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Original Article

Serum iron levels and Parkinson's disease risk: evidence from a meta-analysis

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Abstract: Background: Whether the serum iron level in Parkinson's disease (PD) patients was higher than those in health controls was not consistent in the reported studies. Thus, we conducted a meta-analysis to summarize the evidence from observational studies between them. Methods: Pertinent studies were identified by a search in PubMed and Web of Knowledge up to July 2015. Standardized mean difference (SMD) was performed to combine the results. Random-effect model was used. Publication bias was estimated using Egger's regression asymmetry test. Results: In our study, ten articles involving 591 PD cases and 917 health controls were included in the analysis. Our pooled results suggested that PD patients had a significantly higher serum iron levels compared with those in health controls [summary SMD = 0.28, 95% CI = 0.16, 0.39, P<0.001]. The associations were also significant both in Europe [SMD = 0.60, 95% CI = 0.37, 0.83] and in Asia population [SMD = 0.48, 95% CI = 0.32, 0.65]. No publication bias was found. Conclusions: The current study suggested that serum iron level in PD patients was significantly higher than those in health controls, both in Europe and Asia populations.

Keywords: Serum, iron level, Parkinson's disease, meta-analysis

Introduction

Parkinson's disease (PD) is a multi-factorial disease with the involvement of age, genetic and environmental factors [1]. Moreover, it is the second most common form of neurodegenerative disease. PD affects 2% of the population over the age of 65 years [2, 3]. Primary prevention of PD is a critical matter in the current society. Metal elements such as iron, zinc, and copper-which contribute to the function of metalloenzymes that participate in free radical control and antioxidant defense-have been associated with the development of neurodegenerative disorders [4-6].

Dietary iron intake had been associated with PD [7]. However, a number of epidemiologic studies have been published exploring the relationship between serum iron level and PD risk, with inconsistent results. We therefore conducted a meta-analysis in order to assess the association of serum iron levels in PD patients compared with those in health controls and also assess the between-study heterogeneity and publication bias among the studies we analyzed.

Methods

Literature search

Two authors independently searched the databases of PubMed and Web of Knowledge for related articles published before July 2015 using the following search terms: 'serum' OR 'Plasma' AND 'iron' OR 'Fe' AND 'Parkinson's disease' OR 'Parkinson' OR 'PD' with written in English. In addition, we reviewed references of relevant articles. Disagreements between the two authors were resolved by consensus with a third author.

Study selection

Studies were eligible for included if they met the following criteria: (1) the studies were of case-control design or prospective design or cross-sectional design or randomized controlled trials; (2) the exposure was serum iron levels; (3) the outcomes was PD; (4) available

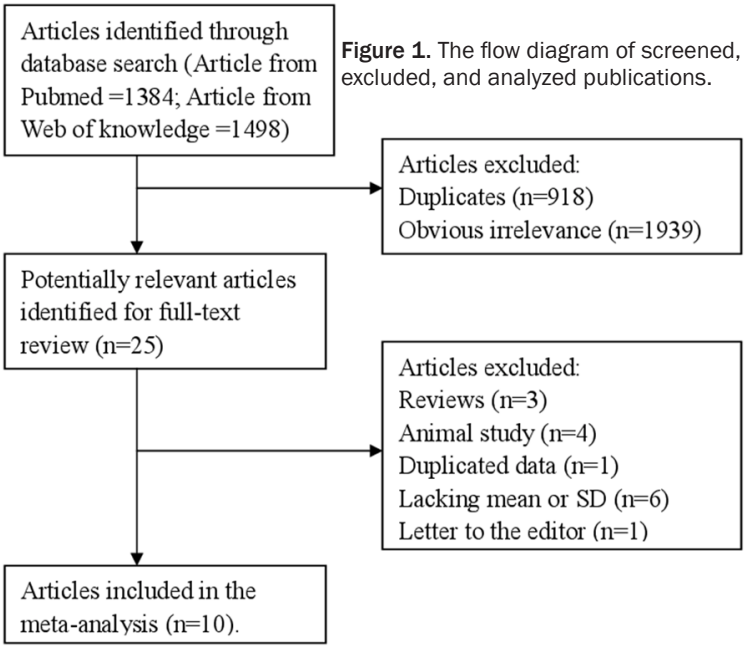

Figure 1. The flow diagram of screened, excluded, and analyzed publications.

sample size, mean and standard deviation (SD) of serum iron level or data provided from which mean and SD could be calculated; and (5) written in English. Accordingly, the following exclusion criteria were also used: (1) reviews and (2) repeated or overlapped publications.

Data extraction

We extracted data from the included articles, with the following information: the first author' last name, year of publication, country of region, study design, study population, age for cases and controls, sample size and the mean ± SD on serum iron levels, and statistical adjustment for the main confounding or mediating factors.

Statistical analysis

Pooled measure was performed on the standardized mean difference (SMD) with 95% confidence interval (CI) to assess the association between serum iron level and risk of PD. Random-effects model was used to combine study-specific SMD (95% CI), which considers both within-study and between-study variation [8]. The Q test and I^2 of Higgins and Thompson [9] were used to assess heterogeneity among included studies. I^2 describes the proportion of total variation attributable to between-study heterogeneity as opposed to random error or chance, with suggested thresholds for low (25%-50%), moderate (50%-75%) and high (>75%) heterogeneity, respectively [10]. Meta-regression and subgroup analyses were performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity [11]. We used the Egger regression asymmetry test to evaluate the publication bias [12]. Sensitivity analysis was conducted to describe how robust the pooled estimator was to removal of individual studies [13]. An individual study is suspected of excessive influence, if the point estimate of its omitted analysis lies outside the 95% CI of the combined analysis. All statistical analyses were performed using Stata 12.0 (Stata Corp, College Station, Texas, USA). Two-tailed $P \leq 0.05$ was accepted as statistically significant.

Results

Literature search

A total of 1384 articles from PubMed and 1498 articles from Web of knowledge following the databases search. After initial screening of titles and abstracts using the aforementioned criteria, 23 articles were identified for full-text review. Hand searching of references listed within these articles identified 2 additional articles. Of these, 15 were further excluded, leaving 10 eligible articles (**Figure 1**). Hence, ten articles [14-23] involving 591 PD cases and 917 health controls were included in our meta-analysis. Two studies were come from India, 2 from Spain, 1 from United States, 1 from Norway, 1 from China, 1 from Turkey, 1 from Italy and 1 from Sweden. The characteristics of these included studies are presented in **Table 1**.

Serum iron level and PD risk

Three of these included studies reported an increased risk for PD of serum iron levels in PD cases compared with health controls, while no significant association was reported in 4 studies. However, three studies suggested that

Table 1. Characteristics of studies on the association between serum iron levels and Parkinson's disease risk

Study, year	Country	Study type	Parkinson's disease			Health controls		
			n	Age (Mean ± SD)	Serum iron: Mean ± SD (μg/mL)	n	Age (Mean ± SD)	Serum iron: Mean ± SD (μg/ml)
Ahmed et al. 2010	India	Case-control	45	57.62 ± 9.10	1.104 ± 0.006	42	55.62 ± 3.25	1.230 ± 0.080
Cabrera-Valdivia et al. 1994	Spain	Case-control	61	65.8 ± 0.96	0.827 ± 0.048	60	65.80 ± 1.00	0.709 ± 0.039
Forte et al. 2004	Italy	Case-control	26	64.9 ± 10.8	1.318 ± 0.481	13	63.80 ± 13.70	1.136 ± 0.393
Fukushima et al. 2013	China	Case-control	58	64.30 ± 9.40	2.100 ± 0.840	81	63.70 ± 9.40	1.510 ± 0.780
Gellein et al. 2008	Norway	Prospective	33	Na	1.275 ± 0.551	99	Na	1.146 ± 0.463
Jimenez-Jimenez et al. 1998	Spain	Case-control	37	65.70 ± 8.80	1.010 ± 0.330	37	62.40 ± 17.8	0.950 ± 0.300
Kumudini et al. 2014	India	Case-control	150	55.70 ± 10.60	0.554 ± 0.124	170	53.73 ± 10.90	0.422 ± 0.126
Logroscino et al. 1997	America	Case-control	104	Na	0.283 ± 0.116	352	Na	0.339 ± 0.152
Madenci et al. 2012	Turkey	Case-control	60	68.50 ± 8.30	0.746 ± 0.293	42	66.90 ± 8.30	0.748 ± 0.271
Qureshi et al. 2006	Sweden	Case-control	17	72.00 ± 17.00	1.020 ± 0.110	21	62.00 ± 11.00	1.160 ± 0.050

SD: standard deviation; Na: not available.

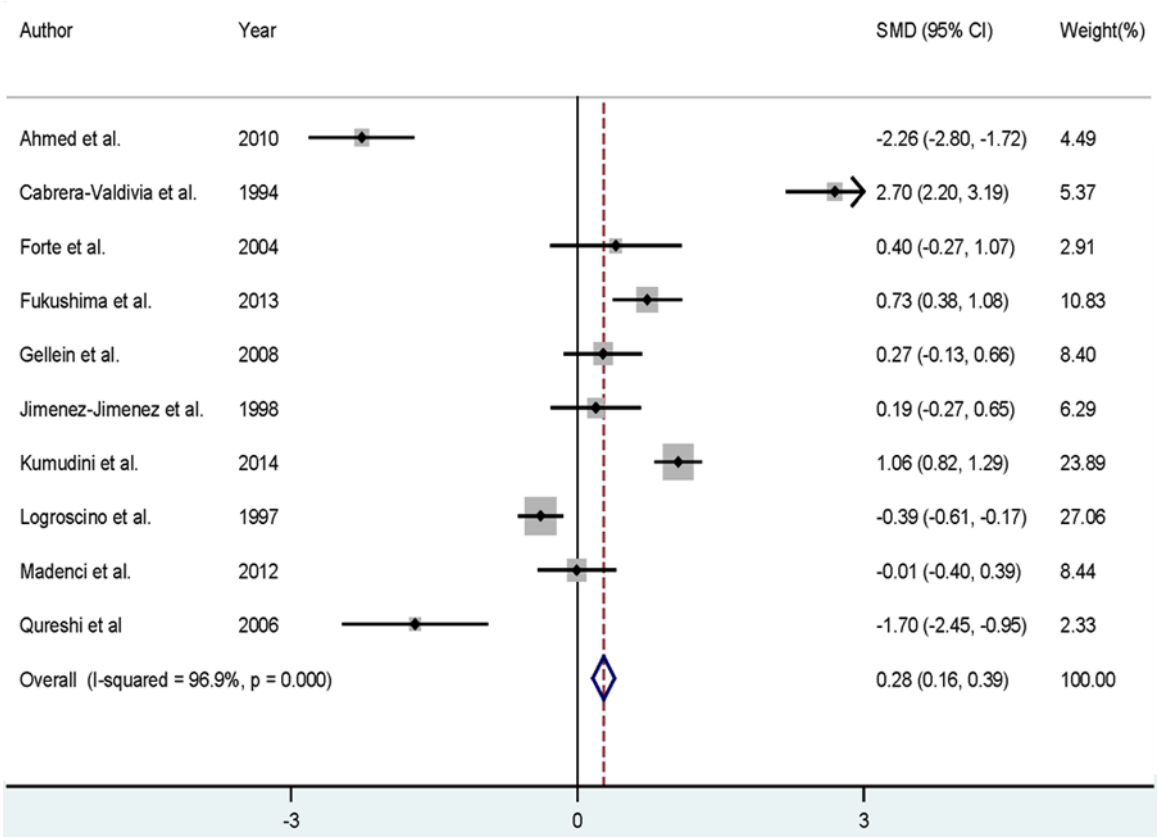

Figure 2. The forest plot of the association between serum iron level and PD risk.

serum iron level was significantly lower in PD cases than those in health controls. Our pooled results suggested that PD patients had a significantly higher serum iron level compared with health controls [summary SMD = 0.28, 95% CI = 0.16, 0.39, P<0.001], with high between-study heterogeneity detected (I^2 = 96.9%, $P_{heterogeneity}$ = 0.000) (**Figure 2**).

Meta-regression and subgroup analysis

In our pooled results, evidence of high between-study heterogeneity (I^2 = 96.9%, $P_{heterogeneity}$ = 0.000) was found in the analysis. In order to explore the high between-study heterogeneity founded in the analysis, univariate meta-regression with the covariates of publication

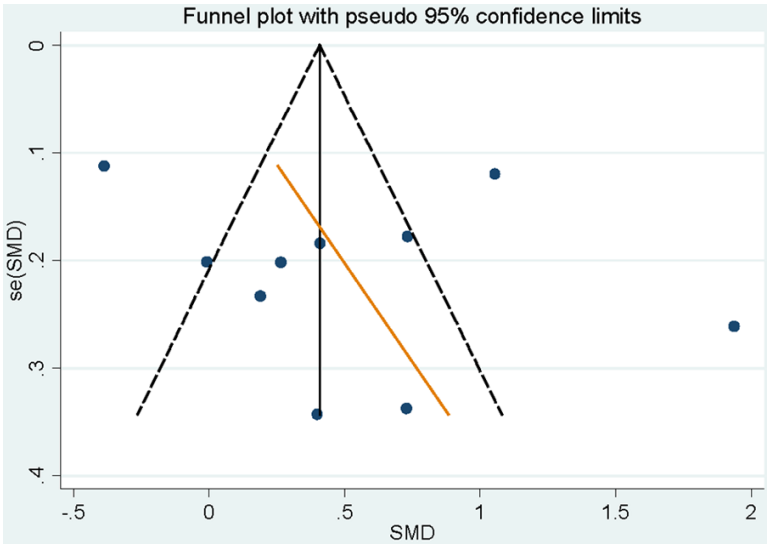

Figure 3. Funnel plot for the analysis of publication bias between serum iron level and PD risk.

year, study design and geographic locations were performed. No significant findings were found in the above-mentioned analysis.

For the subgroup analyses by study design, the association was also significant in the case-control studies [SMD = 0.28, 95% CI = 0.16, 0.40; I^2 = 97.2%] of serum iron levels in PD patients compared with the health controls. There is only one study was prospective design, no pooled results for other study design was combined. In subgroup analyses of geographic locations, when we restricted the analysis to Europe and Asia, the associations were significant both in Europe [SMD = 0.60, 95% CI = 0.37, 0.83; I^2 = 96.4%] and in Asia [SMD = 0.48, 95% CI = 0.32, 0.65; I^2 = 97.7%]. We did not combine the results for other countries while only one study was conducted from United States.

Sensitivity analysis and publication bias

Sensitivity analysis showed that no individual study had excessive influence on the association of serum iron levels with the risk of PD. Egger's regression asymmetry test and funnel plot (**Figure 3**) showed no evidence of significant publication bias between serum iron levels and PD risk (P = 0.677).

Discussion

In this study, data were available from 591 PD cases and 917 health controls for the analysis. This work provided convincing evidence that serum iron level in PD patients was significantly higher than those in health controls. There are 9 case-control studies and 1 prospective study included in the analysis. We only combined the results for case-control studies because only one study was prospective design. Significant association was found in the case-control studies between serum iron levels and PD risk. Five studies were conducted from Europe and 4 studies conducted from Asia. However, only one study was conducted from United States. Therefore, we only pooled the results for the population from Europe and Asia. The associations were significant both in Europe and in Asia population.

In our pooled analysis, high between-study heterogeneity was found between serum iron levels and PD risk. Previous study [24] had indicated that heterogeneity is common in the meta-analyses. The high degree of heterogeneity might have arisen from publication year, study design, geographic locations and so on. Therefore, we used meta-regression to explore the causes of heterogeneity by covariates. However, no covariate had significantly impact on the high between-study heterogeneity among those mentioned above. Subgroup analyses by study design and geographic locations were conducted to explore the source of heterogeneity. However, high heterogeneity were detected both in the subgroup analyses of case-control studies and in the subgroup analyses of Europe and Asia population. Thus, other genetic and environment variables, as well as their possible interaction, may well be potential contributors to the heterogeneity observed.

Some advantages were shown in this meta-analysis. First, a highlight of this study was that we found a significant association between serum iron levels and the risk of PD. Second, the current study included more PD cases and health controls; this may derive a more precise estimation of the relationship between serum

iron levels and PD risk. Third, no significant publication bias was detected in this meta-analysis, indicating our results are stable.

However, some limitations in this meta-analysis should be concerned. First, nine of the 10 studies were case-control design and only one study was prospective design. Although case-control studies may suffer from recall bias and selection bias, they are important methods in etiology research. More studies with other study design are wanted in the future studies. Second, for the subgroup analysis by geographic locations, the associations were significant both in Europe and in Asia between serum iron levels and PD risk. We did not combine the results for other populations while only 1 study was conducted from United States. Thus, the results are applicable to Europe and Asia, but cannot be extended to populations elsewhere. More studies original in other countries are required to assess the association between serum iron levels and PD risk. Finally, as a meta-analysis of observational studies, we could not rule out that individual studies may have failed to control or adjust for potential confounders, which may introduce bias in an unpredictable direction.

In summary, findings from this meta-analysis suggested that serum iron level in PD patients was significantly higher than those in health controls. Further studies are wanted to confirm this result.

Disclosure of conflict of interest

None.

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