

Institution: St George's, University of London		
Unit of Assessment: 2		
Title of case study: Early introduction of allergenic foods and the prevention of food allergy in infancy		
Period when the underpinning research was undertaken: 2006 to 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Michael Perkin	Reader in Clinical Epidemiology	01/09/2018 – 2020 (present)
	Previously: Senior Lecturer in Clinical Epidemiology	01/05/2016 – 31/08/2018
	Honorary Research Fellow and Consultant in Paediatric Allergy, St George's University Hospitals NHS Foundation Trust (SGUHT)	01/02/2008 – 30/04/2016
	Clinical Lecturer in Paediatrics	02/09/2002 – 31/01/2008
	Wellcome Training Fellowship in Clinical Epidemiology	07/09/1999 – 01/09/2002
	David Strachan	Professor of Epidemiology
	Reader in Epidemiology	01/11/1995 – 31/10/1997
	Senior Clinical Lecturer in Epidemiology	01/01/1990 – 31/10/1995
Period when the claimed impact occurred: 2016 to 2020		
Is this case study continued from a case study submitted in 2014? No		
1. Summary of the impact (indicative maximum 100 words)		
<p>Food allergies are common, affecting approximately 6% of children in high-income countries. The Enquiring About Tolerance (EAT) Study demonstrated that the early introduction of allergenic foods including egg and peanut into an infant's diet appreciably reduced the likelihood of food allergies developing, in participants who adhered to the early introduction regimen. Previous infant feeding guidelines have recommended delaying the introduction of allergenic food. The EAT Study findings have contributed to a paradigm shift, with many countries around the world changing their infant feeding recommendations to advise active introduction of allergenic foods into infants' diets from the time of complementary food introduction. This research has the potential to prevent thousands of children worldwide from developing food allergies every year.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>Food allergies are an important child health challenge, affecting approximately 6% of children in high-income countries. Having a food allergy reduces quality of life and increases risk of potentially fatal adverse reactions. National guidelines in the USA and UK previously</p>		

recommended delaying the introduction of allergenic foods into the infant diet. In the 2010 United Kingdom Infant Feeding Survey, 45% of mothers of infants 8 to 10 months of age reported not feeding their infant specific foods, especially nuts, eggs and dairy items because of concerns about allergies.

Recognition of the reduction of allergies in children due to early food introduction

Observational studies showed that Israeli infants, who had peanut introduced into the diet early, had a risk of peanut allergy one tenth of that in North London Jewish infants, suggesting that early allergic food introduction might protect against food allergy.

Following this observation, in 2006 Perkin (at St George's, University of London [SGUL] as Clinical Lecturer and Co-Principal Investigator) developed a proposal with Lack (at King's College London [KCL] as Principal Investigator) to conduct a unique randomised controlled trial in 1,303 exclusively breastfed infants recruited from the general population to determine whether early introduction of 6 common dietary allergens (peanut, cooked hen's egg, cow's milk, sesame, white fish and wheat) from 3 months of age (Early Introduction Group – EIG) would prevent food allergies, as compared with the Standard Introduction Group (SIG) who followed the UK Infant feeding recommendation of exclusive breastfeeding for around 6 months [1].

Perkin and Lack successfully applied for funding for the proposed trial (Enquiring about Tolerance [EAT]) to the Food Standards Agency in 2006. Perkin led the design of the study protocol, at SGUL and then led trial recruitment and the clinical trial team (12 staff) throughout the trial period (Jan 2008 to May 2015) at KCL, while working half-time as a Consultant in Paediatric Allergy at SGUHT and being an Honorary Research Fellow at SGUL. Perkin then returned to SGUL to direct the analysis and publication of the EAT Study results in 2016, with continuing FSA grant support. The EAT study Trial Steering Committee Vice-Chair was Professor David Strachan (SGUL).

Perkin was lead author of the EAT study primary results publication in the New England Journal of Medicine [2]. The key per-protocol analysis showed that among EIG participants adhering to early food allergen introduction, the risk of allergy to any food was 67% (95% CI 17% to 87%, $P=0.01$) lower than in the SIG (2.4% vs. 7.3%). For specific food allergies the risk reductions were particularly marked: peanut was 100% lower (0% vs. 2.5%, $P=0.003$) and egg 75% lower (1.4% vs. 5.5%, $P=0.009$) [3]. The early introduction of all 6 foods was not easily achieved but was safe.

Building understanding of early food introduction in specific groups

Further EAT reports have reinforced these findings, showing that early allergen introduction intervention was effective in an intention-to-treat analysis in EIG infants at high risk of developing food allergy (those with early onset eczema or early onset food sensitization) [3]. The intervention was also associated with improved infant sleep and fewer serious sleep problems [4], and prevented the development of coeliac disease [5].

The group also identified that Black, Asian and Minority Ethnic (BAME) groups, who are at increased risk of food allergy, were significantly less likely to adhere to early allergenic food introduction and will require additional support to achieve early introduction [6]. EAT remains the largest completed and published trial of early allergenic food introduction to date.

3. References to the research (indicative maximum of six references)

1. Perkin, MR, Logan, K, Marrs, T, Radulovic, S, Craven, J, Flohr, C, Lack, G, and on behalf of the EAT Study Team, *Enquiring About Tolerance (EAT) study: Feasibility of an early allergenic food introduction regimen*. *J Allergy Clin Immunol*, 2016. 137(5): p. 1477-1486 DOI: S0091-6749(16)00135-4 [pii];10.1016/j.jaci.2015.12.1322 [doi]. Journal article cited 60 times (WOS 05.02.2021).

2. Perkin, MR, Logan, K, Tseng, A, Raji, B, Ayis, S, Peacock, J, Brough, H, Marrs, T, Radulovic, S, Craven, J, Flohr, C, Lack, G, and for the EAT Study Team, *Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants*. N. Engl. J Med, 2016. 374(18): p. 1733-1743 DOI: 10.1056/NEJMoa1514210 [doi]. Journal article cited 338 times (WOS 05.02.2021).

3. Perkin, MR, Logan, K, Bahnson, HT, Marrs, T, Radulovic, S, Craven, J, Flohr, C, Mills, EN, Versteeg, SA, van Ree, R, Lack, G, and on behalf of the Enquiring About Tolerance (EAT) study team, *Efficacy of the Enquiring About Tolerance (EAT) study among infants at high risk of developing food allergy*. J Allergy Clin Immunol, 2019. 144(6): p. 1606-1614 e2 DOI: 10.1016/j.jaci.2019.06.045. Journal article cited 12 times (WOS 05.02.2021).

4. Perkin, MR, Bahnson, HT, Logan, K, Marrs, T, Radulovic, S, Craven, J, Flohr, C, and Lack, G, *Association of Early Introduction of Solids With Infant Sleep: A Secondary Analysis of a Randomized Clinical Trial*. JAMA Pediatr, 2018 172(8): p. e180739 DOI: 2686726 [pii];10.1001/jamapediatrics.2018.0739 [doi]. Journal article cited 20 times (WOS 05.02.2021).

5. Logan, K, Perkin, MR, Marrs, T, Radulovic, S, Craven, J, Flohr, C, Bahnson, HT, and Lack, G, *Early Gluten Introduction and Celiac Disease in the EAT Study: A Prespecified Analysis of the EAT Randomized Clinical Trial*. JAMA Pediatr, 2020 174(11) DOI: 10.1001/jamapediatrics.2020.2893. Altmetric score 976 (19.03.2021).

6. Perkin, MR, Bahnson, HT, Logan, K, Marrs, T, Radulovic, S, Knibb, R, Craven, J, Flohr, C, Mills, EN, Versteeg, SA, van Ree, R, Lack, G, and on behalf of the Enquiring About Tolerance (EAT) study team, *Factors influencing adherence in a trial of early introduction of allergenic food*. J Allergy Clin Immunol, 2019. 144(6): p. 1595-1605 DOI: 10.1016/j.jaci.2019.06.046. Journal article cited 4 times (WOS 22.03.2021).

4. Details of the impact (indicative maximum 750 words)

The main results of the EAT Study (reference [2], above) showed that adherence to early introduction of allergenic foods reduced the risk of food allergy and were reinforced by an accompanying New England Journal of Medicine editorial which concluded that "early consumption rather than delayed introduction of foods is likely to be more beneficial as a strategy for the primary prevention of food allergy". EAT is one of only two early introduction trials which attempted introduction of multiple foods (including foods other than peanut and egg) and it remains the largest completed early introduction trial to date. A subsequent widely cited systematic review and meta-analysis including EAT Study data confirmed a significant reduction in both egg and peanut allergy from the early introduction of these foods [A]. The EAT study was one of only two peanut trials and one of five egg trials included in the systematic review. For both categories EAT was the largest study included [A].

Influencing international guidelines for infant food introduction

The EAT study results have led to a systematic re-appraisal of how infants are introduced to allergenic foods and many countries have consequently changed their infant feeding recommendations since May 2016, potentially affecting every infant. Where guidelines have recommended the earlier introduction of allergenic foods other than peanut and egg, this is entirely based on results from the EAT Study, since no other study has yet investigated the effects of early introduction of these foods.

United States: The US National Institute of Allergy and Infectious Diseases issued 3 addendum guidelines (January 2017) for infants at differing risk levels for development of peanut allergy. Guideline 2 proposes peanut introduction from around 6 months of age in children with mild-to-moderate eczema. Guideline 3 proposes peanut be freely introduced into the diet in infants without eczema or any food allergy in accordance with family preferences and cultural practices. Both guidelines 2 and 3 referenced the per-protocol protective effect seen with early peanut introduction in the EAT study in support of these recommendations [B].

Australia: Updated guidelines from the Australasian Society of Clinical Immunology and Allergy (May 2016) recommend that all infants, including those at high risk of allergy, should be given allergenic solid foods including peanut butter, cooked egg, dairy and wheat products in the first year of life and referenced the EAT study in support of these recommendations [C].

Canada: New Canadian Paediatric Society guidance (January 2019) referenced the EAT per-protocol findings and recommends that common allergenic solids be introduced at around 6 months of age in infants at high risk of developing food allergy, but not before 4 months of age, and guided by the infant's developmental readiness for food [D].

UK: New UK guidelines developed by the Food Allergy Specialist Group of the British Dietetic Association and Paediatric Allergy Group of the British Society for Allergy & Clinical Immunology (May 2018, Perkin a member), referencing the EAT study, concluded that the deliberate exclusion or delayed introduction of specific allergenic foods may increase the risk of developing food allergy to the same foods. It recommended that allergenic foods should be introduced to the family diet before 12 months of age, potentially including egg, foods containing peanut and tree nuts, pasteurised dairy foods, fish/seafood and wheat [E]. The Scientific Advisory Committee on Nutrition (SACN) issued new guidance for government (July 2017) citing EAT and stating that the deliberate exclusion of peanut or hen's egg beyond 6 to 12 months of age may increase the risk of allergy to the same foods [F].

EU: The European Commission requested that the European Food Safety Authority Panel on Nutrition, Novel Foods and Food Allergens (NDA) review the appropriate age for introduction of complementary feeding into an infant's diet [G]. In contrast to their previous paradigm of allergenic food avoidance, the report concluded that there is no reason to postpone the introduction of potentially allergenic foods (egg, cereals, fish and peanut) to a later age than that of other complementary foods as far as the risk of developing atopic diseases is concerned. In investigating the safety of introduction of complementary foods before 6 months, the report referenced the EAT study 38 times.

Influence on food industry and formulation

Several food companies have been established since the initial publication of the EAT Study, particularly in the US, to manufacture infant food products containing individual or multiple allergenic foods including Lil Mixins, SpoonfulOne and Ready, Set, Food! These products specifically aim to facilitate early allergenic food introduction and reference the EAT study on their websites [H, I].

Impact on feeding behaviour

Evidence that infant feeding behaviour has changed following the introduction of the new guidelines is now available. In Australia, the introduction of new guidelines citing the EAT Study and recommending allergenic food introduction before 12 months for all infants in 2016 [C] was followed by an increase in early allergenic food introduction in Australia from November 2016 onwards, particularly for peanut. Compared with the period 2007 to 2011 when previous guidelines were in operation, the prevalence of peanut introduction by 12 months of age had increased from 28.4% to 88.6%, while the prevalence of egg introduction by 6 months had increased from 25.0% to 57.9% [J].

If the same proportion of Australian infants consumed peanut at the EAT per-protocol level that was achieved by 61% of EAT early introduction participants, then one would anticipate the prevalence of peanut allergy in Australia decreasing by 54%. With currently 1.9% of Australian children developing a peanut allergy, this would prevent approximately 3,200 children every year in Australia alone from developing a potentially life-threatening condition. Globally, a much larger number of cases of food allergy could be prevented by changes in infant feeding behaviour.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. Ierodiakonou, D, Garcia-Larsen, V, Logan, A, Groome, A, Cunha, S, Chivinge, J, Robinson, Z, Geoghegan, N, Jarrold, K, Reeves, T, Tagiyeva-Milne, N, Nurmatov, U, Trivella, M, Leonardi-Bee, J, and Boyle, RJ, Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. JAMA, 2016. 316(11): p. 1181-1192 DOI: 2553447 [pii];10.1001/jama.2016.12623 [doi].

B. Togias, A, Cooper, SF, Acebal, ML, Assa'ad, A, Baker, JR, Jr., Beck, LA, Block, J, Byrd-Bredbenner, C, Chan, ES, Eichenfield, LF, Fleischer, DM, Fuchs, GJ, III, Furuta, GT, Greenhawt, MJ, Gupta, RS, Habich, M, Jones, SM, Keaton, K, Muraro, A, Plaut, M, Rosenwasser, LJ, Rotrosen, D, Sampson, HA, Schneider, LC, Sicherer, SH, Sidbury, R, Spergel, J, Stukus, DR, Venter, C, and Boyce, JA, Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. J Allergy Clin Immunol, 2017. 139(1): p. 29-44.

C. Australasian Society of Clinical Immunology and Allergy (ASCIA) Infant feeding and allergy prevention guidelines. Available from: https://www.allergy.org.au/images/pcc/ASCIA_Guidelines_infant_feeding_and_allergy_prevention.pdf. Last accessed: 10/03/2021.

D. Canadian Paediatric Society Timing of introduction of allergenic solids for infants at high risk. Available from: <https://www.cps.ca/documents/position/allergenic-solids>. Last accessed: 10/03/2021.

E. British Society of Allergy and Clinical Immunology. Early Feeding Guidance 2018 [Available from: <https://www.bsaci.org/professional-resources/resources/early-feeding-guidelines/> (Last accessed 07/03/2021).

F. Scientific Advisory Committee on Nutrition, Committee on Toxicity of Chemicals in Food Consumer Products and the Environment. Assessing the health benefits and risks of the introduction of peanut and hen's egg into the infant diet before six months of age in the UK 2017 [updated 17/07/2017. Available from: <https://cot.food.gov.uk/sites/default/files/jointsacncotallergystatementfinal2.pdf>. (Last accessed 10/03/2021).

G. European Food Safety Authority (EFSA) Panel on Nutrition Novel Foods and Food Allergens (NDA), Castenmiller, J, de Henauw, S, Hirsch-Ernst, K-I, Kearney, J, Maciuk, A, Mangelsdorf, I, McArdle, HJ, Naska, A, Pelaez, C, Pentieva, K, Siani, A, Thies, F, Tsabouri, S, Vinceti, M, Bresson, J-L, Fewtrell, M, Kersting, M, Przyrembel, H, Dumas, C, Titz, A, and Turck, D, Appropriate age for introduction of complementary feeding into an infant's diet. EFSA Journal, 2019.

H. Ready. Set. Food! Available from: <https://readyssetfood.com/pages/education>. Last accessed: 18/11/2020.

I. SpoonfulOne. Available from: <https://www.spoonfulone.com/pages/the-research>. Last accessed: 18/11/2020.

J. Soriano, VX, Peters, RL, Ponsonby, AL, Dharmage, SC, Perrett, KP, Field, MJ, Knox, A, Tey, D, Odoi, S, Gell, G, Perez, BC, Allen, KJ, Gurrin, LC, and Koplin, JJ, Earlier ingestion of peanut following changes to infant feeding guidelines: The EarlyNuts Study. J Allergy Clin Immunol, 2019 DOI: S0091-6749(19)31028-0 [pii];10.1016/j.jaci.2019.07.032 [doi].