

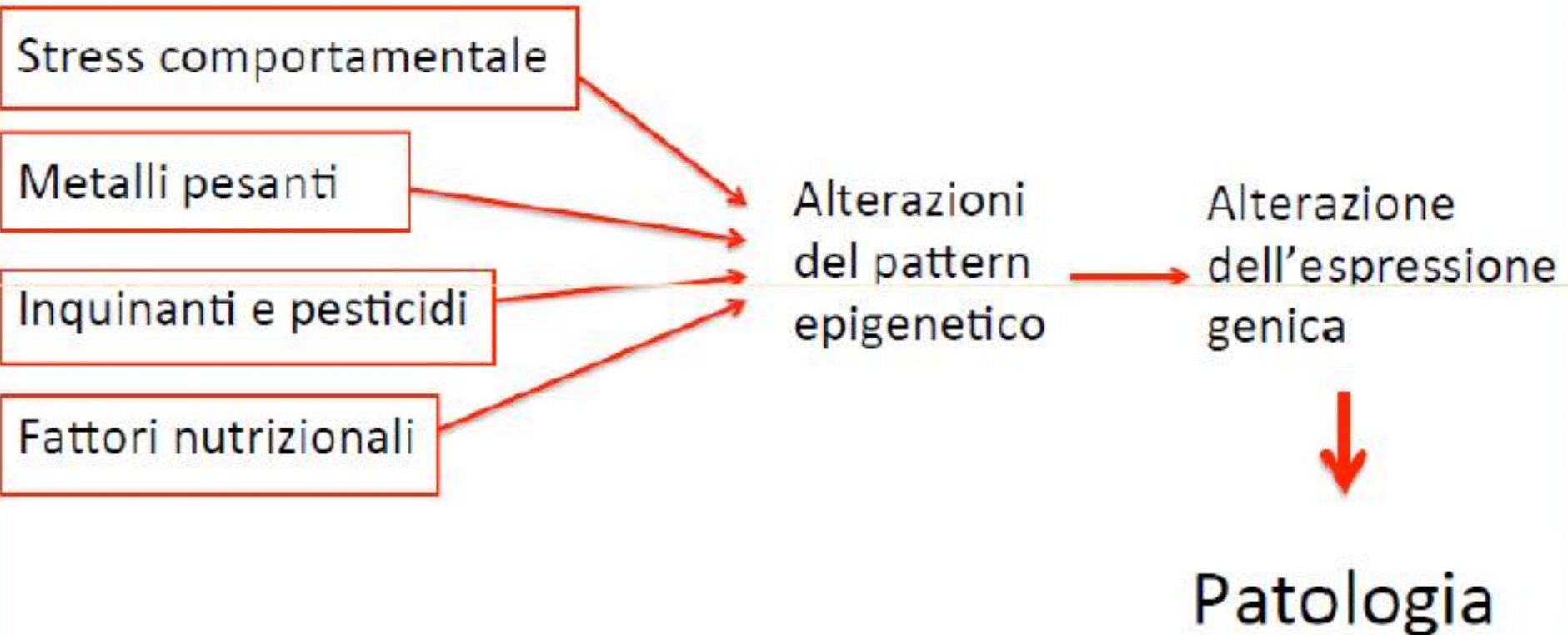


1

Adverse caregiving environment

La rivoluzione epidemiologica del xx secolo

l'Ipotesi di Barker



The long-term impact of adverse caregiving environments on epigenetic modifications and telomeres

Early childhood is a sensitive period in which infant-caregiver experiences have profound effects on brain development and behavior.

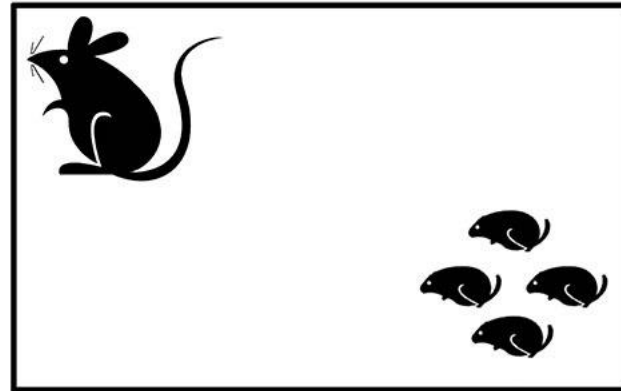
Bambini che vivono condizioni di avversità e stress nel contesto del «caregiving» hanno un rischio aumentato di sviluppare patologie psichiatriche.

Environmentally-driven epigenetic modifications may be an important mediator between adverse caregiving environments and psychopathology.

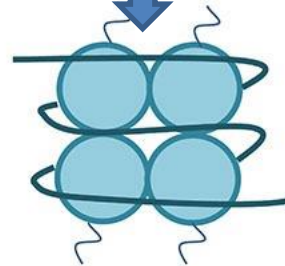
Blaze J, Asok A, Roth TL .
Front Behav Neurosci. 2015

CRH: corticotropin releasing hormone
AVP: arginina vasopressin
Pomc: Pro-opiomelanocortina
GR: glucocorticoid receptor
Bdnf: brain derived neurotrophic factor

Adverse Care during Infancy

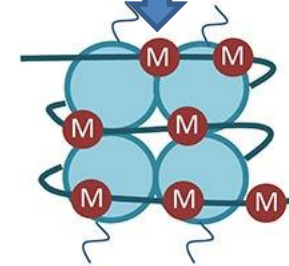


ipometilazione



CRH (hippocampus)
AVP (hypothalamus)
Pomc (pituitary)

ipermetilazione



GR (hippocampus)
Bdnf (prefrontal cortex)

Adulthood

Front Behav Neurosci, 2015. Blaze J.: **The long-term impact of adverse caregiving environments**

Epigenetic modifications such as **DNA methylation**, which normally represses gene transcription, and **microRNA processing**, which interferes with both transcription and translation, show long-term changes throughout the brain and body following adverse caregiving.

Recent evidence has also shown that telomeres (TTAGGG nucleotide repeats that cap the ends of DNA) exhibit **long-term changes in the brain and in the periphery** following exposure to adverse caregiving environments

Front Behav Neurosci, 2015: Blaze J.: **The long-term impact of adverse caregiving environments on epigenetic modifications and telomeres.**

Association With Child Abuse and Adult Psychiatric Symptoms

Childhood abuse can alter biological systems and increase risk for adult psychopathology. Epigenetic mechanisms, alterations in DNA structure that regulate the gene expression, are a potential mechanism underlying this risk.

Il «Child abuse» si associa alla metilazione di certi geni, in particolare quelli coinvolti nel sistema della risposta allo stress.

**Child Development,
28 JAN 2016**



2

Fumo in gravidanza



Smoking in mothers alters neurodevelopmental processes in the fetus.

Maternal smoking alters the DNA methylation of genes involved in **placental and fetal development**, leading to neurodevelopmental disorders in the offspring.

Banik et al.: Maternal Factors that Induce Epigenetic Changes Contribute to Neurological Disorders in Offspring. *Genes*, 24/05/2017

MATERNAL SMOKING



Alteration in DNA methylation pattern of fetal gene pools

Funzione placentare

Neurosviluppo

Neurotrasmissione

Sviluppo del sistema immune

Regolatori della trascrizione

Capacità legante il Calcio



- Distacco della placenta, Aborto spontaneo, morte perinatale del feto, parto pretermine
- Disturbi comportamentali: **ADHD, Autismo, Sindrome di Tourette, Tics, disordine ossessivo-compulsivo**

Banik et al.: Maternal Factors that Induce Epigenetic Changes Contribute to Neurological Disorders in Offspring. *Genes*, 24/05/2017



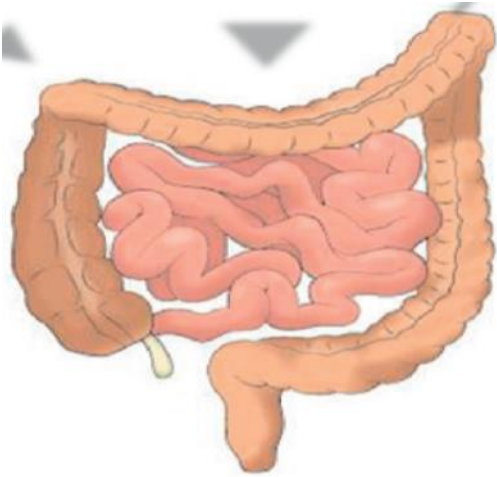
Le ragazze le cui **nonne** materne avevano fumato in gravidanza avevano un rischio aumentato del 67% di sviluppare **tratti autistici**, come scarse capacità di comunicazione sociale e comportamenti ripetitivi.

Lo studio su 14.500 partecipanti ha riscontrato inoltre che, se le **nonne materne** avevano fumato in gravidanza, il rischio di avere nipoti con **disturbo dello spettro autistico (ASD)** aumentava del 53%.

Se una femmina è esposta al fumo di sigaretta quando è in utero, ciò può alterare lo sviluppo degli ovuli.

Smoking can damage the DNA of mitochondria which are only transmitted to the next generation via the mother's egg.

Golding J. Et al.:Scientific Reports; 27/04/2017



6

Gut-microbiota

Beneficial functions of gut microbiota

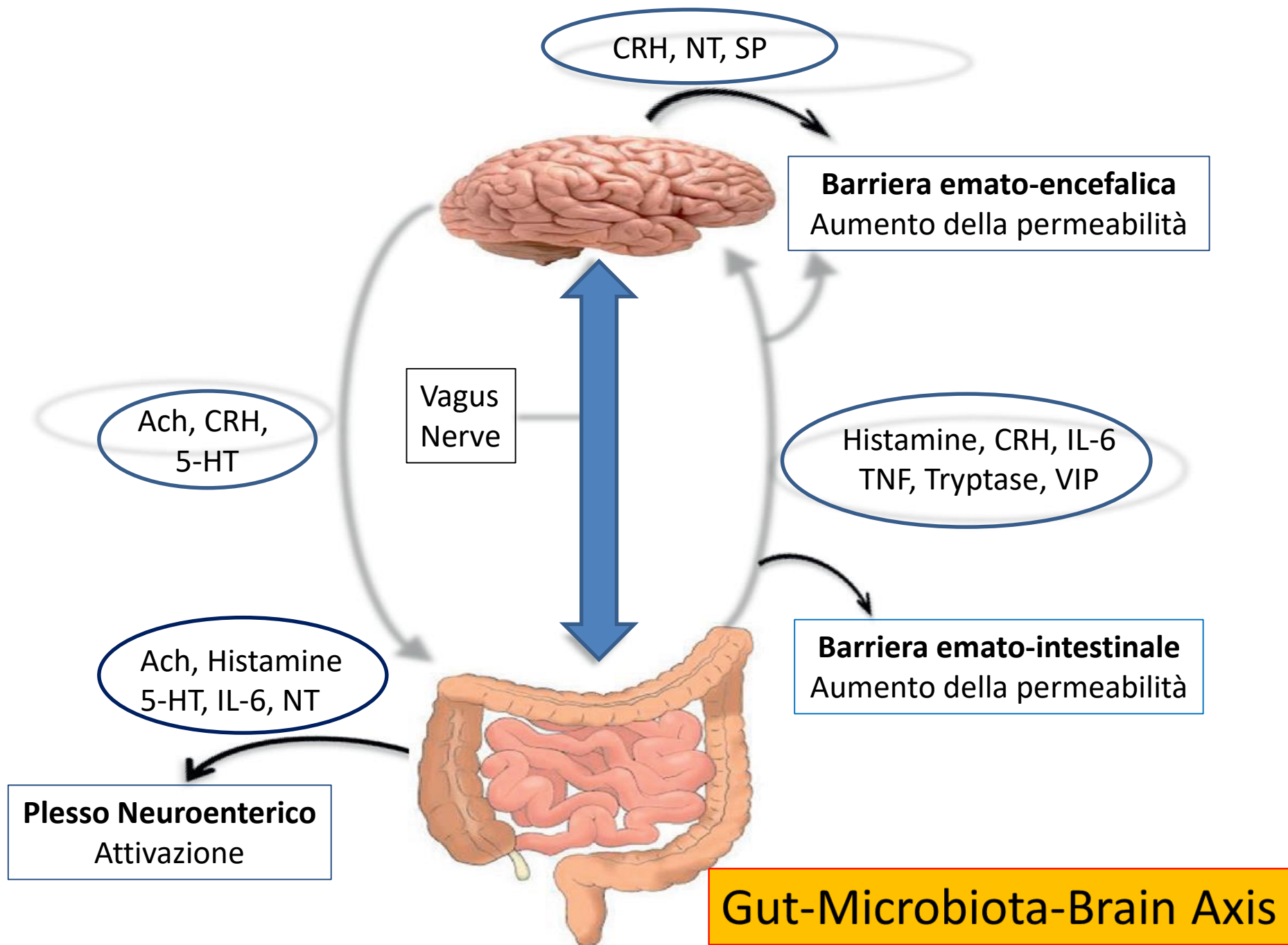
Difesa contro la colonizzazione di patogeni attraverso la competizione per i nutrienti e la produzione di sostanze antimicrobiche

Fortificazione della barriera epiteliale intestinale e induzione della sintesi delle IgA secretorie per limitare la penetrazione dei batteri patogeni nei tessuti

Facilitazione dell'assorbimento dei nutrienti tramite la metabolizzazione dei componenti indigeribili della dieta

Partecipazione nella maturazione e funzionalità del sistema immune fornendo diversi segnali per la «modulazione» dello stato immunitario dell'ospite

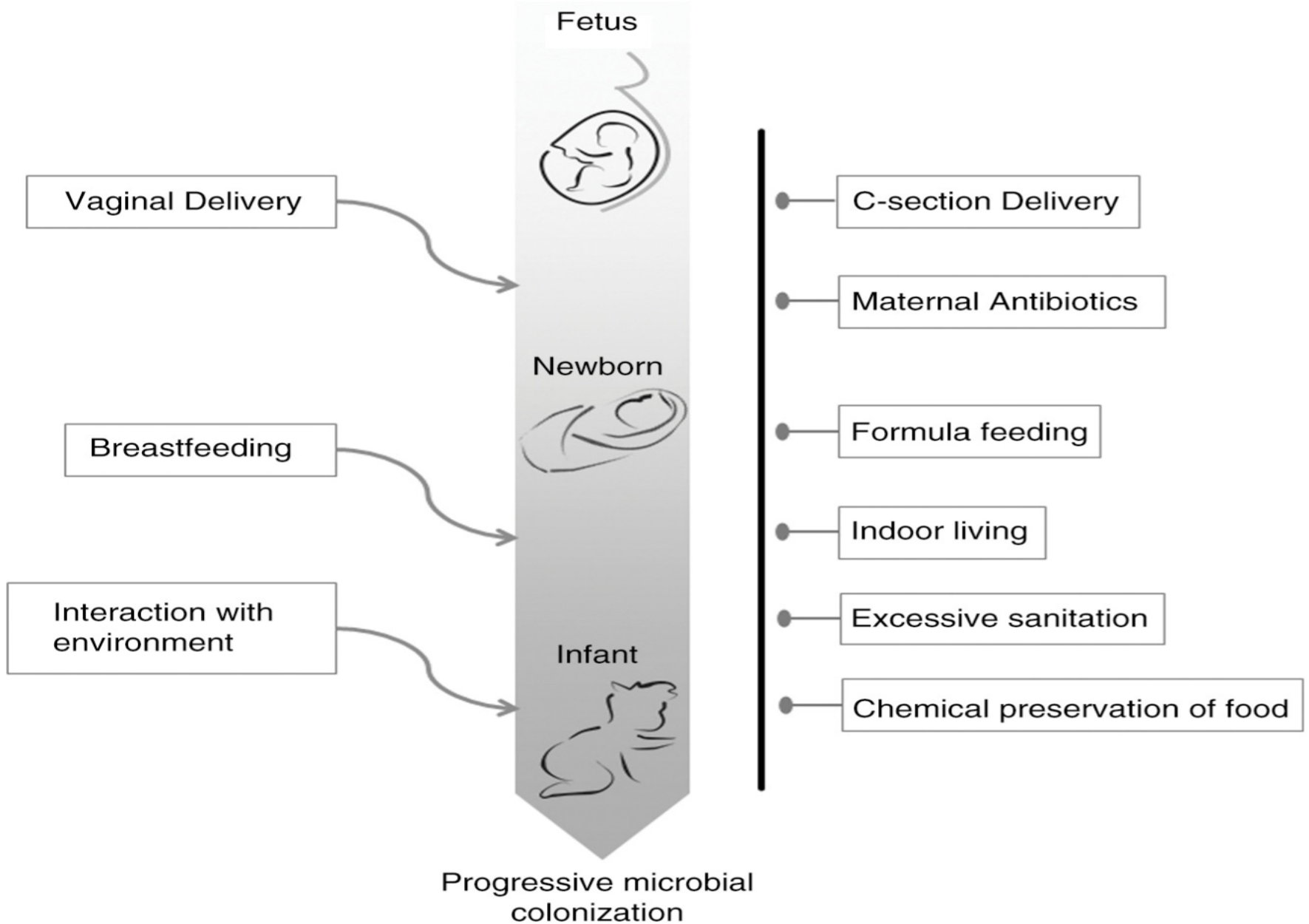
A.I. Petraetal: Clinical therapeutics,
May 2015



Gut-Microbiota-Brain Axis

Antibiotici, agenti infettivi e ambientali, , citokine e metaboliti essenziali, neurotrasmettitori/neuromodulatori intestinali, fibre sensoriali vagali tutti inviano informazioni al SNC sullo stato intestinale. Al contrario, l'asse ipotalamo-ipofisi-surrene, le aree del SNC regolatrici della sazietà e i neuropeptidi rilasciati dalle fibre dei nervi sensoriali influenzano la composizione del microbiota intestinale direttamente o attraverso la disponibilità dei nutrienti.

Queste interazioni sembrano influenzare la patogenesi di un elevato numero di disordini nei quali è implicata l'infiammazione, quali disturbi dell'umore, disordini dello spettro autistico, ADHD, sclerosi multipla e obesità.



Pictorial representation of the routes for, and blockages of, microbial colonization of Westernized humans during early life.



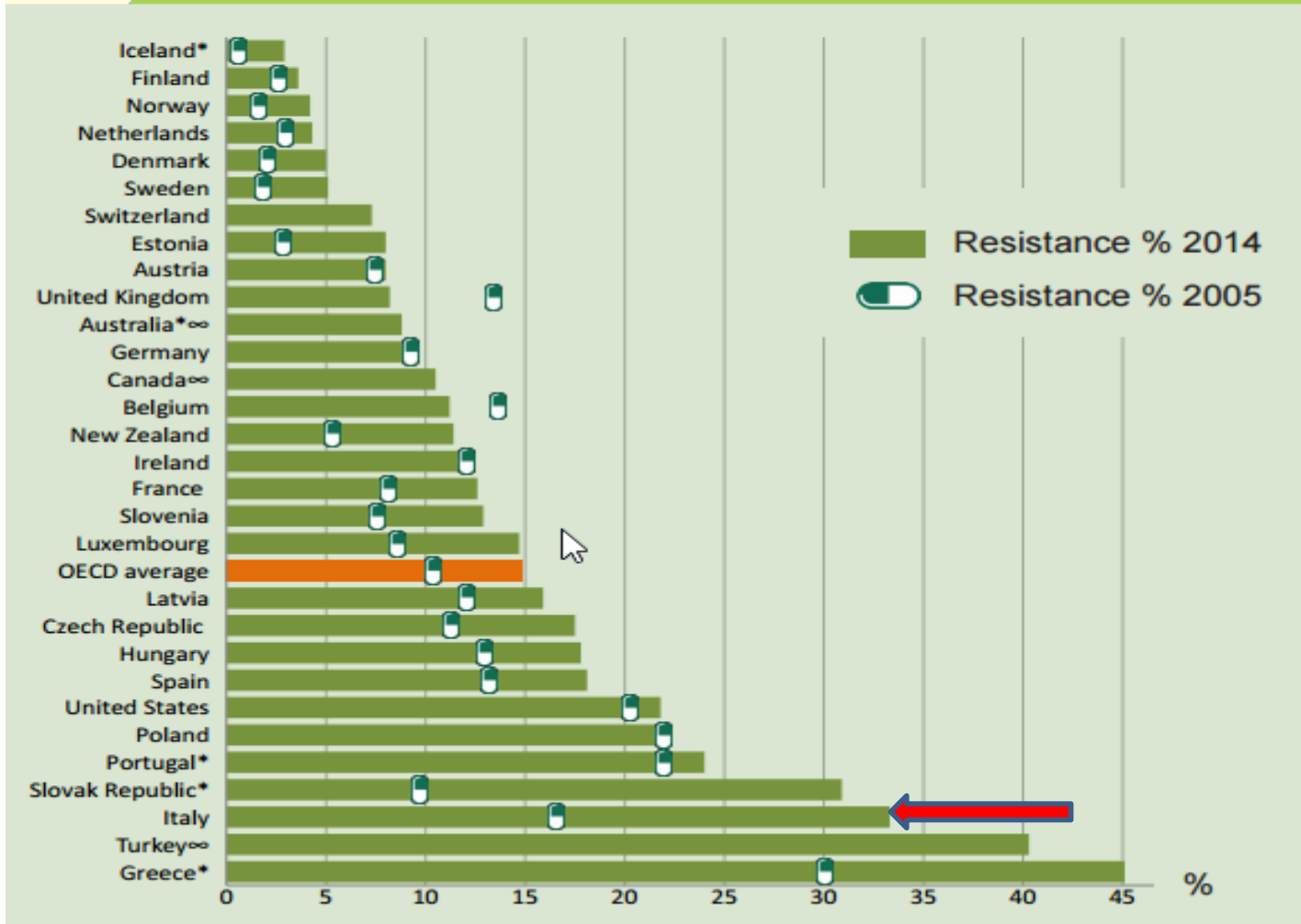
Gli ecosistemi in cui è ridotta la **ridondanza funzionale** sono più predisposti a collassare in presenza di perturbazioni indotte da stress.

Insufficient colonization of an infant (e.g. due to Caesarean section) and/or inadequate nursing with breastmilk; exposure to antibiotics, both as short-term therapy as well as long-term pervasive exposure through the food chain; infection with pathogenic microbes; and consumption of a refined, Western-style diet with little fiber (which is an important food source for colonic bacteria)

The human gut microbiota with reference to autism spectrum disorder. Michael C. Toh: Microbial Ecology, 2015

Trends across OECD countries

Antibiotic resistance is growing

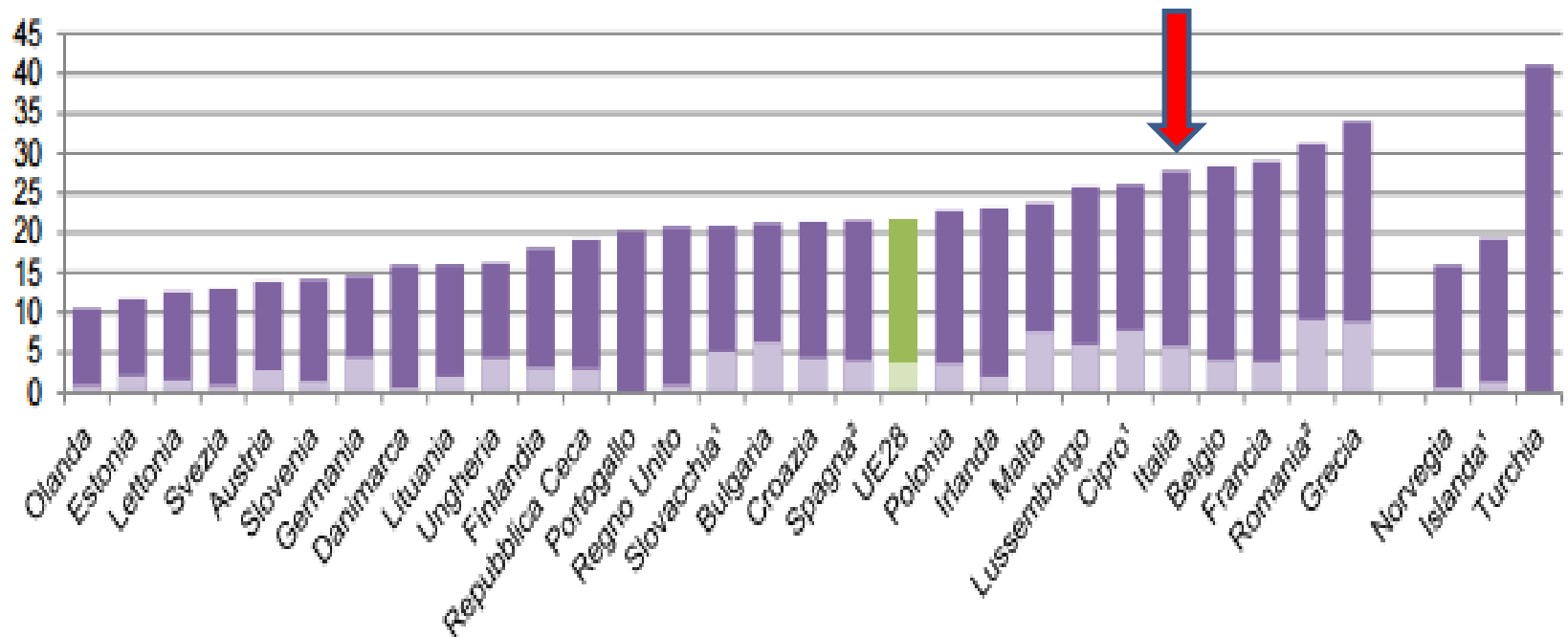


Volume totale di antibiotici prescritti, 2014

DDDs per 1000 per diem (Dose giornaliera definita)

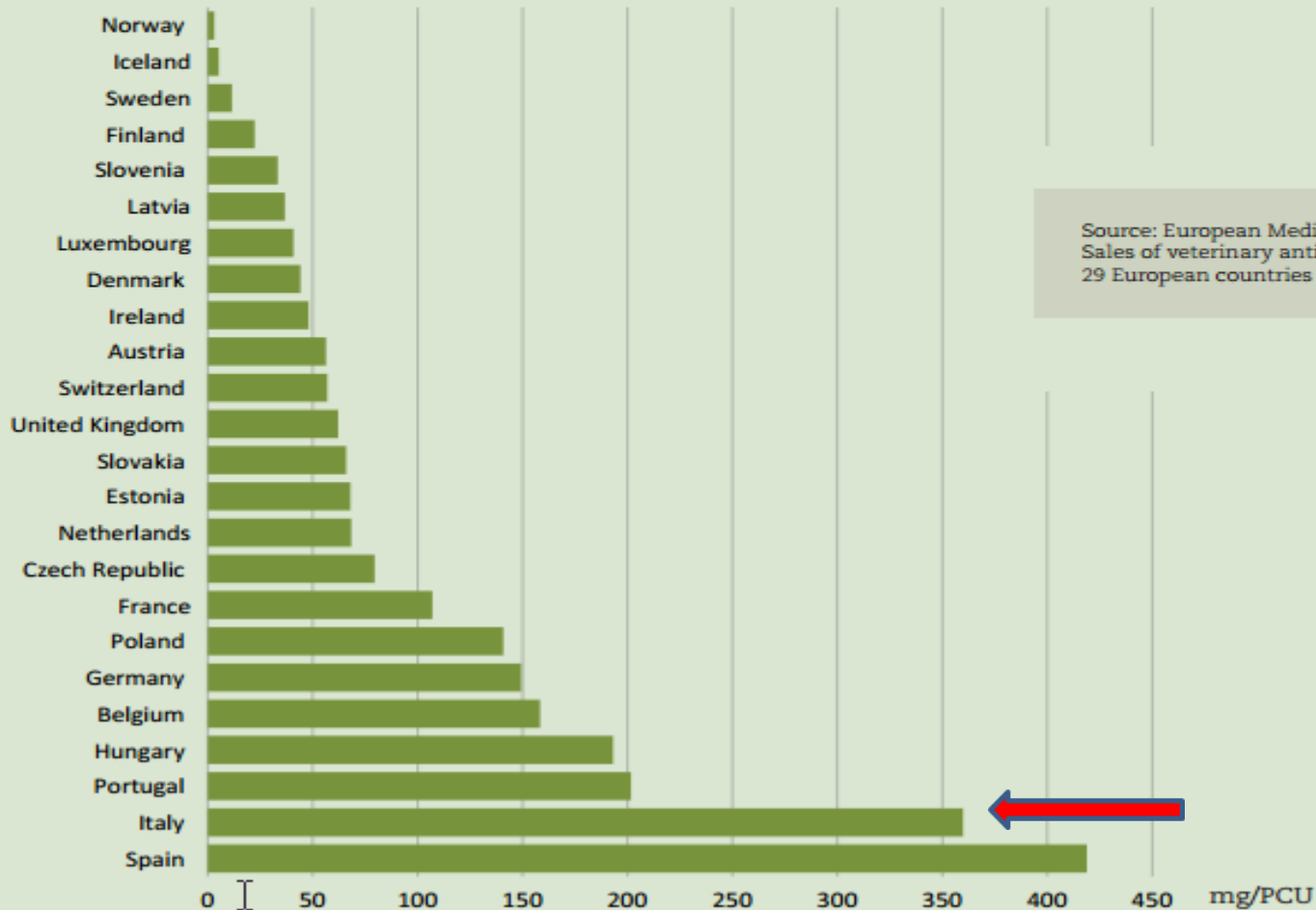
■ Totale

■ Seconda linea



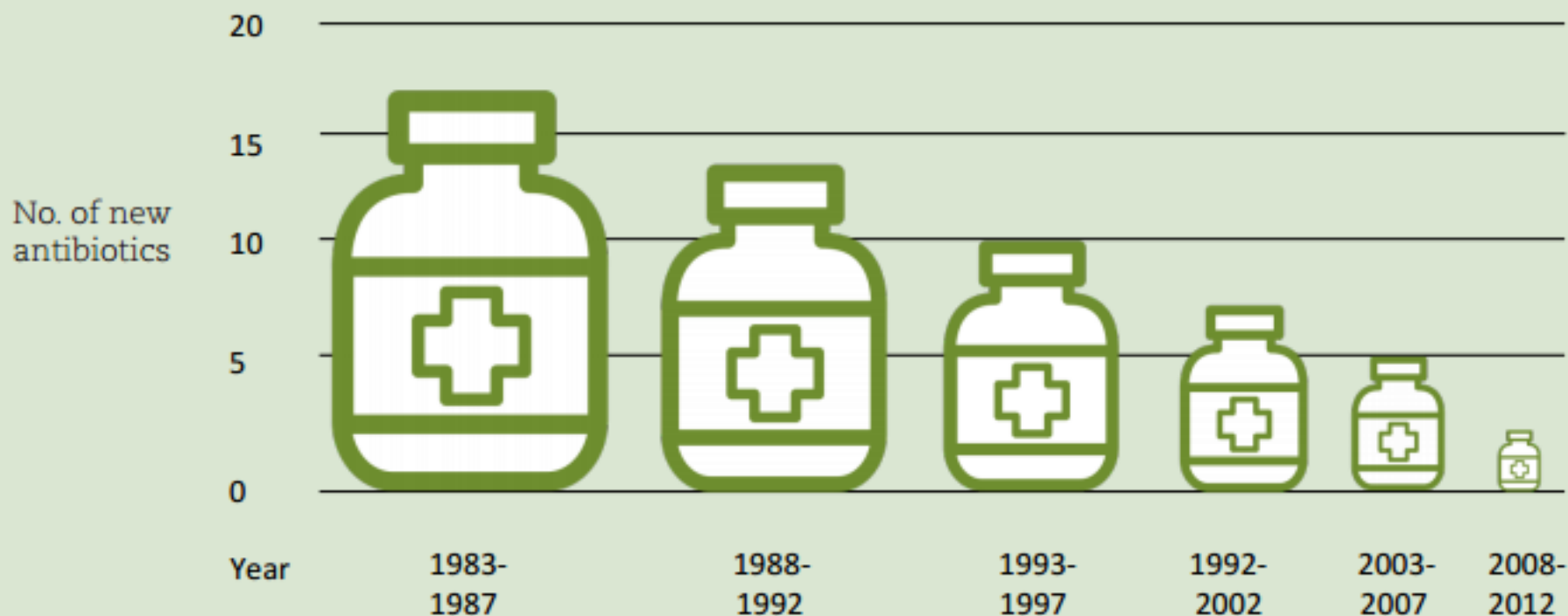
Consumption of antibiotics in agriculture accounts for the majority of total antibiotic use

Sales of antimicrobial agents marketed mainly for food-producing animals in mg/population correction unit (PCU), 2014



Source: European Medicines Agency (2016).
Sales of veterinary antimicrobial agents in
29 European countries in 2014.

Number of new antimicrobials approved by the United States Food and Drug Administration since 1983



Source: OECD (2015). Antimicrobial resistance in G7 countries and beyond: economic issues, policies and options for action.



7

Vitamina D

We found no association between predicted or measured maternal vitamin D status and offspring forearm fractures. But surprisingly we found that the offspring of women who reported intake of dietary vitamin D supplements of more than 10 µg/day in mid-pregnancy, had a 31% significantly increased risk of fractures compared to offspring of women who reported no intake.

Hypothesis

Il feto è in grado di diminuire l'attività di conversione (downregulation) dalla forma inattiva alla forma attiva della vitamina D se il tasso materno di vitamina in circolo è elevato. Nel concetto del "FETAL PROGRAMMING" questa downregulation può produrre conseguenze sulla salute umana che durano tutta la vita.



10

Età paterna,
stato socioeconomico

Le cellule germinative primordiali, l'embrione e il feto sono altamente suscettibili alla disregolazione epigenetica indotta da sostanze chimiche ambientali.

 L'esposizione prenatale alle diverse sostanze chimiche ambientali altera l'epigenoma fetale, con potenziali conseguenze sullo sviluppo di disordini e malattie che si possono manifestare nell'**infanzia**, nel **corso della vita** o anche **transgenerazionalmente**.

F. Perera, J. Herbstman *Prenatal environmental exposures, epigenetics, and disease.*

Reproductive Toxicology, 2011

Frans EM. ***Advanced paternal and grandpaternal age and schizophrenia: a three-generation perspective***. Schizophr Res. 2011;

Harlap Susan, et al. ***Advancing paternal age and autism***. Arch Gen Psychiatry. 2006

Reichenberg A. ***Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies***. Mol Psychiatry. 2011

Yeargin-Allsopp M, et al. ***Parental age and autism spectrum disorders***. Ann Epidemiol. 2012

Sandin S. ***Autism risk across generations: A population-based study of advancing grandpaternal and paternal age***. JAMA Psychiatry. 2013

Even before a child is conceived, the parents' exposure to environmental stressors can alter the way genes are expressed and ultimately harm the child's health when those genes are **passed down to the next generation**

Parents' preconception exposure to environmental stressors can disrupt early development. The Endocrine Society, Aug 2015

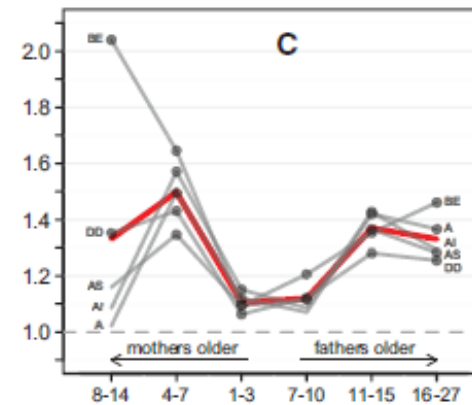
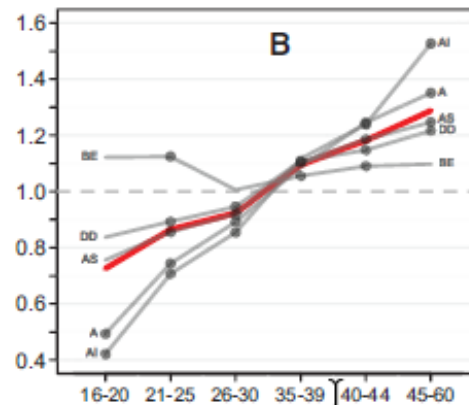
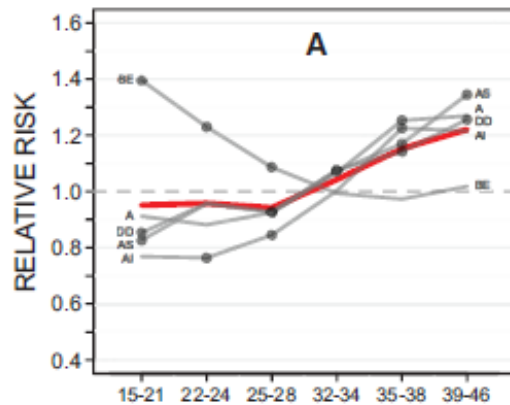
Individuals whose fathers, grandfathers and great-grandfathers fathered their lineage on average under age 30 were **~13% more likely to survive** to adulthood than those whose ancestors fathered their lineage at over 40 years. In addition, females had a lower **probability of marriage** if their male ancestors were older.

These findings are consistent with an increase of the number of accumulated *de novo mutations* with male age, suggesting that **deleterious mutations acquired from recent ancestors** may be a substantial burden to fitness in humans.

If the observed effect, or fraction thereof, is mediated by accumulation of *de novo* mutations, it also supports the view that **the ongoing increase in the mean age of reproduction in modern societies may lead to a higher prevalence of genetic disorders.**

[Bazykin GA](#)³ *Fitness Consequences of Advanced Ancestral Age over Three Generations in Humans.* [PLoS One](#). 2015

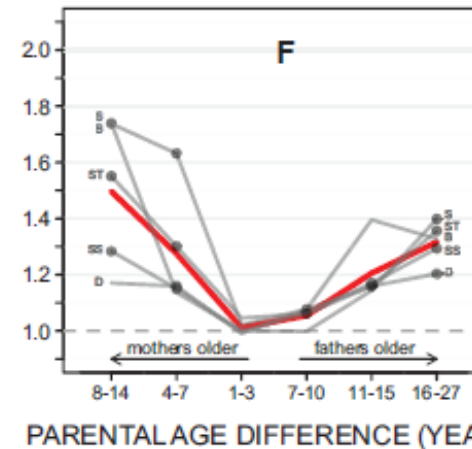
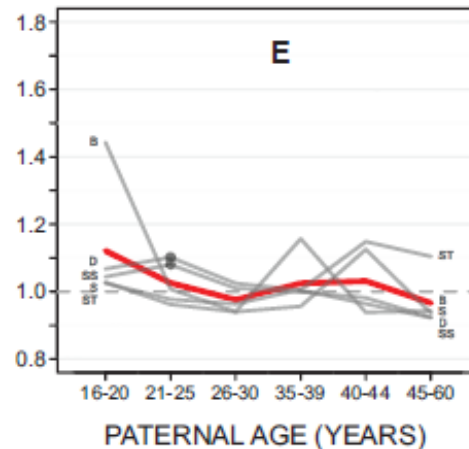
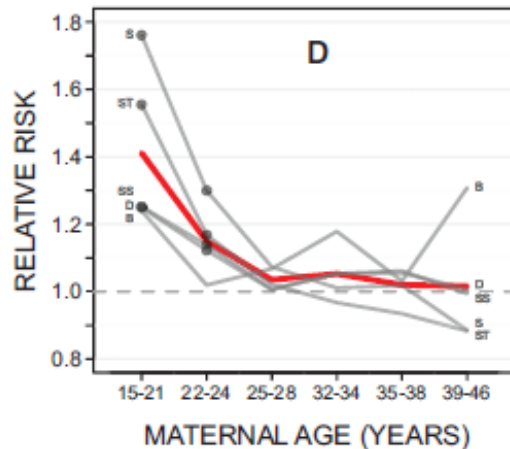
AUTISTIC



AUTISTIC
AI autism, infantile
A autism, infantile and atypical
AS autism-spectrum
DD disorders of psychological development
BE behavioral, emotional disorders

SCHIZOPHRENIC
B bipolar disorder
D depression, major
S schizophrenia
SS schizophrenia-spectrum
ST schizophrenia, schizotypal, delusional

SCHIZOPHRENIC



Sean G. Byars, Jacobus J. Boomsma: **Opposite differential risks for autism and schizophrenia based on maternal age, paternal age, and parental age differences.**
 Evolution, Medicine, and Public Health, 2016

Parenting, Socioeconomic Status Risk, and Later Young Adult Health: Exploration of Effects via DNA Methylation

A sample of 398 African American youth, residing in rural counties with **high poverty and unemployment**, were followed from ages 11 to 19. Protective parenting was associated with better health, whereas elevated socioeconomic status (SES) risk was associated with poorer health at age 19. Three categories of genes were identified whose methylation was associated with parenting, SES risk, and young adult health.

La Metilazione è un mediatore significativo sull'impatto sulla salute dei giovani adulti della genitorialità e dello stato socioeconomico a rischio.



9

Cellule cerebrali

Development of the Cell Population in the Brain White Matter of Young Children

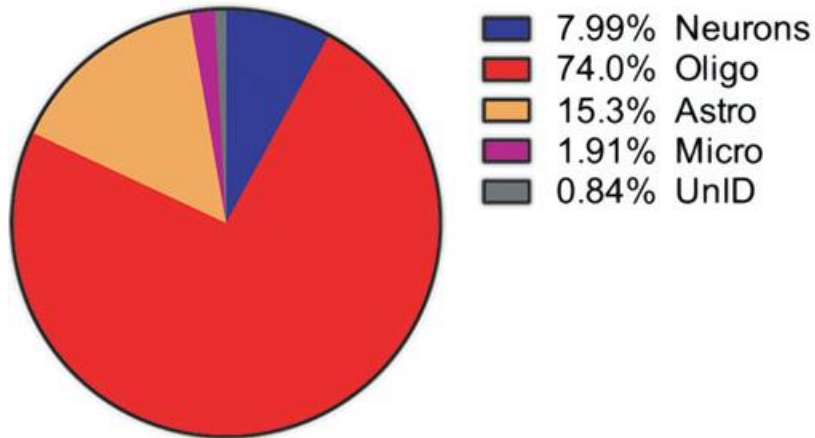
Mentre la **sostanza grigia** è essenzialmente associata ai processi cognitivi e sensorimotori, la **sostanza bianca** modula la distribuzione dei potenziali d'azione, coordina la comunicazione fra le diverse aree del cervello e agisce come un interruttore per i segnali input/output.

L'alterata microstruttura della sostanza bianca nell'autismo e nei disordini bipolari può originare da un sovvertimento della organizzazione assonale e della sostanza bianca durante lo sviluppo.

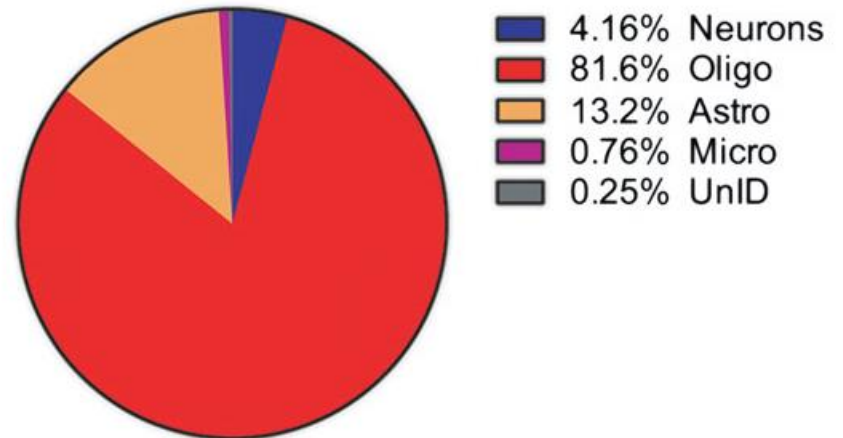
Development of the Cell Population in the Brain White Matter of Young Children

Linear increases with age in the numbers of oligodendrocytes (7–28 billion) and astrocytes (1.5–6.7 billion) during the first 3 years of life, thus attaining two-thirds of the corresponding numbers in adults. The numbers of neurons (0.7 billion) and microglia (0.2 billion) in the white matter did not increase during the first 3 years of life, but showed large biological variation.

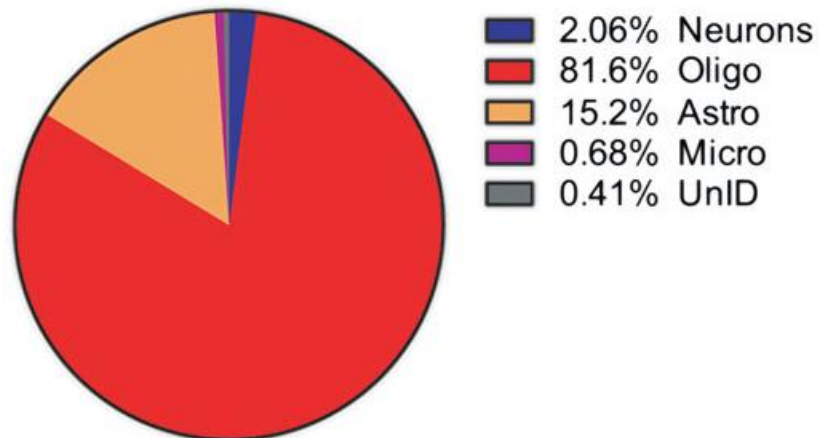
Newborn



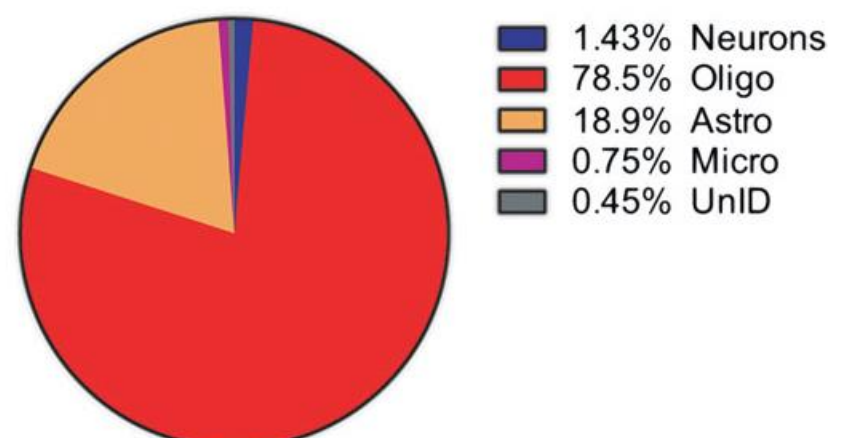
8 months



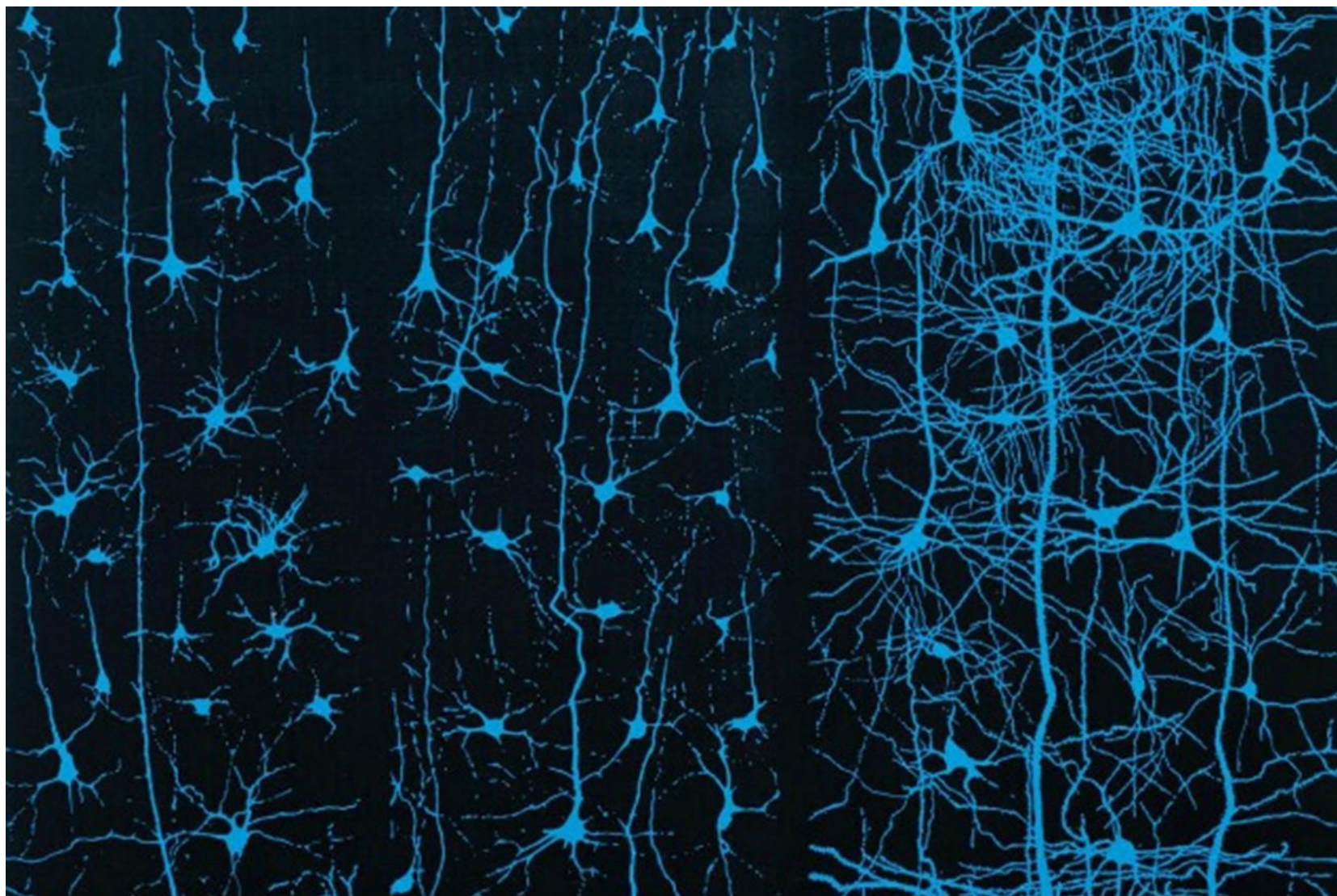
19 months



33 months



Cell distribution in 4 infants: newborn, and aged 8, 19, and 33 months. Oligo, oligodendrocytes; astro, astrocytes; micro, microglia; UnID, unidentified cells.



neonato

3 mesi

2 anni



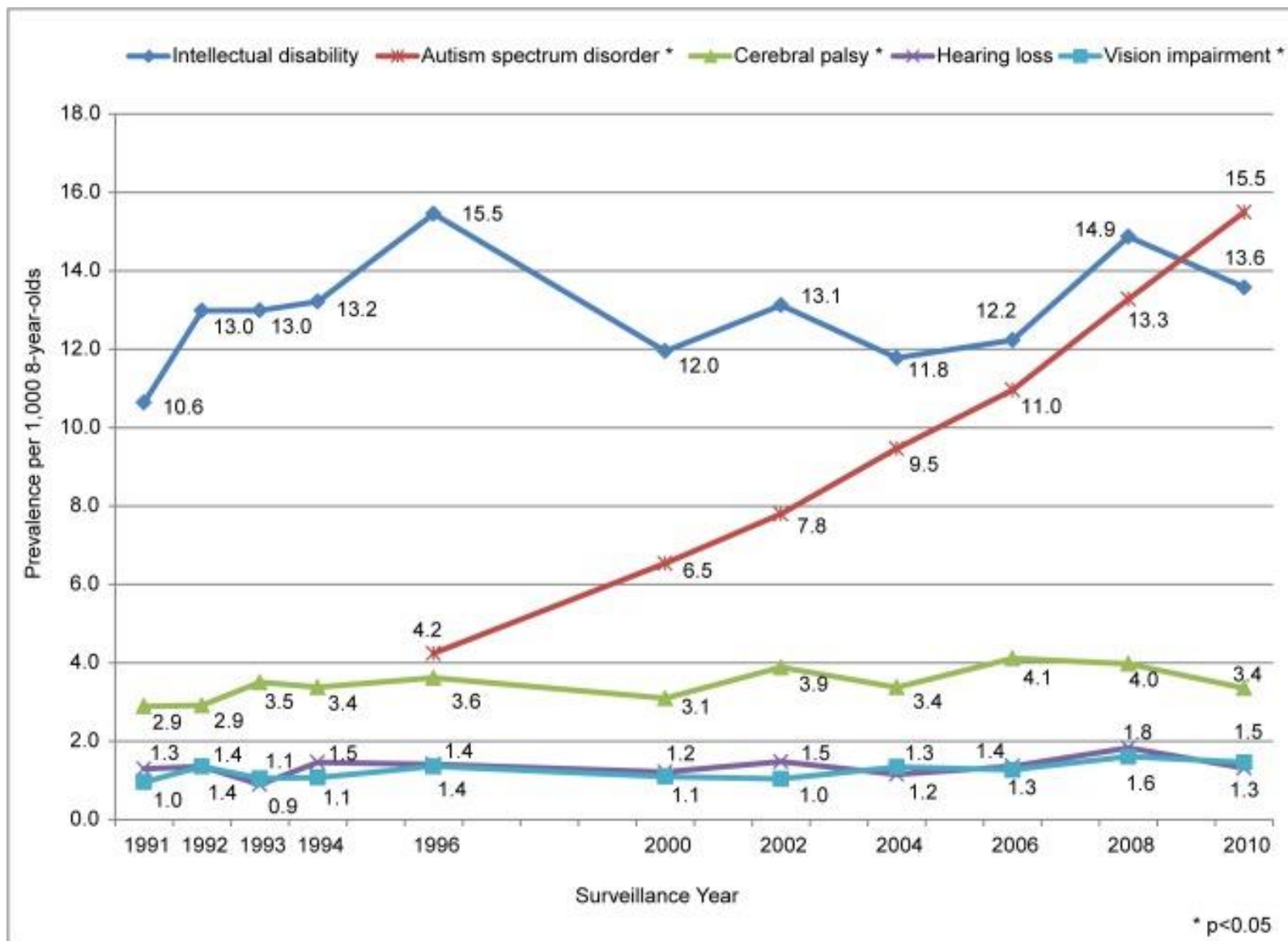
11

autismo

The average annual **increase in ASD** prevalence was 9.3% per year from 1996-2010, with a **269% increase** from 4.2 per 1,000 in 1996 to 15.5 per 1,000 in 2010. From 2000-2010, the prevalence of **ID** without ASD was **stable**.

ASD prevalence increases were found among both males and females, and among nearly all racial/ethnic subgroups and levels of intellectual ability.

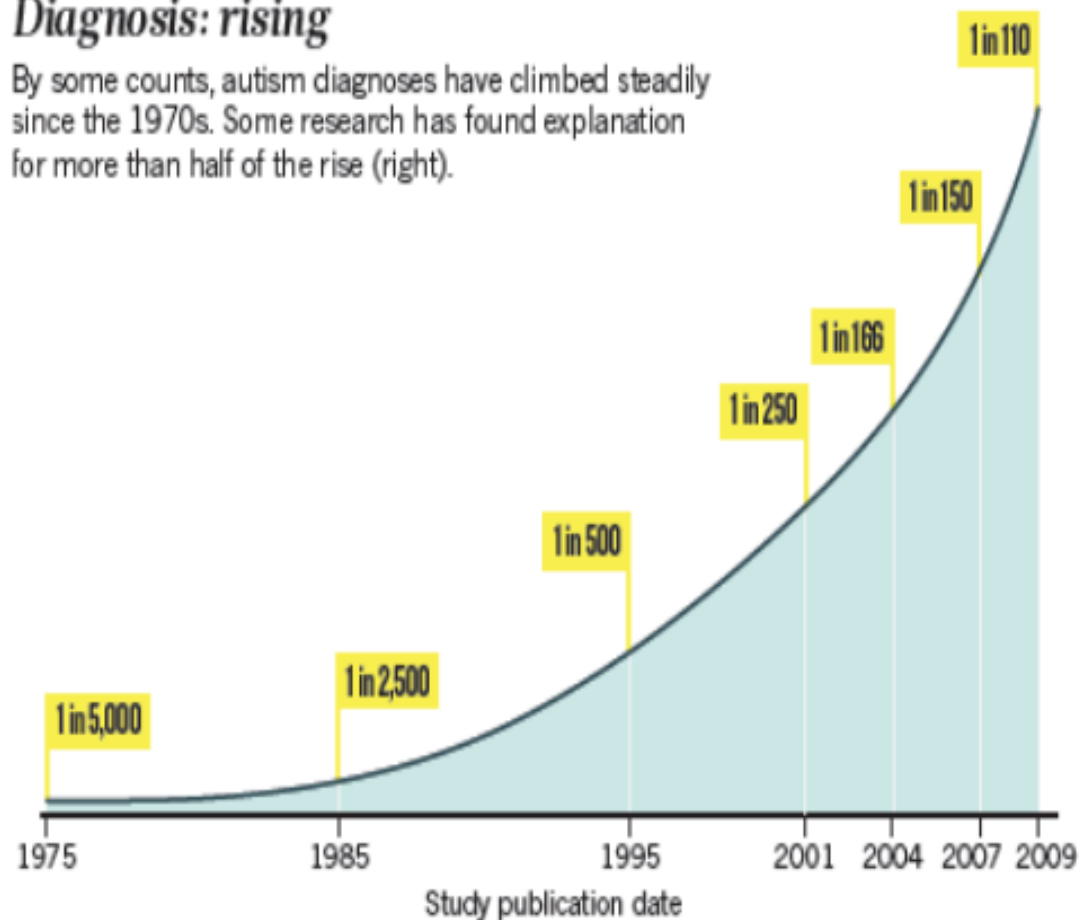
Yeargin-Allsopp M *Trends in the prevalence of autism spectrum disorder, cerebral palsy, hearing loss, intellectual disability, and vision impairment, metropolitan atlanta, 1991-2010* PLoS One. 2015



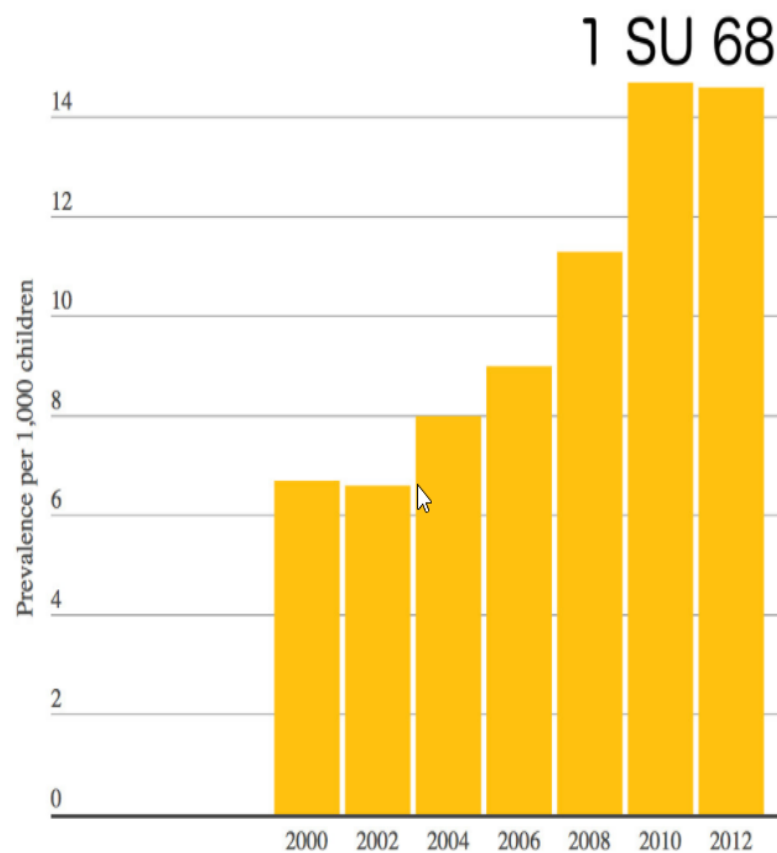
**Prevalence of Five Developmental Disabilities, Metropolitan Atlanta
Developmental Disabilities Surveillance Program, 1991–2010.**

Diagnosis: rising

By some counts, autism diagnoses have climbed steadily since the 1970s. Some research has found explanation for more than half of the rise (right).



PREVALENZA DELL'AUTISMO

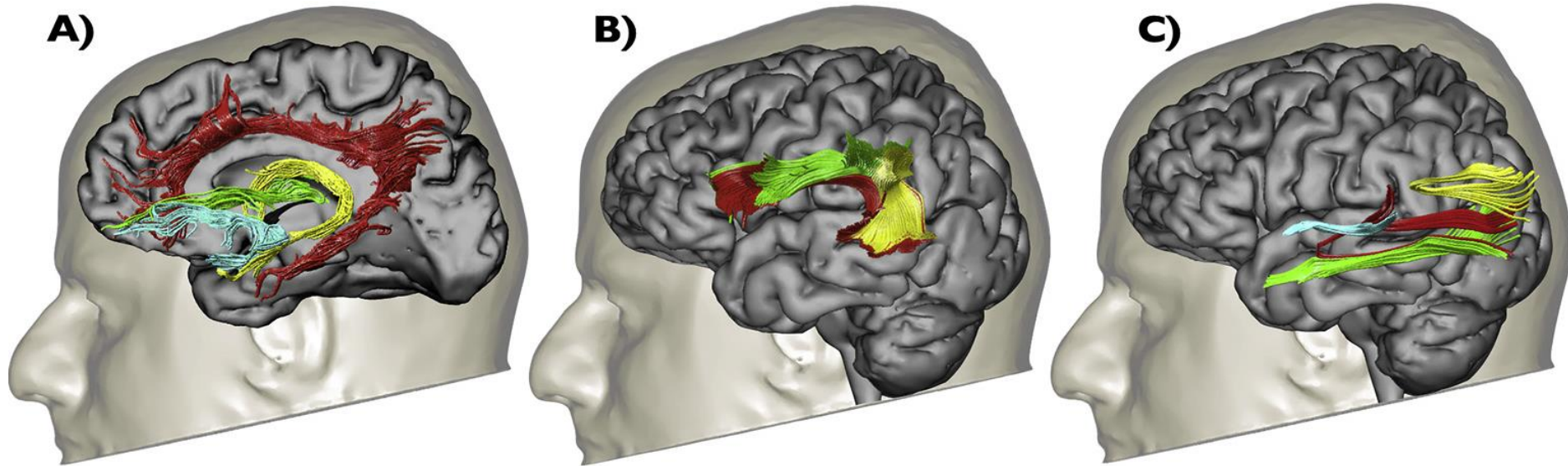


*Centro Statunitense per il Controllo delle
Malattie e la Prevenzione (CDC), 01/04/2016*

Dati diretti **post mortem** rilevano una alterazione della mielina della sostanza bianca e della densità assonale nelle regioni corrispondenti alla **sostanza bianca fronto- limbica** (fascicolo uncinato, fascio cingolato) nell' ASD.

I risultati della MRI strutturale indicano uno **sviluppo cerebrale atipico nei primi anni di vita**, con prevalenti e persistenti effetti sulla **struttura della sostanza bianca frontale, particolarmente delle porzioni frontali dei fascicoli arcuato e uncinato.**

S. H. Ameis, M. Catani: **Altered white matter connectivity as a neural substrate for social impairment in Autism Spectrum Disorder.** Cortex 2015



White matter tracts of the socio-emotional processing system.

- A. **Limbic system**: giro cingolato, fascicolo uncinato, fornice, tratto mammillo-talamico, proiezione talamica anteriore.
- B. **Sistema dei neuroni specchio**: segmenti del fascicolo arcuato: lungo, anteriore, posteriore.
- C. **Sistema di riconoscimento faciale**: fascicolo longitudinale inferiore collegato all'area visuale: splenium (corpo calloso), radiazioni ottiche (corpo genicolato laterale), tratto ottico.

S. H. Ameis, M. Catani: **Altered white matter connectivity as a neural substrate for social impairment in Autism Spectrum Disorder.** Cortex 2015

Risk of Psychiatric and Neurodevelopmental Disorders Among Siblings of Probands With ASD

Among the 3578 cases with **ASD**, Autism spectrum disorders were also associated with schizophrenia spectrum disorders, affective disorders, anxiety disorders, and other neurotic and personality disorders among siblings.

Questa è un'ulteriore evidenza che diversi disordini psichiatrici e neuroevolutivi hanno **comuni fattori di rischio**.

For children with autism and the presence of copy number variations, **exposure to diagnostic ultrasound in the first trimester of pregnancy is linked to increased autism severity.**

Many environmental stressors may interact with genetic vulnerabilities. If we can better identify the neural development periods most vulnerable to environmental insults, it may be possible to quickly reduce the severity of ASD in future children.

Sara Jane Webb et al: ***Severity of ASD symptoms and their correlation with the presence of copy number variations and exposure to first trimester ultrasound.*** Autism Research, 2016;

Extremely low gestational age and very low birthweight for gestational age are risk factors for autism spectrum disorder in a large cohort study of 10-year-old children born at 23-27 weeks' gestation.

Low gestational age



ASD
ID

Severe fetal growth



ASD

cervical-vaginal infection

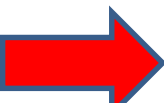


ASD
ID

peripartum maternal fever



ASD

A thick red arrow pointing from the left towards the summary text.

Immaturity, epigenetic phenomena, and inflammation contribute to the occurrence of ASD.

Joseph R.M. et al.: American Journal of Obstetrics & Gynecology MARCH 2017

Pediatricians play an important role in the early recognition of ASDs, because they are usually the first point of contact for children with ASDs.

In ASD patients, the appropriate behavioral therapies and rehabilitation treatments significantly affect the prognosis. Therefore, this makes early diagnosis and treatment very important. In conclusion, pediatricians need to be able to recognize the signs and symptoms of ASDs and be attentive to them in order to make an early diagnosis and provide treatment.

Recent update of autism spectrum disorders.
Korean J Pediatr. 2015

Sintomi di autismo nei bambini < 1 anno

COMUNICAZIONE

1 Balbettio in ritardo. In genere, verso i sei mesi un neonato produce una vasta gamma di suoni e catene di sillabe. Si chiama stadio della lallazione o balbettio (babbling). Nei bebè autistici, questa fase manca oppure si presenta in ritardo.

2 Non indica con il dito. Entro l'anno, il bambino non indica quasi mai con il dito ciò che vuole o su cui desidera attirare attenzione.

3 Non si volta al suo nome. Spesso i genitori temono che il bebè sia sordo, perché rimane indifferente al richiamo e, in generale, alla voce degli altri.

INTERAZIONE SOCIALE E AFFETTIVITÀ

1 Non mantiene il contatto visivo. Il bimbo autistico manifesta una sorta di indifferenza verso l'altro, mamma compresa. Ha uno sguardo "assente". Quando piange, è difficile da calmare o, addirittura, è inconsolabile.

2 Non risponde al sorriso. Intorno ai 3 mesi, il neonato inizia a sorridere a chi gli sorride. All'inizio è soltanto un riflesso, poi diventa intenzionale. Se c'è qualcosa che non va, questo riflesso è assente o saltuario.

3 Non ti abbraccia. Nei piccoli a rischio autistico manca questo riflesso empatico caratteristico dei bambini. Ed è assente persino il riflesso di aggrappamento. Il bimbo, insomma, assume un atteggiamento statico, simile a quello di una "bambola di pezza".

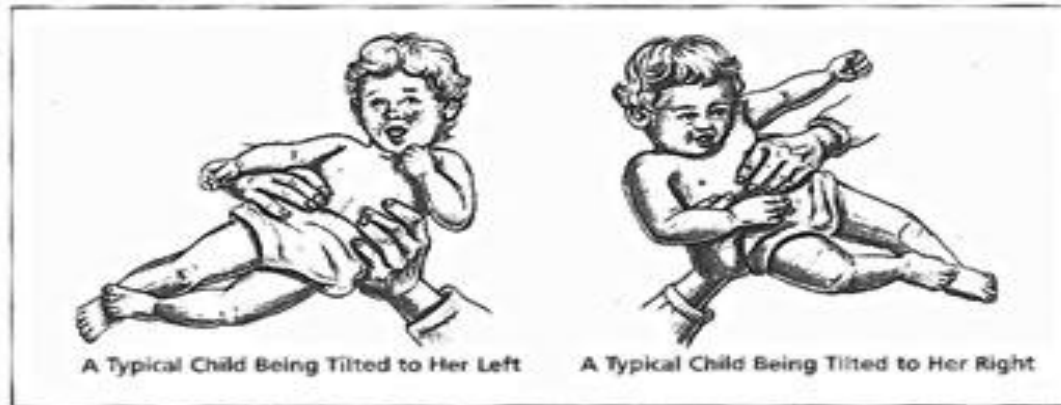
COMPORTEMENTO

1 Ignora i suoi giochi. Il disinteresse coinvolge anche i giocattoli che gli vengono messi a disposizione. Oppure il bambino manifesta un attaccamento insolito per un determinato oggetto.

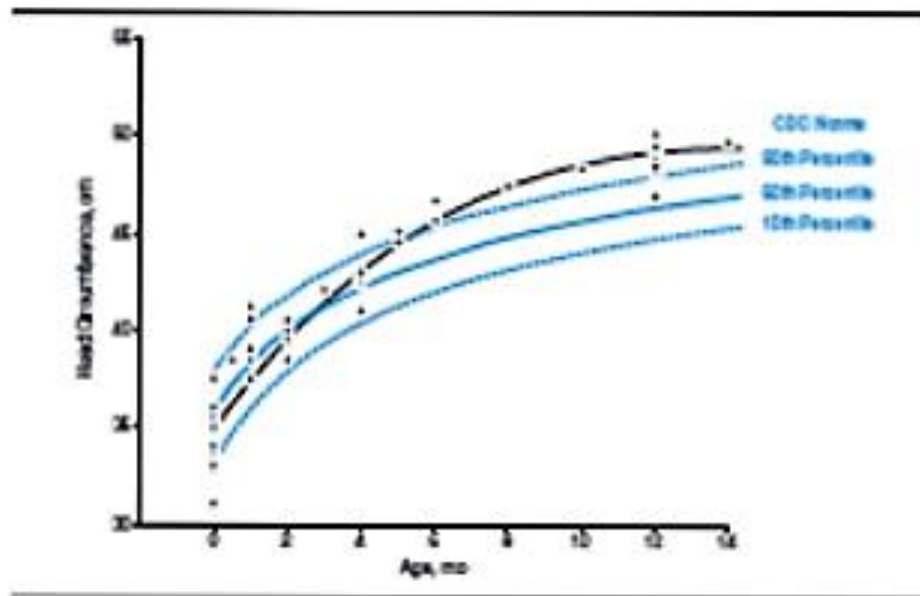
2 Fa sempre la stessa cosa. Agisce in modo stereotipato: l'esempio classico è il dondolio continuo o un interesse esagerato per le mani.

3 Non mantiene l'attenzione. Non è capace di focalizzare il suo interesse su un gioco che si sta facendo o su un oggetto.

An increased **head circumference** and the absence of the **head tilt reflex** is a possible risk factors for autism spectrum disorder, allowing for early detection at 12 months.



Samango-Sprouse C. A. et al.: **Identification of infants at risk for autism spectrum disorder and developmental language delay prior to 12 months.** Autism 2015,



La linea nera indica la crescita media della circonferenza cranica nell'autismo. La media è costruita a partire dai valori, indicati dai puntini, nelle singole età e per ciascun bambino.

Muratori F.: **La diagnosi precoce di autismo : una guida pratica per i pediatri** I. Settembre 2009

In **typical development** progress in motor and gesture repertoire rely on the **inhibition of primitive reflexes**, particularly those involving the hand or mouth.

- Children with autism have often **difficulty in performing skilled movements** and show **poor gesture repertoire**.
- In 12- to 17-month-old infants we evaluated the relationships between **persistence of primitive reflexes**, motor repertoire, and autistic-like traits.

Indipendentemente dall'età, **la persistenza dei riflessi primari altera il repertorio motorio dei bambini e correla con lo sviluppo di tratti di tipo autistico.**

Chimello et al.: **Persistent primary reflexes affect motor acts: Potential implications for autism spectrum disorder.** *Research in Developmental Disabilities*, 2016

BIOMARKERS

Developmental pediatricians, psychologists and other professionals can effectively use the wealth of information provided by **psychometric instruments** to diagnose and evaluate patients with ASD. However, these tests **can rarely diagnose children under two years old** since they are based solely on behavioral assessment.

As it is generally acknowledged that an **earlier diagnosis** can lead to a more favorable outcome in the long run, the identification of **biomarkers** which can be used in conjunction with psychometric measurements would be of significant importance for ASD diagnosis.

These biomarkers may not simply be measurements of certain metabolites but may require nonlinear statistical analysis of the measurements

D.P. Hosmon: Classification and adaptive behavior prediction of children with autism spectrum disorder based upon multivariate data analysis of markers of oxidative stress and DNA methylation. PLOS ONE, 16 Marzo 2017



Questi metaboliti sono **fortemente correlati** con una diagnosi di ASD.

FOCM=folate-dependent one-carbon metabolism

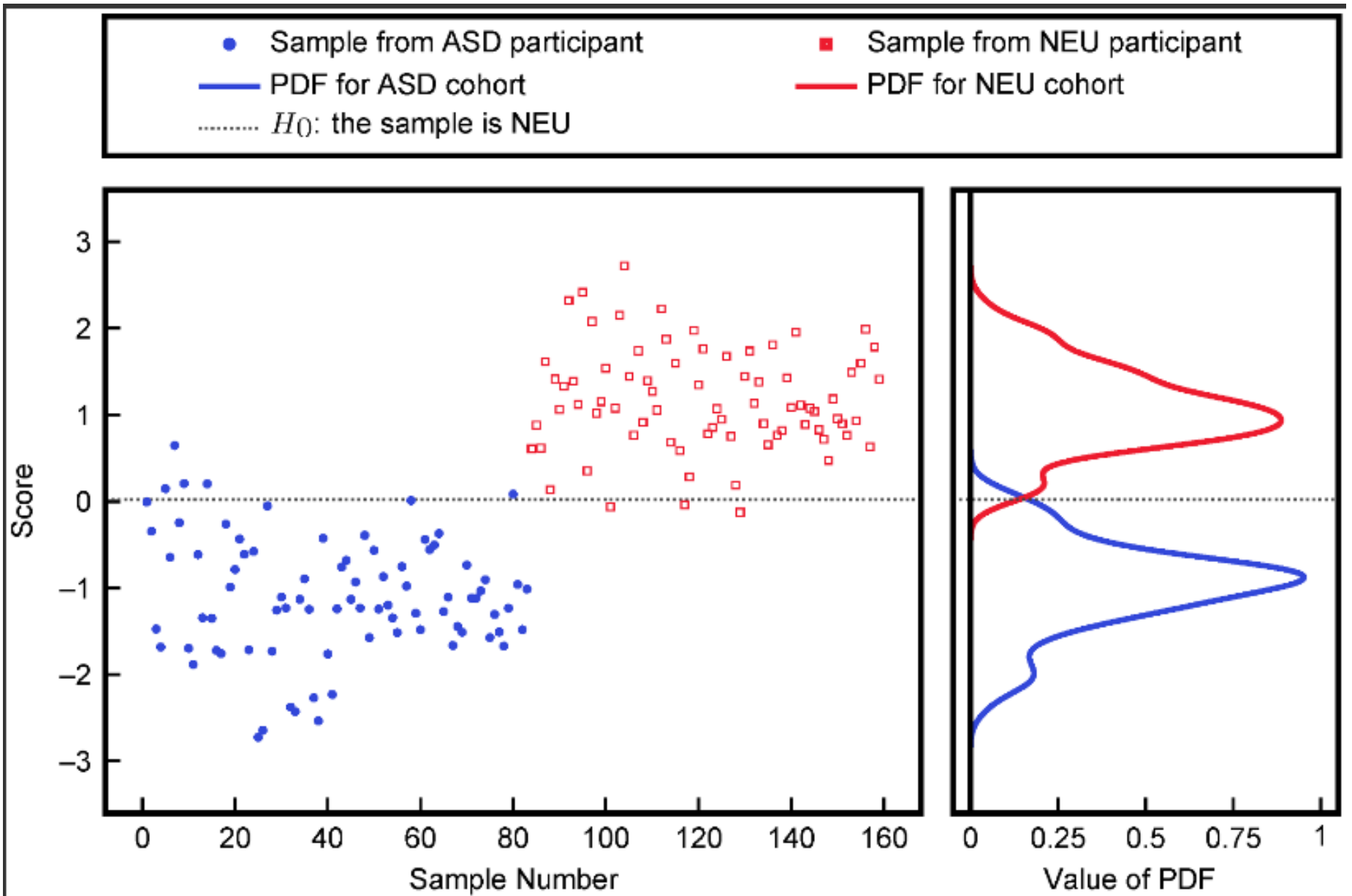
TS= transsulfuration

D.P. Hosmon: Classification and adaptive behavior prediction of children with autism spectrum disorder based upon multivariate data analysis of markers of oxidative stress and DNA methylation. PLOS, 16 Marzo 2017

Methionine	SAM	SAH
SAM/SAH	% DNA methylation	8-OHG
Adenosine	Homocysteine	Cysteine
Glu.-Cys.	Cys.-Gly.	tGSH
fGSH	GSSG	fGSH/GSSG
tGSH/GSSG	Chlorotyrosine	Nitrotyrosine
Tyrosine	Tryptophane	fCystine
fCysteine	fCystine/fCysteine ⁺	% oxidized glutathione

doi:10.1371/journal.pcbi.1005385.t001

FOCM/TS metabolites considered for analysis.



Classification into ASD and NEU cohorts using FDA on all FOCM/TS metabolites



3

Esposizione prenatale e perinatale a
inquinanti ambientali

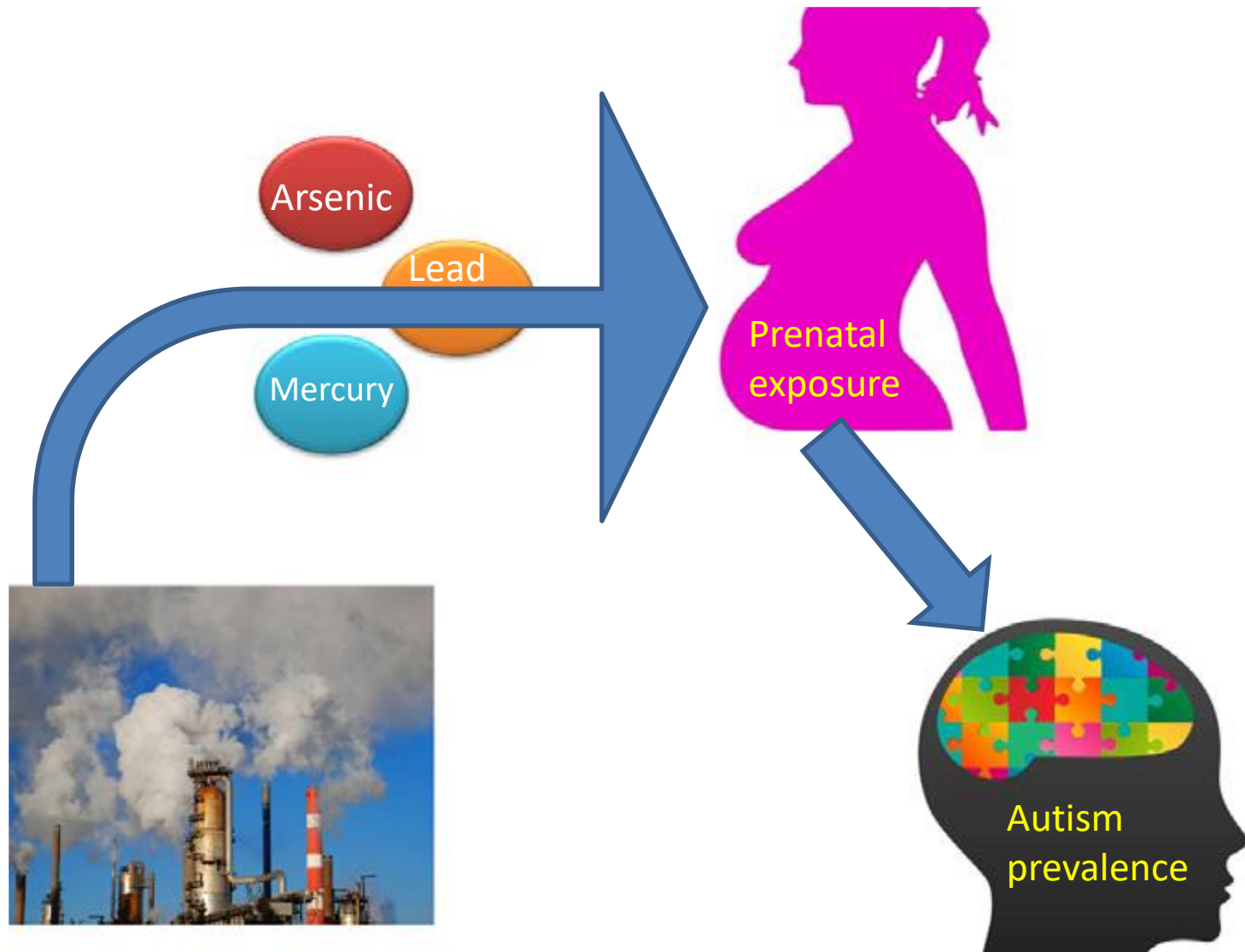
Prenatal and perinatal exposures to air pollutants have been shown to adversely affect birth outcomes in offspring and may contribute to prevalence of autism spectrum disorder (ASD).

ASD prevalence was **higher** in children located in the *closest 10th percentile* compared of distance to those in the *furthest 50th percentile* from the industrial facilities releasing arsenic, lead or mercury during the 1990s (adjusted RR = **1.27**, 95% CI: (1.00, **1.61**), $P = 0.049$).

I risultati di questo studio suggeriscono che **esiste un'associazione tra la prossimità residenziale dalle industrie che emettono inquinanti aerei nell'ambiente e una prevalenza di ASD più elevata.**

Autism spectrum disorder prevalence and proximity to industrial facilities releasing arsenic, lead or mercury
Science of The Total Environment Volume 536, 1 Dec 2015

Autism spectrum disorder prevalence and proximity to industrial facilities releasing arsenic, lead or mercury Science of The Total Environment Volume 536, 1 Dec 2015





4

Particolato sottile, ozono,
idrocarburi policiclici aromatici

DIOSSIDO DI AZOTO - PARTICOLATO SOTTILE – OZONO – CARBONE NERO

Maternal exposure to **NO₂** in early pregnancy was associated with reduced fetal growth.
Iniguez: Environmental Health Perspectives Feb 2016

Maternal exposure to **particulate pollution** was associated with LBW at term across study populations.
Environmental Health Perspectives Apr 2016

Third-trimester antenatal exposures to **BC** (black carbon) and, to a lesser extent, **PM2.5** were associated with higher newborn BP, whereas concentrations of **O3** (Ozone) in the third trimester were associated with lower BP.
Van Rossem: Environmental Health Perspectives; Aprile 2015

Long-term maternal **PM10** and **NO2** exposure during pregnancy was associated with elevated fetal CRP levels at delivery. Our results suggest that air pollution exposure may lead to maternal and fetal inflammatory responses.
Van den Hooven: Environmental Health – May 2012

PAH → ADHD

L'esposizione prenatale agli inquinanti aerei contenenti **Idrocarburi Policiclici aromatici** contribuisce al **rallentamento della velocità di processazione, ai sintomi ADHD e ai problemi di esternalizzazione** attraverso l'alterazione dello sviluppo della sostanza bianca dell'*emisfero sinistro*, mentre l'esposizione postnatale contribuisce a ulteriori disturbi dello sviluppo della sostanza bianca nelle *regioni dorsali*.

Lilian Calderón-Garcidueñas, MA, MD, PhD;
Ricardo Torres-Jardón, PhD **The Impact of Air
Pollutants on the Brain** JAMA Psychiatry. 2015

Particulate matter (PM) and ozone (O3) concentrations close or above their respective air quality standards during the last 20 years affect 24 million people living in the **Mexico City Metropolitan Area**.



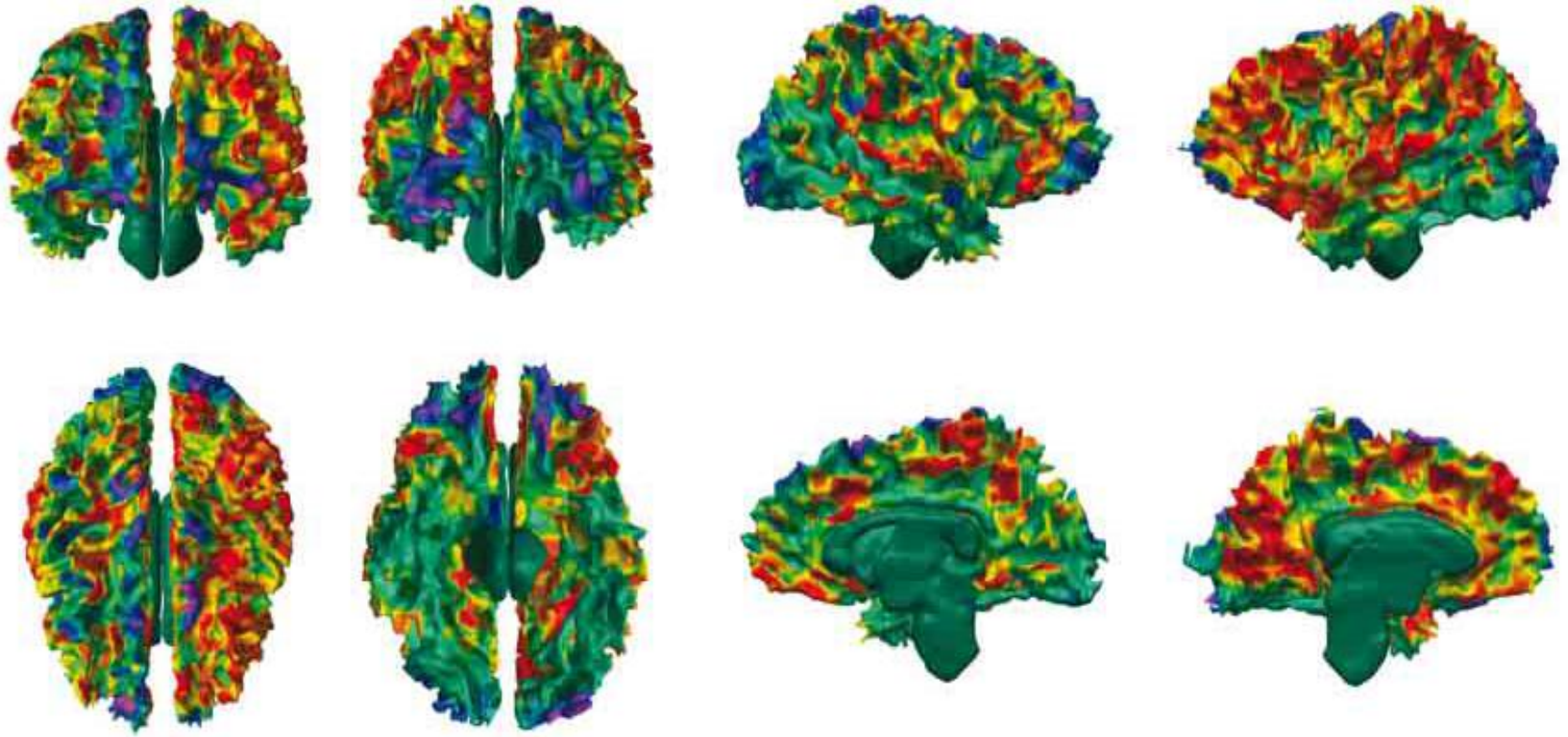
Systemic inflammation, immunodysregulation at both systemic and brain levels, oxidative stress, neuroinflammation, small blood vessel pathology, and an intrathecal inflammatory process,  **early neuropathological hallmarks for Alzheimer and Parkinson's diseases**



Structural and volumetric changes,  **cognitive, olfactory, auditory and vestibular deficits and long term neurodegenerative consequences.**

Megacities air pollution problems: Mexico City Metropolitan Area critical issues on the central nervous system pediatric impact .Lilian Calderón-Garcidueñas et al. Environmental Research, 2015

Prenatal Polycyclic Aromatic Hydrocarbon (PAH) Effects on Processing Speed



Warm colors (yellow, orange, and red) represent significant positive correlations in which white matter reductions associate with lower indexes for processing speed from the Wechsler Intelligence Scale for Children IV (WISC-IV).

Lilian Calderón-Garcidueñas: **The Impact of Air Pollutants on the Brain.** JAMA Psychiatry. 2015;

FETAL PROGRAMMING

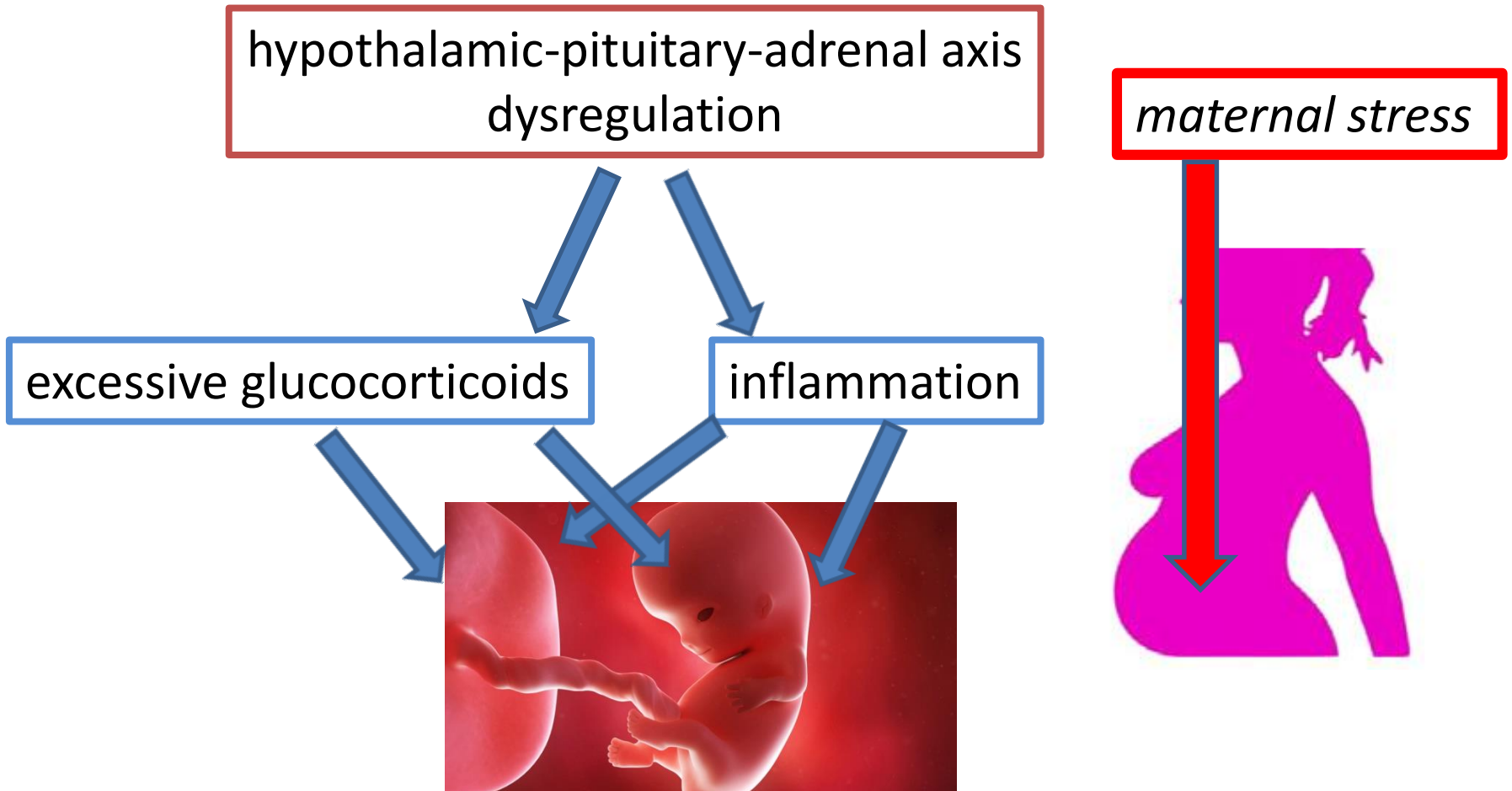


PSYCHIATRIC DISORDERS

Maternal malnutrition, early-life adversities, immune-activation, atmospheric and alimentary chains pollution can increase risk to psychiatric illnesses through epigenetic modifications interacting with a genetic predisposing background

Kim DR et al. *Prenatal programming of mental illness: current understanding of relationship and mechanisms*. Curr Psychiatry Rep. (2015);

Prenatal programming is implicated in the development of psychiatric disorders in offspring exposed to *maternal stress during pregnancy*.



Kim DR et al. ***Prenatal programming of mental illness: current understanding of relationship and mechanisms***. Curr Psychiatry Rep. (2015);



5

Antidepressivi e autismo

Antidepressant use during the second or third trimester of pregnancy, particularly use of selective serotonin reuptake inhibitors (**SSRIs**), nearly doubles the risk of the child's developing autism spectrum disorder (ASD) by age 7 years.

No increased risk for ASD was observed with the use of antidepressants during the first trimester.

Antidepressants in Pregnancy Linked to Increased Autism Risk: Nancy A. Melville ; JAMA Pediatrics, |
December 14, 2015

Treatment of depression with antidepressants in the second and/or third trimester of pregnancy was independently associated with an 87% increase risk of having a child with autistic spectrum disorder.

A history of maternal depression was an independent risk factor for having a child with ASD, increasing the risk by 20%.

Antidepressants in Pregnancy Linked to Increased Autism Risk: Nancy A. Melville ; JAMA Pediatrics, |
December 14, 2015



12

Obesità materna

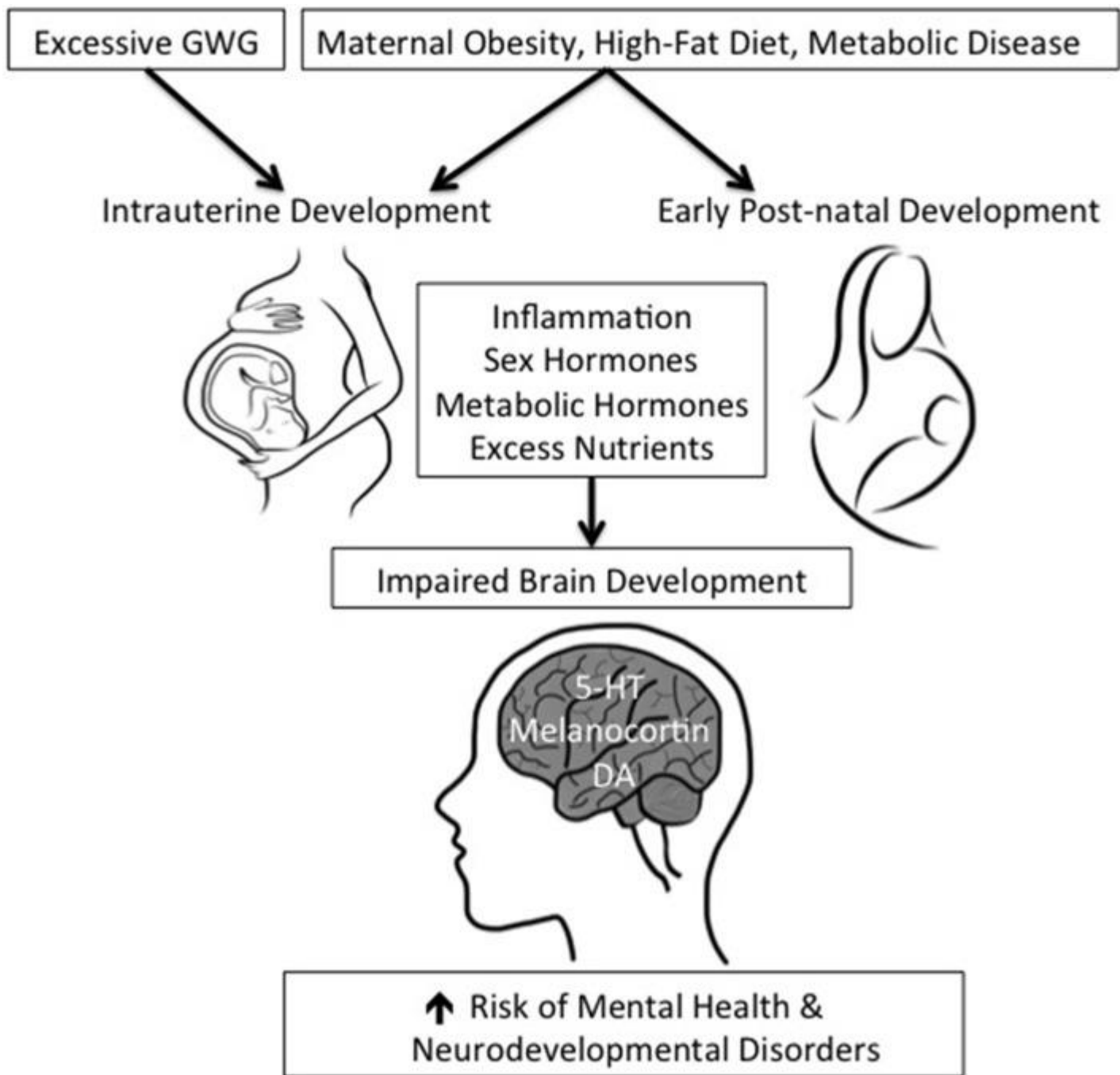
Maternal obesity and metabolic complications increase the risk of attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, anxiety, depression, schizophrenia, eating disorders (food addiction, anorexia nervosa, and bulimia nervosa), and impairments in cognition in offspring.

Rivera H.M.:**The role of maternal obesity in the risk of neuropsychiatric disorders.** Front Neurosci, june2015

During development, these offspring are **exposed to elevated levels** of nutrients (**fatty acids, glucose**), hormones (**leptin, insulin**), and inflammatory factors (**C-reactive protein, interleukin, and tumor necrosis factor**).

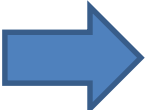
Questi fattori sembrano **cambiare in modo permanente la regolazione neuroendocrina e lo sviluppo del cervello nei figli di madri obese**. Inoltre, l'infiammazione del cervello del feto altera lo sviluppo delle vie nervose che hanno un **ruolo critico nella regolazione del comportamento**, come i sistemi serotoninergici, dopaminergici e melanocortinergici.

Rivera H.M.: **The role of maternal obesity in the risk of neuropsychiatric disorders**. Front Neurosci, June 2015



The Association of Maternal Obesity and Diabetes With Autism

Maternal prepregnancy obesity and maternal diabetes in combination were associated with increased risk for ASD and ID.



Leading theory about autism: the risk likely develops before the child is even born.

Maternal obesity may be associated with an **inflammation** in the developing fetal brain.

Mengying Li et al.: *The association of maternal obesity and diabetes with autism and other developmental disabilities*. Pediatrics. Feb. 2016

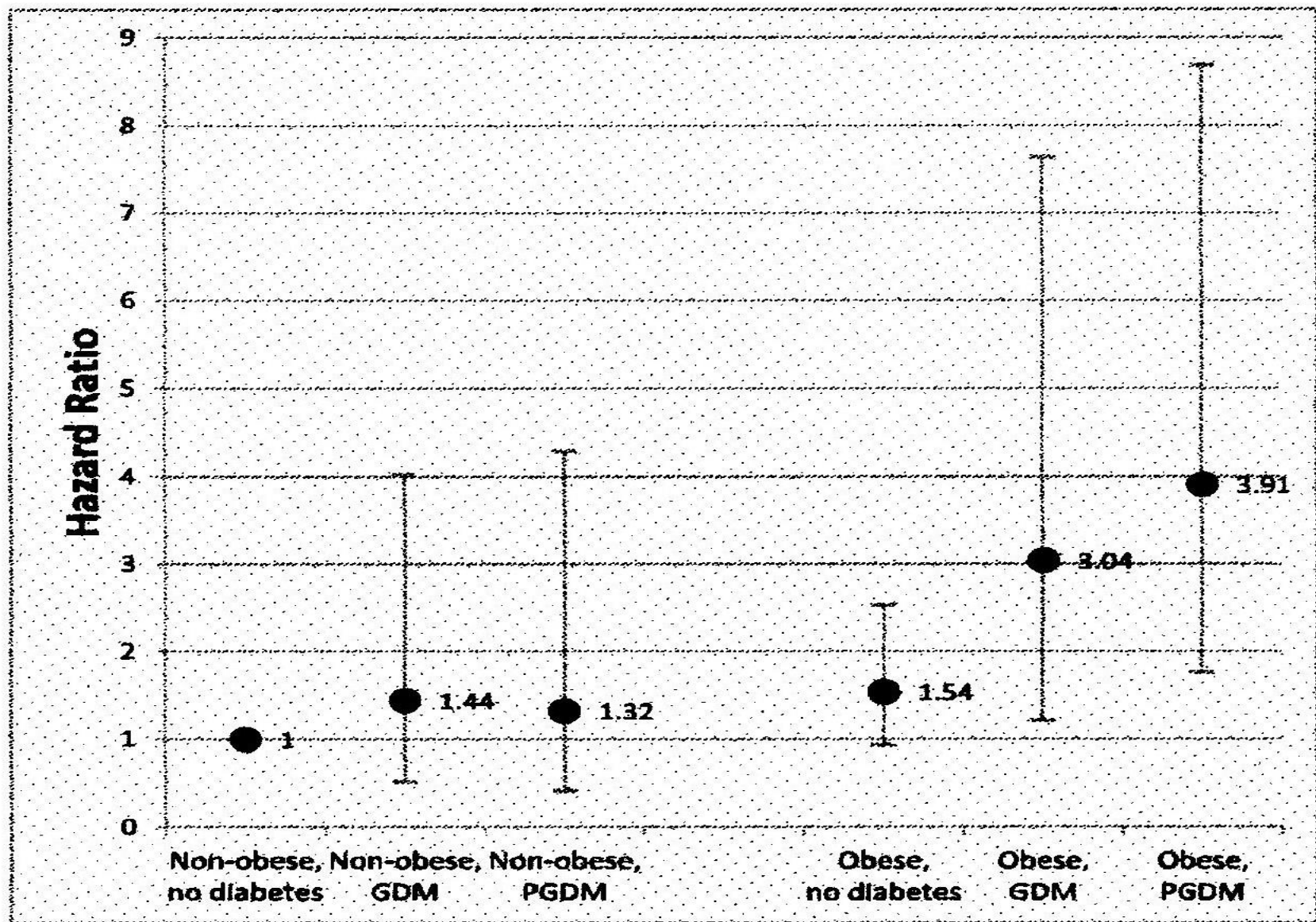


FIGURE 1

Adjusted HR and 95% CI for ASD associated with maternal obesity and diabetes. The models adjusted for child year of birth, child gender, maternal age, parity, smoking during pregnancy, and preterm birth.



13

Fattori materni

It is well established that the regulation of epigenetic factors, including chromatin reorganization, histone modifications, DNA methylation, and miRNA regulation, is critical for the normal development and functioning of the human brain. There are a number of **maternal factors** influencing epigenetic pathways such as lifestyle, including **diet, alcohol consumption, and smoking**, as well as **age and infections** (viral or bacterial).

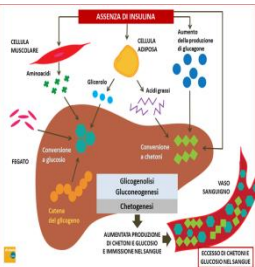
Banik et al.: Maternal Factors that Induce Epigenetic Changes Contribute to Neurological Disorders in Offspring. *Genes*, 24/05/2017



Gestational alcohol exposure induces histone modification, alteration in DNA methylation pattern and miRNA targets, and expression of genes associated with fetal developmental process, **leading to neurodevelopmental disorders.**



The **absence of essential dietary supplements** in maternal diet during gestation leads to a disruption in metabolic pathways and several epigenetic alterations in the fetus, triggering **abnormal intrauterine development and neurodevelopmental disorders.**



Metabolic conditions at gestation such as **GDM, obesity, and hypothyroidism** induce epigenetic alterations in the fetus, leading to a series of metabolic and immunogenic changes triggering neuroanatomical and neuropsychological **deficits in the developing brain**



In our **daily diet** there are macronutrient derivatives (choline, methionine, betaine), micronutrient elements (Vitamin A, D and B), microminerals (iron, selenium, zinc), and bioactive compounds (polyphenols) that have been found to play a significant role in embryonic development through different epigenetic processes.

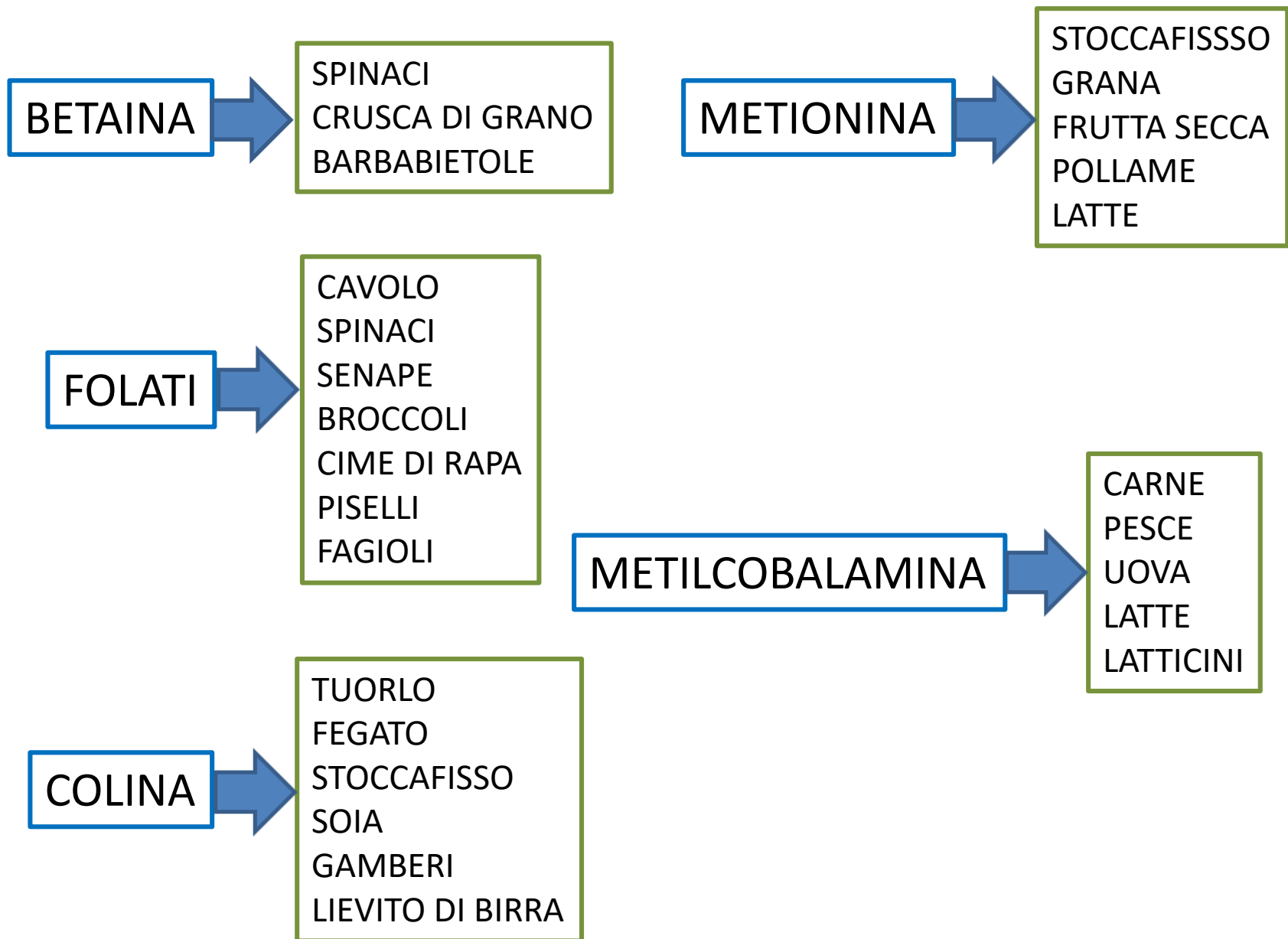


Maternal dietary deficiency

Absence of dietary methyl group donors such as folate, choline, methionine, betain and methylcobalamine

- Imbalance in folate-mediated one-carbon metabolism (FOCM) pathway [98]
- Mutation in methionine synthase reductase (*Mtrr*) gene, essential for deployment of methyl groups from the folate cycle [104]
- Down-regulation of genes related to fetal brain development: *BDNF*, *CREB*, *NGF* and *TrkB* [105]
- H3K9 and H4K20 methylation [114]
- Altered expression of miRNAs linked to FOCM pathway : miR-29c, miR-183, miR-422b, miR-189 [115]; miR-22, miR-24, miR-29b, miR-34a, miR-125, miR-344-5p/484, miR-488 [116-118]

Abnormal uterine development and congenital malformation [104]





14

Digital Media

Children and Adolescents and Digital Media

La prima infanzia è un periodo di rapido sviluppo del cervello, quando i bambini hanno bisogno di **giocare, dormire, imparare a gestire le emozioni e costruire relazioni.**

I ricercatori ci informano che un uso eccessivo dei media può interferire con queste importanti attività.

Y.Chassiakos, J. Radesky: Children and Adolescents and Digital Media. PEDIATRICS 2016

Prospective cohort analysis of cellphone use... emotional and behavioural difficulties in children

Children have higher specific absorption rates of RF (radiofrequency fields) than adults.

Associations between mothers' prenatal cellphone use and emotional and behavioral difficulties at **age 7 years**.

The strongest association was seen among children exposed both prenatally (mother used a cellphone while pregnant) and postnatally

Children without emotional and behavioural difficulties at age 7 years, but who had cellphone exposures, had increased odds of emotional and behavioural difficulties at **age 11 years**.

Guidelines for parents of children 0-5 years

1

- **Avoid** digital media use (except video chatting) in children **younger than 24 months**.
- If digital media is introduced to children between 18 and 24 months, **choose high-quality programming** and use the media **with** your child. Avoid solo use by the child.
- **Do not feel pressured to introduce technology early**. Interfaces are so intuitive that children will figure them out quickly once they start using them.
- For children ages 2 to 5, limit screen use to **one hour a day of high-quality programming**. Watch with your child and help them understand what they are seeing.
- Avoid **fast-paced programs** and apps with lots of distracting content or violence.
- **Turn off** TVs and other devices when not in use

Guidelines for parents of children 0-5 years

2

Avoid using media as the **only way to calm** your child. This could lead to problems with limit setting and ability to self-soothe and regulate emotions.

- **Test** apps before your child uses them, and play together.
- Keep bedrooms, mealtimes and parent-child playtimes **screen free**. Parents can set a "do not disturb" option on their phones during these times.
- Set a rule: No screen time **an hour before bed**.
- Ask your pediatrician if you need help.



15

Rapporti cronologici tra malattie
mentali e malattie fisiche

Chronology of Onset Mental Disorders-Physical Diseases in Adolescents

DEPRESSIONE

Artriti

*Disturbi del
sistema digestivo*

DISTURBI D'ANSIA

Malattie della pelle

EPILESSIA

Disordini alimentari



15

Campi elettromagnetici
Radiazione radiofrequenziale pulsata

The wide array of pathophysiological effects of EMF and RFR exposures from wireless sources do not require “the breaking of molecular bonds” *as done by ionizing radiation* in order for physiologically damaging effects to occur.

Epigenetic mechanisms alone can change fetal development in profound ways, disrupting health by causing **changes in gene activation and expression** without change in gene sequences.

RADIOFREQUENCY (RF) POWER DENSITY

Reported to cause tissue damage, changes in health status, neurological function, cognition and behaviour problems.

C. Sage, E. Burgio: *Electromagnetic Fields, Pulsed Radiofrequency Radiation, and Epigenetics: How Wireless Technologies May Affect Childhood Development* (Child Development, 2017)

Study	RF power density ($\mu\text{W}/\text{cm}^2$)	Reported health impacts
Zwamborn et al. (2003)	0.13	Anxiety, hostility, impaired cognition
Navarro et al. (2003)	0.01–0.11	Fatigue, headaches, sleeping problems
Oberfeld et al. (2004)	0.01	Sleep and concentration disruption, fatigue and cardiovascular problems
Hutter et al. (2006)	0.05–1.0	Headache, sleep, concentration problems, other neurological problems
Thomas et al. (2008)	0.005–0.04	Headaches and concentration difficulties with short-term cell phone radiation
Kundi and Hutter (2009)	0.05–0.1	Headaches, cardiac symptoms, fatigue, sleep and concentration disruption, and other impairments
Heinrich et al. (2010)	0.003–0.02	Headache, irritation, and concentration difficulties in schoolchildren and adolescents (8–17 years old) with short-term exposure to base-station level radiofrequency radiation
Thomas et al. (2010)	0.003–0.02	Conduct and behavioral problems in schoolchildren and adolescents (8–17 years old) exposed to short-term cell phone radiation
Mohler et al. (2010)	0.005	Sleep disturbances in adults with chronic cell phone tower exposure
Buchner and Eger (2011)	0.006–0.01	Significant impact on stress hormones, especially in children and chronically ill adults
Avendano et al. (2012)	0.5–1.0	Decreased sperm viability and DNA breakage in human sperm with 4 hr exposure to Wi-Fi from laptop in wireless mode
Sage and Carpenter et al. (2012)	0.00034–0.07	DNA damage, impaired sperm quality, motility, and viability from cell phones on standby mode and wireless laptop use

E' impressionante la somiglianza tra gli effetti documentati dell'esposizione ai EMF/RFR e i sintomi presenti nel ASD e ADHD.

(Herbert and Sage 2013a, 2013b)

Sintomi quali deficit della memoria, alterazioni cognitive, dell'apprendimento, dell'attenzione e del comportamento, che sono altresì presenti nell' *AUTISMO* e nell' *ADHD*, sono stati riportati in numerosi studi scientifici come risultato di esposizioni a CAMPI ELETTROMAGNETICI e RADIAZIONE FREQUENZIALE PULSATA.

Le cause più probabili di ciò sono da ricercare nei *meccanismi epigenetici*.

L' esposizione persistente contribuisce a una cronica disfunzione, stravolgendo i meccanismi biologici di adattamento.

C. Sage, E. Burgio: *Electromagnetic Fields, Pulsed Radiofrequency Radiation, and Epigenetics: How Wireless Technologies May Affect Childhood Development* (Child Development, 2017)

Numerosi studi dimostrano effetti dannosi sul **feto, lattante, bambino** (Aldad, Gan, Gao, & Taylor, 2012; Divan, Kheifets, Obel, & Olsen, 2008, 2012), **e adolescente** in termini di **sviluppo neurologico, memoria, apprendimento, attenzione, concentrazione, problemi comportamentali e qualità del sonno.**

(Carter, Rees, Hale, Bhattacharjee, & Paradkar, 2016)

Prospective cohort analysis of cellphone use... emotional and behavioural difficulties in children

I bambini hanno dei tassi specifici di assorbimento delle radiazioni radiofrequenziali più elevate rispetto agli adulti.

Esiste un'associazione tra l'uso da parte della madre in gravidanza del cellulare e la comparsa nel bambino di **disturbi emozionali e comportamentali** all'età di 7 anni.

La maggiore associazione è stata riscontrata nei bambini esposti sia **in utero** che **dopo la nascita**.

I bambini che non mostravano disturbi emozionali e comportamentali all'età di 7 anni ma che erano stati esposti al telefono cellulare avevano un aumentato rischio di sviluppare disturbi emozionali e comportamentali all'**età di 11 anni**.

In adults, the evidence points to increased **cancer and neurodegenerative diseases** (chronic degenerative and inflammatory diseases). **Fertility and reproductive harm** is rather consistently documented in men with damage to the DNA of sperm and deterioration of the testes (Sage & Carpenter, 2012)



17

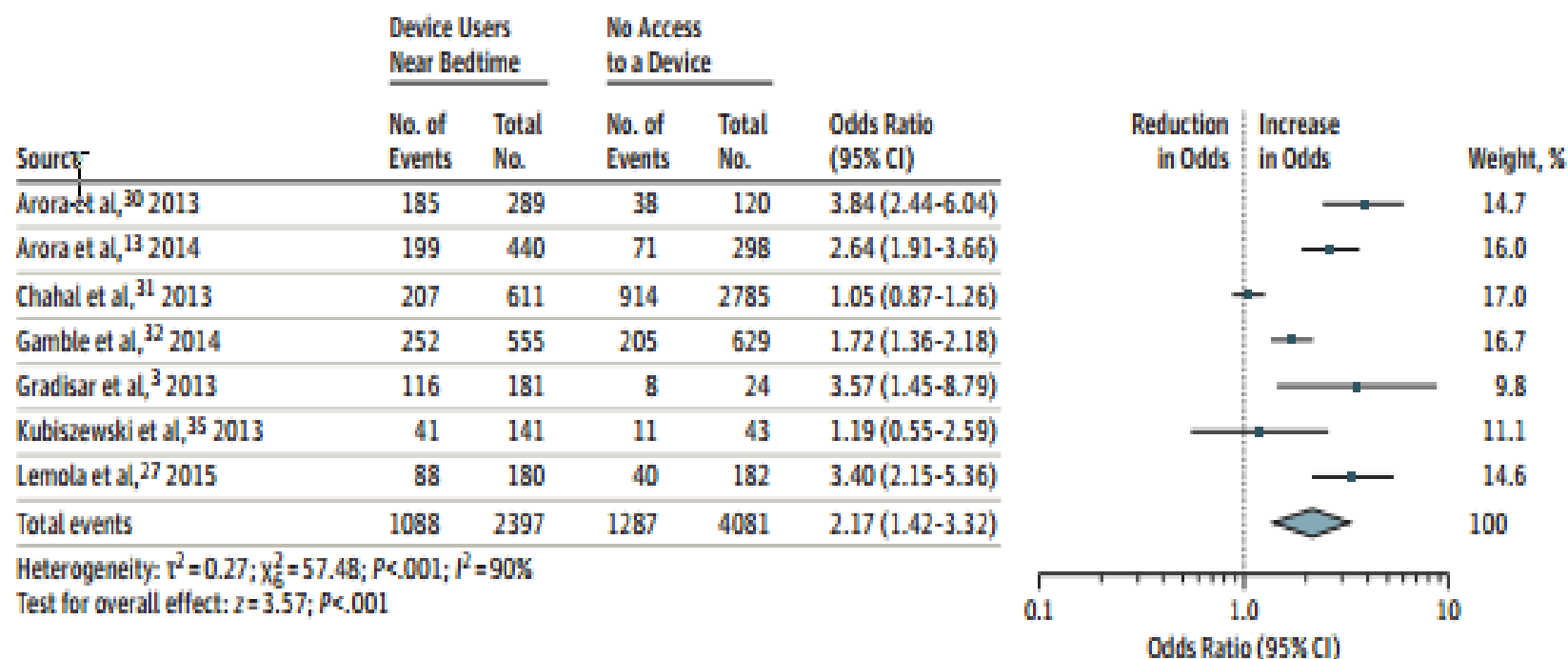
Dispositivi multimediali e sonno

This study is the first systematic review and meta-analysis (**125.128 children**) of the association of access to and the use of media devices with sleep outcomes.

Children with bedtime access to a media device **at least 3 times a week** were categorized as having access to a media device.

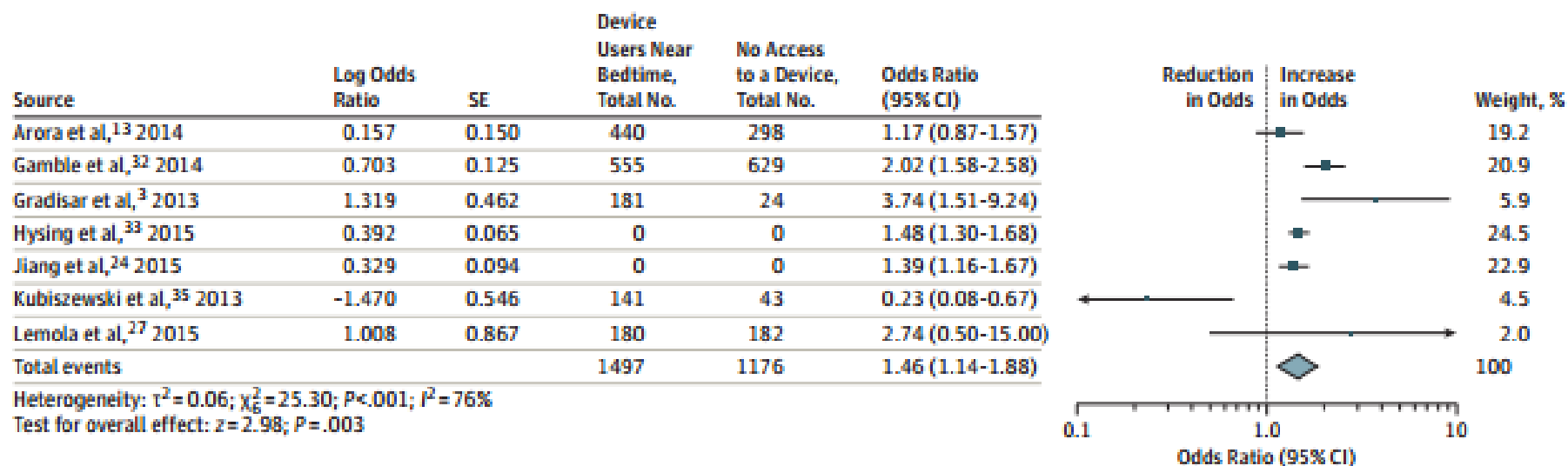
Carter, B., Rees, P., Hale, L., Bhattacharjee, D., Paradkar, M.S. (2016). *Association between portable screen-based media device access or use and sleep outcomes: A systematic review and meta-analysis. JAMA Pediatr. 2016 Dec*

Figure 2. Children With Inadequate Sleep Quantity



We compared children having bedtime media device use with children not having access to a device.

Figure 3. Children With Poor Sleep Quality



We compared children having bedtime media device use with children not having access to a device. The number of participants was not provided by Hysing et al³³ or Jiang et al²⁴; only the results from the statistical analysis were reported.

Figure 4. Alternate Comparison of Children With Inadequate Sleep Quantity