Current evidence: early determinants of food allergy

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Trends in allergic diseases

*Rising prevalence of allergic disease since 1960- Nature Reviews(2006).*
Food allergy – the new kid on the block: are the drivers of disease different?

Food Anaphylaxis Admissions in Australia

Liew WK, Williamson E, Tang MLK. JACI. 2009
Trends in pediatric food allergy in US

Corinne et al Annals of Allergy, Asthma & Immunology, 2014-03-01
Web of Science search – May 2013

**Reviews**

**Systematic Reviews**

*Published Items in Each Year*
## NHMRC Evidence Hierarchy: designations of ‘levels of evidence’ according to type of research question

Merlin T, Weston A, Tooher R. Extending an evidence hierarchy to include topics other than treatment: revising the Australian ‘levels of evidence’. BMC Medical Research Methodology, 2009.

<table>
<thead>
<tr>
<th>Level</th>
<th>Intervention 1</th>
<th>Diagnostic accuracy 2</th>
<th>Prognosis</th>
<th>Aetiology 3</th>
<th>Screening Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>I 4</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
<td>A systematic review of level II studies</td>
</tr>
<tr>
<td>II</td>
<td>A randomised controlled trial</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation</td>
<td>A prospective cohort study</td>
<td>A prospective cohort study</td>
<td>A randomised controlled trial</td>
</tr>
<tr>
<td>III-1</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
<td>A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation</td>
<td>All or none</td>
<td>All or none</td>
<td>A pseudorandomised controlled trial (i.e. alternate allocation or some other method)</td>
</tr>
</tbody>
</table>
| III-2 | A comparative study with concurrent controls:  
  - Non-randomised, experimental trial  
  - Cohort study  
  - Case-control study  
  - Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence | Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial | A retrospective cohort study | A comparative study with concurrent controls:  
  - Non-randomised, experimental trial  
  - Cohort study  
  - Case-control study |
| III-3 | A comparative study without concurrent controls:  
  - Historical control study  
  - Two or more single arm study  
  - Interrupted time series without a parallel control group | Diagnostic case-control study | A retrospective cohort study | A case-control study | A comparative study without concurrent controls:  
  - Historical control study  
  - Two or more single arm study |
| IV    | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard) | Case series, or cohort study of persons at different stages of disease | A cross-sectional study or case series | Case series |
What is a systematic overview?

- Review of systematic reviews
- Cochrane collaboration in 2009
- **Aim** – generate summary of evidence from more than one systematic review
- **Method** – systematic appraisal and comparison of systematic reviews
- **Outcome** - best evidence is made available to clinical decision-makers.
Overview of evidence in prevention and aetiology of food allergy: a review of systematic reviews

C J Lodge, KJ Allen, AJ Lowe, SC Dharmage
Methods- Search Criteria

- Primary prevention of or early life associations with food allergy in human children.
- **Systematic review defined as review with predetermined and transparent search strategy**
- **Inclusion criteria:** Systematic reviews of observational and interventional studies in both high risk and population based children.
- **Exclusion criteria:** not systematic review, adult populations, definition of food allergy not explicit.
Methods - Flow Chart of Search Process

**Figure 1. Flow Chart of the Search Process**

Records identified through searching PUBMED, EMBASE, Cochrane and DARE databases
(n=425)

51 Duplicates, protocols or initial reviews which have been updated removed
(n=374)

Titles and abstracts screened by 2 reviewers
(n=374)

Records excluded
1. Not food allergy
2. Not Systematic review
3. Not prevention or causation
(n=319)

Full-text articles assessed by 2 reviewers for eligibility
(Adjudication by 3rd reviewer)
(n=55)

Full-text articles excluded
(n=41)
1. No transparent, documented systematic search (n=23)
2. No individual food allergy outcomes (n=7)
3. Protocol only (n=2)
4. Abstract only (n=3)
5. Searched directed to atopic dermatitis in outcome (n=1)
6. Searched directed to asthma in outcome (n=2)
7. Withdrawn review (n=1)
8. Not English (Chinese) (n=1)
9. Earlier version of updated systematic review (n=1)

Eligible systematic reviews
(n=14)
<table>
<thead>
<tr>
<th>Question</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Was an ‘a priori’ design provided?</td>
</tr>
<tr>
<td>2</td>
<td>Was there duplicate study selection and data extraction?</td>
</tr>
<tr>
<td>3</td>
<td>Was a comprehensive literature search performed?</td>
</tr>
<tr>
<td>4</td>
<td>Was the status of publication (i.e. grey literature) used as an inclusion criterion?</td>
</tr>
<tr>
<td>5</td>
<td>Was a list of studies (included and excluded) provided?</td>
</tr>
<tr>
<td>6</td>
<td>Were the characteristics of the included studies provided?</td>
</tr>
<tr>
<td>7</td>
<td>Was the scientific quality of the included studies assessed and documented?</td>
</tr>
<tr>
<td>8</td>
<td>Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
</tr>
<tr>
<td>9</td>
<td>Were the methods used to combine the findings of studies appropriate?</td>
</tr>
<tr>
<td>10</td>
<td>Was the likelihood of publication bias assessed?</td>
</tr>
<tr>
<td>11</td>
<td>Was the conflict of interest stated?</td>
</tr>
</tbody>
</table>

- Overview Quality Assessment Questionnaire – 37 items – Oxman-Guyatt) and Sacks checklist along with 3 extra items based on methodological advances in the field. (language restriction, publication bias, publication status)

- 150 reviews appraised by 2 reviewers then performed principal component analysis
Broad groups of systematic reviews for prevention of food allergy

1. Infant formulas (n=5)

2. Maternal and infant diet and dietary supplements (n=6)

3. Hygiene hypothesis related interventions (probiotics, caeserean section) (n=3)
## Results – 1. Formula for prevention

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Design</th>
<th>Intervention/s / comparisons</th>
<th>Population/s studied</th>
<th>search dates</th>
<th>Outcome/s measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szajewska (2010)</td>
<td>RCTs</td>
<td>Partially hydrolysed 100% whey formula (pHF) vs. Standard infant formula (SF)</td>
<td>Increased risk</td>
<td>1985-2010</td>
<td>Food Allergy symptoms (FA) at 6 months.</td>
</tr>
<tr>
<td>Osborn (2006) update (2009)*</td>
<td>RCTs</td>
<td>Soy Formula vs. Cow's milk formula</td>
<td>Increased risk</td>
<td>1980-2006</td>
<td>Food Allergy - GI symptoms and IgE characterized as Obvious, Probable or possible atopic disease</td>
</tr>
<tr>
<td>Osborn (2006)*</td>
<td>RCT</td>
<td>Partially or extensively hydrolysed formula vs. human milk or cow's milk formula Partially vs. extensively hydrolysed milk</td>
<td>3 studies high risk 2 studies population based</td>
<td>Updated search March 2009</td>
<td>Mostly clinical allergy ascertained by questionnaire or doctors' assessment 1 study unknown 2 studies unblinded food elimination/challenge 2 studies used symptoms with specific IgE</td>
</tr>
<tr>
<td>Hays (2005)</td>
<td>RCT</td>
<td>Hydrolysed formulas vs: breastfeeding, cow's milk formula, soy formula or combinations</td>
<td>High-risk (22) Unselected (1)</td>
<td>*</td>
<td>Objective measure in the presence of GI symptoms – open food challenge, DBPCFC, SPT IgE “Atopy” Not defined</td>
</tr>
<tr>
<td>Schoetzau (2001)</td>
<td>RCT Cohort</td>
<td>Hydrolysed formulas to cow's milk formula</td>
<td>Increased risk studies up to 2001*</td>
<td>Food allergy based on strict, well-defined food elimination and challenge procedures including double-blind placebo controlled food challenge.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AMSTAR Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (9) N=67, diarrhoea and colic</td>
</tr>
<tr>
<td>High (11) N=3473 RR 0.62 (0.38-1.00) Decrease in CMA</td>
</tr>
<tr>
<td>Low (2)</td>
</tr>
<tr>
<td>Medium (5)</td>
</tr>
</tbody>
</table>
Formulas - summary

• No evidence to support the use of hydrolysed formulas over breast milk for food allergy/sensitization prevention
• Insufficient evidence to conclude that the use of hydrolysed formulas may reduce food allergy/sensitization when compared with standard formula in high atopy risk children

Lodge et al Overview of evidence in prevention and aetiology of food allergy: a review of systematic reviews IJERPH 2013
Analysis 14.3. Comparison 14 Prolonged feeding: Partially hydrolysed whey formula vs cow’s milk formula, Outcome 3 Eczema.

Review: Formulas containing hydrolysed protein for prevention of allergy and food intolerance in infants

Comparison: 14 Prolonged feeding: Partially hydrolysed whey formula vs cow’s milk formula

Outcome: 3 Eczema

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight %</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy (incidence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chirico 1997</td>
<td>0/21</td>
<td>2/14</td>
<td></td>
<td>3.0 %</td>
<td>0.14 [0.01, 2.64]</td>
</tr>
<tr>
<td>de Seta 1994</td>
<td>3/23</td>
<td>5/39</td>
<td></td>
<td>3.7 %</td>
<td>1.02 [0.27, 3.87]</td>
</tr>
<tr>
<td>Lam 1992</td>
<td>13/44</td>
<td>15/48</td>
<td></td>
<td>14.5 %</td>
<td>0.95 [0.51, 1.76]</td>
</tr>
<tr>
<td>Marini 1996</td>
<td>4/42</td>
<td>8/40</td>
<td></td>
<td>8.3 %</td>
<td>0.48 [0.16, 1.46]</td>
</tr>
<tr>
<td>Tsai 1991</td>
<td>8/15</td>
<td>11/18</td>
<td></td>
<td>10.1 %</td>
<td>0.87 [0.48, 1.59]</td>
</tr>
<tr>
<td>von Berg 2003</td>
<td>53/483</td>
<td>60/483</td>
<td></td>
<td>60.5 %</td>
<td>0.88 [0.62, 1.25]</td>
</tr>
</tbody>
</table>

Subtotal (95% CI) 628 642 100.0 % 0.84 [0.65, 1.09]

Total events: 81 (Treatment), 101 (Control)
Heterogeneity: Chi² = 2.75, df = 5 (P = 0.74); I² = 0.0%
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MACS</th>
<th>GINI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study number</td>
<td>620</td>
<td>2252</td>
</tr>
<tr>
<td>High Risk antenatal recruitment</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Study design</td>
<td>Single blind</td>
<td>Double blind</td>
</tr>
<tr>
<td></td>
<td></td>
<td>But taste and smell of formula differ</td>
</tr>
<tr>
<td>% Exclusively breastfeeding up to 4mth</td>
<td>40.2%</td>
<td>43.1%</td>
</tr>
<tr>
<td>Compliance with feeding protocol:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 4 mth</td>
<td>91.5% (526/575)</td>
<td>93% (1834/1972)</td>
</tr>
<tr>
<td>At 6mth</td>
<td>88.5% (509/575)</td>
<td>Not reported</td>
</tr>
<tr>
<td>At 12 mth</td>
<td>73.7% (424/575)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Study participant retention:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 12 mth</td>
<td>88.5%</td>
<td>82.5%</td>
</tr>
<tr>
<td>Age 2 years</td>
<td>88.5%</td>
<td>79.8%</td>
</tr>
<tr>
<td>Age 6/7 years</td>
<td>79.8%</td>
<td>74.6%</td>
</tr>
<tr>
<td>Differential participation by factors that influence allergic outcomes</td>
<td>None</td>
<td>Higher loss to follow up in pHWF group in GINI, particularly those with early life eczema.</td>
</tr>
<tr>
<td>Intention to treat analysis for eczema at age 1 years</td>
<td>1.14 (0.75-1.75)</td>
<td>0.88 (0.61-1.26)</td>
</tr>
<tr>
<td>Per Protocol analysis for eczema at age 1 years</td>
<td>1.03 (0.55-1.93)</td>
<td><strong>0.49 (0.27-0.88)</strong></td>
</tr>
</tbody>
</table>
### 2.a. Results - Maternal and Infant Dietary Supplements

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Design</th>
<th>Intervention/s / comparisons</th>
<th>Population/s studied and numbers</th>
<th>Number studies &amp; search dates</th>
<th>Outcome measures</th>
<th>Main results</th>
<th>Conclusions</th>
<th>AMSTAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klemens (2011)</td>
<td>RCT</td>
<td>Omega-3 (n-3 PUFA) supplementation during pregnancy and/or lactation vs placebo (olive or soy oil)</td>
<td>451 children from both high allergy risk and population based studies</td>
<td>3 studies 1950-2010</td>
<td><strong>Egg Allergy:</strong> Skin prick test, <strong>Food Allergy:</strong> Clinical diagnosis</td>
<td>Egg SPT up to 12 months reduced - CR 0.33 (0.16, 0.70) (187 children from 2 studies) Food Allergy up to 12 or 30 months - CR 0.46 (0.16, 1.38) (264 children from 3 studies) Supplementation started in pregnancy Food Allergy (2 studies on 200 children) - CR 0.34 (95% CI 0.10, 1.15)</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>Anandan (2009)</td>
<td>RCT</td>
<td>Omega-3 (n-3 PUFA) supplementation during pregnancy and/or lactation vs placebo (olive oil)</td>
<td>148 children from both high allergy risk and population based studies</td>
<td>2 studies 1966-2008</td>
<td><strong>Food Allergy:</strong> not defined in SR. Source papers - not clear in one study and clinical diagnosis in other.</td>
<td>Food Allergy up to 12 or 30 months RR 0.51 (0.10, 2.55) (148 children from 2 studies)</td>
<td>Medium</td>
<td></td>
</tr>
<tr>
<td>Osborn (2007)*</td>
<td>RCT</td>
<td>Probiotics (various types and mixtures) vs no probiotics given to infants</td>
<td>247 infants from both high allergy risk and population based studies</td>
<td>2 studies 1966-2007</td>
<td><strong>Food Allergy:</strong> immediate symptoms on food exposure and specific SPT, <strong>Cow's Milk Allergy (CMA):</strong> DBPCFC (if suggestive symptoms, signs or SPT)</td>
<td>Infant Food Allergy RR 1.54 (0.70, 3.37) (175 children from 1 high risk allergy study using Lactobacillus acidophilus) Infant Cow's Milk Allergy RR 0.41 (0.02, 9.84) (72 children from 1 population based study using Lactobacillus rhamnosus)</td>
<td>High</td>
<td></td>
</tr>
</tbody>
</table>
The WAO guideline panel suggests: a) using probiotics in pregnant women at high risk for having an allergic child; b) using probiotics in women who breastfeed infants at high risk of developing allergy; and c) using probiotics in infants at high risk of developing allergy. All recommendations are conditional and supported by very low quality evidence.
<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Design</th>
<th>Intervention/s and comparisons</th>
<th>Population/s studied and numbers</th>
<th>search dates</th>
<th>Outcome measures</th>
<th>Main results</th>
<th>Conclusions</th>
<th>AMSTAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kramer (2012)*</td>
<td>RCT</td>
<td>Maternal dietary antigen avoidance diet (different regimens) during third trimester of pregnancy (2 studies, n=383), and pregnancy and lactation (1 study n=497)</td>
<td>Children of 497 mothers with family history of allergy</td>
<td>6th July 2012</td>
<td>SPT for cow’s milk, egg and peanut at ages 6 months, 1, 2 and 7 years</td>
<td>Many SPTs showed no evidence of association. Those of note: Avoidance during pregnancy: Infant egg sensitization at 6mo RR 0.58 (0.32, 1.05) in 2 studies (n=340) Avoidance during pregnancy and lactation: Child egg sensitization at 2 yr RR 1.91 (1.03, 3.53) in 1 study (n=497) Child milk sensitization at 2 yrs RR 4.30 (0.94, 19.67) in 1 study (n=473)</td>
<td></td>
<td>High</td>
</tr>
<tr>
<td>Thomps on (2010)</td>
<td>RCTs, case controls</td>
<td>Mother’s exposure to peanut (more or less than once per week)</td>
<td>Children exposure to peanut RCT – Exclusion diets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medium</td>
</tr>
<tr>
<td>Tarini (2006)</td>
<td>Prospective cohort</td>
<td>Exclusive breastfeeding for 6 months (n=70) vs introduction solids at 3 months (n=65)</td>
<td>135 breastfed children of allergic parents</td>
<td>1966-2005</td>
<td>Food allergy - defined as: rash or vomiting At 5 years food allergy was defined as the above plus positive skin prick test</td>
<td>37% of infants fed solids at 3 months of age had a history of food allergy up to the age of 1 compared to 7% who were fed breast milk exclusively (P&lt;0.001) At 5 years no difference between the two groups</td>
<td></td>
<td>Low</td>
</tr>
</tbody>
</table>
Associations between maternal intake of food allergens during the first trimester and current allergy and asthma outcomes at mid-childhood

Food allergy defined as sensitisation and Epipen prescribed

Models were adjusted for child age, sex, breastfeeding, parental atopy, and maternal education

Bunyavanich et al JACI 2014
## Results - Hygiene hypothesis related factors

<table>
<thead>
<tr>
<th>First Author (Year)</th>
<th>Design</th>
<th>Population/s studied and numbers</th>
<th>Number of studies included</th>
<th>Intervention/s</th>
<th>Outcome measures</th>
<th>Main results</th>
<th>Conclusions</th>
<th>AMSTAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arnoldussen (2011)</strong></td>
<td>Randomized prospective single blind study</td>
<td>High allergy risk children BCG=62 Placebo=59</td>
<td>2 studies</td>
<td>BCG vaccination</td>
<td>Food allergy defined as: 1. symptoms of allergy (skin reactions, wheezing, vomiting, or diarrhoea on more than one occasion after ingestion or contact with a particular type of food or allergen 2. Symptoms of feeding induced vomiting diarrhoea or abdominal pain</td>
<td>Results not pooled because outcomes were judged to be too heterogeneous on clinical grounds</td>
<td>Neither study individually showed a significant association with food allergy</td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Bager (2008)</strong></td>
<td>Retrospective Cohort study</td>
<td>Atopic hereditary children 17 and under 216 cases, 358 controls</td>
<td>No search dates stated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Koplin (2008)</strong></td>
<td>Cohort studies</td>
<td>32565 children aged 0-17 Populations not defined</td>
<td>6 Studies Between 1966 &amp; 1 May 2007</td>
<td>Delivery by CS section</td>
<td>Food Allergy/Antioply definitions 1. Hospital admission for food anaphylaxis or epipen prescription (age 0-6) 2. Physician diagnosis (age 8-17) 3. Parent or self report to foods or drugs (age 8-17) 4. Parent or self report to egg, fish or nuts (age 1-2) 5 specific IgE to food (age 1-2)</td>
<td>Food allergy or Food atopy OR 1.32 (95% CI 1.12, 1.55) (6 studies (n=32565))</td>
<td></td>
<td>Medium</td>
</tr>
<tr>
<td><strong>Koplin (2008)</strong></td>
<td>Prospective Cohorts 8. Retrospective cohorts</td>
<td>15121 children</td>
<td>4 Studies Published before July 2007</td>
<td>Delivery by GSection</td>
<td>Symptoms of food allergy IgE antigen-specific levels</td>
<td>Results were not pooled due to small number of papers included in study</td>
<td></td>
<td>Medium</td>
</tr>
</tbody>
</table>
Hygiene hypothesis related interventions

• Modest evidence that Caesarean Section increases the risk of food allergy/sensitisation
Summary

• Only 14 systematic reviews

• No robust evidence in any of the areas studied (soy formula, hydrolysed formulas, Omega 3 supplementation, probiotics, maternal or infant diets, Caesarean Section, BCG vaccination)
Breastfeeding and risk of food allergy contracted by WHO

• There was no risk or protective association between breastfeeding and food allergy (OR 1.02; 0.88, 1.18, 12 studies, I² 86%),

• although this estimate had high heterogeneity and low quality.

Lodge C et al, Archives Disease Childhood 2015
Cross-sectional studies from low income countries more likely to show protection
Conclusions on systematic reviews

- Vast majority of Food Allergy reviews narrative rather than systematic
- Scant evidence in areas reviewed systematically
- Need more primary studies with greater numbers better food allergy definition
  - Special issues for feeding prevention trials regarding ethics of randomising to breastfeeding
- Further systematic reviews in areas not covered by these topics
What are some of the emerging concepts for why food allergy is on the rise?
Epidemiological evidence for the current leading hypotheses for the rise in food allergy

Parents’ country of birth (Asian infants at increased risk)
- Koplin et al. Allergy 2012 – egg allergy
- Martin et al. CEA 2013 – eczema
- Koplin et al. Allergy 2014 – food allergy

Maternal diet during pregnancy (consumption of egg)
- Koplin et al. JACI 2010

Cesarean section delivery
- Koplin et al. Allergy 2012
- Koplin et al. PAI 2008

Infant dietary factors
- Later introduction of allergenic foods
- Du Toit et al. JACI 2008
- Poole et al. Pediatrics 2006
- Szeffler et al. JACI 2008
- Koplin et al. JACI 2010
- Duration of breastfeeding
- Maternal consumption of egg during breastfeeding
- Age at first introduction of solids
- Koplin et al. JACI 2010

Family history of allergy
- Koplin et al. IJERPH 2013

Genetic factors – FLG null mutation
- Brown et al. JACI 2010 (food allergy)
- Tan et al. JACI 2012 (food sensitisation alone)

Fetal epigenetic modification Through maternal exposure
- Elevated maternal folate
- Dunstan et al. Allergy 2012

Factors associated with the “hygiene hypothesis”
- Presence of siblings
- Early childcare attendance
- Cat exposure
- Dog exposure
- Use of antibiotics
- Koplin et al. Allergy 2012

Environmental factors
- Cutaneous exposure to food allergens
- Fox AT et al. JACI 2009
- Brough HA, Santos AF et al. JACI

Vitamin D insufficiency
- Allen et al. JACI 2013

Blue = no association
Green = possibly protective
Red = possible risk factor

G Lack and KJ Allen 2014
Current leading hypotheses of postnatal modifiable factors for the rise in food allergy

1. Skin barrier function and allergen exposure
   - the “Dual Allergen Exposure” or Lack hypothesis
2. Vitamin D hypothesis
3. Hygiene hypothesis (microbial diversity, migration and the modern lifestyle)
Current leading hypotheses for the rise in food allergy

1. Skin barrier function and allergen exposure (the “Dual Allergen” or Lack hypothesis)
2. Vitamin D hypothesis
3. Hygiene hypothesis (microbial diversity, migration and the modern lifestyle)
Earlier onset and more severe eczema more likely to develop food allergy

Martin PJ et al CEA 2014
Neonatal moisturising trials to prevent eczema and sensitisation

- Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention
  - Simpson E et al JACI 2014

- Application of moisturizer to neonates prevents development of atopic dermatitis.
  - Horimukai et al JACI 2014

- Oral application of bacterial lysate in infancy diminishes the prevalence of atopic dermatitis in children at risk for atopy
  - Lau et al Benef Microbes 2014
Dual Allergen Exposure or Lack Hypothesis

- Allergic sensitization results from exposure through the skin
- Tolerance occurs as a result of oral exposure to food

(Gideon Lack 008)
Current leading hypotheses for the rise in food allergy

- What about allergen exposure and infant feeding?

**Can early introduction of egg prevent egg allergy in infants?**

*A population-based study*

Jennifer J. Koplin, BSc (Hons), Nicholas J. Osborne, PhD, Melissa Wake, MD, FRACP, MBBS, Pamela E. Martin, BBiomedSc (Hons), Lyle C. Gurrin, PhD, Marnie N. Robinson, MBBS, FRACP, Dean Tey, MBBS, FRACP, Marjolein Slaa, MBBS, Leone Thiele, BA, RN, RM, MNSc, Lucy Miles, BNurs, Deborah Anderson, BNurs/BAppSc, Tina Tan, BSc, Thanh D. Dang, BBiomedSc (Hons), David J. Hill, MBBS, FRACP, Adrian J. Lowe, PhD, Melanie C. Matheson, PhD, Anne-Louise Ponsonby, MBBS, FAFPHM, FRACP, PhD, Mimi L. K. Tang, MBBS, FRACP, FRCPA, FAAAAI, PhD, Shyamali C. Dharmage, MBBS, MD, PhD, and Katrina J. Allen, MBBS, FRACP, PhD Melbourne, Australia

*JACI 2010*
Population responses to change in infant feeding guidelines in Australia

Tey D et al JACI 2014
Solids introduction between 4-6 months
91.7% (95%CI [90.9-92.5])

Egg introduction between 7-12 months
70.6% (95%CI [69.4-71.9])

Peanut introduction >12 months
71.6% (95%CI [70.3-72.8])
Figure 3a. Kaplan Meier graphs for recruitment year and solids introduction

Log rank test p=0.001

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Post-2009* Crude multinomial OR (95%CI)</th>
<th>P</th>
<th>Post-2009* Adjusted multinomial OR† (95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of solids introduction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 months old</td>
<td></td>
<td></td>
<td>0.76 (0.54-1.09)</td>
<td>0.135</td>
</tr>
<tr>
<td>4 months old</td>
<td></td>
<td></td>
<td>1.21 (1.02-1.45)</td>
<td><strong>0.032</strong></td>
</tr>
<tr>
<td>5 months old</td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>6 months old</td>
<td></td>
<td></td>
<td>0.80 (0.69-0.92)</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>&gt; 6 months old</td>
<td></td>
<td></td>
<td>0.90 (0.68-1.20)</td>
<td>0.468</td>
</tr>
</tbody>
</table>
Figure 3b. Kaplan Meier graphs for recruitment year and egg introduction

<table>
<thead>
<tr>
<th>Age of egg introduction*</th>
<th>Post-2009* Crude multinomial OR (95%CI)</th>
<th>Post-2009* Adjusted multinomial OR† (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 6 months old</td>
<td></td>
<td>1.00</td>
</tr>
<tr>
<td>7-9 months old</td>
<td></td>
<td>0.84 (0.72-0.98)</td>
</tr>
<tr>
<td>10-12 months old</td>
<td></td>
<td>0.80 (0.68-0.94)</td>
</tr>
<tr>
<td>&gt; 12 months old</td>
<td></td>
<td>0.65 (0.48-0.88)</td>
</tr>
</tbody>
</table>

Log rank test p < 0.001
Preliminary analysis suggests that the change in population behaviour towards infant feeding has not affected food allergy prevalence in Australia.
Current leading hypotheses for the rise in food allergy

1. Skin barrier function and allergen exposure (the “Dual Allergen” or Lack hypothesis)
2. Vitamin D hypothesis
3. Hygiene hypothesis (microbial diversity, migration and the modern lifestyle)
Regional EpiPen prescriptions in United States and Australia


The Longitudinal Study of Australian Children (n=10,000)

Osborne NJ et al. JACI, 2012
Australian born infants with Vitamin D insufficiency at 12 months are much more likely to have food allergy

<table>
<thead>
<tr>
<th>Outcome and stratification variables</th>
<th>aOR (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No food allergy (n = 140)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Single food (n = 96)</td>
<td>1.82 (0.38-8.77)</td>
<td>.46</td>
</tr>
<tr>
<td>Multiple foods (n = 32)</td>
<td>10.48 (1.60-68.61)</td>
<td>.014</td>
</tr>
<tr>
<td>No food allergy (n = 140)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Egg allergy (n = 110)</td>
<td>3.79 (1.19-12.08)</td>
<td>.025</td>
</tr>
<tr>
<td>No food allergy (n = 140)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Peanut allergy (n = 33)</td>
<td>11.51 (2.01-65.79)</td>
<td>.006</td>
</tr>
</tbody>
</table>

Allen KJ et al JACI 2013
Is the timing of rise in food allergy consistent with Vitamin D insufficiency rising?

Vitamin D insufficiency is associated with challenge-proven food allergy in infants

JACI 2013
Current leading hypotheses for the rise in food allergy

1. Skin barrier function and allergen exposure (the “Dual Allergen” or Lack hypothesis)
2. Vitamin D hypothesis
3. Hygiene hypothesis (microbial diversity, migration and the modern lifestyle)
Infants with siblings and dogs at home are much less likely to develop food allergy

<table>
<thead>
<tr>
<th></th>
<th>Adjusted†</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of siblings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1.0</td>
<td>(1.0, 1.0)</td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>0.72</td>
<td>(0.57, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Two</td>
<td>0.56</td>
<td>(0.38, 0.81)</td>
<td></td>
</tr>
<tr>
<td>Three or more</td>
<td>0.31</td>
<td>(0.14, 0.68)</td>
<td></td>
</tr>
<tr>
<td>Per sibling</td>
<td>0.72</td>
<td>(0.62, 0.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cat ownership</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cat</td>
<td>1.0</td>
<td>(1.0, 1.0)</td>
<td></td>
</tr>
<tr>
<td>Cat outside only</td>
<td>0.93</td>
<td>(0.49, 1.77)</td>
<td>0.83</td>
</tr>
<tr>
<td>Cat allowed inside</td>
<td>0.75</td>
<td>(0.52, 1.09)</td>
<td>0.13</td>
</tr>
<tr>
<td>Dog ownership†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No dog</td>
<td>1.0</td>
<td>(1.0, 1.0)</td>
<td></td>
</tr>
<tr>
<td>Dog outside only</td>
<td>1.09</td>
<td>(0.75, 1.57)</td>
<td>0.66</td>
</tr>
<tr>
<td>Dog allowed inside</td>
<td>0.72</td>
<td>(0.52, 0.99)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

Environmental and demographic risk factors for egg allergy in a population-based study of infants

J. J. Koplin¹,², S. C. Dharmage¹,³, A.-L. Ponsonby¹, M. L. K. Tang¹,²,⁴, A. J. Lowe¹,³, L. C. Gurrin¹,³, N. J. Osborne¹,²,³,⁵, P. E. Martin¹,², M. N. Robinson¹,⁴, M. Wake¹,²,⁶, D. J. Hill¹, K. J. Allen¹,²,⁴ & for the HealthNuts Investigators

¹Murdoch Childrens Research Institute, ²Department of Paediatrics, The University of Melbourne, ³The University of Melbourne, Centre for Molecular, Environmental, Genetic and Analytic Epidemiology, School of Population Health, ⁴Department of Allergy and Immunology, Royal Children’s Hospital, Parkville, Vic., Australia ⁵European Centre for Environment and Human Health, Peninsula College of Medicine and Dentistry, University of Exeter, Exeter, UK ⁶Royal Children’s Hospital, Centre for Community Child Health, Parkville, Vic., Australia

Allergy 2012
Migration
Infants of parent’s born overseas are much more likely to have food allergy – especially those from Asia

*but risk of allergy amongst parents is reversed*

*Adjusted for family history of allergy, eczema, timing of egg introduction, pet ownership and number of siblings*

Koplin JJ et al, Allergy 2014
Increased risk of peanut allergy in infants of Asian-born parents compared to those of Australian-born parents

J. Koplin\textsuperscript{1,2}, R. Peters\textsuperscript{1,3}, A. -L. Ponsonby\textsuperscript{1}, L. Gurrin\textsuperscript{1,2}, D. Hill\textsuperscript{1}, M. Tang\textsuperscript{1,3,4}, S. Dharmage\textsuperscript{1,2} & K. Allen\textsuperscript{1,3,4,5} for the HealthNuts Study Group

\textsuperscript{1}Murdoch Childrens Research Institute, Parkville; \textsuperscript{2}Centre for Epidemiology and Biostatistics, The University of Melbourne, Melbourne; \textsuperscript{3}Department of Paediatrics, University of Melbourne; \textsuperscript{4}Department of Allergy and Immunology, The Royal Children’s Hospital, Parkville, Vic., Australia; \textsuperscript{5}University of Manchester, Manchester, UK
Are risk factors different for Asians in Australia?

• Asian infants born in Australia have the highest rates of food allergy

however

• Asian infant born in Asia and move to Australia in the first few years of life are protected from food allergy (manuscript in prep)
Could removal of the protective Asian environment increase the expression of genetically at risk infants?

Migration may be associated with changes to:

- **humidity**, changes in *washing* practices — may increase early onset eczema
- **microbial exposure** — cleaner water supply, more antibiotics
- **dietary changes** — timing of introduction, boiled vs roasted peanuts
- **changes in lattitude/UV/non-Western diet** — changes to Vitamin D status
Moving from **describing the problem** to **prescribing the solution**

**Describe the clinical problem**
- Population-based observational studies
- Retrospective clinic audits

**Predict the development of disease and/or resolution**
- Identifying mechanisms, modifiable factors, biomarkers

**Prescribe preventions and cures**
- Prevention trials
- Treatment trials
- Optimising management pathways

[Centre for Food & Allergy Research](http://www.centrefoodallergy.com) An NHMRC Centre of Research Excellence
1) Vitamin D for prevention of food allergy – the Vitality trial (n=3000)

2a) BCG for prevention of allergic disease - the mis-BAIRS trial (n=1200)
   b) Modified H pylori led by Barry Marshall

3) Early introduction of solids – including egg and peanut
   - STAR, STEP, BEAT studies (n=1200)
Acknowledgements

HealthNuts Investigators
• Chief Investigators: Katie Allen (PI), Melissa Wake, Shyamali Dharmage, Mimi Tang, Lyle Gurrin, Melanie Matheson, Terry Dwyer, Colin Robinson
• Associate Investigators: Anne-Louise Ponsonby, David Hill, Adrian Lowe

Postdoctoral Fellows
• Jennifer Koplin, David Martino, Thanh Dang, Nick Osborne

Students
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www.foodallergyresearch.com