

ORIGINAL ARTICLE Epidemiology of Allergic Disease

Prevalence and risk factors of wheeze and eczema in 1-year-old children: the Butajira birth cohort, Ethiopia

Y. Belyhun¹, A. Amberbir^{2,3}, G. Medhin¹, B. Erko¹, C. Hanlon⁴, A. Venn³, J. Britton³ and G. Davey²¹Aklilu Lemma Institute of Pathobiology, ²School of Public Health, Addis Ababa University, Addis Ababa, Ethiopia, ³Division of Epidemiology & Public Health, University of Nottingham, Nottingham, UK and ⁴King's College London (Institute of Psychiatry), London, UK

Clinical & Experimental Allergy

Summary

Background The rising global prevalence of asthma and other allergic conditions has been linked to potential aetiological factors influencing the developing immune system.

Objective To investigate the prevalence and associated risk factors for wheeze and eczema in 1-year-old children in a birth cohort from Butajira, Ethiopia.

Methods In 2005/6, a population-based cohort of 1065 pregnant women was established. At 1 year of age, data on wheeze and eczema in the children were collected from the mother via an interview-administered questionnaire, along with numerous demographic and lifestyle factors. A stool sample was also obtained from the child for geohelminth analysis.

Results The prevalence of wheeze was 11.5% (103/899) and eczema 8.6% (77/899). Independent predictors of wheeze were maternal allergic history [adjusted OR (AOR) = 3.00, 95% CI 1.23–7.36], paternal allergic history (AOR = 2.59, 95% CI 1.08–6.25), increasing household size (P for trend = 0.023; AOR = 3.54, 95% CI 1.31–9.56 for 7+ vs. 1–3 individuals) and paracetamol use by the child (overall $P < 0.001$; AOR 11.04, 95% CI 4.30–28.31 for 4+ tablets in past month vs. never). Factors independently associated with eczema were maternal allergic history (AOR = 3.68, 95% CI 1.54–8.77), household size (overall $P = 0.035$; AOR = 0.45, 95% CI 0.23–0.87 for 4–6 individuals relative to 1–3) and place of sleeping (overall $P < 0.001$; AOR = 0.29, 95% CI 0.10–0.82 for floor vs. bed/platform).

Conclusion These findings support the hypothesis that eczema in early life in these children is a manifestation of allergy, while wheezing is probably due to infection as well as allergy.

Keywords allergy, Ethiopia, helminth, infants, paracetamol

Submitted 3 September 2009; revised 30 November 2009; accepted 11 January 2010

Correspondence:

Dr Gail Davey, School of Public Health, Addis Ababa University, PO Box 26905/1000 Addis Ababa, Ethiopia.

E-mail: gailinaddis@hotmail.com

Cite this as: Y. Belyhun, A. Amberbir, G. Medhin, B. Erko, C. Hanlon, A. Venn, J. Britton and G. Davey, *Clinical & Experimental Allergy*, 2010 (40) 619–626.

Introduction

There is continued interest in the hypothesis that increasing prevalence of asthma and other allergic manifestations in many countries might be due to differences in socio-economic standards, environmental exposures, improved hygiene, childhood infections, antibiotic use and immunization [1, 2]. Although allergy has increased in recent decades, lower levels of allergic disorders are reported in developing countries than developed countries [3, 4] but reasons for the differences between developed and underdeveloped countries have yet to be fully established [5].

Epidemiological studies have implicated a large number of factors as being associated with the risk of childhood asthma and allergic symptoms, some of which are well

established such as parental history of allergic disease [6], and others less established. The role of geohelminth infections, for example, has proven controversial [3, 4, 7, 8] although the evidence for hookworm infection in particular is more consistent and appears to be associated with a reduced risk of asthma [9]. The available epidemiological evidence on geohelminth infection and allergy is derived predominantly from cross-sectional surveys of adults or school-age children, and studies among infants, the age at which first geohelminth infection usually occurs, are lacking. Also attracting recent interest has been the role of paracetamol in the aetiology of asthma and allergic disease, with increasing and consistent evidence from a range of independent studies of an adverse effect of paracetamol intake [10–13]. The possibility that paracetamol and asthma, however, are associated through reverse

causation, in turn arising from medical advice to avoid aspirin use in individuals with asthma, is difficult to exclude.

In view of these inconsistencies in the epidemiological evidence particularly in young infants, we report data from an Ethiopian birth cohort with the objective of assessing the prevalence of wheeze and eczema and associated risk factors in 1-year-old children.

Methods

Study population

The study site was the Butajira area, which is located in southern Ethiopia. The capital, Butajira town, lies at a distance of 130 km from the capital, Addis Ababa. The area is predominately rural and the participants live in villages and are agriculturists growing coffee, maize, *teff* (*Eragrostos tef*), pepper, the stimulant *khat* (*Catha edulis forskal*) and *enset* (false banana) [14].

Study design

The birth cohort is nested in the Butajira Rural Health Program, a Demographic Surveillance Site (DSS) established in 1987 [14]. The DSS population is currently around 60 000 with more than 13 000 women of reproductive age. The study was based on mother–child pairs enrolled in a Butajira birth cohort, from nine rural Peasant Associations and one administrative unit (*Kebele*) from Butajira town. Between July 2005 and February 2006, 1065 pregnant women were recruited to the birth cohort. Mother–child pairs were followed up from July 2006, at the time of the child's first birthday, where 932 singleton babies were available for study. The birth cohort has been described in detail elsewhere [15].

Data collection

The International Study of Asthma and Allergies in Children (ISAAC) questionnaire [5] was administered to each mother by an interviewer and questions were asked about wheeze ('Has your child ever had wheezing or whistling in their chest?'), asthma ('Has your child ever had asthma?') and eczema ('Has your child ever had an itchy skin rash which has affected the skin creases, eg, front of the elbow, behind the knees, the front of the ankles, around the neck, or around the eyes?'). Parental history of allergy was measured by using three questions on asthma ('In the last 12 months have you or your husband had asthma?'), rhinitis ('In the last 12 months have you or your husband had problems with sneezing or running nose without cold or flu, or problems with itchy watery eyes?') and eczema ('In the last 12 months have you or your husband had an itchy skin condition affecting the skin creases (front of the elbow, behind the knees, the

front of the ankles, around the neck, or around the eyes?')]. 'Allergic symptom' was defined as any one or more of the three reported symptoms.

Questions on various potential risk factors, including immunization and breastfeeding history, family history of asthma, number of siblings, insecticide use, domestic fuel use, number of individuals living in the household, paracetamol intake by the child since birth, child's sleeping arrangement and other socio-economic characteristics were included. Information on symptoms of respiratory tract infection (cough, fast breathing and fever) was collected at 2 months and 1 year of age. Birth weight was available in a subsample of children whose weight had been measured immediately after birth. Stool samples were taken from each child for parasitological examination at age 1. The samples were placed in labelled plastic tubes with 10% formalin and transported for analysis to the Aklilu Lemma Institute of Pathobiology, Addis Ababa University. Samples were analysed qualitatively using the formol–ether concentration method [16]. Field and laboratory work was conducted between July 2006 and June 2007.

Ethical approval

Approval for the study was granted by Addis Ababa University, through the Aklilu Lemma Institute of Pathobiology.

Statistical analysis

Questionnaire data were double-entered into EpiData version 3, and parasite data into an Excel file; after export the two databases along with other variables from pregnancy, birth and 2 months were merged. The data then were cleaned, coded and analysed using SPSS 12.0.1 (SPSS Inc., Chicago, IL, USA). We first computed the prevalence of the primary outcome variables *wheeze*, *asthma* and *eczema*. Crude odds ratios with 95% confidence intervals were first computed using logistic regression to determine the univariate associations between potential risk factors and the outcome variables, although the number of asthma cases proved too small for this outcome to be analysed. The independent risk factors for wheeze and eczema were then determined using multiple logistic regression analysis. Gender and place of residence (urban or rural) were treated as *a priori* confounders and included in the final models regardless of significance.

Study power

Our sample size of 933 children provided 80% power at the 5% significance level to detect an odds ratio of 1.70 and 1.85 between the outcomes wheeze and eczema, respectively, and a given risk factor assuming a ratio of exposed to unexposed individuals of 1 : 1.

Results

Demographic characteristics of the birth cohort

Of the 932 mother–child pairs studied, stool samples were either not provided or were not successfully analysed in 27 and for six of them outcome data were not available. A total of 899 (89.4%) children were therefore included in this analysis (Fig. 1). Just over half were males (50.5%) and the majority (87.0%) were from rural areas. The age range of mothers was 15–44 years, with almost half (46.8%) in the age group 25–34 years, and 70.3% had had no formal education.

Prevalence allergic symptoms

Asthma was only reported in 0.8% (7/899) of children and an asthma diagnosis confirmed by a doctor in only two

cases so no further analysis was carried out on this outcome. Eczema was reported in 8.6% (77/899) of children and wheeze was reported in 11.5% (103/899), most of these reporting 1–3 episodes over their first year of life (Table 1).

Table 2 shows that symptoms of respiratory infections (cough, fast breathing and fever) were commonly reported at age 2 months and 1 year, and that these symptoms were more prevalent in the infants with ever wheeze than those without.

Distribution of potential risk factors

The distributions of the potential confounders and risk factors under investigation are shown in Tables 3 and 4. Maternal and paternal history of allergy (wheeze, eczema or hay fever) was reported in 3.7% and 3.6% of the cases, respectively. Paracetamol had been used at some time in the child's first year of life in 38.9% and in the last month in 27.9% of infants. Geohelminth infection was detected in the stool of 3.9% of the children, with hookworm infection being the most prevalent (2.3%) followed by *Ascaris* (1.5%) (Table 4).

Predictors of wheeze in children

In the unadjusted analyses, maternal and paternal history of allergy, insecticide use, animals living in the household, number of individuals in the house and child's use of paracetamol were significantly associated with wheeze in children (Table 4). In multivariate analysis, significant positive associations were seen with maternal allergic history [adjusted OR (AOR) = 3.00, 95% CI 1.23–7.36, $P = 0.016$], paternal allergic history (AOR = 2.59, 95% CI 1.08–6.25, $P = 0.034$), increasing number of individuals in the household [AORs (95% CIs), 3.10 (1.18–8.11) for 4–6 individuals and 3.54 (1.31–9.56) for 7+ individuals, compared with 1–3 number of individuals; P for trend < 0.027], and child's use of paracetamol [AORs (95% CIs) 3.08 (1.60–5.91) for ever users but not in the past month, 3.85 (2.36–6.29) for 1–3 tablets in past month and 11.04

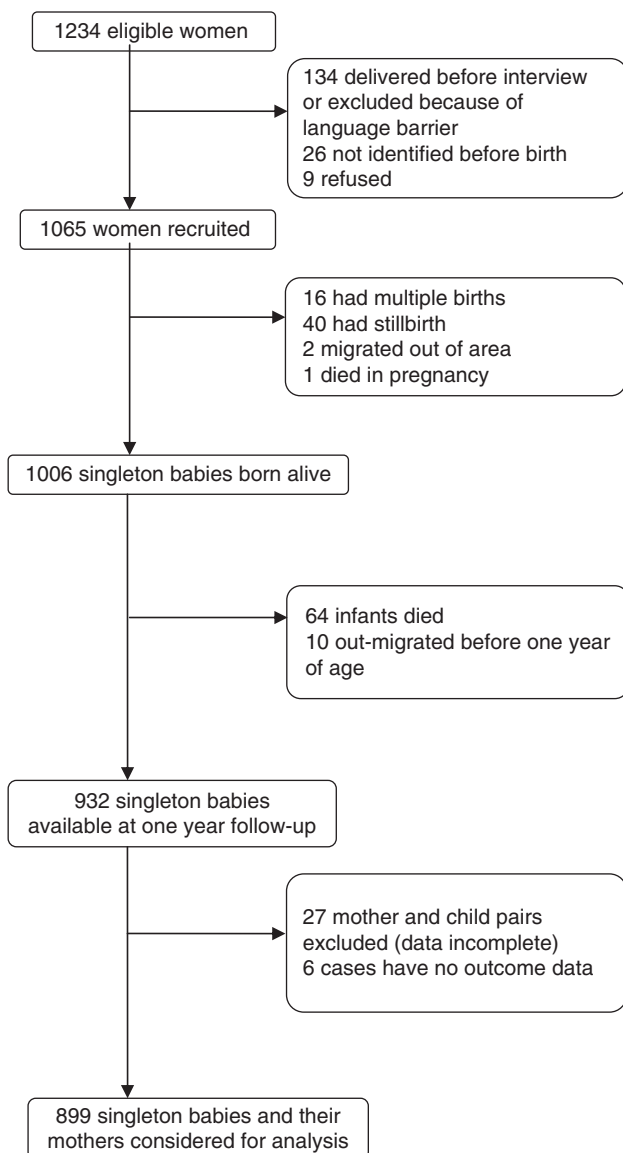


Fig. 1. Study cohort.

Table 1 Maternal reported allergic symptom in 1-year-old infants in the Butajira birth cohort, Ethiopia ($N = 899$)

Allergic symptoms	Number (%)
Ever had wheeze	103 (11.5)
If yes, number of episode ($n = 98^*$)	
1–3	70 (71.4)
4–12	25 (25.5)
≥ 13	3 (3.1)
Ever had eczema	77 (8.6)
Ever had asthma	7 (0.8)
If yes, confirmed by a doctor? ($n = 7$)	2 (28.6)

*Five mothers did not remember the number of episodes.

(4.30–28.31) for 4+ tablets in the past month, all compared with non-use; $P < 0.001$] (Table 5).

Predictors of eczema in children

Factors significantly associated with eczema in univariate analyses were maternal and paternal history of allergy, number of individuals in the household and child's sleeping

place. In multivariate analysis, all these remained independent factors except paternal history of allergy. Maternal allergic history was associated with an increased risk of eczema (AOR 3.68, 95% CI 1.54–8.77, $P = 0.003$) whereas a significant reduction in risk was observed with more number of individuals living in the house [AORs (95% CIs) 0.45 (0.23–0.87) for 4–6 individuals in the household and 0.75 (0.38–1.48) for 7+ individuals, compared with 1–3 number of individuals; overall $P = 0.035$] and with sleeping on the floor (AOR 0.29, 95% CI 0.10–0.82, compared with bed/platform; overall $P < 0.001$) (Table 5).

Table 2 Prevalence of symptoms of respiratory infections overall and by ever wheeze status in the Butajira birth cohort, Ethiopia

		Wheeze		
Symptoms of respiratory infections	<i>N</i> (%)	Yes <i>n</i> (%)	No <i>n</i> (%)	<i>P</i> -value
Respiratory infection-related symptoms at 2 months (<i>N</i> = 895)				
Cough	370 (41.3)	56 (54.4)	314 (39.7)	0.004
Fast breathing	228 (25.5)	37 (35.9)	191 (24.1)	0.01
Fever	319 (35.6)	57 (55.3)	262 (33.1)	<0.001
Respiratory infection-related symptoms at 1 year (<i>N</i> = 899)				
Cough	555 (61.7)	84 (81.6)	471 (59.2)	<0.001
Fast breathing	337 (37.5)	73 (70.9)	264 (33.2)	<0.001
Fever	704 (78.3)	96 (93.2)	608 (76.4)	<0.001

Discussion

This is the first of a series of follow-up studies of a unique birth cohort which aims to investigate prospectively the effects of potential aetiological exposures in early life on the risk of allergic disease in Ethiopian children. The study results at this first point of follow-up, namely 1 year of age, support the concept of an allergic march with characteristic risk factors for wheeze and eczema during infancy. We found that eczema was related to parental allergy and that the risk factors for this outcome broadly fit with the 'hygiene hypothesis' including the protective effect of sleeping on the

Table 3 The distribution of demographic factors and their associations with wheeze and eczema in 1-year-old infants in the Butajira birth cohort ($N = 899$)

Variable	Overall N (%)	Wheeze			Eczema		
		n (%)	Crude OR (95% CI)	P-value	n (%)	Crude OR (95% CI)	P-value
Maternal age				0.167			0.621
15–24	346 (38.5)	32 (9.3)	0.57 (0.31, 1.04)	0.058*	30 (8.7)	0.80 (0.41, 1.56)	0.687*
25–34	421 (46.8)	51 (12.1)	0.77 (0.44, 1.35)		33 (7.8)	0.71 (0.37, 1.38)	
35–44	132 (14.7)	20 (15.2)	1		14 (10.6)	1	
Child's gender							
Male	454 (50.5)	55 (12.1)	1.14 (0.76, 1.72)	0.532	39 (8.6)	1.01 (0.63, 1.61)	0.978
Female	445 (49.5)	48 (10.8)	1		38 (8.5)	1	
Place of residence							
Urban	117 (13.0)	10 (8.6)	0.69 (0.35, 1.37)	0.292	7 (6.0)	0.65 (0.29, 1.44)	0.228
Rural	782 (87.0)	93 (11.9)	1		77 (7.0)	1	
Maternal Education				0.558			0.732
No education	632 (70.3)	70 (11.1)	1.00 (0.59, 1.70)	0.828*	57 (9.0)	1.18 (0.64, 2.18)	0.519*
Read and write [†]	86 (9.6)	13 (15.1)	1.43 (0.68, 3.04)		6 (7.0)	0.89 (0.33, 2.41)	
Formal education	181 (20.1)	20 (11.1)	1		14 (7.7)	1	
Maternal occupation							
Housewife	755 (84.0)	86 (11.4)	1		70 (9.3)	1	
Any other jobs [‡]	144 (16.0)	17 (11.8)	1.04 (0.60, 1.81)	0.886	7 (4.9)	0.50 (0.23, 1.11)	0.089
House ownership							
Yes	813 (90.4)	97 (11.9)	1.81 (0.77, 4.25)	0.176	71 (8.7)	1.28 (0.54, 3.03)	0.581
No	86 (9.6)	6 (7.0)	1		6 (7.0)	1	
TV/radio ownership ($N = 898$)							
Yes	463 (51.6)	45 (9.7)	0.70 (0.46, 1.06)	0.091	43 (9.3)	1.21 (0.75, 1.93)	0.432
No	435 (48.4)	58 (13.3)	1		34 (7.8)	1	

*P-value for trend.

[†]Read and write but have no formal education.

[‡]Farm, trade and profession related and daily labourer.

Table 4 Distribution of potential risk factors and their association with wheeze and eczema in 1 year birth cohort, Butajira Ethiopia ($N = 899$)

Risk factor	Overall <i>N</i> (%)	Wheeze			Eczema		
		<i>n</i> (%)	Crude OR (95% CI)	<i>P</i> -value	<i>n</i> (%)	Crude OR (95% CI)	<i>P</i> -value
Exclusive breastfeeding at 2 months (<i>N</i> = 895*)							
Yes	753 (84.1)	89 (11.8)	1.23 (0.68, 2.22)	0.503	62 (8.2)	0.82 (0.45, 1.51)	0.524
No	142 (15.9)	14 (9.9)	1		14 (9.9)	1	
Vaccination at 2 months (<i>N</i> = 895*)							
Vaccinated	532 (59.4)	66 (12.4)	1.25 (0.81, 1.91)	0.309	44 (8.3)	0.93 (0.58, 1.50)	0.774
Not vaccinated	363 (40.6)	37 (10.2)	1		32 (8.8)	1	
Birth weight (<i>N</i> = 598*)							
Low	42 (7.0)	5 (11.9)	0.99 (0.37, 2.60)	0.978	2 (4.8)	0.55 (0.13, 2.37)	0.426
Normal	556 (93.0)	67 (12.1)	1		46 (8.3)	1	
Maternal history of allergic disease							
Yes	33 (3.7)	9 (27.3)	3.08 (1.39, 6.82)	0.006	8 (24.2)	3.70 (1.61, 8.50)	0.002
No	866 (96.3)	94 (10.9)	1		69 (8.0)	1	
Paternal history of allergic disease (<i>N</i> = 891*)							
Yes	32 (3.6)	9 (28.1)	3.19 (1.43, 7.09)	0.005	6 (18.8)	2.56 (1.02, 6.43)	0.045
No	859 (96.4)	94 (10.9)	1		71 (8.3)	1	
Insecticide use							
Yes	748 (83.2)	94 (12.6)	2.27 (1.12, 4.60)	0.023	66 (8.8)	1.23 (0.63, 2.39)	0.538
No	151 (16.8)	9 (6.0)	1		11 (7.3)	1	
Total number of people in house							
				0.045			0.055
1–3	115 (12.8)	5 (4.3)	1	0.029 [‡]	15 (13.0)	1	0.857 [‡]
4–6	506 (56.3)	61 (12.1)	3.02 (1.18, 7.68)		34 (6.7)	0.48 (0.25, 0.92)	
7+	278 (30.9)	37 (13.3)	3.38 (1.29, 8.83)		28 (10.1)	0.75 (0.38, 1.46)	
Older siblings							
				0.139			0.104
0	138 (15.4)	9 (6.5)	1	0.080 [‡]	17 (12.3)	1	0.687 [‡]
1–3	492 (54.7)	59 (12.0)	1.95 (0.94, 4.05)		34 (6.9)	0.53 (0.29, 0.98)	
4–10	269 (29.9)	35 (13.0)	2.14 (1.00, 4.60)		26 (9.7)	0.76 (0.40, 1.46)	
Child's sleeping place (<i>N</i> = 898*)							
				0.166			<0.001
Bed/Platform	68 (7.6)	5 (7.4)	1		6 (8.8)	1	
Floor	382 (42.5)	38 (9.9)	1.39 (0.53, 3.67)		15 (3.9)	0.42 (0.16, 1.13)	
Grass matting	448 (49.9)	60 (13.4)	1.95 (0.75, 5.04)		56 (12.5)	1.48 (0.61, 3.57)	
Cooking site							
Inside	727 (80.9)	83 (11.4)	0.98 (0.58, 1.65)	0.938	64 (8.8)	1.18 (0.64, 2.20)	0.600
Outside	172 (19.1)	20 (11.6)	1		13 (7.6)	1	
Indoor kerosene use							
Yes	98 (10.9)	8 (8.2)	0.66 (0.31, 1.40)	0.281	8 (8.2)	0.94 (0.44, 2.03)	0.880
No	801 (89.1)	95 (11.9)	1		69 (8.6)	1	
Type of roof							
Thatched	689 (76.6)	83 (12.0)	1.30 (0.78, 2.18)	0.316	65 (9.4)	1.72 (0.91, 3.25)	0.095
Corrugated iron sheet	210 (23.4)	20 (9.5)	1		12 (5.7)	1	
Type of toilet							
Toilet of any type [†]	558 (62.1)	68 (12.2)	1	0.380	53 (9.5)	1	0.203
Open field	341 (37.9)	35 (10.5)	0.82 (0.54, 1.27)		24 (7.0)	0.72 (0.44, 1.19)	
Household own water source							
Yes	311 (34.6)	36 (11.6)	1.02 (0.66, 1.57)	0.935	31 (10.0)	1.30 (0.81, 2.10)	0.275
No	588 (65.4)	67 (11.4)	1		46 (7.8)	1	
Animals living in the home (<i>N</i> = 898*)							
Yes	569 (63.4)	75 (13.2)	1.63 (1.03, 2.58)	0.036	51 (9.0)	1.15 (0.70, 1.88)	0.585
No	329 (36.6)	28 (8.5)	1		26 (7.9)	1	
Child's paracetamol use							
				<0.001			0.211
Never	549 (61.1)	33 (6.0)	1		43 (7.8)	1	
Yes but not in past month	99 (11.0)	16 (16.2)	3.01 (1.59, 5.72)		12 (12.1)	1.62 (0.82, 3.20)	
1–3 times in past month	229 (25.5)	45 (19.7)	3.82 (2.37, 6.18)		18 (7.9)	1.00 (0.57, 1.78)	
4+ times in past month	22 (2.4)	9 (40.9)	10.83 (4.32, 27.16)		4 (18.2)	2.61 (0.85, 8.07)	

continued

Table 4. continued

Risk factor	Overall <i>N</i> (%)	Wheeze			Eczema		
		<i>n</i> (%)	Crude OR (95% CI)	<i>P</i> -value	<i>n</i> (%)	Crude OR (95% CI)	<i>P</i> -value
Hook worm in stool							
Yes	21 (2.3)	4 (19.0)	1.85 (0.61, 5.61)	0.276	4 (19.0)	2.59 (0.85, 7.91)	0.094
No	878 (97.7)	99 (11.3)	1		73 (8.3)	1	
<i>Ascaris lumbricoides</i> in stool							
Yes	13 (1.5)	2 (15.4)	1.41 (0.31, 6.47)	0.656	2 (15.4)	1.97 (0.43, 9.04)	0.385
No	886 (98.6)	101 (11.4)	1		75 (8.5)	1	
Any geohelminth infection [§]							
Yes	35 (3.9)	5 (14.3)	1.30 (0.49, 3.44)	0.593	6 (17.1)	2.31 (0.93, 5.75)	0.072
No	864 (96.1)	98 (11.3)	1		71 (8.2)	1	

*There are missing cases for these exposures.

[†]Pit, improvised and flush type latrine.

[§]*Ascaris lumbricoides*, Hookworm and *Tricuris tricuris*.

[‡]*P*-value for trend.

floor and large household size. It is also now acknowledged that eczema is not simply a transient disease of infancy but also a strong marker of current and future allergy [17].

In contrast, it appears that wheezing in these infants was probably predominantly due to infection, as we observed that symptoms of respiratory infection were more common in those with wheezing, and risk factors including the strong positive dose-response effect of paracetamol and overcrowding best fit this hypothesis. While the observed association with parental allergy implies that some wheezing was allergic, the aetiological portion is likely to be small as the number of children with reported parental allergy was low. It is also established that most childhood wheezing arises in early childhood and that most of this wheezing is transient with good prognosis [18–20]. Further follow-up of the cohort will help to distinguish these different influences.

We have made use of a population-based birth cohort to make very early measurements of potential exposures and allergic outcomes. Approaching mothers at this early stage minimizes recall and reporting bias. However, our findings must be interpreted in the light of certain limitations. Primarily, temporality could not be established as data were collected cross sectionally. Wheeze and eczema were ascertained by maternal self-report, in which information bias is likely to be a problem. Moreover, the use of the ISAAC questionnaire constructed for 6–7 years old children may not work well in an infant population. The short-lived wheezing reported in this early age may represent a disease of different pathogenesis [18–20]. Atopic eczema identified using the ISAAC questionnaires may also represent misclassified infestations such as scabies. However, our previous validation work in Ethiopia provided evidence that the ISAAC questionnaire identified cases with little loss in positive predictive value compared with a clinical examination [21]. Quantitative geohelminth egg estimations to

measure the intensity of infections to look for dose-related effects were not performed.

This study suggests that the prevalence of wheeze and eczema in this young developing country population is low compared with children living in other developed countries like the United Kingdom, Australia and New Zealand [5]. However, our prevalence estimate of wheeze is four times higher than that seen in children of the same age in Jimma, Ethiopia [3], and our eczema prevalence twice that seen in children aged 1–5 years (mean age 3 years) using the ISAAC criteria also in Jimma, Ethiopia [21, 22]. Reasons for the differences may relate to environmental differences between the populations, or may reflect a temporal change in prevalence in Ethiopia as the Jimma studies were carried out 5–8 years ago.

In contrast with existing evidence that helminth infection and atopic diseases are inversely related [3, 4, 8, 9], we found no evidence that helminth infections were associated with a reduced risk of eczema or wheeze. The low prevalence of hookworm and other geohelminth infection observed is likely to limit the statistical power available to show an effect at this time point. Our findings may also be attributed to the evidence that this period of life is critical for the reversal of the Th1/Th2 balance. Studies have reported that the immune response of infants is polarized to a Th2 pattern maintained for a significant period during infancy [23].

A range of studies using the ISAAC questionnaire have reported various factors associated with allergy [3, 4, 7, 22, 24, 25]. Wheeze and eczema and parental allergic history were found to be strongly associated. Several other studies have reported that maternal allergic history (in particular asthma) predicts asthma and eczema in infancy [6, 26]. Sears [6] also showed that children with a positive family history required less exposure to develop sensitization than those with a negative family history. This suggests that hereditary

Table 5 Multivariate analysis: factors independently associated with wheeze and eczema

Outcome	Risk factor	Adjusted OR	95% CI	P-value
Wheeze (N = 899)	Maternal history of allergic disease	3.00	1.23, 7.36	0.016
	Paternal history of allergic disease	2.59	1.08, 6.25	0.034
	Child's paracetamol use			<0.001
	Never	1		
	Yes but not in past month	3.08	1.60, 5.91	
	1–3 times in past month	3.85	2.36, 6.29	
	4+ times in past month	11.04	4.30, 28.31	
	Number of people in the home			0.016
	1–3	1		$P_{\text{trend}} = 0.027$
	4–6	3.10	1.18, 8.11	
Eczema (N = 899)	7+	3.54	1.31, 9.56	
	Urban place of residence*	0.77	0.37, 1.57	0.467
	Male gender*	1.12	0.73, 1.72	0.608
	Maternal history of allergic disease	3.68	1.54, 8.77	0.003
	Number of people in the home			0.035
	1–3	1		$P_{\text{trend}} = 0.927$
	4–6	0.45	0.23, 0.87	
	7+	0.75	0.38, 1.48	
	Child's sleeping place			<0.001
	Bed/Platform	1		
	Floor	0.29	0.10, 0.82	
	Grass matting	1.05	0.41, 2.67	
	Urban place of residence*	0.46	0.19, 1.08	0.074
	Male gender*	1.01	0.63, 1.63	0.969

*Urban place of residence and gender were *a priori* confounders therefore included in the model regardless of significance.

factors play a major role in allergic development and manifestations are expressed at early age.

We have assessed paracetamol exposure and allergic outcomes in a population who use paracetamol irrespective of affluence, who can distinguish paracetamol from other analgesics, and in which aspirin avoidance is not pronounced [10, 11]. Wheeze was strongly associated with paracetamol use in a dose-response manner. Similar findings have been reported elsewhere among Mexican 6–7-year-olds [12], while among children in Singapore, paracetamol intake between birth and 6 months was associated with asthma at 3–10 years, but other allergic symptoms were not separately investigated [13]. The possibilities that paracetamol and wheeze in this study are associated through reverse causation, or paracetamol is given to treat symptoms of respiratory infection that also causes wheeze, remain.

A number of factors were assessed in the study that might provide an indication of the burden of exposure to infections. For example, eczema was less common in those children who slept on the floor compared with those on a bed or platform. Our study in Jimma showed that the use of synthetic bedding materials increased the risk of wheeze and atopy [25]. Mattresses are a recognized reservoir of house-dust mites [25], and inhalation of house-dust mite allergen in early life results in immediate hypersensitivity and allergic symptoms [27].

Consistent with the literature, overcrowding was found to reduce eczema [28], but there was no clear trend in this study. However, in Jimma, Ethiopia, no protective effect of family size on the risk of atopic eczema was found [22]. Overcrowding reflects a number of lifestyle factors which together increase the risk of cross-infection with common childhood illness. This finding, however, was not seen for wheeze symptoms for which the risk increased with increasing number of individuals in the household. The effect of overcrowding on wheeze was likely mediated through its positive association with infection [29]. Broadly the protective effects of floor as the child's sleeping place and overcrowding on eczema fit with the 'hygiene hypothesis', but the mechanisms by which this effect is mediated are not clarified by our study. We have also explored the issue of co-morbidity by assessing the effects of the exposures on the outcome 'wheeze but no eczema', and 'eczema but no wheeze'; the effects seen were similar to those in the main analyses.

In conclusion, in this birth cohort of very young children, eczema was related to recognized risk factors for allergic disease, while wheezing at this age was predominantly related to risk factors linked to infection. No associations between geohelminth infection and allergic outcomes (wheeze and eczema) were seen at this early age, and whether geohelminth infection does protect against allergic disease remains to be seen as the cohort matures and more

children become infected. The significant dose-response association between paracetamol use and wheeze may arise from reverse causation. The group is continuing to follow the cohort to explore whether critical periods exist for a range of biological and environmental exposures including paracetamol and geohelminth infection.

Acknowledgements

We are grateful to the mothers and children who participated in the Butajira birth cohort and the data collectors for their stamina during the field work. We thank Addis Ababa University; the Department of Biology, the Wellcome Trust, Asthma UK and UK Association of Physicians for funding the project.

Competing interests: We declare that we do not have any conflict of interest.

Authors' contributions: G. D., J. B., A. V. & C. H. designed the study. G. M., Y. B., G. D., B. E. and C. H. participated in the conduct of the study. Y. B. and G. M. were responsible for the accuracy of the data. A. A. and Y. B. drafted the manuscript. A. A. and A. V. guarantee the statistical analysis. A. A., A. V., G. D., J. B. and Y. B. interpreted the findings. All authors contributed to the final report.

References

- Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma. A review. *J Epidemiol Community Health* 2002; **56**:209–17.
- Kemp A, Bjorksten B. Immune deviation and the hygiene hypothesis: a review of the epidemiological evidence. *Pediatr Allergy Immunol* 2003; **14**:74–80.
- Dagoye D, Bekele Z, Woldemichael K *et al*. Wheezing, allergy and parasite infection in children in urban rural Ethiopia. *Am J Respir Crit Care Med* 2003; **167**:1369–73.
- Davey G, Venn A, Belete H *et al*. Wheeze allergic sensitization and geohelminth in Butajira, Ethiopia. *Clin Exp Allergy* 2005; **35**:301–7.
- Asher MI, Montefort S, Björkstén B *et al*. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; **368**:733–43.
- Sears MR. Epidemiology of childhood asthma. *Lancet* 1997; **350**:1015–20.
- Cooper FJ, Chico ME, Bland M *et al*. Allergic symptoms, atopy, and geohelminth infections in a rural area of Ecuador. *Am J Respir Crit Care Med* 2003; **168**:313–7.
- Flohr C, Quinnell R, Britton J. Do helminth parasites protect against atopy and allergic diseases? *Clin Exp Allergy* 2009; **39**:20–32.
- Leonardi-Bee J, Pritchard D, Britton J *et al*. Asthma and current intestinal parasite infection. Systematic review and meta-analysis. *Am J Respir Crit Care Med* 2006; **174**:514–23.
- Davey G, Berhane Y, Duncan P, Aref-Adib G, Britton J, Venn A. Use of acetaminophen and the risk of self-reported allergic symptoms and skin sensitization in Butajira, Ethiopia. *J Allergy Clin Immunol* 2005; **116**:863–8.
- Duncan P, Aref-Adib G, Venn A, Britton J, Davey G. Use and misuse of aspirin in rural Ethiopia. *East Afr Med J* 2006; **83**:31–6.
- Barragan-Mejueiro MM, Morfin-Maciél B, Nava-Ocampo AA. A Mexican population-based study on exposure to paracetamol and the risk of wheezing, rhinitis and eczema in childhood. *J Invest Allergol Clin Immunol* 2006; **16**:247–52.
- Riece K, Huak CY, Ning TT, van Bever HP. A matched patient--sibling study on the usage of paracetamol and the subsequent development of allergy and asthma. *Pediatr Allergy Immunol* 2007; **18**:128–34.
- Berhane Y, Wall S, Kebede D *et al*. Establishing an epidemiological field laboratory in rural areas – potentials for public health research and interventions. *Ethiop J Health Dev* 1999; **S13**:3–19.
- Hanlon C, Medhin G, Alem A *et al*. Impact of antenatal common mental disorders upon perinatal outcomes in Ethiopia: the P-MaMiE population-based cohort study. *Trop Med Int Health* 2009; **14**:1–11.
- WHO. *Basic laboratory methods in medical parasitology*. Geneva: World Health Organization, 1991.
- Kurukulaarachy R, Fenn M, Matthews M, Arshad SH. The prevalence, characteristics of and early life risk factors for eczema in 10-year old children. *Pediatr Allergy Immunol* 2003; **14**:178–83.
- Martinez DF, Wright LA, Toussing ML *et al*. Asthma and wheezing in the first six years of life. The group health medical associates. *N Engl J Med* 1995; **332**:133–8.
- Ball MT, Jose A, Castro-Rodriguez MD *et al*. Siblings' day care attendance and the risk of asthma and wheezing during childhood. *New Engl J Med* 2000; **343**:538–43.
- Illi S, Won E, on behalf of the MAS group *et al*. Perennial allergen sensitization early in life and chronic asthma in children: a birth cohort study. *Lancet* 2006; **368**:763–70.
- Haileamlak A, Lewis S, Britton J *et al*. Validation of the International Study of Asthma and Allergies in Children (ISAAC) and U.K. criteria for atopic eczema in Ethiopian children. *Br J Dermatol* 2005; **152**:735–41.
- Haileamlak A, Dagoye D, Williams H *et al*. Early life risk factors for atopic dermatitis in Ethiopian children. *J Allergy Clin Immunol* 2005; **115**:370–6.
- Holt PG, Sly PD, Bjorksten B. Atopic versus infectious diseases in childhood: a question of balance? *Pediatr Allergy Immunol* 1997; **8**:53–8.
- Galassi C, Sario M, Biggeri A *et al*. Changes in prevalence of asthma and allergies among children and adolescents in Italy. *Pediatrics* 2006; **117**:34–42.
- Yemaneberhan H, Flohr C, Lewis SA *et al*. Prevalence and associated risk factors of atopic dermatitis symptoms in rural and urban Ethiopia. *Clin Exp Allergy* 2004; **34**:779–85.
- Sunyer J, Menendez C, Ventura PJ *et al*. Prenatal risk factors of wheezing at the age of four years in Tanzania. *Thorax* 2001; **56**:290–5.
- Platt-Mills TA, Rakes G, Heymann PW. Environmental and inflammatory mechanisms: the relevance of allergen exposures to the development of asthma in childhood. *J Allergy Clin Immunol* 2000; **150**:S503–8.
- Cooper PJ, Chico ME, Rodriguez LC *et al*. Risk factors for atopy among school children in a rural area of Latin America. *Clin Exp Allergy* 2004; **34**:845–52.
- von Mutius E. Influences in allergy: epidemiology and the environment. *J Allergy Clin Immunol* 2004; **113**:373–80.