# Laryngopharyngeal Reflux and Olfaction Disorders. Is There Any Connection? A Scoping Review

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*ABSTRACT*

*Objectives: To review the evidence regarding olfaction in patients with laryngopharyngeal reflux.*

*Methods: Conducting a scoping review of studies evaluating olfactory sense in patients with laryngopharyngeal reflux. Online databases were searched and studies evaluating laryngopharyngeal reflux impact on other nasal functions were excluded. Other exclusion criteria were the presence of severe nasal anatomical issues, rhinosinusitis, allergic rhinitis and nasal polyps in the study group.*

*Results: Seven studies, between 2016 and 2019, met our inclusion criteria. Olfaction threshold was significantly lower in patients with laryngopharyngeal reflux than controls in three studies and in two of these studies, all three assessed parameters, including threshold, identification and discrimination, were significantly affected in the laryngopharyngeal reflux group. In three other studies, where the Connecticut Chemosensory Clinical Research Center test had been used, smell test scores were also statistically significantly lower in the reflux group. Finally, in a survey-based study evaluating olfaction, olfactory anomalies were positively related to gastroesophageal reflux disease and gastroparesis symptom severity.*

*Conclusion: There is scarce evidence regarding the effect of laryngopharyngeal reflux on olfaction, but preliminary evidence shows that laryngopharyngeal reflux may cause olfactory abnormalities. Thus, olfactory abnormalities can be an additional reflux manifestation. Gastroparesis, gastroesophageal reflux disease, laryngopharyngeal reflux and* Helicobacter pylori *infection are factors that can potentially cause olfactory sensory disturbance.*

**Keywords**: olfaction and laryngopharyngeal reflux, nasal congestion and reflux, gastroparesis, surveys and questionnaires, smell.

## INTRODUCTION

In gastroesophageal reflux disease (GERD), the exposure of esophageal epithelial to gastric juice exceeds what can be tolerated by the patient (1).

Reflux may also affect other areas such as the larynx, pharynx, nasopharynx, paranasal sinuses and nasal cavity (2), oral cavity and even the middle ear (3). Reflux that acts upon the laryngopharyngeal area is called laryngopharyngeal reflux (LPR) (4).

The commonest LPR symptoms seen in a General ENT clinic are throat pain, globus type symptoms and hoarseness (5), whilst more recently several researchers have suggested a relation between LPR and chronic rhinosinusitis, post nasal drip, middle ear effusion, halitosis and smelling and tasting problems (6, 7).

Lately, the effect of LPR in olfaction has gained an increased research interest among otolaryngologists (7-9). A critical role of olfaction is the recognition of environmental hazards, which is mediated by the olfactory and trigeminal neural pathways, consisting of a surveillance mechanism of the inhaled air. Moreover, smell adds in pleasure perception, meaning nourishment, mood and sexuality. Currently, the olfactory system is under investigation regarding a possible new function, linking olfaction to various processes such as pheromone detection (10, 11), kin recognition and mating , mother–infant bonding (11), food preferences, central nervous system physiology (12) and longevity (13).

The objective of this study is to review the existing evidence between LPR and olfaction. Does LPR result in alteration of the sense of smell? Currently, there is no robust evidence on the matter. However, since there is significant impact on the quality of life, this should not be overlooked. ❑

## MATERIALS AND METHODS

### Eligibility of relevant studies

Data recording was independently done by two reviewers, who mapped, examined and revised all selected data.

Only case control clinical studies were retrieved. The search was performed in English language and only studies with English abstract or written in English were included.

Critical analysis of the literature was performed focusing on the impact of LPR on olfactory function only. Studies stating the impact of LPR on other nasal functions such as nasal breathing, nasal airway, rhinosinusitis, rhinitis, allergic rhinitis, fungal rhinosinusitis, nasal polyps, were excluded from this review. Studies evaluating olfaction in patients with neurodegenerative diseases, systemic diseases and anatomical issues, such as significant deviated nasal septum, facial dysmorphism, congenital anomalies, post-traumatic injuries, were also excluded. Furthermore, paediatric LPR cases were excluded too. In all included papers there had to be a clear statement on the inclusion and exclusion criteria and clinical tools used for assessment of LPR and olfaction. The review was performed in agreement with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocol (PRISMA) extension for scoping reviews (Figure 1. MSOffice).

### Search strategy

A computerized search of PubMed, Cochrane Library, Google scholar, Scopus, Research Gate and Europe MPC databases was conducted for relevant publications in English, or with English abstracts. The following terms were used: olfaction and reflux, nasal congestion, and reflux, (laryngopharyngeal reflux OR reflux OR GERD) AND (olfaction OR smell). Several other terms, including supraesophageal reflux, laryngeal reflux, pharyngoesophageal reflux, atypical reflux, reflux laryngitis, and extraesophageal reflux, were also used as synonymous with LPR.

### Data extraction

After a preliminary search, 179 articles were identified and one more article was traced by another source. After duplicate removal, abstracts of the remaining 94 articles were reviewed. Of these 94 studies, 86 were not relevant to our review aim and one study, though relevant, was a case report (14). Thus, only seven studies met our criteria and were included in the present review. ❑

## RESULTS

### Study evaluation

All studies were prospective case-control clinical surveys. The evaluation of the olfactory
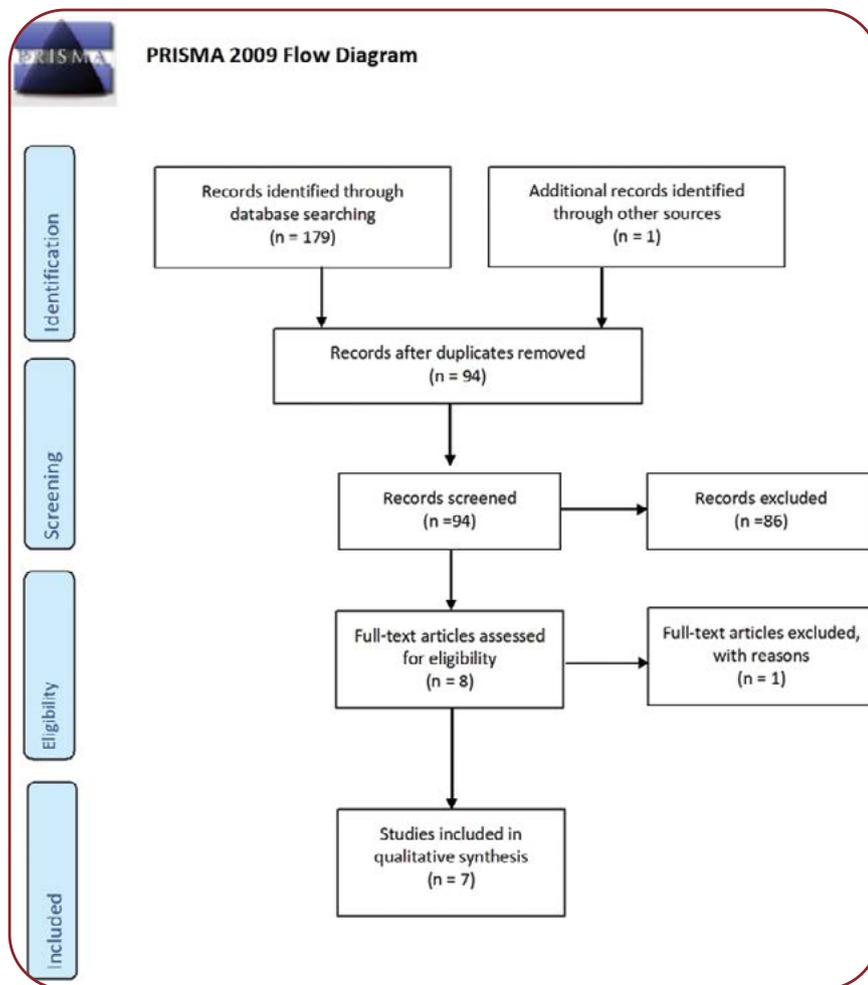
**FIGURE 1.** Article selection by PRISMA criteria

function was conducted by olfactory tests in all selected studies, except for one study, in which the evaluation of smell and taste was based on a 14-item validated questionnaire, initially developed to assess sensory alterations in HIV patients (15).

Assessment of scientific quality of the included studies was done and appropriately documented based on the Quality Assessment Tool for Case-Control Studies from the National Heart, Lung, and Blood Institute (APPENDIX – Table a) (16) and the Critical Appraisal Skills Program (CASP) Qualitative Checklist (APPENDIX – Table b) (17).

Based on GRADE from the four levels of evidence, the case-control studies included in the present review belong to level 3, which is considered a low level.

The study objective was clearly stated and the study population appropriately specified and selected in all studies. However, no power analysis was conducted and no sample size justification was declared in any of the studies.

Control groups were recruited from healthy people at the same period with the study populations, with caution regarding matching age. Inclusion criteria were clearly stated for both study and control populations. Exclusion criteria referring to nasal diseases such as rhinitis, polyps, rhinosinusitis, neurological degenerative diseases, head trauma, neurosurgical operations, or digestive system procedures were strictly used.

Diagnostic criteria regarding LPR and olfactory ability were prespecified and implemented in all subjects of the reviewed studies.

Bias may have occurred, hence there is no evidence to support that the appraisers of LPR condition were blinded to the case or control status of participants. In addition, the period of LPR symptoms was not accurately determined to minimize bias. Finally, the design of those studies

did not allow random control selection from eligible cases.

## Study characteristics

The seven studies that evaluate olfaction in patients with LPR or GERD, which have been published between 2016 and 2019, are presented in Table 1.

Laryngopharyngeal reflux was certified using reflux symptom index (RSI) and reflux finding score (RFS) criteria and olfaction was assessed by olfactory tests or using a survey in one study.

In all six studies using olfactory tests, the results were significantly affected in LPR patients.

In 2016, three authors (7, 8, 18) conducted prospective case-control clinical studies.

Altundag et al (7) examined the effects of LPR on taste and smell. They evaluated the olfactory function of 60 patients with LPR, conducting a prospective multicenter case-control clinical study with 50 controls. The study group consisted of patients who presented with deteriorated quality of voice, persistent cough, and stickiness in the pharynx, and with RFS>11 and RSI>13. The validated Sniffin' Sticks test (SST; Burghart Medical Technology, Wedel, Germany) was used to assess olfactory function.

There were significant differences in odor threshold scores between groups (P<.001), but no differences were detected between identification and discrimination scores. An overall significant difference was recorded in the composite score (TDI) between groups.

In 2016, Mehmet Emre Dinc et al (18) examined 60 individuals (30 LPR and 30 controls) using 24-h dual-probe pH monitoring in addition to clinical evaluation (RFS>7) and history subjective symptomatology (RSI>13). Patients included in the study were assessed by RSI and RFS indexes. If scores were at least 13 and 7, respectively, they had a 24-h pH monitoring to confirm the diagnosis of LPR. Olfactory function was measured using the validated Sniffin' Sticks test (SST; Burghart Medical Technology, Wedel, Germany). All olfactory parameters were significantly lower in the LPR group comparative to the control one (p<0.05).

In October 2015, the results of a study evaluating olfaction in GERD patients were published online by Emre Gunbey et al (8). The study group inclusion criteria were GERD confirmed by 24-h pH monitoring (pH-MII) or reflux esophagitis diagnosed by gastro-esophagoscopy and persistent complaints for at least six months. In the study group, the mean RFS was 9.8±3.7 and the mean RSI 15.2±5.4. All odor tests in the GERD group, including odor threshold (10.1; 9.5, p=0.016), odor identification (9.6; 8.1, p<0.001) and odor discrimination (10.7; 8.9, p<0.001), were significantly lower comparatively to the control group.

However, the results did not detect any correlation among the clinical findings of the larynx and olfactory parameters. The authors declared as limitation the evaluation of chronic rhinosinusitis by clinical criteria only, excluding the use of computed tomography due to ethical reasons.

Two more studies that used the Connecticut Chemosensory Clinical Research Center (CCCRC) test showed a statistically significant difference between LPR and normal subjects, revealing a negative effect of LPR on the olfactory function (9, 19).

In 2018, Kumbul et al (9) used the modified olfactory test of CCCRC, where the odor identification test was applied using the essence of arachis oil in place of peanut butter. The test was used to evaluate olfaction in subjects who were considered LPR patients after achieving a score of 13 and 7 on the RSI and RFS tests, respectively. The following exclusion criteria were used for patient selection: anatomic abnormalities like septal deviation, active upper respiratory tract infection, allergic rhinitis, chronic rhinosinusitis with or without nasal polyposis and history of head trauma. Exclusion from the study was also applied in cases of hyposmia or anosmia after upper respiratory tract infection, intracranial malignancies, radiotherapy for head and neck malignancies, drug use, nasal surgery, neurological or psychiatric diseases. The results showed statistically significantly lower olfactory and taste scores compared with the control group. The mean total CCCRC scores in the control and reflux groups were 5.93±0.10 (range: 4 to 7) and 5.01±0.13 (range 2.5 to 7) points, respectively (p<0.001). In conclusion, the authors endorse the opinion that LPR disease has negative effects on olfaction, without however leading to total anosmia.

In 2019, Kumral et al studied the effect of *Helicobacter pylori* on nasal functions. Multiple tests were used to assess nasal functions. The nasal patency was objectively evaluated by peak nasal inspiratory flowmeter (PNIF) and mucociliary clearance (MCC). However, the sinonasal

**TABLE 1.** Summary of study results

| | Authors | Year | Level of evidence | Study design | Study groups LPR | controls | Results | Conclusion |
|---|---|---|---|---|---|---|---|---|
| 1. | Altunda, *et al* | 2016 | Level 3-low | Case control | 60 | 50 | The differences in odor threshold scores were significant (p<001), but no change was detected for odor identification or discrimination scores (DIS p=0.8, ID p=0.8, TDI, p<0.001)* | Laryngopharyngeal reflux has negative effects on smell function. |
| 2. | Mehmet Emre Dinc, *et al* | 2016 | Level 3-low | Case control | 30 | 30 | The differences were significant in odor threshold (p<0.05), odor discrimination (p<0.05), odor identification (p<0.05) and TDI scores (p<0.05) of the laryngopharyngeal reflux group.* | LPR may affect olfactory physiology and may be one of the reasons of olfactory dysfunction. |
| 3. | Emre Gunbey, *et al* | 2015 | Level 3-low | Case control | 35 (GERD) | 45 | All odor tests in the GERD group, meaning odor threshold (10.1; 9.5, p=0.016), odor identification (9.6; 8.1, p<0.001) and odor discrimination (10.7; 8.9, p<0.001), were significantly lower comparatively to the control group* | Diminished olfactory function in adults with GERD |
| 4. | Bezgin, *et al* | 2017 | Level 3-low | Case control | 32 (*H. pylori* +) | 30 | There were significant lower odor scores in the patient group (*H. pylori* infection) compared to the control group (p<0.05)** | There is an association of *H. pylori* infection with olfactory dysfunction. |
| 5. | Kabadi, *et al* | 2017 | Level 3-low | Case control | 63 n=30 gastroparesis n=10 GERD n=23 both | 13 | Patients with gastroparesis and/or GERD completed questionnaires evaluating taste and smell (Taste and Smell Survey, Patient Assessment of Upper Gastrointestinal Symptom Severity Index. Smell score was strongly correlated to heartburn and regurgitation score (HB/RG) (r=0.513, p<0.001) and gastroparesis cardinal symptom index (GCSI) (r=0.495, p<0.001). | Abnormalities in taste and smell are prominent in gastroparesis and GERD patients and are significantly correlated with both gastroparesis and GERD symptom severity. |
| 6. | Kumbul, *et al* | 2018 | Level 3-low | Case control | 50 | 50 | Mean butanol threshold scores of the control and reflux groups were 6.7±0.09, and 5.77±0.09 points, respectively (p<0.001). Mean scores of the identification tests were 5.41±0.18 and 4.24±0.19 points in the control and reflux groups (p<0.001). Mean total CCCRC scores were calculated as 5.84±0.13 and 5.20±0.11 points in the control and reflux groups, respectively (p<0.001)*** | Laryngopharyngeal reflux disease has a negative effect on olfactory functions without total loss in olfactory functions. |
| 7. | Kumral, *et al* | 2019 | Level 3-low | Case control | 64 (LPR+/GERD +, *H. pylori* +) Pylori colonization point-scale after antral biopsy: mild (grade 1), moderate (grade 2), severe (grade 3) | 36 (LPR-/GERD+ *H. pylori* +) Pylori colonization point-scale after antral biopsy: mild (grade 1) moderate (grade 2) severe (grade 3) | There was a significant difference in the olfactory test scores between the groups (p=0.046; p<0.05). "Mild" group had significantly higher measurements compared with "severe" group (P= 012; P<.05; P<.05). There was no such difference in the results between "mild" and "moderate" groups for the control group (p>.05)*** | Olfactory tests differed between LPR disease and GERD. The density of *H. pylori* colonization in the gastric mucosa influenced nasal function. |

*Sniffin' Sticks test; **The 12-item screening test Sniffin' Sticks;
***Olfactory test of Connecticut Chemosensory Clinical Research Center

outcome test-22 (SNOT-22) and visual analog scale (VAS) were used for the assessment of subjective sense of nasal breathing. The CCCRC olfaction test was used to objectively evaluate olfactory function. A first selection for the LPR diagnosis was based on Reflux Symptom Index (RSI) and Reflux Finding Score (RFS). When RSI >13 and RFS >7, patients were assumed to have LPR and were offered an upper gastrointestinal endoscopy and biopsy. Second selection of patients was based on gastric antral biopsy with histology for *H. pylori* diagnosis. Those with a negative result were excluded from the study. The remaining ones were divided into groups according to the guidelines of the Sydney system, categorized on a four-point scale of none (grade 0), mild (grade 1), moderate (grade 2), or severe (grade 3), depending on the colonization of *H. pylori* on the gastric mucosa (20). Results showed a significant difference of olfactory test scores between categories. The "Mild" group had significantly higher scores than the "severe" group, meaning that olfactory test results worsened as *H. pylori* colonization increased in the antral epithelium (P < .05).

The sixth study (21) investigated the role of Helicobacter pylori in olfactory function using a screening odor test. Patients with dyspeptic symptoms and a positive gastric biopsy for *H. pylori* underwent the Burghart screening test. It was assumed that *H. pylori* could reach the nasal cavity *via* oronasal course or gastroesophageal reflux. The score of odor test in the *H. pylori* group was significantly lower than the control group, suggesting that *H. pylori* infection was a potential etiological factor for olfactory dysfunction.

The conclusion that abnormalities in taste and smell were present in GERD patients has been also retrieved by the seventh study using the "Taste and Smell Survey" (TSS) (22). Anomalies in taste and smell were significantly associated with the severity of GERD symptoms.

The limited number of reviewed studies and their lack of homogeneity as well as the diversity of olfactory diagnostic tests used by the study investigators precluded the conduct of a meta-analysis. ❑

## DISCUSSION

The extraesophageal reflux (EER) affects various organs, including the larynx (hoarseness), ears (otitis media) and lungs (chronic bronchitis, chronic cough, asthma, recurrent pneumonia, idiopathic pulmonary fibrosis). Even sudden infant death syndrome (SIDS) (23) could be attributed to the direct (aspiration) or indirect (vagally mediated) mechanisms. Reflux-related chronic cough, connected to chronic pressure alterations between the abdominal and thoracic cavities, leads to a vicious cycle between reflux and cough, adding an additional burden on the laryngeal structures (23, 24).

**Olfaction and laryngopharyngeal reflux**
Normal olfaction depends on complicated interacting functions and essential physiological processes. First, the anatomy of the olfactory epithelium has a crucial role. The epithelium is located along the olfactory cleft, the posteriosuperior septum, and the lateral nasal wall at the level of superior portion of the middle and superior turbinates (25). Any disturbances or trauma to these areas can potentially harm olfactory function, as there are complex poorly understood neurosignaling processes resulting in the perception of smell (26). Usually, olfactory dysfunction occurs after the implementation of a local pathologic factor leading to distraction of the regional anatomy and physiology. As a consequence, prevention of odorous molecules to reach the olfactory region and stimulate olfactory receptors decreases the sensation of smell (27).

Recently, the link between LPR and chronic sinusitis as well as the nasal consequences of LPR have attracted considerable attention (28). Laryngopharyngeal reflux has been shown to directly affect nasal physiology and functions. Several studies have examined the relation among reflux and nasal pathologies, still other than olfactory function.

Gastroesophageal reflux disease is believed to affect olfactory function *via* two mechanisms. According to the first one, patients with chronic nasal inflammation demonstrate increased nasal pepsin secretions. There is evidence of nasopharyngeal reflux in one-third of GERD patients, supporting a direct toxic effect on the olfactory mucosa (2, 4, 29). The second mechanism supports the fact that reflux stimulates the vagal nerve and may cause dysfunction of the autonomic nervous system, leading to olfactory dysfunction of conductive-type, possibly due to severe sinonasal mucosal edema and chronic rhinosinusitis
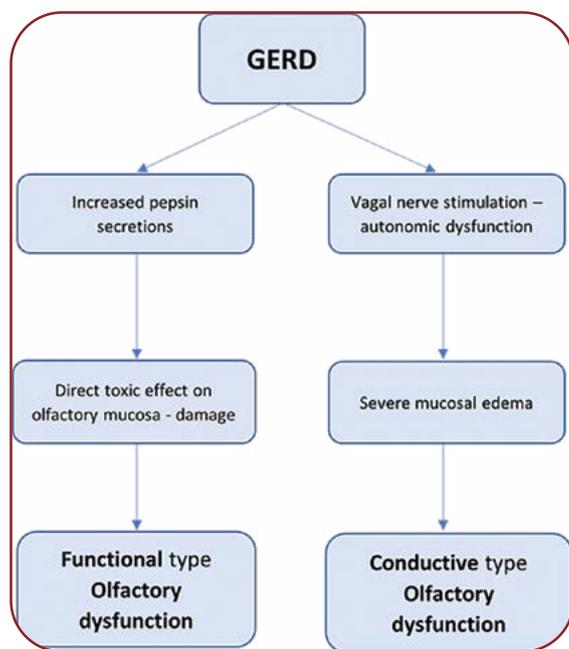
**FIGURE 2.** Potential mechanisms of GERD affecting olfaction

(Figure 2. MSOffice). Holmes *et al* supported that patients with GERD and chronic upper airway inflammation demonstrate significant autonomic nervous system dysfunction with adrenergic hypofunction (30). In addition, patients with known extra-esophageal reflux present with an increased rate of vasomotor rhinitis (31). The role of chronic allergic conditions in triggering both GERD-LPR and rhinitis, affecting smell, is analysed in a comprehensive review by Berghi *et al* (32). This could be a major limitation of the studies trying to connect LPR to olfactory changes.

Similarly to gastroesophageal reflux, but with fewer reflux episodes and attenuated acid concentrations, LPR causes quick and severe deterioration in mucosa of the oral cavity and larynx. Taste buds can be injured, resulting in an adverse foul odor and a general deterioration of oral hygiene (33).

In the above studies there was no reported power analysis to estimate the number of cases needed for a valid conclusion. Most of the authors did not report any limitations. The only exception was found in the study conducted by Gunbey *et al* (8), which posed limitations regarding the clinical and technical methods in diagnosing sinusitis.

The degree of LPR severity was evaluated by clinical findings (RFS) and symptom scale (RSI) in the context of the inclusion criteria, in three of the reviewed studies. Emre Dinc *et al* used additionally 24-hour dual probe pH-monitoring and Gunbey *et al* set a six-month period of continuous complaints important for LPR diagnosis (8, 18). Bezgin *et al* made the assumption that *H. pylori* could reach the nasal cavity *via* oronasal course or gastroesophageal reflux and they used gastric biopsies to identify *H. pylori* infection (21). The fact that there is no gold standard in LPR diagnosis together with the lack of data about the management/treatment of LPR leads to diversity in diagnostic methods and affects the quality of studies which were included in our review. In addition, there is a lack of data regarding further study direction concerning laryngopharyngeal reflux and olfaction disorders. ❏

## CONCLUSION

Although there is little evidence regarding LPR effect on olfaction, current data support the hypothesis that LPR may cause olfactory abnormalities. Thus, olfactory dysfunction could be an additional extraesophageal reflux manifestation. Gastroparesis, GERD, LPR and *Helicobacter pylori* infection are factors that cause disturbance of the olfactory sense.

The causal role of GERD in the pathophysiology of LPR symptoms remains controversial and studies questioning the benefits of PPIs in LPR have been published. Nevertheless, many patients seem to respond to anti-reflux therapy. Similarly, patients with gastric disorders such as LPR and olfaction problems may benefit from anti-reflux treatment.

The lack of a gold standard diagnostic tool for LPR, along with the variability in tests used for olfactory evaluation limit the synthesis of results as well as the display of a safe conclusion.

Another drawback is the low level of evidence of the reviewed studies. However, recommendations from observational studies are sometimes the only available evidence which may trigger a new approach to certain clinical questions.

Likewise, the limited number of the relevant publications highlights the need for further meticulously designed studies to address the impact of LPR in olfaction. ❏

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# APPENDIX

TABLE a. Quality assessment of case-control studies according to NHLBI

| | Alt 2016 | Dinc 2016 | Günbey 2016 | Bezgin 2017 | Kabadi 2017 | Kumbul 2018 | Kumral 2019 |
|---|---|---|---|---|---|---|---|
| 1. Was the research question or objective in this paper clearly stated and appropriate? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2. Was the study population clearly specified and defined? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 3. Did the authors include a sample size justification? | - | - | - | - | - | - | - |
| 4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 6. Were the cases clearly defined and differentiated from controls? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? | - | - | - | - | - | - | - |
| 8. Was there use of concurrent controls? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 11. Were the assessors of exposure/risk blinded to the case or control status of participants? | ? | ? | ? | ? | ? | ? | ? |
| 12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |

**TABLE b.** Risk of bias of included non-experimental studies using the Critical Appraisal Skills Program (CASP) Qualitative Checklist

| | Alt 2016 | Dinc 2016 | Günbey 2016 | Bezgin 2017 | Kabadi 2017 | Kumbul 2018 | Kumral 2019 |
|---|---|---|---|---|---|---|---|
| 1. Did the study address a clearly focused issue? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 2. Did the authors use an appropriate method to answer their question? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 3. Were the cases recruited in an acceptable way? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 4. Were the controls selected in an acceptable way? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 5. Was the exposure accurately measured to minimise bias? | NA | NA | NA | NA | NA | NA | NA |
| 6. (a) Aside from the experimental intervention, were the groups treated equally? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 7. How large was the treatment effect? | NA | NA | NA | NA | NA | NA | NA |
| 8. How precise was the estimate of the treatment effect? | NA | NA | NA | NA | NA | NA | NA |
| 9. Do you believe the results? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 10. Can the results be applied to the local population? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| 11. Do the results of this study fit with other available evidence? | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |