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This is a Peer Reviewed Accepted version of the following article, accepted for publication in *Allergy*.

2018-11-26

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Allergy. 2019 Mar;74(3):625-628.

Wiley

<http://doi.org/10.1111/all.13662>

<http://hdl.handle.net/10616/46574>

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

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28 **Word count:** 1080

29

30 **Summary**

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

35 **Keywords:** IgE, change, pregnancy, cohort

36 **Abbreviations:**

37 asIgE = allergen-specific IgE

38 LOQ = limit of quantification

39 **To the Editor:**

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

52 In the prospective longitudinal cohort study Born into Life, we followed 106 women during
53 2010-2013 living in Stockholm before, during and after pregnancy (6). In total 413 blood
54 samples were collected at baseline (before conception, n=102), at gestational week 10-14
55 (n=64) and 26-28 (n=93), at admission to hospital (n=74), and 3 days after delivery (n=80).
56 Plasma from these blood samples at all time-points were analyzed for IgE-reactivity against a
57 mixture of 11 inhalant allergens, Phadiatop® and 6 food allergens, fx5® (Thermo Fisher
58 Scientific, Uppsala, Sweden). If the test screened positive for Phadiatop® ≥ 0.35 kU_A/L, asIgE
59 antibodies to the most common single airborne allergens; cat, dog, horse-epithelium, birch and

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

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

74 Figure 1a and Table E2 in this article's online supporting information displays the geometric
75 mean for IgE airborne allergens concentration over time with 95% Confidence Interval (CI). The
76 highest geometric mean concentration of asIgE for all time points was found for birch. The
77 geometric mean concentration of IgE to birch was 0.57 (95% CI 0.39-0.83) kU_A/L. At baseline,
78 before conception, the IgE concentration to birch was 0.41 (0.19-0.88) kU_A/L and 3 days after
79 delivery 0.72 (0.31-1.70) kU_A/L. The geometric mean concentration of IgE to cat was 0.21 (0.16-
80 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
81 pregnancy. Figure 1b shows the specific food allergens over time with 95% CI where IgE to soy

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

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

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

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

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

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

122

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141 **Funding sources:** The Swedish Research Council, partly through the Swedish initiative for

142 Research on Microdata in the Social And Medical Sciences (SIMSAM) framework grant no 340-

143 2013-5867, grants provided by the Stockholm County Council (ALF-projects), the Strategic
144 Research Program in Epidemiology at Karolinska Institutet, the Department of Clinical Sciences
145 at Danderyd Hospital, the Swedish Medical Research Council, the Swedish Heart-Lung
146 Foundation, and the Swedish Asthma and Allergy Association's Research Foundation.

147 **Competing financial interests:** The authors declare no financial conflict of interest

148 **Author Contributions:** CA, GP and EA wrote the proposal, AH analysed the data and drafted the
149 paper, CL helped with analysis. AS, JA, EA, GP, CA and CL helped in study conception and
150 designing, data interpretation and gave significant inputs in revising the manuscript. All authors
151 read and approved the final manuscript.

152

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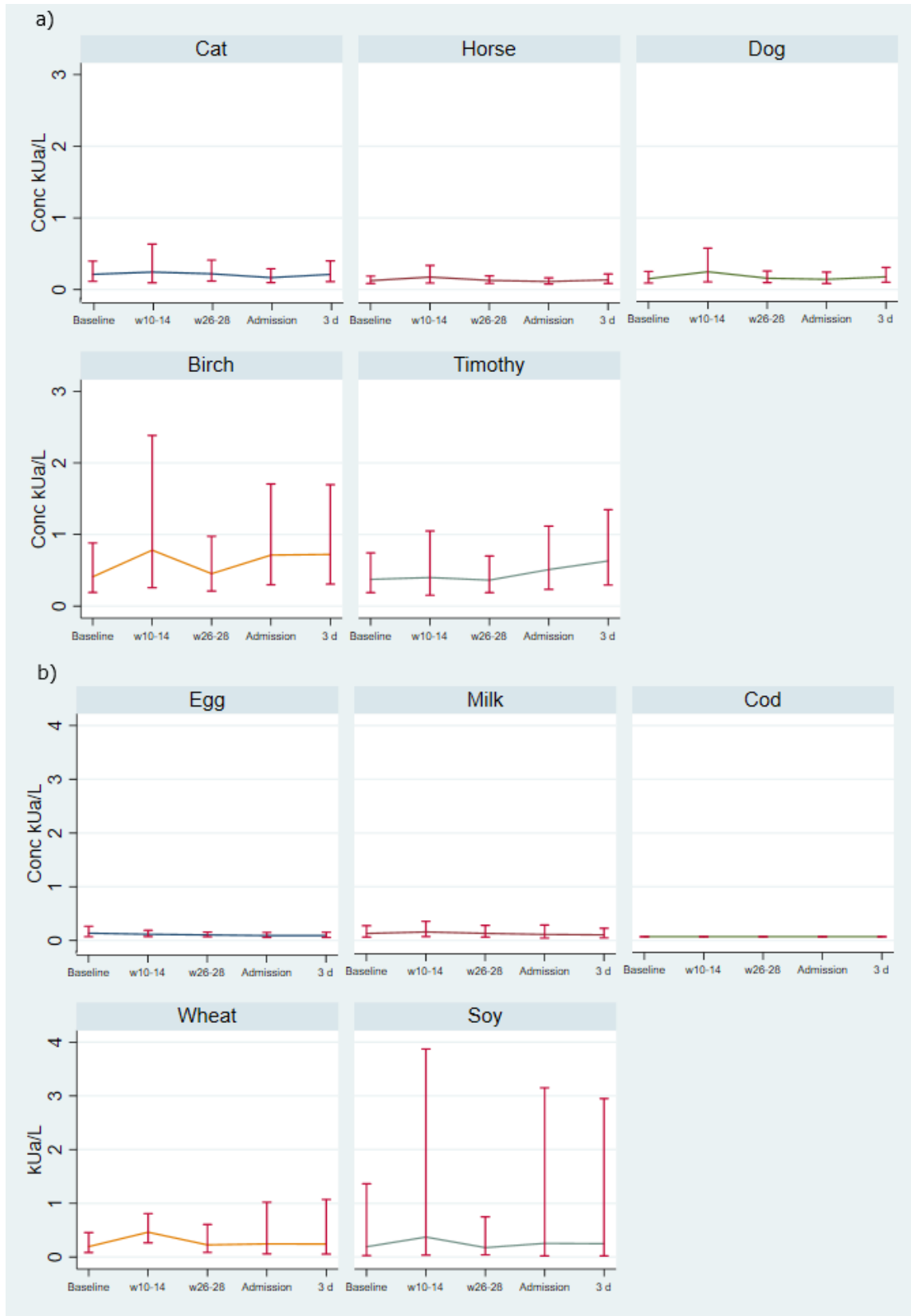
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 180 w = week during pregnancy
 181 3 d = 3 days after delivery

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

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

Allergen	All				At least one above 0.10 kU _A /L			
	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

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1 **Online Supporting Information**

2 **Study Population**

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

12 **Blood samples and analyses of IgE-reactivity to allergens**

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

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

26 **Data sources and variables**

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

33 **Statistical analyses**

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

40 The tobit model is a regression model for truncated data method, analyzing laboratory
41 measurements subject to detection or quantification limits (i.e., where non-detects are values
42 below a given detection limit, which may not be observed, in this case from zero to 0.10 kU_A/L)
43 (4). In the mixed tobit model we assume an intercept, α_i , for each woman, where $\alpha_i \sim N(0, \sigma^2)$
44 and that data are missing at random. Our explanatory variable was time, measured in weeks.
45 The analyses were adjusted for season (at which season the measurement was taken), since it
46 has been found that seasonal exposure to pollen influences IgE antibody levels in allergic
47 individuals (5). For ease of interpretation, the regression coefficients ($\log\beta$) and the
48 corresponding CIs were exponentiated back to the original scale. Thus $(1-\beta) \times 100$ can be
49 interpreted percentage increase in asIgE geometric mean concentration associated with one
50 week progression in pregnancy. We first included all data (everyone above the cut-off ≥ 0.35
51 kU_A/L for Phadiatop[®] and fx5[®]) in our analyses and then did sensitivity analyses using subjects
52 with at least one test above the lower limit of quantification (LOQ) for each specific allergen
53 (i.e., ≥ 0.10 kU_A/L.) Data management was performed using SAS 9.4 (SAS Institute, Cary, NC,
54 USA) and data analyses was conducted using STATA/IC 15.0 for Windows (StataCorp LLC,
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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