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Review article

Volatile organic compounds analysis as promising biomarkers for Parkinson's disease diagnosis: A systematic review and meta-analysis

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ABSTRACT

Objective: Researchers are investigating the potential of volatile organic compounds (VOCs) obtained from exhaled breath and sebum as non-invasive tools for early Parkinson's disease (PD) diagnosis. The present study aims to assess the feasibility of using VOC analysis for PD diagnosis and determine the overall diagnostic accuracy of the proposed tests.

Methods: We performed systematic searches based on the PRISMA guidelines to identify relevant studies on VOCs in PD diagnosis using exhaled breath or sebum samples. The selected articles were described, and meta-analysis was conducted on those that provided the sensitivity and specificity data.

Results: Out of 1268 articles initially identified, 8 met the inclusion criteria and provided specific sensitivity and specificity data for PD, which were included in the current meta-analysis. The pooled analysis of these findings showed a mean area under the receiver operating characteristic curve of 0.85, a sensitivity of 0.81 (95% confidence interval (CI): 0.72, 0.88), and a specificity of 0.76 (95% CI: 0.66, 0.84).

Conclusion: The analysis of VOCs in exhaled breath and sebum has shown promise as a new avenue for non-invasive diagnosis of PD. VOCs' ability to distinguish PD from healthy controls suggests their potential clinical application in screening for the disease. Consequently, VOCs hold significant potential as biomarkers for PD diagnosis and offer a promising novel approach to identifying and diagnosing the condition.

1. Introduction

Parkinson's disease (PD) is the second-most common neurodegenerative disease, with a significant rise in prevalence over the past three decades [1]. PD is characterized by the progressive degeneration of both dopaminergic and non-dopaminergic neurons, predominantly in the brainstem [2]. The spectrum of PD symptoms varies from one individual to another, depending on the extent of impairment in motor and non-motor functions. Nonmotor manifestations of PD are very diverse, including cognitive decline, psychiatric problems, autonomic dysfunction, gastrointestinal issues, sensory symptoms, sleep disturbance, fatigue, and impaired sense of smell [3]. Moreover, the primary motor symptoms are slowed movement (bradykinesia), tremors, muscle rigidity, and postural instability [4].

Early detection, coupled with timely medical, psychological, and social interventions, holds the potential to greatly benefit PD patients and enhance their overall quality of life. Timely management of PD will alleviate symptoms, and extend their survival time, despite the presence of no effective cure. Therefore, it is crucial to diagnose PD accurately. Several diagnostic tools, including dopamine transporter single-photon emission computed tomography (DAT-SPECT), magnetic resonance imaging (MRI) morphometry, brainstem auditory evoked response

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(BAER), and cardiac iodine meta-iodobenzylguanidine (MIBG) scan have been used for identifying PD in the early stages. However, each of these tools has its advantages and disadvantages, and none of them has the accuracy for a definite PD diagnosis [5–8]. Therefore, due to the lack of a specific diagnostic tool, PD diagnosis is clinical-based, and the efforts for the development of the biomarkers for the definite diagnosis are ongoing [9].

Volatile Organic Compounds (VOCs) refers to a diverse assemblage of carbon-derived compounds, encompassing ketones, alcohols, aldehydes, hydrocarbons, isocyanates, terpenes, sulfides, and amines. VOCs are emitted by the human body and introduced into the circulatory system, where they are distributed through biofluids or respired into the lungs. VOCs have been extensively investigated across various matrices, such as exhaled breath, blood, urine, saliva, sweat, and fecal matter [10]. Despite the increasing clinical attention toward VOCs and body odors, research to validate these volatiles as diagnostic markers remains limited concerning quantity or quality. The potential use of VOCs, as non-invasive biomarkers for disease has been recognized since the time of Hippocrates, who described the distinctive scent of Melaena in 400 BC. Diabetes patients are described in ancient Chinese medicine as having decaying apple odor in their urine [11]. Recent research has explored the possibility of detecting various diseases, including tuberculosis, cystic fibrosis, and various types of cancer, through the analysis of volatile metabolites [12,13]. Studies have shown that people with PD have unique "odor fingerprints" that can be detected using specialized equipment [14]. PD can cause the production of a distinctive odor through changes in the body's metabolic processes. As reported in a study by Shao and Le [15], there have been a few metabolomics studies on PD using various biofluids such as blood, fecal, mouth saliva, urine, and cerebrospinal fluid. As a Super Smeller whose husband Les had been diagnosed with PD in 1986, Joy Milne has shown an unusual capability to detect Parkinson's disease by smell [16].

There have been several investigations to discover volatile biomarkers of PD [14,17,18]; Tisch et al. [19] conducted a study investigating the utilization of VOCs to diagnose PD patients in comparison to healthy controls (HC). The research on the diagnostic characteristics of VOCs in PD is still in its early stages, and VOCs are not widely available as a diagnostic tool. However, VOC analysis has the potential to offer a cost-effective and non-invasive way to diagnose PD. VOC analysis may allow future disease stratification by providing insights into molecular alterations.

The body of research on VOCs for the early diagnosis of PD is steadily expanding. In this study, we summarized current knowledge regarding their potential clinical applications. We performed a meta-analysis to assess the diagnostic power of these studies as a stepping stone for future research.

2. Method

2.1. Search strategies

This systematic review was completed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [20] with a PROSPERO ID: CRD42023426573.

Literature searches were conducted until 19 April 2023 in PubMed, EMBASE, Scopus, and Web of Science. At the same time, the references were manually checked for related articles and previous reviews to obtain relevant information. Keywords such as Parkinson, Parkinson's disease, PD, idiopathic Parkinson's disease, IPD, breath, and sebum, e-nose, electronic nose, volatile organic compounds, VOC, diagnosis, sensitivity and specificity, and ROC curve were applied as MeSH (Medical Subject Headings) terms and keywords, combined using AND/OR operators.

2.2. Study selection

The inclusion criteria of the related studies about VOCs in PD diagnosis were as follows: 1) observational studies: cohort, cross-sectional, or case-control; 2) population: confirmed PD; 3) studies that reported sufficient data to construct the 2×2 contingency table, including, true-, false-positive or true-, false-negative; 4) articles that examined VOCs in sebum or breath to diagnose PD.

The exclusion criteria were as follows: 1) review articles; 3) animal studies; 4) studies that analyzed VOCs from other biomarkers (including urine, blood, and/or feces).

2.3. Data extraction

Two reviewers used predefined inclusion and exclusion criteria to conduct a systematic screening and data extraction process. If there were any disagreements, discussions were held to reach an agreement. The extracted data included author details, country of origin, participant characteristics (such as drug-naive or medicated), disease type, methodologies used, techniques used, and the conclusions drawn in the respective studies. Furthermore, sensitivity and specificity values that could be used in meta-analysis were extracted.

2.4. Quality assessment

The methodological quality of the chosen articles was evaluated using a modified version of the Quality Assessment of Diagnostic Studies 2 tool (QUADAS-2). Hanna et al. [21] constructed this tool to enhance the quality assessment of the articles. The modifications made to the QUADAS-2 tool primarily focused on the importance given to the inclusion of benign conditions and healthy controls, internal and/or external validation of results, assessment before the therapeutic intervention, and reproducibility of the chosen index test.

Two independent reviewers (A.H. and R.T.) performed the quality assessment of the articles. Any disagreements were resolved through a consensus between them or discussed with a third author (V-R.O).

2.5. Statistical analysis

All statistical analyses were conducted using Stata MP 16.0 and MetaDiSc 1.40 statistical software. Effect sizes such as positive likelihood ratio (PLR), negative likelihood ratio (NLR), sensitivity, specificity, and diagnostic odds ratio (DOR) were computed based on the numbers of true positives, false positives, true negatives, and false negatives in PD patients and HC. Bivariate meta-analyses were conducted using the MIDAS package in Stata software to generate pooled point estimates of the summary receiver operating curve (SROC) for VOC analysis [22,23]. The Spearman correlation coefficient was applied using MetaDiSc 1.40 software to evaluate the threshold effect between the pooled sensitivity and 1-specificity. Inter-study heterogeneity was evaluated using the Q statistic (with a significance level of $P < 0.1$) and the I-square statistic (with an I^2 value $> 50\%$). Sensitivity analysis was performed using the leave-one-out method to assess the stability of the pooled results after removing each article. The potential evidence of publication bias was assessed using the Deeks funnel plot asymmetry test [24]. Furthermore, additional analyses, including meta-regression analysis and subgroup analysis, were conducted to detect sources of heterogeneity based on moderator variables in our meta-analysis.

3. Result

3.1. Description of included studies

The PRISMA flowchart (Fig. 1) showed our search strategy for this review. The present study included eight studies, including eight case control studies [14, 17, 19, 25–29]. As the research conducted by

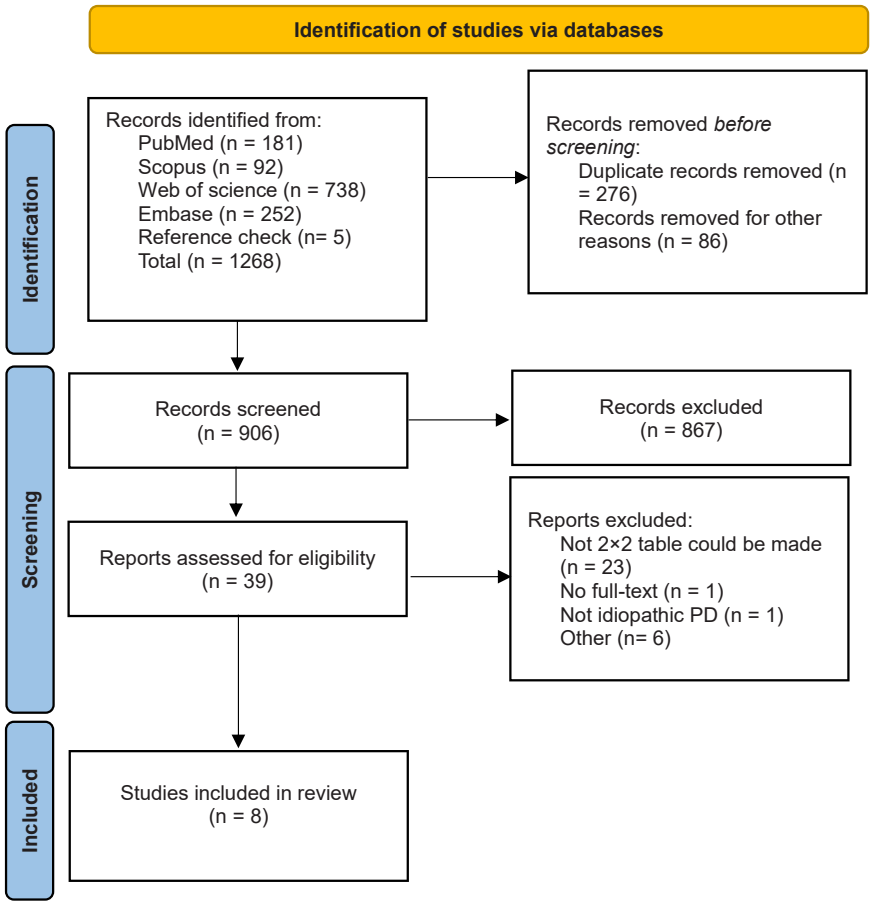

Fig. 1. PRISMA flow diagram for eligibility of studies.

Sinclair et al. was designed in 2 datasets [25], we analyzed nine datasets, including 886 participants. The eight studies were all published between 2012 and 2022. Fig. 1 shows the step by step of the search procedure. The main characteristics of the included articles were presented in Table 1. Of these articles, four were carried out in the United Kingdom (UK) [14,17,25,29], 2 in Israel [19,26], and the others were from Germany [27] and China [28]. Concerning the VOC sources, 4 studies measured VOCs in sebum [14,17,25,28] and four in breath [19,26,27, 29]. Concerning the analytical method, three studies (4 datasets) used the partial least squares discriminant analysis (PLSDA) modeling [14,17, 25], 3 studies used discriminant factor analysis (DFA) [19,26,29], and two studies [27,28] used other analytical methods, including machine learning. These studies utilized several analytical platforms, including gas chromatography-mass spectrometry (GC-MS), coupled with thermal Desorption (TD) or liquid chromatography (LC), ion mobility spectrometer (IMS), and sensor arrays. Assessment of biases and applicability on outcomes using QUADAS-2 are summarized in Table 2. No significant concerns regarding the applicability of the index test, reference standard, and flow and timing were identified, indicating that the overall methodological quality of the included articles was moderately high.

3.2. Diagnostic accuracy

Diagnostic accuracy assessment involves various indicators, including sensitivity, specificity, PLR, NLR, and DOR [30]. Fig. 2 presents the findings, indicating a pooled sensitivity of 0.81 (95% CI: 0.72 – 0.88) and specificity of 0.76 (95% CI: 0.66 – 0.84). Heterogeneity was

Table 1
Characteristics of included studies.

			Participants								
First Author	Year	Country	PD	HC	PD type	TP	FN	FP	TN	VOC source	Analytical platform
Trivedi et al.,[14]	2019	UK	43	21	PD mix	39	4	7	14	Sebum	TD–GC–MS
Tisch et al.,[19]	2012	Israel	30	12	PD medicated	21	9	0	12	Breath	GC-MS- SPME
Sinclair et al.,[17]	2020	UK	100	29	PD mix	90	10	10	19	Sebum	TD–GC–MS
Sinclair et al.,[25]	2021	UK	80	56	PD medicated	57	23	17	39	Sebum	MS
Sinclair et al.,[25]	2021	UK	138	56	PD naive	97	41	18	38	Sebum	MS
Finberg et al.,[26]	2018	Israel	29	19	PD naive	20	9	3	16	Breath	GC-MS and sensors
Bach et al.,[27]	2015	Germany	16	19	PD mix	16	0	0	19	Breath	IMS
Fu et al.,[28]	2021	China	12	12	PD mix	11	1	4	8	Sebum	GC
Stott et al.,[29]	2022	UK	177	37	PD mix	13	41	10	27	Breath	GC-MS

Abbreviations: Parkinson's disease (PD), Healthy controls (HC), Volatile organic compound (VOC), True positive (TP), True negative (TN), False positive (FP), False negative (FN), United Kingdom (UK), chromatography-mass spectrometry (GC-MS), thermal Desorption (TD), liquid chromatography (LC), ion mobility spectrometer (IMS), solid-phase micro-extraction (SPME).

Table 2
Quality assessment of included studies by using the QUADAS-2 tool.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Trivedi et al.	☺	☺	☺	☺	☺	☺	☺
Tisch et al.	☺	☺	☺	☺	☺	☺	☺
Sinclair et al.	?	☺	☺	☺	?	☺	☺
Sinclair et al.	?	☺	☺	☺	?	☺	☺
Sinclair et al.	?	☺	☺	☺	?	☺	☺
Finberg et al.	☺	☺	☺	☺	☺	☺	☺
Bach et al.	☹	☺	?	☺	☹	☺	?
Fu et al.	?	☺	☺	☺	?	☺	☺
Stott et al.	☺	☺	☺	☺	☺	☺	☺

☺ Low Risk ☹ High Risk ? Unclear Risk.

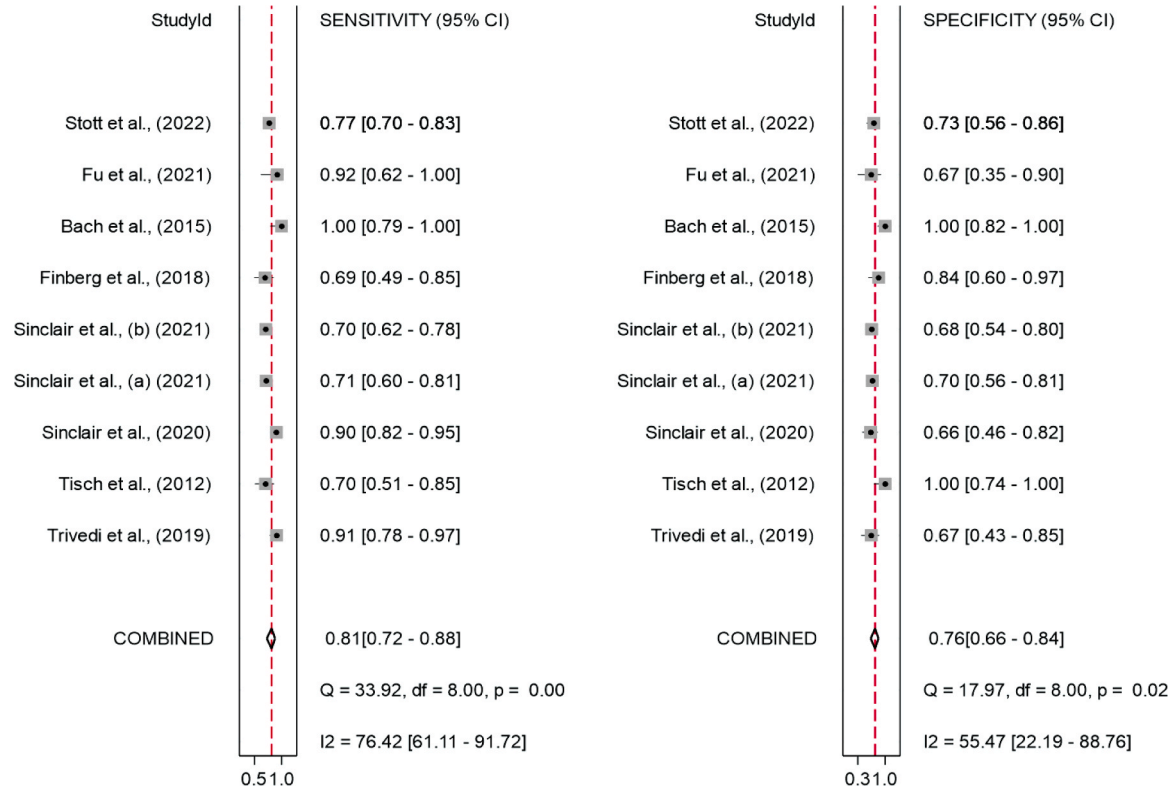

Fig. 2. Forest plots of the sensitivity and specificity for VOC analysis in the diagnosis of PD. Different heterogeneity was shown for pooled sensitivity and specificity (I2 =30.63% and I2 =67.59%, respectively). VOC = volatile organic compounds, PD= Parkinson's disease.

observed in the pooled specificity (I^2 = 55.47%, P = 0.02), and the pooled sensitivity showed even higher heterogeneity (I^2 = 76.42%, P < 0.01). The corresponding values for PLR, NLR, and DOR were 3.4 (95% CI: 2.3 – 5.0), 0.25 (95% CI: 0.16 – 0.38), and 14 (95% CI: 7 – 28), respectively [Suppl. FigS1 **A-B**]. In addition to these calculated measures, the SROC curve demonstrated satisfactory diagnostic

performance of VOC analysis in differentiating PD patients from HC, with an area under the curve (AUC) of 0.85 (95% CI: 0.82 – 0.88) (Fig. 3). Analyzing the included studies demonstrated moderate heterogeneity with a likelihood ratio test Chi-square (LRT-Q) P-value of 0.1 and an LRT-I^2 of 38%. Furthermore, no evidence of a threshold effect was found based on the Spearman correlation coefficient (P = 0.50) [Suppl. Table S1].

3.3. Meta-regression analysis

Meta-regression analysis was performed based on some of the moderator variables such as the location of study, type of substance, type of disease, and analysis method among included studies to detect sources of heterogeneity among studies. As shown in Table 3, meta-regression findings indicated that the location of the study, source of VOCs, and analysis method might be the source of inter-study heterogeneity. We could not conduct subgroup analyses due to insufficient included studies.

3.4. Sensitivity analysis and publication bias

We also conducted a sensitivity analysis among studies after removing each study to determine the reliability of the pooled results. The results showed that the pooled findings were reminded consistently without any change [Suppl. Fig S2]. The Deeks' regression test was performed to examine the evidence of potential publication bias. The test showed a significant publication bias among studies (P = 0.03) [Suppl. Fig S3].

4. Discussion

This study is the first meta-analysis to quantitatively examine the VOCs' capability as a novel biomarker for PD. It was discovered that sebum and exhaled breath VOCs efficiently discriminated individuals with PD from HC in 9 datasets, including 886 participants. The ROC curve was utilized to evaluate overall diagnostic performance. The AUC derived from the ROC curve was 0.85, indicating that VOC analysis has a moderate diagnostic value (AUC: 0.82–0.88). The DOR, which serves as a comprehensive measure of test accuracy [31], was found to be 14 in our included studies (DOR >10), indicating high discriminatory test performance. Additionally, likelihood ratios and post-test probabilities can provide insights into the presence or absence of PD based on positive or negative test results. In our pooled data, the PLR was 3.4, suggesting that individuals with PD are approximately 3.4 times more likely to yield a positive test result compared to HC. Similarly, the NLR was 0.25. These findings imply that VOC analysis is a potential and stable technique for screening for Parkinson's disease, but it is not a diagnostic tool in and of itself.

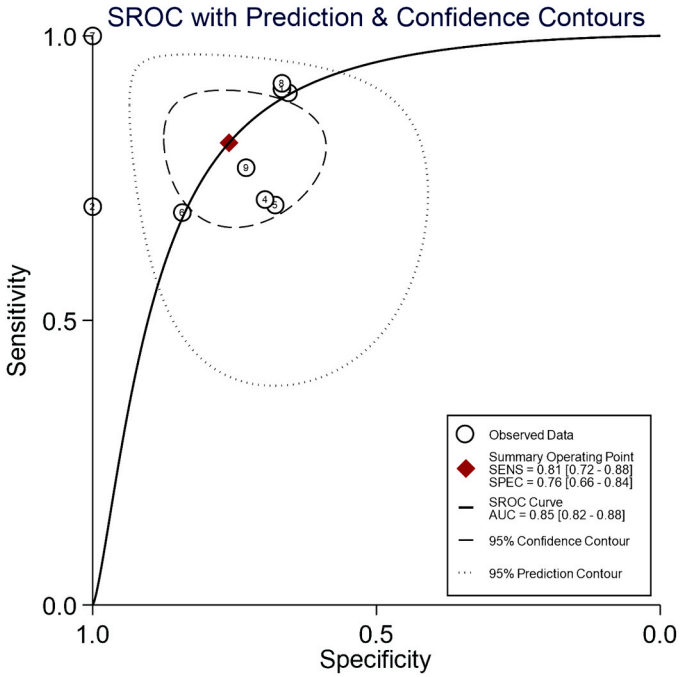

Fig. 3. Summary receiver operating characteristic graph of included studies.

These studies have revealed significant dysregulation of several compounds, shedding light on potential disease biomarkers. According to these studies, the average chemical composition of breath samples from PD patients differs from that of healthy controls. Notably, perillic aldehyde and eicosane have emerged as key differentiators, with perillic aldehyde levels found to be lower in PD samples and eicosane significantly higher in PD patients [32]. Furthermore, ceramide, triacylglycerol, and fatty acyl metabolites were downregulated in PD, whereas glycosphingolipid and fatty acyl metabolites were upregulated [33]. Further study focused on specific target compounds, such as octadecanal, eicosane, hippuric acid, and perillaldehyde, which are by-products of lipid peroxidation and have been linked to elevated levels in PD [34]. These findings highlight the complex interplay of VOCs in PD pathophysiology, as well as the potential for these compounds to serve as valuable diagnostic and investigative tools.

Previous meta-analysis supported VOCs' diagnostic potential as biomarkers for various diseases, including cancer [35], asthma [36], and other conditions [37].

A meta-analysis conducted by Wenchuan Zhou et al. yielded a pooled sensitivity of 0.82, a specificity of 0.79, a PLR of 3.8, and an NLR of 0.23. The AUC was 0.87. This study suggested the VOC analysis's potential as a colorectal cancer screening tool [38].

Another study by Hanna et al. assessed the diagnostic accuracy of VOCs breath tests for cancer detection. They found a sensitivity of 0.79 and a specificity of 0.89. This review emphasizes the importance of establishing standardized protocols for collecting breath samples and validating the accuracy of breath tests in diagnosing cancer [39].

Xiang et al. performed a meta-analysis of exhaled VOCs for the gastrointestinal cancer (GIC) diagnosis. Along with previous studies, they demonstrated that VOCs are promising new biomarkers for the GIC detection. The sensitivity, specificity, and AUC were 0.85, 0.89, and 0.93, respectively [40].

The main advantage of VOCs as biomarkers is the non-invasiveness and convenience of the sample collection. VOC analysis is appealing for clinical applications since breath, urine, and other biological fluids can be acquired relatively readily and non-invasively. This non-invasive approach decreases patient discomfort and allows for repeated assessments in the follow-up, allowing for longitudinal disease progression tracking [41].

PD diagnosis is heavily dependent on clinical evaluation, which is intrinsically subjective. Diagnoses can differ because different healthcare professionals interpret symptoms differently [42]. Aside from the subtle clinical presentations that are difficult to distinguish from other conditions, it can also be challenging to diagnose PD in its early stages [43]. The absence of objective biomarkers limits diagnostic accuracy and reliability, especially in the early stages of the disease. Diagnosis depends on clinical observations and excludes other conditions with similar symptoms. Healthcare settings are not universally accessible to particular diagnostic tools, such as dopamine transporter imaging with single-photon emission computed tomography (DaTSCAN) [44]. As a result of this limited availability and cost of the procedure, diagnosis may be delayed, particularly in the early stages of the disease[43]. Researchers are actively exploring biomarkers that could help diagnose PD. According to studies, individuals with PD may exhibit altered VOC patterns compared to healthy individuals and those with other neurodegenerative conditions [45,46].

Despite the potential benefits, several challenges must be overcome

Table 3
Meta-regression analysis of diagnostic effect.

Parameter	Category	Number of studies	Sensitivity	p-value	specificity	p-value
VOC source	Sebum	5	0.83	0.25	0.68	0.00
	Breath	4	0.79		0.85	
PD type	PD mix	5	0.87	0.53	0.75	0.19
	Naïve/medicated	4	0.71		0.77	
Country	UK	5	0.81	0.13	0.69	0.00
	Other	4	0.82		0.89	
Analysis method	PLSDA	4	0.82	0.14	0.68	0.00
	Other	5	0.80		0.83	

Data selection in meta-regression analysis of VOCs source: Samples in five datasets were from the same VOCs source group. Data selection in meta-regression analysis of PD type: Samples in five datasets were from patients with mixed or not mentioned status of the disease (naïve or medicated). Data selection in meta-regression analysis of countries: Five datasets were from the same countries. Data selection in meta-regression analysis of analysis method: Samples in five datasets were analyzed using PLSDA.

before VOCs can be established as reliable biomarkers for PD. Standardization of VOC analysis techniques and protocols is a crucial challenge [47]. Inconsistent and contradictory results can result from differences in sample collection, storage, and analytical methods between studies. It is critical to standardize findings in order to ensure reproducibility and comparability, allowing for robust and reliable diagnostic applications. [48,49]. Another challenge is identifying specific VOC biomarkers or patterns consistently associated with PD. Because of the complexity of VOCs profiles and the potential influence of confounding factors such as age, gender, medications, and comorbidities, identifying reliable and disease-specific VOCs signatures is critical. Large-scale studies with diverse populations, including both early- and late-stage PD patients, are necessary to validate and refine these biomarkers. Moreover, VOC-based diagnostic translation into clinical practice requires user-friendly and cost-effective analytical platforms. VOC analysis integration into routine clinical workflows necessitates the development of standardized, automated, and high-throughput technologies that reliably detect and quantify specific VOCs.

Study locations in volatile extraction and analysis play a significant role because specific methods employed in volatile extraction and analysis significantly influence their findings. Therefore, in future studies conducted in different countries, it is advisable to use the technique that demonstrates the highest diagnostic accuracy in PD detection. By doing so, heterogeneity among studies can be reduced, resulting in more precise conclusions regarding volatile compounds' diagnostic accuracy in PD. By considering potential regional variations, this approach facilitates a more accurate understanding of volatiles' diagnostic accuracy in PD.

The current study did not find the role of VOC analysis in discriminating between drug-naïve and medicated PD patients. Consequently, further studies are needed to identify specific VOCs that play a discriminatory role between these two groups. By focusing on this aspect, researchers can potentially discover VOCs that exhibit distinct patterns or levels in drug-naïve PD patients compared to those receiving medication. Our meta-analysis has some limitations. Firstly, the number of included studies and participants was small, which may have resulted in reduced statistical power. This limitation can be attributed to the novelty of employing VOCs for PD detection. Furthermore, different sampling methods, VOC analysis techniques, and patient characteristics may have influenced overall diagnostic performance in the included studies. As we found moderate heterogeneity, we performed further meta-regression to discover the heterogeneity's origin, which showed the location of study, source of VOCs, and analysis method might be the source of heterogeneity. The existing research on VOCs in PD lacks standardization in sample collection and analysis methods. This lack of standardization introduces variability in VOC analysis results, making it challenging to compare findings across studies. Therefore, future research efforts for establishing standardized protocols for VOC collection and analysis are mandatory to improve the results' reliability and comparability.

5. Conclusion

VOC analysis represents a promising avenue for the development of non-invasive and objective diagnostic tools in PD. Ongoing progress in the field of VOC analysis techniques, combined with collaborative research endeavors, holds significant promise for enhancing detection, precise diagnosis, and personalized management of PD. These advancements have the potential to significantly increase the quality of life for individuals affected by this neurodegenerative disorder.

Ethics approval

Not applicable.

Ethics approval and consent to participate

Not applicable.

CRediT authorship contributors statement

AH, V-R.O and RT completed the design, data analysis, and manuscript writing. A.H, O.K, and S.K contributed to the conception and revised the manuscript. R.T, S-S.M, and M-R.Z provided suggestions for revision of the manuscript. All authors contributed to the article and approved the submitted version.

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Declaration of Competing Interest

The authors declare that there is no conflict of interest.

Data Availability

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

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This study was conducted at the Noncommunicable Diseases Research Center of Fasa University of Medical Sciences, Fasa, Iran, with number: 402117.

Code availability

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2023.108022.

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