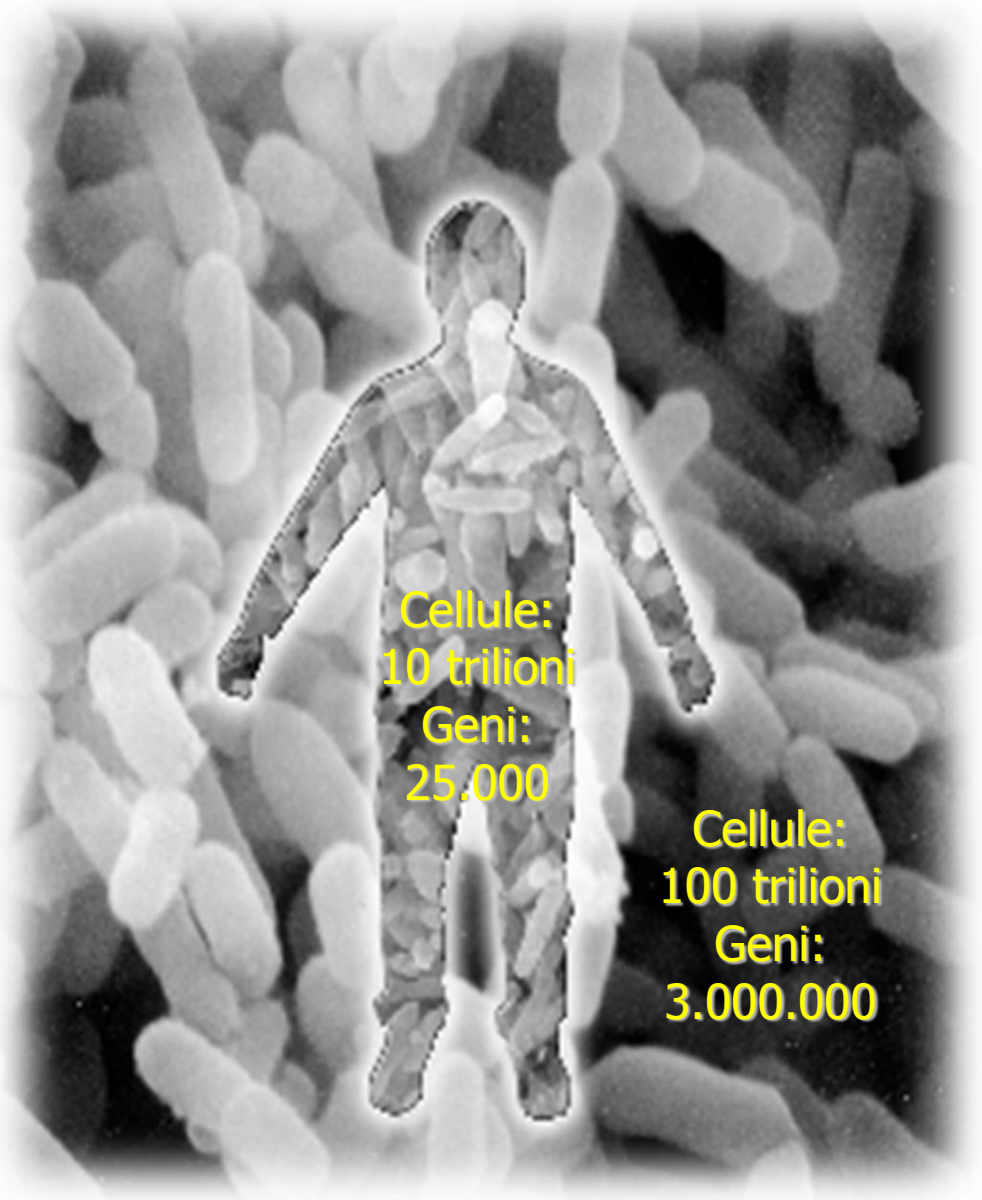
34 Congresso Nazionale di
ANTIBIOTICOTERAPIA
in età pediatrica

Biomodulatori e disbiosi nelle prime epoche di vita

Vito Leonardo Miniello

Università di Bari "Aldo Moro"

Superorganismo



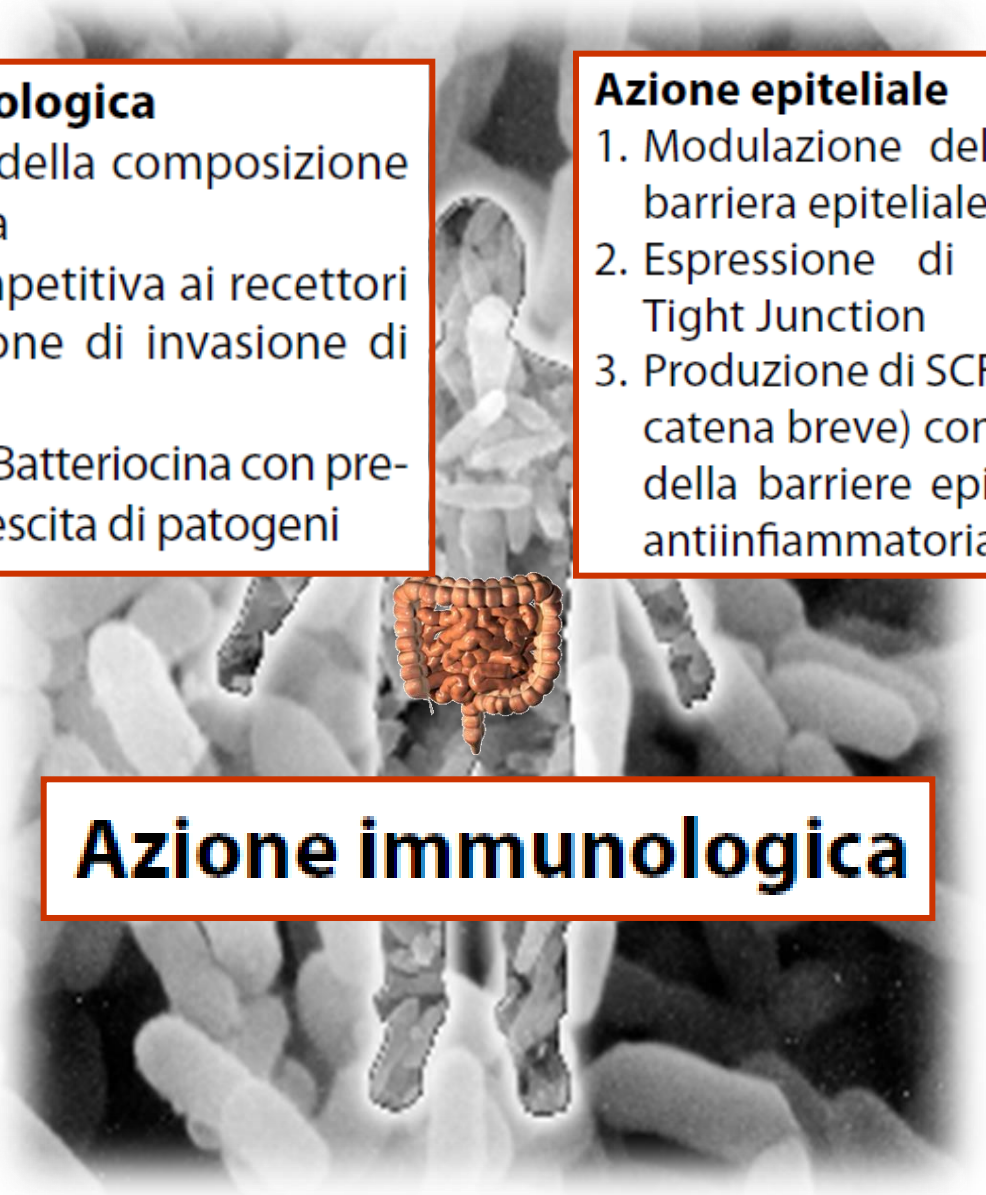
Microbiota Intestinale

Azione microbiologica

1. Modulazione della composizione del Microbiota
2. Adesione competitiva ai recettori con prevenzione di invasione di patogeni
3. Produzione di Batteriocina con prevenzione di crescita di patogeni

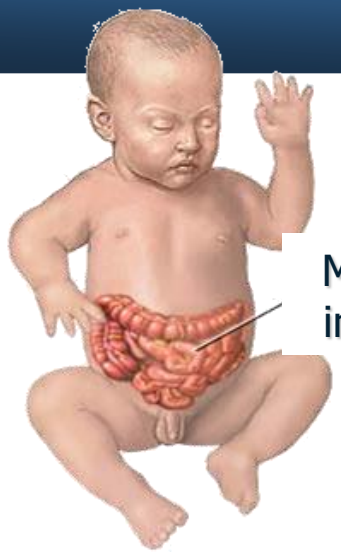
Azione epiteliale

1. Modulazione delle cellule della barriera epiteliale
2. Espressione di proteine delle Tight Junction
3. Produzione di SCFA (Acidi Grassi a catena breve) con miglioramento della barriere epiteliale e azione antiinfiammatoria



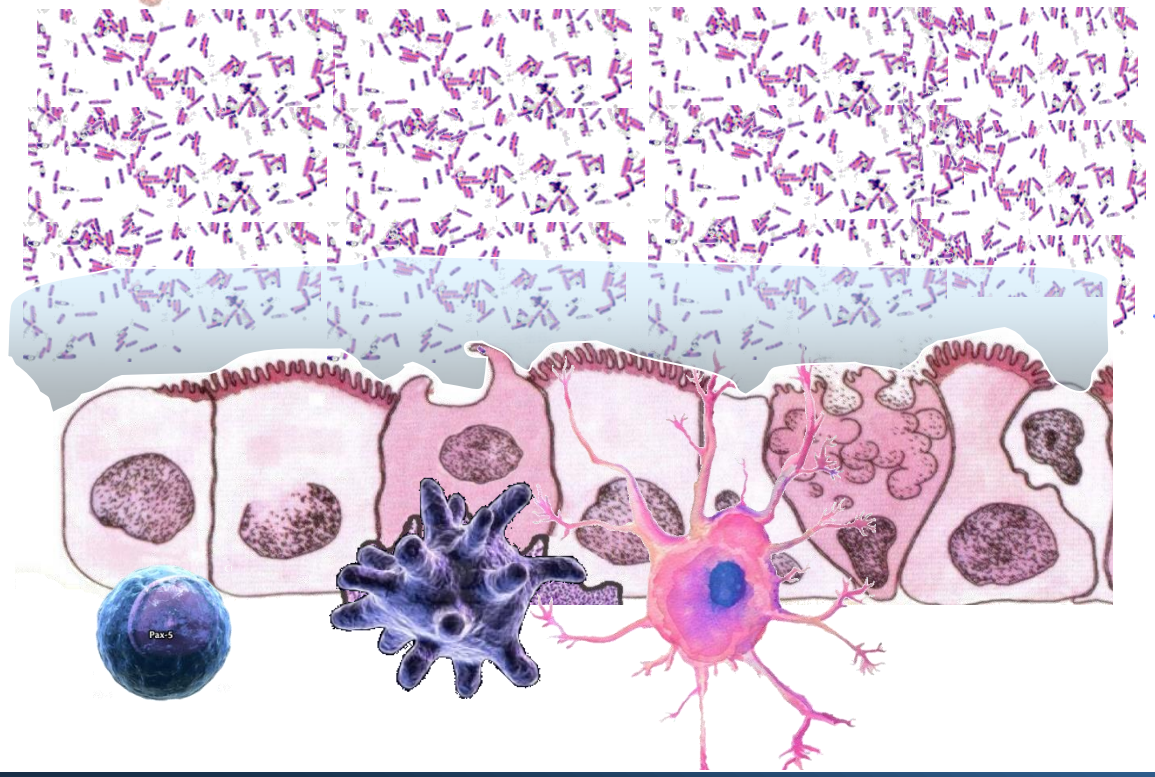
Azione immunologica

Microbiota Intestinale

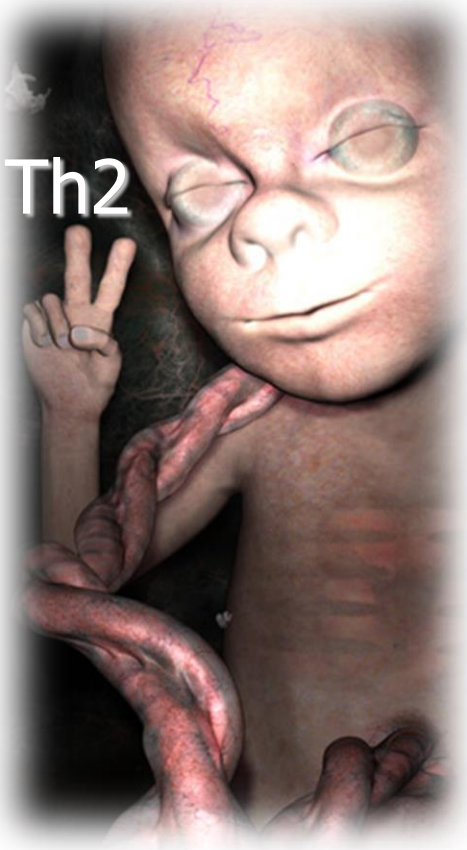


Microbiota intestinale

Il microbiota intestinale è un "organo batterico" **immuno-modulante**



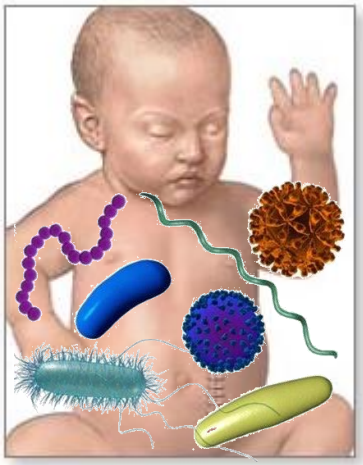
The HYGIENE Hypothesis



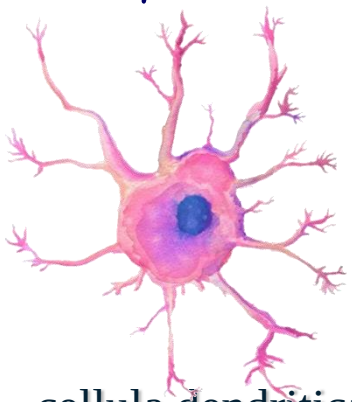
Th2

Th1

INF-γ IL-12



infezioni

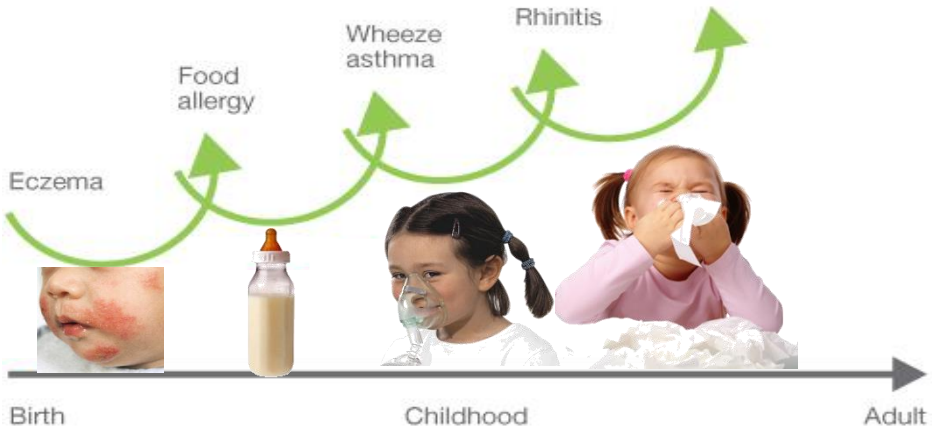


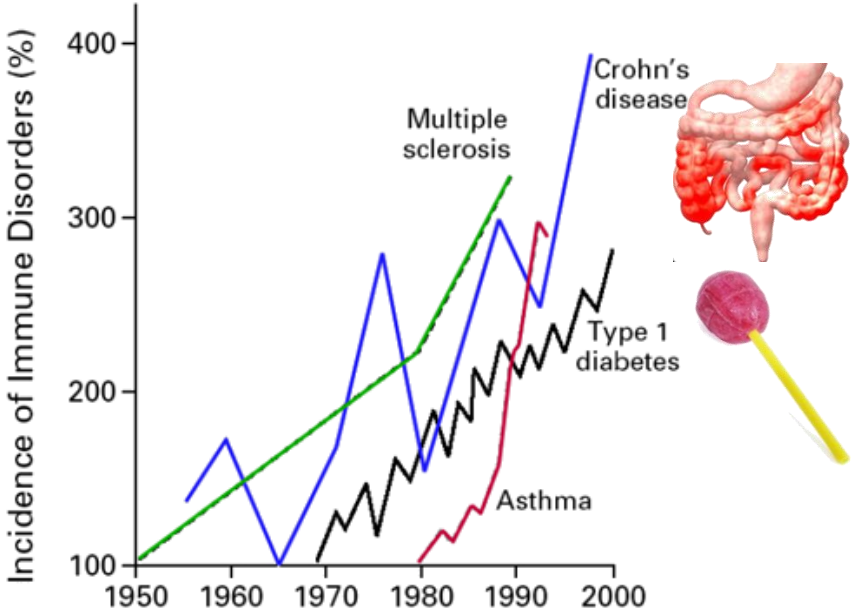
cellula dendritica
(MHCII^{+} CD11C^{+})

Strachan DP, 1989

WA Walker, 2009


Th1
Th2
Th2
Th1

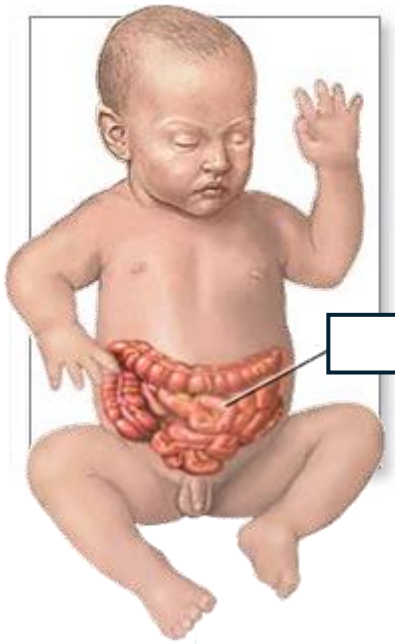

Eczema
Food allergy
Wheeze asthma
Rhinitis
Birth
Childhood
Adult


Incidence of Immune Disorders (%)
400
300
200
100
1950
1960
1970
1980
1990
2000
Multiple sclerosis
Crohn's disease
Type 1 diabetes
Asthma

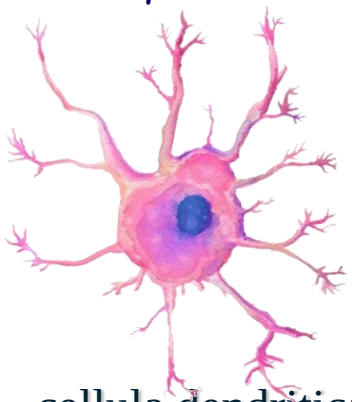
The MICROBIOTA Hypothesis

Th2

Th1

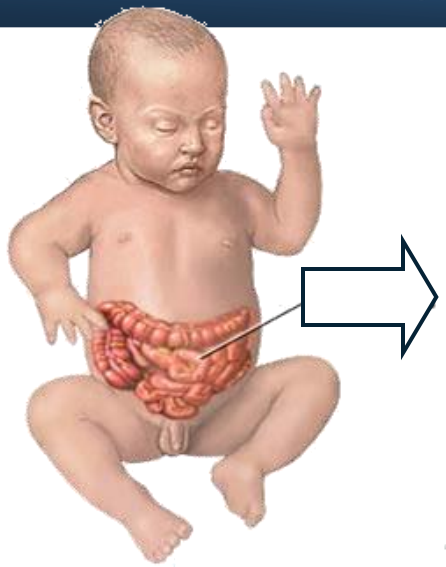


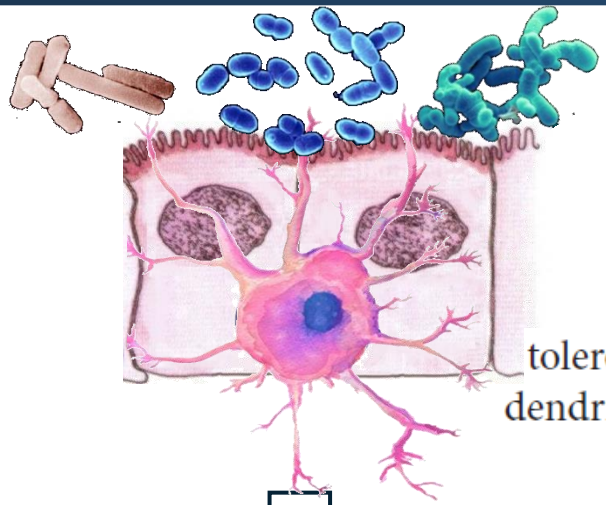
INF-γ IL-12



cellula dendritica
(MHCII^{+} CD11C^{+})

The BIODIVERSITY Hypothesis





tolerogenic dendritic cell

IL-10

TGF β

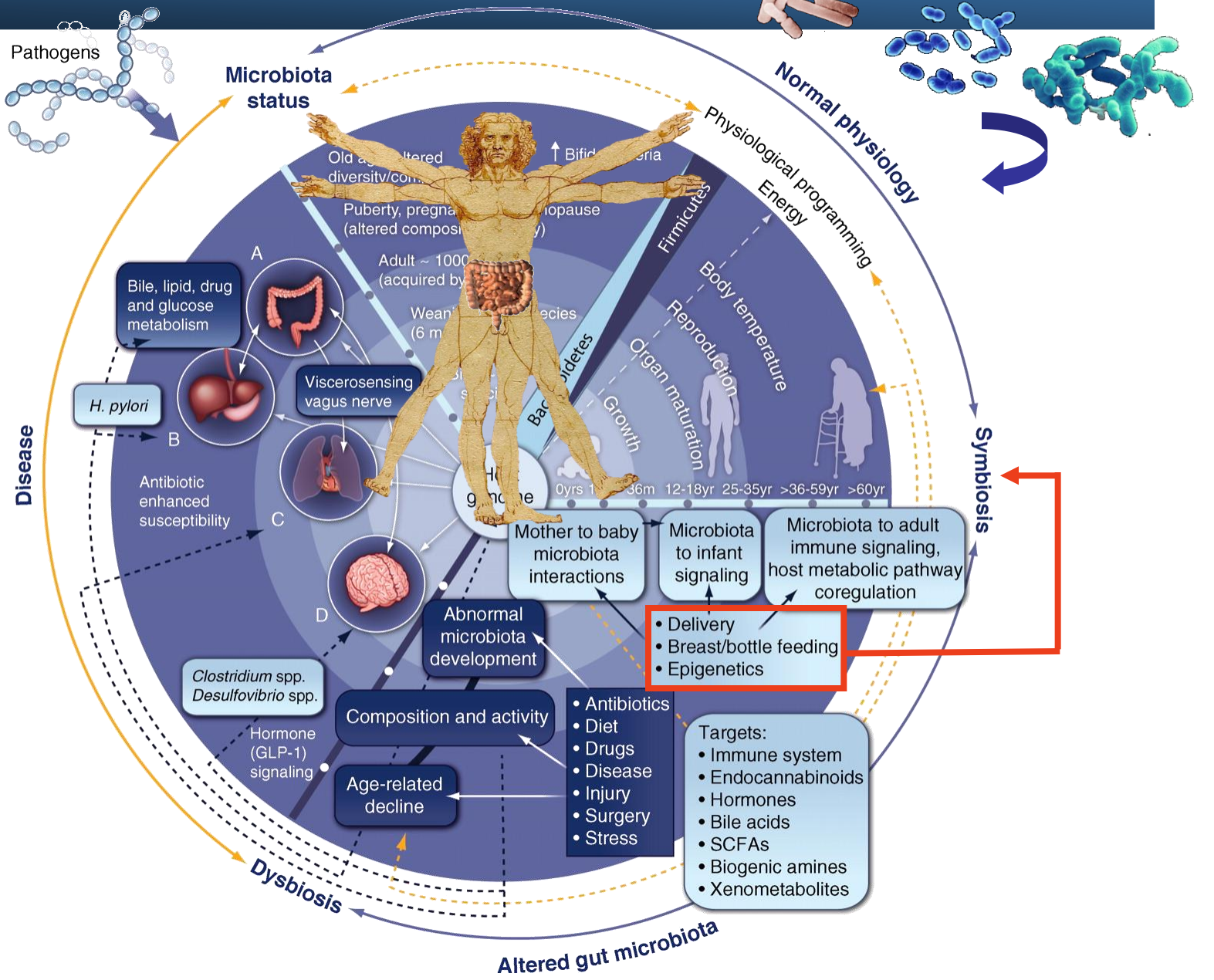
Regulatory $CD4^+$ T

Autoimmunità

Allergia

Trends in Allergic Conditions Among Children: United States, 1997–2011

Kristen D. Jackson, M.P.H.; LaJeana D. Howie, M.P.H., C.H.E.S.; Lara J. Akinbami, M.D.



JK. Nicholson Host-Gut Microbiota Metabolic Interactions Science 2012

Parto Cesareo

World Health Organization

in 1985 the World Health Organization (WHO) stated:

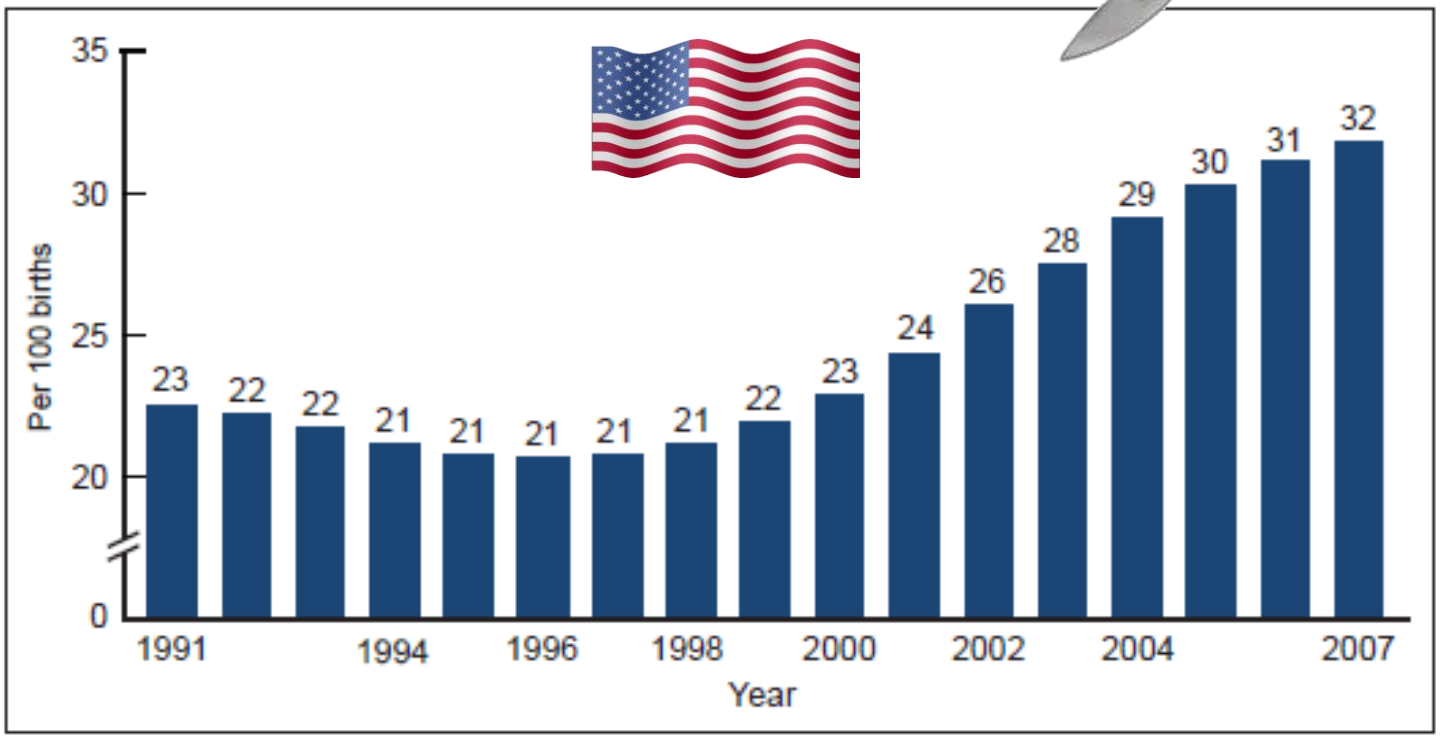
"There is no justification
to have CS rates higher than 10-15%"

Updated December 2012

More recent studies reaffirm earlier World Health Organization recommendations about optimal rates of cesarean section. The best outcomes for women and babies appear to occur with cesarean section rates of 5% to 10%. Rates above 15% seem to do more harm than good

Parto Cesareo

Cesarean delivery rates: United States, 1991–2007



SOURCE: CDC/NCHS, National Vital Statistics System.

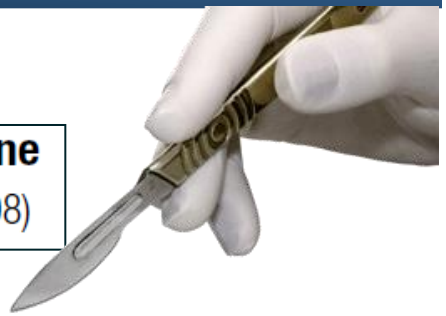
Parto Cesareo

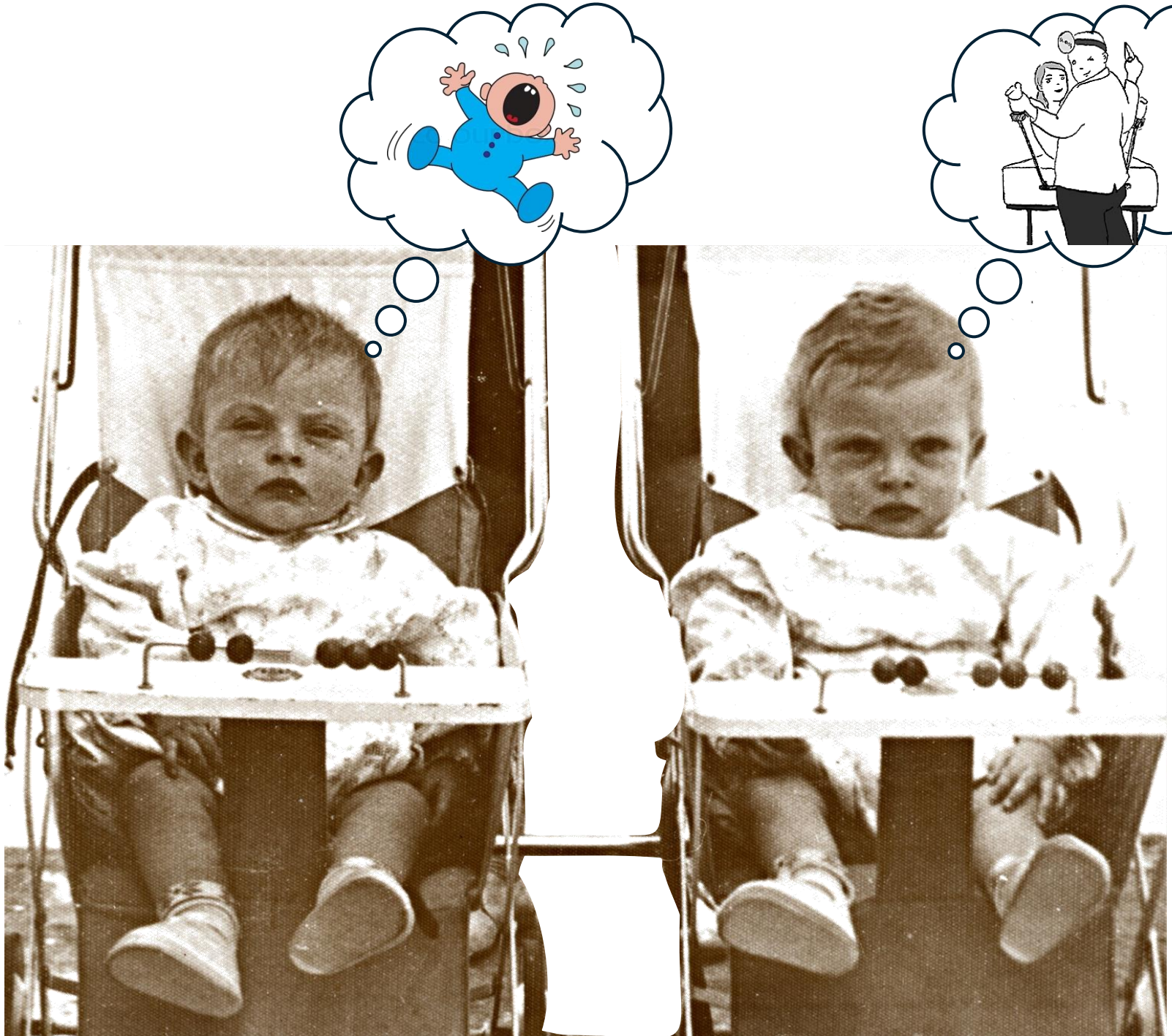
Co-funded by
the Health Programme
of the European Union

Percentuale di tagli cesarei in Europa (Fonte: European Perinatal Health Report, dicembre 2008).

Percentuale di taglio cesareo nelle regioni italiane

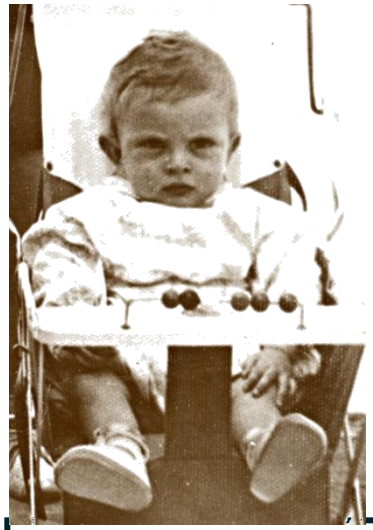
(fonte: Ministero della salute, Sistema informativo sanitario CeDAP, anno 2008)



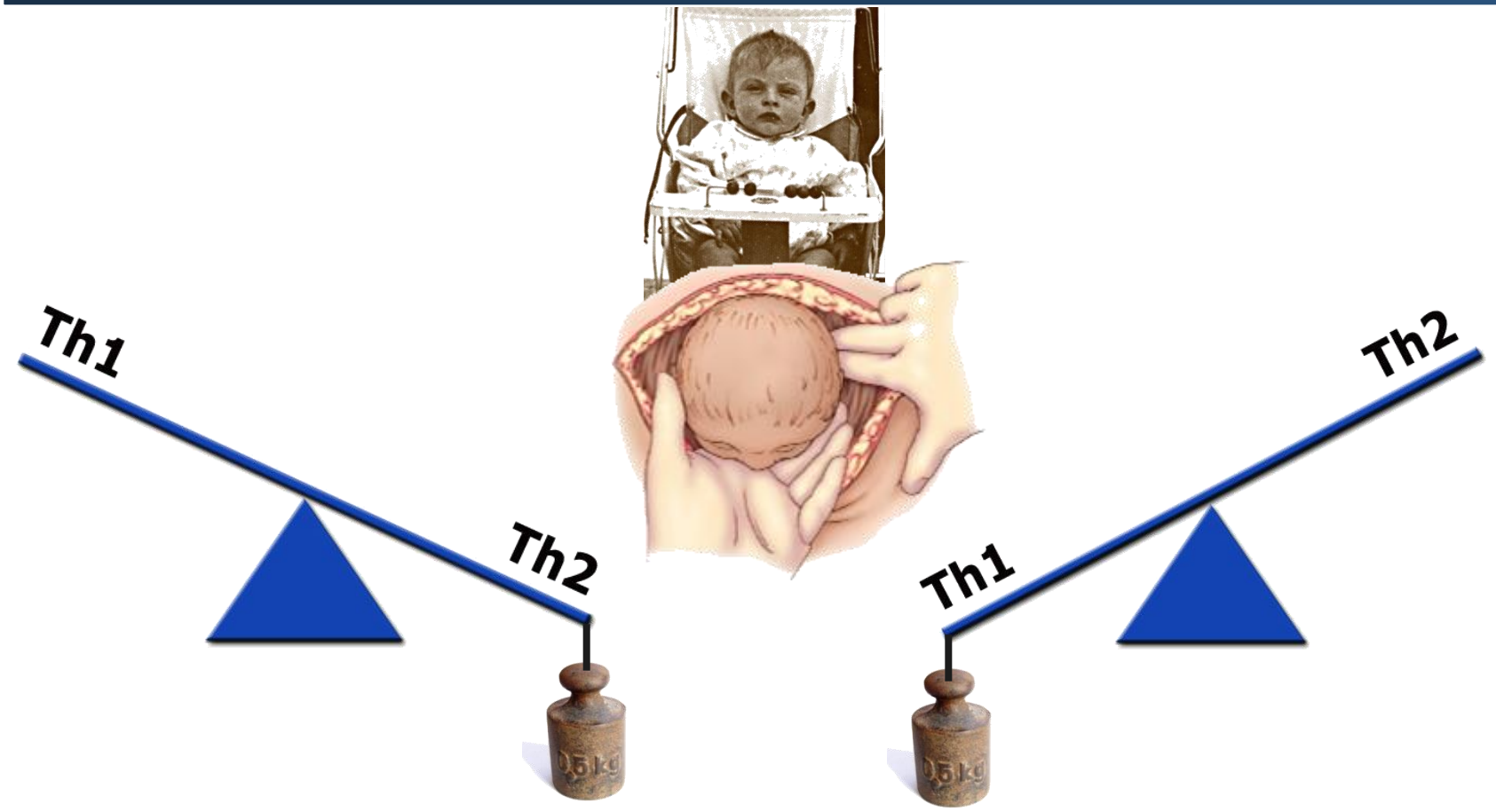


Ministero della Salute

LINEA GUIDA



Taglio cesareo: una scelta appropriata e consapevole



Allergie

Diabete Mellito tipo 1

Celiachia

Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies

C. R. Cardwell

Diabetologia (2008) 51:726–735

First author [reference]	Type 1 DM % Caesarean (*n*/*N*)	Controls % Caesarean (*n*/*N*)	OR (95%CI)	OR (95% CI)
Dahlquist [42]	11 (293/2710)	8 (687/8,148)		1.32 (1.14–1.52)
Patterson [24]	13 (34/270)	8 (112/1,355)		1.60 (1.06–2.42)
McKinney [25]	15 (33/220)	10 (43/433)		1.59 (0.98–2.59)

Conclusions/interpretation This analysis demonstrates a 20% increase in the risk of childhood-onset type 1 diabetes after Caesarean section delivery that cannot be explained by known confounders.

Šipetić [38]	9 (9/105)	5 (11/210)		1.70 (0.68–4.23)
Svensson [37]	15 (71/477)	12 (79/679)		1.33 (0.94–1.88)
Malcova [39]	9 (78/833)	8 (107/1,414)		1.26 (0.93–1.71)
Tenconi [40]	20 (16/77)	19 (32/166)		1.25 (0.61–2.56)
Ievins[b] [18]	6 (23/396)	7 (18,583/281,641)		0.77 (0.51–1.17)
		Overall[a]		1.23 (1.15–1.32)

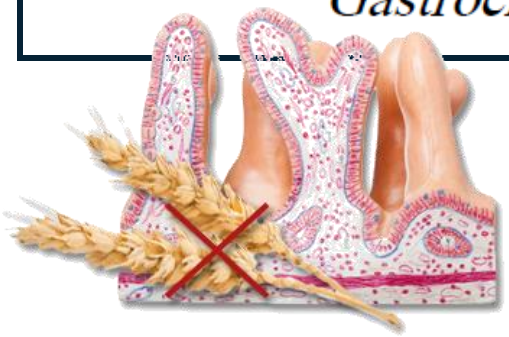
0.5 0.66 1 1.5 2

Reduced risk of diabetes after Caesarean section

Increased risk of diabetes after Caesarean section

Pregnancy outcome and risk of celiac disease in offspring: A nationwide case-control study **Karl Mårild**

Gastroenterology. 2012 January ; 142(1): 39–45

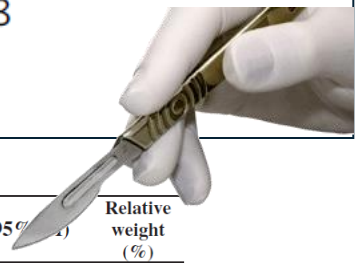


The positive association with *elective*, but not emergency, cesarean delivery is consistent with the hypothesis that the bacterial flora of the newborn plays a role in the development of celiac disease.

A meta-analysis of the association between Caesarean section and childhood asthma

Clinical and Experimental Allergy, **38**, 629–633 2008

S. Thavagnanam*, J. Fleming†, A. Bromley‡, M[illegible]nd C. R. Cardwell§



First author	Asthma C-sect./tot	(%)	C C-sect./[illegible]		Odds ratio (95% CI)	OR (95%[illegible])	Relative weight (%)
Oliveti	33/131	(25)	31/131			1.09 (0.62,1.91)	1.1
Xu	49/282	(17	1098/7804			1.28 (0.94,1.76)	2.9
Nafstad	20/160	(13)	259/2312	[illegible]		1.13 (0.70,1.84)	1.4
Xu	14/98	(14)	89/1855	(5)		3.31 (1.81,6.05)	0.9
Bager						[illegible] (0.98,1.65)	3.9
Hakansson						[illegible] (1.16,1.31)	12.6
Negele						[illegible] (0.03,1.86)	0.1
Debley	385/2028	(19)	1239/8292	(15)		1.33 (1.18,1.51)	8.9
Al-Kubaisy	41/644	(6)	111/1618	(7)		0.92 (0.64,1.34)	2.2
Hagendorens	26/196	(13)	62/592	(10)		1.31 (0.80, 2.13)	1.4
Bernsen	10/144	(7)	71/1507	(5)		1.51 (0.76, 3.00)	0.7
Juhn	41/469	(9)	673/6637	(10)		0.85 (0.61,1.18)	2.7
Renz-Polster	132/698	(19)	1154/7174	(16)		1.22 (1.00 ,1.49)	5.6
Salam	129/508	(25)	584/2928	(20)		1.37 (1.10,1.70)	5.0
Rusconi	247/844	(29)	3916/14 765	(27)		1.15 (0.98,1.34)	7.5
			Overall[a]			**1.22 (1.14, 1.29)**	
			Childhood studies[b]			**1.20 (1.14, 1.26)**	

0.2 0.5 1 2 5

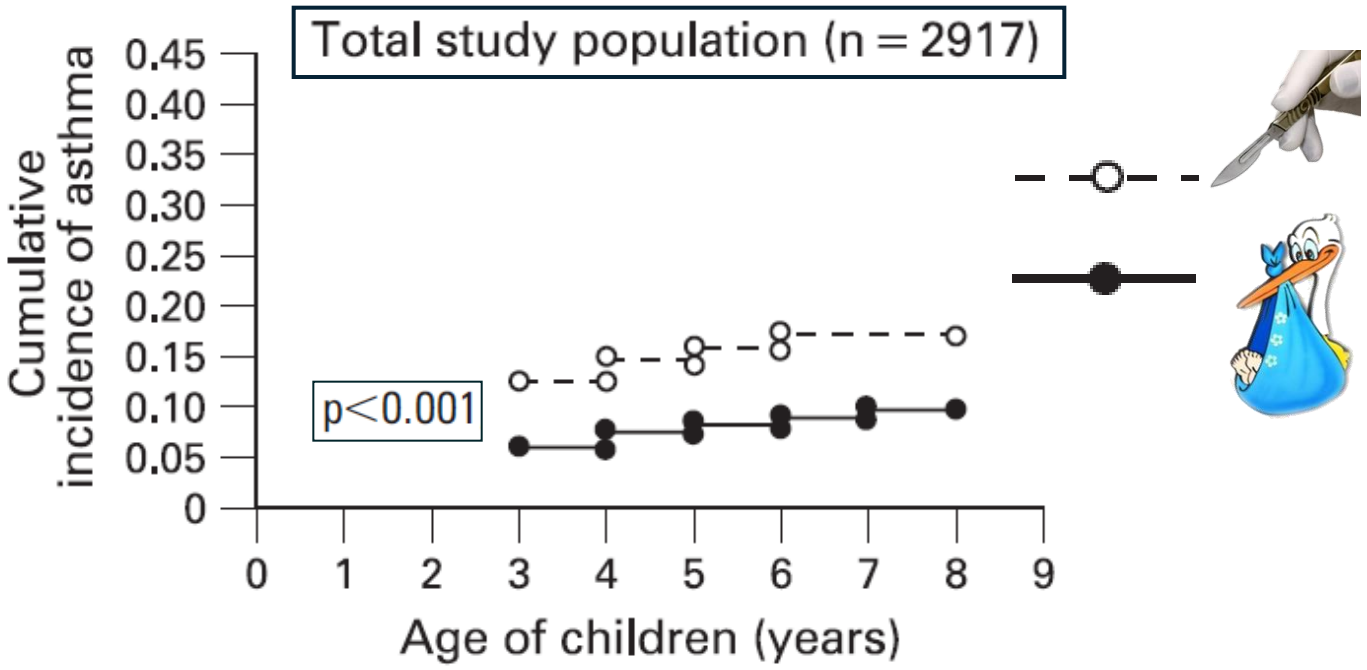
Reduced risk of asthma after Caesarean *Increased risk of asthma after Caesarean*

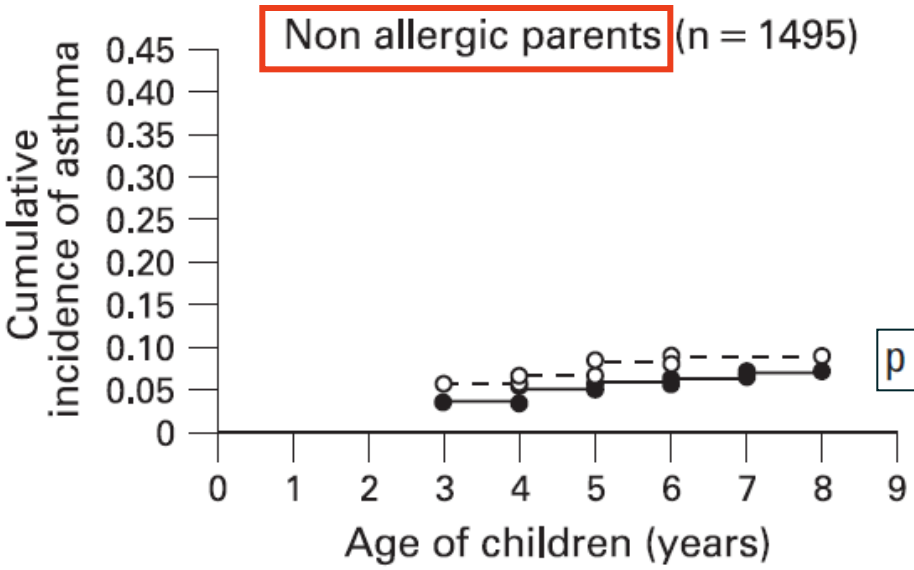
Conclusion In this meta-analysis, we found a 20% increase in the subsequent risk of asthma in children who had been delivered by Caesarean section.

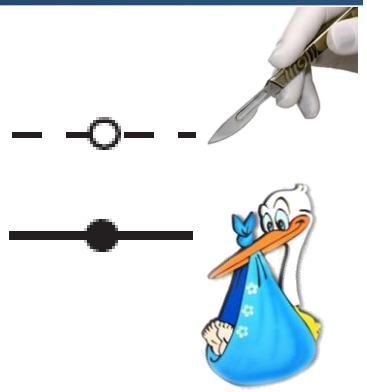
Asthma at 8 years of age in children born by caesarean section

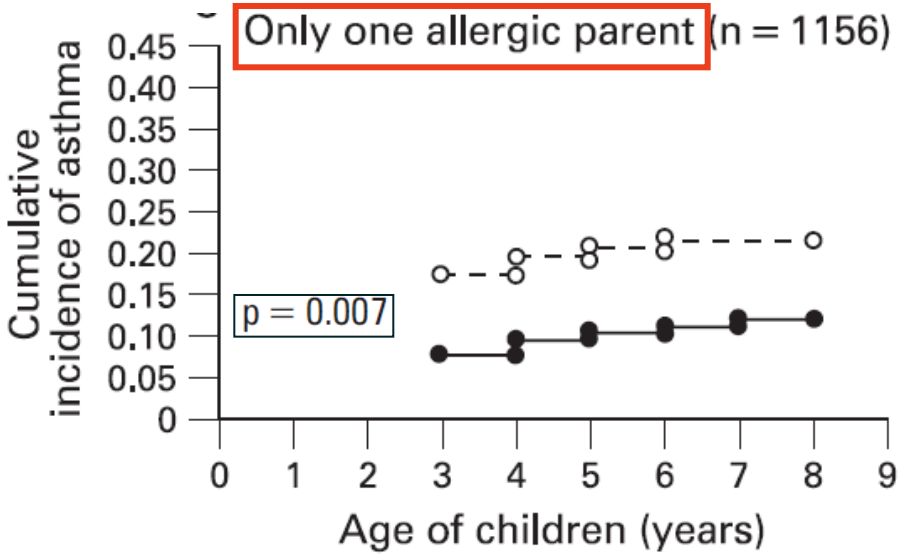
C Roduit *Thorax* 2009;**64**:107–113

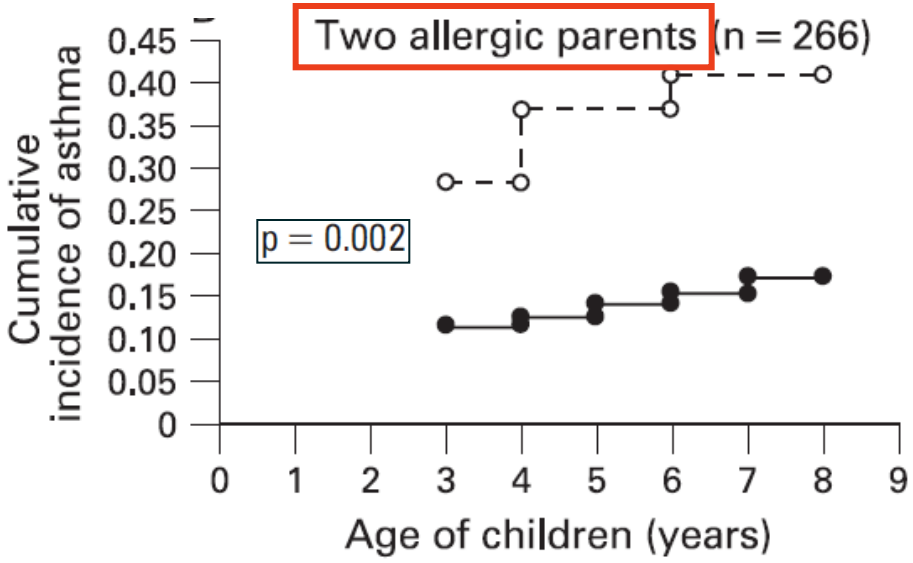
Caesarean section, with a total prevalence of 8.5%, was associated with an increased risk of asthma (OR 1.79; 95% CI 1.27 to 2.51). This association was stronger among predisposed children (with two allergic parents:



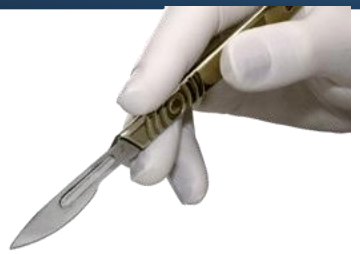

Non allergic parents (n = 1495)
Cumulative incidence of asthma
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0 1 2 3 4 5 6 7 8 9
Age of children (years)
p = 0.12



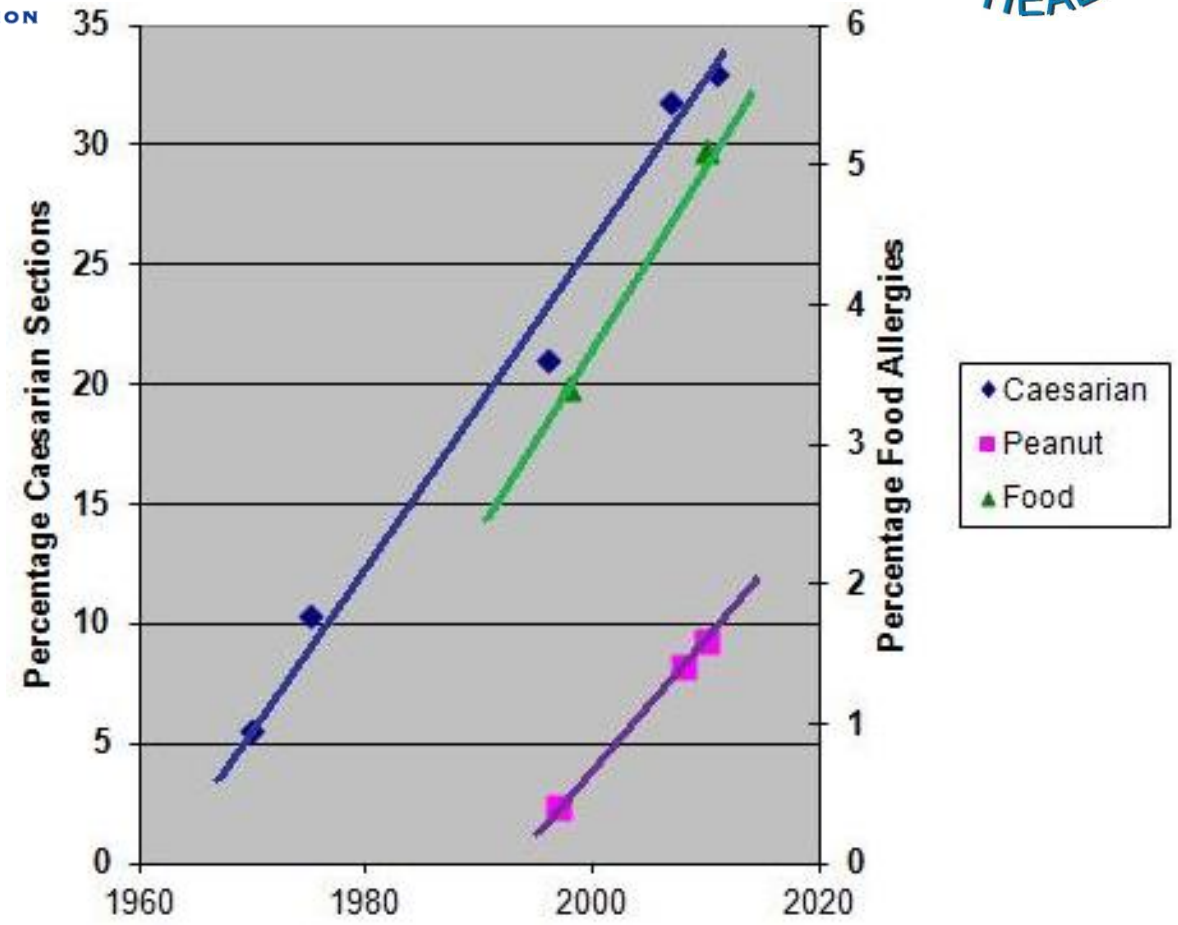

Only one allergic parent (n = 1156)
Cumulative incidence of asthma
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0 1 2 3 4 5 6 7 8 9
Age of children (years)
p = 0.007

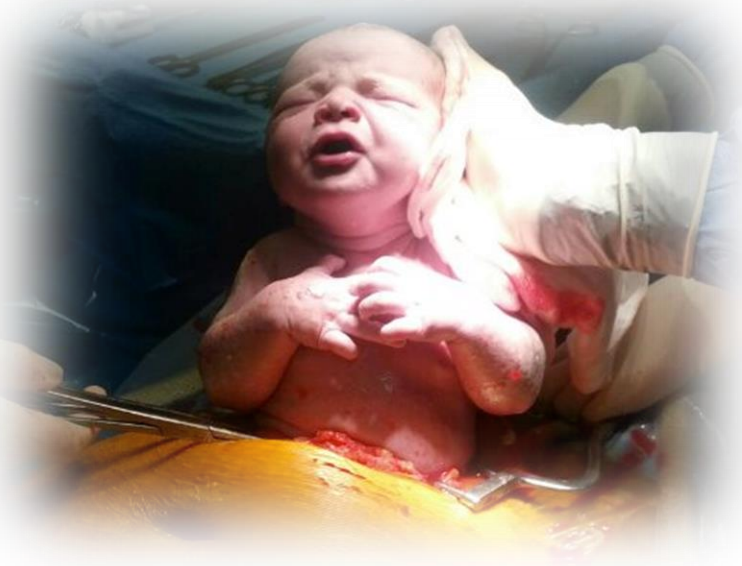

Two allergic parents (n = 266)
Cumulative incidence of asthma
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0 1 2 3 4 5 6 7 8 9
Age of children (years)
p = 0.002

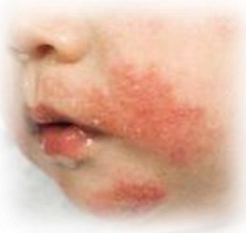
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

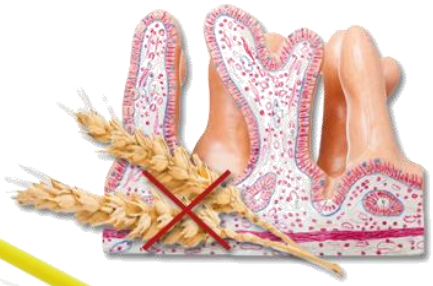


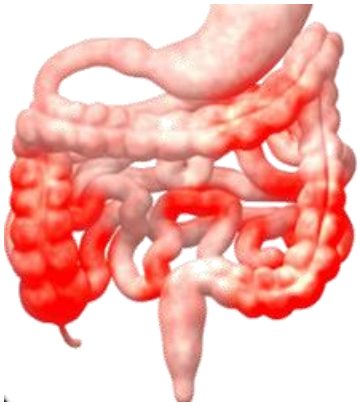
NATIONAL INSTITUTES OF HEALTH

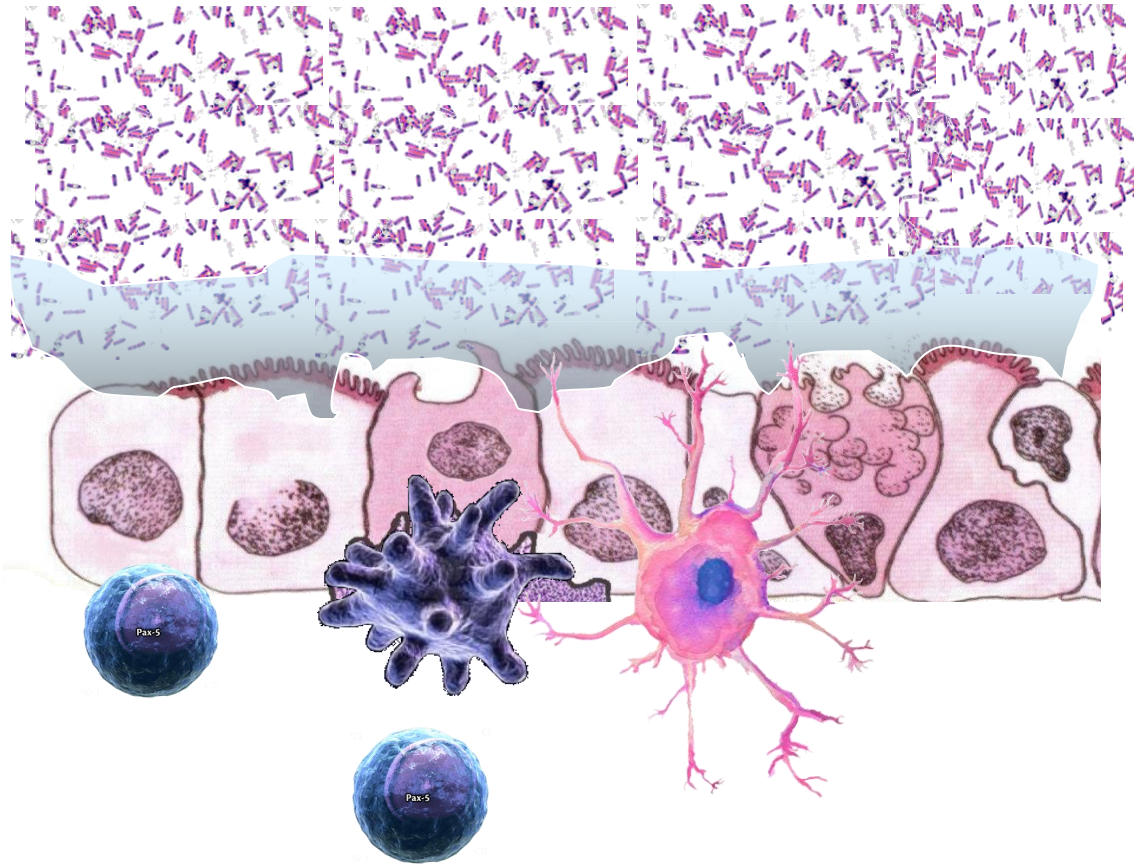











Pax-5
Pax-5


Cross-talk

Eredità Microbica

Microbial influence on tolerance and opportunities for intervention with prebiotics/probiotics and bacterial lysates

J Allergy Clin Immunol
2013;131:1453-63

Petra Ina Pfefferle, PhD, DrPH,[a,b] Susan L. Prescott, MD, PhD,[b,c] and Matthias Kopp, MD[d] *Marburg and Lübeck, Germany,*

Gut Microbiota

Vaginal Microbiota

Eredità Microbica

Microbial influence on tolerance and opportunities for intervention with prebiotics/probiotics and bacterial lysates

J Allergy Clin Immunol
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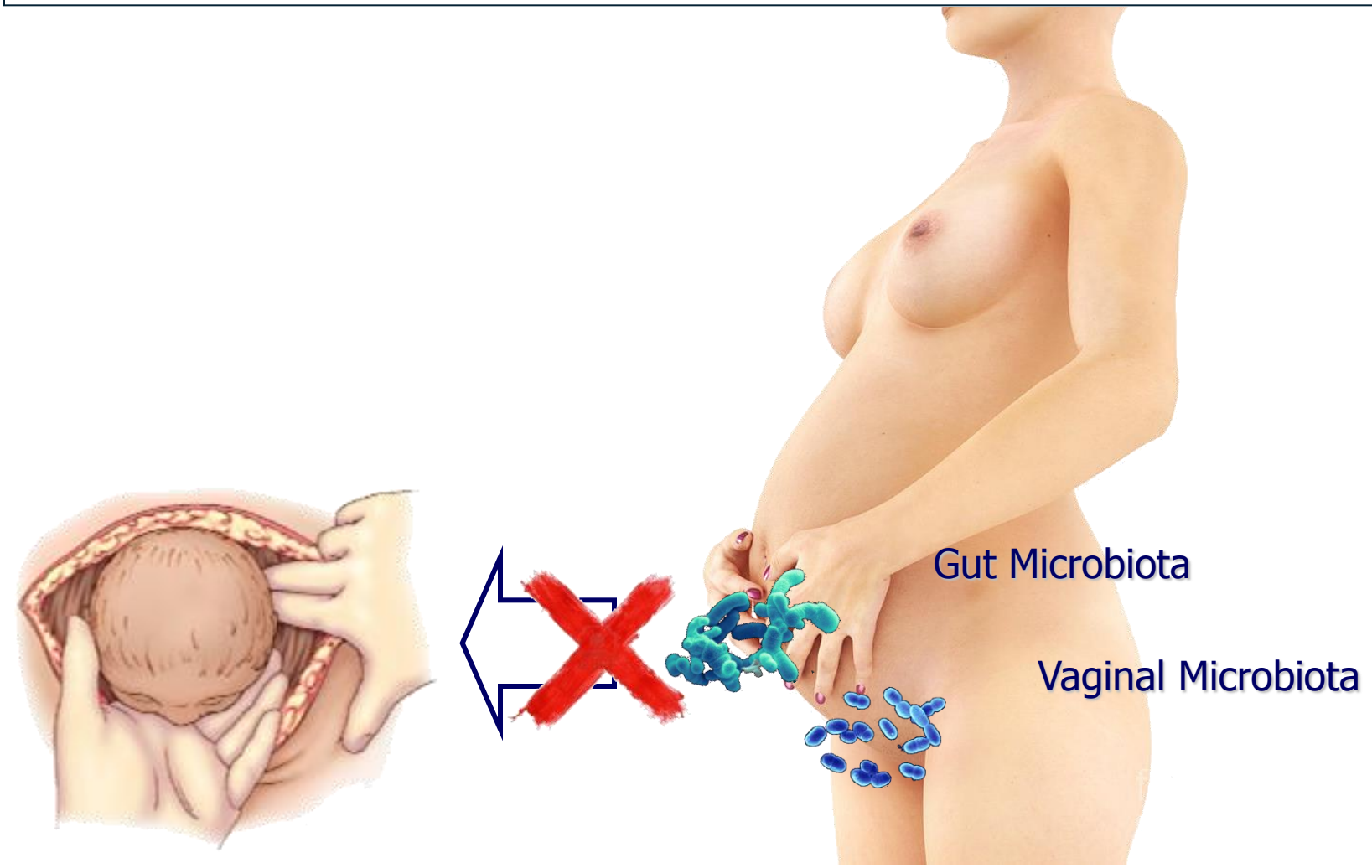
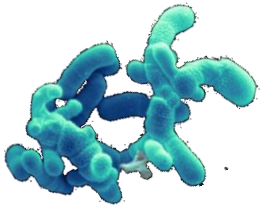
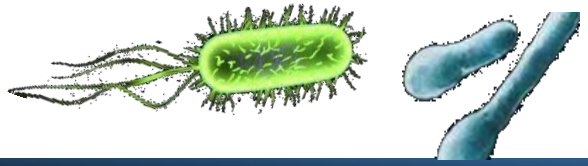


Colonisation of the gut by bifidobacteria is much more common in vaginal deliveries than Caesarean sections Musilova et al. Acta Pædiatrica 2015.

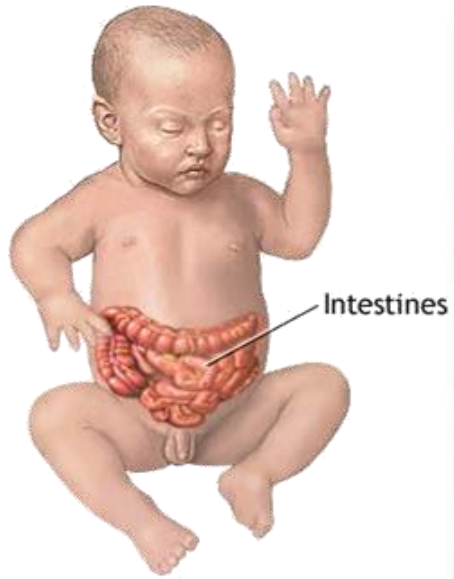


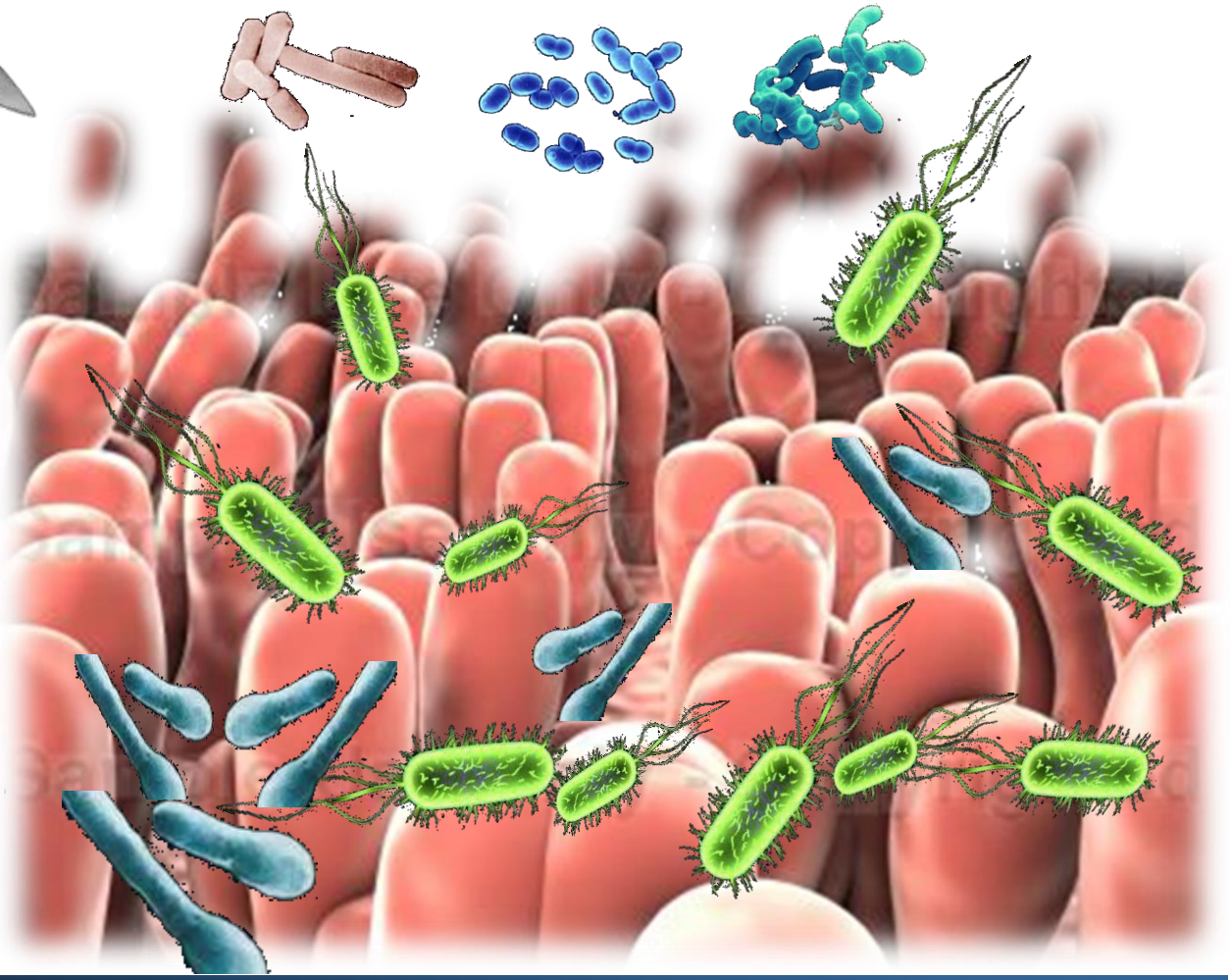
In conclusion, colonisation of the gut by bifidobacteria in vaginally delivered infants is much more common than in infants delivered by Caesarean section.

However, if infants born by Caesarean section did not have bifidobacteria in their gut microbiota, *E. coli* was relatively dominant along with clostridia and gram-negative bacteria.



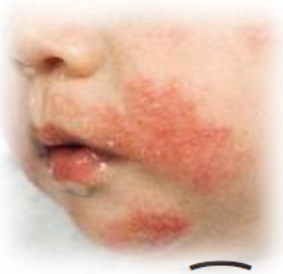
Disbiosi

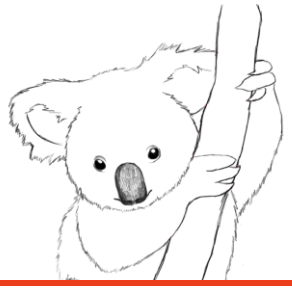




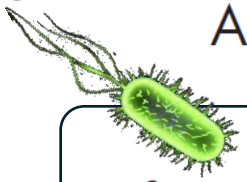
Gut microbiota composition and development of atopic manifestations in infancy: the KOALA Birth Cohort Study

John Penders *Gut* 2007;**56**:661–667





In conclusion, we demonstrated that differences in the gut microbiota composition precede the manifestation of atopic symptoms and atopic sensitisation.



numbers of *Escherichia coli* in faecal samples of 1 month old infants

Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy J Allergy Clin Immunol 2011;128:948-55

Frederika A. van Nimwegen, MSc,[a] John Penders, PhD,[a,b] Ellen E. Stobberingh, PhD,[b] Dirkje S. Postma, MD, PhD,[c]

colonization rates

vaginally home-born } 19.1%
vaginally hospital-born } 27.2%

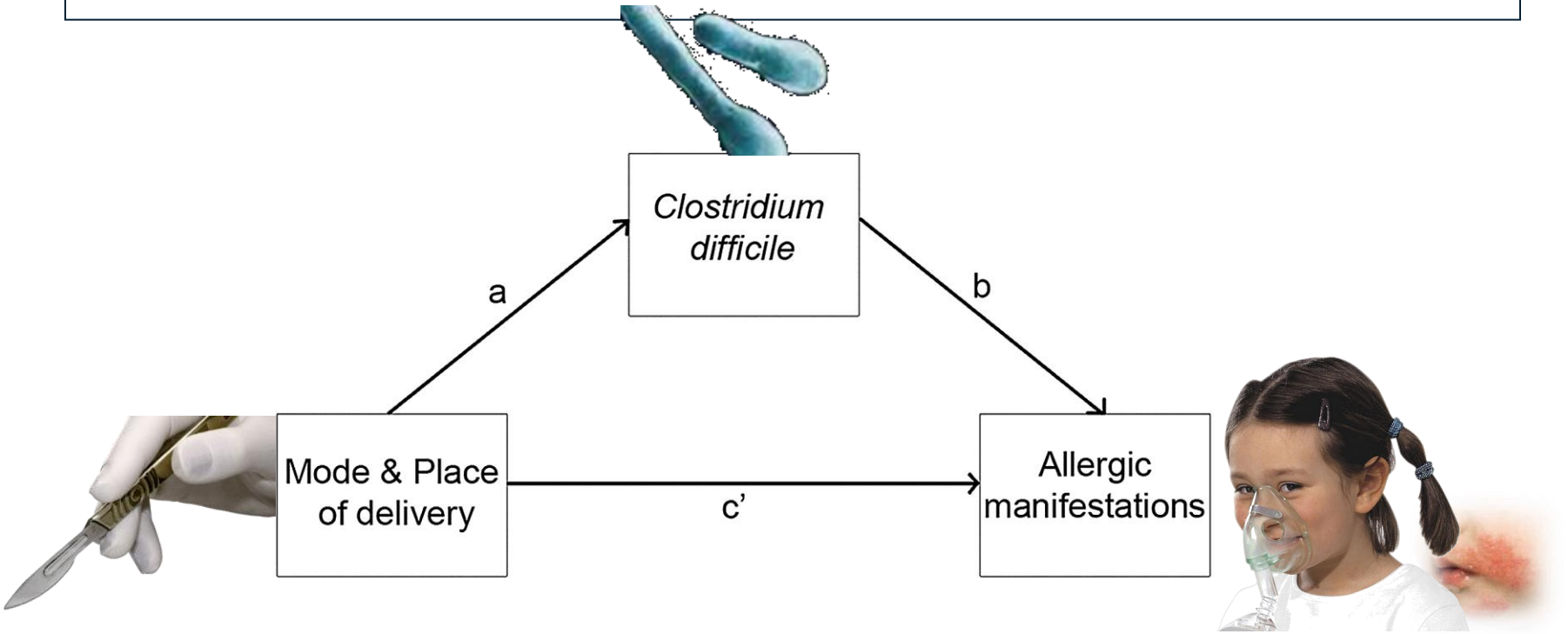
cesarean section–delivered 43.4%

($P_{trend} < .001$)

Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy

J Allergy Clin Immunol 2011;128:948-55

Frederika A. van Nimwegen, MSc,[a] John Penders, PhD,[a,b] Ellen E. Stobberingh, PhD,[b] Dirkje S. Postma, MD, PhD,[c]



Results: Colonization by *Clostridium difficile* at age 1 month was associated with wheeze and eczema throughout the first 6 to 7 years of life and with asthma at age 6 to 7 years.

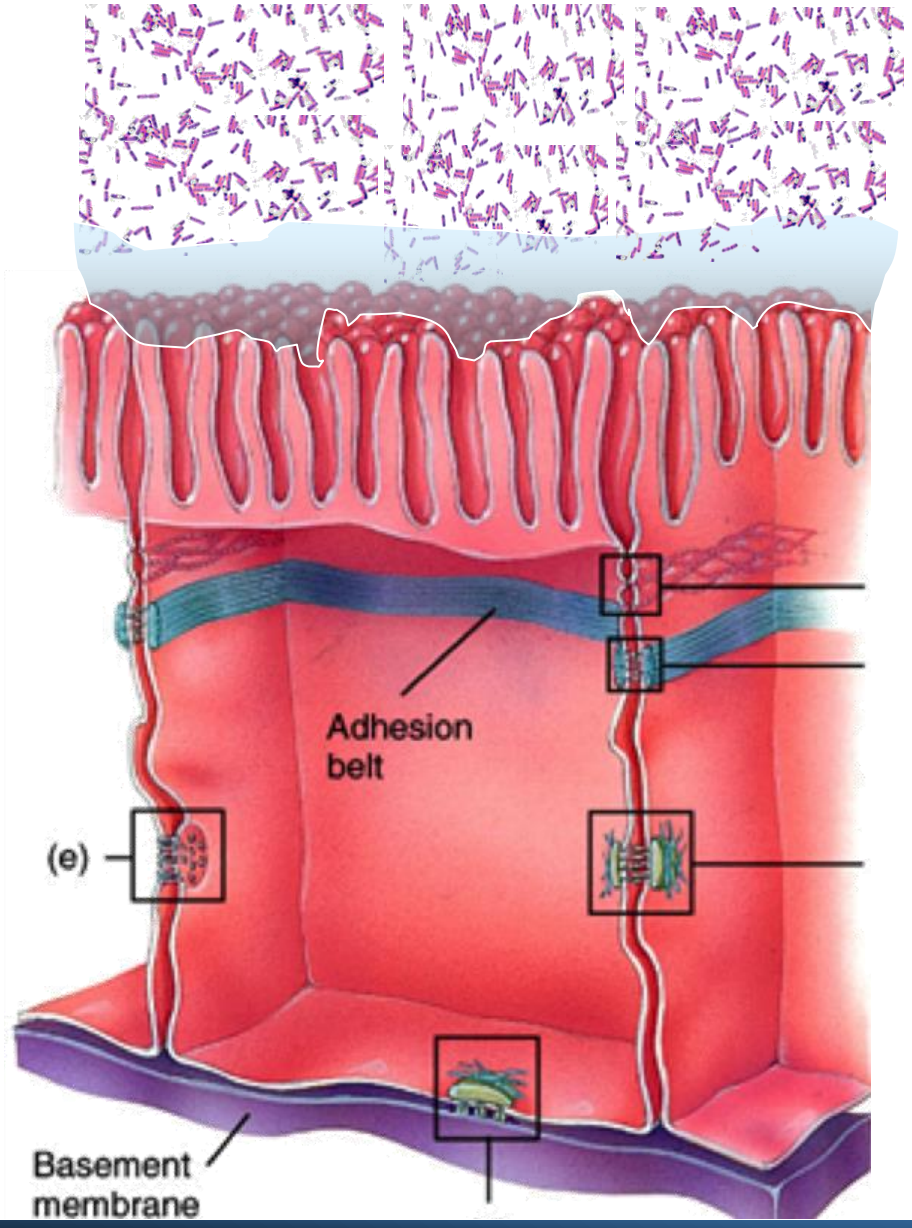
Initial Intestinal Colonization in the Human Infant and Immune Homeostasis

W. Allan Walker Ann Nutr Metab 2013;63

There is strong evidence that disruption of the normal colonization process can lead to alterations in the important symbiotic relationship that is necessary for immune homeostasis. For example, infants born by cesarean section or receiving excessive perinatal antibiotics have inadequate initial colonization and aberrant mucosal immune function.

Permeabilità Intestinale

Permeabilità Intestinale



JPGN
Journal of Pediatric Gastroenterology and Nutrition

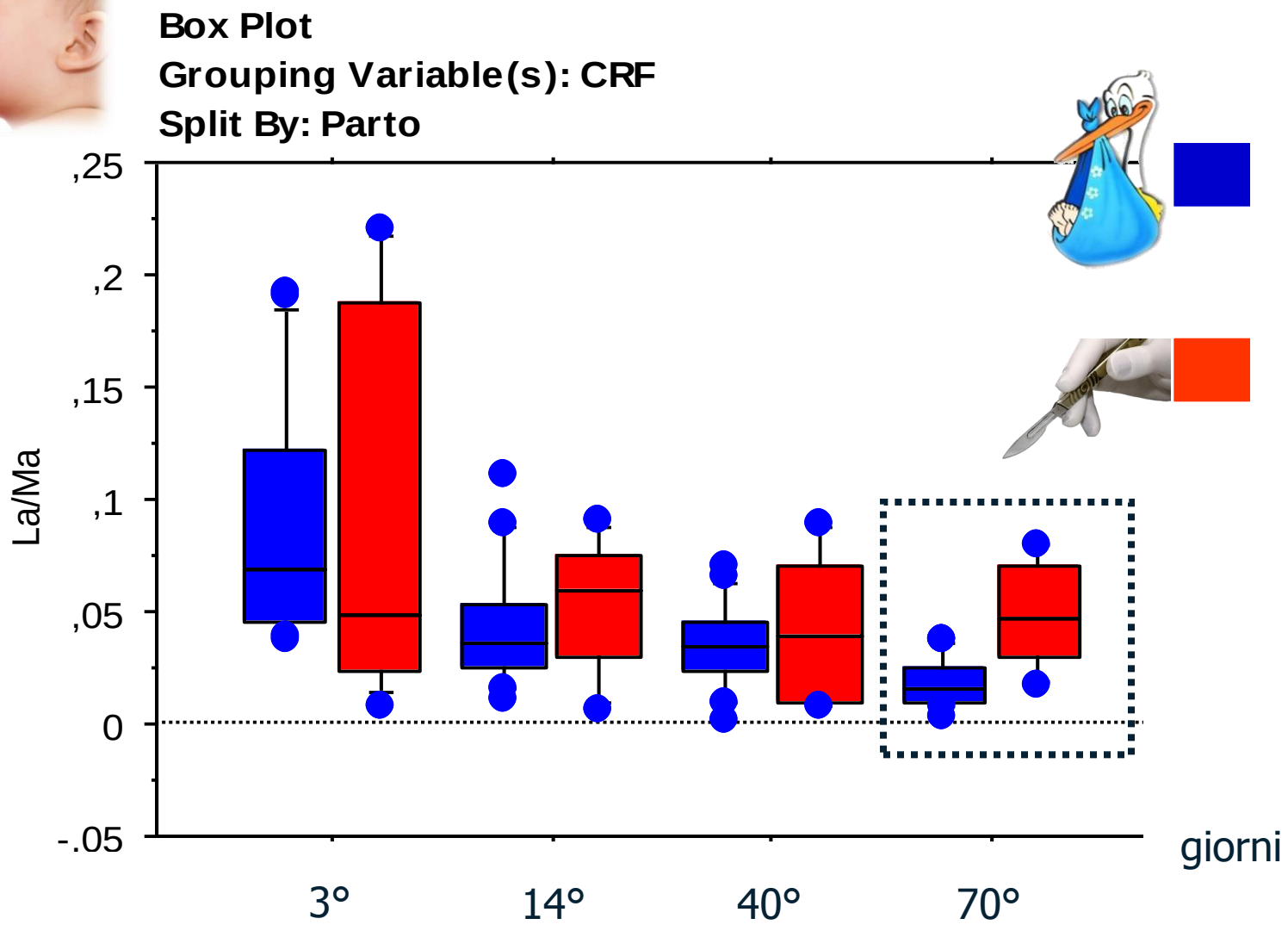
INTESTINAL PERMEABILITY IN HEALTHY BREAST-FED INFANTS, DURING THE POSTNATAL PERIOD

SP Castellaneta[1], A Masciale[1], A Zaccaro[1], S Straziuso[2], V Miniello[2], F Gatti[3], L Polimeno[3], R Francavilla[3].

Journal of Pediatric Gastroenterology and Nutrition
40:616–706 © May 2005 Lippincott Williams & Wilkins

Background and Aim: The maturation of the intestinal epithelial barrier play an important role during the postnatal period and few data are available on the exact timing of gut closure in neonates. The aim of our study was to assess the timing of maturation of the gut barrier by the measure of the intestinal permeability (IP) in full term infants.

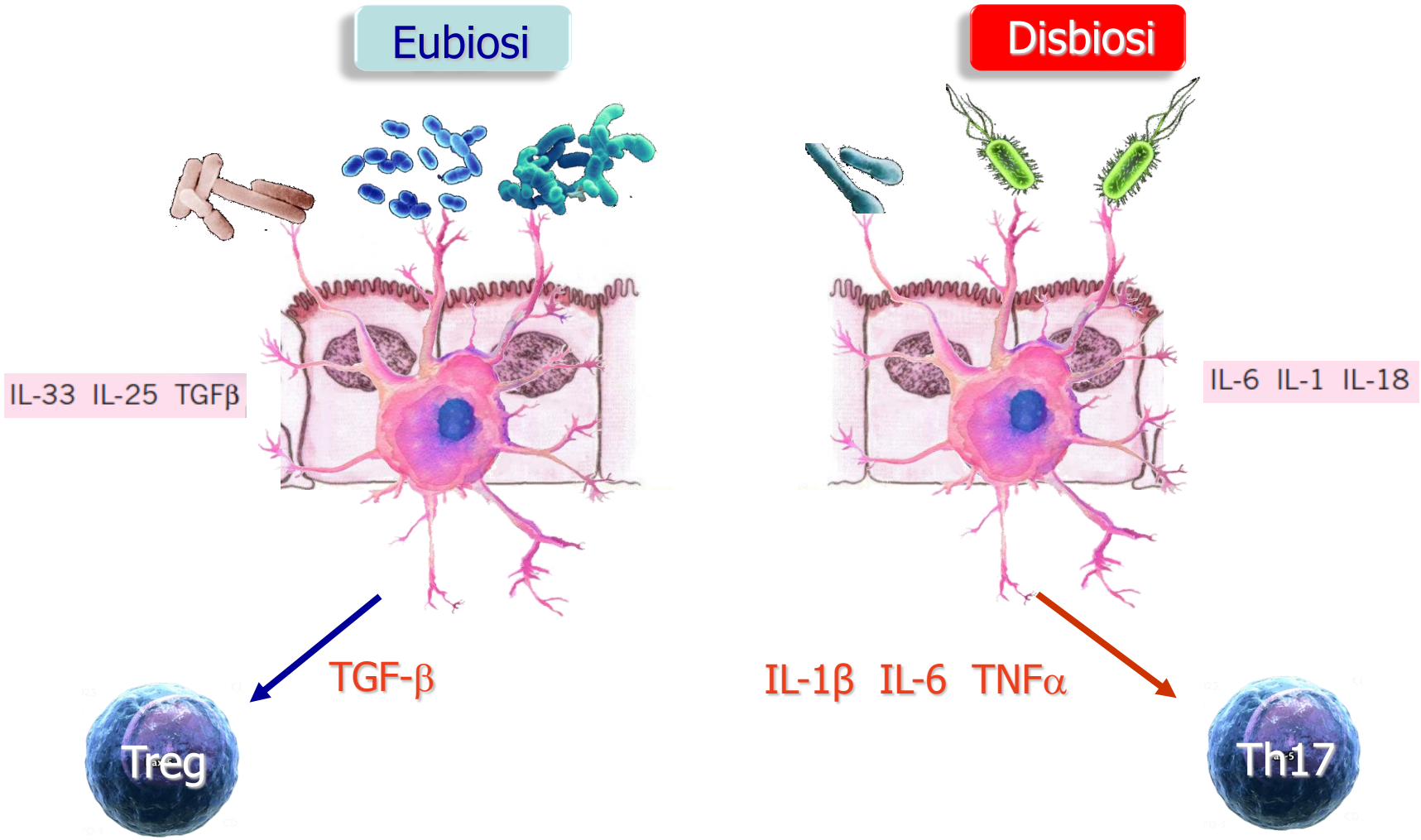
Summary and conclusion: Our study show that the IP to sugar probes in healthy breast fed infants is high at birth and progressively decrease during the first two months of life: however yet at 20 days the maturation of the IP and the gut closure seems to be completed.

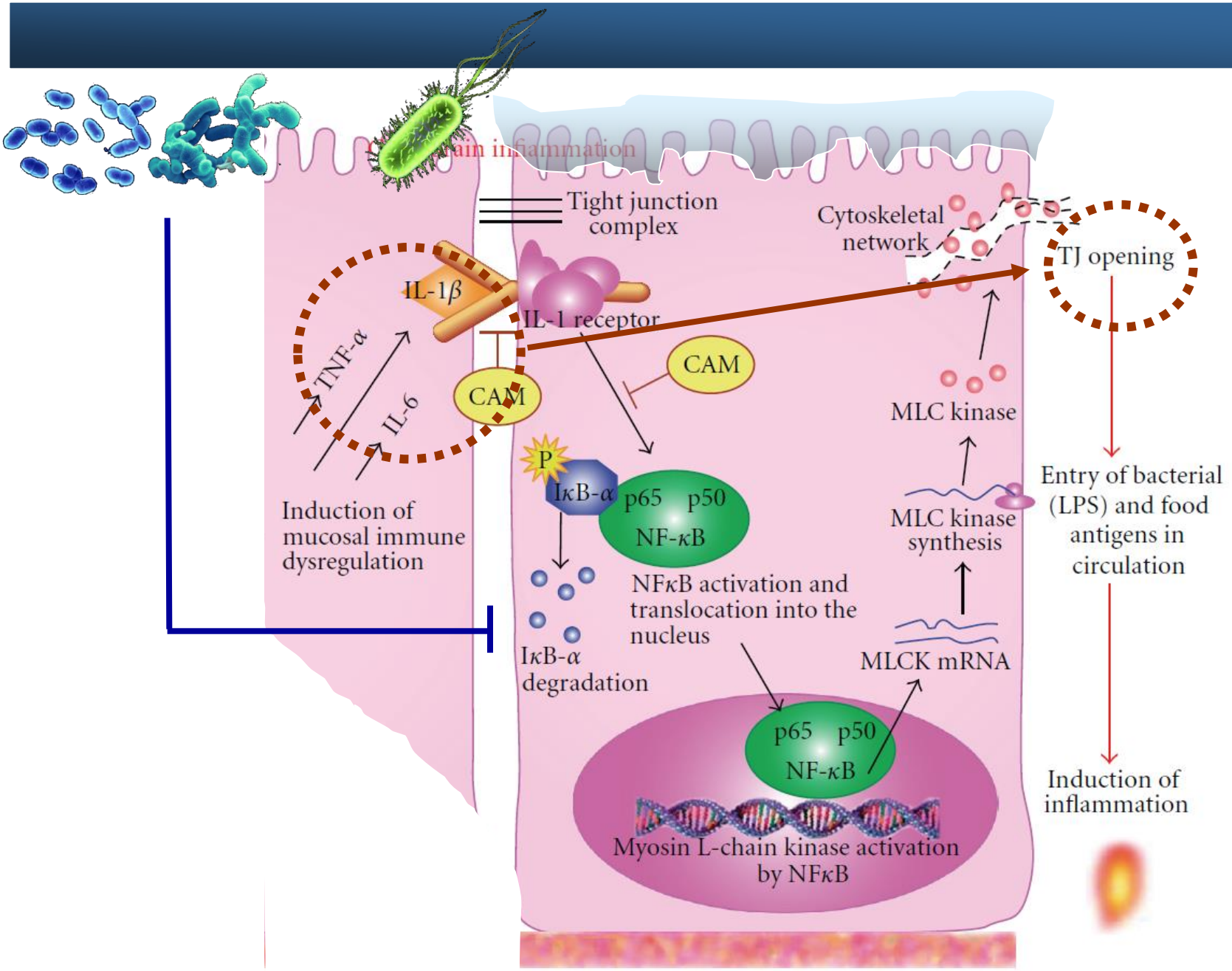

Box Plot
Grouping Variable(s): CRF
Split By: Parto
,25
,2
,15
,1
,05
0
-.05
La/Ma
3°
14°
40°
70°
giorni

Reciprocal interactions of the intestinal microbiota and immune system

2012 | VOL 489 | NATURE

Craig L. Maynard[1], Charles O. Elson[2], Robin D. Hatton[1] & Casey T. Weaver[1]



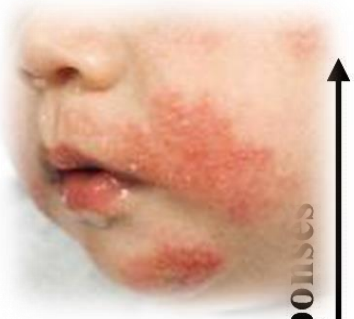


Vojdani A, Lambert J - (2011)

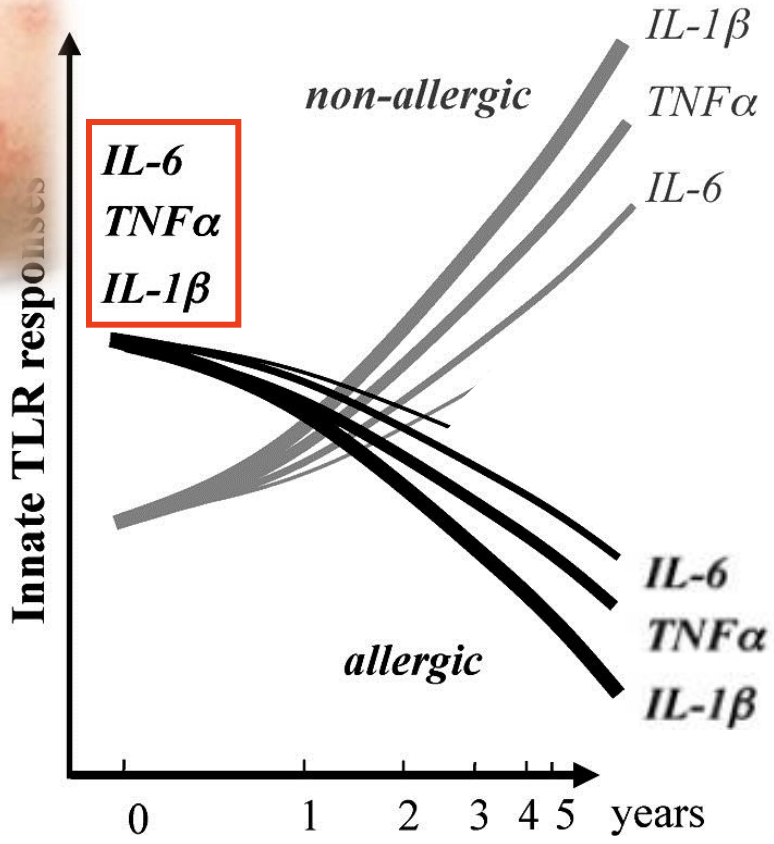
Differences in innate immune function between allergic and nonallergic children: New insights into immune ontogeny

Meri K. Tulic, BSc, PhD,[a] Megan Hodder, BSc,[a] Anna Forsberg, MSc,[b] Suzi McCarthy, BSc,[a] Tara Richman, BSc,[a] Nina D'Vaz, BSc,[a] Anita H. J. van den Biggelaar, BSc, PhD,[c] Catherine A. Thornton, BSc, PhD,[d] and Susan L. Prescott, MD, PhD[a] *Perth, Australia, Linkoping, Sweden, and Swansea, United Kingdom*

J Allergy Clin Immunol 2011;127:470-8.

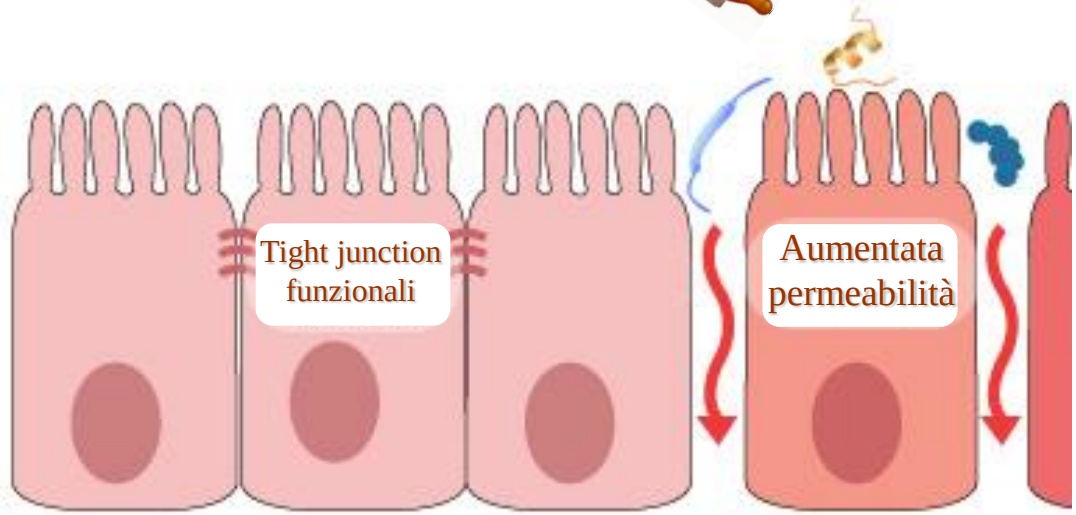


innate immune development

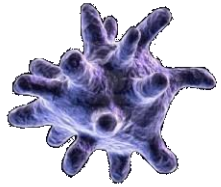


Barriera Intestinale

Disbiosi

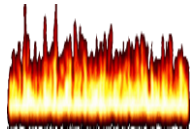


Barriera Normale **Barriera Alterata**



Disregolazione immunitaria

- ✓ **Attivazione Immunitaria**
- ✓ **Infiammazione**



T. Suzuki Regulation of intestinal epithelial permeability by tight junctions. 2013

The intestinal microflora in allergic Estonian and Swedish 2-year-old children.

Björ[illegible] et Al. Clin Exp Allergy. 1999; 29: 342-6.

Distin[illegible]atterns of [illegible]microflora in infants in whom atopy was and was not developing.

[illegible], et Al. J Allergy Clin Immunol. 2001; 107: 129-34.

Diffe[illegible]tween patients wit[illegible]is and healthy control subjects.

[illegible]t al. J Allergy C[illegible]1: 587–91.

Finestra di opportunità

BIOMODULATORI DEL MICROBIOTA INTESTINALE: tra realtà e futuro

Vito Leonardo Miniello

EDITEAM
GRUPPO EDITORIALE

biomodulatori del microbiota intestinale

World Health Organization

Food and Agriculture Organization of the United Nations

"Microrganismi vivi che, assunti in quantità adeguata, conferiscono all'organismo ospite un effetto salutare"

"Costituenti alimentari non vitali che conferiscono un beneficio alla salute, mediante una modulazione del microbiota"

biomodulatori del microbiota intestinale

World Health Organization

Food and Agriculture Organization of the United Nations

Associazione di Prebiotici e Probiotici”

Prodotti batterici o derivati metabolici di microrganismi probiotici con attività biologica per l’ospite

Initial Intestinal Colonization in the Human Infant and Immune Homeostasis

W. Allan Walker Ann Nutr Metab 2013;63(suppl 2):8–15

Abnormal colonization (dysbiosis) and its accompanying increase in disease expression can be prevented by pre- and probiotics.

Probiotici

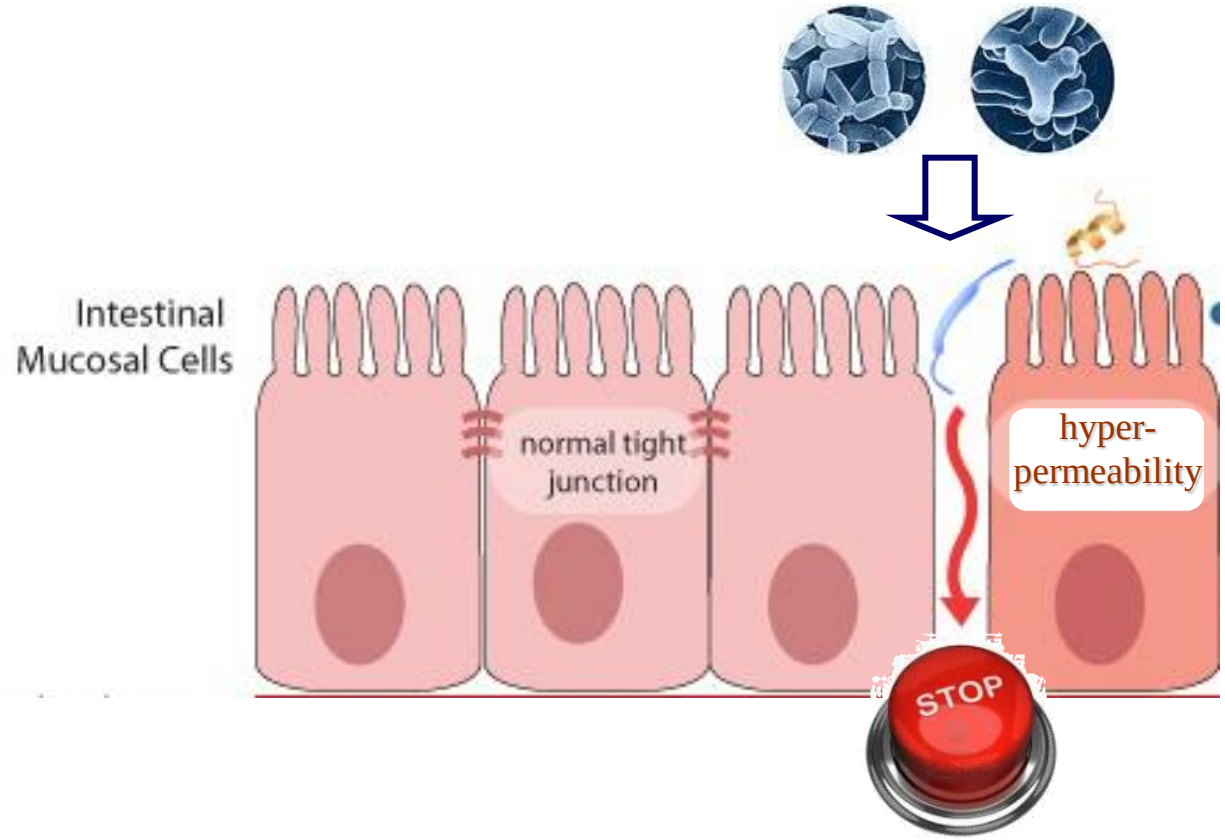
Probiotics for the prevention or treatment of allergic diseases J Allergy Clin Immunol 2007;120:255-62.

Susan L. Prescott, MD, PhD,[a] and Bengt Björkstén, MD, PhD[b] /

L'azione dei probiotici sull'ospite viene esercitata con:

- ✓ ottimizzazione della composizione del microbiota intestinale
- ✓ mantenimento dell'integrità della barriera intestinale
(prevenzione della traslocazione batterica e del passaggio di molecole antigeniche)
- ✓ modulazione delle risposte immunitarie del GALT

Probiotici



Probiotics for the prevention or treatment of allergic diseases J Allergy Clin Immunol 2007;120:255-62.

Susan L. Prescott, MD, PhD,[a] and Bengt Björkstén, MD, PhD

Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: A randomized, double-blind, placebo-controlled trial

(J Allergy Clin Immunol 2007;119:192-8.)

Kaarina Kukkonen, MD,[a] Erkki Savilahti, MD, PhD,[b] Tari Haahtela, MD, PhD,[a]

1223 gravide
(ultimo mese di gestazione)

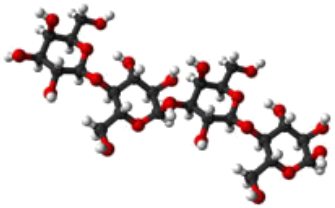
461

- *Bifidobacterium breve* Bb99 (DSM 13692)
- *Lactobacillus rhamnosus* GG (ATCC 53103)
- *Lactobacillus rhamnosus* LC705 (DSM 7061)
- *Propionibacterium freudenreichii* (DSM 7076)

464

PLACEBO

Lattanti ad elevato
rischio di atopia
(per 6 mesi)



GOS

PLACEBO

Outcome a 2 anni

-incidenza cumulativa di malattie allergiche
(allergia alimentare, eczema, asma, rinite allergica)

- sensibilizzazione
(skin prick test + o IgE sieriche antigene-specifiche >0.7 kU/L).

CONCLUSIONI

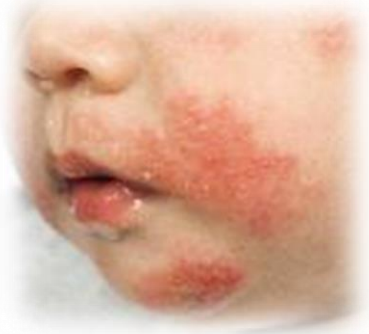
Nessun effetto dei Simbiotici sull'incidenza cumulativa delle malattie allergiche e sulla sensibilizzazione.

Nel gruppo attivo riduzione significativa dell'eczema

(OR, 0.74; 95% CI, 0.55-0.98; p=0.035)

e dell'eczema atopico

(O.R. 0,66; 95% CI, 0,46-0,95; P=0.025)



Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort

(J Allergy Clin Immunol 2009;123:335-41.)

Mikael Kuitunen, MD, PhD,[a] Kaarina Kukkonen, MD,[a] Kaisu Juntunen-Backman, MD, PhD,[a] Riitta Korpela, PhD,[c,d]

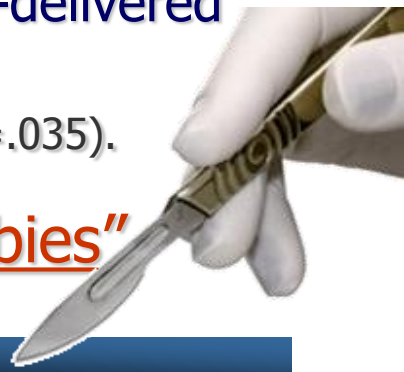
Outcome a 5 anni

-incidenza cumulativa di malattie allergiche
(allergia alimentare, eczema, asma, rinite allergica)

"No allergy-preventive effect is extended to age 5 years by perinatal supplementation with probiotics in babies at risk for developing allergies".

Less IgE-associated allergic disease occurred in cesarean-delivered children receiving probiotics.
(24.3% vs 40.5%; odds ratio, 0.47; 95% CI, 0.23% to 0.96%; p=.035).

"Protection is conferred only to C-section babies"



Clinical Use of Probiotics in Pediatric Allergy (CUPPA): A World Allergy Organization Position Paper

WAO POSITION PAPER *WAO Journal* 2012; 5:148–167

However, the conclusions of this trial appear relevant for prevention and not treatment purposes, as the main difference was lower rates of allergy among infants born by caesarean section.[80]

Gut microbiota biomodulators

when the stork comes by the scalpel

Clinica Chimica Acta

Vito Leonardo Miniello

Under these dysbiosis conditions probiotics could act as 'surrogate' colonizers to prevent immune-mediated diseases.

- Ottimale composizione del Microbiota Intestinale
- Prevalenza di Bifidobatteri

↓

Eubiosi

↓

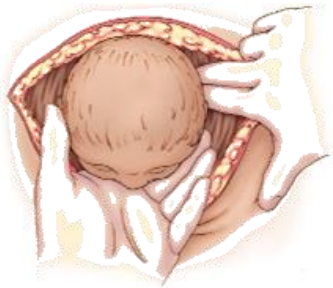
Interazione tra Microbiota e tessuto linfoide intestinale (GALT)

↓

Omeostasi Immunitaria
Protezione per Infezioni
Malattie Allergiche
Malattie Autoimmuni

Antibiotico-terapia perinatale

Parto Cesareo



Prematurità

Disbiosi
Ritardata colonizzazione con ridotta diversità microbica
- Anomala composizione del Microbiota (prevalenza di *Clostridia ed E. coli* con deficit di Bacteroidetes, Bifidobatteri e Lattobacilli)

↓

Alterata Omeostasi immunitaria

↓

Aumentata Prevalenza Malattie Allergiche e Malattie Autoimmuni


“Prega per noi adesso
e nell'ora della nostra nascita”
Thomas Stearns Eliot