Impact of the season of birth on the development of juvenile idiopathic arthritis in the United States: A nationwide registry-based study

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Abstract:

Objective: Autoimmune disorders result from the interplay of genetic and environmental factors. Many autoimmune disorders are associated with specific seasons of birth implicating a role for environmental determinants in their etiopathology. We investigated if there is an association between the season of birth and development of Juvenile idiopathic arthritis (JIA).

Methods: Birth data from 10,913 children with JIA enrolled at 62 Childhood Arthritis and Rheumatology Research Alliance Registry sites was compared with 109,066,226 US births from the same period using a Chi-square goodness-of-fit test. Season of birth of the JIA cohort was compared to the US population estimate using a two-sided one-sample test for a binomial proportion and corrected for multiple comparisons. Secondary analysis was performed for JIA categories, age of onset, and months of birth.

Results: A greater proportion of children with JIA were born in Winter (January to March) compared to the US population (25.72% vs 24.08%; $p_c < 0.0001$). This observation was also true after stratifying for age of onset ($\leq$ or > 6 years). When analyzed by the month of birth, a greater proportion of children with JIA were born in January compared to the US population (9.44% vs 8.13%; $p_c < 0.0001$).

Conclusion: Relative to the general population, children with JIA are more often born in Winter, and specifically the month of January. These observations support the hypothesis that seasonal variations in exposures during the gestational and/or early postnatal periods may contribute to development of JIA.

Introduction: Juvenile Idiopathic Arthritis (JIA) refers to a group of chronic arthritis categorized by history, clinical and laboratory findings to include oligoarthritis, systemic JIA, rheumatoid factor (RF) positive polyarthritis, RF-negative polyarthritis, psoriatic arthritis, enthesitis related arthritis (ERA), and undifferentiated arthritis.(1) JIA, like other autoimmune disorders, is believed to result from genetic and environmental determinants. A role for genetic variants contributing to JIA risk has been confirmed by large genome-wide studies of JIA.(2) Environmental factors in early life have also been implicated in susceptibility to JIA.(3) Prior antibiotic use, hospitalizations in the first-year, and decreased duration of breastfeeding have all been postulated to be associated with an increased risk of JIA.(4-6)

Environmental exposures during gestation and/or postnatal periods could plausibly influence susceptibility to autoimmunity. An association between autoimmune disorders and the season of birth has been proposed on the basis that factors such as infection rates or sunlight exposure vary seasonally. While investigations of smaller cohorts have yielded mixed results, large cohort-based studies with thousands of subjects demonstrate that the month/season of birth is associated with the risk of multiple sclerosis, inflammatory bowel disease (IBD), celiac disease and autoimmune thyroid disease.(7-10) The month of birth peaked in January in a small JIA cohort compared to August for the Israeli population.(11) We sought to determine if the distribution of season and month of birth in a large JIA multicenter cohort differed from that of the US general population.

Methods:

JIA Cohort: Deidentified data were obtained on 11,345 JIA cases enrolled in two Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registries (Legacy Registry 2010-2014, 58 sites; New CARRA Registry 2015-2018, 62 sites).(12, 13) Subjects were enrolled after informed consent under protocols approved by institutional review boards at Emory

University (IRB # 83836, #42709), and the participating centers. Consent to publication of non-identifying information was included in the informed consent. This project was approved by Data and Publications committees of CARRA.

Population Data: Data on all US births between 1990 – 2016 (n = 109,066,226) were obtained from the National Vital Statistics Reports at the Centers for Disease Controls (CDC) at https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm to calculate the population estimates.

Statistical Methods: Birth-month, birth-year, gender, and JIA category data was extracted from the JIA patients in the CARRA Registry. Age of onset information was available on 8623 subjects. Subjects included in both registries were identified and duplicate entries were removed prior to analysis. To match the birth-year data of the US population, 27 subjects in the CARRA Registry born before 1990 or after 2016 were excluded. We excluded 405 subjects who reported living outside the US at the time of JIA onset. Seasons were defined as: Winter: January to March; Spring: April to June; Summer: July to September; and Autumn: October to December as previously defined.(8)

First, the distribution of birth month was tabulated and described using counts and percentages. Population estimates of birth percentages by month were calculated by computing the distribution of births for each calendar year between 1990 to 2016, resulting in 27 proportions for each calendar month. Population estimates for each month were then computed by averaging the monthly proportions across all years. In this method, each year was given an equal weight. In a sensitivity analysis, the distribution of births was recalculated by computing the percentage of all births from a specific month across all years. This was done by summing

number of births per month for all years and dividing by the total number reported births during the study period (n=109,066,226 births).

The distribution of birth by season in the JIA cohort was compared to the US population estimate using a Chi-Square goodness-of-fit test. Percentages of births of children with JIA by individual season of birth were compared to the population value using a two-sided one-sample test for a binomial proportion, where the CDC estimate was treated as the population estimate. To investigate if the observed results for the association between season of birth and JIA were due to changes affecting the population as a whole, we analyzed births by decade, 1990-1999 (n=3719), 2000-2009 (n=5951) and 2010-2016 (n=1243). Secondary analyses were performed to investigate if there was an association between month of birth and JIA categories, as well as age of onset (≤ 6 years vs > 6 years). Since the CDC data was not broken down by gender, analyses stratified by gender were deferred. We performed Chi-Square tests with Yates correction to determine if the male to female ratio of the JIA cohort differed between Winter or January compared to the rest of the year. Statistical significance was assessed at the 0.05 level. For all analyses, we controlled the family-wise error rate at 0.05 for each subgroup analysis (season, month, JIA category, age of onset) using a Bonferroni correction. Specifically, the p value was set to 0.05 divided by the number of pair-wise tests performed. All analyses were performed using SAS v. 9.4 (SAS Institute, Cary, NC).

Results:

Season of birth:

A total of 10,913 JIA patients were included in the analyses, with a mean onset age of 6. When distribution of births by season between subjects with JIA was compared against the US population (Figure 1), we found that the JIA cohort had a had a significantly greater proportion of births in winter compared to the US population (25.72% vs. 24.08% $p_c < 0.0001$). Births in

spring, summer and autumn were not significantly different between the JIA cohort and the US population (Table 1). When analyzed by decade (Table **S1**), in 1990s 24.39% of the JIA cohort was winter-born compared to 24.09% of the population (p = 0.65). However, JIA births in winter were significantly greater compared to the US population in the 2000s (26.16% vs 24.14%, p_c = 0.0016) and 2010s (27.59% vs 23.95%, p_c = 0.032). There were no significant differences between the JIA cohort and the US population for the other seasons.

After stratifying by onset-age, JIA births in winter was increased in the ≤ 6 years (p_c = 0.04) and > 6 years (p_c =0.016) cohorts (Table 2). When stratified by JIA category (**Table 2**), children with oligoarticular JIA (26.04%; p = 0.003, p_c = 0.08), RF-positive polyarticular JIA (27.1%, p = 0.008, p_c = 0.22), and psoriatic JIA (28.38%, p = 0.009, p_c = 0.25) had increased births in winter compared to the US population (24.08%),.

Month of birth

A greater percentage of births occurred in January in the JIA cohort compared to the US population (9.44% vs 8.13%; p_c <0.0001), (Figure S2). The percentage of births in JIA cohort was lower in August compared to the US population (8.32% vs 8.88%, p = 0.04; p_c = 0.48). No other month showed a significant difference between the JIA cohort and the US population (Table 2).

When the month of birth of different JIA categories were compared against the US population, 14.33% of children with undifferentiated JIA were born in January compared to 8.13% for the US population, a difference that was significant after Bonferroni correction (Table 2). While the other observed differences lost significance after Bonferroni correction, it was notable that increased births were observed in the winter months: January for oligoarticular JIA (9.57%, p = 0.002; p_c = 0.67), RF-negative polyarticular JIA (9.36%, p = 0.009; p_c = 0.76) and systemic JIA

(9.91% = 0.045; p_c = 1.0); February for RF-positive polyarticular JIA (10.08% vs. 7.59%, p = 0.007; p_c = 0.59); and March for Psoriatic JIA (10.4% vs 8.36%, p = 0.05; p_c = 1.0). Psoriatic JIA had decreased births in August (6.32% vs. 8.88%, p = 0.019; p_c =1.0) and undifferentiated JIA had decreased births in June (4.9% vs. 8.32%, p = 0.02; p_c = 1.0).

Gender

There were 3133 (28.7%) male and 7778 (71.2%) female JIA subjects. The gender distribution in Winter did not differ from that of the rest of the year (27.6% males vs 29.1%, p = 0.15). Similarly, the gender distribution in January did not different from that of the rest of the year (27.9% vs 28.8%, p = 0.52).

Discussion:

Environmental exposures during the prenatal/perinatal period could influence the development of autoimmunity in genetically susceptible individuals. Several investigations of autoimmune disorders have shown associations with month/season of birth.(14) While studies with small sample sizes show mixed results, studies including large or population-based cohorts have shown associations between autoimmune disease and season of birth. A pooled analysis of multiple sclerosis datasets from Canada, Great Britain, Denmark and Sweden (n = 42,405) showed significantly increased births in May and decreased births in November compared to population controls.(10) Being born in spring was associated with a risk of IBD in a Canadian study of 11,145 cases and 108,633 controls.(8) Summer birth was associated with a risk of Celiac disease in a Swedish study of 29,096 cases and 144,522 controls, with the highest risk in those diagnosed before age 2.(7) A large cohort of 111,565 Danish autoimmune thyroiditis cases compared to 446,260 controls found an association with being born in June.(9) Together, these studies suggest that seasonal variations in exposures during the gestational and/or early postnatal periods may contribute to development of autoimmune disorders.

To our knowledge, the association between season of birth and JIA has been investigated in only two small cohorts.(11, 15) Berkun et al., investigated the seasonality of birth in an Israeli JIA cohort.(11) The authors analyzed 558 children with JIA (68% female) seen in a clinic between 2000 and 2010. The month of birth pattern of the JIA cohort was compared with that of the general population of Israel of over 1 million births over a 13-year period. Overall, the authors reported that the JIA patients showed a different birth pattern compared to the general population, with excess births in the winter. The JIA cohort had peak births in January, with a nadir in June. In contrast, for the general population births peaked in August. After stratification, the association was primarily seen in boys and in those with ERA. Our results using a much larger cohort of JIA and the US population, also point to January being the peak month of birth for JIA. Unlike the Israeli study, we did not see an association with ERA, although it should be noted that their cohort only had 35 subjects with ERA and was mostly comprised of children with oligoarticular JIA (68%).

Alterations in the amount of sun exposure could influence vitamin D levels which might be associated with risk or protection from autoimmunity. To investigate if there was an association between sun-exposure and the development of JIA, Chiaroni-Clarke et al. studied 202 cases of JIA and matched controls from Australia.(15) The authors reported that higher cumulative pre-diagnosis ultraviolet radiation exposure was associated with a reduced risk of JIA. Similarly, ultraviolet radiation exposure at 12 weeks of pregnancy was inversely associated with JIA. These authors also explored if there was an association between JIA and season of birth and found no association. However, the small JIA cohort likely lacked power to detect an association. By contrast, our results are based on a much larger cohort with adequate statistical power, though we did not address sun exposure.

To investigate fetal and perinatal risk factors and their association with the development of JIA Carlens et al performed a case-control study using a Swedish national registry.(4) They found that hospitalization for infection during the first year of life was significantly associated with the development of JIA compared to controls, and the risk was greatest for children hospitalized with gastrointestinal infections, followed by respiratory and skin infections. This is notable because the peak birth month of January coincides with peak transmission of numerous infectious pathogens, including respiratory syncytial virus and influenza.(16) Not surprisingly, peak respiratory viral transmission also coincides with peak *Streptococcus pneumoniae* infections(17) and peak antibiotic prescriptions(18) for presumed secondary bacterial infections. Microbial diversity is essential for maintenance of intestinal homeostasis and education of the developing immune system.(19) The administration of antibiotics during the perinatal period is a known risk factor for the development of dysbiosis and alteration of both the respiratory and intestinal microbiome. Intestinal dysbiosis has been associated with myriad autoimmune conditions, including type-1 diabetes mellitus, (20) spondyloarthritis, (21) and JIA.(22) A recent large cohort study of antibiotic use in Denmark suggested that winter born babies are more likely to be exposed to antibiotics later in the first year rather than shortly after birth, and by 12 months of age 44.8% of babies born in spring had at least 1 antibiotic prescription compared to 39.6% for winter and 34% for Autumn born babies.(23) These observations suggest that the season of birth might influence the age at which babies are first exposed to antibiotics, which could conceivably influence the dysbiosis of the microbiome and consequent development of autoimmunity. Thus, the extent to which early infectious exposures, subsequent antibiotic exposures, or resultant dysbiosis in the perinatal period might contribute to the development of autoimmune diseases remains an area of active research.

Our study has some limitations. Although the CARRA registry is the largest of its kind for JIA, enrollment is subject to physician preference as well as willingness of subjects and their families

to participate and might not be representative of all children with JIA. Given the large geographic area, even in the same season, different parts of the US have differences in timing of infections, climate, amount of sunlight and precipitation, which could limit the generalizability of our findings. We did not have information available on perinatal infections, sun exposure, vitamin D levels or antibiotic use in our study. It has been reported that there are seasonal differences in peak birth rates between Northern and Southern US States.(24) Since the US population birth data obtained from the CDC was not broken down by States we were precluded from comparing seasonality of birth differences between the Northern and Southern states. We also observed that the seasonal differences and winter excess in JIA births appeared to increase over time despite no apparent secular changes in the US population. Future studies in JIA cohorts from other countries might address if this trend is reproducible.

The sex ratio at birth has been reported to be affected by multiple factors.(25) The male to female ratio at birth in the US has been steady at 1.05 in 1990, 2000, 2010 and 2017.(26) Though our JIA cohort, like others, had a female predominance, the male to female ratio in the JIA cohort did not differ significantly between Winter or January compared to the rest of the year. Our results show that the JIA cohort has a 1.64% excess of births in winter compared to the US population. This finding is of a greater magnitude than observed in IBD (1.4% excess for spring births), and for celiac disease (1.35% excess for Summer births).(7, 8) The large size of the JIA cohort, the use of the US population estimates, the apparent concordance of findings with the prior Israeli study and the consistency across birth cohorts suggest that our observed findings represent true associations, which are strengths of this study. However, like other epidemiological studies, our results imply correlation and not causation.

In conclusion, the season and month of birth distribution of JIA patients significantly differs from that of the US population. The peak of JIA births seen in January/Winter supports the

hypothesis that seasonal environmental factors may initiate autoimmune processes during either the critical period of fetal development, which would likely be in spring, or during the first year of life. These are important avenues for future research.

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Figure 1 legend:

Title: Season of birth among children with JIA compared to the US population

The percentages of birth in each season are shown for the JIA cohort (yellow) compared to the US population estimate (blue) for the study period. While the US population percentages remained relatively stable over the study period, the JIA cohort showed a significant increase in Winter.

Supplementary Figure S2 Legend:

Title: Percentage of JIA cohort born in January compared to the US population estimate.

The percentages of birth in January for the JIA cohort (yellow) compared to the US population estimate (blue) for the study period (1990-2016) are shown.

Table 1: Percentages of birth by season for the JIA cohort compared to the US population estimate.

Season	US (95 % CI)	JIA (95 % CI)	P_c-value
Winter	24.08 (24.03 – 24.11)	25.72 (24.90 – 26.54)	**< 0.0001**
Spring	24.74 (24.70 – 24.78)	24.24 (23.43 – 25.04)	0.872
Summer	26.34 (26.31 – 26.35)	25.48 (24.67 – 26.31)	0.168
Autumn	24.84 (24.80 – 24.89)	24.56 (23.75 – 25.37)	1.000

The difference in percentages of births between the JIA cohort (n=10913) and US population (n=109,066,226) in winter was statistically significant (p_c<0.0001) after Bonferroni correction.

Table 2: Season and month of birth percentages in JIA categories and by age of onset compared to the US population estimate.

Season/ Month	US n=109M	JIA n=10913	Oligo n=3617	Poly RF- n=3354	ERA n=1127	Systemic n=949	Poly RF+ n=823	Psoriatic n=680	Undiff JIA n=363	≤ 6 years n= 4286	> 6 years n=4337
Winter	24.08	***25.72$***	26.04^	25.22	23.96	24.55	27.10*	28.38^	27.55	***25.92^***	***26.12^***
Spring	24.74	24.24	24.08	24.42	26.18	25.61	23.21	23.09	19.01*	24.78	23.63
Summer	26.34	25.48*	26.24	24.78*	25.38	25.29	25.64	23.82	28.10	25.48	25.32
Autumn	24.84	24.56	23.64	25.58	24.49	24.55	24.06	24.71	25.34	23.82	24.93
Jan	8.13	***9.44$***	9.57^	9.36^	7.45	9.91*	8.63	10.15	***14.33$***	9.36^	9.36^
Feb	7.59	7.68	7.75	7.51	7.63	6.74	10.09^	7.79	5.51	7.77	8.05
Mar	8.36	8.60	8.71	8.35	8.87	7.90	8.38	10.44*	7.71	8.80	8.72
Apr	8.01	7.71	7.39	7.87	8.96	7.48	7.17	7.94	6.89	7.51	7.63
May	8.41	8.43	8.82	8.53	8.08	9.06	7.66	7.21	7.16	9.31*	8.14
Jun	8.32	8.10	7.88	8.02	9.14	9.06	8.38	7.94	4.96*	7.96	7.86
Jul	8.78	8.69	8.71	8.68	9.05	7.80	8.14	8.97	10.47	8.52	8.44
Aug	8.88	8.32*	8.85	7.93	9.05	7.69	8.63	6.32*	9.09	7.91*	8.74
Sep	8.68	8.47	8.66	8.17	7.28	9.80	8.87	8.53	8.54	9.05	8.14
Oct	8.49	8.92	8.66	8.53	8.96	10.01	8.87	9.85	10.47	8.82	8.83
Nov	8.03	7.69	7.44	8.08	6.66	7.06	8.02	8.53	9.09	7.14*	8.09
Dec	8.32	7.96	7.55	8.97	8.87	7.48	7.17	6.32	5.79	7.86	8.00

Oligo: Oligoarticular JIA; Poly: polyarticular JIA: RF: Rheumatoid Factor; ERA: Enthesitis related arthritis Undiff: Undifferentiated JIA;

Uncorrected p values: * p <0.05: ^ p <0.01: $ p <0.001;
P values significant at p_c <0.05 after Bonferroni correction are ***bolded and italicized***
Bonferroni correction for season of birth analysis: All JIA (p x 4 seasons); categories (p X 28: 4 seasons, 7 categories); age of onset (p X 8: 4 seasons, 2 categories)
Bonferroni correction for month of birth analysis: All JIA (p x 12 months); categories (p X 84: 12 months, 7 categories); age of onset (p X 24: 12 months, 2 categories)

Figure 1: Season of birth among children with JIA compared to the US population