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

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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

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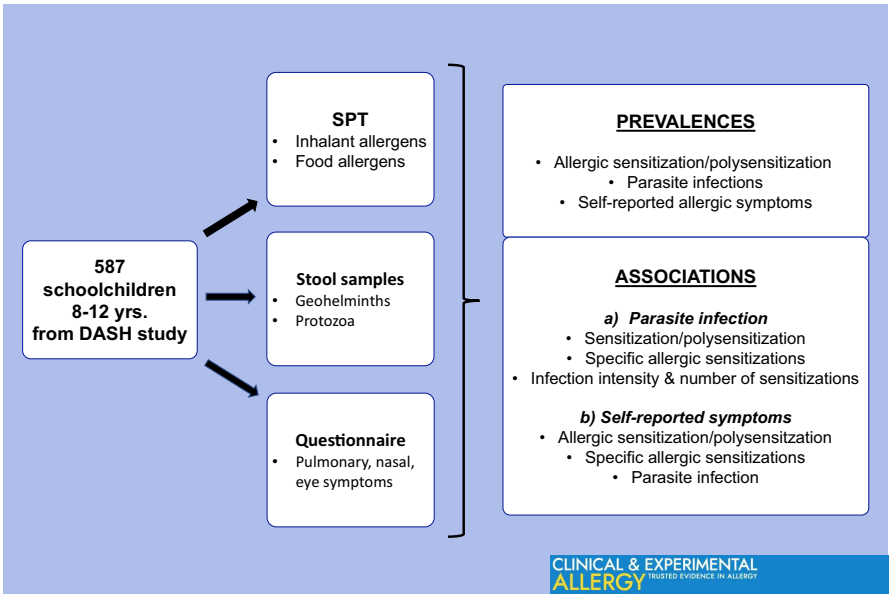
associations were not significant when adjusted for false discovery. Geohelminth infection and intensity of geohelminth infection were both associated with reduced risk of polysensitization (OR 0.41, 95% CI 0.21–0.86), and this association remained significant with adjustment for false discovery. Reported respiratory symptoms were associated with HDM sensitization (ORs from 1.54 to 2.48), but not with parasite infection.

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.

1 | INTRODUCTION

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.[1] The socio-economic changes related to urbanization and rapid industrialization, resulting in a "westernized" lifestyle, are assumed to be responsible for this phenomenon.[2–5] Accordingly, several studies from different African regions recently reported high prevalence of atopic diseases[6,7] ranging from 7.2% to 54.1%.[8] As the onset of atopic disorders commonly occurs early in life, children are particularly affected[9,10] and frequently develop comorbidities, e.g., recurrent sinusitis and nasal polyps, which have a significant impact on their quality of life.[11–13]

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

The most common allergens in sub-Saharan Africa are grass pollen, but house dust mite (HDM) and cockroaches have greatest clinical relevance.[14] In a Ghanaian study examining schoolchildren, both HDM and cockroaches were found to be risk factors for the development of asthma.[15] 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.[16,17]

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.[18–20] 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[21,22] or rather suppress their development.[23,24] 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.[25,26]

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[27,28]). 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[29] with standardized allergen extracts (ALK-Abelló, Hørsholm, Denmark): HDM mix containing *Dermatophagoides* (*Der*) *pteronyssinus* and *farinae*, *Blomia tropicalis* (*Blo*), *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.[30] 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.[31] Additionally, stool samples were screened for the protozoans *Cryptosporidium* spp. and *Giardia intestinalis* using the Crypto-Giardia Duo Strip® 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[32] (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).

TABLE 1 Demographic data and sensitization prevalences

Girls	303 (51.6%)
Boys	281 (47.9%)
Missing sex/age/descent	3 (0.5%)
Age, median (IQR)	11.0 (10.5–11.6)
Body mass index, median (IQR)	17.2 (15.7–19.3)
Ethnicity	
Black	317 (54.0%)
Mixed, black/white descent	241 (41.1%)
Other (Indian, other mixed ethnicities)	26 (4.4%)
Allergic sensitization	
Sensitized	237/587 (40.4%)
Monosensitized	81/237 (34.2%)
Polysensitized	156/237 (65.8%)

Abbreviation: IQR, interquartile range.

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 *Cryptosporidia* (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

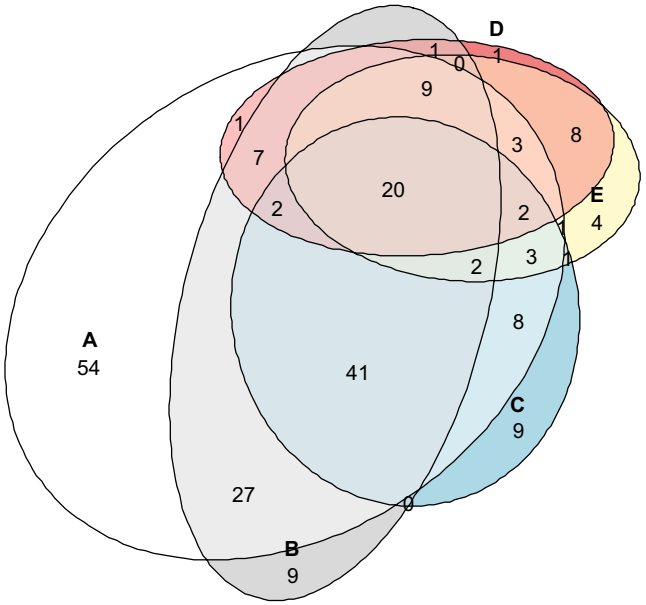


FIGURE 1 Euler-Venn diagram illustrating the overlap of the five major atopic sensitizations: A.) *Dermatophages* spp., B.) *B. tropicalis*, C.) cockroach, D.) grass mix and E.) *Bermuda grass*. The subsets of children with A, B, C, D and E, respectively, are represented by ellipses. Figures within the intersection areas indicate the numbers of children with the respective combinations of sensitizations, with the sizes of the intersection areas roughly proportional to these numbers. For instance, there were 20 children with all 5 sensitizations and 41 children sensitized to *Dermatophages* spp., *B. tropicalis* and cockroach, but to none of the grass allergens. Three combinations could not be represented: A&B&E without C and D ($n = 4$), A&C&D without B and E ($n = 3$) and B&C&D&E without A ($n = 1$)

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).

TABLE 2 Prevalence of stool parasites and infection intensities

Stool parasites	
Any stool parasite	206 (35.1%)
Helminth infection	157 (26.7%)
A. lumbricoides monoinfection	47 (8.0%)
T. trichiura monoinfection	45 (7.6%)
Double infection	65 (11.1%)
T. trichiura	110 (18.7%)
Light (1–999 EPG)	94 (16.0%)
Moderate (1000–9999 EPG)	16 (2.7%)
Heavy (≥10,000 EPG)	0 (0.0%)
A. lumbricoides	112 (19.1%)
Light (1–4999 EPG)	69 (11.8%)
Moderate (5000–49,999 EPG)	37 (6.3%)
Heavy (≥50,000 EPG)	6 (1.0%)
Protozoa	82 (13.9%)
Giardia intestinalis antigen positive	50 (8.5%)
Cryptosporidia spp. antigen positive	37 (6.3%)

Abbreviation: EPG, eggs per gram

Regarding monosensitization and polysensitization (Table 4), children with parasite infection were significantly less likely polysensitized (OR 0.47, 95%-CI 0.25–0.86, $p = 0.014$), and this association was stronger, albeit not significantly, for *T. trichiura* infection (OR: 0.47, 95%-CI 0.20–1.08, $p = 0.08$) than for *A. lumbricoides* (OR 0.66, 95%-CI 0.29–1.48, $p = .31$).

However, none of these associations remained statistically significant after adjustment for false discovery.

3.4 | Helminth infection severity and number of sensitizations

While no dose–response relationships were found for any vs. no sensitization, light helminth infection was associated with a nonsignificant decreased risk of polysensitization (OR 0.48, 95%-CI 0.21–1.08, $p = .08$), whereas moderate/severe infections were associated with a significantly reduced probability of polysensitization (OR 0.14, 95%-CI 0.04–0.48, $p = .002$) (Table 5), a finding that remained significant even after false discovery rate (FDR) adjustment. For association of the two helminth species and the intensity of infection with the number of sensitizations, see Supplementary Material.

3.5 | Associations between allergic sensitizations and protozoa infections

In participants exclusively infected with protozoa, we found an inverse association with allergic sensitization (OR 0.44, 95%-CI 0.22–0.88, $p = .06$ after FDR adjustment). However, they were not less likely to be polysensitized (OR 0.87, 95%-CI 0.25–3.06).

TABLE 3 Estimated adjusted associations of infections with sensitization to specific allergens

	Parasite infection		Helminth infection[1]		*A. lumbricoides*[2]		*T. trichiura*[3]		Protozoa[4]	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Aeroallergens										
Any aeroallergen	0.74 (0.51–1.08)	.12	0.89 (0.54–1.47)	.66	0.68 (0.33–1–42)	.31	0.50 (0.22–1.18)	.11	0.44 (0.22–0.88)	.02
Der	0.65 (0.43–0.96)	.03	0.69 (0.41–1.15)	.15	0.73 (0.34–1.55)	.41	0.26 (0.08–0.78)	.02	0.48 (0.23–1.00)	.05
Blo	0.54 (0.33–0.89)	.02	0.46 (0.25–0.87)	.02	0.44 (0.16–1.20)	.11	0.08 (0.01–0.64)	.02	0.55 (0.24–1.29)	.17
Cockroach	0.64 (0.36–1.13)	.12	0.72 (0.37–1.41)	.34	0.66 (0.24–1.85)	.43	0.60 (0.19–1.87)	.38	0.30 (0.09–1.01)	.05
Bermuda grass	0.50 (0.24–1.03)	.06	0.55 (0.21–1.45)	.23	0.65 (0.18–2.34)	.51	0.45 (0.09–2.18)	.32	0.47 (0.14–1.60)	.22
Grass mix	0.76 (0.38–1.52)	.44	1.14 (0.47–2.80)	.77	1.32 (0.42–4.12)	.63	0.44 (0.08–2.34)	.34	0.51 (0.15–1.76)	.29
Mould mix	0.23 (0.03–2.05)	.19	0.00 (0.00–1.36)	.13*	0.00 (0.00–4.30)	.61*	0.00 (0.00–5.10)	1.00*	0.83 (0.10–6.70)	.86
Cat dander	0.84 (0.34–2.09)	.71	0.76 (0.21–2.71)	.67	0.57 (0.07–4.67)	.60	0.00 (0.00–2.30)	.39*	1.14 (0.32–4.05)	.84
Dog dander	0.75 (0.20–2.80)	.67	0.66 (0.12–3.66)	.63	0.00 (0.00–4.30)	.61*	1.48 (0.15–15.0)	.74	0.71 (0.08–5.90)	.75
Food allergens										
Any food allergen	0.52 (0.23–1.19)	.12	0.75 (0.31–1.81)	.52	0.93 (0.26–3.26)	.91	1.21 (0.34–4.31)	.77	0.24 (0.03–1.84)	.17
Peanut	0.42 (0.12–1.50)	.18	0.42 (0.09–1.92)	.26	1.17 (0.25–5.47)	.84	0.00 (0.00–3.20)	.62*	0.58 (0.07–4.60)	.61
Cow`s milk	0.35 (0.07–1.66)	.19	0.65 (0.13–3.20)	.60	0.00 (0.00–3.90)	.61*	1.23 (0.15–10.5)	.58	0.00 (0.00–3.12)	.62*
Hen`s egg	0.59 (0.06–5.80)	.65	0.91 (0.09–9.58)	.93	0.00 (0.00–14.7)	1.00*	6.17 (0.51–75.2)	.15	0.00 (0.00–11.9)	1.00*
Wheat	0.00 (0.02–146)	1.00*	3.09 (0.04–243)	.43	9.74 (0.12–767)	.18*	0.00 (0.00–437)	1.00*	0.00 (0.00–303)	1.00*
Soy	0.00 (0.00–2.80)	.30*	0.00 (0.00–4.70)	.58*	0.00 (0.00–14.7)	1.00*	0.00 (0.00–17.3)	1.00*	0.00 (0.00–11.9)	1.00*
Cod fish	0.44 (0.10–2.07)	.30	0.72 (0.15–3.42)	.67	0.91 (0.11–7.56)	.93	1.11 (0.13–9.54)	.92	0.00 (0.00–3.12)	.62*

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.

TABLE 4 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			
b.) Helminths	1.07 (0.68–1–68)	.77	582	0.96 (0.58–1.57)	.87	502
Protozoa	0.63 (0.37–1.05)	.08				
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	414
Protozoa	0.62 (0.37–1.04)	.07		0.44 (0.22–0.88)	.02	428
II. Polysensitization vs. monosensitization						
a.) Any parasite	0.47 (0.25–0.86)	.014	232			
b.) Helminths	0.41 (0.21–0.78)	.007	232	0.34 (0.17–0.64)	.003	207
Protozoa	1.24 (0.49–3.11)	.65				
c.) *A. lumbricoides*	0.66 (0.29–1.48)	.31	232	0.50 (0.16–1.61)	.24	171
T. trichiura	0.47 (0.20–1.08)	.08		0.37 (0.10–1.37)	.14	168
Protozoa	1.14 (0.46–2.86)	.77		0.87 (0.24–3.13)	.84	170

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.

TABLE 5 Estimated adjusted association of helminth infection severity with sensitization in general and polysensitization

	Helminths		*A. lumbricoides*		*T. trichiura*	
Infection severity	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Sensitized vs. nonsensitized						
Light	0.89 (0.52–1.54)	.69	0.98 (0.43–2.26)	.97	0.49 (0.20–1.20)	.12
Moderate/severe	1.14 (0.54–2.44)	.73	0.27 (0.06–1.29)	.10	2.67 (0.23–31.5)	.43
Polysensitization vs. monosensitization						
Light	0.48 (0.21–1.08)	.08	0.76 (0.21–2.77)	.67	0.63 (0.14–2.81)	.54
Moderate/severe	0.14 (0.04–0.48)	.002	n.a.		n.a.	

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 whistling 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, $p = .006$). 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. tropicals* 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 symptoms and parasitic infections (Tables S4 and S5). While we were unable to detect any risk reduction in children infected with helminths, protozoa 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 parasites. We found that about 40% were sensitized to at least one allergen 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 protozoa 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.[4] 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.[34,35] European cohort studies found prevalences between 34.8% and 47.9% for children aged 8–10 years,[36] with even higher rates reported in studies from The Netherlands[37] and the Chinese city of Guangzhou.[38] Although such studies can only be compared to a limited extent,[39,40] 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,[41,42] 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 monosensitized 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.[43–45] In a study from northeastern Greece, where climatic conditions are similar to those in Ggeberha, 60% of the children exhibiting allergic sensitizations were polysensitized, with *Der* being the most prevalent allergen.[46] 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 significantly more likely to be sensitized to HDM but also exhibited significantly more frequent polysensitizations.[47] 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.[48–50]

Differences in the prevalence of HDM sensitization across geographical regions are well known. As proliferation and survival of HDM depend on adequate humidity (maximal at relative humidity of 75%[51]), sensitization rates are highest in regions with a tropical and/or maritime climate.[52] Consistent with this, studies found that high HDM concentrations in damp homes[17] and poor hygienic and socioeconomic living conditions were positively associated with HDM and cockroach sensitization.[53–57] As such an exposure is likely to be of relevance in our population due to their poor living conditions, 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. lumbricoides* 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.[58,59] However, it clearly exceeds the average global rates (*A. lumbricoides* 14.5% and *T. trichiura* 8.3%) as described by Pullan et al.[60] Infections with the protozoans *G. intestinalis* and/or *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%)[61,62] and Uganda (8.5%),[63] respectively, but numbers vary widely in the literature.[64,65]

The immune modulatory effects of parasites on the development of sensitization and allergies have been studied intensively. In their meta-analysis, Feary et al.[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,[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 *Der*, *Blo*, *Bermuda grass* and cockroach. Moreover, stratification for the two helminths showed that *T. trichiura* decreased the odds for sensitization in general, as well as the probability for sensitization to the HDMs *Der* and *Blo*, whereas *A. lumbricoides* markedly decreased the SPT reactivity to *Blo* only. Similar observations of such a selective effect were made in cross-sectional studies from Ghana[68] and Zimbabwe,[69] which demonstrated negative associations between infections with *Schistosoma mansoni* and *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 *A. lumbricoides*.[70]

Interestingly, in two surveys,[71,72] increased SPT reactivity was reported after successful antihelminthic therapy, which particularly affected *Der* in those studies exploring the influence on individual allergens. While Lynch et al.[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 helminth infections, found a doubling of the number of SPT reactivity to *Der* spp. (and additionally to grass and olive tree pollen) after successful eradication treatment.[74] Staal et al.[75] recently investigated the outcome of mass drug administration of albendazole in Indonesian schoolchildren in an area endemic for *T. trichiura*, *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 *Der. pteronyssinus*, whereas no significant change was observed for *Der. farinae* or cockroaches. The reason for this phenomenon is obscure. It is, however, conceivable that constant exposure to high concentrations of a specific HDM/*Der* antigen(s) is a prerequisite for effective induction of immunomodulatory mechanisms in individuals whose immune systems have already been deviated by chronic helminth infection towards a protolerogenic network involving regulatory T and B cells as well as high levels of the anti-inflammatory cytokine IL-10.[76] Stimulation by cross-reactive allergens, such as tropomyosin (*Der p10*) and glutathione S-transferase (GST), which occur both in helminths and in *HDM* and cockroaches,[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 helminths, which should be validated by future studies. Our hypotheses, though, do not explain why we also found a reduced sensitization risk for *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.[42,53] Although similar observations were reported in the abovementioned Israeli study,[74] our data must be interpreted with caution, as only 10% of children were sensitized to *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 helminth infection and SPT reactivity.[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.[70,72,80] In our investigations, both light and moderate/severe infections with helminths were negatively associated with polysensitization, while moderate/severe infections with *A. lumbricoides* markedly lowered the odds of being sensitized to an allergen. No such effect was detectable for *T. trichiura*, which is most likely due to the low number of children ($n = 3$) who were exclusively infected with this helminth and who had moderate/severe infections. Indeed, Rodriguez et al.[18] found that severe *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 *G. intestinalis* and/or *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.[81,82] In our literature review, we did not find any studies investigating the relationship between *Cryptosporidium* infections and allergic sensitizations. However, several studies have described an inverse relationship between infections with *Toxoplasma gondii*, which is closely related to *Cryptosporidium* spp.,[83] and atopic sensitization both in humans and in animal models.[26,84] For both protozoa, however, induction of IL-10 synthesis in the host organism has been described. Furthermore, Summan et al.[85] recently reported that *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,[86] this could be a possible link to the reduced sensitization risk observed in our study.

4.3 | Self-reported symptoms and allergic sensitizations

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.[87–89] As part of the ISAAC II study, Weinmayr et al.[89] 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 allergen 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 Ethiopia[94] and a study from Brazil exclusively investigating children with *T. trichiura* and those without helminth infections as controls.[95] Cooper et al.,[96] 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 be chance findings, we additionally performed false discovery rate adjustments, revealing that the positive associations of "Wheezing and whistling" with *B. tropicalis* 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.[98] 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.

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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; IM and BW managed data entry and prepared the database; statistical analysis was done by CS; NDL and BW contributed to data analyses. OB interpreted the study data with the support of CS and wrote and edited the manuscript; SM, AAN, IM, CW, BW, MG and JU provided comments on the drafts.

DATA AVAILABILITY STATEMENT

Data will be made available on request from the authors.

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SUPPORTING INFORMATION

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

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