

Is maternal age at delivery related to childhood food allergy?

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The prevalence of food allergies is increasing. Concurrently, the average maternal age at birth is also increasing. We conducted a preliminary study to evaluate whether maternal age at the time of delivery is associated with a food allergy in children. Case and control patients were identified among consecutive patients seen by one of us (AD) in the Allergy/Immunology program at the Children's Hospital Boston between 11/1/98 and 2/28/00. Case patients were born in Massachusetts and had evidence of clinical sensitivity and IgE to one or more food allergens ($n = 58$). Control patients were those born in Massachusetts who had a negative skin test and/or RAST to inhalant and/or food allergens ($n = 96$). A second comparison group consisted of all live births in Massachusetts in 1999 ($n = 80,866$). Information on maternal age at birth was missing from 3/58 (5%) of patients with a food allergy and 4/96 (4%) of the control patients, so these patients were not included in the analysis. The proportion of children whose mother was aged 30 and over at their birth was significantly higher in children with a food allergy than control patients (78% vs. 55% $p = 0.005$) and higher than all births in Massachusetts (78% vs. 53% $p = 0.0002$). Mothers of children with a food allergy had about three times greater odds of being aged 30 or over at the time of delivery than mothers in either of the comparison groups. Further exploration of the data using logistic regression showed that maternal age over 30 at delivery and being first born were independent predictors of the child having a food allergy. In this study, the presence of a food allergy in children was related to older maternal age at delivery. Additional studies are needed to further evaluate this relationship and its potential implication in preventive strategies for food allergies in children.

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Atopic diseases including food allergies are increasing in prevalence worldwide, particularly in western countries (1–5). It is intriguing that nationwide the mean maternal age at birth has increased from 24.9 years in 1968 to 27.1 years in 1998 (6). In Massachusetts, the proportion of births that had mothers aged 30 and older has been steadily increasing (7), and by 1996, for the first time since births were recorded, more births occurred to women aged 30 and older than to women under 30 (Fig. 1).

Several studies report that hay fever and eczema/atopic dermatitis are increasing among

the offspring of older mothers (2, 8–11). These studies used self-report of allergic symptoms (2, 8–10) or physician diagnosis of atopic dermatitis (11). Except for one study that assessed skin test reactivity to grass (10), objective measures of IgE-mediated allergy (skin testing and/or RAST) were not performed and none of these studies evaluated whether there is an increase in food allergies in the children of older mothers.

We conducted a preliminary study to evaluate whether maternal age at birth is higher in children with IgE-mediated food allergy than in those without a food allergy.

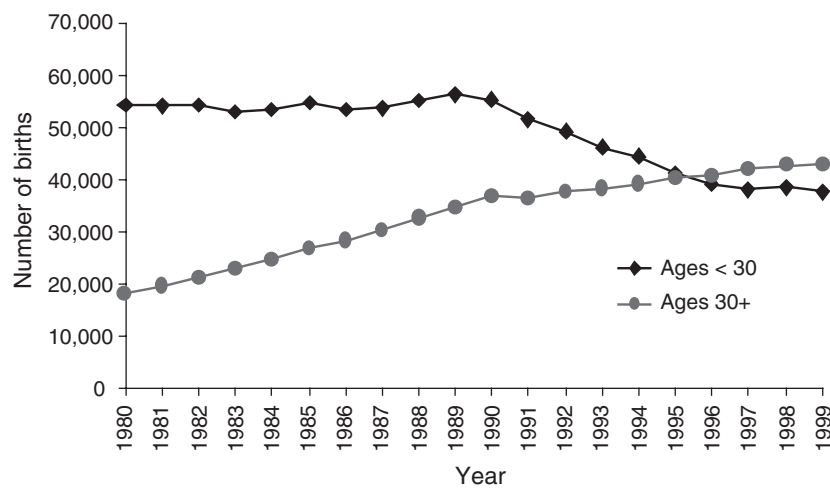


Fig. 1. Trends in the number of births in Massachusetts by mother's age group: 1980–99.

Methods

Children's Hospital case and control patients

Case and control patients were identified among consecutive patients seen by one of us (AD) in the Allergy/Immunology program at the Children's Hospital Boston between 11/1/98 and 2/28/00. Case patients were born in Massachusetts and met both of the following criteria for diagnosis of a food allergy:

1. Clinical sensitivity to one or more food allergens based on a documented history of acute allergic reactions (urticaria, wheezing and/or angioedema with or without vomiting and/or diarrhea) associated with the intake of one or more particular food allergens.
2. Elevated specific IgE to one or more foods detected by either skin prick testing and/or RAST assay performed as indicated by the patient's history. All skin prick tests were done with a Multi-Test[®] device (Lincoln Diagnostics, Decatur, IL, USA) using commercial food extracts (Greer Laboratories, Inc., Lenoir, NC or Bayer Corporation, Spokane, WA, USA). All RAST assays were performed using the UniCAP Pharmacia CAP system[®] (Pharmacia & Upjohn, Uppsala, Sweden).

Control patients were those born in Massachusetts who had negative skin test and/or RAST to inhalant and/or food allergens performed as indicated by their clinical history.

Demographic data [age, sex, parent's insurance carrier (private insurance vs. not)], child's medical history including the perinatal history, birth order of the child and information on allergy tests were abstracted from the child's medical record. This study was reviewed and approved by the Children's Hospital's Institutional Review Board

(IRB). The IRB waived the requirement for informed consent for this chart review study.

General population comparison group

Another comparison group consisted of live births provided by the Massachusetts Department of Public Health's Registry of Vital Records (7). State births for 1999 were selected because this year had the greatest proportion of older mothers (ages 30 or over). This comparison cohort provides the most conservative test of our hypothesis that our case patients have a higher maternal age than the general population.

Statistical methods

Statistical analyses were performed using SPSS version 11.0 (SAS Institute, Chicago, IL, USA). The mother's age at delivery was analyzed as a continuous variable and also collapsed into two categories, under 30 and 30 and over. This categorization was based on the age being tracked by the state of Massachusetts to evaluate trends for maternal age at birth (Fig. 1). A two-sided chi-square test was then used to compare the ages of mothers of children with a food allergy with the ages of mothers in the comparison groups. Crude odds ratios and 95% confidence intervals were also generated comparing the likelihood of mothers being 30 years or older at the time of delivery among patients with a food allergy compared with control patients and with all Massachusetts births in 1999. The effect of potential confounders of the relationship between maternal age at birth and presence of a food allergy in the child, including socioeconomic status and birth order of the child, were analyzed. Maternal age at birth (under 30 vs. 30 and older), type of insurance

(private vs. not) as a proxy for socioeconomic status (12) and birth order (first born vs. all others) were explored using multivariable logistic regression. We used forward variable selection with entry criteria set at $p < 0.05$. We assessed model discrimination using the area under the receiver operating characteristic curve (13) and model calibration using the Hosmer and Lemeshow goodness-of-fit test (14).

Results

Fifty-eight patients met criteria for diagnosis of a food allergy and 96 patients were in the control group. Information on maternal age at birth was missing from 3/58 (5%) patients with a food allergy and 4/96 (4%) of those without a food allergy so these patients were not included in our analysis. The average age of patients with a food allergy at the time of their initial evaluation was 2.9 years with a range of 0.6–11.8 years. There were 33% females, 67% males and 50% of patients had atopic dermatitis.

The mean maternal age at birth of children with a food allergy was 31.2 years (standard deviation 5.3 years) compared with the mean maternal age of children without a food allergy of 29.2 years (standard deviation 5.5 years) ($p = 0.03$).

Table 1 presents the numbers and percentages of mothers by age at delivery in 5-year age groups for patients with a food allergy and the two comparison groups. Crude odds ratios (OR), their 95% confidence intervals, and p -values are listed in Table 2. As shown in Tables 1 and 2,

Table 1. Maternal age at the time of delivery in cases and controls

Maternal age	Patients with a food allergy n (%)	Control patients n (%)	All Massachusetts births in 1999 n (%)
≤24 years	5 (9)	19 (21)	17,401 (22)
25–29 years	7 (13)	22 (24)	20,382 (25)
30–34 years	28 (51)	36 (39)	26,330 (32)
≥35 years	15 (27)	15 (16)	16,753 (21)
<30 years	12 (22)	41 (45)	37,783 (47)
≥30 years	43 (78)	51 (55)	43,083 (53)

Table 2. Crude odds ratios (95% confidence intervals) for likelihood of mother being 30 years or older at the time of delivery

Comparison	Crude odds ratios (95% CI)	p-value
Control patients	1.00	0.005
Patients with a food allergy	2.88 (1.35–6.16)	
All Massachusetts births in 1999	1.00	0.0002
Patients with a food allergy	3.14 (1.66–5.96)	

Table 3. Effect of maternal age on diagnosis of a food allergy in clinic cases and controls – multivariate analysis

Variable	Unadjusted odds ratio (95% confidence interval)	Covariate adjusted odds ratio (95% confidence interval)
Maternal age at birth (> 30 vs. <30 years)	2.88 (1.35–6.16)	3.70 (1.67–8.20)
Birth order (first born vs. all others)	1.73 (0.86–3.46)	2.22 (1.06–4.66)
Type of insurance (private vs. government or none)	3.11 (0.85–11.36)	*

*Not significantly associated with diagnosis of a food allergy after adjustment for maternal age and birth order.

mothers of children with a food allergy were significantly more likely to have been aged 30 or over at the time of delivery compared with mothers of control patients (78% vs. 55%, $p = 0.005$), as well as mothers of all 1999 births in Massachusetts (78% vs. 53%, $p = 0.0002$). Mothers of children with a food allergy had about three times greater odds of being aged 30 or over at the time of delivery than mothers in either one of the comparison groups. There was no difference in the proportion of children whose mother was 30 and over at their birth between control patients and all births in Massachusetts (55% vs. 53%, $p = 0.57$).

Controlling for potential confounders

In the logistic regression model (Table 3), maternal age 30 and over increased the risk of having a child with a food allergy (covariate adjusted odds ratio of 3.70, 95% confidence interval 1.67–8.20, $p = 0.001$) and being first born also increased the risk of having a food allergy (covariate adjusted odds ratio of 2.22, 95% confidence interval 1.06–4.66, $p = 0.035$). Type of insurance was not independently associated with having a child with a food allergy after adjusting for maternal age and birth order. The interaction term between maternal age and birth order was not statistically significant. The goodness-of-fit test p -value was 0.86 and the area under the receiver operating characteristic curve was 0.69.

Discussion

In our patient population, increased maternal age at birth and being first born were independently associated with the presence of a food allergy in their children. To our knowledge, this is the first report of such an association.

Increased maternal age during pregnancy is a well-established risk factor for genetic diseases. Although specific genes for food allergies have not yet been identified, the higher prevalence of food allergies in children with parents who have food allergies is a well-recognized pattern. It is possible that children with older mothers have a higher genetic predisposition for developing a food allergy.

A strong inverse relationship between atopy and increased number of siblings has been observed (8, 9, 15–19). Our study did confirm that being first born increased the risk of developing a food allergy even after adjusting for increased maternal age.

Environmental factors may also increase the risk of atopy in children. Atopy is more prevalent in children of small and relatively affluent families and children with professional parents (2, 8, 15, 20). One explanation for these observations is reduced cross-infection in smaller families, as early infection may protect against allergic sensitization. Our study raises the possibility of an additional explanation that a risk factor for atopy is increased maternal age, as mothers of smaller and more affluent families are more likely to have children at an older age.

As we noted in the introduction section, several studies report an increasing prevalence of hay fever and atopic dermatitis among the offspring of older mothers (2, 8–11). However, we believe that our paper is the first report of a possible association between food allergies and older maternal age at delivery.

One potential limitation of our study is the approach used to diagnose a food allergy. Although a double-blind, placebo-controlled food challenge was not performed in our study, all patients had a history of an acute allergic reaction associated with the intake of one or more foods to which they had mounted an IgE response, documented by a positive skin prick test and/or RAST. At least in the case of patients with a peanut allergy, it has been suggested that in the majority of clinical situations in patients with a good history and a positive skin prick test, a food challenge may not be necessary for diagnosis (21). A second limitation of our study is that the information about maternal age was not available for seven patients. We attempted to address this limitation by assuming the worst case scenario (biasing towards the null hypothesis) for the missing information. We assumed that children with a food allergy for whom there was no information on their mother's age at birth, had mothers under age 30, while we assumed that children without a food allergy

for whom there was no information on their mother's age at birth, had mothers aged 30 and over. Even using these conservative and unlikely assumptions, the p-value for this comparison was 0.035, still showing an association between increased maternal age at birth and diagnosis of a food allergy in their offspring. A third limitation is that patients attending our clinic may be atypical of patients with a food allergy. However, it is reassuring that our control children appeared more like mothers in Massachusetts with respect to age at their child's birth. Also the referral pattern of children with a food allergy was not different than the other patients mostly because we excluded patients born outside Massachusetts who tend to be those presenting for a second opinion or had traveled a long distance to be seen in our clinic. We do recognize that a high proportion of our patients [130/147 (88%)] had private insurance, but the proportion with private insurance in our clinic cases and controls was similar (95% and 85%, respectively). A fourth limitation was our attempt to evaluate whether socioeconomic status was an independent predictor of a food allergy being diagnosed in children. We recognize that using type of insurance as a proxy for socioeconomic status has numerous well-recognized limitations. In addition, because 88% of our patients had private insurance, we had limited power to evaluate whether type of insurance as a proxy for socioeconomic status was associated with occurrence of a food allergy.

In summary, in our patient population, having a mother aged 30 or older at the time of delivery was associated with diagnosis of a food allergy in their children. The recent trend of increasing maternal age at birth may be contributing to the increased prevalence of food allergies reported in western countries. Additional studies are needed to further evaluate this association and, if it is confirmed, strategies to prevent food allergies in young children may need to target older pregnant women.

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