

GUT FEELINGS
The Microbiome and Our Health
ALESSIO FASANO
SUSIE FLAHERTY

The Intestinal Microbiome And The Developing Immune System.

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1

The Epidemics of Chronic Inflammatory Diseases (CID) In The Western Hemisphere: The Hygiene Hypothesis

A

Autoimmune disorders incidence

B

Helminths infestation incidence


Personal communication from Dr. Joel Weinstock

2

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Pathogenesis CID

We May Be “Predisposed”, but Are Not Born “Destined” to Develop Chronic Inflammatory Diseases



MGH 1881

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The Yin and Yang Between Tolerance and Immune Response Leading To CID

Human Genome

Environmental Factors

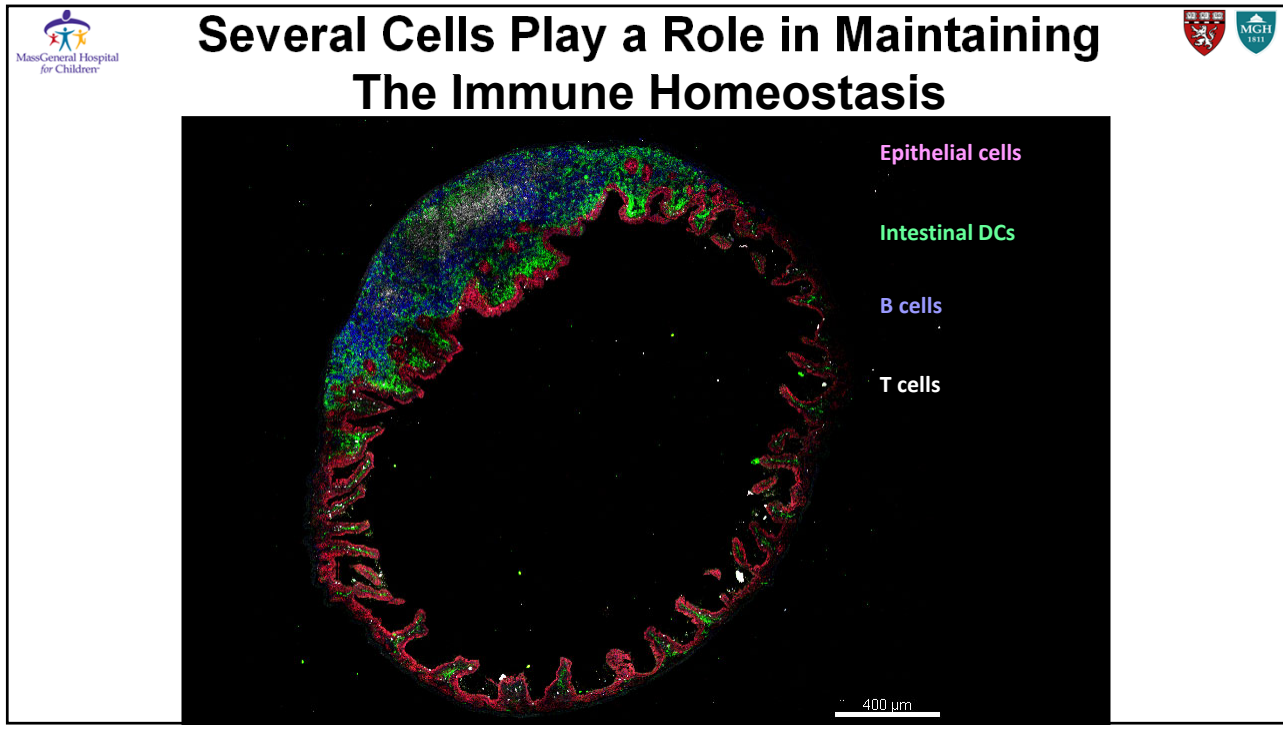
Increased Gut Permeability

Immune Response

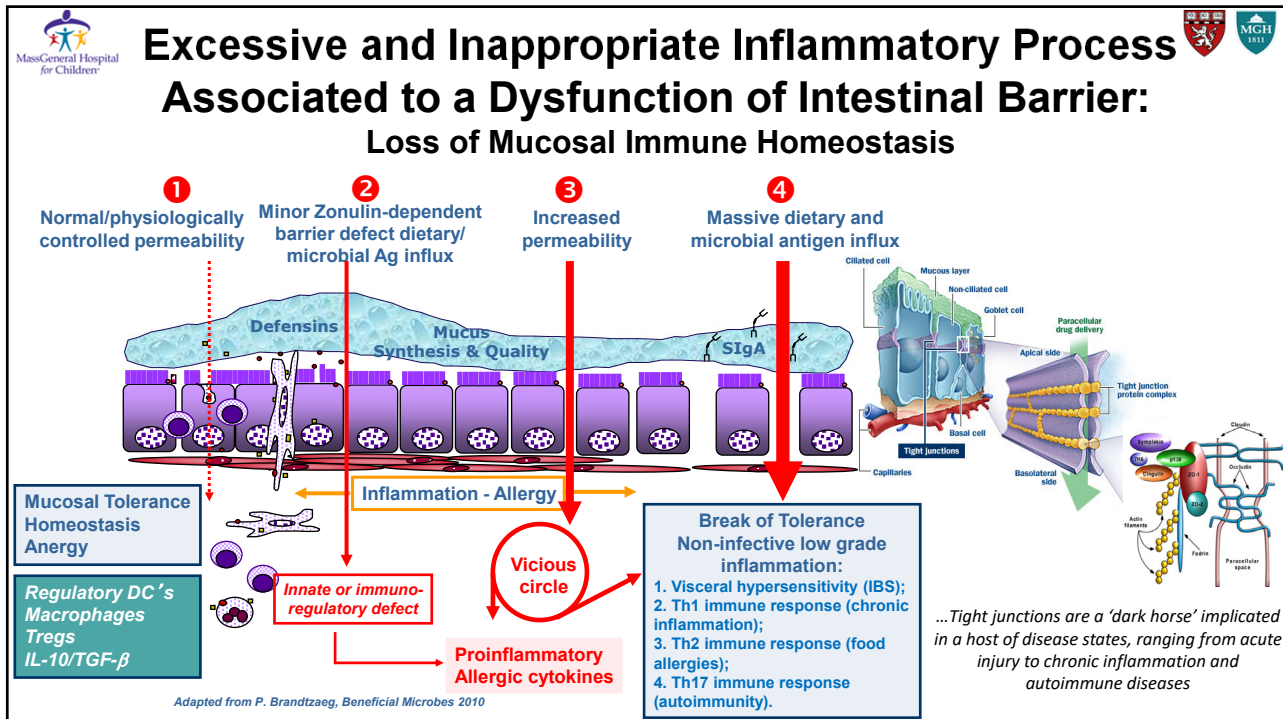
Microbiome

Clinic Outcome

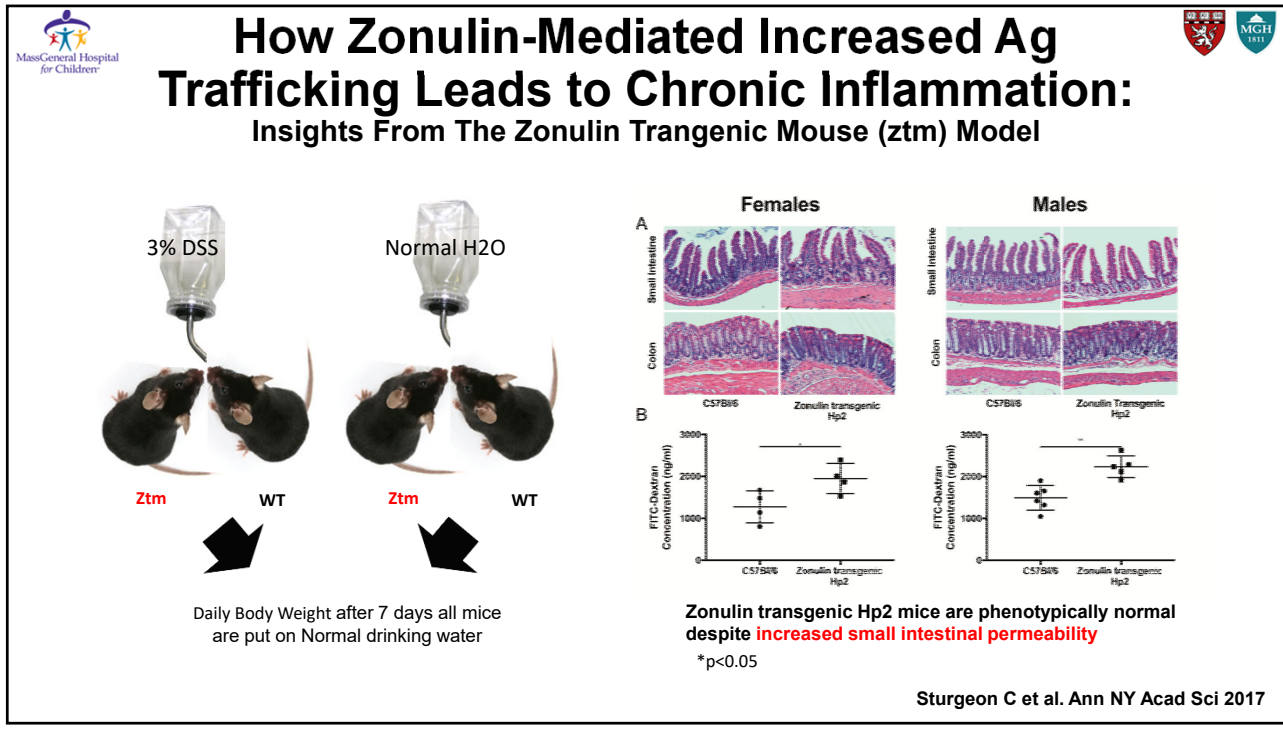
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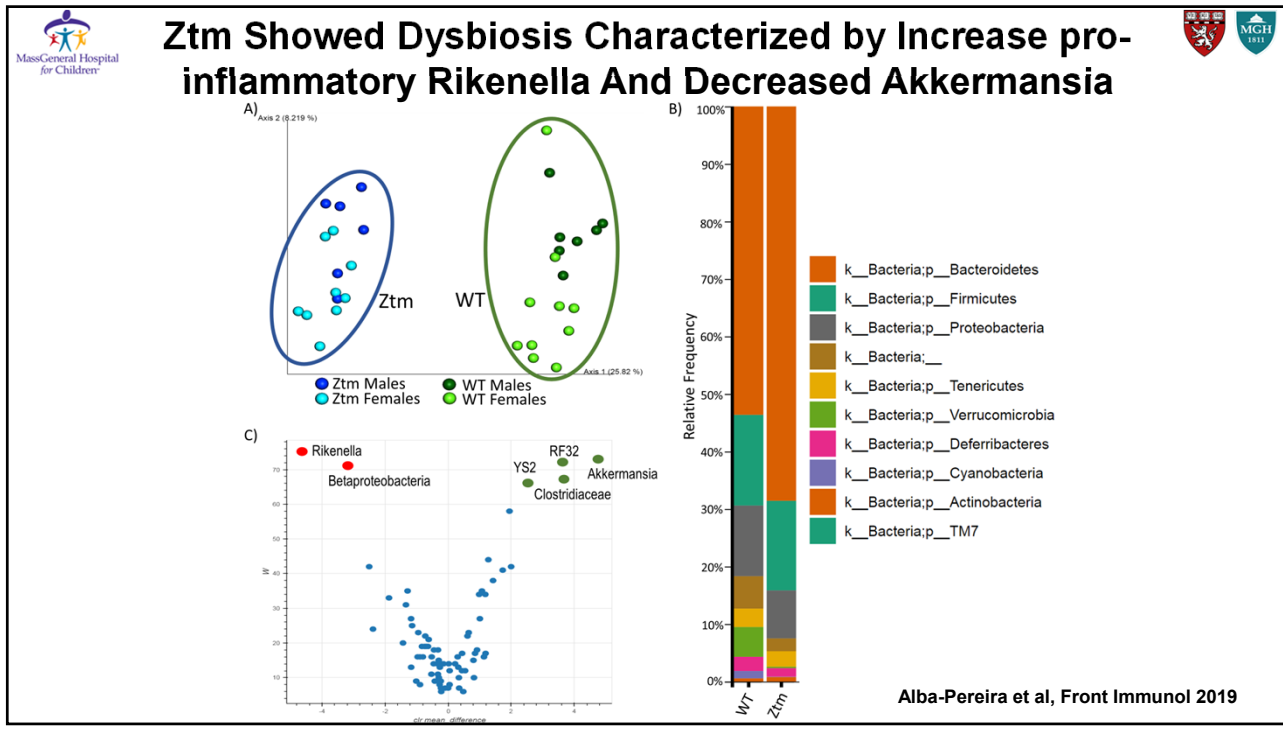
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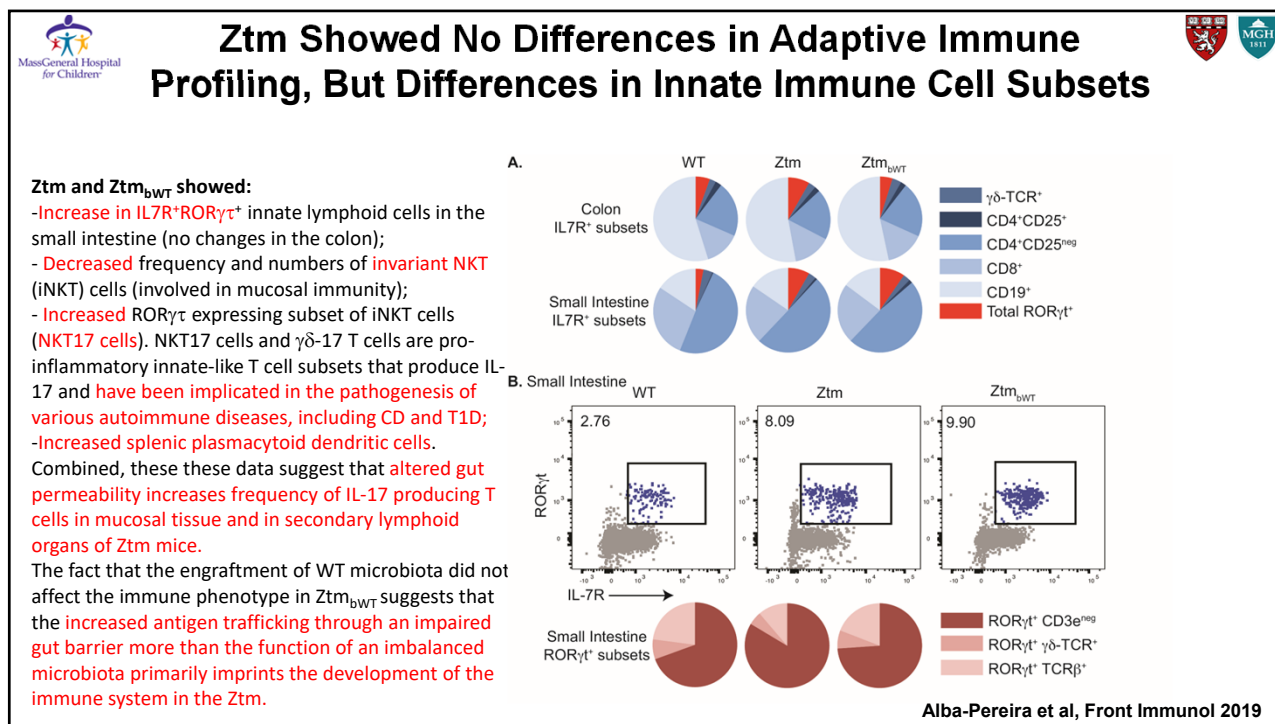
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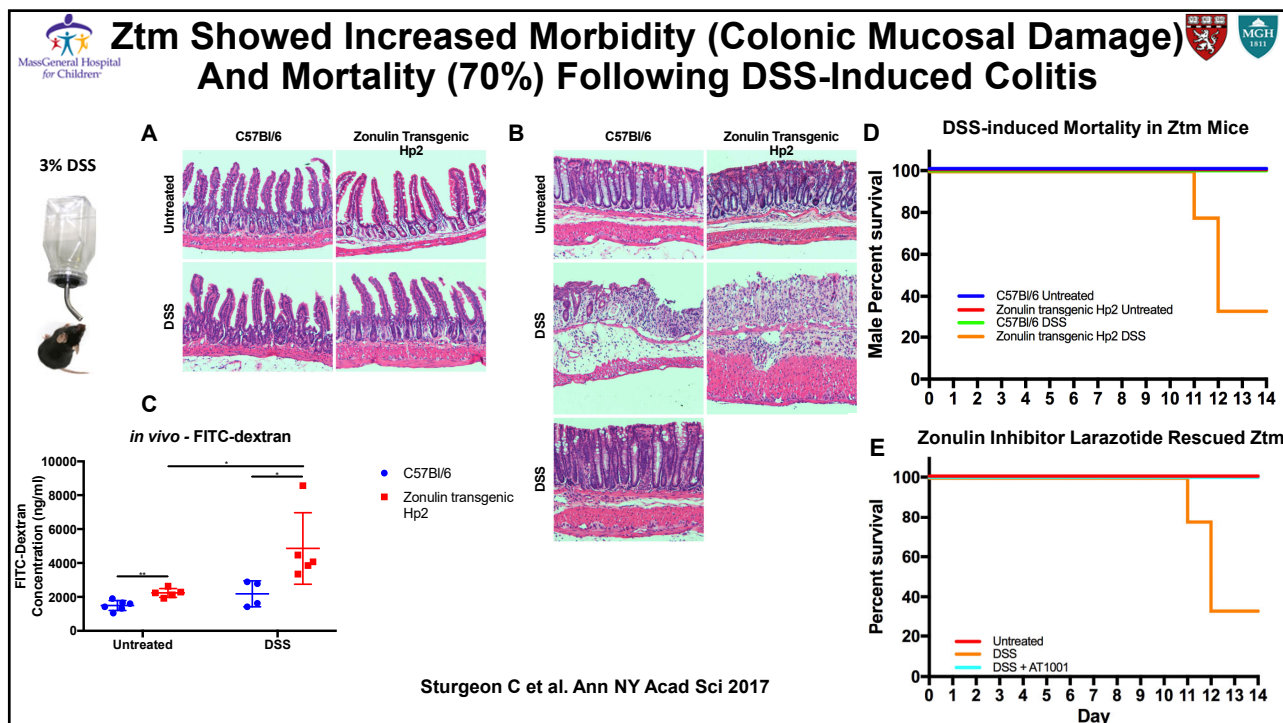
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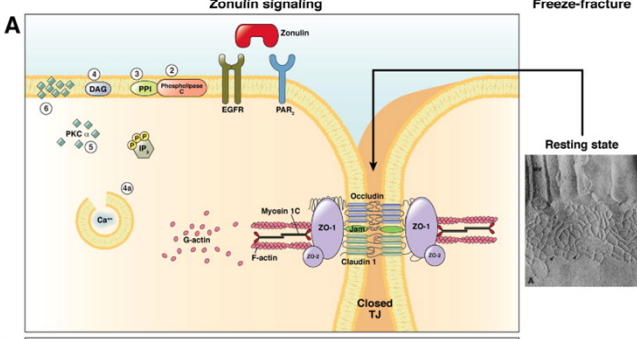
10



Literature Report On Zonulin Association With CID



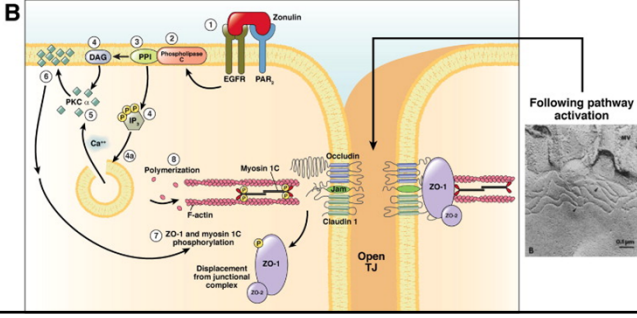
Disease	Model	Zonulin Shown to be Involved
ADHD	Human	YES
Aging	Human	YES
Ankylosis spondylitis	Human	YES
Autism	Human	YES
Bipolar Disorders	Human	YES
Celiac Disease	Human	YES
Colitis/IBD (Crohn's disease)	Human	YES
Colitis	Mouse	YES
Depressive Disorders	Human	YES
Fe metabolism in heart transplant	Human	NO
Glioma	Human	YES
Glioma	Cell	YES
Irritable bowel syndrome	Human	YES
HIV	Human	YES
Multiple sclerosis	Mouse	YES
Necrotizing Enterocolitis (NEC)	Rat	YES
Nonalcoholic fatty liver disease	Human	YES
Non-Celiac Gluten Sensitivity	Human	YES
Obesity/Insulin resistance	Human	YES
Post-surgery Sepsis	Human	YES
Post-surgery Sepsis	Mouse	YES
Psoriasis	Human	NO
Sepsis	Human	YES
Type 1 diabetes	Human	YES
Type 2 diabetes	Human	YES



Zonulin signaling

Freeze-fracture

Resting state



Following pathway activation

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The Changing Face Of Gut Microbes





ASTROPHYSICS
Antimatter-Sparked SUPERNOVAE

NEUROSCIENCE
Building a MACHINE BRAIN

PHYSICS
The Rough Road to FUSION ENERGY

SCIENTIFIC AMERICAN

July 2012

Your Inner Ecosystem

In your body, bacteria outnumber your own cells 10 to 1. Who's in control?

MOBILISM.ORG



nature

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

First results from the Human Microbiome Project highlight the healthy variation in our microbial selves

PAGES 194, 207 & 215

FELLOW TRAVELLERS

FEELING THE PRESSURE
The quest for a comprehensive genetic blueprint

GET USED TO UNCERTAINTY
Climate modelling faces its limits

TITAN'S ELUSIVE METHANE
Trophic links on Saturn's hydrocarbon moon?

NATURE.COM/NATURE

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The Microbiome Is Essential To Health

100 TRILLION


The human microbiome is made up of more than 100 trillion bacteria, fungi, protozoa, and viruses that live in and on the human body
 >10,000 different species of bacteria are resident in the human intestinal microbiota (400-500/person)

2-5x More

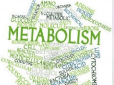
Microbial cells than human cells and the majority live in our gut

150x More

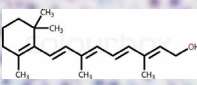
Genes than the human genome




Energy From Food




Regulates Metabolism




Producing Essential Vitamins



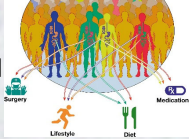
Regulate Immune System



Protection from pathogenic bacteria

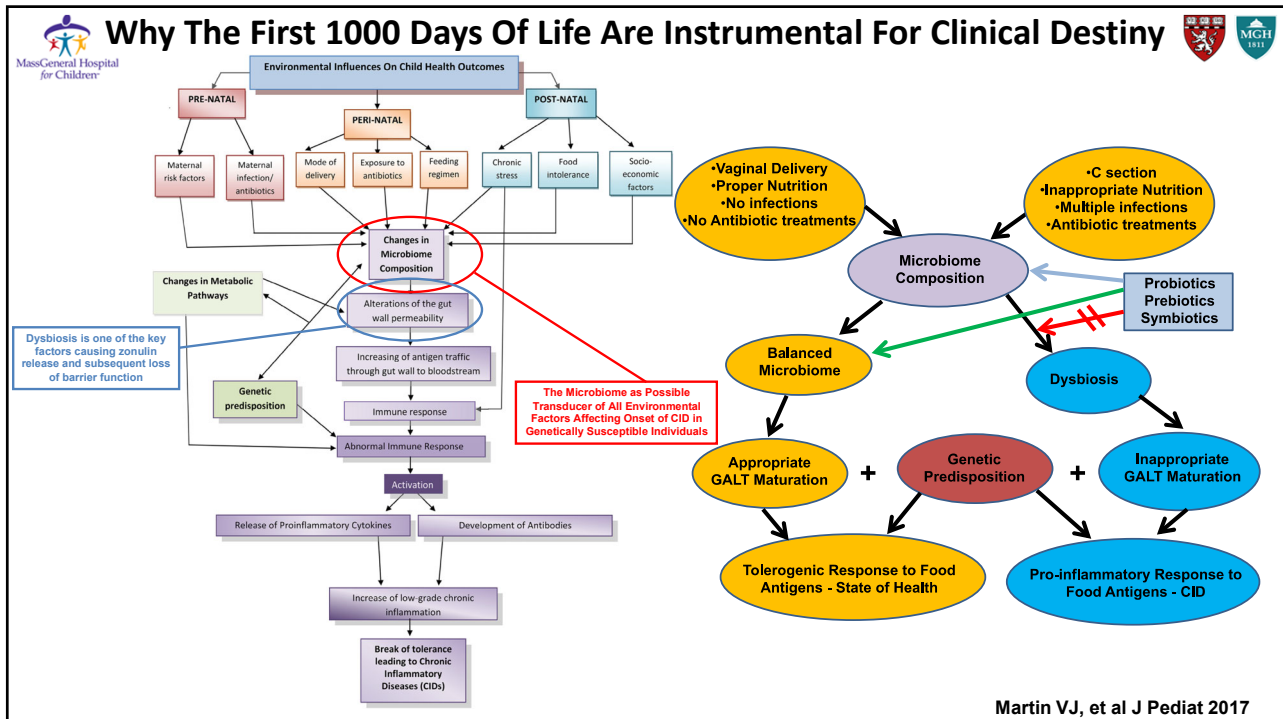


Symbiotic



Personalized

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Role of Breastmilk

Maternal Milk:
 Antigen
 Free
 Complexed to IgA
 Complexed to IgG
 Tolerogenic immune mediators
 TGF- β , IL10, Vit A, ...
 Microbiota modulating factors
 Prebiotics (oligosaccharides, glycoproteins)
 Antimicrobial (lysozyme, lactoferrin, IgA, ...)
 Gut growth factors (EGF, TGF- β , ...)

Impact of human milk glycomiome on the infant intestinal microbiota

Component	Concentration (g/L)	Percentage
Lactose	70	20%
Lipids	40	17%
Proteins	8	11%
HMO	5-15	8%
Other	23%	3%
1585.6	5%	4%
1877.7	4%	3%
2096.7	3%	3%
1731.6	6%	3%
1074.4	8%	3%
1366.5	11%	1%
1511.6	3%	1%
855.3	1%	1%
709.3	17%	20%
1220.4	20%	

<http://www.nature.com>

Zivkovic AM, et al. *PNAS* 2011;108: 4653-58

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Cycle of Microbiota Transmission

Interferences

Interference	Impact
Antibiotics	Taken by girl and boy, gravid woman, prepartum and postpartum, infant
C-section	Baby does not go through birth canal
Washing of skin with antibacterials	Intrapartum, baby (vernix), baby, girls, women
Oral ingestion of antibacterials	Children, women, men


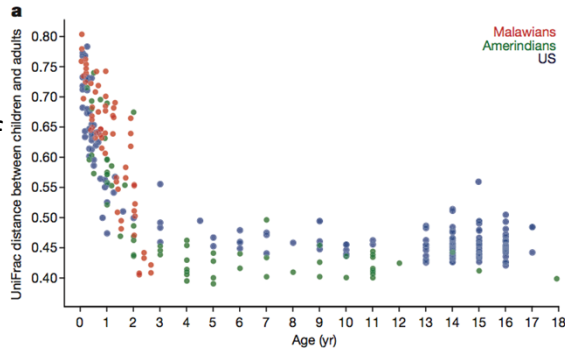
Dominguez-Bello et al Science Trans Med 2015;7:307-39
Fischbach et al Cell 2016;164:1288-1300

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Baby's first bacteria

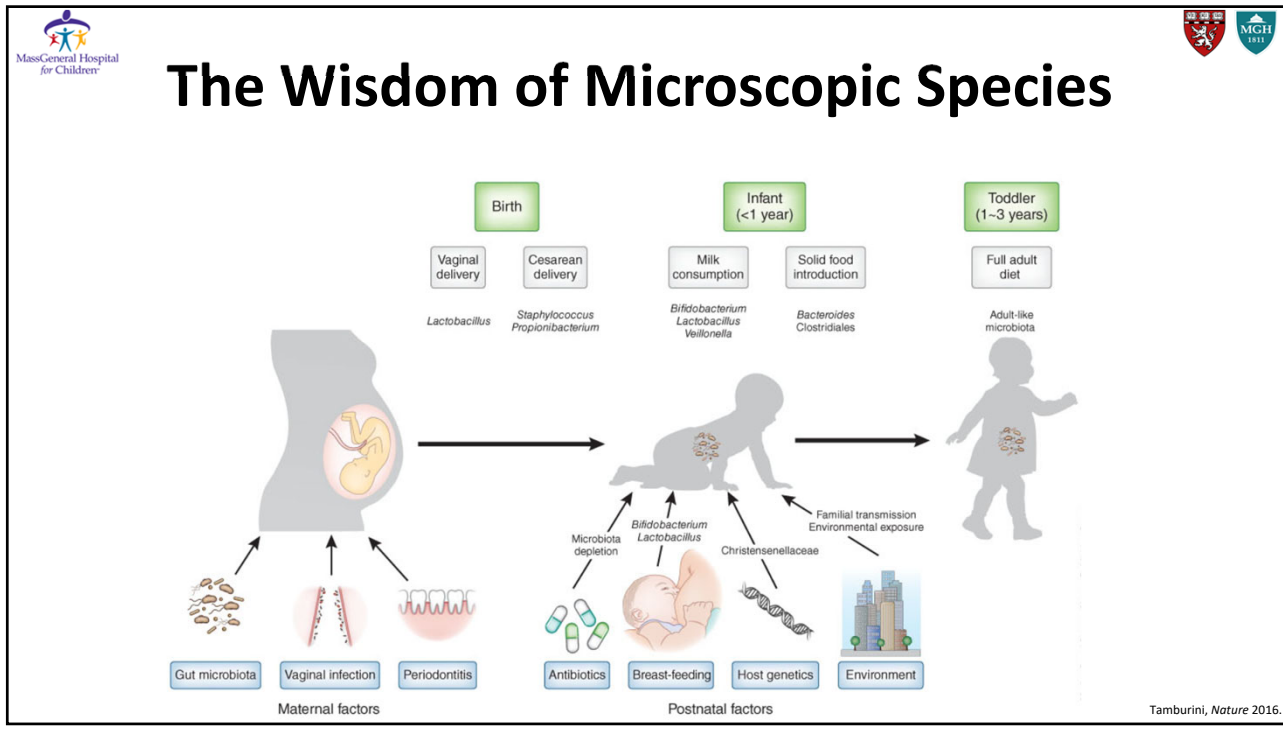
THE WOMB WAS THOUGHT TO BE STERILE. SOME SCIENTISTS ARGUE IT'S WHERE THE MICROBIOME BEGINS.

- Exactly when an infant is first exposed to microbes is still under debate
- Largest microbial transfer occurs at birth
- Microbial colonization of the newborn intestine contributes to the development of the host's immune function
- The first 1-3 years of an infant's microbiome development is characterized by chaotic and dramatic shifts until stabilization at approximately age 3

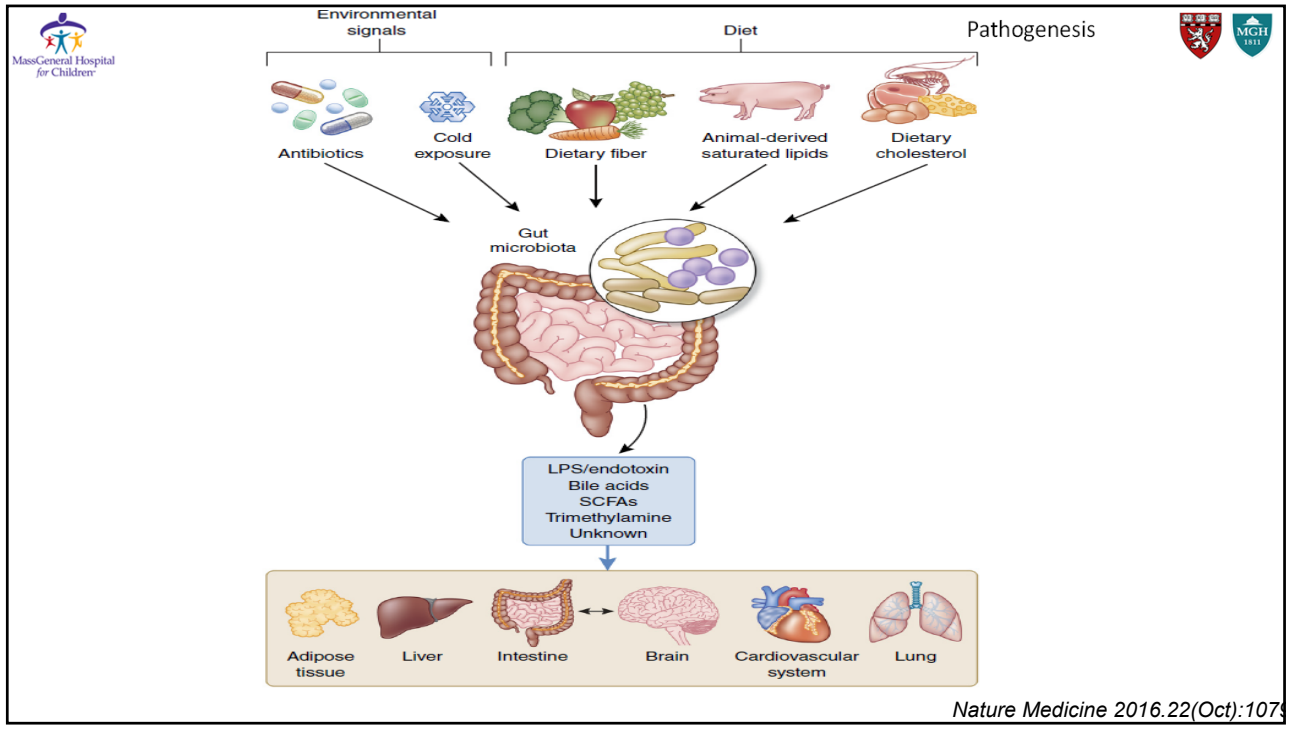
Nature, News Feature 1/18/2018
Yatsunenکو, Nature ,2012

17

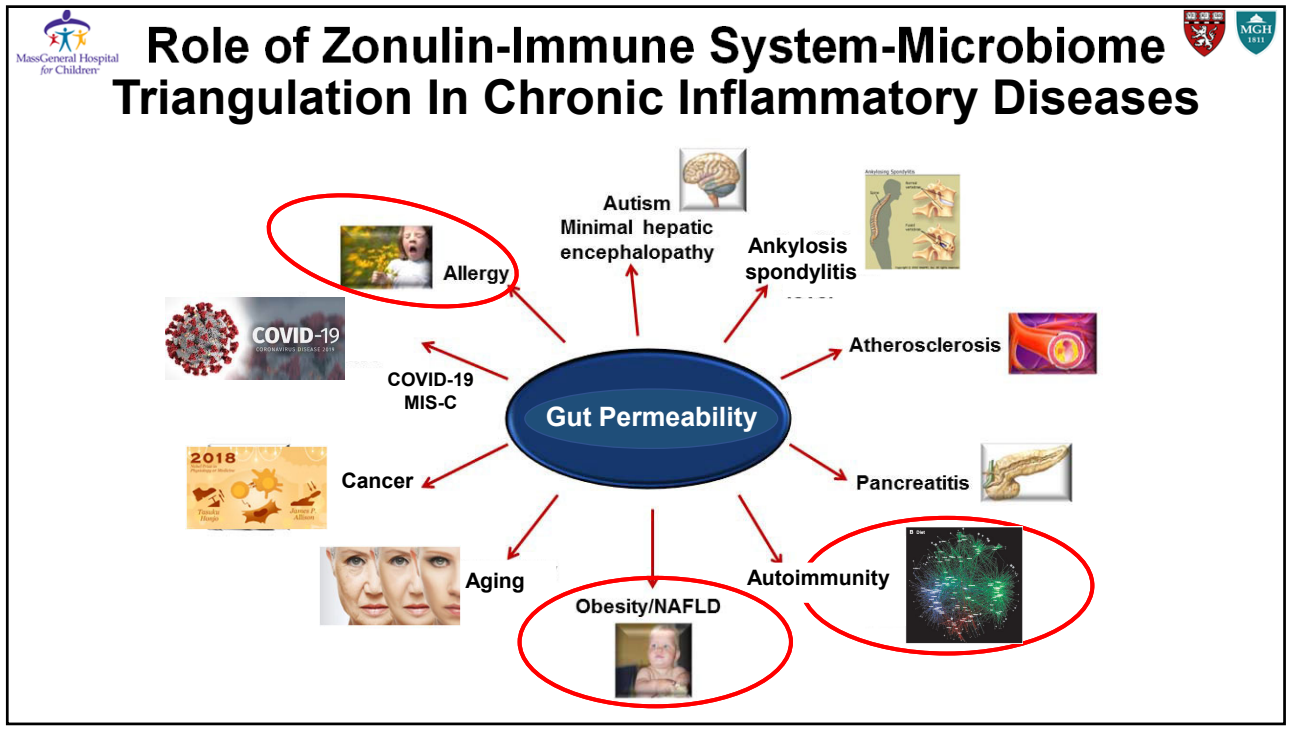


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The Intestinal Microbiome and the Developing Immune System



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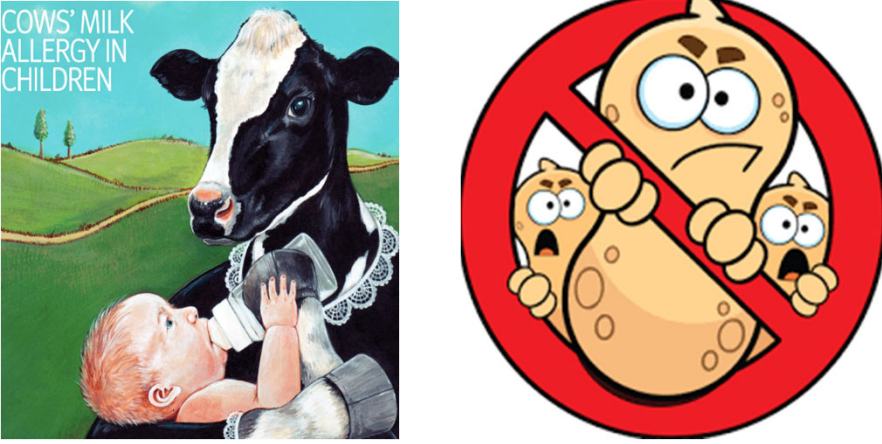


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Food Allergies



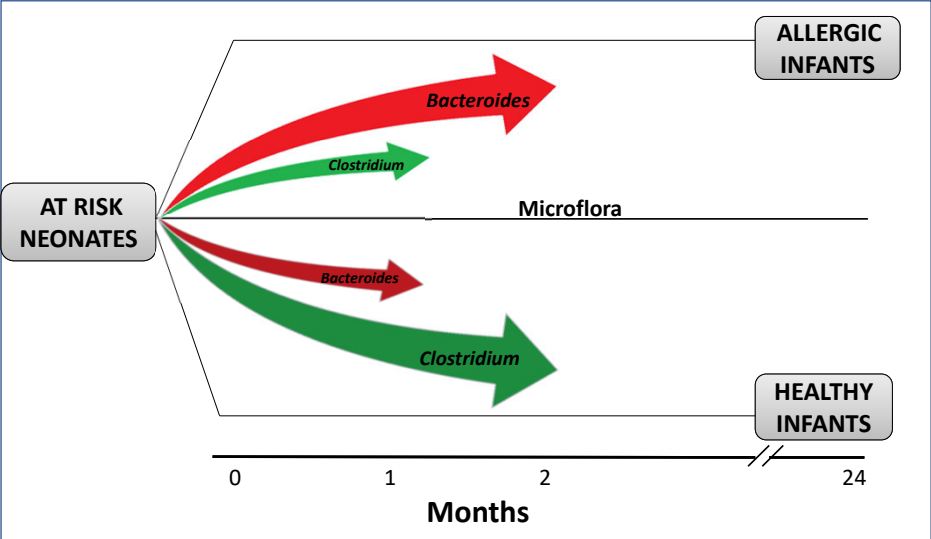
COWS' MILK ALLERGY IN CHILDREN

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Gut Dysbiosis Correlates With Allergy Development



AT RISK NEONATES

ALLERGIC INFANTS

HEALTHY INFANTS

Microflora

Bacteroides

Clostridium

Months

0 1 2 24

Nakayama OC, et al. FEMS Immunol Med Microbiol 2011

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MassGeneral Hospital for Children | OPEN ACCESS Freely available online | PLOS one | MGH 1811

Lactobacillus casei Abundance Is Associated with Profound Shifts in the Infant Gut Microbiome

Michael J. Cox^{1,3}, Yvonne J. Huang^{2,3}, Kei E. Fujimura¹, Jane T. Liu², Michelle McKean³, Homer A. Boushey², Mark R. Segal⁴, Eoin L. Brodie⁵, Michael D. Cabana^{2,3}, Susan V. Lynch^{1*}

16S rRNA PhyloC₂p
High-density, culture-independent microarray that can identify ~8,500 bacterial taxa

Restoring Microbial Health
Lactobacillus GG (LGG) restores the normal microflora composition in infants with CMA

Change in Abundance
Phyla
 Gammaproteobacteria
 Betaproteobacteria
 Alphaproteobacteria
 Epsilonproteobacteria
 Bacteroidetes
 Delephyloproteobacteria
 Actinobacteria
 Cyanobacteria
 Firmicutes
 Planctomycetes
 Verrucomicrobia
 Lentisphaera
 Chloroflexi
 Spirochaetes
 Gemmatimonadetes
 Acidobacteria
 Other Phyla
 -0.01

January 2010 | Volume 5 | Issue 1 | e8745

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MassGeneral Hospital for Children | THE JOURNAL OF Allergy AND Clinical Immunology | MGH 1811

LGG Accelerates CMA Recovery

Months	EHCf (%)	EHCf + LGG (%)
6 m	~20	~55
12 m	~60	~80

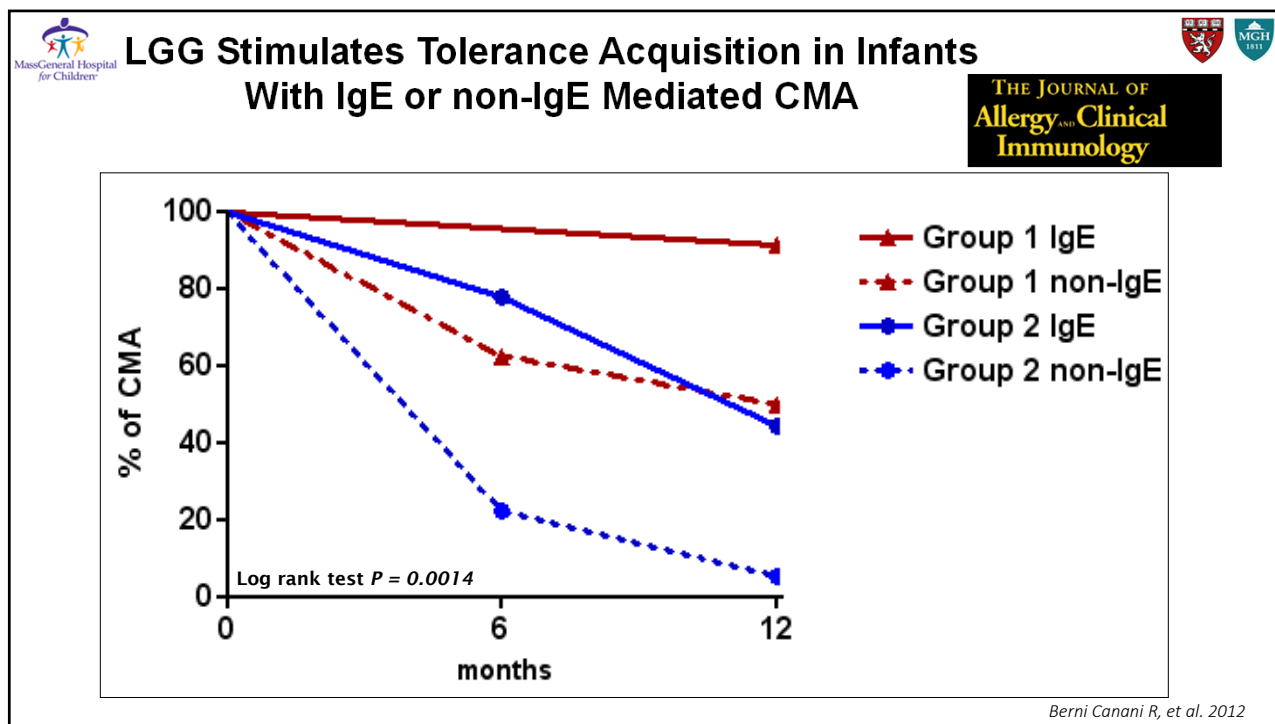
EHCf = extensively hydrolyzed casein formula

Berni Canani R, et al. 2012

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Slide 23

- 2 Fixed spelling of independent
Owner, 7/13/2012
- 1 Added abbreviation LGG for Lactobacillus GG since he uses it later.
Owner, 7/13/2012



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MassGeneral Hospital for Children | SCIENTIFIC REPORTS | MGH 1811

Corrected: Publisher Correction

OPEN Randomized controlled trial on the influence of dietary intervention on epigenetic mechanisms in children with cow's milk allergy: the EPICMA study

Received: 28 September 2018
Accepted: 9 January 2019
Published online: 26 February 2019

Lorella Paparo^{1,4}, Rita Nocerino^{1,4}, Cristina Bruno^{1,4}, Carmen Di Scala^{1,4}, Linda Cosenza¹, Giorgio Bedogni², Margherita Di Costanzo¹, Maurizio Mennini³, Valeria D'Argenio^{4,5,7}, Francesco Salvatore^{4,5,7} & Roberto Berni Canani^{1,4,6,7}


Epigenetic mechanisms could drive the disease course of cow's milk allergy (CMA) and formula choice could modulate these pathways. We compared the effect of two different dietary approaches on epigenetic mechanisms in CMA children. Randomized controlled trial on IgE-mediated CMA children receiving a 12-month treatment with extensively hydrolyzed casein formula containing the probiotic *L. rhamnosus* GG (EHCF + LGG) or with soy formula (SF). At the baseline, after 6 and 12 months of treatment *FoxP3* methylation rate and its expression in CD4⁺ T cells were assessed. At same study points IL-4, IL-5, IL-10, and IFN- γ methylation rate, expression and serum concentration, miRNAs expression were also investigated. 20 children (10/group) were evaluated. Baseline demographic, clinical and epigenetic features were similar in the two study groups. At 6 and 12 months, EHCF + LGG group showed a significant increase in *FoxP3* demethylation rate compared to SF group. At the same study points, EHCF + LGG group presented a higher increase in IL-4 and IL-5 and a higher reduction in IL-10 and IFN- γ DNA methylation rate compared to SF group. A different modulation of miR-155, -146a, -128 and -193a expression was observed in EHCF + LGG vs. SF. Dietary intervention could exert a different epigenetic modulation on the immune system in CMA children.

Key message:
EHCF+LGG induces a stronger modulation of epigenetic mechanisms associated with a trend toward higher rate of immune tolerance acquisition in children

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Obesity



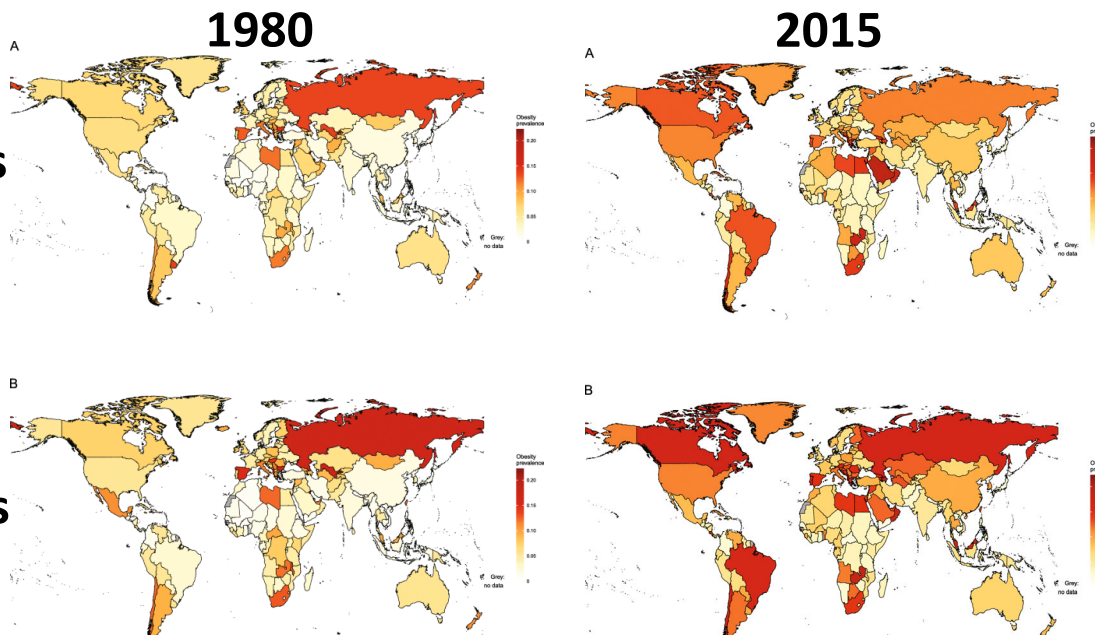
MGH 1811

This slide features the title "Obesity" in a large, bold, black font. In the top left corner is the logo for MassGeneral Hospital for Children, and in the top right corner is the MGH 1811 logo. The central focus is a photograph of a marble statue of a woman, which is significantly overweight, illustrating the concept of obesity. The statue is shown from the waist up, standing in a classical pose.

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Pediatric Obesity Epidemics



MGH 1811

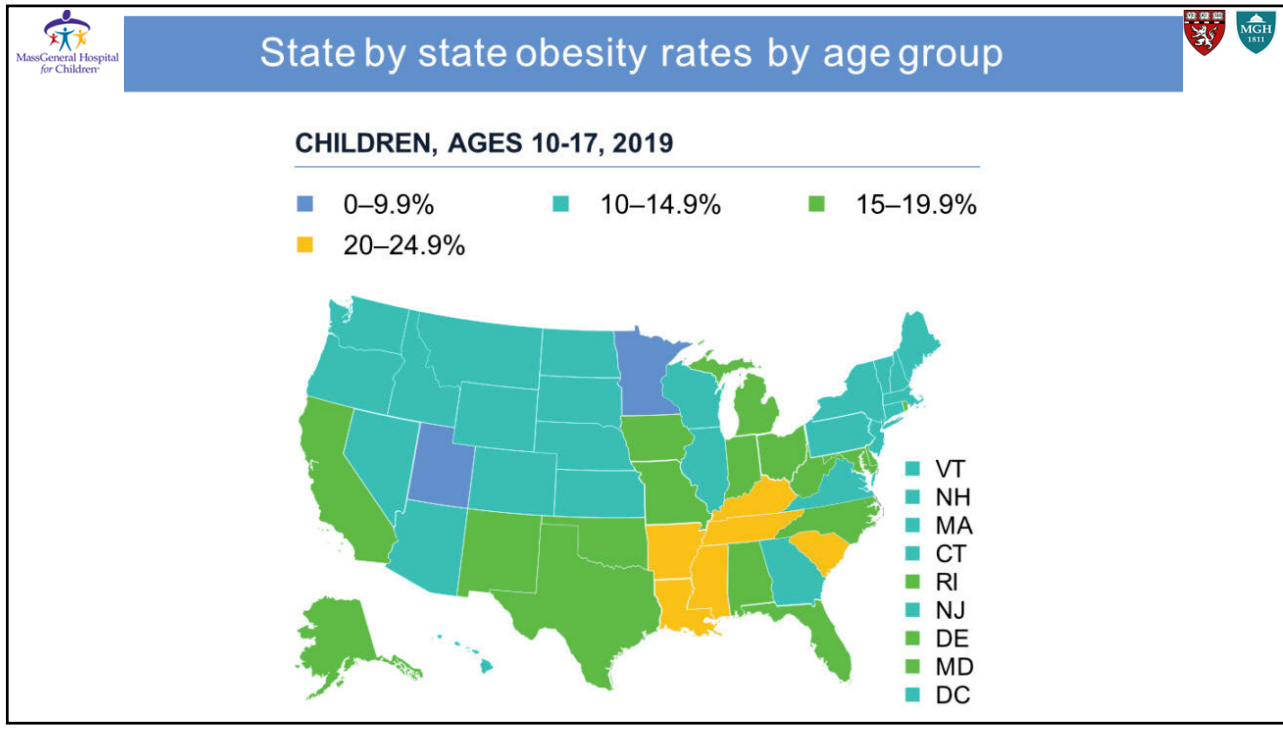
Girls

Boys

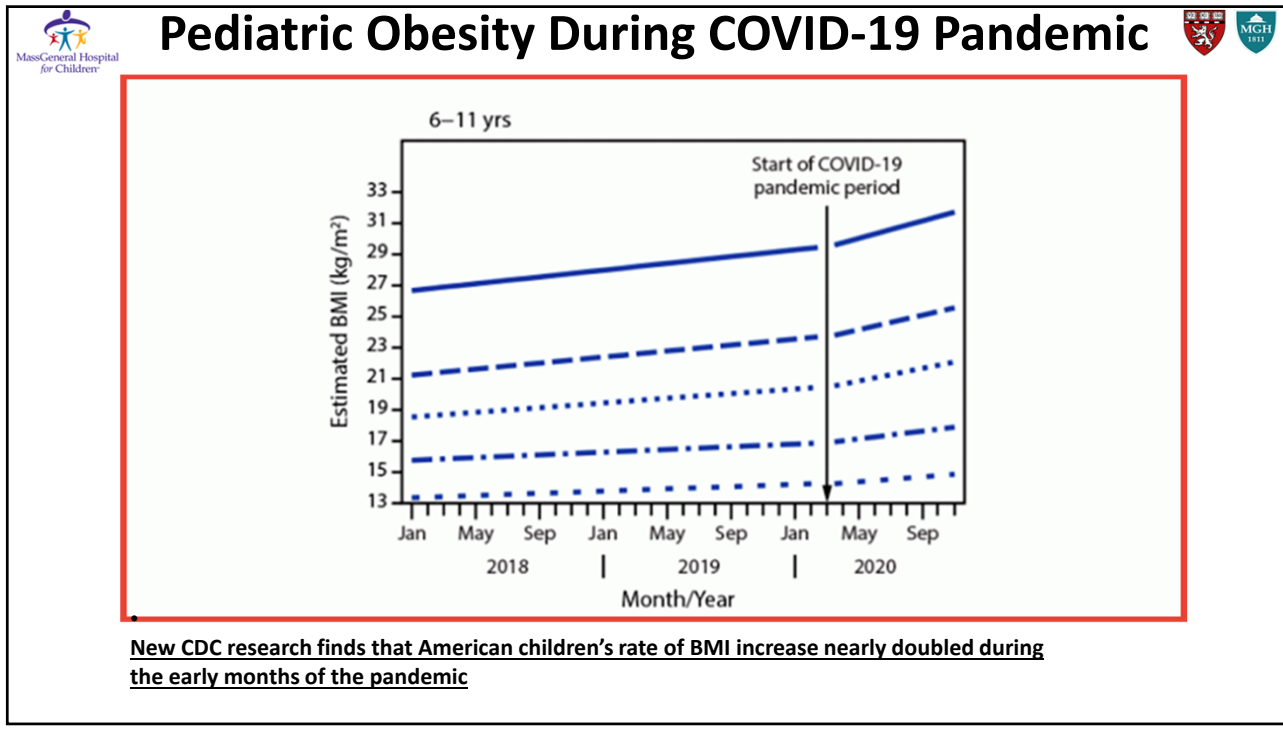
1980 **2015**

This slide is titled "Pediatric Obesity Epidemics" and contains four world maps arranged in a 2x2 grid. The top row is labeled "Girls" and the bottom row is labeled "Boys". The left column shows data for the year 1980, and the right column shows data for 2015. Each map is color-coded to represent the prevalence of obesity, with a legend on the right of each map showing a scale from 0 (yellow) to 0.20 (dark red). The maps show a clear increase in obesity prevalence across most regions, particularly in North America, Europe, and parts of Asia, between 1980 and 2015. The legend for each map includes the text "Obesity prevalence" and "if Grey no data".

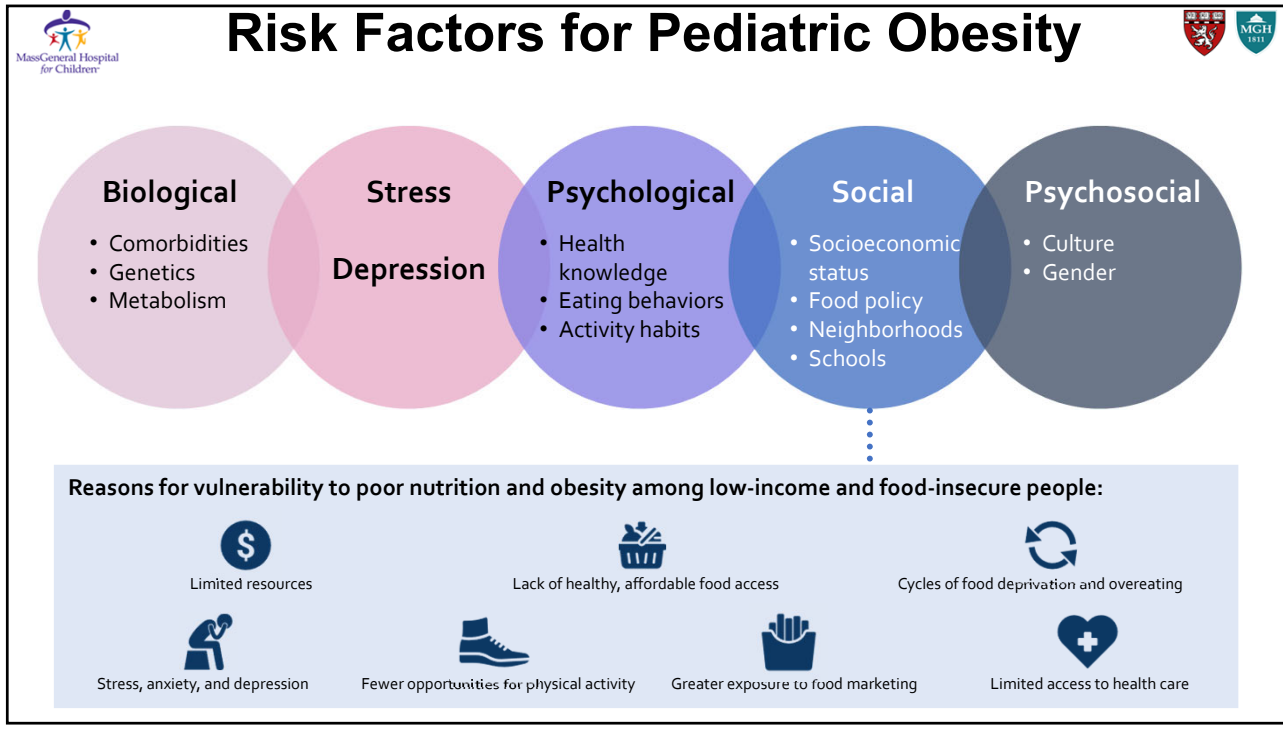
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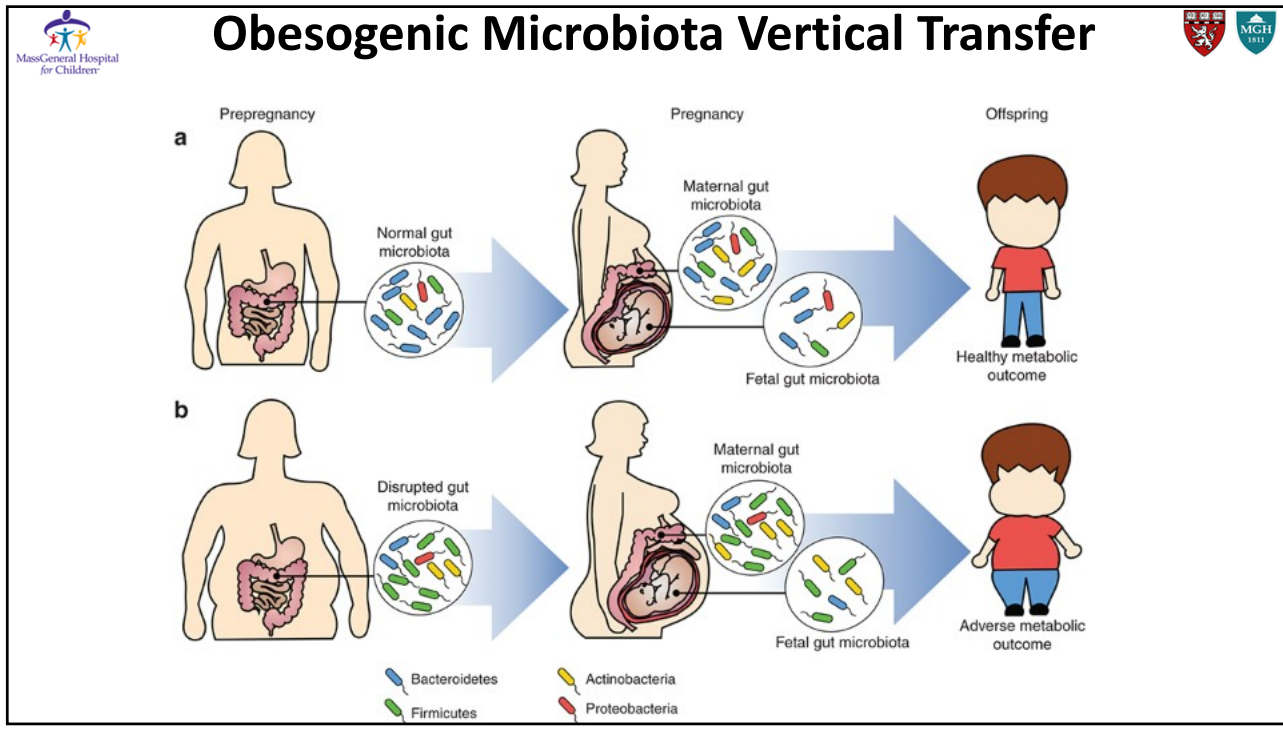
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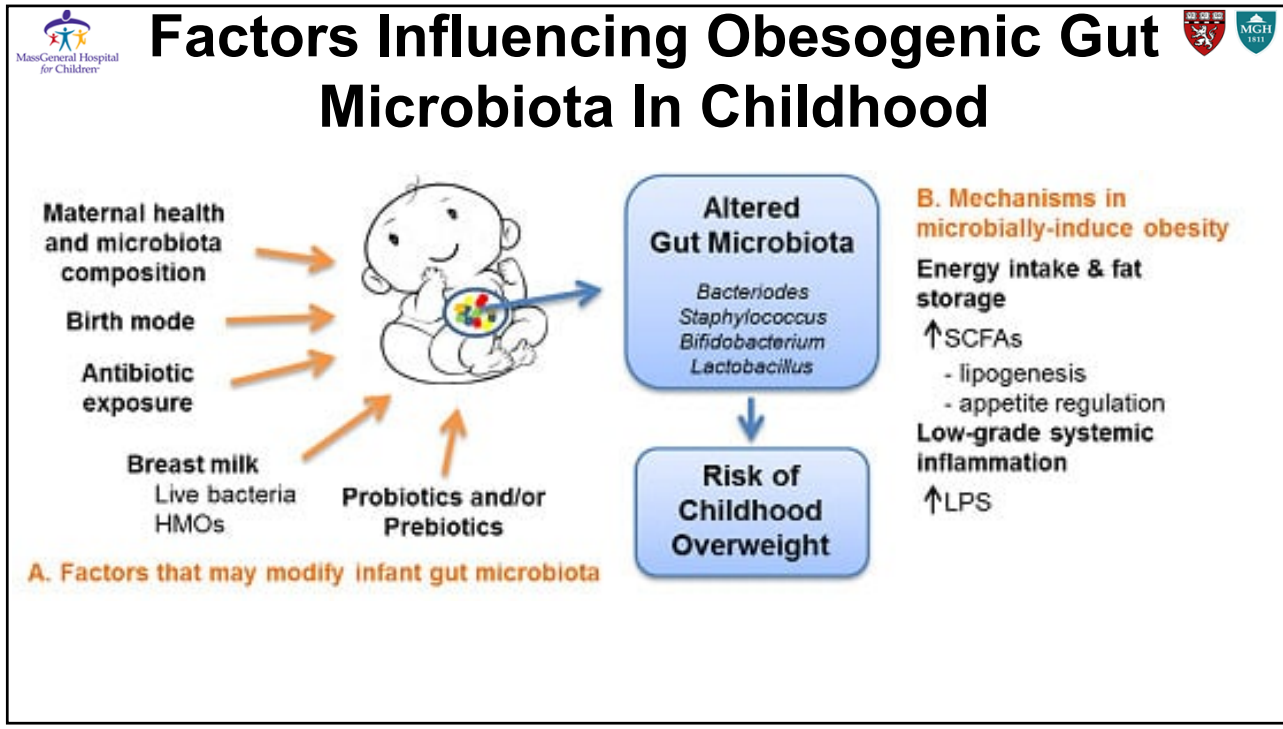
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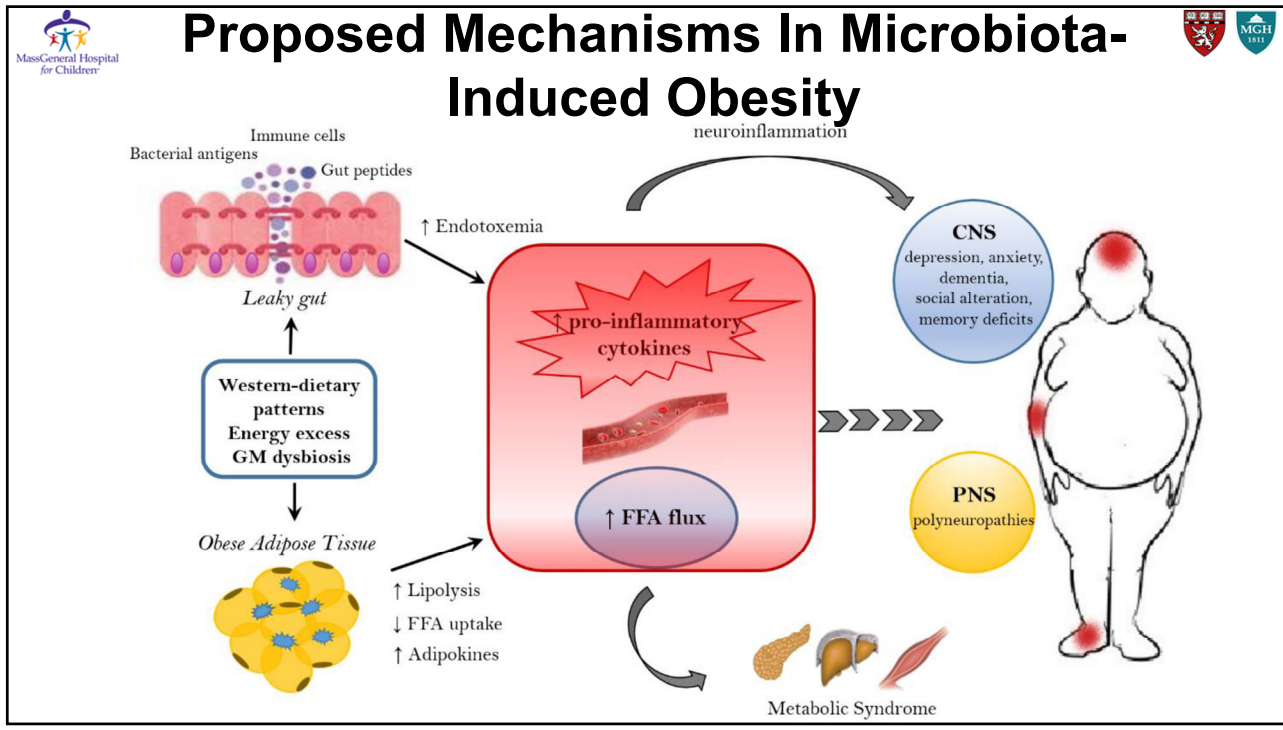
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Celiac Disease Genome, Environment, Microbiome, and Metabolomic Studies

C

D


G


E



M


M

www.CDGEMM.org








**Aspetti un bambino?
Hai un familiare di primo grado
con celiachia?**

Aiutaci a prevenire la celiachia.

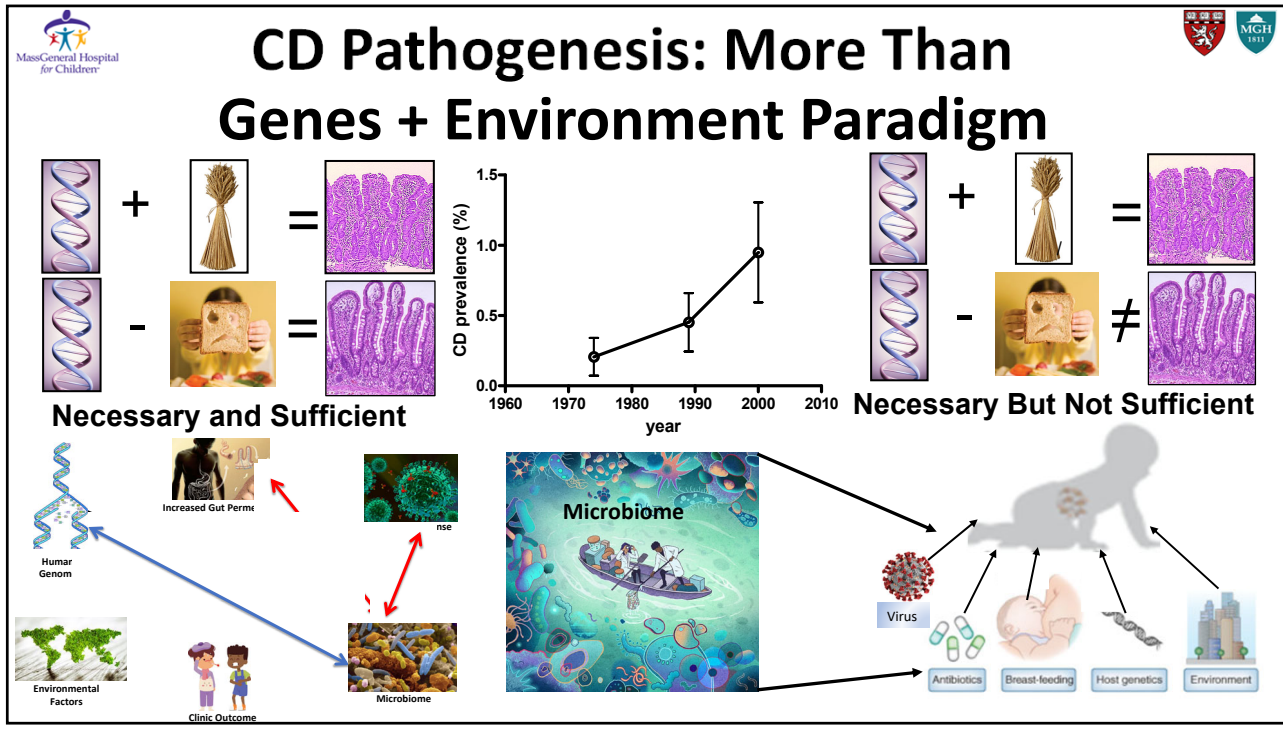
In collaborazione con l'Università di Harvard,
il centro di riferimento per la celiachia e per le malattie
glutine-dipendenti dell'Ospedale Giovanni XXIII di Bari
coordinato dal Prof. R. Francavilla mette a disposizione
i propri specialisti per il follow-up dei nuovi nati

SENZA liste di attesa!

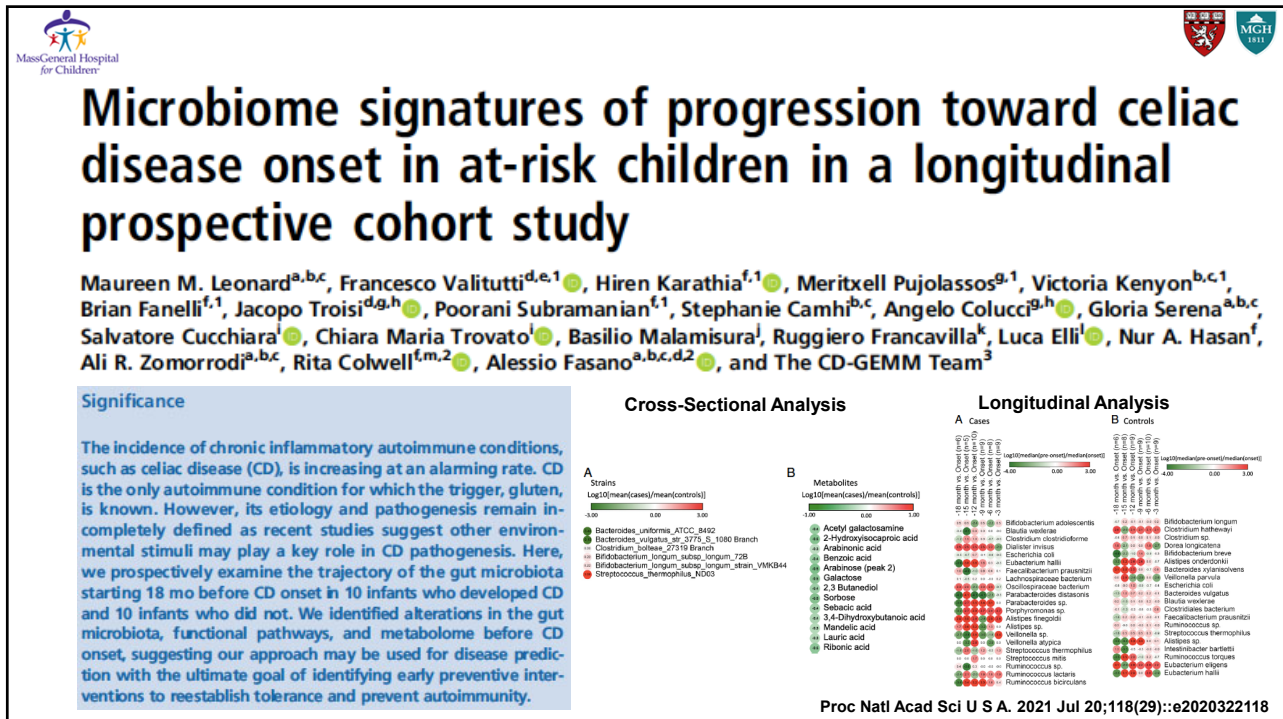


Non esitare a contattarci per maggiori informazioni
328 328 43 23
cdgemmbari@gmail.com pagina facebook


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Longitudinal analysis provided more in-depth data by identifying microbes, pathways and metabolites with differential abundance CD onset



Cases


- ↑ Abundance of microbes/pathways/metabolites
 - Previously linked to autoimmune and inflammatory conditions
- ↓ Abundance of microbes/pathways/metabolites
 - Previously reported as probiotics or having anti-inflammatory properties
 - Previously unreported microbes/pathways/metabolites that may serve as CD-specific biomarkers

Controls


- ↑ Abundance of microbes/pathways/metabolites
 - Previously linked to protection against allergic, autoimmune and inflammatory conditions


Laparra JM, Plosone, 2012.
 Wong CB et al. Nutrients 2019
 Klemenak M et al. Dig Dis Sci 2015
 Stewart, Nature, 2018.
 Ye, Microbiome 2018.
 Pianta, J Clin Invest, 2017
 Menard S et al, Gut, 2004.
 Chien Mw et al, Int j of Mol sci, 2018

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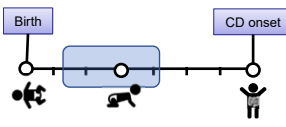


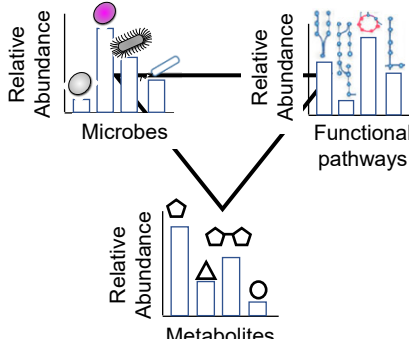
In silico modeling of host-microbiota interactions to study celiac disease pathogenesis and progression

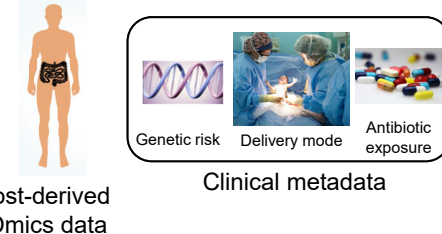




Prospective birth cohort study

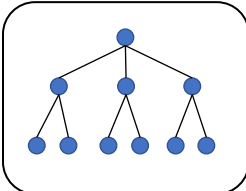







Early prediction of CD development using various data types and machine learning

Machine learning

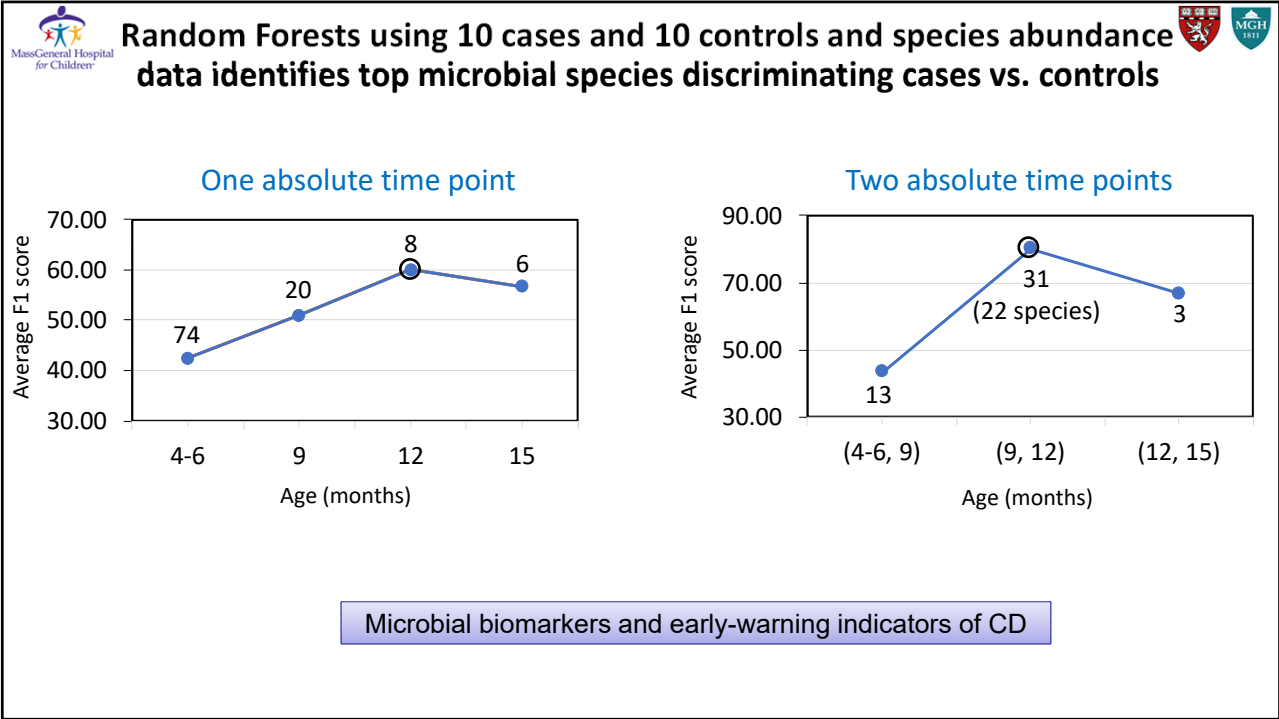


Predict CD onset in unseen subjects

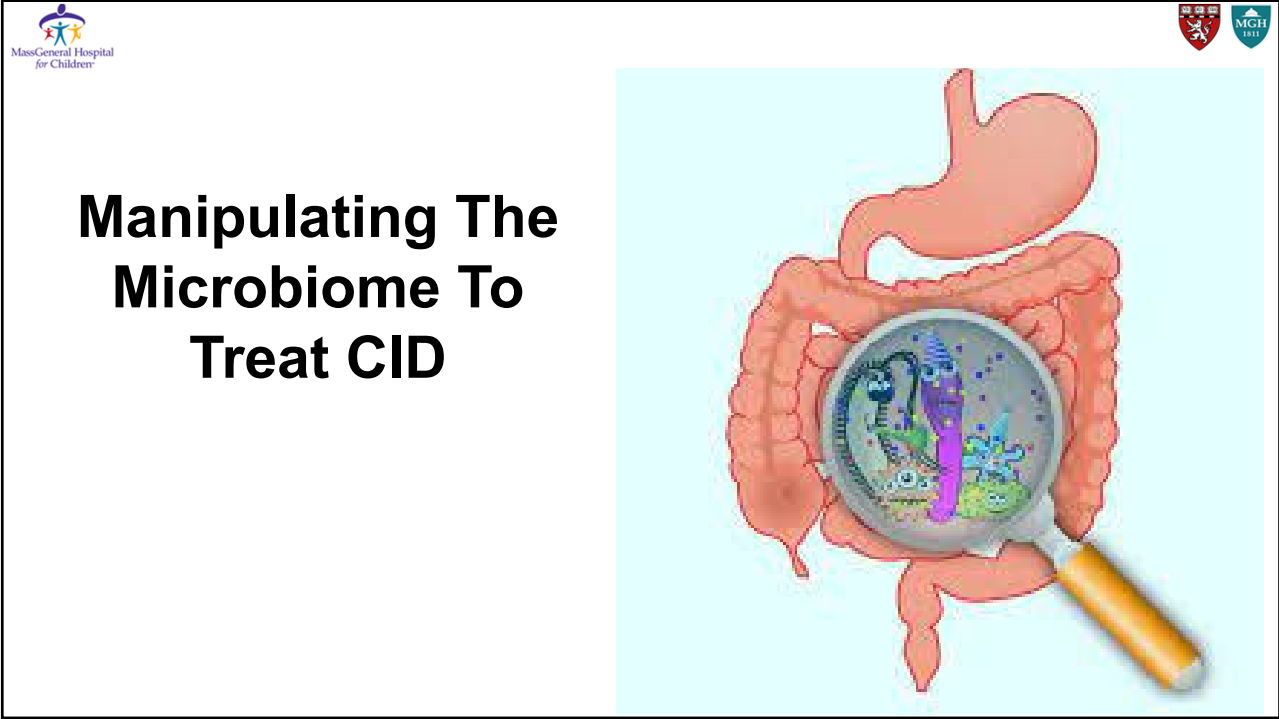


70% develops CD


40




41



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Microbiome Disruption by Condition Summary




CONDITION	RELEVANT FINDINGS
Prematurity	↑ Proteobacteria ↓ Microbial diversity
Necrotizing enterocolitis	Blooms of <i>Proteobacteria</i> prior to disease onset
Sepsis	Altered microbiota structure and composition prior to disease onset has been reported, but specific microbiota reported is inconsistent across studies
Colic	Decreased microbial diversity and increased anaerobic bacteria
Malnutrition	Anaerobic depletion, early dysbiosis, and intestinal pathogenic overabundance with decreased bacterial diversity
Eczema	Early colonization with opportunistic species may be important in disease initiation
Allergies	↓ Species diversity
Asthma	No clear pattern
Inflammatory bowel disease	Data is sparse, no consistent pattern
Type I diabetes	↑ <i>Bacteroidetes:Firmicutes</i> ratios, ↑ <i>Clostridia</i> species ↓ Butyrate-producing bacteria ↓ Bacterial diversity ↓ Community stability Alterations in the microbiome seem to precede disease onset
Type II diabetes and obesity	↑ <i>Firmicutes:Bacteroidetes</i> ratio ↑ SCFAs
Autism spectrum disorder	↑ <i>Clostridial</i> species ↑ <i>Suttetrella</i> and <i>Desulfovibrio</i> species

Limitations of microbiome studies are related to unknowns if microbiota changes occur prior to disease onset, prodromal periods of disease, active disease processes. For the most part it is unknown if microbiota changes are causal to disease or are merely associated with most diseases.

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EVIDENCE FOR USE OF PROBIOTICS IN PEDIATRICS



What the evidence tells us about probiotic use for these conditions in children

Condition	Prevention*	Treatment*	Probiotic species	Typical daily dose (CFU/d)
Colic (breastfed) ⁶⁻⁸	0	+	<i>Lactobacillus reuteri</i>	100 million
Atopic eczema ¹³⁻¹⁷	+	0	<i>Lactobacillus rhamnosus</i> , <i>Lactobacillus paracasei</i> , <i>Bifidobacterium lactis</i>	3-6 billion
URI ⁹⁻¹²	+	+	<i>Lactobacillus</i> and <i>Bifidobacterium</i> spp	2-10 billion
IBS ¹⁸⁻²⁰	Not studied	+	<i>L. rhamnosus</i> VSL#3 [†]	6 billion 450-900 billion
AAD ²¹⁻²⁴	+	+	<i>L. rhamnosus</i> , <i>Saccharomyces boulardii</i>	20 billion
AID ²³⁻²⁹	Not studied	+	<i>L. rhamnosus</i> , <i>S. boulardii</i> , <i>Bifidobacterium bifidum</i> , <i>Bifidobacterium infantis</i>	10 billion

AAD, antibiotic-associated diarrhea; AID, acute infectious diarrhea; CFU/d, colony forming units per day; IBS, irritable bowel syndrome; URI, upper respiratory infection.
* 0=no effect; +=positive effect.
[†]*Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*.

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PRACTICE RECOMMENDATIONS FOR THE USE OF PROBIOTICS



- › Recommend a trial of *Lactobacillus reuteri* for breastfed infants with colic. **A**
- › Consider *Lactobacillus* and *Bifidobacterium* species for the prevention of upper respiratory infections (URIs) and to shorten the course of URI illness. **B**
- › Do not recommend probiotics for the prevention of respiratory or gastrointestinal allergies. **A**
- › Consider probiotics for the reduction of abdominal pain in pediatric irritable bowel syndrome, as well as to reduce diarrhea associated with antibiotic use and acute gastroenteritis. **A**

Strength of recommendation (SOR)

A Good-quality patient-oriented evidence


B Inconsistent or limited-quality patient-oriented evidence

C Consensus, usual practice, opinion, disease-oriented evidence, case series


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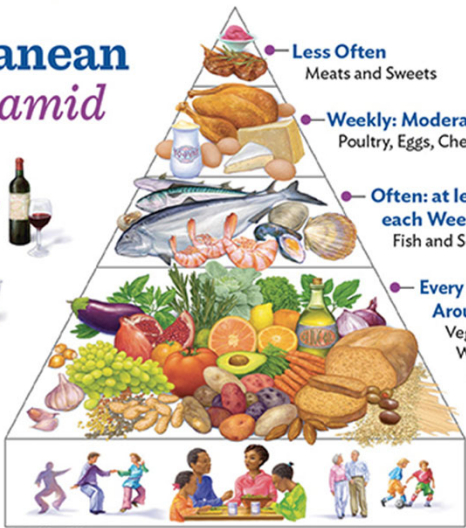
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The Mediterranean Lifestyle



Mediterranean Diet Pyramid



Less Often
Meats and Sweets

Weekly: Moderate Portions
Poultry, Eggs, Cheese and Yogurt

Often: at least Twice each Week
Fish and Seafood

Every Day: Base Each Meal Around these Foods
Vegetables, Fruits, Whole Wheat Grains, Olive Oil, Beans, Nuts, Legumes and Seeds, Herbs and Spices

Every Day
Be Physically Active; Enjoy Meals with Others

In Moderation
Wine

Every Day
Water

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Raffaella de Franchis

La Dieta Mediterranea nel primo anno di vita

Presentazione
Salvatore Auricchio



CUZ SOLIN

Raffaella de Franchis

La Dieta Mediterranea e il bambino: tra scienza e pratica

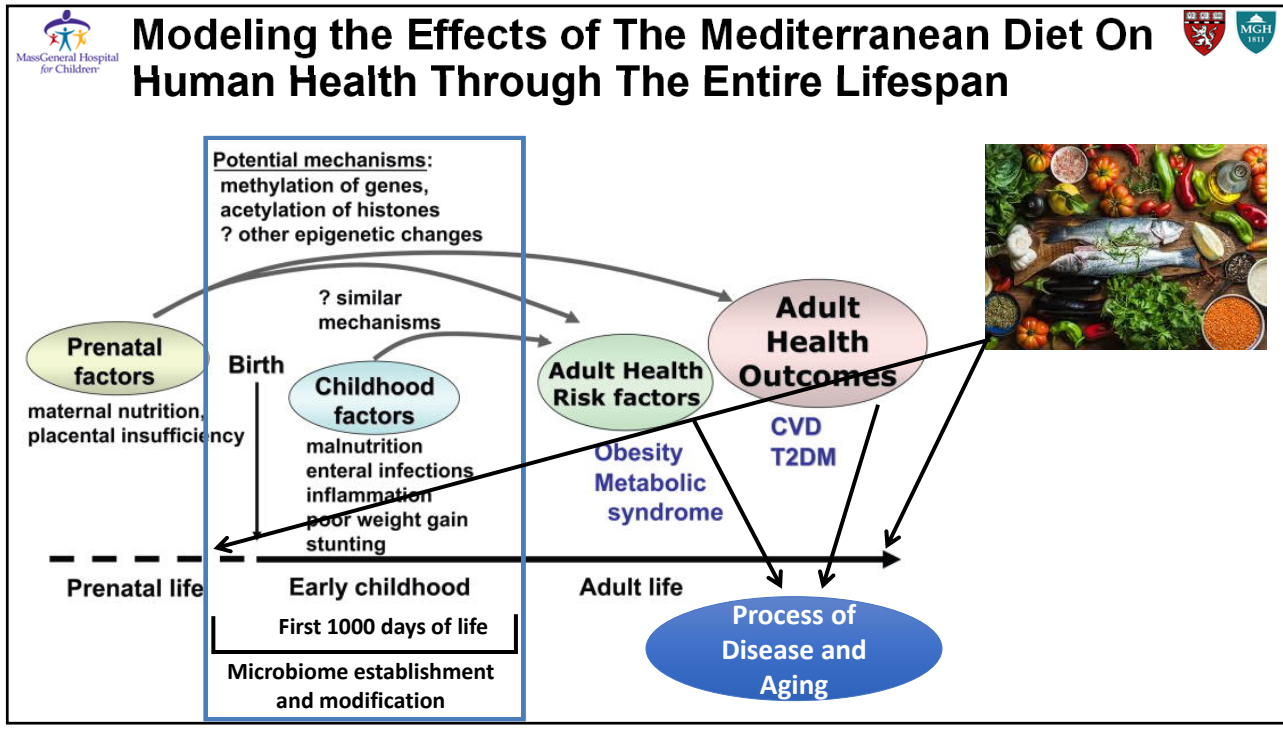


FIAP
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