Striking the balance between primary prevention of allergic disease and optimal infant growth and nutrition.

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To the editor:

The timing of introduction of solids and/or complementary feeds continues to be an area of intense interest with respect to allergy prevention and general optimal infant nutrition. There is recent evidence from RCTs (1-3) and a meta-analysis(1), that the earlier introduction of peanut (between 4 and 11 months) and egg (between 4 and 6 months), in infants at higher risk of allergic disease, may be beneficial. However, concerns have been raised over the impact this may have on duration of breastfeeding, nutrition and growth, when a high protein and calorie-containing food, such as egg or peanut, is introduced. Duration of breast feeding appears to have little impact on development of allergic disease, but is important for protection against overweight and obesity, diabetes and childhood infections (particularly in resource poor settings)(4).

We recently reported results from a primary prevention RCT (the BEAT study) which examined the effect of dietary introduction of egg, from 4 months of age, on sensitization and allergy to egg at age 12 months. Methods and results have been published elsewhere(3), but briefly infants were randomized (in a double-blind fashion) to receive either 350mg of whole pasteurized powdered egg or placebo (rice powder) daily following successful weaning on to appropriate solids from 4 months of age, until dietary liberalization at 8 months. Infants were otherwise on a strict egg-free diet from 4-8 months of age.

We were interested to explore any possible impact of the intervention (or introduction of solids) from 4 months of age on growth or duration of breastfeeding. Differences in proportions between groups was analysed by Chi-squared tests, and growth parameters at 4, 8 and 12 months between groups were compared using non-parametric rank test.

319 infants attended the initial visit at approximately 4 months of age (mean=3.9, SD= 0.5). Detailed feeding data were collected at this visit, and at 8 and 12 months. As might be expected, parents of study infants were generally well-educated and had higher combined annual household incomes than the general population. 65% of mothers had tertiary qualifications and 56% of families had a combined income greater than $AUD100,000/year. 44% of infants had at least one parent born outside Australasia, with parents born in Greater Asia (South East Asia, India, China) constituting the largest group of those with non-Australasian region of birth.

At the initial 4 month visit, 72% (230) of infants were receiving breast milk and 45% (142) exclusively breastfed. 9% (30) had never been breastfed and 29% (66) of breastfeeding mothers were avoiding specific allergenic foods in their own diets-despite receiving no medical advice to do so. In the 177 infants not exclusively breastfed at 4 months, formula was started at a median age of 1 month (IQR- 0.0-2.0) and the majority receiving formula were on a standard cow's milk based formula (142/177). Across the cohort, 69 (22%) of 319 infants had already recently commenced solids prior to the first study visit at 4 months (median 4 months IQR-

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3.8-4.0). The median age at introduction of the study intervention was 4.0 months (IQR-4.0-4.8) for egg and 4.0 (IQR4.0-4.5) for placebo respectively.

At 8 months all infants were receiving solids (as part of the study protocol) and the majority (201, 63%) had introduced solids successfully between 4 and 5 months of age. The most common first weaning foods were fruits and vegetables, with over 80-100% of infants having been successfully introduced to grains, vegetables, fruits and meat by 8 months of age. 45% (118) and 23% (57) infants were still receiving breast milk at 8 and 12 months respectively; this did not vary by study intervention (p=0.78 and p=0.068 at 8 and 12 months, respectively).

Growth parameters for the infants are shown in Table 1. There were no differences in weight, length or weight-for-length (WFL) between those randomised to receive egg or placebo at baseline (4 months), 8 or 12 months of age. Infants in the egg-introduction arm had slightly lower head circumference at baseline prior to any intervention, which persisted throughout the study. There was no difference in weight, length, WFL or head circumference between those 69 infants who had received solids prior to the first visit (4 months) and the remainder of the cohort at 4, 8 or 12 months.

In our cohort, duration of breastfeeding did not differ between those receiving early introduction of egg and those in the placebo arm (receiving rice), and is in line with recent Australian population data(5). Both groups in our study had a median age of introduction of the allocated intervention of 4.0 months. There are a number of caveats to interpreting growth and feeding data from this study cohort. Firstly, this was not a primary outcome measure of the study, and the study was not specifically powered to examine growth or duration of breastfeeding. The study was blinded, so any potential effects on growth or breastfeeding duration are unlikely to be related to parental knowledge of the allocated intervention, but rather could be due to the higher fat, protein and overall caloric content of the egg (weight for weight, rice powder has 70% of total energy of egg, 20 times less fat and approximately 7 times less protein). Both study groups were encouraged to introduce solids from 4 months of age, so it is not possible to draw any direct conclusions about how growth or breastfeeding duration may have been altered by delaying introduction of solids to after 6 months of age. This is in contrast to the EAT study(6), where infants were either randomised to introduce 6 allergenic foods from 3 months of age, or encouraged to follow UK infant feeding guidelines (solids from 6 months of age). No impact on growth(7) or duration of breastfeeding(8) were noted between the early intervention and conventional introduction groups in the EAT study, and growth patterns between studies were very similar (Table 2); however higher rates of breast feeding were achieved in both groups in the EAT study at 9 and 12 months, compared to our cohort.

It is possible to make some comparisons between growth and feeding parameters of infants from our study and known Australian population norms; however, our study infants may not be wholly representative of the general population, with higher maternal education and household income both being associated with longer duration of *exclusive* and *any* breastfeeding in high resource settings such as Australia(9). In 2010 the Australian National Infant Feeding Survey (ANIFS)(5) reported that only 39% of infants were exclusively breastfed after 3 months of age, and 60% were still receiving some breast milk at 6 months. These rates were higher in mothers with a higher level of education: 80% and 62% with degree or diploma respectively were

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exclusively breastfeeding their infants at 4 months of age, with 53% and 36% continuing to breastfeed to some degree between 7-12 months (exact breastfeeding rates at 8 months were not reported in ANIFS). These rates are very similar to those in our study, suggesting that within this demographic, neither encouragement to introduce solids from 4 months nor introduction of a high protein food (egg) from 4 months appeared to greatly influence the duration of breastfeeding. It is noteworthy that 22% of infants in our cohort had already commenced solids prior to 4 months of age, which was contrary to Australian infant feeding guidelines, nor encouraged by the study coordinators. This is also at odds with ANIFS data, where only 2% of mother with a tertiary education, and 5% of infants with a family income >AUD$88,000 had solids introduced before age 4 months.

We did not observe any differences in growth between groups by allocation, something consistent with both the unblinded EAT and LEAP studies in the UK(10) (7)(Table 2). There was some suggestion of an increasing median weight trajectory from randomization at 4 months to 12 months, based upon WHO growth charts in our study infants. The median weight in both groups at baseline (4 months) corresponded to the 36-44th centile for males and 63-71st centile for female; at age 8 months, 46-62nd centile for males and 72-82nd for females; and at 12 months, 57-69th for males and 78-85th for females. Similar trends were not obviously apparent for length, with median length at baseline, 8 and 12 months corresponding to the 22-34th, 39-55th and 54th centile, respectively, for males, and 51-67th, 70-82nd and 78th centile, respectively, for females.

However, WHO charts for children age 0-2 years are based upon infants who were exclusive breast feeding for 4 months, and continued partial breast feeding up to at least 12 months and such infants are recognized to have different weight/length trajectories in their second 6 months of life, when compared to infants who have been weaned prior to this time(11). Whether our cohort is different from similar Australian infants introduced to solids at 6 months or older is unclear (as these data are not currently available), but does suggest that a closer inspection of possible effects of early introduction to solid foods on growth trajectory is warranted. Determining the approximate balance between optimal growth patterns, promotion of breastfeeding and primary prevention of allergic disease will not be straightforward. It will depend upon risk stratification at the individual family level. It is encouraging that few detrimental effects on duration of breastfeeding have been noted to date in the EAT and LEAP studies, nor in our cohort. Further exploration of this outcome in population-based cohorts, outside the confines of a supported trials setting, is required to support these initial observations.

Yours sincerely

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TABLE 1: Comparison of growth parameters from infants in BEAT cohort at 4, 8 and 12 months of age

	Placebo (rice) Median (IQR)	Egg (intervention) Median (IQR)	P value
Weight-4 months	6.88 kg (6.25-7.27)	6.70 kg (6.17-7.31)	0.89
Weight- 8 months	8.89 kg (8.10-9.48)	8.53 kg (7.97- 9.40)	0.28
Weight- 12 months	10.20kg (9.40-10.90)	9.85 kg (9.3-10.70)	0.10
Length- 4 months	63.0 cm (61.0-65.0)	62.1 cm (61.0-64.2)	0.70
Length -8 months	70.9 cm (69.0-72.5)	70.0 cm (67.0-72.0)	0.06
Length- 12 months	76.0 cm (73.8-78.0)	76.0 cm (74.0-77.5)	0.44
Head Circumference- 4 months	41.5 cm (40.5-42.5)	41.1 cm (40.5-42.0)	0.041
Head circumference- 8 months	45.0 cm (44.0-46.0)	44.0 cm (43.0-45.0)	0.0006
Head circumference –12 months	46.5 cm (45.5-48.0)	46.0 cm (45.0-47.0)	0.013

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TABLE 2: COMPARISONS BETWEEN EARLY INTRODUCTION STUDIES WITH GROWTH DATA PUBLISHED

		BEAT STUDY (egg)		**EAT STUDY** (multiple foods)(7)		**LEAP STUDY** (peanut) (10)	
		ACTIVE introduction (from 4 months)	PLACEBO	EARLY introduction (before 6 months)	STANDARD introduction (after 6 months)	EARLY introduction (from 4 months)	Peanut avoidance
Baseline (randomisation)	Assessed at:	4 months		3 months		4-11 months	
	Breastfeeding - ever - any current - exclusive	 91% 75% 42%	 90% 75% 47%	 100% 100% 100%	 100% 100% 100%	 93.4% 44.2% N/A	 91% 39.6% N/A
	Weight (kg) mean (SD) z-score (SD)	 6.8 (0.89) 0.11 (0.98)	 6.82 (0.81) 0.09 (0.93)	 6.27 (0.77) -0.14 (0.92)	 6.29 (0.76) -0.15 (0.94)	 0.0 (0.9)	 0.1 (1.0)
	Length (cm) mean (SD) z-score(SD)	 62.8 (2.8) 0.0 (1.19)	 62.9 (2.8) 0.0 (1.23)	 62.0 (2.3) 0.25 (0.98)	 62.2 (2.3) 0.26 (1.00)	 0.1 (1.1)	 0.2 (1.1)
	Weight-for length z-score (SD)	 0.24 (1.15)	 0.21 (1.09)	 -0.37 (1.02)	 -0.39 (1.02)	 NA	 NA
	HC (cm) mean, (SD)	 41.3 (1.4)	 41.7 (1.7)	 41.1 (1.3)	 41.1 (1.3)	 NA	 NA
@6mths	**Breastfeeding** - any - exclusive	 ND	 ND	 97.2% nil	 97.8% 28.6%	 NA	 NA
@8 mths	**Breastfeeding** - any - exclusive	 46% nil	 47% nil	 NA	 NA	 NA	 NA
@12 mths	**Breastfeeding** - any - exclusive	 18% nil	 28% nil	 NA	 NA	 NA	 NA
@12 months	**Duration of breastfeeding (weeks)** - Median, IQR - Mean (SD)	 NA	 NA	 52 (36-66)	 53 (38-68)	 35.1 (25.1)	 32.5 (25.1)
	Weight (kg) mean (SD) z-score (SD)	 9.99 (1.14) 0.65 (1.46)	 10.25 (1.27) 0.71 (1.25)	 10.03 (1.20) 0.28 (0.90)	 9.94 (1.17) 0.20 (0.92)	 ND 0.2 (0.9)	 ND 0.3 (1.0)
	Length (cm) mean (SD) z-score (SD)	 75.6 (3.5) 0.35 (2.24)	 75.9 (3.6) 0.30 (1.73)	 76.78 (3.1) -0.02 (1.00)	 76.6 (3.0) -0.01 (1.02)	 ND 0.1 (1.1)	 ND 0.3 (1.1)
	Weight-for length z-score (SD)	 0.62 (1.15)	 0.78 (1.09)	 0.39 (0.91)	 0.28 (0.92)	 NA	 NA
	HC (cm) mean, (SD)	 46.2 (1.5)	 46.7 (1.7)	 46.8 (1.5)	 46.8 (1.5)	 ND	 ND

ND- not done, SD- standard deviation, IQR- interquartile range, NA- not available

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