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Atopy risk factors at birth and in adulthood

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Abstract

Objective: To study the association between atopy and variables such as weight, length, and socioeconomic level at birth and in young adulthood.

Methods: A total of 2,063 subjects were investigated in a prospective birth cohort study of individuals born in Ribeirão Preto, Brazil, in 1978/1979, and examined at the age of 23-25 years. Skin prick tests (SPT) for eight common allergens in Brazil were performed. Subjects with a wheal reaction ≥ 3 mm to one or more of the eight allergens tested were considered to be atopic. We used the log-binomial model (generalized linear model) in order to assess the association between atopy and birth or adult variables.

Results: The prevalence of positive SPT was 47.6%. Male gender was associated with an increased risk of atopy (relative risk [RR] = 1.18; 95% confidence interval [95%CI] 1.07-1.30). Low level of schooling was a protective factor against atopy, with a RR = 0.74; 95%CI 0.62-0.89. Living with a smoker in childhood was also associated with lower risk of atopy (RR = 0.87; 95%CI 0.79-0.96). Birth weight, length and order, maternal age, and intrauterine growth restriction were not associated with positive SPT.

Conclusions: This study showed that male gender was associated with an increased risk of atopy. Low socioeconomic status, assessed by low level of schooling, was a protective factor against atopy. These data agree with the hygiene hypothesis.

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Introduction

There is increasing interest in the prenatal origin of health and disease as initially suggested by Barker.[1] According to this hypothesis, fetal growth and maturation characteristics (programming) may influence the likelihood of several diseases later in life. The implication of this new line of thinking for the study of allergic disease became immediately apparent, since preliminary evidence has already indicated an active involvement of the prenatal environment in the development of allergic states among children.[2] Because anthropometric parameters at birth reflect fetal growth and, to some extent, intrauterine and nutritional status, several studies have examined the relationship between these measures and atopic disease.[2-7]

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Genetic factors alone are insufficient to explain the substantial differences in the prevalence of allergic diseases between ethnically similar populations or their increased prevalence. Thus, the expression of allergic diseases may be strongly influenced by environmental factors. A long list of environmental and/or lifestyle factors associated with atopy includes indoor and outdoor pollution,[8] nutrition,[9] exposure to allergens,[10] socioeconomic status,[11] infections, family size,[12] and gestational and perinatal factors.[3,5,6,11,13] However, most of these factors have not demonstrated so far a clear and consistent association with atopic phenotypes in epidemiological studies.

Birth and adult characteristics and their associations with the risk of atopic sensitization in young adulthood were therefore investigated in a birth cohort, in order to test the hypothesis that birth factors may interfere with the prevalence of atopy.

Subjects and methods

Ribeirão Preto, a city located 250 miles (approximately 402 kilometers) from the sea, latitude 21° 11' south and longitude 47° 49' west, is one of the wealthiest cities in Brazil, with approximately 550,000 inhabitants.

The original cohort consisted of 6,827 live births from Ribeirão Preto, and covered 98% of the children born in that city between June 1, 1978 and May 31, 1979. Data collection was started at birth, and follow-up data on the health status of the subjects were collected at various ages. For the follow-up in early adulthood in 2002-2004, individuals whose mothers did not reside in Ribeirão Preto at the time of delivery (2,094) were excluded from the study. Thus, 6,973 liveborn subjects remained in the study, 6,827 singletons and 146 twins. Of the 6,827 singletons, 343 died up to 20 years of age. From the 6,484 alive at 20 years, 5,665 were identified for the follow-up. The follow-up sample was reconstituted from original birth charts containing addresses of the liveborn babies included in the study and from updated addresses retrieved from a number of databases, including the Unified Health System electronic database, lists of users of private health plans, school charts from the follow-up performed in 1987-1989, and military recruitment charts belonging to the original cohort. One out of three of the remaining 5,665 individuals living in the same geographical area were randomly selected for evaluation at age 23-25 years, based on a list of names of participants previously built and drawn from the databases described above. The selection was made based on the geo-economic characterization of the city, which is composed of four geographic regions defined by the income of the head of the family and classified as "poor," "middle-poor," middle-rich," and "rich."[14] Losses (705) occurred because of refusal to participate, imprisonment, death after 20 years of age, and failure to attend for interview. In case of refusal or impossibility to participate, contact was made with the next name on the list using the same sampling frame. The final sample resulted in 2,063 young adults (Table 1). The full description of the sample characteristics and methods has been published elsewhere.[15] The sample flow chart is shown in Figure 1.

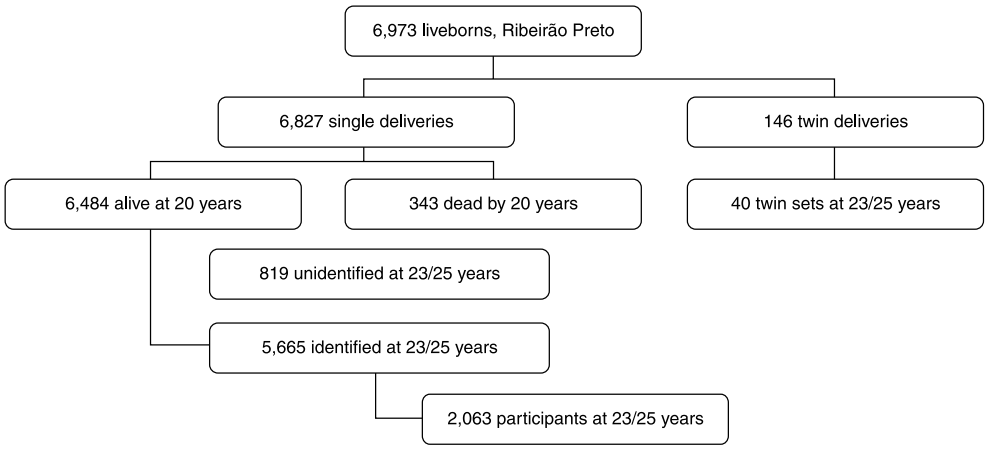
The objectives of the initial investigation were to analyze the behavior of some indicators of perinatal health and their associations with the social and biological variables of mothers and newborns, to measure the utilization of health services for prenatal, delivery and newborn care, and to relate these data to mortality during the first year of life.[17] Study participants were followed until 2002/2004 specifically to investigate the contribution of early life events to non-communicable diseases.[18]

Among the 2,063 subjects who attended the examinations, 1,915 performed skin prick test (SPT), which means that data on response to allergens were missing for 148 participants due to refusal or due to use of medication that could interfere with SPT, and five subjects were excluded due to reaction to the diluent. Therefore, the analyzed sample was 1,910.

Table 1 - Sociodemographic characteristics of young adults aged 23-25 years, Ribeirão Preto, Brazil, 2002/2004

Variables	n	%
Sex		
Male	995	48.2
Female	1,068	51.8
Skin color*		
White	1,367	66.3
Mulatto	666	32.3
Yellow	30	1.5
Years of schooling		
Less than 8	320	15.5
From 9 to 11	1,039	50.4
12 or more	704	34.1
Occupation		
Non-manual	434	21.0
Skilled manual	342	16.6
Semi-skilled manual	366	17.7
Unskilled manual	429	20.8
Outside the EAP	490	23.8
Unknow	2	0.1
Marital status†		
Cohabiting	661	32.0
Non-cohabiting	1,402	68.0
Children		
Have children	562	27.2
Have no children	1,501	72.8
Total	2,063	100

EAP = economically active population.
* According to racial measurements in the Brazilian census, which considers self-reported skin color.
† Cohabiting includes married and living with a companion but not married.



Source: Barbieri et al.[16].

Figure 1 - Sampling frame of the 1978/1979 birth cohort

The variables studied were birth length (categorized as < 47 cm, 47-48.9 cm, 49-50 cm, and ≥ 51 cm) and weight (categorized as < 2,500 g, 2,500-2,999 g, 3,000-3,999 g, and ≥ 4,000 g), intrauterine growth restriction (IUGR) (categorized as no or yes), gender (categorized as female or male), birth order (categorized as first, second, third, and ≥ fourth child), maternal age (categorized as < 20 years, 20-34 years, and ≥ 35 years), parental smoking during pre-school age (categorized as yes or no), and education (categorized as 1-8 years, 9-11 years, and ≥ 12 years of schooling). The analysis of home smoking was limited to pre-school age and to parents in order to select significant second-hand smoking exposure, since exposure to smoking at home should decrease during school years and possible exposure to other smoking relatives would not be very important. The study was approved by the Ethics Committee of the University Hospital, Medical School of Ribeirão Preto, University of São Paulo. All participants gave written informed consent to participate in the study.

The concept of IUGR was based on the birth weight ratio (BWR), that is, the ratio between the newborn's weight and the local population's sex-specific mean birth weight for each gestational age. Individuals were classified as non growth restricted (BWR ≥ 0.85), moderately growth restricted (BWR < 0.85 and ≥ 0.75), and severely growth restricted (BWR < 0.75).[16]

The SPT for allergy was performed using eight extracts of inhalant allergens common in Brazil, namely grass, dog, cat, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Penicillium notatum*, *Alternaria alternata*, and *Aspergillus fumigatus*, plus normal saline as a negative control. Skin reactions to each allergen tested were recorded after 15 min as the average of the maximum wheal diameter and the diameter perpendicular to the maximum. Subjects with a wheal reaction ≥ 3 mm to one or more of the eight allergens tested were considered to be atopic.[19] The tests and measurements were carried out at the University Hospital, Medical School of Ribeirão Preto, and stringent safety procedures were observed at all times.[20]

Statistical analysis

Exploratory analysis was first performed using frequency tables. The log-binomial model (generalized linear model) was used to determine the association between birth weight (or length) and atopy, as well as the relation among control variables. The link function of this model is the logarithm of the proportion under study, and the error distribution is binomial. The measure of the effect of this model is also relative risk (RR).[21]

For k covariables, the model is written as follows:

$\log(\pi) = \beta 0 + \beta 1\ x1 + \beta 2\ x2 + \ldots + \beta k\ xk,$

where π is the probability of success, i.e., the proportion of sick individuals in the group, xi are the covariables, and βi the parameters of the model. The RR estimate of a given variable is exp (βi).

Results

Among subjects who performed SPT (n = 1,910), gender distribution was 48.8% (933/1,910) males and 51.2% (977/1,910) females; 6.4% (123/1,910) of the subjects had low birth weight (< 2,500 g), 11.1% (211/1,901) had low birth length (< 47 cm), and 14.3% (273/1,910) had IUGR; 38.9% (736/1,894) were first born, and 12.1% (229/1,898) were children of mothers aged less than 20 years; 63.0% (1,187/1,884) lived with a smoker during childhood, and 15.3% (292/1,910) of the subjects had less than 8 years of study.

The overall prevalence of atopy (at least one positive SPT reaction) was 47.6% (Table 2). The most common sensitizations were to *D. pteronyssinus*, *D. farinae*, cat, and dog (43.5, 38.4, 8.6, and 3.8%, respectively).

Table 2 - Prevalence rates of atopic sensitization to inhalant allergens among 23-25 years old Brazilians

	n	%
Grass	42	2.2
Dog	73	3.8
Cat	164	8.6
Dermatophagoides farina	734	38.4
Dermatophagoides pteronyssinus	830	43.5
Penicillium notatum	35	1.8
Alternaria alternate	14	0.7
Aspergillus Fumigatus	12	0.6
Positive skin prick test	910	47.6

The prevalence of positive SPT was 51.1% among males subjects, 52.1% among the subjects with high birth weight (≥ 4,000 g), 50.3% among the subjects with high birth length (≥ 51 cm), 48.5% among those without IUGR, 49.4% among second and third borns, 49.2% among children of mothers aged between 20 and 34 years, 52.4% among those who did not have a smoker at home during childhood, and 52.4% among those with more than 12 years of study (Table 3).

The associations of risk factors with atopic sensitization in separate analysis and mutually adjusted analysis are shown in Table 3. At age 23-25 years, male subjects showed a significantly increased prevalence of atopic sensitization compared to female subjects (p = 0.0029). Level of schooling in adulthood was also influential. Low schooling level (compared with ≥ 12 years of study) and living with a smoker during pre-school age were inversely related to atopic sensitization (p < 0.0001 and 0.0022, respectively). Birth weight and length, IUGR, birth order, and maternal age did not have a significant association with atopy in separate analysis or mutually adjusted analysis.

Discussion

The present 23-25 year follow-up study showed that male gender was associated with an increased risk of atopic sensitization, as measured by SPT. In addition, low level of schooling was a protective factor against sensitization. Having a smoker at home in childhood was also associated with protection against atopy, which may be a case of inverse causality. Birth weight, length, birth order, maternal age, and IUGR were not associated with a positive SPT.

Perinatal factors, especially intrauterine growth,[22] have been proposed as "programming" influences on the developing immune system. Our findings do not suggest an important influence of any of these factors, although we lack the specific information required to evaluate the effect of neonatal head circumference or prolonged, exclusive breastfeeding in this cohort.

In studies on children, adolescents, and adults in the United Kingdom (UK)[5] and New Zealand,[7] birth weight was not associated with total serum IgE level or positive SPTs to common allergens. Neither was there an association between birth weight and allergic rhinitis or atopic dermatitis in 9-year-old Italian children[23] nor in a cohort of adolescents from New Zealand.[4] Leadbitter et al.[7] also found no association between these variables. However, a body of evidence showed that there is an inverse relationship between birth weight and SPT reactivity or atopic disease.[6] Low birth weight was associated with more allergic rhinitis and positive SPT in a UK study of 2-year-old children.[3]

Children who lived with smoking parents during pre-school age (first 7 years of life) presented a mild reduction of the prevalence of atopy (RR = 0.87). We explained this finding by inverse causality. Disease-related modification of exposure (inverse causality) concerns the interaction between cause and effect. The effect from breastfeeding is a classic example in which inverse causation might lead to erroneous conclusions. Debut of symptoms of eczema or wheezy disorder tends to prolong the duration of exclusive breastfeeding because of the general belief in its protective effect.[24] Such inverse causation could be misinterpreted as the duration of breastfeeding leading to eczema or wheezy disorder, when, in fact, the disorders lead to longer breastfeeding.[25] In the case of smoking and atopy, the early presence of atopy could have led to smoking cessation at home, with a reduction of the number of smoking parents in allergic children's homes, while this number was larger in healthy children's homes.

The hygiene hypothesis was proposed 2 decades ago and recently revisited. Strachan[12] postulates that the protection against the development of allergic disease provided by

Table 3 - Atopy prevalence and risk factors in separate analysis and mutually adjusted analysis of Brazilian young adults

Variable*	Prevalence (%)	Crude RR (95%CI)	Adjusted RR (95%CI)†
Birth weight (g)			
< 2,500	50/123 (40.7)	0.83 (0.67-1.03)	1.04 (0.76-1.43)
2,500-2,999	166/380 (43.7)	0.89 (0.78-1.01)	0.97 (0.83-1.15)
3,000-3,999	621/1,267 (49.0)	1.0	1.0
≥ 4,000	73/140 (52.1)	1.06 (0.90-1.26)	1.04 (0.87-1.24)
Birth length (cm)			
< 47	84/211 (39.8)	0.87 (0.72-1.06)	0.85 (0.68-1.05)
47-48.9	210/459 (45.8)	1.0	1.0
49-51	380/772 (49.2)	1.08 (0.95-1.22)	1.03 (0.90-1.18)
≥ 51	231/459 (50.3)	1.10 (0.96-1.26)	0.98 (0.83-1.14)
IUGR			
No	794/1,637 (48.5)	1.0	1.0
Yes	116/273 (42.5)	0.88 (0.76-1.01)	0.95 (0.78-1.16)
Gender			
Female	433/977 (44.3)	1.0	1.0
Male	477/933 (51.1)	1.15 (1.05-1.27)	1.18 (1.07-1.30)
Birth order			
First child	355/736 (48.2)	1.0	1.0
Second and third child	440/891 (49.4)	1.02 (0.93-1.13)	1.00 (0.91-1.11)
≥ forth child	106/267 (39.7)	0.82 (0.70-0.97)	0.84 (0.70-1.01)
Maternal age (years)			
< 20	95/229 (41.5)	0.84 (0.72-0.99)	0.88 (0.74-1.04)
20-34	743/1,509 (49.2)	0.83 (0.68-1.00)	0.86 (0.70-1.06)
≥ 35	65/160 (40.6)	1.0	1.0
Smoking‡			
Yes	535/1,187 (45.1)	0.86 (0.78-0.95)	0.87 (0.79-0.96)
No	365/697 (52.4)	1.0	1.0
Level of schooling (years)			
1-8	108/292 (37.0)	0.71 (0.60-0.83)	0.74 (0.62-0.89)
9-11	460/965 (47.7)	0.91 (0.82-1.01)	0.94 (0.85-1.04)
≥ 12	342/653 (52.4)	1.0	1.0

95%CI = 95% confidence interval; IUGR = intrauterine growth restriction; RR = relative risk.
* The total is different for some variables due to missing values.
† Adjusted for IUGR, birth weight and length.
‡ Parental smoking before the 7 years.

a large family and/or the presence of older siblings was mediated by infection acquired from contact with siblings. Over the last decade, it appeared that there is a rather consistent and statistically independent protective effect of larger family size, domestic crowding, and low socioeconomic status on hay fever and atopic sensitization.[11,12] However, these factors may also be regarded as indirect measures of some other factors which increase in the presence of low socioeconomic status and/or large family size. In the present study, low socioeconomic status was indicated by low level of schooling.

Our results were consistent with those of many other studies in demonstrating a higher prevalence of atopy among males than females.[6,7,11] Therefore, we corroborated the involvement of both principal determinants of atopy: environment (represented by schooling) and genetics (represented by male sex). If the hygiene hypothesis is the most reasonable explanation for our findings, its immunologic basis has been controversial. For many years, the hygiene hypothesis was recognized to result from the lack of shifting of allergen-specific responses from the TH2 to the TH1 phenotype (i.e., a missing immune deviation).

However, after the discovery of regulatory T cells, another proposed mechanism has been the decreased activity of these cells (reduced immune suppression).[26]

The pattern of allergic inheritance is complex. Recent results showed the effect of different gene polymorphisms on an individual's predisposition to allergic diseases. The most important linkages produced, to date, include those among the genes for IL-4, IL-13, HLA-DRB, TNF, LTA, FCER1B, IL-4RA, ADAM33, TCR alpha/delta, PHF11, GPRA, TIM, p40, CD14, DPP10, T-bet, GATA-3, and FOXP3 and allergic disorders. The two parallel research efforts, epidemiologic and genetic, are only recently starting to converge, producing fascinating results on the gene-environment interactions that might have in the development of atopy. The lesson learned through this research effort is that not only a small number but many separate risk factors act in concordance in the production of the allergic phenotype.[27]

Among the strengths of this study is the use of a standardized and objective test (prick test) and of objective measurements such as weight and height. The criteria used in this study are international, which allows us to compare our results with those from other countries.[28] Moreover, we looked at a random sample of 36% of the original cohort, a fairly large population, a fact that allowed us to exclude any case with methodological doubts. Although the differences are significant, the RRs are very close to 1, which may indicate a not very potent relationship. For multifactorial diseases, cross-sectional analysis is rather limited by variable selection, and only long-term observations of the start and end of exposure and disease can account for bias. However, the fact that our findings are consistent with other studies indicates they are valid. Despite the study represents only two life stages, birth and early adulthood, very few studies from the developing world have such data.

The onset of asthma in children may be caused by virus infection. Viral etiologies were identified in 90% of wheezing illnesses in children from birth to age 3 years. In this same study, approximately 90% of children who had infection with wheezing by rhinovirus up to age 3 were asthmatic at age 6 years.[29] The respiratory syncytial virus (RSV) infection is also associated with the subsequent development of wheezing in childhood, as shown in a pioneer study.[30] Several other studies have addressed the association of RSV infections in early life and the subsequent development of recurrent wheezing and asthma later in life. In our sample cohort, we have no data on virus etiology of previous respiratory infections. Specific virus tests and follow-up studies would be necessary to evaluate the role of virus infection in childhood. Thus, this major risk factor for asthma could not be assessed. However, our study was aimed at atopic sensitization instead of asthma or wheezing, and few data have associated childhood infection with atopy. According to Jartti et al.,[31] allergic sensitization is positively linked to rhinovirus, but not to other viruses.

In conclusion, this study showed that male gender was associated with an increased risk of atopic sensitization, and low socioeconomic status, assessed by level of schooling, was a protective factor against atopy in a prospective birth cohort study of subjects at age 23-25 years. These data agree with the hygiene hypothesis. Living with a smoker during pre-school age was negatively associated with sensitization, which may be a case of inverse causality.

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