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Original Article

Cigarette Smoking and Parkinson's Disease: A Meta-Analysis

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Abstract Many but not all studies have indicated that smoking is inversely associated with Parkinson's disease (PD). Meta-analysis of epidemiological studies on smoking and PD was performed to summarize data from published studies. Fifty-four epidemiological studies (48 case-control and 6 cohort studies, 53 publications) were identified for potential inclusion in meta-analysis. The summary risk estimates for current smokers, former smokers, and ever (current and former) smokers were 0.31 (95% confidence interval (CI) = 0.25-0.38), 0.72 (95% CI = 0.63-0.83) and 0.55 (95% CI = 0.51-0.59), respectively. In stratified analysis by study design, smoking had a somewhat greater impact on PD risk in cohort studies than in case-control studies. However, meta-regression indicated that the study design did not significantly contribute to heterogeneity. Additional analyses were restricted to case-control studies because of the sufficient number of studies. Stratified analysis by ethnicity indicated that the summary OR for ever-smokers was nonsignificantly smaller in Asian populations than in Caucasian populations. In stratified analysis by source of controls, former smoking was significantly associated with a decreased risk of PD in hospital-based case-control studies but was marginally associated with a decreased risk in population-based case-control studies. The source of controls did not contribute significantly to heterogeneity. PD risk associated with ever-smoking was significantly lower for a hospital-based approach than a population-based approach. Among current smokers, the association held true to the same extent for both approaches. This meta-analysis indicated that smokers have a lower risk of PD. As PD is a multifactorial disease, further investigation of the smoking-gene interaction on PD risk may lead to a better understanding of the pathogenesis of PD.

Key words : Smoking, Parkinson's disease, Meta-analysis

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that can cause significant disability and decreased quality of life. It is the second most common neurodegenerative disease after Alzheimer's disease. Most cases (about 90%) are considered to be sporadic[1)]. PD is an age-related disease : it is rare before age 50 and its prevalence increases with age[1)]. The prevalence of PD is generally lower in Asian populations than in Caucasian populations[1)2)]. For example, PD is estimated to have a prevalence of 0.3% (300/100,000) in the U.S. population and about 1% in people over 60 years of age[3)]. Similarly, the prevalence of PD in the UK was estimated to be 200/100,000[4)]. The corresponding figure in Japan has been estimated to be 100-150/100,000[5)]. The etiology of PD is largely unknown, although there is a growing body of evidence implicating environmental risk factors such as pesticides, heavy metals (iron, manganese, copper, lead, amalgam, aluminium, and zinc), cigarettes, coffee,

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alcohol, dietary antioxidants (vitamin E, vitamin C or beta-carotene), dietary fat and fatty acids (total calories, total fat, saturated fat, animal fat, cholesterol, monosaturated fatty acids, polysaturated fatty acids, dairy products, and milk)[1]. Cigarette smoking is among the most studied risk factors for PD. Many epidemiological studies have revealed a reduced risk of developing PD among users of cigarettes or other tobacco products[6]. Similarly, the incidence of PD decreases with increasing number of cigarettes smoked per day and number of years of smoking but the incidence of PD increases with an increasing number of years since quitting[6].

To comprehensively evaluate the role of cigarette smoking on the risk of PD, this study performed a meta-analysis to summarize findings from epidemiological studies.

Materials and Methods

MEDLINE, Current Contents, and Web of Science searches were conducted using combinations of the search terms 'smoking,' 'Parkinson's disease,' 'case-control,' and 'cohort' (the last search took place on December 2010). Additional articles were identified through the references cited in the first series of articles selected. The MOOSE statement was used to perform meta-analysis[7]. Studies eligible for this analysis had to meet the following inclusion criteria : written in English, published as an original article, with human subjects, reported risk estimate of the association between PD and smoking status (we took the definition of "never," "former," and "current" smokers used in the original report), physician-confirmed diagnosis of PD (incident or prevalent cases), absence of significant cognitive impairment (cases within 10 years of the onset of PD because the mean period from onset of PD to development of dementia is reported to be approximately 10 years[8]), and no obvious overlap of subjects with other studies. When the results of a study were published more than once, only the most complete data were included. For each study, two investigators (SK and CK) independently extracted the following characteristics : authors, year of publication, ethnic group of the study population, source of controls, number of cases and controls, adjusted relative risk (RR) or odds ratio (OR), and confounding factors.

Data were combined using both fixed effects (Mantel-Haenszel method) and random effects (DerSimonian and Laird method) models[9]. As the random effects model is more appropriate when heterogeneity is present[9], the summary risk estimates (OR or RR) were essentially based on the random effects model. The authors assessed heterogeneity with I^2, which describes the percentage of total variation across studies due to heterogeneity rather than chance[10]. An I^2 of more than 75% was considered to represent high heterogeneity, an I^2 of 50% to 75% was considered to represent moderate heterogeneity, and an I^2 of less than 25% was considered to represent low heterogeneity[10]. Publication bias was evaluated by both Begg's[11] and Egger's tests[12]. Subgroup analysis was stratified by study design, ethnicity, and source of controls. Meta-regression was performed to investigate these potential sources of heterogeneity. Statistical significance (publication bias and meta-regression) was defined as a $P < 0.10$ because of the relatively weak statistical power. All calculations were performed using STATA Version 10.1 (Stata Corporation, College Station, TX) software.

Results

In total, 59 publications describing an association between smoking and PD risk were identified using the MEDLINE database. An additional article was indentified through Web of Science. After duplicate studies (2 sets of publications) and studies that did not report ORs for smoking status (5 publications) were excluded, 53 publications (54 epidemiological studies : 48 case-control[13)~60)] and six cohort[61)~65)] studies) were identified for potential inclusion in meta-analysis. The main

characteristics of the case-control studies and results of the studies based on multivariate analysis are shown in Table 1. Most case-control studies (46/48) reported OR of PD for ever-smokers versus never-smokers. The first study[13] reported that ever-smoking was significantly associated with a decreased risk of PD (OR = 0.44, 95% confidence interval (CI) = 0.27-0.74). Twenty-five of 45 subsequent studies showed a significant protective effect of ever-smoking on PD[14)15)17)18)25)27)28)31)36)~38)41)42)45)47)48)51)~54)56)~60)]. Fifteen studies were associated with a modest decrease in risk of PD[19)~24)29)30)32)~35)40)46)55)]. Five studies found no substantial relationship between ever-smoking and PD risk[16)26)39)44)49)]. As for current smokers, most studies reported that smoking was significantly (14 of 19 studies)[15)18)19)21)25)34)35)38)43)50)53)54)56)60)] or nonsignificantly (four of 19 studies)[16)39)44)55)] associated with a decreased risk of PD. One study showed no association between smoking and PD risk[46)]. However, results in terms of the association between the former smokers and PD yielded mixed, variously reporting a significant decreased risk[35)53)54)60)], modest decreased risk[18)38)43)46)56)], no association[15)19)21)34)39)50)] or a nonsignificant increased risk[16)55)]. Table 2 shows the selected characteristics of the cohort studies and results of the studies based on multivariate analysis. Six studies (five publications)[61)~65)] showed a protective effect of smoking, regardless of smoking status, on PD, with the exception of the OR of former smoking reported by Tan et al.[65)]. The summary risk estimates for the association between smoking status and PD are shown in Table 3. The summary risk estimate for ever-smokers versus never-smokers was 0.55 (95% CI = 0.51-0.59) for all studies combined. As shown in Figure 1, studies included in the meta-analysis were sorted in ascending order of risk estimate for ever-smokers. Current smokers (summary risk estimate = 0.31, 95% CI = 0.25-0.38) and former smokers (summary risk estimate = 0.72, 95% CI = 0.63-0.83) had also a significantly decreased risk of PD. The summary risk estimate for former smokers was between that for current smokers and that for never-smokers. Stratified analysis by study design indicated that the summary risk estimates for ever-smoking (current or former smoker) in case-control studies and cohort studies were 0.56 (95% CI = 0.51-0.60) and 0.51 (95% CI = 0.40-0.61), respectively. Similarly, significantly decreased risk estimates for current smokers were noted in case-control studies (summary OR = 0.33, 95% CI = 0.25-0.42) and cohort studies (summary RR = 0.29, 95% CI = 0.20-0.38). The summary risk estimates for former smokers in case-control studies and cohort studies were 0.79 (95% CI = 0.65-0.92) and 0.64 (95% CI = 0.50-0.78), respectively. Although the impact of smoking on PD risk was somewhat greater in cohort studies than in case-control studies, meta-regression indicated that study design did not significantly contribute to heterogeneity. Additional analyses were restricted to case-control studies because of the sufficient number of studies. In the stratified analysis by ethnicity, summary OR for ever-smoking was nonsignificantly smaller in Asian populations (summary OR = 0.47, 95% CI = 0.37-0.57) than in Caucasian or mostly Caucasian populations (summary OR = 0.58, 95% CI = 0.53-0.62). The summary ORs for current smokers and former smokers were not calculable because the ORs for those subjects were not available from six of seven studies. The summary ORs for current smokers and former smokers among Caucasians were 0.35 (95% CI = 0.27-0.43) and 0.81 (95% CI = 0.68-0.95), respectively. Stratified analysis by source of controls indicated that the summary ORs for ever-smokers were 0.57 (95% CI = 0.51-0.63) according to data from population-based studies and 0.50 (95% CI = 0.43-0.56) according to data from hospital-based studies. Meta-regression showed that the PD risk associated with ever-smoking was significantly lower for a hospital-based approach than for a population-based approach (P = 0.07).

Table 1 Association between smoking and Parkinson's disease in case-control studies

Author, year	Ethnicity	Number of Cases/controls	Source of controls	Odds ratio (95% confidence interval)			Confounder
				Current smokers	Former smokers	Ever-smokers	
Nefzger et al 1968[13]	Not specified	198/198	Hospital	-	-	0.44 (0.27-0.74)	Age (male only)
Kessler & Diamond, 1971[14]	Caucasian*	468/468	Hospital	-	-	0.64 (0.48-0.86)	Age, sex, ethnicity
Marrtila & Rinne, 1980[15]	Caucasian	443/443	Population	0.38 (0.23-0.62)	1.40 (0.73-1.49)	0.74 (0.55-1.00)**	Age, sex
Duvoisin et al., 1981[16]	Caucasian	12/12	Population	0.28 (0.03-2.48)	5.50 (0.19-158)	1.00 (0.15-6.68)	(Twin study)
Haack et al., 1981[17]	Caucasian*	237/474	Population	-	-	0.48 (0.32-0.70)	Age, sex, ethnicity
Godwin-Austen et al., 1982[18]	Caucasian	383/383	Hospital	0.40 (0.25-0.64)	0.71 (0.46-1.09)	0.56 (0.38-0.82)	Age, sex
Barbeau & Pourcher, 1982[19]	Caucasian	135/30	Population	0.19 (0.07-0.53)	1.44 (0.40-5.21)	0.50 (0.20-1.23)	Not specified
Bharucha et al., 1986[20]	Caucasian	31/3	Population	-	-	0.30 (0.05-1.65)	(Twin study)
Rajput et al., 1987[21]	Caucasian	118/236	Hospital	0.46 (0.23-0.92)	1.10 (0.60-2.03)	0.7 (0.4-1.2)	Age, sex
Tanner et al., 1987[22]	Caucasian	35/19	Not specified	-	-	0.68 (0.19-2.39)	Age
Ho et al., 1989[23]	Asian	35/105	Hospital	-	-	0.6 (0.2-1.3)	Age, sex
Ngim & Devathasan, 1989[24]	Asian	54/95	Hospital	-	-	0.61 (0.18-2.03)	Age, sex, ethnicity
Hofman et al., 1989[25]	Caucasian	86/172	Hospital	0.70 (0.30-1.00)	-	0.60 (0.30-1.00)	Age, sex
Sasco & Paffenbarger, 1990[26]	Caucasian	96/384	Population	-	-	0.97 (0.57-1.7)	Age, residence (male only)
Hertzman et al., 1990[27]	Caucasian	57/122	Population	-	-	0.40 (0.19-0.86)	Age, sex
Stern et al., 1991[28]	Caucasian	149/149	Population	-	-	0.5 (0.3-0.9)	Age, sex, head injury
Wechsler et al., 1991[29]	Caucasian	34/22	Hospital	-	-	0.57 (0.16-1.96)	Not specified
Jiménez- Jiménez et al 1992[30]	Caucasian	128/256	Hospital	-	-	0.72 (0.45-1.13)	Age, sex, economic status
Butterfield et al., 1993[31]	Caucasian*	63/68	Hospital	-	-	0.32 (0.15-0.67)	Age, sex, ethnicity, education
Semchuk et al., 1993[32]	Caucasian	130/260	Population	-	-	0.58 (0.33-1.20)	Age, sex, family history of PD
Wang et al., 1993[33]	Asian	93/186	Hospital	-	-	0.85 (0.54-1.36)	Age, sex, hospital
Mayeux et al., 1994[34]	Caucasian	285/416	Population	0.2 (0.1-0.5)	0.9 (0.5-1.6)	0.8 (0.4-1.5)	Age, sex
Martyn & Osmond, 1995[35]	Caucasian	172/343	Hospital	0.49 (0.26-0.91)	0.61 (0.40-0.94)	0.58 (0.33-1.20)	Age, sex
De Michele et al., 1996[36]	Caucasian	116/116	Population	-	-	0.36 (0.17-0.73)	Age, sex
Liou et al., 1997[37]	Asian	120/240	Hospital	-	-	0.42 (0.25-0.70)	Age, sex
Hellenbrand et al., 1997[38]	Caucasian	380/379	Population	0.2 (0.1-0.4)	0.8 (0.5-1.2)	0.5 (0.3-0.7)	Age, sex, education
Tzourio et al., 1997[39]	Caucasian	193/579	Population	0.7 (0.4-1.3)	1.4 (0.9-2.1)	1.1 (0.7-1.8)	Age, sex, dementia
McCann et al., 1998[40]	Caucasian*	224/310	Population	-	-	0.7 (0.4-1.1)	Age, sex, ethnicity, residence
Smargiassi et al., 1998[41]	Caucasian	86/86	Hospital	-	-	0.41 (0.22-0.75)	Age, sex
Gorell et al., 1999[42]	Caucasian*	144/464	Population	-	-	0.58 (0.42-0.81)	Age, sex, ethnicity
Fall et al., 1999[43]	Caucasian	113/263	Population	0.17 (0.06-0.43)	0.82 (0.44-1.51)	-	Age, sex
Kuopio et al 1999[44]	Caucasian	123/246	Population	0.5 (0.20-1.24)	-	0.91 (0.55-1.52)	Age, sex, municipality
Werneck & Alvarenga, 1999[45]	Not specified	92/110	Hospital	-	-	0.39 (0.16-0.95)	Age, sex
Beneditti et al, 2000[46]	Caucasian	196/196	Population	1.14 (0.41-3.15)	0.62 (0.38-1.01)	0.73 (0.41-1.32)	Age, sex, coffee, alcohol, education
Preux et al., 2000[47]	Caucasian	140/280	Hospital	-	-	0.5 (0.3-0.8)	Age
Vanacore et al., 2000[48]	Caucasian	140/134	Population	-	-	0.50 (0.29-0.87)	Age, sex, center
Elbaz et al., 2000[49]	Caucasian	127/306	Population	-	-	1.0 (0.6-1.7)	Age, sex, center
Paganini-Hill, 2001[50]	Caucasian	395/2,320	Population	0.42 (0.25-0.69)	0.92 (0.73-1.16)	-	Age, sex
Behari et al., 2001[51]	Asian	318/289	Hospital	-	-	0.55 (0.36-0.84)	Age, sex
Herishanu et al., 2001[52]	Caucasian	93/93	Hospital	-	-	0.36 (0.19-0.69)	Age, sex, pesticide exposure, job
Checkoway et al., 2002[53]	Caucasian*	210/347	Population	0.3 (0.1-0.7)	0.6 (0.4-0.9)	0.5 (0.4-0.8)	Age, sex, ethnicity, education
Galanaud et al., 2005[54]	Caucasian	247/676	Population	0.5 (0.2-1.0)**	0.7 (0.4-1.0)**	0.6 (0.4-0.9)	Age, sex, region
Wirdefeldt et al., 2005[55]	Caucasian	415/415	Population	0.64 (0.37-1.10)	2.14 (0.90-5.08)	0.81 (0.49-1.33)	Age, sex, alcohol, coffee, education
Scott et al., 2005[56][58]	Caucasian	140/168	Population	0.23 (0.09-0.61)	0.55 (0.27-1.14)	0.41 (0.21-0.80)	Age, sex
Powers et al., 2008[57]	Caucasian*	1,186/928	Population (451) and hospital (477)	-	-	0.77 (0.64-0.93)	Age, sex, ethnicity, coffee, NASIDs, residence
Sanyal et al., 2010	Asian	175/350	Hospital	-	-	0.45 (0.26-0.79)	Age, sex
De Palma et al., 2010[59]	Caucasian	767/1,989	Population and hospital			0.59 (0.51-0.69)	Age, sex
Tanaka et al., 2010[60]	Asian	249/369	Hospital	0.12 (0.05-0.27)	0.51 (0.32-0.82)	0.38 (0.24-0.60)	Age, sex, residence, education

Population, population-based controls included other healthy groups such as friends and relatives.
NSAID, nonsteroidal anti-inflammatory drug
*Mostly white.
**$P < 0.05$

Table 2 Association between smoking and Parkinson's disease in cohort studies

Author, year	Ethnicity	Cases/cohort subjects	Name of Cohort study	Relative risk (95% confidence interval)			Confounder
				Current smokers	Former smokers	Ever-smokers	
Grandinetti et al., 1994[61]	Asian	58/8,006 men	Honolulu Heart Program	0.25 (0.14-0.46)	0.50 (0.28-0.87)	0.39 (0.22-0.70)	Age
Willems-Giesbergen et al., 2001[62]	Caucasian	53/6,969	Rotterdam Study	-	-	0.54 (0.20-1.00)**	Age, sex
Hernán et al., 2001[63]	Caucasian*	153/121,700 women	Nurses' Health Study	0.4 (0.2-0.7)	0.7 (0.5-1.0)**	0.59 (0.43-0.81)	Age
Hernán et al., 2001[63]	Caucasian*	146/51,529 men	Health Professionals Follow-up Study	0.3 (0.1-0.8)	0.5 (0.4-0.7)	0.49 (0.35-0.69)	Age
Thacker et al., 2007[64]	Caucasian*	413/184,190	Cancer Prevention Study II Nutrition Cohort	0.27 (0.13-0.56)	0.78 (0.64-0.95)	-	Age, sex
Tan et al., 2008[65]	Asian	157/63,257	Singapore Chinese Health Study	0.29 (0.16-0.52)	0.77 (0.48-1.23)	-	Age, sex, education, year of interview, dialect

*Mostly white.
**$P < 0.05$

Table 3 Summary risk estimate for the association between smoking and Parkinson's disease

	No. of study	Risk estimate (95% confidence interval)					
		Current smokers (No. of available studies)	I^2 (%)	Former smokers (No. of available studies)	I^2 (%)	Ever-smokers (No. of available studies)	I^2 (%)
All studies	54	0.31 (0.25-0.38) (24)	36.8	0.72 (0.63-0.83) (22)	48.1	0.55 (0.51-0.59) (50)	6.3
Study design							
Case-control study	48	0.33 (0.25-0.42) (19)	49.0	0.79 (0.65-0.92) (17)	45.0	0.56 (0.51-0.60) (46)	9.5
Cohort study	6	0.29 (0.20-0.38) (5)	0.0	0.64 (0.50-0.78) (5)	50.2	0.51 (0.40-0.61) (4)	0.0
		P for meta-regression=0.30		P for meta-regression=0.12		P for meta-regression=0.26	
Case-control study							
Ethnicity							
Caucasian	39	0.35 (0.27-0.43) (18)	30.2	0.81 (0.68-0.95) (16)	39.7	0.58 (0.53-0.62) (37)	7.7
Asian	7	- (1)		- (1)		0.47 (0.37-0.57) (7)	0.0
						P for meta-regression=0.16	
Source of controls							
Population-based	25	0.30 (0.22-0.39) (14)	22.4	0.85 (0.68-1.01) (13)	45.2	0.57 (0.51-0.63) (23)	0.0
Hospital-based	20	0.40 (0.18-0.62) (5)	77.8	0.62 (0.46-0.77) (4)	0.0	0.50 (0.43-0.56) (20)	0.0
		P for meta-regression=0.79		P for meta-regression=0.18		P for meta-regression=0.07	

Former smoking was significantly associated with a decreased risk of PD in hospital-based case-control studies (summary OR = 0.62, 95% CI = 0.46-0.77) but marginally associated with a decreased risk in population-based case-control studies (summary OR = 0.85, 95% CI = 0.68-1.01). For current smokers, the summary ORs among population-based and hospital-based controls were 0.30 (95% CI = 0.22-0.39) and 0.40 (0.18-0.62), respectively.

Heterogeneity (Table 3) and publication bias (according to Begg's and Egger's tests, data not shown) were absent from analyses of data based on ever-smokers. Heterogeneity and publication bias were also absent in cohort studies (the data based on current smokers), population-based case-control studies (the data based on current smokers), and hospital-based case-control studies (the data based on former smokers). Evidence of heterogeneity ($I^2 \geq 25\%$) was statistically significant and significant publication bias was noted in the remaining analyses.

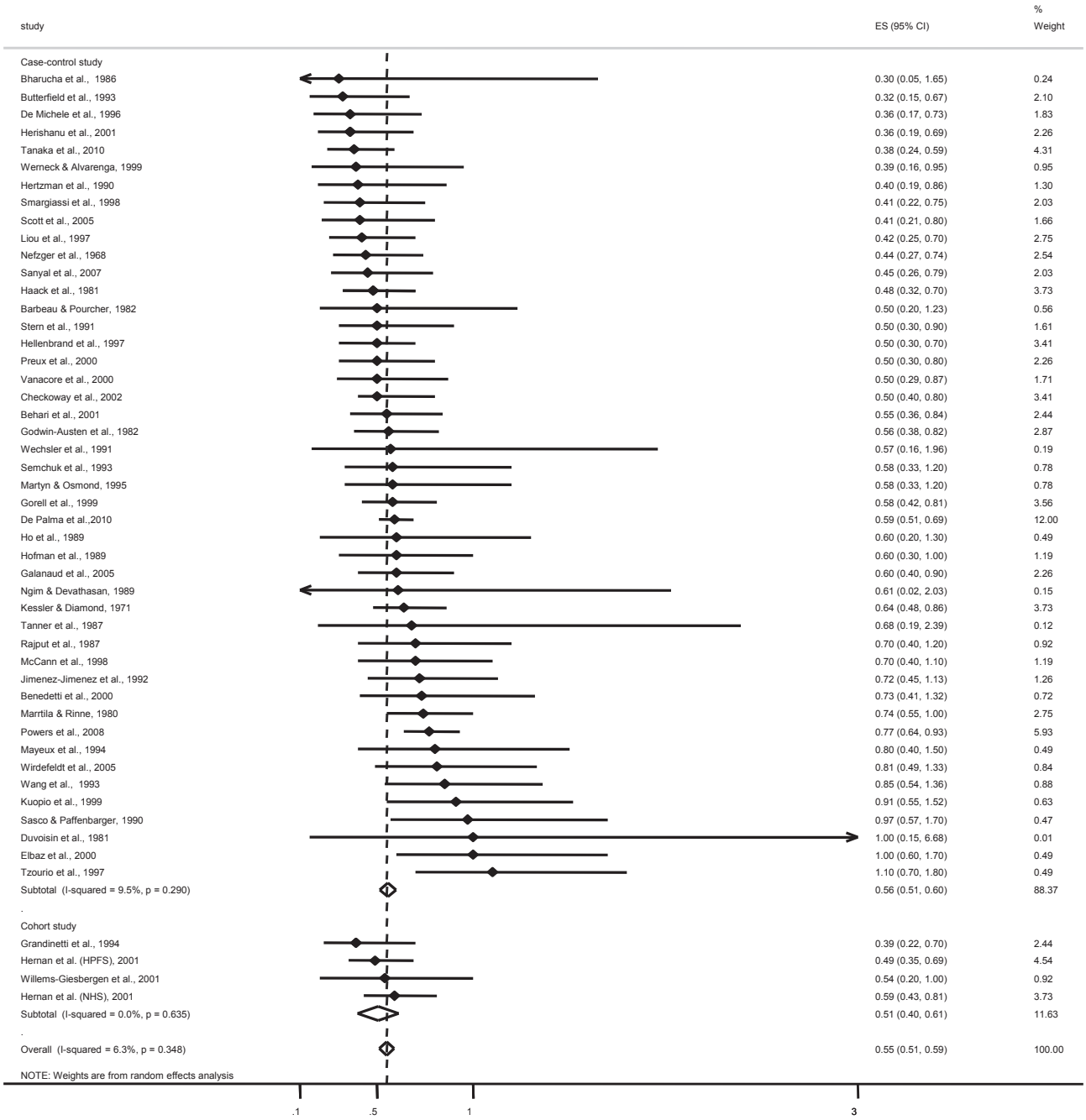

Fig. 1 Meta-analysis of 46 case-control and 4 cohort studies of smoking and Parkinson's disease (ever vs. never). The center of a diamond and the horizontal line (logarithm) indicate the risk estimate and the 95% confidence interval (CI) in each study. The summary OR base on random effects model is represented by the middle of a diamond, with its width indicating the 95%CI.

Discussion

The etiology of PD is largely unknown, although there is growing body of evidence implicating environmental risk (protective) factors. Cigarette smoking is a well-known health hazard and a leading avoidable cause of mortality and morbidity. That said, cigarette smoking appears to confer beneficial effects against PD. A meta-analysis by Hernán et al. in 2002[6] indicated that smoking was associated with a decreased risk of PD. We performed a meta-analysis of published studies (the last search took place on December 2010) to evaluate the association

between smoking and PD. In total, the meta-analysis involved 54 studies on smoking and PD. Results revealed that the PD risk was 63% lower in current smokers and 41% lower in ever-smokers in comparison to never-smokers.

Heterogeneity was noted in several stratified analyses. The presence of significant heterogeneity suggests that the estimated OR in each study is not homogeneous and the estimated ORs are close to 1.0 in the larger studies. Possible sources of heterogeneity would be not only study design but source of controls and ethnicity. The selection of a control group has a major impact on the results of a case-control study. Although hospital inpatients are relatively easy, convenient, and economical to recruit as controls, they may simply represent a sample of a diseased population and suffer from potential biases. Smoking behavior varies widely among different ethnic groups[66]. In most metabolic polymorphisms, allele frequencies vary widely among ethnic groups[67]. Variation in genes such as cytochrome P450 2A6 that are involved in the metabolism of nicotine in different ethnic groups may account in part for differences in smoking behavior (the depth and frequency of inhalation). Although the current study performed stratified analysis by study design, ethnicity, and source of controls, statistically significant heterogeneity was seen in some situations. As residual heterogeneity may exist, the random-effects model was used to account for heterogeneity. Publication bias was present in some analyses. The presence of publication bias indicates that nonsignificant or negative findings remain unpublished. Although publication bias is always a possible limitation of combining data from various sources in an approach like a meta-analysis, Sutton et al. concluded that publication or related biases did not affect the conclusions of most meta-analyses[68].

Meta-regression analysis revealed no significant heterogeneity in risk estimates among study designs. In stratified analysis by source of controls, the inverse effect of ever-smoking was significantly greater in hospital-based studies than in population-based studies (P = 0.067). In general, hospital-based controls are more likely to engage in risk behaviors than is the general population, potentially leading to underestimation of true risk. The generally held view is that smokers are more prevalent among hospital patients than in the general population because many conditions that lead to hospitalization are caused by or associated with smoking; this increased prevalence may bias results of case-control studies of smoking-related diseases[69]. Actually, hospital controls are reportedly more often former smokers than are community controls[70]. Furthermore, former and current male smokers serving as hospital controls tend to smoke more cigarettes per day than do population controls[70]. Since smoking may be a protective factor for PD, it is plausible that the summary OR for ever-smoking was lower in hospital-based studies than in population-based studies.

The biological mechanisms by which smoking affects PD have yet to be elucidated. Cigarette smoke consists of several thousand compounds and one or more of the compounds may have a neuroprotective effect. 4-phenylpyridine and nicotine are potential candidates. 4-phenylpyridine decreases monoamine oxidase B (MAOB) activity. Parkinsonism-inducing neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is oxidized in the brain to the active metabolite 1-methyl-4-phenylpyridine (MPP +) by MAOB[71)72)]. Therefore, 4-phenylpyridine may lower MPP + concentrations by inhibiting the biotransformation of MPTP to MPP +. Nicotine itself might have a direct neuroprotective effect such as an antioxidant effect[71]. Therefore, the hypothesis that smoking decreases PD risk is biologically plausible.

In conclusion, the current meta-analysis indicated that smoking serves as a protective factor for PD. Mechanistic studies in the future will

undoubtedly lead to a more thorough understanding of the role of smoking in PD development.

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（和文抄録）

喫煙とパーキンソン病：メタ分析

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喫煙はパーキンソン病リスクを低下させることが多くの研究で認められているが，すべての研究でその関連性が認められているわけではない．本研究の目的は，喫煙とパーキンソン病についての研究結果を統合するために，公表された研究についてのメタ分析を行うことである．54 の疫学研究（48 症例対照研究と６コホート研究，53 論文）がメタ分析の対象としての適格基準をみたしていた．非喫煙に対する現在喫煙，過去喫煙および喫煙経験（現在喫煙＋過去喫煙）の統合リスクはそれぞれ 0.31（95％信頼区間（95% CI)= 0.25–0.38），0.72（95% CI = 0.63–0.83）および 0.55（95% CI = 0.51–0.59）であった．次に，研究デザインによる層別解析（症例対照研究あるいはコホート研究）を行った．喫煙のパーキンソン病に対する予防効果はコホート研究において，症例対照研究よりもやや強く認められたが，統計学的な有意差は認められなかった．症例対照研究に限ってさらに層別解析を行った．人種（白人あるいはアジア人）による層別解析では，喫煙経験の統合リスクはややアジア人の方が白人よりも小さかった．対照の種類（住民対照あるいは病院対照）による層別解析では，病院対照を用いた場合は過去喫煙は有意にパーキンソン病のリスクを低下させていたが，住民対照を用いた場合はリスクを有意に低下させていなかった．しかし，両者の間に統計学的な有意差は認められなかった．喫煙経験によるリスク低下は病院対照を用いた症例対照研究の方が住民対照を用いた症例対照研究よりも有意に大きかった．現在喫煙のリスクは両者間で有意差はなかった．パーキンソン病は多因子疾患であるので，今後，喫煙－遺伝子交互作用についての研究を行うことによって，パーキンソン病の病因についてよりよい理解が得られると考えられる．