How Early Nutrition Can Shape Gut Microbiota And Its Implications In The Autoimmunity Epidemics: The Lesson Learned From Celiac Disease

Alessio Fasano, M.D.

W. Allan Walker Professor of Pediatric Gastroenterology and Nutrition

Mucosal Biology and Immunology Research Center

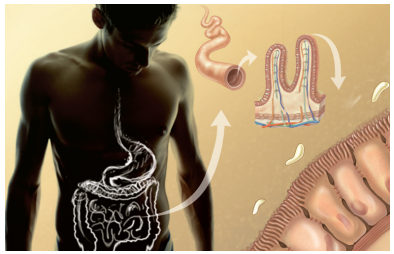
And Center for Celiac Research

Massachusetts General Hospital for Children

MassGeneral Hospital for Children

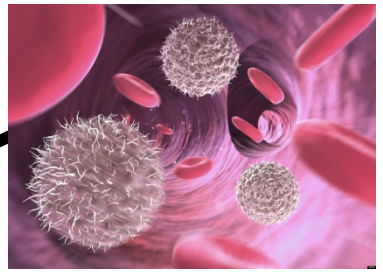
Harvard Medical School

The Yin and Yang Between Tolerance and Immune Response Leading To Immune-Mediated Diseases

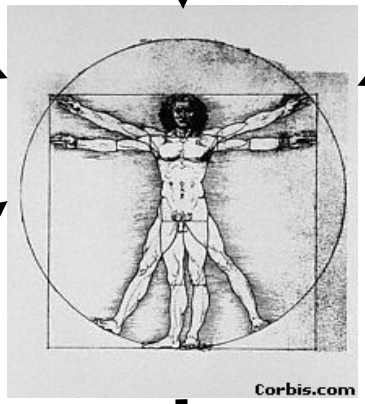


Increased Gut Permeability

Human Genome

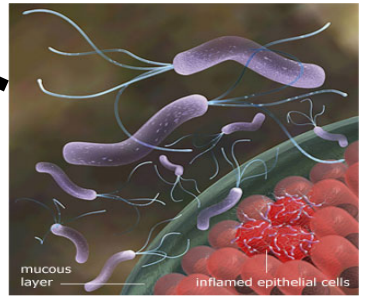


Immune Response



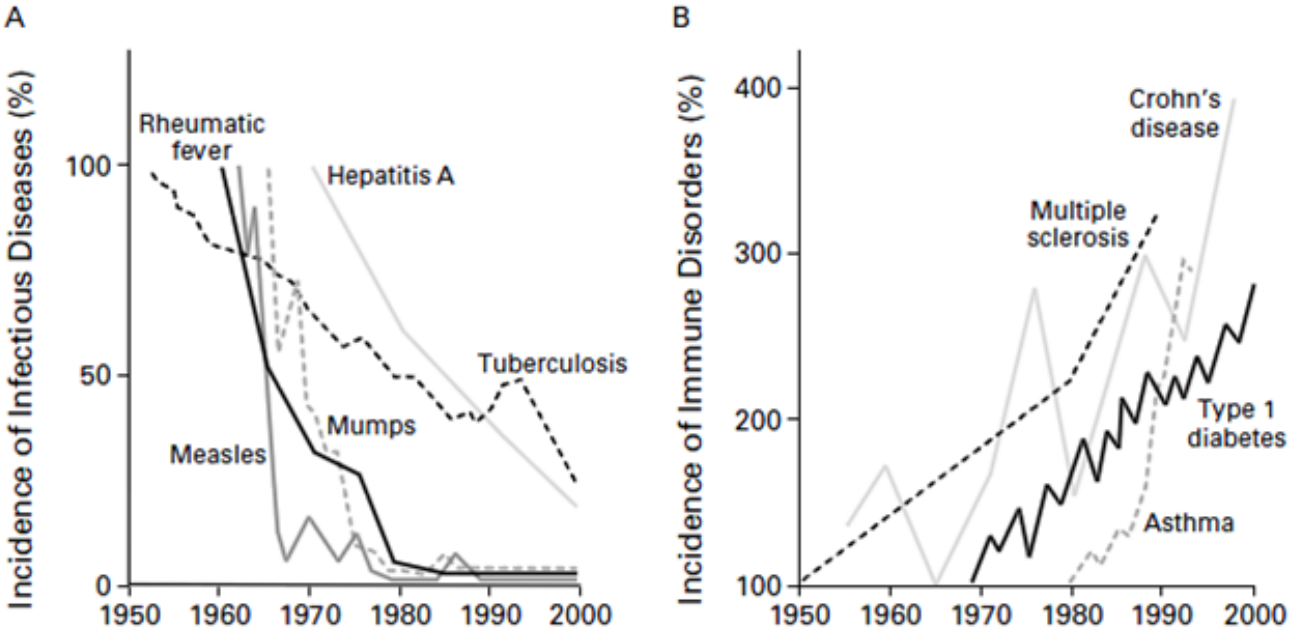
Environmental Factors

Clinic Outcome

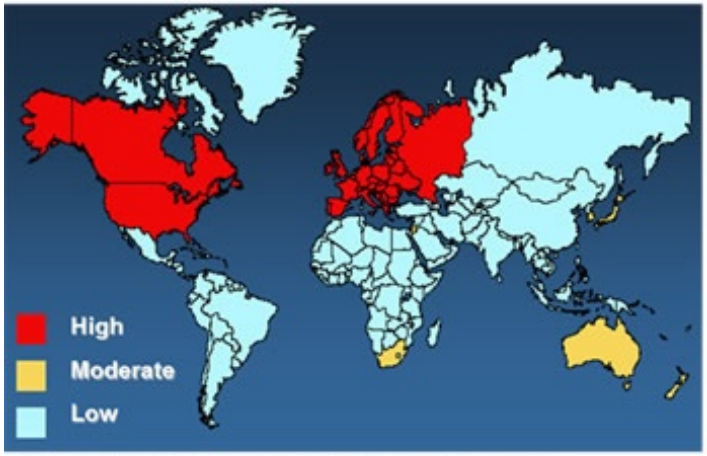


Microbiome

The Epidemics of Immune-Mediated Diseases In The Western Hemisphere: The Hygiene Hypothesis



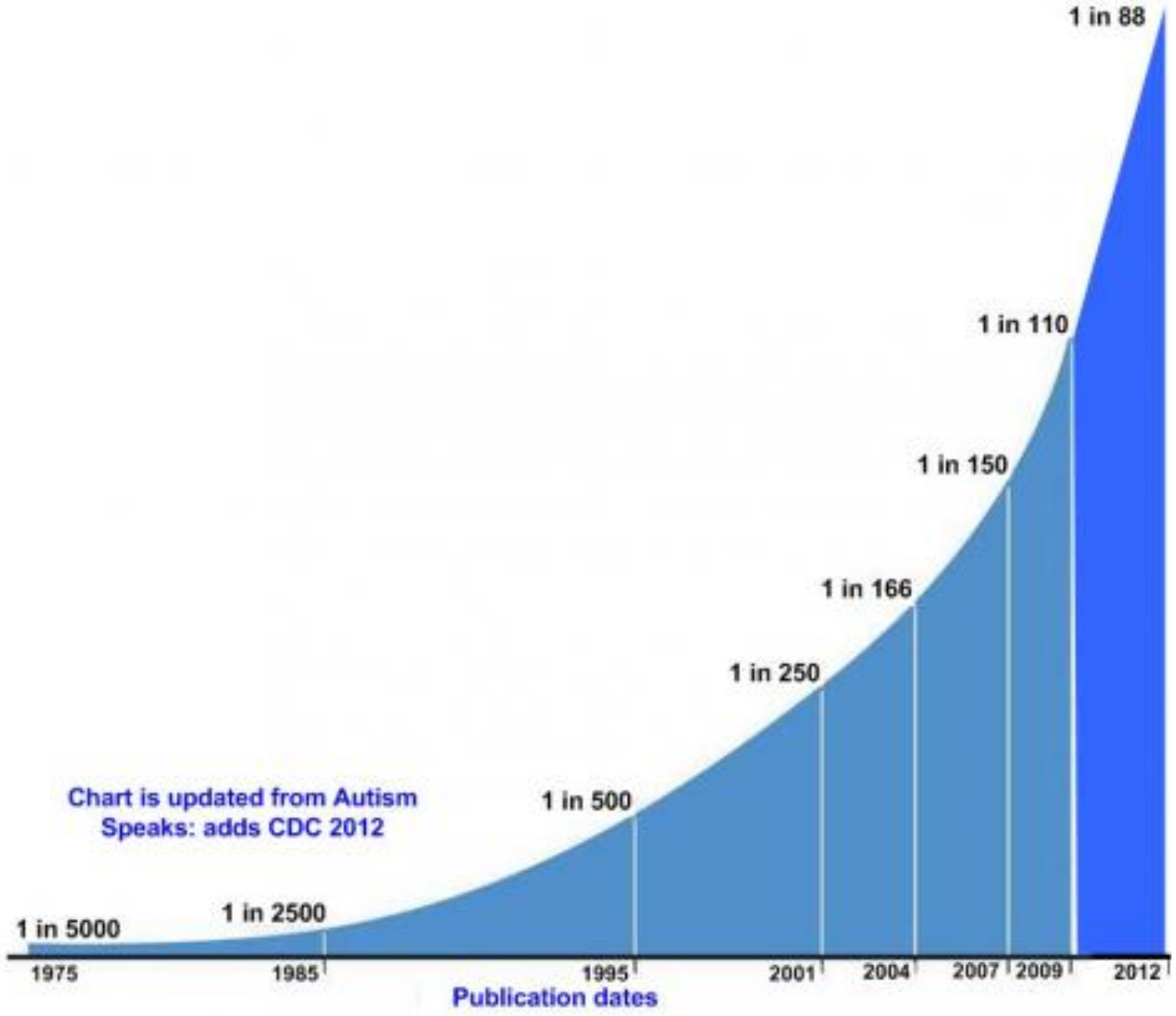
Autoimmune disorders incidence



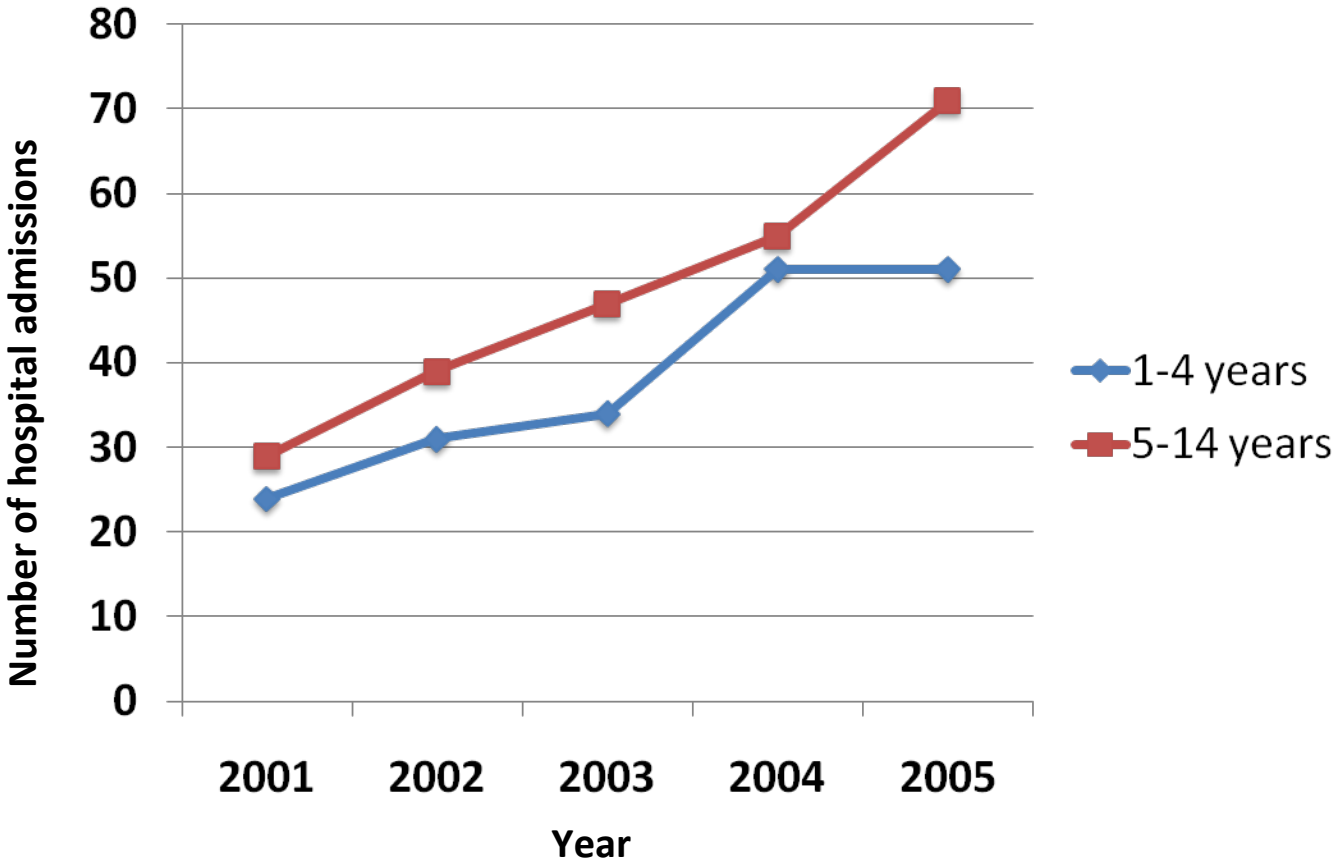
Helminths infestation incidence

Personal communication from Dr. Joel Weinstock

Autoimmunity Epidemics: Autism



Food anaphylaxis in Italy

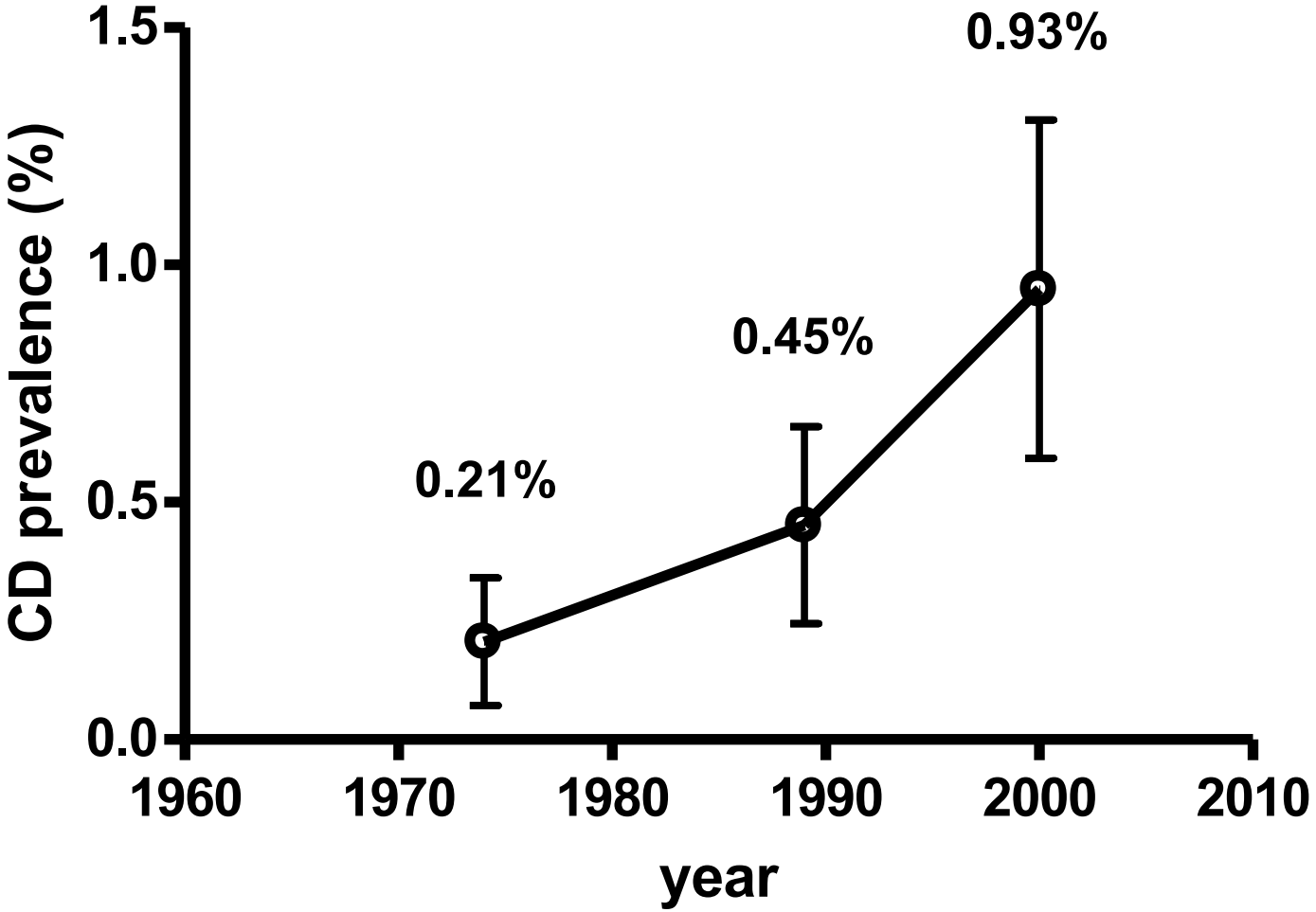


42% CMA

Ministry of Health, Health planning, essential levels of care and ethical principles of the system - Office VI. http://www.salute.gov.it/ricoveriOspedalieri/ric_informazioni/sceltadia.jsp.

Berni Canani R et al. Clin Exp Allergy 2012

Autoimmunity Epidemics: Celiac Disease

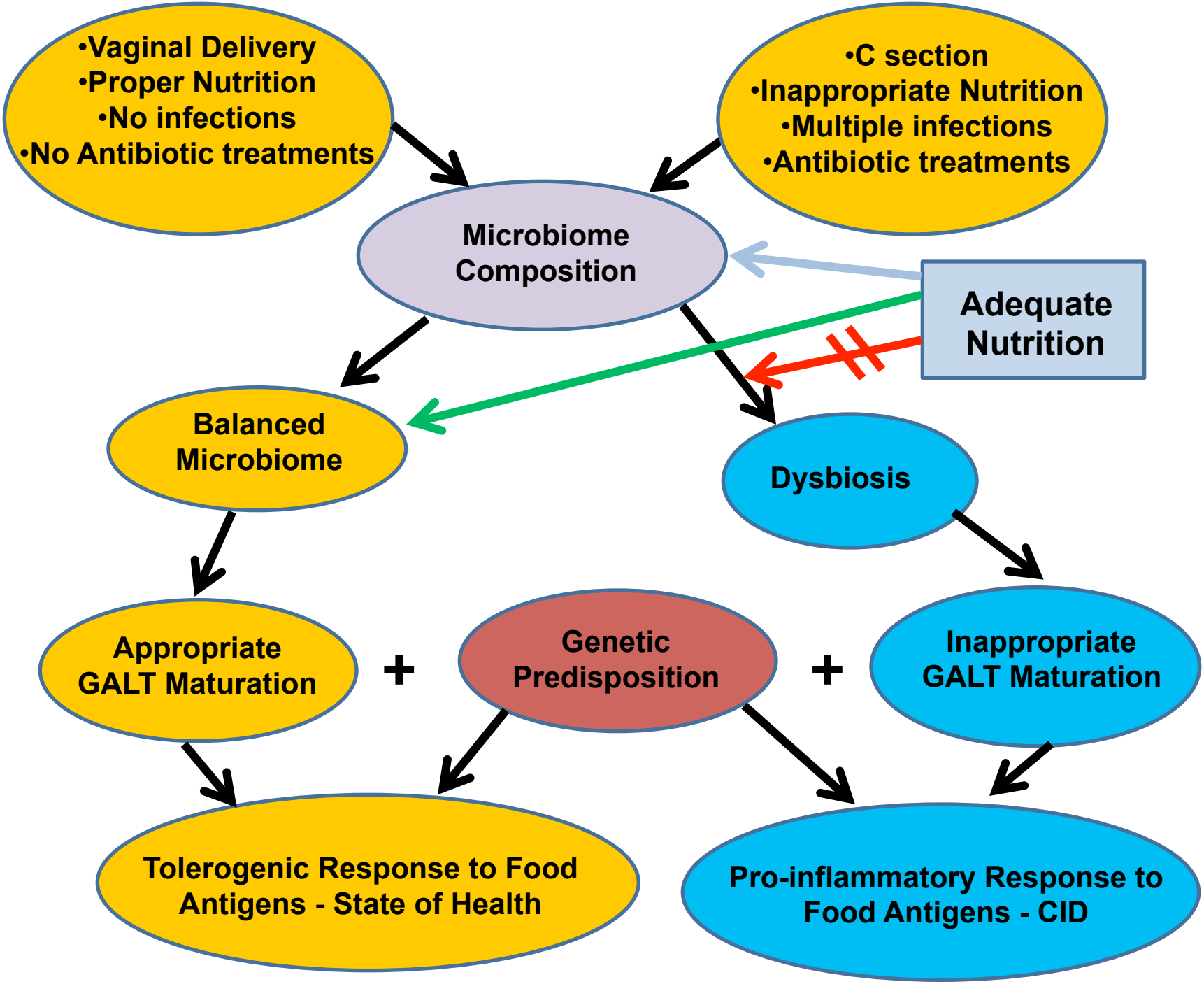


During the past 35 years the true prevalence of CD in USA doubled every 15 years.

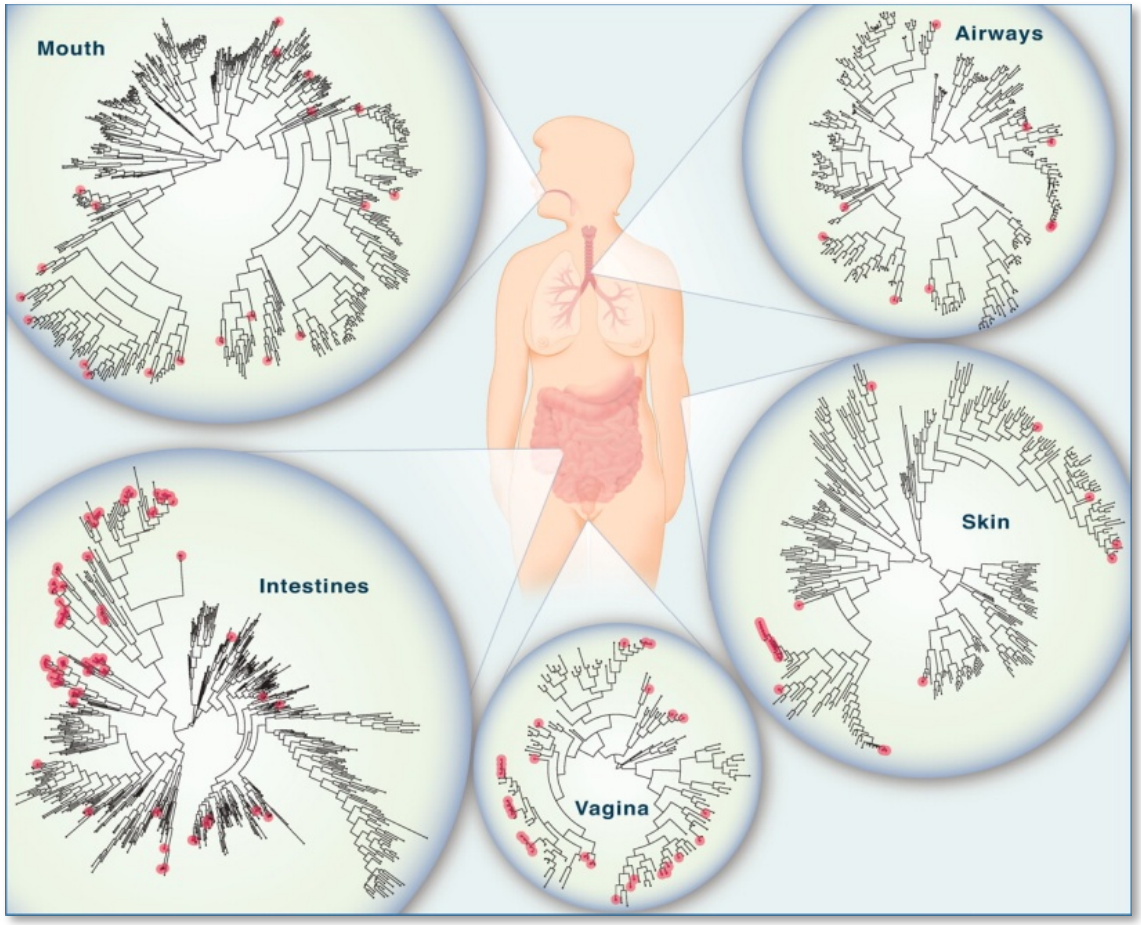
C. Catassi et al, Annal Med 2010;42:530-8.

The Hygiene Hypothesis Has Been Recently Questioned

Improved Hygiene In Some Developing Countries Was Not Paralleled by Increased Immune-Mediated Diseases


•Vaginal Delivery
•Proper Nutrition
•No infections
•No Antibiotic treatments
•C section
•Inappropriate Nutrition
•Multiple infections
•Antibiotic treatments
Microbiome Composition
Adequate Nutrition
Balanced Microbiome
Dysbiosis
Appropriate GALT Maturation
+
Genetic Predisposition
+
Inappropriate GALT Maturation
Tolerogenic Response to Food Antigens - State of Health
Pro-inflammatory Response to Food Antigens - CID

The human microbiome



- The human gut harbors 10^{11}-10^{12} bacteria per gram colonic content (>10^{14} total bacteria)
- Total bacteria outnumber human cells 10:1
- Total bacterial genes outnumber human genes >150:1
- >10,000 different species of bacteria are resident in the human intestinal microbiota (400-500 per person)

Lee & Mazmanian, *Science* (2010)

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PLoS one

Proof of Concept of Microbiome-Metabolome Analysis and Delayed Gluten Exposure on Celiac Disease Autoimmunity in Genetically At-Risk Infants

Maria Sellitto[1¤], Guoyun Bai[2], Gloria Serena[1], W. Florian Fricke[2], Craig Sturgeon[1], Pawel Gajer[2], James R. White[2], Sara S. K. Koenig[2], Joyce Sakamoto[2], Dustin Boothe[1], Rachel Gicquelais[1], Deborah Kryszak[1], Elaine Puppa[1], Carlo Catassi[1,3], Jacques Ravel[2]*, Alessio Fasano[1]*

1 Mucosal Biology Research Center, Center for Celiac Research and Departments of Pediatrics, Medicine and Physiology, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, **2** Institute for Genome Sciences and Department of Microbiology and Immunology, University of Maryland School of Medicine, Baltimore, Maryland, United States of America, **3** Department of Pediatrics, Università Politecnica delle Marche, Ancona, Italy

Abstract

Celiac disease (CD) is a unique autoimmune disorder in which the genetic factors (DQ2/DQ8) and the environmental trigger (gluten) are known and necessary but not sufficient for its development. Other environmental components contributing to CD are poorly understood. Studies suggest that aspects of gluten intake might influence the risk of CD occurrence and timing of its onset, i.e., the amount and quality of ingested gluten, together with the pattern of infant feeding and the age at which gluten is introduced in the diet. In this study, we hypothesize that the intestinal microbiota as a whole rather than specific infections dictates the switch from tolerance to immune response in genetically susceptible individuals. Using a sample of infants genetically at risk of CD, we characterized the longitudinal changes in the microbial communities that colonize infants from birth to 24 months and the impact of two patterns of gluten introduction (early vs. late) on the gut microbiota and metabolome, and the switch from gluten tolerance to immune response, including onset of CD autoimmunity. We show that infants genetically susceptible to CD who are exposed to gluten early mount an immune

The Real Story of Our Genetic Complexity:

We Inherit two Parallel Genomes

Human Genome:

Inherited from both parents, stable, never change in its composition

Microbiome:

Inherited from the mother, extremely dynamic, changes from individual to individual and in the same individual over time

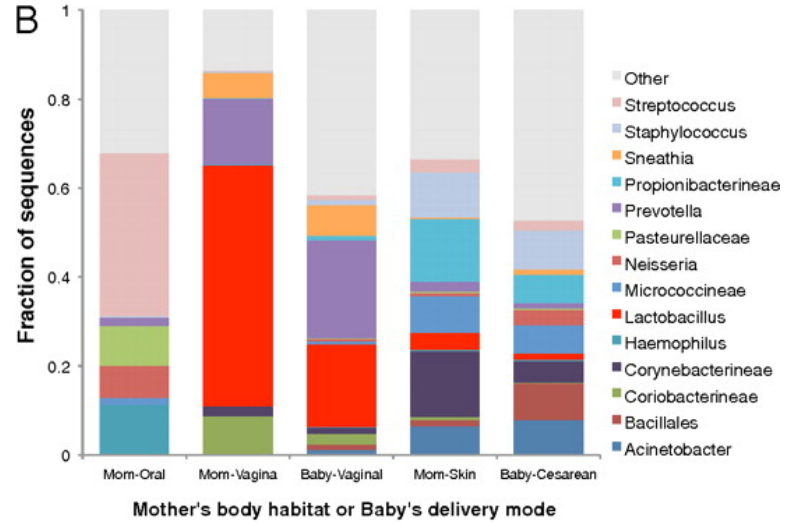
Higher Risk of Celiac Disease After Elective Cesarean Delivery

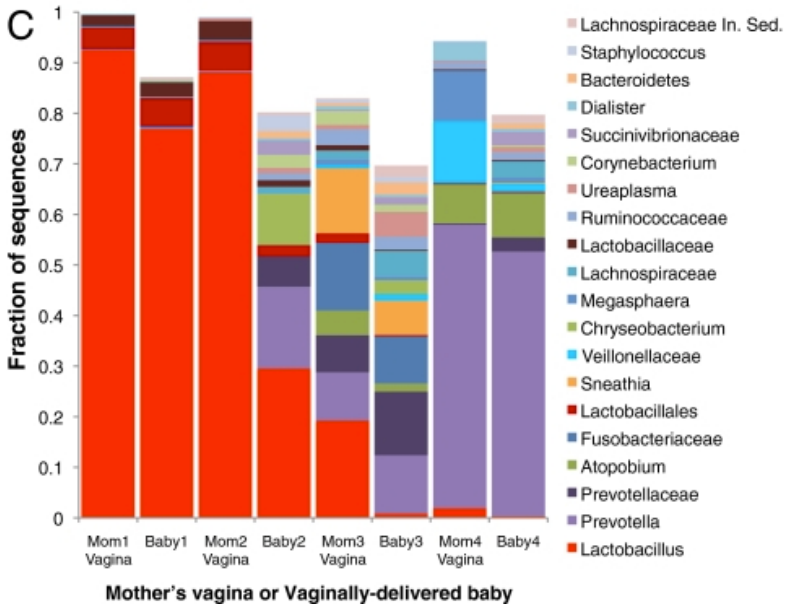
Risk of celiac disease after cesarean delivery.

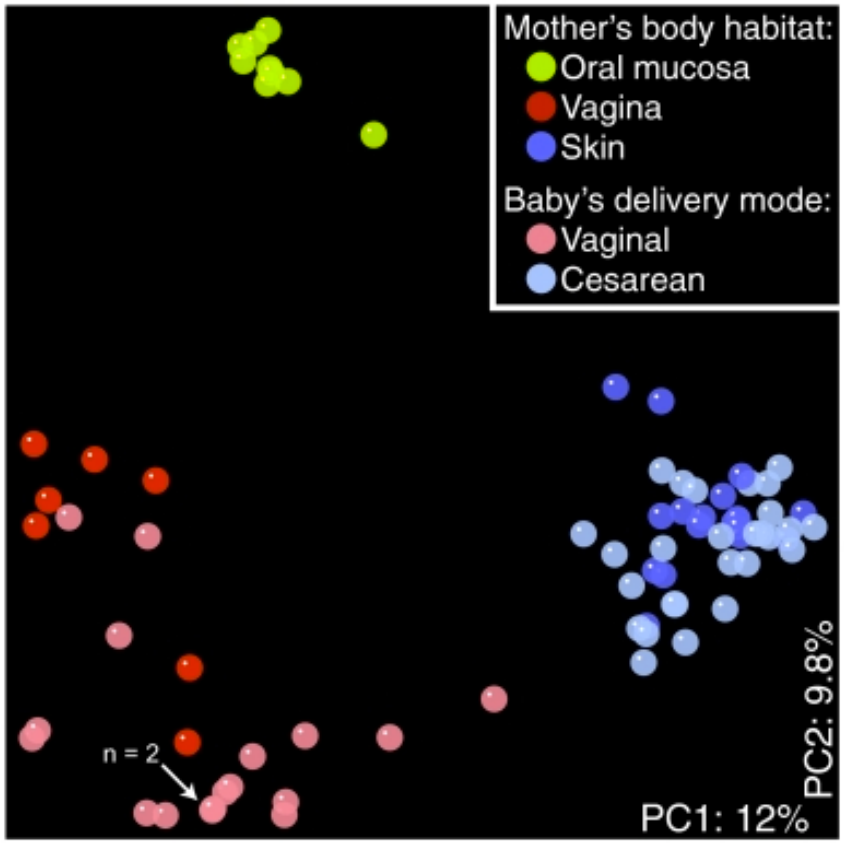
	Matched controls (%)	Celiac disease (%)	Odds ratio; 95% CI OR	P-value	Adjusted odds ratio*, 95% CI AOR	P-value
Cesarean delivery	5,766/53,887 (10.7)	1,299/11,749 (11.1)	1.04; 0.98-1.10	0.232	1.06; 0.99-1.13	0.074
Number of participants			65,636		65,493	
Emergency cesarean delivery †	2,136/41,699 (5.1)	444/8,827 (5.0)	0.99; 0.90-1.10	0.857	1.02; 0.92-1.13	0.749
Number of participants			50,526		50,415	
Elective cesarean delivery †	2,125/41,688 (5.1)	508/8,891 (5.7)	1.11; 1.01-1.22	0.027	1.15; 1.04-1.26	0.005
Number of participants			50,579		50,471	

Mårild et al *Gastroenterology* 2012;*142*(1):39

Infants intestinal microbiome is influenced by mode of delivery







Dominguez-Bello et al *PNAS* 2010;107(26):11971-5

Microbiome
(140-fold Human Genome)
Dynamic

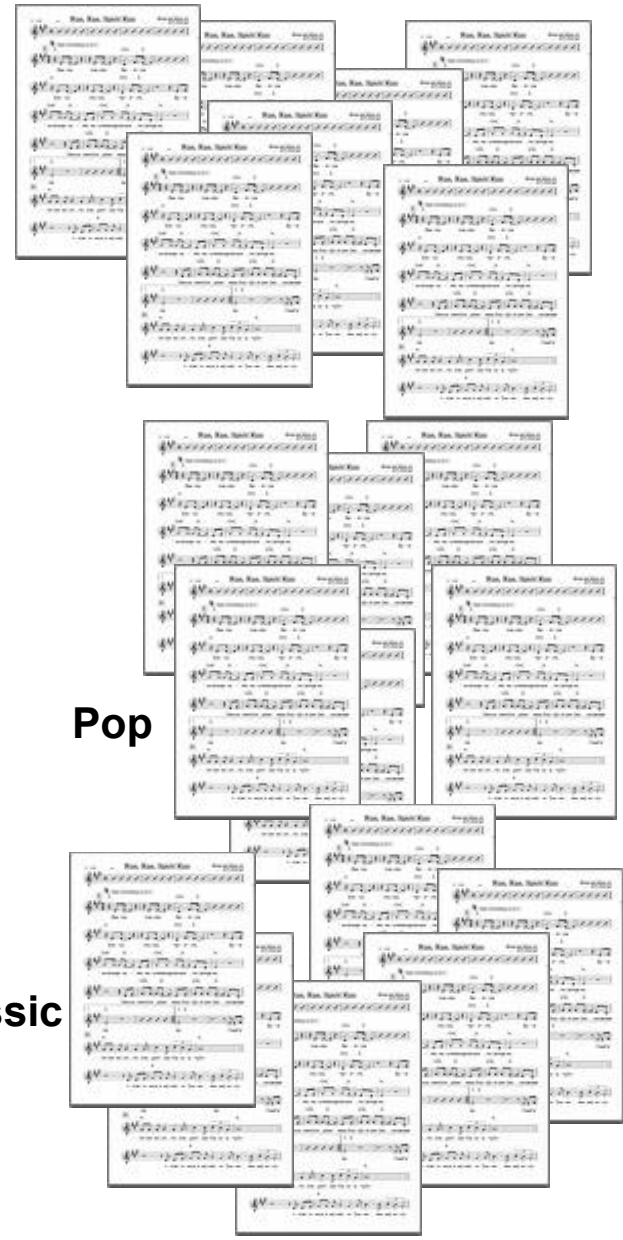
Human Genome
(~30,000 genes)
Stable

Metabonome

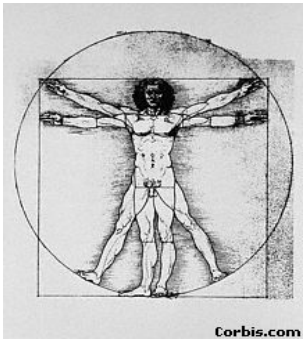
Jazz

Pop

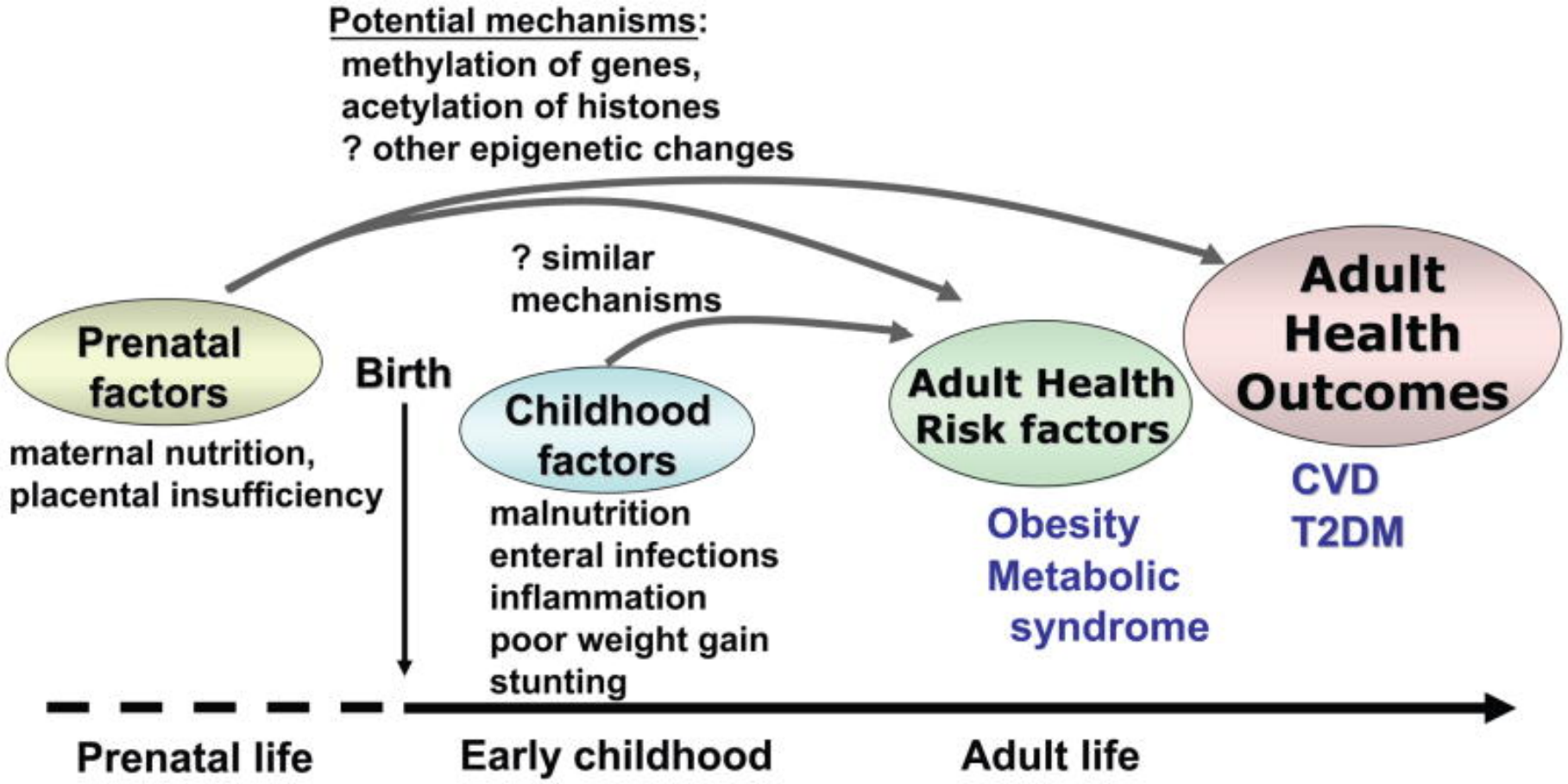
Classic

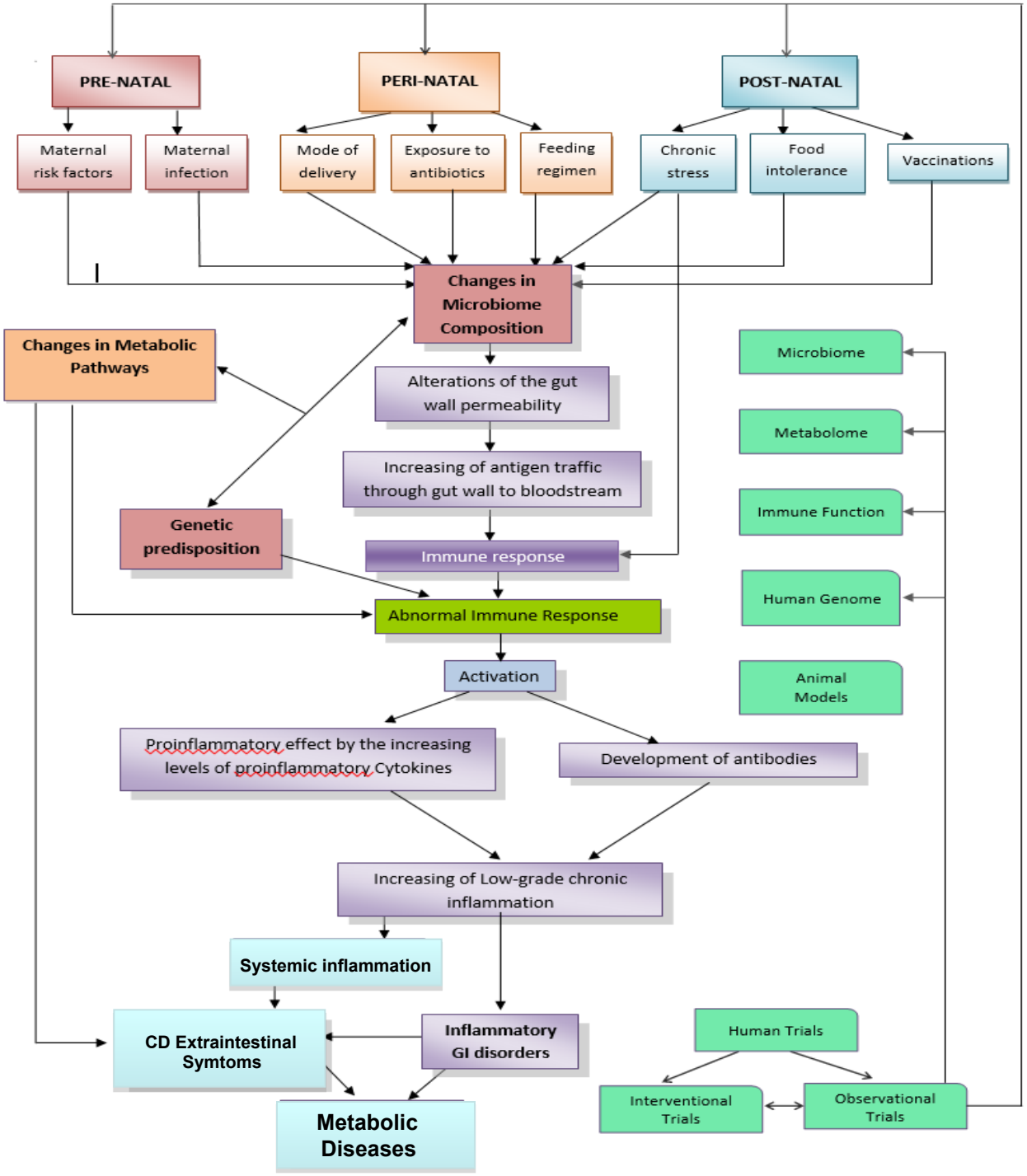


Clinical Outcome



Model for the Effects of Early Childhood Nutrition on Adult Health




PRE-NATAL
PERI-NATAL
POST-NATAL
Maternal risk factors
Maternal infection
Mode of delivery
Exposure to antibiotics
Feeding regimen
Chronic stress
Food intolerance
Vaccinations
Changes in Microbiome Composition
Changes in Metabolic Pathways
Alterations of the gut wall permeability
Increasing of antigen traffic through gut wall to bloodstream
Genetic predisposition
Immune response
Abnormal Immune Response
Activation
Proinflammatory effect by the increasing levels of proinflammatory Cytokines
Development of antibodies
Increasing of Low-grade chronic inflammation
Systemic inflammation
CD Extraintestinal Symtoms
Inflammatory GI disorders
Metabolic Diseases
Microbiome
Metabolome
Immune Function
Human Genome
Animal Models
Human Trials
Interventional Trials
Observational Trials

Celiac **D**isease **G**enomic **E**nvironmental **M**icrobiome and **M**etabolomic Study

www.CDGEMM.org

Hypothesis

Combination of introduction of gluten into the diet and particular microbiota composition of infants genetically at risk for CD activates specific metabolic pathways that can contribute to the loss of tolerance to gluten and to the onset of autoimmunity, as reflected by specific metabolomic phenotypes