Acta Neuropsychiatrica

Acta Neuropsychiatrica 2012: 24: 109–114

DOI: 10.1111/j.1601-5215.2011.00593.x

ACTA NEUROPSYCHIATRICA

Cigarette smoking, coffee intake and alcohol consumption preceding Parkinson's disease: a case–control study

Sipetic SB, Vlajinac HD, Maksimovic JM, Marinkovic JM, Dzoljic ED, Ratkov IS, Kostic VS. Cigarette smoking, coffee intake and alcohol consumption preceding Parkinson's disease: a case–control study.

Objective: A case–control study was performed in Belgrade in order to investigate the association between Parkinson's disease (PD) and smoking, coffee and alcohol consumption.
Methods: During the period 2001–2005, 110 new PD cases and 220 hospital controls were interviewed. Cases and controls were matched by sex, age and place of residence (urban/rural). For the analysis of data conditional univariate and multivariate logistic regression methods were used.
Results: With PD were associated, independently from each other, current smoking [odds ratio (OR) = 0.44; 95% confidence interval (CI) = 0.23–0.82], alcohol consumption (OR = 4.78; 95% CI = 2.67–8.55) and coffee consumption (OR = 2.54; 95% CI = 1.36–4.75). In ever smokers the risk for PD significantly decreased with the increasing number of cigarettes smoked and with increasing duration of smoking. The risk for PD significantly increased with the increasing quantity of alcohol consumption. PD risk was significantly higher in subjects whose average daily consumption of coffee was 1 and 2–3 cups, and it was lower (but not significantly) in those whose daily coffee consumption was 4+ cups. Cases and controls did not differ in duration of alcohol and coffee consumption. The results of multivariate analyses did not substantially change after adjustment on family history positive on PD.
Conclusion: The findings of this study support the hypotheses of inverse association of smoking with PD, but an inverse association with coffee was not confirmed. PD was found to be positively associated with coffee and alcohol consumption.

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Keywords: alcohol consumption; case–control study; cigarette smoking; coffee intake; Parkinson's disease

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Accepted for publication July 8, 2011

Significant outcomes

- Smoking was inversely associated with Parkinson's disease (PD), as well as the average number of cigarettes smoked and duration of smoking.
- Coffee consumption was more frequent in patients with PD.
- Alcohol consumption was positively related to PD both when ever/never consumption and the total dose of alcohol consumed were analysed. The risk for PD significantly increased with the increasing quantity of alcohol consumption.

Limitations

- The principal limitation of this study is the possibility of inaccurate exposure data and resulting misclassification bias. However, as there is no reason to expect differences between cases and controls in their recall of past exposure it is reasonable to assume that possible misclassifications were non-differential and biased the analysis towards conservative findings, deriving the odds ratio (OR) towards 1.0.
- The number of PD cases included in the study was relatively small.
- This study cannot answer the question whether smoking directly protect against the development of PD.

Introduction

Aetiology of PD is not known, but both genetic and environmental factors have been proposed to be related with the disease occurrence (1–3).

Among environmental factors the most consistent findings were inverse relationship of PD and smoking. This association has been found in majority of case–control and cohort studies and in some of them strong inverse dose–response gradient was present (4–7).

Similar inverse relationship with PD has been found for coffee consumption (4,8–10), and in two cohort studies inverse PD risk gradients with the amount of caffeine were seen (11,12).

There are few data about relationship between PD and alcohol consumption. Inverse association of PD with alcohol consumption, primarily with heavy drinking or alcoholism, was reported only in several studies (7,13,14).

Aims of the study

In this paper we report on smoking, coffee and alcohol consumption from case–control study conducted in Belgrade, Serbia.

Methods

Case–control study was conducted in Belgrade from January 2001 to November 2005. Case group comprised 110 consecutive newly diagnosed PD cases treated at the Institute of Neurology, Faculty of Medicine, Belgrade University. Diagnosis was made by a neurologist and was based on the presence of at least two cardinal signs (tremor, akinesia, rigidity) plus unequivocal response to L-DOPA: Unified Parkinson's Disease Rating Scale (15). For each case two controls were chosen among patients with degenerative joint disease (spondylosis, arthrosis and discus herniae) and some diseases of digestive tract like cholelitiasis, hernia umbilicalis and inguinalis, pancreatitis chronica and fistula rectovaginalis, and who were treated at the University Clinical Center, Belgrade. Cases and controls were matched by sex and age (±2 years). As Institute of Neurology and University Clinical Center serve broad territory (patients come from any part of Serbia), cases and controls were also matched according to the place of residence (urban/rural). PD cases and controls were invited to participate in the study and none of them refused participation. The Institutional Ethics Committee approved this study.

Two physicians using a structured questionnaire interviewed all participants within a month of their diagnosis. Data were collected on demographic characteristics (age, sex, education – incomplete primary, primary, secondary, higher, occupation and marital status), occupational exposure to metallic and non-metallic toxins, occupational and residential exposure to pesticides, living conditions, rural living, well water drinking, habits (smoking, coffee and alcohol consumption), diet (consumption frequency of various food items), stressful life events, past medical history and family history. In this study only data on participants habits are presented. Data about smoking (current and former) comprised average number of cigarettes smoked per day by participants, as well as how long participants smoked. Current smokers were defined as individuals who smoked in the 12 months before the disease and included those who quit within that year. Former smokers were defined as those who had quit more than a year before the disease occurrence. For alcohol consumption (ever drinking), data about the type of beverages and their average weekly consumption were obtained. It was assumed that alcohol content in the beverages was as follows: 30% in brandy, 40% in hard liquor, 12% in wine and 3.5% in beer. The total dose of alcohol consumption for each participant was calculated by adding all the individual beverages weighted according to their alcohol content. The cut-off for categories of alcohol consumption was chosen according to sample distribution as well as defined critical values (of greatest significance).

For the analysis of data conditional univariate and multivariate logistic regression methods were used. All variables significantly associated ($p \leq 0.10$) with

https://doi.org/10.1111/j.1601-5215.2011.00593.x Published online by Cambridge University Press

PD in univariate analysis were included in the multivariate analysis.

Results

The basic demographic characteristics of PD cases and their controls are presented in Table 1. Sex, age and place of residence were matching variables. The mean age (standard deviation) was 60.75 (8.64), for cases, and 60.57 (8.78), for controls. The place of residence was urban for 66.4% of participants and rural for the remaining 33.6%. Cases and controls did not significantly differ in their marital status and level of formal education.

Smoking habit was less frequent among PD cases than among controls (Table 2). Significantly lower percent of cases were current smokers ($p < 0.05$). The percent of former smokers was only somewhat greater in control group ($p > 0.05$). For both current and former smokers, presented in Table 2 together as ever smokers, differences between cases and controls increased with the increasing number of cigarettes smoked (p for trend <0.05), and with increasing duration of smoking (p for trend <0.05). In comparison to controls, significantly lower percent of PD cases smoked 21 and more cigarettes per day ($p < 0.05$), and significantly lower percent of PD cases smoked 31 and more years ($p < 0.05$).

Alcohol consumption was more frequently reported by cases than by controls (Table 3). Differences were significant ($p < 0.001$) for any alcoholic beverage and for each type of alcoholic beverages (brandy, hard liquor, wine and beer). The total dose of alcohol consumed was significantly higher in cases than in controls when various quantities of alcohol consumption were compared (p for trend <0.001). There were no differences in duration of alcohol consumption.

Coffee consumption (ever/never) was significantly more frequent among PD cases than among controls ($p < 0.01$) (Table 3). Significantly greater number of cases than controls consumed 1 and 2–3 cups of coffee per day. Average coffee consumption of 4+ cups daily was higher in controls, but the difference was

Table 1. Basic demographic characteristics of Parkinson's disease cases and their controls

Variable	No. of cases (%)	No. of controls (%)	p-Value*
Sex			Matched
Male	63 (57.3)	126 (57.3)	—
Female	47 (42.7)	94 (42.7)	—
Age			Matched
<50	8 (7.3)	20 (9.1)	—
50–59	48 (43.6)	92 (41.8)	—
60–69	35 (31.8)	71 (32.3)	—
≥70	19 (17.3)	37 (16.8)	
Place of residence			Matched
Urban	73 (66.4)	146 (66.4)	—
Rural	37 (33.6)	74 (33.6)	—
Marital status			0.273
Single	4 (3.6)	6 (2.7)	—
Married	91 (82.7)	170 (77.3)	—
Divorced	4 (3.6)	14 (6.4)	—
Widowed	11 (10.0)	30 (13.6)	—
Education			0.961
Incomplete primary	19 (17.3)	34 (15.4)	—
Primary	27 (24.5)	53 (24.1)	—
Secondary	38 (34.6)	90 (40.9)	—
Higher	26 (23.6)	43 (19.6)	—

*According to univariate logistic regression analysis.

Table 2. Smoking habits of PD cases and their controls

	Cases		Controls		
	No.	%	No.	%	OR (95% CI)*
Non-smokers	66	60.0	107	48.6	1.0
Former smokers	26	23.6	55	25.0	0.77 (0.44–1.34)
Current smokers	18	16.4	58	26.4	0.55 (0.30–0.98)
Ever smokers					
Number of cigarettes smoked per day					
0	66	60.0	107	48.6	1.0
1–10	12	10.9	21	9.6	0.85 (0.40–1.84)
11–20	22	20.0	55	25.0	0.77 (0.57–1.03)
21+	10	9.1	37	16.8	0.75 (0.58–0.97)
p for trend <0.05					
Years of smoking					
0	66	60.0	107	48.6	1.0
1–20	19	17.3	31	14.1	0.94 (0.49–1.79)
21–30	13	11.8	29	13.2	0.81 (0.56–1.17)
31+	12	10.9	53	24.1	0.71 (0.56–0.90)
p for trend <0.05					

*According to univariate logistic regression analysis.

Table 3. Alcohol and coffee consumption by PD cases and their controls

	Cases		Controls		
	No.	%	No.	%	OR (95% CI)*
Consumption of:					
Any alcoholic beverages	43	39.1	25	11.4	5.00 (2.84–8.81)
Brandy	33	30.0	21	9.5	4.06 (2.21–7.45)
Hard liquor	16	14.5	3	1.4	13.31 (3.50–43.3)
Wine	23	20.9	2	0.9	28.28 (6.65–125.0)
Beer	22	20.0	6	2.7	9.02 (3.54–22.99)
Average weekly alcohol consumption (dl)					
0	67	60.9	195	88.6	1.0
0.1–3.49	25	22.7	23	10.5	3.15 (1.67–5.91)
3.5+	18	16.4	2	0.9	5.11 (2.43–10.72)
p for trend <0.001					
Coffee consumption	93	84.5	159	72.3	2.45 (1.35–4.42)
Average number of cups per day					
0	17	15.5	61	27.7	1.0
1	31	28.2	29	13.2	3.84 (1.83–8.03)
2–3	57	51.8	103	46.8	1.99 (1.06–3.72)
4+	5	4.5	27	12.3	0.54 (0.22–1.99)

*According to univariate logistic regression analysis.

https://doi.org/10.1111/j.1601-5215.2011.00593.x Published online by Cambridge University Press

Table 4. Risk factors for PD according to multivariate logistic regression analysis

Variable	OR	95% CI
Model a		
Current smoking (yes/no)	0.44	0.23–0.82
Alcohol consumption (ever/never)	4.78	2.67–8.55
Coffee consumption (ever/never)	2.54	1.36–4.75
Model b		
Ever smokers – average number of cigarettes smoked per day (0; 1–10; 11–20; 21+)	0.62	0.48–0.79
Average weekly alcohol consumption (dl) (0; 0.1–3.49; 3.5+)	4.68	2.79–7.84
Coffee consumption (ever/never)	2.49	1.32–4.71

not significant. Cases and controls did not differ in duration of coffee consumption.

Several multiple logistic regression analyses were performed and the results of the two final models are presented in Table 4. Smoking, coffee consumption and alcohol consumption were significantly and independently from each other related to PD. Smoking was significantly inversely related to PD, either current smoking or average number of cigarettes smoked per day was included in the model. Alcohol consumption was significantly positively related to PD, either consumption of any beverage (ever/never) or average weekly alcohol consumption (dl) was included in the model. Coffee consumption (ever/never) was significantly positively related to PD in both models.

The results of multivariate analyses did not substantially change after adjustment on family history positive on PD.

Discussion

In this study smoking was inversely related to PD. Association was significant only for current smokers, but in ever smokers the risk for PD significantly decreased with the increasing number of cigarettes smoked and with increasing duration of smoking. This apparent negative association of smoking and PD is similar to what has been reported in the literature. In meta-analysis comprising 44 case–control and 4 cohort studies on smoking, Hernán et al. (4) found significantly decreased risk for PD among both current smokers (OR = 0.39) and former smokers (OR = 0.80), as well as an inverse dose–response gradient also reported by some other authors (5–7). Further support to protective role of prolonged exposure to cigarette smoke was the finding that among ex-smokers PD risk was most markedly reduced among recent quitters (5,6), although the possibility that patients with PD quit smoking because of prediagnostic symptoms is an alternative explanation (5). There are only few studies in which inverse relationship between PD and smoking was not so pronounced. In Chan et al. study (16) inverse association of PD with current smokers only reached borderline significance at the 5% level. In Italy (8) cigarette smoking (ever vs. never) was inversely related to PD, but the relationship was not statistically significant. Similarly, in Benedetti et al. study (7) inverse association between cigarette smoking and PD was not significant and dose–effect analysis did not show significant trend. Ma et al. (17) even found significantly increased risk for PD among those who smoked more than 3-pack years. As the most probable explanation for such unexpected results they suggested the fact that their PD cases were old (mean age of disease onset 68.56 years). Namely, Tzourio et al. (18) noted that ever smoking was inversely related to PD among younger patients, but PD risk significantly increased with advancing age.

According to the results of already mentioned meta-analysis conducted by Hernán et al. (4), which comprised eight case–control and five cohort studies on coffee consumption, relative risk of PD was 0.69 for coffee drinkers, compared with non-coffee drinkers. Ragonese et al. (8) also reported an inverse association between PD and coffee consumption (ever vs. never), and a dose–dependent protective effect of coffee drinking on PD was found in an ethnic Chinese population (9). Ascherio et al. (10) found that coffee consumption was inversely associated with PD mortality in men, but not in women. In women this association was dependent on postmenopausal oestrogen use and authors suggested that hypothetical beneficial effect of coffee might be prevented by the use of oestrogen replacement therapy. Checkoway et al. (5) did not confirm an inverse association for either coffee or total caffeine consumption. Swedish twins study (19) also did not confirm previous findings of a protective effect of coffee on PD and authors explained that because of the high level of coffee consumption in their population the possibility to detect an association between caffeine and PD was somewhat decreased. In this study inverse association of coffee consumption with PD was not confirmed. Significantly more PD cases than controls reported coffee intake. Greater number of controls than cases consumed 4+ cups of coffee per day, but this difference was not significant. This unexpected finding could be a result of some unknown confounding factor(s) effect.

There are few data about relationship between PD and alcohol consumption. In two large cohorts (Nurses' Health Study and Health Professionals' Follow-up Study) there was no significant association between total alcohol intake and PD, but protective effect was found for beer (14). Inverse association of PD and alcohol was found in some studies (13),

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but there are more studies in which this association was not confirmed (5,19,20). In this study alcohol consumption was positively related to PD both when ever/never consumption and the total dose of alcohol consumed were analysed.

Although inverse association between smoking and PD has been found in many studies, the nature of this association is not quite clear. Several explanations were broadly discussed. One of them was that the association could account for by differential survival between smokers and non-smokers. As Gale and Martyn (21) pointed, the results of cohort studies showing reduced risk of PD among those who smoke similar to that of case–control studies, rules out this possibility.

The other possibility is that predestined patients with PD have genetic predisposition, which makes them less likely to smoke (22). They are either intolerant to pharmacological stimulating effect of smoking or they not experience the rewarding effect of smell involved in this consumption habit (7). Rybicki et al. (23) found that ever smoking cigarettes was inversely associated with PD in those without a PD family history, but was positively, although non-significantly, related to PD in those with a PD family history. In this study, inverse association of smoking with PD did not change after the adjustment on family history positive on PD. In the study of Scott et al. (24) individuals with PD were significantly less likely to have smoked regularly than their unaffected siblings. Tanner et al. (25) found that within twin pairs risk of PD was inversely correlated with the dose (in pack years) of cigarette smoking and the effect was most pronounced in monozygotic twins. The effect remained even when smoking dose was calculated only until 10 years before PD onset, which suggested that lower dose of smoking in the twin with PD was not the result of undiagnosed disease. In a study of Swedish twins, inverse relationship between smoking and PD was found when co-twins were used as controls, but it was not as strong as using external control subjects. When examining monozygotic twins only, the pattern was similar to using all twins, although the number of pairs was small. The authors concluded that, according to study results, the association of smoking and PD was only partially explained by genetic and familial environmental factors. Interesting are the results of Elbaz et al. study (26) suggesting that smoking and family history interact synergistically on a multiplicative scale in determining the risk of PD in individuals older than 75 years. The joint exposure to both risk factors was associated with a significant increase in the risk of PD.

Some studies have implied that predestined patients with PD have premorbid personality characterised by reducing novelty seeking (27,28), which makes them to avoid behaviour that are addicting or negatively sanctioned by society or that may jeopardise their health. Benedetti et al. (7) found that significant association of PD with tobacco and alcohol referred to patterns of extreme or unusual exposure (tobacco chewing or snuff use, alcoholism) rather than to more usual exposures, and stated that unusual behaviour may depend on the presence of a specific personality trait. However, Hernán et al. (20), using General Practice research Database of the United Kingdom, did not find a lower incidence of PD among alcoholics compared with non-alcoholics.

According to accumulating data it seems as the most plausible that inverse association of smoking with PD is the result of the action of some substances in tobacco – nicotine, or probably some other components. Possible pharmacologic action of nicotine has been investigated and discussed by many authors (5,7,11,21,22,29–31). With the prospect of its neuroprotective effect some of the new pharmacological treatments have been recently developed and they have been tested in clinical trials.

Inverse association of smoking with PD and significant dose–response effect, found in this study, are in agreement with the results of majority of other both case–control and cohort studies. However, this study cannot answer the question whether smoking directly protects against development of PD, but the results obtained are not in line with the hypothesis that this habit is genetically predisposed. The inverse association of tobacco with PD was not influenced by family history positive on PD. At the same time the fact that alcohol consumption was positively related to PD is against hypotheses that inverse association of tobacco with PD was underlined by personality trait. If premorbid personal characteristics were responsible for such relationship one would expect that alcohol consumption was inversely related to PD.

Acknowledgement

This work was supported by the Ministry of Science and Technological Development of the Republic of Serbia, through the Contract No. 175042 (2011-2014).

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https://doi.org/10.1111/j.1601-5215.2011.00593.x Published online by Cambridge University Press