

LETTER

House dust mite sensitization and frequent antibiotic courses may suppress remission of rhinosinusitis and asthma symptoms in young children

To the Editor

The reduced morbidity of chronic inflammatory disorders of airways in children during the COVID-19 pandemic has been observed^{1,2}; however, the restriction related to the lockdown may also have a long-lasting negative impact on the clinical care of patients.³ Despite this dichotomy, pandemic isolation offers a unique opportunity to understand better the phenomenon of remission (or progression) of chronic rhinosinusitis (CRS) and asthma symptoms in young children. We aimed to determine clinical, immunological, and microbiological factors that could affect the clinical course of CRS and asthma in young children during pandemic isolation.

Our cohort of young children with chronic rhinosinusitis with or without asthma was fully described before the COVID-19 pandemic.⁴ Children aged 4–8 years with CRS diagnosed by otorhinolaryngologists according to the EPOS (European Position Paper on Rhinosinusitis and Nasal Polyps) criteria were included. Asthma was suspected according to the positive modified Asthma Predictive Index and confirmed by a pulmonologist after clinical improvement during anti-inflammatory therapy and/or positive bronchial reversibility test. The following procedures were performed in all participants before the pandemic: Face-to-face standardized Sinus and Nasal Quality of Life questionnaire, skin prick test, nasopharynx swab, and nasal scrapes collected using Rhino-Probe plastic nasal curettes (Figure 1A). Recruitment for the study took place during two subsequent autumn-winter seasons (2017–2018). During the current study, a telephone follow-up visit was performed after 5 months of pandemic isolation. Details on study methods are given in the Appendix S1. (ClinicalTrials.gov Identifier: NCT03011632).

One hundred and eleven children of the original cohort (84%) of children with CRS were included in the current follow-up analysis. The clinical characteristics of participants are presented in Table 1. In the fall-winter 2020 season, compared to the 2019 and 2017/2018 seasons, we observed a significant reduction in SN-5 score in our patients (Figure 1B). At inclusion during the first study season, asthma was diagnosed in 82 (61.6%) participants. In the fall-winter 2020 season, asthma symptoms and/or antiasthma therapy were reported in 31(27.9%) children (Figure 1C). Children

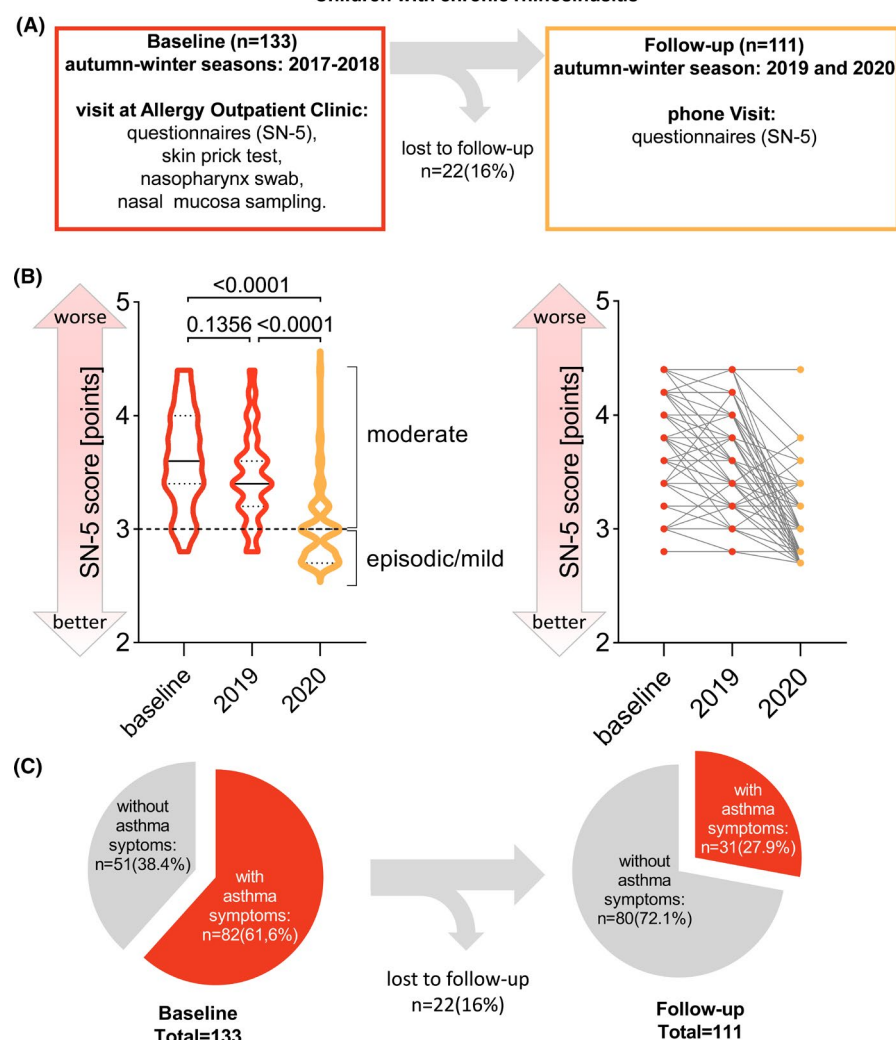
with SN-5 score below the median value (3.0) at fall-winter season 2020 were defined as having *mild/episodic* CRS, and patients above the median as having *moderate* CRS (Figure 1B). Children without asthma symptoms, and any antiasthma treatment during last year, including fall-winter season 2020, were defined as *patients without asthma symptoms* (Figure 1C). Both outcomes (CRS and asthma) were included in logistic regression analysis as dependent variables (Tables S1 and S2). The logistic regression analysis in a multivariate approach showed that independent risk factors of moderate CRS were house dust mites (HDM) sensitization and the number of courses of antibiotic therapy at baseline; sensitization to HDM increased the risk nearly fourfold (OR: 3.85; 95% CI: 1.37–10.79), and each course of antibiotic therapy by over 40% (OR: 1.44; 95% CI: 1.08–1.93). The logistic regression analysis in a multivariate approach showed that independent risk factors of asthma symptoms were food allergy in infancy (OR: 2.57; 95% CI: 1.08–6.16) and moderate symptoms of CRS during pandemic isolation (OR: 2.77; 95% CI: 1.12–6.89). Children with vs. children without HDM sensitization had more frequently reduced biodiversity (reduced Shannon index, one of the features of dysbiosis) in the upper airways at baseline (Table S3). Before the pandemic, we did not observe significant associations between HDM sensitization and CRS severity, antibiotics prescribing frequency, nor the prevalence of asthma symptoms. However, during pandemic isolation, children with HDM sensitization had at least one antibiotic course during fall-winter 2020 and moderate CRS symptoms more frequently compared to those without HDM sensitization (Table S3). We did not observe any association between the size of the skin reaction to HDM in sensitized children and study outcomes (Figure S1).

The nasal mucosa in children with moderate CRS was characterized at baseline by a higher expression of IL-17 ($p = .04$; after adjustment for multicomparison $p = .046$) and Muc5AC ($p = .046$; after adjustment $p = .046$) (Figure S2A). In children with asthma symptoms, the nasal mucosa at baseline was characterized by a lower expression of beta-defensin 2 ($p = .017$; after adjustment $p = .038$) and lower Muc5B expression ($p = .029$; after adjustment $p = .038$) (Figure S2A).

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Children with chronic rhinosinusitis

FIGURE 1 A study flow diagram, (A). SN-5 score at baseline (2017–2018) and follow-up (2019 and 2020), (B). Pie chart of asthma symptoms before (autumn–winter 2017–2018) and after (autumn–winter 2020) (C)**TABLE 1** Baseline characteristics of study cohort at inclusion and follow-up season

	Participants included in the analysis (n = 111)		Patients lost to follow-up (n = 22)		p
	N	%	N	%	
Inclusion data					
Age (years), median (quartiles Q1-Q3)	6 (5-7)		6 (5-7)		.3965
Male gender	70	63.1%	11	50.0%	.3390
Preterm delivery	22	19.8%	5	22.7%	.7743
Natural delivery	54	48.6%	9	40.9%	.6413
Family history of allergy	73	65.8%	15	68.2%	1.0000
Food allergy in infancy	49	44.1%	9	40.9%	.8184
Environmental tobacco smoke (ETS)*	16	14.4%	2	9.1%	.7364
Atopy	54	48.6%	7	38.9%	.6110
Asthma	65	58.6%	17	77.3%	.1489
Atopic dermatitis	15	13.9%	2	10.5%	.6398
BMI (kg/m ²), median (quartiles Q1-Q3)	15.4 (14.6-16.6)		16.2 (14.1-18.6)		.1872
Total number of antibiotic courses/year before inclusion, median (quartiles Q1-Q3)	2 (1-3)		2.25 (1.4-3.3)		.4085

(Continuous)

TABLE 1 (Continued)

	Participants included in the analysis (n = 111)		Patients lost to follow-up (n = 22)		p
	N	%	N	%	
Antibiotic courses/year > median	63	56.8%	11	50.0%	.6411
SN-5 score, median (quartiles Q1-Q3)	3.6 (2.8–4.2)		3.3 (2.4–4.0)		.4154
Pathogens, relative frequency > 0					
<i>Staphylococcus</i>	21	18.9%	5	22.7%	.7689
<i>Haemophilus</i>	109	98.2%	22	100.0%	1.0000
<i>Moraxella</i>	42	37.8%	6	27.3%	.4675
<i>Pseudomonas</i>	24	21.6%	2	9.1%	.2441
Shanon index, median (quartiles Q1-Q3)	4.9 (4.3–5.2)		4.7 (4.0–5.1)		.2240
Reduced Shannon index (<Q1)	28	25.2%	0	0.0%	1.0000
Follow-up data (fall-winter 2020 season)					
SN-5 score, median (quartiles Q1-Q3)	3.0 (2.7–3.0)		-	-	-
Intranasal steroid	38	34.2%	-	-	-
Adenoidectomy (in the period 2017–2020)	32	28.8%	-	-	-
Antibiotic therapy – single episode	10	9.0%	-	-	-
Antibiotic therapy – two or more episode	4	3.6%	-	-	-
Asthma symptoms and/or antiasthma therapy	31	27.9%	-	-	-
Inhaled corticosteroid	13	11.7%	-	-	-
Montelukast sodium	13	11.7%	-	-	-

*One or more smoking person at home.

Children with more frequent antibiotic courses before the pandemic had a lower Shannon index in the upper airways. However, this association was not linear (Figure S2B).

Under natural conditions, the effects of allergic rhinitis and dysbiosis as a consequence of being in a preschool environment interact, making clinical interpretation difficult.⁵ We believe that our research model enabled us to show the consequences of HDM sensitization in young children. Unfortunately, a follow-up visit during the pandemic isolation was only possible by phone. This is a limitation of our study since a considerable discordance between reported allergic conditions and diagnosed disease has been previously reported.⁶

In conclusion, our data suggest that contact with peers determines the natural history of CRS and asthma in young children. Importantly, we described the group of children at risk of persistent symptoms despite isolation from peers. Children with HDM sensitization and more frequent antibiotic courses are at risk of moderate CRS and, consequently, the persistence of asthma symptoms (Figure S3). Atopic sensitization and frequent infections are the epiphenomena of CRS in young children. In this study, we pointed out the possible link between these inflammatory pathways. HDM-sensitized children had the feature of upper-airways dysbiosis at baseline and antibiotic courses more frequent during pandemic social isolation. Our results suggest that both aspects: atopy, especially

sensitization to HDM and frequent infections, should be included in the clinical approach to CRS/asthma in young children. However, further research is required for functional studies to elucidate the molecular mechanisms of these associations. Also, further trials are needed to confirm the efficacy of HDM AIT in young children with allergic asthma.

KEYWORDS

asthma, chronic rhinosinusitis, HDM sensitization, remission

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CONFLICT OF INTEREST

The other authors have no conflicts of interest to declare.

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REFERENCES

1. Cahal M, Amirav I, Diamant N, et al. Real-time effects of COVID-19 pandemic lockdown on pediatric respiratory patients. *Pediatr Pulmonol.* 2021;56(6):1401-1408. doi:10.1002/ppul.25310
2. Papadopoulos NG, Mathioudakis AG, Custovic A, et al. Childhood asthma outcomes during the COVID-19 pandemic: findings from the PeARL multi-national cohort. *Allergy.* 2021;76:1765-1775.
3. Eguluz-Gracia I, van den Berge M, Boccabella C, et al. Real-life impact of COVID-19 pandemic lockdown on the management of pediatric and adult asthma: a survey by the EAACI asthma section. *Allergy.* 2021;76(9):2776-2784.
4. Majak P, Molińska K, Latek M, et al. Upper-airway dysbiosis related to frequent sweets consumption increases the risk of asthma in children with chronic rhinosinusitis. *Pediatr Allergy Immunol.* 2021;32(3):489-500.
5. Depner M, Ege MJ, Cox MJ, et al. Bacterial microbiota of the upper respiratory tract and childhood asthma. *J Allergy Clin Immunol.* 2017;139(3):826-834.
6. Buslau A, Voss S, Herrmann E, Schubert R, Zielen S, Schulze J. Can we predict allergen-induced asthma in patients with allergic rhinitis? *Clin Exp Allergy.* 2014;44(12):1494-1502.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

Appendix S1

Supplementary materials

House dust mite allergy and frequent antibiotic courses suppress remission of rhinosinusitis and asthma symptoms in young children

Molińska K, Latek M, Rychlik B, Lach J, Strapagiel D, Majak J, Błażowski Ł, Jerzyńska J, Kuna P, Majak P

Patients and methods

Our cohort of children aged 4-8 years with chronic rhinosinusitis (CRS) with or without asthma was fully described before the COVID-19 pandemic (1). We followed this cohort up during pandemic isolation.

Recruitment for the study took place in our Allergy Outpatient Clinic during two subsequent autumn-winter seasons (2017-2018). The following exclusion criteria were considered: food allergy with symptoms affecting the respiratory tract, contraindication to nasal endoscopy or contraindication to nasal mucosa biopsy, hypertrophy of the third tonsil exceeding 60% of the nasopharynx (confirmed by endoscopy of the upper-respiratory-tract), confirmed immunodeficiency, exacerbation of asthma requiring systemic administration of glucocorticosteroids, obesity, exposure to tobacco smoke or other chronic illnesses and clinical conditions, which in the opinion of the researcher may influence the evaluation and the course of the study. Receiving intranasal corticosteroids within 4 weeks and/or acute respiratory tract infection within 2 weeks before the visit were temporary exclusion criteria.

During the visit, the following procedures were performed in all patients: i) standardized questionnaire - Sinus and Nasal Quality of Life Survey (SN-5), ii) questionnaire which assessed the treatment used, iii) skin prick test with common inhalant allergens, iv) nasopharynx swab for microbiome analysis by NGS, v) and nasal mucosa sampling for nasal expressions of preselected molecules by qPCR.

In the current study, a telephone visit was performed after five months of pandemic isolation to obtain the following information: i) the severity of CRS symptoms based on the SN-5 scale, ii) the asthma symptoms, and iii) the treatment used during the fall-winter 2019 and 2020 season in the pandemic isolation.

Questionnaires

SN-5: A validated questionnaire to assess the quality of life in children with CRS (5 symptom-cluster items covering the domains of sinus infection, nasal obstruction, allergy symptoms, emotional distress, and activity limitations) was carried out (2). Additionally,

parents were asked to report the incidence of asthma symptoms and treatment used over the past year.

NGS library preparation and sequencing and Nasal mucosa sampling, mRNA isolation, and Q-PCR were described previously (1), but briefly:

DNA was extracted from nasal swabs using the PowerSoil DNA Isolation Kit (Mo Bio Laboratories Inc., Carlsbad, CA, USA). NGS libraries preparation was performed according to Illumina's "16S Metagenomic Sequencing Library Preparation".

Nasal mucosa was sampled using a plastic curette (Rhino-probe™, ASI, Arlington, TX, USA) from the anteromedial aspect of the inferior turbinate (according to the manufacturer's instructions). Total RNA was isolated by the method of Chomczynski and Mackey¹⁴. Reverse transcription reaction was performed in triplicate by the protocol of Wiame et al.¹⁵ using random primers and Maxima™. The expression of specific genes was compared to 18SrRNA as a reference gene and expressed as $\Delta\Delta Ct$.

Ethics

The protocol has been approved by the Medical University of Lodz Ethics Committee. Written consent from the patients and their parents was obtained.

Statistical methods

Between-groups comparisons at baseline were followed using Fisher exact test, Mann-Whitney test, or Kruskal-Wallis test. The main part of the analysis was carried out in three stages. First, dependent variables were defined. Next, logistic regression analysis was used to define variables independently associated with moderate CRS and the presence of asthma symptoms separately. Logistic regression analysis was performed in the univariate model followed by the multivariate model. The multivariate model was built according to the step-forward selection approach; coefficients associated with the dependent variable in the univariate model with P-level < .1 were only included. Finally, nasal expressions of preselected molecules were compared between defined subgroups of patients using the Mann-Whitney test with Benjamini and Hochberg correction for multiple comparisons. A P-value of less than .05 was assumed as statistically significant. Statistica 13.1 (TIBCO Software Inc) was used to perform all analyses.

References

1. Majak P, Molińska K, Latek M, et al. Upper-airway dysbiosis related to frequent sweets consumption increases the risk of asthma in children with chronic rhinosinusitis. *Pediatr Allergy Immunol*. 2021 Apr;32(3):489-500.

2. Ni JS, Kompelli AR, Nguyen SA, et al. The Sinus and Nasal Quality of Life Survey (SN-5) in the management of pediatric chronic rhinosinusitis: a systematic review and meta-analysis. *Int J Pediatr Otorhinolaryngol.* 2018;111:162-169.

Table S1 Clinical and microbiological data at baseline (before pandemic) of children with moderate vs. mild/episodic symptoms of chronic rhino-sinusitis during pandemic isolation. Data are presented by number (%) of observation unless otherwise indicated. Odds ratios with 95%confidence intervals from univariate logistic regression analysis are given.

	mild-episodic CRS (n=52)		moderate CRS (n=59)		p	OR ^a	95%CI	
	N	%	N	%				
age (years), median(quartiles Q1-Q3)	6(5-7)		6(5-7)		0.650 8	1.072	0.794	1.446
age>6 years (school children)	17	32.7%	19	32.2%	0.956 2	0.98	0.44	2.17
male gender	33	63.5%	37	62.7%	0.934 9	0.968	0.447	2.097
preterm delivery	7	13.5%	15	25.4%	0.119 9	2.192	0.815	5.891
natural delivery	27	51.9%	27	45.8%	0.517 3	0.781	0.370	1.649
family history of allergy	29	55.8%	44	74.6%	0.039 0	2.326	1.043	5.187
food allergy in infancy	21	40.4%	28	47.5%	0.454 4	1.333	0.628	2.833
environmental tobacco smoke (ETS)*	8	15.4%	8	13.6%	0.784 8	0.863	0.299	2.490
atopic dermatitis	3	5.9%	12	21.1%	0.032 4	4.267	1.130	16.115
BMI (kg/m2), median(quartiles Q1-Q3)	15.3(14.5-16.6)		15.5(14.8-17.3)		0.597 5	0.957	0.815	1.125
total number of antibiotic courses/year, before inclusion, median(quartiles Q1-Q3)	1.5(0.9-2.5)		2.4(1.4-3.6)		0.010 1	1.456	1.093	1.939
antibiotic courses/year>2 (median)	23	44.2%	40	67.8%	0.013 3	2.654	1.225	5.751
adenoidectomy	18	34.6%	14	23.7%	0.208 4	0.588	0.257	1.345
atopy	19	36.5%	35	59.3%	0.017 6	2.533	1.176	5.455
sensitization profile:								
tree or grass	12	23.1%	23	39.0%	0.074 5	2.130	0.928	4.887
molds or cat or dog	4	7.7%	5	8.5%	0.580 1	1.111	0.282	4.377
house dust mite	6	11.54%	20	33.9%	0.007 7	3.932	1.436	10.764
pathogens, relative frequency>0								
<i>Staphylococcus</i>	10	19.2%	11	18.6%	0.937 2	0.963	0.372	2.492
<i>Haemophilus</i>	52	100%	57	96.6%	-	-	-	-
<i>Moraxella</i>	23	44.2%	19	32.2%	0.193 7	0.599	0.276	1.298
<i>Pseudomonas</i>	11	21.2%	13	22.0%	0.910 5	1.053	0.425	2.608
pathogens, relative frequency>median								

<i>Staphylococcus</i>	6	60.0%	5	45.5%	0.506 6	0.556	0.098	3.149
<i>Haemophilus</i>	30	57.7%	29	50.9%	0.476 1	1.317	0.618	2.806
<i>Moraxella</i>	14	60.9%	8	42.1%	0.228 4	0.468	0.136	1.611
<i>Pseudomonas</i>	3	27.3%	9	69.2%	0.047 8	6.000	1.018	35.375
reduced Shannon index	8	15.4%	20	33.9%	0.028 2	2.821	1.117	7.122

^a dependent variable: moderate vs. mild/episodic symptoms of chronic rhino-sinusitis

*one or more smoking person at home

Table S2 Clinical and microbiological data at baseline (before pandemic) of children with vs. without asthma symptoms during pandemic isolation. Data are presented by number (%) of observation unless otherwise indicated. Odds ratios with 95%confidence intervals from univariate logistic regression analysis are given.

	without asthma symptoms (n=80)		with asthma symptoms (n=31)		p	OR ^a	95%CI	95%CI
	N	%	N	%				
age (years), median(quartiles Q1-Q3)	6(5-7)		5(5-7)		0.1887	0.793	0.562	1.120
age>6 years (school children)	28	35%	8	26%	0.3470	0.65	0.26	1.63
male gender	46	57.5%	24	77.4%	0.0554	2.534	0.979	6.562
preterm delivery	14	17.5%	8	25.8%	0.3275	1.640	0.609	4.412
natural delivery	40	50.0%	14	45.2%	0.6474	0.824	0.358	1.893
family history of allergy	50	62.5%	23	74.2%	0.2470	1.725	0.685	4.342
food allergy in infancy	30	37.5%	19	61.3%	0.0257	2.639	1.125	6.191
environmental tobacco smoke (ETS)*	11	13.8%	5	16.1%	0.7491	1.206	0.382	3.807
atopic dermatitis	9	11.5%	6	20.0%	0.2602	1.917	0.618	5.949
BMI (kg/m2), median(quartiles Q1-Q3)	15.4(14.7-17.3)		15.1(14.1-16.5)		0.1850	0.876	0.721	1.065
total number of antibiotic courses/year, before inclusion, median(quartiles Q1-Q3)	1.8(0.9-2.9)		2.3(1.6-3.6)		0.1139	1.226	0.952	1.579
antibiotic courses/year>2 (median)	43	53.8%	20	64.5%	0.3060	1.564	0.664	3.686
moderate vs. mild/episodic CRS	37	46.3%	22	71.0%	0.0217	2.841	1.165	6.928
adenoidectomy	24	30.0%	8	25.8%	0.6620	0.812	0.318	2.069
atopy	33	41.3%	21	67.7%	0.0141	2.991	1.247	7.173
sensitization profile:								
tree or grass	23	28.8%	12	38.7%	0.3128	1.565	0.656	3.736
molds or cat or dog	4	5.0%	5	16.1%	0.113	3.654	0.912	14.642
house dust mite	16	20.0%	10	32.3%	0.1750	1.905	0.751	4.834
spirometry**								
FEV1 (%pred.) median(quartiles Q1-Q3)	102(96-107)		88.5(89-106)		0.1180	0.82	0.64	1.05

FEV1 (%change after SABA), median(Q1-Q3)	6(4-8)		10(5-12)		0.1168	1.72	0.87	3.41
pathogens, relative frequency>0								
<i>Staphylococcus</i>	16	20.0%	5	16.1%	0.6410	0.769	0.255	2.317
<i>Haemophilus</i>	79	98.8%	30	96.8%	0.4985	0.380	0.023	6.267
<i>Moraxella</i>	31	38.8%	11	35.5%	0.7503	0.869	0.367	2.059
<i>Pseudomonas</i>	18	22.5%	6	19.4%	0.7183	0.827	0.294	2.325
pathogens, relative frequency>median								
<i>Staphylococcus</i>	8	50.0%	3	60.0%	0.6969	1.500	0.195	11.536
<i>Haemophilus</i>	17	54.8%	5	45.5%	0.5933	0.686	0.172	2.732
<i>Moraxella</i>	47	59.5%	12	40.0%	0.0710	0.454	0.193	1.070
<i>Pseudomonas</i>	9	50.0%	3	50.0%	1.0000	1.000	0.158	6.347
reduced Shannon index	19	23.8%	9	29.0%	0.5660	1.313	0.518	3.332

^a dependent variable: presence vs. absence of asthma symptoms

*one or more smoking person at home

** reliable spirometry results obtained at inclusion in 21 children

Table S3 Clinical and microbiological data at baseline (inclusion data, before pandemic) and during pandemic (fall-winter 2020 season) of children with (+) vs. without (-) house dust mite (HDM) sensitization. Data are presented by number (%) of observation unless otherwise indicated. Odds ratios with 95%confidence intervals from univariate logistic regression analysis are given.

	HDM (-) (n=86)		HDM(+) (n=26)		p	OR ^a	95%CI	
	N	%	N	%				
inclusion data								
age (years), median(quartiles Q1-Q3)	6(5-7)		6(5-7)		p=,5555	0.89	0.63	1.28
age>6 years (school children)	29	33.7%	7	26.9%	P=,5165	0.72	0.27	1.92
male gender	54	62.8%	17	65.4%	p=,5012	1.12	0.45	2.81
preterm delivery	14	16.3%	8	30.8%	p=,1561	2.29	0.83	6.28
natural delivery	44	51.2%	11	42.3%	p=,5048	0.70	0.29	1.70
family history of allergy	55	64.0%	18	69.2%	p=,8146	1.27	0.49	3.25
food allergy in infancy	35	40.7%	14	53.8%	p=,2652	1.70	0.70	4.11
environmental tobacco smoke (ETS)*	13	15.1%	3	11.5%	p=,7598	0.73	0.19	2.80
BMI (kg/m2), median(quartiles Q1-Q3)	15.5(14.5-16.5)		15.1(14.9-18.1)		p=,3799	1.08	0.90	1.30
SN-5>3.6(median)	45	52.3%	17	65.4%	p=,2682	1.72	0.69	4.28
asthma	47	54.7%	19	73.1%	p=,1142	2.25	0.86	5.91
antibiotic courses/year before inclusion>2 (median)	46	53.5%	17	65.4%	p=,3682	1.64	0.66	4.09
pathogens, relative frequency>0								
<i>Staphylococcus</i>	16	18.6%	6	23.1%	p=,5856	1.31	0.45	3.79
<i>Haemophilus</i>	85	98.8%	25	96.2%	p=,4120	0.29	0.02	4.87
<i>Moraxella</i>	35	40.7%	7	26.9%	p=,2516	0.54	0.20	1.41
<i>Pseudomonas</i>	17	19.8%	7	26.9%	p=,4265	1.50	0.54	4.13
pathogens, relative frequency>median								
<i>Staphylococcus</i>	7	43.8%	4	66.7%	p=,6351	2.57	0.36	18.33
<i>Haemophilus</i>	47	55.3%	12	48.0%	p=,6490	0.75	0.31	1.82

<i>Moraxella</i>	19	54.3%	3	42.9%	p=,6909	0.63	0.12	3.25
<i>Pseudomonas</i>	8	47.1%	4	57.1%	p=1,000	1.50	0.25	8.84
reduced Shannon index	15	17.6%	13	50.0%	p=,0042	4.52	1.68	12.15
follow-up data (fall-winter 2020 season)								
SN-5>3 (median)	39	45.9%	20	76.9%	p=,0068	3.93	1.44	10.76
asthma symptoms	21	24.7%	10	38.5%	p=,2128	1.90	0.75	4.83
antibiotic courses/year>0	7	8.2%	7	26.9%	p=,0192	4.11	1.29	13.11

^a dependent variable: presence vs. absence of house dust allergy

*one or more smoking person at home

Figure legends:

Figure S1

ROC curve visualization of the association between house dust mite skin prick test results [mm] and two study outcomes: i) moderate vs mild chronic rhinosinusitis (CRS) (left panel) and ii) with vs without asthma symptoms (right panel)

Figure S2

Relative expression of various molecules in the nasal mucosa of children with mild-episodic vs. moderate chronic rhinosinusitis (left panel) and with vs. without asthma symptoms (right panel), A. Shannon index across percentiles of the total number of antibiotic courses/year (before inclusion), B. Data are presented as individual values (points), lower-upper quartiles (boxes), and min-max values (whiskers).

Figure S3

Study results visualization. The pandemic isolation unmasks the clinical significance of house dust mite (HDM) sensitization, which was associated with more frequent antibiotics courses, more severe chronic rhinosinusitis (CRS), and consequently more frequent asthma symptoms.

Figure S1

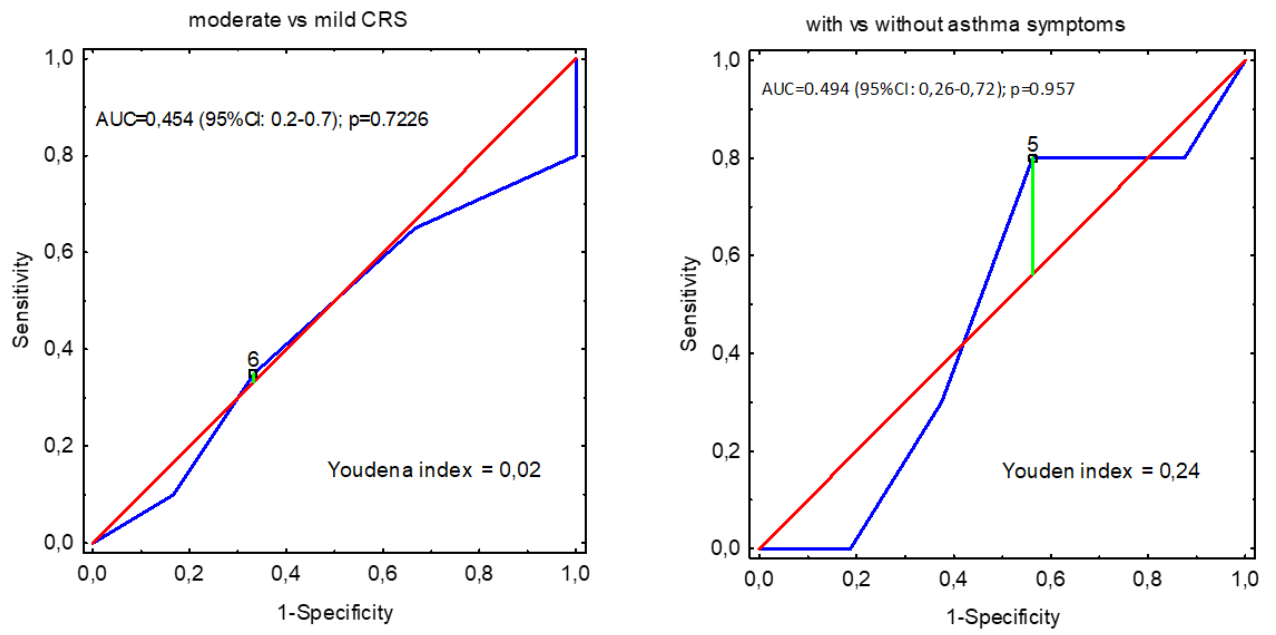


Figure S2

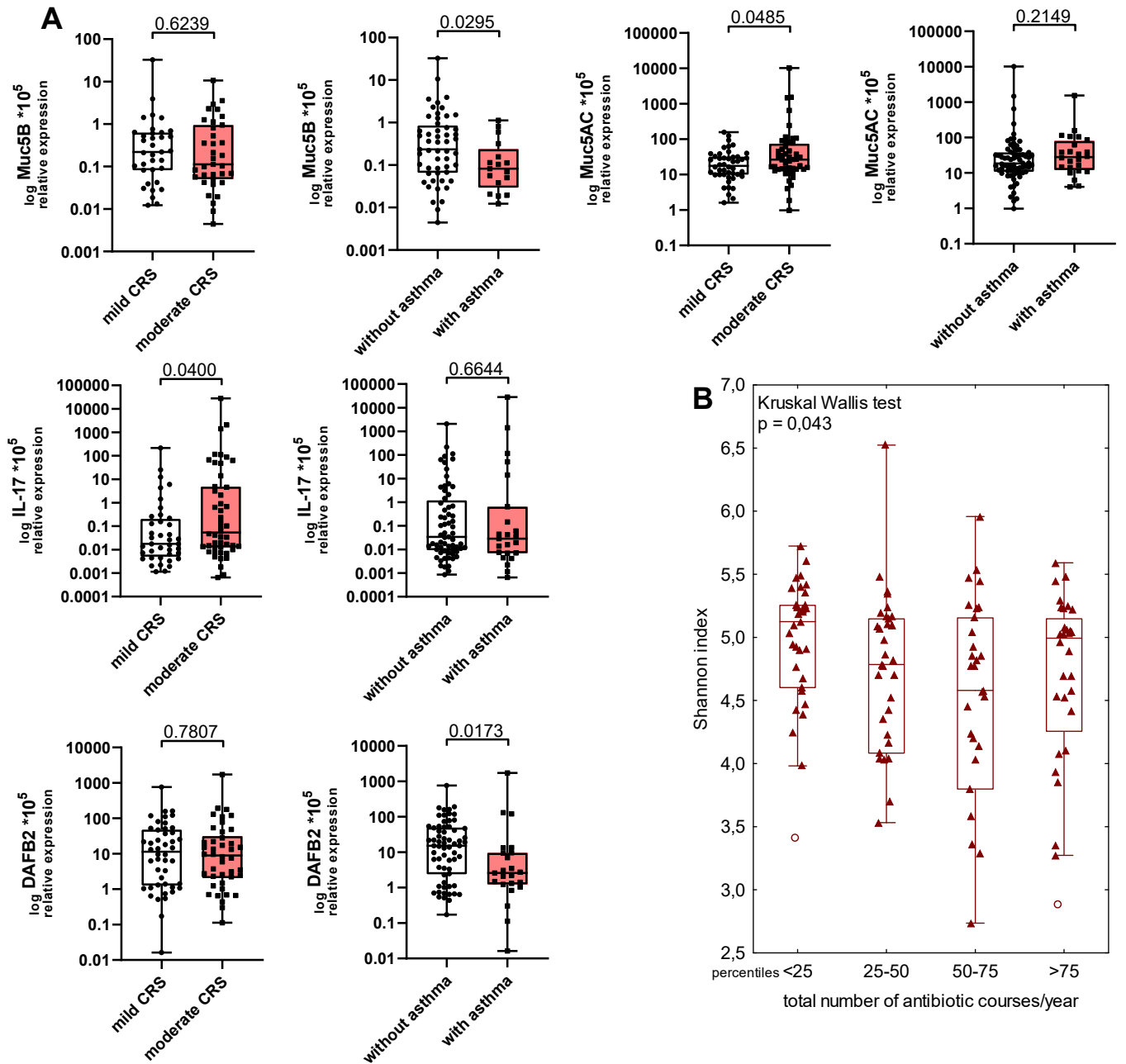


Figure 33

Preschoolers with moderate CRS and asthma in 61% (n=133)

- nasal:
 - ↑IL-17
 - ↑Muc-5C
 - ↓DAFB2
 - ↓Muc-5B
- non-atopic
- HDM (+)
- antibiotic courses

PANDEMIC ISOLATION

follow-up (n=111)

mild-episodic CRS

moderate CRS

ASTHMA 17%

ASTHMA 37%

The flowchart illustrates the PANDORA study's progression. It begins with a group of preschoolers (n=133) who have moderate CRS and asthma in 61%. This group is characterized by being non-atopic, having HDM (+), and taking antibiotic courses. A nasal analysis shows increased IL-17 and Muc-5C, and decreased DAFB2 and Muc-5B. The study then moves to a pandemic isolation phase with follow-up (n=111). From this phase, two outcomes are shown: mild-episodic CRS, which leads to asthma in 17% of cases, and moderate CRS, which leads to asthma in 37% of cases.