Head Injury and Parkinson Disease: Updated Evidence from Meta-Analysis Studies

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Abstract

Background Published studies on head injury and Parkinson's risk(PD) were inconsistent. We performed a meta-analysis study to explore the association.

Methods We retrieved articles published in English from PubMed, Web of Science, Scopus and ScienceDirect between January 1, 1990 and December 31, 2019. The pooled effect of head injury and PD risk was calculated by a random effect model.

Results In the meta-analysis, there were 21 studies, including 214763 individuals and 39209 PD patients. The pooled OR estimates(ORs) showed an increased risk of PD was correlated with head injury(OR = 1.46, 95% CI 1.29–1.66). Considering the unconscious state, head injury with LOC showed significant association with PD(OR = 1.49, 95%CI 1.28–1.74). However, head injury without LOC had no significant association with PD (OR = 0.57, 95% CI 0.29–1.12). Sensitivity analysis showed that, when any one study was excluded, the results did not change significantly.

Conclusions Our research shows that head injury was associated with PD risk.This study provides a basis and reference for further study on head injury and PD.

Background

As a serious global public health problem, head injury have received great attention from various countries. Head injury had become the main cause of deaths and mutilations and more than 10 million people were affected each year, leading to death or hospitalization [1]. Parkinson's disease (PD) is a common neurodegenerative disease that can cause progressive dyskinesia, such as resting tremor, stiffness and bradykinesia, which were often reported in patients with head injury[2, 3]. A person with head injury will increase the risk of PD, this possibility has great social and medical significance.

Studies have shown that neuroinflammation is one of the pathogenesis of PD [4]. Head injury could cause neuroinflammation, which may be the most reasonable explanation for the correlation between them. Moreover, some researches show that head injury would damage the blood-brain barrier, leading to leukocyte infiltration and microglia activation[5]and could damage mitochondrial function, causing glutamate excitotoxicity, which are related to Neurodegenerative diseases, including PD [6–8]. To date, many studies related to head injury and PD have been published. Although some studies have reported head injury can increase the PD risk [9–11], there are also studies that cannot confirm the association [12–13]. In view of the inconsistency between the existing research literature, we conducted a meta-analysis to quantitatively evaluate the correlation.

Methods

We completed the meta-analysis following the guidelines published by the MOOSE group [14] (S1Table) and PRISMA group (S1Appendix) in this meta-analysis studies [36].

Literature Search

We retrieved relevant articles published in English from PubMed, Scopus, Web of Science and ScienceDirect between January 1, 1990 and December 31, 2019. The search terms include“head injury”, “head injuries”, “Parkinson disease”,“brain injury”, “Parkinson’s disease”,“brain injuries”, “parkinsonism”,“head trauma”, “traumatic brain injury”, two reviewers(N.L.and J.X.)independently checked the full text articles to extract data on study characteristics. Only cohort studies and case-control studies were retrieved. We also retrieved a reference list of related studies. The flowchart of literature search was showed in Fig. 1.

Eligibility Criteria

If the following conditions were met, the study was eligible for inclusion: (1) head injury was taken as the target variable; (2)PD diagnosed by doctors was defined as the target result; and (3)provided ORs and corresponding 95% CIs or provided enough information to calculate.

Data Extraction and Quality Evaluation

We extracted the data included author, publication year, sample size, study design, PD definition, exposure variables or CI and adjustment factors. When multiple estimates were reported, adjusted estimates are included. If no other factors are adjusted, rough risk estimates were included.

The Newcastle-Ottawa Quality Assessment Scale [15] was used to evaluate the quality of studies. It included 9 questions and the full score was 9 points, each satisfied answer received 1 point. Only most questions are considered satisfactory (ie not less than 7 points), we considered the study as high methodological quality. There had two independent researchers (Y.L. and C.S.)performed the data extraction and quality assessment. Discrepancies between these results were resolved with a joint reassessment and a consensus was reached.

Statistical Analysis

Considering the heterogeneity between studies, we performed a random-effect model to calculate the pooled ORs. Heterogeneity of the included studies between head injury and PD was quantified by I-squared (I^2) statistic and Q-statistic. When the I^2 value is 25%, 50% and 75%, it can represent low, medium and high heterogeneity levels. Prespecified subgroup analyses were conducted according to unconsciousness status, publication year (before2005 versus after 2005(included)), study region (Europe, America and Asia)and study quality score (≥ 7 versus < 7). Sensitivity analyses were conducted by removing researches one by one. Funnel plots was used to assess the publication bias, a symmetric inverted funne-shaped or egger test($P \geq 0.05$) indicated no publication bias. All the analyses were undertaken using Stata 12.0 software (StataCorp, College Station, TX).

Results

Study characteristics

After a full-text evaluation, a total of 21 case-control studies[2, 10–11, 16–33] met the inclusion criteria. Among these studies, 9 studies carried out in America[10, 11, 17, 18, 20, 21, 22, 26, 28], 9 studies in Europe[2, 16, 19, 23, 24, 25, 27, 31, 33]and3 studies in Asia[29, 30, 32]. Eight studies were published before 2005[10, 11, 19, 22, 25, 31, 32, 33]and 13 afterwards[2, 16, 17, 18, 20, 21, 23, 24, 26, 27, 28, 29, 30]. The study quality scores of 15 studies were greater than or equal to 7[2, 11, 16, 17, 18, 20, 21, 23, 24, 25, 26, 27, 30, 31, 32]and the scores of 6 studies were less than 7[10, 19, 22, 28, 29, 33]. There were 21 studies,including 214763 individuals and 39209 PD patients. Table 1 shows the include studies characteristics. We evaluated the quality of the included studies, including those with a score of 7 or above [2, 11, 16, 17, 18, 20, 21, 23, 24, 25, 26, 27, 30, 31, 32] and those with a score of less than 7[10, 19, 22, 28, 29, 33].Quality assessment was presented in the supplementary material (S2 Table).

Table 1
Characteristics of included studies

Author	Region	Study design	Sample size	Definition of PD	Exposure variable	OR(95%CI)	Adjustment
Baldereschi et al.,2003	Italian	case-control	113 cases, 4383 controls	at least two of the four cardinal signs (rest tremor, rigidity, bradykinesia, and impaired postural reflexes)	head trauma with LOC	0.85(0.45–1.66)	age,sex,years of schooling,smoking,pesticideuse license
Bower et al.,2003	American	case-control	196 Cases, 196 controls	at least two of the four cardinal signs (rest tremor, rigidity, bradykinesia, and impaired postural reflexes)	any head trauma	4.3 (1.2–15.2)	Not-reported
					mild traumas without LOC	1.0 (0.1–7.1)	
					mild traumas with LOC	11.0(1.4–85.2)	
Dick et al., 2007	Scotland, Italy, Sweden, Romania and Malta	case-control	767 Cases, 1989 controls	cases were defined using the United Kingdom Parkinson's Disease Society Brain Bank criteria, and those with drug-induced or vascular parkinsonism or dementia were excluded	ever knocked unconscious	1.35(1.09–1.68)	age, sex, country, ever having used tobacco, ever having been knocked unconscious and first degree family history of Parkinson's disease
Fang et al.,2012	Sweden	Nested case-control	18,648 cases, 93,240 controls	defined as hospitalization for head injury	any head injury	1.42 (1.30–1.54)	year of birth, sex
Goldman et al.,2006	American	case-control	93 Twin pairs and Twenty-six of 93 discordant pairs had at least 1 head-injured twin	core assessment program for intracerebral transplantations diagnostic criteria were used	any head injury	3.8(1.3–11)	adjusted for respondent type (proxy, subject), cigarette pack-years quartile.
Goldman et al.,2012	American	case-control	89 cases and 329 controls	final diagnosis was by consensus of two movement disorder specialists using all available information including medical records, applying NINDS/UK Brain Bank criteria.	head injury	1.3 (0.9–1.8)	age, gender, race, and smoking
					head injury with unconsciousness	1.3 (0.9-2.0)	
Kupio et al.,1999	Finland	case-control	123 Cases, 246 controls	diagnostic criteria of the UK Parkinson's Disease Society	head injury with unconsciousness	1.37(0.8–2.33)	Not-reported
					head injury without unconsciousness	0.53(0.26–1.09)	
Lee et al.,2012	American	case-control	357 incident idiopathic PD cases and 754 population controls	cases with a PD diagnosis	head trauma	2.00(1.28–3.14)	age, gender, ever smoked, race, county, education (school years).

OR = odds ratio. CI = confidence interval. YOPD = The young onset Parkinson's disease. PD = Parkinson's disease. ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification. ICD-8 = The International Classification of Diseases, Eighth Revision. ICD-10 = The International Classification of Diseases, Tenth Revision. NHIRD = The National Health Insurance Research Dataset. NINDS = National Institute of Neurological Disorders and Stroke. LOC:loss of consciousness

Author	Region	Study design	Sample size	Definition of PD	Exposure variable	OR(95%CI)	Adjustment
Tanner et al.,2009	North America	case-control	119 cases and 99 controls	defined as 2 or more signs (resting tremor, bradykinesia, rigidity, and postural reflex impairment), 1 of which must be resting tremor or bradykinesia;	head injury ever	1.25(0.92–1.69)	age,sex,race/ethnicity, smoking, caffeine use, alcohol use
Werneck andAlvarenga, 1999	Brazil	case-control	92 PD and 110 controls	all subjects were examined at least more than once by the same neurologist. Subjects with atypical features suggesting other forms of secondary parkinsonism, severe dementia or any history of cerebrovascular disease were excluded	trauma	1.55(0.67–3.62)	Not-reported
Zorzon et al., 2002	Italy	case-control	136 cases, 272 controls	two or more of the following clinical features of PD: resting tremor, rigidity, bradykinesia, one of them starting asymmetrically and, in addition, history of chronic progression of symptoms, absence of obvious pyramidal, and/or supranuclear oculomotor, and/or autonomic, and/or amyotrophic, and/or cerebellar signs.	head trauma	1.6(0.8–2.5)	pack-years of smoking
Nicoletti et al.,2017	Italy	case-control	492 patients and 459 controls	severity of disease was investigated through both the Unified Parkinson Disease Rating Scale–Motor Evaluation (UPDRS-ME) and the Hoehn-Yahr (HY) scale	head trauma	1.5(1.04–2.17)	age, sex, family history, coffee smoking, and alcohol consumption
Kenborg Et al.,2015	Denmark	case-control	1,705 patients and 1,785 controls	ICD-8 code 342 and ICD-10 code G20	any head injury	0.99 (0.85–1.16)	sex, year of birth, age at first cardinal symptom, alcohol (continuous), pack-years of smoking (continuous), education, family history of Parkinson disease, and urbanization

OR = odds ratio. CI = confidence interval. YOPD = The young onset Parkinson's disease. PD = Parkinson's disease. ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification. ICD-8 = The International Classification of Diseases, Eighth Revision. ICD-10 = The International Classification of Diseases, Tenth Revision. NHIRD = The National Health Insurance Research Dataset. NINDS = National Institute of Neurological Disorders and Stroke. LOC:loss of consciousness

Author	Region	Study design	Sample size	Definition of PD	Exposure variable	OR(95%CI)	Adjustment
Taylor et al.,2016	American	case-control	379 patients and 230 controls	case status was confirmed using U.K. Brain Bank criteria	head injury with LOC	1.58(0.85–2.95)	gender, age, age squared, race, education, smoking status.
Taylor et al.,1999	American	case-control	100 patients and 147 controls	patients had at least two of the following: tremor, rigidity, and bradykinesia. They also had one of the following: gait disturbance, postural instability, or hypomimia, and were levodopa responsive	head injury	6.23(2.58–15.07)	birth cohort and sex
Harris et al.,2013	Canada	case-control	(403 cases, 405 controls	the following clinical diagnostic criteria for PD were used: (1) two of the following symptoms present on examination: parkinsonian tremor, rigidity, bradykinesia, masked facies, micrographia or postural imbalance; (2) absence of specific signs of other diseases that would account for these findings	head injury with LOC	2.64 (1.39–5.03)	age, sex and smoking history
Georgiou et al.,2019	Cyprus	case-control	235 PD patients and 464 controls	patients were included in the study after clinical diagnosis of PD by a board certified neurologist. Diagnosis was followed by a clinical evaluation, using the UPDRS rating scale by a board certified CING neurologist. Patients that had clinical signs suggestive of Parkinsonian syndromes were excluded	severe head injury accompanied with fainting	1.94 (1.28–2.94)	Not-reported

OR = odds ratio. CI = confidence interval. YOPD = The young onset Parkinson's disease. PD = Parkinson's disease. ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification. ICD-8 = The International Classification of Diseases, Eighth Revision. ICD-10 = The International Classification of Diseases, Tenth Revision. NHIRD = The National Health Insurance Research Dataset. NINDS = National Institute of Neurological Disorders and Stroke. LOC: loss of consciousness

Author	Region	Study design	Sample size	Definition of PD	Exposure variable	OR(95%CI)	Adjustment
Chen et al.,2017	China	case-control	1060 PD patients and 1240 controls	PD cases were identified from patients diagnosed with Parkinson's disease (ICD-9-CM: 322) in at least three outpatient visits within one year or in a one-time hospital admission.	head injury	1.77 (1.49–2.10)	urbanization levels and comorbid diseases
Tsai et al.,2002	China	case-control	60 PD patients, 30 YOPD patients and the same number of age- and sex matched young controls were included.	at least two of the three cardinal parkinsonian features, including akinesia, rigidity, and tremor, must be present	head injury	9.27(1.02–84.10)	YOPD with family history of PD excluded; age and sex matched
Rugbjerg et al.,2008	Denmark	case-control	13,695 Patients, 68,445 controls	(ICD-8 code 342; ICD-10 code G20)	head injury with Concussion	1.5(1.4–1.7)	age,sex
Martyn et al 1995	England	case-control	172cases,343controls	patients who had been seen by a consultant neurologist or geriatrician and given a definite diagnosis of Parkinson's disease were included.	head injury	0.6(0.29–1.27)	Not-reported
OR = odds ratio. CI = confidence interval.YOPD = The young onset Parkinson's disease. PD = Parkinson's disease. ICD-9-CM = The International Classification of Diseases, Ninth Revision, Clinical Modification .ICD-8 = The International Classification of Diseases, Eighth Revision. ICD-10 = The International Classification of Diseases, Tenth Revision. NHIRD = The National Health Insurance Research Dataset.NINDS = National Institute of Neurological Disorders and Stroke. LOC:loss of consciousness							

Head injury and PD risk

In the results, the combined ORs for the PD risk was 1.46 (95% CI 1.29–1.66) (Fig. 2). The statistical value ($I^2 = 68.7\%$, $P < 0.001$) between the studies indicated that there was substantial heterogeneity. When considering the unconsciousness status, head injury with LOC was association with the increased PD risk (OR = 1.49, 95%CI 1.28–1.74). The results of five studies did not adjust for other factors, when these five studies were excluded, the OR estimates were not changed (1.48, 95%CI 1.30–1.68), nor did the heterogeneity between studies be reduced ($I^2 = 70.9\%$, $P < 0.001$) (S1 Fig).

Subgroup analysis and Sensitivity analyses

We grouped the literature according to years of publication (before 2005 or after 2005 (included)), study region (America, Europe or Asia), and study quality scores (≥ 7 or < 7) to identify sources of heterogeneity. In the Post-2005 studies, the ORs of PD associated with head injury was 1.46 (1.30–1.64), while in Pre-2005 studies, it was 1.62 (0.98–2.7) (Fig. 3). When considering the study region, the ORs of PD associated with head injury in Europe, America and Asia were 1.24 (1.07–1.44), 1.91 (1.44–2.53) and 1.83 (1.49–2.26), respectively (Fig. 5). The ORs of PD in study quality score ≥ 7 group was 1.43 (1.27–1.62), while in study quality score < 7 group, it was 1.53 (0.9–2.61) (Fig. 4). In addition, by removing a study take turns, the pooled OR of PD change from 1.43 (95% CI 1.27–1.61) to 1.51 (95% CI 1.34–1.70) and did not substantially change the positive correlation (S2 Fig). Sensitivity analysis showed that our research results were robust.

Publication bias

Visual evaluation of funnel chart display that the size distribution of the study was fairly symmetrical relative to the merger effect (Fig. 6), suggesting that our meta-analysis had little published bias. Furthermore, the Egger test ($P = 0.325$) and Begg' test ($P = 0.154$) further proved that there did not have potential publication bias.

Discussion

Our meta-analysis include 21 case control studies, with more than two hundred thousand individuals and 39209 PD patients. Persons with head injury had a 46% increased risk of PD, compared to people without head injury. Tanner [21] found people who work in the agricultural field and agricultural industry have an increased PD risk, if they ever exposed to significant head injury. Goldman et al [17] found that people who are unconscious for more than 5 minutes were twice as likely to have PD as normal people. A recent study [18] explored the combined effects of α -synuclein gene polymorphism length and head injury on

PD. In the study, persons with head injury were not correlated with PD, but they were significantly more at risk of PD compared to other groups. These results provide more evidence that head injury can cause Neurodegenerative diseases.

One study[34] performed a meta-analysis using the literature before 2012 and showed that head injury with LOC was associated with PD risk. Our meta-analysis results were partially consistent with that. Our analysis included six studies with high quality published since 2012. In addition, in this study, we took the unconscious state into consideration and performed a sensitivity analysis on more factors than the quality score. Compared with other studies, the summary estimate of PD risk was more accurate (OR = 1.46, 95% CI 1.29–1.66).

Subgroup analysis showed that head injury with LOC was significantly associated with PD, while head injury without LOC had no significantly associated with PD. The results of five studies did not adjust for other factors, after removing them, head injury without LOC group did not contain any studies. Some studies failed to differentiate head injury with or without LOC, leading to few studies in the without LOC group and a low statistical power. The next phase of researches require to assess the odds ratios (ORs) of PD with and without LOC for head injury separately.

Different studies have different assessment methods for head injury. Some of the included studies about head injury assessment were mainly obtained through questionnaires and medical records, and there was a recall bias for PD patients. In addition, the current data does not explain whether a single or multiple head injury could increase the PD risk, and whether a recent or early head injury have different effects on PD. The current research data does not allow for a more accurate classification of head injury. The random effects method provides some heterogeneity allowance in addition to sampling error [34]. Using a random effects model, the impact of heterogeneity can be expected to be very limited, although it may not exclude the influence of inter-study heterogeneity. Sensitivity analysis was conducted through some research-level factors to seek heterogeneity source, However, heterogeneity remained after sensitivity analysis.

Several limitations exist in the study. First, there have recall bias in case-control study participants, which may affect the quality of information. Second, different studies may have different definitions of head injury, leading to misclassification. Third, in our study, case-control studies from Europe and the Americas accounted for the largest proportion, so the meta-analysis results need to be interpreted cautiously, when they are extended to other populations and regions.

Conclusions

In conclusion, our research showed that head injury was association with an increasing PD risk. When the unconsciousness status was considered, head injury with LOC also showed significant correlated with PD risk. Furthermore, head injury would increase the PD risk, which was closely related to higher quality score studies, euramerica studies and papers published since 2005.

Declarations

Ethics approval and consent to participate Not applicable

Consent for publication Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare that they have no conflict of interest.

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Figures

Figure 1

Flowchart for the selection of eligible studies

Figure 2

The forest plot of head injury and PD

Figure 3
Subgroup analysis of head injury and PD by publication year

Figure 4
Subgroup analysis of head injury and PD by study quality score

Figure 5

Subgroup analysis of head injury and PD by study region

Figure 6

Funnel plot to explore publication bias in the estimates of head injury and PD

Supplementary Files

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