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ORIGINAL RESEARCH

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ACE2 and TAS2R38 receptor expression in pediatric and adult patients in the nasal and oral cavity

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Abstract

Objective: To investigate differences in angiotensin-converting-enzyme-2 (ACE2) and bitter taste receptor (TAS2R38) expression between patient age groups and comorbidities to characterize the pathophysiology of coronavirus 19(COVID-19) pandemic. ACE2 is the receptor implicated to facilitate SARS-CoV-2 infections and levels of expression may correlate to the severity of COVID-19 infection. TAS2R38 has many non-gustatory roles in disease, with some evidence of severe COVID-19 disease in certain receptor phenotypes.

Methods: We conducted a prospective cohort study and collected nasal and lingual tissue from healthy pediatric ($n = 22$) and adult ($n = 25$) patients undergoing general anesthesia for elective procedures. RNA isolation and qPCR were performed with primers targeting ACE2 and TAS2R38.

Results: A total of 25 adult (52% male; 44% obese) and 22 pediatric (50% male; 36% obese) patients were enrolled, pediatric tissue had 43% more nasal ACE2 RNA expression than adults with a median fold change of 0.69 (IQR 0.37, 0.98) in adults and 0.99 (IQR 0.74, 1.43) in children ($p < .05$). There were no differences between the age groups in ACE2 expression of lingual tissue ($p = .14$) or TAS2R38 expression collected from either nasal ($p = 049$) or lingual tissue ($p = .49$). Stratifying for obesity yielded similar differences between nasal ACE2 expression between adults and children with median fold change of 0.56 (IQR 0.32, 0.87) in adults and 1.0 (IQR 0.82, 1.52) in children ($p < .05$).

Conclusions: ACE2 receptor expression is higher in nasal tissue collected from children compared to adults, suggesting COVID-19 infectivity is more complicated than ACE2 and TAS2R38 mRNA expression.

Level of Evidence: NA.

KEYWORDS
ACE2, bitter taste receptor, coronavirus, COVID-19, obesity

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1 | INTRODUCTION

The respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent for coronavirus disease 2019 (COVID-19) and since its global emergence in late 2019, has infected more than 769 million and killed 6.9 million people.[1] Studies have shown that the angiotensin-converting-enzyme-2 (ACE2) may play a role in the pathophysiology of COVID-19 infection, specifically facilitating the ability of the virus to enter the cell and contributing to the severity of the disease. The ACE2 receptor, along with transmembrane serine protease 2 (TMPRSS2), binds to the virus and prime the virus's spike protein for cell entry, respectively.[2] Initial infection occurs within in the upper airway with increased levels of ACE2 within the neuroepithelium of the nose,[3] explaining the high incidence of anosmia and hyposmia in SARS-CoV-2 infections. Studies have implicated ACE2 as major participant in innate immunity[4] and suggested patients on renin-angiotensin system (RAS) blockers are less likely to have severe disease,[5–7] which re-enforces how function or prevalence of the receptor may explain disease severity.

Prior to the COVID-19 pandemic, research efforts were underway to understand the non-gustatory functions of bitter taste receptors (T2Rs) and expression of their subsequent genes (TAS2Rs). T2Rs are found throughout the body, including the small intestine, oral cavity and nasal cavity, and pulmonary neutrophils.[8] Specifically, subtype T2R38 plays a significant role in airway immunity by increasing ciliary beat frequency,[9] muco-ciliary clearance,[10] and neutrophil binding activity[11] and has been implicated in the pathophysiology of several diseases including chronic rhinosinusitis (CRS),[9,12] obesity,[13] and asthma.[14] While T2R38 is not a direct co-receptor for SARS-CoV-2, it is known to regulate sinonasal innate immunity by increasing nitric oxide (NO) and ciliary beat frequency in particular. Increased levels of NO and increased beat frequency lead to increased clearance of pathogens which play an important role in infection prevention.[15–18] Given the known role in upper and lower airway immunity, recent studies have implicated that severity of SARS-CoV2 in adults can be predicted based on their T2R38 expression.[19,20] This interaction between T2R38 expression and SARS-CoV2 disease has also led to investigation of chloroquine, a known T2R agonist, as a possible treatment COVID-19.[21] Obesity is a well-established risk factor for severe SAR-CoV-2 infections in adults,[22] and several studies have found that obesity status alters TAS2R expression in oral and extraoral tissues.[23,24]

Several risk factors are known to influence infection rate and severity of SARS-CoV-2 infections. The clinical phenomenon of markedly decreased severity and infection rates of COVID-19 in pediatric patients has been well documented[25] and the physiologic explanation for this is an active topic of research. A few preliminary studies have sought to elucidate the variability of receptor expression of ACE2 between adults and children.[26–29] Obesity is also a well-established risk factor for severe COVID-19, but an association with ACE2 expression somewhat limited. One study described increased ACE2 in obese mice lung tissue[30] and another demonstrates increased levels of ACE2 in adipose tissue when compared to other human tissues.[31] To our knowledge, the effects of age on TAS2R38 expression and function have not been investigated. Thus, the objective of this study was to evaluate ACE2 and TAS2R38 receptor expression and whether they differ based on age and the presence of obesity. We hypothesized that ACE2 and T2R38 receptor expression would be diminished those at low risk of serious COVID-19 infections, including children compared to adults as well as healthy compared to obese adults and children.

In this study, we performed the first study investigating both ACE2 and TAS2R38 expression variability by prospectively sampling the sinonasal and oral cavities of pediatric and adult patients. To evaluate the effects of obesity in both age groups, we stratified the data to evaluate how receptor expression is altered by increased body mass index (BMI).

2 | METHODS

2.1 | Patient selection

After obtaining Institutional Review Board approval from the Johns Hopkins School of Medicine (IRB00249371), pediatric and adult patients undergoing elective surgery within the department of Otolaryngology—Head and Neck surgery were selected by convenience sampling and were screened for eligibility. Eligibility was determined by age (≤9 years or ≥ 18 years), BMI category, and the surgical procedure being performed. Patients were excluded if they were unable to consent or no guardian available to provide consent, history of ionizing radiation, and current active oral cavity or sinonasal cavity infection or malignancy. Patients were approached pre-operatively and consent was obtained for study participation. After consent was obtained, data was collected including age, weight, demographics, type of surgical procedure, and co-morbidities. Obesity was defined at a BMI greater than 30 in adults and weight-for-age percentile >95% in children.

2.2 | Sample collection

In order to provide consistent and reliable sampling with minimal trauma, patients were sampled shortly after induction of general anesthesia. In the nose, a cotton tip applicator was applied to nasal vestibule to remove mucous. Then a cytobrush swab was applied by the study otolaryngologist between the middle turbinate and near the olfactory epithelium of the spheno-ethmoid recess. The swab was then rotated gently for 15 s and removed. In the oral cavity, the tongue was atraumatically retracted, saliva removed with absorbable gauze and samples taken with cytobrush by swabbing the middle one-third of the tongue. Once samples were acquired, they were placed in DNA/RNA shield (Zymo Research, Irvine CA, USA) and stored at −80°C for later RNA extraction.

TABLE 1 Patient demographics and selected co-morbidities.

	Adults ($n = 25$)	Children ($n = 22$)
Age in years, mean ± SD	55 ± 16	4.0 ± 2.2
Male, % (*n*)	52% (13)	50% (11)
Obese, % (*n*)	44%[a] (11)	36%[b] (8)
Asthma, % (*n*)	4% (1)	18% (4)
Hypertension, % (*n*)	44% (11)	0
Coronary artery disease, % (*n*)	8% (2)	0

[a]Obesity defined as a body mass index >30.
[b]Obesity defined as weight for age percentile >95%.

TABLE 2 Elective surgeries of recruited patients.

Adults ($n = 25$)	Children ($n = 22$)
DL/SML + biopsy (6)	Tonsillectomy and adenoidectomy (12)
Thyroid surgery (5)	+ Tympanostomy tube/EUA ears (4)
+ neck dissection (2)	+ nasal endoscopy
Parathyroid surgery (2)	+ EGD
Parotidectomy (2)	Tympanostomy tube (4)
Septorhinoplasty, ITR	+ adenoid surgery (3)
Septoplasty, ITR	+ ABR
Endoscopic sinus surgery	Ear FB removal
Cochlear Implant	SML/Bronchoscopy, frenotomy
Eustachian Tube Dilation	Branchial cyst excision, tympanoplasty
Wide Local Excision, SLN Biopsy	Neck mass excision
Radical Tonsillectomy, Neck Dissection	Cleft palate repair, EUA ears
Nasal advancement flap	Lip lesion excision
Tonsillectomy	
Sialendoscopy	

Abbreviations: DL, direct laryngoscopy; EUA, exam under anesthesia; ITR, inferior turbinate reduction; SLN, sentinel lymph node; SML, suspension microlaryngoscopy.

2.3 | Data collection and analysis

RNA was then isolated using Quick RNA microprep kit (Zymo Research, Irvine CA, USA, cat#R1050) according to manufacturer's instruction. Total RNA was converted to cDNA using High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Waltham, MA, USA. The real-time quantitative PRC (qPCR) was performed on CFX real-time machine (Biorad, Philadelphia, PA, USA) using SsoAdvanced Universal Supermixes (Biorad, Philadelphia, PA, USA). The primers used for the analysis were as follows: for ACE2, 5′-GGGAT CAGAGATCGGAAGAAGAAA-3′ and 5′-AGGAGGTCTGAACATCAT-CAGTG-3′; for TAS2R38 5′-GTGCTGCCTTCATCTCTGTGCC-3′ and 5′-GCTCTCCTCAACTTGGCATTGC-3′; for 18s ribosomal RNA, 5′-GCAATTATTCCCCATGAACG-3′ and 5′-GGCCTCACTAAACCATC CAA-3. The fold change in expression was analyzed via $2^{-\Delta\Delta CT}$ method using 18S ribosomal RNA as a housekeeping gene and non-obese pediatric patients as the reference population. Additionally, FOXJ1, a ciliated olfactory epithelium regulatory gene, RNA fold change was analyzed to confirm consistency in nasal epithelium sampling. Fold change data was analyzed for outliers via Tukey method and outliers were removed from further statistical testing. Six ACE2 samples and 5 TAS2R samples were identified as outliers. In order to evaluate receptor mRNA expression differences between age groups and different comorbidities, Mann–Whitney–Wilcoxon test statistical analysis was done with Prism GraphPad (San Diego, CA, USA).

3 | RESULTS

3.1 | Patient demographics

The patients were recruited from October 2020 to March 2021. Twenty-five adults (52% male, mean age 55 ± 16 years) and 22 children (50% male, mean age 4 ± 2.2 years) were recruited undergoing elective otolaryngologic surgery (Table 1). 44% of adults were obese and 36% of children were obese.18% of children and 4% of adults had an underlying diagnosis of asthma. For hypertension, 0% of children and 44% of adults had an underlying diagnosis. A majority of the adult elective procedures were for laryngeal surgery ($n = 6$, 24%) and head and neck endocrine surgery ($n = 9$, 36%). Most pediatric elective procedures were tonsillectomy and adenoidectomy (T&A) ($n = 12$, 55%) followed by tympanostomy tube placement ($n = 4$, 18%). For a complete list of the procedures, please see Table 2. Raw data for qPCR reported in Supplemental Figure 1 and FOXJ1 reported in Supplemental Figure 2. No difference in FOXJ1 was identified in pediatric versus adult nasal samples.

3.2 | ACE2 expression

In this cohort, we found that children have significantly more nasal ACE2 RNA expression when compared to adults. Utilizing qPCR and the $2^{-\Delta\Delta CT}$ method with normal-weight children as our reference population, we found that the median fold change was 0.69 (IQR 0.37, 0.98) in adults and 0.99 (IQR 0.74, 1.43) in children ($p = .03$) (Figure 1A). Children have approximately 43% more ACE2 RNA expressed in their nasal epithelium than adults. When evaluating tongue tissue, ACE2 median values were higher in children, but the results were not significant ($p = .14$) (Figure 1C).

3.3 | TAS2R38 expression

For TAS2R38 RNA expression, there were no significant differences when comparing adults and children for both nasal and tongue tissue. For nasal tissue, adults had a median fold change of 0.72 (IQR 1.20,

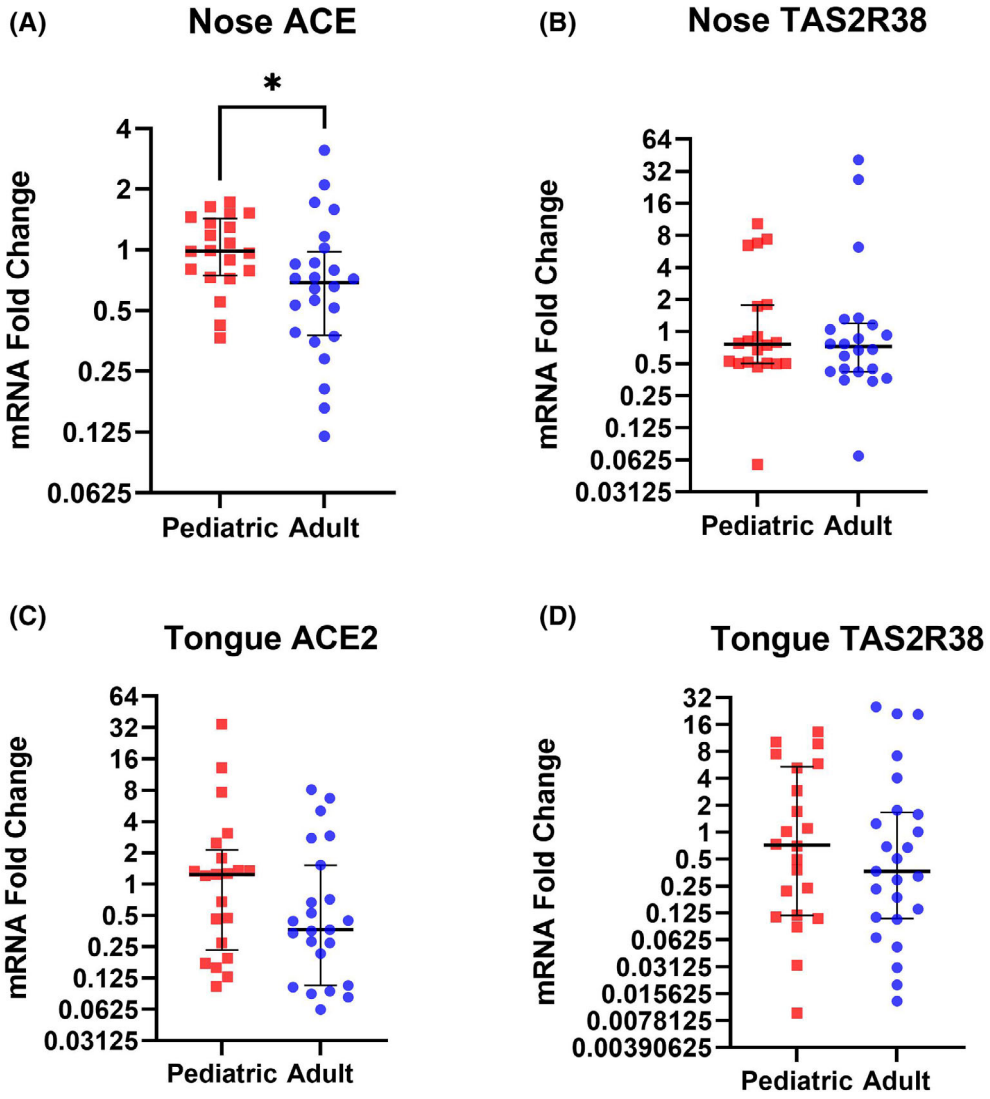

FIGURE 1 Ribonucleic acid (RNA) expression of angiotensin-converting-enzyme-2(ACE2) and bitter taste receptors (TAS2R38) via quantitative polymerase chain reaction (qPCR) in the oral and sinonasal cavity. *-$p < 0.05$.

0.42) and children 0.76 (IQR 0.50, 1.78; $p = .49$) (Figure 1B). For tongue tissue, adults have a median fold change of 0.37 (IQR 0.11, 1.67) and children 0.71 (IQR 5.37, 0.12; $p = .49$) (Figure 1D).

3.4 | Receptor expression in obese patients

Pediatric and adult cohorts were analyzed on obesity status. When comparing non-obese adults to non-obese children, ACE2 RNA expression was increased in pediatric nasal tissue. The median fold change for non-obese adults was 0.56 (IQR 0.32, 0.87) and 1.0 (IQR 0.82, 1.52; $p = .022$) in children (Figure 2A), indicating non-obese children on average have 78% more nasal ACE2 RNA expression. Furthermore, nasal tissue in obese adults had a median fold change of 0.79 (IQR 0.39, 1.17) and children 0.90 (IQR 0.59, 1.577) and these results were not significant ($p = .44$) (Figure 2A). We also stratified obesity for ACE2 expression in tongue tissue, TAS2R38 in nasal tissue, and TAS2R38 in tongue tissue, and no significant differences were noted (Figure 2B–D).

4 | DISCUSSION

The role of ACE2 in SARS-CoV-2 cell entry and infection has been well documented, but the role of this receptor expression in disease severity and virulence is an ongoing area of research. Additionally, the understanding of T2R38 in non-gustatory roles of physiology and pathophysiology throughout the body continues to expand. This is the first prospective analysis of targeted gene expression of both ACE2 and TAS2R38 in the same patient cohort in the oral and sinonasal cavities comparing children and adults. In this study, we investigated the hypothesis that the higher observed virulence and infection rate adults as well as comorbidities including obesity may be explained by receptor gene expression integral to viral entry into the body. We found that children have approximately 43% *more* ACE2 RNA expressed in their nasal epithelium than adults and no observed differences in ACE2 within the oral cavity or TAS2R38 expression in the sinonasal and oral cavity. When we stratified the data for obesity, similar patterns were found with non-obese children having 78% *more* ACE2 RNA than non-obese adults expressed in their nasal epithelium.

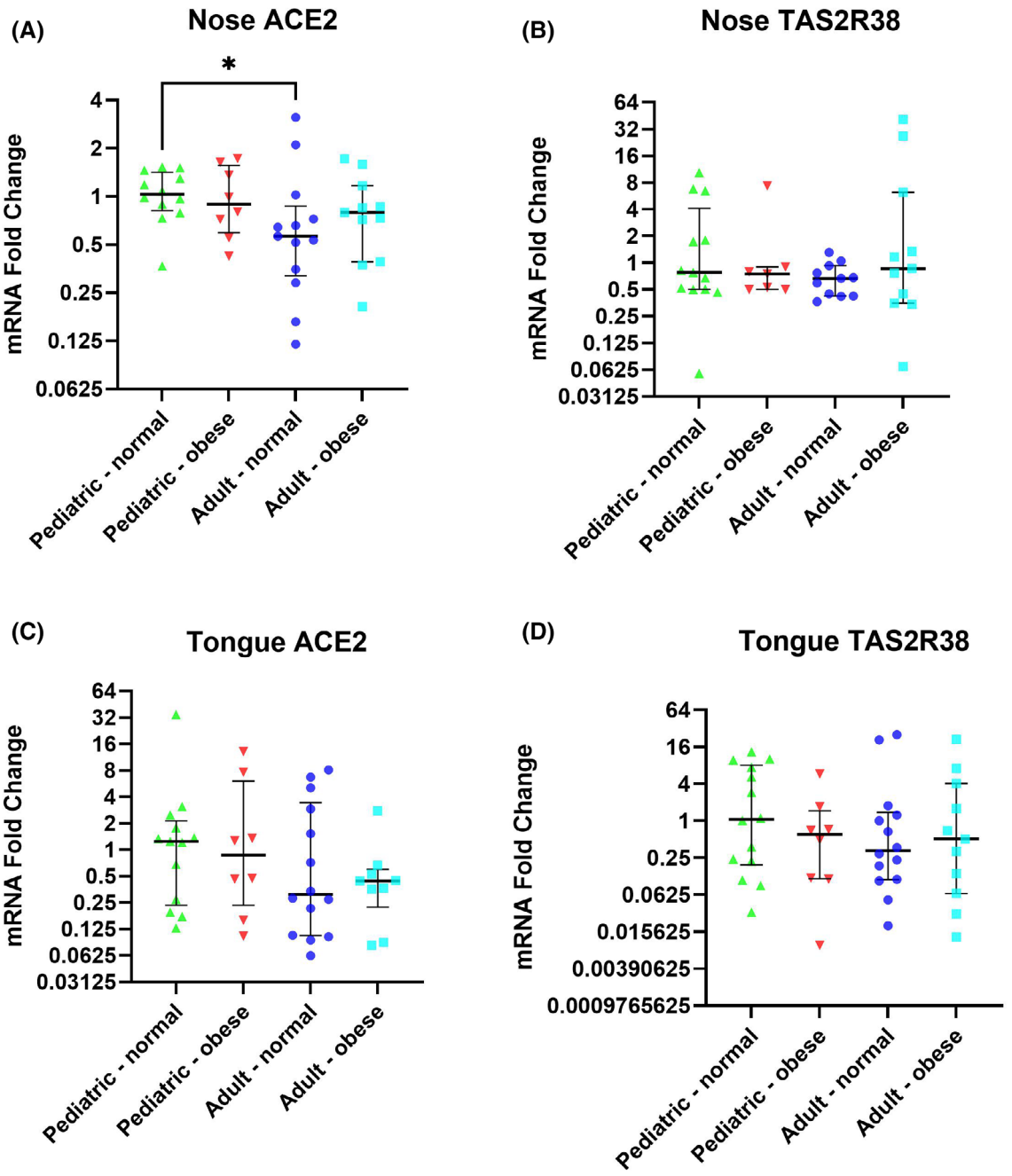

FIGURE 2 Ribonucleic acid (RNA) expression of angiotensin-converting-enzyme-2 (ACE2) and bitter taste receptors (TAS2R38) via quantitative polymerase chain reaction (qPCR) in the oral and sinonasal cavity with obesity stratification. *-$p < 0.05$.

When comparing obese children vs non-obese children and obese adults to non-obese adults, we saw no differences in ACE2 or TAS2R38 RNA expression in the nasal and oral cavities.

4.1 | Age and ACE2 expression

These data indicate that virulence and infection rates are not directly correlated with gene expression levels of receptors in the upper respiratory tract that are active in COVID-19 infectivity. In fact, our results of ACE2 nasal expression are contradictory to several studies that have been published since the start of the pandemic that show decreased[26–28] or no difference[29] in sinonasal expression of ACE2 in children when compared to adults. The majority of these studies utilized retrospective data from collected nasal scrapings[27] or retrospective transcriptome data from nasal scrapings[26,28] with the exception of Canani et al. who also performed a prospective nasal swab qPCR to look at ACE2 sinonasal expression. Their data showed increased sinonasal ACE2 expression in children, but the results were not significant and they used a smaller sample size collection ($n = 15$).[29]

Additionally, the methods for nasal swabbing are not well described in previous studies and a recent study[3] has shown that the levels of ACE2 within the sinonasal cavity vary on the cell type and anatomic location. For instance, the neuroepithelium/olfactory epithelium, which increases in concentration toward the skull base was shown to have the highest level of ACE2 receptors in the nose, suggesting a cause for the high rate of anosmia and hyposmia in SARS-CoV-2 infections.[3] Given these findings, we collected nasal swab samples in the region of the middle turbinate and olfactory epithelium rather than the traditional nasopharyngeal, nasal vestibule, or inferior meatus swab that has been performed in other studies. We posit that this method may be more accurately able to evaluate level of ACE2 in the sinonasal cavity.

Interestingly, results in this study may correlate ACE2 expression as protective of severe COVID-19. Studies from the first coronavirus outbreak (SARS-CoV) demonstrated how coronavirus infections cause a decreased ACE2 expression leading to RAS dysfunction and acute lung injury[32] and the same is thought to occur in SARS-CoV-2 infections.[2] SARS-CoV-2 infection leads to an internalization, downregulation, and shedding of ACE2 which leads to RAS imbalance. ACE2 functions as a major inhibitor of inflammation and its downregulation and shedding are thought to push the RAS toward the inflammatory cytokine storm often seen in severe COVID-19.[33] Increased nasal ACE2 expression we see in children may be protective of severe disease, but this does not fully explain why children are less likely to contract COVID-19.

On the other hand, the differences seen in ACE2 expression may have to do with a patient population skewed toward increased inflammation. We recruited patients undergoing elective surgery and 55% percent of our pediatric patients were undergoing T&A. Chronic inflammation of the oropharyngeal and nasopharyngeal tissue is usually what leads to an indication for T&A. The oral and nasal cavities are in close proximity to these tissues and likely associated with increased inflammation as well. Given ACE2's connection to innate immunity and inflammation,[4] it may be upregulated in this patient population.

Finally, ACE2 RNA expression may have a minor role in actual protein expression and function in infectivity of SARS-CoV-2. Multiple proteins such as TMPRSS2 are involved in SARS-CoV-2 activity and virulence[2] and may play an equal or more important role in describing the differences in age virulence. Additionally, multiple polymorphisms exist for ACE2 and have been shown to alter disease severity among many pulmonary diseases, including acute respiratory distress syndrome in COVID-19.[34] Given these data and that our results are contradictory to several other published studies, the differences in COVID-19 severity by may have to do more with changes in ACE-2 protein function as patients age.

4.2 | Age and TAS2R38 expression

To our knowledge, no previous studies have evaluated TAS2R38 expression in relation to age and our results were unexpected since we anticipated a correlation with expression and age. Previous correlative studies have suggested that children have a decreased appeal for bitter-tasting foods that change as they become adults[35] and have correlated lingual mRNA expression with bitter taste perception in adults.[36] The pediatric bitter taste perception and aversion may not be strongly correlated to receptor expression in the oral cavity and is may have alternative biologic explanations by a biological and behavioral aversion to possibly poisonous foods and increased desire for sweeter foods[35] and is unlikely to be fully explained by receptor expression. Furthermore, TAS2R38 has a significant impact on the innate immunity of the sinonasal cavity through release of antiviral NO and increases pathogen clearance through increased mucociliary function[15–18] and certain genotypes and phenotypes demonstrate worse outcomes with COVID-19[19,20] or increased risk for CRS.[12] Given lack of difference in TAS2R38 RNA expression, it's association with disease severity in COVID-19 likely has to with altered receptor function and/or protein expression.

4.3 | Obesity and ACE2 and TAS2R38 expression

We hypothesized that expression of ACE2 in oral and extra oral tissue may be altered by obesity and therefore may affect innate immunity in response to SARS-CoV-2 infection. Studies have shown higher concentrations of ACE2 protein in adipose tissue;[31] however, our results are not unexpected given that these studies showed no differences in ACE2 concentration in adipose tissue when comparing obese patients to lean patients. Furthermore, studies have correlated obesity and altered taste perception in both children[37] and adults[38] and we had hypothesized that obese children and adults would have decreased TAS2R38 expression and the lack of differences in expression do not correlate with obese patients getting COVID-19 at higher rates and with increased severity.[22] This lack of a difference may also be explained by different polymorphism genotypes of the TAS2R38 gene and their phenotypic expression leading to obesity[39] or altered levels of severity in COVID-19 infections.[19,20]

4.4 | Limitations

There are several limitations to our study. First, like other previous studies[26–29] utilizing gene expression or transcriptome data as the method of estimating receptor function may fail to adequately describe ACE2 and TAS2R38 protein levels and function. Expression alone may be inadequate to describe the complex interaction of ACE2, TAS2R38, and infectiousness of the SARS-CoV-2 virus. Second, another limitation could be the location of sample collection. We used two clinicians to collect the samples and the method was consistent and more accurate than previous studies; however, these collections were not done under direct visualization and we cannot be absolutely certain sampling was performed at the olfactory epithelium, which is believed to have the highest concentration of ACE2 in the nasal cavity. Third, studies evaluating the role of TAS2R38 in

SARS-CoV-2 infectivity showed differences in functional and non-functional phenotypes of the receptor; however, in this study, we only evaluated overall receptor expression. Therefore, receptor function and not overall expression may be more involved in COVID-19 pathophysiology. Lastly, our pediatric sampling was performed predominantly on children presenting for adenotonsillectomy. These children have high rates of airway inflammation from obstructive sleep apnea, which may have led to higher rates of ACE2 receptor expression. Further studies should be conducted on children without airway co-morbidities to determine age as a sole predictor of ACE2 receptor expression.

5 | CONCLUSIONS

In conclusion, correlating ACE2 and TAS2R38 genetic expression levels within the upper respiratory tissues to the severity of SARS-CoV-2 infections in adults may be an oversimplification of a complicated process. In this prospective study utilizing a standardized technique for sample collection, we performed targeted qPCR and found that children, when compared to adults, have up to 78% more ACE2 in the sinonasal cavity. Furthermore, we found no differences in TAS2R38 expression between healthy adults and children. Obesity had little effect on TAS2R38 and ACE2 mRNA expression in adults and children. To better understand these interactions and elucidate discrepancies in our findings and previously reported findings of RNA expression, further studies for protein expression, function, and phenotype of ACE2 and TAS2R38 are needed.

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CONFLICT OF INTEREST STATEMENT

Jonathan M. Walsh reports educational consultant relationship with Smith & Nephew regarding Coblation technology. No direct conflict of interest for this project.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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