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Egg Sensitisation, Allergy and Component Patterns in African Children with Atopic Dermatitis

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Running Title: Egg allergy in African children with AD

Material for electronic repository:

E1. Risk factors for egg allergy

E2. Epitope diversity and egg allergy

Figure E1: Epitope diversity and egg allergy

Table E1: Diagnostic decision points for SPT diameter (egg white) in predicting egg allergy

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Table E2: Diagnostic decision points for ImmunoCAP to egg white in predicting egg allergy

Table E3: ROC area under curves for SPT and ISAC components for predicting egg allergy in all participants (n=100)

Table E4 ROC area under curves for SPT, ImmunoCAP and ISAC components size for predicting egg allergy in egg-sensitised participants (n=54)

Table E5: Egg component patterns amongst egg allergic versus tolerant participants in the population overall (n=100)

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Pediatr Allergy Immunol

Abstract

Background: Egg allergy is the most common food allergy in children with atopic dermatitis (AD).

This study aimed to determine the prevalence of, component patterns and predictive values of screening tests in egg allergy in South African children with AD.

Methodology: This was a prospective, observational study in a paediatric university hospital in Cape Town. Children with AD, aged 6 months to 10 years, were recruited randomly. They were assessed for sensitisation and allergy to egg by questionnaire, skin prick tests (SPT), Immuno Solid Phase Allergen Chip (ISAC 103) test, ImmunoCAP component tests to egg and ovomucoid (*Gal d 1*); and incremental food challenges.

Results: 100 participants (59 black Africans and 41 of mixed ethnicity) were enrolled, median age 42 months. There was a high rate of egg sensitisation of 54% and prevalence of confirmed egg allergy of 25%. History and screening laboratory tests overestimated egg allergy significantly. SPT to fresh egg white was significantly more sensitive in diagnosing egg allergy than SPT to the commercial egg white extract, and produced the highest area under the receiver operator characteristics (ROC) curve

of all the screening tests in predicting true egg allergy. In those participants sensitised to egg, the component ovomucoid was best at differentiating true egg allergy from tolerance. Commonly used 95% Positive Predictive Values (PPV) for SPT to egg and ImmunoCAP egg white produced low PPV of 57% and 74% respectively in this population overall, with generally poorer predictive values amongst the black Africans than the mixed ethnicity participants. A SPT to fresh egg of 17 mm and ImmunoCAP egg white of 13 kU/L produced the best PPV for egg allergy in this population.

Conclusion: The prevalence of egg allergy is high in African children with AD, but history of egg allergy and sensitisation to egg significantly overestimate the true egg allergy rate. SPT to fresh egg white was more sensitive than that to commercial egg white extract, hence fresh egg white should be recommended in an egg allergy screening panel. The component ovomucoid was useful for differentiating allergy from tolerance in egg-sensitised participants. Population specific 95% PPV for egg allergy tests may need to be established in developing world populations.

KEY WORDS

Atopic Dermatitis, Egg Allergy, Egg components, Ethnic differences, Skin prick tests, South Africans, 95% Positive Predictive values,

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Introduction

Egg allergy is one of the most common allergies in infants and young children. The estimated prevalence of egg allergy is 0.5-8.9% in early childhood.¹⁻⁶ Owing to the high degree of natural acquisition of tolerance to egg over time, the prevalence of egg allergy is lower in older children and adults at less than 0.5%.^{1,4,7}

Atopic dermatitis (AD) is a major risk factor for egg allergy. Egg allergy may comprise up to 2/3 of food allergies in children with AD.⁸ Studies in Europe and the United States have shown the prevalence of egg sensitisation in participants with AD to be 35-73%, and egg allergy 16-22%.⁹⁻¹²

Egg allergy and sensitisation are risk factors for aeroallergen sensitisation (especially indoor perennial allergens such as house dust mite) and asthma.¹³⁻¹⁵ Therefore egg allergy may be an important association with the progression of the atopic march.

The major allergenic proteins in hen's (*Gallus domesticus*) egg have been designated *Gal d 1*-*Gal d 5*, with most of the allergenic proteins being found in egg white (*Gal d 1*-*Gal d 4*), and *Gal d 5* in egg yolk.^{16, 17}

Measurement of specific IgE antibodies to individual egg white components has been shown to predict different clinical patterns of egg allergy.¹⁸ Ovomucoid (*Gal d 1*) is a heat and protease-stable antigen and is the dominant allergen in egg allergy.^{19,20} High IgE levels to ovomucoid are associated with persistence of egg allergy.²¹ Ovalbumin (*Gal d 2*) is heat labile, and children who are mainly sensitised to ovalbumin tend to tolerate the "baked" (heat denatured) form of egg.^{22,23} Sensitisation to a high diversity of egg allergen components has also been found to be correlated with an increased chance of egg allergy.²⁴

Quantitative measurements of specific IgE to egg white, either by ImmunoCAP test or by skin prick test (SPT), have been used to create 95% positive decision points for egg allergy. Internationally derived and widely used decision points were described by Sampson (showing 95% PPV for ImmunoCAP to egg white ≥ 7.0 kU/L in over 2 year olds and ≥ 2.0 kU/L in under 2 year olds)²⁵ and Sporik (showing a 100% PPV for SPT ≥ 7 mm in over 2 year olds ≥ 5 mm in under 2 year olds).²⁶ However, such decision points may be age-dependent and may not be applicable to all populations.²⁷ Commonly used 95% PPV for the diagnosis of peanut allergy (SPT, ImmunoCAP and ISAC) have been shown to perform less well in Black African children than in children of mixed ethnicity,²⁸ hence decision points may also be affected by ethnicity.

Tables E1 and E2 in the online repository show PPVs for SPT and ImmunoCAP egg white derived from various studies.

The prevalence of egg allergy in South African children with atopic dermatitis is unknown, and there are no previous studies on challenge-proven egg allergy in this region. Moreover, egg component patterns and value of commonly used 95% PPV have not previously been explored in African children. This study therefore aims to determine egg sensitisation and allergy patterns, component

patterns, the value of 95% PPVs and ethnic differences in egg allergy in a cohort of South African children with AD.

Methodology

This was part of the wider study investigating food sensitisation and allergy patterns in South African children with atopic dermatitis, including 59 children of black African origin, and 41 of mixed ethnicity.²⁹

Screening tests for egg allergy were performed in all 100 participants by taking a thorough history of previous reactions, performing SPT to commercial egg white extract (ALK), a modified SPT to fresh (raw) egg white, and an Immuno Solid Phase Allergen Chip (ISAC 103®, Phadia) test, which included components *Gal d 1*, 2, 3 and 5. SPT results were recorded as mean wheal diameter (largest diameter and perpendicular) minus mean wheal diameter of the negative control.

In those children who were sensitised to egg by the screening tests (n=54), bloods were sent for ImmunoCAP (Phadia) egg white and ovomucoid (*Gal d 1*). In all participants in whom there was uncertainty regarding egg allergy, an incremental open food challenge was performed as a day case at the Red Cross Children's Hospital. The challenge food was given in the form of scrambled egg, starting with a lip challenge, then incremental increases every 15-20 minutes from 0.5g to 30g scrambled egg over 2 hours.

Study definitions

IgE-mediated egg sensitisation was defined as a positive SPT to egg white extract or fresh egg white (3 mm or more above the negative control) and/ or positive egg specific IgE by ISAC (≥ 0.3 ISAC units)

IgE-mediated egg allergy was defined as either:

- Positive food challenge
- A convincing clinical history of significant type I allergic reactions after isolated ingestion of egg-containing food in the preceding 6 months, with significantly positive SPT/sIgE above the internationally derived 95% positive predictive value for egg of 7mm for SPT²⁶ and 7 kU/L for ImmunoCap.²⁵

Results

All of the participants completed the screening tests and food challenges where indicated, hence screening data for SPT and ISAC components from all 100 participants was utilised. ImmunoCAP to egg and ovomucoid were performed on the 54 participants who were sensitised to egg on screening tests.

Egg Sensitisation and Allergy Patterns

Overall, 54 (54%) participants were sensitised to egg, 35/59 (59%) of black Africans and 19/41 (46%) of mixed ethnicity, $p=0.2$.

Overall, 25 participants (25%) were found to be allergic to egg: 14/59 (24%) Xhosas and 11/41 (27%) mixed race participants ($p=0.7$). All 25 cases of egg allergy had a positive SPT to fresh egg white. Twenty out of 25 (80%) of participants with egg allergy had a positive SPT to egg white extract, hence SPT to egg white extract missed 5/25 (20%) cases of egg allergy. 21/25 (84%) participants with egg allergy were positive to any one or more ISAC components to egg, hence ISAC missed 16% of egg allergy cases. Overall, 46% of egg sensitised patients were found to be egg allergic. (Table 1)

Risk factors for egg allergy were young age < 2 years, severe eczema and early age of onset of eczema < 6 months (see online repository for details of risk factors).

Thirty-one participants underwent an egg challenge, of whom 14 were positive and 17 negative. Eleven participants diagnosed with egg allergy did not have a challenge but had a significant recent history of a reaction and a SPT or specific IgE above the frequently used 95% PPV of 7mm for SPT and 7 kU/L for ImmunoCAP.

A history of symptoms of allergy in response to the ingestion of egg was not in itself a reliable predictor of egg allergy: of the 43 (43%) participants who reported symptoms of egg allergy, only 56% were found to be truly egg allergic.

The median age of participants with an egg allergy was 18 months (interquartile range 15-37 months). The median age of introduction of egg into the diet was 12 months in both ethnic groups (interquartile range 8-18 months).

Sensitivity, specificity and Receiver Operating Characteristic (ROC) Curves for SPTs and ISAC tests as screening tests for egg allergy (n=100)

All 100 participants participating in the study underwent screening tests to egg allergy by SPT to egg extract and fresh egg white, as well as ISAC 103 test to egg components *Gal d 1,2,3* and 5.

Receiver Operating Curves (ROC curves) showed that the size of the SPT to fresh egg white was superior in the prediction of egg allergy (ROC area under the curve (AUC) 0.92). This was followed by ISAC to *Gal d 1* (ROC AUC 0.84) and SPT to egg white extract (ROC AUC 0.79), with poorer performance of components *Gal d 2, 3* and 5 (ROC AUC 0.69, 0.67 and 0.66 respectively). The difference in ROC AUC between fresh egg white and egg white extract SPT was significant (p=0.005). There was no significant ethnic difference in the pattern of the ROC prediction curves.

ROC curve results for various screening tests in the overall study population are depicted in figure 1, and table E3 in the online repository.

The SPT to fresh egg white was the most sensitive screening test for egg allergy (100% sensitive in both ethnic groups), but positive predictive value (PPV) for egg allergy was poor (PPV 52 % overall). SPT to egg white extract performed sub-optimally in both sensitivity (80%) and PPV for egg allergy (50%). ISAC to *Gal d 1* had poor sensitivity (72%) but good specificity (93%), and the best PPV of all the screening tests (78%).

Sensitivity, specificity and Receiver Operating Curves (ROC) for SPTs and ISAC tests in predicting egg allergy in egg-sensitised participants (n=54)

Those participants who were found to be egg-sensitised by screening SPT/ISAC tests (n=54) underwent ImmunoCAP screening to Egg White and Ovomucoid (*Gal d 1*).

ROC curves in egg-sensitised participants showed that ImmunoCAP *Gal d 1* was superior in the prediction of egg allergy (ROC area under the curve 0.83). This was followed closely by ISAC to *Gal d 1* (ROC area under curve 0.81), SPT to raw egg white (0.78), and ImmunoCAP to egg white (0.77). The difference in ROC AUCs for ImmunoCAP *Gal d 1*, ISAC *Gal d 1*, SPT raw egg and ImmunoCAP egg white was not significant at p=0.81, hence these tests had comparable value in differentiating egg allergy from tolerance in sensitised participants. SPT to egg white extract performed poorly (AUC 0.60), statistically significantly lower than the other parameters (p=0.005). There were no significant ethnic difference in the pattern of the ROC prediction curves.

ROC curves for various tests in predicting egg allergy in the egg-sensitised population are depicted in figure 2, and table E4 in the online repository.

In the 54 egg-sensitised participants who underwent further ImmunoCAP tests, the SPT to fresh egg showed the highest sensitivity in diagnosing egg allergy (100% in both ethnic groups) but poor specificity 25%, and a PPV of 54%. A positive ImmunoCAP to egg white also showed high sensitivity of 96% (100% in black Africans and 91% in mixed ethnicity) but poor specificity 18% in both ethnic groups with a PPV 51%. ISAC test to *Gal d 1* showed poor sensitivity (72%) but the highest specificity (82%) and PPV (78%).

The overall trend for all 3 screening tests was towards a lower specificity and PPV in black African participants, but this did not reach statistical significance.

Median values of SPT, ISAC and ImmunoCAP tests in tolerant versus allergic participants who were egg -sensitised

The median values in allergic versus tolerant egg-sensitised participants were significantly higher for all tests except SPT egg white extract (Table 2). These trends were similar between ethnic groups with no statistically significant differences.

The median SPT to fresh egg was significantly higher than the median SPT value to egg white extract ($p < 0.001$ by Wilcoxon sign-rank test). Moreover, when comparing ImmunoCAP and ISAC median values, the median ImmunoCAP *Gal d 1* was found to be significantly higher than the median ISAC levels ($p < 0.001$ by Wilcoxon sign rank test) in both tolerant and allergic participants.

Egg component patterns

In the overall population, the proportion of participants with positive reactivity to the component *Gal d 1* was significantly higher in egg allergic (72%) versus egg tolerant participants (7%), $p < 0.001$. Significant differences between allergic and tolerant participants ($p < 0.001$) were also found for all of the other egg components: for *Gal d 2* 40% versus 3%; for *Gal d 3* 40% versus 8%; for *Gal d 5* 36% versus 5%, with insignificant differences between ethnic groups. The greater the number of positive ISAC components, the greater was the risk of egg allergy (see section on epitope diversity and figure E1 in online repository).

In the subgroup of egg-sensitised participants, ISAC *Gal d 1*, ISAC *Gal d 2* and ImmunoCAP *Gal d 1* were statistically significantly higher in the egg allergic versus egg tolerant group (Figure 3).

Value of 95% Positive Predictive Values (PPVs)

Internationally derived 95% PPVs for a positive food challenge to egg described by Sporik for SPT²⁶ and Sampson for specific IgE²⁵ were used in this study to assess their value in egg allergy prediction in our study population. Values of 7mm for SPT and 7 kU/L for specific IgE to egg white were assessed.

For the population overall, a SPT egg white extract of ≥ 7 mm had a positive predictive value of 53% (46% in black African and 75% in mixed ethnicity participants); a SPT to fresh raw egg white of ≥ 7 mm had a PPV of 57% (52% in black African and 65% in mixed ethnicity); and an ImmunoCAP of ≥ 7 mm had a PPV of 74 % (75% in black African and 73% in mixed ethnicity), as summarised in Table 3.

Further analysis looking into optimal values for this population to establish local 95% PPV showed for SPT, an optimal PPV of 100% was reached at 12 mm for egg white extract. Overall, for SPT fresh raw egg, the value of 17 mm achieved the highest PPV for the overall study population of 87.5% (at this level PPV was 67% in black Africans and 100% in mixed ethnicity). By ethnic group, maximal PPVs were achieved at values of 21 mm in black Africans (100%) and 16 mm in mixed ethnicity participants (100%).

For ImmunoCAP to egg, a value of 13 kU/L obtained a PPV of 93% overall (PPV 88% for black Africans and 100% for mixed ethnicity at this level).

Discussion

In this study of food allergy in children with AD, hen's egg was the most common allergen overall causing sensitisation (54% overall) and allergy (25%), comparable with previous results from westernised countries.²⁻⁹ Analysis by ethnic group showed that sensitisation and allergy rates did not differ significantly between black African and mixed ethnicity participants.

Young age at the time of assessment (< 2 years), age of onset of eczema below 6 months and severe eczema were significant risk factors for egg allergy.

The median age of egg introduction was 12 months in both ethnic groups, which is relatively late. Recent studies have shown that in an unselected population, earlier introduction of egg was associated with a trend towards lower allergy rates;³⁰ this may be of even greater significance in a high-risk population as has been demonstrated for peanut.³¹

Overall, egg sensitisation by SPT or ISAC test significantly overestimated true egg allergy, with 46% of participants who are sensitised to egg actually having a clinically significant IgE mediated food allergy. This proportion was even lower in black African participants (40% versus 58% in mixed ethnicity participants) but the ethnic difference did not reach statistical significance ($p=0.08$). A participant-reported history of symptoms of egg allergy also significantly overestimated egg allergy. This emphasises the risk of over-diagnosing egg allergy significantly by relying on screening allergy tests or participant history alone. A significant proportion of sensitised cases may require a food challenge for clarification.

As a screening test for egg allergy, a SPT to fresh raw egg white was significantly more sensitive than a SPT to commercial egg white extract (100% versus 80% respectively). This is in agreement with data that fresh foods may be more effective for detecting sensitivity to food allergens.³² A positive ISAC to the egg component *Gal d 1* was specific for egg allergy (specificity 93%) but not adequately sensitive as a screening test (sensitivity 72%). In prediction of egg allergy in the population overall, SPT to fresh raw egg white had the highest receiver operating curve (ROC) area under the curve.

In participants who were sensitised to egg (54 of the 100 participants), similar areas under the ROC curve were obtained for ImmunoCAP *Gal d 1*, ISAC *Gal d 1* and SPT raw egg in the prediction of true egg allergy, but SPT egg extract performed sub-optimally with a significantly lower predictive value by ROC curve.

Our results suggest that SPT to fresh egg and egg white extract are not interchangeable; and that ISAC and ImmunoCAP to egg are not directly comparable.

Egg component pattern analysis showed that the components *Gal d 1* (ovomucoid) and *Gal d 2* were significantly more positive in egg allergic patients versus tolerant egg-sensitised patients.

The greater the number of positive egg components, the greater was the probability of egg allergy, in keeping with previous studies which have shown that increased component diversity is a risk factor for egg allergy.²⁴

The commonly used “95% PPV levels” of ≥ 7 mm in SPT to egg white produced poor results overall for both egg white extract (PPV 53%) and fresh raw egg white (57%); with PPVs even lower in black African participants. For ImmunoCAP egg white ≥ 7 kU/L, the PPV did not vary significantly by ethnicity, but were still suboptimal at 75% for black African and 73% for mixed ethnicity participants. Highest PPV for egg allergy were attained at 17 mm for SPT to raw egg (88% PPV) and 13 kU/L for immunoCAP egg white (PPV 93%).

These findings suggest that PPVs are not only population specific but may even vary according to ethnicity within the same geographical area. This effect may be due to genetic differences, epigenetic phenomena, differences in skin reactivity or differences in exposures, and requires further exploration. Furthermore, the vast difference in values producing “optimal PPVs” between skin prick to commercial egg extract and fresh egg white suggest that studies to determine population-specific 95% PPVs must take into account whether fresh or commercial extracts are used.

Conclusion

In this population of children with moderate to severe AD, the prevalence of egg allergy is high in both black African and mixed ethnicity participants, and equivalent to those in developed countries.

⁹⁻¹² Egg allergy reduction strategies in this high risk population should be explored further and may include selective earlier introduction of egg.

SPT to fresh raw egg white is significantly more sensitive than SPT to commercial egg white extract in the diagnosis of egg allergy, thus addition of fresh raw egg white is recommendable in a screening SPT panel for food allergy. In resource-poor or remote areas, fresh raw egg white could be used as the sole screening test for egg allergy without the need for more expensive commercial extracts or blood tests.

The component *Gal d 1* (ovomucoid) is the superior component in differentiating asymptomatic sensitisation from egg allergy. Internationally derived widely used 95% PPVs for egg allergy performed sub-optimally in both black African and mixed ethnicity participants. This means that, especially in black Africans, false positive screening tests for egg allergy are common and food challenges may be needed more frequently to confirm or refute allergy. Population specific and ethnic specific PPVs may need to be explored in other settings.

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TABLES

Table 1: Egg sensitisation and allergy patterns by ethnicity

	Sensitised to egg	Allergic to egg	Ratio of allergic: sensitised
Overall (n=100)	54%	25%	46%
Black African (n=59)	59%	24%	40%
Mixed ethnicity (n=41)	46%	27%	58%
Difference between ethnic groups (p-value)*	0.2	0.7	0.08

*by chi-squared test

Table 2: Median values of SPT, ISAC and ImmunoCAP tests in allergic versus tolerant participants who are egg-sensitised

	Overall (n=54) Median (interquartile range)	Black African (n=35) Median (interquartile range)	Mixed ethnicity (n=19) Median (interquartile range)	Difference between ethnic groups (p-value)*
SPT egg white in egg-allergic participants	6 mm (4-7mm)	5 mm (4-7mm)	6 mm (1-9mm)	0.68
SPT egg white in egg-tolerant participants	5 mm (0- 6.5mm)	5mm (0-7mm)	0mm (0-6mm)	0.31
Difference between allergic and tolerant participants (p-value)	0.21	0.61	0.15	
SPT fresh egg white in egg- allergic participants	13mm (10-17mm)	12 mm (10-15mm)	15 mm (10-20mm)	0.14
SPT fresh egg white in egg-tolerant participants	8 mm (2.5-12mm)	8 mm (5-12mm)	10 mm (0-12mm)	0.7
Difference between allergic and tolerant participants (p-	P<0.001**	0.01**	0.02**	

value)				
ImmunoCAP egg white in egg- allergic participants	14.6 kU/L (5.15-53.6 kU/L)	14.34 kU/L (5.15-100 kU/L)	14.6 kU/L (0.56-53.6 kU/L)	0.87
ImmunoCAP egg white in egg-tolerant participants	1.54 kU/L (0.68-3.72 kU/L)	1.51 kU/L (0.65-3.57 kU/L)	1.79 kU/L (0.7-8.5 kU/L)	0.92
Difference between allergic and tolerant participants (p-value)	0.003**	0.001**	0.06	
ImmunoCAP <i>Gal d 1</i> in egg- allergic participants	8 kU/L (1.33-52.6 kU/L)	7.2 kU/L (2.1-100 kU/L)	11.7 (0.85-45)	0.43
ImmunoCAP <i>Gal d 1</i> in egg- tolerant participants	0.32 kU/L (0.01-2.06 kU/L)	0.53 kU/L (0.01-3.48 kU/L)	0.17 kU/L (0.02-2 kU/L)	0.57
Difference between allergic and tolerant participants (p-value)	P<0.001**	P<0.001**	0.001**	
ISAC n<i>Gal d 1</i> in egg- allergic participants	0.9 ISU/L (0-2.5 ISU/L)	1.3 ISU/L (0-7.7 ISU/L)	0.7 ISU/L (0.4-2.2 ISU/L)	0.76
ISAC n<i>Gal d 1</i> egg- tolerant participants	0 ISU/L (0-0)	0 ISU/L (0-0)	0 ISU/L (0-0)	0.44
Difference between allergic and tolerant participants (p-value)	P<0.001**	0.004**	0.002**	

*by Mann-Whitney test

** statistically significant

Table 3: Sensitivities, specificities and Positive Predictive Values of tests in predicting egg allergy in egg-sensitised participants (n=54)

	Overall	black African	Mixed ethnicity	Difference (p-value)*
SPT egg white extract ≥ 7mm				
Sensitivity	32%	36%	27%	0.5
Specificity	75%	68%	89%	0.09
PPV	53%	46%	75%	0.04**
NPV	55%	59%	50%	0.53
SPT fresh egg white ≥ 7mm				
Sensitivity	96%	93%	100%	0.24
Specificity	36%	37%	33%	0.77
PPV	57%	52%	65%	0.34
NPV	91%	88%	100%	0.12
RAST egg white ≥ 7 kU/L				
Sensitivity	68%	64%	73%	0.50
Specificity	79%	84%	67%	0.15
PPV	74%	75%	73%	0.87
NPV	73%	76%	67%	0.88

*chi-squared test

** statistically significant

Figures

Egg Sensitisation, Allergy and Component Patterns in African Children with Atopic Dermatitis

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Figure 1: ROC curves for SPT and ISAC components for predicting egg allergy in overall population (n=100)

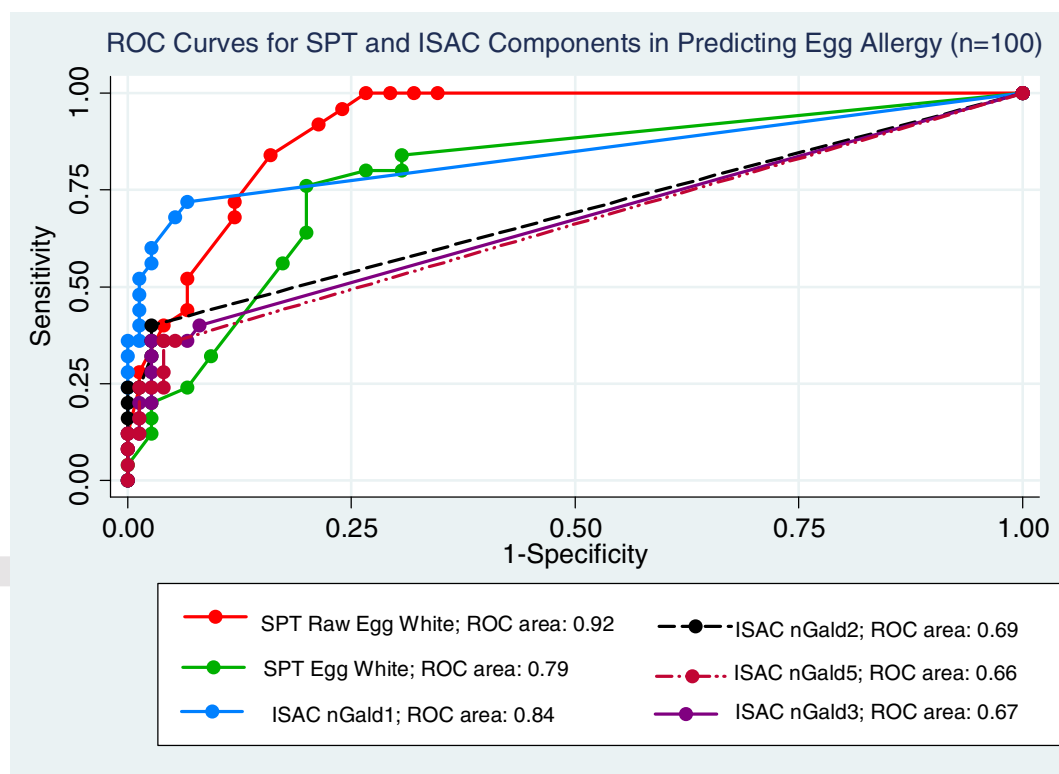
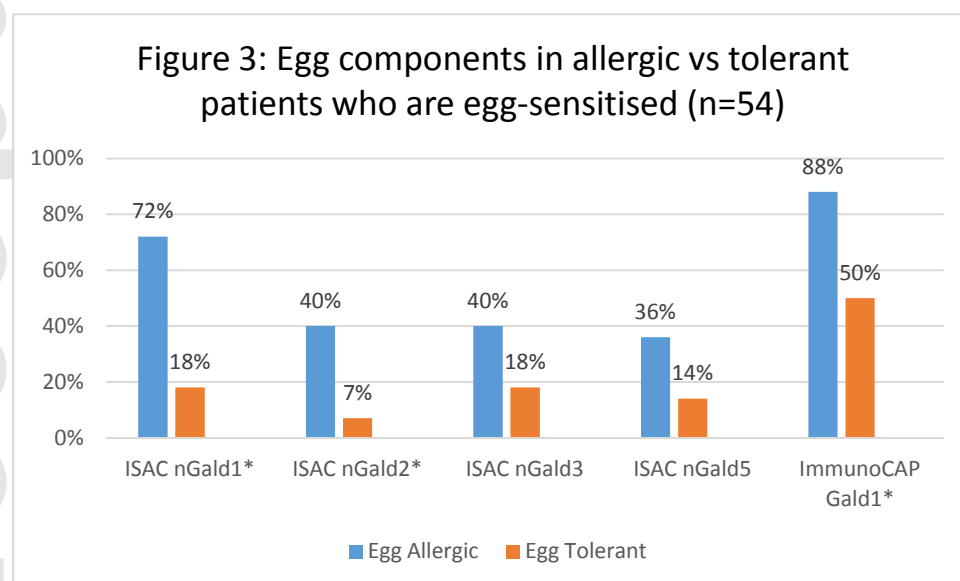
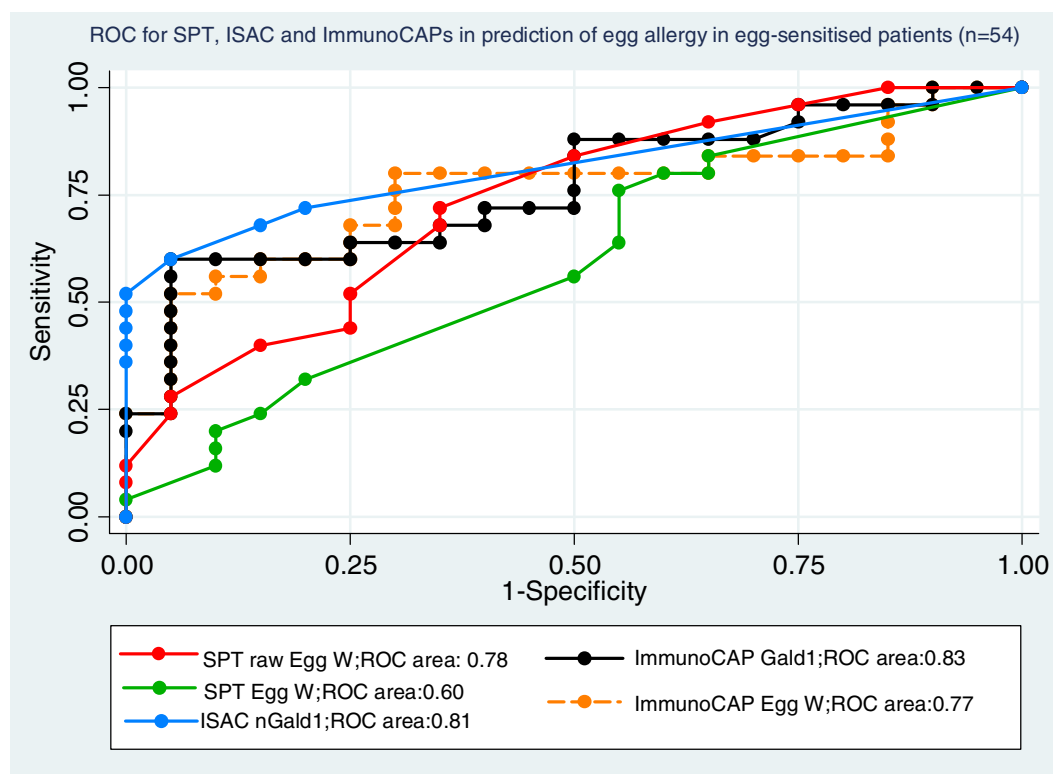


Figure 2: ROC curves for SPT and ISAC components for predicting egg allergy in egg-sensitised participants



*Denotes statistically significant difference (χ^2 test)