Allergen-specific IgE over time in women before, during and after pregnancy

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Summary

The trajectory of IgE levels before, during and after pregnancy in sensitized individuals is characterized by significant increase in specific IgE to birch allergens but not to other allergens after multiple testing. This increase may warrant some surveillance in the antenatal care for those with clinical symptoms.

Keywords: IgE, change, pregnancy, cohort

Abbreviations:

asIgE = allergen-specific IgE

LOQ = limit of quantification

To the Editor:

A strong association has been found between IgE reactivity to allergens and asthma, eczema and rhinitis but these diseases also exist in non-sensitized individuals (1). During pregnancy, IgG, IgM and IgA have been found to decrease between first and third trimester and to increase postpartum but the decrease in IgG was mainly due to hemodilution (2). For IgE, studies report a decrease in total IgE concentration in plasma from pregnancy to after delivery in allergic mothers (3), however, this decrease was not observed for allergen-specific IgE (asIgE) to common inhalant allergens (3). In order to tolerate the semiallogeneic fetus a regulated homeostasis between the Th1/Th2/Th17 (with additional Th9 and Treg) cell subsets and their dynamic and complex inter-relationship is essential during pregnancy (4, 5)To our knowledge, no study has included measures of asIgE *before* conception to study the trajectory of asIgE in sensitized women. Our aim was to investigate changes of asIgE before, during and after pregnancy.

In the prospective longitudinal cohort study Born into Life, we followed 106 women during 2010-2013 living in Stockholm before, during and after pregnancy (6). In total 413 blood samples were collected at baseline (before conception, n=102), at gestational week 10-14 (n=64) and 26-28 (n=93), at admission to hospital (n=74), and 3 days after delivery (n=80). Plasma from these blood samples at all time-points were analyzed for IgE-reactivity against a mixture of 11 inhalant allergens, Phadiatop® and 6 food allergens, fx5® (Thermo Fisher Scientific, Uppsala, Sweden). If the test screened positive for Phadiatop® ≥0.35 kU_A/L, asIgE antibodies to the most common single airborne allergens;cat, dog, horse-epithelium, birch and

timothy were analysed. We did not include house dust mite allergens, since they are not abundant in Sweden. If screening positive for fx5® ≥0.35 kU_A/L the sample was subsequently analysed for asIgE antibodies to the single allergens extract of egg, milk, cod, wheat and soy. To investigate change over time in each specific allergen (as well as all airborne allergens taken together), a mixed tobit-model was applied. Correction for multiple testing was made by the Bonferroni method. Since very few women (n=5) tested positive for fx5® we only present descriptive statistics for these food allergens. Details on study population, data-sources, variables and statistical analyses are provided in this article's online supporting information. The Regional Ethics Review Board in Stockholm, Sweden, granted ethical approval. Written informed consent was obtained from the study participants.

In total, n=38 women screened positive for Phadiatop®, n=5 women screened positive for fx5®, n=4 women screened positive for both Phadiatop® and fx5® and n=67 women were negative for both Phadiatop® and fx5®. See Table E1 for baseline descriptive in this article's online supporting information.

Figure 1a and Table E2 in this article's online supporting information displays the geometric mean for IgE airborne allergens concentration over time with 95% Confidence Interval (CI). The highest geometric mean concentration of asIgE for all time points was found for birch. The geometric mean concentration of IgE to birch was 0.57 (95% CI 0.39-0.83) kU_A/L. At baseline, before conception, the IgE concentration to birch was 0.41 (0.19-0.88) kU_A/L and 3 days after delivery 0.72 (0.31-1.70) kU_A/L. The geometric mean concentration of IgE to cat was 0.21 (0.16-0.28) kU_A/L, at baseline 0.21 (0.11-0.40) kU_A/L and 0.24 (0.09-0.63) kU_A/L week 10-14 during pregnancy. Figure 1b shows the specific food allergens over time with 95% CI where IgE to soy

displays the highest concentration although low in numbers (max n=5) for all food-allergens, Table E2.

Table 1 shows results from the multivariate mixed tobit model. Levels of IgE to birch increased significantly over time, with β=1.006 (95% CI: 1.002-1.010), which means that by one week progress in pregnancy the IgE geometric mean concentration increased by 0.6%. This remained significant after correction for multiple testing using Bonferroni, with similar results for those with at least one test above 0.10 kU_A/L. The largest regression coefficient was found when all airborne allergens were taken together in one analysis, β=1.007, and the smallest was seen for timothy, β=1.003 however non-significant.

In summary, we report a small but statistically significant increase over time from preconception to postpartum for asIgE to birch allergen, but no changes for other allergens. This finding is in line with previous findings that birch-induced cytokine levels were increased during pregnancy compared to post-partum in sensitized women with allergic symptoms (7). While they measured Th2-like cytokines and we assessed levels of asIgE, Th2-like cytokines and IgE has been shown to be related in a series of cellular reactions (5). Th2 cells are suggested to be the key T-helper cell subset responsible for allergic disease (5), and normal pregnancies have been described as an adequate balance for Th1/Th2 immunity which is slightly shifted to Th2-type immunity with additional regulation of the Th17 and Treg cells (4). Thus, the Th2-like immunity associated with allergic disease could be beneficial for the maintenance of a successful pregnancy. On the other hand, pregnancy might enhance the already Th2-skewed immunity of allergic women, expose the foetus to a strong Th2 environment, and perhaps lead to allergy development later in life (8). Since there is a strong correlation between sensitization and

allergic symptoms, our findings may warrant some surveillance of allergic women with clinical symptoms in the antenatal care.

The strength of this study is the longitudinal design with repeated measurements before conception, during pregnancy and after delivery. In addition, our study population was very homogeneous regarding age, geography and education. We also controlled for season, which is particularly important for the specific birch and timothy allergens at this geographical latitude, and we applied multiple test correction, making type I error less likely. The limitations include a small cohort size resulting in low statistical power. Normal aging could be an issue, however, findings from the follow-up by European Community Respiratory Health Survey rather showed that aging was associated with decreased levels of sensitization (9). Methodological issues relating to the analyses of biological samples could affect the results although the analyses were all performed on the same instrument, randomized and using the same batch reagents. Furthermore, being sensitized to birch is very common in this region and we can not rule out that there is also an effect for the other allergens, including timothy, although not statistically significant due to lower power.

In conclusion, we found a small but statistically significant increase in IgE levels to birch allergens in women over time before, during and after pregnancy but no statistically significant change in levels of asIgE for other inhalant allergens or food allergens.

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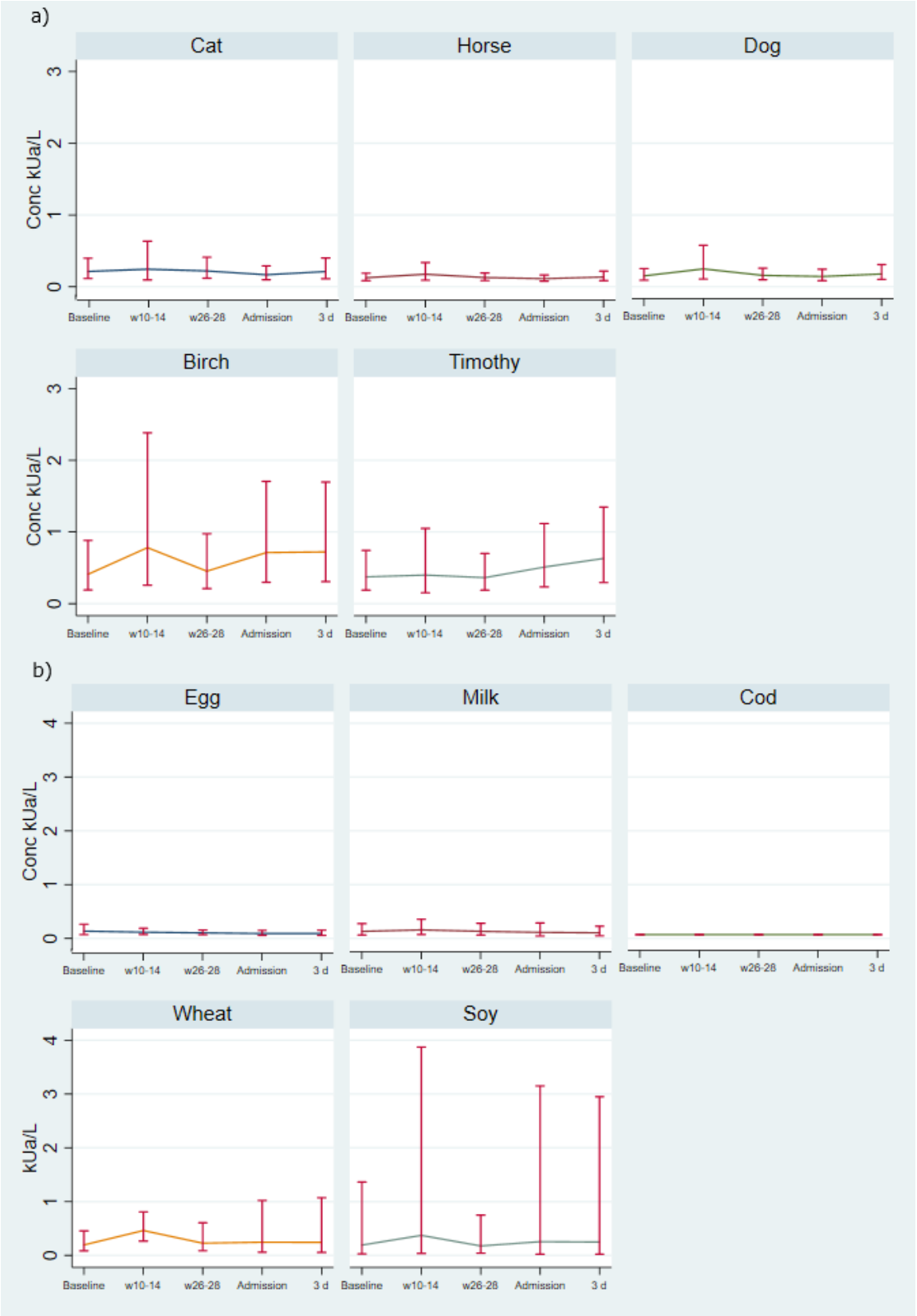

w = week during pregnancy

3 d = 3 days after delivery

Figure 1a-b. IgE-reactivity to airborne (a) and food (b) allergens over time in women pre, during and post pregnancy, presented as geographic means with 95% Confidence Intervals**.**

Table 1. Regression coefficients for time from mixed tobit model with 95% Confidence Intervals.

	All				**At least one above 0.10 kU_A/L**			
Allergen	β	95% CI		p-value	β	95% CI		p-value
Airborne allergens (all)	1.007	0.991	1.024	0.388	1.006	0.993	1.020	0.346
Cat	1.005	0.998	1.012	0.136	1.005	0.998	1.012	0.142
Horse	1.005	0.998	1.011	0.160	1.005	0.998	1.011	0.170
Dog	1.004	0.998	1.009	0.208	1.004	0.998	1.009	0.215
Birch	**1.006**	**1.002**	**1.010**	**0.004**	**1.006**	**1.002**	**1.010**	**0.004**
Timothy	1.003	0.999	1.008	0.143	1.003	0.999	1.008	0.140

β = Exponentiated regression coefficient for time (weeks) from analysis on log-transformed data

p-value cut-off with Bonferroni correction = 0.008

Online Supporting Information

Study Population

Born into Life originates from the larger LifeGene study which has been described in detail elsewhere (1). In short, LifeGene included index persons between 18-45 years who were also encouraged to invite their household members. At enrollment each participant was invited to a test center where biosamples were taken as well as physical measurements. A web-based questionnaire based on multifaceted questions regarding health, diet, lifestyle and diseases was administered at baseline and annually thereafter with a shorter version. Women who became pregnant in LifeGene in Stockholm during 2010-2013 were recruited to Born into Life. The women answered a web-based questionnaires at gestational week 10-14 and 26-18 regarding health, diseases, lifestyle and pregnancy.

Blood samples and analyses of IgE-reacivity to allergens

Blood samples from 106 women were collected before conception, at gestational week 10-14 and 26-28, at admission to the hospital for delivery (cord-blood), and 3 days after delivery in conjunction with the Phenylketonuria screening of the child (2). A positive screening test for either common inhalant allergens (Phadiatop®) or food allergens (fx5®) is fulfilled if the concentration is ≥ 0.35 kU_A/L. A total of n=155 tests from 38 women screened positive for Phadiatop® and n=15 tests from 5 women screened positive for fx5®. Based on this information we selected samples to analyse allergen-specific IgE (asIgE). We selected the samples from women who screened positive for one test and had at least one other test at another time-point

(regardless if this test was screened positive or not), in total n=131 tests from 33 women regarding airborne allergens and n=19 tests from 5 women regarding food allergens. These specific allergens were reported as continuous values, from <0.10 to >100 kU_A/L, i.e. the lower limit of quantification (LOQ) was 0.10 kU_A/L. All samples were analyzed at the Centre for Child Research, Södersjukhuset, Stockholm, Sweden.

Data sources and variables

Maternal age was retrieved from the medical birth records for each mother and child. Highest attained educational level (from mandatory secondary school to high school, university or other) was derived from LifeGene questionnaires. Educational level was used as a proxy for socioeconomic status (3). The covariate season of the year was coded as 1, if the sample was taken during the pollen season of the year in this geographical region (i.e., May-June-July) and 0 otherwise (i.e., all other months).

Statistical analyses

Baseline descriptive statistics included frequencies and percentages for count variables. Chi-squares with Fisher's exact test were applied to the categorical variables. All data were initially analyzed for normality and extreme values. Due to positively skewed distribution of the IgE concentration, the values of the IgE were logarithmically transformed. For the descriptive statistics, samples less than LOQ (i.e., <0.10 kU_A/L) were exchanged with fill values equal to LOQ/ √2.

The tobit model is a regression model for truncated data method, analyzing laboratory measurements subject to detection or quantification limits (i.e., where non-detects are values below a given detection limit, which may not be observed, in this case from zero to 0.10 kU_A/L) (4). In the mixed tobit model we assume an intercept, α_i, for each woman, where $\alpha_i \sim N(0, \sigma^2)$ and that data are missing at random. Our explanatory variable was time, measured in weeks. The analyses were adjusted for season (at which season the measurement was taken), since it has been found that seasonal exposure to pollen influences IgE antibody levels in allergic individuals (5). For ease of interpretation, the regression coefficients ($\log\beta$) and the corresponding CIs were exponentiated back to the original scale. Thus $(1-\beta)\times100$ can be interpreted percentage increase in asIgE geometric mean concentration associated with one week progression in pregnancy. We first included all data (everyone above the cut-off ≥0.35 kU_A/L for Phadiatop® and fx5®) in our analyses and then did sensitivity analyses using subjects with at least one test above the lower limit of quantification (LOQ) for each specific allergen (i.e., ≥0.10 kU_A/L.) Data management was performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and data analyses was conducted using STATA/IC 15.0 for Windows (StataCorp LLC, College Station, TX, USA).

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Online Supporting Information

Table E1. Baseline descriptive characteristics of the cohort.

	Phadiatop® negative and fx5® negative n=67	Phadiatop® positive n=38 (>0.35 kU_A/L)	fx5® positive n=5 (>0.35 kU_A/L)
Age (years)	n(%)	n (%)	n(%)
<19	0	0	0
20-24	1 (1.5)	1 (2.6)	0
25-29	9 (13.4)	11 (29.0)	1 (20.0)
29-34	36 (53.7)	17 (44.7)	2 (40.0)
>34	21 (31.3)	8 (21.1)	2 (40.0)
missing	0	1 (2.6)	0
Education (years)			
<9	0	0	0
10-12	4 (6.0)	5 (13.2)	1 (20.0)
>13	59 (88.1)	27 (71.1)	3 (60.0)
other	2 (3.0)	1 (2.6)	1 (20.0)
missing	2 (3.0)	5 (13.2)	0

n = nr of participants

Table E2. Quantification of the specific allergens with geometric mean, 95% confidence interval and number of individuals.

Allergen	Geometric mean (95% CI)	n	Baseline	n	Week 10-14	n	Week 26-28	n	Admission for delivery	n	3 days after delivery	n
Cat	0.21 (0.16-0.28)	131	0.21 (0.11-0.40)	31	0.24 (0.09-0.63)	17	0.22 (0.12-0.41)	32	0.17 (0.10-0.29)	25	0.21 (0.11-0.40)	26
Horse	0.13 (0.11-0.16)	131	0.13 (0.08-0.19)	31	0.17 (0.09-0.34)	17	0.13 (0.09-0.19)	32	0.11 (0.08-0.16)	25	0.14 (0.09-0.22)	26
Dog	0.17 (0.13-0.21)	131	0.15 (0.09-0.25)	31	0.25 (0.11-0.58)	17	0.16 (0.10-0.26)	32	0.14 (0.08-0.24)	25	0.18 (0.10-0.31)	26
Birch	0.57 (0.39-0.83)	131	0.41 (0.19-0.88)	31	0.78 (0.26-2.38)	17	0.45 (0.21-0.97)	32	0.71 (0.30-1.70)	25	0.72 (0.31-1.70)	26
Timothy	0.44 (0.32-0.62)	127	0.37 (0.19-0.74)	30	0.40 (0.15-1.05)	17	0.36 (0.19-0.70)	31	0.51 (0.23-1.12)	23	0.63 (0.30-1.35)	26
Egg	0.11 (0.09-0.14)	19	0.14 (0.07-0.26)	5	0.12 (0.07-0.19)	3	0.10 (0.07-0.16)	5	0.09 (0.06-0.15)	3	0.09 (0.06-0.15)	3
Milk	0.13 (0.09-0.18)	19	0.13 (0.06-0.27)	5	0.16 (0.07-0.36)	3	0.13 (0.06-0.28)	5	0.11 (0.04-0.29)	3	0.10 (0.05-0.23)	3
Cod	0.07 (0.07-0.07)	19	0.07 (0.07-0.07)	5	0.07 (0.07-0.07)	3	0.07 (0.07-0.07)	5	0.07 (0.07-0.07)	3	0.07 (0.07-0.07)	3
Wheat	0.25 (0.16-0.39)	19	0.20 (0.08-0.46)	5	0.46 (0.27-0.81)	3	0.23 (0.09-0.60)	5	0.25 (0.06-1.02)	3	0.24 (0.06-1.07)	3
Soy	0.23 (0.10-0.52)	18	0.19 (0.03-1.36)	4	0.37 (0.04-3.87)	3	0.18 (0.04-0.75)	5	0.25 (0.02-3.15)	3	0.25 (0.02-2.95)	3

CI=Confidence Interval

n =number of individuals