Quitting smoking: An early non-motor feature of Parkinson's disease?

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ABSTRACT

Introduction: Epidemiological studies report a 60–70% reduced risk of Parkinson's disease (PD) in smokers as compared to non-smokers. However, relationships between former smoking and PD have been poorly investigated.
Methods: We recruited 116 de novo PD subjects, and investigated current, former and never smoking, and reasons for smoking cessation among former smokers. Two hundred and thirty-two controls were matched by Propensity Score.
Results: PD subjects and controls were found to be current smokers (7.7 vs. 39.6%), former smokers (43.9 vs. 6.5%) and never smokers (48.2 vs. 53.9%). Logistic regression showed that current smokers were less likely to have PD ($p < 0.001$; OR: 0.22; 95% CI: 0.10–0.46), while former smokers were more likely to have PD ($p < 0.001$; OR: 7.6; 95% CI: 4.09–15.75), as compared to never smokers. Fifty-one PD patients reported quitting smoking before PD diagnosis (mean time since cessation 9.4 ± 7.3 years). Most important reasons to quit smoking in PD group were illness different from PD (26 subjects, 51.0%), knowledge of the harmful effects of smoking (24 subjects, 47.0%), and physician's advice (1 subject, 2.0%).
Conclusion: The reduced prevalence of current smokers among PD subjects as compared to healthy controls is consistent with previous findings, suggesting a possible neuroprotective effect of smoking. However, it could be due, at least in part, to the increased prevalence of former smokers among PD patients, that were more prone to quit smoking as compared to healthy controls. We suggest that smoking cessation could be an early preclinical condition occurring in PD.

1. Introduction

Parkinson's disease (PD) presents different possible determinants, and environmental factors such as lifestyle-related factors, seem to play a significant etiologic role [1]. Among different possible environmental factors, cigarette smoking has been widely studied. In particular, several epidemiological studies reported a 60–70% reduced risk of PD in smokers, when compared to non-smokers [1–4]. Apparently, this association is dose-dependent with reduced PD risk in relation to intensity and duration of smoking [4–6]. Furthermore, a positive effect of smoking on motor features has been reported with a delayed time to disability requiring dopaminergic therapy [7], and on non-motor symptoms (NMS), with an improvement of smell in PD [8].

Association between quitting smoking and PD is an intriguing matter, that has been poorly investigated so far. We may assume

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that quitting smoking could be either a consequence of personality changes occurring in PD [9], or causative as one of the factors increasing the risk of developing PD over time. Large epidemiological surveys grouped former with current smokers, missing a separate analysis [2,10,11]. Some other studies suggested an overall reduced risk of PD for former smokers, lower than never smokers but higher than current ones [1,2,4], but the rate of former smokers is reported to be extremely variable among PD subjects, ranging from 15% up to 50% [5,12]. Interestingly, a recent study suggested that patients with PD are able to quit smoking more easily than controls and, thus, proposed that ease of smoking cessation is an aspect of premanifest PD [13].

The aims of our study are: 1) to assess the prevalence of current, former and never smokers between newly diagnosed and drug naïve PD subjects, and healthy controls; 2) to describe reasons for quitting smoking in PD, that have never been previously reported; 3) to evaluate the relationship between smoking status and motor and non-motor features of PD.

2. Materials and methods

2.1. Study design

Our study was designed to evaluate differences in smoking habits between de novo PD subjects and healthy controls. Secondary endpoints were describing reasons for quitting smoking, and evaluating possible relationships between smoking status and motor and non-motor symptoms of PD. The study was performed according to the good clinical practice guidelines and the Declaration of Helsinki.

2.2. PD subjects

We enrolled de novo, drug-naïve patients with parkinsonism who were consecutively referred to the Centre for PD and Movement Disorders at the Department of Neurosciences at the University "Federico II" of Naples, Italy, within 2008 and 2009. The local ethical committee approved the study and all subjects provided written informed consent. Inclusion criteria were: presence of a parkinsonian syndrome according to the United Kingdom Parkinson's Disease Society Brain Bank Diagnostic Criteria [14,15]; onset less than 2 years before; no previous or current treatment with dopaminergic drugs. Additional criteria for inclusion were lack of significant cerebral lesions on MRI or CT. Exclusion criteria were: diagnosis of secondary (such as vascular and drug-induced) or familial parkinsonism, diagnosis of atypical parkinsonism, namely, multiple system atrophy, progressive supranuclear palsy, corticobasal syndrome, and dementia with Lewy bodies, according to current diagnostic criteria [16–20]. Parkinsonism was diagnosed by movement-disorder specialists experienced in parkinsonian disorders. All subjects were evaluated after 2 years in order to exclude subjects with symptoms and/or signs of atypical parkinsonism, as previously reported [16–20].

Demographics and clinical data were recorded. An expert physician evaluated motor features by means of Unified Parkinson's Disease Rating Scale (UPDRS) part III. In addition, all patients completed the NMS Questionnaire (NMSQ), a validated tool for detection of NMS [21]. The NMSQ consists of 30 questions with dichotomous (yes/no) answers and of a total score, which ranges between 0 and 30, with higher scores reflecting more NMS [21]. None of the patients was treated with anti-parkinsonian drugs, anticholinergic agents, choline esterase inhibitors, antidepressants, anxiolytic drugs, or other centrally acting substances that might have affected both motor and non-motor evaluation.

Smoking habits were recorded (smoking duration and intensity), and PD subjects were categorized according to self-reported smoking status as never, former, or current smoker [22]. In particular, current smokers were defined as those who had smoked 100 or more cigarettes in their lifetime and were smokers when the survey took place. Former smokers were those who reported as being smokers during their lifetime but currently did not smoke. In addition, ever smokers PD patients were asked about their age at starting and the number of cigarettes smoked per day. Moreover, former smokers were asked to report the age at quitting and the most important reason that led them to quit. For ever smokers (current and former smokers), we calculated pack-years, as previously suggested (packs of cigarettes per day multiplied by years smoked) [22]. Reasons to quit were categorized as previously suggested in similar surveys conducted in Italy [22–24]: illness and current health-related conditions (different from PD); physician's advice; knowledge of the harmful effects of smoking; pregnancy/birth of a child; economic reasons (cigarettes too expensive); pressure to quit by partner/relatives; other reasons.

2.3. Controls

Controls were recruited at the Occupational Medicine Unit of the same hospital within the same period. Concomitant diseases and treatments were recorded. All controls underwent physical examination according to clinical practice. Smoking habits were recorded, and controls were categorized according to participant self-report smoking status as never, former, or current smoker, as previously reported [22–24]. Since, unfortunately, reasons for quitting smoking were not assessed in our control group, an Italian survey on a large population presenting similar age range and geographical distribution was used for comparison with PD group [24].

2.4. Statistical analysis

First of all, PD subjects were matched to controls extracted from database of the Occupational Medicine Unit considering covariates (age and gender), by using the Propensity Score Matching (PSM), with a case/control matching ratio of 1/2. Demographic differences between groups were evaluated by χ^2, *t*-test or Mann–Whitney test, as appropriate. Comparisons between PD subjects and controls in relation to smoking status were conducted by a preliminary χ^2 test and by logistic regression analysis with odds ratio and 95% confidence intervals calculation. In order to study other possible factors interfering with smoking status, the latter model was corrected for age and gender. Subsequently, an additional categorization was performed and a logistic regression model analyzed difference in prevalence of ever smokers (former + current smokers) and never smokers between PD subjects and controls.

In order to examine secondary endpoints, a descriptive analysis was performed with different reasons to quit smoking in PD group. Differences in pack-years between current and former smokers have been analyzed by *t*-test and analysis of variance (ANOVA) corrected for age and gender. Furthermore, motor symptoms were evaluated by regression analysis studying the relationship between UPDRS part III and smoking status. In order to evaluate the quantitative relationship between smoking and motor symptoms in ever smokers (current and former), we performed a regression model considering pack-years and UPDRS part III. Among former smokers, time from cessation was related to UPDRS part III by regression analysis. With regard to non-motor symptoms, NMSQ total score was related to smoking status by regression analysis, and NSMQ single items were related to smoking status by χ^2 test or Fisher's exact test, as appropriate. Subsequently, Bonferroni correction for multiple comparisons was performed. In order to evaluate the quantitative relationship between smoking and NMS in ever smokers (current and former), we performed a regression model considering pack-years and NMSQ total score. Among former smokers, time from cessation was related to NMSQ total score by regression analysis.

Stata 12.0 and Microsoft Excel 2011 software were used for data processing and statistical analysis. Results were considered statistically significant for $p < 0.05$.

3. Results

We recruited 116 PD subjects that were matched to 232 healthy controls by PSM. No differences were found between cases and controls for age and gender (Table 1).

PD subjects and controls were found to be current smokers (7.7 vs. 39.6%), former smokers (43.9 vs. 6.5%) and never smokers (48.2 vs. 53.9%) (Table 2; Fig. 1). With regard to our primary endpoint, χ^2 test showed an association between PD diagnosis and smoking status ($p < 0.001$). In particular, at logistic regression analysis current smoking was less likely associated to PD diagnosis ($p < 0.001$), while smoking cessation was more likely associated to PD diagnosis ($p < 0.001$) (Table 2; Fig. 1). Age and gender did not appear to influence smoking status differences between PD subjects and controls ($p = 0.708$ and $p = 0.366$, respectively). Logistic regression failed to show any association between ever smoking (current and former) and PD diagnosis ($p = 0.324$), since there was no difference in prevalence of ever smokers and never smokers between PD subjects and controls.

Table 1
Demographics and clinical features of PD subjects and controls.

	PD subjects ($n = 116$)	Controls ($n = 232$)	*p*-value
Gender			
Male (%)	69 (59.5)	138 (59.5)	*0.945*
Female (%)	47 (40.5)	95 (40.5)	
Age ± SD (range)	59.4 ± 8.4 (40–74)	58.7 ± 7.5 (40–72)	*0.789*
UPRDR part III	15.2 ± 7.1		
NMSQuest total score	4.2 ± 3.2		

p-values from χ^2, *t*-test or Mann–Whitney test, as appropriate.
PD: Parkinson's disease; SD: standard deviation; UPDRS: unified Parkinson's disease rating scale; NMSQuest: non-motor symptom questionnaire.

Table 2
Smoking status of PD subjects and controls. Results are shown from logistic regression analysis before and after correction for age and gender.

	PD subjects (n = 116)	Controls (n = 232)	Unadjusted model				Adjusted model			
			OR	95% CI		*p*-value	OR	95% CI		*p*-value
				Lower	Upper			Lower	Upper	
Smoking status										
Never (%)	56 (48.2)	125 (53.9)								
Current (%)	9 (7.7)	92 (39.6)	0.22	0.10	0.46	*<0.001*	0.23	0.11	0.48	*<0.001*
From years ± SD (range)	32.2 ± 11.6 (10–40)									
Cigarettes per day ± SD (range)	14.6 ± 9.9 (5–40)									
Pack-years	21.4 ± 15.7 (7.5–60)									
Former (%)	51 (43.9)	15 (6.5)	7.6	3.39	14.63	*<0.001*	8.03	4.09	15.75	*<0.001*
From years ± SD (range)	9.4 ± 7.3 (0.5–21)									
Pack-years	12.5 ± 9.5 (2–50)									
Covariates										
Age							0.78	0.46	1.33	*0.708*
Gender							1.00	0.97	1.04	*0.366*

PD: Parkinson's disease; OR: odds ration; 95% CI: 95% confidence interval; SD: standard deviation.

Fifty-one PD patients reported quitting smoking before PD diagnosis (mean time since cessation 9.4 ± 7.3 years, range 0.5–21). In PD patients, most important reasons to quit smoking were illness and current health-related conditions (different from PD) (26 subjects, 51.0%), knowledge of the harmful effects of smoking (24 subjects, 47.0%), and physician's advice (1 subject, 2.0%). In a general population sample from Southern of Italy [24], the most important reasons to quit smoking were illness and current health-related conditions (41.1%), knowledge of the harmful effects of smoking (32.3%), and pregnancy (6.1%).

In PD subjects, smoking intensity evaluated by means of pack-years, resulted to be significantly higher in current smokers when compared to former ones at *t*-test ($p = 0.036$) and ANOVA corrected for age and gender ($p = 0.002$).

Clinical features are shown in Table 1. Regression analysis failed to show any association between UPDRS part III and smoking status, considering never, former and current smokers. There was no quantitative relationship between pack-year and UPDRS part III ($p = 0.815$) among ever smokers (current and former). Time from cessation did not relate to UPDRS part III in former smokers ($p = 0.164$).

NMSQ total score did not relate to smoking status ($p = 0.357$). For NMSQ single item evaluation, in consideration of small sample size and zero values for some items, Fisher's exact test was performed and showed former smokers frequently reporting dribbling saliva ($p = 0.044$), while current and former smokers frequently reporting difficulty concentrating or staying focused ($p = 0.021$), and difficulties in having sex ($p = 0.032$) (Table 3). However, these results were no longer significant after correction for multiple comparisons. A quantitative relationship was found between pack-year among ever smokers (current and former) and NMSQ total score, with subjects smoking more pack-year presenting more NMS ($p = 0.042$; coefficient: 0.08; 95% CI: 0.03–0.15). Time from cessation did not relate to NMSQ total score in former smokers ($p = 0.991$).
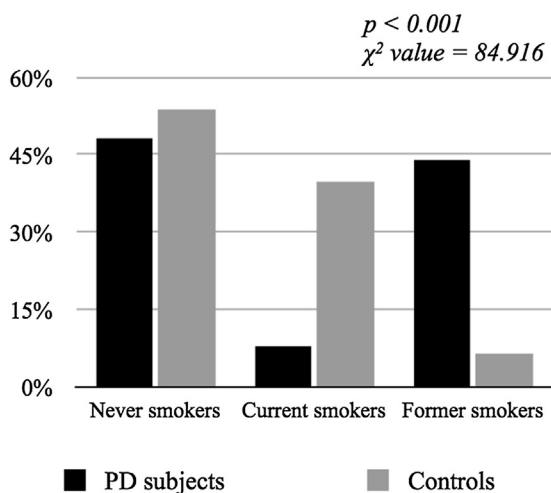
4. Discussion

This is the first study evaluating smoking habits among newly diagnosed and drug naïve PD subjects in relation to healthy controls, recruited and categorized with highly selective criteria. Considering our primary endpoint (difference in smoking status between PD subjects and controls), the reduced prevalence of current smokers among PD subjects is in line with previous studies investigating similar outcomes, but the evaluation of de novo untreated PD subjects significantly strengthens our findings. From this view, we found that different smoking habits are present since early phases of PD and, thus, they are not a consequence of PD diagnosis, progression or treatment. In fact, concomitant health problems can strongly modify smoking habits among general population and, thus, previous studies evaluating treated or advanced PD patients, could have been biased by PD diagnosis or

$$p < 0.001$$
$$\chi^2 \ value = 84.916$$

Fig. 1. Bar chart showing differences in smoking status between PD subjects and healthy controls. *p*-value from χ^2 test is shown.

Table 3
NMSQ single items related to smoking status.

NMSQ items			*p*-values
Dribbling saliva during the day time:	No	Yes	*0.044*
Never smokers	47	7	
Current smokers	9	0	
Former smokers	35	14	
Difficulty concentrating or staying focused:	No	Yes	*0.021*
Never smokers	50	4	
Current smokers	6	3	
Former smokers	37	12	
Finding it difficult to have sex when you try:	No	Yes	*0.032*
Never smokers	52	4	
Current smokers	6	3	
Former smokers	40	9	

p-values from Fisher's exact test are reported.
NMSQ: non-motor symptom questionnaire.

progression, triggering a change in smoking habits [24]. A possible explanation for the reduced prevalence of smokers in PD is a neuroprotective effect of smoking, that has been investigated in several studies suggesting different mechanisms [25,26]. In particular, substances contained in cigarette smoking may interact with MAO-B in dopaminergic neurons possibly reducing oxidative stress [25]. In addition, nicotine modulates dopamine release, with a possible overall functional protective effect against nigrostriatal degeneration [25]. Furthermore, genetic polymorphisms of MAO-B and glutathione S-transferase (GST) may variably interact with cigarette smoking, modifying the risk of PD [27]. More recently, cigarette smoking has been suggested to change the composition of the gut microbiota with reduced misfolding of alpha-synuclein in enteric nerves and decreased propagation of the protein aggregates to the central nervous system [28].

Interestingly, our study did not only show a decreased prevalence of current smokers, but also an increased prevalence of former smokers among PD subjects when compared to controls. Notably, in a large longitudinal study, Chen and colleagues found that PD subjects are more likely than controls to quit smoking earlier and the earliest they quitted smoking, the highest was the risk of developing PD [12]. In addition, among almost 300 PD subjects described by Kandinov and colleagues, former smokers represents over 90% of ever smokers, confirming that smoking cessation frequently happens among PD subjects [6]. However, both studies considered only two subgroups (never and ever smokers) thus, missing a full analysis. In particular, at least in our PD population, current and former smokers appeared to be significantly different for overall smoking exposure and, so, deserved to be separately considered. By analyzing the prevalence of the three different subgroups (never, former and current smokers) in PD patients as compared to healthy controls, we could hypothesize that the reduced prevalence of current smokers among PD subjects could be attributed, at least in part, to the increased prevalence of former smokers. The latter is supported by the fact that prevalence of ever smokers (former and current smokers evaluated together) is not different between our PD subjects and controls. In this view, we may hypothesize that those who quit smoking are more prone to develop PD, or alternatively pre-symptomatic PD subjects are more prone to quit smoking. It is interesting that a recent study supports the latter hypothesis, suggesting that ease of smoking cessation could be considered a premotor feature of PD [13]. In particular, in a large population Ritz and colleagues found that subjects easily quitting smoking presented an increased risk of developing PD, and, more in general, that PD patients were less likely to become habitual smokers [13]. In addition, they found that subjects with greater difficulty quitting (and more prone to use nicotine substitutes) were less likely to develop PD [13]. This is in line with the possibility that quitting cigarettes might be a marker for PD onset, rather than smoking itself having a neuroprotective effect. Anyway, in both cases smoking cessation could be considered a condition that predates the onset of PD.

Interestingly, the average period since former smokers quitted smoking is around 10 years, so that their smoking cessation could possibly date during 1 or 2 Braak stage of PD timeline [29]. Those stages are characterized by sympathetic nervous system changes and, thus, quitting smoking could represent a way of restoring sympathetic-parasympathetic balance by reducing the nicotinic receptor-mediated parasympathetic stimulation. Alternatively, reduced sensation seeking due to mesocorticolimbic dopaminergic system degeneration may lead to a suppression of linked behaviors (i.e. smoking) in a prodromal phase of PD [9]. Both hypotheses are of course speculative, but our findings represent an initial clue for further investigations.

With regard to our secondary endpoints, this is the first study reporting reasons for quitting smoking among PD subjects. In particular, we found that health and knowledge of the harmful effects of smoking are the main reasons that led PD subjects to quit smoking. Comparing our PD subjects to a large Italian population screened with the same questionnaire for smoking cessation reasons, it seems that PD subjects are apparently more sensitive to the harmful consequences of smoking and, thus, possibly more prone to quit smoking. We recognize that this is a preliminary result and that comparing our PD subjects to the general population might have been biased by differences in age and gender distribution. Therefore, further studies in different countries should be performed to confirm our results and to be trans-culturally reliable. However, it has already been reported that PD subjects tend to be more passive, more introspective, less likely to take risks, and more self-controlled, and in turn may choose not to smoke or to quit smoking [6,9].

When evaluating motor features of PD, we failed to find relationships between UPDRS part III and smoking status or pack/year. This is possibly due to the reduced sample size and to the lack of longitudinal motor data, not allowing clearly assessing the efficacy of smoking on motor symptoms [7]. However, it has been suggested that smoking possibly does not have a neuroprotective effect in patients already diagnosed with PD [30]. It has to be reported that early differences in personality, leading to variable smoking habits, could be associated with subsequent development of different PD motor phenotypes. Unfortunately, we did not found this difference in our PD population due to the reduced sample size with a low rate of akinetic-rigid subjects (data not shown) [1,31].

An additional secondary endpoint of the present study is the evaluation of the relationship between non-motor symptoms of PD and smoking status. Interestingly, the intensity of smoking positively related to NMSQ total score in both current and former smokers. In addition, our pilot study seems to suggest that PD subjects complaining daytime dribbling were more frequently former smokers and that PD subjects complaining more difficulties in having sex, a well-known side effect of cigarette smoking, were more frequently current and former smokers. While increased dribbling may have been involved in the decision of quitting smoking in order to reduce additional stimuli to salivation, it is difficult to explain the increased difficulties in concentrating among former smokers. Unfortunately, due to small sample size, these results were no longer significant after multiple test correction, and thus have to be considered very preliminary.

We must acknowledge some limitations. First of all, we did not perform any genetic analysis in our subjects, even though it has been suggested that one or more susceptibility genes act as a background to the effect of smoking [11]. Furthermore, there are limits in the clinical diagnosis of PD and, therefore, we cannot exclude some contamination in our population due to other causes of parkinsonian features. In addition, information on smoking was based on self-reports and, consequently, recall bias may exist. Moreover, we did not assess passive smoking in both cases and controls [10].

In conclusion, the present study broadens our knowledge on the relationship between smoking and PD. In line with previous studies, we found a reduced prevalence of current smokers among PD subjects, supporting a possible neuroprotective efficacy of smoking. In addition, we showed that smoking cessation is a frequent behavior in preclinical PD, and may represent an early non-motor condition occurring in PD and preceding PD diagnosis up to 10 years. Moreover, we presented for the first time reasons for quitting smoking in PD and possible relationships between smoking and NMS of PD. Present results strongly encourage additional studies to evaluate the reasons for different smoking habits in PD.

Conflict of interest

Funding

References

[1] Nicoletti A, Pugliese P, Nicoletti G, Arabia G, Annesi G, Mari MD, et al. Voluptuary habits and clinical subtypes of Parkinson's disease: the FRAGAMP case–control study. Mov Disord 2010;25(14):2387–94. http://dx.doi.org/10.1002/mds.23297.

[2] Tanaka K, Miyake Y, Fukushima W, Sasaki S, Kiyohara C, Tsuboi Y, et al. Active and passive smoking and risk of Parkinson's disease. Acta Neurol Scand 2010;122(6):377–82. http://dx.doi.org/10.1111/j.1600-0404.2010.01327.x.

[3] Powers KM, Kay DM, Factor SA, Zabetian CP, Higgins DS, Samii A, et al. Combined effects of smoking, coffee, and NSAIDs on Parkinson's disease risk. Mov Disord 2008;23(1):88–95. http://dx.doi.org/10.1002/mds.21782.

[4] Hernán MA, Takkouche B, Caamaño-Isorna F, Gestal-Otero JJ. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. Ann Neurol 2002;52(3):276–84. http://dx.doi.org/10.1002/ana.10277.

[5] Ritz B, Ascherio A, Checkoway H, Marder KS, Nelson LM, Rocca WA, et al. Pooled analysis of tobacco use and risk of Parkinson disease. Arch Neurol 2007;64(7):990–7. http://dx.doi.org/10.1001/archneur.64.7.990.

[6] Kandinov B, Giladi N, Korczyn AD. Smoking and tea consumption delay onset of Parkinson's disease. Parkinsonism Relat Disord 2009;15(1):41–6. http://dx.doi.org/10.1016/j.parkreldis.2008.02.011.

[7] Marras C, McDermott MP, Marek K, Rochon P, Naglie G, Tanner CM, et al. Predictors of time to requiring dopaminergic treatment in 2 Parkinson's disease cohorts. Mov Disord 2011;26(4):608–13. http://dx.doi.org/10.1002/mds.23581.

[8] Moccia M, Picillo M, Erro R, Vitale C, Amboni M, Palladino R, et al. How does smoking affect olfaction in Parkinson's disease? J Neurol Sci 2014;340(1–2):215–7. http://dx.doi.org/10.1016/j.jns.2014.02.018.

[9] Evans AH, Lawrence AD, Potts J, MacGregor L, Katzenschlager R, Shaw K, et al. Relationship between impulsive sensation seeking traits, smoking, alcohol and caffeine intake, and Parkinson's disease. J Neurol Neurosurg Psychiatr 2006;77:317–21. http://dx.doi.org/10.1136/jnnp.2005.065417.

[10] Searles Nielsen S, Gallagher LG, Lundin JI, Longstreth Jr WT, Smith-Weller T, Franklin GM, et al. Environmental tobacco smoke and Parkinson's disease. Mov Disord 2012;27(2):293–6. http://dx.doi.org/10.1002/mds.24012.

[11] Elbaz A, Manubens-Bertran JM, Baldereschi M, Breteler MM, Grigoletto F, Lopez-Pousa S, et al. Parkinson's disease, smoking, and family history. EUROPARKINSON study group. J Neurol 2000;247(10):793–8.

[12] Chen H, Huang X, Guo X, Mailman RB, Park Y, Kamel F, et al. Smoking duration, intensity, and risk of Parkinson disease. Neurology 2010;74(11):878–84. http://dx.doi.org/10.1212/WNL.0b013e3181d55f38.

[13] Ritz B, Lee PC, Lassen CF, Arah OA. Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease. Neurology 2014. http://dx.doi.org/10.1212/WNL.0000000000000879.

[14] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinic- pathological study of 100 cases. J Neurol Neurosurg Psychiatr 1992;55:181–4.

[15] Fahn S, Elton RL. UPDRS program members. Unified Parkinson's disease rating scale. In: Recent developments in Parkinson's disease, vol. 2. Florham Park. NJ: Macmillan Healthcare Information; 1987. p. 153–63.

[16] Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013;80(5):496–503. http://dx.doi.org/10.1212/WNL.0b013e31827f0fd1.

[17] Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008;71(9):670–6. http://dx.doi.org/10.1212/01.wnl.0000324625.00404.15.

[18] Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. Eur J Neurol 2013;20(1):16–34. http://dx.doi.org/10.1111/ene.12022.

[19] Litvan I, Agid Y, Calne D, Campbell G, Dubois B, Duvoisin RC, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996;47(1):1–9.

[20] McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. J Alzheimers Dis 2006;9(3 Suppl.):417–23.

[21] Chaudhuri RK, Martinez-Martin P. Quantitation of non-motor symptoms in Parkinson's disease. Eur J Neurol 2008;15(Suppl. 2):2–7. http://dx.doi.org/10.1111/j.1468-1331.2008.02212.x.

[22] Lugo A, La Vecchia C, Boccia S, Murisic B, Gallus S. Patterns of smoking prevalence among the elderly in Europe. Int J Environ Res Public Health 2013;10:4418–31. http://dx.doi.org/10.3390/ijerph10094418.

[23] Carreras G, Gorini G. Time trends of Italian former smokers 1980–2009 and 2010–2030 projections using a bayesian age period cohort model. Int J Environ Res Public Health 2014;11:1–12. http://dx.doi.org/10.3390/ijerph110100001.

[24] Gallus S, Muttarak R, Franchi M, Pacifici R, Colombo P, Boffetta P, et al. Why do smokers quit? Eur J Cancer Prev 2013;22(1):96–101. http://dx.doi.org/10.1097/CEJ.0b013e3283552da8.

[25] Quik M, Perez XA, Bordia T. Nicotine as a potential neuroprotective agent for Parkinson's disease. Mov Disord 2012;27(8):947–57. http://dx.doi.org/10.1002/mds.25028.

[26] Ross GW, Petrovitch H. Current evidence for neuroprotective effects of nicotine and caffeine against Parkinson's disease. Drugs Aging 2001;18:797–806.

[27] De Palma G, Dick FD, Calzetti S, Scott NW, Prescott GJ, Osborne A, et al. A case-control study of Parkinson's disease and tobacco use: gene-tobacco interactions. Mov Disord 2010;25(7):912–9. http://dx.doi.org/10.1002/mds.22980.

[28] Derkinderen P, Shannon KM, Brundin P. Gut feelings about smoking and coffee in Parkinson's disease. Mov Disord 2014. http://dx.doi.org/10.1002/mds.25882.

[29] Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. Parkinsonism Relat Disord 2010;16(2):79–84. http://dx.doi.org/10.1016/j.parkreldis.2009.08.007.

[30] Alves G, Kurz M, Lie SA, Larsen JP. Cigarette smoking in Parkinson's disease: influence on disease progression. Mov Disord 2004;19:1087–92. http://dx.doi.org/10.1002/mds.20117.

[31] Skeie GO, Muller B, Haugarvoll K, Larsen JP, Tysnes OB. Differential effect of environmental risk factors on postural instability gait difficulties and tremor dominant Parkinson's disease. Mov Disord 2010;25(12):1847–52. http://dx.doi.org/10.1002/mds.23178.