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Tea consumption and risk of Parkinson's disease: A meta-analysis

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Abstract

The results of studies on the association between tea consumption and Parkinson's disease (PD) have been inconsistent. Therefore, the aim of this study was to perform an updated meta-analysis to better resolve any association between tea consumption and PD. We searched PubMed, Embase, and the Cochrane Library – from their commencement to November 2016 – for qualified studies that evaluated the associations between tea drinking and risk of PD. A total of nine case–control studies and three prospective cohort studies were included. The meta-analysis showed that tea consumption was associated with a reduced risk of developing PD(OR, 0.82; 95% CI, 0.69–0.98) when case–control studies and prospective cohort trials were considered together. Subgroup analysis on the category of tea consumption and risk of PD showed that black tea was not associated with PD (OR: 0.89; 95% CI, 0.64–1.24; I^2=0.0%), but other kinds of tea was associated with a reduced risk of developing PD (OR: 0.67; 95% CI, 0.48–0.95; I^2=0.0%). Subgroup analysis on the dose of tea consumption and PD risk showed that drinking more than one cup of tea daily was associated with a reduced risk of developing PD in case–control studies (OR: 0.38; 95% CI, 0.22–0.66; I^2=0.0%). No indication of publication bias was found.
In *conclusion*, the current evidence showed that tea consumption was associated with a reduced risk of developing PD. The results of our subgroup analysis suggested that people who drinking more than one cup of non-black tea daily might have a reduced risk of developing PD.

Keywords: Tea consumption, Parkinson's disease, risk factor, systematic review, meta-analysis

INTRODUCTION

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder and affects approximately 1% of individuals over the age of 60.[1,2] The number of PD patients over the age of 50 is expected to reach between 8.7 and 9.3 million by 2030.[3] As the population ages, PD may place an increasing economic burden on caregivers and society. To date, the causes of PD are not very clear. It is widely believed that genetic and environmental factors are responsible for PD.[4] Tea – which consists of flavonoids, theanine, and caffeine – is a popular beverage consumed worldwide, and it has many biological activities. Gao *et al*. performed a follow-up study that followed patients for 20–22 years. They found that men exposed to the highest concentration of flavonoids had a 40% lower risk of PD than the participants exposed to the lowest concentration of flavonoids.[5] Interestingly, flavonoids exert neuroprotective, neuroreparative, and antioxidant stress effects, and they can restore mitochondrial function in animal models of PD.[6-10] However, tea also contains 4-phenylpyridine, an analog of 1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine (MPTP), which can deplete neurons of dopamine.[11] So far, some studies have found tea consumption to be related to a reduced risk of PD[12-17], but others have not.[18-23] A meta-analysis found that tea drinking could protect from PD but did not indicate any visible dose–response relationship.[24] In contrast, another meta-analysis concluded that there was a linear relationship between tea drinking and a decreased risk of PD.[25] In recent years, the association between tea consumption and the risk of PD has been evaluated in several studies[16,17,22,23], but the results have been contradictory. For this reason, we performed an updated meta-analysis to assess this association.

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METHODS

Search strategy

We carried out a systematic literature search in PubMed, Embase, and the Cochrane library – from their commencement to November 2016 – with the terms: ("Parkinson Disease" or "Idiopathic Parkinson's Disease" or "Lewy Body Parkinson Disease" or "Lewy Body Parkinson's Disease" or "Primary Parkinsonism" or "Parkinsonism, Primary" or "Parkinson Disease, Idiopathic" or "Parkinson's Disease" or "Parkinson's Disease Idiopathic" or "Parkinson's Disease, Lewy Body" or "Idiopathic Parkinson Disease" or "Paralysis Agitans") and ("Tea" or "Green Tea" or "Green Teas" or "Tea, Green" or "Teas, Green" or "Black Tea" or "Black Teas" or "Tea, Black" or "Teas, Black"). Additional studies were searched from meta-analysis and the reference lists of all relevant publications.

Selection criteria

The eligibility criteria for included studies were as follows: (1) written in English or Chinese, (2) included comparisons of the risk of PD between subjects with and without tea consumption, (3) PD individuals were diagnosed based on the clinical diagnostic criteria of the U.K. Parkinson's Disease Society Brain Bank, (4) original data were provided, such as the number of PD cases and controls, the odds ratio (OR) or relative risk (RR), 95% confidence intervals (CIs), or enough raw data to allow calculation of the risk estimates.

Quality assessment

The observational studies were assessed for methodological quality using the Newcastle-Ottawa Scale (NOS) criteria. The criteria included three items: patient selection, comparability between groups and exposure (case–control studies) or outcome (cohort studies), with a score ranging from zero to nine, and higher scores means better quality of the study.

Data abstraction

The following data were extracted from each paper: first author; year of publication; study design; country of origin; number of participants; number of cases and controls; adjusted RRs or ORs, and 95% CI (or complete information needed to calculate these values); as well as information required to implement the NOS questionnaire. All this information was extracted independently by investigators, and conflicting results were resolved by discussion between investigators.

Statistical analysis

We used the STATA 14.0 statistics software to calculate the available data from each study. The random-effect model was used to calculate the summary OR and its 95% CI. We assessed heterogeneity using I^2 statistics. Subgroup analysis was performed to explore the differences across tea categories and the daily dose of tea drinking. We also used meta-regression analysis to explore the potential sources of heterogeneity for the classified variable. We used graphical examination of funnel plots and Begg's test to appraise the publication bias. A two-tailed p-value of <0.05 was considered indicative of statistical significance, except in the presence of heterogeneity.

RESULTS

Literature search and characteristics of eligible studies

Our literature search yielded 298 potentially relevant articles (83 articles from PubMed, 210 articles from Embase, and 5 articles from other sources). First, we excluded 29 duplicate articles, leaving 269 articles for title and abstract review, after which we had 84 articles for full-text screening. Finally, 12 articles, 9 case–control articles and 3 prospective articles were deemed eligible and included further for our study. The details of the search and literature review process are shown in Figure 1. Among the included articles, three were from China [12,18,23], two were from the U.S.[14,21], one each was from France[20], Sweden[13], Spain[19], Japan[16], U.K.[22], Finland[15], and Argentina.[17] Detailed characteristics of the included studies are presented in Table 1. We also evaluated the quality of the included studies, all of which scored equal to or greater than five in NOS indicating high methodological quality.

Tea consumption and PD risk

The forest plot of the analysis is shown in Figure 2. The pooled ORs of PD with 95% CIs were 0.83 (0.64-1.07) for tea consumers compared to non-consumers in the case–control studies, and heterogeneity was readily visible (I^2=59.6%) with ORs of 0.85 (0.70–1.04) in the cohort studies (I^2=24.9%) and 0.82 (0.69–0.98) when considering all of the studies (I^2 = 52.1%). After conducting both sensitivity analysis and a Galbraith plot for

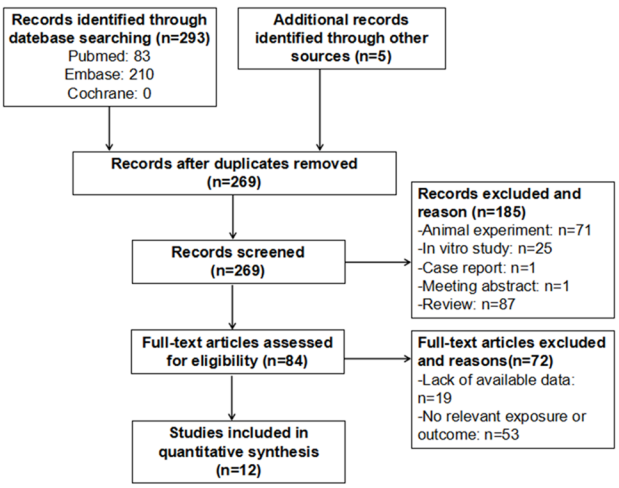

Figure 1. Flow diagram of literature research and selection process.

heterogeneity, we removed one case–control study from the original analysis.[20] Ultimately, the pooled ORs with 95% CIs were 0.74 (0.61–0.89) in the case–control studies with decreased heterogeneity (I^2=24.2%), and 0.78 (0.67–0.90) in all of the studies (I^2 = 28.4%). The case-control studies indicated that tea consumption was associated with a reduced risk of developing PD; however, the prospective cohort studies suggested that tea consumption had no significant association with PD risk.

Subgroup analysis: type of tea consumed and PD risk

Among all included studies, two articles referred to the relationship between tea consumption (people who drink black tea, people who drink

Table 1: Characteristics of studies included in this meta-analysis

Author	Year of Publication	Country	Design	Sample		OR (95%CI)
				Cases	Controls	
Ho *et al*.	1989	China	case-control study	35	105	0.81 [0.36,1.80]
Morano *et al*.	1994	Spain	case-control study	74	148	2.09 [0.65,6.71]
Chan *et al*.	1998	China	case-control study	215	313	0.66 [0.46,0.94]
Fall *et al*.	1999	Sweden	case-control study	113	263	0.45 [0.28,0.72]
Preux *et al*.	2000	France	case-control study	140	280	1.67 [1.04,2.68]
Paganini-Hill *et al*.	2001	U.S.	prospective cohort study	395	2320	1.16 [0.93,1.44]
Checkoway *et al*.	2002	U.S.	case-control study	210	347	0.73 [0.51,1.04]
Hu *et al*.	2007	Finland	prospective cohort study	200	29135	0.31 [0.23,0.42]
Tanaka *et al*.	2011	Japan	case-control study	249	368	0.91 [0.63,1.31]
McGhee *et al*.	2012	U.K.	case-control study	205	264	0.91 [0.46,1.78]
Gatto *et al*.	2015	Argentina	case-control study	223	406	0.74 [0.50,1.10]
Chen *et al*.	2015	China	prospective cohort study	95	74	0.91 [0.43,1.91]

OR, odds ratio; CI, confidence interval.

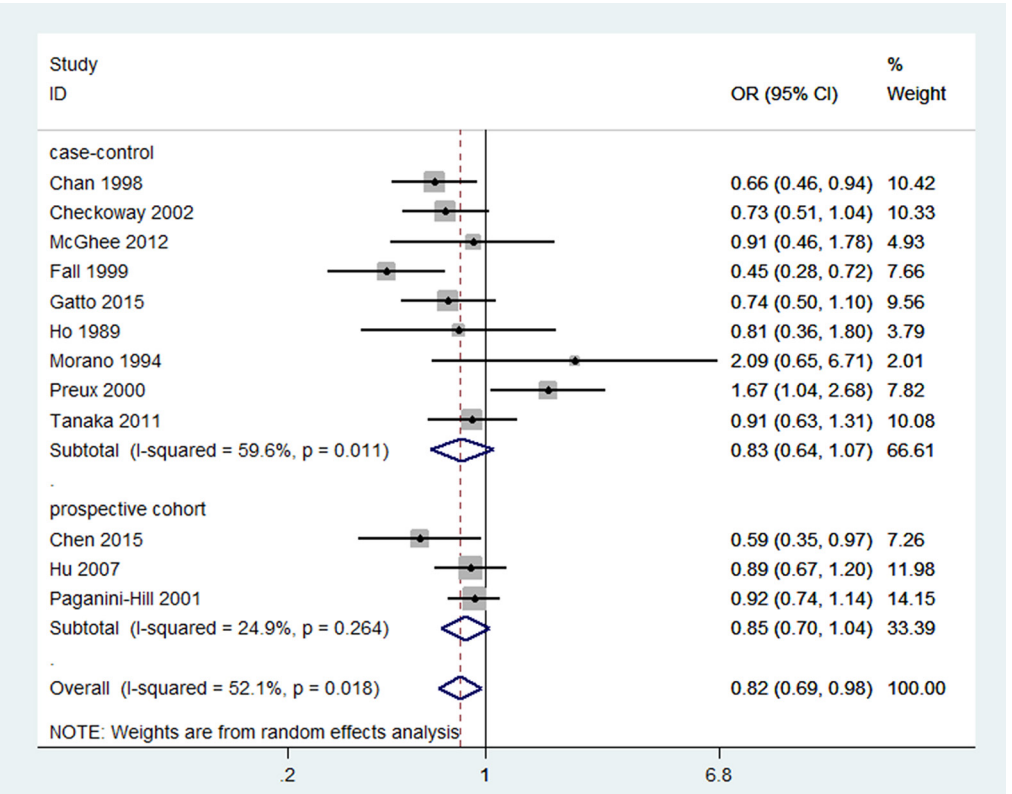

Figure 2. Forest plot showing the association between tea consumption and PD. Analysis model: random effects; OR: odds ratio, CI: confidence interval.

other kinds of tea, and non-consumers) and the risk of PD.[16,18] However, these results have been inconsistent. The information about the type of tea consumed is presented in Table 2. Based on Figure 3, we can see that for black tea consumers versus non-consumers, the pooled OR (OR: 0.89, 95% CI=0.64–1.24, I^2=0.0%) showed that black tea was not associated with the risk of PD. But for people who consumed other kinds of tea versus non-consumers, the overall OR (OR: 0.67, 95% CI=0.48–0.95, I^2=0.0%) showed a protective effect against PD. In summary, we conclude that non-black tea is associated with a reduced risk of developing PD.

Subgroup analysis: dose of tea consumed and risk of PD

Among the twelve studies, four articles referred to the relationship between the dose of tea consumed and the risk of PD[13,14,21]; the subgroup information is presented in Table 3. As shown in Figure 4, we can see that for consumers who drank up to one cup of tea daily versus non-consumers, the pooled OR was 0.64 (0.39, 1.06) in case–control studies (I^2=62.4%), 0.90 (0.74, 1.08) in prospective cohort studies (I^2=0.0%), and 0.80 (0.63, 1.02) in all studies (I^2=50.5%). In the sensitivity analyses and Galbraith plot which omitted one case–control study[13], the pooled OR for consumers who drank up to one cup of tea daily versus non-consumers was 0.94 (0.91–0.97) (I^2 = 0.0%) in cohort studies. For consumers of more than one cup of tea daily versus non-consumers, the summary ORs were 0.38 (0.22, 0.66) in case–control studies (I^2=0.0%), 0.57 (0.28, 1.15) in cohort studies (I^2=79.6%), and 0.57 (0.28, 1.15) in all studies (I^2=80.3%) (Figure 5). After conducting both sensitivity analysis and a Galbraith plot for heterogeneity, we omitted one cohort study[21] and the resultant pooled OR was then 0.52 (0.26, 1.02) for prospective cohort studies. In conclusion, drinking up to one cup of tea daily showed no significant association with the risk of PD in either case–control or prospective cohort studies, whereas drinking more than one cup of tea daily was associated with a reduced risk of developing PD in case–control studies, but not prospective studies.

Table 2: Relationship between type of tea and risk of PD

Type of Tea	Author	Year of Publication	Country	Design	Cases		Controls		OR (95%CI)
					N	n	N	n	
Black tea	Ho *et al*.	1989	China	case-control study	34	17	105	57	0.84 [0.39,1.83]
	Tanaka *et al*.	2011	Japan	case-control study	249	182	368	276	0.91 [0.63,1.31]
Others	Ho *et al*.	1989	China	case-control study	34	4	105	13	0.94 [0.29,3.11]
	Tanaka *et al*.	2011	Japan	case-control study	249	165	368	276	0.65 [0.46,0.93]

OR, odds ratio; CI, confidence interval.

Evaluation for publication bias and meta-regression

We conducted a Funnel plot and Begg's test to evaluate the publication bias of the twelve studies. Visual inspection of the graph showed symmetric distribution, and Begg's test indicated no significant publication bias (p = 0.770).

To explore the potential sources of heterogeneity, we conducted a random-effects meta-regression analysis of the 12 studies. The independent variables included the year of publication, sample sizes, origins of the study population (Asian countries were scored as 1; countries in Europe and the Americas as 2), quality scores of the studies, and study types. None of these variables were significantly responsible for heterogeneity (p> 0.05). However, adjusted variables were different across studies and may be the sources of the heterogeneity.

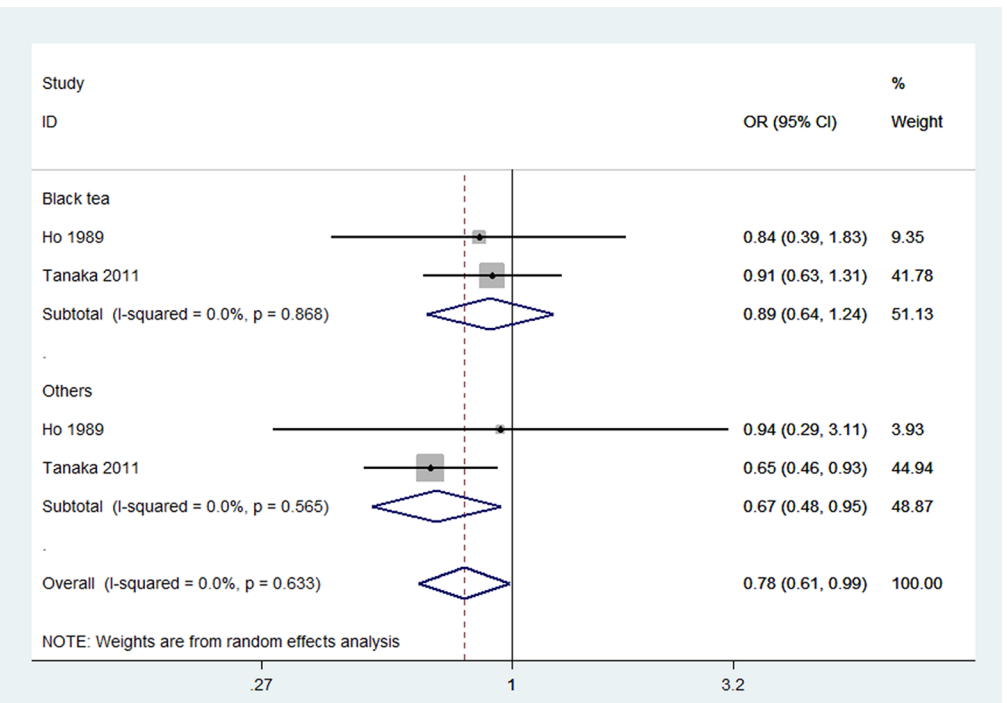

Figure 3. Forest plot showing the association between type of tea and risk of PD. Form of analysis: random effects; OR: odds ratio, CI: confidence interval.

Table 3: Relationship between amount of tea consumed and risk of PD.

Amount of Tea consumed	Author	Year of Publication	Country	Cases N	Cases n	Controls N	Controls n	OR (95%CI)
≤1cup per day	Fall *et al*.	1999	Sweden	111	57	231	143	0.65 [0.41,1.03]
	Paganini-Hill *et al*.	2001	U.S.	391	132	2313	892	0.81 [0.65,1.02]
	Checkoway *et al*.	2002	U.S.	210	61	347	110	0.88 [0.61,1.28]
≥2 cups per day	Fall *et al*.	1999	Sweden	111	7	231	31	0.43 [0.18,1.02]
	Paganini-Hill *et al*.	2001	U.S.	391	50	2313	234	1.30 [0.94,1.81]
	Checkoway *et al*.	2002	U.S.	210	11	347	35	0.49 [0.24,0.99]

OR, odds ratio; CI, confidence interval.

DISCUSSION

This meta-analysis covered 12 studies with 107,608 participants (2,154 cases and 105,454 controls), and the results suggest that tea consumption is associated with an 18% reduction in the risk of PD. Subgroup analysis indicated that drinking non-black teas was associated with a 33% reduction in the risk of PD, and drinking more than one cup of tea daily was associated with a 62% reduction in the risk of PD in case–control studies. However, the pooled prospective cohort studies produced conflicting results.

In the meta-analysis of the association between tea consumption and the risk of PD, although all studies revealed that tea consumption could prevent PD, neither the case–control nor cohort studies showed this association, and a significant heterogeneity was observed in the case–control studies. After we constructed a Galbraith plot

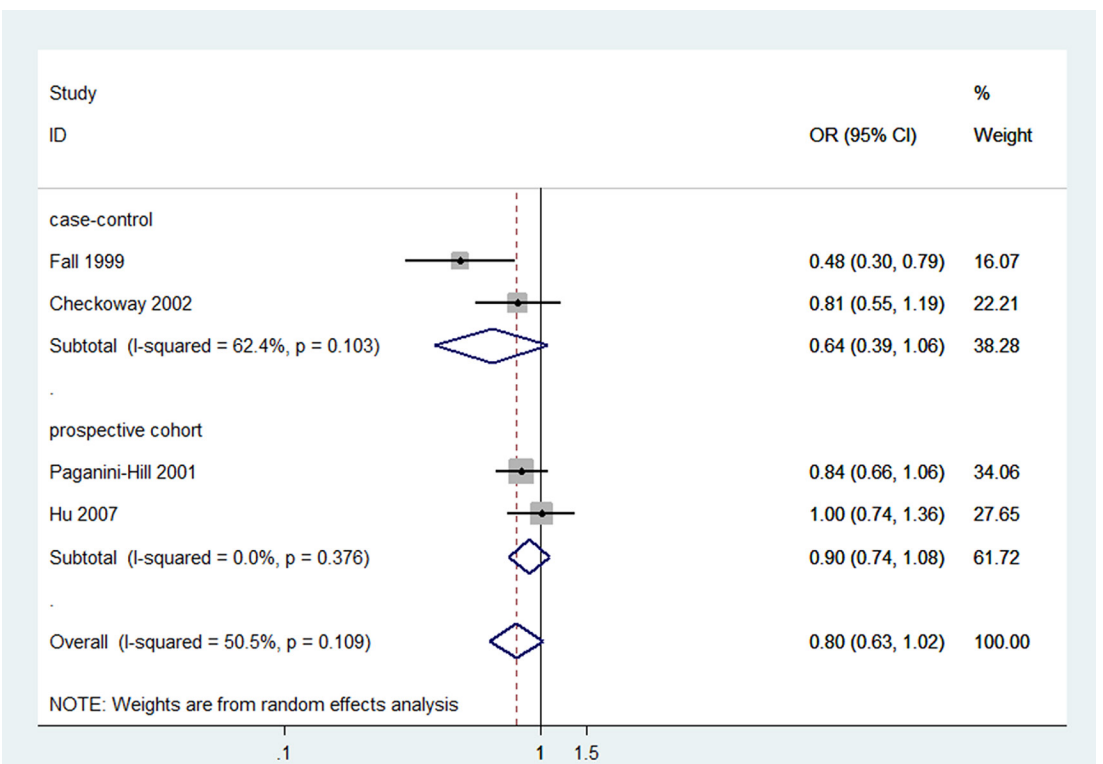

Figure 4. Forest plot showing the association between drinking one cup of tea daily or less and the risk of PD. Analytical model: random effects; OR: odds ratio, CI: confidence interval.

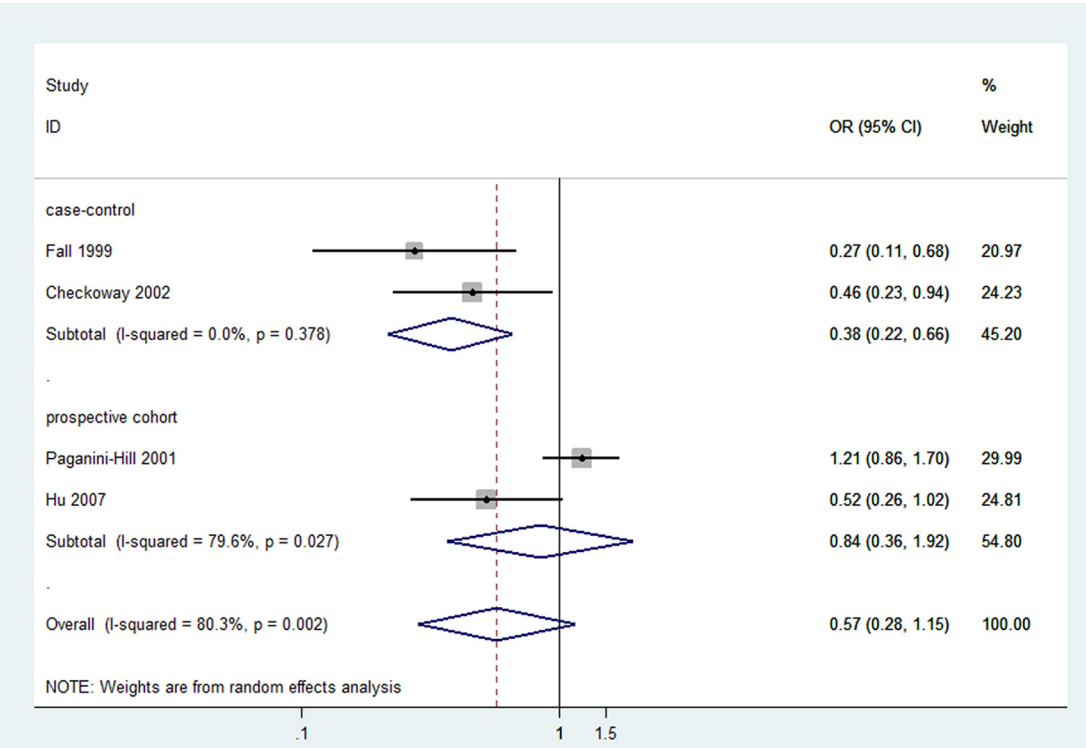

Figure 5. Forest plot showing the association between drinking more than one cup of tea daily andrisk the of PD. Analysis model: random effects; OR: odds ratio, CI: confidence interval.

and conducted sensitivity analysis that removed one case–control study from our analysis[20], the heterogeneity decreased visibly and the result of the case–control studies changed in a way that showed a protective effect of tea consumption on the risk of PD. The protective effect of tea consumption was still present in all studies, indicating that the effect of tea consumption on PD was acceptable and sound. There were two differences between the omitted study and the other studies. First, this was the only study to require that all participants had lived locally for at least 20 years. Second, the omitted study did not exclude cases with a history of cerebrovascular accidents or use of medications, such as haloperidol or reserpine (known to cause drug-induced Parkinsonism), preceding the onset of PD. Therefore, these may be the sources of heterogeneity. Although we omitted studies in the subgroup analysis, the protective effect that was shown for drinking more than one cup of non-black tea daily in case–control studies was still present, indicating that the protective effect on PD was stable.

The etiology of PD is not clearly defined; several studies have suggested that oxidative stress leads to lipid peroxidation and synuclein aggregates, and then synuclein forms Lewy bodies, which lead to further neuronal dysfunction.[26-29] Some studies have proposed that neuroinflammation is also associated with the pathogenesis of PD.[30,31] Furthermore, mitochondrial dysfunction can also lead to the onset of PD.[32]

Tea, derived from *Camellia sinensis*, is rich in polyphenols, caffeine and theanine. Caffeine has been proven to alleviate the destruction of dopaminergic neurons by MPTP in mouse models of PD.[33] A meta-analysis showed a 25% reduced risk of PD among caffeine consumers.[34] Polyphenol flavonoids have been proven to activate an endogenous antioxidant state in neurons[35], suppress lipid peroxidation[36,37], and inhibit inflammation and apoptosis [37,38], thereby protecting neurons from neurodegeneration. Animal studies have shown that quercetin, a flavonoid compound, can repair mitochondrial electron-transport defects in a rat model of Parkinsonism.[39] L-theanine, a free amino acid found in green tea, can cross the blood-brain barrier[40], suppress the excitatory action of caffeine[41], and exert antioxidant properties.[42] Some studies have demonstrated that L-theanine could

protect neurons from β-amyloid-induced cognitive dysfunction, cell death[43], and neurotoxicity induced by environmental toxins related to Parkinson's disease, as observed in SH-SY5Y cells cultured with dieldrin and rotenonein.[44] In addition, tea also contains 4-phenylpyridine, an analog of MPTP, which could deplete neurons of dopamine.[45] Overall, the components of tea are complex and their roles in PD differ from one another. Several studies have been conducted to evaluate the association between tea consumption and the risk of PD, but yielded inconsistent results. We performed this meta-analysis to assess this aforementioned association. Fortunately, the results of the present meta-analysis showed that tea consumption was associated with a reduced risk of developing PD. However, because different teas are manufactured in different ways, the concentrations of these components can differ from one another. For example, in the process of manufacturing green tea, after the fresh tea leaves are harvested, they are immediately heated or steamed which leads to slight oxidation of polyphenols. Therefore, the main flavonoids in green tea are the flavonol sepicatechin and its gallate derivatives. However, in the manufacturing process of black tea, after tea leaves are harvested, they are dried and crushed to enhance oxidation. Consequently, the main flavonoids in black tea are the aflavins and thearubigins.[45] An epidemiological study by Chan *et al*. showed that drinking more than two cups of green tea daily had a protective effect against PD.[12] A study by Tan *et al*. showed that drinking black tea, but not green tea, was associated with a reduced risk of PD.[46] Because only two studies specified the type of tea (black tea, other teas)[16,18] and only four studies investigated the daily amount of tea consumed[13-15,21], subgroup analysis for type and amount of tea were conducted. Based on our results, we suggest that drinking more than one cup of non-black tea daily may have a reduced risk of developing PD.

This work has several limitations that should be taken into account. First, because some otherwise qualified studies lacked sufficient data, only a few could be included here. Second, the included studies were all observational studies, so there may be some residual confounding effects in this meta-analysis.[47] However, confounding bias can be more obvious, and the adjustment variables of the qualified studies were not identical. In this meta-analysis, several studies have specific weaknesses in their design. For example, some did not list the type of tea. Also, most included studies adjusted for several important confounding factors – such as smoking, coffee, and alcohol – but not all studies adjusted for other factors (e.g. sex, age, fruit in the diet, vegetables in the diet, and level of education). These were also important variables. Overall, statistical adjustments for confounding factors may not completely resolve these problems. Third, in this meta-analysis, eight case–control studies were included in which information about tea consumption was obtained by questionnaires from patients; therefore, recall bias in cases and controls may limit the accuracy of these original eight studies. Fourth, in this meta-analysis, we conducted subgroup analysis on the dose of daily tea consumed with the risk of PD. The dose was mainly evaluated by the number of cups drank daily. However, cup size and tea concentration could both vary considerably. Only two studies were suitable for subgroup analysis of the association between the type of tea and the risk of PD. Too few studies specified the type of tea, and many other issues have not been addressed. Different teas may have different effects on PD. More well-designed studies on different types of tea and their effects on the risk of PD are needed. Lastly, even though a funnel plot and Begg's test showed no publication bias in our meta-analysis, we did not search for unpublished studies, so publication bias is certainly present to some extent. These limitations should be taken into consideration when assessing the reliability of our meta-analysis.

In conclusion, the current work shows that tea consumption is associated with a reduced risk of developing PD. The results of our subgroup analysis results suggest that people who drinking more than one cup of non-black tea daily may have a reduced risk of developing PD. Further well-designed research, listing the type of tea and the amount consumed, are required to elaborate these issues and further determine the utility of tea for the primary prevention of PD.

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DISCLOSURE

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