

ORIGINAL ARTICLE

Epidemiology, Genetics & Prevention

Nutrition and allergic diseases in urban and rural communities from the South African Food Allergy cohort

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Abstract

This study describes and compares allergic diseases and sensitization in urban and rural children in the SAFFA study cohort as well as infant feeding patterns and nutritional status. We assessed the relationship between nutritional status, breastfeeding, complementary feeding patterns, and atopic diseases including aeroallergen and food allergen sensitization, self-reported atopic dermatitis, allergic rhinitis, asthma, and challenge-proven food allergy (FA).

Methodology: A total of 1185 urban and 398 rural toddlers aged 12–36 months were screened for food sensitization (FS) and FA using skin prick testing and oral food challenges. Of these, 535 and 347, respectively, were additionally screened for aeroallergen sensitization. Information was collected on infant feeding practices, and anthropometric measurements and clinical signs for atopy were documented.

Results: Markedly higher rates of allergy (asthma 9.0% vs 1.0%, eczema 25.6% vs 2.0%, rhinitis 25.3% vs 3.3%, and FA 2.5% vs 0.5%) exist in urban vs rural children. 13.1% unselected urban South African children were sensitized to aeroallergens compared to 3.8% of their rural counterparts and 9.0% to any food compared to 0.5%. Exclusive breastfeeding duration was longer, and there was a later introduction

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; BA, black African; Blo t, *Blomia tropicalis*; BMI, body mass index; C, Caucasian/white; Der p, *Dermatophagoides pteronyssinus*; ECD, early child development; FA, food allergy; FS, food sensitization; HDM, house dust mite; IgE, immunoglobulin E; LFA, length for age; MA, mixed ancestry; OFC, oral food challenge; SAFFA study, South African Food Allergy study; SPT, skin prick test; WFA, weight for age; WFL, weight for length; ZAR, South African rands.

of allergenic foods in rural communities. Obesity rates were similar between the two groups, but rural children were more likely to be stunted. Being overweight was associated with asthma in urban but not rural settings. In the urban cohort, children with FS and allergy were thinner than their peers.

Conclusion: Allergy and sensitization rates are significantly higher in unselected urban South African toddlers than their rural counterparts. Risk and protective factors for allergy and atopy may differ between urban and rural settings.

KEYWORDS

aeroallergen, aeroallergen sensitization, Africa, allergic rhinitis, asthma, atopic dermatitis, breastfeeding, complementary feeding, weaning age, eczema, food allergy, obesity, prevalence, sensitization, stunting, weaning

1 | BACKGROUND

Many studies have shown an association between nutrition and allergic diseases.¹⁻³ Obesity has been most strongly associated with aeroallergen sensitization and asthma.⁴ Conversely, established food allergy (FA) has been shown to cause malnutrition.⁵ Few studies have assessed the association between growth and multiple atopic outcomes including both aeroallergen sensitization and respiratory disease, atopic dermatitis, food sensitization (FS), and challenge-proven FA.

The significant difference in FS and FA prevalence in urban and rural South Africa⁶ is unlikely to result from ethnic differences between the cohorts. We hypothesized that differences would exist in infant feeding practices as well as nutrition between urban and rural communities. To examine the inter-relationship of allergy and nutrition, data on breastfeeding and complementary feeding as well as nutritional status were collected and assessed for associations with aeroallergen sensitization, allergic diseases, FS, and challenge-proven FA.

2 | METHODS

2.1 | Study design and setting

Between June 2013 and December 2016, 1185 urban and 398 rural children aged 12-36 months were screened for FS and challenge-proven FA in the South African FA (SAFFA) study, which was conducted in the rural Eastern Cape and the City of Cape Town.^{6,7} A subsection of this cohort was also assessed for aeroallergen sensitization.

2.2 | Sampling frame

In Cape Town, registered early childhood development (ECD) centers were approached in random order and parents of all enrolled children aged 12-36 months were invited to participate. As ECD centers are rarely found in the rural area, we conducted study days

Key Message

Rural 1-3 year old children have a markedly lower rates of aeroallergen and food sensitisation as well as asthma, rhinitis, eczema and challenge proven food allergy than urban children. This effect is due to environment and exposures, not due to ethnic differences. Growth, nutrition and complementary feeding are associated with allergy outcomes in urban, but not rural settings. Other factors in the rural environment are likely associated with the protective effect.

at 10 primary healthcare clinics recruiting all children of eligible age from the surrounding area.

2.3 | Sample size

The SAFFA study sample size was calculated to determine and compare the prevalence of FS and FA in urban Cape Town and in the rural Eastern Cape.⁷ Aeroallergen sensitization was added into our assessments when we estimated an equal number of rural and urban participants would still be recruited and we aimed to enroll 400 participants in each group.

2.4 | Recruitment and assessment

A questionnaire captured information on family history of allergic diseases, family size, breastfeeding and weaning, infant diet, socioeconomic status, household number, parental education, and parental employment.

Participants' allergic diseases were determined by self-reported symptoms according to modified ISAAC criteria and through clinical examination for signs of allergic rhinitis (allergic shiners, nasal crease, Dennie's lines, and enlarged turbinates) and atopic dermatitis (xerosis, visible skin lesions). AD was diagnosed by a dermatologist

based on diagnostic criteria proposed by the American Academy of Dermatology including essential features of pruritus and eczematous rash with typical morphology and age-specific patterns, and a chronic or relapsing history.⁸

Weight was measured without shoes and outer clothing and recorded to the nearest 0.1 kg. Length was measured using a measuring mat with the child supine and without shoes and recorded to the nearest 0.5 cm.

Triceps skinfold thickness was measured using Medi-Q skinfold calipers at the mid-upper arm in millimeters (mm) with the child sitting or standing and the arm hanging free.

Abdominal circumference was measured in a supine position, at the level just above the right iliac crest using a stretch-resistant tape.

Skin prick tests (SPTs) were performed for food allergens in the entire cohort and for aeroallergen sensitization in the smaller cohort. SPTs were performed using ALK-Abello SPT solutions (Thermo Fisher) to seven common food allergens (egg white extract, peanut, cow's milk, cod-fish, soya, wheat (flour), and hazelnut) and four aeroallergens (*Dermatophagoides pteronyssinus*, *Blomia tropicalis*, German cockroach (*Blatella germanica*), and Grass Mix containing *Dactylis glomerata*, *Festuca elatior*, *Lolium perenne*, *Phleum pratense*, and *Poa pratensis*). In addition, fresh egg white, peanut butter, and fresh cow's milk as well as positive (10 mg/mL histamine) and negative (saline) controls were used. SPT results were read at 15 minutes and recorded as the mean wheal diameter in millimeters. For aeroallergens, a mean wheal diameter of ≥ 3 mm >the negative control was considered positive. Participants with any reactive food SPT (≥ 1 mm) and who were not (on questionnaire) tolerating a full age-appropriate portion of the specific food were qualified for an open oral food challenge (OFC) performed at Red Cross Children's Hospital in Cape Town and Zithulele Hospital in the Eastern Cape.⁶

A subset of participants completed a 24-hour dietary recall administered by study staff trained in the multiple pass method, including first inquiring to ascertain a quick list of foods consumed, followed by forgotten foods and a detailed description of each food.⁹ This inquiry was done using culturally appropriate portion size illustrations to obtain accurate quantities. The individual food items from these completed 24-hour recalls were entered into the Food Processor Nutrition software program (created by Elizabeth Stewart, Hands and Associates), a nutrient analysis program utilizing the USDA Standard Reference database, manufacturer's data, restaurant data, and data from literature sources to determine nutrient values for individual food items. Data were entered by registered dietitians, generating key nutrients of interest, including total fat, saturated fat, protein, fiber, and total sugar. This study was approved by the Human Research Ethics Committee of the University of Cape Town (HREC REF: 038/2012). Informed consent was obtained from parents or legal guardians of participants.

2.5 | Statistical analysis

Data were entered into a Microsoft Access database and analyzed using Stata version 11.1 (Stata Corp). The Mann-Whitney test was

used to investigate differences between numerical variables, Fisher's exact test was used to assess associations between categorical variables, and the Z test was used to investigate differences in proportions. Multivariate analysis was performed to assess the association between the different allergy outcomes and toddler nutritional status as exposure variables. Confounders chosen a priori that were adjusted for in the regression analyses included sex, ethnicity, family history of allergy, and family size. The analyses were performed for both numerical and categorical versions of the nutritional status variables. A P-value of <0.05 was considered statistically significant.

Overweight and obesity were defined according to the WHO child growth standards.¹⁰ Z-scores for BMI, WFA, WFL, LFA, and triceps skinfold thickness were calculated using WHO anthropometry software. For abdominal circumference, we calculated sample-specific z-scores as no relevant population-based standardized z-scores exist for abdominal circumference in this age group (as opposed to waist circumference measured at the level of the umbilicus).

3 | RESULTS

A total of 1230 urban and 410 rural children were screened for inclusion. Of these, 1200 urban and 410 rural children were eligible for the study. Fifteen urban and 12 rural children did not complete the questionnaire or skin tests. A total of 1185 urban and 398 rural participants completed the study (Table S1). Five hundred and thirty-five and 347 participants in the urban and rural cohorts, respectively, completed SPT for aeroallergens.

The median age of enrollment of the urban cohort was 26 months (IQR 22-32), significantly older than the rural cohort (21 months, IQR 17-28, $P < 0.001$).

In both the urban and the rural cohorts, more male than female participants were enrolled. The proportions however were not significantly different between the two cohorts (Table S2).

The urban cohort reflected the ethnic composition of children under five in the City of Cape Town according to the 2011 census. The rural cohort was entirely black African.

Household income shows significant discrepancy between urban and rural participants with the median household income in our urban cohort being ZAR7000 per month compared to ZAR1380 in the rural cohort ($P < 0.001$). Rural households tended to be larger than urban with the median total number of people living in a rural household being seven (IQR 5-8) compared to four (IQR 4-6) in the urban cohort ($P < 0.001$). Urban parents were more likely to have completed tertiary education than their rural counterparts (43.3% vs 5%, $P < 0.001$) and were more likely to be employed.

Urban participants had significantly higher rates of a family history of allergy than rural participants.

The smaller cohort of participants who had aeroallergen testing did not differ significantly from the larger cohort in terms of these differences in age, ethnicity, household income, household number, parental employment, parental education, and personal and family history of atopy (Table S2).

3.1 | Infant feeding

Breastfeeding rates were similar between urban and rural mothers (88.2% vs 88.4%, $P = 0.60$). Duration of exclusive breastfeeding was longer in rural mothers and in urban black African mothers, but the total duration of breastfeeding did not differ significantly between study sites. Formula (or fresh milk) and first solid complementary foods were introduced earlier in urban settings (Table 1) with 19.7% of urban mothers introducing solids before 4 months compared to 15.3% of rural mothers ($P = 0.05$). 29.9% of rural mothers introduced solids only after 6 months compared to 11.2% of urban mothers ($P < 0.001$).

Urban and rural diets differed significantly in many ways.⁹ Energy intake and grams of protein, carbohydrates, fiber, simple sugars, and fat were significantly lower in rural South African children than in urban children. In addition, fiber and sugar intake was significantly lower in rural children compared to urban children.

Exposure to allergenic foods most relevant to this population (egg and peanut) was significantly higher in the urban cohort

(Table 2). 6.3% of the rural participants had never been exposed to egg compared to 1.4% of the urban children ($P < 0.001$). More than half of the rural children had never been exposed to peanut (53.0%) compared to 6.3% of urban children ($P < 0.001$). Even though exposure was lower, the rural children who did receive egg and peanut tended to receive it earlier than the urban cohort. Urban black African participants more closely resembled the rest of the urban population than the rural black African population, apart from a low exposure to tree nuts.

We found no association between age of introduction of allergenic food and atopic diseases including FS and FA in this cohort (Tables S10 and S12).

3.2 | Growth and nutrition

Rural children had higher BMIs than the urban cohort (BMI z-score median 1.15 vs 0.72, $P < 0.001$). 16.3% of rural participants were overweight (BMI z-score > 2) compared to 11.0% of urban children

TABLE 1 Infant feeding practices by study site

Infant feeding variables	Urban n = 1185 (%)	Urban black African n = 551 (%)	Rural n = 398 (%)	P-value*	P-value**
Ever breastfed (categories)	1045 (88.2)	455 (82.6)	352 (88.4%)	0.60	0.01
Duration of exclusive breastfeeding in months, median (IQR)	3.0 (0.5-5.0)	3.0 (0.5-6.0)	3.5 (1-6)	<0.001	0.004
Age exclusively breastfed (categories)					
Never breastfed exclusively	137 (11.6)	95 (17.2)	46 (11.6)	1.0	0.02
<4 mo	594 (50.8)	233 (42.3)	159 (40.0)	<0.001	0.47
4-6 mo	402 (34.4)	193 (35)	170 (42.7)	0.002	0.02
>6 mo	36 (3.1)	19 (3.5)	23 (5.8)	0.01	0.09
Duration of breastfeeding in months, median (IQR)	6 (2-16)	6 (2-17)	6.5 (2-15)	0.55	0.45
Duration of breastfeeding (categories)					
Never breastfed	137 (11.6)	95 (17.2)	46 (11.6)	1.0	0.02
Duration <4 mo	318 (26.8)	118 (21.4)	83 (20.9)	0.02	0.83
4-6 mo	188 (15.9)	73 (13.3)	70 (17.6)	0.42	0.07
6-12 mo	178 (15.0)	90 (16.3)	65 (16.3)	0.57	1.0
>12 mo ^a	352 (29.7)	169 (30.7)	134 (33.7)	0.15	0.33
Age of introduction of formula/fresh milk in months, median (IQR)	3 (0.5-6)	3 (0.5-6)	4 (1-6)	0.07	0.45
Age at first introduction of weaning foods in months, median (IQR)	6 (4-6)	6 (4-6)	6 (5-7)	<0.001	<0.001
Weaning age (categories)					
<4 mo	233 (19.7)	119 (21.6)	61 (15.3)	0.05	0.02
4-6 mo	817 (69.0)	354 (64.3)	218 (54.8)	<0.001	0.003
>6 mo	133 (11.2)	77 (14.0)	119 (29.9)	<0.001	<0.001

^aTotal duration of breastfeeding includes the children who were still breastfeeding at the time of the study. Their total duration is captured as their age of enrollment. They therefore all fall in the >12-mo group.

*P from z test for proportions for categorical values and Mann-Whitney test for continuous variables for the total urban population vs the rural population.

**P from z test for proportions for categorical values and Mann-Whitney test for continuous variables for the urban black population vs the rural population.

TABLE 2 Exposure to highly allergenic foods in urban and rural children

Highly allergenic foods	Urban n = 1185 median (IQR)	Urban black n = 551 median (IQR)	Rural n = 398 median (IQR)	P-value*	P-value**
Egg					
Never exposed to egg	17 (1.4)	12 (2.2)	25 (6.3)	<0.001	0.001
Age of egg introduction	12 (8-12)	12 (8-14)	12 (8-12)	<0.001	<0.001
Peanuts					
Never exposed to peanut	79 (6.7)	58 (10.5)	211 (53.0)	<0.001	<0.001
Age of peanut introduction	12 (12-18)	12 (12-18)	12 (8-13)	<0.001	<0.001
Cow's milk					
Never exposed to cow's milk	3 (0.3)	2 (0.4)	3 (0.8)	0.16	0.41
Age of cow's milk introduction	7 (6-9)	7 (6-9)	7 (6-9)	0.03	0.02
Cow's milk formula					
Never exposed to cow's milk formula	105 (8.9)	53 (9.6)	16 (4.0)	0.002	0.001
Age of cow's milk formula introduction	3 (0.3-6)	3 (0-6)	3 (1-6)	0.001	0.018
Any cow's milk exposure (including formula)					
Never exposed to any cow's milk	108 (9.1)	55 (10.0)	18 (4.5)	0.003	0.002
Age of any cow's milk introduction	7 (6-9)	7 (6-8)	7 (6-12)	0.50	0.60
Other nuts					
Never exposed to other nuts	680 (57.4)	416 (75.5)	315 (79.2)	<0.001	0.188
Age of other nuts introduction	18 (12-24)	18 (12-24)	12 (9-15)	<0.001	<0.001
Soya					
Never exposed to soya	362 (30.6)	107 (19.4)	6 (1.5)	<0.001	<0.001
Age of soya introduction	12 (10-18)	12 (10-18)	8 (6-12)	<0.001	<0.001
Wheat					
Never exposed to wheat	1 (0.1)	0	7 (1.8)	<0.001	0.002
Age of wheat introduction	8 (6-12)	8 (6-12)	11 (7-12)	<0.001	<0.001
Fish					
Never exposed to fish	56 (4.7)	44 (8.0)	116 (29.2)	<0.001	<0.001
Age of fish introduction	12 (10-18)	12 (12-18)	12 (9-13)	0.001	<0.001

*P from z test for proportions for categorical values and Mann-Whitney test for continuous variables for the total urban population vs the rural population.

**P from z test for proportions for categorical values and Mann-Whitney test for continuous variables for the urban black population vs the rural population.

($P = 0.01$). However, obesity was not significantly higher (3.9% vs 4.5%, $P = 0.62$). Rural participants had significantly lower median length-for-age z-score (-0.635 vs -0.01 , $P < 0.001$) and higher rates of stunting and severe stunting than the urban cohort (8.8% vs 5.8%, $P = 0.04$ and 4.5% vs 1.9%, $P = 0.01$, respectively; Figure 1). Stunted rural children had significantly higher BMIs than those who were not stunted ($P = 0.007$); however, there was no significant difference in urban children ($P = 0.47$; Figure 2).

Urban participants were more likely to be wasted (<-2 weight-for-length z-score; 1.2% vs 0%, $P = 0.03$).

Median triceps skinfold thickness in rural and urban communities fell within 0 and +1 z-scores but was significantly lower in the urban cohort than the rural cohort (0.7 vs 1.0 vs $P < 0.001$).

There was no difference in median z-scores for abdominal circumference between the urban and rural cohorts (-0.07 vs 0.073, $P = 0.50$; Table S3).

3.3 | Urban vs rural allergy

Significantly higher rates of allergic diseases were seen in urban than rural participants. Rates of self-reported asthma were 9.0% in the urban cohort vs 1.0% in the rural cohort ($P < 0.001$) with 25.3% urban vs 3.3% rural children having allergic rhinitis ($P < 0.001$) and 25.6% vs 2.0% atopic dermatitis. Overall, 45.1% of urban children had asthma, allergic rhinitis, or atopic dermatitis compared to 5.8% of their rural counterparts (Table 3; $P < 0.001$). Fourteen urban

children and one rural child did not complete one or more food challenge. To calculate adjusted prevalence rates, multiple logistic regression was performed with OFC as the outcome and each SPT for each allergen used as the predictor variables, using this dataset. A probability of a positive OFC was then calculated and used for each participant who did not complete an indicated OFC in order to add them to the analysis of adjusted prevalence.⁶ The prevalence of FS and challenge-proven FA was significantly higher in the urban cohort (9.0% vs 2.8%, $P = 0.001$ and 2.5% vs 0.5%, $P = 0.006$).

The prevalence of (any) aeroallergen sensitization was 13.1% (CI: 10.2-16.0) in the urban cohort, significantly higher than the rural cohorts (3.8%, CI: 1.7-5.8, $P < 0.001$). Der p sensitization in the urban cohort (12%, CI: 9-15) was three times higher than in the rural cohort (3.8%, CI: 1.5-5.4, $P < 0.001$). Prevalence rates for *Blomia tropicalis*, *Blattella germanica*, and Grasses were much lower overall, and statistically significant differences were not seen (Figure 3).

Aeroallergen sensitization was significantly higher in urban children with any allergic disease than those without (22.7% vs 7.1%, $P < 0.001$) as well as in those with asthma, AR, and AD than those without any allergies (Table 3). The urban black African participants more closely resembled their urban contemporaries rather than the rural black African participants. Sensitization rates were highest in urban children with clinically confirmed allergic rhinitis (14.1%) and atopic dermatitis (27.9%) (Table 4).

Higher sensitization rates to Der p were seen in urban subjects with any asthma, AR, or AD combined (20.7%, $P < 0.001$), as well as self-reported asthma (25.0%, $P = 0.03$), allergic rhinitis (21.3%, $P = 0.002$), and atopic dermatitis (26.2%, $P < 0.001$) in urban participants compared to non-allergic participants (Table S4).

There were low rates of aeroallergen sensitization in rural children. Aeroallergen sensitization was not significantly higher in rural children with allergic diseases than rural children without allergic diseases. Urban subjects without allergic diseases had significantly higher aeroallergen sensitization and Der P sensitization than rural children without allergic diseases.

3.4 | Association between nutrition and atopy

In the urban cohort, logistic regression analysis of the relationship between atopy and allergic diseases with nutritional status (adjusted for sex, ethnicity, family history of allergy, and family size) shows significant associations between asthma and measures of overweight/fatness (Table 5). There were no significant associations in the rural cohort (Table S5).

Analysis of continuous nutritional variables at the extremes of <2 or >2 standard deviations showed an association between overweight (>2 z-scores weight for age, weight for length, BMI) and self-reported asthma in the urban cohort (Table S6). There was no association between asthma and nutritional status in the rural cohort (Table S7).

In the urban cohort, measures of thinness were associated with FS (underweight-for-age OR 3.4, CI: 1.2-9.4, $P = 0.02$ and low abdominal girth OR 5.1, CI = 2.0-12, $P = 0.001$) and FA (low abdominal girth

OR = 4.9, CI = 1.1-22.7, $P = 0.04$), and fatness was associated with reduced FA (high triceps skinfold thickness OR = 0.3, CI 0.04-2.5, $P = 0.04$; Table S6). In the rural cohort, however, bigger children (WFA, WFL, and LFA z-score $>+2$) showed significantly increased odds of FS (Table S7). There was no significant association with triceps skinfold thickness and abdominal circumference and allergic diseases in the rural cohort.

We evaluated the effect of area of residence (urban vs rural study site) on the association between asthma outcome and toddler nutritional status by including a cross-product interaction term between the nutrition variable and the study site. Effect modification was considered to be significant if the cross-product interaction term P -value was <0.05 . None of the interaction terms (nutritional status $\times$ study site) were statistically significant when we analyzed the pooled cohort of urban and rural participants (Table S8). In the association between the exposure of nutritional status and asthma outcome, the toddler's place of residence is not an effect modifier. We stratified according to study site and performed multivariate analysis adjusting for a priori confounders to evaluate the association between nutrition and atopy (Tables 5, S6 and S7).

3.5 | Association between breastfeeding and weaning practices and atopy

The ages of introduction of egg and peanut did not differ in urban and rural settings (Table S10). In the urban cohort, increased duration of exclusive breastfeeding and later age of introduction of cow's milk formula or fresh milk were associated with a small increase in odds ratio of FS (Table S9). Later age of introduction of formula or cow's milk was associated with a slightly reduced OR for aeroallergen sensitization (Table S10). No significant associations were found in the rural cohort (Tables S11 and S12).

4 | DISCUSSION

This study explores the relationships between allergic diseases and food and aeroallergen sensitization, in the context of nutritional parameters in urban and rural settings. The rural participants comprised black African subjects, and the rural participants reflected the ethnic diversity of urban Cape Town. Urban black African subjects more closely resembled the rest of the urban cohort than the rural cohort, indicating that environmental exposures have more effect than genetic determinants of allergic sensitization and disease and that the differences found in urban and rural participants in allergic sensitization and allergy cannot be ascribed to ethnicity.

South African indoor allergens include house dust mites, cockroaches, and pet dander. Der p is ubiquitous, but mite numbers are lower in inland areas with lower humidity.¹¹ Der p sensitization is common in atopic South African children.¹² Sensitization to *Blomia* has been shown to be high in children with asthma and allergic rhinitis in the city of Durban where the climate is subtropical compared to the dryer Johannesburg.¹³

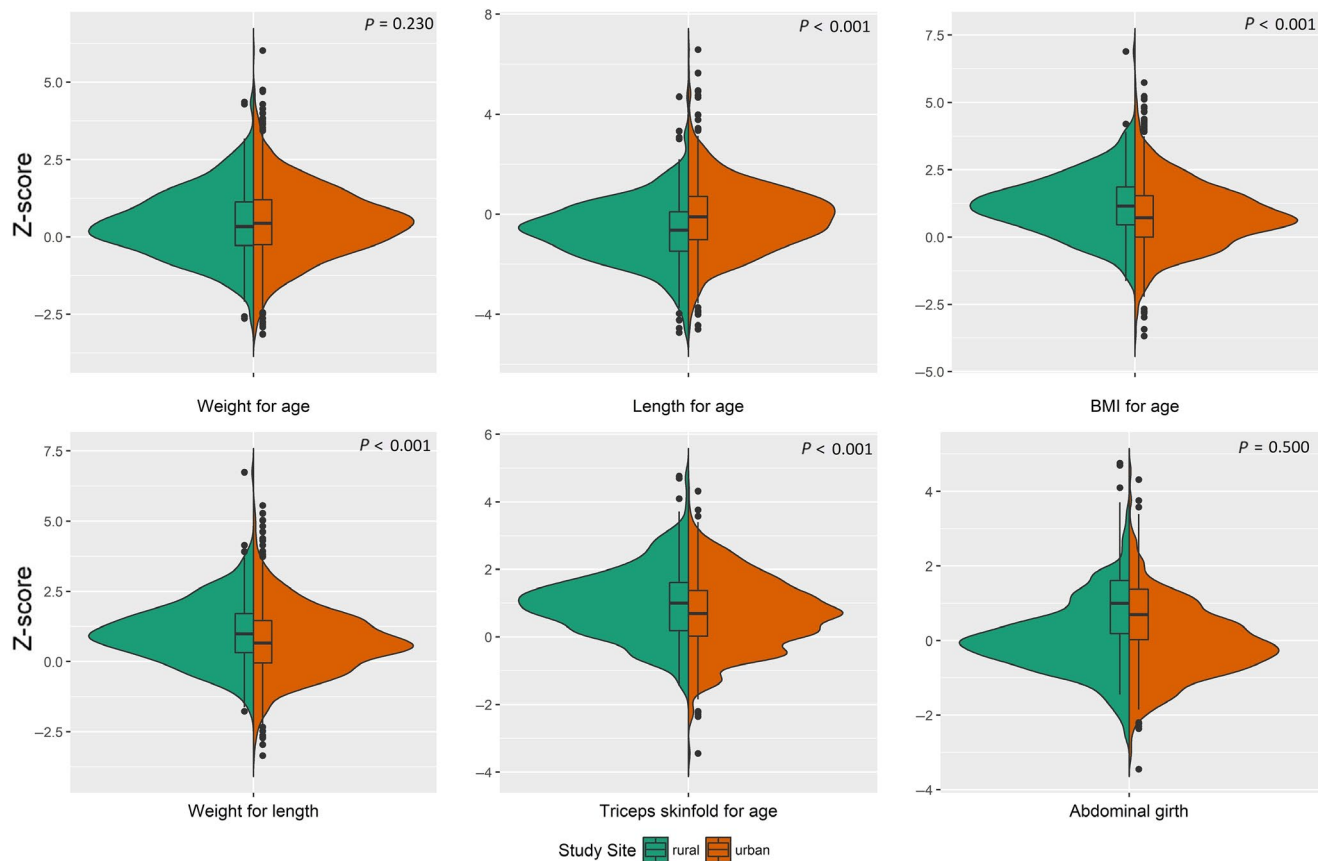
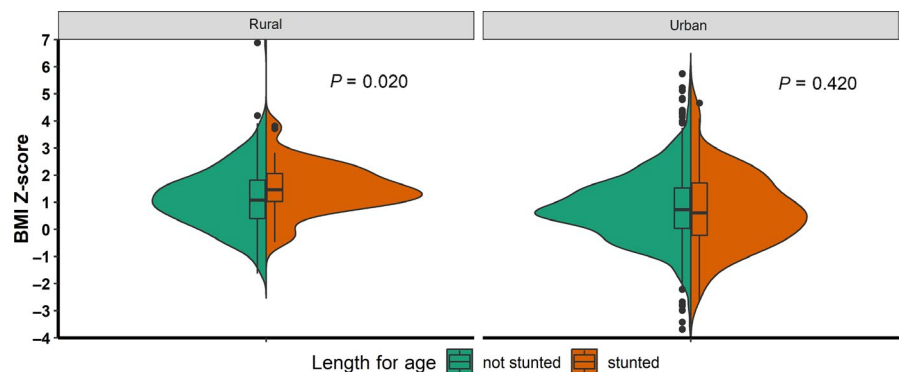


FIGURE 1 Comparison of nutritional status of the urban vs rural cohort

FIGURE 2 BMI in stunted vs non-stunted rural and urban children



South African studies point toward an increasing prevalence of allergic sensitization over time. Studies in South Africa in the 1970s reported very low rates of aeroallergen sensitization especially in rural settings¹⁴ with no sensitization to house dust mite in rural black asthmatics, but 65% sensitization in urban black asthmatic children and teenagers.¹⁴ Later studies showed increasing prevalence rates of asthma in urban¹² and rural black communities,^{15,16} narrowing of the urban-rural gradient and markedly different patterns of sensitization in those with or without bronchial hyper-responsiveness.¹²

The lower aeroallergen sensitization in this study probably reflects the very young age of our study cohort and predominant exposure to indoor aeroallergens such as HDM. The low prevalence of cockroach

sensitization, even in the urban cohort, is unexpected. Similar to other studies of urban-rural sensitization patterns in Africa,¹⁷ the association between aeroallergen sensitization and allergic diseases is strong in the urban population, but weak in the rural population.

This may partially be explained by small numbers in the rural population reducing power, but also reflects the strong protective effect against atopy in the rural setting, evidenced by the lower rates of aeroallergen sensitization in rural non-allergic than urban non-allergic subjects.

In both the urban and the rural cohorts, most children were exposed to first foods in the 4- to 6-month period. Rural mothers were more likely to start weaning foods after 6 months (29.9% vs 11.2%, $P < 0.001$) as per governmental health messaging around infant feeding. Increased

TABLE 3 Prevalence of atopy and allergy in urban vs rural participants

	Urban	Urban black	Rural	P-value*	P-value**
Any positive aeroallergen SPT% (95% CI)	13.1 (10.3-16.2)	12.8 (8.9-17.6)	3.7 (2.0-6.3)	<0.001	<0.001
Asthma% (95% CI)	9.0 (7.4-10.7)	6.0 (4.2-8.3)	1.0 (0.3-2.6)	<0.001	<0.001
Allergic rhinitis% (95% CI)	23.5 (21.2-26.1)	16.0 (13.0-19.3)	3.3 (1.8-5.5)	<0.001	<0.001
Atopic dermatitis% (95% CI)	23.5 (21.2-26.1)	19.6 (16.4-23.2)	1.8 (0.7-3.6)	<0.001	<0.001
Any asthma, AR, or AD% (95% CI)	45.1 (42.3-48.0)	34.7 (30.7-38.8)	5.8 (3.7-8.5)	<0.001	<0.001
Any positive food SPT% (95% CI)	9.0 (7.5-10.8)	10.2 (7.8-13.0)	2.8 (1.4-4.9)	0.001	0.001
Food allergy% (95% CI)	2.3 (1.5-3.3)	2.7 (1.5-4.5)	0.5 (0.1-1.8)	0.006	0.005

*P from z test for proportions for categorical values in the total urban population vs the rural population.

**P from z test for proportions for categorical values in the urban black population vs the rural population.

duration of exclusive breastfeeding has beneficial effects on immunity, nutritional status, and protection against infectious diseases, but also implies delayed introduction of formula and solids, which may be a risk factor for FS and FA.¹⁸ Increased duration of exclusive breastfeeding and later introduction of cow's milk or formula was associated with FS in the urban setting, and increased duration of breastfeeding was associated with reduced aeroallergen sensitization, indicating that different factors may impact food and aeroallergen sensitization.

This is the first South African study reporting on the timing of introduction of allergenic foods in an unselected population. Introduction is later than advised by current international allergy prevention guidelines^{19,20} and indicates a possible gap in our health-care messaging around complementary feeding in a rapidly urbanizing setting where FA prevalence is likely on the increase.

The most significant food allergens in this population of children, egg and peanut, were introduced late with more than half of rural children never being exposed to peanut at the time of assessment.

The explanation for a protective effect against FS and FA in the rural cohort²¹ is unlikely to result from "early" (4-11 months) exposure to allergenic foods.^{22,23} The late introduction of these foods in both the urban and rural cohorts may not directly cause the development of FA or FS, given the low prevalence of allergies in the rural cohort, but they may play a role when individuals migrate to a non-protective urban environment.

Because this is not a randomized trial, the direction of these effects cannot be ascertained, and it is possible that reverse causation could account for some of the findings. This is unlikely to be the explanation as breastfeeding uptake and duration and the age of introduction of complementary foods were not different in subjects with atopic parents or siblings with allergy.

The most significant nutritional finding is the lower length in the rural vs urban cohort, manifesting as increased rates of stunting and severe stunting but without significant differences in weight for age. This results in a higher BMI (being weight/length²) and a higher

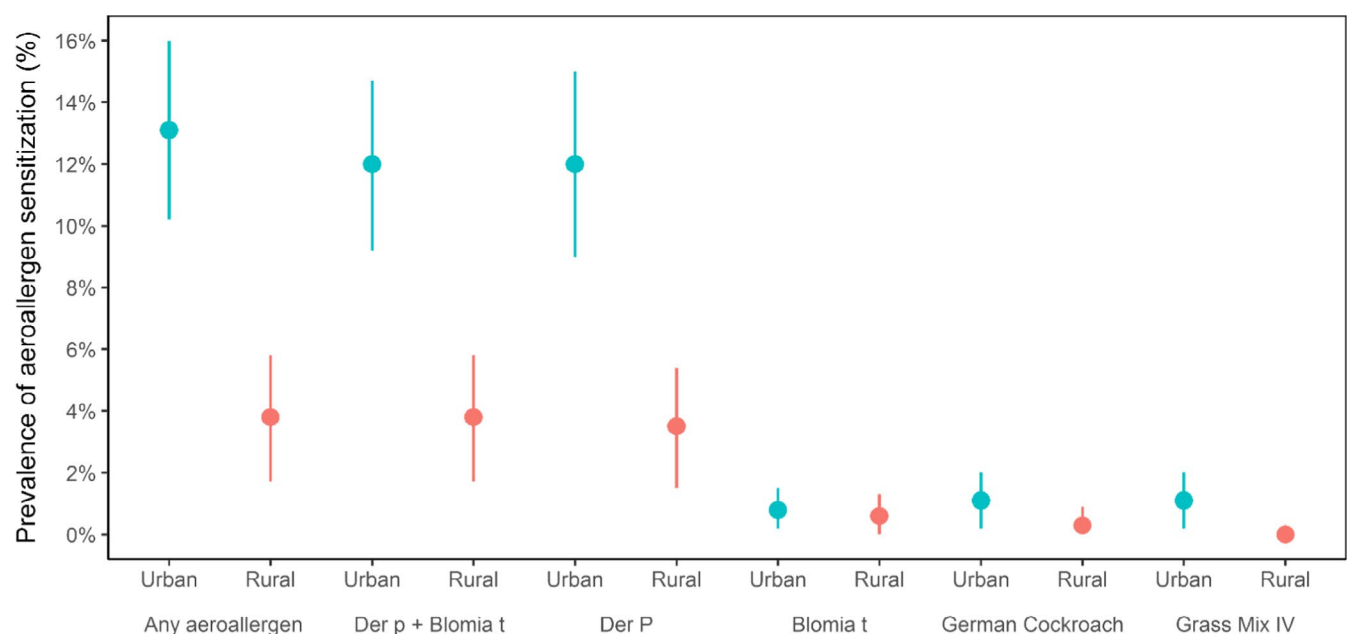
**FIGURE 3** Prevalence of aeroallergen sensitization in urban and rural participants [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Aeroallergen sensitization in participants with and without allergic disease

	Urban (n = 535)			Rural (n = 347)			
Any asthma, AR, or AD, n (%)	No (322)	Yes (213)	P-value	No (329)	Yes (18)	P-value	P-value no; yes
	23 (7.1%)	47 (22.1%)	<0.001	12 (3.7%)	1 (5.6%)	0.51	0.055; 0.098
Asthma	No (507)	Yes (28)	P-value	No (345)	Yes (2)	P-value	P-value no; yes
	62 (12.2%)	8 (28.6%)	0.01	13 (3.8%)	0 (0%)		<0.001; 0.38
Allergic rhinitis	No (427)	Yes (108)	P-value	No (334)	Yes (13)	P-value	P-value no; yes
	45 (10.5%)	25 (14.1%)	0.001	12 (3.6%)	1 (7.7%)	0.40	<0.001; 0.52
Atopic dermatitis	No (413)	Yes (122)	P-value	No (342)	Yes (5)	P-value	P-value no; yes
	36 (8.7%)	34 (27.9%)	<0.001	12 (3.5%)	1 (20.0%)	0.18	0.004; 0.70

prevalence of overweight (>1 z-score) but not in obesity (>2 z-scores). Urban children are slightly thinner than rural children with a lower weight for length and lower triceps skinfold thickness.

The most significant relationship between nutritional status and allergy is the associations between self-reported asthma and multiple measures of overweight/fatness. In the urban cohort, measures of thinness were associated with FS and FA and fatness was associated with a reduced FA. In the rural cohort, however, bigger children (WFA, WFL, and LFA z-score >+2) showed significantly increased odds of FS. A possible explanation of these findings is the bidirectional influences of nutrition and FA. In the urban community, where FA approximates 2.5%,²¹ awareness of FA is high, and some participants were on exclusion diets, possibly influencing their nutritional status. Conversely in the rural environment, FA prevalence is low, and children do not limit foods from choice. In this community, nutritional status may be having a direct effect on risk of FS or may serve as a proxy for more affluent individuals with different living environments and exposures.

In addition, the lack of association between breastfeeding and weaning patterns or nutritional status with any other measure of sensitization or allergy in the rural cohort implies that there may be other, more potent risk and protective factors in rural environments. These may include differences in birth mode, time spent outside in nature and sunlight, farm milk, parasite infestations, cooking and heating methods, pet and farm animal exposures, and exposure to different microbiomes.

4.1 | Weaknesses of this study

There is wide variability in reported measurements of abdominal or waist circumference as a measure of abdominal fatness. Methods used depend mainly on the age of the participants with infant measurements at the level of the iliac crest being a continuation of antenatal methods to determine fetal growth (as per the NHANES III protocol). Measurements for older children such as the WHO STEPwise approach to Surveillance (STEPS) protocol are more

TABLE 5 Association of nutritional status with allergy outcomes in urban participants

	Aeroallergen sensitization	Allergic rhinitis	Atopic dermatitis	Asthma	Food sensitization	Food allergy
Urban	OR (95% CI) P-value	OR (95% CI) P-value	OR (95% CI) P-value	OR (95% CI) P-value	OR (95% CI) P-value	OR (95% CI) P-value
Weight for age	1.0 (0.8-1.3) 0.81	1.0 (0.9-1.1) 0.81	1.0 (0.9-1.1) 0.91	1.4 (1.2-1.6) <0.001	1.0 (0.8-1.2) 0.93	0.9 (0.6-1.2) 0.41
Length for age	1.0 (0.8-1.2) 0.84	1.0 (0.9-1.2) 0.36	1.1 (1.0-1.2) 0.33	1.3 (1.1-1.5) 0.001	1.0 (0.8-1.1) 0.58	0.8 (0.6-1.0) 0.06
Weight for length	1.0 (0.8-1.3) 0.67	1.0 (0.9-1.1) 0.80	1.0 (0.9-1.1) 0.54	1.2 (1.1-1.5) 0.01	1.1 (0.9-1.2) 0.55	1.1 (0.8-1.5) 0.72
BMI	1.1 (0.9-1.3) 0.60	1.0 (0.9-1.1) 0.65	1.0 (0.9-1.1) 0.48	1.2 (1.0-1.4) 0.03	1.1 (0.9-1.2) 0.51	1.1 (0.8-1.5) 0.50
Triceps skinfold thickness	1.1 (0.8-1.4) 0.53	1.0 (0.8-1.1) 0.63	0.9 (0.8-1.1) 0.42	1.1 (0.9-1.3) 0.50	0.9 (0.7-1.1) 0.25	0.8 (0.6-1.2) 0.33
Abdominal girth (sample-specific z-scores)	1.1 (0.9-1.4) 0.46	1.0 (0.9-1.2) 0.92	1.1 (1.0-1.3) 0.19	1.2 (1.0-1.5) 0.05	0.8 (0.6-1.0) 0.05	0.6 (0.4-1.0) 0.05

closely aligned to adult waist measurements, which are taken at the level of the umbilicus or halfway between the last palpable ribs and the iliac crests. Standardized charts exist for these measurements, but our cohort fell in the age gap that straddles these two methodologies, and therefore, no standardized reference values exist for that age range at which our cohort was assessed. We therefore calculated sample-specific z-scores.

Furthermore, the relatively smaller samples size of the rural cohort limited our ability to show clearer correlations between breastfeeding and weaning practices and allergy outcomes.

5 | CONCLUSION

Urban infants have higher prevalence of eczema, higher food and aeroallergen sensitization, and higher FA as well as asthma and allergic rhinitis. Further work needs to be done to delineate the specific protective factors that are significant in the rural environment. Breastfeeding and complementary feeding practices may have an impact on tolerance in urban but not rural populations. Further research should be conducted on dietary content and allergies.

CONFLICT OF INTEREST

Maresa Botha, Wisdom Basera, Heidi E. Facey-Thomas, Ben Gaunt, Jon Genuneit, Claudia L. Gray, Wanjiku Kiragu, Jordache Ramjith, and Alexandra Watkins declared no conflicts of interest. Michael E. Levin declared conflicts of interest in research funded by Medical Research Council of South Africa, Nestle, Mylan, Thermo Fisher.

AUTHOR CONTRIBUTIONS

Maresa Botha, Wisdom Basera, Heidi E. Facey-Thomas, Ben Gaunt, Jon Genuneit, Claudia L. Gray, Wanjiku Kiragu, Jordache Ramjith, Alexandra Watkins, and Michael E. Levin designed the study. Maresa Botha, Heidi E. Facey-Thomas, Wanjiku Kiragu, Alexandra Watkins, and Michael E. Levin gathered the data. Maresa Botha, Wisdom Basera, Heidi E. Facey-Thomas, and Wanjiku Kiragu contributed to data entry. Maresa Botha, Wisdom Basera, Jon Genuneit, Jordache Ramjith, Alexandra Watkins, and Michael E. Levin analyzed the data. Maresa Botha and Michael E. Levin wrote the article. Maresa Botha, Wisdom Basera, Heidi E. Facey-Thomas, Ben Gaunt, Jon Genuneit, Claudia L. Gray, Wanjiku Kiragu, Jordache Ramjith, Alexandra Watkins, and Michael E. Levin reviewed the article.

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REFERENCES

- Hooper R, Calvert J, Thompson RL, Deetlefs ME, Burney P. Urban/rural differences in diet and atopy in South Africa. *Allergy Eur J Allergy Clin Immunol*. 2008;63(4):425-431.
- Kelishadi R, Roufarshbaf M, Soheili S, Payghambarzadeh F, Masjedi M. Association of childhood obesity and the immune system: a systematic review of reviews. *Child Obes*. 2017;13(4):332-346.
- Berents TL, Carlsen K, Mowinckel P, et al. Weight-for-length, early weight-gain velocity and atopic dermatitis in infancy and at two years of age: a cohort study. *BMC Pediatr*. 2017;17(1):141.
- Calvert J, Burney P. Effect of body mass on exercise-induced bronchospasm and atopy in African children. *J Allergy Clin Immunol*. 2005;116(4):773-779.
- Meyer R, De Koker C, Dziubak R, et al. Malnutrition in children with food allergies in the UK. *J Hum Nutr Diet*. 2014;27(3):227-235.
- Botha M, Basera W, Facey-Thomas HE, et al. Rural and urban food allergy prevalence from the South African Food Allergy (SAFFA) study. *J Allergy Clin Immunol*. 2019;143(2):662-668.e2.
- Basera W, Botha M, Gray CL, et al. The South African Food Sensitisation and Food Allergy population-based study of IgE-mediated food allergy: validity, safety, and acceptability. *Ann Allergy Asthma Immunol*. 2015;115(2):113-119.
- Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis Work Group. *J Am Acad Dermatol*. 2014.
- Mahdavinia M, Rasmussen HE, Engen P, et al. Atopic dermatitis and food sensitization in South African toddlers. *Ann Allergy Asthma Immunol*. 2017;118(6):742-743.e3.
- World Health Organization. WHO child growth standards: training course on child growth assessment. World Health Organization;2008:1-116.
- Potter PC. Common indoor and outdoor aero-allergens in South Africa. *Contin Med Educ*. 2010;28(9):426-432.
- Levin ME, Muloiwa R, Motala C. Associations between asthma and bronchial hyper-responsiveness with allergy and atopy phenotypes in urban black South African teenagers. *South African Med J*. 2011;101(7):472-476.
- Jeevarathnum AC, van Niekerk A, Green RJ, Becker P, Masekela R. Prevalence of *Blomia Tropicalis* allergy in two regions of South Africa. *South African Med J*. 2015;105(7):567-569.
- Van Niekerk CH, Weinberg EG, Shore SC, Heese HV, Van Schalkwyk J. Prevalence of asthma: a comparative study of urban and rural Xhosa children. *Clin Allergy*. 1979;9(4):314-319.
- Calvert J, Burney P. Ascaris, atopy, and exercise-induced bronchoconstriction in rural and urban South African children. *J Allergy Clin Immunol*. 2010;125(1):100-105.e1-5.
- Steinman HA, Donson H, Kawalski M, Toerien A, Potter PC. Bronchial hyper-responsiveness and atopy in urban, peri-urban and rural South African children. *Pediatr Allergy Immunol*. 2003;14(5):383-393.
- Obeng BB, Hartgers F, Boakye D, Yazdanbakhsh M. Out of Africa: what can be learned from the studies of allergic disorders in Africa and Africans? *Curr Opin Allergy Clin Immunol*. 2008;8(5):391-397.
- Levin M, Goga A, Doherty T, et al. Allergy and infant feeding guidelines in the context of resource-constrained settings. *J Allergy Clin Immunol*. 2017;139(2):455-458.
- Fleischer DM, Sicherer S, Greenhawt M, et al. Consensus communication on early peanut introduction and prevention of peanut allergy in high-risk infants. *Pediatr Dermatol*. 2016;33(1):103-106.
- Muraro A, Halken S, Arshad SH, et al. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. *Allergy Eur J Allergy Clin Immunol*. 2014;69(5):590-601.

21. Botha M, Basera W, Facey-Thomas HE, et al. Rural and urban food allergy prevalence from the South African Food Allergy Study (SAFFA). *J Allergy Clin Immunol*. 2018;143:662-668.
22. Perkin MR, Logan K, Marrs T, et al. Enquiring about Tolerance (EAT) study: feasibility of an early allergenic food introduction regimen. *J Allergy Clin Immunol*. 2016;137(5):1477-1486.
23. Koplin JJ, Osborne NJ, Wake M, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. *J Allergy Clin Immunol*. 2010;126(4):807-813.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Supplementary Table 1

CONSORT TABLE FOR STUDY COHORT		
	URBAN	RURAL
Responders	1230	410
Nonparticipants	25	0
Participants	1205	410
Ineligible (>36 months)	5	0
Eligible Participants	1200	410
Questionnaire incomplete	4	0
SPT Incomplete	11	12
TOTAL	1185	398
Sensitised	136 (11.5%)	18 (4.5%)
OFC Indicated	64 (5.5%)	7 (1.8%)
OFC Incomplete (none done at all)	7	1
OFC Partially Complete	7	0

Supplementary Table 2: Characteristics of the study population by study site															
	Total Urban N=1185			Total rural N=398			p- value	Urban aeroallergen N=535			Rural aeroallergen N=347			p- value	Urban;rural
	n	% or median	95% CI or IQR	n	% or median	95% CI		n	% or median	95% CI or IQR	n	% or median	95% CI		
Enrolment age (months)	1185	26	22-32	398	21	17-28		535	26	21-31	437	21	16-27	<0.001	
Sex															
Male	622	52.5%		225	56.5		0.162	287	51.6%		198	57.1%		0.11	0.73;0.87
Female	563	47.5%		173	43.5			259	48.4%		149	42.9%			0.73; 0.87
		p=0.01			p=0.01										
Ethnicity															
Black African	549	46.3%		398	100%				46.4%			100%			0.97
Mixed Ancestry	551	46.5%		0	0				51.4%						0.06
Caucasian	85	7.2%		0	0				2.2%						<0.001
Socioeconomic status															
Household income (Median in R)		7000	3000-6250		1380	990-2390	<0.001	534	7000	3500-15000	347	1450	990-2390	<0.001	
Total number of people living in the household		4	4-6		6	5-8	<0.001	534	5	4-6	346	7	5-9	<0.001	
Parental education															
Secondary education only		55.4%			77.4%		<0.001	305	57.0%		274	79.0%		<0.001	0.52; 60
Tertiary education		43.1%			5.0%		<0.001	225	42.1%		18	5.2%			0.70; 0.90
Parental employment															
• Both parents unemployed	41	3.7%		190	49.0%			19	3.7%		162	47.9%			1.0; 0.785
• One parent employed/studying	260	23.2%		165	42.5%		<0.001	136	26.8%		147	43.4%		<0.001	0.11;0.978
• Both parents employed/studying	819	73.1%		33	8.3%			353	69.5%		29	8.6%			0.30;0.912
Family History of atopy															
First degree relative with any allergy	578	48.8%	45.9-51.6	30	7.5%	(4.9-10.1)	<0.001	265	50.0%	45.3-53.8	23	6.6%	4.0-9.3	<0.001	0.65; 0.54
Atopy/Allergy															
Asthma	106	9.0%	7.4-10.7	4	1.0%	0.3-2.6	<0.001	28	5.2%	3.3-7.1	2	0.6%	0.2-1.4	<0.001	0.01 ; 0.54
Allergic rhinitis	300	25.3%	22.8-27.8	13	3.3%	(1.5-5.0)	<0.001	108	20.2%	16.8-23.6	13	3.8%	1.7-5.8	<0.001	0.02 ; 0.71
Atopic dermatitis	303	25.6%	23.1-28.1	8	2.0%	(0.6-3.4)	<0.001	122	22.8%	9.2-26.4	5	1.4%	0.2-2.7	<0.001	0.213; 0.53
Sensitisation (spt≥3mm)	107	9.0%	7.5-10.8	11	2.8%	(1.4-4.9)	<0.001	43	8.0%	5.7-10.4	11	3.3%	1.3-5.0	0.002	0.50; 0.72

Food Allergy	27	2.5%	1.5-3.7	2	0.5%	(0.1-1.8)	<0.006	12	2.2%	0.9-3.5	2	0.6%	0.2-1.4	0.04	0.71; 0.85
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Supplementary Table 3: Comparison of nutritional status of the urban vs rural cohort			
Z-scores	Urban	Rural	p-values
Weight-for-age			
Median (IQR)	0.44 (-0.26-1.21)	0.34 (-0.28-1.13)	0.23
Underweight	21 (1.8%)	3 (0.8%)	0.14
Normal weight	1042 (88.9%)	364 (91.5%)	0.15
Overweight	109 (9.3%)	31 (7.8%)	0.36
Length-for-Age			
Median (IQR)	-0.1 (-1.02-0.71)	-0.635 (-1.48-0.1)	<0.001
Severely stunted	22 (1.9%)	17 (4.3%)	0.01
Stunted	68 (5.8%)	35 (8.8%)	0.04
Normal	1062 (91.1%)	342 (85.9%)	<0.001
Very tall	14 (1.2%)	4 (1.0%)	0.75
Weight-for-length			
Median (IQR)	0.66 (-0.06-1.46)	0.99 (0.32-1.71)	0.028
Wasted	14 (1.2%)	0 (0)	0.03
Normal	992 (85.2%)	329 (82.6%)	0.22
Overweight	117 (10.1%)	54 (13.6%)	0.05
Obese	41 (3.5%)	15 (3.8%)	0.82
BMI			
Median (IQR)	0.72 (0.00-1.54)	1.15 (0.44-1.86)	<0.001*
Wasted	15 (1.3%)	0 (0%)	<0.02**
Normal weight	975 (83.8%)	315 (79.2%)	0.04**
Overweight	128 (11.0%)	65 (16.3%)	0.01**
Obese	46 (3.9%)	18 (4.5%)	0.62**
Triceps skin fold thickness			
Median (IQR)	0.7 (0.01-1.38)	1.0 (0.19-1.61)	<0.001
<-2	9 (0.9%)	0 (0)	0.06
Normal	894 (87.1%)	336 (85.5%)	0.44
>+2	124 (12.1%)	57 (14.5%)	0.22
Abdominal girth			
Median (IQR)	-0.07 (-0.62-0.48)	-0.073 (-0.49-0.48)	0.50
<2(lower limits)	24 (2.3%)	7 (1.8%)	0.53
Normal	980 (94.2%)	379 (95.7%)	0.27

>2(upper limits)	36 (3.5%)	10 (2.5%)	0.37
*MannWhitney, **z test for proportions			

Supplementary Table 4: Der P sensitisation in participants with and without allergic disease

	URBAN (535)			RURAL (347)			p-value rural vs urban no;yes
	NO (322)	YES (213)	p-value	NO (329)	YES (18)	p-value	
Any asthma, AR or AD	20 (6.2%)	44 (20.7%)	<0.001	11 (3.3%)	1 (5.7%)	0.48	0.08;0.12
Asthma	NO (507)	YES (28)	0.06	NO (345)	YES (2)	0.93	<0.001; 0.42
	57 (11.2%)	7 (25.0%)		12 (3.5%)	0 (0%)		
Allergic Rhinitis	NO (427)	YES (108)	0.002	NO (334)	YES (13)	0.37	<0.001;0.26
	41 (9.6%)	23 (21.3%)		11 (3.3%)	1 (7.7%)		
Atopic Dermatitis	NO (413)	YES (122)	<0.001	NO (342)	YES (5)	0.16	0.007;0.76
	32 (7.8%)	32 (26.2%)		11 (3.2%)	1 (20.0%)		

Supplementary Table 5: Association of nutritional status with allergy outcomes in rural participants						
RURAL	Aeroallergen sensitisation	Allergic Rhinitis	Atopic Dermatitis	Asthma	Food sensitisation	Food Allergy
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
Weight for age	1.0 (0.6-1.6) 0.91	1.1 (0.7-1.9) 0.68	1.2 (0.7-2.3) 0.51	1.6 (0.7-3.9) 0.29	1.6 (0.9-2.6) 0.08	0.5 (0.1-2.0) 0.31
Length for age	0.9 (0.6-1.4) 0.70	0.9 (0.5-1.3) 0.49	1.1 (0.6-1.9) 0.77	1.6 (0.7-3.5) 0.27	1.4 (0.9-2.2) 0.16	0.5 (0.2-1.4) 0.20
Weight for length	1.0 (0.6-1.7) 0.93	1.3 (0.8-2.1) 0.31	1.2 (0.7-2.2) 0.53	1.4 (0.6-3.2) 0.48	1.4 (0.8-2.2) 0.20	0.8 (0.2-2.9) 0.69
BMI	1.0 (0.6-1.7) 0.87	1.3 (0.8-2.1) 0.25	1.2 (0.7-2.2) 0.56	1.3 (0.5-3.0) 0.59	1.3 (0.8-2.2) 0.27	0.9 (0.3-3.3) 0.89
Triceps skinfold thickness	0.9 (0.5-1.7) 0.83	1.1 (0.6-1.9) 0.79	0.8 (0.4-1.6) 0.51	0.5 (0.1-1.8) 0.30	0.8 (0.4-1.5) 0.51	0.7 (0.2-3.0) 0.62
Abdominal girth (sample specific z-scores)	0.8 (0.4-1.4) 0.44	0.9 (0.5-1.6) 0.63	1.0 (0.5-2.1) 0.95	1.7 (0.6-5.2) 0.32	1.4 (0.7-2.5) 0.32	1.0 (0.2-4.2) 0.98

Supplementary Table 6: Association of nutritional status with allergy outcomes in urban participants						
URBAN	Aeroallergen sensitisation	Allergic Rhinitis	Atopic Dermatitis	Asthma	Food sensitisation	Food Allergy
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
WEIGHT FOR AGE						
Underweight Weight-for-age z-score<-2	0.5 (0.1-4.1) 0.54	0.7 (0.2-2.1) 0.51	1.1 (0.4-3.0) 0.80	**	3.3 (1.2-9.3) 0.02	**
Upper limit Weight-for-age z-score>+2	0.5 (0.2-1.4) 0.19	0.7 (0.4-1.2) 0.17	0.6 (0.4-1.0) 0.06	1.9 (1.1-3.4) 0.02	1.0 (0.5-2.1) 0.92	0.4 (0.05-2.7) 0.31
WEIGHT FOR LENGTH						
Wasted Weight for length z-score<-2	**	0.4 (0.1-1.7) 0.20	2.0 (0.7-5.9) 0.21	0.7 (0.1-5.5) 0.74	2.8 (0.8-10.3) 0.12	**
Overweight Weight for length z-score>+2	0.7 (0.3-1.7) 0.43	0.7 (0.4-1.1) 0.16	0.9 (0.6-1.4) 0.68	2.3 (1.3-3.9) 0.003	1.7 (1.0-3.0) 0.07	1.5 (0.5-4.4) 0.47
Obese	1.1 (0.3-3.8) 0.92	0.8 (0.4-1.7) 0.52	0.6 (0.3-1.4) 0.21	0.3 (0.04-2.0) 0.20	0.9 (0.3-2.8) 0.79	**
LENGTH FOR AGE						
Severely stunted	0.5 (0.1-4.1) 0.54	1.1 (0.4-3.0) 0.93	0.5 (0.1-1.7) 0.27	**	**	**
Stunted Length for age z-score<-2	1.4 (0.6-3.5) 0.48	0.8 (0.4-1.5) 0.44	1.1 (0.6-1.9) 0.76	0.1 (0.02-1.1) 0.06	2.0 (1.0-4.0) 0.04	2.9 (1.0-8.6) 0.06
Very tall Length for age z-score<+2	5.4 (0.9-33.6) 0.07	2.9 (0.9-9.1) 0.06	1.8 (0.6-5.5) 0.31	3.2 (0.8-12) 0.09	0.8 (0.1-6.4) 0.86	**
BODY MASS INDEX						
Normal weight BMI z-score -1 to +1	Used as reference category					
Wasted BMI z-score<-2	**	0.8 (0.2-2.7) (0.74)	1.8 (0.6-5.0) 0.30	0.6 (0.1-5.0) 0.67	1.5 (0.3-6.9) 0.58	**
Overweight BMI z-score>+2	1.0 (0.5-2.1) 0.98	0.7 (0.4-1.1) 0.09	1.0 (0.6-1.5) 0.97	2.1 (1.2-3.7) 0.006	1.4 (0.8-2.5) 0.25	1.8 (0.7-4.8) 0.25
Obese BMI z-score>+3	1.1 (0.3-3.8) 0.91	0.8 (0.4-1.6) 0.52	0.6 (0.3-1.3) 0.23	0.2 (0.03-1.8) 0.16	1.0 (0.4-2.9) 0.99	**
TRICEPS SKINFOLD THICKNESS						
Lower limit (z-score<-2)	5.8 (0.4-95.0) 0.22	1.2 (0.3-5.1) 0.79	2.2 (0.6-8.2) 0.26	4.7 (1.1-19.7) 0.04	3.1 (0.6-15.2) 0.17	**
Upper limit (z-score>+2)	1.0 (0.4-2.4) 0.94	1.1 (0.7-1.7) 0.74	1.2 (0.7-1.8) 0.53	1.2 (0.6-2.3) 0.63	0.7 (0.3-1.5) 0.30	0.3 (0.05-2.6) 0.30
ABDOMINAL GIRTH (sample specific z-scores)						
Lower limit (z-score<-2)	1.8 (0.4-8.7) 0.47	0.6 (0.2-2.0) 0.44	2.0 (0.8-4.6) 0.11	1.7 (0.5-6.0) 0.40	4.8 (1.9-11.9) 0.001	4.2 (0.9-19.2) 0.06

Upper limit (z-score>+2)	1.3 (0.4-4.7 0.67	1.0 (0.4-2.3) 0.97	1.5 (0.7-3.1) 0.27	1.6 (0.5-4.7) 0.40	0.7 (0.2-2.9) 0.60	**
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Supplementary Table 7: Association of nutritional status with allergy outcomes in rural participants

RURAL	Aeroallergen sensitisation	Allergic Rhinitis	Atopic Dermatitis	Asthma	Food sensitisation	Food Allergy
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
WEIGHT FOR AGE						
Underweight Weight-for-age z-score<-2	**	**	**	**	**	**
Upper limit Weight-for-age z-score>+2	0.9 (0.1-7.6) 0.96	2.2 (0.5-10.3) 0.33	**	3.7 (0.4-39.8) 0.28	7.8 (2.1-28.7) 0.002	**
WEIGHT FOR LENGTH						
Wasted Weight for length z-score<-2	**	**	**	**	**	**
Overweight Weight for length z-score>+2	1.9 (0.5-7.1) 0.35	1.2 (0.3-5.6) 0.82	2.6 (0.5-14.1) 0.26	1.8 (0.2-18.8) 0.61	4.1 (1.2-15) 0.03	**
Obese	**	2.1 (0.3-18) 0.49	4.2 (0.5-39.1) 0.21	**	**	**
LENGTH FOR AGE						
Severely stunted	**	2.0 (0.2-16.9) 0.52	**	**	2.4 (0.3-21) 0.42	**
Stunted Length for age z-score<-2	0.8 (0.1-6.8) 0.88	**	**	**	**	**
Very tall Length for age z-score<+2	**	**	**	**	11.9 (1.1-128.4) 0.04	**
BODY MASS INDEX						
Normal weight BMI z-score -1 to +1	Used as reference category					
Wasted BMI z-score<-2	**	**	**	**	**	**
Overweight BMI z-score>+2	2.2 (0.7-7.6) 0.19	1.0 (0.2-4.6) 0.98	2.1 (0.4-11.5) 0.37	1.8 (0.2-18.4) 0.62	3.3 (0.9-12) 0.07	**
Obese BMI z-score>+3	**	1.6 (0.2-13.7) 0.66	3.3 (0.4-30.5) 0.29	**	**	**
TRICEPS SKINFOLD THICKNESS						
Lower limit (z-score<-2)	**	**	**	**	**	**
Upper limit (z-score>+2)	1.0 (0.2-4.6) 0.98	0.5 (0.1-3.9) 0.50	**	**	0.6 (0.1-4.9) 0.65	**
ABDOMINAL GIRTH (sample specific z-scores)						
Lower limit (z-score<-2)	4.1 (0.5-36.4) 0.21	**	**	**	**	**
Upper limit (z-score>+2)	**	**	**	**	**	**

Supplementary Table 8: Association of nutritional status with asthma outcomes
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COMBINED COHORT	Asthma		
	OR	(95%CI)	p-value
Weight for age	1.6	0.7-3.8	0.25
WFA*site interaction	0.8	0.4-2.0	0.70
Urban setting	5.7	1.4-22.7	0.01
Length for age	1.5	0.7-3.2	0.26
LFA*site interaction	0.8	0.4-1.8	0.64
Urban setting	4.2	1.5-12.1	0.01
Weight for length	1.4	0.6-3.1	0.43
WFL*site interaction	0.9	0.4-2.0	0.81
Urban setting	5.9	1.2-29	0.03
BMI	1.3	0.6-2.9	0.55
BMI*site interaction	0.9	0.4-2.2	0.87
Urban setting	5.7	1.1-29.6	0.04
Triceps skinfold thickness	0.5	0.1-1.7	0.27
TST*site interaction	2.2	0.6-7.7	0.23
Urban setting	3.5	1.0-12.6	0.06
Abdominal girth (sample specific z-scores)	1.6	0.6-4.2	0.37
ABDO*site interaction	0.8	0.3-2.2	0.66
Urban setting	4.8	1.5-15	0.01

Supplementary Table 9: Association of breastfeeding practice with allergy outcomes in urban participants						
	Aeroallergen sensitisation	Allergic rhinitis	Atopic dermatitis	Asthma	Food sensitisation	Food allergy
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
Ever breastfed yes	0.87 (0.4-1.9) 0.72	1.1 (0.8-1.7) 0.79	1.5 (0.9-2.3) 0.11	0.87 (0.5-1.7) 0.68	0.9 (0.5-1.7) 0.76	0.61 (0.2-1.7) 0.34
Duration of exclusive breastfeeding	0.91 (0.8-1.0) 0.11	1.0 (1.0-1.1) 0.83	1.0 (1.0-1.1) 0.42	0.95 (0.9-1.0) 0.23	1.1 (1.0-1.2) 0.02	1.1 (1.0-1.2) 0.24
Duration of breastfeeding	1.0 (0.97-1.0) 0.60	0.99 (0.98-1.0) 0.23	1.0 (0.99-1.0) 0.55	0.98 (0.96-1.0) 0.06	1.0 (1.0-1.0) 0.92	1.0 (0.96-1.0) 0.93

Supplementary Table 10: Association of weaning practices with allergy outcomes in urban participants						
	Aeroallergen sensitisation	Allergic rhinitis	Atopic dermatitis	Asthma	Food sensitisation	Food allergy
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
Age of introduction of formula/fresh cow's milk	0.91 (0.8-1.0) 0.03	1.0 (0.99-1.1) 0.24	1.0 (1.0-1.1) 0.31	0.99 (0.9-1.0) 0.58	1.1 (1.0-1.1) 0.03	1.0 (1.0-1.2) 0.30
Median age at first introduction of weaning foods	1.0 (0.9-1.2) 0.93	1.0 (0.96-1.1) 0.33	1.0 (0.9-1.1) 0.93	0.95 (0.8-1.1) 0.44	1.0 (0.9-1.2) 0.50	1.0 (0.8-1.3) 0.80
Age of introduction to egg	1.0 1.0-1.0 0.60	1.0 1.0-1.0 0.45	1.0 1.0-1.0 0.18	1.0 1.0-1.0 0.46	1.0 1.0-1.0 0.89	1.0 1.0-1.0 0.47
Age of introduction to peanut	1.0 0.99-1.0 0.47	1.0 1.0-1.0 0.83	1.0 1.0-1.0 0.06	1.0 1.0-1.0 0.43	1.0 1.0-1.0 0.84	1.0 1.0-1.0 0.79

Supplementary Table 11: Association of breastfeeding practice with allergy outcomes in rural participants						
	Aeroallergen sensitisation	Allergic rhinitis	Atopic dermatitis	Asthma	Food sensitisation	Food allergy
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
Ever breastfed yes	0.77 (0.1-3.2) 0.62	**	**	**	1.3 (0.2-10.5) 0.80	**
Duration of exclusive breastfeeding	0.9 (0.7-1.2) 0.45	1.0 (0.8-1.3) 0.84	1.0 (0.8-1.3) 0.93	0.96 (0.6-1.4) 0.82	1.1 (0.9-1.4) 0.41	1.6 (0.8-23.0) 0.17
Duration of breastfeeding	1.0 (0.9-1.1) 0.82	0.98 (0.9-1.1) 0.53	1.0 (1.0-1.1) 0.42	1.0 (0.9-1.2) 0.67	1.0 (0.9-1.1) 0.89	1.1 (0.9-1.3) 0.53
** empty categories (numbers too small)						

Supplementary Table 12: Association of weaning practices with allergy outcomes in rural participants						
	Aeroallergen sensitisation	Allergic rhinitis	Atopic dermatitis	Asthma	Food sensitisation	Food allergy
	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value	OR (95%CI) p-value
Age of introduction of formula/fresh cow's milk	0.9 (0.8-1.1) 0.44	1.0 (0.9-1.2) 0.90	1.0 (0.8-1.3) 0.94	1.0 (0.7-1.4) 0.94	1.1 (0.9-1.3) 0.56	1.2 (0.9-1.5) 0.30
Median age at first introduction of weaning foods	1.0 (0.7-1.3) 0.85	0.8 (0.6-1.1) 0.15	1.1 (0.8-1.5) 0.62	0.9 (0.5-1.4) 0.61	1.1 (0.8-1.4) 0.70	1.3 (0.7-2.4) 0.36

Age of introduction of egg	0.9 (0.7-1.1) 0.18	1.0 (1.0-1.0) 0.85	0.8 (0.7-1.1) 0.13	0.9 (0.7-1.4) 0.71	1.0 (0.8-1.2) 0.82	0.7 (0.4-1.3) 0.24
Age of introduction of peanut	0.9 (0.8-1.1) 0.45	1.0 (0.9-1.2) 0.70	0.8 (0.6-1.2) 0.26	1.2 (0.9-1.6) 0.33	0.8 (0.7-1.1) 0.12	0.7 (0.4-1.2) 0.18