Risk factors for asthma among schoolchildren who participated in a case-control study in urban Uganda

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Abstract

Data on asthma aetiology in Africa are scarce. We investigated the risk factors for asthma among schoolchildren (5-17 years) in urban Uganda. We conducted a case-control study, among 555 cases and 1,115 controls. Asthma was diagnosed by study clinicians. The main risk factors for asthma were tertiary education for fathers [adjusted OR (95% CI); 2.32 (1.71-3.16)] and mothers [1.85 (1.38-2.48)]; area of residence at birth, with children born in a small town or in the city having an increased asthma risk compared to schoolchildren born in rural areas [2.16 (1.60-2.92)] and [2.79 (1.79-4.35)], respectively; father’s and mother’s history of asthma; children’s own allergic conditions; atopy; and cooking on gas/electricity. In conclusion, asthma was associated with a strong rural-town-city risk gradient, higher parental socio-economic status and urbanicity. This work provides the basis for future studies to identify specific environmental/lifestyle factors responsible for increasing asthma risk among children in urban areas in LMICs.

Background

Asthma is estimated to affect more than 235 million people globally, and is the most common non-communicable condition among children(1). In Africa, the prevalence of asthma appears to be increasing(2-6), particularly in urban areas(3, 7), but the causes of this increase are not fully understood. Moreover, asthma has various phenotypes which may have different aetiologies(8). Asthma risk factors appear to vary internationally, and to differ between high-income countries (HICs) and low-and-middle income countries (LMICs)(9).

There is little previously published data on asthma risk factors from Africa. The few studies reported have suggested that current residence in urban areas is associated with a higher risk of asthma than rural residence in Africa (10, 11) and other LMICs (12, 13). The association
between helminth infections and asthma has been investigated in Africa and other LMICs, but
the findings have been inconsistent across studies (14, 15). Other risk factors for asthma in
Africa and other LMICs, similar to those in HICs, include maternal smoking (16, 17), maternal
history of asthma (18), childhood atopic sensitisation (11, 19) and history of allergy (18, 20).
Previous reports suggest no association between biomass fuels and asthma risk (21, 22), but
increased asthma symptoms (22, 23). Unlike in HICs, higher parental education and
socioeconomic status has been associated with asthma among children in Africa (3, 18, 24).
We undertook a case-control study among schoolchildren in an urban area in Uganda, to
investigate the main risk factors for asthma and the patterns of allergic sensitisation.

Results

Reference characteristics of participating schools and participant flow

We enrolled participants from 55 schools (32 primary, 23 secondary). Of the 6,385 children
initially identified from the pre-screening exercise, we were unable to contact 4,550
parents/guardians in time for them to attend the parents’ meeting; most of these children were in
the boarding section (Figure 1). Of the 1,835 who attended the meeting, 97% provided written
informed consent for their child to participate in the study. We screened 1,779 participants and
of these, 77 who had initially reported breathing problems either did not have an asthma
diagnosis or did not have asthma symptoms in the last 12 months and were excluded. We
enrolled 562 children with and 1,140 without asthma, but excluded thirty-two with incomplete
data (Figure 1). At enrolment, 477 asthma cases successfully performed the spirometry, and
only three of these had FEV₁ values less than 80% of predicted values.
Early life risk factors for asthma

Participants had mean age 11 years (range 5-17 years); children with asthma were slightly older, and more likely to have parents with a tertiary education and a reported history of asthma (Table 1). Compared to children born in rural Uganda, children born in any town in Uganda or in the city had an increased risk of asthma [adjusted OR (95% confidence interval (CI)) 2.16 (1.60-2.92)] and [2.79 (1.79-4.35)], respectively. The same pattern was observed for the area where the child spent most of their early life (0-5 years) (Table 1). There were no differences in reported exposure to farm animals, or to cigarette smoke during pregnancy. Children with asthma were less likely to have a BCG scar [0.67 (0.51-0.89)] (Table 1), but the TST response (induration ≥10mm) at enrolment was similar between cases (15.6%) and controls (14.4%) [1.03 (0.67-1.58)]. There was no statistical evidence of interaction between parental education and the children’s area of residence in early life, nor interaction between age and any of the asthma risk factors.

Current features of asthma cases versus controls

Asthma cases were more likely to report a high frequency of ‘trucks passing on the street near their home’ [2.28 (1.52-3.43)]; to come from homes that used electricity/gas for indoor cooking [1.58 (1.16-2.17)]; and to report having used de-worming medication more than twice in the last 12 months [2.18 (1.62-2.93)] than controls. There was weak evidence for an inverse association between asthma and infection with any helminths species [0.75 (0.53-1.07)] (Table 2); overall this was not statistically significant as shown by the fact that the confidence interval included the null value of 1, but it was significant for *T. trichiura* [0.33 (0.13-0.89)] (Supplementary File 1a). Children with asthma were more likely to report a history of allergic diseases such as allergic rhinitis, conjunctivitis, eczema and urticarial rashes (Table 1) and to have these conditions currently (Table 2). The prevalence of current exposure to cigarette smoke (in the household) was similar among cases and controls, although only about 11% were exposed (Table 2).
Atopy and asthma

Children with asthma were more likely to have allergic sensitisation: SPT positive to at least one of seven whole allergen extracts [2.40 (1.92-3.00)]; and elevated asIgE levels to any of three whole allergen extracts [2.45 (1.53-3.91)], and higher total IgE (Table 3). The most common allergens were dust mites and cockroach. Asthma cases were more likely to have elevated FENO levels [2.57 (2.01-3.29)] (Table 3).

Assessment of different combinations of risk factors for asthma

We investigated the relative importance of area of residence at birth versus the first years of life, on the asthma risk, by looking at children who migrated between rural and urban areas during these two periods. Children born and raised in rural areas had the lowest risk (the reference group); children born and raised in urban areas had the highest risk [2.55 (1.80-3.61)], children born in the urban area who migrated and spent most of 0-5 years in rural areas still had an increased risk of asthma [2.11 (1.14-3.91)], unlike children who were born in rural areas but migrated and spent most of 0-5 years in urban areas (Table 4).

We investigated the combined effects of the child’s area of residence at birth and parental history of allergic disease. Even among children with no parental history of allergic disease, compared to being born in a rural area, being born in a town [2.15 (1.35-3.44)] or in the city [3.33 (1.61-6.90)] was associated with an increased risk of asthma, Table 5. Compared to the same reference group, children with a parental history of allergic disease had a higher risk of asthma that increased steadily from among children born in rural areas [2.78 (1.58-4.89)], in a town [5.16 (3.25-8.17)] and in the city [5.54 (2.99-10.26)] (Table 5).
We also investigated the combined effects of area of residence at birth and children’s atopic status (positive SPT to any of seven allergens). Taking non-atopic children born in rural areas as the reference group, we found that non-atopic children born in town had a modest increase in asthma risk [1.72 (1.16-2.55)], which increased further among city-born children [2.63 (1.41-4.91)], Table 6. However, atopic children had a modestly increased risk of asthma even if they were born in the rural area [1.77 (1.02-3.05)], which increased substantially among atopic children born in town [4.61 (3.07-6.90)] or in the city [4.67 (2.56-8.52)], Table 6.

We investigated the combined effects of parental education and urbanicity on asthma risk, by looking at the father’s education level in combination with the child’s area of residence at birth. We found that for each level of father’s education, there was an increasing risk gradient from rural-town-city; for each area of residence, increasing father’s education level was associated with increased asthma risk; the highest risk of asthma was among children born in the city whose fathers had a tertiary education [6.95 (3.52-13.71)] (Table 7). The same pattern in Table 7 was seen for mother’s education and for child’s area of residence in the first five years of life.

For the combined effect of atopy (SPT positive) and parental history of allergic disease, we found that asthma risk was more than five times among children with both atopy and a parental history of allergic disease [5.74 (4.07-8.10)] (Supplementary File 1b). However, children who had both parents with a history of allergic disease had an effect size similar to children who had only one parent with a history of allergic disease [2.49 (1.74-3.58)] (Supplementary File 1c).

**Discussion**

We found a step-wise increase in asthma risk according to the child’s area of residence at the time of birth and in their first five years of life. Children born and raised in rural areas had the lowest risk, children born and raised in small towns had a 2-fold increase in risk, while children born and raised in the city had a 3-fold increase in asthma risk. This is the first study in Africa to show such a strong gradient in asthma risk by place of birth. Previous studies have been mostly
cross-sectional and conducted in either rural or urban settings, and therefore focusing on
current residence; these have shown that the prevalence of asthma is lower among rural
residents compared to urban residents (6, 7, 10).

Our findings confirm that the area where a child is born (usually the same as the area where the
mother was resident during pregnancy) is important for asthma risk. Indeed, we found that when
children moved to other environments, they carried with them the asthma risk related to their
area of residence in pregnancy: children born in urban areas who were subsequently raised in
rural areas still had a 2-fold increase in asthma risk, similar to their counterparts born and raised
in urban areas. These findings are comparable to observations from Europe showing that
children born on a farm (usually in rural areas) have a lower risk of asthma in later life, even
when they subsequently moved to urban areas (25), and that children who migrated to Europe
after age five had a lower prevalence of asthma, similar to their country of origin, than children
who were either born in Europe or migrated before the age of five (26, 27). However, there are
also studies that show increased risk of wheezing and allergy among children following
migration (28, 29). Unlike studies from Europe and North America which have reported a lower
risk of asthma for children born or raised on farms (30, 31), our study found no association
between asthma risk and exposure to farm animals either during pregnancy or in early life. We
hypothesise that this may be due to ubiquitous farm animal exposure due to subsistence
farming, a widespread practice in Uganda, even in towns.

Our observation that children with asthma were more likely to have parents with tertiary
education and to use gas or electricity for indoor cooking (as opposed to charcoal stoves) has
been made by an earlier study in Uganda (18). Similarly, our finding that children with asthma
reported the highest frequency of ‘trucks passing on the street near their home’ has been
reported elsewhere (32-34). We suggest that these factors are proxy measures of a higher
socio-economic status of asthma cases and of urbanicity, consistent with findings from other
LMICs that have found a higher prevalence of asthma among children (and adults) in urban than rural areas\textsuperscript{(7, 12, 13)}. However, our findings contradict those from HICs in which asthma is associated with lower parental education\textsuperscript{(35)} and socio-economic status\textsuperscript{(36)}. This suggests that there may be similarities in lifestyle and environmental factors between the highly educated and high socio-economic status families in LMICs with the low educated and low socio-economic status families in HICs, which increase asthma risk, and therefore require further investigation.

Although children with asthma were more likely to be sensitised to allergens than controls, the pattern of allergic sensitisation was similar among cases and controls; majorly sensitised to house-dust mites and cockroach, and least sensitised to peanut, cat, pollen and mould. This SPT response pattern was similar to other studies from Africa\textsuperscript{(19, 37)}, but different from Europe where the main allergens are dust mite, cat and pollen\textsuperscript{(38)}.

Although maternal smoking is a known risk factor for childhood asthma\textsuperscript{(39)}, our study found no association between maternal smoking and asthma. We attribute this to the low prevalence of smoking in this population, by the mothers during pregnancy (2.5\%) and by any household members currently (11\%). The lack of association between asthma and indoor cooking with biomass fuels in this study is consistent with other studies from Africa\textsuperscript{(21, 22)}. Indeed, this is consistent with the general pattern of lower risk of asthma in rural areas (where biomass fuel use is highest) than urban areas.

We found an inverse association between asthma and current infection with any helminths, particularly \textit{T. trichuria}. However, the association between asthma and current infections in Africa has been inconsistent across studies\textsuperscript{(15)}. What was novel in this study is that we also collected data on history of using de-worming medication in the last 12 months. We found that children with asthma were more likely to have used de-worming medication more than twice in the last 12 months compared to controls, and this was de-worming with albendazole (for geo-helminths) not with praziquantel (for schistosomiasis). This implies that the inverse association
we noted between asthma and helminths may be partly explained by increased de-worming among children with asthma. The current de-worming schedule in this age-group in Uganda includes mass-deworming in schools, bi-annually for albendazole and once a year for praziquantel. We did not establish whether the additional de-worming was self-medicated or prescribed by medical workers.

We found that children with asthma were less likely to have a BCG scar, but there was no association with tuberculin skin test at enrolment. In Uganda, BCG vaccination is routinely given at birth. A lack of BCG scar does not mean the vaccine was not administered, but may indicate differences in immune responses among children who will eventually develop asthma. Alternatively, BCG vaccination may be protective against asthma, as suggested by previous studies(40).

The other important risk factors for asthma, that have been previously described, included parental history of allergic disease(41), a child’s atopy status and concomitant other allergic disease(42). The strength of this study was to demonstrate that having a combination of any two of these known risk factors for asthma had an additive effect of asthma risk, and that this risk also increased in relation to area of residence in early life, with an increasing rural-town-city gradient. This gradient and independent effects of parental education provide strong evidence for the role of environmental and lifestyle factors associated with urbanisation that are responsible for the increasing asthma risk in urban areas. More investigations are required to identify the specific factors, in order to design interventions to modify them so as to prevent the establishment of asthma risk in early life.

This study had limitations inherent to all case-control studies, such as potential recall bias, selection bias and confounding. We minimised recall bias by focusing on major early life events that a parent was likely to remember. It was re-assuring to note a strong correlation between the recalled events and objective measures such as SPT. We minimised the selection bias for
controls by randomly selecting controls from the same class register where the cases were
obtained, and by randomly selecting the 400 participants for the asIgE assay. We minimised
confounding by adjusting for measured confounders in all our analyses, but cannot rule out the
possible role of unmeasured confounders. Finally, a large number of potential participants were
not included in this study, mostly because they were in the boarding school section and were
unable to contact their parents/guardians in time to attend the parents’ meeting (to provide
consent). We do not have information on whether these parents were more likely to reside in
rural areas or the city, where the asthma risk is either lower or higher than the town where this
study was conducted, respectively. Our results may or may not be generalisable to similar urban
areas in Uganda and Sub-sahara Africa.

Our findings support concept that environmental factors during early life may influence the risk
of development of NCDs in later life (43). However, our study does not involve information
sufficiently detailed to identify whether exposures in utero or in early life are most relevant.
Further research in this setting is required to investigate these hypotheses, and this would have
important implications for the life course approach in the prevention of asthma globally.

Conclusion

The risk of asthma among schoolchildren in urban Uganda is strongly predicted by their area of
residence in early life, particularly at birth, with the highest risk among children whose early life
is spent in small towns and in the city. This risk increases further in the presence of other
asthma risk factors such as parental history of allergic disease, children’s own atopy, higher
measures of socio-economic status and urbanicity. Given the current rapid urbanisation in Africa
and other LMICs, the prevalence of asthma is likely to increase further. This study provides the
basis for future studies investigating environmental and lifestyle factors that increase asthma
risk in the urban areas of LMICs.
Methods

Study design

We conducted an un-matched case-control study among schoolchildren, and report following STROBE guidelines [44].

Study population, sampling and consent

The study base was determined a priori as schoolchildren, 5-17 years old, in primary and secondary schools in Entebbe Municipality and Katabi zone in Wakiso District, Central Uganda. This was a predominantly urban (town) setting. All schools in the study area were invited and 96% participated. Study enrolment was between May 2015 and July 2017. We estimated that a sample size of 2,112 would have 80% power to detect odds ratio (OR) <0.5 or >1.5 for exposures with prevalence 10% among controls.

At each school, we pre-screened by registering all children with any breathing problems. We concurrently randomly selected from the class register two children without any breathing problems, using a random number generator programme in STATA (StataCorp, Texas, USA). The children delivered invitation letters to their parents; parents/guardians with telephones were invited to attend a meeting during which those interested provided written informed consent, and children aged ≥8 years provided written informed assent.

Definition of cases and controls

Following consent and assent, we screened all participants with the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire [45]. Children with a history of wheezing in the last 12 months underwent a detailed medical history and examination by study clinicians, to diagnose asthma. Asthma was defined as a history of recurrent symptoms of wheezing, cough (mostly dry, worse at night and morning) and/or difficulty in breathing
experienced in the last 12 months, with or without forced expiratory volume in the first second (FEV₁) ≤80% expected for age, sex and height for African children. Additional medical history included a prior physician diagnosis and good response to asthma medication. If the diagnosis was not straightforward, two clinicians reviewed the participant and if they disagreed, that participant was excluded in order to ensure proper case ascertainment. Children with a history of wheeze or any asthma symptoms but not in the last 12 months were excluded. Controls were defined as having no history of wheeze or any other asthma symptoms. There were no other exclusion criteria.

**Ethical approval**

The study was approved by the Uganda Virus Research Institute Research and Ethics Committee, and the Uganda National Council for Science and Technology.

**Clinical assessments**

We collected data about asthma risk factors and allergic conditions identified in literature using interviewer-led questionnaires to parents and adolescents, including the ISAAC questionnaire (45). When a parent was not available in person and the participant answering the questionnaire did not know that parent’s history of allergy, we telephoned the parent for the relevant information. We looked for the presence of a Bacillus Calmette–Guérin (BCG) scar since BCG vaccination has been inversely associated with asthma previously(40). We tested for fractional exhaled nitric oxide (FENO), using a hand-held device (NoBreath® from Bedfonf Scientific, Maidstone, United Kingdom), and used the manufacturer’s cut-off for children of >35 parts per billion. FENO is considered a biomarker of allergic airway inflammation(46). We conducted lung function tests for asthma cases using a hand-held spirometer (Micro 1 Diagnostic Spirometer, CareFusion, Chatham Marine, United Kingdom).
Skin prick tests (SPT) and allergen-specific IgE (asIgE) are important measures of allergic sensitisation(47). We conducted (SPT) following standard procedures(47, 48), and crude extracts of seven allergens (*Dermatophagoides* mix of *D. farinae* and *D. pteronyssinus*, *Blomia tropicalis*, *Blattella germanica*, peanut, cat, pollen mix of weeds, mould mix of *Aspergillus* species; ALK Abello, Hoersholm, Denmark). A positive response was a wheal diameter ≥3mm measured after 15 minutes, with a negative saline control and positive histamine. We collected blood samples which we processed to obtain plasma that we stored at -80°C. At the end of the study, we randomly selected 200 plasma aliquots from all asthma cases and 200 from all controls for measurement of asIgE to whole allergen extracts (*D. pteronyssinus*, *B. germanica* and peanut), using ImmunoCAP® (Phadia, Uppsala, Sweden). The standard cut-off for allergic sensitisation of ≥0.35 allergen-specific kilo units per litre (kUA/L) was used (Table 8).

Because previous studies have reported an association between asthma and helminths (15), we collected three fresh stool samples from each participant and tested for intestinal helminths using the Kato Katz method(49). The findings on the association between tuberculin skin test (TST) and allergy/asthma have been inconsistent(50, 51). We investigated this association by performing the TST using standard procedures, as we have previously described(52).

**Data management and statistical analysis**

Data were double-entered using OpenClinica open source software version 3.1.4 (OpenClinica LLC and collaborators, Waltham, MA, USA). Data were analysed in STATA.

For continuous variables with clinically relevant cut-off points such as for SPT, asIgE, FENO and TST, we used the dichotomous variables in the analysis. Total IgE was analysed as a continuous variable. The variable for maternal or paternal history of ‘allergic disease’ combines the history of asthma, eczema, allergic rhinitis, allergic conjunctivitis and any other allergies(53).

We conducted a complete case analysis, and did not impute missing values.
The key variables adjusted for (see below) were age, sex, area of residence at time of birth and father’s education. Each of these variables (except sex) had small numbers of missing values (the largest number was 29 for father’s education). We therefore created a ‘complete case’ data set, comprising the 555 cases and 1,115 controls which had no missing values for these variables. This ‘complete case’ data set was used for all analyses.

The odds ratio was the main outcome measure (as is appropriate for a case-control study), and we also estimated the 95% CIs. We identified age and sex as a priori confounders, and all analyses were adjusted for these variables. We identified area of residence at time of birth and father’s education as potential confounders; we did not also adjust for area where the child spent most of the first five years or mother’s education, since these were strongly associated with the above two factors, and therefore would have introduced collinearity. Previous studies in this setting have found that father’s and mother’s education are significantly associated with socioeconomic status (54).

We did not identify any factors which were likely to be on the causal pathways (and therefore were not potential confounders and should not be adjusted for). We conducted initial logistic regression analyses for each exposure of interest, adjusted for age and sex, with random effects to allow for any clustering by school. We then ran the adjusted random effects logistic regression model (i.e. adjusted for the above factors in addition to age and sex) for each exposure of interest, and checked for collinearity by comparing the standard error of the exposure coefficient in the adjusted model and in the basic model (53, 55). We did not find any problems of collinearity, so we reported the findings for the adjusted model for each exposure.
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Competing interests

No competing interests were disclosed.

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### Table 1: Early life risk factors for asthma among schoolchildren enrolled in a case-control study between 2015-17 (N=1,670)

| Risk factors                              | Asthma cases N=555 | Non-asthma controls N=1,115 | Adj. OR (95% CI)‡ |
|-------------------------------------------|--------------------|------------------------------|-------------------|
| Age, years, Mean (Range)                  | 11.42 (3.26)       | 10.98 (3.05)                 | 1.07 (1.03-1.11)  |
| Sex: Girls (933)                          | 294 (53.0)         | 639 (57.3)                   | 0.79 (0.63-0.99)  |
| Mother’s history of asthma [m=164]        |                    |                              |                   |
| Yes (102)                                 | 61 (12.0)          | 41 (4.1)                     | 3.05 (1.97-4.71)  |
| Father’s history of asthma [m=175]        |                    |                              |                   |
| Yes (85)                                   | 65 (12.8)          | 20 (2.0)                     | 6.64 (3.90-11.30) |
| Fathers’ highest education level           |                    |                              |                   |
| None/Primary (437)                        | 99 (17.8)          | 338 (30.3)                   | 1                 |
| Secondary (594)                           | 193 (34.8)         | 401 (36.0)                   | 1.61 (1.20-2.16)  |
| Tertiary (639)                             | 263 (47.4)         | 376 (33.7)                   | 2.32 (1.71-3.16)  |
| Mothers’ highest education attained [m=4]  |                    |                              |                   |
| None/Primary (577)                        | 158 (28.6)         | 419 (37.6)                   | 1                 |
| Secondary (601)                           | 185 (33.4)         | 416 (37.4)                   | 1.11 (0.85-1.44)  |
| Tertiary (488)                             | 210 (38.0)         | 278 (25.0)                   | 1.85 (1.38-2.48)  |
| Child’s residence at birth                 |                    |                              |                   |
| Rural (352)                               | 74 (13.3)          | 278 (24.9)                   | 1                 |
| Town (1,169)                              | 412 (74.2)         | 757 (67.9)                   | 2.16 (1.60-2.92)  |
| City (149)                                | 69 (12.5)          | 80 (7.2)                     | 2.79 (1.79-4.35)  |
| Child’s residence for most of 0-5 years    |                    |                              |                   |
| Rural (337)                               | 72 (13.0)          | 265 (23.8)                   | 1                 |
| Town (1,247)                              | 434 (78.2)         | 813 (72.9)                   | 1.96 (1.44-2.66)  |
| City (86)                                 | 49 (8.8)           | 37 (3.3)                     | 3.74 (2.19-6.39)  |
| Maternal regular contact with farm animals during pregnancy [m=252] | | | |
| Yes (500)                                 | 152 (30.2)         | 348 (38.0)                   | 0.82 (0.64-1.06)  |
| Maternal cigarette smoking during pregnancy [m=302] | | | |
| Yes (36)                                  | 13 (2.7)           | 23 (2.6)                     | 1.07 (0.51-2.22)  |
| Breast feeding duration [m=402]            |                    |                              |                   |
| ≤1year (328)                              | 114 (25.3)         | 214 (26.2)                   | 1                 |
| >1year (940)                              | 337 (74.7)         | 603 (73.8)                   | 1.12 (0.85-1.49)  |
| Allergic rhinitis ever                     |                    |                              |                   |
| Yes (862)                                 | 429 (77.3)         | 433 (38.8)                   | 5.53 (4.31-7.09)  |
| Allergic conjunctivitis ever              |                    |                              |                   |
| Yes (766)                                 | 361 (65.0)         | 405 (36.3)                   | 3.12 (2.50-3.90)  |
| Eczema ever                               |                    |                              |                   |
| Yes (764)                                 | 126 (22.7)         | 138 (12.4)                   | 2.08 (1.56-2.77)  |
| Urticarial rash ever                      |                    |                              |                   |
| Yes (569)                                 | 222 (40.0)         | 347 (31.1)                   | 1.42 (1.13-1.79)  |
| Presence of a BCG scar on child’s arm at enrolment [m=83] | | | |
| Yes (1,315)                               | 413 (78.4)         | 902 (85.1)                   | 0.67 (0.51-0.89)  |

Adj. OR=adjusted odds ratio; CI=confidence interval; N=number; m=missing; number (%) in 2nd and 3rd column unless indicated otherwise. ‡adjusted for child’s age, sex, residence at birth and father’s education level. #Test for trend p-value <0.0001. For parental history of allergy, 6.6% mothers and 3.4% fathers responded by telephone.
Table 2: Current risk factors and features of schoolchildren enrolled in an asthma case-control study between 2015-17 (N=1,670)

| Current features | Asthma cases N=555 | Non-asthma controls N=1,115 | Adj. OR (95% CI)‡ |
|------------------|---------------------|-----------------------------|-------------------|
| Frequency of ‘Trucks’ passing on street near child’s home | | | |
| Rarely (931) | 264 (47.6) | 667 (59.8) | 1 |
| Frequently (618) | 232 (41.8) | 386 (34.6) | 1.60 (1.27-2.01) |
| Almost all the time (121) | 59 (10.6) | 62 (5.6) | 2.28 (1.52-3.43)# |
| Cooking fuel most frequently used indoor | | | |
| No indoor cooking (390) | 120 (21.6) | 270 (24.2) | 1 |
| Charcoal stove (890) | 262 (47.2) | 628 (56.3) | 1.04 (0.79-1.37) |
| Gas/Electricity (390) | 173 (31.2) | 217 (19.5) | 1.58 (1.16-2.17) |
| Child’s reported regular physical activity levels as recommended by WHO [m=1] | | | |
| Yes (999) | 300 (54.0) | 699 (62.7) | 0.71 (0.56-0.90) |
| Current exposure to cigarette smoke by a household member§ | | | |
| Yes (187) | 68 (12.2) | 119 (10.7) | 1.26 (0.90-1.76) |
| Use of de-worming medication in last 12 months [m=1] | | | |
| None (570) | 151 (27.2) | 419 (37.6) | 1 |
| Once (724) | 231 (41.6) | 493 (44.3) | 1.37 (1.06-1.77) |
| ≥Twice (375) | 173 (31.2) | 202 (18.1) | 2.18 (1.62-2.93)# |
| Infection with any helminths at enrolment† [m=127] | | | |
| Yes (206) | 53 (10.3) | 153 (14.9) | 0.75 (0.53-1.07) |
| Allergic rhinitis in last 12 months [m=1] | | | |
| Yes (215) | 119 (21.4) | 96 (8.6) | 2.91 (2.13-3.97) |
| Allergic conjunctivitis in last 12 months | | | |
| Yes (177) | 86 (15.5) | 91 (8.2) | 2.10 (1.51-2.92) |
| Eczema in last 12 months | | | |
| Yes (60) | 41 (7.4) | 19 (1.7) | 4.52 (2.54-8.06) |
| Urticarial rash in last 12 months | | | |
| Yes (36) | 18 (3.2) | 18 (1.6) | 1.92 (0.96-3.84) |

† adj. OR=adjusted odds ratio; CI=confidence interval; N=number; m=missing; WHO=World Health Organisation. Number (%) in 2nd and 3rd column. ‡ adjusted for child’s age, sex, residence at birth and father’s education level. § Test for trend p-value <0.0001. † Helminths infections included mainly *Schistosoma mansoni, Trichuris trichuria, Hookworm, and Ascaris lumbricoides*; this variable was additionally adjusted for reported worm treatment in the last 12 months. #This included the adolescents’ own smoking history.
Table 3: Atopy among schoolchildren enrolled in an asthma case-control between 2015-17 (N=1,635)

| Atopy characteristics                                      | Asthma cases N=546 | Non-asthma controls N=1,089 | Adj. OR (95% CI)‡ |
|------------------------------------------------------------|--------------------|------------------------------|------------------|
| Any positive skin prick test to any of 7 allergens         |                    |                              |                  |
| Yes (653)                                                  | 302 (55.3)         | 351 (32.2)                   | 2.40 (1.92-3.00) |
| *Blomia tropicalis* (dust mite) SPT                        |                    |                              |                  |
| Positive (478)                                             | 241 (44.1)         | 237 (21.8)                   | 2.51 (1.98-3.19) |
| *Dermatophagoides* mix (dust mite) SPT                     |                    |                              |                  |
| Positive (535)                                             | 262 (48.0)         | 273 (25.1)                   | 2.46 (1.95-3.10) |
| *German cockroach* SPT                                     |                    |                              |                  |
| Positive (354)                                             | 150 (27.5)         | 204 (18.7)                   | 1.59 (1.23-2.06) |
| *Peanut SPT [m=4]                                          |                    |                              |                  |
| Positive (57)                                              | 27 (5.0)           | 30 (2.8)                     | 1.73 (0.99-3.05) |
| *Cat SPT*                                                  |                    |                              |                  |
| Positive (45)                                              | 22 (4.0)           | 23 (2.1)                     | 1.94 (1.02-3.69) |
| *Pollen mix (weeds) SPT [m=2]                              |                    |                              |                  |
| Positive (43)                                              | 22 (4.0)           | 21 (1.9)                     | 2.14 (1.11-4.11) |
| *Mould mix SPT                                             |                    |                              |                  |
| Positive (19)                                              | 8 (1.5)            | 11 (1.0)                     | 1.40 (0.52-3.76) |
| *Fractional exhaled nitric oxide (FENO) [m=42]             |                    |                              |                  |
| Elevated (>35ppb) (378)                                    | 199 (36.7)         | 179 (17.0)                   | 2.57 (2.01-3.29) |
| *Any positive allergen-specific IgE* (of 3 allergens, N=392) |        |                              |                  |
| Atopic level (249)                                         | 143 (72.6)         | 106 (54.4)                   | 2.45 (1.53-3.91) |
| *Dermatophagoides-IgE*                                     |                    |                              |                  |
| Atopic level (186)                                         | 116 (58.6)         | 70 (35.9)                    | 2.32 (1.49-3.63) |
| *Cockroach IgE*                                            |                    |                              |                  |
| Atopic level (198)                                         | 110 (55.8)         | 88 (45.1)                    | 1.69 (1.08-2.63) |
| *Peanut IgE*                                               |                    |                              |                  |
| Atopic level (63)                                          | 39 (19.7)          | 24 (12.3)                    | 1.92 (1.05-3.50) |
| *Total IgE*: Mean (SD) kU/L                               | 930.25 (1246.60)   | 640.88 (1146.61)             | 1.00024 (1.00005-1.00043) |

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; SD=standard deviation; m=missing; ppb=parts per billion; number (%) shown in 2nd and 3rd column unless indicated otherwise. ‡adjusted for child’s age, sex, residence at birth and father’s education level. Skin prick test using whole allergen extracts. *allergen-specific IgE levels were obtained using ImmunoCAP®, on a random sample of 200 cases and 200 controls; standard cut-off for allergic sensitisation (≥0.35 allergen-specific kilo units per litre (kU/L)).
Table 4: Residence in early life as a risk factor for asthma among schoolchildren enrolled in a case-control study between 2015-17 (N=1,670)

| Child's residence in early life                          | Asthma cases N=555 | Non-asthma controls N=1,115 | Adj. OR (95% CI)‡ |
|---------------------------------------------------------|--------------------|-----------------------------|------------------|
| Born and spent first 5 years in rural (265)             | 50 (9.0)           | 215 (19.3)                  | 1                |
| Born in rural, spent first 5 years in urban (87)        | 24 (4.3)           | 63 (5.6)                    | 1.54 (0.86-2.75) |
| Born in urban, spent first 5 years in rural (72)        | 22 (4.0)           | 50 (4.5)                    | 2.11 (1.14-3.91) |
| Born and spent first 5 years in urban (1,246)           | 459 (82.7)         | 787 (70.6)                  | 2.55 (1.80-3.61) |

N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; number (%) shown in 2nd and 3rd column
‡Adjusted for age, sex, and father’s education level.

Table 5: Combined effects of residence at birth and parental history of allergic disease as risk factors for asthma among schoolchildren in a case-control study from 2015-17 (N=1,532)

| Child's residence at birth | Parental history of allergy | Asthma cases N=526 | Non-asthmatic controls N=1,006 | Adj. OR (95% CI)‡ |
|----------------------------|-----------------------------|--------------------|--------------------------------|------------------|
| Rural                      | -                           | 27 (5.1)           | 158 (15.7)                     | 1                |
| Town                       | -                           | 137 (26.1)         | 383 (38.1)                     | 2.15 (1.35-3.44) |
| City                       | -                           | 20 (3.8)           | 31 (3.1)                       | 3.33 (1.61-6.90) |
| Rural                      | +                           | 42 (8.0)           | 85 (8.4)                       | 2.78 (1.58-4.89) |
| Town                       | +                           | 253 (48.1)         | 306 (30.4)                     | 5.16 (3.25-8.17) |
| City                       | +                           | 47 (8.9)           | 43 (4.3)                       | 5.54 (2.99-10.26) |

Adj. OR=adjusted odds ratio; CI=confidence interval; N=number; “-” refers to no history of parental allergy, “+” refers to positive history of parental allergy. number (%) in 3rd and 4th column. ‡Adjusted for child’s age, sex, and father’s education level. Parental history of allergic disease included a history of asthma, eczema, allergic rhinitis, allergic conjunctivitis and any other allergies.
Table 6: Combined effects of residence at birth and atopy as asthma risk factors among schoolchildren in a case-control study between 2015-17 (N=1,635)

| Child’s residence at birth | Atopy (SPT to any of 7 allergens) N=546 | Asthma cases N=1,089 | Non-asthmatic controls N=1,089 | Adj. OR (95% CI)‡ |
|---------------------------|----------------------------------------|----------------------|-------------------------------|-----------------|
| Rural                     | -                                      | 42 (7.7)             | 191 (17.5)                    | 1               |
| Town                      | -                                      | 177 (32.4)           | 504 (46.3)                    | 1.72 (1.16-2.55)|
| City                      | -                                      | 25 (4.6)             | 43 (4.0)                      | 2.63 (1.41-4.91)|
| Rural                     | +                                      | 31 (5.7)             | 81 (7.4)                      | 1.77 (1.02-3.05)|
| Town                      | +                                      | 228 (41.7)           | 236 (21.7)                    | 4.61 (3.07-6.90)|
| City                      | +                                      | 43 (7.9)             | 34 (3.1)                      | 4.67 (2.56-8.52)|

‡ Adjusted for child’s age, sex and father’s education level.

Table 7: Combined effects of father’s education and residence at birth as asthma risk factors among schoolchildren in a case-control study from 2015-17 (N=1,670)

| Father’s education level | Child’s residence at birth | Asthma cases N=555 | Non-asthma controls N=1,115 | Adj. OR (95% CI)‡ |
|--------------------------|----------------------------|---------------------|-----------------------------|-----------------|
| Primary                  | Rural                      | 20 (3.6)            | 115 (10.3)                  | 1               |
| Primary                  | Town                       | 67 (12.1)           | 206 (18.5)                  | 2.13 (1.22-3.74)|
| Primary                  | City                       | 12 (2.2)            | 17 (1.5)                    | 4.98 (2.02-12.31)|
| Secondary                | Rural                      | 26 (4.7)            | 109 (9.8)                   | 1.39 (0.72-2.66)|
| Secondary                | Town                       | 156 (28.1)          | 268 (24.0)                  | 3.97 (2.34-6.76)|
| Secondary                | City                       | 11 (1.9)            | 24 (2.2)                    | 2.80 (1.16-6.76)|
| Tertiary                 | Rural                      | 28 (5.0)            | 54 (4.8)                    | 3.22 (1.64-6.33)|
| Tertiary                 | Town                       | 189 (34.1)          | 283 (25.4)                  | 4.96 (2.89-8.53)|
| Tertiary                 | City                       | 46 (8.3)            | 39 (3.5)                    | 6.95 (3.52-13.71)|

‡ Adjusted for child’s age and sex. Similar pattern was observed for mother’s education level and child’s residence at birth.
Table 8: Key Resources Table

| Reagent type (species) or resource | Designation                      | Source or reference                      | Identifiers                                                                 | Additional information                                                                 |
|-----------------------------------|----------------------------------|------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Commercial assay or kit           | ImmunoCAP® specific IgE test     | Thermo Fisher Scientific, Uppsala, Sweden |                                                                            | http://www.phadia.com/en/Products/Allergy-testing-products/ImmunoCAP-Assays/sIgE/      |

Figure legends

Figure 1. Participant flow diagram for an asthma case-control study, conducted among 1,670 schoolchildren aged 5-17 years, between 2015 and 2017 in Uganda.

Supplementary file 1. Tables of results for risk factors for asthma among schoolchildren involved in an asthma case-control study in Uganda, between 2015-17.

File 1a. The association between infection with different species of helminths and asthma among 1,543 schoolchildren. Three fresh stool samples per child were examined for helminths using the Kato Katz method. We used multiple logistic regression method, adjusted for child’s age, sex, residence at birth, father’s education level and reported worm treatment in the last 12 months. "Other helminth infections included Hymenolepis nana and Enterobius vermicularis. N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; number (%) in 2nd and 3rd column.

File 1b. The association between individual and combined effects of child’s atopy and parental history of allergic disease, and asthma risk among 1,501 schoolchildren. Skin prick test (SPT) performed using standard procedures and seven crude extracts of Blomia tropicalis, Dermatophagoides mix, cockroach, peanut, cat, weeds pollen mix, and mould mix. Parental history of allergic disease included a history of asthma, eczema, allergic rhinitis, allergic conjunctivitis and any other allergies. We used multiple logistic regression analysis, and adjusted for child’s age, sex, residence at birth and father’s education level. N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; “-” refers to none, “+” refers to present. Number (%) in 3rd and 4th column.
The individual and combined effects of mother’s and father’s history of allergic disease, and asthma risk among 1,498 schoolchildren. Parental history of allergic disease included a history of asthma, eczema, allergic rhinitis, allergic conjunctivitis and any other allergies. We conducted multiple logistic regression analysis, and adjusted for child’s age, sex, residence at birth and father’s education level. N=number; Adj. OR=adjusted odds ratio; CI=confidence interval; number (%) shown in 2\(^{nd}\) and 3\(^{rd}\) column.
Figure 1: Participant flow diagram for 1,670 schoolchildren enrolled in an asthma case-control study between 2015-17

- Prescreening to identify children with any breathing problems N=2,284
  - Randomly selected from the class register children without any breathing problems (ratio 1:2) N=4,101
  - Total number provided with invitation cards N=6,385

- Attended Parents’ meeting to discuss study details and consent N=1,835

- Provided consent for the study N=1,786

- Screened for study eligibility N=1,779

- Enrolled into the study N=1,702
  - Cases=562; Controls=1,140

- Included in this analysis N=1,670
  - Cases=555, Controls=1,115

N=4,550 children whose parents did not attend the Parents’ meeting. This mainly affected children in the boarding school section who were unable to deliver invitations to parents or whose parents resided outside the study area.

N=49 parents did not provide consent

N=7 children did not provide assent

N=77 not asthma diagnosis or no asthma symptoms in the last 12 months

N=32 incomplete data