

Maternal atopy and changes in parity

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Summary

Background Atopic women tend to have fewer children, although atopy may favour conception.

Objective To assess whether atopy is associated with the number of new births and whether changes in parity are associated with a change in atopy in a cohort of young women.

Methods Women had atopy (defined as the presence of serum-specific IgE against common aeroallergens) measured in the European Community Respiratory Health Study during the years 1991–92 ($n = 4580$). About 9 years later, 2844 (62.1%) were recontacted and 2414 (52.7%) had atopy measured again.

Results Atopic women had fewer children at baseline than non-atopic women but the association disappeared at the end of the follow-up. Atopy tended to increase parity during the follow-up, but in a non-statistically significant way (relative risk = 1.08; 0.86–1.35, after adjusting for number of children at baseline, age, length of follow-up, education or social class). Prevalence of atopy during the follow-up changed by the same magnitude whatever the birth cohort and the change in the number of children (P for interaction > 0.7).

Conclusion Atopic women did not have a significantly higher fertility rate but they may postpone having their first child compared with non-atopic women. We are unable to confirm the hypothesis that atopy in women may decrease with successive pregnancies.

Keywords atopy, fertility, IgE sensitization, parity

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Introduction

Previous studies have shown that atopy decreases with birth order which has been explained by changes in environmental exposures early in life at different birth order (the hygiene hypothesis) [1]. Alternatively, mothers with more children were less likely to be atopic as demonstrated by skin prick test [2], or suffer from allergic rhinitis (AR) [3, 4] and atopic diseases [5] after controlling for age and social class. Possible explanations for this observation may be that atopy decreases the rate of conception/birth or that pregnancy decreases atopic sensitization in the mother [6]. A recent study in 31 145 pregnant women showed a shorter time to pregnancy among allergic women [3] suggesting that atopy *per se* increases the chance of conception, but with increasing numbers of pregnancies the rate of atopic sensitization decreases [6]. In fact, in a small prospective study, women tended to lose allergy after successive pregnancies [7]. Maternal atopic sensitization may confer reproductive advantages [8]. Pregnant women have a propensity for T-helper type 1 (Th1)

function suppression [9, 10] and local production of Th2 cytokines may contribute to the maintenance of pregnancy [11]. On the other hand, post-partum rebound of cytokines in favour of a Th1 balance in the maternal circulation may protect against atopy with increasing parity [8]. These changes may persist after the post-partum period.

Our aim was to assess, in an international follow-up study, whether atopic sensitization is associated with an increase of full-term pregnancies and whether changes in parity were associated with a decrease in atopic sensitization.

Methods

Design and subjects

The European Community Respiratory Health Study (ECRHS) was an international survey carried out during the years 1991–1992 in randomly selected individuals from the general population aged 20–44 years old in 36 centres in 16 countries [12]. Populations and subjects participating in the study have been described in detail elsewhere [12]. All participants attending the clinical examination, including blood extraction for IgE sensitization measurement (ECRHS-I) were invited to participate in a follow-up study during the years 1999–2002 (ECRHS-II) [13].

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Women recruited for the present study were the 4580 who were selected at random and had data on IgE sensitization in ECRHS-I from the 21 centres participating in the women's study in ECRHS-II (South Antwerp, Antwerp city in Belgium; Bordeaux Grenoble, Montpellier, Paris in France; Reykjavik in Iceland; Bergen in Norway; Ipswich, Norwich in the UK; Portland in the USA; Albacete, Barcelona, Galdakao, Huelva, Oviedo in Spain; Goteborg, Umea, Uppsala in Sweden; Basel in Switzerland; and Tartu in Estonia). Of these, 2844 (62.1%) completed the questionnaire in ECRHS-II and 2414 (52.7%) had IgE sensitization measured again. Differences between participants in the present study and those lost to follow-up ($n = 4580 - 2844 = 1736$) were not significant in terms of age (mean age 34.2 vs. 33.5), asthma prevalence (4.2% in both groups) or number of children at baseline (1.3% in both groups), but participants were better educated (50% had tertiary education in comparison with 40%) and less atopic (24.6% vs. 28.7%).

Variables Respiratory symptoms, reported maternal and paternal allergy, social class (based on the woman's occupation), employment, years of education and smoking were assessed by questionnaire both at baseline and at follow-up [13]. Data on the number of children at baseline, number of full-term pregnancies (including still births) during follow-up, date of the last delivery, months taking oral contraceptives since ECRHS-I, age of menarche and age of menopause was measured by questionnaire at follow-up. Specific IgEs were measured by using the Pharmacia CAP system. All assays for specific IgE were judged to be positive if they had in excess of 0.35 kU/L of the specific allergen, the limit of detection of the assay. In all centres specific IgE against house dust mite (*Dermatophagoides pteronissinus*), cat dander, timothy grass and *Cladosporium herbarum* were measured, and atopy defined as a positive response to any of the allergens. Asthma was defined based on respiratory symptoms derived from questionnaire [12].

Statistical methods In order to analyse the risk of having new children among atopic and non-atopic women logistic regression models were used. Secondly, to analyse the changes in atopy after changes in parity we measured the incidence of atopy at the follow-up among women who were non-atopic at baseline and the remission of atopy at follow-up among women who were atopic at baseline. In addition, data was analysed using generalized estimated equations (GEE) with atopy as the outcome. This method accounts for repeated data (i.e., two observations of atopy at different times for each subject) and changes in atopy according to pregnancies in the interim can be determined, using interaction between the time of follow-up in years with number of preceding and new children. All the above regression models were adjusted for education, social class, number of children at baseline, maternal allergy, current asthma, taking oral contraceptives, age of menarche, smoking, and centre. Variables were retained in the models if the P -value was lower than 0.1. Heterogeneity between centres was not tested because of a small number of new births.

Results

Among women of any given age, the number of children per woman before the age of 40 years was lower for those in the youngest birth cohort (born between the years 1962 and 1973) than in the oldest cohorts (1945–1961). Table 1 provides a description of the participant characteristics. At baseline, 37.6% of women were nulliparous. Changes in number of children occurred in 27.4% of women during the follow-up (15.3% had one child and 12.2% at least two). At the end of follow-up, only 22.3% of women were nulliparous.

The mean number of years of follow-up was 8.86 (range 6.04–11.8) and the mean age of menopause among the 8% reporting it 45.2 years. At baseline atopic women were younger and more likely to report current asthma, maternal allergy, never smoking, high education, use of oral contraceptives during the follow-up and smaller families compared with non-atopic women ($P < 0.05$). By contrast, woman's occupation, being a housewife or unemployed, age of menarche, age of menopause, and maternal age were unrelated with atopy (the lowest P -value = 0.3).

Table 1. Distribution of descriptive variables in 2844 women in ECRHS II

	Baseline (1991–1993) (%)	Follow-up (1999–2002) (%)
<i>N</i> children		
0	37.60	22.27
1	17.78	16.53
2	25.98	34.33
≥3	18.63	26.87
Current asthma	4.23	4.87
Smoking status		
Never	48.52	47.92
Ex	20.32	25.32
Current	31.16	26.76
Age at end of formal education (years)		
< 16	10.13	9.67
16–20	33.47	32.98
> 20	42.23	55.56
Unknown	14.17	1.79
Social class		
Professional/managerial	29.50	*
Non-manual clerical	22.68	*
Skilled manual	7.35	*
Semi-skilled manual/unskilled	13.40	*
Unclassifiable	27.07	
Atopy	24.68	23.24†
Two allergens	9.35	7.95†
Der p 1	11.85	11.56†
Cat	8.51	7.95†
Grass	14.49	13.63†
Oral contraceptive	*	28.97
	Mean (SE)	Mean (SE)
Age (in years)	33.98 (0.13)	42.84 (0.13)
Age of menarche	*	12.89 (0.03)

*No information. †Among 2414 women.

Table 2. Changes in number of children according to changes in atopy

Atopy			Mean number of children (SE)		Change in number of children from baseline (%)		
Baseline	Follow-up	N	At baseline	At follow-up	0 (n = 2014)	1 (n = 434)	≥2 (n = 346)
No	—	2037	1.38 (0.03)	1.79 (0.03)	76.9	75.3	65.6
Yes	—	657	1.19 (0.05)	1.75 (0.06)	23.1	24.6	34.4
No	No	1625	1.42 (0.03)	1.81 (0.03)	62.4	57.6	48.3
No	Yes	108	1.51 (0.14)	1.99 (0.13)	3.8	4.8	4.3
No	Unknown	304	1.14 (0.07)	1.63 (0.08)	10.6	12.9	13.0
Yes	No	140	1.08 (0.11)	1.62 (0.12)	5.0	4.1	6.9
Yes	Yes	425	1.22 (0.06)	1.75 (0.07)	14.9	16.8	19.4
Yes	Unknown	92	1.17 (0.15)	1.98 (0.17)	3.2	3.7	8.1

Changes in parity in immunoglobulin E sensitized and non-sensitized women at baseline

At baseline, the number of children was higher in non-atopic women than in atopic women (means 1.38 and 1.19, respectively, $P < 0.01$) (Table 2), a difference that was not explained by age. At the end of the follow-up the number of children was similar among non-atopic and atopic at baseline (means 1.79 and 1.75, respectively, $P = 0.35$). Similarly, women non-atopic in both examinations (baseline and follow-up) had more children at baseline than those atopic at baseline and/or at follow-up (means 1.42 and 1.22, respectively, $P < 0.01$), but this difference disappeared at the end of the follow-up (means 1.81 and 1.75, respectively, $P = 0.31$). Women atopic at baseline have a higher increase in number of children during the follow-up period than non-atopic women (23% of those not having new children were atopic vs. 34% of those increasing at least twice, P for trend < 0.01) (Table 2). However, this difference disappeared after adjusting for age, number of children at baseline, length of follow-up and education (odds ratio of having new children = 1.08; (0.86–1.35)). Definition of atopy using a cut-off of 0.70 instead of 0.35 provided the same results.

Changes in immunoglobulin E sensitization following child birth

Changes in atopy occurred in 6.2% of those negative at baseline, who became positive at follow-up, while 24.5% of those positive at baseline became negative at follow-up. Among women non-atopic at baseline, those who had new children during follow-up tend to become positive at follow-up in a higher proportion than women who did not have any

new children during follow-up, although differences were not statistically significant (Table 3). Among women atopic at baseline there were no differences at follow-up in the proportion of those who became negative. Accordingly, in the GEE model, after adjusting for the potential confounding variables, the prevalence of atopy decreased moderately per year (1%, 95% confidence interval 0–2%) by the same magnitude whatever the birth cohort and the change in the number of children during the follow-up (P for interaction > 0.7) (i.e. the decrease was similar in women with and without an intervening child). Similar findings were observed when atopy was defined as being positive to at least two allergens or suffering nasal allergy instead of by IgE sensitization (data not shown).

Discussion

In the present study atopic women at baseline had fewer children, which agrees with other studies [2–5]. However, the association disappeared at the end of the follow-up, as atopic women tended to have more children during the follow-up, that would be consistent with the protective influence of Th2 cytokines during pregnancy [8], although the association between atopy and parity during follow-up was not significant after considering age and other variables. At baseline, atopic women had fewer children, a finding that could be interpreted as a delay (either intentional or unintentional) in the conception of the first child among atopic women. The women in this study had a similar change in atopy whatever number of new children during the follow-up, and hence we are unable to confirm the hypothesis that

Table 3. Changes in atopy (from baseline to follow-up) by changes in number of children during the follow-up and by parity at baseline

Changes in atopy		Increase in number of children from baseline			P for trend	Adjust† P for trend
		0	1	≥2		
Incidence* (%)	0	4.7	7.1	9.1	0.06	0.21
	≥1	6.1	7.8	7.1	0.46	0.98
Remission* (%)	0	26.9	25.7	25.4	0.82	0.87
	≥1	24.8	16.4	28.0	0.71	0.57

*Incidence as the proportion of positive atopy at follow-up among women negative at baseline. Remission as the proportion of negative atopy at follow-up among women positive at baseline. †Adjusted for age at baseline in years, education and social class.

atopy in women may decrease with successive full-term pregnancies

A limitation of the present study is that we only had the date of birth for the last child and that not all women have finished their reproductive period. Therefore, we cannot measure whether atopic women postpone having their first child, and we cannot separate a potential age effect (a delay in childbearing) from a cohort effect (a different relationship between atopy and parity at different generations). Secondly, we did not take into account the time when new pregnancies occurred which did not allow to control for censoring, although survival analysis incorporating exact dates for women only having one child resulted in results similar to those obtained via logistic regression models restricted to those increasing only once. Different definitions of atopy (i.e., positive to at least two allergens or IgE positivity to each specific allergen) did not change our findings. Finally, we did not adjust for changes in lab procedures when measuring changes in atopy between the two examinations, which could explain the 1% decrease in atopy prevalence per year. The strengths of the present study, in addition to its prospective nature, are its size and the use of repeated data on IgE sensitization.

An age or a cohort effect of atopy in childbearing might have two main explanations a defect in the conception process related to atopy and hormonal levels [14], or that socio-demographic characteristics related to voluntary infertility are more common in atopics than in non-atopics [15]. Among the latter we may partially exclude the use of oral contraceptives as an explanation, as adjustment for both taking oral contraceptives during the follow-up and for duration of the reported months taking it during the follow-up did not confound the results.

Although it is possible that atopy may confer some advantage regarding the rate of conception, because of immunological factors related with implantation of the embryo [6], one study showed a decrease of IgE concentration among women during the periovulatory phase [16]. In an earlier study with pregnant Danish women, atopics had a shorter time to pregnancy [3]. In that study, early age of menarche was associated with AR [3], which was also suggested in a cohort study including 2590 Finnish women [17]. Young age of menarche could be a consequence of higher estrogen levels [18] and estrogen levels have an affect on the immune system promoting a shift towards the Th2 phenotype [19]. Consistently, among multiparous women in our study, age of menarche was earlier in atopic than in non-atopic women. However, among those without children the atopic women had later menarche than the non-atopic (P for interaction = 0.01) (data not shown). It is unlikely that atopy could be related with unsuccessful pregnancy after conception, given the immunological bases related with pregnancy [8, 9] and the findings of a lack of relation between atopy and poor reproductive outcomes or increased abortions in general population studies [2, 3]. Only asthma has been associated with poor full-term pregnancies [20], but our findings on atopy and parity were independent of having asthma. One hypothesis could be that hormonal levels may be related with atopy and with conception which may be the underlying mechanism of our findings. This includes either a potential delayed conception or potential increase of infertility among atopics from recent generations.

An alternative explanation refers to the fact that atopy is more prevalent in high socio-economic classes and well educated people [15] among whom delayed pregnancies and smaller families may be more frequent. In our study, social class based on maternal occupation was unrelated with atopy in contrast to maternal education that is positively related with atopy in a moderate way (59% of atopic women were highly educated vs. 52% of non-atopic women). The potential of a residual confounding of these factors could not be excluded, although neither education in years (as a continuous variable) in either of the two examinations, nor social class based on woman's occupation, marital status, being a housewife or maternal unemployment explain our findings. Similar results have been found in previous studies relating the number of offspring with IgE sensitization [2] or nasal allergy [3, 4] adjusted for social class. Maternal smoking showed an immunological impact at birth [21], however adjustment for smoking did not modify the present findings.

Findings of the present study would have consequences for the offspring as maternal atopy might be inherited. Thus, cord blood total IgE [22] and T-helper cell proliferative responses [23], both related with further atopy, have been found to decrease with birth order. Another hypothesis is that children exposed to higher levels of maternal hormones have a higher risk of atopy [24]. Therefore, the present findings might explain in part the sibling effect on atopy (i.e., atopy decreases with birth order) [1].

Overall, taking into account the prospective nature of the data (i.e., the fact that it deals with a large range of co-factors in an international follow-up study) we found no evidence of increased parity in atopics and no evidence for a decrease in atopic sensitization with successive pregnancies. However, atopic women had fewer children at baseline which might be explained by a delay in childbearing. Only a cohort study followed-up to the menopause and including the exact dates of all births could assert it.

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