	-0.14 (-0.89, 0.62)	0.35	0.724	94.9	0.000
America	1	0.08 (-0.33, 0.48)	0.38	0.705	-	-
Africa	1	1.18 (0.80, 1.55)	6.13	0.000	-	-
<b>Analysis method</b>						
ICP-MS/ICP-AES	10	1.13 (0.17, 2.09)	2.30	0.021	97.3	0.000
AAS	4	0.41 (-0.06, 0.89)	1.70	0.090	86.6	0.000
Colorimetry	2	-0.08 (-2.79, 1.04)	0.90	0.369	95.6	0.000

**Abbreviations:** AAS, atomic absorption spectrometry; ICP-AES, inductively coupled plasma-atomic emission spectrometer; ICP-MS, inductively coupled plasma-mass spectrometry; PD, Parkinson's disease; SMD, standardized mean difference.

by Mg transporter proteins into the cell and accumulated in mitochondria.<sup>39</sup> Thus, intracellular Mg levels are higher than those in extracellular fluid. However, many degenerative diseases including PD, often cause protein expression alterations or gene variant of these transporter proteins, thus finally lead to deranged Mg homeostasis.<sup>40</sup> For example, in substantia nigra area PD patients, the mRNA and protein expression levels of TRPM7 significantly decreased, suggesting that the Mg influx was reduced during the progress of PD.<sup>41</sup> Moreover, SLC41A1 is a coding region of the novel PD susceptibility locus PARK16. Its coding variant p.A350V that only occurred in the PD patients enhanced Mg efflux and then decreased intracellular Mg levels.<sup>42,43</sup> Furthermore, previous clinical study also showed that due to mitochondrial cytopathies, intracellular Mg concentration in brain tissues of patients with neurologic disorders was lowered.<sup>44</sup> Although the reason is unknown, we hypothesized that this phenomenon might be related to Mg efflux from impaired mitochondria. Finally, the joint action of above-mentioned various mechanisms leads to the higher Mg levels in PD patients. Consequently, we further performed meta-analysis to investigate the CSF Mg levels in PD patients. The results showed that Mg levels significantly increased in PD patients compared with healthy population (SMD =0.55, 95% CI =0.21, 0.88). However, the limited number of studies (only five publications) and the small sample size (180 PD

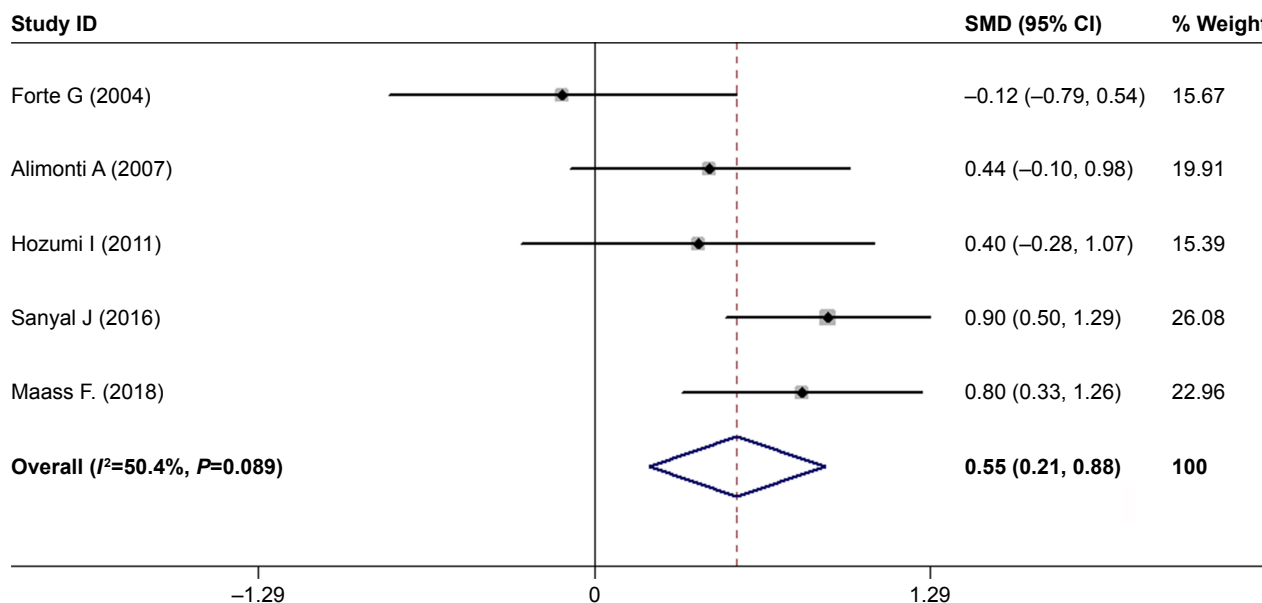
patients and 144 healthy individuals) conducted on CSF perhaps lead to an unreliable meta-analysis result. In CNS, Mg transporters across the blood-brain barrier transport Mg ion from blood into CSF, which create the phenomena that Mg levels in CSF are high like that in serum.<sup>45</sup> Finally, peripheral high concentration of Mg gets into the CNS, causing CSF Mg levels rise, which could partly explain the origin of higher Mg CSF levels. In general, CSF Mg levels keep relatively steadily state even if their serum levels has been changed, thus estimating CSF Mg levels may be more precise than its blood levels.<sup>46</sup> It was worth noting that high Mg CSF concentrations, in turn, accelerated the formation of  $\alpha$ -synuclein oligomers, both from reaction rate and from formation size, that exacerbated dopamine neurons damage and contributed to the progression of PD.<sup>47-49</sup> For the future, continuous investigations are necessary to assess the CSF Mg levels of PD patients and expound its impact on the progression of PD.

Nevertheless, this meta-analysis still included several limitations and shortcoming despite the strengths. First, we cited the most recent and comprehensive papers, but, the number of included studies was still limited, especially those for blood and CSF Mg levels. Future studies are necessary to confirm our conclusion with larger sample sizes. Second, we limited the search range to articles written in Chinese and English, and therefore several important papers

**Table 5** The meta-regression of studies reporting peripheral blood Mg levels in PD

Covariates	Coefficients	95% CI	Std. Err.	P-value	Adj I <sup>2</sup> (%)
Duration (years)-PD	-0.15	-1.07, 0.78	0.39	0.717	-12.9
Mean age (years)-PD	-0.37	-0.78, 0.04	0.19	0.073	20.3
Female (%)-PD	0.04	-0.07, 0.15	0.05	0.466	-4.6

**Abbreviations:** PD, Parkinson's disease; Std. Err., standard error.



**Figure 4** Forest plot of CSF Mg levels between PD patients and HC subjects.

**Notes:** The horizontal lines represent 95% CI. The sizes of the shaded squares are proportional to study weight. Weights are from random-effects analysis.

**Abbreviations:** CSF, cerebrospinal fluid; HC, healthy control; PD, Parkinson's disease; SMD, standardized mean difference.

published in other languages were not inevitably included. However, these cited articles probably met our inclusion criteria. Third, confounding factors, including the severity of PD, time of taking L-dopa, dietary or drug-induced Mg intake, socioeconomic status, and risky lifestyles (eg, alcohol, tobacco, and obesity) were difficult to collect from most of the included studies. Fourth, we only studied Mg levels in blood, serum, and CSF in the meta-analysis. However, most of total body Mg is intracellular, which makes examining Mg levels in erythrocytes of PD patients to comprehensively evaluate Mg possible implication in the pathology.

## Conclusion

To our knowledge, this is the first comprehensive and systematic meta-analysis that evaluated the association between circulating Mg levels and PD patients to deeply understand the role of Mg homeostasis in PD. This meta-analysis emphasized that Mg serum, peripheral blood, and CSF levels in PD patients were obviously higher than those in healthy individuals. Due to the high heterogeneity, further investigations are needed to verify the results with large-scale cohort studies.

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## Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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