INTRODUCTION

In the original ‘hygiene hypothesis’, Strachan proposed that increased microbial exposure in early life could protect children from developing immune hypersensitivities later in life.1 Decades later, the increase in allergic and autoimmune diseases in the industrialized world was also suggested to be associated with a decline in childhood infections due to effective vaccination, use of antibiotics, improved sanitation and personal hygiene.2 Immunologically, the concept was explained by the differential function of T helper (Th) cells with polarized cytokine profiles that counter-regulate each other.3 This proposed a Th1-dominant immune phenotype induced and imprinted by early life microbial exposures which was thought to inhibit the Th2-atopic immunopathology.4

Received: 19 February 2021 | Revised: 14 February 2022 | Accepted: 16 February 2022

DOI: 10.1111/pim.12913
2 | METHODS

2.1 | Study design

The study was approved by the South African Medical Research Council (SAMRC) and the University of Stellenbosch Ethics Committees (NO04/02/045). Permission to conduct the study was provided by the Matthew Goniwe Clinic management team. This cross-sectional analysis used data obtained from the prospective study that were tracking the immune profile of adults during helminthic infection and anthelmintic treatment (n = 218), partly described in detail elsewhere.15–17

2.2 | Study population and setting

Study participants were Xhosa adults (18 years and above) who were clinic attendees, presenting for different ailments, some were accompanying their relatives to the clinic and others were attending the clinic’s HIV/AIDS support group. This is a Health District clinic of the Metro Region and is the largest in this region, servicing the informal settlement. These individuals were recruited by convenience sampling and participated in a larger prospective immunology and deworming study published in part elsewhere.15 With the exception of a few (approximately 10%, who were born in the City of Cape Town and elsewhere) the majority of the participants (approximately 90%) had moved from rural villages in the neighbouring Eastern Cape province of South Africa to a suburb of Cape Town within an informal settlement in the Western Cape province of South Africa. The area is poorly resourced, with lack of clean water and proper sanitation, overcrowded and previous reports showed high prevalence of helminth infections.18 Both *Ascaris lumbricoides* and *Trichuris trichuria* are the most predominant intestinal helminths in the Western Cape Province and Cape Town19 and Eastern Cape.20

2.3 | Data collection

2.3.1 | Allergy and previous worm infection recall

Lifetime history and current experience of asthma and rhinitis symptoms and treatment as well as current use of asthma inhalers and rhinitis nasal sprays or other treatment were collected through questionnaires administered in the local isiXhosa language. Clinical records were also used to confirm clinician-diagnosed allergies and treatment where available. Asthma and rhinitis recall and clinical diagnosis were also recorded based on the use of prescribed medications including inhalers such as Ventolin and its generics (e.g., asthavent, venteze etc.), nasal sprays such as Beclomethasone (Beconase) nasal spray and its generics and other rhinitis prescriptions also recorded from patient files to confirm asthma and rhinitis, respectively, where data were available in case record files, as...
well as those carrying these medications to the clinic at the time of interviewing.

Similarly, history of worm infection, as described in a previous study that enquired about history of intestinal helminth infection, more than 70% reported a recall of worm infection either as a child or an adult, more often both as a child or adult. Most had reported infection as a child before relocating from the rural home. The common practice of defecating in the open field, both in the rural villages and informal settlement made the experience of passing worms easy to recall and describe the worms. The description of the worms passed fitted mostly A. lumbricoides and a few others such as T. trichuria and tapeworm species. These data were elaborated in detail in a previous publication but for purposes of this work, this information is relevant as it qualitatively confirms the lifetime history (from childhood to adulthood) of worm exposure in this population, previously residing in rural areas then moved to poorly resourced informal settlements. This context also relates to the proposed concept early life or prior, and current helminth exposure and co-occurrence of allergy in an under resourced population.

### 2.3.2 Detection of current helminth infection

Both A. lumbricoides and T. trichuria are the most common helminths in the study area and were thus the focus of this study. Two stool samples, collected on two different days, were used for detection of helminth infection. Coproscopy, using Kato-Katz and the modified formol-ether concentration (Mini-Parasep) by two independent microscopists, were used to detect the presence of helmint eggs. Mebendazole and praziquantel for schistosomiasis treatment were provided for all participants found to be infected with worms.

Serology was also used to increase the sensitivity of microscopy for intestinal helminth infection or exposure. A. lumbricoides-specific IgE levels were thus analysed. Antibody cross reactivity with T. trichuria has been documented, and therefore this antibody is an appropriate proxy indicator of worm exposure for this setting where both these helminths are most common. However, the ability of ascariasis to increase allergic sensitization (atopy) is acknowledged, and in this section, the presence of high Ascaris IgE is used (in part, with stool parasitology) in the context of describing exposure/non-exposure in order to classify those who had past or present helminthiasis infection. This analyte may be either a confounder or an intermediate factor in the association between helminth infection and allergy.

### 2.3.3 Biochemical measures and allergy screening

The primary exposure variables were faecal A. lumbricoides and/or T. trichuria egg excretion plus serum A. lumbricoides-specific IgE (used as a proxy to indicate helminth exposure) as well as demographic variables such as age, gender and locality type (place of birth). The study biological outcomes included eosinophil counts, serum total IgE, total IgE, defined as overall quantity of all immunoglobulin E subtypes in blood. High total IgE for the study methodology are levels equal to or above the defined cut-off value of 70 kU/L. Allergic disorder outcome variables included four measures: (1) IgE atopy (a positive test for evidence of allergen sensitization by specific IgE using Phadiatop), (2) asthma, (3) rhinitis and (4) food allergy (Table 1). Allergic sensitization or atopy was screened using the ImmunoCAP™ Phadiatop assay. Positive allergen IgE reactivity was measured on discs containing locally relevant inhalant allergens (dog and cat epithelium, house dust and house dust mites and cockroaches); mixed trees (olive, willow, pine, eucalyptus, acacia and melaleuca); mixed weeds (marguerits, dandelion, plantain, goosefoot and golden rod); Bermuda and Timothy grass and mixed mould (Pennisetum notatum, Cladosporium herbarum, Aspergillus fumigatus and Alternaria alternata). Total serum IgE, food sensitivity and A. lumbricoides-specific IgE levels were determined by ImmunoCAP Total IgE, ImmunoCAP allergen-specific fx3 IgE, and Ascaris IgE radioallergosorbent (RAST) tests respectively. Food allergens included egg whites, milk, soya, peanuts, wheat and fish (cod and shrimp).

### 2.4 Statistical analysis

Descriptive statistics frequencies and percentages were used to summarize the data. Pearson chi-square test was used to test for differences between categorical variables. Bivariate and multivariate logistic regressions were used to analyse the association between measures of allergy-related disorders and helminth parasitic infection exposure. Crude (OR) and adjusted odds ratios (aOR) and 95% confidence intervals (95% CI) with a p-value ≤.05 were used to determine the level of statistical significance. Data were analysed using STATA version 15.0 (Stata Corporation).

## 3 RESULTS

### 3.1 Characteristics of the study population

Table 2 highlights the demographics and biological characteristics of the study population. A third of participants were aged 30–39 years (34.4%), and the majority were females (86.2%). Total IgE levels were generally high, with a mean serum total IgE of 419.5 kU/L (reference value is <70 kU/L) with a high proportion of study participants having a high total IgE (64.2%), and 19.3% had high eosinophil counts.
Regarding helminthiasis, a quarter had active worm infection as shown by *Ascaris* (24.1%) and *Trichuris* (24.8%) eggs in stool and 33.9% had high *Ascaris* IgE. The overall prevalence of helminth infection was 43%, by egg excretion positivity; however, the prevalence as measured by either high *Ascaris*-specific IgE, and/or *Trichuris/Ascaris* egg excretion was 66% in this sample population. In terms of allergic disorders, overall, asthma, rhinitis, IgE atopy and food allergy prevalence were 17.5%, 54.7%, 39.9% and 11.5% respectively (Table 2).

The majority of participants (88.5%) had migrated from rural villages in the Eastern Cape (their place of birth) to the Western Cape Province’s City of Cape Town informal settlement. Tables 3 and 4 show the prevalence of helminth exposure and allergy-related disorders, respectively, in relation to participants’ place of birth (Cape Town, Eastern Cape and other Provinces). A significant association between participants’ place of birth and (i) helminth exposure (high *Ascaris* IgE: \( \chi^2 p = .002 \) and *Trichuris* eggs: \( \chi^2 p < .0001 \)) and (ii) allergy-related disorder outcomes (IgE atopy: \( \chi^2 p = .006 \) and food allergy: \( \chi^2 p = .007 \)) were observed. Those born in Cape Town had the highest prevalence of high *Ascaris* IgE (66.7%) and *Trichuris* eggs (83.3%) while *Ascaris* eggs were most prevalent in participants originally from the Eastern Cape (26%). Asthma prevalence was similar across all the places of birth and ranged between 16% and 18%. The Eastern Cape had the highest prevalence of rhinitis (55.6%) while IgE atopy (72.2%) and food allergy (33.3%) was most prevalent among those born in Cape Town (Tables 3 and 4; Figures S1 and S2).

### 3.2 Concurrent occurrence of helminth exposure and allergy-related outcomes

Overall, IgE atopy (78.4%), rhinitis (51.4%) and food allergy (27%) were most prevalent among the group with high *Ascaris* IgE. Rhinitis prevalence was similar and higher in participants that had active worm infection as shown by stool positivity for *Ascaris* eggs (65.3%) and *Trichuris* eggs (62.5%). All helminth exposed groups (high *Ascaris* IgE and positive stool *Ascaris* and *Trichuris* eggs) had a similar prevalence of asthma ranging between 24.3%, 24.5 and 25% respectively (Figure 1).

### 3.3 Association between participants’ demographic characteristics and helminth exposure with allergy-related outcomes

Males had a higher prevalence of asthma (\( p < .001 \)), IgE atopy (\( p < .001 \)) and food allergy (\( p < .001 \)). The biological reactants, eosinophilia and high total serum IgE are characteristic biological markers.
TABLE 2 Characteristics of study participants including proxy variables for parasitic infections (n = 218)

| Variables | N   | %   |
|-----------|-----|-----|
| Age groups in years |     |     |
| 18–25     | 37  | 17.5|
| 25–29     | 56  | 26.4|
| 30–39     | 74  | 34.9|
| 40+       | 45  | 21.2|
| Gender    |     |     |
| Male      | 30  | 13.8|
| Female    | 188 | 86.2|
| Province  |     |     |
| Cape Town | 18  | 8.3 |
| Eastern cape | 193 | 88.5|
| Others    | 7   | 3.2 |
| Total IgE |     |     |
| Low (<70 kU/L) | 78  | 35.8|
| High (>70 kU/L) | 140 | 64.2|
| Eosinophils |     |     |
| Low (<0.35 cells/ml) | 176 | 80.7|
| High (>0.35 cells/ml) | 42  | 19.3|
| Ascaris IgE |     |     |
| Low (<0.35 kU/L) | 144 | 66.1|
| High (≥0.35 kU/L) | 74  | 33.9|
| Trichuris eggs |     |     |
| Yes       | 48  | 24.8|
| No        | 152 | 75.2|
| Ascaris eggs |     |     |
| Yes       | 49  | 24.1|
| No        | 154 | 75.9|
| Asthma    |     |     |
| Yes       | 37  | 17.5|
| No        | 175 | 82.5|
| Rhinitis  |     |     |
| Yes       | 116 | 54.7|
| No        | 96  | 45.3|
| IgE atopy |     |     |
| Yes       | 87  | 39.9|
| No        | 131 | 60.1|
| Food allergy |     |     |
| Yes       | 25  | 11.5|
| No        | 193 | 88.5|

Note: Subtotals are not always equal due to some missing data. Abbreviation: IgE, immunoglobulin E.

associated with both exposure variables (parasitic infections) and outcome variables (allergy-related disorders). As expected, participants with high total IgE levels significantly associated with allergy-related disorders (IgE atopy: $p < .001$ and food allergy: $p < .001$). Likewise, high eosinophil levels were associated with asthma: $p < .001$, rhinitis: $p = .012$, IgE atopy: $p = .001$ and food allergy: $p = .024$ (Table 5).

Table 6 shows the association between helminth exposure and allergy-related outcomes. Models adjusted for age, gender and locality show that asthma was significantly less likely among those with *Ascaris* eggs (aOR = 0.43, 95% CI: 0.24–0.99, $p = .048$) and those with *Trichuris* eggs (aOR = 0.36, 95% CI: 0.15–0.87, $p = .024$) but more likely among those with high *Ascaris* IgE (aOR = 2.20, 95% CI: 0.66–3.75, $p = .047$). IgE atopy was significantly more likely among those with high *Ascaris* IgE (aOR = 18.18, 95% CI: 8.02–41.19, $p < .0001$). Food allergy was also significantly more likely among those with high *Ascaris* IgE (aOR = 14.47, 95% CI: 4.17–50.14, $p < .0001$).

4 | DISCUSSION

This study investigated the effects of exposure to *A. lumbricoides* (and by proxy, *T. trichuria*) and egg excretion on allergic disorders including atopy, asthma, food allergy and rhinitis in participants from a socioeconomically deprived rural population that had moved to urban informal areas. In the present study, the overall prevalence of ascariasis and trichuriasis was 43% as measured by egg excretion only and 66% by egg excretion plus high *Ascaris*-specific IgE. More than 20% had active worm infection shown by *Ascaris* (24.1%) and *Trichuris* (24.6%) eggs in stool and approximately a third (33.9%) had high *Ascaris*-specific IgE. Overall occurrence of allergic disorders in the study sample ranged between 11.5% (food allergy) and 39.9% (atopy), as measured by allergen specific IgE screen; and asthma (18%) and 55% rhinitis according to recall of disease symptoms and treatment. The study population generally had high serum total IgE. This is expected since helminth infections induce a polyclonal stimulation of IgE synthesis via IL-4, giving rise to high serum total IgE. During assay of the latter and *Ascaris*-specific IgE, there could be cross-reactivity.

Regarding the concurrent manifestation of allergic disorders and helminth exposure, the majority (78.4%) of those with high *Ascaris* IgE also had high IgE atopy, and more than 50% had rhinitis. Those with active worm infection had more than 60% rhinitis, and all helminth exposed groups had more than 20% prevalence of asthma. In the present study, high *Ascaris* IgE showed a significant association with atopy and food allergy, both of which were increased after adjustment for demographic characteristics. Likewise, high *Ascaris* IgE was also significantly associated with asthma but significantly less likely among those with *Ascaris* and *Trichuris* eggs in stool (active worm infection). These results present high prevalence of both helminth infection and allergic disorders, and concurrent manifestation of both, in a population that has moved from rural villages into an urban informal settlement, with a history of childhood and/or adult worm infection and current evidence of worm infection. These findings do not support the hypothesis of an inverse relationship between parasite infection and allergic sensitization.
Contrary to previous studies that have suggested that helminth parasites protect against atopy, 27–30 in our study, multivariate analysis showed that individuals with high Ascaris-specific IgE were fourteen times more likely to be atopic. This association was highly statistically significant. The significant association between atopy and high Ascaris IgE is a typical reflection of the documented presence of elevated Ascaris IgE being a risk factor for atopy or a genetic tendency towards allergic sensitization and asthma or wheezing. 29

Other findings showed that male gender was associated with Ascaris infection. In addition, active worm infection (Ascaris and Trichuris eggs in stool) was also significantly associated with males, although they only constituted a smaller proportion (14%) of the study sample. This is in keeping with the general finding that males are generally more susceptible to parasite infections. 31,32

The findings of the current study also add another layer of ambiguity to the rephrased hygiene hypothesis that incorporates the acquisition of ‘old friends’ such as helminths, and microbiota early in life as primers of immunoregulation that results in an appropriately responsive immune response later in life. 8 The individuals in the study had recalled childhood worm infection, while also growing up in rural settings, as the majority were born in rural Eastern Cape villages. Seventy percent of these adult participants had reported previous exposure to helminths in childhood and/or as adults, the majority of whom had moved to the city but within resource-constrained informal settlement less than 10 years before, after previous residence in a rural setting. 15 However, a significant proportion of these individuals also had allergic disorders.

### TABLE 3 Prevalence of helminth exposure stratified according to place of birth (Cape Town, Eastern Cape and other Provinces) (n = 218)

| Variables | High Ascaris IgE (n = 74) | Ascaris eggs (n = 49) | Trichuris eggs (n = 48) |
|-----------|---------------------------|----------------------|------------------------|
|           | Yes (≥0.35 kU/L)          | No (<0.35 kU/L)      |                        |
| Cape Town (n = 18) | n (%) | 12 (66.7) | 6 (33.3) | 3 (16.7) | 15 (83.3) | 15 (83.3) | 3 (16.7) |
| Eastern Cape (n = 193) | n (%) | 62 (32.1) | 131 (67.9) | 46 (26) | 131 (74) | 30 (16.9) | 147 (83.1) |
| Other Provinces (n = 7) | n (%) | 0 (0) | 7 (100) | 0 (0) | 7 (100) | 3 (42.8) | 2 (28.6) |

χ² p-value .002 .213 <.0001

Note: Subtotals are not always equal due to some missing data. χ²: chi-square test p-value.

Abbreviation: IgE, immunoglobulin E.

*aDenotes sample size for high Ascaris IgE.

*bDenotes sample size for Ascaris eggs and Trichuris eggs.

### TABLE 4 Prevalence of allergy-related disorders stratified according to place of birth (Cape Town, Eastern Cape and other Provinces) (n = 218)

| Variables | Asthma (N = 212) | Rhinitis (N = 212) | IgE atopy (N = 218) | Food allergy (N = 218) |
|-----------|------------------|-------------------|---------------------|-----------------------|
|           | Yes | No | Yes | No | Yes | No | Yes | No |
| Cape Town (n = 18) | n (%) | 3 (17.6) | 14 (82.4) | 8 (47.1) | 9 (52.9) | 13 (72.2) | 5 (27.8) | 6 (33.3) | 12 (66.7) |
| Eastern Cape (n = 193) | n (%) | 33 (17.5) | 156 (82.5) | 105 (55.6) | 84 (44.4) | 73 (37.8) | 120 (62.2) | 19 (9.8) | 174 (90.2) |
| Other Provinces (n = 7) | n (%) | 1 (16.7) | 5 (83.3) | 3 (50) | 3 (50) | 1 (14.3) | 6 (85.7) | 0 (0) | 7 (100) |

(χ²) p-value .999 .775 .006 .007

Note: Subtotals are not always equal due to some missing data. χ²: chi-square test p-value.

Abbreviation: IgE, immunoglobulin E.

*aDenotes sample size for asthma and rhinitis.

*bDenotes sample size for IgE Atopy and food allergy.
These findings both oppose and agree with two main notions of the hygiene hypothesis that (i) individuals residing in rural settings with poor sanitation and geohelminth infection are less prone to allergy\textsuperscript{33} and (ii) helminth infections protect against allergy.\textsuperscript{5,6} However, this study shows that those with high \textit{Ascaris} IgE were significantly more likely to have asthma, food allergy and atopy, opposing the first point. Nonetheless, those with active worm infection were found to be significantly less likely to have asthma, which is in agreement with the second point. Some epidemiological reports suggest that allergy risk is reduced in high geohelminth infection settings as is the case with the current study area.\textsuperscript{29,34}

There are contradictory reports on the occurrence of allergic diseases in low- and middle-income countries; however, urban areas are reported to be most affected than rural areas.\textsuperscript{35} Urbanization has been shown to cause allergy through air pollution and higher exposure to allergens and endotoxin.\textsuperscript{30,36} Individuals in the current study have lived in rural settings as well as urban informal settlements with limited sanitation and clean water. The notions that reduced infections due to improved health care and personal hygiene and decreased exposure to helminths in the urban environment suggested to lead to insufficient stimulation of the immune system and increased susceptibility to allergy\textsuperscript{37} are discordant with our findings.

However, the study has several limitations. Firstly, it is limited by an interviewer-administered, retrospective questionnaire which may have possible recall bias for asthma and rhinitis. However, there were several steps in mitigating some of these limitations. For example, in addition to the fact that for the history of worm infection, the worms described mostly resembled \textit{Ascaris}, due to their conspicuous size, egg excretion and \textit{Ascaris}-specific IgE were also measured and confirmed high prevalence of the two helminth species. Likewise, for the history of asthma and rhinitis symptoms and treatment, current symptomatology and treatment were also recorded and confirmed through clinic records to mitigate the recall and self-reporting bias. In addition, for allergic disorders, blood measurements for IgE atopy and food allergy as well as total and \textit{Ascaris}-specific IgE were undertaken. The study was also limited by the small sample size which is reflected by the wide confidence intervals in some of the associations. An additional confounder was gender bias since the majority of participants were females. This was a default representative of a healthcare sample, as is a common phenomenon where females are more likely to be healthcare seekers than males. Demographically, most participants were born in the Eastern Cape villages.

A spurious finding was the significant negative association between \textit{Ascaris} egg excretion and asthma. During the early phase of \textit{Ascaris} infection, the larvae migrate to the lungs before being coughed up, causing an eosinophilic pneumonia-like symptom that may present as asthma.\textsuperscript{38} A possible explanation could be that asthma is a heterogenous disease which includes atopic and non-atopic forms.\textsuperscript{39} In particular, the non-atopic form is more prevalent among older people, as similar to the age of the population studied here. The present study, however, did not distinguish or control for these different endotypes since the objective was to record any form of asthma in the presence or absence of helminthiasis. Others suggest that chronic but not acute helminth infections protect against allergy.\textsuperscript{29} In our study, active worm infections that were negatively associated with asthma cannot be classified as either chronic or acute. Further study with adequate sampling and power is required.

Although limited by several factors, the study highlights that early and current infection with helminths and exposure to rural and later, unhygienic environments (in the city informal settlements) do not preclude the occurrence of allergies induced by food and inhalant allergens, and asthma and rhinitis.

5 | CONCLUSION

We have shown more than 20% concurrent active worm infection and allergy in adults with evidence of lifelong exposure to environmental stimulation factors (rural and informal settlements with lack of clean water and proper sanitation) as well as helminthiasis. This finding seems to be in agreement with the proposition that complex factors interact to determine the occurrence of allergic and autoimmune diseases in the context of helminth infections. This report
| Variables          | Asthma N | n (%) | P-value | Rhinitis N | n (%) | P-value | IgE Atopy N | n (%) | P-value | Food allergy N | n (%) | P-value |
|--------------------|----------|-------|---------|-----------|--------|---------|-------------|-------|---------|----------------|-------|---------|
| **Age group in years** |          |       |         |           |       |         |             |       |         |                |       |         |
| 18–25              | 36       | 5 (13.9) | .114    | 36        | 14 (38.9) | .096    | 37          | 17 (45.9) | .691    | 37          | 4 (10.8) | .370    |
| 25–29              | 54       | 5 (9.3)   |         | 54        | 33 (61.1) |         | 56          | 21 (37.5) |         | 56          | 6 (10.7) |         |
| 30–39              | 73       | 12 (16.4) |         | 73        | 45 (61.6) |         | 74          | 26 (35.1) |         | 74          | 11 (14.9) |         |
| 40+                | 44       | 2 (27.3)  |         | 44        | 22 (50.0) |         | 45          | 19 (42.2) |         | 45          | 2 (4.4)  |         |
| **Gender**         |          |       |         |           |       |         |             |       |         |                |       |         |
| Male               | 29       | 12 (41.4) | <.001   | 29        | 19 (65.5) | .209    | 30          | 24 (80.0) | <.001   | 30          | 10 (33.3) | <.001   |
| Female             | 183      | 25 (13.7) |         | 183       | 97 (53.0) |         | 188         | 63 (33.5) |         | 188         | 15 (8.0)  |         |
| **Total IgE**      |          |       |         |           |       |         |             |       |         |                |       |         |
| Low (<70 kU/L)     | 75       | 10 (13.3) | .242    | 75        | 41 (54.7) | .991    | 78          | 9 (11.5)  | <.001   | 78          | 0 (0)    | <.001   |
| High (>70 kU/L)    | 137      | 27 (19.7) |         | 137       | 75 (54.7) |         | 140         | 78 (55.7) |         | 140         | 25 (17.9) |         |
| **Eosinophils**    |          |       |         |           |       |         |             |       |         |                |       |         |
| Low (<0.35 cells/ml) | 172     | 21 (12.2) | <.001   | 172       | 87 (50.6) | .012    | 176         | 61 (34.7) | .001    | 176         | 16 (9.1)  | .024    |
| High (>0.35 cells/ml) | 40      | 16 (40.0) |         | 40        | 29 (72.5) |         | 42          | 26 (61.9) |         | 42          | 9 (21.4)  |         |

Note: Subtotals are not always equal due to some missing data.

Abbreviation: IgE, immunoglobulin E.
| Helminth exposure | Allergy-related disorders |  |
|-------------------|--------------------------|---|
|                   | Asthma                   | Rhinitis | IgE atopy | Food allergy |
|                   | Yes  | No   | Yes  | No   | Yes  | No   | Yes  | No   | Yes  | No   |
| High Ascaris IgE  | 18   | 56.7 | 37   | 51.4 | 35   | 48.6 | 58   | 78.4 | 16   | 21.6 |
| Not high (<0.35 kU/L) (Reference group) | 18 | 14.6 | 79 | 56.4 | 61 | 43.6 | 28 | 19.6 | 115 | 80.4 |
| p-value           | .1268 |      |      |      | <.0001 |      |      |      | <.0001 |      |
| OR (95% CI)       | 1.88 (0.90–3.9) |      |      |      | 14.89 (7.46–29.7) |      |      |      | 12.87 (4.2–39.4) |
| p-value           | .047 |      |      |      | <.0001 |      |      |      | <.001 |      |
| OR (95% CI)       | 2.20 (0.66–3.75) |      |      |      | 18.18 (8.02–41.19) |      |      |      | 14.47 (4.17–50.14) |
| Ascaris eggs      | 12   | 24.5 | 32   | 65.3 | 17   | 34.7 | 14   | 28.6 | 35   | 71.4 |
| Yes, n (%)        |      |      |      |      |      |      |      |      |      |      |
| No (Reference group), n (%) | 23 | 15.5 | 78 | 52.7 | 70 | 47.3 | 63 | 41.4 | 89 | 58.6 |
| p-value           | .195 |      |      |      | <.0001 |      |      |      | <.0001 |      |
| OR (95% CI)       | 1.76 (0.80–3.88) |      |      |      | 0.57 (0.28–1.14) |      |      |      | 0.28 (0.06–1.25) |
| p-value           | .48 |      |      |      | .323 |      |      |      | .530 |      |
| OR (95% CI)       | 0.43 (0.24–0.99) |      |      |      | 0.49 (0.24–1.01) |      |      |      | 0.64 (0.16–2.54) |
| Trichuris eggs    | 12   | 25.0 | 30   | 62.5 | 18   | 37.5 | 14   | 29.2 | 34   | 70.8 |
| Yes, n (%)        |      |      |      |      |      |      |      |      |      |      |
| No (Reference group), n (%) | 23 | 15.4 | 80 | 53.7 | 69 | 46.3 | 63 | 41.2 | 90 | 58.8 |
| p-value           | .135 |      |      |      | .173 |      |      |      | .297 |      |
| OR (95% CI)       | 1.83 (0.83–4.03) |      |      |      | 0.59 (0.29–1.19) |      |      |      | 0.47 (0.13–1.66) |
| p-value           | .024 |      |      |      | .563 |      |      |      | .666 |      |
| OR (95% CI)       | 0.36 (0.15–0.87) |      |      |      | 0.79 (0.39–1.58) |      |      |      | 0.74 (0.19–2.92) |

Note: Subtotals are not always equal due to some missing data.
Abbreviations: aOR, adjusted odds ratio (adjusted for age, gender and locality); IgE, immunoglobulin E.
adds to the ever-contradictory studies of the interactions between helminths and hyperimmune disorders. More insights into the extension of the reformulated hygiene hypothesis and old friends’ theory are needed which require more in-depth studies in different geographic settings. This knowledge is important for better diagnosis, treatment and prevention of allergy-related diseases and the potential therapeutic or exacerbating significance of helminthiasis. Therefore, more studies are needed in order to gain a better understanding of this phenomenon.

ACKNOWLEDGEMENTS
The South African Medical Research Council is acknowledged for providing funding support for this study (ZLM-K) and the South African National Research Foundation (NRF) for a travel grant support (ZLM-K). Prof TFHG Jackson, Dr John Fincham, Dr Vera Adams and Ms Celia Anderson are acknowledged for their support during the project. The Health Service of the City of Cape Town and study participants are highly acknowledged for authorizing and supporting the acquisition and provision of data respectively.

CONFLICT OF INTEREST
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR CONTRIBUTIONS
Zilungile Lynette Mkhize-Kwitshana contributed to conceptualization, laboratory and field work and writing—original draft preparation. Pragalathan Naidoo contributed to conceptualization and writing—reviewing and editing. Ntombifikile M. Nkwanyana contributed to data analysis and validation. Musawenkosi L. H. Mabaso contributed to conceptualization, data analysis and writing—reviewing and editing.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**How to cite this article:** Mkhize-Kwitshana ZL, Naidoo P, Nkwanyana NM, Mabaso MLH. Concurrent allergy and helminthiasis in underprivileged urban South African adults previously residing in rural areas. *Parasite Immunol*. 2022;44:e12913. doi:10.1111/pim.12913