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Daily egg intake may reduce sensitisation to common allergenic foods among six- to nine-month-old south African infants: A randomized controlled trial

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Abstract

Background: This study aimed to investigate sensitization to eggs and other common allergenic foods, allergic symptoms, and fatty acid status among infants after introducing daily eggs as a complementary food for 6 months.

Methods: This secondary analysis used data from a randomized controlled trial of 500 infants aged 6–9 months in Jouberton, South Africa, who were randomly assigned to receive one egg daily, $n = 250$ (treatment) or no egg, $n = 250$ (control) for 6 months. Clinical allergy symptoms were assessed with the Childhood Allergy and Immunology Research questionnaire. Infants were tested with a skin prick test for egg sensitization at baseline and at the end of the study for additional food allergens. The fatty acid composition was analyzed in whole blood at the endpoint.

Results: At the endpoint, egg sensitization was 1.9% in the egg intervention group and 2.0% in the control group (aOR 0.936 [95% CI 0.229, 3.822]; $p = .926$) and all foods sensitization was 7.5% in the egg intervention group and 12.9% in the control group (aOR 0.515 [0.264, 1.005]; $p = .052$). There were no reported acute egg-related allergy symptoms at baseline and midpoint in the two groups. The incidence of allergic disease during the study was 7.5% in the egg intervention group and 13.4% in the control group (aOR = 0.545 [95% CI: 0.283, 1.048]; $p = .069$). The total and long-chain polyunsaturated fatty acid omega-6/omega-3 ratios were higher in the intervention group ($\beta = .173$ [0.291, 2.898], $p = .021$ and $\beta = .198$ [0.149, 0.902], $p = .007$) with no effect on omega-3 fatty acid composition.

Conclusion: Complementary feeding with daily eggs may reduce overall allergic sensitization to common allergenic foods.

KEYWORDS
allergy, complementary feeding, eggs, fatty acids, infants, sensitisation

1 | INTRODUCTION

Globally, pediatric allergic diseases are on the rise, especially in low- and middle-income countries, as reported by the Global Asthma Network (GAN) Phase 1.[1] A survey among children (6–7 years) and adolescents (13–14 years) between 2015 and 2020 in 25 countries reported that over 9.1% of children (6–7 years) had asthma, 7.7% had rhino-conjunctivitis, and 5.9% had eczema.[2] In Sub-Saharan Africa, the prevalence of allergic diseases is increasing.[3] Food allergies are an emerging second wave of allergies for children due to modern lifestyles.[4] The exact burden of food allergies is hard to ascertain because of differences in geographical areas, the population studied, methodologies used, allergens tested, and definitions used to determine food allergies, and many other factors affecting their prevalence.[5] Generally, a rate of food allergies of up to 10% has been reported, but that is increasing in both developed and developing countries.[5–9] In developing regions, food allergies are underrecognized, with suboptimal diagnosis and management.[10,11]

South Africa is undergoing a so-called "food allergy epidemic" because of economic transition and the adoption of modern lifestyles and diets.[12] A large food allergy study involving 1200 children aged 12–36 months reported higher food sensitisation rates in urban areas (9.0%) compared to rural areas (2.8%), and 2.5% of urban children had challenge-proven food allergies.[13] In 2014, a study involving 100 children aged 6 months to 10 years with atopic dermatitis reported almost half of the children with challenge-proven food allergies.[14] A pediatric anaphylaxis study conducted between 2014 and 2016 involving 73 children under 14 years admitted at a South African public children's hospital, reported about 95% of admitted children with severe allergic reactions, had a known food trigger, of which the most common trigger was peanuts at 30.1%, followed by hen's eggs at 21.2%.[15]

Egg allergy is the most common food allergy in South Africa, with a prevalence of 1.9% for raw eggs.[13] A study done in 2014 at a Cape Town pediatric hospital among 100 children between 6-month- to 10-year-old children found that egg allergy was highest in children with atopic dermatitis, with about 54% sensitized to eggs and 25% having confirmed egg allergy.[16] About 50% of children with an egg allergy usually have a spontaneous resolution by two to 9 years.[6] In South Africa, 72.2% of children with an egg allergy outgrew their allergy by 5 years.[17]

Eggs introduced in the infants' diet between four to 6 months have been associated with a 40% lower risk of egg allergies (relative risk 0.60, 95% CI 0.44–0.82, $p = .002$) in a systematic review of six randomized controlled trials.[18] The Healthnuts study, although it was an observational study, also found a reduced risk of egg allergy confirmed by oral challenge with the early introduction of eggs between four to 6 months.[19] However, a previous randomized controlled trial in Ecuador, the first study that introduced one egg daily to infants from a low socioeconomic community between the ages of six and nine months for a period of 6 months, found no effect on egg allergy symptoms during the follow-up period.[20] Likewise, a randomized controlled trial in Australia found no effect of the early introduction of eggs between the ages of 4 and 6 months on the risk of egg allergy at 1 year.[21]

Key message

Early introduction of eggs during infancy may reduce allergic sensitization to common allergenic foods. These results provide evidence to incorporate the introduction of allergenic foods, such as eggs, into infants' diets before 1 year into the South African infant feeding guidelines to improve food diversity and minimize the risk of sensitization to these foods.

Long-chain polyunsaturated fatty acids (LCPUFA), especially n-3 LCPUFA, are important in alleviating allergic reactions by modulating inflammatory responses.[22–24] Diets rich in oily fish and fish oil, the main source of omega-3 LCPUFA, are not consumed in adequate amounts in most complementary diets in low-income countries.[25,26] In South Africa, a low consumption (17%) of energy-dense animal products like eggs, meat, and fish was reported among 6- to 12-month-old infants.[27] However, since eggs are readily available and affordable, they can be an alternative source of n-3 LCPUFA, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). A randomized controlled trial in Ecuador reported improved DHA status in daily egg consumers.[28] In the USA, infants who consumed eggs in their complementary diets had a higher fatty acid status, including DHA, compared to non-egg consumers.[29]

The Eggcel-growth study was a randomized controlled trial that hypothesized that daily egg consumption for 6 months would improve linear growth (primary outcome) among infants aged six to 9 months in a low socioeconomic community. The main finding was the lack of intervention effect on growth.[30] To address a secondary objective, we investigated sensitization to eggs and other allergenic foods including cow's milk, fish, wheat flour, soya flour, peanuts, and corn flour, allergic symptoms, and assessed arachidonic acid (AA), DHA, EPA, and total n-6 and n-3 LCPUFA status among infants after introducing one egg per day as a complementary food for 6 months.

2 | METHODS

2.1 | Study procedure and outcomes

The design and primary outcomes of the trial have been described in detail elsewhere.[30] In summary, the study took place in the peri-urban area of Jouberton, located within the greater Matlosana Municipality in Klerksdorp, South Africa, from 16th February 2021 to 21st December 2021. Infants aged six to 9 months with no severe illnesses requiring hospitalization, weight-for-length Z-scores >−3, hemoglobin >7 g/dL, no congenital abnormalities, or known allergies/sensitivities to eggs were included in the study. Additionally, mothers/caregivers/legal guardians above the age of 18 years or not planning to relocate

from the study area were also included. Participants were randomly allocated to two groups in a 1:1 ratio using a randomization sequence generated with the RANNOR function in SAS software version 9.4. A dataset consisting of 500 tags (250 for each group) was created. These tags were paired with a sequence of pseudo-random numbers generated from a normally distributed variable. The random numbers were then sorted to produce a randomized list of codes and tags, which was used by a research assistant to assign 250 participants to each group. The intervention group ($n=250$) received one chicken egg per day for 6 months, and the control group ($n=250$) did not receive eggs; both groups were followed up for 6 months. The intervention group received a dozen eggs weekly, seven eggs for the infant, and five eggs for the rest of the family, whereas the control household received 5 kg of maize flour monthly and four dozen eggs after the study as an incentive for participation in the study. The mothers were educated on egg preparation methods, and the eggs were prepared according to the mothers' choice of cooking method, usually boiled, fried, or scrambled. The mothers were also trained to cook the eggs well for denaturation of possible allergic proteins and to prevent possible undesirable microorganisms from surviving. The intervention group had a compliance form for recording when the eggs were given/not given, and this data was collected weekly by the fieldworkers. The study was not blinded to the participants because of the nature of the food intervention but was blinded to the enumerators who measured child anthropometric variables and dietary intake, the laboratory staff, and the data analyst.

Egg intake was neither promoted nor prohibited in the control group. An egg intake estimation was therefore calculated for all study participants regardless of group to further explore associations of actual egg intake with morbidity in the total sample. A weekly food frequency questionnaire (FFQ) conducted in both groups was used. It had four options: Every day, most days (4–6 days), once a week (1–3 days) and never. The options were scored as never=0; 1–3 days=2; 4–6 days=5; and every day=7, which was then multiplied by the number of eggs eaten at a time (usually one egg, but also ½ or 2 eggs) and by the number of times eaten per day (usually once or twice).

Information on the infants' birthdates, birth weight, and length was transcribed from the infant health booklet. The sociodemographic status, such as education, and mothers' age, were collected by the trained fieldworkers using a structured questionnaire at baseline. In addition, data on anthropometric status, dietary intake, and morbidity were collected. Breastfeeding data was recorded from a weekly FFQ. The Eggcel-growth study sample size powered for growth was described in detail elsewhere.[30]

2.2 | Allergy symptoms and sensitization outcomes

History of allergy diagnosis by a medical practitioner and clinical allergy symptoms including acute food reactions (hives, angioedema, anaphylaxis, acute abdominal pain, vomiting and/or diarrhea; tightness in the throat, difficulty breathing, wheezing and/or noisy breathing) and delayed symptoms (allergic cough, wheezing, eczema, allergic rhinitis, and enlarged or removal of adenoids and/or tonsils) were assessed at baseline (enrolment), midpoint (after 3 months of intervention) and endpoint (after 6 months of intervention) with the Childhood Allergy and Immunology Research (CAIR) questionnaire.[31]

All infants were tested for egg allergen sensitization with a skin prick test (SPT) at baseline. The food allergens were procured from ImmunoSpec Pty (Ltd) (Midrand, South Africa). A trained nurse and/or trained research assistant inquired if the mother had given any antihistamine in the past 2 days; for those infants who had not used antihistamines, a small amount of whole egg allergen extract was applied to the skin, either on the forearm or back, and then the skin was scratched to introduce the allergen. A positive control consisting of histamine and a negative control consisting of saline were placed alongside the allergen for comparison. The presence of a wheal (raised, reddened bump) of >3 mm at the test site indicated a positive reaction. Infants with a positive SPT were excluded from the study. Those who were enrolled in the study had the oral egg challenge done on the same day with a small amount of cooked egg given to the infant for consumption; the infants were monitored for allergy symptoms at the study site, and those who developed any signs of allergy were treated and excluded from the study. The mother/caregiver was then contacted on the second day to assess if the baby had any delayed reaction. The positive indication of clinical allergy symptoms together with a positive SPT confirmed egg allergy (no tolerance). A positive SPT without clinical symptoms confirmed sensitization with tolerance. However, since eggs were provided daily, which may cause tolerant sensitization to evolve into allergy, all babies with positive SPT to eggs were excluded. Babies who showed clinical symptoms of egg allergy during the study were tested again by SPT followed by an egg challenge test if positive. At the end of the study, the babies were tested again for egg sensitization, and mothers who consented to additional SPT had their infants tested for additional food allergens (cow's milk, cod fish, peanuts, wheat flour, soybean flour, maize flour) to determine if they were sensitized to any of those foods. The mothers received information and counseling on how to manage their sensitized/allergic baby and were referred to the pediatric clinic at the Department of Pediatrics at the Klerksdorp Hospital.

A child was classified as having allergic disease if diagnosed during the study (excluding baseline) by a medical practitioner and/or if the child was sensitized as assessed by SPT at the endpoint of the study in combination with having any acute or delayed allergy symptoms during the study.

2.3 | Whole blood dried blood spot fatty acid analysis

A trained nurse collected a capillary blood sample from a finger or heel prick at the endpoint. Two 50 µL volumes of whole blood were spotted on EDTA-soaked dried blood spot (DBS) cards (Lipomic Healthcare) immediately after collection and dried. Total lipid fatty acids were analyzed at the CEN NWU chromatography laboratory.[32] Briefly, one dried blood spot was punched from the DBS. The lipids were transmethylated with 2 mL methanol: sulfuric acid (95:5, v:v) by vortexing for 30 s and incubating at 70°C for 3 h to yield fatty acid methyl esters (FAMEs).

The resulting FAMEs were extracted with water and heptane. The sample was allowed to stand for a few minutes for the layers to separate. The supernatant containing FAMEs was extracted and aliquoted into a glass tube containing sodium sulfate to absorb any water and vortexed. The top heptane layer was then pipetted and aliquoted into a GC vial. FAMEs were analyzed with an Agilent Technologies 7890A gas chromatograph system equipped with an Agilent Technologies 7000B triple quad mass selective detector (Agilent Technologies). The gas chromatography separation of FAMEs was carried out on an HP88 capillary column (100 m × 0.25 mm × 0.20 mm; Agilent) by using helium as the carrier gas at a flow rate of 2.2 mL/min. The gas chromatography injector was held at a temperature of 270°C, and the mass spectrometry source at 250°C. The injection volume of the sample solution was 1 μL using a split ratio of 1:20. The oven temperature was programmed from 50°C to 170°C at 30°C/min, then from 170°C to 215°C at 2°C/min, and it rose at 4°C/min to 230°C. After that, the temperature was held isothermally at 230°C for 7 min. The total analysis time was 38.25 min. Mass spectrometry with 70 eV electron ionization was carried out in multiple reaction monitoring mode, with at least two transitions per compound. Quantification of FAME was done with Masshunter (B.06.00). FAME peaks were identified and calibrated against a standard reference mixture of 33 FAMEs (Nu-Check-Prep) and two single FAME standards (Larodan Fine Chemicals AB). Relative percentages of fatty acids were calculated by taking the concentration of a given fatty acid derivative as a percentage of the total concentration of all fatty acids identified in the sample, namely palmitic acid (16:0), palmitoleic acid (16:1n7), stearic acid (18:0), elaidic acid (18:1n9T), vaccenic acid (18:1n7T), oleic acid (18:1n9), vaccenic acid (18:1n7cis), linoleic acid (18:2n6), eicosanoic acid (20:0), gamma linolenic acid (18:3n6), alpha linolenic acid (18:3n3), eicosenoic acid (20:1n9), stearidonic acid (18:4n3), eicosadienoic acid (20:2n6), behenic acid (22:0), 20:3n3, dihomo-gamma-linolenic acid (20:3n6), mead acid (20:3n9), AA, erucic acid (22:1n9), EPA, lignoceric acid (24:0), docosatrienoic acid (22:3n3), nervonic acid (24:1n9), adrenic acid (22:4n6), osbond acid (22:5n6), docosapentanoic acid (22:5n3), and DHA. Total n-3 PUFA was calculated as the sum of alpha linolenic, stearidonic, 20:3n3, EPA, docosatrienoic, docosapentanoic, and DHA, and total n-3 LCPUFA as the sum of stearidonic, 20:3n3, EPA, docosatrienoic, docosapentanoic, and DHA. Total n-6 PUFA was calculated as the sum of linoleic, gamma linolenic acid, eicosadienoic, dihomo-gamma-linolenic, AA, adrenic, and osbond acid; and total n-6 LCPUFA as the sum of gamma linolenic acid, eicosadienoic, dihomo-gamma-linolenic, AA, adrenic, and osbond acid.

2.4 | Data analysis

Data was analyzed on an intention-to-treat basis, but for infants with missing data for allergy symptoms at midpoint or endpoint, the baseline data was considered in a per-protocol analysis. Baseline characteristics were described as counts and percentages for categorical data. Continuous data was described as median and 25th and 75th percentiles for non-normally distributed data and as mean with standard deviation for normally distributed data. Non-normally distributed data was log-transformed before statistical analysis. The effects of the intervention on allergy symptoms over the combined 6 months were assessed with multivariable logistic regression, adjusted for age and sex of the infant, baseline breastfeeding, and maternal age (years). Effects of the egg intervention at each time point were assessed using chi-square tests. Linear regression analysis, unadjusted and adjusted for age, sex, baseline breastfeeding, and maternal age, was performed to assess the association between the estimated egg intake, regardless of intervention group, with fatty acid status. $p < .05$ was considered significant for all inferential analyses.

2.5 | Ethical approval

Ethical approval was granted by the Health Research Ethics Committee of North-West University (NWU-00452-19-A1), and the study was registered on ClinicalTrials.gov (NCT05168085) on February 13, 2020. Goodwill permission was obtained from the South African National and Provincial Departments of Health, local clinics in the study area, and community leaders. Written informed consent was secured from all parents or legal guardians.

3 | RESULTS

Figure 1 shows the flow of participants during the study. Six infants were excluded from the study due to sensitisation to eggs. Out of the 446 infants who completed the study, endpoint SPT results for the egg were available for 415 (93%) and for 400 (90%) to other foods, as 15 infants' mothers/caretakers declined additional food tests at the endpoint. Table 1 shows the baseline characteristics of the infants and mothers by treatment group. Similar proportions of infants in the intervention group (58.0%) and the control group (55.2%) had previously consumed eggs or food containing eggs before the study. There was a high estimated adherence of 96.3% to daily egg intake by the egg group.[30] The egg group had a median weekly egg intake of 7 eggs, while the control group had 0.5 eggs.[33]

3.1 | Effect of 6 months egg intervention on reported allergy symptoms

Table 2 shows the effect of 6 months of egg intervention on egg allergy among six- to nine-month-old infants.

There were no reported acute egg-related allergy symptoms at baseline and midpoint in the two groups. At the endpoint, 2 (0.8%) of the participants in the intervention group reported itching around the mouth after eating an egg with spices, but no symptoms when eggs were provided subsequently without the spices. Mothers/caregivers reported acute reactions like itching around the mouth to fish (12 infants), fruit and vegetables (10 infants), spices (9 infants), infant cereals (9 infants), snacks (4 infants), milk and yoghurt (3 infants), chicken liver (1 infant), and cured meat (1 infant).

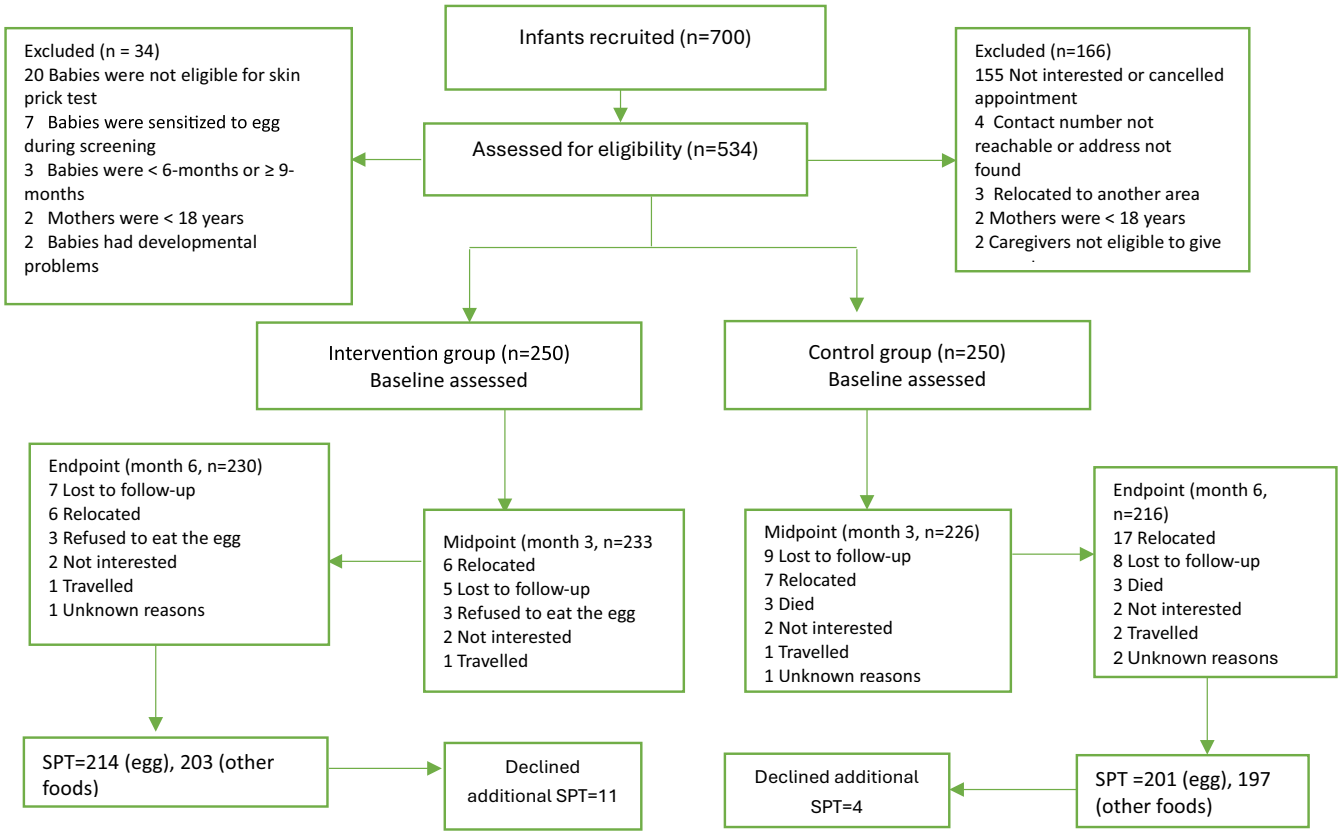

FIGURE 1 Flow diagram of participation through the randomized controlled trial during the 6 months intervention.

TABLE 1 Baseline characteristics of infants and their mothers by treatment group.

Characteristics	Egg group ($n=250$) n (%)	Control group ($n=250$) n (%)
Infant		
Age (months)	6.5 (6.1, 7.7)[a]	6.6 (6.1, 7.5)
Female	133 (53.2)	125 (50.0)
Baseline breastfeeding rate	151 (60.4)	157 (62.8)
Previous consumption of egg or food with egg	145 (58.0)	138 (55.2)
HIV exposure	75 (30.0)	78 (31.2)
Mother		
Age (years)	29 (23, 36)	27 (23, 33)
Married (legal or traditional)	34 (13.6)	22 (8.6)
Education (grade 10 or higher)	194 (77.6)	209 (83.6)

[a]Data reported as median (25th, 75th percentile), all such values.

3.2 | Effect of 6 months egg intervention on allergic sensitisation

Table 3 shows the effect of six months of egg intervention on allergic disease and sensitisation among six-nine-month-old infants. The incidence of allergic disease during the study was 7.5% in the egg intervention group and 13.4% in the control group (aOR = 0.545 [95% CI: 0.283, 1.048]; $p = .069$). At endpoint egg sensitisation was 1.9% in the egg intervention group and 2.0% in the control group (aOR = 0.936 (95% CI: 0.229, 3.822; $p = .926$). At the endpoint, sensitisation to all foods was 7.5% in the egg intervention group and 12.9% in the control group (aOR = 0.515 [95% CI: 0.264, 1.005]; $p = .052$). No sensitisation to eggs was found in infants who presented with potential allergy symptoms and were tested with SPT during the study, thus none of them were tested with an egg challenge test during the study.

TABLE 2 Effect of 6-month egg intervention on the number of 6- to 9-month-old infants with allergy symptoms.

	Baseline		Midpoint		Endpoint			
Allergy symptoms	**Egg (*n* = 250) *n* (%)**	**Control (*n* = 250) *n* (%)**	**Egg (*n* = 233) *n* (%)**	**Control (*n* = 226) *n* (%)**	**Egg (*n* = 230) *n* (%)**	**Control (*n* = 216) *n* (%)**	**Adjusted OR (95% CI)**	***p*-Value[a]**
Acute food allergy symptoms[b]	7 (2.8)	6 (2.4)	8 (3.4)	11 (4.9)	12 (5.2)	12 (5.6)	1.142 (0.623, 2.091)	.668
Acute egg allergy symptoms[b]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–	–
Delayed[c] allergy symptoms	53 (21.2)	51 (20.4)	49 (21.0)	48 (21.2)	67 (29.1)	61 (28.2)	1.101 (0.770, 1.576)	.598
Cough	9 (3.6)	5 (2.0)	20 (8.7)	14 (6.2)	31 (13.5)	30 (14.0)	1.311 (0.840, 2.047)	.233
Wheeze	4 (1.6)	5 (2.0)	5 (2.2)	4 (1.8)	6 (2.6)	3 (1.4)	1.554 (0.643, 3.753)	.382
Eczema	38 (15.2)	38 (15.2)	29 (12.6)	34 (15.0)	37 (16.1)	28 (13.0)	1.042 (0.704, 1.542)	.838
Runny nose/ sneezing	14 (5.6)	10 (4.0)	13 (5.7)	13 (5.8)	33 (14.3)	33 (15.3)	1.100 (0.709, 1.707)	.670
Adenoids/tonsilitis	0 (0.0)	0 (0.0)	2 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	0.581 (0.046, 5.647)	.507

Abbreviations: CI, Confidence interval; OR, Odds ratio.

[a]Effects of the intervention over the combined 6 months were assessed with multivariable logistic regression, adjusted for the age and sex of the infant, baseline breastfeeding, and maternal age (years). Effects of the egg intervention at each time point were assessed using chi-square tests, showing no significant differences. $p < .05$ was considered significant.

[b]Acute food allergy symptoms included symptoms occurring within 2 h of ingesting a food. Symptoms included swelling and itching of lips, hands or feet, itchy rash or welts (hives), swelling of any part of the body (angioedema); dizziness, passing out, collapse or pallor (anaphylaxis), acute abdominal pain, vomiting, diarrhea or tightness in the throat, difficulty breathing, wheezing and/or noisy breathing.

[c]Delayed allergy symptoms included persistent allergic cough, wheezing, and/or runny nose/sneezing without acute respiratory infection and/or eczema and/or enlarged or removed tonsils or adenoids.

TABLE 3 Effect of 6-month egg intervention on allergic disease and sensitisation among 6- to 9-month-old infants.

	Egg (*n* = 214) *n* (%)	**Control (*n* = 201) *n* (%)**	**Total (*n* = 415) *n* (%)**	**Adjusted OR (95% CI)**	***p*-Value**
Allergic disease	16 (7.5)	27 (13.4)	43 (10.4)	0.545 (0.283, 1.048)	.069
Sensitisation					
All foods	16 (7.5)	26 (12.9)	42 (10.2)	0.515 (0.264, 1.005)	**.052**
Egg[a]	4 (1.9)	4 (2.0)	8 (1.9)	0.936 (0.229, 3.822)	.926
Cod fish[b]	3 (1.5)	5 (2.5)	8 (2.0)	0.410 (0.086, 1.960)	.264
Wheat[b]	7 (3.4)	6 (3.0)	13 (3.3)	0.971 (0.310, 3.044)	.959
Maize[b]	2 (1.0)	5 (2.5)	7 (1.8)	0.213 (0.033, 1.385)	.106
Cow milk[b]	5 (2.5)	9 (4.6)	14 (3.5)	0.540 (0.175, 1.666)	.284
Peanut[b]	6 (3.0)	10 (5.1)	16 (4.0)	0.544 (0.191, 1.548)	.254
Soy[b]	3 (1.5)	8 (4.1)	11 (2.8)	0.334 (0.085,1.313)	.116

Note: Data were analyzed with multivariable logistic regression, adjusted for infant age and sex, baseline breastfeeding, and maternal age. $p < .05$ was considered significant and indicated in bold.

Abbreviations: CI, 95% confidence intervals; OR, odds ratios.

[a]Egg allergen – Intervention group – 214 infants tested; Control group – 201 infants tested.

[b]Other food allergens – Egg group – 203 infants tested; Control group-197 infants tested; 15 infants declined additional food allergen tests.

TABLE 4 Association of estimated egg intake regardless of group allocation with infant fatty acid status.

Fatty acid	Egg group ($n=89$)	Control group ($n=101$)	p^*	Standardized β (95% CI)	p^{**}
Linoleic acid (LA, C18:2n6)	22.43 ± 3.3d4	21.97 ± 3.24	.340	0.886 (0.327,1.482)	.210
Gamma-linolenic acid (GLA, C18: 3n6)[a]	0.04 (0.03, 0.07)	0.04 (0.03, 0.07)	.882	0.002 (−0.103,0.106)	.977
Alpha linolenic acid (ALA, C18:3n3)[a]	0.04 (0.02, 0.10)	0.04 (0.03, 0.08)	.355	0.062 (0.066,0.177)	.370
Arachidonic acid (ARA, C20:4n6)	7.12 ± 2.07	6.78 ± 2.27	.298	0.086 (−0.226,0.976)	.220
Eicosapentaenoic acid (EPA, C20:5n3)[a]	0.10 (0.06, 0.15)	0.11 (0.07, 1.58)	.633	−0.042 (−0.108,0.059)	.588
Docosahexaenoic acid (DHA, C22:6n3)	1.72 ± 0.77	1.75 ± 0.58	.755	−0.014 (−0.203,0.167)	.847
Total n-3 PUFA	2.37 ± 0.89	2.42 ± 0.67	.625	−0.029 (−0.267,0.177)	.691
Total n-3 LCPUFA	2.29 ± 0.90	2.36 ± 0.67	.554	−0.35 (−0.277,0.166)	.622
Total n-6 PUFA	31.41 ± 4.67	30.71 ± 4.42	.288	0.096 (−0.363,2.100)	.166
Total n-6 LCPUFA	8.93 ± 2.32	8.69 ± 2.37	.481	0.062 (−0.369,0.945)	.388
Total n-6 /n-3 PUFA ratio	14.92 ± 5.75	13.39 ± 3.13	**.021**	0.173 (0.291, 2898)	**.017**
Total n-6/n-3 LCPUFA ratio	4.31 ± 1.64	3.80 ± 0.93	**.007**	0.198 (0.149, 0.902)	**.006**

Note: Association of estimated egg intake irrespective of group allocation with fatty acid composition was analyzed using linear regression, *unadjusted and **adjusted for age, sex, baseline breastfeeding, and maternal age. Data reported as mean ± standard deviation (SD) or median (25th, 75th percentile). $p<.05$ was considered significant and indicated in bold. n-3: omega-3, n-6: omega-6.

Abbreviations: LCPUFA, long-chain polyunsaturated fatty acid; PUFA, polyunsaturated fatty acid.

[a]Non-normally distributed data was log-transformed.

3.3 | Effect of daily egg intake on whole blood fatty acid status

Table 4 shows the effect of daily egg intake on fatty acid status after six-month intervention period. The total whole blood n-6/n-3 PUFA and LCPUFA ratios were higher in the intervention group compared to the control group ($p=.017$ and $p=.006$). There was no effect of daily egg intake on omega-3 status.

4 | DISCUSSION

In this study, we hypothesized that providing one egg a day for 6 months would reduce sensitization to egg and other common allergenic foods, and egg-related allergy symptoms, as well as improve the fatty acid status among six- to nine-month-old infants from a low socioeconomic community in South Africa.

Our study showed that the overall sensitization to common foods, including egg, cod, wheat, cow's milk, maize, peanut, and soy, was 10.2% at ages 12–15 months. This figure closely aligns with findings from the South Africa Food Allergy (SAFFA) study, which reported a food sensitization rate of 9.0% among urban South African toddlers aged 12–36 months.[13] The present prevalence of food sensitization in our study is also consistent with rates observed in high-income countries.[7–9]

We observed sensitization to all foods tested after 6 months of follow-up tended to be lower in the intervention group compared to the control group. Although it was an observational study, a similar finding was reported among Taiwanese children introduced to allergenic foods, such as cow's milk, peanuts, and egg white, between six to 12 months. Specifically, for egg white, there was a significant reduction in sensitisation to other foods (cow's milk and peanut) at 12 months compared to those who did not consume eggs.[34] In addition, a Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study also reported that early introduction of allergenic foods, especially eggs, decreased the risk of sensitization to other tested foods as well (cow's milk and peanut) at 1 year.[35] The reason for this finding is unclear, but we speculate this might have been linked to other theories; for example, the leaky gut and altered gut microbiome associated with environmental enteric dysfunction (EED). Impaired intestinal permeability and gut microbiota disturbances have been linked to the development of food allergies.[36] Prolonged egg consumption for 35 weeks has been reported to enhance gut microbiota in children.[37] In our study, we postulated that the 26 weeks of egg consumption might have improved gut microbial diversity and a possible improvement of intestinal barrier integrity and hence reduced allergic sensitization and symptoms.

We report no significant differences in acute food allergy and egg allergy symptoms in the two groups. This is in agreement with a clinical trial in Ecuador where infants who had daily egg provision showed no evidence of increased egg allergy symptoms and sensitization and had similar egg-specific IgE levels in the egg and control groups.[38] Similarly, other trials that investigated the effect of egg consumption during the complementary feeding period on egg allergy displayed no significant differences in IgE-mediated egg allergy at 12 months.[21,39–41] In our study, there was a lower incidence of overall allergic disease in the egg group than in the control group, but it was not statistically significant. Though it was an observational study, Hua et al. reported the introduction of egg white and yolk in infancy before 12 months was associated with a lower risk of atopic dermatitis.[34] Other observational studies reported no significant

associations between the age of introduction of the egg during the complementary feeding period and allergic diseases. For example, Turati et al. found no significant association between the age of introduction of egg and atopic dermatitis at 24 months. Alma et al. found no significant association between the age of introduction of egg and allergic rhinitis at 4 years,[42] and Roduit et al. found no association between the age of egg introduction and asthma at 6 years.[43]

Furthermore, our study observed a rise in food allergy symptoms from baseline to endpoint, possibly attributable to increased exposure to various foods as infants matured. We did not exclude infants who were allergic to other foods apart from the egg. Although dietary diversity has been reported to be low in infants in South Africa,[44] egg consumption has been found to have the potential to improve dietary diversity in this population.[45,46]

Eggs are also a source of n-3 fatty acids that may exert protective properties against allergy.[47–49] We found whole blood n-6/n-3 PUFA and n-6/n-3 LCPUFA ratios were higher in the intervention group, with no remarkable effect on total n-3 fatty acids, EPA, and DHA. We did not find an increase in the DHA levels, as was reported in other studies.[28,29] This might be explained by the fact that the Ecuador study measured plasma DHA, and we used whole blood. The sensitivity to show changes in DHA status may differ between the different blood pools used. In addition, the eggs utilized in our study were not enriched with DHA, and the PUFA content of eggs is dependent on the chicken feeds, which normally provide n-6 (LA and oleic acid), and we speculate it is higher in South Africa due to high sunflower production. Although eggs contributed to both n-6 and n-3, the conversion of ALA to DHA may have been low in these infants, as reflected by the n-6/n-3 ratio. The possible high linoleic acid in infants' diets inhibits the conversion of ALA to n-3 LCPUFA.[50]

Our results contribute to available evidence reported from a pooled analysis of studies, which found the early introduction of eggs to infants between four to 6 months of age was associated with a reduced risk of egg allergy.[18] Numerous studies have also demonstrated the protective effects of the introduction of allergenic foods, such as milk and eggs, between four to 6 months against allergic conditions.[51–53] Consequently, many international food allergy prevention guidelines now recommend introducing well-cooked eggs and other allergenic foods into infants' complementary diets between four to 6 months of age to prevent the development of egg and food allergy.[54,55] However, the South African Infant and Young Child Feeding (ICYF) guidelines currently advocate for the introduction of solid foods from 6 months of age without providing a clear consensus on the timing for introducing allergenic foods.[56]

Our study had several strengths, including being a randomized controlled trial, which helped minimize the risk of potential confounders. SPT has a high sensitivity to screen for potential food allergies. Nonetheless, we also had limitations in this study. SPT only tests IgE-mediated allergies, and therefore non-IgE-mediated food allergies could have been missed. There were no food challenges at the intervention endpoint to confirm food allergies, including no egg challenges. Additionally, there might have been over-reporting of allergic cough and rhinitis symptoms due to confusion with respiratory symptoms, possibly infectious. Lastly, we did not analyze the fatty acid concentrations of the eggs used in the study.

In conclusion, our study provides additional evidence that early introduction of eggs in infancy may reduce overall allergic sensitization to common allergenic foods but has no effect on egg allergy symptoms. These results provide evidence to incorporate the early introduction of allergenic foods, such as eggs ideally between six to 9 months of age, into South African infant feeding guidelines to improve food diversification, which is low in this population and potentially mitigate the risk of food sensitization.

AUTHOR CONTRIBUTIONS

Regina Nakiranda: Conceptualization; methodology; project administration; writing – review and editing; writing – original draft; investigation; validation; data curation. **Linda Malan:** Conceptualization; methodology; supervision; resources; writing – review and editing; funding acquisition; investigation; data curation; project administration. **Hannah Ricci:** Conceptualization; investigation; writing – review and editing; project administration; methodology; validation. **Herculina S. Kruger:** Conceptualization; methodology; supervision; writing – review and editing; investigation; validation. **Arista Nienaber:** Writing – review and editing; validation; supervision. **Marina Visser:** Writing – review and editing; project administration; methodology; validation; investigation. **Cecile Cooke:** Methodology; investigation; writing – review and editing. **Cristian Ricci:** Formal analysis; software; validation; visualization. **Mieke Faber:** Conceptualization; investigation; methodology; funding acquisition; writing – review and editing; supervision; validation. **Cornelius M. Smuts:** Funding acquisition; investigation; conceptualization; methodology; validation; supervision; resources; writing – review and editing; project administration.

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CONFLICT OF INTEREST STATEMENT

None.

PEER REVIEW

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