ORIGINAL ARTICLE

The role of Caesarean section in childhood asthma

Al Yassen AQ, Al-Asadi JN, Khalaf SK

Al Yassen AQ, Al-Asadi JN, Khalaf SK. The role of Caesarean section in childhood asthma. *Malays Fam Physician.* 2019;14(3);10–17.

Keywords:
asthma, Basrah, childhood, Caesarean section, role

Authors:

Shukrya K. Khalaf
(Corresponding author)
FRACGP
College of Medicine, Basrah University, Iraq
E-mail: Shukryakamil@gmail.com

Asaad Q. Al Yassen
M.Sc.
College of Medicine, Basrah University, Iraq
E-mail: asaad.alyassen66@gmail.com

Jasim N. AL-Asadi
Ph. D.
College of Medicine, Basrah University, Iraq

Abstract

Objective: As indicated by previous studies, children born via Caesarean section may have an increased risk of developing asthma compared with those born via vaginal delivery. The aim of this study is to assess the association between a Caesarean section and the risk of childhood asthma.
Methods: This was a case-control study carried out in Basrah, Iraq including 952 children aged 3-12 years. Four hundred and seven asthmatic cases and a control group of 545 age-matched non-asthmatic children were enrolled. Binary logistic regression was used to assess the relationship between asthma and birth via Caesarean section.
Results: The mean age of the children was 6.7±2.5 years. Two-hundred eighty-three children (29.7%) were delivered via Caesarean section. The binary logistic regression analysis showed that delivery via Caesarean section was found to be an independent significant risk factor for asthma (OR=3.37; 95% CI=1.76-6.46; p<0.001). In addition, many other risk factors were found to be significant predictors of asthma, including bottlefeeding (OR=27.29; 95% CI=13.54-54.99; p<0.001) and low birth weight (OR=16.7; 95% CI=6.97-37.49; p<0.001).
Conclusion: Caesarean section is significantly associated with an increased risk of childhood asthma.

Introduction

Vaginal delivery is acknowledged to be a harmless and more advantageous method of childbirth for both mother and child than Caesarean section (CS). In recent years, there has been an upsurge in the proportion of children born via CS, exceeding the 15% level recommended by the World Health Organization (WHO)[1] and making CS the most common operation undergone by women of reproductive age.[2]

Authorities and clinicians have conveyed their alarm over the rise in the number of CS births and the possible adverse effects for maternal and child health.[3] The CS rate for all births in Iraq was 18% in 2008 and rose to 24.4% in 2012, well above the 15% recommended by WHO and mainly as a result of the increasing number of private hospitals and the inclinations of both women and gynecologists towards CS.[4]

Asthma is one of the common diseases of childhood and is characterized predominantly by the tightening of the bronchioles, which then leads to coughing and breathlessness. In some cases, it may be caused by contact with particular recognized allergens, but, in other cases, there is no single known causal factor. However, there is still a lot to learn about its etiology and what attributers are related to vulnerability to it.[5]

The incidence of allergies and asthma in childhood has increased noticeably over the last few years, mostly in developed countries and in parallel with the increased rate of CS deliveries.[6] According to a study that was done in Basrah ity on preschool children, the prevalence of asthma, which is considered a common health problem among children in Iraq,[7] was 15.8%.[8] Many studies, which have been done to assess the effect of mode of delivery on the development of asthma have differed in their conclusions. The researchers involved in these studies have hinted that the inclusion criteria and disease explanation standards have significant consequences on the results of such reports.[9,10] Since the medium and long-term health impacts of CSs on children are unclear, the relationship between CS and asthma remains controversials.[11-17]

Though the relationship between the method of delivery and the occurrence of asthma has been investigated in many countries, there have been no published reports in Basrah. The effect of delivery mode on the future health of the children has also not been reviewed in Basrah due to an absence of accessible information. Therefore, with the rising

number of children who have been delivered by CS, this gap needs to be addressed

The purpose of the present study is to assess the association between CS and current asthma in children in Basrah. Our original hypothesis was that children born through CS would be at greater risk for the development of asthma in comparison with those born via vaginal delivery.

Methdos

Patients

A case-control study was conducted in Basrah, Iraq for the period between April and October 2017. The study included children aged 3-12 years attending primary health care centers allover Basrah City. A list of the primary health centers was obtained from the General Directorate of Health. Out of 40 health centers distributed throughout Basrah City, ten were chosen randomly. The study included 407 asthmatic cases and 545 non-asthmatic children as a control group. The groups were frequency matched for age. The purpose of the current study was explained to the parents who accompanied their children to the primary health care centers, and their informed consent was obtained before their children were enrolled in the study.

Data collection

The parents were interviewed using a structured questionnaire, which was especially designed for the purpose of the study. The first part of the questionnaire dealt with demographic characteristics such as age, gender, maternal and paternal education, income, family size and family history of asthma. The questions in the second part concentrated on the mode of the delivery of the children. For statistical analysis, mode of delivery was classified into CS and vaginal delivery. Possible confounders for the development of asthma, including feeding patterns, cotton-filled mattress use, antibiotic use in the first year of life, family history of asthma, exposure to cigarette smoking, complications during pregnancy (such as antepartum hemorrhage, hypertension), pets and carpet usage, were also enquired about.

Using the Global Initiative for Asthma guidelines,[18] asthma was defined as recurrent pediatrician-diagnosed asthma requiring treatment resulting in at least one episode of wheezing in the previous year.[19]

The control group included children without asthma attending the same primary health care centers for other unrelated health problems. To exclude potential asthma among the controls, the core questionnaire-wheezing module for 6–7 year olds from the International Study of Asthma and Allergies in childhood was used.[20]

The Ethical Committee of the College of Medicine, Basrah University approved the study.

Statistical analysis

Univariate analysis was done to compare differences between the asthmatic and control groups, using X2 or Fisher Exact tests (where appropriate) for categorical variables. Moreover, the strength of the association was evaluated through comparing odds ratios (ORs) and 95% confidence intervals (CIs). Furthermore, a binary logistic regression analysis was performed to assess the independent risk factors of asthma. All independent variables were entered in the regression model. A p-value of <0.05 was considered to be statistically significant.

Results

Girls in this study constitute more than half of the sample (53.5%), and about 56% of the mothers had less than 12 years of education. Only 23.7% of the children were from families with a monthly income of more than 1 million Iraqi Dinar. [**Table 1**]

Table 1. Socio-demographic characteristics of the study population

Character	No.	%
Age (years)		
< 6	354	37.2
≥ 6	598	62.8
Gender		
Male	443	46.5
Female	509	53.5
Maternal education (Years)		
< 12	538	56.5
≥ 12	414	43.5
Paternal education (Years)		
< 12	509	53.5
≥ 12	443	46.5
*Monthly income (Iraqi Dinar) **		
< 500,000	379	39.8
500,000 - 1,000,000	347	36.5
> 1,000,000	226	23.7
Birth order		
First	323	33.9
Second or after	629	66.1
Family size		
< 5	516	54.2
≥ 5	436	45.8
Total	**952**	**100**

I US $= 1250 Iraqi Dinar

Table 2 presents the associations of asthma with the socio-demographic characteristics. Higher proportions of asthmatic children were girls (OR=1.67; 95% CI=1.28-2.17; p<0.001).

Lower maternal and paternal education levels were significantly associated with asthma. Similarly, low family monthly income and large family size were also significantly associated with asthma.

Table 2. Association of asthma with socio-demographic characteristics

Characteristic	Cases (n=407) No. (%)	Controls (n=545) No. (%)	OR (95% CI)	p-value
Gender				
Male	160 (39.3)	283 (51.9)	0.60 (0.46-0.78	< 0.001
Female	247 (60.7)	262 (48.1)		
Maternal education (Years)				
< 12	275 (67.6)	263 (48.3)	263 (48.3) 282 (51.7)	< 0.001
≥ 12	132 (32.4)	282 (51.7)		
Paternal education (Years)				
< 12	244 (60.0)	265 (48.6)	1.58 (1.22-2.10)	< 0.001
≥ 12	163 (40.0)	280 (51.4)		
*Monthly income (ID) **				
<500,000	140 (34.4)	239 (43.9)	1	0.009
500,000 - 1,000,000	167 (41.0)	180 (33.0)	0.63 (0.58-0.71)	
> 1,000,000	100 (24.6)	126 (23.1)	0.74 (0.67-0.82)	
Birth order				
First	138 (33.9)	185 (33.9)	0.99 (0.76-1.30)	0.990
Second or after	269 (66.1)	360 (66.1)		
Family size				
< 5	109 (26.8)	407 (74.4)	8.06 (6.02-10.80)	< 0.001
≥ 5	298 (73.2)	138 (25.3)		

* ID= Iraqi Dinar, I US $= 1250 ID

Two-hundred eighty-three children (29.7%) were delivered via CS, and 669 children (70.3%) were delivered via vaginal delivery. Delivery via CS was found to be significantly associated with asthma (OR=3.64; 95% CI=2.72-4.81; p<0.001)

Other risk factors, which were found to be significantly associated with asthma, include exposure to cigarette smoke, family history of asthma, type of feeding, and use of antibiotics during the first year of life.

No significant association was found between exposure to pets and asthma in children. [**Table 3**]

Table 3. Association of mode of delivery and other factors with asthma

Factor	Cases (N=407) No. (%)	Controls (N=545) No. (%)	p-value OR (95% CI)
Mode of delivery			
Caesarean section	183 (45.0)	100 (18.3)	< 0.001
Vaginal	224 (55.0)	445 (81.7)	3.64 (2.72-4.85)
Gestational age at delivery			
< 37 weeks	283 (69.5)	21 (3.9)	< 0.001
≥ 37 weeks	124(30.5)	524 (96.1)	10.93 (6.73-17.75)
Child history of allergy to drugs			
Positive	77 (18.9)	24 (4.4)	< 0.001
Negative	330 (81.1)	521 (95.6)	5.07 (3.14-8.17)
Family history of asthma			
Positive	267 (65.6)	145 (26.6)	< 0.001
Negative	140 (34.4)	400 (73.4)	5.26 (3.98-6.95)
Cigarette smoke exposure			
Positive	219 (53.8)	155 (28.4)	< 0.001
Negative	188 (46.2)	390 (71.6)	2.93 (2.24-3.84)
Kitchen smoke exposure			
Positive	251 (61.8)	52 (9.5)	< 0.001
Negative	156(38.2)	493 (90.5)	5.89 (4.19-8.35)
Pet exposure			
Positive	155 (38.1)	215 (39.4)	0.669
Negative	252 (60.9)	330 (60.6)	0.94 (0.73-1.23)
Cotton-filled mattress use			
Positive	186 (45.7)	142 (26.1)	< 0.001
Negative	221 (44.3)	403 (73.9)	2.39 (1.82-3.13)
Carpet use			
Positive	153 (37.6)	282 (51.7)	< 0.001
Negative	254 (62.4)	263 (48.3)	0.56 (0.43-0.73)
Type of feeding during 1st six months of life			
Bottle	338 (83.0)	97 (17.8)	< 0.001
Breast	69 (17.0)	448 (82.2)	22.62 (16.11-31.76)
Maternal antibiotic use			
Positive	205 (50.4)	152 (27.9)	< 0.001
Negative	202 (49.6)	393 (72.1)	2.62 (2.00-3.44)
Pregnancy complications			
Positive	243 (59.7)	120 (22.0)	< 0.001
Negative	164 (40.3)	425 (78.0)	5.24 (3.95-6.96)
Child use of antibiotics			
Positive	304 (74.4)	119 (21.8)	< 0.001
Negative	103 (25.3)	426 (78.2)	10.57 (7.81-14.79)
Birth weight (Kg)			
< 2.5	241(59.2)	32 (5.9)	< 0.001
≥ 2.5	166(40.8)	513 (94.1)	11.04 (7.34-16.61)

In order to examine the independent effect of method of delivery on the development of asthma, a binary logistic regression analysis was done. The method of delivery was found to be an independent significant risk factor with an OR of 3.37 (95% CI=1.76-6.46, p<0.001).

Many other risk factors were found to be significant predictors of asthma. The excluded variables were: exposure to pets, exposure to cigarette smoke, pregnancy complications, maternal used of antibiotics, carpet usage, cotton mattress, child's history of allergies to drugs, and kitchen smoke exposure. [**Table 4**]

Table 4. Logistic regression analysis

Variable	β	P-value	Expected B	95% CI of expected B
Female	0.892	0.006	2.44	1.30 - 4.59
Family size	0.506	< 0.001	1.66	1.41 - 1.96
Income	- 0.701	< 0.001	0.496	0.34 - 0.73
Low birth weight	2.783	< 0.001	16.17	6.97 - 37.49
Low gestational age at delivery	1.556	< 0.001	4.74	2.00 - 11.22
Family history of asthma	0.803	< 0.001	2.23	1.75 - 2.85
Child use of antibiotics	1.234	< 0.001	3.44	1.89 - 6.23
Mode of delivery (CS)	1.214	< 0.001	3.37	1.76 - 6.46
Type of feeding (bottle feeding)	3.307	< 0.001	27.29	13.54 - 54.99

CS= Caesarean section

Discussions

Both the univariate and multivariate analyses in our study showed that CS was significantly associated with more than a three-fold increase in the risk of childhood asthma. This result disagrees with a study done previously in Iraq, which showed no relationship between asthma in children and CS delivery.[7] This discrepancy might be due to the difference in the age group chosen for the study (they chose primary school children, and we chose younger children). Our study agrees with the result of a meta-analysis study that showed a positive relationship between asthma and CS.[21] However, other studies could not exclude the probable confounding effects of the underlying medical indications for CS[22] as well as the effect of other factors, such as parental asthma, gestational age,[17] and breast-feeding,[18] that were found to attenuate the effect of CS and make the interpretation of such an association difficult. The complicated interactions between genetic factors and environment exposures could also contribute to this inconsistency of results.[6]

Gut microbiotica has been found to play a crucial role in the development of the immune system. There is wide individual variation in the microbial colonization pattern of the infant gut.[1]

Altered microbial colonization and types during early life in the gut of infants delivered by CS may prolong the immaturity of the immune system and thereby link the development of asthma with this mode of delivery.[23-26] Infants delivered by CS are exposed to maternal skin and hospital environment microbes which differ from those in the maternal vagina.[27] It was reported that manual exposure of CS-delivered infants to vaginal microbes might partially restore their normal microbiota.[28] Furthermore, increased airway inflammation reflected by higher fractional exhaled nitric oxide levels might be another explanation for the relation between CS and asthma.[29] Epigenetic modification of gene expression in the infant immune system and a distorted perinatal stress response induced by emergency CS might influence the developing immune system.[30] During vaginal delivery, uterine contractions and infant hypoxia stimulate a stress response, leading to a high concentration of cortisol and catecholamine in infants.[31] In contrast, this stress-based hormone secretion is lacking in CS-delivered infants.[32]

In addition, anesthetic drugs used during CS are thought to cross the placental barrier and alter the immune system of the infant.[33]

Similar to the results indicated by previous studies,[14,34] our study showed that asthma

is common among children with lower gestational age. The significant relationship between asthma and low gestational age may be attributed to lung underdevelopment and increased susceptibility to respiratory infection.[35]

In agreement with other studies,[12,36,37] this study showed that breastfeeding in early infancy provides a protective effect against asthma. Breastfeeding could prevent asthma through the maturation and regulation of gut barrier function and through transmitting immunologically active cells, immune modulatory cytokines, and immunoglobulin to the infant, which could enhance immune system development.[38,39]

Although the relation between use of antibiotics in early life and asthma has been debated,[40] our study showed that antibiotic use in the first year of life is significantly associated with the risk of childhood asthma, a result that had been reported before[41,42] and may further support the hygiene theory. Alteration of microbiota through the use of antibiotics in early infancy may compromise the infant immune system, resulting in the development of asthma.[40]

The role of low birth weight as a risk factor for childhood asthma found in this study has been confirmed previously.[43] Matheson et al. demonstrated the continuing effect of low birth weight on the risk of asthma into middle age.[44] Children born with low birth weight could suffer varying degrees of lung problems, such as lower volume and lung function, which cause greater bronchial hypersensitivity to external environmental stimuli.[45,46] To the contrary, several studies showed no significant association between low birth weight and asthma,[47] at least during the first 6 years of life.[48] Such inconsistencies in results could be attributed to use of different definitions of low birth weight or a lack of control of confounding factors.[49]

In conclusion, children delivered by CS are at increased risk of developing asthma. Bottlefeeding in the first year of life, low birth weight, gestational age<37 weeks, family history of asthma, and the use of antibiotics were also associated with risk of asthma.

Limitations of the study

Our study is limited in that we were not able to control for the type of CS, and we were unable to obtain any information on whether or not vaginal delivery had been attempted in CS cases. Yet, we believe that these limitations do not affect our findings, not even in the case that an effect of type of CS is assumed, which is controversial.[50,51] In addition, the risk of occurrence of asthma was reported to be significantly associated with general anesthesia.[52] However, it is still possible that some residual confounders may have affected the results of this study; therefore, a large-scale prospective study is recommended to examine the effect of type CS, elective or emergency, on the development of childhood asthma.

Another limitation is that a skin prick test was not used to ascertain the diagnosis of asthma due to its non-availability. Furthermore, recall bias cannot be excluded. However, mothers of children with the disease or with an adverse obstetric history tend to better recall past exposure. A previous study showed that the maternal recall accuracy of a CS occurring 3 to 9 years ago was 100%, and maternal recall of severe obstetric complications was also reliable.[53]

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

References

1. Sevelsted A, Stokholm J, Bønnelykke K, et al. Caesarean section and chronic immune disorders. *Paediatrics*. 2015; 135(1): e92-8.
2. Declercq E, Menacker F, Macdorman M. Maternal risk profiles and the primary caesarean rate in the United States, 1991-2002. *Am J Public Health*. 2006; 96:867-72.
3. World Health Organization. Statement on caesarean section rates. Available from: (http://apps.who.int/iris/bitstream/10665/161442/1/WHO_RHR_15.02_eng.pdf?ua=1) Accessed on 8/1/2018.
4. Shabila NP. Rates and trends in caesarean sections between 2008 and 2012 in Iraq. *BMC Pregnancy Childbirth*. 2017;17(1):22. doi: 10.1186/s12884-016-1211-6

5. Davidson R, Roberts SE, Wotton CJ, et al. Influence of maternal and perinatal factors on subsequent hospitalization for asthma in children: evidence from the Oxford record linkage study. *BMC Pulm Med*. 2010;10:14. doi: 10.1186/1471-2466-10-14

6. Roduit C, Scholtens S, de Jongste JC, et al. Asthma at 8 years of age in children born by caesarean section. *Thorax*. 2009; 64:107–13. doi: 10.1136/thx.2008.100875

7. Al-Kubaisy W, Ali SH, Al-Thamiri D. Risk factors for asthma among primary school children in Baghdad, Iraq. *Saudi Med J*. 2005;26(3):460-66.

8. Salem MB, Al-Sadoon IO, Hassan MK. Prevalence of wheeze among preschool children in Basra governorate, southern Iraq. *East Mediterr Health J*. 2002;8(4-5): 503-8.

9. Ayanci E, Sancak R, ÖzturkF, et al. Does mode of delivery affect asthma developing in children who had neonatal sepsis? *Asthma Allergy Immunol*. 2012;10:31-7.

10. Kero J, Gissler M, Grönlund M, et al. Mode of delivery and asthma-is there a connection? *Pediatr Res*. 2002;52(1):6-11.

11. Magne F, Puchi Silva A, Carvajal B, et al. The elevated rate of caesarean section and its contribution to non-communicable chronic diseases in Latin America: the growing involvement of the microbiota. *Front Pediatr*. 2017;5:192. doi: 10.3389/fped.2017.00192

12. Chu S, Chen Q, Chen Y, et al. caesarean section without medical indication and risk of childhood asthma, and attenuation by breastfeeding. *PLoS One*. 2017;12(9):e0184920. doi: 10.1371/journal.pone.0184920

13. Black M, Bhattacharya S, Philip S, et al. Planned repeat caesarean section at term and adverse childhood health outcomes: a record-linkage study. *PLoS Med*. 2016;13(3):e1001973. doi: 10.1371/journal.pmed.1001973

14. Chen G, Chiang WL, Shu BC, et al. Associations of caesarean delivery and the occurrence of neurodevelopmental disorders, asthma or obesity in childhood based on Taiwan birth cohort study. *BMJ Open*. 2017;7(9):e017086. doi: 10.1136/bmjopen-2017-017086

15. Brix N, Stokholm L, Jonsdottir F, et al. Comparable risk of childhood asthma after vaginal delivery and emergency caesarean section. *Dan Med J*. 2017; 64(1).

16. Leung JY, Li AM, Leung GM, et al. Mode of delivery and childhood hospitalizations for asthma and other wheezing disorders. *Clin Exp Allergy*. 2015;45(6):1109-17. doi: 10.1111/cea.12548

17. Brüske I, Pei Z, Thiering E, et al. Caesarean section has no impact on lung function at the age of 15 years. *Pediatr Pulmonol*. 2015;50(12):1262-9. doi: 10.1002/ppul.23196

18. Global Initiative for Asthma. Global strategy for asthma management and prevention 2017. 2017. Available from: Available from: https://ginasthma.org/wp-content/uploads/2019/04/wmsGINA-2017-main-report-final_V2.pdf Accessed on 16/5/2018

19. Pistiner M, Gold RG, AbdulkerimH, et al. Birth by caesarean section, allergic rhinitis, and allergic sensitization among children with a parental history of atopy. *J Allergy Clin Immunol*.2008;122:274-9.

20. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8:483-91.

21 Thavagnanam S, Fleming J, Bromley A, et al. A meta-analysis of the association between caesarean section and childhood asthma. *Clin Exp Allergy*. 2008; 38(4):629-33. doi: 10.1111/j.1365-2222.2007.02780.x

22 Chu S, Zhang Y, Jiang Y, et al. Caesarean section without medical indication and risks of childhood allergic disorder, attenuated by breastfeeding. *Sci Rep*. 2017;7(1): 9762. doi: 10.1038/s41598-017-10206-3

23. Lee E, Kim BJ, Kang MJ, et al. Dynamics of gut microbiota according to the delivery mode in healthy Korean infants. *Allergy Asthma Immunol Res*. 2016;8(5): 471-7. doi: 10.4168/aair.2016.8.5.471

24 Stokholm J, Thorsen J, Chawes BL, et al. Caesarean section changes neonatal gut colonization. *J Allergy Clin Immunol*. 2016;137(3):881-9. doi: 10.1016/j.jaci.2016.01.028

25. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA*. 2010; 107:11971–5.

26. Weng M, Walker WA. The role of gut microbiota in programming the immune phenotype. *J Dev Orig Health Dis*. 2013;4(3):203-14. doi:10.1017/S2040174412000712

27. Kaplan JL, Shi HN, Walker WA. The role of microbes in developmental immunologic programming. *Pediatr Res*. 2011; 69:465-72.

28. Dominguez-Bello MG, De Jesus-Laboy KM, Shen N, et al. Partial restoration of the microbiota of caesarean-born infants via vaginal microbial transfer. *Nat Med*. 2016; 22:250-3.

29. van Berkel AC, den Dekker HT, Jaddoe VW, et al. Mode of delivery and childhood fractional exhaled nitric oxide, interrupter resistance and asthma: the Generation R study. *Pediatr Allergy Immunol*. 2015;26(4):330-6. doi: 10.1111/pai.12385

30. Cho CE, Norman M. Caesarean section and development of the immune system in the offspring. *Am J Obstet Gynecol*. 2013;208(4):249-54.

31. Lagercrantz H. Stress, arousal and gene activation at birth. *News Physiol Sci*. 1996;11:214-8.

32. Lagercrantz H, Slotkin TA. The "stress" of being born. *Sci Am*. 1986;254:100-7.

33. Rizzo A, Campanile D, Spedicato M, et al. Update on anesthesia and the immune response in newborns delivered by caesarean section. Immunopharmacol Immunotoxicol. 2011; 33:581-5.

34. Tollånes MC, Moster D, Daltveit AK, et al. Caesarean section and risk of severe childhood asthma: a population-based cohort study. J *Pediatr*. 2008;153(1):112–6.

35. Doyle LW, Anderson PJ. Adult outcome of extremely preterm infants. *Pediatrics*. 2010;126(2):342–51.

36. Soto-Ramirez N, Karmaus W, YousefiM, et al. Maternal immune markers in serum during gestation in breast milk and the risk of asthma-like symptoms at ages 6 and 12 months: a longitudinal study. *Allergy Asthma Clin Immunol*. 2012;8(1):11. doi: 10.1186/1710-1492-8-11

37. Krenz-Niedbała M, Kościński K, Puch EA, et al. Is the relationship between breastfeeding and childhoodrisk of asthma and obesity mediated by infant antibiotic treatment? *Breastfeed Med*. 2015;10(6):326-33.

38. Politis I, Chronopoulou R. Milk peptides and immune response in the neonate. *Adv Exp Med Biol*. 2008; 606:253-69. doi: 10.1007/978-0-387-4_10.

39. Munblit D, Verhasselt V. Allergy prevention by breastfeeding: possible mechanisms and evidence from human cohorts. *Curr Opin Allergy Clin Immunol*. 2016;16(5):427-33.

40. Pitter G, Ludvigsson JF, Romor P, et al. Antibiotic exposure in the first year of life and later treated asthma, a population based birth cohort study of 143,000 children. *Eur J Epidemiol*. 2016;31(1):85-94.

41. Yamamoto-Hanada K, Yang L, Narita M, et al. Influence of antibiotic use in early childhood on asthma and allergic diseases at age 5. *Ann Allergy Asthma Immunol*. 2017;119(1):54-8.

42. Xie MY, Yuan YH, Liu LM, et al. Association between use of antibacterial agents in the first year of life and childhood asthma: a meta analysis. *Zhongguo Dang Dai Er Ke Za Zhi*. 2016;18(10):995-1000.

43. Raheleh Z, Ahmad A, Abtin H, et al. The association between birth weight and gestational age and asthma in 6-7- and 13-14-year-old children. *Scientifica*. 2016; 2016:3987460. doi: 10.1155/2016/3987460

44. Matheson MC, D´ Olhaberriague AL, Burgess JA, et al. Preterm birth and low birth weight continue to increase the risk of asthma from age 7 to 43. *J Asthma*. 2017; 54(6):616-23.

45. Anand D, Stevenson CJ, West CR, et al. Lung function and respiratory health in adolescents of very low birth weight. *Arch Dis Child*. 2003;88(2):135–38.

46. Murk W, Risnes KR, Bracken MB. Prenatal or early-life exposure to antibiotics and risk of childhood asthma: a systematic review. *Pediatrics*. 2011;127(6):1125–38.

47. Mallen CD, Mottram S, Wynne-Jones G, et al. Birth-related exposures and asthma and allergy in adulthood: a population based cross-sectional study of young adults in North Staffordshire. *J Asthma*. 2008;45(4):309–12.

48. Yang HJ, Qin R, Katusic S, et al. Population-based study on association between birth weight and risk of asthma: a propensity score approach. *Ann Allergy Asthma Immunol*. 2013;110(1):18-23.

49. Villamor E, Iliadou A, Cnattingius S. Is the association between low birth weight and asthma independent of genetic and shared environmental factors? *Am J Epidemiol*. 2009;169:1337-43. doi: 10.1093/aje/kwp054.

50. Almqvist C, Cnattingius S, Lichtenstein P, et al. The impact of birth mode of delivery on childhood asthma and allergic diseases—a sibling study. *Clin Exp Allergy*. 2012;42(9):1369–76. doi: 10.1111/j.1365-2222.2012.04021.x

51. Black M, Bhattacharya S, Philip S, et al. Planned repeat caesarean section at term and adverse childhood health outcomes: a record-linkage study. *PLoS Med*. 2016;13(3):e1001973. doi: 10.1371/journal.pmed.1001973

52. Chen G, Chiang WL, Shu BC, et al. Associations of caesarean delivery and the occurrence of neurodevelopment disorders, asthma or obesity in childhood based on Taiwan birth cohort study. *BMJ Open*. 2017;7:e017086. doi:10.1136/bmjopen-2017-017086

53. Sou SC, Chen WJ, Hsieh WS, et al. Severe obstetric complications and birth characteristics in preterm or term delivery were accurately recalled by mothers. *J Clin Epidemiol*. 2006;59:429–35. doi: 10.1016/j.jclinepi.2005.08.010