Origen prenatal de las enfermedades no transmisibles

Nutrición y embarazo: prevención de enfermedades no transmisibles.

Dra. Miriam Tonietti

- Actualmente está bien establecida la influencia de eventos tempranos sobre la salud en etapas posteriores de la vida.
- Aunque inicialmente se reconoció el impacto sobre la salud metabólica (DM, enfermedad cardiovascular) el espectro de condiciones asociadas a exposiciones tempranas se ha extendido (salud mental, función inmune)

- La prevalencia de obesidad y alteraciones metabólicas se ha incrementado dramáticamente en cada período de la vida en la mayoría de los países del mundo.
- Más allá de la mayor disponibilidad de alimentos densamente energéticos y de la reducción de los niveles de actividad física, hoy resulta claro el importante rol del ambiente temprano

Magnitud del problema

Más del 80% de las muertes debidas a las ECNT ocurren en países en desarrollo y se espera que este número aumente en las próximas décadas . (OMS,2005)

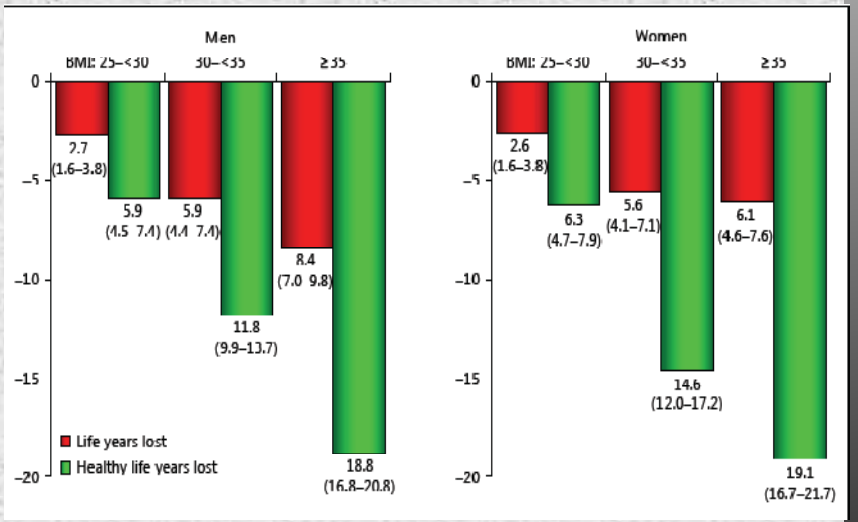
Las consecuencias de la OBESIDAD

- La OMS concluyó que actualmente la Obesidad es la 5° causa de las muertes globales y responsable de:
- 44% de la carga de DM
- 23% de enfermedad coronaria
- 7-41% de algunos cánceres

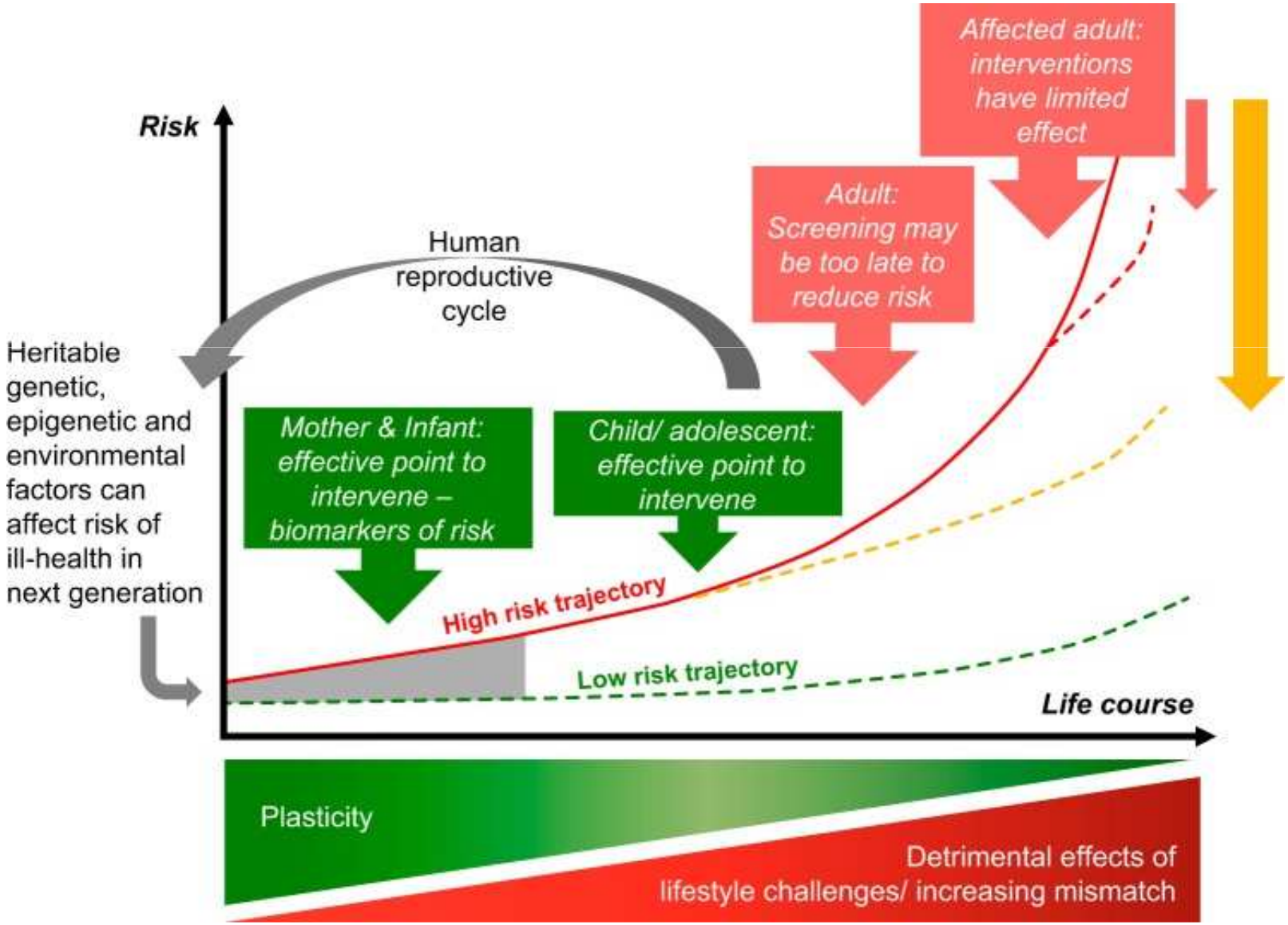
Morbilidad y calidad de vida

- Hay fuerte evidencia de la programación del desarrollo de las ECNT y su importancia en años de vida perdidos y principalmente años de vida saludables perdidos

Carga de enfermedad del Sp/Ob en sujetos de 20-39 años. Lancet Diabetes Endocrinol 2015



Teoría del curso de la vida para el desarrollo de las ECNT



The New England
Journal of Medicine

Volume 295 AUGUST 12, 1976 Number 7

OBESITY IN YOUNG MEN AFTER FAMINE EXPOSURE IN UTERO AND EARLY INFANCY

GIAN-PAOLO RAVELLI, M.D., M.S., ZENA A. STEIN, M.A., M.B., B.CH., AND MERVYN W. SUSSER, M.B., B.CH., F.R.C.P.

Abstract In a historical cohort study of 300,000 19-year-old men exposed to the Dutch famine of 1944-45 and examined at military induction, we tested the hypothesis that prenatal and early postnatal nutrition determines subsequent obesity. Outcomes were opposite depending on the time of exposure. During the last trimester of pregnancy and the first months of life, exposure produced significantly lower obesity rates ($P<0.005$). This result is consistent with the inference that nutritional deprivation affected a critical period of development for adipose-tissue cellularity. During the first half of pregnancy, however, exposure resulted in significantly higher obesity rates ($P<0.0805$). This observation is consistent with the inference that nutritional deprivation affected the differentiation of hypothalamic centers regulating food intake and growth, and that subsequent increased food availability produced an accumulation of excess fat in an organism growing to its predetermined maximum size. (N Engl J Med 295:349-353, 1976)

IN a historical cohort study of the Dutch famine of 1944-45, we examined prenatal and postnatal levels of nutrition as determinants of obesity in 19-year-old men. Early nutrition has been thought by some to influence adipose cell number and cell size, and in turn, adult obesity.[1,2] Others have proposed that the conditions prevailing in the prenatal period during hypothalamic differentiation can influence appetite, growth and subsequent obesity.[3] This study provides indirect tests of both hypotheses.

During the last six months of World War II, from October, 1944, until liberation, on May 7, 1945, an acute famine affected the western Netherlands. The Allied Forces had freed the Netherlands south of the Rhine, but in the west, which was still under Nazi occupation, an embargo was placed on all incoming transport, including food supplies. The embargo was a reprisal for a general strike by the Dutch railroad workers, who had responded to an appeal by the Dutch government-in-exile in London for support of the Allied Forces. Food supplies were already short, and the embargo, worsened by an unusually early and hard winter, soon resulted in famine. The famine was particularly severe in the large cities.

Available indexes of famine include the records of official food rations, measures of fetal growth, and subsequent infant mortality and general cause-specific mortality. A full description of the famine and its effects and of the data on which this study is based is given by Stein and her associates.[4] According to this account:

> At the beginning of the occupation the average daily ration for anyone not falling into a special category was about 1,800 calories. Rations were maintained at the same level in all three regions (West, North and South) until September 1944. By that time, the average daily ration had fallen to about 1,400 calories. With the onset of the famine in the West, rations were down to 1,200 calories in November, and by the turn of the year to less than 800 calories. Toward the end of February 1945, the food ration had dropped to 580 calories. Between February and April 1945, bread and potatoes formed almost the entire ration. Rations elsewhere were lower than in previous years of the occupation, but did not reach the low levels of the West. In the North, the average daily ration varied between 1,350 and 1,400 calories, and in the South between 1,375 and 1,700 calories...Supplements were given to pregnant women, mothers with young infants and the sick. During the famine however the SHAEF (Supreme Headquarters of the Allied Expeditionary Forces Report) states that "it was not always possible actually to provide these rations." Referring to conditions in The Hague the SHAEF team reports: "In the middle of November 1944 the additional supplies for mothers who were feeding their babies stopped...the allowances for pregnant women were not met."

Famine exposure in the third trimester of gestation sharply reduced post-partum maternal weight, retarded fetal growth and was followed by an excess of infant deaths in the first three months of life. Famine exposure in the first trimester of gestation, combined with some other unknown factor, was followed by an excess of premature deliveries, infants of very low birth weight, perinatal deaths and malformations of the central nervous system. Deaths during the famine, attributed to malnutrition as the primary cause and taking no account of deaths in which malnutrition was a contributing factor, numbered about 10,000.[4] Table 1 shows the average daily caloric ration in three-month averages for each region of the country.

From the Division of Epidemiology, Faculty of Medicine, Columbia University School of Public Health, and the Psychiatric Institute, New York State Department of Mental Hygiene (address reprint requests to Dr. Susser at the Division of Epidemiology, Faculty of Medicine, Columbia University School of Public Health, 600 W. 168th St., New York, NY 10032).

Supported in part by grants (5R01-HD-06751-02, 5R01-HD-06751-03, 3T01-HD-00325-9S2) from the U.S. Public Health Service and by a grant (940-199.73) from the Swiss National Science Foundation.

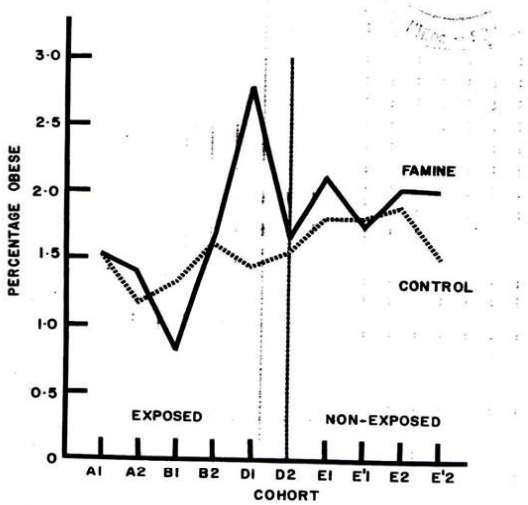


Figure 2. Obesity Prevalence Rates among Birth Cohorts in Famine and Control Areas.

Table 2. Obesity among 307,700 Military Inductees, According to Period of Birth, in Famine-Area and Control-Area Birth Cohorts.

PERIOD OF BIRTH*	FAMINE AREA			CONTROL AREA			P VALUE†
	TOTAL BIRTHS	TOTAL OBESE	% OBESE	TOTAL BIRTHS	TOTAL OBESE	% OBESE	
A_1	8,100	124	1.53	20,400	311	1.52	NS‡
A_2	9,500	132	1.39	21,600	250	1.16	NS
B_1	6,200	51	0.82	11,200	148	1.32	<0.005
B_2	7,500	126	1.68	17,600	286	1.63	NS
D_1	4,300	119	2.77	15,900	230	1.45	<0.0005
D_2	2,500	41	1.64	10,500	162	1.54	NS
E_1	15,800	333	2.11	35,200	636	1.81	<0.025
E'_1	17,500	305	1.74	29,200	527	1.80	NS
E_2	14,500	294	2.03	26,600	502	1.89	NS
E'_2	8,900	179	2.01	24,700	370	1.50	<0.005
Totals	94,800	1,704	1.80	212,900	3,422	1.61	<0.001

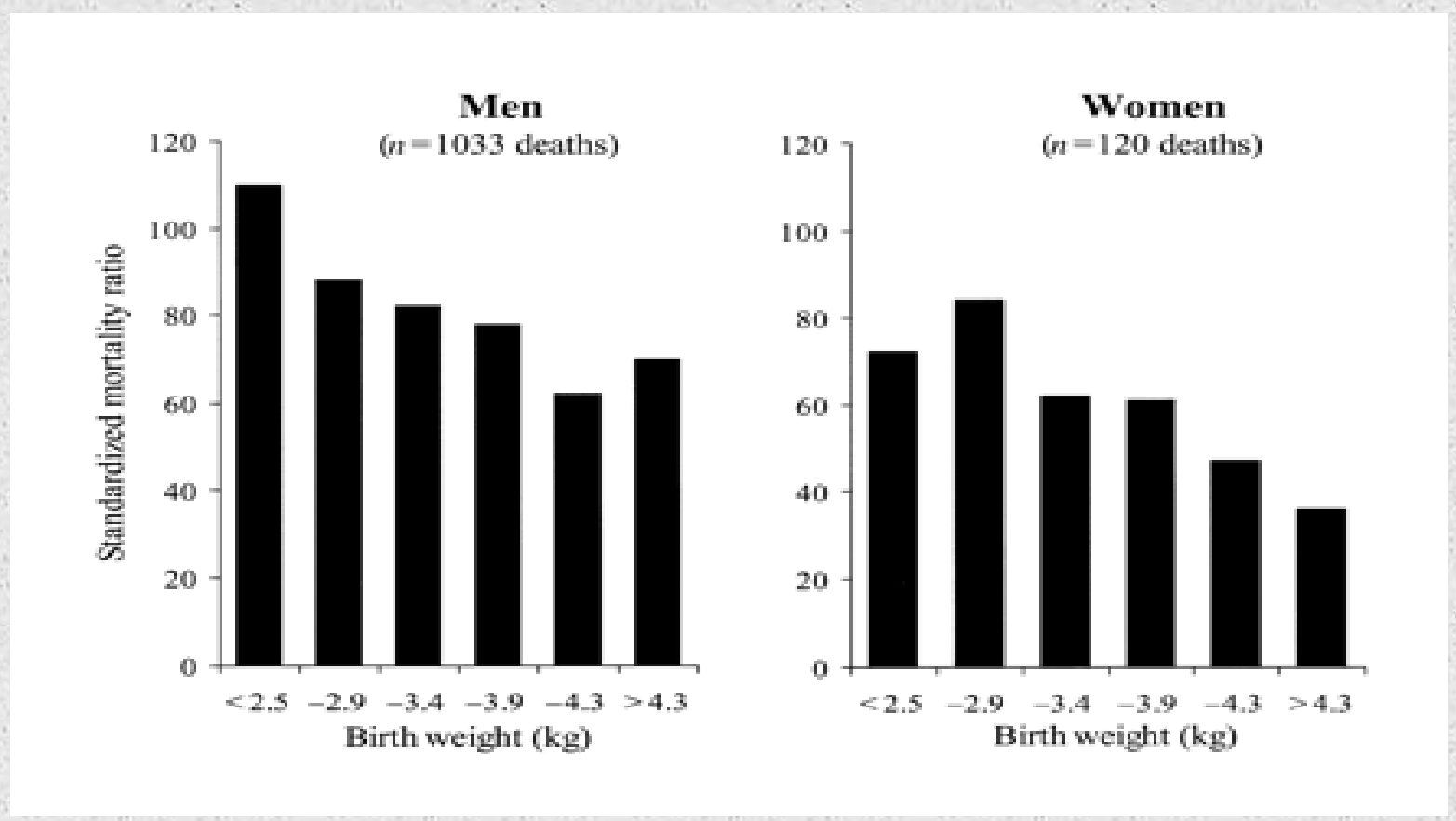
*A_1 denotes Jan-May 44, A_2 Jun-Oct 44, B_1 Nov 44-Jan 45, B_2 Jan-May 45, D_1 Jun-Sept 45, D_2 Oct-Dec 45, E_1 Jan-Jun 46, E'_1 Jun-Dec 46, E_2 Jan-Jun 47, & E'_2 Jul-Dec 47.

†Tested by chi-square, with 1 degree of freedom.

‡Not significant.

Tasas de mortalidad coronaria según PN. Hertfordshire

BMJ 1993. Osmond y col



Prevalencia de IGT y Diabetes 2 en hombres de 65 a de cohorte de Hertfordshire (n=370)

Diabetologia 1993; 36: 225–28.

IGT y diabetes hombres a los 64 años

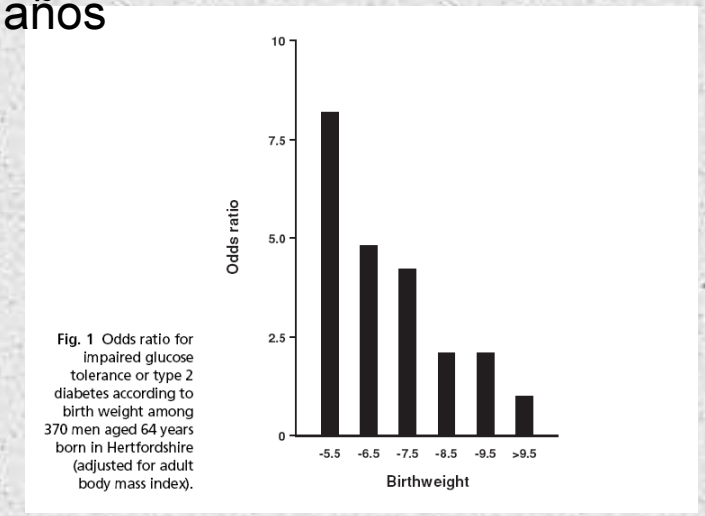


Fig. 1 Odds ratio for impaired glucose tolerance or type 2 diabetes according to birth weight among 370 men aged 64 years born in Hertfordshire (adjusted for adult body mass index).

Síndrome metabólico

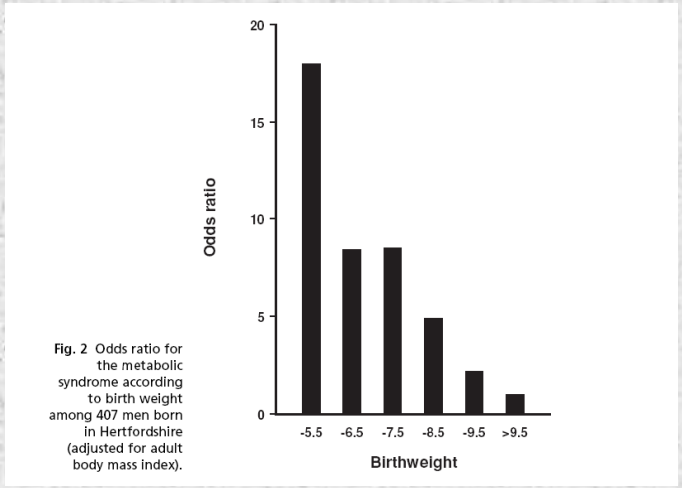


Fig. 2 Odds ratio for the metabolic syndrome according to birth weight among 407 men born in Hertfordshire (adjusted for adult body mass index).

Glucose tolerance in adults after prenatal exposure to famine

THE LANCET • Vol 351 • January 17, 1998

Findings Glucose concentrations were increased 2 h after a standard glucose load among exposed participants (p=0·006), and were highest in men and women exposed during mid and late gestation. Mean 2 h glucose concentration among non-exposed participants was 5·8 mmol/L; concentrations were 0·5 mmol/L (95% CI 0·1–0·9) higher among participants exposed during late gestation, 0·4 mmol/L (0–0·8) higher among those exposed during mid gestation, and 0·1 mmol/L (−0·4 to 0·6) among those exposed during early gestation. Participants born as thin babies to mothers with low bodyweights had the highest concentrations and concentrations were especially high among people exposed to famine who became obese as adults. Prenatal exposure to famine was related to increased fasting proinsulin (p=0·05) and 2 h insulin concentrations (p=0·04), which suggests an association with insulin resistance.

Poblaciones en las que se encontró correlación entre PN y IGT o Síndrome X

Table 1 Populations in which relationships between birth weight, shortness or thinness at birth and altered glucose and insulin metabolism or the metabolic syndrome have been described

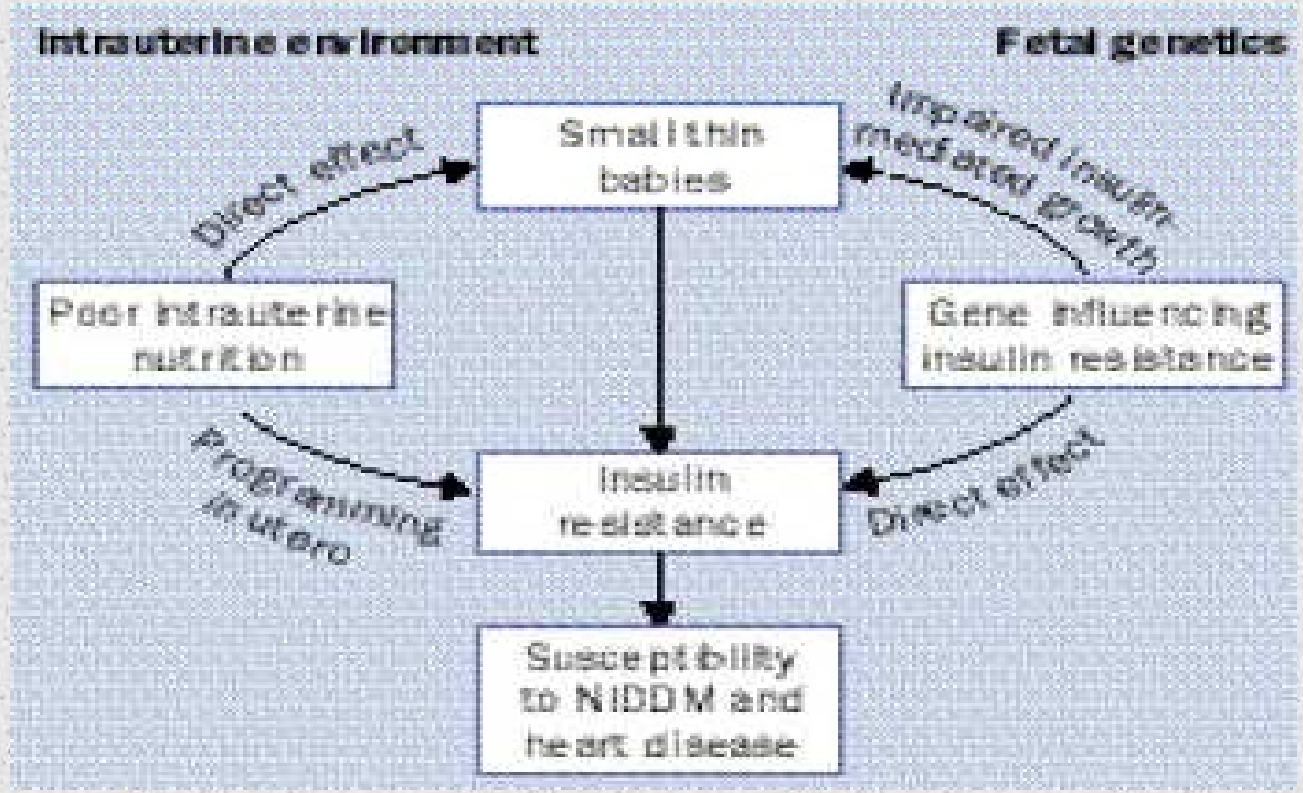
	Age (years)
Indian children	4[6]
Pima Indians (USA)	5–29[7]
Black South African children	7[8]
Jamaican school children	6–10[9]
Salisbury children (UK)	7[10]
Prepubertal children (New Zealand)	8.5[11]
British children	10–11[12]
Italian children	8–14[13]
Southampton men (UK)	18–25[14]
French adults	21[15]
Australian men	21[16]
Danish men and women	18–32[17]
British pregnant women	27[18]
Pima Indians (USA)	20–38[19]
Mexican Americans and non-Hispanic whites	32[20]
Indian men and women	39–60[21]
Health professional men (USA)	40–75[22]
Oxford men and women (UK)	43[23]
Chinese men and women	45[24]
Danish men and women	48[25]
Preston men and women (UK)	46–54[26]
Preston men and women	47–55[27]
Swedish men	40–60[28]
Swedish men	50–76[29]
Dutch men and women	50[30]
Postmenopausal women (USA)	50–84[31]
Sheffield men and women (UK)	52[32]
Danish twins	55–74[33]
Hertfordshire men (UK)	55–74[2]
Nurses' health study (women USA)	59[34]
British women	65[35]
Swedish men	70[36]

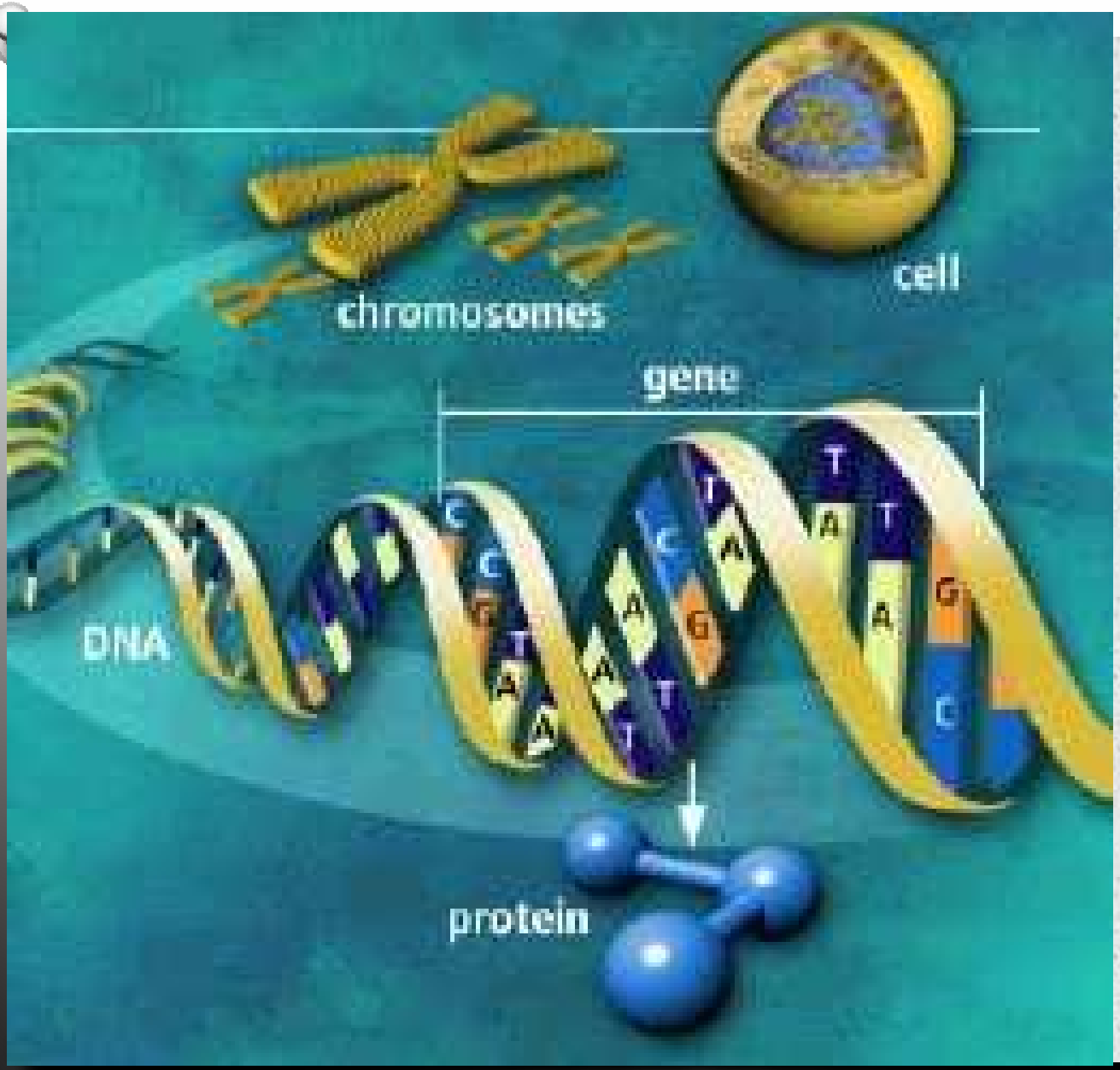
Diabetes Mellitus: A "Thrifty" Genotype Rendered Detrimental by "Progress"?

JAMES V. NEEL
Department of Human Genetics,
University of Michigan Medical School,
Ann Arbor, Mich.

FOR THE POPULATION GENETICIST, diabetes mellitus has long presented an enigma. Here is a relatively frequent disease, often interfering with reproduction by virtue of an onset during the reproductive or even pre-reproductive years, with a well-defined genetic basis, perhaps as simple in many families as a single recessive or incompletely recessive gene (cf. Allan, 1933; Pincus and White, 1933, 1934; Harris, 1950; Steinberg and Wilder, 1952; Lamy, Frézal and de Grouchy, 1957; Steinberg, 1959; Post, 1962a). If the considerable frequency of the disease is of relatively long duration in the history of our species, how can this be accounted for in the face of the obvious and strong genetic selection against the condition? If, on the other hand, this frequency is a relatively recent phenomenon, what changes in the environment are responsible for the increase? Current developments in the study of this disease suggest an explanation with important biological ramifications.

Dos hipótesis alternativas para la asociación entre pequeño al nacer e IR, NIDDM y Enfermedad Coronaria (genes y ambiente intrauterino)





PolimorfismoGenes

Thrifty gen

FNTα

Receptorβ3

PPARy2Pro12Ala

INS VNTR

IGF1y2

Receptor de IGF

•

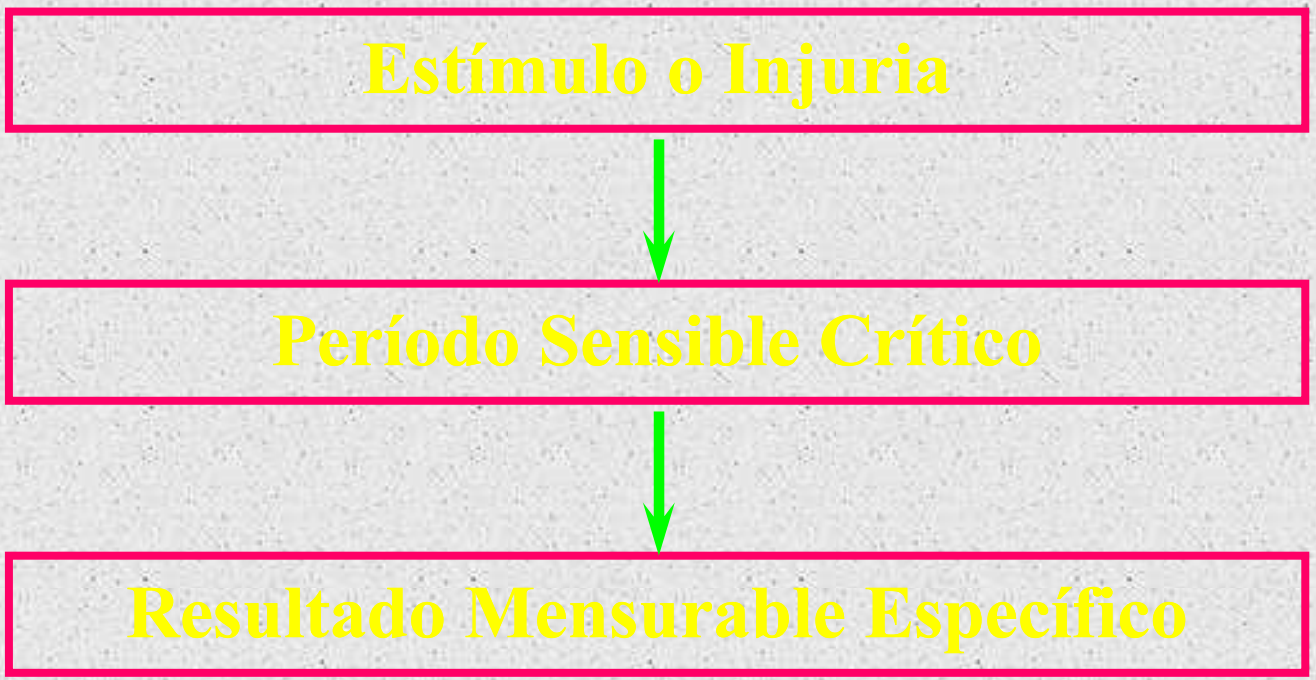
Low birth weight is associated with NIDDM in discordant monozygoticand dizygotic twin pairs.

Diabetologia. 1997;40:439–46.

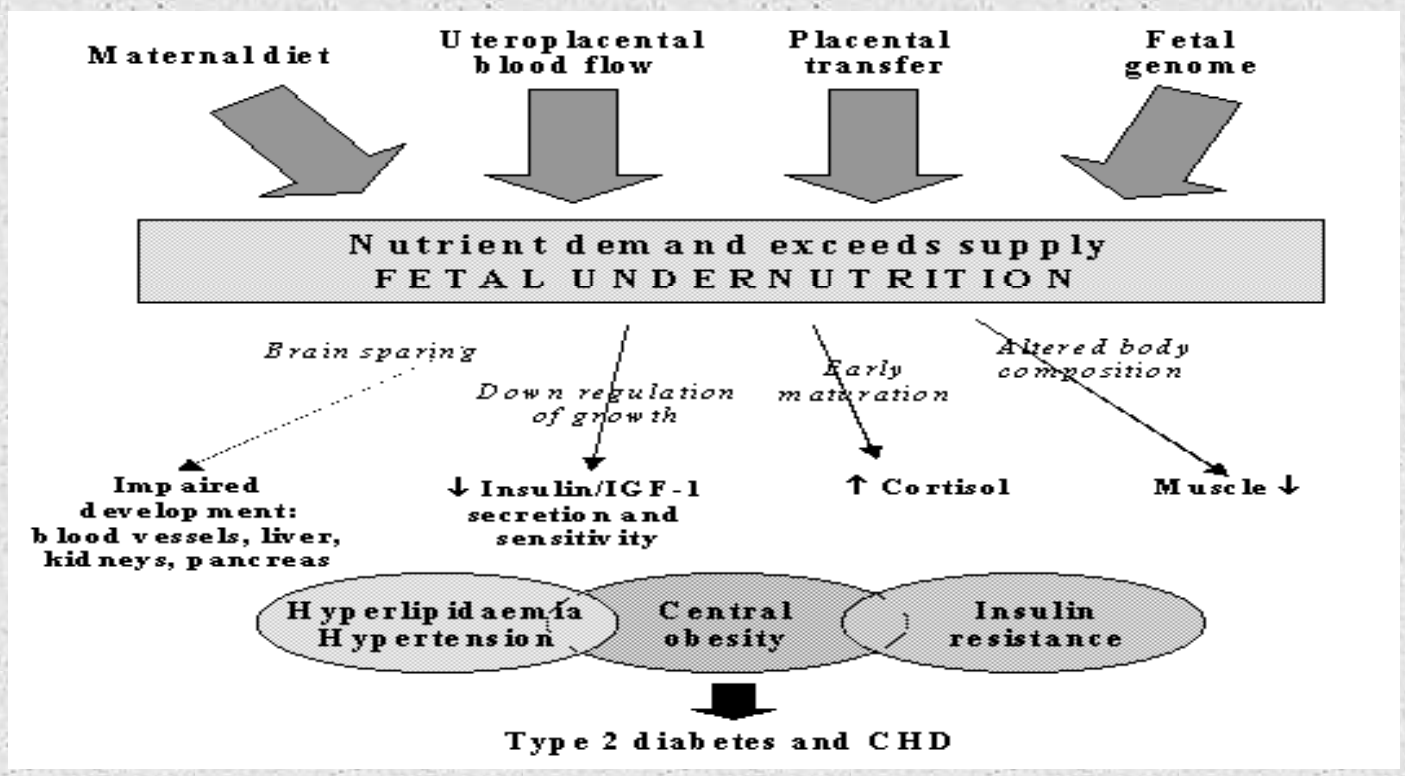
- Estudio en Dinamarca demostró que tanto en gemelos monocigotas como dicigotas discordantes para DM2, el gemelo diabético tuvo PN significativamente más bajo.

Este estudio refuerza la importancia del ambiente temprano

Programming



Hipótesis del origen fetal



Hipótesis del fenotipo thrifty

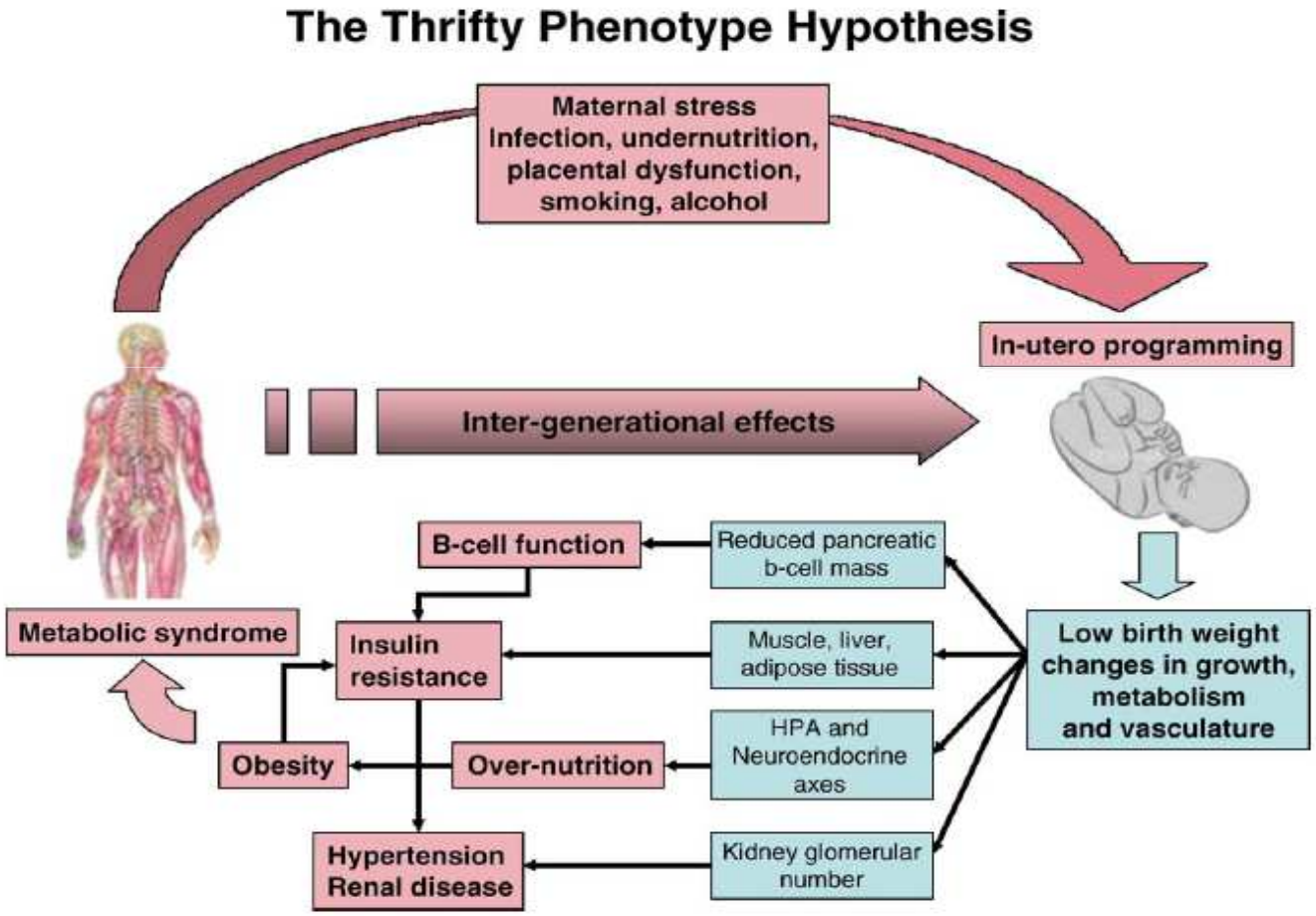
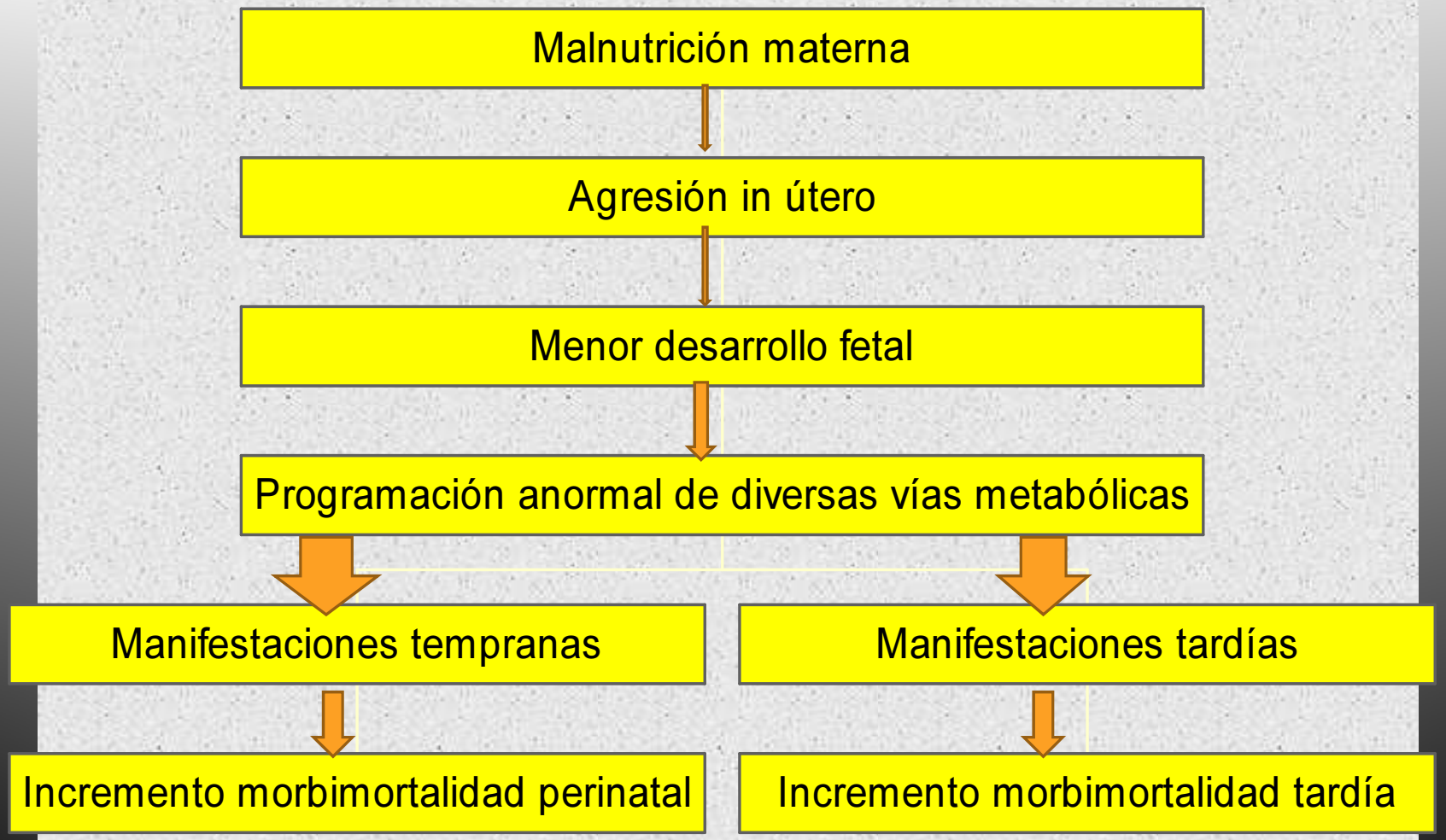


Fig. 1. A schematic representation of the Thrifty Phenotype Hypothesis, illustrating the programming effects of a suboptimal in-utero environment, nutritional or otherwise, on early growth and subsequent development of the metabolic syndrome (adapted from Hales and Barker [16]).

Teoría de la programación



Por qué la nutrición como estímulo programador?

Fenómeno biológico básico consistente en respuestas adaptativas a condiciones nutricionales específicas que se producen en un momento ontogénico sensible y que tiene un efecto persistente y duradero en la adultez

¿Por qué la nutrición? Programación nutricional en animales

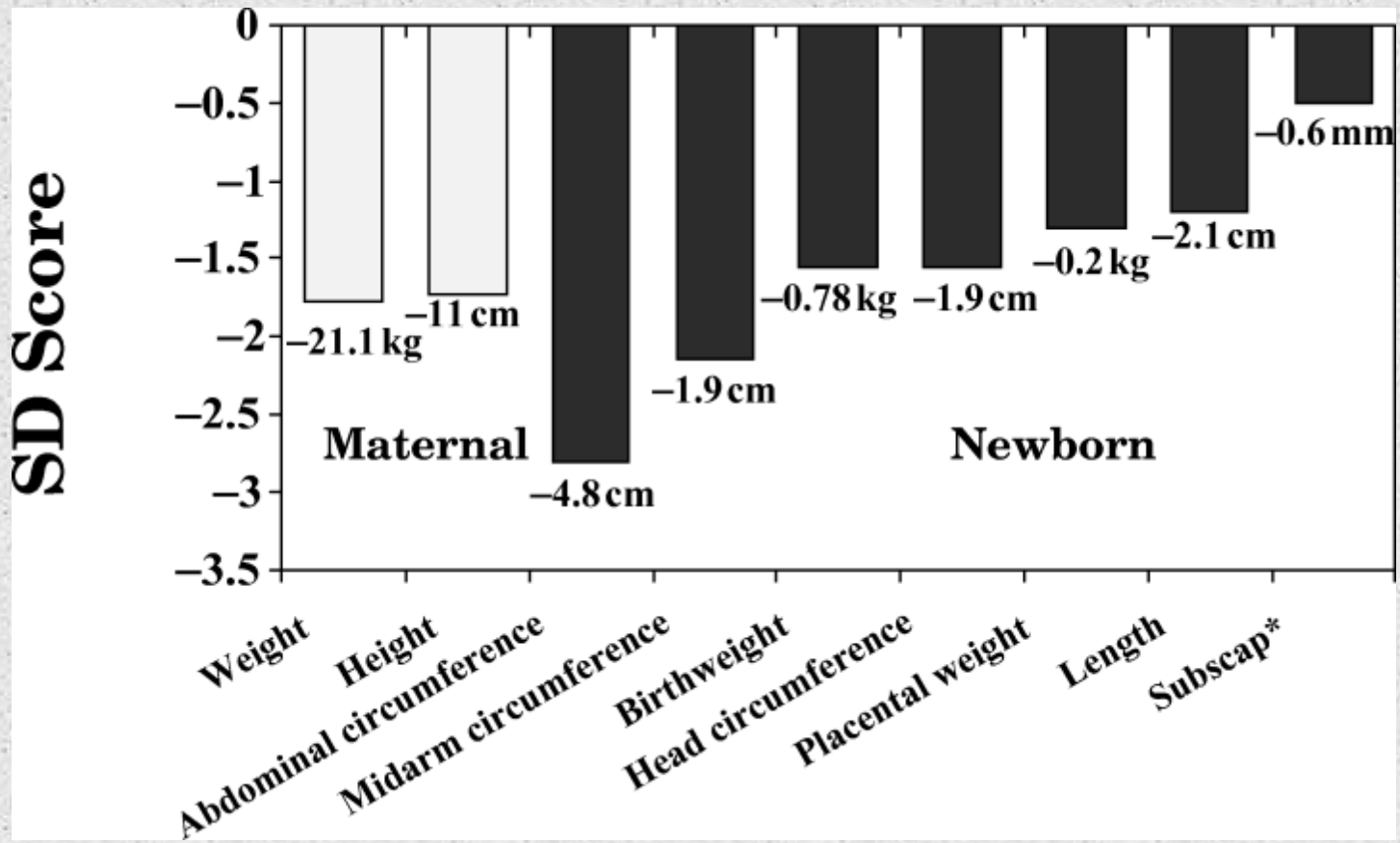
La manipulación dietaria en animales durante el embarazo produce muchos de los fenómenos observados en los estudios epidemiológicos (McCance,1962)

Ej: < prot madre embarazo:<tamaño al nacer >TA e IGT adultez

Por qué la nutrición?

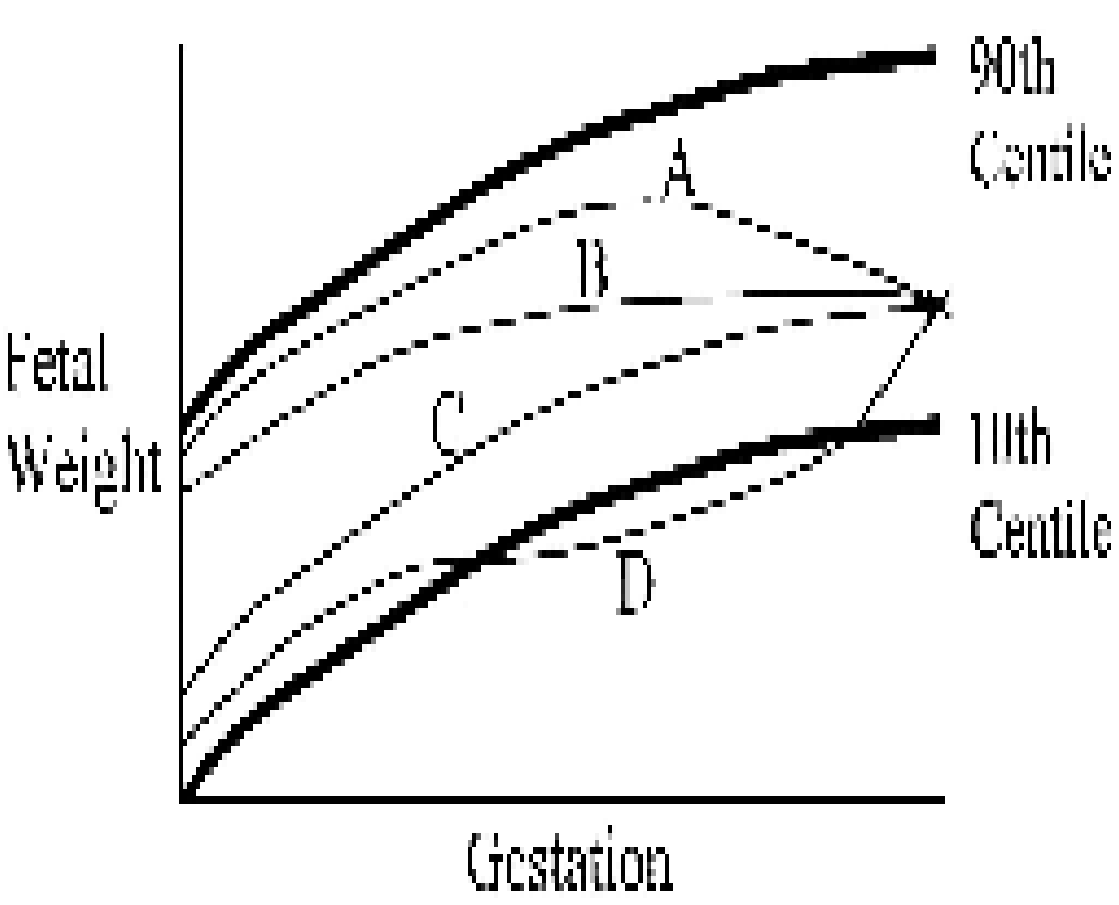
- Los principales mediadores hormonales del crecimiento fetal son la Insulina y los factores insulino-símiles (IGF), los cuales están regulados por la suplencia de nutrientes al feto. Ej: bajo aporte de glucosa al feto resulta en bajas concentraciones de insulina e IGF y en disminución del crecimiento fetal

Es el PN un buen predictor de riesgo ??



Yajnik CS.American Society for Nutritional Sciences, 2004

Trayectorias posibles de crecimiento fetal



DESARROLLO NORMAL

Procesos que restringen el desarrollo hacia un fenotipo particular

Variaciones en el fenotipo de acuerdo a señales ambientales tempranas

- El crecimiento es un proceso continuo
- Cualquier fenómeno que produzca una alteración temprana en la trayectoria de crecimiento puede determinar el riesgo de enfermar mucho tiempo después de ocurrida la injuria
- Fenómenos que tienen lugar en momentos posteriores en la vida pueden amplificar el riesgo de desarrollar enfermedad

- Las condiciones de salud en la adultez son dependientes, en parte, de la salud nutricional de la madre y del crecimiento en la vida temprana.

Ambos factores independientemente afectan la sensibilidad a la insulina, la composición corporal y la homeostasis energética en general

Diabetes en el embarazo

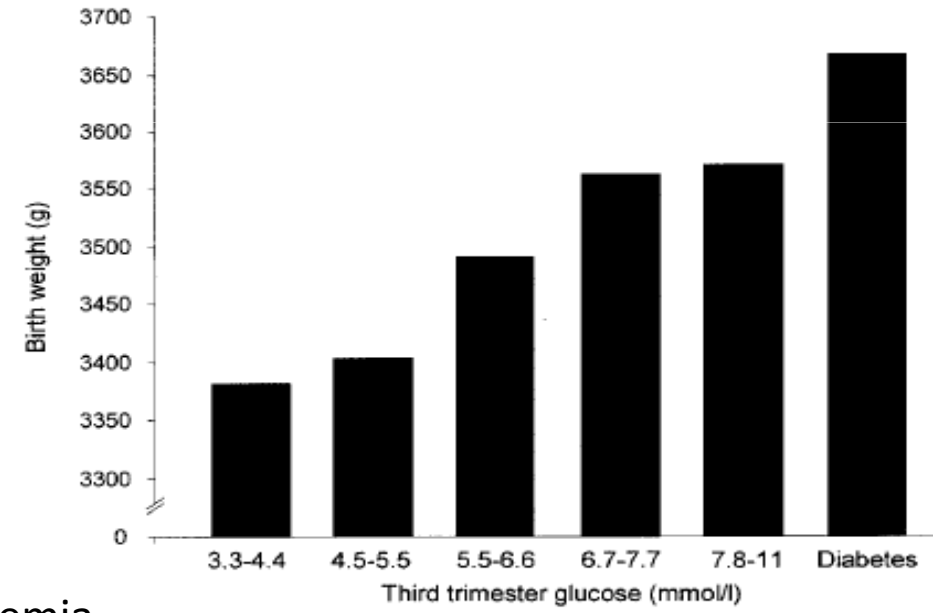
- Expone al feto a una hiperglucemia a la cual debe adaptarse.
- Repercute sobre sus patrones de crecimiento (macrosomía o RCIU), sobre la estructura y función endócrina del páncreas (hiperplasia e hipertrofia de islotes) y agotamiento precoz del contenido insulínico.
- Efecto transgeneracional: El feto mujer expuesto en útero a DG tiene mayor riesgo de DG en su embarazo

- Los RN de madres con DM 1 y 2 tienen alteración en la función de la célula β demostrado por mayor insulina en líquido amniótico.
- > insulina fetal----- > crecimiento fetal

(> glucosa, Aa y lípidos cruzando placenta)

Macrosomía con > adiposidad

Asociación entre PN y glucemia materna en el tercer trimestre



1SD de > glucemia materna aumento 57 g PN

Diferencias en el IMC en hermanos expuestos y no expuestos a DG.

Dabelea, Diabetes 2000

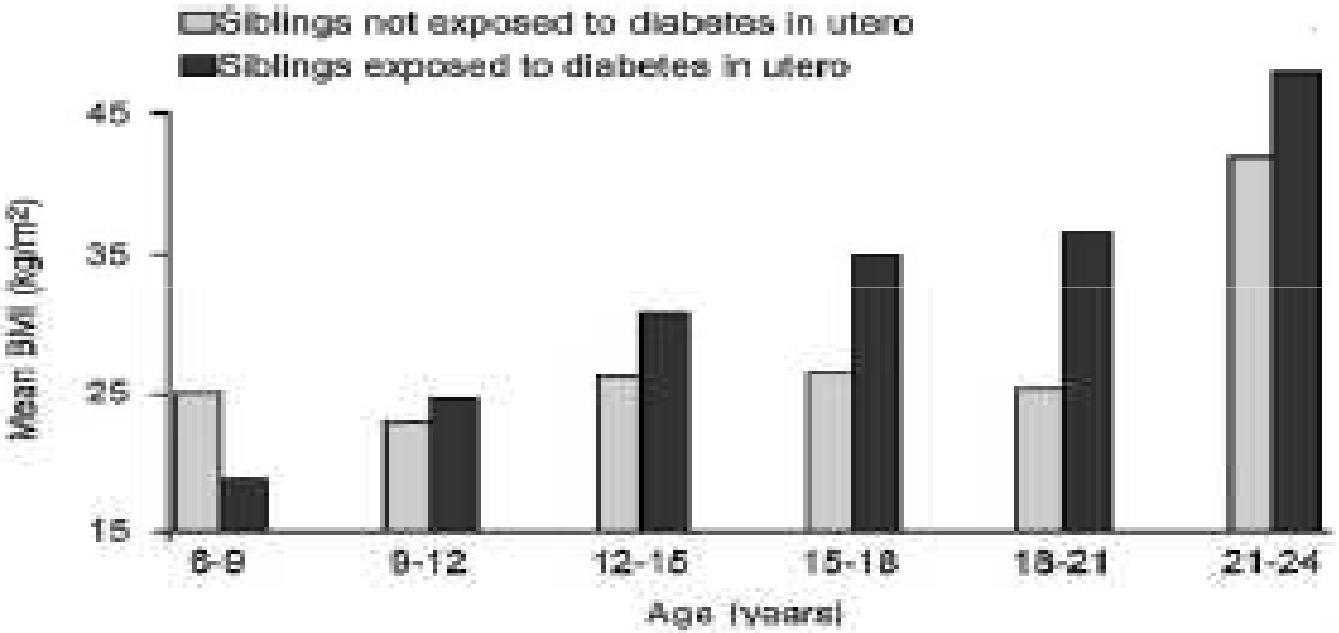


Figure 4: Mean BMI in Pima Indian siblings exposed and not exposed to diabetic intrauterine environment, separated into 3-year age intervals. Siblings exposed have a higher BMI than those unexposed ($p = 0.003$, controlled for sibship by ANOVA) (63). Reproduced with permission of the journal *Diabetes*. © American Diabetes Association.

Childhood Obesity and Metabolic Imprinting

The ongoing effects of maternal hyperglycemia

Diabetes Care 30:2287–2292, 2007

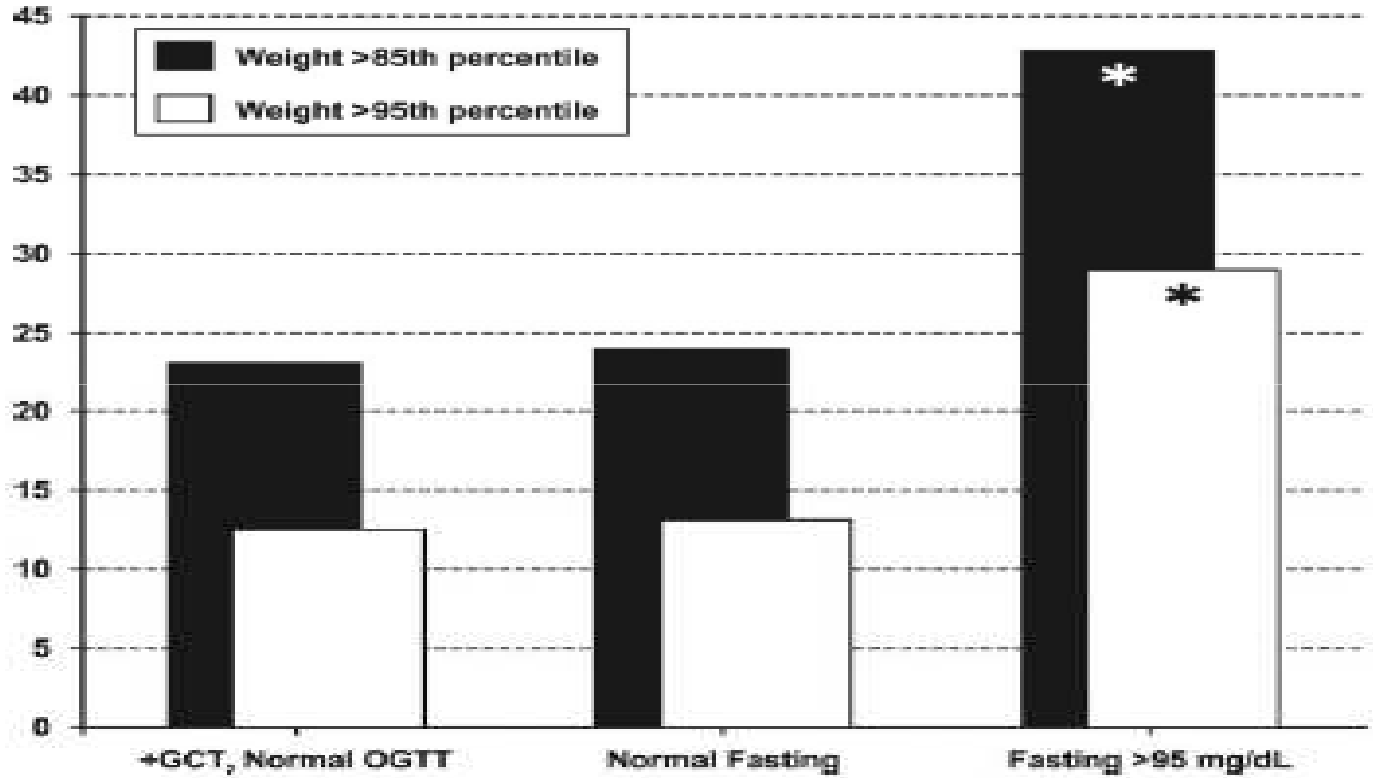
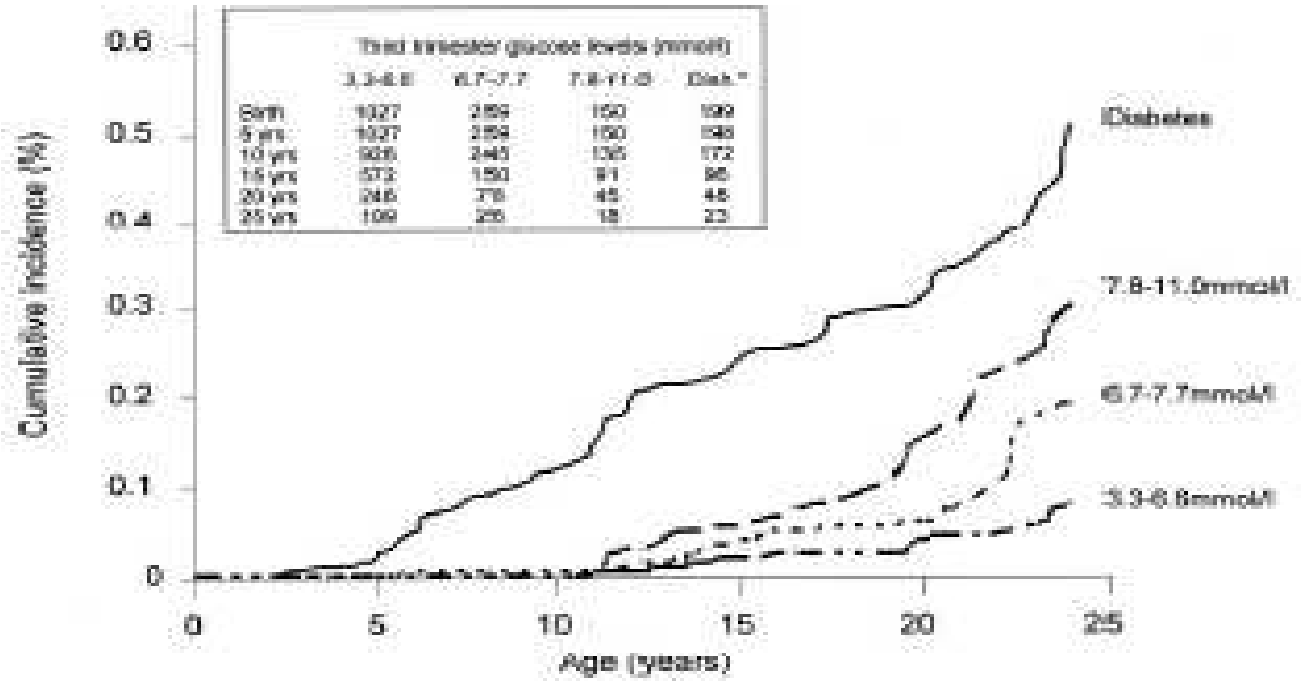


Figure 1—*Relationship of fasting maternal hyperglycemia in pregnancy with childhood obesity at age 5–7 years, among the subsample with abnormal GCT and complete follow-up OGTT results: 1) GCT >140 mg/dl (7.7 mmol/l) but follow-up OGTT normal at all 4 time points (fasting, 1 h, 2 h, and 3 h post-OGTT) by Carpenter and Coustan criteria (22,24) (n = 731); 2) normal fasting glucose (≤95 mg/dl [5.3 mmol/l]) but ≥1 Carpenter and Coustan postprandial values equaled or exceeded on OGTT (n = 547); and 3) elevated fasting glucose (>95 mg/dl [n = 184]) on OGTT and 0, 1, or 2 Carpenter and Coustan postprandial values equaled or exceeded. Categories 2 and 3 are stratified on the basis of fasting glucose on the OGTT irrespective of whether the woman met the criteria for GDM (2 of 4 values exceeded by either Carpenter and Coustan or NDDG criteria).*

Incidencia de Diabetes 2 en el RN estratificado por categoría de glucemia materna en tercer trimestre



1SD de glucemia materna aumenta
1.6 riesgo de diabetes

Franks PW, Diabetes, 2006

Maternal Lipids as Strong Determinants of Fetal Environment and Growth in Pregnancies With Gestational Diabetes Mellitus.

Schaeffer –Graf U. *Diabetes Care* 31:1858–1863, 2008

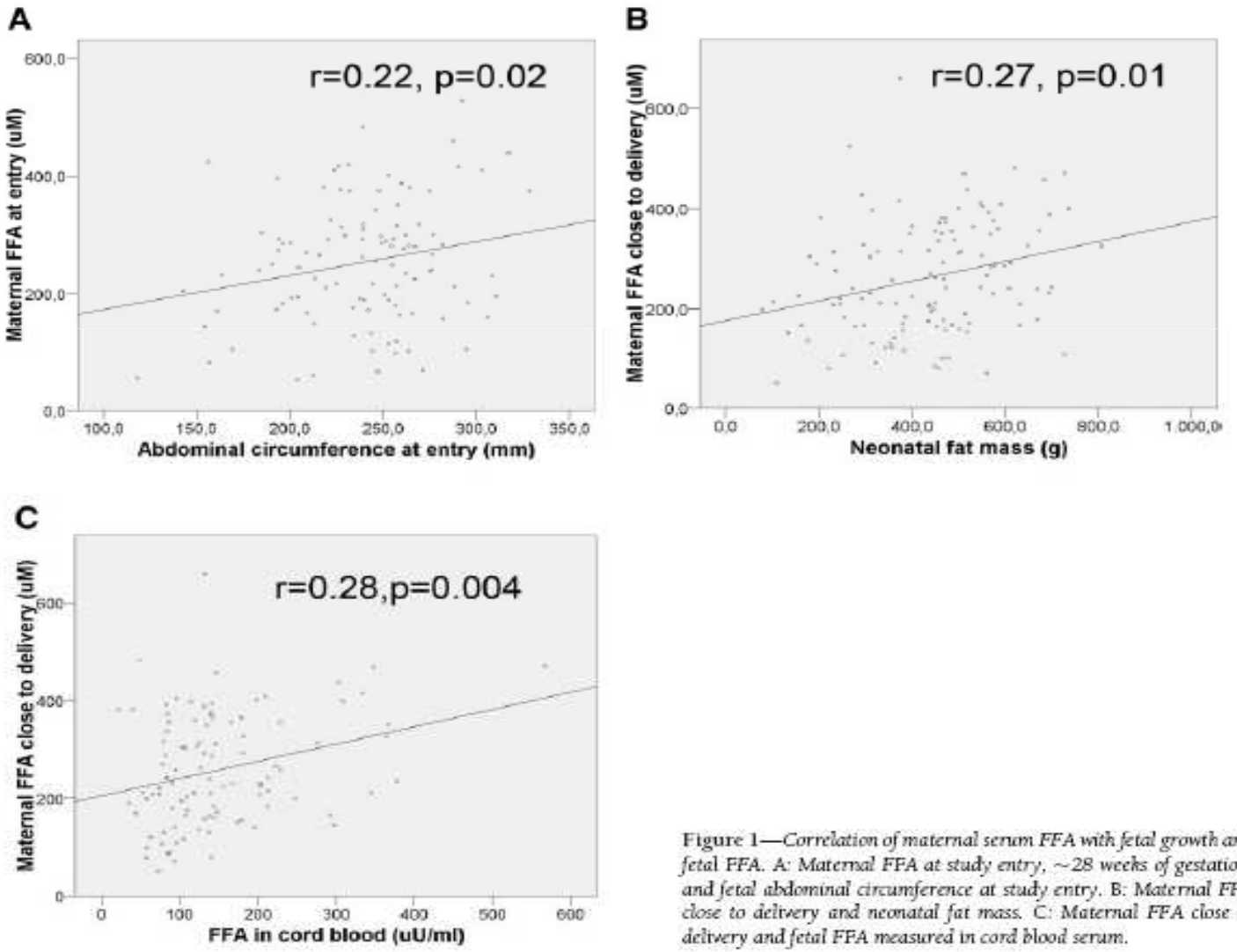


Figure 1—*Correlation of maternal serum FFA with fetal growth and fetal FFA. A: Maternal FFA at study entry, ~28 weeks of gestation, and fetal abdominal circumference at study entry. B: Maternal FFA close to delivery and neonatal fat mass. C: Maternal FFA close to delivery and fetal FFA measured in cord blood serum.*

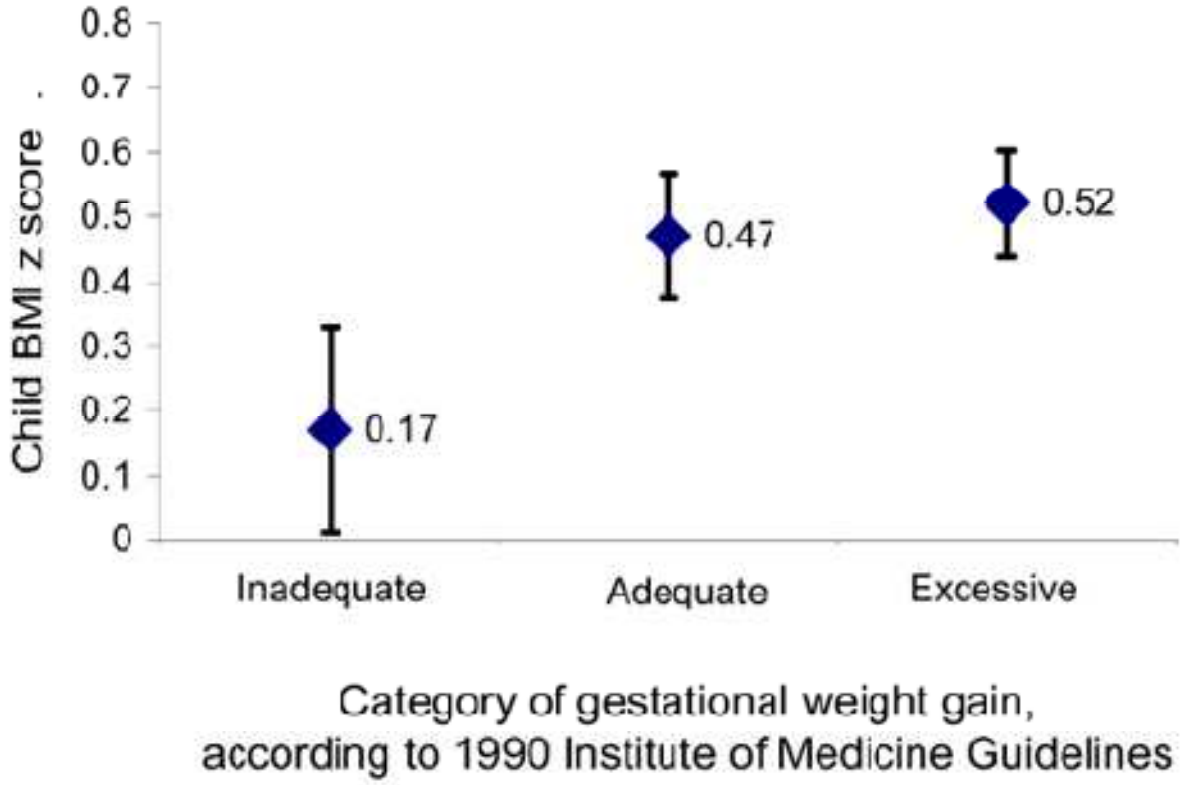
Obesidad materna y riesgo en los hijos

Table 1
A summary of studies which have reported a relationship between maternal BMI/obesity and offspring BMI/obesity or measures thereof.

Citation	Cohort size	Follow up age	Conclusion
Knight et al. 2007 [54]	547	2 years	Maternal BMI associated with offspring weight at birth, 1 year and 2 years. Maternal prepregnancy BMI is correlated with offspring BMI at 2years ($r=0.18$, $p<0.001$) during the first two years of life. After 1 year post-birth offspring BMI is also correlated with paternal BMI (at 2 years: $r=0.23$, $p<0.001$).
Whitaker et al. 2004 [123]	8494	4 years	The risk of childhood obesity at 4years is associated with maternal obesity (measured during first trimester; BMI >30) (OR: 2.3; 95% CI: 2.0–2.6)
Burdette et al. 2006 [124]	313	5 years	Children of obese mothers (pre-pregnancy BMI >30) have 0.54 kg more fat mass than children of non-obese mothers as determined by dual-energy x-ray absorptiometry.
O'Callaghan et al. 1997 [125]	4062	5 years	Pre-pregnancy maternal obesity (≥95 percentile) (OR: 4.7; 95% CI: 3.3–6.8) and paternal obesity (≥95 percentile) (OR: 2.9; 95% CI: 1.9–4.5) are independent predictors of severe obesity (≥95 percentile) at 5 years.
Salsberry and Reagan (2005) [126]	3022	2–7 years	Maternal pre-pregnancy BMI >30 associated with an increased odds ratio for overweight in the offspring (OR: 1.37; 95% CI: 1.02–1.84)
Danzelzik et al. 2002 [74]	3306	5–7 years	Children's BMI is significantly correlated with parental BMI, although a closer correlation was observed between maternal ($r=0.249$; $p<0.01$) than paternal ($r=0.159$; $p<0.01$) BMI. Also there was a closer correlation between the BMI of boys and parental BMI than that for girls.
Blair et al. 2007 [127]	871	7 years	Maternal obesity (BMI >30) results in higher offspring body fat measured by bioelectrical impedance analysis (OR: 4.0 (95% CI: 0.4–7.7)
Fisch et al. 1975 [128]	1779	7 years	Maternal index (kg/cm) is associated with offspring obesity at 7 years of age ($p<0.5$)
Reilly et al. 2005 [129]	8234	7 years	Maternal BMI during pregnancy and Paternal BMI are independent predictors of obesity at 7 years (both parents: adjusted OR: 10.44; 95% CI: 5.11–21.32).
Davey Smith et al. 2007 [130]	4654	7.5 years	Child BMI is associated equally with maternal ($r=0.295$ (0.267 to 0.322)) and paternal ($r=0.250$ (95% CI: 0.218 to 0.274)) BMI
Gale et al. 2008 [83]	216	9 years	For 1 standard deviation increase in maternal pre-pregnancy BMI, fat mass index increased by 0.26 standard deviations.
Li et al. (2005) (131)	2636	2–14 years	Maternal pre-pregnancy BMI >30 associated with an increased odds ratio for overweight in the offspring (adjusted OR: 4.1; 95% CI): 2.6–6.4)
Lawlor et al. 2007 [132]	3340	14 years	Pre-pregnancy maternal BMI (β 0.353 (95% CI: 0.304–0.401) a stronger predictor of offspring BMI than paternal BMI (β 0.251 (95% CI: 0.199–0.304) (difference between maternal and paternal: $p=0.009$)
Koupil and Toivanen 2008 [133]	1103	18 years	Maternal pre-pregnancy BMI is the strongest predictor of offspring obesity (OR: 0.39; 95% CI: 0.28–0.49)
Parnon et al. 2001 [134]	17,414	33 years	Pre-pregnancy maternal BMI explained association between birth weight and adult BMI

- Niños nacidos de madres obesas tienen 2 veces más riesgo de ser obesos a los 2 años (Whitaker 2004).
- El peso de la madre anterior a la concepción es un factor de riesgo adicional para obesidad en la adolescencia (Yogev & Langer 2008).
- Adolescentes nacidos de madres obesas o con DM tienen doble riesgo de tener sindrome metabólico (Boney et al. 2005).
- Hay una fuerte correlación entre el IMC materno y el IMC del hijo en la adultez

Gestational weight gain and child adiposity at age 3 years. Oken E, *Am J Obstet Gynecol*. 2007 ;196(4):e1–e8



- Varios estudios demuestran que la excesiva GPG está asociada a:
- > riesgo de GEG (Obstet Gynecol 2014;123:737–44 Am J Obstet Gynecol 2010;202:574.e1–8.)
- Sp/adiposidad en niñez (Am J Clin Nutr 2008;87:1818–24. . Circulation 2010;121:2557–64.)
- Sp/adiposidad adolescencia (Obstet Gynecol 2008;112:999–1006)
- Sp/adiposidad adultez (Circulation 2009;119:1720–7)

GPG y riesgo de Sp en hijos.

Lau E, J Obes 2014

- Revisión sistemática sobre 23 estudios
- Variables: GPG e IMC del hijo entre 2 y 18.9 años

Los niños de madres con excesiva GPG (IOM) tuvieron significativamente > z-IMC (0.74 a 1.73) y elevado riesgo de Sp/Ob (1 a 57%)

Association of excessive GWG with adiposity indicators and metabolic diseases of their offspring: systematic review.

Perez Morales ME . Nutr Hosp. 2015;31(4):1473-1480

Hay asociación entre la GPG y los indicadores de adiposidad u otros componentes del síndrome metabólico en la niñez, durante la adolescencia

o la edad adulta.

Associations of maternal BMI and gestational weight gain with neonatal adiposity in the Healthy Start study.

Am J Clin Nutr 2015;101:302–9

- cada 1kg/m2 de aumento en IMC materno se asoció con aumento de la masa grasa neonatal (5.2 g; 95% CI: 3.5, 6.9 g), masa libre de grasa (7.7 g; 95% CI: 4.5, 10.9 g), y porcentaje de grasa corporal (0.12%; 95% CI: 0.08%, 0.16%).
- Cada 0.1-kg/semana de mayor aumento en la GPG se asoció con aumento de la masa grasa (24.0 g; 95% CI: 17.4, 30.5 g), MLG (34.0 g; 95% CI: 21.4, 46.6 g), y % de grasa corporal(0.55%; 95% CI: 0.37%, 0.72%).
- El IMC pregestacional y la GPG se asocian positiva e independientemente con la adiposidad neonatal

Obesidad en mujeres en el mundo

- Prevalencia mundial en mujeres > 20 años de SP 35% y Ob 14%
- En América: 62% Sp y 26% Ob
- Europa: 50% Sp y 23% Ob
- EEUU:64% Sp y 35% Ob

Importancia de la obesidad en el padre

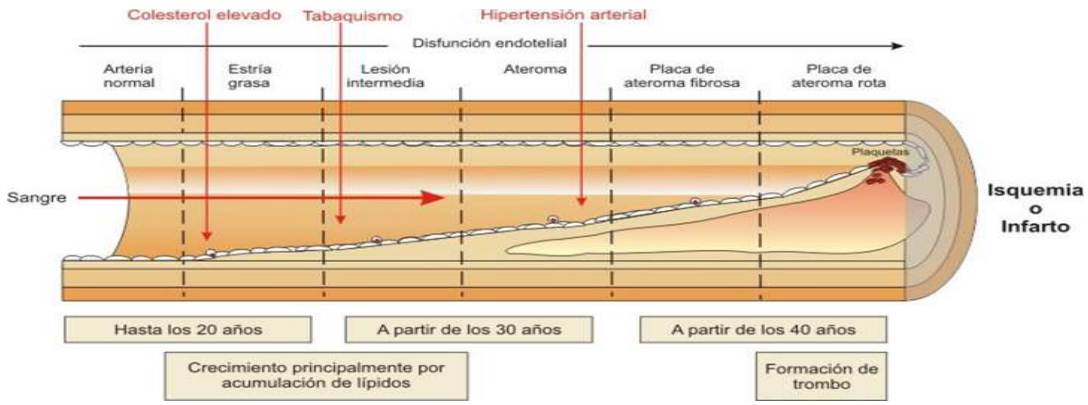
- El peso y la dieta alta en grasa del padre afectan la posibilidad para el desarrollo en el RN de obesidad y enfermedades metabólicas
- La obesidad afecta la concentración, motilidad y morfología del esperma y aumenta la probabilidad de daño de su ADN
- Independientemente ligada a menor PN del RN y a mayores niveles de adiposidad en niñas pre-puberales

Ng SF, Nature,2010;467:963–6.

Maternal diet during pregnancy and carotid intima-media thickness in children.

Gale, C.R. et al. (2006) Arterioscler. Thromb. Vasc. Biol.26, 1877–1882

La estructura vascular en niños, tan temprano como a los 9 años, es dependiente de la dieta materna antes y durante el embarazo, independientemente del peso al nacer



Estado nutricional en micronutrientes

- El estado nutricional materno de Fe, I, Ca, B12, Fólico, vitamina A y C influencian el tamaño y composición corporal del hijo
- Niños de madres con bajas concentraciones de B12 y altas de folatos, más adiposos e insulino-resistentes (Yajnik 2006 Nutr Rev 64 (5))

Epigenética

- 30000 genes codificantes
- Estado de cromatina: crítico para determinar cuándo, cómo y dónde se establece la transcripción de un gen en un producto determinado
- Heterocromatina: altamente condensada, impide el acceso de los elementos activadores de la transcripción y determina silenciamiento génico de la zona
- Eucromatina: más laxa, permite acoplamiento de activadores en regiones promotoras y la transcripción

3 mecanismos básicos

- Metilación del ADN
- Modificación de histonas
- Secuencias de pequeños ARNs no codificantes

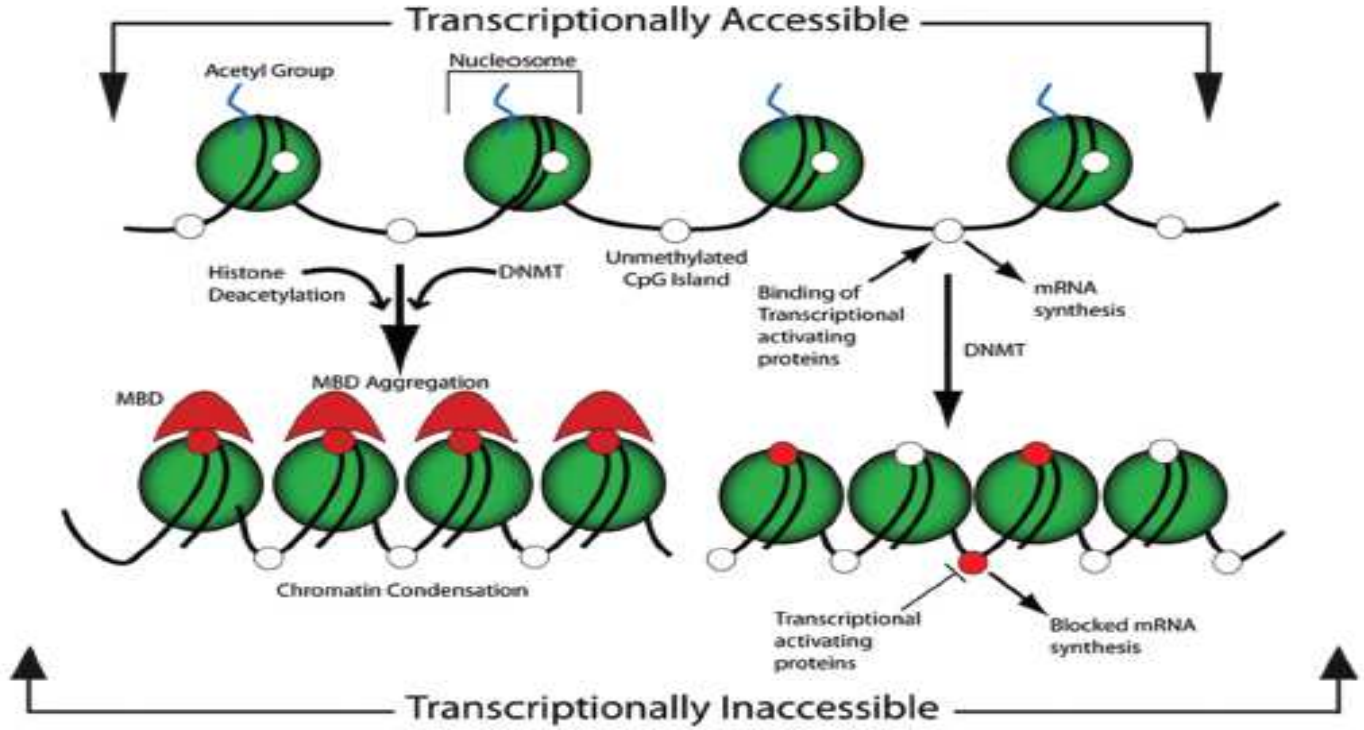


Figure 2. The shaded sphere depicts the octameric histone complex, which forms the nucleosome with the acetylated tails of histones and the cytosines of the CpG sites in an unmethylated state, shown as open white circles. In this conformation, the chromatin is loosely packed and available for the binding of transcriptional activating proteins, which, by the action of RNA polymerase II, synthesize mRNA. The action of DNA methyl transferase (DNMT) methylates the cytosine residues, depicted as red circles, which provide a docking site for the methyl binding domain proteins (MBD), which aggregate in conjunction with the action of the histone deacetylase, which cleaves the histone acetyl group. Both of these serve to alter the structure of the chromatin by causing a condensation that impedes the access of the transcriptional activating proteins and thereby blocks mRNA synthesis. Alternatively, the normal active structure of chromatin can become inaccessible for the binding of transcriptional activating proteins by the action of CpG methylation at sites that sterically hinder the binding of activating proteins, independent of MBD aggregation.

Alteraciones en el epigenoma inducidas por experiencias nutricionales

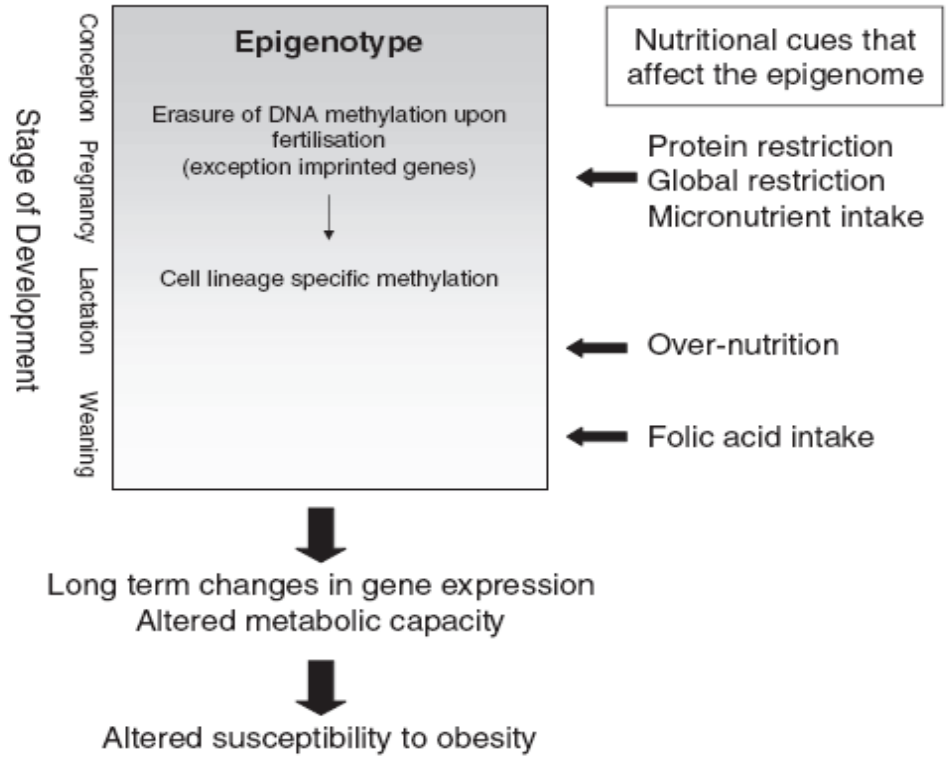


Figure 1 Alterations in the epigenome induced by nutritional challenges results in an altered metabolic capacity and altered susceptibility to developing obesity in later life. The sensitivity of the epigenome to the environment (represented by the shading) decreases during postnatal life.

International Journal of Obesity

Epigenetic marks at birth predict childhood body composition at age 9 years. Godfrey, K.M. et al. (2009) DOHaD 1, S44

- Recientemente se ha demostrado que el perfil epigenético en sangre de cordón al nacer puede predecir las variantes fenotípicas posteriores independientemente del PN.
- En 2 cohortes independientes el estado de metilación del factor de transcripción RXR se asoció con adiposidad en la infancia en ambos sexos, explicando > del 25% de la masa grasa

Maternal pregestational BMI is associated with methylation of the PPARGC1A promoter in newborns. Obesity 2009 :1032-9.

Gemma C[1], Sookoian S, Alvariñas J, et al

Correlación positiva entre el IMC materno y la metilación del promotor del PPARGC1A en sangre de cordón (p = 0.0007) lo que sugiere un rol potencial del promotor del PPARGC1A en la programación metabólica del hijo

Recientemente fue demostrada la hipometilación en el ADN en el gen de IGF2 seis décadas después en los que sufrieron exposición preconcepcional a la hambruna durante el invierno holandés de 1944-45. IGF2 juega un rol clave en la división y diferenciación celular y en la regulación metabólica.(Heijman)

- Folatos, metionina, betaína, colina y vitamina B12 participan en metabolismo monocarbonado que incluye la metilación

Cohorte de Helsinski

Eriksson J et al . BMJ1999

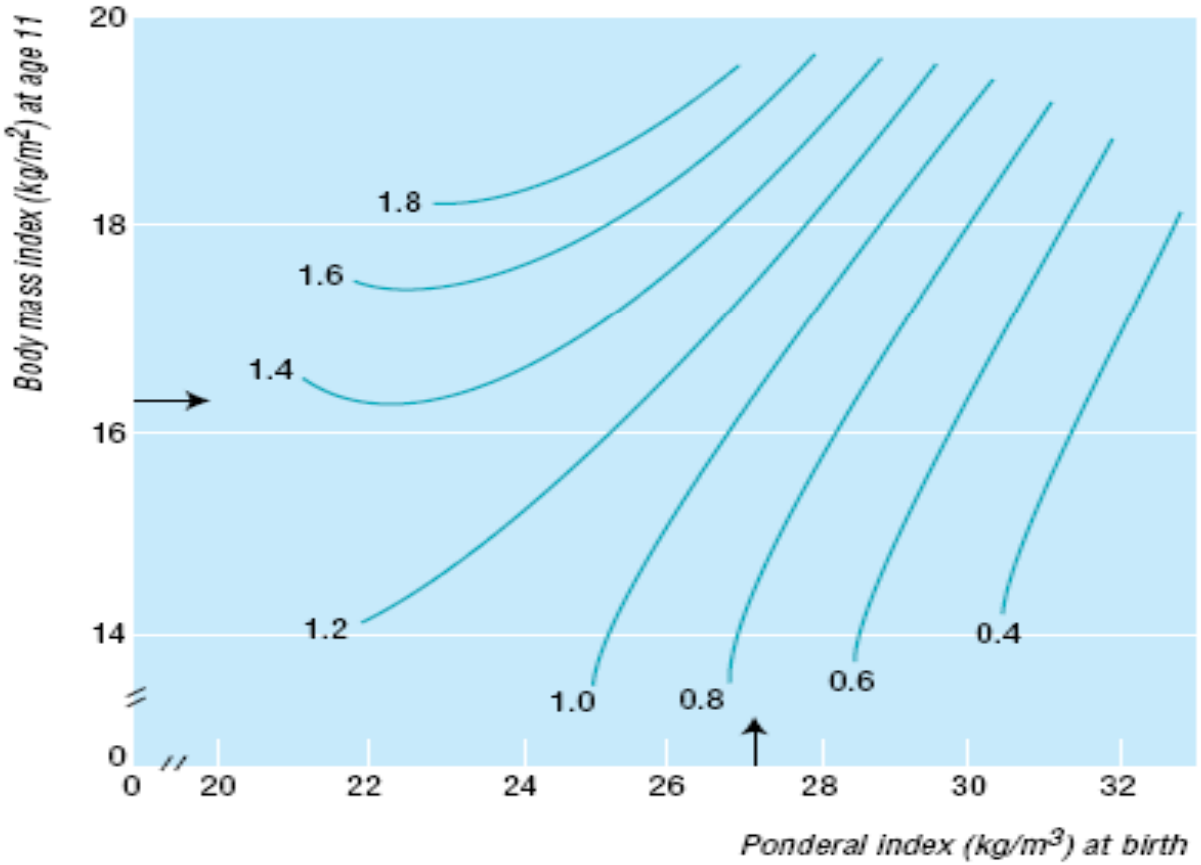


Fig 2 Hazard ratios for death from coronary heart disease according to ponderal index at birth and body mass index at age 11 years, adjusted for length of gestation. Arrows indicate average values

Early Nutrition Project

UPBEAT Trial

Poston L Lancet Diabetes Endocrinol 2015;3:767-777

- 1555 embarazadas obesas
- Randomizadas a tratamiento convencional vs intervención conductual de 8 lecciones sobre alimentación y AF
- Reducción de GPG pero no afectó la prevalencia de DG ni GEG
- Sin embargo…

Menor carga glucémica y grasas saturadas + AF

Skinfolds	Z-score (95% CI)	*p* value
Triceps	−0.14 (−0.38 to 0.10)	ns
Subscapular	−0.26 (−0.49 to −0.02)	<0.001

ns, not significant.

Conclusiones

El crecimiento es un proceso continuo.

Hay períodos sensibles en los que un estímulo o injuria es capaz de provocar adaptaciones que pueden determinar un riesgo para el desarrollo de enfermedades crónicas en la adultez

Desde hace algunos años está emergiendo un nuevo modelo conceptual en el desarrollo de la enfermedad modelado no sólo por nuestro bagaje genético y nuestro estilo de vida sino también por el camino que seguimos para arribar hasta allí: la trayectoria del crecimiento

- Prevención primordial es la mejor estrategia para la prevención de las enfermedades crónicas no transmisibles.
- La adolescencia es una ventana de oportunidad para la consejería nutricional para optimizar la salud presente y futura de madre e hijo

GRACIAS