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Article

# Influence of Birth Season Climate on Adult Total Serum IgE Levels

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**Abstract:** *Objective:* To determine the effect of birth season climate on adult total serum IgE (TSIgE) levels. *Study design:* The study is a retrospective chart review with the following inclusion criteria: TSIgE measurement, age  $\geq 16$ , and northeastern Tennessee birthplace. Main outcome measures include TSIgE levels, birth season climatic conditions, and regional pollen-producing plant and pollen counts. *Results:* The records of 1,274 women (mean age  $40.8 \pm 17.5$ , age range 16-96) and 762 men (mean age  $38.1 \pm 17$ , age range 16-82) seen in our Allergy Clinic were reviewed. Persons born in the spring and summer, the seasons with the highest pollen counts and the most favorable climatic conditions for plant growth, had nearly twice the odds of having TSIgE levels  $>1\sigma$  above the mean of the study group when compared to those born in the fall or winter (odds ratio (OR) 1.75, 95% confidence interval (CI) 0.96-3.17 and OR 1.93, 95% CI 1.04-3.57, respectively); odds were highest for those born in March (OR 2.55, 95% CI 1.37-4.74) and July (OR 2.38, 95% CI 1.25-4.51) and lowest for those born in November (OR 0.11, 95% CI 0.0068-1.79). When averaged over the 95-years of study and five 30-year climate cycles TSIgE levels increased linearly as the seasons progressed from fall to summer ( $r^2=0.9475$ ,  $P=0.0266$ ). Of the climatic factors, TSIgE levels correlated most strongly with levels of precipitation ( $r^2=0.9145$ ,  $P=0.0437$ ). *Conclusion:* Climatic conditions that increase birth season exposure to environmental allergens may have a life-long effect on TSIgE production.

**Keywords:** total serum IgE; birth month; birth season; birth climate; neonates; allergy

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## 1. Introduction

A number of reports have suggested that allergen exposure in the month of birth or season of birth may be important in determining the subsequent development of IgE-mediated hypersensitivity disorders, including asthma and allergic rhinitis [1-35]. This suggests that the epigenetic bias toward Th2 function can persist beyond the postnatal period and is in keeping with reports that epigenetic modifications favoring either Th1- or Th2-mediated immunity can occur following neonatal exposure to a variety of environmental factors, including pollens, mites, bacteria, and cat or dog dander [36-38].

Using measurements of total serum IgE (TSIgE), birth season climatic conditions, and regional allergenic plant and pollen counts, this study investigated the possibility that the immunological effects of allergen exposure during one's birth month can persist into adulthood and that the degree of exposure is influenced by climatic conditions.

## 2. Methods

This retrospective review was approved by the Institutional Review Board of James H. Quillen College of Medicine, East Tennessee State University, Johnson City, TN.

The author reviewed the Division of Allergy and Immunology's laboratory and clinic records for patients born between the years 1898 and 1995. TSIgE levels were measured by the Phadebas IgE paper immunosorbent test (PRIST) (detection range, 0.5 to  $\geq 800$  kU IgE/L) (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden). Serum levels of IgE antibody to 60 regional seasonal and nonseasonal allergens were measured using a Phadebas radioallergosorbent test (RAST) (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden).

Epicutaneous and intradermal skin tests were done using 66 regional seasonal and non-seasonal allergens (Miles Inc., Spokane, WA).

Climatic information for the region of study was obtained from the National Climatic Data Center in Asheville, North Carolina [39], the National Oceanic and Atmosphere Administration National Centers for Environmental Information [40], and from Weathersparks [41]. Included are measurements of temperature, precipitation, relative humidity, kilowatt hours of incident shortwave solar radiation reaching ground level, growing degree days (a measure of heat accumulation used to predict plant developmental rates), the percent of growing season, and wind speeds. Regional pollen counts were obtained from the National Allergy Bureau in Knoxville, Tennessee. Regional allergenic plant numbers were detailed in a book by the Tennessee Chapter of the Sierra Club [42].

### 3. Statistical analysis

The threshold p value (alpha) is set at 0.05. Two-tailed Fisher's exact test for matched pairs was used to analyze the significance of observed versus expected frequency of attributes and for calculation of odds ratios. Probability testing was done using a two-tailed paired t test. Multiple regression analysis was done to confirm the significance of the correlation between outcomes. GraphPad, version 6.03 from GraphPad Software, 2365 Northside Drive, Suite 560, San Diego, CA 92108, was used as statistical software.

### 4. Results

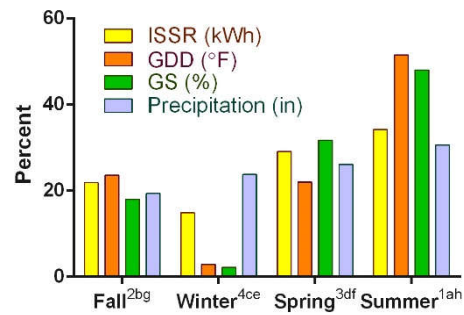
#### 4.1. Patient demographics

The study includes 2,036 patients, 1,274 women (mean age  $40.8 \pm 17.5$ , age range 16-96) and 762 men (mean age  $38.1 \pm 17$ , age range 16-82) all of whom were referred to our clinic for evaluation of allergic symptoms and had one or more TSIgE measurements. Medical records were available for 500 patients (24.6% of total) whose diagnoses include rhinosinusitis (44.4%), bronchitis and asthma (25.6%), food allergies (6.5%), eczema (3%), urticaria (2.8%), hymenoptera allergy (1%), and non-allergic conditions (16.7%). Results of RAST and/or skin tests were available in 38.4% of these patients, an insufficient number to derive statistically significant results.

#### 4.2. Climate and pollen-producing plants

The region supports the growth of 140 pollen-producing plants, including 81 species of trees, 37 species of grasses, and 22 species of weeds. Of the 140 different pollens produced by these plants, 74 are considered mildly allergenic, 36 moderately allergenic, and 30 highly allergenic.

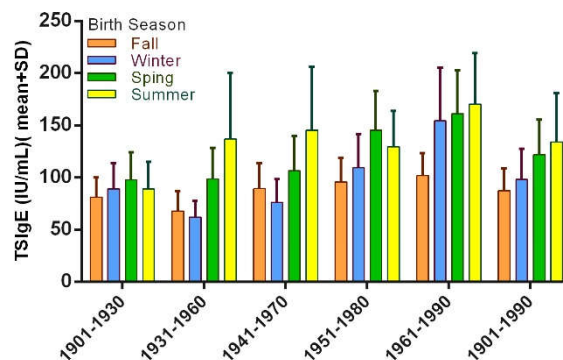
Thirty-year seasonal percentages of temperature, precipitation, relative humidity, kilowatt hours of incident shortwave solar radiation reaching ground level, growing degree days, growing season and wind speeds indicate that the most favorable conditions for plant growth in the region of study occur in the summer followed by the spring, fall and winter. High levels of relative humidity and temperature make summer the most favorable season for the growth, survival and fecundity of dust mites and mold (Figure 1).



**Figure 1.** 30-year seasonal percentages of kilowatt hours (kWh) of incident shortwave solar radiation reaching ground level (ISSR), growing degree days (GDD), growing season (GS) and precipitation. Superscript X-axis labels indicate the seasons with the highest to lowest levels of temperature (1-4), the seasons with the highest to lowest levels of relative humidity (a-d), and the seasons with the highest to lowest wind speeds (e-h).

#### 4.3. Birth season and TSIgE levels

TSIgE levels tabulated over 30-year intervals from 1901 to 1990 indicate that in each interval the lowest levels of TSIgE occurred in persons born in the fall and winter and the highest levels occurred in persons born in the spring and summer. Over the ninety years of study, TSIgE levels increased linearly as the seasons progressed from fall to summer ( $r^2=0.9475$ ,  $P=0.0266$ ) (Figure 2).



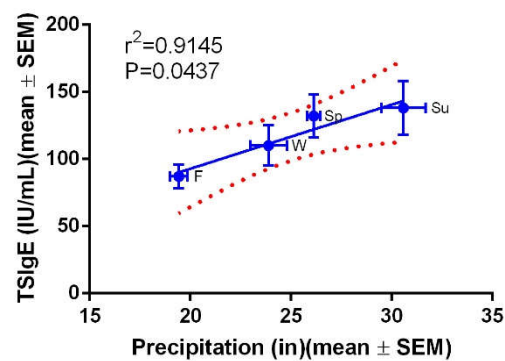
**Figure 2.** Over five 30-year climate cycles (1901-1990) TSIgE levels increased linearly as the seasons progressed from fall to summer.

#### 4.4. Birth month and TSIgE levels

Persons born in March and July had over twice the odds of having TSIgE levels  $\geq 2\sigma$  above the mean of the study group (odds ratio (OR) 2.55, confidence interval (CI) 1.37-4.74,  $P=0.0046$ ; and OR 2.38, CI 1.25-4.51,  $P=0.0121$ , respectively), whereas those born in November had one-tenth the odds of having similar increases in TSIgE levels (OR 0.11, CI 0.0068 - 1.79,  $P=0.0315$ ).

#### 4.5. Climatic factors and TSIgE levels

Over the 95-year period of study precipitation levels in northeastern Tennessee correlated with TSIgE levels measured over the same time period ( $r^2=0.9145$ ,  $P=0.0437$ ) (Figure 3).



**Figure 3.** Over the 95-year period of study, TSIgE levels correlated with regional precipitation levels.

## 5. Discussion

Newborns go through a critical period of development in which their T and B cells first encounter environmental antigens [43]. During the first several weeks of this “window of sensitization” the neonatal immune system is intrinsically biased toward T helper 2 (Th2)-type immune responses. This bias is generated in utero by the secretion of Th2-type cytokines at the maternal-fetal interface and includes the suppression of Th1-type immune responses by regulatory T cells, IL-10 and IL-4 [43-49]. It is posited that this Th2 bias is necessary to prevent fetal-maternal alloimmune reactions and to provide a beneficial time window for the newborn infant to develop tolerance to autoantigens [43].

When bolstered by heritable factors that predispose to allergy, such as the nature of one’s MHC class II haplotypes, the integrity of genes encoding the beta chain of the high affinity IgE receptor and the IL-4 gene cluster [50], the newborn infant is placed at high risk of developing an allergic disorder when exposed to environmental allergens.

In this study, adult TSIgE levels are shown to correlate with birth month climatic conditions that favor the growth and survival of allergenic plants, dust mites, and molds. The findings are in keeping with reports that epigenetic modifications favoring Th2-mediated immunity can occur following neonatal exposure to a variety of environmental allergens, including pollens, dust mites, and animal dander [28-31]. The findings are also in keeping with a report showing an association between 92 CpG sites involved in the epigenetic regulation of TSIgE and the season of birth; 20 of the 92 CpG sites were associated with allergic outcomes [51]. Genetic determinants controlling TSIgE levels include 1q23 (FCER1A), 5q31 (RAD50, IL13, IL4), 12q13 (STAT6), 6p21.3 (HLA-DRB1) and 16p12 (IL4R, IL21R) [52].

Climate is a long-term characterization or averaging of weather variables, the most important of which are the amount and type of precipitation, the air temperature, the amount of solar radiation reaching ground level, and the humidity. Studies on crop yields have shown that precipitation is the main determinant of crop productivity, air temperature is the main determinant of when and for how long a crop will grow, and the amount of solar radiation reaching ground level (in combination with soil water) is the main determinant of crop photosynthesis [53]. High levels of humidity are also known to promote the growth, survival, and fecundity of house dust mites [54] and molds [55]. In the current study, birth season levels of precipitation, which are expected to increase with global warming [56, 57], had the greatest effect on adult TSIgE levels.

## 6. Conclusion.

The results of this study support the hypothesis that birth month climate may affect the child beyond the post-natal period and provide an additional reason for advising parents to take steps to minimize their newborn infant’s exposure to environmental allergens. These precautions should resonate most strongly in families with a history of Type I hypersensitivities.

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