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Early life exposure to farm animals and symptoms of asthma, rhinoconjunctivitis and eczema: an ISAAC Phase Three Study

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Background Associations between early life exposure to farm animals and respiratory symptoms and allergy in children have been reported in developed countries, but little is known about such associations in developing countries.

Objective To study the association between early life exposure to farm animals and symptoms of asthma, rhinoconjunctivitis and eczema in a worldwide study.

Methods Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC) was carried out in 6- to 7-year-old children in urban populations across the world. Questions about early life exposure to farm animals (at least once/week) were included in an additional questionnaire. The association between such exposures and symptoms of asthma, rhinoconjunctivitis and eczema was investigated with logistic regression. Adjustments were made for gender, region of the world, language, gross national income and 10 other subject-specific covariates.

Results A positive association was found between early exposure to farm animals and the prevalence of symptoms of asthma, rhinoconjunctivitis and eczema, especially in non-affluent countries. In these countries, odds ratios (ORs) for 'current wheeze', 'farm animal exposure in the first year of life' and 'farm animal exposure in pregnancy' were 1.27 [95% confidence interval (CI) 1.12–1.44] and 1.38 (95% CI 1.21–1.58), respectively. The corresponding ORs for affluent countries were 0.96 (95% CI 0.86–1.08) and 0.95 (95% CI 0.84–1.08), respectively.

Conclusion Exposure to farm animals during pregnancy and in the first year of life was associated with increased symptoms of asthma, rhinoconjunctivitis and eczema in 6- to 7-year-old children living in non-affluent but not in affluent countries.

Keywords Farm animals, early life, asthma, eczema, rhinoconjunctivitis

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Introduction

Studies in farming communities have shown that children in these communities have less allergic disease; several factors could explain this protective effect, including exposure to farm animals during pregnancy of the mother and/or in early life as discussed in a recent review based on studies which were mostly conducted in Europe and North America.[1]

The large majority of studies on farm animal exposure have been conducted in affluent countries, and it is not clear to what extent the findings can be extrapolated to child populations living in other parts of the world. A small number of studies have addressed the relationship between farm animal exposure and childhood allergic symptoms in non-Western populations, and, interestingly, these have in some cases found positive relationships between various measures of farm animal exposure (including exposure to farm animals in pregnancy) and childhood symptoms. As an example, one of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three centres in Mexico reported a positive association between cumulative asthma in 6- to 7-year-old children and exposure of the mother to farm animals in pregnancy in boys [odds ratio (OR) 1.86, 95% confidence interval (CI) 1.14–3.03] as well as girls (OR 1.73, 95% CI 0.92–3.26).[2]

In this article, we present findings on farm animal exposure from Phase Three of ISAAC, which was a questionnaire-based assessment conducted in a total of 1 187 495 children from 238 centres located in 98 countries in all parts of the world. The analyses in this article are restricted to 194 794 6- to 7-year-old children for whom data on exposure to farm animals were collected.

Methods

ISAAC Phase Three is a repetition and expansion of the first phase of ISAAC, which documented large differences in the prevalence of childhood symptoms of asthma and allergy across the world.[3,4]

As in ISAAC Phase One, parents of the 6- to 7-year olds completed the written questionnaire at home. Schools were randomly selected from within a defined geographical area. Centres obtained ethical approval from their local ethics committee, or, for the minority of centres that did not have an ethics committee, some other approving body such as The Ministry of Health. The method of consent was determined by the local ethics committee and informed consent was obtained from parents of all participating children. Centres obtained their own funding. Adherence to the ISAAC Protocol was assessed and centres with serious discrepancies were excluded. Minor deviations from the protocol were identified with footnotes to the results tables in the publications presenting the Phase Three results.[5,6] In this article, we focus on 'current wheeze' ('Has your child had wheezing or whistling in the chest in the past 12 months?'), 'asthma ever' ('Has your child ever had asthma?'), symptoms of 'rhinoconjunctivitis' ('In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when you (he/she) did not have a cold or the flu?' and 'In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?') and symptoms of 'eczema' ('Has your child had this itchy rash at any time in the past 12 months?' and 'Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?'). The eczema questions were preceded by the question 'Has your child ever had an itchy rash coming and going for at least 6 months?' We have also analysed 'symptoms of severe asthma', defined as participants who, according to the written questionnaire, in the past 12 months, have had four or more attacks of wheeze, or >1 night per week sleep disturbance from wheeze, or wheeze affecting speech. This definition is based on previous ISAAC analyses that showed a combination of these features of more severe wheezing episodes correlated significantly more closely with asthma mortality and hospital admissions than current wheeze alone.[7] In ISAAC Phase Three, an optional environmental questionnaire (EQ) was administered in addition to the core symptom questionnaire to test a number of specific aetiological hypotheses.[3] The environmental questionnaire included questions on diet, heating and cooking fuels, exercise, exposure to farm animals and pets, family size, birth order, socio-economic status, use of antibiotics and anti-pyretics, breastfeeding, birth weight, immigrant status, environmental tobacco smoke and frequency of truck traffic in street of residence. The complete questionnaire can be found on the ISAAC website (www.isaac.auckland.ac.nz). The questions that this article relates to are:

(1) In your child's first year of life did he/she have regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry) (Y/N)?
(2) Has this child's mother had regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry) while being pregnant with this child (Y/N)?

These questions were only included in the questionnaires for the 6- to 7-year olds, so our analysis was restricted to this age category and could not be extended to the 13- to 14-year olds.

ORs have been calculated using generalized linear-mixed models (GLMMs) for a binomial distribution and logit link and with the centres being modelled as a random effect. The analyses on all study participants were adjusted for gender, region of the world,

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language and gross national income (GNI). Regions of the world were: Africa, Asia-Pacific, Eastern Mediterranean, Latin America, North America, Northern and Eastern Europe, Oceania, Indian Subcontinent and Western Europe. The written questionnaire was translated from English into 53 languages, according to the ISAAC Phase Three protocol[3] that required back translation to English and comparison with the original.[8] For the analysis, languages were categorized as Arabic, Chinese, English, Hindi, Indonesian, Portuguese, Spanish and 'other' (comprising many different languages). In addition to the combined analyses, further analyses were conducted after stratification for gender and GNI. For GNI, countries were classified as 'affluent' or 'non-affluent' using a 2001 GNI value of US$ 9205 per capita as cut-off, which separates high-income countries from the low- ($\leqslant$US$ 745), lower middle- (746–2975 US$) and upper middle- (2976–9205 US$) income countries.[9] Finally, multivariate analyses (GLMM) were conducted to check whether associations between symptoms and farm animal exposure were confounded by certain other variables in the environmental questionnaire such as maternal education, cooking fuel, maternal and paternal smoking, television watching, exercise, siblings (older and younger), fast food, truck traffic exposure and paracetamol use. In a sensitivity analysis, the effect of additional adjustment for cat and dog exposure in the first year of life was investigated. Centres were treated as simple random effects but region was included in the model as a fixed effect to account for the differences in level between regions.

The final worldwide data set comprised 144 centres from 61 countries with 388 811 6- to 7-year-old children. Centres that had not undertaken the EQ were then excluded from the data set leaving a final EQ data set of 75 centres from 32 countries with 220 408 children. For inclusion in this analysis, centres were required to have $\geqslant$70% of participants with data on reported animal exposure. Six centres were accordingly excluded leaving 69 centres in 28 countries with 194 794 children with data on farm animal exposure. In the fully adjusted analyses, we excluded centres with <70% response rates. Missing values on covariables led to further reductions in the number of children included in the analyses and we documented to what extent results were influenced by these selections and adjustments.

Results

Data from 6- to 7-year-old children from 69 centres in 28 countries are included in the analyses of farm animal exposures. The analysis of exposure to farm animals in the first year includes 194 794 children and the analysis of maternal exposure to farm animals during pregnancy includes 194 598 children. Table 1 shows the range of reported percentages of farm animal exposure by area of the world. The highest farm animal exposure was found in the one participating centre from Africa; the lowest in North America. The average percentage of children in all centres whose mothers had been exposed to farm animals in pregnancy (10%) and of children exposed to farm animals in the first year of life (11.5%) shows that these exposures were relatively uncommon in the ISAAC Phase Three populations.

Table 2 shows the associations between farm animal exposure in the first year of life and symptoms. There was a positive association with most symptoms (especially severe symptoms of asthma and eczema) after adjustment for all covariates. Similar findings were obtained in the analysis of farm animal exposure during pregnancy of the mothers of the index children (Table 3). Additional adjustment for cat and dog exposure in the first year of life made virtually no difference to these associations (results not shown). As these tables show, the largest differences in ORs were generally found when centres were excluded that had insufficient data on covariates.

When the analyses were stratified by country affluence, it became clear that most of the associations were much stronger in the non-affluent than in the affluent countries (Table 4). In fact, most ORs in the affluent countries became close to unity, indicating no effect. Results were generally similar for boys and girls (results not shown).

Table 5 shows the results of an analysis in which children with farm animal exposure in pregnancy only, during the first year of life only, and during both periods are compared with children without farm animal exposure in either period. The frequencies of exposure mentioned in the footnote to Table 5 show that exposure during pregnancy and in the first year was most frequent (5.5% in affluent countries, 6.3% in non-affluent countries), but considerable frequencies were also found in categories of exposure during pregnancy only or during the first year only (4.6% affluent, 7.0% non-affluent). The strongest positive associations were found in children in non-affluent countries with exposure to farm animals during both periods. In affluent countries, symptoms of rhinoconjunctivitis and eczema were positively associated with exposure in pregnancy only, which was reported for only 1.4% of the children in this group of countries. The strongest associations were found in the non-affluent countries. Adjustment for cat and dog exposure in the first year of life again did not change the findings (results not shown).

Discussion

This study found a positive global relationship between childhood symptoms of current asthma, rhinoconjunctivitis and eczema and farm animal exposure in the first year of life as well as farm animal exposure of the child's mother during pregnancy. The

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Table 1 Frequency of reported farm animal contact in pregnancy and during first year of life in the various regions of the world where 6- to 7-year-old children were studied as part of the ISAAC Phase Three study

	Number of countries	Number of centres	*N*	Farm animal contact first year (%)	Farm animal contact pregnancy (%)
All centres	28	69	194 794	11.5	10.0
Africa	1	1	2304	25.6	23.5
Asia-Pacific	5	8	26 923	11.4	10.3
Eastern Mediterranean	3	5	15 012	15.5	14.9
Indian Sub-Continent	1	14	42 523	11.3	8.9
Latin America	6	16	43 388	11.1	9.8
North America	2	2	3921	8.6	7.7
Northern and Eastern Europe	5	6	15 115	12.0	12.4
Oceania	1	4	10 753	11.2	8.9
Western Europe	4	13	34 855	9.6	7.8

Table 2 Association between exposure to farm animals in the first year of life and symptoms of asthma, rhinoconjunctivitis and eczema in 6- to 7-year-old children

	OR (95% CI)		
Outcome	Model 1[a] (all children)	Model 2[b]	Model 3[c]
Current wheeze	1.27 (1.20–1.35)	1.14 (1.05–1.24)	1.09 (1.00–1.18)
Current symptoms of severe asthma	1.39 (1.29–1.50)	1.33 (1.19–1.49)	1.22 (1.09–1.37)
Asthma ever	1.14 (1.07–1.21)	1.01 (0.93–1.10)	0.98 (0.90–1.07)
Current symptoms of rhinoconjunctivitis	1.31 (1.24–1.40)	1.22 (1.12–1.34)	1.18 (1.08–1.30)
Current symptoms of severe rhinoconjunctivitis	1.43 (1.19–1.72)	1.42 (1.06–1.91)	1.21 (0.89–1.63)
Hay fever ever	1.18 (1.11–1.26)	1.12 (1.02–1.22)	1.10 (1.00–1.20)
Current symptoms of eczema	1.33 (1.25–1.41)	1.19 (1.10–1.30)	1.16 (1.07–1.27)
Current symptoms of severe eczema	1.89 (1.65–2.16)	1.48 (1.19–1.83)	1.31 (1.05–1.63)
Eczema ever	1.10 (1.04–1.17)	0.98 (0.91–1.06)	1.02 (0.94–1.10)

[a]Adjusted for sex, region of the world, language and GNI per capita.
[b]Adjusted for sex, region of the world, language and GNI. Including only centres with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed.
[c]Multivariate analysis including centres with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, GNI, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings and truck traffic in street of residence.

associations were driven by the non-affluent countries (especially upper and lower middle income) as there was little relationship between farm animal exposure and symptoms in the affluent countries that were studied. There was no evidence for protective effects of farm animal exposure in affluent countries.

The strengths of the ISAAC study are worldwide coverage, the use of standardized and validated methods of symptom reporting, and an extremely large population size. Limitations include the reliance on parent-completed questionnaires and absence of objective measurements of exposure and allergy status.

Could these results have been produced by bias? It seems unlikely that parents of children with allergic symptoms over-report exposure to farm animals in pregnancy or the first year of life, as this exposure is not widely discussed in the media or by physicians treating their children. There was also little evidence of selection bias when children who had insufficient data on potential confounding variables were excluded from the analyses. If anything, the crude analyses for the complete populations produced higher ORs than the crude analyses that were restricted to children with full confounder data (comparing column 1 with column 2 in Tables 2 and 3). There was little evidence of confounding by the individual or community-level confounders that were assessed in these analyses (comparing column 2 with column 3 in Tables 2 and 3). We cannot exclude the possibility of residual confounding by unmeasured or

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Table 3 Association between maternal exposure to farm animals during pregnancy and symptoms of asthma, rhinoconjunctivitis and eczema in 6- to 7-year-old children

Outcome	OR (95% CI)		
	Model 1[a] (all children)	Model 2[b]	Model 3[c]
Current wheeze	1.36 (1.28–1.44)	1.19 (1.09–1.30)	1.13 (1.03–1.24)
Current symptoms of severe asthma	1.47 (1.36–1.59)	1.36 (1.20–1.54)	1.23 (1.09–1.40)
Asthma ever	1.15 (1.08–1.22)	1.01 (0.92–1.10)	0.97 (0.88–1.06)
Current symptoms of rhinoconjunctivitis	1.33 (1.25–1.42)	1.29 (1.17–1.43)	1.24 (1.12–1.37)
Current symptoms of severe rhinoconjunctivitis	1.57 (1.30–1.90)	1.76 (1.30–2.37)	1.50 (1.11–2.03)
Hay fever ever	1.22 (1.14–1.30)	1.19 (1.08–1.31)	1.17 (1.06–1.29)
Current symptoms of eczema	1.30 (1.22–1.39)	1.21 (1.10–1.32)	1.17 (1.07–1.29)
Current symptoms of severe eczema	1.86 (1.61–2.16)	1.46 (1.15–1.85)	1.28 (1.00–1.62)
Eczema ever	1.06 (1.00–1.13)	0.98 (0.90–1.07)	1.01 (0.93–1.10)

[a]Adjusted for sex, region of the world, language and GNI per capita.
[b]Adjusted for sex, region of the world, language and GNI. Including only centres with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed.
[c]Multivariate analysis including centres with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, GNI, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings and truck traffic in street of residence.

Table 4 Associations between farm animal contact and current symptoms of asthma, rhinoconjunctivitis and eczema in 6-to-7-year-old children in affluent and non-affluent countries[a]

Region	Number of countries	Number of centres	*n*	OR[b] (95% CI) asthma (wheeze)	OR[b] (95% CI) rhinoconjunctivitis	OR[b] (95% CI) eczema
Farm animal exposure in the first year of life						
Affluent	6	19	41 782	0.96 (0.86–1.08)	1.06 (0.93–1.20)	0.95 (0.84–1.08)
Non-affluent	14	24	53 534	1.27 (1.12–1.44)	1.35 (1.18–1.55)	1.38 (1.23–1.55)
Farm animal exposure during pregnancy						
Affluent	6	19	41 877	0.95 (0.84–1.08)	1.12 (0.98–1.29)	0.96 (0.84–1.11)
Non-affluent	14	24	53 558	1.38 (1.21–1.58)	1.38 (1.20–1.60)	1.37 (1.21–1.56)

Multiple regression analyses in children with complete covariate data.
[a]World Bank classification for 2001.
[b]Multivariate analysis including centres with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, GNI per capita, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings and truck traffic in street of residence.

inadequately measured risk factors but the pattern just described is also compatible with some underestimation of the ORs related to non-random missing values.

Growing up on a farm has been associated with protection against allergic sensitization and disease in several studies (for instance[10,11]). Exposure to farm animals during pregnancy and during the first years of life has been suggested as one of the possible factors to explain this association. A European study conducted in five different countries found protective associations between pig exposure on farms and asthma, but a positive association with sheep on the farm.[12] The same study found protective associations with living on a farm for wheeze and rhinitis but not eczema,[13] and a protective association with farm milk consumption for symptoms of rhinoconjunctivitis but not wheeze and eczema.[14] A recent study found that a higher diversity of microbial exposure on farms was associated with less asthma and atopy.[15] Very few studies from non-affluent countries have been reported on this subject. A study from China[16] has analysed exposure to farm animals and found a strongly positive association with childhood wheezing, asthma, cough and phlegm but not with rhinitis. One explanation given to explain not finding a protective effect was that the Chinese children in this study were still growing up in less hygienic circumstances with

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Table 5 Association between maternal and first-year exposure to farm animals and current symptoms of asthma, rhinoconjunctivitis and eczema in 6- to 7-year-old children in affluent and non-affluent countries[a]

	Outcome									
	Pregnancy only OR[b] (95% CI)			First year only OR[b] (95% CI)			Pregnancy and first year OR[b] (95% CI)			
	Asthma (wheeze)	Rhinoconjunctivitis	Eczema	Asthma (wheeze)	Rhinoconjunctivitis	Eczema	Asthma (wheeze)	Rhinoconjunctivitis	Eczema
Affluent[c]	1.14 (0.88–1.48)	1.44 (1.10–1.89)	1.37 (1.05–1.78)	1.08 (0.91–1.29)	1.10 (0.90–1.34)	1.11 (0.91–1.35)	0.91 (0.79–1.05)	1.05 (0.90–1.23)	0.87 (0.74–1.03)
Non-affluent[c]	1.30 (1.04–1.62)	1.26 (0.98–1.61)	1.18 (0.96–1.47)	1.10 (0.90–1.33)	1.21 (0.98–1.50)	1.24 (1.05–1.48)	1.44 (1.23–1.68)	1.46 (1.23–1.73)	1.51 (1.31–1.76)

Multiple regression analyses in children with complete covariate data. The reference category for the ORs is no exposure to animals in pregnancy and in the first year at either time.

[a]World Bank classification for 2001.

[b]Multivariate analysis including centres with at least 70% data available for all covariates. All children who had a missing value for any of the covariates have been removed. Adjusted for sex, region of the world, language, gross national income per capita, cooking fuel, maternal education, current maternal and paternal smoking, exercise, television viewing, consumption of fast food, current paracetamol use, older and younger siblings and truck traffic in street of residence.

[c]Frequency of exposure: pregnancy only 1.4% (affluent), 2.7% (non-affluent); first year only 3.2% (affluent), 4.3% (non-affluent); pregnancy and first year 5.5% (affluent), 6.3% (non-affluent).

ubiquitous exposure to microbial agents. A small study among urban and rural children living in Nepal found a protective effect on asthma of cattle being indoors at night but not from cattle kept outdoors.[17] Interestingly, keeping poultry indoors (which was more frequently reported than keeping cattle indoors at night) was associated with increased asthma prevalence in this study. A large study from Belarus found protective associations between exposure to farm animals and symptoms of wheeze, rhinoconjunctivitis and eczema in 6-year-old children as established with the ISAAC questionnaire.[18] The population was described as mixed urban–rural, and a high percentage of parents (61.2%) reported contact with farm animals. It was suggested that the level of hygiene in Belarus was already very high at the time of this study, reducing exposure to microbial agents in general in this population. A population study from Russia and Finland found a positive association between allergic asthma and exposure to farm animals in pregnancy and early in life in both the countries.[19] The explanation offered was that the children and their mothers, not living on farms themselves, had had occasional rather than frequent or continuous exposure to farm animals, limiting exposure to agents that may confer protection at higher exposures. In the ISAAC study, most children were studied in urban or semi-urban areas rather than in farming communities. In fact, almost half of the study centres were located in cities with more than one million inhabitants. Exposure to farm animals in pregnancy and the first year of life may have been occasional rather than frequent or continuous in most of these populations as well. This is supported by our finding that equally large proportions of subjects were exposed in pregnancy only, or during the first year only, compared with subjects being exposed in both periods as indicated in Table 5. Urban livestock farming is widespread in many cities in developing countries[20] and exposure to farm animals may exhibit different patterns in such countries compared with the developed world.

How could a positive relationship between early farm animal exposure and childhood allergic symptoms be explained? Some farm animals, such as horses, produce allergens to which children may become sensitized.[21] However, asthma and rhinitis are predominantly non-allergic in non-affluent compared with in affluent countries[22,23] and it seems unlikely that early life exposure to farm animals would noticeably increase Immunoglobulin-E (IgE)-mediated allergic symptoms at age 6–7 years. High exposure to endotoxin in the farming environment has been associated with increased non-atopic airway symptoms and bronchial hyper-responsiveness in farmers.[24] Endotoxin was also associated with increased non-atopic wheeze in farm children studied in Germany, Switzerland and Austria[10] and early-life exposure to endotoxin was associated with increased

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wheeze at ages 1–7 years in an urban birth cohort followed in Boston, USA.[25] This suggests that increased endotoxin exposure associated with early life contact with farm animals in mostly urban children could possibly be responsible for the associations seen in our study. It is also possible that contact to farm animals increases exposure to certain helminths which may produce respiratory symptoms later in childhood.[26–29] Farm cats and dogs have been found with high prevalence of Toxocara and Toxoplasma[30,31] in some studies, and toxocara infections have been associated not only with wheezing symptoms but also with but also with allergic rhinitis[32] and with skin manifestations.[33] A study from China documented high rates of helminth infections in dogs posing a threat to public health.[34] We adjusted our analyses for early life cat and dog exposure and found that the associations between farm animal exposure and symptoms were independent of early cat and dog exposure. Small-scale livestock farming is common in many cities in non-affluent countries in the world, and may produce a different type of exposure to farm animal products than is encountered on traditional farms located in affluent countries.

Whether such observations help to explain the associations we show in this article remains speculative, however. More detailed studies on farm animal exposure and childhood symptoms of wheeze, rhinoconjunctivitis and eczema among children living in non-affluent countries are needed.

We conclude that exposure to farm animals during pregnancy and in the first year of life is associated with increased symptoms of asthma, rhinoconjunctivitis and eczema in 6- to 7-year-old children living in non-affluent countries.

Supplementary Data

Supplementary Data are available at *IJE* online.

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Conflict of Interest: None declared.

KEY MESSAGE

- In low- and middle-income countries, early life exposure to farm animals in urban settings is a risk factor for childhood symptoms of asthma, rhinoconjunctivitis and eczema.

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Urban livestock farming
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