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ORIGINAL ARTICLE

Influence of chronic diseases on the olfactory function in children

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Abstract

The association between smell impairment and chronic diseases has been reported in some studies in adults. Such information is not available for chronic diseases in children. The aim of this study was to examine olfactory function of children with chronic diseases such as diabetes mellitus type 1, hypothyroidism, and bronchial asthma in combination with allergic rhinitis in comparison to healthy controls. The data were obtained from $n = 205$ participants (104 boys, 101 girls) between the age of 6 and 17 years. Seventy-eight of the participants were healthy controls, $n = 43$ had diabetes mellitus type 1, $n = 50$ suffer from allergic rhinitis or bronchial asthma, and 34 presented a reduced function of their thyroid in medical history. All participants underwent olfactory testing including olfactory threshold using "Sniffin' Sticks" and odor identification using the "U-Sniff" test. In addition, a depression inventory and cognitive testing using the Ravens Progressive Matrices was performed. No significant difference in olfactory function was observed for any of the chronic diseases in children in comparison to healthy controls. Further analysis showed a trend in significance for a subpopulation of children with bronchial asthma and comorbidities performed worse on the olfactory threshold test compared to patients with bronchial asthma without comorbidities. Pediatric patients suffering from chronic diseases scored higher on the depression inventory compared to healthy controls.

Conclusion: In conclusion, this study demonstrates that the influence of chronic diseases (bronchial asthma, diabetes mellitus type 1 and hypothyroidism) on olfactory function in childhood, if any, seems to be insignificant. This is partly in contrast to adult patients. Further research should be conducted in a subgroup of patients with bronchial asthma, allergic rhinitis, and atopic dermatitis or other comorbidities to better understand the association of allergic diathesis and olfactory function and the putative pathogenesis of olfactory dysfunction.

What is known:

- The association between smell impairment and chronic diseases has been reported in some studies in adults.
- Such information is not available for chronic diseases in children.

What is new:

- The influence of chronic diseases (bronchial asthma, diabetes mellitus type 1, and hypothyroidism) on olfactory function in childhood, if any, seems to be insignificant.
- In patients with bronchial asthma and allergic rhinitis, only a subgroup of patients with additional comorbidity (atopic dermatitis) showed a tendency to a reduced sense of smell.

Keywords Olfactory threshold · Odor identification · "Sniffin' sticks" · Chronic diseases children · Bronchial asthma · Allergic rhinosinusitis · Hypothyroidism · Diabetes mellitus type 1 · Children

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Abbreviations

CPM	Colored progressive matrices
F	Degrees of freedom
fT3	Free triiodothyronine
fT4	Tetraiodothyronine
HbA1c	Glycohemoglobin A1c
MANOVA	Multivariate variance analysis
n	Amount
p	Significance level
r	Correlation coefficient
SD	Standard deviation
SPM	Standard progressive matrices
SPSS	Statistical Package for the Social Sciences
TSH	Thyroid-stimulating hormone
U-Sniff	universal Sniffin' Sticks Test for children

Introduction

Only little is known about the role of olfactory function in childhood, whereas in adults, olfactory function has a major impact on at least three areas in everyday life: social communication, food intake, and detection of danger [44]. Olfactory dysfunction in adults can be associated with several risks like an increase of food poisoning or household accidents. People with olfactory dysfunction are known to be more likely to develop depression [20].

Although these mentioned difficulties could occur, some patients do not recognize their smell impairment or do not seek medical help [33]. Especially patients with chronic diseases seem to be at risk to develop an olfactory dysfunction caused for instance by chronic inflammation [1] or hormonal imbalance [13].

The association between olfactory impairment and chronic diseases has been reported in previous studies in adults: For example, chronic renal failure and inflammatory bowel disease can be associated with olfactory dysfunction [12, 27, 43]. Furthermore, allergic rhinitis and bronchial asthma can lead to a decreased olfactory function [7, 16], caused not only by nasal blocking but also by the length of disease and the severity of inflammatory agents leading to destruction of the olfactory epithelium [17]. This is evident by facing that patients suffering from persistent allergic rhinitis seem to be more affected by decreased olfactory function than patients with intermittent allergic rhinitis [30, 45].

Moreover, untreated chronic reduced thyroid function is a disease, which is suspected to cause a decreased olfactory function. It can be assumed that the neuronal development in the olfactory epithelium is disturbed by a lack of thyroid hormones [32]. No olfactory dysfunction was detected in patients, which were treated with L-thyroxine and had balanced hormonal levels [9, 34]. Regarding patients with diabetes mellitus, the current literature is controversial: Some studies observed olfactory impairment in patients with diabetes mellitus type 1 and 2 [13, 46], while others could not detect any difference between healthy controls and patients with diabetes mellitus type 1 and 2 in regard to olfactory function [3, 35]. It has to be emphasized that patients with diabetes mellitus type 2 seem to be more affected in olfaction than patients with diabetes mellitus type 1 [13]. Previous literature assumes that especially in patients suffering from diabetes mellitus type 2, olfactory dysfunction is based on a peripheral neuropathy [15].

While several studies investigated the olfactory function in adults with chronic diseases, the knowledge about this issue in children is limited. Nevertheless, previous reports about olfactory function in children suffering from chronic disease are available: Armstrong and colleagues described taste impairment but unchanged olfactory function in children with renal failure in comparison to healthy children [4]. Another study addressing a chronic disease in childhood is presented by Langdon and colleagues, reporting smell dysfunction in association with allergic rhinitis [30].

Diabetes mellitus type 1, hypothyroidism, bronchial asthma, and allergic rhinitis are chronic diseases, which frequently occur in childhood. The influence of these diseases on olfaction in children has not or only little been reported in the current literature. Based upon the literature found for adults [7, 13, 34, 46], an impairment of olfactory function in children suffering from these diseases could be possible. The aim of this study was to investigate whether these chronic diseases are associated with olfactory dysfunction in children and whether these patients might benefit from olfactory testing.

Material and methods

This retrospective case-control study received the approval of the local Ethics Committee of the Medical Faculty of the Technical University Dresden (EK 355092014). The study was conducted in accordance with the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. The purpose and the procedure of the examination were explained to the children and their parents or legal guardians in verbal and written form. Children under an age of 8 years only received a verbal explanation of the procedure. Prior to the study, written informed consent was obtained from parents/legal guardians. Every child gave its assent to participate in this study.

Participants

Power calculation was performed using G*Power to detect differences in olfactory test performance between two groups. Power calculations are based on previous studies using olfactory threshold [14] and odor identification testing (Gellrich

et al. accepted). Using a two-tailed *t* test with alpha 0.05 and a power of 0.95 and an effect size of 0.8 (based on previous studies), a size of $n = 42$ for each group is necessary to detect group differences in olfactory threshold and odor identification performance.

Patients were consecutively selected based on their routine appointments in the pediatric outpatient clinics. Patient recruitment was started in May 2015 and was finished after reaching the necessary, and prior determined number of patient after 28 months. Patients were included in our study based on pre-defined inclusion and exclusion criteria to avoid any selection bias.

The data were obtained from 205 participants (104 boys, 101 girls) between an age of 6 and 17 years. Fifty children had bronchial asthma or allergic rhinitis, 43 had diabetes mellitus type 1, and 34 patients were diagnosed suffering from hypothyroidism. The control group consisted of 78 healthy children. All participants and patients completed the study. A detailed medical history was obtained from all participants, and their olfactory function was assessed using the "Sniffin' Sticks." In addition, the standard progressive matrices (SPM) was performed as a measurement of frontal brain function and the "Depressionsinventar für Kinder und Jugendliche" was applied to account for depression because it has to be assumed that cognitive function has an impact on olfactory testing in children and that depression is associated with a poor olfactory function [8, 36].

Olfactory assessment

The olfactory threshold subtest of the validated Sniffin' Sticks [22, 26] and the U-Sniff odor identification test for children [40] were used to measure olfactory function of the pediatric participants. The odorants were presented in felt tip pens (Sniffin' Sticks, Burkhardt GmbH, Wedel, Germany).

For the olfactory threshold test, a rose-like odor—phenylethylalcohol—was used. The test was executed in the staircase-procedure starting with the highest dilution of phenylethylalcohol. The test consisted of 16 triplets of Sniffin' Sticks. One felt tip pen of each triplet contained the phenylethylalcohol dilution while the other two pens were odorless. The possibility of visual identification of the odor-containing pen received attention by blindfolding the subjects. Applying a three-alternative forced-choice paradigm, the children had to identify the odor-containing pen out of the triplet. After two successful or one false identification, the next higher or lower threshold staircase was induced. The staircase-procedure was repeated until seven reversal points were obtained. The average of the last four reversal points yielded the individual olfactory threshold. Sixteen points were the maximum score, which could be achieved in the olfactory threshold test [21].

In addition, a pediatric suprathreshold test, the U-Sniff odor identification test was applied [40]. Each of the 12 odorants was administered separately to the participant. The task was to identify the odorant with the help of four descriptors given in picture and writing. Whenever a participant was not able to read, the examiner read out the displayed cards and showed the labeled pictures. The interval between the odorant presentations was approximately 20 s. The number of correctly identified odors was summed up for the odor identification score. The participants' scores could range from 0 to 12 [40]. The administration of both olfactory tests, olfactory threshold, and odor identification together took about 25 min.

Medical history

A detailed medical history of all patients was obtained. In addition to general medical questions, disease-specific data were obtained. The following data were recorded: data of initial diagnosis, comorbidities, current medication, surgeries, in addition laboratory results such as HbA1c (for patients with diabetes mellitus type 1), fT4, fT3, TSH (for patients with hypothyroidism). Allergic rhinitis was assessed using medical history and prick test while bronchial asthma was assessed using pulmonary function diagnosis.

Progressive matrices

To measure the nonverbal intelligence, the logical concluding and thinking in analogies, the progressive matrices test was administered. Reason for the use of this test was the necessity to exclude the possibility of a decreased olfactory score caused by a reduced executive function instead of the potential influence the chronic diseases. The test is available in three forms: the standard progressive matrices (SPM) for children 11 years and above, the colored progressive matrices (CPM) for children age 6 to 11 years and the advanced progressive matrices. In this study, the SPM and the CMP were applied according to the age of the participant.

The SPM consists of 5 sections with 12 tasks in each. The tasks contain a pattern with a missing puzzle piece, which completes the pattern. The participant had to decide which puzzle piece completes the pattern best. The solution of the first pattern of each section is immediately comprehensible. While the difficulty is increasing from task to task, the participants trained the approach of each section. The individual raw score counted from 0 to 60 and was converted to age depending percentile rank regarding to the German normative data [28].

The ability to think in analogies is not fully developed in younger children; therefore, the CPM was applied to examine children between an age of 6 and 11 years. The CPM consists only of 36 tasks in 3 separate sections. The task model of the CPM in comparison to the SPM is

easier to analyze and colored in order to simplify the task. This should make it easier to understand the task without reading abilities or excessive verbal explanations. The SPM and the CPM were applied without time limitation. The possible scores of the CPM ranged from 0 to 36 points [37–39].

Depressionsinventar für Kinder und Jugendliche

The Depressionsinventar für Kinder und Jugendliche is a German self-assessment questionnaire to measure a depressive disorder in children and adolescents. This test was administered in order to detect a possible influence of depression on olfactory function in the study population. Twenty-six items had to be answered targeting different everyday situations. The answer for each question is transformed into points ranging from two to zero. The given answers were added to an individual result, ranging from 0 to 52. A higher score refers to a more depressive mood of the child or adolescent. All scores were converted to percentile scores [25].

Statistical analysis

Analyses were performed using SPSS 23.0 software (SPSS Inc., Chicago, IL, USA) with the level of significance set at $p < 0.05$. This study aimed to detect differences between olfactory testing in healthy children and children suffering from chronic diseases. To compare psychophysical testing, one-way MANOVA was used to investigate differences between patient and control group. Post hoc Bonferroni testing was used to examine subgroup differences. Because of the age difference between the control group and participants suffering from chronic diseases, all measurements were age corrected. The association between variables was analyzed using Pearson's and partial correlation. Whenever appropriate, non-parametric tests were applied. The study was designed to analyze group differences in olfactory function of patients suffering from hypothyroidism, allergic rhinitis or bronchial asthma, and diabetes mellitus type 1 in comparison to a healthy control group. Furthermore, analyses of potentially influencing factory of disease-specific parameters like HbA1c for diabetes mellitus type 1 or intake of medication for hypothyroidism were made in addition. These analyses showed clinically significant separations into subgroups especially in the group of patients with allergic rhinitis or bronchial asthma. Although this study was not powered to analyze subgroups, the statistical analysis was undertaken to show possible future research direction regarding this topic.

Results

Participants

A total of 205 participants completed the examination. No participant had to be excluded from the study. None of the participants had kidney insufficiency, epilepsy, or reported any olfactory disorder. For more details about descriptive statistics, see Table 1. In the following, statistical analysis regarding olfactory function comparing healthy controls to each of the reported diseases should be reported.

Bronchial asthma/allergic rhinitis

Fifty of the patients suffered from bronchial asthma and/or allergic rhinitis: Four of them had only bronchial asthma, none of them had only allergic rhinitis, and 46 suffered from both and were positively tested on allergy tests (Prick test or specific IgE antibody testing). The most common allergies were house dust mite allergy ($n = 22$), grass pollen allergy ($n = 18$), and tree pollen allergy ($n = 17$).

Table 1 Results on olfactory testing for different study-groups, descriptive data for all four subgroups given in mean and standard deviation, p is age corrected for olfactory threshold, odor identification, and "Depressionsinventar" and given in comparison to healthy controls, significance level

	healthy controls	bronchial asthma/ allergic rhinitis	diabetes mellitus type 1	hypothyroidism
Age in years *n*	9.6 ± 2.65 78	11.1 ± 2.73 50	11.2 ± 2.1 43	12.5 ± 2.44 34
Duration of illness in years n		5.4 ± 3.82 50	4.4 ± 2.57 43	6.3 ± 5.06 34
Threshold *n*	8.67 ± 3.38 78	10.02 ± 3.69 50 n.s.	9.26 ± 3.18 43 n.s.	9.83 ± 3.37 34 n.s.
Identification n	9.63 ± 1.86 78	9.94 ± 1.62 50 n.s.	10.3 ± 1.06 43 n.s.	10.24 ± 1.44 34 n.s.
Depressionsinventar, Percentile n	31.74 ± 25.68 75	34.44 ± 24.99 50 n.s.	42.61 ± 26.53 43 $p = 0.031$*	42.92 ± 24.95 34 $p = 0.035$*
Depressionsinventar, T-score n	43.37 ± 9.09 75	46.68 ± 8.84 50 $p = 0.046$*	47.35 ± 9.02 43 $p = 0.024$*	47.91 ± 8.19 34 $p = 0.012$*
CPM/SPM Percentile n	52.0 ± 27.42 78	54.74 ± 29.01 50 n.s.	60.95 ± 31.95 43 n.s.	52.41 ± 25.77 34 n.s.

n.s. not significant

*$p \leq 0.05$

In comparison to healthy controls, no significant difference regarding olfactory threshold or odor identification has been found (olfactory threshold: bronchial asthma 10.02 ± 3.69 healthy controls 8.67 ± 3.38 F(1,128) = 1.99 $p = 0.16$; odor identification: bronchial asthma 9.94 ± 1.62 healthy controls 9.63 ± 1.86 F(1,128) = 0.02 $p = 0.9$). All results were age corrected.

Neither disease-specific medication (gradual therapy) nor co-medication significantly influenced results of olfactory threshold and odor identification testing in this subgroup (olfactory threshold: gradual therapy F(3,46) = 0.33 $p = 0.80$, co-medication F(1,49) = 0.01 $p = 0.93$; odor identification: gradual therapy F(3,46) = 0.88 $p = 0.46$, co-medication F(1,49) = 0.02 $p = 0.89$). No correlation (partial correlation controlled for age) between the duration of disease and olfactory threshold (r = − 0.024 $p = 0.87$) or odor identification (r = 0.209 $p = 0.154$) scores has been found.

Because patients with bronchial asthma and allergic rhinitis often also suffer from other diseases, the influence of comorbidities on olfactory function was analyzed. The most frequent comorbidity in patients with bronchial asthma and allergic rhinitis in our study population was atopic dermatitis ($n = 18$), other comorbidities were, e.g., lactose intolerance, celiac disease, psoriasis (all $n = 1$), or obesity ($n = 2$). Patients with bronchial asthma and allergic rhinitis without comorbidities ($n = 25$) achieved higher olfactory threshold scores than patients with comorbidities ($n = 25$). This difference nearly missed significance (olfactory threshold: patients with comorbidity 9.0 ± 3.65 points; without comorbidity 11.03 ± 3.52 points F(1,50) = 4.01, $p = 0.051$). For odor identification, no significant difference has been found (odor identification: patients with comorbidity 10.08 ± 1.75; patients without comorbidity 9.8 ± 1.5 points F(1,50) = 0.37, $p = 0.55$). Patients with comorbidity showed no significant difference to healthy controls (olfactory threshold F(1,103) = 0.01 $p = 0.91$; odor identification F(1,103) = 0.33 $p = 0.57$). As already mentioned, the most frequently observed comorbidity was atopic dermatitis. No significant difference between patients with bronchial asthma and atopic dermatitis and patients suffering from bronchial asthma without comorbidities could be found regarding olfactory function, but the comparison for olfactory threshold showed a strong trend and nearly missed significance (Mann-Whitney U: olfactory threshold z = − 1.911 $p = 0.056$ patients with atopic dermatitis 9.49 ± 3.49 patients without comorbidities 11.03 ± 3.52; odor identification z = − 0.72 $p = 0.47$ patients with atopic dermatitis 10.0 ± 1.72 patients without comorbidities 9.8 ± 1.5). Comparing bronchial asthma patients with atopic dermatitis with healthy controls, no significant difference could be found (olfactory threshold F(1,96) = 0.64 $p = 0.43$, odor identification F(1,96) = 0.35 p = 0.55).

Diabetes mellitus type 1

Forty-three of the patients suffered from diabetes mellitus type 1, eight of them had comorbidities. The most frequent comorbidity was celiac diseases ($n = 5$); other comorbidities like psoriasis or lactose intolerance were only found in single individuals.

In comparison to healthy controls, no significant difference for diabetic patients regarding olfactory threshold or odor identification has been found (olfactory threshold: diabetes mellitus type 1 9.26 ± 3.18 healthy controls 8.67 ± 3.38 F(1,121) = 0.062 $p = 0.804$; odor identification: diabetes mellitus type 1 10.3 ± 1.06 healthy controls 9.63 ± 1.86 F(1,121) = 0.954 $p = 0.331$). All results were age corrected.

For the patients with diabetes mellitus type 1, the age-corrected correlation between the duration of disease, the HbA1c, and olfactory function was analyzed. No significant correlations between these factors, olfactory threshold, and odor identification were observed (olfactory threshold: duration r = − 0.157 $p = 0.32$, HbA1c r = − 0.037 $p = 0.82$; odor identification: duration r = 0.24 $p = 0.12$, HbA1c r = 0.005 $p = 0.98$). Patients with diabetes mellitus type 1 and comorbidities showed no significant difference compared to patients without comorbidities in regard to olfactory threshold and odor identification performance (olfactory threshold Mann-Whitney U z = − 0.69, $p = 0.49$, odor identification z = − 0.05, $p = 0.96$). In comparison to healthy controls, also no significant differences between patients with or without comorbidities in regard to olfactory threshold or odor identification could be found (Mann-Whitney U, patient without comorbidity vs. healthy control: olfactory threshold z = − 0.58, $p = 0.57$ odor identification z = − 1.761, $p = 0.078$, patients with comorbidity vs. healthy control olfactory threshold z = − 1.108, $p = 0.27$, odor identification z = − 0.82, $p = 0.41$).

Hypothyroidism

Thirty-four of the patients suffered from hypothyroidism. Fourteen of them showed connatal hypothyroidism and 12 of them had Hashimoto Thyroiditis. Seventeen of the patients had comorbidities. The most frequent comorbidities were diabetes mellitus type 1 ($n = 6$) and celiac disease ($n = 3$). Other comorbidities had only a frequency of one or two in the case of obesity.

In comparison to healthy controls, no significant difference for patients suffering from hypothyroid disease regarding olfactory threshold or odor identification has been found (olfactory threshold: hypothyroid 9.83 ± 3.37 healthy controls 8.67 ± 3.38 F(1,112) = 1.255 $p = 0.265$; odor identification: hypothyroid 10.24 ± 1.44 healthy controls 9.63 ± 1.86 F(1,112) = 0.081 $p = 0.776$). All results were age corrected.

All patients were treated with L-Thyroxin. Sixteen of them were *euthyroid* under treatment. Ten were slightly below the age depending on normal values for the TSH, while eight patients had an elevated TSH. The subgroup of patients with hypothyroidism consisted of patients suffering from congenital hypothyroidism ($n = 14$), acquired hypothyroidism ($n = 12$), and Hashimoto thyroiditis ($n = 8$). Results of olfactory testing did not differ significantly between these three groups with $F(2,34) = 0.04$ $p = 0.96$ for olfactory threshold and $F(2,34) = 0.86$ $p = 0.43$ for odor identification (congenital: olfactory threshold 10.09 ± 3.7 points, odor identification 9.79 ± 1.37 points, acquired hypothyroidism: olfactory threshold 9.73 ± 2.92 points, odor identification 10.58 ± 1.62 points, Hashimoto thyroiditis: olfactory threshold 9.53 ± 3.83 points, odor identification 10.5 ± 1.2 points). Patients suffering from hypothyroidism and comorbidities showed no significant difference compared to patients without comorbidities for olfactory threshold ($F(1,34) = 0.35$, $p = 0.56$) and odor identification testing ($F(1,34) = 1.35$, $p = 0.25$). Also, no significant difference between patients with comorbidity and healthy controls occurred (olfactory threshold $F(1,95) = 1.30$ $p = 0.26$; odor identification $F(1,95) = 0.60$ $p = 0.44$).

Neuropsychological testing

No significant difference in CPM/SPM between patients suffering from chronic diseases and healthy children was found $F(3,283) = 1.08$ $p = 0.36$ (for additional information see Table 1). Besides the cognitive testing, a depression inventory was applied. Patients suffering from chronic diseases scored higher on the depression inventory compared to healthy children $F(3,241) = 3.09$ $p = 0.03$) (for additional information see Table 1).

Discussion

The results of this study showed no significant difference in olfactory function for pediatric patients suffering from any of the three chronic diseases in comparison to healthy children and adolescents.

Only in the subgroup of pediatric patients with bronchial asthma and allergic rhinitis, a nearly missed significant difference has been observed between patients with and without comorbidities with the comorbidity group achieving lower olfactory test scores.

An interesting result was displayed in the test Depressioninventar für Kinder und Jugendliche with higher scores for children suffering from chronic diseases. One could hypothesize that due to restrictions and difficulties in daily life of children with chronic diseases, this result seems to be comprehensible. Härter et al. concluded that not only necessary lifestyle changes due to chronic diseases resulted in a higher likelihood of depression but that the disease itself, for example the metabolic state of patients with diabetes mellitus, could influence the likelihood for depression [18].

Allergic rhinitis as well as bronchial asthma are known to cause olfactory dysfunction in adults and children [17, 29, 30, 42]. One reason for the decreased olfactory function is the obstruction of the upper airway for example through polyposis but also the chronic inflammation and the resulting epithelial damage [10, 17]. In this study, we could not observe any significant differences between healthy controls and pediatric patients suffering from bronchial asthma and chronic allergic rhinitis in regard to olfactory function. A potential reason for the findings contradicting the current literature could be the fact that the olfactory epithelium, which is impaired in bronchial asthma and allergic rhinitis [17], is able to regenerate itself [41]. Based on the observations that cell regeneration within the olfactory epithelium decreases with age, the cell turnover and regeneration is probably higher in children than in adults [11, 31]. The regeneration of the olfactory epithelium could also benefit from the intermittent nature of allergic rhinitis in children in contrast to a more continuous form in adults [24]. Consequently, it has to be assumed that a discontinued inflammatory process is less damaging than a more continuous destruction of olfactory epithelium. It also had to be considered that some of the patients were treated with steroids like prednisolone to relieve symptoms of asthma, which is also used to treat sinunasal olfactory disorders [23].

Although the total group of patients with bronchial asthma and allergic rhinitis did not differ significantly from the control group in regard to olfactory function, a strong tendency for lower scores could be observed in the group of asthmatic patients with comorbidities. In this comparison, patients with comorbidities scored lower than patients without comorbidities. The most frequent comorbidity in patients with allergic rhinitis and bronchial asthma was atopic dermatitis. Comparing bronchial asthma patients with atopic dermatitis with healthy controls, no significant difference could be found. The comparison of olfactory threshold scores between this group and patients without comorbidities nearly missed significance with patients additionally suffering from atopic dermatitis scoring lower on the olfactory threshold test. The lower olfactory threshold score, although it missed statistical significance, could possibly be due to a higher severity of disease associated with comorbidities such as atopic dermatitis, possible higher IgE antibody levels in the blood, and more inflammation and nasal congestion causing an additive damaging effect on the olfactory epithelium. Furthermore, the results of a reduction of olfactory threshold are more in favor for a peripheral damage of the olfactory system [19, 47] possibly resulting from a chronic epithelia destruction. Further

studies with larger patient groups suffering from allergic rhinitis or atopic dermatitis are necessary to investigate this issue in more detail.

Diabetes mellitus is a disease which was suspected to be associated with a reduced sense of smell due to microvascular damage similarly to the pathophysiology of diabetic neuropathy [15]. The results of former literature are controversial: Early literature on this topic indicates a significant difference between patients with diabetes mellitus type 1 and 2 and healthy controls [13, 46] with adult patients suffering from diabetes mellitus type 2 scoring lower in olfactory tests than patients suffering from diabetes mellitus type 1 [13]. It was shown in the recent literature that uncomplicated diabetes mellitus type 1 in young adult patients was not associated with a decreased olfactory function if no other influencing factors (higher age, smoking or high blood pressure) are prevalent [2, 35]. This is in line with our findings in children with diabetes mellitus type 1 in regard to their olfactory function. We also examined the influence of HbA1c and the duration of the diabetes mellitus type 1 and could not find any correlation to the olfactory function in the cohort of pediatric patients. Weinstock et al. and Altundag et al. reported similar results for adult patients [2, 46].

As a third and common disease in children, the olfactory function in children with hypothyroidism was analyzed. In previous studies, olfactory dysfunction was observed for untreated primary hypothyroidism in adults and patients showed an increase of olfactory function after treatment with L-thyroxine [9, 34]. Similar results were reported for an animal model: Mice with congenital hypothyroidism were anosmic and recovered after hormonal treatment [5]. On the other hand, propylthiouracil treatment-induced hypothyroidism in rats showed no olfactory impairment in rats [6]. In our study, we observed no olfactory impairment in young patients suffering from hypothyroidism. Recruiting patients with hypothyroidism was difficult because many patients in the outpatient department suffered from both hypothyroidism and type 1 diabetes mellitus. Since we were able to demonstrate that diabetes mellitus type 1 does not appear to affect olfactory function in children, we accepted the comorbidity of diabetes mellitus type 1 in our study participants with hypothyroidism in our study. No significant difference to healthy controls in regard to olfactory function was observed. Because not all of our patients showed euthyroid function under treatment at the time of examination, thyroid hormone levels were measured and the association to olfactory function was analyzed. No significant influence of thyroid hormone level on olfactory function was detectable. Potential reasons for our findings could be that only severe long-lasting hypothyroidism influences the olfactory function and that the duration of disease is too short in a population of children. In addition, all of our patients were treated with L-thyroxine and a previous study showed an increase in olfactory function in adult patients with hypothyroidism after treatment [9, 34].

In conclusion, olfactory function in patients with diabetes mellitus type 1 and in pediatric patients with hypothyroidism was not altered in comparison to the olfactory function of a healthy control group. In children with bronchial asthma and allergic rhinitis, only a subgroup of patients with additional comorbidity (e.g., atopic dermatitis) showed a tendency of a reduced sense of smell.

The results of olfactory studies in adulthood cannot be simply transferred to children. One potential reason for this could be the longer duration of disease in adults. Further studies with a more longitudinal approach should be conducted in children and adolescents with bronchial asthma, allergic rhinitis, and atopic dermatitis to gain more knowledge on this issue.

Authors' contributions Janine Gellrich: author, data management, statistical analysis of the data.Marie-Luise Dabow: Recruitment of volunteers, data collection, data management, critical review. Christian Vogelberg: critical review and advice in relation to allergic rhinitis and asthma.Felix Reschke: critical review and advice in relation to endocrinological issues.Andrea Näke: critical review and advice in relation to diabetes.Maja von der Hagen: critical review and planning of the study.Valentin A. Schriever: planning of the study, statistical analysis, critical review.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical consent The study was conducted in accordance with the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. The consent of all individuals involved in the study has been obtained after information. This article does not include studies with animals conducted by any of the authors.

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