The effects of farming and birth order on asthma and allergies

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ABSTRACT: A farm childhood is apparently protective in allergic disease, but studies of this issue in Europe have been confined to particular types of farming practice. This study addressed whether or not this effect was generalisable.

A cross-sectional survey of 800 schoolchildren living in rural Crete was undertaken. Standard questions relating to allergic disease were included and atopy was measured through skin-prick tests involving 10 local aeroallergens.

The prevalence of atopy was 24%, but associated symptoms were far less common. At all ages, children from farming families had more frequent contact with farm animals (mainly goats), but were no less likely to be atopic. Atopy and seasonal rhinitis were significantly and independently more common among first-born children.

This community has an intermediate prevalence of atopy but a very low frequency of allergic disease; farming does not seem to be an important determinant, possibly because it is of the wrong sort. Thus farming effects may be specific to local practices. First-born children in this community also appear to be at increased risk of allergic disease.

KEYWORDS: Allergic disease, atopy, birth order, farming, Greece

Childhood asthma and allergic disease are distributed unevenly across Europe, with a decreasing prevalence from north to south and from west to east [1]. The reasons for this variation are unclear but are often, if loosely, attributed to westernisation, in itself perhaps a reflection of lower rates of microbial contact in early childhood, leading to inappropriate regulation of a developing immune system. In keeping with this, several studies have reported that European children brought up against a farming background have lower risks of atopy and some associated allergic diseases, particularly hay fever [2, 3]. Also widely reported is the observation that children from small sibships show increased risk of such allergies, a phenomenon consistent with a protective effect of early infection [4].

For the most part, studies that have examined farming have involved children living in communities in which cows are kept, often in close proximity to the family home. Farming on Crete, an Eastern Mediterranean island, is very different from that in Central and Northern Europe. Cows are absent from the island, and, where livestock are kept, they are invariably goats or sheep, put out to graze on distant mountain slopes; animals are not kept in barns. Arable farming is of olives, vegetables or citrus fruits. For the most part,

farmers live in villages some distance from their land. The distinction between farmers and their nonfarming neighbours is not always clear and villagers who do not consider themselves chiefly to be farmers frequently have a small plot of land and often keep a few animals. In addition, many rural families keep one or two goats in their courtyard at home, frequently accompanied by chickens or caged rabbits. Pet dogs and cats live outside.

In an earlier survey, it was reported that the prevalence of childhood atopy in a rural Cretan community was half that in Iráklion, the capital city [5]. Among rural children, however, there was no relationship between atopy and parental farming. In order to investigate this further, a second, more detailed cross-sectional survey was designed in order to include children living in a variety of rural settings on the island. In addition to atopy, the rural distribution of allergic symptoms consistent with asthma or hay fever was examined.

METHODS

In 2001, all schoolchildren aged 7–18 yrs and living in four previously unsurveyed areas of rural Crete were invited to take part in a study of the relationships between atopy or associated

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diseases and a farm upbringing. Ethical approval was obtained from The Scientific Committee at the Venetian Hospital (Iraklion, Crete) and the Ethics Committee at Royal Brompton and Harefield NHS Trust (London, UK). All parents gave written informed consent.

Parents were asked to complete a questionnaire that elicited information about the respiratory health of their participating children, any siblings and the child's parents. Where possible, questions were translated directly from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [6]. Information was requested about levels of parental education and occupation, and about their children's exposure to and contact with farm animals or pets and consumption of farm milk at three different stages of life: infancy, at 5 yrs of age, and during the past year.

Each child was invited to undergo skin-prick tests, in accordance with the ISAAC protocol, involving a series of 10 common aeroallergens: grass pollen (Mediterranean mix), *Parietaria*, olive blossom, cat fur, *Dermatophagoides pteronyssinus* and *D. farinae*, goat epithelium, *Cladosporium*, cockroach, and poultry, all purchased from ALK Abelló (Hungerford, UK). The negative and positive controls were saline and histamine respectively. A skin-prick test result was considered positive if it produced a mean wheal diameter of ≥ 3 mm greater than that produced by the saline control.

Statistical analysis

Complete data were available for 797 children, 93% of those eligible. Children were categorised as atopic if they gave one or more positive immediate skin-prick test results. In order to permit comparison with the earlier survey in Crete, a further category (standard atopy), defined by the presence of one or more positive test results to any of the three pollens, either dust mite or cat fur, was formed. Children were considered to suffer from current seasonal rhinitis when they were reported to have had a runny or blocked nose (while not having a cold or influenza) over the past year during the months of March to September. Parents were defined as full-time farmers if either was a full-time farmer; part-time farming indicated that either parent was a part-time farmer but neither was involved full-time. Only when neither the father nor the mother was involved in any kind of farming was the child considered to come from a nonfarming family.

All information was entered on to a computer database, and analyses were performed after data checking and cleaning. The Pearson Chi-squared test was used to test for associations between categorical variables, and the medians of continuous variables were compared between groups by means of the Kruskal-Wallis or Mann-Whitney test. Where appropriate, Cuzick's trend test was used for ordered exposure variables.

Explanatory variables associated with the outcome of interest ($p < 0.15$) were included in multivariate logistic regression models and adjusted for those factors that either were significantly associated with atopy or confounded the association between atopy and the main exposure of interest. Effect modification was assessed between the variables retained in the final models.

RESULTS

Comparisons between farming and nonfarming households

A minority (14%) of the children were currently living in a nonfarming home; equal proportions of the remainder were from full- or part-time farming families (table 1). Almost all (95%) current full-time farmers, but only 30% of part-time farmers and 8% of current nonfarmers reported that farming was their primary occupation at the time their child was born.

The distributions of age and sex of the surveyed children did not differ across the three levels of farming. Levels of parental education, conversely, varied systematically, with mothers and fathers who farmed having completed fewer years of schooling than other parents ($p < 0.005$ for both). Children from nonfarming households tended to be from smaller families and were more often the first-born. These differences were significant. Reported asthma is rare in this community but was more common in the siblings of those children whose parents were farmers. This difference was not apparent for seasonal rhinitis, reported by 5.9% of the total population. Parents who were current full-time farmers almost always reported that their primary occupation at the time of their child's birth was farming. Children from farming homes, either full- or part-time, were more likely to have current contact with sheep or goats and live in a home where these animals were kept in close proximity. This was also the case during infancy, at age 5 yrs (data not shown) and for all species of farm animals (goats, sheep, chickens, pigs and rabbits; data shown only for goats/sheep). Of children who currently lived in a home where goats or sheep were kept in the courtyard, 53% were reported to have daily contact with the animals, 35% weekly contact and 13% no contact. During infancy, these proportions were reversed: 24, 18 and 58%, respectively.

Atopy, allergic disease and farming

Of the children, 24% were atopic; 19% showed standard atopy (table 1). These frequencies were the same in each of the four study areas. Atopic children were most often sensitised to *D. pteronyssinus* (12% of all children) or cockroach (10%); prevalences of positive tests to *D. farinae*, any pollen or cat fur were 3–6%. Of the children, $< 1\%$ tested positive to any of the remaining allergens. Symptoms of allergic diseases were far less common than atopy. Only 10 (1%) children were both atopic and wheezy over the past year, and just 15 (2%) had seasonal rhinitis and a positive skin-prick test result for one of the three pollens.

None of these outcomes were obviously related to habitation in a farming home. When separate allergens were examined, the prevalence of cat fur sensitisation was almost three times higher among nonfarming children (9 versus 4 and 3% for full- and part-time farming children, respectively; $p_{\text{trend}} = 0.06$). Only children from full-time farming families were sensitised to *Cladosporium* (2%). Furthermore, neither atopy nor current wheeze was associated with the frequency of consumption of home-produced milk, boiled or otherwise, during any stage of the child's upbringing (data not shown).

Children with regular animal contact, at any stage of life, were equally likely to be atopic or have current wheeze than children with less frequent or no contact (table 2). Conversely, children who currently lived in homes where sheep or goats

TABLE 1 Demography, farm animal exposures currently and in infancy, and allergic outcomes by current parental farming

	Total	Current farming			p-value
		Full-time	Part-time	None	
Subjects	797	346	336	115	
Male	382 (48)	168 (49)	161 (48)	53 (46)	0.9
Age yrs	12 (9–14)	12 (10–14)	11 (9–14)	12 (9–14)	0.57
Age at child's birth yrs					
Mother	24 (21–29)	24 (21–29)	24 (21–28)	24 (21–28)	0.07 [†]
Father	32 (28–36)	34 (28–38)	32 (28–35)	31 (27–34)	<0.005 [†]
Education yrs					
Mother	9 (6–12)	8 (6–12)	9 (6–12)	12 (7–12)	<0.005 [†]
Father	6 (6–10)	6 (6–9)	8 (6–12)	9 (6–12)	<0.005 [†]
Asthma					
Mother	32 (4)	13 (4)	13 (4)	6 (5)	0.79
Father	22 (3)	11 (3)	10 (3)	1 (1)	0.40
≥ 1 sibling	53 (7)	28 (8)	23 (7)	2 (2)	0.03 [†]
Children in family	3 (2–4)	3 (2–4)	3 (2–4)	2 (1–3)	<0.0005
Older siblings					
0	332 (42)	132 (38)	141 (42)	59 (51)	
1	243 (31)	99 (29)	109 (32)	35 (30)	
2	118 (15)	57 (17)	45 (13)	16 (14)	
≥ 3	104 (13)	58 (17)	41 (12)	5 (4)	0.013
Father farmer[#] at child's birth	433 (55)	324 (95)	100 (30)	9 (8)	<0.0005
Current goat/sheep contact					
Almost daily	122 (16)	64 (19)	52 (16)	6 (5)	
Once/twice weekly	264 (34)	130 (38)	117 (35)	17 (15)	
Almost never	401 (51)	149 (43)	162 (49)	90 (80)	<0.0005
Goats/sheep location					
Courtyard	87 (11)	37 (11)	45 (14)	5 (4)	
Away from home	453 (58)	257 (75)	179 (54)	17 (15)	
Not kept	245 (31)	49 (14)	106 (32)	90 (80)	<0.0005
Goat/sheep contact in year 1					
Almost daily	37 (5)	22 (6)	13 (4)	2 (2)	
Once/twice weekly	101 (13)	48 (14)	46 (14)	7 (6)	
Almost never	653 (82)	273 (80)	275 (82)	105 (92)	0.027
Goats/sheep location in year 1					
Courtyard	76 (10)	42 (12)	31 (9)	3 (3)	
Away from home	415 (53)	245 (72)	151 (45)	19 (17)	
Not kept	298 (38)	55 (16)	152 (46)	91 (80)	<0.0005
Atopy (any)	182 (24)	80 (24)	76 (24)	26 (24)	0.99
Standard atopy	144 (19)	62 (18)	59 (18)	23 (21)	0.62
Ever wheeze	132 (17)	53 (16)	67 (20)	12 (11)	0.72
Current wheeze	35 (4)	18 (5)	13 (4)	4 (4)	0.46
Atopic current wheeze	10 (1)	5 (2)	5 (2)	0	0.36
Seasonal rhinitis	43 (6)	20 (6)	19 (6)	4 (4)	0.46
Seasonal rhinitis and pollen SPT+	15 (2)	4 (1)	7 (2)	4 (4)	0.11

Data are presented as n, n (%) or median (interquartile range). SPT+: skin-prick test positive. #: primary occupation; †: trend.

were kept nearby were less likely to be atopic ($p=0.01$), although they had an equal prevalence of current wheeze. Children who lived in a home where goats or sheep were kept in the courtyard during either of the two earlier periods of life were also less often atopic, although these associations could easily have arisen by chance.

Birth order

Of the children, 42% were the first-born (table 3). They were older, albeit not greatly so, than other children but no more likely to be male. Unsurprisingly, mothers and fathers of first-born children were younger at the time of their child's birth. Mothers with three or more children had received significantly

TABLE 2 Prevalence of atopy and current wheezing by animal exposure during three periods of life

	Infancy		Age 5 yrs		Current year	
	Atopy	Current wheeze	Atopy	Current wheeze	Atopy	Current wheeze
Animal contact						
Sheep/goats						
Daily	12 (33)	3 (8)	23 (27)	7 (8)	23 (24)	5 (4)
Weekly	20 (20)	3 (3)	60 (22)	12 (4)	58 (23)	10 (4)
Never	147 (23)	29 (4)	95 (23)	16 (4)	92 (24)	19 (5)
ptrend	0.49	0.65	0.65	0.10	0.83	0.65
Chickens						
Daily	9 (24)	2 (5)	25 (25)	8 (8)	26 (21)	5 (4)
Weekly	20 (23)	2 (2)	52 (21)	13 (5)	62 (23)	13 (5)
Never	150 (23)	31 (5)	103 (25)	14 (3)	90 (25)	16 (4)
ptrend	0.99	0.63	0.68	0.04	0.42	0.93
Rabbits						
Daily	5 (33)	1 (7)	13 (24)	3 (5)	18 (23)	3 (4)
Weekly	11 (19)	2 (3)	27 (18)	12 (8)	41 (21)	11 (6)
Never	163 (24)	31 (4)	139 (25)	20 (3)	118 (24)	20 (4)
ptrend	0.93	0.95	0.26	0.07	0.60	0.65
Animal location						
Sheep/goats						
Courtyard	13 (17)	5 (7)	16 (18)	4 (5)	12 (14)	5 (6)
Away from home	95 (24)	11 (3)	102 (24)	11 (3)	100 (23)	14 (3)
Not kept	70 (25)	19 (6)	62 (25)	19 (7)	66 (28)	15 (6)
ptrend	0.24	0.26	0.25	0.04	0.01	0.38
Chickens						
Courtyard	28 (22)	8 (6)	32 (23)	9 (7)	31 (22)	12 (8)
Away from home	82 (23)	13 (4)	88 (23)	16 (4)	91 (23)	12 (3)
Not kept	69 (24)	14 (5)	60 (25)	10 (4)	54 (25)	9 (4)
ptrend	0.53	0.78	0.68	0.31	0.43	0.09
Rabbits						
Courtyard	16 (20)	5 (6)	18 (18)	7 (7)	16 (16)	10 (10)
Away from home	70 (25)	11 (4)	68 (24)	11 (4)	72 (24)	12 (4)
Not kept	93 (23)	19 (5)	93 (25)	17 (4)	90 (25)	12 (3)
ptrend	0.89	0.83	0.25	0.45	0.09	0.01

Data are presented as n (%), unless otherwise indicated.

fewer years of education ($p_{\text{trend}}=0.02$). Reported parental asthma and allergies showed no association with birth order.

Atopy was more prevalent ($p_{\text{trend}}=0.01$) amongst the first-born children, but there were no differences at higher birth orders. Similar results were observed for standard atopy ($p_{\text{trend}}=0.02$). Of the remaining outcomes, only seasonal rhinitis ($p_{\text{trend}}=0.07$) and seasonal rhinitis accompanied by a positive skin-prick test result for pollen were associated with birth order ($p_{\text{trend}}=0.01$).

Logistic regression analysis of the birth order association indicated three independent determinants of atopy: male sex (odds ratio (OR) 2.3, 95% confidence interval (CI) 1.6–3.2; $p<0.0005$), age (OR 1.06, 95% CI 1.0–1.13·yr⁻¹; $p=0.07$) and first-born birth order (OR 1.68, 95% CI 1.2–2.4; $p=0.003$).

DISCUSSION

Childhood atopy, as measured by response to skin-prick testing, is not uncommon in this rural Cretan community.

Symptoms consistent with associated allergic disease, conversely, are rarely reported. Despite clear differences in their contact with farm animals at all ages, no consistent differences in the rates of atopy and allergic disease were found between those children whose parents were or were not farmers. Children who live in houses where goats or sheep are kept adjacent to the home were significantly less often atopic (but not wheezy); given the large number of statistical tests carried out, this finding may have occurred by chance. Atopy was more common among first-born children, an association independent of the other variables measured.

Several explanations were considered for the apparent lack of a protective effect of a farm upbringing in this population. First is the possibility that a rural childhood in Crete is such that every child receives sufficient exposure to the protective factor(s), and that, in this setting, a categorisation by parental farming status is insufficiently discriminatory. Table 4 summarises seven earlier farming studies in which childhood

TABLE 3 Demographics and outcomes by number of older siblings

	Total	Number of older siblings				p-value
		0	1	2	≥ 3	
Subjects	797	332	243	118	104	
Variable						
Male	382	168 (51)	115 (47)	47 (40)	52 (50)	0.23
Age yrs	12 (9–14)	12 (10–14)	11 (9–13)	12 (10–14)	11 (9–14)	0.05 [#]
Age at child's birth yrs						
Mother	24 (21–29)	22 (20–27)	24 (21–28)	26 (22–30)	28 (25–33)	<0.005 [#]
Father	32 (28–36)	30 (26–35)	32 (28–35)	33 (29–38)	37 (34–41)	<0.005 [#]
Education yrs						
Mother	9 (6–12)	9 (6–12)	9 (6–12)	9 (6–12)	6 (6–12)	0.02
Father	6 (6–10)	6 (6–10)	7 (6–12)	7 (6–11)	6 (6–9)	0.11
Asthma						
Mother	32	13 (4)	7 (3)	7 (6)	5 (5)	0.48 [#]
Father	22	8 (3)	6 (3)	3 (3)	5 (5)	0.29 [#]
Outcome						
Atopy (any)	182 (24)	94 (30)	46 (19)	22 (20)	20 (20)	0.01
Standard atopy	144 (19)	74 (23)	38 (16)	16 (14)	16 (16)	0.02
Ever wheeze	132 (17)	52 (16)	41 (17)	22 (19)	17 (16)	0.72
Current wheeze	35 (4)	11 (3)	16 (6)	4 (3)	4 (4)	0.85
Atopic current wheeze	10 (1)	4 (1)	4 (1)	1 (1)	1 (1)	0.76
Seasonal rhinitis	43 (6)	24 (8)	11 (5)	5 (5)	3 (3)	0.07
Seasonal rhinitis and pollen SPT+	15 (2)	13 (4)	1 (0.4)	0 (0)	1 (1)	0.01

Data are presented as n, n (%) or median (interquartile range). SPT+: skin-prick test positive. [#]: trend.

atopy was assessed through use of skin-prick tests along with the present findings, using comparable age groupings where possible. Among children aged 7–8 yrs, the prevalence of atopy in the children of Cretan farmers was far higher than that among farming children in Austria [7] but not dissimilar to estimates among farming children living in Sweden, Australia or Finland [8, 11, 12]. Conversely, the prevalence of atopy among children of nonfarmers in Crete is consistently lower than that among similar children living in any of the other communities studied. Responses to the present questionnaire suggest that children of farming parents in Crete received systematically greater exposure to all farm animals at every stage of life, but, unlike in other studies [9–12], no systematic evidence of any association between animal contact and the frequency of atopy could be found. Thus, the present authors think it improbable that there is a universal protective factor in this rural population.

A second explanation lies in the design of the present survey. Although primary education is essentially universal on Crete, an estimated 5% of rural children leave school at the age of 12 yrs. Many of these take work in farming, often as goatherds. No differences were found between farm and nonfarm children aged <12 yrs, but it is conceivable that there is a small population of older children, missed through the present method of recruitment, who have both an intense farm exposure and a low prevalence of atopy.

A third, and perhaps most plausible, explanation is that farming of this type is indeed not protective. To date, all

reports of a low prevalence of allergic respiratory disease in farm children have been in communities in which cows (primarily) are kept and, for part of the year at least, housed in barns close to the family home. In these communities, the consumption of home-produced milk, often unpasteurised, is common. On Crete, in contrast, no cows are farmed and animals are kept outdoors throughout almost the entire year; moreover, goat's milk is universally boiled before it is drunk, being otherwise considered unpalatable. Thus, a childhood farm exposure there is probably different both qualitatively and quantitatively. If this is the case, then it may provide important clues as to the specificity of the protective farm effect observed elsewhere. Following the ecological observation that a protection against atopy in Australian children of farmers is confined to those living in a region in which livestock are commonly kept, DOWNS *et al.* [11] suggested that regional differences (perhaps in climate or soil type) may be relevant, or that nonanimal (in that case, cows or sheep) farms do not confer protection.

Although a high prevalence of atopy was found, the present findings suggest that current symptomatic allergic disease, atopic asthma or hay fever, is uncommon in this community, although the frequency of "ever wheeze" was high. Since the present assessment of clinical disease was based on parental responses to a self-completed questionnaire, some caution should be exercised in the interpretation of these observations. There are, with little doubt, important cultural and linguistic influences that determine symptom reporting and it may be that these are, at least in part, responsible for the apparently

TABLE 4 Studies of childhood atopy, as determined by skin-prick testing (SPT), in farming/nonfarming populations

First author [Ref.]	Age yrs	SPT allergens n	Atopy			Current wheeze			Country
			FT farming	PT farming	Nonfarming	FT farming	PT farming	Nonfarming	
HORAK [7]	7–8	7	6	11	26				Austria
KLINTBERG [8]	7–8	15	31		33	8		13	Sweden
RIEDLER [9]	8–10	7	19		33	5		8	Austria
VON EHRENSTEIN [10]	5–7					6	5	8	Germany
DOWNS [11]	7–12	8	30		49	20		28	Australia
REMES [12]	6–13	6	28		40				Finland
ERNST [13]	12–19	24	41		53	17		25	Canada
Present survey	7–8	10	24	18	15	9	8	7	Crete, Greece
Present survey	8–10	10	23	17	17	7	4	7	Crete, Greece
Present survey	7–12	10	23	20	24	4	4	5	Crete, Greece
Present survey	12–18	10	25	27	25	5	4	0	Crete, Greece

Data are presented as %, unless otherwise indicated. FT: full-time; PT: part-time.

low prevalence of disease in Crete. The English word wheeze, for example, has only an approximate equivalent in Greek. However, a similar dissociation between atopy and allergic disease has been observed elsewhere in South-East Europe [14] and further afield [15]; it may represent a transitional stage between populations with low frequencies of atopy and disease and those with high frequencies of both, such as in North-West Europe. In turn, these may reflect gradations in important causative or protective environmental exposures. The present authors suggest that the high frequency of “ever wheeze” reflects the probable high incidence of early respiratory infection, a pattern common among rural communities in many parts of the world.

Children in the present population who were first-born showed significantly increased rates of atopy and seasonal rhinitis, an association that was independent of the other factors examined. No differences were observed between children of lower birth orders. Similar observations have often been made previously, but, for the most part, in communities with high overall frequencies of childhood allergic disease. If it is argued that the lack of a farming effect in rural Crete is due to every child receiving sufficient exposure to a putative protective and probably microbial factor, then an additional explanation is required for the observed birth order effect. There is now increasing evidence that it may be determined before birth and perhaps reflect pregnancy-related changes in maternal immunity [16–18].

In several but not all respects, the observations reported here confirm those made in an earlier study [5], in which parental farming did not explain apparently lower rates of atopy among children living in rural Crete than those living in the capital city. One important difference is that the prevalence of rural atopy in the present study is approximately twice that measured 3 yrs previously in a different, but not distant, part of the island. The rate reported here was unvarying over four separate districts, which suggests that it is a valid estimate for the rest of the island. It is possible that the original study area had a peculiarly low prevalence of atopy, in which case further

study there would be valuable. Alternatively, there has been a sharp increase in the frequency of atopy among children in rural Crete. Although the interval for this seems implausibly short, a similar increase over a similar period was observed among children living in Leipzig, Germany [19]. There, the rise was attributed tentatively to (unidentified) changes consequent on the reunification of Germany; no such major events have been apparent in Crete.

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