

PRENATAL AND POSTNATAL RISK FACTORS IN OVERWEIGHT CHILDREN WITH ASTHMA

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Abstract

There is undoubtedly an increased risk of asthma in overweight children. The aim of this study was to evaluate the relationship between prenatal exposure and postnatal events and the development of asthma in overweight children. A total of 112 children aged 7-17 years were included in this prospective study. Thirty-eight had asthma and a normal body mass index (BMI), 33 were overweight with asthma, and 41 were overweight children. A medical history was taken from every child's parent. No significant association between premature birth, gestational age, birth weight, delivery mode, maternal smoking status during pregnancy within the groups was found. Mothers of overweight children with asthma were most likely using antibiotics (12.1%) in the first 3 months of pregnancy. Familial atopy was significantly more associated with asthma as well overweight and asthma compared to overweight [OR=3.937 (1.46-10.61) 95%CI] vs. [OR=5.880 (1.89-18.23) 99%CI], respectively. According to the analysis, most children born as small for gestational age (SGA) 7(17.1%) were in the overweight group. For $p < 0.05$, a significant difference in the number of older siblings was determined between overweight/asthma/overweight + asthma groups for consecutive Mann-Whitney U Test: $Z = -2.619$; $p = 0.009$. Breastfeeding, vaccination, attendance at kindergarten, having pets and annual frequency of antibiotic treatment in the first 3 years, have no statistical significance.

Conclusion: Familial atopy was confirmed as one of the prenatal risk factors for asthma in childhood, independent of BMI. We did not confirm the "hygiene hypothesis" probably due to the small number of subjects for epidemiological analysis.

Keywords: asthma, body mass index, children, obesity, overweight, risk factors

Introduction

Asthma and obesity are two of the most common chronic diseases. More than 340 million people with asthma are reported worldwide, with an increasing prevalence among low-income and middle-income countries. In recent decades asthma prevalence has been gradually increasing in childhood as well^[1]. During the period of 2002-2004, in Macedonia within the International Study of Asthma and Allergies in Childhood (ISAAC), a low prevalence of asthma was reported^[2]. Obesity is also a global public health problem, with more than 2,5

billion people overweight, and about 890 million obese adults worldwide^[3]. Obesity is also a health problem in children, and the prevalence among them is increasing at an alarming rate. In 2022, 37 million children under the age of 5 were overweight and over 390 million aged 5–19 years, including 160 million who were living with obesity^[3]. The ISAAC study in Macedonia reported a moderately low prevalence of overweight and a low prevalence of obesity^[4]. A decade later, a significantly higher prevalence of overweight/ obese children aged 5 to 15 years was recorded^[5].

A parallel epidemic of asthma and obesity has erupted worldwide over the past few decades, but their association is still being investigated. Several hypotheses underly their association^[6]. Although genetic susceptibility can contribute to the development of both asthma and obesity, and predisposition to both appears to begin *in utero*. Various environmental risk factors can affect the fetus *in utero*, the infant after birth (perinatal period), or the child in early childhood, which can subsequently lead to childhood asthma in overweight children. Epigenetic mechanisms associated with obesity and asthma have been proposed^[7-11].

The aim of this study was to examine the relationship between various prenatal exposure and postnatal events in later development of asthma in overweight children.

Material and methods: A prospective study with 112 children aged 7-17 years was performed at the University Children's Clinic, Skopje, Republic of North Macedonia, during 2020. Ethical approval was obtained by the Ethics Committee at the Faculty of Medicine in Skopje and written informed consent for inclusion in the study was signed by the parents. A medical history was taken from every child's parent and then each child was examined. Patients were divided in three groups. The Overweight group consisted of 41 overweight children, the Asthma group consisted of 38 children with asthma and normal BMI, and the Overweight with asthma group consisted of 33 overweight children with asthma. Exclusion criteria were: the presence of other diseases, obesity due to other conditions, and administration of systemic corticosteroid therapy three months before being included in the study. The diagnosis of asthma was assessed by the Global Initiative for Asthma (GINA) and International Consensus on (ICON) Paediatric Asthma guidelines^[12,13]. Body mass index (BMI) was calculated according to the standard formula, defining overweight for those over 25 kg/m² and obesity for those above 30 kg/m² at 18 years of age^[14].

Statistical analysis was performed with SPSS 22.0 (SPSS, Chicago, IL, USA). The qualitative series were processed by determining the coefficient of relations, proportions, and rates. These were shown as absolute and relative numbers. Quantitative series were analysed with measures of central tendency (average, median), as well as with dispersion measures (standard deviation, standard error). The Pearson Chi square, Fischer exact, and Fisher Freeman Halton exact tests were used to determine the association between certain attributive variables. To test the significance of the difference between certain analyzed parameters, depending on the frequency distribution, Mann Whitney U test was used. A two-sided analysis with a significance level of $p < 0.05$ was used to determine the statistical significance.

Results

The study included 112 children, aged 7-17 years, who were divided in three groups, 41(36.6%) children with high BMI - Overweight group, 38 (33.9%) children with asthma and normal BMI - Asthma group and 33 (29.5%) children with asthma and high BMI - Overweight + Asthma group. The average age was 11.1 ± 2.4 years with a minimum/maximum age of 7 to 17 years, and did not show any differences between the groups. There was no significant association between premature birth, gestational age, birth weight, delivery mode, maternal smoking during pregnancy within the groups. Mothers from Overweight + Asthma group were most likely to use antibiotic treatment (12.1%) in the first 3 months of pregnancy, but there was no significant association between the groups ($p=0.4163$). Familial atopy (asthma, allergic

rhinitis, atopic dermatitis, food allergy, drug allergy in first-grade relatives) was significantly more associated with asthma as well overweight + asthma compared to overweight [OR=3.937

Table 1. Prenatal risk factors

Parameter		Groups			P
		Overweight N=41	Asthma N=38	Overweight + asthma N=33	
Smoking status of the mother during pregnancy					
No	N	31	32	22	Pearson Chi-square: 2.9741; df=2; p=0.2260
	%	75.61 %	84.21 %	66.67 %	
Yes	N	10	6	11	
	%	24.39 %	15.79 %	33.33 %	
Familial atopy					
No	N	21	8	5	Pearson Chi-square test=13.606; df=2; p=0.0011*
	%	51.22 %	21.05 %	15.15 %	
Yes	N	20	30	28	
	%	48.78 %	78.95 %	84.85 %	
Antibiotic therapy in the first 3 months of pregnancy					
No	N	39	36	29	Fisher Freeman Halton exact test: p=0.4163
	%	95.12 %	94.74 %	87.88 %	
Yes	N	2	2	4	
	%	4.88 %	5.26 %	12.12 %	
Premature birth					
No	N	32	34	31	Fisher Freeman Halton exact test: p=0.1115
	%	78.05 %	89.47 %	93.94 %	
Yes	N	9	4	2	
	%	21.95 %	10.53 %	6.06 %	
Birt weight					
≤ 2.500	N	2	4	0	O/O+A (p=0.9456)^ O/A (p=0.2092)^ A/O+A (p=0.2095)^
	%	4.9 %	10.5%	0 %	
> 2.500 < 3.500	N	17	29	15	
	%	41.5%	50%	45.5%	
≥ 3.500	N	22	15	18	
	%	53.7%	39.5%	54.5%	
Born by cesarean section					
No	N	32	30	22	Pearson Chi- square:1.7413; df=2; p=0.4187
	%	78.05 %	78.95 %	66.67 %	
Yes	N	9	8	11	
	%	21.95 %	21,05 %	33.33 %	

*significant for p<0.05

(1.46-10.61) 95%CI] vs. [OR=5.880 (1.89-18.23) 99%CI], respectively. No percentage difference was found between the groups related to the birth weight ≥ 3.500 g, although the proportion of patients with this birth weight in Overweight as well as Overweight + Asthma group was higher compared to Asthma group. Prenatal risk factors are summarized in Table 1.

The analysis of postnatal risk factors included seven parameters: small for gestational age (SGA), breastfeeding, vaccination, attendance at kindergarten, having pats, number of older siblings and annual frequency of antibiotic treatment in the first 3 years. According to the analysis, most children with SGA diagnosis on birth 7 (17.1%) were in the Overweight group. But, for $p>0.05$, the analysis did not indicate a significant association between the groups ($p=0.1447$). Postnatal risk factors are summarized in Table 2.

Table 2. Postnatal risk factors

Parameters		Groups			P
		Overweight N=41	Asthma N=41	Overweight + asthma N=33	
Small for gestational age– SGA					
No	N	34	32	32	Fisher Freeman Halton exact test: p=0.1447
	%	82.93 %	84.21 %	96.97 %	
Yes	N	7	6	1	
	%	17.07 %	15.79 %	3.03 %	
Vaccination					
No	N	/	/	/	/
	%	/	/	/	
Yes	N	41	38	33	
	%	100 %	100 %	100 %	
Going to kindergarten					
No	N	16	20	10	Pearson Chi-square: 3.7502; df=2; p=0.1533
	%	39.02 %	52.63 %	30.30 %	
Yes	N	25	18	23	
	%	60.98 %	47.37 %	69.70 %	
Pets (cat dog)					
No	N	18	23	21	Pearson Chi-square:3.5030; df=2; p=0.1735
	%	43.90%	60.53%	63.64%	
Yes	N	23	15	12	
	%	56.10%	39.47%	36.36%	
Breastfeeding					
Non breast feed	N	4	5	1	≤ 4 M/ > 4 ≤ 6 M/ > 6 ≤ 12 M Pearson Chi-square: 3.125; df=4; p=0.5371
	%	9.76 %	13.16 %	3.03 %	
> 1 ≤ 4 months	N	4	1	0	
	%	9.76%	2.63%	0 %	
> 4 ≤ 6 months	N	10	9	9	
	%	24.39 %	23.68 %	27.27 %	
> 6 ≤ 12 months	N	23	23	23	
	%	56.10 %	60.53 %	69.70 %	
Antibiotic therapy – annual frequency in the first 3 years					
Non used	N	11	12	8	Pearson Chi-square: 7.219; df=4; p=0.1248
	%	26.83 %	31.58 %	24.24 %	
< 4 times	N	18	7	9	
	%	43.90 %	18.42 %	27.27 %	
≥ 4 times	N	12	19	16	
	%	29.27 %	50 %	48.48 %	

*significant for p<0.05

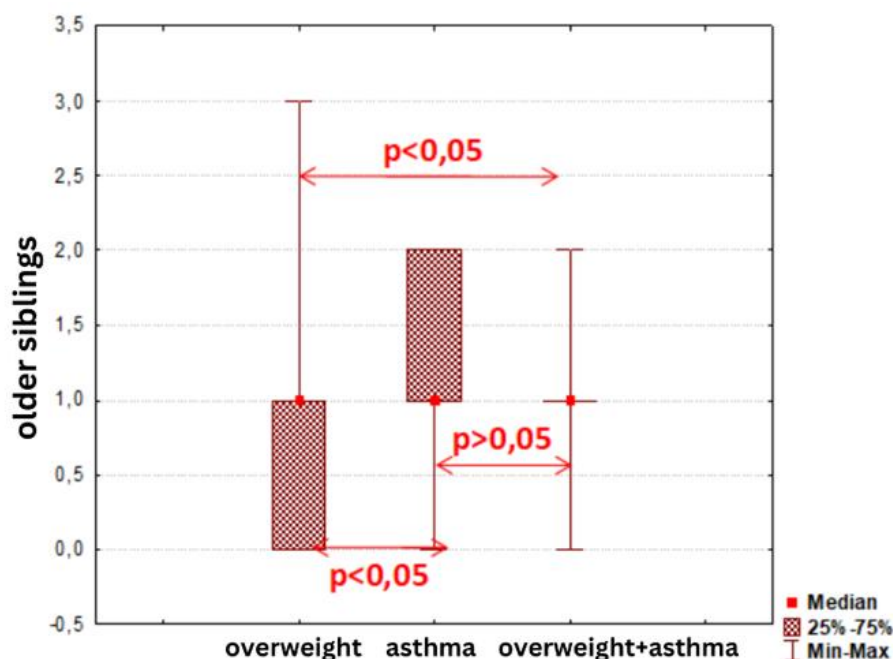


Fig. 1. Intergroup comparison of number of older siblings

For $p < 0.05$, a significant difference in the number of older siblings was determined between Overweight / Asthma / Overweight + Asthma groups for consecutive Mann-Whitney U Test: $Z = -2.619$; $p = 0.009$ and Mann-Whitney U Test: $Z = -2.433$; $p = 0.015$, in addition to a significantly lower number of older siblings in the Overweight group compared to the other two groups. Intergroup comparison of number of older siblings is presented in Figure 1.

Discussion

Many studies have confirmed the increased risk of asthma in overweight children and adolescents^[14-16]. The relationship between these two conditions is not coincidental, so determining possible hypotheses for their association is a real challenge.

A meta-analysis from 11 case-control studies revealed OR of asthma and overweight as $OR = 1.64$; (95% Confidence Interval (CI): 1.13–2.38) and from 14 case-control studies, OR for asthma and obesity was $OR = 1.92$ (95% CI: 1.39–2.65), which indicated that risk of asthma in overweight and obese children and adolescence was significantly higher (1.64 and 1.92 times) than that of individuals with (p-value < 0.01 for underweight/normal weight in both cases)^[18].

However, after adjusting for some factors that may have an impact on both asthma and obesity (age, gender, family and personal atopy, duration of breastfeeding, diet, physical activity), this dependence was decreased to 1.3 times. In this study, according to BMI, almost half of the children with asthma were overweight, with no significant difference in terms of gender. After evaluating the role of prenatal factors in the development of childhood asthma later in preschool and school years, we found a significant relationship between family history of allergy in first-grade relatives. The association of BMI with atopy was examined by Henkin *et al.*, but not confirmed^[19]. Papoutsakis *et al.* confirmed a positive association, but only with maternal familial atopy^[20]. Lawson *et al.* confirmed, however, an increased risk of asthma in overweight children only with asthma in the family^[10]. Regarding the familial atopy, it was present in 69.6% of children in the entire sample, and there was statistical significance in the groups of children with asthma, with normal and increased BMI, compared to the overweight group. It is well known that more than 80% of childhood asthma is atopic.

The impact of breastfeeding on the development of asthma is contradictory. There are studies that confirm the transient protective effect of breast milk on the development of eczema, food allergies and wheezing in the first three years of life^[21,22], but also studies that show the opposite. Most studies and meta-analyses indicate a protective effect against obesity as well^[23,24]. Breastfeeding helps in self-regulating satiety, and breast milk contains proteins and hormones that help regulate energy metabolism^[9,25]. In our study, we did not find a statistically significant difference between the groups in terms of the duration of breastfeeding during the first year of life, nor a protective effect of breastfeeding on asthma and being overweight. Namely, the largest percentage of children in the groups were breastfed for 6-12 months. In addition to the length of breastfeeding, the study also examined other factors of the "hygiene hypothesis" of asthma, such as the frequency of antibiotic therapy use in the first three years of life, attendance at a kindergarten during the same period, the number of older siblings, vaccination status, as well as passive exposure to cigarette smoke and having a pet in the home (dog, cat). Lawson *et al.* determined that frequent respiratory infections in the first three years of life, maternal smoking during pregnancy, and a dog in the home were associated with asthma in childhood^[10]. ISAAC reported a positive association of BMI with frequent use of antibiotics in the first years of life, as well as passive exposure to cigarette smoke^[9]. Fong *et al.* recently published an article demonstrating that asthma was significantly associated with antibiotic use in children. Particularly, a relationship between early antibiotic exposure and gut microbiota of the human immune system has been suggested^[26].

In our study, we did not find statistical significance with each of the examined postnatal risk factors in relation to the three study groups. Going to kindergarten, annual frequency of antibiotic therapy in the first three years of life, vaccination status and length of breastfeeding, have not been confirmed as a significant postnatal risk factor for being overweight in children with asthma. The exception is the parameter older siblings, despite the significantly lower number of older siblings in the group of overweight children compared to the other two asthma groups. This may be due to the greater attention expressed by offering food from the youngest age by parents, in families with fewer children or with one child.

What is noteworthy is that 100% of the respondents had a full vaccination status.

No statistical significance was determined between the three groups and birthweight. However, the proportion of subjects with a birth weight ≥ 3500 grams was non-significantly higher in the overweight groups compared to the asthma group. Several studies suggest an association between high birth weight (LGA ≥ 4000 g) and an increased risk of being overweight in childhood^[27-29]. The association with small birth weight (SGA ≤ 2500 g) is contradictory. There are studies that indicate a reduced risk of being overweight, studies that have shown no association, but also studies that have shown a positive association^[9,30,31]. Kochova *et al.* reported, however, that SGA infants were particularly vulnerable to developing metabolic syndrome later in life, which is a risk factor for obesity^[32]. Low birth weight was also associated with an increased risk of asthma^[33].

We aimed to identify the perinatal factors that may induce the risk of asthma development.

Conclusions

Asthma and obesity are chronic diseases with a moderately low prevalence in childhood in Macedonia, but with an increasing trend in the last two decades.

Familial atopy was confirmed as one of prenatal risk factors for asthma in childhood, independent of BMI. We did not confirm an association of asthma in overweight children in terms of prenatal exposure to maternal smoking, antibiotic therapy in the first 3 months of pregnancy, prematurity, SGA, and cesarean delivery, as prenatal risk factors. We did not confirm the "hygiene hypothesis" regarding examined postnatal risk factors, which is probably

due to the small number of subjects for epidemiological analysis. Therefore, new epidemiological studies are needed to determine the influence of possible prenatal and postnatal risk factors to clarify the complex association of obesity in children with asthma.

Conflict of interest statement. None declared.

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