DOI: *http://dx.doi.org/10.18502/cjn.v22i4.14530*

Current Journal of Neurology

Review Paper

Curr J Neurol 2023; 22(4): 249-54

Olfactory dysfunction in patients with Parkinson's disease: A systematic review and meta-analysis

Received: 09 June 2023
Accepted: 13 Aug. 2023

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Keywords
Parkinson Disease; Olfactory; Prevalence; Review

Abstract

Background: Parkinson's disease (PD) is a progressive neuro-degenerative disease and olfactory dysfunction is considered as an important issue in these patients. The prevalence of olfactory dysfunction in patients with PD was reported variously in previous studies. Therefore, we designed this systematic review and meta-analysis to estimate the pooled prevalence of olfactory dysfunction in patients with PD.

Methods: Two expert researchers systematically searched PubMed, Scopus, EMBASE, Web of Science, Google Scholar, references of the papers, and conference abstracts. The titles and abstracts of the potential studies were evaluated after deleting the duplicates. We extracted data regarding the total number of participants, first author, publication year, the country of origin, mean age, mean disease duration, female/male, number with olfactory dysfunction, and name of the test. We evaluated the risk of potential bias by the Newcastle-Ottawa Quality Assessment Scale (adapted for cross-sectional studies). All statistical analyses were done using Stata software. To determine heterogeneity between the findings of included studies, inconsistency (I^2) was calculated. We applied random effect model when I^2 was more than 50%. P-value less than 0.05 was considered significant.

How to cite this article: Bagherieh S, Arefian NM, Ghajarzadeh M, Tafreshinejad A, Zali A, Mirmosayyeb O, et al. Olfactory dysfunction in patients with Parkinson's disease: A systematic review and meta-analysis. Curr J Neurol 2023; 22(4): 249-54.

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Results: The literature search revealed 1546 studies; after deleting duplicates, 894 remained. Finally, twelve studies remained for meta-analysis. Studies were published between years of 2009 to 2021, the sample size of studies ranged between 30 and 2097, and the mean age ranged between 61 and 70 years. The pooled prevalence of olfactory dysfunction in patients with PD was estimated as 64% [95% confidence interval (CI): 44-84, I^2 = 99.7%, P < 0.001]. The pooled prevalence of olfactory dysfunction using Sniffin's test was 67% (95% CI: 51-83) and using other tests was 60% (95% CI: 28-92).

Conclusion: The results of this systematic review and meta-analysis showed that the pooled prevalence of olfactory dysfunction in patients with PD was 64% which should be considered by physicians.

Introduction

Parkinson's disease (PD) is a progressive neuro-degenerative disease characterized mostly by bradykinesia, rest tremor, and rigidity.[1,2] Its prevalence is estimated between 113 and 873 cases per 100000 people, while its prevalence is reported to be higher in Europe and the lowest in Asia.[1] In addition to motor dysfunction, patients with PD suffer from autonomic, olfactory, and sensory changes, although they are not fully understood and considered.[3-8] These symptoms affect the quality of life and may interfere with daily activities. Olfaction is impaired since the early stages of the disease and is markedly reduced in PD. The prevalence of olfactory deficit is reported between 45%-90% in PD.[7,9,10] It has been shown that olfactory dysfunction does not fluctuate during ON and OFF periods of levodopa which indicates that it is not fully related to dopaminergic dysfunction[9] and cholinergic pathways degeneration is considered the underlying pathologic explanation.[11] In a post-mortem study which was conducted by Ross et al., it was suggested that patients with olfactory deficits had greater risk of developing symptomatic PD.[12] On the other hand, olfactory dysfunction was associated with a cognitive deficit and a marker of cortical atrophy.[13,14] Therefore, it appears that considering olfactory dysfunction is crucial in patients with PD from the early stages.

The prevalence of olfactory dysfunction in patients with PD was reported variously in previous studies. Hence, we designed this systematic review and meta-analysis to estimate pooled prevalence of olfactory dysfunction in patients with PD.

Materials and Methods

Two expert researchers systematically searched PubMed, Scopus, EMBASE, Web of Science, Google Scholar, references of the papers, and conference abstracts. The titles and abstracts of the potential studies were evaluated after deleting the duplicates. Afterward, they screened the full texts and examined the potential to include them in the study. Discripancies between two researchers were solved by the third expert researcher. Each researcher extracted data independently which were checked by the third party.

We extracted data regarding the total number of participants, first author, publication year, the country of origin, mean age, mean disease duration, female/male, number with olfactory dysfunction, and name of the test.

The Medical Subject Headings (MeSH) terms which were used for searching in the PubMed were:

("olfaction disorder", "smell disorder", "smell dysfunction", "olfactory agnosia", "agnosias for smell", "dysfunction AND smell", "olfactory impairment", "impairment AND olfactory", "sense of smell", "smell sense", "loss of smell", "smell loss", "cacosmia", "dysosmia", "anosmia", "paraosmia", "hyposmia", "agnosias", "agnosia AND olfactory") AND ("idiopathic Parkinson disease" OR "Lewy body Parkinson disease" OR ("Parkinson disease" AND idiopathic) OR ("Parkinson disease" AND "Lewy body") OR ("Parkinson disease" AND Idiopathic) OR "Parkinson disease" OR "idiopathic Parkinson disease" OR "Lewy Body Parkinson Disease" OR "primary parkinsonism" OR (Parkinsonism AND primary) OR "paralysis agitans" OR "Parkinson").

Inclusion criteria were: Studies reporting the prevalence of olfactory dysfunction in patients with PD and studies published before February 2022.

Exclusion criteria were: Case reports, case series, studies which were published in other languages except for English.

Risk of bias assessment: We evaluated the risk of potential bias by the Newcastle-Ottawa Quality Assessment Scale (adapted for cross-sectional studies). It includes 4 questions regarding screeening (maximum: 5 scores), one about comparability (maximum: one score), and two about outcome (maximum: three scores). Final score is the sum of all scores, and the higher the score, the better the quality of the study.[15]

All statistical analyses were done using Stata software (version 14, Stata Corporation, College Station, TX, USA).

To determine heterogeneity between the findings of included studies, inconsistency (I^2) was calculated. We applied random effect model when I^2 was more than 50%. Forest plot was drawn to demonstrate the prevalence of olfactory dysfunction as well as showing heterogeneity.

We did subgroup analysis by considering two groups (group one studies which had used Sniffin' Sticks for olfactory evaluation and the group two which had used other tests for olfaction). P-value less than 0.05 was considered significant.

Results

Two independnet researchers conducted systematic search on January 31, 2022. They imported the results in EndNote.

A literature search revealed 1546 studies, after deleting duplicates, 894 remained. They screened titles and abstarcts, and deleted 661 (475 were not relevant, 34 were animal studies, 18 were review articles, and 56 were published in other languages). They also screened full texts and excluded 221 studies. In the case of discrepancies, they asked the third one to help them. Finally, twelve studies remained for meta-analysis (Figure 1).

Studies were published between 2009-2021, the sample size ranged between 30 and 2097, and mean age ranged between 61 and 70 years

The most common sites of the studies were Germany and the United States of America (USA), and in all studies, men were dominant. The Newcastle-Ottawa Scale (NOS) of included studies ranged between 6 and 8 indicating that high quality studies were included (Table 1).

The prevalence of olfactory dysfunction in included studies ranged between 6%-96%, and the pooled prevalence of olfactory dysfunction in patients with PD was estimated as 64% [95% confidence interval (CI): 44-84, I^2 = 99.7%, P < 0.001] (Figure 2).

The pooled prevalence of olfactory dysfunction using Sniffin's test was 67% (95% CI: 51-83) and using other tests was 60% (95% CI: 28-92) (Figure 3).

Discussion

The results of this systematic review and meta-analysis showed that the pooled prevalence of olfactory dysfunction in patients with PD was 64%, ranging between 40% and 98%.

The difference between the results of the included studies is based on the types of applied tests, various inclusion and exclusion criteria, and different duration and severity of the disease.

In a study by Camargo et al. in Brazil, forty two patients with PD were selected. The prevalence of olfactory dysfunction was 95% among patients.[16]

Using Sniffin's test, Haehner et al.[17] enrolled 400 patients with PD and reported olfactory dysfunction in 45%, while in a later study, Casjens et al.[18] found olfactory dysfunction in 56%. Application of University of Pennsylvania Smell Identification Test (UPSIT) by Kanavou et al.[1] and Haugen et al.[19] demonstrated the prevalence of olfactory dysfunction as 96% and 98% in patients with PD, respectively.

Our sub-group analysis showed that the pooled prevalence of olfactory dysfunction was higher when researchers used Sniffin's test versus other tests [UPSIT, non-motor symptoms questionnaire (NMSQ), and non specific test].

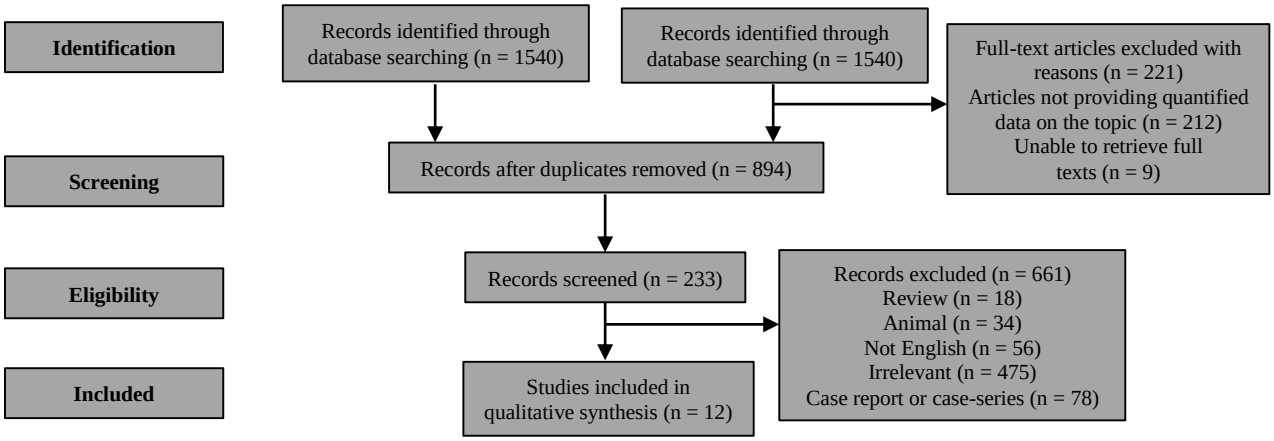

Figure 1. Flow diagram of included studies

Table 1. Data extracted from included studies

Author	Country	PD total	Female/ male	Mean age (year)	Mean disease duration (year)	Olfactory dysfunction	Name of the test	NOS score
Kanavou et al.[1]	UK	2097	735/1362	NA	NA	2023	UPSIT	7
Domellof et al.[13]	Sweden	125	NA	NA	NA	91	Sniffin' Sticks	6
Camargo et al.[16]	Brazil	42	16/26	70.6 ± 10.6	NA	40	Sniffin' Sticks	7
Haehner et al.[17]	Germany	400	137/263	64.3, range: 33-85	6.6, range: 0.5-30	180	Sniffin' Sticks	8
Casjens et al.[18]	Germany	148	70/78	Median: 67 (IQR: 59-73)	NA	84	Sniffin' Sticks	7
Haugen et al.[19]	USA	183	44/139	67.0 ± 8.3	6.4 ± 4.3	179	UPSIT	6
Roos et al.[20]	Netherlands	63	21/42	65.9 ± 8.5	10.6 ± 6.5	43	Sniffin' Sticks	8
Kulick et al.[21]	USA	199	84/115	NA	NA	12	NMSQ	7
Krismer et al.[22]	Austria	67	23/44	NA	NA	41	Sniffin' Sticks	8
Zhang et al.[23]	China	1119	542/577	61.3 ± 10.3	NA	450	NMSQ	7
Lopez et al.[24]	Spain	30	8/22	70.0 ± 10.0	2.1 ± 0.9	21	Sniffin' Sticks	6
Muller et al.[25]	Norway	207	NA	NA	NA	122	Olfactory test (vanilla, coffee)	7

UPSIT: University of Pennsylvania Smell Identification Test; NMSQ: Non-motor symptoms questionnaire; IQR: Interquartile range; PD: Parkinson's disease; NOS: Newcastle-Ottawa Scale; NA: Not available

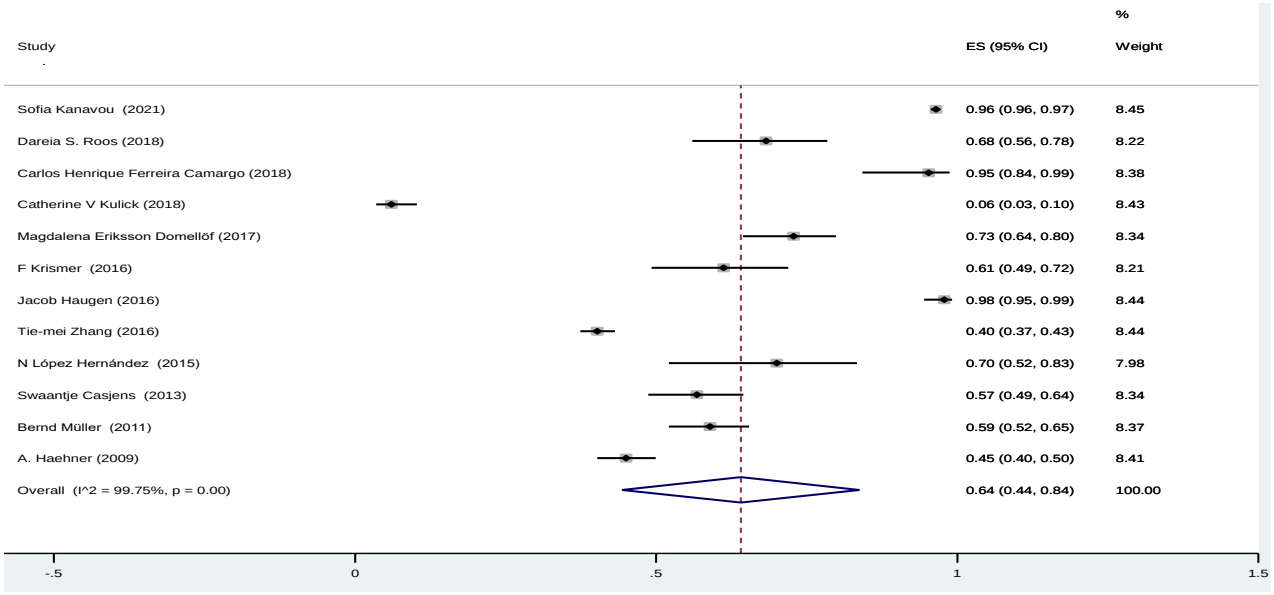

Figure 2. The pooled prevalence of olfactory dysfunction in patients with Parkinson's disease (PD)

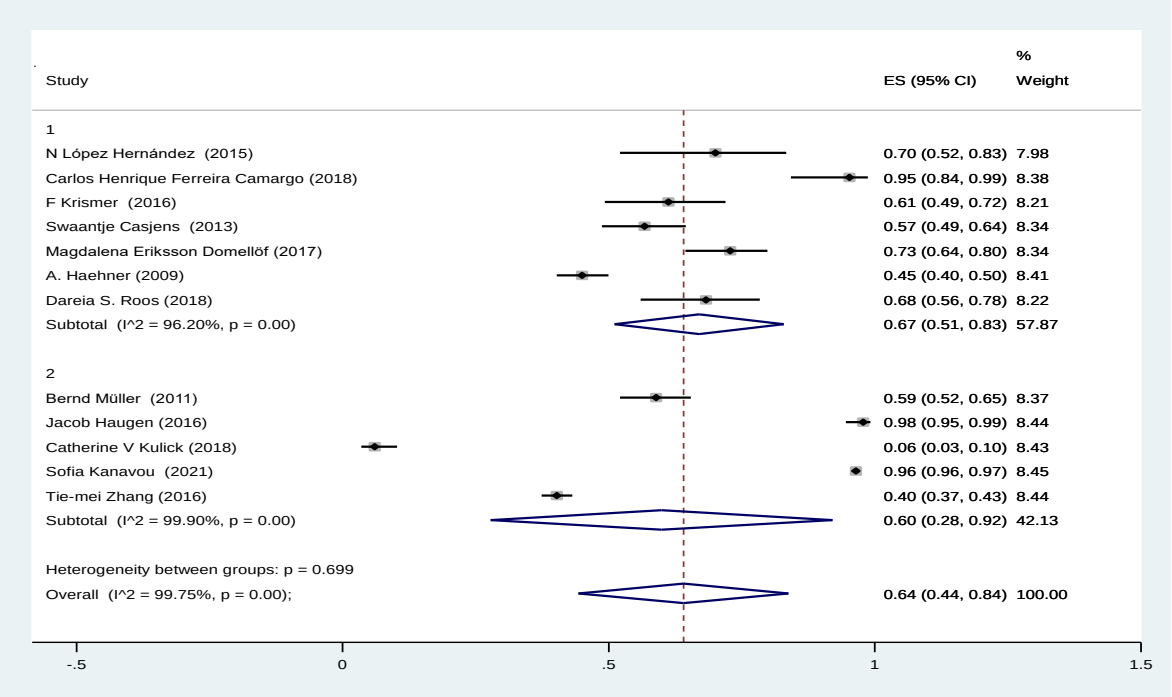

Figure 3. The pooled prevalence of olfactory dysfunction using different tests

The Sniffin' Sticks test was developed in 1997, which is a semi-objective evaluation of the patient's olfactory performance. It has three subtests: threshold test, identification test, and discrimination test. It could be used to monitor the course of these performances during chronic diseases such as PD.[26]

Olfactory dysfunction usually occurs during aging and the odds is 15 times higher at age 90 over 60, and men are more affected.[27] It is shown that regardless of applied test, more than 80% of patients with PD with smell loss are functionally anosmic or severely hyposmic.[17] It is also demonstrated that there is no consensus regarding the relationship between olfactory dysfunction and disease duration, or severity of the disease.[17,28,29]

Olfactory dysfunction in patients with PD includes impairments of odor identification and discrimination performance[30] which could be perceived at the early stages of PD when motor symptoms are detected. Camargo et al. found a correlation between olfactory deficit and attention loss while they investigated no correlation betweeen cognitive tests and the Sniffin' Sticks test.[16]

It should be noted that olfaction is based on learning and memory.[16] In patients with PD, dopaminergic denervation in the hippocampus as well as cholinergic pathways reduction in the archicortex will result in reduced archicortex capacity to recognize odors and finally hyposmia.[11,31]

In a neuroimaging study, Hanganu and Monchi found that in patients with PD who had a cognitive deficit, the parahippocampal gyrus, and middle and superior temporal gyri were affected, which play role in memorization and olfaction processes.[32] In another study, Damholdt et al. enrolled three groups (PD with anosmia, PD without anosmia, and healthy subjects). They found that memory, processing speed, and language were declined in the first group.[33] Fullard et al. suggested that in early stages of PD, olfaction could be noticed as the sensitive marker of memory deficit.[34] For olfaction, sensory processing as well as cognitive well-being (memory) is required. Therefore, olfactory dysfunction could be indicative of extranigral pathology which is related with cortical impairment.[34] Olfactory evaluation should be considered by physicians in patients with PD.

This study had some limitations. First, all studies did not apply the same test. Second, data regarding disease duration and disease severity were not provided by all studies. If they were available, we could do more subgroup analysis.

Conclusion

The results of this systematic review and meta-analysis showed that the pooled prevalence of olfactory dysfunction in patients with PD was 64% which should be considered by physicians.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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