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NUTBRO NUTRICIÓN Y BROMATOLOGÍA

CENTUM CMM CAMPUS MARE NOSTRUM

www.um.es/nutbro

5th European Nutrition and Dietetics Conference

June 16-18, 2016 Holiday inn Rome- Aurelia, Rome, Italy

Early life nutrition associated with healthy life?

And if not, what to do?

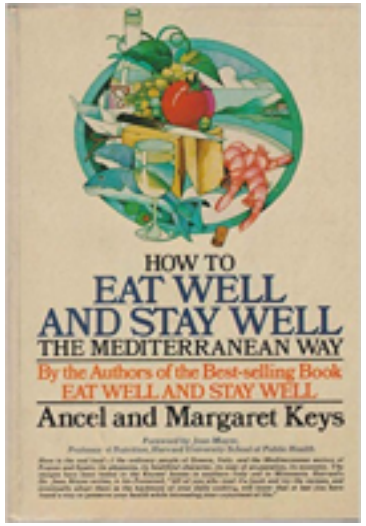
Gaspar Ros Berruezo gros@um.es

Prof. Human Nutrition & Food Science

University of Murcia



Early life nutrition associated with healthy life?

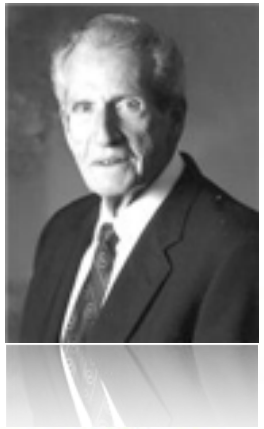


1975

Ancle Keys



Joseph W. Voegtlin



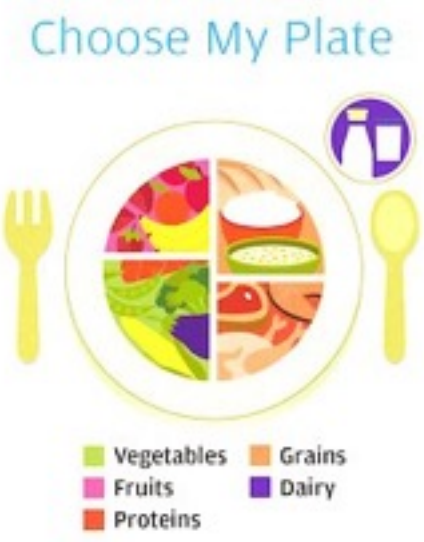


1975

Loren Cordain

2010









OLDWAYS
HEALTH THROUGH HERITAGE

Mediterranean Diet Pyramid

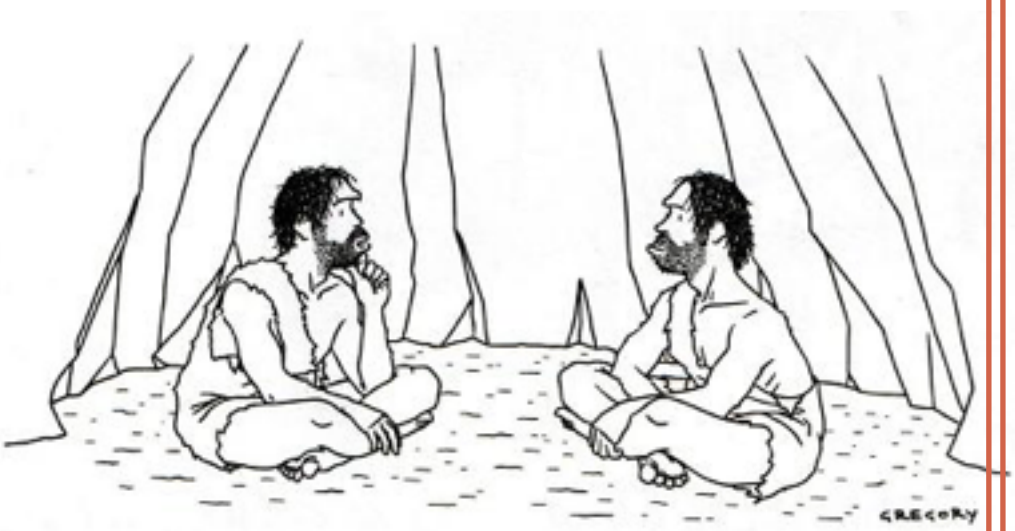


MEDITERRANEAN FOODS ALLIANCE



THE PALEO DIET FOOD PYRAMID



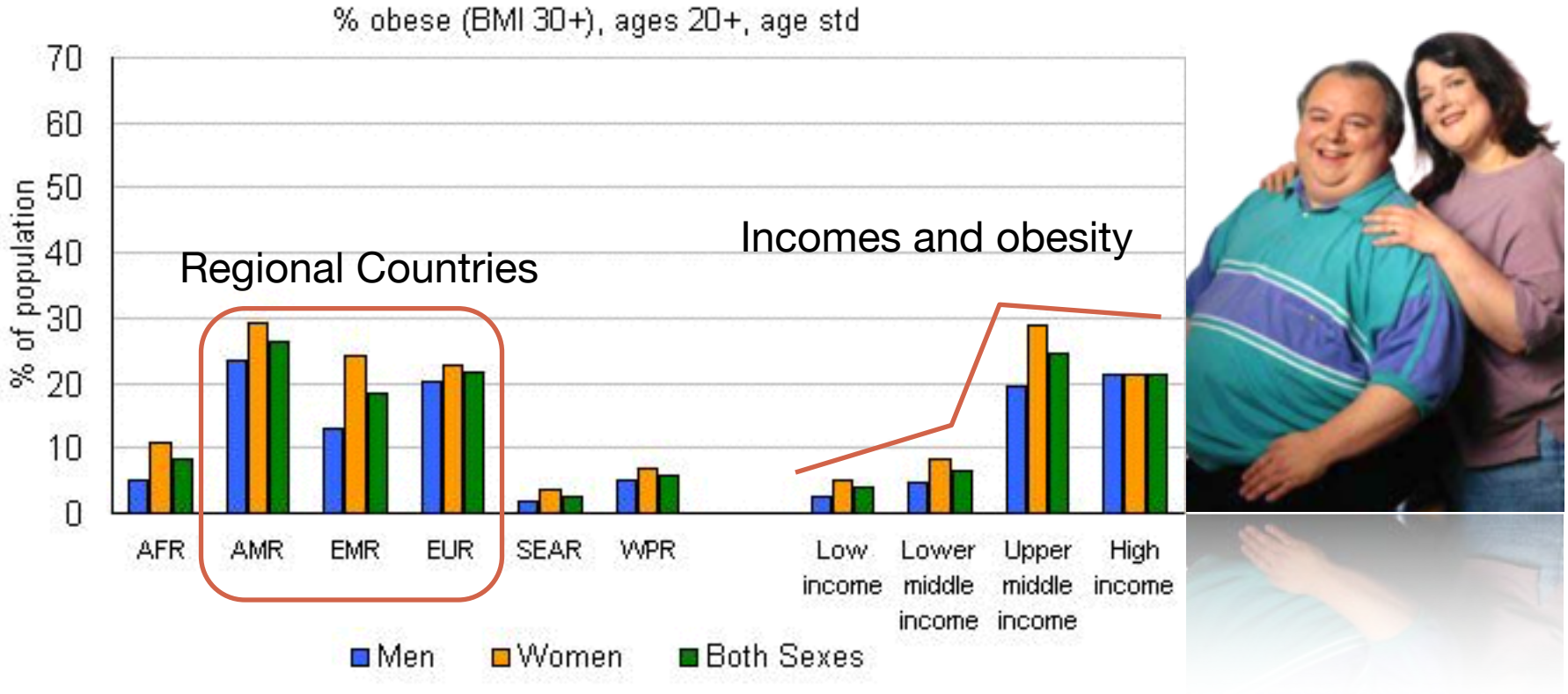


"Something's just not right—our air is clean, our water is pure, we all get plenty of exercise, everything we eat is organic and free-range, and yet nobody lives past thirty."



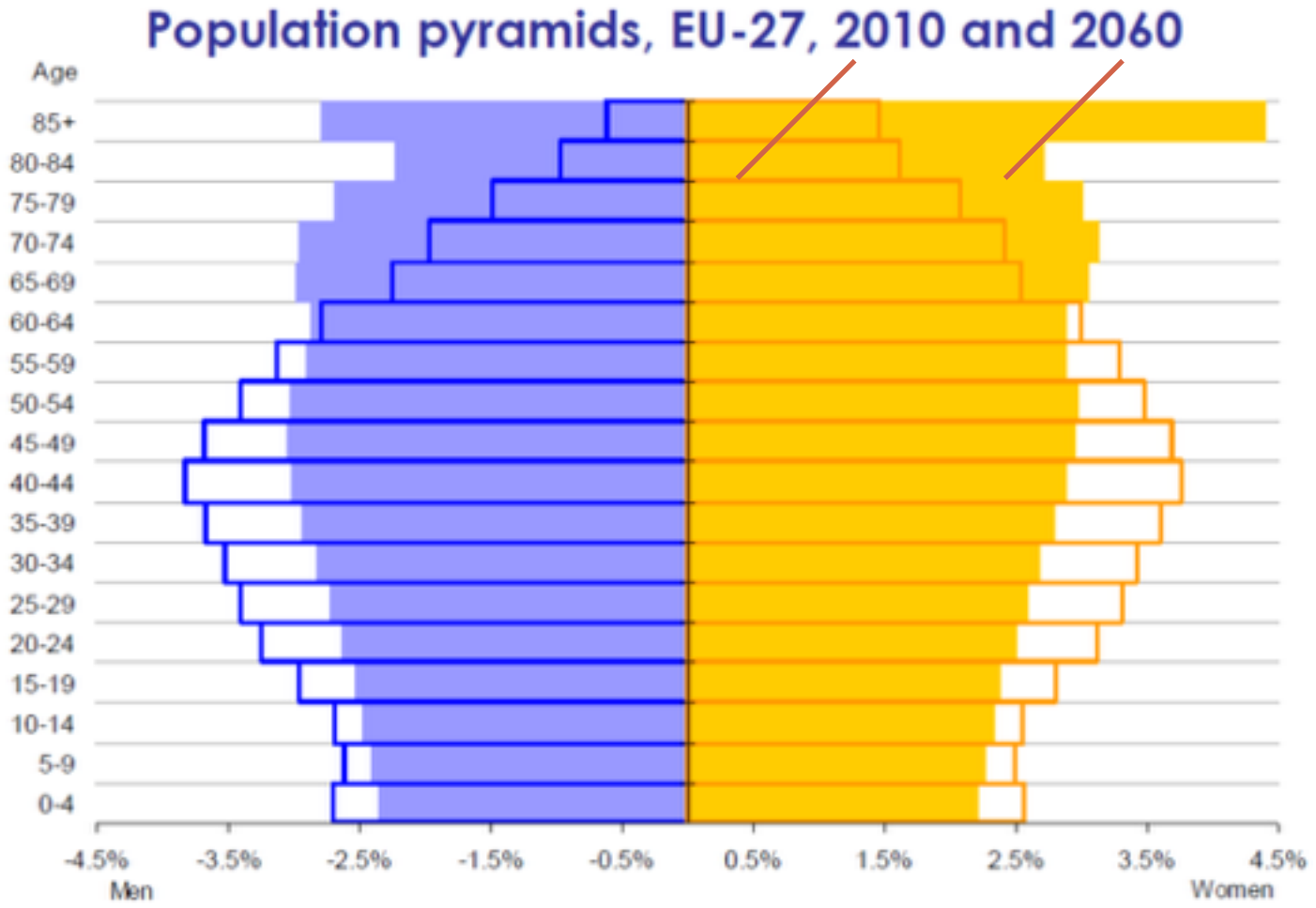
"The 'Humungo Meal' comes with your choice of 2 sides...heart disease, high blood pressure, diabetes or obesity."

search ID: mbcn2649



AFR= Africa; AMR=Americas; EMP= Eastern Mediterranean; EUR= Europe; SEAR= South-East Asia; WPR= Western Pacific

Demographic change needs early prevention for



- But people still struggle to find the right balance between energy intake and energy expenditure.
- The public is looking for disease preventing and health promoting foods and beverages that match their lifestyles, cultures and genetics.
- Evidence for the trans-generational impact of epigenetics on health is beginning to emerge.
- Nutritional genomics is providing new insights into diet-genome interactions that will enable us to achieve optimal health and well-being earlier, and maintain it longer.

Early programming:

an established concept in biology

Behavioural programming

Hatching geese accept first moving object as “parent“.

Konrad Lorenz 1952



Metabolic programming

Metabolic and nutritional factors acting during limited, sensitive time periods of early development induce lasting effects on physiology, function, health and disease risks



Early programming:

an established concept in biology

Metabolic programming

- Undernutrition of animals at early, but not at later ages, determines adult body size

Elsie Widdowson & McCance, Cambridge 1970

- Programming of human adult functions and diseases by hormones, metabolites and neuro-transmitters during critical development periods

Günther Dörner, Berlin, Germany 1975

- Programming by early nutrition in man

Alan Lucas, Cambridge, UK 1991

- Fetal Programming of adult disease by poor fetal nutrition and low birth weight

Nick Hales, David Barker, Oxford, Southampton, UK 1986

***The Fetal Origins (formerly the Barker) Hypothesis**: Fetal environmental exposures, especially nutrition, can directly affect embryonic development and "program" the child for adult health outcomes. D. Barker, 1986*

Developmental Origins of Health and Disease (DOHaD)



Dutch Famine, 1944-45: 18 thousand dead

Chinese Famine, 1959-60: 20-40 million dead

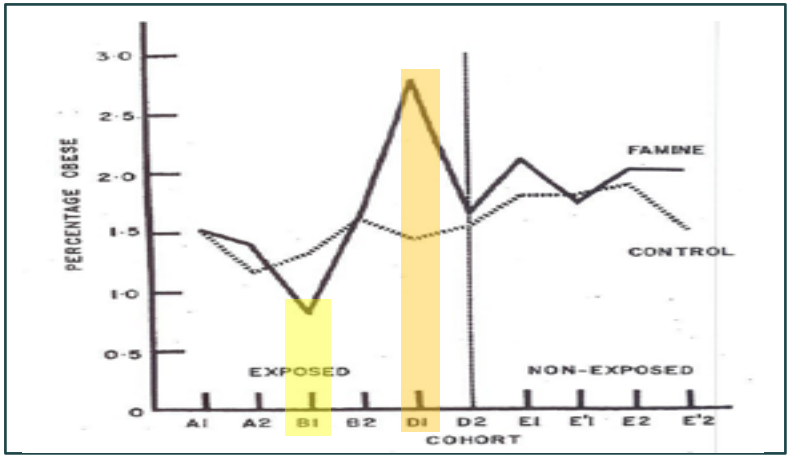
Dutch Famine

- During the Dutch Famine, the average caloric intake for an adult was about 400 – 800 calories, compared to 1800 calories before the famine.
- People who were in early gestation (**exposure in first 2 trimesters)** during the Dutch Famine showed a higher risk of obesity (80% higher prevalence of overweight ($p<0.0005$)), higher levels of lipids in the bloodstream, 3-fold higher risk of cardiovascular disease than people who were not exposed to the famine.
- Cohort B1: Conceived and gestated at time of moderate caloric restriction, Born into time of famine, Low rates of adult obesity
- Cohort D1: Conceived and gestated at a time of famine, Born into food sufficiency, High rates of adult obesity

Ravelli et al (1976) NEJM

Roseboom et al. (2001) Mol. & Cell. Endocrinol; 93-98

Obesity in Young Men after Famine Exposure in Utero and early Infancy





What does this mean for us?

- Further proof of relevance of nutrition during pregnancy

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Healthy Birthweight = Healthy Life

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"Birthweight is a strong indicator not only of a birth mother's health and nutritional status but also a newborn's chances for survival, growth, long-term health and psychosocial development."

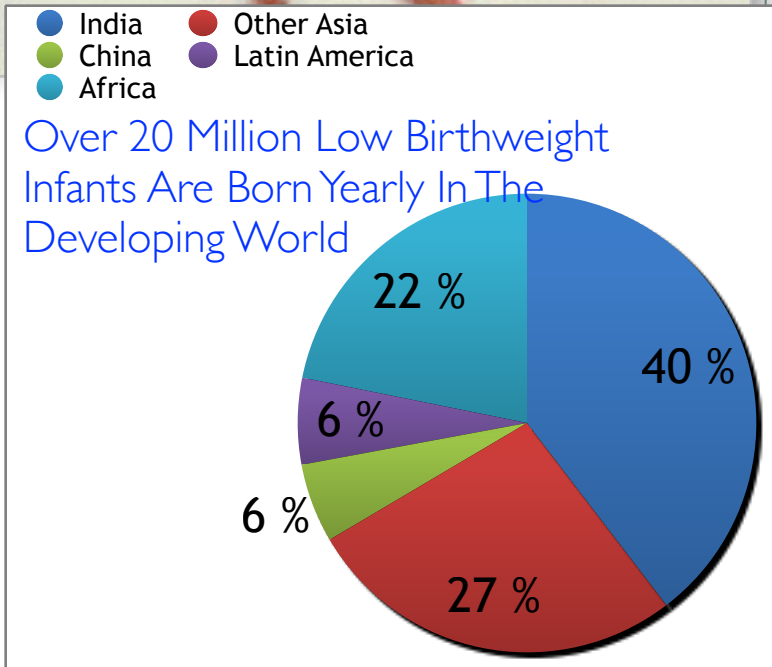
- UNICEF



Low Birthweight (LBW)

- Definition: birthweight <2500 g (5.5 lbs)
- Low birthweight babies are more than 20 times likely to die during infancy than heavier babies.

Over 20 Million Low Birthweight Infants Are Born Yearly In The Developing World

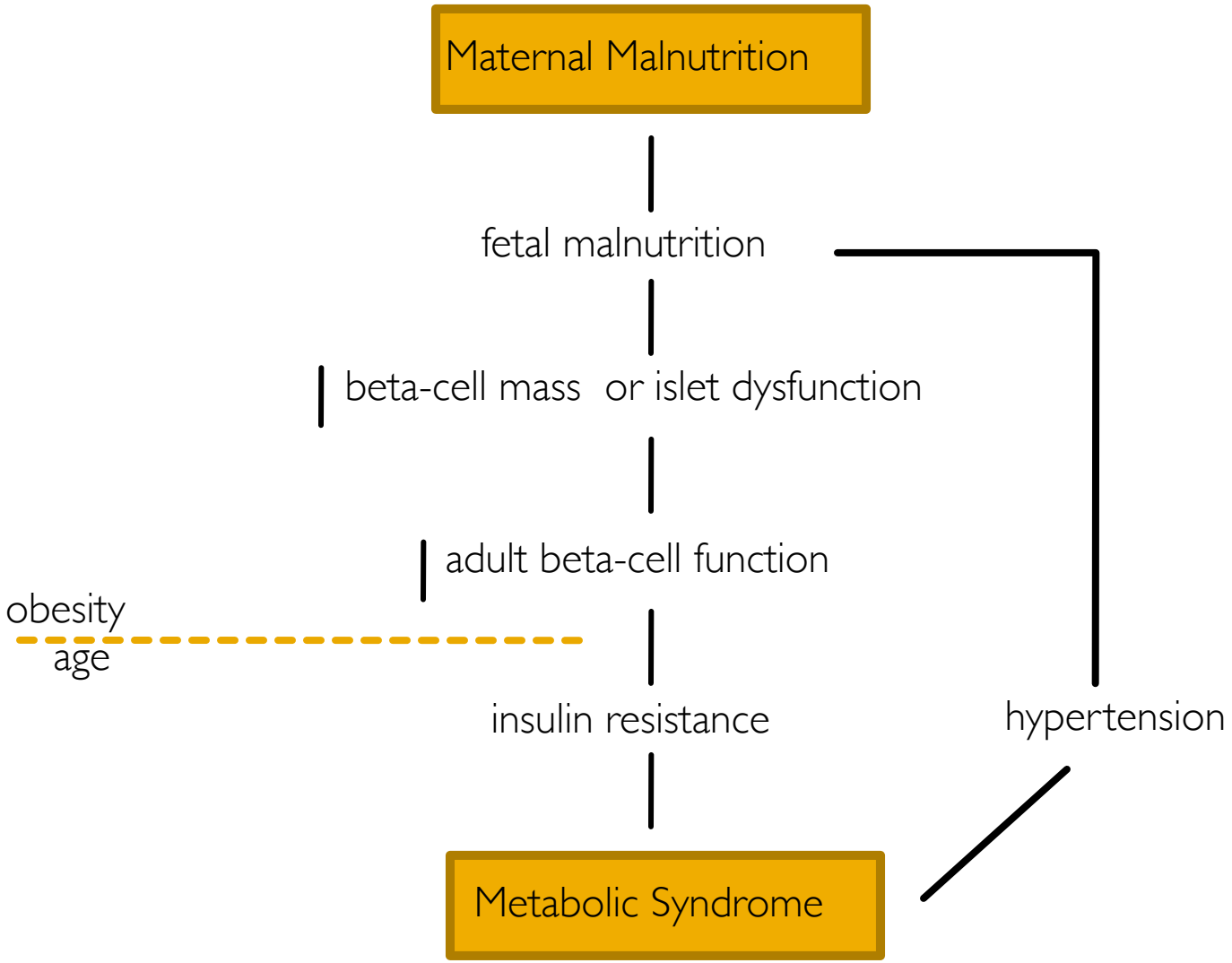


Fetal Programming

Stimulus



Adaptation


Maternal Malnutrition
fetal malnutrition
beta-cell mass or islet dysfunction
adult beta-cell function
obesity
age
insulin resistance
hypertension
Metabolic Syndrome

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Predictive Adaptive Response

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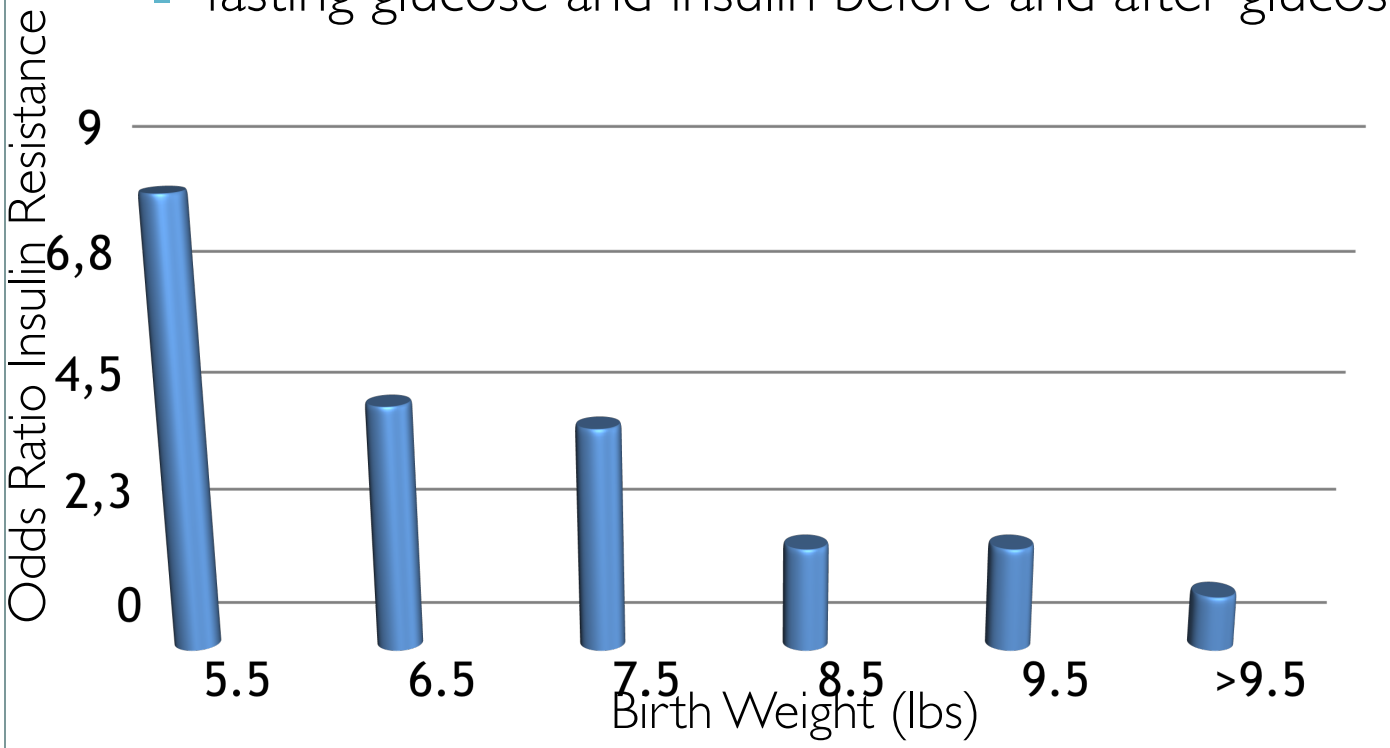
FETAL ENVIRONMENT	POSTNATAL ENVIRONMENT	ADULT HEALTH



- Adequate Nutrition
  - Adequate Nutrition → HEALTHY
  - Poor Nutrition → MALNOURISHED
- Poor Nutrition
  - Adequate Nutrition → METABOLIC SYNDROME
  - Poor Nutrition → MALNOURISHED

Hertfordshire Studies: Insulin Resistance

- Published in early 1990s (Hales, Barker et al.)
- 468 men born in Hertfordshire 1920-1930 and still living there
- Birthweights recorded
- Tests for insulin resistance performed:
  - fasting glucose and insulin before and after glucose drink

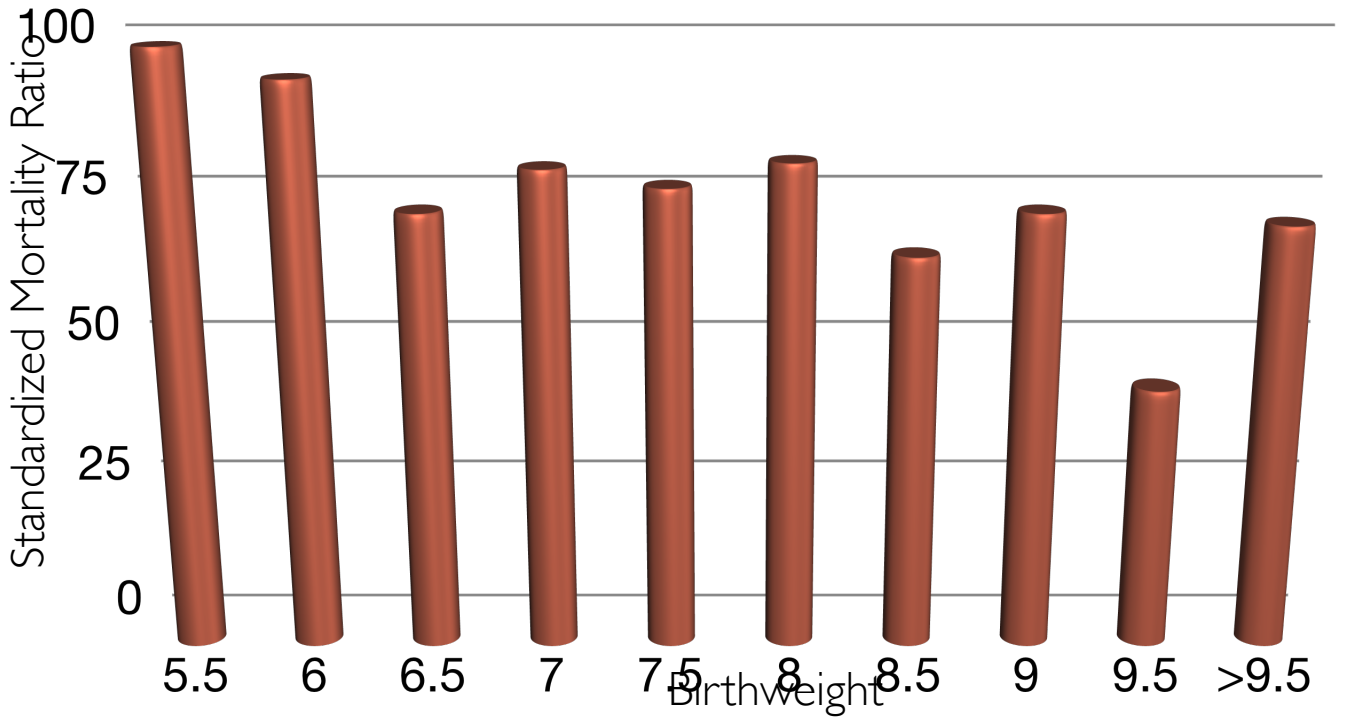


Low Birthweight Increases Risk of Insulin Resistance in Adulthood

Hales CN et al. BMJ 1991; 303:1019-22

Sheffield Study: Cardiovascular Mortality

- 5585 men and 10,141 women born in Sheffield, UK 1911-1930.
- **Low birthweight** infants had higher risk of coronary artery disease in adulthood



- Similar trends in risk for hypertension and type 2 diabetes

Osmond et al. BMJ 1993

Nutrition like shoes, clothes,… —

one size does not fit all.



You are what you eat.

You are what your mother ate.

You are what your grandmother ate.

You are what your microbiome ate.

Nutrition in early life of greater importance than at any other time in life

Rapid growth,

nutrient needs/kg,

body stores

Nutrition affects development, structure & function

First months: one food must cover all needs

Important consequences short term

(*e.g. growth, infections)* and

long term

(e.g. brain function, mental and physical performance, risk of obesity & associated disorders)



First 1000 days: developmental programming of adult health

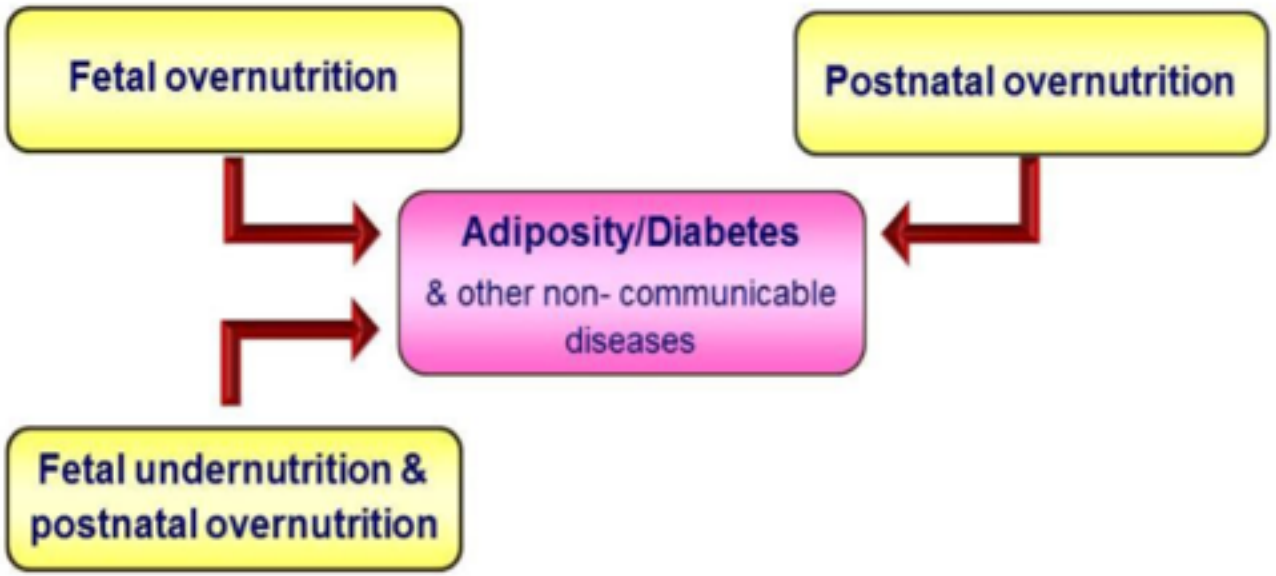
During limited time periods of early developmental plasticity, nutrition and other factors induce lasting effects on physiology, function, health and disease risks .



Programming of obesity & assoc. diseases

EARLYNUTRITION
Long-term effects of early nutrition on later health

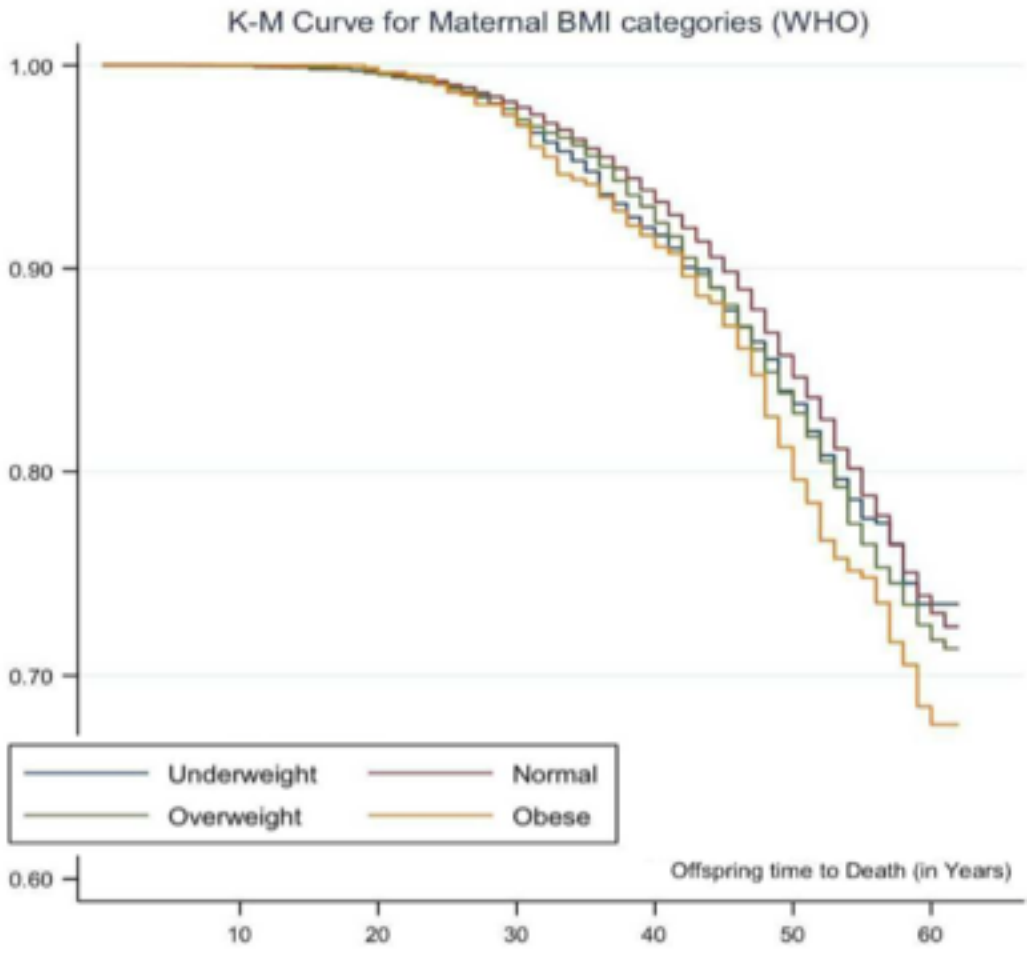
Long term effects of early nutrition on later health (2012-2017) FP7-289346-*EarlyNutrition*



Koletzko B et al. The Power of Programming..., Ann Nutr Metab 2014;64:141-50.

Maternal obesity in pregnancy and premature offspring mortality from CVD

37 709 Scottish people with birth records from 1950, follow-up of 1 323 275 person years

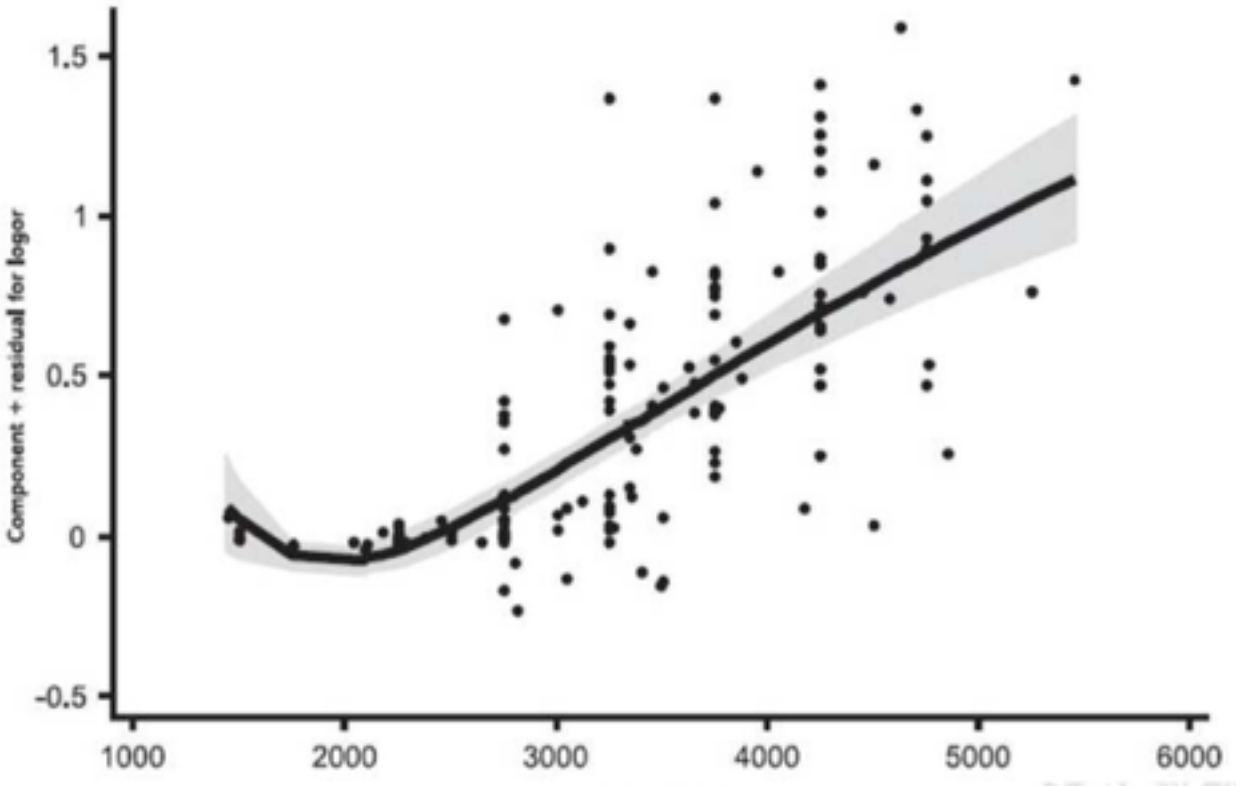


EARLYNUTRITION

Reynolds et al, BMJ 2013 Systematic review & meta-analysis

Birthweight predicts later overweight

66 studies, >640 000 subjects 1-75 J., 26 countries, 5 continents



EARLYNUTRITION

Schellong et al. PLoS One 2012;7(10)e47776.

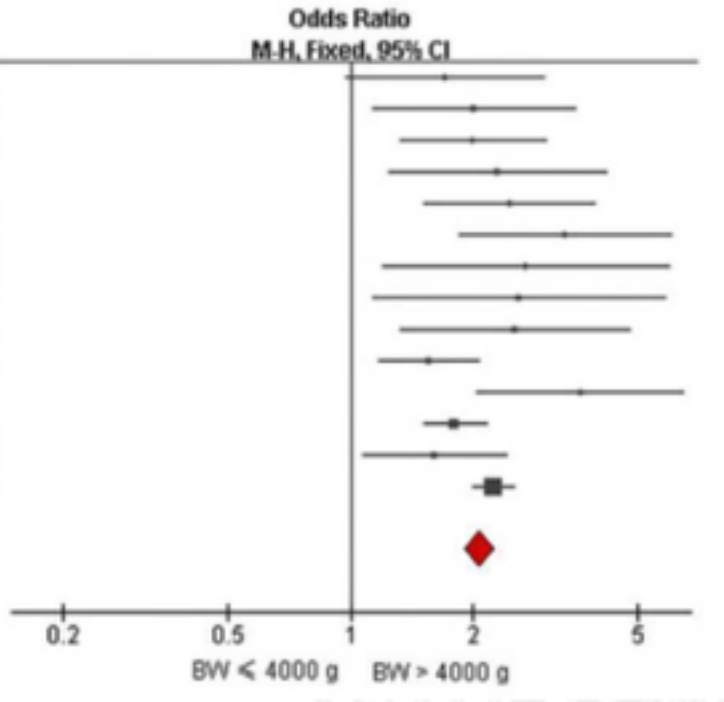
Birthweight >4 kg doubles: 2x adult obesity

Systematic review & meta-analysis

Study or Subgroup	BW > 4000 g Events	Total	BW ⩽ 4000 g Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Che 2010	16	142	106	1526	2.2%	1.70 [0.98, 2.97]
Gu 2003	16	163	69	1336	1.9%	2.00 [1.13, 3.53]
He (a) 2000	74	114	388	805	4.7%	1.99 [1.32, 2.99]
He (b) 2005	14	143	57	1256	1.5%	2.28 [1.24, 4.21]
Hirschler 2008	28	95	136	932	2.5%	2.45 [1.52, 3.94]
Li 2007	36	141	20	214	1.6%	3.33 [1.83, 6.04]
Lu 2008	8	52	52	819	0.7%	2.68 [1.20, 5.99]
Mao 2007	21	30	115	242	1.1%	2.58 [1.13, 5.85]
Monteiro 2003	13	81	70	992	1.2%	2.52 [1.33, 4.78]
Ruan 2009	82	260	488	2135	10.0%	1.55 [1.17, 2.06]
Shi 2007	54	75	80	193	1.7%	3.63 [2.03, 6.49]
Wang 2009	179	1537	640	9360	22.0%	1.80 [1.51, 2.14]
Yang 2009	72	120	290	601	5.3%	1.61 [1.08, 2.40]
Zhang 2009	456	1977	1642	13875	43.6%	2.23 [1.99, 2.51]
Total (95% CI)		**4930**		**34286**	**100.0%**	**2.07 [1.91, 2.24]**
Total events	1069		4153			

Heterogeneity: Chi² = 17.87, df = 13 (P = 0.16); I² = 27%

Test for overall effect: Z = 17.75 (P < 0.00001)



EARLYNUTRITION

Yu et al. Obes Rev. 2011;12:525-42. doi: 10.1111/j.1467-789X.2011.00867

Limit milk protein supply in infancy

Breastfeeding reduces later obesity risk **promote, protect & support breastfeeding**

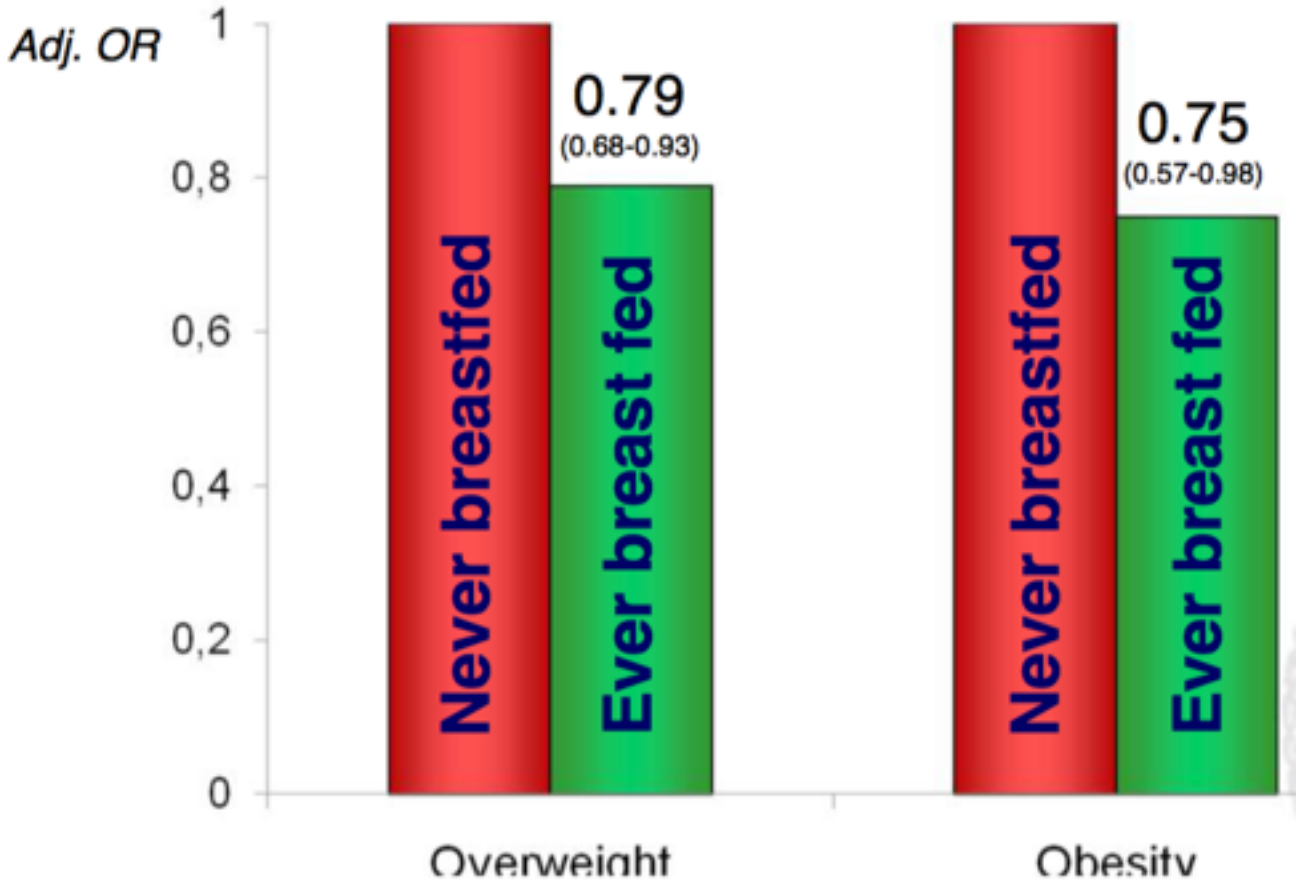
Avoid high protein supply
Infants not (fully) breast fed**: infant formula**

with reduced protein, but high protein quality
All infants: **no cows‘ milk/animal milk as a drink**

in infancy if feasible and affordable

Breast feeding less overweight & obesity in >9000 children at school entry

(Bavaria, Germany)



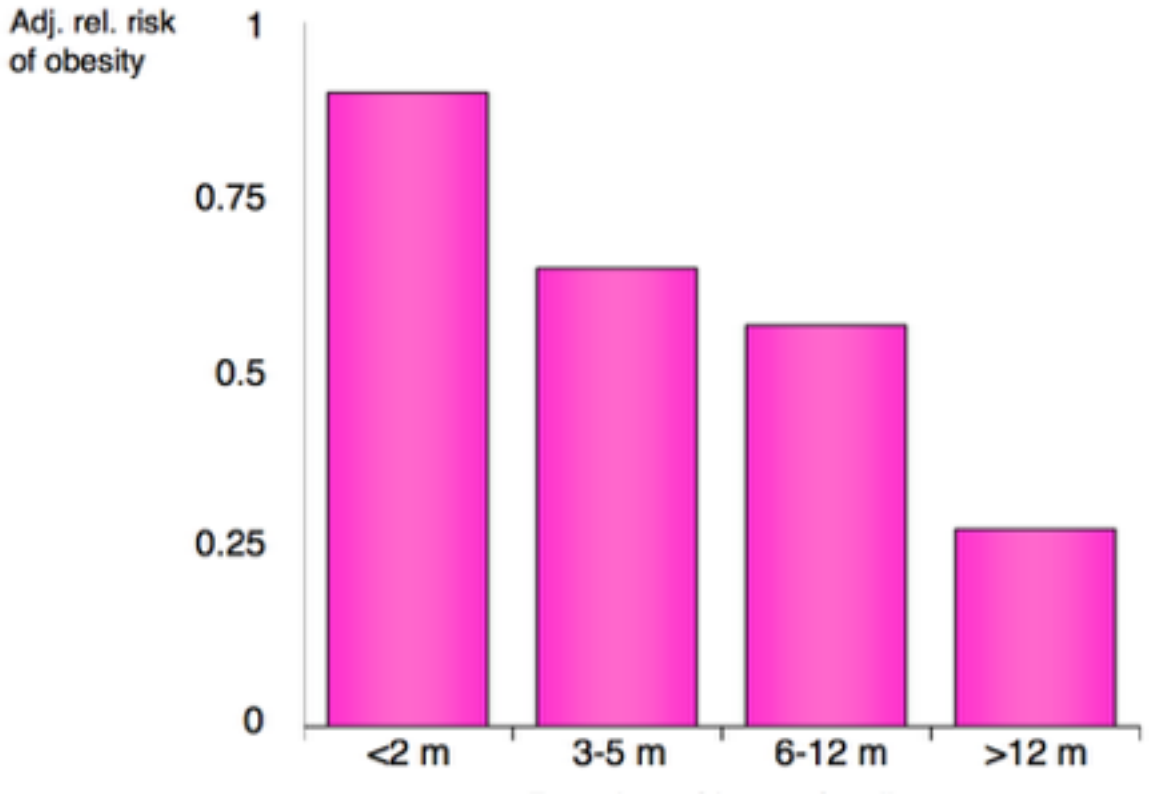
EARLYNUTRITION

v. Kries et al. Brit Med J 1999,319:147-50. Koletzko et al. Ann Nutr Metab 2014;65:99–107

Longer breastfeeding less obesity

in >9000 children at school entry

(Bavaria, Germany)



Meta-analyses of observational studies agree: consistent protection by breastfeeding

- 2004: 22% obesity Arenz S et al. Int J Obes Relat Metab Disord 2004; 28:1247–56.
- 2012: 15% obesity Weng S et al. Arch Dis Child 2012;97:1019–1026.
- 2013: 24% obesity Horta BL, Victora CG. WHO Syst Rev. 2013.
- 2014: 22% obesity *Yan J et al. BMC Public Health 2014, 14:1267.*

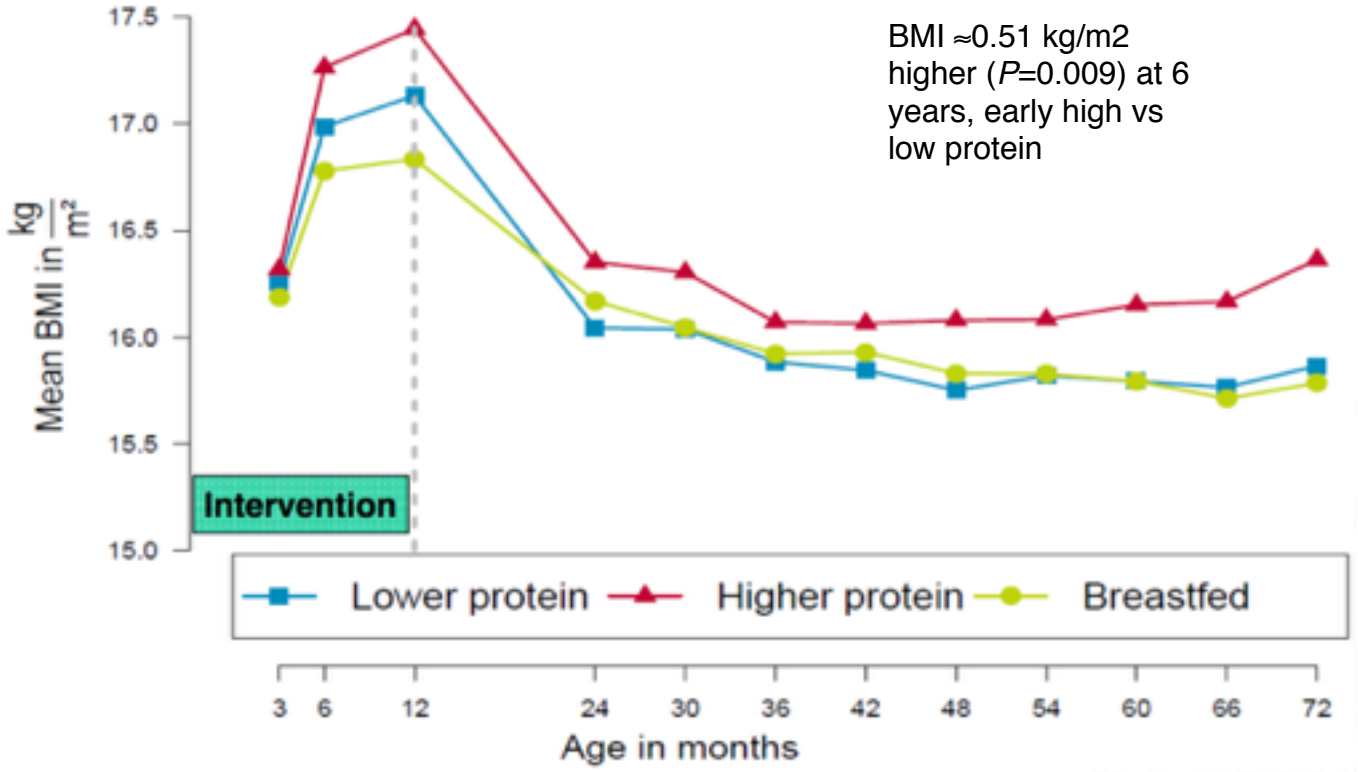
EARLYNUTRITION

v. Kries et al. Brit Med J 1999,319:147-50. Koletzko et al. Ann Nutr Metab 2014;65:99–107

Early Protein Hypothesis

Excessive protein intake in infancy promotes high early weight gain and later obesity.

Infant diet and BMI until early school age



EARLYNUTRITION

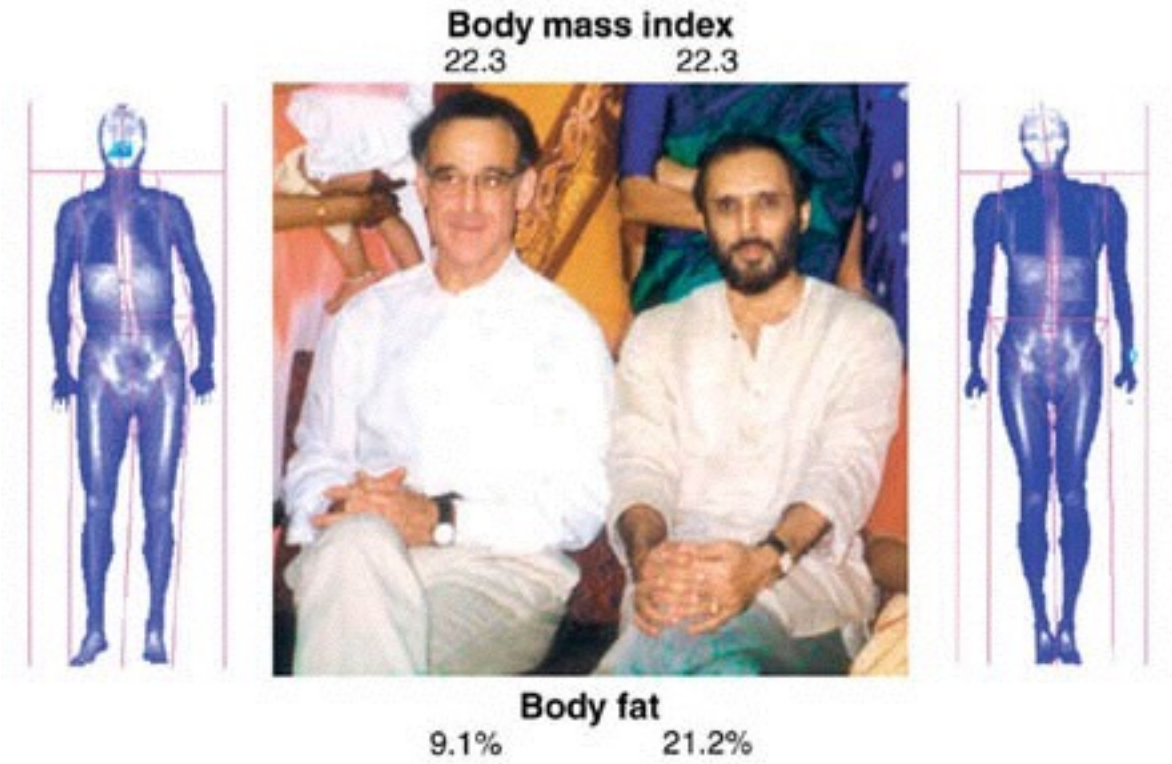
Weber et al, Am J Clin Nutr 2014.

Yajnik - India's Diabetes Paradox & the Thin-Fat Indian



↑ prevalence of diabetes in Rural Indians
↑ prevalence of LBW in India
LBW = more insulin resistance
The Thin fat indian phenotype
Related to Nutrition in Preganancy





Yajnik (1995) Diabet Med 12:330–336,
Yajnik et al. (2002) JCEM 87 (12): 5575
Yajnik & Yudkin (2004) The Lancet 363
Yajnik et al (2008). Diabetologia (51):29-38

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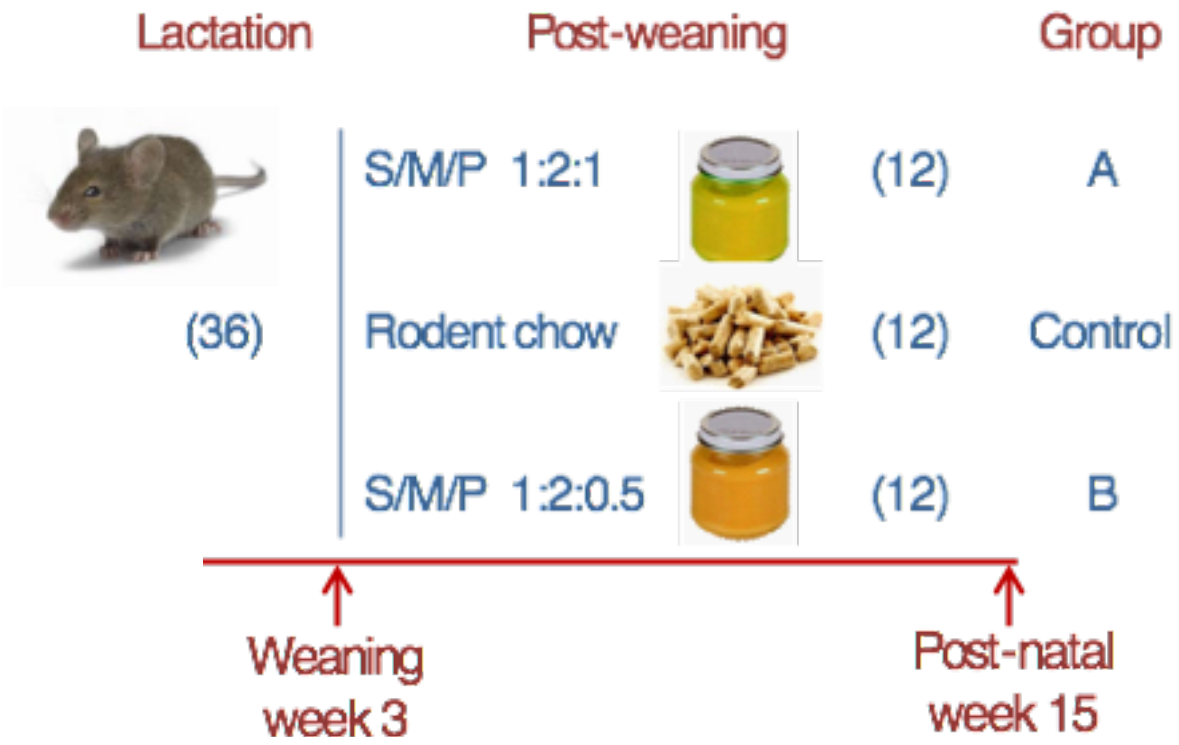
8-9 October 2015 Cesena-Italy 4th Foodomics International Conference

5th European Nutrition and Dietetics Conference

OBESITY: Omic Expression In Mice In Lipid Tissue Fed With Two Homogenized Baby Foods With High and Low Protein and Fat Contents and Profiles.

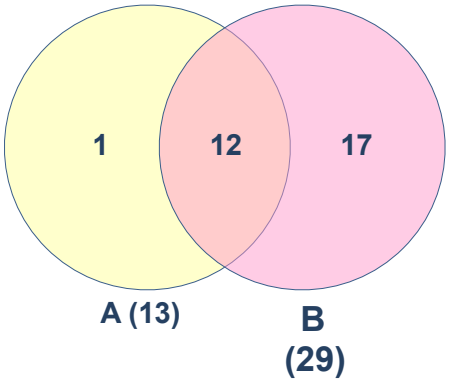
E. Sánchez-Samper, M.J. Bernal, C. Gómez-Gallego and G. Ros

Thirty-six weaned C57BL/6J mice were randomly separated in three different experimental groups for a 12-week intervention groups. The groups were divided into group **"A" fed with homogenized baby food which profile was: 67 kcal per 100 g, 3.6% proteins, 2.7% fat and a fatty acids profile 1:2:1; (S/M/P), and group "B" which baby food profile was 87 kcal for 100 g, 4.2% proteins, 2.9% fat, and a fatty acids profile 1:2:0.5 (S/M/P); and a group "C" (control group) fed with rodent chow** (*"14% Protein Rodent Maintenance Diet"*, Harland). All groups had free access to rodent chow to avoid deficiencies in micronutrients. A and B groups developed overweight compared with C. At the end of the study, samples of **epididymal lipid tissu**e were collected and expression of **84 genes** related to obesity was analyzed by qPCR array (*Qiagen, Cat. No. PAMM 017Z*).



Experimental design.

Gene expression and cluster diagram showing genes that were up- or down-regulated in **epididymal lipid tissue**. Similar expression profiles are grouped together to form a clustering tree. The colour map represents the normalized intensity values (normalized to the median of all samples) if the genes (rows), where red and green represent the up- and down-regulated genes, respectively.



Venn diagram. Relations between genes with significant differences

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Fold regulation on obesity-related genes in A and B groups comparing with control group. The table represents only genes with fold differences minor than -1.5 and higher than 1.5 with significant differences ($p<0.05$).

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Gene	Gene description	B	A	General function
Adra2b	Adrenergic receptor, α2b	-2.03		Orexigenic receptors
Oprk1	Opioid receptor, κ1	-3.05	-2.03	
Oprm1	Opioid receptor, μ1	-2.92	-6.24	
Sigmar1	Sigma non-opioid intracellular receptor 1	-6.33	-2.69	
Ghrl	Ghrelin	-2.07		Orexigenic gut hormone
Nmb	Neuromedin B	-2.74		
Ucn	Urocortin	-2.07	-2	
Sort1	Sortilin 1	-2.89		
Trh	Thyrotropin releasing hormone	-1.24		Anorectic neuropetides and receptors
Hrh1	Histamine receptor H1	-2.90	-2.59	
Htr2c	5-hydroxytryptamine (serotonin) receptor	-1.89		
Il6ra	Interleukin 6 receptor, α	-3.20		
Nmur1	Neuromedin U receptor 1	-2.77	-3.12	
Ntrk2	Neurotrophic tyrosine kinase, receptor, type 2	-8.73	-3.13	
Prlhr	Prolactin releasing hormone receptor	-2.39	-4.64	
Apoa4	Apolipoprotein A-IV	-4.16	-3.30	Anorectic gut hormone
Iapp	Islet amyloid polypeptide		-2.70	
Ramp3	Receptor (calcitonin) activity modifying protein 3	-3.46	-2.88	
Sst	Somatostatin	-2.07	-4.06	Anorectic Pancrease Derived Peptides Receptors
Sstr2	Somatostatin receptor 2	-3.85	-3.41	
Gcgr	Glucagon receptor	-3.16		
Insr	Insulin receptor	-2.63		
Adrb1	Adrenergic receptor, β1	-2.48		
C3	Complement component 3	-2.96		
Ptpn1	Protein tyrosine phosphatase, non-receptor type 1	-3.76		
Adipor1	Adiponectin receptor 1	-2.07		
Ppara	Peroxisome proliferator-activated receptor α	-2.95		
Ppargc1a	Peroxisome proliferative activated receptor γ, coactivator 1α	-2.03		
Cpd	Carboxipeptidase D	-3.08		
Thrb	Thyroid hormone receptor β	-3.18		

Adipocyte-derived Peptides and Receptors

CNS-derived Peptide and Receptor

Genes Related to Energy Expenditure

These **underexpressed** genes are involved in the regulation of energy intake and expenditure. Theses genes incode for orexigenic peptides, hormones and receptors; anorectic peptides, hormones and receptors; and central and peripheral signaling molecules involved in energy expenditure.

CONCLUSION:

Our results suggest that the intake of homogenized baby food with the highest fat and protein percentage produces down-regulation of larger number of genes. Such an effect should be further studied in human infants to learn more about the composition of beikost on early programming.



And if not, what to do?







First 1000 days: developmental programming of adult health

During limited time periods of early developmental plasticity, nutrition and other factors induce lasting effects on physiology, function, health and disease risks .

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Comisión Europea

Aprender Juntos

5th European Nutrition and Dietetics Conference



Comprar Juntos

Cocinar Juntos

Comer Juntos

Moverse Juntos

Programming:
some potential mechanisms

- Epigenetic modification
- Cell number ⇒ metabolic differentiation
- *Chromatin structure eu-/heterochromatin*
- *DNA binding proteins*
- Apoptosis
- Hepatocyte polyploidization
- Clonal selection
- Cell size cause or effect?
- Organ structure *e.g. cell juxtaposition*
- Body size & tissue composition
- Tissue vascularization
- Endocrine regulation

➢ *Epigenetics (soft inheritance)*: The ability to change gene activity — *without changing gene sequence (no mutations involved)*.

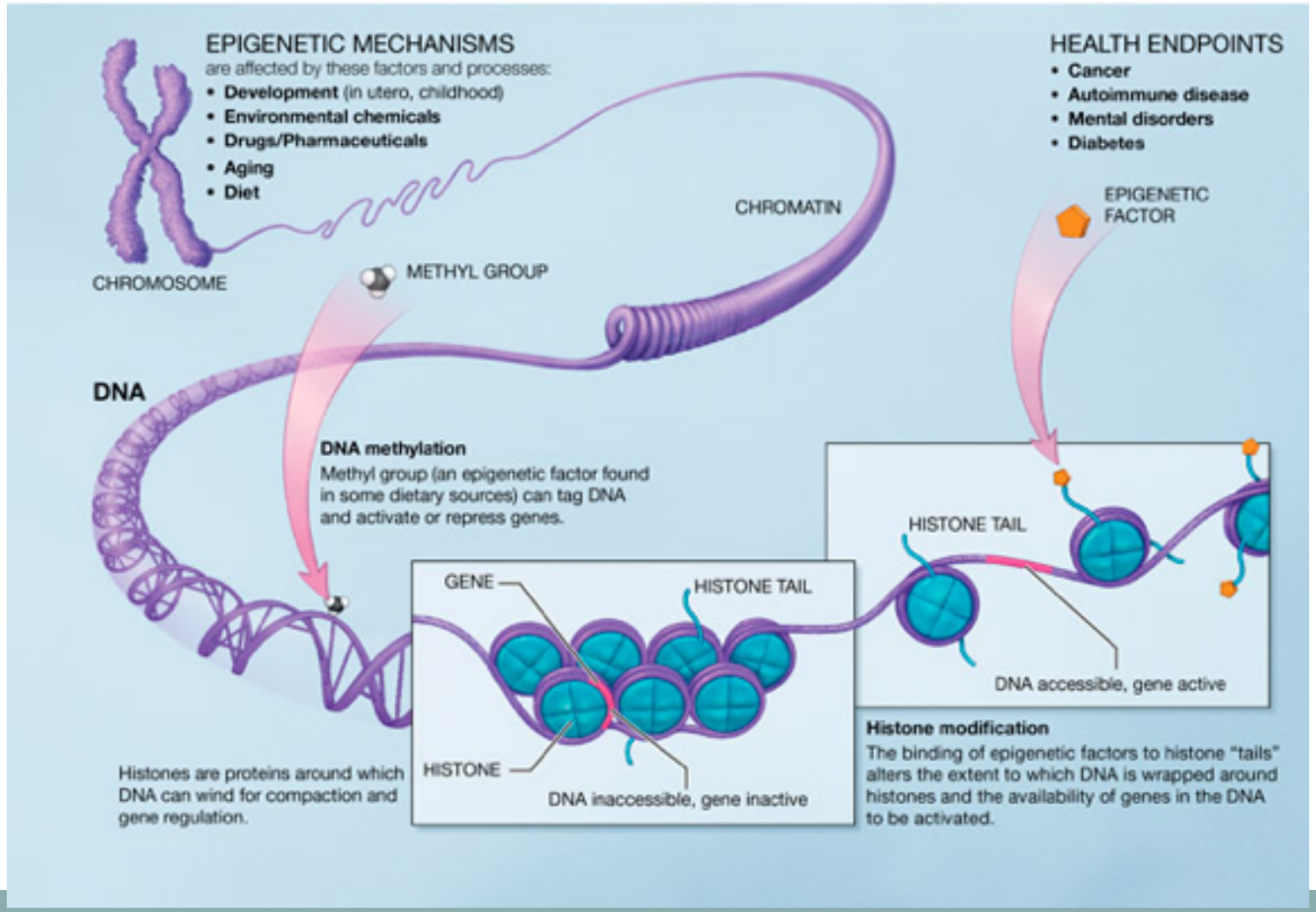
➢ Typical epigenetic affects include DNA methylation (gene silencing) and Histone acetylation (gene activation)

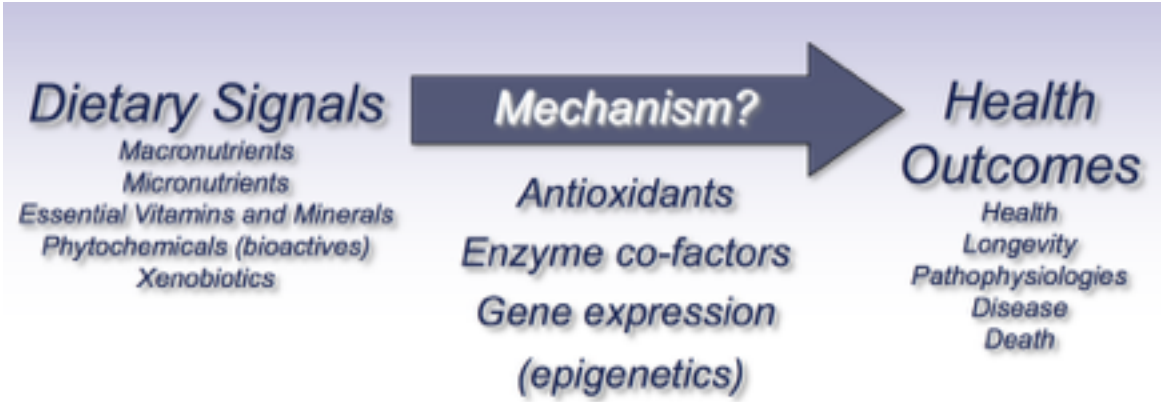
Koletzko et al 2009

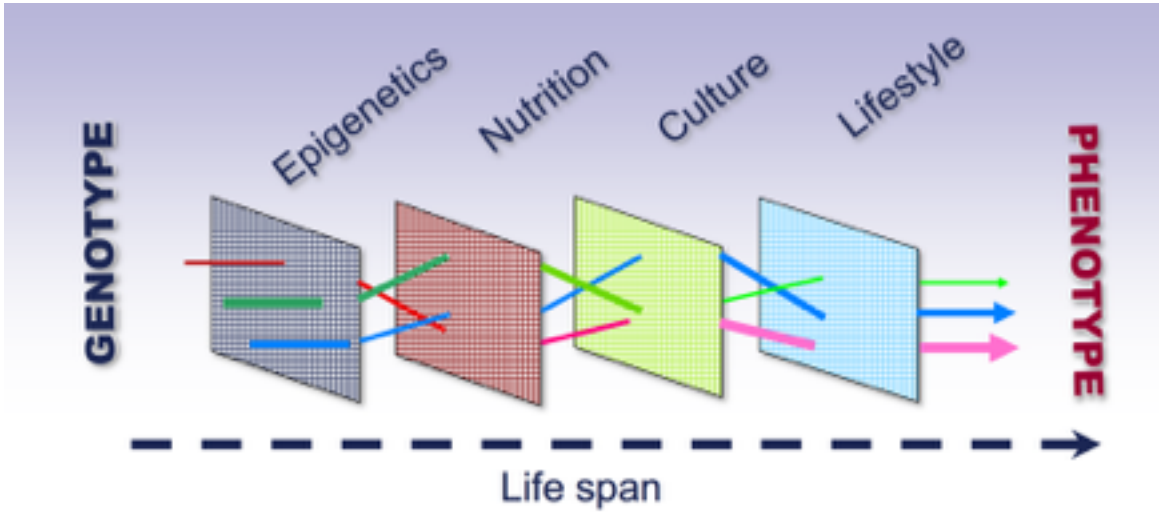

Joe Klein: The CIA's Afghan Disaster
Yemen: The New Center Of Terror
Why the Recession Hasn't Been Cool To Teens
TIME
WHY YOUR DNA ISN'T YOUR DESTINY
The new science of epigenetics reveals how the choices you make can change your genes —and those of your kids
BY JOHN CLOUD
January 6, 2010

Epigenetics: Methylation "Silences" Genes

"The study of heritable changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence."







Because of these filters, we are not slaves to our genes nor are we victims of genetic determinism.

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EARLY INTRODUCTION of F&V and acceptance

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In short-term experimental studies

Exposure to F&V variety in the early weaning period has been found to influence later acceptance of foods (Gerrish & Manella., 2001; Birch et al., 1998)

Longitudinal studies have found that early introduction to F&V has been associated with an increased consumption of F&V at :

- 2–6 years of age (Cooke et al., 2004)
- 6–8 years of age (Skinner et al., 2002)
- 7 years (Coultard et al., 2010)

Experimental

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Observational

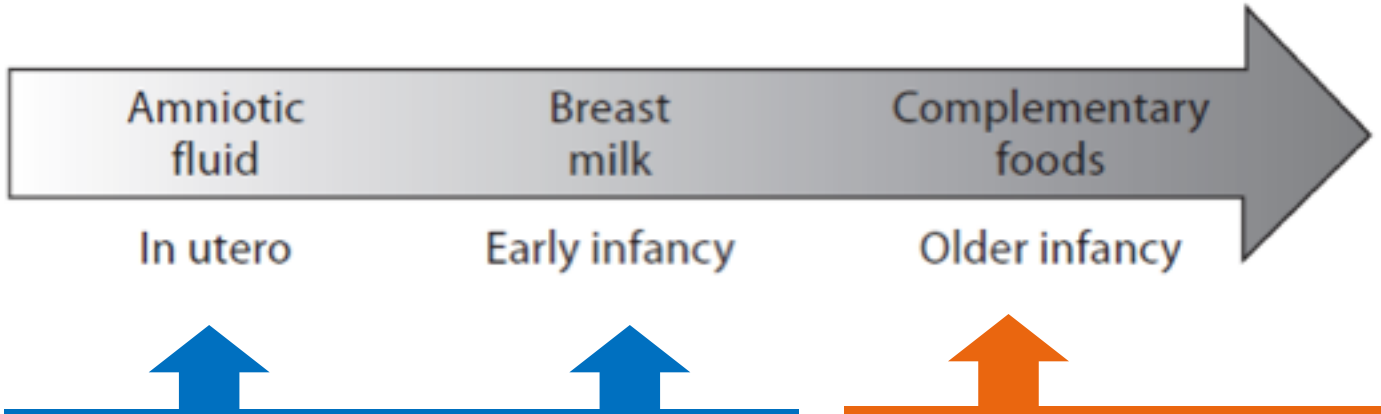
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THE SENSITIVE PERIOD HYPOTHESIS
Opportunities for early exposure

Exposure to different flavors begins early in life.



Infants learn about flavor prior to their first taste of solid food via amniotic fluid/breast milk.

Maternal/family diet plays a critical role in the timing and types of flavors and types of complementary foods offered to the infant.

The varied sensory experiences with food flavors in mother's milk may explain why children who are breastfed tend to be less picky and more willing to try new foods during childhood

Key Messages

- Nutritional and metabolic factors during sensitive, limited periods of early human development have a long-term programming effect on health, well-being and performance in later age, extending into adulthood and old age.
- Evidence for early programming effects arises from in vitro experiments, animal models, retro- and prospective epidemiological studies, and first con-trolled intervention trials.
- Obstetric and pediatric medicine are expected to achieve a much greater future role for prevention of long-term disease risks in the population.
- The important effects on health of early nutrition programming justify major investments into re- search and improvement of practice.

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