

Bottle Feeding and Exposure to *Toxocara* as Risk Factors for Wheezing Illness among Under-five Amazonian Children: A Population-based Cross-sectional Study

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Summary

We investigated the prevalence and risk factors for wheezing and asthma in young Amazonian children. A population-based cross-sectional survey of 606 children aged 6–59 months was performed in two small towns in Acre State, Northwestern Brazil. Information on outcome variables (recent wheezing and medical diagnosis of asthma) and demographic, socioeconomic, environmental, maternal and nutritional variables was obtained by interviewing children's mothers or guardians. Infections with intestinal parasites and antibodies to the zoonotic nematode *Toxocara* were diagnosed using standard laboratory techniques. Multiple unconditional logistic regression models were used to describe associations between independent variables and outcomes. The prevalence of recent wheezing (one or more reported episodes in the past 12 months) was 42.6%, but only 19.8% of wheezing children were also reported to have a medical diagnosis of asthma (prevalence, 8.5%); 21.5% of the children examined had antibodies to *Toxocara*. Increased risk of asthma was independently associated with early introduction of bottle feeding, defined as <4 months of exclusive breastfeeding [adjusted odds ratio (aOR)=2.21, 95% confidence interval (95% CI), 1.07–4.59, $P=0.033$], and seropositivity to *Toxocara* (aOR=2.37, 95% CI 1.17–4.77, $P=0.016$), suggesting two potential targets for public health interventions.

Key words: asthma, wheezing, *Toxocara*, helminthes, breastfeeding, population-based studies, Amazonia

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Introduction

The recent rise in the prevalence of asthma has been attributed to an increased exposure to environmental allergens, air pollution and new foods, as well as to the reduced exposure to microbes due to more 'hygienic' living conditions [1]. Although asthma is less frequent in developing countries [2], high prevalence rates are common in tropical metropolitan areas [3–5]. The epidemiology of asthma in small towns and rural areas of the tropical world, where the infectious burden tends to be greater than in large cities, has attracted little attention.

Although most children wheeze in early childhood, only 20% of them will develop asthma until their sixth birthday [6]. Asthma symptoms usually appear in early childhood, but transient wheezing disorders may mimic asthma in this age group [7].

Nonatopic, transient wheeze differs in both pathogenesis and risk factors from asthma [8]; it may be triggered, for example, by respiratory tract infections and larval migration of helminths, which are common in the tropics. Risk factors for transient wheeze in young children, such as exposure to siblings at home and attendance at day care, may protect them from asthma in later childhood [9, 10].

Here, we report the results of a population-based survey of early childhood asthma and wheezing in two Amazonian towns in Brazil. Early introduction of bottle-feeding and exposure to the zoonotic helminth *Toxocara*, both of them currently under intense investigation and debate as risk factors for asthma, were found to be significantly associated with wheezing illnesses in this population.

Subjects and Methods

Study design and methodology

A cross-sectional survey was carried out in the urban areas of Acrelândia and Assis Brasil, Acre State, northwest Brazil. Acrelândia (urban population, 3700) is a frontier town inhabited by migrants from southeast and south Brazil engaged in commercial agriculture and cattle raising. Assis Brasil (urban population, 2300) is a traditional town mostly inhabited by families formerly involved in rubber and Brazil nut collection; cattle raising and wood extraction are currently the main sources of income. Child health indicators in both towns are substantially below the country average; infant mortality rates are 70.7/1000 in Acrelândia and 67.4/1000 in Assis Brasil, compared with 27.7/1000 in Brazil (unpublished data, Ministry of Health of Brazil).

The field survey is described in detail elsewhere [11]. The census performed in December 2002 by the local teams of the Family Health Program of the Ministry of Health of Brazil identified 724 under-five children in the urban areas of these towns. All households with under-five children in Acrelândia ($n=334$) and Assis Brasil ($n=157$) were visited by trained field workers in January 2003, when mothers or guardians were invited to participate in this study. The Ethical Review Board of the School of Public Health, University of São Paulo, approved the study protocol; all mothers or guardians gave written informed consent.

A questionnaire was administered to the mothers or guardians of 720 (99.4%) under-five children who lived in the 491 dwellings visited. Data on birth weight, breastfeeding practices, housing quality, household assets, number of persons per bedroom, maternal smoking, maternal age (at the time of the delivery) and paternal education were recorded. Exclusive breastfeeding was defined according to the World Health Organization criteria [12]. Housing quality was defined according to the

material (bricks, wood or construction scraps) used to build the dwellings. Recent wheezing was defined as one or more episodes of wheeze in the past 12 months; this information was obtained as standardized for the International Study on Asthma and Allergies in Children (ISAAC) and validated in Brazil [13]. Information on previous medical diagnosis of asthma was also obtained from the mothers or guardians, but no attempt was made to investigate familial history of asthma or atopy. Each mother or guardian was given a plastic container for each of their under-five children and asked to provide, at a scheduled visit to the local Family Health clinic, a stool sample from each child in this age group in her or his dwelling. Each container was identified with the name of the child enrolled in the study.

Next, 677 children (93.5% of the original sample) were examined by a field physician and had their clinical history taken. Analyses were restricted to the 606 children who were aged between 6 and 59 months, since younger children often failed to provide stool and/or blood samples. Of them, 497 children provided stool samples, which were examined for intestinal parasites, and 483 provided venous blood samples, which were used to measure antibodies to *Toxocara*. No significant differences were found between demographic and socioeconomic parameters of children who provided a stool or blood sample and those of the children who did not provide such samples.

Stool samples were examined in field laboratories in Acrelândia and Assis Brasil as described [11]. Logistic limitations prevented the collection of more than one stool sample from each subject, but prevalence estimates derived from the examination of a single sample have been shown to be accurate for most geohelminths [14]. Since variable volumes of faeces were mixed with formalin for preservation, no attempt was made to perform egg counts. Infected children were given free treatment [15].

IgG antibodies to *T. canis* excreted-secreted larval antigens [16] were measured by ELISA as described [17]; serum samples were diluted at 1:320. To remove non-specific antibodies, test samples were incubated with an extract of adult *Ascaris suum* prior to serology [17]. Test samples were considered positive when they yielded absorbance values greater than the mean plus three SD of the absorbance values obtained by testing 96 samples from apparently healthy controls [17].

Statistical analysis

The ownership of 14 household assets (television set, stereo set, videotape player/recorder, gas stove, refrigerator, radio, blender, bicycle, electric iron, motor vehicle, sofa set, washing machine, telephone and parabolic antenna) was used to derive a wealth

index [11, 18]. Principal component analysis was used to define the household asset weights; the first principal component explained 32.7% of the variability and gave greatest weight to ownership of a blender, a washing machine and a refrigerator. After standardization of these weighed asset variables [18], the highest scores were given to the ownership of a videotape player/recorder (2.865), a motor vehicle (2.835) and a telephone (1.350). Lowest scores were given to households without a gas stove (−4.141), a refrigerator (−1.876) and a television (−1.833). The asset scores were summed to a wealth index for each household, which was divided into quartiles for further analysis [11].

Prevalence data are presented as proportions, and compared with χ^2 tests or χ^2 tests for linear trend, as appropriate; unadjusted odd ratios (OR) were also calculated. Multiple unconditional logistic regression models were used to describe associations between potential risk factors (independent variables) and two outcomes: (i) recent wheezing and (ii) recent wheezing in children with a medical diagnosis of asthma. Variables associated with P -values <0.20 in unadjusted analysis were maintained in the logistic regression models. The SPSS software package (version 13.0, SPSS Inc., Chicago, IL, USA) was used in all analyses.

Results

The prevalence of recent wheezing was 42.6%, but a previous diagnosis of asthma was reported for 8.5% of the children. No significant difference was found in the prevalence of recent wheezing and asthma among boys and girls. Children from Acrelândia and Assis Brasil had similar prevalence rates of reported recent wheezing (42.9 and 41.7%, respectively) and asthma (8.6 and 8.1%, respectively); data for both towns were combined in subsequent analyses. The proportion of recently wheezing children who were reported to have a medical diagnosis of asthma varied across age groups (8.8 and 31.5% in the youngest and oldest groups, respectively; average, 19.8%).

Current maternal smoking was not associated with increased risk of either wheezing or asthma, but the presence of other smokers in the household was not investigated. Because only eight mothers reported to have smoked during the pregnancy, the impact of prenatal tobacco exposure could not be properly assessed. Crowding (>5 persons per bedroom) was associated with an increased risk of asthma, but without clear dose–response relationship (Table 1). Early introduction of bottle-feeding (<120 days of exclusive breastfeeding), reported for 61.0% of the children, was associated with an increased risk for both wheezing and asthma (Table 1).

Geohelminths infected 4.8% of the children examined; the predominant species were *Ascaris lumbricoides* and *Trichuris trichiura* [11]. Although wheezing and asthma were more frequent among children with geohelminth infection, these associations did not reach statistical significance (Table 1). In contrast, seropositivity to *Toxocara* was frequent (21.5% of the children examined), emerging as a risk factor for asthma (Table 1).

Multiple logistic regression analysis showed early bottle-feeding to be independently associated with increased risk of recent wheezing [adjusted OR (aOR)=1.78, 95% confidence interval (95% CI), 1.20–2.63, $P=0.004$], while both early bottle-feeding (aOR=2.21, 95% CI, 1.07–4.59, $P=0.033$) and exposure to *Toxocara* (aOR=2.37, 95% CI, 1.17–4.77, $P=0.016$) were independently associated with increased risk of asthma. Age and the number of persons per bedroom were entered in logistic models as either continuous or categorical variables (categories as in Table 1); in neither case a significant association with asthma was found in adjusted analysis.

Discussion

This is the first population-based survey of asthma and wheezing in early childhood in Amazonia, and one of the few surveys of asthma in this age group to be conducted in small tropical towns. Parent-reported medical diagnosis of asthma was slightly less prevalent in this study (8.5%) than in under-five children living in São Paulo (11.6%) [5], the largest metropolitan area of Brazil, but rarer than in urban pre-school children in southern Brazil (18.4%) [19]. Recent wheeze reported by the mothers and guardians was unusually prevalent (42.6%), but <20% of these children had a previous diagnosis of asthma made by a physician. Similar findings were reported for 12–24-month old Canadian children: only 26% of those with recent wheeze had a medical diagnosis of asthma [20]. Transient wheeze in our population is particularly prevalent during the dry season (May–October), when both towns are involved by a dense smoke produced by traditional slash-and-burn agricultural practices in surrounding rural areas. In addition, the prevalence of wheezing in our population may have been overestimated, because the term ‘wheezing’ is frequently misunderstood by parents; other lung sounds (snoring, stridor and stertors) may be misreported as wheezing [21].

Early introduction of bottle-feeding and exposure to *Toxocara* have been previously associated with wheezing conditions in children, but conflicting evidence is abundant. Exclusive breastfeeding may protect from atopy and lower respiratory infections with the respiratory syncytial virus, which are associated with asthma in early childhood [22–24], but recent data suggest that protecting young

TABLE 1
Prevalence of recent wheezing and a medical diagnosis of asthma, reported by the mother or guardian, among young children according to putative risk factors. Acre, Brazil, 2004

Putative risk factor	No. of subjects ^a	Wheezing in the past 12 months	OR (95% CI)	No. of subjects ^a	Wheezing in the past 12 months and asthma	OR (95% CI)
Demographic variables						
Age (months)						
6–12	70	48.6%	1.00	69	4.3%	1.00 ^c
13–24	126	47.6%	0.96 (0.51–1.80)	126	4.8%	1.10 (0.23–7.01)
25–36	141	44.0%	0.83 (0.45–1.54)	140	10.7%	2.64 (0.71–14.67)
37–48	141	38.3%	0.66 (0.35–1.22)	141	9.3%	2.05 (0.53–11.65)
>48	128	37.5%	0.64 (0.34–1.19)	127	11.8	2.95 (0.79–16.39)
Sex						
Boys	301	44.8%	1.20 (0.86–1.68)	300	10.3%	1.63 (0.88–3.05)
Girls	305	40.3%	1.00	303	6.6%	1.00
Social variables						
Wealth index (quartile) ^b						
1 (poorest)	146	41.8%	0.87 (0.52–1.41)	146	9.6%	1.63 (0.63–4.23)
2	150	41.3%	0.85 (0.52–1.38)	148	10.1%	1.73 (0.68–4.45)
3	156	41.0%	0.84 (0.52–1.36)	156	7.7%	1.28 (0.48–3.41)
4 (least poor)	148	44.7%	1.00	147	6.1%	1.00
Education of father (years of schooling)						
0	55	47.3%	1.25 (0.64–2.44)	55	14.5%	2.50 (0.82–7.73)
1–4	191	45.0%	1.14 (0.72–1.81)	189	5.8%	0.91 (0.34–2.46)
5–8	149	42.3%	1.02 (0.62–1.67)	148	10.1%	1.65 (0.65–4.26)
>8	141	41.8%	1.00	141	6.4%	1.00
Environmental variables						
House construction						
Brick walls	47	51.1%	1.00	48	8.3%	1.00
Wooden walls	472	41.9%	0.69 (0.36–1.31)	469	8.3%	1.00 (0.34–4.02)
Another material	77	41.6%	0.68 (0.31–1.51)	76	9.2%	1.12 (0.27–5.50)
Number of persons per bedroom						
1–2	286	44.7%	1.00	285	7.7%	1.00 ^d
3–5	264	38.6%	0.78 (0.55–1.10)	262	7.2%	0.93 (0.47–1.85)
>5	46	52.2%	1.35 (0.69–2.63)	46	19.6%	2.91 (1.14–7.28)
Maternal smoking						
Yes	41	48.8%	1.31 (0.66–2.58)	40	5.0%	0.55 (0.06–2.25)
No	565	42.1%	1.00	563	8.7%	1.00
Maternal and nutritional factors						
Maternal age at delivery (years)						
≤20	97	52.6%	1.70 (1.01–2.85) ^c	96	10.4%	1.53 (0.60–3.84)
>20	200	39.5%	1.00	198	7.1%	1.00
Birth weight (g)						
≤2500	51	39.2%	0.86 (0.46–1.60)	49	10.2%	1.25 (0.37–3.38)
>2500	555	42.9%	1.00	554	8.3%	1.00
Duration of exclusive breastfeeding (months)						
≤4	344	47.4%	1.58 (1.10–2.26) ^f	341	10.6%	2.05 (1.01–2.42) ^g
>4	220	36.4%	1.00	220	5.4%	1.00
Exposure to helminths						
Current infection with intestinal helminths						
Yes	24	45.8%	1.14 (0.46–2.77)	24	16.7%	2.42 (0.57–7.75)
No	473	42.7%	1.00	471	7.6%	1.00
Positive serology for <i>Toxocara</i>						
Yes	104	45.2%	1.23 (0.78–1.95)	103	18.4%	2.39 (1.17–4.85) ^h
No	379	40.1%	1.00	378	7.1%	1.00

Note. OR, odds ratio; 95% CI, 95% confidence interval.

^aNumbers of subjects assessed for each risk factor differ because of missing values for some variables.

^bWealth index derived from information on household assets; see 'Subjects and Methods' section.

^c $P=0.034$, χ^2 test for trend.

^d $P=0.018$, χ^2 test.

^e $P=0.045$, χ^2 test.

^f $P=0.012$, χ^2 test.

^g $P=0.050$, χ^2 test.

^h $P=0.014$, χ^2 test.

children against infections through exclusive breastfeeding might increase the risk of atopy in later childhood and adolescence [25, 26]. The public health implications of these findings remain unclear, since the benefits of breastfeeding for young children outweigh potential risks in later life [25].

Since the pioneering report by Tullis in 1970 [27], intestinal helminths have been reported to both trigger or inhibit asthma expression [28], but the biological basis for this dual effect is disputed [29]. Helminths elicit T_H2 -type T-cell responses, with high levels of IgE, eosinophilia, mastocytosis and allergic reactions to parasite and nonparasite antigens [29]. Moreover, some intestinal nematodes of humans, such as *Ascaris* and hookworm, may elicit asthma-like symptoms during the pulmonary phase of larval migration (Loeffler's syndrome). However, children heavily exposed to helminths may have their inflammatory responses suppressed by mast cell saturation, induction of blocking IgG₄ antibodies, tolerization to aeroallergens that are cross-reactive with parasite antigens, and T-cell hyporesponsiveness [30]. The animal nematodes *T. canis* and *T. cati*, whose larval stages infect humans and may cause eosinophilic pneumonitis, were suggested as possible etiologic agents of childhood asthma in the 1990s [31, 32], but contradictory findings have been reported since then [33, 34]. Infection with intestinal nematodes is relatively rare in our population [11], but exposure to *Toxocara* is very common (seropositivity rate, 21.5%) and may represent a major target for primary prevention of asthma in this and other similar tropical populations with frequent exposure to *Toxocara* [35].

Limitations of our study include its cross-sectional design, the lack of information on familial history of asthma (which may modify the protective effect of exclusive breastfeeding [36]) and exposure to smoking at home, as well as the uncertainties regarding the diagnosis of wheezing and asthma in young children [7, 21]. The high illiteracy rates among adults in Acrelândia and Assis Brasil may have affected the quality of parental reports; in addition, chest radiography, sweat chloride and allergy skin testing and pulmonary function tests are not locally available to confirm the clinical diagnosis of asthma and rule out other causes of wheeze [7]. Despite these limitations, this study identified potential risk factors that warrant further investigation and may represent targets for primary prevention of early childhood asthma in the tropics.

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