Fattori socioeconomici e sviluppo di malattie allergiche.

(….. qualche idea per la prevenzione?)

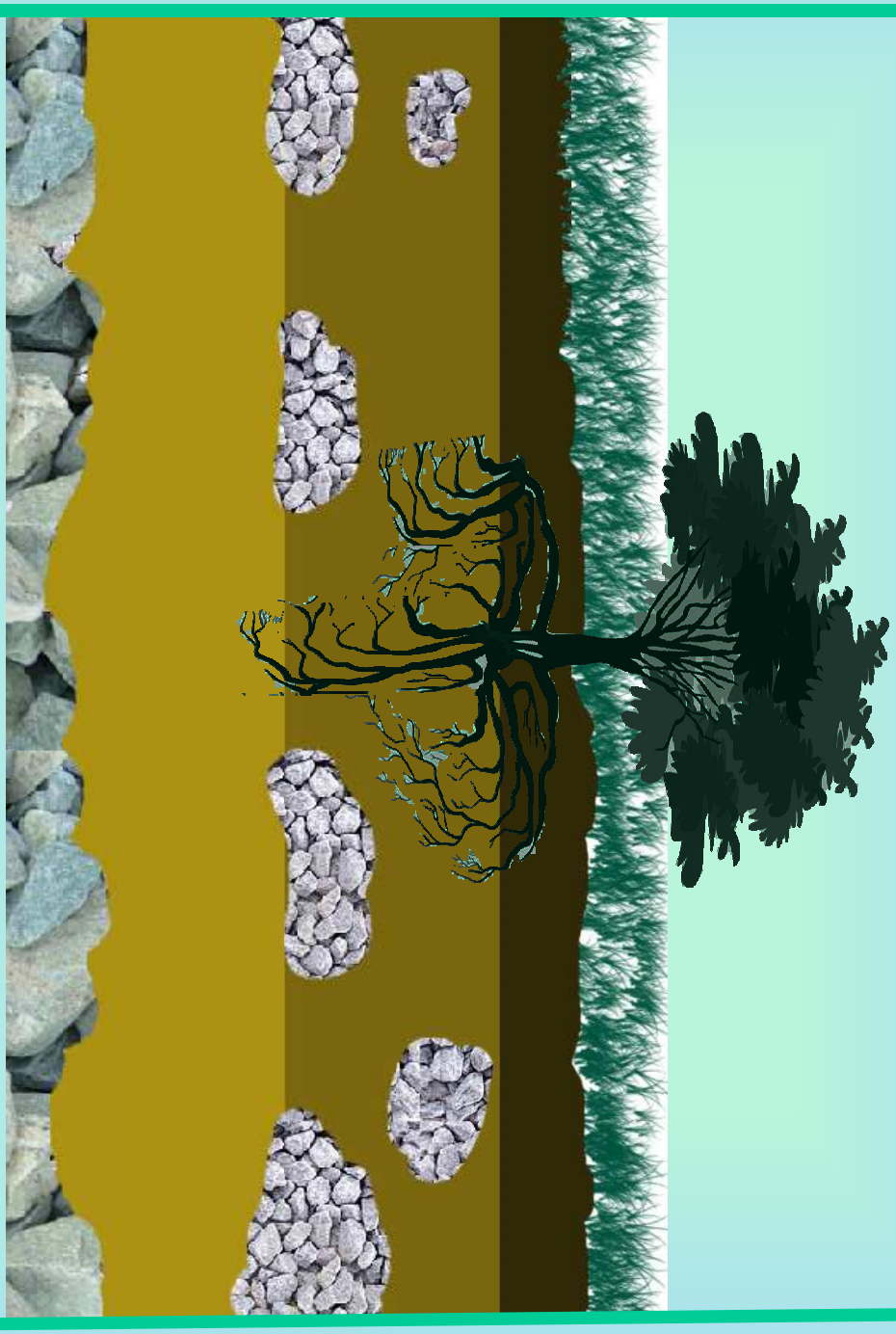
Alessandro Fiocchi
Melloni Pediatria
Milano

Fattori socioeconomici & allergie

a. Epidemiologia delle allergie negli ultimi 20 anni
b. Ambiente prenatale e sviluppo delle allergie
c. Indicatori di sviluppo ed allergie: analisi ecologiche
d. Il sibship size effect
e. Possibili effetti di questi fattori sullo sviluppo di allergie
f. Conclusioni

Trends in hospital admission rates of food allergy by age (1990-2003)

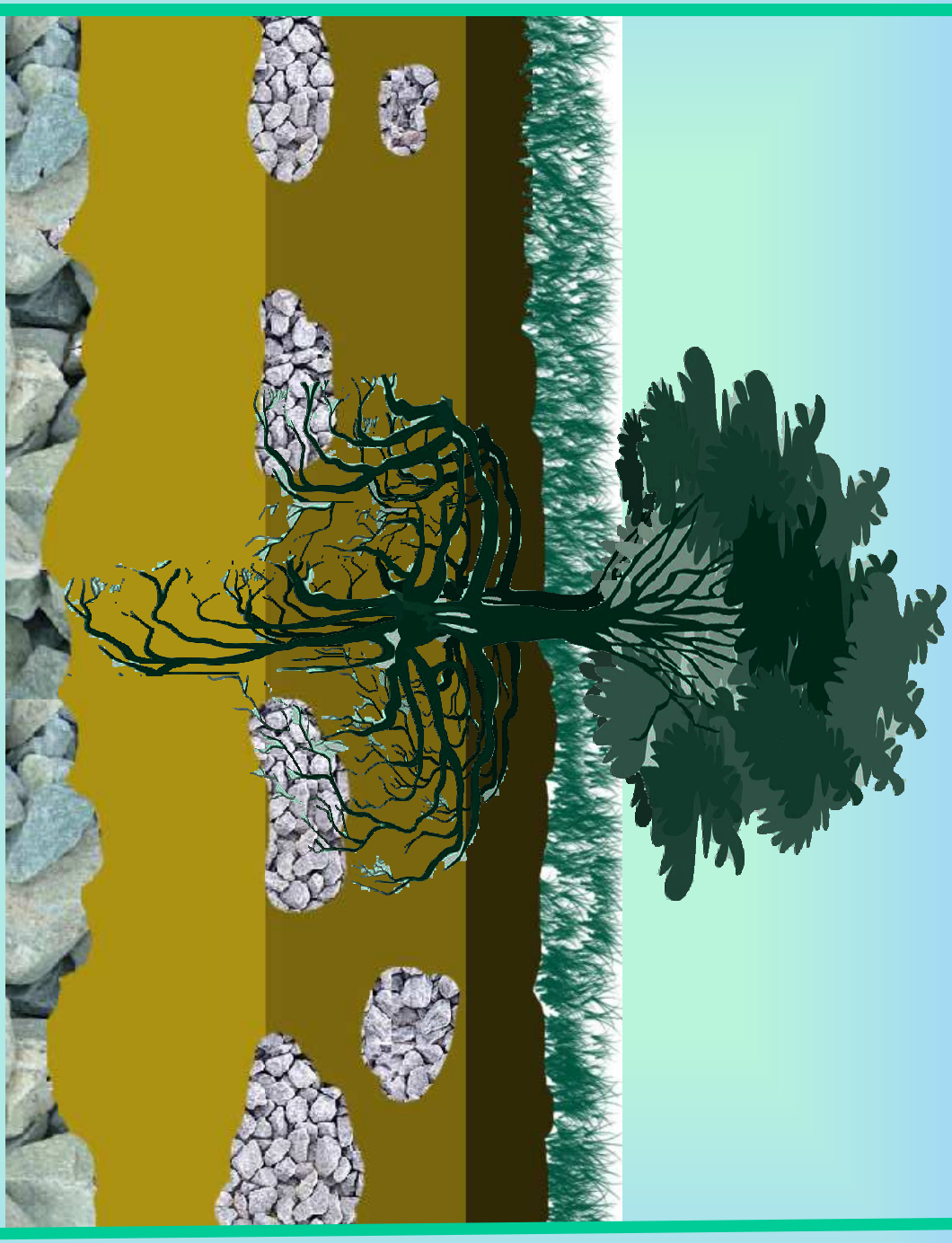
1990 – 20:1.000.000



Gupta R. Time trends in allergic disorders in the UK. Thorax 2007; 62:91-6

Trends in hospital admission rates of food allergy by age (1990-2003)

1995 – 60:1.000.000



Gupta R. Time trends in allergic disorders in the UK. Thorax 2007; 62:91-6

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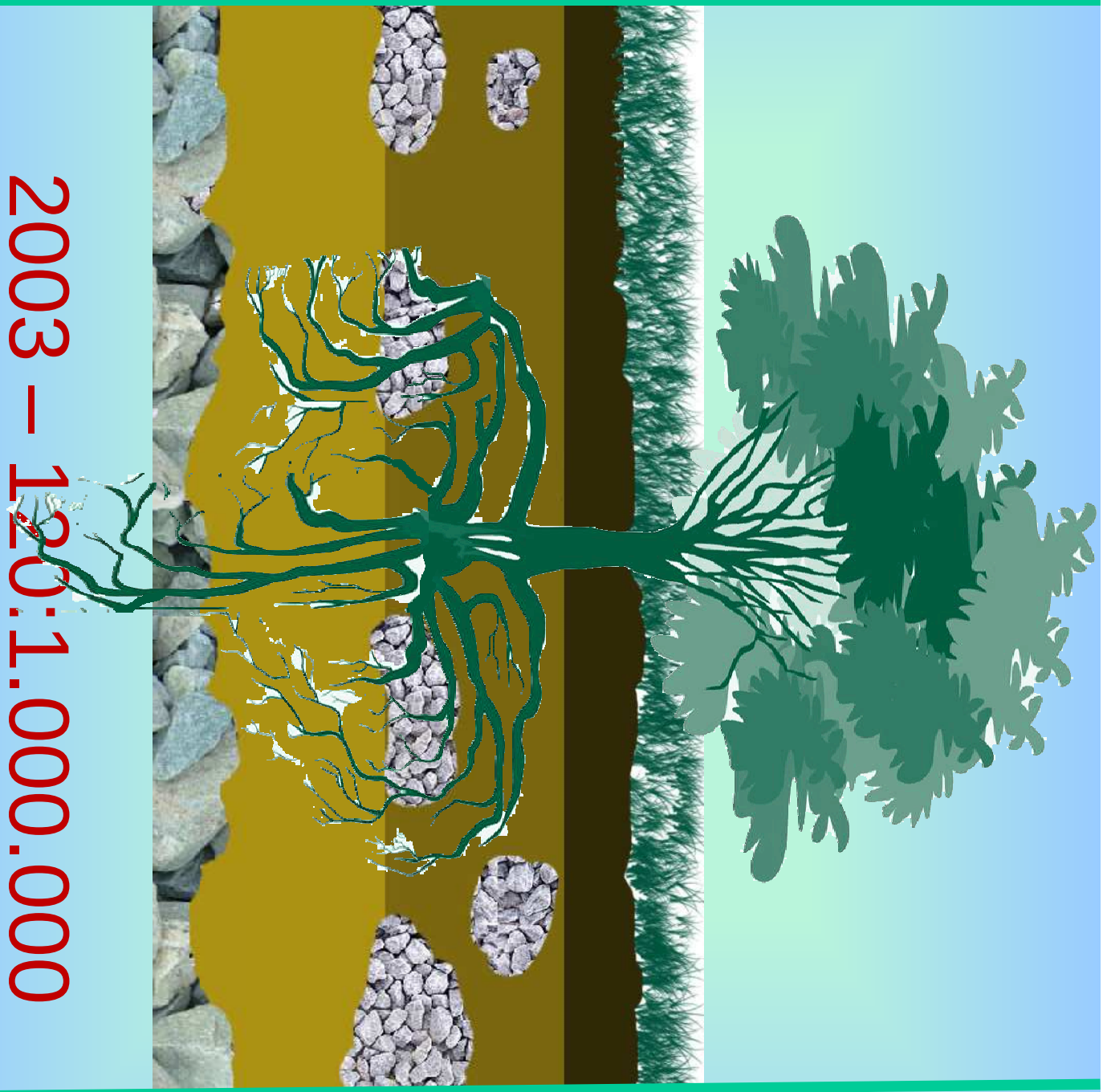
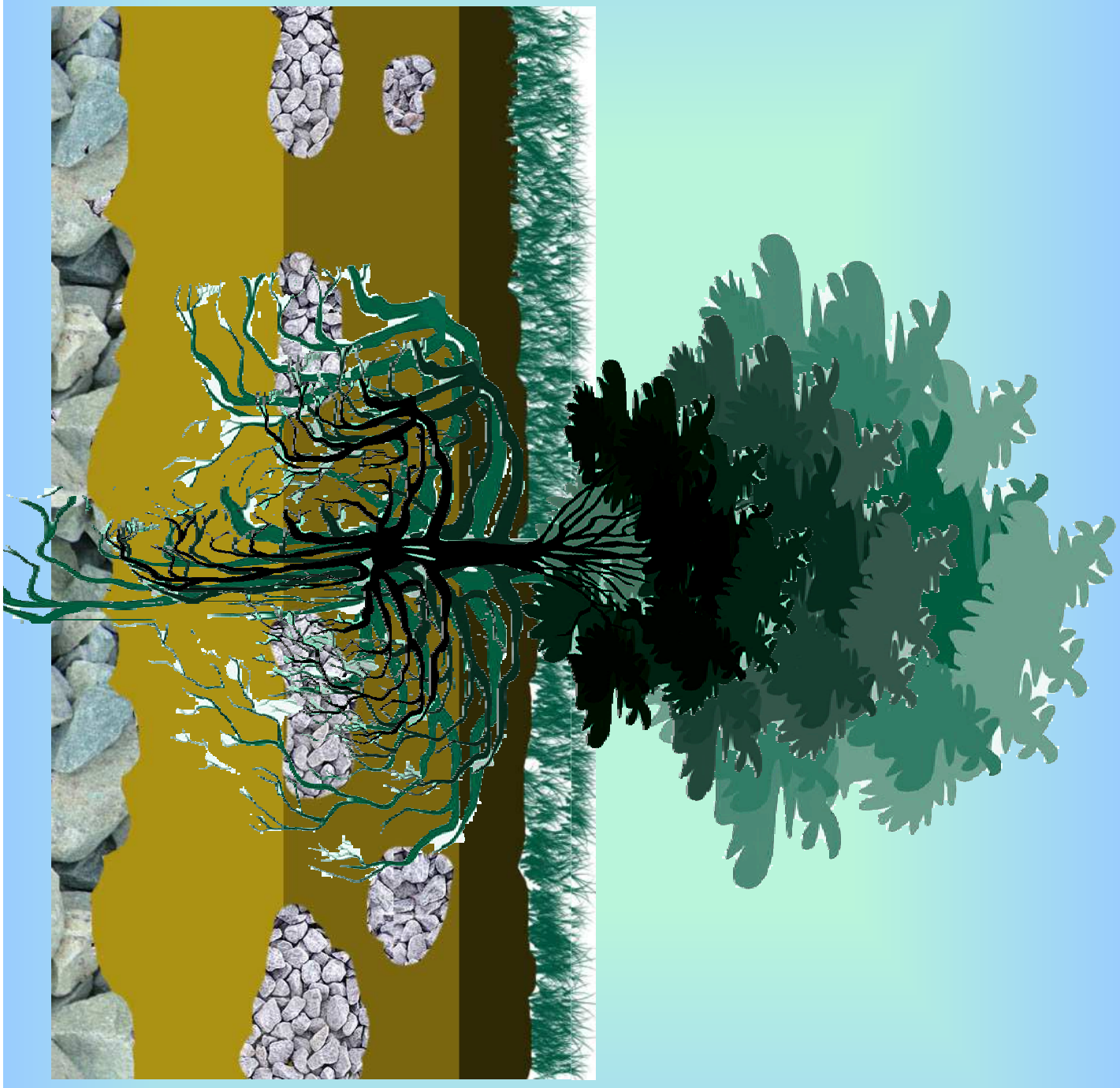


2003 – 120.1.000.000

Gupta R. Time trends in allergic disorders in the UK. Thorax 2007; 62:91-6

2012 – ??:1.000.000



The ‘Allergy Epidemic’

as part of a much bigger problem:

- In the last 50 years: there has been a dramatic rise in a wide range of NCDs

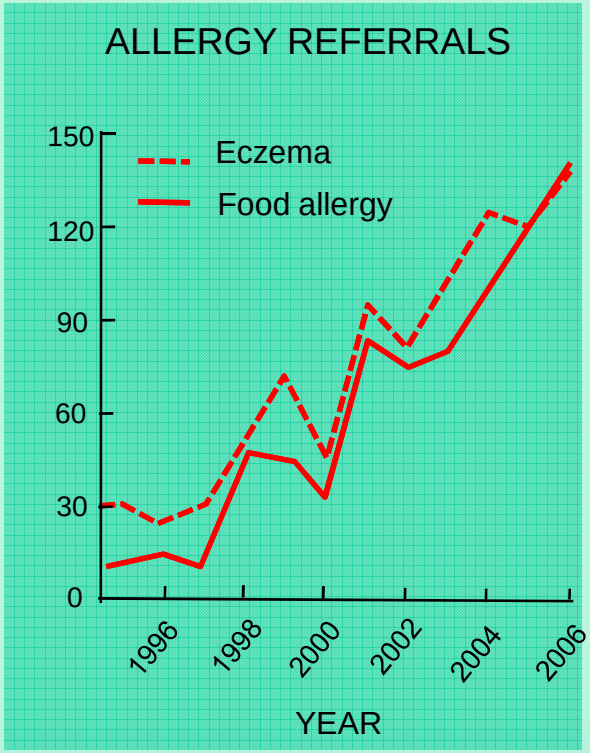
- Obesity	- Cardiovascular disease
- COPD	- Metabolic disease (NIDDM)
- Asthma	- Psychiatric disorders
- Allergy	- Autoimmunity
- Cancer	- Chronic liver/renal disease

- United nations: Major global threat
- Now rising in *developing* countries
- Many linked with *inflammation*
- *All* linked with modern lifestyle changes

Need for prevention strategies with multi-system benefits

United Nations General Assembly
Prevention of NCDs
in developing regions
(September 2011)

The dramatic rise in allergic disease must be environmental



Mullins, MJA 2007; 186: 618-621 *(Australian data)*

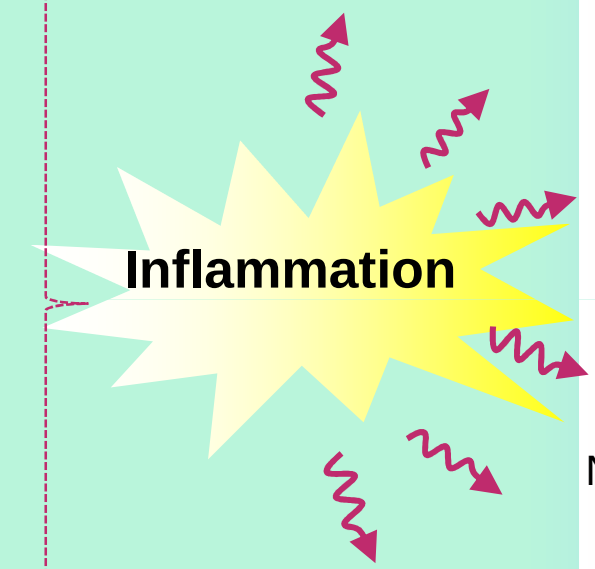
Seems to be getting worse with each generation

So what are the main driving factors?

Common risk factors

For many modern diseases

- Δ microbial balance
- Δ dietary profile
  - ↑ Saturated fat
  - ↓ Dietary fibre
  - ↓ n3/n-6 PUFA
  - ↓ Fresh foods
- Δ Sunlight (vitamin D)
- Δ Stress patterns
- Δ Exercise patterns
- Δ Pollutants
  - Smoking
  - Toxins & POPs
  - EM radiation?



- Allergy
- Autoimmunity
- Obesity
  Metabolic disease
  Diabetes
- Cardiovascular Disease
- Neurodegenerative Disease
- Inflammatory Bowel Disease
- Cancer

= Common interventions for prevention

Other suspects!

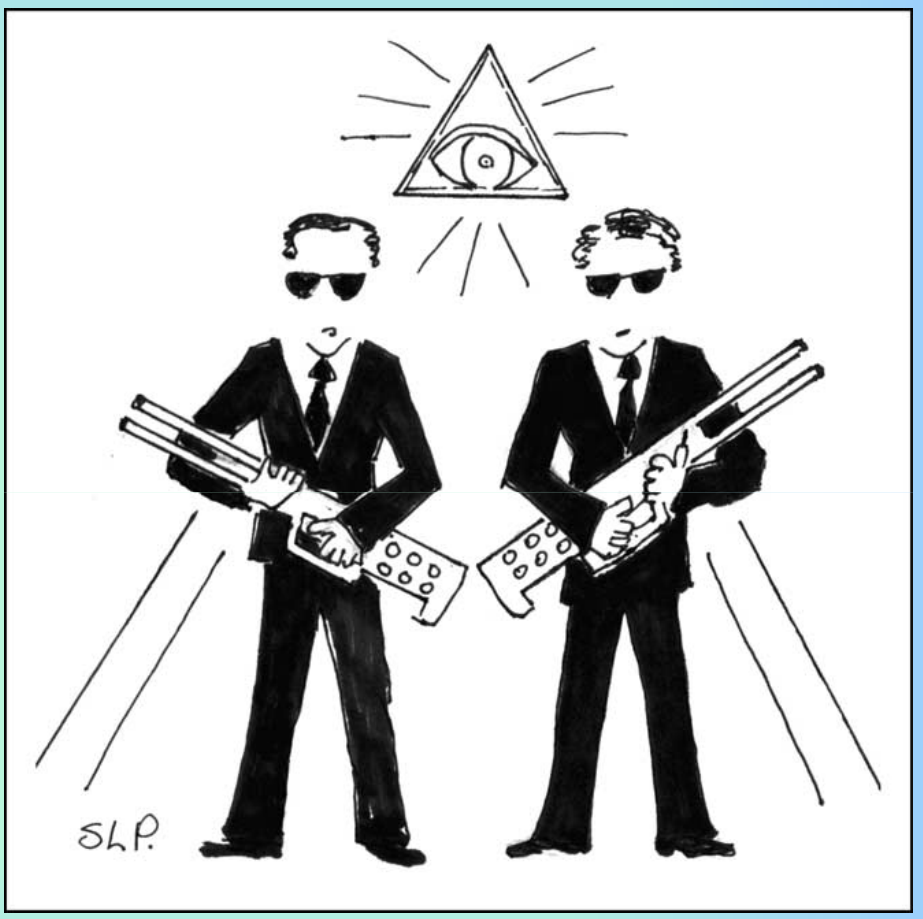
Modern epidemic of immune disease is multi-factorial:

Not the work of one agent, but an organised crime network

Conspiracy of westernisation

Can arguments over when food allergens arrived on the crime scene explain the crime?

Are not they distracting us from the real perpetrators?



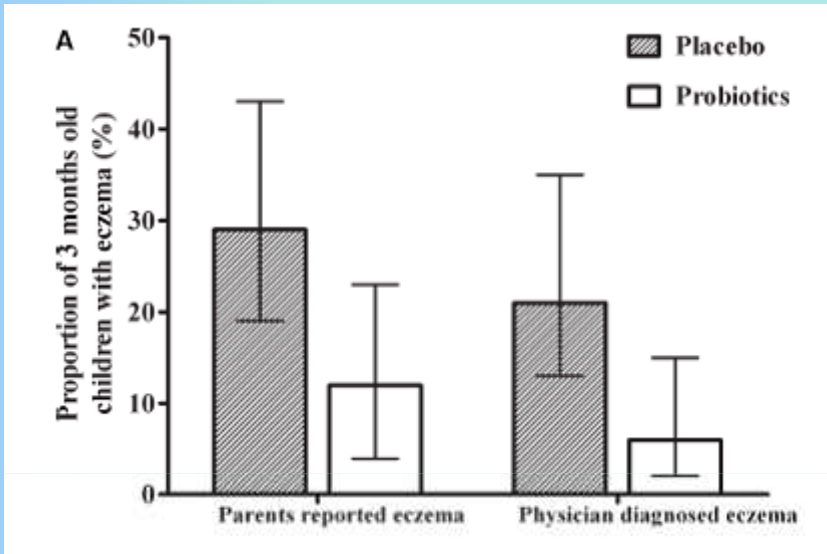
Prescott S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? Curr Opin Allergy Clin Immunol 2010,10:258–66

The hygiene hypothesis

The hygiene hypothesis proposes that as a result of modern public health practices, individuals living in the industrialized world experience a relative deficiency in immune stimulation by microbes, rendering them vulnerable to the development of allergic hypersensitivities and their associated diseases.

Prescott S, Fiocchi A. Avoidance or exposure to foods in prevention and treatment of food allergy? Curr Opin Allergy Clin Immunol 2010,10:258–66

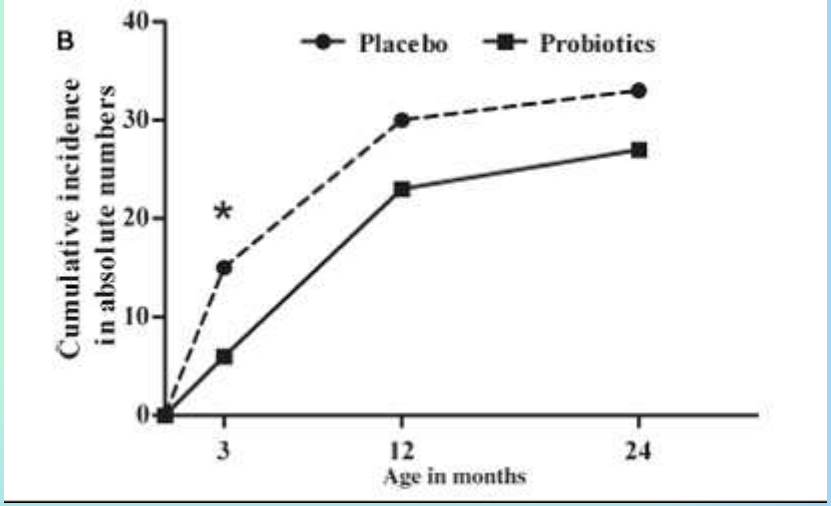
Ecologic PandA and eczema



AD:

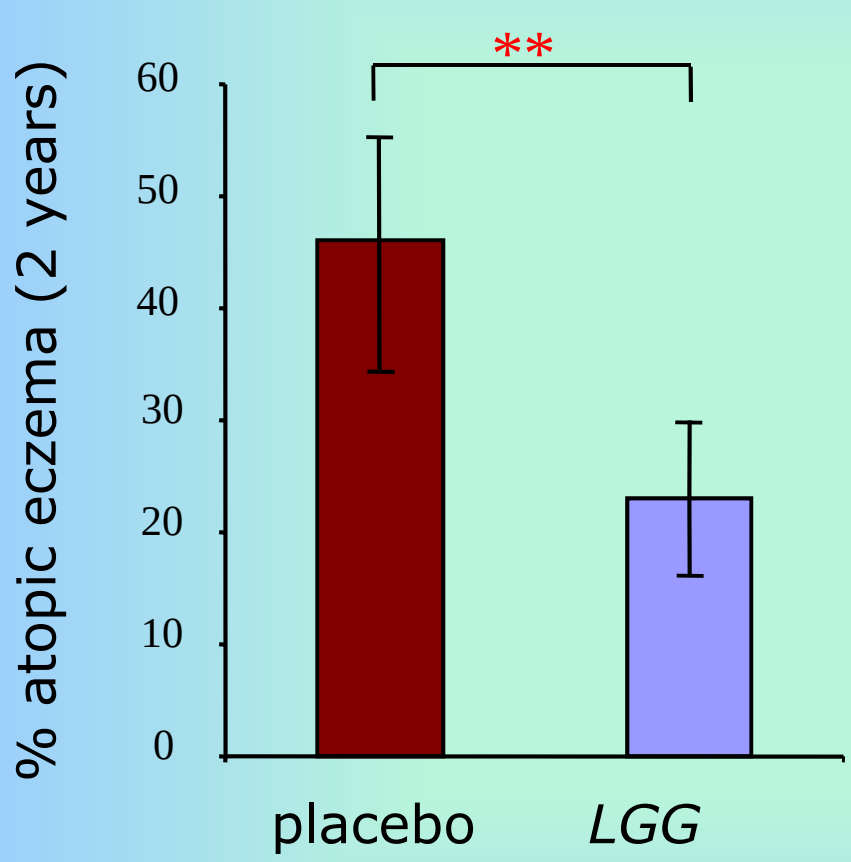
6/50 (**12%**) in treated vs. 15/52 (**29%**) in placebo. ***P = 0.035***

RR reduction: 58%

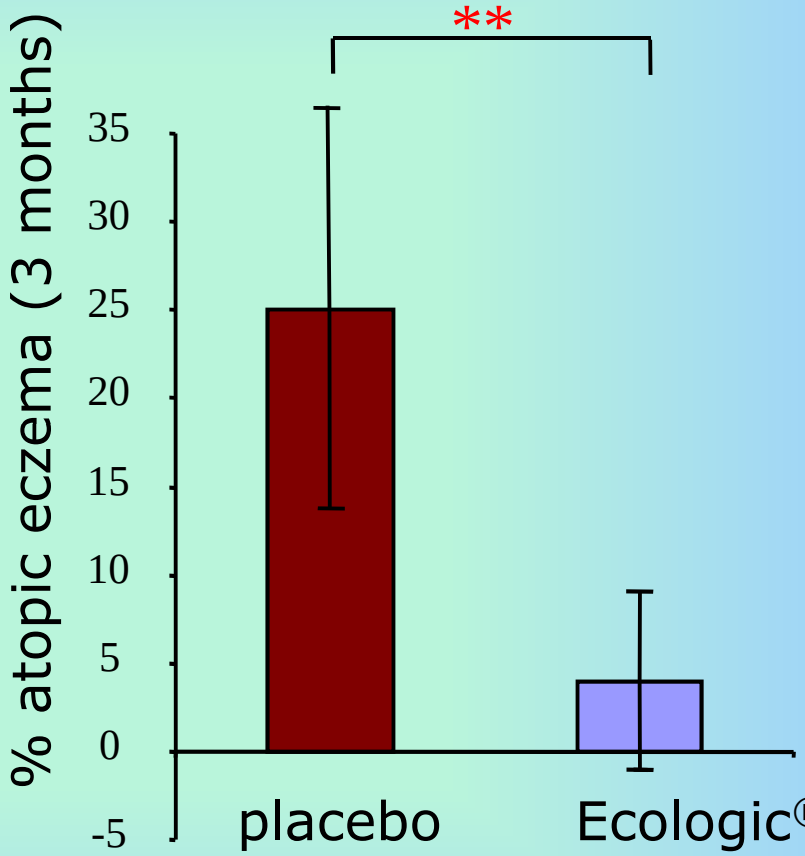


Njers R. the effects of selected probiotic strains on the development of eczema . The PandA study. Allergy 2009: 64:256-61

Reduction of eczema: 3 months



Kalliomaki et al.
Lancet 357 (2001) 1076



Niers et al.
Allergy 125 (2009) 256

B. bifidum
B. lactis
Lc. lactis

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Food sensitisation is a very early event

Community survey (Melbourne):

- **n=5000 1yr old infants** attending community clinics for routine checks
- Allergy skin prick tests
- Any child with a positive test referred for a food challenge at hospital to determine if there was a clinical reaction

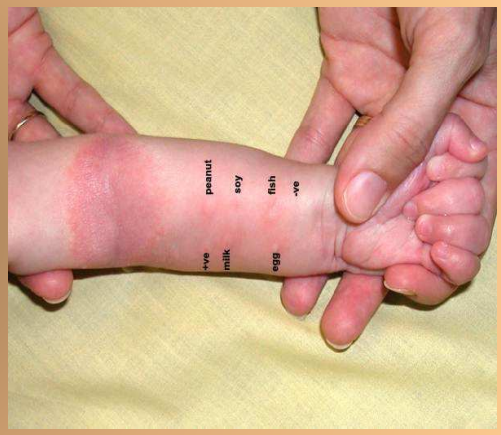
Osborne et al. JACI **2011**; 127: 668-678 (Australian data)

More than 20% with food sensitisation

Rate of ‘sensitisation’ (positive allergy tests):
= Children with allergic antibodies to foods

- egg: 16%
- peanut: 9%
- cows milk: 6%

- **TOTAL: >20%**



But not all children with allergic antibodies will have a reaction: so need to ‘challenge’ to determine clinical reactivity

Osborne et al. JACI 2011; 127: 668-678 (Australian data)

Over 10% with challenge-proven food allergy

Osborne et al. JACI 2011; 127: 668-678

Reactions on challenge:

(hives, swelling, noisy breathing, choking, vomiting, pallor, floppiness)

- egg: 9%
- peanut: 3%
- other: 2%

- **TOTAL: >10%**

More than 1 in 10 of all 1 year olds in Australia have clinical food allergy

Now: significant rates of food allergy *prior* to starting foods at 4-6 months

DB-RCTs: early egg feeding

(n=1512 high risk infants)

- RCTs: start egg/placebo at 4-6months
- **22% reaction rate** at randomization (*prior* to the intervention)
- **1.2% anaphylaxis** Rx adrenaline
- On ‘first’ known oral exposure to ‘egg’
- ‘Early feeding’ already too late in these children

Implies much earlier allergen exposure:
pregnancy, lactation, transcutaneous

Pregnancy and fetal immunity

Pregnancy is the most critical period of developmental programming

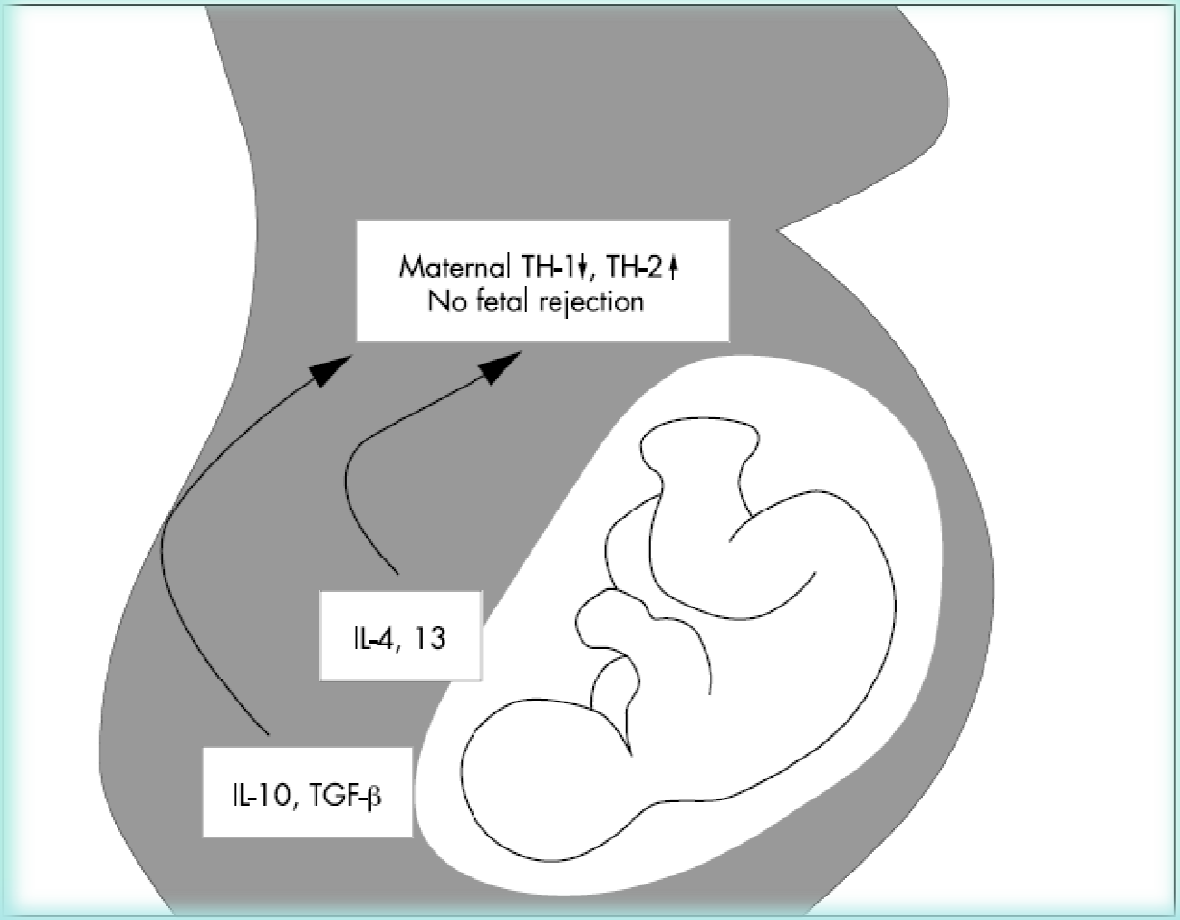
Pregnancy modifies maternal cytokine production

⇓Th1 responses to environmental antigens

⇓Th1 responses to fetal alloantigens

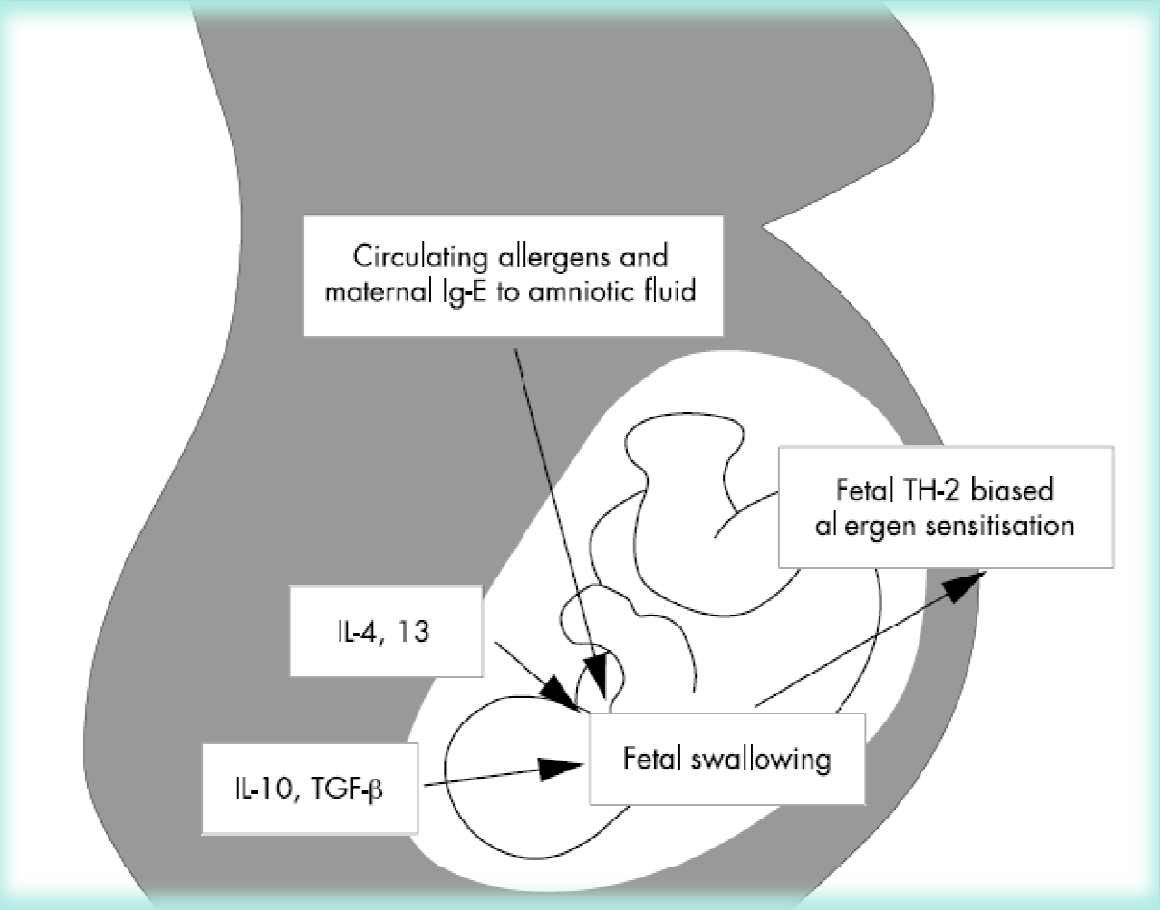
Prescott SL, Clifton V. Asthma and pregnancy: emerging evidence of epigenetic interactions in utero. Curr Opin Allergy Clin Immunol 2009;9:417–426

The conceptus down-regulates maternal Th-1 immune responses to feto-paternal antigens



Warner JO. The early life origins of asthma and related allergic disorders. Arch Dis Child 2004;89:97–102.

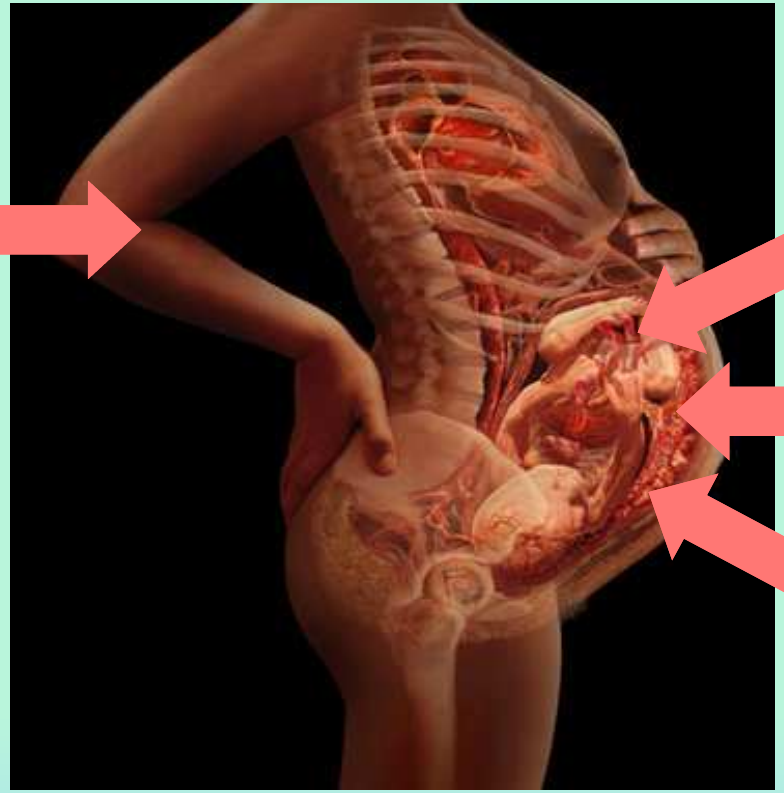
Th-2 + maternal IgE + allergens from maternal circulation= potential for fetal allergic sensitisation



Warner JO. The early life origins of asthma and related allergic disorders. Arch Dis Child 2004;89:97–102.

Allergen detection in pregnancy
first encounter with allergen

Maternal blood



Placental tissues

Fetal blood

Amniotic Fluid

Contact with fetal skin, gut, airways

Holloway, J. A., et al. Lancet 356(9245): 1900-2.
Vance GH, et al. Clin Exp Allergy 2005; 35:1318-26.
Szepfalusi Z, et al. Clin Exp Allergy 2006; 36:1130-7.

Szepfalusi Z, et al. Pediatr Res 2000; 48:404-7.
Loibichler C, et al. Clin Exp Allergy 2002; 32:1546-51.

Pregnancy modifies maternal cytokine production

- ⇓Th1responses to environmental antigens

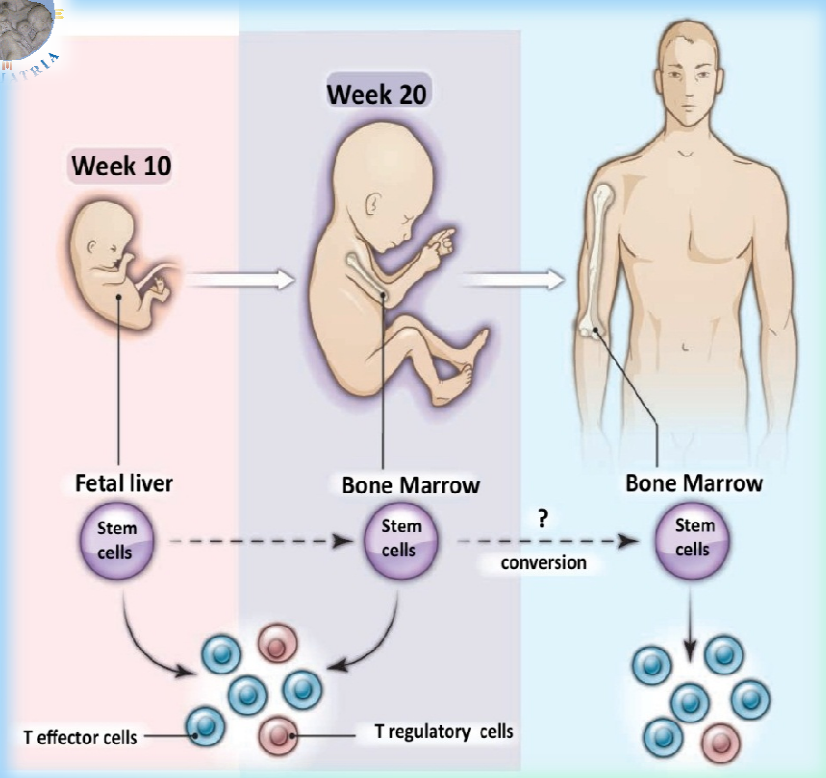
- ⇓Th1responses to fetal alloantigens.

In allergic mothers:

– ⇓ IFNγ responses

- ⇧ Immunosuppressive and regulatory cytokines (IL-10 and TGF-β)

Prescott SL, Clifton V. Asthma and pregnancy: emerging evidence of epigenetic interactions in utero. Curr Opin Allergy Clin Immunol 2009;9:417–426



Fetus: highly developed regulatory responses

- Not inert or passively unresponsive!
- Not an 'immature' version of adults [1-2]

- Highly responsive to antigens
- Strong bias to Treg differentiation
  (tolerogenic milieu : TGFβ, TSLP)

- Higher % circulating Treg than adults[3]

→ Wave of promiscuously responsive cells
→ Gives rise to a broad repertoire of Treg (self antigens)

1. Betz, A. G. (2010). Science 330(6011): 1635-6.
2. Mold, J. E. and J. M. McCune (2011).." Chimerism 2(2): 35-41
3. Darrasse-Jeze, G., G. Marodon, et al. (2005). Blood 105(12): 4715-21..

Dispels myth that the fetus has 'reduced ability' to respond

Regulatory responses are initiated prior to conception

⇧ $CD4^+/CD25^+/FoxP3^+$ regulatory cells following exposure to paternal antigens in seminal fluid

Robertson SA, Guerin LR, Bromfield JJ, et al. Seminal fluid drives expansion of the $CD4^+CD25^+$ T regulatory cell pool and induces tolerance to paternal alloantigens in mice. Biol Reprod 2009; 21; 76-9

Exposure to paternal antigens in previous pregnancies may influence regulatory T-reg activity

Bernsen RM, Nagelkerke NJ. Impairment of regulatory T cells in cord blood of atopic mothers. J Allergy Clin Immunol 2008; 122:841

Bernsen RM, Does paternal antigen-induced secretion of interleukin-10 by T regulatory cells mediate the birth order effect? Medical Hypotheses 2006;67:740–3

Allergen-specific responses in pregnancy

- Detectable as early as 22 weeks[1]
- Responses to foods and inhalants, but not to vaccines (not exposed) [2,3]
- But not classical memory [4], and
- Lymphoproliferation does not correlate with exposure [5,6]

But may not be surprising, if the dominant fetal response is regulatory rather than classic memory recall

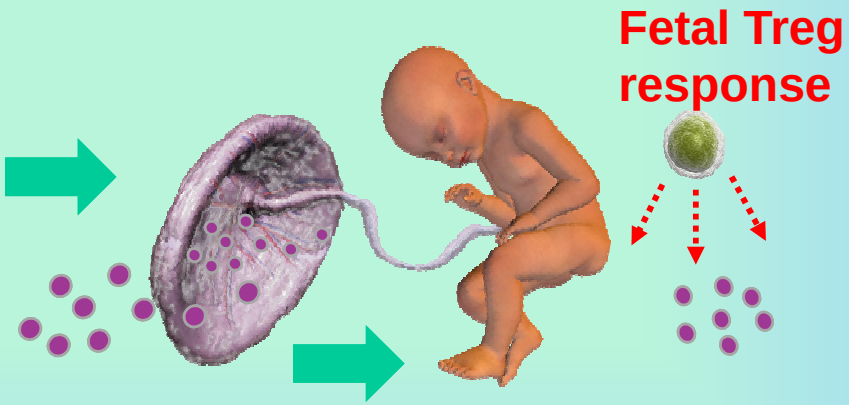
1. *Jones, A. et al. Pediatric Allergy Immunol 1996 7: 109-116.*
2. *Prescott, S. et al. J Immunol 1998 160: 4730-4737.*
3. *Piccinni, M. et al. Int Arch Allergy Immunol 1993 102: 301-303.*
4. *Thornton, C. A. et al. J Immunol 2004 173(5): 3084-92.*
5. *Smillie, F. I. et al. Clin Exp Allergy 2001 31(8): 1194-204.*
6. *Marks, G. B., et al. Clin Exp Allergy 2002 32(3): 355-60*

Tolerance to exogenous antigens also begins during this period

- Fetus can generate long-lived CD4+CD25+FoxP3+ Tregs
  - → to exogenous antigens (alloantigens, microbial Ag)[1,2]
  - → can modulate postnatal responses

- Fetal allergen-specific responses
  - → generate Treg in vitro[3]

- Alloantigens
- Microbial antigens
- Allergens



1. *Mold JE, et al. Science 2008; 322:1562–1565*
2. *Mackroth, M. S. et al. J Immunol 2011:186(5): 2780-91.*
3. *Thornton C. et al. J Immunol 173(5): 3084-92.*

Role of antenatal allergen exposure in *initiation* of allergen-specific tolerance?

Must be a strong focus on early life:

Very early exposures have greater implications for the risk (and prevention) of future diseases

Early environment
(diet, microbes, toxins, stress)

Risk of later disease
(heart disease, obesity, dementia
diabetes, allergy, asthma)

Early environmental exposures can alter the tissue milieu

(pregnancy and early postnatal period)

- **Influence the patterns of response to 'new' antigens**
- **Factors known to alter immune function** [1,2]

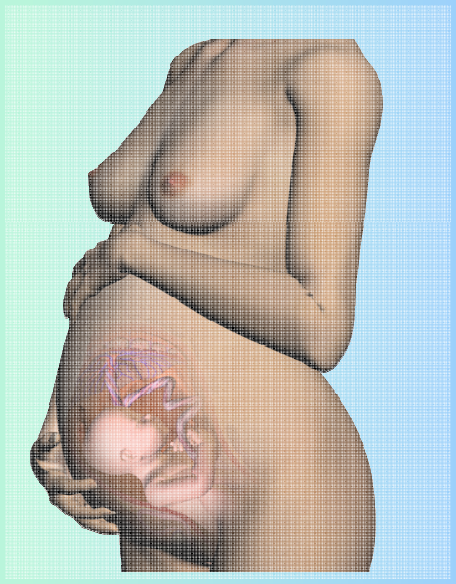
  also have known effects of TSLP

  and other tissue factors

  - Smoking / pollutants [3]
  - Dietary patterns / nutrients [4]
  - Microbial exposure [5,6]

Epigenetic effects

Effects on milieu (TSLP)



- **May contribute to emergent differences in immune function at birth**

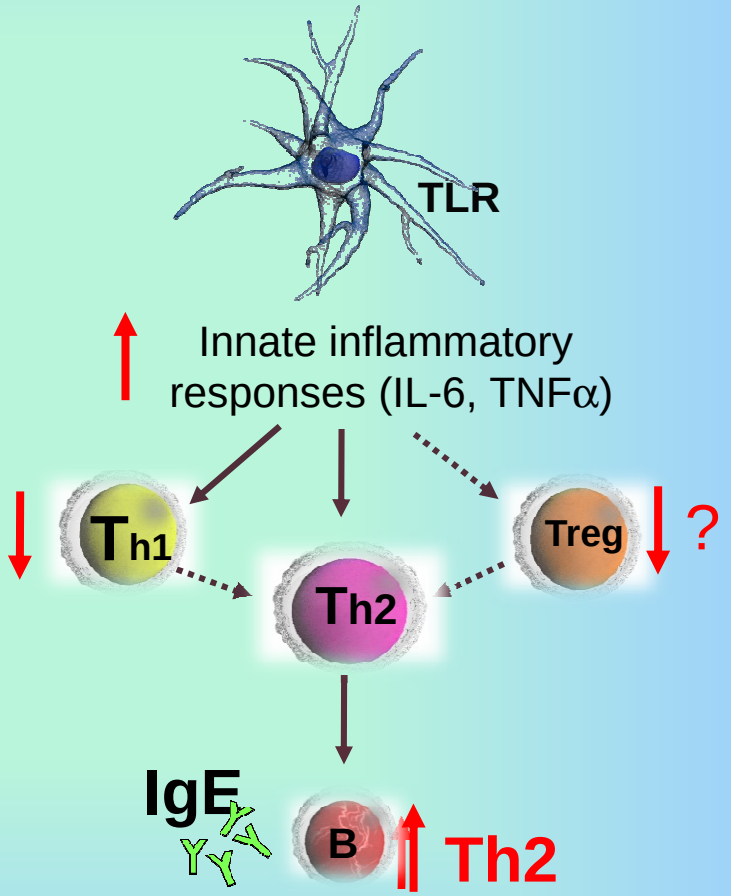
1. *Martino and Prescott (2010). Allergy 65(1): 7-15.*
2. *Martino and Prescott (2011). Chest 139(3): 640 – 647*
3. *Nakamura Y, et al. JACI 2008; 122:1208-14..*
4. *Weise C, et al. PAI 2011; 22:497-504.*
5. *Mileti E, et al. PLoS One 2009; 4:e7056.*
6. *Kawasaki J, et al. J Dermatol Sci 2011; 62:131-4.*

Neonatal differences in immune function
point to the importance of in utero events

Presymptomatic differences at birth in allergic individuals:

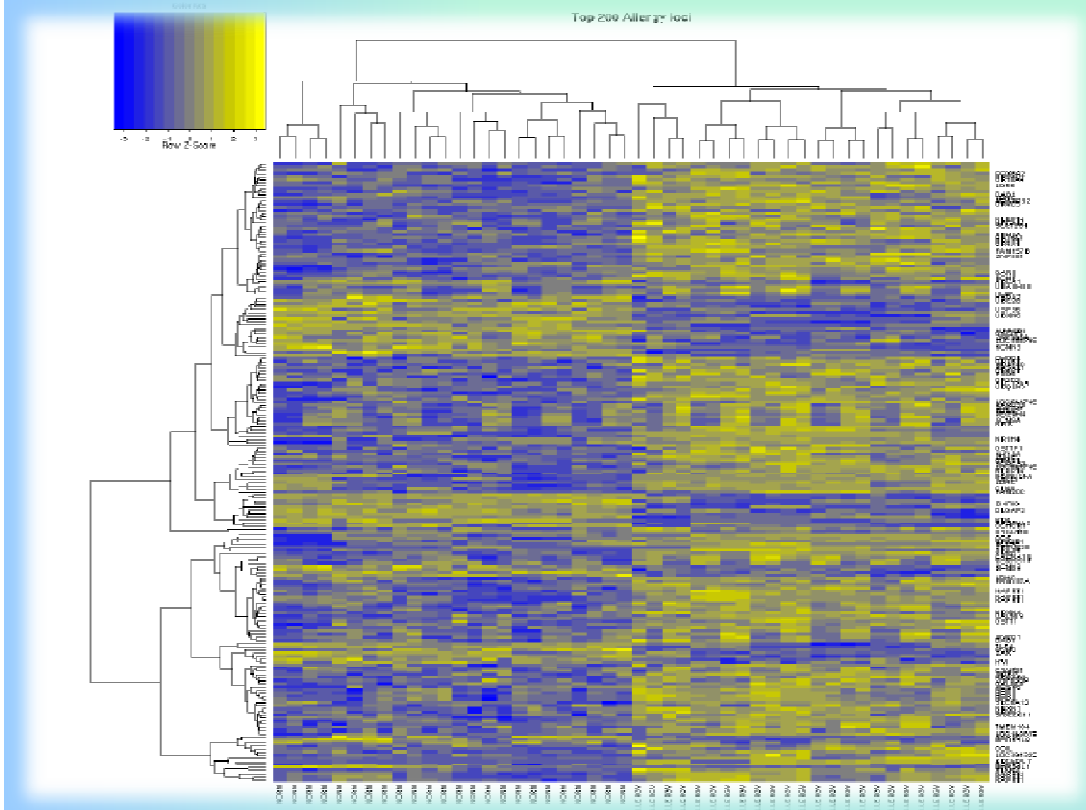
- **Increased inflammatory** responses
  Prescott JACI 2008;122:391
  Tulic JACI 2011;122:391
- **Immature Th1 function**
  Tang 1994, Warner 1994, Kondo 1998,
  Prescott 1998, and others
- **Immature T reg function** (?)
  Smith/Prescott 2008;121:1460
  Schaub 2008;121:1491
  Tulic JACI 2012;122:391
- **T cells: Epigenetic differences**
  Martino/Prescott (under review) 2012

Gene-environmental interactions in utero.



Epigenetic differences in food allergy

Differences in methylation patterns evident <u>at birth</u>



Global methylation patterns in CD4+ T cells

2090 probes differentially methylated
122 vary >15% (biologically meaningful)

Differences present at birth and consistent with differences at 1 year when symptomatic

Genes of interest include HLADR genes, Protein Kinases, IL5R (Th2)

Martino, Saffery, Prescott et al. in prep 2011

Further highlights antenatal events

Breast milk: early source of allergen exposure

- Allergens in breast milk (with TGFβ / tolerogenic factors)[1-3]
- Allergen-IgG complexes (foods & inhalants) [4]
  → antigen-specific Treg cells in animals
  → also detected in human milk

Individual differences in secretion

- DB-RCT lactating women[1]
  (55g/day egg vs placebo for 21 days)
  → Some (25%) do not secrete OVA

1. *Palmer DJ, et al. Clin Exp Allergy 2008; 38:1186-91*
2. *Vance GH, et al. Clin Exp Allergy 2005; 35:1318-26*
3. *Verhasselt, V. et al. Nat Med 2008 14 (2): 170-175.*
4. *Mosconi E, et al. Mucosal Immunol 2010; 3:461-74.*

Variations in maternal milk (allergens / cytokines / other)
may contribute to the efficacy of oral tolerance

Links between breast milk and the thymus

- **IL-7 in breast milk** → Important role in generation of thymic Treg[1]
- Greater thymus size in breastfeed infants;
  correlations with breast milk IL-7 levels.[2]

breast milk IL-7

IL-7 in maternal milk
→ crosses the neonatal intestine
→ increases T cell production
in the thymus [2]

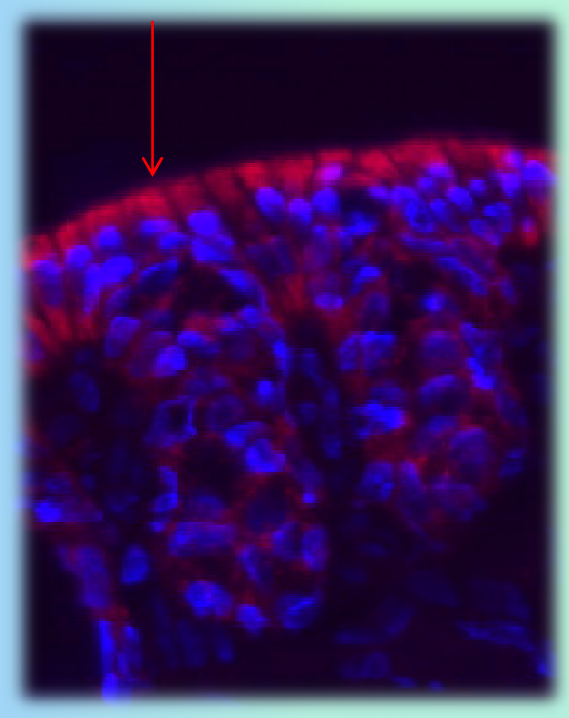
TSLP also in breast milk [3]
→ Emerging role in oral tolerance[4]
(Not simply a 'Th2' cytokine)

1.Aspinall R, et al. PLoS One 2011; 6:e20812.
2.Prentice AM, et al. Acta Paediatr 2000; 89:8–12.
3. Macfarlane T, et al. PAI 2010; 21:e454-6
4. Spadoni, II et al. Mucosal Immunol. 2012 epub

Suggests a hitherto unrecognized link between
gut and systemic tolerance mechanisms: role of milk variations?

A ‘new’ role for TSLP in the gut: Emerging importance in oral tolerance

TSLP staining in intestine[1]



Produced by DC and epithelial cells (IEC) in the intestine[1]:

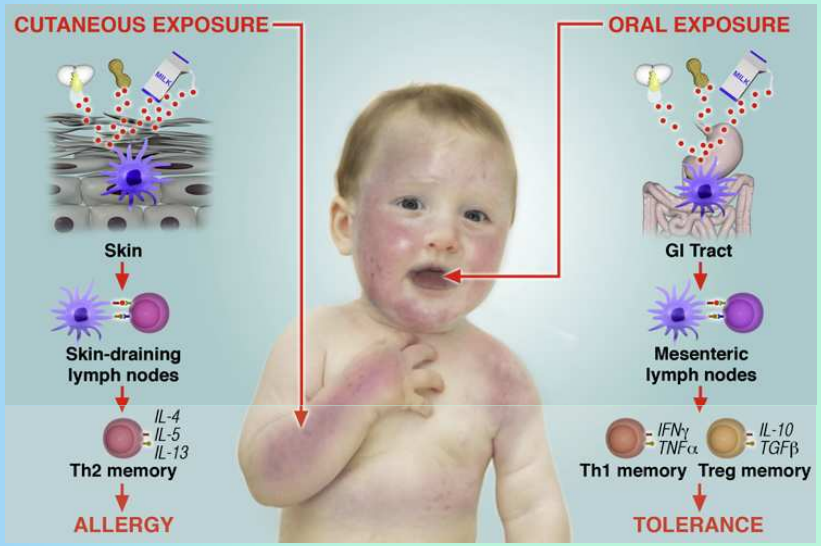
- Promotes tolerogenic DCs[2]
- Acts directly on T cells (TSLP-R)
  → promote Treg differentiation[3]
  → inhibit Th17 cell development[3]

Role in suppressing inflammation

1. *Taylor et al. J Ex Med. 2009 206(3): 655-67*
2. *Iliev, et al.. Gut 2009 58 , 1481 – 1489.*
3. *Spadoni et al. Mucosal Immunology 2012 ePub*

Needs to be explored in early origins of allergic disease

Cutaneous exposure: another route of early sensitisation



Allergens: surfaces, dust.
Transcutaneous sensitisation
Less tolerogenic than the oral route
(hypothesis unconfirmed)

Fox, A. et al. J Allergy Clin Immunol 123(2): 417-23.
Lack, G. (2008) J Allergy Clin Immunol 121(6): 1331-6.

Most relevant in children with eczema
Impaired cutaneous barrier function
Already have ‘allergy phenotype’: earlier events already set the scene

More likely to be a secondary, amplifying event?
Role in children without eczema?

Fattori socioeconomici & allergie

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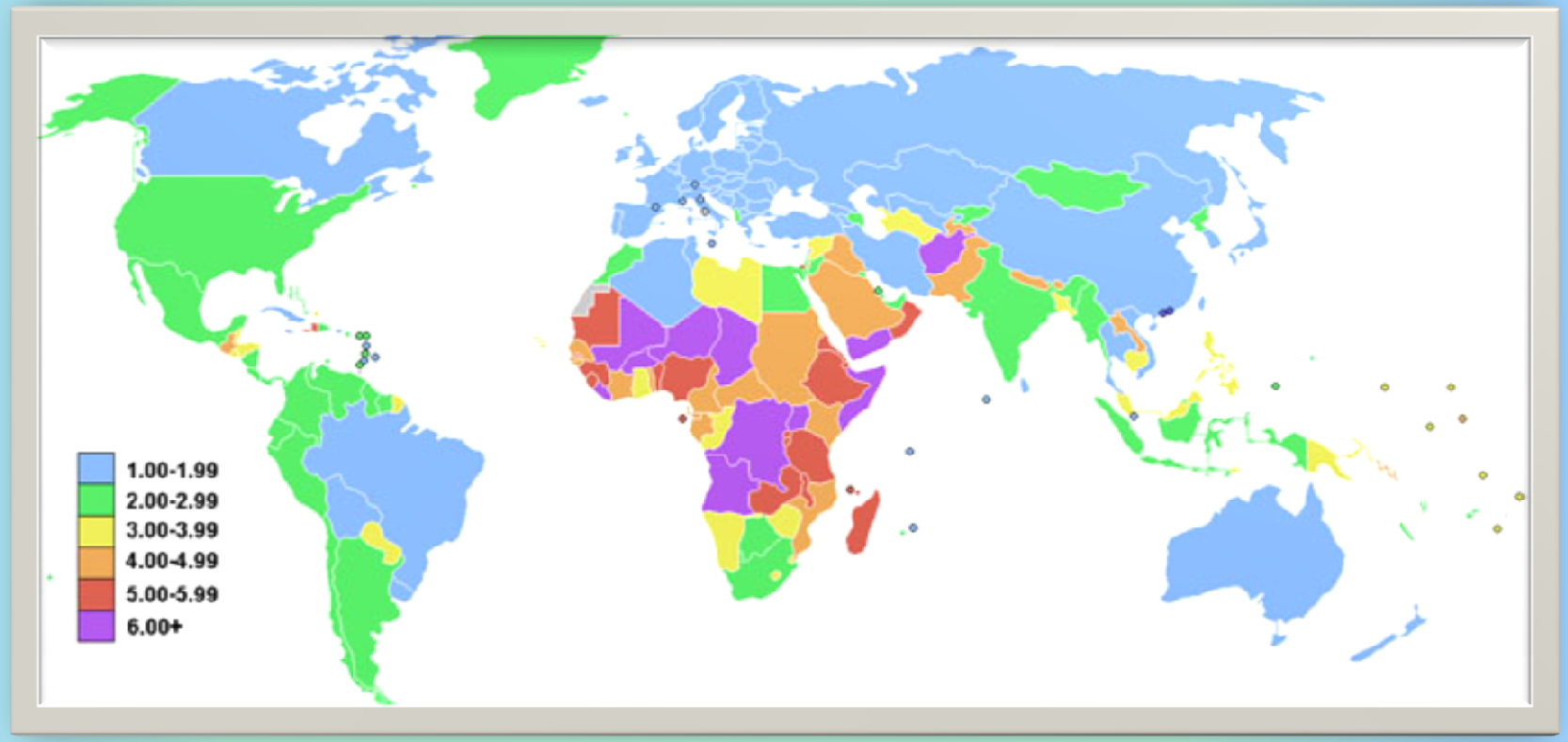
Indicators of human well-being

1	Hunger	kCal/capita/day
		% Childhood malnutrition
2	Fertility rate	Births per woman
3	Infant mortality	% of live births
4	Life expectancy	Years
5	Health-adjusted LE	Healty years
6	Economic development	GDP/capita
7	Education	% literacy
8	HDI	4+6+7

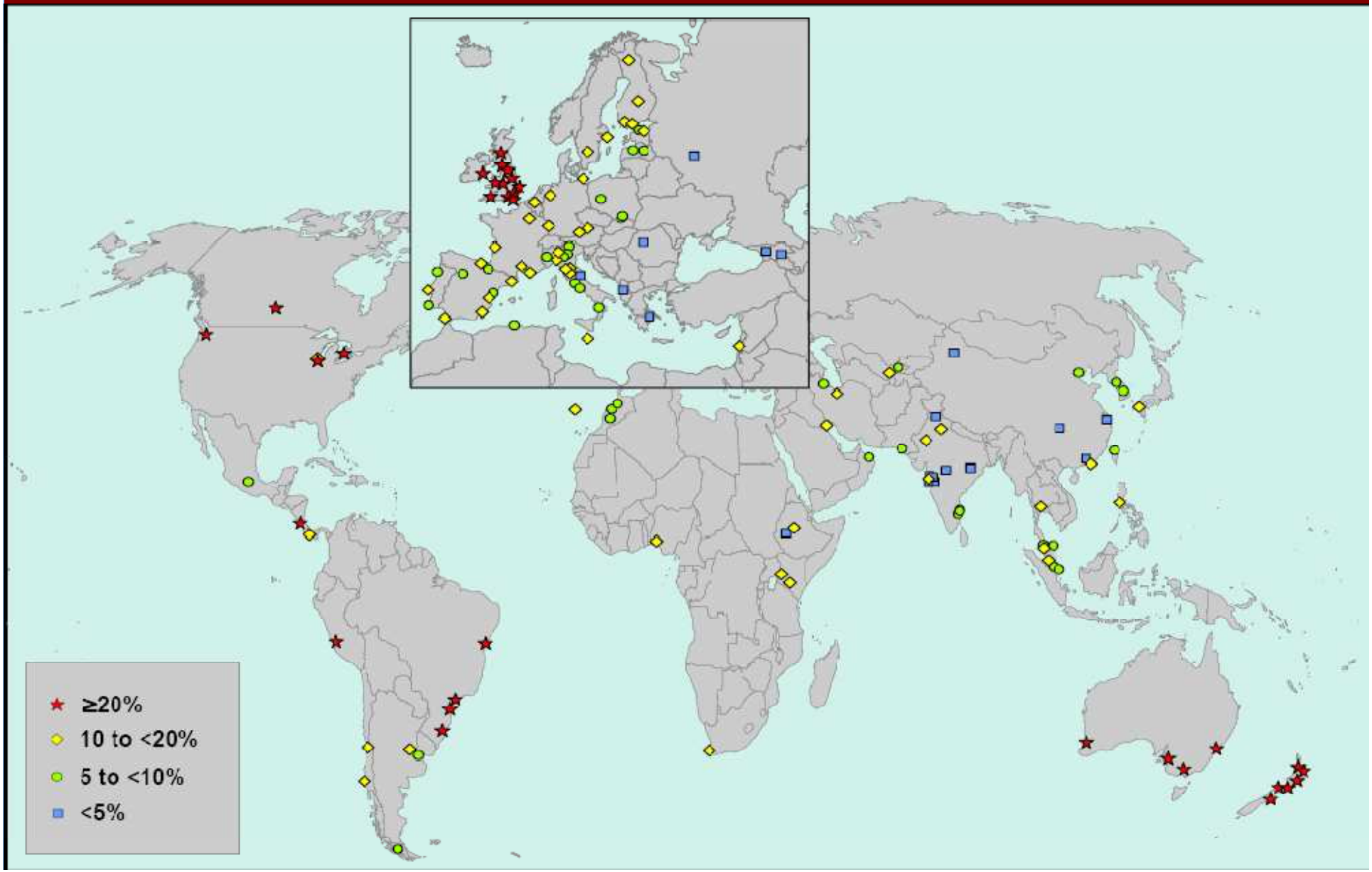
Golkany IM. The improving state of the world. Washington D.C. Cato Institute, 2006

Fertility rate

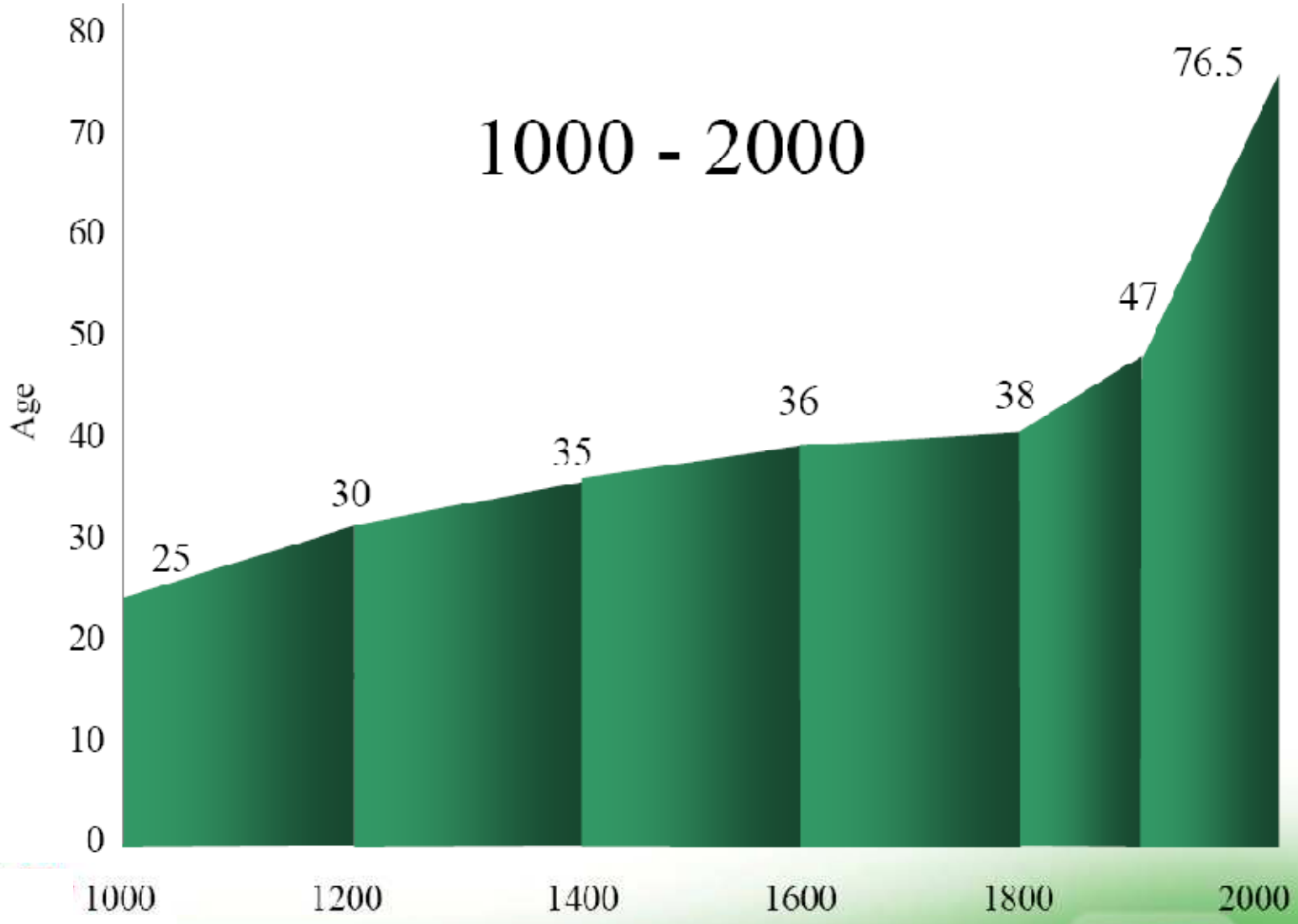


http://www.census.gov/ipc/prod/wp96/wp96033.pdf

12 month period prevalence of asthma symptoms in 13-14 year old children

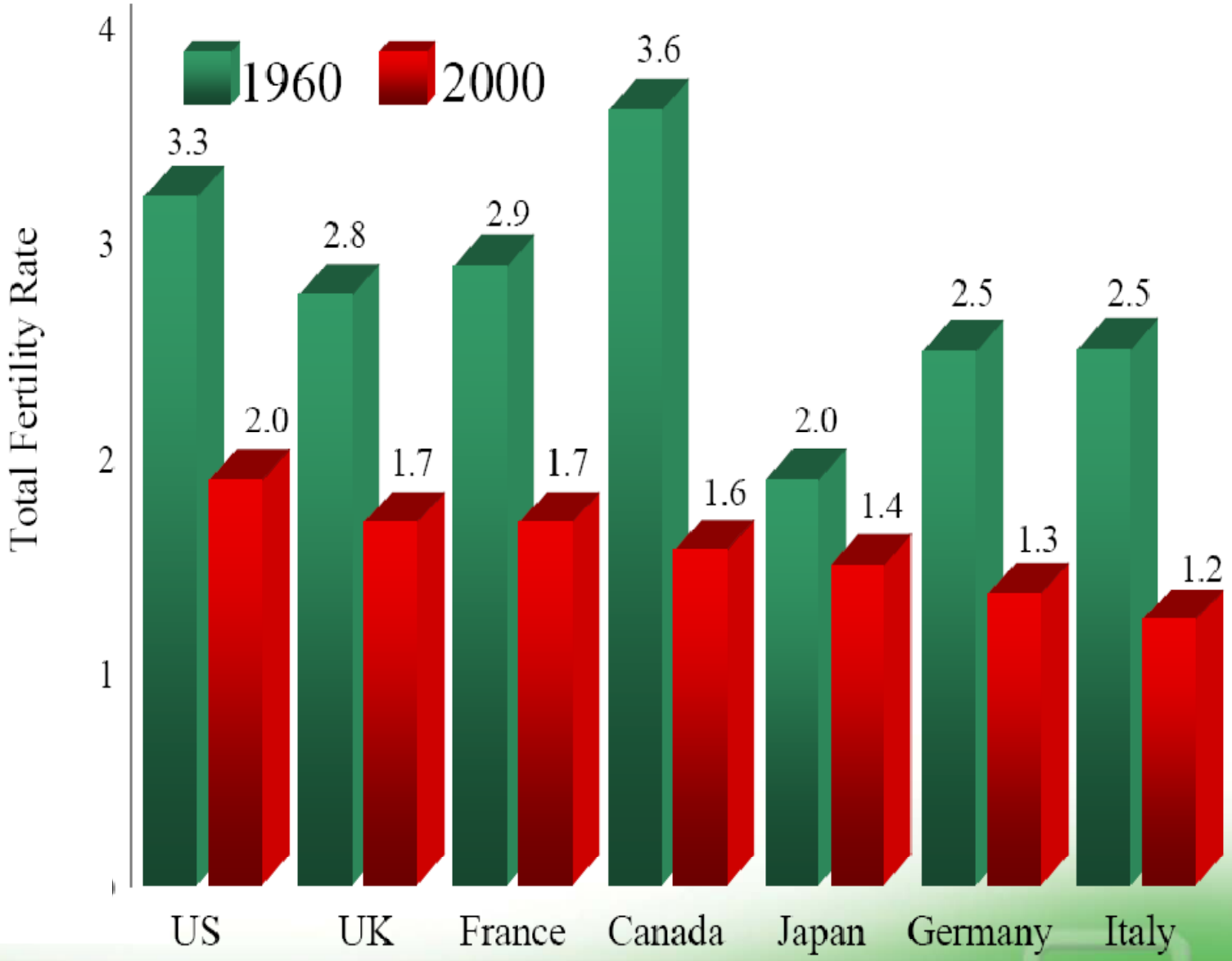


Life Expectancy at Birth



http://www.census.gov/ipc/prod/wp96/wp96033.pdf

Declining Fertility Rates



http://www.census.gov/ipc/prod/wp96/wp96033.pdf

Paternal education and atopy in Italy

None: 15,6%

Matricardi PM. Sibship size, birth order, and atopy in 11,371 Italian young men. J Allergy Clin Immunol 1998;101:439–44

Gross national product and ISAAC

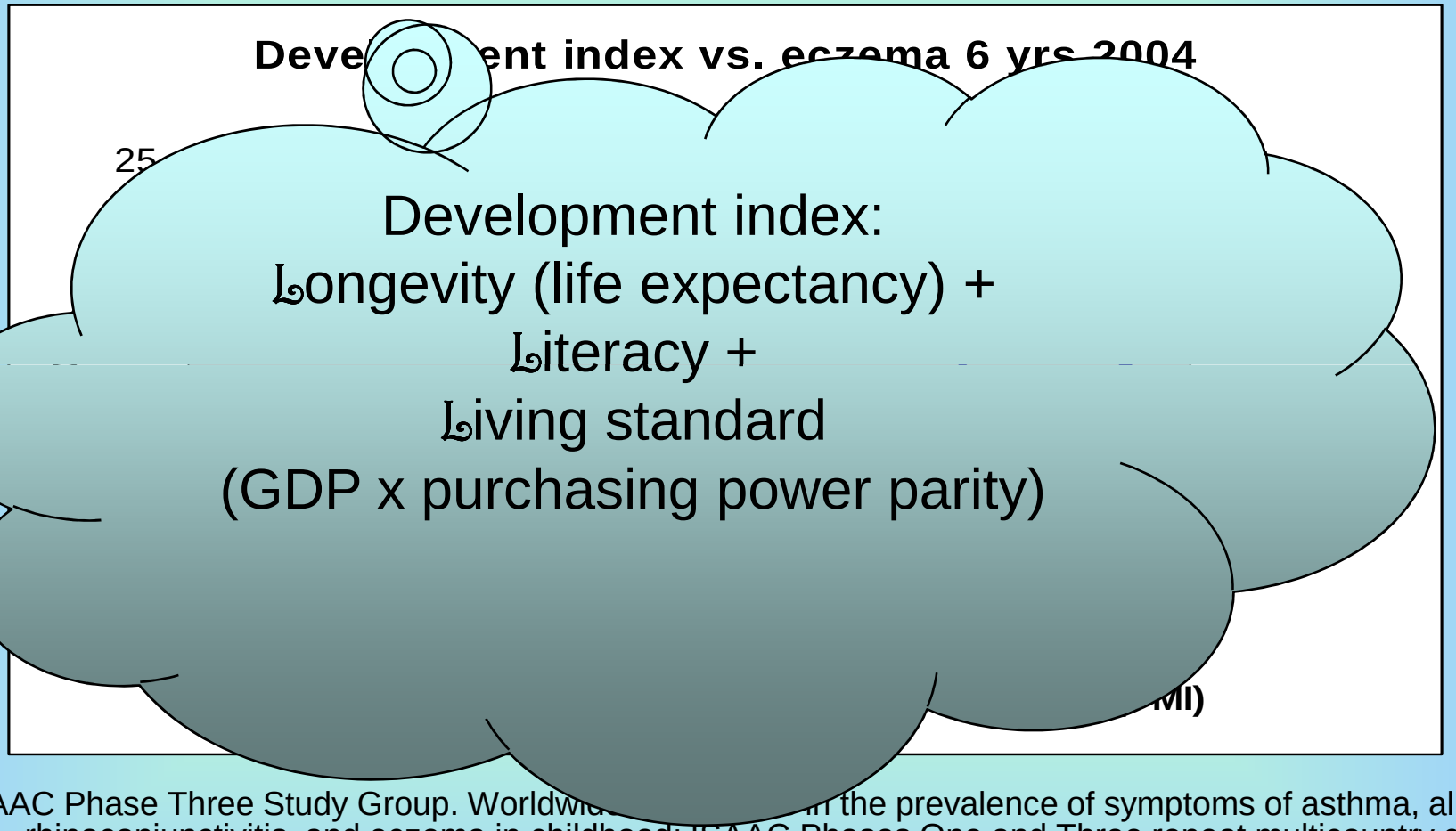
An evaluation of the relationship of symptoms of asthma, rhinitis and eczema with GNP per capita

ISAAC data related to 1993 GNP per capita for each country (World Bank)

The countries in the lowest quartile of GNP per capita have the lowest median positive responses to all the questions on symptoms of asthma, rhinitis and eczema.

Stewart AW. The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC). Int J Epidemiol. 2001;30:173-9

Human Development Index, 1998, *vs.* reported rate of eczema at 6 years, 2004. R=0.67, P = 0.18



ISAAC Phase Three Study Group. Worldwi… in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368:733-43

IMF, World Economic Outlook database. Accessed Aug 28°, 2007, at http://www.imf.org/external/pubs/ft/weo/2007/01/data/WEOApr2007all.xls

Fattori socioeconomici & allergie

a. Ambiente prenatale e sviluppo delle allergie
b. Epidemiologia delle allergie negli ultimi 20 anni
c. Indicatori di sviluppo ed allergie: analisi ecologiche
d. Il sibship size effect
e. Conclusioni

OR for inhalant allergy by maternal age

Maternal age at delivery	Any inhalant allergy	3+ inhalant allergies
< 20	1.00	1.00
20-	1.17	1.21
25-	1.22	1.34
30-	1.33	1.44
35+	1.54	1.60

Strachan DP, Harkins LS, Golding J, et al. Sibship size and self-reported inhalant allergy among adult women. Clin Exp Allergy 1997;27:151–5

Caratteristiche delle mamme milanesi che potrebbero predisporre i loro bambini all'allergia

- Età al parto 33.6 anni: la puerpera italiana è la più attempata dell'intera comunità europea (la più giovane è la lituana che partorisce mediamente a 28.2 anni).

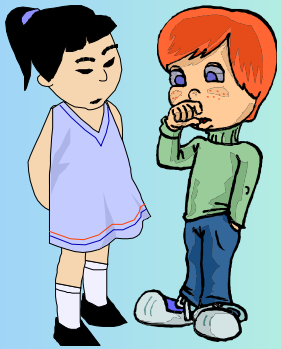
	Nordic	*Maritime*		*Central European*			*Mediterranean*		
	Iceland	United Kingdom	The Netherlands	Germany	Poland	Lithuania	Spain	Italy	Greece
Caesarian section (%)	12.8	30.8	11.0	31.1	37.5	15.6	2.5	30.8	44.2
Mother									
Age (year ± sd)	30.1 ± 4.8	31.8 ± 5.2	29.9 ± 4.8	31.4 ± 5.4	28.8 ± 4.4	28.2 ± 5.2	31.4 ± 5.1	33.6 ± 4.7	30.9 ± 4.9
Allergy (%)	44.1	51.0	36.4	35.2	9.7	5.9	24.7	23.3	14.0
Antibiotic use (%) in pregnancy	23.4	20.0	19.0	18.6	27.6	16.6	7.5	26.5	31.0

McBride D. *The EuroPrevall birth cohort study on food allergy: baseline characteristics of 12,000 newborns and their families from nine European countries.* Pediatr Allergy Immunol. 2011 Dec 23 - Epub ahead of print

EuroPrevall

Sibship size, birth order, and atopy in Italy

24,9%



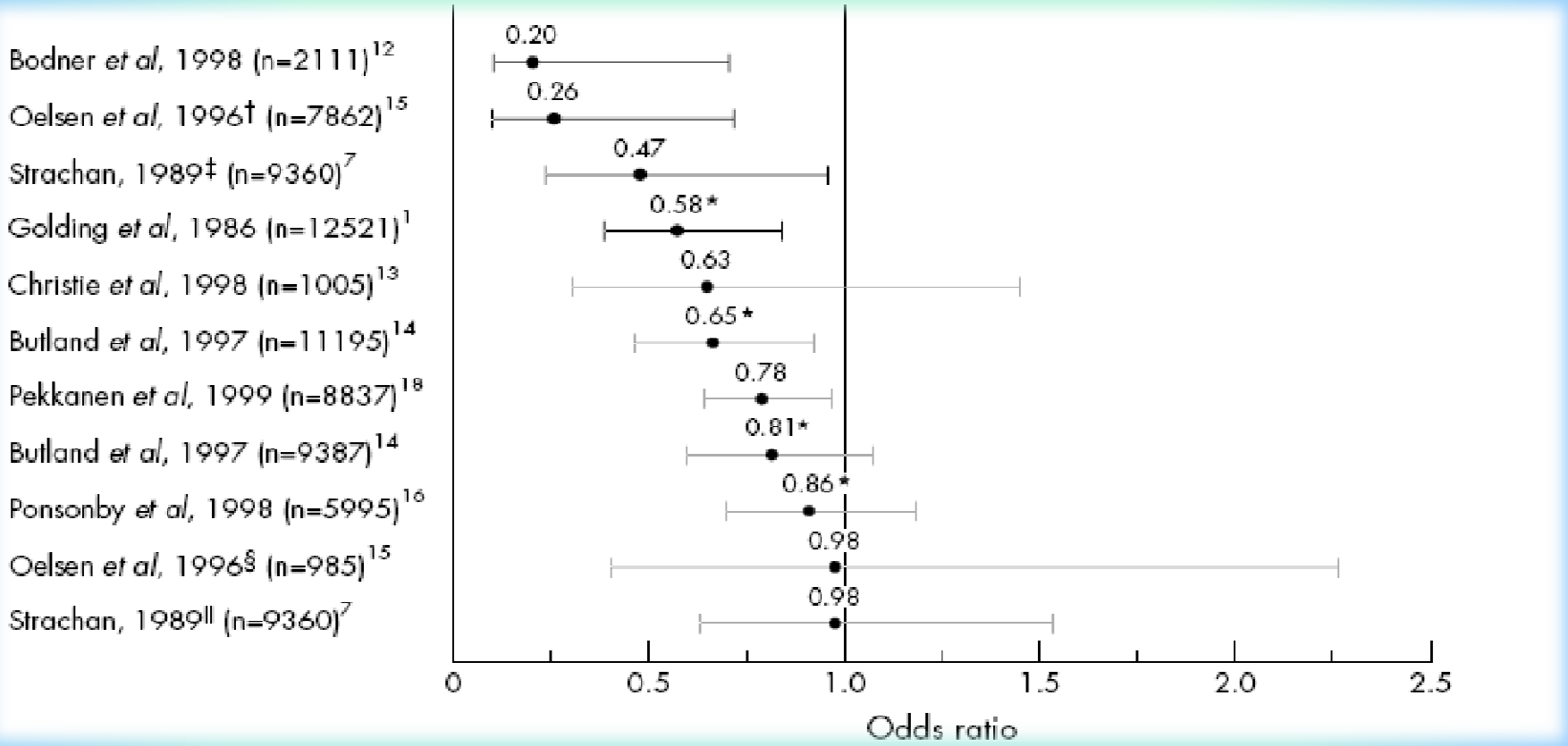
23,7%

9,3%

18,9%

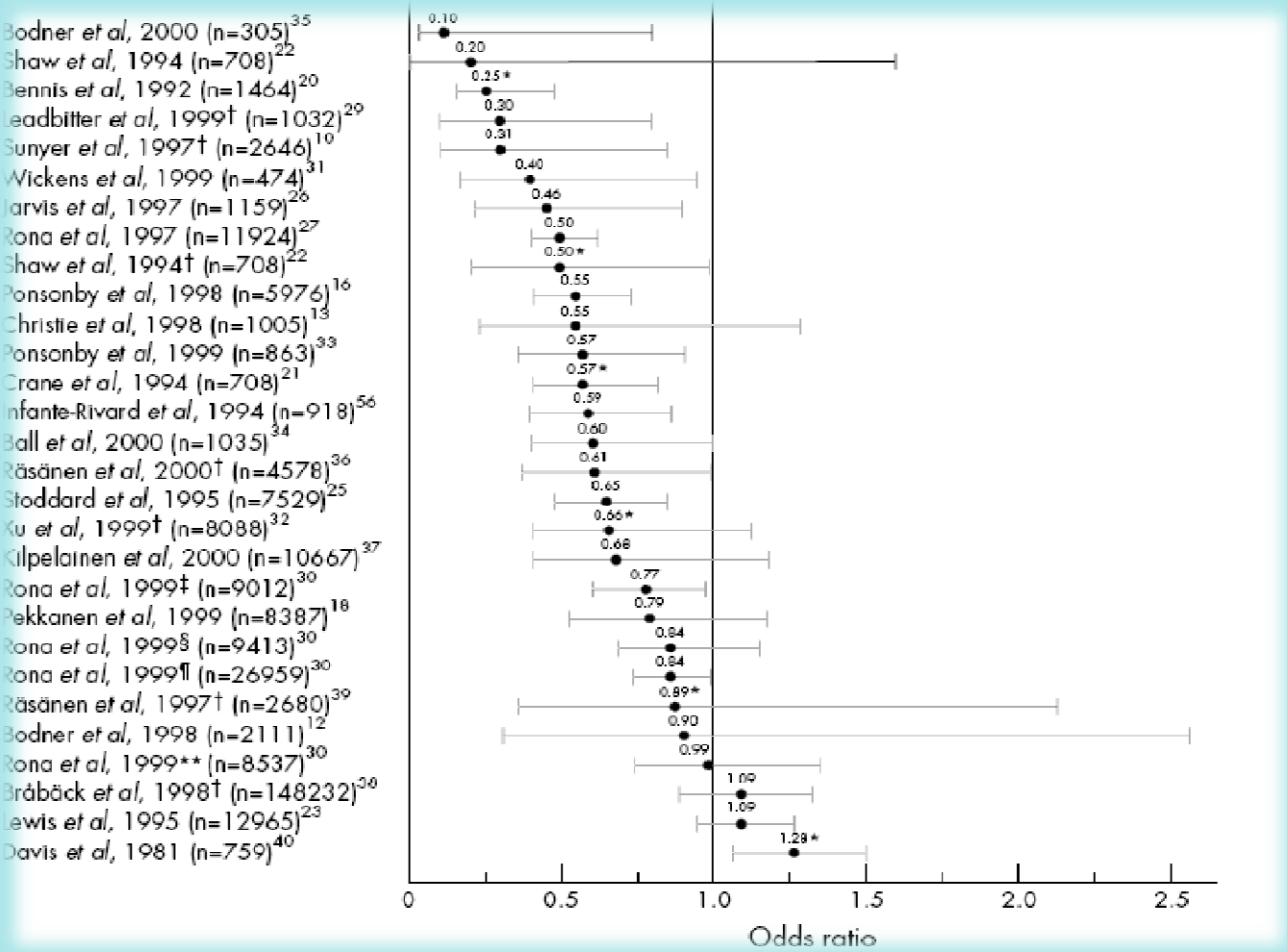
Matricardi PM. Sibship size, birth order, and atopy in 11,371 Italian young men. J Allergy Clin Immunol 1998;101:439–44

Eczema and number of siblings: 3+ vs. none



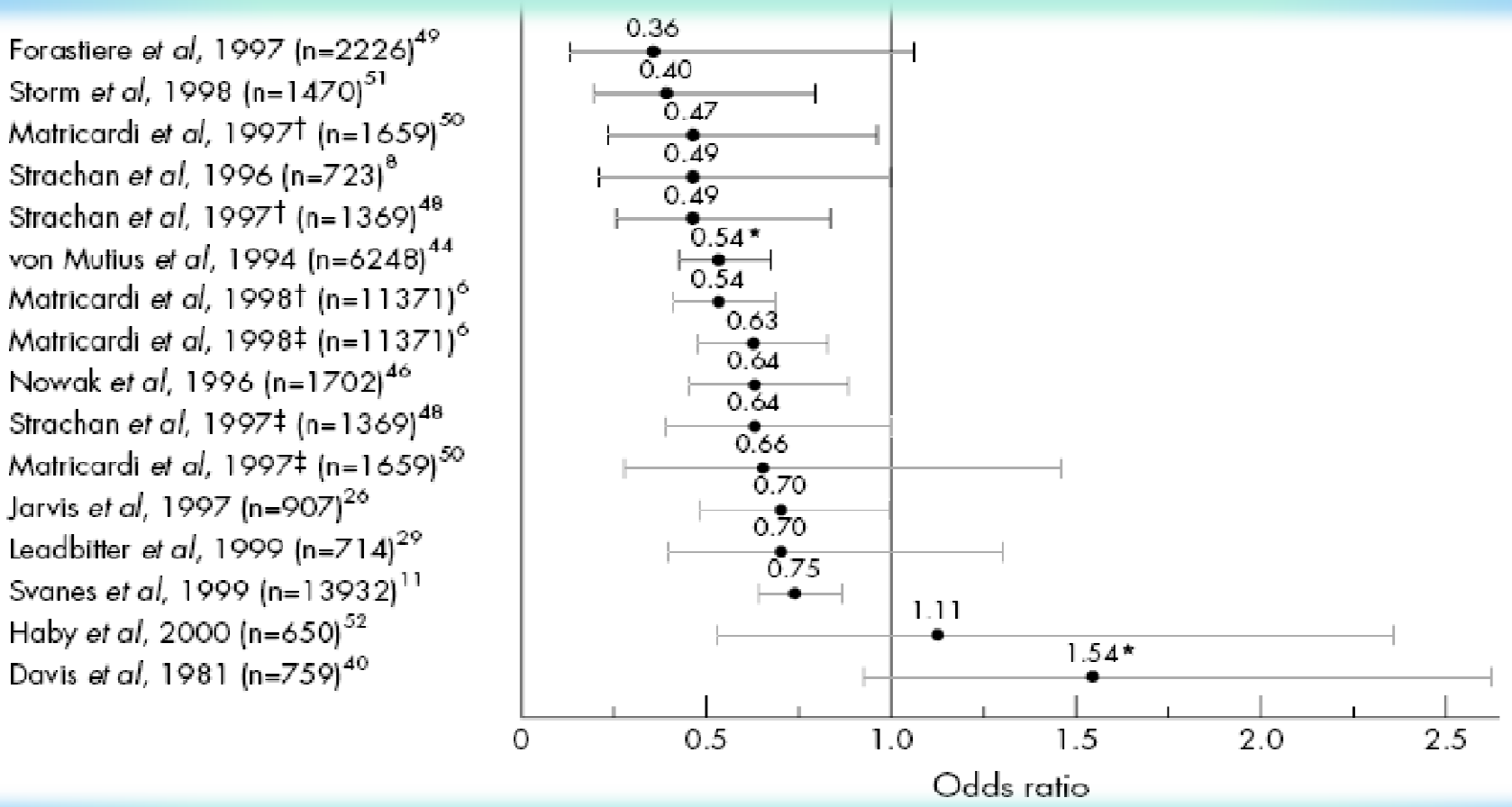
Karmaus W. Does an higher number of siblings protect against the development of allergy and asthma? J. Epidemiol. Community Health 2002;56;209-217

Asthma and number of siblings: 3+ vs. none



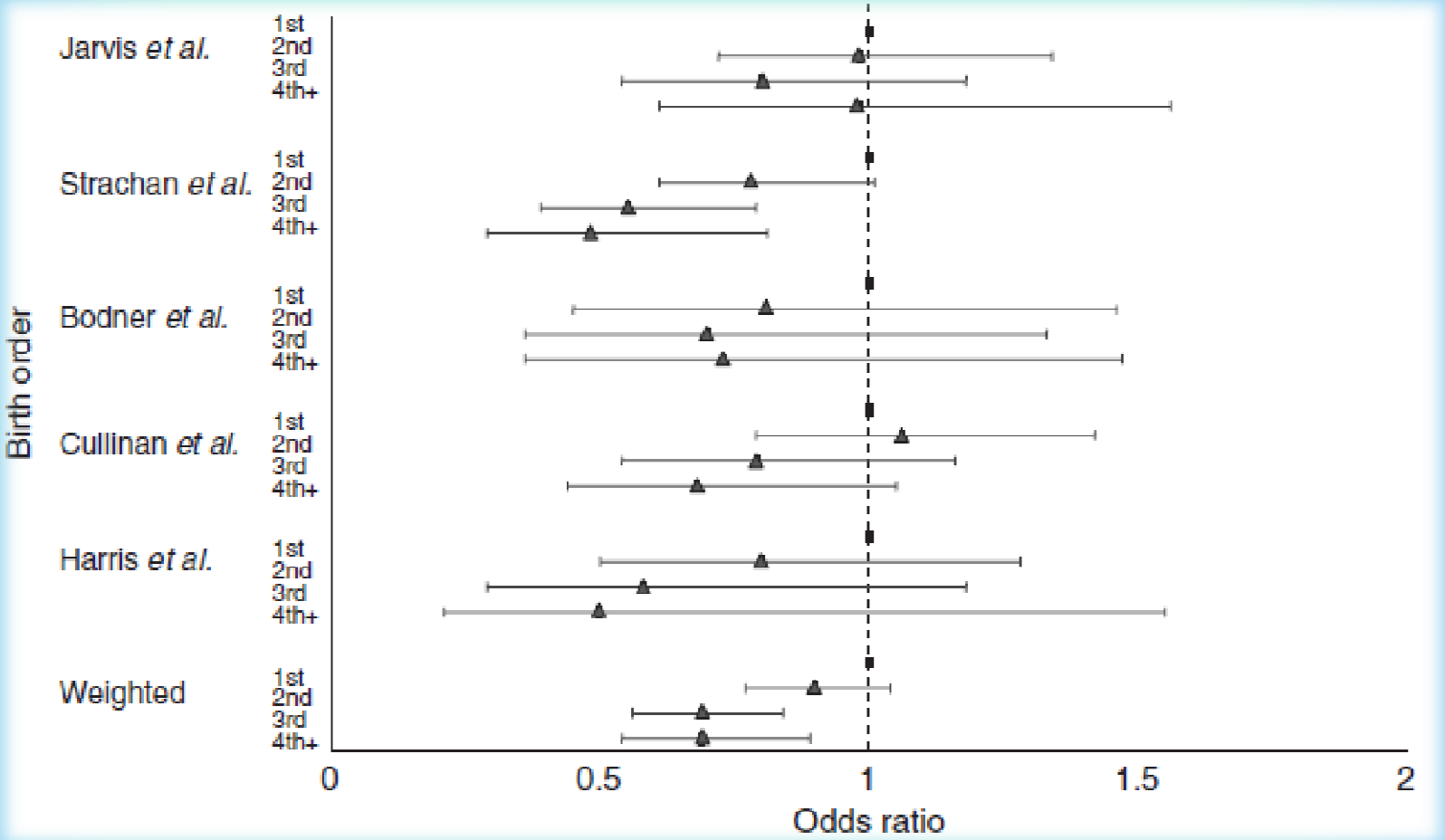
Karmaus W. Does an higher number of siblings protect against the development of allergy and asthma? J. Epidemiol. Community Health 2002;56;209-217

SPT+ and number of siblings: 3+ vs. none



Karmaus W. Does an higher number of siblings protect against the development of allergy and asthma? J. Epidemiol. Community Health 2002;56;209-217

Atopy by order of birth



Upchurch S. . Temporal changes in UK birth order and the prevalence of atopy. Allergy 2010; 65: 1039–1041.

The sibship size effect: importance

If we were to identify the factors that cause the phenomenon of the sibling effect and if these factors were applied to children with a low number of siblings, the cases in this group might be diminished by:

- 28% for asthma
- 34% for eczema
- 56% for hay fever
- 38% for SPT reactivity

Karmaus W. Does an higher number of siblings protect against the development of allergy and asthma? J. Epidemiol. Community Health 2002;56;209-217

Interpregnancy interval might affect the risk of childhood atopy

Children born after inter-pregnancy intervals of less than 2 years are less likely to have a positive SPT.

Since a successful pregnancy is a fine balance between a mother's tolerance for her fetus' foreign genetic material and the fetus' ability to survive the maternal immunologic defenses, it is suggested that prior pregnancies and their spacing might influence the intrauterine environment.

Closely spaced pregnancies may provide a higher maternal tolerance.

Wegienka R. Interpregnancy interval might affect the risk of childhood atopy. J Allergy Clin Immunol 2004,113:169-171.

IL13 polymorphisms, birth order and allergic sensitization at ages 4, 10 and 18 years.

1456 participants.

Atopy 19.7% at age 4, 26.7% at 10 and 41.1% at age 18.

Firstborns had ⇧ IgE at age 10 (p = 0.007)
⇧ inhalant screen (p = 0.034)

Interaction between Ileu 13 rs20541 on SPT

This effect was restricted only to first-born children (p = 0.007)

Gluckman PD. Effect of in utero and early-life conditions on adult health and disease. N Engl J Med 2008, 359:61-73.

Ogbuanu IU. Birth order modifies the effect of IL13 gene polymorphisms on serum IgE at age 10 and skin prick test at ages 4, 10 and 18: a prospective birth cohort study. Allergy, Asthma & Clinical Immunology 2010, 6:1-13

IL13 polymorphisms, birth order and allergic sensitization at ages 4, 10 and 18 years.

A statistically significant interaction between IL13 polymorphisms and birth order for

- elevated serum IgE at age 10
- serum inhalant specific IgE at age 10
- SPT at ages 4, 10 and 18 years

The predictive value of IL13 genotypes on the atopic markers was restricted only to first born children.

Genetic polymorphisms in the IL13 gene may undergo epigenetic changes in utero due to conditions specific to a first pregnancy compared to subsequent pregnancies.

Ogbuanu IU. Birth order modifies the effect of IL13 gene polymorphisms on serum IgE at age 10 and skin prick test at ages 4, 10 and 18: a prospective birth cohort study. Allergy, Asthma & Clinical Immunology 2010, 6:1-13

IL13 polymorphisms, birth order and allergic sensitization: epigenetic interpretation

DNA provides the blueprint for the manufacture of all the proteins necessary to create a living organism.

Epigenetic modifications provide additional instructions on how, where, and when the genetic information will be used (gene expression).

These epigenetic changes involve DNA modification such as methylation and acetylation, histone protein modifications, and regulation of gene expression by microRNAs

Ogbuanu IU. Birth order modifies the effect of IL13 gene polymorphisms on serum IgE at age 10 and skin prick test at ages 4, 10 and 18: a prospective birth cohort study. Allergy, Asthma & Clinical Immunology 2010, 6:1-13

Sibship size effect: interpretations 1 – hygiene hypothesis

⇓ cross-infection in small families could increase allergic conditions during childhood

Th2 /Th1

If so, older children = younger children

.

Strachan DP. Allergy and family size: a riddle worth solving. Clin Exp Allergy 1997: 27: 235–6.

Martinez FD. Role of microbial burden in aetiology of allergy and asthma. Lancet 1999: 354 SII12–5.

Strachan DP. Family structure, neonatal infection, and hay fever in adolescence. Arch Dis Child 1996: 74: 422–6.

Illi S. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort study. BMJ 2001: 322: 390–5.

Sibship and hygiene hypothesis

Infections? TB?... Not confirmed

RSV can trigger allergic diseases (*bronchial susceptibility* hypothesis)

Vaccination effect not confirmed for MMR and DTP

Early day care attendance: when confirmed, the effect is not related to infections

Karmaus W. Does an higher number of siblings protect against the development of allergy and asthma? J. Epidemiol. Community Health 2002;56;209-217

Sibship size effect: interpretations 2 – IUP hypothesis

Maternal immune tolerance may increase with increasing order of birth of live offspring

The maternal immune status may be communicated to the child

If so, younger children more protected than older

.

Karmaus W. Does the sibling effect have its origin in utero? Investigating birth order, cord blood immunoglobulin E concentration, and allergic sensitization at age 4 years. Am J Epidemiol 2001: 154: 909–15

Harris JM. New pregnancies and loss of allergy. Clin Exp Allergy 2004: 34: 369–72.

Karmaus W. Does maternal immunoglobulin E decrease with increasing order of live offspring? Investigation into maternal immune tolerance. Clin Exp Allergy 2004: 34: 853–9

la Fattori socioeconomici & allergie

a. Le allergie sono in aumento soprattutto nei paesi sviluppati
b. La natalità è in diminuzione dovunque
c. Frequenza di allergie tra i bambini ed indicatori di sviluppo: analisi ecologiche
d. Il sibship size effect
e. Conclusioni

Conclusion:

Early life: critical for all aspects of development

pregnancy

"sets the scene"

postnatal

"culminating events"

Opportunities for prevention (many NCDs)

Need for more inter-disciplinary collaborative research

Conclusioni

1. L’esplosione del problema “allergie” è legata allo stile di vita
2. Meno figli non significa bambini più sani
3. I figli minori sono più protetti dei figli maggiori
4. Questo effetto probabilmente passa attraverso una maturazione del sistema immune materno
5. Per questa via potrebbero essere identificati:

- Markers
- Bersagli terapeutici
- Strategie di prevenzione.

Conclusioni

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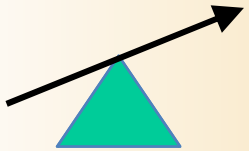
Logical preventive approaches

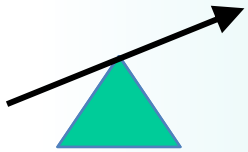
Restoring environmental balance

↓ **Traditional diets**



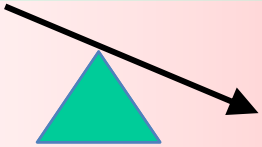
↑ **Anti-inflammatory nutrients**
n-3 PUFA, fibre, antioxidants,

↓ **Microbial exposure**



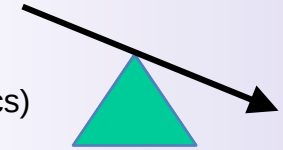
↑ **Strategies to restore balance**
probiotics, prebiotics, other?

↑ **Pollutants**
(smoking, particulates, POPs)



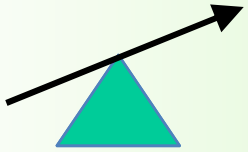
↓ **Reduce avoidable exposure**
(individual and societal)

↑ **Pharmaceutics**
(panadol, antacids antibiotics)



↓ **Reduce unnecessary use**
(individual and HCP)

↑ **Sedentary lifestyles**



↑ **Behavioural strategies**
exercise, reduce stress,
sun in moderation, vitamin D?