DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2023;70(5):A09220520

Evaluation of subjective and tested olfactory dysfunction as a screening tool for COVID-19 in children

Laura Marie Aalkjær Danielsen[1, 2], Alexander Wieck Fjældstad[1, 2] & Therese Ovesen[1, 2]

1) Flavour Clinic, University Clinic for Flavour, Balance and Sleep, Department of

Otorhinolaryngology, Regional Hospital Gødstrup, Central Denmark Region, 2) Flavour Institute, Department of Clinical Medicine, Aarhus University, Denmark

Dan Med J 2023;70(5):A09220520

ABSTRACT

INTRODUCTION. Olfactory dysfunction (OD) is an extremely frequent symptom of SARS-CoV-2 infection in adults. However, the symptomatology in the paediatric population remains understudied and heavily reliant on questionnaires. The aims of this study were to evaluate the prevalence of OD in children with SARS-CoV-2 infection and to assess the use of olfactory testing in predicting COVID-19 in children. Furthermore, we aimed to investigate the correlation between subjective and objective sense of smell in children.

METHODS. Children aged 6-12 years presenting at Test Centre Aarhus for a reverse transcription PCR for SARS-CoV-2 were invited to participate during the study period (from 8 January to 22 February 2022). They underwent olfactory testing with Sniffin' Sticks 16 Identification Kit and they were asked about their subjective assessment of smell and any confounding factors.

RESULTS. A total of 78 children completed inclusion of whom 51 had a positive SARS-CoV-2 PCR test. We found no correlation between either current SARS-CoV-2 status and Sniffin' Sticks Identification score (p = 0.500) or previous self-reported infection. We also found no correlation between subjective and objective sense of smell (p = 0. 109).

CONCLUSION. The lack of correlation between SARS-CoV-2 infection and OD may indicate that OD is not a dominant symptom in children. Therefore, olfactory testing is not recommended as a screening method for SARS-CoV-2 as was suggested in adults. Likewise, subjective questioning is not a reliable tool in assessing olfactory function in children.

FUNDING. *Laura Danielsen* received funding for salary from Forskningsfond Hospitalsenheden Vest (now Forskningsfond Regionshospitalet Gødstrup). *Alexander Wieck Fjældstad* wishes to acknowledge research salary funding for other projects from Velux Fonden. The sponsors had no say, roles or responsibilities in relation to the study, including (but not limited to) the study design, data collection, management, analysis or decision to publish.

TRIAL REGISTRATION. Not relevant.

The sense of smell is of vital importance in the everyday life of humans [1], and its impact is reflected in a deranged quality of life when the olfactory function is disturbed. Furthermore, loss of olfactory function affects a varied range of everyday tasks from food enjoyment to personal hygiene and even causing personal endangerment from lack of awareness of spoiled food, fire or gas leaks [2].

Olfactory dysfunction (OD) may be caused by a variety of conditions, of which post-infectious OD is the most prevalent aetiology. This has gained attention in the past pandemic-ridden years as patients suffering from COVID-19 often report a lack of gustatory and olfactory function. Thus, OD has been shown to be the best predictor of COVID-19 in comparison with all other symptoms in both adults and children [3]. Apparently, children are more frequently asymptomatic than adults [3]. Even so, they carry the infection and contribute to the chains of infection that push the virus through society. Hence, a thorough understanding of the paediatric population's symptomatology is of great interest. The literature on paediatric COVID-19 is rather scarce - especially with regard to OD prevalence. This is striking considering the problems arising if the dysfunction is carried into adulthood [1], highlighting the importance of collecting further data on the paediatric population and gaining a deeper understanding of evaluation methods. Questionnaires are an easy and quick method of assessing a potential dysfunction and were widely used during the COVID-19 pandemic [4, 5]. However, the reliability of the answers provided is not well documented, and the use of subjective assessment of olfactory function in adults has been questioned [6, 7]. Furthermore, similar data on subjective olfactory and gustatory function in the paediatric COVID-19 population are lacking.

Therefore, the aims of this study were to evaluate the prevalence of OD in children with SARS-CoV-2 infection and to assess the use of olfactory testing in predicting COVID-19 in children. Furthermore, we aimed to investigate the correlation between subjective and objective sense of smell in children.

METHODS

Inclusion took place at Test Center Aarhus from 8 January to 22 February 2022. Test Center Aarhus is a government-funded SARS-CoV-2 test centre using reverse transcription (RT)-PCR-based testing.

Children aged 6-12 years who showed up for testing at Test Center Aarhus were invited to participate in the study after having been swabbed for their RT-PCR SARS-CoV-2 test. Upon agreeing to participate, the children underwent examination in an adjacent office to minimise any disturbance. Parents and siblings were present because of the young age of the participants.

Before olfactory and gustatory testing, the following baseline questions were asked:

subjective sense of smell (normal, slightly poorer than average, poorer than average, much poorer than average, completely absent),

subjective sense of taste (same categories),

comorbidities and medications.

If the children did not know or did not understand the questions, explanations such as "Do you think you can smell the same things as your classmates?" were used for exemplification.

After testing, the following baseline questions were asked:

vaccine status,

previous SARS-CoV-2 infection,

symptoms (nasal secretion and/or cough),

reason for contact to the Test Center.

Before leaving, the children and/or parent(s) were given an anonymous ID-number and a link to a questionnaire to fill out with their COVID-19 status when they received the SARS-CoV-2 PCR test result.

The psychophysiological olfactory testing was performed with Burghart Messtechnik Sniffin' Sticks 16 Identification kit (SIT-16). These are felt tipped pens containing odours that have been validated in Denmark [8] with normative test scores on children aged 12-15 years [9]. Before each pen was presented, the four answer options were read out loud and also pointed out on a small poster with illustrations of the items. The participants were told to let the tester know if they did not know one of the answer options before the scent was presented. If the participant did not know an answer option, the word was explained. The most common explanations were:

turpentine: "It is used for cleaning and prickles in the nose",

cloves: "Used in various Christmas traditions",

aniseed: "Smells a bit like liqourice",

curry: "The spice used in many of the yellow-coloured meals you eat."

Each pen was then applied underneath the participants' nostrils for approximately two seconds before the cap was put back on the pen. Two applications of each pen were allowed before a descriptor had to be chosen (forced multiple choice test).

The gustatory testing was performed using the Spray Test [10], which is based on spray bottles with four above-threshold concentrations of the tastants sweet (1 g sucrose in 10 ml water), sour (1 g citric acid in 10 ml water), salty (1 g sodium chloride in 10 ml water) and bitter (1 g quinine hydrochloride in 10 ml water). Examples were given for each of the four options both verbally and with pictures (sweet like candy, sour like lemon, salty like salt, and bitter like dark chocolate and grape), and the tastants were sprayed on the participants' tongue in a pseudo-randomised order.

We used the statistical parameters mean, median, standard deviation (SD). Comparison of groups based on SARS-CoV-2 positivity was calculated by means of Student's t-test and the Wilcoxon rank-sum test. Adjustment for possible confounders was calculated by a standard regression analysis with Pearson's χ^2 test. The p value for statistical significance was set at $p < 0.05$. All analyses were conducted in STATA (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.).

Trial registration: not relevant.

RESULTS

A total of 90 children participated of whom 12 were lost to follow-up as they did not respond to the questionnaire concerning their SARS-CoV-2 status. Among the remaining 78, 51 had positive and 27 had negative RT-PCR SARS-CoV-2 tests, respectively (**Table 1** and **Table 2**). A post-hoc analysis showed that with an SD of ± 1.77 [11] and 80 children, the power in the present study was 0.7 to identify a difference of one, which is the least measurable difference of the SIT-16 kit.

TABLE 1 Demographics.

		RT-PCR SARS-CoV-2 test response		
	All (N_{all} = 78)	negative (N_n = 27)	positive (N_p = 51)	p value
Age, median (± SD), yrs	9.0 (± 1.8)	9.4 (± 1.8)	8.7 (± 1.8)	0.093[d]
Vaccinations, n (%)[a]				0.15[e]
0	13 (16.7)	2 (9)	11 (24)	
1	13 (16.7)	3 (14)	10 (22)	
2	41 (52.6)	17 (77)	24 (53)	
Comorbidity, n (%)[b]	17 (22.0)	5 (18.5)	12 (23.5)	0.580[e]
Medicine, n (%)[c]	11 (14.1)	1 (3.7)	10 (19.6)	0.055[e]
Previous COVID-19, n (%)	9 (11.5)	2 (7.4)	7 (13.7)	0.419[e]

RT = reverse transcription.
a) 0, 1, or 2 shots.
b) Asthma (n = 5), allergies (n = 7), autism (n = 3), migraine (n = 1), psoriasis (n = 1), heart failure (n = 1), immunocompromised (n = 1), hard of hearing (n = 1), overactive bladder (n = 1).
c) Cetirizin (n = 3), salbutamol (n = 1), solifenacin (n = 1), allergy vaccine (n = 1), asthma spray unspecified (n = 3), trimethoprim (n = 1), montelukast (n = 1).
d) Student's t-test.
e) Pearson's χ^2 test.

TABLE 2 Analyses for sense of smell and SARS-CoV-2-positivity based on reverse transcription (RT)-PCR response.

	RT-PCR SARS-CoV-2 test response		
	negative (N_n = 27)	positive (N_p = 51)	p value
Identification score, mean (range)	14 (12-15)	14 (12-15)	0.5[a]
Identification score < 13, n (%)	8 (29.6)	18 (35.3)	0.16[b]
Taste spray, n (%)			0.16[b]
1 correct	0	1 (2)	
2 correct	7 (26)	4 (8)	
3 correct	2 (7)	7 (14)	
4 correct	18 (67)	37 (76)	
Subjective normal sense of smell, n (%)	25 (93)	46 (90)	0.72[b]
Subjective normal sense of taste, n (%)	27 (100)	50 (98)	0.419[b]

a) Wilcoxon rank-sum test.
b) Pearson's χ^2 test.

Age had a significant impact on olfactory identification score, with an increased score correlating with increased age ($p < 0.001$). No correlation was observed between SARS-CoV-2 status and SIT-16 score when adjusted for confounders (age, vaccine status, previous COVID-19, comorbidities and medicine intake) ($p = 0.760$.)

Furthermore, no correlation was recorded between subjective and objective sense of smell (p = 0.109).

Children who reported previous SARS-CoV-2 infection had a SIT16 score of –0.832 (–2.667-1.008) when adjusted for age, vaccination status and current SARS-CoV-2 status, which was not statistically significant from children without previous SARS-CoV-2 infection.

DISCUSSION

Our study showed that children infected with SARS-CoV-2 did not have a significantly lower sense of smell based on SIT-16 scores, though other reports have indicated that smell loss may serve as an indicator of SARS-CoV-2 in adults [12]. Therefore, we conclude that olfactory testing should not be used as a screening tool to identify infected children. Previously, only a few studies have been conducted on COVID-19 and the sense of smell in children. In 2021, Rusetsky et al. [13] found hyposmia in 86.1% of 79 children admitted to the National Medical Research Centre for Children's Health (Moscow, Russia) in April and May 2020 with COVID-19. The method of testing was SIT-16 similar to that used in our study. However, the two studies are not directly comparable. While Rusetsky et al. examined hospitalised children, our study was conducted while the test strategy in Denmark recommended testing all children with a quick test at the school premises or completing a home test twice a week [14]. This resulted in children included in our study being at the test centre due to a positive quick or home test or because they were a close contact to a SARS-CoV-2-infected individual and presented only mild to no symptoms. Therefore, it is very possible that the children included in this study, while infected with SARS-CoV-2, did not, in fact, suffer from COVID-19. Nonetheless, the aim of this study was to assess the usefulness of olfactory testing in predicting SARS-CoV-2 positivity, and therefore our evaluation of children showing little to no symptoms was highly relevant as this group constituted the vast majority of infected children in Denmark.

Our test period started on 8 January 2022, and at this time approximately 96-97% of all SARS-CoV-2 positive cases were infected with the Omicron variant [15]. While loss of sense of smell has been reported as a prevalent sign in historical SARS-CoV-2 infection, it has been reported to be significantly less prevalent with the Omicron variant [16]. Thus, it is possible that the prevalence of the Omicron variant altered the expected prevalence of the loss of sense of smell.

All the children included in our study were tested for SARS-CoV-2 with an RT-PCR test, making the risk of false positives or negatives low, which strengthens the lack of association we found. According to our power calculation, our group of 79 children should provide a 70% likelihood of finding any difference. Furthermore, we believe that the children included have a high representability to the population as we included all children arriving at the test centre.

Statistically, we found a poor reliability of the subjective measures of olfactory function.

Thus, 29.5% of children had an SIT-16 score below 13, which has historically been used as a cut off value for hyposmia [11, 13]. However Gellrich et al. [17] set the cut off value between normosmia and hyposmia as an SIT-16 score of 7-9 in children 6-11 years of age but also caution against the use of cut off values in children, and encourage individual assessment of the child as the prevalence of OD remains unknow in children. Therefore, we have chosen to evaluate the small number of children who reported a subjectively reduced sense of smell. Only one of the seven had a SIT-16 score below ten (with a score of eight). This also means that while eight children scored ≤ 10 on the SIT-16 score, only one (mentioned above) was able to subjectively identify this. We found no predictive value in olfactory symptoms, which runs rontrary to Nikolopoulou et al. [3]. However, the study by Nikolopoulou et al. used a subjective measurement of olfactory function [18], which is not uncommon in research concerning symptoms of SARS-CoV-2 in children [4, 5]. Based on our results, subjective measurements of olfactory function should be used with great caution in the paediatric population as we found a

poor reliability.

The lack of self-reporting of olfactory symptoms in younger children is not unique to our study [19]. Therefore, great care was taken to ensure that all the children understood what was meant by "normal sense of smell", so as not to skew the subjective assessment of olfactory function based on an age-related increase in understanding. However, the focus in this study was on obtaining a statistically useful number of participants for an overview assessment and therefore it was highly prioritised to keep the inclusion time to a minimum as an incentive for both children and parents to agree to participate. Therefore, we kept the questions to a maximum of ten and did not use standardised questionnaires such as SNOT-22 as they would have prolonged the inclusion period. Thus, while our results are in line with previous findings [13, 19], further studies are needed to both validate and elaborate on the lack of coherence between the subjective and psychophysiological olfactory ability.

The difference in SIT-16 scores between the children reporting a previous SARS-CoV-2 infection and those not reporting such an infection was not significant. However, only nine out of 79 (11.39%) children were aware of any previous infection. According to the Danish health authorities (Statens Serum Institut), only one third of all seropositive adults were aware of their infection [20]. As we were unable to check for seropositivity, it is likely that a number of the children reporting no previous infection had, in fact, been infected, thereby causing type 2 error.

CONCLUSION

We found no difference in the sense of smell between the 51 SARS-CoV-2-positive and 27 SARS-CoV-2-negative children, and thus do not recommend using olfactory testing as a screening method for SARS-CoV-2 – either objectively or subjectively. However, in the case of possible OD in children, olfactory testing is important as we found subjective measures to be unreliable. We found no correlation between previous SARS-CoV-2 infection and measured olfactory function, but cannot exclude a possible correlation being hidden in the lack of acknowledged previous infection.

Correspondence *Laura Marie Aalkjær Danielsen*. E-mail: lauraaalkjaer@hotmail.com

Accepted 15 February 2023

Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2023;70(5):A09220520

REFERENCES

1. Calvi E, Quassolo U, Massaia M et al. The scent of emotions: a systematic review of human intra- and interspecific chemical communication of emotions. Brain Behav. 2020;10(5):e01585.
2. Hummel T, Nordin S. Olfactory disorders and their consequences for quality of life. Acta Otolaryngol. 2005;125(2):116-21.
3. Nikolopoulou GB, Maltezou HC. COVID-19 in Children: where do we stand? Arch Med Res. 2022;53(1):1-8.
4. Qiu C, Cui C, Hautefort C et al. Olfactory and gustatory dysfunction as an early identifier of COVID-19 in adults and children: an international multicenter study. Otolaryngol Head Neck Surg. 2020;163(4):714-21.
5. Roge I, Smane L, Kivite-Urtane A et al. Comparison of persistent symptoms after COVID-19 and other non-SARS-CoV-2 infections in children. Front Pediatr. 2021;9:752385.
6. Philpott CM, Wolstenholme CR, Goodenough PC et al. Comparison of subjective perception with objective measurement of olfaction. Otolaryngol Head Neck Surg. 2006;134(3):488-90.

7. Wehling E, Lundervold AJ, Espeset T et al. Even cognitively well-functioning adults are unaware of their olfactory dysfunction: implications for ENT clinicians and researchers. Rhinology. 2015;53(1):89-94.
8. Niklassen AS, Ovesen T, Fernandes H et al. Danish validation of sniffin' sticks olfactory test forthreshold, discrimination, and identification. Laryngoscope. 2018;128(8):1759-66.
9. Hald M, Hald MO, Stankovic J et al. Positive association between bitter taste threshold and preference of vegetables among adolescents. Acta Paediatr. 2021;110(3):875-880.
10. Hummel T, Hummel C, Welge-Luessen A. Assessment of olfaction and gustation. In: Welge-Luessen A, Hummel T, eds. Management of smell and taste disorders: a practical guide for clinicians. Thieme, 2013:58-75.
11. Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol. 2007;264(3):237-43.
12. Meng X, Deng Y, Dai Z, Meng Z. COVID-19 and anosmia: a review based on up-to-date knowledge. Am J Otolaryngol. 2020;41(5):102581.
13. Rusetsky Y, Meytel I, Mokoyan Z et al. Smell status in children infected with SARS-CoV-2. Laryngoscope. 2021;131(8):E2475-E2480.
14. Skanderborg Kommune. Information om samtykke til test for Covid-19 på skolerne. www.skanderborg.dk/borger/familie-boern-og-unge/skole/information-om-samtykke-til-test-for-covid-19-paa-skolerne (22 Feb 2022).
15. Our World In Data. SARS-CoV-2 variants in analyzed sequences. https:// ourworldindata.org/grapher/covid-variants-area?country=~FRA (22 Feb 2022).
16. Boscolo-Rizzo P, Tirelli G, Meloni P et al. Coronavirus disease 2019 (COVID-19)-related smell and taste impairment with widespread diffusion of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) Omicron variant. Int Forum Allergy Rhinol. 2022;12(10):1273-81.
17. Gellrich J, Sparing-Paschke LM, Thieme T et al. Normative data for olfactory threshold and odor identification in children and adolescents. Int J Pediatr Otorhinolaryngol. 2019;123:5-9.
18. King JA, Whitten TA, Bakal JA, McAlister FA. Symptoms associated with a positive result for a swab for SARS-CoV-2 infection among children in Alberta. CMAJ. 2021;193(1):E1-E9.
19. Concheiro-Guisan A, Fiel-Ozores A, Novoa-Carballal R et al. Subtle olfactory dysfunction after SARS-CoV-2 virus infection in children. Int J Pediatr Otorhinolaryngol. 2021;140:110539.
20. SSI. Seroprævalensundersøgelse af bloddonorer - 5. runde. Updated 29 March 2022. https://covid19.ssi.dk/-/media/arkiv/subsites/covid19/overvaagningsdata/moerketal/seropraevalensundersoegelse-af-bloddonorer_runde5.pdf?la=da (Apr 2022).