



Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Spring season birth is associated with higher emergency department admission for acute allergic reactions

Gianfranco Cervellin^a, Fabio Schirosa^a, Ruggero Buonocore^b, Antonio Nouvenne^c, Loris Borghi^c, Tiziana Meschi^c, Giuseppe Lippi^{b,*}^a Emergency Department, Academic Hospital of Parma, Parma, Italy^b Laboratory of Clinical Chemistry and Hematology, Academic Hospital of Parma, Parma, Italy^c Department of Clinical and Experimental Medicine, Academic Hospital of Parma, Parma, Italy

ARTICLE INFO

Article history:

Received 25 April 2015

Received in revised form 18 August 2015

Accepted 1 November 2015

Available online xxxx

Keywords:

Allergy

Anaphylaxis

Emergency medicine

Emergency department

Epidemiology

ABSTRACT

Background: Acute allergic reactions are important causes of emergency department (ED) admission, imposing a significant clinical and organizational burden. Since the season of birth is linked with early exposure to allergens, this study was aimed to establish whether an association exists between season of birth and incidence and severity of acute allergic reactions in the ED.

Methods: The electronic hospital database was searched to identify all consecutive adult patients who were admitted to the ED for acute allergic reactions compared to those born in autumn and in all other seasons, respectively during a 1-year period.

Results: The final study population consisted in 588 patients (328 women and 260 men; mean age 43 ± 18 years, range 16–96 years). Increased frequency of ED admission was observed for patients born in spring, whereas the lowest frequency was found for those born in autumn. Patients born in spring exhibited 1.19 and 1.12 higher risk of ED admission for acute allergic reactions compared to those born in autumn and in all other seasons, respectively. This difference remained significant in patients with allergic reaction attributable to drugs and in those with unknown triggers, whereas no pattern of seasonality was observed in patients with allergic reactions attributable to aliments, hymenoptera, chemicals or inhalants. Patients born in spring also exhibited 1.86 and 1.52 higher risk of being admitted to the ED for severe acute allergic reactions compared to those born in autumn and in all other seasons, respectively.

Conclusions: Patients born in spring appear particularly vulnerable to allergic reactions requiring ED visit.

© 2015 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

1. Introduction

Acute allergic reactions represent an important cause of Emergency Departments (ED) visit, exhibiting an incremental trend in the past decades [1,2]. Beside allergic rhinitis (a rare cause of presentation to the ED) and asthma (representing a distinct disease), the most common forms of acute allergic reactions include acute urticaria, acute angioedema, and anaphylaxis. Acute urticaria is a self-limited condition, which may be associated with angioedema or more serious disorders such as anaphylaxis [3]. A recent survey concluded that cases of urticaria may account for as many as 1% of all ED visits [4].

Angioedema involves the reticular (deep) dermis and subcutaneous and submucosal tissues. When the affected areas involve the upper respiratory tract, angioedema becomes a true medical emergency. Anaphylaxis is a serious, rapidly developing and often life-threatening

allergic reaction [5]. Reliable epidemiological data on incidence of anaphylactic reactions are scarce, mostly emerging from heterogeneous clinical settings such as the general population [6,8], ED patients [7], hospital admitted patients [9], and specialist allergy clinics [10–12]. It has been reported that only 1% of ED visits for acute systemic allergic reactions may receive a final diagnosis of anaphylaxis, whereas a large number of cases are classified as “acute allergic reactions” or “acute hypersensitivity reactions” [13–15].

The current knowledge about predisposing factors for acute severe allergic reactions is limited [16–19]. An association between the date of birth and the frequency of allergy in childhood has been described in the past decades [16]. More specifically, previous epidemiological investigations described a relationship between season of birth and prevalence of allergy in the childhood age, in that autumn/winter births were occasionally found to be more frequent than spring/summer births in patients with different forms of childhood allergy including asthma, atopy, food allergies and skin sensitization [20–28]. However, this data mostly emerged from prevalence studies (e.g., surveys) or allergy clinic-based, whereas no specific information has been published on the relationship between season of birth and ED visits for acute

* Corresponding author at: U.O. Diagnostica Ematochimica, Dipartimento di Patologia e Medicina di Laboratorio Azienda Ospedaliero-Universitaria di Parma, Via Gramsci, 14, 43126 Parma, Italy.

E-mail addresses: gliippi@ao.pr.it, ulippi@tin.it (G. Lippi).

allergic reactions in adults to the best of our knowledge. Since in many climatic settings early exposure to allergens depends on the season of birth, this study was hence aimed to establish whether an association exists between season of birth, incidence and severity of acute allergic reactions in adult patients visiting the ED.

2. Materials and methods

The study population consisted in all consecutive adult patients admitted to the ED of the University Hospital of Parma (Italy) for acute allergic reactions, during the entire year 2013. The facility is a 1250-bed teaching general hospital, serving a population of approximately 435,000 inhabitants. The information about ED visits for acute allergic reaction was identified from the electronic hospital database during a 1-year period (1st January to 31st December 2013), using a double extraction key, i.e., ICD-9 codes 999, 995, 716, 708, 477 and 287 (including all the 4th and 5th digits), as well as verbal “strings”, i.e. “allergy”, “anaphylaxis”, “urticaria”, “angioedema”, “shock”. Each acute allergic reaction was classified as “severe” when the “Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium” criteria for anaphylaxis were met [6].

The statistical analysis included Pearson's χ^2 statistics and calculation of the relative risk (RR) with 95% confidence interval (95% CI) using Analyse-it (Analyse-it Software Ltd, Leeds, UK) and MedCalc Version 12.3.0 (MedCalc Software, Mariakerke, Belgium). The RR was calculated from the difference between the frequency distribution of the month of birth of patients admitted to the ED with acute allergic reactions and the frequency distribution of the month of birth of the resident population (official data obtained from the National Institute for Statistics (Istat). <http://demo.istat.it/altridati/IscrittiNascita/>. Last Access 25 April 2015). The study was performed in accordance with the Declaration of Helsinki, under the terms of relevant local legislation.

3. Results

A total number of 3237 records were retrieved and analyzed after first extraction by two separate physicians, to exclude incorrect or dubious records. Children aged 16 years or younger ($n = 273$ cases) were not included in this analysis, since most of children patients with acute allergic reactions (even severe reactions) in our hospital visit outpatient Pediatric Clinic instead of visiting the ED. Almost two-thirds of study subjects ($n = 2376$) were excluded due to other disease entities (i.e., allergic rhinitis, $n = 267$; asthma, $n = 1475$; chronic urticaria, $n = 634$), thus limiting our analysis to adult patients admitted with acute urticaria, acute angioedema, urticaria–angioedema and anaphylaxis. Overall, the final study population consisted in 588 patients (328 women and 260 men; mean age 43 ± 18 years, range 16–96 years), representing 0.65% of all ED visits recorded during the study period. All patients were admitted to the ED within 12 h from the onset of symptoms and none of them was visited twice for the same problem during the study period. Fifty-six patients met the diagnostic criteria for anaphylaxis (9.5%), 75 for angioedema (12.7%), 363 for urticaria (61.7%), and 95 for urticaria–angioedema (16.1%). The suspected triggers of the allergic reaction included drugs ($n = 123$; 20.9%), foods ($n = 88$; 15.0%), hymenoptera ($n = 58$; 9.9%), chemicals ($n = 26$; 4.4%), and inhalants ($n = 6$; 0.01%), whereas a specific cause could not be recognized in nearly half of the cases ($n = 287$; 48.9%). The frequency distribution of the month of birth of the resident population and patients admitted to the ED with acute allergic reactions is shown in Table 1. Compared to the resident population, patients admitted to the ED for acute allergic reactions were more frequently born in the Italian spring season (March, April and May) than in the Italian autumn season (September, October and November) (Pearson's χ^2 statistics, 4.47; $p = 0.034$) (Fig. 1). This difference remained statistically significant in

Table 1

Frequency of month of birth of the Italian resident population and patients admitted to the emergency department for acute allergic reactions.

	Resident population	Allergic patients	Difference
January	8.6%	9.2%	0.5%
February	7.4%	7.3%	−0.1%
March	7.8%	7.7%	−0.1%
April	7.2%	8.8%	1.6%
May	8.1%	9.7%	1.6%
June	8.0%	9.0%	1.0%
July	9.1%	9.0%	−0.1%
August	8.8%	9.2%	0.4%
September	9.1%	7.5%	−1.6%
October	8.9%	7.7%	−1.3%
November	8.3%	6.8%	−1.5%
December	8.7%	8.2%	−0.5%

patients with allergic reaction attributable to drugs and in those without known triggers, whereas no pattern of seasonality was observed in patients with allergic reactions attributable to foods, hymenoptera, chemicals or inhalants (Table 2). The RR for ED admission for total allergic reactions of patients born in spring was 1.19 (95% CI, 1.01–1.41) compared to those born in autumn. A similar trend was observed comparing spring births with births in the three other seasons (RR, 1.12; 95% CI, 0.99–1.27). Even more importantly patients admitted to the ED for severe acute allergic reactions (i.e., anaphylaxis) were also more frequently born in spring than in autumn season (Pearson's χ^2 statistics, 5.16; $p = 0.023$) (Fig. 1). The RR for ED admission for severe allergic reactions of patients born in spring was 1.86 (95% CI, 1.02–3.42) compared to those born in autumn. A similar trend was observed comparing spring births with births in the three other seasons (RR, 1.52; 95% CI, 1.07–2.17).

4. Discussion

The pathogenesis of allergy is still incompletely acknowledged and is probably multifactorial, involving genetic predisposition, nutritional habits, obstetric practices (i.e., caesarean delivery in allergic mothers), maternal age, exposure to tobacco smoke, vitamin D status, and environmental factors such as air pollution [17–19]. The results of our study also show that adult patients born in spring appear more vulnerable to acute allergic reactions requiring ED visit than those who were born in all other seasons. At variance with our findings, a number of previous investigations based on epidemiologic surveys or allergy clinic visits reported an association between fall/winter birth and mild allergic reactions during childhood, or else failed to find any significant relationship between birth age and allergy.

In the EuroPrevall birth cohort investigation, the largest study using the reference diagnostic criteria for food allergy in children, country-specific differences were found for a broad range of factors playing a role in the development of food allergy, including family history, obstetric practices, pre- and post-natal environmental exposures [20]. Vassallo et al. first reported that fall and winter season birth was associated with a larger prevalence of allergy in US children (aged <5 years) treated in the ED for non-food allergy reasons but not in older children or adults [21]. In another Australia-based study, Mullins et al. failed to identify birth seasonal patterns in a general population of children aged 0–4 years referred to a specialist allergy/immunology medical practice for all types of allergy, whereas autumn/winter births were more common than spring/summer births among food allergy patients, especially those diagnosed with peanut and egg allergy [22]. Keet et al. studied 5862 children (i.e., aged 17 or younger) from the National Health and Nutrition Examination Survey (NHANES) III and 1514 well-characterized food allergic children (i.e., aged 21 or younger) from the Johns Hopkins Pediatric Allergy Clinic (JHPAC) [23], and found that fall birth was more frequent among food allergic subjects in both cohorts. Similar results were recently reported by Pyrhönen

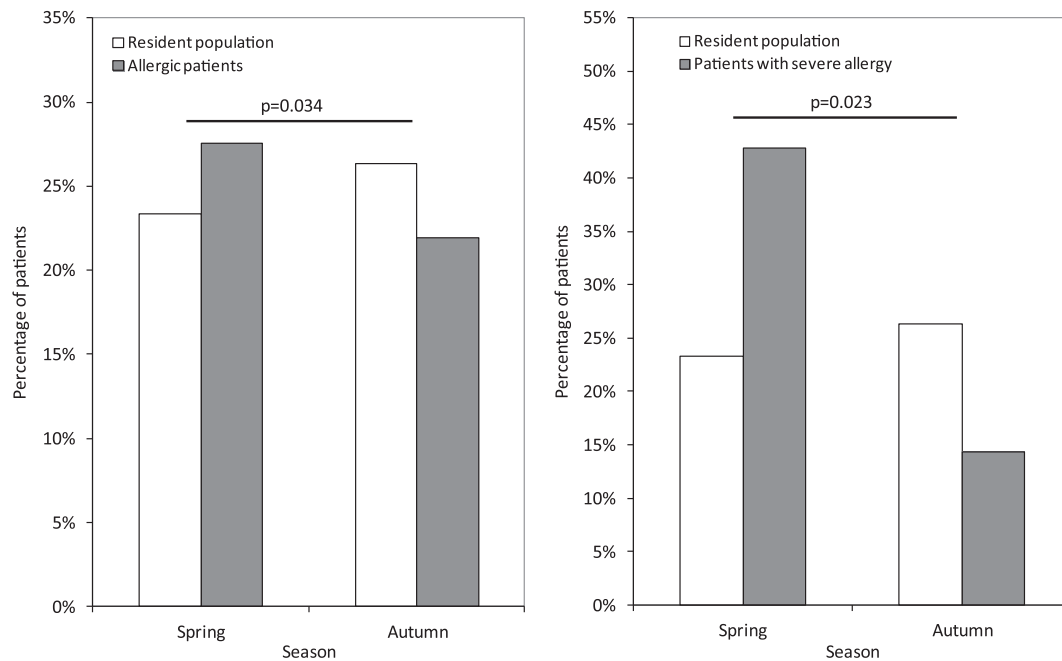


Fig. 1. Frequency of birth season of the Italian resident population and patients admitted to the emergency department for total and severe allergic reactions. Percentages are compared by Pearson's χ^2 statistics.

et al. in 5920 Finland children, observing that the prevalence of milk and egg allergy and specific IgE antibodies to these food items were significantly higher in children born in winter than in those born in other seasons [24]. Opposite results were recently published by Clark et al. [25]. The study, based on administration of a self-administered survey followed by telephone interviews of parents of 962 US children, emphasized that no statistically significant association could be observed between season of birth and allergy. Similarly, Wjst et al. studied 6535 10-year-old German children [26], and found that the risk of developing allergic skin sensitization for grass pollen was higher in children born in May and June, whereas the risk of developing hay fever was higher in those born in May. Other studies showed different and often controversial patterns of birth seasonality in other immune-mediated disorders, such as atopy [27] and asthma [28].

Unlike previous studies based on childhood populations, our investigation demonstrates for the first time the existence of a significant association between spring birth and increased frequency of ED admission for any form of acute allergic reactions in the adulthood age. Interestingly, this association appeared to be stronger in patients with severe allergy (i.e., anaphylactic reactions) than in those with urticaria and/or angioedema. In accord with these findings, Pedersen and Weeke reported that the prevalence of asthma and/or allergic rhinitis in a general population of Danish outpatients was higher in subject born in spring than those born in July–January [29]. In another study that investigated

the potential association between allergy and latitude or birth date by means of a questionnaire distributed to 200,682 participants worldwide, Wjst et al. failed to find any relationship between month of birth and prevalence of allergic rhinitis [30].

There are several reasons which may justify the difference between our findings and those previously published, showing a relationship between autumn or winter birth and allergy. First, our population included subjects aged 17 years or older, whereas fall birth was found to be a significant predictor of allergic reactions only in children. The geographical setting of our investigation was also different, since we enrolled a resident Italian population, whereas previous studies were based in Northern Europe, US and Australia. It has been demonstrated that the prevalence of allergy varies widely according to the country of birth [31], and it is hence conceivable that different triggers in specific geographical area of birth may generate a different risk of sensitization to certain allergens later in life. Then, all types of acute allergic reactions were included in our epidemiological investigation, whereas the association between allergy and fall or spring birth could only be demonstrated in food allergic subjects in previous studies. It is also noteworthy that the study of Mullins et al. showed an increased risk of ED admission for food allergy in children but not in adults [22], and this is hence in agreement with our findings that birth seasonality was not significantly associated with food allergy (RR, 1.15; 95% CI, 0.49–2.73). Finally, unlike previous studies which investigated the overall prevalence of allergy or IgE positivity in the general population, our study was limited to ED admissions, thus excluding mild forms of allergic reactions, not requiring ED visit.

Although the association between season of birth and prevalence of childhood allergy has been tentatively explained with a greater prevalence of vitamin D deficiency due to shorter daylight and sunlight exposure of children born in winter, which would ultimately contribute to impair immune system maturation, this hypothesis remains largely debated [32–34]. We cannot identify a reliable biological explanation for our finding of an association between spring season birth and ED visits for acute allergic reactions in adults, but we hypothesize that the pathogenesis might differ between childhood-onset and adult-onset disease, when a number of different precipitating factors such as adult infections, dietary patterns and outdoor pollutants may play a more significant role in triggering acute allergic reactions. Interestingly, a recent

Table 2

Comparison of the distribution (number of subjects and relative percentage) of patients admitted to the emergency department for acute allergic reactions and potential triggers causing emergency department visit between spring and autumn. Distributions are compared by Pearson's χ^2 statistics.

	n	Spring	Autumn	p
All patients	588	27.6%	21.9%	0.034
Trigger				
- Foods	88	22.7%	21.6%	0.746
- Chemicals	26	15.4%	30.8%	0.513
- Drugs	123	30.1%	15.4%	0.043
- Hymenoptera	58	24.1%	29.3%	0.809
- Inhalants	6	33.0%	0.0%	0.136
- Unknown	287	30.0%	22.6%	0.008

study exploring the association between season of birth and celiac disease in 1964 patients reported that more patients with this condition were born in the spring compared to other seasons [35]. Interestingly, spring birth has also been associated with an increased risk of developing type 1 diabetes [36]. This evidence may be explained with fetus exposure to lower levels of maternal vitamin D from 3 to 7 months before birth (i.e., October to February), a time window that may impact on optimal prenatal development of the immune system, and determine a greater predisposition to developing acute and severe allergic reactions later in life. Conversely, fetus exposure to maternal vitamin D is higher for subjects born in autumn, so that the development of immune system may be more efficient. This would then explain the lower frequency of ED admission for acute allergic reactions in adulthood. The different birch pollen/inhalant exposure is another potential explanation for our findings, since allergic reactions especially due to pollen and mold are typically higher in Spring than in Autumn in our country.

5. Conclusions

Recent data shows that allergic reactions caused by food and anaphylaxis cause a considerable economic burden, approximating half a billion dollars in the US, 20% of which is attributable to ED visits [37]. Due to their challenging diagnostic and therapeutic management, especially in the presence of severe cases of anaphylaxis, they also contribute to increased overcrowding and resource utilization [38]. Therefore, the identification of subjects more vulnerable to severe allergic problems leading to ED visit appears a mainstay for both clinical and economical reasons. Since asthma exacerbation is apparently related with exposure to allergen, which is also associated with season of birth, the exclusion of subjects with asthma may be regarded as a potential weakness of our analysis. It is also worthwhile mentioning here that the main aim of this study was to provide a general overview of the impact on the ED imposed by acute allergic reaction visits, and therefore we do not analyzed data for potential confounding factors such as age, gender and especially, the socioeconomic status which may have indeed influenced the perception of severity of the allergic reaction.

Provided that our findings can be replicated in additional studies and other areas, this study identified that patients born in spring season appear particularly vulnerable, with increased risk of ED admission for acute and severe allergic reactions. We also showed that the relationship between season of birth and allergy remains largely controversial, probably depending from a large number of variables such as the age of the patient, the geographical setting, the type and severity of the allergic reaction.

Learning points

- We analyzed frequency of ED admission for acute allergic reactions according to birth season.
- An excess ED admission was found for adult patients born in spring.
- Spring birth was also associated with 1.5 greater risk of ED admission for anaphylaxis.
- Patients born in spring may be more predisposed to develop severe allergic reactions.

Conflict of interests

All authors have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

References

- [1] Ewan PW. Anaphylaxis. *Br Med J* 1998;316:1442–5.
- [2] Estelle F, Simons R. Anaphylaxis. *J Allergy Clin Immunol* 2010;125:S161–81.
- [3] Kaplan AP. Urticaria and angioedema. In: Adkinson NF, Bochner BS, Busse WW, et al, editors. *Middleton's Allergy: Principles and Practice*, 7th., St Louis, MO: Mosby; 2009. p. 1063.
- [4] Losappio L, Heffler E, Bussolino C, Cannito CD, Carpentiere R, Raie A, et al. Acute urticaria presenting in the emergency room of a general hospital. *Eur J Intern Med* 2014;25:147–50.
- [5] Kaplan AP, Greaves MW. Angioedema. *J Am Acad Dermatol* 2005;53:373–88.
- [6] Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson Jr NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391–7.
- [7] Lieberman P, Camargo Jr CA, Bohlke K, Jick H, Miller RL, Sheikh A, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol* 2006;97:596–602.
- [8] Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol* 2004;113:536–42.
- [9] Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993–1994 to 2004–2005. *J Allergy Clin Immunol* 2007;120:878–84.
- [10] Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy* 2004;34:285–90.
- [11] Panesar SS, Nwaru BI, Hickstein L, Rader T, Hamadah H, Fawz D, et al. The epidemiology of anaphylaxis in Europe: protocol for a systematic review. *Clin Transl Allergy* 2013;3:9.
- [12] Simons FER, Sampson HA. Anaphylaxis epidemic: fact or fiction? *J Allergy Clin Immunol* 2008;122:1166–8.
- [13] Clark S, Gaeta TJ, Kamrathi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol* 2006;16:696–700.
- [14] Gaeta TJ, Clark S, Pelletier AJ, Camargo CA. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol* 2007;98:360–5.
- [15] Ross MP, Ferguson M, Street D, Klontz K, Schroeder T, Luccioli S. Analysis of food-allergic and anaphylactic events in the National Electronic Injury Surveillance System. *J Allergy Clin Immunol* 2008;121:166–71.
- [16] Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. *Pediatr Allergy Immunol* 2004;15(Suppl. 16):4–5.
- [17] Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol* 2003;112:420–6.
- [18] Dioun AF, Harris SK, Hibberd PL. Is maternal age at delivery related to childhood food allergy? *Pediatr Allergy Immunol* 2003;14:307–11.
- [19] West CE, Prescott SL. Role of diet in the development of immune tolerance in the context of allergic disease. *Curr Opin Pediatr* 2010;22:635–41.
- [20] McBride D, Keil T, Grabenhenrich L, Dubakiene R, Drasutiene G, Flocchi A, et al. The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries. *Pediatr Allergy Immunol* 2012;23:230–9.
- [21] Vassallo MF, Banerji A, Rudders SA, Clark S, Mullins RJ, Camargo Jr CA. Season of birth and food allergy in children. *Ann Allergy Asthma Immunol* 2010;104:307–13.
- [22] Mullins RJ, Clark S, Katelaris C, Smith V, Solley G, Camargo Jr CA. Season of birth and childhood food allergy in Australia. *Pediatr Allergy Immunol* 2011;22:583–9.
- [23] Keet CA, Matsui EC, Savage JH, Neuman-Sunshine DL, Skripak J, Peng RD, et al. Potential mechanisms for the association between fall birth and food allergy. *Allergy* 2012;67:775–82.
- [24] Pyrhönen K, Läärä E, Hiltunen L, Kaila M, Hugg T, Näyhä S. Season of the first trimester of pregnancy predicts sensitisation to food allergens in childhood: a population-based cohort study from Finland. *J Epidemiol Community Health* 2012;66:49–56.
- [25] Clark NM, Baptist AP, Ko YA, Leo HL, Song PX. The relationship of season of birth to asthma and allergy in urban African American children from 10 to 13 years of age. *J Asthma* 2012;49:1037–43.
- [26] Wjst M, Dold S, Reitmeir P, Stiepel E, Von Mutius E. Month of birth and allergic disease at the age of 10. *Clin Exp Allergy* 1992;22:1026–31.
- [27] Kusunoki T, Asai K, Harazaki M, Korematsu S, Hosoi S. Month of birth and prevalence of atopic dermatitis in schoolchildren: dry skin in early infancy as a possible etiologic factor. *J Allergy Clin Immunol* 1999;103:1148–52.
- [28] Gazala E, Ron-Feldman V, Alterman M, Kama S, Novack L. The association between birth season and future development of childhood asthma. *Pediatr Pulmonol* 2006;41:1125–8.
- [29] Pedersen PA, Weeke ER. Month of birth in asthma and allergic rhinitis. *Scand J Prim Health Care* 1983;1:97–101.
- [30] Wjst M, Dharmage S, André E, Norback D, Raherison C, Villani S, et al. Latitude, birth date, and allergy. *PLoS Med* 2005;2:e294.
- [31] Silverberg JL, Simpson EL, Durkin HG, Joks R. Prevalence of allergic disease in foreign-born American children. *JAMA Pediatr* 2013;167:554–60.
- [32] Camargo Jr CA, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol* 2007;120:131–6.

- [33] Zittermann A, Tenderich G, Koerfer R. Vitamin D and the adaptive immune system with special emphasis to allergic reactions and allograft rejection. *Inflamm Allergy Drug Targets* 2009;8:161–8.
- [34] Erkkola M, Kaila M, Nwaru BI, Kronberg-Kippilä C, Ahonen S, Nevalainen J, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009;39:875–82.
- [35] Tanpowpong P, Obuch JC, Jiang H, McCarty CE, Katz AJ, Leffler DA, et al. Multicenter study on season of birth and celiac disease: evidence for a new theoretical model of pathogenesis. *J Pediatr* 2013;162:501–4.
- [36] Kahn HS, Morgan TM, Case LD, Dabelea D, Mayer-Davis EJ, Lawrence JM, et al. Association of type 1 diabetes with month of birth among U.S. youth: the SEARCH for Diabetes in Youth Study. *Diabetes Care* 2009;32:2010–5.
- [37] Patel DA, Holdford DA, Edwards E, Carroll NV. Estimating the economic burden of food-induced allergic reactions and anaphylaxis in the United States. *J Allergy Clin Immunol* 2011;128:110–5.
- [38] Ben-Shoshan M, La Vieille S, Eisman H, Alizadehfar R, Mill C, Perkins E, et al. Anaphylaxis treated in a Canadian pediatric hospital: incidence, clinical characteristics, triggers, and management. *J Allergy Clin Immunol* 2013;132:739–41.