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Asthmatic/wheezing phenotypes in preschool children: Influential factors, health care and urban-rural differences

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ABSTRACT

Background: Different wheezing and asthmatic phenotypes turned out to indicate differences in etiology, risk factors and health care. We examined influential factors and urban-rural differences for different phenotypes.

Methods: Parents of 4732 children filled out a questionnaire concerning children's health and environmental factors administered within the Health Monitoring Units (GME) in a cross-sectional study in Bavaria, Germany (2014/2015). To classify respiratory symptoms, five phenotype groups were built: episodic, unremitting and frequent wheeze, ISAAC (International Study of Asthma and Allergies in Children) – asthma and physician-diagnosed asthma (neither of the groups are mutually exclusive). For each phenotype, health care variables were presented and stratified for residence. Urban-rural differences were tested by Pearson's chi-squared tests. Multivariable logistic regression was performed to analyze associations between influential factors and belonging to a phenotype group, and to compare groups with regard to health care variables as outcome.

Results: Risk factors for wheezing phenotypes were male gender (OR = 2.02, 95%-CI = [1.65–2.48]), having older siblings (OR = 1.24, 95%-CI = [1.02–1.51]), and preterm delivery (OR = 1.61, 95%-CI = [1.13–2.29]) (ORs for unremitting wheeze). 57% of children with ISAAC asthma and 74% with physician-diagnosed asthma had performed allergy tests. Medication intake among all groups was more frequent in rural areas, and physician's asthma diagnoses were more frequent in urban areas.

Conclusions: In accordance with previous research this study confirms that male gender, older siblings and preterm delivery are associated with several wheezing phenotypes. Overall, low numbers of allergy tests among children with physician's diagnoses highlight a discrepancy between common practice and current knowledge and guidelines. Residential differences in health care might encourage further research and interventions strategies.

1. Introduction

Asthma is the most common chronic disease in children. About 10% of children in Western Europe have asthma (The Global Asthma Report 2014, 2014; Schladt et al., 2007) and around 40% of children under six years of age have had at least one wheezing episode (Weiss, 2008; Mallol et al., 2010). Asthma is an umbrella term, and according to the Global Initiative for Asthma, a heterogeneous disease characterized by a variety of symptoms (Anon, 2017).

In children younger than six years it is difficult to diagnose asthma, as among other things, pulmonary function tests cannot be performed reliably before the age of six. In this age, wheezing remains one of the main symptoms of asthma, although it is not clear whether young children who wheeze will develop asthma or not. Different wheezing phenotypes have been defined and investigated in several epidemiological studies (Henderson et al., 2008; Savenije et al., 2011). Although there is increasing evidence that different forms of wheezing may be associated with different risk factors and prognosis, so far neither the

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Table 1
Description of wheezing groups.

Groups	Definition	Prevalence
1. Episodic Wheeze (N = 438)	Ever having wheezing episodes concomitantly together with a cold with fever or rhinitis and no symptoms between those wheezing episodes	9.3%
2. Unremitting Wheeze (N = 491)	Having symptoms between distinct wheezing episodes or having wheeze without a cold with fever or rhinitis.	10.4%
3. Frequent Wheeze (N = 61)	Having more than 4 attacks (wheeze, shortness of breath, asthma or bronchitis) in the last 12 months	1.3%
4. Asthma diagnosis (ISAAC) (N = 371)	A physician's diagnosis of asthma at least once per lifetime or recurrent diagnoses of asthmatic, spastic or obstructive bronchitis	7.8%
5. Physician diagnosed asthma (N = 129)	A physician's diagnosis of asthma	2.7%

Annotation: Wheezing groups are not mutually exclusive.

pathogenesis of wheezing phenotypes nor their relation to asthma have been completely elucidated. Phenotypes in childhood may differ in the likelihood of persisting asthma in later life. Several cohort studies have followed children with respiratory symptoms into their adult life. In the Melbourne Asthma Study (Kelly et al., 1990) children with severe degrees of asthma had a higher probability of persistent asthma in adulthood than children with mild infrequent asthma. There are still deficits in asthma diagnostics. Yeatts et al. (2003), for instance, found that 28% of children between 12 to 14 years of age (North Carolina, USA) from their study had current asthma-like symptoms, and that out of this group, more than 60% had no diagnosis of asthma.

Good medical care in wheezing children is important. Insufficient medical diagnoses may lead to missing therapeutic consequences, e.g. sleep disturbances and absence from school (Yeatts et al., 2003). Tariq et al. (2000) followed a birth cohort and discovered that an early IgE sensitization to hen's egg proteins increases a later risk for asthma. As allergies are a main cause of childhood asthma, allergy anamnesis and testing are recommended (Bundesärztekammer (BÄK), 2009). If the child is allergic, an early intervention may improve children's health considerably or prevent the progression of the disease (Høst et al., 2003).

Further we were interested in comparing residences, as at the time, we were not aware of any data describing urban-rural differences in the health care situation of wheezing preschool children in Bavaria, Germany.

There are two main aims of this study: first, to describe characteristics and potential influential factors of different asthmatic/wheezing phenotypes in preschool children and second to ascertain differences in health care for those phenotypes, also with regard to urban-rural differences.

2. Methods

2.1. Data collection

Health monitoring units (GME) were first established in 2004 by the Bavarian Health and Food Safety Authority with the intention to periodically collect standardized health data of preschool children in order to develop and evaluate intervention and prevention strategies. In the course of a compulsory school entrance examination, parents of preschool children were asked to fill out a questionnaire regarding their children's health and socioeconomic issues. The data analyzed in the present study was collected in 2014/2015 from three urban (Munich, Ingolstadt, Bamberg city) and three rural (Schwandorf, Günzburg, Bamberg rural district) regions within Bavaria with the GME questionnaire. There are regular meetings with school medical assistants and consultation of all involved local health authorities to ensure a standardized data collection. The GME have the approval of the local ethics committees. Bolte et al.'s publication provides further information on the health monitoring units (Bolte et al., 2007).

2.2. Demographic and socioeconomic variables and influential factors

The following variables were analyzed: region of data collection was categorized ("rural" or "urban"), having older siblings ("yes" or "no"), parental school education refers to the highest education of mother or father (low = "Hauptschulabschluss" or no graduation, middle = "Realschulabschluss", "POS" or others, high = "Fachhochschulreife" or "Abitur"), parental smoking habits ("prenatal smoking exposure", "current smoking exposure at home" and "both prenatal smoking exposure and current smoking exposure at home"), country of birth ("Germany" versus "other countries") and underweight at birth or preterm delivery ("yes" or "no"). In addition, age and sex of the children were recorded.

2.3. Asthmatic/wheezing phenotypes and health care

In the questionnaire parents were asked whether their child had ever wheezed, had ever wheezed without having a cold with fever or sniff, wheezed in the last 12 months, had wheeze attacks during the past 12 months ("no attacks", "1–3 attacks", "4–12 attacks" or "more than 12 attacks"), had gasped for breath while talking after one or two words (dyspnea) during the past 12 months, had been symptom free between wheeze attacks, and at what age it had first wheezed. Furthermore, they were asked whether their children had medical diagnoses of asthma ("once", "several times" or "no") or asthmatic/spastic/obstructive bronchitis ("once", "several times" or "no").

Five phenotype groups were constructed similarly to the clinical phenotypes stated in a publication of 2014 by Depner et al. (2014): episodic, unremitting and frequent wheeze, asthma according to ISAAC definition (definition of Asthma according to the ISAAC study (The International Study of Asthma and Allergies in Childhood): either one time physician-diagnosed asthma or more than one time physician-diagnosed obstructive bronchitis) and medically diagnosed asthma (for details see Table 1). A healthy control group was built out of those children who were in none of the five groups. The five phenotype groups are not mutually exclusive, as a child can belong to more than one group at the same time.

Concerning health care, the questionnaire comprised questions about the use of a peak-flow-meter for the assessment of pulmonary function, the intake of medication for airway-related symptoms during the past 12 months, as well as the intake of regular or emergency medication. The parents were also asked whether an allergy test had been performed, whether it had been positive for any allergens and whether the test had been performed by a specialized physician (allergist).

2.4. Statistical analysis

Sociodemographic characteristics of phenotype groups and health care stratified by residency are summarized in two descriptive tables

Table 2
Sociodemographic characteristics and influential factors.

Characteristics/influential factors	Total population N = 4732		Healthy controls N = 3689		Episodic wheeze N = 438		Unremitting wheeze N = 491		Frequent wheeze N = 61		ISAAC Asthma N = 371		Physician-diagnosed Asthma N = 129	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	5.3	0.5	5.3	0.5	5.2	0.4	5.4	0.5	5.5	0.7	5.4	0.5	5.4	0.4
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex male	2418	51.1	1780	48.3	252	57.5	324	66.0	38	62.3	244	65.8	86	66.7
Urban residency	2512	53.1	1998	54.2	215	49.1	248	50.5	28	45.9	181	48.8	75	58.1
Rural residency	2215	46.8	1686	45.7	223	50.9	243	49.5	33	54.1	190	51.2	54	41.9
Older siblings	2206	46.6	1694	45.9	203	46.4	253	51.5	32	52.5	198	53.4	76	58.9
Underweight at birth or preterm delivery	293	6.2	199	5.4	47	10.7	42	8.6	8	13.1	47	12.7	9	7.0
Prenatal smoking exposure and current smoking exposure at home	61	1.3	47	1.3	7	1.6	6	1.2	1	1.6	2	0.5	0	0.0
Current smoking exposure at home	127	2.7	92	2.5	8	1.8	22	4.5	1	1.6	10	2.7	2	1.6
Prenatal smoking exposure	322	6.8	246	6.7	23	5.3	44	9.0	2	3.3	24	6.5	9	7.0
Country of birth Germany	4440	93.8	3442	93.3	427	97.5	467	95.1	60	98.4	350	94.3	117	90.7
Parental education														
low ^a	850	18.0	668	18.1	55	12.6	106	21.6	12	19.7	48	12.9	19	14.7
middle ^a	1425	30.1	1075	29.1	148	33.8	161	32.8	24	39.3	127	34.2	48	37.2
high ^a	2295	48.5	1797	48.7	232	53.0	217	44.2	24	39.3	192	51.8	60	46.5

Annotations: ^a refers to highest education of mother or father: 'low' is "Hauptschulabschluss" or no graduation, 'middle' is "Realschulabschluss, POS or other, 'high' is "Fachhochschulreife oder Abitur.

(Tables 2 and 4). Urban-rural differences were tested using Pearson's chi-squared test. In order to explore multivariate associations between influential factors and phenotypes, ORs were calculated with a multivariable logistic regression analysis. To compare unremitting to episodic wheeze and frequent to episodic wheeze, a logistic regression model adjusted for age, sex, older siblings, preterm delivery, parental education, and country of birth was calculated.

Significance was tested at a 0.05 significance level. Results are presented as ORs with 95% confidence intervals (95%-CI). All statistical analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Description of the study population

Data from 4732 children (mean age 5.3 years, 51.1% males) were available (response rate 56.9%), and just over half of them (53.1%) lived in urban areas. There were 438 children assigned to "Episodic Wheeze" (9.3%), 491 to "Unremitting Wheeze" (10.4%), 61 to "Frequent Wheeze" (1.3%), 371 to "Asthma diagnoses (ISAAC)" (7.8%) and 129 to "Physician diagnosed asthma" (2.7%) (Table 1). Between 51.5% (unremitting wheeze) and 58.9% (physician diagnosed asthma) of children had older siblings. Prevalence of preterm deliveries varied between 7.0% and 13.1% in the phenotype groups. For more details see Table 2. For the proportion of the phenotype groups in the six different study regions see Supplement Table 2.

3.2. Associations between influential factors and wheezing phenotypes

Odds ratios describing associations between influential factors and phenotype groups are presented in Table 3. Boys are statistically significantly more likely to belong to one of the groups. The greatest effect can be observed for boys with unremitting wheeze (OR = 2.02; 95%-CI: [1.65–2.48]) and for children with ISAAC asthma (OR = 2.04; 95%-CI: [1.62–2.57]). There was a positive association between rural residency and belonging to any of the groups, except for children with physician-diagnosed asthma. Having older siblings was a significant risk factor for unremitting wheeze (OR = 1.24; 95%-CI: [1.02–1.51]), ISAAC asthma (OR = 1.38; 95%-CI: [1.11–1.72]) and physician-diagnosed asthma

(OR = 1.70; 95%-CI: [1.18–2.45]). Preterm children turned out to have a higher risk for phenotypes, particularly for frequent wheeze (OR = 2.83; 95%-CI: [1.31–6.11]) and ISAAC asthma (OR = 2.62; 95%-CI: [1.85–3.70]). Smoking exposure at home was statistically significantly associated with unremitting wheeze (OR = 1.79; 95%-CI: [1.09–2.95]).

3.3. Health care and urban-rural differences

As shown in Table 4, the percentage of children with a physician's asthma diagnosis was 36.1% for frequent, 17.1% for unremitting and 4.3% for episodic wheeze. Asthma diagnoses were more likely to be made in urban areas. A statistically significant difference in residences was observed for episodic wheeze (urban: 6.5%, rural: 2.2%) and ISAAC asthma (urban: 41.4%, rural: 28.4%). 90.2% of the children with frequent wheeze, 70.6% with ISAAC asthma and 61.5% with unremitting wheeze took medication for airway-related symptoms. Medication intake was more frequent in rural areas. There was a significant urban-rural difference for medication intake for the total population (urban: 10.4%, rural: 13.9%) and for episodic wheeze (urban: 40.0%, rural: 53.4%).

Prevalence rates of allergy tests were 29.2% (episodic wheeze), 56.9% (ISAAC asthma) and 75.4% (frequent wheeze). The incidence of allergic sensitization was 39.3% for frequent wheeze, 28.3% for ISAAC asthma, 48.8% for physician-diagnosed asthma, 21.1% for unremitting wheeze and 10.7% for episodic wheeze. More allergy tests were performed in rural areas, but with no significant difference to urban areas.

Children with frequent wheeze were 19 times (OR = 19.12, CI = [8.53–42.85]) more likely and children with unremitting wheeze 5 times (OR = 5.23, CI = [3.09–8.86]) more likely to have an asthma diagnosis than those with episodic wheeze (see Supplement Table 1).

4. Discussion

Children were divided into five phenotype groups and examined with regard to potential influential factors and health care in urban and rural areas. Main risk factors for asthmatic/wheezing phenotypes were male gender, having older siblings and preterm delivery. The percentage of performed allergy tests in children with ISAAC asthma was 56.9%. Medication intake was more frequent in rural areas, and asthma

Table 3
Adjusted Odds Ratios—associations between influential factors and wheezing groups.

Influential factor	Odds ratio (95% CI)	Episodic wheeze (n = 438)	Unremitting wheeze (n = 491)	Frequent wheeze (n = 61)	ISAAC asthma (n = 371)	Physician's diagnosed asthma (n = 129)
Age		0.89 (0.72–1.09)	1.18 (0.98–1.42)	1.57 (0.98–2.50)	1.18 (0.96–1.47)	1.21 (0.86–1.68)
Sex (male vs. female)		1.45 (1.18–1.77)	2.02 (1.65–2.48)	1.65 (0.97–2.80)	2.04 (1.62–2.57)	1.87 (1.29–2.72)
Residency (rural vs. urban)		1.25 (1.01–1.54)	1.07 (0.87–1.31)	1.19 (0.70–2.04)	1.22 (0.97–1.54)	0.74 (0.51–1.07)
Older Siblings		1 (0.82–1.23)	1.24 (1.02–1.51)	1.32 (0.78–2.21)	1.38 (1.11–1.72)	1.7 (1.18–2.45)
Underweight at birth or preterm delivery		1.64 (1.14–2.37)	1.61 (1.13–2.29)	2.83 (1.31–6.11)	2.62 (1.85–3.70)	1.3 (0.65–2.60)
Smoking during pregnancy and current smoking at home vs. never smoking		1.28 (0.57–2.89)	0.82 (0.34–1.95)	0.88 (0.12–6.61)	0.41 (0.10–1.70)	n.a.
Current smoking at home vs. never smoking		0.74 (0.35–1.54)	1.79 (1.09–2.95)	0.54 (0.07–4.03)	1.08 (0.55–2.12)	0.47 (0.11–1.94)
Smoking during pregnancy vs. never smoking		0.77 (0.48–1.23)	1.35 (0.95–1.92)	0.4 (0.10–1.69)	1.04 (0.66–1.63)	0.93 (1.44–1.94)
Country of birth Germany		2.23 (1.20–4.14)	1.3 (0.82–2.08)	3.49 (0.48–25.43)	0.97 (0.61–1.56)	0.54 (0.29–1.00)
Parental education		1.58 (1.14–2.17)	0.86 (0.66–1.13)	0.76 (0.37–1.57)	1.62 (1.14–2.29)	1.01 (0.59–1.73)
High vs. low		1.64 (1.18–2.28)	1.01 (0.77–1.32)	1.25 (0.62–2.53)	1.7 (1.19–2.43)	1.48 (0.86–2.55)

Annotations: Subjects without a given risk factor were assigned a value of 0 and those with the risk factor a value of 1; logistic regressions were performed comparing each of the groups with the “healthy control group”; Odds ratios have been adjusted in the model for all the other risk factors listed; CI denotes confidence interval.

diagnoses were more frequent in urban areas.

For defining phenotype groups, we drew upon a classification used by Depner et al. (2014), which analyzed data from the PASTURE birth cohort study (N = 953) in five European countries with annual surveys until children reached the age of six. As our data was derived from a cross-sectional study, the longitudinal design of PASTURE may serve as an explanation for the continuously higher prevalence of corresponding groups compared to the present study. While defining the phenotypes, they asked for symptoms occurring during at least one or two of eight follow-up periods. In a cross-sectional design, the likelihood of a symptom to be reported is reduced due to the data not being collected multiple times. As expected, with percentages of 19.5% compared to 9.3% for episodic wheeze, 22.6% compared to 10.4% for unremitting wheeze, 8.5% compared to 1.3% for frequent wheeze, 8.4% compared to 7.8% for ISAAC asthma and 8.4% compared to 2.7% for physician-diagnosed asthma, higher prevalences were found in the PASTURE study. The KIGGS study (German Health Interview and Examination Survey for Children and Adolescents) (2009–2012) reported a 6.7% lifetime prevalence of asthma diagnoses in 3–6 year old German children (Schmitz et al., 2014). In the present study, the prevalence of asthma diagnoses was lower (2.7%).

More males were found in all groups. This result is consistent with previous research (Granell et al., 2016; Mandhane et al., 2005; Garcia-Marcos et al., 2005; Castro-Rodriguez et al., 2000).

Having older siblings was a significant risk factor for unremitting wheeze and ISAAC asthma in our study. Results of previous studies are inconsistent. One study from Ball et al. (2000) showed a protective effect regarding the development of asthma in American children (6–13 years old) with older siblings, while others showed that wheezing was positively related to having older siblings as in the PASTURE birth cohort (Loss et al., 2016).

We were also able to show that preterm children are at a higher risk of being in one of the phenotype groups. This matches results observed in previous studies summarized in a meta-analysis of childhood wheezing disorders by Been et al. (2013).

In this study, rural residence was a risk factor particularly for phenotypes with episodic wheeze. Although a study from Cyprus found

an increase in asthmatic symptoms specific to rural areas (Kolokotroni et al., 2011), most studies reveal that urban living environment are the risk factor; this is mainly based on the hygiene hypothesis already postulated by Strachan (1989) in 1989. Microbial stimuli in rural living environments could lead to a preventive effect on the development of asthma in children. Information about residence in the first years of life is not available in our study.

Smoking behavior of parents sometimes even showed a negative association with wheezing phenotypes, particularly with frequent wheeze. One possible explanation may be that the child's disease influences the smoking behavior of parents (Jaakkola et al., 1994) so that they might smoke less or quit smoking (Meinert et al., 1994). This is known as the “healthy passive smoker”-effect (Meinert et al., 1994).

Appropriately, those with the most severe phenotype in our study, children with frequent wheeze, were more likely to receive a medical asthma diagnosis, while children with episodic wheeze were less likely to have a diagnosis.

Physician-diagnosed asthma showed urban-rural differences, being more frequent in urban areas among all phenotypes. So far, results regarding this topic are inconsistent. No difference in residence for current asthma was found in Portuguese children aged 0–17 (Ferreira-Magalhaes et al., 2016), as well as for “asthma diagnoses ever” in Greek children aged 8–10 (Priftis et al., 2007). On the other hand, Solé et al., who analyzed ISAAC data of 13- to 14-year-olds in Brazil, found a significantly higher rate of “lifetime asthma diagnosis” in children living in urban areas (Solé et al., 2007). In our study, we identified significantly more asthma diagnoses in urban areas for episodic wheeze and ISAAC asthma. A possible explanation for this urban-rural gap may be that there are more specialized physicians in urban areas. Another possible reason for the higher rate of asthma diagnosis in urban environments of Brazil and Germany could be that their cities are more dense and have higher levels of indoor (e.g., second-hand smoke infiltrating from units within multi-family buildings) and outdoor (e.g., proximity to high traffic and diesel exhaust) asthma triggers.

In our study, 90.2% of children with frequent wheeze took medication. However, about half of the children with episodic wheeze and about 38% of those with unremitting wheeze did not. Those children

Table 4
Parental report of health care stratified by urban-rural residency.

	Total population			Episodic wheeze			Unremitting wheeze			Frequent wheeze			ISAAC asthma			Physician-diagnosed asthma		
	Total n = 4732 n%	Urban n = 2512 n%	Rural n = 2215 n%	Total n = 438 n%	Urban n = 215 n%	Rural n = 223 n%	Total n = 491 n%	Urban n = 248 n%	Rural n = 243 n%	Total n = 61 n%	Urban n = 28 n%	Rural n = 33 n%	Total n = 371 n%	Urban n = 181 n%	Rural n = 190 n%	Total n = 129 n%	Urban n = 75 n%	Rural n = 54 n%
Airway related symptoms																		
Current wheeze	401	196	205	123	58	65	256	127	129	61	28	33	165	80	85	77	42	35
(in the last 12 months)	8.5	7.8	9.3	28.1	27.0	29.2	52.1	51.2	53.1	100.0	100.0	100	44.5	44.2	44.7	59.7	56.0	64.8
Dyspnea after one or two words while talking (in the last 12 months)	55	25	30	5	4	1	49	21	28	19	9	10	32	14	18	20	12	8
Medical Supply																		
Physician-diagnosed asthma	129	75	54	19	14	5	84	44	40	22	11	11	129	75	54	–	–	–
Medication intake for airway related symptoms (in the last 12 months)	2.7	3.0	2.4	4.3	6.5	2.2	17.1	17.7	16.5	36.1	39.3	33.3	34.8	41.4	28.4	105	61	44
-regular medication intake	117	54	63	23	10	13	79	38	41	56	10	16	82	39	43	51	28	23
-emergency medication intake	2.5	2.2	2.8	5.3	4.7	5.8	16.1	15.3	16.9	91.8	35.7	48.5	22.1	21.6	22.6	39.5	37.3	42.6
Child owns peak-flow meter	76	33	43	16	6	10	51	23	28	21	5	16	61	27	34	40	21	19
Allergy test performed	932	473	459	128	61	67	223	108	115	46	21	25	211	100	111	95	56	39
– and positive for an allergen	19.7	18.8	20.7	29.2	28.4	30.0	45.4	43.6	47.3	75.4	75.0	75.8	56.9	55.3	58.4	73.6	74.7	72.2
– and diagnosed by an allergist	347	173	174	47	26	21	104	54	50	24	14	10	105	57	48	63	40	23
	7.3	6.9	7.9	10.7	12.1	9.4	21.2	21.8	20.6	39.3	50.0	30.3	28.3	31.5	25.3	48.8	53.3	42.6
	134	77	57	17	10	7	47	27	20	14	10	4	50	29	21	32	22	10
	2.8	3.1	2.6	3.9	4.7	3.1	9.6	10.9	8.2	23.0	35.7	12.1	13.5	16.0	11.1	24.8	29.3	18.5

Annotation: Over the whole study population there are 5 children, where information about residency was not available.

* Numbers marked by an asterisk are significant with $p < 0.05$; Chi-square test (urban-rural difference).

might benefit from a preventive potential of medical treatment. A population-based survey in Portugal reported that children with current asthma from rural areas were less likely to have used any inhalation therapy in the previous 12 months (OR = 0.20; 95%-CI: [0.09–0.43]) (Eigenmann et al., 2013). This is contrary to our observation that medication intake was significantly higher for all children in rural areas. One possible explanation could be that there are fewer specialists in rural areas who would prescribe medication. No urban-rural difference for medication intake could be observed for frequent wheeze and ISAAC asthma, indicating no urban-rural difference in medical treatment of severe cases. On the other hand, moderate phenotypes, such as episodic wheeze, showed a difference in favor of children in rural areas. However, it is difficult to differentiate whether differences are due to overtreatment in one area or undertreatment in another. At this point, further research is needed.

One important finding of this study was that allergy testing was performed less often than recommended (Høst et al., 2003; Eigenmann et al., 2013), especially in the children with medical diagnoses. The diagnosis asthma or obstructive bronchitis implies that these children have been seen by a medical doctor, but 43.1% of children with ISAAC asthma did not undergo allergy testing. This may conceivably indicate an insufficient health care situation in those areas where the study was conducted. In a Portuguese study by Ferreira-Magalhaes et al. (Ferreira-Magalhaes et al., 2016), 79.9% of children with current asthma reported prior allergy testing. In our study, 73.6% of children with physician-diagnosed asthma had allergy testing. In another German-Dutch study, 37.6% of 6- to 7-year old German children had medically diagnosed allergies (Mommers et al., 2005), while in our study, 7.3% of all children had a positive allergy test.

Usage of a parental questionnaire in order to monitor children's health can result in recall bias or selection bias. Parents with chronically ill children could be more interested in answering a questionnaire concerning the health of their children. We have a response rate of 56.9%, which could lead to differences between those who participated and those who didn't. This could create a participation bias. Because of the cross-sectional study design, statements about temporal relationships or changes of environmental exposures in the children's development cannot be made.

Due to the limited number of questions in the GME questionnaire, some questions reflecting important influential factors regarding wheezing and asthma outcomes are missing, e.g. family history of asthma, pollution or breast feeding. A change in the odds ratios by adjusting for these missing factors is conceivable.

Large sample size, a reasonable response rate and data of good quality data are powerful factors of our study. Questions about asthma and wheezing symptoms have a high comparability, as they are in part identical to the ISAAC questionnaire used by many studies.

5. Conclusion

In accordance with previous research, this study confirmed that male gender, older siblings and preterm delivery were associated with different wheezing patterns and physician-diagnosed asthma, revealing differences in wheezing phenotypes. Addressing health care, overall low rates of allergy tests in children with medical diagnoses highlight a discrepancy to current knowledge and guidelines. Therefore, health care of Bavarian preschoolers concerning airway-related disorders and allergies needs improvement. We observed that severe cases (frequent wheeze) report more medication intake and medical diagnoses of asthma, while medication intake was less frequently accompanied by doctors diagnosis in rural than in urban areas.

Conflict of interest

None declared.

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None.

Appendix A

GME Study Group: Health Authority of the District Office of Bamberg (Wiltrud Doerk, Angelika Pfister, Rosemarie Sittig, Winfried Strauch, Heidi Thamm, Anita Wunder); Health Authority of the District Office of Günzburg (Tatjana Frieß-Hesse, Franziska Lang, Dagmar Rudolph, Roland Schmid, Gudrun Winter); Health Authority of the City Ingolstadt (Isabella Bockmann, Christine Gampenrieder, Margot Motzet, Elisabeth Schneider, Traudl Tontsch, Gerlinde Woelk); Department of Health and Environment, City of Munich (Sylvia Kranebitter, Heidi Mayrhofer, Gertraud Rohrhirsch, Brigitte Weise, Luisa Wolf); Health Authority of the District Office of Schwandorf (Kornelia Baranek, Gitte Koch-Singer, Maximilian Kühnel); Institute of Social Pediatrics and Adolescent Medicine, Ludwig-Maximilians-University Munich (Ladan Baghi, Otmar Bayer, Rüdiger von Kries); Bavarian Health and Food Safety Authority, Munich and Oberschleißheim (Gabriele Bolte, Hermann Fromme, Annette Heißenhuber, Lana Hendrowarsito, Caroline Herr, Martina Kohlhuber, Joseph Kuhn, Bernhard Liebl, Anja Lüders, Nicole Meyer, Christine Mitschek, Gabriele Morlock, Michael Mosetter, Uta Nennstiel-Ratzel, Dorothee Twardella, Manfred Wildner, Angelika Zirngibl).

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ijheh.2017.12.001>.

References

- <http://ginasthma.org/>. Global initiative for Asthma.
- Ball, T., Castro-Rodriguez, J., Siblings, Griffith K., et al., 2000. Day-care attendance, and the risk of asthma and wheezing during childhood. *N. Engl. J. Med.* 343, 538–543.
- Been, J., Marlies, J., Smets, E., et al., 2013. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. *PLoS Med.* 11 (1), e1001596.
- Bolte, G., Heissenhuber, A., von Kries, R., et al., 2007. Health monitoring units in Bavaria Concept, aims and thematic focus of the first survey on children's environment and health. *Bundesgesundheitsbl* 50, 476.
- Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBK), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Asthma – Kurzfassung, 2. Auflage. Version 5. 2009, zuletzt geändert: August 2013. Available from: <http://www.versorgungsleitlinien.de/themen/asthma> [cited: 18.07.2016].
- Castro-Rodriguez, J., Holberg, C., Wright, A., Martinez, F., 2000. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am. J. Respir. Crit. Care Med.* 162, 1403–1406.
- Depner, M., Fuchs, O., Genuneit, J., et al., 2014. Clinical and epidemiologic phenotypes of childhood asthma. *Am. J. Respir. Crit. Care Med.* 189 (2), 129–138.
- Eigenmann, P., Atanaskovic-Markovic, M., O'B Hourihane, J., et al., 2013. Testing children for allergies: why, how, who and when: an updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) section on pediatrics and the EAACI-Clemens von Pirquet Foundation. *Pediatr. Allergy Immunol.* 24 (2), 195–209.
- Ferreira-Magalhaes, M., Sa-Sousa, A., Morais-Almeida, M., et al., 2016. Asthma-like symptoms, diagnostic tests, and asthma medication use in children and adolescents: a population-based nationwide survey. *J. Asthma* 53 (3), 269–276.
- Garcia-Marcos, L., Castro-Rodriguez, J., Suarez-Varela, M., Garrido, J., et al., 2005. A different pattern of risk factors for atopic and non-atopic wheezing in 9–12-year-old children. *Pediatr. Allergy Immunol.* 16 (6), 471–477.
- Granell, R., Henderson, A., Sterne, J., 2016. 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.* 138 (4), 1060–1070.
- Høst, A., Andrae, S., Charkin, S., et al., 2003. Allergy testing in children: why, who, when and how. *Allergy* 58, 559–569.
- Henderson, J., Granell, R., Heron, J., et al., 2008. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. *Thorax* 63 (11), 974–980.
- Jaakkola, N., Ruotsalainen, R., Jaakkola, J., 1994. What are the determinants of children's exposure to environmental tobacco smoke at home? *Scand. J. Soc. Med.* 2, 107–112.
- Kelly, W., Hudson, P., Phelan, et al., 1990. Atopy in subjects with asthma followed to the age of 28 years. *J. Allergy Clin. Immunol.* 85, 548–557.
- Kolokotroni, O., Middleton, N., Nicolaou, N., et al., 2011. Temporal changes in the

- prevalence of childhood asthma and allergies in urban and rural areas of Cyprus: results from two cross sectional studies. *BMC Public Health* 11, 858.
- Loss, G., Depner, M., Hose, A., et al., 2016. The early development of wheeze: environmental determinants and genetic susceptibility at 17q21. *Am. J. Respir. Crit. Care Med.* 193 (8), 889–897.
- Mallol, J., García-Marcos, L., Solé, D., et al., 2010. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. *Thorax* 65, 1004–1009.
- Mandhane, P., Greene, J., Cowan, J., Taylor, D., Sears, M., 2005. Sex differences in factors associated with childhood- and adolescent-onset wheeze. *Am. J. Respir. Crit. Care Med.* 172 (1), 45–54.
- Meinert, R., Fischer, T., Kuehr, J., 1994. The “healthy passive smoker”: relationship between bronchial hyper-reactivity in school children and maternal smoking. *J. Epidemiol. Community Health* 48, 325–326.
- Mommers, M., Swaen, G., Weishoff-Houben, M., Dott, W., van Schayck, C., 2005. Differences in asthma diagnosis and medication use in children living in Germany and the Netherlands. *Prim. Care Respir. J.* 14 (1), 31–37.
- Priftis, K., Anthracopoulos, M., Paliatatos, A., et al., 2007. Different effects of urban and rural environments in the respiratory status of Greek schoolchildren. *Respir. Med.* 101 (1), 98–106.
- Savenije, O., Granell, R., Caudri, D., et al., 2011. Comparison of childhood wheezing phenotypes in 2 birth cohorts: ALSPAC and PIAMA. *J. Allergy Clin. Immunol.* 127 (6), 1505–1512.
- Schlaud, M., Atzpodien, K., Thierfelder, W., 2007. Allergic diseases. results from the german health interview and examination survey for children and adolescents (KiGGS). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 50 (5), 701–710.
- Schmitz R., Thamm M., Ellert U.M., et al. Verbreitung häufiger Allergien bei Kindern und Jugendlichen in Deutschland - Ergebnisse der KiGGS-Studie - Erste Folgebefragung (KiGGS Welle1) *Bundesgesundheitsbl* 2014;57 (7):771-8.
- Solé, D., Cassol, V., Silva, A., et al., 2007. Prevalence of symptoms of asthma, rhinitis, and atopic eczema among adolescents living in urban and rural areas in different regions of Brazil. *Allergol. Immunopathol.* 5 (6), 248–253.
- Strachan, D., 1989. Hay fever, hygiene, and household size. *BMJ* 299, 1259.
- Tariq, S., Matthews, S., Hakim, E., Arshad, S., 2000. Egg allergy in infancy predicts respiratory allergic disease by 4 years of age. *Pediatr. Allergy Immunol.* 11, 162–167.
- The Global Asthma Report 2014. Auckland, New Zealand: Global Asthma Network, 2014.
- Weiss, L., 2008. The diagnosis of wheezing in children. *Am. Fam. Phys.* 77 (8), 1109–1114.
- Yeatts, K., Shy, C., Sotir, M., et al., 2003. Health consequences for children with undiagnosed asthma-like symptoms. *Arch. Pediatr. Adolesc. Med.* 157, 540–544.

Supplement Table 1: Comparison of single groups concerning health care

Odds ratio (95% CI)	PHYSICIAN- DIAGNOSED ASTHMA	MEDICATION			CHILD OWNS PEAK-FLOW METER	ALLERGY TEST PERFORMED
		INTAKE FOR AIRWAY RELATED SYMPTOMS *	REGULAR MEDICATION INTAKE	EMERGENCY MEDICATION INTAKE		
Unremitting ^a (n=491) vs. episodic wheeze ^b (n=438)	5.23 (3.09 - 8.86)	1.68 (1.26 - 2.25)	2.72 (1.60 - 4.62)	0.97 (0.63 - 1.50)	2.88 (1.61 - 5.18)	1.93 (1.46 - 2.55)
Frequent ^c (n=61) vs. episodic wheeze (n=438)	19.12 (8.53 - 42.85)	7.53 (2.91 - 19.46)	7.12 (3.19 - 15.88)	0.87 (0.42 - 1.79)	10.97 (4.98 - 24.19)	6.97 (3.57 - 13.62)

Annotations: CI denotes confidence interval; Odds ratios have been adjusted in the logistic-regression model for age, sex, older siblings, preterm delivery, parental education and country of birth; ^a unremitting wheeze: symptoms between the attacks or wheezing ever without having a cold or the flu; ^b episodic wheeze: Wheezing ever without a cold and symptom-free between attacks; ^c frequent wheeze: More than 4 attacks in last 12 months; Intersections between the applied groups were: unremitting wheeze $\cap$ episodic wheeze = 0, frequent wheeze $\cap$ episodic wheeze = 8,

Supplement Table 2: Proportion of phenotype groups in six different study regions

	Urban 1 (München)	Urban 2 (Ingolstadt)	Urban 3 (Bamberg -urban)	Rural 1 (Günzburg)	Rural 2 (Bamberg -rural)	Rural 3 (Schwandorf)	Total population
	n %	n %	n %	n %	n %	n %	n %
Episodic wheeze	108 24.7	75 17.1	32 7.3	80 18.3	73 16.7	70 16.0	438 100
Unremitting wheeze	136 27.7	95 19.6	17 3.5	92 18.7	68 13.9	83 16.9	491 100
Frequent wheeze	15 24.6	12 19.7	1 1.6	16 26.2	9 14.8	8 13.1	61 100
ISAAC asthma	114 30.7	53 14.3	14 3.8	75 20.2	48 12.9	67 18.1	371 100
Physician- diagnosed asthma	46 35.7	26 20.2	3 2.3	20 15.5	9 7.0	25 19.4	129 100
Medication intake for airway related symptoms (in the last 12 months)	153 26.8	88 15.4	21 3.7	123 21.6	83 14.6	102 17.9	570 100