Association between Hypertension and the Risk of Parkinson's Disease: A Meta-Analysis of Analytical Studies

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Keywords

Hypertension · Parkinson's disease · Meta-analysis

Abstract

Background: The results of analytical studies show that the association between hypertension and the risk of Parkinson's disease (PD) remains controversial. **Method:** We searched studies related to the association between hypertension and the risk of PD. We pooled the ORs and risk ratios (RRs) with 95% confidence interval (CI) with random effects model and conducted meta-regression to explore potential sources of heterogeneity. Publication bias was estimated by Egger's test and the funnel plot. **Results:** Twenty-six articles containing 27 studies were included, involving 9 cohort studies and 18 case-control studies. In cohort studies, compared with the non-hypertension participants, the pooled RR for the risk of PD was 1.70 (95% CI 1.60–1.80) for the patients with hypertension. In case-control studies, compared with the non-hypertension participants, the pooled OR for the risk of PD was 0.85 (95% CI 0.78–0.92) for the patients with hypertension. There were no publication bias in cohort

studies and case-control studies. **Conclusion:** Based on population-based cohort studies, this meta-analysis indicated that hypertension might increase the risk of PD. In view of both hypertension and PD having an association with aging, case-control studies, especially the studies based on hospital records, were not suitable for similar studies.

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Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders, which is characterized by tremor, rigidity, bradykinesia, and postural instability [1]. Globally, the prevalence of PD is about 0.3% in individuals aged over 40 years [2, 3]. PD has complex etiology with combined effects of genetic and environmental factors [2, 4]. In some environmental exposure factors, alcohol intake [5, 6], drinking coffee [7], vitamin E intake [8], and use of nonsteroidal anti-inflammatory drugs [9] could reduce the PD risk; however, pesticide exposure [10–12] and milk intake [13] could increase the PD risk.

And studies founded that some diseases might have an effect on the risk of PD, such as asthma [14], diabetes [15, 16], and hypercholesterolemia [16], and so on.

Hypertension is one of the most common chronic diseases. According to World Health Organization, the global prevalence of hypertension was approximately 22% among adults in 2014, and the prevalence is expected to rise to 29.2% in 2025 without intervention [17]. Meanwhile, hypertension was strongly associated with the risk of stroke, cardiovascular disease, and kidney failure [18, 19].

Hypertension might cause hypertensive vasculopathy in the thalamus, brain stem, and basal ganglia [20], thus perhaps affecting the dopaminergic cells in the pars compacta and the connections between neurons in the substantia nigra and the putamen portion of the striatum. That might further cause the prevalence of PD. There were some studies about the association between hypertension and the risk of PD. Some studies [14, 16, 21, 22] founded hypertension could reduce the risk of PD. However, some studies [23–26] founded hypertension could increase the risk of PD. Given the different effects, we carried out this meta-analysis to assess the relationship between hypertension and the risk of PD.

Methods

Literature Search and Selection

A search of the literature up to 13 July 2018 was performed from the databases of PubMed, Web of Science, EMBASE, China National Knowledge Infrastructure, Wan fang, VIP (Database of Chinese Scientific and Technical Periodicals) and CBM (China biology medical literature database), using the following search terms: (hypertension or “high blood pressure”) and (Parkinson’s disease or Parkinson disease). The language was restricted to English and Chinese. Moreover, we also reviewed the references of the included studies to identify additional studies which were not captured by our database searches.

Two investigators (J.C. and Y.W.) reviewed all identified studies independently, and studies were included in this meta-analysis if they met the following criteria: (1) analytical studies (cohort studies and case-control studies); (2) the exposure of interest was hypertension; (3) the outcome of interest was PD; (4) multivariate-adjusted hazard ratio (HR) or risk ratio (RR) or odds ratio (OR) with 95% confidence interval (CI) were provided; (5) the most recent and complete article was chosen if a study had been published more than once.

Data Extraction

Two investigators (J.C. and C.Z.) extracted the following data from each study: (1) name of the first author; (2) year; (3) continent; (4) mean age of cases; (5) study type; (6) source of controls; (7) design of study; (8) number of cases; (9) sample size; (10) hypertension assessment; (11) OR, RR or HR with 95% CI and (12) adjusted covariates.

Statistical Analysis

We weighted the study-specific log RRs and log ORs by the case number, to calculate pooled RRs and ORs with corresponding 95% CI of the association between hypertension and risk of PD. The I^2 was used to assess heterogeneity (I^2 values of 0, 25, 50, and 75% represent no, low, moderate and high heterogeneity respectively) [27]. The fixed-effect model was used as the pooling method if moderate or lower heterogeneity ($I^2 \leq 50\%$) was found; otherwise ($I^2 > 50\%$), the random-effect model was adopted. Meta-regression with restricted maximum likelihood estimation was performed to assess the potentially important covariates that might exert substantial impact on between-study heterogeneity. After meta-regression, if we found a positive result, we further performed the permutation test to verify the accuracy of the results [28]. Subgroup analysis was performed based on the results of meta-regression. An influence analysis [29] was performed with one study removed at a time to assess whether the results could be markedly affected by a single study. Leave-one-out sensitivity analysis [30] was carried out to evaluate the key studies that have substantial impact on between-study heterogeneity. Publication bias was estimated using Egger regression asymmetry test [31] and the funnel plot.

All statistical analyses were performed with STATA version 15.0 (Stata Corporation, College Station, TX, USA). A 2-tailed $p \leq 0.05$ was considered statistically significant.

Results

Literature Search and Study Characteristics

The search strategy identified 1,141 articles from PubMed, 212 articles from Web of Science, 2,800 articles from EMBASE, 64 articles from China National Knowledge Infrastructure, 407 articles from Wan fang, 83 articles from VIP and 260 articles from CBM. After duplicates being removed, 3,205 articles were excluded on screening of titles and/or abstract. After reading full text, 102 articles were excluded for the following reasons: duplicated reports from the same study population ($n = 7$); lacking OR, RR or HR and 95% CI ($n = 60$); inverse exposure and outcome ($n = 26$); review ($n = 9$). Finally, 26 articles [14–16, 21–26, 32–48] were included in this meta-analysis. The detailed literature search for article inclusion is shown in Figure 1.

Twenty-six articles containing 27 studies were included, involving 1,230,085 participants for population-based cohort studies and 32,121 participants for case-control studies. In population-based cohort studies, 2 studies were conducted in North America, 4 studies in Asia, and 3 studies in Europe. As for hypertension assessment, 6 studies were based on medical record, 2 studies on questionnaire, and one study on measurement of blood pressure. In case-control studies, 5 studies were conducted in North America, 8 studies in Asia, 4 studies in Europe and one study in

Fig. 1. Selection of studies for inclusion in this meta-analysis. RR, risk ratio; HR, hazard ratio.

Oceania. As for the source of participants, 9 studies based on non-hospital, 6 studies based on hospital and 3 studies based on both hospital and non-hospital samples. As for hypertension assessment, 5 studies were based on medical record, 11 studies on questionnaire, and 2 studies on the measurement of blood pressure. The detailed characteristics of the included studies are shown in Table 1.

Quantitative Synthesis

In population-based cohort studies, the pooled RR of PD for the hypertension vs. non-hypertension was 1.70 (95% CI 1.60–1.80; $I^2 = 97.3\%$).

In case-control studies, the pooled OR of PD for the hypertension vs. non-hypertension was 0.85 (95% CI 0.78–0.92; $I^2 = 87.8\%$). In the subgroup analysis by the source of participants, the pooled OR was 0.95 (95% CI 0.88–1.03; $I^2 = 89.7\%$, $p_{\text{heterogeneity}} < 0.001$) in studies based on non-hospital, 0.58 (95% CI 0.48–0.70; $I^2 = 34.7\%$, $p_{\text{heterogeneity}} = 0.176$) in studies based on hospital and 0.48

(95% CI 0.27–0.84; $I^2 = 68.9\%$, $p_{\text{heterogeneity}} = 0.040$) in studies based on non-hospital and hospital records (Table 2).

Sources of Heterogeneity

In population-based cohort studies, high heterogeneity among studies was found for hypertension with the risk of PD ($I^2 = 97.3\%$, $p_{\text{heterogeneity}} < 0.001$; Fig. 2). To explore the sources of heterogeneity, meta-regression with the covariates of year, continent, sample size, case number, hypertension assessment, and the number of confounding factors were performed. The p value was 0.268, 0.178, 0.932, 0.331, 0.240, and 0.838, respectively, which suggested that no covariates were the important sources of heterogeneity.

In case-control studies, high heterogeneity among studies was also found for hypertension with the risk of PD ($I^2 = 87.8\%$, $p_{\text{heterogeneity}} < 0.001$; Fig. 3). Meta-regression analysis was conducted with the covariates of year, continent, case number, sample size, hypertension assessment, the

Table 1. Characteristics of studies on hypertension and the risk of PD

Author	Year	Country	Continent	Case age	Control age	Study type	Sources of participant	Design of study	Case number	Control number	Sample size	Hypertension assessment	OR/RR/HR (95% CI)	Adjustment for covariates
Rajput et al. [32]	1987	USA	North America	None	None	Case-control	Non-hospital	Retrospective	118	236	354	Medical record	0.60 (0.30–1.10)	Age, sex
HO et al. [33]	1989	China	Asia	None	None	Case-control	Non-hospital and hospital	Retrospective	35	105	140	Questionnaire	0.90 (0.30–2.40)	Age, sex
Morano et al. [34]	1994	Spain	Europe	68.2±0.97	67.5±0.65	Case-control	Hospital	Retrospective	74	148	222	Questionnaire	1.14 (0.61–2.15)	Age, sex
McCann et al. [35]	1998	Australia	Oceania	70.3±0.6	68.9±0.7	Case-control	Non-hospital and hospital	Retrospective	224	310	534	Questionnaire	0.30 (0.18–0.42)	Age, sex, ethnicity, area, family history, stroke
Paganini-Hill [21]	2001	USA	North America	75±6.1	75±6.0	Case-control	Non-hospital	Retrospective	395	2,320	13,979	Questionnaire	0.71 (0.56–0.89)	Sex, age, vital status
Herishanu et al. [22]	2001	Israel	Asia	None	None	Case-control	Hospital	Retrospective	93	93	186	Questionnaire	0.48 (0.26–0.88)	Age, sex
Powers et al. [15]	2006	USA	North America	69	71	Case-control	Non-hospital	Retrospective	217	298	515	Questionnaire	0.80 (0.55–1.17) men	Age, sex, area
Powers et al. [15]	2006	USA	North America	69	71	Case-control	Non-hospital	Retrospective	135	186	321	Questionnaire	1.62 (1.00–2.62) women	Age, sex, area
Scigliano et al. [36]	2006	Italy	Europe	58.1±11.4	59.8±10.2	Case-control	Hospital	Retrospective	178	533	711	Medical record	0.59 (0.37–0.92)	Age, sex, area
Ascherio and Tanner [14]	2009	UK	Europe	72	72	Case-control	Non-hospital	Retrospective	3,637	3,637	7,274	Medical record	0.83 (0.74–0.92)	Age, sex, smoking, BMI, DM, asthma, IHD, CHF, stroke, arrhythmia, hyperlipidemia, epilepsy, affective disorders, schizophrenia, neurotic and somatoform disorders, dementia
Chen et al. [37]	2009	China	Asia	67.3±0.7	68.4±1.0	Case-control	Non-hospital and hospital	Retrospective	211	135	346	Measure blood pressure	0.70 (0.20–2.10)	Age, sex, BMI, DM, hyperlipidemia, medications including ACEI/ARB, statins, antiplatelet, anti-diabetes drugs, tea and coffee drinking, alcohol use, smoking, vitA/E supplement
Das et al. [24]	2010	India	Asia	None	None	Case-control	Non-hospital	Retrospective	41	123	164	Questionnaire	2.45 (1.03–5.84)	Age, sex

Table 1. (continued)

Author	Year	Country	Continent	Case age	Control age	Study type	Sources of participant	Design of study	Case number	Control number	Sample size	Hypertension assessment	OR/RR/HR (95% CI)	Adjustment for covariates
Miyake et al. [16]	2010	Japan	Asia	68.5±8.6	66.6±8.5	Case-control	Hospital	Retrospective	249	368	617	Questionnaire	0.43 (0.29–0.64)	Sex, age, area, smoking, years of education, leisure-time exercise, BMI, dietary intake of energy, cholesterol, vitamin E, alcohol, coffee, the dietary glycemic index
Cereda et al. [38]	2012	Italy	Europe	61.5±10.2	58.6±9.1	Case-control	Non-hospital	Retrospective	80	80	160	Measure blood pressure	0.83 (0.30–2.28)	Age, sex, BMI
Savica et al. [39]	2012	USA	North America	71	71	Case-control	Non-hospital	Retrospective	196	196	392	Medical record	0.99 (0.63–1.55) 1.05 (0.59–1.88) men 0.83 (0.40–1.74) women	Age, sex, cigarette smoking, coffee consumption
Miao [40]	2015	China	Asia	70.89±6.62	70.05±7.16	Case-control	Hospital	Retrospective	372	372	744	Questionnaire	0.61 (0.44–0.84)	Age, sex, ethnicity
Chen et al. [23]	2017	China	Asia	≥40	≥40	Case-control	Non-hospital	Retrospective	1,060	4,240	5,300	Medical record	1.65 (1.42–1.91)	Age, sex, urbanization level, diabetes, dementia, stroke, depression, renal disease, sleep disorder, alcohol-related disease, head injury
Pinzon [41]	2017	Japan	Asia	None	None	Case-control	Hospital	Retrospective	54	108	162	Questionnaire	0.75 (0.38–1.49)	Age, sex
Grandinetti et al. [42]	1994	USA	North America	69.6±0.6	None	Cohort	Population based	Prospective cohort	58	None	8,006	Medical record	1.25 (0.68–2.28)	Age, smoking
Simon et al. [43]	2007	USA	North America	66.6	None	Cohort	Population based	Retrospective cohort	530	None	171,879	Questionnaire	0.96 (0.80–1.15)	Age, smoking
Qiu et al. [26]	2011	Finland	Europe	66.6±11	None	Cohort	Population based	Retrospective cohort	794	None	59,540	Measure blood pressure	1.18 (0.91–1.54) 0.90 (0.63–1.28) men 1.62 (1.09–2.42) women	Age, sex, study year, education, smoking, alcohol consumption, BMI, physical inactivity, diabetes mellitus, consumption of coffee, tea, total cholesterol
Friedman et al. [25]	2013	Israel	Asia	73.69	None	Cohort	Population based	Retrospective cohort	1,035	None	94,308	Medical record	1.10 (0.93–1.29)	LDL, stain use

Table 1. (continued)

Author	Year	Country	Continent	Case age	Control age	Study type	Sources of participant	Design of study	Case number	Control number	Sample size	Hypertension assessment	OR/RR/HR (95% CI)	Adjustment for covariates
Lai et al. [44]	2014	China	Asia	73.4±5.5	None	Cohort	Population based	Retrospective cohort	252	None	25,132	Medical record	1.70 (1.26–2.30)	Sex, age, hearing loss, head injury, diabetes, hyperlipidemia, dementia, cerebrovascular disease, depression, chronic kidney disease
Lai et al. [45]	2015	China	Asia	40–84	None	Cohort	Population based	Retrospective cohort	1,268	None	51,968	Medical record	1.42 (1.26–1.61)	Sex, age, cataracts, cerebrovascular disease, chronic kidney disease, dementia, depression, diabetes mellitus, head injury, hyperlipidemia
Saaksjarv et al. [46]	2015	Finland	Europe	30–79	None	Cohort	Population based	Retrospective cohort	86	None	6,490	Questionnaire	1.13 (0.58–2.20)	Age, sex, education, smoking, alcohol consumption, exercise, serum vitamin D, coffee consumption, BMI, serum triglycerides, serum cholesterol, plasma fasting glucose
Hsu et al. [47]	2016	China	Asia	65–74	None	Cohort	Population based	Retrospective cohort	188	None	20,472	Medical record	1.65 (1.10–2.46)	Diabetes, hyperlipidemia, and cardiovascular disease
Pupillo et al. [48]	2016	Italy	Europe	75–84	None	Cohort	Population based	Retrospective cohort	2,204	None	792,290	Medical record	3.09 (2.85–3.35)	Age, sex

BMI, body mass index; DM, diabetes mellitus; IHD, ischemic heart disease; CHF, congestive heart failure; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; LDL, low density lipoprotein; RR, risk ratio; HR, hazard ratio.

Table 2. Pooled ORs of the relationship between hypertension and the risk of PD

Study characteristics	Number of studies	OR (95% CI)	<i>p</i> value	<i>I</i> ² , %	<i>p</i> value
All case-control studies	18	0.85 (0.78–0.92)	<0.001	87.8	<0.001
The source of participants					
Based on non-hospital	9	0.95 (0.88–1.03)	0.204	89.7	<0.001
Based on non-hospital and hospital	3	0.48 (0.27–0.84)	0.011	68.9	0.040
Based on hospital	6	0.58 (0.48–0.70)	<0.001	34.7	0.176

PD, Parkinson's disease.

Fig. 2. Forest plot of the RRs with corresponding 95% CIs of studies on hypertension and PD. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs. RR, risk ratio.

source of controls, and the number of confounding factors. The *p* value of the covariates was 0.937, 0.168, 0.937, 0.309, 0.531, 0.037, and 0.479, respectively. We further performed permutation test, and the *p* value for the source of controls was 0.044, which suggested that the source of controls was the important sources of heterogeneity.

Influence Analysis

In population-based cohort studies, influence analysis showed that 4 studies [25, 43, 45, 48] had an excessive influence on the pooled RR (Fig. 4). After excluding the excessive influential studies, the pooled results did not change obviously (RR 1.32; 95% CI 1.11–1.58; *I*² = 17.2%).

In case-control studies, influence analysis showed that one study [23] had an excessive influence on the pooled OR (Fig. 5). After excluding the excessive influential study, the pooled results was 0.76 (95% CI 0.69–0.83; *I*² = 70.7%).

Sensitivity Analyses

By using the leave-one-out sensitivity analysis, 2 articles contributed to high between-study heterogeneity in population-based cohort studies. After further excluding these 2 articles [43, 48], low heterogeneity (*I*² = 47.2%) was found and the pooled RR was 1.29 (95% CI 1.17–1.41).

The results from case-control studies showed that 3 articles contributed to high between-study heterogeneity. After further excluding these 3 articles [16, 23, 35], the pooled OR was 0.81 (95% CI 0.73–0.88; *I*² = 46.5%).

Publication Bias

Egger test showed no evidence of significant publication bias for the analysis between hypertension and the risk of PD (*p* = 0.121 for population-based cohort studies, *p* = 0.313 for case-control studies; Figs. 6, 7).

Fig. 3. Forest plot of the OR with corresponding 95% CIs of studies on hypertension and PD. The size of gray box is positively proportional to the weight assigned to each study, and horizontal lines represent the 95% CIs.

Fig. 4. Influence analysis of individual study on the pooled RR for studies on hypertension and PD.

Fig. 5. Influence analysis of individual study on the pooled OR for studies on hypertension and PD.

Fig. 6. The funnel plot of hypertension and the risk of PD of cohort studies. Each dot represents a different study.

Fig. 7. The funnel plot of hypertension and the risk of PD of case-control studies. Each dot represents a different study.

Discussion

This meta-analysis provides a comprehensive evaluation of the association between hypertension and the risk of PD. The results from population-based cohort studies indicated that hypertension might increase the risk of PD. But the results from case-control studies indicated that hypertension might decrease the risk of PD. There was inconsistency between population-based cohort studies and case-control studies.

In population-based cohort studies, the pooled RR indicated that hypertension might increase the risk of PD. And the results from leave-one-out sensitivity analysis also indicated that hypertension might increase the risk of PD. And these results were the same as those of the previous study, which included 6 cohort articles conducted by Hou et al. [49]. Meanwhile, compared with Hou et al. [49], our meta-analysis contained influence analysis. In influence analysis, 4 studies had an excessive influence on the pooled RR. After removing

these 4 articles, the pooled results were still significant, indicating the pooled RR was not significantly affected by these 4 studies and the positive results were stable.

In case-control studies, the pooled OR indicated that hypertension could decrease the risk of PD, and the results from leave-one-out sensitivity analysis and influence analysis also supported this association. However, in subgroup analysis, the result from studies based on non-hospital records indicated there were no association between hypertension and the risk of PD.

We found the results from case-control studies were opposite to the results from population-based cohort studies. Here are some possible reasons for the inconsistency: First, PD is a typical senile disease with an average onset age of about 60 years old. According to the World Health Organization in 2014, the global prevalence of hypertension was about 50% among people aged more than 60 years old, and about 22% among general population. The above data indicated both hypertension and PD had close association with aging. So in the age-matched control group, it was more likely to select the elderly with hypertension. Especially in the case-control studies based on hospital records, the proportion of hypertension in control group was higher; for example, in the study conducted by Pinzon et al. [41], the proportion of hypertension in control group was 69.44%. There were more hypertension patients in the control group; thus, we were more likely to get the protective results. Similarly, case-control studies were not suitable for the studies about analogous diseases and PD. Second, both hypertension and PD were diseases with a long course; it was difficult to determine the sequence of onset of PD and hypertension in case-control studies. Moreover, there were recall bias in case-control studies [50], especially in the studies based on questionnaire in this meta-analysis. Thus, the evaluation of the relationship between hypertension and PD was inevitably affected.

Between-study heterogeneity occurs frequently in meta-analysis [27]. In this meta-analysis, high heterogeneity were found ($I^2 = 97.3\%$ for cohort studies; $I^2 = 87.8\%$ for case-control studies). However, the between-study heterogeneity in population-based cohort studies was not successfully explained. But in case-control studies, the results from meta-regression and permutation test suggested that the source of controls was the important sources of heterogeneity. The results from subgroup analysis also revealed the sources of heterogeneity. In different sources of participants, the controls from hospital tended to have

increased frequency of hypertension [37], so the pooled OR based on hospital records was lower.

As a meta-analysis of relevant published studies, our study has several strengths. First, though there were one prospective cohort study and 8 retrospective cohort studies, all of these 9 were prospective studies from exposure to outcome, so the significant positive result was more persuasive. Second, these 9 cohort studies were general population-based studies, so the results can be better extended to the general population. Third, the sample size in this meta-analysis was large, enabled a much greater possibility of reaching reasonable conclusions. Fourth, we extracted RRs, ORs, or HRs that reflected the greatest degree of control for potential confounders, increasing the credibility of the conclusions.

Nevertheless, our study also has limitations. First, the confounder of usage of antihypertensive drugs could not be adjusted, which is a very important factor affecting the association between hypertension and the risk of PD. Some studies [14, 51] found the use of antihypertensive drugs could reduce the risk of PD. Second, confounders adjusted in studies were different, which could affect the association between hypertension and the risk of PD. Third, the pooled results of population-based cohort studies and case-control studies were contrary, so we could not calculate the total pooled results of analytical studies. Finally, high between-study heterogeneity in cohort study was found, but it was not completely explained by meta-regression and subgroup analysis.

Based on population-based cohort studies, this meta-analysis indicated hypertension might increase the risk of PD. In view of both hypertension and PD had association with aging, case-control studies especially the studies based on hospital records were not suitable for similar studies.

Ethics Statement

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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