Corso Formativo di base per il counselling nutrizionale in gravidanza per Ginecologi e Ostetriche.

L'ALIMENTAZIONE, L'OBESITÀ E LE GRANDI SINDROMI **OSTETRICHE.**

26 FEBBRAIO 2016
ore 9.00 - 16.00
MILANO
Auditorium Ospedale dei Bambini V. Buzzi

Epigenetica & Fetal Programming

Anna Maria Marconi
Università degli Studi di Milano - DiSS San Paolo
annamaria.marconi@unimi.it

Ospedale San Paolo
Polo Universitario
Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

90 LA STATALE
UNIVERSITÀ DEGLI STUDI DI MILANO

Epigenetica

- Nasce nei primi anni ’40, termine coniato dal biologo genetista inglese **Conrad H. Waddington** ad indicare il collegamento tra genetica e altre branche della biologia come la citologia, l’embriologia, l’evoluzionismo e la biologia cellulare
- *… «epigenetica» derivato dalla parola Aristotelica «epigenesis» che era passata in disuso, ed un termine adatto ad indicare quella branca della biologia che studia* ***l’interazione causale tra geni e i loro prodotti e che porta il fenotipo ad essere***

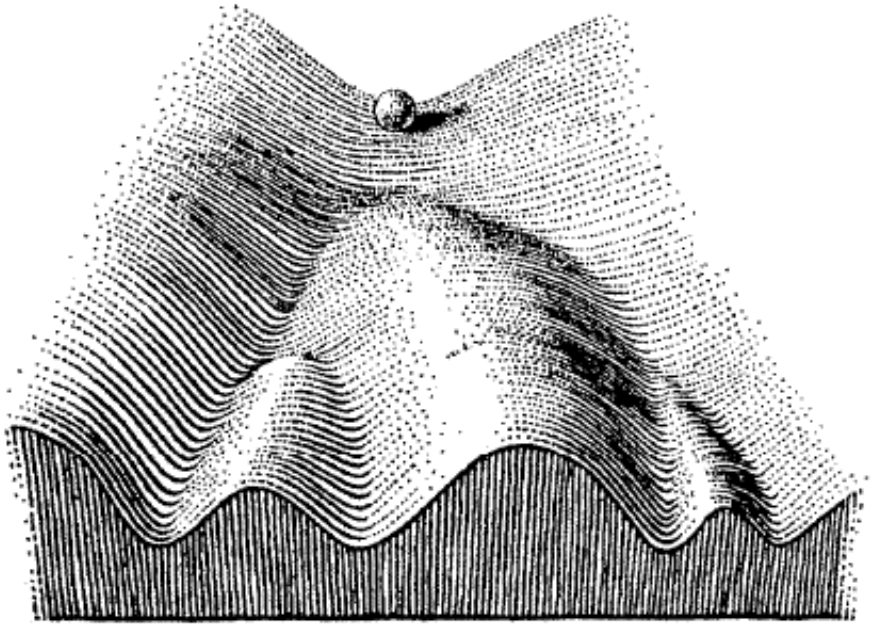
Development as an *epigenetic process*

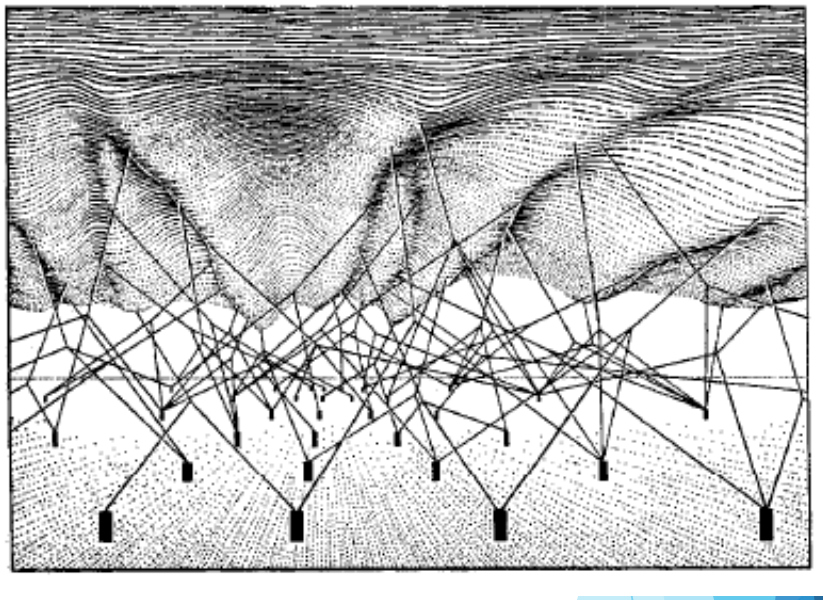
FROM
Genotype + environment = phenotype
TO
Genotype + *epigenotype* + environment = particular phenotype

Epigenetic constitution of tissue/cell
Set of organizers and organizing relations to which tissue is subject during development

L Van Speybroeck, Ann NY Acad Sci 2002

Epigenetica





La relazione tra gene e fenotipo non è semplice perché **se un gene muta**, alterando la tensione in un determinato set di tiranti, il risultato non dipenderà da quel particolare gene ma dall'**interazione** che ha con tutti gli altri

Waddington, C.H. 1957. *The Strategy Of The Genes* (London: Allen & Unwin).

Epigenetica

- **Hall 1992**: il controllo epigenetico è la somma dei **fattori genetici e non genetici** che agiscono sulle cellule per controllare selettivamente **l'espressione dei geni** che produce la crescente complessità fenotipica durante lo sviluppo
- **Russo 1996**: lo studio delle modificazioni mitotiche e/o meiotiche ereditabili nella funzione dei geni che **non può essere spiegata da modificazioni nella sequenza del DNA**
- **Science 2001**: lo studio delle modificazioni nella funzione dei geni che sono mitoticamente e/o meioticamente ereditabili e che **non implicano un cambiamento nella sequenza del DNA**

Fetal Programming
[developmental origins hypothesis]

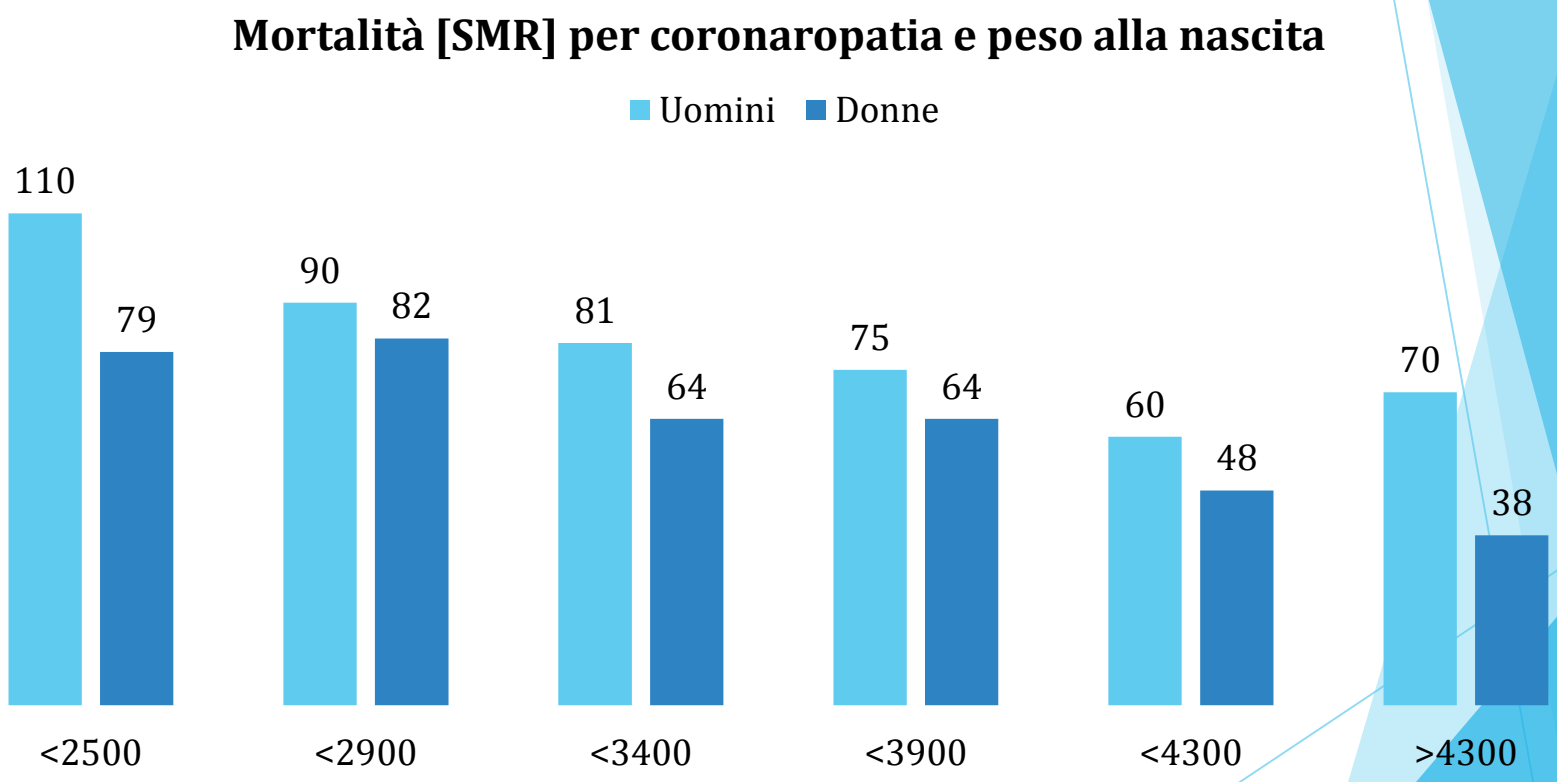
- **Ipotesi**: poiché la maggior parte delle **morti neonatali** avvengono entro 1 settimana dalla nascita e sono associate al **basso peso**, quindi ad influenze intrauterine, i nati di basso peso che sopravvivono potrebbero essere a maggior rischio di patologia coronarica da adulti

Table 1 Standardized mortality ratios for stroke, coronary heart disease and chronic bronchitis in the 212 local authority areas of England and Wales grouped by neonatal and postneonatal mortality (1911–25)

	Postneonatal mortality				
Neonatal mortality	1 (lowest)	2	3	4	5 (highest)
Stroke					
1 (lowest)	85	81	79	78	79
2	86	90	98	74	76
3	102	100	104	104	104
4	–	108	110	115	117
5 (highest)	124	–	121	123	117
Coronary heart disease					
1 (lowest)	84	89	91	88	98
2	85	93	95	88	91
3	86	94	99	106	113
4	–	98	109	111	115
5 (highest)	83	–	114	119	116
Chronic bronchitis					
1 (lowest)	67	78	106	115	161
2	64	84	85	104	126
3	69	65	89	88	151
4	–	91	99	120	142
5 (highest)	41	–	108	123	144

DJP Barker, J Intern Med 2007

Fetal Programming
[developmental origins hypothesis]



Osmond et al, BMJ 1993

Svezia: nei maschi nati ‘20-’30 relazione inversa tra peso alla nascita e mortalità coronarica

Finlandia: nei maschi nati ‘20-’30 relazione inversa tra IP alla nascita e mortalità da CHD

GB: nei maschi nati ‘20-’30 relazione inversa tra ipertrofia ventricolare e peso ad un anno

India: in maschi e femmine CHD da 18% nei nati ≤2500 gr a 4% nei nati ≥3200 gr

GB: per ogni kg in meno di peso alla nascita il rischio di morte dei genitori per CVD raddoppia

USA: la coronaropatia è 2 volte meno frequente nei nati normopeso

USA: l’altezza si correla inversamente all’infarto miocardico

Fetal Programming
[developmental origins hypothesis]

David Barker
29.6.1938 – 27.8.2013

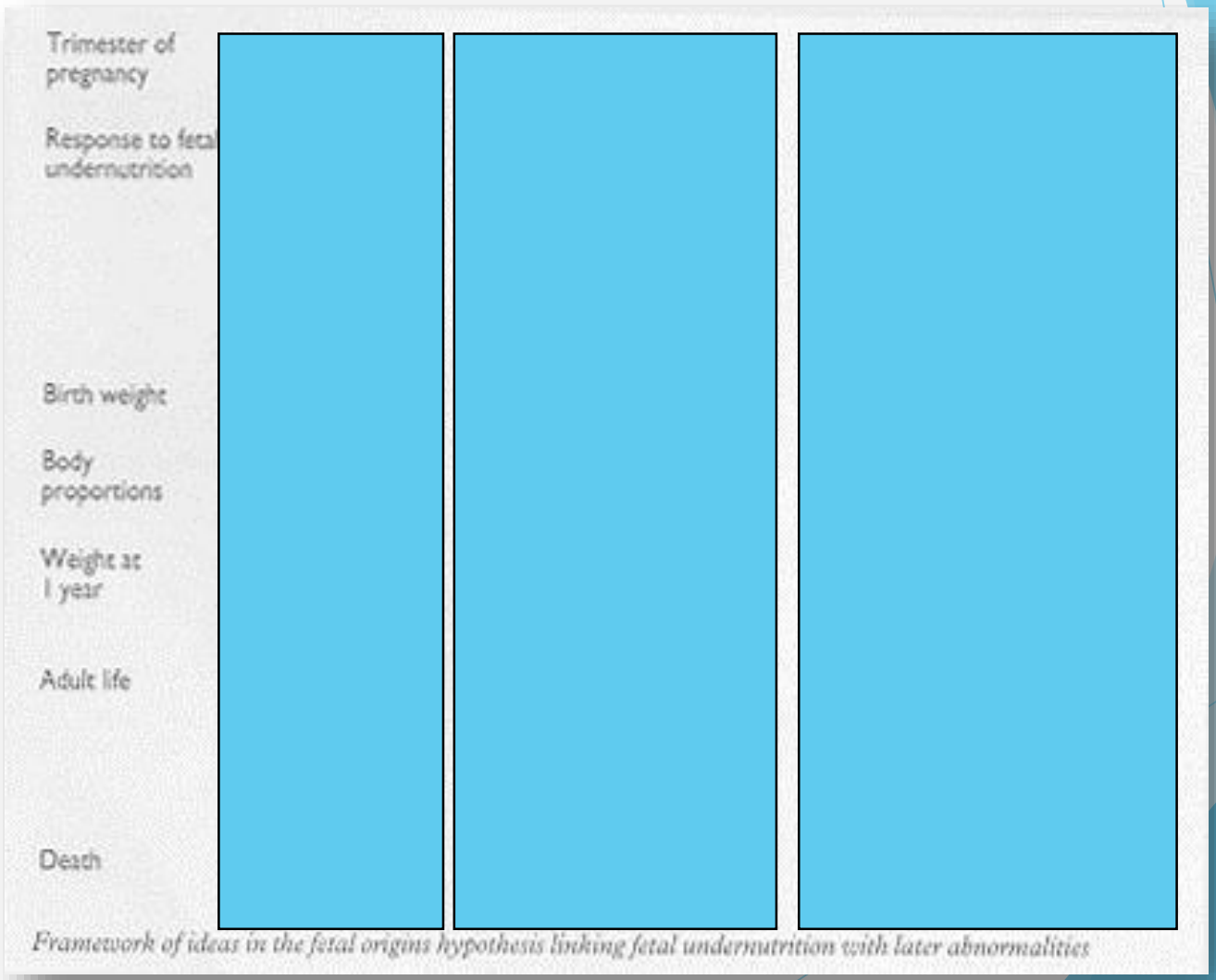
- L'ipotesi delle **«origini fetali»** propone che alterazioni nella nutrizione e nello stato endocrino del feto esitino in **adattamenti** nello sviluppo che modificano in modo permanente **struttura, fisiologia e metabolismo**, in tal modo **predisponendo** gli individui all'insorgenza di patologie cardiovascolari, metaboliche e endocrinologiche nella vita adulta

“Fetal Programming”

- Durante lo sviluppo prenatale, si verificano periodi di rapida divisione cellulare, in diversi momenti, nei diversi tessuti corporei.
- Durante questi “periodi critici” il milieu di nutrienti ed ormoni del prodotto del concepimento può **modificare l’espressione del genoma fetale** e ciò può avere conseguenze per tutta la vita.

Lucas A: In “The childhood environment and adult disease”, JW&S, 1991

Ipotesi di Barker: conseguenze del basso peso alla nascita



Framework of ideas in the fetal origins hypothesis linking fetal undernutrition with later abnormalities

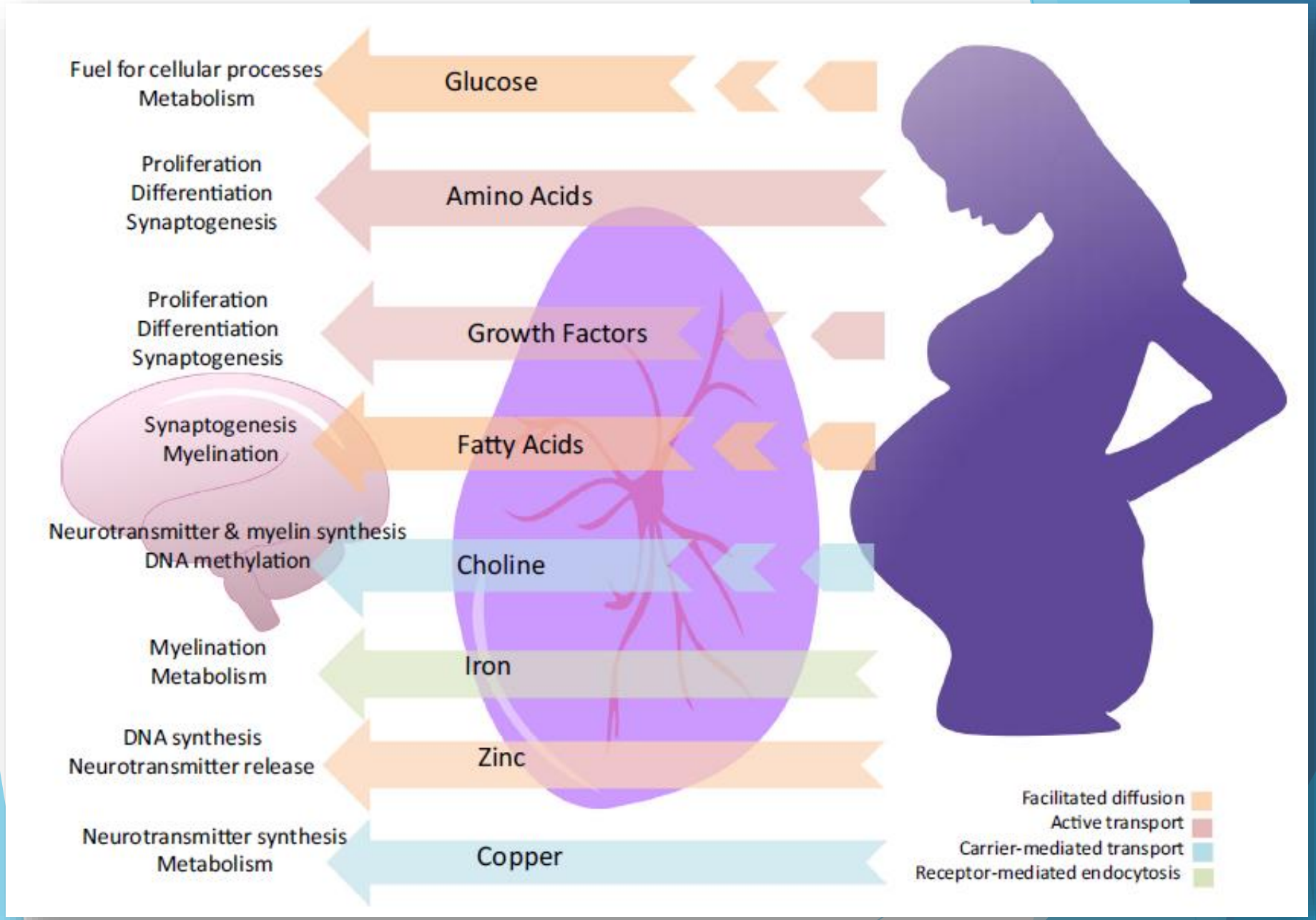
DJP Barker, BMJ 1995

Tissues and systems for which there is evidence of programming in humans[1]

Tissue or system	Examples of programming	Reference
Cardiovascular system	Vascular compliance	17
	Endothelial function	18
Respiratory system	Lung volume	19
Endocrine system	Hypothalamic-pituitary-adrenal axis	20
	Glucose-insulin metabolism	21, 22
	Growth hormone–IGF-I axis	23
Reproductive system	Age at menarche	24
	Polycystic ovary syndrome	25
Central nervous system	Schizophrenia	26
Skeletal muscle	Insulin resistance	8
	Glycolysis during exercise	27
Bone	Bone mineral content	28
Kidney	Renin-angiotensin system	29
Liver	Cholesterol metabolism	30
	Fibrinogen and factor VII synthesis	31
Immune system	Thyroid autoantibodies	32
	IgE concentrations	33

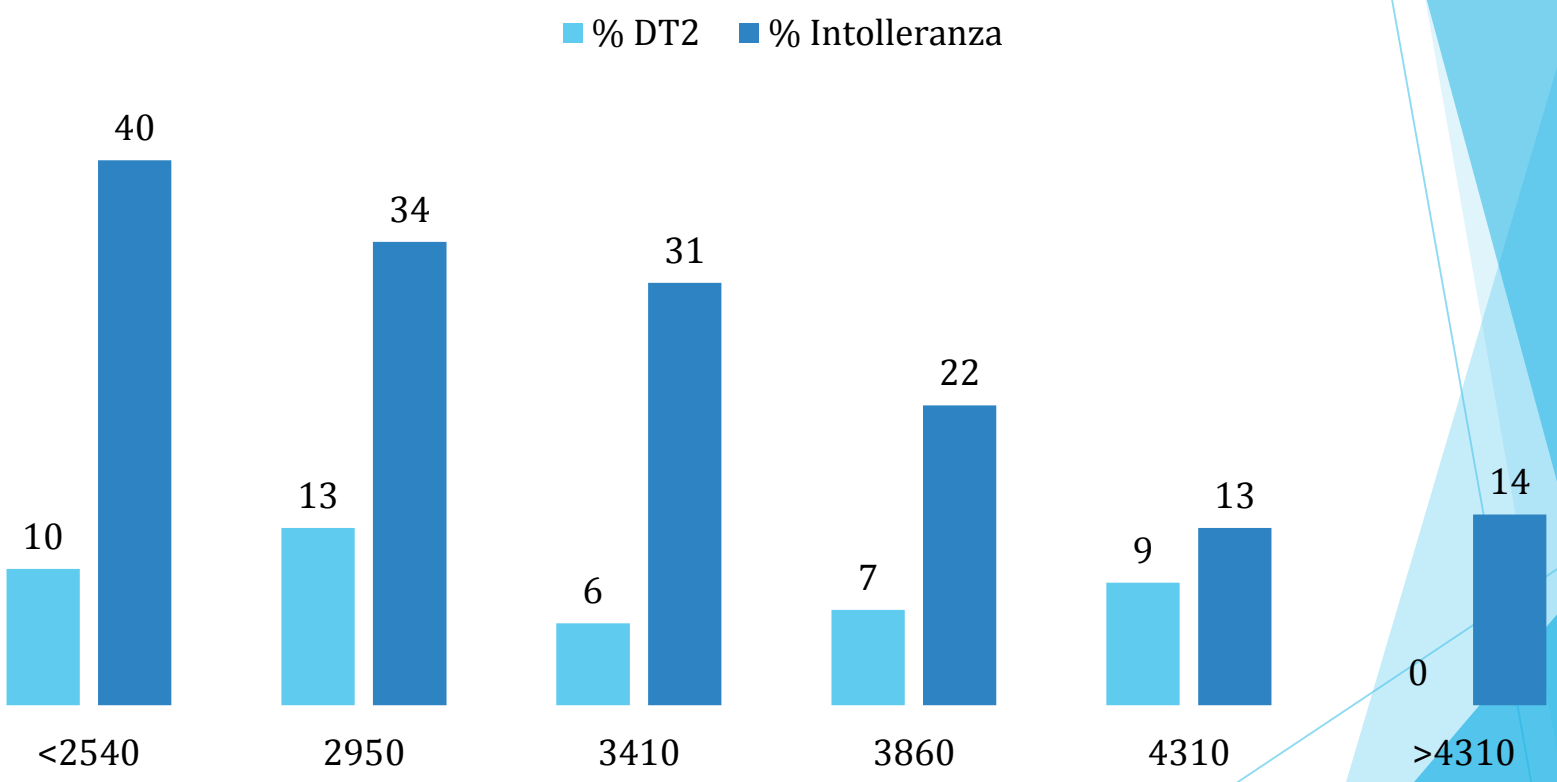
[1] IGF-I, insulin-like growth factor I; Ig, immunoglobulin.

KM Godfrey & DJP Barker, Am J Clin Nutr 2000



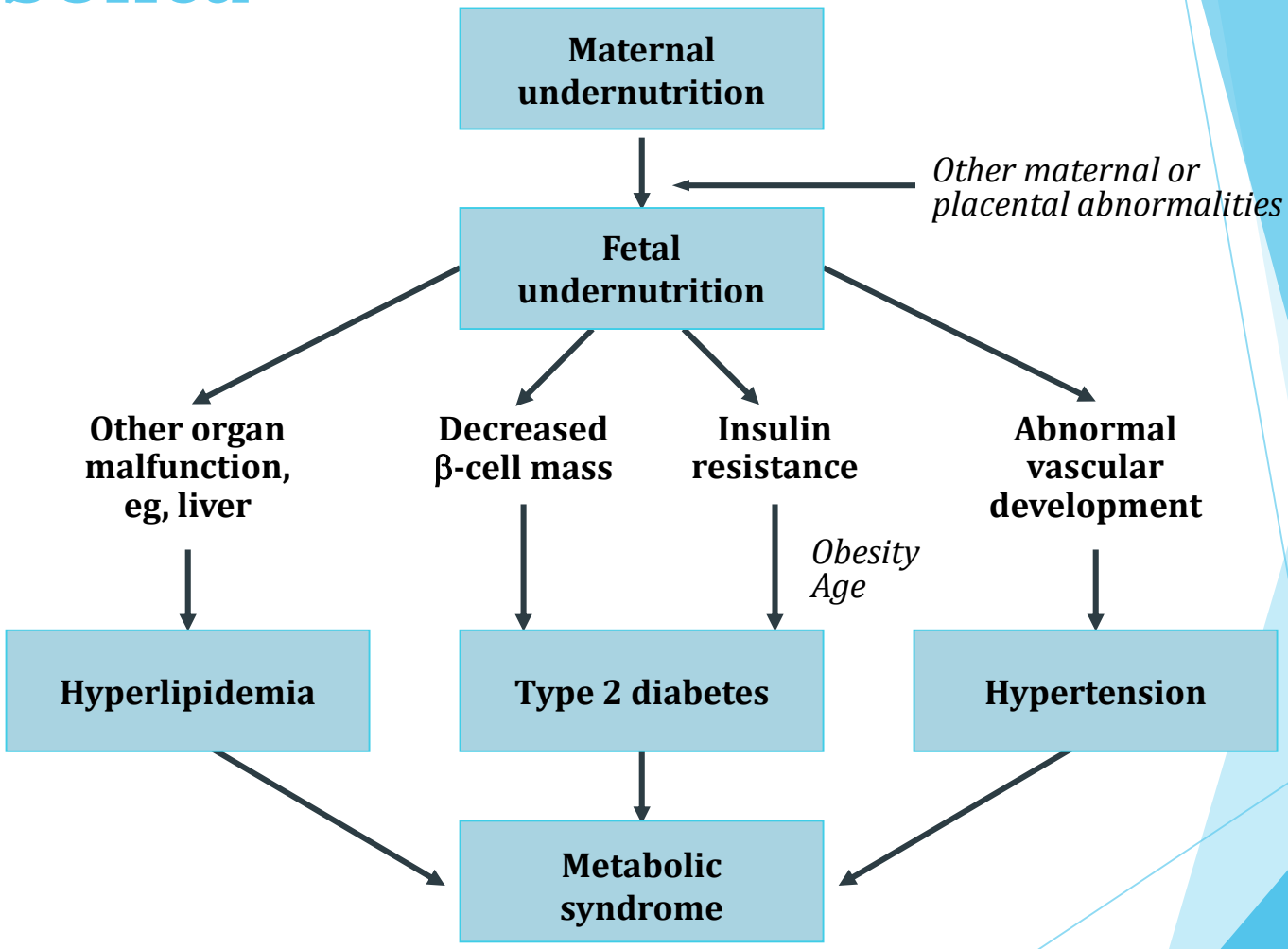
BM Nugent & TL Bale, Front Neuroendocrinol 2015

Fetal Programming
[developmental origins hypothesis]

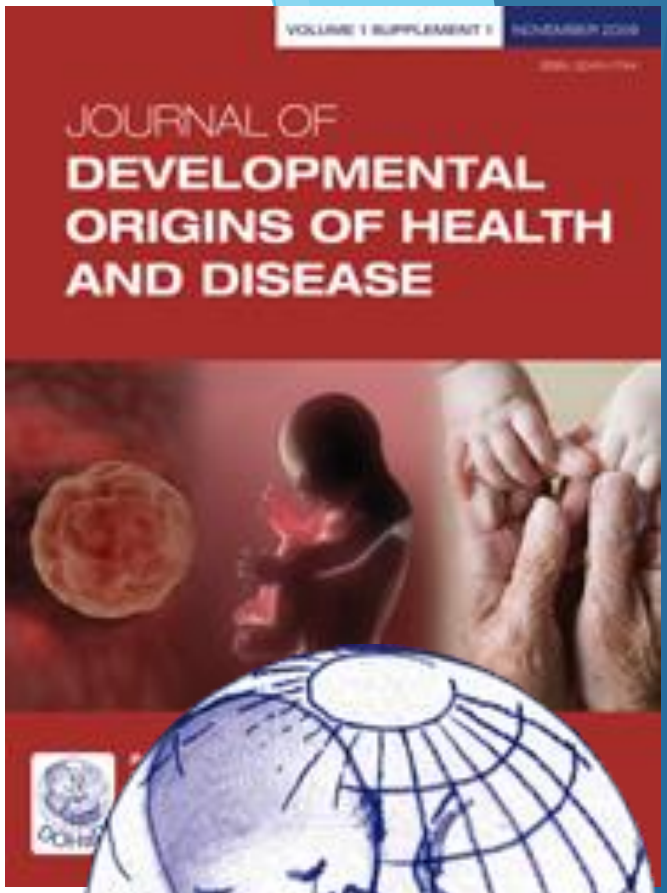


CN Hales et al, BMJ 1991

L'origine fetale della Sindrome Metabolica

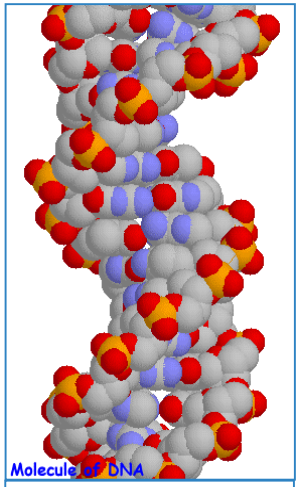


Barker DJP et al. *Diabetologia.* 1993;36:62. Barker DJP. *BMJ.* 1995;311:171.



- Il processo per cui uno stimolo/insulto in un periodo sensibile o critico dello sviluppo abbia **effetti a lungo termine** viene chiamato ***programming***

Crescita fetale



genoma

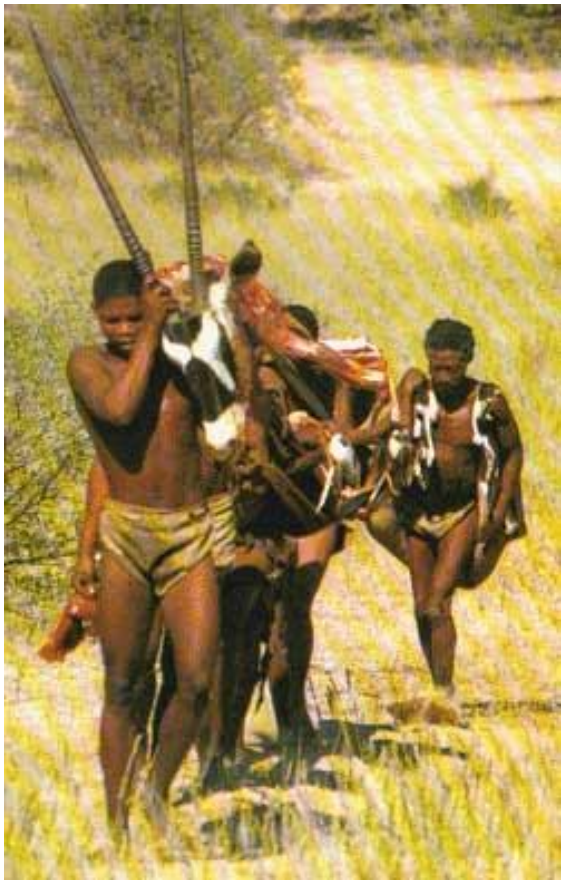
fattori ambientali

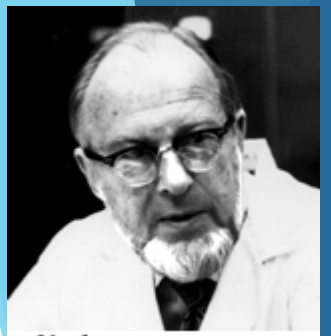
infezioni

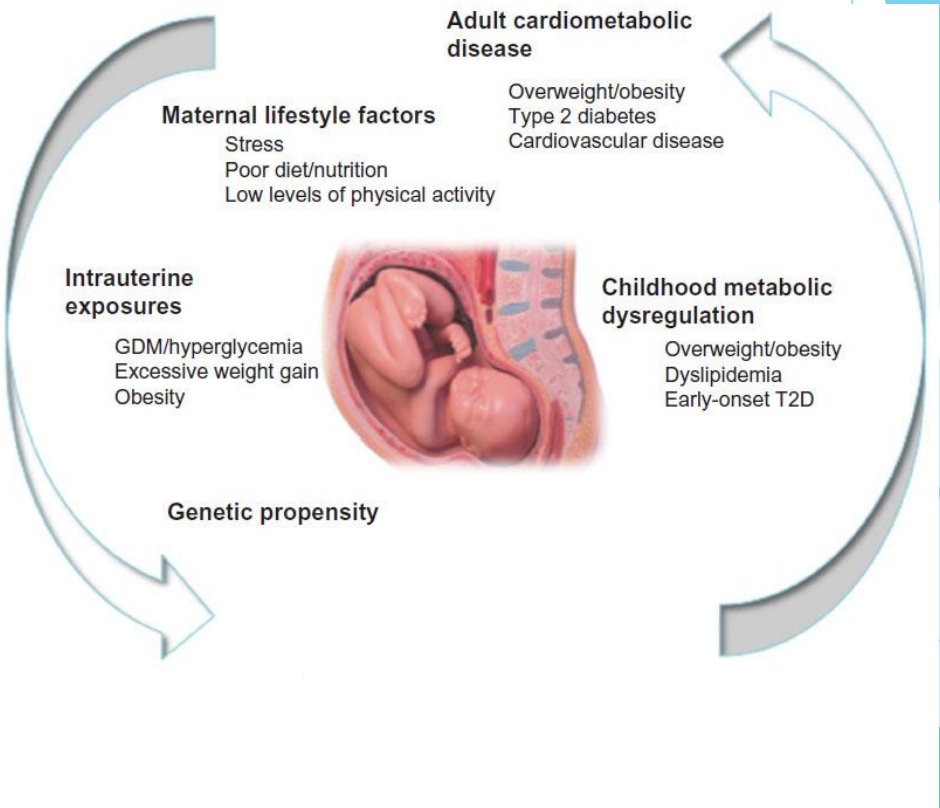
status materno

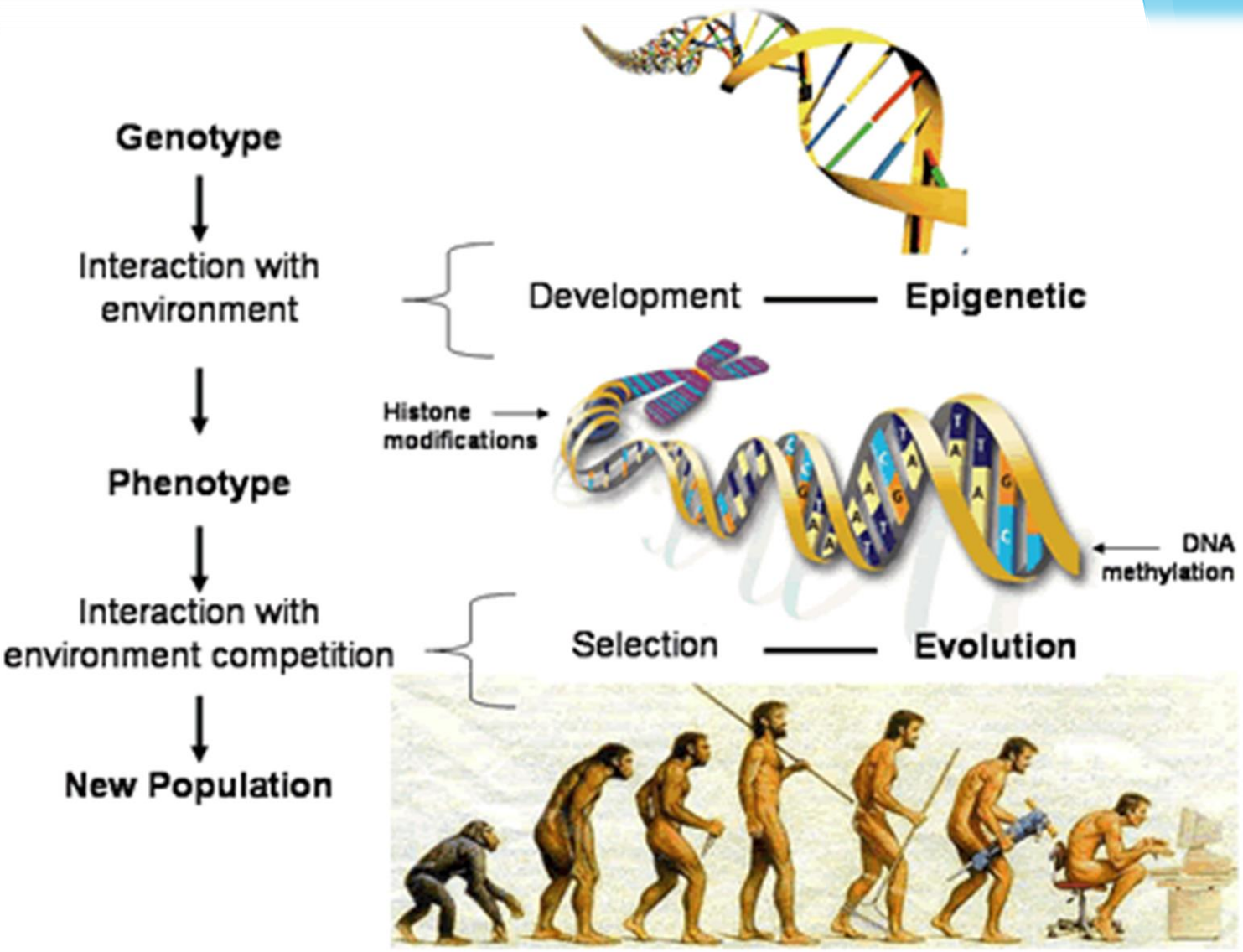
alimentazione

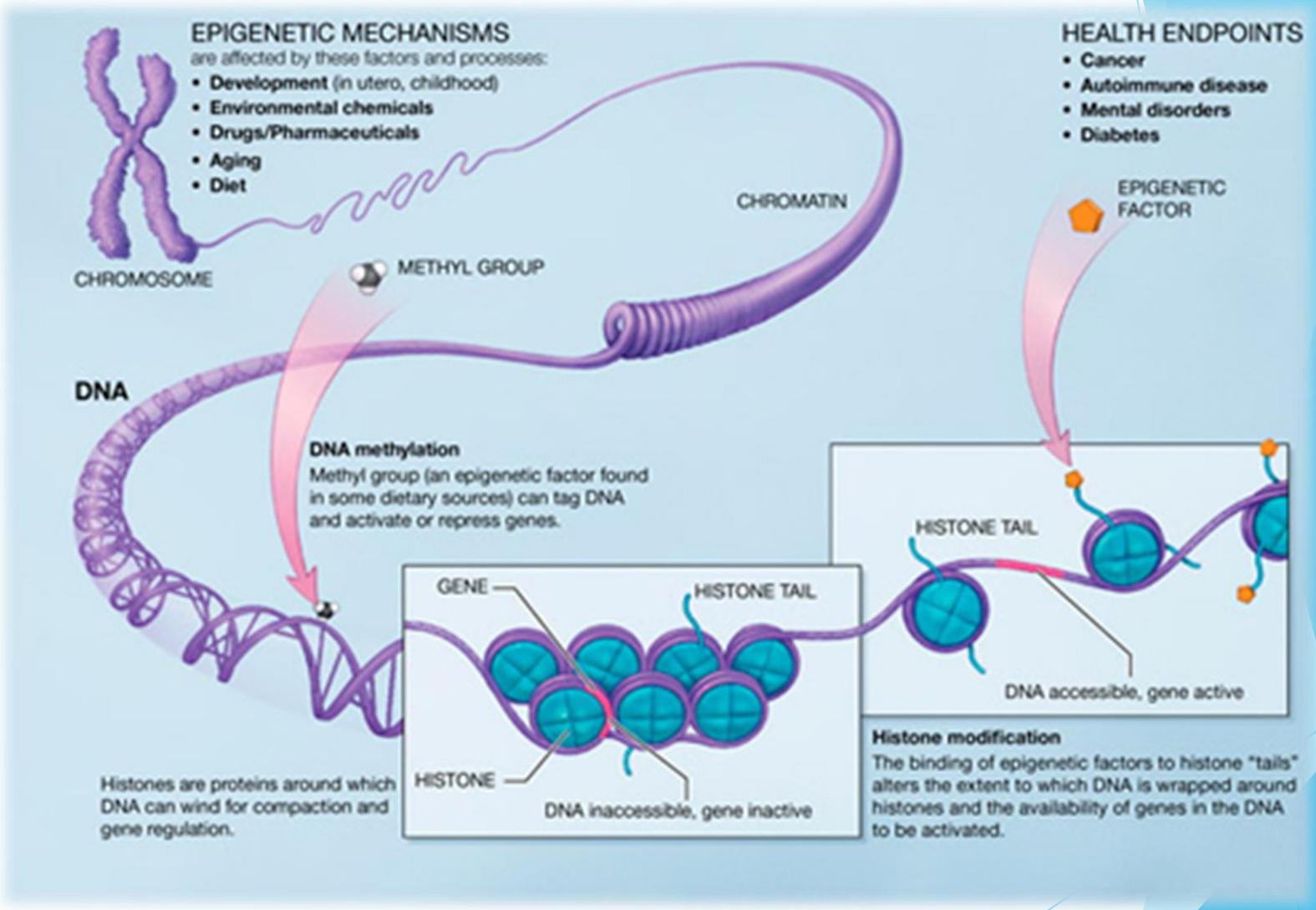
«Thrifty genotype-phenotype»

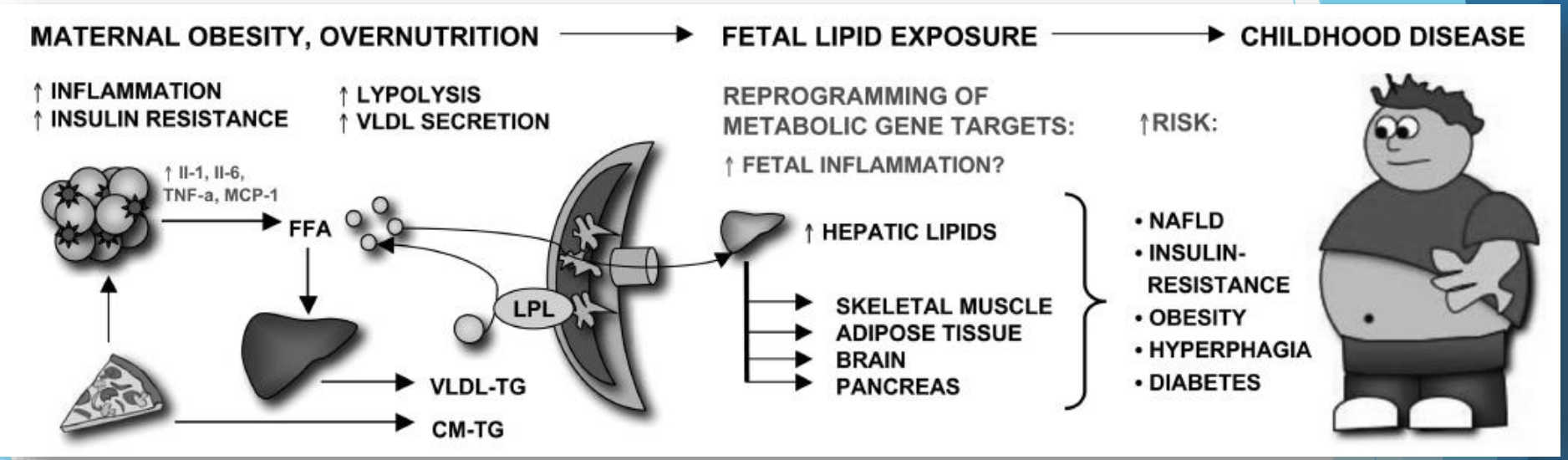







Genotype
Interaction with environment
Development
Epigenetic
Histone modifications
Phenotype
DNA methylation
Interaction with environment competition
Selection
Evolution
New Population


EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
HISTONE TAIL
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.



MJR Heerwagen et al, Am J Physiol Regul Integr Comp Physiol 2010

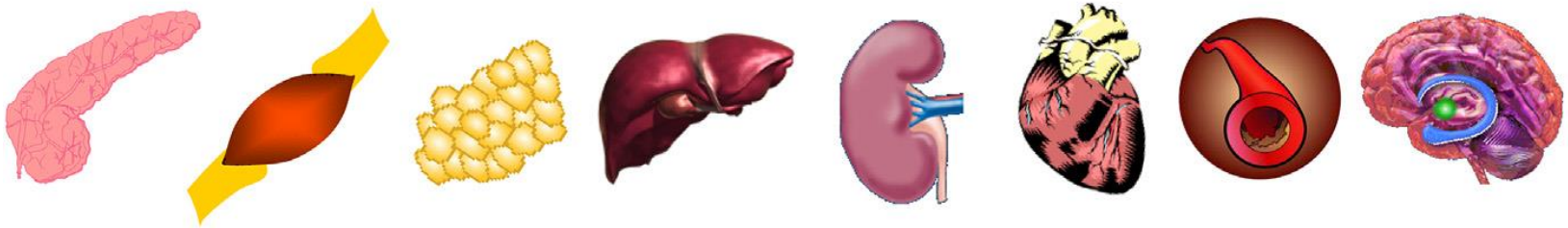
Maternal obesity

Gestational weight gain

Maternal DM/ GDM

In-utero over-nutrition

Epigenetic changes in genes e.g. *MEST*, *PPARA*, *ABCA1*



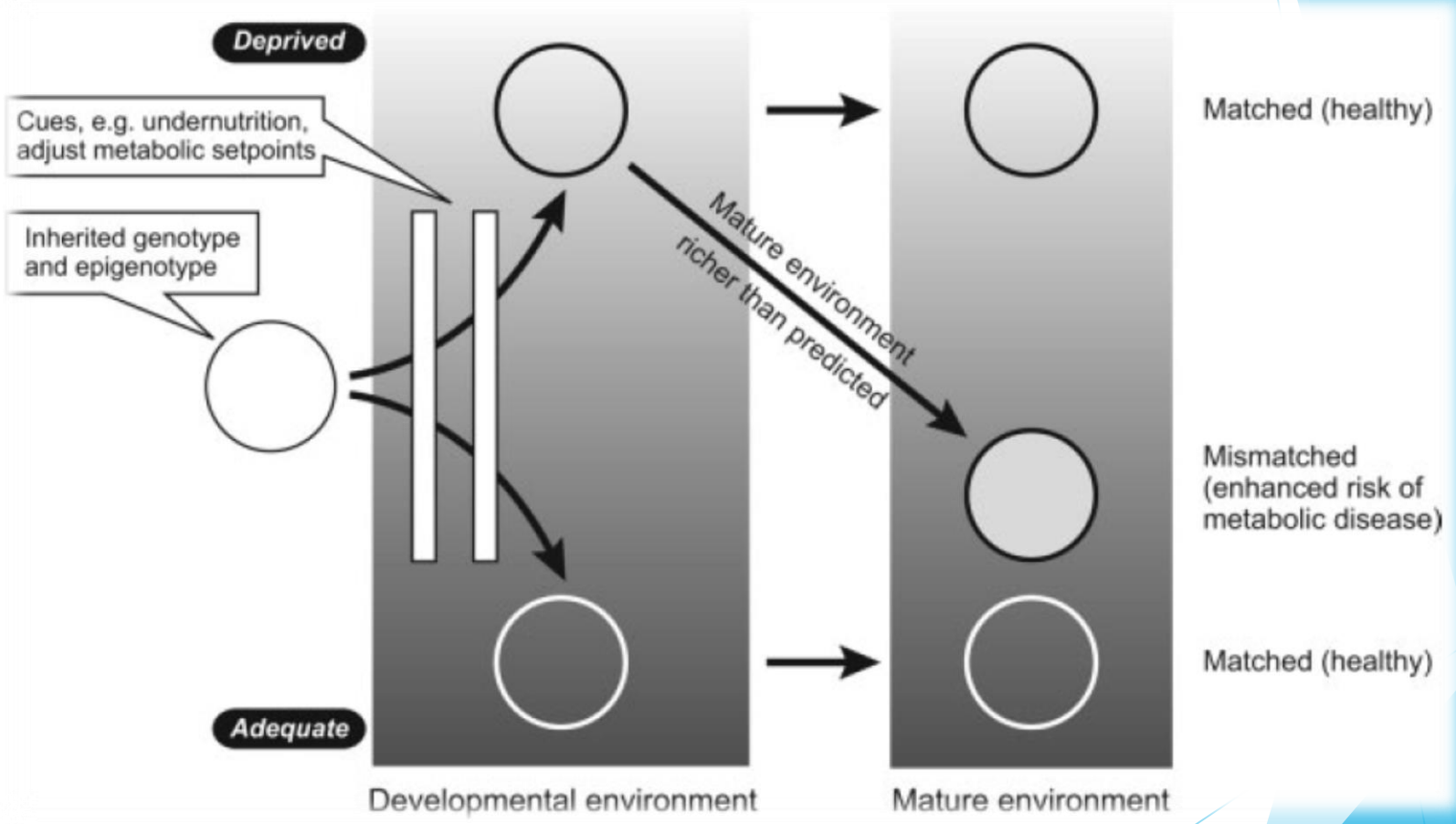
Altered physiology e.g. insulin resistance, β- cell dysfunction

↑ Risk of obesity, DM ,CVD in offspring

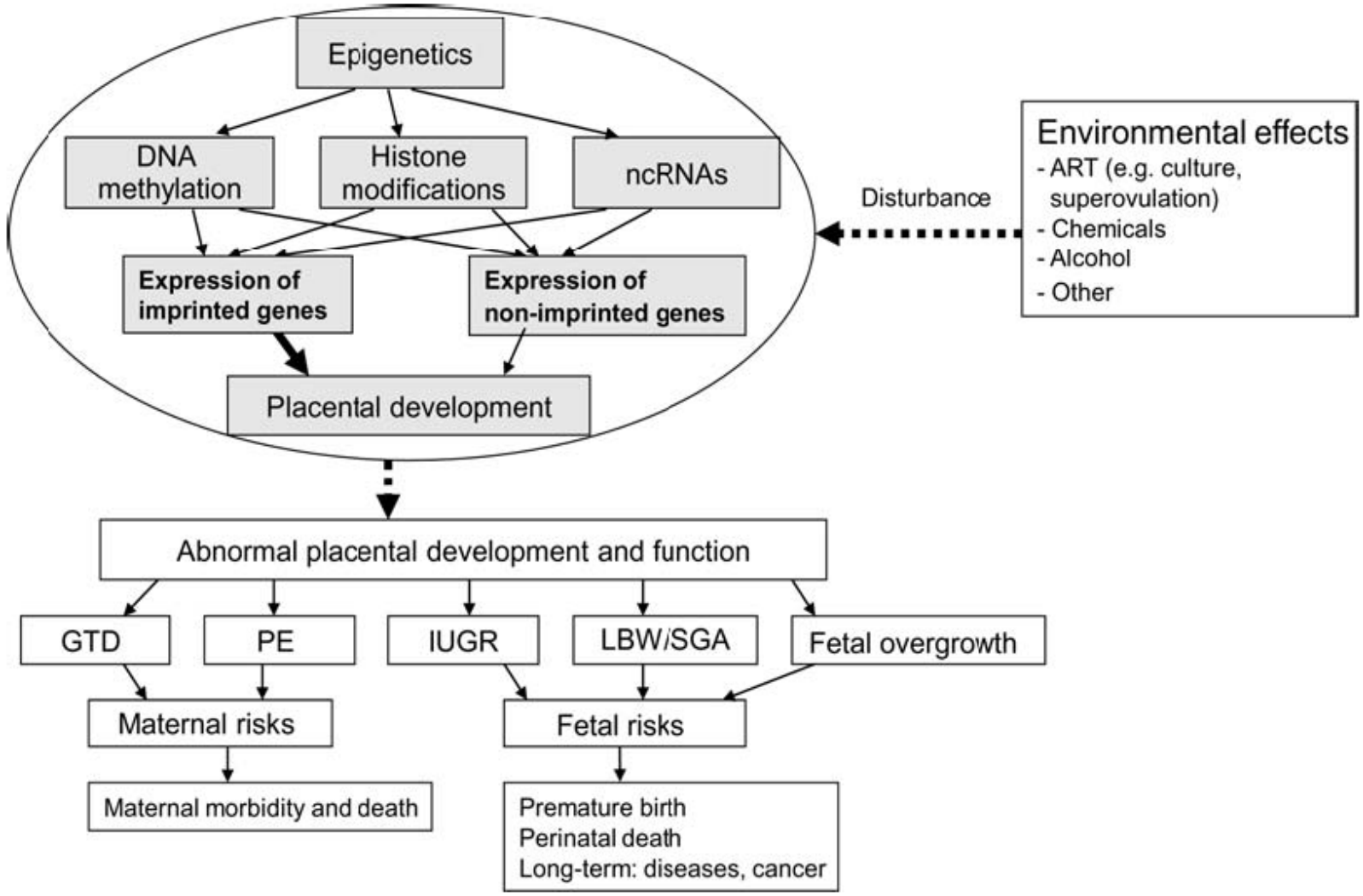
Intergenerational effects and long-term NCD risk

Intergenerational Risk / Burden of NCD

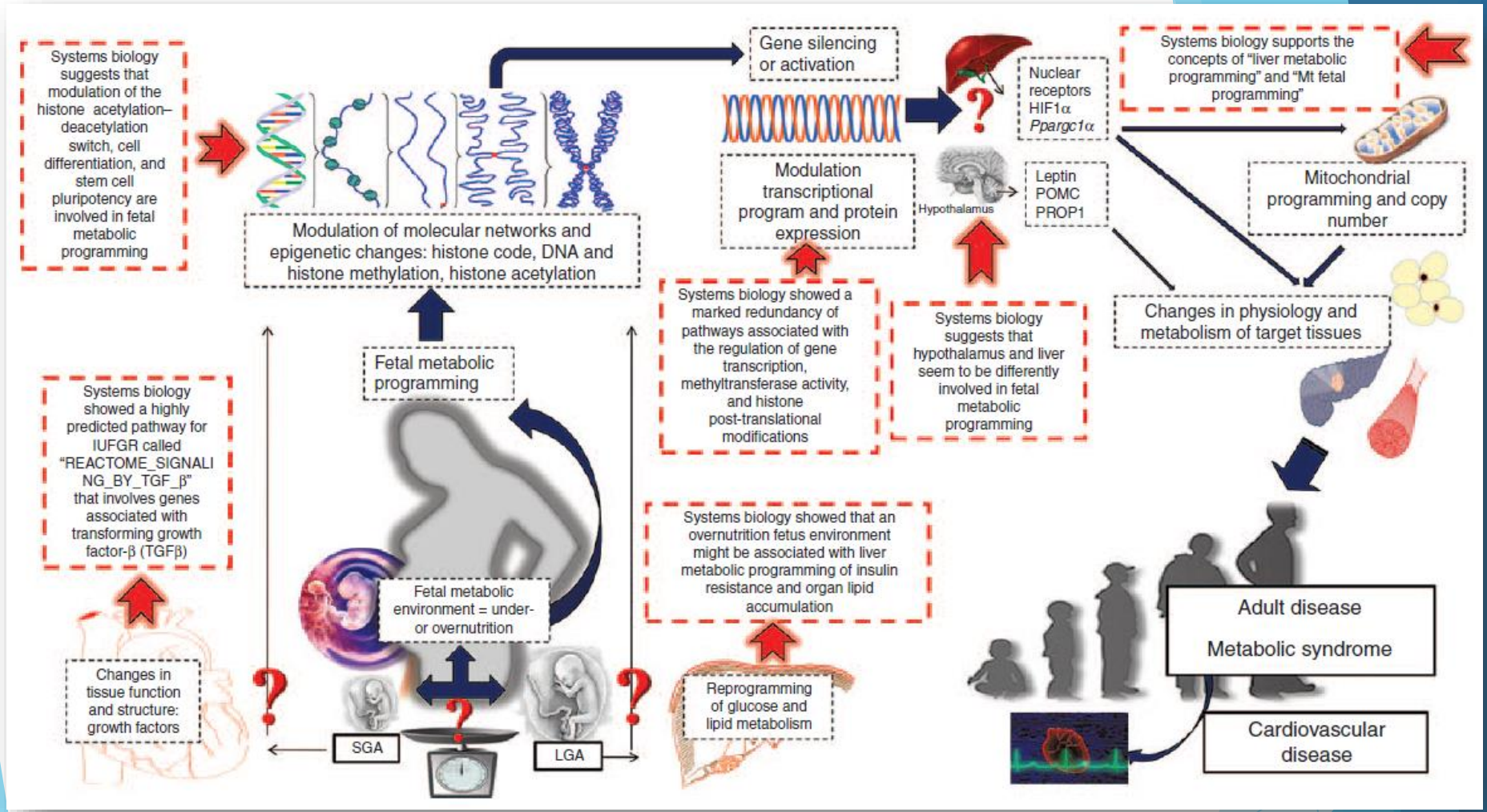
RCW Ma et al, Prog Biophys Mol Biol 2015



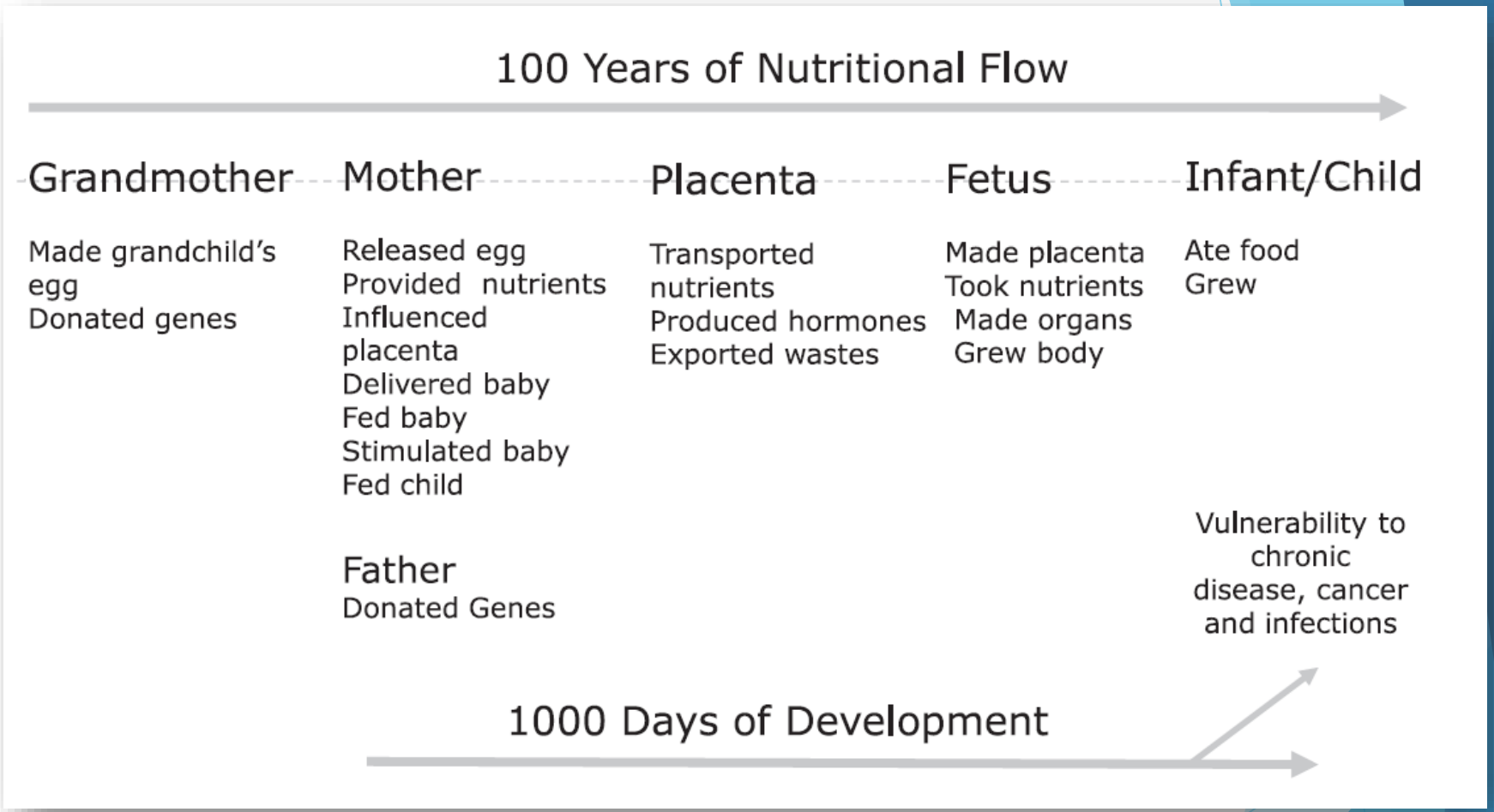
PD Gluckman et al, Am J Hum Biol 2007



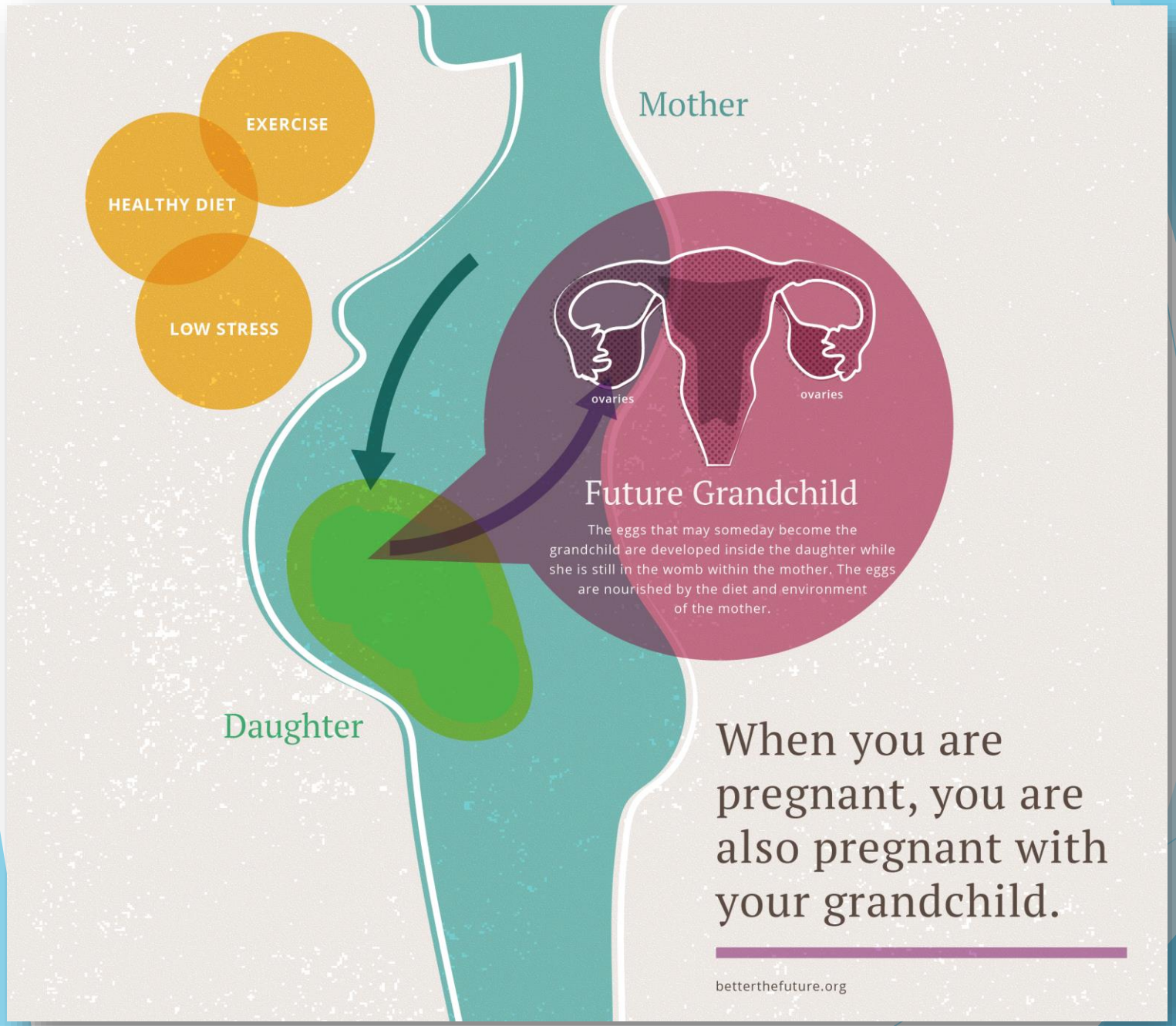
ECM Nelissen et al, Hum Reprod update 2010

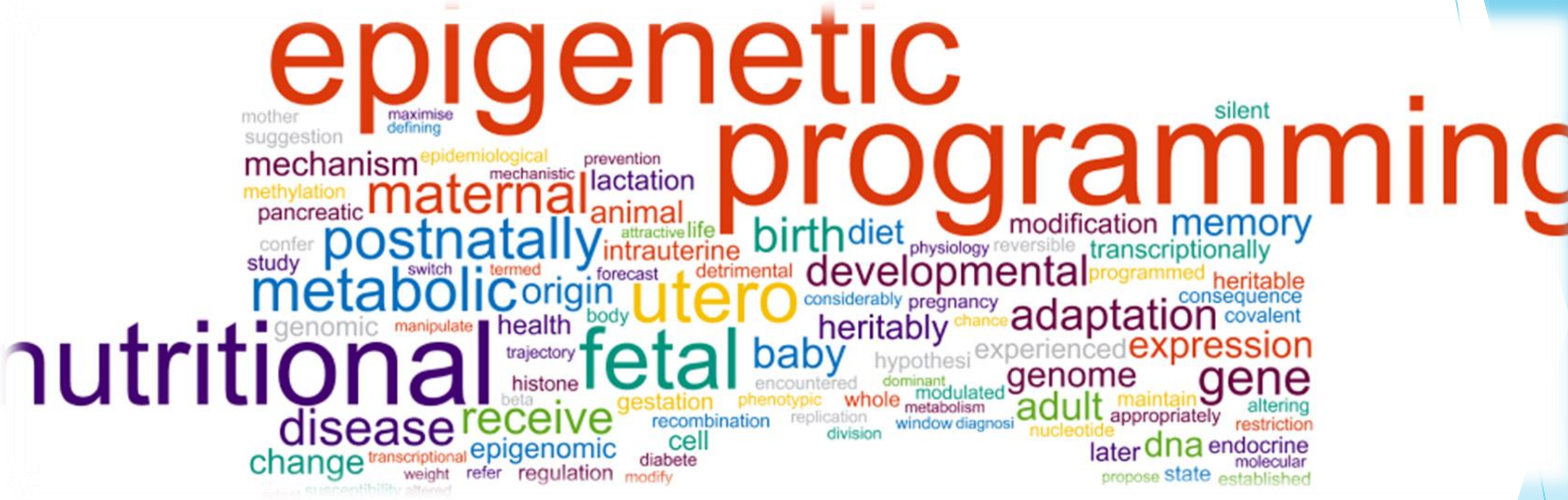


S Sookoian et al, Pediatr Res 2013



DJP Barker et al, Placenta 2012


EXERCISE
HEALTHY DIET
LOW STRESS
Mother
ovaries
ovaries
Future Grandchild
The eggs that may someday become the grandchild are developed inside the daughter while she is still in the womb within the mother. The eggs are nourished by the diet and environment of the mother.
Daughter
When you are pregnant, you are also pregnant with your grandchild.
betterthefuture.org


epigenetic
mother
maximise
defining
suggestion
silent
mechanism
epidemiological
prevention
mechanistic
lactation
methylation
maternal
pancreatic
animal
attractive
life
birth
diet
modification
memory
confer
postnatally
intrauterine
physiology
reversible
transcriptionally
study
switch
termed
forecast
detrimental
developmental
programmed
heritable
metabolic
origin
utero
considerably
pregnancy
consequence
genomic
manipulate
health
body
heritably
chance
adaptation
covalent
trajectory
fetal
baby
hypothesi
experienced
expression
histone
encountered
dominant
genome
gene
beta
gestation
phenotypic
whole
modulated
metabolism
adult
maintain
altering
disease
receive
recombination
replication
division
window
diagnosi
nucleotide
appropriately
restriction
change
transcriptional
epigenomic
cell
diabete
later
dna
endocrine
weight
refer
regulation
modify
molecular
propose
state
established

Grazie!