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Impact of peanut consumption in The LEAP Study: feasibility, growth and nutrition

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ABSTRACT

BACKGROUND

Early introduction of peanut is an effective strategy to prevent peanut allergy in high-risk infants; however, feasibility and effects on growth and nutritional intake are unknown.

OBJECTIVE

To evaluate the feasibility of introducing peanut in infancy and explore effects on growth and nutritional intake up to 60 months of age.

METHODS

In the Learning Early About Peanut Allergy (LEAP) trial, 640 atopic infants aged 4-11 months were randomly assigned to consume (6g peanut protein/week) or avoid peanut until 60 months of age. Peanut consumption and early feeding practices were assessed by questionnaire. Dietary intake was evaluated with prospective food diaries. Anthropometric measurements were taken at all study visits.

RESULTS

Peanut was successfully introduced and consumed until 60 months with median peanut protein intake of 7.5g/week (IQR 6.0-9.0) in the consumption group compared to 0g in the avoidance group. Introduction of peanut in breastfeeding infants did not affect the duration of breastfeeding. There were no differences in anthropometric measurements or energy intakes between groups at any visits. Regular peanut consumption led to differences in dietary intakes. Consumers had higher intakes of fat and avoiders had higher carbohydrate intakes; differences were greatest at the upper quartiles of peanut consumption. Protein intakes remained consistent between groups.

CONCLUSIONS

Introduction of peanut proved feasible in infants at high-risk of peanut allergy and did not affect the duration of breastfeeding nor impact negatively on growth or nutrition. Energy balance was achieved in both groups through variations in intakes from fat and carbohydrate while protein homeostasis was maintained.

Key words: food allergy, allergy prevention, peanut, infant feeding, breast feeding, nutrition, growth, prospective food diary, protein homeostasis

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Abbreviations used:

LEAP: Learning Early About Peanut Allergy

FFQ: Food frequency questionnaire

BMI: Body mass index

DRV: Dietary reference value

RNI: Reference nutrient intake

LRNI: Lower reference nutrient intake

%TE: Percentage of total energy

ITT: Intent to treat

IQR: Interquartile range

CAPSULE SUMMARY

Our results demonstrate that the dietary intervention of regular peanut consumption from infancy as a strategy to prevent peanut allergy in high-risk infants is easily achieved and has no adverse effects on growth or nutrition.

CLINICAL IMPLICATIONS STATEMENT

Peanut consumption as a strategy to prevent peanut allergy, introduced in infancy and maintained to 5 years of age, is nutritionally safe even when consumption occurs at high levels.

INTRODUCTION

We recently reported that early introduction of dietary peanut results in a marked reduction in the development of peanut allergy in high-risk infants.(1) The LEAP Study intervention disagrees with current WHO advice which recommends that infants should be exclusively breastfed for the first six months of life (no other food or water).(2) Similar to the dietary practices in the USA and Australia, the mean age of introduction of peanut-containing foods in the UK is 36 months and only around 8-10% of infants eat peanut before one year of age.(3-5)

Many professional allergy societies now recommend the LEAP Study intervention of early peanut introduction in infancy followed by ongoing regular consumption until 60 months of age for the prevention of peanut allergy in high-risk infants.(6-8) This advice may in time be extended to encompass all children regardless of their risk of peanut allergy. Whilst regular consumption of peanut from an early age appears to be an effective strategy for the prevention of peanut allergy in high-risk infants as well as in infants recruited from a general population, there could be unexpected consequences for growth and nutrition. (1,9) Anecdotally, no adverse health consequences have been associated with this practice in countries such as Israel, where peanut is regularly consumed by infants and young children. Epidemiological studies describe beneficial health effects of regular nut consumption in children and adolescents including a lower body mass index (BMI), a higher healthy eating index and higher intakes of micronutrients.(10,11). Furthermore, there is a long tradition of using peanut as the mainstay of nutritional fortification programs in developing countries and even in the USA as part of the supplemental nutrition program for Women, Infants and Children.(12) Despite these dietary practices, intervention studies involving regular consumption of peanut or similar energy-dense foods in early childhood are lacking in the literature.

The LEAP intervention recommended an intake of 6g peanut protein/week, equivalent to 3 teaspoons of peanut butter, based on the upper quartile of intake observed in infants in Israel (7.1g peanut protein/month).(3) It is unknown if this dietary recommendation is challenging to incorporate into the diet of the infant, or will lead to an imbalanced diet if eaten throughout childhood.

The objectives of this study were to evaluate the feasibility of introduction of peanut in infancy and the effects of regular ongoing consumption on growth, nutrition and diet of atopic infants enrolled onto a randomized controlled trial. Using data from the LEAP study, we compare infants randomized to consumption or avoidance of peanut during the first 5 years of life.

METHODS

Study Design

This study represents a planned secondary analysis from the LEAP trial, a randomized, open-label, controlled trial comparing two strategies to prevent peanut allergy: consumption or avoidance of peanut in high-risk infants. The primary outcomes and adverse event profile of this trial have been previously published.(1)

Dietary intervention

Infants aged 4 to <11 months with severe eczema and/or egg allergy were randomly assigned to consume or avoid peanut until 60 months of age. Participants randomized to peanut consumption (except those who were diagnosed with peanut allergy) were advised to eat at least 6g peanut protein/week distributed over three or more meals/week until age 60 months. The preferred peanut source was Bamba®, a snack-food manufactured from peanut butter and puffed maize; this snack was suitable for infants and could also be easily softened to a smooth texture (with warm milk or water) and added to other infant foods, such as oatmeal. Smooth peanut butter (Sunpat® and Duerr's® brands) was also provided by the study center; for safety, it was advised that this be loosened using warm (cooled, boiled) water prior to feeding infants.(13) Due to choking risk, it was also recommended that whole peanuts be avoided during early childhood.(13) Participants randomized to avoidance (and participants who were diagnosed with peanut allergy) were given detailed dietary advice on how to avoid exposure to peanut during study participation. They were advised that avoidance of products with peanut precautionary allergen labelling (where peanut was not a listed ingredient) was unnecessary unless diagnosed peanut allergic. Further details of the dietary advice provided are available in this article's Online Repository (Figure E1 and Figure E2).

Peanut consumption monitoring

Peanut consumption was monitored using a validated food frequency questionnaire (FFQ) at intervals as detailed in the schedule of events; adherence criteria are detailed elsewhere.(1,14) For subgroup analyses, peanut consumers were divided into quartiles based on average peanut consumption throughout the study as measured by FFQ.

Growth and anthropometric measurements

Anthropometric measurements were taken in duplicate and the mean value recorded by trained staff at each study visit. Length and height were measured to the nearest 0.1cm, using an infant measuring table (<2 years) or wall-mounted stadiometer (Harpenden, Crymych, UK) and weight to the nearest 0.1kg using an electronic scale (Marsden M700, Rotherham, UK). Waist circumference was measured to the nearest 0.1cm using an anthropometric measuring tape, triceps and subscapular skinfold thickness were measured to the nearest 0.1mm using skinfold calipers (Holtain, Crymych, UK). Body Mass Index (BMI) was calculated as weight/(height*height). Measurements were transformed into z-scores using the WHO Child Growth Standards.(15)

Nutritional intake monitoring

A 3-day food diary was completed prior to (or shortly after) each study visit. Detailed instructions were provided by study dietitians on how to complete the diary accurately. Food diaries were checked for completeness by a dietitian/dietetic assistant at the study visit and additional information or clarification sought where required including cooking methods and portion sizes. Those who had not completed some or all of the food diary were asked to return the diary by mail after the clinic visit.

Foods and drinks were entered into Dietplan 6 (Forestfield Software Limited, UK) and analyzed to produce average daily energy, macronutrient and micronutrient intakes. Portion weights were assigned based on information from manufacturers, food packaging and/or estimated from standard food portion sizes all scaled down for age based on the details recorded in the food diary and portion size resources.(16-21)

Nutrient intakes were compared with UK Dietary Reference Values (DRVs) by age and sex.(22-24) Further details on nutritional intake monitoring are available in this article's online repository.

Types of foods consumed (average daily consumption in grams) over the duration of the study were compared between avoidance and consumption groups. All food codes entered into Dietplan were mapped to 61 food groups based on those reported elsewhere.(25) In addition, we separated out peanut-containing foods and specialist allergen-free products (e.g. wheat/gluten free cereals) which are more frequently eaten in this population compared to the general population.

Statistical analysis

All analyses were carried out in the intention to treat (ITT) population comparing the two randomized treatment groups cross-sectionally. Anthropometry and skin fold measurements were compared using general linear models adjusted for treatment assignment and gender. Percentage of total energy intakes were compared using equivariance t-tests. The proportion of participants with micronutrient intakes below lower reference nutrient intake (LRNI) levels were compared with Fisher's exact tests. Micronutrient intakes, total protein intake, percent of total protein intake, and average daily consumption of different types of foods were compared using Wilcoxon tests.

RESULTS

Study participants

The median age of participants at screening was 7.8 months (IQR, 6.3 to 9.1). The median duration of study participation was 4.4 years. Additional baseline characteristics have been previously published.(1)

Peanut consumption

In the consumption group, average peanut intake exceeded the recommended study intake within the first month (median 7.5g/week; IQR 6.0-9.0g/week) post-randomization, was sustained during the first six months of the intervention (median 7.9g/week; IQR 6.6-9.2g/week) and on average increased throughout the study (**Table I and Fig 1**). Median peanut intake in the avoidance group remained at 0g throughout the study.

The main sources of peanut changed over time **(see Fig E3 in this article's Online Repository):** up until 21 months of age, participants consumed Bamba as their predominant source of peanut protein with peanut butter becoming the main source as participants got older. Other sources, including peanut-containing breakfast cereals and confectionary (e.g. cookies, chocolate or snack bars containing peanut) were minor sources of peanut protein. Crushed or ground whole peanuts were eaten by some participants from 12 months of age.

Infant feeding pre- and post-randomization

There were no differences in breastfeeding characteristics between treatment groups before or after randomization (**Table I**). The introduction of peanut did not result in a significantly shorter duration of breastfeeding in the peanut consumption group, even when adjusted for maternal highest level of education, gestational age at birth, and ethnicity. The mean duration of breastfeeding post-randomization was 4.7 months in the consumption group and 4.9 months in the avoidance group (p=0.56). At the time of randomization, 290 participants had introduced infant formula in the consumption and 287 in the avoidance group. Solid foods were introduced at a mean age of 5 months (range 2.0-7.0 months) in both groups. There were no differences in the age at which the following food allergens were introduced pre-randomization: dairy foods (excludes infant formula), egg, wheat, fish, soya, tree nuts.

Growth, anthropometry and nutritional intakes

Anthropometric measures and nutrient intakes were compared between randomized groups and in subgroup analyses which compared the highest quartile of peanut consumers with the peanut avoidance group.

There were no differences in weight, height, BMI or other anthropometric measurements (waist circumference, subscapular and triceps skin fold thickness) between the consumption and avoidance groups at any time during the study (**Fig 2**). Even when comparing the highest quartile of peanut consumers to peanut avoiders, there were no differences in anthropometric measures (**see Fig E4 in this article's**

Online Repository). There were also no differences in anthropometric measurements when compared to WHO child growth standards (**see Table E1 in this article's Online Repository**).

Food diary return rates

There were no differences between randomized groups in the numbers of food diaries returned **(see Table E2 in this article's Online Repository)**.

Energy and macronutrient intakes

There were no differences in total energy intakes between randomized groups at any study time points and for the highest quartile of peanut consumers compared to peanut avoiders (**see Fig E5 in this article's Online Repository**).

The percentage of total energy (%TE) from carbohydrate was higher in the avoidance group compared to the consumption group at all post-randomization time points. Conversely, the %TE from fat was higher in the consumption group compared to the avoidance group at all post-randomization time points (**Fig 3B**). A cross-sectional comparison of macronutrient intakes across quartiles of peanut consumption found that small differences in contributions of carbohydrate and fat to %TE were accentuated in the upper quartiles of peanut consumption whereas %TE from protein remained consistent at all post-randomization time points for all quartiles of peanut consumption (**Fig 3C**) and in the avoidance group. When macronutrient subgroups were compared, %TE from starch was significantly higher at 21 and 30 months and %TE from sugars was significantly higher at 30 and 60 months in the avoidance group (**see Fig E6a in this article's Online Repository**). There were no differences between randomized groups in %TE from saturated or polyunsaturated fatty acids at any time point. Intakes of monounsaturated fatty acids were significantly higher in the consumption group at 60 months. (**see Fig E6b in this article's Online Repository**).

When compared with UK DRVs, mean protein intakes in both groups were well above the RNI whilst fat intakes met DRVs at all study visits.(22) Mean carbohydrate intakes fall just above the recommended 50%TE for children aged 2 years and older in the avoidance group at all post-randomization time points. In the consumption group carbohydrate intakes fall just below the DRV at 12 and 21 months, are at the DRV at 30 months and just above at 60 months.(23)

Sodium, calcium, iron, zinc, vitamin D

As peanut-containing foods often have added sodium, we assessed this intake between peanut avoiders and consumers. Sodium intake was elevated for all participants (144-244% above UK recommendations); this intake was not significantly different between randomized groups or in the highest peanut consumers compared to peanut avoiders. (**see Tables E3a, E3b and E3c in this article's Online Repository Table**).(24,26)

Calcium, iron, zinc and vitamin D intakes (expressed as a percentage of the RNI) were compared as intakes of these micronutrients are often compromised in children with food allergies.(27-29) There were no differences in intakes for calcium (except at 12 months), iron or zinc. There were no differences between groups in intakes of vitamin D; however, intake decreased over time. There is no RNI for vitamin D above 3 years of age so intake as a percentage of RNI at 60 months could not be calculated (**Table II**).

There were no differences in the proportion of participants with intakes of iron, calcium or zinc below the lower reference nutrient intake (LRNI) (**Table III**). A higher than expected proportion of participants in both randomized groups had intakes of iron and zinc below the LRNI; at baseline, 12, 21 and 30 months of age for iron and at all time points for zinc (apart from peanut avoidance group at 21 months).

Foods consumed

Participants randomized to consumption ate significantly less of the following food groups: 'crisps/chips and savory snacks', 'high fiber bread', 'fruit juices and smoothies', 'spreads' (e.g. jam, yeast extract), 'low energy dense sauces' (includes gravy, ketchup, mustard, tomato-based pasta sauce), 'sunflower/other oils and fat spreads' and 'dairy free spreads' (**see Table E4 and Table E5 in this article's Online Repository**).

To see whether the consumption of peanut, a source of vegetable protein, led to a reduced intake of protein from other sources in order to maintain overall protein

homeostasis, we compared the sources of protein (expressed as total intake in grams and percent of total protein intake) in the avoidance and consumption groups. There were no differences between randomized groups in protein intake from different sources at any post randomization time point (except for 'other' sources at 12 months) (**Table IV**). However, when we compared the highest quartile of peanut consumers to the avoiders, we found significantly higher intakes of vegetable protein and lower intakes of animal protein expressed as a percent of total grams at 21, 30, and 60 months. (**Table V**).

DISCUSSION

The LEAP Study successfully introduced peanut to the diet of infants randomized to peanut consumption. The recommended intake was achieved in the first month of the study and maintained throughout, confirming the ease with which peanut can be introduced to the infant diet. Whilst Bamba and peanut butter accounted for the majority of peanut intake during the early years of the trial, peanut butter consumption increased after 21 months, showing that the intervention can be undertaken using a variety of peanut products. Despite eating different peanut-containing foods, even whole peanuts from the age of 12 months, no episodes of participant choking or aspiration were reported. However, clinicians should still emphasize that whole peanuts and chunks of peanut butter are a choking hazard in young children and should not be consumed before 5 years of age.(6-8,13)

The timing of introduction of other allergenic foods was equivalent between groups prior to randomization. A high proportion of LEAP infants were breastfeeding at the time of introducing peanut and, reassuringly, peanut consumption did not affect the duration of breastfeeding. Whilst the study intervention does not comply with WHO guidelines on exclusive breastfeeding, it did not negatively impact breastfeeding itself. This is important due to concerns that introduction of solid foods before 6 months of age will reduce breastfeeding duration.(30) Our finding is supported by other studies.(31,32) We know that in the UK, 30% of infants have already introduced solid foods by 4 months and 75% by 5 months of age i.e. do not comply with WHO guidelines on exclusive breastfeeding.(5) In addition, for some infants the introduction of allergenic foods between 4-6 months may be important for allergy prevention.(33-

35) Our results show that in high-risk infants, early consumption of peanut from 4 months of age is safe and effective for allergy prevention.

Peanut consumption did not lead to differences in weight, height, BMI, or other anthropometric measurements even amongst the highest quartile of peanut consumers.

Macronutrient intakes in both groups were in line with UK recommendations apart from carbohydrate which fell close to the recommended intake (DRV for 2-5 year olds defined in 2015). When compared to US dietary reference intakes, which have wider ranges than the UK, both groups meet acceptable macronutrient distribution ranges for protein, fat and carbohydrate at all study visits.(36) Sodium intakes were above UK recommended maximum intakes in both groups but below US recommended maximum intakes.(26) Although iron and zinc intakes were low for some participants, similar proportions of young children with intakes below the LRNI have been reported by the recent UK national dietary survey.(37)

Nutritional priorities of maintenance of energy and protein homeostasis are achieved in different ways in peanut consumers compared to avoiders. Peanut consumption led to a higher fat intake and a lower carbohydrate intake compared to avoidance while energy balance was maintained in both groups. These differences in fat and carbohydrate intakes were accentuated in the highest quartile of peanut consumers while protein intake stayed constant across quartiles of peanut consumption and in the avoidance group. We believe this shows evidence of protein regulation occurring in children from an early age. The addition of peanut-containing foods did not affect %TE intake from protein because intake from other sources (animal protein sources) was decreased to maintain protein homeostasis; energy balance was maintained by adjusting non-protein energy intakes (i.e. fat and carbohydrate). Similarly, an experimental study found that adult participants restored protein homeostasis through increased selection of high protein foods such that they had a 13% higher protein intake after a 14 day low protein diet compared to after a high protein diet. (38)

Peanut consumers made different food choices to peanut avoiders. They had a lower intake of fat spreads and oils than the avoidance group; however, their overall intake of fat as %TE was higher. This likely reflects their using peanut butter in place of fat

spreads. Peanut butter tends to be spread more generously and also parents/caregivers may have given larger portions to ensure the participant achieved their target peanut protein intake (a generous teaspoon or 8g of smooth peanut butter contains approximately 2g of peanut protein).

Peanut consumers also ate significantly less crisps/chips and savory snacks, high fiber bread, fruit juices and smoothies, spreads (e.g. jam, yeast extract), low energy dense sauces (includes gravy, ketchup, mustard, tomato-based pasta sauce), than peanut avoiders. Many of these foods have a high carbohydrate content supporting the lower carbohydrate intakes found in the consumption group. We are unable to say whether reduced consumption of these foods is due to development of different taste preferences through repeat peanut exposure from infancy (increased liking for fruit and vegetables has been observed in children with repeat exposure from infancy), or whether having a predetermined snack means that other popular snack choices are not selected. Alternatively, regulatory processes may influence self-selection of specific foods to avoid imbalances in protein and total energy intake which we observe occurs with intakes of different protein sources in the highest peanut consumers.(39-41)

The nutritional intake data is subject to the limitations of estimated food diaries which are well described including the challenges of accurately quantifying portion sizes, over-, under- and mis-reporting of dietary intakes by participants and missing nutritional data in UK food tables.(42) Nonetheless this method provides a level of detail about dietary intake that cannot be obtained by other methods such as FFQs.(43) We have also previously described the limitations associated with the use of FFQ's for the accurate determination of peanut intake.(14) The favorable LEAP nutritional 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.

Our study has several strengths. The high study retention over 5 years (98%), high adherence to the randomized intervention (92%), regular collection of peanut consumption and avoidance information by FFQ (median number of 80 phone contacts per participant) ensure robust data were gathered. This is enhanced by the high return

rate of food diaries (83% returned ≥4 food diaries) with collection on 5 occasions from infancy to 60 months alongside detailed growth data. In addition, we show that infants and young children not only maintain energy balance in response to dietary manipulation but also regulate their protein intakes.

In conclusion, this is the first randomized trial to introduce peanut in infancy and demonstrates that the intervention is easily achieved and has no adverse dietary sequelae. In addition to a reduction in peanut allergy at 60 months of age, peanut consumption did not negatively impact growth in childhood even at the highest quartile of consumption. These findings are reassuring in the context of new consensus communications to feed peanut early to high-risk, atopic infants.(6-8) Interestingly, we found that despite peanut consumers making different food choices to peanut avoiders, both achieved nutritional priorities of energy and protein homeostasis. This occurs through a trade-off between carbohydrate and fat contributions to energy intake.

Implications for clinicians:

Peanut consumption as a strategy to prevent peanut allergy, introduced in infancy is nutritionally safe even when consumption occurs at high levels. However, parents/caregivers must be reminded that whole peanuts should not be given to children below 5 years due to choking risk.

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REFERENCES

(1) Du Toit G, Roberts G, Sayre PH, Bahnson HT, Radulovic S, Santos AF, et al. Randomized Trial of Peanut Consumption in Infants at Risk for Peanut Allergy. N Engl J Med 2015 02/26; 2015/08;372(9):803-813.

(2) World Health Organization (WHO) Fifty-fifth World Health Assembly. Infant and young child nutition. Global strategy on infant and young child feeding. 2002;A55/15.

(3) Du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, et al. Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. J Allergy Clin Immunol 2008 Nov;122(5):984-991.

(4) Hourihane JO, Aiken R, Briggs R, Gudgeon LA, Grimshaw KEC, DunnGalvin A, et al. The impact of government advice to pregnant mothers regarding peanut avoidance on the prevalence of peanut allergy in United Kingdom children at school entry. J Allergy Clin Immunol 2007 5;119(5):1197-1202.

(5) Health and Social Care Information Centre (HSCIC). Infant Feeding Survey 2010. 2012.

(6) Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, et al. Consensus Communication on Early Peanut Introduction and the Prevention of Peanut Allergy in High-Risk Infants. Allergy 2015 Jul 5.

(7) Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. Ann Allergy Asthma Immunol 2015 Aug;115(2):87-90.

(8) Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. J Allergy Clin Immunol 2015 Aug;136(2):258-261.

(9) Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. N Engl J Med 2016 Mar 4.

(10) Griel AE, Eissenstat B, Juturu V, Hsieh G, Kris-Etherton PM. Improved diet quality with peanut consumption. J Am Coll Nutr 2004 Dec;23(6):660-668.

(11) Moreno JP, Johnston CA, El-Mubasher AA, Papaioannou MA, Tyler C, Gee M, et al. Peanut consumption in adolescents is associated with improved weight status. Nutr Res 2013 Jul;33(7):552-556.

(12) United States Department of Food and Agriculture. Food and Nutrition Service. The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). Available at: http://www.fns.usda.gov/wic/women-infants-and-children-wic. Accessed January, 2016.

(13) Committee on Injury, Violence, and Poison Prevention. Prevention of choking among children. Pediatrics 2010 Mar;125(3):601-607.

(14) Sofianou-Katsoulis A, Mesher D, Sasieni P, Du Toit G, Fox AT, Lack G. Assessing Peanut Consumption in a Population of Mothers and Their Children in the UK. World Allergy Organ J 2011;4(2):38-44.

(15) WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization.; 2006.

(16) Nelson M, Atkinson M, Meyer J. A Photographic Atlas of Food Portion Sizes. London: Ministry of Agriculture, Fisheries and Food.; 1997.

(17) The Caroline Walker Trust. Eating Well for 1-4 Year Olds: Practical Guide.: The Caroline Walker Trust; 2010.

(18) The Caroline Walker Trust. Eating Well for 5-11 Year Olds: Practical Guide.: The Caroline Walker Trust; 2010.

(19) Crawley H, Mills A, Patel S, Food Standards Agency. Food portion sizes. 3rd ed. London: The Stationery Office; 2002.

(20) Wrieden WL, Longbottom PJ, Adamson AJ, Ogston SA, Payne A, Haleem MA, et al. Estimation of typical food portion sizes for children of different ages in Great Britain. Br J Nutr 2008 Jun;99(6):1344-1353.

(21) Cheyette C, Balolia Y. Carbs and Cals. Chello Publishing Limited; 2010.

(22) Great Britain. Working Party on the Composition of Foods for Infants and Young Children, Whitehead RG, Panel on Dietary Reference Values, Great Britain. Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom: report of the Panel on Dietary Reference Values of the Committee on Medical Aspects of Food Policy. London: H.M.S.O.; 1991.

(23) Scientific Advisory Committee on Nutrition. Carbohydrates and Health. The Stationery Office; 2015.

(24) Scientific Advisory Committee on Nutrition. Salt and Health. The Stationery Office; 2003.

(25) Johnson L, Mander AP, Jones LR, Emmett PM, Jebb SA. Energy-dense, low-fiber, high-fat dietary pattern is associated with increased fatness in childhood. Am J Clin Nutr 2008 Apr;87(4):846-854.

(26) U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans 2010. 7th ed. Washington DC: U.S. Government Printing Office; 2010.

(27) Christie L, Hine RJ, Parker JG, Burks W. Food allergies in children affect nutrient intake and growth. J Am Diet Assoc 2002 Nov;102(11):1648-1651.

(28) Noimark L, Cox HE. Nutritional problems related to food allergy in childhood. Pediatr Allergy Immunol 2008 Mar;19(2):188-195.

(29) Meyer R, De Koker C, Dziubak R, Godwin H, Dominguez-Ortega G, Shah N. Dietary elimination of children with food protein induced gastrointestinal allergy - micronutrient adequacy with and without a hypoallergenic formula? Clin Transl Allergy 2014 Oct 3;4(1):31-7022-4-31. eCollection 2014.

(30) Grummer-Strawn LM, Scanlon KS, Fein SB. Infant feeding and feeding transitions during the first year of life. Pediatrics 2008 Oct;122 Suppl 2:S36-42.

(31) Jackson DA, Imong SM, Wongsawasdii L, Silprasert A, Preunglampoo S, Leelapat P, et al. Weaning practices and breast-feeding duration in Northern Thailand. Br J Nutr 1992 Mar;67(2):149-164.

(32) Hornell A, Hofvander Y, Kylberg E. Solids and formula: association with pattern and duration of breastfeeding. Pediatrics 2001 Mar;107(3):E38.

(33) Prescott SL, Smith P, Tang M, Palmer DJ, Sinn J, Huntley SJ, et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. Pediatr Allergy Immunol 2008 Aug;19(5):375-380.

(34) Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. J Allergy Clin Immunol 2010 Jul;126(1):77-82.e1.

(35) Koplin JJ, Osborne NJ, Wake M, Martin PE, Gurrin LC, Robinson MN, et al. Can early introduction of egg prevent egg allergy in infants? A population-based study. J Allergy Clin Immunol 2010 Oct;126(4):807-813.

(36) Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington DC: National Academies Press; 2002/2005.

(37) Food Standards Agency, Public Health England. National Diet and Nutrition Survey Headline Results from Years 1, 2, 3 and 4 (Combined) of the Rolling Programme (2008/2009–2011/12). https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/310995/NDNS_Y1_to_4_UK_report.pdf . 2014.

(38) Griffioen-Roose S, Mars M, Siebelink E, Finlayson G, Tome D, de Graaf C. Protein status elicits compensatory changes in food intake and food preferences. Am J Clin Nutr 2012 Jan;95(1):32-38.

(39) Cooke LJ, Wardle J, Gibson EL, Sapochnik M, Sheiham A, Lawson M. Demographic, familial and trait predictors of fruit and vegetable consumption by pre-school children. Public Health Nutr 2004 Apr;7(2):295-302.

(40) Forestell CA, Mennella JA. Early determinants of fruit and vegetable acceptance. Pediatrics 2007 Dec;120(6):1247-1254.

(41) Maier A, Chabanet C, Schaal B, Issanchou S, Leathwood P. Effects of repeated exposure on acceptance of initially disliked vegetables in 7-month old infants. Food Quality and Preference 2007;18:1023-1032.

(42) Livingstone MB, Robson PJ, Wallace JM. Issues in dietary intake assessment of children and adolescents. Br J Nutr 2004 Oct;92 Suppl 2:S213-22.

(43) Emmett P. Assessing diet in longitudinal birth cohort studies. Paediatr Perinat Epidemiol 2009 Jul;23 Suppl 1:154-173.

FIGURE LEGENDS

Table I. Infant feeding characteristics

[1] P-value is from a Chi-Square test comparing the percentage of subjects in the Avoidance to the Consumption group. [2] P-value is from a Wilcoxon Rank Sum Test comparing the distributions in the Avoidance to the Consumption group. [3] Dairy refers to solid foods (e.g. yogurt or cheese). [4] Source of Peanut Consumption comes from the Food Frequency Questionnaire (FFQ).

Fig 1. Average peanut consumption over time (grams peanut protein per week)

Peanut consumption summarized throughout the study from FFQs completed at baseline and between study visits. Median weekly consumption during the first 2 years of life (per-protocol adherence) has been previously published.(1) Grey dots denote subjects randomized to the avoidance group. Green dots denote subjects randomized to the consumption group. Red circles denote participants who were peanut allergic at 60 months.

Fig 2. Growth & anthropometry in avoidance and consumption groups (ITT sample)

Measures are weight, height, body mass index (BMI), subscapular skinfold thickness, triceps skinfold thickness, waist circumference. The bottom panel displays the difference in means (consumption – avoidance) and 95% confidence intervals between the two randomized groups resulting from a model adjusted for randomization assignment and gender.

Fig 3. Macronutrient intakes in avoidance & consumption groups as percentage of total energy intake (ITT sample) and differences in mean macronutrient intakes by quartile of peanut consumption

Panel A displays all data for both randomized groups. Panel B displays the difference in means (consumption – avoidance) and 95% confidence intervals between the two randomized groups resulting from equivariance T-tests. Panel C displays the difference in means (consumption – avoidance) and 95% confidence intervals between the avoidance group and each quartile of peanut consumption resulting from equivariance T-tests.

Table II. Average daily intake of select micronutrients as percentage of the reference nutrient intake (RNI[1]).

P values are based on Wilcoxon tests comparing all avoiders to all consumers within each visit. Summary Statistics are displayed as Mean (SD), Median, and Interquartile Range respectively.
1. The RNI is the amount of a nutrient sufficient for 97% of the population.

Table III. Proportion of participants with average daily intakes of select micronutrients below the lower reference nutrient intake (LRNI[1]).

Percentages are calculated from the total number of participants in each treatment group with available data within each visit. P-values are based on Fisher's Exact tests.
1. The LRNI is the amount that is adequate for only around 2.5% of the population.

Table IV. Comparison of sources of protein (animal or vegetable) in avoidance and consumption groups (total grams consumed and percent of total protein intake).

Animal sources included the following food groups: milk/milk products, infant formula, eggs/egg dishes, meat/meat products, fish/fish products

Vegetable sources included: cereal/cereal products, milk substitutes, meat alternatives, vegetables/potatoes, nuts/seeds, savory snacks, fruit

Other sources included: fat spreads/oils, sugar and confectionery, non-alcoholic beverages, miscellaneous
P-values are based on Wilcoxon tests comparing all avoiders to all consumers within each visit.

Table V. Comparison of sources of protein (animal or vegetable) for all avoiders compared to the highest quartile of peanut consumption (total grams consumed and percent of total protein intake).

P-values are based on Wilcoxon tests comparing all avoiders to the highest quartile of peanut consumers within each visit.