Association between allergic sensitization and intestinal parasite infection in schoolchildren in Gqeberha, South Africa

Oliver Brandt1,2,3,4 | Benjamin Wegenstein1,3,5 | Ivan Müller5,6 | Danielle Smith7 | Siphesihle Nqweniso7 | Larissa Adams7 | Simon Müller2 | Rosa du Randt7 | Uwe Pühse6 | Markus Gerber6 | Alexander A. Navarini2 | Jürg Utzinger3,5 | Niklaus D. Labhardt3,5,8 | Christian Schindler3,5 | Cheryl Walter7

1Department of Dermatology, Allergy Unit, University Hospital, University of Basel, Basel, Switzerland
2Department of Dermatology, University Hospital Basel, Basel, Switzerland
3University of Basel, Basel, Switzerland
4Pediatric Respiratory Medicine, Children’s University Hospital of Bern, University of Bern, Bern, Switzerland
5Swiss Tropical and Public Health Institute, Allschwil, Switzerland
6Department of Sport, Exercise and Health, University of Basel, Basel, Switzerland
7Department of Human Movement Science, Nelson Mandela University, Gqeberha, South Africa
8Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland

Abstract

Background: Inconsistent data exist regarding the influence of parasitic infection on the prevalence of allergic sensitization and disorders.

Objective: To investigate the impact of geohelminth and protozoan infections on sensitization patterns and allergic symptoms of children living in low-income communities in Gqeberha, South Africa.

Methods: In a cross-sectional study, 587 schoolchildren aged 8–12 years were recruited in June 2016 and screened for reactivity to common allergens by skin prick tests (SPTs) and for parasitic infections by stool examination. Additionally, questionnaires were completed to record allergic symptoms the children may have experienced.

Results: Positive SPTs were found in 237/587 children (40.4%), and about one-third of whom were polysensitized. Sensitizations were most frequently detected against the house dust mites (HDM) Dermatophagoides spp. (31.9%) and Blomia tropicalis (21.0%). Infections with geohelminths (Ascaris lumbricoides, Trichuris trichiura) were found in 26.8% and protozoan infections (Giardia intestinalis, Cryptosporidia spp.) in 13.9% of study participants. Mixed logistic regression analyses revealed negative associations between parasite infection and sensitization to Blomia tropicalis (OR: 0.54, 95% CI 0.33–0.89) and to Dermatophagoides spp. (OR 0.65, 95% CI 0.43–0.96), and between protozoan infection and allergic sensitization to any aeroallergen, although these associations were not statistically significant.
For decades, allergies have been considered as disorders of Western civilization and were, due to the lack of epidemiological data, underestimated in regions beyond Europe and North America. It has become obvious, however, that allergies constitute a significant and increasing health problem across the Global South, exhibiting similar rates to high-income countries.\textsuperscript{1} The socio-economic changes related to urbanization and rapid industrialization, resulting in a “westernized” lifestyle, are assumed to be responsible for this phenomenon.\textsuperscript{2-5} Accordingly, several studies from different African regions recently reported high prevalence of atopic diseases\textsuperscript{6,7} ranging from 7.2\% to 54.1\%.\textsuperscript{8} As the onset of atopic disorders commonly occurs early in life, children are particularly affected\textsuperscript{9,10} and frequently develop comorbidities, e.g., recurrent sinusitis and nasal polyps, which have a significant impact on their quality of life.\textsuperscript{11-13}

**Conclusions and clinical relevance:** Our data suggest that geohelminth infection and high geohelminth infection intensity are associated with a reduced risk of polysensitization.

---

**GRAPHICAL ABSTRACT**

Schoolchildren from low-income communities in Gqeberha, South Africa, were investigated for intestinal parasite infections and its impact on allergic sensitization. A questionnaire was used to report previous and current allergic symptoms. About 40\% exhibited at least one sensitization with HDMs being the most prevalent allergen. While helminth infections were associated with a reduced risk of polysensitization, inverse associations between sensitization in general and protozoa infection were found.

**Key messages**

- 40\% of schoolchildren from low-income South African communities were sensitized, most commonly to dust mite.
- Helminth infection and infection intensity were inversely associated with polysensitization.
- Parasite infections were not associated with allergic sensitization when adjusted for false discovery rate

---

**1 | INTRODUCTION**
The most common allergens in sub-Saharan Africa are grass pollen, but house dust mite (HDM) and cockroaches have greatest clinical relevance.\(^1\) In a Ghanaian study examining schoolchildren, both HDM and cockroaches were found to be risk factors for the development of asthma.\(^1\) This is of special importance as poor housing conditions supporting dampness provide optimal growth and reproduction conditions for mites and moulds, respectively, increasing the corresponding allergen levels and thus sensitization rates.\(^1\)

According to the "hygiene hypothesis," chronic exposure to microbes and parasites during early childhood induces regulatory immune mechanisms that inhibit the development of inflammation-associated disorders. Indeed, in numerous studies, chronic infections with helminths demonstrably influenced the development and course of autoimmune and allergic diseases in humans and in animals.\(^2\) As both helminth infections and atopic diseases are associated with a T-helper cell type 2–driven immune response, it is an on-going contention as to whether infections with helminths predispose to atopic diseases\(^3\) or rather suppress their development.\(^4\) More evident, though much less studied thus far, seems to be the influence of protozoa on atopy. Infections with these parasites appear to have protective effects on the development of allergic sensitization and disease via an enhanced Th1-type immune response.\(^5\)

As South Africa is one of the most "westernized" nations on the African continent, we wondered whether atopy is as common amongst children in South Africa as it is in countries of the so-called Western world and how it relates to other African countries. We therefore investigated the prevalence of atopy in schoolchildren from disadvantaged neighbourhoods in Gqeberha (formerly Port Elizabeth), South Africa, and studied potential effects of environmental factors, notably parasitic infections, on allergic sensitizations and clinical manifestations.

## 2 | METHODS

### 2.1 | Study setting

This cross-sectional study was conducted amongst black African learners and learners of mixed-race ancestry (a complex of predominantly indigenous Khoi and black African, European or Asian) at 7 schools situated in socio-economically disadvantaged urban neighbourhoods in different areas of Gqeberha, South Africa. The Indian Ocean port has a subtropical, oceanic climate with an annual average temperature of 17.5° Celsius (13.5–22.3°C) and an average relative humidity of 77% (73–81%).

### 2.2 | Subject population and study design

Participants were 8- to 12-year-old children who were part of the "Disease, Activity and School children’s Health" (DASH) cohort survey that explored the physical and psychological well-being of learners from disadvantaged districts (described in detail elsewhere\(^7\)). For the current study, participants were examined for sensitizations to common allergens typical of the region and for the presence of parasite infections. A detailed description of the information for participants, exclusion criteria and the management of parasite infections is provided in the Supplement.

Informed consent was provided by the child’s legal caregiver(s) and the survey was approved as a part of the DASH study by the Ethics Committee Northwest/Central Switzerland (reference number 2014-179), the Nelson Mandela University Human Ethics Committee (study number H14-HEA_HMS002 and H14-HEA-HMS-002/Amendment), the Eastern Cape Department of Education and the Eastern Cape Department of Health in Gqeberha, South Africa.

### 2.3 | Skin prick testing

Skin prick testing (SPT) was performed using standard procedures\(^8\) with standardized allergen extracts (ALK-Abelló, Hørsholm, Denmark): HDM mix containing Dermatophagoides (Der) pteronyssinus and farinae, Blomia tropicalis (Bio), German cockroach, grass mix, Bermuda grass, mould mix, cat and dog epithelia, cow’s milk, egg white, wheat, peanut, soy and cod fish (for details see Supplementary Material). Participants with one positive reaction were classified as "monosensitized," those with two or more as "polysensitized."

### 2.4 | Parasitological examinations

Intestinal helminth infections were determined in morning stool samples using the Kato-Katz technique and evaluated as described previously.\(^9\) According to the World Health Organization (WHO) classification, infection intensity with the soil-transmitted helminths (STH) Ascaris lumbricoides (A. lumbricoides) and Trichuris trichiura (T. trichiura) was based on the number of eggs per gram (EPG) of stool.\(^10\) Additionally, stool samples were screened for the protozoans Cryptosporidium spp. and Giardia intestinalis using the Crypto-Giardia Duo Strip\(^6\) rapid diagnostic test (Coris, BioConcept, Gembloux, Belgium).

For more details on parasitological examinations, see Supplement.

### 2.5 | Prevalence of allergies/allergic symptoms

To investigate the prevalence of allergic symptoms, learners were asked to answer questions regarding respiratory, rhinoconjunctival and cutaneous symptoms taken from the International Study of Asthma and Allergies in Childhood (ISAAC) II questionnaire\(^11\) (Supplementary Material S1). Study nurses especially trained for this study assisted the children in answering the questionnaire.
2.6 | Statistical analyses

Data were double-entered and cross-checked using EpiData version 3.1 (EpiData Association, Odense, Denmark) and subsequently merged into a single database. Only children with complete data on infections and atopic sensitizations were included in the final analyses. Associations between binary outcomes and predictor variables were analyzed using mixed logistic regression models with random intercepts for schools if the outcome frequency was sufficiently large. Otherwise, unadjusted odds ratios (ORs) were computed from 2 by 2 tables, and the Fisher’s exact test was used to determine their statistical significance. All regression analyses were adjusted for sex and age of the child and for socio-economic status (SES; for details on estimation of SES, see the Methods section in the Supplement) of the parents, and in models of respiratory symptoms, body mass index (BMI) was additionally included. In analyses of atopic sensitizations, predictors of interest were parasitic infections to *A. lumbricoides*, *T. trichiura* and protozoa, respectively, whereas predictors of interest in analyses of respiratory symptoms were atopic sensitizations. Factors influencing the number of atopic sensitizations were assessed in two steps. First, children with and without atopic sensitization were compared, and subsequently, predictors of having more than one sensitization were assessed amongst children with at least one atopic sensitization. Results are presented as ORs with 95%-confidence intervals. Nominal p-values are reported for primary and secondary outcomes, as they correspond with the 95% confidence intervals. Additionally, for secondary outcomes, p-values adjusted for multiple comparisons were calculated using the Stata module AEFDR,\(^33\) which provides false discovery rate-adjusted p-values. Analyses were conducted using Stata Statistical Software, Release 15.0, College Station (Stata Corp. Texas, USA) and the level of significance was set at \(p < .05\) across all analyses.

3 | RESULTS

Of the 913 learners who were invited to participate, 640 were enrolled and data of 587 of which were suitable for analyses. Median age was 11.0 years (IQR 10.5–11.6); 303 (51.6%) were females, 281 (47.9%) males, three children had missing data on sex, age and ethnicity. Slightly more than half of the children were black South Africans, children of mixed descent accounted for 41.3%, and 4.4% had other ethnic backgrounds (Table 1).

### 3.1 | Prevalence of sensitizations

Of the 587 children, 237 (40.4%) responded to at least one allergen, with reactions to HDM (52.9%) being by far the most frequent sensitizations (Der 31.9%, Blo 21.0%, both 19.1%), followed by cockroach (15.7%), grass mix and Bermuda grass (9.9% each). Sensitization prevalence neither differed significantly between females and males (\(p = .26\)) nor between black children and children of mixed descent (\(p = .37\)).

Of the 237 children with at least one positive SPT, 65.8% were polysensitized. Of those exhibiting monosensitization, Der (58.0%) followed by cockroach (11.1%) and Blo (9.9%) were the most common allergens, while in the polysensitized children, respective percentages were 89.7%, 53.2% and 73.7%.

Sensitization to Der was most frequently accompanied by sensitization to Blo (59.9%), followed by cockroach (43.3%) and grass mix (25.1%). Blo, in turn, was nearly always combined with Der (91.1%) and frequently with cockroach sensitization (53.7%). The latter also showed a strong association with Der sensitization (88.0%) and in 71.7% with Blo. Both grass mix and Bermuda grass sensitizations were detectable in about one in ten children and exhibited exactly the same prevalence (9.9%; in polysensitized 36.5% and 34.6%, respectively), most likely due to cross-reactivities between grasses (Figure 1 and S1). We found a nonsignificant positive association between male sex and a nonsignificant negative association between age and number of sensitizations (\(p = .32\) and .34, respectively). Sensitization to food allergens was rare (6.8%), with peanut (3.1%) being the most common food allergen.

### 3.2 | Prevalence of parasite infections

35.1% of the children were infected with parasites, 26.8% with *A. lumbricoides* and *T. trichiura* (monoinfection in 8.0 and 7.6%, respectively) and 13.9% with the protozoans *Gardia lamblia* (*G. intestinalis*) and Cryptosporidium (monoinfections in 8.5% and 6.3%, respectively). Infections with helminths other than those mentioned above were detected in 6 children (see Supplementary Results). Light infections were more common (*A. lumbricoides* 11.8%, *T. trichiura* 16.0%) than moderate ones (6.3 and 2.7%, respectively) or heavy infections (1.0% and 0% respectively) (Table 2). Since the number of children

---

**TABLE 1** Demographic data and sensitization prevalences

| Ethnicity                      | Girls                  | Boys                   |
|--------------------------------|------------------------|------------------------|
| Black                          | 303 (51.6%)            | 281 (47.9%)            |
| Mixed, black/white descent     | 81/237 (34.2%)         | 26 (4.4%)              |
| Other (Indian, other mixed ethnicities) | 156/237 (65.8%)     |                        |

Abbreviation: IQR, interquartile range.
with severe helminth infections was low, we combined moderate and heavy infection groups for further calculations.

### 3.3 Associations between allergic sensitization and parasitic (helminths and/or protozoa)/ helminthic infections (A. lumbricoides and/or T. trichiura)

Statistically significant negative associations with parasite infection were found for sensitization to Blo (OR 0.54, 95%-CI 0.33–0.89, \( p = .02 \)) and Der (OR 0.65, 95%-CI 0.43–0.96, \( p = .03 \)), and to a non-significant extent, to cockroach (OR 0.64, 95%-CI 0.36–1.13, \( p = .12 \)) and Bermuda grass (OR 0.50, 95%-CI 0.24–1.03, \( p = .06 \)). Helminth infection in general was negatively associated with Blo sensitization (OR 0.46, 95%-CI 0.25–0.87, \( p = .02 \)), whereas selective analysis of T. trichiura and A. lumbricoides yielded contrasting results. While no significant association with sensitizations was detected for the latter, T. trichiura infection was negatively associated with sensitization to both Der (OR 0.26, 95%-CI 0.08–0.78, \( p = .02 \)) and Blo (OR 0.08, 95% CI: 0.01–0.64, \( p = .02 \)) (Table 3 and Table S1, Supplementary Material).
| Aeroallergens                                      | Parasite infection | Helminth infection | A. lumbricoides | T. trichiura | Protozoa |
|---------------------------------------------------|--------------------|--------------------|-----------------|--------------|----------|
| Any aeroallergen                                   | 0.74 (0.51–1.08)   | 0.89 (0.54–1.47)   | 0.68 (0.33–1.42) | 0.50 (0.22–1.18) | 0.44 (0.22–0.88) |
| Der                                               | 0.65 (0.43–0.96)   | 0.69 (0.41–1.15)   | 0.73 (0.34–1.55) | 0.26 (0.08–0.78) | 0.48 (0.23–1.00) |
| Blo                                               | 0.54 (0.33–0.89)   | 0.46 (0.25–0.87)   | 0.44 (0.16–1.20) | 0.08 (0.01–0.64) | 0.55 (0.24–1.29) |
| Cockroach                                         | 0.64 (0.36–1.13)   | 0.72 (0.37–1.41)   | 0.66 (0.24–1.85) | 0.60 (0.19–1.87) | 0.30 (0.09–1.01) |
| Bermuda grass                                     | 0.50 (0.24–1.03)   | 0.55 (0.21–1.45)   | 0.65 (0.18–2.34) | 0.45 (0.09–2.18) | 0.47 (0.14–1.60) |
| Grass mix                                         | 0.76 (0.38–1.52)   | 1.14 (0.47–2.80)   | 1.32 (0.42–4.12) | 0.44 (0.08–2.34) | 0.51 (0.15–1.76) |
| Mould mix                                         | 0.23 (0.03–2.05)   | 0.00 (0.00–1.36)   | 0.00 (0.00–4.30) | 0.00 (0.00–5.10) | 0.83 (0.10–6.70) |
| Cat dander                                        | 0.84 (0.34–2.09)   | 0.76 (0.21–2.71)   | 0.57 (0.07–4.67) | 0.00 (0.00–2.30) | 1.14 (0.32–4.05) |
| Dog dander                                        | 0.75 (0.20–2.80)   | 0.66 (0.12–3.66)   | 0.00 (0.00–4.30) | 1.48 (0.15–15.0) | 0.71 (0.08–5.90) |

| Food allergens                                    | Parasite infection | Helminth infection | A. lumbricoides | T. trichiura | Protozoa |
|---------------------------------------------------|--------------------|--------------------|-----------------|--------------|----------|
| Any food allergen                                 | 0.52 (0.23–1.19)   | 0.75 (0.31–1.81)   | 0.93 (0.26–3.26) | 1.21 (0.34–4.31) | 0.24 (0.03–1.84) |
| Peanut                                            | 0.42 (0.12–1.50)   | 0.42 (0.09–1.92)   | 1.17 (0.25–5.47) | 0.84           | 0.58 (0.07–4.60) |
| Cow’s milk                                        | 0.35 (0.07–1.66)   | 0.65 (0.33–3.20)   | 0.00 (0.00–3.90) | 0.123 (0.15–10.5) | 0.00 (0.00–3.12) |
| Hen’s egg                                         | 0.59 (0.06–5.80)   | 0.91 (0.09–9.58)   | 0.00 (0.00–14.7) | 6.17 (0.51–75.2) | 0.00 (0.00–11.9) |
| Wheat                                             | 0.00 (0.02–146)    | 3.09 (0.04–243)    | 9.74 (0.12–767)  | 0.00 (0.00–437) | 0.00 (0.00–303) |
| Soy                                               | 0.00 (0.00–2.80)   | 0.00 (0.00–4.70)   | 0.00 (0.00–14.7) | 0.00 (0.00–17.3) | 0.00 (0.00–11.9) |
| Cod fish                                          | 0.44 (0.10–2.07)   | 0.72 (0.15–3.42)   | 0.91 (0.11–7.56) | 1.11 (0.13–9.54) | 0.02 (0.00–3.32) |

Note: If case numbers were large enough, odds ratios (ORs) and 95%-confidence intervals (95% CI) were estimated from mixed logistic regression models adjusting for sex, age and socio-economic status and including random school intercepts. Otherwise, unadjusted ORs (with exact CI) and p-values from the Fisher's exact test are given (cases marked with *). Numbers of children investigated were 587 for parasite infection (at least one of the protozoa or helminths), 505 for helminth infection (one or both helminths), 421 for A. lumbricoides, 415 for T. trichiura and 430 for protozoa, including the uninfected children in each case. For ORs equaling 0, one-sided 95% CI are given. (1) comparison between children with helminth infection only and children without any parasite infection, (2) comparison between children infected with A. lumbricoides only and children without any parasite infection, (3) comparison between children infected with T. trichiura only and children without any parasite infection and (4) comparison between children with protozoa infection only and children without any parasite infection. None of these results remains statistically significant after adjustment for false discovery.
Estimated adjusted associations of parasite infections with sensitization in general and polysensitization

|                      | All subgroups combined | Monoinfected vs. uninfected |
|----------------------|------------------------|----------------------------|
|                      | OR (95% CI)            | p-Value                    | N | OR (95% CI)                  | p-Value                  | N |
| I. Sensitized vs. nonsensitized |                        |                            |   |                            |                          |   |
| a.) Any parasite     | 0.77 (0.53–1.13)       | .18                        | 582| 0.96 (0.58–1.57)            | .87                      | 502|
| b.) Helminths        | 1.07 (0.68–1.68)       | .77                        | 582| 0.58 (0.25–1.34)            | .20                      | 414|
| c.) A. lumbricoides  | 1.23 (0.74–2.06)       | .43                        | 582| 0.68 (0.33–1.42)            | .31                      | 419|
| T. trichiura         | 1.11 (0.64–1.93)       | .72                        |    | 0.58 (0.25–1.34)            | .20                      |    |
| Protozoa             | 0.62 (0.37–1.04)       | .07                        |    | 0.44 (0.22–0.88)            | .02                      |    |
| II. Polysensitization vs. monosensitization |                     |                            |   |                            |                          |   |
| a.) Any parasite     | 0.47 (0.25–0.86)       | .014                       | 232| 0.34 (0.17–0.64)            | .003                     | 207|
| b.) Helminths        | 0.41 (0.21–0.78)       | .007                       | 232| 0.50 (0.16–1.61)            | .24                      | 171|
| Protozoa             | 1.24 (0.49–3.11)       | .65                        |    | 0.37 (0.10–1.37)            | .14                      |    |
| c.) A. lumbricoides  | 0.66 (0.29–1.48)       | .31                        | 232| 0.87 (0.24–3.13)            | .84                      | 170|
| T. trichiura         | 0.47 (0.20–1.08)       | .08                        |    |                            |                          |    |
| Protozoa             | 1.14 (0.46–2.86)       | .77                        |    |                            |                          |    |

Note: Odds ratios (ORs) and 95% confidence intervals (95% CI) between (I) being sensitized to at least one of the allergens tested, (II) being polysensitized (among children with at least one sensitization), on the one hand, and parasite infections, on the other hand, were estimated from mixed logistic regression models adjusting for sex, age and socioeconomic status and including random school intercepts. The results in the left part of the table are from three different models. Model (a) contained a single indicator variable for all parasite infections, model (b) separate indicator variables for helminth and protozoa infections and model (c) separate indicator variables for A. lumbricoides, T. trichiura and protozoa infections. The right-hand part of the table provides results from comparing children with the indicated type of parasite infection only and children without any parasite infection. The significant negative association between polysensitization vs. monosensitization and heminth infection stands up to adjustment for false discovery rate.

Estimated adjusted association of helminth infection severity with sensitization in general and polysensitization

| Infection severity | Helminths | A. lumbricoides | T. trichiura |
|--------------------|----------|----------------|-------------|
| NOR (95% CI)       |          |                |             |
| Sensitized vs. nonsensitized |         |                |             |
| Light              | 0.89 (0.52–1.54) | .69            |             |
| Moderate/severe    | 1.14 (0.54–2.44) | .73            |             |
| Polyosensitization vs. monosensitization |         |                |             |
| Light              | 0.48 (0.21–1.08) | .08            |             |
| Moderate/severe    | 0.14 (0.04–0.48) | .002           |             |
| Note: Odds ratios (ORs) and 95% confidence intervals (95% CI) between (a) being sensitized to at least one of the allergens tested, resp. (b) being polysensitized (amongst children with at least one sensitization), on the one hand, and the severity of parasite infections, on the other hand, were estimated from mixed logistic regression models adjusting for sex, age and socio-economic status and including random school intercepts. Analyses were restricted to children who either had no parasite infection or just had the respective type of infection but no additional parasite infection(s). Numbers (Ns) of the different analyses were 502, 419 and 414, respectively, for helminths, A. lumbricoides and T. trichiura as predictors of "any atopic sensitization" in monoinfected or uninfected children, and 207, 171 and 168, respectively, for helminths, A. lumbricoides and T. trichiura as predictors of a polysensitization in monoinfected or uninfected children with at least one atopic sensitization. The significant negative association between polysensitization vs. monosensitization and moderate/severe helminth infection stands up to adjustment for false discovery.

3.6 | Prevalence of self-reported symptoms (ISAAC questionnaire) and association with allergic sensitizations

Approximately 40% of the participants reported that they had experienced respiratory (15.8–38.7%) and/or rhinoconjunctival symptoms (9.3–39.2%), and 22.0% stated that they had suffered from an itchy rash in the past (Table S2). Children sensitized to at least one allergen were more likely to report "Dyspnoea at rest" (OR 1.81, 95%-CI 1.14–2.87, p = .012), "Wheezing or whistling in the chest" (OR 1.60, 95%-CI 1.00–2.55, p = .048) or "Wheezing during or after exercise" (OR 1.37, 95%-CI 0.95–1.90, p = .09) than those without sensitization, while children exhibiting polysensitization were significantly more likely to report "Wheezing or whistling in the chest" (OR 3.34, 95%-CI 1.40–7.94, p = .006). In contrast, the respiratory sign “Dry cough” showed only a weak positive association with any sensitization (OR 1.23, 95%-CI
0.85–1.77, p = .27). After adjustment for false discovery, however, only the association between polysensitization and "Wheezing and whis- tling in the chest" remained statistically significant (p = .042).

Considering sensitizations individually (Table S3), "Dyspnoea at rest" exhibited significant positive associations with responses to Blo (OR 1.89, 95%-CI 1.13–3.18; p = .02), Der (OR 1.68, 95%-CI 1.04–2.70; p = .03) and cat dander (OR 2.56, 95%-CI 1.08–6.05; p = .03), while for "Dry cough," a nonsignificant positive association with cockroach sensitization (OR 1.58, 95%-CI 0.98–2.55; p = .06) was detected. "Wheezing or whistling in the chest" exhibited positive associations with sensitizations to Blo (OR 2.48, 95%-CI 1.48–4.16, p < .001) and Der (OR 1.95, 95%-CI 1.21–3.14, p = 0.006). Similar associations were found for "Wheezing during or after exercise," with ORs of 1.54 (95%-CI 1.05–2.25, p = .03) for Der and of 1.49 (95%-CI 0.97–2.30, p = .07) for Blo. However, only the association of "Wheezing and whistling in the chest" with B. tropicalis sensitization holds up to adjustment for false discovery (p = .04 after FDR-adjustment). For the results of non-pulmonary signs, see Supplementary Material.

Finally, we tested potential associations between reported symp- toms and parasitic infections (Tables S4 and S5). While we were unable to detect any risk reduction in children infected with helminths, protozoan infection was significantly associated with a reduced risk of reported "Dyspnoea at rest" (OR 0.36, 95%-CI 0.13–0.95, p = .04) and "Itchy rash during the last 6 months" (OR 0.43, 95%-CI 0.20–0.91, p = .03). Infection with protozoa (OR 1.79, 95%-CI 1.03–3.10, p = .04) and also with parasite infection in general (OR 1.65, 95%-CI 1.04–2.62, p = .03), however, were significantly positively associated with "Wheezing during or after exercise." Yet, none of these associations remained statistically significant after adjustment for false discovery.

4 | DISCUSSION

In this study, we examined schoolchildren from marginalized urban districts in Gqeberha (formerly Port Elizabeth), South Africa, for sensitizations to common allergens and investigated whether and in which way these sensitizations are affected by infections with para- sites. We found that about 40% were sensitized to at least one aller- gen of which two-thirds were polysensitized. Der and Blo, cockroach and grasses were the most prevalent allergens and parasite infections significantly affected the risk of sensitization to Blo and Der. Interestingly, protozoan and helminth infections exhibited different associations with atopic sensitization risks: while protozoan significantly reduced the risk of sensitization in general, T. trichiura and, to a lesser extent, A. lumbricoides were associated with a significantly reduced risk of polysensitization amongst sensitized children.

4.1 | Prevalence of sensitization and polysensitization

With a sensitization rate of 40.4%, our results fall in the upper third and are well in line with those reported by other authors. Steinman et al. examined rural and urban children aged 10–14 years from different regions in South Africa and found prevalences ranging from 42.3% in black to 55.2% in white urban participants, and two more recent surveys from Douala, Cameroon, reported sensitization rates to aeroallergens of 32.3% in children and adolescents, and of 42.8% in young university students. European cohort studies found prevalences between 34.8% and 47.9% for children aged 8–10 years, with even higher rates reported in studies from The Netherlands and the Chinese city of Guangzhou. Although such studies can only be compared to a limited extent, our results and those of others show that sensitization rates even in low-income communities in Africa have reached similar dimensions to more industrialized nations.

Similar to other surveys, the majority in our cohort showed polysensitization, with Der being the most prevalent allergen in both monosensitized and polysensitized participants, followed by Blo, cockroach and grass mix/Bermuda grass. However, while monosen- sitized children exhibited 58.0% sensitizations to Der, this appeared in 89.7% of the polysensitized children, underlining the high sensitization potency of this indoor allergen. Notably, sensitization to Blo appeared in less than 10% of monosensitized participants but was nearly almost associated with Der in polysensitized individuals. This finding is in accordance with previous studies, which showed that monosensitization to Blo was rare, while co-sensitization to Der was present in approximately 70% of the cases. In a study from northeastern Greece, where climatic conditions are similar to those in Gqeberha, 60% of the children exhibiting allergic sensitizations were polysensitized, with Der being the most prevalent allergen. Furthermore, a survey examining the sensitization patterns of nearly 6,500 children from 6 French cities found Der to be the dominant allergen and that children from coastal regions were not only sig- nificantly more likely to be sensitized to HDM but also exhibited significantly more frequent polysensitizations. This finding is of particular importance since both polysensitization and dust mite sensitization are associated with an increased risk of developing or suffering from asthma and/or allergic multimorbidity.

Differences in the prevalence of HDM sensitization across geo- graphical regions are well known. As proliferation and survival of HDM depend on adequate humidity (maximal at relative humidity of 75%), sensitization rates are highest in regions with a tropical and/or maritime climate. Consistent with this, studies found that high HDM concentrations in damp homes and poor hygienic and socioeconomic living conditions were positively associated with HDM and cockroach sensitization. As such an exposure is likely to be of relevance in our population due to their poor living con- ditions, the high sensitization prevalence to these indoor allergens may be at least partly due to these circumstances.

4.2 | Prevalence of parasitic infections and its association with allergic sensitization

Approximately 25% of the children were infected with A. lumbrico- ides and/or T. trichiura, and the majority of these infections were of light intensity. This value is well below the overall infection rates
reported for these helminths for schoolchildren from Cape Town in 2005 and recently in a meta-analysis of Nigerian children.\textsuperscript{58,59} However, it clearly exceeds the average global rates (\textit{A. lumbricoides} 14.5\% and \textit{T. trichiura} 8.3\%) as described by Pullan et al.\textsuperscript{60} Infections with the protozoans \textit{G. intestinalis} and/or \textit{Cryptosporidium} spp. were present in 13.9\% of the children, of whom 8.5\% and 6.3\%, respectively, were diagnosed with monoinfections. Similar rates have been reported in asymptomatic children in Ghana (5–10\%)\textsuperscript{61,62} and Uganda (8.5\%),\textsuperscript{63} respectively, but numbers vary widely in the literature.\textsuperscript{44,65}

The immune modulatory effects of parasites on the development of sensitization and allergies have been studied intensively. In their meta-analysis, Feary et al.\textsuperscript{66} reported substantial evidence that intestinal parasite infections reduce the risk of allergic sensitization and that this effect was particularly pronounced for STH. As coinfections with STH and protozoa are common in endemic regions and particularly affect children,\textsuperscript{67} we wondered about any associations with allergy-related outcomes in combined infections, despite the opposing immune responses induced by these parasites. Remarkably, while we found a weak relationship between the presence of a parasite infection and a reduced sensitization risk in general, mixed logistic regression analysis revealed that parasites selectively influenced the likelihood of sensitizations to \textit{Der}, \textit{Blo}, \textit{Bermuda grass} and cockroach. Moreover, stratification for the two helminths showed that \textit{T. trichiura} decreased the odds for sensitization in general, as well as the probability for sensitization to the HDMs \textit{Der} and \textit{Blo}, whereas \textit{A. lumbricoides} markedly increased the SPT reactivity to \textit{Blo} only. Similar observations of such a selective effect were made in cross-sectional studies from Ghana\textsuperscript{68} and Zimbabwe,\textsuperscript{69} which demonstrated negative associations between infections with \textit{Schistosoma mansoni} and \textit{Der} sensitization, while the risk of sensitization to other allergens was not affected. Furthermore, a Vietnamese study found a significantly reduced risk of a positive SPT for HDM amongst schoolchildren infected with \textit{A. lumbricoides}.\textsuperscript{70}

Interestingly, in two surveys,\textsuperscript{71,72} increased SPT reactivity was reported after successful antihelminthic therapy, which particularly affected \textit{Der} in those studies exploring the influence on individual allergens. While Lynch et al.\textsuperscript{73} described an increase in the reactivity to house dust from 17\% to 68\%, a study from Israel, investigating newly arrived immigrants from Ethiopia with helmints infections, found a doubling of the number of SPT reactivity to \textit{Der} spp. (and additionally to grass and olive tree pollen) after successful eradication treatment.\textsuperscript{74} Staal et al.\textsuperscript{75} recently investigated the outcome of mass drug administration of albendazole in Indonesian schoolchildren in an area endemic for \textit{T. trichiura}, \textit{A. lumbricoides} and hookworm and observed a significant increase in positive SPTs, especially for HDM, in those successfully treated. Interestingly, the significance of this effect was confined to \textit{Der}, \textit{peteronysinus}, whereas no significant change was observed for \textit{Der}, \textit{farinae} or cockroaches. The reason for this phenomenon is obscure. It is, however, conceivable that constant exposure to high concentrations of a specific HDM/\textit{Der} antigen(s) is a prerequisite for effective induction of immunomodulatory mechanisms in individuals whose immune systems have already been deviated by chronic helmints infection towards a protolerogenic network involving regulatory T and B cells as well as high levels of the anti-inflammatory cytokine IL-10.\textsuperscript{76} Stimulation by cross-reactive allergens, such as tropomyosin (\textit{Der} \textit{p}10) and gluthione S-transferase (GST), which occur both in helmints and in HDM and cockroaches,\textsuperscript{77} may additionally be important for adequate tolerance induction. The fact that we and the abovementioned studies did not observe a general effect on the sensitization risk but predominately on reactions to HDM suggests the induction of a specific tolerance by helmints, which should be validated by future studies. Our hypotheses, though, do not explain why we also found a reduced sensitization risk for \textit{Bermuda grass}. However, the fact that grasses are the most important outdoor allergens in many world regions—just as HDM are the most relevant indoor allergens—emphasizes their equally high allergenic potential.\textsuperscript{42,53} Although similar observations were reported in the abovementioned Israeli study,\textsuperscript{74} our data must be interpreted with caution, as only 10\% of children were sensitized to \textit{Bermuda grass}, and despite high cross-reactivity, such an effect was not detectable for grass mix.

Some studies found no negative or even positive associations between helmhmint infection and SPT reactivity.\textsuperscript{5,78,79} However, few of these studies investigated infection intensity that, in various studies, has been demonstrated to considerably influence the risk of sensitization.\textsuperscript{70,72,80} In our investigations, both light and moderate/severe infections with helmints were negatively associated with polysensitization, while moderate/severe infections with \textit{A. lumbricoides} markedly lowered the odds of being sensitized to an allergen. No such effect was detectable for \textit{T. trichiura}, which is most likely due to the low number of children (n = 3) who were exclusively infected with this helmint and who had moderate/severe infections. Indeed, Rodriguez et al.\textsuperscript{18} found that severe \textit{T. trichiura} infections in early childhood significantly reduced the prevalence of one positive SPT in later childhood by more than 50\% and the risk of polysensitization by even 80\%.

When we compared children infected exclusively with the protozoa \textit{G. intestinalis} and/or \textit{Cryptosporidium} spp. with children without parasite infections, we found that protozoa infection was associated with a reduced sensitization risk in general, whereas there were no associated odds for polysensitization. These findings contrast with the results of the few other studies that investigated the influence of these protozoa on allergic sensitization.\textsuperscript{81,82} In our literature review, we did not find any studies investigating the relationship between \textit{Cryptosporidium} infections and allergic sensitizations. However, several studies have described an inverse relationship between infections with \textit{Toxoplasma gondii}, which is closely related to \textit{Cryptosporidium} spp.,\textsuperscript{83} and atopic sensitization both in humans and in animal models.\textsuperscript{25,84} For both protozoa, however, induction of IL-10 synthesis in the host organism has been described. Furthermore, Summan et al.\textsuperscript{85} recently reported that \textit{G. intestinalis} trophozoites not only affect DC activity by modulating their cytokine secretion, but are also capable of rapidly inducing their apoptosis. Since these cells are of crucial importance as antigen presenters, and thus for sensitization to allergens—and depending on their phenotype—are also important producers of IL-10,\textsuperscript{86} this could be a possible link to the reduced sensitization risk observed in our study.
Asthma-, rhinoconjunctivitis- and eczema-related symptoms were commonly reported in the ISAAC questionnaire in our study. Prevalence rates appeared to be well in line with those of a survey from Cape Town that compared data gathered from 1995 to 2002 in 13- to 14-year-old adolescents,6 and with prevalences found in other African regions and globally.97-99 As part of the ISAAC II study, Weinmayr et al.98 reported positive relationships between allergic sensitizations and asthma in nearly all participating countries, with affluent countries exhibiting stronger associations than nonaffluent ones (combined OR 4.0, 95%-CI 3.5–4.6 and 2.2, 95% CI 1.5–3.3 respectively). With ORs between 1.23 and 1.81 for respiratory symptoms, our results concur with these findings and the considerably higher probability of polysensitized children (OR 3.26) who reported “Wheezing or whistling” is consistent with surveys, which observed that the risk of developing/suffering from asthma, rhinitis and eczema increases with the number of positive SPTs.90,91 The above-cited and other research, like our study, identified HDM and, to a lesser extent, cat allergens as important risk factors for asthma, highlighting the importance of these indoor allergens.92,93 The allergological relevance of HDM was additionally emphasized in our investigations by the fact that corresponding sensitizations were positively associated with reported “Sneezing/blocked nose,” symptoms typical for HDM allergy. In contrast to the impact on allergic sensitization, we did not find negative associations for helminth infections with allergic symptoms, which is in line with a survey from Ethiopia94 and a study from Brazil exclusively investigating children with T. trichiura and those without helminth infections as controls.95 Cooper et al.,76 on the other hand, found no association between infections with a specific helminth species nor with the intensity of infection but observed that only nonatopic children who became infected with helminths at a later age had a lower risk of wheeze, while Stein et al.74 described a significant inverse relationship between egg burden and the presence of allergic symptoms in general.

The negative associations we found between protozoa infections and atopic sensitization were not conclusively reflected in the allergic symptoms reported. Although protozoa infection was inversely associated with a risk of “Dyspnoea at rest” and “Itchy rash,” protozoa and parasite infection in general were positively associated with the odds of reported “Wheezing.” So far, only few studies have investigated such associations, and apart from the abovementioned association with food allergies,82 none of these studies showed negative associations between allergies/allergic symptoms and infections with Giardia intestinalis or Cryptosporidium spp.81,97 Taken together, these inconsistent results once again suggest the existence of numerous influencing factors that should be investigated in future studies.

4.4 | Strengths and limitations

This study has some limitations. Firstly, as this is a cross-sectional study, we do not know the time of initial infections and sensitizations nor their duration, which would have been required for a deeper understanding of the observed associations. Additionally, a higher number of participants with severe helminth infections, especially with T. trichiura, may have underscored the protective effect of these parasites on the risk of developing sensitization and allergy symptoms/signs. Secondly, we have applied the Kato–Katz method for the detection of helminth eggs. This is currently the most commonly used diagnostic procedure for detection of STH in stool samples, which, however, entails the risk of false negative results due to day-to-day variation in helminth egg excretion. Hence, we cannot exclude the possibility that some of the “negative” participants were actually infected. Thirdly, due to subgroup analyses, the number of some cases has become small, which limits the validity of the respective results. Fourthly, as results for the multiple secondary outcomes (i.e., specific sensitizations) are prone to chance findings, we additionally performed false discovery rate adjustments, revealing that the positive associations of “Wheezing and whistling” with B. tropicais sensitization and polysensitization with “Wheezing and whistling,” and the inverse association between moderate/severe helminth infection and polysensitization withstood such adjustment, while the negative association between sensitization and infection with protozoa was only marginally significant (FDR-adjusted p-value of .06). However, none of the studies cited by us with a comparable design performed such an adjustment. Finally, although the questionnaire was answered by the children with the help of especially trained members of the study team, we cannot exclude that certain terms were not understood properly and that questions were thus answered incorrectly. However, it is unlikely that the strong associations we found for example between HDM sensitization and the corresponding clinical symptoms could be explained by reporting bias. Strengths of the study are the high homogeneity of the examined population, which in turn limits the transferability of its results to other settings. Additionally, in contrast to many other surveys, we did not confine outcomes to the dichotomy “sensitized vs. nonsensitized” and “infected vs. noninfected,” but examined intensities of sensitization and infection and have thoroughly investigated the effects of protozoa infections on allergic sensitizations and symptoms. Moreover, unlike the majority of studies on this topic cited by us, we performed adjustments for potential confounders, such as BMI and SES.

5 | CONCLUSION

This study shows that allergic sensitization is very common amongst children in South Africa living in poor socio-economic conditions and, as demonstrated previously, that HDM play a prominent role in this regard. It is noteworthy that helminth infections were not associated with a reduced risk of sensitization in general, but—apparently selectively—for HDM. This finding could suggest an approach for the development of therapeutic measures, as experimental therapies for the treatment of allergies and autoimmune diseases with Trichuris suis have shown promising results in animal models.96 In addition,
Further studies are necessary to confirm the first-ever observed negative association between sensitization and protozoan infection. If confirmed in future studies, combined application of microbial structures from different parasites could represent a novel therapeutic approach for the prevention of allergic sensitization and polysensitization and thus allergies.

ACKNOWLEDGEMENT
This study was supported by grants of the Freiwillige Akademische Gesellschaft, Basel, Switzerland, and Mundipharma Medical Company, Basel, Switzerland, and falls under the umbrella of the UNESCO Chair on Physical Activity and Health Educational Settings. The authors are grateful to Claudia Gray, University of Cape Town, Cape Town, South Africa, for valuable suggestions. Open Access Funding provided by Universitat Basel. [Correction added on 17 May 2022, after first online publication: CSAL funding statement has been added.]

CONFLICT OF INTEREST
The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS
OB, NDL and IM designed this study; CW, MG, RDR and UP designed the DASH study, on which the present study is based. BW, IM, DS, SN and LA conducted the field work; statistical analysis was done by CS; NDL and BW contributed to data analyses. OB interpreted data entry and prepared the database; statistical analysis was done by IM, DS, SN and LA; fieldwork was conducted by IM and BW; BW, OB, NDL and IM designed this study; CW, MG, RDR and UP contributed to data analyses.

DATA AVAILABILITY STATEMENT
Data will be made available on request from the authors.

ORCID
Oliver Brandt https://orcid.org/0000-0003-2461-4843
Ivan Müller https://orcid.org/0000-0002-6397-9979
Danielle Smith https://orcid.org/0000-0002-7374-9034
Siphelele Nqweniso https://orcid.org/0000-0001-8793-9624
Larissa Adams https://orcid.org/0000-0003-1459-1916
Simon Müller https://orcid.org/0000-0002-0200-4254
Rosa du Randt https://orcid.org/0000-0003-1033-9908
Uwe Pühse https://orcid.org/0000-0003-1228-316X
Markus Gerber https://orcid.org/0000-0001-6140-8948
Alexander A. Navarini https://orcid.org/0000-0001-7059-632X
Niklaus D. Labhardt https://orcid.org/0000-0003-3599-1791
Christian Schindler https://orcid.org/0000-0003-3059-7613
Cheryl Walter https://orcid.org/0000-0001-8422-4105

REFERENCES
1. Ait-Khaled N, Odhiambo J, Pearce N, et al. Prevalence of symptoms of asthma, rhinitis and eczema in 13- to 14-year-old children in Africa: the International Study of Asthma and Allergies in Childhood Phase III. Allergy. 2007;62(3):247-258.
2. Niekerk CH, Weinberg EG, Shore SC, Heese HDV, Schalkwyk DJ. Prevalence of asthma: a comparative study of urban and rural Xhosa children. Clin Allergy. 1979;9(4):319-314.
3. Mavale-Manuel S, Joaquim O, Macome C, et al. Asthma and allergies in schoolchildren of Maputo. Allergy. 2007;62(3):265-271.
4. 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.
5. Levin ME, Botha M, Basera W, et al. Environmental factors associated with allergy in urban and rural children from the South African Food Allergy (SAFFA) cohort. J Allergy Clin Immunol. 2020;145(1):415-426.
6. Zar HJ, Ehrlich RI, Workman L, Weinberg EG. The changing prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. Pediatr Allergy Immunol. 2007;18(7):560-565.
7. Mercer MJ, van der Linde GP, Joubert G. Rhinitis (allergic and nonallergic) in an atopic pediatric referral population in the grasslands of inland South Africa. Ann Allergy Asthma Immunol. 2002;89(5):503-512.
8. Katelaris CH, Lee BW, Potter PC, et al. Prevalence and diversity of allergic rhinitis in regions of the world beyond Europe and North America. Clin Exp Allergy. 2012;42(2):186-207.
9. Roduit C, Frei R, Depner M, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. JAMA Pediatr. 2017;171(7):655-662.
10. Kulig M, Bergmann R, Klettke U, Wahn V, Tacke U, Wahn U. Natural course of sensitization to food and inhalant allergens during the first 6 years of life. J Allergy Clin Immunol. 1999;103(6):1173-1179.
11. Said SA, Mchember MD, Chalya PL, Rambau P, Gilyoma JM. Allergic rhinitis and its associated co-morbidities at Bugando Medical Centre in Northwestern Tanzania; a prospective review of 190 cases. BMC Ear Nose Throat Disord. 2012;12:13.
12. Maspero J, Lee BW, Katelaris CH, et al. Quality of life and control of allergic rhinitis in patients from regions beyond western Europe and the United States. Clin Exp Allergy. 2012;42(12):1684-1696.
13. Colás C, Galera H, Allebarro B, et al. Disease severity impairs sleep quality in allergic rhinitis (The SOMNIAAR study). Clin Exp Allergy. 2012;42(7):1080-1087.
14. Westtritsch-King C, Sibanda E, Thomas W, et al. Analysis of the sensitization profile towards allergens in central Africa. Exp Clin Immunol. 2003;33(1):22-27.
15. Addo-Yobo EO, Custovic A, Taggart SC, Craven M, Bonnie B, Woodcock A. Risk factors for asthma in urban Ghana. J Allergy Clin Immunol. 2001;108(3):363-368.
16. Keall MD, Crane J, Baker MG, Wickens K, Howden-Chapman P, Cunningham M. A measure for quantifying the impact of housing quality on respiratory health: a cross-sectional study. Environ Health. 2012;11:33.
17. Weimayr G, Gehring U, Genuneit J, et al. Dampness and moulds in relation to respiratory and allergic symptoms in children: results from Phase Two of the International Study of Asthma and Allergies in Childhood (ISAAC Phase Two). Clin Exp Allergy. 2013;43(7):762-774.
18. Rodrigues LC, Newcombe PJ, Cunha SS, et al. Early infection with Trichuris trichiura and allergen skin test reactivity in later childhood. Clin Exp Allergy. 2008;38(11):1769-1777.
19. Smallwood TB, Giacomini PR, Loukas A, Mulvenna JP, Clark RJ, Miles JJ. Helminth immunomodulation in autoimmune disease. Front Immunol. 2017;8:453.
20. Cruz AA, Cooper PJ, Figueiredo CA, Alcantara-Neves NM, Rodrigues LC, Barreto ML. Global issues in allergy and immunology: parasitic infections and allergy. J Allergy Clin Immunol. 2017;140(5):1217-1228.
lumbricoïdes IgE antibodies and of Trichuris trichiura infection are risk factors for wheezing and/or atopy in preschool-aged Brazilian children. *Respir* *Res*. 2010;11:114.

22. Hunninghake GM, Soto-Quiros ME, Avila L, et al. Sensitization to Ascaris lumbricoïdes and severity of childhood asthma in Costa Rica. *J Allergy Clin Immunol*. 2007;119(3):654-661.

23. Scrivener S, Yemaneberhan H, Zebenigus M, et al. Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. *Lancet*. 2001;358(9292):1493-1499.

24. Yazdanbakhsh M, van den Biggelaar A, Maizels RM. Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease. *Trends Immunol*. 2001;22(7):372-377.

25. de Andrade CM, Carneiro VL, Cerqueira JV, et al. Parasites and allergy: observations from Brazil. *Parasite Immunol*. 2019;41(6):e12588.

26. Fernandes JF, Taketomi EA, Mineo JR, et al. Antibody and cytokine responses to house dust mite allergens and Toxoplasma gondii antigens in atopic and non-atopic Brazilian subjects. *Clin Immunol*. 2010;136(1):148-156.

27. Yap P, Müller I, Walter C, et al. Disease, activity and schoolchildren's health (DASH) in Port Elizabeth, South Africa: a study protocol. *BMC Public Health*. 2015;15:1285.

28. Gall S, Müller I, Walter C, et al. Associations between selective atopy and soil-transmitted helminth infections, socioeconomic status, and physical fitness in disadvantaged children in Port Elizabeth, South Africa: an observational study. *PLoS Negl Trop Dis*. 2017;11(5):e0005573.

29. Heinzerling LM, Burbach GJ, Edenharter G, et al. GA2LEN skin test study I: GA2LEN harmonization of skin prick testing: novel sensitization patterns for inhalant allergens in Europe. *Allergy*. 2009;64(10):1498-1506.

30. Müller I, Gall S, Beyleveled L, et al. Shrinking risk profiles after deworming of children in Port Elizabeth, South Africa, with special reference to Ascaris lumbricoïdes and Trichuris trichiura. *Geospat Health*. 2017;12(2):601.

31. Montresor A, Crompton DWT, Hall A, Bundy DAP, Savioi L. *Guidelines for the Evaluation of Soil-Transmitted Helminthiasis and Schistosomiasis-Asia at Community Level*. A Guide for Managers of Control Programmes. World Health Organization; 1998: 1-45.

32. Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW. ISAAC Phase Three Manual. ISAAC International Data Centre; 2000.

33. Phillips R, Cro C. AEDFR: Stata module to perform false discovery rate p-value adjustment for adverse event data," *Statistical Software Components*. 2020; https://ideas.repec.org/c/boc/bocod/s458733.html.

34. Mbatchou Nganghe BH, Noah D, Nganda Motto M, Mapoure A. Sensitization to common aeroallergens in a South African urban children population cohort. *J Allergy Asthma Clin Immunol*. 2019;52(6):571-575.

35. Pefura-Yone EW, Mbela-Onana CL, Balkissou AD, et al. Perennial aeroallergens sensitisation and risk of asthma in African children and adolescents: a case-control study. *J Asthma*. 2015;52(6):571-575.

36. Gruzieva O, Gehring U, Aalberse R, et al. Meta-analysis of air pollution exposure association with allergic sensitization in European birth cohorts. *J Allergy Clin Immunol*. 2014;133(3):767-776 e767.

37. Koet LBtM, Brand PLP. Increase in atopic sensitization rate among Dutch children with symptoms of allergic disease between 1994 and 2014. *Pediatr Allergy Immunol*. 2018;29(1):78-83.

38. Chen Y, Wang H, Wong GWK, Zhong N, Li J. Allergen sensitization affected the change trend of prevalence of symptoms of rhinitis co-existing with wheeze among adolescents in Guangzhou City from 1994 to 2009. *Pediatr Allergy Immunol*. 2017;28(4):340-347.

39. Salam N, Azam S. Prevalence and distribution of soil-transmitted helminth infections in India. *BMC Public Health*. 2017;17(1):201.

40. Parija SC, Chidambaram M, Mandal J. Epidemiology and clinical features of soil-transmitted helminths. *Trop Parasitol*. 2017;7(2):81-85.

41. de Jong AB, Dikkeschel LD, Brand PL. Sensitization patterns to food and inhalant allergens in childhood: a comparison of non-sensitized, monosensitized, and polysensitized children. *Pediatr Allergy Immunol*. 2011;22(2):166-171.

42. Raciborski F, Bousquet J, Bousquet J, et al. Dissociating polyclonality and multiformity in children and adults from a Polish general population cohort. *Clin Allergy*. 2019;9:4.

43. Liu X, Zheng P, Zheng SG, et al. Co-sensitization and cross-reactivity of Blomia tropicalis with two Dermatophagoides species in Guangzhou, China. *J Clin Lab Anal*. 2019;33(9):1-8.

44. Castro Almarales RL, Mateo Morejon M, et al. Correlation between skin tests to Dermatophagoides pteronyssinus, Dermatophagoides siboney and Blomia tropicalis in Cuban asthmatics. *Allergol Immunopathol (Madr)*. 2006;34(1):23-26.

45. Andriappan AK, Puan KJ, Lee B, et al. Allergic airway diseases in a tropical urban environment are driven by dominant mono-specific sensitization against house dust mites. *Allergy*. 2014;69(4):501-509.

46. Katomichelakis M, Danielsies G, Illou T, et al. Allergic sensitization prevalence in a children and adolescent population of northeastern Greece region. *Int J Pediatr Otorhinolaryngol*. 2016;89:33-37.

47. Charpin D, Ramadour M, Lavaud F, et al. Climate and allergic sensitization to airborne allergens in the general population: data from the French six cities study. *Int Arch Allergy Immunol*. 2017;172(4):236-241.

48. Boulet LP, Turcotte H, Laprise C, et al. Comparative degree and type of sensitization to common indoor and outdoor allergens in subjects with allergic rhinitis and/or asthma. *Clin Exp Allergy*. 1997;27(1):52-59.

49. Ha RK, Baek JH, Lee SY, et al. Association of polysensitization, allergic multimorbidty, and allergy severity: a cross-sectional study of school children. *Int Arch Allergy Immunol*. 2016;171(3-4): 250-260.

50. Gabet S, Just J, Couderc R, Bousquet J, Seta N, Moma S. Early polysensitization is associated with allergic multimorbidity in PARIS birth cohort infants. *Pediatr Allergy Immunol*. 2016;27(8):831-837.

51. Miller JD. The role of dust mites in allergy. *Clin Rev Allergy Immunol*. 2019;51(3):312-329.

52. Jeevarathnum AC, van Niekerk A, Green RJ, Becker P, Masekela M. Prevalence of Blomia tropicalis allergy in two regions of South Africa. *S Afr Med J*. 2015;105(7):567-569.

53. Kim J, Hahm MI, Lee SY, et al. Sensitization to aeroallergens in Korean children: a population-based study in 2010. *J Korean Med Sci*. 2011;26(9):1165-1172.

54. Sarpong SB, Hamilton RG, Eggleston PA, Adkinson NF Jr. Socioeconomic status and race as risk factors for cockroach allergen exposure and sensitization in children with asthma. *J Allergy Clin Immunol*. 1996;97(6):1393-1401.

55. Salo PM, Arbes SJ Jr, Jaramillo R, et al. Prevalence of cockroach allergy in the United States: results from the National Health and Nutrition Examination Survey (NHANES) 2005–2006. *J Allergy Clin Immunol*. 2014;134(2):350-359.

56. Zakzuk J, Mercado D, Bornacelly A, et al. Hygienic conditions influence sensitization to Blomia tropicalis allergenic components: results from the FRAAT birth cohort. *Pediatr Allergy Immunol*. 2019;30(2):172-178.

57. Olmedo O, Goldstein IF, Acosta L, et al. Neighborhood differences in exposure and sensitization to cockroach, mouse, dust mite, cat, and dog allergens in New York City. *J Allergy Clin Immunol*. 2011;128(2):284-292 e287.

58. Karshima SN. Prevalence and distribution of soil-transmitted helminth infections in Nigerian children: a systematic review and meta-analysis. *Infect Dis Poverty*. 2018;7(1):69.

59. Adams VJ, Markus MB, Adams JF, et al. Paradoxical helminthiasis and giardiasis in Cape Town, South Africa: epidemiology and control. *Afr Health Sci*. 2005;5(3):276-280.
60. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors. 2014;7:37.

61. Anim-Baidoo I, Narh CA, Oddei D, et al. Giardia lamblia infections in children in Ghana. Pan Afr Med J. 2016;24:217.

62. Forson AO, Arthur I, Olu-Taiwo M, Glover KK, Pappoe-Ashong PJ, Ayeh-Kumi PF. Intestinal parasitic infections and risk factors: a cross-sectional survey of some school children in a suburb in Accra, Ghana. BMC Res Notes. 2017;10(1):485.

63. Tumwine JK, Kekitiinwa A, Nabuкеere N, et al. Cryptosporidium parvum in children with diarrhea in Mulago Hospital, Kampala, Uganda. Am J Trop Med Hyg. 2003;68(6):710-715.

64. Quihui-Cota L, Morales-Figueroa GG, Valverde-Duarte A, Ponce-Martínez JA, Valbuena-Gregorio E, López-Mata MA. Prevalence and associated risk factors for Giardia and Cryptosporidium infections among children of northwest Mexico: a cross-sectional study. BMC Public Health. 2017;17(1):852.

65. Squire SA, Ryan U. Cryptosporidium and Giardia in Africa: current and future challenges. Parasit Vectors. 2017;10(1):195.

66. Feary J, Britton J, Leonardi-Bee J. Atopy and current intestinal parasite infection: a systematic review and meta-analysis. Allergy. 2011;66(4):569-578.

67. Vaca M, Cooper PJ, Cortés AA, et al. Comparison of cytokine responses in Ecuadorian children infected with giardia, ascaris, or both parasites. Am J Trop Med Hyg. 2017;96(6):1394-1399.

68. Obeng BB, Amoah AS, Larbi IA, et al. Schistosome infection is negatively associated with mite atopy, but not wheeze and asthma in Ghanaian school children. Clin Exp Allergy. 2014;44(7):965-975.

69. Rujeni N, Nausch N, Bourke CD, et al. Atopy is inversely related to schistosome infection intensity: a comparative study in Zimbabwean villages with distinct levels of Schistosoma haematobium infection. Int Arch Allergy Immunol. 2012;158(3):288-298.

70. Flohr C, Tuyen LN, Lewis S, et al. Poor sanitation and helminth infection protect against skin sensitization in Vietnamese children: a cross-sectional study. J Allergy Clin Immunol. 2006;118(6):1305-1311.

71. Endara P, Vaca M, Chico ME, et al. Long-term periodic anthelmintic treatments are associated with increased allergen skin reactivity. Clin Exp Allergy. 2010;40(11):1669-1677.

72. Flohr C, Tuyen LN, Quinnell RJ, et al. Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam. Clin Exp Allergy. 2010;40(1):131-142.

73. Lynch N, Hagel I, Perez M, Diprisco M, Lopez R, Alvarez N. Effect of anthelmintic treatment on the allergic reactivity of children in a tropical slum. J Allergy Clin Immunol. 1993;92(3):404-411.

74. Stein M, Greenberg Z, Boaz M, Handzel ZT, Meshesha MK, Bentwich Z. The role of helminth infection and environment in the development of allergy: a prospective study of newly-arrived Ethiopian immigrants in Israel. PLoS Negl Trop Dis. 2016;10(1):e0004208.

75. Staal SL, Hogendoorn SKL, Voets SA, et al. Prevalence of atopy following mass drug administration with albendazole: a study in school children on Flores Island, Indonesia. Int Arch Allergy Immunol. 2018;177(3):192-198.

76. van den Biggelaar AH, van Ree R, Rodrigues LC, et al. Decreased atopy in children infected with Schistosoma haematobium: a role for parasite-induced interleukin-10. Lancet. 2000;356(9243):1723-1727.

77. Mpaiwe H, Amoah AS. Parasites and allergy: observations from Africa. Parasite Immunol. 2019;41(6):e12589.

78. Webb EL, Nampijja M, Kaweesa J, et al. Helminths are positively associated with atopy and wheeze in Ugandan fishing communities: results from a cross-sectional survey. Allergy. 2016;71(8):1156-1169.

79. Moncayo AL, Vaca M, Oviedo G, et al. Effects of geohelminth infection and age on the associations between allergen-specific IgE, skin test reactivity and wheeze: a case-control study. Clin Exp Allergy. 2013;43(1):60-72.

80. Hamid F, Wira AE, Wammes LJ, et al. Risk factors associated with the development of atopic sensitization in Indonesia. PLoS One. 2013;8(6):e67064.

81. Souza VM, Sales IR, Peixoto DM, et al. Giardia lamblia and respiratory allergies: a study of children from an urban area with a high incidence of protozoan infections. J Pediatr (Rio J). 2012;88(3):233-238.

82. Prisco MCD, Hagel I, Lynch NR, et al. Association between giardiasis and allergy. Ann Allergy Asthma Immunol. 1998;81(3):261-265.

83. Chakraborty S, Roy S, Mistry HU, et al. Potential sabotage of host cell physiology by apicomplexan parasites for their survival benefits. Front Immunol. 2017;8:1261.

84. Fenoy IM, Sánchez VR, Soto AS, Picchio MS, Martin V, Goldman A. Toxoplasma gondii infection modulate systemic allergic immune response in BALB/c mice. Exp Parasitol. 2015;154:47-50.

85. Summan A, Nejsum P, Williams AR. Modulation of human dendritic cell activity by Giardia and helminth antigens. Parasite Immunol. 2018;40(5):e12525.

86. Schulke S. Induction of interleukin-10 producing dendritic cells as a tool to suppress allergen-specific T helper 2 responses. Front Immunol. 2018;9:455.

87. Ayuk AC, Ramjith J, Zar HJ. Environmental risk factors for asthma in 13-14 year old children. Pediatr Pulmonol. 2018;53(11):1475-1484.

88. Asher MI, Montefort S, Björkstén B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-743.

89. Weinmayr G, Weiland SK, Björkstén B, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. Am J Respir Crit Care Med. 2007;176(6):565-574.

90. Arshad SH, Tariq SM, Matthews S, Hakim E. Sensitization to common allergens and its association with allergic disorders at age 4 years: a whole population birth cohort study. Pediatr. 2001;108(2):E33.

91. Simpson BM, Custovic A, Simpson A, et al. NAC Manchester Asthma and Allergy Study (NACMAAS): risk factors for asthma and allergic disorders in adults. Clin Exp Allergy. 2001;31(3):391-399.

92. Li J, Wang H, Chen Y, Zheng J, Wong GW, Zhong N. House dust mite sensitization is the main risk factor for the increase in prevalence of wheeze in 13- to 14-year-old schoolchildren in Guangzhou city, China. Clin Exp Allergy. 2013;43(10):1171-1179.

93. Gabet S, Ranciere F, Just J, et al. Asthma and allergic rhinitis risk depends on house dust mite specific IgE levels in PARIS birth cohort children. World Allergy Organ J. 2019;12(9):100057.

94. Davey G, Venn A, Belete H, Berhane Y, Britton J. Wheeze, allergic sensitization and geohelminth infection in Butajira. Ethiopia. Clin Exp Allergy. 2005;35(3):301-307.

95. Goncalves JP, Nobrega CGO, Nascimento WRC, et al. Cytokine production in allergic and Trichuris trichiura-infected children from an urban region of the Brazilian northeast. Parasitol Int. 2020;74:101918.

96. Cooper PJ, Chico ME, Vaca MG, et al. Effect of early-life geohelminth infections on the development of wheezing at 5 years of age. Am J Respir Crit Care Med. 2018;197(3):364-372.

97. Guangorena-Gomez JO, Maravilla-Dominguez A, Garcia-Arenas G, et al. Modulation of the immune response by infection with Cryptosporidium spp. in children with allergic diseases. Parasite Immunol. 2016;38(8):468-480.
98. Jouvin MH, Kinet JP. Trichuris suis ova: testing a helminth-based therapy as an extension of the hygiene hypothesis. *J Allergy Clin Immunol*. 2012;130(1):3-10; quiz 11-12.

**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

**How to cite this article:** Brandt O, Wegenstein B, Müller I, et al. Association between allergic sensitization and intestinal parasite infection in schoolchildren in Gqeberha, South Africa. *Clin Exp Allergy*. 2022;52:670–683. doi:10.1111/cea.14100