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EXHALED VOLATILE ORGANIC COMPOUNDS (VOCs) FOR PREDICTION OF ASTHMA EXACERBATION IN CHILDREN

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Abstract
Objectives: To find possible relationship between asthma exacerbation and metabolomic profile of airways, assessed by non-invasive method – free volatile organic compounds (VOCs) in exhaled air in children. **Material and Methods:** The study included 80 children aged 4–18 years with asthma: 42 children with a min. 3 asthma exacerbations in the past 12 months, and 38 children without a history of exacerbations in the past year. During the study visit, each patient was examined, medical history (including information regarding atopy and eosinophil blood count) was taken, spirometry and fractional exhaled nitric oxide (FeNO) were tested, an exhaled air sample was taken to test for the presence of VOCs, and the patient also completed standardized form – *Asthma Control Questionnaire*. Volatile organic compounds were measured by combined gas chromatography coupled to mass spectrometry. **Results:** The obtained results of VOCs were correlated with the history of the disease. The 2 gas profiles were defined and they formed 2 clinically distinct clusters ($p = 0.085$). Cluster 2 was characterized for children with a higher number of bronchial asthma exacerbations and worse lung function parameters (predicted percentage forced expiratory volume in 1 s [FEV_1] [$p = 0.023$], FEV_1/ forced vital capacity ratio [FVC] [$p = 0.0219$]). The results were independent of the age, sex, BMI, atopy (house dust mite allergy) and eosinophil blood count. **Conclusions**: The study findings suggest that a relative group of gases may be a useful predictor of having asthma exacerbations in children. Additionally, a single FeNO value was unlikely to be clinically useful in predicting asthma exacerbations in children. The VOCs profile reflecting the metabolism of the airway epithelium and local microbiota was associated with the course of asthma, which strongly justifies further prospective validation studies. Int J Occup Med Environ Health. 2024;37(3):351–59

Key words:
children, asthma, atopy, lung function tests, asthma monitoring, VOCs

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INTRODUCTION

Asthma is the most common chronic airway disease diagnosed in children [1]. There is not only an increase in the incidence of bronchial asthma worldwide, but also the appearance of its symptoms in increasingly younger age groups. The disease is characterized by chronic inflammation in the airways, resulting in swelling of the mucous membrane, overproduction of mucus and bronchospasm [1,2]. This inflammation can be assessed directly using invasive techniques (bronchial biopsy, bronchoalveolar lavage) and non-invasive techniques such as exhaled air analysis and induced sputum. However, neither sputum-based techniques nor bronchoscopy are feasible in routine clinical practice. Currently, only measurement of exhaled nitric oxide is included in international guidelines. In addition to nitric oxide, human breath has thousands of molecules, including volatile organic compounds (VOCs) which are then secreted through the asthmatic airways. Therefore, a new method of particular interest in the diagnosis, monitoring and prediction of asthma exacerbations appears to be the assessment of VOCs in exhaled air [3,4]. Endogenous VOCs are formed by human metabolic processes and colonizing microorganisms. The profile of VOCs can reflect the type of inflammation in the airways and exacerbation of the disease through mechanisms that cause oxidative stress in cells [3].

Volatile organic compounds are included in a diverse group of chemical compounds containing carbon in their structure. They are formed by protein metabolism, lipid peroxidation, or cholesterol biosynthesis, among others. They are characterized by a volatile state of aggregation at ambient temperature and poor solubility, so that once they enter the lungs with the blood, they are easily removed with exhalation [4]. Endogenous VOCs are formed not only in the cells of the human body, but are also produced during the metabolism of microorganisms that reside in the body, so they can be used as biomarkers for many diseases [4].

Many diseases involving acute or chronic inflammation produce certain VOCs that can be identified in exhaled air by mass spectrometry (endogenous VOCs). Currently, the usefulness of VOCs profile in the diagnosis and monitoring of diseases such as bronchial asthma, chronic obstructive pulmonary disease, cystic fibrosis, inflammatory bowel disease and non-alcoholic steatohepatitis is increasingly emphasized [4]. The study of VOCs can allow not only the prediction of the course of asthma, but also its early diagnosis [4,5].

Asthma exacerbation is defined as a loss of symptom control requiring treatment modification and, in severe exacerbations, hospitalization. The most common triggers of asthma exacerbations in children include viral infections and exposure to allergens (especially perennial allergens such as house dust mites) and tobacco [1,2]. It is possible that VOCs could be used to predict with a high degree of accuracy which patients with asthma will have exacerbations of the disease in the future compared to those who will not present with symptoms. Moreover, combining VOC testing with fractional exhaled nitric oxide (FeNO) and blood eosinophil counts may increase the specificity, sensitivity and accuracy of the results compared to tests performed alone. No published evidence showing an association between asthma exacerbations and objective testing in children was found. No published evidence showing the relationship between asthma exacerbations and objective testing in children was found. Therefore, the aim of the present study was to evaluate the relationship between changes in metabolomic profile assessed by non-invasive testing methods – assessment of free VOCs in exhaled air as well as spirometry and FeNO, and asthma exacerbation in children.

MATERIAL AND METHODS

Patients

The study included 80 children with asthma, aged 4–18 years, under the care of an allergy clinic or hospitalized due to asthma exacerbation. Asthma was diagnosed

according to international standards – Global Initiative for Asthma (GINA) [1,6].

The study was conducted in 2 groups. The study group (with asthma exacerbations) consisted of 42 children of both sexes, with documented at least 3 asthma exacerbations in the past 12 months; 27 children had documented house dust mite (HDM) allergy. The control group (without asthma exacerbations) consisted of 38 children of both sexes, without bronchial asthma exacerbations in the past 12 months; 18 children had documented HDM allergy.

Exclusion criteria for the study included age <4 years and >18 years, the presence of anatomical and functional anomalies in the upper and lower airways, known hypertrophy of the pharyngeal tonsil, meeting eligibility criteria for adenotomy, chronic diseases affecting respiratory function, including cystic fibrosis and diabetes, cancer and humoral or cellular immune deficiencies, chronic use of systemic corticosteroids, and lack of cooperation during the tests performed.

Study design

After a positive medical history, fulfilling all inclusion criteria, with or without exacerbations within last 12 months, written consent was obtained from parents/patients. During the first study visit, each patient underwent spirometry testing, fractional exhaled nitric oxide (FeNO) testing, an exhaled air sample was taken to test for the presence of VOCs, and the patient also completed standardized *Asthma Control Questionnaire* (ACQ) [7,8]. Due to the fact that nitric oxide is flushed out during forced expiration, which alters the other test result. The nitric oxide test was performed before spirometry and the VOCs test in exhaled air.

Eosinophilia was assessed retrospectively from medical records, based on the result of the latest tests ordered by the attending physician at the allergy clinic or hospital ward. Atopy, defined as allergy to HDM, was also collected retrospectively from the medical records.

A positive opinion of the Bioethics Committee of the Medical University of Lodz, Poland, with the number RNN/104/21/KE, dated 11.05.2021, was obtained for conducting the study. Written consent was obtained from the parents before the patient's participation in the study, as well as from the patient if he/she was >16 years old.

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Statistical analysis

An unsupervised cluster analysis was performed that enabled the authors to stratify the data set of VOCs without any previously defined hypothesis. Before analysis all VOCs were transformed according to Box-Cox algorithm. Next, cluster analysis using the k-means algorithm was done. The number of clusters was selected according to the results of v-fold cross-validation. Finally, between-cluster comparisons were performed by using the Mann-Whitney U test for continuous data and the 2-tailed Fisher's or Pearson χ^2 tests for categorical data. Holm-Bonferroni correction for multiple comparisons was used. Differences were considered statistically significant at a p-value ≤0.05. Statistica 13.1 (TIBCO Software Inc.) was used to perform all analyses.

Methods

Collecting medical history

A general medical examination included a detailed medical history of the disease (atopy, number of exacerbations, eosinophil blood count), and standardized asthma control questionnaire, the ACQ [1].

Pulmonary function testing

Resting spirometry (flow-volume curves) using a MasterScreen device from Jeager (Hoechberg, Germany). All pulmonary function tests were performed in the Respiratory Function Testing Laboratory, always between 9–11 in the morning. The patient performed intensified exha-

lations preceded by maximal inhalations. Measurements were made in accordance with the recommendations of the American Thoracic Society (ATS) [6,9].

Measurement of NO concentration in exhaled air

Measurement of NO concentration in exhaled air was performed using an NO analyzer, model 280i from Sievers Instruments, Inc. (Boulder, Colorado, USA), according to the recommendations of the ATS [9].

The test was performed using the restricted exhaled breath (REB) technique, in which the test subject exhales calmly for the maximum length of time through a mouthpiece with individually selected resistance (this elevates the soft palate and avoids the influence of air from the nasal cavities on the test result). The result is the average of 3 consecutive measurements expressed in parts per billion (ppB).

VOCs measurement

Volatile organic compounds were measured in the exhaled air of each child by combined gas chromatography (GC) coupled with mass spectrometry (MS). The test was always conducted in the same room, which had not been washed with disinfectants for the preceding 24 h, so as not to falsify the results. The subject remained without food or drink, did not chew gum, did not smoke, did not brush his teeth, and limited physical activity for a period of 3 h before the test. During the test, the patient took 5 calm, maximally long exhalations through a mouthpiece into a special bag (Tedlar Bags, Push Lock Valve 5 liter, Supelco, St. Louis, USA) in a sitting position, which was then immediately sent to a science and technology laboratory for analysis. The gas sample was evaluated by GC/MS, taking advantage of the fact that VOCs are partitioned based on their chemical properties, after being subjected to an ionization process, partitioning was performed according to their mass-to-charge ratio (m/z).

RESULTS

The study was completed by all 80 children, assigned to the study group (N = 42) and the control group (N = 38), according to the inclusion criteria.

Based on the obtained results and their correlation with medical history, a non-supervised statistical cluster analysis was performed that enabled the authors to stratify the data set of VOCs without any previously defined hypothesis. Clustering of all gases showed 2 clinically distinct phenotypes with significantly different symptoms predominance, as indicate p-values (Holm-Bonferroni sequential adjustment) (Table 1). Baseline characteristics of all children in both clusters are presented in Table 2.

Cluster 1, defined as a phenotype without exacerbations, included 47.5% (N = 38) of the cohort, with a milder asthma course and no exacerbations, e.g., cyclohexane P96, (4E)-5-methyl-4-hepten-3-one (Figure 1). Cluster 2, defined as the exacerbation phenotype, included 52.5% (N = 42) of the cohort with predominantly more bronchial asthma exacerbations and worse lung ventilation parameters (forced expiratory volume in 1 s [FEV_1]/ forced vital capacity ratio [FVC] and FEV_1) (Figure 1). Gases belonging to cluster 2 included 1-propanol, 1-butanol, cinnamaldehyde, benzaldehyde.

No differences were observed between clusters in age, sex, BMI, FeNO, house dust mite allergy, ACQ and eosinophil blood count of the studied children (Table 2).

DISCUSSION

In recent years, there has been a growing interest in studying the profiles of VOCs in exhaled air as a diagnostic tool in various diseases, including chronic respiratory diseases. A wide variety of compounds belonging to VOCs have been identified in exhaled air, and a correlation has been noted between changes in their concentrations and the course of abnormalities in the physiological processes of the human body [4].

Table 1. Clusters characteristics by volatile organic compounds (VOCs) profile, measured in children (N = 80) aged 4–18 years with asthma, the Institute of Natural Products and Cosmetics of Lodz University of Technology, Łódź, Poland, 2022–2023

Cluster	Volatile organic compounds
Cluster 1	(4e)-5-methyl-4-hepten-3-one; 2-oxabicyclo [2,2,2] octane, 1,3,3-trimethyl-; 4-hexen-2-one, 3,4-dimethyl-; 5-hepten-3-one, 5-methyl-, (Z)-; benzene, propoxy-; cyclohexane P96; dodecane; heptane, 2,2,4,6,6-pentamethyl-; hexanoic acid, butyl ester; p-xylene; undecane
Cluster 2	1-butanol, 2-methyl-, acetate; 1-propanol; 2-butanone, 3-hydroxy-; 2-pinen-4-one, (1s,5s)-(–)-; 2-undecanone; 3-heptanone, 5-methylene- (CAS); 3-methyl-2(5h)-furanone; 4-hepten-3-one, 5-methyl-, (Z)-; α-pinene; benzaldehyde, 2-hydroxy-; benzene; benzene, 1,2-dimethyl-; benzenemethanol, α,α-dimethyl-; benzothiazole; cyclohexanol, 5-methyl-2-(1-; ethylethyl)-, [1r-(1a,2α,5a)]-; cyclopentane, methyl-; decanal; heptane; heptane, 2,4-dimethyl-; hexadecanoic acid, methyl ester; limonene; methane, thiobis-; N,N-dimethylacetamide; nonane; pentasiloxane, dodecamethyl-; propanedioic acid; dihydroxy-
Cluster 1 and 2	α-pinene; 2-pentanone, 4-methyl-; acetone; cinnamaldehyde; n-hexane octane, 4-methyl-

Cluster 1 – the phenotype without exacerbations, included 47.5% (N = 38) of the cohort, with a milder asthma course and no exacerbations; cluster 2 – the exacerbation phenotype, included 52.5% (N = 42) of the cohort with predominantly more bronchial asthma exacerbations and worse lung ventilation parameters.

In the presented study, the relationship between the profiles of VOCs in exhaled air and the course of asthma in children was demonstrated. A correlation was found between VOCs characterized by cluster 2 and a worse course of asthma, including worse lung parameters (FEV_1/FVC and FEV_1) and higher number of asthma exacerbations in children. In contrast, VOCs classified in cluster 1 occurred in children with a milder course of asthma and better lung function. The results were independent of the age, sex, BMI, FeNO, house dust mite allergy, *Asthma Control Questionnaire* (ACQ) and eosinophil blood count of the children studied. There was no difference between 2 clusters in terms of FeNO, ACQ and eosinophil blood count.

Detection of specific VOCs can predict the severity of the asthma course. Volatile organic compounds that were present in the highest concentrations in children with more frequent asthma exacerbations included cyclohexanol, benzene, benzaldehyde. Ibrahim et al. [10] described 13 compounds that differentiated adults' patients with uncontrolled asthma (ACQ ≥1) with 89% accuracy (area under the ROC curve [AUC] 0.90). The study also showed that adult patients with bronchial asthma, compared to healthy subjects, showed increased concentrations of compounds such as benzyl alcohol, 3,4-dihydroxybenzonitrile, benzene, butanoic acid, benzoic acid, cyclohexanol, pentadecane, and lower concentrations of 2-butanone, cyclohexene, butanoic acid, dodecane and 2,5-cyclohexadiene. In this study, dodecane was present in higher concentrations in children with milder asthma [10].

A clinical study of VOCs in exhaled air also shows the presence of a specific profile of VOCs in pediatric patients with a current asthma exacerbation. In a study by Brickman et al. [11], monitoring of metabolites in exhaled air was shown to distinguish between loss of asthma control and clinically stable episodes in adult patients (a significantly statistical increase in methanol, acetonitrile, bicyclo-octan-1-ol, 4-methyl-C9H16O was observed). The researchers showed significant associations between exhaled metabolites captured by GC/MS and the presence of eosinophilia in sputum (Pearson's r ≥0.46, $p < 0.01$). In the present study, there was no correlation of VOCs with eosinophilia in pediatric patients ($p = 0.5059$).

In contrast, van Vliet et al. [12] in a 1-year, prospective, observational cohort study involving 94 children

Table 2. Baseline characteristics of participants – children aged 4–18 years with asthma, the Institute of Natural Products and Cosmetics of Lodz University of Technology, Łódź, Poland, 2022–2023

Variable	Participants (N = 80)								p[a]
	cluster 1 (N = 38)				cluster 2 (N = 42)				
	n (%)	Me	Q25	Q75	n (%)	Me	Q25	Q75	
Age [years]		10.0	9.0	12.0		11.0	9.0	14.0	0.1831
Male gender [n (%)]	30 (78)				33 (75)				0.7948
BMI [kg/m^2]		20.0	17.0	22.0		19.0	17.0	21.5	0.2299
House dust mite (HDM) allergy [n (%)]	18 (47.4)				27 (61.4)				0.2668
FEV_1 [%pred]		104.0	93.0	117.0		97.5	86.0	107.0	0.0241
FEV_1/FVC [%pred]		103.0	96.0	107.0		98.0	90.0	103.0	0.0223
FeNO [ppb]		39.8	30.0	65.0		39.7	33.2	54.0	0.9373
Eosinophil blood count									
%		5.0	3.0	8.0		4.0	3.0	6.0	0.5059
cells/mm^3		340	200	550		309	200	505	0.7497
Asthma Control Questionnaire [pts]		22.0	18.0	23.0		22.0	18.0	24.0	0.9889

FeNO – fractional exhaled nitric oxide; FEV_1 – forced expiratory volume in 1 s; FVC – forced vital capacity ratio.
[a] Mann-Whitney.
Cluster 1 and cluster 2 explanation as in Table 1.

aged 6–18 years, 76% of whom had atopy and 65% of whom had controlled asthma at the start of the study, described 7 VOCs (6,10-dimethyl-5,9-undecadien-2-one 2-ethylhexanal; 1,2-dimethylcyclohexane; 2(or 3)-methylfuran; octanal; nonanal, 1 compound unknown) that showed a correlation with the presence of asthmatic airway inflammation. The presented profile of 7 VOCs predicted 88% of asthma exacerbations within 14 days of sampling. The predictive power was inversely proportional to the time from sample collection to exacerbation onset [12].

As early as 1997, Olopade et al. [13] showed a significant increase in exhaled pentane in acute asthma exacerbations and a higher risk of hospitalization compared to control subjects. In the present study, cyclopentane was present in cluster in children with more frequent asthma exacerbations.

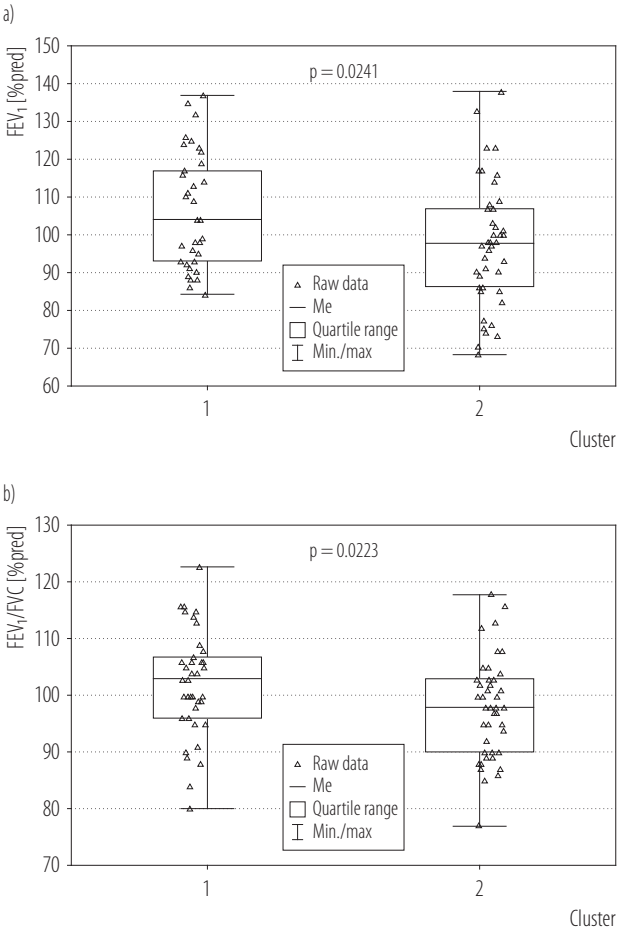
Robroeks et al. [14] also demonstrated an association of VOCs with the prediction of bronchial asthma exacerbations in children. Higher concentrations of p-xylene, 3-methylpentane, 2-ethyl-4-methyl-1-pentanol, 1-phenyl-1-butene, 4,6,9-nonadecatrien and 1 unknown compound were detected in children with a current asthma exacerbation (correct classification 96%, sensitivity 100% and specificity 93%). It is noteworthy that, in the authors' study, p-xylene was detected in children with milder asthma, while methylpentane was present in the group of children with asthma exacerbations. In the above-mentioned study, 2-ethyl-1,3-butadiene, cyclohexane, 2-octen-1-ol, 1,2-methyl-4H-1,3-benzoxacin and benzene distinguished children with asthma exacerbations from those without exacerbations (correct classification 91%, sensitivity 79% and specificity 100%) [14]. In the present study conducted cyclohexane was found

in statistically significant concentrations in children with milder asthma, whereas benzene was found in children with at least 3 asthma exacerbations in the past year.

There are some limitations to this study. The main source of the asthma exacerbation in the children studied was a respiratory tract infection. Due to the production of VOCs by the microbiome, the presence of bacteria alters the patterns of exhaled VOCs, so breath analysis can be used to diagnose infections of bacterial aetiology. Exposure to the allergen during the pollen season increases allergic inflammation in the airways, which may affect the VOCs profile. In this study, however, no correlation was found between sensitisation to house dust mites (a year-round allergen) and the VOCs profile. Due to the limited study group, other allergens were not considered.

In the authors' study, there was no validation cohort, moreover, the results published to date on VOCs are not consistent and the number of variables confounding the obtained VOCs profile is large, which clearly limits the clinical utility of VOCs at the current level of knowledge.

In the present study, no differences were observed between the clusters in terms of ACQ, which can be explained by good symptoms control of patients included in the study. Worsening spirometry and FeNO are good indicators of worsening asthma severity, however higher FeNO level is usually associated with typical, steroid-responsive, type II airway inflammation. In the study, worse spirometry outcomes correlated with asthma course in children with exacerbations (Cluster 2). Fractional exhaled nitric oxide levels were also not observed to be higher in the group of children with exacerbations. The above results suggest that change in lung function parameters can be used to assess asthma risk, while the role of change in FeNO is less clear. Moreover, no differences in FeNO and the number of eosinophils in peripheral blood were observed between the defined clusters. This observation suggests that the gas profile in defined clusters in the



Cluster 1 and 2 explanantion as in Table 1.
Concentrations of the indicated gases from cluster 1 (Table 1) were higher in a given concentration compared to the second concentration.

Figure 1. Characteristics of cluster 1 and 2 according to lung function: a) forced expiratory volume in 1 s – FEV_1 b) FEV_1 to forced vital capacity ratio – FEV_1/FVC, and number of asthma exacerbations in children aged 4–18 years with asthma, the Institute of Natural Products and Cosmetics of Lodz University of Technology, Łódź, Poland, 2022–2023

study may not be dependent on type II inflammation in the airways. This observation is consistent with previous findings highlighting the role of type III inflammation in the upper respiratory tract of preschool children with asthma, where local dysbiosis seems to be one of the most important immunologic backgrounds of asthma [15]. This confirms that exhaled nitric oxide reflects only a distinct, albeit important, endotype of asthma, which is

induced via interleukins 4 and 13 therefore cannot fully encompass the entire burden of asthmatic inflammation such as that in the authors' study.

The study findings suggest that a relative group of gases (cluster 2) may be a useful predictor of having asthma exacerbations. Furthermore, the results suggest that a single FeNO value shows little clinical utility in predicting asthma exacerbations in children. Diagnosis of asthma exacerbation by VOCs was better than diagnosis made by FeNO and eosinophil count. The authors' results are in agreement with another group that also showed, using univariate Cox regression analysis, that FeNO was unable to predict exacerbations [14]. The study shows that specific VOCs can predict with a high degree of accuracy which asthma patients are likely to experience exacerbations compared to those who remain stable.

Profiling of VOCs in exhaled air provides information on ongoing pathophysiological processes and appears to be a promising new method in diagnosing asthma, monitoring its course and response to treatment [16].

In conclusion, this study of VOCs appears to hold promise for exacerbation prevention in children, distinguishing from comorbidities (such as obesity). To achieve these goals, however, improvement and standardization of the technique is necessary. Finally, it will be fundamental to discover stable VOCs biomarkers that show greater disease specificity so that they can be detected reproducibly, independent of comorbidities or other factors. It is important, however, that VOCs result from oxidative stress caused by numerous inflammatory processes, so a better elucidation of the inflammatory processes underlying diseases is essential for their proper detection by VOCs.

CONCLUSIONS

Exacerbations of bronchial asthma occurring when the control of disease symptoms is destabilized, necessitate the search for new methods of predicting them. A promising non-invasive method in the diagnosis and monitoring the course of asthma is the measurement of VOCs in exhaled air. The authors' study findings suggest that a relative group of gases may be a useful predictor of having asthma exacerbations. Additionally, a single FeNO value is unlikely to be clinically useful in predicting asthma exacerbations in children. The diagnosis of asthma exacerbation based on the VOCs test was better than the diagnosis made by measuring FeNO and eosinophil count. Determining the profiles of VOCs that may correlate with a higher incidence of asthma exacerbations and its more severe course allows for more effective treatment and improves patients' quality of life. However, there is a need for more research to develop standards useful in clinical practice.

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