Accepted Article

DR HARRIET MPAIRWE (Orcid ID : 0000-0003-1199-4859)

DR GYAVIIRA NKURUNUNGI (Orcid ID : 0000-0003-4062-9105)

Article type : Original Article-Epidemiology of Allergic Disease

Title: Risk factors associated with rhinitis, allergic conjunctivitis and eczema among schoolchildren in Uganda

Running title: Risk factors for allergy-related diseases in Uganda

Manuscript word count: 3706 words

Figure and Tables count: 6 main tables, 4 supplementary tables

Author's institutional affiliation*: Medical Research Council/Uganda Virus Research Institute and London School of Hygiene and Tropical Medicine Uganda Research Unit. Plot 51-59 Nakiwogo Road, Box 49, Entebbe, Uganda

Corresponding author: Harriet Mpairwe, MRC/UVRI and LSHTM Uganda Research Unit, Plot 51-59 Nakiwogo Road, Box 49, Entebbe, Uganda. Tel. +256 417 704000. Email harriet.mpairwe@mrcuganda.org

*Author now also at London School of Hygiene and Tropical Medicine. Keppel St, Bloomsbury, London WC1E 7HT, UK.

Conflict of interest

None of the authors had any conflict of interest to declare.

Author contributions

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CEA.13769

This article is protected by copyright. All rights reserved

Mpairwe H - made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, in drafting the manuscript and revising it critically for important intellectual content.

Nkurunungi G - made substantial contributions to acquisition of data, drafting the manuscript and revising it critically for important intellectual content.

Tumwesige P, Akurut H, Namutebi M, Nambuya I, Nnaluwooza M, Apule B, Onen C, Katongole T, Niwagaba E, Mukasa M - made substantial contributions to acquisition of data, and revising manuscript critically for important intellectual content

Webb E L - made substantial contributions to analysis and interpretation of data and revising manuscript critically for important intellectual content.

Elliott A M, Pearce N - made substantial contributions to conception and design, analysis and interpretation of data, and revising manuscript critically for important intellectual content.

All authors have given final approval of the version to be published.

Accepted Article

This article is protected by copyright. All rights reserved

Abstract

Background: The prevalence of allergy-related diseases (ARDs), including rhinitis, allergic conjunctivitis and eczema, is on the increase globally. The causes of this increase are not well established.

Objectives: To investigate the risk factors associated with ARDs among schoolchildren in Uganda.

Methods: We conducted a secondary data analysis of a large asthma case-control study involving 1,700 schoolchildren, 5-17 years, in urban Uganda. ARDs were defined according to the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire. Skin prick testing (SPT) was conducted using standard procedures and allergen-specific IgE (asIgE) using ImmunoCAP®. We employed inverse probability weighted analysis to generate estimated prevalence data and weighted odds ratios.

Results: The lifetime estimated weighted prevalence of reported rhinitis, allergic conjunctivitis and eczema was 43.3%, 39.5%, and 13.5%; weighted prevalence in 12 months was 10.1%, 9.1% and 2.3%, respectively. There was overlap of ARDs, with 66.3% of 1,193 schoolchildren who reported having ever an ARDs (including asthma) reporting two or more. Risk factors associated with reported rhinitis in the last 12 months were city residence at birth [adjusted odds ratio (95% confidence interval) 2.66 (1.42-4.99) compared to rural]; father's [2.62 (1.79-3.83)] and mother's history of allergic disease [2.12 (1.48-3.02)]; frequent de-worming in the last 12 months [2.01 (1.30-3.11), >2 versus none]; current high frequency of 'trucks passing on the street near home' [2.59 (1.48-4.52), 'almost all the time' versus rarely] and positive SPT [1.54 (1.09-2.18)] but not asIgE [1.38 (0.60-3.15)]. The same pattern of risk factors was observed for allergic conjunctivitis and eczema.

Conclusion:

We found extensive multi-morbidity of, and overlap in the risk factors for, rhinitis, conjunctivitis, and eczema - similar to asthma risk factors - among schoolchildren in urban Uganda. This suggests a similar underlying cause for all ARDs, associated with exposure to urban lifestyles and environment in Uganda.

This article is protected by copyright. All rights reserved

Accepted Article

Introduction

Allergy-related diseases (ARDs) including rhinitis, allergic conjunctivitis and eczema are on the increase in most parts of the world[1, 2], but the causes of these diseases are generally not established[3]. These chronic recurrent conditions cause significant physical and psychological distress, sleep disturbance and reduced quality of life among people of all ages, but particularly among children[3, 4]. The worldwide prevalence is estimated as 42% for rhinitis[2], 25% for allergic conjunctivitis[4], and 8% for eczema[5]. Studies from high-income countries have demonstrated that these ARDs often co-exist[6, 7], but data from population studies in sub-Saharan Africa are scarce.

In Africa, and other low and middle income countries (LMICs), the prevalence of these conditions is higher in urban than rural areas[8-11]. Although data on risk factors for ARDs from Africa is scarce, there is evidence to suggest that there may be important differences in risk factors between high income countries (HICs) and LMICs. For example, the International Study of Asthma and Allergies in Childhood (ISAAC) study reported a weaker association between ARDs and allergic sensitisation in LMICs than in HICs[12]. These differences were also supported by results from our own work on risk factors for asthma, another important ARD, among Ugandan schoolchildren[13]. Children born in rural areas had the lowest asthma risk, but this was not associated with exposure to farm animals in early life[13] as has been found in Europe[14, 15] and North America[16, 17]. Childhood asthma was also associated with a higher parental education and social-economic status[13], in contrast to HICs where asthma is associated with low parental education and social economic status[18, 19]. Understanding the risk factors for ARDs in Africa is key to identifying the causes of these conditions and will inform local intervention strategies for prevention and treatment. We therefore undertook a secondary data analysis of a large asthma case-control study involving schoolchildren in urban Uganda, in order to investigate the risk factors associated with rhinitis, allergic conjunctivitis and eczema.

Accepted Article

This article is protected by copyright. All rights reserved

Methods

This was a secondary analysis of data from an asthma cross-sectional case-control study (i.e. disease status – case or control – is measured at one point in time)[13]. For this paper, we used statistical tools that enabled us to analyse the data as a general cross-sectional study. The statistical tool is inverse probability weighted analysis (detailed explanation in the statistics section below). The data that support the findings of this study are available in London School of Hygiene & Tropical Medicine Data Compass at http://datacompass.lshtm.ac.uk/1761/. Data access is restricted due to the presence of potential identifiers. To gain access, interested parties are asked to complete a data request, indicating the requested values (codebook for details freely available), and sign a data agreement. We report our findings according to the STROBE guidelines[20].

Study population and enrolment procedures

Schoolchildren, 5-17 years, were enrolled from both primary and secondary schools in an urban area of Wakiso district in central Uganda between May 2015 and July 2017; further details of the study are described elsewhere[13, 21]. For each child with asthma ("cases"), two children without a history of asthma symptoms ("controls") were randomly selected from the class register, using a random number generator programme in STATA (StataCorp, Texas, USA). The parents or guardians of potential participants were contacted to attend a meeting, using invitation cards delivered by the children or telephone calls by the study team. During the meeting, parents/guardians who were interested in having their children participate provided written informed consent. Children eight years or older provided written informed assent.

The study conforms to the standards of the Declaration of Helsinki, and was approved by the Uganda Virus Research Institute Research and Ethics Committee (reference number GC/127/14/09/481), and by the Uganda National Council for Science and Technology (reference number HS 1707).

Accepted Article

This article is protected by copyright. All rights reserved

Study procedures

Data on rhinitis, allergic conjunctivitis and eczema were collected using the widely used and validated ISAAC questionnaire[22], which was administered by the study team in either English or Luganda (a language widely understood by the study population). Rhinitis was defined as 'a problem with sneezing, or a runny, or a blocked nose when you did not have a cold or the flu'; allergic conjunctivitis was defined as 'recurrent itchy-watery eyes'; eczema was defined as 'an itchy rash which was coming and going for at least 6 months, and in 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'. We included an additional question for urticarial rash which was defined as 'itchy rash associated with wheals (*ebilogologo* in Luganda, a well-known terminology). Questions were answered by either the parents or the participant themselves (for adolescents). We used the ISAAC environmental questionnaire[23] to collect data on risk factors for ARDs, and added questions relevant to this setting, such as residence at birth and in the first five years of life [rural or urban (small town or the city Kampala)], and frequency of de-worming in the last 12 months.

We conducted assessments for allergic sensitisation. Skin prick testing (SPT) was conducted using standard procedures[24] with seven crude allergen extracts [*Dermatophagoides* mix of *D. farinae* and *D. pteronyssnus* (dust mite), *Blomia tropicalis* (dust mite), *Blattella germanica* (cockroach), *Arachis hypogaea (*peanut), cat, pollen mix of weeds, mould mix of *Aspergillus* species; ALK Abello, Hoersholm, Denmark]. Fractional exhaled nitric oxide (FENO) was measured using a handheld device (NoBreath®, Bedfonf Scientific, Maidstone, United Kingdom). We used the manufacturer's cut-off for children of >35 parts per billion. For allergen-specific IgE (asIgE), 200 aliquots of plasma were randomly selected from all participants for testing by ImmunoCAP® (Phadia, Uppsala, Sweden)[25] using three crude allergen extracts (*D. pteronyssinus*, *B. germanica* and *Arachis hypogaea*). The standard cut-off for allergic sensitisation of >0.35 allergen-specific kilo units per litre (kU_A/L) was used. Total IgE was also measured using ImmunoCAP®.

Other assessments included the tuberculin skin test (TST), stool examinations and HIV testing. TST was conducted using standard procedures we have described previously[26].

This article is protected by copyright. All rights reserved

Examination for helminths was conducted on three stool samples freshly collected on different days, using the Kato Katz method[27], and these included *Schistosoma mansoni, Trichuris trichuria,* hookworm, and *Ascaris lumbricoides*. As part of the Uganda Ministry of Health (MoH) directive, all children enrolled in the study were tested for HIV, using rapid test kits, according to the MoH algorithm[28].

Statistical considerations

Data were collected on paper questionnaires and double data-entered into OpenClinica open source software version 3.1.4 (OpenClinica LLC and collaborators, Waltham, MA, USA). Cleaned data were transferred to STATA version 15 for analysis. Variables with clinically-relevant standard cut-off points, such as SPT, asIgE, FENO and TST, were analysed as binary variables. Total IgE was analysed as a continuous variable. The variable father's and mother's 'history of allergic disease' included a history of asthma, rhinitis, conjunctivitis, eczema and any other allergies such as urticaria.

We generated an additional variable for any allergy-related disease which we defined as existence of any of rhinitis, allergic conjunctivitis, eczema and asthma. This was in recognition of the evidence from literature that these conditions frequently coexist[6, 7], suggesting the possibility of similar underlying risk factors that this study aimed to investigate.

This was a secondary analysis of data from an asthma case-control study, and therefore it was not a random population sample. We therefore used inverse probability weighting which takes into account the fact that asthma cases and non-asthma controls were sampled with different probabilities of selection into the case-control study[29]. This tool uses differential weighting, by giving each individual's data a weight inversely proportional to their probability of selection. Inverse probability weighting was implemented as follows. The population prevalence of asthma in urban Uganda is approximately 12%[30], and the original asthma case-control study enrolled all identified asthma cases in the population under study [in Wakiso District] and randomly selected twice the number of controls[13]. One might therefore expect that for every 100 children in the source population, there would be 12 asthma cases

This article is protected by copyright. All rights reserved

and 24 non-asthmatic controls (out of 88 non-asthmatics) selected. We therefore assumed that all cases in the source population were sampled, and that the sampling fraction in the non-asthmatics was 24/88 (0.273). We used inverse probability weighting to account for these sampling fractions in all our analyses, i.e. asthma cases received a weight of 1, whereas non-asthmatics received a weight of 3.67 (=1/0.273).

Using the weighted analysis, we estimated the weighted prevalence of rhinitis, allergic conjunctivitis and eczema. We used chi squared tests for comparison of the different risk factors among children with or without a given allergy-related condition. We built each multiple logistic regression model by adding one confounder (identified in literature, and in preliminary analyses of the data) at a time and noted the change in effect side, we stopped adding when there was no change in effect size[31]. Variables that were strongly related (such as mother's and father's education, or area of residence at birth and area of residence in the first five years) were not included in the same model in order to minimize problems of collinearity[31].

In order to investigate whether the results on risk factors associated with rhinitis, allergic conjunctivitis and eczema were being driven by asthma comorbidity, we conducted a sub-group analysis among schoolchildren with and without asthma separately, and obtained similar findings. We present results from the weighed analysis.

Accepted Article

This article is protected by copyright. All rights reserved

Results

We present results from the weighted analysis that included all 1,700 schoolchildren enrolled in the original asthma case-control study[32]; the detailed participant flow diagram has been published previously[13].

Weighted prevalence of rhinitis, allergic conjunctivitis and eczema

The lifetime estimated weighted prevalence of reported rhinitis, allergic conjunctivitis and eczema was 43.3%, 39.5%, and 13.5%, respectively, while the weighted prevalence in the last 12 months was 10.1%, 9.1% and 2.3% respectively (Table 1). There was overlap of these ARDs (Table 1); of the 1,193 schoolchildren who reported having ever had ARDs, 791 (66.3%) reported either two, three or four ARDs. The lifetime weighted prevalence of urticarial rash and weighted prevalence in the last 12 months was 31.9% and 1.8%, respectively (Table 1). The overall weighted prevalence of positive skin prick test (to any of seven allergens) at enrolment was 34.7%.

For the rest of the analysis, the main outcomes are reported rhinitis in the last 12 months, the lifetime history of allergic conjunctivitis, eczema (because of larger numbers compared to the prevalence of these same conditions in the last 12 months), and the combined variable of any allergy-related diseases (that includes asthma).

Risk factors associated with rhinitis

Schoolchildren with reported rhinitis in the last 12 months were more likely than their counterparts without rhinitis to report a father's [adjusted odds ratio (95% confidence interval), 2.62 (1.79-3.83)]; and mother's history of allergic disease [2.12 (1.48-3.02)]; residing in the city at birth [2.66 (1.42-4.99)]; using firewood/charcoal stove as main fuel for indoor cooking [2.46 (1.53-3.97)]; the highest reported frequency of de-worming in the last 12 months [2.01 (1.30-3.11)] and the highest reported frequency of 'trucks passing on the street near their home' currently [2.59 (1.48-4.52)] (Table 2). They were more likely to have a positive skin prick test [1.54 (1.09-2.18)] and elevated FENO levels [1.66 (1.14-2.40)], but there were no differences for asIgE and total IgE (Table 2). Similar results were observed for

Accepted Article

This article is protected by copyright. All rights reserved

lifetime history of rhinitis, albeit narrower confidence intervals were observed, due to bigger numbers (Supplementary Table 1).

Risk factors associated with allergic conjunctivitis

Schoolchildren with a lifetime history of allergic conjunctivitis were more likely than their counterparts without allergic conjunctivitis to report a father's [2.06 (1.56-2.71)] and mother's history of allergic disease [1.57 (1.24-1.98)]; residing in the city at birth [1.69 (1.09-2.64)]; being exposed to farm animals in early life [1.33 (1.05-1.67)]; having a father with tertiary education [1.35 (1.03-1.79)]; the highest reported frequency of de-worming in last 12 months [1.94 (1.44-2.63)] and the highest reported frequency of 'trucks passing on the street near their home' currently [1.60 (1.03-2.48)] (Table 3). They were more likely to have a positive SPT [1.76 (1.40-2.21)] and elevated FENO levels [1.57 (1.20-2.05)], but there was no difference for asIgE and total IgE (Table 3). Similar results were observed for allergic conjunctivitis in the last 12 months, albeit with wider confidence intervals due to much smaller numbers.

Risk factors associated with eczema

Children with a lifetime history of eczema were more likely than their counterparts without eczema to report a father's [2.19 (1.56-3.09)] and mother's history of allergic disease [1.94 (1.42-2.67)]; residing in the city at birth [1.55 (0.91-2.63)]; the highest reported frequency of de-worming in last 12 months [1.63 (1.10-2.43)] and the highest reported frequency of 'trucks passing on the street near their home' currently [1.94 (1.14-3.32)], but there were no differences for SPT, asIgE and total IgE (Table 4). Numbers for eczema in the last 12 months were small.

Risk factors associated with ARDs combined

Because of the high rate of multi-morbidity of ARDs (Table 1) and the high overlap of risk factors associated with these conditions (Tables 2-4), we created a new variable that combined all the ARDs (including asthma), and compared children with any ARD to children who did not report any ARDs. We found the risk factors associated with 'any ARD ever' to include a father's [2.64 (1.89-3.70)] and mother's history of allergic disease [2.21 (1.70-

Accepted Article

This article is protected by copyright. All rights reserved

2.86)]; city residence at birth [2.12 (1.26-3.57)]; exposure to farm animals in first five years of life [1.41 (1.11-1.80)]; the highest reported frequency of de-worming in the last 12 months [2.12 (1.51-2.99)] and 'trucks passing on the street near home' currently [2.18 (1.25-3.78)]; positive SPT [1.91 (1.49-2.46)] and elevated FENO [1.92 (1.40-2.64)], but not asIgE or total IgE (Table 5). These results were similar for ARDs in the last 12 months, except this time the association with asIgE was statistically significant [1.85 (1.14-3.01)] (Supplementary Table 2). Similar results were observed for risk factors associated with ARDs among non-asthma controls only (Supplementary Table 3).

Risk factors associated with positive skin prick test

Children with positive SPT were more likely than SPT-negative children to report having a father [1.36 (1.02-1.81)] and/or a mother with tertiary education [1.72 (1.29-2.30)]; a father's [1.41 (1.06-1.87)] and mother's history of allergic disease [1.28 (1.00-1.63)]; residing in the city at birth [1.83 (1.17-2.86)]; the highest reported frequency of 'trucks passing on the street near their home' currently [2.26 (1.45-3.55)]; and were more likely to have elevated FENO [4.38 (3.29-5.82)], allergen-specific [25.91 (10.53-63.80)] and total IgE (Table 6). Similar results were observed in the sub-group analysis of only children without asthma.

For urticarial rash, the statistically significant associated risk factors were a father's and mother's history of allergic disease, reported increased frequency of de-worming and of 'trucks passing on the street near home' in the last 12 months, but not SPT, asIgE and total IgE (Supplementary Table 4).

Other potential factors, including maternal smoking during pregnancy (3%), current smoking by anyone in the household (including the child, 11%), and breastfeeding history (74% of children breastfed to more than one year) were not associated with ARDs. Of the 1,700 children enrolled in the study and tested for HIV, only 12 were positive and all were already receiving the recommended antiretroviral therapy.

Accepted Article

This article is protected by copyright. All rights reserved

Discussion

We found extensive multi-morbidity and substantial overlap of the risk factors for rhinitis, allergic conjunctivitis, eczema, urticarial rash and atopic sensitisation among schoolchildren in urban Uganda. The most consistent risk factors included parental history of allergic disease, city residence at birth, current proximity to a busy road, frequent de-worming, positive SPT and elevated FENO, but not allergen specific-IgE or total IgE to crude allergen extracts.

We found that children born in the city (a proxy for mother's residence during pregnancy) were at a higher risk of ARDs than their counterparts born in the village. Of note, the schools were situated in an urban setting, and most of the schoolchildren enrolled were in the 'day section' of school and commuted daily within the study area (a predominantly urban setting). Thus current residence was considered as reasonably uniform, and urban. This highlights the importance of exposures in early life and is consistent with the observation that the prevalence of ARDs is higher among children in urban than rural areas in Africa[33] and other LMICs[11]. This observation is also consistent with studies from Europe and North America that report a lower risk of ARDs among children raised on farms (which are predominantly in rural areas), and this has been attributed to early life exposure to farm animals[14, 34]. However, we observed a positive association between reported early life exposure to farm animals and ARDs. This implies that the observed 'protective rural effect' in this setting could not be explained by exposure to farm animals, consistent with studies from other developing countries[35, 36].

We found a positive association between ARDs and positive SPT responses and with elevated FENO, which is consistent with underlying allergic inflammation that is common to these conditions[3, 4]. However, there was a lack of association between asIgE (to three crude allergen extracts) and rhinitis, conjunctivitis and eczema, despite the standard asIgE assessments and cut-off points used, and a strong association between asIgE and SPT reactivity. This lack of association may be explained, at least in part, by high levels of cross-reactive IgE to other environmental allergens, particularly to cross-reactive carbohydrate determinants[37], as reported by studies in Ghana[38]. Indeed, our recent work in Uganda

This article is protected by copyright. All rights reserved

showed that associations between asIgE or SPT sensitization and clinical allergy outcomes were weak among participants from rural, compared to urban, settings[39]. Rural residents had a higher prevalence of helminths - an important source of 'environmental' antigens[39]. Our observations are consistent with the ISAAC study, which reported a weaker association between ARDs and atopic sensitisation in LMICs than in HICs[12]. This weak/lack of association between ARDs and asIgE has important implications for diagnosis and treatment of these conditions in this setting: what proportion of these conditions are *allergic*, and, would immunotherapy or biologicals treat as effectively as in HICs? To answer these question would require the use of component-resolved diagnosis (using purified single protein allergens) to determine IgE sensitisation, with high cost implications that may be prohibitive for routine use in this setting.

The participant characteristics that were consistent across all ARDs were the reported high frequency of 'trucks on the street near home' and reported frequent use of de-worming medication. We think 'trucks near home' is a proxy for proximity to a busy road, and this has been previously found to be positively associated with ARDs[40, 41] and asthma morbidity[42], and this is probably related to increased pollution. Air pollution as a possible risk factor is further supported by our observation that children with current rhinitis were more likely to report indoor cooking with firewood/charcoal stove as main fuel sources, similar to a South African study[43]. With regards to the reported increased frequency of deworming among children with the different ARDs including asthma[13], we have no ready explanation. In Uganda, schoolchildren routinely receive mass drug administration with albendazole once a year, but in this study, children with ARDs were more likely to report being dewormed twice or more in the last one year. There was a trend towards low prevalence of helminths among children with ARDs but this was statistically significant for only 'rhinitis ever'. The inverse association between rhinitis and the tuberculin skin test has been reported previously in South Africa[44].

Among the study limitations, first, we performed standard tests for asIgE and total IgE on a randomly selected 400 schoolchildren, not the entire sample size of 1,700, limiting our power to detect weaker associations with rhinitis, conjunctivitis and eczema (we had good power to

This article is protected by copyright. All rights reserved

detect strong associations). Secondly, the average age of the participants was 10 years and as such, we could not obtain detailed information on some exposures in early life. Nevertheless, we highlight the importance of environmental exposures in early life in increasing the risk of ARDs in the urban setting. Thirdly, we acknowledge that estimates obtained by design weights tend to be less precise than the unweighted estimates from an unweighted study. Nevertheless, this statistical approach has enabled us to cost-effectively contribute valuable information on risk factors for ARDs from sub-Saharan Africa, using existing data from an asthma case-control study. Lastly, the variable 'father's (and mother's) history of allergy' included 'history of urticaria'. This may have reduced the overall effect sizes, because urticaria may not be comparable to other allergy outcomes. However, in terms of risk factors, we observed that overall, the risk factors associated with urticaria among children were similar to the risk factors associated with the other ARDs.

The strength of this study is the large sample size and the weighed analysis, which make our findings generalisable to schoolchildren in urban areas in Uganda, and probably in sub-Saharan Africa. The risk factors associated with rhinitis, conjunctivitis, eczema and atopic sensitisation (SPT) were similar to the risk factors for asthma reported in our earlier work[13], even in the subgroup analysis of children without asthma. Given the similarity in risk factors, and the extensive overlap of these ARDs among children, it is possible that these conditions have the same underlying cause and as such, should be investigated as one entity in population studies. Multi-morbidity of the ARDs has been extensively demonstrated in birth cohorts in HICs[6, 7, 45]. The hypothesis of shared underlying disease mechanisms for the different ARDs is supported by studies that show the role of shared genetic and environmental factors[46]. The specific shared early life lifestyle and environmental risk factors have not been identified, but there are important differences with findings from HICs: in LMICs setting, there is possibly a reduced role of asIgE and exposure to farm animals, an increased risk associated with higher parental education and socio-economic status[47], and urbanisation[9]. Investigating these differences will increase our understanding of underlying causes of all allergy-related diseases.

This article is protected by copyright. All rights reserved

Accepted Article

Conclusion

We found extensive multi-morbidity of, and overlap in the risk factors associated with, rhinitis, conjunctivitis, and eczema - similar to asthma risk factors - among schoolchildren in urban Uganda. This suggests a similar underlying cause for all ARDs, associated with early-life exposure to urban lifestyles and environment in Uganda. The rapid urbanisation and population growth in Africa provides an excellent opportunity to identify the specific cause. This calls for epidemiological research to investigate the causes of ARDs in urban Africa, as one disease entity.

Acknowledgements

Many thanks to the study participants, their parents, guardians and teachers for their enthusiasm and support during this study. We acknowledge the contribution of Ronald van Ree from Amsterdam University Medical Centers (AMC), The Netherlands, who worked with GN on the asIgE ImmunoCAP® assays. This study was funded by Wellcome (reference no. 102512 Training fellowship to HM; 204928/Z/16/Z Institutional Strategic Support Fund to HM; 095778 Senior fellowship to AE), European Research Council (reference no. 668954 to NP), African Partnership for Chronic Disease Research (to GN) and UK Medical Research Council (reference no. MR/K012126/1 to EW).

This article is protected by copyright. All rights reserved

References

1. Asher MI, Montefort S, Bjorksten 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 (London, England)* 2006; **368**(9537): 733-43.
2. Bjorksten B, Clayton T, Ellwood P, Stewart A, Strachan D. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* 2008; **19**(2): 110-24.
3. Pawankar R, Canonica G, Holgate S, Lockey R, Blaiss M. WAO white book on allergy: update 2013. *World Allergy Organization* 2013: 11-9.
4. Akdis CA, Agache I. Global atlas of allergy: European Academy of Allergy and Clinical Immunology; 2014.
5. Davies E, Rogers NK, Lloyd-Lavery A, Grindlay DJC. What's new in atopic eczema? An analysis of systematic reviews published in 2015. Part 1: epidemiology and methodology. 2018; **43**(4): 375-9.
6. Pinart M, Benet M, Annesi-Maesano I, et al. Comorbidity of eczema, rhinitis, and asthma in IgE-sensitised and non-IgE-sensitised children in MeDALL: a population-based cohort study. *The Lancet Respiratory Medicine* 2014; **2**(2): 131-40.
7. Gough H, Grabenhenrich L, Reich A, et al. Allergic multimorbidity of asthma, rhinitis and eczema over 20 years in the German birth cohort MAS. *Pediatric Allergy and Immunology* 2015; **26**(5): 431-7.
8. Robinson CL, Baumann LM, Romero K, et al. Effect of urbanisation on asthma, allergy and airways inflammation in a developing country setting. *Thorax* 2011; **66**(12): 1051-7.

Accepted Article

This article is protected by copyright. All rights reserved

9. Morgan BW, Siddharthan T, Grigsby MR, et al. Asthma and Allergic Disorders in Uganda: A Population-Based Study Across Urban and Rural Settings. *The journal of allergy and clinical immunology In practice* 2018.

10. Botha M, Basera W, Facey-Thomas HE, et al. Nutrition and allergic diseases in urban and rural communities from the South African Food Allergy cohort. *Pediatric Allergy and Immunology* 2019; **30**(5): 511-21.

11. Gaviola C, Miele CH, Wise RA, et al. Urbanisation but not biomass fuel smoke exposure is associated with asthma prevalence in four resource-limited settings. *Thorax* 2016; **71**(2): 154-60.

12. Weinmayr G, Weiland SK, Bjorksten B, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med* 2007; **176**(6): 565-74.

13. Mpairwe H, Namutebi M, Nkurunungi G, et al. Risk factors for asthma among schoolchildren who participated in a case-control study in urban Uganda. *eLife* 2019; **8** **e49496**.

14. Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2000; **30**(2): 187-93.

15. Timm S, Frydenberg M, Janson C, et al. The Urban-Rural Gradient In Asthma: A Population-Based Study in Northern Europe. *International journal of environmental research and public health* 2015; **13**(1): 93.

16. Christensen SH, Timm S, Janson C, et al. A clear urban-rural gradient of allergic rhinitis in a population-based study in Northern Europe. *European clinical respiratory journal* 2016; **3**: 33463.

Accepted Article

This article is protected by copyright. All rights reserved

17. Parsons MA, Beach J, Senthilselvan A. Association of living in a farming environment with asthma incidence in Canadian children. *The Journal of asthma : official journal of the Association for the Care of Asthma* 2017; **54**(3): 239-49.

18. Lewis KM, Ruiz M, Goldblatt P, et al. Mother's education and offspring asthma risk in 10 European cohort studies. *European journal of epidemiology* 2017; **32**(9): 797-805.

19. Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality: United States, 2005-2009. *National health statistics reports* 2011; (32): 1-14.

20. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. *International Journal of Surgery* 2014; **12**(12): 1495-9.

21. Mpairwe H, Tumwesige P, Namutebi M, et al. Asthma control and management among schoolchildren in urban Uganda: results from a cross-sectional study [version 1; peer review: 1 approved with reservations]. *Wellcome Open Research* 2019; **4**(168).

22. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *The European respiratory journal* 1995; **8**(3): 483-91.

23. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW. The international study of asthma and allergies in childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis* 2005; **9**(1): 10-6.

24. Mpairwe H, Muhangi L, Ndibazza J, et al. Skin prick test reactivity to common allergens among women in Entebbe, Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2008; **102**(4): 367-73.

25. http://www.phadia.com/da/Products/Allergy-testing-products/ImmunoCAP-Lab-Tests/sIgE/.

Accepted Article

This article is protected by copyright. All rights reserved

26. Nkurunungi G, Lutangira JE, Lule SA, et al. Determining Mycobacterium tuberculosis Infection among BCG-Immunised Ugandan Children by T-SPOT.TB and Tuberculin Skin Testing. *PLoS ONE* 2012; **7**(10).

27. Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick-smear technique in Schistosomiasis mansoni. *Rev Inst Med Trop Sao Paulo* 1972; **14**(6): 397-400.

28. Ministry of Health Uganda. National HIV Testing Services Policy and Implementation Guidelines Uganda, 2016.

29. Mansournia MA, Altman DG. Inverse probability weighting. *BMJ (Clinical research ed)* 2016; **352**: i189.

30. Kirenga BJ, de Jong C, Katagira W, et al. Prevalence and factors associated with asthma among adolescents and adults in Uganda: a general population based survey. *BMC public health* 2019; **19**(1): 227.

31. Greenland S, Daniel R, Pearce N. Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. *International journal of epidemiology* 2016; **45**(2): 565-75.

32. Mpairwe Harriet, Emily WL. SONA project - Risk factors for allergy-related diseases among schoolchildren in Uganda. London School of Hygiene & Tropical Medicine, London, United Kingdom; 2020.

33. Botha M, Basera W, Facey-Thomas HE, Gaunt B, Genuneit J. Nutrition and allergic diseases in urban and rural communities from the South African Food Allergy cohort. 2019.

34. Lampi J, Canoy D, Jarvis D, et al. Farming environment and prevalence of atopy at age 31: prospective birth cohort study in Finland. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2011; **41**(7): 987-93.

35. Ma Y, Zhao J, Han ZR, Chen Y, Leung TF, Wong GW. Very low prevalence of asthma and allergies in schoolchildren from rural Beijing, China. *Pediatric pulmonology* 2009; **44**(8): 793-9.

Accepted Article

This article is protected by copyright. All rights reserved

36. Brunekreef B, Von Mutius E, Wong GK, Odhiambo JA, Clayton TO. Early life exposure to farm animals and symptoms of asthma, rhinoconjunctivitis and eczema: an ISAAC Phase Three Study. *International journal of epidemiology* 2012; **41**(3): 753-61.

37. Nkurunungi G, Mpairwe H, Versteeg SA, et al. Cross-reactive carbohydrate determinant-specific IgE obscures true atopy and exhibitsα-1, 3-fucose epitope-specific inverse associations with asthma. *Allergy* 2020.

38. Amoah AS, Obeng BB, Larbi IA, et al. Peanut-specific IgE antibodies in asymptomatic Ghanaian children possibly caused by carbohydrate determinant cross-reactivity. *The Journal of allergy and clinical immunology* 2013; **132**(3): 639-47.

39. Nkurunungi G, Lubyayi L, Versteeg SA, et al. Do helminth infections underpin urban-rural differences in risk factors for allergy-related outcomes? *Clinical & Experimental Allergy* 2019; **49**(5): 663-76.

40. Shirinde J, Wichmann J, Voyi K. Allergic rhinitis, rhinoconjunctivitis and hayfever symptoms among children are associated with frequency of truck traffic near residences: a cross sectional study. *Environmental health : a global access science source* 2015; **14**: 84.

41. Venn A, Yemaneberhan H, Lewis S, Parry E, Britton J. Proximity of the home to roads and the risk of wheeze in an Ethiopian population. *Occupational and environmental medicine* 2005; **62**(6): 376-80.

42. Hauptman M, Gaffin JM, Petty CR, et al. Proximity to major roadways and asthma symptoms in the School Inner-City Asthma Study. *The Journal of allergy and clinical immunology* 2020; **145**(1): 119-26.e4.

43. Bidassey-Manilal S, Mbonane TP, Rathebe PC, Senekane MF. Household Fuel Use and Prevalence of Self-reported Allergic Rhinitis in Rural Areas of Mpumalanga, South Africa. 2019 Open Innovations (OI); 2019 2-4 Oct. 2019; 2019. p. 241-6.

Accepted Article

This article is protected by copyright. All rights reserved

44. Obihara CC, Kimpen JL, Gie RP, et al. Mycobacterium tuberculosis infection may protect against allergy in a tuberculosis endemic area. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology* 2006; **36**(1): 70-6.

45. Ballardini N, Kull I, Lind T, et al. Development and comorbidity of eczema, asthma and rhinitis to age 12: data from the BAMSE birth cohort. *Allergy* 2012; **67**(4): 537-44.

46. Khan SJ, Dharmage SC, Matheson MC, Gurrin LC. Is the atopic march related to confounding by genetics and early-life environment? A systematic review of sibship and twin data. *Allergy* 2018; **73**(1): 17-28.

47. Mercer MJ, Joubert G, Ehrlich RI, et al. Socioeconomic status and prevalence of allergic rhinitis and atopic eczema symptoms in young adolescents. *Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology* 2004; **15**(3): 234-41.

Accepted Article

This article is protected by copyright. All rights reserved

Table 1: Weighted prevalence of allergy-related diseases among schoolchildren in Uganda (N=1,700)

Allergy-related diseases (ARDs)	Ever		Last 12 months	
	n	Weighted %	n	Weighted %
1. Overall,				
Rhinitis	870	43.3	216	10.1
Allergic conjunctivitis	772	39.5	179	9.1
Eczema	265	13.5	60	2.3
Urticarial rash	572	31.9	36	1.8
2. ARDs overlap,				
None (of the four ARDs)	498	38.8	959	74.8
Asthma only	60	1.3	388	8.3
Rhinitis only	171	13.3	63	4.9
Conjunctivitis only	144	11.2	59	4.6
Eczema only	27	2.1	16	1.3
2 ARDS	396	21.6	134	4.5
3 ARDs	308	9.9	63	1.4
4 ARDs	87	1.8	7	0.2
Total	1691[a]	100	1689[b]	100

N=number, %=percentage. Missing numbers: [a]=9, [b]=11. Overall, 1,193 (61.2%) reported at least one ARD ever, and 730 (25.2%) in the last 12 months

Accepted Article

This article is protected by copyright. All rights reserved

Table 2: Risk factors for current rhinitis among Ugandan schoolchildren (N=1,691)

Characteristics	Rhinitis, last 12-months		Adj. OR‡ (95% CI)	P-value
	Yes (N=216)	**No** (N=1,475)		
Age, years Mean (SD)	11.71	11.00	1.05 (0.99-1.12)	0.10
Girls (941)	122 (56.5)	819 (55.5)	0.88 (0.62-1.23)	0.45
Father's history of allergic disease [m=149]				
Yes (363)	80 (41.4)	283 (21.0)	2.62 (1.79-3.83)	<0.0001
Mother's history of allergic disease [m=126]				
Yes (592)	102 (51.8)	490 (35.8)	2.12 (1.48-3.02)	<0.0001
Area of residence at the time of the child's birth [m=1]				
Rural (354)	33 (15.3)	321 (21.8)	1	
Town (1,187)	154 (71.3)	1,033 (70.1)	1.49 (0.95-2.34)	
City (149)	29 (13.4)	120 (8.1)	2.66 (1.42-4.99)[a]	0.01
Child's area of residence in first five years of life [m=1]				
Rural (339)	28 (13.0)	311 (21.1)	1	
Town (1,265)	174 (80.5)	1,091 (74.0)	1.91 (1.19-3.06)	
City (86)	14 (6.5)	72 (4.9)	1.99 (0.86-4.60)[b]	0.03
Exposure to animals in first five years of life [m=58]				
Yes (614)	90 (43.1)	524 (36.8)	1.43 (1.00-2.05)	0.05
Frequency of 'trucks passing on street near child's home' at enrolment [m=1]				
Rarely (943)	108 (50.0)	835 (56.6)	1	
Frequently (624)	79 (36.6)	545 (37.0)	1.03 (0.71-1.48)	
Almost all the time (123)	29 (13.4)	94 (6.4)	2.59 (1.48-4.52)[c]	0.003
Main source of fuel used for indoor cooking [m=1]				
No indoor cooking (394)	33 (15.3)	361 (24.5)	1	
Firewood/charcoal stove (906)	144 (66.6)	762 (51.7)	2.46 (1.53-3.97)	
Paraffin stove (145)	14 (6.5)	131 (8.9)	1.47 (0.68-3.18)	
Electricity or gas (245)	25 (11.6)	220 (14.9)	1.13 (0.59-2.17)	0.0007
Use of de-worming medication in last 12 months [m=2]				

Accepted Article

This article is protected by copyright. All rights reserved

None (577)	63 (29.3)	514 (34.9)	1	
Once (732)	79 (36.7)	653 (44.3)	1.02 (0.68-1.53)	
>Twice (380)	73 (34.0)	307 (20.8)	2.01 (1.30-3.11)[d]	0.002
Any helminth infection at enrolment [m=130]				
Yes (212)	23 (11.5)	189 (13.9)	0.86 (0.50-1.47)	0.58
Tuberculin skin test induration at enrolment [N=960]				
Positive (>10mm) (143)	19 (15.4)	124 (14.8)	0.74 (0.39-1.40)	0.36
Skin Prick Test response to any of 7 allergens at enrolment [m=36]				
Positive (>3mm) (657)	108 (51.4)	549 (38.0)	1.54 (1.09-2.18)	0.01
Fractional exhaled nitric oxide levels at enrolment [m=80]				
Elevated (>35ppb) (381)	75 (34.9)	306 (21.9)	1.66 (1.14-2.40)	0.007
Allergen-specific IgE at enrolment (N=397)[§]				
Atopic (>0.35 kU_A/L) (251)	38 (70.4)	213 (62.1)	1.38 (0.60-3.15)	0.45
Total IgE (N=398) Median (95%CI) kU/L	468.2 (178.0-828.7)	330.5 (271.5-410.7)	1.0001 (0.9998-1.0003)	0.61

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%). [‡]Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-valve: [a]=0.08; [b]=0.004; [c]=0.006; [d]=0.02; [e]=0.005. [§]ImmunoCAP® cut-off >0.35kU_A/L.

Accepted Article

This article is protected by copyright. All rights reserved

Table 3: Risk factors for allergic conjunctivitis among schoolchildren in Uganda (N=1,691)

Characteristics	Conjunctivitis ever		Adj. OR‡ (95% CI)	P-value
	Yes (N=772)	**No** (N=919)		
Age, years Mean (SD)	11.45 (3.10)	10.80 (3.12)	1.06 (1.02-1.10)	0.002
Girls (942)	430 (55.7)	512 (55.7)	1.02 (0.82-1.27)	0.83
Father's education [m=20]				
None/Primary (437)	172 (22.4)	265 (29.3)	1	
Secondary (595)	284 (37.1)	311 (34.4)	1.28 (0.97-1.69)	
Tertiary (639)	310 (40.5)	329 (36.3)	1.35 (1.03-1.79)[a]	0.08
Father's history of allergic disease [m=148]				
Yes (363)	222 (31.2)	141 (17.0)	2.06 (1.56-2.71)	<0.0001
Mother's history of allergic disease [m=125]				
Yes (592)	315 (43.4)	277 (32.9)	1.57 (1.24-1.98)	<0.0001
Area of residence at the time of the child's birth				
Rural (354)	158 (20.5)	196 (21.3)	1	
Town (1,188)	523 (67.7)	665 (72.4)	0.89 (0.68-1.16)	
City (149)	91 (11.8)	58 (6.3)	1.69 (1.09-2.64)[b]	0.006
Exposure to animals in first five years of life [m=58]				
Yes (615)	296 (39.7)	319 (35.9)	1.33 (1.05-1.67)	0.02
Frequency of 'trucks passing on street near child's home' at enrolment				
Rarely (944)	411 (53.2)	533 (58.0)	1	
Frequently (624)	290 (37.6)	334 (36.3)	1.06 (0.84-1.34)	
Almost all the time (123)	71 (9.2)	53 (5.7)	1.60 (1.03-2.48)[c]	0.05
Use of de-worming medication in last 12months [m=1]				
None (578)	228 (29.6)	350 (38.1)	1	
Once (732)	320 (41.5)	412 (44.8)	1.09 (0.85-1.40)	
>Twice (380)	223 (28.9)	157 (17.1)	1.94 (1.44-2.63)[d]	<0.0001
Any helminth infection at enrolment [m=129]				
Yes (212)	87 (12.1)	125 (14.8)	0.88 (0.63-1.22)	0.44

Accepted Article

This article is protected by copyright. All rights reserved

Tuberculin skin test induration at enrolment [N=960]				
Positive (>10mm) (143)	58 (13.9)	85 (15.6)	0.68 (0.45-1.05)	0.08
Skin Prick Test response to any of 7 allergens at enrolment [m=35]				
Positive (>3mm) (657)	368 (48.9)	289 (32.0)	1.76 (1.40-2.21)	<0.0001
Fractional exhaled nitric oxide levels at enrolment [m=79]				
Elevated (>35ppb) (381)	227 (30.2)	154 (17.9)	1.57 (1.20-2.05)	0.001
Allergen-specific IgE at enrolment (N=397)[§]				
Atopic (>0.35 kU_A/L) (251)	136 (67.3)	155 (59.0)	1.22 (0.75-1.98)	0.41
Total IgE at enrolment (N=398)				
Median (95%CI) kU/L	335.2 (250.7-457.6)	335.8 (270.9-420.0)	0.9999 (0.9997-1.0001)	0.28

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%), unless stated otherwise. [‡]Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-value: [a]=0.03; [b]=0.22; [c]=0.09; [d]<0.0001[§] ImmunoCAP®, cut-off >0.35 kU_A/L.

Accepted Article

This article is protected by copyright. All rights reserved

Table 4: Risk factors for eczema among schoolchildren in Uganda (N=1,691)

Characteristics	Eczema ever		Adj. OR‡ (95% CI)	P-value
	Yes (N=265)	**No** (N=1,426)		
Age, years Mean (SD)	11.55 (3.20)	11.02 (3.11)	1.06 (1.01-1.12)	0.01
Girls (942)	161 (60.7)	781 (54.8)	1.24 (0.92-1.69)	0.16
Father's history of allergic disease [m=148]				
Yes (363)	87 (34.8)	276 (21.3)	2.19 (1.56-3.09)	<0.0001
Mother's history of allergic disease [m=125]				
Yes (592)	124 (49.6)	468 (35.6)	1.94 (1.42-2.67)	<0.0001
Area of residence at the time of the child's birth				
Rural (354)	60 (22.6)	294 (20.6)	1	
Town (1,188)	168 (63.4)	1,020 (71.5)	0.81 (0.56-1.17)	
City (149)	37 (14.0)	112 (7.9)	1.55 (0.91-2.63)[a]	0.03
Frequency of 'trucks passing on street near child's home' at enrolment				
Rarely (944)	137 (51.7)	807 (56.6)	1	
Frequently (624)	96 (36.2)	528 (37.0)	1.14 (0.82-1.59)	
Almost all the time (123)	32 (12.1)	91 (6.4)	1.94 (1.14-3.32)[b]	0.05
Use of de-worming medication in last 12months [m=1]				
None (578)	84 (31.7)	494 (34.7)	1	
Once (732)	97 (36.6)	635 (44.5)	0.89 (0.62-1.27)	
>Twice (380)	84 (31.7)	296 (20.8)	1.63 (1.10-2.43)[c]	0.006
Any helminth infection† at enrolment [m=129]				
Yes (212)	28 (11.2)	184 (14.0)	0.76 (0.47-1.25)	0.28
Skin Prick Test response to any of 7 allergens at enrolment [m=35]				
Positive (>3mm) (657)	121 (46.0)	536 (38.5)	1.26 (0.92-1.72)	0.15
Allergen-specific IgE at enrolment (N=397)§				
Atopic (>0.35 kU_A/L) (251)	48 (73.8)	203 (61.1)	1.41 (0.69-2.88)	0.34
Total IgE at enrolment (N=398)				
Median (95%CI) kU/L	431.4 (183.7-	335.4 (274.0-	1.00 (0.9998-1.0002)	0.94

Accepted Article

This article is protected by copyright. All rights reserved

	639.4)	413.5)		

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%), unless stated otherwise. ‡Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-value: [a]=0.50; [b]=0.04; [c]=0.04. §ImmunoCAP®, cut-off >0.35 kU_A/L.

Accepted Article

This article is protected by copyright. All rights reserved

Table 5: Risk factors for having ever had any of rhinitis, conjunctivitis, eczema and asthma among Ugandan schoolchildren (N=1,693)

Characteristics	Allergy-related diseases – ever		Adj. OR‡ (95% CI)	P-value
	Yes (N=1,195)	**No** (N=498)		
Age, years Mean (SD)	11.29	10.64	1.06 (1.02-1.10)	0.003
Girls (942)	680 (56.9)	262 (52.6)	1.28 (1.02-1.61)	0.03
Father's history of allergic disease [m=150]				
Yes (363)	313 (28.5)	50 (11.2)	2.64 (1.89-3.70)	<0.0001
Mother's history of allergic disease [m=127]				
Yes (592)	483 (43.1)	109 (24.4)	2.21 (1.70-2.86)	<0.0001
Area of residence at the time of the child's birth [m=1]				
Rural (355)	234 (19.6)	121 (24.3)	1	
Town (1,188)	835 (69.9)	353 (70.9)	1.06 (0.81-1.40)	
City (149)	125 (10.5)	24 (4.8)	2.12 (1.26-3.57)[a]	0.01
Exposure to animals in first five years of life [m=60]				
Yes (615)	454 (39.2)	161 (33.8)	1.41 (1.11-1.80)	0.005
Frequency of 'trucks passing on street near child's home' at enrolment [m=1]				
Rarely (945)	626 (52.4)	319 (64.1)	1	
Frequently (624)	464 (38.9)	160 (32.1)	1.40 (1.10-1.78)	
Almost all the time (123)	104 (8.7)	19 (3.8)	2.18 (1.25-3.78)[b]	0.001
Use of de-worming medication in last 12 months [m=3]				
None (578)	384 (32.2)	194 (39.0)	1	
Once (732)	491 (41.2)	241 (48.4)	0.95 (0.75-1.22)	
>Twice (380)	317 (26.6)	63 (12.6)	2.12 (1.51-2.99)[c]	<0.0001
Any helminth infection at enrolment [m=130]				
Yes (212)	133 (12.0)	79 (17.3)	0.73 (0.53-1.02)	0.06
Tuberculin skin test induration at enrolment [N=961]				
Positive (>10mm) (143)	88 (13.1)	55 (19.0)	0.60 (0.39-0.90)	0.01
Skin Prick Test response to any of 7 allergens at enrolment [m=36]				

Accepted Article

This article is protected by copyright. All rights reserved

Positive (>3mm) (657)	529 (45.2)	128 (26.3)	1.91 (1.49-2.46)	<0.0001
Fractional exhaled nitric oxide levels at enrolment [m=80]				
Elevated (>35ppb) (381)	321 (27.7)	60 (13.2)	1.92 (1.40-2.64)	<0.0001
Allergen-specific IgE at enrolment (N=398)[§]				
Atopic (>0.35 kU_A/L) (252)	203 (67.2)	49 (51.0)	1.54 (0.92-2.56)	0.10
Total IgE (N=398) Median (95%CI) kU/L	348.2 (279.9-465.3)	310.0 (187.6-381.5)	0.9998 (0.9996-1.0001)	0.22

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%), unless stated otherwise. [‡]Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-valve: [a]=0.02; [b]<0.0001; [c]<0.0001. [§] ImmunoCAP, cut-off >0.35 kU_A/L.

Accepted Article

This article is protected by copyright. All rights reserved

Table 6: Risk factors for skin prick test reactivity among schoolchildren in Uganda (N=1,661)

Characteristics	Skin prick test[#]		Adj. OR[‡] (95% CI)	P-value
	Pos. (N=658)	**Neg.** (N=1,003)		
Age, years Mean (SD)	11.18 (3.10)	11.08 (3.14)	1.03 (1.00-1.07)	0.08
Girls (930)	308 (46.8)	622 (62.0)	0.57 (0.45-0.71)	<0.0001
Father's highest education level [m=25]				
None/Primary (425)	147 (22.5)	278 (28.3)	1	
Secondary (585)	215 (32.9)	370 (37.6)	0.92 (0.68-1.23)	
Tertiary (626)	291 (44.6)	335 (34.1)	1.36 (1.02-1.81)[a]	0.01
Mother's highest education level [m=26]				
None/Primary (569)	186 (28.5)	383 (39.0)	1	
Secondary (590)	229 (35.1)	361 (36.8)	1.26 (0.96-1.64)	
Tertiary (476)	238 (36.4)	238 (24.2)	1.72 (1.29-2.30)[b]	0.001
Father's history of allergic disease [m=125]				
Yes (356)	178 (29.2)	178 (19.7)	1.41 (1.06-1.87)	0.02
Mother's history of allergic disease [m=95]				
Yes (577)	264 (39.7)	331 (36.1)	1.28 (1.00-1.63)	0.05
Area of residence at the time of the child's birth [m=4]				
Rural (348)	113 (17.2)	235 (23.5)	1	
Town (1,164)	467 (71.1)	697 (69.7)	1.19 (0.89-1.59)	
City (145)	77 (11.7)	68 (6.8)	1.83 (1.17-2.86)[c]	0.03
Frequency of 'trucks passing on street near child's home' at enrolment [m=4]				
Rarely (923)	340 (51.8)	583 (58.3)	1	
Frequently (615)	255 (38.8)	360 (36.0)	1.21 (0.95-1.54)	
Almost all the time (119)	62 (9.4)	57 (5.7)	2.26 (1.45-3.55)[d]	0.001
Use of de-worming medication in last 12months [m=6]				
None (572)	221 (33.6)	351 (35.2)	1	
Once (713)	281 (42.8)	432 (43.3)	0.97 (0.75-1.25)	
>Twice (370)	155 (23.6)	215 (21.5)	0.87 (0.64-1.19)[e]	0.68

Accepted Article

This article is protected by copyright. All rights reserved

Any helminth infection† at enrolment [m=119]				
Yes (211)	73 (11.9)	138 (14.8)	0.76 (0.54-1.08)	0.13
Fractional exhaled nitric oxide levels at enrolment [m=74]				
Elevated (>35ppb) (380)	261 (41.3)	119 (12.5)	4.38 (3.29-5.82)	<0.0001
Allergen-specific IgE at enrolment (N=395)§				
Atopic (>0.35 kU_A/L) (251)	156 (94.5)	95 (41.3)	25.91 (10.53-63.80)	<0.0001
Total IgE at enrolment (N=396)				
Median (95%CI) kU/L	733.2 (587.6-892.7)	179.0 (123.1-238.7)	1.0004 (1.0001-1.0008)	0.01

N=number; Pos=positive; Neg=Negative; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%), unless stated otherwise. #whole allergen extracts of *Blomia tropicalis*, Dermatophagoides mix, cockroach, peanut, cat, weeds pollen mix, and mould mix. ‡Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-value: [a]=0.03; [b]=<0.0001; [c]=0.02; [d]=0.001; [e]=0.43. §3 allergen extracts (Dermatophagoides, cockroach and peanut), using ImmunoCAP® on a random sample of 400; standard cut-off >0.35 kU_A/L.

Accepted Article

This article is protected by copyright. All rights reserved

Supplementary Table 1: Risk factors for rhinitis among schoolchildren in Uganda (N=1,692)

Characteristics	Rhinitis ever		Adj. OR‡ (95% CI)	P-value
	Yes (N=870)	**No** (N=822)		
Age, years Mean (SD)	11.51 (3.12)	10.65 (3.08)	1.08 (1.04-1.12)	<0.0001
Girls (942)	511 (58.7)	431 (52.4)	1.39 (1.12-1.74)	0.003
Father's education [m=21]				
None/Primary (437)	198 (22.9)	239 (29.6)	1	
Secondary (595)	307 (35.6)	288 (35.6)	1.14 (0.87-1.50)	
Tertiary (639)	358 (41.5)	281 (34.8)	1.37 (1.03-1.80)[a]	0.08
Father's history of allergic disease [m=149]				
Yes (363)	242 (30.1)	121 (16.4)	2.08 (1.57-2.75)	<0.0001
Mother's history of allergic disease [m=126]				
Yes (592)	384 (46.9)	208 (27.8)	2.29 (1.81-2.91)	<0.0001
Area of residence at the time of the child's birth [m=1]				
Rural (354)	159 (18.3)	195 (23.7)	1	
Town (1,188)	612 (70.3)	576 (70.2)	1.22 (0.93-1.60)	
City (149)	99 (11.4)	50 (6.1)	1.97 (1.26-3.10)[b]	0.01
Exposure to animals in first five years of life [m=57]				
Yes (615)	331 (39.2)	284 (36.0)	1.23 (0.98-1.55)	0.07
Frequency of 'trucks passing on street near child's home' at enrolment [m=1]				
Rarely (944)	442 (50.9)	501 (61.0)	1	
Frequently (624)	346 (39.8)	278 (33.9)	1.42 (1.13-1.79)	
Almost all the time (123)	81 (9.3)	42 (5.1)	1.90 (1.19-3.03)[c]	0.001
Use of de-worming medication in last 12 months [m=1]				
None (578)	276 (31.8)	302 (36.8)	1	
Once (732)	345 (39.7)	387 (47.1)	0.85 (0.67-1.09)	
≥Twice (380)	248 (28.5)	132 (16.1)	1.80 (1.32-2.45)[d]	<0.0001
Any helminth infection at enrolment [m=130]				
Yes (212)	90 (11.2)	122 (16.0)	0.70 (0.50-0.97)	0.03
Tuberculin skin test induration at enrolment [N=960]				
Positive (≥10mm) (143)	66 (13.4)	77 (16.4)	0.66 (0.44-1.01)	0.05
Skin Prick Test response to any of 7 allergens at enrolment [m=36]				
Positive (≥3mm) (657)	392 (45.8)	265 (33.1)	1.56 (1.24-1.96)	<0.0001
Fractional exhaled nitric oxide levels at enrolment [m=80]				
Elevated (≥35ppb) (381)	254 (30.2)	127 (16.4)	2.06 (1.57-2.70)	<0.0001
Allergen-specific IgE to any of 3 allergens at enrolment (N=397)[§]				
Atopic (≥0.35 kU_A/L) (251)	142 (66.4)	109 (59.6)	1.33 (0.81-2.18)	0.26
Total IgE (N=398) Median (95%CI) kU/L	414.8 (281.1-537.5)	304.3 (213.6-359.3)	1.00002 (0.99983-1.00020)	0.87

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%), unless stated otherwise. ‡Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-value: [a]=0.03; [b]=0.006; [c]<0.0001; [d]=0.002. § ImmunoCAP®, cut-off ≥0.35 kU_A/L.

Supplementary Table 2: Risk factors for currently having any of rhinitis, conjunctivitis, eczema and asthma among Ugandan schoolchildren (N=1,693)

Characteristics	Allergy-related disease in last 12-months		Adj. OR‡ (95% CI)	P-value
	Yes (N=734)	**No** (N=959)		
Age, years Mean (SD)	11.34	10.91	1.05 (1.01-1.09)	0.01
Girls (942)	388 (52.9)	554 (57.8)	0.83 (0.66-1.03)	0.09
Father's history of allergic disease [m=150]				
Yes (363)	217 (32.2)	146 (16.8)	2.06 (1.57-2.70)	<0.0001
Mother's history of allergic disease [m=128]				
Yes (592)	312 (45.3)	280 (31.9)	1.66 (1.31-2.11)	<0.0001
Area of residence at the time of the child's birth [m=1]				
Rural (355)	117 (16.0)	238 (24.8)	1	
Town (1,188)	531 (72.4)	657 (68.5)	1.32 (0.99-1.77)	
City (149)	85 (11.6)	64 (6.7)	1.91 (1.22-2.99)[a]	0.01
Child's area of residence in first five years of life [m=1]				
Rural (339)	110 (15.0)	229 (23.9)	1	
Town (1,267)	570 (77.8)	697 (72.7)	1.41 (1.04-1.89)	
City (86)	53 (7.2)	33 (3.4)	1.78 (1.03-3.06)[b]	0.04
Exposure to animals in first five years of life [m=60]				
Yes (615)	276 (38.8)	339 (36.8)	1.45 (1.14-1.84)	0.002
Frequency of 'trucks passing on street near child's home' at enrolment [m=1]				
Rarely (945)	370 (50.5)	575 (60.0)	1	
Frequently (624)	287 (39.1)	337 (35.1)	1.18 (0.93-1.49)	
Almost all the time (123)	76 (10.4)	47 (4.9)	2.15 (1.38-3.35)[c]	0.003
Use of de-worming medication in last 12 months [m=3]				
None (578)	210 (28.7)	368 (38.4)	1	
Once (732)	304 (41.6)	428 (44.6)	1.16 (0.89-1.50)	
≥Twice (380)	217 (29.7)	163 (17.0)	1.87 (1.38-2.53)[d]	0.0002
Any helminth infection at enrolment [m=130]				
Yes (212)	78 (11.5)	134 (15.1)	0.87 (0.61-1.24)	0.45
Skin Prick Test response to any of 7 allergens at enrolment [m=36]				
Positive (≥3mm) (657)	364 (50.6)	293 (31.3)	1.70 (1.35-2.14)	<0.0001
Fractional exhaled nitric oxide levels at enrolment [m=80]				
Elevated (≥35ppb) (381)	238 (33.2)	143 (16.0)	1.99 (1.53-2.59)	<0.0001
Allergen-specific IgE at enrolment (N=398)§				
Atopic (≥0.35 kU_A/L) (252)	159 (71.3)	93 (53.1)	1.85 (1.14-3.01)	0.01
Total IgE (N=398) Median (95%CI) kU/L	432.4 (306.5-595.7)	274.9 (207.4-339.7)	1.0001 (0.9999-1.0003)	0.23

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%), unless stated otherwise. [‡]Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-valve: [a]=0.004; [b]=0.01; [c]=0.002; [d]<0.0001. [§]ImmunoCAP® cut-off ≥0.35 kU_A/L.

Supplementary Table 3: Risk factors for having ever had any of rhinitis, conjunctivitis and eczema among Ugandan schoolchildren without asthma (N=1,132)

Characteristics	Allergy-related disease ever		Adj. OR‡ (95% CI)	P-value
	Yes (N=634)	**No** (N=498)		
Age, years Mean (SD)	11.19	10.64	1.05 (1.01-1.09)	0.02
Girls (646)	384 (60.6)	262 (52.6)	1.37 (1.07-1.75)	0.01
Father's education [m=17]				
None/Primary (338)	183 (29.2)	155 (31.8)	1	
Secondary (401)	231 (36.8)	170 (34.8)	1.13 (0.84-1.51)	
Tertiary (376)	213 (34.0)	163 (33.4)	1.16 (0.32-1.00)[a]	0.61
Father's history of allergic disease [m=113]				
Yes (188)	138 (24.0)	50 (11.2)	2.44 (1.71-3.48)	<0.0001
Mother's history of allergic disease [m=95]				
Yes (346)	237 (40.1)	109 (24.4)	2.10 (1.59-2.77)	<0.0001
Area of residence at the time of the child's birth				
Rural (280)	159 (25.1)	121 (24.3)	1	
Town (772)	419 (66.1)	353 (70.9)	0.96 (0.72-1.27)	
City (80)	56 (8.8)	24 (4.8)	1.88 (1.09-3.25)[b]	0.02
Exposure to animals in first five years of life [m=46]				
Yes (426)	265 (43.4)	161 (33.8)	1.49 (1.15-1.93)	0.002
Frequency of 'trucks passing on street near child's home' at enrolment				
Rarely (676)	357 (56.3)	319 (64.1)	1	
Frequently (392)	232 (36.6)	160 (32.1)	1.30 (1.01-1.69)	
Almost all the time (64)	45 (7.1)	19 (3.8)	1.92 (1.08-3.42)[c]	0.02
Use of de-worming medication in last 12 months [m=1]				
None (427)	233 (36.8)	194 (39.0)	1	
Once (500)	259 (40.9)	241 (48.4)	0.90 (0.69-1.17)	
≥Twice (204)	141 (22.3)	63 (12.6)	1.91 (1.33-2.74)[d]	0.0001
Any helminth infection at enrolment [m=87]				
Yes (157)	78 (13.2)	79 (17.3)	0.76 (0.53-1.07)	0.12
Skin Prick Test response to any of 7 allergens at enrolment [m=26]				
Positive (≥3mm) (354)	226 (36.4)	128 (26.3)	1.66 (1.27-2.17)	<0.0001
Fractional exhaled nitric oxide levels at enrolment [m=66]				
Elevated (≥35ppb) (181)	121 (19.8)	60 (13.2)	1.61 (1.14-2.27)	0.007
Allergen-specific IgE at enrolment (N=199)§				
Atopic (≥0.35 kU_A/L) (109)	58 (56.3)	49 (51.0)	1.20 (0.68-2.14)	0.53
Total IgE (N=398) Median (95%CI) kU/L	234.8 (178.3-328.5)	310.0 (187.6-381.5)	0.9997 (0.9994-1.0000)	0.06

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%). ‡Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-valve: [a]=0.76; [b]=0.17; [c]=0.005; [d]=0.006. §ImmunoCAP® cut-off $\geq$0.35 kU_A/L.

Supplementary Table 4: Risk factors for urticarial rash among schoolchildren in Uganda (N=1,691)

Characteristics	Urticarial rash ever		Adj. OR‡ (95% CI)	P-value
	Yes (N=572)	**No** (N=1,119)		
Age, years Mean (SD)	12.01 (3.04)	10.64 (3.07)	1.18 (1.13-1.23)	<0.0001
Girls (942)	339 (59.3)	603 (53.9)	1.16 (0.91-1.47)	0.22
Fathers' highest education attained [m=20]				
None/Primary (437)	168 (29.5)	269 (24.4)	1	
Secondary (595)	195 (34.3)	400 (36.3)	0.71 (0.53-0.94)	
Tertiary (639)	206 (36.2)	433 (39.3)	0.79 (0.59-1.05)[a]	0.06
Father's history of allergic disease [m=148]				
Yes (363)	147 (27.8)	216 (21.3)	1.68 (1.25-2.25)	0.001
Mother's history of allergic disease [m=128]				
Yes (592)	235 (43.8)	357 (34.7)	1.58 (1.23-2.02)	<0.0001
Area of residence at the time of the child's birth				
Rural (354)	126 (22.0)	228 (20.4)	1	
Town (1,188)	395 (69.1)	793 (70.9)	1.15 (0.87-1.53)	
City (149)	51 (8.9)	98 (8.7)	1.08 (0.67-1.74)[b]	0.60
Exposure to animals in first five years of life [m=58]				
Yes (615)	237 (42.9)	378 (35.0)	1.29 (1.01-1.66)	0.04
Frequency of 'trucks passing on street near child's home' at enrolment				
Rarely (944)	292 (51.1)	652 (58.3)	1	
Frequently (624)	218 (38.1)	406 (36.3)	1.19 (0.93-1.52)	
Almost all the time (123)	62 (10.8)	61 (5.4)	2.19 (1.37-3.48)[c]	0.003
Use of de-worming medication in last 12months [m=1]				
None (578)	181 (31.7)	397 (35.5)	1	
Once (732)	237 (41.5)	495 (44.2)	0.96 (0.74-1.25)	
≥Twice (380)	153 (26.8)	227 (20.3)	1.40 (1.02-1.92)[d]	0.04
Any helminth infection at enrolment [m=129]				
Yes (212)	77 (14.7)	135 (13.0)	1.19 (0.84-1.67)	0.33
Skin Prick Test response to any of 7 allergens at enrolment [m=35]				
Positive (≥3mm) (657)	241 (42.9)	416 (38.0)	1.26 (0.99-1.61)	0.06
Allergen-specific IgE at enrolment (N=397)[§]				
Atopic (≥0.35 kU_A/L) (251)	94 (67.6)	157 (60.8)	1.17 (0.70-1.95)	0.55
Total IgE at enrolment (N=398)				
Median (95%CI) kU/L	421.3 (234.2-596.0)	323.3 (271.0-384.8)	1.00 (0.9998-1.0002)	0.70

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; Columns 2 and 3 represent number (%), unless stated otherwise. ‡Adjusted for child's age, sex, area of residence at birth and father's education. Test for trend p-value: [a]=0.12; [b]=0.48; [c]=0.002; [d]=0.08. [§] ImmunoCAP®, cut-off ≥0.35 kU_A/L.