Published online (http://hsm.umsu.ac.ir)



Investigating risk factors related to asthma in children before school age in rural and urban areas of West Azerbaijan province

Hamidreza Houshmand *1, Mehdi Talebi 1

Abstract

Background & Aims: Allergic disorders are one of the most critical health problems in the world. This study aimed to investigate the prevalence of childhood asthma and its related factors among urban-rural preschool children.

Materials & Methods: In this descriptive cross-sectional study, children under 5 years referred to the Asthma, Allergy, and Immunology Clinic of Motahari Hospital were included. The children were divided into two groups: urban and rural group. A checklist in the form of a questionnaire (consisting of information about demographics, parental asthma, exposure to farm animals, and tobacco, adequate home air conditioning, use of antibiotics during the first year of life, maternal gestational age, type of delivery, birth weight, age of wheezing onset, length of breastfeeding, and siblings number) was filled by the parents of the children. Data were analyzed by using SPSS 21 software.

Results: Of 149 children with asthma, 85 were boys (40.3%) and 61 were girls (59.7%). Among the compared risk factors of asthma between urban and rural patients, the statistically significant variables were Body Mass Index (BMI) which was high among urban children (p = 0.002), the number of siblings of children (urban = 74, rural = 75) (p < 0.001), age of wheezing onset (urban = 74, rural = 75) (p = 0.014), animal exposure (urban = 28.4%, rural = 46.7%) (p = 0.021), and cesarean section delivery (urban = 63.5%, rural = 37.3%) (p = 0.001) were statistically significant.

Conclusion: The risk of asthma among preschool children is strongly predicted by their area of residence in early life. This risk increases further in children accompanied with other asthma risk factors such as passive smoking, type of delivery, exposure to animals, and other discussed factors.

Keywords: Asthma, Children, Risk factors, Rural areas, Urban areas

Received 22 April 2023; accepted for publication 15 August 2023

This is an open-access article distributed under the terms of the Creative Commons Attribution-noncommercial 4.0 International License, which permits copy and redistribute the material just in noncommercial usages as long as the original work is properly cited

Introduction

Asthma is a chronic inflammatory disease that results in recurrent episodes of increased responses in the tracheobronchial tract when exposed to various stimuli (1). It affects more than 235 million individuals worldwide, primarily impacting children as the most

¹ Department of Allergy and Clinical Immunology, Faculty of Medicine, University of Medical Sciences, Urmia, Iran

^{*}Corresponding author: Hamidreza Houshmand, Address: Department of Pediatrics, Faculty of Medicine, University of Medical Sciences, Urmia, Iran, Email: hamidrezahoushmand1347@gmail.com, Tel: +989143433913

common non-communicable condition (2). The prevalence rates differ due to the varying epidemiological definitions of asthma, differences in measurement methods and environment between countries (3). Additionally, asthma has different phenotypes with varying causes and risk factors that vary internationally and differ between high-income and low-to-middle income countries (4). To mitigate the costs imposed on health systems, significant efforts are made towards preventing and managing asthma (5).

Asthma, a respiratory disease, may manifest at any age, but it primarily develops during childhood when the immune system is still in its developmental stages. The majority of children experiencing asthma showcase their first symptom by age 5 (6). Over the last few decades, the prevalence of childhood asthma has increased considerably. The reasons behind this surge are not well-established; however, several factors such as amplified exposure to environmental allergens, both indoor and outdoor air pollutants, mounting obesity rates, and inadequate early immune system exposures may play a role (7).

Disparities in sociodemographic, economic, and geographic conditions between urban and rural areas contribute to differences in asthma prevalence (8). Childhood asthma is predominantly studied in rural and farming locations due to varying exposures that are linked to the disease and differ between the urban and rural environments (9-10, 11-12). In addition, access to healthcare differs between urban and rural populations, possibly accounting for variations in disease prevalence. Previous research suggests that asthma prevalence is lower in rural or farming areas (10, 13).

The topic of asthma incidence across urban and rural areas among children and adolescents has received limited attention, with only a few studies conducted on the subject (10, 14-15). Prior research carried out in Iran has reported asthma prevalence rates ranging from 2.1% to 20.3% among children aged 13-14 years old (16-18). However, there is a lack of detailed study regarding the differences between asthmatic children residing in urban versus rural areas in West Azerbaijan province. Thus, this study aimed to

investigate the discrepancies between preschool children with asthma and allergies living in rural and urban areas in West Azerbaijan province, Iran.

Materials & Methods

In this descriptive cross-sectional study, children under 5 years of age referred to Asthma, Allergy, and Immunology Clinic of Motahari Hospital were In the method section of the article, included. participants were recruited based on specific inclusion and exclusion criteria. A single specialist in asthma and allergy visited potential participants to confirm their eligibility for the study. To be included, children needed to have a history of wheezing attacks occurring more than three times in the past year, with at least one such attack having been diagnosed by a doctor, or they needed to have had wheezing that responded to salbutamol spray and met either one of the primary criteria or two of the minor Asthma Predictive Indexes criteria. The children were divided into two groups: urban and rural. Urban children were defined as those who had access to safe drinking water and a bath at home, while rural children were involved in farming or animal husbandry. Children with certain medical conditions or whose parents did not provide written consent were excluded from the study. Ultimately, out of 150 eligible children, one was excluded due to parental non-consent, leaving a final sample size of 149 children.

A validated and reliable questionnaire was administered to the parents of participating children at the onset of the study. The questionnaire comprised of various factors such as demographic information, parental asthma status, exposure to animals, and tobacco, appropriate home air conditioning, use of antibiotics during infancy, length of pregnancy, mode of delivery, birth weight, age of wheezing onset, duration of breastfeeding, number of siblings, and Body Mass Index (BMI). Due to financial limitations, the skin prick test could not be performed. The study received ethical approval from the Urmia University of Medical Sciences Ethics Committee (NO IR.UMSU.REC.1397.492), and a single pediatric

asthma specialist evaluated the children to ensure they fit the inclusion criteria.

Home air conditioning:

It is a process in which air temperature, air humidity, ventilation rate, flow shape, airspeed, pollutants in the air, and in some cases, the pressure difference between the desired space and adjacent spaces are controlled to create comfortable conditions for people or suitable conditions for the production of the product. According to the study of Marfortt et al., the home air conditioning index is calculated through the relationship between bedroom ventilation index = (windows meters) / bedrooms (cubic meters) × 100. The lowest average level was 10.2%. More than this amount was considered proper air conditioning, and less than this amount was considered inadequate air conditioning (19).

Statistical analysis:

Data have been analyzed by IBM's Statistical Package for the Social Sciences (SPSS) after a thorough check to exclude any incomplete or inconsistent data. Data have been double-checked and scrutinized before and after entry into the SPSS program. Categorical variables have been presented as proportions, whereas non-categorical variables have been presented as means and standard deviations (SD). Qualitative data between children with asthma symptoms have been compared by Chi-square test. The statistical significance level was considered less than 0.05.

Results

One hundred and forty-nine children from urban and rural areas (74 urban and 75 rural) participated in this study. The mean age of urban and rural children was 3.22 ± 1.21 and 3.72 ± 1.18 years, respectively. There was a statistically significant difference between the two groups (p = 0.011). Gender distribution was 41 boys (55.4%) and 46 girls (61.3%). No statistically significant difference was observed between the two groups (p = 0.463) (Table 1).

Table 1. Early life risk factors for asthma among enrolled children

	Location	Numbers (%)	Mean	p value	
Sex Boy	Urban	41 (55.4%)	Total = 46 (61.3%)	0.463	
Girl	Rural	33 (44.6%)	Total = $29 (38.7\%)$	0.403	
Ann	Urban	74	3.22 ± 1.21	0.011 *	
Age	Rural	75	3.72 ± 1.18	0.011	
DMI	Urban	74	49.30 ± 83.9	0.002 *	
BMI	Rural	75 12.84 ± 77.56		0.002	
No	Urban	74	0.74 ± 0.70	0.001 *<	
Number of siblings	Rural	75	$1/69\pm1/04$	0.001	
The number of people	Urban	74	$0/62 \pm 0.54$		
Sleeping in the same room with the person	Rural	75	$2/25\pm1/19$	0.001 *<	
Number of months of	Urban	74	$19/78 \pm 3/46$		
breastfeeding/formula milk	Rural	75	$20/27\pm2/62$	0.338	

	Location	Numbers (%)	Mean	p value
Age of starting wheezing (months/old)	Urban	74	$10/09 \pm 2/53$	0.014*
	Rural	75	$9/10\pm1/70$	0.014 *
Birth weight in grams	Urban	74	2575/54 ± 249/96	0.073
	Rural	75	$2662/80 \pm 332/82$	
Gestational age per week	Urban		$37/26 \pm 0/89$	
	Rural	75	$37/03\pm0/54$	0.059

Chi-Square = 0.539, df = 1

The BMI of urban children was 83 ± 30.49 kg, and the mean of rural children was 84.12 ± 56.7 kg, which indicate a higher BMI among urban children. A statistically significant difference was observed between the two groups (p = 0.002). The mean number of siblings of urban and rural children was 0.74 ± 0.7 and 1.69 ± 1.04 , respectively. The results showed a statistically significant difference between the two groups (p < 0.001). The mean duration of breastfeeding/formula was 19.78 ± 3.48 months for urban children and 20.27 ± 2.62 months for rural children. Results showed no statistically significant difference between the two groups (p = 0.338). The mean age of wheezing onset was 10.09 ± 2.53 months for urban children and 9.10 ± 1.70 for rural children. The results showed a statistically significant difference between the two groups (p = 0.014). The mean birth body weight was 2575.54 ± 249.96 kg for urban children and 2662.80 \pm 332.82 kg for rural children. There was no significant difference between the two groups (p = 0.073). The mean length of pregnancy per week was 37.26 ± 0.89 for urban children and $37.03 \pm$ 0.54 for rural children. There was no statistical significance difference between the two groups (p = 0.059).

The comparison of distribution of different variables among asthma children according to location is shown in Table 2. The statistical analysis displayed no significant difference between the two groups in comparison of parents' smoking (p = 0.946), asthma history among mothers (p = 0.951), asthma history among fathers (p = 0.752), antibiotics usage in the first year of children (p = 0.159), and proper ventilation status of children (p = 0.964) according to the location (Urban or rural). Therefore, comparison of the distribution of animal exposure history of children with asthma according to location showed that, 21 (28.4%) urban patients and 35 (46.7%) rural patients had a history of exposure to animals. The results showed a difference between the two groups (p = 0.021). Furthermore, the comparison of type of delivery of mothers showed that 47 (63.5%) urban patients and 28 (37.3%) rural patients were born by cesarean section which was statistically significant (p = 0.001) (Table 2).

Table 2. Comparison of distribution of asthmatic risk factors between urban and rural asthmatic children

	<u>-</u>	Location		T. ()	_
		Urban N (%)	Rural N (%)	Total	p value
Parents' tobacco use at home	Yes	30 (40.5%)	30 (0.60%)	60 (40.3%)	0.946
	No	44 (59.5%)	45 (40%)	89 (59.7%)	
History of asthma in the mother	Yes	9 (12.3%)	9 (12%)	18 (12.2%)	0.051
	No	65 (87.7%)	66 (88%)	131 (87.8%)	0.951

		Location			
		Urban N (%)	Rural N (%)	Total	p value
History of asthma in the father	Yes	7 (9.5%)	6 (8%)	13 (8.7%)	0.770
	No	67 (90.5%)	69 (92%)	136 (91.3%)	0.752
Exposure to animals	Yes	21 (28.4%)	35 (46.7%)	56 (37.6%)	
	No	53 (71.6%)	40 (53.3%)	93 (62.4%)	0.021
Taking antibiotics in the first year	Yes	33 (44.6%)	25 (33.3%)	58 (38.9%)	0.4.50
	No	41 (55.4%)	50 (66.1%)	91 (61.1%)	0.159
Suitable ventilation of the home air	Yes	57 (77%)	58 (77.3%)	115 (77.2%)	0.064
	No	17 (17%)	17 (22.7%)	34 (22.8%)	0.964
Type of delivery	Yes	27 (36.5%)	47 (62.7%)	74 (49.7%)	0.004
	No	47 (63.5%)	28 (37.3%)	75 (50.3%)	0.001

Discussion

Allergic disorders represent a significant global health problem and are associated with substantial costs for healthcare systems. As a result, much effort is made to prevent and control these disorders, which include asthma, allergic rhinitis, and eczema, among others (20). Asthma, in particular, is a recurrent chronic condition that affects a significant proportion of children worldwide. Its prevalence varies across different countries and regions, with rates in Latin America ranging from 8.4% to 37.6% among 6-7 yearolds and 11.6% to 27.3% among 13-14 year-olds (19). In Iran, the reported prevalence of asthma is between 5% and 15%, affecting around 6.5 million people (20). These differences in prevalence may be attributed to various factors such as socioeconomic status. environmental exposures, psychosocial stress, access to healthcare, and urbanization.

The etiology of asthma is multifactorial and involves both genetic and environmental factors. Early life, particularly during pregnancy and infancy, is a critical period for the development of allergies and asthma (21). Important exposures such as breastfeeding, diet, use of antibiotics, indoor allergens and microbes, and air pollutants can alter the immune system profile of infants and potentially trigger allergy and asthma (22). Urban-rural differences and the farming effect have also been investigated in relation to asthma, with generally lower prevalence observed in

rural or farm indwelling individuals (10, 23, 24). Consistent with previous findings from Europe, our study confirms that the area of birth is an important factor in determining asthma risk, even when individuals subsequently move to urban areas (25).

The current research findings demonstrated a significant difference in the mean age of asthmaaffected children living in urban and rural areas. The results indicated that urban children tend to develop asthma at comparatively later ages compared to their rural counterparts. This finding diverges from a prior study by Pesek et al. (26), which reported similar age and gender patterns in asthmatic children living in urban and rural regions. Nonetheless, our study's results align with Pesek et al.'s observations regarding the gender distribution of asthmatic children. However, several studies have revealed that wheezing and allergies are more prevalent among urban children (27). In contrast, our study indicates that rural children tend to experience early onset of wheezing attacks, corroborating Marfortt et al.'s research (28), which found that rural children exhibited premature wheezing compared to urban children.

Previous research has identified parental history of allergic disease as a significant risk factor for asthma (29). Studies have suggested that parental history of allergy, in particular, is strongly associated with early onset persistent asthma (29, 30, 31). However, our study did not find any significant difference in the

prevalence of parental history of allergy among urban and rural asthmatic children. Our findings indicated that urban children had higher BMI compared to rural children, which can be attributed to the higher prevalence of overweight individuals in urban areas. Overweight is considered a comorbid risk factor for asthma, and studies have shown a higher prevalence of asthma in urban children (21, 32, 33). Conversely, birth weight did not differ significantly between urban and rural asthmatic children in our study. In contrast, some studies have reported a strong association between low birth weight and asthma among children born in large cities (34, 35).

In the present study, it was found that urban children had fewer siblings compared to their rural peers. This finding is consistent with the results reported by Marfortt et al. (28) who suggested that living in a rural environment and having more siblings can reduce the risk of asthma which was justified by the studies of Feng, et al. (35). Marfortt et al.'s (28) study further showed that sharing a room with other siblings was more common in rural populations than in urban populations, which is consistent with our findings. However, our results were inconsistent with those reported by another study (36), which found that the prevalence of vaginal delivery, breastfeeding, and consumption of unpasteurized milk was higher in the rural population compared to the urban population. The only exception was the delivery route, as cesarean delivery was more common in the urban population than in the rural population.

While it is widely acknowledged that maternal smoking poses a considerable risk for childhood asthma, as evidenced in a study (37), our investigation reveals no meaningful correlation between passive smoking and asthma among children. This lack of association may be attributable to the relatively low incidence of smoking observed within the population under study, particularly by expectant mothers and other household members. Notably, prior research has established that maternal smoking during pregnancy leads to impaired respiratory function in neonates - a phenomenon evident even before postnatal exposure to

smoke (38). Furthermore, empirical evidence from this and similar studies highlights the negative impact of maternal smoking during pregnancy on pulmonary function in school-aged children (39).

In contrast to previous research that has indicated a reduced risk of asthma in children who were either born or raised on farms (40, 41), our study did not find any significant difference between asthmatic urban and rural children with respect to early-life exposure to farm animals. Our hypothesis is that this lack of difference may be due to the fact that farm animal exposure is widespread even in urban areas as a result of subsistence farming practices. This is supported by a study which found that rural populations had a higher risk of asthma compared to urban populations when exposed to animals (28). However, the present study has limitations in that only data provided by the parents of patients was used, and recall accuracy may have been impacted by the passage of time when asking about asthma risk factors dating back several years.

Conclusion

The likelihood of asthma in preschool-aged children residing in urban and rural areas is heavily influenced by their location of residence during early life, particularly at the time of birth. Children born in small towns or cities have the highest risk, which further increases when accompanied by other risk factors such as passive smoking, delivery method, and animal exposure. Therefore, additional research is necessary to identify these specific risk factors and develop interventions to modify them, ultimately preventing the onset of asthma during early childhood.

Acknowledgments

The authors would like to express their gratitude to the Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, for English editing.

Conflict of interest

The authors have no conflict of interest in this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability

The raw data supporting the conclusions of this article are available from the authors upon reasonable request

References

- Doeing DC, Solway J. Airway smooth muscle in the pathophysiology and treatment of asthma. J Appl Physiol (1985). 2013 Apr;114(7):834-43. https://doi.org/10.1152/japplphysiol.00950.2012.
- 2. World Health Organization. Asthma Fact Sheet. 2017.
- Kuruvilla ME, Vanijcharoenkarn K, Shih JA, Lee FE. Epidemiology and risk factors for asthma. Respir Med. 2019 Mar 1;149:16-22.
- Lotvall J, Akdis CA, Bacharier LB, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011;127(2):355-60.
- Mortimer K, Reddel HK, Pitrez PM, Bateman ED. Asthma management in low and middle income countries: case for change. Eur Respir J. 2022 Sep 15;60(3):2103179. https://doi.org/10.1183/13993003.03 179-2021.
- Pedersen SE, Hurd SS, Lemanske Jr RF, et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. Pediatr Pulmonol. 2011 Jan;46(1):1-7.
- Serebrisky D, Wiznia A. Pediatric Asthma: A Global Epidemic. Ann Glob Health. 2019 Jan 22;85(1):6. https://doi.org/10.5334/aogh.2416.
- Desalu OO, Adeoti AO, Ojuawo OB, Aladesanmi AO, Oguntoye MS, Afolayan OJ, et al. Urban-Rural Differences in the Epidemiology of Asthma and Allergies in Nigeria: A Population-Based Study. J Asthma Allergy. 2021;14:1389-1397. doi: 10.2147/JAA.S333133.
- Illi S, Depner M, Genuneit J, Horak E, Loss G, Strunz-Lehner C, et al. Protection from childhood asthma and

- allergy in Alpine farm environments the GABRIEL Advanced Studies. J Allergy Clin Immunol. 2012;129(6):1470-1477. doi: 10.1016/j.jaci.2012.03.041.
- Lawson JA, Janssen I, Bruner MW, Madani K, Pickett W. Urban-rural differences in asthma prevalence among young people in Canada: the roles of health behaviours and obesity. Ann Allergy Asthma Immunol. 2011;106(3):220-228. doi: 10.1016/j.anai.2010.12.003.
- Barnig C, Reboux G, Roussel S, Casset A, Sohy C, Dalphin J-C, et al. Indoor dust and air concentrations of endotoxin in urban and rural environments. Lett Appl Microbiol. 2012;56(2):161-167. doi: 10.1111/j.1472-765X.2012.03390.x.
- Vlaski E, Lawson J. Urban-rural differences in asthma prevalence among young adolescents: The role of behavioural and environmental factors. Allergologia et immunopathologia (Madr). 2015;43(2):131-141. doi: 10.1016/j.aller.2014.02.007.
- Genuneit J. Exposure to farming environments in childhood and asthma and wheeze in rural populations: a systematic review with meta-analysis. Pediatr Allergy Immunol. 2012;23(6):509-518. doi: 10.1111/j.1399-3038.2012.01327.x.
- Horak E, Morass B, Ulmer H, Genuneit J, Braun-Fahrlander C, Von Mutius E. Prevalence of wheezeing and atopic diseases in Austrian schoolchildren in conjunction with urban, rural, or farm residence. Wien Klin Wochenschr. 2014;126(13-14):532-536. doi: 10.1007/s00505-014-2422-1.
- Kausel L, Boneberger A, Calvo M, Radon K. Childhood asthma and allergies in urban, semiurban, and rural residential sectors of Chile. Sci World J. 2013;2013:4.
- 16- Boskabady MH, Kolahdoz GH. Prevalence of asthma symptoms among the adult population in the city of Mashhad (north-east of Iran). Respirology 2002;7(3):267-72.
- 17- Rahimi Rad M, Hejazi M, Behrouzian R. Asthma and other allergic diseases in 13-14-year-old schoolchildren in Urmia: an ISAAC study. East Mediterr Health J. 2007;13(5):1005-16.
- 18- Nasiri Kalmarzi R, Shekari A, Tajik M, Ataee P, Homagostar G, Roshani D, et al. The prevalence of asthma symptoms in elementary and middle school

- students in Kurdistan province, the West of Iran. Int J Pediatr. 2016;4(2):1323-30. doi: 10.22038/ijp.2016.6488.
- 19- McCormack K, Leo H. Differences Between Preschoolers with Asthma and Allergies in Urban and Rural Environments. Pediatrics. 2018 Dec;142(Suppl 4):S255-6. doi: 10.1542/peds.2018-3059S.
- 20- Alatawi AM, Alanazi AMM, Almutairi ABS, Albalawi RFA, Alhakami AAM, Alnuaman AAS, et al. Prevalence and Risk Factors of Allergic Diseases Among School Students in Tabuk: A Cross-Sectional Study. Cureus. 2023 Mar 24;15(3):e36658. doi: 10.7759/cureus.36658.
- 21- Sole D, Aranda CS, Wandalsen GF. Asthma: epidemiology of disease control in Latin America - short review. Asthma Res Pract. 2017;3:4. doi: 10.1186/s40733-017-0035-8.
- 22- Wang H, Li N, Huang H. Asthma in Pregnancy: Pathophysiology, Diagnosis, Whole-Course Management, and Medication Safety. Can Respir J. 2020;2020:9046842. doi: 10.1155/2020/9046842.
- 23- Mpairwe H, Namutebi M, Nkurunungi G, Tumwesige P, Nambuya I, Mukasa M, et al. Risk factors for asthma among schoolchildren who participated in a case-control study in urban Uganda. Elife. 2019;8:e49496. doi: 10.7554/eLife.49496.
- 24- Pawankar R, Canonica GW, Holgate ST, Lockey RF. Allergic diseases and asthma: a major global health concern. Curr Opin Allergy Clin Immunol. 2012;12(1):39-41. doi: 10.1097/ACI.0b013e32834dd1e9.
- 25- Kantomaa MT, Tolvanen M, Halonen M, Svanes C, Järvelin MR, Sebert S. Influence of Farm Environment on Asthma during the Life Course: A Population-Based Birth Cohort Study in Northern Finland. Int J Environ Res Public Health. 2023;20(3):2128. doi: 10.3390/ijerph20032128.
- 26- Pesek RD, Vargas PA, Halterman JS, Jones SM, McCracken A, et al. A comparison of asthma prevalence and morbidity between rural and urban schoolchildren in Arkansas. Ann Allergy Asthma Immunol. 2010;104(2):125-31. doi: 10.1016/j.anai.2009.11.004.

- 27. Grant TL, Wood RA. The influence of urban exposures and residence on childhood asthma. Pediatric Allergy and Immunology. 2022;33(5):e13784. https://doi.org/10.1111/pai.13784
- Marfortt DA, Josviack D, Lozano A, Cuestas E, Agüero L, Castro-Rodriguez JA. Differences between preschoolers with asthma and allergies in urban and rural environments. J Asthma. 2018;55(5):470-6.https://doi.org/10.1080/02770903.2017.1339800
- Paaso E, Jaakkola MS, Rantala AK, Hugg TT, Jaakkola
 JJ. Allergic diseases and asthma in the family predict the
 persistence and onset-age of asthma: a prospective
 cohort study. Respir Res. 2014;15(1):1.
 https://doi.org/10.1186/s12931-014-0152-8
- London SJ, Gauderman WJ, Avol E, Rappaport EB, Peters JM. Family history and the risk of early onset persistent, early onset transient and late onset asthma. Epidemiology. 2001;12(5):577-8. https://doi.org/10.1097/00001648-200109000-00019
- Slob EM, Longo C, Vijverberg SJ, Beijsterveldt TC, Bartels M, Hottenga JJ, et al. Persistence of parentalreported asthma at early ages: A longitudinal twin study. Pediatric Allergy and Immunology. 2022;33(3):e13762. https://doi.org/10.1111/pai.13762
- O'Connor GT, Lynch SV, Bloomberg GR, Kattan M, Wood RA, Gergen PJ, et al. Early-life home environment and risk of asthma among inner-city children. J Allergy Clin Immunol. 2018;141(5):1468-75. https://doi.org/10.1016/j.jaci.2017.06.040
- Ege MJ. The Hygiene Hypothesis in the Age of the Microbiome. Ann Am Thorac Soc. 2017;14(Suppl 5):S348-53. https://doi.org/10.1513/AnnalsATS.201702-139AW
- 34. Zhang J, Ma C, Yang A, Zhang R, Gong J, Mo F. Is preterm birth associated with asthma among children from birth to 17 years old?-A study based on 2011-2012 US National Survey of Children's Health. Ital J Pediatr. 2018;44(1):90. https://doi.org/10.1186/s13052-018-0583-9
- 35. Xu XF, Li YJ, Sheng YJ, Liu JL, Tang LF, Chen ZM. Effect of low birth weight on childhood asthma: a metaanalysis. BMC Pediatr. 2014;14:271. https://doi.org/10.1186/1471-2431-14-275

- Ulfa Y, Maruyama N, Igarashi Y, Horiuchi S. Early initiation of breastfeeding up to six months among mothers after cesarean section or vaginal birth: A scoping review. Heliyon. 2023;9:e09981. https://doi.org/10.1016/j.heliyon.2023.e16235
- 37. Silvestri M, Franchi S, Pistorio A, Petecchia L, Rusconi F. Smoke exposure, wheezing, and asthma development: a systematic review and meta-analysis in unselected birth cohorts. Pediatr Pulmonol. 2015;50(4):353-62. https://doi.org/10.1002/ppul.23037
- 38. González-Luis GE, van Westering-Kroon E, Villamor-Martinez E, Huizing MJ, Kilani MA, Kramer BW, Villamor E. Tobacco smoking during pregnancy is associated with increased risk of moderate/severe bronchopulmonary dysplasia: a systematic review and meta-analysis. Front Pediatr. 2020;8:160. https://doi.org/10.3389/fped.2020.00160
- 39. Jansone K, Eichler A, Fasching PA, Kornhuber J, Kaiser A, Millenet S, et al. Association of Maternal Smoking during Pregnancy with Neurophysiological and ADHD-Related Outcomes in School-Aged Children. Int J Environ Res Public Health. 2023;20(6):4716. https://doi.org/10.3390/ijerph20064716
- 40. Genuneit J. Exposure to farming environments in childhood and asthma and wheeze in rural populations: a systematic review with meta-analysis. Pediatr Allergy Immunol. 2012;23(6):509-18. https://doi.org/10.1111/j.1399-3038.2012.01312.x
- 41. Timm S, Frydenberg M, Janson C, Campbell B, Forsberg B, Gislason T, et al. The Urban-Rural Gradient In Asthma: A Population-Based Study in Northern Europe. Int J Environ Res Public Health.