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Diagnosis of Anosmia and Hyposmia: A Systematic Review

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Abstract

Background: Anosmia and hyposmia have many etiologies, including trauma, chronic sinusitis, neoplasms, and respiratory viral infections such as rhinovirus and SARS-CoV-2. We aimed to systematically review the literature on the diagnostic evaluation of anosmia/hyposmia.

Methods: PubMed, EMBASE, and Cochrane databases were searched for articles published since January 1990 using terms combined with Medical Subject Headings (MeSH). We included articles evaluating diagnostic modalities for anosmia, written in the English language, used original data, and had two or more patients.

Results: A total of 2065 unique titles were returned upon the initial search. Of these, 226 abstracts were examined, yielding 27 full-text articles meeting inclusion criteria (Level of evidence ranging from 1 to 4; most level 2). The studies included a total of 13,577 patients. The most utilized diagnostic tools were orthonasal smell tests (such as the Sniffin' Sticks and the UPSIT, along with validated abridged smell tests). Though various imaging modalities (including MRI and CT) were frequently mentioned in the workup of olfactory dysfunction, routine imaging was not used to primarily diagnose smell loss.

Conclusion: The literature includes several studies on validity and reliability for various smell tests in diagnosing anosmia. Along with a thorough history and physical, validated orthonasal smell tests should be part of the workup of the patient with suspected olfactory dysfunction. The most widely studied modality was MRI, but criteria for the timing and sequence of imaging modalities was heterogenous.

Keywords

anosmia, hyposmia, diagnosis, viral, COVID-19, SARS-CoV-2, smell loss, smell test, MRI, fMRI, SPECT, OERP, trauma, infection

Introduction

The sense of smell has an enormous impact on a patient's quality of life, and olfactory dysfunction has been associated with alterations in appetite and mood.[1,2] With increasing attention to smell disturbance as a symptom of SARS-CoV-2 infection, the medical community should be prepared to accurately diagnose olfactory dysfunction. To this end, focused history and physical exam are imperative, and ancillary tests such as smell tests [including orthonasal (smell through sniffing)[3] and retronasal (smell through eating/drinking)[3]] and imaging (including CT and MRI) have been utilized in the past. However, numerous diagnostic tests exist, and there remains variability in the clinical diagnosis of anosmia and hyposmia.

To confirm suspected common etiologies of anosmia and hyposmia due to head trauma, chronic rhinosinusitis (CRS) with or without polyposis, congenital

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syndromes, or neoplasms, physicians have utilized computed tomography (CT) or magnetic resonance imaging (MRI) in the past. Alternatively, viral upper respiratory infection (URI) and idiopathic anosmia/hyposmia are diagnoses of exclusion after appropriate testing has been completed.[2,4] Regardless of etiology, clinicians must be prepared to properly diagnose and manage patients with smell disturbance in everyday practice.

To this aim, we performed a systematic review of the literature focusing on diagnosis of anosmia and hyposmia in the clinical setting. Our goal was to identify which diagnostic modalities of olfactory dysfunction have the strongest evidence, and to provide guidance to clinicians for approaching anosmia, particularly in the current climate of increased prevalence secondary to COVID-19.

Materials and Methods

A systematic review of English-language published literature was conducted to investigate diagnosis of anosmia and hyposmia. Our study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and statement recommendations.[5] The following PICOS (Participants, Interventions, Comparisons, Outcomes, and Study Design) criteria were utilized: [Patients: those with hyposmia or anosmia; Intervention: established or novel diagnostic smell tests and imaging modalities; Comparison: assessing the validity/utilization of various smell tests and imaging modalities between anosmics and normosmics; Outcomes: classifying the severity of anosmia accurately for smell tests as well as determining common findings on imaging for anosmics; Setting: one retrospective study and numerous prospective cohort studies]

On March 10th, 2020, we searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE databases for relevant publications, beginning after January 1990 through March 2020. We again performed the search on April 30th, 2020 to identify COVID-19-related articles on anosmia, which had been published since the March search. An electronic search strategy was utilized for each database. The search included combined key terms and exploded medical subject headings (MeSH), including: *anosmia, hyposmia, smelling disorder, olfaction disorder, diagnosis, microbiology, prevention, disease management, drug therapy, drug administration, pharmacology, imaging, history, rehabilitation, statistics and numerical data, surgery, virology*.

Eligibility Criteria

The articles utilized in this review were limited to those written in the English language that included original data. These articles included cohort studies, case-control studies, and pilot studies. Two members of the investigation team (A.N. and A.S.) independently reviewed the articles to include in this study. A third member of the team (M.S.) then reviewed the articles as well. The following inclusion criteria were applied: original data; English language; at least 2 patients included in the study; well-defined and measurable outcomes obtained; and published after January 1990. Studies with no measurable outcomes; review articles; articles with little relevance to our study aims; studies focused on chronic rhinosinusitis with or without polyposis; and all basic science, cadaver, and animal-model studies were excluded.

Data Extraction

Data were extracted and reviewed independently. Any disagreement in inclusion or exclusion of articles was re-reviewed for a consensus between investigators. Articles were then evaluated for time of study, etiology of smell loss, number of patients, age of patients, and diagnostic modality used. The level of evidence was then assigned based on the published guidelines by the Oxford Centre for Evidence-based Medicine, Levels of Evidence.[6]

Risk of Bias

Risk of bias was assigned by evaluating each individual paper for its methodology and outcomes. Nonrandomized studies were assigned a risk of bias: "low", "moderate", "serious", or "critical", based on the ROBINS-I Cochrane risk of bias tool.[7]

Statistical Analysis

Due to the heterogenous nature of outcome measurements in studies meeting inclusion criteria and underpowered diagnostic modality groups, quantitative analysis was not possible per our statistician.

Results

The article selection process is illustrated in Figure 1. A total of 2065 unique titles were returned upon initial search, after which 226 abstracts were selected and examined, yielding 33 full-text articles for review and ultimately 27 articles that met inclusion criteria (Figure 1). 24 studies were level II evidence, and the other 3 studies were level I, III, and IV, respectively. The studies included a total of 13,577 patients (Table 1). Endpoints were based on diagnostic test findings among anosmic/hyposmic patients. Diagnostic methods discussed in the studies included Orthonasal smell tests,[8–18] Retronasal smell tests,[19,20] Olfactory Event Related Potentials (OERP),[21,22] Functional MRI

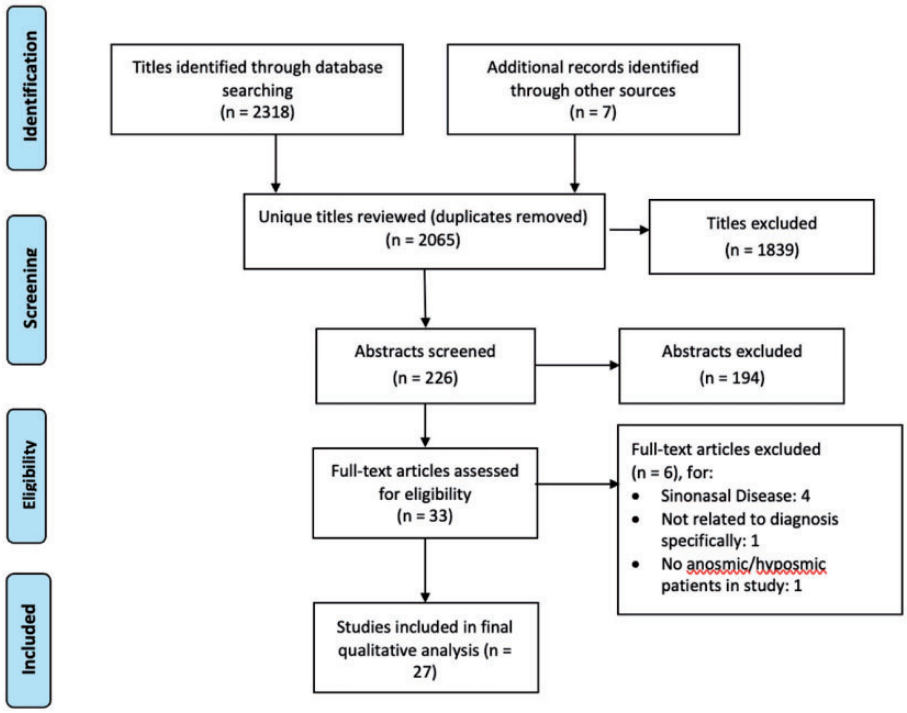

Figure 1. PRISMA diagram illustrating literature search algorithm.

(fMRI),[23–25] MRI,[19,26–29] Single-Photon Emission CT (SPECT),[29–32] CT,[32] and Positron Emission Tomography (PET) Scans[33,34] (Table 1). Per the exclusion criteria, any diagnostic studies focusing strictly on CRS were excluded.

Smell Tests

Orthonasal smell tests with cutoffs. A total of 11 studies using orthonasal smell tests[8–18] were included, totaling 12,257 patients (Table 1). 7/11 studies specified cutoffs differentiating normosmia from hyposmia.[8–14] Among these, Lotsch et al.[8] reported that cinnamon, banana, and fish odors provided enough specificity and sensitivity (84.3% and 80.4%, respectively) to establish normal olfactory function compared to Sniffin' Sticks (SS) (Table 1). Jackman et al.[9] similarly reported findings comparing the Q-SIT, a 3-item smell test, to the University of Pennsylvania Smell Identification Test (UPSIT) (Table 1). Similarly, Takebayashi et al.[10] found a positive correlation between the scores of the Self-Administered Odor Questionnaire (SAOQ) and the well-established Visual Analogue Scale (VAS) (Table 1). Tsukatani et al.[11] compared the Connecticut Chemosensory Clinical Research Center (CCCRC) test and the Jet Stream Olfactometer (JSO) and found a significant correlation between them for detection threshold and identification and recognition scores ($P < .01$). Welge-Lussen et al.[12] found a significant difference in threshold detection identification (TDI) score in 23.4% of anosmics between the right and left nostrils when using SS (Table 1). Oleszkiewicz et al.[13] investigated the relationship between SS scores and age, concluding that overal TDI score decreases most between 61-70 years (Table 1). Poletti et al.[14] correlated SS TDI scores with the Olfactory Cleft-Specific Lund-Kennedy (OC-LK) score among various etiologies of anosmia and found that post-traumatic anosmics had the lowest TDI scores, and as a group overall, anosmic patients had higher OC-LK scores when compared to normosmics (Table 1).

Orthonasal smell tests without cutoffs. Four orthonasal smell test studies did not specify cutoffs.[15–18] Kobal et al.[15] performed a "random" test consisting of varying concentrations of rose and citrus and found a correlation with TDI (SS) ($r = .82$) (Table 1). Villwock et al.[16] compared a novel smell test, AROMA, with UPSIT and SNOT-22 and found significant correlations between them. Robson et al.[17] used a butanol threshold smell test and found that anosmic patients had significantly lower scores than normosmics. Davidson and Murphy[18] developed a smell test with 70% isopropyl alcohol in which the distance where a subject first identifies the odor is measured, and found significantly lower scores for anosmic patients (Table 1).

Retronasal smell tests. Two studies using retronasal smell tests[19,20] were included, totaling 211 patients. Rombaux

Table 1. Summary of Articles.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
Orthonasal Smell Tests with Cutoffs .	18–96	n = 613 Normosmic (179) Hyposmic (251) 63/251 post-viral 47/251 post-traumatic Anosmic (183) 18/183 post-viral, 66/183 post-traumatic	Goal was to determine minimum number of, and which specific, odor identification items would establish normal olfactory function and still be sensitive and specific enough compared to well-established smell tests	Cinnamon: incorrectly identified by anosmics 84% of the time Banana: incorrectly identified by anosmics 75% of the time Fish: incorrectly identified by anosmics 73% of the time	At beginning of study, patients' olfactory acuity was evaluated via nasal endoscopy and Sniffin' Sticks to establish a baseline. Cinnamon correctly identified by 156/179 normosmics (87.2 %). Fish odor correctly identified by remaining 23 normosmics (12.8%). For diagnosis of normosmia (correctly identifying cinnamon, banana, fish), sensitivity and specificity = 80.4% and 84.3%, respectively, and NPV of 91.3%.	Lotsch et al.[8] 2016 (Level II, Prospective Cohort Study) (Low)
	15–88	n = 264 Control (40) Anosmic/Hyposmic: URI (61) Idiopathic (52) Sinusitis (36) Medication-related (26) Post-traumatic (24) Other (25)	Goal was to determine whether the Quick Smell Identification Test (Q-SIT, 3 items) was a valid smell test in comparison to the 40 item UPSIT	Using Q-SIT, number who identified 2 or less odors: Anosmia: 67/68 (99%) Severe Microsmia: 35/41 (85%) Moderate Microsmia: 31/41 (76%) Mild Microsmia: 17/34 (50%)	Of 40 control patients, 62.5% (25/40) correctly identified all odors, 25% (10/40) had one wrong answer, and 12.5% (5/40) had two wrong answers. None of the normosmic patients missed all three items. For detecting anosmia, sensitivity = 99% and specificity = 40%. NPV = 98%, PPV = 43%.	Jackman et al.[9] 2005 (Level II, Prospective Cohort Study) (Low)
	19–65	N = 652 patients who responded to surveys and were well-followed Healthy = 403 Olfactory Disorders: 170 managed conservatively with topical steroids 79 managed with ESS due to CRS Otherwise, etiology of anosmia not specified	Goal was to determine how the novel self-administered odor questionnaire (SAOQ) consisting of 20 smell-related items compares to the previously-established visual analogue scale (VAS), another self-administered odor questionnaire, and also to the T&T Olfactometer	Among the 249 patients with olfactory disorders who underwent management: Post treatment, there was significant improvement in SAOQ scores, from 20.4 ± 28.1% pre-treatment, to 46.7 ± 36.5% after treatment VAS score significantly improved as well, from 16.5 ± 23.2% to 41.1 ± 32.4%	For normal patients (403), the SAOQ was 99% sensitive and 90.1% specific for identifying normosmia, when using a cutoff value of 66.7% = Normosmia. NPV was 88.7% and PPV was 99.1% for the questionnaire. For the VAS (cutoff of 47%) the numbers were Sn 95.5%, Sp 88%, NPV 86.1%, PPV 96.2%. There was significant positive correlation between SAOQ and VAS scores	Takebayashi et al.[10] 2010 (Level II, Prospective Cohort Study) (Low)

(continued)

Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
	18–78	n = 75 Healthy = 50 Anosmic/ Hyposmic = 25 Etiology not specified	This study aimed to compare two smell tests: The Connecticut Chemosensory Clinical Research Center (CCCRC) test and the Jet Stream Olfactometer (commonly used in Japan)	Study did not specifically comment on the test findings among healthy patients vs anosmics/hyposmics Instead, study focused on comparison between the two tests	Significant correlation between the two tests for detection threshold ($P < .01$; $r_s = .683$) and identification and recognition scores ($P < .01$; $r_s = .788$). When categorizing patients as either anosmic or normosmic, the CCCRC and JSO were in agreement 75.9-91.7% of the time. When comparing hyposmics (mild, moderate, and severe), the tests were in agreement only 22% of the time	Tsukatani et al.[11] 2005 (Level II, Prospective Cohort Study) (Low)
	9–93	n = 518 Post-traumatic (177) Post-URTI (97) Sinonasal (59) Idiopathic (84) Congenital (16) Other (85)	Sniffin' Sticks used on each nostril of patients with olfactory dysfunction to determine lateralized dysfunction in olfaction based on TDI score	23.4% (121/518) of patients had significant difference in TDI score between right and left nares Side-specific differences in thresholds were found significantly more in post-URTI patients than post-traumatic patients	Study found odor threshold score was correlated significantly with overall TDI, odor discrimination, and odor identification. The authors argue for testing each nostril, rather than doing birhinal testing, specifically if threshold scores in each nostril differ by 3 or more. TDI < 16 = anosmia and TDI < 31 is hyposmia.	Welge-Lussen et al.[12] 2010 (Level III, Cross-Sectional Study) (Serious – selection bias and lack of control group – all normosmic patients were excluded)
	5–96	n = 9139 Self-identified normosmic patients with no history of olfactory disturbance	Goal was to administer Sniffin' Sticks on self-identified healthy patients and validate diagnostic method	Did not comment on a preselected cohort of anosmics; instead, this study focused on demographic variations of Sniffin' Sticks results, along with validation of the smell test. Significant effect of age on overall TDI score, suggesting older individuals typically score worse Percentage of hyposmic/ anosmic patients increased most significantly from 61-70 years old	– Women scored higher than men by about 1.3 points. – Large jump in olfactory capabilities from 5-10 years old (90%+ of whom were "hyposmic") to 11-20 years old (19.5% hyposmic), – Age-related difficulty in testing was noted in the younger group. – Hyposmia defined as less than 30.75 points on TDI score Test-retest: $r = .8$ for odor discrimination; $r = .88$ for odor identification; $r = .92$ for odor threshold.	Oleszkiewicz et al.[13] 2019 (Level I, Testing of Previously developed diagnostic criteria) (Low)

(continued)

Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
	18–89	n = 288 5 groups (0-4) G0: control (48) G1: idiopathic (116) G2: sinonasal (33) G3: post-infectious (59) G4: post-trauma (32)	Correlation of Sniffin' Sticks with modified olfactory cleft specific Lund-Kennedy (OC-LK) score looking at olfactory mucosa through nasal endoscopy among 5 different groups of patients	G0: mean TDI 30.9; mean OC-LK 0.4 (SD 0.6); olfaction rating 8.3; airflow rating 7.9 G1: mean TDI 18.5; mean OC-LK 0.6 (SD 0.8); olfaction rating 3.3; airflow rating 7.1 G2: mean TDI 17; mean OC-LK 2.5 (SD 1.5); olfaction rating 3.6; airflow rating 5.8 G3: mean TDI 20.2; mean OC-LK 0.4 (SD 0.6); olfaction rating 3.0; airflow rating 7.2 G4: mean TDI 13; mean OC-LK 0.4 (SD 0.7); olfaction rating 2.0; airflow rating 7.7	Sniffin' Sticks test showed difference in TDI score between controls and each of smell impaired groups. Significantly higher OC-LK and cLK scores in all patients combined when compared with normosmic controls (although sinonasal seemed to be only group skewing that difference) Significant negative correlation found between OC-LK and cLK on both sides and discrimination scores from Sniffin' Sticks smell test Significant negative correlation between OC-LK on right side and TDI scores	Poletti et al.[14] 2008 (Level II, Prospective Cohort Study) (Low)
Orthonasal Smell Tests with no Cutoffs	12–85	n = 273 All subjects in the study had no history of olfactory disturbances	"Random" test compared to Sniffin' Sticks. 16 concentrations of PEA (rose smell) or CIT (citrus smell) were presented in a pseudo-random order in a non-forced choice test as opposed to stair-stepped threshold method of Sniffin' Sticks	Did not provide information on anosmics/hyposmics individually. The cohort was a self-reported normosmic cohort, and this study's goal was to introduce a novel smell testing method	"Random" Test correlates with Sniffin' sticks overall and among subsets, with the strongest correlation being the combined PEA/CIT score with the TDI score of Sniffin Sticks ($r = .82$). – Test takes 10 minutes as opposed to 20-30 minutes for Sniffin' Sticks – "Random" test includes 'no odor' choice – Did not provide what cutoff values would be used to define anosmia vs hyposmia vs normosmia.	Kobal et al.[15] 2001 (Level II, Prospective Cohort Study) (Low)
	49 (mean)	n = 68 38 'sinonasal' patients with a history of CRS or allergic rhinitis 30 healthy controls Excluded post-surgical	This test described a novel essential-oil-based smell test, AROMA, which can be done at home in a forced choice manner, and	Sinonasal cohort: 28/38 hyposmic per UPSIT Mean SNOT-22 = 50.6 AROMA score: mean 47% (95% CI, 40%-53%). Healthy cohort: 8/22 hyposmic per UPSIT	– Correlated significantly with UPSIT and SNOT-22 – AROMA correlation to UPSIT is strong ($r = .75$) – SNOT-22, age, and perceived sense of smell all significantly correlated with both AROMA	Villwock et al.[16] 2020 (Level IIb, Prospective Cohort Study) (Moderate –control and experimental group mean ages

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Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
		and congenital anosmics	compared patient findings with UPSIT and SNOT-22	Mean SNOT-22 = 7.3 AROMA score: mean 82% (95% CI 77-87%)	($\rho = -0.548$, -0.557, -0.642, respectively) and UPSIT ($\rho = -0.367$, -0.460, -0.552, respectively). Anosmic population was avg 55 years while normal was avg 41 years.	significantly different)
	12–83	n = 227 Normosmia (133) Anosmia (94): idiopathic (32), congenital (18), rhinosinusitis (11), post-trauma (9), post-surgical (15), post-URTI (7), Other (2)	Utilized a nine dilute butanol threshold test averaged with the score from a nine question forced choice identification test (score 0-9).	Mean score for anosmic patients was 2.7 with 2.2 SD; range 0-7.5 Mean score for normosmic was 7.1 with SD 1.08; range 5-9	Test able to differentiate normosmia from anosmia, and hyposmia from anosmia, but differentiating normosmia from hyposmia needs further study. Did not explicitly give cutoffs for what they would consider normosmia vs hyposmia vs anosmia. Anosmic population was avg 58 years while normal was avg 37.5 years.	Robson et al.[17] 1996 (Level II, Prospective Cohort Study) (Moderate –control and experimental group mean ages significantly different
	47 (mean)	n = 100 64 Anosmic/Hyposmic patients with a history of CRS or idiopathic olfactory disturbance 36 Healthy Controls	Alcohol sniff test (AST) compared to butanol threshold test. 70% isopropyl alcohol used on alcohol prep pad and distance needed to smell measured = AST score	Normosmics scored close to 15 on the AST whereas anosmics scored around 5 with a wider SD	AST scores significantly differ between anosmics, hyposmics, and normosmics (who have been previously classified as such per the butanol threshold test). The distance cutoff for the AST was not explicitly stated.	Davidson and Murphy[18] 1997 (Level II, Prospective Cohort Study) (Low)
Retronasal Smell Tests	20–63	n = 44 normal controls (NL) = 11 Nasal polyposis (NP) = 11 Post-infectious (PI) = 11 Post-traumatic (PT) = 11	4 equal sized groups of patients underwent MRI of olfactory bulb, chemosensory event-related potentials (trigeminal and olfactory), and smell tests (ortho- and retronasal)	Orthonasal testing showed NL individuals had higher scores than NP, PT, and PI patients ($P < .001$). The same was found for retronasal testing ($P < .001$). Retronasal scores for NP patients were higher compared with PT and PI patients ($P < .001$). MRI showed decreased olfactory bulb volume	Of the five testing modalities, normal individuals were statistically significantly different than the other three groups in all cases except trigeminal ERP. Normal patients had higher amplitude olfactory ERP, and higher scores on ortho and retronasal smell tests compared to the other three groups. The study found that the ROC curves for the tests were high for orthonasal testing	Rombaux et al.[19] 2006 (Level II, Prospective, Cohort Study) (Moderate – Low Sample sizes in the groups potentially limits well-powered analysis)

(continued)

Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
				among NP, PI, and PT patients compared to NL	(0.99) and retronasal testing (0.98). Suggests test is good at discriminating normal from abnormal olfactory function. Age was not significantly different between groups ($P = .68$).	
	12–81	n = 167 Controls (71) Smell loss (96): Sinonasal (31) Post-URTI (26) Post-traumatic (17) Idiopathic (14) Other (8)	Candy Smell Test was investigated, which compares 23 industrially produced candy smells with Sniffin' Sticks smells Hyposmia defined as <16/23 Anosmia defines as <13/23	Olfactory Dysfunction group: Mean (SD) TDI = 16.2 (0.7) CST score = 11.6 ± 0.4 Controls had mean (SD) TDI of 33.2 (0.4) CST score 19.0 ±0.3	Olfactory Dysfunction: 30 (31.3%) were found to be hyposmic and 51 (53.1%) were found to be anosmic. 15.6% were normosmic Healthy controls: 97.2% normosmic, 2.8% hyposmic	Haxel et al.[20] 2011 (Level II, Prospective Cohort Study) (Low)
OERP	19–89	n = 123 Normal smell: 43 Anosmic: 40 Hyposmic: 40 Where etiology was specified: congenital anosmia (6) , Parkinson's disease (1), head trauma (10), URTI (30), sinonasal disease (17), idiopathic (16)	Olfactory event-related potentials (OERP) in relation to Sniffin Sticks	A TDI score of 22.6, equivalent to "pronounced hyposmia", was identified as the turning point at which the probability of detection of OERP was higher than 50%. Its 95% confidence interval of 16.1–27.8 well reflected the range of hyposmia, i.e., was above significant loss of olfactory function (functional anosmia, TDI score < 15.5) and below normal olfactory function (TDI score > 30.5).	OERP detection lies within the clinical boundaries of hyposmia, but is above that of anosmia, and so can be a tool to detect present olfactory function. Absence of OERP has little to no diagnostic value as even some hyposmic and normosmic patients could not record the OERP, possibly due to the methodology of getting OERP requiring multiple stimulations.	Lotsch and Hummel[21] 2006 (Level II, Prospective Cohort Study) (Low)
	15–79	n = 65 post-URTI (15) post-trauma (26) nasal polyps (15) mixed (9)	Likelihood of recording olfactory event-related potentials (OERP) in comparison to orthonasal and retronasal olfactory tests	33/65 patients categorized as hyposmic based on orthonasal (Sniffin' Sticks) and retronasal smell tests 32/65 patients categorized as anosmic 22/33 hyposmic patients recorded an OERP	OERPs are still recorded in those categorized as hyposmic. OERPs are more likely to be detected in hyposmics who have a retronasal score that is closer to norm. The point at which OERP detection disappears is within the range of hyposmia, although OERPs are	Rombaux et al.[22] 2007 (Level II, Prospective Cohort Study) (Moderate – no control group)

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Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
				0/32 anosmic patients recorded an OERP	absent in all anosmics, indicating its use as a screening tool.	
fMRI	6–68 (one patient under 18)	n = 23 2 control patients 16 Type I hyposmia Post-trauma (5) congenital (4) post-URTI (2) Allergic rhinitis (2) Idiopathic (2) Drug-induced (1) 5 Type II hyposmia Post-URTI (2) Diabetes (1) Sarcoma (1) Stroke (1)	fMRI measuring brain activation in response to olfactory stimuli in type I and II hyposmics using a new rapid fMRI technique Type I hyposmia: Could detect but not recognize odors Type II hyposmia: Could detect and recognize odors, but with lower acuity than normosmics	Type I had average total activated pixel numbers of .50, .40, and .71 for amyl acetate, menthone, and pyridine, respectively. Type II had average total activated pixel numbers of 11.7, 7.2, and 17.1 for amyl acetate, menthone, and pyridine, respectively. Normal subjects had 48 for amyl acetate and 260 for pyridine.	Each patient with Type I hyposmia treated with theophylline had improved smell function to Type II hyposmia, and after treatment demonstrated activation in inferior frontal and cingulate cortex bilaterally, whereas before treatment, no activation in these regions was apparent. Activation in patients with Type I hyposmia reduced in the middle frontal, orbitofrontal, and temporal cortex; totally absent in regions of inferior frontal, insular, and cingulate cortex. Activation in patients with Type II hyposmia was greatest in the middle frontal cortex and the orbitofrontal cortex bilaterally and was present in regions of inferior frontal, temporal, and cingulate cortex.	Levy et al.[23] 1999 (Level II, Prospective Cohort Study) (Serious – Inadequate size of control group, precludes well-powered analysis)
	20–76	n = 25. 17 normosmic 8 hyposmics: post-trauma (3), allergic rhinitis (3), congenital (1), and oncologic (1)	fMRI using pyridine, menthone, and amyl acetate to observe activation of brain regions	Less activation of inferior frontal and cingulate gyral regions of frontal lobes and medial and posterior temporal cortices within hyposmic patients when compared to normosmics ($P < .01$).	This was the preliminary study that showed that these three odors can lead to brain activation in fMRI and that there is a difference between hyposmics and normosmics.	Levy et al.[24] 1998 (Level II, Prospective Cohort Study) (Moderate - Small sample sizes)
	42.2 +/– 10.4 (average and SD)	n = 35 16 post-traumatic anosmics 19 healthy controls	fMRI comparing brain activation using BME (unpleasant odor) and citral (pleasant odor) stimulation All patients underwent olfactory smell	Decreased brain activation in the bilateral temporal cortex and left superior parietal lobe of patients with traumatic anosmia in response to an unpleasant odor was noted, relative to normal controls. Specific	Anosmic patients had previously been diagnosed as such per the Korean version of Sniffin Sticks (KVSS) Anosmia group mean age: 42.2 ± 10.4 y Normosmia group mean age:	Moon et al.[25] 2018, (Level II, Prospective Cohort study) (Moderate –control and experimental group ages significantly differ)

(continued)

Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
			testing and nasal endoscopy	values were not provided	29.3 ± 8.5 y	
MRI	Mean 58 years	n = 564 patients with olfactory dysfunction per UPSIT Idiopathic = 247 130 of 247 underwent MRI. No patients in other groups underwent MRI. Post-viral = 230 Post-traumatic = 87	All patients had a baseline UPSIT diagnostic of olfactory dysfunction. Goal of study was to determine MRI feasibility and cost-effectiveness for identifying an etiology of idiopathic olfactory loss.	4.6% of MRIs were considered abnormal, but only 1 patient had an MRI that potentially could explain *causation* of olfactory loss (multiple sclerosis) Abnormalities seen on MRI: hypertensive encephalopathy, left frontal lobe vascular malformation, right third ventricle mass, left olfactory bulb atrophy, possible left posterior fossa schwannoma, and multiple white matter abnormalities suggestive of multiple sclerosis (MS).	Estimated cost per MRI finding that could potentially be causative of olfactory loss was $3,25,000, if average cost per MRI is $2500. Authors considered olfactory bulb atrophy as a result of, rather than a cause of, olfactory loss; thus, its presence on an MRI was not deemed to add value in a patient's workup.	Hoekman et al.[26] 2014, (Level IV, Retrospective Review) (Low – study focused on utilizing MRI to help diagnose idiopathic anosmia; control group unnecessary)
	Mean 52 years	n = 24 Post-viral (10), Post-trauma (5), and idiopathic (9)	MRI to determine if findings among olfactory dysfunction patients can be correlated to objective (Chemosensory evoked potentials) and subjective olfactometry (Sniffin' Sticks)	The study concluded that trauma affects olfactory filaments, while virus-induced olfactory dysfunction is associated with damage to olfactory epithelium, in particular olfactory mucosa.	Statistically significant correlation found between objective olfactometry and bulb volume determined by MRI, [$P < .001$, r (PEARSON) = .85]. No correlation identified between subjective olfactometry and bulb volume [r(PEARSON = .58]. Inverse correlation between bulb volume and duration of olfactory dysfunction [$P = .06$, r (PEARSON) = −.38].	Goektas et al.[27] 2009 (Level II, Prospective Cohort Study) (Moderate – no control group)
	16–84	n = 127 All Post-Traumatic 81 with anosmia 44 with hyposmia 2 with normosmia	Analysis of brain lesion patterns using MRIs (flair, Epi, SWI, T2-weighted)	In anosmic patients, lesions in right olfactory bulb region were much more frequent than in patients with preserved sense of smell	77/143 patients had lesions overall. Of these, 75/77 had orbitalfrontal abnormalities	Lotsch et al.[28] 2016 (Level II, Prospective Cohort Study) (Serious – inadequate size of control group)
	20–63					

(continued)

Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
		n = 44 Normal controls (NL) = 11 Nasal polyposis (NP) = 11 Post-infectious (PI) = 11 Post-traumatic (PT) = 11	4 equal sized groups of patients underwent MRI of olfactory bulb, chemosensory event-related potentials (trigeminal and olfactory), and smell tests (ortho- and retronasal)	Olfactory Bulb (OB) volumes higher in NL individuals compared with NP, PT, and PI patients ($P < .001$) OB volumes in PT patients significantly lower than those from NP and PI patients ($P < .001$)	For the entire cohort, a significant correlation was found between orthonasal testing and OB volume, be- tween retronasal testing and OB volume, and between both orthonasal and retronasal testing and olfactory ERP am- plitudes. Olfactory ERPs were recorded in the 11 NL in- dividuals and in 3 NP, 3 PT, and 4 PI patients, defined as responders.	Rombaux et al.[19] 2006 (Level II, Prospective, Cohort Study) (Low)
	14–65	n = 40 21 with post-traumatic anosmia 19 with normosmia (per Cain's identification test) – 19/19 underwent SPECT, 10/19 underwent MRI	MRI and SPECT performed on anosmic patients to determine if any areas of the brain are abnormal	Brain MRIs abnormal in 18/21 patients (85.7%), 13 of whom (61.9%) had olfactory bulb abnormalities (10 patients [47.6%] had olfactory bulb injury and 3 had olfactory bulb atrophy [14.3%]). Frontal lobe abnormalities were seen in 15/21 patients (71.4%). Main abnormality was in the anterior inferior frontal lobe. Qualitative SPECT abnormal in 17/21 patients (80.9%), and semiquantitative SPECT abnormal in 18/21 patients (85.7%). Frontal hypoperfusion was the most common finding (76.19%)	Frontal abnormalities in SPECT had good correlation with MRI, with a 0.81 correlation (contingency coefficient = 0.217), but not significant ($P = .309$). Poor correlation between MRI and SPECT in parietal and temporal lobes (0.71 correlation, contingency coefficient = 0.152). When MRI and SPECT considered together, there is a 90.4% chance of finding an abnormality in at least one of these images.	Atighechi et al.[29] 2009 (Level II, Prospective Cohort Study) (Moderate – selection bias – patients with very severe head trauma selected, potentially exaggerating results)
SPECT	19–48	n = 29 16 post-traumatic anosmics 13 nontraumatic controls	Qualitative and Semi-quantitative SPECT to investigate findings among post-traumatic anosmia patients (diagnosed per Cain's smell test)	Qualitative SPECT: Orbitofrontal abnormalities in 6/16 (38%) anosmic patients. Of these, 4 patients also had abnormalities in other regions Semi-quantitative SPECT: Orbitofrontal region abnormal in the 14/16 (87.5%)	Overall, 25/32 calculated orbital frontal rations (78%) were abnormal. Hypoperfusion noted in inferior orbital cortex in 5 patients (16%), superior frontal pole in 5 patients (16%), posterior superior frontal region in 1 patient (3%), and parasagittal cortex in 4 patients (12.5%).	Eftekhari et al.[30] 2005 (Level II, Prospective Cohort Study) (Moderate – results not generalizable given very specific group of patients under study)

(continued)

Table 1. Continued.

Diagnostic Modality	Age Range (Years)	Patient Population	Description and Objective of Study	Diagnostic Test Findings Among Anosmics/Hyposmics	Expanded Notes	Author, Year (Level of Evidence, Risk of Bias)
				anosmic patients unilaterally (3) or bilaterally (11).	There were 9 abnormal CT scans and/or MRIs in the target group (56%).	
	Mean 38.1 +/– 11.9	n = 23 18 post-traumatic anosmics 5 healthy controls	Quantitative SPECT findings in post-traumatic anosmics	Count ratios significantly lower ($P < .01$) in anosmics in orbital frontal cortex. Anosmics had count density of .87 (SD .13) vs .98 (SD.06) in normosmics in the orbital front cortex	Study suggests that post-traumatic anosmia is associated with hypoperfusion of the orbital frontal cortex.	Varney et al.[31] 1998 (Level II, Prospective Cohort Study) (Moderate – results not generalizable given very specific group of patients under study)
SPECT-CT (Thallium)	26–71	n = 31 Anosmia: Head trauma (n = 7), URTI (n = 7), and CRS (n = 7) 10 healthy controls	SPECT-CT used to evaluate Migration of nasal (201) Tl to the olfactory bulb compared to T&T olfactometry	Nasal (201) Tl migration was significantly lower in olfactory-impaired patients (n = 21) compared with healthy volunteers (n = 10). No significant difference between the three anosmic patient groups (post-trauma, URTI, CRS).	Migration of (201) Tl to the olfactory bulb significantly correlated with odor recognition thresholds obtained with T&T olfactometry ($r = -.62$) and correlated with volume of olfactory bulb determined from MRI images ($r = .73$) when all subjects were included.	Shiga et al.[32] 2013 (Level II, Prospective Cohort Study) (Low)
PET Scan	Mean 57 +/– 9 years	n = 18 9 post-viral olfactory disfunction 9 healthy controls	PET scan utilized to detect abnormalities in the central auditory pathway of patients with post-viral anosmia	Significant hypometabolism found in right piriform gyrus (Brodmann area 34) and parahippocampus (Brodmann area 37) of anosmics. Hypometabolism was also shown in the bilateral insular cortices and medial and lateral temporal cortex	Right piriform gyrus and parahippocampus are where olfactory neurons primarily project. Bilateral insular cortices and medial and lateral temporal cortex are where olfactory information is integrated to produce the sensation. Regional metabolism inversely correlated with the BTT (butanol threshold test) score in right cingulate cortex, basal ganglia, and left insular and left temporal cortex.	Kim et al.[33] 2012 (Level II, Prospective Cohort Study) (Low)
	Mean 47 +/– 9.6 years	n = 22 Post-trauma anosmics (11) and control (11)	PET to determine metabolism differences among post-trauma anosmics and normosmic controls	Significant decreases in metabolic activity in bilateral orbitofrontal cortex (Brodmann's area 11) and rectal gyrus among anosmics. Also, decrease in frontal pole (Brodmann's area 10) metabolism	Areas that had statistically significant differences ($P < .05$) among post-trauma vs control: orbitofrontal (left and right), frontal pole, medial prefrontal, temporal tip, and medial prefrontal gyri. Areas that showed no differences were putamen (left and right, occipital radiation, and visual association cortex).	Varney et al.[34] 2001 (Level II, Prospective Cohort Study) (Low)

et al.[19] found that post-infectious (PI), post-traumatic (PT), and nasal polyposis (NP) anosmic patients had significantly lower retronasal smell test scores than normosmics ($P < .001$), with PI and PT patients scoring worse than NP patients ($P < .001$). Haxel et al.[20] compared the novel Candy Smell Test (CST) to SS and found a significant correlation between the two, defining anosmia as <13/23 and hyposmia as (13-16)/23 on CST (Table 1).

Olfactory event related potentials (OERP). Two studies investigated OERP detection[21,22] in patients with various etiologies of anosmia/hyposmia. Lotsch and Hummel[21] found that OERP can be used to detect existing olfactory function, but is not very effective in diagnosing anosmia/hyposmia (Table 1). Rombaux et al.[22] found that OERPs were recorded in 22/33 hyposmic patients and 0/32 anosmic patients, indicating it can be used to screen for anosmia but is not effective for determining a definitive diagnosis.

Imaging modalities

Functional MRI. Three studies (83 patients) investigated fMRI[23–25] findings in patients with known olfactory dysfunction. Levy el al[23,24] measured brain activation in response to amyl acetate, menthone, and pyridine, reporting reduced activation in orbitofrontal, middle frontal, inferior frontal, and temporal cortices in hyposmics relative to normosmics (Table 1). Moon et al.[25] reported reduced activation in bilateral primary and secondary olfactory cortices in post-traumatic anosmics (Table 1).

Magnetic resonance imaging. Five studies (365 patients) utilized conventional MRI[19,26–29] to evaluate findings among known anosmics/hyposmics. Hoekman et al.[26] investigated the feasibility of MRI as a diagnostic tool for anosmia and reported that only 4.6% of MRIs were abnormal in patients with idiopathic olfactory loss, concluding that MRI is not cost-effective in diagnosing anosmia (Table 1). Goektas et al.[27] found a significant correlation between objective (Chemosensory evoked potentials), but not subjective (Sniffin' Sticks), olfactometry and olfactory bulb volume on MRI. Further, this suggests that trauma affects olfactory filaments and thus decreases olfactory bulb volume, while virus-induced olfactory dysfunction is associated with damage to olfactory epithelium, in particular olfactory mucosa, and does not result in loss of olfactory bulb volume (Table 1). Lotsch et al.[28] analyzed brain lesion patterns in post-traumatic anosmics and found that, when compared to normosmics, these patients tended to have lesions in the right olfactory bulb region. Rombaux et al.[19] found that olfactory bulb volumes were higher in normosmics when compared to nasal polyposis, post-trauma, and post-infectious anosmics ($P < .001$). Atighechi et al.[29] found that 86% of post-traumatic anosmic patients had abnormal MRIs, of which 71.4% entailed frontal lobe abnormalities (Table 1).

SPECT/CT. Four studies used SPECT,[29–32] one of which also used CT,[32] totaling 123 patients. Atighechi et al.[29] found that SPECT identified abnormalities (typically frontal hypoperfusion) in over 80% of post-traumatic anosmics (Table 1). Eftekhari et al.[30] corroborated these findings. Varney et al.[31] found significantly lower count ratios in post-traumatic anosmics in the orbital frontal cortex when compared to normosmics. Shiga et al.[32] used SPECT and CT to evaluate migration of nasal thallium to the olfactory bulb, and found that olfactory-impaired patients had significantly lower migration when compared to normosmics (Table 1).

PET scans. Two studies used PET[33,34] to observe differences among olfactory impaired patients, totaling 40 patients. Kim et al.[33] found significant hypometabolism in the right piriform gyrus and parahippocampus among post-viral anosmic patients. Varney et al.[34] found decreased metabolic activity in the bilateral orbitofrontal cortices, rectal gyrus, and frontal pole in post-traumatic anosmics when compared to normosmics (Table 1).

Risk of bias. Among the studies in this systematic review, 14 had a low risk of bias, 10 had a moderate risk of bias, and 3 had a serious risk of bias.

Discussion

Olfactory dysfunction has profound effects on quality of life, impacting both the ability to experience reward related to smell and the ability to detect potentially harmful odors and substances.[35,36] This dysfunction can range from a slightly diminished sense of smell (hyposmia) to a complete loss of smell (anosmia).[37] Smell dysfunction has numerous etiologies, including viral infections, trauma, obstruction, CRS, and idiopathic causes.[37] Notably, the SARS-CoV-2 pandemic has been shown to cause olfactory dysfunction in patients who might otherwise be asymptomatic,[38,39] highlighting the crucial need for clinicians to be able to properly diagnose and manage individuals with smell disturbance.

Based on this systematic review, orthonasal smell tests (such as Sniffin' Sticks and UPSIT) should be utilized as an initial diagnostic tool for smell dysfunction.[8,12–15,20] UPSIT, the most widely-used diagnostic smell test, entails presenting 40 odors in a forced multiple-choice manner (scored up to 40); a score <18 is consistent with anosmia, whereas >33 in men or >34

in women is considered normosmia, with varying levels of microsmia in between.[40] SS involves utilizing 12 smells to produce a TDI score, encompassing odor threshold, discrimination, and identification[13]; a score of 31 or greater indicates normal olfactory function, while <16 indicates anosmia, with anything in between being hyposmia.[13] Although SS and UPSIT are widely-used and validated tests, they are often considered tedious. In light of this, providers may consider utilizing more efficient tests, such as those presenting odors in randomized order,[15] or tests presenting a limited subset of odors,[8,9] which have been utilized with comparable results to SS and/or UPSIT (Table 1).

Of note, Landis et al.[3] determined that patients with smell loss, without a loss of taste, have diminished orthonasal olfaction but intact retronasal olfaction, indicating that orthonasal and retronasal olfaction might be processed differently. Thus, retronasal smell tests are an important method to consider when diagnosing anosmia or hyposmia if orthonasal smell tests do not fully explain the patient's clinical picture.

In addition to diagnostic smell tests, imaging has been used to investigate findings among patients with smell disturbance, but imaging is not commonly used as a primary diagnostic tool. The most widely used imaging modality is MRI, including both traditional and fMRI.[19,23–29] Other imaging modalities include SPECT and PET,[29–34] however mostly in academic settings and not in routine use, and findings among studied patients are detailed in Table 1. Overall, the most common finding in anosmics and hyposmics, across multiple imaging modalities was abnormality within the orbitofrontal region. When excluding control patients, this was present in 29/45 subjects in the fMRI studies,[23–25] 92/351 conventional MRI subjects,[19,26–29] 34/55 SPECT subjects,[29–32] and 11/20 PET subjects[33,34] (Table 1). The orbitofrontal cortex is known to be involved in the conscious perception and processing of smell, and lesions here have been linked to anosmia.[41] Trauma is a very common cause of lesions to the orbitofrontal region and may explain the loss of smell in these individuals.[41]

An important study included in this systematic review discusses the cost-effectiveness and feasibility of using MRI to diagnose idiopathic anosmia/hyposmia.[26] Among 130 patients who underwent MRI, only six MRIs were considered abnormal, only one of which could potentially explain anosmia. Assuming an average MRI cost of $2500, the authors determined that the expense associated with identifying a single abnormality potentially explaining anosmia on MRI is $3,25,000 (Table 1). It is important to note, however, that all patients in the study had an idiopathic etiology of olfactory loss, which could explain why the MRI results of this study vary widely from the other imaging studies included in this systematic review.

Based on the most feasible and reliable diagnostic tools reviewed in this paper, we propose an algorithm that can assist the clinician in working up the patient with suspected anosmia/hyposmia (Figure 2). In the current climate, screening for symptoms of COVID-19 should be considered given this has been identified as an early marker for disease.[37] For patients with concern for COVID-19 infection, referral for testing is prudent prior to in-office evaluation, if possible. For all patients, appropriate personal protective equipment precautions should be followed.[42–44] Then, in order to determine the etiology of olfactory loss, a detailed history and physical examination should be performed. Patients with a sudden onset of olfactory loss are typically those with post-viral or post-traumatic etiologies, although post-traumatic anosmia can present a few weeks after the incident.[37] We suggest patients should be evaluated using a well-established diagnostic orthonasal smell tests such as SS or UPSIT, if available, prior to any topical nasal medications or manipulation. Alternatively, a clinician may choose among the less time-consuming validated methods discussed, such as the three odors determined by Lotsch et al.[8] or the Q-SIT.[9] If possible, these smell tests should be performed individually for each nostril to rule out lateralized dysfunction.[12] Next, as part of the physical exam, nasal endoscopy should be performed to rule out an obstructive anatomic/pathologic cause of anosmia.[37] Following these diagnostic measures, fMRI or SPECT may be considered if there is post-traumatic etiology to localize the abnormality, though it is unclear if findings on either imaging modality would change clinical management. This systematic review did not find that benign or malignant tumors were a significant finding in patients with reduced sense of smell, which brings into question whether imaging is necessary for routine workup of isolated reduced smell without other neurologic or rhinologic symptoms. Based on the evidence available, this review does not support the routine use of imaging in working up smell disturbance.

There are a few limitations of this systematic review. First, we excluded papers solely focusing on CRS-related anosmia. Given the large body of literature available on CRS, we felt it prudent to concentrate on post-infectious and post-traumatic etiologies and evaluate these independently. Additionally, due to the varying studies using different methods to diagnose anosmia, a meta-analysis on the data was unable to be performed. In addition, many of the studies included had small sample sizes and very specific populations, which may limit generalizability of the study. Furthermore, many of the imaging studies in this systematic review focused on post-traumatic anosmia, which presents with different imaging findings than the other etiologies of olfactory dysfunction. This limits our ability to draw definitive

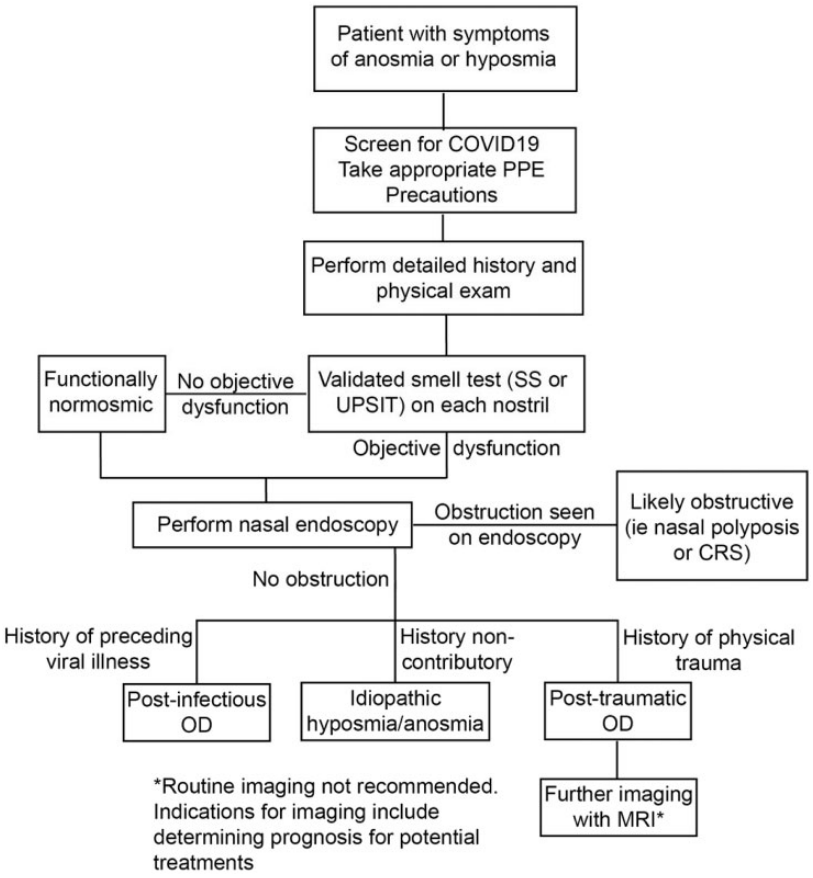

Figure 2. Diagnostic algorithm for patients presenting with anosmia. CRS = Chronic Rhinosinusitis, OD = Olfactory Dysfunction, MRI = Magnetic Resonance Imaging, UPSIT = University of Pennsylvania Smell Identification Test, SS = Sniffin' Sticks.

and broad conclusions on the role of imaging in working up smell dysfunction. Finally, many of the imaging studies included were not necessarily diagnostic, as the patients had already been diagnosed with olfactory dysfunction, and the imaging was subsequently performed for characterizing imaging findings or ruling out intracranial neoplasms.

Conclusion

The literature on the diagnosis of anosmia and hyposmia includes diagnostic smell tests and imaging modalities. A thorough history and physical, followed by orthonasal smell tests such as SS or UPSIT should be used as a first-line method to diagnose anosmia, although validated abridged smell tests may be used as well. Although imaging modalities can be used to investigate olfactory dysfunction, their feasibility is questionable and is not cost-effective in the patient without suspicion for underlying mass or neurological disorder. One potential benefit for using imaging modalities includes localizing an abnormality, which can then potentially lead to better prognostic accuracy or guidance on potential future treatments such as olfactory epithelium transplantation or electronic olfactory implant.[45] Further study is needed on these topics.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

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Ethical Approval

This study was deemed exempt by our institutional review boards.

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