Risk Factors for Allergic Sensitisation and Asthma

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Manchester, UK
Asthma has increased in prevalence

Beasley R, JACI 2000; 105: S466-472
Asthma is heritable – and complex

Linkage in >1 study

Linkage in 1 study
Environment And Respiratory Allergic Diseases

- Environment – everything that is not me
  - Albert Einstein

- Hygiene hypothesis

- The role of environmental allergen exposure
Hygiene Hypothesis

- Improved hygienic conditions
- Less microbial exposure during early childhood
- Slower post-natal maturation of the immune system
- Delayed development of the optimal balance between TH-1 and TH-2-like immune response
Atopy And EIB Amongst Urban Rich, Urban Poor and Rural Children in Ghana in 1993

EOD Addo Yobo & A Custovic, Thorax 1997
Atopy and Exercise-Induced Bronchospasm in Ghana: 1993-2003

EOD Addo Yobo & A Custovic, 2006
Odds Ratios for Wheeze and Hookworm Quartiles

Scrivener et al

Lancet 2001; 358: 1493-1499

OR (95% CI)

\[ p = 0.04 \]

Range: (eggs/g)

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td>0</td>
<td>&lt;5.79</td>
<td>5.80-48.87</td>
<td>48.88-1458</td>
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</tbody>
</table>
Geohelminthic Parasites are Protective Against Skin Test Reactivity in Ecuador

A lumbricoides
OR 0.74 (0.60-0.91)

T trichiura
OR 0.82 (0.67-1.01)
70-700 eggs
>700 eggs

A duodenale
OR 0.39 (0.18-0.85)

Any geohelminth
OR 0.64 (0.52-0.78)

P=0.005
P=0.07
P=0.01
P=0.02
P<0.001

Cooper PJ et al, JACI 2003; 111: 995-1000
Treatment of Intestinal Helminths Increases Mite Skin-Test Reactivity

- **Treatment group (163):**
  - Praziquantel +
  - Mebendazole 3 monthly

- **Placebo group (178)**

*Van den Biggellar et al, JID 2004; 182: 892-900*
Inverse Association Between Family Size, Atopy and Asthma

- Number of older siblings more important compared to younger siblings

- No such difference
  - Strachan & ALSPAC Study Team, Clin Exp Allergy 1997; 27: 151-5

- Stronger effect of family size than of birth order
  - Jarvis et al., Clin Exp Allergy 1997; 27: 240-5

- Protective effect of greater number of brothers
  - Svanes et al, J Allergy Clin Immunol 1999; 103: 415-20

- Older siblings inversely correlated to atopic disorders only for the children with a history of parental atopy
  - Mattes et al., Clin Exp Allergy 1998; 28: 1480-6

- Very little association between asthma and family size
  - Rona et al., J Epidemiol Community Health 1999; 53: 15-19

Strachan et al

Prevalence of Asthma or Wheezy Bronchitis at Age 16 (%)

Hay Fever and Asthma at Age 16 in Two British Cohorts by Birth Order

Strachan et al
BCG, Allergy and Asthma

- Association between positive tuberculin responses and less allergy & asthma

**But**

- Inverse relationship dependant on a small number of children with florid tuberculin response not being allergic

- ? reverse hypothesis correct - the tuberculin reaction size is reduced in asthmatic children because they have lower IFN-\(\gamma\) secretion

Shirakawa et al., Science 1997; 275: 77-9
BCG and Atopy

- 216 children with atopic parents who received a BCG vaccination (<6 months of age) and 358 matched controls without a BCG vaccination
- No differences between the 2 groups

*But*

- Powered to detect a 50% reduction in the frequency of atopy in the BCG group
- BCG vaccination alone may produce such a large reduction in disease
- ? timing of the BCG vaccination

Alm et al., Allergy 1998; 53: 537
Gut Microbiota: Large and Continuous Microbial Pressure

$10^5-7$

$10^9-11$
Probiotics in Primary Prevention of Allergic Diseases

Kalliomaki M et al, Lancet 2001; 357: 1076-9
Probiotics in Primary Prevention of Allergic Diseases

**Diagram:**

- **Eczema Sensitisation (IgE):**
  - Placebo
  - Lactobacillus GG
  - *P* < 0.05

- **Sensitisation (SPT):**
  - Placebo
  - Lactobacillus GG

*Kalliomaki M et al, Lancet 2001; 357: 1076-9*
**Paradoxical Effects Of Exposure To Domestic Animals**

**Decreased sensitization to cat amongst cat owners**

<table>
<thead>
<tr>
<th>Researcher</th>
<th>Country</th>
<th>Journal</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesselmar, Bjorksten <em>et al</em></td>
<td>Sweden</td>
<td>CEA 1999</td>
<td></td>
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<tr>
<td>Roost <em>et al</em></td>
<td>ECRHS</td>
<td>JACI 1999</td>
<td></td>
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<tr>
<td>Sporik <em>et al</em></td>
<td>USA</td>
<td>Thorax 1999</td>
<td></td>
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<tr>
<td>Custovic <em>et al</em></td>
<td>UK</td>
<td>JACI 2002</td>
<td></td>
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**Production of IgG and IgG4 (without IgE):**

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<th>Year</th>
</tr>
</thead>
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<tr>
<td>Platts-Mills <em>et al</em></td>
<td>USA</td>
<td>Lancet 2001</td>
<td></td>
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<tr>
<td>Erwin <em>et al</em></td>
<td>USA</td>
<td>JACI 2003</td>
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</table>

**Non-specific effects on other allergens:**

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<th>Researcher</th>
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<th>Journal</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ownby <em>et al</em></td>
<td>USA</td>
<td>JAMA 2002</td>
<td></td>
</tr>
<tr>
<td>Perzanowski <em>et al</em></td>
<td>Sweden</td>
<td>AJRCCM 2002</td>
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</table>

* More than one animal.
Decreased Risk of Sensitisation to Cats With High Exposure to Cat Allergen

Custovic et al.
J Allergy Clin Immunol 2001; 108: 537-9
Exposure to Stables and/or Farm Milk in the First Year of Life

- Asthma diagnosis:
  - No exposure: 11.8%
  - Milk only: 14.8%
  - Stable only: 2.8%
  - Stable and milk: 16%

- Asthma symptoms:
  - No exposure: 3.2%
  - Milk only: 12.4%
  - Stable only: 5.1%
  - Stable and milk: 19.8%

- Hay fever diagnosis:
  - No exposure: 5.1%
  - Milk only: 12.4%
  - Stable only: 11.8%
  - Stable and milk: 14.8%

- Hay fever symptoms:
  - No exposure: 0%
  - Milk only: 32.9%
  - Stable only: 10%
  - Stable and milk: 20%

- Atopy:
  - No exposure: 32.9%
  - Milk only: 12.4%
  - Stable only: 11.8%
  - Stable and milk: 14.8%

*Riedler et al. Lancet 2001*
Exposure to Farm Environment in Pregnancy among children exposed to stables and milk in 1. year of life

- Asthma diagnosis: 0.9%
- Asthma symptoms: 0.8%
- Hay fever diagnosis: 0.8%
- Hay fever symptoms: 0.8%
- Atopy: 8.4%

Mother not daily exposed n=58
Mother daily exposed n=119

Riedler et al. Lancet 2001

ALEX-Study
A tale of two molecules

Kim et al JBC 2005
Endotoxin Exposure, Hay Fever & Allergic Sensitisation

**A**
Adjusted Prevalence of Hay Fever (%)

**B**
Adjusted Prevalence of Hay-Fever Symptoms (%)

**C**
Adjusted Prevalence of Atopic Sensitisation (%)

Endotoxin Load in Mattress (units/m²)

Braun-Fahrländer et al, NEJM 2002;347:869-79
Endotoxin and allergy — Associated in Sweden, but not in Estonia

Bottcher et al CEA
2003; 33: 295
CD14

- Pattern recognition receptor
- Part of receptor complex for LPS (endotoxin)
- Soluble or membrane bound CD14
- Maps to 5q32 - region of linkage to asthma
sCD14 varies with \textit{CD14} genotype

Baldini et al, AJRCMB 1999; 20: 976
No association between CD14 and IgE in German children

Kabesch et al, Allergy 2004; 59: 520
CD14/-159 in the Hutterites

- Founder population South Dakota
- Descended from 64 founders (1700s)
- Communal agrarian lifestyle
- Asthma very common
- T allele associated with positive skin tests ($p<0.001$)
Studies of CD14/-159 Genotype

- C allele associated
- T allele associated
- No association
Inconsistencies in results for CD14 and endotoxin

- CD14 polymorphisms associated with allergic sensitisation in some populations but not other
  - Risk allele different in different populations
- Endotoxin protective in some populations but not others

Sengler et al Clin Exp Allergy 2003 33 166 -169
Goa et al : Clin Genetic 1999 56 (2) 164-5
Endotoxin Exposure and IgE Mediated Sensitisation

Endotoxin Load (EU/m²)

Predicted probability for sensitisation

P=0.005

Simpson et al, AJRCCM 2006
CD 14 Promoter Polymorphism, Endotoxin Exposure and Sensitization

Predicted probability for sensitisation

P=0.004
P=0.2
P=0.7

Endotoxin Load (EU/m²)

Simpson et al, AJRCCM 2006
Relationship Between Allergen Exposure and the Development of Sensitization, Wheeze & Lung Function
Odds Ratios for Wheeze and Der p 1 Quartiles

Scrivener et al
Lancet 2001; 358: 1493-1499

OR (95% CI)

Range: (µg/g)  
<1.01  1.01-2.17  2.18-4.52  >4.52

p=0.05
Mite Allergen Exposure Increases the Risk of Specific Sensitisation

Predicted probability for mite sensitisation

Cumulative Der p 1 exposure (mcg)

0.0 0.2 0.4 0.6 0.8 1.0

0 7.4 54.5 403.4 2980

HR  MR  LR
No Association Between Exposure to Dust Mite and Wheeze at Age 3 Years

- Wheeze ever
- Wheeze with colds
- Wheeze apart from colds
- Wheeze in previous 6 months

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Wheeze ever</th>
<th>Wheeze with colds</th>
<th>Wheeze apart from colds</th>
<th>Wheeze in previous 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>35%</td>
<td>31%</td>
<td>14%</td>
<td>18%</td>
</tr>
<tr>
<td>Never exposed</td>
<td>35%</td>
<td>31%</td>
<td>14%</td>
<td>18%</td>
</tr>
</tbody>
</table>
No Effect of Allergen Exposure on Lung Function at Age 3 Years

- Not exposed (n=139)
- Exposed any (n=359)
- Exposed mite (n=290)
- Exposed cat (n=102)
- Exposed dog (n=97)

Lowe et al, Arch Ped Adolesc Med 2004; 158: 996-1001
• Allergen exposure increases the risk of IgE-mediated sensitisation
• No effect of allergen exposure on wheeze or lung function

• Successful allergen avoidance should:
  – Reduce sensitisation
  – Have no effect on wheeze
  – Have no effect on lung function
INTERVENTION STUDY: CLINICAL EFFECT OF ALLERGEN AVOIDANCE
Age 3: Effect of Environmental Control on Sensitisation to Allergens (IgE)

Woodcock et al, AJRCCM 2004; 170: 433-9
Age 3: Effect of Environmental Control on Respiratory Symptoms

Woodcock et al, AJRCCM 2004; 170: 433-9
Lung Function in Pre-School Children

- No effect of allergen exposure on lung function
  
- Lung function significantly worse in:
  - High risk children (irrespective of the reported symptoms or atopic status)
  - Sensitized children (irrespective of the reported symptoms)

Lung Function in the Active and Control Group at Age 3 Years

Woodcock et al, AJRCCM 2004; 170: 433-9
Lung Function in Infancy: Rapid Thoraco-Abdominal Compression (RTC) Technique
Lung Function in the Active and Control Group in Infancy and at Age 3 Years

Lung function (VmaxFRC) at age 4 weeks

P = 0.49

Lung function (sRaw) at age 3 years

P = 0.003

Woodcock et al, AJRCCM 2004; 170: 433-9
Primary Prevention:
From the whole population to individuals at risk
Endotoxin and Der p 1 Exposure and Probability for Mite Sensitisation in Children With CD14 -159 CC Genotype

Simpson et al, AJRCCM 2006
Conclusions

- Totality of evidence on risk factors remains conflicting
  - No clear indication of the types of microbes that might be “protective”
  - Relationship between allergen exposure and development of clinical phenotypes inconsistent
- Elucidate protective exposures
- Determine environmental and genetic basis for subsequent disease
- To understand risk factors for asthma and allergies, study the interaction between the inherited risk and the environment
Conclusions-Prevention

• Some of the results encouraging
  – Longer follow-up is required before we can be sure that the interventions cause no harm
  – We cannot as yet give any advice within the public health context.

• The selection of subjects needs to be refined
  – Identify particular genetic polymorphisms which confer an increase in risk

• This will results in tailor made approaches for individuals.

Custovic and Simpson, ABC of Allergies, BMJ 2006