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REVIEW ARTICLE

Gustatory dysfunction is related to Parkinson's disease: A systematic review and meta-analysis

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Abstract

Background: Olfactory dysfunction has been reported to be involved in Parkinson's disease (PD) pathogenesis. However, gustatory dysfunction in PD has not been evaluated as in-depth as olfactory dysfunction. We reviewed the previously published studies regarding gustatory function in PD patients and suggested the possibility that gustatory dysfunction may also be associated with PD.

Methods: MEDLINE, Cochrane Library, Embase, and PubMed databases were searched for studies evaluating gustatory function in PD patients. We used the standardized mean difference and a 95% confidence interval (CI) as the effect analysis index regarding the taste strip test. The relative risk and 95% CI were used as the effect analysis index for the questionnaires and propylthiouracil (PTU)/phenylthiocarbamide (PTC) perception test. Statistical heterogeneity was assessed using forest plots, Cochran's Q, and the I^2 statistic; heterogeneity was considered high when I^2 was over 75%. Publication bias was assessed by funnel plots and the Egger bias test.

Results: We identified 19 articles that reported the results of gustatory function tests in PD patients and healthy controls. Most of these studies used various gustatory tests, including taste strips, questionnaires, taste solutions, PTU/PTC perception tests, and electrogustometry, and reported significantly lower gustatory function in PD patients than in the controls. However, several articles reported contradictory results.

Conclusions: Based on these studies, gustatory dysfunction is closely related to PD. However, the number of studies and enrolled subjects was small, and a unified gustatory function test was lacking. Therefore, further studies with larger populations and normalized gustatory function tests are needed.

KEYWORDS
gustatory dysfunction, meta-analysis, Parkinson's disease, systematic, taste

1 | INTRODUCTION

Parkinson's disease (PD) is clinically diagnosed when motor symptoms are visible. Yet, sensory symptoms may precede or present with the development of parkinsonism and are regarded as an integral part of PD-associated neurodegeneration.[1] Preceding or concurrent sensory symptoms can be helpful in the early diagnosis and understanding of PD pathophysiology.

Olfactory dysfunction (OD) is one of the most evaluated sensory symptoms and has been identified as a common symptom of PD. The prevalence of OD in PD has been reported to be between 75% and 90%, which is much higher than the 25% prevalence in the general population.[2] The presence of OD increases the risk of future development of PD.[3] OD usually occurs during the early stages and is helpful in the differential diagnosis of PD from other conditions, such as essential tremor and atypical parkinsonian disorders.[4–6] Therefore, OD is frequently evaluated, and olfactory function tests are usually recommended in patients suspected or diagnosed with PD.

More recently, gustatory dysfunction (GD) has been reported to be associated with PD; however, studies regarding GD in PD are relatively limited and report heterogeneous and contradictory findings. Several studies have reported that gustatory function was decreased in PD compared with the general population, and the prevalence has been reported to be between 9% and 54%.[7–9] However, in some studies, patients with PD showed a higher sensitivity in gustatory functions. For example, the identification test scores for all stimuli measured by whole-mouth taste were significantly lower for PD patients than the healthy controls, which suggests that PD patients had a more sensitive gustatory function than the controls.[10]

Therefore, we performed a meta-analysis to review published papers regarding GD in PD to evaluate whether GD is significantly associated with PD.

2 | MATERIALS AND METHODS

A systematic review was conducted using the meta-analysis protocol (PRISMA-P)[11] and Preferred Reporting Items for Systematic Reviews (PROSPERO CRD42021243325).

2.1 | Inclusion and exclusion criteria

All randomized controlled, cohort, cross-sectional, and case-control studies, including nested case–control studies, reporting gustatory function in patients with PD were included. We included only studies that performed gustatory function tests in patients with PD and compared the results with healthy control subjects. The exclusion criteria were: (1) review articles, case reports, commentaries, proceedings, laboratory studies, and other nonrelevant studies; (2) studies that did not include the result of gustatory function tests; and (3) studies reporting GD in animals. No language limitations or date restrictions were imposed.

2.2 | Search strategy

Two authors (IYK and HJM) searched publications from January 2000 to August 2022 in Cochrane Library, Embase, and PubMed using the keywords "Parkinson" AND "gustatory" OR "taste" OR "gustation." We also screened existing systematic reviews. The reference lists of the identified studies and eligible articles were searched manually.

2.3 | Study selection

The titles and abstracts of the collected studies were independently scanned by two authors (HJM and KSK) via the search strategies. The full paper was retrieved upon determining the study's eligibility. Potentially relevant studies selected by at least one author were retrieved, and the full-text versions were evaluated. The relevance of each study was discussed by the two authors (HJM and KSK) to arrive at a consensus regarding study inclusion or exclusion. Disagreements were settled via discussion with a third investigator (IYK). There were no objections to the final included studies by the three authors.

2.4 | Data extraction and quality assessment

All interrelated data were independently extracted from the included studies through a standardized form by two authors (HJM and KSK). The extracted data were cross-checked by the two authors (HJM and KSK). Article identifiers (authors, year of publication, and published journal), study identifiers (sample size, study design, country, inclusion criteria, definition, and criteria used for gustatory function), population information (age and sex), and outcome measurements (taste strip test scores, questionnaire scores, propylthiouracil [PTU]/phenylthiocarbamide [PTC] perception, whole-mouth spray test results, and electrogustometry [EGM] results were included in the standardized form. To evaluate the quality of case-control studies we utilized the Newcastle–Ottawa Quality Assessment Scale (NOS). The NOS evaluates the selection of cases and controls, comparability of cases and controls, and ascertainment of exposure. A study can be awarded a maximum of four stars for selection, two stars for comparability, and three stars for exposure. A higher number of stars means better quality of a study.[12]

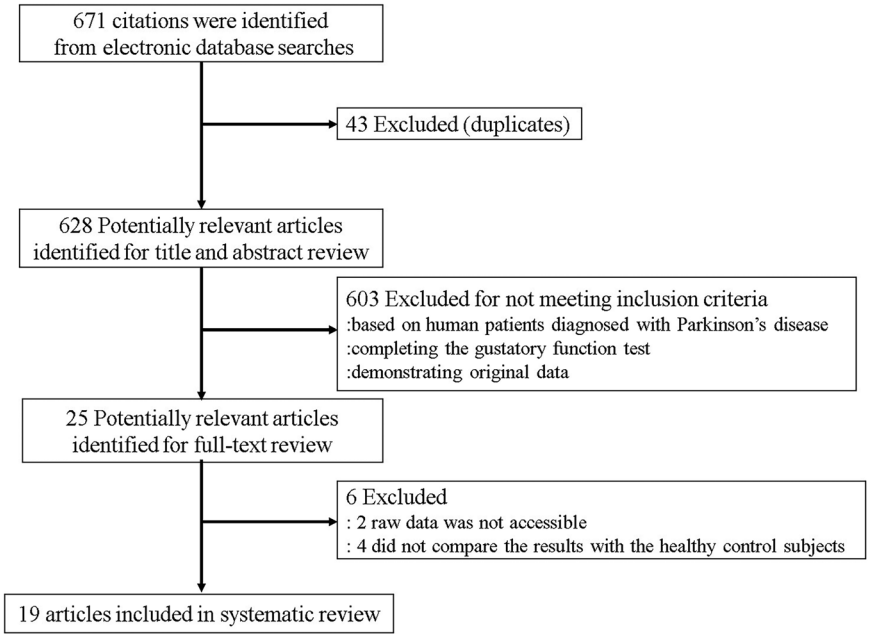

FIGURE 1 A flow diagram of the study selection process.

2.5 | Outcome measurements

Studies, including the results of taste strip tests, whole-mouth spray tests, and EGM, were reviewed. The raw data were expressed in continuous variables, and the bigger the scores were, the worse the gustatory function. Other studies, including questionnaires, were reviewed as binary outcomes, in which "yes" means there was subjective GD. Any results of PTU/PTC perception tests were reviewed as binary outcomes, in which "yes" means the subjects were tasters.

2.6 | Statistical analysis

A frequency analysis was performed on the outcomes used to measure the decrease in taste ability since there is no standardized research procedure for gustatory function. For the taste strip test, the standardized mean difference (SMD) and its corresponding 95% confidence interval (CI) were used as the effect analysis index. For the questionnaires, the relative risk (RR) and its corresponding 95% CI were used as the effect analysis index. Statistical heterogeneity was visually assessed using forest plots and formally assessed using Cochran's Q and the *I*2 statistic; heterogeneity was considered high for I^2 values greater than 75%.[13] Publication bias was assessed using funnel plots and calculating the Egger bias test.[14] Sensitivity analysis was not considered due to the small number of papers used for the meta-analysis. There were only five papers that utilized taste stripe tests, four that utilized questionnaires, and two that utilized PTU/PCT perception tests. All analyses were performed using metafor and meta packages in R version 4.2.1.[15]

3 | RESULTS

3.1 | Search results

We identified 671 potentially relevant studies from the database search. After excluding 43 duplicates, 628 records were screened based on their titles and abstracts. Of these, 603 studies were excluded because they did not meet the inclusion criteria or they met the exclusion criteria. The full texts of the remaining 25 studies were reviewed in detail. Six studies were excluded for the following reasons: (1) raw data were not accessible ($n = 2$)[14,15,6] and (2) the gustatory function was not compared with the healthy control subjects ($n = 4$).[16–19] Therefore, 19 studies were included in this systematic review and meta-analysis (Figure 1, Supplementary Table S1).[7,10,20–36] No studies were found to have a high risk of bias after performing a quality assessment using the NOS (Supplementary Table S2).

3.2 | Frequency analysis on outcomes

The studies included in this meta-analysis used various taste-testing methods to measure gustatory function, including taste strip tests, questionnaires, PTU/PTC perception tests, EGM, and whole-mouth spray tests. Figure 2 represents the number of relevant studies based

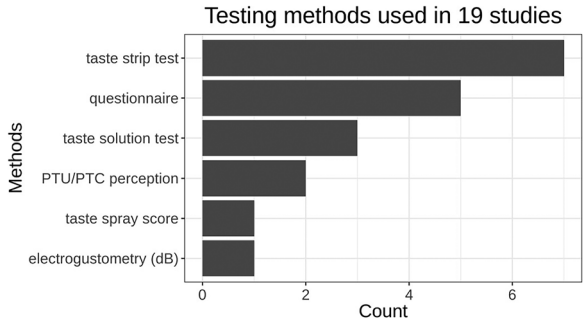

FIGURE 2 The number of different taste-testing methods used in the studies comparing taste changes in the Parkinson's disease (PD) and the non-PD groups. PTU, propylthiouracil; PTC, phenylthiocarbamide.

on taste-testing methods. Among the various methods, the taste strip test was the most common taste-testing method (seven studies).[20,21,23,27,32,34,36] Questionnaires were the second most common method (five studies),[24,25,30,31,35] followed by taste solution tests (three studies)[10,22,28] and PTU/PTC perception tests (two studies).[7,29] One study used taste spray scores,[26] and another performed an EGM.[33]

3.3 | Gustatory dysfunction in PD using the taste strip test

A meta-analysis was performed using five studies[20,21,27,32,34] since two of the seven papers that used taste strip tests to measure gustatory function were excluded because they lacked detailed information.[23,36] The total population across these five studies was 939 subjects (657 in the control group and 282 in the PD group). As the concentration of each taste solution was not identical in all studies, we evaluated and compared the total score of each taste solution between the PD patients and the control subjects. Figure 3A shows the funnel plot, and the Egger's test on the funnel plot asymmetry was not significant ($p = 0.7774$). Figure 3B is the forest plot of the five papers using taste strip test scores. The mean and variance of taste strip test scores between the PD patient group and the control group and the 95% CI using SMD were reported in the forest plot. The taste ability of patients with PD was significantly lower than that of the control groups in three of the five papers.[21,23,27] Both the common- and random-effect models showed that taste ability was reduced in patients with PD with an SMD of −0.4058 and −0.4130, respectively, compared with the controls. Cochran's Q test rejected the hypothesis that heterogeneity did not exist, and the $I2$ was 72%.

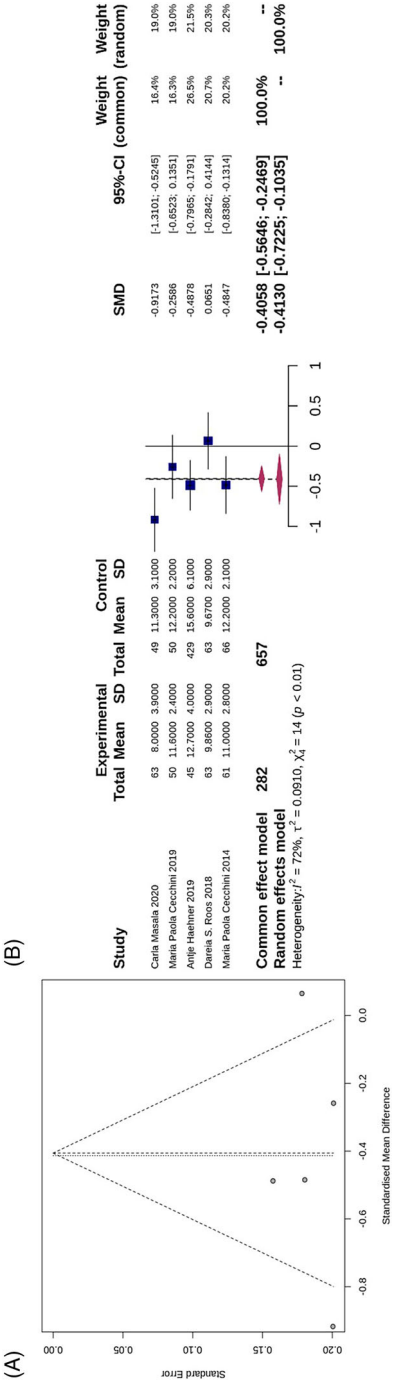

FIGURE 3 Analysis regarding the taste strip test. (A) Funnel plot of five papers using the taste strip test. (B) The forest plot of standardized mean difference (SMD) using taste strip test scores. The common- and random-effect models showed that taste ability was reduced in the Parkinson's disease (PD) group.

3.4 | Gustatory dysfunction in PD using questionnaires

A meta-analysis was performed using four papers of the five papers that used the questionnaire method[25,30,31,35] since one study that lacked detailed information was excluded.[24] Although the wording was not the same, all the questionnaires evaluated the presence or absence of taste disturbance. Therefore, a meta-analysis was performed on the binary outcomes. The total study population across the four studies was 928 subjects (342 in the control group and 586 in the PD group). Figure 4A shows the funnel plot, and the Egger's test on the funnel plot asymmetry was significant ($p = 0.0385$). However, since the number of samples was only four, the reliability of the test was not high. Figure 4B shows the forest plot of the four papers using the binary outcomes from the questionnaires. The number of events and the total number of patients with PD or the controls, the RR, 95% CI for RR, and RR of the common- and random-effect models were reported in the forest plot. The taste loss in patients with PD was significantly higher than the controls in three of the four studies with RR criteria.[25,30,35] The common- and random-effect models showed that taste loss was higher in patients with PD with RRs of 3.8969 and 6.4797, respectively, compared with the controls. Cochran's Q test rejected the hypothesis that heterogeneity did not exist, and the I^2 was 61%.

3.5 | Gustatory dysfunction in PD using the taste solution test

Among the three studies that used the taste solution test, one study, which included 74 subjects, reported no significant difference between the patients with PD and without PD. However, we could not obtain the raw data for each taste solution test.[22] Although this study also reported that the taste strip test score was significantly lower in patients with PD compared with the patients without PD, it was not involved in the taste strip test analysis. In another study, which included 83 subjects, taste performance was significantly decreased in patients with PD compared with the controls, which was demonstrated by a z-score difference.[28] In another study, only the NaCl solution showed a significant difference between the patients with PD and the controls.[10] Since the raw data in these studies were described heterogeneously, we could not perform a statistical analysis.

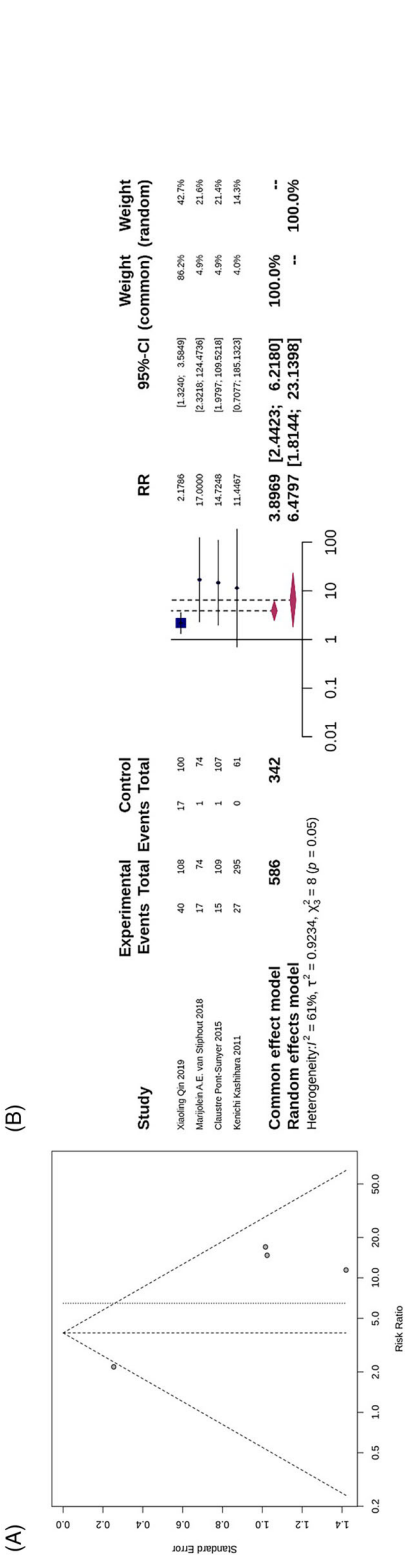

FIGURE 4 Analysis regarding the questionnaire method. (A) Funnel plot for the questionnaire method. (B) The forest plot of relative risk (RR) using the questionnaire method. The common- and random-effect models showed the presence of taste loss in the Parkinson's disease (PD) group.

3.6 | Gustatory dysfunction in PD using PTU/PTC perception tests

A meta-analysis was performed on two papers[7,29] using the PTU/PTC perception method. The total study population across these two studies was 296 subjects (151 in the control group and 145 in the PD group). We evaluated and compared the percentage of tasters between the patients with PD and the control subjects. Figure 5 shows the forest plot for the two papers using the PTU/PTC perception binary outcomes. The number of events and total events for patients with PD and the controls, RR, 95% CI for RR, and RR of the common- and random-effect models were reported in the forest plot. In both studies, the taste loss in patients with PD was significantly higher than that of the controls with the RR criteria. The common- and random-effect models showed that PTU/PTC perception was lower in patients with PD with RRs of 0.6777 and 0.6734, respectively, compared with the controls. Cochran's Q test could not reject the hypothesis that heterogeneity did not exist, and the $I2$ was 0%. However, since the number of samples was only two, the reliability of the heterogeneity and asymmetry tests was low.

3.7 | Gustatory dysfunction in PD using other tests

One study employed a whole-mouth test using taste sprays for gustatory evaluation.[26] When patients scored in the range of ageusia or hypogeusia or when they scored with a significant decrease in gustatory function, taste strips were used for further evaluation.[26] In this study, 41 patients with PD and 206 control subjects were evaluated. There was no significant reduced gustatory function or parageusia in patients with PD compared with the controls. In another study, EGM was applied to evaluate the gustatory function.[33] In this study, 75 patients with PD and 74 control subjects were evaluated, and there was a significant impairment of taste threshold in patients with PD compared with the controls.

4 | DISCUSSION

Based on the meta-analysis, we suggest that GD is significantly higher in patients with PD than those without PD. Although several studies reported contradictory results, most currently reviewed studies have concluded that GD was significantly associated with PD.

Olfactory dysfunction has long been evaluated in PD, and it has been well established that OD is closely related to PD.[37] Specifically, the prevalence of OD has been shown

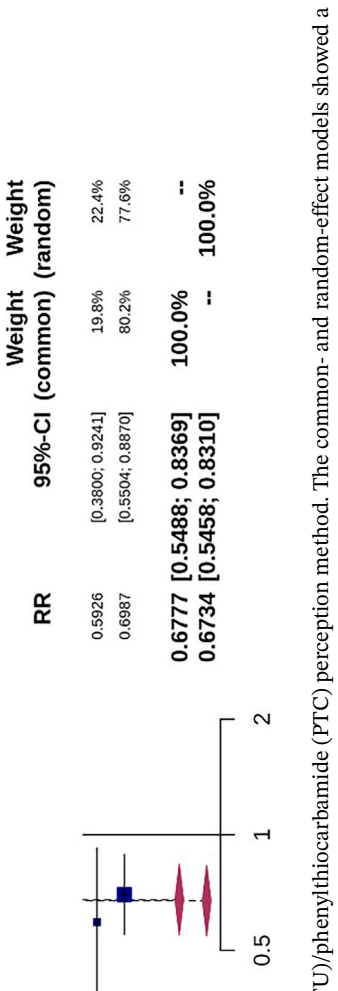

FIGURE 5 The forest plot of relative risk (RR) using the propylthiouracil (PTU)/phenylthiocarbamide (PTC) perception method. The common- and random-effect models showed a decrease in PTU/PTC perception in the Parkinson's disease (PD) group.

to be significantly higher in patients with PD compared with the controls, and OD increases the risk of future development of PD.[1,3] Furthermore, assessment of olfactory function has been suggested to be a useful diagnostic tool in differentiating PD from other conditions related to PD, such as essential tremors.[1,5] Therefore, olfactory function tests are recommended in patients who are suspected of or diagnosed with PD.[38] However, compared with OD, studies regarding GD in PD are very limited. Based on this current study, we suggest that GD may be related to PD similarly to OD, and further studies, such as a longitudinal follow up study, need to be performed to further support this.

The mechanisms of GD in PD have not yet been fully clarified. During the process of taste signal transduction from the periphery to the cortex of the brain, the primary gustatory cortex involves the frontal operculum, insula, and other cortical lesions, including the orbitofrontal cortex, which could be affected during the pathogenesis of PD.[39] Genetic studies have demonstrated a dysregulation of taste receptor genes in PD patients compared with controls.[40] Recently, it has been reported that dysbiosis of gut microbiota in PD affects the expression of specific taste receptors.[41] Although more studies are needed, based on current and previous studies, we suggest that GD could be one of the chemosensory symptoms observed in the pathogenesis of PD.

We found that the most commonly used gustatory function test was chemical gustatory function tests, which utilize various tools, such as taste strips, taste solutions, or sprays. These tests consist of chemical solutions with four or five tastants (including umami) and several gradient concentrations. However, the specific concentrations of each tastant could be culture specific. Subjective questionnaires regarding the presence of GD were the second most commonly used test. In a previous study, we found that subjective recognition of a patient's self-reported discomfort does not always correspond to the objective measurement outcome of chemical gustatory function tests.[42] PTU/PTC perception tests were used in Western countries, and the perception of PTU/PTC has been known to be associated with general taste perception and food preferences at the same time. However, the ability to taste these chemicals has been reported to be a heritable trait.[7,43] Although EGM has been thought to be an objective measurement tool in GD, the result of EGM is dependent on various other factors, such as mucosal dryness and the condition of the electrode, and the usefulness of EGM is not conclusive.[44,45] Therefore, we suggest that chemical gustatory function tests, including subjective questionnaires, are recommended to truly evaluate the presence of GD. Furthermore, since lifestyle factors, such as consumption of a Western-style diet, can result in variations in chemosensory abilities,[46] culture-specific gustatory function tests with corresponding normal ranges should be established and implemented for the proper diagnosis of GD in PD.

Olfactory function tests usually consist of threshold, discrimination, and identification subsets. It has been reported that general OD and the ability to identify specific odorants have been closely related to PD,[47,48] and these findings suggest that more simple olfactory function tests with specific identification subsets could be used for quick and easy screening of OD. Similarly, gustatory function tests composed of detection and recognition thresholds of tastants have been developed and applied.[49] Traditionally, it has been known that taste consists of sweet, sour, bitter, salty, and umami, and recently, the taste of fatty acids has been described as a sixth taste.[50] Therefore, we suggest that future studies evaluating the relationship between the subsets of gustatory function tests (detection or recognition thresholds) with PD are needed. Furthermore, identifying the relationship between the ability to taste each taste component (sweet, sour, bitter, salty, umami, and fatty acids) with PD could elucidate a reduced perceptivity for a specific tastant in PD and may be helpful in further understanding the pathogenesis of PD and early screening of gustatory function in those who are suspected of having PD.

There are limitations in this current study. First, we have found that the studies performing gustatory function tests in PD include relatively small sample sizes. Compared with olfactory function tests, studies containing the results of gustatory function tests are scarce. In the current evaluation, the number of patients included in the studies that met our inclusion criteria was 2559. The relatively small sample size of the reported studies regarding GD could be due to the lack of established gustatory function tests at each institute and the possibility that GD is less frequently associated with PD compared with OD. More evidence is needed to draw a definite conclusion about the clinical relevance of GD in PD. Based on the current analysis, we suggest that GD is closely associated with PD, and clinicians should pay attention to gustatory function in patients who are suspected of having PD. In addition, more gustatory function testing needs to be applied. Second, olfactory function was not considered in this current study. The relationship between gustatory and olfactory function has been long evaluated. It has been reported that GD is closely related to OD.[51] However, one study suggested that OD has no influence on GD when the effects of sex, age, and etiology are adjusted for.[52] As evaluating the relationship between gustatory and olfactory function was not our primary goal, we did not consider olfactory function in the enrolled study population in the current analysis. We instead evaluated the results of gustatory function tests in

patients with PD compared with controls. Therefore, the inter-relationship and interactive mechanisms of GD and OD in PD would be interesting in future studies.

5 | CONCLUSION

We found that GD is frequently reported in patients with PD compared with the controls suggesting the high possibility of a close relationship between GD and PD. As currently published studies have limitations, further studies should be performed to demonstrate the involvement of GD in the pathogenesis of PD.

AUTHOR CONTRIBUTION

Il-Youp Kwak performed the statistical analysis and initial drafting of the manuscript. Kyung Soo Kim collected the data and reviewed the manuscript. Hyun Jin Min participated in study conceptualization, data collection, initial writing of the manuscript, and final submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

This study's data are available from the corresponding author upon reasonable request. The data are not publicly available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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