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Medical care and treatment of children with asthmatic or wheezing health outcomes and urban–rural differences in Bavaria – a cross-sectional study

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ABSTRACT

Introduction: Asthma is among the most common chronic conditions in children. The aim of this publication is to describe prevalence rates and factors associated with asthmatic or wheezing preschoolers and to evaluate medical care and treatment with regard to urban–rural differences.

Methods: Data for this cross-sectional study were collected through a questionnaire, which was distributed to parents within the Health Monitoring Units in Bavaria (HMU), Germany. Data from 4767 children were available (2016/17). Those children were classified into four diagnostic groups: Unremitting Wheeze, International Study of Asthma and Allergies in Children (ISAAC) Asthma, Physician-diagnosed Asthma, and healthy control group. Urban–rural differences were tested by Pearson's chi-squared test or by Fisher's exact test. Independent variables were factors associated with health outcomes, for example, residency or migrant status. To examine associations between independent and outcome variables multivariate logistic regression analysis was performed.

Results: Prevalence rates were 6.3% for 'Unremitting Wheeze', 5.2% for 'ISAAC Asthma', and 1.2% for 'Physician-diagnosed Asthma'. Factors associated with health outcomes were the occurrence of asthma in first-degree relatives, male sex, and migrant status. Generally, higher rates of doctor's visits, positive allergy tests, and corticosteroids intake in the diagnostic groups in rural compared to urban areas were observed. Rates of performed allergy tests were 55.6% for 'ISAAC Asthma' and 74.6% for 'Physician-diagnosed Asthma'.

Conclusions: Prevalence rates of the diagnostic groups decreased compared to the HMU 2014/15. According to previous studies, factors associated with asthmatic or wheezing health outcomes could be confirmed. Children in rural areas generally received more medical care.

Abbreviations: HMU: Health Monitoring Units in Bavaria; ISAAC: International Study of Asthma and Allergies in Children; OR: odds ratio

KEY POINTS

- Children's prevalence rates of asthma or wheezing disorders decreased in the past 2 years within Bavaria.
- This study is consistent with risk factors for asthma from the literature: asthma in the family, male gender, and migrant status.
- Children in rural areas receive more medical care than children in urban areas.
- There should be more allergy tests among children with medical diagnosis in Bavaria as low rates indicate gaps in care.

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Asthma; preschool children; medical care; treatment; unremitting wheeze; urban–rural differences

Introduction

Asthma is a chronic bronchial inflammatory reaction and the most common chronic disease in children. It is also among the top 20 chronic conditions in the

global ranking of disability-adjusted life years (1). The etiology is multifactorial and mutual influences of genetic and environmental factors are of great importance for the development of asthma (2). Due

to differences in the pathophysiology and clinical phenotypes, asthma is considered as a heterogeneous disease (3). Main clinical manifestations of asthma are wheezing, breathlessness (dyspnea), chest tightness, coughing, sputum production, and variable limitation of expiratory airflow (2). However, it remains difficult to diagnose asthma in children younger than six years of age. This is because, among other things, lung function tests often cannot be completed (3,4). Without a diagnosis of asthma, wheezing remains one of the leading symptoms of asthma at this age (5,6). For this reason, alternative approaches to the possible presence of asthma in preschool children have emerged. Besides clinical wheezing phenotypes, the asthma definition according to the ISAAC study has also become established in recent years (6). Wheezing disorders have a multifactorial nature as well and occur frequently in preschool children. The cumulative prevalence rate of 'Wheeze' is almost 50% within the first 6 years of life and mainly associated with viral respiratory infections (7). In Germany, about 6% of all children suffer from Asthma (8). Medical treatment in preschool children involves different therapeutic strategies, including pharmacological and non-pharmacological measures. Regarding wheezing disorders, medical treatment is similar to those in asthma guidelines, for instance recommendations for drug interventions or control of external variables as avoidance of allergens and reduction of tobacco smoke exposure (3,7,9,10). Although national and international guidelines have been developed to improve healthcare for asthmatic children and most children can be easily treated with medication that is both safe and effective, asthma in children is still poorly controlled (11). Internationally, many studies have been conducted on asthma control, while in Germany and particularly in Bavaria there is little literature on the medical care of respiratory diseases in preschool children. Consequently, more research is needed to identify possible deficits in this important public health field. For structural analyses and health policy measures, it can be important to know the differences in the health care situation between urban and rural areas.

The aim of this study is to describe current prevalence rates and factors associated with unremitting wheezing, ISAAC asthma, physician-diagnosed asthma, and a healthy control group in Bavarian preschoolers. Additionally, the study aimed to

evaluate respective medical care and treatment for each group with a focus on rural and urban differences.

Materials and methods

Data collection

The data for the present study were obtained from a cross-sectional study performed in 2016–17 and were provided by the Health Monitoring Units in Bavaria (HMU). The German name of the study is 'Gesundheits Monitoring Einheiten' (GME). The HMU were established in 2004 by the Bavarian Health and Food Safety Authority and are supported by the Bavarian State Ministry of Health and Care. The HMU surveys are conducted every two years in three urban (Munich, Ingolstadt, Bamberg city) and three rural (Schwandorf, Guenzburg, Bamberg rural district) regions. The questionnaire was developed as a tool to collect data on important health and socioeconomic aspects in preschool children. The HMU have been approved by the local ethics committees (13th September 2004, Nr. 04157, Bayerische Landesärztekammer/Ethikkommission). The informed consent has been given in writing. For more information on the HMU and the study regions please refer to Bolte et al. (12). Parents were asked to fill out a paper questionnaire. Participation was voluntary.

Health outcome variables

Based on the parent responses to the surveys, four diagnostic groups were defined. 'Unremitting Wheeze', which was defined as 'having symptoms between distinct wheezing episodes' or 'having wheeze without a cold with fever or rhinitis'; 'Physician-diagnosed Asthma' was defined as 'physician's diagnosis of asthma at least once per lifetime'; 'ISAAC Asthma' was specified as 'physician's diagnosis of asthma at least once per lifetime or recurrent diagnoses of asthmatic, spastic, or obstructive bronchitis'. The definition of 'ISAAC Asthma' followed the definition of the International Study of Asthma and Allergies in Children (ISAAC). Children who did not belong to any of the three groups formed the 'healthy control group'. Due to the nature of the disease progression, a child could belong to more than one diagnostic group at the same time.

Sociodemographic variables

The following variables were analyzed to describe the study population: 'age', 'sex', 'siblings' (no siblings, at

least one older sibling, younger siblings, or twins), 'migrant status' (both parents born abroad or child born abroad and at least one parent born abroad), 'parents smoking at home' (yes or no), 'mother smoking during pregnancy' (yes or no), 'asthma in first-degree relatives' (yes or no), and 'parental school education' (low, middle, or high).

Medical care and treatment

In terms of medical care and treatment, the questionnaire comprised information on the 'frequency of visits to general practitioners or pediatricians within the past 12 months', the 'presence of a peak-flow-meter' to assess pulmonary function, performance and results of 'allergy tests' (positive or negative), 'inpatient or outpatient medical treatment for respiratory conditions', and the 'daily intake of medication for the treatment of respiratory symptoms during the past 12 months' (only Corticosteroids, Corticosteroids and Beta2-adrenergic antagonist, and Beta2-adrenergic antagonist and Leucotriens).

Descriptive and statistical analysis

Sociodemographic characteristics as well as medical care and treatment variables were stratified by residency for the total population and diagnostic groups. The data were described using absolute and relative frequencies. Urban-rural differences were tested by Pearson's chi-squared test or in case of group sizes smaller than five cases by Fisher's Exact test. In order to investigate the association between factors associated with health outcomes and diagnostic groups as well as medical care and treatment variables and diagnostic groups, multiple multivariable logistic regression analysis have been performed. In the logistic regression analysis the independent variables were 'residency' (urban vs. rural), 'sex' (male vs. female), 'having older siblings' (yes vs. no), 'migrant status' (yes vs. no), 'asthma in first-degree relatives' (yes vs. no), 'parental education' (high vs. low), 'smoking at home' vs. 'never smoking' and 'smoking during pregnancy' vs. 'never smoking'. The outcome variables were 'Unremitting Wheeze', 'ISAAC Asthma', 'Physician-diagnosed Asthma', 'visit pediatrician or general practitioner' (>4 times in the last 12 months), 'positive allergy test', and 'intake only corticoids' (in last 12 months). Odds ratios (OR) have been adjusted in the model for all the other independent variables listed. Factors associated with health outcomes were used as independent variables in both cases and diagnostic groups respectively

medical care and treatment variables were used as dependent variables. The 'healthy control group' served as reference group.

In the logistic regression analysis with medical care and treatment variables, the authors excluded the variables 'smoking at home' and 'mothers smoking in pregnancy' due to the small sample size. Significance was tested at a 0.05 significance level. Results were presented as OR with 95% confidence intervals (95% CI). All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Description of the study population

As shown in Table 1, data from 4767 children (response rate = 54,3%) were available with a mean age of 5.4 years, 51.3% of all children were male and 51.5% lived in urban areas. 6.3% of the children belonged to 'Unremitting Wheeze', 5.2% to 'ISAAC Asthma', and 1.2% to 'Physician-diagnosed Asthma'. Children of migrants (either both parents were born abroad or the child was born abroad and at least one parent was born abroad) accounted for 22.3% of the total population and between 14.0% ('ISAAC Asthma') and 28.5% ('Unremitting Wheeze') of the diagnostic groups. Statistically significant more migrants lived in urban compared to rural areas in the total population and in the group 'Unremitting Wheeze' compared to the healthy control group. Those children who had first-degree relatives with asthma diagnoses accounted for 45.8% in the group 'Physician-diagnosed Asthma', which was the highest proportion among the diagnostic groups. Urban-rural differences in parental education, most of which were statistically significant, could be observed both in the study population and in diagnostic groups with higher levels of parental education in urban areas.

Medical care and treatment

In general, higher rates of positive allergy tests results and corticosteroids intake were observed for diagnostic groups in rural compared to urban areas (see Table 2). Frequent visits of general practitioners or pediatrician within the previous year were higher in children with 'Unremitting Wheeze' (23.5%), 'ISAAC Asthma' (28.4%), or 'Physician-diagnosed Asthma' (30.5%) compared to the total population (11.9%) and were observed more often in rural areas. A statistically significant difference in residencies, with higher proportions in rural areas, was observed for children with 'ISAAC Asthma' and 'Physician-diagnosed Asthma' for

Table 1. Sociodemographic characteristics and factors associated with health outcomes.

Groups	Total population		Healthy control group				Unremitting Wheeze				ISAAC Asthma				Physician-diagnosed Asthma			
	4767 (100)		4313 (90.5)				298 (6.3)				250 (5.2)				59 (1.2)			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (in years)	5.4	0.6	5.3	0.5	5.4	0.6	5.4	0.6	5.4	0.6	5.4	0.6	5.5	0.6	5.5	0.6	5.5	0.6
N (% of total population)	Total	Urban	Total	Urban	Total	Urban	Total	Urban	Total	Urban	Total	Urban	Total	Urban	Total	Urban	Total	Urban
	N = 4762	n = 2453	N = 4313	n = 2225	N = 2983	n = 2083	N = 298	n = 148	N = 250	n = 126	N = 250	n = 126	N = 124	n = 59	N = 124	n = 59	N = 31	n = 31
Definition	Rural	n (%)	Rural	n (%)	Rural	n (%)	Rural	n (%)	Rural	n (%)	Rural	n (%)	Rural	n (%)	Rural	n (%)	Rural	n (%)
All completed questionnaires 2016/17	Urban	n (%)	Urban	n (%)	Urban	n (%)	Urban	n (%)	Urban	n (%)	Urban	n (%)	Urban	n (%)	Urban	n (%)	Urban	n (%)
Children who do not belong to the diagnostic groups	Total	N	Total	N	Total	N	Total	N	Total	N	Total	N	Total	N	Total	N	Total	N
Sex male	2417 (50.8)	1244 (50.7)	1173 (50.8)	1105 (49.7)	1047 (50.3)	167 (56.0)	89 (60.1)	78 (52.0)	154 (61.6)	79 (62.7)	75 (60.5)	38 (64.4)	18 (64.3)	20 (64.5)	38 (64.4)	18 (64.3)	20 (64.5)	18 (64.3)
Siblings	924 (19.4)	507 (20.7)	417 (18.1)	456 (20.5)	376 (18.1)	64 (21.5)	35 (23.6)	29 (19.3)	48 (19.2)	26 (20.6)	22 (17.7)	12 (20.3)	7* (25.0)	5* (16.1)	12 (20.3)	7* (25.0)	5* (16.1)	5* (16.1)
No siblings	2077 (43.6)	1026 (41.8)	1051 (45.5)	929 (41.8)	946 (45.4)	133 (44.6)	67 (45.3)	66 (44.0)	109 (43.6)	52 (41.3)	57 (46.0)	30 (50.8)	12 (42.9)	12 (38.7)	30 (50.8)	12 (42.9)	12 (38.7)	12 (38.7)
Older sibling(s)	1593 (33.5)	833 (34.0)	760 (32.9)	758 (34.1)	686 (32.9)	92 (30.9)	41 (27.7)	51 (34.0)	90 (36.0)	47 (37.3)	43 (34.7)	17 (28.8)	9 (32.1)	14 (45.2)	17 (28.8)	9 (32.1)	14 (45.2)	14 (45.2)
Younger sibling(s) or twins	1064 (22.3)	724* (29.5)	340* (14.7)	656* (29.5)	307* (14.7)	85 (28.5)	60* (40.5)	25* (16.7)	35 (14.0)	22 (17.5)	13 (10.5)	12 (20.3)	7 (25.0)	5 (16.1)	12 (20.3)	7 (25.0)	5 (16.1)	5 (16.1)
Migrant ^a	115 (2.4)	59 (2.4)	56 (2.4)	53 (2.4)	48 (2.3)	13 (4.4)	5 (3.4)	8 (5.3)	4 (1.6)	2 (1.6)	2 (1.6)	1 (1.7)	1 (3.6)	0 (0.0)	1 (1.7)	1 (3.6)	0 (0.0)	0 (0.0)
Smoking at home	284 (6.0)	113 (4.6)	171 (7.4)	99 (4.4)	152 (7.3)	25 (8.4)	12 (8.1)	13 (8.7)	14 (5.6)	4 (3.2)	10 (8.1)	5 (8.5)	2 (7.1)	3 (9.7)	5 (8.5)	2 (7.1)	3 (9.7)	3 (9.7)
Mother smoking during pregnancy	674 (14.2)	352 (14.3)	322 (13.9)	293 (13.2)	264 (12.7)	72 (24.2)	32 (21.6)	40 (26.7)	80 (32.0)	44 (34.9)	36 (29.0)	27 (45.8)	13 (46.4)	14 (45.2)	27 (45.8)	13 (46.4)	14 (45.2)	14 (45.2)
Asthma in first-degree relatives ^b	819 (17.2)	334* (13.6)	485* (21.0)	304 (13.7)	431 (20.7)	63 (21.1)	23* (15.5)	40* (26.7)	38 (15.2)	11* (8.7)	27* (21.8)	14 (23.7)	3* (10.7)	11* (35.5)	14 (23.7)	3* (10.7)	11* (35.5)	11* (35.5)
Parental education ^c	1342 (28.2)	490* (20.0)	852* (36.9)	437* (19.6)	769* (36.9)	98 (32.9)	41* (27.7)	57* (38.0)	69 (27.6)	26* (20.6)	43* (34.7)	13 (22.0)	6 (21.4)	7 (22.6)	13 (22.0)	6 (21.4)	7 (22.6)	7 (22.6)
Low	2415 (50.7)	1540* (62.8)	875* (37.9)	1400* (62.9)	791* (38.0)	131 (44.0)	80* (54.1)	51* (34.0)	138 (55.2)	88* (69.8)	50* (40.3)	30 (50.8)	18* (64.3)	12* (38.7)	30 (50.8)	18* (64.3)	12* (38.7)	12* (38.7)
Middle																		
High																		

*Both parents were born abroad or child born abroad and at least one parent born abroad.

^aParents or siblings diagnosed with asthma.

^bLow is 'Hauptschulabschluss' or no graduation, 'middle' is 'Realschulabschluss', POS or other, 'high' is 'Fachhochschulreife oder Abitur'; % include missing values.

^cNumbers marked with asterisk are relevant with $p < 0.05$ for Chi-square test or Fisher's Exact Test as stratification (urban-rural differences).

Table 2. Medical care and treatment.

	Total population						Unremitting Wheeze						ISAAC Asthma			Physician-diagnosed Asthma								
	Total		Urban		Rural		Total		Urban		Rural		Total		Urban		Rural		Total		Urban		Rural	
	N	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)	N	(%)	n	(%)	n	(%)
Visit of general practitioner or pediatrician within the last 12 months	4153	(87.2)	2143	(87.4)	2010	(87.1)	264	(88.6)	126	(85.1)	138	(92.0)	229	(91.6)	118	(93.7)	111	(89.5)	49	(83.1)	25*	(89.3)	24*	(77.4)
	3249	(68.2)	1718	(70.0)	1531	(66.3)	160	(53.7)	80	(54.1)	84	(56.0)	130	(52.0)	75*	(59.5)	55*	(44.4)	21	(35.6)	12*	(42.9)	9*	(29.0)
	568	(11.9)	276	(11.3)	292	(12.6)	70	(23.5)	31	(20.9)	39	(26.0)	71	(28.4)	32	(25.4)	39	(31.5)	18	(30.5)	8	(28.6)	10	(32.3)
	44	(0.9)	19	(0.8)	25	(1.1)	24	(8.1)	11	(7.4)	13	(8.7)	27	(10.8)	8*	(6.3)	19*	(15.3)	13	(22.0)	4*	(14.3)	9*	(29.0)
Presence of a peak-flow-meter	756	(15.9)	349	(14.2)	407	(17.6)	135	(45.3)	59*	(39.9)	76*	(50.7)	139	(55.6)	61*	(48.4)	78*	(62.9)	44	(74.6)	19*	(67.9)	25*	(80.7)
	444	(9.3)	212	(8.6)	232	(10.0)	65	(21.8)	29	(19.6)	34	(22.7)	67	(26.8)	27	(21.4)	38	(30.6)	14	(23.7)	7	(25.0)	7	(22.6)
	312	(6.6)	137	(5.6)	175	(7.6)	70	(23.5)	32	(21.6)	42	(28.0)	72	(28.8)	32	(25.4)	40	(32.3)	30	(50.8)	12*	(42.9)	18*	(58.1)
	851	(17.7)	425	(17.3)	426	(18.5)	296	(99.3)	146	(98.7)	147	(98.0)	187	(74.8)	94	(74.6)	91	(73.4)	48	(81.4)	24*	(85.7)	23*	(74.2)
condition ^a																								
Outpatient																								
General practitioner	656	(13.8)	320	(13.1)	336	(14.6)	207	(69.5)	103	(69.6)	103	(68.7)	166	(66.4)	84	(66.7)	80	(64.5)	40	(67.8)	21*	(75.0)	18*	(58.1)
Emergency service	65	(1.4)	38	(1.6)	27	(1.2)	33	(11.1)	20	(13.5)	13	(8.7)	19	(7.6)	11	(8.7)	8	(6.5)	6	(10.2)	2	(7.1)	4	(12.9)
Inpatient																								
Hospitalization for 1 day	40	(0.8)	20	(0.8)	20	(0.9)	25	(8.4)	12	(8.1)	13	(8.7)	16	(6.4)	7	(5.6)	9	(7.3)	7	(11.9)	3	(10.7)	4	(12.9)
Hospitalization for >1 day	102	(2.1)	54	(2.2)	48	(2.1)	47	(15.8)	24	(16.2)	23	(15.3)	42	(16.8)	21	(16.7)	21	(16.9)	13	(22.0)	4*	(14.3)	9*	(29.0)
Daily medication intake for respiratory conditions within the last 12 months	307	(6.5)	140	(5.7)	167	(7.2)	122	(40.9)	55	(37.2)	67	(44.7)	137	(54.8)	61*	(48.4)	76*	(61.3)	47	(79.7)	22	(78.6)	25	(80.7)
Corticosteroids ^b	34	(0.7)	12	(0.5)	22	(1.0)	25	(8.4)	7	(4.7)	18	(12.0)	25	(10.0)	10	(7.9)	15	(12.1)	14	(23.7)	6	(21.4)	8	(25.8)
Cort. & B2AA ^c	26	(0.5)	10	(0.4)	16	(0.7)	11	(3.7)	5	(3.4)	6	(4.0)	17	(6.8)	6	(4.8)	11	(8.9)	8	(13.6)	5*	(17.9)	3*	(9.7)
B2AA&Leucotriens ^d	30	(0.6)	11	(0.4)	19	(0.8)	12	(4.0)	4	(2.7)	8	(2.7)	14	(5.6)	5	(4.0)	9	(7.3)	5	(8.5)	2	(7.1)	3	(9.7)

^aRespiratory conditions include children who have ever had shortness of breath, wheezing, asthma, or asthmatic, spastic, or obstructive bronchitis.^bExclusive intake of corticosteroids.^cExclusive intake of corticosteroids and Beta2-adrenergic agonist, 4 only intake of beta 2 adrenergic agonist and leukotrienes.^dExclusive intake of Beta2-adrenergic agonist and leukotriens.*Numbers marked with asterisk are relevant with $p < 0.05$ for Chi-square test or Fisher's Exact Test as stratification (urban–rural differences).

the 'presence of a peak-flow-meter'. Prevalence rates of performed allergy tests were 45.3% ('Unremitting Wheeze'), 55.6% ('ISAAC Asthma'), and 74.6% ('Physician-diagnosed Asthma'), with statistically significant more allergy tests were performed in rural compared to urban areas in 'Unremitting Wheeze' and 'ISAAC Asthma'. 50.8% of children in 'Physician-diagnosed asthma', 28.8% of children in 'ISAAC Asthma', and 23.5% of children in 'Unremitting Wheeze' had a positive allergy test with a tendency to higher shares in rural areas. The diagnostic group that used medical care services the most due to respiratory conditions was 'Unremitting Wheeze' with a percentage of 99.3%. More frequent use of outpatient care services was observed in urban compared to rural areas and significantly more in children with 'Physician-diagnosed Asthma'. 79.7% of children with 'Physician-diagnosed Asthma' took daily medication for respiratory conditions and thus represent the group with the highest proportion among the diagnostic groups. Further results can be found in Table 2.

Associations between factors associated with health outcomes and diagnostic groups

Boys were more likely to belong to 'Unremitting Wheeze' (OR = 1.45; 95% CI: [1.08–1.95]) and

'ISAAC Asthma' (OR = 1.60; 95% CI: [1.17–2.18]) compared to girls. Children with migrant status were significantly 1.5 times more likely to suffer from 'Unremitting Wheeze' (OR = 1.54; 95% CI: [1.10–2.15]) compared to non-migrants. Children with a first-degree family member with asthma were more likely to belong to any of the three diagnostic groups ('Unremitting Wheeze': OR = 2.02; 95% CI: [1.44–2.84], 'ISAAC Asthma' (OR = 2.74; 95% CI: [1.97–3.81]), 'Physician-diagnosed Asthma' (OR = 4.12; 95% CI: [2.19–7.76]) compared to children with no asthma cases in first-degree relatives. Further associations, represented as OR can be found in Table 3.

Associations between factors associated with health outcomes and medical care and treatment variables

Children from urban areas took up less health care compared to children from rural areas. They visited pediatricians or general doctors less often (OR = 0.76; 95% CI: [0.60–0.96]), performed allergy tests less often (OR = 0.80; 95% CI: [0.66–0.99]) and have taken corticosteroids only a third as frequently in the last 12 months (OR = 0.29; 95% CI: [0.10–0.81]). Children with migrant status as well as children with asthmatic first-degree relatives had a significant higher likeliness

Table 3. Association between factors associated with health outcomes/medical care variables and diagnostic groups.

	Diagnostic group			Medical care		
	Unremitting Wheeze	ISAAC Asthma	Physician-diagnosed Asthma	Visit pediatrician or general practitioner (>4 times in the last 12 months)	Positive allergy test ^a	Intake only corticoids (last 12 months)
	N=298	N=250	N=59	N=568	N=312	N=34
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Residency (urban vs. rural)	0.96 (0.70–1.32)	1.07 (0.77–1.49)	0.86 (0.44–1.68)	0.76 ^a (0.60–0.96)	0.80 ^a (0.66–0.99)	0.29 ^a (0.10–0.81)
Sex (male vs. female)	1.45 ^a (1.08–1.95)	1.60 ^a (1.17–2.18)	1.70 (0.89–3.22)	0.81 (0.65–1.00)	1.25 ^a (1.04–1.51)	1.26 (0.55–2.88)
Having older siblings (yes vs. no)	0.90 (0.62–1.31)	0.94 (0.63–1.43)	0.89 (0.41–1.92)	0.66 ^a (0.49–0.87)	0.55 ^a (0.43–0.70)	0.74 (0.25–2.21)
Migrant (yes vs. no)	1.54 ^a (1.10–2.15)	0.71 (0.47–1.08)	1.49 (0.72–3.09)	1.46 ^a (1.14–1.87)	1.32 ^a (1.06–1.66)	0.76 (0.25–2.38)
Asthma in first-degree relatives (yes vs. no)	2.02 ^a (1.44–2.84)	2.74 ^a (1.97–3.81)	4.12 ^a (2.19–7.76)	1.41 ^a (1.07–1.85)	1.70 ^a (1.35–2.15)	3.02 ^a (1.287.12)
Parental education (high vs. low)	0.81 (0.58–1.13)	1.15 (0.80–1.65)	1.32 (0.60–2.91)	0.88 (0.69–1.13)	0.96 (0.77–1.20)	1.02 (0.40–2.60)
Smoking at home vs. never smoking	1.78 (0.81–3.88)	1.09 (0.38–3.15)	0.71 (0.09–5.50)	n.a. (0.69–1.13)	n.a. (0.77–1.20)	n.a. (0.40–2.60)
Smoking during pregnancy vs. never smoking	0.97 (0.51–1.83)	1.21 (0.64–2.31)	1.96 (0.72–5.30)	n.a.	n.a.	n.a.

Annotations: Variables were code as 0 when the factors associated with health outcomes were not present and 1 when it was present; Logistic regression analysis were performed comparing each of the diagnostic groups with the 'healthy control group'. Medical care variables were coded binary and thus compared as the following: 'Visit pediatrician or general practitioner (>4 times in the last 12 months) vs. ≤4 times', 'Positive allergy test vs. negative allergy test', 'Intake only corticosteroids vs. no medication'; Odds ratios have been adjusted in the model for all the other factors associated with health outcomes listed; OR, odds ratio; CI, confidence interval.

^aAn allergy test was done and the child had at least one allergy.

to have visited the pediatrician or general doctor (OR = 1.46; 95% CI: [1.14–1.87] and OR = 1.70; 95% CI: [1.35–2.15]) or have done an allergy test (OR = 1.32; 95% CI: [1.06–1.66] and OR = 1.70; 95% CI: [1.35–2.15]).

Discussion

In comparison to the prevalence rates two years earlier within the framework of the HMU in 2014/15, the results of the present study show lower prevalence rates among the diagnostic groups: 6.3% vs. 10.4% for ‘Unremitting Wheeze’, 5.2% vs. 7.8% for ‘ISAAC Asthma’, and 1.2% vs. 2.7% for ‘Physician-diagnosed Asthma’ (5). This study is partly an update of the publication about the HMU study from 2014/15 (5) and gives a good insight into the developments affecting healthcare of asthmatic or wheezing children, also with regard to urban–rural differences. In contrast to the previous study, this study adds detailed information on medication. In the previous study, logistic regression analyses were used to examine the association between socioeconomic factors and the different wheezing groups, whereas this study uses logistic regression analysis to examine the association between factors associated with health outcomes and diagnostic groups and medical care variables. As the aim of this study was not to focus on different wheezing patterns, the authors only chose one wheezing phenotype (‘Unremitting Wheeze’). According to Depner et al. the clinical phenotype of ‘Unremitting Wheeze’ has evolved as a promising alternative asthma definition for epidemiological studies. (6). In 2016, the HMU group published an asthma prevalence rate (physician’s diagnose) of 2.8% in children for the year 2012/13 (13). The KiGGS Study (‘German Health Interview and Examination Survey for Children and Adolescents’) published 12-month prevalence rates of physician-diagnosed bronchial asthma of 3.0% in girls and 5.0% in boys (14). The asthma definition according to the ISAAC study (International Study of Asthma and Allergies in Childhood) is often used for children. It states that children up to 6 years of age are considered to have asthma if they have either been diagnosed with asthma by a doctor or have been diagnosed several times as having ‘asthmatic, spastic, or obstructive bronchitis’. The reason for this is that in the German language the term asthma was previously avoided and replaced by spastic or obstructive bronchitis (6).

Risk factors for children to be in a diagnostic group compared to the healthy group included male sex, migrant status, and family history of asthma. Male children comprised a greater proportion amongst diagnostic groups which is consistent with other

studies (5,14,15), although male sex was no longer a significant risk factor for ‘Physician-diagnosed Asthma’ in this study. In accordance with previous research, a diagnosis of asthma in first-degree relatives was determined to be a relevant risk factor for ‘Unremitting Wheeze’, ‘ISAAC Asthma’, and ‘Physician-diagnosed Asthma’ (16–18). In our study, there were more children with a migrant’s status in the group ‘unremitting wheeze’, than without. This could reflect a health seeking behavior of this group and possibly reflect undiagnosed asthma.

In this study, migrant status was a risk factor for ‘Unremitting Wheeze’, but not for ‘Physician-diagnosed Asthma’ compared to non-migrants. Possible explanations could be language barriers, leading to poor asthma education or reduced access to health services. Asthma and allergy prevalence rates among migrants are higher compared to their country of origin (19–21). The explanations given for this phenomenon were amongst other things population genetic factors and the adaptation time for the immunological system. This could explain our findings that migrants have more contact with the health care system and more positive results in the allergy test compared to non-migrants. Nevertheless, asthma is not diagnosed more frequently among migrant children than among children without a migration background.

Among the diagnostic groups, we observed more visits to general practitioners or pediatricians and more medical care required due to respiratory conditions in urban compared to rural areas. We have also seen more peak-flow meters, more frequent and more positive, allergy tests and higher daily medication intake for respiratory diseases in rural areas. With regard to medical care for asthma and wheeze the guidelines recommend regular follow-up care for children (3,9,10). The ‘Global Initiative for Asthma’ for instance recommends follow-up examinations every 3–6 months in children 5 years and younger (10). According to our results, visits to pediatricians or general practitioners (more than 4 times a year) were more frequent in children belonging to the diagnostic groups compared to the total population. The Association of Statutory Health Insurance Physicians of Bavaria calculated the doctor–inhabitant ratio, which defines for how many inhabitants a doctor is available. If this ratio is perfect, the rate is 100%. For our study regions, the ratio of pediatricians in relation to the number of children under 18 years are higher than 100%: 129.3% in Munich (urban), 119.4% in Ingolstadt (urban), 193.7% in Bamberg (urban), 115.4% in Schwandorf (rural), and 144.7% in Günzburg (rural) (22). This suggests that children living in urban and rural areas have equal

opportunities to access healthcare. To our knowledge, there is no further Bavarian data on visits to physicians of asthmatic or wheezing children available.

Being exposed to pesticides, farm animals or crops (rural areas) proved to be relevant risk factors for early onset of persistent asthma (23–25). In the present study, this could explain the higher rates of doctor visits in rural areas compared to urban areas, although rural children did not have increased rates of diagnosed asthma, either by their physicians or by ISAAC criteria.

However, there are studies from central Europe (including Bavaria) that have shown that exposure to animals and stables at an early age is associated with less allergic diseases and asthma, which is in contrast to the study from Salam et al. At this point, it is important to highlight that there are many cross-sectional studies that support the so-called hygiene hypothesis. These studies show that increased exposure to bacteria, fungi, respiratory infections, dogs, cats, and other animals in childhood is associated with a reduced risk of asthma and allergies (26). Other studies show a lower incidence of allergic diseases in children raised on farms (27,28).

An important result of this study is that allergy tests were performed less often than it is recommended for children with physician's diagnoses. Compared to the results from the HMU in 2014/15 (5) rates of allergy tests did not change 56.9% vs. 55.6% for 'ISAAC Asthma' and 74.7% vs. 74.6% for 'Physician-diagnosed Asthma'. Since these children were examined by a doctor and diagnosed with asthma or obstructive bronchitis, this still indicates an insufficient healthcare situation. Guidelines (7,29) clearly recommend and emphasize the importance of performing allergy tests in asthmatic children as part of the diagnose process (3,9,10).

In our study, hospital stays of more than one day were more frequent in the diagnostic groups compared to the total population. A meta-analysis by Kaiser et al. in 2016 revealed that treatment with corticosteroids prevents hospital care and reported that rates of asthma-related emergency department visits and hospitalizations were highest among preschool children (30). This might explain the occurrence of low rates in daily medication among the present diagnostic groups and simultaneously high rates of hospitalization. Furthermore, Engelkes et al. (31) stated in 2014 that a better treatment adherence was associated with fewer severe asthma exacerbations. The estimated adherence was 20–34% (medication possession rate) for inhaled corticosteroids in children. This was related to a lack of parental knowledge about asthma medications, parental beliefs, and

fears, and the child's self-image. According to the guidelines, children in the first stage of asthma should be treated with a bronchodilator usually based on the substance beta2-adrenergic agonist, which is required for wheezing attacks. 'The global asthma insights and reality survey', a cross-sectional study from 2004 including 29 countries worldwide, revealed that children with persistent asthma, from mild to severe, reported a low use of preventative medication and a high use of quick-relief medication, which is suggestive of poor asthma control (32).

Despite the availability of effective asthma treatments, the compliance to most of the asthma medication recommendations is generally poor. Poor adherence is characterized by an undersupply of inhaled corticosteroids and often accompanied by excessive use of short-acting beta2-adrenergic agonist for symptom relief. The potent anti-inflammatory corticosteroids play a central role in asthma treatment (33–35). In our study, the exclusive use of corticosteroids was higher compared to the other drugs listed and was mainly used in rural areas. To our knowledge and at the time of publication of this study, no further data on pharmacological treatment in asthmatic or wheezing children in Bavaria is available.

In closing, a number of potential limitations need to be considered. The data were based on information provided by the parents, which could lead to reporting bias or misclassification due to recall bias. Since the surveys were conducted in German, the language barrier may have been a limitation for non-native speakers. Moreover, it is not possible to specify reasons for the doctor's visits from our data retrospectively and the medication doses are unknown. It should also be noted that in Tables 1 and 2, the numerical values of the sociodemographic and medical care and treatment variables are after stratification for residency in some extent small, except for the variable 'Migrant'. The resulting limited relevance value should be taken into account when interpreting the results.

Our work has some limitations, but also powerful factors like a large sample size and good quality data. Another strength is that questions about asthma and wheezing symptoms have a high level of comparability, as they are in part identical to the ISAAC questionnaire used by many studies in this field.

Conclusions

In 2016/2017, we found generally lower prevalence rates of asthmatic/wheezing diagnostic groups in Bavarian preschool children than previously reported and were able to confirm genetic risk factors for

asthma and wheeze in children. Medical care and treatment in urban and rural areas generally seem to differ for children with unremitting wheeze or diagnosed asthma, with greater use in rural areas. The different regional results of our study suggest the importance of evaluating urban and rural healthcare policies. Low rates of performed allergy tests in children with physician's diagnoses of respiratory diseases indicate a discrepancy to the current guidelines.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. No potential competing interest are reported by the authors. There are no relevant financial or non-financial competing interests to report.

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References

- Ferrante G, La Grutta S. The burden of pediatric asthma. *Front Pediatr*. 2018;6:186.
- Hoch HE, Houin PR, Stillwell PC. Asthma in children: a brief review for primary care providers. *Pediatr Ann*. 2019;48(3):e103–e9. doi:10.3928/19382359-20190219-01.
- Buhl R, Bals X, Baur D, Berdel C-P, Criée M, Gappa A, Gillissen T, Greulich P, Haidl E, Hamelmann P, Kardos A, et al. Zacharasiewicz S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit Asthma. AWMF online: Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V., Deutsche Atemwegsliga e.V.; 2017.
- Horak F, Doberer D, Eber E, Horak E, Pohl W, Riedler J, Szépfalusi Z, Wantke F, Zacharasiewicz A, Studnicka M. Diagnosis and management of asthma – statement on the 2015 GINA Guidelines. *Wien Klin Wochenschr*. 2016;128(15–16):541–554. doi:10.1007/s00508-016-1019-4.
- Kutzora S, Weber A, Heinze S, Hendrowarsito L, Nennstiel-Ratzel U, von Mutius E, Fuchs N, Herr C. Asthmatic/wheezing phenotypes in preschool children: Influential factors, health care and urban–rural differences. *Int J Hyg Environ Health*. 2018;221(2):293–299. doi:10.1016/j.ijheh.2017.12.001.
- Depner M, Fuchs O, Genuneit J. Clinical and epidemiologic phenotypes of childhood asthma. *Am J Respir Crit Care Med*. 2014;15(189):129–138.
- Brand PL, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, de Blic J, de Jongste JC, Eber E, Everard ML, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*. 2008;32(4):1096–1110. doi:10.1183/09031936.00002108.
- Thamm R, Poethko-Müller C, Hüther A, Thamm M. Allergische Erkrankungen bei Kindern und Jugendlichen in Deutschland–Querschnittergebnisse aus KiGGS Welle 2 und Trends. 2018.
- Schulz M, Martin E, Dalhoff K, Worth H, Criée CP, Lommatzsch M, Hammelmann E, Schneider A. Nationale VersorgungsLeitlinie Asthma Langfassung. 3. Auflage ed: Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2018.
- Boulet LP, Bateman ED, Brusselle G, Cruz AA, FitzGerald M. Pocket guide for asthma management and prevention (for children 5 years and younger). Global Initiative for Asthma; 2015.
- Guenter K, Boeselt T, Kroenig J, Hildebrandt O, Koehler N, Viniol C, Koehler U. [Asthma control in adults and children must be improved!]. *Pneumologie*. 2018;72(10):681–686. doi:10.1055/a-0629-4242.
- Bolte G, Heissenhuber A, von Kries R, Liebl B, Zapf A, Wildner M, Fromme H, GME-Studiengruppe. [Health monitoring units in Bavaria. Concept, aims and thematic focus of the first survey on children's environment and health]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2007;50(4):476–483. doi:10.1007/s00103-007-0191-0.
- Weber A, Herr C, Hendrowarsito L, Meyer N, Nennstiel-Ratzel U, von Mutius E, Bolte G, Colon D, Kolb S, GME Study Group. No further increase in the parent reported prevalence of allergies in Bavarian preschool children: results from three cross-sectional studies. *Int J Hyg Environ Health*. 2016;219(4–5):343–348. doi:10.1016/j.ijheh.2016.02.001.
- Poethko-Mueller C, Thamm M, Thamm R. Allergic rhinitis and asthma among children and adolescents in Germany. Results of the cross-sectional KiGGS Wave 2 study and trends. *J Health Monit*. 2018;3(1):52–56.
- Granell R, Henderson AJ, Sterne JA. Associations of wheezing phenotypes with late asthma outcomes in the Avon Longitudinal Study of Parents and Children: a population-based birth cohort. *J Allergy Clin Immunol*. 2016;138(4):1060–1070. doi:10.1016/j.jaci.2016.01.046.
- Garcia-Marcos L, Mallol J, Sole D, Brand PL, the EISL Study Group. International study of wheezing in infants: risk factors in affluent and non-affluent countries during the first year of life. *Pediatr Allergy Immunol*. 2010;21(5):878–888. doi:10.1111/j.1399-3038.2010.01035.x.
- von Mutius E, Hartert T. Update in asthma 2012. *Am J Respir Crit Care Med*. 2013;188(2):150–156. doi:10.1164/rccm.201303-0468UP.
- Hallit S, Leynaert B, Delmas MC, Rocchi S, De Blic J, Marguet C, Scherer E, Dufourg MN, Bois C, Reboux G, et al. Wheezing phenotypes and risk factors in early life: the ELFE cohort. *PLoS One*. 2018;13(4):e0196711. doi:10.1371/journal.pone.0196711.
- Cabieses B, Uphoff E, Pinart M, Anto JM, Wright J. A systematic review on the development of asthma and allergic diseases in relation to international immigration: the leading role of the environment confirmed. *PLoS One*. 2014;9(8):e105347. doi:10.1371/journal.pone.0105347.

20. Holguin F, Moughrabieh MA, Ojeda V, Patel SR, Peyrani P, Pinedo M, Celedón JC, Douglas IS, Upson DJ, Roman J. Respiratory health in migrant populations: a crisis overlooked. *Ann Am Thorac Soc*. 2017;14(2):153–159. doi:[10.1513/AnnalsATS.201608-592PS](https://doi.org/10.1513/AnnalsATS.201608-592PS).
21. Tham EH, Loo EXL, Zhu Y, Shek LP. Effects of migration on allergic diseases. *Int Arch Allergy Immunol*. 2019;178(2):128–140. doi:[10.1159/000494129](https://doi.org/10.1159/000494129).
22. Krombholz S. Ritter-Rupp Versorgungsatlas Kinder- und Jugendärzte. Darstellung der regionalen Versorgungssituation sowie der Altersstruktur in Bayern KVB Kassenärztliche Vereinigung Bayerns; 2018.
23. Baldi I, Robert C, Piantoni F, Tual S, Bouvier G, Lebailly P, Raherison C. Agricultural exposure and asthma risk in the AGRICAN French cohort. *Int J Hyg Environ Health*. 2014;217(4–5):435–442. doi:[10.1016/j.ijheh.2013.08.006](https://doi.org/10.1016/j.ijheh.2013.08.006).
24. Pechlivanis S, von Mutius E. Effect of farming on asthma. *Acta Med Acad*. 2020;49(2):144–155. doi:[10.5644/ama2006-124.293](https://doi.org/10.5644/ama2006-124.293).
25. Tarmure S, Alexescu TG, Orasan O, Negrean V, Sitar-Taut AV, Coste SC, Todea DA. Influence of pesticides on respiratory pathology – a literature review. *Ann Agric Environ Med*. 2020;27(2):194–200. doi:[10.26444/aaem/121899](https://doi.org/10.26444/aaem/121899).
26. Ege MJ, Mayer M, Normand A-C, Genuneit J, Cookson WOCM, Braun-Fahrlander C, Heederik D, Piarroux R, von Mutius E, GABRIELA Transregio 22 Study Group. Exposure to environmental microorganisms and childhood asthma. *N Engl J Med*. 2011;364(8):701–709. doi:[10.1056/NEJMoa1007302](https://doi.org/10.1056/NEJMoa1007302).
27. Strömbeck A, Nordström I, Andersson K, Andersson H, Johansen S, Maglio C, Rabe H, Adlerberth I, Wold AE, Hesselmar B, et al. Allergic disease in 8-year-old children is preceded by delayed B cell maturation. *Clin Exp Allergy*. 2017;47(7):918–928. doi:[10.1111/cea.12922](https://doi.org/10.1111/cea.12922).
28. von Mutius E, Vercelli D. Farm living: effects on childhood asthma and allergy. *Nat Rev Immunol*. 2010;10(12):861–868. doi:[10.1038/nri2871](https://doi.org/10.1038/nri2871).
29. Ren CL, Esther CR, Debley JS, Sockrider M, Yilmaz O, Amin N, Bazzi-Asaad A, Davis SD, Durand M, Ewig JM, ATS Ad Hoc Committee on Infants with Recurrent or Persistent Wheezing, et al. Official American Thoracic Society clinical practice guidelines: diagnostic evaluation of infants with recurrent or persistent wheezing. *Am J Respir Crit Care Med*. 2016;194(3):356–373. doi:[10.1164/rccm.201604-0694ST](https://doi.org/10.1164/rccm.201604-0694ST).
30. Kaiser SV, Huynh T, Bacharier LB, Rosenthal JL, Bakel LA, Parkin PC, Cabana MD. Preventing exacerbations in preschoolers with recurrent wheeze: a meta-analysis. *Pediatrics*. 2016;137(6):e20154496–e20154496. doi:[10.1542/peds.2015-4496](https://doi.org/10.1542/peds.2015-4496).
31. Engelkes M, Janssens HM, de Jongste JC, Sturkenboom MC, Verhamme KM. Medication adherence and the risk of severe asthma exacerbations: a systematic review. *Eur Respir J*. 2015;45(2):396–407. doi:[10.1183/09031936.00075614](https://doi.org/10.1183/09031936.00075614).
32. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, Weiss ST. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol*. 2004;114(1):40–47. doi:[10.1016/j.jaci.2004.04.042](https://doi.org/10.1016/j.jaci.2004.04.042).
33. Amin S, Soliman M, McIvor A, Cave A, Cabrera C. Usage patterns of short-acting β_2 -agonists and inhaled corticosteroids in asthma: a targeted literature review. *J Allergy Clin Immunol Pract*. 2020;8(8):2556–2564. doi:[10.1016/j.jaip.2020.03.013](https://doi.org/10.1016/j.jaip.2020.03.013).
34. Nwaru BI, Ekström M, Hasvold P, Wiklund F, Telg G, Janson C. Overuse of short-acting β_2 -agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. *Eur Respir J*. 2020;55(4):1901872. doi:[10.1183/13993003.01872-2019](https://doi.org/10.1183/13993003.01872-2019).
35. Masaki K, Miyata J, Kamatani T, Tanosaki T, Mochimaru T, Kabata H, Suzuki Y, Asano K, Betsuyaku T, Fukunaga K. Risk factors for poor adherence to inhaled corticosteroid therapy in patients with moderate to severe asthma. *Asian Pac J Allergy Immunol*. 2020. doi:[10.12932/AP-311219-0731](https://doi.org/10.12932/AP-311219-0731).