Zeynep Kamil Med J 2024;55(3):162–167
DOI: 10.14744/zkmj.2024.39269

ORIGINAL ARTICLE

The association of phototherapy for neonatal hyperbilirubinemia and childhood allergic disease

[1,2]Mehtap KAYA
[2,3]Fatih ÇİÇEK
[2]Feyza Mediha YILDIZ
[4,5]Mahmut DOĞRU

[1]Division of Pediatric Nephrology, Department of Pediatrics, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey

[2]Department of Pediatrics, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

[3]Department of Pediatric Allery and Immunology, Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey

[4]Department of Pediatric Allergy and Immunology, Memorial Sisli Hospital, Istanbul, Turkey

[5]Division of Pediatric Allergy and Immunology, University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center, Istanbul, Turkey

ORCID ID
MK : 0000-0002-6750-5172
FÇ : 0000-0001-7348-7081
FMY : 0000-0002-8684-0101
MD : 0000-0001-9728-8028

ABSTRACT

Objective: The prevalence of allergic diseases is increasing worldwide. Phototherapy has been identified as a potential risk factor associated with childhood allergic diseases, including allergic asthma, allergic rhinitis (AR), and atopic dermatitis (AD). In this study, our aim is to assess the relationship between phototherapy and these common childhood allergic diseases.

Material and Methods: We analyzed 621 children between the ages of 3-17, including a patient group of 371 who received phototherapy during the neonatal period and a control group of 250 who did not receive phototherapy. The International Study of Asthma and Allergy in Childhood (ISAAC) survey was administered to all cases. For participants with allergic diseases, plasma eosinophil and total immunoglobulin (Ig) E levels were analyzed, and a skin prick test was conducted.

Results: There was no statistically significant association between the patient and control groups in terms of the diagnosis of wheeze/asthma, AR, AD, and phototherapy treatment. The percentage of eosinophilia was significantly higher in the patient group ($p=0.01$). Cesarean section was more frequent in the control group ($p<0.05$).

Conclusion: According to our study, there was no significant relationship between phototherapy treatment and the incidence of childhood asthma, AR, and AD.

Keywords: Allergic asthma, allergic rhinitis, atopic dermatitis, children, phototherapy.

Cite this article as: Kaya M, Çiçek F, Yıldız FM, Doğru M. The association of phototherapy for neonatal hyperbilirubinemia and childhood allergic disease. Zeynep Kamil Med J 2024;55(3):162–167.

Received: February 26, 2024 **Revised:** March 29, 2024 **Accepted:** April 01, 2024 **Online:** August 14, 2024
Correspondence: Mehtap KAYA, MD. Kartal Dr. Lutfi Kırdar Şehir Hastanesi, Çocuk Sağlığı ve Hastalıkları Kliniği, Çocuk Nefrolojisi Bölümü, İstanbul, Türkiye.
Tel: +90 505 949 21 09 **e-mail:** mehtap_ky@hotmail.com

INTRODUCTION

Allergy can be defined as an exaggerated immune response of the body against allergens and antigens. Allergic diseases, including asthma, allergic rhinitis (AR), and atopic dermatitis (AD), are frequently observed in childhood, and their frequency has been increasing over the last 30 years, especially in developing countries.[1] They represent a significant cause of morbidity in children. Therefore, it is essential to identify and prevent risk factors associated with allergic diseases. These risk factors include genetic predisposition, obesity, gender, and emotional and environmental factors.[2] Additionally, several perinatal and neonatal factors have been linked to childhood allergic diseases, such as low gestational age, preterm birth, low birth weight, breastfeeding, hyperbilirubinemia, and phototherapy.[3]

Neonatal hyperbilirubinemia/jaundice results from the production of unconjugated bilirubin in newborns. This condition results from a metabolic dysregulation that leads to increased bilirubin production surpassing the capacity of bilirubin elimination via the liver and intestines, posing a risk of neurological impairment if not adequately managed.[4] Every year 60% of term and 80% of preterm babies develop neonatal hyperbilirubinemia within the first two weeks of life.[5] Therefore, it is crucial for clinicians to evaluate the short-term and lasting impacts of elevated bilirubin levels and phototherapy.

Bilirubin is produced as the final result of breaking down heme, a process initiated by the enzyme heme oxygenase, which catalyzes the decomposition of heme. This is followed by the conversion of biliverdin into bilirubin through reduction.[6] At a physiological level, bilirubin has been shown to be a naturally occurring antioxidant.[6] The mainstay of hyperbilirubinemia treatment is phototherapy. It converts unconjugated bilirubin into water-soluble forms.[7] Phototherapy has both acute and late side effects. Acute side effects involve disruption of the relationship between child and mother, imbalances in body temperature and fluid-electrolyte levels, bronze baby syndrome, skin damage, changes in blood composition, intestinal paralysis, an open ductus arteriosus, and eye problems. Late side effects involve tumors, skin damage, and allergic conditions.[8]

The pathophysiology of allergic diseases is based on the balance between oxidants and antioxidants. Phototherapy leads to an increase in pro-inflammatory cytokines and a decrease in the T helper 2 (Th2) to T helper 1 (Th1) switching, as well as a decrease in interleukin 6 (IL-6), which is an anti-inflammatory cytokine.[9] These changes all contribute to an increased risk of allergic diseases and inflammatory conditions. Many studies have demonstrated that phototherapy can cause damage to DNA and induce lymphocyte apoptosis.[10] Additionally, phototherapy suppresses T lymphocyte activity, resulting in DNA chain breaks and mutations.[11] It is also reported that bilirubin suppresses T-cell proliferation, activation, and IL-2 production. The inhibition of T-cell function leads to an increased risk of developing allergic diseases by reducing regulatory T cells (Treg).[12] Despite the effects of hyperbilirubinemia and phototherapy on the development of allergic diseases, the results of the studies are challenging.

In our study, we aimed to assess the relationship between phototherapy and common childhood allergic diseases: allergic asthma, AR, and AD.

MATERIAL AND METHODS

This is a prospective study conducted at Zeynep Kamil Maternity and Children Training and Research Hospital. We analyzed a total of 621 children between the ages of three and 17, comprising 366 males and 255 females. This cohort included a patient group of 371 who received phototherapy during the neonatal period and a control group of 250 patients who did not receive phototherapy. The International Study of Asthma and Allergies in Childhood (ISAAC) survey was administered to all 621 cases to assess allergic diseases.

We planned to analyze eosinophil and total IgE levels and conduct a skin prick test in cases with allergic diseases. The questionnaire included the ISAAC survey and information on demographics, birth data, maternal pregnancy history, and family history of allergies.

The study received approval from the Zeynep Kamil Maternity and Children Training and Research Hospital Ethical Committee (date, 25.04.2014; decision number: 54). All procedures adhered to the ethical principles outlined in the Declaration of Helsinki. Written consent forms were obtained from the parents.

Skin Prick Test

Skin prick tests with common aeroallergens, including Dermatophagoides pteronyssinus, Dermatophagoides farinae, Alternaria alternata, cockroaches (Blattella germanica), cat dander, dog dander, a mixture of grass pollens (Lolium perenne, Dactylis glomerata, Phleum pratense, Anthoxanthum odoratum, Poa pratensis, Festuca elatior, Agrostis vulgaris, Holcus lanatus, Cynodon dactylon, Avena sativa, Avena fatua, Lotus corniculatus), a mixture of grain pollens (oats, wheat, barley, corn), a mixture of tree pollens (Acer pseudoplanatus, Aesculus hippocastanum, Robinia pseudoacacia, Tilia platyphyllos, Platanus vulgaris), and weed mix pollens (Medicago sativa, Trifolium pratense, Brassica nigra, Urtica dioica, Rumex acetosa; Stallergenes SA, Antony, France), were conducted with a lancet. The anterior surface of the forearm was used for administration. Histamine (10 mg/ml) and physiological saline were used as positive and negative references, respectively. Skin reactions were assessed 20 minutes after the skin test application, with indurations of ≥3mm deemed to signify a positive response.

Serum Total Immunoglobulin E and Eosinophil Counts

Serum total IgE levels were analyzed using the nephelometry system (Siemens Healthcare Diagnostics Inc., Deerfield, Germany), and values over 100 IU/ml were considered high. The total number of eosinophils and blood eosinophils percentage were determined through an automated blood analyzer, the ABX Pentra 80 (HORIBA Medical, Montpellier, France), with percentages above 4% regarded as elevated.

Statistical Analysis

All analyses were conducted using Statistical Package for the Social Sciences (SPSS) Version 15. For statistical analyses of qualitative data and comparisons between two groups, the Pearson chi-squared test and the independent Mann-Whitney U test were employed, respectively. Findings were estimated with a 95% confidence interval, and statistical significance was determined with a two-tailed corrected p-value of <0.05.

Table 1: Age and gender distribution of patient and control groups

	Patient group (n=371)	Control group (n=250)	p
Gender			0.578*
Boys, n (%)	222 (%59.8)	144 (%57.6)	
Girls, n (%)	149 (%40.2)	106 (%42.4)	
Age (years)	7.65±3.75	7.19±1.79	0.563**

*: Chi-Square Test; **: Mann-Whitney U test.

Table 2: Demographics, birth data, background of mother's pregnancy and family history of allergy of patient and control groups

	Patient group (n=371)		Control group (n=250)		p
	n	%	n	%	
Consanguinity	61	16.4	51	20.4	>0.05
Family history of allergic disease	117	31.5	75	30	>0.05
Gestational diabetes	18	4.8	20	8	>0.05
Pre-eclampsia	14	3.7	7	2.8	>0.05
Maternal smoking during pregnancy	34	9.1	31	12.4	>0.05
Delivery method					
Vaginal delivery	216	58.2	102	40.8	>0.05
Caesarean section	149	40.1	143	57.2	*0.01

*: Significant difference between the patient and control groups, p<0.05.

RESULTS

In total, 621 children were evaluated: 366 boys (58.9%) and 255 girls (41.1%). Among them, 371 children received phototherapy for neonatal jaundice, with 222 boys (59.8%) and 149 girls (40.2%). The control group consisted of 250 children, including 144 boys (57.6%) and 106 girls (42.4%). There was no significant difference in gender distribution (p=0.578). The mean age of the patient group was 7.19±1.79 years, and for the control group, it was 7.65±3.75 years. There was no significant difference in age distribution (Table 1).

There were no statistically significant differences in consanguinity, a family history of allergic disease, gestational diabetes, a history of preeclampsia, tobacco smoke exposure, or tobacco smoking during pregnancy between the patient and control groups (p>0.05). Cesarean section was more frequent in the control group (p<0.05) (Table 2).

The mean total serum bilirubin (TSB) level of the patient group was 19.6±3.7 mg/dL. Children received phototherapy for an average of 58.7±28.6 hours (ranging from 24 to 240 hours). We analyzed the etiology of hyperbilirubinemia in the patient group; the reason was unknown in 227 patients (61.2%), ABO incompatibility was detected in 62 patients (16.7%), Rh incompatibility in 28 patients (7.5%), dehydration in 22 patients (5.9%), subgroup incompatibility in 16 patients (4.3%), sepsis in 13 patients (3.5%), glucose-6-phosphate dehydrogenase deficiency (G6PD) in two patients (0.5%), and hereditary spherocytosis in one patient (0.3%). There was no statistically significant association between the patient and control groups in terms of the diagnosis of wheeze/asthma, nighttime coughing, exercise-induced wheeze, AR, and AD, with a p-value >0.05 (Table 3).

Doctor-diagnosed allergic asthma and/or allergic rhinitis and/or atopic dermatitis were detected in 87 (23.5%) children in the patient group and 68 (27.2%) children in the control group; however, there was no statistical significance with a p-value of 0.29 (Table 3).

The prick test could be applied to 32 of the 82 cases in the patient group and 38 of the 68 cases in the control group with doctor-diagnosed allergic disease. Additionally, total IgE levels and the percentage of eosinophilia were analyzed. The percentage of eosinophilia was higher in the patient group (p=0.012). On the other hand, the presence of atopy detected in the prick test and total IgE levels showed no difference between the patient and control group (p=0.509 and p=0.327, respectively) (Table 4).

DISCUSSION

Phototherapy/hyperbilirubinemia has been mentioned as a potential risk factor for the development of allergy.[13] However, we did not find a significant association between phototherapy and the risk of developing childhood asthma, AR, and AD in our study. Despite the

Table 3: Comparison of diagnosis of allergic disease according to ISAAC questionnaire between patient and control groups

	Patient group		Control group		p
	n	%	n	%	
Diagnosis of wheeze/asthma	137	36.9	96	38.4	0.710*
Nighttime coughing	21	5.7	17	68	0.568*
Exercise induced wheeze	23	6.2	15	6	0.907*
Allergic rhinitis	58	15.6	52	20.8	0.098*
Atopic dermatitis	25	6.7	13	5.2	0.433*
Doctor diagnosed allergic asthma	57	15.4	38	15.3	0.972*
Doctor diagnosed allergic rhinitis	45	12.1	36	14.4	0.399*
Doctor diagnosed atopic dermatitis	15	4	11	4.4	0.820*

*: Chi-Square Test.

Table 4: Values of eosinophilia and immunoglobulin E levels

	Patient group (n=22)	Control group (n=32)	p
Percentage of eosinophilia (%)	4.1+2.8	3.2+2.9	0.012*
Immunoglobulin E levels (IU/mL)	232+404	222+397	0.327

*: Significant difference between patient and control group, p<0.05.

potential enhancing effects of phototherapy/hyperbilirubinemia on allergic inflammation, different results have been obtained on this issue. These discrepancies may be attributed to variations in factors such as study design, patient population, and diagnostic criteria for allergic diseases.

The first study about the relationship between asthma and neonatal phototherapy/hyperbilirubinemia was conducted in 2007 by Aspberg et al.[9] They assessed children admitted to the hospital diagnosed with asthma and showed that neonatal phototherapy or neonatal hyperbilirubinemia was independently associated with an increased risk for developing childhood asthma. In another study conducted by Aspberg et al.,[13] any prescribed asthma medication was accepted as a diagnosis of asthma, and they obtained results similar to their previous study. Kuzniewicz et al.[14] conducted a study involving 109,212 infants. For the diagnosis of asthma, they used the criteria of at least two physician-diagnosed asthma attacks and/or at least two prescriptions for asthma medication after the age of two years. According to their study, even though modest levels of hyperbilirubinemia were associated with asthma, higher bilirubin levels were not associated with it. In 2018, Tham et al.[15] did not observe any association between phototherapy and the frequency of allergic diseases in the first five years of life in a prospective study involving 135 children. Similarly, we did not find a relationship between asthma and phototherapy treatment, which is consistent with this study. These differences among studies in this area may be attributed to the parabolic relationship between hyperbilirubinemia and asthma, in addition to factors such as study design, diagnostic criteria, and sample selection. It is exceedingly challenging to separate the impacts of high bilirubin levels and phototherapy treatment on allergic diseases due to their strong association. There is a need for more comprehensive studies.

Allergic rhinitis was another allergic condition we evaluated in our study. The first study investigating the relationship between neonatal hyperbilirubinemia and allergic rhinitis was conducted by Sun et al.[16] In this study, 11,328 children born between 1997 and 2000 were followed up until the age of ten. They discovered a significant association between neonatal hyperbilirubinemia and AR.[16] In another study, babies born between 2000 and 2007 were monitored until 2008. Across all age groups, the incidence of all allergic diseases was higher in the neonatal jaundice cohort than in the non-neonatal jaundice cohort.[17] Safar et al.[18] compared 300 allergic children with a mean age of 3.4–3.7 years to 300 controls. They concluded that hyperbilirubinemia and phototherapy have a statistically significant association with the development of allergic diseases. In contrast to these studies, Tham et al.[15] followed 1058 infants up to the age of five years and found no difference in AR between those who received phototherapy and those who did not. Our results were consistent with this study.

The last allergic disease we investigated in our study was AD. The most comprehensive study on this subject is the study by Egeberg et al.[19] They encompassed 85,743 children who developed AD within the first five years of their life and concluded that neonatal hyperbilirubinemia was associated with an increased risk of AD. A population-based study conducted in Taiwan revealed similar results to Egeberg et al.[19,20] In contrast to these studies, Tham et al.[15] found no relationship between receiving phototherapy and the development of AD. Likewise, we did not find a significant association between AD and phototherapy treatment.

Additionally, there are two systematic reviews that have evaluated the association between allergic diseases and hyperbilirubin-

emia/receiving phototherapy. One of these systematic reviews was conducted by Das et al.[21] They published a systematic review that included seven high-quality studies on childhood allergic diseases and neonatal hyperbilirubinemia. They concluded that there was a significant association between childhood allergic diseases and neonatal hyperbilirubinemia and/or neonatal phototherapy. However, the evidence obtained was deemed to be 'low-quality'.[21]

The review conducted by Kuniyoshi et al.[22] included fourteen studies. This review revealed that neonatal hyperbilirubinemia was associated with a higher risk of childhood asthma. Neonatal phototherapy was also linked to an increased likelihood of developing asthma and AR in childhood. In conclusion, this review suggests that neonatal hyperbilirubinemia and phototherapy may be considered as potential etiological factors for allergic diseases developing in childhood; however, the associations appear to be weaker than previously estimated.[22]

In 2010, Gloria-Bottini et al.[23] conducted a study on Adenosine Deaminase locus 1 (ADA1) polymorphisms. The study has shown that the ADA12 allele was linked to elevated bilirubin levels in newborn infants and it was a defense mechanism against asthma. Individuals carrying the ADA12 allele are found to be less common in people with asthma compared to those in the control group ($p<0.05$). In the group analyzed from birth, allergic rhinitis and/or conjunctivitis occurred more often in newborns who underwent phototherapy than among those who did not receive it ($p=0.046$). In conclusion, these findings back the theory that the ADA12 allele, by raising bilirubin levels in newborns, could shield infants from oxidative stress. This genetic trait may lead to a shift towards a Th1 immune response, hence reducing the likelihood of allergic symptoms in later life. The ADA12 allele may play an effective role in the parabolic relationship between allergic diseases and jaundice/phototherapy.[23] There is a need for further research to obtain more precise information.

One of the limitations of our study is the small number of patients. Additionally, there was a high frequency of caesarean section deliveries in our control group, which is known to be a risk factor for allergic diseases.[24] While there were no differences in other factors that may influence the development of allergic diseases between our control and patient groups, the disparity in caesarean section deliveries may have an impact on the prevalence of allergic diseases in our control group.

The strength of our study lies in the inclusion of patients across a wide age range, from three to 18 years old. In other studies examining the relationship between the development of allergic diseases and neonatal hyperbilirubinemia, cases within a limited age range were assessed. Due to the broad age range in our study, we believe it is important in providing a more accurate reflection of real-life data.

CONCLUSION

In conclusion, our study did not find a significant relationship between phototherapy treatment and the incidence of childhood asthma, AR, and AD. This result, which contradicts the findings of most previous studies, may be attributed to the inclusion of only patients who received phototherapy in our study. More extensive research is required in this area.

Statement

Ethics Committee Approval: The University of Health Sciences, Turkey. Istanbul Zeynep Kamil Maternity and Children's Diseases Health Training and Research Center Clinical Research Ethics Committee granted approval for this study (date: 25.04.2014, number: 54).

Author Contributions: Concept – MK, FÇ, MD, FMY; Design – MK, FÇ, MD, FMY; Supervision – MK, FÇ, MD, FMY; Resource – MK, FÇ; Materials – MK, FÇ; Data Collection and/or Processing – MK, FÇ; Analysis and/or Interpretation – MK, FÇ, MD, FMY; Literature Search – MK, FÇ; Writing – MK; Critical Reviews – MD, FMY.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study has received no financial support.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Kansen HM, Lebbink MA, Mul J, van Erp FC, van Engelen M, de Vries E, et al. Risk factors for atopic diseases and recurrent respiratory tract infections in children. Pediatr Pulmonol 2020;55:3168–79.
2. Hallit S, Raherison C, Malaeb D, Hallit R, Kheir N, Salameh P. The AAA risk factors scale: A new model to screen for the risk of asthma, allergic rhinitis and atopic dermatitis in children. Med Princ Pract 2018;27:472–80.
3. Yu B, Dai L, Chen J, Sun W, Chen J, Du L, et al. Prenatal and neonatal factors involved in the development of childhood allergic diseases in Guangzhou primary and middle school students. BMC Pediatr 2019;19:479.
4. Olusanya BO, Kaplan M, Hansen TWR. Neonatal hyperbilirubinaemia: A global perspective. Lancet Child Adolesc Health 2018;2:610–20.
5. UNICEF. The state of the world's children 2017. Children in a digital world. December, 2017. Available at: https://www.unicef.org/reports/state-worlds-children-2017. Accessed Mar 25, 2018.
6. Maruhashi T, Kihara Y, Higashi Y. Bilirubin and endothelial function. J Atheroscler Thromb 2019;26:688–96.
7. Bhutani VK; Committee on Fetus and Newborn; American Academy of Pediatrics. Phototherapy to prevent severe neonatal hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics 2011;128:e1046–52.
8. Faulhaber FRS, Procianoy RS, Silveira RC. Side effects of phototherapy on neonates. Am J Perinatol 2019;36:252–7.
9. Aspberg S, Dahlquist G, Kahan T, Källén B. Is neonatal phototherapy associated with an increased risk for hospitalized childhood bronchial asthma? Pediatr Allergy Immunol 2007;18:313–9.
10. Yahia S, Shabaan AE, Gouida M, El-Ghanam D, Eldegla H, El-Bakary A, et al. Influence of hyperbilirubinemia and phototherapy on markers of genotoxicity and apoptosis in full-term infants. Eur J Pediatr 2015;174:459–64.
11. Rosenstein BS, Ducore JM. Enhancement by bilirubin of DNA damage induced in human cells exposed to phototherapy light. Pediatr Res 1984;18:3–6.
12. Liu Y, Li P, Lu J, Xiong W, Oger J, Tetzlaff W, et al. Bilirubin possesses powerful immunomodulatory activity and suppresses experimental autoimmune encephalomyelitis. J Immunol 2008;181:1887–97.

13. Aspberg S, Dahlquist G, Kahan T, Källén B. Confirmed association between neonatal phototherapy or neonatal icterus and risk of childhood asthma. Pediatr Allergy Immunol 2010;21:e733–9.
14. Kuzniewicz MW, Niki H, Walsh EM, McCulloch CE, Newman TB. Hyperbilirubinemia, phototherapy, and childhood asthma. Pediatrics 2018;142:e20180662.
15. Tham EH, Loo EXL, Goh A, Teoh OH, Yap F, Tan KH, et al. Phototherapy for neonatal hyperbilirubinemia and childhood eczema, rhinitis and wheeze. Pediatr Neonatol 2019;60:28–34.
16. Sun HL, Lue KH, Ku MS. Neonatal jaundice is a risk factor for childhood allergic rhinitis: A retrospective cohort study. Am J Rhinol Allergy 2013;27:192–6.
17. Wei CC, Lin CL, Shen TC, Kao CH. Neonatal jaundice and risks of childhood allergic diseases: A population-based cohort study. Pediatr Res 2015;78:223–30.
18. Safar H, Elsary AY. Neonatal jaundice: The other side of the coin in the development of allergy. Am J Perinatol 2020;37:1357–63.
19. Egeberg A, Andersen YM, Gislason G, Skov L, Thyssen JP. Neonatal risk factors of atopic dermatitis in Denmark - Results from a nationwide register-based study. Pediatr Allergy Immunol 2016;27:368–74.
20. Gau C-C, Lee WF, Lu I-C, Lin LL, Wu CY, Tsai HJ, et al. Neonatal jaundince and risk of allergic diseases by 6 years of age: A cohort study. J Allergy Clin Immunol 2018;141:AB5.
21. Das RR, Naik SS. Neonatal hyperbilirubinemia and childhood allergic diseases: A systematic review. Pediatr Allergy Immunol 2015;26:2–11.
22. Kuniyoshi Y, Tsujimoto Y, Banno M, Taito S, Ariie T. Neonatal jaundice, phototherapy and childhood allergic diseases: An updated systematic review and meta-analysis. Pediatr Allergy Immunol 2021;32:690–701.
23. Gloria-Bottini F, Bottini E. Is there a role of early neonatal events in susceptibility to allergy? Int J Biomed Sci 2010;6:8–12.
24. Gerlich J, Benecke N, Peters-Weist AS, Heinrich S, Roller D, Genuneit J, et al. Pregnancy and perinatal conditions and atopic disease prevalence in childhood and adulthood. Allergy 2018;73:1064–74.