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The South African Food Sensitisation and Food Allergy population-based study of IgE-mediated food allergy: validity, safety, and acceptability

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ABSTRACT

Background: Few studies exist on food sensitization and challenge-proven food allergy in low- and middle-income countries.

Objective: To describe the study design and methodology to recruit infants from an African population for skin prick testing and oral food challenges and the use of preliminary data to investigate the extent to which the study sample is representative of the target population.

Methods: Children 12 to 36 months old were recruited from childcare education facilities in Cape Town. Children underwent skin prick testing to foods. Those with a reactive wheal of at least 1 mm larger than the negative control and not clearly tolerant according to history to a full age-appropriate portion to at least 1 food underwent oral food challenges. Parents who chose not to participate completed a nonparticipant questionnaire. Interim analysis of at least 500 respondents was performed. Demographic features of participating children were compared with those of nonparticipants and the population demographics of the most recent Cape Town census data.

Results: The response rate was 60.1%, with high participation and completion rates of 96.5% and 97.5%, respectively. Demographics of the completed participant sample were similar to those of the Cape Town census. Use of a nonrespondent questionnaire indicated no selection bias in favor of increased participation of participants with allergy. No ethnic differences in sensitization or food allergy were evident.

Conclusion: The study was safe and feasible and the recruitment was effective and representative of the target population. Future studies will aim to increase the precision of the prevalence of food sensitization and allergy, describe environmental risk factors, and include a rural black African cohort.

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Introduction

Epidemiologic data on food allergy (FA) is predominantly from high-income countries.¹ Reports suggest there could be a "second wave" of the allergy epidemic, with FAs increasing in a similar fashion, albeit a few decades later, as other allergic diseases (allergic rhinitis, eczema, and asthma).²

Studies on FA have a high degree of heterogeneity because of small-sample studies, selection bias, varying response rates,

differential reports of FA, inconsistent FA definitions, and differences in data analysis.³ Many studies have based FA on self-reports and few have used objective measurements such as oral food challenges (OFCs) to diagnose FA.^{4–6} This leads to an overestimation of FA, with estimates varying from 20% to 35%.^{7–9} However, recent findings in children younger than 5 years have reported that prevalence varies from 1% to 2% to higher than 10% based on OFC-confirmed IgE-mediated FA.^{10–12}

In South Africa, an increase in respiratory allergies has been reported similar to that in high-income countries but following it by several years.¹³ There also are differences in the prevalence of respiratory allergy, eczema, and aeroallergen sensitization among different ethnic and socioeconomic groups that might reflect diverse environmental exposures, genetic influences, or epigenetic phenomena.¹⁴ Studies performed in Africa have reported food sensitization (FS) rates or FA rates based on questionnaire surveys mostly in selected populations.^{15,16} There are no data on the point prevalence of FS and OFC-proven FA in unselected African populations.

Food allergy is considered rare in South Africa especially in the black African population; however, the documented increase in respiratory allergy in this population (in rural and urban settings), believed to be associated with changes in living environment (including urbanization), could indicate a similar increase in FS and IgE-mediated FA.¹⁷

Therefore, there is a need to determine the prevalence of FS and FA in young South African children and to compare this with global measurements. The authors report on the methodology and interim analysis of the broader South African Food Sensitisation and Food Allergy (SAFFA) study of unselected 12- to 36-month-old children in Cape Town to determine the preliminary prevalence of FS and challenge-proven IgE-mediated FA, accurately assess power calculations for the parent study, and determine its feasibility.

Methods

Design and Setting

This was a cross-sectional study conducted from February 2013 to December 2014 in childcare education facilities (CCFs) in the Cape Town metropolis. Participants recruited from CCFs were assessed using a questionnaire and skin prick test (SPT) results and, if they qualified, were invited to the Red Cross Hospital Paediatric Allergy Clinic (RCHPAC) for further investigations.

Sampling Frame

From an online database of Cape Town CCFs registered by the provincial department of social development, a random sequence of numbers was generated using Excel (Microsoft, Redmond, Washington) and 150 CCFs were selected. Of these, 63 were contactable, had eligible children, and agreed to participate. Once a CCF agreed to host a study day, the parents or legal guardians of eligible children 12 to 36 months old were invited to participate. Enrollment was curtailed once a predetermined number for feasibility evaluation and interim analysis of at least 500 participants was achieved. Participants who responded to the study invitation but decided not to participate or who could not complete the study were considered nonparticipants. In the broader SAFFA study, it is envisaged that sampling from this frame will continue until a sample of 1,200 participants is achieved.

Recruitment and Assessment

Participants were assessed by the study team with a standardized allergy questionnaire¹⁸ and a general physical examination for signs of eczema, hay fever, and asthma. The questionnaire included information on history of other allergic diseases, family history of

allergy, number of siblings, family position, tobacco smoke exposure during pregnancy and postnatally, infant feeding patterns including breastfeeding duration, exposure to unpasteurized milk, exposure to domestic or farm animals, antibiotics, paracetamol, immunizations, and past infections. Nonparticipants completed a shortened questionnaire with questions on demographics, history of other allergic diseases, and family history of allergy to assess whether those declining the offer to participate differed from study participants.

Respondents (participants and nonparticipants) were asked about the history of their child's current or past comorbid allergy using modified from the International Study of Asthma and Allergies in Childhood¹⁹ for self-reported asthma, eczema, and allergic rhinitis. Respondents who answered in the affirmative were recorded as their child having "caregiver-reported comorbid allergic conditions." Children were examined for clinical signs of comorbid allergic conditions (atopic dermatitis, allergic rhinitis, and asthma) whether or not they had caregiver-reported comorbid allergic conditions. Children with clinical signs were designated as "clinically confirmed comorbid allergy." Children who met the criteria of these 2 groups were designated as "any form comorbid allergy."

Skin Prick Test

The SPTs were performed using standardized solutions from ALK-Abelló (Thermo Fisher; Hørsholm, Denmark) and ALK lancets to egg white extract, peanut, cow's milk, wheat (flour), soy, hazelnut, fish (cod), and positive (10 mg/mL of histamine) and negative (saline) controls. In addition, modified SPTs for egg, milk, and peanut were performed using raw egg white, fresh cow's milk, and fresh peanut butter. The skin on the forearm was pricked with a drop of the extract. The SPT results were read at 15 minutes and recorded as average wheal diameter in millimeters.

Indications for OFCs

Participants who had tolerated a full age-appropriate food portion (within 1 month) with no history of any reaction to that food were considered tolerant irrespective of whether the SPT result was reactive. All participants with any level of sensitization (SPT wheal ≥ 1 mm larger than the negative control) for whom tolerance was not clearly reported by clinical history (or had never ingested the food) were eligible for a food challenge, even if a reaction had been reported unless such a reaction was recent (<6 months for peanut and <2 months for all other allergens) and severe (according to World Allergy Organization criteria for anaphylaxis)²⁰ and the participant had SPT reactive wheals larger than previously published 95% positive predictive values (PPVs; >24 months old: milk ≥ 8 mm, egg ≥ 7 mm, peanut ≥ 8 mm; <24 months old: milk ≥ 6 mm, egg ≥ 5 mm, peanut ≥ 4 mm).²¹

Oral Food Challenges

Challenges were performed as open incremental oral challenges at the RCHPAC using a standardized protocol adapted from the Australian HealthNuts study (egg and peanut),¹⁸ the PRACTALL guidelines (hazelnut),²² and the RCHPAC (milk, soy milk, fish, and wheat)²³ by adding lower initial doses as suggested by the European Academy of Allergy and Clinical Immunology guidelines.²⁴ The dosing schedule was 0.1, 0.5, 1.0, 2.0, 5.0, 10, and 20 mL for egg¹⁸; 0.1, 0.5, 1, 5, 10, 20, 40, and 100 mL for milk and soy milk²³; smear on the lip, 1/16, 1/8, 1/4, 1/2, and 1 teaspoon for peanut butter¹⁸; 10 mg, 0.25, 0.5, 2, 5, 10, and 30 g for fish²³; 10, 20, and 70 mg, 0.2, 0.7, 2.2, 7.3, and 22 g for hazelnut (crushed)²²; and 10 mg, 0.5, 1, 2, 5, 10, and 20 g for wheat.²³ Cumulative doses of the native food and protein were 38.6 mL and 4.8 g for egg, 176.6 mL and 6.5 g for milk, 176.6 mL and 5.0 g for soy, 9.7 and 2.8 g for peanut butter,

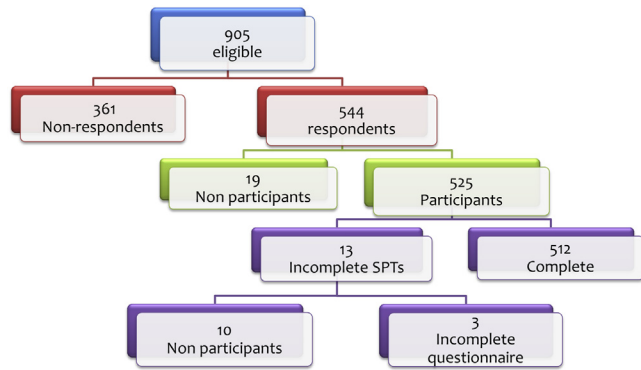


Figure 1. Flow chart detailing the status of the study population. SPTs, skin prick tests.

47.8 and 7.6 g for fish, 32.5 and 4.7 g for hazelnut, and 38.5 and 5.5 g for wheat, respectively. After the initial dose, the challenge food was given in gradual increments every 15 minutes.

Predetermined objective criteria for a positive reaction comprised 1 of the following: at least 3 concurrent noncontact hives (urticarial lesions) lasting longer than 5 minutes, perioral or periorbital angioedema, vomiting (excluding gagging or vomiting immediately after ingestion), or evidence of circulatory or respiratory compromise within 2 hours of the last dose within the food challenge.¹⁸ Other less specific signs of allergic reactions were recorded but not used to terminate food challenges, including (but not restricted to) transient urticaria (<3 hives lasting <5 minutes), erythema, diarrhea, and any of following lasting longer than 3 minutes: abdominal pain, persistent rubbing of eyes or nose, persistent rhinorrhea, and persistent scratching. Participants were observed for a minimum of 2 hours after a negative challenge reaction. Participants with a positive challenge reaction were treated by the protocol according to the severity of the reaction and observed for 4 hours. Participants with indeterminate challenge reactions (who refused or were unable to complete a challenge) were scheduled for a repeat challenge.

After a negative challenge reaction, parents were advised to give a full age-appropriate portion as a single serving on the following day and report any reactions at consumption. The participant's family was contacted by telephone 48 to 72 hours after the challenge to enquire about delayed symptoms. Participants with FA were referred for ongoing care by the authors' allergy service.

Definitions of FS and FA

Correlation with sensitization was assessed at 3 "cutoff" levels, with participants in the higher levels also included in the counts of the lower-level categories.

Any (low-level) sensitization: at least 1 SPT reaction with a wheal at least 1 mm larger than the negative control.

Moderate-level sensitization: at least 1 SPT reaction with a wheal at least 3 mm larger than the negative control.

High-level sensitization: at least 1 SPT reaction with a wheal at least 7 mm larger than the negative control.

IgE-mediated FA: any sensitization and a positive food challenge reaction OR a history of a recent (<6 months for peanuts and <2 months for other allergens) anaphylactic reaction with an SPT reactive wheal larger than the previously published 95% PPV.

Ethics

This study was approved by the University of Cape Town's Faculty of Health Sciences Human Research Ethics Committee (reference number HREC REF: 497/2013). Written informed consent was obtained from the parent or guardian for participation and food challenges.

Data Entry and Statistical Analysis

The data were entered into a Microsoft Access database by the authors and cleaned using pivot tables before being exported to STATA 11.1 (Stata Corp, College Station, Texas) for analysis. Statistical tests were performed according to whether the variable was continuous or categorical. Because most of the data were categorical, the χ^2 test or Fisher exact test and the Z test were used to test for a statistical difference between variables and proportions, respectively. A P value less than or equal to .05 was considered statistically significant.

Results

The sample for interim analysis of 544 responding children was achieved from a total possible pool of 905 eligible children (60.1% response rate). The remaining children were not at the CCF on the study day or parents had not responded to invitations to the study days. There was a high participation rate among the responders of 96.5% (525 of 544), and 19 responders completed the nonparticipant questionnaire. Of those who participated, the completion rate of having SPTs after the questionnaire was 97.5% (512 of 525). Of those who did not have SPTs (13), 10 had filled in the questionnaire and were considered additional nonparticipants (Fig 1).

The completed study population consisted of 512 participants with a median age of 27 months (interquartile range 21–32 months). More than half (268 of 512, 52.3%; 95% confidence interval [CI] 48.0–56.7) were boys. There was no significant difference between participants and nonparticipants regarding a history of a first-degree relative (ie, mother, father, and siblings) with asthma (93 of 512 vs 6 of 29, $P = .73$), hay fever (181 of 512 vs 7 of 29, $P = .22$), eczema (89 of 512 vs 4 of 29, $P = .62$), FA (17 of 512 vs 1 of 29, $P = .97$), or any allergy (243 of 512 vs 10 of 29, $P = .17$).

Table 1
IgE-mediated food allergy and food sensitization patterns

Food tested	Prevalence sensitization SPT reactive wheal						Positive OFC result, n	IgE-mediated food allergy prevalence, % (95% CI)
	Any sensitization (≥ 1 mm)		≥ 3 mm		≥ 7 mm			
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI		
Overall	63 (12.3)	9.4–15.2	49 (9.6)	7.0–12.1	23 (4.5)	2.7–6.3	13	2.5 (1.4–4.3)
Any egg	53 (10.4)	7.7–13.0	35 (6.8)	4.6–9.0	19 (3.7)	2.1–5.4	9	1.8 (0.6–2.9)
Any peanut	33 (6.4)	4.3–8.6	18 (3.5)	1.9–5.1	9 (1.8)	0.6–2.9	6	1.2 (0.2–2.1)
Any cow's milk	33 (6.4)	4.3–8.6	14 (2.7)	1.3–4.2	2 (0.4)	0–0.9	1	0.2 (0–0.6)
Soy	14 (2.7)	1.3–4.2	5 (1.0)	0.1–1.8	0		0	—
Wheat	12 (2.3)	1.0–3.7	2 (0.4)	0–0.9	0		0	—
Fish	9 (1.8)	0.6–2.9	2 (0.4)	0–0.9	0		1	0.2 (0–0.6)
Hazelnut	9 (1.8)	0.6–2.9	3 (0.6)	0–1.2	1 (0.2)	0–0.6	0	—

Abbreviations: CI, confidence interval; OFC, oral food challenge; SPT, skin prick test.

Table 2
Sensitization and proven allergy status using skin prick test categories and ethnicity

	Any food			Any egg			Any peanut			Any cow's milk			Soy			Wheat			Fish			Hazelnut		
	n (%)	95% CI	n (%)	n (%)	95% CI	n (%)	n (%)	95% CI	n (%)	n (%)	95% CI	n (%)	n (%)	95% CI	n (%)	n (%)	95% CI	n (%)	n (%)	95% CI	n (%)	n (%)	95% CI	
Black African (n = 246)	≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm		≥1 mm	
	≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm		≥3 mm	
	≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm		≥7 mm	
	OFC positive		OFC positive		OFC positive		OFC positive		OFC positive		OFC positive		OFC positive		OFC positive		OFC positive		OFC positive		OFC positive		OFC positive	
	32 (13.0)	9.1–17.9	31 (12.6)	8.7–17.4	20 (8.1)	5.0–12.3	16 (6.5)	3.8–10.3	7 (2.8)	0.7–4.7	1.2–5.8	5 (2.0)	0.4–4.1	1 (0.4)	0.0–2.2	0	0	0	0	0	0	0		
	25 (10.2)	6.7–14.6	21 (8.5)	5.4–12.8	11 (4.5)	2.3–7.9	4 (1.6)	0.4–4.1	4 (1.6)	0.0–2.6	0	0	0	0	0	0	0	0	0	0	0	0		
	12 (4.9)	2.5–8.4	11 (4.5)	2.3–7.9	6 (2.4)	0.9–5.2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	8 (3.3)	1.4–6.3	6 (2.4)	0.9–5.2	4 (1.6)	0.4–4.1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
Mixed ancestry (n = 211)	26 (12.3)	8.2–17.5	18 (8.5)	5.1–13.1	12 (5.7)	3.0–9.7	16 (7.6)	4.4–12.0	7 (3.3)	1.3–6.7	7 (3.3)	1.3–6.7	7 (3.3)	1.3–6.7	7 (3.3)	1.3–6.7	7 (3.3)	1.3–6.7	7 (3.3)	1.3–6.7	7 (3.3)	1.3–6.7		
	19 (9.0)	5.5–13.7	10 (4.7)	2.3–8.5	6 (2.8)	1.1–6.1	9 (4.3)	2.0–7.9	1 (0.5)	0.0–2.6	0	0	0	0	0	0	0	0	0	0	0	0		
	8 (3.8)	1.7–7.3	6 (2.8)	1.1–6.1	3 (1.4)	0.3–4.1	1 (0.5)	0.0–2.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
	3 (1.4)	0.3–4.1	1 (0.5)	0.0–2.6	2 (1.0)	0.1–3.4	1 (0.5)	0.0–2.6	0	0	0	0	0	0	0	0	0	0	0	0	0	0		
White (n = 55)	5 (9.1)	3.0–20.0	4 (7.3)	2–17.6	1 (1.8)	0.0–9.7	1 (1.8)	0.0–9.7	1 (1.8)	0.0–9.7	0	0	0	0	0	0	0	0	0	0	0	0		
	5 (9.1)	3.0–20.0	4 (7.3)	2–17.6	1 (1.8)	0.0–9.7	1 (1.8)	0.0–9.7	1 (1.8)	0.0–9.7	0	0	0	0	0	0	0	0	0	0	0	0		
	3 (5.5)	1.1–15.1	2 (3.6)	0.4–12.5	0	0	1 (1.8)	0.0–9.7	1 (1.8)	0.0–9.7	0	0	0	0	0	0	0	0	0	0	0	0		
	2 (3.6)	0.4–12.5	2 (3.6)	0.4–12.5	0	0	0	0.0–9.7	0	0.0–9.7	0	0	0	0	0	0	0	0	0	0	0	0		
P values (χ ² test)	.7 ^b		3 ^b		2 ^b		3 ^b		0		0		0		0		0		0		0		0	
	.9 ^b		3 ^a		.6 ^b		.6 ^b		.3 ^b		.3 ^b		.3 ^b		.3 ^b		.3 ^b		.3 ^b		.3 ^b		.3 ^b	
	.7 ^a		.7 ^a		.6 ^b		.6 ^b		.1 ^b		.1 ^b		.1 ^b		.1 ^b		.1 ^b		.1 ^b		.1 ^b		.1 ^b	
	.4 ^b		1 ^a																					

Abbreviations: CI, confidence interval; OFC, oral food challenge.

^aDifference nonsignificant by Fisher exact test.^bDifference nonsignificant by Pearson χ^2 test.**Table 3**

Sensitization and proven food allergy patterns by SPT level and comorbid allergy

	Any comorbid allergy (n = 245)		No comorbid allergy (n = 267)		P value ^a
	n (%)	95% CI	n (%)	95% CI	
SPT wheal ≥1 mm (n = 63)	45 (18.4)	13.7–23.8	18 (6.7)	4.0–10.4	<.0001
SPT wheal ≥3 mm (n = 49)	36 (14.7)	10.5–19.8	13 (4.9)	2.6–8.2	<.0001
SPT wheal ≥7 mm (n = 23)	19 (7.8)	4.7–11.8	4 (1.5)	0.4–3.8	.001
Food allergic (n = 13)	12 (4.9)	2.6–8.4	1 (0.4)	0–2.1	.001

Abbreviations: CI, confidence interval; SPT, skin prick test.

^aDifference significant by Pearson χ^2 test.

The study was comprised of participants from different parts of Cape Town with different ethnicities. The proportion of black African participants was 246 of 512 (48.1%), that of mixed-ancestry participants was 211 of 512 (41.2%), and that of white participants was 55 of 512 (10.7%). The distribution of participants in the study sample was similar to the 0- to 4-year-old population in the most recent Cape Town census of 2011 (black Africans, 48.1% vs 46.4%, $P = .71$; those with mixed ancestry, 41.2% vs 45.4%, $P = .48$; whites, 10.7% vs 8.2%, $P = .41$).

Sensitization Prevalence

Sixty-three participants (12.3%; 95% CI 9.5–15.2%) were sensitized to at least 1 food and 449 had negative reactions to all foods (87.7%). One child experienced a generalized urticarial rash after the SPT, which responded to antihistamines alone. Table 1 presents the prevalence of sensitization among the participants in categories of degree of sensitization (namely SPT reactive wheals ≥ 1 , ≥ 3 , and ≥ 7 mm). Overall, 12.3%, 9.6%, and 4.5% had a SPT reactive wheal of at least 1, at least 3, and at least 7 mm, respectively, to at least 1 of the 7 foods tested. Of the entire group, 31 of 512 (7.6%) were polysensitized, with 16 of 512 (3.1%) sensitized to 2 foods and 23 of 512 (4.5%) sensitized to at least 3 foods. Of those sensitized, 35 of 63 (55.6%) were tolerant to the foods by history and 28 of 63 (44.4%) underwent OFCs.

Spectrum of Sensitization

Levels of any (SPT reactive wheal ≥ 1 mm) and moderate-level (SPT reactive wheal ≥ 3 mm) sensitization were detectable in decreasing frequency to egg, peanut, cow's milk, soy, wheat (flour), hazelnut, and fish. Only 4 foods (hen's egg, peanut, cow's milk, and hazelnut) were detectable at high-level FS (SPT reactive wheal ≥ 7 mm) in decreasing frequency (Table 1).

Perceived FA

The rate of perceived FA was 7.4% because 38 of 512 participants reported having a prior reaction to at least 1 of the foods. The higher rate of perceived FA in nonparticipants than in participants (5 of 29, 17.2%, vs 38 of 512, 7.4%) was statistically significant ($P = .05$). Perceived fish allergy was present in 12 of 512 participants (2.3%), cow's milk allergy in 15 of 512 (2.9%), egg allergy in 8 of 512 (1.6%), peanut allergy in 5 of 512 (1.0%), soy in 2 of 512 (0.4%), and wheat in 1 of 512 (0.2%). There were no reports of anaphylactic reactions²⁵ within the past 6 months. Thus, no participants were excluded from food challenges based on a recent anaphylactic allergic reaction.

Prevalence of IgE-Mediated FA

Thirty-five of 63 sensitized participants were tolerant to the food by history and by eating a full age-appropriate portion of the relevant food. All participants who were sensitized and in whom tolerance had not been established by history or who had never

Table 4

Sensitization and proven food allergy patterns by skin prick test level and tertile age group

	12–23 mo (n = 177)		24–30 mo (n = 176)		31–36 mo (n = 159)		P value
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
SPT wheal ≥ 1 mm (n = 63)	28 (15.8)	10.8–22.0	15 (8.5)	4.8–13.7	20 (12.6)	7.9–18.8	.11 ^a
SPT wheal ≥ 3 mm (n = 49)	24 (13.6)	8.9–19.5	12 (6.8)	3.6–11.6	13 (8.2)	4.4–13.6	.08 ^a
SPT wheal ≥ 7 mm (n = 23)	14 (7.9)	4.4–12.9	1 (0.6)	0–3.1	8 (5.0)	2.2–9.7	.004 ^b
Food allergic (n = 13)	5 (2.8)	0.9–6.5	1 (0.6)	0–3.1	7 (4.4)	1.8–8.9	.05 ^c

Abbreviations: CI, confidence interval; SPT, skin prick test.

^aDifference nonsignificant by Pearson χ^2 test.^bDifference significant by Pearson χ^2 test.^cDifference significant by Fisher exact test.

ingested the food (28 of 63 sensitized) had an OFC. Challenge-proven IgE-mediated FA to any food was 2.5% (95% CI 1.2–3.9), to raw egg was 1.8% (95% CI 0.6–2.9), to peanut butter was 1.2% (95% CI 0.2–2.1), and to cow's milk and fish (hake) was 0.2% (95% CI 0–0.6). Three of the 28 participants (10.7%) undergoing food challenges experienced an anaphylactic reaction requiring adrenalin treatment.²⁰

Eight of 246 black African (3.3%), 3 of 211 mixed-ancestry (1.4%), and 2 of 55 white (3.6%) participants had challenge-proven IgE-mediated FA (Table 2). No participants were classified as having FA based on recent anaphylactic reactions with a SPT reactive wheal larger than previously described 95% PPVs.²¹

Sensitization and Ethnicity

Patterns of sensitization did not vary among the different ethnic groups. There were no significant ethnic differences at low, medium, and high levels of sensitization for any foods (Table 2). There was a larger proportion of multiply sensitized black African participants (20 sensitized to 1 food, 10 to 2 foods, and 13 to ≥ 3 foods) compared with the other ethnic groups combined (20 sensitized to 1 food, 6 to 2 foods, and 10 to ≥ 3 foods).

Although a larger proportion of black African participants had a cumulative SPT reactive wheal of at least 1 mm compared with the other ethnic groups, this did not achieve statistical significance ($P = .61$).

Sex and Sensitization

There was a small but statistically significant difference in the prevalence of low and medium levels of sensitization in boys (40 of 268, 14.9%, vs 33 of 268, 12.3%, $P = .05$) and girls (23 of 244, 9.4%, vs 16 of 244, 6.6%, $P = .03$), respectively, but at higher-level sensitization, this difference lost statistical significance. The higher rate of FA in boys also did not achieve statistical significance.

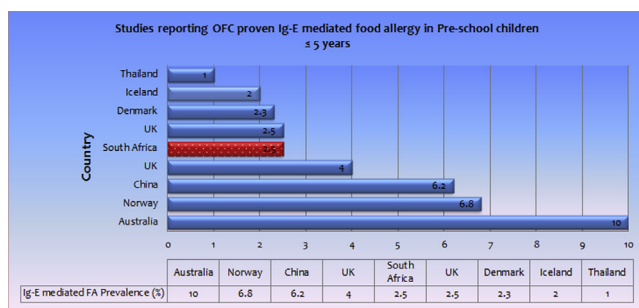


Figure 2. Summary of IgE-mediated food allergy (FA) proved by oral food challenges (OFCs) from studies that have data for children younger than 5 years.^{3,11,29–33}

Comorbid Allergy and Prevalence of Sensitization

Two hundred forty-nine of 512 (48.6%), 238 of 512 (46.5%), and 113 of 512 (22.1%) participants had any comorbid allergy, caregiver-reported comorbid allergy, and clinically confirmed comorbid allergy, respectively. Sixty-nine of 512 (13.5%), 135 of 512 (26.4%), and 134 of 512 (26.2%) were classified as caregiver-reported any asthma, any hay fever, and any eczema, respectively. There was no significant difference between participants and nonparticipants regarding their caregiver report of asthma (69 of 512 vs 5 of 29, $P = .57$), hay fever (135 of 512 vs 9 of 29, $P = .58$), eczema (134 of 512 vs 7 of 29, $P = .80$), or any allergy (238 of 512 vs 16 of 29, $P = .36$).

Of those with any SPT reactive wheal of at least 1 mm, 45 of 63 (71.4%) had any comorbid allergy (43 of 63 caregiver reported and 22 of 63 clinically confirmed). Participants with any comorbid allergy had higher rates of all levels of sensitization and of challenge-proven FA compared with those without comorbid allergies (Table 3).

Sensitization by Tertile Age Groups

There was no significant difference in low and medium level of sensitization according to age tertiles; however, at the 2 extremes of age, there was a statistically significant higher rate of high-level FS ($P = .001$) and FA ($P = .05$; Table 4).

Discussion

This is the first study in Africa to investigate the prevalence of FS and IgE-mediated FA in an unselected community through a sampling frame of CCFs and using formal food challenges to characterize the allergic status of participants. The authors delineated the interim rates of FS and IgE-mediated FA in the study population.

In this population-based sample, a large proportion of parents approached in a community setting agreed to participate. To assess selection bias in individual study participation, a nonparticipant questionnaire was administered. Most of those who chose not to participate did not have time owing to work commitments. The stronger history of FA in nonparticipating than in participating children and the similar rates of comorbid atopy in participating and nonparticipating children make it unlikely that selection bias had an effect on participation rates.

Because these participating children were not patients and most parents had not reported a previous allergic reaction, the authors anticipated that the completion rate might be lowered by the need to travel for food challenges to the RCHPAC on at least 1 occasion. Participants who attended the clinic for challenges did so for a median of 2 visits. However, the extremely high completion rate indicates that the study is feasible and the methodology is acceptable to participants.

The ethnic distribution of the preset sample was similar to that reported in the most recent Cape Town population census of 2011, indicating that the sample is representative of the source

population. Using CCFs rather than health care facilities ensured that health-seeking behavior did not influence the sample. However, children not at CCFs were excluded and factors affecting the likelihood of CCFs being registered with the department of social development, having contact details on the register, and consenting to be part of the study could contribute to selection bias. In poorer communities, there is likely to be a higher registration of CCFs because subsidies are given by the department of social development for such CCFs; however, some of these CCFs had incorrect contact details or were inaccessible. If they were contactable, then CCFs from poorer communities often agreed to participate, possibly owing to unmet needs in health provision and the perception that they would benefit from having physicians and nurses visit the CCF. The CCFs in more affluent communities had reliable contact details but were less likely to agree to participate and often had a poorer response rate from parents. These factors resulted in a sample that reflects a good representation from all areas.

A potential limitation of the study is that open food challenges were performed instead of double-blinded, placebo-controlled food challenges; however, predetermined objective symptoms were used to define a positive result, and the use of open OFCs in infants is much less likely to be confounded by psychosomatic reactions than in older groups.²⁶ A strength of the study is that all participating children with any level of sensitization who had not tolerated the food in the previous month were challenged to assess FA rather than using previously described SPT cutoff values with high PPVs for food reactions as a surrogate for proven food allergy. Internationally derived 95% PPVs derived from specialty centers in which children have a history of food allergy and/or have atopic dermatitis might not be applicable in an unselected cohort in Africa. In this sample, all subjects with FA were diagnosed based on a food challenge.

Because sensitization is a continuous variable and levels of sensitization that have high PPVs for food reactions differ according to the food and the population studied, 3 levels of sensitization were analyzed. The prevalence of any sensitization to at least 1 of the common allergic foods was 12.3% (highest for egg, peanut, cow's milk, and soy). The prevalence of FS at the 3-mm level (9.6%) is much higher than what has been previously observed in older unselected populations in South Africa²⁷ and Ghana²⁸ at 5.4% and 5%, respectively.

South Africa appears to have among the lower levels of challenge-proven FA reported, with data from unselected populations confirmed by food challenges being in the range of 1% to 10%.¹¹ The 2.5% prevalence rate of FA in the present population is similar to that reported in unselected cohorts in Thailand (1%),²⁹ Denmark (2.3%),³⁰ and Iceland (2%)³¹ (Fig 2).^{3,11,29–33} At this preliminary analysis, the CIs for FS and FA are wide; however, a sample of 1,200 will increase the precision of these estimates, making the CIs narrower.

Immunoglobulin E-mediated FA and FS have been considered rare in the black African population, but there is a suggestion of an emergence of allergies in this group as reported by a recent study showing high rates of FS and FA in black African children with atopic dermatitis.³⁴ These results confirm the impression that FS and FA are no longer less common in urbanized black African children. Indeed, black African participants had a larger proportion of multiple sensitizations and larger cumulative SPT reactive wheals compared with the other ethnic groups; however, this did not achieve statistical significance. Further studies will be conducted in a rural black African cohort to assess the influence of the rural environment.

In this study, high-level FS and challenge-proven FA were more common at the 2 extremes of age. This might be because egg allergy was more prevalent in the younger group (median age of children with egg OFC positive reaction 22 months) and peanut allergy in

the older group (median age of children with peanut OFC positive reaction 32.5 months).

Comorbid allergy was strongly associated with FS and IgE-mediated FA. With documented increases in the prevalence of other allergic conditions (allergic rhinitis, eczema, and asthma) in the South African context mimicking the global trend of the first wave of allergy,¹³ there is potential for an increase in the complexity and severity of FA as the allergy epidemic advances.

This study provides preliminary data on the community prevalence of IgE-mediated FA in South African children 12 to 36 months of age. The study was safe and feasible and recruitment was effective in this setting. The projected sample of 1,200 respondents in the larger SAFFA study is sufficient to determine the prevalence of FS and FA in an unselected population with a high degree of precision.

This stage of the study did not detect an expected lower rate of FS or FA in black African participants. The second phase of the study will focus on describing the modifiable and unmodifiable environmental and exposure-related risk factors for FA and will be expanded to include a rural black African cohort.

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