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Smoking exposure and Parkinson's disease: A UK Brain Bank pathology-validated case-control study

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ABSTRACT

Introduction: Epidemiological studies have consistently shown an inverse association between cigarette smoking and Parkinson's disease. Literature indicates that both current and former smokers have a reduced risk of developing PD compared to non-smokers. If smoking protects against Parkinson's disease risk or, conversely, smoking habit is abated due to the disease itself, according to the reverse causation, is still an unsolved question.
Methods: 118 patients from the UK Brain Bank with an alive clinical diagnosis of Parkinson's disease were enrolled. Post-mortem validation served as the gold standard for diagnosis to divide the population into true positive and false positive groups. Patient charts were reviewed to extract smoking exposure information and statistical analyses were conducted to determine the odds associated with smoking in the two diagnostic groups.
Results: Among alive clinically diagnosed patients with Parkinson's disease, 53 % had no smoking exposure. In the True Positive group, 58 % had no smoking exposure, while this proportion was lower in the False Positive group at 46 %. The Odds Ratio for the association between smoking exposure and the two groups was 0.63 (95 % CI: 0.32–1.37). The Chi-square test yielded a p-value of 0.2804.
Conclusions: Our findings emphasize the role of smoking exposure in Parkinson's diagnosis. The results indicate that the observed association is not specific to idiopathic Parkinson's disease but rather a broader phenomenon encompassing various parkinsonian disorders. This suggests a potential common neuroprotective effect of smoking, shared risk factors, or supports the reverse causation hypothesis where parkinsonian symptoms reduce smoking exposure.

1. Background

Current literature and previous epidemiological studies have consistently shown an inverse association between cigarette smoking and risk of developing Parkinson's disease (PD). However, the nature of this association is controversial and still poorly understood, since it is under debate if it represents a truly biological effect or a mere artifact of study design related to selection bias or confounding factors. Additionally, also the number of cigarettes that should be smoked to reach a potential protective effect is not defined and literature has poorly addressed this issue. In fact, alternative explanations to an apparent true protective role of smoking for PD involve study design artifact of diagnostic displacement, selection bias related to increased selective mortality of smokers who would have developed PD or a cause-and-effect bias related to decreased smoking due to PD itself [1].

Interestingly, factors other than smoking and caffeine, raised attention as potential protective agents against PD. Especially drugs like statins, terazosin, angiotensin receptor blockers (ARBs) and glucagon-like peptide-1 (GLP-1) receptor agonists have been summoned to play an apparently protective role on PD with a variable strength of evidence. However, controversial results have been published on the topic and a true biological effect still seems questionable. Therefore, retrospective and prospective studies are still needed to assess potentialities of the aforementioned drugs as PD protective factors.

Addressing the uncertainty around the documented link between smoking exposure and Parkinson's disease (PD) is crucial. This

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ambiguity arises from an open question: Is there a true protective impact of low smoking exposure against Parkinson's disease (PD) development, or is there a reverse causal relationship, where early-stage PD causes a decrease in inclination or capacity to smoke? This distinction is important because it has a significant impact on our comprehension of the causes of Parkinson's disease (PD) and the possibilities for preventive measures. A strong counterargument to the protective hypothesis is the occurrence of reverse causation, which postulates that PD symptoms like olfactory impairment or changed reward circuits could cause smokers to cut back on their smoking.

A meta-analysis of 61 case-control and 8 cohort studies found that ever smokers had a 41 % lower risk of PD compared to never smokers [2]. The risk reduction was even greater for current smokers (58 % lower risk) and showed a dose-response relationship with higher cumulative smoking exposure [2]. Additionally, Allam, Del Castillo [3] conducted a systematic review of published observational studies on PD and cigarette smoking stratified by PD family history: three case–control studies were carried out between 1996 and 2000 and reported risk was estimated in one of them. In this work, authors found that the odds ratio for ever smoker in subjects with a positive PD family history was 0.82 (95 % CI, 0.44–1.53), while in patients with a negative PD family history the odds ratio was 0.77 (95 % CI, 0.59–1.01). Despite such results, Authors concluded that further studies evaluating the interaction between smoking and PD family history are strongly needed. Similar risk reductions were reported in a pooled analysis of 11 case-control and cohort studies by Ritz, Ascherio [4], including over 2000 PD cases. Ritz, Ascherio [4] have confirmed an inverse association between PD onset and smoking and found this protective role to be generally stronger in current compared with former smokers and the association was stronger in cohort than in case-control studies. Authors stratified pooled adjusted odds ratios taking pack-year of cigarette smoking into account and found odds ratios of 0.82 in women and 0.90 in men for the 0–9 pack-years group, while odds ratios dropped to 0.52 in women and 0.64 in men for the >60 pack-years group. Furthermore, Authors showed inverse trends with pack-years smoked at every age at onset, except for people over 75 years of age, and the reduction of risk lessened with years since quitting smoking. Importantly, estimated effects were not influenced by sex or education, but were stronger among those with younger age at onset. These data have been observed in the white and Asian population but not in the African American and Hispanic population and possible race-related differences need to be explored. In addition to smoking, caffeine intake has also been associated with lower PD risk. On this purpose, Liu, Guo [5] prospectively examined the influence of caffeine intake on risk of PD in both men and women among 304,980 participants in the National Institutes of Health-AARP Diet and Health Study and also the possible role of smoking on such relationship. In this work, smoking habit was attributed only if ever smoked 100 cigarettes. Logistic regression models were employed by the Authors to estimate multivariate odds ratios and showed that higher caffeine intake was associated with lower PD risk in both men and women. After adjustment for age, race and physical activity, the odds ratio comparing the highest quintile of caffeine intake with the lowest one was 0.75 (95 % CI, 0.60–0.94) for men and 0.60 (95 % CI, 0.39–0.91) for women. Further adjustment for duration of smoking and analyses carried out among never smokers showed similar results. Authors proposed that smoking and caffeine may act independently in relation to PD risk. Finally, the authors conducted a meta-analysis of 9 prospective studies [1,6–13] and confirmed that caffeine intake was inversely associated with PD risk in both men and women. Authors concluded that the relation between caffeine and PD risk was not influenced by gender difference. In the case-control study of Alves, Kurz [14], a 50 % higher prevalence of smokers in control groups compared to PD patients was found, confirming a protective role of smoking against PD development. However, smoking did not affect disease progression in patients already diagnosed with PD in their longitudinal analysis. A large meta-analysis of Noyce, Bestwick [15] included over 200 studies and found strong associations between reduced PD risk and family history of PD, smoking, caffeine intake and constipation. They found that the strongest predictors of later PD diagnosis were family history, smoking and constipation history [14,15]. Moreover, Noyce, Bestwick [15] concluded that smoking reduces the risk of PD by about 36 %, with the strongest effect in current smokers and weakest in past smokers (56 % for current smokers and 22 % for past smokers). Other meta-analyses of observational studies have reported overall relative risks of 0.24–0.55 (95 % CI, 0.13–0.78) for current smokers compared to never smokers [16–18]. Interestingly, this association appears to demonstrate a dose-response relationship, with heavier smoking associated with lower PD risk [17]. A case-control study by Searles Nielsen, Gallagher [19] demonstrated that passive smoking was associated with a 66 % reduced risk of PD, suggesting that smoke exposure, rather than smoking behavior itself, may be related to PD risk. Overall, the epidemiologic data provide strong evidence for an inverse association between cigarette smoking and PD risk, but do not clearly establish causality for exposures related to rural living and farming. Moreover, a case-control study by Mellick, Gartner [20] with 163 PD patients and 151 matched controls found that passive smoking exposure variables, like ever lived with a smoker (OR 0.58, 95 % CI, 0.29–1.17) and ever worked in a smoky workplace (OR 0.65, 95 % CI, 0.35–1.20), were less common in PD patients compared to controls. These results confirm that passive smoking may also be associated with reduced PD risk, independently from active smoking. Another case-control study by Gorell, Rybicki [21] with 144 PD patients and 464 matched controls found a dose-response relationship between smoking amount and PD risk, with light smokers having lower risk than non-smokers (OR 0.59, 95 % CI, 0.23–1.53) and heavy smokers having the lowest risk (OR 0.08, 95 % CI 0.01–0.62). An inverse association between time since quitting smoking and PD risk was also proved in this study. Additionally, a twin-model study by Tanner, Goldman [22] with 113 twin pairs discordant for PD found that twins without PD smoked more pack-years than their twin siblings with PD (9.8 more pack-years), even when accounting for pre-diagnostic smoking. This difference was greater in identical twins, suggesting a true biological effect of smoking rather than genetic or environmental confounding.

Differently from PD, literature on the relationship between smoking habit and atypical parkinsonisms is quite poor and has been only recently summarized by Lo [23]. Such epidemiological association is controversial, since both multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) patients have been found to smoke non-significantly less than control subjects. However, studies on the topic suffer from possible selection bias due to exclusion of subjects with smoking-related illnesses. As things stand, the link between atypical parkinsonisms and smoking has been poorly explored and displays less solid data than PD [23].

In summary, multiple studies consistently showed a 30–60 % lower risk of PD among smokers compared to never smokers. There appears to be a dose-response relationship, with lower risks associated with higher cumulative smoking exposure. Table 1 summarizes the key risk metrics from studies related to smoking exposure in Parkinson's disease, and Fig. 1A shows literature data about odds ratio of smoking exposure in Parkinson's disease.

Due to the lack of anatomopathological confirmatory studies, it is not clear if the smoke exposure protection is valid more in general for Parkinson's disease syndrome or is specific for idiopathic Parkinson's disease. Our study, aims to investigate this complex relationship and provide light on this important yet unexplored area of PD research.

1.1. *Pathophysiology of smoking as a protective factor against PD*

Biological mechanisms for the protective effects of smoking on risk of PD development are not completely established, since tobacco and tobacco smoke are chemically heterogeneous in composition and not easily establishble. For example, at present, it has been supposed that nicotine or carbon monoxide contained in tobacco smoke may promote

Table 1
Literature key results about smoking exposure and Parkinson's disease.

Reference	Participants	Risk Estimate
Li, Li [1]	13,504 cases (case-control), 3189 cases (cohort)	RR 0.59 (95 % CI, 0.56–0.62)
Allam, Del Castillo [2]	97 cases	(1) OR 0.82 (95 % CI, 0.44–1.53) for ever smokers with positive PD family history
	774 cases	(2) OR 0.77 (95 % CI, 0.59–1.01) for ever smokers with negative PD family history
Ritz, Ascherio [3]	2328 cases (case-control)	(1)OR 0.53 (95 % CI, 0.44–0.63) for current smokers
	4113 controls (case-control)	(2)OR 0.76 (95 % C, 0.68–0.86) for former smokers
		(3) OR 0.70 (95 % CI, 0.63–0.78) for ever smokers
	488 cases (cohort)	(4) OR 0.23 (95 % CI, 0.15–0.36) for current smokers
	4880 controls (cohort)	(5) OR 0.64 (95 % CI, 0.52–0.77) for former smokers
		(6) OR 0.54 (95 % CI, 0.45–0.65) for ever smokers
Liu, Guo [4]	304,980 cases	(1)OR 0.60 (women) (95 % CI, 0.39–0.91)
		(2)OR 0.75 (men) (95 % CI, 0.60–0.94)
Alves, Kurz [5]	239 PD patients, 200 controls	77.9 % prevalence of never smoked in a PD population
Noyce, Bestwick [6]	202 studies	RR 0.44 (95 % CI, 0.39–0.50) for current vs never smokers
Searles Nielsen, Gallagher [7]	154 PD cases, 173 controls	(1)OR 0.34 (95 % CI, 0.16–0.73) for ever passive smoking vs never smoked
		(2)OR 0.35 (95 % CI, 0.17–0.73) for ever active smokers vs never smoked
Ritz, Lee [8]	1808 PD cases, 1876 controls	(1)OR 0.44 (95 % CI, 0.29–0.69) for former smokers who had ever used nicotine substitute vs never smoked
		(2)OR 0.24 (95 % CI, 0.13–0.46) for current smokers who had ever used nicotine substitutes vs never smoked
Domenighetti, Sugier [9]	12,424 PD cases, 9480 controls	OR 0.74 (95 % CI, 0.60–0.93) for current smoking vs never smoked
Breckenridge, Berry [10]	Meta-analysis of 33 studies on smoking	(1)RR 0.54 (95 % CI, 0.47–0.62) using fixed effects model for current smoking vs never smoked
		(2)RR 0.55 (95 % CI, 0.39–0.78) using random effects model for current smoking vs never smoked
Mellick, Gartner [11]	163 PD, 151 controls	(1)OR 0.58 (95 % CI, 0.29–1.17) for ever lived with a smoker
		(2)OR 0.65 (95 % CI, 0.35–1.20) for ever worked in a smoky workplace
Gorell, Rybicki [12]	144 PD, 464 controls	(1)OR 0.59 (95 % CI, 0.23–1.53) for current light smokers vs never smokers
		(2)OR 0.08 (95 % CI 0.01–0.62) for current heavy smokers vs never smokers
Tanner, Goldman [13]	113 twin pairs	Twins without PD smoked 9.8 more pack-years
		OR 0.64 (95 % CI, 0.39–1.05) for all pairs of any zigosity-twins that ever smoked vs never smoked

survival of dopaminergic neurons. Another explanation involves the possible smoke-mediated alteration/competition of the enzyme activity with a subsequent decrease of toxic endogenous (dopamine quinones) or exogenous (MPP+) metabolites [24] Castagnoli and Murugesan [25] explored the possible connection between monoamine oxidase (MAO) inhibitors present in tobacco and tobacco smoke and the implications of their effects in the MPTP mouse PD model. Probably, tobacco-induced cyanomethylation of the reactive amino groups in the MAO protein may reduce its catalytic activity. Consequences of MAO long-term inhibition include direct enhanced dopaminergic neurotransmission and secondary effects on other neurotransmitter systems, such as serotonin and noradrenaline. Additionally, MAO-B inhibition by cigarette smoke has been found to reduce the levels of hydrogen peroxide, a by-product of MAO oxidation and a source of reactive oxygen species. Interestingly, Fowler, Volkow [26] demonstrated that tobacco smokers have lower levels of brain and blood platelet MAO-B activity and a lower incidence of PD compared to non-smokers. Moreover, a PET-based study of Fowler, Volkow [27] demonstrated that smokers have significantly lower brain MAO-A activity than non-smokers in all brain regions examined. Yong and Perry [28] found significantly reduced MAO-B activity in both male and female subjects. This result was confirmed by Norman, Chamberlain [29], who described a 24 % decrease in MAO-B activity in female smokers compared to female non-smokers and a 21 % decrease in male smokers compared to male non-smokers, variably ranging from frontal cortex and basal ganglia. Other studies have focused on the role of nicotine, since this molecule has pleiotropic and neuroprotective effects on dopaminergic neurons [24]. It has been proved that nicotine and another compound present in smoke (hydroquinone) have the potential to inhibit the formation of ***α***-synuclein fibrils, with the subsequent possibility to stabilize soluble oligomeric form of ***α***-synuclein [30]. According to others, PD patients have fewer available nicotinic acetylcholine receptors in the brain with reductions of up to 50 % in the frontal and temporal areas involved in learning, memory and execution of stimulus seeking behaviors [24]. For this reason, PD patients may feel less nicotine-mediated "reward" from stimulus-seeking behaviors or from smoking, which may make it easier to quit smoking. The apparent neuroprotective effect of cigarettes in PD would be expression of the underlying physiologic response that lets PD patients to quit smoking more easily than those without PD. However, it is worth to emphasize that smoking-related reward drops as the number of nicotinic acetylcholine receptors decreases, but addiction is still a possible issue in PD patients on levodopa, as demonstrated by the dopamine dysregulation syndrome. Following this hypothesis, Ritz, Lee [18] have proposed that the ease of quitting smoking could be an early prodromal sign of the disease, identifying the altered sensitivity of the brain's reward system in response to nicotine in affected patients. In conclusion, the relationship between smoking and PD is complex and many hypotheses to explain this inverse correlation are still under discussion.

The aim of this study is to better characterize the relationship of smoking exposure to PD diagnosis through a pathology-validated method, by comparing PD patients with a post-mortem confirmed diagnosis to patients which received a clinical PD diagnosis but not confirmed with a post-mortem pathology analysis.

2. Methods

The present study is a case-control study investigating the association between smoking exposure and PD. In order to avoid the clinical misdiagnosis, we selected PD patients with a post-mortem pathology diagnosis validation (true positive), which is the current gold standard and compared the smoking exposure data to patients which received a clinical PD diagnosis but not confirmed with a post-mortem pathology analysis (false positive). Ethical clearance was granted by the local ethics committee of Campus Bio-Medico University of Rome. The study was made in collaboration with Parkinson's UK Brain Bank at the Imperial College London. Clinical and neuropathological data were supplied by Parkinson's UK Brain Bank at Imperial, funded by Parkinson's UK, a charity registered in England and Wales (258197) and in Scotland (SC037554). This Brain Bank has been approved as a Research Tissue Bank by the Wales Research Ethics Committee.

In the present study were enrolled 118 patients which received a clinical diagnosis of PD, 62 were confirmed with post-mortem pathology analysis (True Positive), while 56 were found to be misdiagnoses (False Positive). Chart review was made in order to explore in the patients'

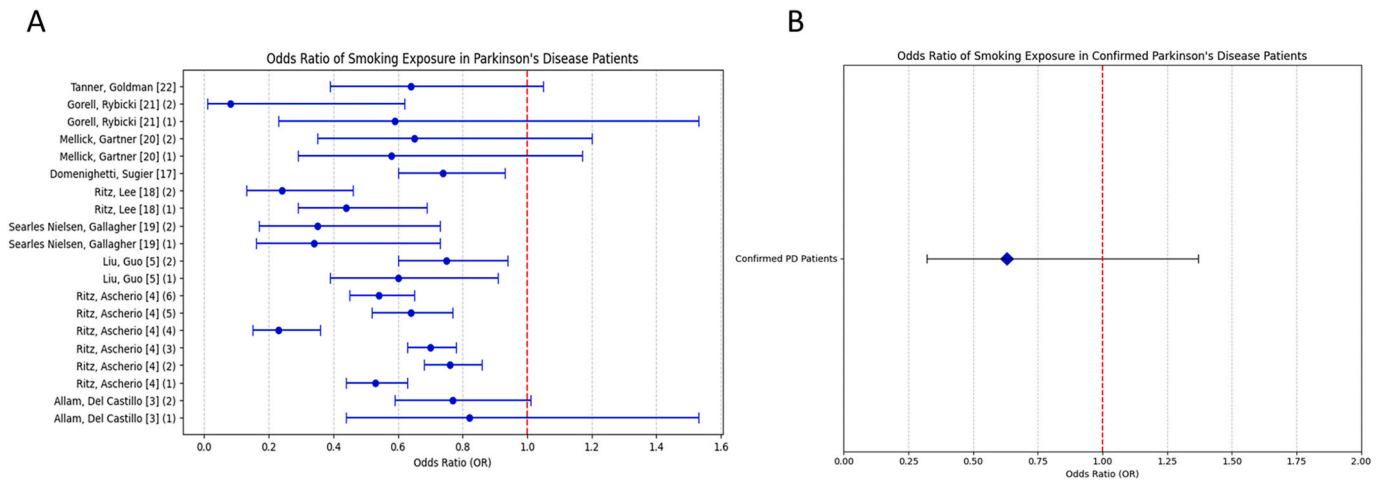

Fig. 1. A. Odds ratio of smoking exposure in PD reported in literature.
-The figure shows the studies references and indicates also in round brackets the number of odds reported (details of data in Table 1) with the points estimate represented by a blue circle:
• The blue circles indicate the odds ratio points estimate.
• The vertical dashed red line at 1.0 is the line of no effect.
- B. Graph of odds ratio of smoking exposure in confirmed Parkinson's disease patients. The figure shows the visualization for the odds ratio with the point estimate represented by a blue diamond: The blue diamond indicates the odds ratio point estimate (0.63), and the black line the 95 % CI range (0.32, 1.37); the vertical dashed red line at 1.0 is the line of no effect. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

clinical history the exposure to smoking. In order to assess the strength of association between smoking exposure and the two groups true positive and false positive PD diagnosis the Odds Ratio was calculate along with the 95 % CI, and Chi-square test was used to check if the results were statistically significant. Python was used as the primary tool for both statistical analysis and the generation of visualizations and graphs.

3. Results

3.1. Population characteristics

Among confirmed post-mortem PD patients (true positive), the average age at death was 79.03 years (SD = ± 7.24 years). Moreover, the average duration of the disease among these patients was 13.37 years (SD = ± 5.72 years), while the average age of onset of the disease was 66.42 years (SD = ± 9.07 years).

Conversely, among misdiagnosed PD patients (false positive), the average age at death was 81.15 years (SD = ± 8.85 years). The average duration of the disease for this subgroup was 13.36 years (SD = ± 15.25 years), while the average age of onset for the disease was 69.92 years (SD = ± 12.07 years). For true positive group, the percentage male was 63 % and for the false positive group of 51 %.

3.2. Statistical analysis

Among the 118 patients with alive clinical diagnosis of PD the 53 % was not exposed to smoke. After anatomophatology post-mortem Parkinson's disease diagnosis confirmation among the True Positive group, 58 % had no exposure to smoking (either as active smokers, ex-smokers, or passive smokers), while this proportion was lower in the False Positive group at 46 %. Table 2 shows the distribution of the subjects in the different subgroups. Dissecting 56 FP cases, 39 % had an isolated post-mortem diagnosis of atypical parkinsonism (9 exposed, 13 never exposed to smoke). Among 56 FP cases, 19.6 % were PSP (4 exposed, 7 never exposed to smoke), 16 % MSA (4 exposed, 5 never exposed to smoke), 1.8 % Dementia with Lewy Body (one exposed to smoke), 1.8 % Corticobasal degeneration (one never exposed to smoke), 11 % Alzheimer's disease (2 exposed, 4 never exposed to smoke), 1.8 % vascular encephalopathy (one never exposed to smoke), while 7 % of cases had other isolated pathological findings (2 exposed, 2 never exposed to smoke). 41 % of FP brains had more than one post-mortem finding (16 exposed and 7 never exposed to smoke). Considering proteinopathies, 23 % of FP cases suffered from an isolated tauopathy (5 exposed, 8 never exposed to smoke), 18 % an isolated synucleinopathy (5 exposed and 5 never exposed to smoke), 11 % an isolated amyloidopathy (2 exposed, 4 never exposed to smoke), 41 % a combined proteinopathy and 7 % of FP cases had no post-mortem finding of proteinopathy (1 exposed and 3 never exposed to smoke). Table 3 summarizes amount and type of pathological diagnoses and relative smoking habits for FP group.

Table 2
Absolute and relative representation of smoking habits among pathology-validated and clinically misdiagnosed PD patients.

	Confirmed PD diagnosis (true Positive) n (%)	Not PD diagnosis (false Positive) n (%)
Not exposed to smoke	36 (58 %)	26 (46 %)
- Never smoking	36 (58 %)	26 (46 %)
Exposed to smoke	26 (42 %)	30 (65 %)
-Passive smoker	2 (3 %)	0 (0 %)
-Actual smoker	1 (2 %)	3 (5 %)
-Ex smoker	23 (37 %)	27 (48 %)
Available total data	62 (100 %)	56 (100 %)

When assessing the strength of association between smoking exposure and the two groups true positive and false positive PD diagnosis the Odds Ratio was 0.63 (95 % CI: 0.32–1.37) (Fig. 1B). The Chi-square test showed a p-value of 0.2804.

4. Discussion

In this pathology-validated case-control study, we explored the association between smoking exposure and the PD gold standard diagnosis. At clinical diagnosis level, in line with literature our data showed an higher frequency of parkinsonian syndrome patients not exposed to smoking. The statistical analysis comparing the smoking exposure between the two groups pathology confirmed and not confirmed PD,

Table 3
Absolute and relative representation of isolated and combined pathological diagnoses with relative smoking habits for clinically misdiagnosed PD patients.

False positive	n (%)	Not exposed to smoke	Exposed to smoke		
Pathological diagnosis			Passive smoker	Actual smoker	Ex smoker
PSP	11 (19.6 %)	7			4
MSA	9 (16 %)	5		1	3
DLB	1 (1.8 %)				1
CBD	1 (1.8 %)	1			
AD	6 (11 %)	4			2
Vascular	1 (1.8 %)	1			
Other isolated	4 (7 %)	2			2
Copathology	23 (41 %)	7		2	14
Total data	56 (100 %)	27 (48.2 %)	0 (0 %)	3 (5.3 %)	26 (46.4 %)
Proteinopathy					
Synucleinopathy	10 (18 %)	5		1	4
Tauopathy	13 (23 %)	8			5
Amyloidopathy	6 (11 %)	4			2
Combined proteinopathy	23(41 %)	7		2	14
No proteinopathy	4 (7 %)	3			1
Total data	56 (100 %)	27 (48.2 %)		3 (5.3 %)	26 (46.4 %)

Abbreviations: PSP = progressive supranuclear palsy; MSA = multiple system atrophy; DLB = dementia with Lewy bodies; CBD = corticobasal degeneration; AD = Alzheimer's disease.

showed no difference between these two groups. The finding that both idiopathic Parkinson's Disease (PD) and other parkinsonian syndromes exhibit a low association with smoking provides significant insight in this field. This result may suggest that the observed association is not specific to idiopathic PD but rather a broader phenomenon encompassing various parkinsonian disorders. The possibility that smoking similarly influences both idiopathic PD and other parkinsonian syndromes opens new questions about the nature of the link between smoking and neurodegenerative diseases. It could, for instance, indicate a common neuroprotective mechanism induced by smoking or reflect shared risk factors or lifestyle patterns influencing both smoking and the development of these disorders. Alternatively, this could also support the reverse causation hypothesis, where early stages of parkinsonian disorders lead to a reduction in smoking exposure.

Multiple studies have consistently shown a 30–60 % lower risk of PD among smokers compared to never smokers [2–5,14–22]. Furthermore, a dose-response relationship has been demonstrated, with lower risks associated with higher cumulative smoking exposure [2,16–18]. Possible biological mechanisms to explain such protective role of smoke on PD risk are still under debate. However, the exact pathophysiological mechanisms by which smoking might influence PD risk remain not understood.

Additionally, our findings confirm a still relevant diagnostic error for PD and unveil the importance of the pathological validation for the scope. Concerning the FP group, we demonstrated that most important clinical misdiagnoses were PSP (4 exposed, 7 never exposed to smoke) and MSA (4 exposed, 5 never exposed to smoke), against which clinicians should pay more attention for a correct differential diagnosis. We also found that 11 % of clinically misdiagnosed patients were AD (2 exposed, 4 never exposed to smoke), pointing out its relevant role as a movement disorder mimicker.

Notably, we found a grossly similar relative representation of pathological isolated synucleinopathies (5 exposed and 5 never exposed to smoke) and tauopathies (5 exposed, 8 never exposed to smoke), respectively 18 % and 23 % of FP brains. However, the subgroups sample size of our cohorts doesn't allow subanalysis, and a possible protective role of smoking for synucleinopathy as a whole cannot be evaluated and further confirmatory longitudinal studies are required for the scope.

According to a more recent point of view and in line with Movement Disorders Society (MDS) clinical diagnostic criteria for PD [31], besides the classical description that depicts some specific clinical and pathology differences, PD, Parkinson's disease Dementia (PDD) and DLB should be considered a continuum alongside the spectrum of intraneuronal α-synucleinopathies lying within the umbrella term of "Lewy body disease".

Our findings highlight also the importance of copathology in the context of a correct diagnosis of PD: the presence of multiple pathologies is now recognized as the rule rather than the exception in neurodegenerative disorders. Concordantly, we found more than one postmortem diagnosis in 41 % of clinically misdiagnosed patients.

Our study has limitations. The sample size, while significant, may not be representative of the broader population. Also, potential recall biases related to self-reported smoking history could influence the results.

In order to further confirm that the exposure to smoking is statistically a protective factor for the whole group of parkinsonian syndrome and that there is no difference between idiopathic Parkinson's disease and all other parkinsonisms, new studies are needed with higher sample size and with parkinsonian syndromes subgroups further comparison.

5. Conclusions

In conclusion, our findings emphasize the role of smoking exposure for Parkinson's diagnosis. The results show that the observed association is not specific to idiopathic Parkinson's disease but rather a broader phenomenon encompassing various parkinsonian disorders, suggesting a broader phenomenon that may indicate a common neuroprotective effect of smoking, shared risk factors, or support the reverse causation hypothesis where parkinsonian symptoms reduce smoking exposure.

CRediT authorship contribution statement

Lazzaro di Biase: Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Pasquale Maria Pecoraro:** Writing – original draft. **Simona Paola Carbone:** Writing – original draft. **Francesca Alessi:** Writing – original draft. **Vincenzo Di Lazzaro:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Lazzaro di Biase reports a relationship with Bial that includes: consulting or advisory. Lazzaro di Biase reports a relationship with AbbVie Inc that includes: consulting or advisory. Lazzaro di Biase reports a relationship with Boston Scientific Corp that includes: consulting or advisory. Lazzaro di Biase reports a relationship with Zambon SpA that includes: funding grants. Lazzaro di Biase reports a relationship with Brain Innovations that includes: equity or stocks. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] K. Wirdefeldt, et al., Risk and protective factors for Parkinson's disease: a study in Swedish twins, Ann. Neurol.: Off. J. Am. Neurol. Assoc. Child Neurol. Soc. 57 (1) (2005) 27–33.

[2] X. Li, et al., Association between cigarette smoking and Parkinson's disease: a meta-analysis, Arch. Gerontol. Geriatr. 61 (3) (2015) 510–516.

[3] M. Allam, A. Del Castillo, R.C. Navajas, Parkinson's disease, smoking and family history: meta-analysis, Eur. J. Neurol. 10 (1) (2003) 59–62.

[4] B. Ritz, et al., Pooled analysis of tobacco use and risk of Parkinson disease, Arch. Neurol. 64 (7) (2007) 990–997.

[5] R. Liu, et al., Caffeine intake, smoking, and risk of Parkinson disease in men and women, Am. J. Epidemiol. 175 (11) (2012) 1200–1207.

[6] A. Ascherio, et al., Prospective study of caffeine consumption and risk of Parkinson's disease in men and women, Ann. Neurol.: Off. J. Am. Neurol. Assoc. Child Neurol. Soc. 50 (1) (2001) 56–63.

[7] G. Hu, et al., Coffee and tea consumption and the risk of Parkinson's disease, Mov. Disord.: off. J. Move Disord. Soc. 22 (15) (2007) 2242–2248.

[8] G.W. Ross, et al., Association of coffee and caffeine intake with the risk of Parkinson disease, JAMA 283 (20) (2000) 2674–2679.

[9] K. Sääksjärvi, et al., Prospective study of coffee consumption and risk of Parkinson's disease, Eur. J. Clin. Nutr. 62 (7) (2008) 908–915.

[10] L.C. Tan, et al., Differential effects of black versus green tea on risk of Parkinson's disease in the Singapore Chinese Health Study, Am. J. Epidemiol. 167 (5) (2008) 553–560.

[11] A. Ascherio, et al., Caffeine, postmenopausal estrogen, and risk of Parkinson's disease, Neurology 60 (5) (2003) 790–795.

[12] A. Ascherio, et al., Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: the modifying effects of estrogen, Am. J. Epidemiol. 160 (10) (2004) 977–984.

[13] A. Paganini-Hill, Risk factors for Parkinson's disease: the leisure world cohort study, Neuroepidemiology 20 (2) (2001) 118–124.

[14] G. Alves, et al., Cigarette smoking in Parkinson's disease: influence on disease progression, Mov. Disord. 19 (9) (2004) 1087–1092.

[15] A.J. Noyce, et al., Meta-analysis of early nonmotor features and risk factors for Parkinson disease, Ann. Neurol. 72 (6) (2012) 893–901.

[16] C.B. Breckenridge, et al., Association between Parkinson's disease and cigarette smoking, rural living, well-water consumption, farming and pesticide use: systematic review and meta-analysis, PLoS One 11 (4) (2016) e0151841.

[17] C. Domenighetti, et al., Mendelian randomisation study of smoking, alcohol, and coffee drinking in relation to Parkinson's disease, J. Parkinsons Dis. 12 (1) (2022) 267–282.

[18] B. Ritz, et al., Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease, Neurology 83 (16) (2014) 1396–1402.

[19] S. Searles Nielsen, et al., Environmental tobacco smoke and Parkinson's disease, Mov. Disord. 27 (2) (2012) 293–297.

[20] G.D. Mellick, et al., Passive smoking and Parkinson disease, Neurology 67 (1) (2006) 179–180.

[21] J.M. Gorell, et al., Smoking and Parkinson's disease: a dose–response relationship, Neurology 52 (1) (1999), 115-115.

[22] C. Tanner, et al., Smoking and Parkinson's disease in twins, Neurology 58 (4) (2002) 581–588.

[23] R.Y. Lo, Epidemiology of atypical parkinsonian syndromes, Tzu Chi Med. J. 34 (2) (2022) 169–181.

[24] M. Quik, Smoking, nicotine and Parkinson's disease, Trends Neurosci. 27 (9) (2004) 561–568.

[25] K. Castagnoli, T. Murugesan, Tobacco leaf, smoke and smoking, MAO inhibitors, Parkinson's disease and neuroprotection; are there links? Neurotoxicology 25 (1–2) (2004) 279–291.

[26] J.S. Fowler, et al., Inhibition of monoamine oxidase B in the brains of smokers, Nature 379 (6567) (1996) 733–736.

[27] J.S. Fowler, et al., Brain monoamine oxidase A inhibition in cigarette smokers, Proc. Natl. Acad. Sci. USA 93 (24) (1996) 14065–14069.

[28] V.W. Yong, T.L. Perry, Monoamine oxidase B, smoking, and Parkinson's disease, J. Neurol. Sci. 72 (2–3) (1986) 265–272.

[29] T.R. Norman, K.G. Chamberlain, M.A. French, Platelet monoamine oxidase: low activity in cigarette smokers, Psychiatr. Res. 20 (3) (1987) 199–205.

[30] D.-P. Hong, A.L. Fink, V.N. Uversky, Smoking and Parkinson's disease: does nicotine affect α-synuclein fibrillation? Biochim. Biophys. Acta Protein Proteonomics 1794 (2) (2009) 282–290.

[31] R.B. Postuma, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (12) (2015) 1591–1601.