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Time trends in asthma and atopic diseases in North-West part of Croatia—ISAAC Phase III (2013)

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Abstract
Aim: The authors conducted two cross-sectional studies 8 years apart with the aim of assessing temporal trends in the prevalence of asthma and atopic diseases in Međimurje County, Northwestern Croatia.
Methods: Studies were conducted in children aged 12 years 0 months to 14 years 11 months in 2005 and in 2013; additionally, in adolescents aged 18 years in 2013 according to the international study on asthma and allergies protocol.
Results: In the age group 12–14 years, a significant increase in the prevalence of asthma (5.1% vs 8.31%), allergic rhinitis (10.86% vs 16.24%), allergic rhinoconjunctivitis (7.14% vs 10.95%) and atopic dermatitis (5.34% vs 8.12%) was observed. When the age group 12–14 years in 2005 was compared with the age group 18 years in 2013, a significant increase in symptoms of asthma (5.1% vs 11.5%), allergic rhinitis (10.86% vs 19.59%), allergic rhinoconjunctivitis (7.14% vs 14.25%), and atopic dermatitis (5.34% vs 7.69%) was observed.
Conclusion: This study shows an increasing trend in Međimurje County in the prevalence of all symptoms associated with atopic diseases: Asthma, allergic rhinitis, allergic rhinoconjunctivitis, and atopic dermatitis.

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Introduction

The encumbrance of asthma and atopic diseases continues to increase worldwide. Together with other atopic diseases, it is the most common chronic disease in children. Most of the data in children come from the Multicenter International Study of Childhood Asthma and Allergies (ISAAC), which provided the standardized methodology for international and interregional data comparison. ISAAC Phase III was a repeat of Phase I, 5 or more years after Phase I, with the aim of examining temporal trends in asthma, allergic rhinitis, and eczema.[1,2] The studies conducted in Croatia and different Croatian regions show variability in the prevalence of asthma, allergic rhinitis, and atopic dermatitis.[3–10]

The aim of this study was to evaluate the temporal trends in the prevalence of asthma and atopic diseases in children in Međimurje County, northwestern Croatia, by comparing data from children of the same age in the period of 8 years and data from children who performed ISAAC Phase I and Phase III in the period of 8 years.

Materials and methods

The authors conducted two cross-sectional surveys 8 years apart (Phase I 2005, Phase III 2013) following the ISAAC protocol in the Međimurje region in northwestern Croatia.[11] This region is located between Eastern Alps and Pannonian Plain, which is characterized by a rural environment. The climate is humid continental, with warm summers and cold winters.

The target population was children aged 12 years 0 months to 14 years 11 months (6th to 8th grade). In 2013, the authors conducted the same survey among adolescents aged 18 years. The total population of children in Međimurje County aged 12 years to 14 years 11 months was 4307. The total population of 18-year-olds was 1545.

Data were collected using a standardized ISAAC written questionnaire. All standardized modules were translated from English to Croatian by physicians specialized in asthma and allergies according to the translation guidelines.[12]

The correctness of the questionnaire was verified by back-translation by an independent professional translator. Ethical approval was obtained from the local ethics committee before the start of the study. Any discrepancies found were clarified through telephone conversations with the parents. Data analysis was performed using MedCalc version 19.5.3. Basic descriptive summaries of the data were made, and differences between the groups studied were calculated by cross-tabulation and the chi-square test. A *p* value of 0.05 indicated a statistically significant difference.

Results

The authors included 27 primary schools in the Međimurje region. Phase I included 3111 children and Phase III included 1059 children in the age group of 12 years 0 months to 14 years 11 months. The response rate of Phase I was 84.33% and that of Phase III was 92.41%. In 2013, the authors conducted the same survey among 1067 adolescents aged 18 years. The response rate was 94.84%. Descriptive statistics of the study population are shown in Table 1.

(1) Time trends in asthma, allergic rhinitis, and atopic dermatitis prevalence among 12–14-year-old children:

The results of these two studies showing the time trends in the prevalence (%) of asthma, allergic rhinitis, atopic dermatitis, and their symptoms in 12–14-year-old children (2005 and 2013) are shown in Table 2.

Comparing the results of this study from 2005 with those from 2013, there was a significant increase in the symptom of wheezing ever (11.86 to 21.44%, $p < 0.0001$) and wheezing in the past 12 months (5.11 to 8.31%, $p = 0.0002$). In 2005, the prevalence was statistically higher in the males; while in 2013, the authors observed no gender difference.

When looking at the changes in the prevalence of rhinitis between 2005 and 2013, a statistically significant increase was observed (10.86 to 16.24%, $p < 0.0001$). In 2005, the prevalence was statistically higher in boys than in girls (13.82% in boys vs 10.69% in girls; odds ratio [OR]: 1.34, 95% confidence interval [CI]: 1.08–1.66, $p = 0.0091$), while in 2013 no difference was observed between the genders. The increase is also observed in symptoms of rhinitis combined with conjunctivitis (7.14 to 10.95%, $p = 0.0001$)

The prevalence of itchy skin rash also increased significantly between 2005 and 2013 (5.34% vs 8.12%, $p = 0.0011$). The gender difference changed from a dominant female prevalence (boys: 3.97%, girls: 6.63%; OR: 0.58, 95% CI: 0.42–0.81, $p = 0.0013$) to a male prevalence (boys: 10.86%, girls: 5.43%; OR: 2.12, 95% CI: 1.33–3.37, $p = 0.0015$). When considering lifetime eczema, the authors found significantly higher rates in girls (boys 11.24% vs 16.10% in girls; OR: 0.66, 95% CI: 0.46–0.94, $p = 0.0219$).

The gender differences in the prevalence of asthma, allergic rhinitis, atopic dermatitis, and their symptoms are shown in Table 3.

(2) Time trends in the prevalence of asthma, allergic rhinitis, and atopic dermatitis between 12–14-old children in 2005 and 18-year-old participants in 2013

The results of the two studies showing the time trends in the prevalence (%) of asthma, allergic rhinitis, atopic dermatitis and their symptoms in 12–14-year-olds and 18-year-olds (2005 and 2013) are shown in Table 4.

Table 1 Descriptive statistics of the study population.

	12-14-year-old children						
	Boys		Girls		Total		Response
Survey	N	%	N	%	N	%	rate (%)
2005	1512	48.86	1599	51.14	3111	100	94.33
2013	525	49.58	534	50.42	1059	100	92.41
	18-years-old children						
	Boys		Girls		Total		
	N	%	N	%	N	%	
2013	531	49.77	536	30.23	1067	100	94.86

Table 2 Time trends in the prevalence (%) of asthma, allergic rhinitis, atopic dermatitis, and their symptoms in 12–14-year-old children (2005 and 2013).

	12-14-year-old children				
	2005		2013		
	Total		Total		
	N = 3111		N = 1059		
	N	%	N	%	p*
Wheezing ever	369	11.86	227	21.44	<**0.0001**
Wheezing in the past year	159	5.11	88	8.31	=**0.0002**
Exercise-induced wheezing in the past year	225	7.23	105	9.92	**0.0054**
Night wheezing in the past year	72	2.31	28	2.64	0.5451
Dry night cough in the past year	209	6.71	126	11.89	<**0.0001**
Asthma ever	220	7.07	98	9.25	**0.0212**
Rhinitis symptoms ever	660	12.21	192	18.31	**0.0317**
Rhinitis symptoms in the past year	338	10.86	172	16.24	<**0.0001**
Rhinoconjunctivitis symptoms in the past year	222	7.14	116	10.95	**0.0001**
Itchy rash ever	218	7.01	145	13.69	<**0.0001**
Itchy rash in the past year	166	5.34	86	8.12	**0.0011**
Atopic eczema ever	335	10.77	135	12.75	0.0788

Bold values present statistically significant results

Table 3 Prevalence (%) of asthma, allergic rhinitis, atopic dermatitis, and their symptoms in 12–14-year-old children (2005 and 2013) according to gender.

	12-14-year-old group									
	2005					2013				
	Total N = 3111					Total N = 1059				
	Male		Female			Male		Female		
	N = 1512		N = 1599			N = 525		N = 534		
	N	%	N	%	p	N	%	N	%	p
Wheezing ever	213	14.09	156	9.76	**0.0002**	123	23.43	104	19.48	0.1212
Wheezing in the past year	85	5.62	74	4.63	0.2394	47	8.95	41	7.68	0.6358
Exercise-induced wheezing in the past year	108	7.14	117	7.31	0.9059	56	10.67	49	9.18	0.5302
Night wheezing in the past year	35	2.31	37	2.31	0.9063	31	5.90	29	5.43	0.7387
Dry night cough in the past year	107	7.08	102	6.38	0.4806	62	11.81	64	11.99	0.9297
Asthma ever	123	8.13	97	6.07	**0.0293**	58	11.05	40	7.49	**0.0471**
Rhinitis symptoms ever	209	13.82	171	10.69	**0.0091**	93	17.71	99	18.54	0.7275
Rhinitis symptoms in the past year	180	11.90	158	9.88	0.0792	86	16.38	86	16.10	0.9031
Rhinoconjunctivitis symptoms in the past year	115	7.61	107	6.69	0.3574	56	10.67	60	11.24	0.7668
Itchy rash ever	83	5.49	135	8.44	**0.0016**	59	11.24	86	16.10	**0.0219**
Itchy rash in the past year	60	3.97	106	6.63	**0.0013**	57	10.86	29	5.43	**0.0015**
Atopic eczema ever	140	9.26	195	12.2	**0.0098**	57	10.86	78	14.61	0.0682

**P values for the difference between genders*
Bold values present statistically significant results

The results presented in Table 4 show a statistically significant increase in 18-year-olds in 2013 compared to 12–14-year-olds in 2005 for all asthma symptoms: Wheeze ever (11.86% vs 20.89%, OR: 0.51, 95% CI: 0.42–0.61, $p < 0.0001$), wheeze last year (5.11% vs 11.15%, OR: 0.43, 95% CI: 0.33–0.55, $p < 0.0001$), exertional wheezing in the past year (7.23% vs. 10.78%, OR: 0.65, 95% CI: 0.51–0.82, $p = 0.0003$), dry nocturnal cough in the past year (6.71% vs. 11.43%, OR: 0.56, 95% CI: 0.44–0.71, $p < 0.0001$), and asthma ever (OR: 0.74, 95% CI: 0.58–0.95, $p = 0.0195$). Regarding allergic rhinitis symptoms, the authors observed a statistically significant increase in the prevalence of rhinitis symptoms in the

Table 4 Time trends in the prevalence (%) of asthma, allergic rhinitis, atopic dermatitis, and their symptoms in 12–14-year-old children (2005) and in 18-year-old participants (2013).

	12–14-year-old children		18-year-old children		p*
	2005		2013		
	Total		Total		
	N = 3111		N = 1067		
	N	%	N	%	
Wheezing ever	369	11.86	223	20.89	**<0.0001**
Wheezing in the past year	159	5.11	119	11.15	**<0.0001**
Exercise-induced wheezing in the past year	225	7.23	115	10.78	**0.0003**
Night wheezing in the past year	72	2.31	36	3.37	0.0613
Dry night cough in the past year	209	6.71	122	11.43	**<0.0001**
Asthma ever	220	7.07	99	9.28	**0.0195**
Rhinitis symptoms ever	660	12.21	236	22.12	0.5352
Rhinitis symptoms in the past year	338	10.86	209	19.59	**<0.0001**
Rhinoconjunctivitis symptoms in the past year	222	7.14	152	14.25	**<0.0001**
Itchy rash ever	218	7.01	129	12.09	**<0.0001**
Itchy rash in the past year	166	5.34	82	7.69	**0.0053**
Atopic eczema ever	335	10.77	135	12.65	0.0932

**P values for the difference between genders*
Bold values present statistically significant results

last 12 months (10.86% vs. 19.59%, OR: 0.50, 95% CI: 0.41–0.60, $p < 0.0001$) and rhinoconjunctivitis symptoms (7.14% vs.14.25%, OR: 0.46, 95% CI: 0.37–0.58, $p < 0.0001$).

For atopic dermatitis in 18-year-olds, the authors observed a statistically significant increase in the prevalence of symptoms for both itchy rash ever (7.01% vs 12.09%, OR: 0.49, 95% CI: 0.39–0.61, $p < 0.0001$) and itchy rashes in the past 12 months (5.34% vs. 7.69%, OR: 0.68, 95% CI: 0.51–0.89, $p = 0.0053$).

The gender differences in the prevalence of asthma, allergic rhinitis, atopic dermatitis, and their symptoms among 12–14-year-old participants in 2005 and 18-year-old participants in 2013 are shown in Table 5.

A statistically significant difference between genders was found for symptoms like wheezing ever in life (male: 17.89%, female: 23.88%; OR: 0.69, 95% CI: 0.52–0.94, $p = 0.0164$), wheezing in the last year (male: 7.53%, female: 14.74%; OR: 0.47, 95% CI: 0.32–0.70, $p = 0.0002$), exertion-induced wheezing in the past 12 months (men: 5.84%, women: 15.67%; OR: 0.33, 95% CI: 0.22–0.51, $p = 0.0001$), and dry nocturnal cough in the past 12 months (men: 8.66%, women: 14.18%; OR: 0.57, 95% CI: 0.39–0.85, $p = 0.005$). According to gender, the authors also observed significant gender differences for all symptoms of rhinitis: Rhinitis symptoms ever (male: 19.21%, female: 25%; OR: 0.72, 95% CI: 0.53–0.96, $p = 0.00240$), rhinitis symptoms in the past year (male: 17.14%, female: 22.01%; OR: 0.73, 95% CI: 0.54–0.99, $p = 0.0452$) and rhinoconjunctivitis symptoms in the past year (male: 12.05%, female: 16.42%; OR: 0.69, 95% CI: 0.49–0.99, $p = 0.0421$). Itchy rashes in the past year were also more common in women (men: 5.08%, women: 10.26%; OR: 0.47, 95% CI: 0.29–0.76, $p = 0.0018$), as well as reported itchy rashes ever in their lifetime (men: 8.85%, women: 16.42%; OR: 0.49, 95% CI: 0.34–0.72, $p = 0.0002$)

Discussion

By strictly applying identical study methods, achieving high and similar response rates in both surveys and for both age groups in a large sample representative of children in the general population, the authors believe that they have arrived at credible estimates of temporal trends in the prevalence of asthma symptoms and symptoms of allergic rhinitis, rhinoconjunctivitis, and atopic eczema in the population studied.

The results of this study show an increase in the time trends of all symptoms associated with atopic diseases and lifetime prevalence of asthma in children in Međimurje County.

The advantage of this study is the comparison of the prevalence of atopic symptoms in the age group of 18 years in 2013 with the age group of 12–4 years 11 months in 2005 as the 8-year difference between the studies shows a temporal trend in approximately the same population in the same area at different time points (Table 4). The disadvantage is the smaller number of participants in Phase III, due to limited funding.

The prevalence of wheezing in the last 12 months in the 13–14 age group had increased over the period 2005–2013, with a marked increase in girls. In 2005, wheezing symptoms in the last 12 months were predominantly found in boys and in 2013. The authors found no gender dominance.

The results of this study showed a similar temporal trend in the prevalence of asthma symptoms compared with other Croatian Counties, which published the results of the ISAAC Phase III.[8,9] Compared with Primorsko Goranska County, in Međimurje County the prevalence of asthma ever in life, wheezing ever in life is higher, although

Table 5 Prevalence (%) of asthma, allergic rhinitis, atopic dermatitis, and their symptoms in 12–14-year-old children (2005 and 2013) and in 18-year-old children (2013) according to gender.

	12-14-years-old					18-years-old				
	2005					2013				
	Total *N* = 3111					Total *N* = 1067				
	Male		Female			Male		Female		
	N = 1512		N = 1599			N = 531		N = 536		
	N	%	N	%	p	N	%	N	%	p
Wheezing ever	213	14.09	156	9.76	**0.0002**	95	17.89	128	23.88	**0.0164**
Wheezing in the past year	85	5.62	74	4.63	0.2394	40	7.53	79	14.74	**0.0002**
Exercise-induced wheezing in the past year	108	7.14	117	7.31	0.9059	31	5.84	84	15.67	**<0.0001**
Night wheezing in the past year	35	2.31	37	2.31	0.9063	34	6.40	49	9.14	0.0965
Dry night cough in the past year	107	7.08	102	6.38	0.4806	46	8.66	76	14.18	**0.005**
Asthma ever	123	8.13	97	6.07	**0.0293**	47	8.85	52	9.70	0.6323
Rhinitis symptoms ever	209	13.82	171	10.69	**0.0091**	102	19.21	134	25	**0.0240**
Rhinitis symptoms in the past year	180	11.90	158	9.88	0.0792	91	17.14	118	22.01	**0.0452**
Rhinoconjunctivitis symptoms in the past year	115	7.61	107	6.69	0.3574	64	12.05	88	16.42	**0.0421**
Itchy rash ever	83	5.49	135	8.44	**0.0016**	49	9.28	80	14.93	**0.0047**
Itchy rash in the past year	60	3.97	106	6.63	**0.0013**	27	5.08	55	10.26	**0.0018**
Atopic eczema ever	140	9.26	195	12.2	**0.0098**	47	8.85	88	16.42	**0.0002**

Bold values present statistically significant results

the prevalence of wheezing in the last 12 months is higher in Primorsko Goranska County with male dominance. According to the Croatian authors of Primorsko Goranska County, this may be due to the high proportion of adolescents and school children who smoke.[8] Since adolescence is a very demanding phase of life, it is possible that boys at this age experimentally smoke more than girls.[13]

The prevalence of wheezing in Brod Posavina County is similar to the prevalence of wheezing in Međimurje County.[9]

Compared with other studies based on the ISAAC questionnaire, the increase in asthma prevalence is similar to other low- and middle-income countries that have not yet reached the plateau.[1,14,15] In Phase III of ISAAC, 12-month prevalence of asthma symptoms in adolescents was reported, ranging from 2.1% in Indonesia to 32.2% in the United Kingdom. The highest 12-month prevalence of wheeze was found in westernized, English-speaking countries.[16] Among the most important established risk factors for asthma and wheeze in general is sensitization to house dust mites, which has a high prevalence in Međimurje County and it may be one of the reasons for the increase in the prevalence of all atopic diseases.[16,17]

The lifetime prevalence of rhinitis symptoms has also increased, but with a higher increase than rhinitis with conjunctivitis. This suggests the role of other possible causes of rhinitis symptoms (infection, physical stimuli, air quality), while rhinitis and conjunctivitis are better markers of allergic symptoms.[18] Allergic rhinitis and conjunctivitis have also shown a temporal increase in prevalence in Međimurje County, as in other Croatian regions.[7,9] The increase in 12–14-year-olds is equally observed in both gender. A similar increase without gender dominance in the same age group was reported in children in a German study from Muenster.[19]

Symptoms of atopic dermatitis also showed a significant increase from 2005 to 2013, and in both studies, symptoms were more severe in girls. The results show that the prevalence of atopic dermatitis is higher than that of itchy rashes in general, which is probably due to the fact that the memory of childhood itching has been lost and parents only remember the diagnosis of atopic dermatitis. Compared with other Croatian regions, Međimurje County showed a slight increase in symptoms of atopic dermatitis in the last 12 months, while the prevalence in Brod Posavina County and Primorsko Goranska County remained stable.[7,9] Previously published data from Međimurje County showed the following risk factors: Atopy in the family, female gender, and sleeping on feather pillows.[20]

If children aged 13–14 years in 2005 are compared with young adults aged 18 years in 2013, the authors find that wheezing is even more common in girls. This highlights the increase in the prevalence of wheezing in girls over time. It is consistent with previous studies on gender difference in asthma prevalence showing an increase in asthma symptoms in female adolescents.[19,21–23] This is thought to be related to immunological and hormonal factors and differences in gender-specific responses to environmental factors.[24,25] In addition to wheezing overall, the prevalence of wheezing was also higher in female gender, including exertion-induced wheezing and dry night cough in the last year.

The predominance of female gender in allergic rhinitis also increases with age. This result is observed in this study as well as in other studies. Frolich et al. and Pinart have shown the same gender shift in the prevalence of allergic rhinitis toward adulthood.[22,26]

Conclusion

In this study, the authors show an increasing trend in the prevalence of all symptoms associated with atopic diseases: Asthma, allergic rhinitis, allergic rhinoconjunctivitis, and eczema, as well as the lifetime prevalence of asthma in Međimurje County. The overall prevalence of asthma in Međimurje County has remained moderate, as it has the prevalence of atopic eczema, while the prevalence of allergic rhinitis has increased and remains high. These data provide important information for further interventions in the public health system.

Conflict of interests

The authors declare no potential conflicts of interest with respect to research, authorship and/or publication of this article.

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