Developmental Origins of Health and Diseases: when we become what we are.

Attilio L Boner

University of Verona, Italy

- ✓ **Original findings**
- ✓ Further discoveries & the first 1000 days
- ✓ Maternal diseases
- ✓ Maternal life style-environment
- ✓ Epigenetic
- ✓ More than 1 generation
- ✓ Prevention & Reversibility
- ✓ Public Health Implications
- ✓ Conclusions

ORIGIN OF COMPLEX ADULT ONSET DISEASES

Perhaps the single **most important observation made in the twentieth century** related to the origins of complex adult onset disorders was made by Barker and his colleagues

Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ.
Weight in infancy and death from ischaemic heart disease.
Lancet 1989;2:577–80.

ORIGIN OF COMPLEX ADULT ONSET DISEASES

✓**Barker DJ**, Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;1:1077.

a large positive geographic correlation (~0.7) for standardized rates for **infant mortality from 1921 to 1925 and ischemic heart disease from 1968 to 1978**.

✓**Barker DJ**, Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577.

✓**Barker DJ**, Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341:938.

✓**Barker DJ**. The origins of the developmental origins theory. J Intern Med. 2007;261:412.

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a possible relationship between birthweight and coronary heart disease in adulthood.

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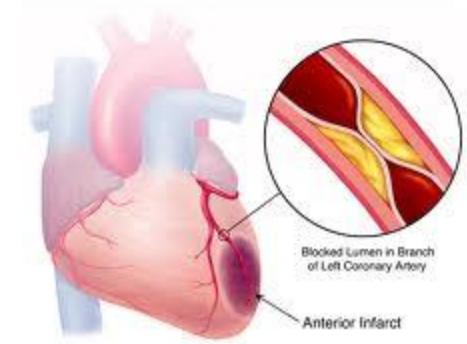

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undernutrition during gestation was an important contributor to low birthweight and an early origin of adult cardiac and metabolic disorders due to **fetal programming** in response to undernutrition that permanently shaped the body's structure, function, and metabolism

ORIGIN OF COMPLEX ADULT ONSET DISEASES

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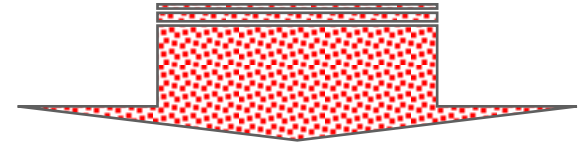
Before ≠ After

profound effects have been demonstrated if there is a **"mismatch"** between the early, developmental environment and the subsequent environment in childhood and adult life



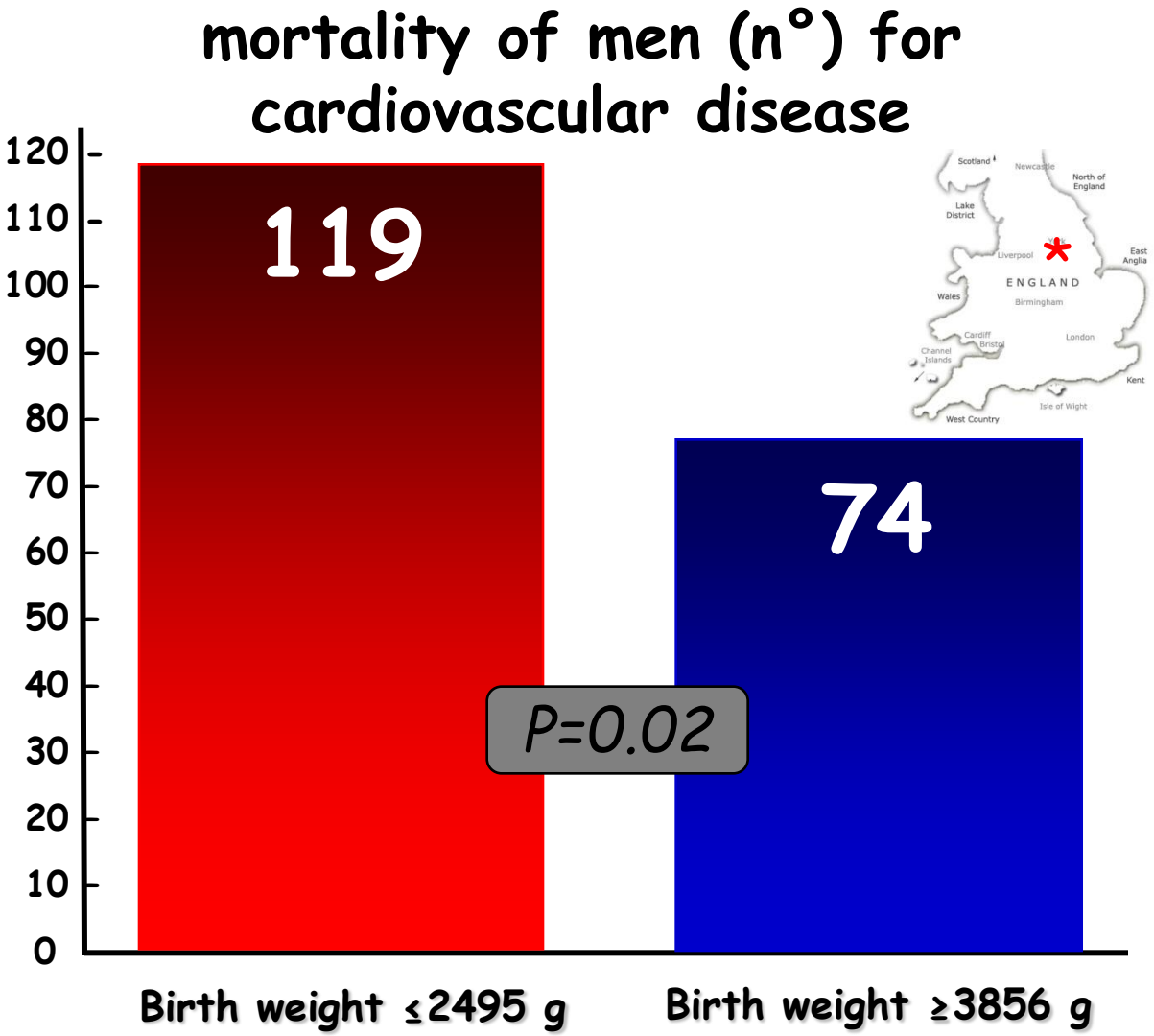
"thrifty phenotype"

The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life

DJ P Barker, BMJ 1993;306:422-6

✓1586 men born in Sheffield, England during 1907-24 whose birth weights, head circumferences, and other body measurements were recorded at birth

✓followed up to adulthood (59-70 years)



Fetal origins of non-insulin dependent diabetes

D J P Barker BMJ 1995;311:171-4

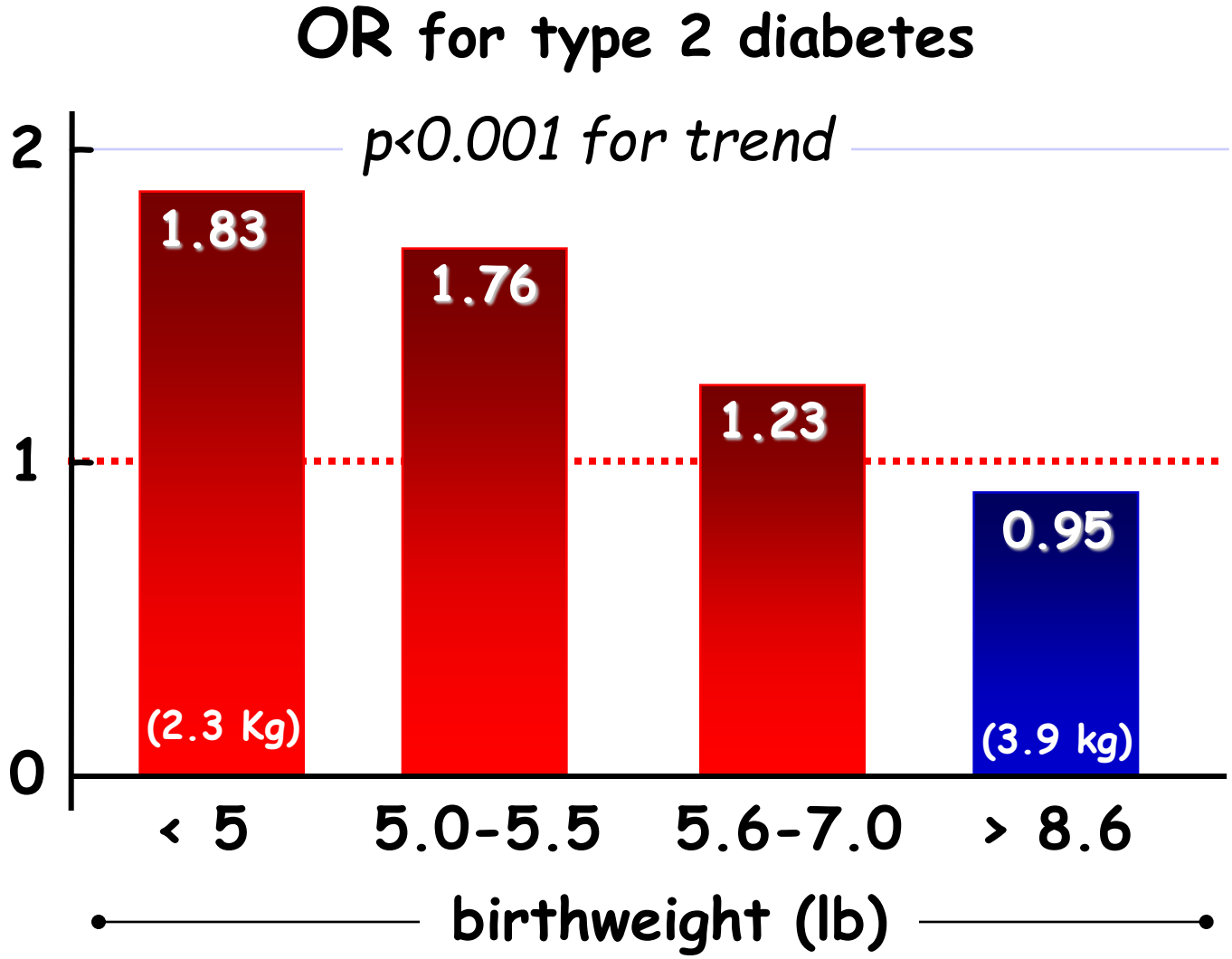
TABLE I—*Prevalence of non-insulin dependent diabetes and impaired glucose tolerance* in men aged 59-70 years*

Birth weight (lb (g))	No of men	No (%) with impaired glucose tolerance or diabetes	Odds ratio (95% confidence interval) adjusted for body mass index
≤5·5 (2500)	20	8 (40)	6·6 (1·5 to 28)
5·6–6·5 (2540-2950)	47	16 (34)	4·8 (1·3 to 17)
6·6–7·5 (2990-3410)	104	32 (31)	4·6 (1·4 to 16)
7·6–8·5 (3450-3860)	117	26 (22)	2·6 (0·8 to 8·9)
8·6–9·5 (3900-4310)	54	7 (13)	1·4 (0·3 to 5·6)
>9·5 (4310)	28	4 (14)	1·0
Total	370	93 (25)	χ^2 for trend=15·4 (P<0·001)

*Plasma glucose concentration >7·8 mmol/l at two hours after challenge.

Birthweight and the risk for type 2 diabetes mellitus in adult women. *Rich-Edwards JW, Ann Intern Med. 1999;130:278*

- ✓The Nurses' Health Study, a cohort of 121,701 U.S. women born from 1921 to 1946 who have been followed since 1976.
- ✓Birthweight and type 2 diabetes
- ✓1lb = 453 g



Not only cardiovascular disease

Those who are
thin at birth,
as measured by a low
ponderal index
(weight/length^3),

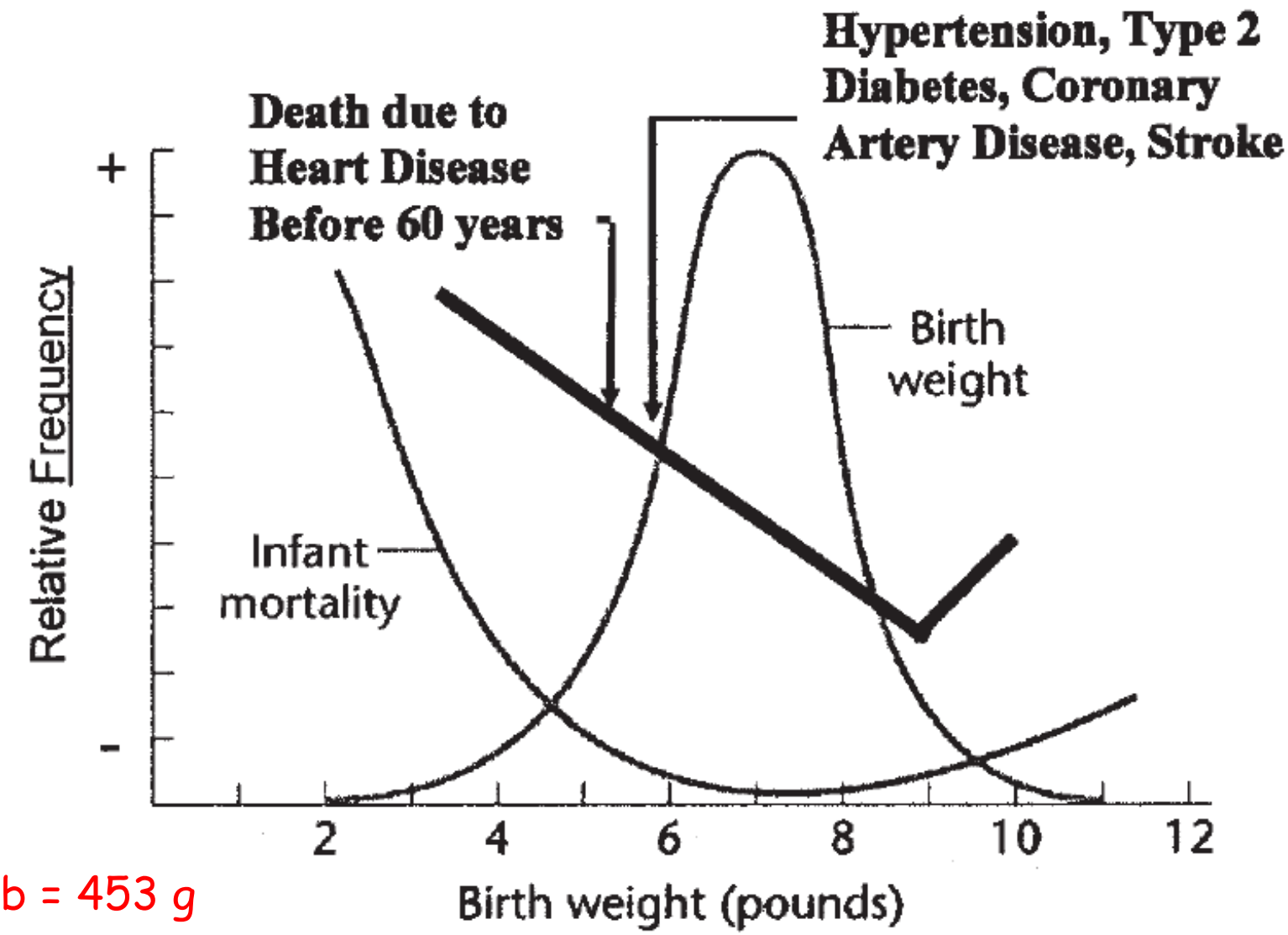
tend to develop the combination of:

- ✓ **hypertension,**
- ✓ **non-insulin-dependent diabetes,**
- ✓ **lipid disorders** known as syndrome X,
- ✓ **Osteoporosis** later in life
- ✓ **Precocious puberty**
- ✓ **Chronic bronchitis**
- ✓ **Some form of cancer**

Barker DJP Lancet 1993;341:938

Relation of birth weight to infant mortality and Complex Adult-Onset Disease

Dover GJ. Trans Am Clin Climatol Assoc. 2009;120:199-207.



1 pound = 1lb = 453 g

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Morbidities associated with intrauterine growth restriction (IUGR) can be split into metabolic and nonmetabolic effects

Joss-Moore Curr Opin Pediatr. 2009; 21:230

Adult phenotypes of intrauterine growth restriction

Metabolic	Nonmetabolic
Dyslipidemia	Attention deficit disorder
Hypertension	Chronic lung disease
Insulin resistance	Immunodeficiency
Poor postnatal growth	Neurodevelopmental delay
Renal insufficiency	Schizophrenia

Dyslipidemia, Hypertension, Insulin resistance + central adiposity = **Metabolic Syndrome**

Birth and the Metabolic Syndrome in Adult Life: A Systematic Review and Meta-analysis

Parkinson, Pediatrics 2013;131:1240-1263

- ✓ Reports of metabolic syndrome–associated features in adults (≥18 years of age) born at <37-week gestational age and at term (37- to 42-week gestational age)
- ✓ BMI, waist-hip ratio, percentage fat mass, systolic (SBP) and diastolic (DBP) blood pressure, flow-mediated dilatation, intima-media thickness, and fasting glucose, insulin, and lipid profiles
- ✓ 27 studies, with a total of 17 030 preterm and 295 261 term-born adults

In adults preterm birth was associated with:

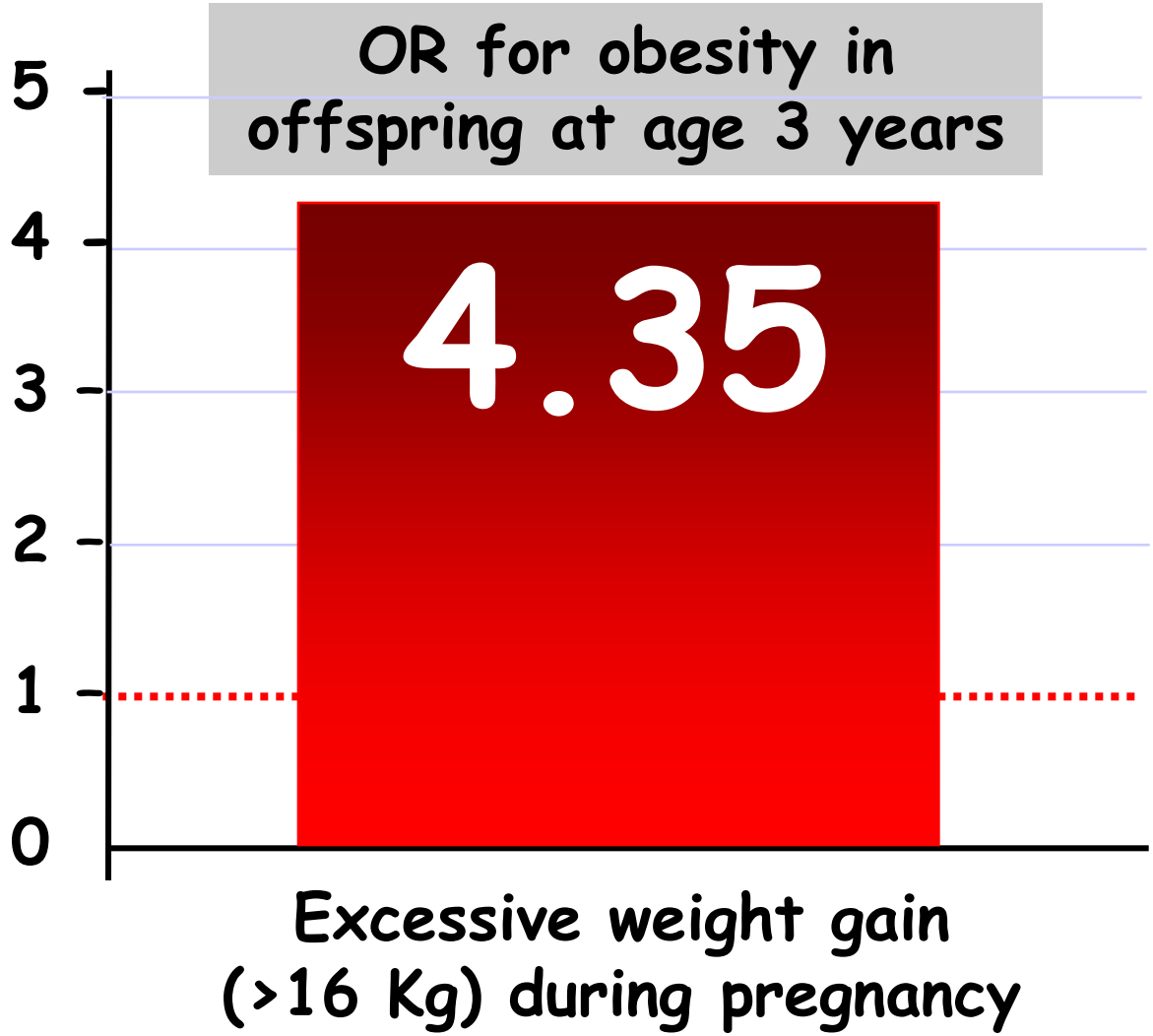
1) Significantly higher SBP (mean difference, 4.2 mm Hg; *P* <*0.001*), DBP (mean difference, 2.6 mm Hg; *P* <*0.001*)

2) Higher low-density lipoprotein (mean difference, 0.14 mmol/L; *P* = *0.01*)

Gestational weight gain and child adiposity at age 3 years. *Oken E, Am J Obstet Gynecol. 2007;196:322.e1-8.*

✓1044 mother-child pairs in Project Viva.

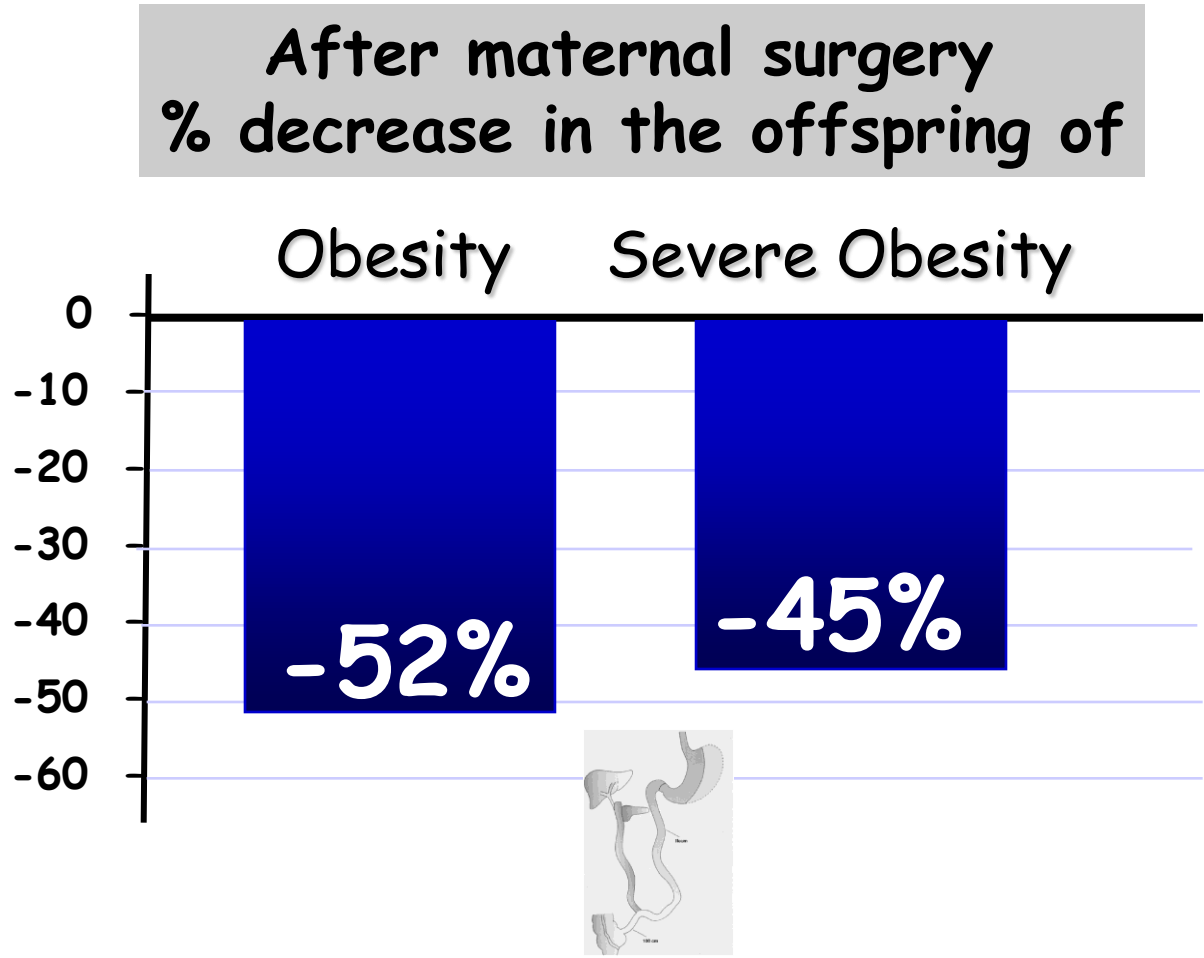
✓associations of gestational weight gain with child adiposity



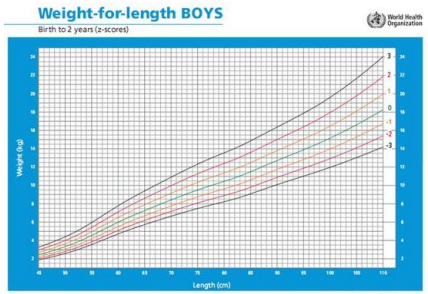
Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. *Kral JG, Pediatrics. 2006;118:e1644-9.*

✓172 children born to 113 previous obese mothers (BMI: 31±9 kg/m^2) with substantial weight loss after **biliopancreatic bypass surgery**

✓45 same-age siblings who were born before maternal surgery (mothers' BMI: 48 ± 8 kg/m^2)

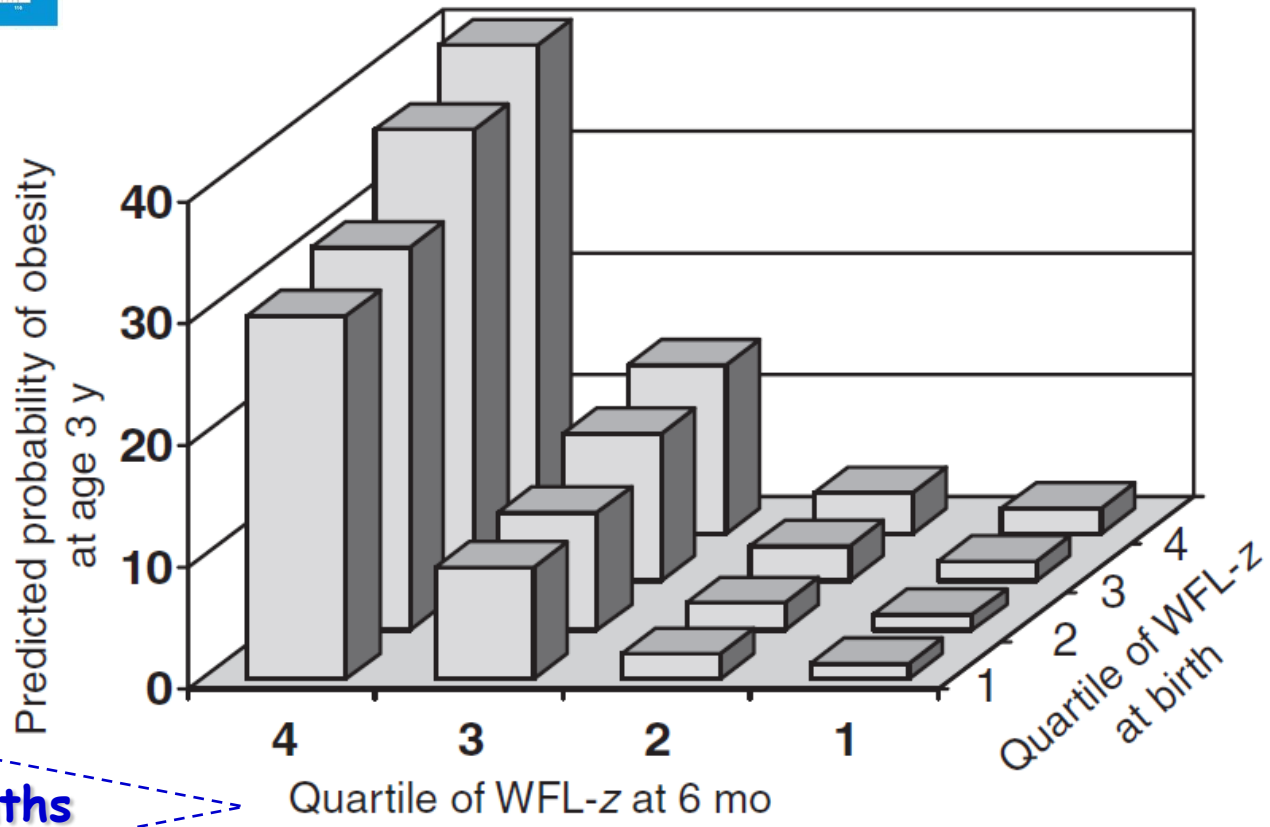


Weight status in the first 6 months of life and obesity at 3 years of age. *Taveras EM Pediatrics 2009;123:1177.*



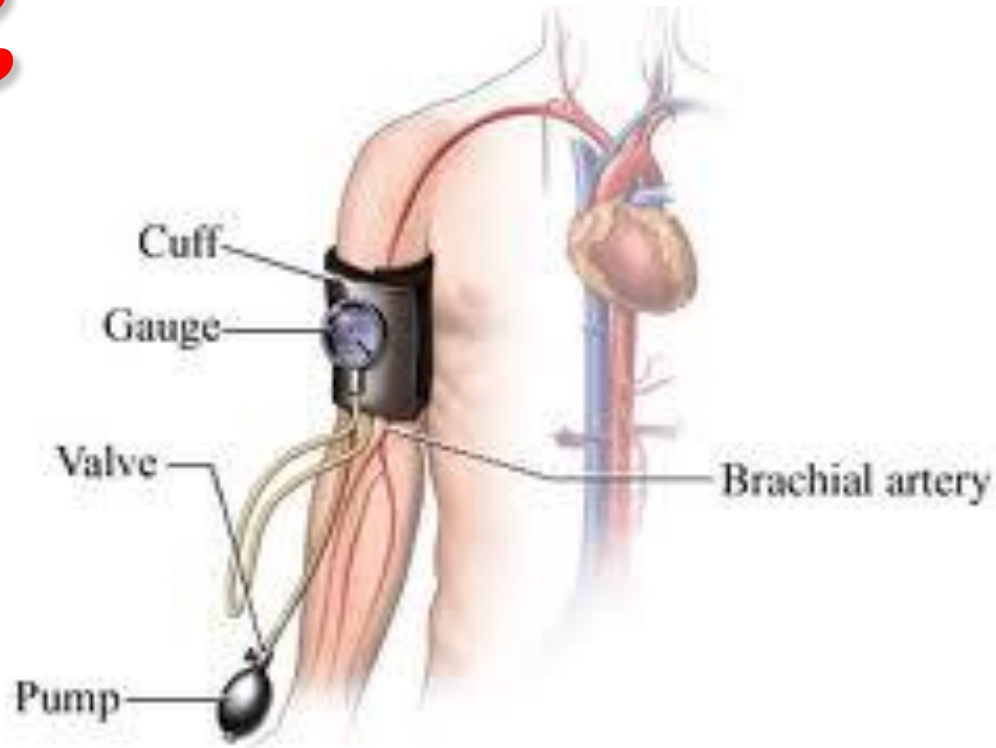
Predicted probability of obesity (BMI of > 95th percentile) at 3 years of age according to quartile of WFL *z* score at birth and at 6 months of age,

- ✓559 children
- ✓weight early in life (weight-for-length –WFL- at birth and 6 months of age)
- ✓obesity (BMI >95th percentile) at 3 years of age.



The importance of the first 6 months

Blood Pressure



Prenatal Factors for Childhood Blood Pressure Mediated by Intrauterine and/or Childhood Growth?

Wen Pediatrics 2011;127:e713

- ✓ 30 461 mother-child pairs in the Collaborative Perinatal Project.
- ✓ Prenatal data and children's SBP measured at 7 years of age.

Significantly associated with higher offspring systolic BP at age 7 years were:

1. Heavy maternal smoking during pregnancy
2. Maternal pregnancy weight gain.

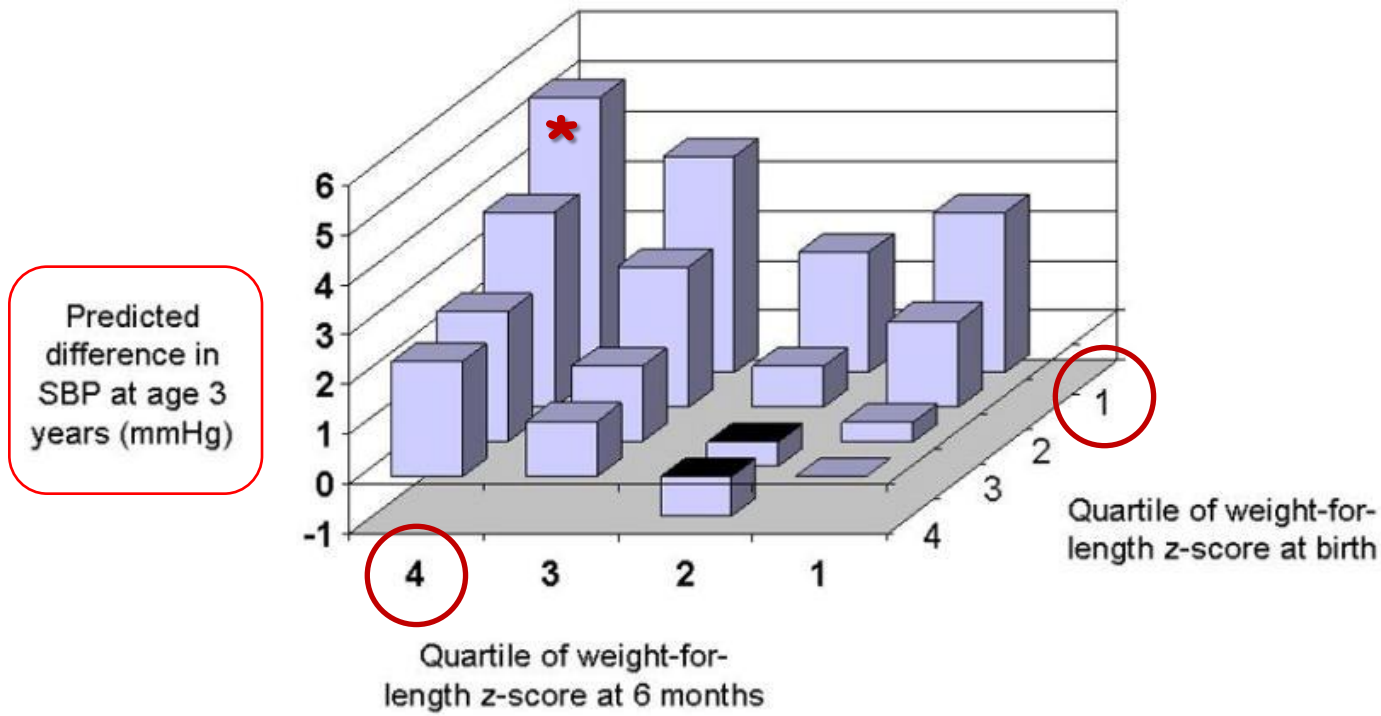
+

3. Child BMI.

Size at birth, infant growth, and blood pressure at three years of age. *Belfort MB, J Pediatr. 2007;151:670-4*

- ✓530 children from the prospective cohort Project Viva,
- ✓birth length and 6-month weight and length
- ✓weight-for-length z-scores (WFL-z)
- ✓SBP at age 3 years

Predicted difference in **systolic blood pressure at age 3 years** according to quartile of weight-for-length z-score at birth and age 6 months



Aterosclerosis

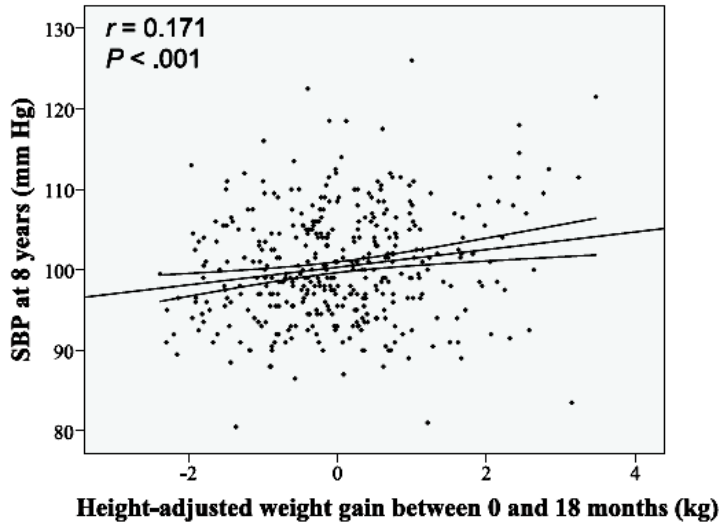
Weight Gain in Infancy and Vascular Risk Factors in Later Childhood

Skilton MR, Pediatrics 2013;131:1821

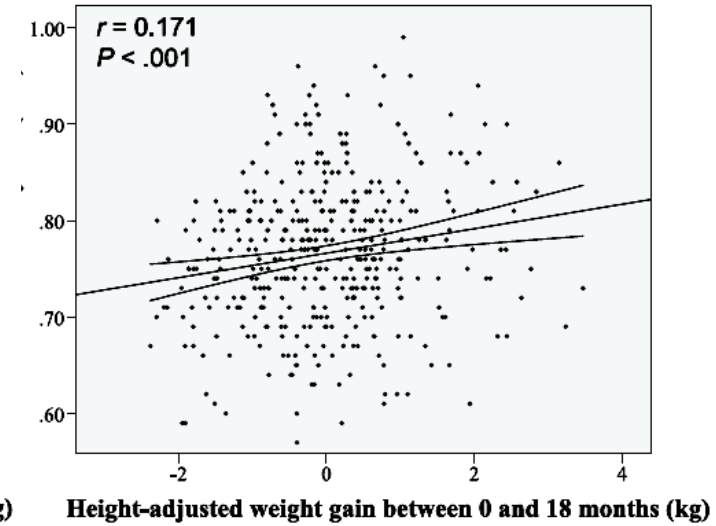
- ✓ A longitudinal birth cohort recruited antenatally
- ✓ 395 nondiabetic children followed to age 8 years
- ✓ Early weight gain and arterial wall thickness

Height-adjusted early weight gain between 0 and 18 months of age and,

Systolic Blood Pressure

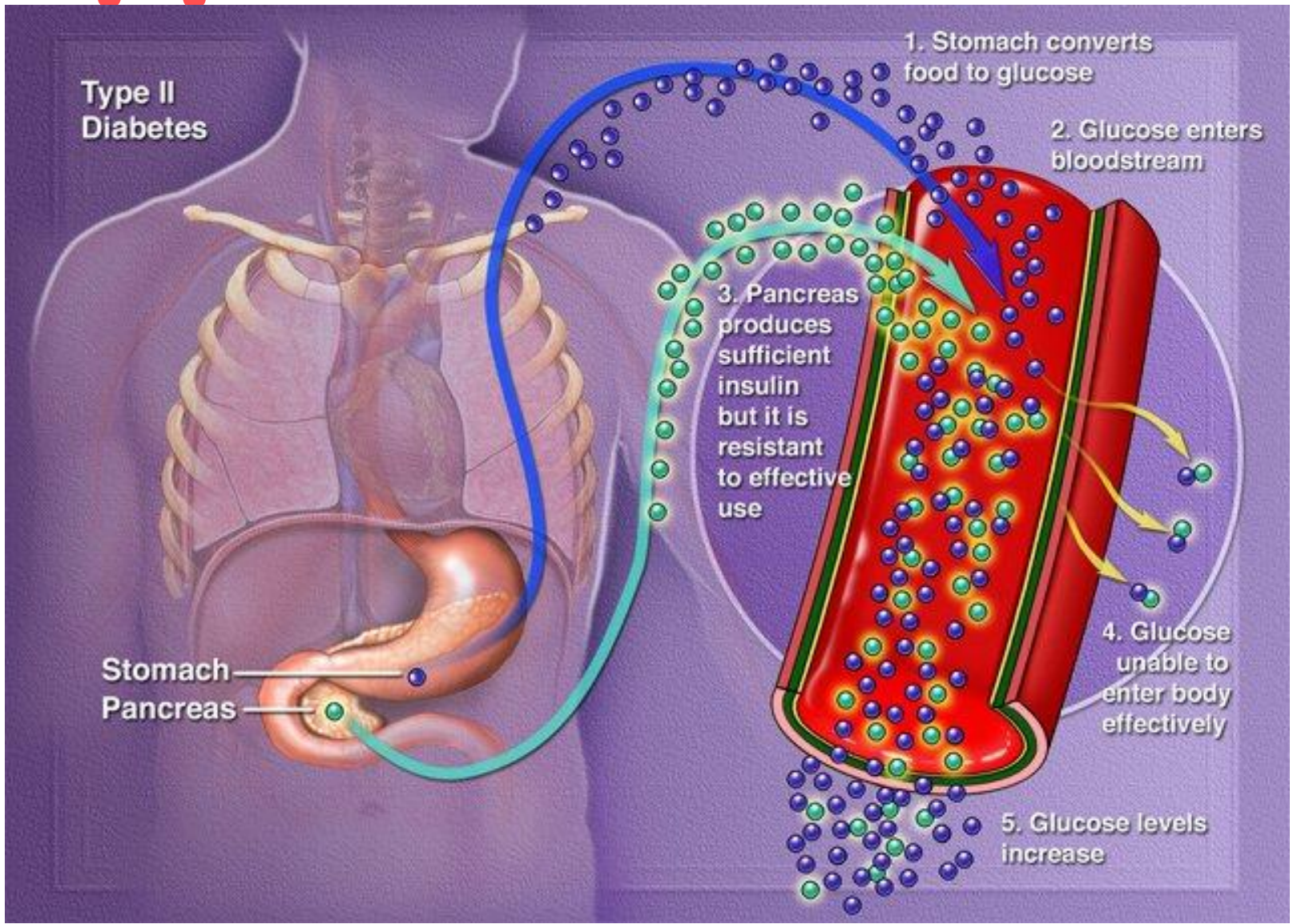


carotid IMT



at age 8 years

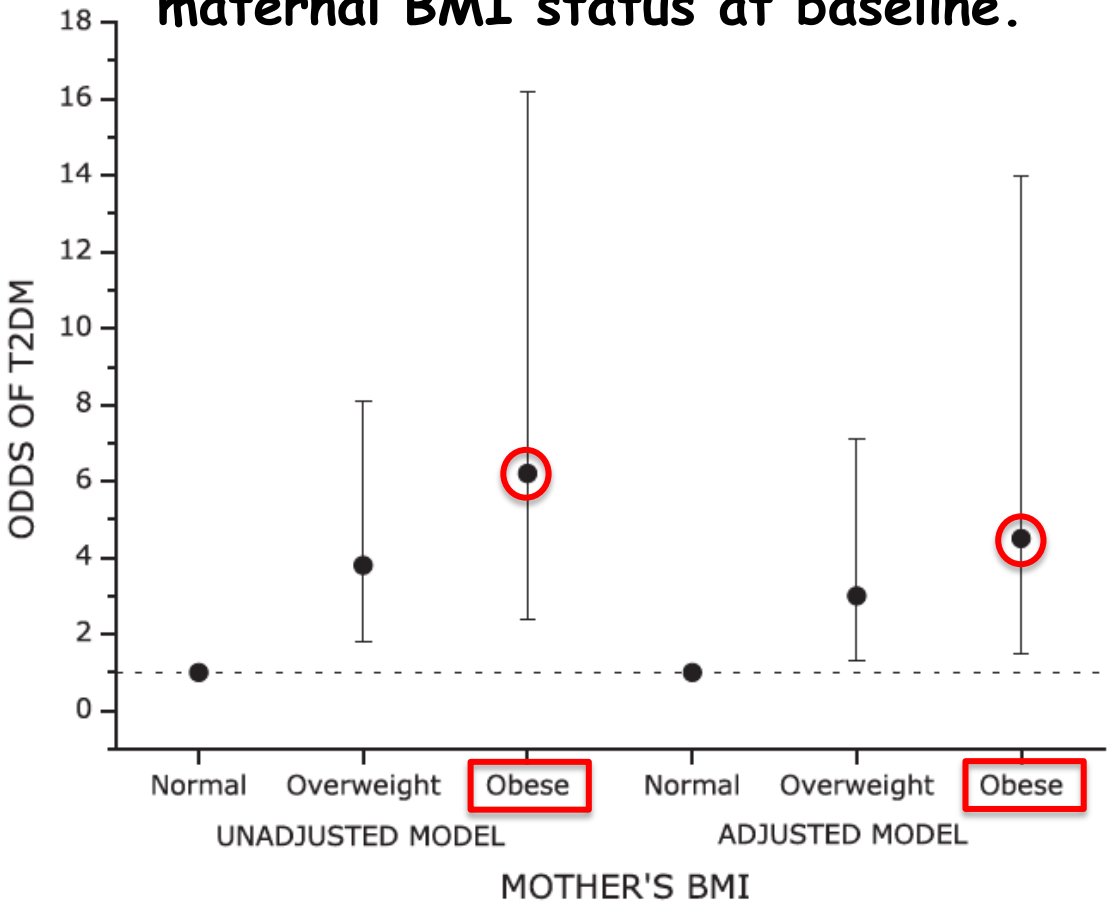
Type 2 diabetes



Higher Maternal Body Mass Index Is Associated with an Increased Risk for Later Type 2 Diabetes in Offspring *Juonala M, J Ped 2013;162:918*

- ✓ 1835 individuals aged 3-18 years;
- ✓ Maternal BMI;
- ✓ Followed-up over 21-27 years.

OR and 95% CI for offspring's type 2 diabetes risk at follow-up according to maternal BMI status at baseline.



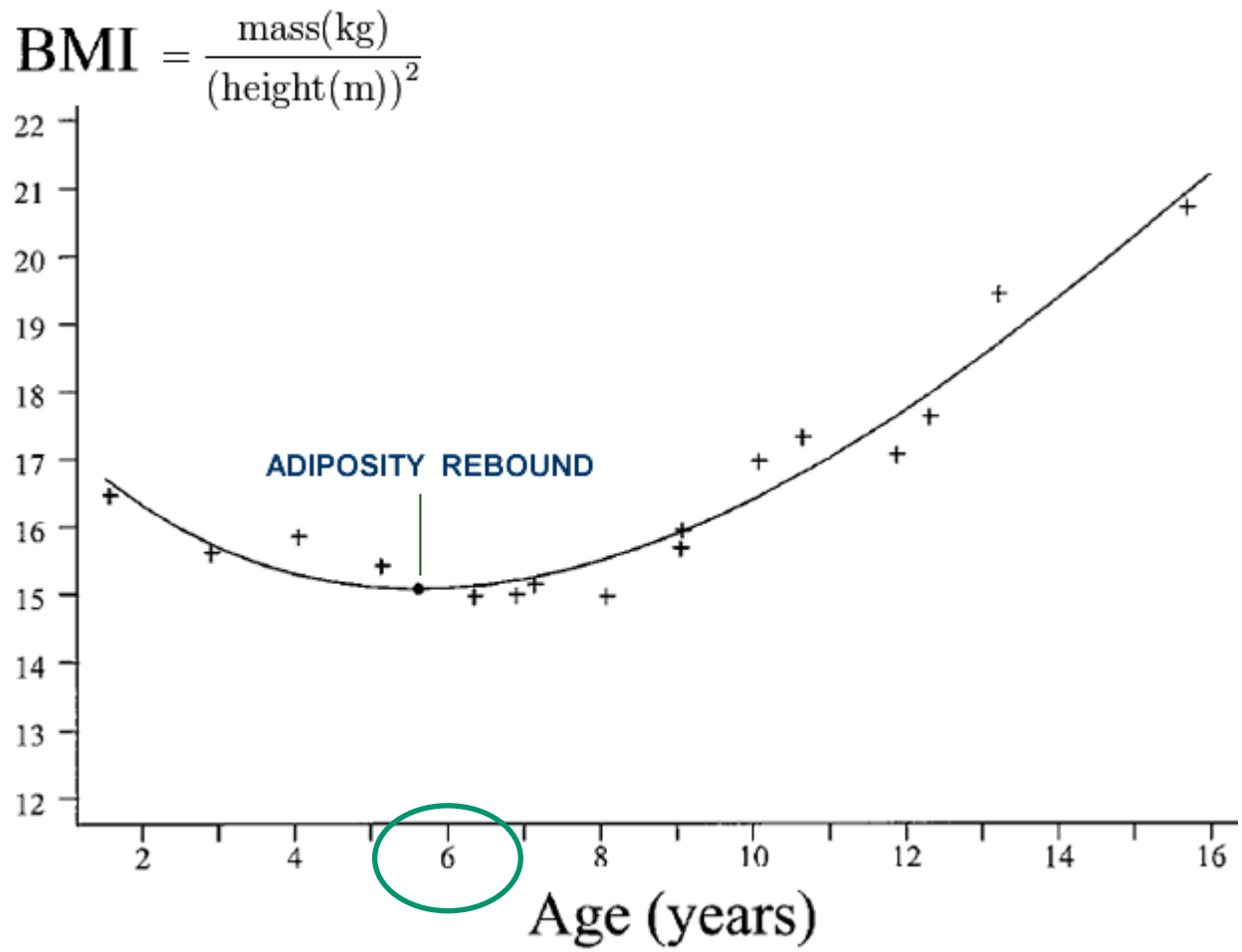
Early adiposity rebound in childhood and risk of type 2 diabetes in adult life.

Eriksson JG, Diabetologia 2003; 46: 190–194.

✓A longitudinal study of 8760 subjects born in Helsinki during 1934 to 1944.

✓On average, they had 18 measurements of height and weight between birth and 12 years of age.

✓In western countries BMI usually decreases after the age of 2 years and rises again at around 6 years--the so-called adiposity rebound.



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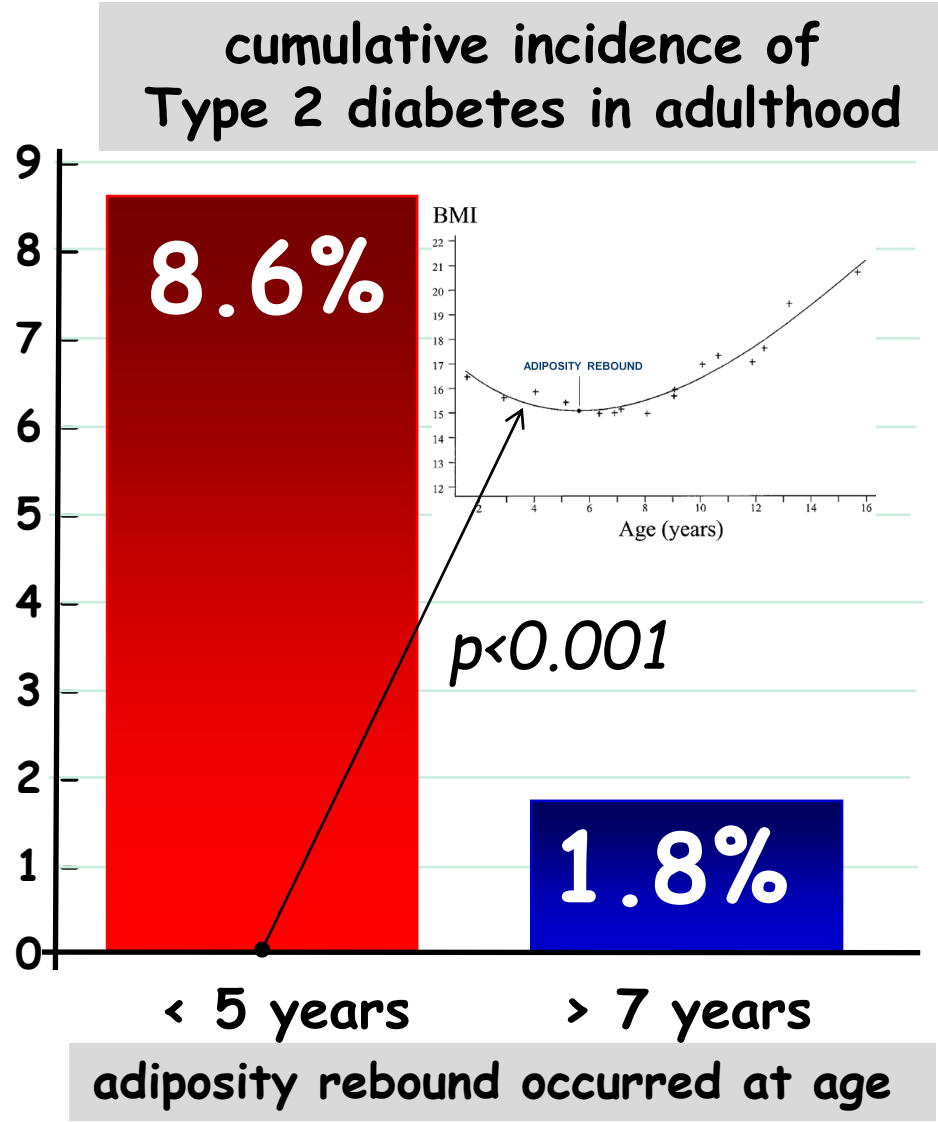


Lung

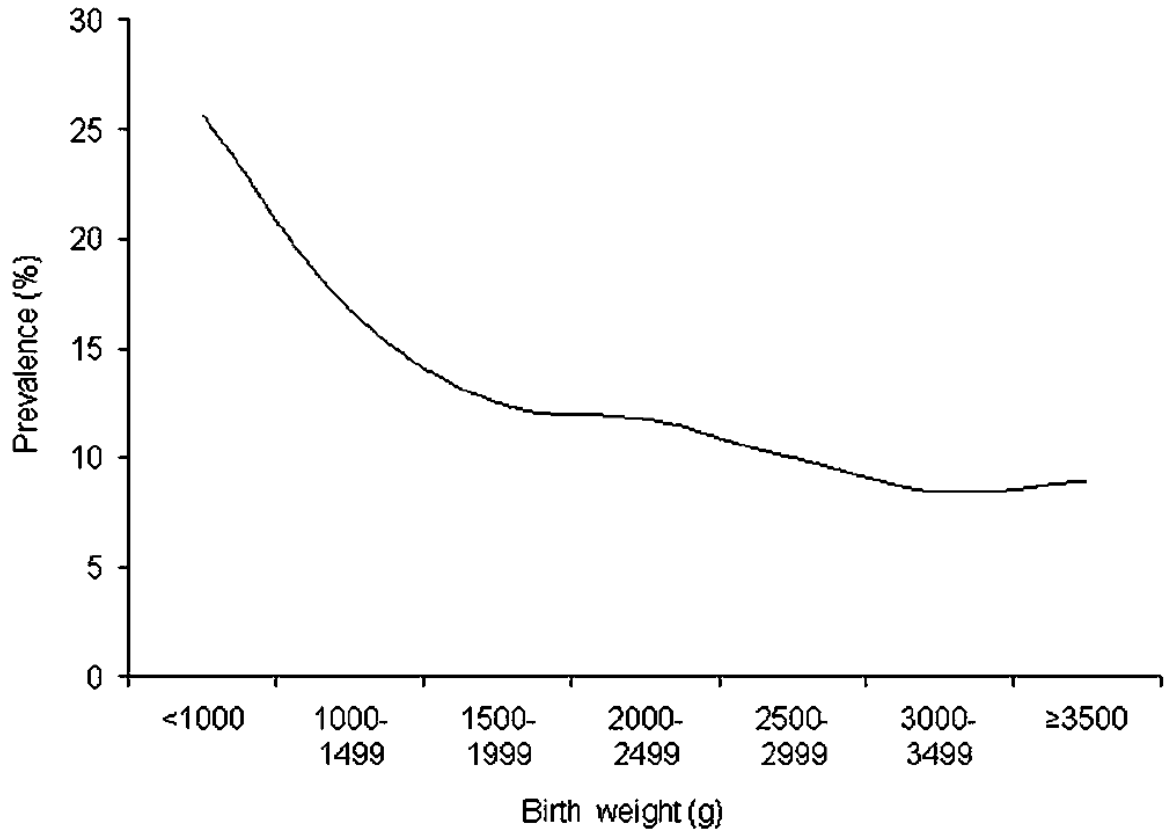

Why asthma makes it hard to breathe
Air enters the respiratory system from the nose and mouth and travels through the bronchial tubes.
In an asthmatic person, the muscles of the bronchial tubes tighten and thicken, and the air passages become inflamed and mucus-filled, making it difficult for air to move.
In a non-asthmatic person, the muscles around the bronchial tubes are relaxed and the tissue thin, allowing for easy airflow.
Inflamed bronchial tube of an asthmatic
Normal bronchial tube
Source: American Academy of Allergy, Asthma and Immunology

Birth weight and risk of asthma in 3-9-year-old twins: exploring the fetal origins hypothesis

Kindlund Thorax 2010;65:146

- ✓ Birth weight of all live twins (8280 pairs) born in Denmark between 1994 and 2000 .
- ✓ Information on asthma from parent-completed questionnaires at age 3-9 years.

Prevalence of asthma according to birth weight in Danish twin pairs, 3-9 years of age.

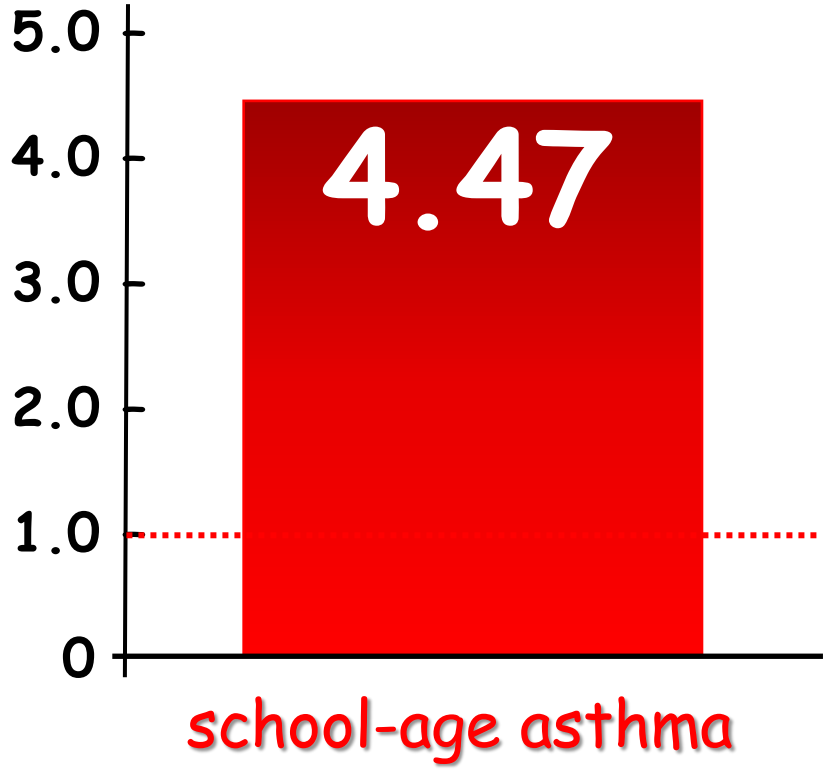


Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children

Sonnenschein-van der Voort AM, JACI 2014;133:1317

- ✓ Meta-analysis for 147,252 children of 31 birth cohort studies.
- ✓ Birth and infant growth characteristics.
- ✓ Risks of preschool wheezing (1-4 years) and school-age asthma (5-10 years).

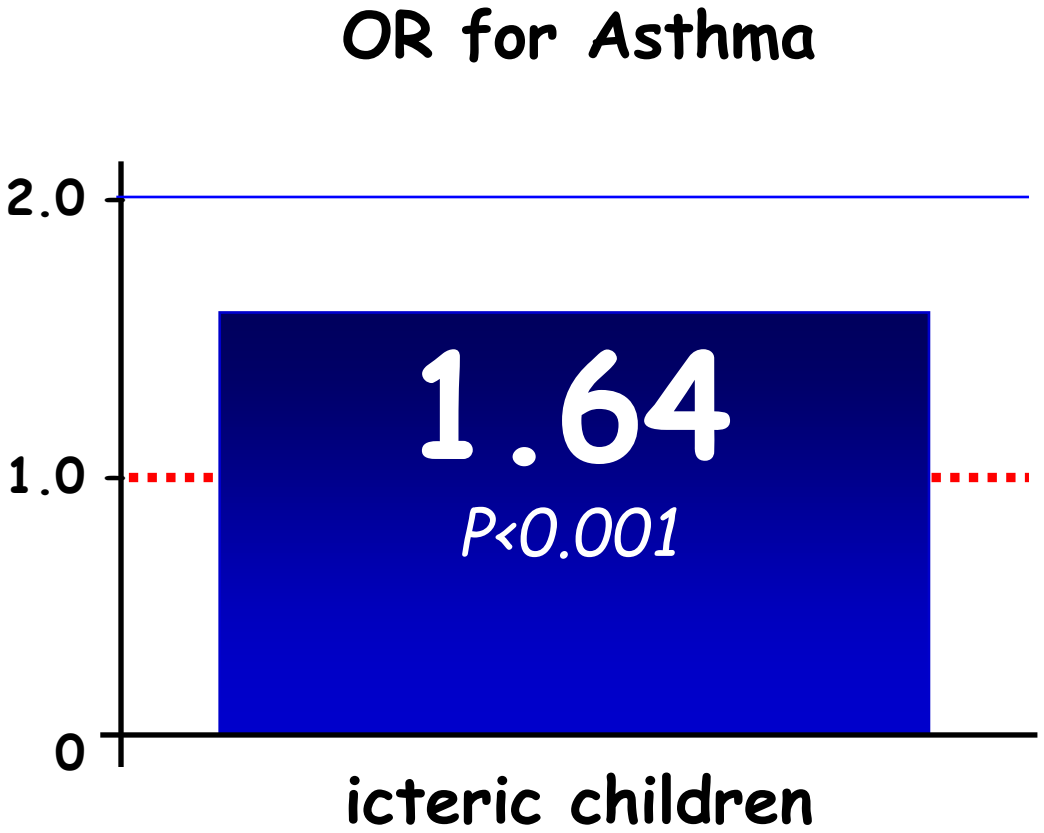
Compared with term-born children with normal infant weight gain, in children born preterm with high infant weight gain *OR* for

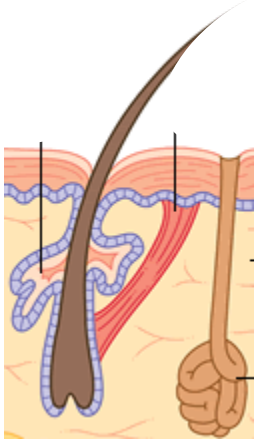


Neonatal jaundice is a risk factor for childhood asthma: a retrospective cohort study

Ku Min-Sho, Pediatr Allergy Immunol 2012;23(7):623-28

- ✓ 11,321 children from birth to 10 yr old.
- ✓ case (those with neonatal jaundice) and controls

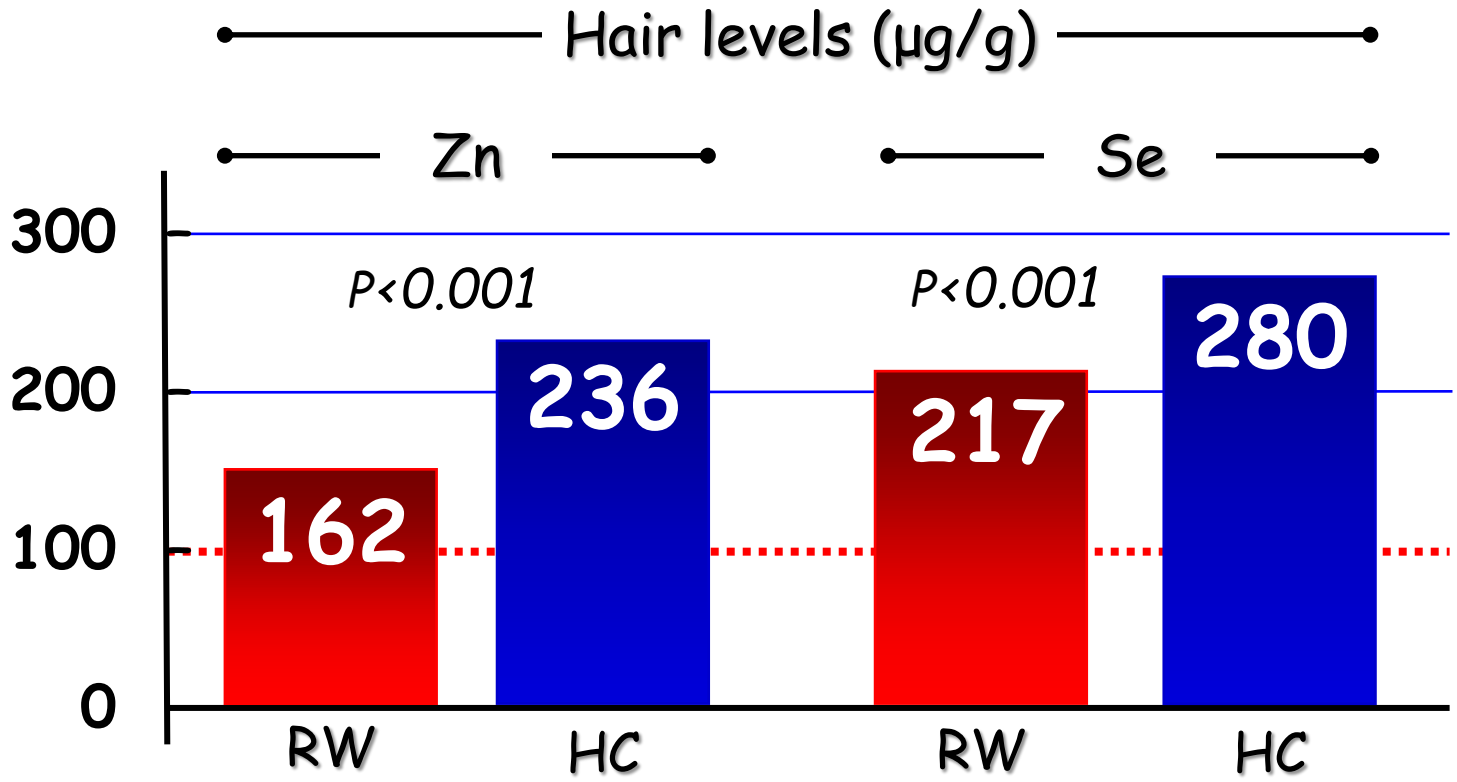


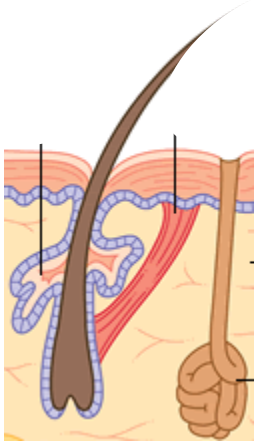


Hair Zinc and Selenium Levels in Children With Recurrent Wheezing

Razi C. H., Pediatr Pulmonol 2012; 47: 1185–1191

- ✓ Zn and Se levels
- ✓ 65 patients with recurrent wheezing (RW) and 65 healthy children (HC)
- ✓ Total antioxidant capacity (TAC) (mmol/L)





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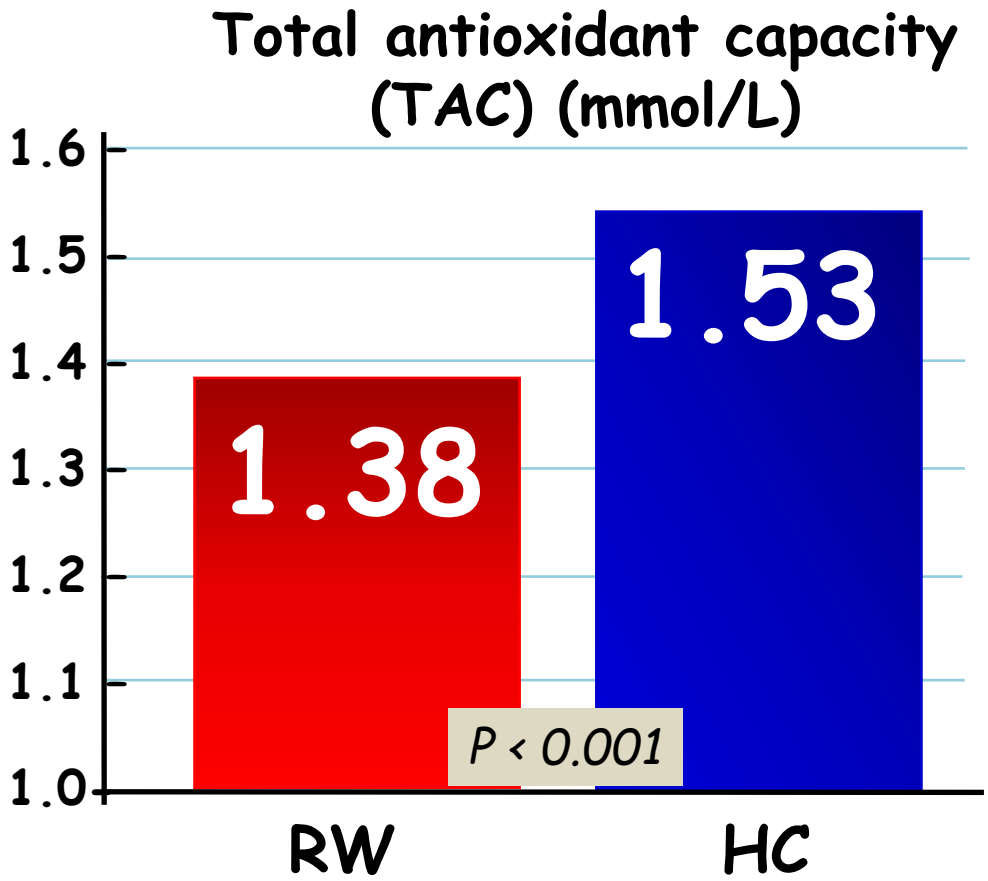
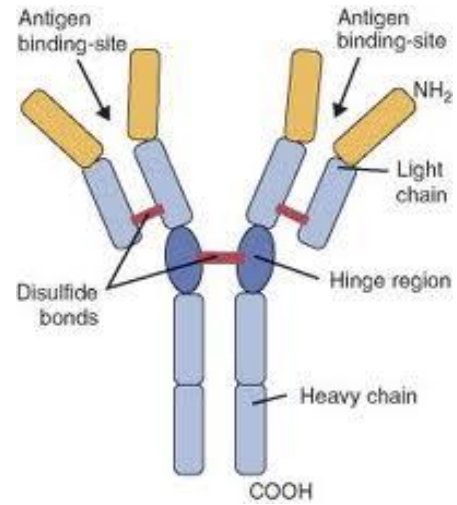
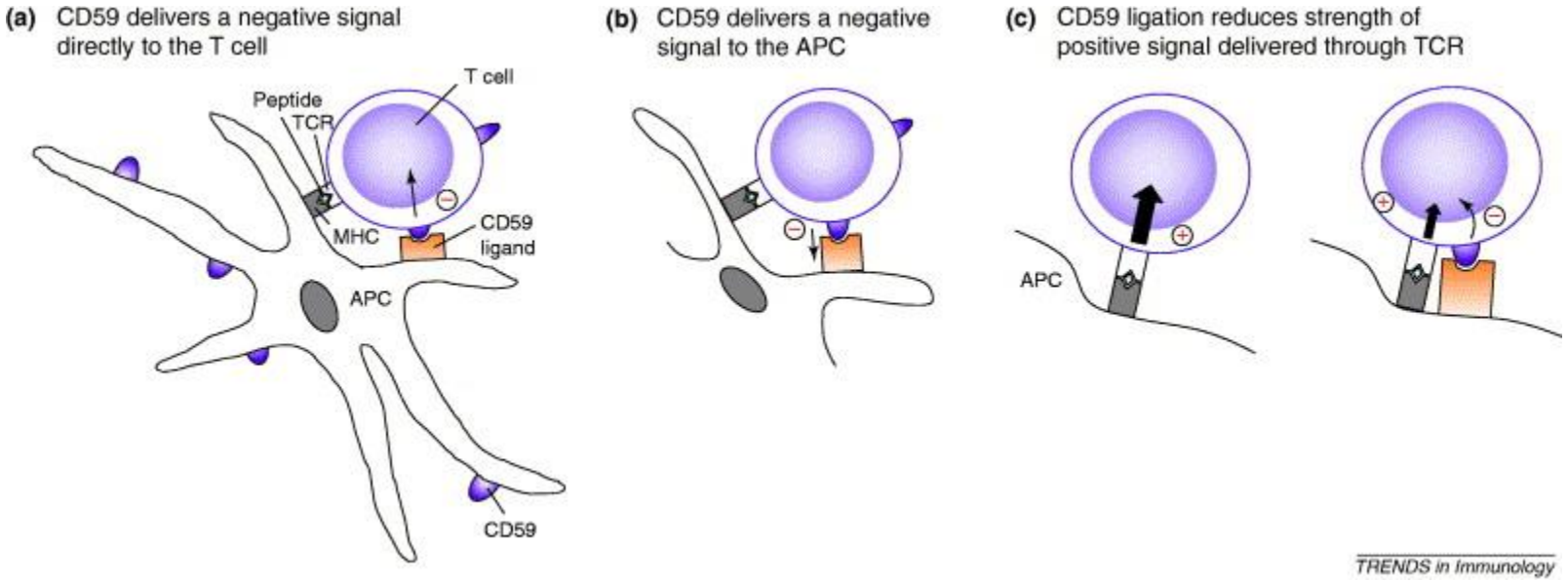


Immune & Allergic responses



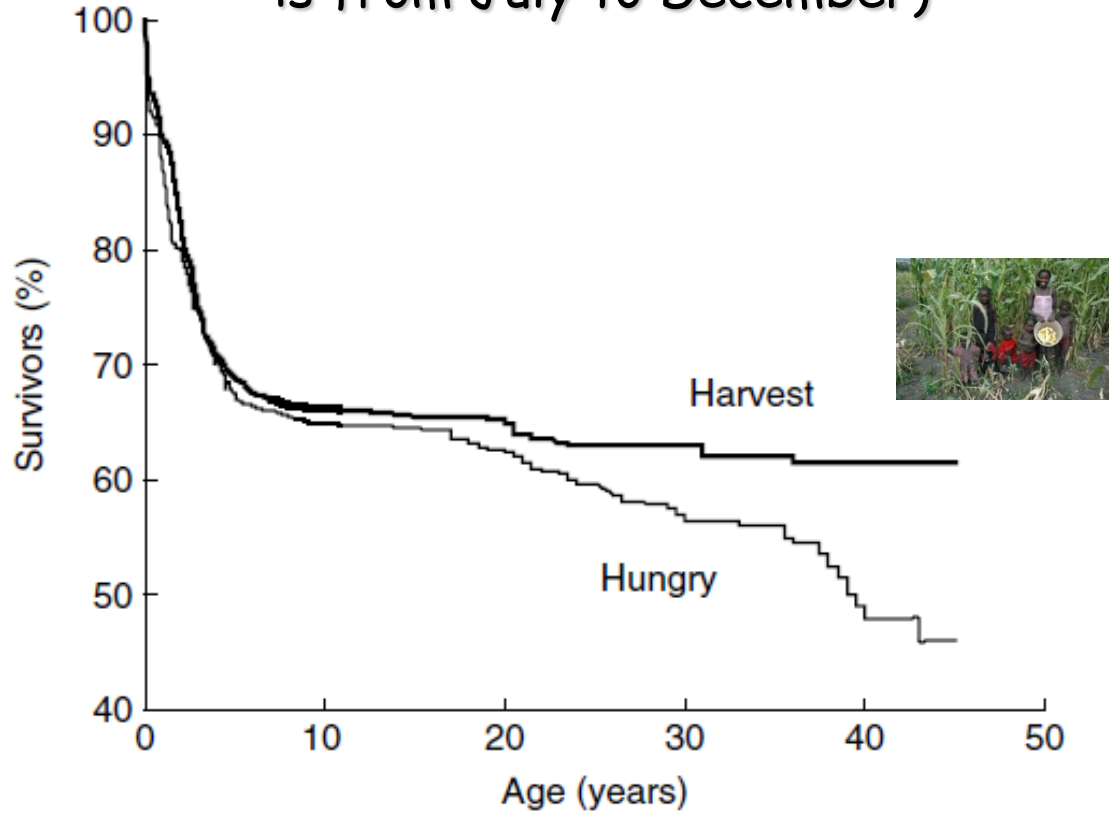


Early immunological development and mortality from infectious disease in later life.

Moore SE, Proc Nutr Soc. 2006;65:311–318.

✓3162 subjects (2059 alive and 1103 dead) resident in three villages in the rural West Kiang region of The Gambia.

Kaplan-Meier survival plots by season of birth (the 'harvest' season is from January to June and the 'hungry' season is from July to December)



Breast-feeding and Allergy

two meta-analyses
Gdalevich M, J Pediatr 2001; 139:261–266.
van Odijk OJ, Allergy 2003; 58:833–843.

protective effect of exclusive breast-feeding for 4–6 months on the risk of allergic disease (eczema and asthma) in early childhood, particularly in high-risk infants (positive family history).

However, there is no evidence that exclusive breast-feeding for **more than 6 months** prevented asthma, eczema or atopy at 5 years of age, and **with prolonged breast-feeding**,

the risk of atopic dermatitis and atopy, and particularly the risk of asthma in later life, may even increase.
Kramer MS, BMJ 2007; 335:815.
Matheson MC, JACI 2007;120:1051.

Breastfeeding and allergies: time for a change in paradigm?

Duncan Curr Opin Allergy Clin Immunology 2008, 8:398-405

✓Although **breastfeeding** is strongly recommended for its **multiple benefits** on child health, most recent studies do not confirm the 'conventional wisdom' that breastfeeding is protective against allergy and asthma.

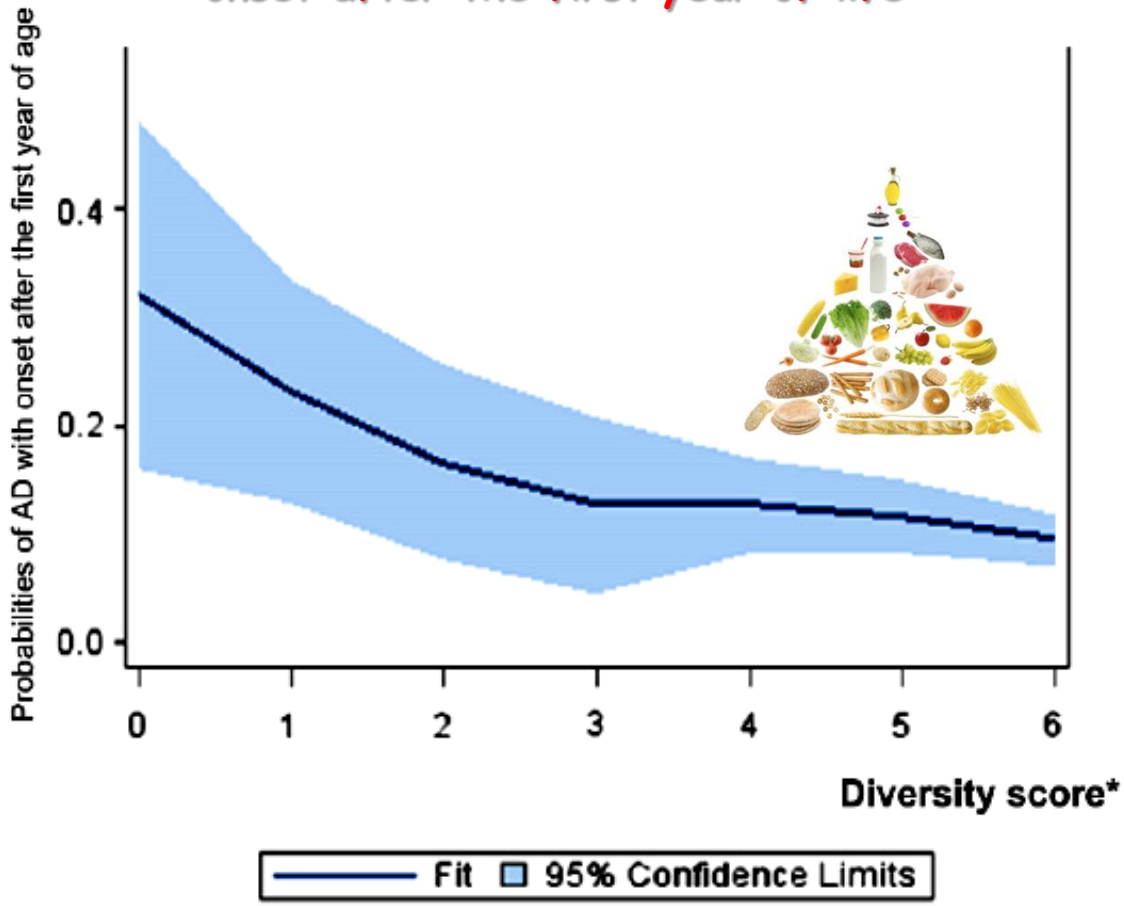
✓Early reduction in childhood wheezing may reflect protection from viral infections, but **allergies and asthma at later ages may be increased**.

Development of atopic dermatitis according to age of onset and association with early-life exposures

Roduit JACI 2012;130:130

- ✓ Introduction to complementary food in the first year of life.
- ✓ Development of atopic dermatitis, taking into account the reverse causality.
- ✓ 1041 children birth cohort study.
- ✓ Feeding practices reported by parents in monthly diaries between the 3rd and 12th months of life.

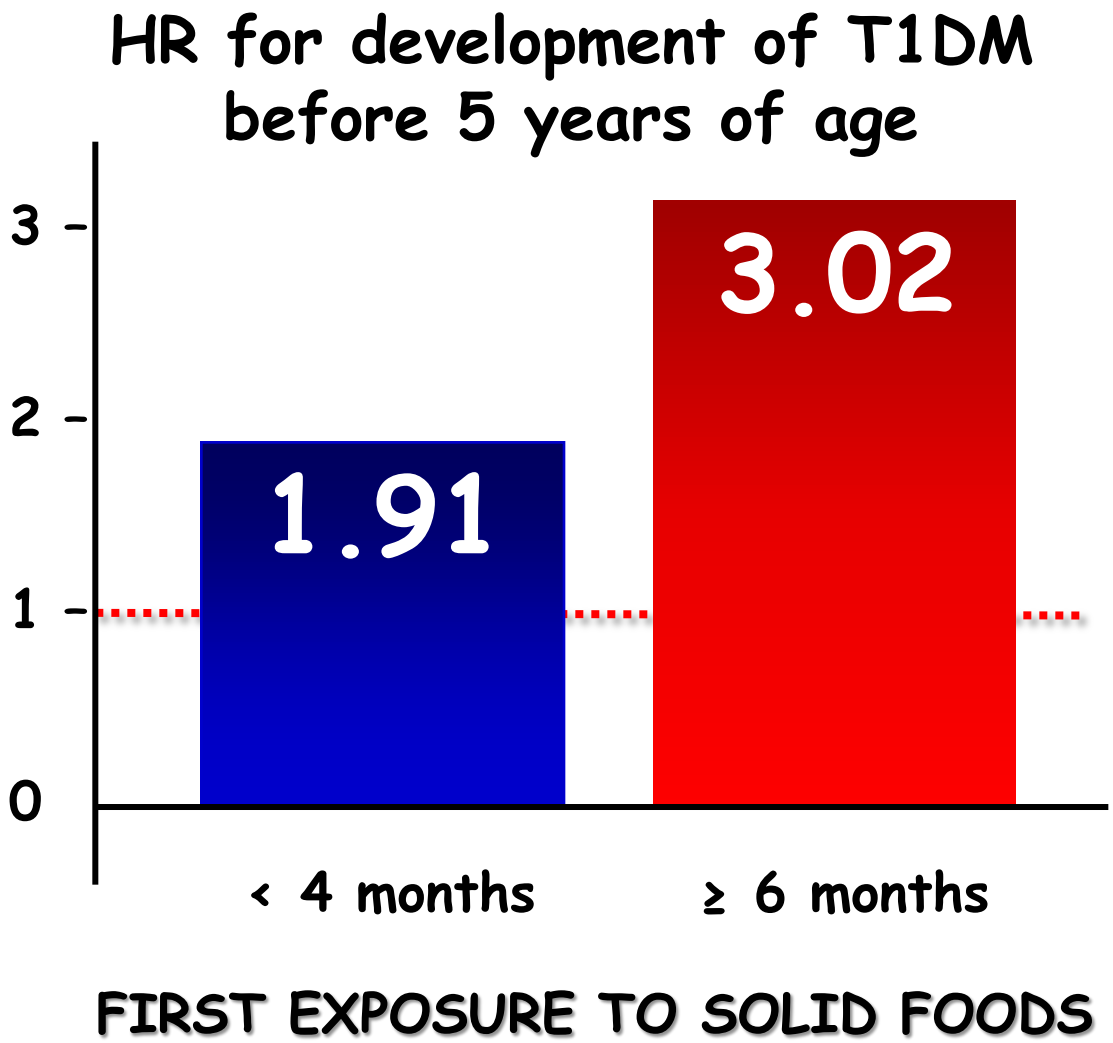
Association between increasing numbers of different major food items (n = 6) introduced in the first year of life and atopic dermatitis with onset after the first year of life.



Infant Exposures and Development of Type 1 Diabetes Mellitus

Frederiksen B., JAMA PEDIATR 2013;167(9):808-15

- ✓ 1835 children at increased genetic risk for T1DM
- ✓ Early (<4 months of age) and late (≥ 6 months of age) first exposure to solid foods compared with first exposures at 4 to 5 months of age.

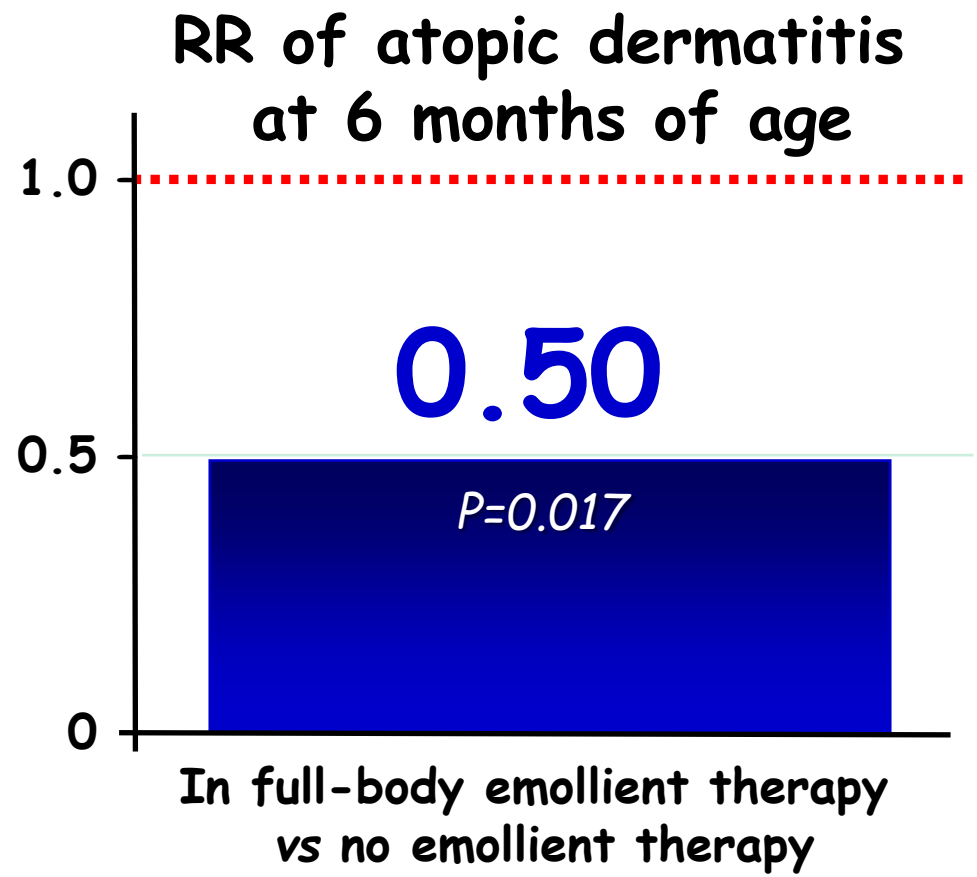


Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention.

Simpson EL, J Allergy Clin Immunol. 2014 Oct;134(4):818-23.

✓124 neonates at high risk for atopic dermatitis defined as having a parent or full sibling who has (or had) physician-diagnosed atopic dermatitis, asthma, or allergic rhinitis.

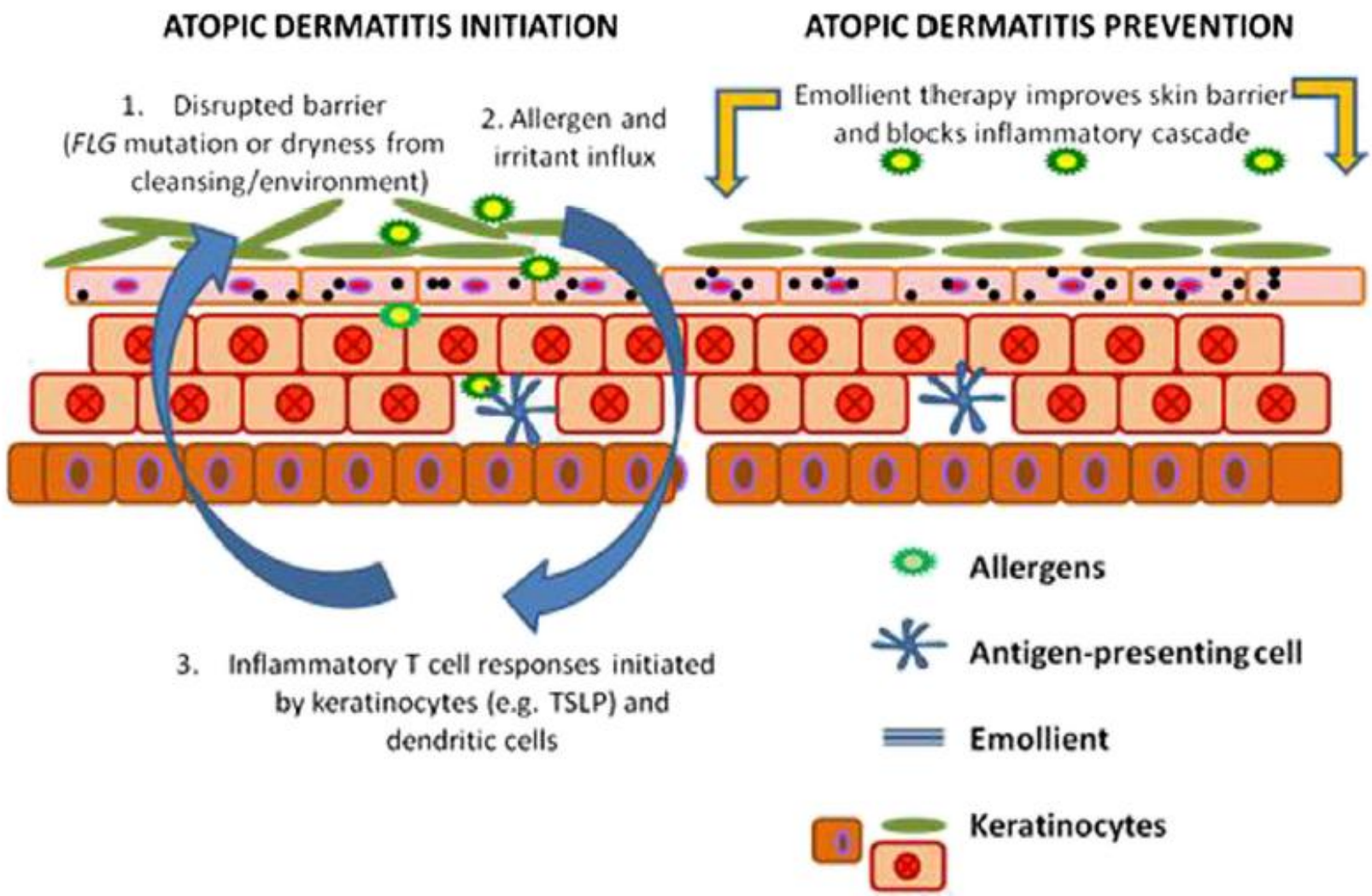
✓full-body emollient therapy (sunflower seed oil plus cream) at least once per day starting at least within 3 weeks of birth and continuing until the infants was 6 months *vs* no emollients.



Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention.

Simpson EL, J Allergy Clin Immunol. 2014 Oct;134(4):818-23.

Skin barrier protection might prevent atopic dermatitis development.

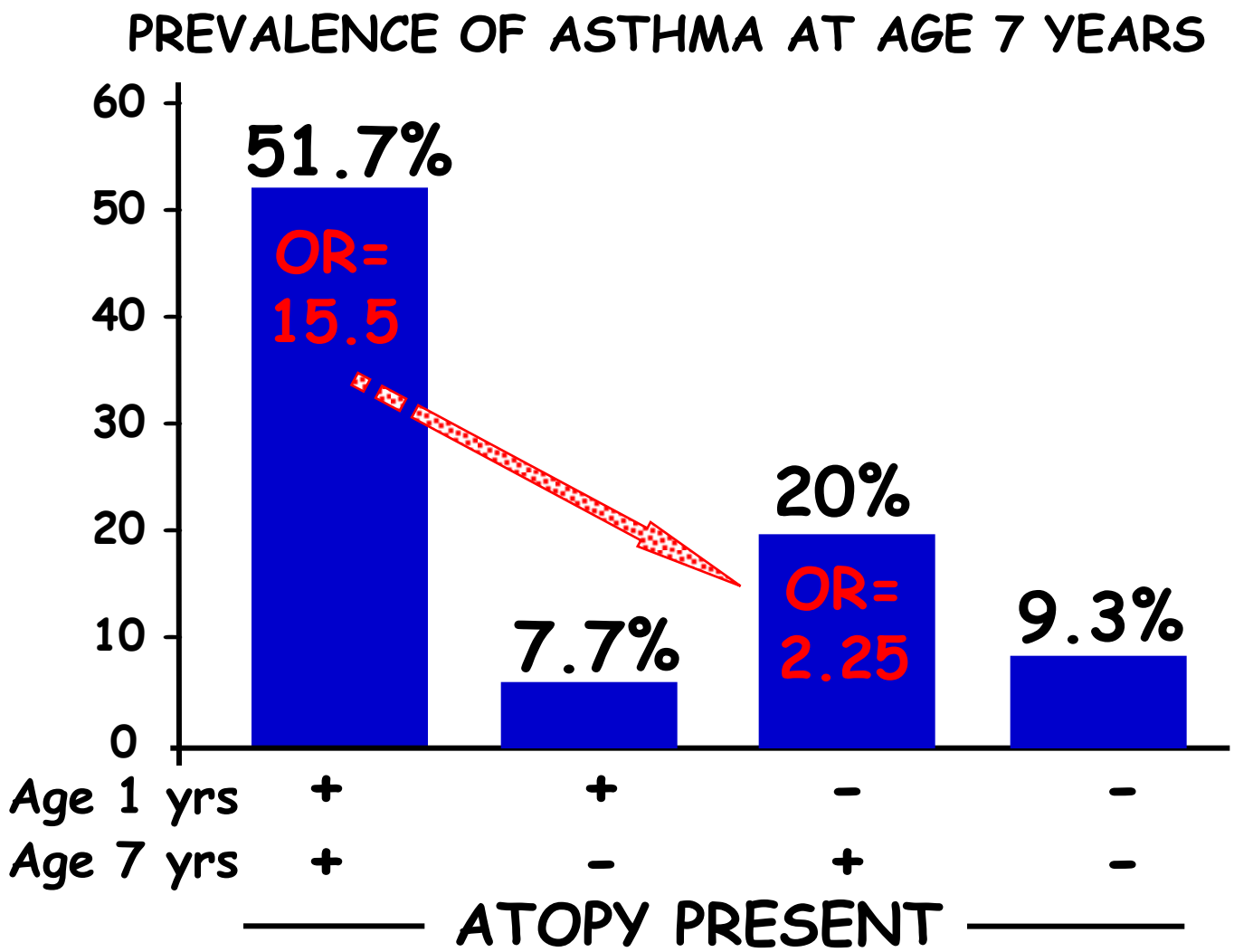


FLG, Filaggrin.

Atopy in early life and effect of a primary prevention program for asthma in a high-risk cohort.

Chan-Yeung M, J Allergy Clin Immunol. 2007;120(5):1221-3.

- ✓ Infants with at least 1 first-degree relative with asthma or 2 first-degree relatives with other IgE-mediated allergic diseases.
- ✓ Intervention group (N=279) or the control group (N=266) before the child's birth.



Mental - Brain health

Early life origins of psychological development and mental health *Raikkonen, Scand J Psychol 2009;50:583–591*

- **smaller body size at birth**
- *Sørensen, H. T., BMJ 1997;315:401*

- **Slower postnatal growth**
- *Gale, C. R., Brain., 2004;127:321–329.*
- *Lundgren, E. M., Ped Res 2001;50:91–96.*
- *Montgomery, S. M., Arch Dis Child 2006;91:61–62*

low cognitive functioning later in life.

Birth weight and the risk of depressive disorder in late life *Thompson C. Br J Psychiatry 2001;179:450-455*

2.900 Kg

✓882 singleton term births in the 1920s records of birth weight and weight at 1 year.

✓At 68 years Geriatric Depression Scale and Geriatric Mental State Examination.

3.850 Kg

Odds ratios for depression according to birthweight and weight at 1 year

♂

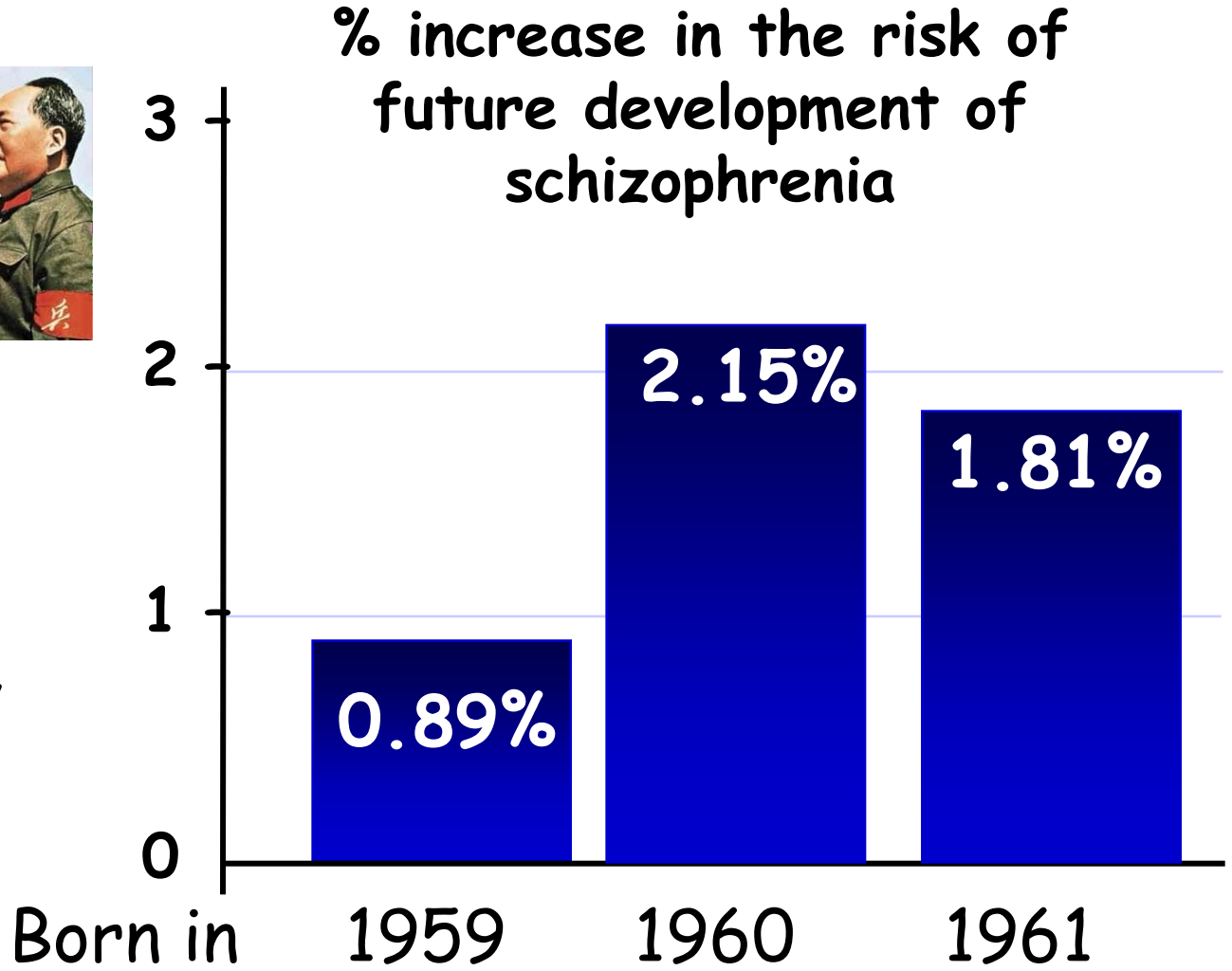
	Men			
	n	% With depression	OR (95% CI)	Adjusted OR (95% CI)
Birthweight (lb)				
<6.5	76	13.2	3.0 (0.9–10.6)	3.5 (1.0–12.8)[1]
6.5–7.5	149	12.1	2.7 (0.9–8.7)	3.2 (1.0–10.5)[1]
7.5–8.5	176	11.4	2.5 (0.8–7.9)	2.8 (0.9–8.9)[1]
>8.5	94	4.3	1.0	1.0
			(*P*=0.02)	(*P*=0.007)
Weight at 1 year (lb)				
<20.5	94	10.6	1.0	1.0
20.5–22.5	160	11.3	1.2 (0.5–2.9)	1.3 (0.5–3.1)[2]
22.5–24.5	132	8.3	0.9 (0.3–2.3)	1.0 (0.4–2.6)[2]
>24.5	109	11.9	1.6 (0.6–4.2)	2.1 (0.8–5.6)[2]
			(*P*=0.37)	(*P*=0.10)

Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961.

St Clair D, JAMA. 2005;294:557-62.

✓massive 1959-1961 famine in China as a cosequence of Mao Zedong's disastrous modernization campaign.

✓Rates of schizophrenia among those born before, during, and after the famine years.

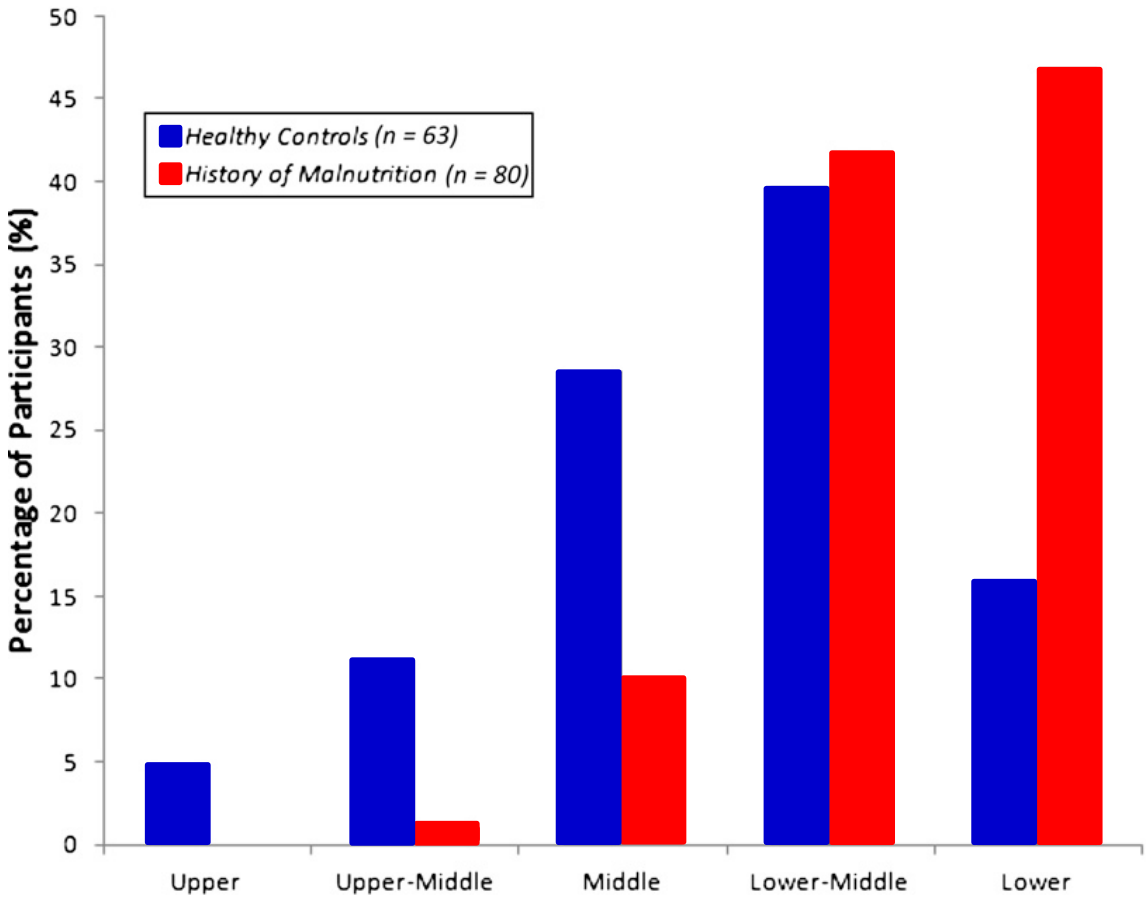


Socioeconomic Outcomes in Adults Malnourished in the first Year of Life: A 40-Year Study

JR Galler, Pediatrics 2012;130:e1

- ✓ Barbadian adults, hospitalized for protein-energy malnutrition (PEM) during 1st yr of life, with good nutrition & health;
- ✓ 40-yr longitudinal case-control study;
- ✓ educational achievement, occupational status & standard of living assessed by Hollingshead scales & a site-specific Ecology Questionnaire.

Malnutrition effects on Adult Hollingshead Index Social Position



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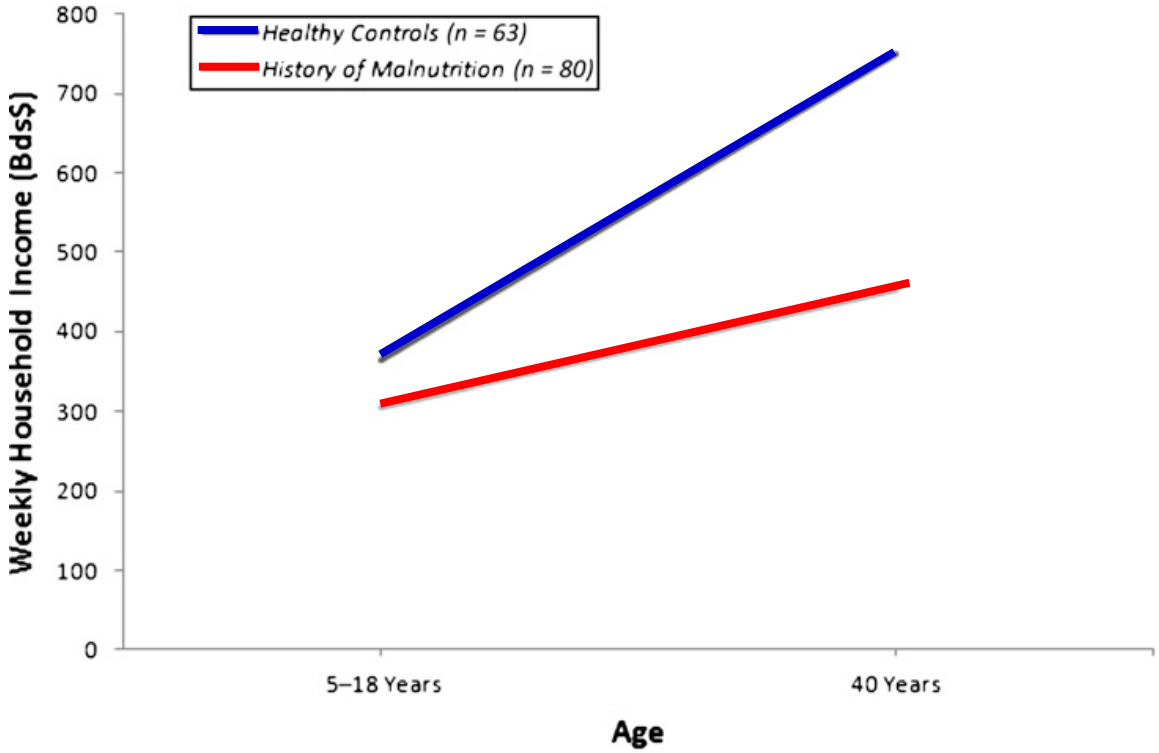
Malnutrition effects on adult weekly household income.



Maternal Prepregnancy BMI and Child Cognition: A Longitudinal Cohort Study

Basatemur E, Pediatrics 2013;131;56

(+)

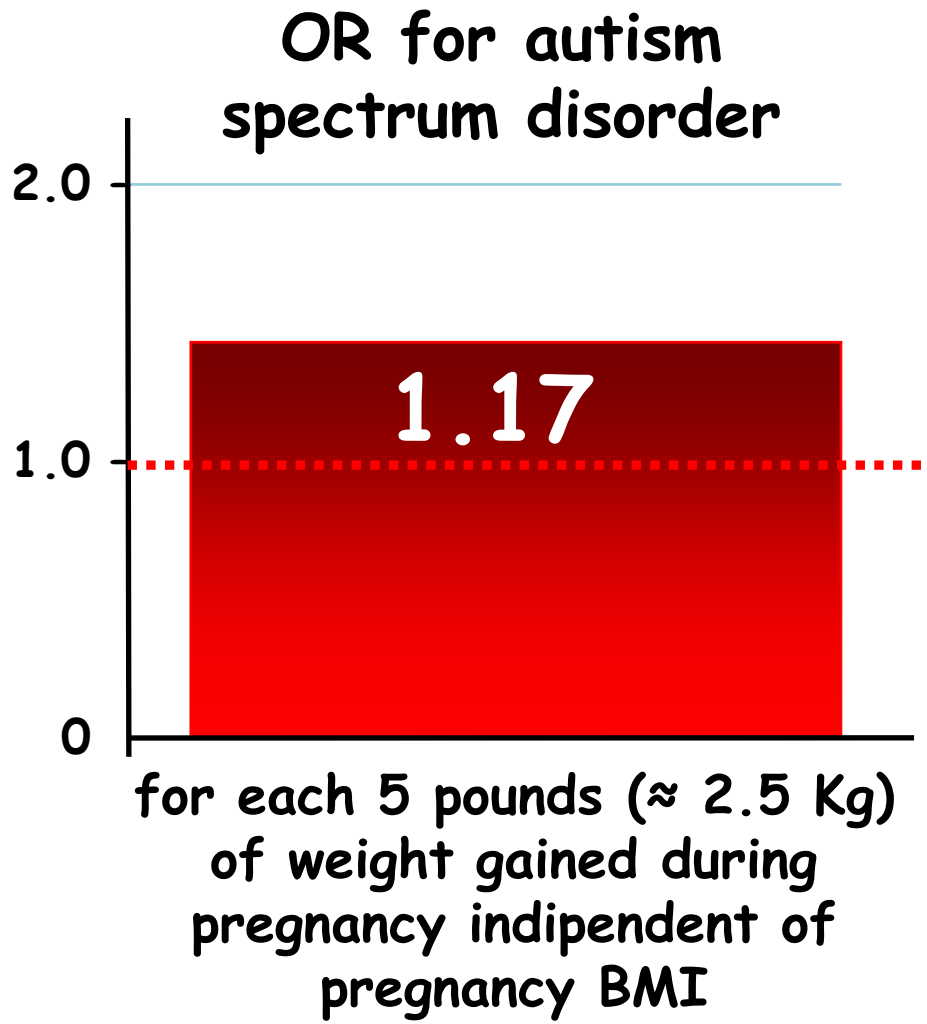
- ✓ Cohort of 19517 children in the United Kingdom.
- ✓ British Ability Scales, second edition and a number skills test performed at 5 and 7 yrs of age.
- ✓ Principal components analysis.
- ✓ Maternal prepregnancy BMI.

Maternal prepregnancy BMI was negatively associated with children's cognitive performance at age 5 *(P = .0069)* and age 7 *(P < .0001)*.

(-)

Maternal Prenatal Weight Gain and Autism Spectrum Disorders *Bilder, Pediatrics 2013;132:e1276*

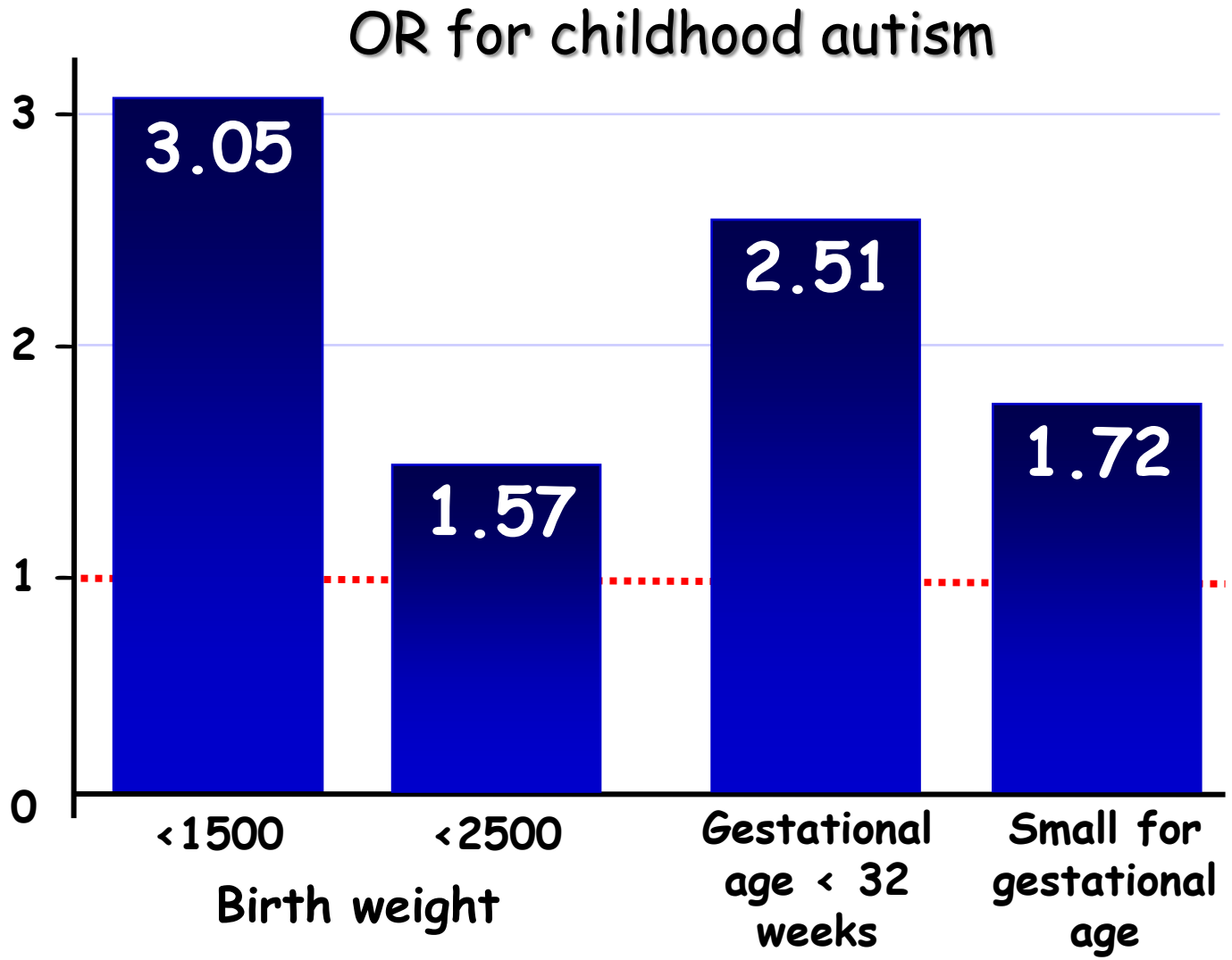
- ✓ A population-based autism spectrum disorder (ASD) cohort (n = 128)
- ✓ 10 920 control subjects
- ✓ A second ASD cohort of children (n = 288) and their unaffected siblings (n = 493)



Risk of Autism Spectrum Disorders in Low Birth Weight and Small for Gestational Age Infants

Lampi K., J Ped 2012;161:830-836

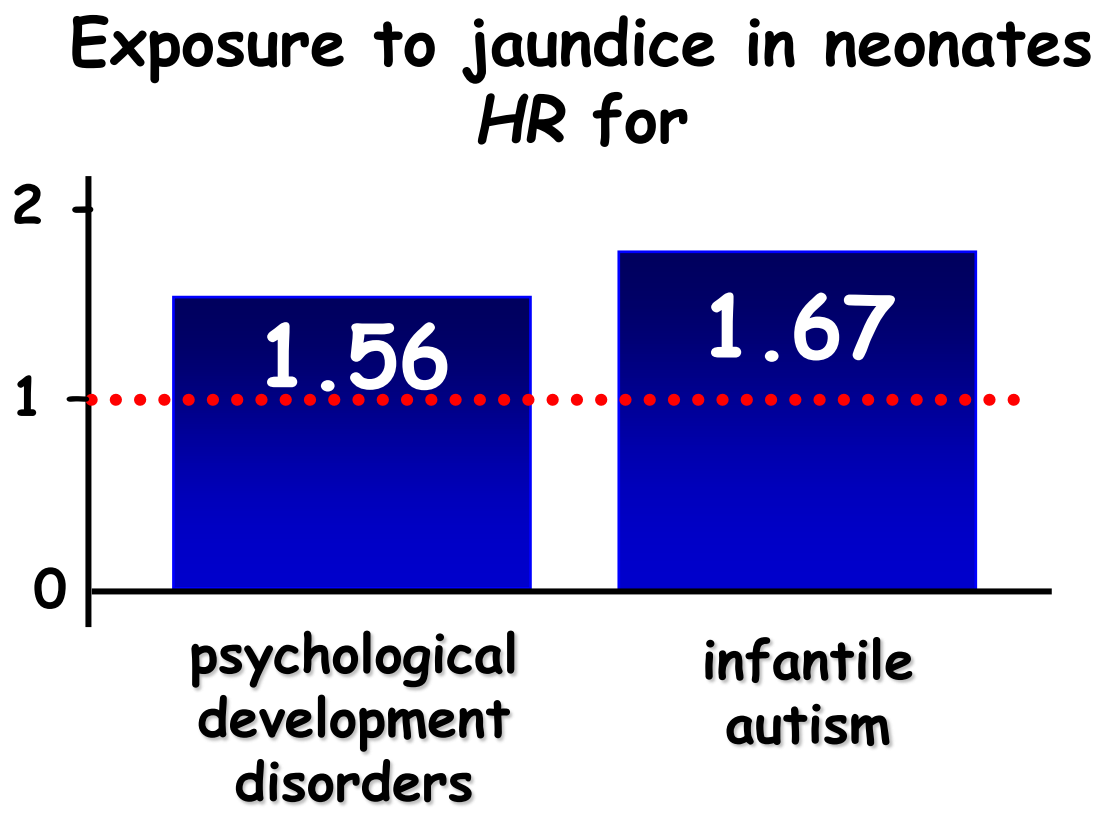
- ✓ 4713 cases born between 1987 and 2005.
- ✓ Childhood autism, Asperger syndrome or pervasive developmental disorder (PDD).



Neonatal Jaundice, Autism, and Other Disorders of Psychological Development

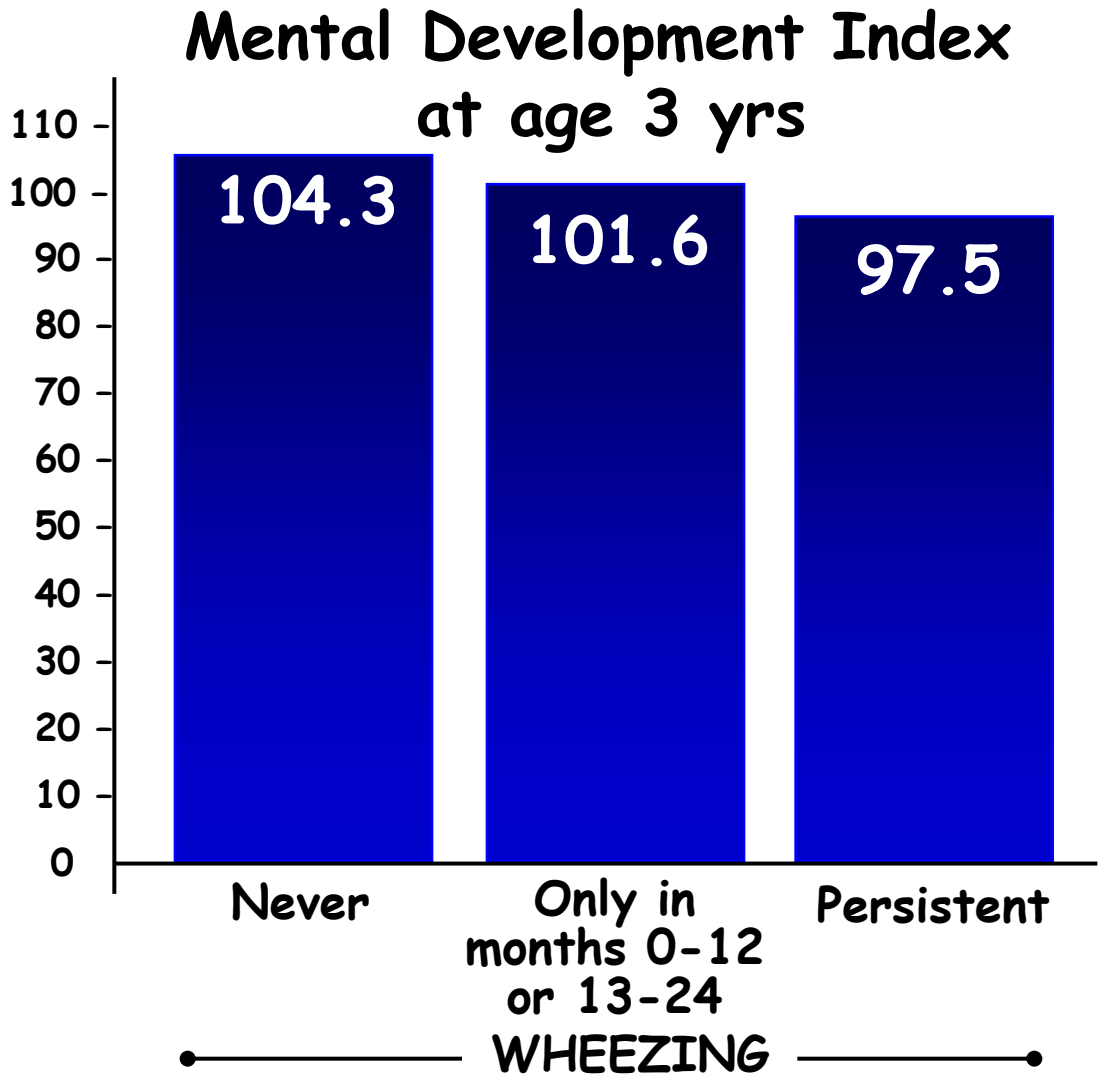
Maimburg Pediatrics 2010;126:872-78

- ✓ All children born alive in Denmark between 1994 and 2004 (*N=733 826*)
- ✓ Hazard ratios (HRs)



Early wheezing phenotypes and cognitive development of 3-yr-olds. Community-recruited birth cohort study *Jedrychowski PAI 2010;21:550*

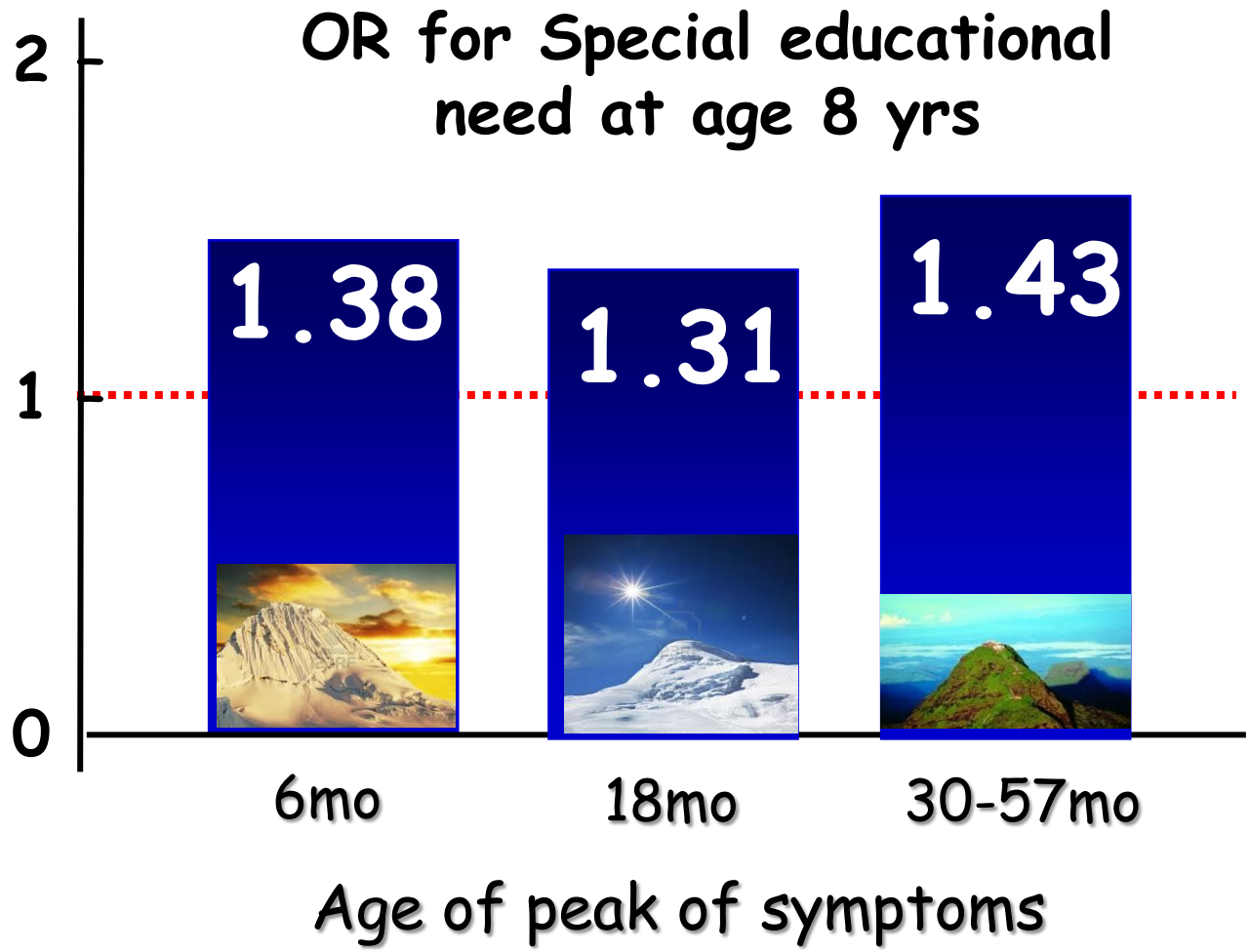
- ✓ Birth cohort.
- ✓ Wheezing symptoms over first two years.
- ✓ Cognitive status of children at the age of 3 yr with the Bayley Mental Development Index (MDI).



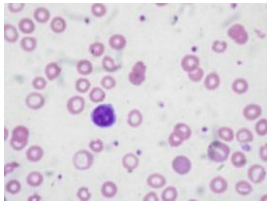
Pediatric Sleep Disorders and Special Educational Need at 8 Years: A Population-Based Cohort Study

Bonuck K., Pediatrics 2012;130:634

- ✓ Sleep disordered breathing (SDB) through 5 years of age (11 049 children).
- ✓ Special educational need (SEN) at 8 years.
- ✓ Parents reported on children's snoring, witnessed apnea, and mouth-breathing at 6, 18, 30, 42, and 57 months.



Dose-Response Relationships between Iron Deficiency with or without Anemia and Infant Social-Emotional Behavior *Lozoff B, J Pediatr. 2008;152:696-702*



- ✓ A cohort of 9- to 10-month-old infants.
- ✓ The infants were given oral iron for 3 months.
- ✓ Behavioral coding from videotape at 12 months

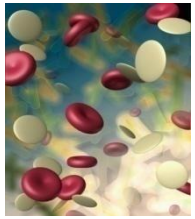
There were significant ($P < 0.05$) linear effects of poorer iron status for:

- **increasing shyness,**
- decreasing orientation/engagement,

- **decreasing soothability,**
- when an examiner attempted to engage the infants in **imitative play**, decreasing positive affect and engagement.

Iron-Deficiency Anemia in Infancy and Social Emotional Development in Preschool-Aged Chinese Children

Chang S, Pediatrics 2011;127:e927



- ✓ Children with iron-deficiency anemia (IDA) in infancy whose ***anemia was not corrected before 24 months (chronic IDA)*** *(n=27).*
- ✓ Children with IDA in infancy whose *anemia* was *corrected* before 24 months (corrected IDA) *(n=70).*
- ✓ Children who were *non-anemic* in infancy and at 24 months *(n =64).*

Children who had **chronic IDA** in infancy displayed:

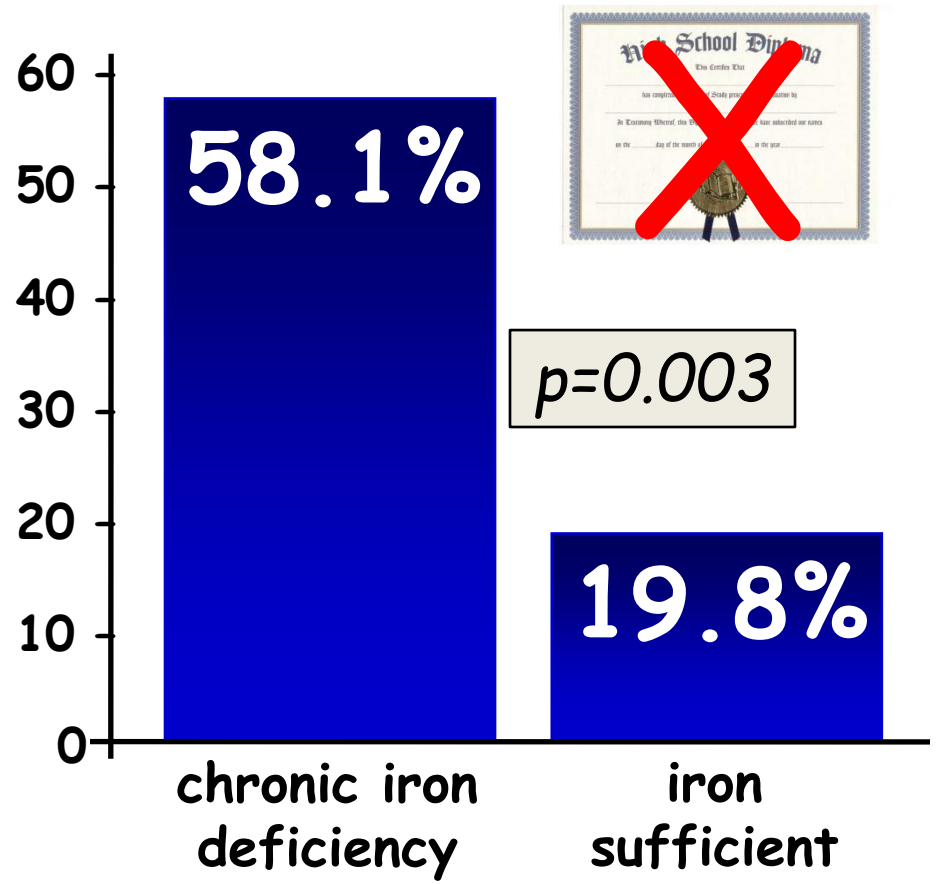
1. less positive affect and frustration tolerance;
2. more passive behavior and physical self-soothing in the stranger approach;
3. delay of gratification.

Functional Significance of Early-Life Iron Deficiency: Outcomes at 25 Years

Lozoff J Ped 2013;163:1260

- ✓ At 25 years, 33 subjects with chronic iron deficiency in infancy *vs* 89 who were iron-sufficient before and/or after iron therapy.
- ✓ Education, employment, marital status, and physical and mental health.

% subjects who did not complete secondary school



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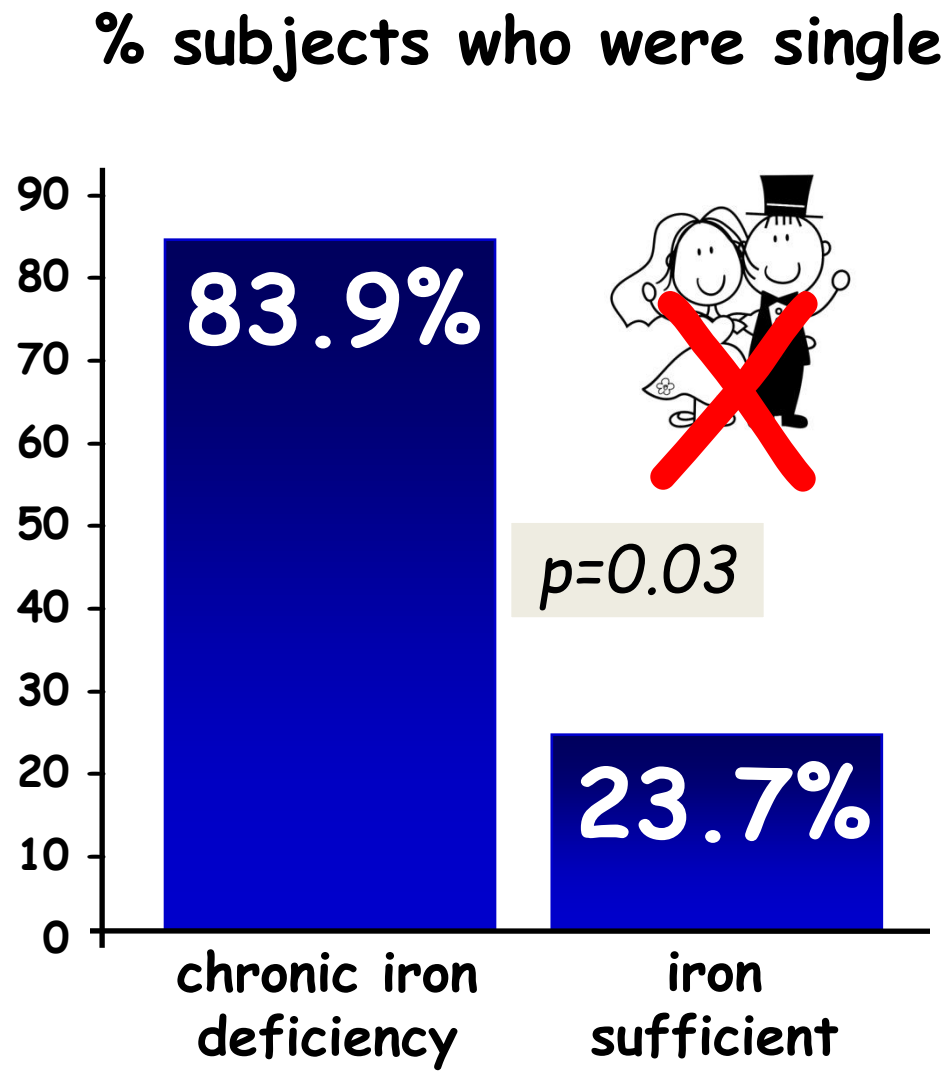
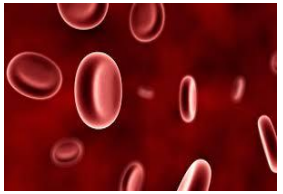
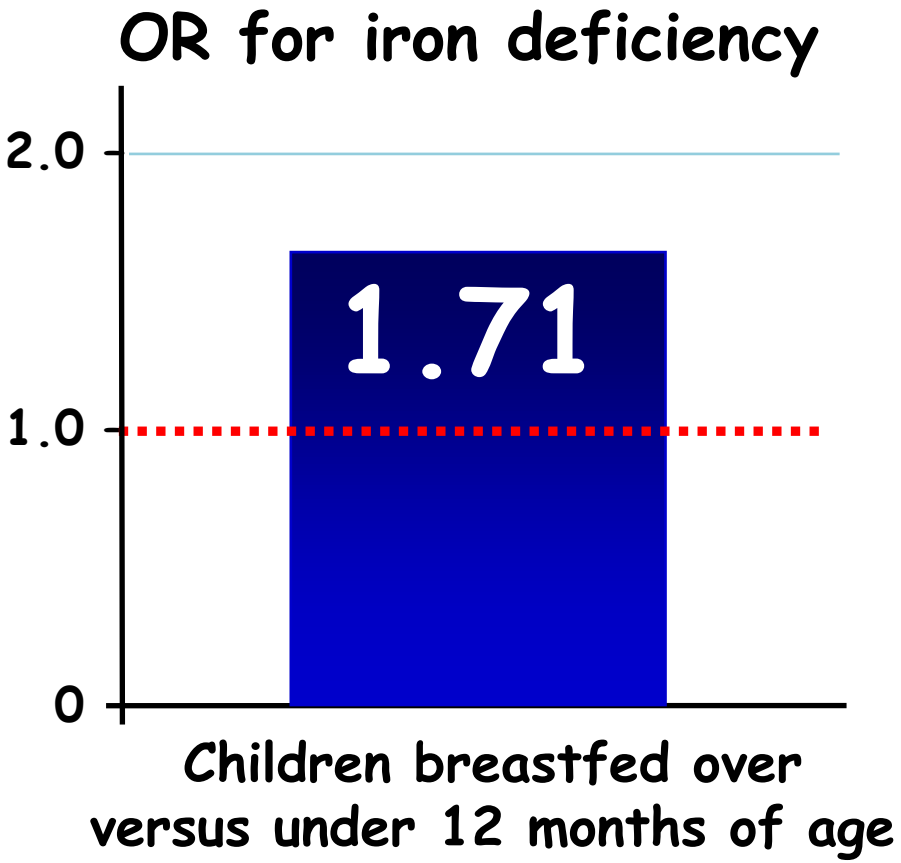


Association Between Total Duration of Breastfeeding and Iron Deficiency

Maguire, Pediatrics 2013;131:1530



- ✓ 1647 healty children, aged 1 to 6 years
- ✓ association between total breastfeeding duration and serum ferritin, iron deficiency, and iron deficiency anemia



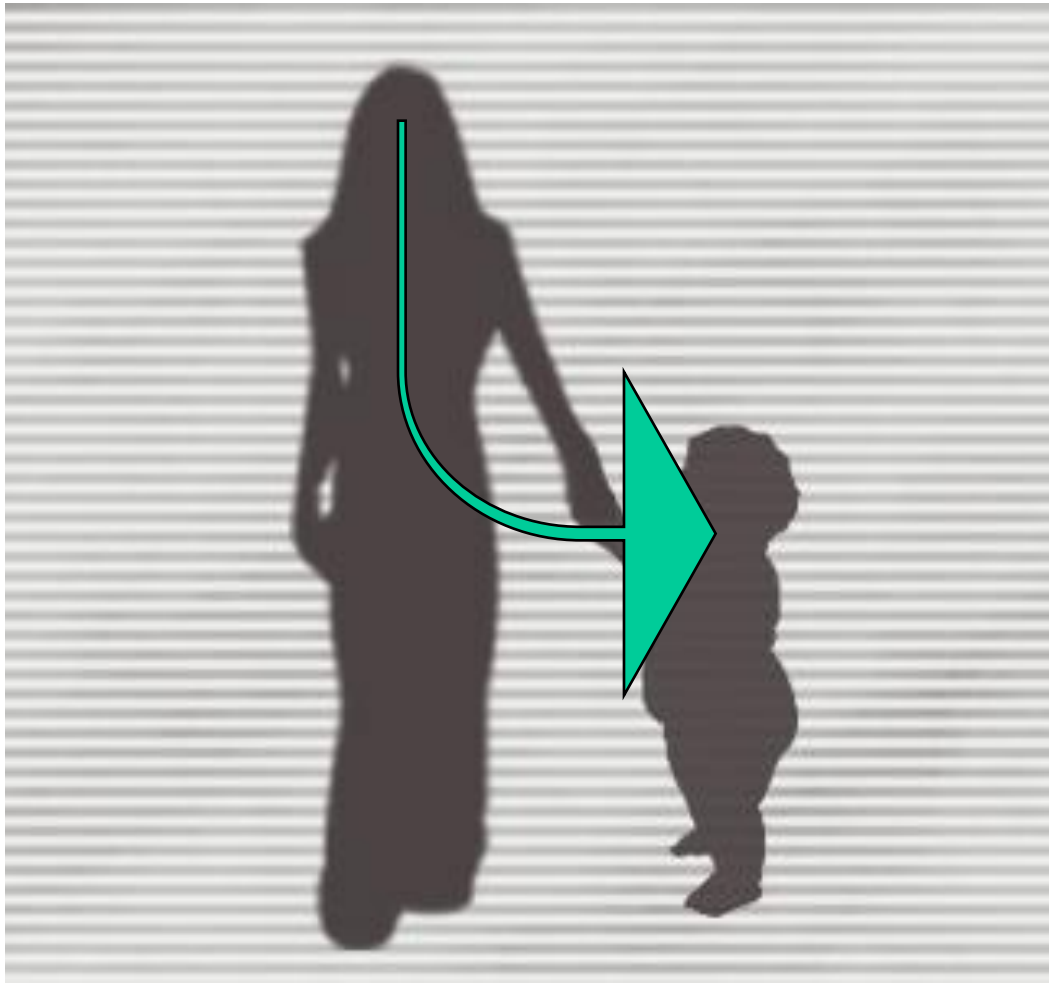
Developmental Origins of Health and Diseases: when we become what we are.

Attilio L Boner

University of Verona, Italy

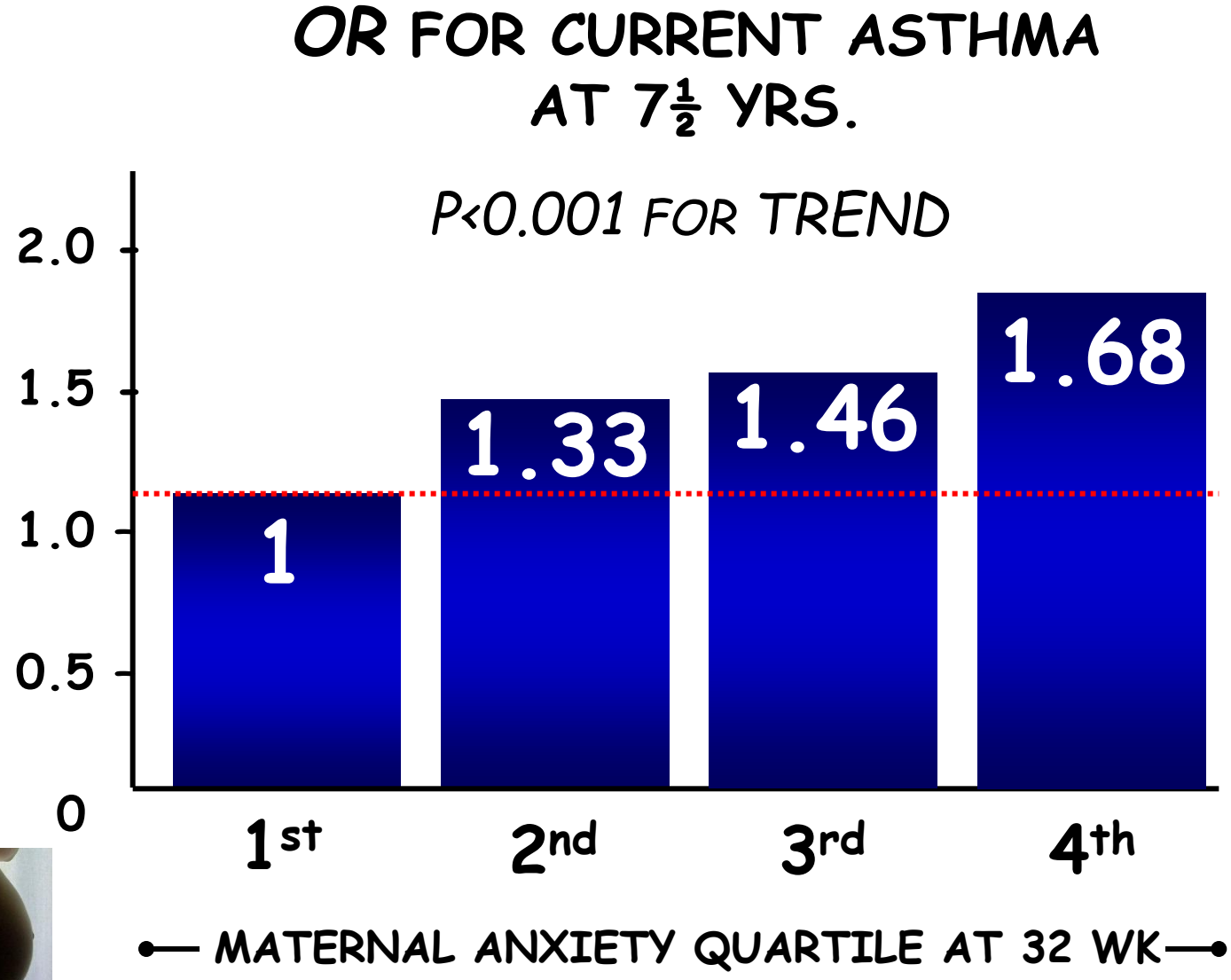
- ✓ Original findings
- ✓ Further discoveries & the first 1000 days
- ✓ **Maternal diseases**
- ✓ Maternal life style-environment
- ✓ Epigenetic
- ✓ More than 1 generation
- ✓ Prevention & Reversibility
- ✓ Public Health Implications
- ✓ Conclusions

Mother's anxiety and depression



Mothers' anxiety during pregnancy is associated with asthma in their children *Cookson JACI 2009; 123:847*

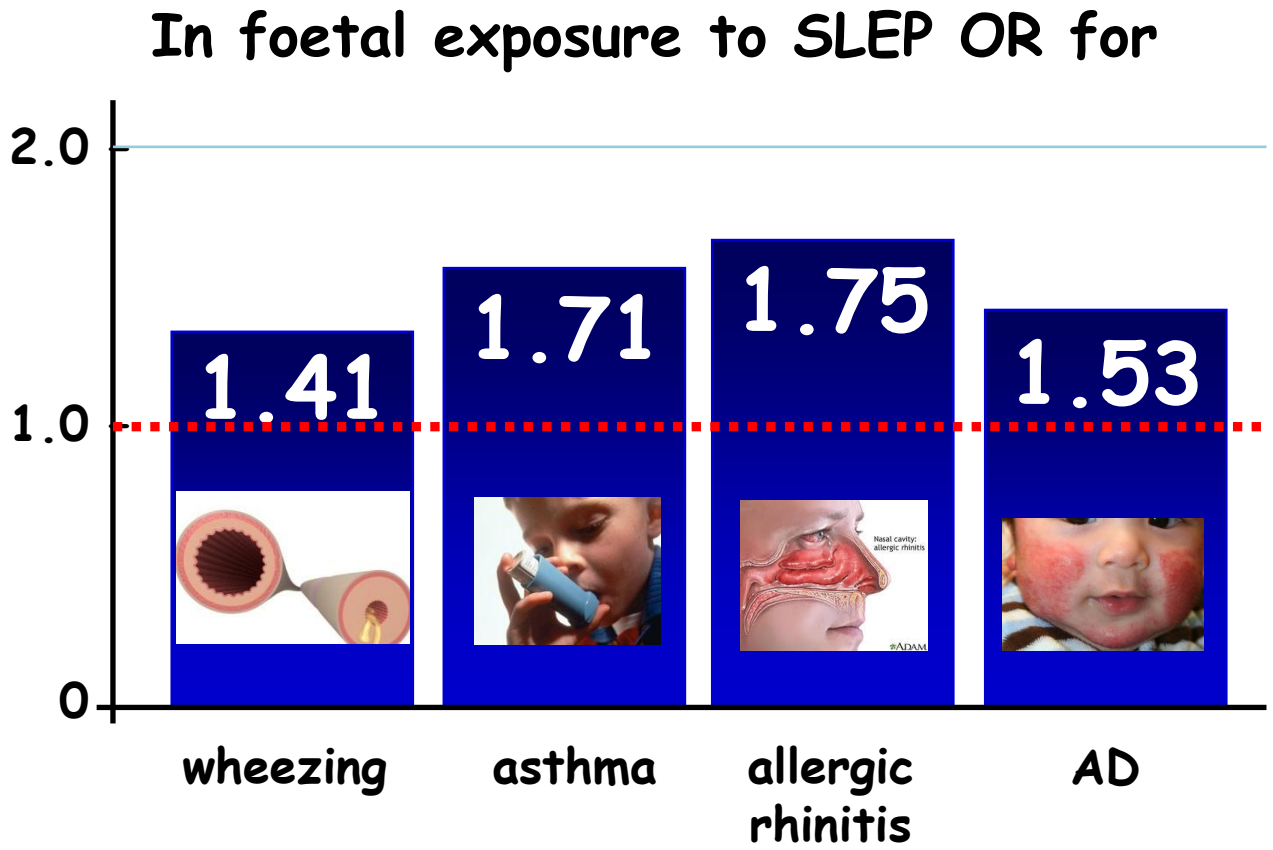
- ✓ Avon Longitudinal Study of Parents and Children (5810 children).
- ✓ Anxiety assessed at 18 and 32 weeks of gestation.
- ✓ Asthma was defined at age 7½ years.



Foetal exposure to maternal stressful events increases the risk of having asthma and atopic diseases in childhood *De Marco R., Pediatr Allergy Immunol 2012; 23:724-29*

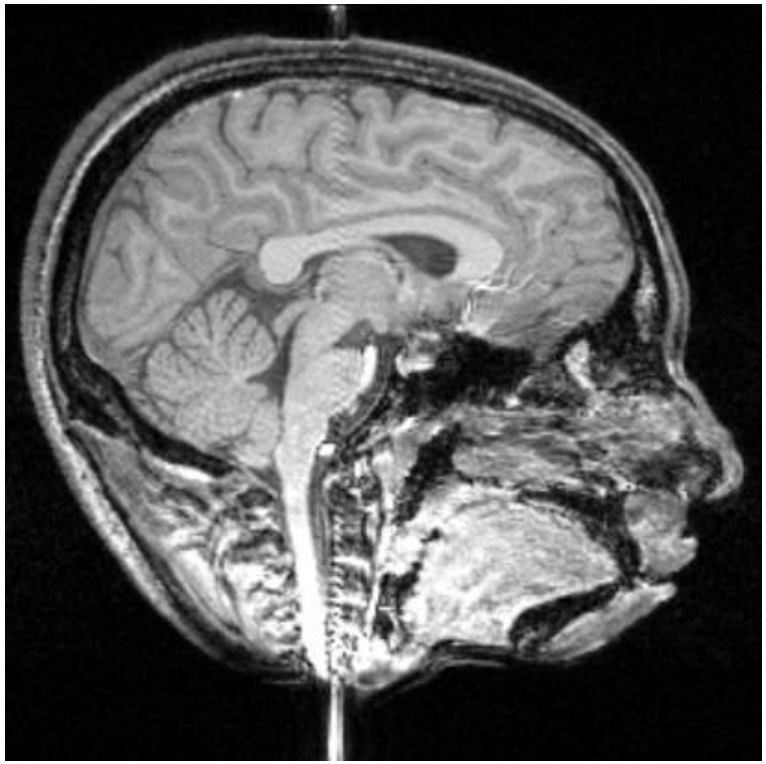
- ✓ Foetal exposure to maternal stressful life events during pregnancy (SLEP), at least one among: divorce, mourning or loss of the job.

- ✓ Occurrence of asthma and atopic diseases in childhood.
- ✓ 3854 children aged 3–14 yrs.



High pregnancy anxiety during midgestation is associated with decreased gray matter density in 6–9-year-old children. *Buss C, Psychoneuroendocrinology 2010; 35:141–153.*

- ✓35 women
- ✓pregnancy anxiety at 19, 25 and 31 weeks gestation.
- ✓offspring evaluated between 6 and 9 years of age,
- ✓neurodevelopmental stage was assessed by a structural MRI scan.

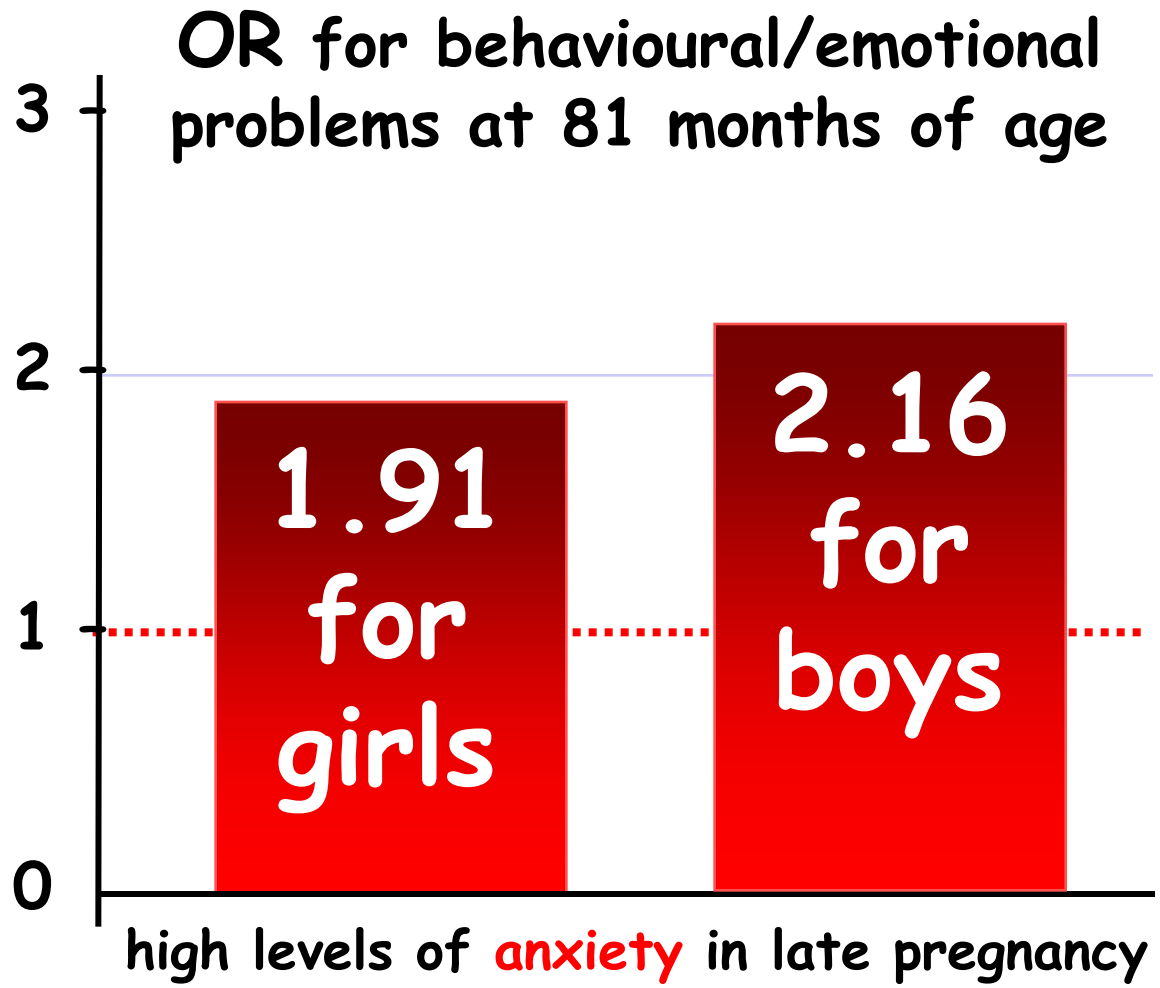


maternal pregnancy-specific anxiety in mid-gestation was associated with gray matter **volume reductions in several child brain regions, including the prefrontal cortex**

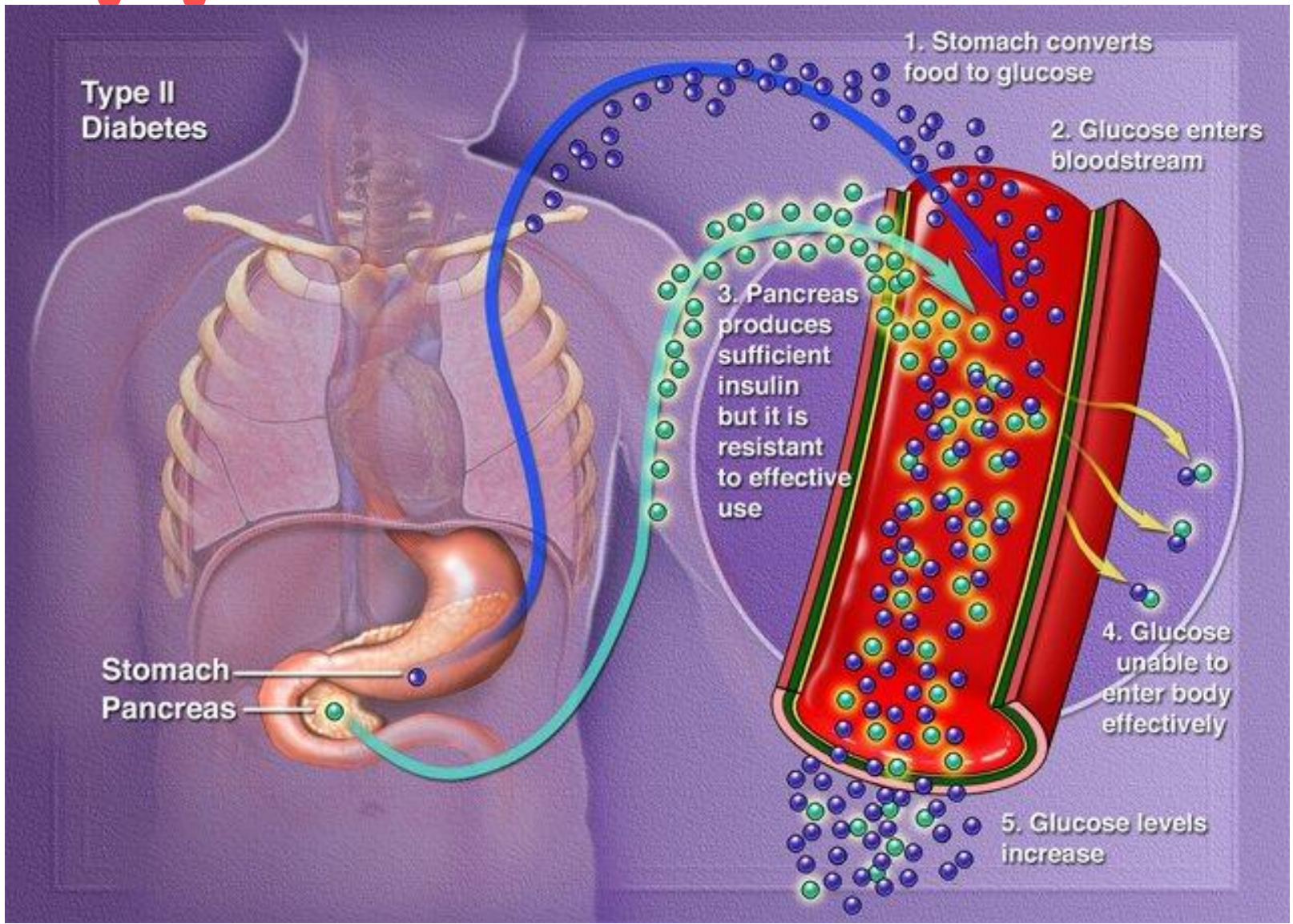
Maternal antenatal anxiety and behavioral/emotional problems in children: a test of a programming hypothesis.

O'Connor TG, J Child Psychol Psychiatry. 2003;44:1025–1036.

- ✓Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective, community-based study that has followed a cohort of women from pregnancy.
- ✓Self-report measures of maternal anxiety and depression were assessed at repeated intervals in pregnancy and the postnatal period.
- ✓Children's behavioural/emotional problems were assessed by parent report at age 47 and 81 months.



Type 2 diabetes

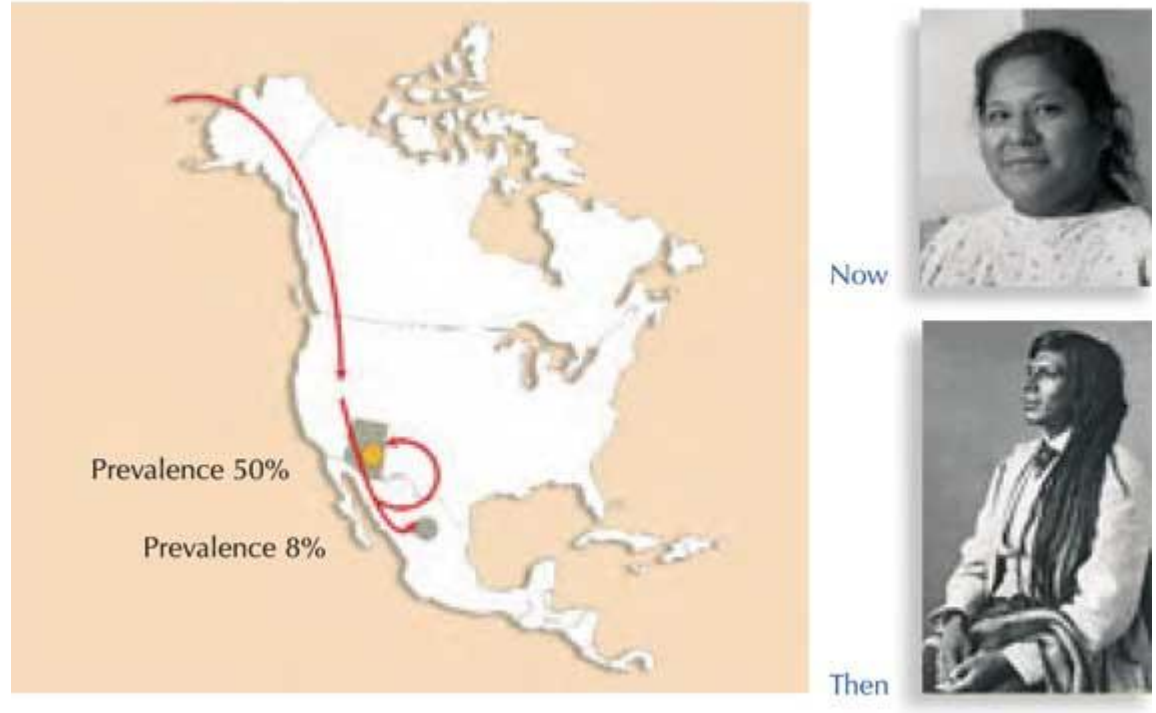


Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians.

Dabelea D J Matern Fetal Med. 2000;9:83-8.

OBJECTIVE: To review data on the long-term effects of prenatal exposure to the diabetic intrauterine environment in the **Pima Indians** of Arizona.

This population has high rates of Type 2 diabetes mellitus that has a strong genetic component and develops at young ages.

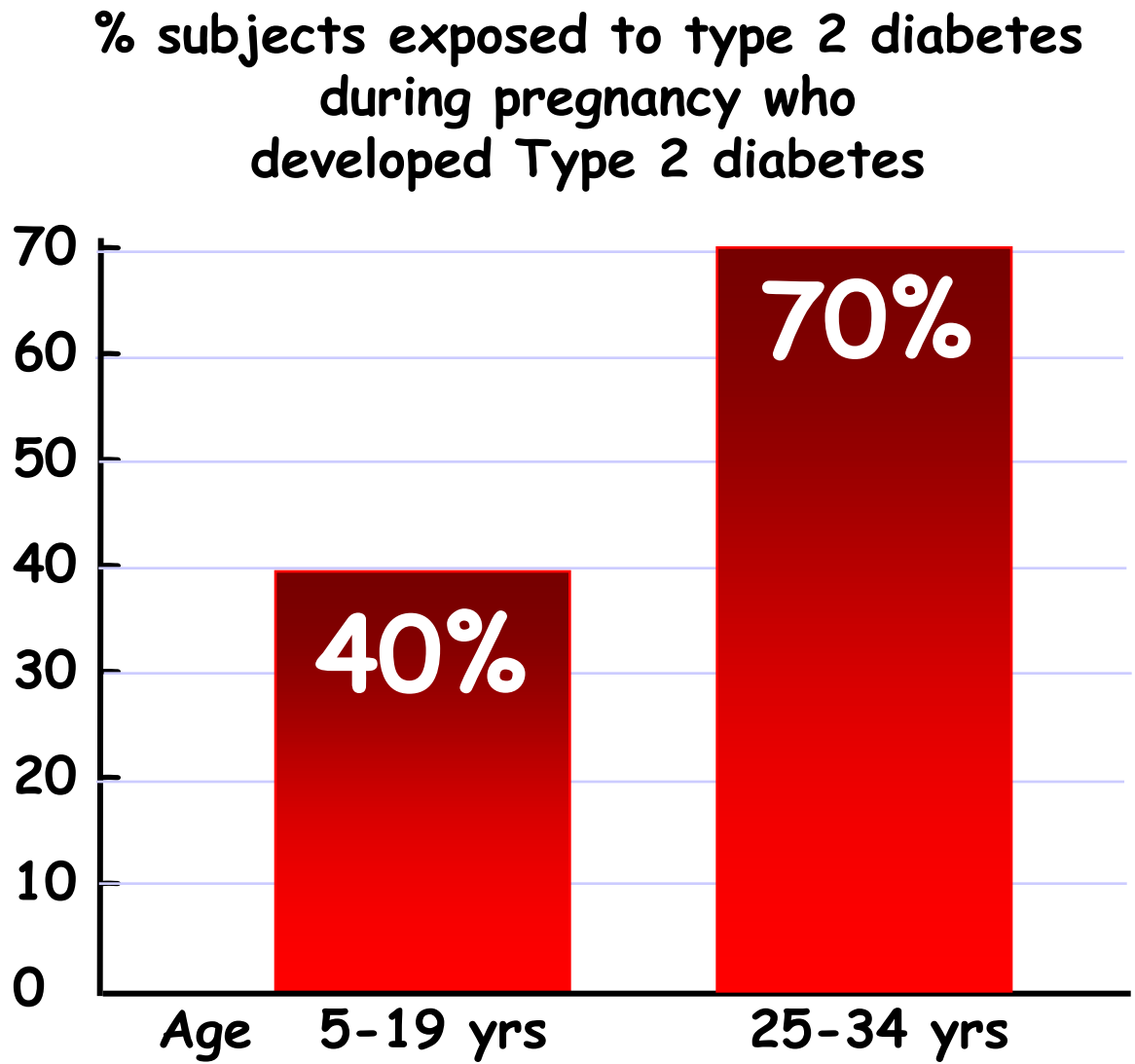


Quelli che vivono in Messico hanno un'incidenza del diabete pari circa all'8%, mentre quelli che sono emigrati negli Stati Uniti, dove lo stile di vita è più sedentario e l'accesso al cibo energetico (grasso) è più semplice, hanno un'incidenza di diabete che raggiunge il 50%.

Effect of diabetes in pregnancy on offspring: follow-up research in the Pima Indians.

Dabelea D J Matern Fetal Med. 2000;9:83-8.

- ✓Since 1965, biennial examinations
- ✓measurements of obesity and glucose tolerance and of glucose tolerance testing during pregnancy.
- ✓Development of type 2 diabetes

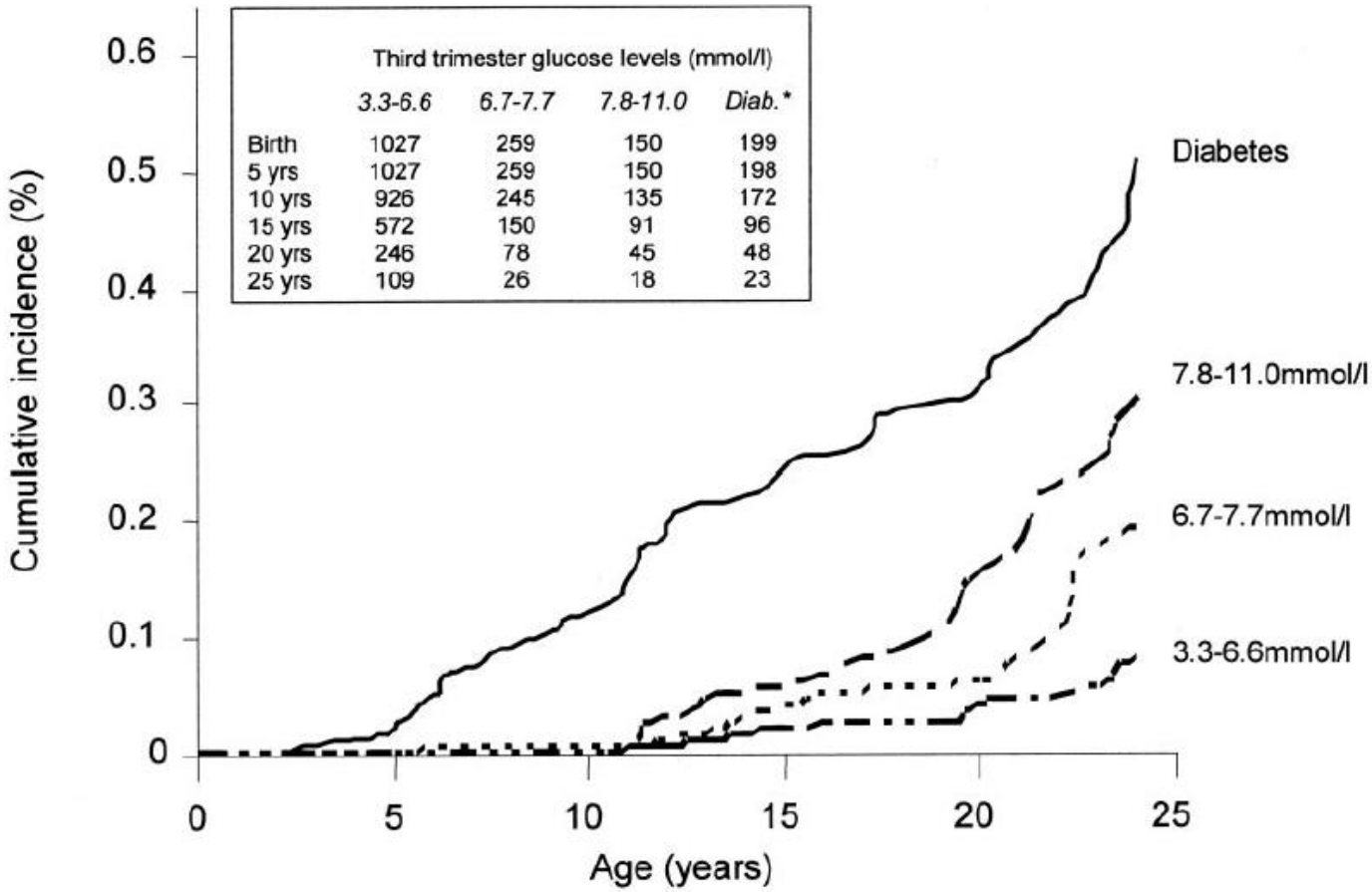


Gestational glucose tolerance and risk of type 2 diabetes in young Pima Indian offspring.

Franks PW, Diabetes. 2006;55:460-5.

- ✓911 nondiabetic Pima Indian mothers and 1,436 of their children.
- ✓maternal third trimester glucose tolerance and indexes of body composition and glycemic control in their children

Cumulative incidence of type 2 diabetes in offspring stratified by category of maternal third trimester 2-h glucose.



	Third trimester glucose levels (mmol/l)			
	3.3-6.6	*6.7-7.7*	*7.8-11.0*	*Diab.**
Birth	1027	259	150	199
5 yrs	1027	259	150	198
10 yrs	926	245	135	172
15 yrs	572	150	91	96
20 yrs	246	78	45	48
25 yrs	109	26	18	23

An understanding of the role of gestational factors in disease can change **individual behavior**, notes *Daniel Benyshek, a medical anthropologist at the University of Nevada at Las Vegas*, who has interviewed members of Arizona's Native American tribes. He finds that those who believe diabetes is their genetic destiny tend to hold fatalistic attitudes about the illness. When Benyshek shared findings about the fetal origins of diabetes with tribe members, however, he noticed a different reaction. *"The idea that some **simple changes made during pregnancy** could reduce the offspring's risk for diabetes fosters a much more hopeful and engaged response,"* he says. *"Young women in particular are enthusiastic about the idea of intervening in pregnancy to break the cycle of diabetes. They say, 'I tried **dieting**, I tried **exercising**, and I couldn't keep it up. But I could do it for nine months if it meant that my baby would have a better chance at a healthy life.'"*

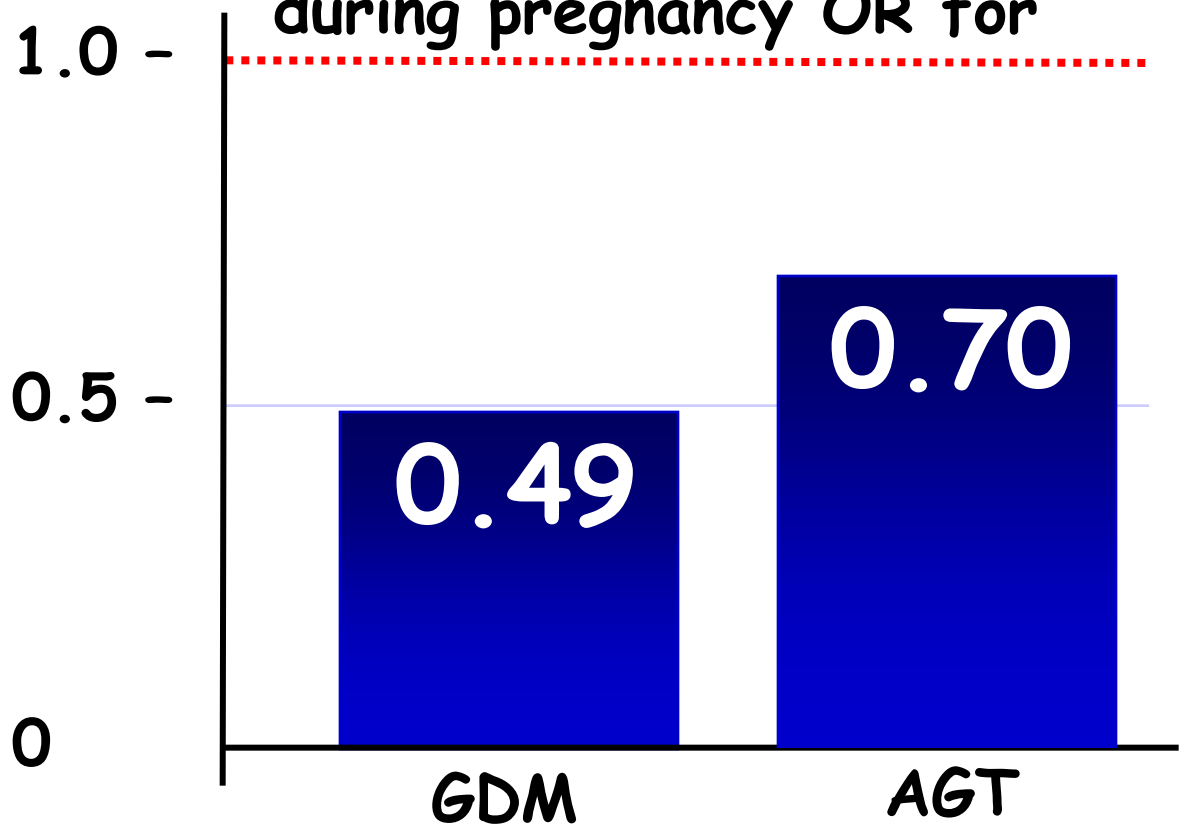
Annie M Paul Time October 4, 2010

Associations of physical activity and inactivity before and during pregnancy with glucose tolerance.

Oken E, Obstet Gynecol. 2006;108:1200-7.

- ✓1,805 women enrolled in Project Viva
- ✓duration and intensity of physical activity and time spent viewing television both before and during pregnancy
- ✓gestational diabetes mellitus (**GDM**) and abnormal glucose tolerance (**AGT**)

In women with vigorous activity before pregnancy and light-to-moderate or vigorous activity during pregnancy OR for

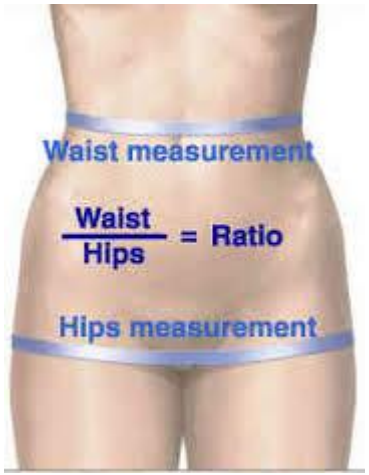


Gestational Diabetes Mellitus, Maternal Obesity, and Adiposity in Offspring

Page KA, J Ped 2014;164;807-810

- ✓ 62 Mexican American mothers and their index offspring
- ✓ Maternal gestational diabetes mellitus (GDM) and glucose status during index pregnancy

Between the ages of 5 and 16 years: GDM-exposed offspring (n = 37) had greater measures of BMI (all $P \leq 0.02$) and greater waist and hip circumferences (both $P = 0.002$) compared with 25 offspring of non-GDM mothers

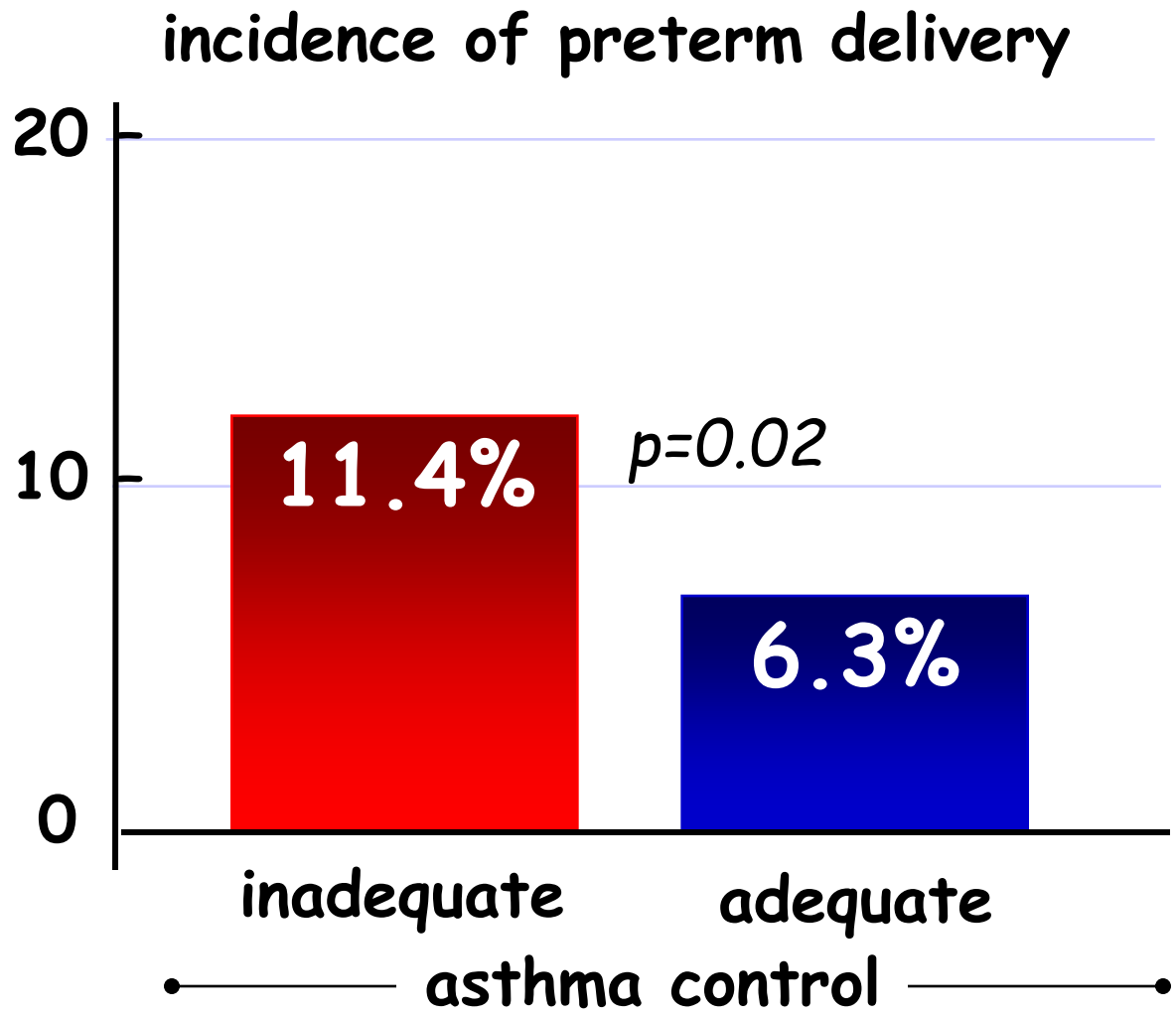


Asthma in pregnancy

Asthma control during pregnancy and the risk of preterm delivery or impaired fetal growth.

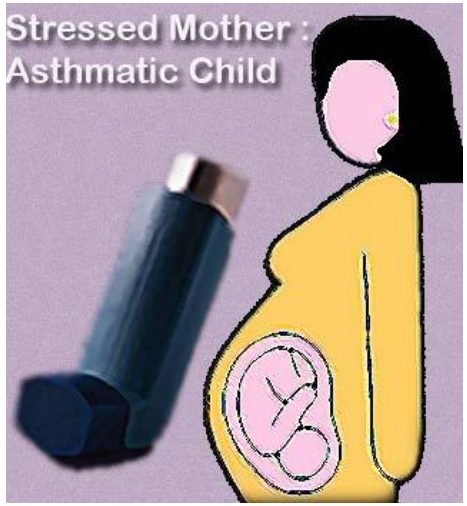
Bakhireva LN, Ann Allergy Asthma Immunol 2008; 101:137–143.

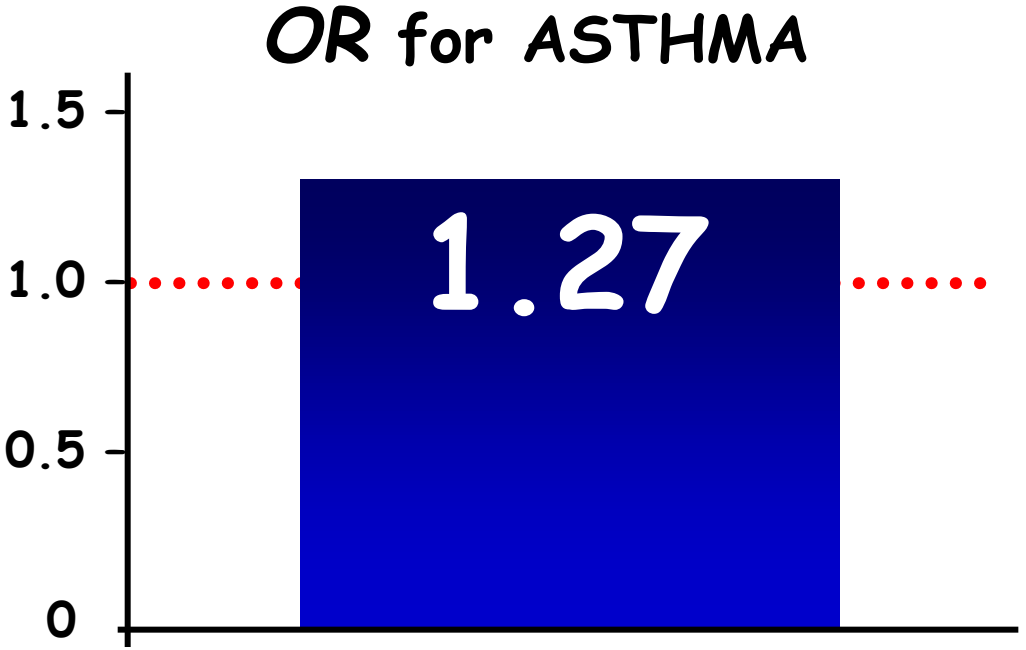
- ✓Pregnant women with physician-diagnosed asthma (n = 719)
- ✓Asthma control during pregnancy



Control and severity of asthma during pregnancy are associated with asthma incidence in offspring: two-stage case-control study *Martel ERJ 2009:34:579*

- ✓ 8,226 children of asthmatic mothers.
- ✓ 30,318 age-matched controls.



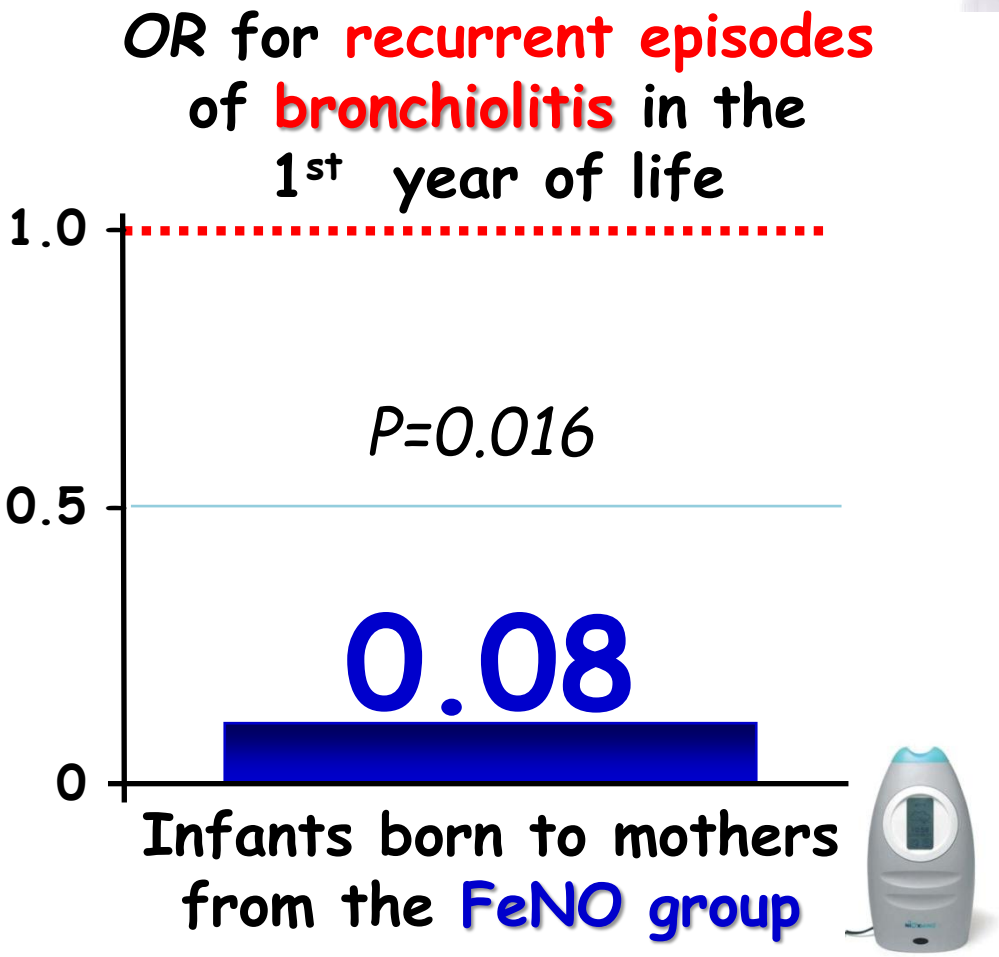


In children whose mothers had moderate-to-severe uncontrolled asthma during pregnancy versus mild controlled asthma.

Prenatal origins of bronchiolitis: protective effect of optimised asthma management during pregnancy

Mattes, Thorax 2014;69:383

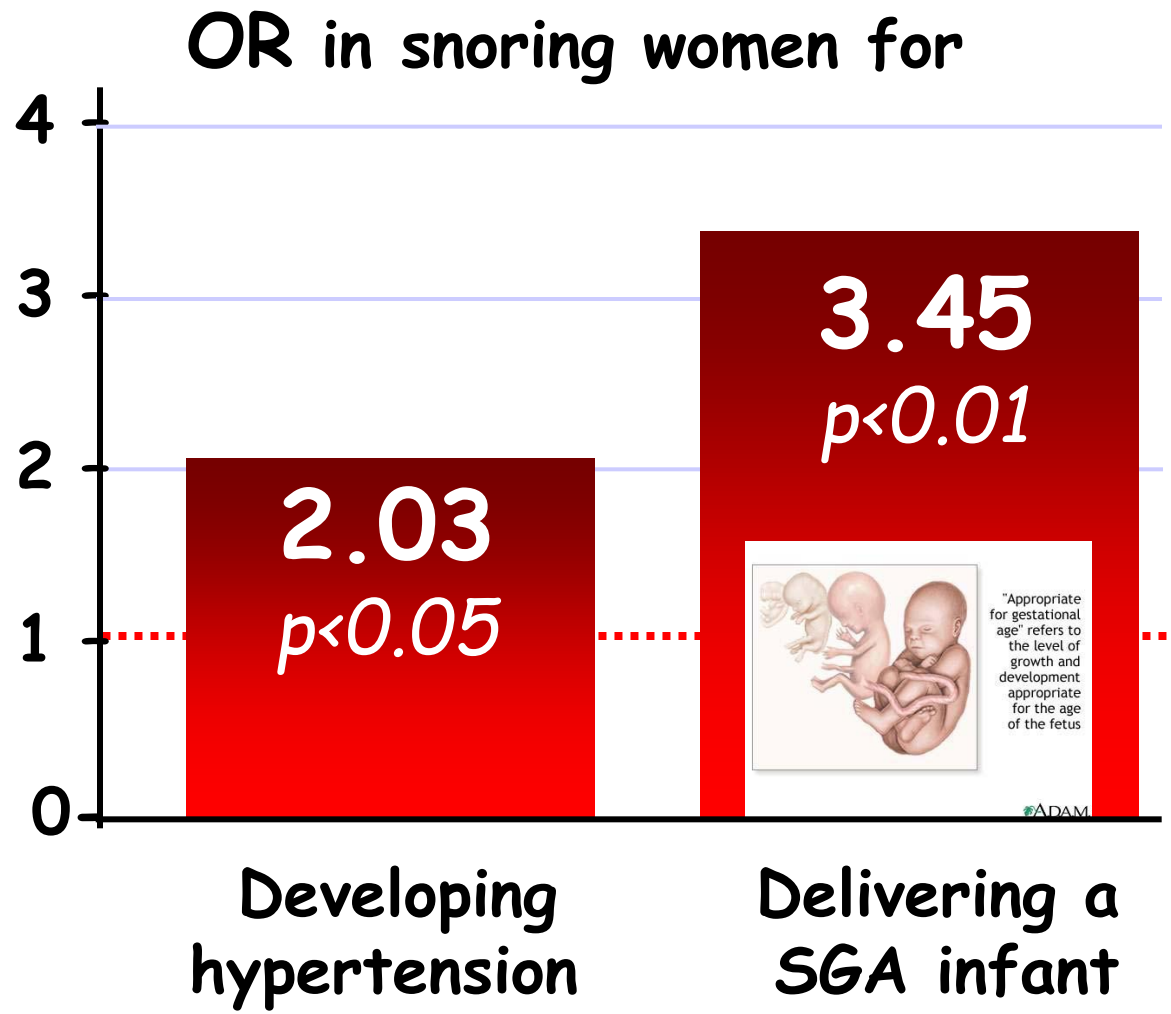
- ✓ Infants born to **women with asthma** assigned to **treatment adjustment** by an algorithm using clinical symptoms (**clinical group**) or the fraction of exhaled nitric oxide (**FeNO group**).
- ✓ 146 **infants** attended the 12-month follow-up visit.



Sleep-disorderd breathing or sleep deprivation during pregnancy

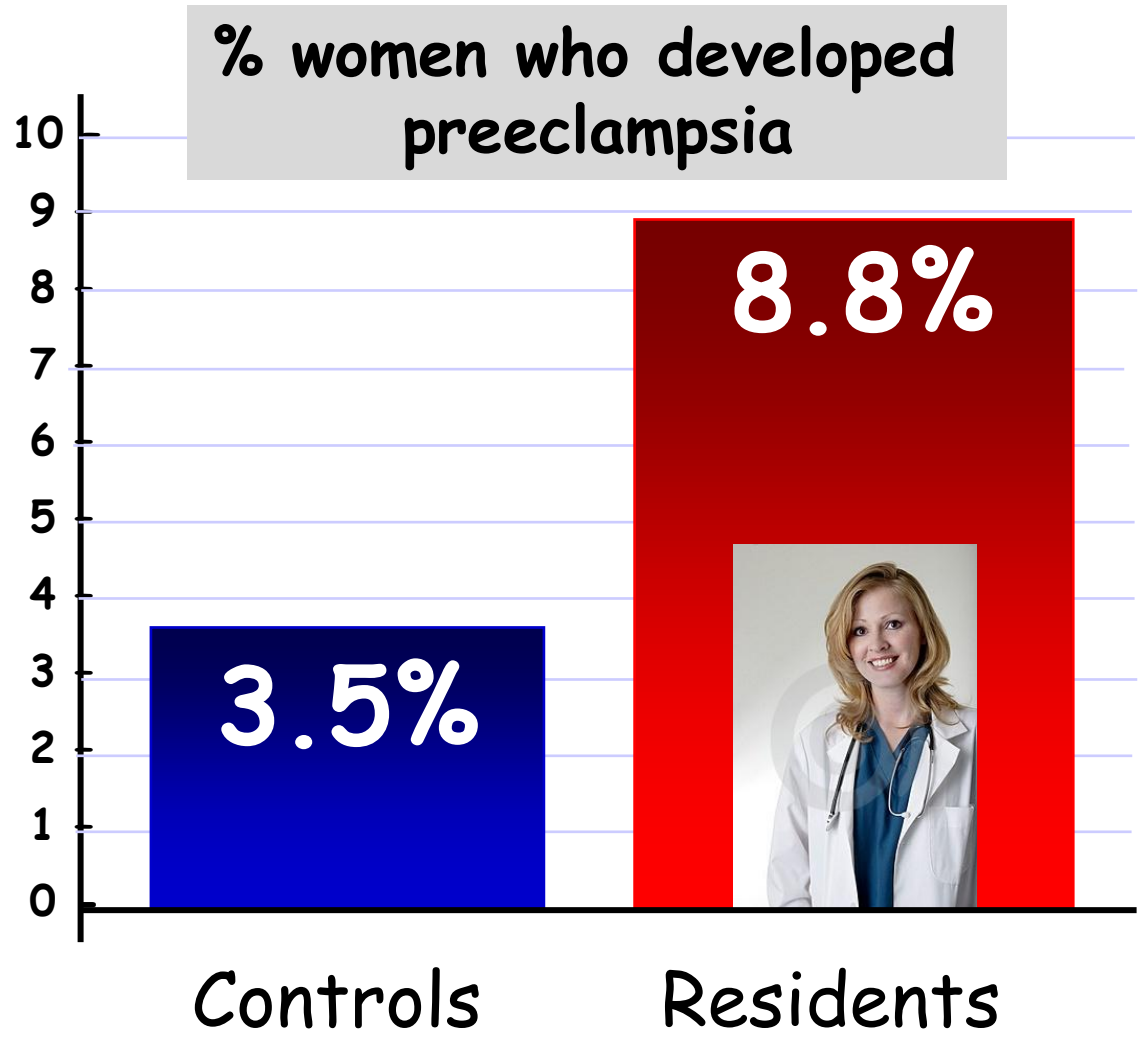
Snoring, pregnancy-induced hypertension, and growth retardation of the fetus. *Franklin KA, Chest 2000; 117:137*

- ✓502 women with singleton pregnancies
- ✓
- ✓questionnaire about snoring, witnessed sleep apneas, and daytime fatigue.



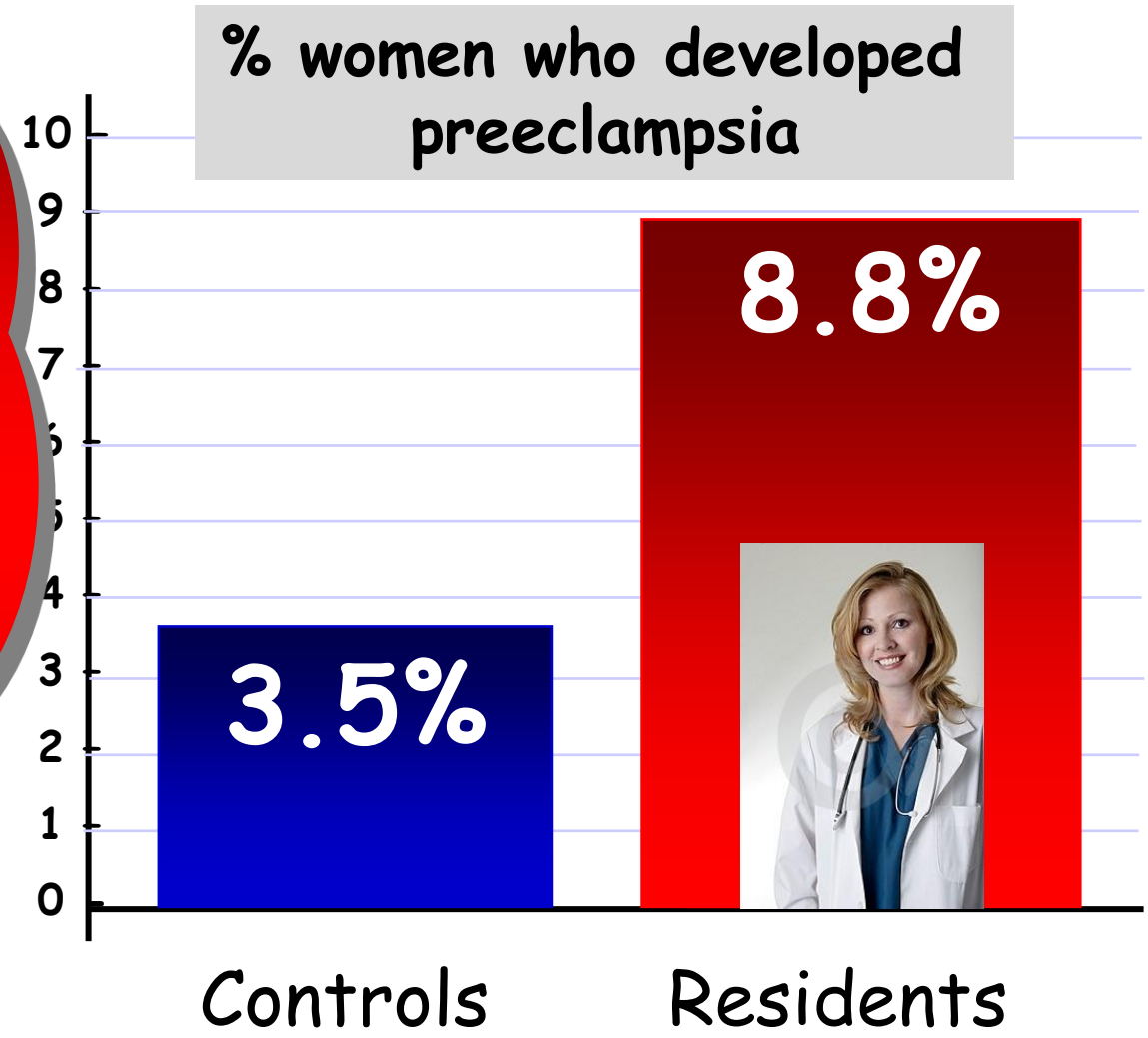
Outcomes of pregnancy in a national sample of resident physicians. *Klebanoff MA, N Engl J Med 1990; 323:1040–1045.*

- ✓4412 women who graduated from medical school in 1985 (sleep deprivation)
- ✓wives of 4236 of their male classmates, who served as controls and who sleeped more



Outcomes of pregnancy in a national sample of resident physicians. *Klebanoff MA, N Engl J Med 1990; 323:1040–1045.*

Sleep-Disordered Breathing has been associated with:
1) increased risks of premature delivery,
2) intrauterine growth restriction,
3) lower infant Apgar scores,
4) infant mortality

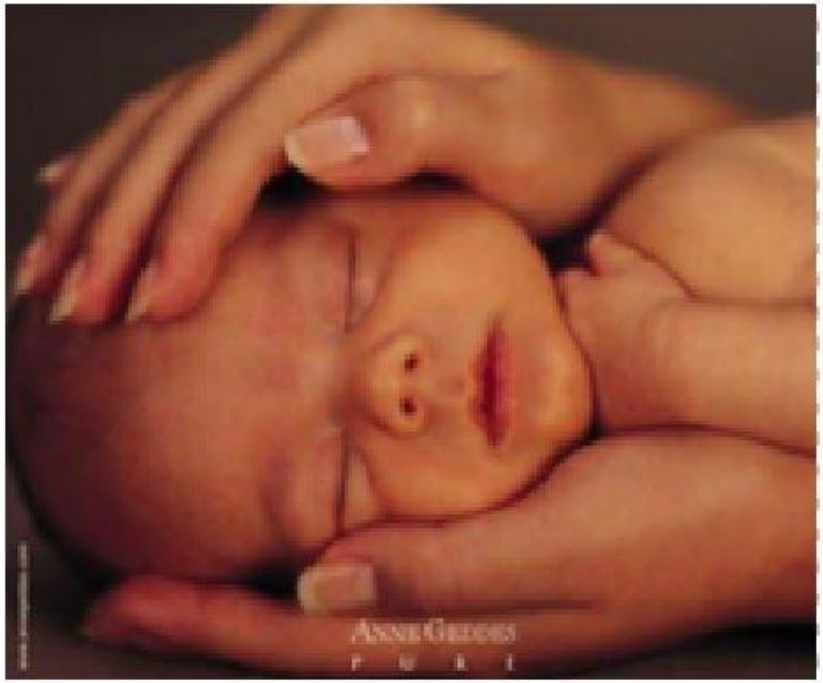


Developmental Origins of Health and Diseases: when we become what we are.

Attilio L Boner

University of Verona, Italy

- ✓ Original findings
- ✓ Further discoveries & the first 1000 days
- ✓ Maternal diseases
- ✓ **Maternal life style-environment**
- ✓ Epigenetic
- ✓ More than 1 generation
- ✓ Prevention & Reversibility
- ✓ Public Health Implications
- ✓ Conclusions

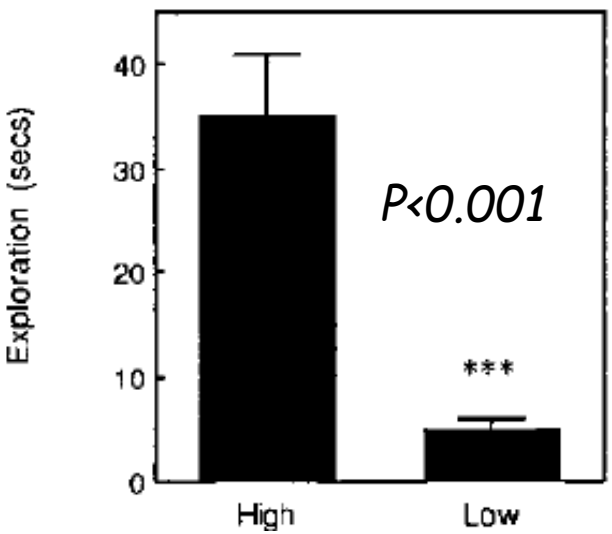

ANNIE GEDDES
PURE

Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat.

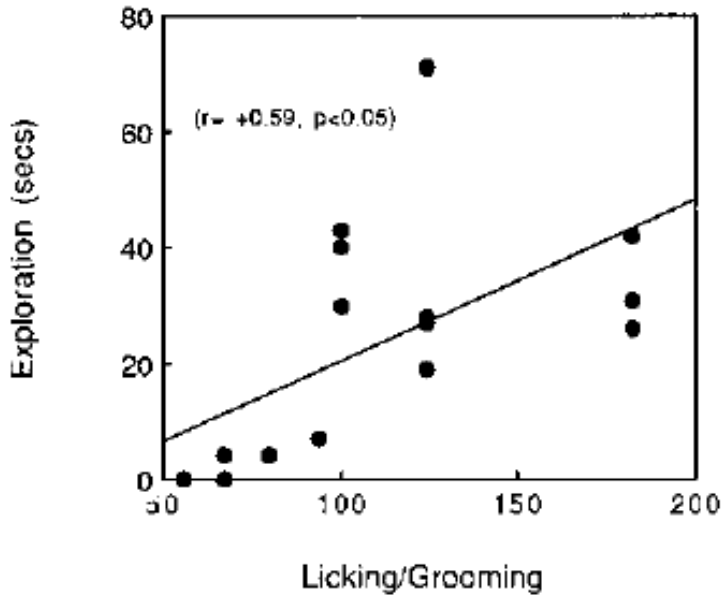
Caldji C, Proc Natl Acad Sci USA 1998; 95:5335–5340.

licking/grooming and arched-back nursing

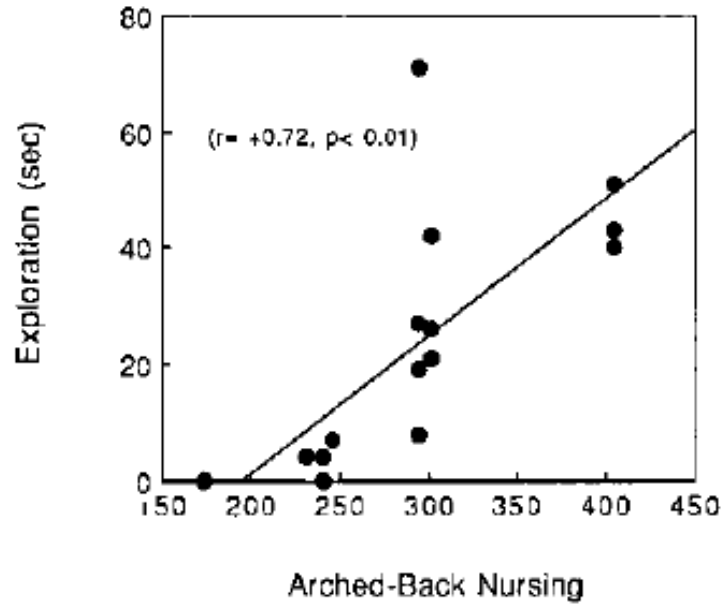
Mean±SEM time spent in exploration of the inner area of an open field in the adult offspring of high versus low LG-ABN mothers.



correlation between maternal licking/grooming and exploration.



correlation between maternal arched-back nursing and exploration.



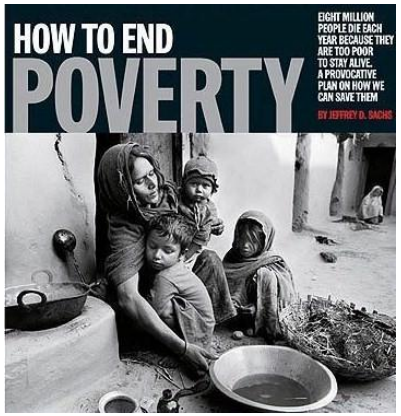
Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat.

Caldji C, Proc Natl Acad Sci USA 1998; 95:5335–5340.

"Mia will become an incredible swimmer"

Uncle Grooming

From the Rat Model of Nurturing to the Child



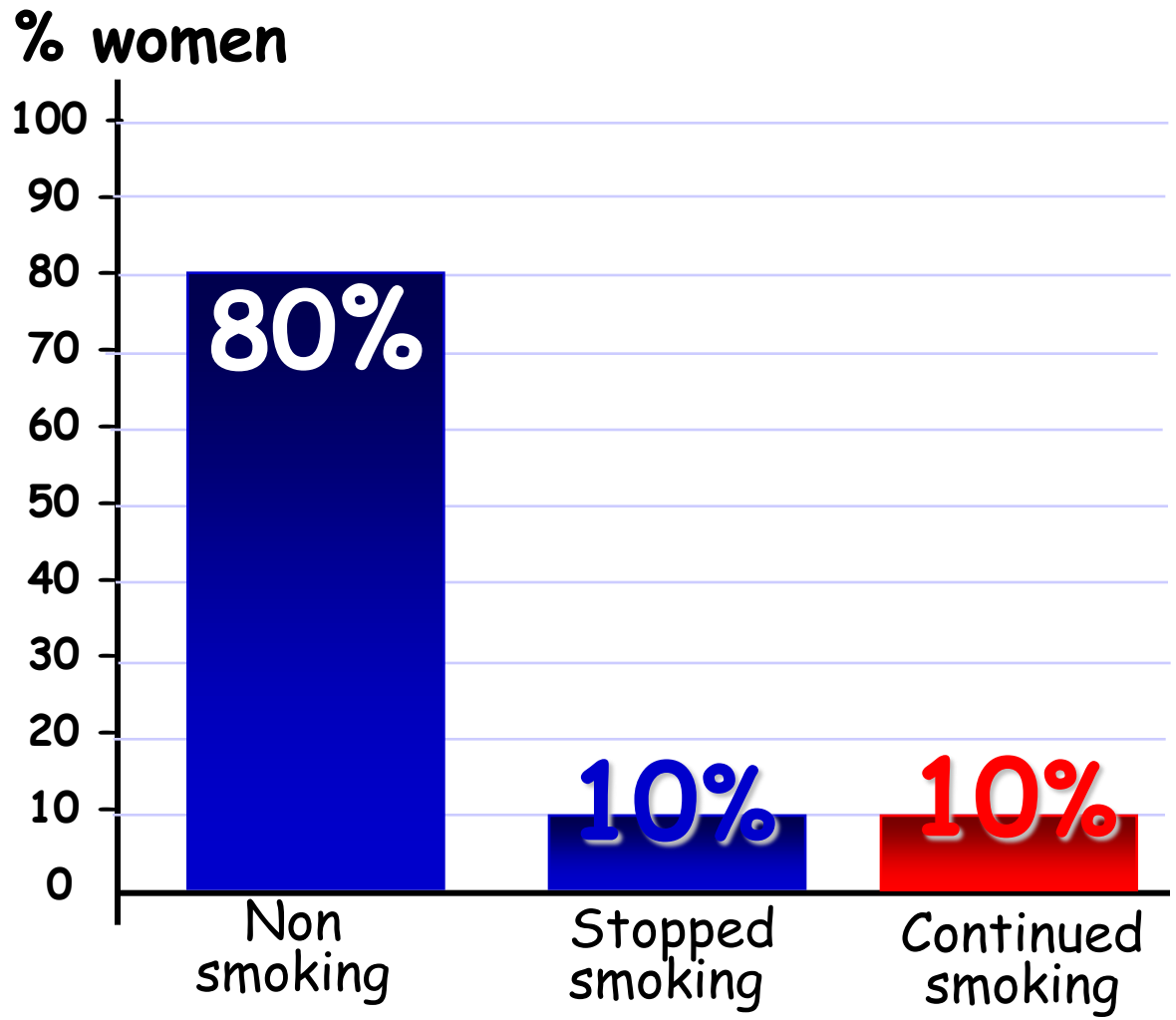
This provides a biological basis for speculations about the **effects of poverty** on early experience, and how exposure to **abuse**, **family strife**, **emotional neglect**, and **harsh discipline** may have epigenetic effects that produce **individual differences in neural and endocrine response to stress** and may **increase the susceptibility to common adult disorders such as depression and anxiety, drug abuse**, and **diabetes**, **heart disease**, and **obesity**.

Smoking in pregnancy

Spontaneous preterm birth and small for gestational age infants in women who stop smoking early in pregnancy: prospective cohort study.

McCowan LM, BMJ 2009;338:b1081.

- ✓2504 nulliparous women (SCOPE study) grouped by maternal smoking status at 15 (+/-1) week's gestation.
- ✓preterm birth and small for gestational age infants (birth weight <10th centile)



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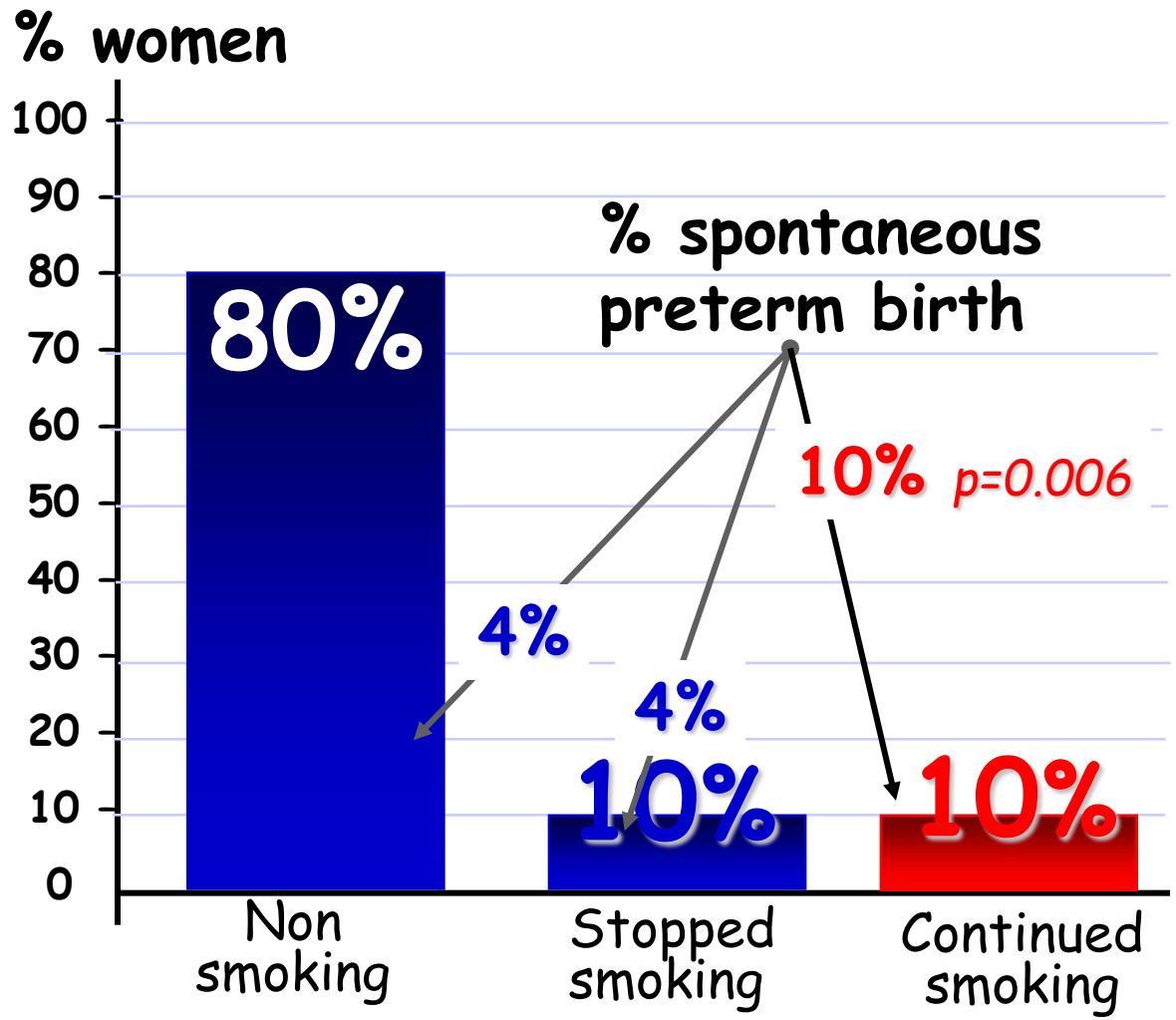

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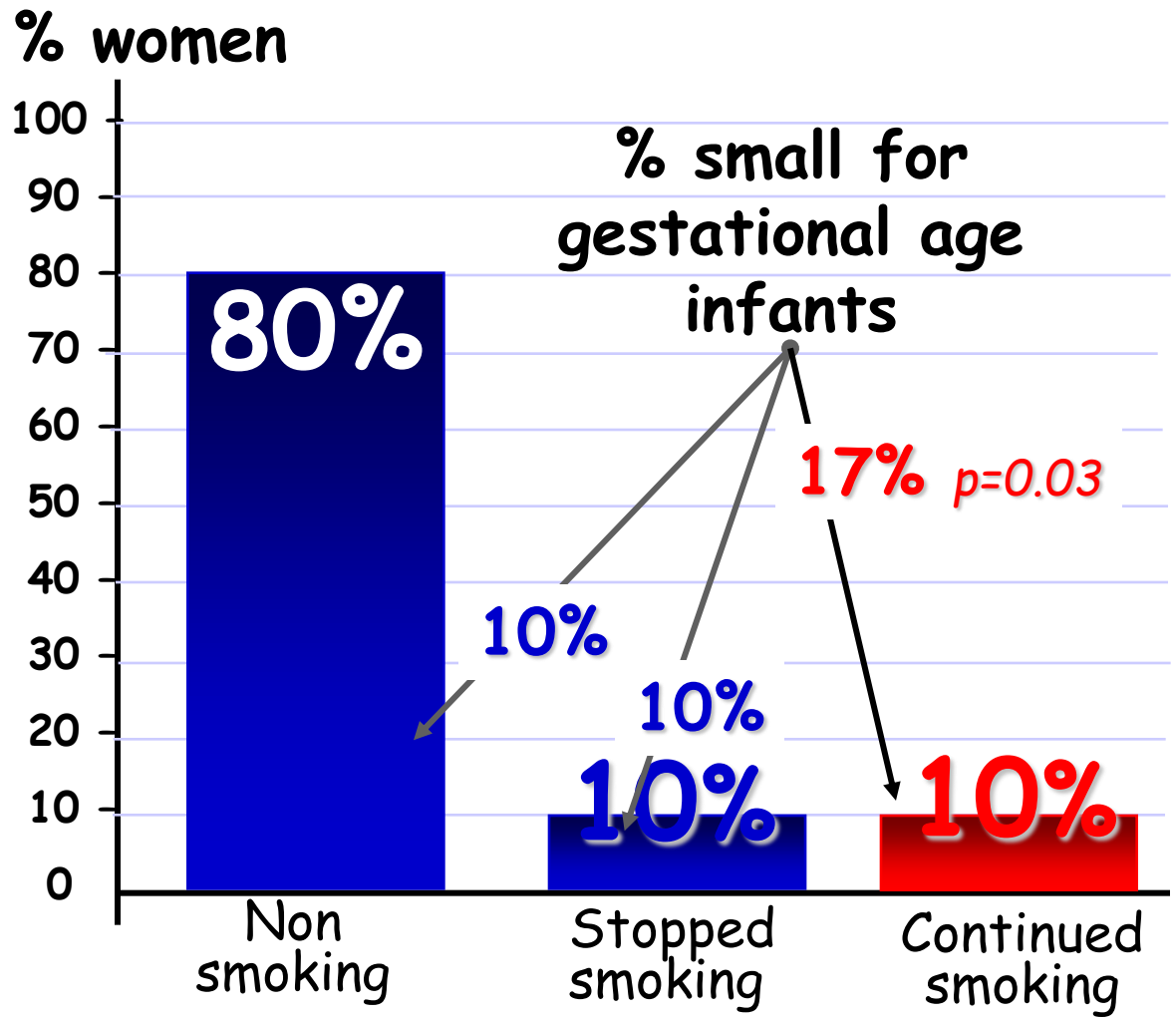
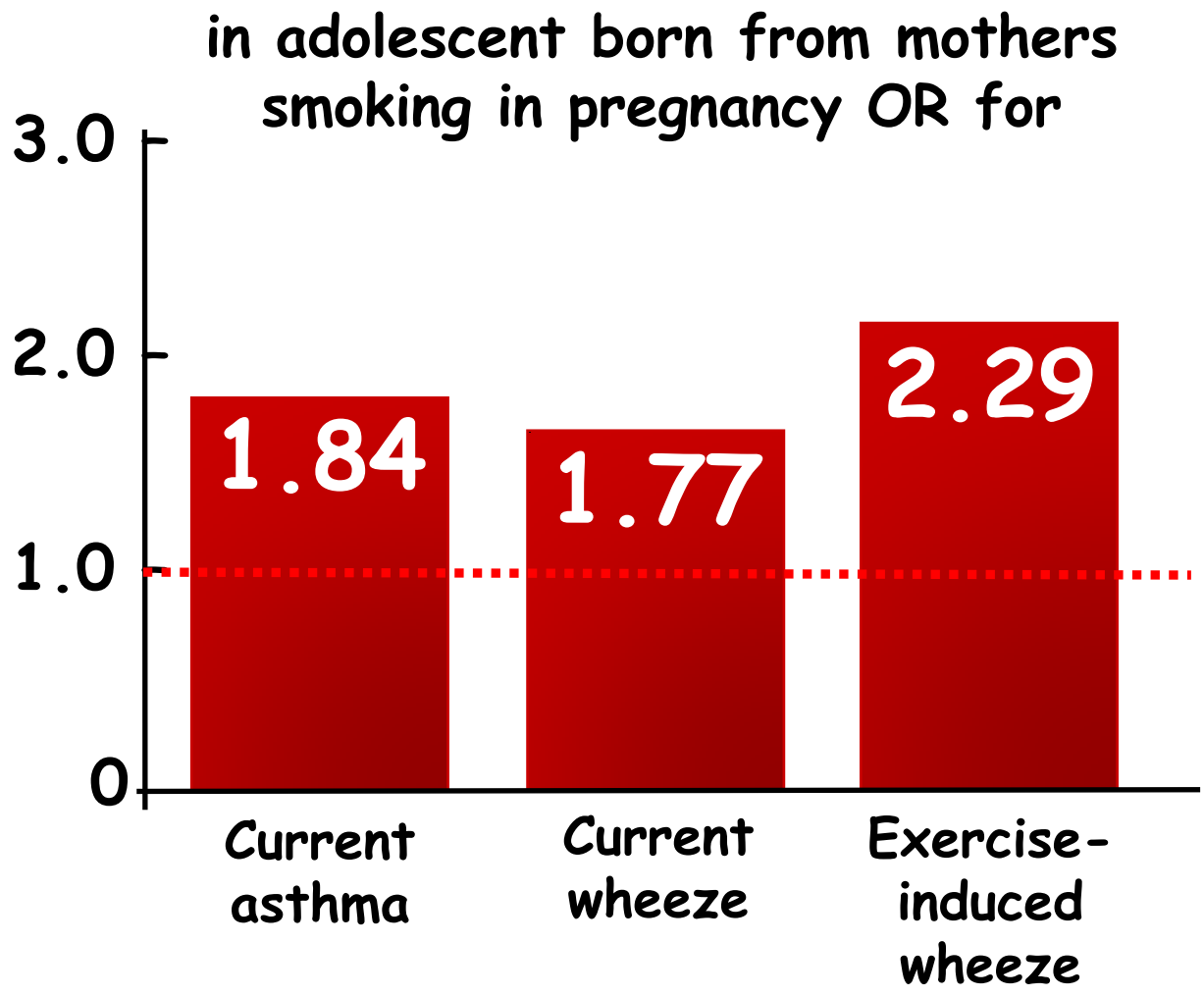


Persistent Effects of Maternal Smoking during Pregnancy on Lung Function and Asthma in Adolescents

Hollams EM, AJRCCM 2014;189:401

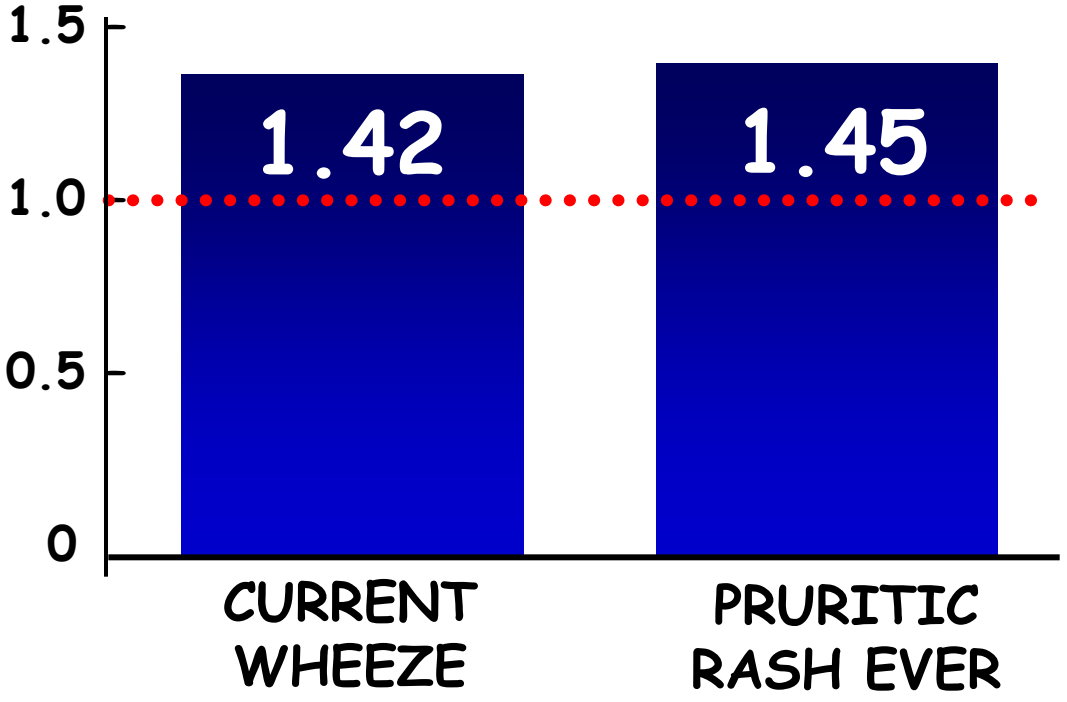
- ✓ maternal smoking in pregnancy (MSP);
- ✓ risk of respiratory disorders in adolescence;
- ✓ bronchial responsiveness, respiratory symptoms,
- ✓ total and allergen-sIgE;
- ✓ 1,129 participants in the 14-year follow-up.



Association of passive exposure of pregnant women to environmental tobacco smoke with asthma symptoms in children. *Xepapadaki Pediatr Allergy Immunol 2009:20:423*

- ✓ Passive exposure of pregnant women to ETS.
- ✓ Questionnaires from 2374 Preschool children.

In Children Born from Mother Passively Exposed to Tobacco Smoke During the 3° Trimester of Pregnancy OR for



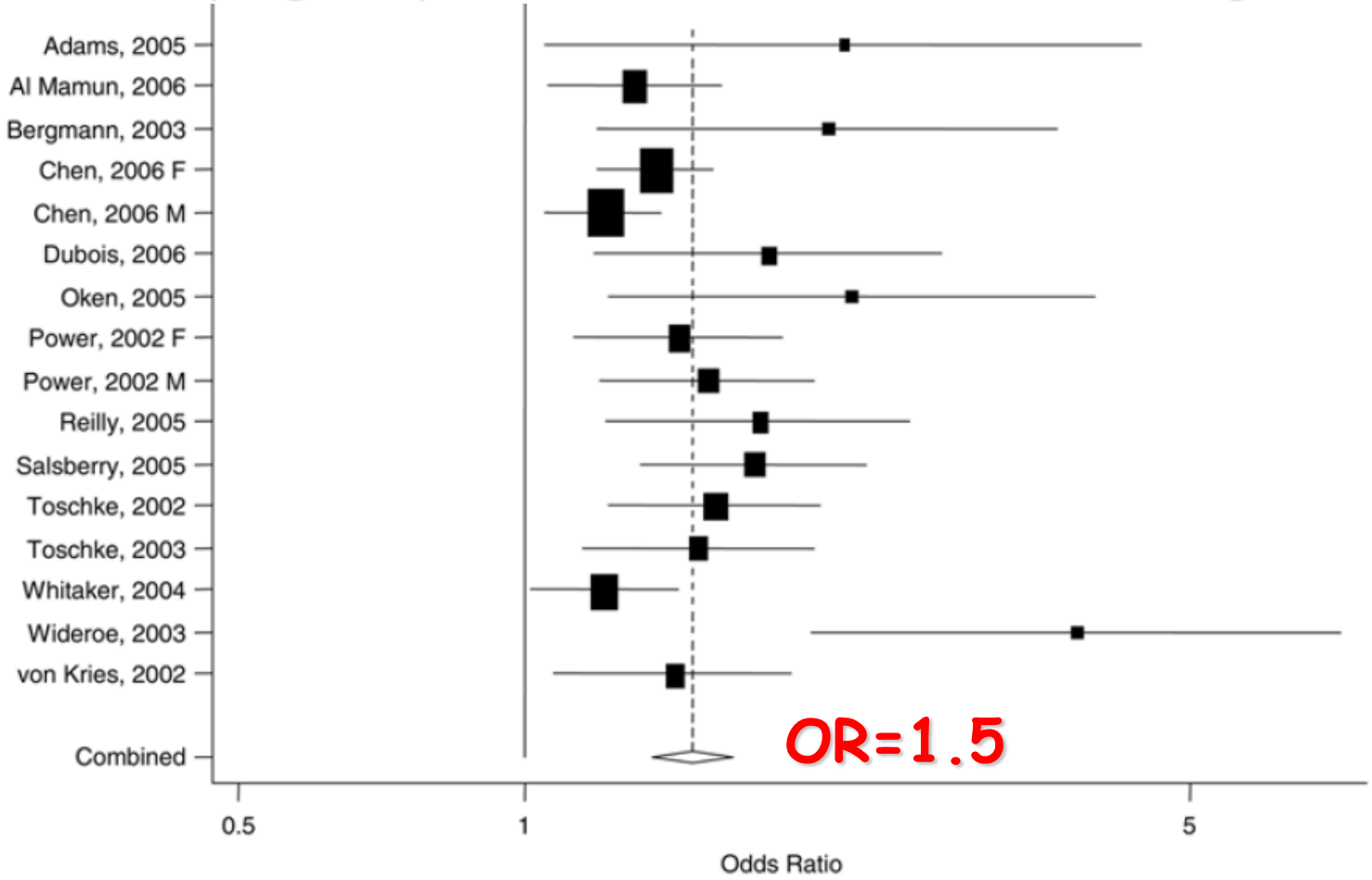
Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis.

Oken E, Int J Obes (Lond) 2008;32(2):201-210.

At age 2 yrs children whose mothers smoked during pregnancy were at elevated risk for overweight

✓84 563 children

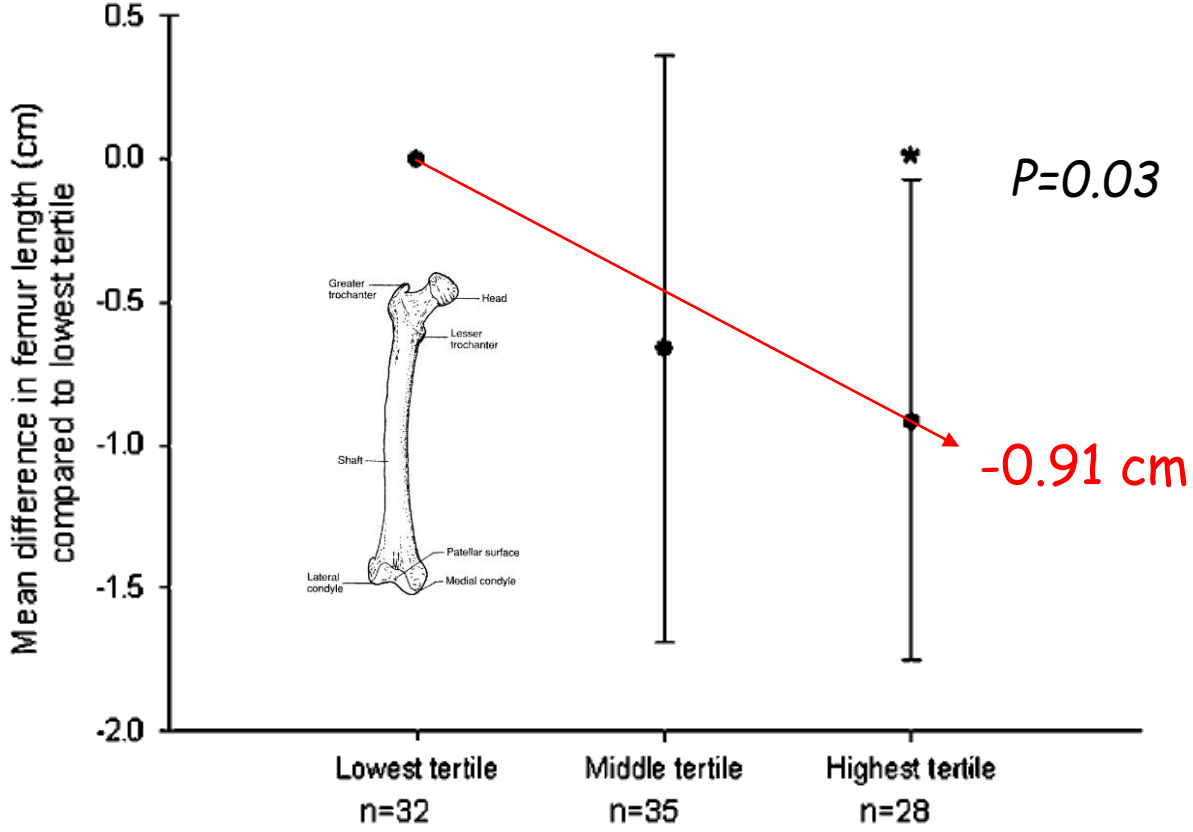
✓14 observational studies



First trimester maternal tobacco smoking habits and fetal growth *Prabhu Thorax 2010;65:235-240*

- ✓ 1924 pregnant women
- ✓ Fetal ultrasound measurements at 11 weeks (crownerump length, CRL) and at 20 weeks gestation (femur length, FL, and biparietal diameter, BPD)

Mean differences in femur length (cm) and 95% CI between 20-week-old fetuses grouped by tertile of maternal daily cigarette consumption

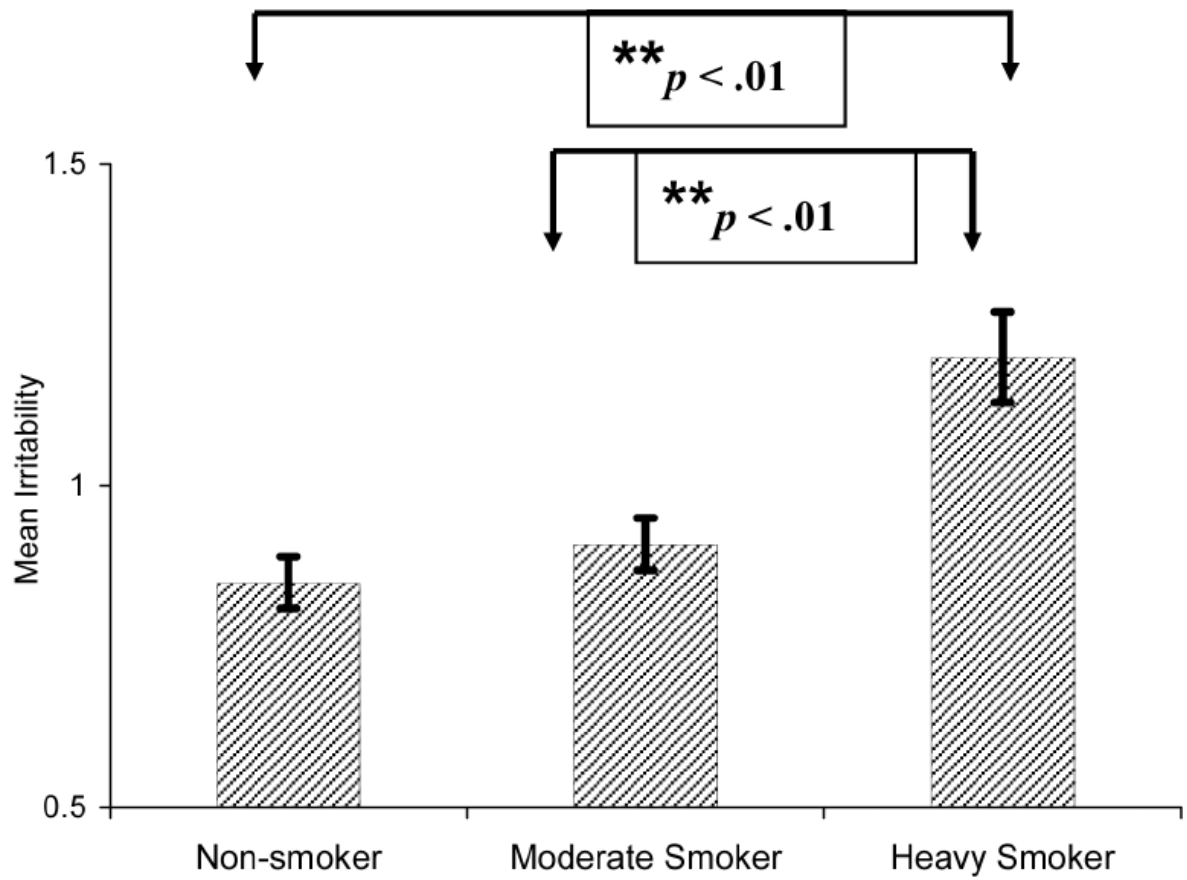


Maternal smoking during pregnancy and neonatal behavior: a large-scale community study.

Stroud LR, Pediatrics 2009;123:e842–e848.

- ✓962 mothers and infants from the Providence Cohort of the National Collaborative Perinatal Project enrolled between 1960 and 1966.
- ✓Neonatal behavior assessed using the Graham-Rosenblith Behavioral Examination of the Neonate.

Significant pair-wise differnces between Maternal Smoking Groups on Infant Irritability



Prenatal Exposure to Nicotine and Impaired Reading Performance *Cho K, J Ped 2013;162:713*

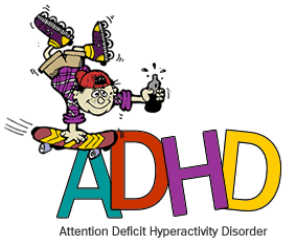
- ✓ A longitudinal sample of 5119 school age children in the Avon Longitudinal Study of Parents and Children;
- ✓ Skill outcomes in the area of speed, fluency, accuracy, spelling, and comprehension in relation to prenatal nicotine exposure;
- ✓ Prenatal nicotine exposure divided: high (>17 mg per day), low (≤ 17 mg per day), and no exposure.

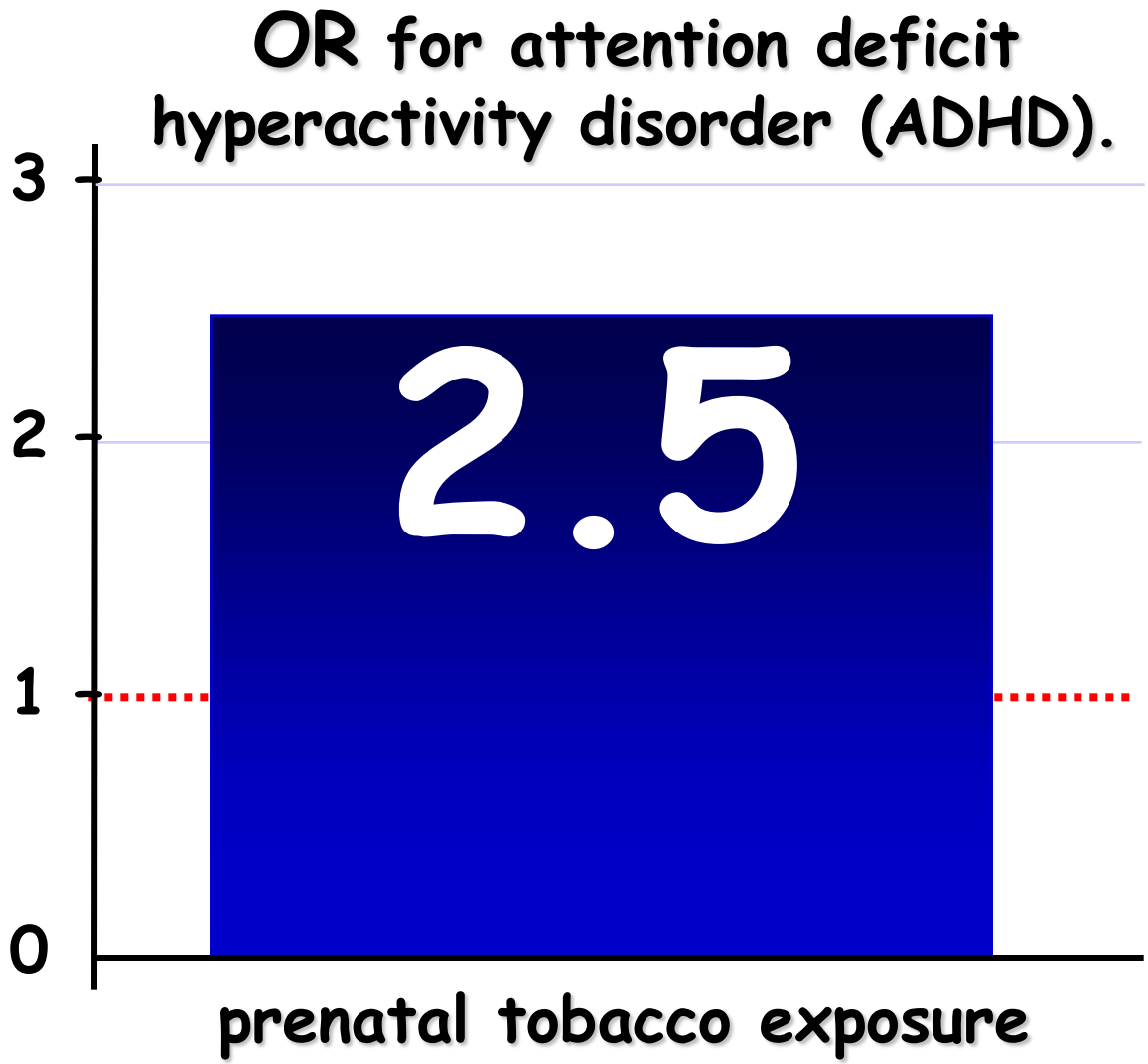
Prenatal nicotine exposure was associated with increased risk of *underperformance in specific reading skill* outcomes after adjusting for potential mediators and confounders *(p = 0.006).*

Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children.

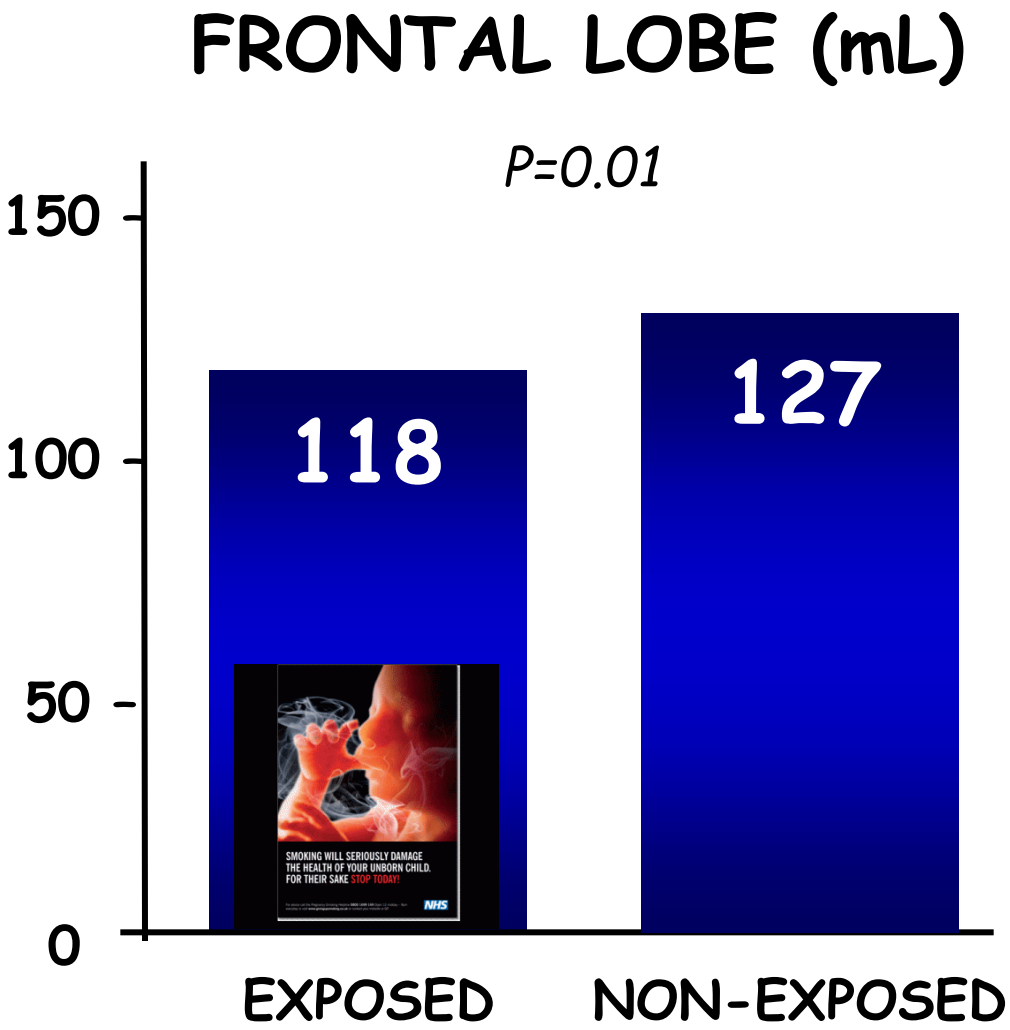
Braun JM, Environ Health Perspect 2006;114:1904–1909.

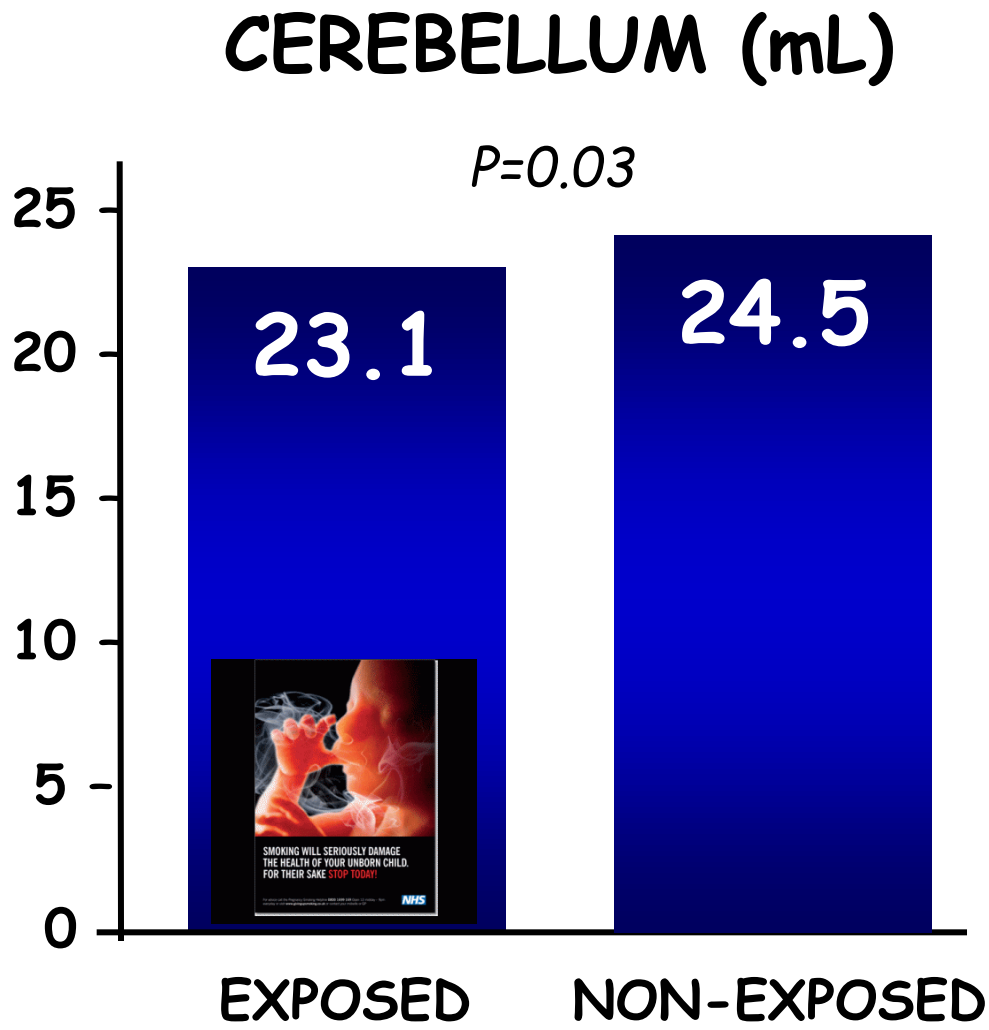
- ✓Prenatal and postnatal tobacco exposure
- ✓4,704 children 4-15 years of age
- ✓**4.2% were reported to have ADHD**





Maternal Smoking during Pregnancy and Regional Brain Volumes in Preterm Infants *Ekblad J Pediatr 2010;156:185*





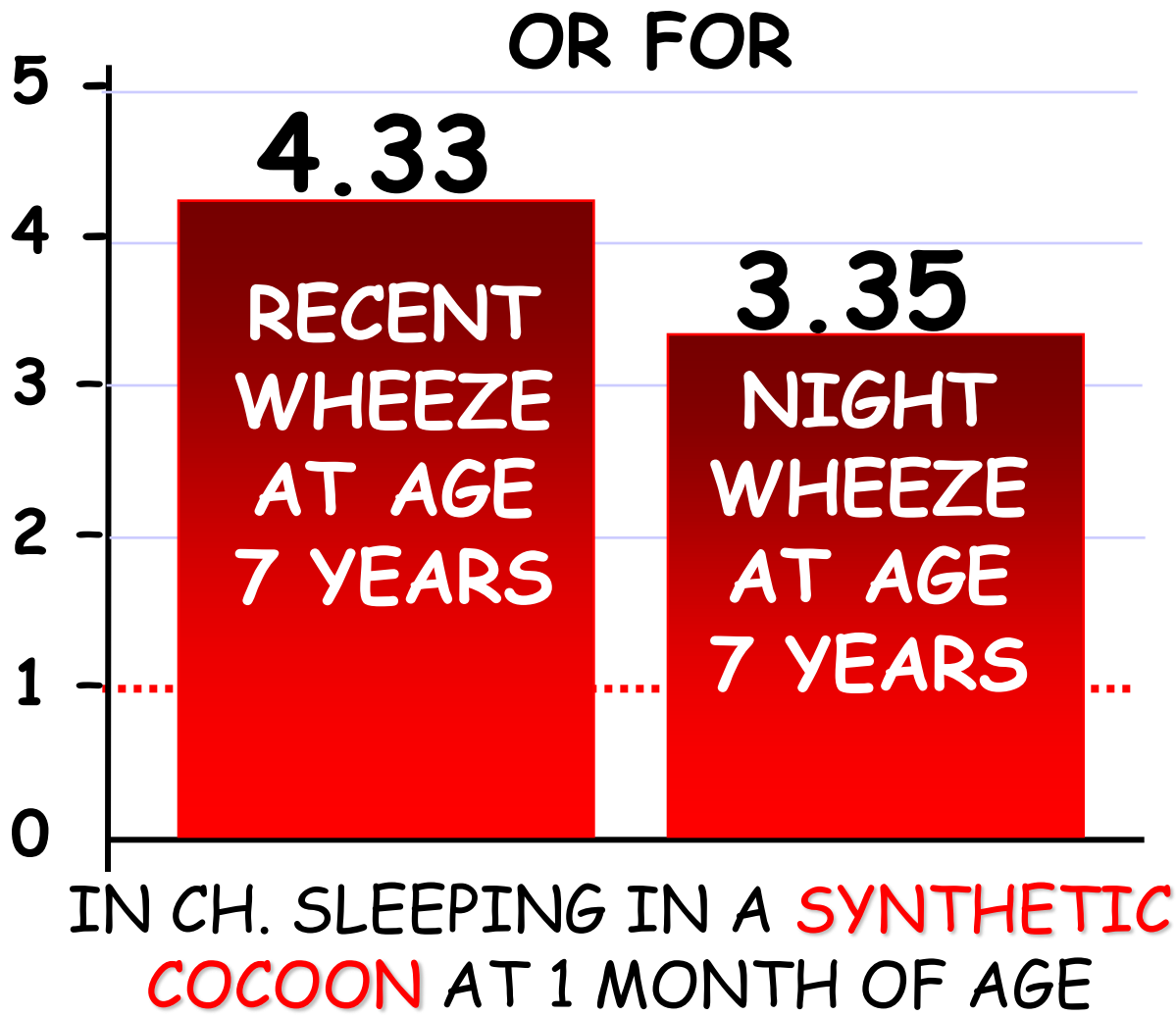
Magnetic Resonance

Indoor Pollution during Pregancy and first years of life

A prospective association between synthetic cocoon use in infancy and childhooh asthma.

Trevillian Paed Perin Epidem 2004:18:281

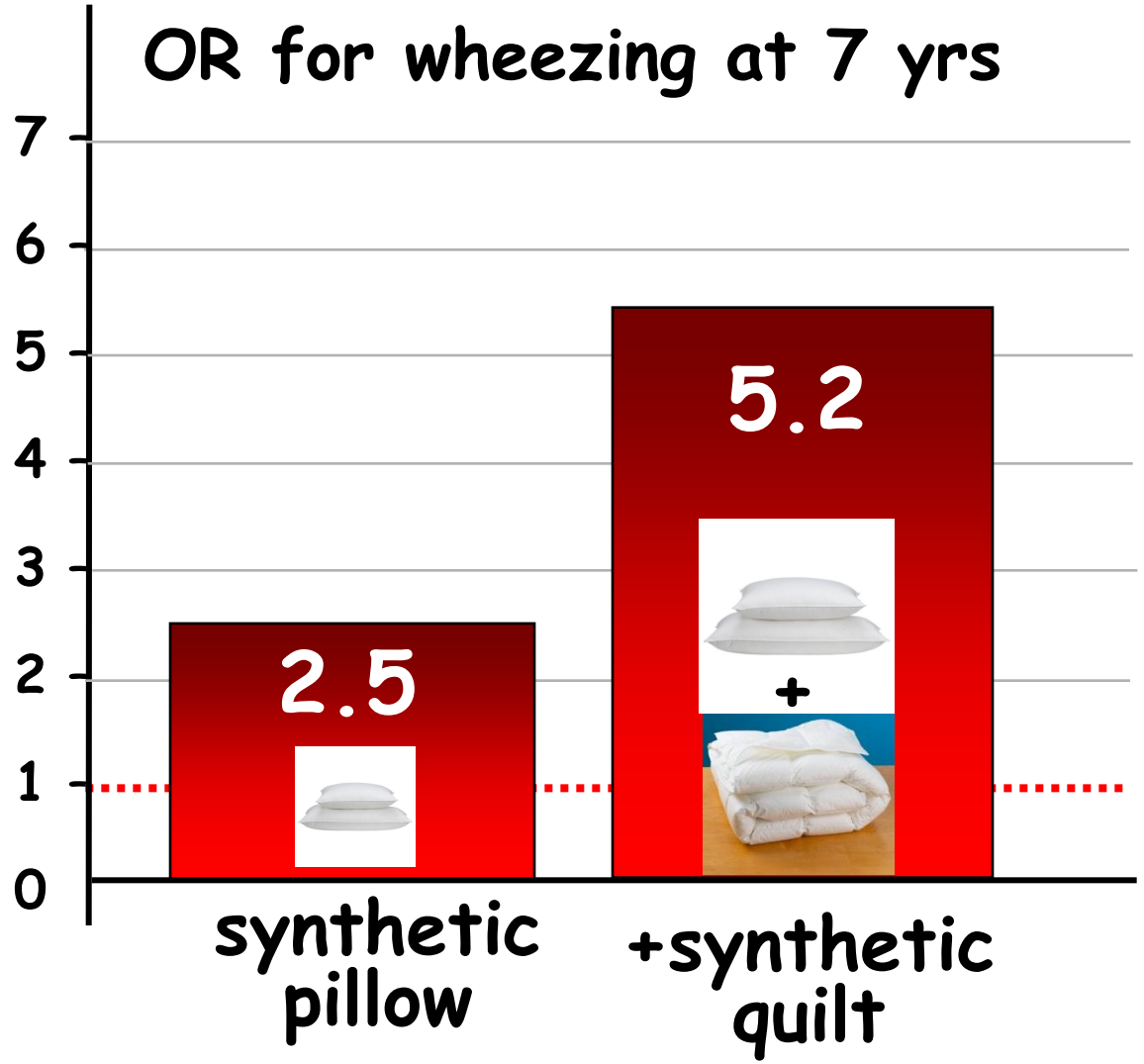
- ✓ Sleeping environment of 863 infants evaluated at 1 month of life
- ✓ Follow-up: 7 years



Synthetic bedding and wheeze in childhood.

Ponsonby AL, Epidemiology. 2003;14(1):37-44

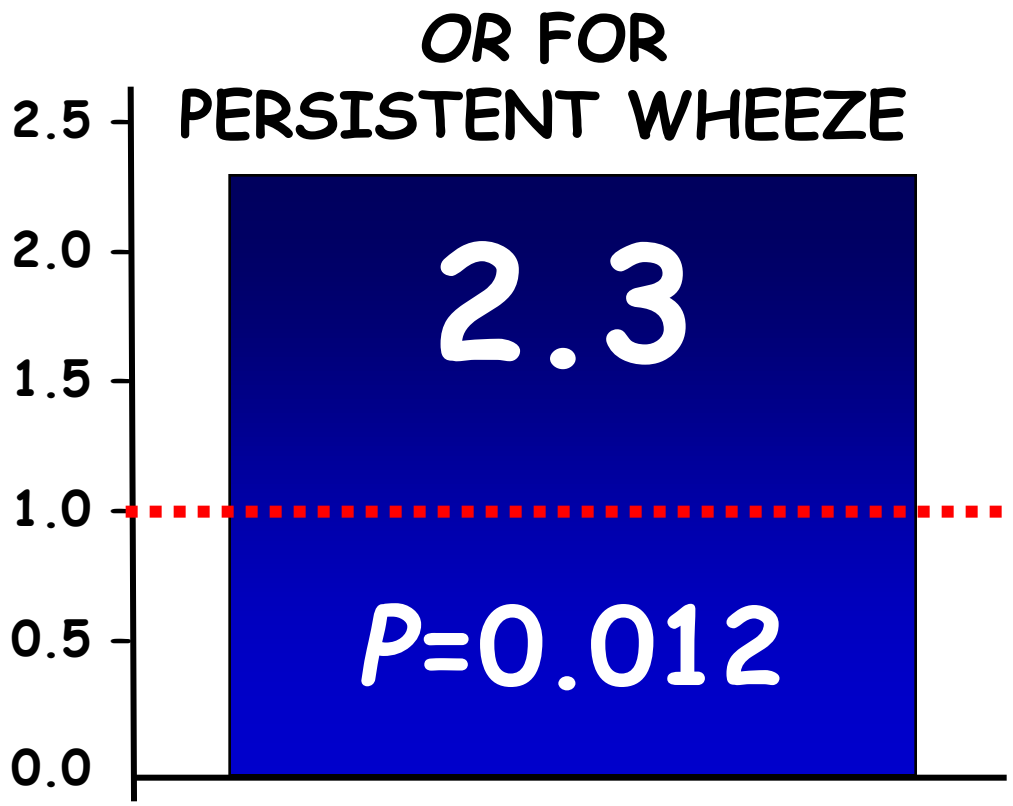
- ✓Bedding type at 1mo
- ✓Wheeze at 7 yrs (n=6,378 ch)



spray detergents
and
atopy-asthma

Frequent use of chemical household products is associated with persistent wheezing in pre-school age children. *Sherriff A, Thorax. 2005;60(1):45-9.*

- ✓ Population based Avon Longitudinal Study of Parents and Children.
- ✓ Frequency of use of 11 chemical based domestic products determined from questionnaires completed by women during pregnancy.
- ✓ A total chemical burden (TCB) score was derived.



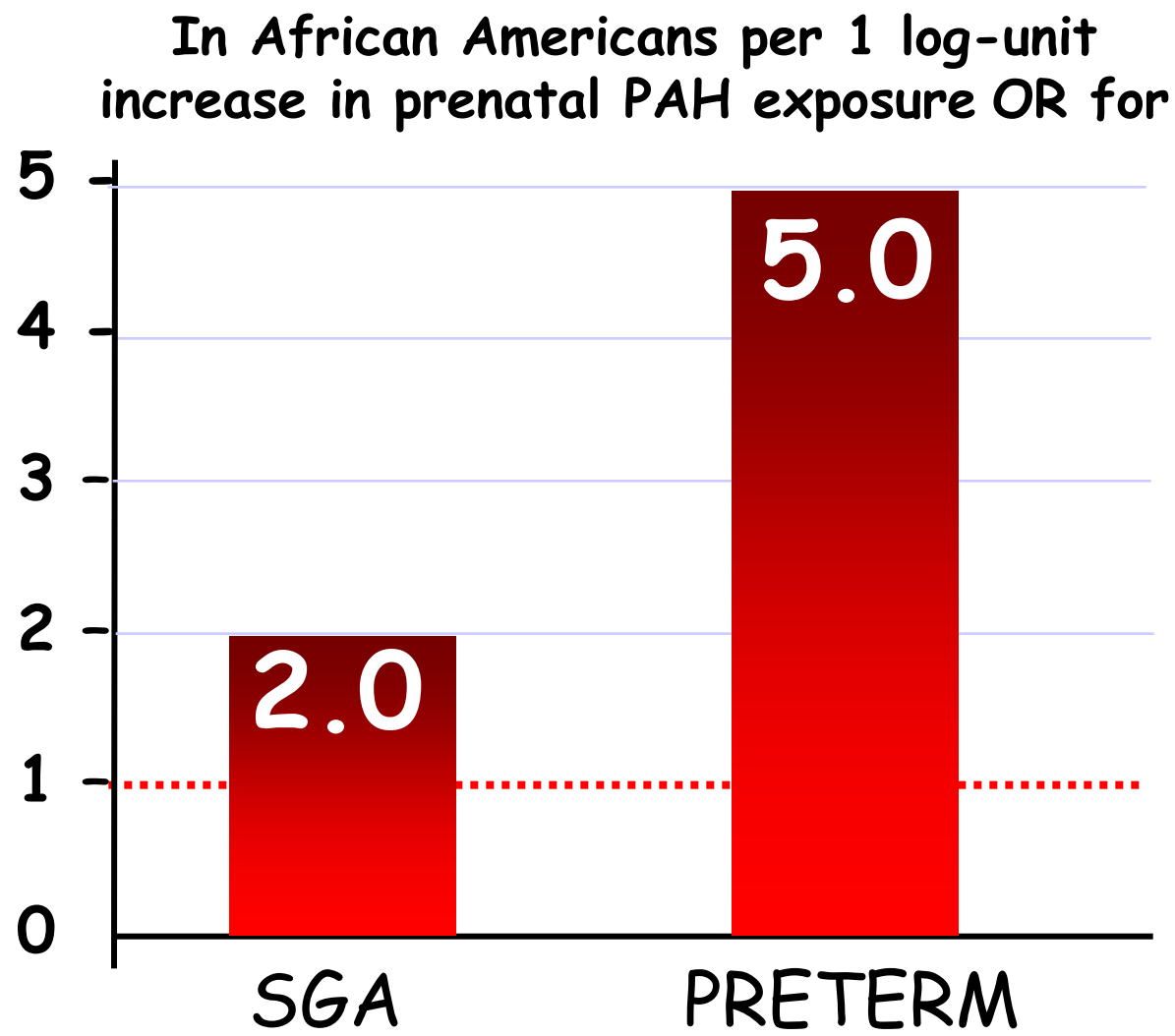
In children whose mothers had high TCB scores (>90th centile) than children whose mothers had a low TCB score (<10th centile).

Outdoor Pollution during pregnancy

Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction.

Choi H, Environ Health Perspect. 2008;116:658-65.

- ✓nonsmoking, healthy African-American (n = 224) and Dominican (n = 392) mother-newborn pairs residing in New York City
- ✓prenatal PAH exposures estimated by personal air monitoring.



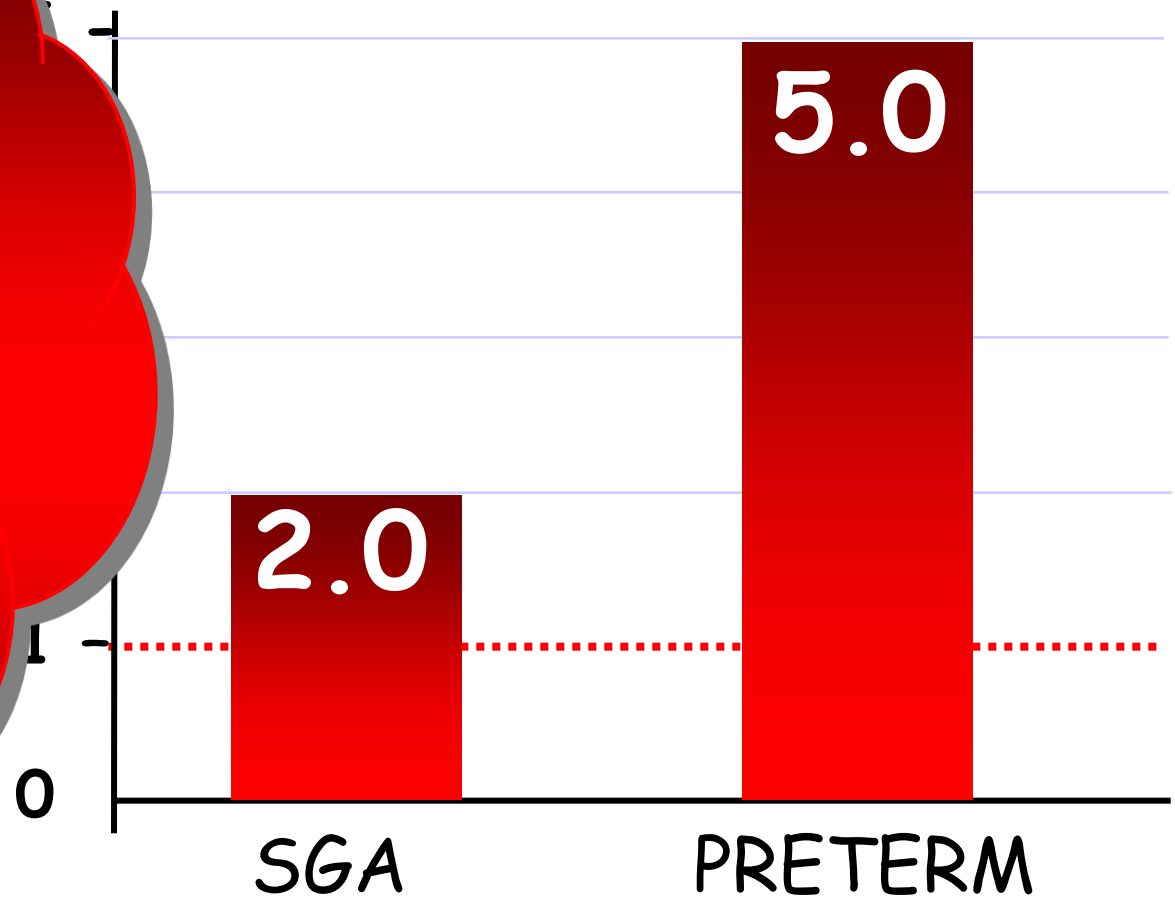
Prenatal exposure to airborne polycyclic aromatic hydrocarbons and risk of intrauterine growth restriction.

Choi H, Environ Health Perspect. 2008;116:658-65.

✓ no
Af
an

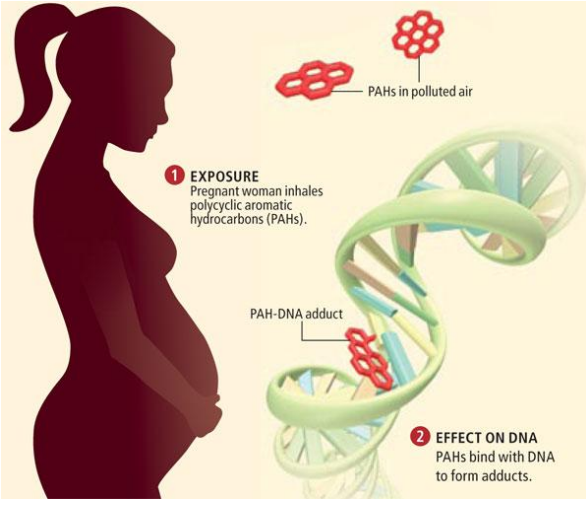
These effects were not observed in Dominicans.

In African Americans per 1 log-unit increase in prenatal PAH exposure OR for



Predictors of personal polycyclic aromatic hydrocarbon exposures among pregnant minority women in New York City. *Tonne CC, Environ Health Perspect. 2004;112:754-9.*

✓personal exposures to **polycyclic aromatic hydrocarbons (PAHs)** among 348 pregnant women in northern Manhattan and the South Bronx, New York.



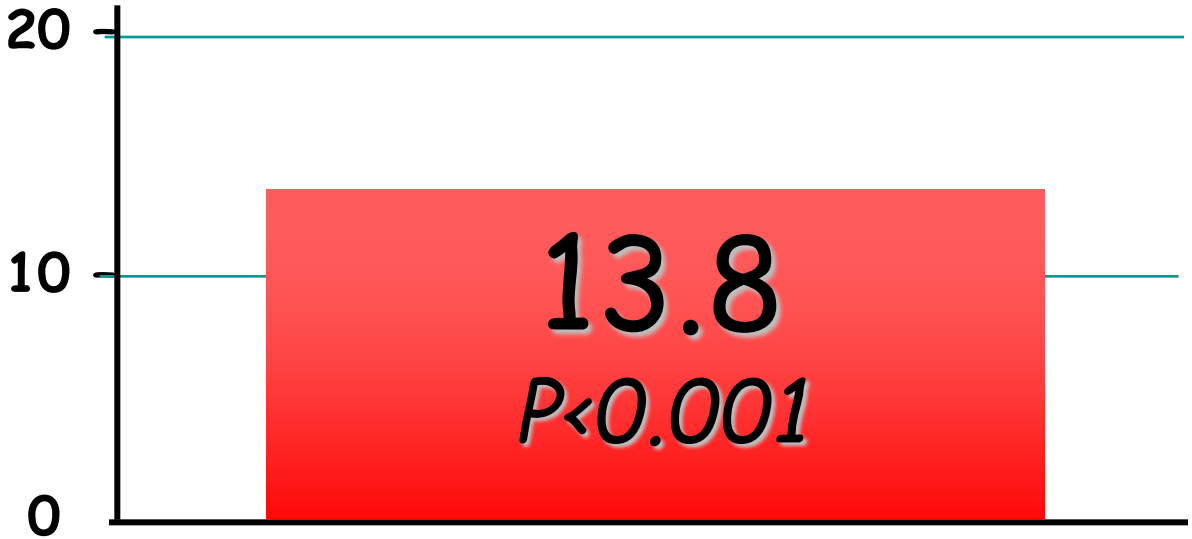
1. **100%** of the women were **exposed** to PAHs during their pregnancies.
2. analyses of cord blood from the **infants** showed that **40% had subtle DNA damage from PAHs — damage** that has been linked to **increased cancer risk**.
3. those exposed prenatally to high levels of PAHs were more than twice as likely to be **cognitively delayed at age 3**, scoring lower on an assessment that predicts performance in school; **at age 5**, these children scored **lower on IQ** tests than children who received less exposure to PAHs in the womb.

Relation of DNA methylation of 59-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma.

Perera F, PLoS One 2009; 4: e4488.

- ✓a longitudinal cohort of approximately 700 children in New York City
- ✓transplacental exposure to traffic-related polycyclic aromatic hydrocarbons (PAHs)
- ✓methylation sensitive restriction fingerprinting was used to analyze umbilical cord white blood cell (UCWBC) DNA

OR for methylation of the acyl-CoA synthetase long-chain family member 3 (ACSL3 5'-CGI) in UCWBC



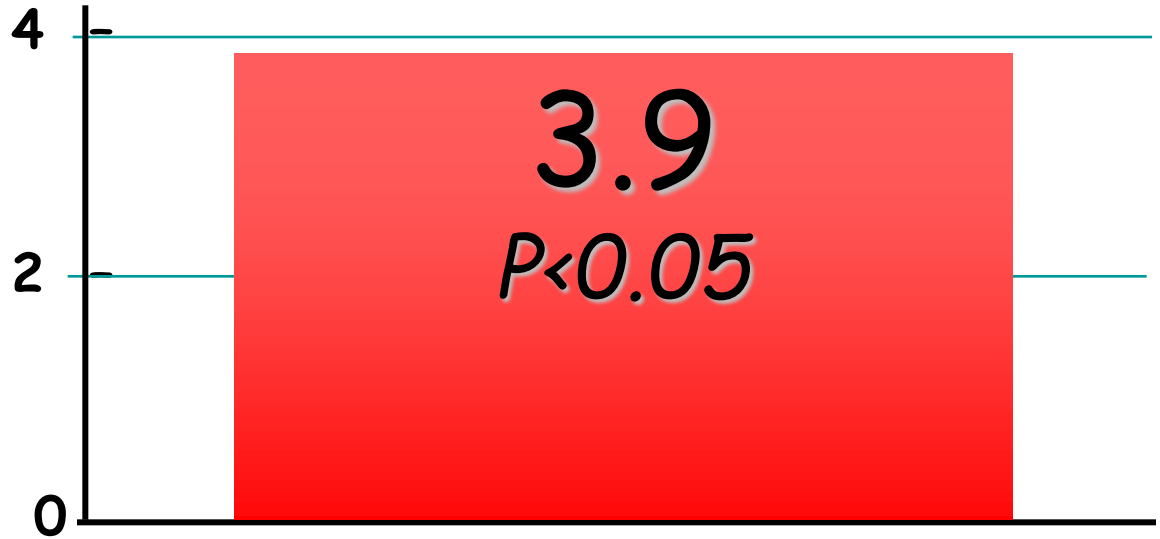
maternal airborne PAH exposure exceeding 2.41 ng/m^3

Relation of DNA methylation of 59-CpG island of ACSL3 to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma.

Perera F, PLoS One 2009; 4: e4488.

- ✓a longitudinal cohort of approximately 700 children in New York City
- ✓transplacental exposure to traffic-related polycyclic aromatic hydrocarbons (PAHs)
- ✓methylation sensitive restriction fingerprinting was used to analyze umbilical cord white blood cell (UCWBC) DNA

OR for a parental report of asthma symptoms in children prior to age 5



methylation of the ACSL3 5'-CGI in UCWBC

Prenatal Exposure to Air Pollution, Maternal Psychological Distress, and Child Behavior

Perera, Pediatrics 2013;132:e1284

- ✓ Longitudinal birth cohort 248 children of nonsmoking white women in the coal-burning region of Krakow, Poland
- ✓ Followed from in utero until age 9
- ✓ Prenatal PAH exposure measured by personal air monitoring
- ✓ Maternal demoralization during pregnancy

Significant interactions between maternal demoralization and PAH exposure (high versus low) were identified for symptoms in children of:

- anxious/ depressed,
- withdrawn/depressed,
- social problems,
- aggressive behavior,
- internalizing problems
- externalizing problems

The Impact of Air

"We used to worry about elderly people and asthma patients," *Perera says.* ***"Now we worry about fetuses."*** *And efforts to reduce environmental toxins can make a measurable difference, she says. "Over the years that we've been tracking exposures, New York City buses have switched to cleaner technology, and restrictions have been placed on the idling of diesel buses and trucks," Perera notes. "As a result, we've seen the levels of pollutants in pregnant women's blood coming down, which means their fetuses are encountering fewer of these substances too."*

Annie M Paul Time October 4, 2010

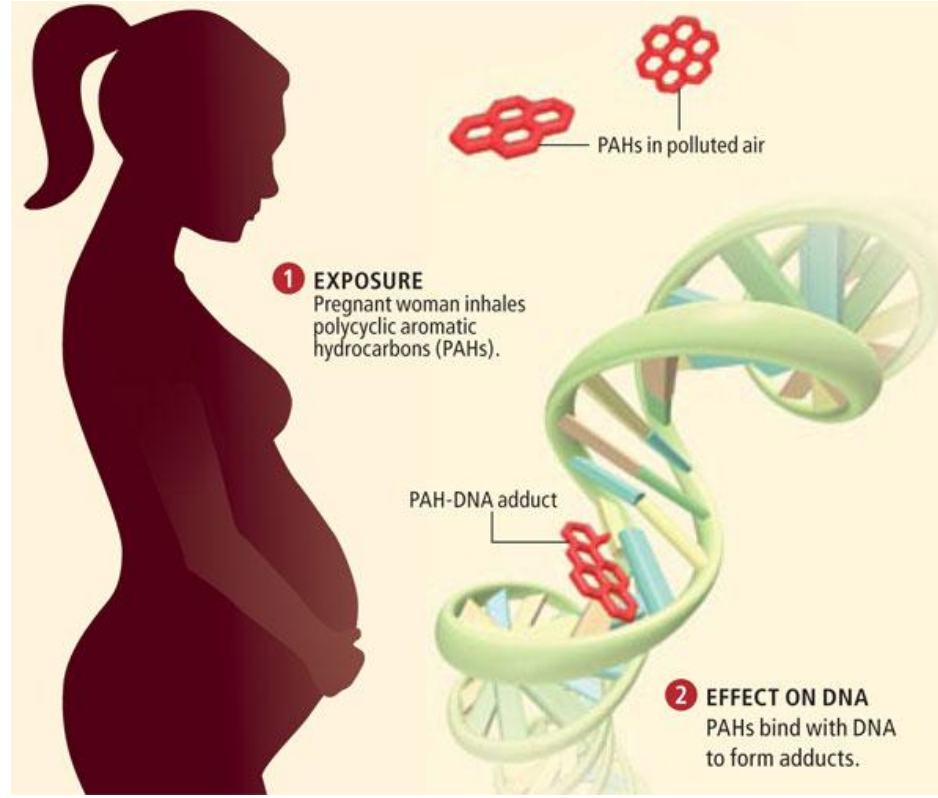
Diet of the mother diuring pregnancy

Modulation of the effect of prenatal PAH exposure on PAH-DNA adducts in cord blood by plasma antioxidants.

Kelvin EA, Cancer Epidemiol Biomarkers Prev. 2009;18:2262-8.

✓The fetus is more susceptible than the adult to the effects of certain carcinogens, such as polycyclic aromatic hydrocarbons (PAH).

✓Nutritional factors, including **antioxidants, have been shown to have a protective effect** on carcinogen-DNA adducts and cancer risk in adults.



Modulation of the effect of prenatal PAH exposure on PAH-DNA adducts in cord blood by plasma antioxidants.

Kelvin EA, Cancer Epidemiol Biomarkers Prev. 2009;18:2262-8.

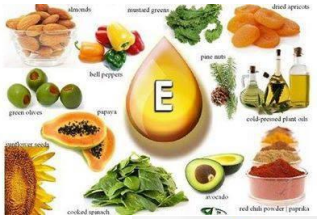
- ✓prenatal airborne PAH exposure, measured by personal air monitoring during pregnancy,
- ✓level of PAH-DNA adducts in a baby's cord blood
- ✓concentration of micronutrients in maternal and cord blood

The association between PAH exposure and PAH-adducts was much stronger among those with low α-tocopherol

(beta = 0.15; P = 0.001)

and among those with low carotenoids

(beta = 0.16; P < 0.001)



compared with babies with high levels of these micronutrients

Nutrients and foods for the primary prevention of asthma and allergy: Systematic review and meta-analysis. *Nurmatov U, JACI. 2011;127:724*

✓62 eligible reports.
✓22 studies reported on the association between **fruit and vegetable** consumption and asthma or atopic outcomes in children

higher consumptions by mothers during pregnancy and children in early life result in

reductions in the risk of children developing asthma and asthma-related symptoms.

Overall, the body of data was **more convincing for fruit** than vegetables.

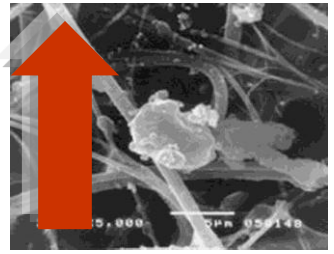
Higher fish consumption in pregnancy may confer protection against the harmful effect of prenatal exposure to fine particulate matter.

Jedrychowski W, Ann Nutr Metab. 2010;56:119-26.

- ✓481 nonsmoking women with singleton pregnancies
- ✓diet during pregnancy.
- ✓PM2.5 by personal air monitoring over 48 h during the second trimester of pregnancy

adjusted birth weight was significantly lower in newborns whose mothers were exposed to particulate matter > 46.3 microg/m^3

(beta coefficient = -97.02, p=0.032).



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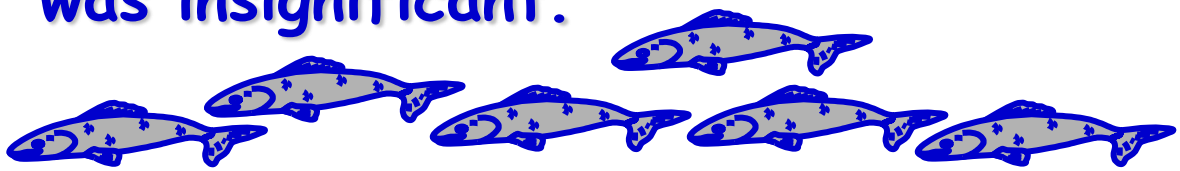
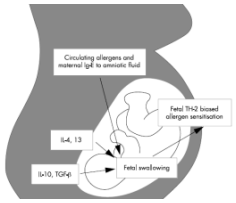
- ✓481 nonsmoking women with singleton pregnancies
- ✓diet during pregnancy.
- ✓PM2.5 by personal air monitoring over 48 h during the second trimester of pregnancy

Deficit in birth weight amounted to 133.26 g ($p = 0.052$) in newborns whose mothers reported low fish intake (<91 g/week).

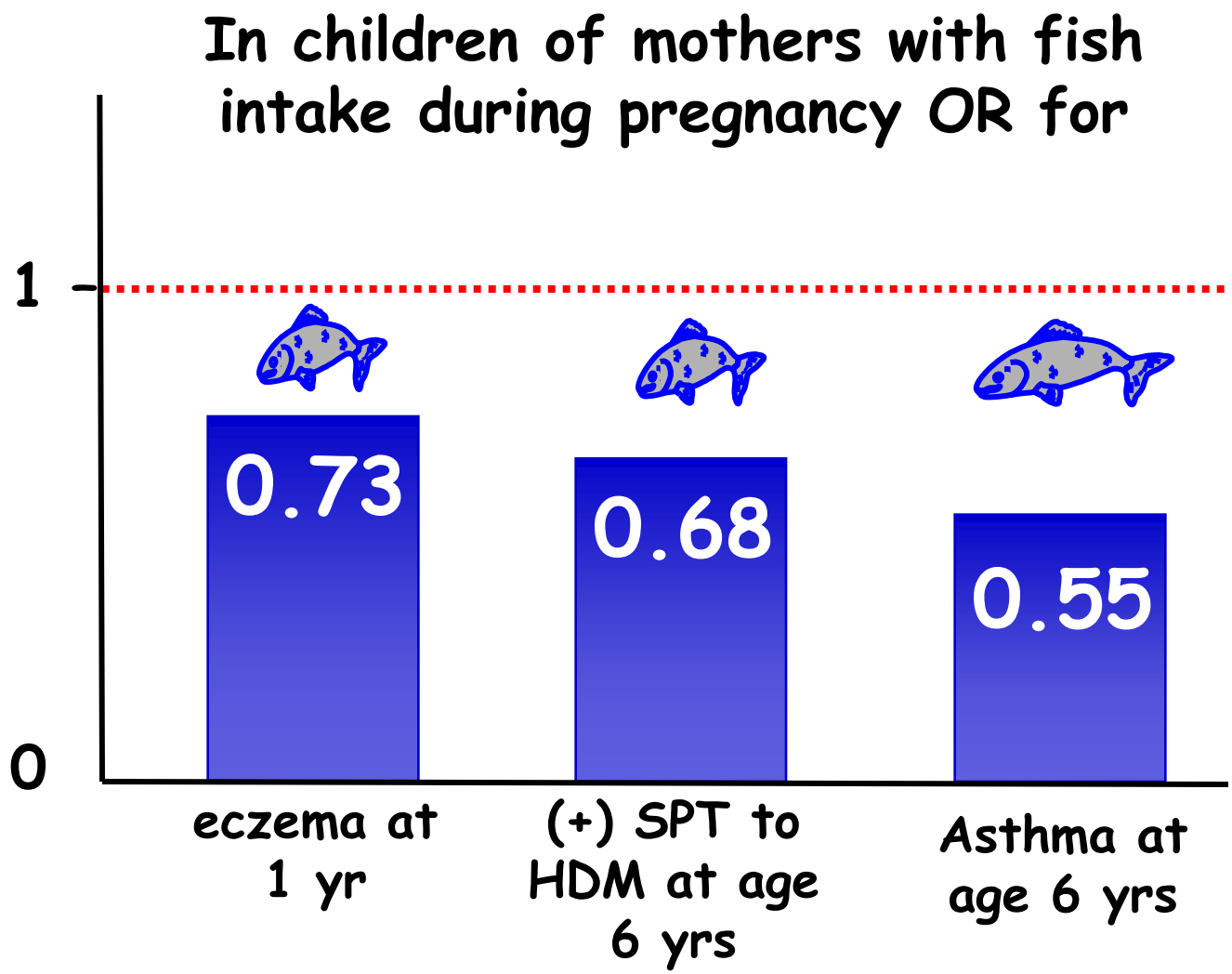
The birth weight deficit in newborns whose mothers reported medium (91-205 g/week) or higher fish intake (>205 g/week) was insignificant.



Maternal fish intake during pregnancy and atopy and asthma in infancy. *Romieu Clin Exp All 2007;37:518*



- ✓ A cohort of women (n=462) enrolled during pregnancy
- ✓ Offspring followed-up to 6 years



Good for your heart but bad for your baby? Revised guidelines for fish consumption in pregnancy.

Bambrick HJ, Med J Aust. 2004;181:61-2.

Revised Australian recommendations for fish consumption*

	One serve per week (no other fish that week)*		One serve per fortnight (no other fish that fortnight)*		Two or three serves per week
Pregnant women, women intending to become pregnant, and children (up to 6 years)	Orange roughy (sea perch), catfish	OR	Shark (flake), billfish (swordfish, broadbill, marlin)	OR	Any fish or seafood not listed to the left
Rest of population	Shark (flake), billfish (swordfish, broadbill, marlin)	OR		OR	Any fish or seafood not listed to the left

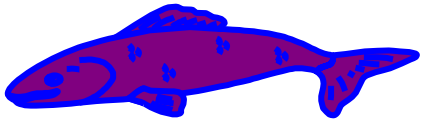
* Serving size = 150 g for adults and older children, 75 g for children aged up to 6 years.[1]

While some species of fish have high levels of MeHg (swordfish, orange roughy, shark), others, such as salmon and hake, have relatively low levels.

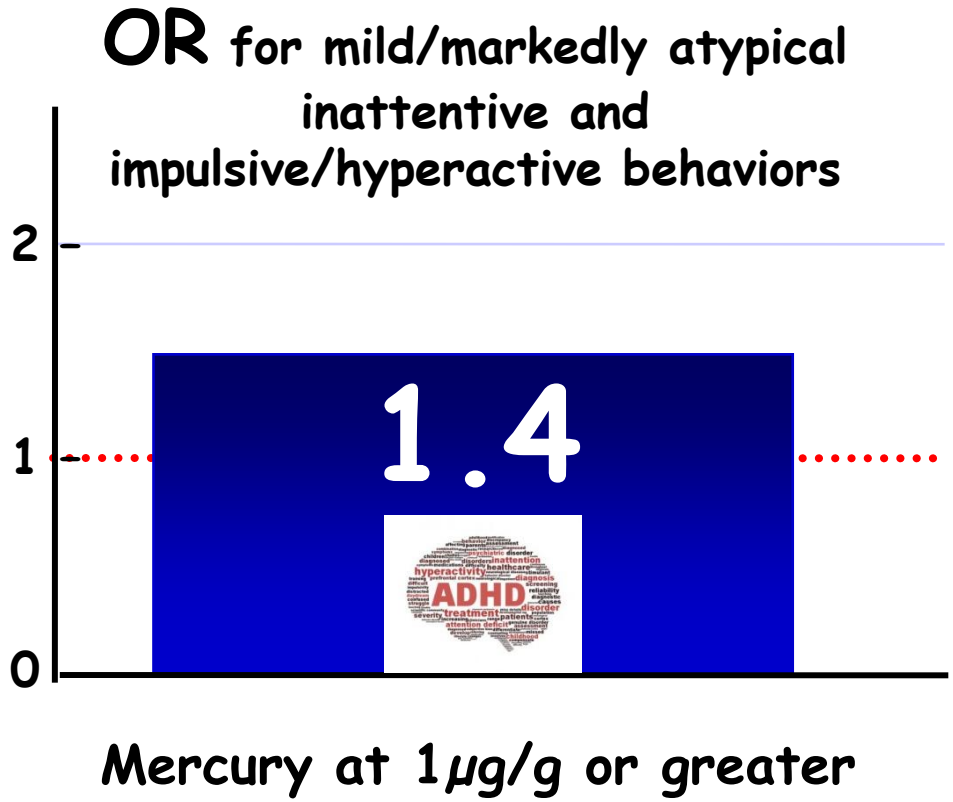
Although canned tuna is usually sourced from smaller, younger fish and is relatively low in mercury, some tuna (albacore, bluefin) has higher concentrations.

Prenatal Exposure to Mercury and Fish Consumption During Pregnancy and Attention-Deficit/Hyperactivity Disorder–Related Behavior in Children

Sagiv K.,APAM 2012;166(12):1123-1131



- ✓birth cohort recruited 1993-1998
- ✓children examined at age 8 years
- ✓peripartum maternal hair mercury measures (n=421) or maternal report of fish consumption during pregnancy (n = 515)



Folic acid

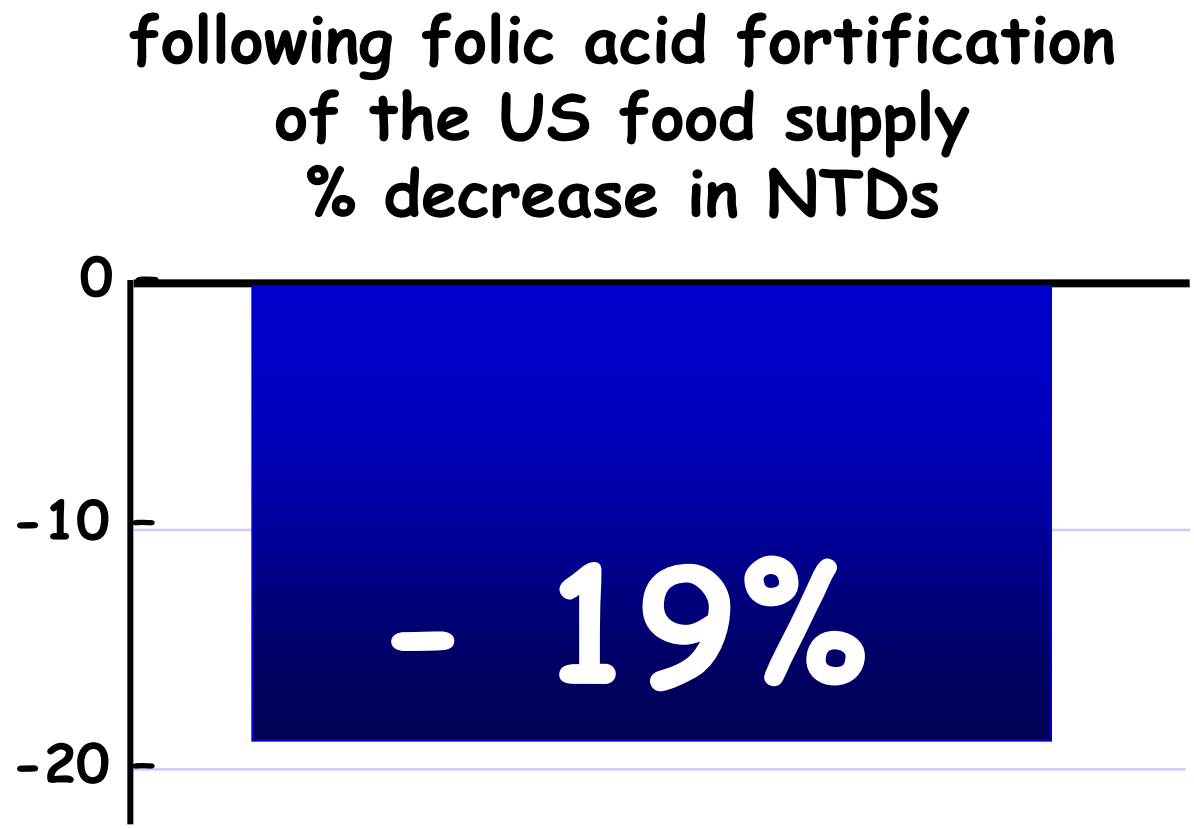
and

DHA

Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects.

Honein MA, JAMA 2001;285:2981-2986.

✓Birth certificate reports of spina bifida and anencephaly
before fortification
(October 1995 through December 1996) compared with after
mandatory fortification
(October 1998 through December 1999).
✓in 45 US states and Washington, DC
✓neural tube defects (NTDs).

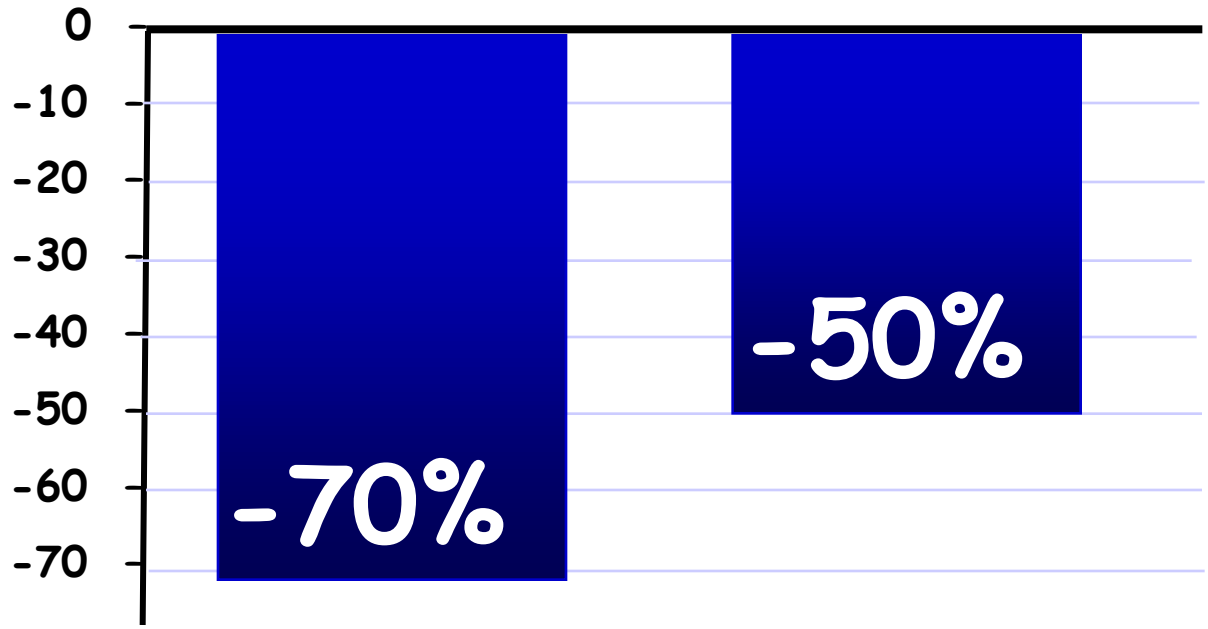


Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study.

Bukowski R, PLoS Med 2009;6(5):e1000061.

- ✓a cohort of 34,480 low-risk singleton pregnancies
- ✓preconceptional folate supplementation prospectively recorded in the first trimester of pregnancy
- ✓Spontaneous preterm birth was defined as duration of pregnancy between 20 and 37 wk

preconceptional folate supplementation associated decreased risk for preterm birth between

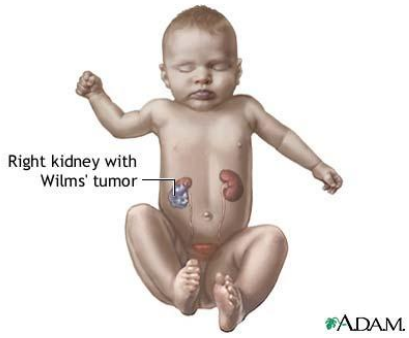


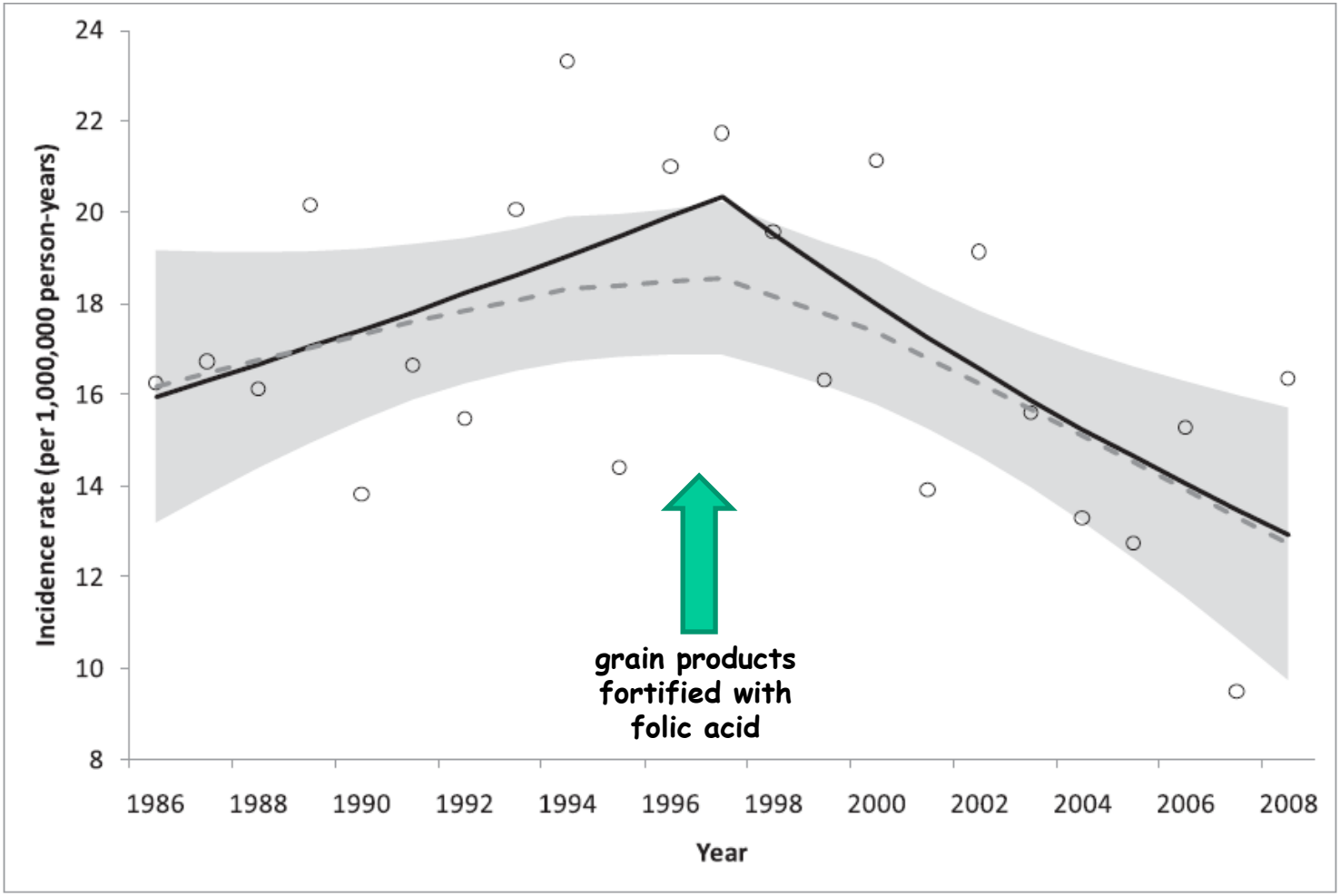
Childhood cancer incidence trends in association with US folic acid fortification (1986-2008)

Amy M. et al Pediatrics 2012;129:1125-1133

Epidemiology (1986 - 2008) in children aged 0 to 4 years

Changes in **WILMS TUMORS**



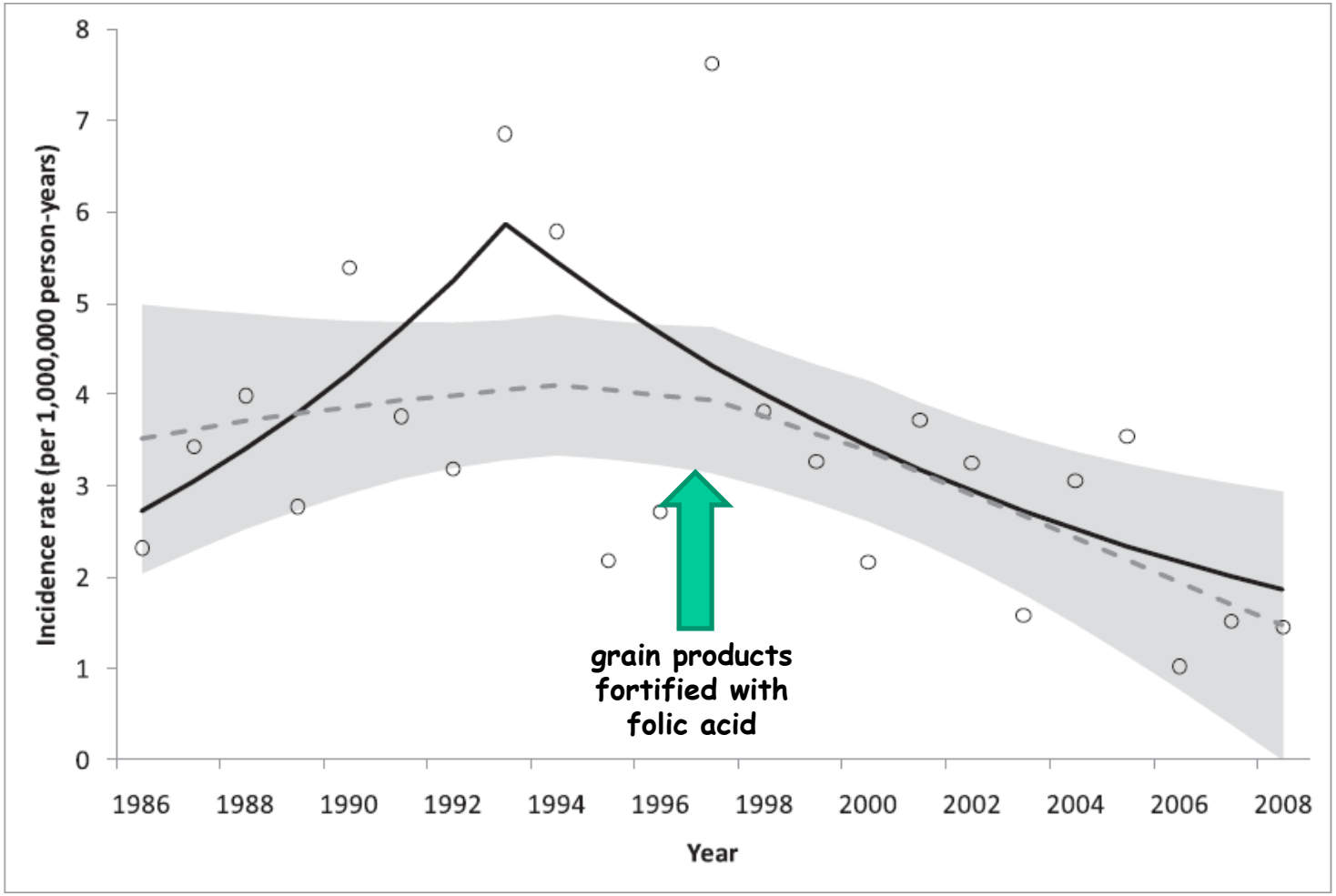


Childhood cancer incidence trends in association with US folic acid fortification (1986-2008)

Amy M. et al Pediatrics 2012;129:1125-1133

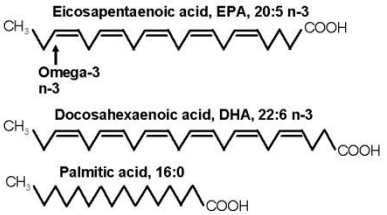
Epidemiology (1986 - 2008) in children aged 0 to 4 years

Changes in **PRIMITIVE NEURO-ECTODERMAL TUMORS**



Meta-analysis of LCPUFA Supplementation of Infant Formula and Visual Acuity

Qawasmi A, Pediatrics 2013; 131;e262



- ✓ 19 studies involving 1949 infants
- ✓ Long-chain polyunsaturated fatty acids (LCPUFAs) supplementation in infant formulas

- We demonstrated a significant benefit of LCPUFA supplementation on infants' visual acuity at 2, 4, and 12 months of age when visual acuity was assessed by using visual evoked potential and at 2 months of age by using behavioral methods

Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age.

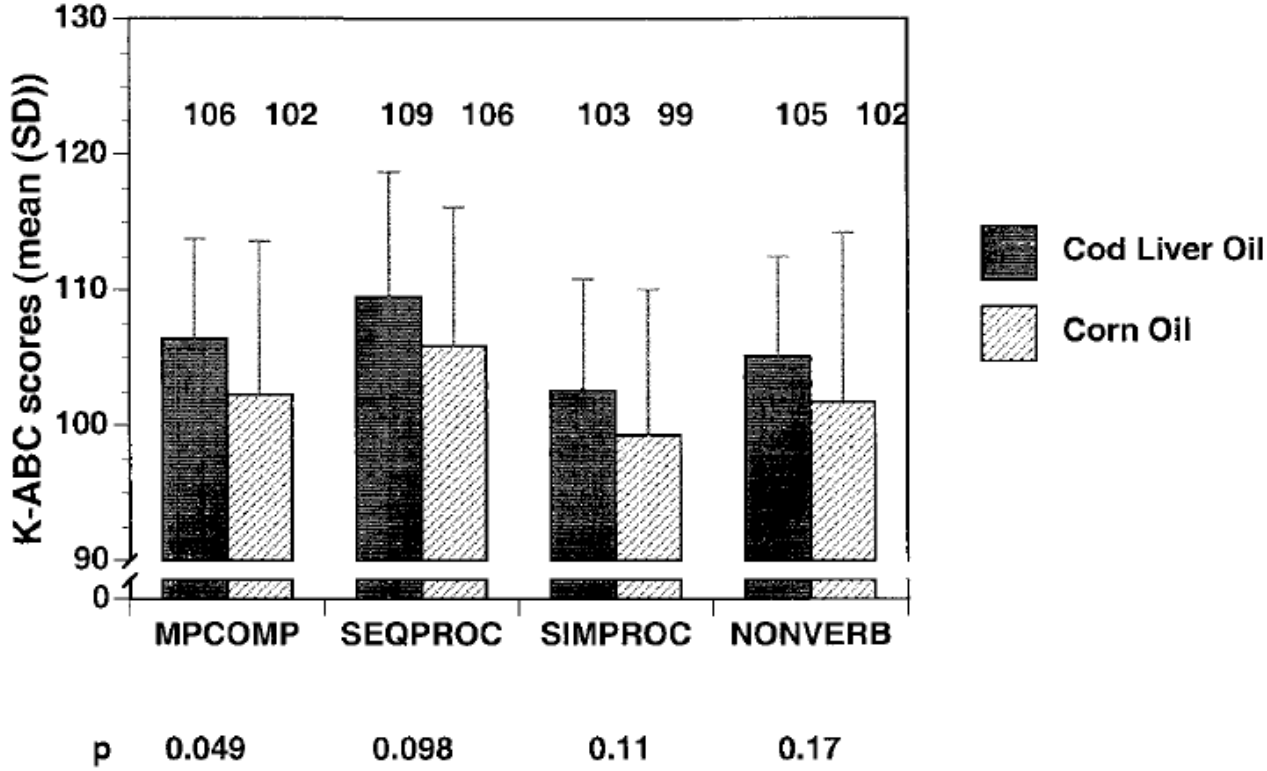
Helland IB, Pediatrics. 2003;111:e39-e44.

✓Pregnant women were recruited in week 18 of pregnancy to take 10 mL of cod liver oil or corn oil until 3 months after delivery

✓The cod liver oil contained 1183 mg/10 mL **DHA**, 803 mg/10 mL **eicosapentaenoic acid** (20:5 n-3)

MPCOMP, Mental Processing Composite; SEQPROC, Sequential Processing; SIMPROC, Simultaneous Processing; NONVERB, Nonverbal Abilities.

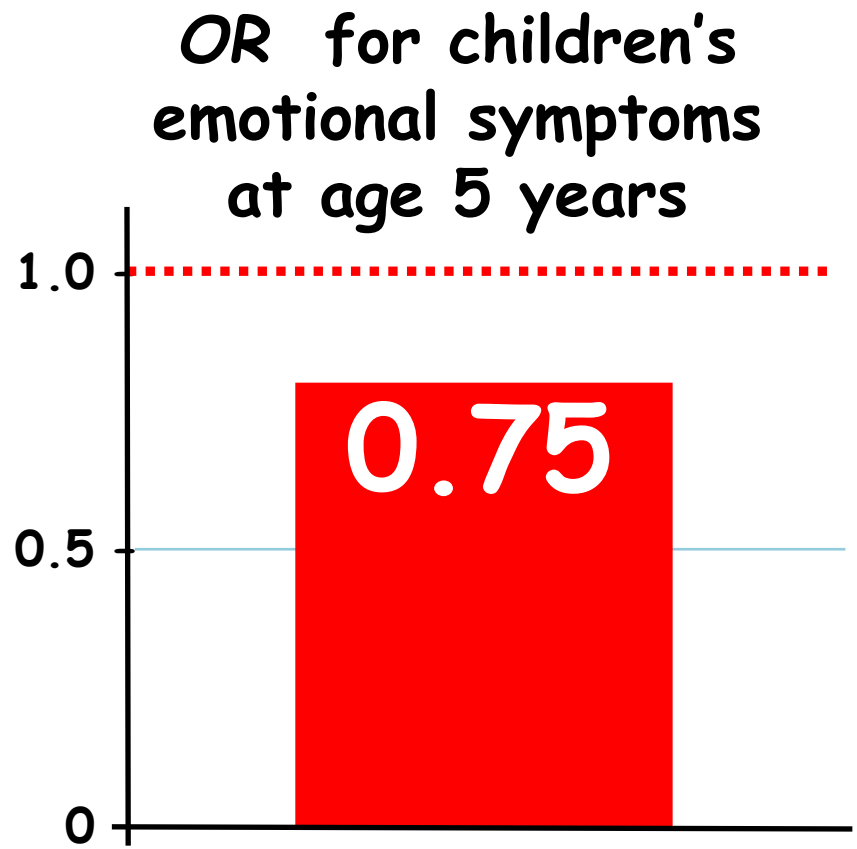
Kaufman Assessment Battery for Children (K-ABC) score at 4 years of age



Maternal Long-Chain Polyunsaturated Fatty Acid Status during Early Pregnancy and Children's Risk of Problem Behavior at Age 5-6 Years

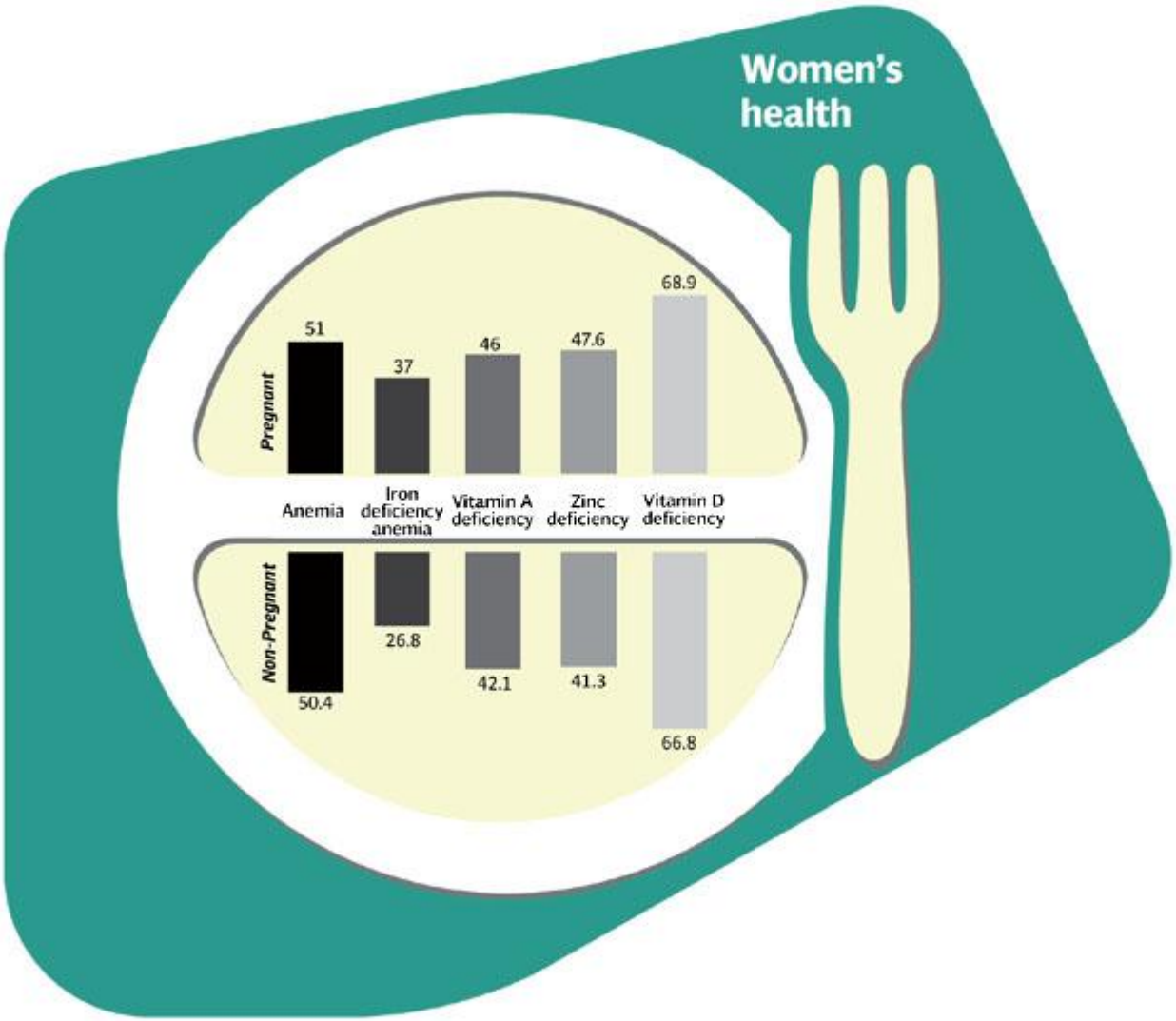
Loomans EM, J Ped 2014;164;762-768

- ✓ Maternal long-chain polyunsaturated fatty acid (LCPUFA) status and ratio during pregnancy (4336 women)
- ✓ Children's risk of problem behavior at 5 years of age rated by their mother (n = 2502) and teacher (n = 2061)



Greater concentrations of omega-3 fatty acid docosahexaenoic acid

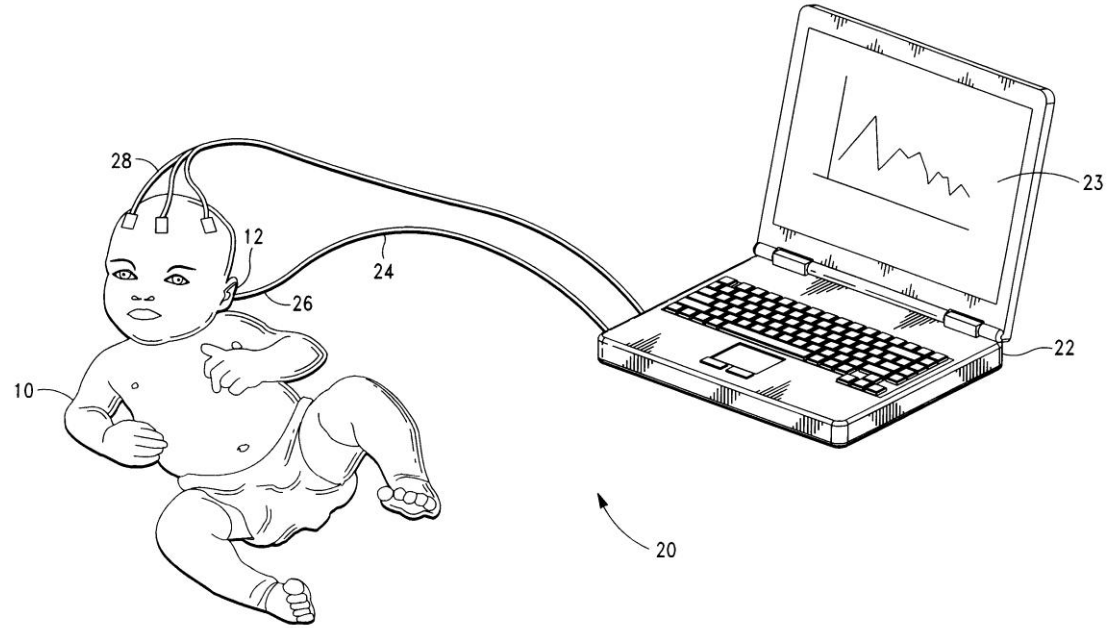
Micronutrients deficency during pregnancy



Latent Iron Deficiency In Utero Is Associated with Abnormal Auditory Neural Myelination in ≥35 Weeks Gestational Age Infants

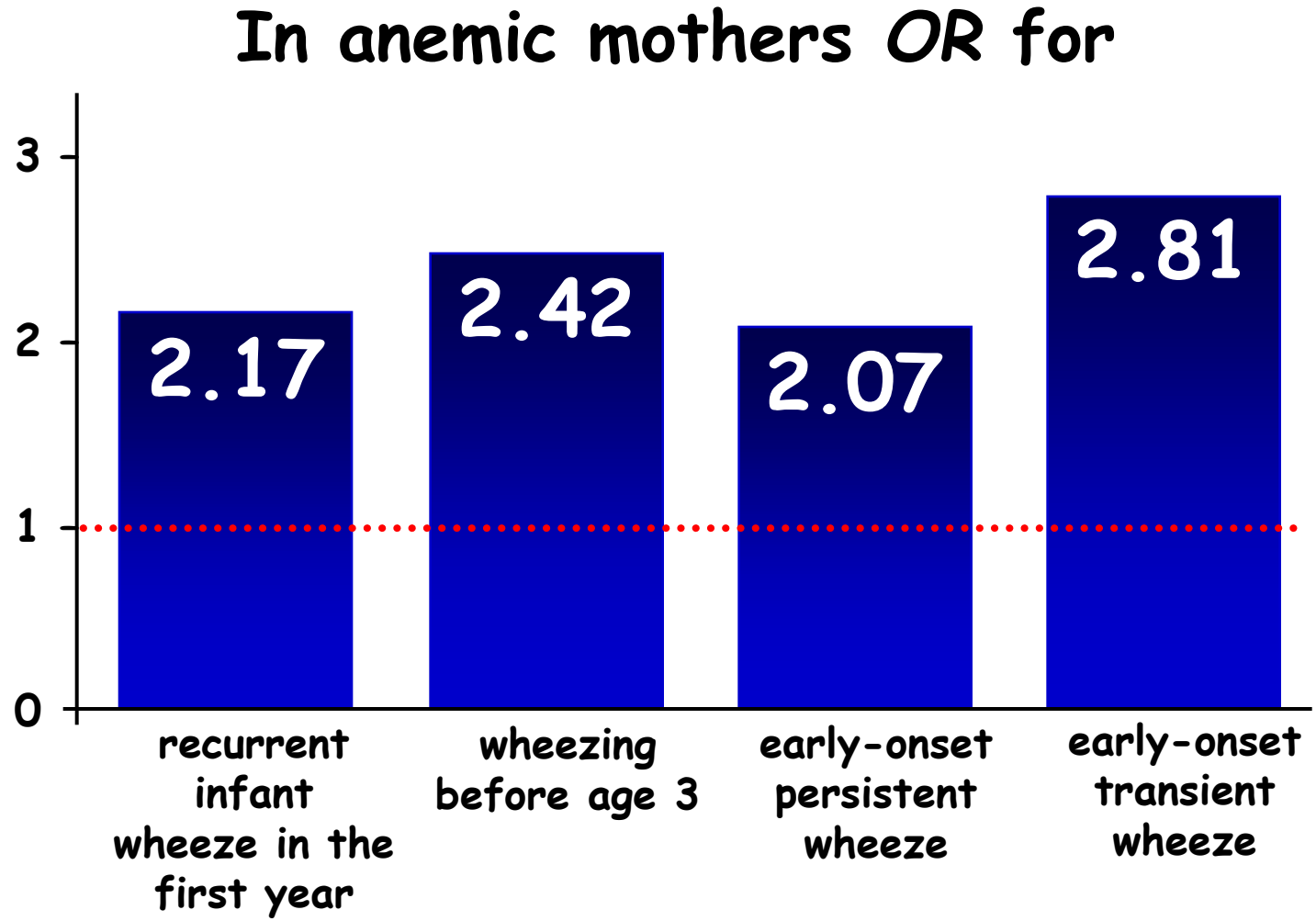
Amin J Ped 2013;163:1267

- ✓ Prospective study.
- ✓ Auditory neural myelination in infants with **latent iron deficiency (cord serum ferritin, 11-75 ng/mL)** and infants with **normal iron status** (cord serum ferritin, >75 ng/mL) at birth.
- ✓ **Risk factors for poor in utero iron status:** maternal diabetes mellitus, pregnancy-induced hypertension, anc intrauterine growth restriction.
- ✓ Auditory brainstem evoked response measured using 80-dB normal hearing level click stimuli at a rate of 69.9/sec within 48 hours after birth.



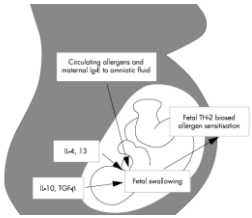
Association of maternal anemia with increased wheeze and asthma in children *Triche Ann All 2011;106:131*

- ✓ Maternal anemia in pregnancy and hemoglobin < 11 g/dl during delivery hospitalization.
- ✓ Patterns of wheeze from birth to age 6.



1) **MATERNAL INTAKE OF VITAMIN D DURING PREGNANCY AND RISK OF RECURRENT WHEEZE IN CHILDREN AT 3 Y OF AGE**

Camargo Am J Clin Nutr 2007; 85: 788



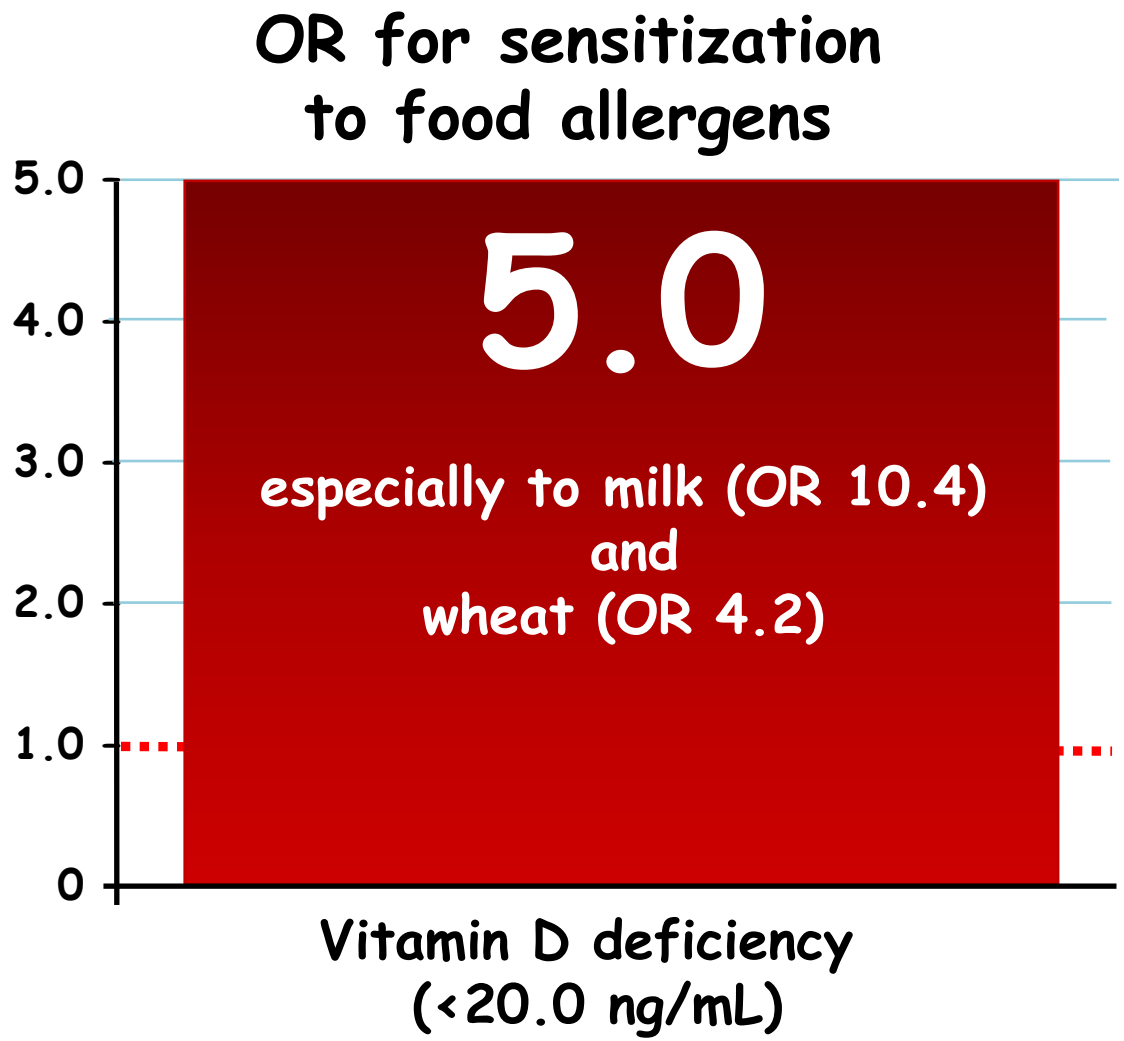
2) **MATERNAL VITAMIN D INTAKE DURING PREGNANCY AND EARLY CHILDHOOD WHEEZING (5 yrs)**

Devereux Am J Clin Nutr 2007; 85: 853

" using data from the two birth cohorts with maternal vitamin D assessment, we estimate that the <u>population attributable risk for asthma incidence</u> caused by vitamin D deficiency in pregancy is about <u>40%</u> of all cases." *Weiss JACI 2007;120:1031*

The link between serum vitamin D level, sensitization to food allergens, and the severity of atopic dermatitis in infancy. *Baek JH, J Pediatr. 2014;165(4):849-54.*

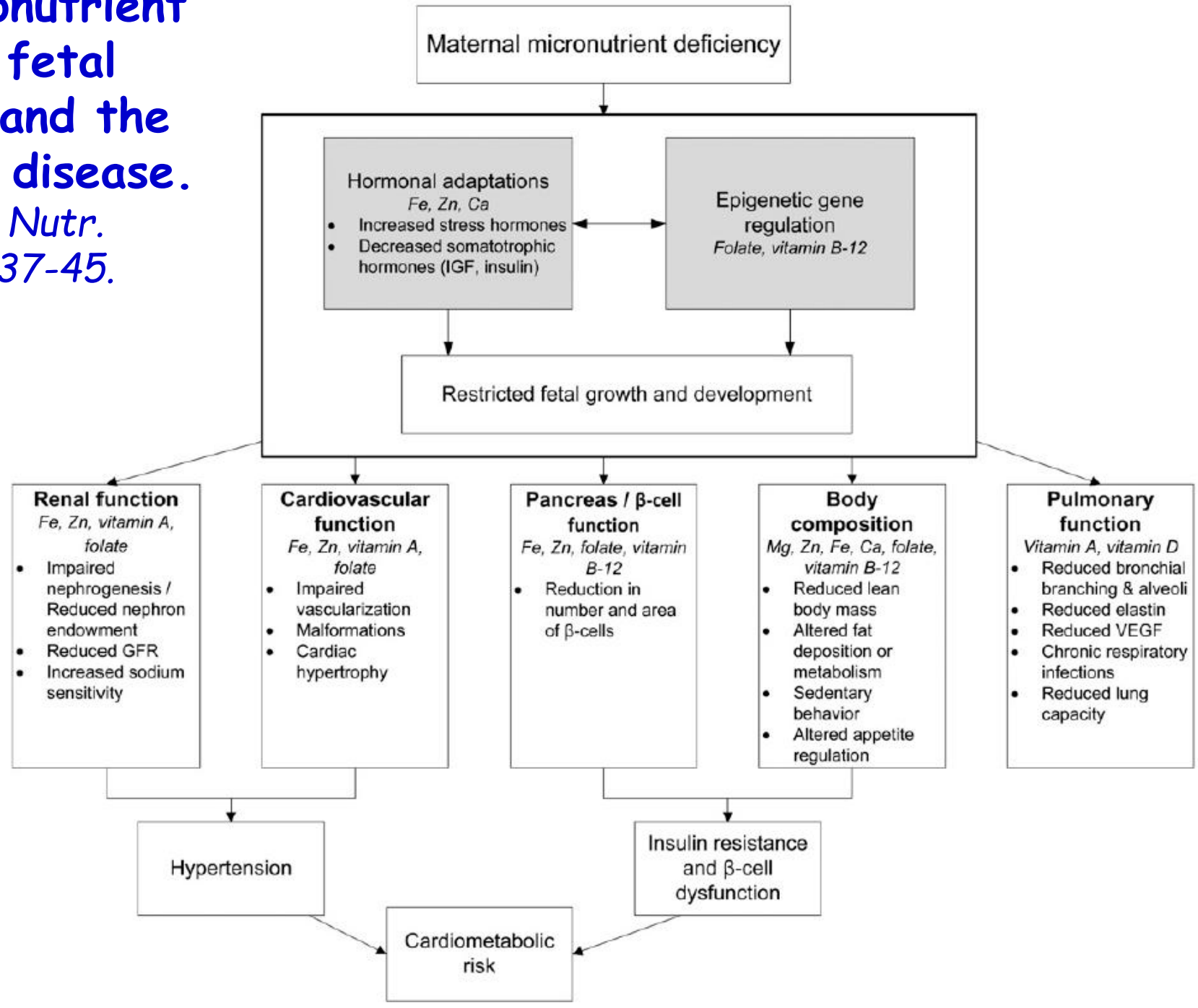
- ✓226 infants with atopic dermatitis or food allergy
- ✓serum 25-hydroxyvitamin D (25[OH]D) and sIgE levels to common or suspected food allergens
- ✓serum 25(OH)D category levels: <20.0 ng/mL (deficiency), 20.0-29.0 ng/mL (insufficiency), ≥ 30.0 ng/mL (sufficiency)



Maternal micronutrient deficiency, fetal development, and the risk of chronic disease.

Christian P, J Nutr. 2010;140(3):437-45.

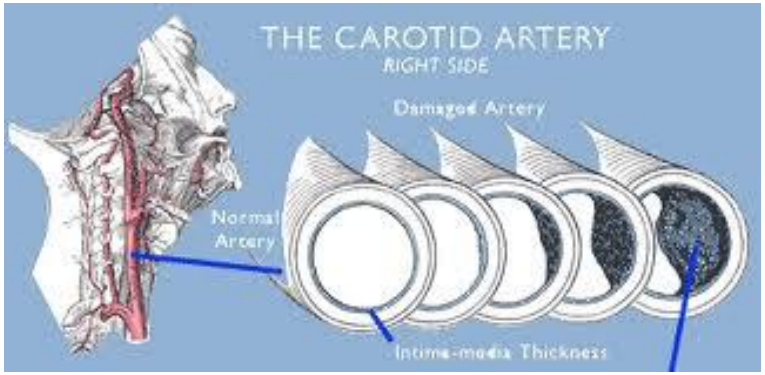
- Fe,
- Zn,
- Ca,
- Folate,
- Vit B12,
- Vit A,
- Vit D



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

Gale CR, Arterioscler Thromb Vasc Biol 2006;26:1877-82.

✓carotid intima-media thickness (IMT) in 216 9-year-old children mothers' nutrition during pregnancy.



IMT was greater

- in boys,
- in children who were heavier,
- in those with higher systolic blood pressure,
- in those who took less exercise.

Increased IMT was associated with a lower maternal energy intake in early (*P*=0.029) or late (*P*=0.006) pregnancy,

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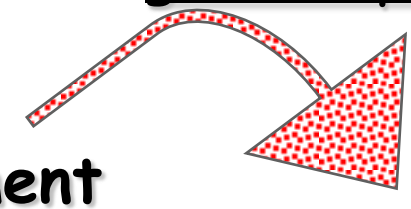
Epigenetics Definition

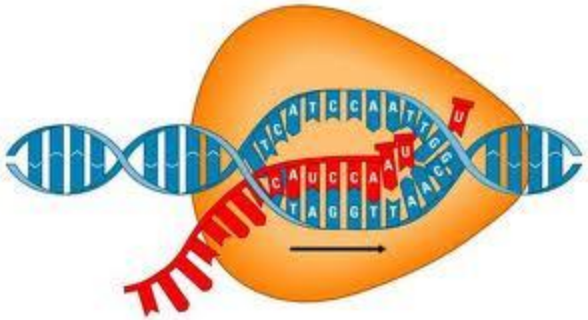
Epigenetics

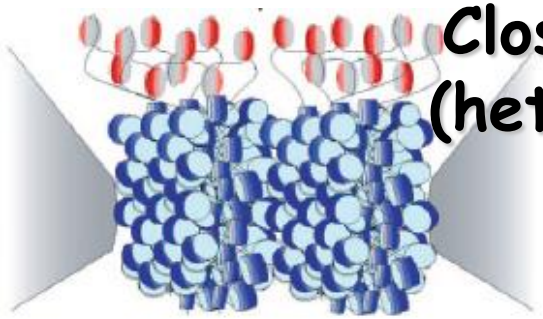
heritable changes of a phenotype that are not caused by changes in the nucleotide sequence of the genetic code itself but are due to a <u>different gene expression</u> patterns of a specific cell type.



environment

genomic adaption





Closed chromatin (heterochromatin)

Transcriptionally silent

Open chromatin (euchromatin)

Transcriptionally active

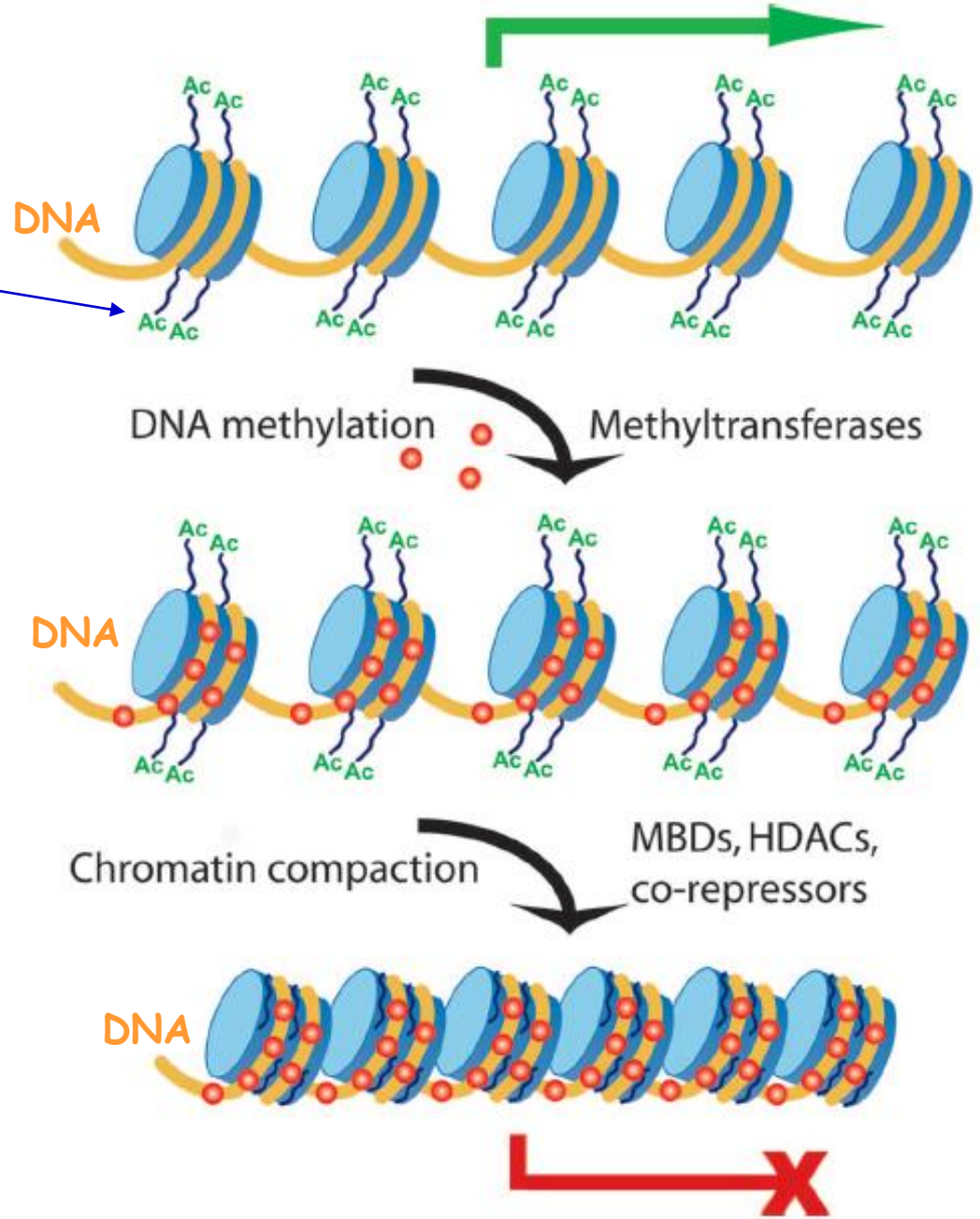
Epigenetic modifications in gene silencing.

Cutfield Ped Res 2007;61:68R

Transcriptionally active chromatin is associated with acetylated histones, (Ac) whereas inactive chromatin has methylated DNA and de-acetylated histones.

DNA methylation, executed by methyltransferases, allows recruitment of methyl-binding domain proteins (MBD), which then recruit **histone deacetylases** (HDAC, transcriptional co-repressors and other chromatin modifying enzymes).

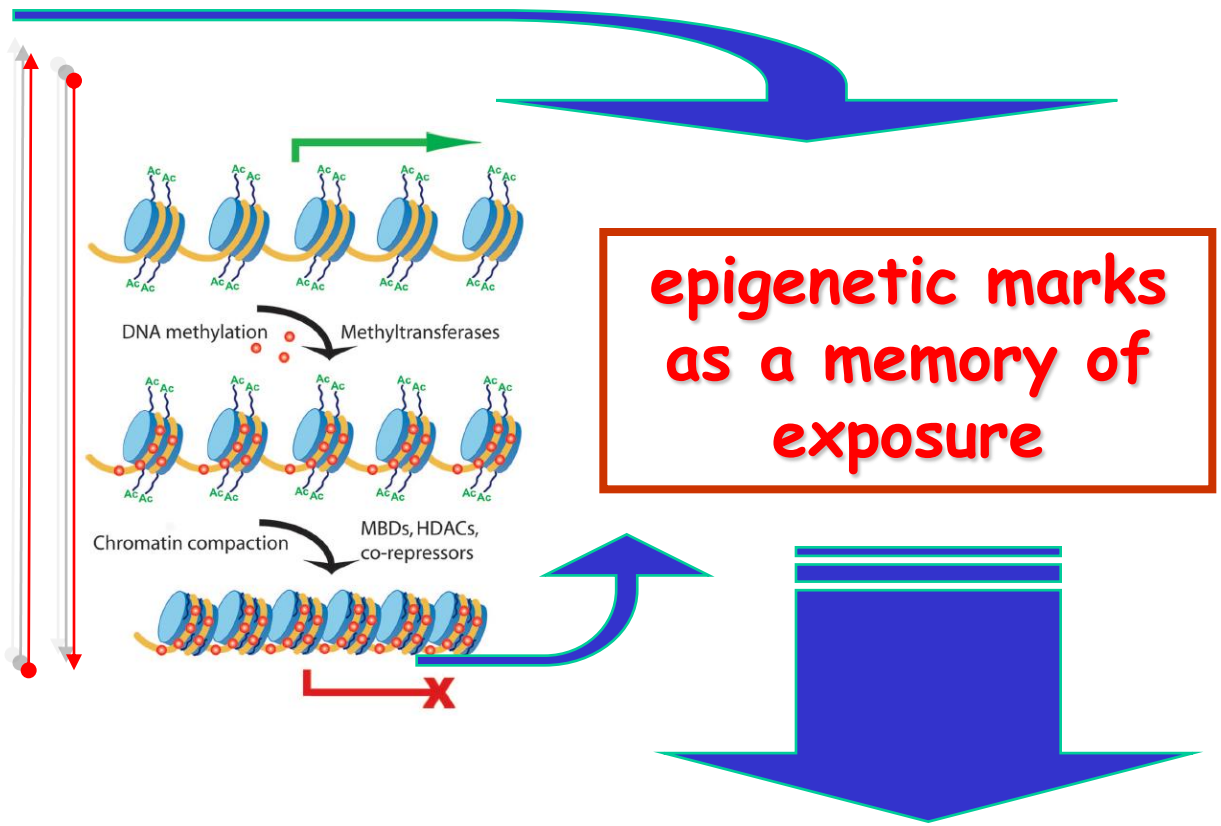
A series of epigenetic modifications transforms transcriptionally active regions of DNA (*top*) into inactive compact chromatin (*bottom*).



Epigenetic Programming: General Concepts

Attig Curr Op Clin Nutr Metab Care 2010;13:284

environmental signals early in life (inadequate or inappropriate chemical/nutritional or nonchemical environments)



epigenetic marks as a memory of exposure

These marks induce long-term changes in gene expression, potentially leading to disease in later life, hence the 'developmental origin of health and disease' (DOHaD) hypothesis

DIETARY FOLATE AND DNA METHYLATION

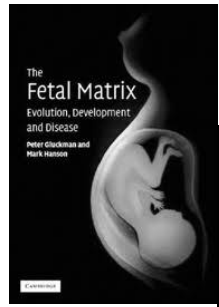
Cutfield, Pediat Res 2007;61:68R

dietary methyl donors are

- methionine
- choline
- folate

folate or methyl group deficiency diets in

late fetal life or early postnatal life



stable long-term total DNA and specific gene hypomethylation

in adults

DNA hypomethylation that reverses with resumption of a normal diet

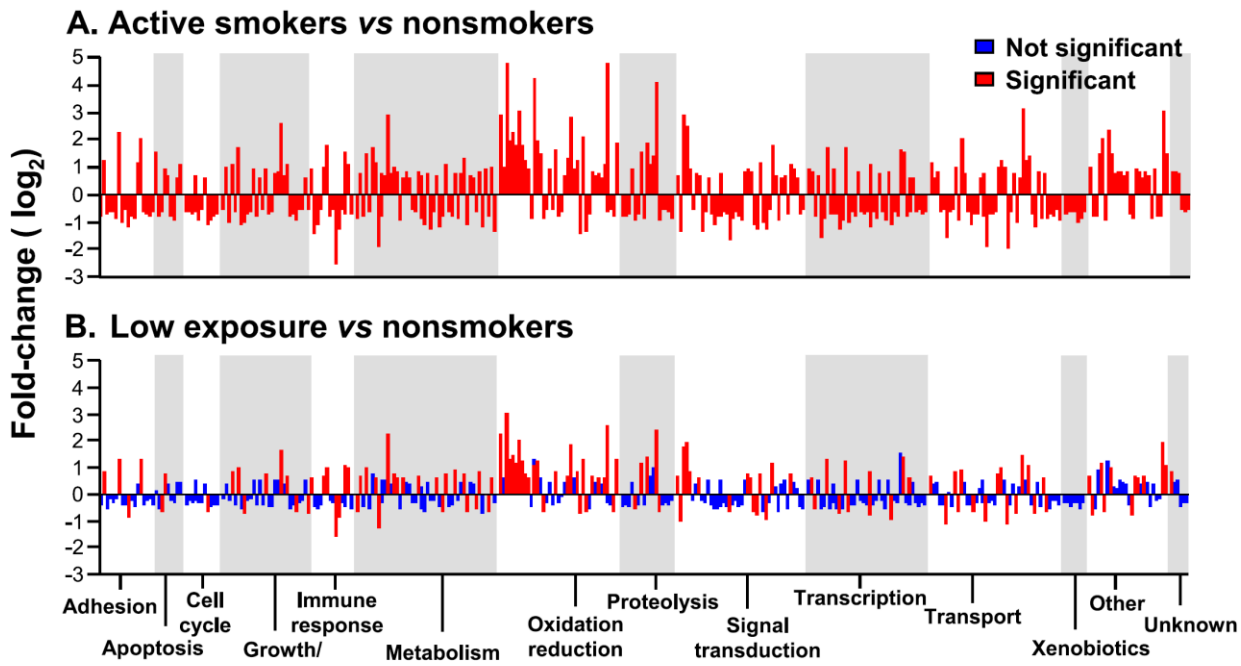
Wilson MJ, Biochem J 218:987–990
Bhave MR, Carcinogenesis 9:343–348

Threshold of Biologic Responses of the Small Airway Epithelium to Low Levels of Tobacco Smoke

Strulovici-Barel Am J Respir Crit Care Med 2011;182:1524

- ✓ 121 individuals.
- ✓ Small airway epithelium by bronchoscopy.
- ✓ Microarrays to assess genome-wide gene expression;
- ✓ Urine nicotine used to categorize subjects as "nonsmokers," "active smokers," and "low exposure."

Genes in the small airway epithelium up- and down-regulated by smoking. (A, B)



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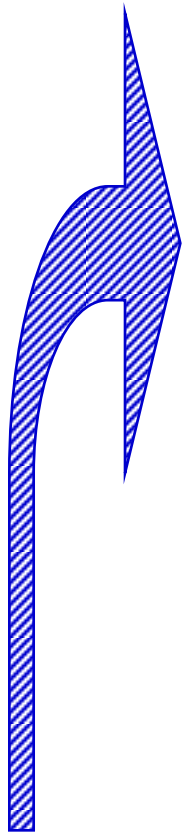
Intergenerational studies of human birthweight from the 1958 birth cohort. 1. Evidence for a multigenerational effect.

Emanuel I, Br J Obst Gynaecol 1992; 99:67–74.

✓longitudinal study of one week's births in 1958 (1638 firstborn).

✓any associations between their birthweight and characteristics of their parents and grandparents



- **Significant positive associations were found between babies' birthweight and parental birthweight** but not gestational age.

- **For the babies born to female cohort members additional findings included associations between their birthweight and the height of the maternal grandmother**

Transmission of risk factors across three generations.

Brook JS, Psychol Rep 1999; 85:227-241

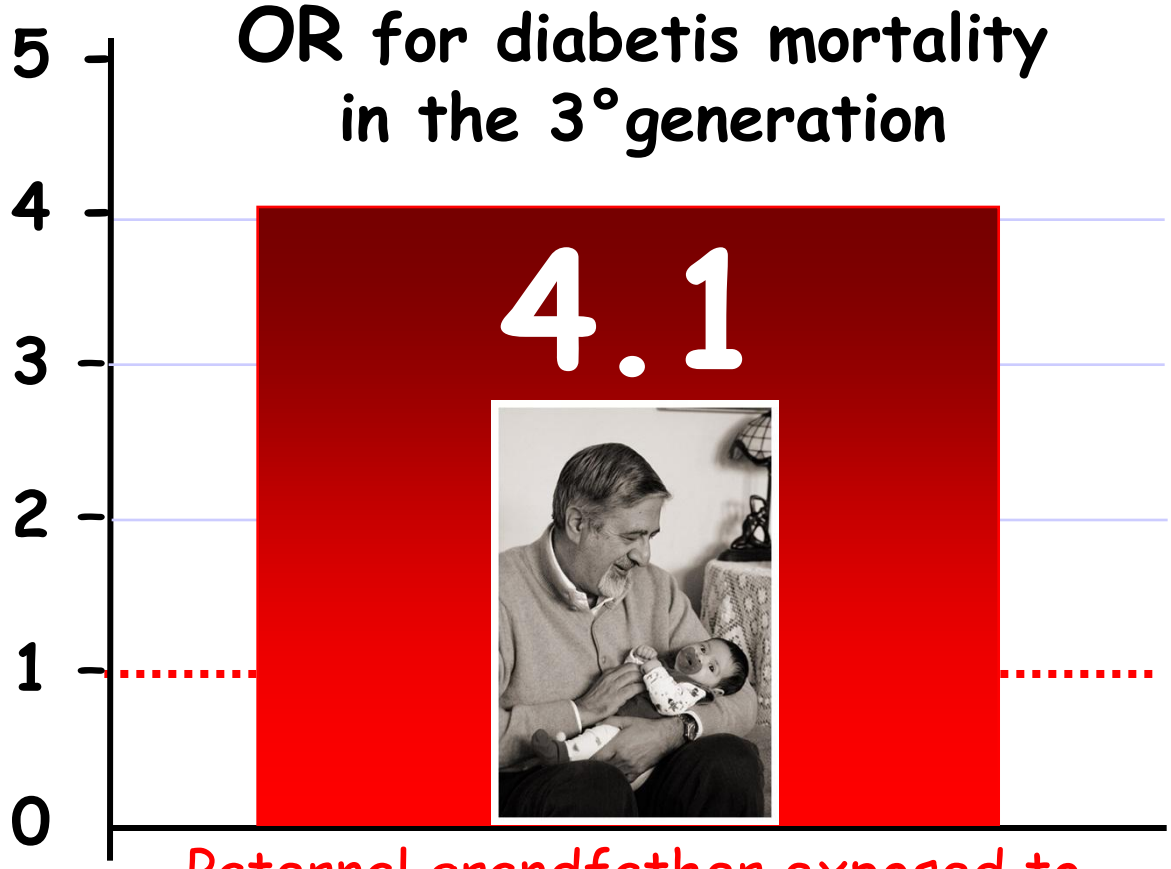
✓association between the parent-grandmother relationship, the parenting of toddlers, and toddlers' anger.

✓185 2-yr-old toddlers, one of the parents of each toddler, and the corresponding grandmother of each toddler

intergenerational transmission of risk factors from grandparents to parents to toddlers.

Cardiovascular and diabetes mortality determined by nutrition during parents' and grandparents' slow growth period. *Kaati G, Eur J Hum Genet 2002; 10:682-688*

- ✓3 cohorts born in 1890, 1905 and 1920 in Sweden
- ✓follow-up until death or 1995.
- ✓parents' or grandparents' access to food during their slow growth period (SGP), before their prepubertal peak in growth velocity

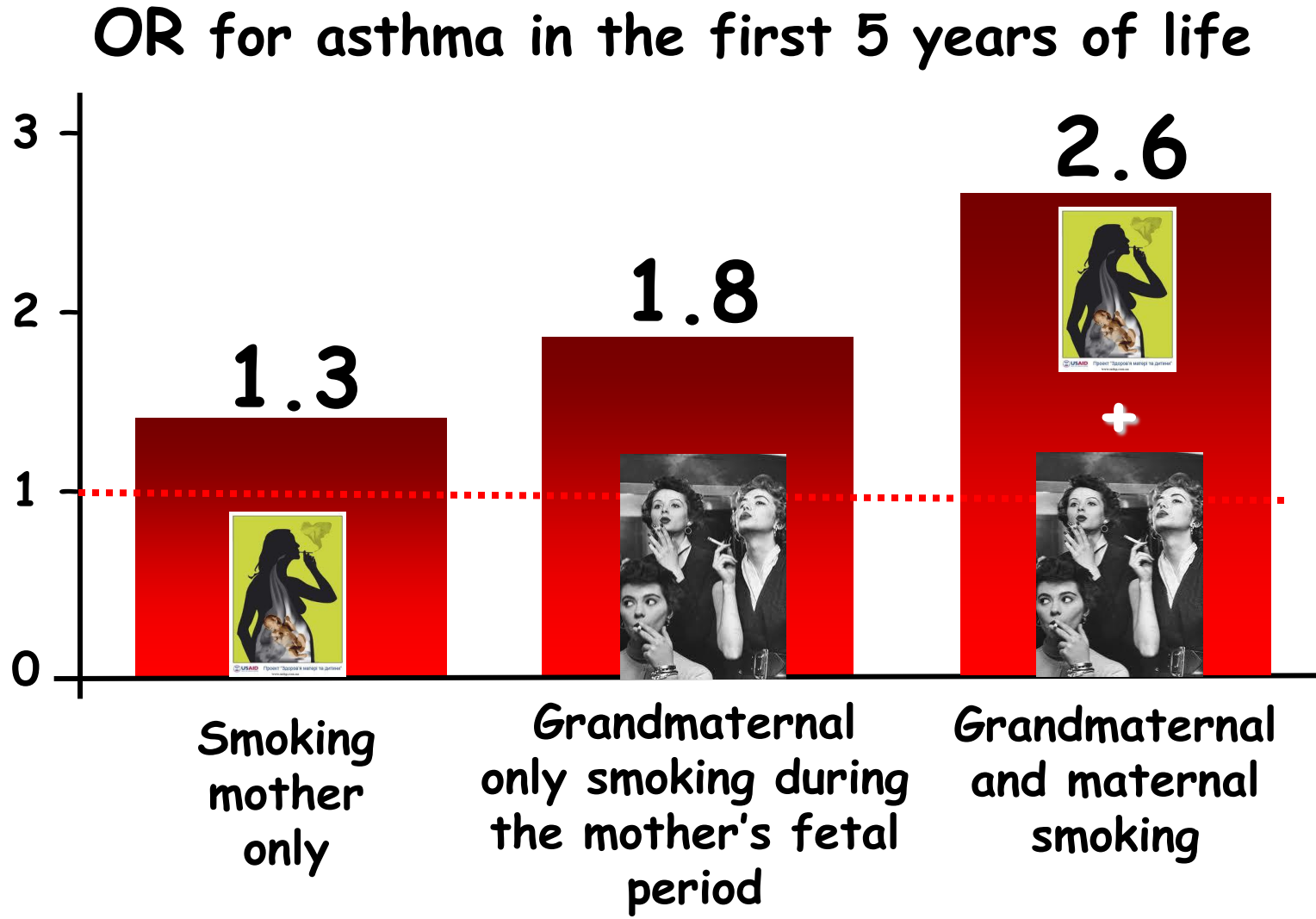


Paternal grandfather exposed to abundant nutrition during his prepubertal growth period

Maternal and grandmaternal smoking patterns are associated with early childhood asthma.

Li YF, Chest. 2005;127(4):1232-41.

- ✓ 338 children with asthma diagnosed in the first 5 years of life
- ✓ 570 control subjects



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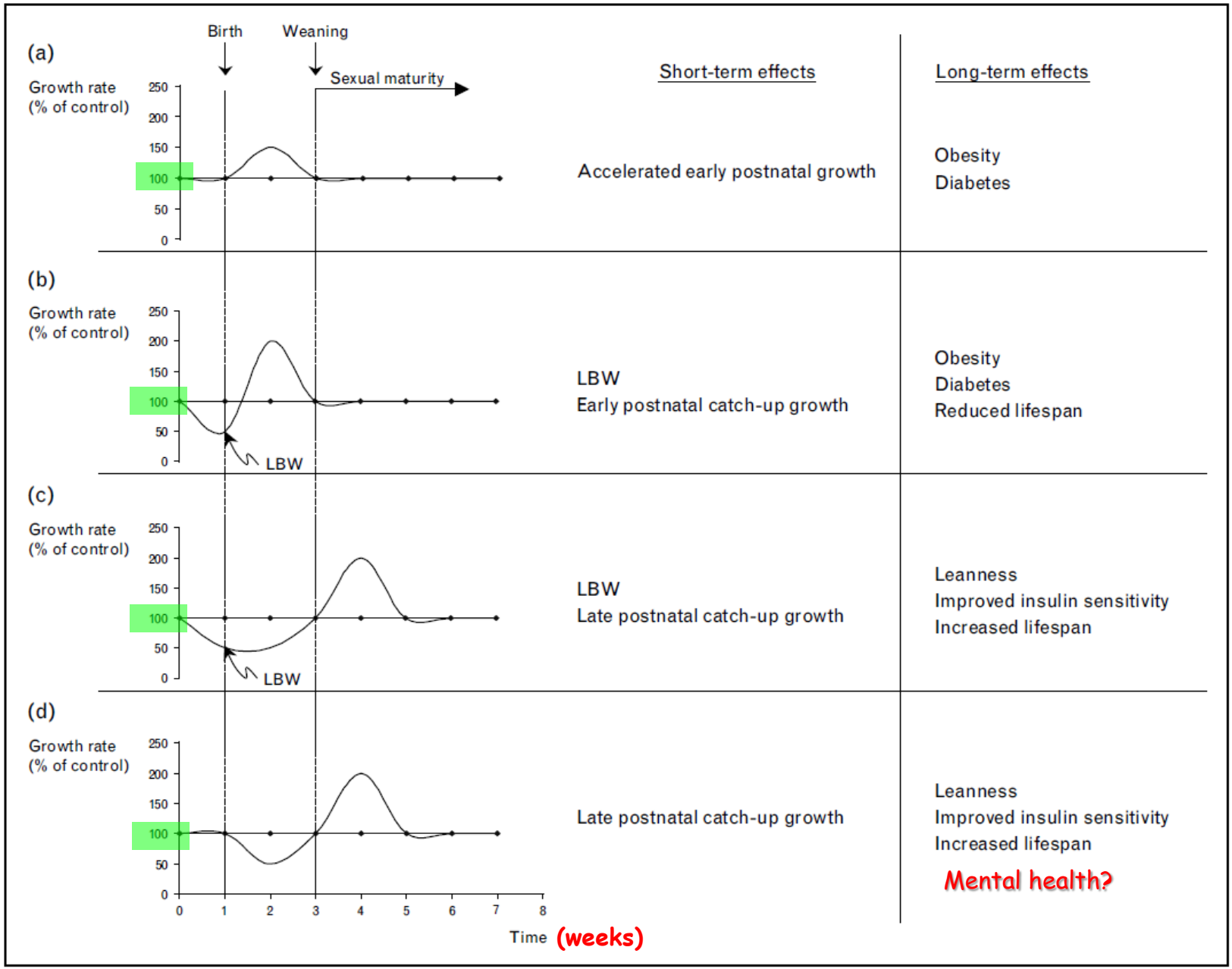
To catch up or not to catch up: is this the question? Lessons from animal models *Jimenez-Chillaron CurrOpinEndocrinol DiabetesObes 2007:14:23-29.*

Values over 100% indicate accelerated growth rate, whereas values below 100% indicate slowed growth rate.



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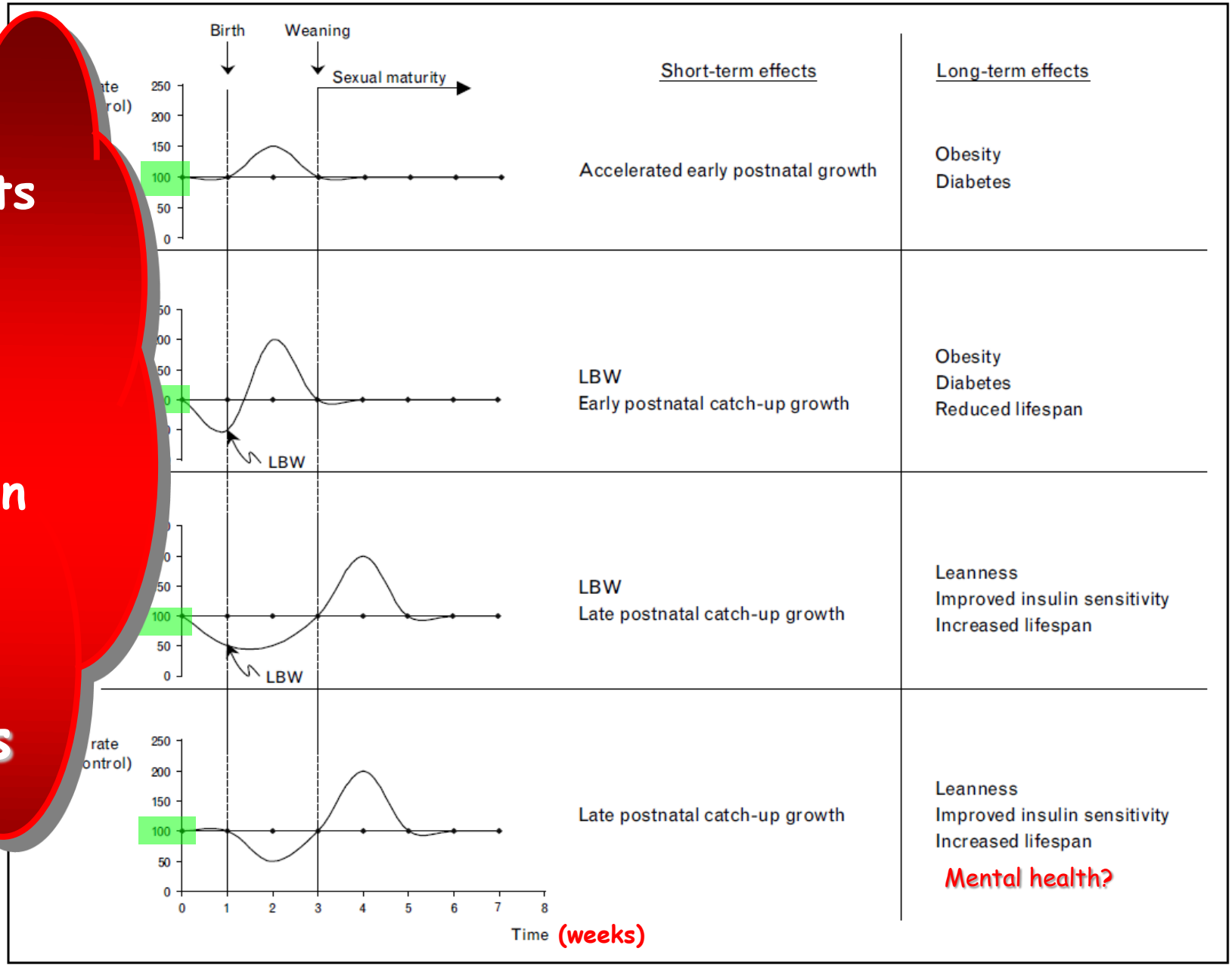
Similar results have been reported in **rats** and, in other nonmammalian organisms including **salmon** or **butterflies**



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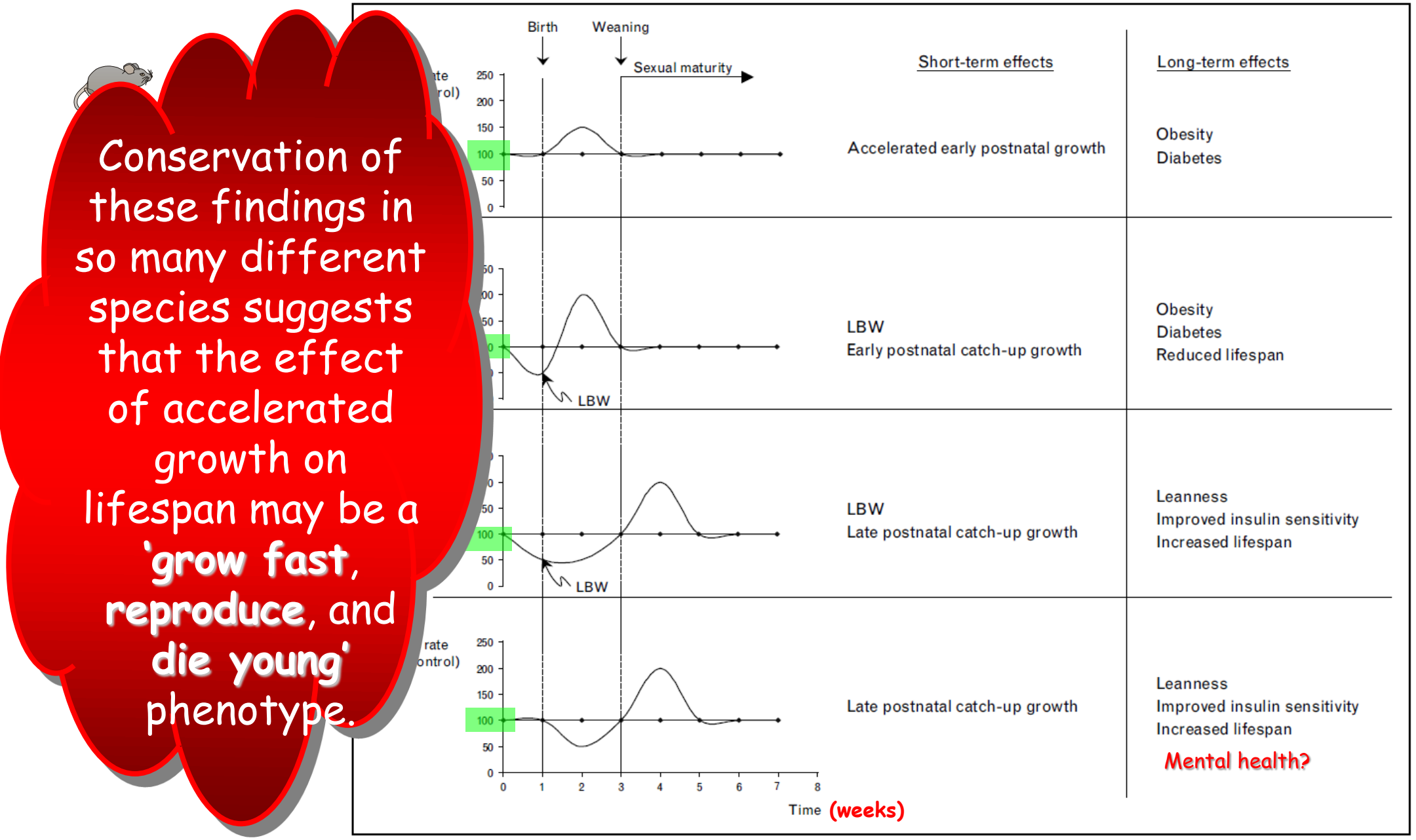

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accelerated postnatal growth

occurring either in the context of previous poor growth (compensatory or catch-up growth) or in the context of previous normal growth

has adverse long-term consequences on:

- metabolism,
- cognition, and
- lifespan.

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In humans the plastic period ranges from the

first weeks of life to 1-3 years

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To catch up or not to catch up: is this the question? Lessons from animal models *Jimenez-Chillaron CurrOpinEndocrinol DiabetesObes 2007:14:23-29.*

This period can become a potential window for therapeutic interventions aimed to prevent late onset of disease.

In humans the plastic period ranges from the first weeks of life to 1-3 years

has adverse long-term consequences on:

- metabolism,
- cognition, and
- lifespan.

Comparison between human milk (from a milk bank) with nutrient-enriched formula in preterm infants or SGA

...or...

provided 60% more protein and energy

marked benefits 13–16 years later for:

- Lipid profile, *Singhal A, Lancet 2004; 363:1571–78.*
- Blood pressure, *Singhal A, Lancet 2001;357: 413–19.*
- Leptin resistance (suggestive of future obesity) *Singhal A, Am J Clin Nutr 2002; 75: 993–99.*
- Insulin resistance. *Singhal A, Lancet 2003; 361: 1089–97.*
- Lower diastolic blood pressure 6–8 years later
- Lower risk for aterosclerosis *Sinhal Circulation 2004;109:1108*

50 Years Ago in THE JOURNAL OF PEDIATRICS February 2011

The Effect of High Caloric Feeding on the Growth of Premature Infants *Snyderman SE. J Pediatr 1961;58:237-40.*

Snyderman, in the February 1961 issue of The Journal, asked whether calorically fortifying enteral feeding improved the linear growth and weight gain of premature infants.

By increasing caloric intake to 155-180 cal/kg/day, daily weight gain improved by approximately 20 g/day.

The investigators noted that the intervention group reached its goal discharge weight earlier and that "the babies all appeared plump and had unusually rounded cheeks for premature infants."

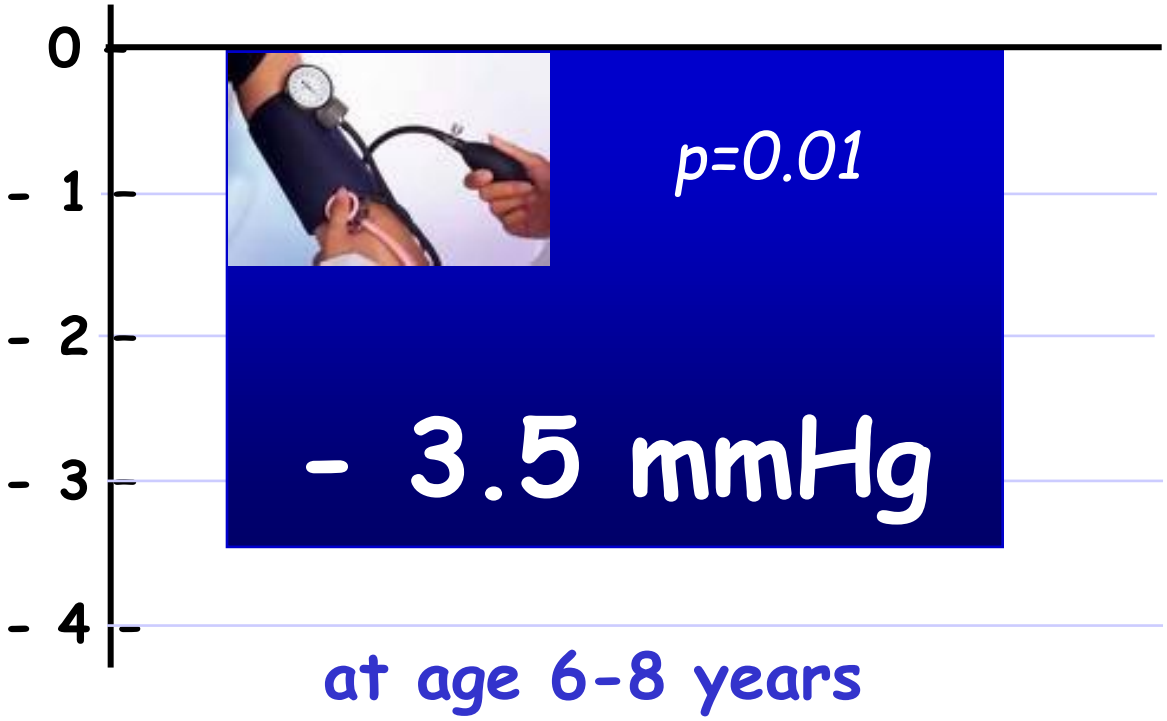
However, there were no differences in linear growth as assessed with fibula length on serial radiography.

The authors concluded that caloric fortification accelerated weight gain caused by fat deposition and resulted in earlier attainment of discharge weight. However, they questioned whether this accelerated weight gain benefited their patients.

Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure? *Singhal A, Circulation. 2007;115:213-220*

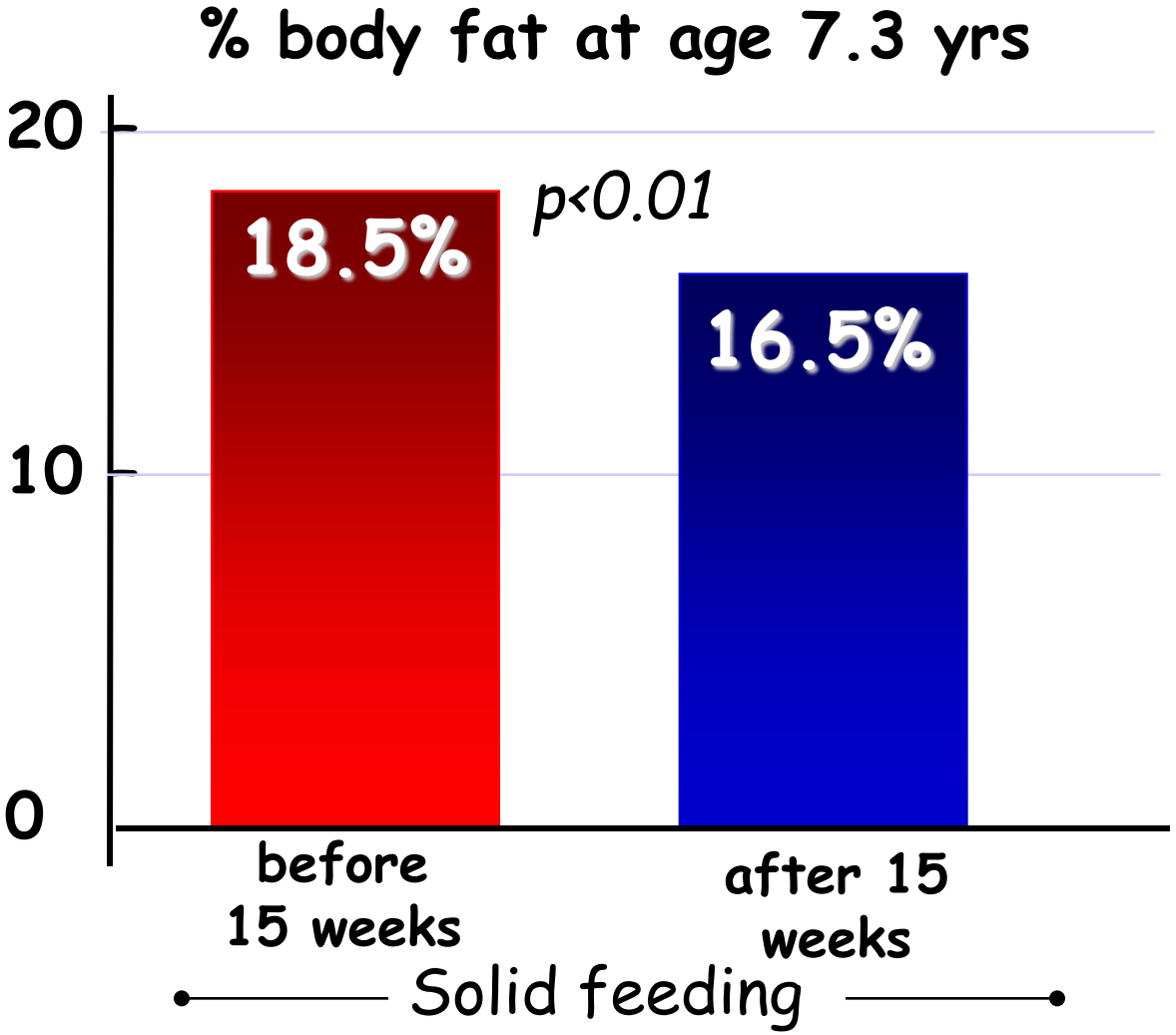
- ✓Blood pressure measured at 6 to 8 years in 153 children born small for gestational age (birth weight 10th percentile)
- ✓randomly assigned at birth to receive either a standard or a nutrient-enriched formula.

Diastolic blood pressure in children assigned to standard compared with nutrient-enriched formula



Relation of infant diet to childhood health: seven year follow up of cohort of children in Dundee infant feeding study. *Wilson AC, BMJ 1998: 316:21-25.*

- ✓674 infants
- ✓follow-up: mean age 7.3
- ✓Age of weaning



Short-term consequences of catch-up growth: an evolutioniary perspective

Jimenez-Chillaron CurrOpinEndocrinol DiabetesObes 2007:14:23

accelerated growth occurs in a wide spectrum of species ranging from mammals to birds and fishes, indicating that **catch-up growth must be an adaptive beneficial response in short-term**

1) in **improving short-term survival**, as small individuals have increased risk of succumbing to a given predator in a particular ecosystem

2) increasing the likelihood of **survival during periods of subsequent food shortage**.

3) fast-growing individuals can **increase reproductive success** either by reaching sexual maturity earlier than their counterparts or by increasing attractiveness to the other sex, thus gaining access to breeding

the question now is whether catch-up growth has a short-term benefit in any given population?

✓In a population with high rates of infant and child mortality rates, as in developing countries, **catch-up growth may be beneficial in the short term**.

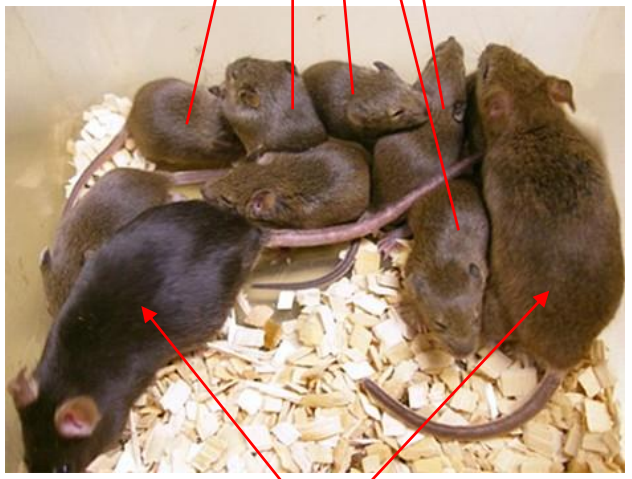
✓In contrast, in a population in which infant mortality rate is low, as in developed countries, the **deleterious long-term effects of catch-up growth might outweigh its benefits.**

Identifying efficacious approaches to chemoprevention with chlorophyllin, purified chlorophylls and freeze-dried spinach in a mouse model of transplacental carcinogenesis. *Williams D, Carcinogenesis. 2009;30:315-20.*

✓We developed a mouse model in which a single treatment with **dibenzopyrene (DBP),** a few days prior to parturition, produced a severe T-cell lymphoma between 3 and 6 months of age in offspring.

✓If the mice do not succumb to the lymphoma, 100% develop multiple lung tumors and the majority of males also exhibit liver tumors.

- lymphoma,
- lung tumors
- liver tumors

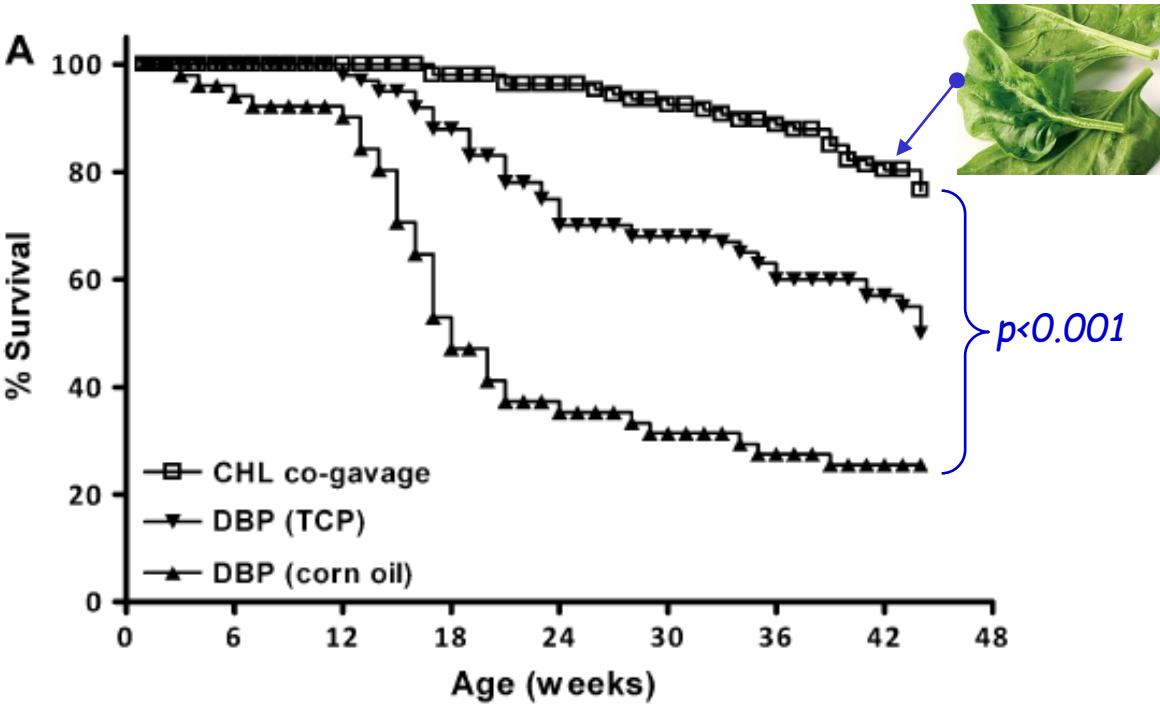


dibenzopyrene

Identifying efficacious approaches to chemoprevention with chlorophyllin, purified chlorophylls and freeze-dried spinach in a mouse model of transplacental carcinogenesis. *Williams D, Carcinogenesis. 2009;30:315-20.*

- ✓Pregnant mice
- ✓purified diets incorporated with either 2000 p.p.m. chlorophyllin (CHL), 2000 p.p.m. chlorophyll (Chl) or 10% freeze-dried spinach beginning at gestation day 9.
- ✓dibenzo[a,l]pyrene (DBP) as carcinogen few days prior parturition

(A) Impact of coadministration of CHL on DBP-dependent mortality in offspring



Cancer prevention with natural compounds.

Gullett NP, Semin Oncol. 2010;37:258-81.

- Popul
asse

-
c

cab onion,
green tea, s, berries, and ginger.

"one day, pregnant women will be prescribed a dietary supplement that will protect their future children from cancer".

David Williams Oregon State University










Developmental Origins of Health and Diseases: when we become what we are.

Attilio L Boner

University of Verona, Italy

- ✓ Original findings
- ✓ Further discoveries & the first 1000 days
- ✓ Maternal diseases
- ✓ Maternal life style-environment
- ✓ Epigenetic
- ✓ More than 1 generation
- ✓ Prevention & Reversibility
- ✓ **Public Health Implications**
- ✓ Conclusions

Evolving Notions of Childhood Chronic Illness

Halfon N, JAMA 2010;303:665

epidemiology of child health

acute illnesses		chronic illnesses
1960	⟶	2010

an increasing body of evidence documents a historic shift in the epidemiology of child health— **from acute to chronic illnesses** —

1. *Van Cleave J, JAMA. 2010;303:623-630.*
2. *Newacheck PW, Am J Public Health. 1986;76:178-184.*
3. *Newacheck PW, Arch Pediatr Adolesc Med. 2000;154:287-293.*
4. *Perrin JM, JAMA. 2007;297(24):2755-2759.*

Evolving Notions of Childhood Chronic Illness

Halfon N, JAMA 2010;303:665

✓ The epidemiologic shift, signified by the increasing number of children with **obesity**, **ADHD**, **asthma**, and other less severe chronic conditions, seems to be associated with a shift in the social ecology of childhood.

This changing ecology includes:

- ✓ **exposures to higher levels of toxic stress,**
- ✓ **increasing rates of absent parents,**
- ✓ **more sedentary and less active lifestyles,**
- ✓ **more television and multimedia use, and the**
- ✓ **ingestion of high caloric and high-fat diets.**

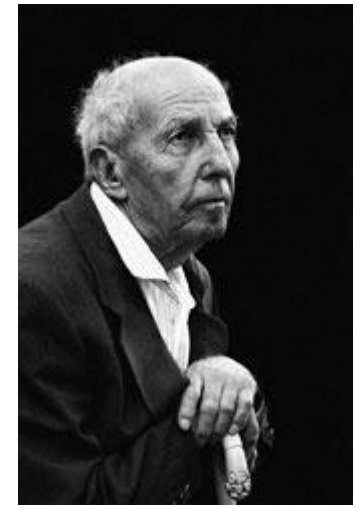
Prescott S, Allergol Int. 2014;63:11-20

Evolving Notions of Childhood Chronic Illness

Halfon N, JAMA 2010;303:665

✓The same adverse childhood experiences that can contribute to the onset of childhood illness can also affect stress-sensitive physiologic systems (nervous, endocrine/metabolic, immune), predisposing the same individuals to develop age-related diseases as adults. *Danese A, Arch Pediatr Adolesc Med. 2009;163:1135.*

✓This suggests that well-designed prevention strategies ✓initiated in childhood could be a **"two-for,"** preventing ✓childhood chronic conditions as well as the adult chronic conditions that are likely to emerge in years to come.



Relevance to public health: Effect size of lower nutrient diet *Singhal Lancet 2004;363:1642*

The effect of early growth and nutrition on later cardiovascular health is substantial.

The **3 mm Hg reduction in diastolic blood pressure in infants fed a lower-nutrient diet**

(versus nutrient-enriched diet)

Singhal A, Lancet 2001;357: 413–19.

is greater than all other non-pharmacological means of reducing blood pressure, including:

- weight loss,

- salt restriction, and

- exercise.

Relevance to public health: Effect size of lower nutrient diet *Singhal Lancet 2004;363:1642*

Indeed, lowering population-wide diastolic blood pressure by only 2 mm Hg (less than we observed)

- reduce prevalence of hypertension by 17%,
- coronary heart disease by 6%, and
- stroke and transient ischaemic attacks by 15%,
- prevent 100 000 cardiovascular events yearly in the USA alone.

Singhal A, Lancet 2001;357: 413–19.

Relevance to public health: Effect size of lower nutrient diet *Singhal Lancet 2004;363:1642*

Similarly, lowering cholesterol concentration by 10% with **breastfeeding**,

Singhal A, Lancet 2004; 363:1571–78.
Owen CG, Pediatrics 2002; 110: 597–608.

would be expected to reduce:
- Cardio Vascular Disease incidence by about 25% and
- mortality by 13–14%.

Relevance to public health: Effect size of lower nutrient diet *Singhal Lancet 2004;363:1642*

Similarly, lowering cholesterol concentration by 10% with **breastfeeding**,

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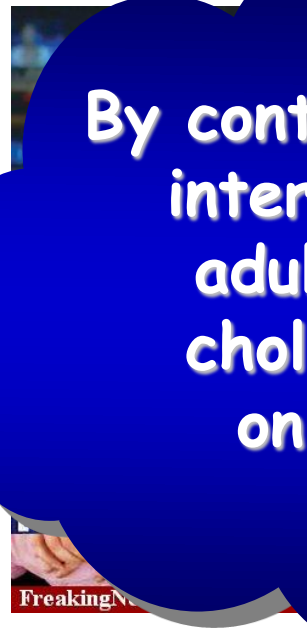


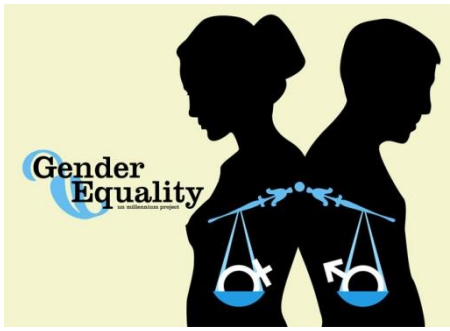
By contrast, dietary interventions in adults reduce cholesterol by only 3–6%.

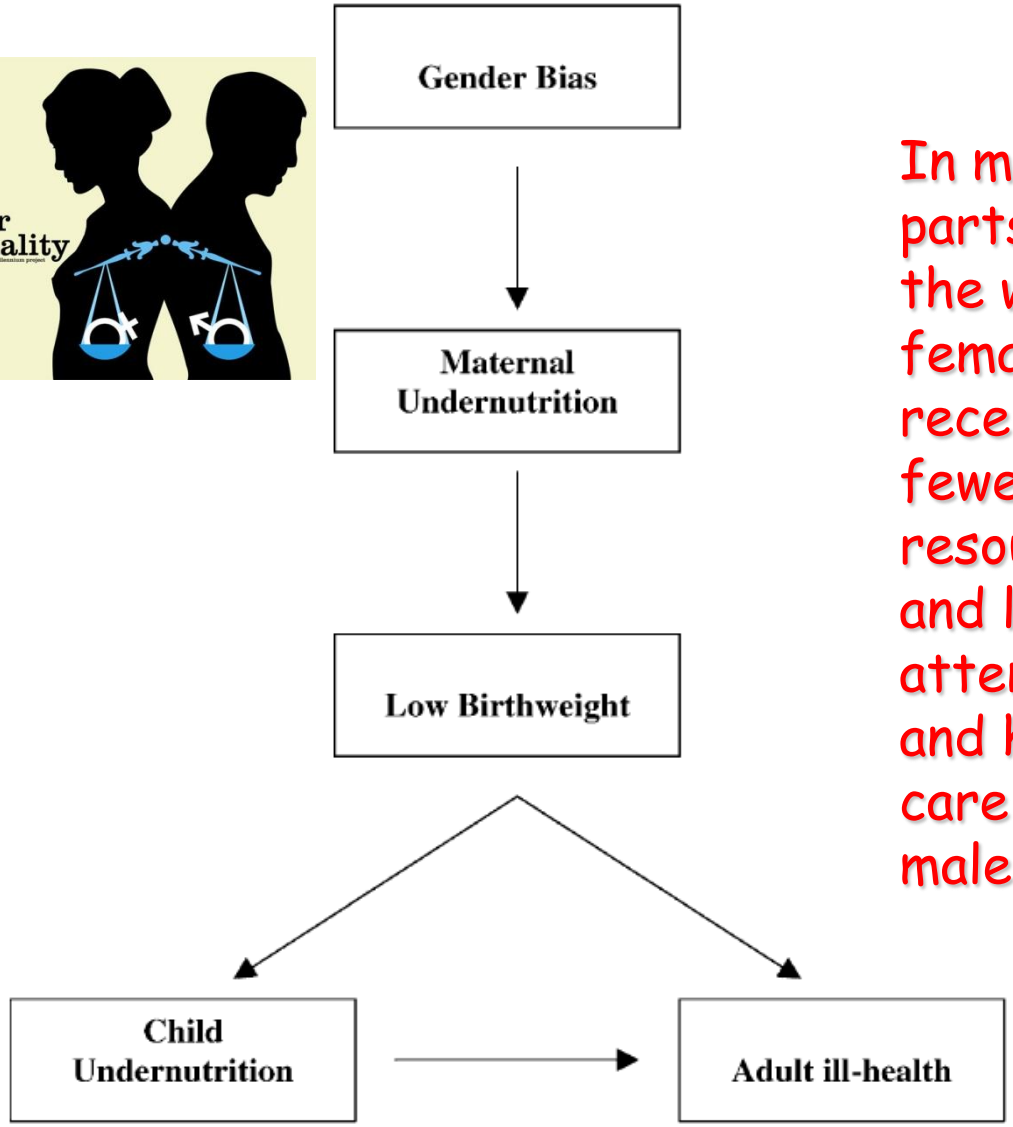
would be expected to reduce:
- Cardio Vascular Disease incidence by about 25% and
- mortality by 13–14%.

The hidden penalties of gender inequality: fetal origins of ill-health. *Osmani S, Econ Hum Biol. 2003;1:105-21.*

The pathways from gender inequality to ill-health.

Gender inequality in some areas, such as North Africa and Asia (including China), inequality directly involves matters of life and death, and takes the brutal form of unusually high mortality rates of women, and a consequent preponderance of men in the total population.





In many parts of the world, females receive fewer resources, and less attention and health care than males do.

The hidden penalties of gender inequality: fetal origins of ill-health. *Osmani S, Econ Hum Biol. 2003;1:105-21.*

The **penalties of gender bias** are indeed extensive:

- increasing the *mortality* rates, of women in particular, but also of others (child mortality relates directly to women's education and literacy);
- limiting the strength and coverage of *economic progress* (many of the successful experiences of rapid economic activities have crucially depended on women's initiative, particularly in East and South-east Asia, but increasingly also in other countries, including Bangladesh);
- impairing *political participation* and the practice of democracy (there is much evidence, not least from South Asia, that a greater role of women in grass-root politics can help to change the agenda of social discourse).

Women and Children Last — The Predictable Effects of Proposed Federal Funding Cuts

George J. Annas, J.D., M.P.H., and Wendy K. Mariner, J.D., M.P.H

N ENGL J MED 364;17 NEJM.ORG APRIL 28, 2011

Nancy Pelosi Democratic Leader of the House of Representatives was succeeded by Republican John Boehner

- **cutting 10%** from the special **supplementary nutrition program for women, infants, and children** (WIC), which serves 10 million low-income women and their children each month; and

- **cutting $50 million** from block grants **supporting prenatal care** for 2.5 million low-income women and health care for 31 million children annually.

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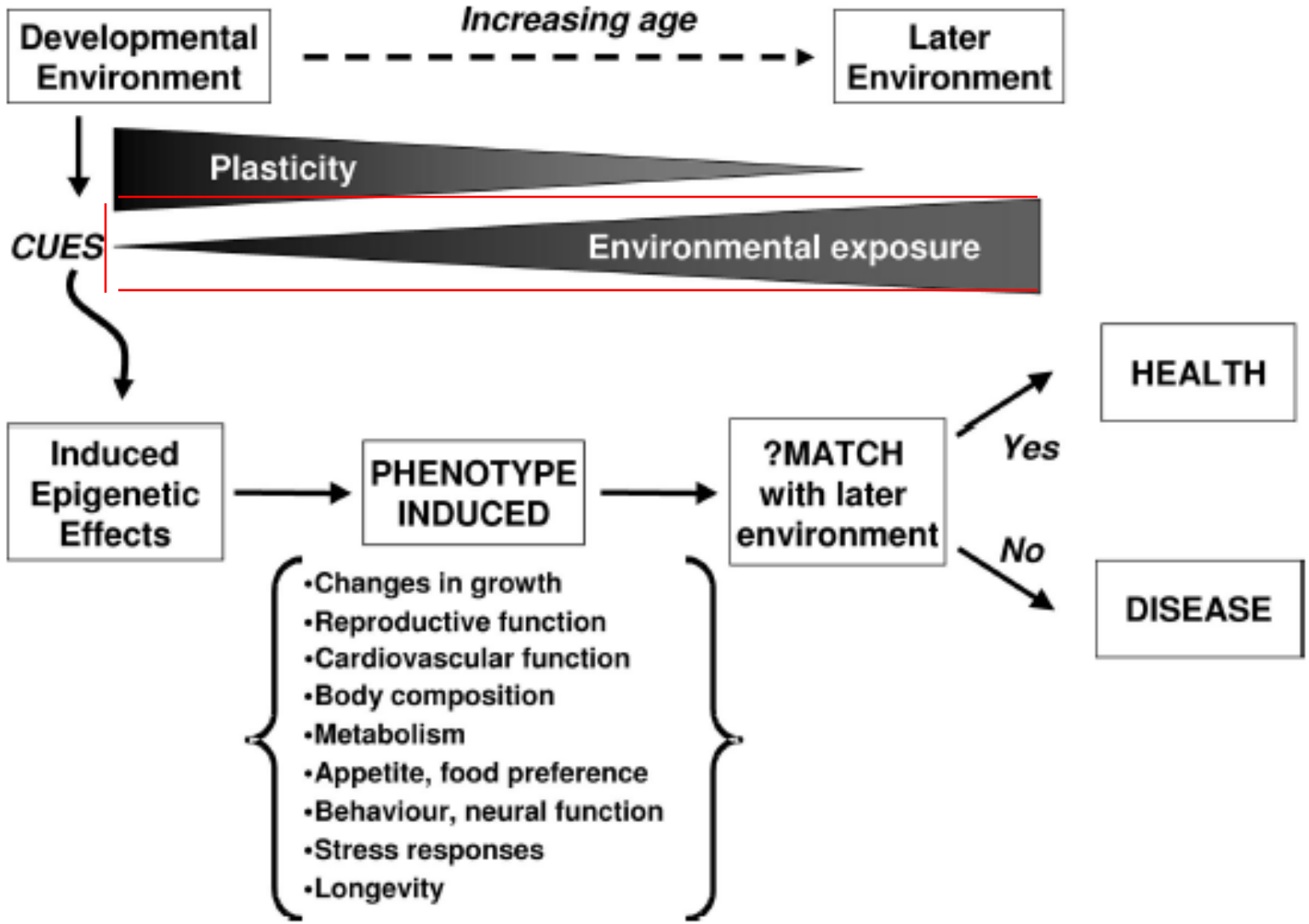
Epigenetic Mechanisms and the Mismatch Concept of the Developmental Origins of Health and Disease.

Godfrey Ped Res 2007;61:5R



Conclusions

- *The kind and quantity of nutrition you received in the womb; the pollutants, drugs and infections you were exposed to during gestation; your mother's health, stress level and state of mind while she was pregnant with you — all these factors shaped you as a baby and a child and continue to affect you to this day.*

- *9 months of gestation constitute the most consequential period of our lives, permanently influencing the wiring of the brain and the functioning of organs such as the heart, lung, liver and pancreas.*

- *The conditions we encounter in utero shape our susceptibility to disease, our appetite and metabolism, our intelligence and temperament.*

Conclusions

✓ *Much of what a pregnant woman encounters in her daily life — the air she breathes, the food and drink she consumes, the chemicals she's exposed to, even the emotions she feels — is shared in some fashion with her fetus.*

✓ *The fetus incorporates these offerings into its own body, makes them part of its flesh and blood.*

✓ *Often it does something more: it treats these maternal contributions as information,* ***biological postcards*** *from the world outside.*

The Womb. Your Mother. Yourself.

Annie M Paul Time October 4, 2010

"No woman who is pregnat today can escape hearing the message that what she does affect the fetus".

The Womb. Your Mother. Yourself.

Annie M Paul Time October 4, 2010

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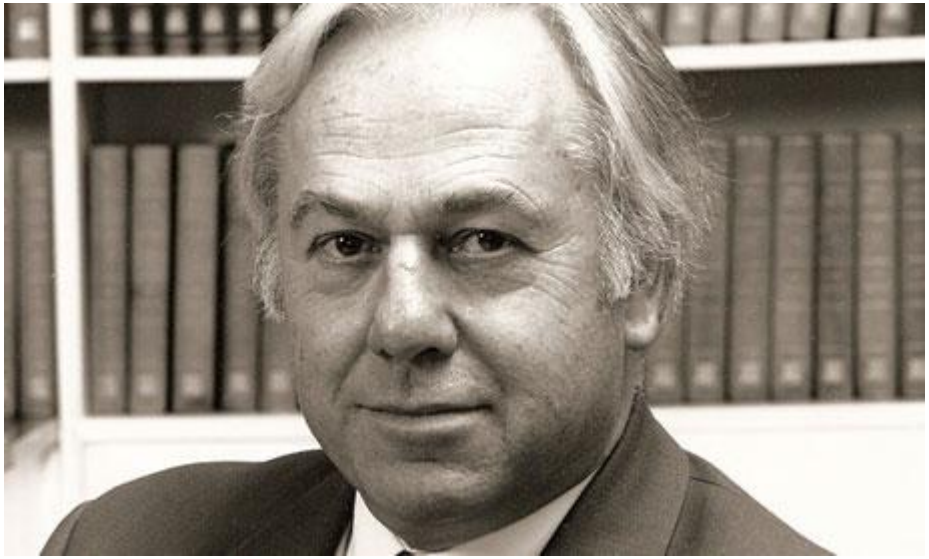


David James Purslove Barker,
physician and epidemiologist,
born 29 June 1938;
died 27 August 2013

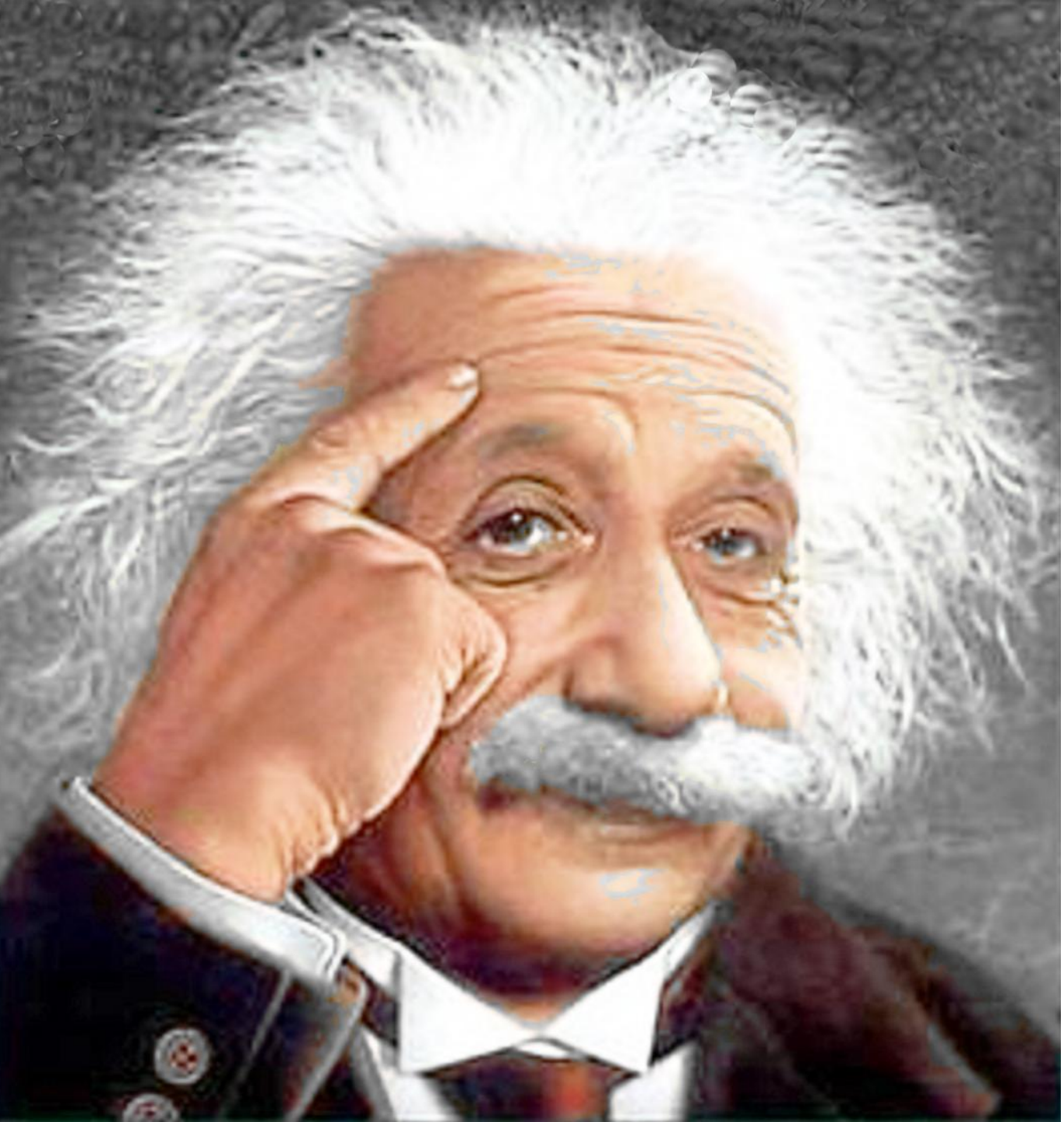
"The next generation does not have to suffer from heart disease or osteoporosis.

These diseases are not mandated by the human genome.

They barely existed 100 years ago.

They are unnecessary diseases.

We could prevent them had we the will to do so."



'The world is a dangerous place to live; not because of the people who are evil, but because of the people who don't do anything about it.'

Taking responsibility at both the individual and the societal level is essential for to address our global health challenges.

Inertia is our greatest enemy in this.


"It Takes A Village To Raise A Child"

Grazie per la vostra attenzione alla storia che vi ha raccontato mio nonno

Mia Charlize Powell

Verona FORMAT 23-24 Aprile 2015