Environmental factors associated with atopic dermatitis in children from urban, peri-urban and rural South Africa

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DECLARATION

I, Janine Dewar, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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AUTHOR CONTRIBUTIONS

Janine Dewar (JD) conceptualised the current study design and methodology, formatted, curated and collated data, conducted data analysis, interpreted findings, wrote up analysis, discussion and conclusions, and compiled full dissertation.

Gail Todd was directly involved in creating and managing the parent study, secured data for author (JD), assisted in formalising current study design and provided feedback on statistical analysis, interpretation of findings and final write-up of the dissertation.

Leslie London was involved in guidance related to research plan, statistical analysis, interpretation of results and dissertation write up, as well as negotiating institutional approval for reanalysis of parent study,

PART A: JOURNAL MANUSCRIPT

Title: Environmental factors associated with atopic dermatitis in children from urban, peri-urban and rural South Africa.

Abstract

Background: Environmental exposures related to modern urban living, and the absence of protective rural exposures, may contribute to the high prevalence of childhood atopic dermatitis (AD).

Objectives: To identify environmental exposures associated with AD in children living in three residential areas of South Africa.

Methods: A total of 3144 children aged 3 to 11 years participated in 1999 in a cross-sectional study involving a suburban area, peri-urban informal settlement, and several villages in a remote rural district in South Africa. Caregivers of children within a modified case control subset of 739 children, consisting of 253 cases and 486 controls, completed a researcher-led 57-point questionnaire on environmental exposures. Bivariate and multivariate logistic regression models were used to determine statistically significant associations between environmental exposures and AD.

Results: A total of 387 children in the urban area, 59 in the peri-urban area and 293 in the rural district were included. Mean age of participants was 6.8 years, and 53.9% were female. Multivariate analysis found that current exposure to mould (aOR 2.79; 95% CI 1.58 – 5.00), pesticides (aOR 1.73; 95% CI 1.24 – 2.42), stress events (aOR 2.37; 95% CI 1.19 – 4.75) and home infestation with fleas (aOR 1.73; 95% CI 1.24 – 2.42) increased odds of AD in our study population, as did weaning after 4 months (aOR 1.83; 95% CI 1.31 – 2.56), compared to earlier weaning.

Conclusion: Our findings underscore the need for targeted interventions addressing indoor environmental air quality, use of indoor pesticides, and the impact of psychological stressors on the development of AD.

Introduction

Atopic dermatitis (AD) is a common inflammatory disease in children[1] with a global prevalence of 15 - 20%.[2] Low and middle-income regions, including sub-Saharan Africa, continue to see increases in AD and other atopic conditions,[3] particularly in urban environments. Between 1999 and 2000, a study conducted among 3- to- 11-year-old amaXhosa children in urban, peri-urban and rural areas in South Africa, using the United Kingdom Working Party (UKWP) criteria, found a low prevalence of AD, but rates that were significantly higher in urban (4.1%) compared to rural (1.5%) children.[4] Nearly twenty years later, in 2018, the South African Food Sensitisation and Food Allergy study (SAFFA) investigated various atopic conditions in urban and rural cohorts of children 12- to- 36 months of age.[5] The prevalence of AD in the urban Cape Town cohort (23.5%), determined by criteria proposed by the American Academy of Dermatology, was far greater than that found in the earlier study. The prevalence of AD in the rural Eastern Cape, however, was largely unchanged (1.8%). Although the two studies utilised different diagnostic criteria for AD and different age inclusion criteria, the results suggest that factors associated with modern urban living may be responsible for triggering disease in predisposed individuals, and account for the increased prevalence of AD reported for urban areas. One theory, coined the Biodiversity Hypothesis, relates to how reduced exposure to an abundance of diverse microbiota, which is commonly found in rural areas, coupled with increasing fetal and childhood exposures to chemical pollutants, is at the heart of the rising burden of atopic conditions such as AD.[6]

Studies evaluating environmental factors' associations with AD in children thus far have indicated that exposures to indoor and outdoor air pollution, tobacco smoke, home cleaning and fragrance products, various chemicals, mould and 'hard' water may be associated with an increased risk of AD development, severity and flares.

Several recent studies conducted in East Asia have investigated the association between AD symptoms and indoor and outdoor air pollution containing particulate matter (PM_{10} and $PM_{2.5}$) and nitrous oxide (NO_2).[7–11] South Korean researchers demonstrated, through generalised linear modelling, a maximum odds ratio of 1.40 for AD symptoms in young children with eczema for a 10 µg/m3 increase in ambient $PM_{2.5}$ exposure (95% CI: 1.22–1.61).[12] Exposure to ambient tobacco smoke (OR 1.18; 95% CI 1.01-1.38) was shown to be associated with AD

in a large meta-analysis of 86 observational studies from 39 countries.[13] This association was not found for *in utero* tobacco smoke exposure (OR 1.06; 95% CI 0.80-1.40).

Household products such as washing detergents, adhesives, fragranced products and biocides, as well as their frequency of use, correlated to onset and severity of AD in children in a 2019 Korean study.[14] Hard water containing high levels of alkaline calcium carbonate (CaCO3) and magnesium carbonate (MgCO3) has been shown to increase risk of AD in infancy,[15] as well as increase self-reported skin dryness and worsening of AD symptoms.[16] Two epidemiological studies conducted in Korea indicated that infants living in homes with visible mould had significantly increased risk of current AD (aOR 1.49; 95% CI: 1.15–1.91; aOR 1.65; 95% CI: 1.30–2.11).[17]

Having regular contact with dogs, or dogs and cats may be protective.[18] Recent analysis of over 84000 children from the Danish National Birth Cohort revealed a marginally lower risk of AD in children with early life exposure to dogs (adjusted hazard ratio 0.81; 95% CI: 0.70–0.94).[19] Recent meta-analysis has not found an association between intestinal helminth infection and clinical atopic disease,[20] despite previous research showing an increase in skin allergen sensitisation in children post anti-helminth treatment, in a Vietnamese population with endemic helminth infestation.[21]

AD is strongly influenced by genetic factors, evidenced by atopic tendencies within families, and high monozygotic twin concordance rates.[22,23] Up to 31 genetic loci have been identified in genome and exome studies as being associated with increased AD risk, with significant variation of expression between population groups.[24]

Despite increasing prevalence and disease burden, AD and its associations within the South African setting is poorly understood, largely due to lack of research. Pinpointing particular exposures as potential risk factors, or indeed protective factors, for AD is extremely difficult owing to the complex exposome and genetic variance which plays a role in disease development. By attempting to identify statistical associations with AD in a single defined group of ethnically and culturally similar children living in different environments, we hope to

recognise potential areas for further research, in order to better understand, and perhaps even prevent, this condition.

Environmental exposures investigated during a first arm of our study, conducted in 1999,[4] are unique and probably not repeatable. The clearly distinguishable and different living conditions of the three geographical areas at the time of investigation, have over the last 25 years, gradually become similar, reflecting widespread urbanisation. By investigating disease associations among participants with a predominantly homogenous ancestral, language and socio-cultural background, this study aimed to examine the influence of environmental factors on the development of AD in a population of South African children, while attempting to limit confounding caused by wide genetic variability.

Methods

Data source and study design

A nested case-control data subset, derived from a community-based cross-sectional questionnaire and examination survey was analysed.[4] The parent study was conducted between 1999 and 2000 as a joint project between the University of Cape Town and the University of Nottingham, United Kingdom (UK) and aimed to assess the prevalence of AD in children residing in three distinct areas of South Africa, and to determine the validity of the UK Working Party Criteria as a diagnostic tool for atopic dermatitis in black amaXhosa children within an African setting. A case control subset was created, and two further questionnaires were utilised, the first to determine the additional financial cost to parents of children with AD, and the second to identify environmental exposures which may be risk factors for developing AD. Only the data collected from the latter questionnaire, along with the first survey data were used for this analysis.

Study population

Three residential area types in South Africa were selected. An established, urban residential suburb in Cape Town (Langa) with full government service provision including sanitation, power and waste management; migrant, peri-urban areas in Cape Town (Joe Slovo and Imizamo Yethu), defined by the presence of predominantly informal infrastructures and limited service delivery; and a traditional rural area, the district of Centane in the Eastern Cape without

service delivery. During the study period between 1999 and 2000, residents in the urban and peri-urban areas were predominantly isiXhosa-speaking people who had migrated from the rural Eastern Cape. Peri-urban settlements consisted largely of residents who had recently migrated to the city from rural areas and moved back and forth between the two areas, with children staying in urban areas with the parents in infancy, and later schooled in the rural area while living with family and grandparents.[25]

The cross-sectional data included 3144 participants 3-to-11-years of age with at least 1000 participants from each of the area types. The sample for this arm of the study was formed by a case-control selection from the original cross-sectional dataset. Cases included all children determined to have AD by fulfilling the criteria for diagnosis via the UK Working Party Criteria.[26] Controls were randomly selected from participants of a similar age group who did not meet criteria for AD diagnosis, approximately 2 controls selected for each case for the urban and rural groups, and 1 control per case in the peri-urban group. In peri-urban areas, repeated fires and the transient nature of the occupants made finding patients and caregivers after the initial interviews difficult, particularly for controls, hence a decision to use a smaller set of controls for peri-urban participants. Only these participants went on to complete the questionnaire for this arm of the study. In total, 739 children were included – 253 cases, and 486 controls (case: control = 1: 1.92).

Covariates

Information about numerous environmental exposures was included in the questionnaire, (see Appendix 2) including prenatal, dietary, household and ambient exposures. Exposures included in the questionnaire were chosen based on exposures hypothesised to be associated with AD, and local knowledge, with few additional modifications from the pilot study. Data related to psychological components, acting either as risk factors or secondary outcome measures, were collected. These included exposure to recent stressful events, such as death in the family, parental separation, experiencing an injury or chronic illness. All information regarding environmental and prenatal exposures was self-reported by interviewees. There was no opportunity to validate caregiver responses through home inspections or corroboration by other family members.

Variables from the original dataset were analysed in existing format, combined or adjusted to produce new variables better able to fulfil the formulated study objectives, and outcomes which allow comparison with previous published research. An example of this is where stressful events, examples as mentioned above, were amalgamated into a single variable, named stress event.

Statistical analysis

Statistical analysis was performed using *R Studio* statistical software. Summary statistics were calculated for the whole case-control study population, and then individually for each of the three geographical areas – rural, urban and peri-urban. Differences in exposure characteristics between areas was evaluated using Pearson's χ^2-test for categorical variables, and the Student's t-test for numerical variables.

Relationships between environmental factors and AD in the entire population sample was first calculated using χ^2-tests. Bivariate logistic regression was used to calculate crude odds ratios (ORs), with 95% confidence intervals (CIs), to estimate the association between AD and individual environmental exposures. This was done for the whole study population, and for each of the three areas individually. Statistically significant findings from bivariate models were then included in a multivariate model. Multivariate logistic regression (MLR) analysis was performed using eight variables. Two variables, age and sex, were chosen *a priori*, and 5 were chosen based on significance of bivariate associations and Akaike models of best fit, with the chosen model having the lowest Akaike Information Criterion (AIC) compared to other models. Variables showing collinearity and likely confounding with others were excluded from the analysis.

Ethics

The original study conducted in 1999 was approved by the Human Research Ethics Committee, University of Cape Town (reference 116/98), and by the Queen's Medical Centre (Nottingham) Ethics Committee. This study was approved by the Human Research Ethics Committee, University of Cape Town, reference 701/2022. All data were anonymized before any analysis.

Results

Demographics and comparison of area exposures

A total of 739 children were included – 293 from the rural area, 387 from the urban area, and 59 from the peri-urban areas (**Table 1**). Of these 739 participants, 253 were cases who fulfilled the diagnostic criteria for AD, while 486 were controls without AD. Male participants accounted for 46.1% of the total, and there was a mean age of 6.8 years across all groups. There was no significant difference in the distribution of participants' sex between the group locations. The median number of people living in the home was 6 in the rural and urban areas, and 5 in the peri-urban area while 82% of the total cohort had at least 1 sibling. More than a third of children in the urban area lived in households of more than 6 people. Of those interviewed, 62% were participant's mothers – 76% in urban area, 61% in peri-urban area, and 44% in the rural area. Grandmothers were interviewed for 14% of children in rural areas, while 38% of interviews in the rural and peri-urban areas were conducted with a non-specified caregiver or family member.

Environmental exposures for all study participants varied substantially across the three geographical areas (see **Table 1**).

Rural area children

Rural children tended to live in mud brick houses with thatched roofs, use pit latrines or no formal toilets. Water was collected predominantly from rivers, streams, dams or rainwater tanks, and almost all had regular contact with a variety of domestic and farm animals. Eighty four percent of children were exclusively breastfed for the first month of life, dropping to 11.6% by 4 months, and half were breastfed for longer than 18 months. As many as 92% of rural children had been fed with formula milk during their infancy, higher than in urban and peri-urban areas. Children living in the rural area were more than three times as likely (54.6% vs 13.7%) to have ever been exposed to tobacco smoke than urban children, with 38% having tobacco smoke exposure at the time of the study. Wood and paraffin were the most common fuels used for cooking and heating in the home. Dampness and mould in rural homes were uncommon, at 6.8% and 2.4% respectively.

Urban area children

In the urban areas, the majority of children lived in brick homes (91.9%) with cement flooring (60.5%) and either asbestos (65.9%) or zinc sheet (26.4%) roofing, used flushed toilets (99.4%) and had access to tap water (96.1%). Almost none had exposures to farm animals. Only 10% owned a dog and 3% a cat. More than 70% of urban children regularly swam in the ocean. Nearly a quarter of children were breastfed for less than 6 months, while mean breastfeeding duration was the lowest of the three areas at 14.9 months and exclusive breastfeeding duration a median of only 1 month. More urban children were exposed to chemicals within the house than those in rural or peri-urban areas, such as perfumed body sprays (83%) and air-fresheners (38%), bleach (86%), and furniture polish (36%). Homes tended to use electricity and paraffin for cooking, and 88% used paraffin for heating in the home. Half of homes had a formal smoke outlet, and over one third of homes were in close proximity to a power station.

Peri-urban area children

Many children living in the peri-urban area lived in homes with earth or cement flooring and zinc roofs, with a high proportion of damp and mould within the home (35.6% and 18.6% respectively) (**Table 2**). Two thirds used flush toilets, and the other third, bucket toilets. Infant feeding and weaning practices were very similar to that in the rural areas, with three quarters of children receiving solid foods before 6 months old, and only 10% received exclusive breastfeeding until 4 months. Nearly 20% of children had regular contact with cats, and 15.3% with dogs, higher than that of urban children. Peri-urban homes had the highest prevalence of infestation with rats (81%), and other pests such as fleas, cockroaches and mosquitos. As a result, 90% of these homes regularly used pesticides and other poisons compared to 70% in urban and 58% in rural areas. Paraffin was the predominant fuel source for cooking and heating, used in 76% of homes, with only 2 homes having formal smoke outlets. Forty five percent of children had been exposed to tobacco smoke at any time, with similar numbers living in close proximity to high volumes of motor vehicle traffic.

Children living in urban and peri-urban areas had higher prevalences of psychological and behavioural difficulties, compared to those in the rural area. Five percent of all children in the study had experienced a stressful event in the preceding 6 months. A stressful event was defined

as having experienced problems within the home or school, a death in the family, parental divorce, severe illness or abuse.

Bivariate analysis

Logistic regression was performed to assess for each variable's association with AD. Bivariate models were used to analyse the data for the whole study population combined, and for each area individually, resulting in crude odds ratios (**Table 2**). Variables from bivariate models found to be statistically significant were later included in a single multivariate regression model (**Table 3**).

In home exposures

The results from regression models indicate that children living in homes where pesticides were used had an 93% increased odds of AD, compared to those living in homes which did not use these products (OR 1.93; 95% CI 1.38 – 2.74) (**Table 2**). Use of pesticide sprays on or around the bed, in particular, were shown to be associated with an increased odds of AD (OR 2.21; 95% CI 1.59 – 3.07 and OR 2.04; 95% CI 1.46 – 2.87 respectively). Perfumed sprays, bleach and furniture polish use in the home were not associated with AD.

Results show that, compared to children living in homes without mould and visible dampness, those living in damp and /or mouldy homes had a significantly greater odds of having AD (OR 3.23; 95% CI 1.88 – 5.67 and OR 2.90; 95% CI 1.92 – 4.43, respectively),

The use of carpets in the home associated with a 50% lower odds of AD in our whole study population (OR 0.50; 95% CI 0.33 – 0.76). This was found in the rural cohort alone, and not in the urban or peri-urban areas. Analysis comparing other housing materials and how they related to AD odds was not performed, as homes tended to be built using different materials in each of the three geographical areas.

With regards to fuels used in the home, odds ratios of all three areas combined showed no significant difference between the use of dirty versus clean household fuels for both cooking and fuel use, and child symptoms of AD. Dirty fuels were defined as wood, coal and paraffin.

In peri-urban areas, however, where homes were not fitted with smoke outlets, children whose families used dirty fuels had significantly increased odds of AD (OR 6.62; 95% CI 2.16 – 22.76), compared to those whose families used mostly clean fuels (gas, electricity or none).

Pests

Having current infestations with fleas (OR 1.93; 95% CI 1.42 – 2.63), as well as with ticks (OR 2.58; 95% CI 1.27 – 5.37) were associated with increased odds of AD. Exposure to other insects such as mosquitos, bedbugs and cockroaches did not affect odds of AD in our study population. Current infestation with rats in homes was also not shown to be associated with AD.

Animals

Our study did not show any protective associations between pet (cat and dog) ownership. In the urban group, the 10% of children who had dogs as pets were more than twice as likely to have AD than the majority without dogs (OR 2.33; 95% CI 1.20 – 4.59). There were no association found between ownership of cats and AD.

In the rural area, regular contact with a specific species of farm animal, such as cows, pigs, sheep or goats, did not indicate an association with AD. Rural children exposed to <u>any</u> farm animal, however, had a strong inverse association with AD (OR 0.20; 95% CI 0.04 – 0.78), compared to those with no exposure. Similarly, current ownership of birds, including chickens and other feathered animals, was also shown to be associated with a lower odds of AD in this rural group. As 98% of children in the rural area had regular close contact to at least one species of farm animal, including birds, this finding may be confounded by other rural exposures. Analysis for children in urban areas and peri-urban areas was not interpreted owing to the low levels of exposure to farm animals among these children.

Smoking

Among the whole study population, when corrected for study area, exposure to smoking - either *in utero* or in childhood – was not associated with AD. In the rural area, however, the 54.6% of children who had any exposure to tobacco smoke, were almost half as likely to have AD compared to those without any previous exposure (OR 0.58; 95% CI 0.35 – 0.96). This finding

may be explained if tobacco smoke exposure in rural areas acts as a surrogate marker for other unmeasured protective factors present in these areas.

Pollution

Pollution exposures assessed included proximity to, and density of motor vehicle traffic, proximity to power stations and whether tyres were regularly burned close to homes. There was no association found between these exposures and AD in our population.

Toilets

There was a large variance in means of ablution between study areas. In rural areas, pit latrines predominated, with no child having access to a flush toilet. There was no difference in the odds of AD in those using no toilet, compared to those using pit latrines. In contrast, flush toilets were available to almost all children in the urban area, and 61% of children residing in the peri-urban area. The remaining 38% of children, who used predominantly bucket toilets, had a much higher odds of AD compared to those using flush toilets (OR 16.47; 95% CI 4.46 – 81.93)

Feeding and weaning

Almost all children in the study received mixed feeding from the time of birth, with 98% of the sample having received breast milk alternatives such as formula milk, cow's milk, goat's milk or water. Despite low number of exclusive breast feeding, children were partially breastfed for an average of 17 months.

Approximately 30% of children were weaned, defined as having solids introduced to their diet, later than 4 months of age. Overall, these children had a higher odds of having AD compared to those weaned earlier (OR 1.84; 95% CI 1.34 – 2.53), however this was not consistent across all three locations. Increasing durations of breastfeeding was associated with a non-significant lowered odds of AD compared to those never breastfed, with odds ratios ranging from 0.53 for those breastfed for 0 to 3 months, 0.57 for 6 to 9 months of breastfeeding, and 0.25 for children breastfed for 12 to 15 months. This association was seen up until the age of 15 months, with a longer duration of breastfeeding suggesting no additional benefit.

Stress exposure

Exposure to a stressful event in the preceding 6 months, defined as having experienced a death in the family, parental divorce, severe illness, abuse or difficulties at school, were shown to significantly increase odds of AD in our study population (OR 2.23; 95% CI 1.16 – 4.34). When comparing between sites, this was shown to be statistically significant in the urban group only, and not in the rural and peri—urban groups.

Multivariate analysis:

The MLR model identified several statistically significant associations with AD, highlighting the importance of environmental and psychological factors in its development. Individuals who commenced solid diets after 4 months were significantly more likely to develop AD (OR 1.75; 95% CI 1.26 – 2.44) compared to those weaned earlier (**Table 3**). Similarly, exposure to fleas increased the likelihood by 68% (OR 1.68; 95% CI 1.21 – 2.34), and exposure to mould more than tripled the odds of AD compared to those without current exposure (OR: 3.01; 95% CI 1.72 – 5.36). Other significant predictors include exposure to pesticides in the home (OR 1.50; 95% CI 1.05 – 2.17) and stressful events (OR 2.37; 95% CI 1.19 – 4.73).

Multivariate analysis using the same 7 variables was performed for each of the geographical areas. In the rural area, mould exposure remained statistically significant, whereas weaning, flea exposure, pesticide use and stress events no longer showing statistical association with AD (see Appendix 3). The MVR model for the urban group showed the inverse, with mould exposure no longer showing statistical significant association with AD. The four other variables were all shown to be associated with AD in this group. In the peri-urban group, none of the 5 chosen variables were shown to have a statistically significant association with AD. Notably, the sample size in the peri-urban areas was about 15-20% of the size of the samples in the other areas. The results of MVR stratified by site were similar to results found in bivariate analysis for each of the areas, apart from mould exposure in urban areas, which had a significantly increased association with AD in the urban area. It is possible that higher levels of exposure to other unknown risk factors, dampened the individual role of mould in this group.

Discussion:

This study delves into the significant impact of indoor environmental exposures on children predisposed to developing atopic dermatitis (AD). Specifically, pesticide sprays and mould were identified as contributors to increased odds of AD among children. Children living in peri-urban areas, where homes were not fitted with smoke outlets, had 6 times higher odds of having AD compared to those using clean fuels. These findings underscore the role of airborne irritants and pollutants within inadequately ventilated spaces, which act upon an impaired skin barrier by stimulating immune cells and exacerbating the allergic response.[27]

Our research did not establish any associations between AD prevalence and proximity to high traffic or emission zones, contrary to findings reported in studies conducted in heavily polluted areas like Korea and China.[11] Notably, our study relied on subjective caregiver estimates of ambient pollution exposure, without independent verification by the research team, potentially introducing measurement bias.

Contrary to large-scale meta-analyses, multivariate analysis in our study did not reveal an association between AD and tobacco smoke exposure (ever).[28,29] No association was detected on bivariate analysis of any pre- or postnatal tobacco exposure.

Factors such as building materials, types of toilets used, and swimming in open bodies of water did not demonstrate significant associations with AD prevalence in this study. This is in keeping with previous research. A study conducted in Vietnam found that having access to flush toilets, compared to no toilet or use of a bucket toilet, inferred a significantly increased risk of dust mite skin allergen sensitisation, however, this did not correlate to an increase in visible signs of eczema.[30] Few studies have found links to household building and furnishings and AD, with a Chinese study finding an association between composite wooden flooring and AD in children.[31] A narrative review published in 2023 discussed existing evidence of swimming and its effect on AD.[32] Proposed effects of swimming on AD included an increase in trans-epidermal water loss, skin irritation and risk of secondary infection, however the researcher found no convincing evidence that swimming worsened or improved eczema in children. In our research, the observed homogeneity of exposures within specific areas, and

significant heterogeneity across different study locations, likely account for the lack of meaningful associations with these environmental factors.

Household infestations with fleas and ticks were shown to be associated with AD in our study population. Flea-allergy dermatitis is a well-documented condition among dogs and cats, as a results of a Type I or Type IV hypersensitivity to flea saliva.[33] Similarly, dermatoses, such a papular urticaria and other urticarial reactions are common in humans exposed to various insects, including ticks, lice, cimex, fleas and mites.[34] This may suggest that exposure to insect saliva may trigger an immune response, resulting in itchy skin, where the itch-scratch-itch cycle exacerbates AD in pre-disposed individuals.

In contrast to earlier research suggesting a protective effect of pet ownership against atopic conditions,[35] our study did not find evidence supporting this hypothesis in our population. In contrast, children living in urban environments who had dogs as pets, had a higher odd of AD compared to those who did not have dogs. This may point to a higher risk of exposure to pests such as fleas and ticks, and indeed pesticides, among these children compared to those with no pets. There were no identified associations between AD and exposure to farm animals, notwithstanding a statistically insignificant negative association noted between AD prevalence and exposure to farm animals in rural settings, where nearly all participants reported such exposure.

Within our study cohort, a high prevalence of mixed feeding practices, low rates of exclusive breastfeeding, and early introduction of solids likely reflect maternal employment and childcare practices within the family network. Cultural norms, and the high prevalence of Human Immunodeficiency Virus (HIV) in South Africa at the time of the study,[36] are also likely to have heavily influenced infant feeding practices. Although multiple studies have explored the impact of breastfeeding duration and weaning practices on atopic conditions,[37–39] our findings, based on an average breastfeeding duration of 17 months, did not reveal any statistical benefits from prolonged breastfeeding. There was noted to be non-significant lowered odds of AD in those children breastfed in the early months, however this was not seen after the age of 15 months. These findings suggest that mixed feeding practises, with early introduction of solids, together with breastfeeding for the first 12 to 15 months, may be instrumental in reducing risk of AD and other atopic conditions.

Results from the study also highlight the potential role of psychological stress on AD, with preceding family or individual stress events correlating to a significantly increased odds of AD in our study population. This relationship was explored within a focus group of 28 participants in Sweden, who reported that both acute and chronic stress contributed to worsening symptoms of AD and pruritus.[40] Research has indicated that chronic stress disrupts the normal hypothalamic-pituitary-adrenal axis, modulating glucocorticoid action within the skin and increasing pro-inflammatory cytokines, resulting in heightened inflammation and dysregulation of skin homeostasis.[41]

Several strengths bolstered the integrity of our study and mitigated researcher bias. Limiting the number of research assistants minimized inter-observer variability and enhanced data reliability. Moreover, the fluency of researchers in both isiXhosa and English, coupled with their deep understanding of local cultures and norms, facilitated effective communication and accurate information gathering from participants.

The reliability of our primary outcome measure was bolstered by dermatologist diagnoses and the use of a partially validated diagnostic tool for AD assessment. Additionally, participant recruitment focused predominantly on areas inhabited by amaXhosa clans from the Eastern Cape, aimed at reducing genetic and cultural heterogeneity within the study population, although the impact on genetic confounding was likely minimal given the complex polygenic nature of AD.

The study design had inherent limitations that warrant consideration. Exposures were primarily assessed through caregiver memory and estimation, potentially introducing recall bias. Furthermore, secondary caregivers or grandparents, lacking a complete exposure history, may have provided incomplete or inaccurate data, particularly regarding breastfeeding duration, weaning practices, and *in utero* exposures. There was no scope for corroboration of data by researchers through home inspections, or additional interviews with mothers.

The cross-sectional nature of our dataset, capturing information at a single time point, precluded causal inferences regarding AD. Given the variable and remitting nature of AD, influenced by seasonal and climatic variations, temporal variations in data collection across different areas may have impacted outcome measures. Nonetheless, our study provides

valuable insights into correlations between previously identified contributing factors and AD outcomes.

Although conducted over two decades ago, this study, which aimed to explore the relationships between AD and various environmental exposures in distinctly different residential environments, still holds relevance as we continue to identify risk factors for AD, specifically in children. The use of this historical dataset offered a unique opportunity to gain a perspective on rural exposures before the widespread urbanization observed globally today. Interestingly, prevalence data from studies conducted nearly 20 years apart, show little difference in prevalence of AD in rural areas, suggesting persistence of protective exposures in these areas despite urbanisation.

Conclusion:

This study revealed that exposure to mould and pesticides in the home, and direct exposure to fleas and ticks are associated with AD, as are stressful events and later initiation of weaning, and may be important modifiable risk factors. This research enhances our understanding of the nuanced interplay between environmental exposures and AD among children in diverse South African settings. By elucidating these associations, our findings underscore the need for targeted interventions addressing indoor environmental air quality, use of indoor pesticides, and the impact of psychological stressors on the development of AD. Future research should involve more targeted research on these subjects to further evaluate causal pathways and refine preventive strategies for this highly prevalent childhood condition.

Tables of results:

Table 1: *Population summary statistics*

		TOTAL	RURAL	URBAN	PERI-URBAN	p-value
TOTAL (n)		N = 739	N = 293	N = 387	N = 59	
POPULATION CHARACTERISTICS						
Eczema N (%)		253 (34.2)	87 (30.0)	137 (35.4)	29 (49.2)	-
Age (years) (mean)		6.8	6.8	7.0	5.9	**0.01**
Sex	Male	341 (46.1)	139 (47.4)	175 (45.2)	27(45.8)	0.85
N (%)	Female	398 (53.9)	154 (52.6)	212 (54.8)	32 (54.2)	
Number of people in the house (median [IQR])		6 [4;8]	6 [5;8]	6 [4;8]	5 [4;6]	**<0.05**
(Missing data)		Na = 183	Na = 182	Na = 1	Na = 0	
0-3 people		69 (9.3)	13 (4.4)	46 (11.9)	10 (16.9)	
3-6 people		276 (37.3)	47 (16.0)	189 (48.8)	40 (67.8)	
6-9 people		145 (19.6)	40 (13.6)	101 (26.1)	4 (6.8)	
>9 people		66 (8.9)	11 (3.8)	50 (12.9)	5 (8.5)	
Has Siblings (Yes) N (%)		607 (82.1)	254 (86.7)	306 (79.0)	47 (79.7)	0.07
	Mother	460 (62.2)	130 (44.4)	294 (76.0)	36 (61.1)	
Adult	Father	16 (2.2)	4 (1.4)	12 (3.1)	0	
Interviewed	Grandmother	43 (5.8)	41 (14.0)	1 (0.3)	1 (1.7)	**<0.05**
N (%)	Grandfather	5 (0.7)	5 (1.7)	0	0	
	Other	214 (29.0)	113 (38.6)	79 (20.4)	22 (37.2)	
FEEDING						
Duration of BF (months)						
Median (months) [IQR]		17.0 [6.3;24.0]	24.0 [12;24]	12.0 [4;24]	24.0 [12;24]	**<0.05**
Mean (months)		17.0	19.1	14.9	19.1	
BF less than 6 months		134 (18.1)	38 (13.0)	87 (22.5)	9 (15.3)	**<0.05**
BF 6 to 12		44 (6.0)	13 (4.4)	29 (7.5)	2 (3.4)	0.09
BF 12 to 18		143 (19.4)	61 (20.8)	69 (17.8)	13 (22.0)	0.89
BF for >= 18 months		322 (43.6)	153 (52.2)	137 (35.4)	32 (54.2)	**<0.05**
EBF duration (months)						
Median [IQR]		2 [1;3]	2 [1;3]	1 [0;3]	3 [1;3]	
Mean		2.2	2.3	2.1	2.6	
EBF >=1 month		486 (65.8)	247 (84.3)	206 (53.2)	33 (55.9)	**<0.05**
EBF >=2 months		303 (41.0)	171 (58.4)	106 (27.4)	26 (44.1)	**<0.05**
EBF >=4 months		61 (8.3)	34 (11.6)	21 (5.4)	6 (10.2)	**<0.05**
EBF >=6 months		20 (2.7)	13 (4.4)	6 (1.6)	1 (1.7)	0.07
Solids after 4 months		241 (32.6)	130 (44.4)	82 (21.2)	29 (49.2)	**<0.05**
Solids after 6 months		113 (15.3)	64 (21.8)	34 (8.8)	15 (25.4)	**<0.05**
Any breastmilk alternative (at any time)		724 (98.0)	287 (98.0)	380 (98.0)	57 (96.6)	0.73
Formula milk (at any time)		602 (81.5)	270 (92.2)	290 (74.9)	42 (71.2)	**<0.05**
TOBACCO SMOKE EXPOSURE						
Maternal smoking during pregnancy		54 (7.3)	38 (13.0)	11 (2.8)	5 (8.5)	**<0.05**
Smoke exposure during pregnancy		42 (5.7)	28 (9.6)	10 (2.6)*	4 (6.8)	**<0.05**
Smoke exposure current		168 (22.7)	112 (38.2)	37 (9.6)	19 (32.2)	**<0.05**
Smoke exposure ever		240 (32.5)	160 (54.6)	53 (13.7)	27 (45.8)	**<0.05**
Mom smoked cigarettes Ever		53 (7.2)	35 (11.9)	12 (3.1)	1 (1.7)	**<0.05**
Mom smoked pipe ever		16 (2.2)	13 (4.4)	1 (0.3)	2 (3.4)	**<0.05**
PEOPLE IN THE HOUSE						
		Na = 183	Na = 182	Na = 1	Na = 0	
Median [IQR]		6 [4;8]	6 [5;8]	6 [4;8]	5 [4;6]	
0-3 people		69 (9.3)	13 (4.4)	46 (11.9)	10 (16.9)	
3-6 people		276 (37.3)	47 (16.0)	189 (48.8)	40 (67.8)	
6-9 people		145 (19.6)	40 (13.6)	101 (26.1)	4 (6.8)	
>9 people		66 (8.9)	11 (3.8)	50 (12.9)	5 (8.5)	
FUEL USE*						

Cooking	Electric (grid)	198 (26.7)	3 (1.0)	181 (46.8)	14 (23.7)	**<0.05**
	Electric (batt)	34 (4.6)	1 (0.3)	25 (6.5)	8 (13.6)	**<0.05**
	Dung	1 (0.1)	1 (0.3)	0	0	**<0.05**
	Coal	1 (0.1)	0	0	1 (1.7)	**<0.05**
	Gas	11 (1.5)	4 (1.4)	7 (1.8)	0	**<0.05**
	Paraffin	286 (38.7)	89 (30.4)	161 (41.6)	36 (61.0)	**<0.05**
	Wood	129 (17.5)	129 (44.0)	0	0	**<0.05**
	Other	69 (9.3)	65 (22.2)	4 (1.0)	0	**<0.05**
	Electric (total)	232 (31.4)	4 (1.4)	206 (53.2)	22 (37.3)	**<0.05**
	Coal/dung/wood	131 (17.7)	130 (44.4)	0	1	**<0.05**
	Paraffin and gas	297 (40.2)	93 (31.7)	168 (43.4)	36 (61.0)	**<0.05**
Heating	Electricity	40 (5.4)	1 (0.3)	32 (8.3)	7 (11.9)	**<0.05**
	Paraffin	433 (58.6)	47 (16.0)	341 (88.1)	45 (76.3)	**<0.05**
	Wood	215 (29.1)	215 (73.4)	0	0	**<0.05**
	Other	8 (1.1)	7 (2.4)	1 (0.3)	0	**<0.05**
	None	18 (2.4)	16 (5.5)	2 (0.5)	0	**<0.05**
Dirty	Cooking	486 (65.8)	284 (96.9)	165 (42.6)	37 (62.7)	**<0.05**
N (%)	Heating	657 (88.9)	269 (91.8)	343 (88.6)	45 (76.3)	0.11
	Both	457 (61.8)	262 (89.4)	161 (41.6)	34 (57.6)	**<0.05**
Clean	Cooking	244 (33.0)	8 (2.7)	214 (55.3)	22 (37.3)	**<0.05**
N (%)	Heating	59 (8.0)	17 (5.8)	34 (9.0)	7 (11.9)	0.16
	Both	42 (5.7)	1 (0.3)	33 (8.8)	7 (11.9)	**<0.05**
Both clean and dirty		211 (28.6)	23 (7.8)	177 (45.7)	11 (18.6)	**<0.05**
Petrochemicals	Cooking	297 (40.2)	92 (31.4)	168 (57.3)	36 (61.0)	**<0.05**
N (%)	Heating	433 (58.6)	46 (15.7)	342 (88.4)	45 (76.3)	**<0.05**
	Both	235 (31.8)	23 (7.8)	163 (55.6)	34 (57.6)	**<0.05**
Smoke outlet in the house		228 (30.8)	23 (7.8)	203 (52.5)	2 (3.4)	**<0.05**
***Fuel use:** **Dirty = coal/wood/paraffin/other** **Clean = electricity/gas/none** **Petrochemicals = gas and paraffin**						
MOULD/DAMP						
Damp		108 (14.6)	20 (6.8)	67 (17.3)	21 (35.6)	**<0.05**
Mould		59 (8.0)	7 (2.4)	41 (10.6)	11 (18.6)	**<0.05**
PESTS						
Rats		586 (79.3)	241 (82.2)	292 (75.5)	53 (89.9)	**<0.05**
Cockroaches		369 (49.9)	37 (12.6)	296 (76.5)	36 (61.0)	**<0.05**
Mosquitos		235 (31.8)	123 (42.0)	87 (22.5)	25 (42.4)	**<0.05**
Fleas		377 (51.0)	124 (42.3)	204 (52.7)	49 (83.1)	**<0.05**
Ticks		32 (4.3)	25 (8.5)	6 (1.6)	1 (1.7)	**<0.05**
Bedbugs		118 (16.0)	74 (25.3)	37 (9.6)	7 (11.9)	**<0.05**
PESTICIDE USE						
Use of pesticides (any)		494 (66.8)	170 (58.0)	271 (70.0)	53 (89.9)	**<0.05**
Types	Doom	206 (27.9)	42 (14.3)	139 (35.9)	25 (42.4)	**<0.05**
N (%)	Fastkill	136 (18.4)	73 (24.9)	56 (14.5)	7 (11.9)	**<0.05**
	Baygon	12 (1.6)	0 (0)	12 (3.1)	0 (0)	**<0.05**
	Target	32 (4.3)	1 (0.3)	29 (7.5)	2 (3.4)	**<0.05**
	Ratex	29 (3.9)	8 (2.7)	8 (2.1)	13 (22.0)	**<0.05**
	Multiple	124 (16.8)	55 (18.8)	33 (8.5)	36 (61.0)	**<0.05**
Insecticide spray for bed surrounds		209 (28.3)	44 (15.0)	148 (38.2)	17 (28.8)	**<0.05**
Insecticide spray for bedding		187 (25.3)	30 (10.2)	141 (36.4)	16 (27.1)	**<0.05**
DETERGENTS AND ODOURANTS						
Air fresheners		165 (22.3)	14 (4.8)	145 (37.5)	6 (10.2)	**<0.05**
Hair spray		394 (53.3)	95 (32.4)	266 (68.7)	33 (55.9)	**<0.05**
Body spray		469 (63.5)	112 (38.2)	321 (83.0)	36 (61.0)	**<0.05**
Perfumed bleach		418 (56.6)	61 (20.8)	332 (85.8)	25 (42.4)	**<0.05**
Furniture polish		166 (22.5)	25 (8.5)	138 (35.7)	3 (5.1)	**<0.05**
ANIMAL EXPOSURES						
Cat		149 (20.2)	126 (43.0)	12 (3.1)	11 (18.6)	**<0.05**
Dog		248 (33.6)	200 (68.3)	39 (10.0)	9 (15.3)	**<0.05**
Birds*		270 (36.5)	269 (91.8)	4 (1.0)	0 (0)	**<0.05**
Goat		136 (18.4)	135 (46.1)	1 (0.3)	0 (0)	**<0.05**
Pig		226 (30.6)	225 (76.8)	1 (0.3)	0 (0)	**<0.05**
Cow		142 (19.2)	141 (48.1)	1 (0.3)	0 (0)	**<0.05**
Any farm mammal		242 (32.7)	239 (81.6)	3 (0.1)	0 (0)	**<0.05**
Any farm animal#		286 (38.7)	285 (95.9)	5 (1.3)	0 (0)	**<0.05**
***Birds (chickens and/or other feathered animals)**						

#Farm animal (goat, pig, cow, chicken)					
WATER SOURCE					
Piped (inside)	241 (32.6)	0	237 (61.2)	4 (6.8)	**<0.05**
Piped (yard)	89 (12.0)	0	58 (15.0)	31 (52.5)	**<0.05**
Piped (public tap - free)	99 (13.4)	1 (0.3)	77 (19.9)	21 (35.6)	**<0.05**
Piped (public tap - paid)	2 (0.3)	0	0	2 (3.4)	**<0.05**
ANY TAP WATER	431 (58.3)	1 (0.3)	372 (96.1)	58 (98.3)	**<0.05**
Borehole	4 (0.5)	4 (1.4)	0	0	**<0.05**
Rainwater tank	14 (1.9)	14 (4.8)	0	0	**<0.05**
River / stream	254 (34.4)	254 (86.7)	0	0	**<0.05**
Dam / stagnant water	13 (1.8)	13 (4.4)	0	0	**<0.05**
Other	2 (0.3)	2 (0.7)	0	0	**<0.05**
TOILETS					
Flush toilet	419 (56.7)	0 (0)	383 (99.4)	36 (61.0)	**<0.05**
Pit latrine	33 (4.5)	21 (11.0)	0 (0)	1 (1.7)	**<0.05**
Bucket toilet	25 (3.4)	2 (0.7)	1 (0.3)	22 (37.3)	**<0.05**
No toilet	258 (34.9)	257 (88.3)	1 (0.3)	0 (0)	**<0.05**
TRAFFIC					
Traffic (low)	285 (38.6)	156 (54.7)	106 (37.2)	23 (8.1)	**<0.05**
Traffic (moderate)	333 (45.1)	123 (42.0)	206 (53.2)	4 (6.8)	**<0.05**
Traffic (high)	107 (14.5)	9 (3.1)	71 (18.3)	27 (45.8)	**<0.05**
Low = less than 20 vehicles per day Moderate = less than 20 vehicles per hour High – Traffic throughout the day or heavy rush hour traffic					
INDUSTRY NEARBY					
Power station	155 (21.0)	0	146 (37.7)	9 (15.3)	**<0.05**
Substation	1 (0.1)	0	1 (0.3)	0	**<0.05**
Power lines	81 (11.0)	8 (2.7)	60 (15.5)	13 (22.0)	**<0.05**
SWIMMING					
Ocean	318 (43.0)	12 (4.1)	282 (72.9)	24 (40.7)	**<0.05**
River	124 (16.8)	118 (40.3)	4 (1.0)	2 (3.4)	**<0.05**
PSYCHOSOCIAL					
STRESS EXPOSURE					
Stress Events in the last 6 months	38 (5.1)	9 (3.1)	26 (6.7)	3 (5.1)	0.10
HOUSING					
Wall materials					
Mud	256 (34.6)	255 (87.6)	0 (0)	1 (1.7)	**<0.05**
Wood	72 (9.7)	0	29	43	**<0.05**
Iron/zinc sheeting	20 (2.7)	0	10	10	**<0.05**
Cardboard	4 (0.5)	0	1 (0.3)	3 (5.1)	**<0.05**
Mud	49 (6.6)	21 (7.2)	28 (7.2)	0	**<0.05**
Brick	374 (50.6)	14 (4.8)	317 (91.9)	43 (72.9)	**<0.05**
Flooring					
Earth	268 (36.3)**	165 (56.3)	1 (0.8)	25 (47.5)	**<0.05**
Tiles	40 (5.4)	0 (0)	40 (10.4)	0 (0)	**<0.05**
Dung	76 (10.2)	72 (24.6)	1 (0.3)	3 (5.1)	**<0.05**
Cement	257 (34.8)	9 (3.1)	234 (60.5)	14 (23.8)	**<0.05**
Wood	104 (14.1)	0 (0)	92 (23.8)	12 (20.3)	**<0.05**
Other	67 (9.1)	45 (15.4)	17 (4.4)	5 (8.5)	**<0.05**
Floor covering					
Carpets	370 (50.1)	27 (9.2)	300 (77.5)	43 (72.9)	**<0.05**
Roofing					
Thatch	227 (30.7)	222 (75.8)	0 (0)	5 (8.5)	**<0.05**
Asbestos	258 (34.5)	0 (0)	255 (65.9)	0 (0)	**<0.05**
Tile	43 (5.8)	30 (10.2)	8 (2.1)	5 (8.5)	**<0.05**
Wood	33 (4.7)	0 (0)	20 (5.2)	13 (22.0)	**<0.05**
Zinc sheeting	174 (23.5)	37 (12.6)	102 (26.4)	35 (59.3)	**<0.05**

***Table 2**: Table depicting crude odds ratios of Bivariate Logistic Regression (BLR) Models of various Environmental Factors to the outcome of AD, with 95% confidence intervals and p-values*

	TOTAL	Rural	Urban	Peri-urban
FEEDING				
Ever breastfed (vs never breastfed)	1.12 0.73 – 1.74 0.613	1.14 0.52 – 2.70 0.747	1.06 0.63 – 1.84 0.819	2.00 0.18 – 44.50 0.580
Weaning initiated after 4 months (compared to earlier than 4 months)	**1.84** **1.34 – 2.53** **<0.001**	1.34 0.81 – 2.21 0.258	**3.21** **1.96 – 5.30** **<0.001**	1.22 0.44 – 3.44 0.698
Exposure to goats milk	1.66 0.83 – 3.28 0.146	**2.44** **1.11 – 5.33** **0.024**	-	2.15 0.19 – 47.79 0.542
Duration of breastfeeding (BF) ***Compared to children never breastfed**				
1-3 months	0.53 0.23 – 1.19 0.126	0.44 0.05 – 2.50 0.375	0.48 0.18 – 1.25 0.136	-
3-6 months	**0.38** **0.14 – 0.95** **0.043**	0.80 0.13 – 4.18 0.794	**0.24** **0.07 – 0.75** **0.019**	-
6-9 months	0.56 0.14 – 1.89 0.368	0.40 0.02 – 3.30 0.447	0.86 0.15 – 4.55 0.856	-
9-12 months	0.57 0.28 – 1.15 0.112	0.70 0.21 – 2.56 0.572	**0.36** **0.14 – 0.90** **0.030**	-
12-15 months	0.25 0.04 – 1.07 0.095	-	0.33 0.04 – 1.62 0.204	-
15-18 months	1.98 0.88 – 4.57 0.102	3.09 0.76 – 13.88 0.124	1.24 0.43 – 3.63 0.694	-
18+ months	0.99 0.53 – 1.88 0.976	1.21 0.42 – 4.00 0.731	0.87 0.39 – 1.98 0.738	-
PEOPLE IN THE HOUSE				
More than 6 (compare to less than 6)	1.27 0.90 – 1.80 0.175	**2.39** **1.08 – 5.49** **0.035**	1.04 0.67 – 1.60 0.856	1.35 0.32 – 6.04 0.677
TOBACCO SMOKE EXPOSURE				
Smoke exposure during pregnancy (compared to none)	1.04 0.52 – 1.99 0.917	0.65 0.23 – 1.59 0.376	**6.68** **1.59 – 45.25** **0.019**	0.32 0.02 – 2.69 0.338
Smoke exposure (current)	0.83 0.57 – 1.20 0.338	0.65 0.38 – 1.10 0.117	1.27 0.63 – 2.53 0.493	1.23 0.41 – 3.72 0.713
Smoke exposure ever (compared to never)	0.80 0.57 – 1.11 0.177	**0.58** **0.35 – 0.96** **0.036**	1.33 0.72 – 2.41 0.356	0.93 0.33 – 2.60 0.887
Mom smoked cigarettes ever				
Mom smoked pipe ever				
FUEL USE£				
Heating, Mostly dirty (compared to mostly clean)	**0.58** **0.34 – 0.99** **0.045**	-	**0.14** **0.06 – 0.31** **<0.001**	**9.00** **1.38 – 177.66** **0.050**
Cooking, Mostly dirty (compared to mostly clean)	0.96 0.69 – 1.32 0.783	0.41 0.10 – 1.78 0.219	1.01 0.66 – 1.54 0.966	**6.28** **1.99 – 22.84** **0.003**
Mostly dirty fuels only (compared to clean or mixed)	1.10 0.81 – 1.51 0.535	1.24 0.55 – 3.07 0.617	1.07 0.70 – 1.62 0.769	**6.62** **2.16 – 22.76** **0.001**
£Fuel use:				

Dirty = coal/wood/paraffin/other, Clean = electricity/gas/none.				
Smoke outlet in the house. (Yes)	0.79 0.57 – 1.11 0.177	3.44 1.45 – 8.39 0.005	0.51 0.33 – 0.77 0.002	-
Dirty fuel use (houses WITH smoke outlet)	1.40 0.77 – 2.51 0.265	-	0.98 0.48 – 1.94 0.954	-
Petrochemicals				
MOULD/DAMP				
Damp in the home (current)	**2.90** **1.92 – 4.43** **<0.001**	**3.17** **1.26 – 8.15** **0.014**	**2.09** **1.22 – 3.58** **0.007**	**6.15** **1.94 – 22.44** **0.003**
Mould in the home (current)	**3.23** **1.88 – 5.67** **<0.001**	**6.22** **1.31 – 44.03** **0.031**	**6.22** **1.31 – 44.03** **0.031**	3.43 0.87 – 17.14 0.095
PESTS				
Rats	0.71 0.49 – 1.03 0.066	0.21 0.11 – 0.38 <0.001	1.34 0.82 – 2.22 0.254	2.08 0.37 – 15.91 0.421
Cockroaches	1.27 0.94 – 1.73 0.121	1.84 0.88 – 3.74 0.097	0.79 0.49 – 1.29 0.343	1.94 0.68 – 5.79 0.221
Mosquitos	1.29 0.94 – 1.77 0.119	1.01 0.61 – 1.68 0.963	1.96 1.22 – 3.14 0.005	0.70 0.24 – 1.97 0.498
Fleas	**1.93** **1.42 – 2.63** **<0.001**	0.84 0.50 – 1.40 0.514	**3.54** **2.27 – 5.60** **<0.001**	0.59 0.14 – 2.32 0.455
Ticks	**2.58** **1.27 – 5.37** **0.009**	**4.08** **1.77 – 9.79** **0.001**	1.84 0.34 – 10.08 0.458	-
Bedbugs	1.15 0.76 – 1.73 0.492	0.77 0.42 – 1.37 0.382	**2.20** **1.12 – 4.36** **0.022**	2.92 0.57 – 21.68 0.225
POISONS				
Use of pesticides (current)	**1.93** **1.38 – 2.74** **<0.001**	1.04 0.62 – 1.73 0.892	**3.20** **1.93 – 5.51** **<0.001**	0.96 0.17 – 5.62 0.965
Pesticide around the bed (current)	**2.21** **1.59 – 3.07** **<0.001**	**4.45** **2.30 – 8.79** **<0.001**	**2.02** **1.32 – 3.10** **0.001**	0.45 0.13 – 1.41 0.180
Pesticides on bedding (current)	**2.04** **1.46 – 2.87** **<0.001**	**8.38** **3.69 – 20.90** **<0.001**	**1.66** **1.08 – 2.55** **0.020**	0.36 0.10 – 1.17 0.100
DETERGENTS AND ODOURANTS				
Air Fresheners	1.03 0.71 – 1.47 0.878	0.94 0.25 – 2.91 0.925	1.00 0.65 – 1.53 0.993	0.48 0.06 – 2.69 0.421
Hair spray	0.80 0.59 – 1.09 0.152	0.68 0.39 – 1.18 0.180	0.77 0.50 – 1.21 0.262	0.41 0.14 – 1.15 0.094
Body spray	1.01 0.74 – 1.39 0.947	0.98 0.58 – 1.64 0.946	0.94 0.54 – 1.67 0.841	0.46 0.15 – 1.32 0.153
Perfumed bleach	1.01 0.75 – 1.38 0.928	**2.72** **1.51 – 4.88** **0.001**	**0.28** **0.16 – 0.50** **<0.001**	0.92 0.33 – 2.60 0.879
Furniture polish	1.22 0.85 – 1.74 0.280	0.73 0.26 – 1.80 0.516	1.46 0.95 – 2.24 0.085	-

ANIMAL EXPOSURES				
Cat	0.94 0.64 – 1.37 0.747	1.13 0.68 – 1.88 0.626	1.31 0.38 – 4.20 0.646	0.83 0.21 – 3.13 0.786
Dog	1.01 0.73 – 1.39 0.943	1.16 0.68 – 2.01 0.601	**2.33** **1.20 – 4.59** **0.013**	0.46 0.09 – 1.96 0.310
Birds[&]	**0.65** **0.47 – 0.89** **0.008**	**0.39** **0.16 – 0.91** **0.027**	1.84 0.22 – 15.45 0.545	-
Goat	0.98 0.66 – 1.44 0.911	1.38 0.84 – 2.29 0.208	-	-
Pig	0.82 0.58 – 1.14 0.237	1.26 0.70 – 2.36 0.454	-	-
Cow	**0.65** **0.43 – 0.97** **0.038**	0.73 0.44 – 1.20 0.214	-	-
Any farm animal (compared to none)	**0.66** **0.48 – 0.91** **0.012**	**0.20** **0.04 – 0.78** **0.025**	1.22 0.16 – 7.45 0.829	-
TOILETS				
Pit latrine (3) (compared to flush toilets)	1.23 0.58 – 2.52 0.579	-	-	
Bucket toilet (4) (compared to flush toilets)	**13.86** **4.70 – 59.24** **<0.001**	-	-	**16.47** **4.46 – 81.93** **<0.001**
No toilet (6) (compared to flush toilets)	**0.73** **0.52 – 1.02** **0.070**	*0.56 ** *0.26 – 1.21* *0.131* **compared to pit latrine*	-	
WATER SOURCE				
Tap water (compared to other water sources)	**1.42** **1.04 – 1.96** **0.031**			
TRAFFIC				
Low traffic (compared to high)	1.38 0.87 – 2.23 0.181	0.51 0.12 – 1.98 0.323	1.61 0.83 – 3.20 0.162	1.89 0.62 – 5.98 0.268
Moderate traffic (compared to high)	0.97 0.61 – 1.55 0.886	0.15 0.04 – 0.63 0.009	**1.93** **1.07 – 3.60** **0.033**	1.45 0.16 – 13.68 0.727
FLOORS				
Carpet (compared to other floor covering)	**0.50** **0.33 – 0.76** **0.001**	**0.36** **0.13 – 0.95** **0.044**	0.61 0.33 – 1.14 0.117	0.40 0.08 – 1.71 0.229
PSYCHOSOCIAL STRESS EXPOSURE				
Any stress Events in the last 6 months (compared to none)	**2.23** **1.16 – 4.34** **0.016**	3.08 0.80 – 12.71 0.100	**2.26** **1.01 – 5.11** **0.046**	0.50 0.02 – 5.51 0.580

Footnotes:

Missing data as a result of unimodal, or nearly unimodal distribution

Table 3: *Table depicting adjusted odds ratios of* ***Multivariate*** *Logistic Regression (MLR) Models of various Environmental Factors to the outcome of AD, with 95% confidence intervals.*

		AD	
Predictors	*Odds Ratios*	*CI*	*p*
(Intercept)	0.24	0.13 – 0.42	**<0.001**
Weaned after 4 months (compared to earlier)	1.75	1.26 – 2.44	**0.001**
Fleas (current)	1.68	1.21 – 2.34	**0.002**
Mould in the home (current)	3.01	1.72 – 5.36	**<0.001**
Use of pesticides in the home (current)	1.50	1.05 – 2.17	**0.029**
Stress events (in last 6 months)	2.37	1.19 – 4.73	**0.014**
Age in years	0.97	0.91 – 1.04	0.378
Sex [M]	1.23	0.89 – 1.69	0.210
Observations	739		
R^2 Tjur	0.080		

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PART B: APPENDICES

SECTION 1: PROTOCOL

AIMS AND OBJECTIVES

1.1 Aims of the Project

This study aims to identify prenatal, home and ambient environmental exposures associated with atopic eczema in amaXhosa children living in three distinct study locations in South Africa – urban and peri-urban areas in Cape Town, Western Cape, and a rural district, Centane, in the Eastern Cape Province.

1.2 Objectives

1) To identify differences in environmental exposures among three study areas**.**

2) To examine associations between environmental exposures and atopic dermatitis in our study population.

3) To determine how differences in environmental exposures in the three study areas relate to atopic dermatitis in each area.

BACKGROUND AND LITERATURE REVIEW

2.1 Background

Atopic dermatitis (AD) (or atopic eczema) is a chronic, relapsing inflammatory skin condition [1] affecting children and adults. It is the most common inflammatory disease in children[2] with a global prevalence of 15 - 20%.[1] Rates in high-income countries appear to be stabilising [3] with low and middle-income regions continuing to see increases in AD and other atopic conditions.[4] The most comprehensive epidemiological data on atopic conditions can be derived from the International Study of Asthma and Allergies in Childhood (ISAAC), which demonstrated that the presence of eczema symptoms in children aged 6-7 years increased between phase 1 (1992 -1997) and phase 3 (1999-2004) in 44 out of 64 study locations around the world,[5] with countries in Latin America and South East Asia seeing the biggest increases. In South Africa, as part of ISAAC phases 1 and 3, in-person and video questionnaires conducted among a sample of 13 to 14 year old adolescents attending schools within the Cape Town metropole, and largely representative of Cape Town socio-economic demographic profile, found an increasing annual prevalence of itchy rash from 11.8% to 19.4% between 1995 and 2002.[6]

AD is associated with substantial quality-of-life and economic implications which may persist into adult life.[7] The Global Burden of Disease Study shows that AD is the skin condition with the highest disease burden calculated in disability adjusted life years (DALYs).[8] A UK-based study found that AD ranked second out of all chronic childhood conditions, behind cerebral palsy, with respect to effect on quality of life.[9] Multiple factors may be implicated in the high burden of disease as well as the effect on quality of life, including the association with other atopic conditions like asthma, hay-fever and food allergy, increased susceptibility to cutaneous and non-cutaneous infections, sleep deprivation from intense itch, high financial cost of treatment, as well as psychological outcomes.[10–13] Chronic scratching, visible skin disease and the associated stigma may play a role in the development of low self-esteem.[14] Developmental delay, attention deficit and hyperactivity disorder (ADHD), conduct disorders, anxiety and depression have all been shown to occur in higher frequency among children with eczema. [12,13,15,16] This may be a direct effect of the multitude of social sequalae affecting both the child suffering from AD, and their parents. In addition, AD and mental illnesses such as ADHD share important risk factors, including dietary and chemical exposures, which may further

account for their comorbid association.[16,17] Exposure to high levels of inflammatory cytokines and stress hormones associated with AD have been postulated to adversely affect cerebral development, and predispose to symptoms of ADHD.[18]

AD may also be associated with comorbidities later in life. A recent analysis of UK electronic health records suggests that adults with severe and predominantly active AD are at a significantly increased risk of experiencing adverse cardiovascular disease (CVD) outcomes, including myocardial infarction, unstable angina, heart failure, atrial fibrillation, stroke, and cardiovascular death, compared to patients without AD.[19] The association between AD and CVD has been postulated to be as a result of higher clotting risk from increased platelet aggregation and decreased fibrinolysis leading to adverse CVD events. Results in this study by Silverwood et al. were adjusted for potential confounders including conventional risk factors for CVD such as high body mass index, smoking and alcohol consumption, which may be greater in people with AD.[19] Studies conducted in Europe, USA and Asia have linked AD to both systemic and dermatological auto-immune conditions including vitiligo, alopecia areata and systemic lupus erythematosus (SLE).[20] Meta-analysis of observational studies suggest that AD may also be associated with kidney and keratinocyte cancers, including squamous cell carcinomas and basal cell carcinomas,[21] although heterogeneity between included studies mean that more evidence is required to substantiate this finding. Furthermore, much of the association seen in these studies may be attributable to the concurrence of ultraviolet (UV)-induced skin malignancies and AD in fair-skinned individuals, who's populations have been shown to have higher carriage of identified gene mutations associated with AD.

2.2 Gene-environment interaction in atopic dermatitis

Aetiology of AD is multifactorial and complex. Genetic and prenatal factors determine skin barrier function and disease susceptibility, which, together with early life environmental exposures, influence an array of immune and inflammatory pathways.[1] The strongest genetic risk factor for AD identified is mutations in the gene encoding for filaggrin,[22] a protein found in the epidermal layer of skin which plays a role in surface moisture retention and skin barrier integrity.[1] Loss-of-function mutations of the *FLG* gene have been found to be common in people of European and Asian ancestry with AD.[7] The role of *FLG* gene mutations in the development of AD in people of African descent, however, is less defined. African Americans

are 6 times less likely than European Americans to have loss-of-function mutations[23] and African-based studies have found no *FLG* loss-of-function mutations in amaXhosa or Ethiopian patients with AD.[24,25]

AD is not a 'monogenetic' disease. Up to 31 genetic loci have been identified in genome and exome studies as being associate with increased AD risk, with significant variation of expression between population groups.[26] Mutations of genes resulting in the downregulation of other proteins within the epidermis, including tight junction protein claudin 1 *(CLDN1)* and a protein closely resembling filaggrin (*FLG2),* have been identified in individuals from varying populations with AD, including Ethiopian and African American subjects.[27–30]

Family history and inheritance patterns of atopic conditions further point to the importance of genetics in AD. European population-based family studies suggest that half of offspring from atopic families will have AD.[31] Twin studies show a concordance rate of 0.75 for monozygotic twins for AD compared to 0.20 for dizygotic twins.[22]

Genetic factors can partially explain geographical differences seen in global trends of AD prevalence, however, the rapidly emerging disparities within countries and socio-cultural groups over the course of just a few generations indicate that development of AD cannot be due to genetics alone.[2,3] Between 1999 and 2000 the University of Cape Town conducted a study to investigate the prevalence of AD among amaXhosa children in urban, peri-urban and rural environments.[32] The validity of the UK Working Party (UKWP) diagnostic criteria for AD diagnosis in African children was simultaneously evaluated. This study found a statistically significant difference in point prevalence of AD diagnosed by UKWP criteria between black amaXhosa children 3- to- 11 years of age living in urban Cape Town (4.1%) and the rural Eastern Cape province (1.5%). The difference in prevalence remained significant when diagnosis was made based on a dermatologist diagnosis.

Nearly twenty years later, in 2018 and 2019, the South African Food Sensitisation and Food Allergy study (SAFFA) investigated various atopic conditions in urban and rural cohorts of

children between 12 and 36 months selected from attendees at early childhood development centres and primary health care clinics.[33] This study found a much higher AD prevalence of 23.5% in the urban Cape Town cohort, with a prevalence in the rural Eastern Cape similar to that of the former study, of 1.8%.[34] Unsurprisingly, risk and protective environmental factors among the urban black African participants more closely resembled those of the rest of the urban cohort, rather than the rural black African cohort. The diagnosis of AD in this study was made by clinical assessment based on the diagnostic criteria proposed by the American Academy of Dermatology.[35] Accurate diagnosis of AD using these criteria relies on the clinical exclusion of other red, scaly skin conditions. Due to high observer variability among multiple examiners, this may have resulted in misclassification of other common eczematous dermatological conditions occurring in children in this age group. This study was also less able to account for genetic variation among black African subjects. The results from both local studies suggest that the environment plays a bigger role in development of AD than that of genetics, and that factors associated with modern urban living may be responsible for triggering disease in predisposed individuals, and account for the rapidly rising global prevalence of AD.

The combined effects of genetics and the environment also affect disease phenotype. In Europeans, *FLG* gene mutations may have provided an evolutionary advantage, whereby enhanced skin barrier permeability associated with low epidermal filaggrin is thought to enhance immunity to infections and improve biosynthesis of Vitamin D in UV-deficient environments.[36] Despite fewer *FLG* mutations in African populations, research conducted in North American and European settings show that AD is in fact more prevalent in people of African ancestry compared to those of European ancestry, accounting for socio-economic and environmental factors, and the disease clinical presentation among the groups may vary substantially.[36–38] African Americans have been shown to have higher levels of Immunoglobulin E (IgE), as well as high-affinity IgE receptor cells, than those of European or Asian descent with AD.[39,40] This IgE-associated skewing of the immune system towards allergen sensitisation and atopic disease may explain the higher AD prevalence and severity in individuals of African ancestry living in urban environments.[41]

2.3 Atopic Dermatitis and the Environment

Based on the above findings, environmental exposures play a key role in development of atopic dermatitis. Prenatal exposures may enhance disease susceptibility in those who are genetically predisposed, while early life exposures can lead to sensitisation and atopic tendency, culminating in expression of disease.[33] A multitude of environmental factors have been investigated for their link to atopic dermatitis. Due to consistently growing prevalence of AD in areas of industrialisation and urbanisation,[42] factors associated with urban living, combined with the resultant reduction in protective rural exposures, are largely accepted to be the driving force responsible for the increasing burden of atopy and eczema seen in modern society.[43]

2.3.1 Prenatal exposures

Various maternal exposures have been linked to the development of atopic disease in offspring, highlighting the importance of innate immunity in allergic conditions.[2] *In utero* tobacco smoke exposure has been shown to be associated with an increased risk of development of asthma and rhinitis in children.[44] However, meta-analysis of 86 observational studies failed to observe an association between maternal smoking and development of AD in infants.[45] Maternal antibiotic use, stress and depression during pregnancy may have a positive correlation with childhood AD,[42,46,47] while perinatal helminth infestation, consumption of unprocessed cow's milk and exposure to farm animals in a rural environment have been shown to be protective.[48–50] In northern Limpopo province of South Africa, a Venda-based study exploring maternal exposure to mosquito insecticides dichloro-diphenyl-trichloroethane (DDT) and dichloro-diphenyl-dichloro-ethylene (DDE), found an association between childhood wheeze, itchy skin and food allergy, although these results were not significant.[51] In the SAFFA study, Levin et al. found that maternal farm animal exposure in the rural Eastern Cape province of South Africa was associated with a reduced incidence of aeroallergen sensitisation, food sensitisation and food allergy in children under the age of 3, but there was no association found with AD.[33]

2.3.2 Early life exposures

A widely accepted current theory is that of the role of urban living, and its effect on the human microbiome in the increasing prevalence of atopic conditions around the world.[2,52,53] The 'biodiversity hypothesis' relates to current understanding of how exposure to diverse microbiota present in rural and farming environments is key to promoting a healthy gut, lung

and skin microbiome, modulating host production of cytokines, and diverting the immune system away from a pro-inflammatory state.[7,24,33,42,53,54] As globalisation evolves, more children are residing in urban settings with less exposure to natural environments, farm animals, soil, and unprocessed milk, where homes and schools are routinely cleaned with antimicrobial chemicals, and improved access to healthcare results in antibiotic and anti-helminth treatment and fewer childhood infections. This 'hygienic' environment, devoid of sufficient microbial biodiversity may lead to gut and skin dysbiosis, and sway an 'immature' or 'under-exposed' immune system towards inflammation and allergen sensitisation, increasing the susceptibility to atopic conditions such as asthma, rhinitis and AD.[33,42,52]

Other exposures related to urban living and industrialisation may also increase the risk of AD, likely via disruption of the skin barrier and immune modulation. High level exposure to ambient and indoor air pollution in pregnancy and the first year of life was shown to be associated with AD in pre-school age children in Hubei, China.[55] A Korean study found a significant positive correlation between AD symptom severity and mean daily ambient particulate matter (PM) PM10 and PM2.5 exposure.[56] Similarly, a Chinese study was able to demonstrate how high levels of ambient sulphur dioxide (SO_2), nitrogen dioxide (NO_2) and PM levels correlated with a 7 day lag increase in local outpatient visits for eczema flares.[57,58] Traffic-related pollutant exposure, which includes PM, NO_2, ozone and carbon monoxide, adjusting for possible confounders, was shown to have a small, but significant association with flexural eczema in a large-scale Taiwanese study of over 300 000 children.[59]

In South Africa, Wichman et al. investigated the prevalence of AD, and associations with household exposures, in 6- to 7-year-old North Sotho black African children living within a 60km radius of Polokwane, Limpopo province using the ISAAC phase I validated questionnaires for caregivers.[60,61] The majority of the source population (73%) was noted to live in rural areas, which was defined as residing in one of the five villages outside of the larger urban centres of Polokwane and Sheshego. The study found a significantly increased risk of 12-month eczema symptoms and 'eczema ever' in children exposed to both 'clean' and 'dirty' home fuel use, including paraffin and coal, compared to exposure to 'clean' fuels only, namely electricity and gas.[60] While 'dirty' fuel use is characteristically associated with rural living, and the otherwise protective exposures present in rural settings, this area is surrounded by

mines and industrial smelters likely to emit high amount of ambient air and environmental pollutants, and introduce other influences related to urbanisation such as vehicle traffic and western food outlets. This resultant 'double-burden' of exposures related to poverty (and poor service delivery) and industrialisation is likely to account for the high prevalence of eczema symptoms seen in this population (38%). Children living in what was regarded as rural areas were also found to having a significantly increased odds of having eczema symptoms in the past year compared to those in the urban area (OR 1.53, 95% CI 1.14 – 2.07).

Exposure to environmental tobacco smoke (ETS) is an important risk factor for AD in both children and adults. A large meta-analysis of 86 observational studies from 39 countries found a significantly increased odds of AD from active smoking (OR 1.87, 95%CI 1.32-2.63) and passive smoking (OR 1.18, 95% CI 1.01-1.38).[42,45] In South Africa a Gauteng-based cross-sectional study of 13- to 14-year-old adolescents from diverse socio-economic and cultural backgrounds, attending 16 high schools found that ETS exposure in the home correlated to self-reported history of eczema ever, and presence of current eczema symptoms.[62]

Several chemical products commonly used in modern households have been linked to AD. A Korean study demonstrated that increasing numbers of any of 23 included household products used in the home, such as washing detergents, adhesives, fragranced products and biocides, as well as their frequency of use, correlated to the onset and severity of AD in children.[63] A second Korean study demonstrated that short-term exposure to chemicals commonly used in the production of plastics, namely phthalates and bisphenol A, aggravates symptoms of eczema in pre-school children.[64]

Hard water containing high levels of alkaline calcium carbonate ($CaCO_3$) and magnesium carbonate ($MgCO_3$) has been shown to increase risk of AD in infancy,[65] particularly in individuals with *FLG* mutations, as well as increase self-reported skin dryness and worsening of AD symptoms.[66] Hard water accumulation in tanks and heating systems can result in limescale build-up and calcium stearate deposition on skin and clothing. This increases skin surface pH and enhances protease activity, causing breakdown of intra-epidermal proteins and impairing skin barrier integrity. Hard water has also been proposed to reduce the solubility of

surfactants commonly found in cleaning agents, such as sodium lauryl sulphate, leading to increased and prolonged deposition of the irritant on the skin surface.[67]

The role of infant feeding on development of atopic dermatitis is controversial, with studies showing conflicting result. A recent systematic review and meta-analysis did not show statistically significant effects of exclusive breastfeeding, or early introduction of cow's milk or infant formula on the development of AD.[68,69] Data from the SAFFA study found that consumption of fermented cow's milk by infants living in urban areas of Cape Town was associated with a lower risk of atopic conditions compared to urban children not exposed to fermented milk (9.7% vs 26.1%, $P < 0.05$).[33] This association was not found in the rural cohort. The authors proposed that the probiotic effect of fermented milk may supplement a deficient gut microbiome common among children living in urban environments, which is likely not present in children living in rural areas. These children may also be exposed to other 'traditional' foods or ways of life which may further protect against gut and skin dysbiosis related to urban living.

Diet during childhood and adulthood may have an effect on AD. Regions with high *per capita* intake of vegetables, cereals and starch appear to have low prevalence of AD.[70] Frequent intake of fast food, high in processed sugar and pro-inflammatory polyunsaturated fats has been shown to increase the risk and severity of AD in children.[71,72] Current evidence suggests that strict dietary limitation and specific food avoidance, however, is not effective in the treatment of AD.[73]

2.3.3 Protective factors

Some early life exposures have been shown to be protective against the development of AD in children. A meta-analysis of studies investigating the association between pets and child AD found that family ownership or regular contact with dogs, or dogs and cats, resulted in a significantly lower risk of AD compared to children without dog exposure.[74] This protection was not associated with exposure to cats alone. Exposure to helminths during childhood may infer protection against allergic skin sensitisation. A large Vietnamese-based study conducted by Flohr et al. found that skin sensitisation to dust mites and cockroaches was significantly

reduced in children with presence of geohelminths in the stool.[75] Having access to flush toilets, compared to no toilet or use of a bucket toilet, inferred a significantly increased risk of dust mite skin allergen sensitisation. These findings were corroborated in a randomised double-blind placebo-controlled trial on the same population which showed that treatment with anti-helminth drugs was associated with increased skin allergen sensitisation.[49] This, however, did not confer to an increase in clinical features of eczema.

2.4 Gaps in the literature

Despite evidence of increasing prevalence and marked disease burden associated with AD, its impact in the African setting is poorly understood.[76] In the context of scarce resources, where infectious diseases and life-threatening conditions remain the priority of public health interventions, resultant scarcity of clinical research, inadequate training of health care professionals and poor access to medical care has likely led to under-reporting of atopic conditions such as AD in Africa.[77] This has also resulted in under-representation of Africa in dermatology literature,[78] and `poor clinical understanding of the diagnostic and treatment considerations in people with darker skin types presenting with eczema.[79] Despite apparent skin-type disparities in disease susceptibility, presentation, and severity, only 10.3% of studies related to AD published between 2000 and 2009 reported results considering skin type.[41] Darker skin types are also under-represented in applied research and therapeutic clinical trials.[80]

In this study, we will explore urban, rural and peri-urban exposures in 3- to 11 -year-old children, including factors such as indoor and outdoor pollution, chemical, pesticide, detergent and animal exposure, stress, smoking and infant feeding and their association with AD. By exploring disease associations among participants with a predominantly homogenous cultural and socio-economic background, we may improve our understanding of how environmental factors, within varied social circumstances, influence the development of AD. This data was collected over 20 years ago, prior to the urban development in rural areas of the Eastern Cape that is apparent today, and when most migratory populations to Cape Town were of amaXhosa heritage from the Eastern Cape. This allows a unique opportunity to investigate how stark contrasts in environmental exposures, uncommon today, impact this disease of modern living.

This could lead to identification of potentially modifiable risk factors for AD in South African children, contribute towards disease prevention and improve patient outcomes.

METHODOLOGY

3.1 Study design

A secondary analysis of a nested 'case-control' data subset, derived from a community-based cross-sectional questionnaire and examination survey, will be conducted. The original study from which data will be analysed, previously approved as HREC 116/98, is now closed.

The study was conducted between 1999 and 2000 as joint project between the University of Cape Town/Groote Schuur Hospital's Department of Dermatology, and the University of Nottingham, United Kingdom (UK). The purpose of the study was to examine the prevalence of atopic dermatitis in children residing in urban, peri-urban and rural areas of South Africa, and to determine the validity of the UK Working Party Criteria as a diagnostic tool for atopic dermatitis in black children within an African setting. The questionnaires for this data set enquired about a variety of environmental factors children may be exposed to – dietary, household, ambient and social.

3.2 Study Setting

Three residential area types in South Africa were selected for analysis. An established, stable, urban residential suburb in Cape Town (Langa) with full services; migrant, peri-urban areas in Cape Town (Joe Slovo and Imizamo Yethu), defined by the presence of predominantly informal infrastructures and limited service-delivery; and a stable, traditional rural area, the district of Centane in the Eastern Cape without service delivery. During the study period *circa* 2000, residents in the urban and peri-urban areas were predominantly isiXhosa speaking people who had migrated from Eastern Cape. Peri-urban settlements consisted largely of residents who had recently migrated to the city from rural areas and constantly moved back and forth between the two areas with children staying with the parents in infancy but often schooled in the rural area, living with family and grandparents. Originally, Joe Slovo, the informal settlement surrounding the urban suburb of Langa, was selected as the peri-urban study population.

Because two fires ravaged the area with resultant relocation of participating families, the site had to be abandoned, and the remainder of the sample recruited from a second site. Imizamo Yethu was chosen due to similarities with Joe Slovo in terms of accessibility, residential structures, service delivery and population demographics.

Potential research participants were identified in Langa by use of cluster sampling by creating blocks from grid lines drawn on aerial photographs, with blocks being selected via a random number selector. All dwellings situated in identified blocks were sequentially eligible for selection until at least 1000 children has been recruited. A similar approach was adopted for the peri-urban area of Joe Slovo but because of lack of formal roads and addresses, researchers went house to house in the selected blocks. Due to Imizamo Yethu being selected as a site at short notice, door-to-door recruiting was performed following no pre-specified pattern until at least 1000 participants had been interviewed from both areas. In the rural setting, all schools in the district were identified and numbered. Selection of schools to include in the study was determined using a random number allocator. With community support, all families in the surrounding area within walking distance from the randomly selected school, were asked to attend the school on a specific day. Research sites were moved daily from school to school until at least 1000 participants had been recruited.

3.3 Study population

The study population comprised children 3-to-11-years of age. Most participants belonged to families which had originated from the Eastern Cape. Children were chosen for participation in the study as atopic dermatitis is predominantly a disease of childhood, which tends to improve or resolve by adolescence. By exploring disease associations in a study population with a relatively homogenous ancestral and cultural background, the study aimed to provide unique insight into how migration from rural to urban environments may affect disease outcomes.

The cross-sectional data included 3144 participants 3-to-11-years of age with at least 1000 participants from each of the area types – urban, peri-urban and rural. The original research proposal calculated the necessary sample size using an assumed prevalence of 8% in urban Cape Town (as determined by local data derived from the ISAAC study) [6] and ensuring a

sample size that would be sufficient to detect a prevalence difference of at least 20% between the three settings, using standard power of 80% and significance of 0.05. [32]

The sample for this arm of the study was formed by a 'case-control' selection from the original cross-sectional dataset. Cases included all children determined to have atopic dermatitis, identified by fulfilling the criteria for diagnosis of AD via the UK Working Party Criteria (Table 2). Controls were randomly selected from participants of a similar age group who did not meet criteria for AD diagnosis, approximately 2 controls being selected for each case for the urban and rural groups, and 1 control per case in the peri-urban group, due to difficulty re-tracing participants in these areas. Only these participants went on to complete the questionnaire for this arm of the study. In total, 739 children were included in this arm of the study – 253 cases, and 486 controls (case: control = 1: 1.92).

3.4 Power for case control study

Table 1: Table of predicted achievable power for data analysis

		Odds of AD if exposed	Odds of Exposure in South Africa (SA)	Power (SA) Alpha=5%	Odds of Exposure in Eastern Cape (Rural)	Power (EC) Alpha=5%	Odds of Exposure in Western Cape (Urban)	Power (WC) Alpha=5%
				SS = 739 Cases:264 C:C: 1.81		*SS = 293 Cases:87 C:C: 2.37*		*SS = 387 Cases:140 C:C: 1.76*
Feeding:	**EBF for 3 months**	0.89[68]	23.7%[81]	**15.3%**	*Not available*		*Not available*	
Farm animals:	**Households owning farm animals**	0.04*[33]	15.2%[81]	**100%**	99.5%[33]	**97.5%**	2.5%[33]	**36.6%**
Pets:	**Regular contact with a dog**	0.72[74]	*Not available*		72.4%[33]	**33.2%**	35.1% [33]	**41.2%**
Housing:	**Formal housing (2002)**	0.77[60]	68.3%[82]	**49.4%**	39.9% [82]	**24.9%**	80.9% [82]	**26.9%**
Tobacco use:	**Households with smokers**	1.18[42]	20.3%[81]	**23.0%**	48%[33]	**15.9%**	26.1%[33]	**17.5%**
Fuel use:	**Households using solid fuels**	1.16[83]	12.5%[81]	**16.6%**	51.0%[33]	**14.2%**	4.1%[33]	**8.5%**
Sanitation:	**Household uses a flush toilet**	4.61**[75]	58.5%[81]	**100%**	21.4% [82] (2002)	**99.9%**	90%[82] (2002)	**91.4%**

***Aero-allergen sensitisation. Information related to AD not available.**
****Skin sensitisation. Information related to AD not available.**

Using the predetermined sample sizes for each group, case to control ratios, as well as measures of association derived from previous research, it is possible to determine the likely power which is achievable for this data set. This has also been calculated for the rural and urban areas individually, due to likely differences in exposures for the different areas. From Table 1, the power which is achievable ranges considerably, depending on the measures of association found between exposures and atopic dermatitis in the literature. Based on information from

Table 1, for this study we can expect to achieve sufficient power for exposures related to farm animals and sanitation. Assuming small measures of effect as found in previous studies, we may not achieve sufficient power related to exposures such as infant feeding, fuel use or tobacco smoke exposure.

3.5 Recruitment and enrolment

All children were recruited, and care givers interviewed by the same three trained isiXhosa speaking research assistants in all 3 areas, in the interest of promoting good inter-observer reliability. In urban Langa, researchers approached each home in the pre-allocated blocks. If there were any children 3-to-11-years of age residing in the household, parents/guardians were informed about the study in their home language and invited to sign up for participation. Questionnaires were conducted in the home with the caregiver. Depending on the child's age, they were either examined in the home or at their school or local community centre.

In peri-urban areas, researchers went house-to-house informing community members about the study, encouraging caregivers with children 3-to-11-years of age to participate. They would then be directed to a study location, where interviews and examinations were conducted. Study location varied from community centres to private dwellings hired for the day.

In the rural study, local community workers circulated through communities in the proximity of the selected school within walking distance, asking family members to bring children to the local school on a predetermined day where questionnaires were completed, and examinations were done.

3.6 Research procedures and data collection methods

The questionnaires were translated into isiXhosa by bilingual research assistants, then back translated to English by other bilingual research assistants to ensure meanings were consistent. Adjustments were made where applicable. Questionnaires were conducted face-to-face by research assistants fluent in both isiXhosa and English. Questions were read out as written, and not interpreted or explained to those being interviewed to ensure consistency of the measurement tool.

Participants were subjected to a physical examination by 1 of 2 dermatologists to identify skin signs and diseases and to make a clinical diagnosis of atopic dermatitis. If children met the case

definition for AD diagnosis per the UKWP criteria, further questionnaires interrogating the costs to the family of having a child with atopic dermatitis, self-reported prenatal habits, infant feeding practices and environmental exposures were completed. For each case of AD identified, 2 controls from the urban and rural areas, and 1 from peri-urban areas, were selected from participants who did not meet AD criteria for diagnosis. These selected controls also completed the additional questionnaires.

Most interviews (consisting of questionnaires and examination) took place at one sitting, with no requirement for further involvement in the study. Some caregivers completed the second questionnaire during a second interview.

All children brought to the sites were seen and treated equally whether or not they had skin disease or fitted criteria for inclusion. Those children with skin disease were treated with topical therapy and referred to the local clinic for long term management and follow-up, or urgently referred for care.

3.7 Data handling and safety

A database of all participants was kept, and incrementally updated, to ensure all necessary and required information for the study had been obtained. Hard copies of the questionnaires were filled out by hand by the research assistants and dermatologists. These were placed in boxes and transported to the research facility where data was manually double captured into a digital format by a data capturing unit of the University of Cape Town. A computer program compared the two sets of data and identified inconsistencies which were then manually checked, and the data appropriately corrected before analysis.

Hard copies of the completed questionnaires remain in a secure, locked storage unit managed by the UCT Dermatology Department, only accessible by prior approval of the principal researcher involved in the primary data collection. These files have been stored in the department since the study was conducted in 2000. Data files are to be kept until all data has been sufficiently analysed. The electronic data has remained only with principal researchers and those conducting analysis of the data, with pre-approval from the principal researcher being required for permission to conduct analysis on the data.

3.8 Data characteristics:

a) Demographics

Demographic characteristics were self-reported by participant caregivers. These included participant age, sex, family clan and area of origin. Current residential location was based on study location.

b) Diagnosis of atopic dermatitis

The main outcome measure, diagnosis of atopic dermatitis, was determined using the UK Working Party Criteria (Table 2). Participants who fulfilled the criteria were determined to be cases. Controls consisted of participants who did not meet diagnostic criteria, randomly selected at a ratio of 2 controls per 1 case for the urban and rural groups, and 1 control per case for the peri-urban group.

Table 2: UK Working Party Criteria for Atopic Dermatitis in children [84]

UK Working Party Criteria for Atopic Dermatitis in children
Must have: (MAJOR Criterium)
1. An itchy skin condition in the last 12 months
Plus, three or more of: (MINOR Criteria)
1. Onset below age 2*
2. History of flexural involvement
3. History of a generally dry skin
4. Personal history of other atopic disease†
5. Visible flexural dermatitis (as per photographic protocol)
* Not used in children under 4 years. † In children aged under 4 years, history of atopic disease in a first-degree relative may be included.

c) Environmental factors

All information regarding environmental and prenatal exposures was self-reported by interviewees. There was no validation of caregiver responses through home inspections or

corroboration by other family members, which may affect accuracy and reliability of information obtained.

Variables from the original dataset will be analysed in existing format or combined or adjusted to produce new variables. This is to provide variables which are better able to fulfil the formulated study objectives, and outcomes which allow better comparison to previous research conducted. The original data set is attached as an addendum. Table 3 depicts variables formulated to fulfil research objective 1.

Table 3: Table of Variables: Environmental Exposures

Variables	Variable type
Demographics	
Study location *Rural/Urban/Peri-urban*	Categorical
Sex *Male/Female*	Binary
Age *Years*	Numerical, discrete
Infant feeding	
Ever breastfed? *Yes/No*	Binary
Exclusively breastfed >3 months *Yes/No*	Binary
Infant feeding (other than breastmilk): *Milk formula* *Unprocessed milk (cow or goat)* *Other*	Categorical
Age of weaning to solids/other milk feed *<4 months* *>4 months*	Binary
Tobacco smoke exposure	
Maternal smoking during pregnancy *Yes/No*	Binary
Childhood smoke exposure ever *Yes/No*	Binary
Childhood smoke exposure current *Yes/No*	Binary
Stress/Behavioural factors	
Stress events in the last 6 months *Yes /No*	Binary
Child behavioural problems *Yes/No*	Binary

Housing	
Housing and roofing material *Thatch* *Asbestos* *Other*	Categorical
Carpets in the house *Yes/No*	Binary
Number of people living in the home *<4* *4- 8* *>8*	Categorical
Pet and animal exposure	
Cat at home *Yes/No*	Binary
Dog at home *Yes/No*	Binary
Farm animals at home *Yes/No*	Binary
Rats in the home *Yes/No*	Binary
Goats *Yes/No*	Binary
Cows *Yes/No*	Binary
Birds *Yes/No*	Binary
Indoor pollutants	
Solid fuel burning inside the home *Yes/No*	Binary
Types of fuels used for cooking/heating *'Clean'* *'Dirty'* *Petrochemicals*	Binary
Is there a smoke outlet /chimney in the house *Yes/No*	
Mould/Damp in the home *Yes/No*	Binary
Household products	
Household chemical products used in the home *Yes/No*	Binary
If household products used: *0-2 products* *>2 products*	Binary
Pesticides used in the home or garden *Yes/ No*	Binary

Outdoor pollutants		
	Refuse removal *Burned* *Dumped locally* *Removed*	Categorical
	Local tyre burning *Yes/No*	Binary
	Motor vehicle traffic near the house *Heavy* *Moderate* *Light*	Categorical
	Nearby polluting industry *Yes/No*	Binary

3.9 Main outcome measures:

All data handling and statistical analysis will be performed in RStudio, Version 1.2.5033.

Hypothesis 1:

H_0: There is no difference in environmental exposures among the three residential areas (urban, per-urban and rural)

Method: Exploratory analysis of the data across the three study locations will be performed to identify significant differences in environmental exposures in the three settings. As all environmental variables are categorical, chi-squared tests can be used to identify significant differences.

Hypothesis 2:

H_0: Environmental factors are not associated with atopic dermatitis in our study population.

Method: Relationships between environmental factors and atopic dermatitis in the entire population sample will calculated by Chi-square tests. Univariate and bivariate regression models calculating odds ratios can be calculated.

Hypothesis 3:

$H_{0:}$ There is no difference in how environmental factors relate to atopic dermatitis in the three settings – urban, peri-urban and rural.

Method: Logistic regression models, for the whole study population, and stratified by study location – urban, peri-urban and rural – can be performed to determine whether the associations between environmental factors and AD are location specific, or similar across locations.

3.10 Ethical considerations

3.10.1 Ethics related to primary data collection:

3.10.1.1 Informed consent

Prior to initiating the study, consent was obtained from local community leaders and authorities, as well as local schools and community centres to gain their support and permission to use their premises for interviews.

Ethical approval for the original study was obtained from the University of Cape Town, Human Research Ethics Committee, *reference 116/98.*

Informed consent was taken from the parent, legal guardian or primary caregiver either via written or verbal method prior to the interview and examination which required the ascent of children older than 10 years of age. Information about the study methods and objectives was provided in the caregivers' primary language, with clarity being provided by the research assistant where appropriate. Caregivers and children were informed of their ability to leave the study at any time or refuse to answer any question should they wish to with the understanding that disclosure of all information was voluntary.

Because of the large numbers of caregivers and children seen daily, a variety of basic refreshments of drinks, biscuits, fruit and sandwiches were offered during the waiting period.

3.10.1.2 Privacy and Confidentiality:

Personal information was recorded on the hard copy for instances where participants required follow-up. The digital dataset used for this study arm includes only a participant number without inclusion of identifying information. Confidentiality was maintained by holding interviews in private areas. To minimise participant discomfort, children were examined fully clothed, examining only legs, arms, face and neck. Where the trunk needed to be exposed,

participants were examined in their undergarments in a private room, accompanied by the caregiver. Genitalia were not examined.

Hard copies of the data remain in a secure location only accessible to the principal researchers. Electronic datasheets are available only to the principal researchers and those conducting secondary analysis.

3.10.1.3 Risks and benefits

Benefits for participants at the time included being able to have skin conditions assessed and diagnosed by a dermatologist and receive necessary treatment. Any children with non-dermatological conditions identified were referred to the local healthcare centre. Participants and their caregivers were encouraged to ask questions, and to seek clarification where needed.

Original analysis of cross-sectional data collection provided the annual prevalence of atopic dermatitis in the three settings, and was used to validate the UK Working Party Criteria in an African setting. [32] Dermatologist assessment of these children also provided point prevalence estimates of many other skin findings and diseases in this age group of children in the various settings.

3.10.2 Ethics related to secondary data analysis:

3.10.2.1 Referencing and objectivity:

Works of other authors used in this study are to be acknowledged and appropriately referenced using a modification of the Vancouver referencing system, as per the MPH Program Handbook. The author will attempt to conduct statistical analysis and discussion of findings in an objective, unbiased manner.

3.10.2.2 Risks and Benefits:

Benefits for society and healthcare systems include the possible identification of modifiable risk factors for atopic dermatitis, including various household exposures. This may lead to behaviour change or educational programs aimed at informing the public on methods to reduce a child's chance of developing eczema.

Findings could be published in medical journals with the hope of informing many clinicians and researchers.

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SECTION 2: STUDY APPENDICES

Appendix 1: Ethics approval documents

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: https://health.uct.ac.za/home/human-research-ethics

28 October 2022

HREC REF: 701/2022

Prof L London
Division of Public Health & Family Medicine
Falmouth Building-FHS
Email: Leslie.london@uct.ac.za
Student: janinedewar@gmail.com

Dear Prof London

PROJECT TITLE: ENVIRONMENTAL FACTORS ASSOCIATED WITH ATOPIC DERMATITIS IN AMAXHOSA CHILDREN IN URBAN, PERI-URBAN AND RURAL SOUTH AFRICA. (MASTER'S DEGREE – DR JANINE DEWAR)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2023.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Janine Dewar will also be involved in this study.

Please quote the HREC REF 701/2022 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007

Hrec ref 701 2022

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Hrec ref 701 2022

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.01.2025
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	23/1/2024

Note: Please email this form and supporting documents (if applicable) in a combined pdf file to hrec-enquiries@uct.ac.za.
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

HUMAN RESEARCH ETHICS COMMITTEE
23 JAN 2024
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

Comments to PI from the HREC
Thank you for your Study Deviation

HREC Chair Signature
Date: 23/1/2024

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	11/01/2024		
HREC REF Number	701/2022	Current Ethics Approval was granted until	30/10/2023
Protocol title	Environmental factors associated with atopic dermatitis in amaXhosa children in urban, peri-urban and rural South Africa		
Protocol number (if applicable)	None		
Are there any sub-studies linked to this study?	☐ Yes	☑ No	
If yes, could you please provide the HREC Reference number for all sub-studies? **Note:** A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Professor Leslie London		
Department / Office Internal Mail Address	Leslie.london@uct.ac.za		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix 2 : Original Study Questionnaire

Appendix 3
Questionnaire - Study 3: Environmental Exposures

UNIVERSITY OF CAPE TOWN SKIN SURVEY
ENVIRONMENTAL FACTORS : CASE/CONTROL STUDY

Study ID **3**				CHILD ID	Case 1
Study Area	URBAN	INFORMAL	RURAL		Control 2
School				Interviewer No:	

IGAMA LOMNTWANA : .....
Name of child:

UBUMNI BONTWANA: YINKWENKWE YINTOMBAZANA
Gender:

IMINYAKA: .....
Age:

NGOKU NOLIZA KUKUBUZA MALUNGA NOMNTWANA KUNYE NENDAWO ENIHLALA KUYO:
We would now like to ask you some questions about your child and the environment in which you live:

1. Umncancise ixesha elingakanani u ...?
   For how many months was *(child's name)* breastfed? .....
2. Ugale ukumtyisa ukutya kwecephe xa engakanani?
   How many months old was *(child's name)* when he/she was first fed with solid food? .....
3. Ugale engakanani ukusela ubisi ngaphandle kolwe bele?
   How old was *(child's name)* when he/she first received drink other than breastmilk? .....

4. Ingaba zeziphi okhe wamnika kwezi zilandelayo?
   Were any of the following given instead of breastmilk?

	EWE	HAYI
01 Amanzi abileleyo Boiled water		
02 Amanzi angabilanga Unboiled water		
03 Amanzi aneswekile Sugar water		
04 Ubisi lwebhokhwe Goats milk		
05 Ubisi lwenkomo Cows milk		
06 Ubisi elingumgubo lwabatwana Milk formula		

1

NGOKU NDIZA KUKUBUZA NGENDIMA YOKUTSHAYA
I am now going to ask some questions about smoking

	EWE	HAYI	ANDAZI
5. Uyatshaya na umama womtwana? Has the child's mother ever smoked cigarettes?			
6. Wakhe wayitshaya inqawe? Has the child's mother ever smoked a pipe?			
7. Wayetshaya na ngoku waye mi thi u .....? Did she smoke when she was pregnant with *(child's name)*?			

If NO or DON'T KNOW go to question **10**

8. Utshaya kangakanani ngosuku? How much does the mother smoke each day?	Cigarettes: Pipe: Grams:
9. Bangaphi abantu abahlala nawe ababetshaya ngexesha wawumithi u .... ? How many people living in the house smoked when *(child's name)* mother was pregnant with *(him/her)*?	
10. Bangaphi abantu ohlala nabo ababetshaya kunye nawe ngexesha u ..... waye ngaphantsi konyaka ezelwe? How many people in the house, including the mother smoked when *(child's name)* was less than 1 year old?	
11. Ngoku bangaphi abantu ohlala nabo abatshaya roqo. How many people in the house smoke regularly at the moment?	

XA NDIZAKUKUBUZA UMBUZO UZUCINGE NGEMPILO YOMNTWANA KULE MINYAKA IPHELILEYO?
When I ask the next questions, think about how (child's name) has been since LAST YEAR?

12. Umntwana wakho ukhe wakhathazwa zezi zinto zilandelayo kwezi nyanga zinta – ndathu ziphambi kokuba abe nengxata yofele?
Has your child experienced any of the following during the **6 MONTHS BEFORE** the skin problem started?

EWE HAYI

UKUBA EWE, ZEZIPHI?
If YES, which ones?

01 = ingxaki zekhaya
02 = uqhawulo mtshato
03 = violence
04 = ingxaki esikolweni
05 = ukufa
06 = isigulo esibi
07 = uhlukumezo
08 = ezinye - chaza

01 = problems in the home
02 = divorce
03 = violence
04 = problems at school
05 = death
06 = serious illness
07 = abuse
08 = other

13. Umntwana wakho ukhe wanazo ezi ngxaki zilandelayo?
Has your child had any of the following problems?

EWE HAYI

UKUBA EWE, ZEZIPHI?
If YES, which ones?

01 =ukulala kakubi ***04 =ukuchama xa elele*** ***07 =umsindo***
02 =ukutefa ***05 =ukoyika*** ***08 =ukungafuni ukutya***
03 =iingxaki esikolweni ***06 =ukusoloko elila*** ***09 =ungankwazi ukuba nabahlobo***

01 =sleep problems *04 =bed wetting* *07 =aggression*
02 =clinging behaviour *05 =being very frightened* *08 =no appetite*
03 =problems at school *06 =crying, sadness* *09 =difficulty making friends*

14. Ingaba u ..... unokutshintsha okungaqhele kanga?
Ukuba EWE, njani?

EWE HAYI

Has (child's name) changed in any other way?
If YES, how?

.....

.....

NGOKU NDIZA KUKUBUZA NGENDAWO OHLALA KUYO
I would now like to ask you some questions about your home

15. Indonga zendlu yakho zakhiwe ngantoni?
What are the walls of your house made of?

01 = Wood ***02 = Mud*** ***03 = Tile***
04 = Iron (Zinc) sheets ***05 = Plastic*** ***06 = Cardboard***
07 = Thatching ***08 = Asbestos*** ***09 = Mud & cement***
10 = Other

.....

16. Kusentyenziswe oluphi uphahla lwendlu?
What is the roof of your house made of?

01 = Thatch ***02 = Cement*** ***03 = Wood*** ***04 = Reeds***
05 = Iron (Zinc) sheets ***06 = Asbestos*** ***07 = Tiles*** ***07 = Other***

.....

17. Kusentyenziswe oluphi umgubo lwendlu?
What is the floor of the house made of?

01 = Tiles ***02 = Cement*** ***03 = Wood*** ***04 = Beaten earth***
05 = Bricks ***06 = Dung*** ***07 = Other***

.....

18. Kusentyenziswe oluphi udidi lwe flori endlwini yakho?
What type of floor covering do you have in your house?

01 = Carpet ***03 = Reed mat***
02 = Cloth mat ***04 = Other***

.....

NDIZA KUKUBUZA NGEZINYE IZINTO OZENZAYO NGAPHAKATHI NANGA PHANDLE ENDLWINI
I am now going to ask you some questions about the different things you do in and around the house

19. Wombatha ntoni umntwana ebusuku? What is the child **covered with** to sleep at night?		
(PLEASE TICK)	EWE	HAYI
01 Ingubo / Blanket?		
02 iSheet / Sheet?		
03 Duvet?		
04 Akembhathi / No covering?		
01 Enye into / Other?		

20. Umntwana ulala phezu kwantoni ebusuku? What does the child sleep **on** at night?	
01=Ebedini enomatrasi **03=Ukhukho** **05=Ingubo** **02=Ematrasini pantsi** **04=iSheet** **06= iPilo** 01=Bed and mattrass 02=Mattrass on the floor 03= Mat 04=Sheet 05=Blanket 06=Pillow	
21. Bangaphi abantu abalala ekamereni? How many people sleep in the same room as the child?	
22. iBedi uye ndlula roqho? Is the bed made up each day?	
23. Uyitshintsha emva kwexesha elingakaka nani? How often is the bedding changed?	
24. Mangaphi amagumbi endlu yakho? How many rooms are there in the house?	
25. Bangaphi abantu abahlala nani? How many people live in the house?	

26. Zeziphi kwezi zilwanyanha ezingenayo endlwini? Which of the following animals come into the house?	EWE	HAYI
01 iKati / Cat		
02 Inja / Dog		
03 Iinkuku / Chicken		
04 Ezinye ezinoboya / Other feathered animals		
05 iHagu / Pig		
06 Inkomo / Cow		
07 iBhokhwe / Goat		
08 Nezinye / Other (specify)		
09 Ezi zilwanyana zivumelekile apho kufalwa khona? Are any of these animals allowed in the sleeping area?		
Ukuba EWE, zeziphi? If yes, which type of animal?		

27. Usebenzisa awaphi amafutha ukufudumeza indlu? What is the main fuel you use for heating the house?	
28. Usebenzisa awaphi amafutha ukupheka nokubilisa amanzi? What is the main fuel you use for cooking and boiling water?	
01 = Electricity - grid ***04 = Electricity - battery/generator*** ***07 = Paraffin*** ***02 = Dung*** ***05 = Gas*** ***08 = Wood*** ***03 = Charcoal/coal*** ***06 = Other*** ***09 = None***	
29. Usebenzisa exiphi izixhobo ukupheka nokubilisa amanzi? What type of appliance do you use for cooking and boiling water?	
01 = LPG Ring Burner ***05 = Wood*** ***08 = Paraffin Primus Stove*** ***02 = Paraffin Wick Stove*** ***06 = Coal Stove*** ***09 = None*** ***03 = Three-Stone Wood Stove*** ***07 = Coal Brazier*** ***010 = Other*** ***04 = Electric stove***	

	EWE	HAYI
30. Ikhona imbhobo yokuphuma umsi? Is there a smoke outlet in the house?		
31. Ngethuba aphekayo umama ubesoloko elubelekile na usana? When (child's name) was a baby was (he/she) carried by their mother while she did the cooking?		
32. Uyibona indlu yakho ifumile? Do you think your house is damp?		
33. Amanzi esitila ngodonga? Does water ever run down the walls?		
34. Amadonga amanzi? Are the walls damp to touch?		
35. Amadonga angundile nemphahla yendlu? Does mould ever grow on the walls or furniture in the house?		
36. Indlu ikhe idame amanzi? Does the house ever flood with water?		
37. Iflori ihlala njalo ifumile? Are the floors ever damp?		

38. Usebenzisa eyiphi i Toilet? What type of toilet does the household use?

01 = Flush toilet	***02 = Improved pit latrine – ventilation (VIP)***
03 = Other pit latrine	***04 = Bucket toilet***
05 = Chemical toilet	***06 = None***

39. iToilet esetyenziswa nangabanye abantu na? Is the toilet shared with other households?	EWE	HAYI

40. Amanzi uwafumana phi? Where does your water come from?

01= Piped (tap) – inside	***02=Piped (tap) – yard***	***03=Water carrier/tanker***
04=Piped-public tap/kiosk (free)	***05=Piped-pub. tap/kiosk (paid)***	***06=Borehole***
07=Rainwater tank	***08=Flowing river/stream***	***09=Dam/Stagnant water***
010=Well (no borehole)	***011=Protected spring***	***012=Other***

41. Ingaba lamanzi usela kuwo, uhlambe kuwo, ude upheke kwangawo? Do you use the same water for drinking, washing, cooking and washing clothes?	EWE	HAYI

IF **YES** GO TO QUESTION **43**

42. Uwafumana phi amanzi owasebenzi sela - Where do you get the water you use for -	
01 Ukuhlamba impahla? / washing clothes?	
02 Ukuhlamba umntwana? / washing your child?	
03 Ukupheka / cooking?	
04 Ukusela / drinking?	

01 =Piped (tap) - internal	***02=Piped (tap) - yard***	***03=Rainwater tank***
04 =Flowing river/stream	***05=Water carrier/tanker***	***06=Dam/Stagnant water***
07 =Piped-public tap (free)	***08=Well (no borehole***	***09=Protected spring***
010=Piped-pub. tap/kiosk (paid)	***011=Borehole***	***012=Other***

43. Zeziphi kwezi zinambkuzane exikhoyo endlwini yakho? What type of pests are a problem where you live?		EWE	HAYI
01	Iimpukane / Rats		
02	Amaphela / Cockroaches		
03	Iingcongconi / Mosquitoes		
04	Iintakumba / Fleas		
05	iTicks / Ticks		
06	Iincukuthu / Bedbugs		
07	Ezinye / Other (Specify)		

44. Ingaba usebenzisa ichiza lokubulala ezi zinambuzane? Do you use any poisons to kill insects, cockroaches, weeds or rats?	EWE	HAYI
Uku EWE, leliphi? If YES, which ones?		

IF **NO** GO TO QUESTION **42**

45. Ulisebenzisa ixesha elingakanani elichiza? How often do you use these products?	
46. Usebenzisa isaitshizi, ichiza elingamanzi okanye umgubo? Do you use a spray, liquid or powder	Spray/Liquid/Powder
47. Ulisebenzisa eli chiza ngaphakathi okanye ngaphandle? Do you use these products inside or outside?	Inside / Outside

48. Usebenzisa eyiphi isepha ukuhlamba impahla yakho? What products do you use to wash your clothes?

49. Usebenzisa eyiphi isepha ukuhlamba u ..... (umntwana) What products do you use to wash (child's name)?

50. Uyazisebenzisa ezi zilandelayo? Do you use any of the following?		EWE	HAYI
01	Isitshizi sendlu esigholiweyo / Air fresheners		
02	Isitshizi senwele / Hair spray		
03	Isitshizi somzimba / Body spray		
04	Isitshizi sebedi / Spray for beds		
05	Isitshizi somandlalo / Spray for bedding		
06	IJik eqholiweyo / Perfumed Jik		
07	IFurniture polish eqholiweyo / Perfumed furniture polish		

51. Uyicoca njani inkunkuma yakho? How do you get rid of your household waste?		
01=Council waste disposal	***02=Private waste removal co.***	***05=Other***
03=Local dump	***04=Burn***	

52. Ingaba kukhe kutshiswe amatayara kufutshane nendlu yakho? Do people often burn tyres near your home?	EWE	HAYI	ANDAZI

53. Kwezi zilandelayo kokuphi okuchaza ngokusondeleyo endlwini yakho?
Which of the following best describes the amount of traffic on the road closest to your house?

01 = Always heavy traffic (vehicles at all times during day-time)
02 = Traffic only at rush-hour, less than 20 vehicles an hour at other times)
03 = Sometimes traffic (less than 20 vehicles an hour at all times)
04 = Almost never (less than 30 vehicles per day)
05 = Less than 20 vehicles per day
06 = Less than 10 vehicles per day

54. Uhlala kufutshane nezi ndawo zilandelayo? Do you live near any of the following?

01 = Power Station
02 = Transfer Station)
03 = Power lines (high voltage)
04 = Industry (specify if possible)
05 = Incinerator/Burner

55. Ingaba umntwana ..... ukhe aqubhe elwandle? Does (child's name) often swim in the sea?	EWE	HAYI
Ukuba EWE, koluphi ulwandle? If YES, at which beach?		
56. Uyaqubha emlanjeni? Does (he/she) swim in the river?	EWE	HAYI
Ikuba EWE, kowuphi? If YES, in which river?		
56. Ikhona enye indawo athi aqubhe kuyo? Is there anywhere else where he/she swims?	EWE	HAYI
Ukuba EWE, phi? If YES, where?		

57. Oko kugqibela, xa uqaphela ungathi woneliseka kangakanani na yindlu yakho, kunye nobomi esiphila kubo namhlanje? Lastly, taking everything into account, how satisfied is your household with the way it lives these days?

01 = Very satisfied
02 = Satisfied
03 = Neither satisfied nor dissatisfied
04 = Dissatisfied
05 = Very dissatisfied

THANK YOU FOR HELPING US TO ANSWER THESE QUESTIONS

NGOKU NDIZA KUKUBUZA NGENDIMA YOKUTSHAYA
I am now going to ask some questions about smoking

	EWE	HAYI	ANDAZI
5. Uyatshaya na umama womtwana? Has the child's mother ever smoked cigarettes?			
6. Wakhe wayitshaya inqawe? Has the child's mother ever smoked a pipe?			
7. Wayetshaya na ngoku waye mi thi u .....? Did she smoke when she was pregnant with *(child's name)*?			

If NO or DON'T KNOW go to question **10**

8. Utshaya kangakanani ngosuku? How much does the mother smoke each day?	Cigarettes: Pipe: Grams:
9. Bangaphi abantu abahlala nawe ababetshaya ngexesha wawumithi u .... ? How many people living in the house smoked when *(child's name)* mother was pregnant with *(him/her)*?	
10. Bangaphi abantu ohlala nabo ababetshaya kunye nawe ngexesha u ..... waye ngaphantsi konyaka ezelwe? How many people in the house, including the mother smoked when *(child's name)* was less than 1 year old?	
11. Ngoku bangaphi abantu ohlala nabo abatshaya roqo. How many people in the house smoke regularly at the moment?	

XA NDIZAKUKUBUZA UMBUZO UZUCINGE NGEMPILO YOMNTWANA KULE MINYAKA IPHELILEYO?
When I ask the next questions, think about how (child's name) has been since LAST YEAR?

12. Umntwana wakho ukhe wakhathazwa zezi zinto zilandelayo kwezi nyanga zinta – ndathu ziphambi kokuba abe nengxata yofele?
Has your child experienced any of the following during the **6 MONTHS BEFORE** the skin problem started?

EWE HAYI

UKUBA EWE, ZEZIPHI?
If YES, which ones?

01 = ingxaki zekhaya
02 = uqhawulo mtshato
03 = violence
04 = ingxaki esikolweni
05 = ukufa
06 = isigulo esibi
07 = uhlukumezo
08 = ezinye - chaza

01 = problems in the home
02 = divorce
03 = violence
04 = problems at school
05 = death
06 = serious illness
07 = abuse
08 = other

13. Umntwana wakho ukhe wanazo ezi ngxaki zilandelayo?
Has your child had any of the following problems?

EWE HAYI

UKUBA EWE, ZEZIPHI?
If YES, which ones?

01 =ukulala kakubi ***04 =ukuchama xa elele*** ***07 =umsindo***
02 =ukutefa ***05 =ukoyika*** ***08 =ukungafuni ukutya***
03 =iingxaki esikolweni ***06 =ukusoloko elila*** ***09 =ungankwazi ukuba nabahlobo***

01 =sleep problems *04 =bed wetting* *07 =aggression*
02 =clinging behaviour *05 =being very frightened* *08 =no appetite*
03 =problems at school *06 =crying, sadness* *09 =difficulty making friends*

14. Ingaba u ..... unokutshintsha okungaqhele kanga?
Ukuba EWE, njani?

EWE HAYI

Has (child's name) changed in any other way?
If YES, how?

.....

.....

NGOKU NDIZA KUKUBUZA NGENDAWO OHLALA KUYO
I would now like to ask you some questions about your home

15. Indonga zendlu yakho zakhiwe ngantoni?
What are the walls of your house made of?

01 = Wood ***02 = Mud*** ***03 = Tile***
04 = Iron (Zinc) sheets ***05 = Plastic*** ***06 = Cardboard***
07 = Thatching ***08 = Asbestos*** ***09 = Mud & cement***
10 = Other

.....

16. Kusentyenziswe oluphi uphahla lwendlu?
What is the roof of your house made of?

01 = Thatch ***02 = Cement*** ***03 = Wood*** ***04 = Reeds***
05 = Iron (Zinc) sheets ***06 = Asbestos*** ***07 = Tiles*** ***07 = Other***

.....

17. Kusentyenziswe oluphi umgubo lwendlu?
What is the floor of the house made of?

01 = Tiles ***02 = Cement*** ***03 = Wood*** ***04 = Beaten earth***
05 = Bricks ***06 = Dung*** ***07 = Other***

.....

18. Kusentyenziswe oluphi udidi lwe flori endlwini yakho?
What type of floor covering do you have in your house?

01 = Carpet ***03 = Reed mat***
02 = Cloth mat ***04 = Other***

.....

NDIZA KUKUBUZA NGEZINYE IZINTO OZENZAYO NGAPHAKATHI NANGA PHANDLE ENDLWINI
I am now going to ask you some questions about the different things you do in and around the house

19. Wombatha ntoni umntwana ebusuku? What is the child **covered with** to sleep at night?		
(PLEASE TICK)	EWE	HAYI
01 Ingubo / Blanket?		
02 iSheet / Sheet?		
03 Duvet?		
04 Akembhathi / No covering?		
01 Enye into / Other?		

20. Umntwana ulala phezu kwantoni ebusuku? What does the child sleep **on** at night?	
01=Ebedini enomatrasi **03=Ukhukho** **05=Ingubo** **02=Ematrasini pantsi** **04=iSheet** **06= iPilo** 01=Bed and mattrass 02=Mattrass on the floor 03= Mat 04=Sheet 05=Blanket 06=Pillow	
21. Bangaphi abantu abalala ekamereni? How many people sleep in the same room as the child?	
22. iBedi uye ndlula roqho? Is the bed made up each day?	
23. Uyitshintsha emva kwexesha elingakaka nani? How often is the bedding changed?	
24. Mangaphi amagumbi endlu yakho? How many rooms are there in the house?	
25. Bangaphi abantu abahlala nani? How many people live in the house?	

26. Zeziphi kwezi zilwanyanha ezingenayo endlwini? Which of the following animals come into the house?	EWE	HAYI
01 iKati / Cat		
02 Inja / Dog		
03 Iinkuku / Chicken		
04 Ezinye ezinoboya / Other feathered animals		
05 iHagu / Pig		
06 Inkomo / Cow		
07 iBhokhwe / Goat		
08 Nezinye / Other (specify)		
09 Ezi zilwanyana zivumelekile apho kufalwa khona? Are any of these animals allowed in the sleeping area?		
Ukuba EWE, zeziphi? If yes, which type of animal?		

27. Usebenzisa awaphi amafutha ukufudumeza indlu? What is the main fuel you use for heating the house?	
28. Usebenzisa awaphi amafutha ukupheka nokubilisa amanzi? What is the main fuel you use for cooking and boiling water?	
01 = Electricity - grid ***04 = Electricity - battery/generator*** ***07 = Paraffin*** ***02 = Dung*** ***05 = Gas*** ***08 = Wood*** ***03 = Charcoal/coal*** ***06 = Other*** ***09 = None***	
29. Usebenzisa exiphi izixhobo ukupheka nokubilisa amanzi? What type of appliance do you use for cooking and boiling water?	
01 = LPG Ring Burner ***05 = Wood*** ***08 = Paraffin Primus Stove*** ***02 = Paraffin Wick Stove*** ***06 = Coal Stove*** ***09 = None*** ***03 = Three-Stone Wood Stove*** ***07 = Coal Brazier*** ***010 = Other*** ***04 = Electric stove***	

	EWE	HAYI
30. Ikhona imbhobo yokuphuma umsi? Is there a smoke outlet in the house?		
31. Ngethuba aphekayo umama ubesoloko elubelekile na usana? When (child's name) was a baby was (he/she) carried by their mother while she did the cooking?		
32. Uyibona indlu yakho ifumile? Do you think your house is damp?		
33. Amanzi esitila ngodonga? Does water ever run down the walls?		
34. Amadonga amanzi? Are the walls damp to touch?		
35. Amadonga angundile nemphahla yendlu? Does mould ever grow on the walls or furniture in the house?		
36. Indlu ikhe idame amanzi? Does the house ever flood with water?		
37. Iflori ihlala njalo ifumile? Are the floors ever damp?		

38. Usebenzisa eyiphi i Toilet? What type of toilet does the household use?

01 = Flush toilet	***02 = Improved pit latrine – ventilation (VIP)***
03 = Other pit latrine	***04 = Bucket toilet***
05 = Chemical toilet	***06 = None***

39. iToilet esetyenziswa nangabanye abantu na? Is the toilet shared with other households?	EWE	HAYI

40. Amanzi uwafumana phi? Where does your water come from?

01= Piped (tap) – inside	***02=Piped (tap) – yard***	***03=Water carrier/tanker***
04=Piped-public tap/kiosk (free)	***05=Piped-pub. tap/kiosk (paid)***	***06=Borehole***
07=Rainwater tank	***08=Flowing river/stream***	***09=Dam/Stagnant water***
010=Well (no borehole)	***011=Protected spring***	***012=Other***

41. Ingaba lamanzi usela kuwo, uhlambe kuwo, ude upheke kwangawo? Do you use the same water for drinking, washing, cooking and washing clothes?	EWE	HAYI

IF **YES** GO TO QUESTION **43**

42. Uwafumana phi amanzi owasebenzi sela - Where do you get the water you use for -	
01 Ukuhlamba impahla? / washing clothes?	
02 Ukuhlamba umntwana? / washing your child?	
03 Ukupheka / cooking?	
04 Ukusela / drinking?	

01 =Piped (tap) - internal	***02=Piped (tap) - yard***	***03=Rainwater tank***
04 =Flowing river/stream	***05=Water carrier/tanker***	***06=Dam/Stagnant water***
07 =Piped-public tap (free)	***08=Well (no borehole***	***09=Protected spring***
010=Piped-pub. tap/kiosk (paid)	***011=Borehole***	***012=Other***

43. Zeziphi kwezi zinambkuzane exikhoyo endlwini yakho? What type of pests are a problem where you live?	EWE	HAYI
01 Iimpukane / Rats		
02 Amaphela / Cockroaches		
03 Iingcongconi / Mosquitoes		
04 Iintakumba / Fleas		
05 iTicks / Ticks		
06 Iincukuthu / Bedbugs		
07 Ezinye / Other (Specify)		

44. Ingaba usebenzisa ichiza lokubulala ezi zinambuzane? Do you use any poisons to kill insects, cockroaches, weeds or rats?	EWE	HAYI
Uku EWE, leliphi? If YES, which ones?		

IF **NO** GO TO QUESTION **42**

45. Ulisebenzisa ixesha elingakanani elichiza? How often do you use these products?	
46. Usebenzisa isaitshizi, ichiza elingamanzi okanye umgubo? Do you use a spray, liquid or powder	Spray/Liquid/Powder
47. Ulisebenzisa eli chiza ngaphakathi okanye ngaphandle? Do you use these products inside or outside?	Inside / Outside

48. Usebenzisa eyiphi isepha ukuhlamba impahla yakho? What products do you use to wash your clothes?

49. Usebenzisa eyiphi isepha ukuhlamba u ..... (umntwana) What products do you use to wash (child's name)?

50. Uyazisebenzisa ezi zilandelayo? Do you use any of the following?		EWE	HAYI
01	Isitshizi sendlu esigholiweyo / Air fresheners		
02	Isitshizi senwele / Hair spray		
03	Isitshizi somzimba / Body spray		
04	Isitshizi sebedi / Spray for beds		
05	Isitshizi somandlalo / Spray for bedding		
06	IJik eqholiweyo / Perfumed Jik		
07	IFurniture polish eqholiweyo / Perfumed furniture polish		

51. Uyicoca njani inkunkuma yakho? How do you get rid of your household waste?
01=Council waste disposal ***02=Private waste removal co.*** ***05=Other*** ***03=Local dump*** ***04=Burn***

52. Ingaba kukhe kutshiswe amatayara kufutshane nendlu yakho? Do people often burn tyres near your home?	EWE	HAYI	ANDAZI

53. Kwezi zilandelayo kokuphi okuchaza ngokusondeleyo endlwini yakho?
Which of the following best describes the amount of traffic on the road closest to your house?

01 = Always heavy traffic (vehicles at all times during day-time)
02 = Traffic only at rush-hour, less than 20 vehicles an hour at other times)
03 = Sometimes traffic (less than 20 vehicles an hour at all times)
04 = Almost never (less than 30 vehicles per day)
05 = Less than 20 vehicles per day
06 = Less than 10 vehicles per day

54. Uhlala kufutshane nezi ndawo zilandelayo? Do you live near any of the following?

01 = Power Station
02 = Transfer Station)
03 = Power lines (high voltage)
04 = Industry (specify if possible)
05 = Incinerator/Burner

55. Ingaba umntwana ..... ukhe aqubhe elwandle? Does (child's name) often swim in the sea?	EWE	HAYI
Ukuba EWE, koluphi ulwandle? If YES, at which beach?		
56. Uyaqubha emlanjeni? Does (he/she) swim in the river?	EWE	HAYI
Ikuba EWE, kowuphi? If YES, in which river?		
56. Ikhona enye indawo athi aqubhe kuyo? Is there anywhere else where he/she swims?	EWE	HAYI
Ukuba EWE, phi? If YES, where?		

57. Oko kugqibela, xa uqaphela ungathi woneliseka kangakanani na yindlu yakho, kunye nobomi esiphila kubo namhlanje? Lastly, taking everything into account, how satisfied is your household with the way it lives these days?

01 = Very satisfied
02 = Satisfied
03 = Neither satisfied nor dissatisfied
04 = Dissatisfied
05 = Very dissatisfied

THANK YOU FOR HELPING US TO ANSWER THESE QUESTIONS

Appendix 3 : Additional statistical results

*Table depicting adjusted odds ratios of **Multivariate** Logistic Regression (MLR) Models of various Environmental Factors to the outcome of AD, with 95% confidence intervals, for **AREA 1 = RURAL***

		Eczema	
Predictors	*Odds Ratios*	*CI*	*p*
(Intercept)	0.35	0.14 – 0.84	**0.020**
Weaned4Months [1]	1.30	0.78 – 2.18	0.310
Fleas [1]	0.80	0.46 – 1.36	0.409
MouldGrow [1]	**5.73**	**1.18 – 41.20**	**0.042**
UsePoisons [1]	1.05	0.61 – 1.80	0.871
StressEvents [1]	2.81	0.66 – 12.53	0.157
AgeInYears x	0.99	0.89 – 1.11	0.920
Gender [M]	1.18	0.70 – 1.97	0.534
Observations	293		
R^2 Tjur	0.035		

*Table depicting adjusted odds ratios of **Multivariate** Logistic Regression (MLR) Models of various Environmental Factors to the outcome of AD, with 95% confidence intervals, for **AREA 2 = URBAN***

		Eczema	
Predictors	*Odds Ratios*	*CI*	*p*
(Intercept)	0.11	0.04 – 0.26	**<0.001**
Weaned4Months [1]	**2.93**	**1.71 – 5.09**	**<0.001**
Fleas [1]	**3.08**	**1.92 – 5.03**	**<0.001**
MouldGrow [1]	2.03	0.99 – 4.22	0.054
UsePoisons [1]	**2.11**	**1.22 – 3.74**	**0.009**
StressEvents [1]	**2.59**	**1.07 – 6.32**	**0.034**
AgeInYears x	0.99	0.90 – 1.09	0.850
Gender [M]	1.26	0.79 – 1.99	0.333
Observations	387		
R^2 Tjur	0.173		

*Table depicting adjusted odds ratios of **Multivariate** Logistic Regression (MLR) Models of various Environmental Factors to the outcome of AD, with 95% confidence intervals, for **AREA 3 = PERI-URBAN***

	Eczema		
Predictors	*Odds Ratios*	*CI*	*p*
(Intercept)	3.83	0.14 – 156.51	0.445
Weaned4Months [1]	1.49	0.44 – 5.24	0.521
Fleas [1]	0.88	0.13 – 6.04	0.895
MouldGrow [1]	3.29	0.62 – 23.69	0.185
UsePoisons [1]	0.54	0.05 – 5.35	0.591
StressEvents [1]	0.54	0.02 – 8.61	0.678
AgeInYears x	0.80	0.60 – 1.04	0.106
Gender [M]	1.72	0.54 – 5.50	0.357
Observations	59		
R^2 Tjur	0.131		

Appendix 4 : Journal submission instructions (Environmental Health Perspectives)

What *EHP* Publishes

Research articles report original research results that are relevant to the relationship between the environment and human health, and that make a substantial advance in the field.

EHP strongly recommends that authors consult the following reporting guidelines while drafting manuscripts:

- For observational research studies, authors should consult an appropriate version of the **STROBE**(Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.
- For research articles involving animal subjects, authors must adhere to the **ARRIVE**(Animals in Research: Reporting *in Vivo* Experiments) guidelines for reporting animal research (**Kilkenny et al. 2010**; **Tilson and Schroeder 2013**).

Regarding papers that consider race or ethnicity:

- As noted by the *AMA Manual of Style* committee, "Continual review of the language used to describe race and ethnicity is critically important" (**Flanagin et al. 2021**). Thus, *EHP* may revise these guidelines as necessary. We recognize that these guidelines represent a change from prior journal practices, and we anticipate and welcome the conversation this may precipitate.
- Racial and ethnic groups should be described using terms used by study participants to describe themselves (e.g., if the study questionnaire options included Black do not describe participants as African American) and designated by capitalization (e.g., Black versus black). For additional guidance on reporting race and ethnicity, we recommend the **APA Racial and Ethnic Identity Style Guidelines**.
- Because race is a social construct, *EHP* generally will not consider research that proposes or assumes a genetic basis as the only explanation for racial health disparities (see **Kaufman and Hajat 2021**). If a genetic explanation is proposed as a basis for health disparities, this explanation should be framed in terms of genetic ancestry rather than "race" (**Oni-Orisan et al. 2021**).
- We urge investigators to develop and use methods to measure racism and/or racist policies and their effects directly whenever possible, instead of using race/ethnicity as a convenient proxy. We expect authors to be thoughtful in considering racism as an underlying reason for downstream impacts, rather than simply attributing health effects to race. Importantly, the absence of data does not imply that disparities in exposures and health do not exist.

Suggested Length

Suggested length is < 7,000 words, excluding the text in the abstract, **references**, **tables**, **figure** captions, acknowledgments, and **Supplemental Material**.

Title

The title should consist of ≤ 300 characters and should state the subject of the paper and include relevant information to help potential readers determine whether the paper might be related to their interests or needs. Relevant information includes the exposure(s) and outcome(s) assessed, and whether the study was observational or experimental. For epidemiological studies, consider key characteristics of the study population (e.g., gender, age, location, cohort) and design. For experimental studies, indicate the experimental model, including species or *in vitro* system(s). The title should not be a declarative statement of the study results or conclusions.

Abstract

Include a structured abstract of ≤ 300 words using the following headings: Background, Objectives, Methods, Results, Discussion.

The abstract should not include references or any information that does not appear in the text of the manuscript. We recommend that authors indicate study names or sources of data that are integral to the study. Summarize major findings in a balanced manner, rather than focusing only on findings that support the study hypothesis.

Main Text Structure

Sections should appear in the following order:

- Introduction
- Methods
- Results
- Discussion
- **References**
- **Tables**
- **Figure** captions

Concise subheadings (≤ 8 words each) may be used to designate major topics within each of these sections. Subheadings should be used to organize information, but should not summarize or interpret results or conclusions.

Introduction

Provide background information to support the motivation for the study, and state the study objectives or hypotheses. Specifically,

- Provide context for the study, including information on the exposures and outcomes and why they are relevant to environmental health.
- Briefly review the literature to summarize current knowledge.
    - Present a balanced review of the literature, and acknowledge inconsistencies, rather than noting only findings that support the present study hypothesis.

    - For each cited study, indicate whether the research was observational or experimental, and note key characteristics of study populations or experimental models.
- Identify knowledge gaps addressed by the current study.
- Provide a clear description of the study questions/hypotheses, aims, or objectives, and, if appropriate, an overview of the approach used to address them.

Do not summarize study results or conclusions in the Introduction.

Methods

EHP requires complete methodological transparency—describe methods in enough detail to ensure that the study or analysis could be repeated by other researchers in the same field (at least in theory), and that the methods can be understood and interpreted by most *EHP* readers. Specifically,

- Thoroughly describe the methods used to generate all results reported in the manuscript, including (as appropriate):

Experimental studies	**Observational studies**

• Study design and experimental model
• Assay methods and conditions
• Justification of exposure and/or doses
• Number of biological and/or technical replicates
• Statistical analyses
• Accession numbers (or "rs" numbers for SNPs)
• All criteria used to interpret results
• Key assumptions and limitations of the methods
• Model numbers of all equipment used
• Company name, catalog number, and lot numbers for all reagents used
• Names/version numbers for data analysis software packages or macros
• All relevant details listed in the latest version of
	• Study design and population
	  ◦ Report how and by whom "race" or "ethnicity" was defined (e.g., self-reported by participants or some other method) and why this information was included in the study design
	• Explain the rationale for treating race as an exposure, confounder, effect modifier, or other type of variable in analyses
	• Disaggregate race and ethnicity data to the fullest extent possible
	• Methods to measure or estimate exposures and covariates
	• Outcome definitions and ascertainment or measurement
	• Assay methods and conditions
	• Statistical analyses, including
	  ◦ Statistical models and assumptions (with equations as appropriate)
	  ◦ Methods/rationale for selecting model covariates (provide directed acyclic graphs as appropriate)
	  ◦ Missing data methods

the **ARRIVE** guidelines • Indication that the protocol was approved by an institutional animal care and use committee	◦ Methods for assessing linearity/non-linearity ◦ Cutpoints for categorical variables • Sensitivity and secondary analyses • All criteria used to interpret results • Key assumptions and limitations of the methods • Names/version numbers for data analysis software packages or macros • Information about institutional review board approval • Describe informed consent protocols or explain why informed consent was not required

- If referring to previous publications for methods details, include a brief description of the approach, key assumptions and limitations, and any deviations from previously described methods.
- Do not report results in the Methods section unless relevant to explain the rationale for the approaches listed.

Results

All results on which study conclusions or inferences are based (in whole or in part), including null findings and results of secondary or sensitivity analyses, must be reported in full in the main text or in supplemental tables or figures (see "**Supplemental Material**" for a list of materials that may be presented in this section).

The "Results" section may be organized using subheadings that describe the nature of the results, but do not use declarative statements indicating your conclusions about the findings.

- Provide a clear and concise description of all findings without extrapolating beyond the study results. Interpretations of the findings should be reserved for the “Discussion” section.
- Do not describe methods for the first time in the "Results" section.
- Do not limit results to statistically significant results or selected findings that support the study hypothesis.
- In general, *EHP* recommends that authors avoid using statistical significance testing as the sole or primary criterion for interpreting their findings, but if significance testing or p-values are used, report numeric p-values (rounded to 1-2 significant digits) for all results instead of indicating whether results are above or below a specific p-value only.
- Clearly indicate the number of observations for each analysis or experiment. Numbers should reflect observations included in each analysis after accounting for missing data.
- Include an appropriate measure of precision or variation (e.g., standard errors, 95% confidence intervals) with all summary estimates and estimates of effect.

- For observational studies, include a table or tables summarizing relevant population characteristics, including all covariates included in primary or secondary models.
    - Indicate numbers of observations with missing data for all covariates.
    - Provide detailed information about exposure distributions, including minimum and maximum values, percentiles, and numbers of samples above/below assay limits of detection or quantification.
- Although *EHP* encourages the use of supplemental tables or figures for secondary findings (see "**Supplemental Material**" for details), present primary results in the main text. This includes results that are mentioned repeatedly, are related to the primary study aims, or are mentioned in the abstract or manuscript conclusions.
- Provide tables with corresponding numeric data for all figures (in the main text or supplemental material, as appropriate) or include numeric data within figures (e.g., as forest plots).

Discussion

Begin with a *brief* overview of the main study findings, without repeating all results in detail.

- Provide a review of the relevant literature and other information needed to put the study findings into context.
- Provide a complete and balanced view of previous research, including findings that are inconsistent with the hypothesis, results, or conclusions of the present study.
- Describe sources in sufficient detail to ensure that readers can assess the quality and extent of the contribution, including:
    - study type or design
    - sample size
    - population or experimental model
    - specific exposures and outcomes
- Provide a frank discussion of study limitations.
    - If race/ethnicity is included in analyses, discuss limitations in its classification, and in its use as a proxy for unmeasured consequences of racism.
- End with a summary of the key findings and their implications for the study question/hypothesis, future research, and policy, as appropriate.
- Do not describe methods or results for the first time in the "Discussion" section.

Acknowledgments

Include sources of funding for the research (if applicable), such as granting agencies, foundations, private support, etc. Authors may also include (as relevant) specific author contributions, acknowledgment of other contributors, information about data sharing, or names of large cohort groups.

Data Sharing

Information about data sharing protocols, options for accessing data, and links to data repositories may be provided in the “Acknowledgments” section, as noted above. Authors may also provide links to data repositories in the “Methods” or “Results” sections of their manuscripts, as appropriate.