Olfactory dysfunction in CHARGE syndrome: a systematic review of prevalence, assessment methods, and clinical correlates

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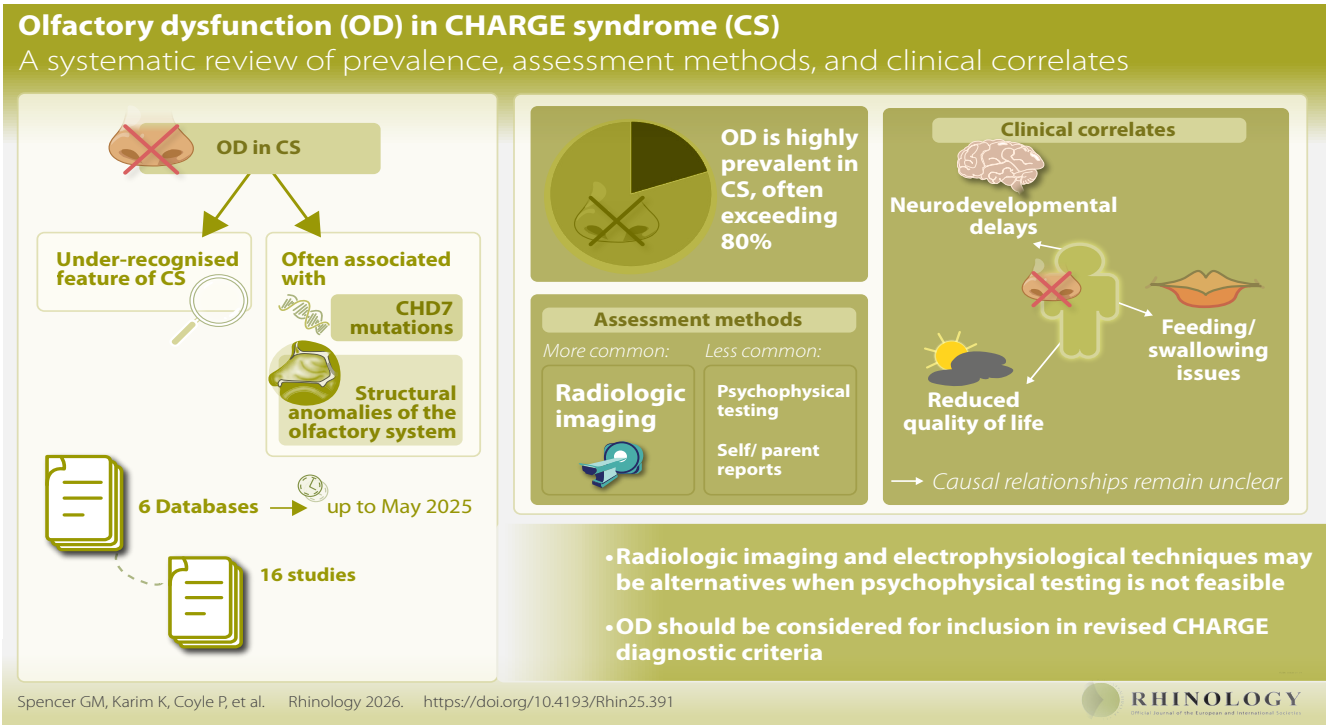

Abstract

Background: Olfactory dysfunction (OD) is an underrecognized feature of CHARGE syndrome (CS), often associated with CHD7 mutations and structural anomalies of the olfactory system. This systematic review examines the burden, assessment methods, and clinical correlates of OD in CS.

Methodology: A systematic review was conducted in accordance with PRISMA guidelines and registered with PROSPERO (CRD420251040500). A comprehensive search of six databases up to May 2025 was performed. Two independent reviewers screened, extracted data, and assessed study quality. A narrative synthesis was performed.

Results: From 1,643 records, 16 studies met inclusion criteria. Most were retrospective cohort studies and employed clinical diagnostic criteria for CS, with a subset reporting CHD7 mutation data. OD was most frequently identified radiologically. Psychophysical testing and self/parent reports were less common. Neurodevelopmental delays, feeding/swallowing issues, and reduced quality of life were reported in association with OD, but causal relationships remain unclear.

Conclusions: OD is highly prevalent in CS, often exceeding 80%, yet remains underrecognized. Radiologic imaging and electrophysiological techniques may be alternatives when psychophysical testing is not feasible. Future research should focus on validating paediatric-specific and developmentally appropriate olfactory assessments and integrating olfaction into quality-of-life frameworks. OD should be considered for inclusion in revised CHARGE diagnostic criteria.

Key words: anosmia, charge syndrome, genetic disorder, olfaction, olfactory dysfunction

Introduction

CHARGE syndrome (CS) is a rare genetic disorder characterized by coloboma, heart defects, choanal atresia, poor growth, genital abnormalities, and ear anomalies [1]. Olfactory dysfunction (OD), including anosmia and hyposmia, is increasingly recognized as part of the CHARGE phenotype, linked to aplasia of the olfactory bulb and tracts, as well as CHD7 gene mutations [2]. Variants of arhinencephaly were reported in autopsy cases as early as 1981 by Pagon et al. [3]. Children with CS commonly have peripheral orofacial anomalies in addition to choanal atresia, such as cleft palate, or upper airway anomalies that may require tracheostomy, all of which may further impair olfaction [4]. Despite its clinical significance, the prevalence of OD in CS remains uncertain, and assessment methodologies vary widely [2].

OD can have significant impact on quality of life, through effects on feeding behaviours, environmental navigation, hazard avoidance, hygiene regulation, and social communication [5,6]. Olfactory deficits may exacerbate the CHARGE phenotype, potentially though its impact on feeding [4,7,8], impaired mother-child bonding, behavioural disturbances, and broader implications on cognitive development [4]. Early identification of OD is therefore important. OD can be assessed through use of subjective patient/parent reporting, but the gold standard is age-appropriate psychophysical testing. Radiological assessment of olfactory structures can add diagnostic or prognostic information, though due to high inter-individual variability, cannot at present be used in isolation as a proxy for olfactory function [6].

Subjective questionnaires, psychophysical testing, and magnetic resonance imaging (MRI) have all been employed in the assessment of olfaction in CHARGE, yet no synthesis of the prevalence or clinical associations of OD currently exists. We conducted a comprehensive systematic review to estimate the burden of OD in this syndrome, evaluate assessment approaches, and explore potential clinical correlates, including genotype-phenotype relationships as well as impacts on neurodevelopmental outcomes and quality of life.

Materials and methods

Search strategy

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines and registered the protocol internationally with PROSPEO (CRD420251040500) [9]. In collaboration with a health sciences librarian, the lead author (G.S.) conducted a search of published literature in the databases listed in Figure 1, up until May 2025. The search strategy included both medical subject headings related to CS and keywords related to OD as the item of interest and are featured in Figure 2. We included studies that were: 1) published in peer-reviewed journals; 2) involved patients diagnosed clinically or genetically with CS that reported on the prevalence of OD using any type of olfactory function assessment 3) reported one of radiologic findings, genotype correlations (e.g., CHD7 mutations), neurodevelopmental outcomes, or quality of life impact; 4) studies published in English. We excluded studies that: 1) were not original research studies; 2) were case reports or case series involving less than four patients diagnosed with CS; 3) focused exclusively on other syndromes (e.g., Kallmann syndrome) without CHARGE-specific data.

We imported identified citations into the Covidence software (Systematic Review Tool, Australia). Two independent reviewers (G.S., K.K.) applied inclusion/exclusion criteria to each title and abstract to determine if the study should be selected for full-text review. Two independent reviewers (G.S., K.K.) performed the full-text review of each of the included studies. Any disagreements between reviewers were resolved via a consensus meeting.

Critical appraisal

We used the Joanna Briggs Institute (JBI) critical appraisal tool for the assessment of risk of bias for analytical cross-sectional studies [10]. Two reviewers (G.S., K.K.) independently evaluated the methodological quality of each study using the JBI tool. The JBI tool does not use a numerical scoring or weighting system; instead, studies are assessed qualitatively on a question-by-question basis, and overall risk of bias is determined through reviewer consensus and narrative judgment rather than point totals [10]. The results of this critical appraisal can be found in Table 1.

Data extraction

Two reviewers (G.S., K.K.) independently extracted data, resolving discrepancies by consensus. Variables included study demographics, CS diagnostic details, olfactory assessment methods, OD prevalence, MRI findings, genotype-olfactory correlations, and other outcomes (neurodevelopment, feeding/swallowing, quality of life). Proposed OD mechanisms were also noted. The full data extraction table is available in Table S1.

Synthesis of the extracted data

We performed a narrative synthesis of the extracted data from 16 studies. We were not able to complete a meta-analysis due to the small number of studies available and heterogeneity in assessment and reporting of olfactory outcomes. To repot both quantitative and qualitative data included in the studies, our narrative synthesis was conducted in a convergent integrated approach. We present integrated findings of a combination of qualitative data and textual descriptions of quantitative data.

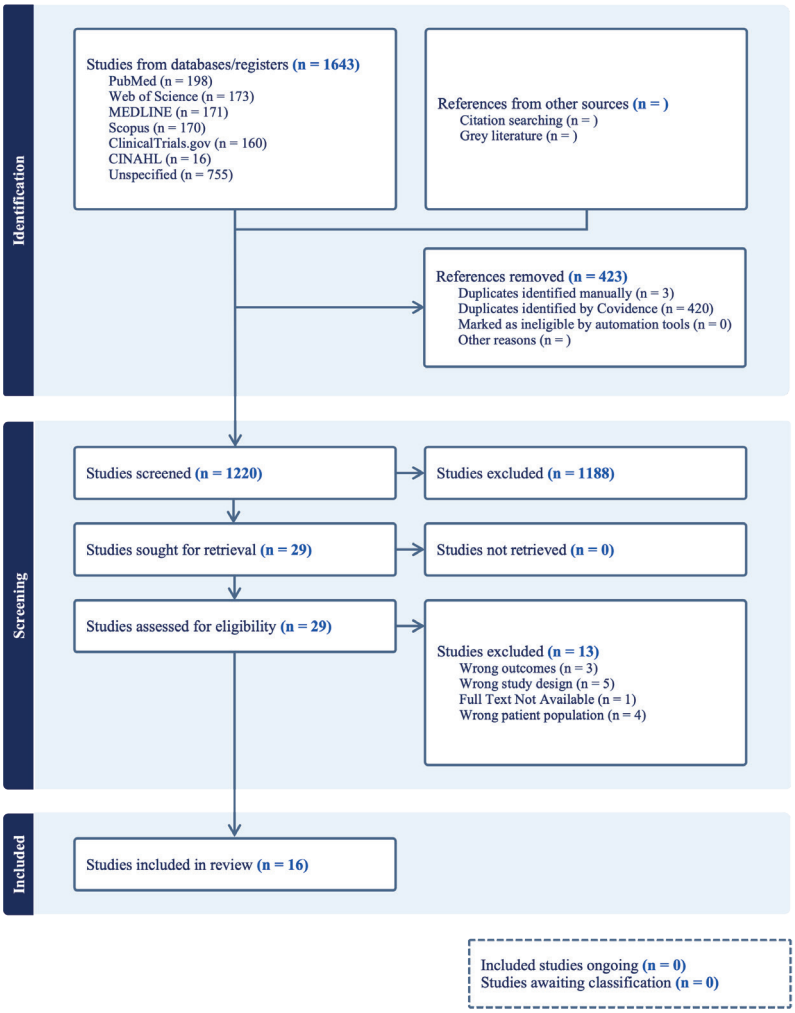

Figure 1. PRISMA Flow Diagram. n = 0 indicates no studies were identified in that category. 'Full text not available' refers to articles that could not be accessed despite institutional library and interlibrary loan searches.

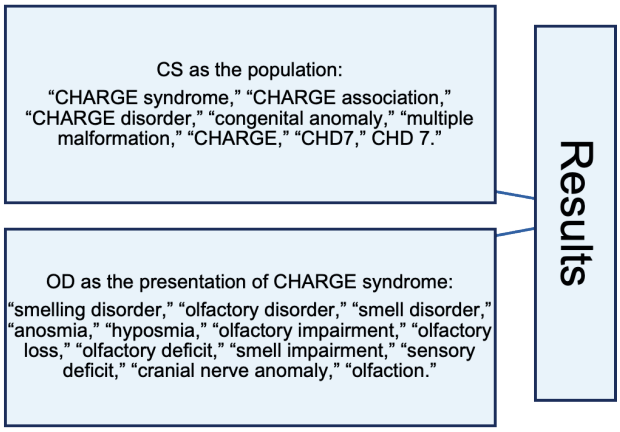

Figure 2. Conceptual framework for literature search strategy. Search terms were categorized into two domains: CHARGE syndrome–related terms and olfactory disorder–related terms. Only studies addressing both domains were included for full-text screening.

Results

We identified a total of 1643 studies through the initial database search. After removal of 423 duplicates, 1220 original studies remained to be screened with title and abstract as shown in the PRISMA study flow diagram (Figure 1). Following title and abstract screening, we identified 29 studies for full-text review and ultimately excluded 13 studies for reasons listed in Figure 1. We were left with 16 studies for data extraction and critical appraisal.

The key study characteristics, study design, study population, and method of CHARGE diagnosis are summarized in Table 2. Included studies were published from 1995 to 2025. Study designs included retrospective cohort (n=10), prospective cohort (n=5) and case control (n=1). The studies were conducted in USA (n=5), France (n=3), Japan (n=2), China (n=1), Denmark (n=1), Australia (n=1), Netherlands (n=1), Korea (n=1), and Spain (n=1). The primary outcome of OD prevalence in CS is presented in Table 3, which shows that over 70% of patients with CHARGE

Table 1. Risk of bias summary using the Joanna Briggs Institute (JBI) critical appraisal tool for analytical cross-sectional studies.

Study ID	Asakura (2008)	Blustajn (2008)	Bocca (2009)	Chalouchi (2005)	Charach (2025)	Harvey (1991)	Hoch (2017)	Husu (2013)
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y	Y	Y
Were confounding factors identified?	Y	Y	Y	Y	Y	Y	Y	Y
Were strategies to deal with confounding factors stated?	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y
Study ID	**Kim (2022)**	**Legendre (2017)**	**Pinto (2005)**	**Shiohama (2019)**	**Shoji (2014)**	**Teixeira (2025)**	**Thelin (2005)**	**Zhang (2021)**
Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y	Y	Y	Y	Y	Y
Were the study subjects and the setting described in detail?	Y	Y	Y	Y	Y	Y	Y	Y
Was the exposure measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
Were objective, standard criteria used for measurement of the condition?	Y	Y	Y	Y	Y	Y	Y	Y
Were confounding factors identified?	Y	Y	Y	Y	Y	Y	Y	Y
Were strategies to deal with confounding factors stated?	Y	Y	Y	Y	Y	Y	Y	Y
Were the outcomes measured in a valid and reliable way?	Y	Y	Y	Y	Y	Y	Y	Y
Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y

Note: "Y" indicates "Yes"; "N" indicates "No".

are diagnosed with OD. Notably, the reported prevalence varied considerably depending on the method used to establish the CHARGE diagnosis.

Methods of CHARGE diagnosis

There were two main categories of CHARGE diagnosis that were reported: clinical and genetic. Most studies involved a clinical diagnostic approach to CS (n=14). Commonly employed scales/types of clinical diagnosis included criterion from: Blake et al. [11] (n=7), Verloes et al. [12] (n=7), Amiel [13] (n=1), and Pagon et al. [3] (n=1). A genetic diagnostic approach to CS was employed in nine studies, seven of which reported the specific CHD7 mutation type.

Methods of olfactory assessment

Four categories of olfactory assessment type were present among the included studies: self or parent reported (including history or specific patient reported outcome measure (PROM)) (n=5), radiological diagnosis (olfactory bulb/tract assessment on MRI or computed tomography (CT) scan) (n=14), psychophysical testing (U-sniff [14], Sniffin' Sticks [15], University of Pennsylvania Smell Identification Test (UPSIT) [16], Biolfa [17]) (n=3). We also looked for the use of electrophysiological testing (olfactory event-related potentials (OERP) [18]/Electrobulbogram (EBG) [19]), but this was not employed in any of the included studies (n=0). The largest burden of OD was assigned radiologically. Details on methods of olfactory assessment and the olfaction-based clinical outcomes reported across studies are summarized in Table 3.

Table 2. Summary of studies reporting olfactory dysfunction in CHARGE syndrome, including study design, patient demographics, comparator groups, diagnostic methods, CHD7 mutation status, and prevalence of olfactory dysfunction.

Study	Study Design	Country	Total Patients Diagnosed with CHARGE	Mean Age (years) ± Standard Deviation	Sex Distribution	Comparator Group and Characteristics	CHARGE Diagnosis: CLINICAL (Y/N)	CHARGE Diagnosis: GENETIC (Y/N)	CHD7 Mutation (Y/N/type)
Asakura (2008)[27]	Cross Sectional Study	Japan	8	7.18 ± 3.31	5M 3F	N	Y Blake	Y	Y 5 nonsense 1 frameshift 2 missense
Blustajn (2008)[2]	Cross Sectional Study	USA	10	4 neonates (14 –21 days), 2 infants (40and 42 days), and 4 young children (3–10 years)	5M 5F	N	Blake Verloes	N	N
Bocca (2009)[21]	Cross Sectional Study	Netherlands	35	14.7 ± 3.05 Y	19M 16F	Y 6M 6F 20-26Y To determine if American UPSIT can be used for Dutch	Blake Verloes	Y	Y Missense, frameshift, nonsense, splice site
Chalouhi (2005)[3]	Cross Sectional Study	France	14	M: 7.8 ± 0.25 Y F: 12.5 ± 4 Y	6M 8F	Y Control group of 25 healthy children (14 girls aged 7–13 years, mean ± SD: 10.6 ± 2.2; 11 boys aged 6–13 years, mean ± SD: 9.5 ± 1.9)	Y Blake	N	N
Charach (2025)[26]	Cross Sectional Study	Spain	4 Fetuses 2 Aborted	30-40 weeks gestation	N	N	N	Y	Y Trio CES: heterozygous de novo mutation in CHD7 in 3 patients Trio CES: normal in 1 patient
Harvey (1991)[63]	Cross Sectional Study	Australia	17 Patients 10 Dead	2-15 Y 7 Died neonatally	8M 7F	N	Y Pagon	N	N
Hoch (2017)[23]	Cross Sectional Study	USA	10	4 ± 5.66 Y	6M 4F	N	Y Verloes	Y 3/6 genetic tested	N
Husu (2013)[31]	Cross Sectional Study	Denmark	18	8.3 Y	6M 12F	N	Y Verloes	Y	Y Nonsense, deletions, frameshift, missense, splice
Kim (2022)[28]	Cross Sectional Study	Korea	30	5 ± 6.4 Y	20M 10F	N	Y Verloes	Y Molecular CHD	Y 11 nonsense 37.9% 11 frameshift 39.9% 3 missesense 10.3% 2 splice 6.9% 2 large deletions 6.9%

Table 2 *continued.*

Study	Study Design	Country	Total Patients Diagnosed with CHARGE	Mean Age (years) ± Standard Deviation	Sex Distribution	Comparator Group and Characteristics	CHARGE Diagnosis: CLINICAL (Y/N)	CHARGE Diagnosis: GENETIC (Y/N)	CHD7 Mutation (Y/N/type)
Legendre (2017)[32]	Cross Sectional Study	France	119	11 ± 10 Y	62F 57M	N	Y Verloes	Y 93/118 79%	Frameshift, Nonsense, splice
Pinto (2005)[22]	Cross Sectional Study	France	10	N	20M 12F	N	Y Blake Amiel	N	N
Shiohama (2019)[30]	Cross Sectional Study	USA	10	15.54 Y	7M 3F	Y Sex and age matched	Y Blake	N	N
Shoji (2014)[33]	Cross Sectional Study	Japan	25	1-25 Y	13M 12F	N	Y Blake Verloes	Y	17/21 7 nonsense 5 frameshift 3 splice site 2 deletions
Teixeira (2025)[24]	Cross Sectional Study	USA	18	Fetal median gestation 26.25 (20.4 – 36.3)	10M 3F 5 unknown	N	Y	N	N
Thelin (2005)[37]	Cross Sectional Study	USA	28	7 Y	11M 17F	N	Y	N	N
Zhang (2021)[29]	Cross Sectional Study	China	7	N	N	N	N	Y – CHD7	N

Note: "Y" indicates "Yes"; "N" indicates "No".

Terminology most used to describe OD or lack thereof amongst study participants included anosmia (n=6), hyposmia (n=3), normosmia (n=1).

Psychophysical assessment of OD

Of 16 studies, three employed psychophysical olfactory assessment. One study utilized the UPSIT [20] and two utilized the Biolfa assessment [17]. Across these studies, psychophysical assessment was performed in 26, 13, and 10 patients, respectively, for a total of 49 tested individuals. The reported prevalence of OD in these cohorts was 81%, 100%, and 100%. When pooled, these findings indicate a prevalence of OD exceeding 90%. Bocca in 2009 found that the UPSIT test could not be administered to patients with a developmental age less than five years, prolonged tube feeding, or uncorrected bilateral choanal atresia [21]. Bocca then suggested that in children unable to complete the UPSIT – whether due to intellectual disability or physical limitations – cerebral MRI could demonstrate olfactory bulb aplasia, serving as a surrogate marker for OD or anosmia [21]. Chalouhi et al. deemed the Biolfa assessment to be appropriate in patients with CS, if they have reached levels of speech and intellectual levels of five years of age [4].

Olfactory bulb and tract morphology on MRI, CT, or ultrasound

Most included studies did not explicitly define olfactory bulb hypoplasia, aplasia, or agenesis, nor did they reference established normative volumetric when describing abnormalities on imaging. Additionally, many studies were published prior to the adoption of normative references. Given the lack of consistent terminology and absence of histological confirmation in these studies, we have chosen to use the term "aplasia" throughout this paper as an umbrella term to describe all reported cases of absent or severely underdeveloped olfactory bulbs on imaging.

Across 14 studies, radiological assessment consistently revealed olfactory system abnormalities in individuals with CS. The primary imaging correlates of anosmia or hyposmia were olfactory bulb aplasia (n = 9); aplasia of the olfactory sulci (n = 5); and aplasia of the olfactory tract (n = 5), with general rhinencephalic malformations described in one study. Table 3 outlines specific radiologic features associated with olfactory dysfunction, which should be interpreted in conjunction with clinical findings.

Proposed mechanisms of OD

Multiple studies proposed mechanisms of the OD observed in CS. First proposed by Pinto et al. in 2005 and later reiterated

Table 3. Overview of olfactory assessment modalities (self/parent report, radiological, psychophysical, electrophysiological, and other) used in CHARGE syndrome studies, including diagnostic definitions and reported prevalence of anosmia, hyposmia, and total olfactory dysfunction.

Study	Olfactory Assessment SELF/PARENT REPORTED Y/N	Olfactory Assessment RADIOLOGICAL DIAGNOSIS Y/N	Olfactory Assessment PSYCHOPHYSICAL TESTING Y/N	Olfactory Assessment OTHER Y/N	Terminology Used (anosmia/hyposmia)	Anosmia Prevalence (%)	Hyposmia Prevalence (%)	Olfactory Dysfunction Prevalence n = X %
Asakura (2008)[27]	N	Y – MRI 100% abnormalities of the olfactory bulb region Olfactory sulci were shallow or absent and asymmetric Olfactory bulbs were hypoplastic or aplastic 3 Hypoplasia 3 Asymmetry 2 Aplasia	N	N	Olfactory Bulb Hypoplasia, Aplasia, Asymmetry	N	N	8/8 100% Radiological Diagnosis
Blustajn (2008)[2]	N	Y – MRI 100% patients with anomalies of olfactory bulb or sulci	N	Y	Olfactory Dysfunction	N	N	10/10 100% Radiological Diagnosis
Bocca (2009)[21]	N	Y – MRI for 3/10 patients 2/3 aplasia of the olfactory bulbs 1/3 asymmetrical olfactory bulbs with aplasia of the right olfactory bulb and hypoplasia of the left olfactory bulb	Y – UPSIT test Completed by 26/35 patients UPSIT scores 60-89%. n = 5 UPSIT scores 9-40% "anosmic" n = 21	N	Anosmia, Hyposmia, Normosmia based on psychophysical	21/26 80% Psychophysical	N	3/10 30% Radiological Diagnosis – were of sufficient quality for olfactory bulb analysis. 21/26 80% Psychophysical Diagnosis
Chalouhi (2005)[3]	Y Questionnaire provided to parents: normal, residual or no olfaction	Y – MRI 100% anomalies of rhinencephalon Olfactory track and bulb anomalies varies from hypoplasia to complete aplasia No direct link to olfactory function	Y – French Biolfa olfactory test, assessed detection threshold and discrimination of 6 odours	N	Anosmia, Hyposmia	7/13 53.8%	6/13 46% 2 severe 3 moderate 1 mild	13/13 100%
Charach (2025)[26]	N	Y – MRI Absent olfactory sulci and olfactory bulbs in ¾ OS hypoplasia with absent olfactory bulbs in ¼	N	N	N	N	N	Radiological diagnosis The authors deemed that all patients with arhinecephaly have congenital anosmia.
Harvey (1991)[63]	Y Interview by authors	N	N	N	Anosmia	9/17 52%	N	9/17 52% 7 From autopsy 2 self/parent reported Limitation: All patients had varying degrees of intellectual disability.
Hoch (2017)[23]	N	Y – MRI olfactory nerve hypoplasia (100%), olfactory sulcus	N	N	Olfactory nerve hypoplasia, olfactory sulcus dysplasia, olfactory groove dysplasia	N	N	10/10 The authors deemed that all patients with arhinecephaly have congenital anosmia.

Table 3 *continued*.

Study	Olfactory Assessment SELF/PARENT REPORTED Y/N	Olfactory Assessment RADIOLOGICAL DIAGNOSIS Y/N	Olfactory Assessment PSYCHOPHYSICAL TESTING Y/N	Olfactory Assessment OTHER Y/N	Terminology Used (anosmia/hyposmia)	Anosmia Prevalence (%)	Hyposmia Prevalence (%)	Olfactory Dysfunction Prevalence n = X %
Husu (2013)[31]	Y – 2/7 patients parents reported, hard to do in neonates	N	N	N	Anosmia	2/7 28.6%	N	2/7 28% Reporting by Parents Limitation: Percentage calculations for specific features are affected by missing data. Results reflect only patients for whom the clinical feature could be assessed.
Kim (2022)[28]	N	Y – MRI Olfactory bulb aplasia (n = 3)	N	Y Unspecified clinical diagnosis revealing 6/29 patients were hyposmic/anosmic	Hyposmia/anosmia based on MRI findings, did not specify the assessment type to assess olfaction	6/29 20.1%	6/29 20.1%	3/17 17.6% Radiological diagnosis 6/29 20.1% Clinical diagnosis
Legendre (2017)[32]	N	Y – MRI Arhinencephaly: 77% (41/53) of patients; 76% (32/42) of CHD7-positive patients Hyposmia/Anosmia: 82% (23/28) of patients; 83% (19/23) of CHD7-positive patients Either/Both Features: 79% (56/71) of patients Olfactory bulb aplasia in 32 of 42 patients with a CHD7 variant and in nine of 11 patients without a CHD7 variant	N	N	Anosmia, Hyposmia, Arhinecephaly	56/71 78.9%	N	93/118 79% Radiological Diagnosis
Pinto (2005)[22]	N	Y – MRI Olfactory Bulb MRI in 18 Patients: 15 absent; 1 hypoplastic, 2 asymmetric	Y – Biolfa Method	N	Anosmia, Hyposmia	Sample = 10 7/10 70%	3/10 30%	18/18 100% Radiological 10/10 100% Psychophysical All psychophysical also had radiological diagnosis. Not all radiological had psychophysical diagnosis.
Shiohama (2019)[30]	N	Y – MRI 6/10 absence of olfactory nerve	N	N	Cranial Nerve Absence	6/10 60%	N	6/10 60% Radiological
Pinto (2005)[22]	N	Y – MRI Olfactory Bulb MRI in 18 Patients: 15 absent; 1 hypoplastic, 2 asymmetric	Y – Biolfa Method	N	Anosmia, Hyposmia	Sample = 10 7/10 70%	3/10 30%	18/18 100% Radiological 10/10 100% Psychophysical All psychophysical also had radiological diagnosis. Not all radiological had psychophysical diagnosis.

Table 3 *continued*.

Study	Olfactory Assessment SELF/PARENT REPORTED Y/N	Olfactory Assessment RADIOLOGICAL DIAGNOSIS Y/N	Olfactory Assessment PSYCHOPHYSICAL TESTING Y/N	Olfactory Assessment OTHER Y/N	Terminology Used (anosmia/hyposmia)	Anosmia Prevalence (%)	Hyposmia Prevalence (%)	Olfactory Dysfunction Prevalence n = X %
Shiohama (2019)[30]	N	Y – MRI 6/10 absence of olfactory nerve	N	N	Cranial Nerve Absence	6/10 60%	N	6/10 60% Radiological
Shoji (2014)[33]	Y – self-evaluation with spicy food, however 6 had severe intellectual disability	Y – temporal head CT in patients with atresia choanae	N	N	Anosmia – impaired sense of smell	24%	N	6/25 24% Self/parent reported Limitation: All patients had varying degrees of intellectual disability. Additionally, hearing loss and craniofacial abnormalities may have affected the reliability of developmental assessment results.
Teixeira (2025)[24]	N	Y – Fetal MRI Olfactory apparatus: 8/10 absent 2/10 hypoplastic Absent olfactory structures in eight of 10 fetuses, with the remainder showing aplasia	N	N	Olfactory apparatus on MRI	100% from MRI	N	10/10 100% Radiological Diagnosis
Thelin (2005)[37]	Y – parents completed a questionnaire	N	N	N	N	3/28 11%	N	3/28 11% Self-parent reported
Zhang (2021)[29]	Y – questionnaire n = 7	Y – nasal sinus MRI Olfactory nerve center (defined as consisting of absent or aplastic olfactory bulbs, olfactory sulci or olfactory tract) maldevelopment in all three patients coincidentally assessed by nasal sinus MRI n = 6	N	N	N	6/7 85%	N	6/6 100% Radiological 6/7 85.7% Self/parent reported One patient did not have an MRI.

Note: "Y" indicates "Yes"; "N" indicates "No".

by Hoch et al. in 2017, deficiency of fibroblast growth factor signaling may be responsible for olfactory bulb dysgenesis and that there may be a functional connection between CHD7 and fibroblast growth factor signaling in olfactory bulb differentiation [22,23]. Teixeira et al. recently in 2025 reemphasized the mesodermal flow theory by Hengerer and Strome, suggesting that impaired development of olfactory structures is due to excess migration of neural crest cells into the developing nasal septum and posterior choanae hinders normal flow into the craniofacial region [24,25]. It was also suggested that the CHD7 gene and protein may play a role in the interaction between neural crest and somite cells [22]. On a molecular level, CHD7 is thought to mediate neural crest-somite cell interactions, providing a plausible developmental mechanism for observed anomalies in the olfactory bulb and clivus, as described in one study (24).

Genotype-phenotype correlations and other clinical outcomes

Genotype–olfactory correlations in CS highlight a frequent association between pathogenic CHD7 variants and olfactory abnormalities, though findings across studies remain heterogeneous. These correlations were discussed in nine studies. Structural anomalies such as absent or hypoplastic olfactory bulbs and sulci have been observed in individuals with CHD7 mutations (n=3) [23,26,27]. These mutations are known to impair the development and migration of olfactory and gonadotropin-releasing hormone (GnRH) neurons, contributing to hypogonadotropic

hypogonadism. Accordingly, OD has been proposed as a clinical predictor of pubertal insufficiency (n=2) [24,28]. However, because most study cohorts are predominantly prepubertal, long-term follow-up is required to confirm these associations (n=1) [28]. In some cases, patients with CHD7 mutations present with severe olfactory deficits consistent with Kallmann syndrome, underscoring phenotypic overlap between olfactory and reproductive pathways (n=1) [29]. Additional neurodevelopmental consequences may include increased regional right brain cortical thickness, potentially linked to disrupted neuronal pruning secondary to CHD7 mutations (n=1) [30].

Despite these findings, no definitive genotype–phenotype correlations have been established (n = 4) [27,29,30,31]. Clinical heterogeneity persists, even among patients with identical CHD7 mutations or deletions, and subtle associations may be overlooked due to small sample sizes, as discussed in three of the included studies [27,29,31]. Some studies suggest that less severe mutations may produce milder or non-classic phenotypes – such as semicircular canal agenesis or olfactory bulb hypoplasia in isolation – raising the possibility that CHD7 mutations may be underrecognized in patients with limited CHARGE features (n=2) [23,27].

Neurodevelopmental outcomes

An apparent association between neurocognitive dysfunction and either OD or CHD7 mutation has been described across several studies. Chalouhi et al. found that all children categorized within the lower intellectual functioning group were also identified as anosmic [4], Shoji (2014) and Kim (2022) found that 100% and 42.9% had an intellectual disability, respectively [28,32], and Legendre et al. identified intellectual disabilities in 62% of those with confirmed CHD7 mutations [33]. The authors noted that evaluating cognitive impairment in patients with multiple sensory deficits was challenging. However, they observed that whenever a sensory deficit – whether visual, auditory, or olfactory – was present, all affected patients exhibited delayed motor milestones [33]. No direct mechanistic explanations for OD-neurocognitive linkage were formally proposed in the included studies.

Feeding and/or swallowing outcomes

Feeding and swallowing difficulties are frequently reported in CS, but their relationship to OD remains unclear. While patients with confirmed OD were frequently reported to have feeding and/or swallowing difficulties across several included studies (n=5) – including gastroesophageal reflux disease (GERD), velopharyngeal dysfunction, esophageal abnormalities, and other nonspecific swallowing issues – the relationship between OD and these manifestations was not explicitly explored or hypothesized in any study [2,28,31,33]. To our knowledge, there are no studies directly linking OD to feeding behavior in individuals with CS.

Discussion

In this systematic review, we identified 16 studies that assessed OD, or radiological features suggestive of OD in CS, whether as a primary (n=5) or secondary (n=11) outcome. Sixteen of 16 studies were of good methodological quality. Across these studies, the pooled prevalence of olfactory dysfunction was over 70%, based on multiple assessment methods – some more accurate than others in this population – as will be discussed in detail below. To center the discussion on olfactory function in CS, we emphasize that OD is a frequent and defining feature of this condition but missing from reviews to date. OD in CHARGE may range from complete anosmia to milder hyposmia, often associated with structural anomalies such as olfactory bulb hypoplasia or aplasia, as reported in early autopsy studies [3] and confirmed by recent MRI investigations [23]. While various forms of olfactory assessment exist, numerous barriers still hinder the incorporation of standardized testing into clinical practice. Psychophysical testing – the current clinical gold standard for assessment of olfactory function – is infrequently reported in the literature. Furthermore, no studies to date have evaluated OD as an isolated measure of quality of life in individuals with CS.

Self- or parent-reported olfactory assessment

Subjective assessment of OD is essential for understanding its impact on daily life [34]. However, tests specifically designed to assess olfactory loss in children have seen limited use, potentially due to developmental limitations such as lower reading levels, shorter attention spans, and unfamiliarity with certain odour references commonly used in adults [35].These challenges may be further compounded in patients with CS, who often experience developmental delays and intellectual disabilities, making standard testing even less accessible or reliable [36]. Despite these limitations, five studies included in this synthesis relied on self- or parent-reported outcome measures to assess for OD.

Chalouhi et al. in 2005 employed a questionnaire (not previously validated) to parents discussing their child's feeding difficulties and ability to both detect and differentiate odours [4]. However, the parents' assessments agreed with the results of the paediatric adapted Biolfa psychophysical olfactory test for only six of 13 children [4]. Another study investigating communication and language development in CS found that parental perceptions of their child's impairment did not correlate with the objectively measured severity of the condition [37]. This suggests that parents may assess their child's challenges based on personal expectations and lived experience rather than in comparison to other children with CHARGE. Consequently, subjective parental assessments may not reliably reflect clinical severity, reinforcing

the need for objective evaluation tools when studying functional outcomes in this population [37]. A minority of parents (14% and 11%) suspected that taste or smell issues might be linked to language delays [37]. It has been suggested in the literature that olfaction plays a foundational role in early infant-caregiver bonding and social development, as maternal odor can be a strong modulator of social perception in human infants [38] – both crucial for language learning [39]. While parent questionnaires may offer valuable context, they cannot replace standardized psychophysical testing.

It is important to distinguish congenital anosmia from acquired anosmia, as they can have distinct consequences for patients' daily functioning and behavior. Accurate assessment of olfactory function is essential, as some deficits may be subtle and not reliably captured by self- or parent-reports. Croy et al. (2012) compared 32 adults with isolated congenital anosmia (ICA) to age-matched controls and found that, while daily functioning was only slightly impaired, ICA patients reported greater social insecurity, a higher risk of depressive symptoms, and an increased risk of household accidents [40]. Besser et al. stated that patients with congenital anosmia often report little to no disease-related complaints, whereas those with postinfectious or posttraumatic olfactory dysfunction – typically of sudden onset – frequently experience significant distress due to their sensory loss [41]. These findings suggest that congenital anosmia may be associated with subtle but meaningful psychosocial and safety-related challenges, which differ from the often more disruptive effects observed in individuals with acquired anosmia.

Psychophysical olfactory assessment

The UPSIT test is a psychophysical test that is commonly employed to assess olfaction and is suitable for use in adults and children ≥five years of age [42]. The UPSIT was employed in one study included in this review, but with limitations. Bergman et al. determined that patients with CS and symptoms of rhinitis could not be tested, nor could those with intellectual disability and a developmental age under five years, uncorrected bilateral choanal atresia, or prolonged feeding difficulties requiring tube feeding [21]. In lieu of this, these patients were tested with a newly designed picture book for the Dutch population, with photographs representing the odour options.

The French Biolfa test, utilized in two studies, measures odour detection threshold and odour identification [4,17]. Chalouhi et al. demonstrated that this was an effective and appropriate tool for assessing olfactory function in patients with CS, with all individuals in their cohort identified as having significantly reduced olfactory thresholds and marked difficulties with odour discrimination [4]. The validated Biolfa method, used by Pinto et al. in 2005, was feasible to administer across the cohort and enabled differentiation of children as either anosmic (n=7) or hyposmic (n=3) [22].

While not examined in the studies included in our review, several other validated olfactory tests for paediatric populations exist besides the UPSIT. These include Sniffin' Sticks [15], U-Sniff, the Lyon Clinical Olfactory Test [43], the Smell Wheel [44], and the Pediatric Barcelona Olfactory Test-6 [45].

Radiological/histological diagnosis of olfactory assessment

Many anomalies that are characteristic of CS can be described by radiological diagnosis of structures within the ear, orbit, nasal cavity, and brain [23]. Much of the neuroimaging literature has focused on CT findings to characterize phenotype [23,46]. Our review included studies that assessed features associated with OD through radiological methods, including MRI (n=12), CT (n=1), as well as autopsy (n=1). MRI is valuable for assessing olfactory complex anomalies, including absence or aplasia of the olfactory nerve and sulcus, first described by Pinto et al. in 2005 [22] and then by Blustajn et al. in 2008 [2]. As formal smell testing is complex in children under the age of five, and due to the plethora of causes of olfactory impairment, radiological evidence of olfactory tract or bulb aplasia/hypoplasia can help to identify CHARGE patients that are at further risk of Kallman syndrome [47], a congenital form of hypogonadism caused by low levels of hypogonadotropic hormones that characteristically manifests with either hyposmia or anosmia [48]. However, because olfactory imaging does not consistently correlate with olfactory function, it should not be used in isolation to determine diagnostic status. In 2020, Weiss et al. demonstrated that two healthy left-handed women without anatomically defined olfactory bulbs on MRI exhibited normal odor detection, discrimination, identification, and representation. Functional MRI showed typical odourant-induced activity in the piriform cortex, and review of a public brain-MRI database identified olfaction without olfactory bulbs in ~0.6% of women and ~4.25% of left-handed women, highlighting remarkable neuroanatomical plasticity [49]. As such, radiological diagnosis may be a surrogate measure until the child is old enough to reliably undergo psychophysical olfactory testing, but it should be interpreted cautiously, given that anatomical absence does not always predict functional impairment.

Zhang et al. believed that when discussing olfactory bulb development, psychophysical or self-reported olfactory assessment might underestimate the true olfactory deficit in these patients and that MRI examination would be more accurate [29]. The authors noted that approximately 50% of patients with hypogonadotropic hypogonadism who self-reported a normal sense of smell were found to be hyposmic or anosmic with standardized testing or definitive imaging [29,50].

Choanal atresia can be life-threatening in complete bilateral cases. Fetal MRI was proposed by Teixeira et al. in 2025 to be crucial when prenatal ultrasound is suspicious [24]. They illustrated that the most important fetal MRI findings subsequently supporting a diagnosis of CS included inner ear dysplasia and olfactory bulb aplasia [24]. It was demonstrated in 2006 by Azoulay et al. that during normal development, olfactory sulci and bulbs are identifiable on MRI from 30 weeks' gestational age and 30-34 weeks onwards respectively [51]. It was therefore proposed that absence of olfactory sulci/bulbs after 30 weeks could be an additional criterion for CS [24].

OD and Quality of Life in CS

Few studies directly assessed quality of life outcomes despite existing literature highlighting the broader impact of sensory deficits on psychosocial well-being. In the general paediatric population, olfactory and gustatory dysfunction can significantly affect nutrition, psychological well-being, and the quality of social interactions [52]. Although the true prevalence of OD in CS has yet to be determined, impairments in other sensory modalities – particularly vision and hearing – have been consistently associated with decreased quality of life, including challenges with social interaction and community acceptance [53]. Additionally, dysfunction of other cranial nerves, such as facial nerve palsy, can impede facial expression, further compromising both verbal and non-verbal communication [53]. Children with CS commonly experience oral-motor skill deficits, which affect their ability to accept food, manipulate it within the mouth, and safely swallow [54]. As a result, eating can require significantly more effort, leading to fatigue and prolonged mealtimes. Children may cry, push food away, or refuse bites due to this increased difficulty. These challenges are often compounded by reduced appetite or food aversion, which may be partially attributable to a diminished ability to perceive flavors (retronasal olfaction) [52]. Blake et al. demonstrated that children with CS exhibit decreased interest in food and reduced gustatory sensation [55]. Choanal atresia, another contributor to OD, can further impair an infant's ability to feed effectively [55].

Although none of the studies in our review directly assessed autism spectrum disorders (ASD), sensory processing is increasingly recognized as relevant in ASD diagnosis. Tonacci et al. (2017) reported that children with high-functioning ASD demonstrated reduced olfactory sensitivity and impaired odor identification, with preserved odor discrimination, and these deficits correlated with social and behavioral difficulties [56]. Given that children with CS may also present with both OD and neurodevelopmental challenges, this overlap raises the possibility that olfactory assessment could contribute to a broader understanding of social and behavioral outcomes in CHARGE, warranting further study.

When co-occurring with other common sensory deficits in CS – such as visual and auditory impairments – OD may contribute to compounded social and communicative challenges through a phenomenon of "sensory stacking," whereby multiple subclinical deficits collectively hinder environmental interaction and engagement [57].

Strengths and limitations

This review offers several notable strengths. First, it represents the most comprehensive synthesis to date of OD in CS, incorporating a wide range of assessment modalities. Collaboration with a health sciences librarian ensured a robust and exhaustive search strategy across multiple databases. Use of the JBI critical appraisal tool provided a standardized framework for assessing methodological quality.

However, several limitations must be acknowledged. Most included studies were observational in nature, with small sample sizes and limited generalizability due to single-center designs. Considerable heterogeneity in diagnostic criteria, olfactory assessment tools, and reporting methods precluded meta-analysis and limited direct comparisons across studies. Some groups demonstrate lower rates of OD which may reflect variability in assessment methods, age, cognitive ability, or diagnostic criteria. Furthermore, the predominance of radiological over functional olfactory testing may have introduced ascertainment bias and underrepresented subjective or behavioral correlates of OD. Finally, the lack of longitudinal data limited insight into developmental trajectories and the potential impact of interventions.

Future directions and implications for clinical practice

OD, or features associated with OD, are highly prevalent in individuals with CS, though reported rates vary across studies, depending on the diagnostic method used. Whilst underutilised, psychophysical testing consistently showed high rates of anosmia or hyposmia (81-100% in included studies), while radiological assessments revealed olfactory bulb abnormalities in 60–100% of patients who underwent imaging, features that are highly suggestive of OD. Studies relying on subjective self/parent-report showed lower prevalence rates (11–28%), likely reflecting under-recognition or reporting bias. Overall, findings were limited by incomplete testing, inconsistent diagnostic criteria, and challenges in assessing patients with intellectual disability and sensory impairments.

Given the high prevalence of olfactory anomalies, the inclusion of OD – supported by both structural and functional evidence – is worth of consideration in future revisions to the CHARGE diagnostic criteria.

Future research should focus on developing and validating

paediatric-specific olfactory tests that accommodate the cognitive and developmental challenges seen in CS. Studies should aim to correlate parent-reported symptoms and radiological findings with psychophysical assessments to improve diagnostic accuracy. Incorporating olfaction into broader sensory assessments may better capture the cumulative impact of multisensory deficits in CHARGE, guiding more holistic and effective interventions.

The limitations of psychophysical and self-reported olfactory assessments, as previously discussed, have led researchers to explore alternative methods such as OERPs, which offer a more objective means of assessing olfactory function, while being less reliant on patient comprehension, communication abilities, or developmental level [18]. Similarly, the EBG is a new technique that uses electrodes positioned on the forehead to measure olfactory bulb activity, which – if issues surrounding anatomical co-registration can be overcome in future, could offer non-invasive insight into OB activity [58]. The electro-olfactogram (EOG) is another electrophysiological measure of olfactory function that measures field potential of the olfactory epithelium. However, this technique requires placement of a receiving electrode within the olfactory cleft, which is impractical in children [59]. Despite the potential utility of these electrophysiological methods – particularly in populations such as individuals with CS, none of the studies included in our review employed OERPs or EBG in their assessment of OD. While they are currently limited by the burden of administration, and high false positive/negative rates, these modalities are promising avenues for objective evaluation of olfaction. Incorporating such tools into future diagnostic pathways or clinical guidelines may improve the accuracy and comprehensiveness of olfactory assessment in this population, ultimately enhancing our understanding of the role of olfaction in the CHARGE phenotype.

None of the included studies employed or evaluated intervention or rehabilitation strategies for OD in individuals with CS. Future research should explore intervention strategies tailored to the unique cognitive and developmental profiles of this patient population. Incorporating such approaches into clinical practice may offer new avenues for improving functional outcomes and overall quality of life. Odours that stimulate the trigeminal nerve to a greater degree, and thereby provide non-olfactory chemosensation, represent promising candidates for targeted sensory intervention [4]. Electrophysiological studies show that odourants co-stimulate both olfactory and trigeminal systems [60]. Flavour or taste training was found to be greatly appreciated by patients with OD, and flavours with high trigeminal components aligning with patients' positive expectations of the training [41]. The idea of an olfactory implant was first patented by Costanzo and Coelho in 2016 [61]. A recent international opinion paper outlined key considerations for olfactory implant candidacy, including patient selection, comprehensive psychophysical and imaging assessments, trial of existing treatments, multidisciplinary counseling, and structured post-implant rehabilitation [62]. While stimulation of the olfactory bulb and central networks shows promise, electrode design, safety, long-term efficacy, and ethical implications remain active areas of research.

Clinicians should consider routine screening for OD as part of the multisystem assessment of patients with CS. While psychophysical testing remains the gold standard, developmental and cognitive limitations may hinder its feasibility in this population. In such cases, parent-reported outcome measures can provide useful insights, and radiological imaging may help confirm clinical suspicion by identifying olfactory bulb aplasia or other structural anomalies. Until validated, developmentally appropriate psychophysical tests become available for this cohort, clinicians and researchers will need to rely on a combination of parent-reported olfactory function, radiologic findings, and where feasible, electrophysiological testing to assess OD in these patients. Regardless of the assessment method used, safety counseling about the inability to detect environmental hazards should be provided to all patients and families. Where appropriate, referrals to allied health services such as speech-language pathology or occupational therapy should also be considered to support feeding, swallowing, and broader sensory needs.

Conclusion

OD in CS is an underrecognized yet potentially significant contributor to morbidity. Cumulative deficits underscore the need to better characterize the impact of OD on the lived experience with CS, particularly in relation to social development, communication, and potentially, feeding/swallowing. Despite these plausible impacts, validated tools for olfactory assessment in children with developmental disabilities are lacking, posing a substantial barrier to diagnosis and appropriate treatment.

Having efficient and standardized methods for olfactory evaluation in patients with CS may change the physician's approach to OD and lead to more effective treatment and rehabilitation for children with disabilities [4]. Future research should aim to systematically evaluate olfactory function of patients with CS within multisensory quality of life frameworks, thereby elucidating its role in the broader neurodevelopmental and psychosocial trajectories of affected individuals.

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Conflict of interest

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Authors' contributions

GMS: Literature search, screening of studies, data extraction, writing of manuscript, editing of manuscript, production of figures, integration of co-author comments. KK: Screening of studies, data extraction, writing of manuscript. PC: Editing of manuscript. EKB: Conceptual design, writing of manuscript, editing of manuscript. KLW: Conceptual design, writing of manuscript, editing of manuscript.

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SUPPLEMENTARY MATERIAL

Table S1. Blank data extraction template used for systematic data collection from included studies.

Study	Study Design	Country	Total Patients Diagnosed with CHARGE	Mean Age (years) ± Standard Deviation	Sex Distribution	Comparator Group and Characteristics	CHARGE Diagnosis: CLINICAL (Y/N)	CHARGE Diagnosis: GENETIC (Y/N)	CHD7 Mutation (Y/N/ type)
X	X	X	X	X	X	X	X	X	X
Study	**Olfactory Assessment SELF/ PARENT REPORTED Y/N**	**Olfactory Assessment RADIOLOGICAL DIAGNOSIS Y/N**	**Olfactory Assessment PSYCHOPHYSICAL TESTING Y/N**	**Olfactory Assessment OTHER Y/N**	**Terminology Used (anosmia/ hyposmia)**	**Anosmia Prevalence (%)**	**Hyposmia Prevalence (%)**	**Olfactory Dysfunction Prevalence n = X %**	
X	X	X	X	X	X	X	X	X	
Study	**Olfactory Bulb/Tract findings on imaging**	**Other findings on imaging**	**Genotype-Olfactory Correlations**	**Neurodevelopmental Outcomes Y/N (specify outcome measure used if Y)**	**Feeding/ Swallowing Outcomes Y/N (specify outcome measure used if Y)**	**Quality of Life Outcomes Y/N (specify outcome measure used if Y)**	**Mechanisms of OD function proposed**		
X	X	X*	X	X	X	X	X		

We extracted the following details regarding CS diagnosis: clinical diagnosis, genetic diagnosis, and CHD7 mutation type. We extracted the following details regarding olfactory assessment: the presence of a) self/parent reported clinical assessment, b) radiological assessment, c) psychophysical assessment, d) electrophysiological assessment, e) other assessment. We extracted the following details regarding OD prevalence: a) definitions used (e.g., anosmia, hyposmia, etc.) based on assessment type, b) anosmia prevalence (%), c) hyposmia prevalence (%), d) normosmia prevalence (%), e) total OD prevalence (%), f) MRI findings involving the olfactory tract/bulb, g) other MRI findings, h) genotype-olfactory correlations. We extracted the following details regarding other relevant outcomes: neurodevelopmental outcomes, feeding/swallowing outcomes, and quality of life outcomes. We also extracted proposed methods of OD if applicable.

* Additional commonly reported neuroimaging abnormalities in patients with CS across the included studies were semicircular canal hypoplasia or agenesis (reported in at least 5 studies, n≥40 patients), cerebellar vermis hypoplasia or dysplasia (n=5), ventriculomegaly (n=3), corpus callosum dysgenesis or agenesis (n=4), and brainstem hypoplasia or abnormalities (n=2). Inner ear anomalies, including cochlear dysplasia, were consistently observed (n=3). Additional common features include choanal atresia or stenosis (n=4), coloboma (n=3), cleft lip/palate (n=2), and cranial nerve dysfunction such as facial palsy or sensorineural hearing loss (n=2). Rare but notable findings include Dandy-Walker malformations (n=2), pituitary hypoplasia (n=2), and parotid gland aplasia or hypoplasia.