

XXXIV Congresso Nazionale SIPPSS

# Dagli albori della vita ... un cammino insieme



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SOCIETÀ AFFILIATA  
ALLA SIP



# *Dagli albori della vita ...un cammino insieme*



**Vassilios Fanos**

**Neonatal Intensive Care Unit  
University of Cagliari - Italy**



Dagli Albori della vita ... un cammino insieme  
Vassilios Fanos, Daniela Lucangeli



***La struttura non determina la funzione o  
viceversa, ma entrambe descrivono la  
stessa cosa***

(Oliver JR, 1968)





Dalla Treccani, albore deriva dal latino tardo *albor-oris*, derivato di *albus* “bianco”; letteralmente significa “bianchezza, chiarore, luminosità”, e più specificatamente **“la prima luce dell’alba”**, quindi un inizio, quando la luce è ancora solo una promessa.





**The Santorini Boxers**

## **Conflict of interest**

**Angelini, Bromatech,  
Chiesi, Menarini,  
Microbiotica, Valeas**

**No conflict of  
interest for this  
talk**





# Agenda

- **«Mille giorni di te e di me»**
- **«La risposta se ne va nel vento»**
- **«Non sappiamo perché, ma ci dicono che...»**
- **«Come si cambia, per non morire»**
- **«E l'acqua si riempie di schiuma, il cielo di fumi...»**
- **«E' il mio corpo che cambia...»**
- **«In questa grande immensità...»**
- **«Aspettiamo che ritorni la luce...»**



# Agenda

- ***Un cammino insieme: madre, feto e bambino***
- ***Più domande che risposte***
- ***La natura conserva gelosamente i suoi segreti***
- ***Viaggio al centro dell'utero***
- ***L'inquinamento penetra dentro di noi***
- ***Le incredibili modificazioni del microbiota materno in gravidanza***
- ***Un esempio di grande complessità: i disturbi dello spettro autistico***
- ***Dagli albori della vita...***





# SECTION 1

***Un cammino insieme:  
madre, feto e bambino***



## Esiste una finestra temporale critica

- **Mille giorni dal concepimento**
- **Fetal programming**
- **Perinatal programming**
- **Developmental Origins of Health and Disease**
- **6 + 9 + 6**



Cataldi L, Fanos V. *Leonardo da Vinci and his studies on the human fetus and the placenta*. Acta Biom ed Ateneo Parmense. 2000;71 Suppl 1:405-6.





## Esiste una finestra temporale critica

➤ Mille giorni dal concepimento

➤ *Fetal programming*

➤ *Perinatal programming\**

➤ *Developmental Origins of Health and Disease*

➤ 6 + 9 + 6

I tre cervelli maturano quasi completamente a tre anni:

- Cervello
- Intestino
- Sist. immune

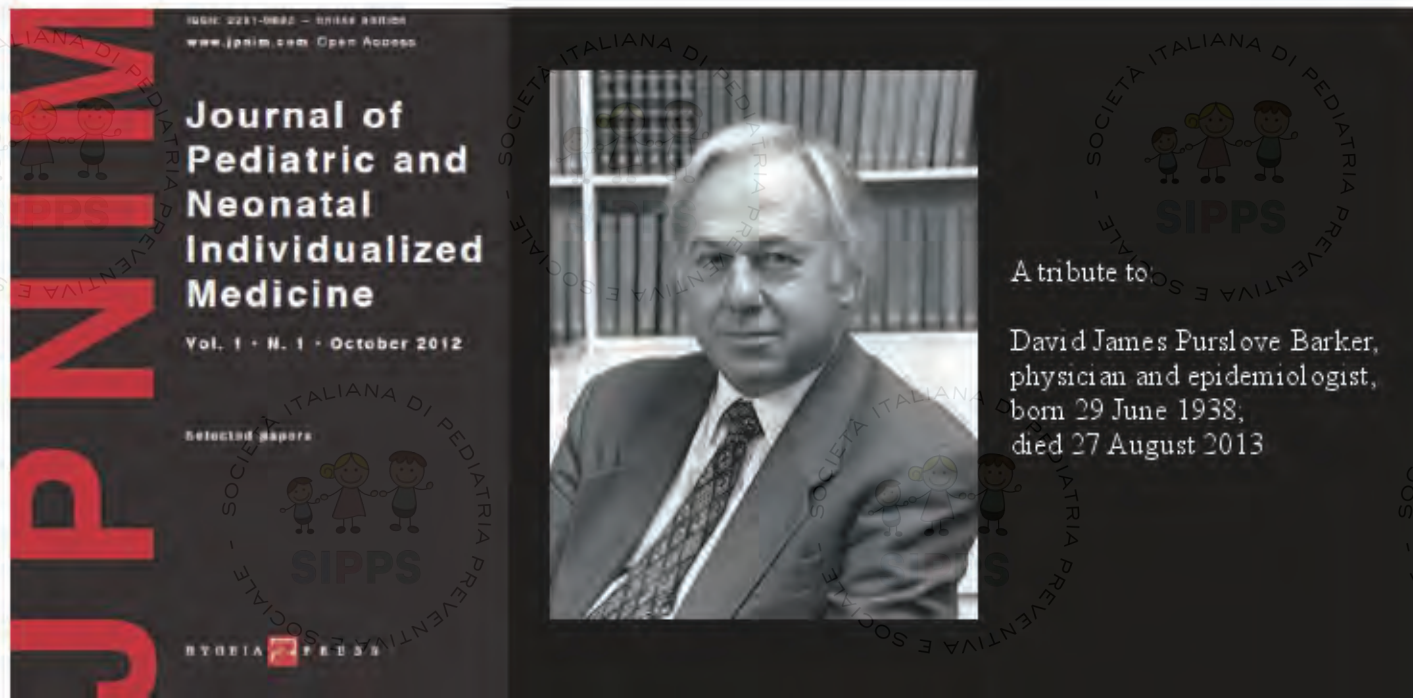
\*Circa 11.500 lavori su PubMed

# David Barker: the revolution that anticipates existence

Italo Farnetani<sup>1</sup>, Vassilios Fanos<sup>2</sup>

<sup>1</sup>Department of Surgery and Interdisciplinary Medicine, University of Milano – Bicocca, Milan, Italy

<sup>2</sup>Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, AOU and University of Cagliari, Italy







# Windows of vulnerability/ Windows of opportunity

## First Trimester



- CV Disease**
- Hypertension**
- Dyslipidemia**
- Obesity**

## Second Trimester

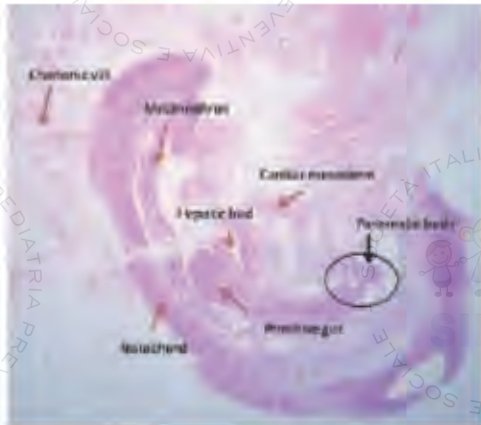


- Pulmonary Disease**
- Renal Disease**

## Third Trimester



- Diabetes**
- Depression**
- Schizophrenia**
- Anti-Social Personality Disorder**
- Autism**

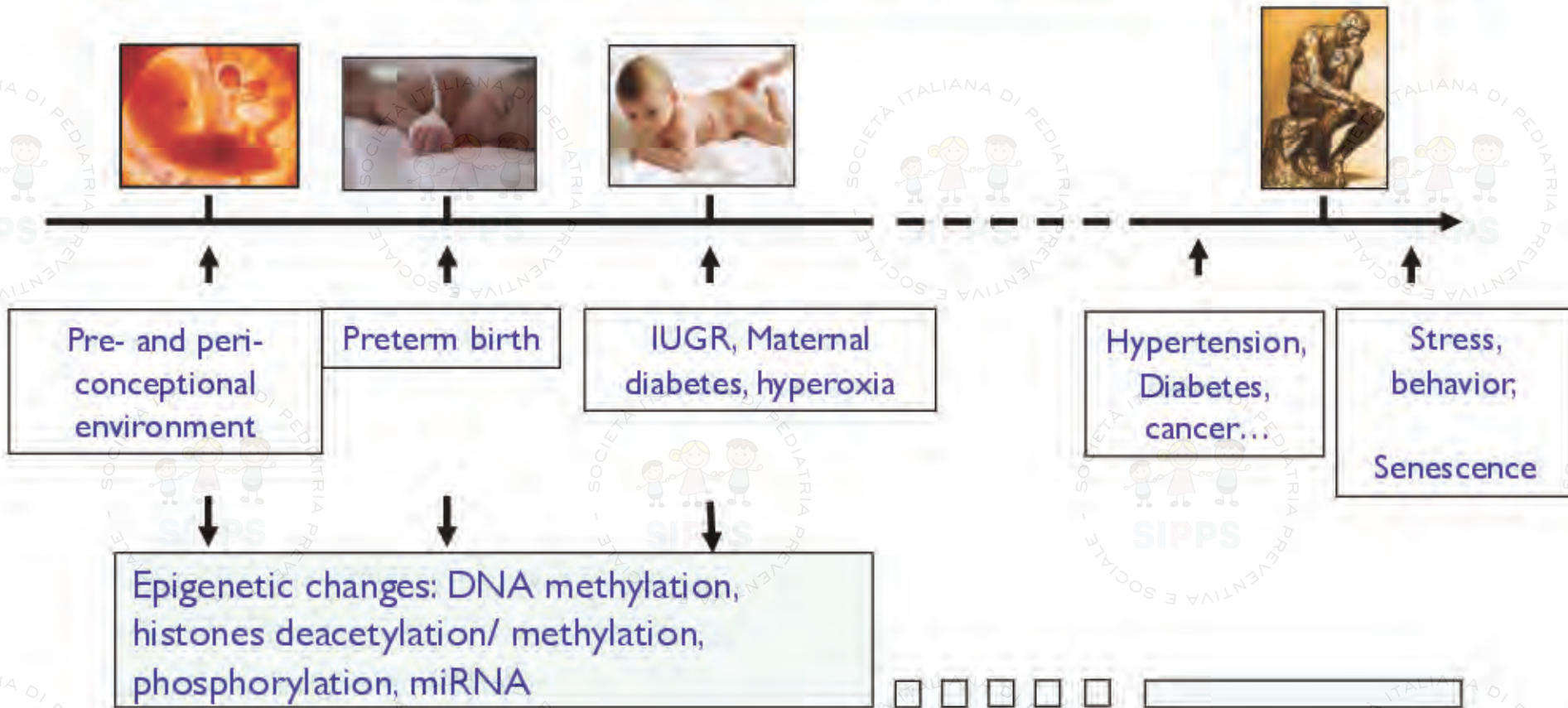


During the Dutch Famine of 1944–1945, energy intake dropped from 1,800 to 400–800 calories per day for about 5 months.

# Developmental Origins of Health and Disease (DOHaD)

## Perinatal programming

La vita è una linea continua!



Simeoni U. et al. 2010



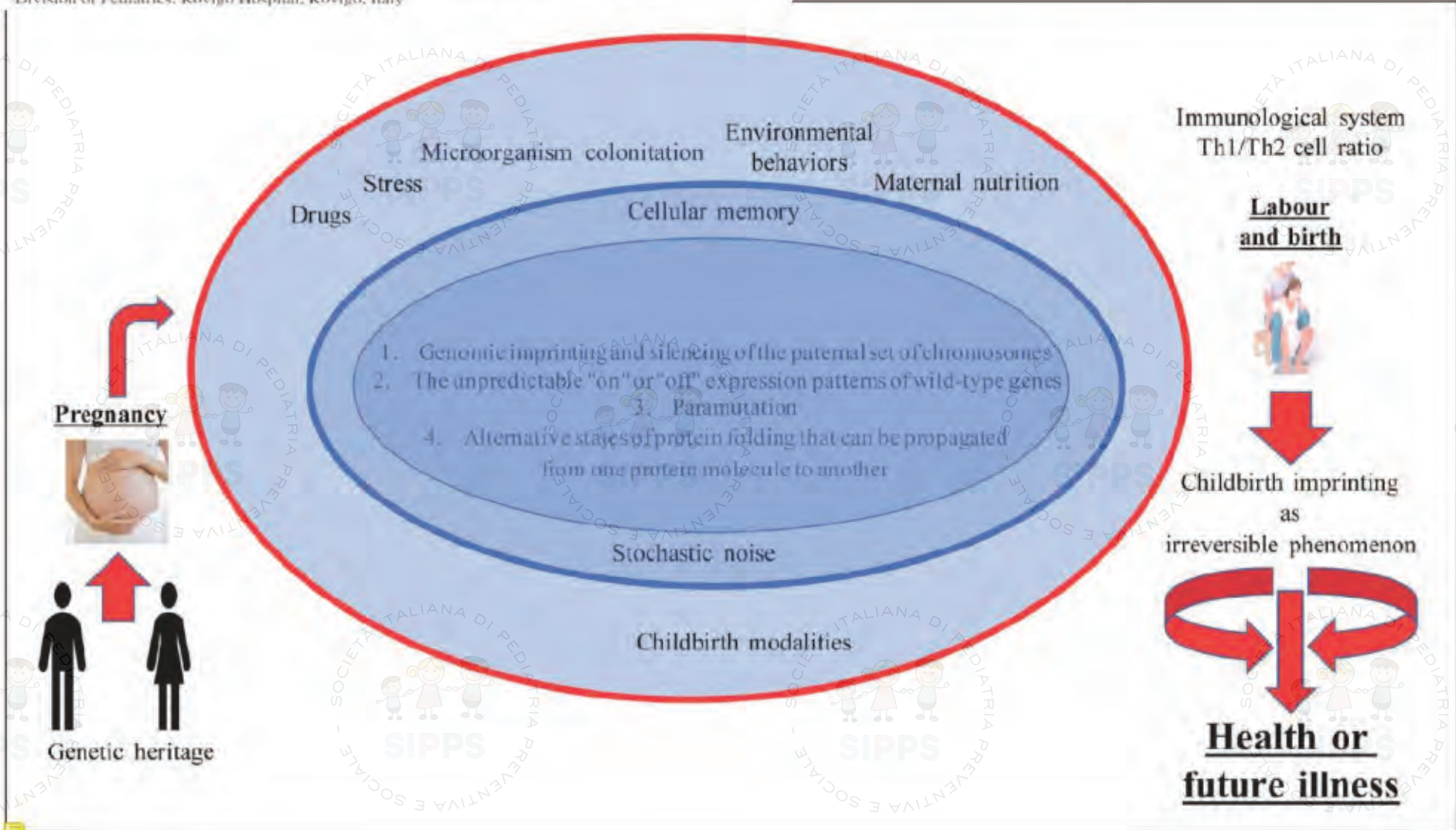
Invited review

# Off to a good start: environmental imprinting in the childbirth period

Antonio Ragusa<sup>1</sup>, Simone Rugolotto<sup>2</sup>, Sara D'Avino<sup>1</sup>, Chiara Incarnato<sup>2</sup>,  
 Alessandra Meloni<sup>4</sup>, Alessandro Svelato<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynecology, Massa Carrara General Hospital, Massa, Italy  
<sup>2</sup>Division of Pediatrics, Rovigo Hospital, Rovigo, Italy

- Una buona partenza
- Partire con il piede giusto
- Essere sulla buona strada





# SECTION 2

***Più domande che risposte***



Environment Special:  
The oceans—why 70%  
of our planet is in danger

Afghanistan:  
After a flawed election,  
how the world can help

# TIME

## How the first nine months shape the rest of your life

The new science  
of fetal origins

BY ANNIE MURPHY PAUL



# Perinatal programming

*«The response by a developing organism to a specific challenge during a critical time window that alters the trajectory of development qualitatively and/or quantitatively with resulting persistent effects on phenotype»*

Environment Special:  
The oceans—why 70%  
of our planet is in danger

Afghanistan:  
After a flawed election,  
how the world can help

# TIME

**How the  
first nine  
months  
shape  
the rest  
of your life**

The new science  
of fetal origins

BY ANNIE MURPHY PAUL



## Perinatal programming



**Are the fetus and the  
newborn father to the  
man?**



# Children are not small adults

Dr. Abraham Jacobi\*

***“Pediatrics does not deal with miniature men and women, with reduced doses and the same class of disease in smaller bodies, but...has its own independent range and horizon”***

***\*1830-1919, founder of Pediatrics in the United States and opened the first children's clinic in the country***

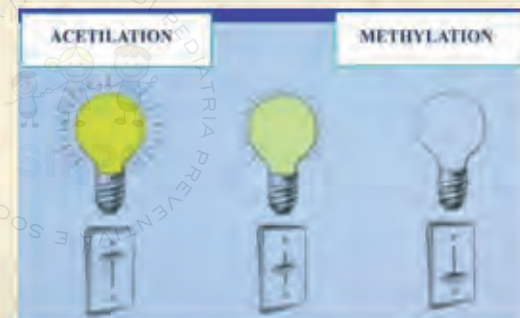
# Adults are big children!

## Ieri: Genetica

*Occorre scegliersi i genitori (oggi diremmo anche i nonni)  
neonato = essere sostanzialmente sano che si deteriora  
progressivamente e inevitabilmente con il tempo*

## Oggi: Genetica + Epigenetica

*La genetica propone, l'epigenetica dispone  
neonato alberga in sé dal momento perinatale la vocazione  
ad ammalarsi. Moltissimo si decide in epoca perinatale*







# TWINS

40 **Leading Edge Review**

## Individualized Medicine from Prewomb to Tomb

Eric J. Topol\*

\*The Scripps Translational Science Institute, The Scripps Research Institute and Scripps Health, La Jolla, CA 92037, USA

**Identical twins  
are not  
identical!  
Same  
Genome/  
Different  
Epigenome**

- **Acetylome**
- **Metylome**
- **Microbiome**
- **Virome**
- **Fungome**
- **Inflammasome**
- **Metabolome**
- **Phenome**
- **Diseasome**



# SECTION 3

***La natura conserva  
gelosamente i suoi segreti***



# 7 recent outstanding titles from papers on placenta

- What is placenta?
- Is placenta an innocent bystander?
- The flight's recorder of pregnancy
- The diplomat of pregnancy
- The omniscient placenta
- How the placenta affects your life, from womb to tomb
- The centre of the chronic disease of the universe



# ***A big secret!*** ***The Mysterious Tree of a Newborn's Life***

**Understanding the Placenta, the least understood human organ**  
**An innocent bystander?**

By **DENISE GRADY** *New York Times* **JULY 14, 2014**



**Placenta is the first of the trees of the organism: when it is strongly involved in pathologies, especially at  $\leq 26$  weeks of gestation, it probably determines a negative influence on all the other trees.**

**A print of a placenta was created by dipping the **organ's treelike branches** in blue acrylic paint. The blood vessels that feed the branches were painted red before the blot was made.**



# Is there a sex of the placenta?

Gian Carlo Di Renzo, Elena Picchiassi, Giuliana Coata, Graziano Clerici, Eleonora Brillo

Department of Obstetrics and Gynecology and Centre for Perinatal and Reproductive Medicine, University Hospital, Perugia, Italy

## *The placenta and neurodevelopment: sex differences in prenatal vulnerability*

Tracy L. Bale, PhD

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[www.dialogues-cns.org](http://www.dialogues-cns.org)

Placenta

Placenta





**«There's a great future in  
plastics. Think about it.  
Will you think about it?»**

Mr. McGuire's advice to Benjamin  
in Mike Nichols' The Graduate (1967)





## L'era del «plasticene»

**«There's a great future in plastics. Think about it. Will you think about it?»**

Mr. McGuire's advice to Benjamin  
in Mike Nichols' *The Graduate* (1967)

Journal of Medical Toxicology (2018) 14:117–119  
<https://doi.org/10.1007/s13181-018-0661-9>

EDITORIAL

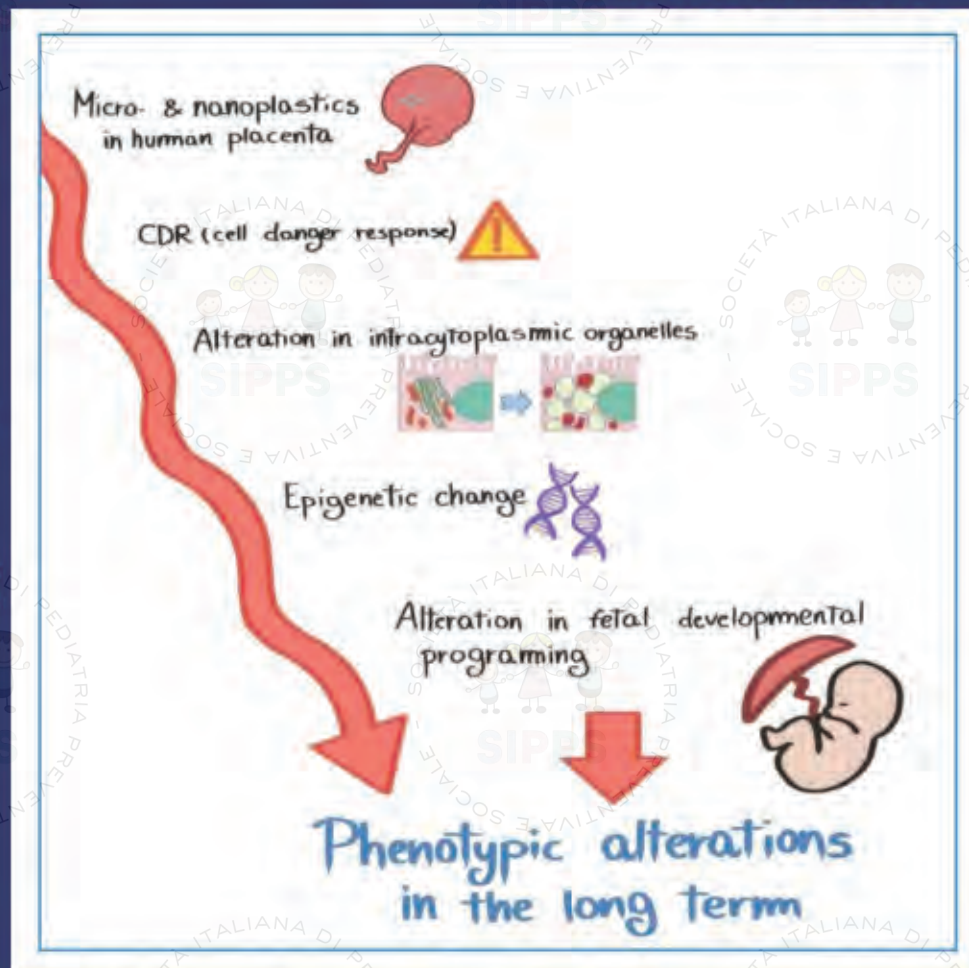
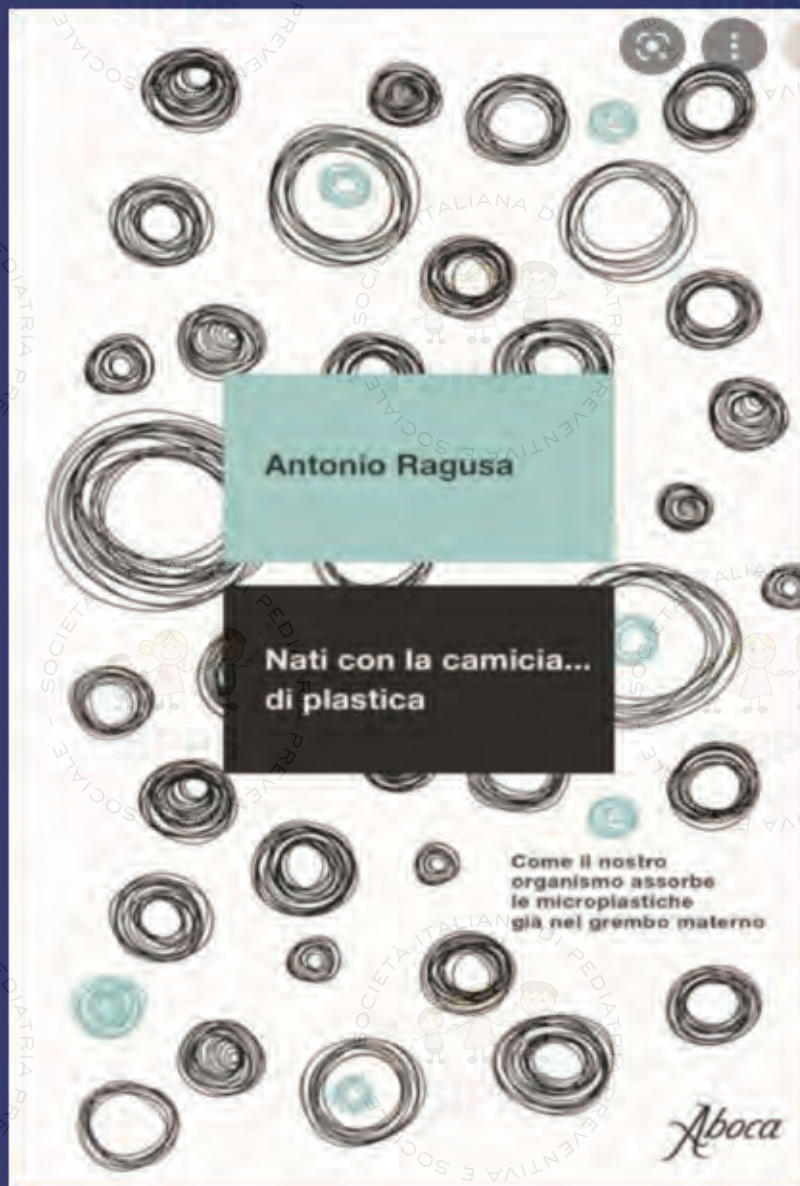


**Microplastics and Human Health: Our Great Future to Think About Now**

Amy V. Kontrick<sup>1</sup>

# Nati con la camicia... di plastica

Da M. Matta 2021



Abbiamo in corso uno studio collaborativo con il Dr. A. Ragusa per valutare anche la **metabolomica placentare** in rapporto alle plastica



# La «plasticenta»

Environment International (2021) 106274

Contents lists available at ScienceDirect

Environment International

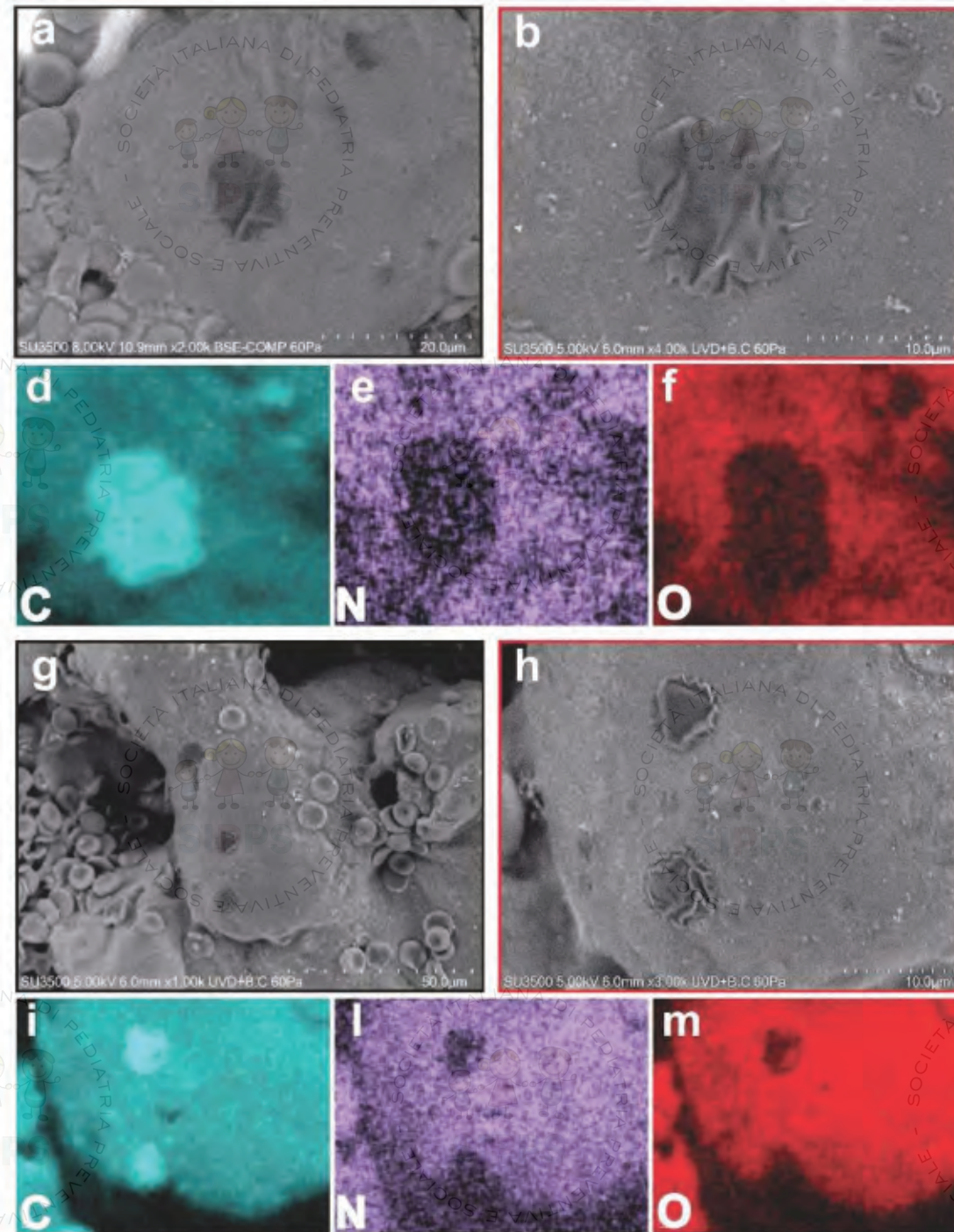
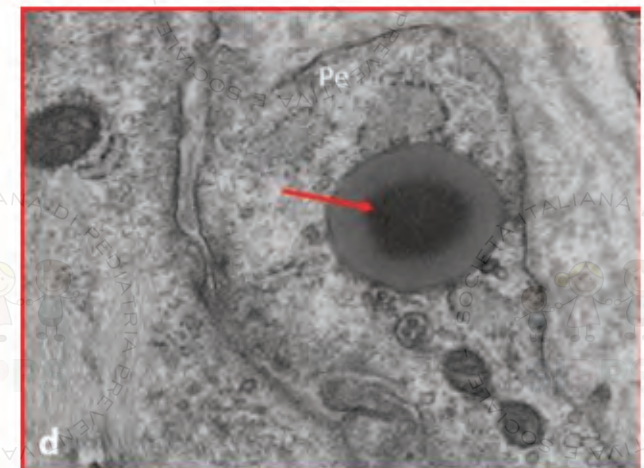
journal homepage: [www.elsevier.com/locate/envint](http://www.elsevier.com/locate/envint)

## Plasticenta: First evidence of microplastics in human placenta

Antonio Ragusa<sup>a</sup>, Alessandro Svelato<sup>a</sup>, Criselda Santacroce<sup>a</sup>, Piera Catalano<sup>a</sup>,  
Valentina Notarstefano<sup>a</sup>, Orlana Carnevali<sup>a</sup>, Fabrizio Papa<sup>a</sup>, Mauro Ciro Antonio Rongioletti<sup>a</sup>,  
Federico Baiocco<sup>a</sup>, Simonetta Draghi<sup>a</sup>, Elisabetta D'Amore<sup>a</sup>, Denise Rinaldo<sup>a</sup>, Maria Marta<sup>a</sup>,  
Elisabetta Giorgini<sup>a</sup>

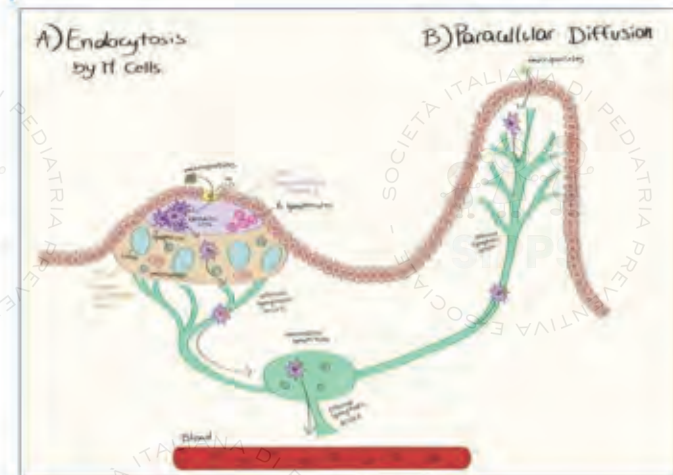
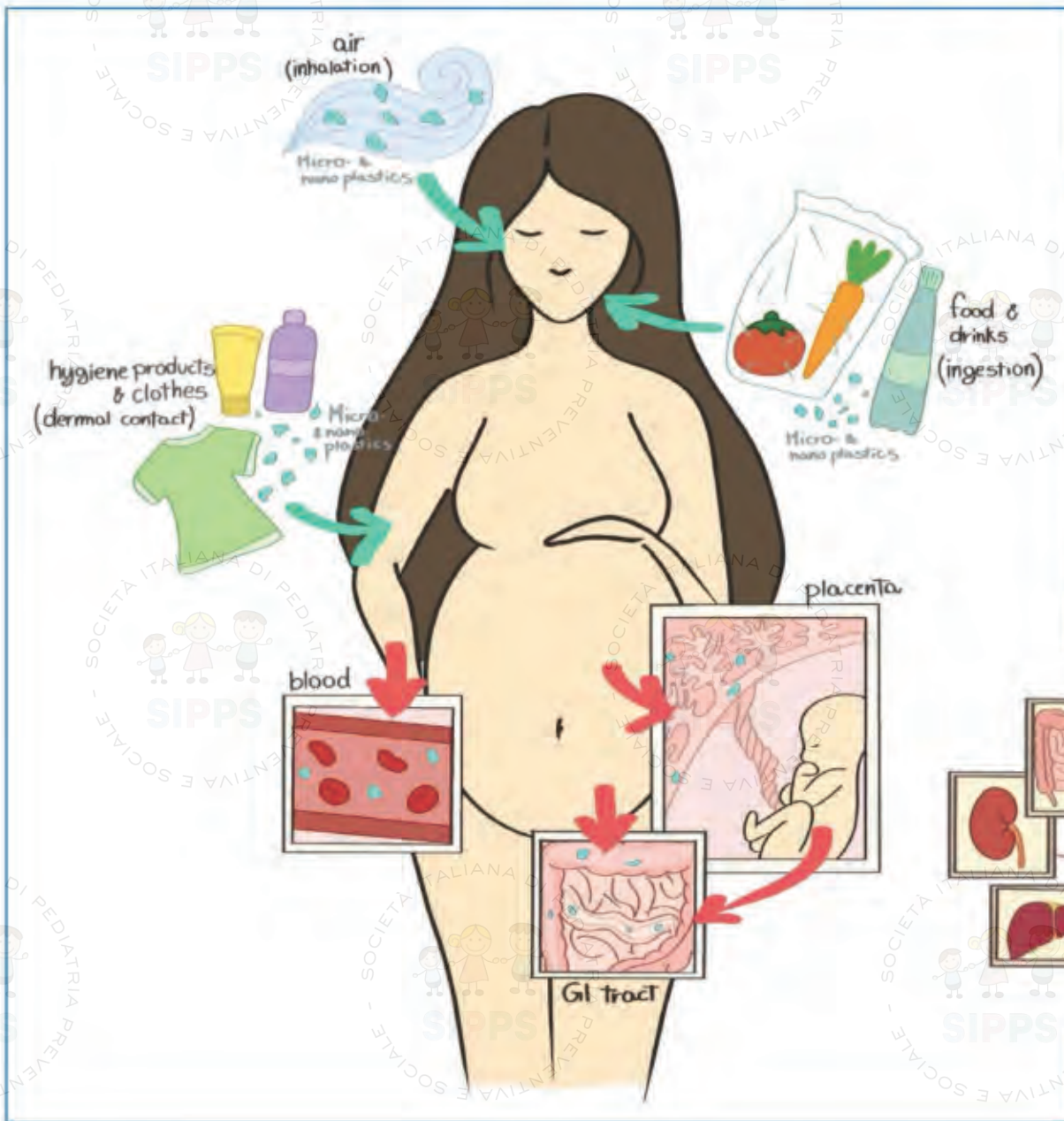
<sup>a</sup> Department of Obstetrics and Gynecology, San Giovanni Calibita Fatebenefratelli Hospital, Viale Pisanelli, 29, 00196 Roma, Italy

## Morpho-chemical study of microplastics on terminal villus surface in hydrated human placenta of different area (SEM)





# Microplastic invasion of the body







## Preliminary metabolomics analysis of placenta in maternal obesity

Claudia Fattuoni <sup>a</sup>, Chiara Mandò <sup>b</sup>, Francesco Palmas <sup>a</sup>, Gaia Maria Anelli <sup>b</sup>, Chiara Novielli <sup>b</sup>, Estefanía Parejo Laudicina <sup>c</sup>, Valeria Maria Savasi <sup>b</sup>, Luigi Barberini <sup>d</sup>, Angelica Dessì <sup>e</sup>, Roberta Pintus <sup>e</sup>, Vassilios Fanos <sup>e</sup>, Antonio Noto <sup>e</sup>, Irene Cetin <sup>b, \*</sup>

<sup>a</sup> Department of Chemical and Geological Sciences, University of Cagliari, Italy

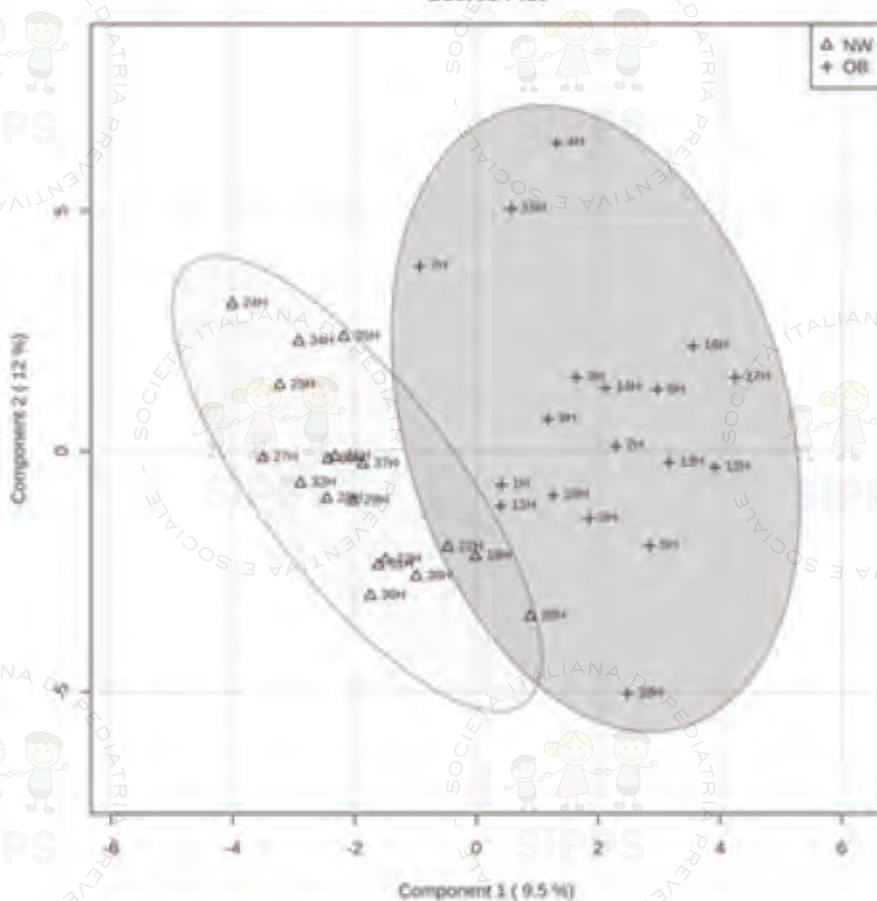
<sup>b</sup> Unit of Obstetrics and Gynecology, Hospital "L. Sacco" and Department of Biomedical and Clinical Sciences, Università degli Studi di Milano, Italy

<sup>c</sup> Centre of Excellence for Pediatric Research EURISTIKOS and Department of Pediatrics, School of Medicine, University of Granada, Granada, Spain

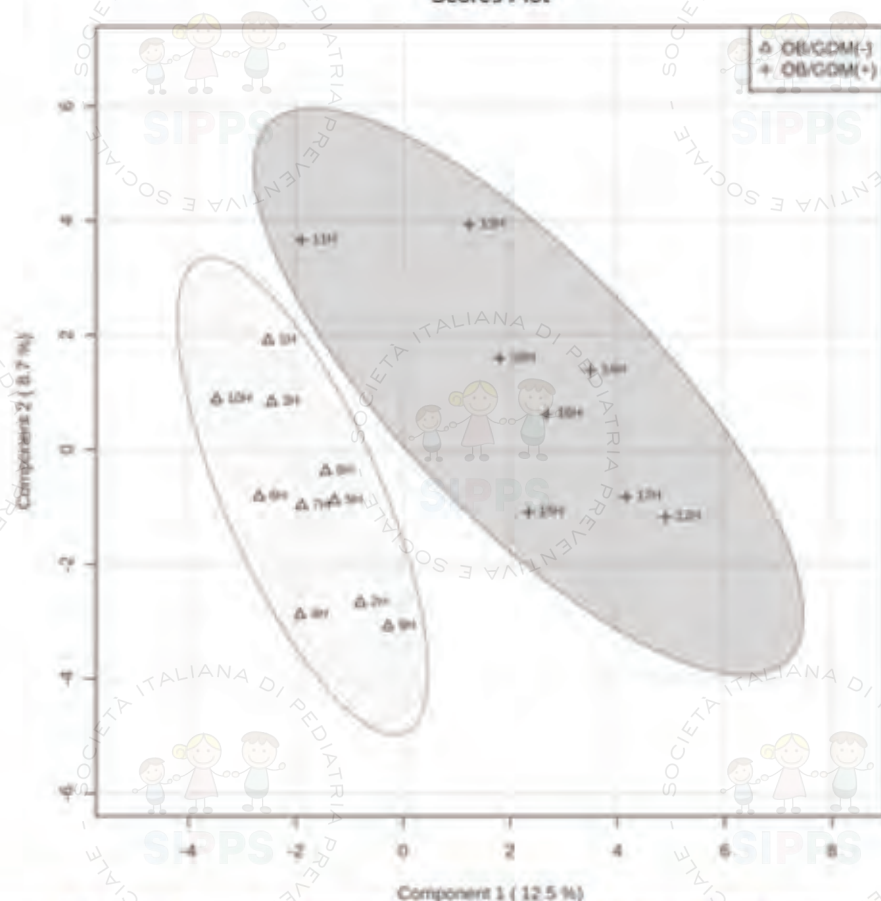
<sup>d</sup> Department of Medical Sciences and Public Health, University of Cagliari, Italy

<sup>e</sup> Maternal-Neonatal Department, Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, AOUC University Hospital of Cagliari, Italy

Scores Plot



Scores Plot



Normal versus Obese

Obese without and with diabetes

# METABOLOMICA PLACENTARE NELLO IUGR: UNA CASISTICA DALL'OSPEDALE UNIVERSITARIO DI LARISSA

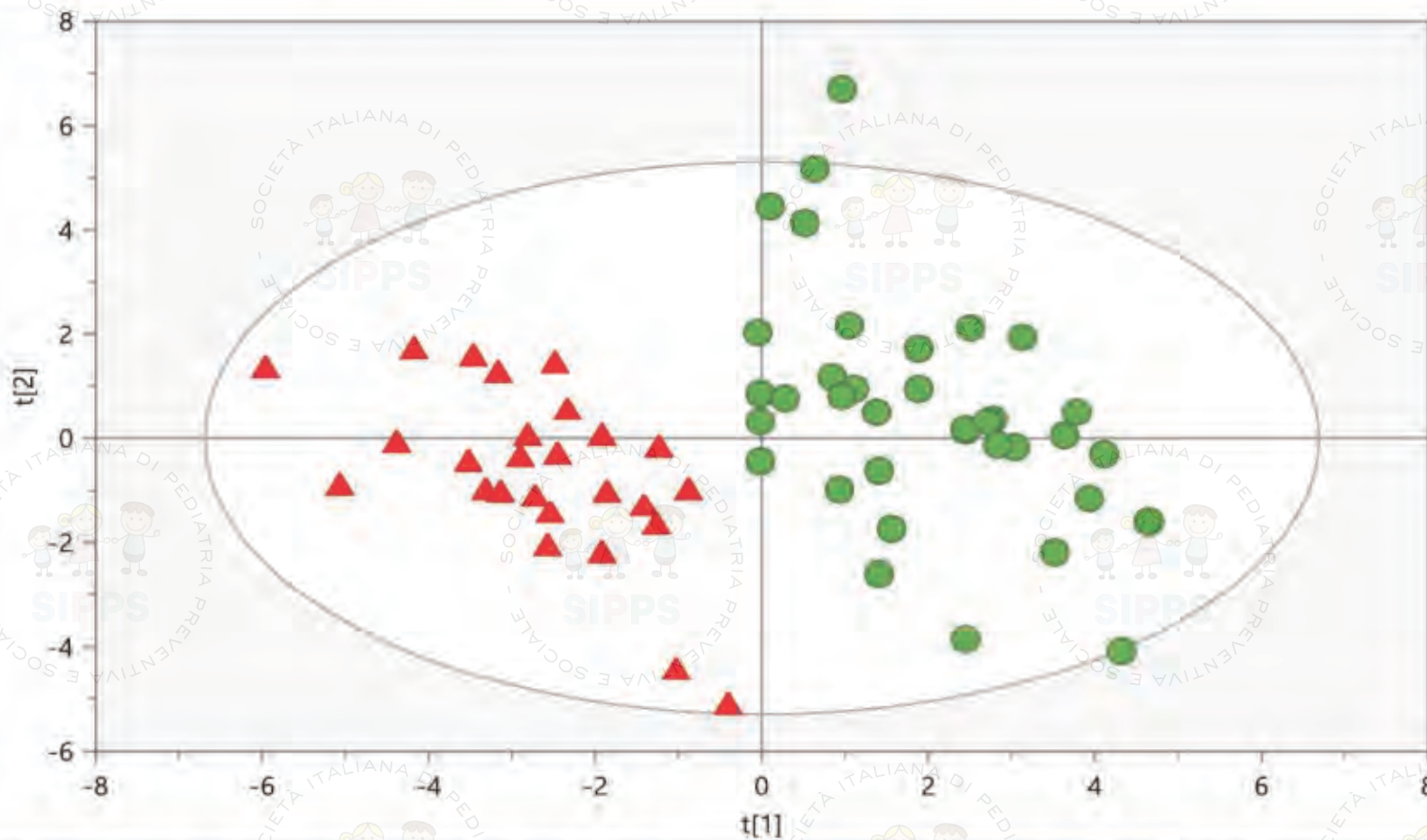
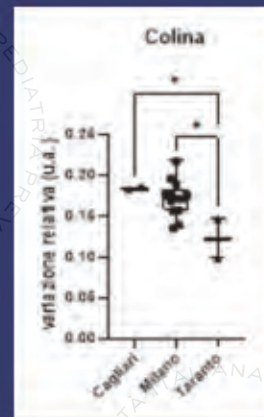
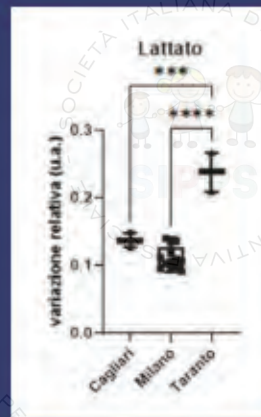
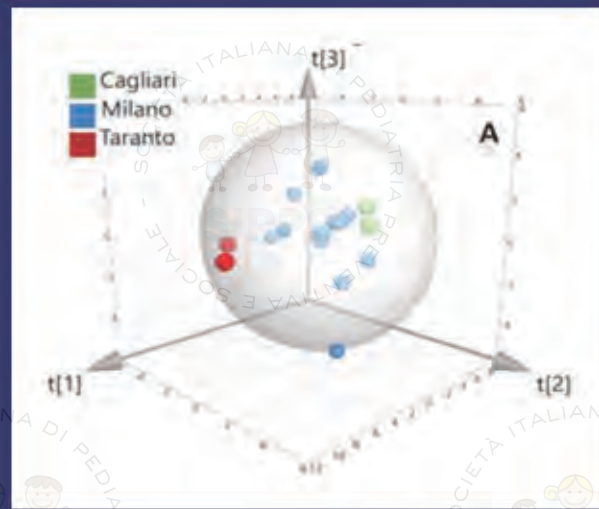


Grafico degli score del modello PCA per il dataset di spettri 1H NMR di campioni di placenta raccolti da madri con IUGR e controlli.

*Nostra Tesi (Luca Sanna, aa 2021-22)*





## Ambiente, programmazione epigenetica fetale e prevenzione delle patologie croniche

A collage of logos for partner institutions and organizations. The logos include:
 

- Università di Pisa (Supreme Dignity 1343)
- ASST Fatebenefratelli Sacco (Sistema Socio Sanitario Regione Lombardia)
- ASL Taranto (Azienda Sanitaria Locale della provincia di Taranto)
- ISTITUTO ZOOFILATTICO SPERIMENTALE DELLA LOMBARDIA E DELL'EMILIA ROMAGNA "BRUNO UBERTINI"
- ISTITUTO SCIENTIFICO BIOMEDICO EURO MEDITERRANEO (ISBEM)
- CCM (Centro di Coordinamento)
- Regione Autonoma della Sardegna





**Placenta**, simbolo del dio Khonsu indicante fertilità (nota come la placenta del Re)

**Gli antichi Egizi la onoravano la placenta come "l'anima esterna".**





# SECTION 4

***Viaggio al centro dell'utero***

# Programmazione dei 1000 giorni

## Mediatori epigenetici

### ORGANISMO

- (Ormonale)
- **Mitocondriale**
- **Microbica**
- **Nutrizionale**  
(latte materno)
- (Immunitaria)

### Organo (esempi)

- **Cerebrale**
- **Cardiaca**
- **Renale**
- **Polmonare**



Do each of these babies have different adult health fates?



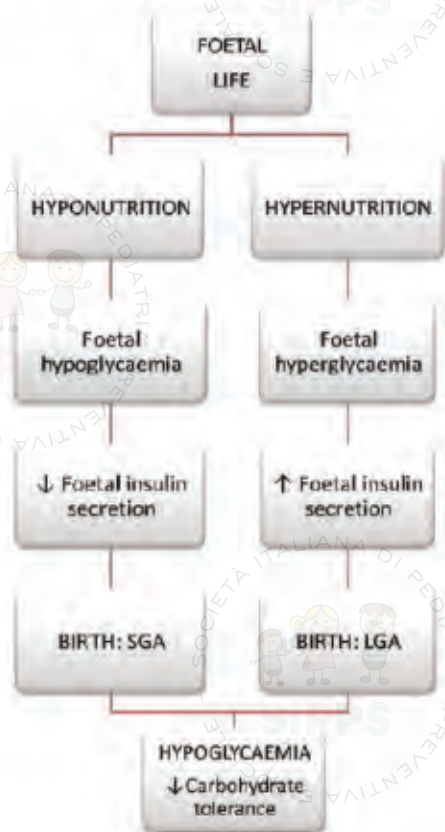
ORIGINAL ARTICLE

## Physiopathology of intrauterine growth retardation: from classic data to metabolomics

Angelica Dessi<sup>1</sup>, Giovanni Ottonello<sup>1</sup> & Vassilios Fanos<sup>1,2</sup>

<sup>1</sup>Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, AO.U. Cagliari, Italy and <sup>2</sup>Department of Surgery, Section of Neonatal Intensive Care Unit and Puericulture, University of Cagliari, Cagliari, Italy

Figure 1. Metabolic state characterizing SGAs and LGAs from foetal life to birth.



REVIEW

## Myo-inositol: A new marker of intrauterine growth restriction?

A. Dessi & V. Fanos

Department of Surgery Science, Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, University of Cagliari, Italy

Molecules 2013, 18, 11724-11732; doi:10.3390/molecules181011724

OPEN ACCESS

molecules

ISSN 1420-3049

www.mdpi.com/journal/molecules

Review

## Metabolomics and Fetal-Neonatal Nutrition: Between “Not Enough” and “Too Much”

Angelica Dessi, Melania Puddu, Giovanni Ottonello and Vassilios Fanos \*

Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, Azienda Ospedaliera Universitaria, Cagliari 09124, Italy

Hindawi Publishing Corporation  
BioMed Research International  
Volume 2014, Article ID 981219, 8 pages  
http://dx.doi.org/10.1155/2014/981219

Review Article

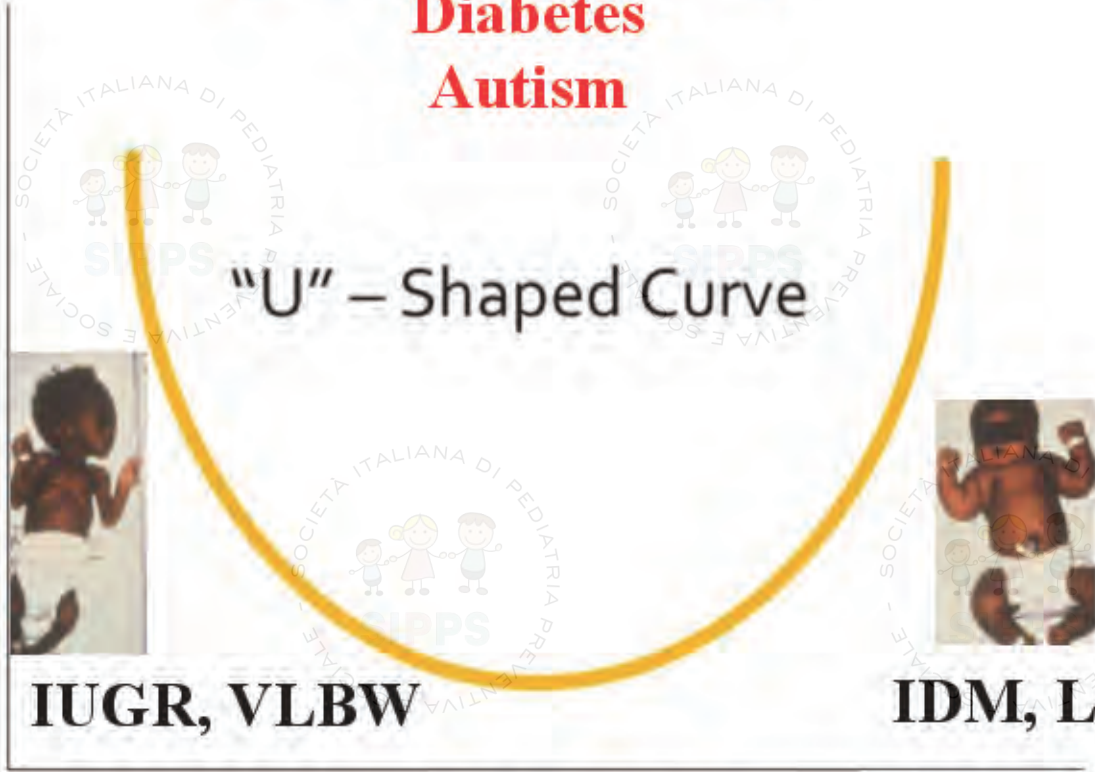
## Clinical Metabolomics and Nutrition: The New Frontier in Neonatology and Pediatrics

Angelica Dessi,<sup>1</sup> Flaminia Cesare Marincola,<sup>2</sup> Alice Masili,<sup>1</sup> Diego Gazzolo,<sup>3</sup> and Vassilios Fanos<sup>1</sup>



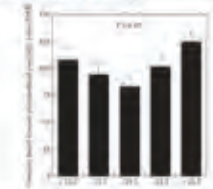
**Mortality**  
**Cardiovascular diseases**  
**Chronic renal failure**  
**Diabetes**  
**Autism**

**METABOLIC SYNDROME RISK**



**BIRTH WEIGHT**  
**PLACENTA WEIGHT**

**Risk of coronary heart disease based on the ratio of placental weight to birthweight**





The figure shows the risk of coronary heart disease based on the ratio of placental weight to birthweight in our English population. Low placental weight is associated to elevated risk measured by the life table curve. The U-shaped curve suggests that, overall, offspring are exposed to the risk for disease. The association has been found to also persist in men.

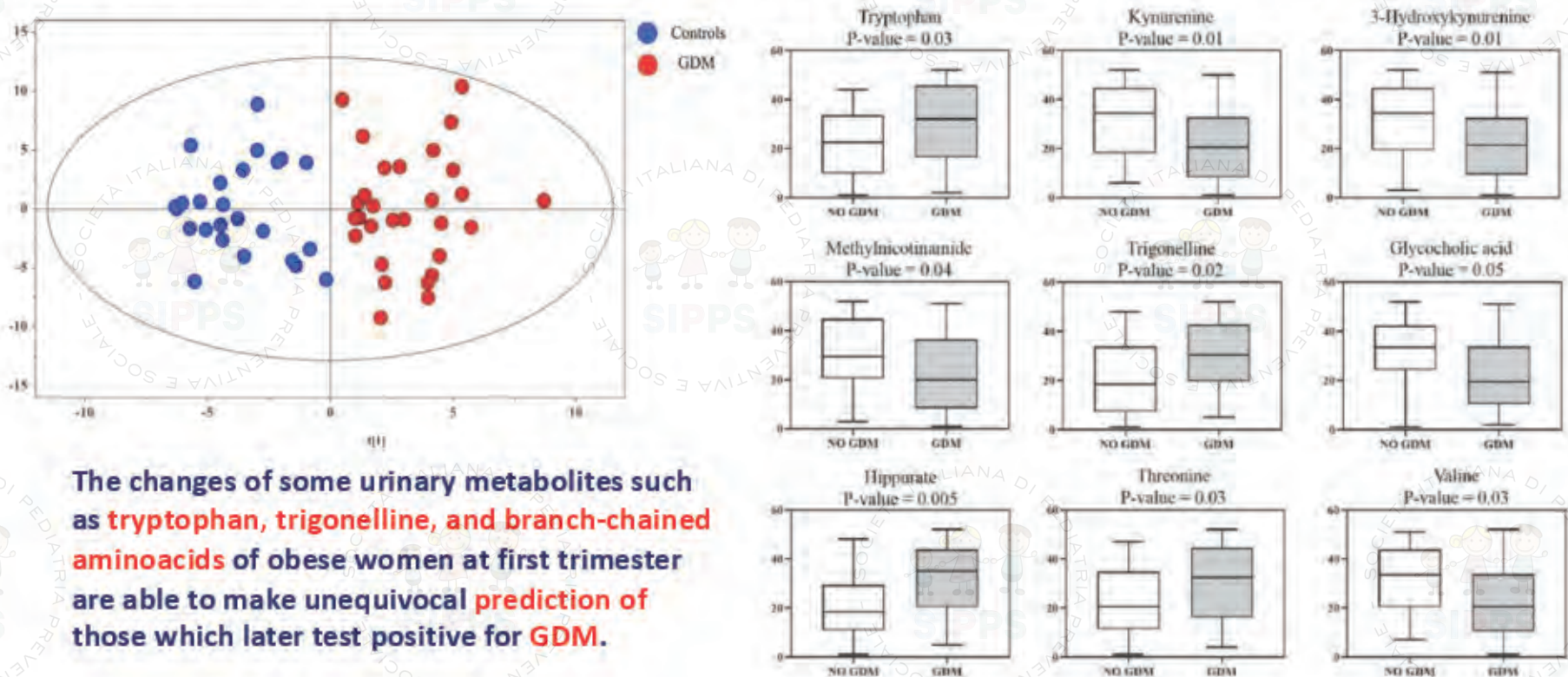
ORIGINAL ARTICLE



# First trimester metabolomics 1H-NMR study of the urinary profile predict gestational diabetes mellitus development, in obese women

† Cristina Piras<sup>a\*</sup>, Isabella Neri<sup>b\*</sup>, Roberta Pintus<sup>c</sup>, Antonio Noto<sup>a</sup> , Elisabetta Petrella<sup>b</sup>, Francesca Monari<sup>b</sup>, Angelica Dessì<sup>c</sup> , Vassilios Fanos<sup>c</sup>, Luigi Atzori<sup>a\*</sup> and Fabio Facchinetti<sup>b\*</sup>

<sup>a</sup>Department of Biomedical Sciences, University of Cagliari, Sardinia, Italy; <sup>b</sup>Department of Medical and Surgical Sciences for Mother, Child and Adult, Azienda Ospedaliero Universitaria Policlinico, University of Modena and Reggio Emilia, Modena, Italy; <sup>c</sup>Department of Surgical Sciences, Neonatal Intensive Care Unit, AOU, University of Cagliari, Monserrato, Italy



The changes of some urinary metabolites such as **tryptophan, trigonelline, and branch-chained aminoacids** of obese women at first trimester are able to make unequivocal prediction of those which later test positive for **GDM**.



Perinatal nutrient restriction reduces nephron endowment increasing renal morbidity in adulthood: A review

V. Fanos <sup>a,\*</sup>, M. Puddu <sup>a</sup>, A. Reali <sup>a</sup>, A. Atzei <sup>a</sup>, M. Zaffanello <sup>b</sup>

<sup>a</sup> Neonatal Intensive Care Unit, Paediatrics Institute and Neonatal Section, University and Azienda Ospedaliera of Cagliari, Italy  
<sup>b</sup> Department of Mother-Child and Biology-Genetics, University of Verona, Verona, Italy

## Cosa succede se non cresco bene nel grembo materno?



- **FENOTIPO RISPARMIATORE:** impariamo velocemente a difenderci
- **TRASMISSIONE TRANSGENERAZIONALE:** gli effetti del *programming* sono transgenerazionali. Dallo slogan paradossale “devi sceglierti i genitori” al “devi sceglierti i genitori, i nonni e i bisnonni!”
- **IL GOAL: LA RIPRODUZIONE.** Il compenso che si verifica vuole farci raggiungere l’immortalità (“*Per nascere son nato*” → “*Per riprodurmi, son nato*”) ma ha dei costi (“una tassa da pagare”).
- **MISMATCHING.** Pericoloso il passaggio da un ambiente troppo poco favorevole a quello troppo favorevole

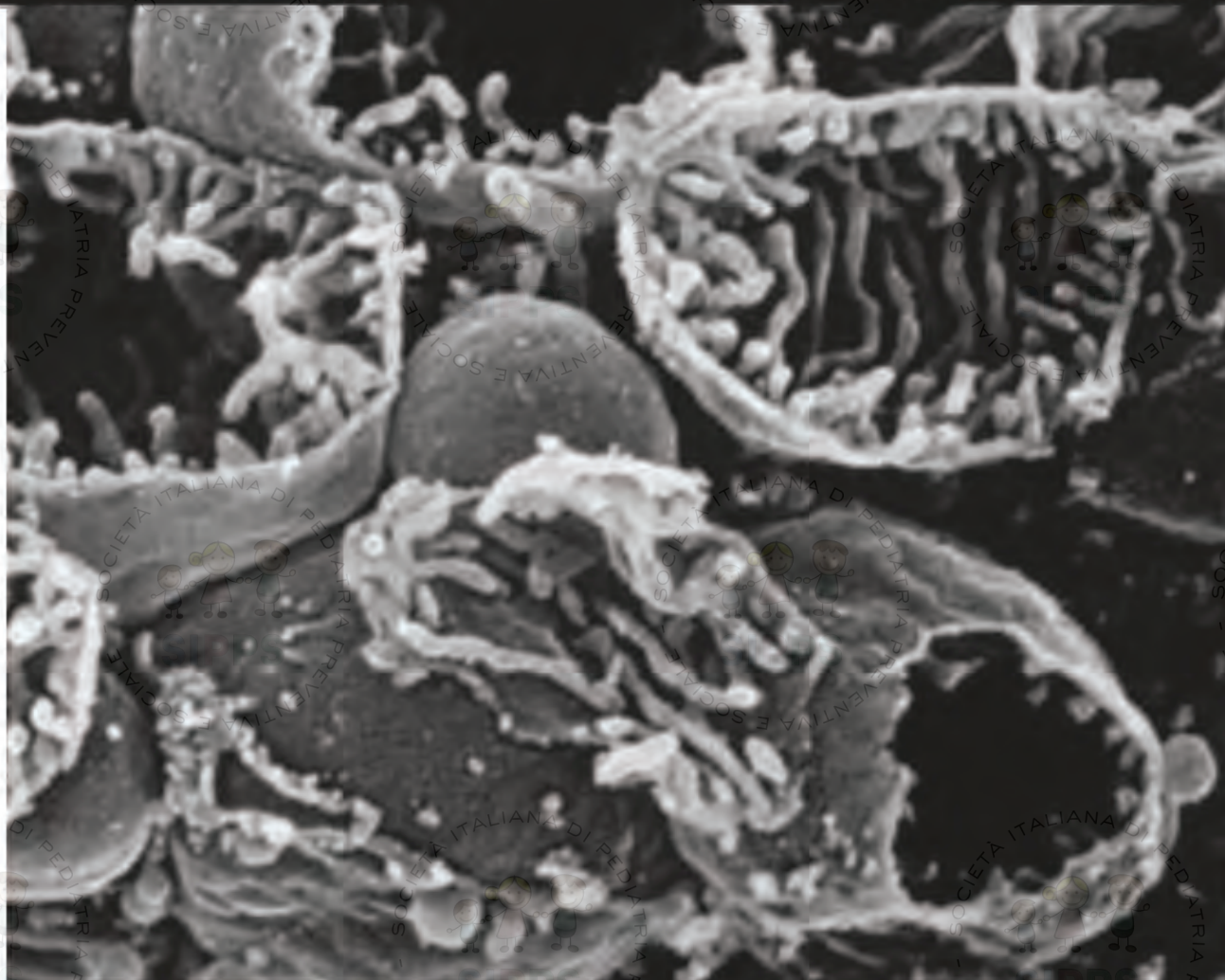
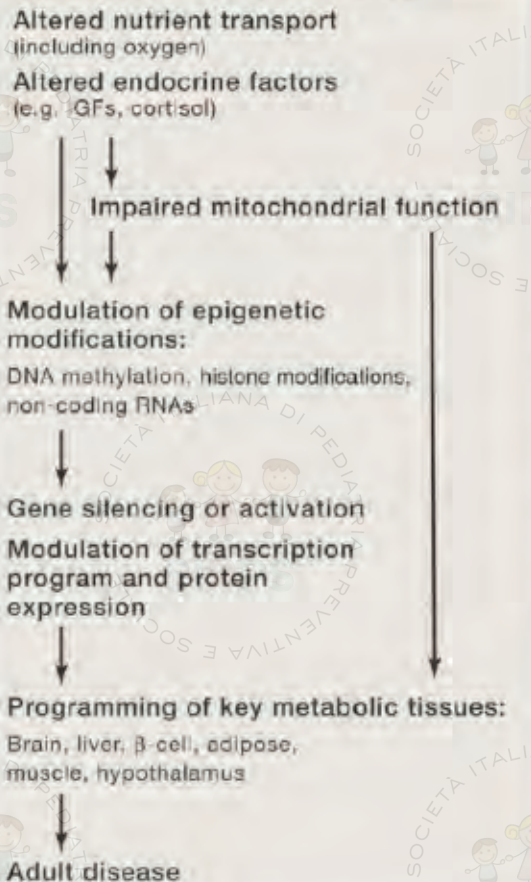


Uteroplacental insufficiency → Reduction in energy supply and oxygen → **activation of mitochondria in the fetus** to satisfy the cellular need of energy → increased production of ROS and oxidative stress → mitochondrial dysfunction → long term problems in all organs

I'm Eating for Two: Parental Dietary Effects on Offspring Metabolism

Oliver J. Rando<sup>1,2</sup> and Rebecca A. Simmons<sup>1,2</sup>  
<sup>1</sup>Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA 01605, USA  
<sup>2</sup>Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

**Mitochondria function and fetal programming**



At high power (13,000X), interior of the **liver mitochondria** is presented, allowing a good evaluation of cristae volume and architecture. Mocci C, J Pediatr Neonat Individual Med. 2014





# SECTION 5

*L'inquinamento  
penetra dentro di noi*

# BodyBurden

## The Pollution in Newborns

A benchmark investigation of industrial chemicals, pollutants, and pesticides in human umbilical cord blood



JANE HOULIHAN  
TIMOTHY KROPP, PH.D.  
RICHARD WILES  
SEAN GRAY  
CHRIS CAMPBELL



JULY 14, 2005

*The gift our mothers  
never wanted to give us*

**In the  
umbilical  
cord:**

- ◆ **Endocrine disruptors**
- ◆ **Heavy metals**
- ◆ **Ultrafine particles**







**A BABY'S ORGANS AND SYSTEMS ARE RAPIDLY DEVELOPING, AND THUS ARE OFTEN MORE VULNERABLE TO DAMAGE FROM CHEMICAL EXPOSURE.**



**A DEVELOPING CHILD'S CHEMICAL EXPOSURES ARE GREATER POUND-FOR-POUND THAN THOSE OF ADULTS.**



**CHILDREN HAVE LOWER LEVELS OF SOME CHEMICAL-BINDING PROTEINS, ALLOWING MORE OF A CHEMICAL TO REACH "TARGET ORGANS."**



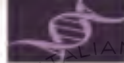
**IN A CHILD, SYSTEMS THAT DETOXYFIFY AND EXCRETE INDUSTRIAL CHEMICALS ARE NOT FULLY DEVELOPED.**



**THE LONGER FUTURE LIFE SPAN OF A CHILD COMPARED TO AN ADULT ALLOWS MORE TIME FOR ADVERSE EFFECTS TO ARISE.**



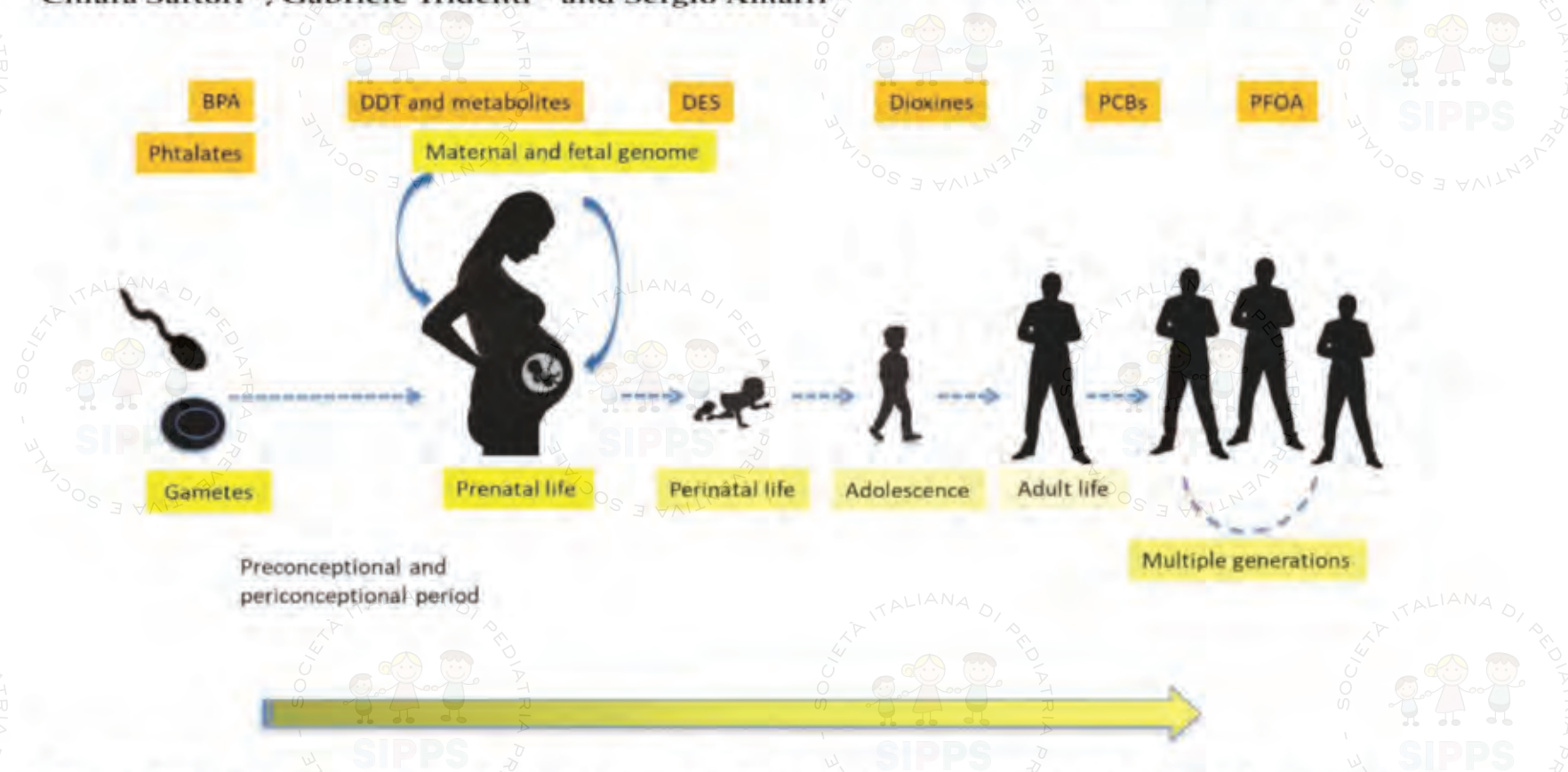
**A CHILD'S IMMATURE, POROUS BLOOD-BRAIN BARRIER ALLOWS GREATER CHEMICAL EXPOSURES TO THE DEVELOPING BRAIN.**



Review

# Current Knowledge on Endocrine Disrupting Chemicals (EDCs) from Animal Biology to Humans, from Pregnancy to Adulthood: Highlights from a National Italian Meeting

Maria Elisabeth Street <sup>1,\*</sup>, Sabrina Angelini <sup>2</sup>, Sergio Bernasconi <sup>3</sup>, Ernesto Burgio <sup>4</sup>,  
Alessandra Cassio <sup>5</sup>, Cecilia Catellani <sup>1</sup>, Francesca Cirillo <sup>1</sup>, Annalisa Deodati <sup>6</sup>,  
Enrica Fabbrizi <sup>7</sup>, Vassilios Fanos <sup>5</sup>, Giancarlo Gargano <sup>1</sup>, Enzo Grossi <sup>9</sup>, Lorenzo Iughetti <sup>10</sup>,  
Pietro Lazzeroni <sup>1</sup>, Alberto Mantovani <sup>11</sup>, Lucia Migliore <sup>12</sup>, Paola Palanza <sup>13</sup>,  
Giancarlo Panzica <sup>14,15</sup>, Anna Maria Papini <sup>16</sup>, Stefano Parmigiani <sup>17</sup>, Barbara Predieri <sup>10</sup>,  
Chiara Sartori <sup>1</sup>, Gabriele Tridenti <sup>1</sup> and Sergio Amarri <sup>1</sup>



**Figure 2.** Importance of EDCs driven epigenetic effects during life course and potential consequences across generations according to the Developmental Origins of Health and Disease (DOHaD) theory.

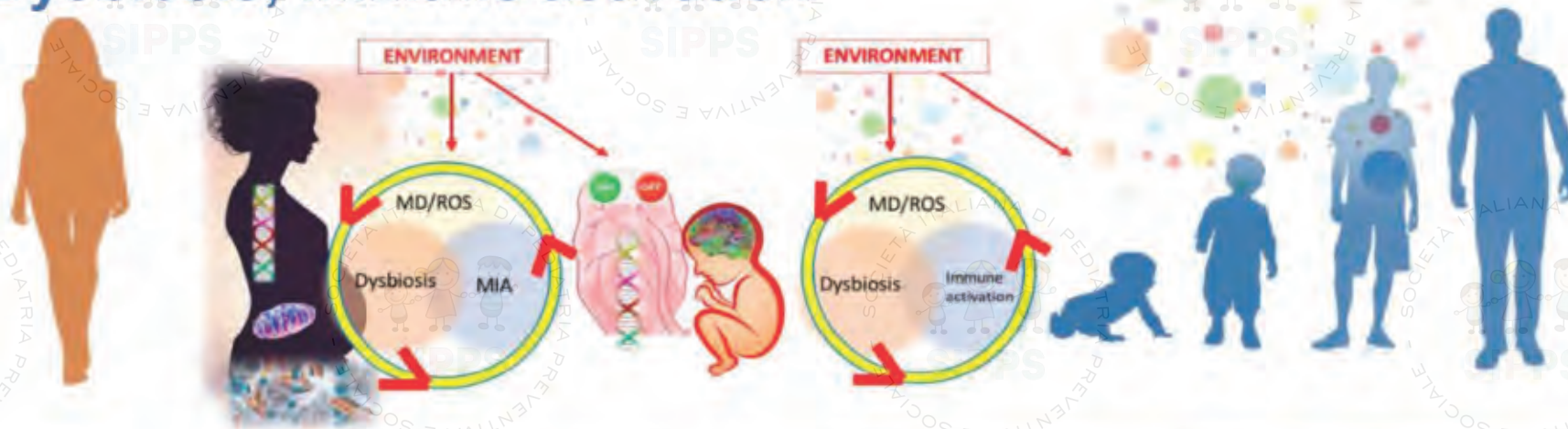


Review

# Autism Spectrum Disorder from the Womb to Adulthood: Suggestions for a Paradigm Shift

Cristina Panisi <sup>1,2,\*</sup>, Franca Rosa Guerini <sup>3,\*</sup>, Provvidenza Maria Abruzzo <sup>4</sup>, Federico Balzola <sup>5</sup>, Pier Mario Biava <sup>6</sup>, Alessandra Bolotta <sup>4</sup>, Marco Brunero <sup>7</sup>, Ernesto Burgio <sup>8</sup>, Alberto Chiara <sup>9</sup>, Mario Clerici <sup>3,10</sup>, Luigi Croce <sup>11</sup>, Carla Ferreri <sup>12</sup>, Niccolò Giovannini <sup>13</sup>, Alessandro Ghezzi <sup>4</sup>, Enzo Grossi <sup>14</sup>, Roberto Keller <sup>15</sup>, Andrea Manzotti <sup>16</sup>, Marina Marini <sup>4,\*</sup>, Lucia Migliore <sup>17</sup>, Lucio Moderato <sup>1</sup>, Davide Moscone <sup>18</sup>, Michele Mussap <sup>19</sup>, Antonia Parmeggiani <sup>20</sup>, Valentina Pasin <sup>21</sup>, Monica Perotti <sup>22</sup>, Cristina Piras <sup>23</sup>, Marina Saresella <sup>3</sup>, Andrea Stoccoro <sup>17</sup>, Tiziana Toso <sup>24</sup>, Rosa Anna Vacca <sup>25</sup>, David Vagni <sup>26</sup>, Salvatore Vendemmia <sup>27</sup>, Laura Villa <sup>28</sup>, Pierluigi Politi <sup>2</sup> and Vassilios Fanos <sup>19,29</sup>

## The “Bad Trio”: Mitochondrial dysfunction/Oxydative stress; Dysbiosis; Immune activation





# SECTION 6

***Le incredibili modificazioni  
del microbiota materno  
in gravidanza***







COMMENTARY

Open Access

### Lessons learned from the prenatal microbiome controversy

Martin J. Blaser<sup>1</sup>, Suzanne Devkota<sup>2,3</sup>, Kathy D. McCoy<sup>4</sup>, David A. Relman<sup>5,6</sup>, Miriam Voskou<sup>7</sup> and Vincent B. Young<sup>8</sup>

Frontiers Endocrinology (2021) 12:1163  
https://doi.org/10.3389/fendo.2020.00948

Microbiome

EDITORIAL

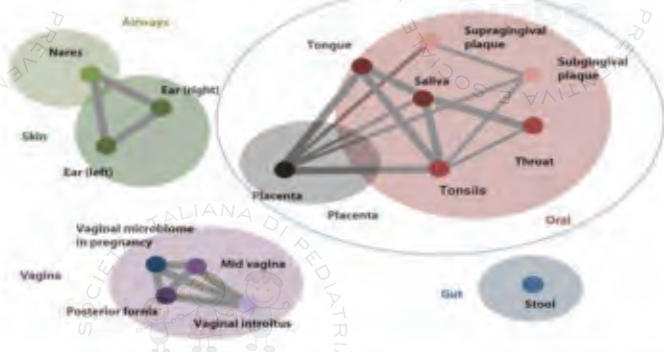
Open Access

### Microbiome or no microbiome: are we looking at the prenatal environment through the right lens?

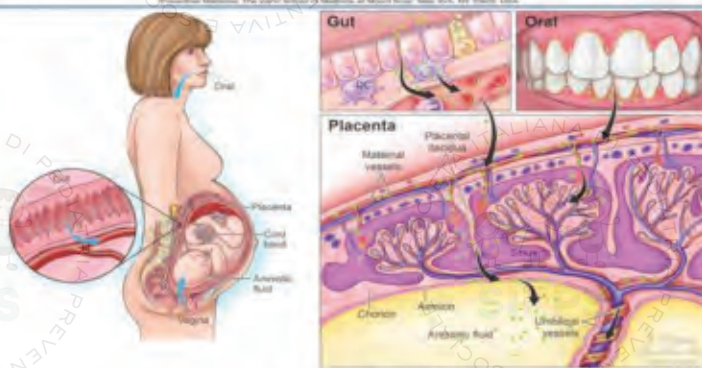
W. Florian Fricke<sup>1,2</sup> and Jacques Razet<sup>1</sup>



**The Placenta Harbors a Unique Microbiome**  
Kjersti Aagaard et al.  
*Sci Transl Med* 6, 237ra65 (2014);  
DOI: 10.1126/scitranslmed.3008599



The prenatal gut microbiome: Are we colonized with bacteria in utero?



REVIEW  
published: 14 July 2020  
doi: 10.3389/fmicb.2020.01031

**frontiers**  
in Microbiology

# Microbial Changes during Pregnancy, Birth, and Infancy

Meital Nuriel-Ohayon<sup>1</sup>, Hadar Neuman<sup>1</sup> and Omry Koren<sup>1\*</sup>

Faculty of Medicine, Bar-Ilan University, Safed, Israel

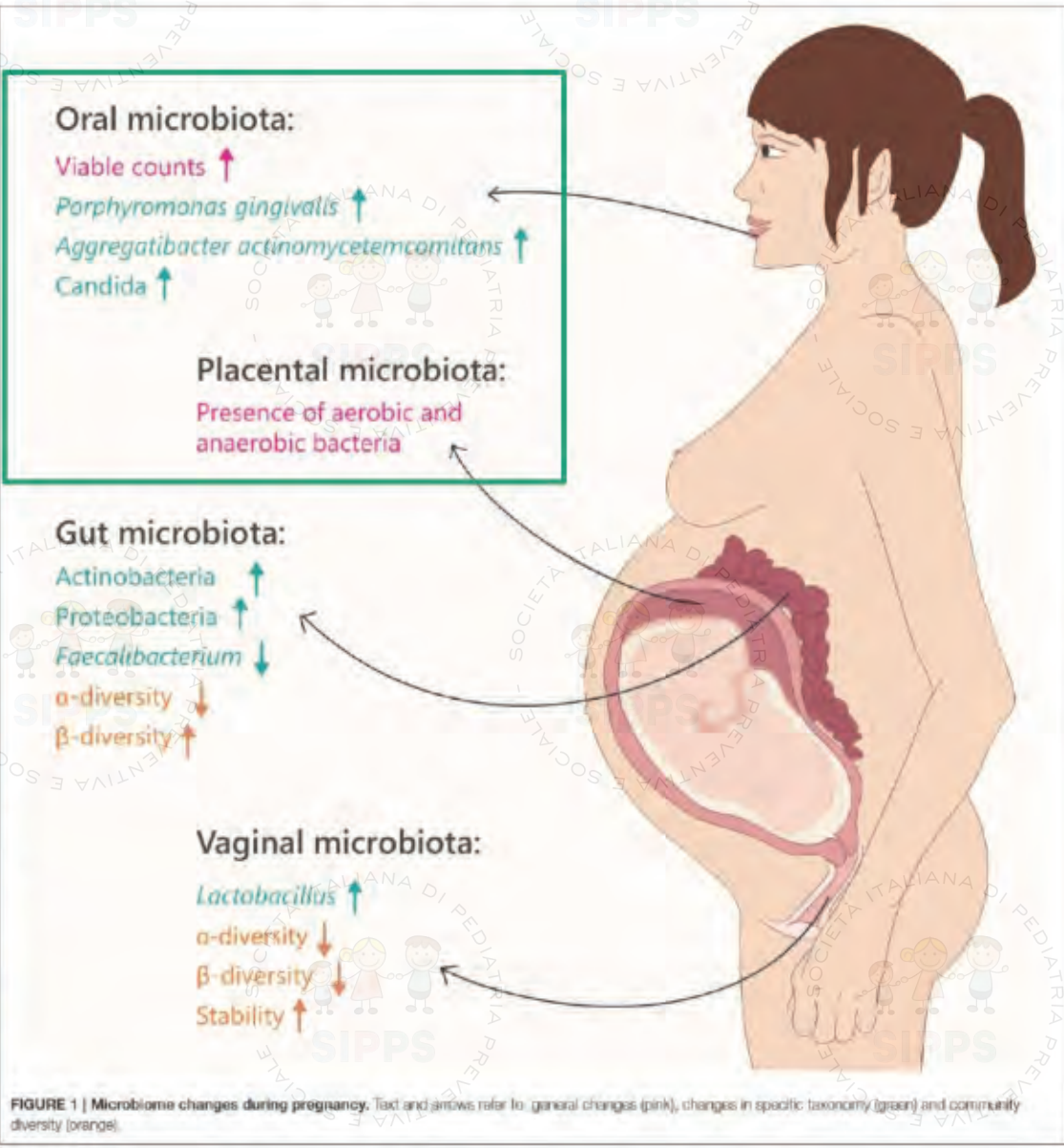
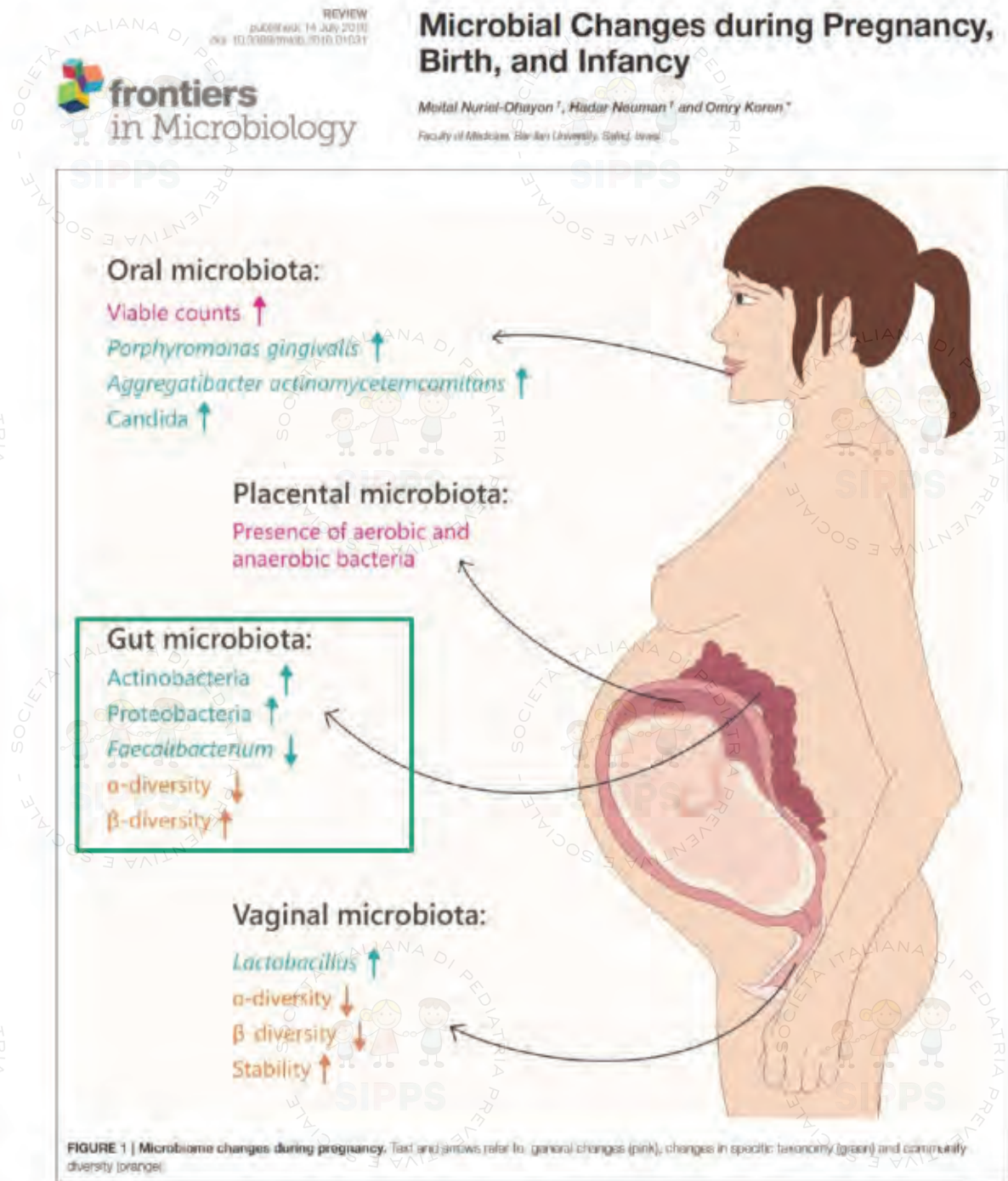


FIGURE 1 | Microbiome changes during pregnancy. Text and arrows refer to: general changes (pink), changes in specific taxonomy (green) and community diversity (orange).



- Ridotta ricchezza individuale
- Aumentata diversità tra le gestanti
- Aumento degli Actinobacteria (Bifidobatteri consumatori di mucina) controbilancia l'aumento dei Proteobacteria
- Aumento dei Proteobacteria = infiammazione e





# I batteri pionieri del neonato

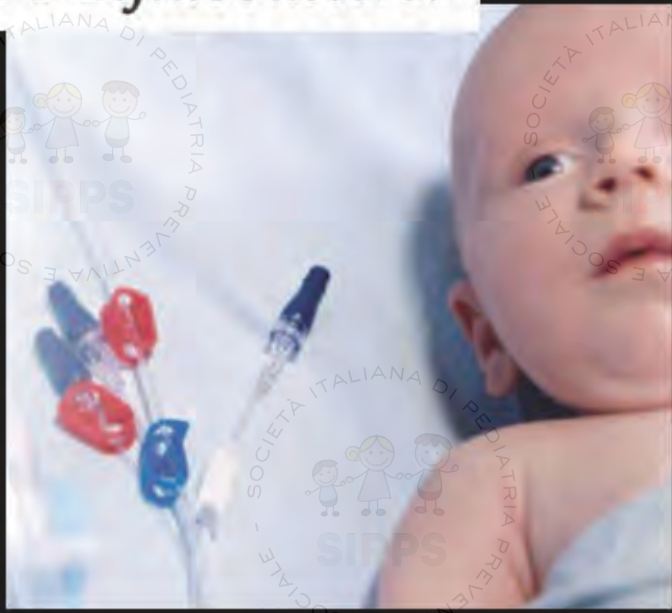
**I batteri pionieri che arrivano per primi hanno una vasta scelta di opzioni e restringono le condizioni per una successiva ondata di colonizzatori.**







**Ma dove vanno i Bifidobatteri?**



# DISBIOSI BIFIDO- BATTERICA

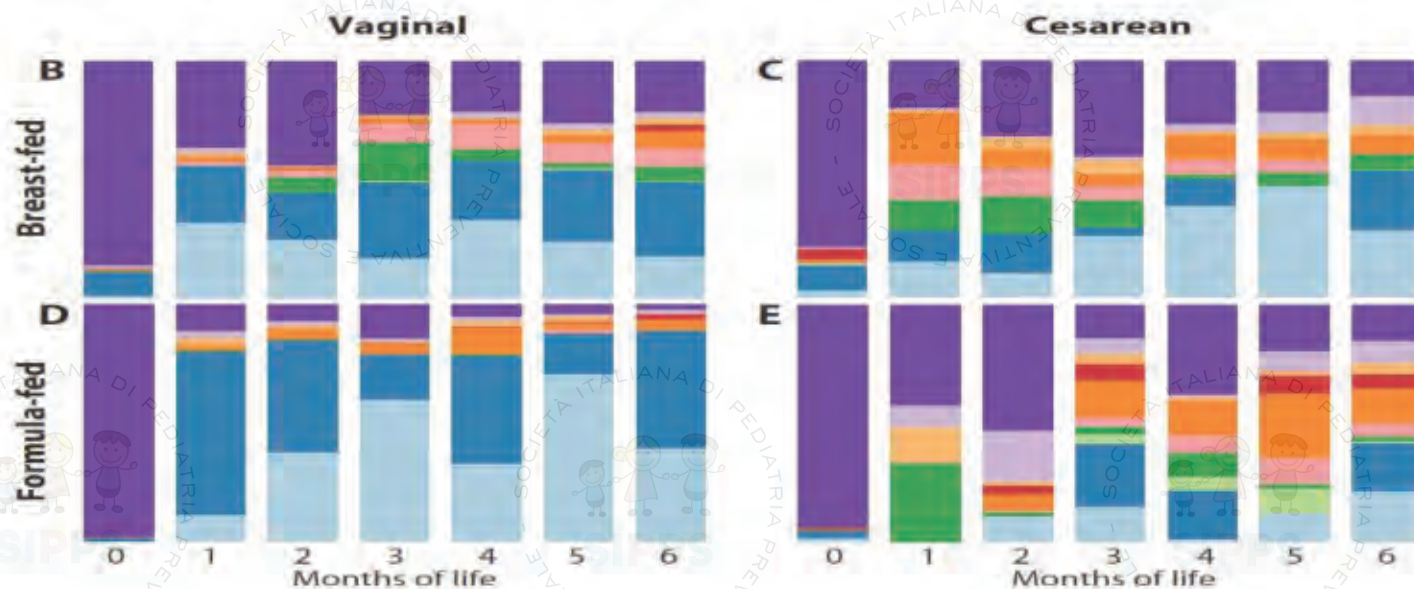
Il confronto tra vecchi e attuali studi sul microbiota mette in evidenza una perdita recente di *Bifidobatteri*, che possono essere quasi considerati "**missing microbes**", batteri perduti, in relazione a un uso inappropriato di antibiotici e di latti formulati, a percentuali elevate di tagli cesarei e a nascite pretermine.



## MICROBIOME

## Antibiotics, birth mode, and diet shape microbiome maturation during early life

Nicholas A. Bokulich,<sup>1</sup> Jennifer Chung,<sup>1</sup> Thomas Battaglia,<sup>1</sup> Nora Henderson,<sup>1</sup> Melanie Jay,<sup>1,2</sup> Huilin Li,<sup>3</sup> Amon D. Lieber,<sup>1</sup> Fen Wu,<sup>1,2</sup> Guillermo I. Perez-Perez,<sup>1,4</sup> Yu Chen,<sup>1,2</sup> William Schweizer,<sup>5</sup> Xuhui Zheng,<sup>4</sup> Monica Contreras,<sup>1</sup> Maria Gloria Dominguez-Bello,<sup>1</sup> Martin J. Blaser<sup>1,4,6\*</sup>







# Why doctors are swiping C-section babies with their mom's microbiome

Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

Maria G. Dominguez-Bello<sup>1,2,\*</sup>, Kassandra M. De Jesus-Laboy<sup>2</sup>, Nan Shen<sup>2</sup>, Laura M. Cox<sup>1</sup>, Amnon Amir<sup>3,7</sup>, Antonio Gonzalez<sup>3,7</sup>, Nicholas A. Bokulich<sup>1</sup>, Se Jin Song<sup>3,4</sup>, Marina Hoashi<sup>5</sup>, Juana I. Rivera-Vina<sup>6</sup>, Keimari Mendez<sup>2</sup>, Rob Knight<sup>3,7</sup>, and Jose C. Clemente<sup>8,9,\*</sup>

<sup>1</sup>School of Medicine, New York University, New York, NY, USA



Image: M.J. Schoen

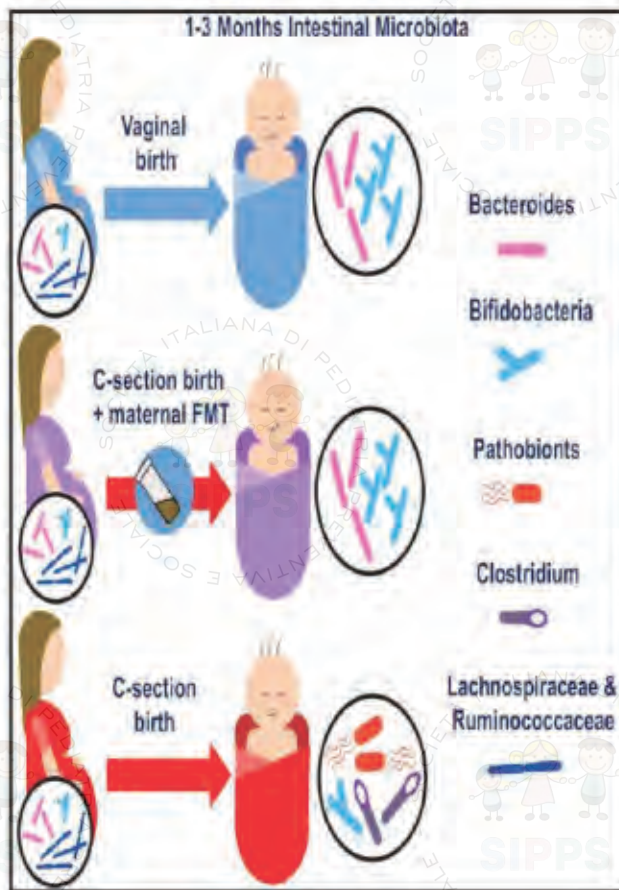


A new study aims to find out whether C-section babies can get the same microbes from their mothers as those born vaginally. Here, NYU senior research coordinator Nora Henderson collects samples of bacteria from twin boys in Mamaroneck, N.Y. (John Abbott / NYU Langone Medical Center via AP)

2020, 1st  
October

# Maternal Fecal Microbiota Transplantation in Cesarean-Born Infants Rapidly Restores Normal Gut Microbial Development: A Proof-of-Concept Study

## Graphical Abstract



## Authors

Katri Korpela, Otto Helve,  
Kaija-Leena Kolho, ..., Anne Salonen,  
Sture Andersson, Willem M. de Vos

## Correspondence

willem.devos@wur.nl

## In Brief

A proof-of-concept safety study shows that oral fecal transplantation can shift the microbiome composition of infants who are born via cesarean section to a profile that is more similar to those born via vaginal delivery.

## Highlights

- Fecal microbiota development of newborns is dependent on the mode of delivery
- The development in cesarean section-born infants deviates from that of vaginally born infants
- This deviation can be prevented by fecal microbiota transplantation from the mother
- Transplanted cesarean section-born infants show normal fecal microbiota development



# Human microbiome and allergy

Vittoria Montecchiani<sup>1</sup> | Vassilios Fanos<sup>2</sup>

## In asthma in stools:

- reduction of 4 species: *Faecalibacterium*, *Lachnospira*, *Veillonella* e *Rothia* (FLVR);
  - increased *Clostridium spp.*
- Thus, the *ratio Lachnospira/Clostridium spp.* is a biomarker for prediction of asthma.

## Key message

Human microbiome has a complex relationship with immune and metabolic networks. It plays a strong role in perinatal programming of environmentally influenced diseases such as allergic disorders.

REVIEW PAPER

# Factors influencing the development of a personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy

G. Faa<sup>1</sup>, C. Gerosa<sup>1</sup>, D. Fanni<sup>1</sup>, S. Nemolato<sup>1</sup>, P. van Eyken<sup>3</sup>, and V. Fanos<sup>2</sup>

<sup>1</sup>Department of Surgical Sciences, Division of Pathology, University Hospital San Giovanni di Dio, University of Cagliari, Cagliari, Italy,

<sup>2</sup>NIC, Puericulture Institute and Neonatal Section, University Hospital San Giovanni di Dio, University of Cagliari, Cagliari, Italy, and <sup>3</sup>Department of Pathology, K.U. Leuven, Leuven, Belgium



**Obesity?**  
**Autism?**



# Cosa siamo?

- Siamo quello che mangiamo
- (Siamo quello che digeriamo)
- Siamo quello che mangiamo nei primi giorni dal concepimento
- Siamo quello i nostri genitori e nonni hanno mangiato
- Siamo anche quello i nostri genitori e nonni non hanno mangiato
- **Siamo quello che mangiamo in rapporto al nostro microbiota!**







## Enterotipo 1

# B

+ frequente

## Enterotipo 2

# P

## Enterotipo 3

# R

Esiste veramente?

**Batterio caratterizzante**  
(who the microbes are?)

**Bacteroides**

**Prevotella**

**Ruminococcus**

**Batteri associati frequentemente**

**Parabacteroides  
Clostridiales**

**Desulfovibrionales  
Streptococcus**

**Akkermansia  
Methanobrevibacter  
Clostridiales**

**Proprietà funzionale di degradazione**  
(what the microbes do?)

**Carboidrati e  
proteine**

**Glicoproteine della  
mucina e  
polisaccaridi vegetali**

**Carboidrati e  
mucina**

**Dieta tipica**

**Carne rossa**

**Frutta e verdura  
Cereali  
Poca carne**

**Effetto**

**Grandi estrattori di  
energia (obesità?)**

**Grandi produttori di  
composti di zolfo  
(odore uova bollite)**

**Coinvolgimento nella biosintesi**

**Biotina (Vit. B7)**

**Tiamina (Vit. B1)**

**Eme (coinvolto in biosintesi Vit. B 12)**

**Consistenza delle feci**

**Dura**

**Molle**

**Dura**





## Invited Review

## The human milk microbiota: Origin and potential roles in health and disease

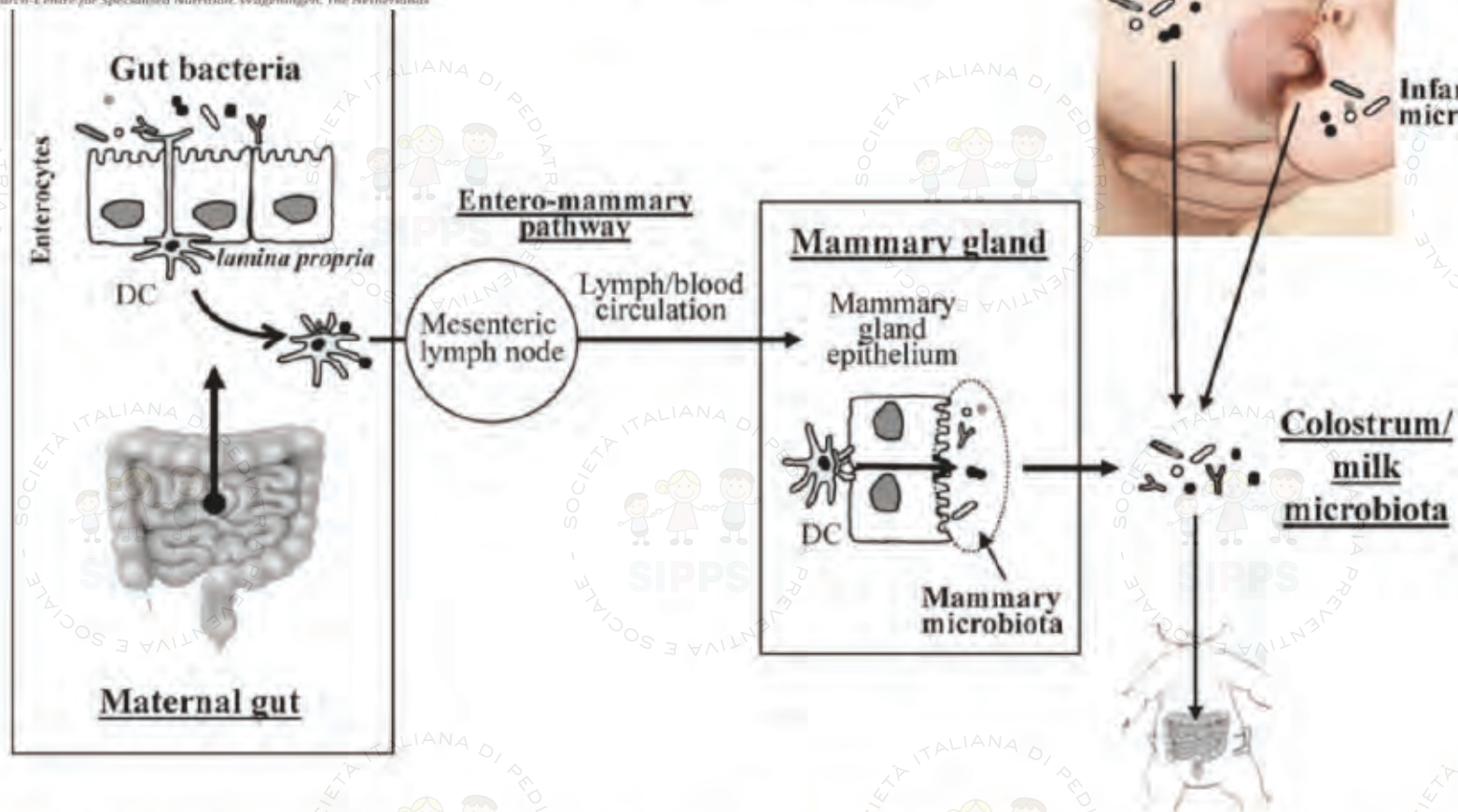
Leónides Fernández<sup>a</sup>, Susana Langa<sup>a,b</sup>, Virginia Martín<sup>a</sup>, Antonio Maldonado<sup>a,c</sup>,  
Esther Jiménez<sup>a</sup>, Rocío Martín<sup>d</sup>, Juan M. Rodríguez<sup>a,\*</sup>

<sup>a</sup> Department of Nutrition, Food Science and Food Technology, Complutense University of Madrid, 28040 Madrid, Spain

<sup>b</sup> Department of Food Technology, Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria, Carretera de la Coruña Km 7.5, 28040 Madrid, Spain

<sup>c</sup> Department of Food Biotechnology, Instituto de la Grasa-CSE, 41012 Sevilla, Spain

<sup>d</sup> Danone Research-Centre for Specialised Nutrition, Wageningen, The Netherlands



Si stima che un lattante che ingerisce 800 ml di latte materno **al giorno** possa recepire, per questa via, **fra i 100.000 e i 10.000.000 di batteri**

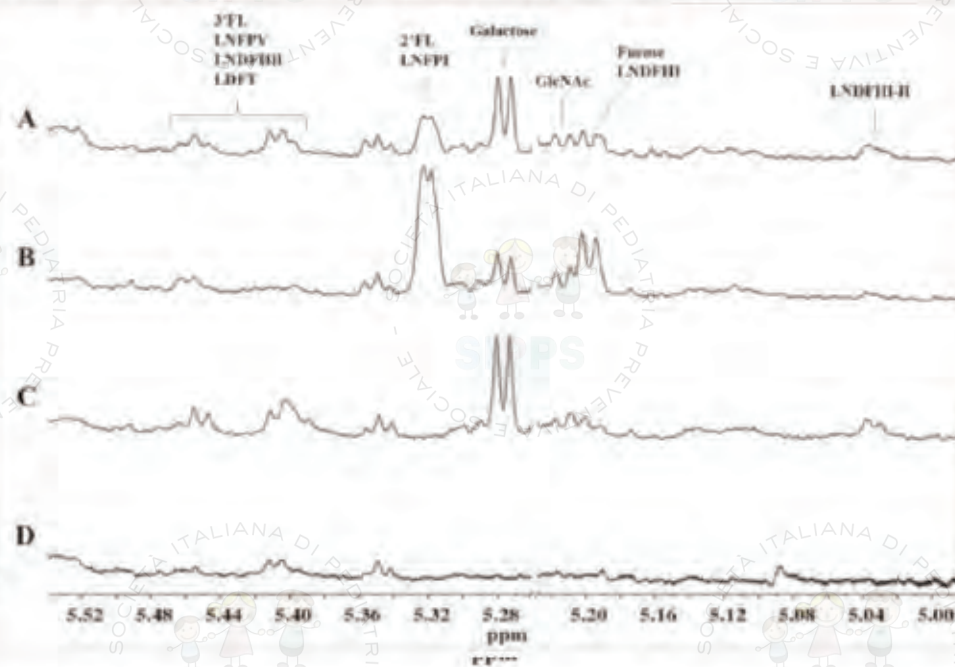
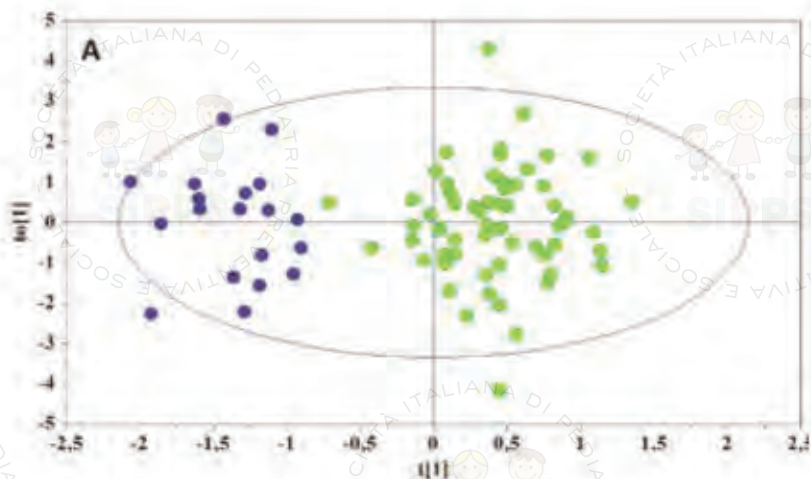


# Metabolomics of Breast Milk: The Importance of Phenotypes

Angelica Dessì <sup>1,\*†</sup>, Despina Briana <sup>2,†</sup>, Sara Corbu <sup>1</sup>, Stavroula Gavrili <sup>3</sup>,  
Flaminia Cesare Marincola <sup>4</sup>, Sofia Georgantzi <sup>3</sup>, Roberta Pintus <sup>1</sup>, Vassilios Fanos <sup>1</sup> and  
Ariadne Malamitsi-Puchner <sup>2</sup>

<sup>1</sup> Neonatal Intensive Care Unit, Neonatal Pathology and Neonatal Section, Azienda University Polyclinic, University of Cagliari, 09124 Cagliari, Italy; sari.crb@gmail.com (S.C.); gomberta@icloud.com (R.P.); vafanos@tin.it (V.F.)

<sup>2</sup> National and Kapodistrian University of Athens, 10679 Athens, Greece; brianadespina@yahoo.com (D.B.);



**Figure 6.** OPLS-DA scores (A) and coefficient (B) plots for the two groups of infants born from a secretor (green) or a non-secretor (blue) mother.  $R^2Y= 0.804$ ,  $Q^2= 0.374$ ,  $p<0.001$











June 2020

## The Human Breast Milk Metabolome in Preeclampsia, Gestational Diabetes, and Intrauterine Growth Restriction: Implications for Child Growth and Development

Flaminia Bardanzellu, MD, Melania Puddu, and Vassilios Fanos

## The Human Breast Milk Metabolome in Overweight and Obese Mothers

Flaminia Bardanzellu<sup>1†</sup>, Melania Puddu<sup>1†</sup>, Diego Giampietro Peroni<sup>2\*</sup> and Vassilios Fanos<sup>1</sup>




frontiers  
in Immunology



SIPPS

Review

## The clinical impact of maternal weight on offspring health: lights and shadows in breast milk metabolome

Flaminia Bardanzellu  , Melania Puddu, Diego Giampietro Peroni & Vassilios Fanos 

Pages 571-606 | Received 09 Apr 2021, Accepted 04 Jun 2021, Accepted author version posted online: 09 Jun 2021, Published online: 18 Aug 2021



International Journal of  
Environmental Research  
and Public Health

MDPI

Review

## Breast Milk and COVID-19: From Conventional Data to “Omics” Technologies to Investigate Changes Occurring in SARS-CoV-2 Positive Mothers

Flaminia Bardanzellu\*, Melania Puddu and Vassilios Fanos





**LIFE18 ENV/IT/000460 – Life MILCH**

**Mother and Infant dyads: Lowering the impact of endocrine disrupting Chemicals in milk for a Healthy Life**



## **Il coordinatore: partners:**



**UNIVERSITÀ DI PARMA**

**Project Leader: Prof.<sup>ssa</sup> Paola Palanza**  
Responsabile tecnico per il Dipartimento di Medicina e Chirurgia UNIPR

**Prof. Francesco Nonnis Marzano**  
Responsabile tecnico per il Dip. di Scienze Chimiche- della Vita e della Sostenibilità Ambientale UNIPR

**Dott. Davide Molena**  
Responsabile amministrativo UNIPR

**Prof.<sup>ssa</sup> Annalisa Pelosi**  
Coordinatrice unità di statistica ed epidemiologia

**I**



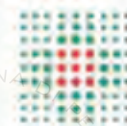
**Cagliari**

**-Prof. Vassilios Fanos**  
Responsabile tecnico UNICA  
**-Dott.<sup>ssa</sup> Patrizia Baire**  
Responsabile amministrativa UNICA



**UNIVERSITÀ  
DEGLI STUDI  
FIRENZE**

**- Prof.<sup>ssa</sup> Anna Maria Papini**  
Responsabile tecnico UNIFI PeptLab-MoD&LS  
**-Dott.<sup>ssa</sup> Giulia Masi**  
Responsabile amministrativa UNIFI



**SERVIZIO SANITARIO REGIONALE  
EMILIA-ROMAGNA**  
Azienda Unità Sanitaria Locale di Reggio Emilia  
IRCCS Istituto di Ricovero e Cura a Carattere Scientifico

**- Prof.<sup>ssa</sup> Maria Street**  
Responsabile tecnico REGGIO  
**- Dott.<sup>ssa</sup> Sara Li Donni**  
Responsabile amministrativa REGGIO

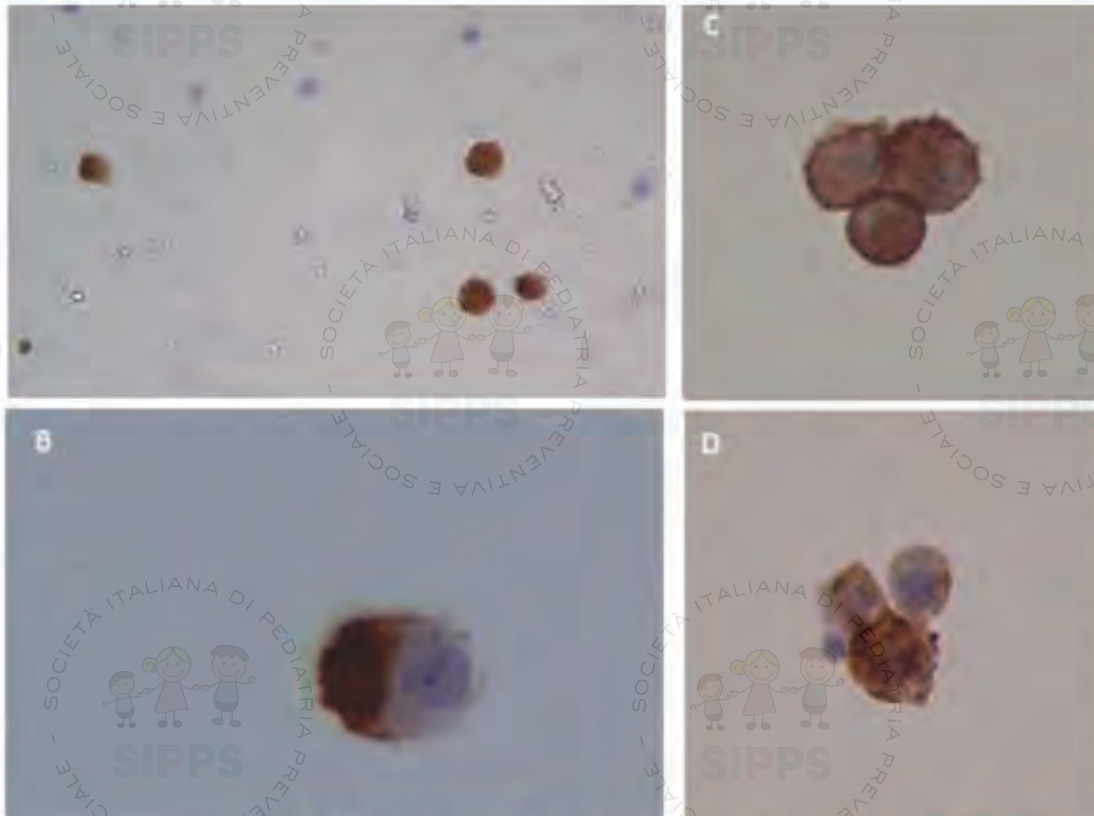


# Human breast milk stem cells: a new challenge for perinatologist

Giuseppina Pichiri<sup>1</sup>, Daniele Lanzano<sup>1</sup>, Monica Piras<sup>1</sup>, Angelica Dessì<sup>2</sup>,  
Alessandra Reali<sup>2</sup>, Melania Puddu<sup>2</sup>, Vassilios Fanos<sup>2</sup>, Gavino Faa<sup>1</sup>,  
Pierpaolo Coni<sup>1</sup>

<sup>1</sup>Department of Surgical Sciences, Section of Pathology, University of Cagliari, Cagliari, Italy

<sup>2</sup>Neonatal Intensive Care Unit, Neonatal Pathology, Puericulture Institute and Neonatal Section, AOU and University of Cagliari, Cagliari, Italy

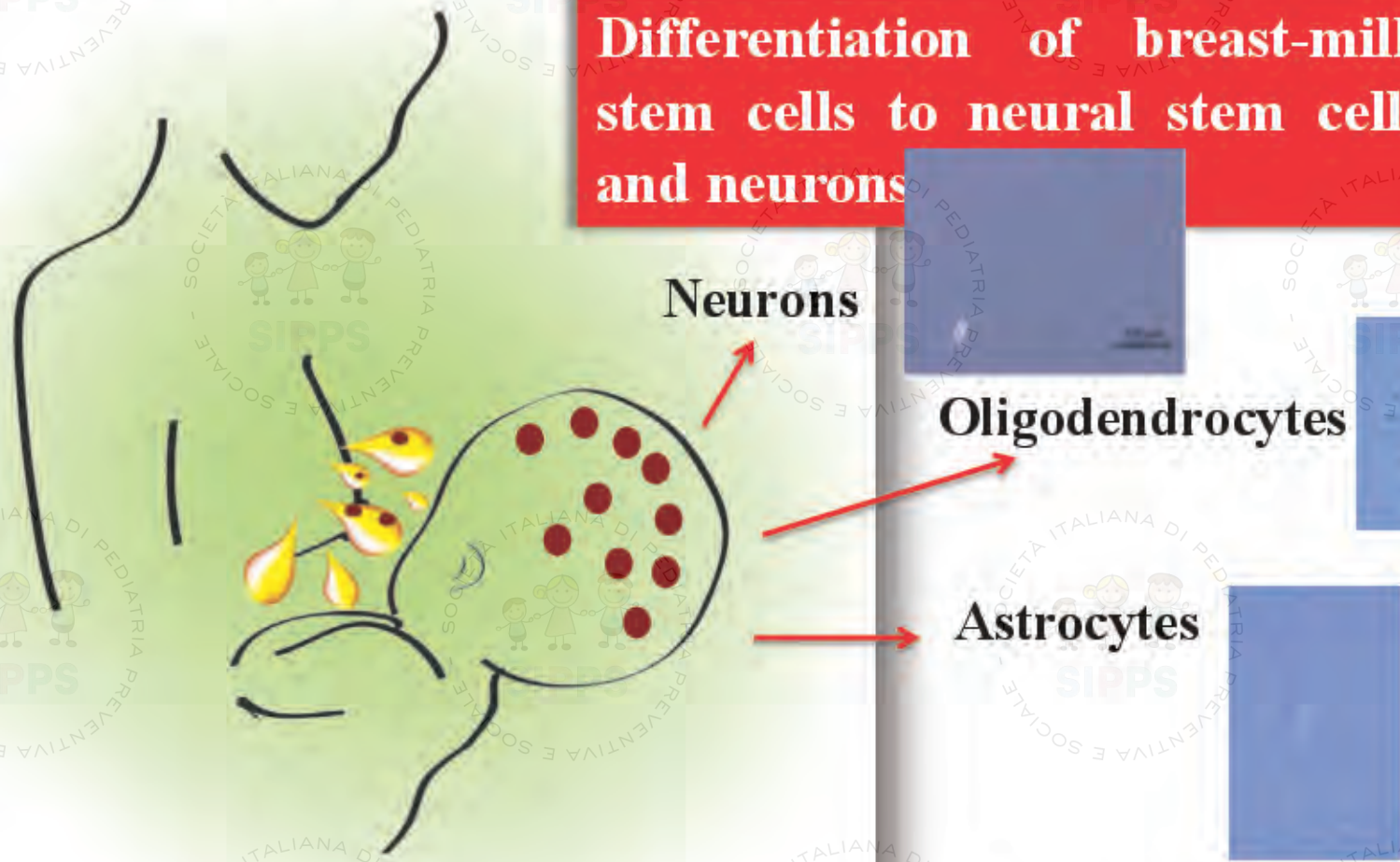


**Only few cells  
are CD44  
positive!  
Metabolomics  
applied to the  
study of stem  
cells**

**CD 44 is a good marker of milk stem**

# FROM BREAST MILK TO BRAIN HUMAN MILK PROGRAMMING (DOHaD)

**Differentiation of breast-milk stem cells to neural stem cells and neurons**



**Neurons**

**Oligodendrocytes**

**Astrocytes**

Metabolomica liquido  
cellule staminali





# SECTION 7

***Un esempio di grande  
complessità: i disturbi dello  
spettro autistico***

# Review

## Fetal Programming of Neuropsychiatric Disorders

Gavino Faa<sup>1</sup>, Mirko Manchia<sup>2,3</sup>, Roberta Pintus<sup>4</sup>, Clara Gerosa<sup>1</sup>,  
Maria Antonietta Marcialis<sup>4</sup>, and Vassilios Fanos<sup>\*4</sup>

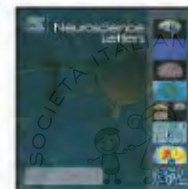
Birth Defects Research (Part C)  
© 2016 Wiley Periodicals, Inc.



Contents lists available at [ScienceDirect](#)

### Neuroscience Letters

journal homepage: [www.elsevier.com/locate/neulet](http://www.elsevier.com/locate/neulet)



#### Review article

### The role of neuropathological markers in the interpretation of neuropsychiatric disorders: Focus on fetal and perinatal programming

Daniela Fanni<sup>a,\*</sup>, Clara Gerosa<sup>a</sup>, Monica Rais<sup>b</sup>, Alberto Ravarino<sup>a</sup>, Peter Van Eyken<sup>c</sup>,  
Vassilios Fanos<sup>d</sup>, Gavino Faa<sup>a</sup>

<sup>a</sup> Division of Pathology, Department of Surgical Sciences, University of Cagliari, Italy

<sup>b</sup> Rudolf Magnus Institute of Neuroscience, Department of Psychiatry, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>c</sup> Department of Pathology, Ziekenhuis Oost Limburg (ZOL), Genk, Belgium

<sup>d</sup> NICU Center and Puericulture Institute and Neonatal Section, Department of Surgical Sciences, University of Cagliari, Italy

Progress in Neuropsychopharmacology & Biological Psychiatry 77 (2017) 32–41



Contents lists available at [ScienceDirect](#)

### Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: [www.elsevier.com/locate/psnp](http://www.elsevier.com/locate/psnp)



### Targeting aggression in severe mental illness: The predictive role of genetic, epigenetic, and metabolomic markers

Mirko Manchia<sup>a,b</sup>, Vassilios Fanos<sup>c,d,\*</sup>

<sup>a</sup> Section of Psychiatry, Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

<sup>b</sup> Department of Pharmacology, Dalhousie University, Halifax, Nova Scotia, Canada

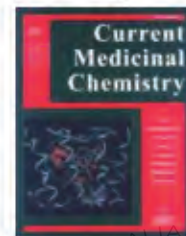
<sup>c</sup> Department of Surgical Sciences, University of Cagliari and Neonatal Intensive Care Unit, Cagliari, Italy

<sup>d</sup> Puericulture Institute and Neonatal Section, Azienda Ospedaliera Universitaria, Cagliari, Italy



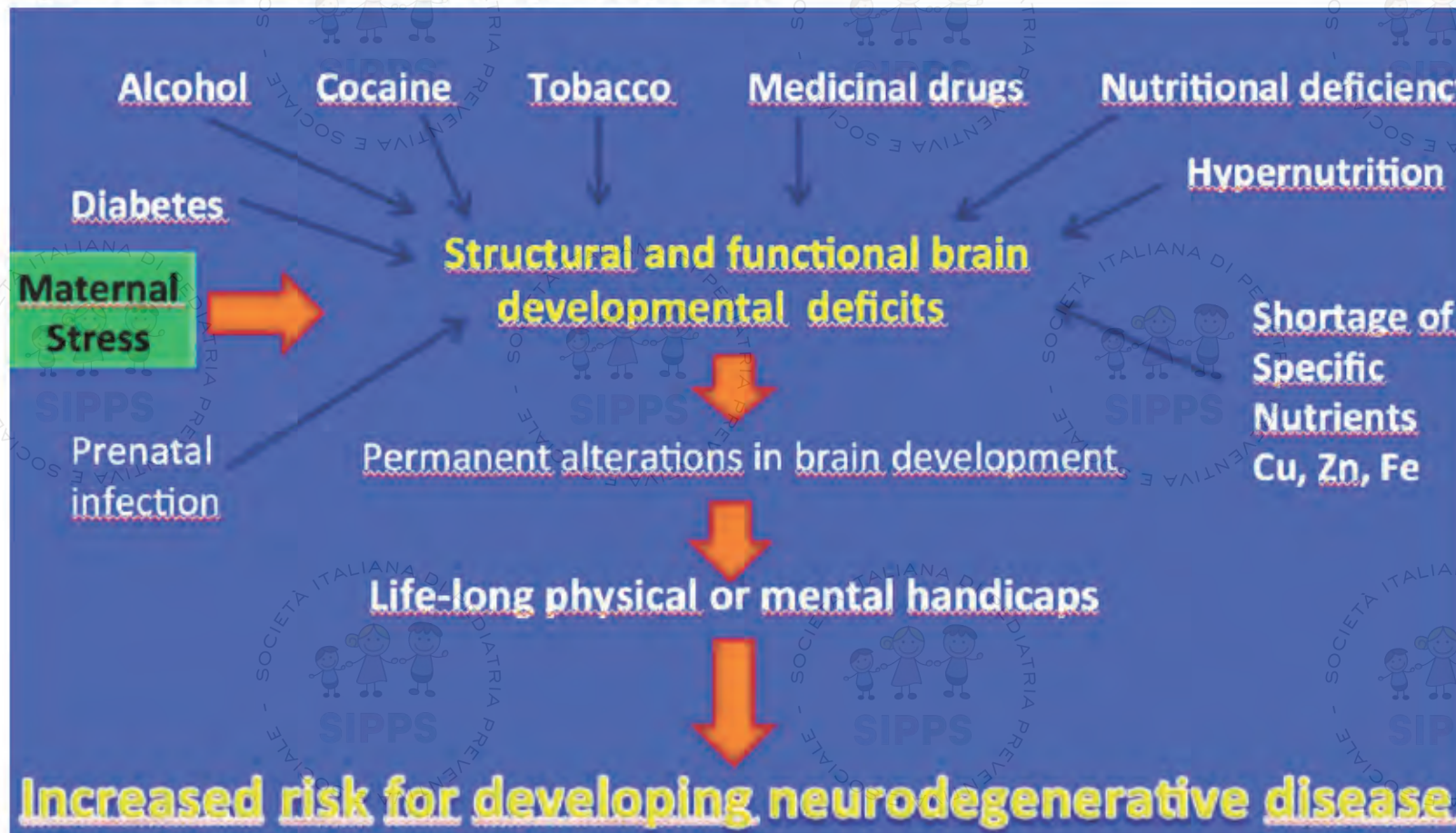


# Fetal Programming of the Human Brain: Is there a Link with Insurgence of Neurodegenerative Disorders in Adulthood?

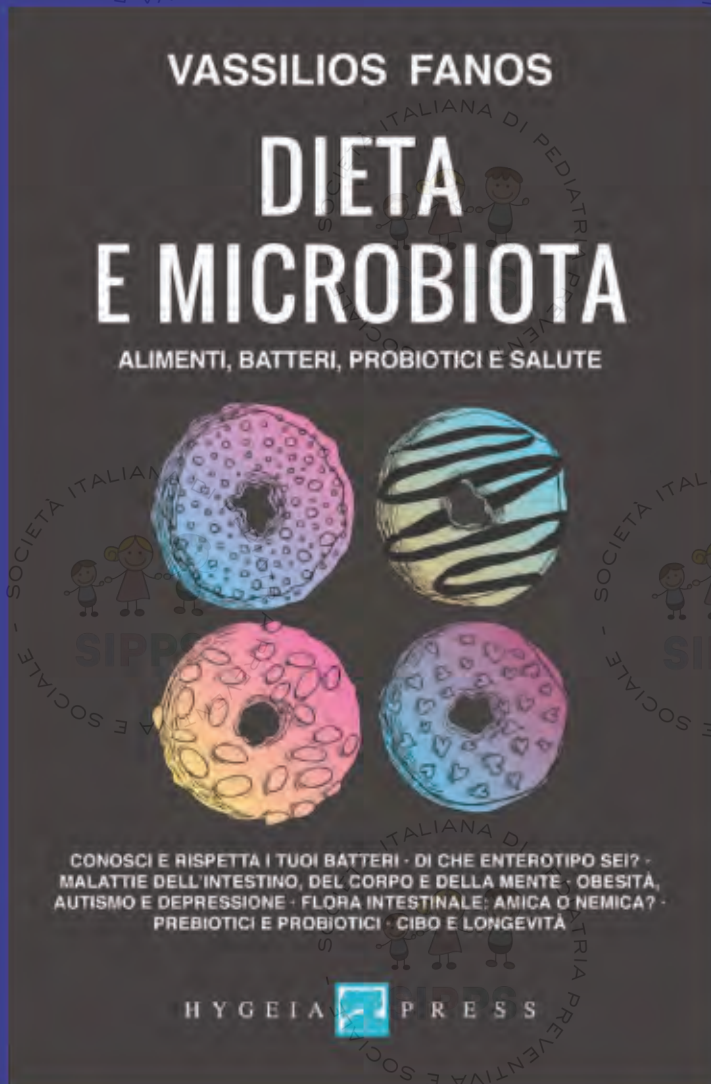


G. Faa<sup>1</sup>, MA. Marcialis<sup>2</sup>, A. Ravarino<sup>1</sup>, M. Piras\*<sup>1</sup>, MC. Pintus<sup>2</sup> and V. Fanos<sup>2</sup>

<sup>1</sup>Division of Pathology; and <sup>2</sup>Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, Department of Surgical Sciences, AOU and University of Cagliari, Cagliari, Italy



# Dieta, batteri, metaboliti, autismo

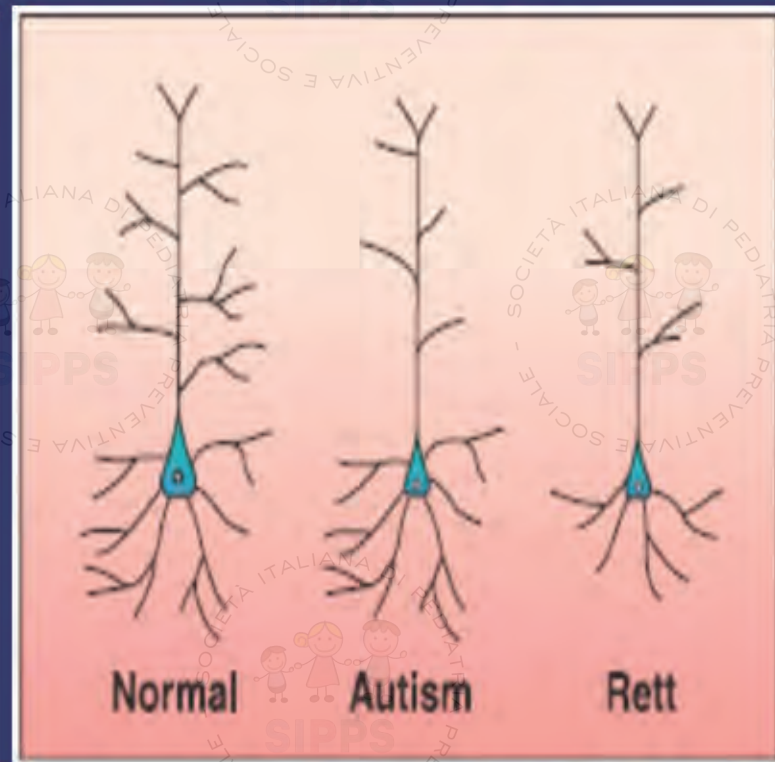
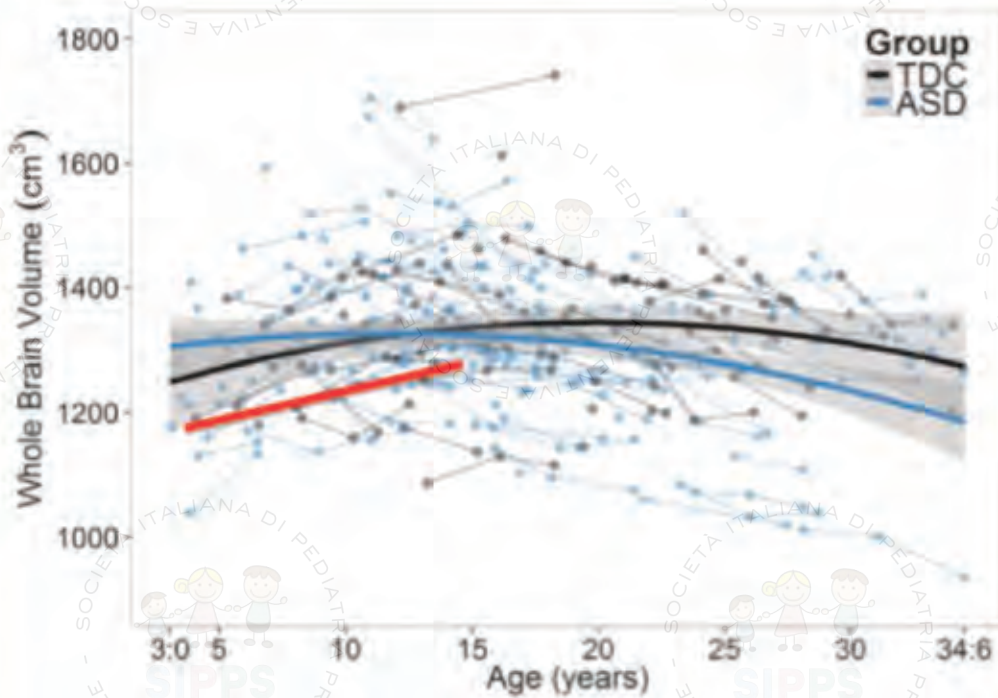


## Autismo Tipo di danno

- prenatale cronico
- prenatale acuto
- postnatale acuto
- postnatale cronico
- combinato



# Brain volume by age and group



<https://dx.doi.org/10.56077/en.2015.24.4.273>  
Exp Neurobiol. 2015 Dec;24(4):273-284.  
pISSN 1226-2560 • eISSN 2093-8114

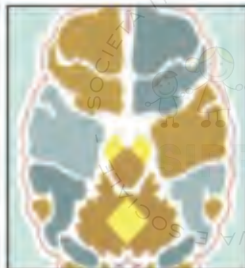
Review Article: Autism Spectrum Disorders

**en**  
Experimental Neurobiology

## Characteristics of Brains in Autism Spectrum Disorder: Structure, Function and Connectivity across the Lifespan

Sungji Ha<sup>1</sup>, In-Jung Sohn<sup>1,2</sup>, Namwook Kim<sup>1,2</sup>, Hyeon Jeong Sim<sup>1</sup> and Keun-Ah Cheon<sup>1,2\*</sup>

<sup>1</sup>Department of Psychiatry, Institute of Behavioral Science in Medicine and Yonsei Autism Laboratory, Yonsei University College of Medicine, Seoul 03722, <sup>2</sup>Division of Child and Adolescent Psychiatry, Severance Children's Hospital, Yonsei University College of Medicine, Seoul 03722, Korea



# THE AUTISM ENIGMA

Sorting fact from fiction

[nature.com/autism](http://nature.com/autism)



SIPPS



Expert Review of Molecular Diagnostics

ISSN: 1473-7159 (print) 1744-8352 (Online) | journal homepage: <http://www.tandfonline.com/loi/hero20>

## Metabolomics of autism spectrum disorders: early insights regarding mammalian-microbial cometabolites

Michele Mussap, Antonio Noto & Vassilios Fanos

### METABOLOMICS AND AUTISM

M. Mussap<sup>1</sup>, C. Moretti<sup>2</sup>, A. Noto<sup>3</sup>, V. Fanos<sup>3</sup>

<sup>1</sup>Laboratory Medicine Service, IRCCS AOU San Martino-IST, University Hospital, Genoa, Italy

<sup>2</sup>Pediatric Emergency and Intensive Care, Department of Pediatrics and Pediatric Neuropsychiatry, Policlinico Umberto I, Sapienza University, Rome, Italy

<sup>3</sup>Neonatal Intensive Care Unit, Neonatal Pathology and Neonatal Section, AOU and University of Cagliari, Cagliari, Italy

THE JOURNAL OF  
MATERNAL-FETAL  
& NEONATAL  
MEDICINE

<http://informahealthcare.com/jmf>  
ISSN: 1476-7058 (print), 1476-8954 (electronic)  
J Matern Fetal Neonatal Med, 2014; 27(52): 1-7  
© 2014 Informa UK Ltd. DOI: 10.3109/14767058.2014.954794

informa  
healthcare

#### ORIGINAL ARTICLE

### The urinary metabolomics profile of an Italian autistic children population and their unaffected siblings

Antonio Noto<sup>1</sup>, Vassilios Fanos<sup>1</sup>, Luigi Barberini<sup>2</sup>, Dmitry Grapov<sup>3</sup>, Claudia Fattuoni<sup>4</sup>, Marco Zaffanello<sup>5</sup>, Andrea Casanova<sup>6</sup>, Gianni Fenu<sup>7</sup>, Andrea De Giacomo<sup>8</sup>, Maria De Angelis<sup>9</sup>, Corrado Moretti<sup>10</sup>, Paola Papoff<sup>10</sup>, Raffaella Dittono<sup>11</sup>, and Ruggiero Francavilla<sup>11</sup>

### Aut Res 2017

### The Urinary <sup>1</sup>H-NMR Metabolomics Profile of an Italian Autistic Children Population and Their Unaffected Siblings

Milena Lussu, Antonio Noto, Alice Masili, Andrea C. Rinaldi, Angelica Dessi, Maria De Angelis, Andrea De Giacomo, Vassilios Fanos, Luigi Atzori, and Ruggiero Francavilla

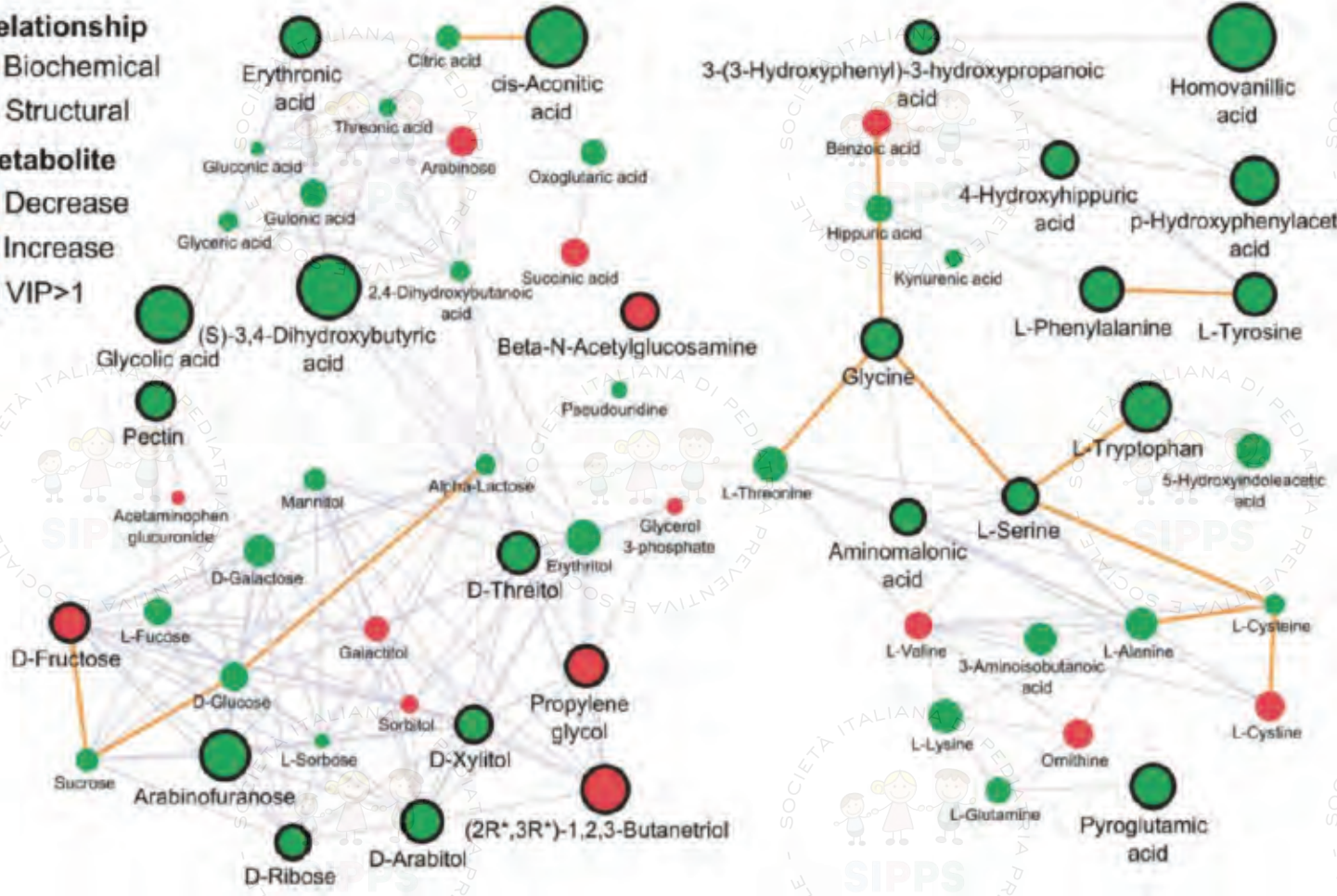




# HOW does it work?

## Scale-Free Networks

- Relationship**
- Biochemical
  - Structural
- Metabolite**
- Decrease
  - Increase
  - VIP > 1



THE JOURNAL OF  
**MATERNAL-FETAL  
& NEONATAL  
MEDICINE**

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healthcare

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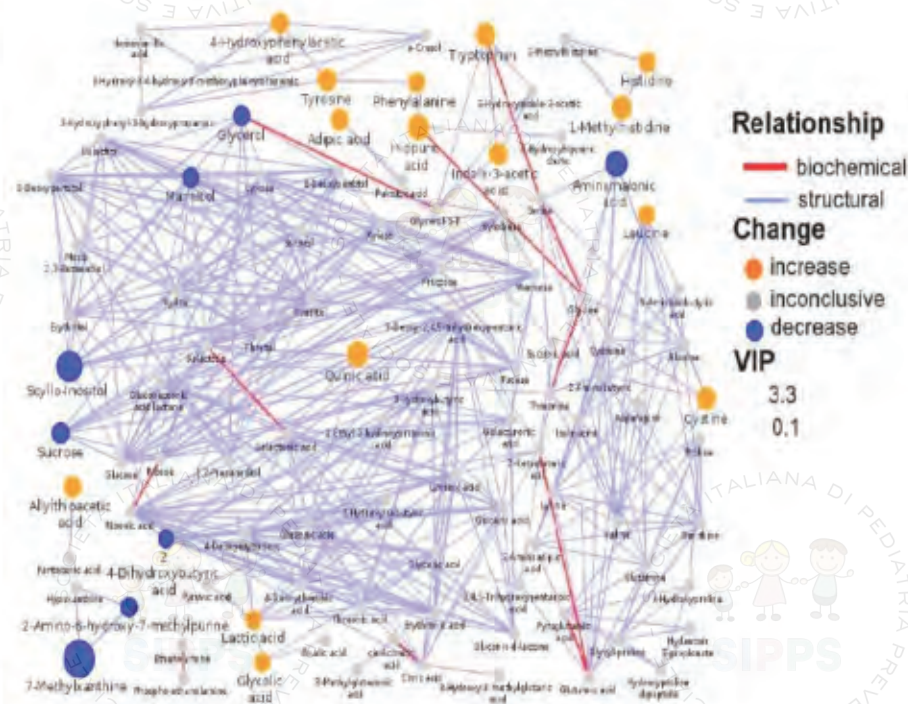
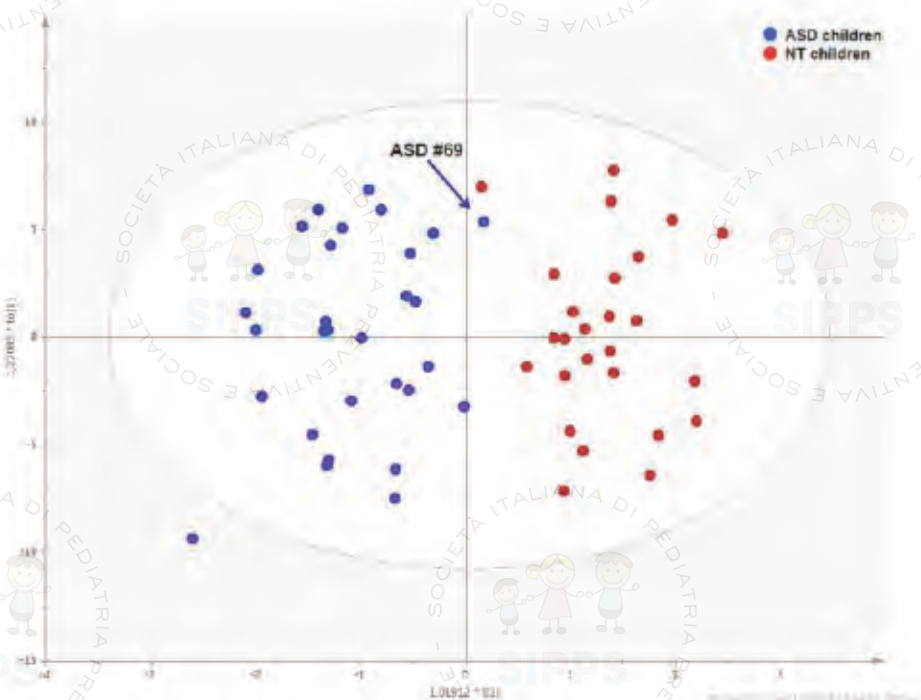




Article

# The Urine Metabolome of Young Autistic Children Correlates with Their Clinical Profile Severity

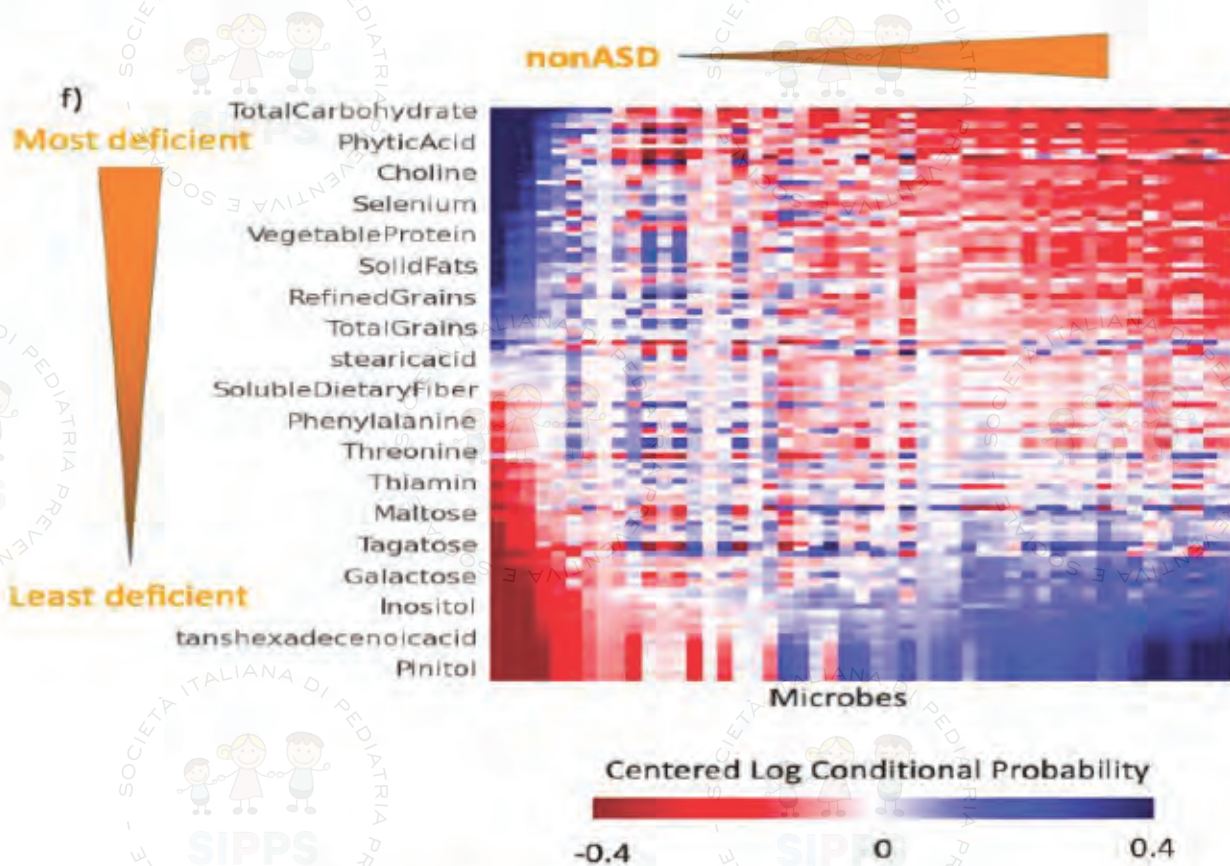
Michele Mussap <sup>1,\*</sup>, Martina Siracusano <sup>2,3</sup>, Antonio Noto <sup>4</sup>, Claudia Fattuoni <sup>5</sup>, Assia Riccioni <sup>6</sup>, Hema Sekhar Reddy Rajula <sup>1</sup>, Vassilios Fanos <sup>1</sup>, Paolo Curatolo <sup>6</sup>, Luigi Barberini <sup>4</sup> and Luigi Mazzone <sup>6</sup>





# Multi-omic analysis along the gut-brain axis points to a functional architecture of autism

James T. Morton<sup>1,2</sup>, Dong-Min Jin<sup>3</sup>, Robert H. Mills<sup>4</sup>, Yan Shao<sup>5</sup>, Gibraan Rahman<sup>6</sup>, Kirsten Berding<sup>7</sup>, Brittany D. Needham<sup>8</sup>, María Fernanda Zurita<sup>9</sup>, Maude David<sup>10</sup>, Olga V. Averina<sup>11</sup>, Alexey S. Kovtun<sup>11, 12</sup>, Antonio Noto<sup>13</sup>, Michele Mussap<sup>13</sup>, Mingbang Wang<sup>14</sup>, Daniel Frank<sup>15</sup>, Ellen Li<sup>16</sup>, Wenhao Zhou<sup>14</sup>, Vassilios Fanos<sup>13</sup>, N. Valery Danilenko<sup>11</sup>, Dennis P. Wall<sup>17</sup>, Paúl Cárdenas<sup>18</sup>, Manuel E. Baldeón<sup>19</sup>, Ramnik J. Xavier<sup>20, 21, 22</sup>, Sarkis Mazmanian<sup>8</sup>, Rob Knight<sup>23, 24, 25</sup>, Jack A. Gilbert<sup>23, 26</sup>, Sharon M. Donovan<sup>27</sup>, Trevor Lawley<sup>5</sup>, Bob Carpenter<sup>1</sup>, Richard Bonneau<sup>1, 3</sup>, and Gaspar Taroncher-Oldenburg<sup>2</sup>



2022 (submitted)



## The juniper bush of autism spectrum disorder (ASD): metabolomics, microbiomics, acetaminophen. What else?

Vassilios Fanos<sup>1</sup>, Antonio Noto<sup>2</sup>, Michele Mussap<sup>3</sup>

<sup>1</sup>Department of Surgical Sciences, Neonatal Intensive Care Unit, Neonatal Pathology and Neonatal Section, University of Cagliari, Cagliari, Italy

<sup>3</sup>Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

EXPERT REVIEW OF CLINICAL PHARMACOLOGY

2020, VOL. 13, NO. 2, 115-134

<https://doi.org/10.1080/17512433.2020.1713750>



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Taylor & Francis Group

REVIEW



### Metabolomics in pharmacology - a delve into the novel field of pharmacometabolomics

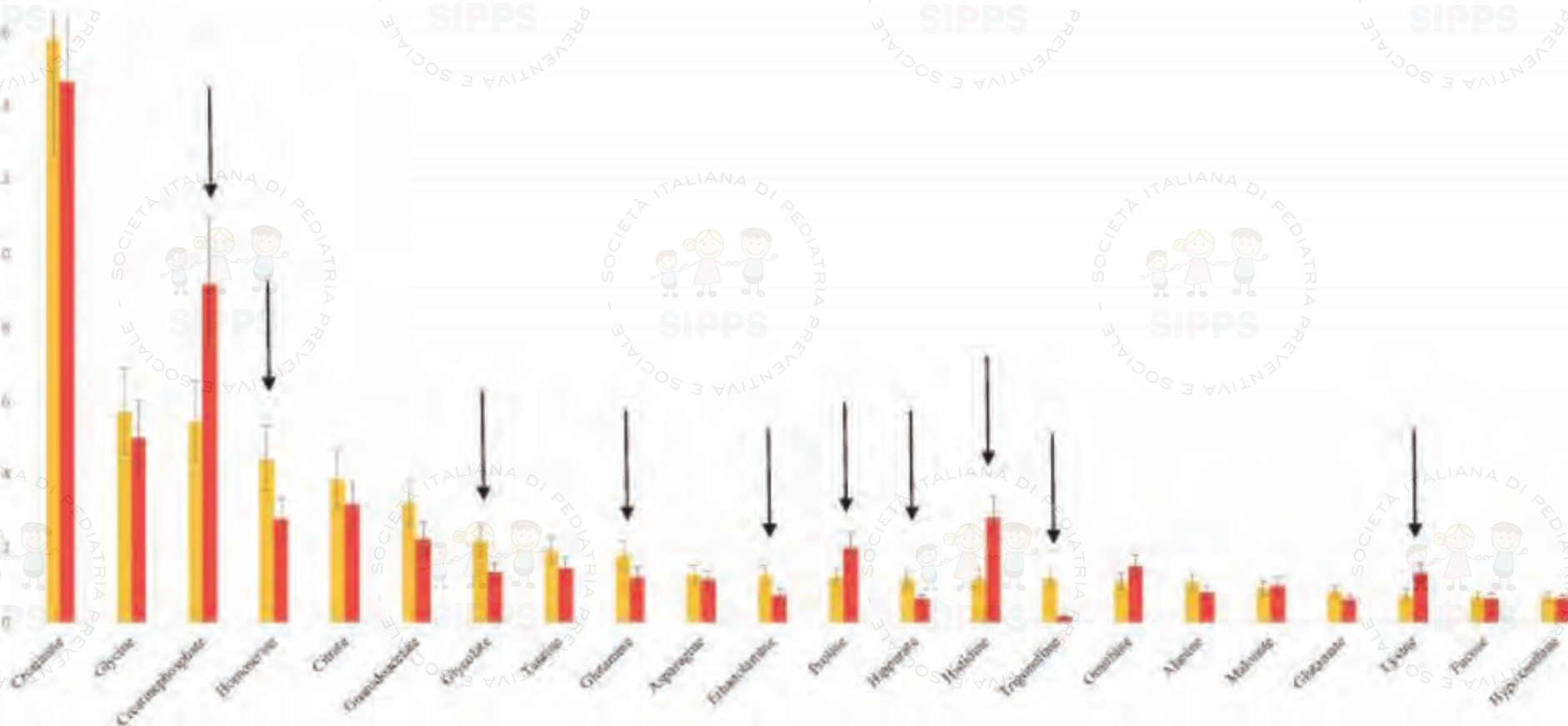
Michele Mussap<sup>a</sup>, Cristina Loddo<sup>b</sup>, Claudia Fanni<sup>b</sup> and Vassilios Fanos<sup>c</sup>



# Pediatric Acute-onset Neuropsychiatric Syndrome and *Mycoplasma Pneumoniae* Infection: A Case Report Analysis with a Metabolomics Approach

Cristina Piras<sup>1</sup>, Roberta Pintus<sup>2</sup>, Dario Pruna<sup>3</sup>, Angelica Dessi<sup>2</sup>, Luigi Atzori<sup>1</sup> and Vassilios Fanos<sup>2,\*</sup>

■ Metabolites before  
■ Metabolites after pharmacological treatment





*medicina*

Review

# Comparison of Conventional Statistical Methods with Machine Learning in Medicine: Diagnosis, Drug Development, and Treatment

Hema Sekhar Reddy Rajula<sup>1,2</sup>, Giuseppe Verlato<sup>3</sup>, Mirko Manchia<sup>4,5,\*</sup>, Nadia Antonucci<sup>3</sup> and Vassilios Fanos<sup>1</sup>

Medicina 2020, 56, 455;

EXPERT REVIEW OF PRECISION MEDICINE AND DRUG DEVELOPMENT  
<https://doi.org/10.1080/23808993.2021.1911639>



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REVIEW



## Slotting metabolomics into routine precision medicine

Michele Mussap<sup>a</sup>, Antonio Noto<sup>b</sup>, Cristina Piras<sup>c,d</sup>, Luigi Atzori<sup>e</sup> and Vassilios Fanos<sup>a</sup>

<sup>a</sup>Department of Surgical Science, University of Cagliari, Monserrato, Italy; <sup>b</sup>Department of Medical Sciences and Public Health, University of Cagliari, Monserrato, Italy; <sup>c</sup>Department of Biomedical Sciences, University of Cagliari, Monserrato, Italy

# PAI

PEDIATRIC ALLERGY  
AND IMMUNOLOGY

Guest Editors

Gian Luigi Marseglia,  
Amelia Licari

Volume 33 Supplement 27 January 2022

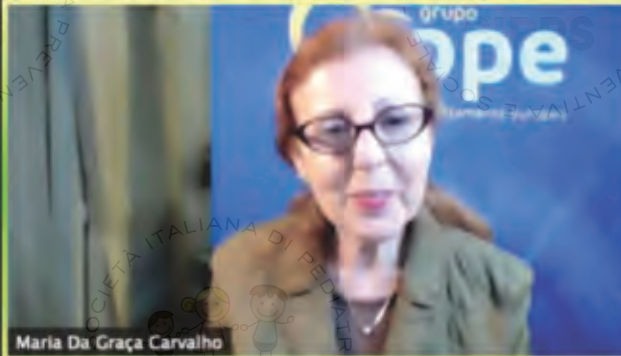
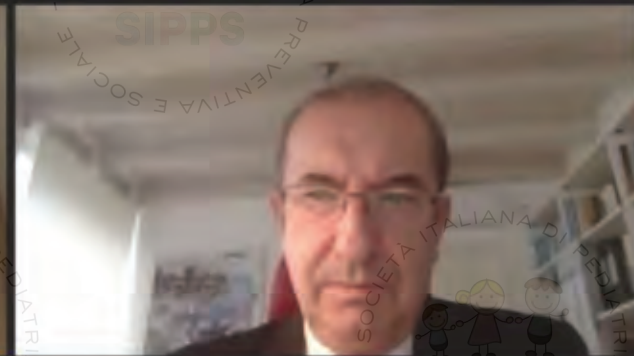
WILEY

## Metabolomics, Microbiomics, Machine learning during the COVID-19 pandemic

Flaminia Bardanzellu<sup>a</sup> | Vassilios Fanos<sup>b</sup> *Riservata al personale sanitario*



# 12th European Innovation Summit, European Parliament



**12TH EUROPEAN INNOVATION SUMMIT**  
TOWARDS A EUROPEAN INNOVATION AREA


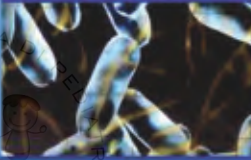
7 - 11 December 2020



**TIME**  
December 7 (Monday) - 11 (Friday)

**LOCATION**  
European Parliament, Brussels

**12th EUROPEAN INNOVATION SUMMIT 2020**  
Towards a European innovation Area



**Metabolomics,  
Microbiomics,  
and  
Artificial Intelligence**

**Vassilios Fanos**  
vafanos@tiscali.it

Neonatal Intensive Care Unit,  
University of Cagliari - Italy



# SECTION 8

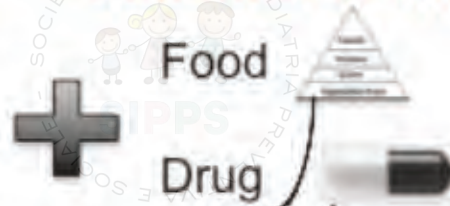
*Dagli albori della vita...*



**Genomica**



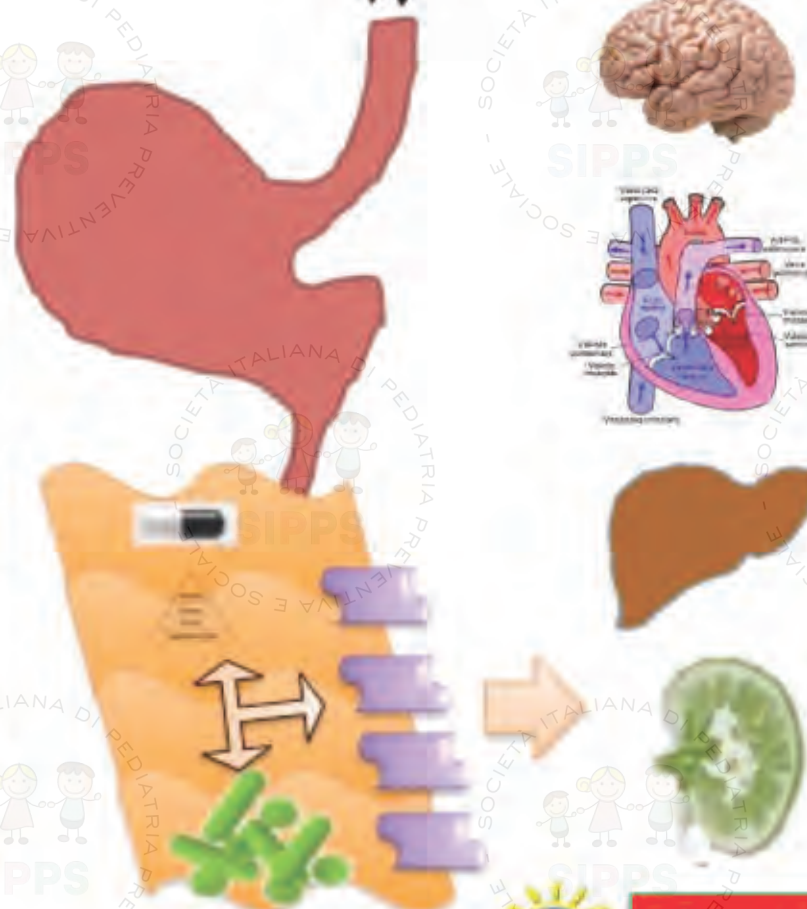
**Nutrimetabolomica**



**Siamo un ecosistema**

Ogni essere umano con i propri batteri (il proprio microbiota) è un olobionte.

La Medicina oggi cura il singolo individuo e non l'intero ecosistema.



Vi è un fitto dialogo tra i batteri tra loro e con i vari organi e, oggi, la metabolomica ci consente di decifrare e capire molte di queste comunicazioni, il linguaggio segreto del nostro corpo



**Nutrimicrobiomica**

**Comprendere la complessità**

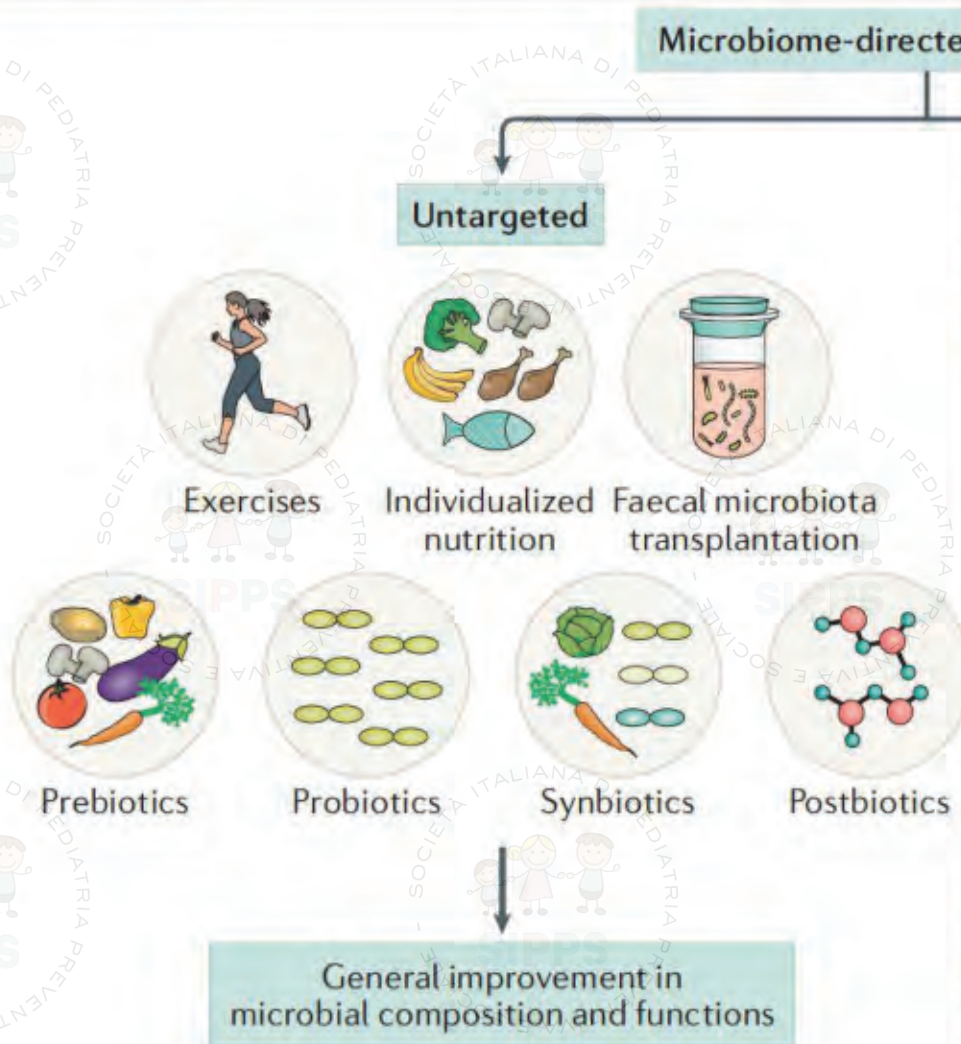


# Gut microbiota in human metabolic health and disease

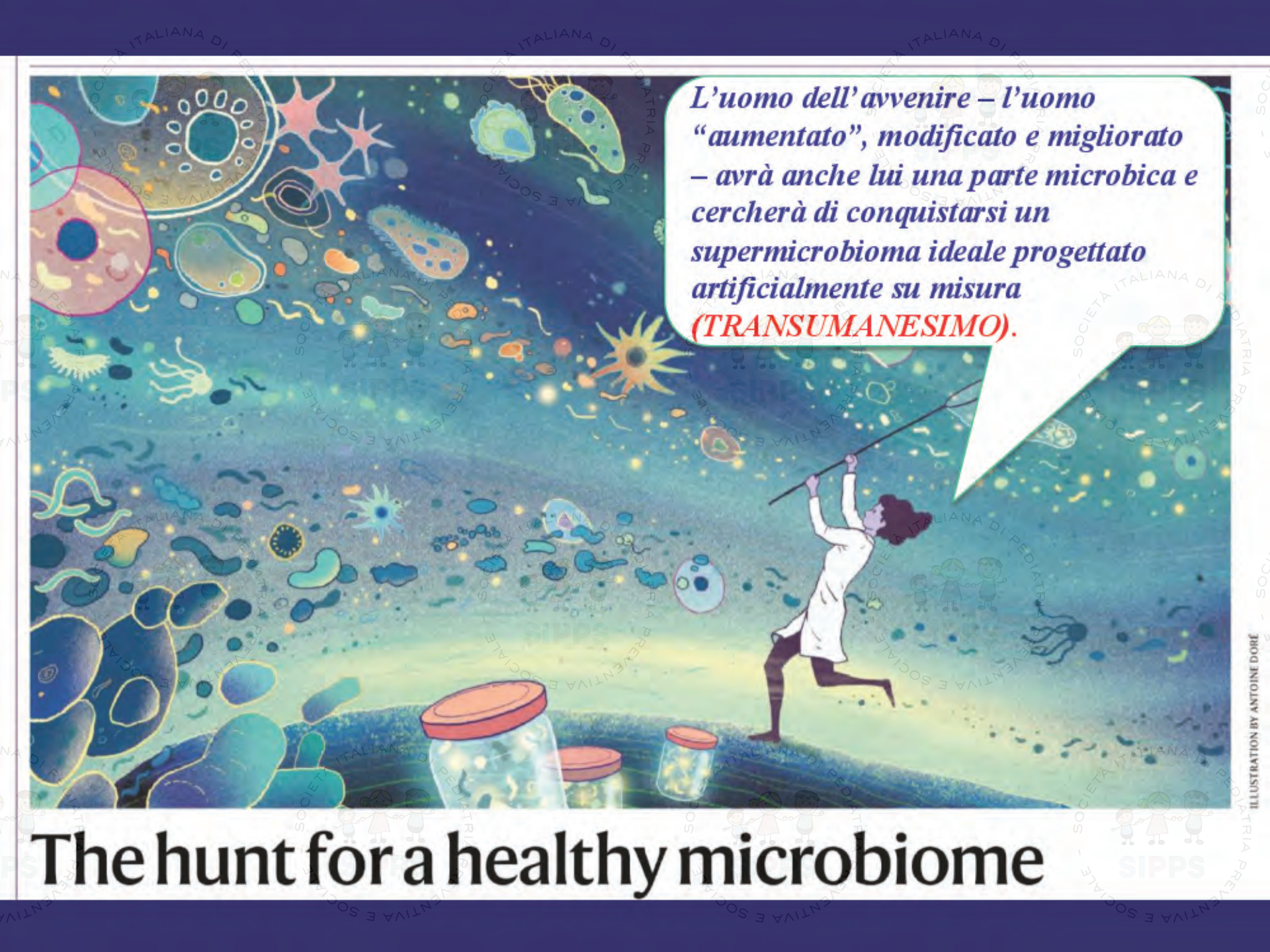
2020

Yong Fan  and Oluf Pedersen  

NATURE REVIEWS | MICROBIOLOGY





An illustration depicting a scientist in a white lab coat running through a vast, colorful field of diverse microorganisms. The scientist is holding a long pole with a net at the end, attempting to catch a specific microbe. In the foreground, there are several glass jars with red lids, some containing microbes, suggesting a collection or storage process. The background is filled with various shapes and colors representing different types of bacteria, fungi, and other microbes. A speech bubble in the upper right corner contains text in Italian.

*L'uomo dell'avvenire – l'uomo  
"aumentato", modificato e migliorato  
– avrà anche lui una parte microbica e  
cercherà di conquistarsi un  
supermicrobioma ideale progettato  
artificialmente su misura  
**(TRANSUMANESIMO).***

**The hunt for a healthy microbiome**

# Biological Programming and Age

**Impact of Environment**

**Opportunity for correction**

**Fetus**

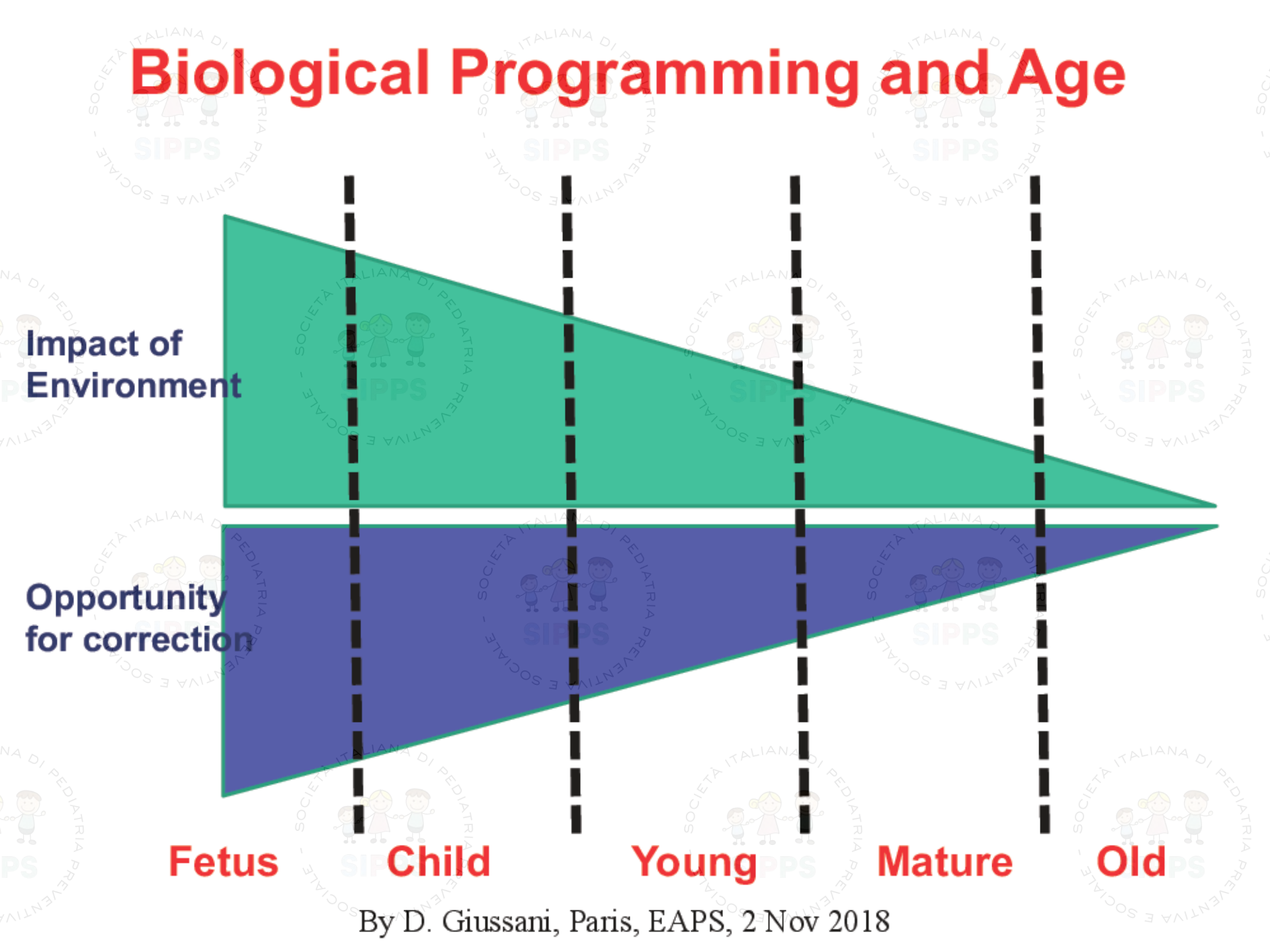
**Child**

**Young**

**Mature**

**Old**

By D. Giussani, Paris, EAPS, 2 Nov 2018

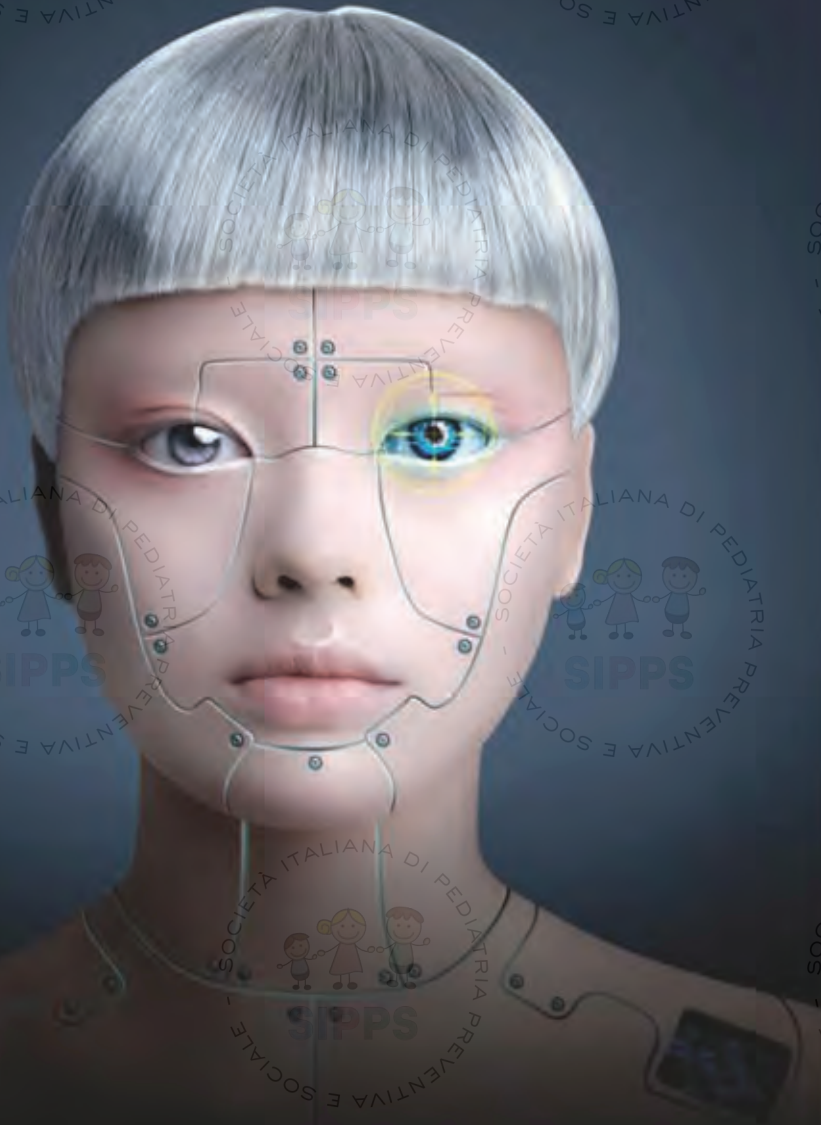




ARTSCIENCE MUSEUM™ PRESENTS

# HUMAN+

THE FUTURE OF OUR SPECIES



***It is better to  
build a healthy  
adult from the  
womb of the  
mother and  
from pediatric  
age rather  
than fix and  
cure an adult  
with illness***

Ciò che non vorremmo mai essere...

# Trasfigurazioni, 2013, opere di Agata Haines

*(il nostro corpo può essere modificato)*

**Plastica dell'epidermide  
a fini termici (da scalpo)  
per ridurre effetti del  
riscaldamento globale**



**Plastica delle guance  
(per aumentare  
l'assorbimento di  
caffaina e affrontare  
meglio lo stress da**



**Stomia  
dell'epidermide (a  
forma di sfintere) per  
assumere meglio  
pillole e farmaci**



Con permesso



# Ciò che forse saremo...

SIPPS

**ispirato dalla tecnologia e dalla biomimesi (imitazione della natura)**

**capace di tollerare un elevato grado di incertezza del futuro**

Apr 18, 2021, 10:55am EDT 1.092 views

## Five Kids From The Future



Cathy Hackl Contributor  
CMO Network

Fun & tech futurist & speaker with expertise in AR, VR & IoT. Metaverse.

Con permesso

### 1. Solarpunk Kid



### 2. Existential Kid



### 3. Designer Baby Kid



### 4. The Digikid



### 5. The Maverick Kid



**esploratore intergalattico, protetto geneticamente dagli effetti della gravità**

**vive, gioca, interagisce e cresce con la realtà virtuale**

**non è interessato all'educazione formale ma solo alla sperimentazione**



**18<sup>th</sup>**  
**International Workshop**  
**on Neonatology and Pediatrics**  
From womb to adulthood

*President: Vassilios Fanos*

**19<sup>th</sup> - 22<sup>th</sup>**  
**october 2022**

**T HOTEL | CAGLIARI**

**18<sup>th</sup>**  
**International Workshop**  
**on Neonatology and Pediatrics**  
From womb to adulthood

**PRESIDENTS**

**PRESIDENT:** VASSILIOS FANOS (Cagliari, Italy)  
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**CO-PRESIDENTS**

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SALVATORE SAVASTA (Cagliari, Italy)  
SANTOSH SOANS (Mangalore, India)

**SATELLITE MEETINGS**

**2<sup>o</sup> Meeting di Cardiologia Perinatale e Pediatrica**  
**IV Take Care of Children**  
**Pediatria Social e Dr. Google**

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**ANGELICA DESSI** (Cagliari, Italy)  
**PAOLA NERONI** (Cagliari, Italy)  
**GIANFRANCO TRAPANI** (Sanremo, Italy)





***In my end is my  
beginning.***

**Thomas S. Eliot.  
Four Quartets**





# Thomas S. Eliot



***...Pray for us now  
and at the hour of our birth.***

***Animula***

















Apr 18, 2021, 10:55am EDT | 3.092 views

# Five Kids From The Future

Cathy Hackl Contributor @

CMO Network

I'm a tech futurist & speaker with expertise in AR, VR & the Metaverse.

## 1. Solarpunk Kid



The Solarpunk Kid of 2030 will be very inspired by technologies like biocommics, AI, VR, AR, and the Metaverse.

## 2. Existential Kid



Existential kid is expected to tolerate a lot of uncertainty. Let's

## 3. Designer Baby Kid



They will be the first galaxy explorers genetically protected from the effects of low gravity and... (1)

## 4. The Digikid



The Digikid lives, plays, interacts and grows in the metaverse. (1)

## 5. The Maverick Kid



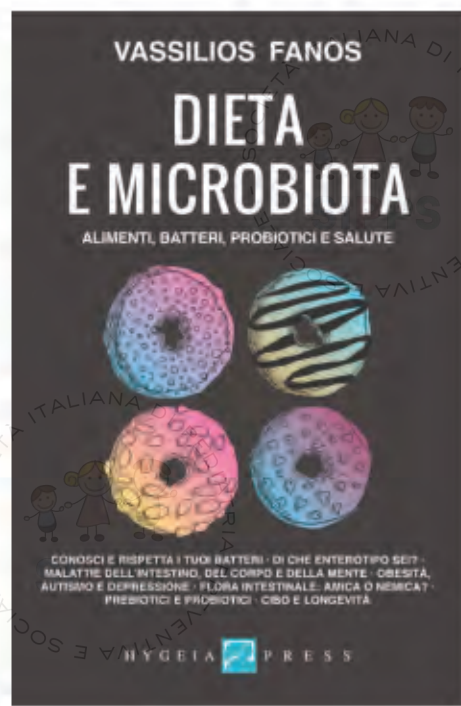
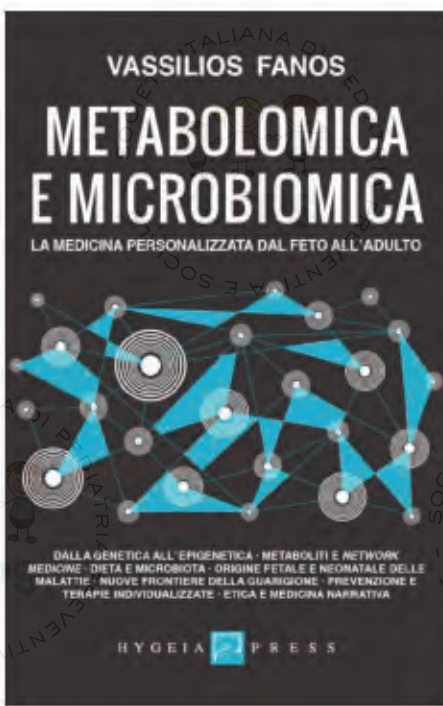
The Maverick kid is interested in virtual education, like many. Enough experimentation... (1)

# Trasfigurazioni, 2013, opere di Agata Haines

*(il nostro corpo può essere modificato)*

- Plastica dell'epidermide a fini termici (da scalpo per ridurre effetti del riscaldamento globale)
- Osteogenesi per estensione (per fini estetici)
- Falangectomia (favorisce infezioni da ancilostoma per ridurre asma e allergie)
- Plastica delle guance (per aumentare l'assorbimento di caffeina a affrontare meglio lo stress da adulti)














# PRAYER

***...Give us this day our daily germs.***

**G. A. W. Rook and J. L. Stanford**

***...Pray for us now  
and at the hour of our birth.***

**T.S. Eliot. *Animula***





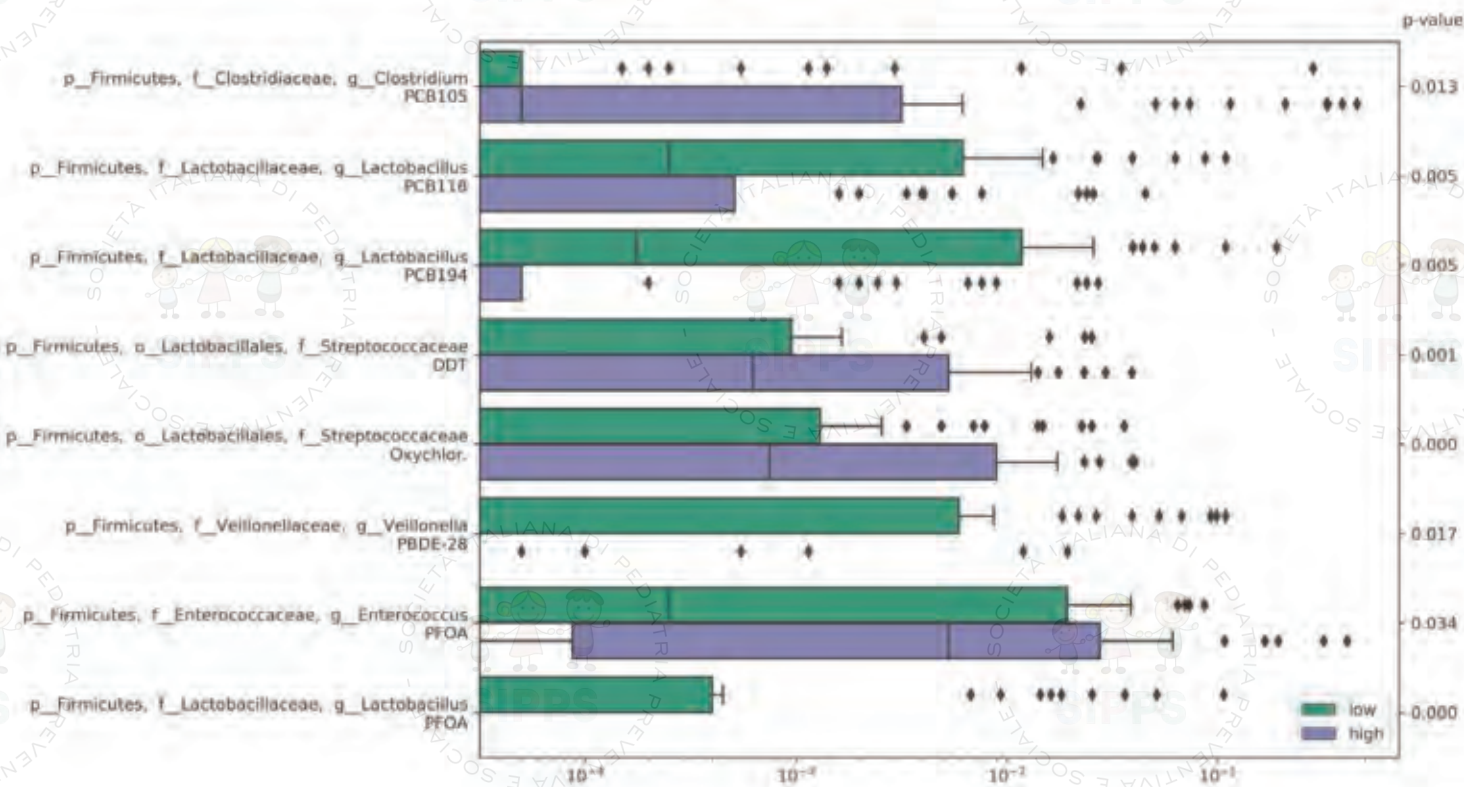
RESEARCH

Open Access

Reduction of  
Lactobacilli

# Environmental toxicants in breast milk of Norwegian mothers and gut bacteria composition and metabolites in their infants at 1 month

Nina Iszatt<sup>1</sup>, Stefan Janssen<sup>2,3</sup>, Virissa Lenters<sup>1</sup>, Cecilie Dahl<sup>4</sup>, Hein Stigum<sup>5</sup>, Rob Knight<sup>6,7</sup>, Siddhartha Mandal<sup>8</sup>, Shyamal Peddada<sup>9</sup>, Antonio González<sup>2</sup>, Tore Midtved<sup>10</sup> and Merete Eggesbø<sup>1\*</sup>



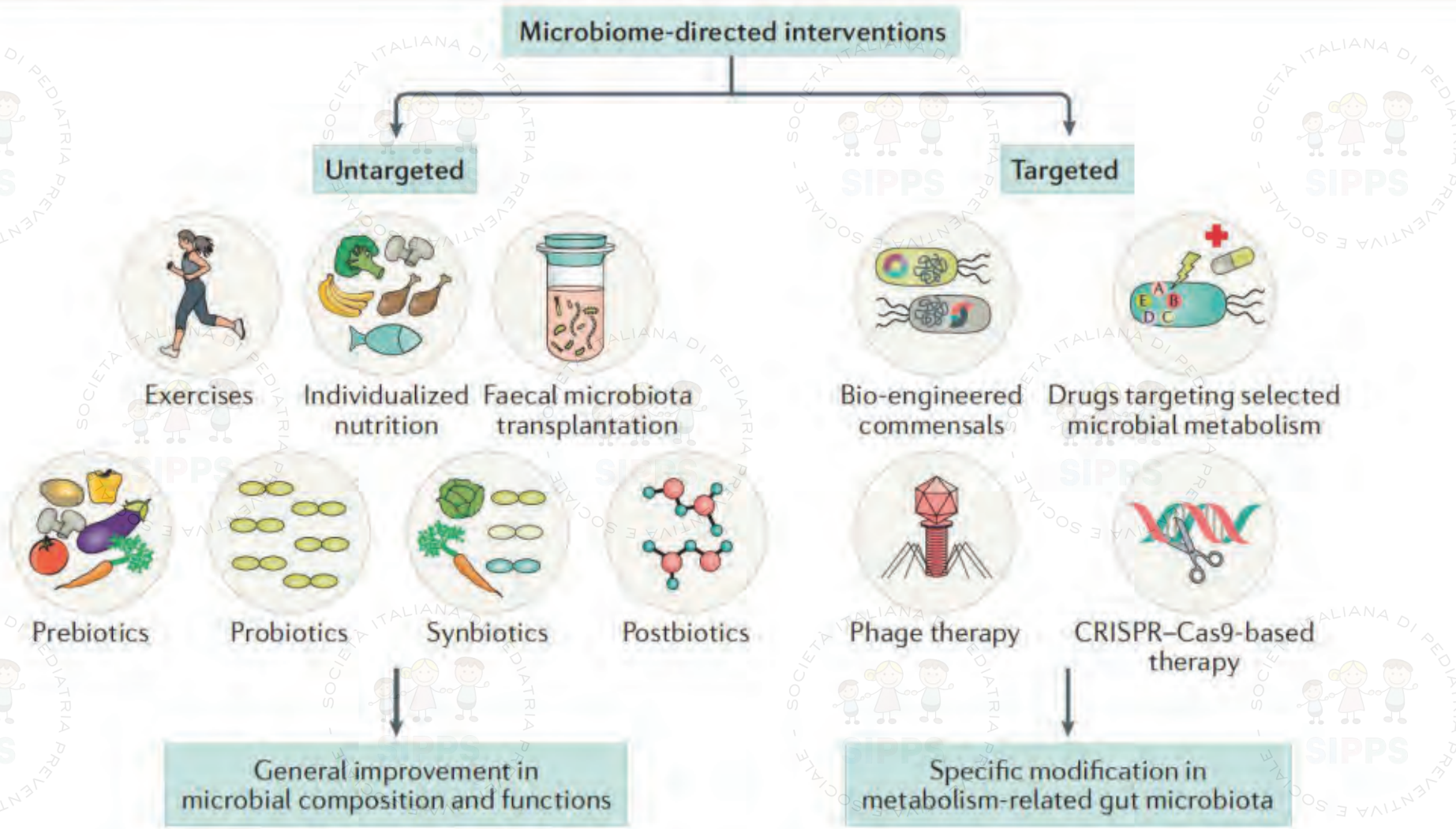
The authors tested 28 chemical exposures: polychlorinated biphenyls (PCBs), polybrominated flame retardants (PBDEs), per- and polyfluoroalkyl substances (PFASs), and organochlorine pesticides.

# Gut microbiota in human metabolic health and disease

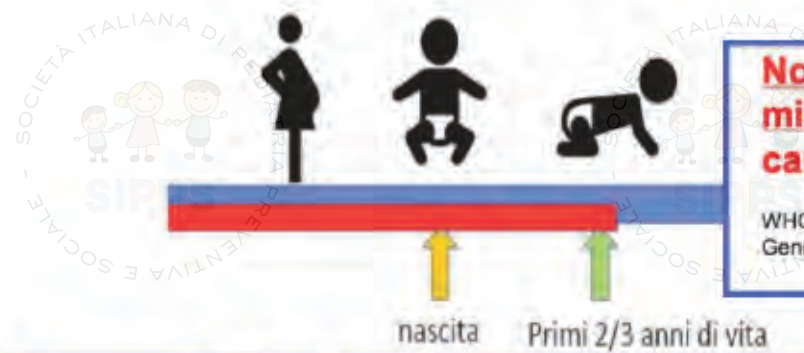
2020

Yong Fan  and Oluf Pedersen  

NATURE REVIEWS | MICROBIOLOGY







**Noncommunicable diseases (NCDs), kill more than 38 million people each year, making them by far the leading cause of death in the world.**

WHO. WHO Global Status Report on Noncommunicable Diseases 2014. World Health Organisation, Geneva, Switzerland, 1-51 (2014).

## Esiste una finestra temporale critica

- Mille giorni dal concepimento
- Fetal programming
- Perinatal programming
- Developmental Origins of Health and Disease

6 + 9 + 6

**I tre cervelli maturano quasi completamente a tre anni:**

- Cervello 1°
- Intestino 2°
- Sist. Immune 3°



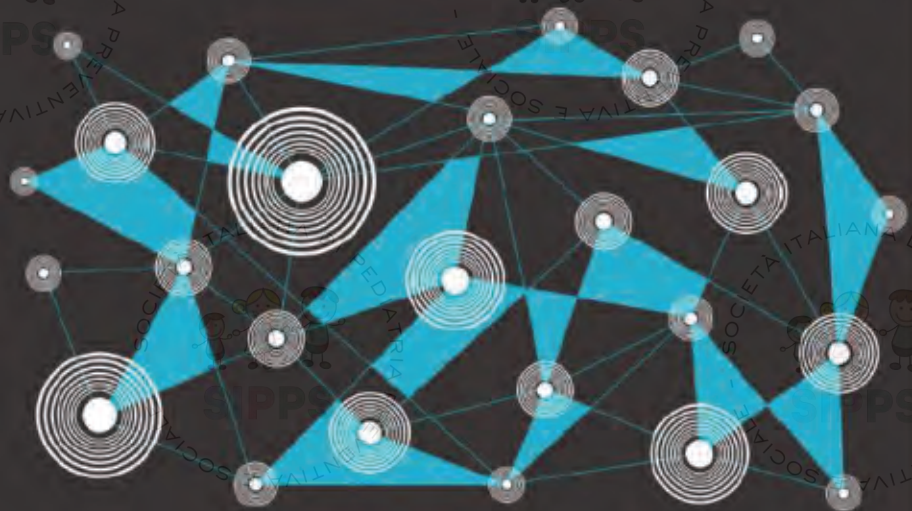




VASSILIOS FANOS

# METABOLOMICA E MICROBIOMICA

LA MEDICINA PERSONALIZZATA DAL FETO ALL'ADULTO



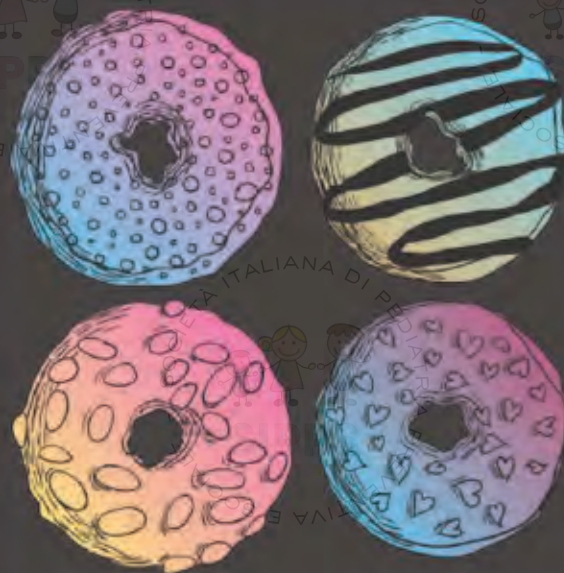
DALLA GENETICA ALL' EPIGENETICA · METABOLITI E NETWORK  
MEDICINE · DIETA E MICROBIOTA · ORIGINE FETALE E NEONATALE DELLE  
MALATTIE · NUOVE FRONTIERE DELLA GUARIGIONE · PREVENZIONE E  
TERAPIE INDIVIDUALIZZATE · ETICA E MEDICINA NARRATIVA

HYGEIA  PRESS


VASSILIOS FANOS

# DIETA E MICROBIOTA

ALIMENTI, BATTERI, PROBIOTICI E SALUTE



CONOSCI E RISPETTA I TUOI BATTERI · DI CHE ENTEROTIPO SEI? ·  
MALATTIE DELL'INTESTINO, DEL CORPO E DELLA MENTE · OBESITÀ,  
AUTISMO E DEPRESSIONE · FLORA INTESTINALE: AMICA O NEMICA? ·  
PREBIOTICI E PROBIOTICI · CIBO E LONGEVITÀ

HYGEIA  PRESS



VASSILIOS FANOS

# MEDICINA DI PRECISIONE

CELLULE, BATTERI, METABOLITI, ENERGIA



HYGEIA  PRESS













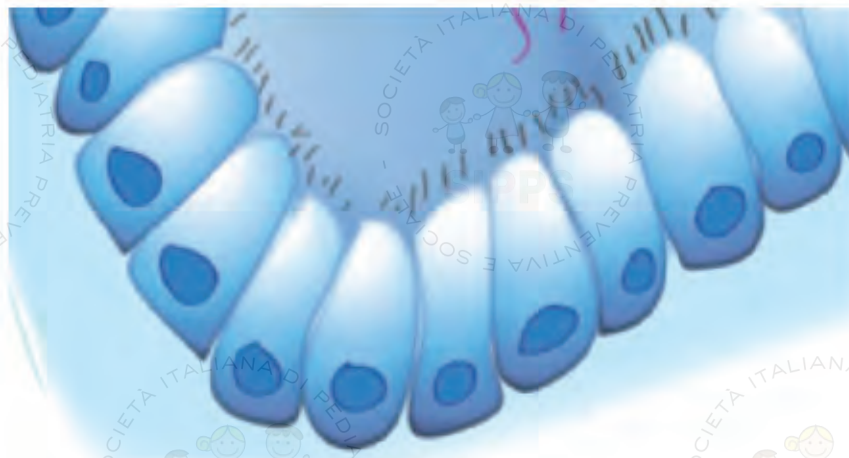




# Dr. Elsie Widdowson (1906-2000)



The suckled pigs  
duodenum gains 42% of  
it's weight in the first 24  
hours of life



# An unborn baby's genetic inheritance, 2006

## Wellcome Library, Cambridge



**Il rovescio della medaglia fa nascere perplessità: questa massa di conoscenze aumenterà il potere dell'uomo sull'uomo e, paradossalmente, porrà problemi cruciali sulla libertà che ciascuno di noi avrà in futuro.**



# An unborn baby's genetic inheritance, 2006

## Wellcome Library, Cambridge



**Il rovescio della medaglia fa nascere perplessità: questa massa di conoscenze aumenterà il potere dell'uomo sull'uomo e, paradossalmente, porrà problemi cruciali sulla libertà che ciascuno di noi avrà in futuro.**



# New hypothesis: 'All healthy microbiomes are similar; each dysbiotic microbiome is dysbiotic in its own way'

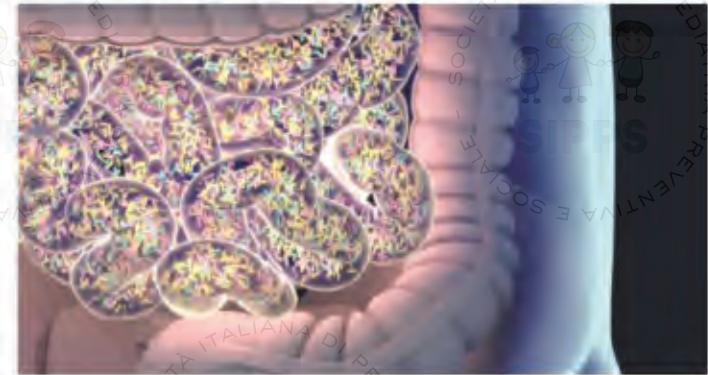
13 NOV 2017 | Kristina Campbell

Dysbiosis, Gut Microbiota, Gut Microbiota Composition, Research & Practice

Tagged: Dysbiosis, Gut microbiota stressor

When Leo Tolstoy wrote the first line of his classic novel Anna Karenina—"All happy families are like one another; each unhappy family is unhappy in its own way"—he probably never thought it would apply to gut microbiomes.

But researchers from [University of Washington](#) (USA) and [Oregon State University](#) (USA) recently put forward the "Anna Karenina principle" as a way of explaining what might happen when microbial communities in many different environments are subject to perturbation: **random variation may occur in microbiota community composition—and compared to baseline, the microbiota may become more varied and unstable.**

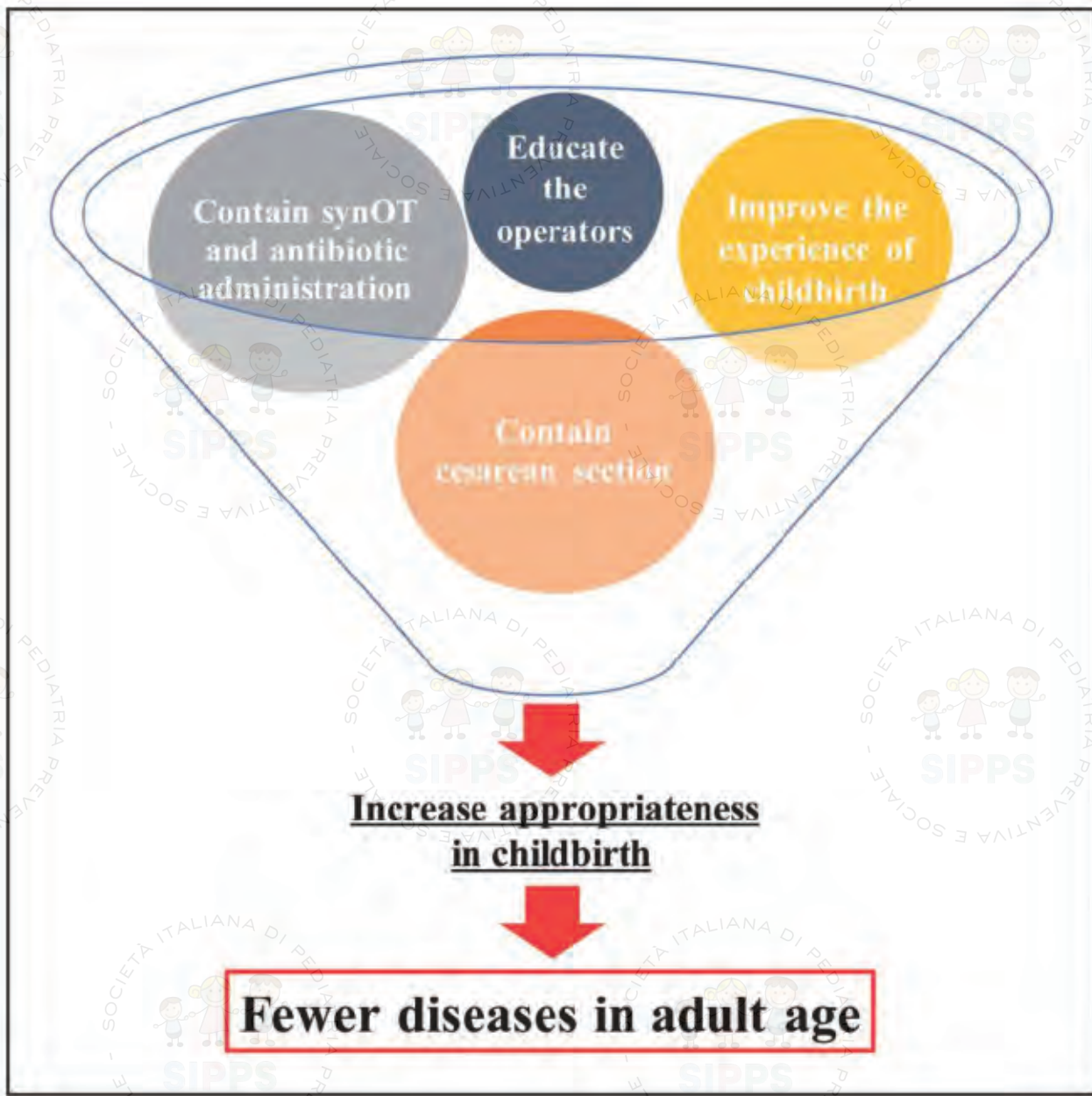


## Precision Medicine

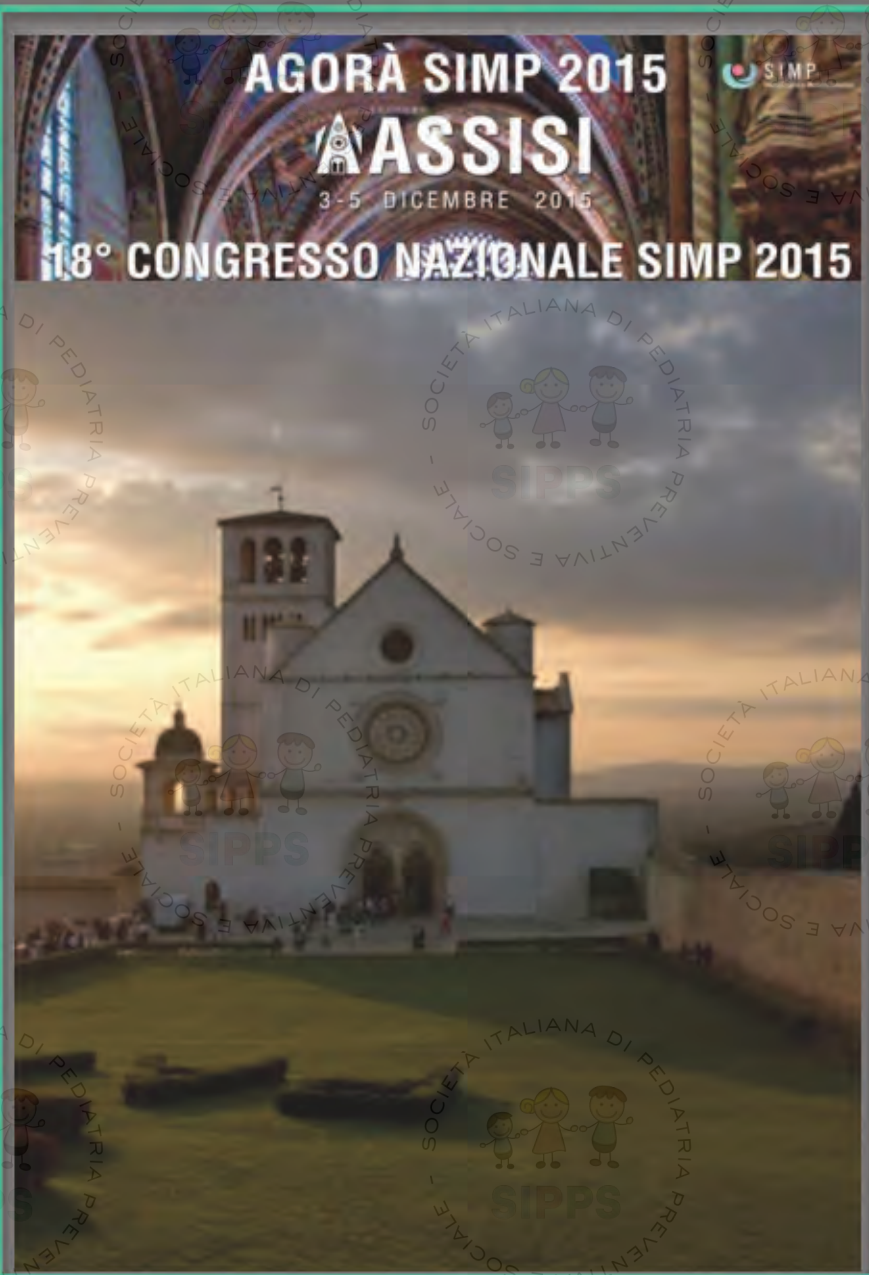
“microbiome-based metabolite treatment” or “postbiotics”











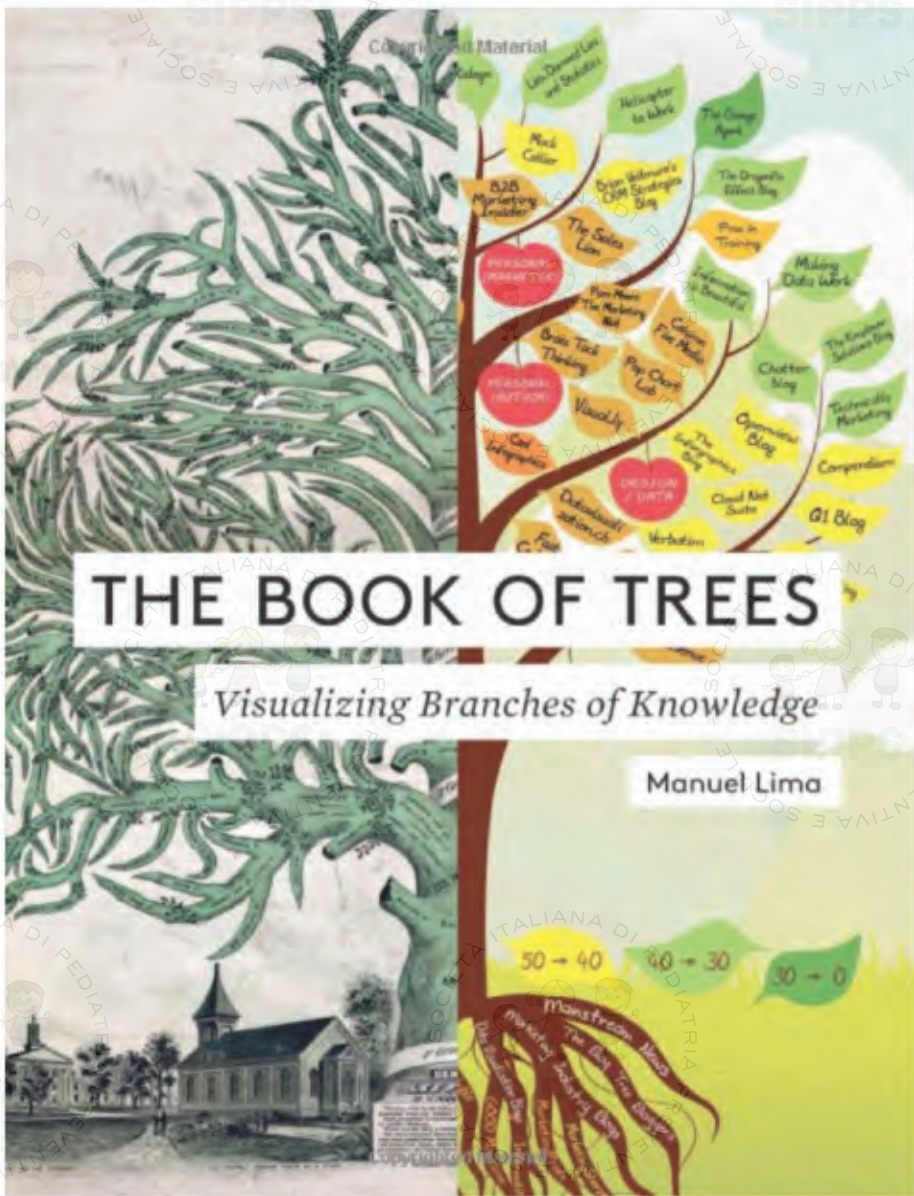
**4 DICEMBRE 2015**

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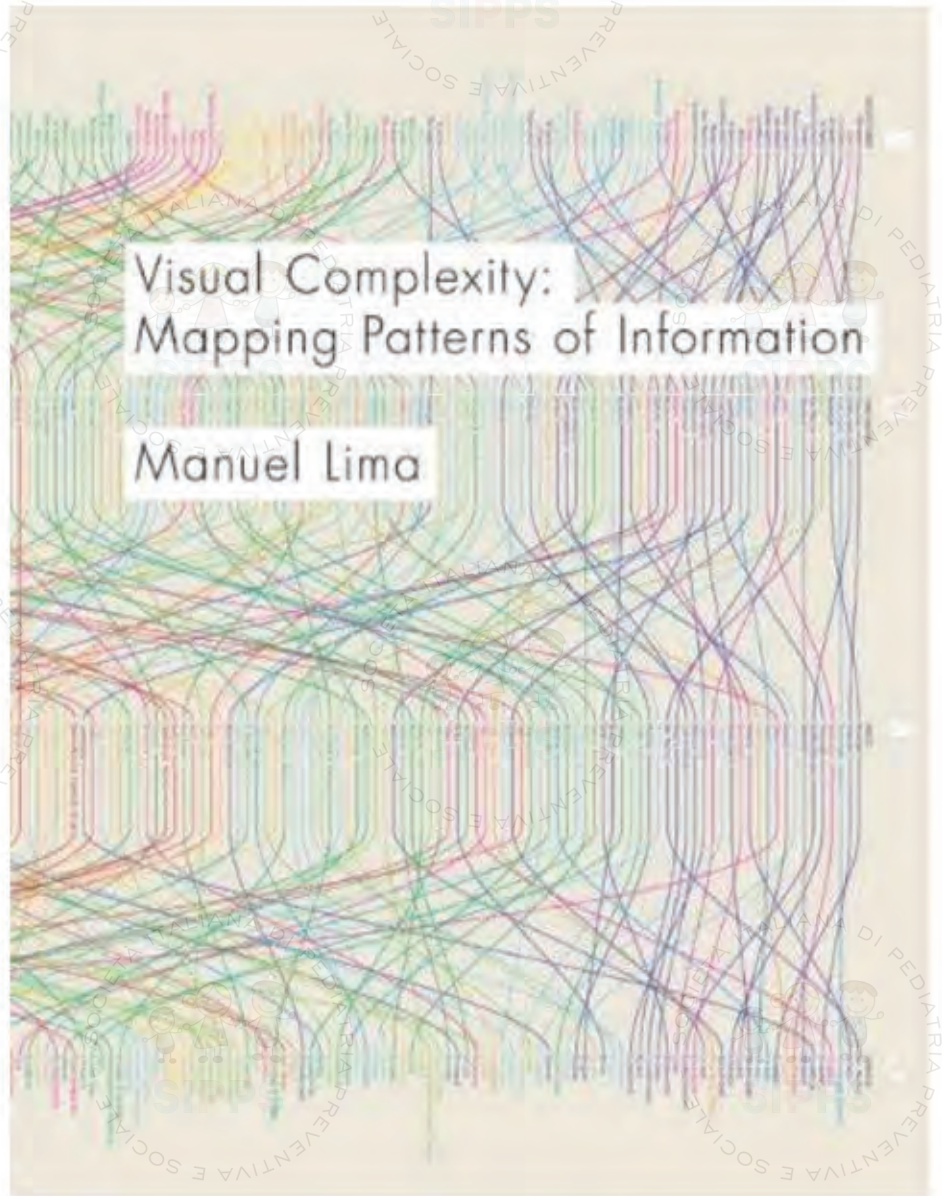




# THE BOOK OF TREES

*Visualizing Branches of Knowledge*

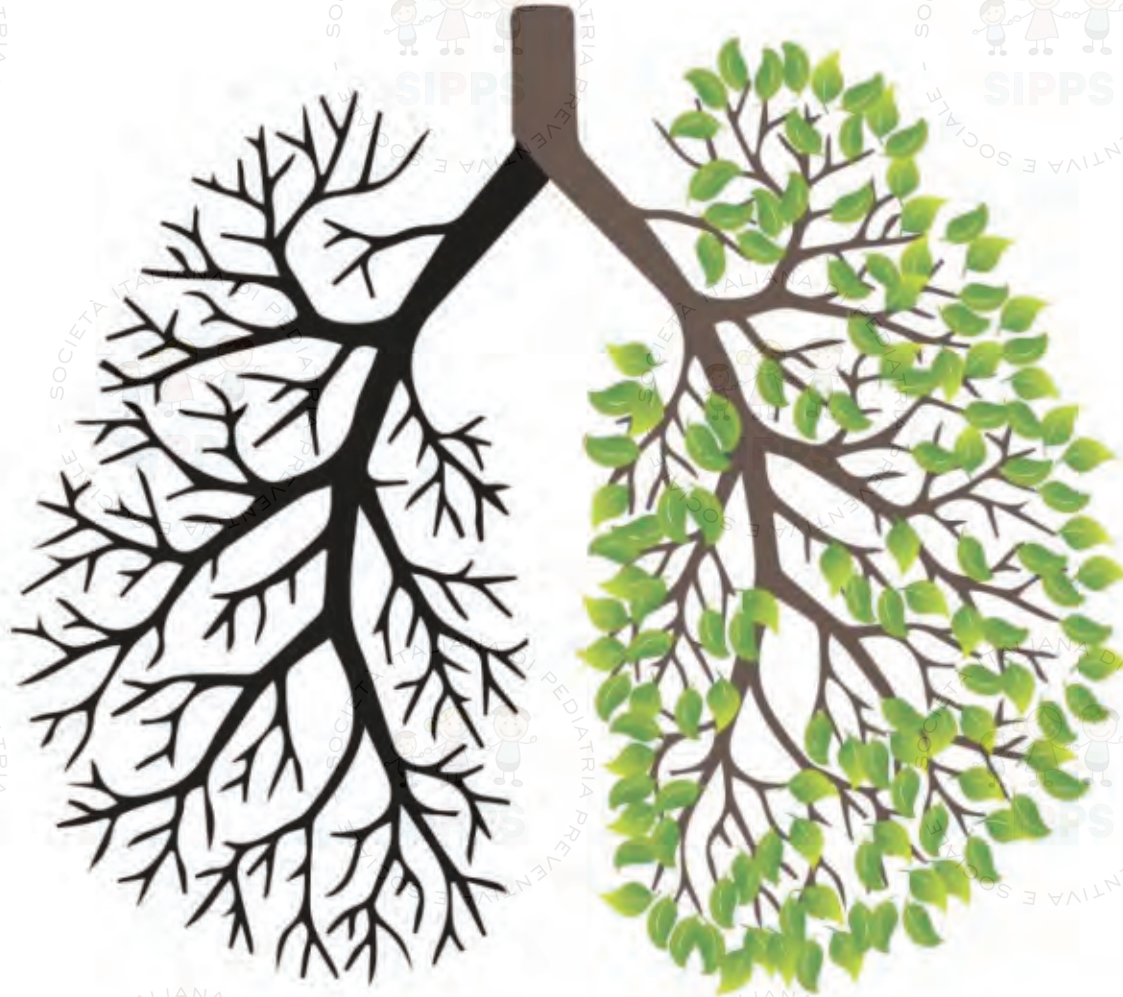
Manuel Lima



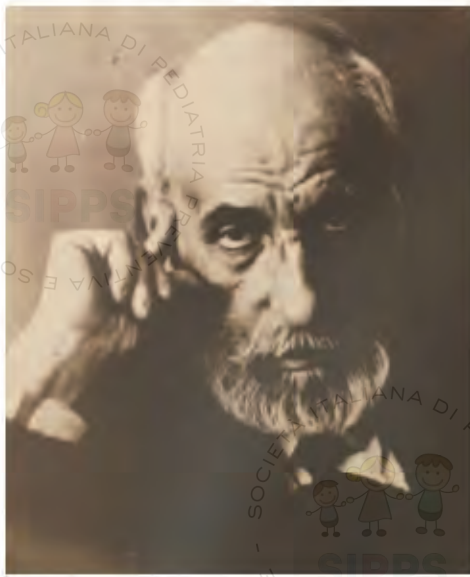
# Visual Complexity: Mapping Patterns of Information

Manuel Lima





**Struttura dell'albero bronchiale: un albero senza foglie, rovesciato, con i rami vuoti internamente.**



***“The total arborization of a neuron represents the graphic history of conflicts suffered during the developmental life”.***

## **NO REGENERATION**

**Santiago Ramon y Cajal (1852 – 1934) Spanish pathologist, histologist, neuroscientist and Nobel laureate, the father of modern neuroscience**







*....we have not yet  
unravellled the mystery  
of what is our brain.*

**Ecole Polytechnique Fèdèrale de  
Lausanne, blue Brain Project 2008**

Thirty millions connections between  
ten thousand neurons.  
The different colors indicate  
distinctive levels of electric activity

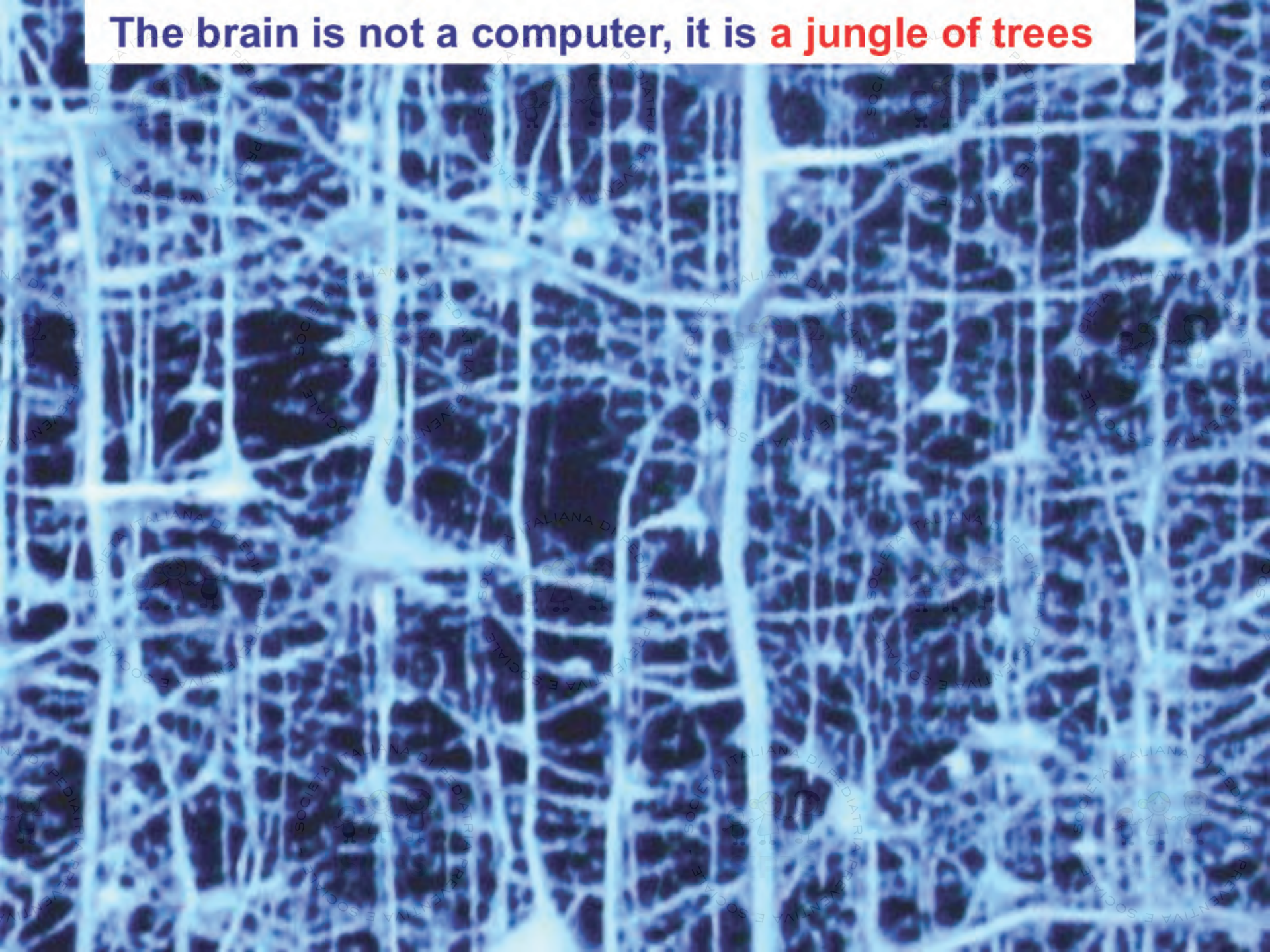




**Jackson Pollock, *Number 5*, 1948**



The brain is not a computer, it is **a jungle of trees**





**Siamo una sola cosa con  
quello che mangiamo**

**Scritture Vimalakirti**





# Aluminum exposure and toxicity in neonates: a practical guide to halt aluminum overload in the prenatal and perinatal periods

Daniela Fanni, Rossano Ambu, Clara Gerosa, Sonia Nemolato, Nicoletta Iacovidou, Peter Van Eyken, Vassilios Fanos, Marco Zaffanello, Gavino Faa Cagliari, Italy

**Background:** During the last years, human newborns have been overexposed to biologically reactive aluminum, with possible relevant consequences on their future health and on their susceptibility to a variety of diseases. Children, newborns and particularly preterm neonates are at an increased risk of aluminum toxicity because of their relative immaturity.

based formulas in which, on the basis of recent studies, there is still too much aluminum.

*World J Pediatr 2014;10(?):??-??*

**Key words:** aluminum;  
fetus;  
newborn;

## Sources

Breast milk

Infant formula

Soy-based formula

Vaccines

Parenteral nutrition

Antiacids

## Amount

10 mg

40 mg

120 mg

4 mg

grams

unknown

**Aluminum sources that infants may receive during the first 6 months of life**

**“Non finiremo mai di cercare/  
e la fine della nostra ricerca/  
sarà l’arrivare al punto da cui siamo  
partiti/ e il conoscere quel luogo per la  
prima volta”.**

**T. S. Eliot**





# Prenatal and postnatal nutrition: impact on child health

Berthold Koletzko<sup>a</sup> and Ranan Shamir<sup>b</sup>

## EARLY PROGRAMMING

Metabolomics

### Genotype

### Phenotype

Conception

Birth

6 Month

Later Life



- Maternal nutrition
- Maternal stress
- Placental development
- Placental transfer

- Infant nutrition

- Obesity
- Diabetes
- CVD
- Allergy
- Cognition
- Behaviour

Environment and Nutrition

# ‘Hormonal imprinting’

The original term, reported by Csaba as has been successively called:

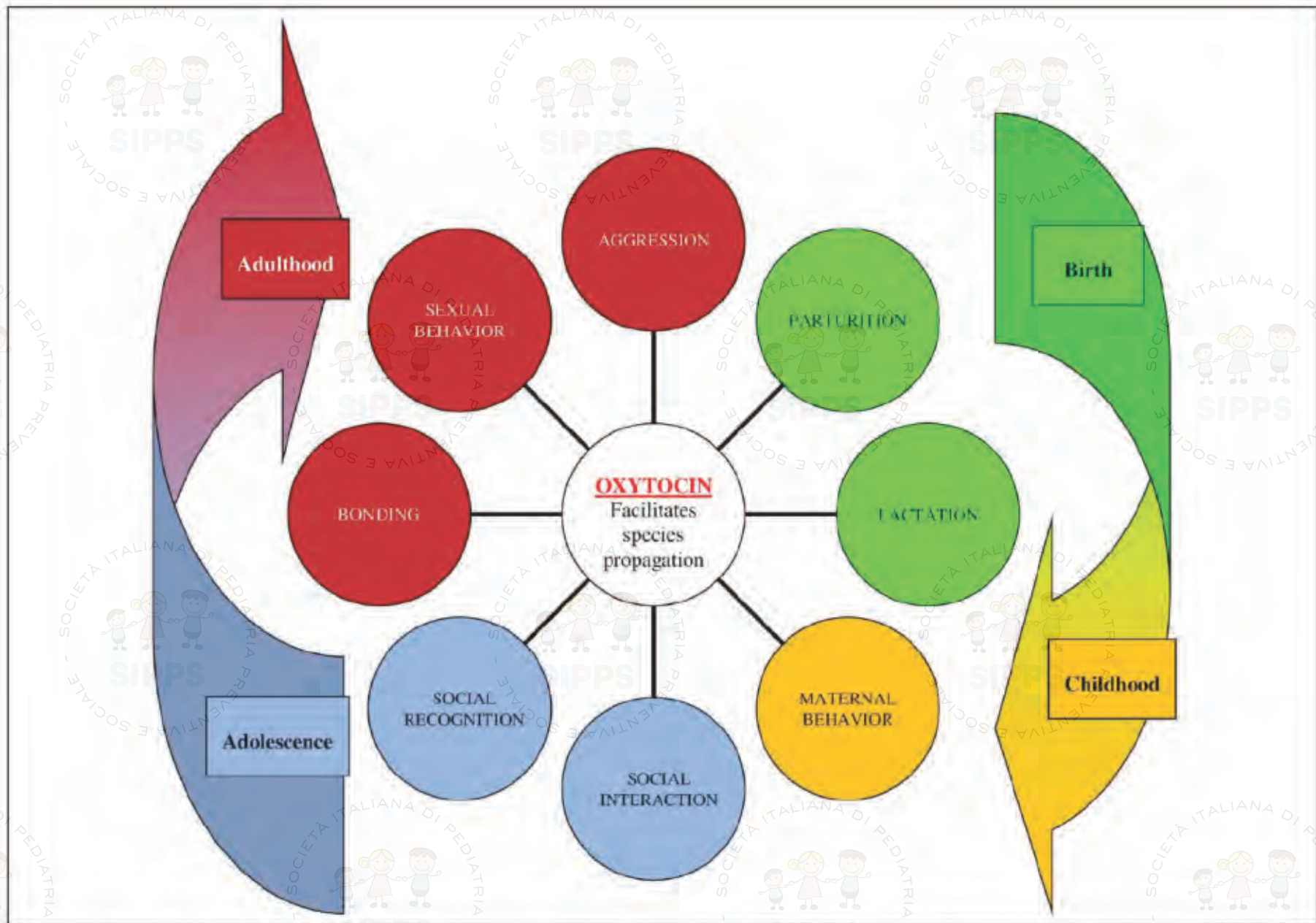
- metabolic imprinting
- epigenetic imprinting
- childbirth imprinting

describing hormonal imprinting-like phenomena caused by hormonal or/and non-hormonal factors.

All of these phenomena are, of course, different from “genome imprinting” .

Csaba G. Phylogeny and ontogeny of hormone receptors: the selection theory of receptor formation and hormonal imprinting. *Biol Rev Camb Philos Soc* 1980; 55(1): 47-63.





**Figure 3.** The spheres of life illustrate numerous areas at which oxytocin may affect behavior and physiology to facilitate the propagation of the species in different periods of life. Modified from Lee et al., 2009 [67].

# I'm Eating for Two: Parental Dietary Effects on Offspring Metabolism

Oliver J. Rando<sup>1,\*</sup> and Rebecca A. Simmons<sup>2,\*</sup>

<sup>1</sup>Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA 01605, USA

<sup>2</sup>Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA

**Dutch famine**



You do not need to eat for two, you need to eat better! I. Cetin 2014

# I'm Eating for Two: Parental Dietary Effects on Offspring Metabolism

Oliver J. Rando<sup>1,\*</sup> and Rebecca A. Simmons<sup>2,\*</sup>

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**Dutch famine**

# Il futuro della salute

*Come la tecnologia digitale sta  
rivoluzionando la medicina (e la nostra vita)*

## Medicina di ieri

Osservativa

Uno a Uno

Descrittiva, Retrospettiva

Frammentata

Non digitale

## Medicina di Oggi/Domani

Basata sui dati

Collettivamente originata

Predittiva

Integrata

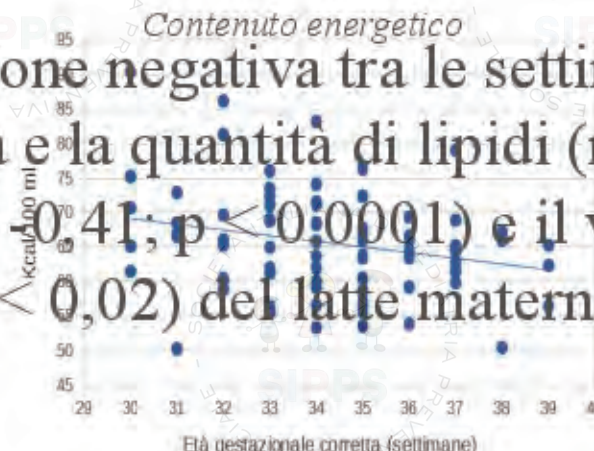
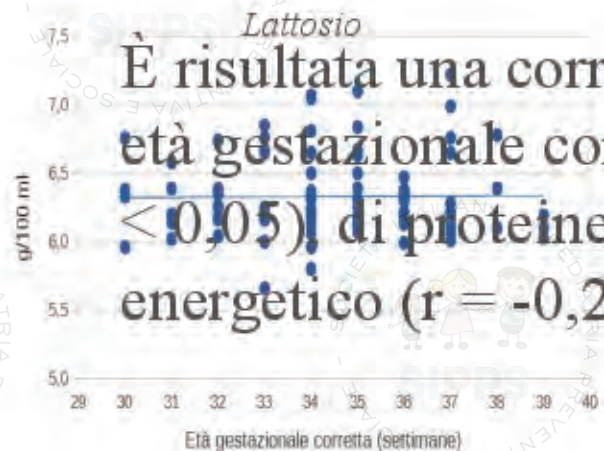
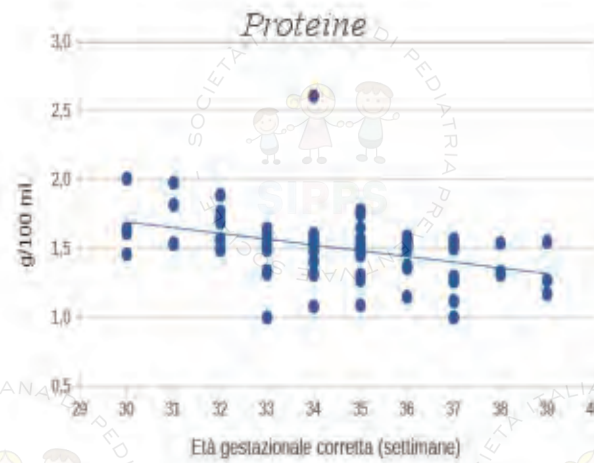
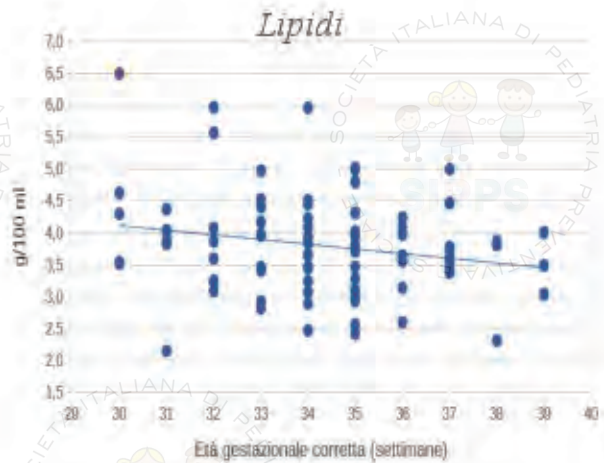
Digitale



Ascione, Hoepli 2018, mod



# Il latte materno dei gemelli: variazione settimanale (secondo l'EG corretta)



È risultata una correlazione negativa tra le settimane di età gestazionale corretta e la quantità di lipidi ( $r = -0,21$ ;  $p < 0,05$ ) di proteine ( $r = -0,41$ ;  $p < 0,0001$ ) e il valore energetico ( $r = -0,25$ ;  $p < 0,02$ ) del latte materno.

# Il latte materno dei gemelli e dei singoli a confronto

Sono stati selezionati esclusivamente le madri di neonati con EG  $\leq 28$  settimane

Componenti del latte e valore energetico	Gemelli	Singoli	p
Lipidi (g/100 ml)	3,91 $\pm$ 0,65	3,87 $\pm$ 0,66	0,71
Proteine (g/100 ml)	1,53 $\pm$ 0,29	1,29 $\pm$ 0,23	<b>0,00</b>
Lattosio (g/100 ml)	6,34 $\pm$ 0,2	6,72 $\pm$ 0,24	<b>0,02</b>
Contenuto energetico (Kcal/100 ml)	66,68 $\pm$ 6,24	66,87 $\pm$ 6,26	0,96

## RISULTATO

Il latte materno dei gemelli contiene più proteine e meno lattosio rispetto a quello dei singoli



# Una possibile spiegazione: la prolattina

- **Le madri dei gemelli producono prolattina in quantità fino a 2 volte superiori rispetto alle madri dei singoli**

Tyson J.E., Freedman R.S., Perez A., Zacur H.A., Zanartu J. – Significance of the secretion of human prolactin and gonadotropin for puerperal lactational infertility – CIBA Foundation Symposium – 1976 – (45):49-71

- **I livelli di prolattina sono direttamente proporzionali alla quota proteica del latte, e inversamente proporzionali alla quantità di lattosio**

Healy D.L., Rattigan S., Hartmann P.E., Herington A.C., Burger H.G. – Prolactin in human milk: correlation with lactose, total protein, and alpha-lactalbumin levels – American Journal of Physiology – 1980 – 238:e83-e86





OCTOBER 26, 2010

**China's Fury:**  
Eyes on the  
Nobel Prize

**Back to Baghdad:**  
A reporter and  
a soldier return

**Chilean Miners:**  
Their amazing  
journey

**U.S. Election 2010:**  
Foreign money  
in the midterms?

# TIME

# Alzheimer's

At last, some progress  
against the most  
stubborn disease

BY ALICE PARK



# Why do an extraordinary number of Chamorro people of Guam island develop Alzheimer's symptoms?





# The Cox's hypothesis, emerging from the Chamorro diet

**Chamorro people have  
Been poisoning  
themselves by their  
greatest culinary delight:**



**a bat (flying wolf) boiled in milk:  
toxin called  $\beta$ -N-methylamino-l-alanine  
(BMAA)**



China

North Korea

Seoul

South Korea

Hiroshima

Fukuoka

Nagasaki

East China Sea

Okinawa

Sea of Japan (East Sea)

Shinano River

Nagano

Nagoya

Kobe

SHIKOKU

KYUSHU

Ryukyu Islands

Philippine Sea

HOKKAIDO

Sapporo

Kushiro

Hakodate

Akita

Niigata

HONSHU

Sendai

Mount Fuji

Tokyo

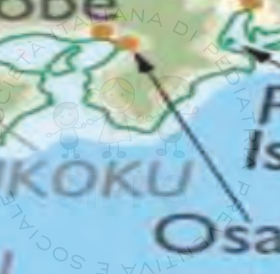
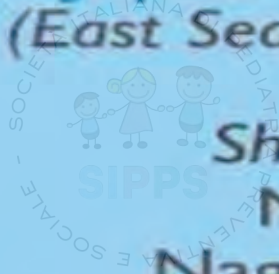
Japan

Yokohama

Osaka

Pearl Island

Bonin Islands





# Ogimi people have the highest L-serine levels in their body





# How does BMAA make its damage in the brain? **Misincorporation**

BMAA insinuates itself into protein chains in place of one of the 20 standard aminoacids, passing for

L-serine



**Misfolding**



**Neuronal death** → **A.D.**



# Role of L-serine in Epigenetics of Brain

- 1. L-serine appears to be neuroprotective against BMAA**
- 2. L-serine given in the perinatal period might be neuroprotective against all neurological diseases presenting in adulthood**
- 3. L-serine could reduce the risk of developing neurodegeneration later in life**

Courtesy Prof. Gavino Faa

# Perinatal programming (I)

## Messaggi da portare a casa

- Periodi critici di vulnerabilità → (“trasformare le finestre di vulnerabilità in finestre di opportunità”).
- Il *programming* ha effetti permanenti sull'organismo a breve e lungo termine e può modificare la suscettibilità alle malattie (“*In my beginning is my end*” T.S. Eliot).
- Il *programming* determina cambiamenti strutturali in organi importanti (*God save the brain...*).
- La placenta svolge un ruolo chiave (“E' la placenta un *innocent bystander*, un testimone innocente? No, non lo è”).
- Il compenso che si verifica vuole farci raggiungere l'immortalità (“*Per riprodurmi, son nato*”) ma ha dei costi (“una tassa da pagare”).



# Perinatal programming (II)

## Messaggi da portare a casa

- I tentativi di correggere gli effetti del *programming* possono avere conseguenze non volute (si pensi alla *early aggressive nutrition*).
- I feti reagiscono in modo diverso alle condizioni subottimali rispetto ai neonati e agli adulti.
- I feti reagiscono in modo molto diverso gli uni dagli altri (straordinaria variabilità interindividuale fetale!).
- Gli effetti del *programming* sono transgenerazionali. Dallo slogan paradossale “devi sceglierti i genitori” al “devi sceglierti i genitori, i nonni e i bisnonni!”
- Il *programming* ha effetti differenti nei maschi e nelle femmine (Medicina di genere).

**Fanos V. Metabolomica e microbiomica. Hygeia Press 2015**

# Una scoperta straordinaria



## Autismo Tipo di danno

- prenatale cronico
- prenatale acuto
- postnatale acuto
- postnatale cronico
  
- combinato

SMS Biologici



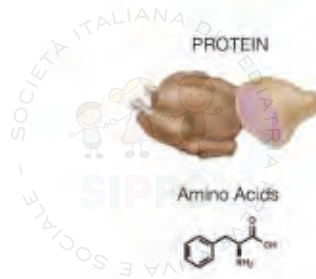
# Maternal dietary patterns and preterm delivery: results from large prospective cohort study

 OPEN ACCESS

Linda Englund-Ögge *medical doctor*<sup>1</sup>, Anne Lise Brantsæter *senior scientist*<sup>2</sup>, Verena Sengpiel

## Three distinct dietary patterns:

- “prudent” (for example, vegetables, fruits, oils, water as beverage, whole grain cereals, fibre rich bread) → **Reduced risk of preterm delivery**
- “Western” (salty and sweet snacks, white bread, desserts, processed meat products)
- “traditional” (potatoes, fish).



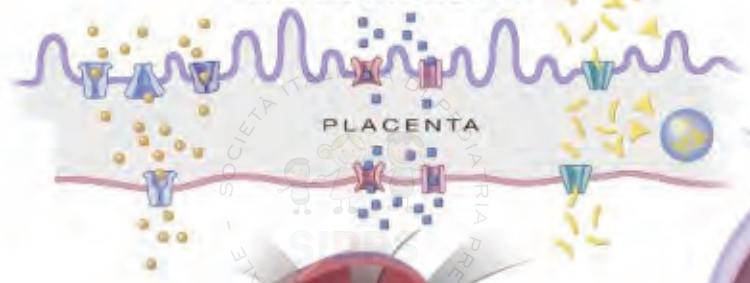
CARBOHYDRATES



Glucose

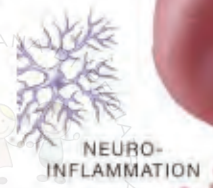


MATERNAL BLOOD

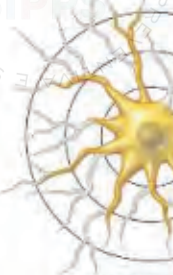


PLACENTA

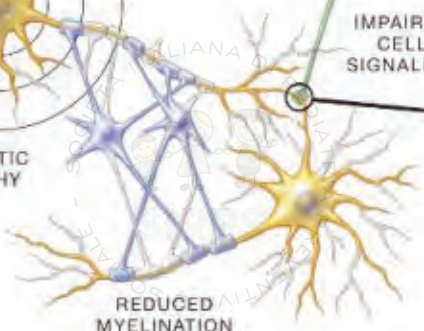
FETAL BLOOD



NEURO-INFLAMMATION

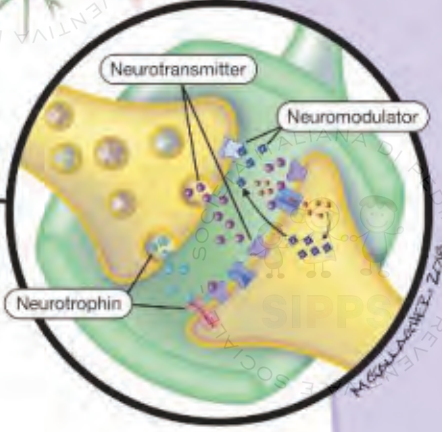


DENDRITIC ATROPHY



REDUCED MYELINATION

IMPAIRED CELL SIGNALING



Review

# Perinatal Nutrition and Programmed Risk for Neuropsychiatric Disorders: A Focus on Animal Models

Madison DeCapo, Jacqueline R. Thompson, Geoffrey Dunn, and Elinor L. Sullivan

2019



	<b>Enterotipo 1</b> <b>B</b> <b>+ frequente</b>	<b>Enterotipo 2</b> <b>P</b>	<b>Enterotipo 3</b> <b>R</b> <b>Esiste veramente?</b>
<b>Batterio caratterizzante</b> (who the microbes are?)	<b>Bacteroides</b>	<b>Prevotella</b>	<b>Ruminococcus</b>
<b>Batteri associati frequentemente</b>	<b>Parabacteroides</b> <b>Clostridiales</b>	<b>Desulfovibrionales</b> <b>Streptococcus</b>	<b>Akkermansia</b> <b>Methanobrevibacter</b> <b>Clostridiales</b>
<b>Proprietà funzionale di degradazione</b> (what the microbes do?)	<b>Carboidrati e proteine</b>	<b>Glicoproteine della mucina e polisaccaridi vegetali</b>	<b>Carboidrati e mucina</b>
<b>Dieta tipica</b>	<b>Carne rossa</b>	<b>Frutta e verdura</b> <b>Cereali</b> <b>Poca carne</b>	--
<b>Effetto</b>	<b>Grandi estrattori di energia (obesità?)</b>	<b>Grandi produttori di composti di zolfo (odore uova bollite)</b>	--
<b>Coinvolgimento nella biosintesi</b>	<b>Biotina (Vit. B7)</b>	<b>Tiamina (Vit. B1)</b>	<b>Eme (coinvolto in biosintesi Vit. B 12)</b>
<b>Consistenza delle feci</b>	<b>Dura</b>	<b>Molle</b>	<b>Dura</b>

# Agenda

# 6 + 9 + 6

- Tre periodi da raccontare
- Finestre: tempo come opportunità
- Formidabile l'epigenetica!
- Il rischio a "U"
- 4 programmazioni: ormonale, mitocondriale, batterica, nutrizionale (immunitaria denominatore comune)
- 3 organi top level (cervello, cuore, rene)
- Autismo: cose che non sappiamo di non sapere
- Alzheimer (dall'isola di Guam all'isola di Okinawa)
- Cosa portare a casa e cosa fare?
- Preghiera finale





# An unborn baby's genetic inheritance, 2006

## Wellcome Library, Cambridge



**Il rovescio della medaglia fa nascere perplessità: questa massa di conoscenze aumenterà il potere dell'uomo sull'uomo e, paradossalmente, porrà problemi cruciali sulla libertà che ciascuno di noi avrà in futuro.**

**Noncommunicable diseases (NCDs), kill more than 38 million people each year, making them by far the leading cause of death in the world.**

WHO. WHO Global Status Report on Noncommunicable Diseases 2014. World Health Organisation, Geneva, Switzerland, 1–51 (2014).

## Epigenetics and noncommunicable diseases

### Epigenomics

“The field in general needs better causal evidence to underpin the mechanistic link between epigenetic variation and noncommunicable diseases.”

*Epigenomics* (2017) 9(6), 789–791



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MRC Integrative Epidemiology Unit,  
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University of Bristol, Oakfield House,  
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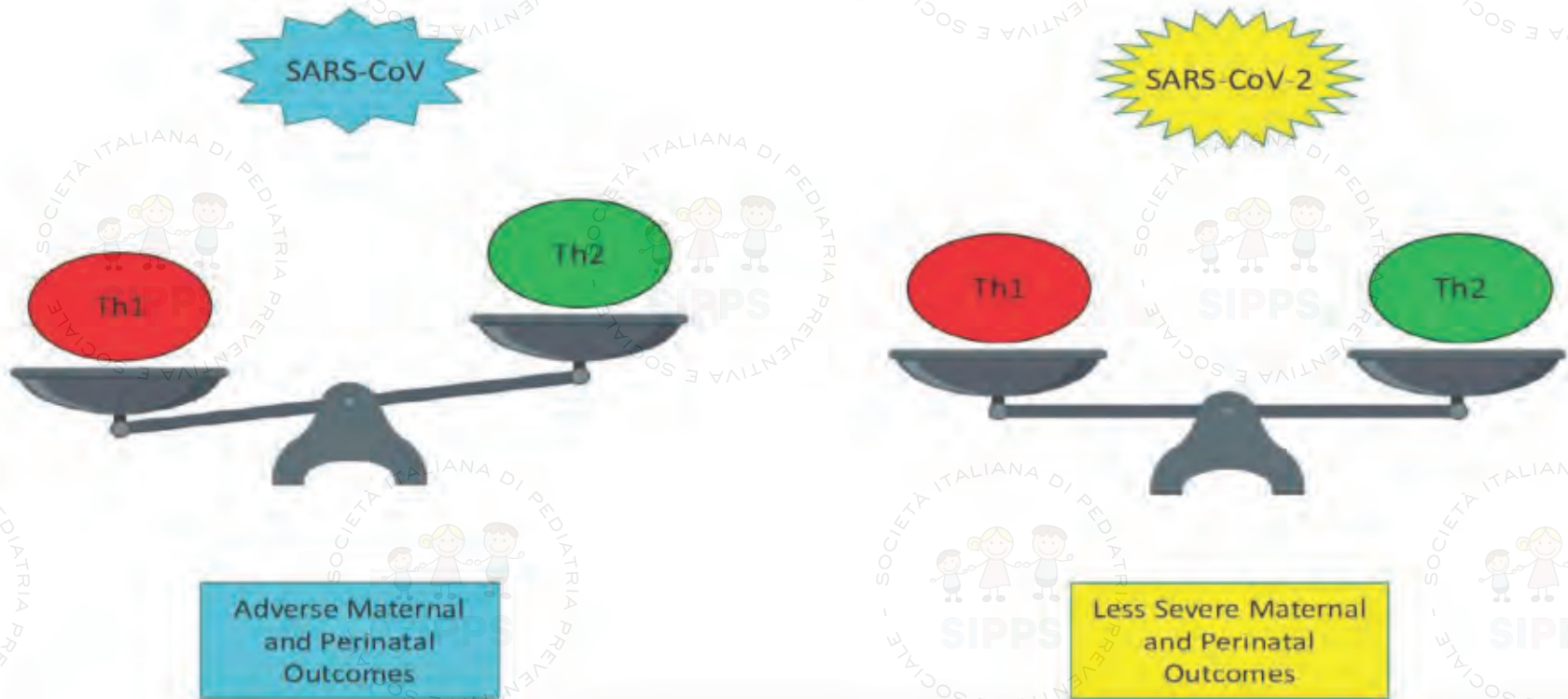
REVIEW ARTICLE



## Relationship between pregnancy and coronavirus: what we know

Stefano Forestieri<sup>a</sup>, Maria Antonietta Marcialis<sup>b</sup>, Lucia Migliore<sup>c</sup>, Cristina Panisi<sup>d</sup> and Vassilios Fanos<sup>b,e</sup>

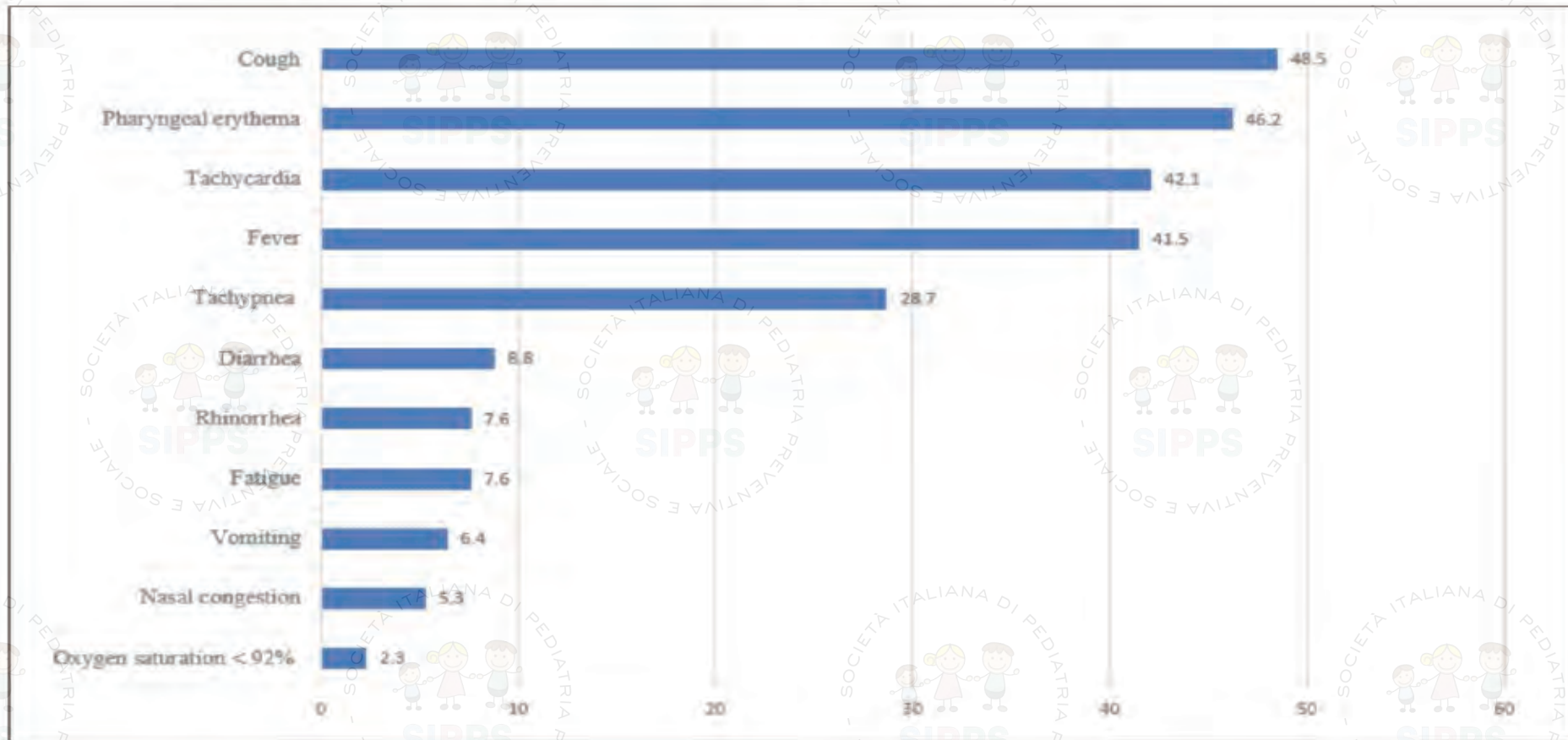
<sup>a</sup>School of Pediatrics, University of Cagliari, Cagliari, Italy; <sup>b</sup>Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy; <sup>c</sup>Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Pisa, Italy; <sup>d</sup>"Sacra Famiglia" Institute, Varese, Italy; <sup>e</sup>Department of Surgery, University of Cagliari, Cagliari, Italy



# COVID-19 in newborns and in children: the state of the art

Valentina Paraluppi<sup>1</sup>, Maria Cristina Pintus<sup>2</sup>, Vassilios Fanos<sup>3</sup>, Maria Antonietta Marcialis<sup>2</sup>

<sup>1</sup>School of Pediatrics, University of Cagliari, Cagliari, Italy





## Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review

Giulia Sanna<sup>1</sup> • Gaia Serrau<sup>1</sup> • Pier Paolo Bassareo<sup>2,3</sup> • Paola Neroni<sup>1</sup> • Vassilios Fanos<sup>1</sup> • Maria Antonietta Marcialis<sup>1</sup>

## THE KIDNEY IN COVID-19: PROTAGONIST OR FIGURANT?

Maria Francesca STAICO, Marco ZAFFANELLO, Giulia DI PIETRO, Vassilios FANOS, Maria Antonietta MARCIALIS

*Panminerva Medica* 2020 May 20

DOI: 10.23736/S0031-0808.20.03965-8

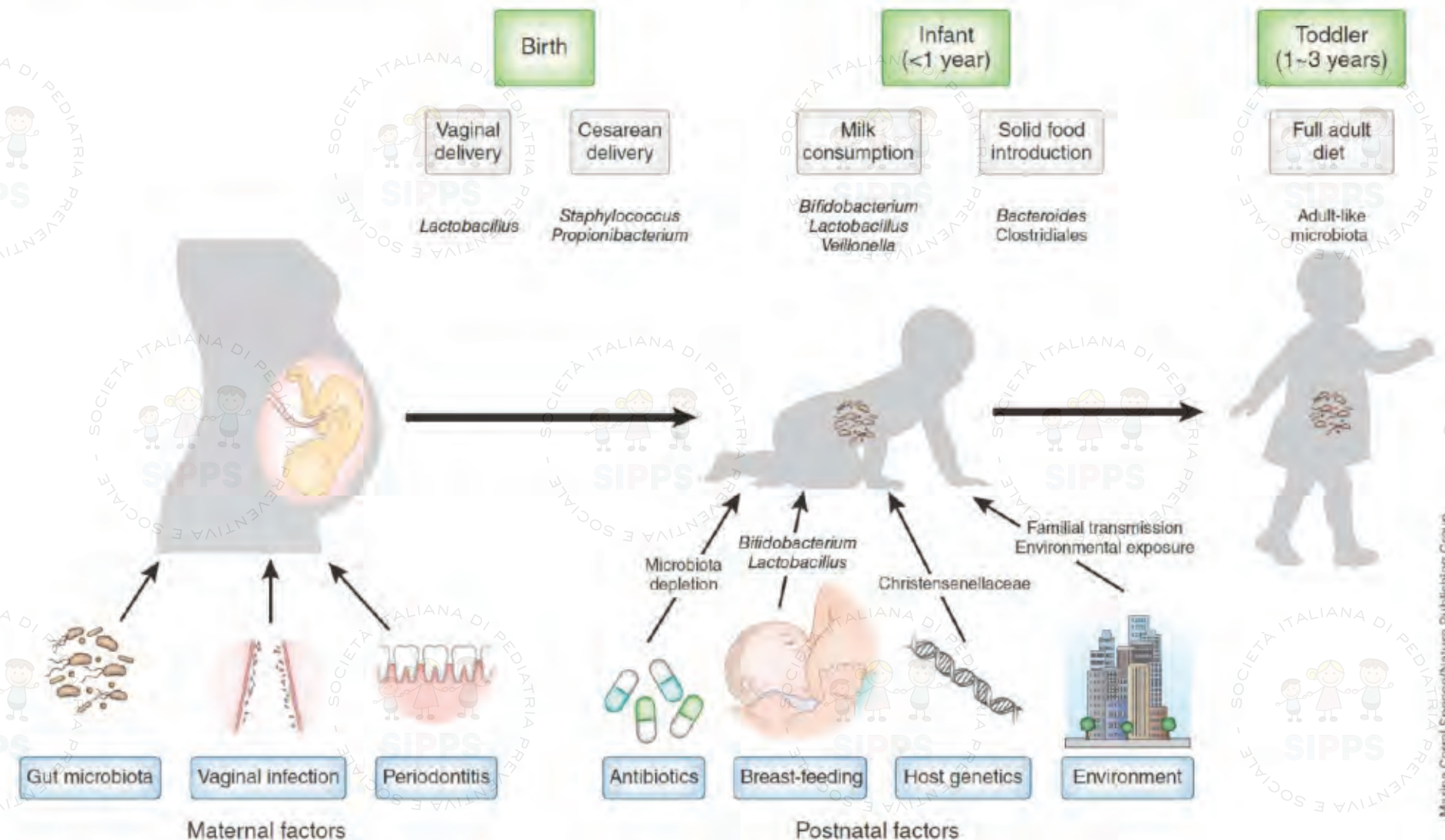
# The microbiome in early life: implications for health outcomes

Sabrina Tamburini<sup>1,4</sup>, Nan Shen<sup>1,4</sup>, Han Chih Wu<sup>2,3</sup> & Jose C Clemente<sup>1-3</sup>

nature  
medicine

NATURE MEDICINE VOLUME 22 | NUMBER 7 | JULY 2016

REVIEW





# Pediatric and neonatal individualized Medicine: care and cure for each and everyone

Vassilios Fanos

Editor in Chief JPNUM

Neonatal Intensive Care Unit, Puericulture Institute and Neonatal Section, AOU and University of Cagliari, Italy

**Metabolomics →**  
**Microbiomics →**

**Medicine of the past**

**Medicine of the future**

**Epidemiologic**

**Individualized**

**Descriptive**

**Predictive**

**Reductionistic**

**Holystic**

**Reactive**

**Prospective**

**Genetics-based**

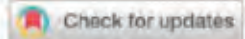
**Epigenetics-based**

**Imprecision**

**Precision**



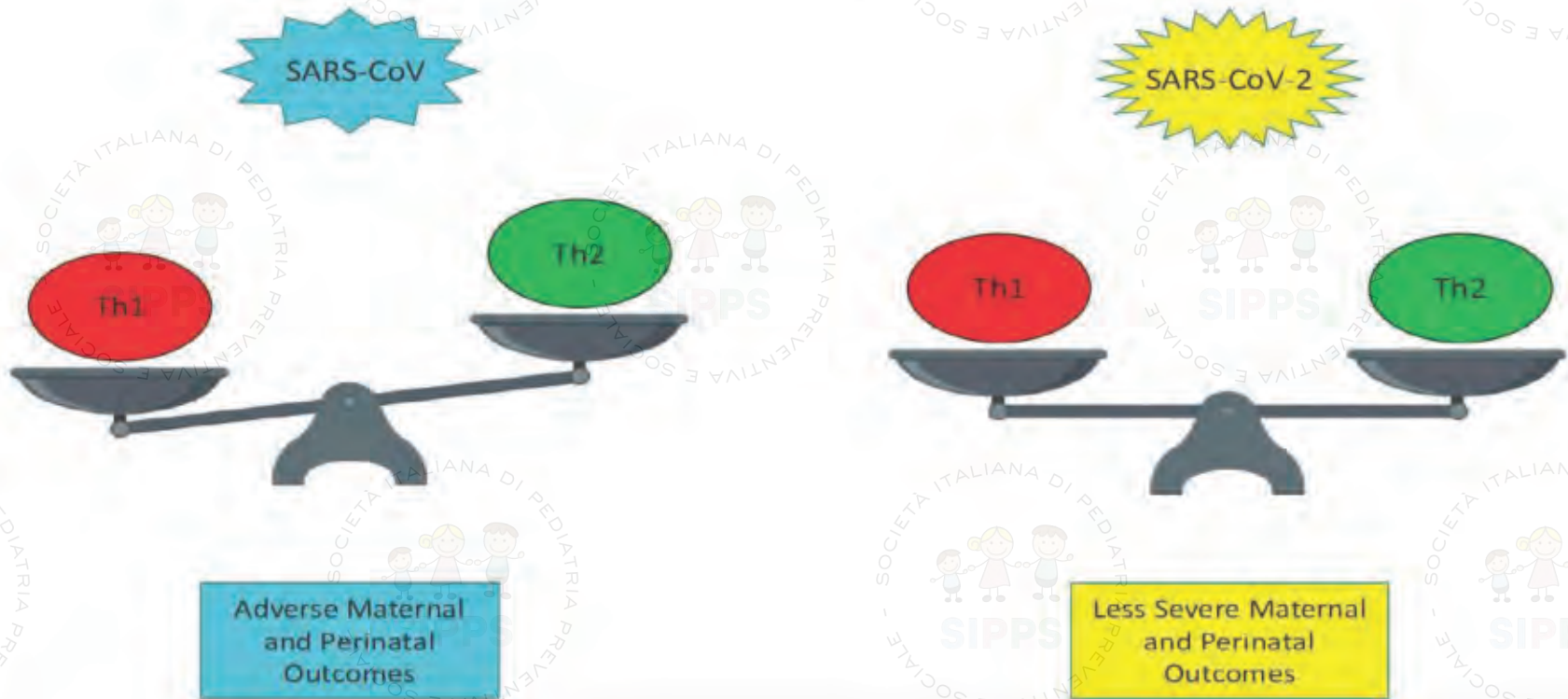
REVIEW ARTICLE



# Relationship between pregnancy and coronavirus: what we know

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<sup>a</sup>School of Pediatrics, University of Cagliari, Cagliari, Italy; <sup>b</sup>Neonatal Intensive Care Unit, AOU Cagliari, Cagliari, Italy; <sup>c</sup>Department of Translational Research and of New Surgical and Medical Technologies, University of Pisa, Pisa, Italy; <sup>d</sup>"Sacra Famiglia" Institute, Varese, Italy; <sup>e</sup>Department of Surgery, University of Cagliari, Cagliari, Italy

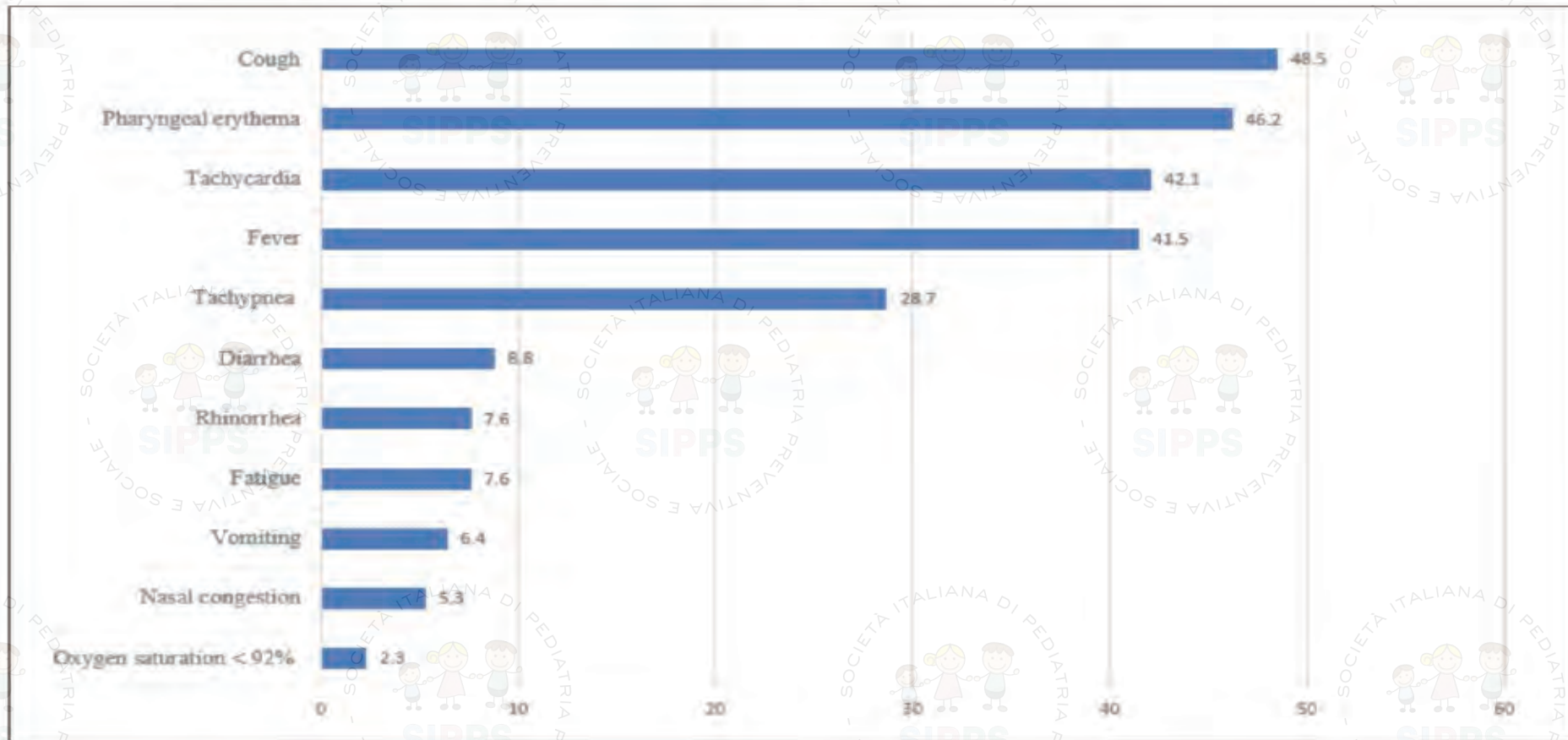




# COVID-19 in newborns and in children: the state of the art

Valentina Paraluppi<sup>1</sup>, Maria Cristina Pintus<sup>2</sup>, Vassilios Fanos<sup>3</sup>, Maria Antonietta Marcialis<sup>2</sup>

<sup>1</sup>School of Pediatrics, University of Cagliari, Cagliari, Italy



## Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review

Giulia Sanna<sup>1</sup> • Gaia Serrau<sup>1</sup> • Pier Paolo Bassareo<sup>2,3</sup> • Paola Neroni<sup>1</sup> • Vassilios Fanos<sup>1</sup> • Maria Antonietta Marcialis<sup>1</sup>

## THE KIDNEY IN COVID-19: PROTAGONIST OR FIGURANT?

Maria Francesca STAICO, Marco ZAFFANELLO, Giulia DI PIETRO, Vassilios FANOS, Maria Antonietta MARCIALIS

*Panminerva Medica* 2020 May 20

DOI: 10.23736/S0031-0808.20.03965-8



# Prenatal – birth

# Infant – early child (birth to 3 years)

## Neuro-immune abnormalities in autism and their relationship with the environment: a variable insult model for autism

Daniel K. Goyal\* and Jaleel A. Miyan  
Faculty of Life Sciences, The University of Manchester, Manchester, UK

	Early acute insult	Early chronic insult	Late acute insult	Late chronic insult
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Congenital abnormalities

++++      ++++      +      +

Severe dysmotility

++++      ++++      ++      ++

Sudden regression

+      ++      +++++      ++++

Insidious regression

++      ++++      +      +++++

Early immune-related issues

+++      +++++      ++      ++

Motor delays

++++      ++++      +      +

Family history of autoimmunity

++      ++      +++++      ++++

Gestational exposure

++++      ++++      +

Early infancy exposure

+      ++      +++++      +++++

# Sintesi delle alterazioni metabolomiche nei bambini autistici

Ambito di studio	Alterazioni metabolomiche
<b>Neurologia</b>	<p>Triptofano e derivati, acido kinurenico, fenilalanina, glicina e acido ippurico, associati a sintomi neurologici e depressione.</p> <p>Incremento nelle urine di galattosio, ribosio, arabitolo, xilitolo, treitolo ed eritritolo come nel deficit di ribosio-5-fosfato isomerasi (sintomi neurologici simili all'autismo).</p>
<b>Gastroenterologia</b>	<p>Pacchetto di metaboliti di ischemia cronica (incremento urinario di acido gluconico, acido treonico, glucosio e ribosio e decremento di arabinosio).</p> <p>Aumento del mannitolo urinario, segno di abnorme permeabilità intestinale.</p> <p>Aumento del fucosio urinario, segno di aggressività delle malattie infiammatorie intestinali croniche.</p>
<b>Microbiologia</b>	<p>Abnorme colonizzazione da parte di <i>Clostridia spp.</i> (e anche di <i>Caloramator</i> e <i>Sarcina</i>).</p> <p>Incremento urinario di acido 3-idrossifenilacetico, L-tirosina e acido 3-3-idrossifenil-3-idrossipropionico (firma dei <i>Clostridia spp.</i>).</p>
<b>Immunologia</b>	<p>Alterazioni aminoacidiche: aumento sierico e urinario della glicina e della serina coinvolti in numerosi <i>pathways</i> metabolici (elevati anche in schizofrenia e psicosi).</p> <p>Stress ossidativo: aumento dell'acido piroglutammico, indice di un deficit di glutazione.</p>
<b>Disfunzione mitocondriale</b>	<p>Alterazione del ciclo di Krebs.</p> <p>Incremento urinario di citrato e isocitrato e diminuzione di succinato (blocco da parte dell'acido propionico, prodotto dai <i>Clostridia spp.</i>).</p>



Egypt Divided / Qatar's Ambition / Rot in the ANC

# TIME

## Want to Know My Future?



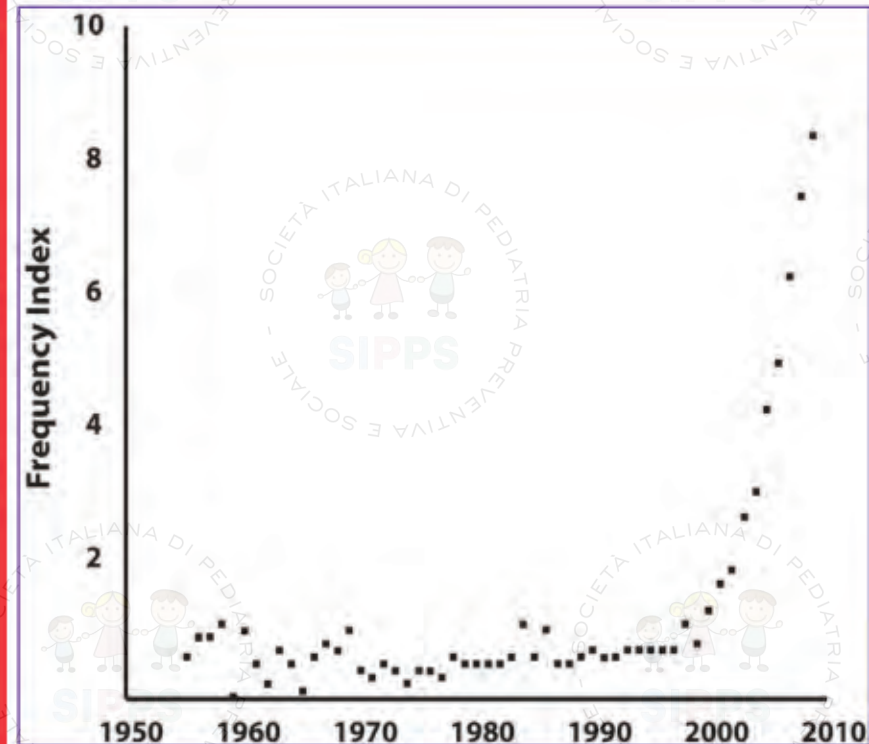
New genetic tests can point to risks—  
but not always a cure

BY BONNIE ROCHMAN



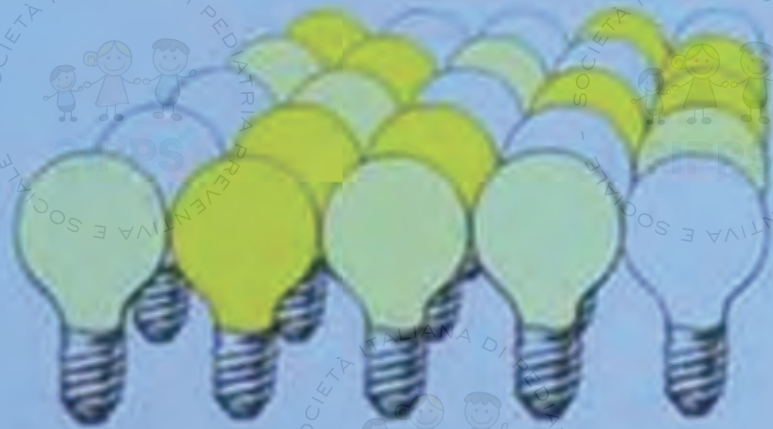
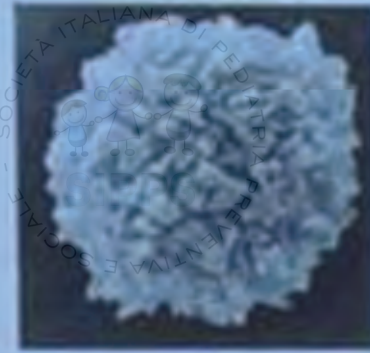


Most of the diseases are multigenic and multifactorial:  
**Epigenetics!**





# Tissue Specificity versus Environmental Effects

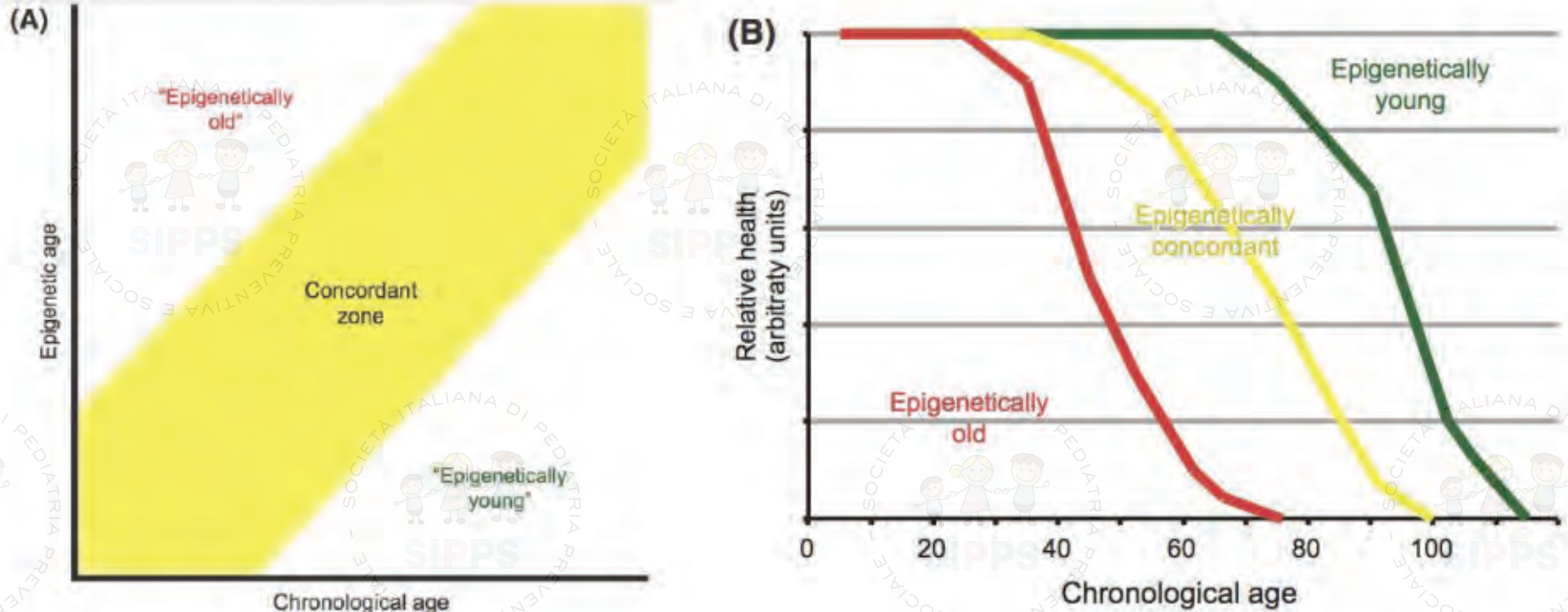


REVIEW

# DNA methylation and healthy human aging

Meaghan J. Jones,<sup>1,2</sup> Sarah J. Goodman<sup>1,2</sup> and Michael S. Kobor<sup>1,2,3</sup>

<sup>1</sup>Centre for Molecular Medicine and Therapeutics, Child and Family Research Institute, <sup>2</sup>Department of Medical Genetics, <sup>3</sup>Human Early Learning Partnership, School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada





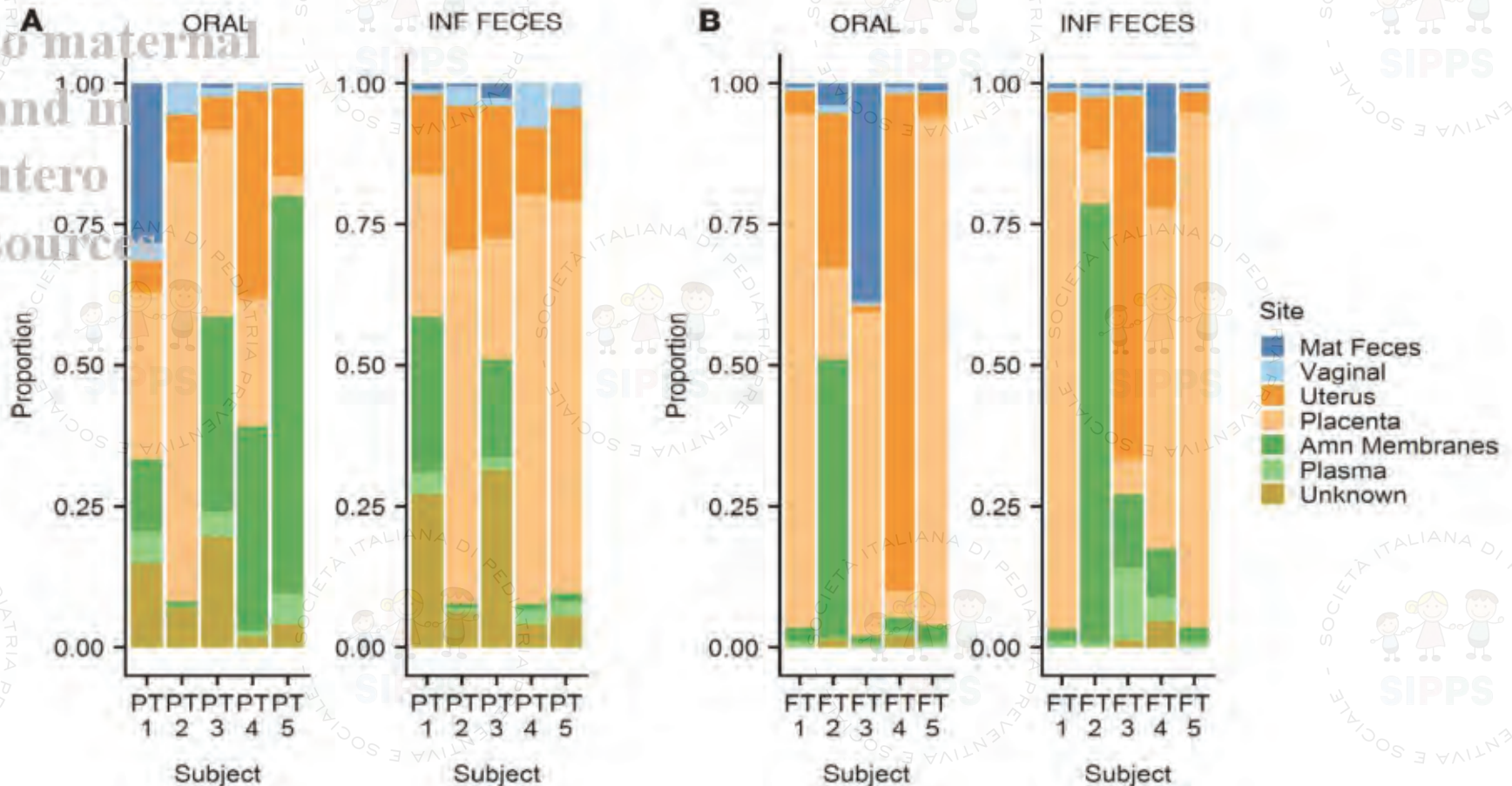
Proportions of the infant microbiota

attributed to maternal and in utero sources

# Fetal exposure to the maternal microbiota in humans and mice

Noelle Younge,<sup>1</sup> Jessica R. McCann,<sup>1</sup> Julie Ballard,<sup>1,2</sup> Catherine Plunkett,<sup>2</sup> Suhail Akhtar,<sup>2</sup> Félix Araújo-Pérez,<sup>1,2</sup> Amy Murtha,<sup>1,3</sup> Debra Brandon,<sup>1,4</sup> and Patrick C. Seed<sup>2</sup>

<sup>1</sup>Department of Pediatrics, Duke University School of Medicine, Durham, North Carolina, USA. <sup>2</sup>Department of Pediatrics,



# Gestational diabetes is associated with changes in placental microbiota and microbiome

Judit Bassols, Matteo Serino, Gemma Carreras-Badosa, Rémy Burcelin, Vincent Blasco-Baque, Abel Lopez-Bermejo & José-Manuel Fernandez-Real

Affiliations | Corresponding author

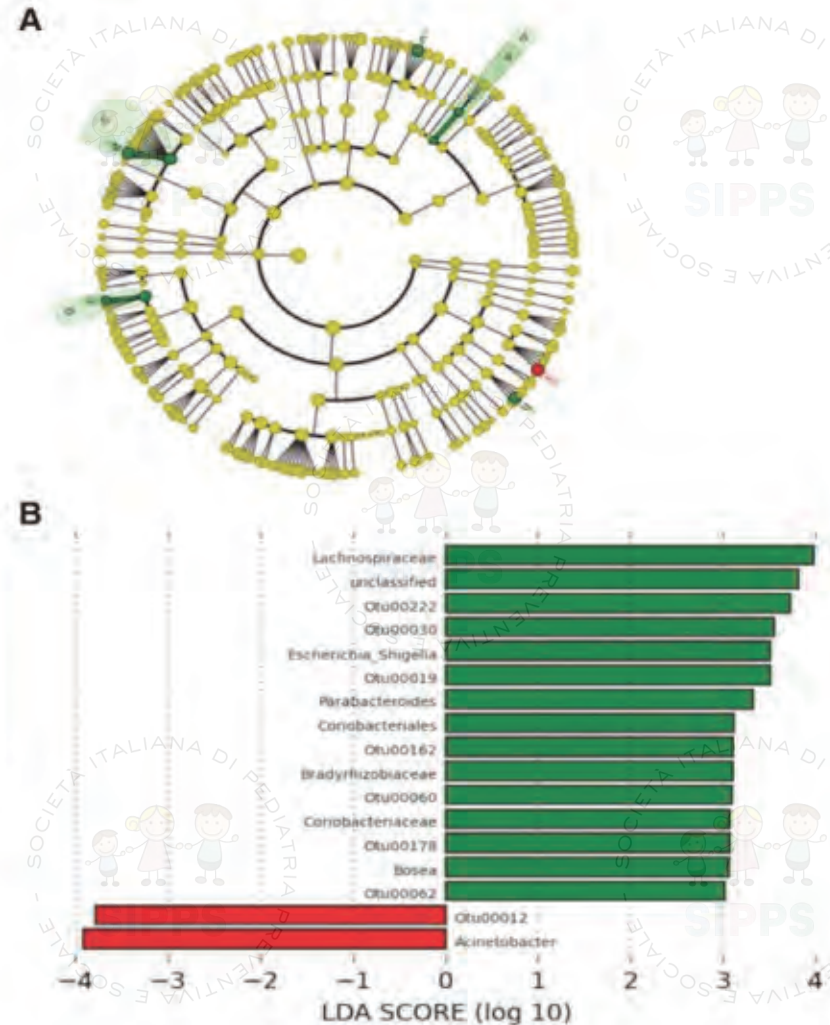
*Pediatric Research* (2016) 80, 777–784 | doi:10.1038/pr.2016.155

Received 12 February 2016 | Accepted 03 June 2016

↓ Acinetobacter



Fenotipo metabolico e infiammatorio sfavorevole





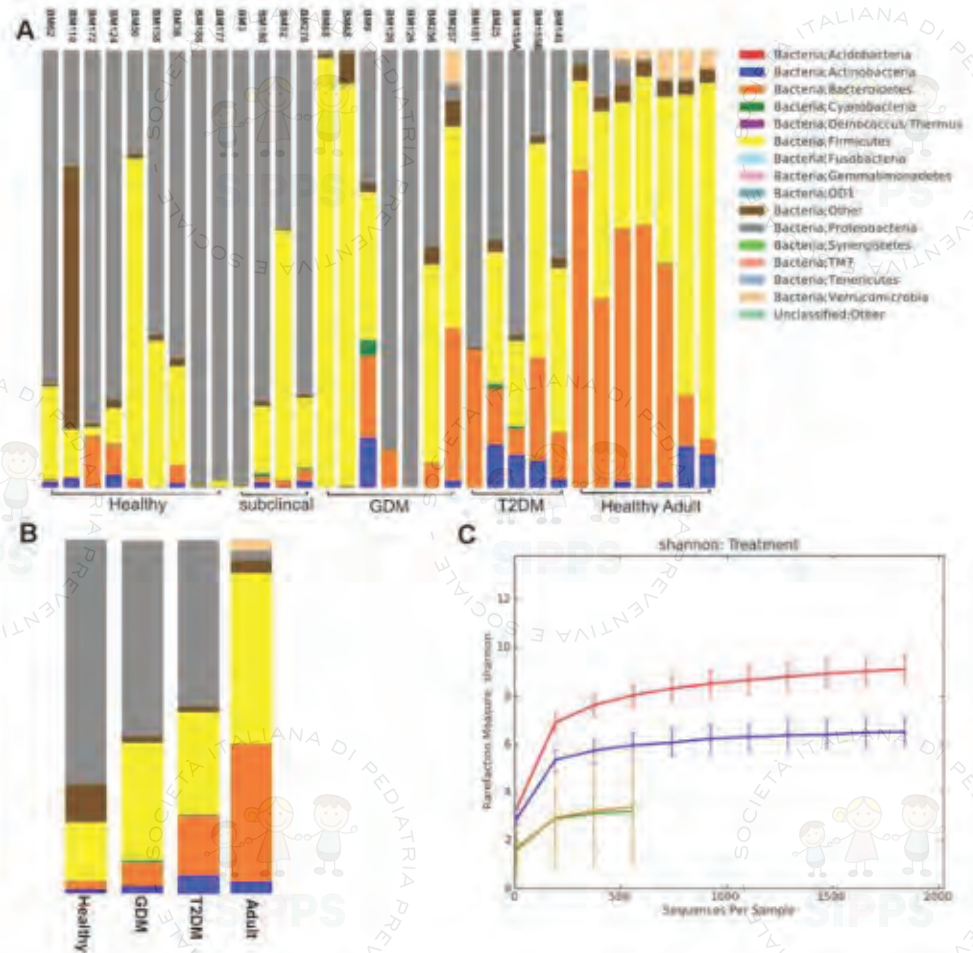
# Diversified Microbiota of Meconium Is Affected by Maternal Diabetes Status

Jianzhong Hu<sup>1\*</sup>, Yoko Nomura<sup>2,3</sup>, Ali Bashir<sup>1</sup>, Heriberto Fernandez-Hernandez<sup>1</sup>, Steven Itzkowitz<sup>4</sup>, Zhiheng Pei<sup>5,6</sup>, Joanne Stone<sup>7</sup>, Holly Loudon<sup>7</sup>, Inga Peter<sup>1</sup>

**1** Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, **2** Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, **3** Department of Psychology, Queens College, CUNY, Flushing, New York, United States of America, **4** Division of Gastroenterology, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America, **5** Department of Veterans Affairs New York Harbor Healthcare System, New York, New York, United States of America, **6** Department of Pathology, NYU Langone Medical Center, New York University School of Medicine, New York, New York, United States of America, **7** Department of Obstetrics, Gynecology, and Reproductive Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, United States of America

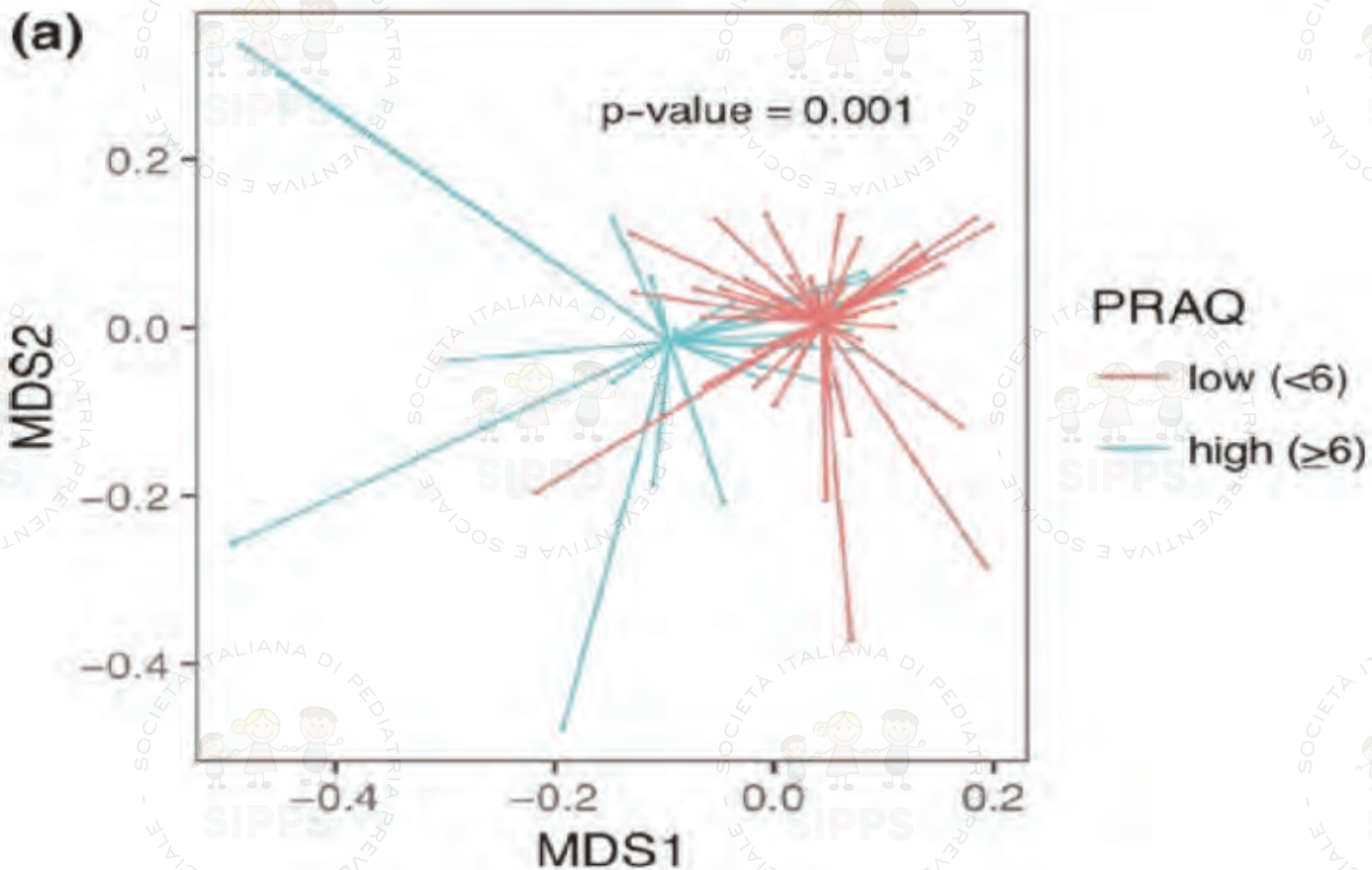
↑ Firmicutes nei figli di mamma diabetica

Microbiota del meconio è simile a quello delle feci di adulti malati di diabete



# Microbiota of newborn meconium is associated with maternal anxiety experienced during pregnancy

Jianzhong Hu<sup>1</sup> | Jenny Ly<sup>2</sup> | Wei Zhang<sup>2,3</sup> | Yonglin Huang<sup>4</sup> | Vivette Glover<sup>5</sup> | Inga Peter<sup>1</sup> | Yasmin L. Hurd<sup>6,7</sup> | Yoko Nomura<sup>2,4,6</sup>



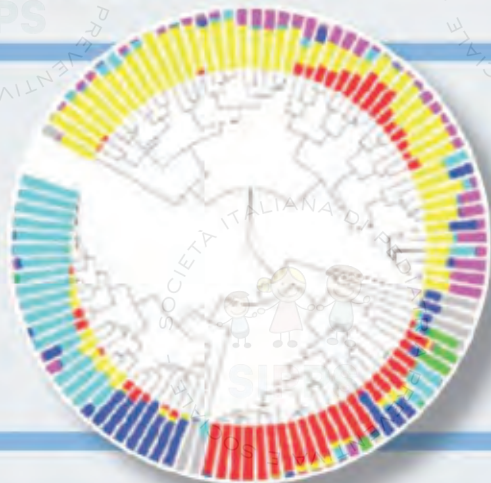


# ISTOGRAMMA DELLA MUCOSA NASOFARINGEA A SEI SETTIMANE E SEI MESI DI VITA NEI SOGGETTI ALLATTATI AL SENO O ALIMENTATI CON FORMULA ADATTATA

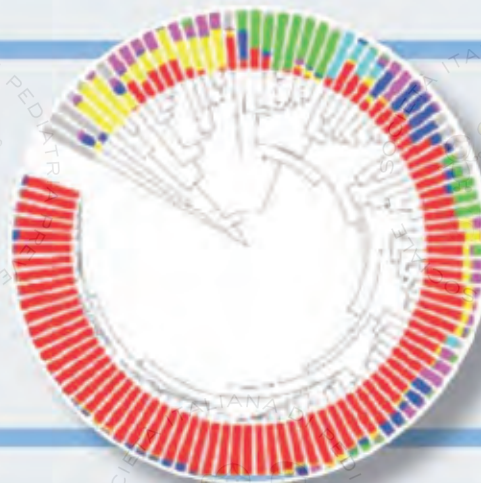
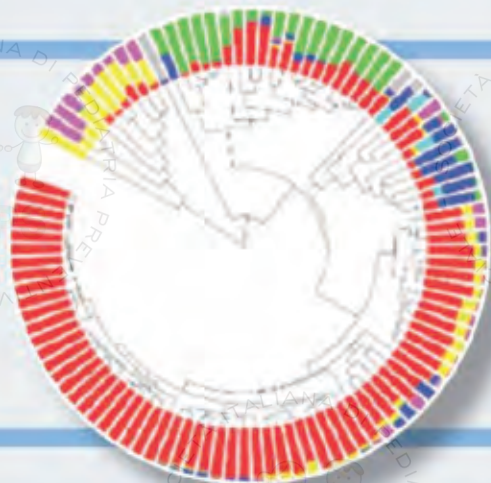
Allattati al seno

Formula adattata

6 SETTIMANE



6 MESI

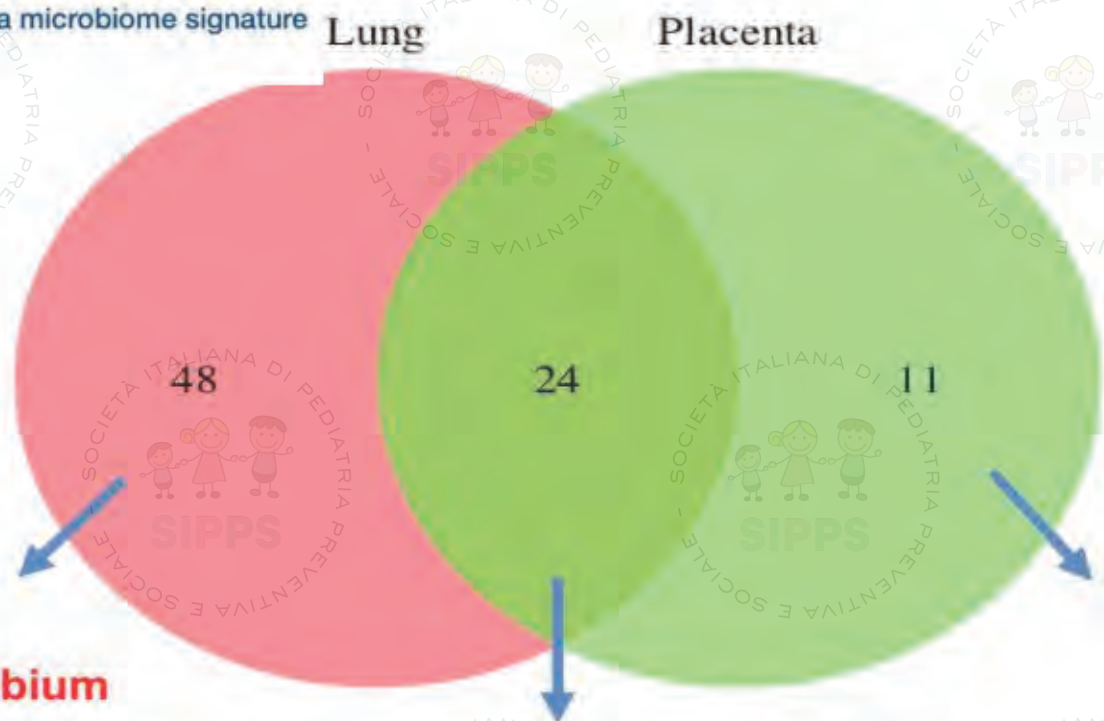


- Moraxella
- Haemophilus
- Streptococcus
- Staphylococcus
- Corynebacterium
- Dolosigranulum
- Altri generi

The Impact of Breastfeeding on Nasopharyngeal Microbial Communities in Infants.  
Biesbroek G1, Bosch AA, Wang X, Keijser BJ, Veenhoven RH, Sanders EA, Bogaert D.  
Am J Respir Crit Care Med. 2014 Aug 1;190(3):298-308

# Human fetal lungs harbor a microbiome signature

Date: January 17, 2020



- Paracoccus**
  - Desemzia**
  - Geobacillus**
  - Nostoc**
  - Burkholderia**
  - Cellulosimicrobium**
  - Balneimonas**
  - Pseudonocardia**
  - Terriglobus**
  - Isoptericola**
- (0.3-3 %)**

- Lactobacillus**
  - Gardnerella**
  - Haemophilus**
  - Shuttleworthia**
  - Megasphaera**
  - Propionibacterium**
  - Enhydrobacter**
  - Atopobium**
  - Sneathia**
  - Chryseobacterium**
- (2-25 %)**

- Flavobacterium**
  - Lysobacter**
  - Bacteroides**
  - Thermus**
  - Chroococcus**
  - Hymenobacter**
  - Kitasatospora**
  - Armatimonas**
  - Hydrocoleum**
  - Myroides**
- (0.8-1.5 %)**

Copyright © 2020

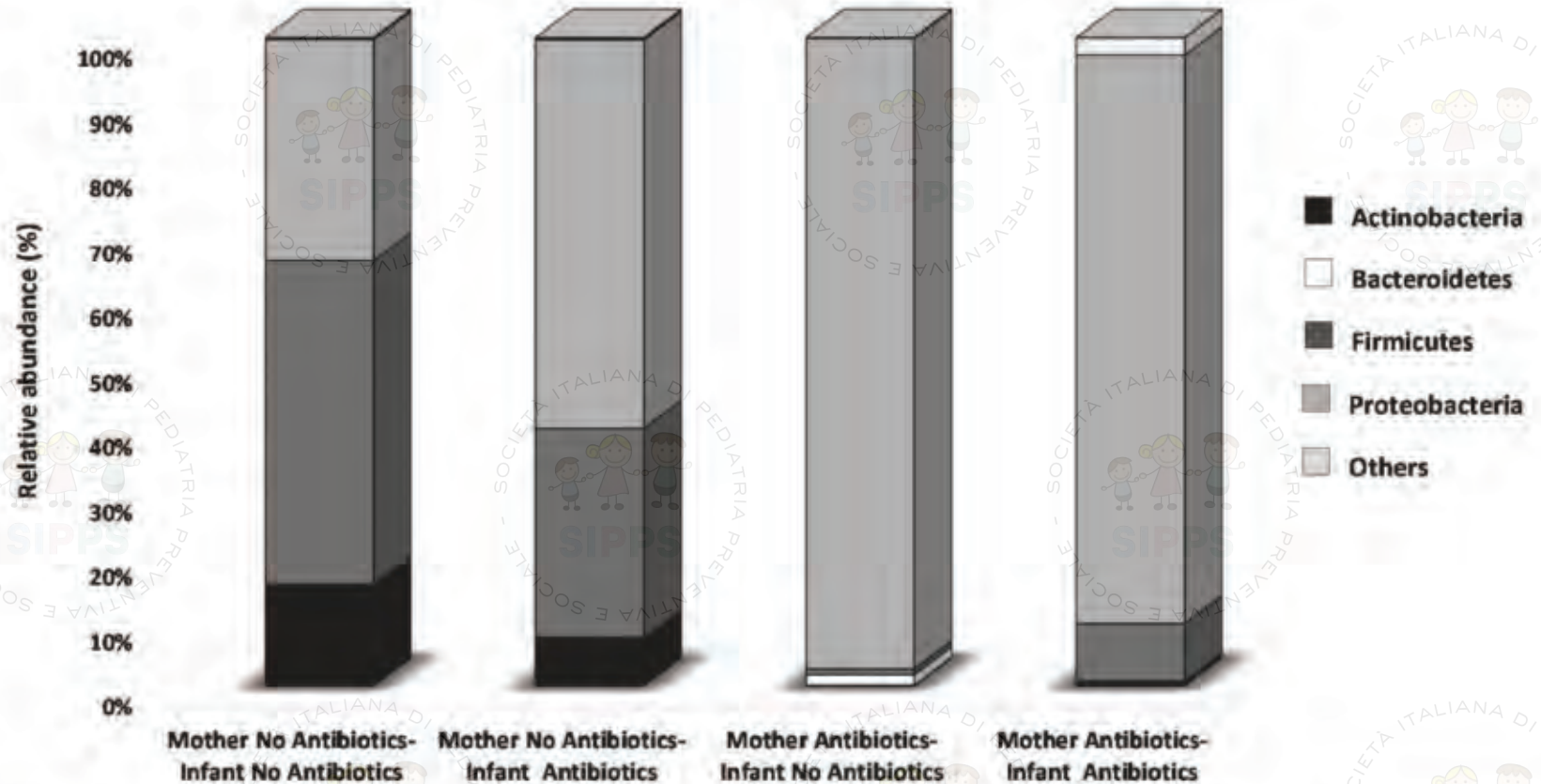
Similar lung microbiome profiles are found after either cesarean or vaginal delivery, which suggests that microbes somehow are able to reach the lungs before birth





# Impact of Prematurity and Perinatal Antibiotics on the Developing Intestinal Microbiota: A Functional Inference Study

Silvia Arboleya <sup>1</sup>, Borja Sánchez <sup>1</sup>, Gonzalo Solís <sup>2</sup>, Nuria Fernández <sup>3</sup>, Marta Suárez <sup>2</sup>, Ana M. Hernández-Barranco <sup>1</sup>, Christian Milani <sup>4</sup>, Abelardo Margolles <sup>1</sup>, Clara G. de los Reyes-Gavilán <sup>1</sup>, Marco Ventura <sup>4</sup> and Miguel Guemonde <sup>1,4</sup>



**Figure 3.** Relative abundance (%) of phylum level distributions of the fecal microbiota in the different antibiotic exposure groups classified into four classes depending on mother and infant antibiotic exposure at 30 days of life.

REVIEW PAPER

# Factors influencing the development of a personal tailored microbiota in the neonate, with particular emphasis on antibiotic therapy

G. Faa<sup>1</sup>, C. Gerosa<sup>1</sup>, D. Fanni<sup>1</sup>, S. Nemolato<sup>1</sup>, P. van Eyken<sup>3</sup>, and V. Fanos<sup>2</sup>

<sup>1</sup>Department of Surgical Sciences, Division of Pathology, University Hospital San Giovanni di Dio, University of Cagliari, Cagliari, Italy,

<sup>2</sup>NIC, Puericulture Institute and Neonatal Section, University Hospital San Giovanni di Dio, University of Cagliari, Cagliari, Italy, and <sup>3</sup>Department of Pathology, K.U. Leuven, Leuven, Belgium



**Obesity?**  
**Autism?**



# Neonatal microbiota development and the effect of early life antibiotics are determined by two distinct settler types

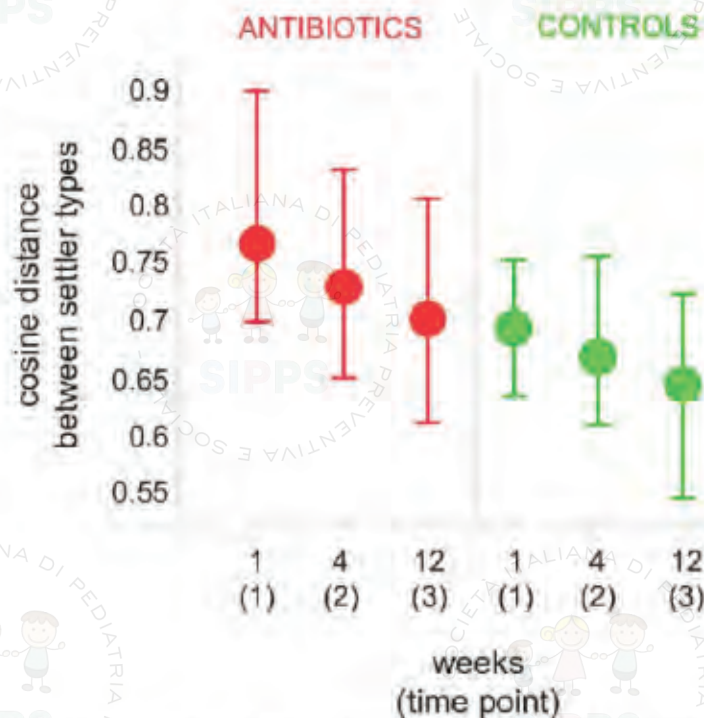
OPEN ACCESS

**Citation:** Eck A, Rutten NBMM, Singendonk MMJ, Rijkers GT, Savelkoul PHM, Meijssen CB, et al. (2020) Neonatal microbiota development and the effect of early life antibiotics are determined by two distinct settler types. PLoS ONE 15(2): e0228133. <https://doi.org/10.1371/journal.pone.0228133>

**Anat Eck<sup>1</sup>**, **Nicole B. M. M. Rutten<sup>2</sup>**, **Maartje M. J. Singendonk<sup>3</sup>**, **Ger T. Rijkers<sup>4</sup>**, **Paul H. M. Savelkoul<sup>1,5</sup>**, **Clemens B. Meijssen<sup>6</sup>**, **Clarissa E. Crijns<sup>7</sup>**, **Johanna H. Oudshoorn<sup>8</sup>**, **Andries E. Budding<sup>1</sup>**, **Arine M. Vlieger<sup>2\*</sup>**

**1** Department of Medical Microbiology and Infection Control, Amsterdam UMC, VU University Amsterdam,

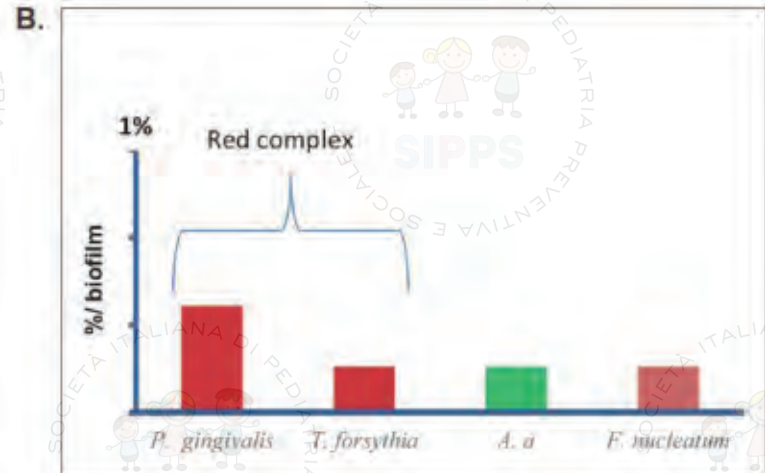
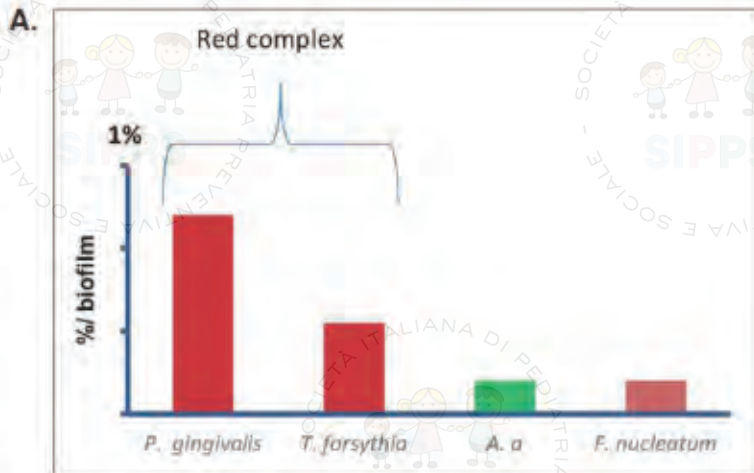
(b)



**Fig 2. Convergence of settler types over time.** A principle coordinate analysis of intestinal microbiota of all untreated infants at week 1 (T = 1), month 1 (T = 2) and month 3 (T = 3). Samples are colored by settler type. (b) Cosine distances, as a measure of community dissimilarity between settler types, displayed over time by treatment group. Dots indicate median cosine distances, bars indicate IQR (inter quartile range). A higher distance indicates the settler types are less similar.

# Periodontal microbiota of Sardinian children: comparing 200-year-old samples to present-day ones

Germano Orrù<sup>1,2</sup>, Maria Paola Contu<sup>1</sup>, Eleonora Casula<sup>1</sup>, Cristina Demontis<sup>1,2</sup>, Cornelio Blus<sup>2</sup>, Serge Sz mukler-Moncler<sup>2</sup>, Gabriele Serrelli<sup>3</sup>, Carla Maserati<sup>4</sup>, Giorgio Carlo Steri<sup>4</sup>, Vassilios Fanos<sup>5</sup>, Ferdinando Coghe<sup>3</sup>, Gloria Denotti<sup>2</sup>



**Figure 3.** Percentage in the biofilm of each periodontal bacterium detected in the recent group (A), and in the ancient one (B).

A. a.: *A. actinomycetemcomitans*.



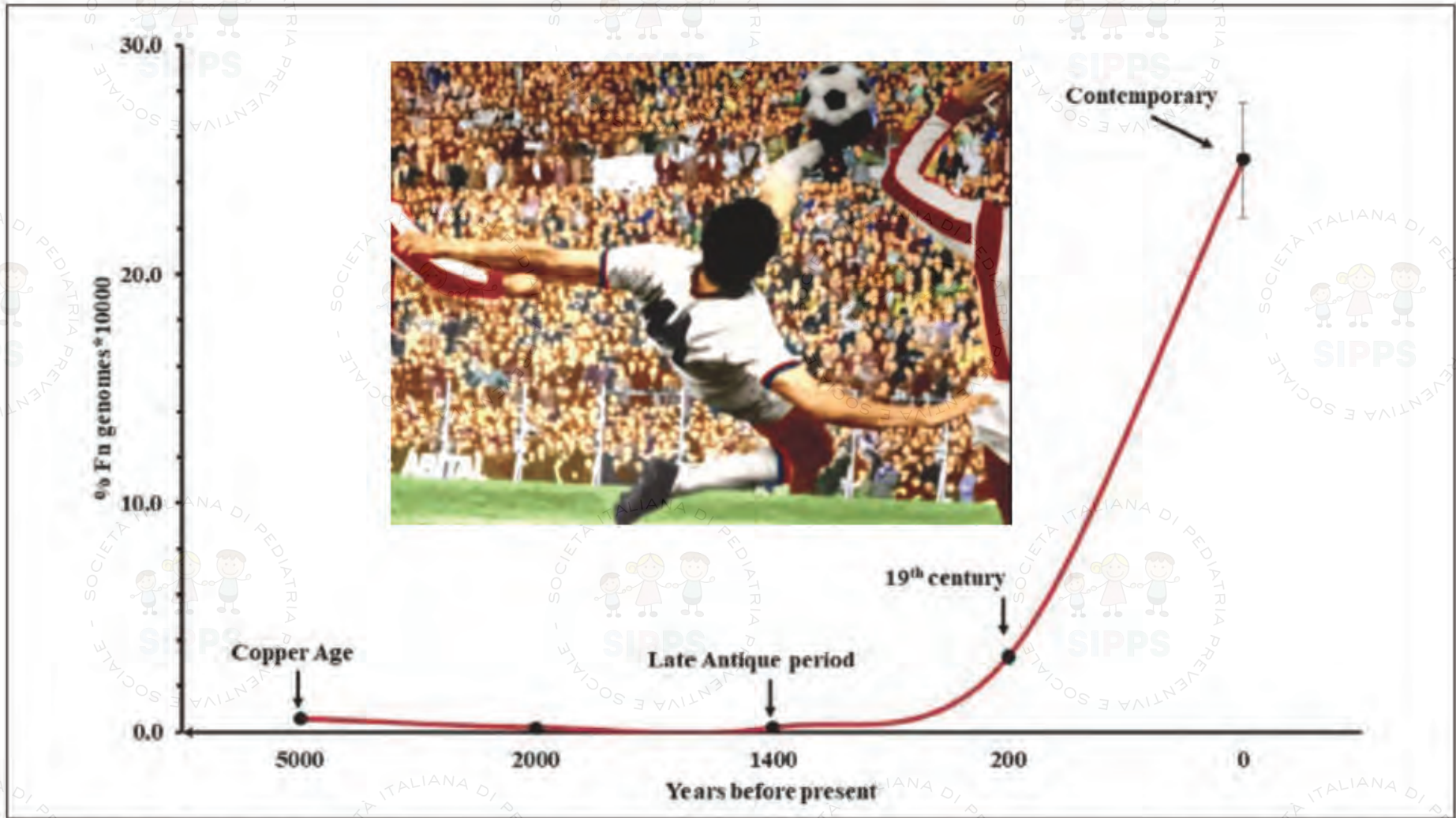


Figure 1 (ABS 21). Relationship between sampling period and Fn titer %, a significant increase is observable from the 19<sup>th</sup> century to the recent period.



Jpn J Med 2018,1:4

217

## Japan Journal of Medicine

2018; 1(4): 217 - 221 . doi: 10.31488/jjm.1000119

Review article

### Kidney development and susceptibility to develop kidney disease in adulthood

Faa G<sup>1</sup>, Fanni D<sup>1</sup>, Gerosa C<sup>1</sup>, Gibo Y<sup>2</sup>, Fanos V<sup>3</sup>

<sup>1</sup> Division of Pathology, University Hospital San Giovanni di Dio, AOU of Cagliari, University of Cagliari, Cagliari, Italy

<sup>2</sup> Hepatology Clinic, Matsumoto, Japan

<sup>3</sup> Neonatology and Neonatal Intensive Care Unit, University of Cagliari, Cagliari, Italy

**THE BLUE STRIP WIDTH**



# Il cervello ha bisogno di un microbiota sano



**Vi è un fitto dialogo tra i vari organi e, oggi, la metabolomica ci consente di decifrare e capire molte di queste comunicazioni, il linguaggio segreto del nostro corpo. La creazione di queste reti da parte dei batteri pionieri, nelle prime fasi della vita, costituisce la fondazione dei pilastri della salute, buona o cattiva.**



RESEARCH

Open Access

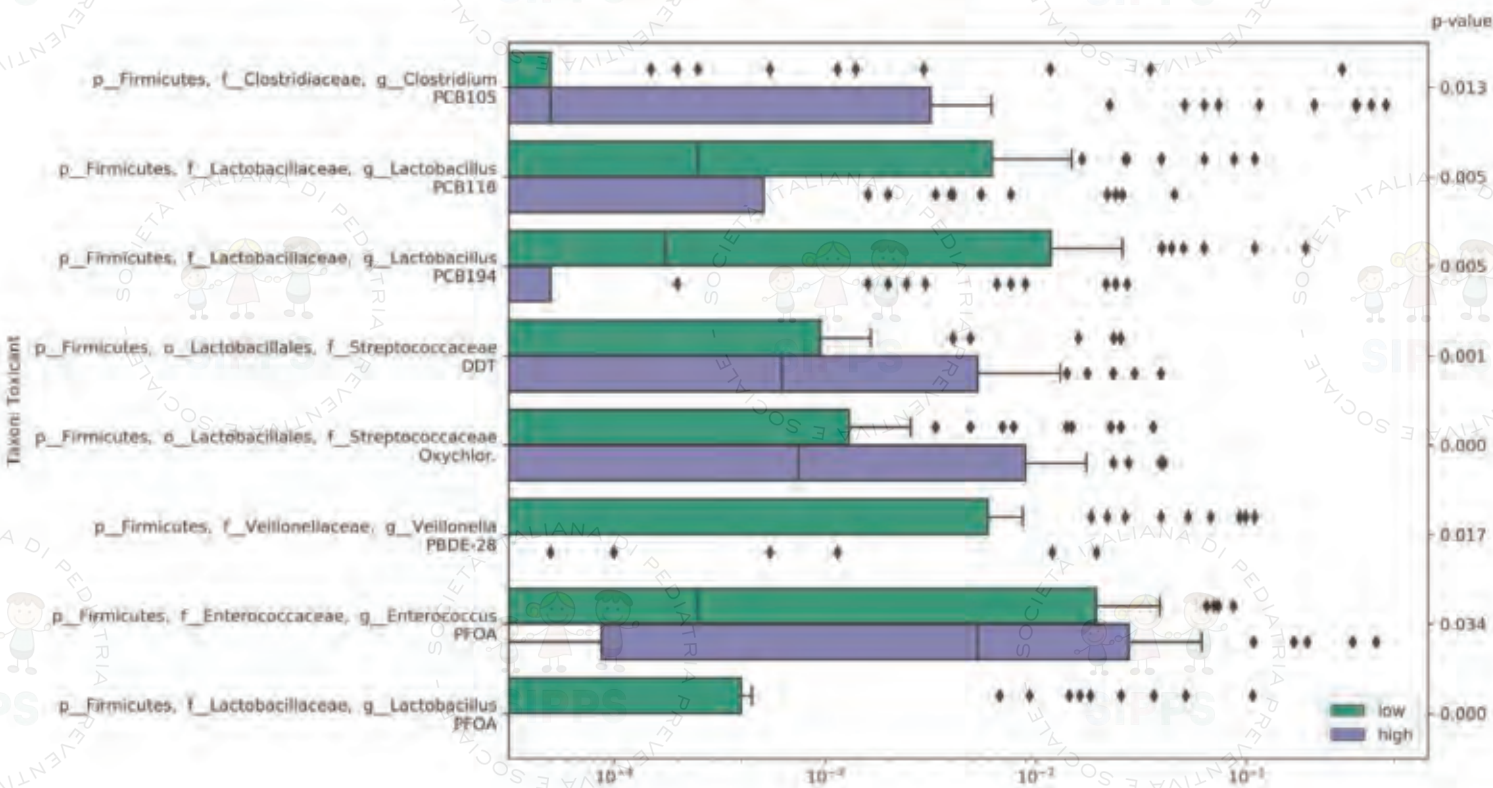
Reduction of  
Lactobacilli

# Environmental toxicants in breast milk of Norwegian mothers and gut bacteria composition and metabolites in their infants at 1 month

Nina Iszatt<sup>1</sup>, Stefan Janssen<sup>2,3</sup>, Virissa Lenters<sup>1</sup>, Cecilie Dahl<sup>4</sup>, Hein Stigum<sup>5</sup>, Rob Knight<sup>6,7</sup>, Siddhartha Mandal<sup>8</sup>, Shyamal Peddada<sup>9</sup>, Antonio González<sup>2</sup>, Tore Midtvedt<sup>10</sup> and Merete Eggesbø<sup>1\*</sup>



The authors tested 28 chemical exposures: polychlorinated biphenyls (PCBs), polybrominated flame retardants (PBDEs), per- and polyfluoroalkyl substances (PFASs), and organochlorine pesticides.







# Friends with social benefits: host-microbe interactions as a driver of brain evolution and development?

Roman M. Stilling<sup>1,2</sup>, Seth R. Bordenstein<sup>3</sup>, Timothy G. Dinan<sup>1,4</sup> and John F. Cryan<sup>1,2\*</sup>

<sup>1</sup> Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland

<sup>2</sup> Department Anatomy and Neuroscience, University College Cork, Cork, Ireland

<sup>3</sup> Departments of Biological Sciences and Pathology, Microbiology, and Immunology, Vanderbilt University, Nashville, TN, USA

<sup>4</sup> Department of Psychiatry, University College Cork, Cork, Ireland

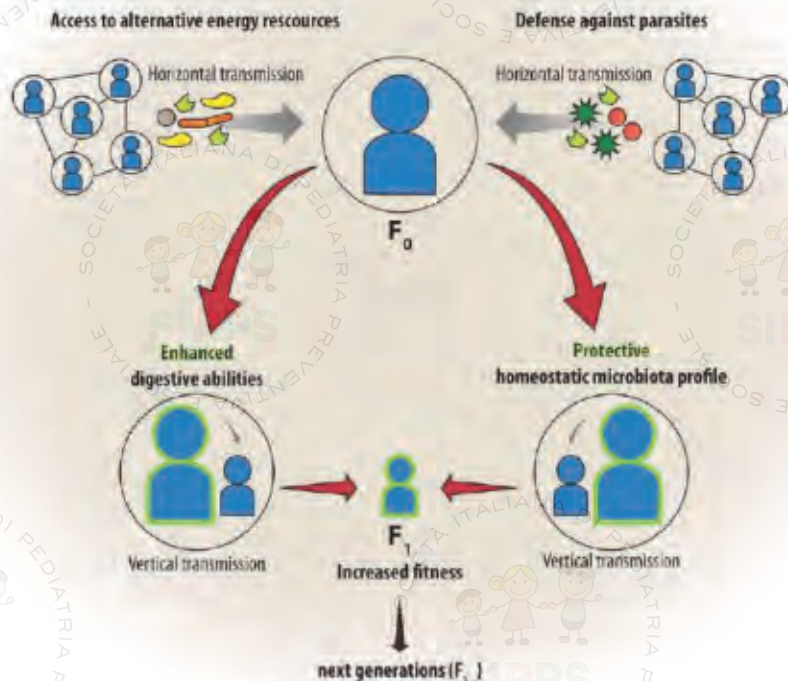
## THE SOCIAL NETWORK: MICROBIOTA, RNA AND THE EVOLUTION OF THE SOCIAL BRAIN

“LIFE DID NOT TAKE OVER THE GLOBE BY COMBAT, BUT BY NETWORKING”

(Margulis and Sagan, 1986)

“ALL EVOLUTION IS CO-EVOLUTION”

(Stuart Kauffman, 1995)

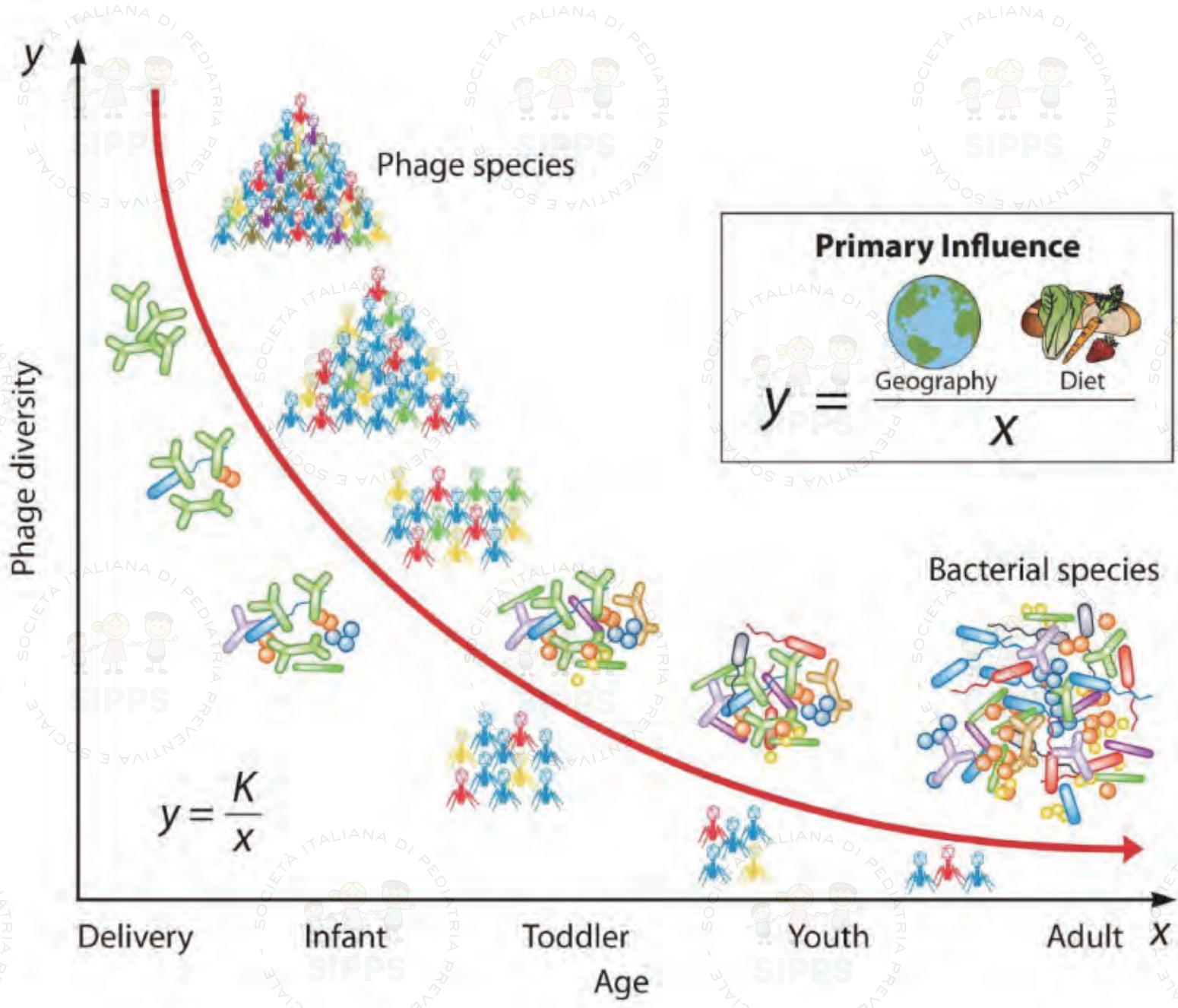


# An unborn baby's genetic inheritance, 2006

## Wellcome Library, Cambridge







SOCIETÀ ITALIANA DI PEDIATRIA PREVENTIVA E SOCIALE - SIPPS

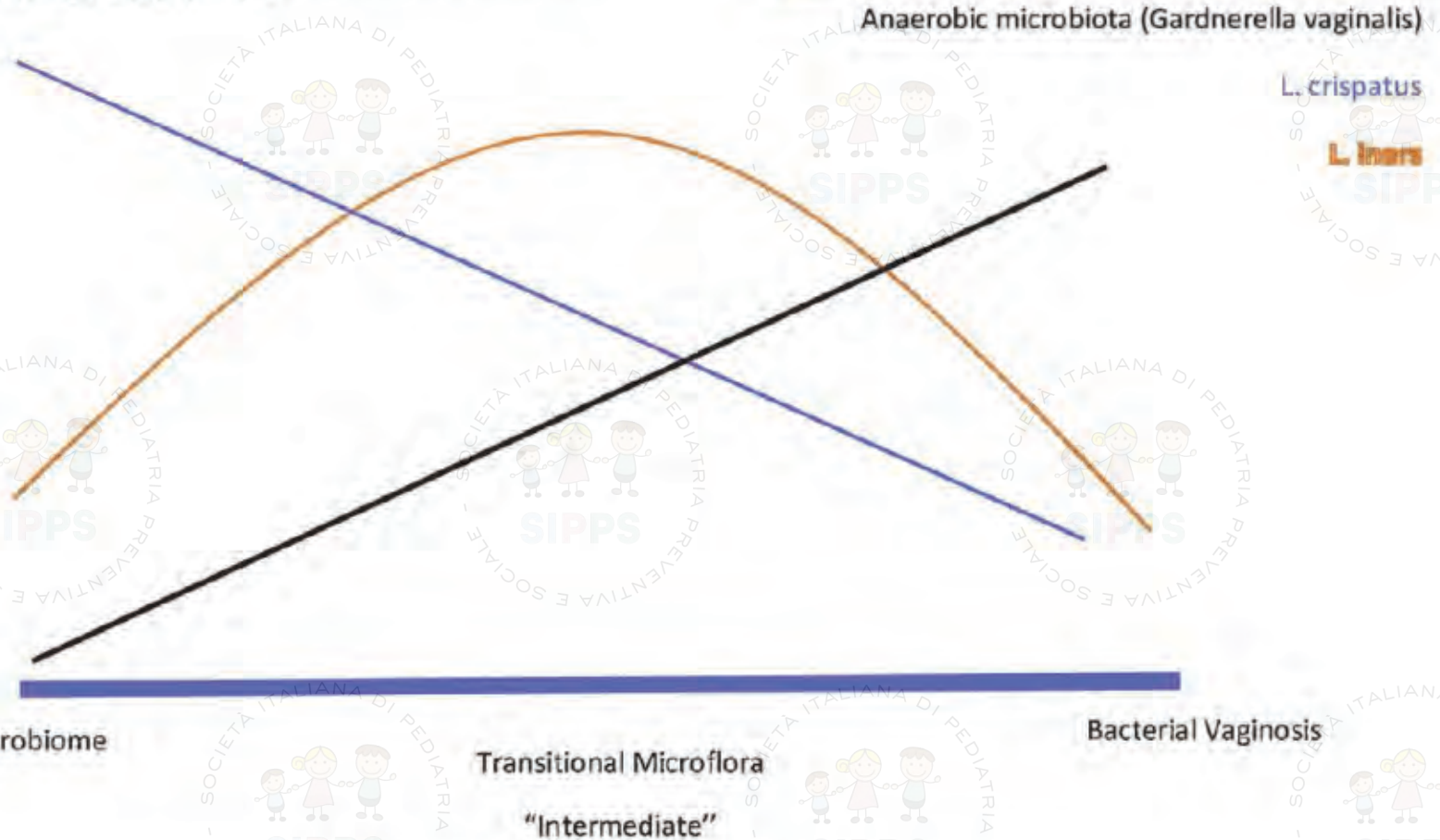
Review article

### Female genital tract microbiota affecting the risk of preterm birth: What do we know so far? A review

O. Tsonis<sup>a,\*</sup>, F. Gkrozou<sup>b</sup>, E. Harrison<sup>b</sup>, K. Stefanidis<sup>c</sup>, N. Vrachnis<sup>d</sup>, M. Paschopoulos<sup>a</sup>

<sup>a</sup>Department of Obstetrics and Gynecology, University Hospital of Ioannina, Greece

**1/3 delle donne con microbiota vaginale povero di Lactobacilli va incontro a un parto altamente pretermine (< 32 settimane); 3/4 delle donne con microbiota vaginale ricco di Lactobacilli hanno un parto a termine.**



**Fig. 1.** Dynamic changes in vaginal microbiome.



# Metabolomics is the "Rosetta Stone" of Microbiomics

## Aromatic Amino Metabolism

p-cresol sulfate  
o-cresol sulfate  
3-indoxyl sulfate  
3-(4-hydroxyphenyl)lactate  
3-(3-hydroxyphenyl)propionate  
3-(4-hydroxyphenyl)propionate  
4-hydroxyphenylacetate  
5-hydroxyindoleacetate  
3-ethylphenylsulfate  
4-ethylphenylsulfate  
4-vinylphenylsulfate  
indolelactate  
indoleacetate  
Indolebutyrate  
indolepropionate  
indoleacetylglutamine  
methyl indole-3-acetate  
phenylacetylglutamine  
phenyllactate  
phenol sulfate

## Vitamins Riboflavin

## Lipid Metabolism:

valerate  
Isovalerate  
Methylpropionate  
Lyso-PC  
lyso-PE  
monacylglycerol  
cholesterol

## Secondary Bile Acids:

cholate  
glycohyocholate  
taurodeoxycholate  
glycodeoxycholate  
glycolithocholate  
glycolithocholate sulfate  
glychoyodeoxycholate  
glycocholenate sulfate  
glycoursodeoxycholate  
hyocholate  
taurocholenate sulfate  
tauroursodeoxycholate  
tauroolithocholate 3-sulfate

## gut bacteria metabolism

## Energy Metabolism

Lactate  
succinate  
glucose  
urea  
creatinine  
Creatinine

## Choline Metabolism

betaine  
dimethylglycine

## Xenobiotic Metabolism:

hippurate  
2-hydroxyhippurate  
3-hydroxyhippurate  
4-hydroxyhippurate  
naringenin

Plasma metabolomic profiles enhance precision medicine for volunteers of normal health

Living Donor? Michael D. Williams<sup>1</sup>, John A. Bock<sup>1</sup>, Steven C. Lammert<sup>1</sup>, Matthew M. Mitchell<sup>1</sup>, David E. Weller<sup>1</sup>, Steven C. Anderson<sup>1</sup>, Anne M. Stone<sup>1</sup>, Brent Brummer<sup>1</sup>, Julia Miller<sup>1</sup>, William J. Bennett<sup>1</sup>, and C. Thomas Casadevall<sup>1</sup>

<sup>1</sup>Department of Medicine, Center for Molecular Systems, Division of Gastroenterology and Hepatology, and Division of Infectious Diseases, Columbia University Medical Center, New York, NY, USA

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May 3, 2017

# The Paternal Epigenome Makes Its Mark

Jennifer Abbasi

Article Information

JAMA. Published online May 3, 2017. doi:10.1001/jama.2017.1566



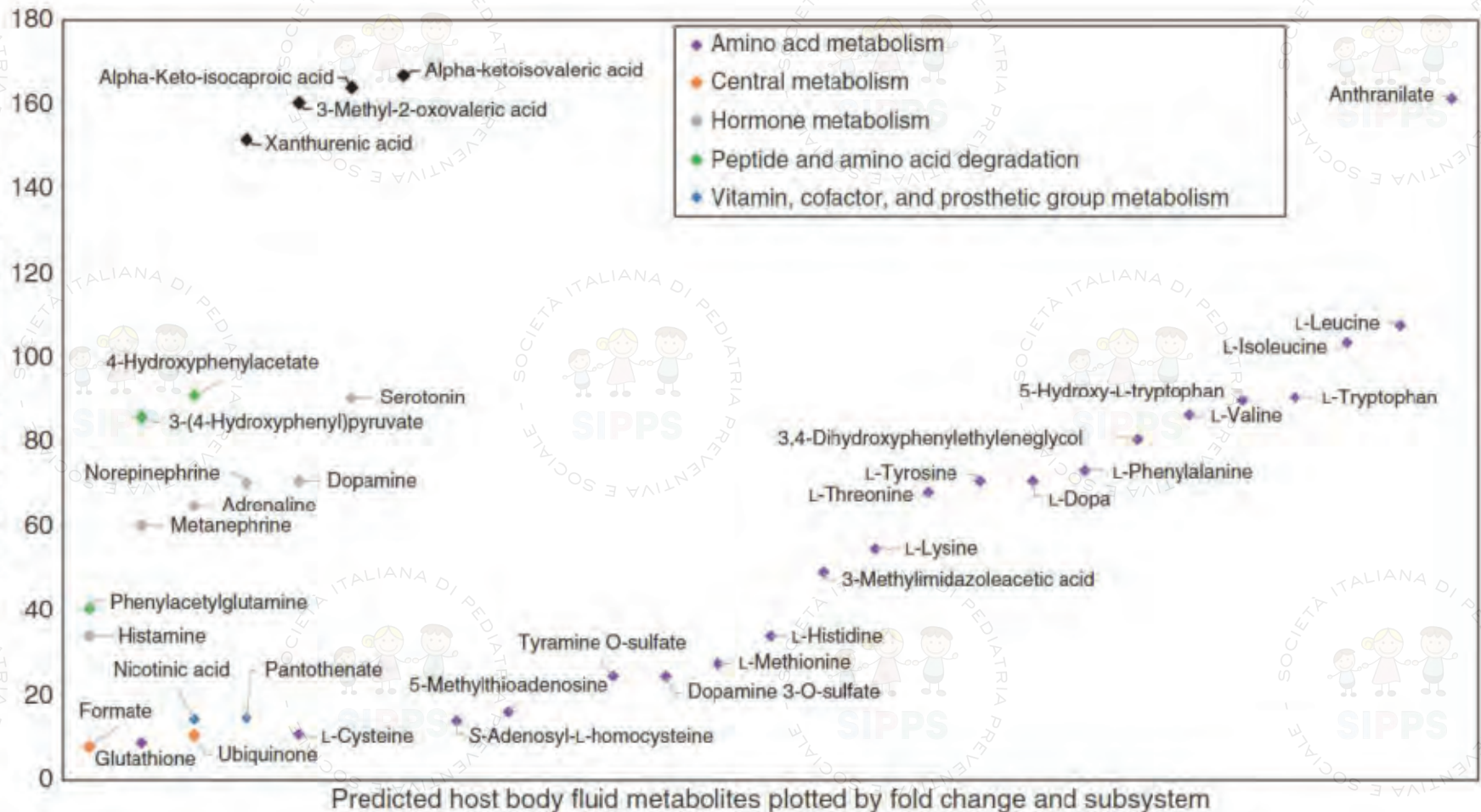




# Systems biology of host–microbe metabolomics

Almut Heinken and Ines Thiele\*

Fold change in body fluid secretion in microbe-associated versus germfree host



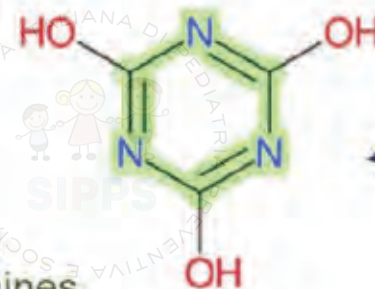
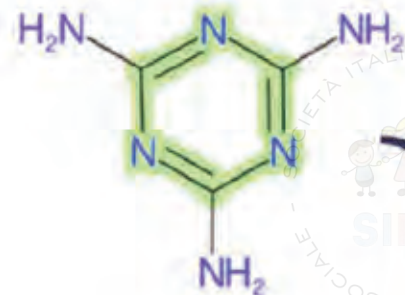
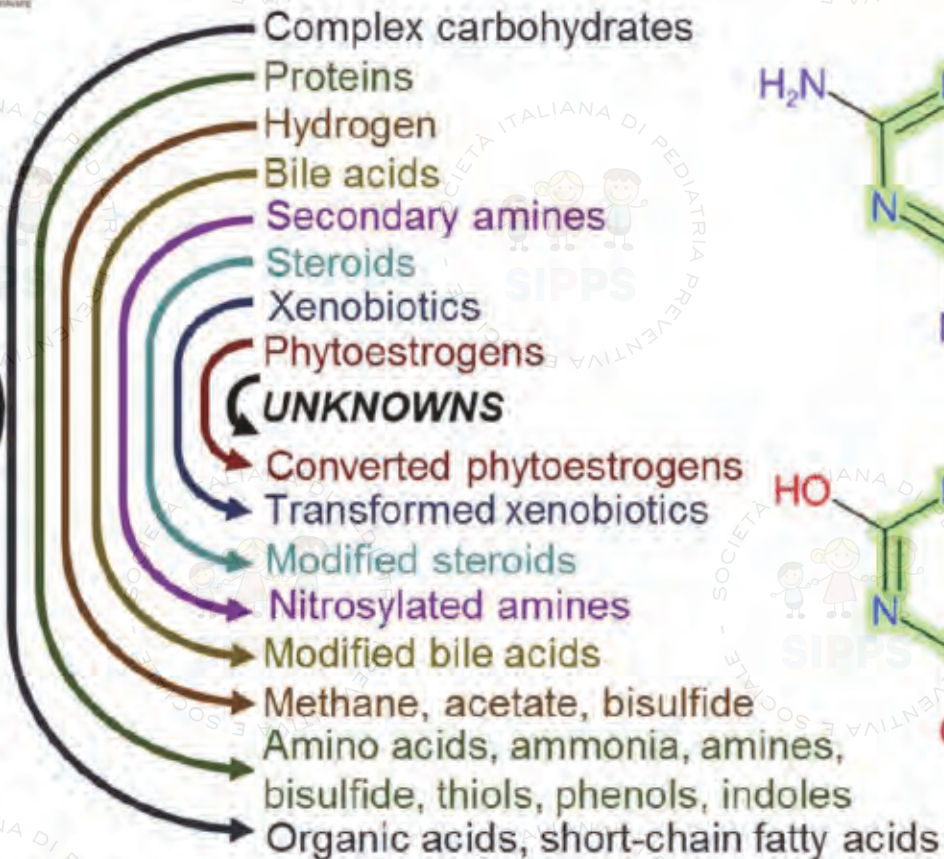
Dark matter in host-microbiome metabolomics: Tackling the unknowns—A review

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Microbiome-driven biotransformations in the gut.  
 The microbiome-mediated transformation of the xenobiotic  
**melamine into cyanuric acid** is shown as an example



# Growth in rats

Robert McCance (1962)

