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Brief Report

A study on the impact of the COVID-19 pandemic on the aetiology of paediatric olfactory dysfunction

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Running title: Impact of COVID-19 pandemic on aetiologies of paediatric olfactory dysfunction.

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Abstract

Introduction Although previous studies have examined olfactory dysfunction in children, the novel coronavirus SARS-CoV-2 has certainly had an unprecedented effect on their olfaction, which could not be taken into consideration. Aim of this report is to present data on the epidemiology of olfactory dysfunction during the pandemic and compare this dataset with a pre-pandemic set. We hypothesized an increase in URTI-related olfactory dysfunction.

Methods Data of paediatric patients consulting a smell and taste clinic between March 2020 and June 2022 were retrospectively analyzed. Frequency of major causes of olfactory dysfunction was examined and compared with three subsets of an older data set.

Results A total of 52 patients were included in the analysis. Most children presented with olfactory dysfunction due to upper respiratory tract infection (URTI) (52%). Congenital olfactory dysfunction was present in 34% of cases. Sinonasal disorders and idiopathic cases accounted for 6 and 4%, respectively, whereas head-trauma was the least common cause (2%). This was in contrast with the results of the older set. The frequency URTI-related olfactory dysfunction increased significantly. The frequency of head-trauma-related or congenital olfactory dysfunction showed marked reductions. There were no significant differences regarding the other aetiologies between our patient cohort and the three subsets.

Conclusion The COVID-19 pandemic has resulted in differences regarding the prevalence of aetiologies between our dataset and the subsets of pre-pandemic times. The surge of the frequency of URTI-related olfactory dysfunction may be ascribed to a novel pathomechanism involving sustentacular cells in the olfactory epithelium.

Introduction

Our sense of smell serves many important functions. It provides us a tool to detect spoiled food or hazardous gases, it plays a role in social relations and maintaining personal hygiene, and it is highly significant for the perception of flavours during eating and drinking. Unsurprisingly, olfactory dysfunction can have a drastic impact on the patients' lives [1]. While research in the clinical field of olfactory dysfunction attracts more and more interest, it still lags behind research of the other senses, especially in the paediatric population. However, Schriever and Hummel [2] recently provided precise information on the prevalence of aetiologies of olfactory dysfunction among children. In their study, it was shown that approximately 2/3 of patients in this age group had a congenital olfactory dysfunction. Acquired olfactory dysfunctions were rare, with head trauma (together with an idiopathic cases) being the second most frequent aetiology of olfactory dysfunction. Furthermore, in their paediatric cohort, post infectious olfactory dysfunction only accounted for 4% of this study population, thereby constituting a rather uncommon aetiology among children. Note that this data only represents the percentage of affected children who sought medical help, the prevalence of the respective aetiologies may differ in the general population (see discussion).

However, the COVID-19 pandemic has had a significant impact on these statistics. As of November 2022, more than 639.000.000 confirmed infections with the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) were registered (Coronavirus Resource Center of John Hopkins University, accessed 23.11.2022). An infection is often accompanied, inter alia, by olfactory dysfunction in adults [3,4]. Also, in children several reports of olfactory dysfunction after SARS-CoV-2 infections were published [5,6]. In fact, there is evidence indicating that children are as commonly affected as adults [6,7]. With such high infection numbers, a shift in the frequency of the distribution of aetiologies of olfactory dysfunction seems certain. Since olfactory dysfunction is a biomarker for an infection with SARS-CoV-2 [3], we predicted an increase in post-infectious olfactory dysfunction. Thus, the aim of this investigation was to provide an update on the epidemiology of olfactory dysfunction among paediatric patients and compare the present data with those before the COVID-19 pandemic.

Methods

Similar to the previous communication by Schriever and Hummel [2], the present article is based on a retrospective analysis of two groups of patients presenting to a specialized smell and taste clinic. Group 1 (herein termed: "pre-COVID-19-population") consisted of a paediatric subset of Schriever and Hummel's [2] initial set of data, collected between 2000 and 2017. The patients were between 6 and 17 years of age and exhibited olfactory dysfunction. In this first report, the focus lied on depicting the prevalence of aetiologies of olfactory dysfunction (primarily in a paediatric population). Aetiologies with a prevalence of at least 5% were considered main causes for olfactory dysfunction and thereby constituted a separate category [congenital, idiopathic, head-trauma, sinonasal, and upper respiratory tract infection (URTI)]. Every other aetiology was comprised under the term "others"(for precise information, see Schriever and Hummel [2]).

Group 2 (herein termed: "peri-COVID-19-population") consisted of a set of data collected between March 2020 and June 2022. This group was purely paediatric, as well, i.e., patients falling below the age of 18 years. As with the initial report, the different aetiologies of olfactory dysfunction were categorized by main causes. To facilitate the comparison of both groups, the same main causes introduced in the pre-COVID-19-population were adopted. A thorough otorhinolaryngological examination was performed in all patients across both groups. Olfactory performance was measured through evaluation of olfactory threshold, odour discrimination, and odour identification (TDI) using the "Sniffin' Sticks" test. Furthermore, all patients of the peri-COVID-19-group had a confirmed detection of SARS-CoV-2 by means of PCR or antigen test. For our comparison, we had to account for the differences in age, sex, and overall number of patients between the pre- and peri-COVID-19-populations. To do that, we generated a randomized age-, sex-, and size-matched subgroup of our pre-COVID-19-population and named it pre-COVID-19-subgroup. The prevalence of the aetiologies was then compared between the pre-COVID-19-subgroup and peri-COVID-19-population.

The program R Studio (version 4.2.2.) was employed for all statistical analyses. To determine whether there was a significant association between the outbreak of the global COVID-19-pandemic and the prevalence of different aetiologies, Fisher's exact test was used. Applying Pearson's χ^2 Test was not possible because of our sample size. Also, to see if age and/or sex plays a role in the epidemiology of olfactory dysfunction, an analysis of the age distribution was conducted for the peri-COVID-population. The children were either divided into a pre-pubertal (ages 6 to 14) or post-pubertal (ages 15 to 17) group.

Results

Our peri-COVID-19-population consisted of 52 paediatric patients. There were more than twice as many post-pubertal (n=35) than pre-pubertal children (n=17), resulting in a mean age of 14.4 ± 2.7 years. The age distribution is shown in Figure 1.

The sex distribution was unequal, as well: There were more than twice as many girls (n=37) than boys (n=15) across both the pre-pubertal and post-pubertal group. The pre-pubertal group consisted of 12 females and 5 males, whereas the post-pubertal group consisted of 25 females and 10 males. Table 1 summarizes the information.

In this population, most patients presented with olfactory dysfunction due to an upper respiratory tract infection (URTI) (52%). Second to that were patients with congenital olfactory dysfunction (34%), followed by sinonasal olfactory dysfunction (6%). Four per cent of the study population showed an idiopathic olfactory dysfunction. The causes "head-trauma" and "others" accounted for 2%, respectively. Taken together, 65% of the patients had an acquired olfactory dysfunction (considering the fact that idiopathic olfactory dysfunction is always associated with an acquired type [2]). This data is visualized in Figure 2. The infection with SARS-CoV-2 was suspected to cause olfactory dysfunction in 89% of URTI-related cases of olfactory dysfunction. In the remaining cases, the pathogenesis of URTI could not be determined.

Because URTI was the most frequent aetiology, the data of all patients suffering from URTI (n=27) were further scrutinized. The sex- and age-distribution was similar to that of the whole patient cohort. This time, there were more than four times as many post-pubertal (n=22) than pre-pubertal children (n=5). Again, more than twice as many females (n=20) than males (n=7) were affected across both the pre- and post-pubertal group. The pre-pubertal group consisted of 4 females and 1 male, whereas the post-pubertal group consisted of 16 females and 6 males. Table 2 summarizes this information.

The prevalence of aetiologies in thepre-COVID-19-subgroup differed considerably from the one in our peri-COVID-19-population: the majority of patients presented with congenital olfactory dysfunction. The second most common cause was head trauma, followed by idiopathic and sinonasal cases. URTI-related olfactory dysfunction was the least common aetiology. Detailed information is shown in Figure 3.

The statistical analyses revealed that there was a statistically significant association between the outbreak of the pandemic and the increased prevalence of URTI ($p < 0.001$). This also applies to the outbreak of the pandemic and the decreased frequency of congenital olfactory dysfunction in our study population ($p < 0.05$). The percentage of head-trauma-associated olfactory dysfunction also showed a significant decrease ($p < 0.01$). There were no statistically significant associations between the outbreak of the COVID-19-pandemic and the prevalence of the remaining aetiologies. For comprehensibility reasons, these results are summarized in Table 3.

Discussion

For the present investigation, we sought to compare the frequencies of aetiologies of olfactory dysfunction of a pre-COVID-19-subgroup with those of a peri-COVID-19-population. This was meant to provide an update on aetiologies of olfactory dysfunction among a paediatric population during the global COVID-19-pandemic and thereby exemplify its impact. Because infection with SARS-CoV-2 has been linked to olfactory dysfunction in adults [3] and children [5,6], we hypothesized that an increase in olfactory dysfunctions due to upper respiratory tract infection (URTI) is likely.

To address this topic, a retrospective analysis concerning the prevalence of different aetiologies of olfactory dysfunction was conducted. The most salient result of this study regards the prevalence of olfactory dysfunction caused by URTI and simultaneously confirms our hypothesis: While URTI had been the least common cause of olfactory dysfunction and merely accounted for 2% of cases in the pre-COVID-19-subgroup, it became the most common cause for olfactory dysfunction in the peri-COVID-19-population, accounting for 52% of cases. Because SARS-CoV-2 typically induces olfactory dysfunction [4,6], this increase is reasonable, and in line with the existing literature: For example, in their meta-analysis, Tong et al. [8] found that more than half the patients (53%), suffering from a SARS-CoV-2 infection, also suffered some form of olfactory dysfunction. Interestingly, this number was much higher when validated tests, such as the University of Pennsylvania Smell Identification Test (UPSIT) or the Sniffin Sticks, were used (87%). Lechien et al. [7] yielded similar results, showing that 86% of patients with a confirmed infection with SARS-CoV-2 had olfactory dysfunction. Arguably the most relevant results related to this brief report come from Rusetsky et al. [6], who examined a solely paediatric cohort of patients with confirmed SARS-CoV-2 infection. In their patient cohort, approximately 86% of paediatric patients had olfactory dysfunction after infection with the virus – a proportion identical to Lechien et al.'s percentage of adult patients [7]. Considering these outcomes, our results seem plausible.

Another aetiology which showed a significant decrease during the pandemic was that of head trauma. Accounting for 19% of cases in the pre-COVID-19-subgroup, head trauma only caused 2% of cases of olfactory dysfunction in the peri-COVID-19-population. This result is in agreement with the existing literature. In fact, one study from Norway found a 43% decrease of injured patients during the first weeks of lockdown, with most noticeable reductions among paediatric patients aged 0-17 years. Head injuries within this group decreased by 51% [9]. Another study from Canada shared even more drastic results (possibly due to the monocentric study design). Keays et al. [10] detected an overall reduction of 72% among paediatric patients visiting the emergency department. If only those patients were considered who were aged 6-17 years and had mild traumatic brain injuries a striking 93% decrease was observed. These differences could be ascribed to the lockdown regulations, which were imposed globally and, for example, restricted outdoor (e.g., sports activities) and nightlife activities. Another consequence of lockdowns was the switch from traditional learning to online formats. This, also, is likely to have played a non-negligible part in the decline of paediatric patients presenting with (olfactory dysfunction due to) head trauma, as Zagel et al. [11] suggest that approximately 21% of unintentional injuries of children (aged 5-18) happened on school grounds.

Overall, our distribution of aetiologies certainly is unusual according to Fark and Hummel's [12] results, in which only a minor proportion of their patient cohort with URTI-related olfactory dysfunction were young people. Actually, they defined the age range of 50 to 65 years to be the most vulnerable time span for developing an URTI related olfactory dysfunction. Indeed, subtracting the patients suffering from olfactory dysfunction due to a SARS-CoV-2 infection from our patient cohort does reflect this outcome, as only 11% of URTI cases would remain. Still, fact is that 89% of URTI cases in our paediatric patient cohort show olfactory dysfunction due to a SARS-CoV-2 infection.

The increase in URTI-related olfactory dysfunction suggests that the infection with SARS-CoV-2 possibly follows a different pathological mechanism than other viruses. It has been established that infection with SARS-CoV-2 mainly relies on two components, namely angiotensin converting enzyme II (ACE2) and trans-membrane protease serine 2 (TMPRSS2) [13]. ACE2 seems to play a more relevant role in viral transmission, as TMPRSS2 may be substituted for other proteases [14]. Additionally, there is a growing body of evidence for the involvement of support cells of the olfactory receptor neurons, such as sustentacular cells, in the pathogenesis of a SARS-CoV-2 infection [15,16]. Because sustentacular cells display an especially high expression of ACE2 (in mice) [15], they potentially constitute a primary route for viral entry. Recently, it was hypothesized that these cells play an essential role in the conservation of olfactory cilia, which are needed for proper signal transduction [16]. Once infected, the sustentacular cells are unable to fulfill their function, which leads to deciliation and consequently to an olfactory dysfunction. Indeed, Khan et al. [17] identified sustentacular cells as main target cells of SARS-CoV-2. Cecchini et al. [18] provide similar results in a paediatric patient. All in all, it seems that the infection of sustentacular cells is a novel pathomechanism of SARS-CoV-2, which probably plays a major role in the surge of URTI-related olfactory dysfunction, as Butowt et al. [16] proposed.

Furthermore, with regards to the age distribution of our peri-COVID-19-population, a considerable increase in the number of patients aged >15 years can be observed (see Fig. 1). This trend could be ascribed to lacking awareness regarding one's dysfunctional sense of smell. Unlike seeing or hearing, olfactory dysfunction is not always accompanied by striking impairments in daily life situations and therefore may not be recognized as early. In fact, a study by Bojanowski et al. [19] suggests that patients suffering from congenital isolated anosmia, i.e., the complete inability to perceive any odours since birth, often become aware of their disorder relatively late (on average around the age of 11). According to their analyses, it usually takes 13 years until these patients obtain their diagnosis. Although they only investigated patients with isolated congenital anosmia, this lack of "olfactory awareness" in young children could explain the noticeable increase in the number of paediatric patients presenting with olfactory dysfunction between 15 and 17 years of age in our patient cohort.

With respect to the observed sex differences among the peri-COVID-population, our cohort consists of more than twice as many girls than boys in both the pre- and post-pubertal group. These results are difficult to put into context because literature on sex differences in paediatric patients suffering from SARS-CoV-2 infection is scarce, and most literature that does relate to this topic (or URTI in general) stands in contrast to our results. Thus, Muenchhoff et al.[20] results suggest that viral infections generally affect boys more frequently than girls, although it should be noted that SARS-CoV-2 had not spread at the time of publication and therefore could not have been included in their analysis. Nevertheless, in a large clinical study with more than 34,000 patients suffering from an infection with SARS-CoV-2, Burn et al. [21] were indeed able to show a male-bias in their US-American and Spanish cohort. Only in South Korean hospitals a female-bias was observed. Note, however, that

the patients included in this study were almost exclusively adult patients. The COVID-19 sex-disaggregated data tracker also provides live and global data on this issue (unfortunately, without data regarding the age), showing that while infection rates seem somewhat equal between sexes, males are at higher risk of a severe outcome, including ICU admissions and deaths (The Sex, Gender and COVID-19 Project, https://globalhealth5050.org/the-sex-gender-and-covid-19-project/the-data-tracker/, accessed 22 August 2023). Different mechanisms have been proposed to underly this bias, including genetic, hormonal, and immunological ones [22].

Nonetheless, there is some evidence corroborating our results. It seems that post-pubertal children not only ascribe greater significance to proper olfaction than pre-pubertal children, but also perform better on odour identification tasks [23,24]. There are many theories that try to explain this age-related increase: It has been suggested that olfactory performance develops together with cognitive abilities, and therefore increases with age [23]. Another prominent theory regards the sense of smell a tool to avoid inbreeding [25]. Nováková et al. [26], on the other hand, postulated that olfactory information of peer-groups become more significant during the transition from child to adolescent, which consequently raises awareness.

Additionally, females attribute greater value to proper olfaction than males, and also perform better on odour identification tasks [23,24]. Sex differences in hygiene norms pose a possible explanation for this phenomenon. In fact, Eriksson et al. [27] found that women have stricter hygiene norms than men in almost every country. Although they only investigated handwashing and spitting, it could be that women (and girls) also place greater importance on having a pleasant body odour than men (and boys) do, and consequently use their olfactory sense to check, leading to an increased awareness. Studies are needed to verify this hypothesis.

Taken together, our results do not display the COVID-related sex-bias observed in previous studies. They do however reflect behavioural age- and sex-differences that were previously verified.

While the current report is an addition to the still relatively small – though, growing – body of literature on olfactory dysfunction in paediatric populations, it is important to note that the data of this study stem from a specialized smell and taste clinic. This, of course, introduces an inherent selection bias, which, due to the scarcity of literature on this topic, seems inevitable but has to be considered.

Additionally, the media coverage on the SARS-CoV-2 virus has probably played a significant role in the publics increasing awareness of the olfactory sense, leading to more appointments in specialized clinics, for example. To put into perspective: In Schriever and Hummel's report [2], 144 children presented to their clinic within a time span of 17 years. In the current report, 52 children (i.e., more than one third) sought medical consultation within a time span of approximately 2 years.

Lastly, although this is the largest paediatric cohort addressing this issue, another limitation of this study is the sample size of n=52 patients. A larger patient cohort could have resulted in less striking or different results. Hence, future studies with more patients over a longer time period should confirm our findings. Future research could also address any changes in the prevalence of different aetiologies of olfactory dysfunction following COVID-19.

Statements

Statement of Ethics:

Study approval statement: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the Faculty of Medicine of the TU Dresden covering anonymized retrospective and pooled analyses.

Consent to participate**:** This study protocol was reviewed and approved by ethics committee of TU Dresden, approval number BO-EK-254062022. Patient consent were not required in accordance with local or national guidelines. This also applies to patients under the age of 18 years.

Conflict of Interest:

The authors declare no conflict of interest.

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Author Contributions:

MD and VAS contributed equally to the preparation of the manuscript. Conceived and designed the study: VAS, TH, collected the data: TH, performed statistical analysis: MD, VAS, wrote the manuscript MD, VAS, TH

Data Availability Statement:

The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

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Figure Legends

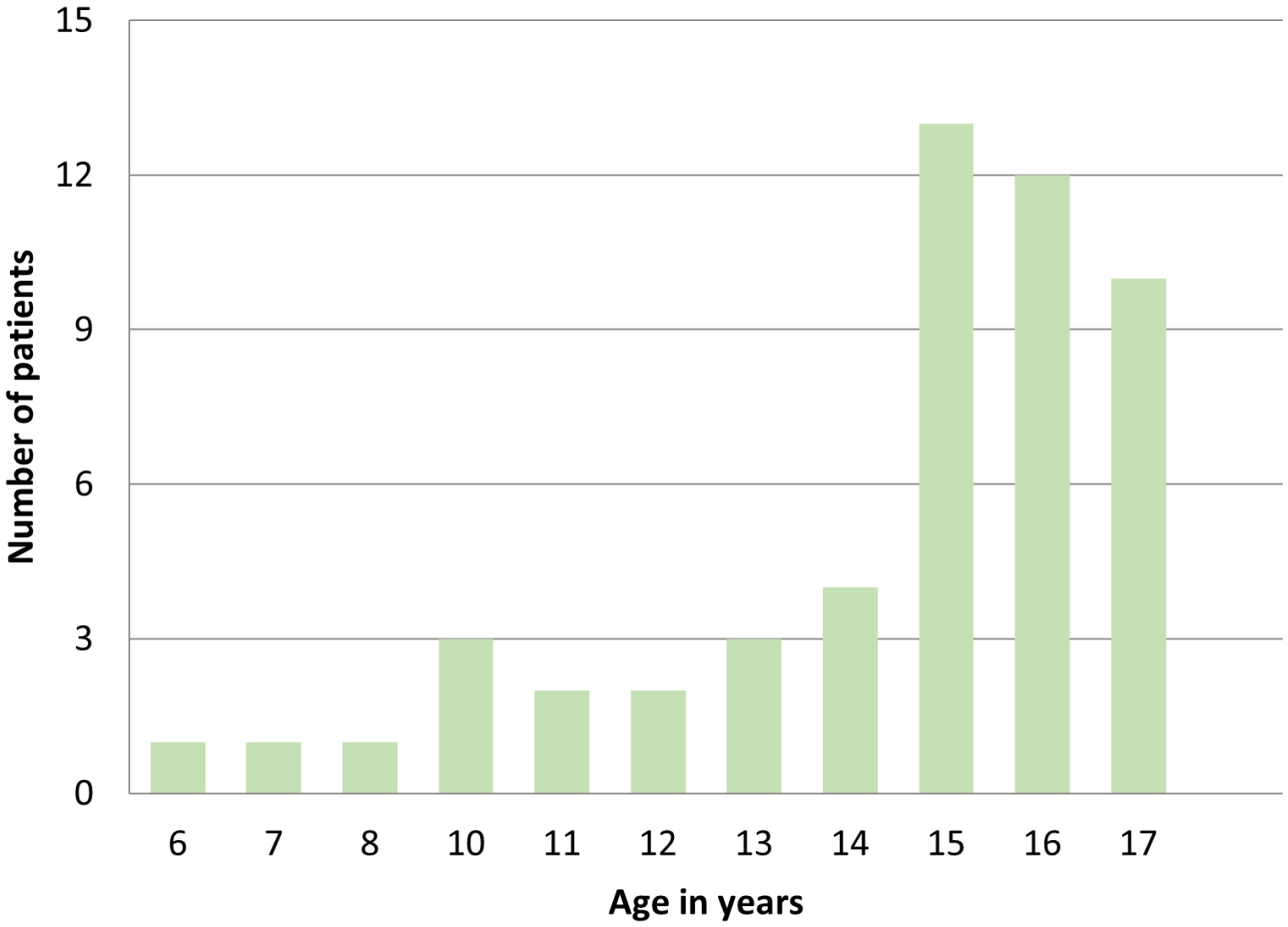
Fig. 1 Distribution of age in the peri-COVID-19-population (n=52).

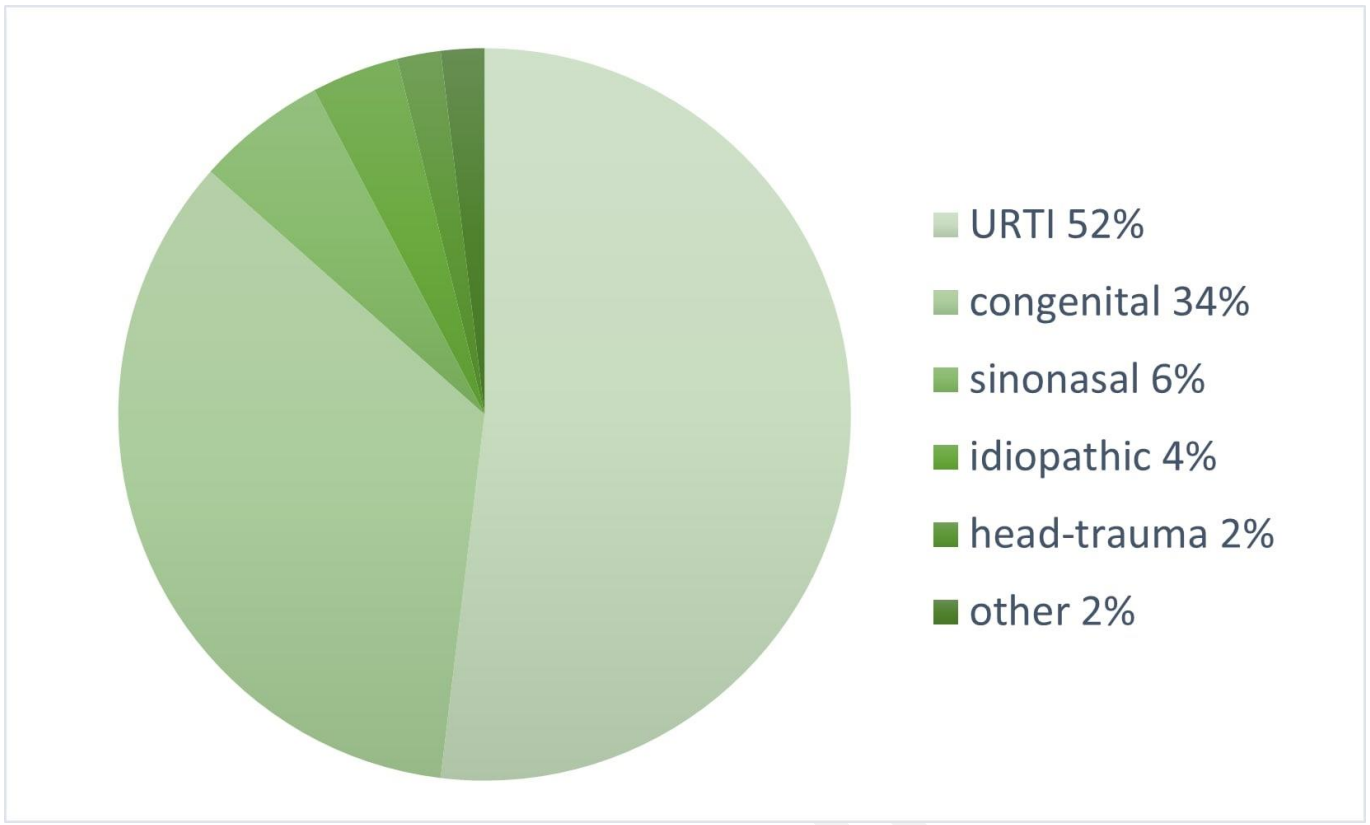
Fig. 2 Prevalence of aetiologies of olfactory dysfunction in the peri-COVID-19-population (n=52) sorted by frequency.

URTI – upper respiratory tract infection.

Fig. 3 Prevalence of aetiologies of olfactory dysfunction in the pre-COVID-19 subgroup sorted by frequency.

URTI – upper respiratory tract infection





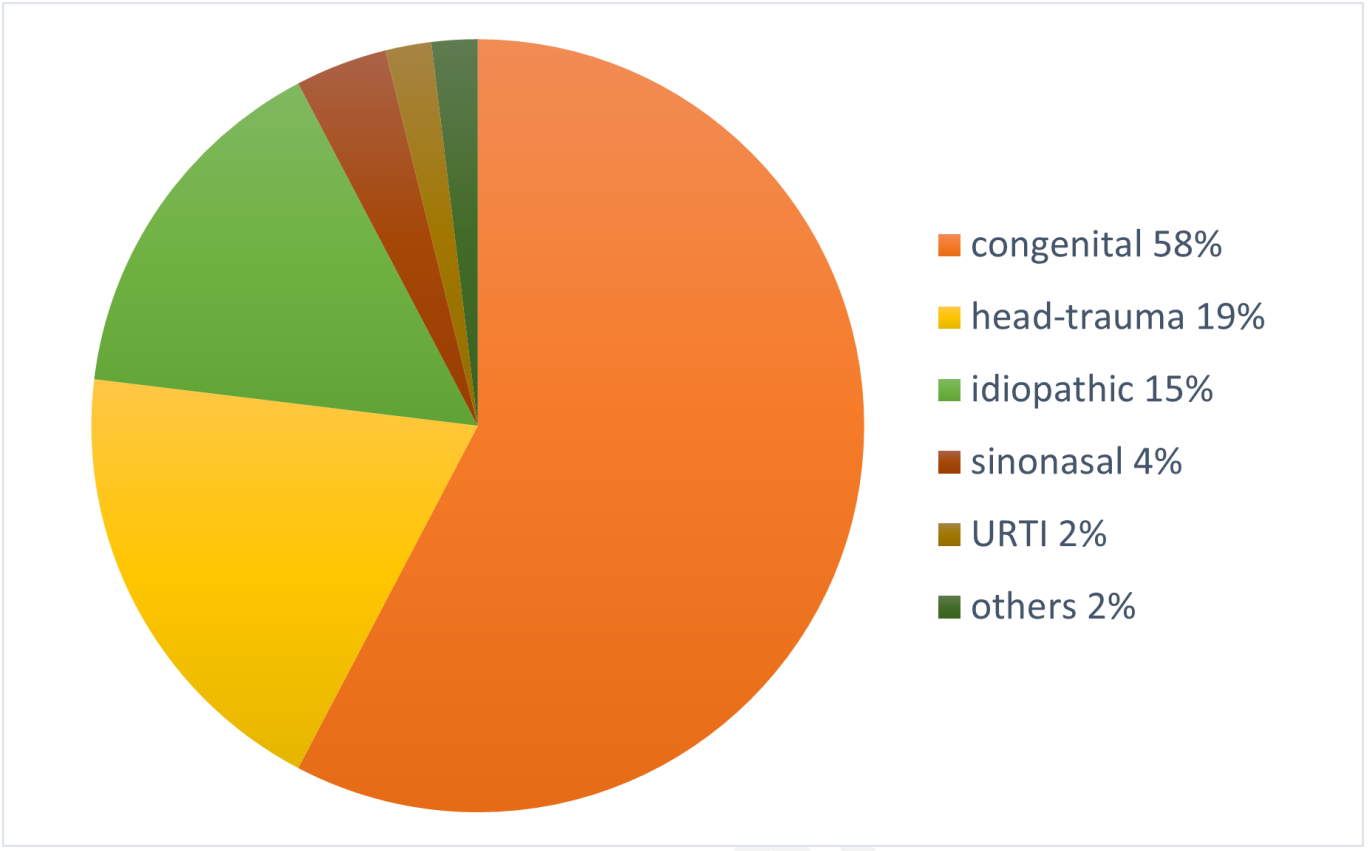


Table 3 Visual summary of the results of the statistical analyses. For comprehensibility purposes, the relevant (i.e., statistically significant) results are highlighted with a *. URTI = upper respiratory tract infection

Aetiology	**Present dataset/peri-COVID-19-population (in %)**	**Schriever & Hummel (2020) dataset/pre-COVID-19-subgroup (in %)**	***p-value***
URTI	52	2	$p < 0.001$*
Congenital	34	58	$p < 0.05$*
Sinonasal	6	4	$p > 0.05$
Idiopathic	4	15	$p > 0.05$
Head-trauma	2	19	$p < 0.01$*
Other	2	2	$p > 0.05$

Table 1 Differences in sex distribution among pre- and post-pubertal children.

Sex/Age		Age		
		Prepubertal (ages 6 – 14)	**Postpubertal (ages 15 – 17)**	**Total**
Sex	**Female**	12	25	37
	Male	5	10	15
	Total	17	35	52

Table 2 Visual summary of the sex- and age distribution of all patients suffering from URTI-related olfactory dysfunction in the peri-COVID-19-population.

Sex/Age		Age		
		Pre-pubertal (ages 6 – 14)	**Post-pubertal (ages 15 – 17)**	**Total**
Sex	**Female**	4	16	20
	Male	1	6	7
	Total	5	22	27