



How and when to introduce eggs to avoid egg allergies

A report for the Australian Egg
Corporation Limited

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Foreword

This project was conducted to determine the association between the age of introducing egg into the infant diet and childhood egg allergies.

This project was funded from industry revenue which is matched by funds provided by the Federal Government.

This report is an addition to AECL's range of research publications and forms part of our R&D program, which aims to support improved efficiency, sustainability, product quality, education and technology transfer in the Australian egg industry.

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Dr Angus Crossan
Program Manager – R&D
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Abbreviations

AOR	Adjusted Odds Ratio
ASCIA	Australasian Society of Clinical Immunology and Allergy
CI	Confidence Interval
mm	Millimetres
IgE	Immunoglobulin-E
IQR	Interquartile Range
LCPUFA	Long chain polyunsaturated fatty acids
NHMRC	National Health and Medical Research Centre
RCT	Randomised Controlled Trial
RR	Relative Risk
SAS	Statistical Analysis System

Executive Summary

Egg allergy is the most common food allergy in Australian young children, with the most recent estimates indicating that about 10% of children are affected. The escalating rates of food allergies in general has also resulted in a >5-fold increase in potentially life-threatening food anaphylaxis in children under four years of age. Food allergy is also one of the first manifestations of allergy and approximately 50% of children with egg allergy go on to develop respiratory allergic diseases (asthma, rhinitis) in childhood. Prevention is therefore the key to reducing the burden on the individual, the family and the health care system.

As recent evidence suggests that early oral exposure of egg may be required to prevent the development of egg allergy, we investigated whether the timing of egg introduction into infant diets was related to egg allergy in early childhood. We also assessed the relationship between the age at first exposure to egg and other early childhood allergies.

We used an existing trial of 706 children assessing the effect of prenatal fish oil supplements on early childhood allergies to prospectively evaluate the timing of egg introduction in the diets of infants and young children. We also tested the association between the time of first egg exposure with egg allergy as well as eczema. There was no relationship between the use of prenatal fish oil supplements and the age at which egg was introduced to the infant diet. The average age of first exposure to egg was nine months of age.

We observed that children introduced to egg in the first 12 months of life were 51% less likely to have a confirmed or suspected egg allergy at one year of age (5.2% vs. 11.5%, Relative Risk, RR 0.49, 95% Confidence Interval, CI, 0.25 to 0.97, $p < 0.05$) and 48% less likely to have a confirmed or suspected egg allergy at one or three years of age (7.0% vs. 14.5%, RR 0.52, 95% CI, 0.28 to 0.98, $p < 0.05$). Similarly, children introduced to egg in the first 12 months of life were 26% less likely to have eczema at one or three years of age (37.2% vs. 50.0%, RR, 0.74, 95% CI, 0.59 to 0.94, $p < 0.05$). Egg exposure in the first year of life did not predict egg sensitisation (a positive result on a skin prick test to egg) at any age. There was also no significant association between egg exposure in the first 12 months and eczema with egg sensitisation at either one year of age or at one or three years of age.

Our data indicates that delaying the introduction of egg to a child's diet after 12 months of age is associated with increased risk in egg allergy and eczema. Eggs should be included in the infant diet before 12 months of age and as the infant is developmentally ready.

1 Introduction, Methods and Results

1.1 Background

In Australia egg allergy is the most common food allergy observed in young children (one and two years of age), with the most recent estimates indicating that about 9% of children at one years of age are affected (Osborne et al. 2011). The escalating rates of food allergies in general has also resulted in a >5-fold increase in potentially life-threatening food anaphylaxis over the last 10 years in children under 4 years of age (Poulos et al 2007). There is no treatment for established egg allergy except egg avoidance, which can be time consuming, socially restrictive and impact on family eating practices. Food allergy significantly impacts on general health perception, parental emotional distress and family activities (Sicherer et al. 2001). It is also one of the first manifestations of allergy and approximately 50% of children with egg allergy go on to develop respiratory (asthma, rhinitis) allergic disease in childhood (Tariq et al. 2000). Prevention is therefore the key to reducing the burden on the individual, the family and the health care system.

Based on the assumption that early exposure to allergenic food proteins like egg contribute to food allergies, expert committees previously recommended delayed introduction of egg until 12-24 months for infants who had an immediate family history of allergic disease (American Academy of Pediatrics 2000). Although these recommendation were not based on systematic studies, fears over early introduction of “allergenic foods” (including egg) were translated to infant feeding guidelines for the whole population, including our current Australian National Health and Medical Research Council (NHMRC) which recommends delaying the introduction of egg yolk to eight months of age and egg white to 12 months of age (NHMRC 2003). However, high quality scientific evidence behind these recommendations is scarce.

Without any randomised controlled trials that solely examine how “age at first introduction to solid foods” influences allergy outcomes, the majority of available scientific evidence comes from non-intervention observations from cohort studies. While these have suggested that early avoidance of solid foods (less than four months of age) reduces the risk of allergic disease (Fergusson 1982), (Zutavern 2006), Zutavern (2008), prolonged avoidance (beyond six months of age) has not been associated with reduced risk of allergic disease (Zutavern 2008). Of particular relevance to this report is the finding by Zutavern et al. (2004) that introduction to egg beyond eight months of age was associated with an increased risk of eczema (aOR=1.6, 95% CI 1.1-2.4). This suggests that there may be an optimal time for introducing potentially allergenic foods. In support of this hypothesis, a recent Australian cohort study observed that introducing egg into an infant’s diet between four-six months of age was associated with a lower risk of subsequent egg allergy (Koplin et al. 2010).

Animal studies provide further support for this notion, showing that tolerance is an allergen-driven process, and that early exposure to repeated doses of food proteins (allergens) can induce oral tolerance (Smith 2000). Thus early oral exposure of egg in infants may be required to induce tolerance and thus prevent the development of egg allergy. Based on this current, albeit limited evidence, the Australasian Society of Clinical Immunology and Allergy (ASCIA) published “Infant Feeding Advice” and suggests introduction of solids from four to six months of age with no restrictions in the introduction of “allergenic” foods such as cow’s milk, egg, nuts, seafood and wheat (ASCIA website). However, they also highlighted the need for specific studies to determine the optimal timing of introduction of allergenic foods.

With this background the purpose of our study was:

- To document the timing and pattern of egg introduction into infant diets and the relationship to egg allergy
- To examine the influence of a child's egg allergy on family egg consumption

1.2 Study Design and Methods

We prospectively evaluated the timing of egg introduction in the diets of infants and young children and assessed the relationship with egg allergy diagnosis at one and three years of age. This was done in a group of infants whose clinical status was well defined through an existing randomised controlled trial (RCT) which was separately funded by the National Health and Medical Research Council (NHMRC) (Palmer et al. 2012).

706 pregnant women with an unborn baby at higher than normal risk of developing allergies (because they have a first degree relative with medically diagnosed allergies) were randomly allocated to a fish oil supplement, providing approximately 1g of n-3 long chain polyunsaturated fatty acids per day, or placebo from 20 weeks gestation until birth. We were in contact with these women (via telephone or appointment) every six months from their infant's birth until their child turned three years of age. Infant feeding practices and all allergy symptoms were prospectively documented. The age of first introduction of any egg or egg containing food into the diet of the infant was recorded from birth to three years of age to the nearest month of age. The specific type of egg or egg containing food first introduced was not recorded.

At one and three years of age the children attended a medical review and physical examination including a skin prick test to common allergens (including egg) to determine diagnosis of allergic disease. As part of the medical and on-going assessments, an Immunoglobulin-E (IgE) mediated egg allergy was defined in two ways.

Firstly, confirmed egg allergy was defined as a history of immediate (within 60 minutes) skin rash (hives, rash or swelling) with or without respiratory symptoms (cough, wheeze, stridor) and/or gastrointestinal symptoms (vomiting, diarrhoea) and/or cardiovascular symptoms (floppy unresponsive, collapse) following ingestion of egg and a positive skin prick test (≥ 3 mm weal) to egg. Secondly, suspected egg allergy was defined as a history of repeatedly spitting out or refusing to eat egg and a positive skin prick test (≥ 3 mm weal) to egg. The suspected egg allergy diagnosis was included as many infants get an initial lip or oral mucosa irritation (which they are too young to verbalise about) when they eat a food they are allergic to and hence naturally spit out or refuse to eat that food. Hence we could not be confident that they are actually tolerant to egg and that they do not in fact have an egg allergy. Both these diagnoses of egg allergy were made on parental reporting of symptoms as we were not able to conduct specific oral egg challenges as part of this trial.

Each participating child was diagnosed with either

- 1) confirmed egg allergy or;
- 2) suspected egg allergy or;
- 3) no egg allergy with no overlap between the three categories.

Eczema was defined as the presence of eczema in criteria according to Hanifin and Rjika (1980) on medical review or a history of an itchy rash distributed to the facial, flexural, or extensor surface of the skin which has followed a fluctuating or chronic course. IgE-associated eczema or atopic eczema was defined as eczema with sensitisation, where the infant had a positive skin prick test to at least one of the allergens assessed.

At the three years of age medical review, we also documented current family egg consumption patterns by recording the frequency per week (over the past month) that common egg and egg containing foods were eaten. The list of egg and egg containing foods included: egg (scrambled, boiled, fried, poached), omelette, quiche, frittata, French toast, egg custard, egg in milk drinks, pasta dishes, mayonnaise and baked goods such as cake, muffin, pavlova, pudding, pancakes. These data were collected for the participating three year old child as well as any household member who lived in the same house as the participating child for at least three days per week. These egg intake data included the consumption of the egg and egg containing foods both at and away from the family home. The age (to the nearest month) of first introduction of any egg or egg containing food into the diet of any (new) younger siblings and whether this younger sibling(s) had any allergic reaction to egg in their diet was also documented at the appointment when the participating child was three years of age.

1.2.1 Statistical Analysis

Associations between the introduction of egg and all allergy outcomes were assessed using log binomial regression models, with effect estimates expressed as relative risks and 95% confidence intervals. Analyses were adjusted for treatment group, maternal age at trial entry (years) and maternal further education (none, certificate/diploma, degree, higher degree). Due to the low incidence of confirmed egg allergy during follow-up, to avoid over-fitting to the data only treatment group was adjusted for in analyses involving this outcome.

The difference in total household egg intake between families with and without a child with egg allergy at three years of age was assessed using the Wilcoxon rank sum test. Participants with missing outcome or egg introduction data were excluded from each analysis. All calculations were performed using Statistical Analysis System (SAS) version 9.3.

1.3 Results and Discussion

Of the 706 children participating in this study, 337 (47.7%) were males and 493 (69.8%) had mothers with a history of allergic disease (eczema, asthma, or allergic rhinitis). Most children had mothers who completed secondary education (454/706, 64.3%) and avoided smoking during pregnancy (614/706, 87%). The median age of the women at the time of birth was 30 years. For 281 (39.8%) women the child included in the study was their first child.

682 of the 706 (96.6%) children contributed data to this study examining the relationship between egg usage in infant diets and allergy outcomes in the first three years of life. At one years of age, 681/706 (96.5%) infants attended their medical review and 666/706 (94.3%) had skin prick testing to determine their sensitization status. At three years of age, 638/706 (90.4%) children attended their medical review, with 587/706 (83.1%) children having skin prick testing. The high participation rate minimises the possibility of bias caused by attrition.

Figure 1-1 illustrates the timing (by month of age) of first egg introduction into the child's diet. Overall the median age of first introduction to egg or egg containing foods into the diet of the children in this cohort was 9.0 months (interquartile range, IQR, 6.0 to 11.0 months). This pattern of egg introduction was comparable with the only other contemporary Australian data in which a family history of allergy was not a prerequisite for inclusion (Koplin et al. 2010). There was no significant relationship between age at first egg

exposure and allocation to the study groups in the original trial, indicating that the fish oil intervention did not change the way egg was introduced in the infant diet.

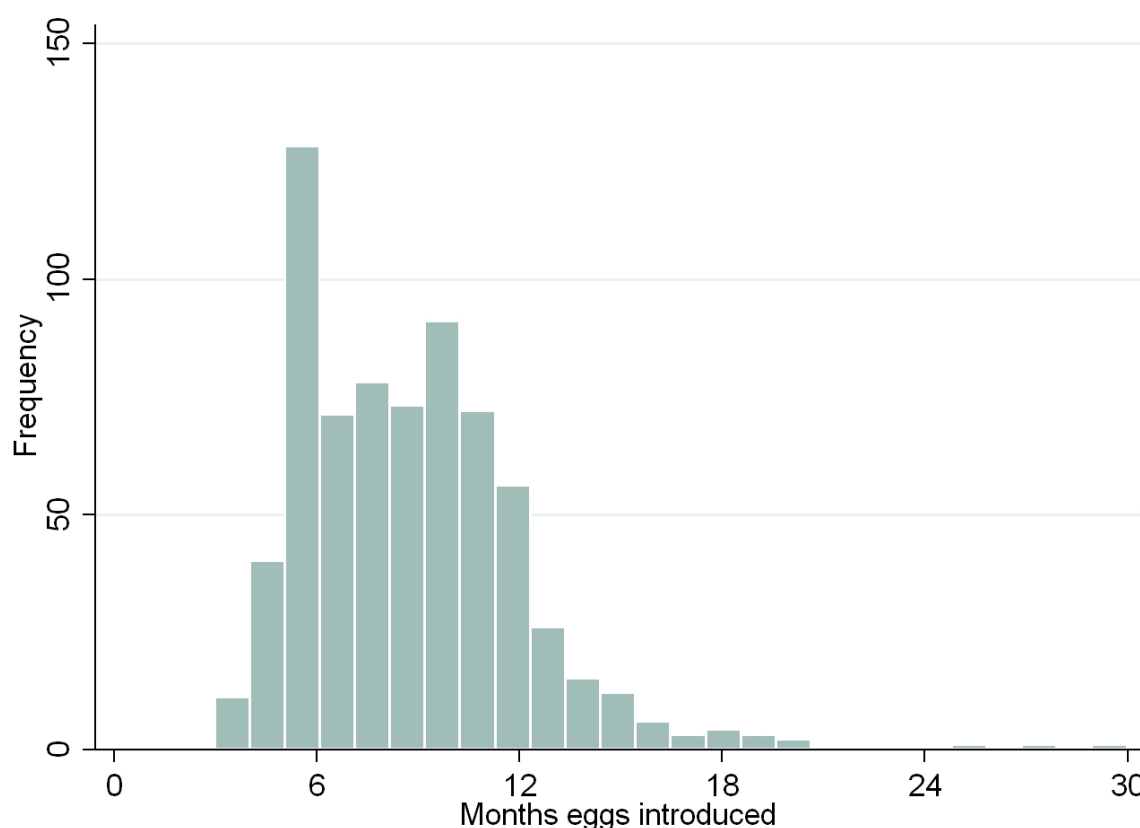


Figure 1-1 - Age in months of first egg introduction into the child's diet

The relationship between the ages at first introduction of egg and allergy outcomes in young children is described in Tables 1 and 1-2. Table 1-1 shows the association between allergy outcomes and whether egg was first introduced to the child's diet before or after 12 months of age. This was the primary analysis and focussed on 12 months as the age of egg exposure because the current NHMRC guideline recommends delaying the introduction of egg white, and therefore whole egg, until 12 months of age. We have also included a secondary analysis, described in Table 1-2, which examined the association between allergy outcomes and whether egg was first introduced to the child's diet before or after eight months of age. This sensitivity analysis was used to examine the other component of the NHMRC guideline, which recommends that egg yolk is not introduced until eight months of age.

We observed that children introduced to egg in the first 12 months of life were 51% less likely to have an egg allergy at one years of age and 48% less likely to have an egg allergy at one or three years of age (Table 1-1). Similarly, children introduced to egg in the first 12 months of life were 26% less likely to have eczema at one or three years of age (Table 1-1). Egg exposure in the first year of life did not predict egg sensitisation (a positive result on a skin prick test to egg) at any age (Table 1-1). There was also no significant association between egg exposure in the first 12 months and eczema with egg sensitisation at either one year of age or at one or three years of age (Table 1-1).

Table 1-1 - Association between allergy outcomes and whether egg was first introduced to the child's diet before or after 12 months of age

Allergy Outcomes	Infants had egg in the first 12 months of life	Infant had no egg in the first 12 months of life	Adjusted Relative Risk (95% confidence interval)
Confirmed egg allergy at 1 yr	12/577 (2.1%)	1/87 (1.2%)	1.82 (0.24, 13.79)
Confirmed egg allergy at 1 or 3 yr	17/498 (3.4%)	3/76 (3.95%)	0.86 (0.26, 2.88)
Confirmed or suspected egg allergy at 1 yr	30/577 (5.2%)	10/87 (11.5%)	0.49 (0.25, 0.97)*
Confirmed or suspected egg allergy at 1 or 3 yr	35/498 (7.0%)	11/76 (14.5%)	0.52 (0.28, 0.98)*
Eczema at 1 yr	148/590 (25.1%)	28/92 (30.4%)	0.83 (0.59, 1.17)
Eczema at 1 or 3 yr	206/554 (37.2%)	44/88 (50.0%)	0.74 (0.59, 0.94)*
Egg sensitisation at 1 yr	75/577 (13.0%)	10/87 (11.5%)	1.20 (0.65, 2.23)
Egg sensitisation at 1 or 3 yr	76/504 (15.1%)	12/76 (15.8%)	1.00 (0.57, 1.74)
Eczema with egg sensitisation at 1 yr	46/588 (7.8%)	9/91 (9.9%)	0.82 (0.42, 1.62)
Eczema with egg sensitisation at 1 or 3 yr	47/536 (8.8%)	10/85 (11.8%)	0.78 (0.41, 1.48)

*indicates statistically significant comparisons, $p < 0.05$

All analyses were adjusted for fatty acid treatment group, maternal age and maternal education, except for confirmed egg allergy that was adjusted for fatty acid treatment group only.

We observed no associations between any allergy outcomes and first egg exposure before 8 months of age (Table 1-2).

Table 1-2 - Association between allergy outcomes and whether egg was first introduced to the child's diet before or after eight months of age

Allergy Outcomes	Infants had egg in the first eight months of life	Infant had no egg in the first eight months of life	Adjusted Relative Risk (95% confidence interval)
Confirmed egg allergy at 1 yr	5/301 (1.6%)	8/354 (2.3%)	0.71 (0.23, 2.15)
Confirmed egg allergy at 1 or 3 yr	10/256 (3.9%)	10/318 (3.1%)	1.25 (0.53, 2.95)
Confirmed or suspected egg allergy at 1 yr	15/310 (4.8%)	25/354 (7.1%)	0.78 (0.42, 1.48)
Confirmed or suspected egg allergy at 1 or 3 yr	20/256 (7.8%)	26/318 (8.2%)	1.07 (0.60, 1.89)
Eczema at 1 yr	82/318 (25.8%)	94/364 (25.8%)	1.02 (0.79, 1.33)
Eczema at 1 or 3 yr	116/292 (39.7%)	134/350 (38.3%)	1.07 (0.88, 1.30)
Egg sensitisation at	40/310 (12.9%)	45/354 (12.7%)	1.08 (0.72, 1.62)

1 yr			
Egg sensitisation at 1 or 3 yr	41/260 (15.8%)	47/320 (14.7%)	1.14 (0.77, 1.69)
Eczema with egg sensitisation at 1 yr	29/318 (9.1%)	26/361 (7.2%)	1.32 (0.78, 2.21)
Eczema with egg sensitisation at 1 or 3 yr	30/280 (10.7%)	27/341 (7.9%)	1.42 (0.85, 2.36)

**There were no statistical significant comparisons*

All analyses were adjusted for fatty acid treatment group, maternal age and maternal education, except for confirmed egg allergy that was adjusted for fatty acid treatment group only.

The lack of an association between egg exposure before eight months of age and egg allergy outcomes and a negative association between delayed egg exposure (after 12 months of age) and allergy outcomes, implies that the first 12 months of life may be an important time to establish egg as part of the diet and minimise the risk of egg allergy and eczema over the first eight years of life.

Our observations were made in a cohort of children at higher than normal risk of developing allergic disease because of a positive family history. Overall the prevalence of eczema during the first year of life was 25.8%, at 12 months of age the egg sensitisation rate was 12.8% (where sensitisation was defined as wheal size ≥ 3 mm) and parental reported confirmed or suspected egg allergy rate was 6.0%. Another recent Australian cohort study of infants in Victoria also born between 2006 and 2008 found that the prevalence of eczema during the first year of life was 26.7%, at 12 months of age the egg sensitisation rate was 11.8% (where sensitisation was defined as wheal size ≥ 3 mm) and the prevalence of challenge-proven raw egg allergy rate was 8.9% (Hanifin (1980)). The study populations were comparable and probably representative of the current generation of Australian children.

While our data are from a well conducted cohort study in which egg exposure was prospectively collected, we cannot exclude the possibility that some other environmental variables may have confounded the relationship between egg exposure and allergy. Randomised controlled trials assessing different windows of egg exposure and their effect on egg allergy are ultimately needed to establish a cause and effect relationship between the time of egg introduction into the infant diet and allergic disease. Such trials are currently in progress in Australia as well as internationally.

Another aspect of our study was to investigate the influence of children's egg allergy on family egg consumption. The median egg intake (from eggs and egg containing foods) per household per week for families in this cohort was 8.46 eggs (IQR 5.13-13.75). No relationship was found between egg allergy at three years of age with the total household egg intake ($p = 0.42$).

By three years of age, 117/641 (18%) of the children in this study had a sibling who had been introduced to egg. The median age when egg was introduced to the sibling was nine months of age (IQR 7 to 12 months of age), which is comparable to the median age of introduction to egg of the study children. Only 3/117 (2.5%) of these siblings introduced to egg had a parental reported allergic reaction to the egg.



2 Conclusions and Recommendations

- Delaying the introduction of egg to a child's diet after 12 months of age is associated with increased risk in egg allergy and eczema.
- Eggs should be included in the infant diet before 12 months of age and as the infant is developmentally ready.

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4 Plain English Compendium Summary

Project Title:

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• Researcher:	Professor Maria Makrides
• Organisation:	Women's & Children's Health Research Institute
• Phone:	08 8161 7443
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• Objectives	To document whether the timing of egg introduction into infant diets is associated with a lower risk of egg allergy.
• Background	In Australia, egg allergy is the most common food allergy affecting young children. There is no treatment for egg allergy except egg avoidance. Strategies to prevent egg allergies are therefore of vital importance. Emerging evidence suggests that early oral exposure of egg may be required to prevent the development of egg allergy. Earlier introduction of egg to infant diets will enhance micro-nutrient status and increase diet variety by avoiding unnecessary dietary restrictions.
• Research	<p>We used an existing trial of 706 children assessing the effect of prenatal fish oil supplements on early childhood allergies to evaluate the timing of egg introduction in the diets of infants and young children.</p> <p>We recorded on the pattern of egg introduction into infant diets every 6 months and also assessed egg and other allergies by a medical examination at 1 and 3 years of age. We then tested the association between the time of first egg exposure with egg allergy as well as eczema.</p>
• Outcomes	We observed that children introduced to egg in the first 12 months of life were 51% less likely to have a confirmed or suspected egg allergy at one year of age and 48% less likely to have a confirmed or suspected egg allergy at one or three years of age. Similarly, children introduced to egg in the first 12 months of life were 26% less likely to have eczema at one or three years of age.
• Implications	<ul style="list-style-type: none"> • Delaying the introduction of egg to a child's diet after 12 months of age is associated with increased risk in egg allergy and eczema. • Eggs should be included in the infant diet before 12 months of age and as the infant is developmentally ready.
• Publications	Pending