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Relationship between Parkinson's and Smoking: A Meta-Analysis

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Abstract*— *Introduction: *Parkinson's disease is one of the most important neurodegenerative disorders affecting 1% of the population above 60 years Oxidative stress in the body is the leading cause of Parkinson's disease which leads to the degeneration of dopaminergic neurons in substantia nigra pars compacta leads to decrease in the level of dopamine and it is shown that there is an association between cigarette smoking and PD.* ***Objective:*** *To evaluate the association between Parkinson's disease (PD) with smoking, and determine whether gender, source of controls, the dose of smoking, and year of studies modify the observed effects of smoking on PD.* ***Materials and methods:*** *The studies which were published between October 2008 to October 2018 were searched and selected from science direct Springer, American journal of epidemiology, PubMed, back-references, and scholarly publications from other science databases. Search strategies like Parkinson's disease and smoking, nicotine and Parkinson's disease and nicotine, tobacco, etc. out of these observational studies were chosen i.e., case-control studies were selected.* ***Results:*** *The data of these obtained studies were pooled and analyzed using comprehensive meta-analysis software the results obtained were as follows OR 0.557 at 95% CI (0.436-0.712) the Z-value obtained was -4.681 and the p-value was 0.000 which showed an association between smoking and Parkinson's disease.* ***Conclusion:*** *from the obtained results and despite extensive evidence from epidemiological and basic research studies suggesting that nicotine may represent an effective agent with potential for prevention and alleviation of PD, clinical data vary to a major extent between individuals.*

I. INTRODUCTION

Parkinson's disease is the second most chronic neurodegenerative disease. It was termed by James Parkinson in 1817 and is otherwise known as shaking palsy. PD prevalence is increasing with age and PD affects 1% of the population above 60 years Oxidative stress in the body is the leading cause of Parkinson's disease which leads to the degeneration of dopaminergic neurons in substantia nigra pars compacta leads to a decrease in the level of dopamine in brain leading to an abnormal brain activity the Clinical manifestations of the disease include tremor, cogwheel rigidity or stiffness of the skeletal muscles and akinesia (poor ability to initiate the movement). This triad is the classic symptom of Parkinson's disease. Increased knowledge about the disease and the developing risk factors and new treatment approaches helps in reducing the incidence of Parkinson's disease.

Many researchers suggest a causal relationship of many factors which get involved in Parkinson's disease such as alcohol, pesticide exposure, caffeine consumption, and smoking it was found to have a positive relationship between smoking and Parkinson's disease as cigarette smoking was found to have a neuroprotective effect in the disease. However, the other environmental factors had a negative relation to increasing the risk of developing Parkinson's disease. Many controversies still exist on this relation. The previous meta-analysis selected which had 69 articles were selected out of which 61 case-control studies and 9 cohort studies were included and a fixed effect model was applied which presented the following results of relative risk of 0.59 (95% CI, 0.56–0.62), which suggested that the risk of PD was 41% lower in ever smokers compared with never smokers. There was a significant decrease in the risk of developing the disease among the current smokers and also those who previously smoked.

These results provide inverse evidence to establish a correlation between smoking and Parkinson's disease. The present meta-analysis is performed to identify the clinical association between cigarette smoking and symptoms of Parkinson's disease from the various observational studies i.e., case-control studies are taken into consideration and the results were obtained accordingly.

II. MATERIALS AND METHODS

Search strategy: Search strategy was developed based on a meta-analysis that had a positive correlation between smoking and reduced risk of Parkinson's disease. The studies which were published between October 2008 to October 2018 were searched and selected from science direct Springer, American journal of epidemiology, Pubmed, back-references, and scholarly publications from other science databases. Search strategies like Parkinson's disease and smoking, nicotine and Parkinson's disease and nicotine, tobacco, etc. out of these observational studies were chosen i.e. case-control studies which were foreseen for bias and were crosschecked for errors, and then these were selected using certain predetermined criteria which had an association between the smoking and Parkinson's disease.

Selection criteria (inclusion and exclusion criteria):

- The present meta-analysis included the studies which were selected depending on the following criteria such as those which presented the results to avoid publication bias.
- Studies were case-control and had cases of those diagnosed with Parkinson's disease by the physician.
- Those which compared the association using odds ratio and 95% CI in their results.
- And subjects without PD and subjects without gout were used as control groups in case-control, respectively.

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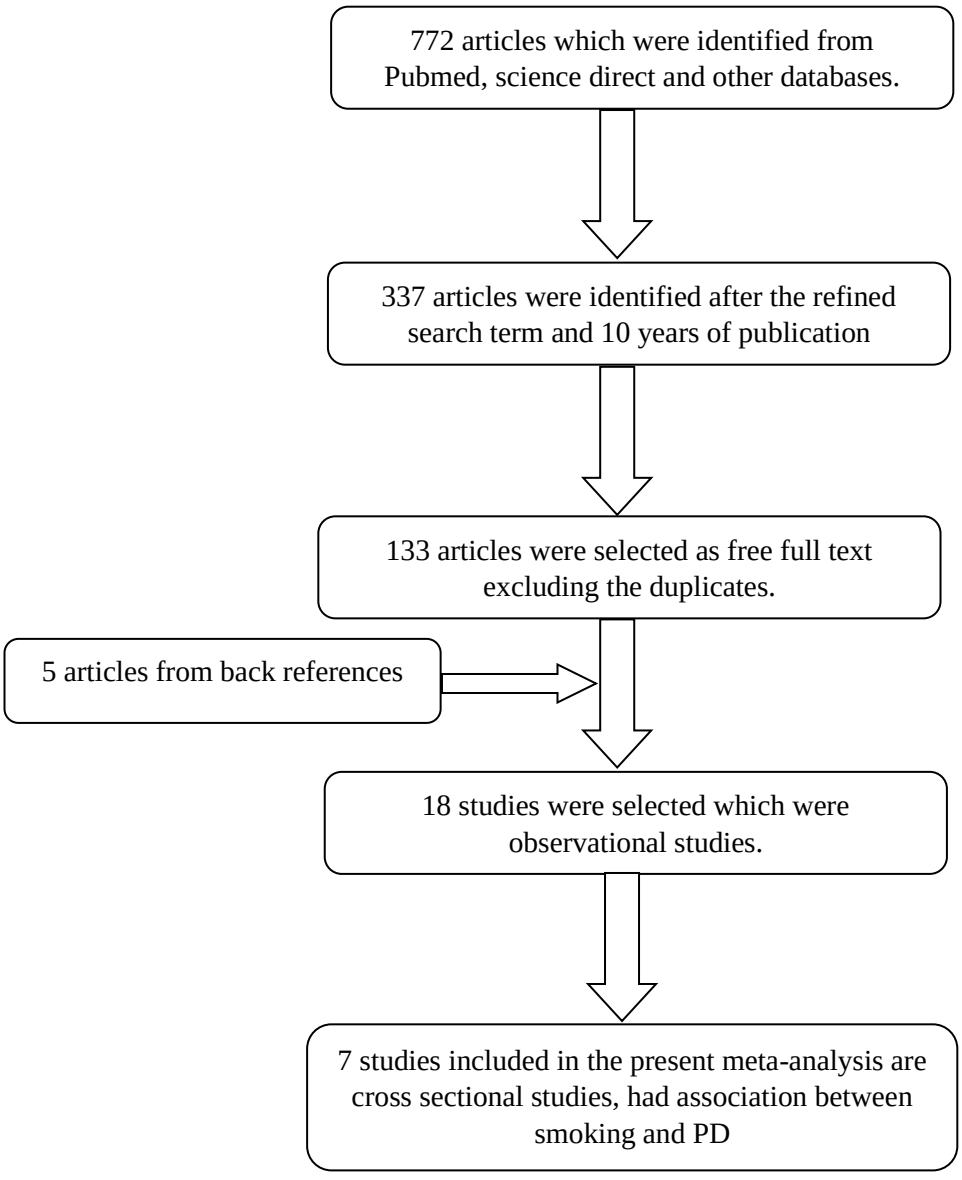
- The exclusion of those studies did not measure the association between smoking and PD.
- Studies were excluded also depending on prominent or early signs of more extensive nervous system involvement not explained otherwise (e.g., dementia, dysautonomia) i.e., which were not related to PD.

Data extraction and statistical analysis:

Data extraction: A standardized data collection strategy was used to extract the following information: last name of the first author, the title of the study, year of publication, the year when the study was conducted, country of study, study size, study population, the method used to diagnose Parkinson's disease, the average duration of follow up, baseline characteristics for each group, confounders that were adjusted and adjusted effect estimates with 95% CI. Those results were published in more than one study the data was extracted only from those studies which had the complete information. And PD risk among never smokers with that among ever, past, or current smokers, and adjustment factors and the association which was calculated by (odds ratio and CI 95%).

Statistical analysis: Statistical analysis was performed using comprehensive meta-analysis software which included the selected studies' pooled odds ratio with a CI of 95% after obtaining all the results of the studies with their upper and lower limits of the confidence interval the data was collated and analyzed for Z-value, p-value, and standard error to find the association between smoking and Parkinson's disease.



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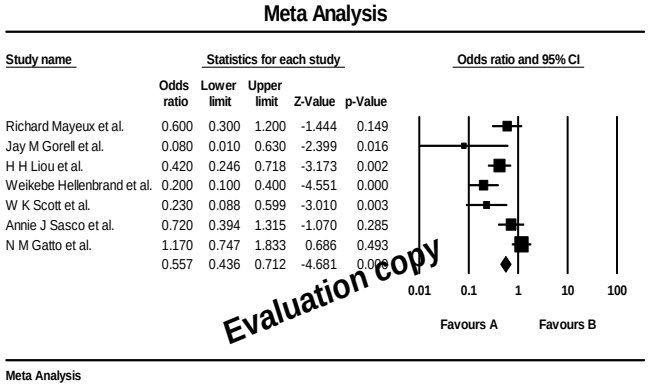
III. RESULTS

772 articles were identified from the refined search strategy which was applied 337 relevant articles were identified (including Pubmed and science direct and other databases) and 157 articles were identified as free full text 5 articles from the back-references were included and only 18 of them were observational studies and 7 out of these were cross-sectional and are included in the present meta-analysis which included the odds ratio and 95% CI and had an association between smoking and Parkinson's disease. The data of these obtained studies were pooled and analyzed using comprehensive meta-analysis software the results obtained were as follows OR 0.557 at 95% CI (0.436-0.712) the Z-value obtained was -4.681 and the p-value was 0.000 which showed an association between smoking and Parkinson's disease i.e., the patients who had Parkinson's disease and who smoke had a lower risk in the progression of their disease when compared with the controls.

IV. DISCUSSION

The etiology of Parkinson's disease is however not well established many factors are found to have an association with Parkinson's disease. Among all these factors cigarette smoking is found to have a relation to PD. The results presented from the previous meta-analysis (Xiao L et al.) show the correlation between smoking and reducing the risk of PD i.e. as smoking has a protective effect in patients with PD.

The present results from the meta-analysis which pooled the results of 7 studies taking into consideration of Odds ratio and CI of 95% had an association between smoking and PD this proves there was a lower risk in the participants with PD who smoked as nicotine had a protective effect on the dopaminergic system and reducing symptoms associated with the disease. When the forest plot was obtained for the results of case-control studies the results were obtained as follows which had a p-value of 0.000 which showed there is a significant association between smoking and Parkinson's disease.



Meta Analysis

Biological mechanisms involved in PD include damage to the dopaminergic neurons. It is characterized by progressive neuronal damage in the nigrostriatal pathway and the prevalence is most among 55-65 years of age leading to symptoms such as rigidity, bradykinesia, etc. cigarette smoke has more than 5000 chemicals in it. Nicotine plays an important role in Parkinson's disease when compared to other chemicals. It is involved in the regulation of the nigrostriatal pathway which is being mediated through the dopaminergic system, cigarette smoking results in the activation of nicotinic acetylcholine receptors (nAChRs) on dopaminergic nerve terminals which modulates dopamine release. Nicotine also plays an important role in preventing striatal damage which is induced due to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) results in further improvement in motor function.

A case-control study with 196 participants had shown tobacco use, including tobacco chewing or snuffing use, is inversely associated with the risk of PD (O'Reilly EJ). In a cohort study with 9 years of follow-up, men who were current users of smokeless tobacco at enrollment had a significantly lower risk of PD mortality (age-adjusted RR = 0.22, 95% confidence interval (CI), 0.07 to 0.67) (O'Reilly EJ). Another prospective cohort study with 307 PD cases also had a similar inverse association between snus use and PD in men (Liu Z, Roosaar A). Subsequently, in a case-control study based on 154 PD cases from Washington State, environmental tobacco smoke exposure was associated with a 64% lower risk of PD (Searles Nielsen S). Among persons with passive smoking as the only tobacco smoke exposure, the risk was inversely associated with years exposed (Searles Nielsen S). One cohort study using parental smoking as tobacco exposure has also shown the dose-response inverse association with PD incidence (O'Reilly EJ).

Since smoke has dependably appeared as a reason for antagonistic well-being results, the reverse relationship between smoking and the danger of PD was bizarre. Some studies yet proved this relation true as an impact of a genuine natural defensive effect of cigarette smoking.

However, some researchers propose the relation between smoking and PD due to bias. For example, a recent study reported that patients with PD were able to quit smoking more easily than controls (Ritz B, Lee PC). This study suggests that the ease of smoking cessation is an early manifestation of pre-motor PD related to the loss of nicotinic rewards. In this case, quitting smoking could be just a pre-clinical marker rather than a risk factor. However, in a case-control study in France, with 247 cases and 676 controls, when smoking was defined as cigarette smoking 18 years before PD onset, the same inverse association was still present (Moccia M, Erro R).

The exact molecular mechanism for the protective effects of smoking in PD remains to be clarified, and more research on these biological mechanisms would be quite necessary.

V. CONCLUSION

The summarized results of the case-control studies from the present meta-analysis prove that there is a correlation between smoking which is a protective factor against Parkinson's disease. Thus the protective effect was found to be to a greater extent in the case-control and cohort studies and the results were proven to be more significant in men than in women according to the no of pack years and the cigarettes smoked. However, it was an inverse relationship was found with the number of pack years. Due to the serious health hazards which are being caused due to cigarette smoking which leads to other co-morbid conditions it is not much recommended. It is more beneficial than pharmacological therapy with different classes

of drugs that can be further adulterated and developed with the constituents derived from tobacco and tobacco and smoke. In addition, the exact molecular mechanism for the protective effect of smoking remains to be clarified. Mechanistic studies in the future will be quite important to understand the role of smoking in PD development and lead to advances in the prevention and treatment of PD.

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Conflict of Interest: There are no specific financial or non-financial potential conflicts of interest.

Author Contribution: Author Study design, data search and collection, statistical analysis, writing manuscript.

Disclosure: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethic: This study did not directly involve human subjects and was exempt from ethical approval.

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