

Accepted Manuscript

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PII: S0091-6749(16)30879-X

DOI: [10.1016/j.jaci.2016.08.001](https://doi.org/10.1016/j.jaci.2016.08.001)

Reference: YMAI 12305

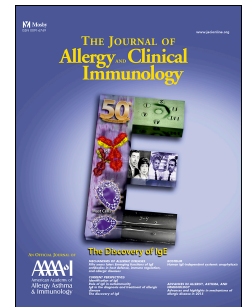
To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 25 July 2016

Accepted Date: 8 August 2016

Please cite this article as: Venter C, Groetch M, LEAPing ahead with early allergen consumption, *Journal of Allergy and Clinical Immunology* (2016), doi: 10.1016/j.jaci.2016.08.001.

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LEAPing ahead with early allergen consumption

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Keywords: Allergy, Food Allergy, Peanut allergy, Dietitian, Nutrition, Prevention

Nutritional interventions aimed at preventing food allergies have been investigated as early as the late 1980s (1). The recommended age for introducing complementary foods, particularly the major allergens, has been a highly debated topic in the field of food allergy. Data from the United Kingdom (UK) and Israel (2) indicated that peanut allergy in Jewish school-age children was about 10 times higher when peanut was introduced later in childhood (North London) than in the first year of life (Israel). This prompted the Learning Early about Peanut (LEAP) trial (3), which recruited infants 4-11 months of age and recommended consuming 2 g of peanut protein (Table 1) 3 times per week in the consumption group and no peanut protein intake (excepting precautionary allergen-

labeled products) in the avoidance group. LEAP showed that introducing peanut in the first year of life significantly reduces the development of peanut allergy, particularly in those sensitized prior to recruitment (3). Consequently, interim guidelines were published (4), and formal guidelines are being finalized at the National Institute of Allergy and Infectious Disease (NIAID).

The early introduction of peanut, however, raises many nutritional dilemmas—feasibility, sufficient dietary monitoring, and the effect on overall nutrition, growth, and allergy outcomes. A LEAP nutrition study led by Feeney(5), a registered dietitian (RD), appears in this *JACI* issue and reassuringly addressed many of these concerns (Figure 1).

Feasibility

LEAP showed that such a challenging intervention was feasible; the weekly target of peanut intake (6 g peanut protein) was achieved within the first month of enrollment and continued by 98% of subjects (628/640) up to 60 months of age(5). Notably, the study invested in having two full-time RDs give practical advice to parents in order to improve adherence.

Dietary monitoring

Two major shortcomings of most dietary trials are not measuring nutritional intake nor adherence to the required intervention, which are fueled by a lack of validated tools to assess intake. LEAP utilized a previously published and validated Food Frequency Questionnaire (FFQ) for measuring peanut intake (6). More than 86% of food diaries were received and analyzed over the course of LEAP, and portion size estimates were calculated according to set criteria to report the best estimate. In the future, electronic food diaries may further improve the data quality.

Nutrition

Feeney et al. report that there were no differences in breastfeeding characteristics before or after randomization. Although mothers breastfed for slightly less long post randomization in the consumption than avoidance group (mean breastfeeding duration post randomization 4.7 vs. 4.9 months, respectively), the mean age of ceasing breastfeeding was slightly higher in the consumption than avoidance group (8.1 vs. 7.5 months, respectively). This finding is extremely important, as early complementary feeding challenges the 6-month exclusive breastfeeding advice from the World Health Organization (7). However, LEAP was not powered to detect a significant difference in breastfeeding trends between groups and is therefore not able to totally reassure that early weaning does not affect breast-feeding duration. Only 45% of subjects were still breastfed at randomization, and 89% of subjects already had exposure to formula.

Weaning is a time of transition when the infant learns about new flavors and textures and develops autonomy in feeding; it is a crucial period for establishing and maintaining an appropriate growth trajectory. The way that we feed infants during the early years also programs long-lasting food preferences (8). Healthy preferences are established by limiting exposure to sweet/salty/fatty foods and exposing children to a wide variety of healthful foods (8). There are concerns that medicalizing and regimenting the weaning process could lead to anxiety in parents and reduce infant diet diversity (9).

LEAP showed no difference in *mean total energy intake* or *mean protein intake* at all time points (Figure 1). Higher protein intake may be a risk factor for developing obesity (10). As plant-based proteins may not yield this effect; longer-term follow-up of LEAP participants is required.

Mean fat intake was higher in the consumption group, and fatty acid intake was similar apart from higher mono-unsaturated fatty acid intake in the consumption group at 60 months. Carbohydrate intake was lower in the consumption group and was below the UK daily recommended value (DRV) at 12 and 21 months, but carbohydrate needs were met at all time points by United States (US) standards.

Interestingly, both groups reported that sodium intake was 144-244% of the UK DRV, but the mean intake did not differ between the groups. There were no differences in the mean % intake for most micronutrients studied (Figure 1), but these data should be interpreted with caution, as nutrient supplementation was not taken into account in the dietary analysis.

Growth

Peanut is naturally considered to be a high-fat, high-protein food, and many peanut-containing products have added fats, sugar/honey, and/or salt. The Bamba snack used in LEAP contains palm oil and added salt; as some other peanut containing foods (Table 1). Notably, however, the LEAP peanut intervention did not affect any measures of growth negatively; there were no differences between groups in weight, height, body mass index, waist circumference, or subscapular and triceps skin folds for up to 5 years of age.

Allergy outcomes

The LEAP intervention significantly reduced the occurrence of peanut allergy in the consumption group compared to the avoidance group. Furthermore, LEAP showed that nutritional interventions can be performed with good adherence and without negatively affecting overall nutritional intake.

Incorporating RDs

Importantly, RD input was essential for the success of LEAP, not only for feasibility of but also for nutritional guidance and safety. Though LEAP demonstrated that early peanut consumption was feasible and did not negatively affect growth and nutrition, the key words “with dietetic supervision” is an unspoken but important addendum to that conclusion. Elements such as lack of breastfeeding, early consumption of complementary foods, high intake of sweetened beverages, and low intake of fruits and vegetables are indicated by the Institute of Medicine (IOM) as risk factors for obesity, which in turn is associated with an increased risk of allergic disease. Interestingly, LEAP observed a daily intake of 5 or more servings of fruit and vegetables in both groups. This finding is unusual, as the Feeding Infants and Toddlers Study (n = 3,273) found that 16-27% of children did not consume any fruit or vegetable in any amount on the survey day and that a sweet or sweetened beverage was more likely to be consumed than a fruit or vegetable by 2 years of age (11). This contrast suggests that incorporating RDs positively influenced the healthiness of the diet.

As peanut is a calorically, protein-, and fat-dense food, it is important that families understand the nutritional contribution of regular peanut intake to the diet and learn how to balance macronutrients appropriately in the foods that they serve. The authors hypothesized that protein homeostasis may be a result of protein regulation occurring in children from an early age; however, infants and young children can only choose from the food that is provided. Thus, caregiver food choices exert a great influence on protein intake, and those feeding infants will likely require guidance. We could not agree more with the author’s statement—“The favorable LEAP results may not be generalizable to children in the general population who have less dietetic support with peanut consumption, less frequent monitoring of peanut intakes and of growth and nutritional

intakes during treatment.” In some countries, such as the USA, access to a pediatric dietitian is rare during the weaning period and throughout childhood, and such an intervention could affect nutritional intake.

The JACI, by including the LEAP nutrition study and this editorial for its readership, highlights the importance of nutritional interventions on allergy outcomes to the allergy field and the public. The future of nutritional outcomes in the conduct of allergy clinical trials therefore seems promising. Pro-actively measuring nutritional intake more accurately and investigating the effect of nutrition and the underlying diet on the genome and immunologic biomarkers would be future steps. This will enable researchers to identify whether dietary factors other than the planned intervention affect trial outcome. One potential dietary factor is advanced glycation end products (AGEs)(12), which could act as mediators of inflammatory disorders. Despite the fact that roasted peanuts are considered to contain high levels of AGEs, the LEAP intervention reduced the development of peanut allergy. Further investigations may elucidate whether a healthy diet, such as that of the LEAP consumption group participants (eating e.g. less crisps/chips/fruit juices/smoothies/jams/ low-energy-dense sauces such as gravy, ketchup, mustard, tomato-based pasta sauce), may have mitigated the effect of any other dietary factors (e.g., AGEs), while allowing the tolerogenic effect of oral peanut protein intake.

In summary, LEAP has set an improved standard for future nutritional intervention trials focusing on diagnosis, management, and/or prevention of food allergies. The success of LEAP was partially due to incorporating RDs as contributors on the research and clinical management team. This is a positive trend that we hope to see continue, as RDs are being welcomed into the AAAAI and actively participating in the Annual Meeting, as well

as being further integrated into research efforts. We hope that the LEAP team-approach model will encourage further support for training, education and funding of RDs, as the overall quality of the diet may be a preventative factor for food allergy.

We would like to thank Shawna Hottinger for assisting with the editing of the document.

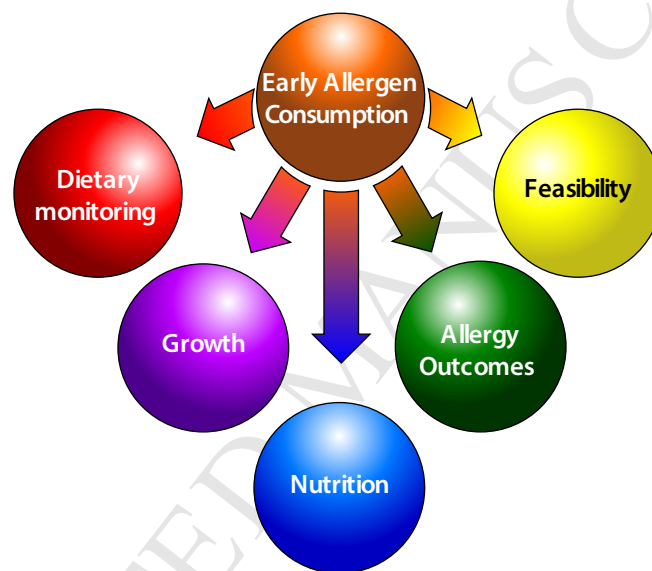
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Table 1. Foods containing 2 g of peanut protein

Per approximately 2 g peanut protein:	Bamba® (17 g)	Peanut butter ^a (10 g)	Peanut butter UK (12 g)	Peanuts (8 g)	Peanut butter powder ^b (4 g)	Peanut flour ^b (4 g)	US cereal (140 g)	UK cereal (100 g)	US chocolate/candy (21 g)
kcal	93	59	80	45	15	13	550	600	105
Sugar (g)	0.4	0.65	0.72	0.38	0.4	0.33	45	35	10.5
Salt (mg)	68	48	0	1	31	7	649	880	75
Fat (g)	6.1	4.95	6.98	3.94	0.49	0.02	7.5	5	6.5

^aUSDA commodity^baverage information from manufacturers

**LEAP**

- Utilized a validated FFQ and 3-day food diaries
- Used standard methods for estimating portion sizes
- Vitamin and mineral supplements were not taken into account.

Further questions

- Would electronic food diaries in future enhance quality of information?

Leap

- No difference in weight, height, BMI, waist circumference, and subscapular and triceps skin fold up to 5 years of age

Further questions

- What is the long-term impact of the LEAP intervention on growth?

LEAP

- No differences in breastfeeding characteristics
- No difference in protein and energy intake
- Protein intake above UK RNI for both groups
- Mean fat intake higher in consumption group but still meeting UK RDV
- Carbohydrate intake lower in consumption group due to eating less starchy (21 and 30 months) and sugary (30 and 60 months) food
- No difference in calcium, zinc, iron and Vitamin D intake, although improvements overall are needed in regard to iron and zinc
- Sodium intake high for both groups
- No difference in fruit and vegetable intake (≥ 5 per day for both groups)

Further questions

- Can we improve dietary iron and zinc to meet recommended intake levels?
- Can we reduce the sodium load in the intervention group by choosing "no salt added" peanut products?
- Does the LEAP intervention have long-term effects on food intake, preference and nutritional status?

LEAP

- Showed that the intervention was feasible with high levels of adherence achieved with essential RD input to provide practical advice to parents and ensure regular follow-up

Further questions/challenges

- Standardize measuring instructions i.e., 1 "well-rounded" teaspoon in LEAP papers vs. 2 leveled teaspoons in upcoming guidelines from NICE and AAAAI

Leap

- Less peanut allergy in consumption group than avoidance group
- No difference between groups in timing of introducing other solid foods or introducing other major allergens

Further questions

- How did intervention and underlying diet interact with genetics, immune system, and microbiome?
- Did other immunomodulating nutrients such as Vitamin D, omega-3 and 6 fatty acids; fruit and vegetable intake; and other dietary factors (e.g., AGEs) affect/amplify the trial outcome?