

SUBMITTED VERSION

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Role of early egg ingestion in induction of tolerance: an unanswered question. Reply

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1 **Reply to Qurat-ul Ain Kamili**

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20 **Funding Declaration:** The trial was supported by a grant from the Women's and Children's
21 Hospital Foundation and a grant from the Ilhan Food Allergy Foundation.

22

23 Kamili et al ¹ have raised some important questions that we are pleased to address regarding
24 our recent randomised control trial (RCT) on the effects of early regular egg exposure in
25 infants with eczema ². First, to address the process of subject recruitment, the RCT
26 participant flow profile is shown in Figure 1. Initial recruitment for our RCT was undertaken
27 by placing newspaper advertisements and flyers at baby health clinics. 243 potential
28 participants were initially screened, of whom 109 infants were ineligible (46 due to infant age
29 >4 months, 37 did not have moderate to severe eczema), 32 did not consent (16 due to
30 parents not wanting to introduce solid foods at 4 months of age) and 16 were lost to follow
31 up after initial contact.

32

33 Second, it is important to note that in Australia breastfeeding rates are higher than those
34 reported by Kamili et al for the United States in their letter to the Editor. In Australia, the
35 initiation of breastfeeding occurs in 95.9% of infants and 60.1% are breastfed at six months
36 of age ³. At the commencement of the study at 4 months of age, >80% of the participating
37 infants in both groups were breastfed as described in our paper. We agree that small doses of
38 egg protein (3.2ng/mL after the consumption of one whole cooked egg ⁴) can be transmitted
39 to the infant via breast milk and maternal dietary egg intake data was collected during this
40 study. For the entire duration of the intervention period (from 4 to 8 months of age), 27/42
41 (64%) of the egg group infants were breastfed with 15/27 (56%) of their breastfeeding
42 mothers consuming >2 eggs per week in their maternal diet compared to 26/35(74%) of the
43 control group infants being breastfed but with only 8/26 (31%) of their mothers were
44 consuming >2 eggs per week.

45

46 In our RCT ², the egg-specific IgG4 levels were significantly ($P<0.001$) higher in the egg
47 group at both 8 and 12 months of age. Allergen-specific IgG4 has been reported to be a
48 useful marker of the development of immune tolerance in oral immunotherapy studies. The
49 favourable changes in these immunological measures are not the same as clinical tolerance,
50 but provide reassurance of the early regular egg allergen exposure approach. We are in
51 complete agreement with Kamili et al regarding the limitations of our trial imposed by the
52 unforeseen logistic issues that resulted in insufficient power to show statistically significant
53 definitive clinical results. Even so, the trend for lower incidence of egg allergy in the egg
54 group (33%) compared to the control group (51%) reduces previous concerns that early
55 introduction of this allergenic food would be associated with increased egg allergy risk. We
56 also agree that the question of whether early egg exposure can reduce egg allergy
57 development requires further investigation before evidence based clinical recommendations
58 can be made and eagerly await the results from current RCTs also investigating this question.

59

60 **Figure Legends:**

61 Figure 1: Participant flow profile.

62

63 **References:**

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