Lessons from Cross-Sectional and Longitudinal Studies in Infants and Children

Luis Garcia-Marcos
Arrixaca University Children’s Hospital
IMIB Research Institute
University of Murcia. Spain
Lessons from data

- Global variations of asthma prevalence
- Time trend of asthma prevalence
- Environmental risk factors
  - Ecological level
  - Individual level
Global variations
ISAAC Phase One

Wheeze in last 12 mths
13-14 yr age grp

≥20%
10 to <20%
5 to <10%
<5%
Some lesson from global variations

• Asthma is not less prevalent in low-income countries
• More severe asthma is more frequent in areas with higher prevalence
• Hygiene hypothesis does not work everywhere
• Prevalence is highly variable in genetically similar areas
• Environmental local factors probably exert a key role in asthma inception
Temporal trends
Some lessons on time trends

- In areas with high prevalence 20 years ago, it tends to decrease or maintain.
- In areas with low prevalence by that time, asthma prevalence tends to increase.
- There might be a cohort effect in some areas by which new generations suffer from more frequent asthma.
Environmental factors
(ecological level)
Air pollution

Environ Health Perspect 2012
Climate

Ocup Environ Med 2004
Some lessons from environmental factors (ecological level)

- It does not seem that pollution or pollen counts explain much of the difference between centres.
- Diet and climate (relative humidity) are good candidates for explaining those differences.
Environmental factors (individual level)
Atopy

OR for the association of current wheeze with skin prick test reactivity

Hong Kong
Dresden
Munich
Athens
Thessaloniki
Reykjavik
Rome
Utrecht
Hawkes Bay
Tromso
Almeria
Cartagena
Madrid
Valencia
Linköping
Oestersund
West Sussex
Combined affluent

Tirana
Uruguayana
Beijing
Guangzhou
Pichincha
Tallinn
Tbilisi
Kintampo
Mumbai
Riga
Ramallah
Ankara
Combined non-affluent
Combined non-affluent without Guangzhou

Odds ratio with 95%-confidence intervals
## Truck traffic

<table>
<thead>
<tr>
<th>Group/symptom</th>
<th>High vs. never</th>
<th>Medium vs. never</th>
<th>Low vs. never</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current wheeze</td>
<td>1.35 (1.23–1.49)</td>
<td>1.24 (1.13–1.35)</td>
<td>1.07 (0.98–1.16)</td>
</tr>
<tr>
<td>Asthma ever</td>
<td>1.18 (1.08–1.28)</td>
<td>1.08 (1.00–1.17)</td>
<td>1.01 (0.94–1.09)</td>
</tr>
<tr>
<td>Current wheeze–video</td>
<td>1.44 (1.26–1.64)</td>
<td>1.28 (1.14–1.44)</td>
<td>1.11 (0.99–1.23)</td>
</tr>
<tr>
<td>Severe asthma symptoms</td>
<td>1.53 (1.36–1.72)</td>
<td>1.26 (1.13–1.41)</td>
<td>1.07 (0.97–1.18)</td>
</tr>
<tr>
<td>Rhinoconjunctivitis</td>
<td>1.39 (1.27–1.52)</td>
<td>1.21 (1.12–1.32)</td>
<td>1.06 (0.98–1.14)</td>
</tr>
<tr>
<td>Eczema</td>
<td>1.54 (1.37–1.73)</td>
<td>1.30 (1.17–1.45)</td>
<td>1.08 (0.97–1.19)</td>
</tr>
</tbody>
</table>
## Breast feeding

<table>
<thead>
<tr>
<th></th>
<th>Affluent countries&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Nonaffluent countries&lt;sup&gt;$&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted&lt;sup&gt;§&lt;/sup&gt;</td>
<td>Adjusted&lt;sup&gt;§&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>Atopic wheeze</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of breastfeeding&lt;sup&gt;¶¶&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not breastfed</td>
<td>1</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>0.89</td>
<td>0.70–1.13</td>
</tr>
<tr>
<td>≥6 months</td>
<td>0.87</td>
<td>0.68–1.11</td>
</tr>
<tr>
<td><strong>Nonatopic wheeze</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of breastfeeding&lt;sup&gt;‡‡&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not breastfed</td>
<td>1</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt;6 months</td>
<td>0.88</td>
<td>0.69–1.11</td>
</tr>
<tr>
<td>≥6 months</td>
<td>1.00</td>
<td>0.79–1.26</td>
</tr>
</tbody>
</table>

Eur Resp J 2010
## Paracetamol

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adjusted*  (all children)</th>
<th>Adjusted† (children with complete covariate data)</th>
<th>Multivariate analysis‡ (children with complete covariate data)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>1.76 (1.58-1.85)</td>
<td>1.77 (1.66-1.89)</td>
<td>1.46 (1.36-1.56)</td>
</tr>
<tr>
<td>Rhinoconjunctivitis</td>
<td>1.78 (1.59-1.86)</td>
<td>1.74 (1.62-1.87)</td>
<td>1.48 (1.38-1.60)</td>
</tr>
<tr>
<td>Eczema</td>
<td>1.54 (1.47-1.61)</td>
<td>1.54 (1.44-1.64)</td>
<td>1.35 (1.26-1.45)</td>
</tr>
</tbody>
</table>

Data are OR (95% CI). *Adjusted for sex, region of the world, language, and gross national income. A total of 194,555 children were included from 69 centres in 29 countries, except in the analysis of eczema (191,915 children from 68 centres in 28 countries). †Adjusted for sex, region of the world, language, and gross national income. ‡Multivariate analysis included centres with at least 70% data available for all covariates. Children who had a missing value for any of the covariates were removed.

*Table 1:* Association between paracetamol use for fever in the first year of life and symptoms of asthma, rhinoconjunctivitis, and eczema at 6-7 years of age

Lancet 2008
Some lessons from environmental factors (individual level)

- The association between asthma and atopy varies between areas, and is much weaker in low income countries.
- Breast feeding seems to protect against asthma only in non-atopic children and only in low income countries.
- Certain drugs are associated to asthma prevalence further to a mere indication bias.
- Oxidative stress might be of more importance in asthma inception that it has been thought until now (paracetamol, diesel, diet).
Some other lessons from environmental factors (individual level)

- **Other positive associations include:**
  - Open fire cooking & tobacco smoke exposure
  - Farm animals
  - Dampness in homes
  - Burger/fast food intake
  - Obesity
  - Migration to higher prevalence country
  - Greater family size (severe asthma)

- **Other negative associations include:**
  - Fresh fruits and vegetables
  - Mediterranean diet
The International Study of Asthma and Allergies in Childhood (ISAAC) is a unique worldwide epidemiological research programme established in 1991 to investigate asthma, rhinitis and eczema in children due to considerable concern that these conditions were increasing in western and developing countries.

ISAAC has become the largest worldwide collaborative research project ever undertaken, involving more than 100 countries and nearly 2 million children and its aim is to develop environmental measures and disease monitoring in order to form the basis for future interventions to reduce the burden of allergic and non-allergic diseases, especially in children in developing countries.

The ISAAC findings have shown that these diseases are increasing in developing countries and that they have little to do with allergy, especially in the developing world. Further population studies are urgently needed to discover more about the underlying mechanisms of non-allergic causes of asthma, rhinitis and eczema and the burden of these conditions.

**New network to continue ISAAC's work in asthma**

The ISAAC Programme formally finished in December 2012. The Global Asthma Network was founded in 2012 and will extend the work of ISAAC in the asthma field.

**The ISAAC Story**

The ISAAC Steering Committee is proud to announce that the ISAAC Story, a 20 year history of ISAAC, is available on the website. This fascinating account contains details from the how ISAAC was first conceived through to the highlights of the very latest papers. Recollections of founding members, full descriptions of all aspects of the methodology and tools, all publications graphs and maps are available as well as pages for each of the 3 phases, 165 countries and 200 centres containing centre information, collaborators and personal stories.
Environmental factors

Epigenetics
(can be modified after conception)

Genetic polymorphisms
(born with)

Inter-individual variability
Over 130 birth cohorts focusing on asthma and allergy have been initiated in the last 30 years.
Endotypes

The Asthma Syndrome
Symptoms of asthma, variable airflow obstruction

Asthma phenotype characteristics
Observable characteristic with no direct relationship to a disease process. Includes physiology, triggers, inflammatory parameters

Asthma Endotypes
Distinct disease entities which may be present in clusters of phenotypes, but each defined by a specific biological mechanism

Endotype 1  Endotype 2  Endotype 3  Endotype 4  Endotype 5
Epi / genotypes?

Internal / Maternal factors:
- Oxidants & Antioxidants
- Diet & Nutritional factors
  (e.g. choline, betaine, folic acid, vitamin B12, vitamin D)

Airway Epithelium

Allergens

Activated DC

Naïve Th Cell

IL-17

Th17 Cell

IL-4
IL-5
IL-9
IL-13

Th2 Cell

Th1 Cell

Treg Cell

TGF-β
Foxp3

DEP
PM
Black carbon
Dust mite

Tobacco smoke
BaP
PAH
Endotoxin (e.g. LPS)
Dust mite

Sm Ho. JACI 2010
Window of opportunity & Foetal programming
New (?) infections
CONCLUSIONS

- Cross-sectional studies have identified a considerable number of factors associated to higher asthma prevalence, but fewer associated to lower prevalence.
- However, no cause-effect relationship can be concluded from cross-sectional studies.
- Birth and prenatal cohort studies add (and will add) important insights on the natural history and mechanisms (including genetic and epigentic) of asthma.
- Cohort studies can identify cause-effect relationship which could be the starting point for primary prevention.