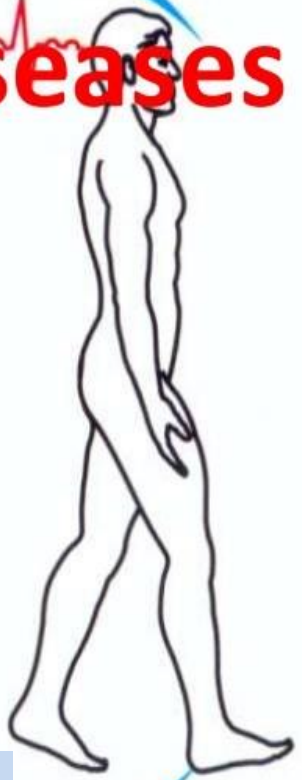
# Fetal Origins of Adult Diseases



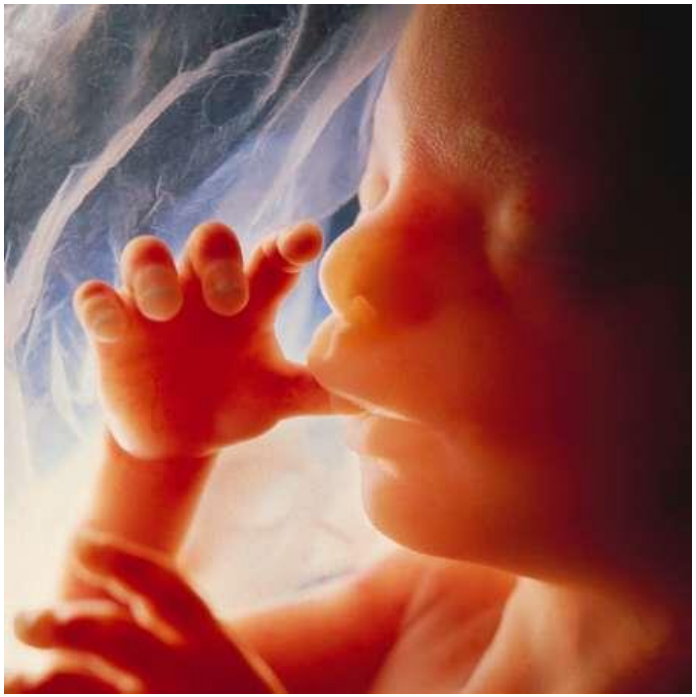

***Prof. Dr. Nguyễn Công Khanh***

***Honorary President of***

***Vietnam Pediatric Association***

# OUTLINE OF PRESENTATION

- *Fetal origins of adult diseases*
  *Barker hypothesis*
- *Possible mechanisms*
- *Prevention of adult disease originized from fetal*



# 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.**

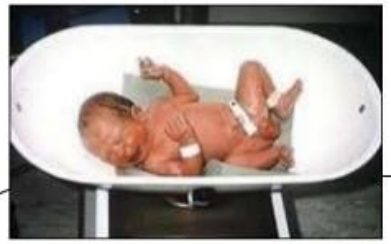

✓**Barker DJ**, Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577.

✓**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.

# ORIGIN OF COMPLEX ADULT ONSET DISEASES

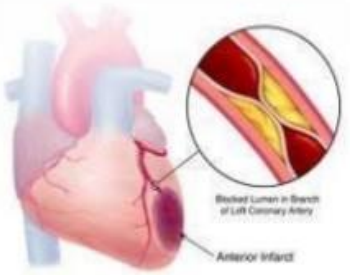
✓**Barker DJ**, Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;1:1077.



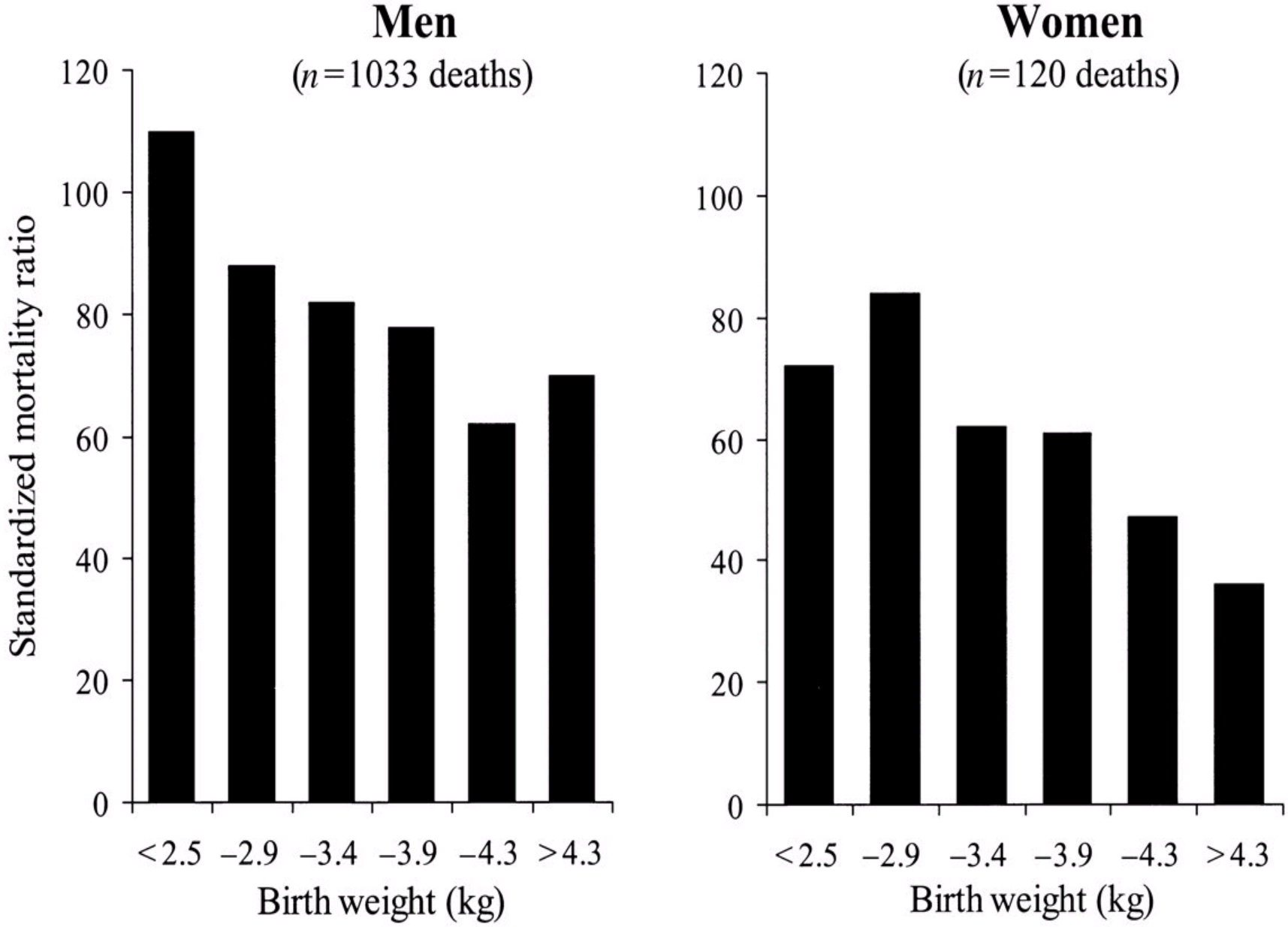
✓**Barker DJ**, Weight in infancy and death from ischaemic heart disease. Lancet 1989;2:577.

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

✓**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.


Men
(n=1033 deaths)
Women
(n=120 deaths)
Standardized mortality ratio
120
100
80
60
40
20
0
<2.5
–2.9
–3.4
–3.9
–4.3
>4.3
Birth weight (kg)

# ORIGIN OF COMPLEX ADULT ONSET DISEASES

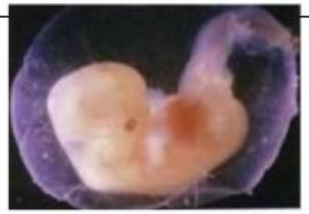
✓**Barker DJ**, Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1986;1:1077.

✓**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.

**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

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

✓**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.

**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"**

# Barker Hypothesis

**DEVELOPMENTAL PROGRAMMING**

*"Whereby a stimulus or insult during a critical period of growth and development has entrained long-term developmental and physiological changes in key tissues or organs"*

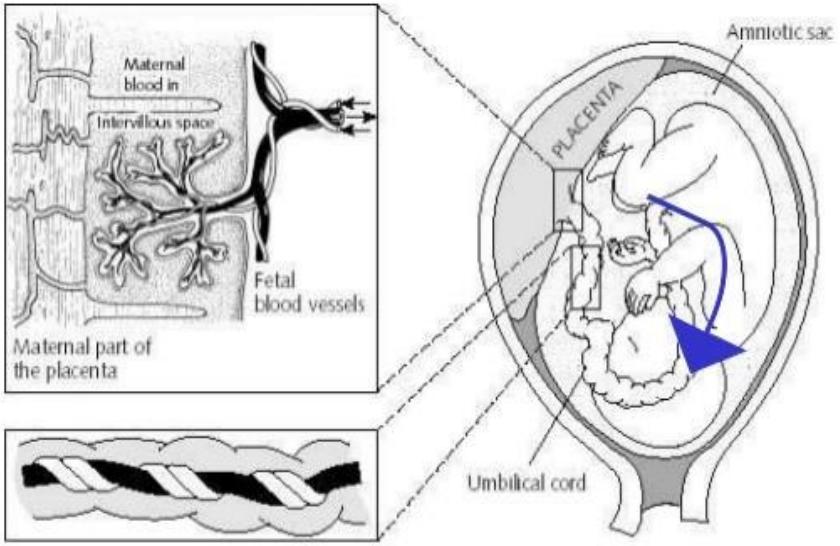
**THE THRIFTY PHENOTYPE HYPOTHESIS**

*"When the fetal environment ís poor, there ís an adaptive response, which optimizes the growth of key body organs to the detriment of others and leads to an altered postnatal metabolism, which is designed to enhance postnatal survival under conditions of intermittent or poor nutritiom".*

**Barker DJ. and Hale CN. (2001). The thrifty phenotype hypothesis. Br.Med.Bull; 60: 5-20**

# Environmental Effects via Developmental Plasticity:
## Types of Response to the Early Environment
*Gluckman Science 2004;305:1733*

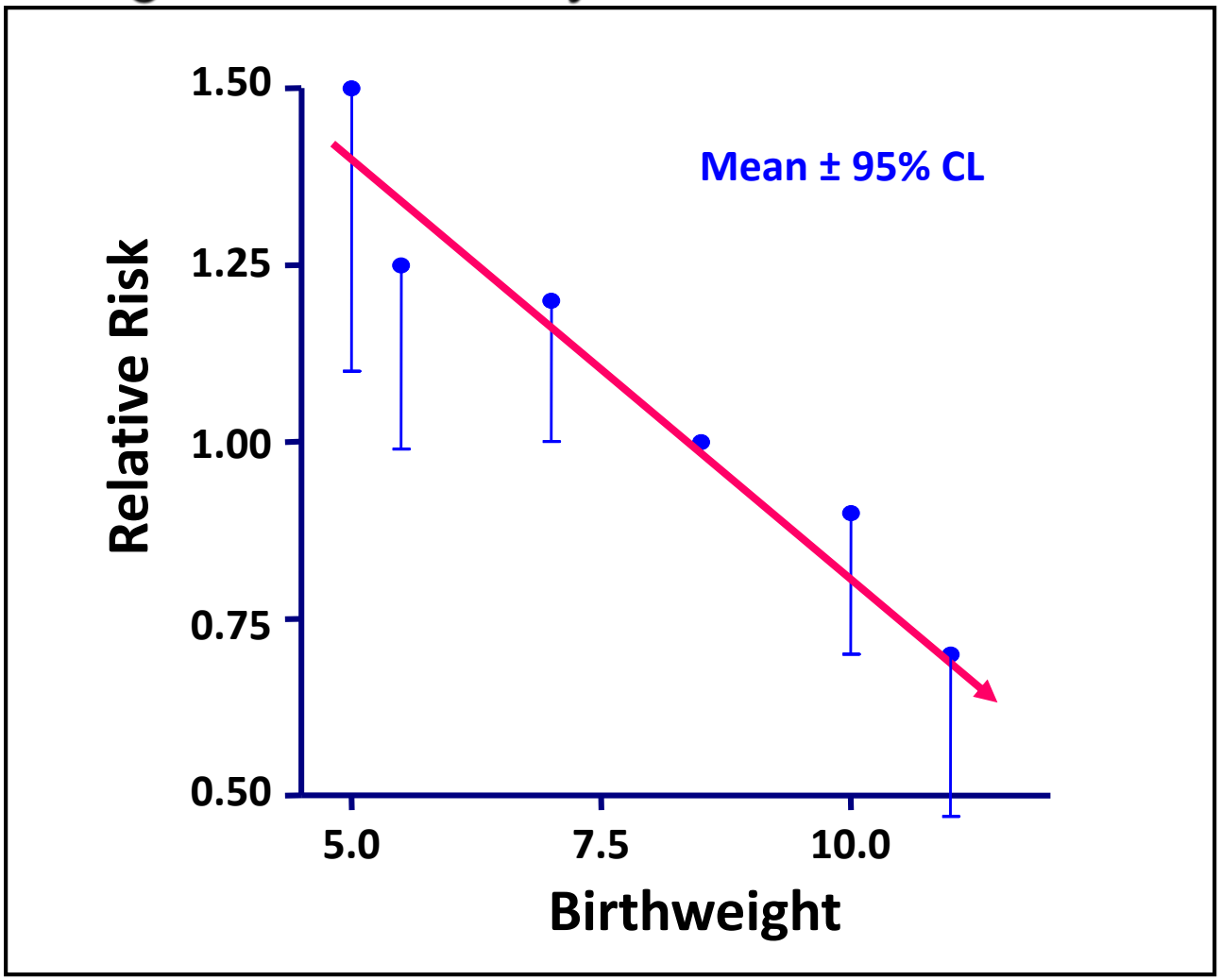
✓the **fetus** has many **homeostatic and homeorhetic*** **mechanisms** that confer **immediate survival advantage** e.g., **alterations in regional blood flows and organ growth when nutrient or oxygen supply is reduced** — even if there may be **subsequent postnatal costs**.




Homeorhesis, derived from the Greek for "similar flow", is a concept encompassing dynamical systems which return to a **trajectory**, as opposed to systems which return to a particular **state**, which is termed **homeostasis**. The word describes the tendency of developing or changing organisms to continue development or change towards a given state.

# BIRTHWEIGHT AND ADULT DISEASES

## Birthweight and Coronary heart Diseases & Strocke

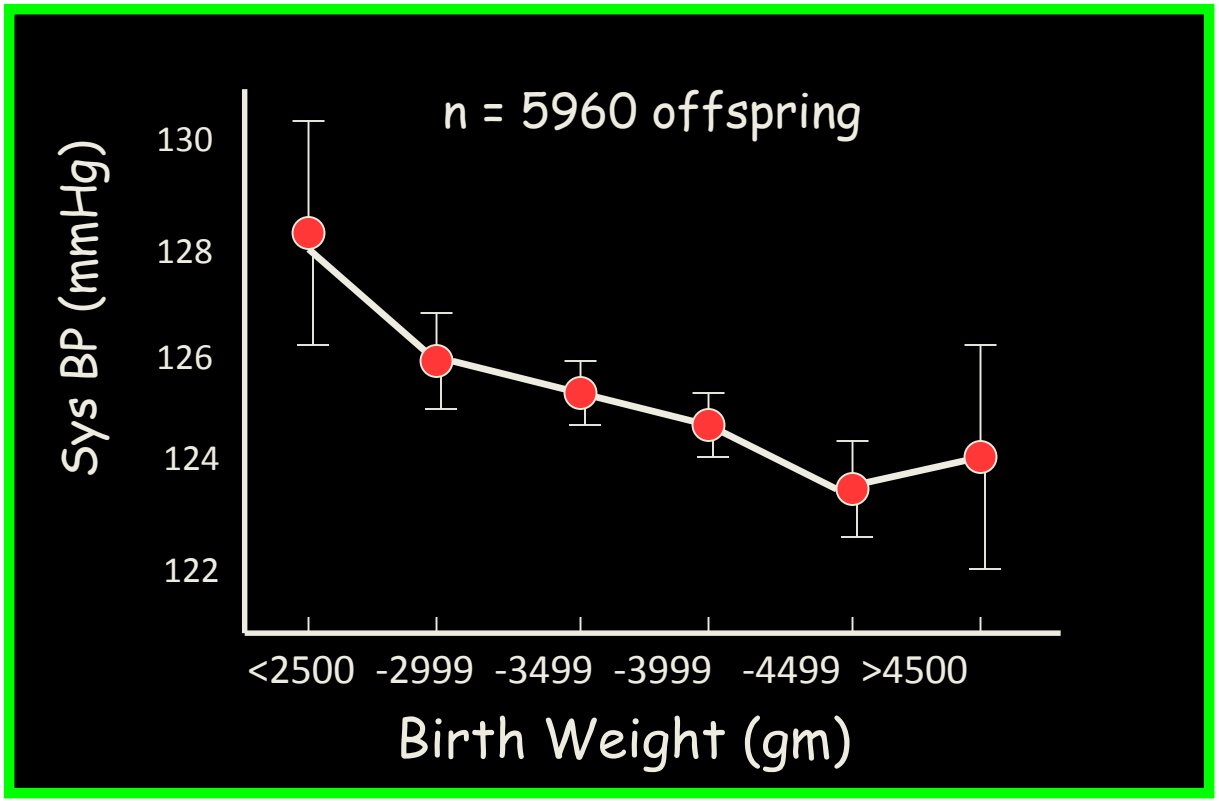



121,700 American Nurses, self report study BMJ 315:396,1997

# Birth Weight Predicts Blood Pressure at Age 31

## 1966 Northern Finland Birth Cohort

**+/- adjust for current BMI**

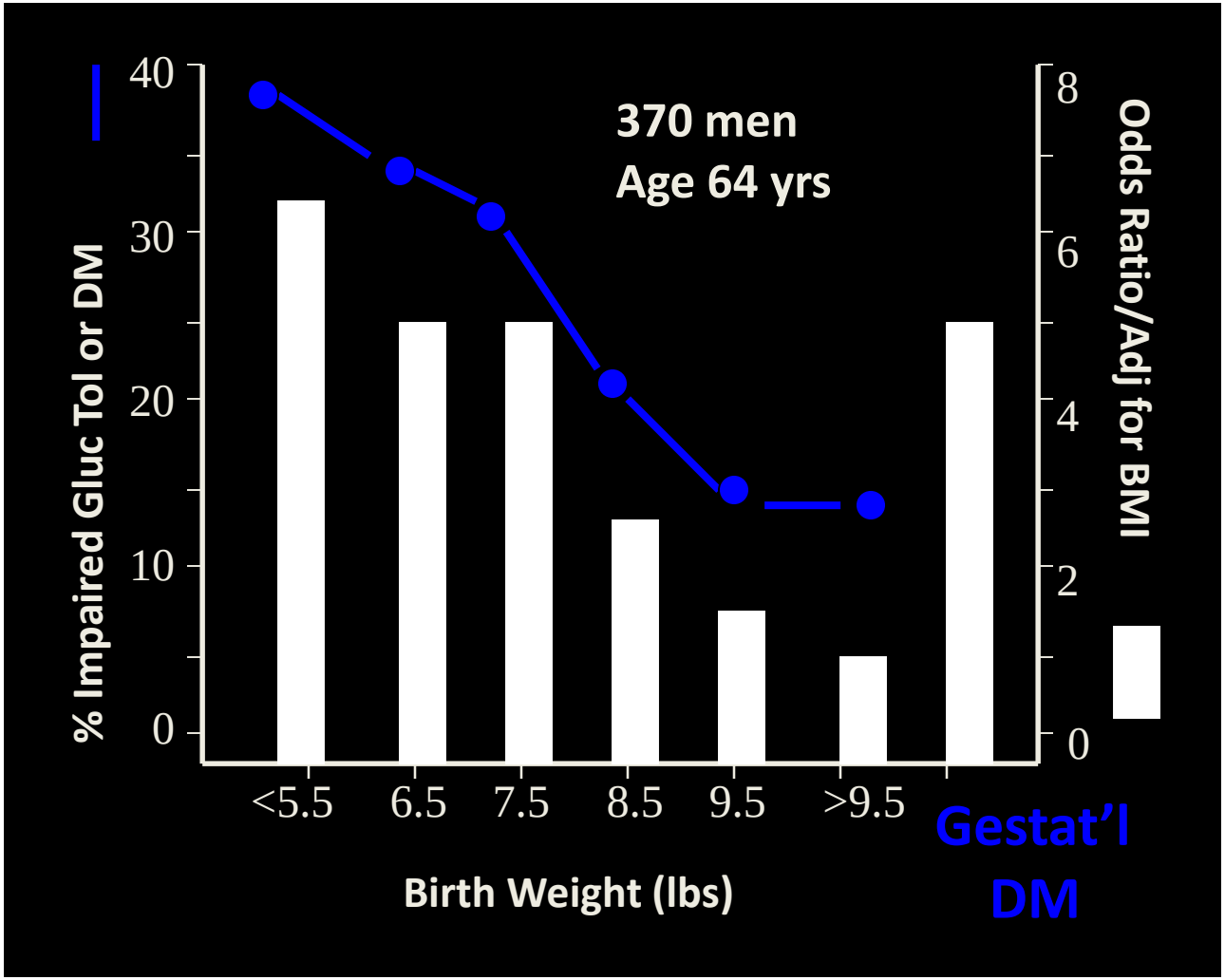



**Variables:**

Birth Weight
Ponderal Index
Sex
Gestational age
Mat'l Ht, Wt
Parity
Socioeconomic
Current BMI

Jarvelin M et al. Hypertension 2004

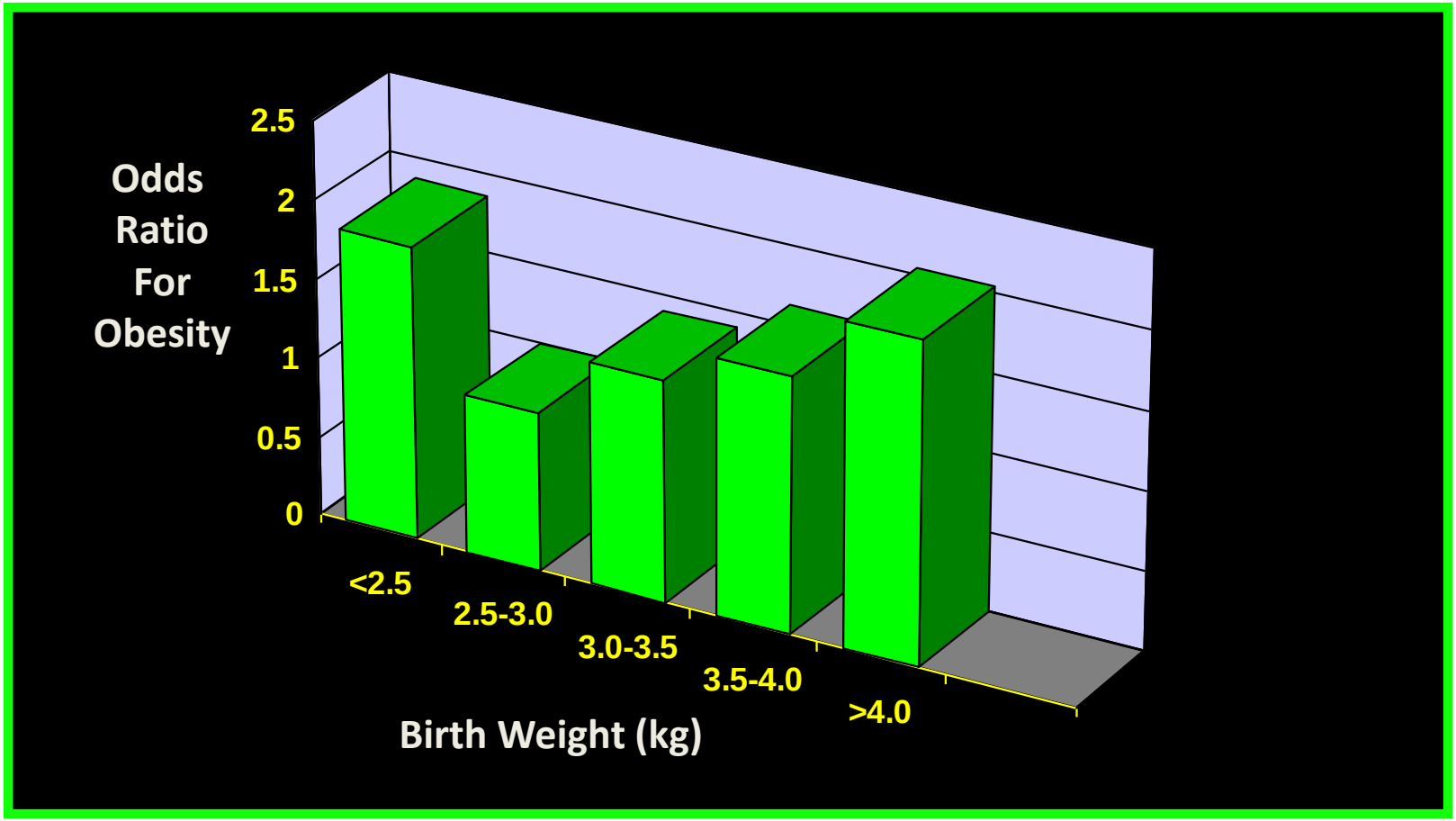
# Birthweight and Diabetes in Men




Hales et al. BMJ 303: 1019, 1991

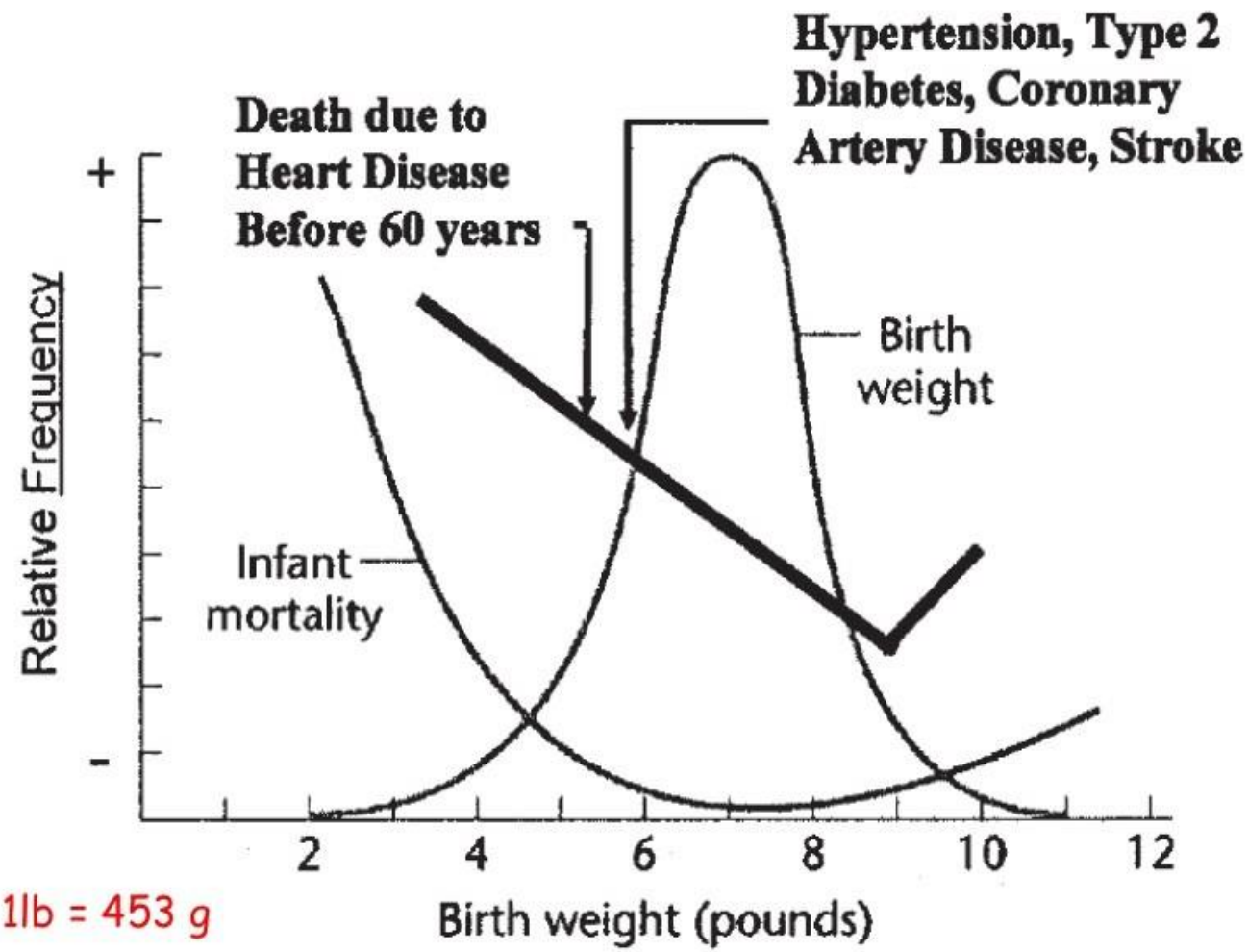
# Birthweight and Obesity Risk

## Trouble at Both Ends of the Birth Weight Spectrum




Eriksson J et al Internatl J Obesity 2001

# 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

# Low Birth Weight and Lung Function in Adulthood: Retrospective Cohort Study in China, 1948–1996

*Pei Pediatrics 2010;125:899-905*

- ✓ A retrospective cohort study
- ✓ A total of 627 men and women born between 1948 and 1954
- ✓ Lung function

- **Significant associations were observed between birth weight and $FEV_1$, FVC, and PEF in adulthood (P <0.001).**
- **$FEV_1$, FVC, and PEF values increased with increasing birth weight.**

# Low Birth Weight and Lung Function in Adulthood: Retrospective Cohort Study in China, 1948–1996

*Pei Pediatrics 2010;125:899-905*

**TABLE 3** Association Between Birth Weight and Adult Lung Function

| Birth Weight | *N* | Adult Lung Function | | edictive |
|---|---|---|---|---|
| | | $FEV_1$, Mean (95% CI), L | FVC, Mean (95% CI), L | |
| <2.5 kg | 38 | 2.62 (2.45–2.79) | 3.30 (3.08–3.53) | |
| ≥2.5 kg | 190 | 2.70 (2.63–2.77) | 3.31 (3.21–3.41) | |
| ≥3.0 kg | 284 | 2.93 (2.87–3.00) | 3.66 (3.57–3.76) | |
| ≥3.5 kg | 115 | 3.00 (2.89–3.11) | 3.79 (3.64–3.94) | |
| Total | 627 | 2.85 (2.81–2.90) | 3.55 (3.49–3.61) | |
| F | | 12.00 | 13.95 | |
| *P* | | .0001 | .0001 | |
| Linear trend, F | | 19.82 | 18.03 | .13 |
| Linear trend, *P* | | .0001 | .0001 | >.05 |

CI indicates confidence interval.

Lung function may be affected by hypogenesis in utero.

# 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) |

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

Foetal undernutrition predisposes men but not women to depression in late adult life.

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

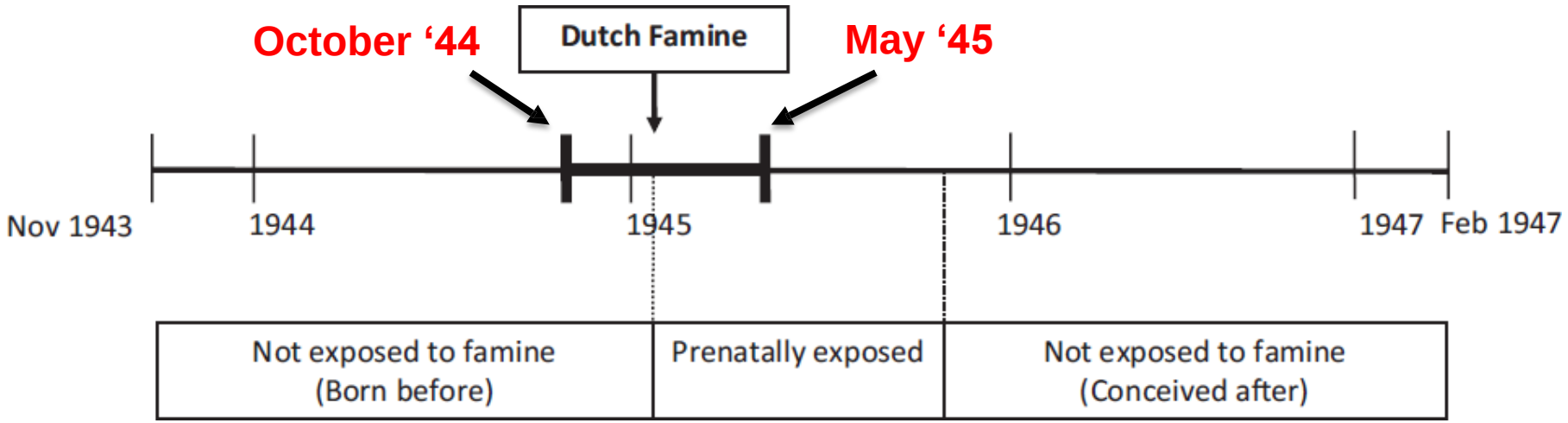
| | Men | | | |
|---|---|---|---|---|
| | *n* | % With depression | OR (95% CI) | Adjusted OR (95% CI) |
| Birthweight (lb) | | | | |
| <6.5 | 76 | 13.2 | 3.0 (0.9–10.6) | 3.5 (1.0–12.8)[1] |
| 6.5–7.5 | 149 | 12.1 | 2.7 (0.9–8.7) | 3.2 (1.0–10.5)[1] |
| 7.5–8.5 | 176 | 11.4 | 2.5 (0.8–7.9) | 2.8 (0.9–8.9)[1] |
| >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) |

# FETAL NUTRITION AND ADULT DISEASES

## Dutch famine 1944 - 1945

Rations were 500 to 1000 kcal per day for adults

5 months




2414 people aged 60 years examined
of which 912 interviewed and 741 with clinical examinations

*Painter et al, Repr Toxicol 20:345-352, 2005*

# After 60 years, adults exposed to Dutch famine during early gestation showed higher incidence of chronic diseases

**Grandmothers** | **Sons** | **Daughters** | **Grandchildren**





**Dutch famine during early gestation**

**Higher birth weight**
**Higher incidence of**
Obesity
Type 2 diabetes
Atherosclerosis
Coronary heart disease
Breast Cancer
Alzheimer

**Higher incidence of**
Obesity

*Painter et al, Repr Toxicol 20:345-352, 2005*
*de Rooij, Roseboom BMJ Open 2013*
*Veenendal et al, Int J Obst Gynaecol 2013*

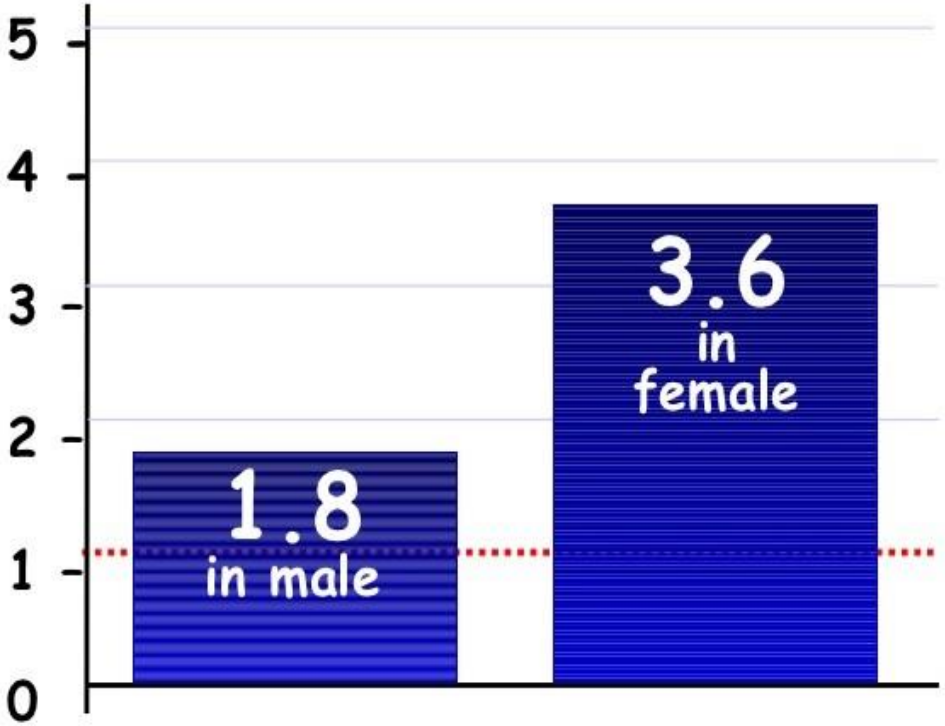
# Acute maternal stress in pregnancy and schizophrenia in offspring: a cohort prospective study.

*Malaspina D, BMC Psychiatry. 2008;8:71.*

✓consequence of an acute maternal stress, through a follow-up of offspring whose mothers were pregnant during the Arab-Israeli Six Day War of 1967.

✓a cohort of 88,829 born in Jerusalem in 1964-76.

**RR** of incidence of schizophrenia for those who were in the **3° month** of fetal life in June 1967



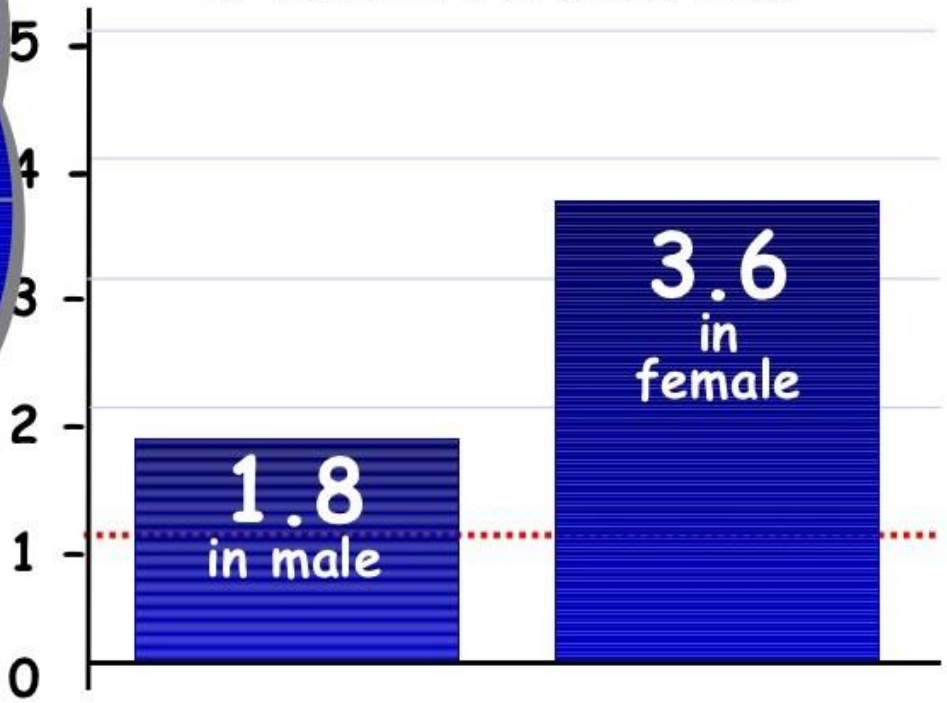
# Acute maternal stress in pregnancy and schizophrenia in offspring: a cohort prospective study.

*Malaspina D, BMC Psychiatry. 2008;8:71.*

Schizophrenia has been linked with intrauterine exposure to maternal stress due to bereavement, famine and major disasters.

✓ c
ac
t
bor
1964

**RR** of incidence of schizophrenia for those who were in the **3°month** of fetal life in June 1967



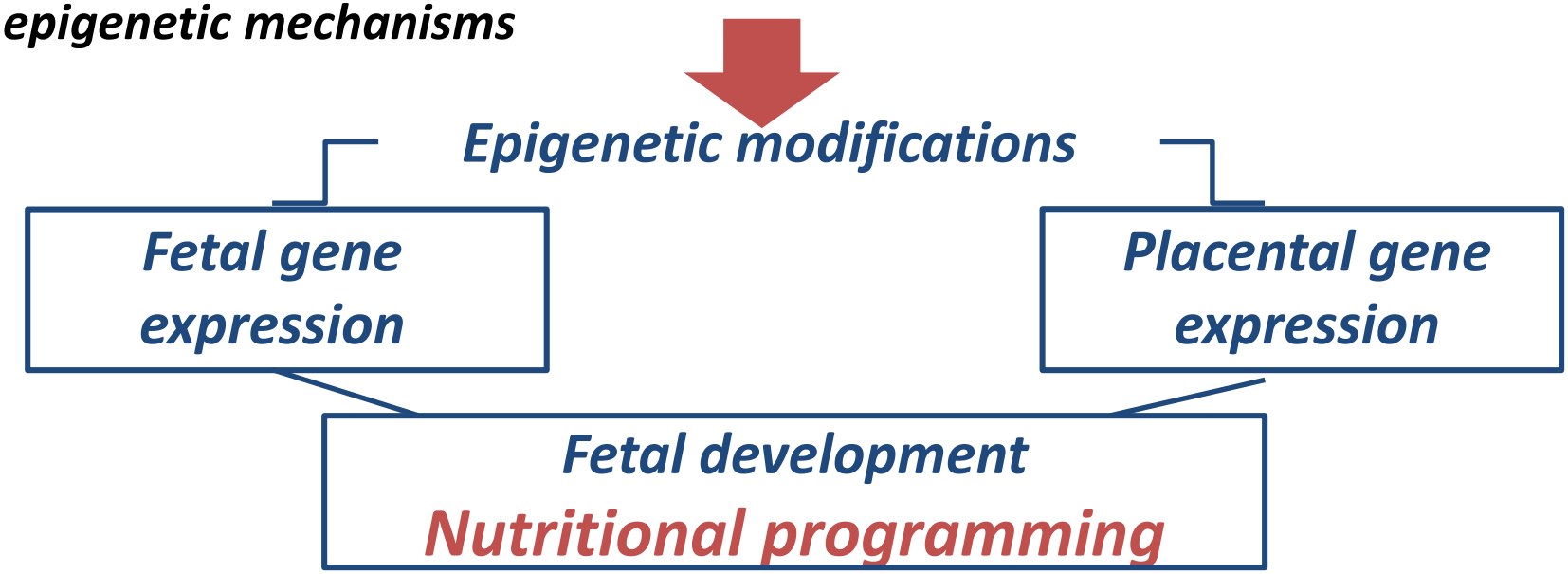
# POSIBLE MECHANISMS

## (1) Altered fetal nutrition

- ***Fetal nutrition is the key regulator of fetal growth, that is to be early programming, influencing to health, adult diseases.***

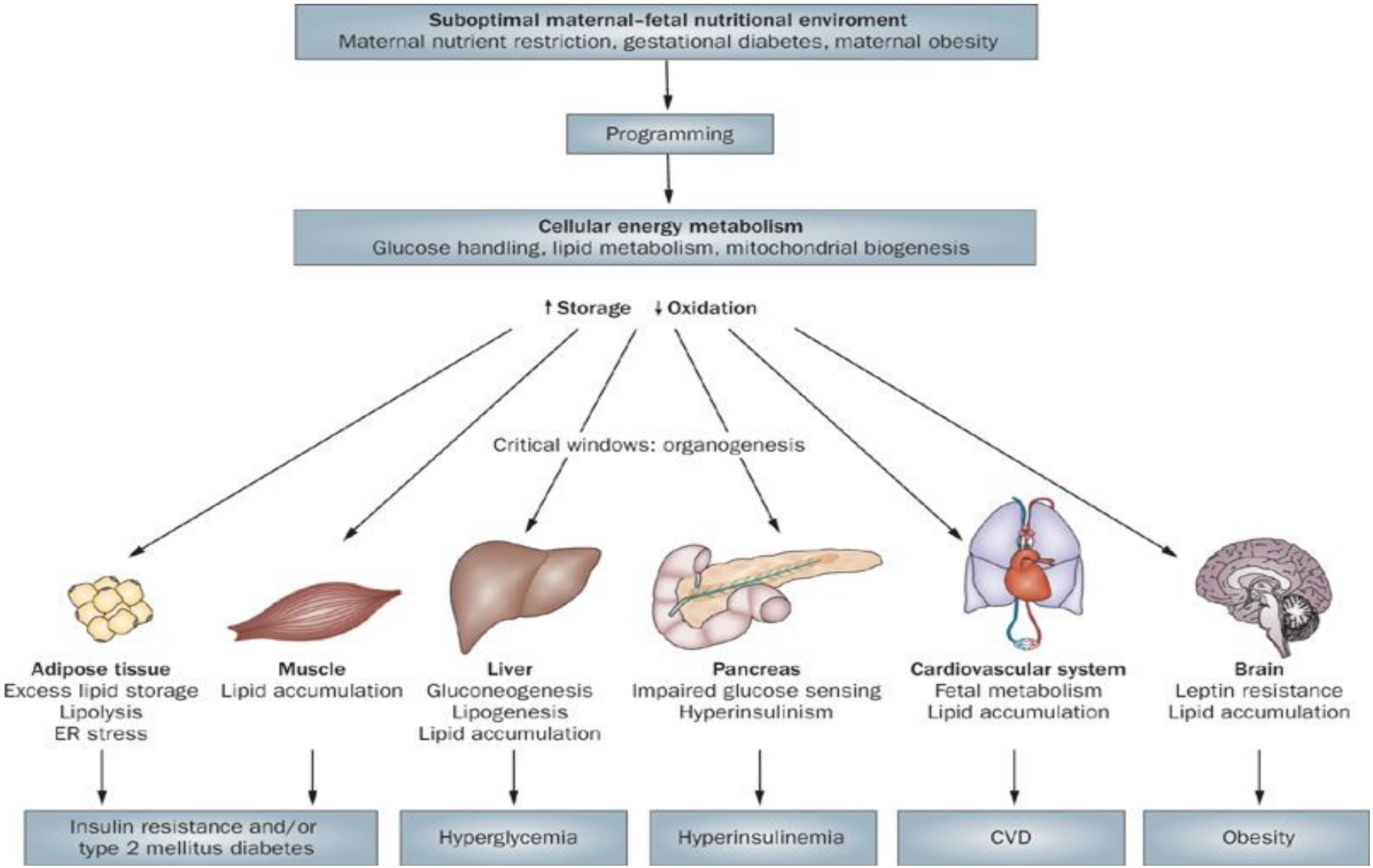
  ***Harding JE. Int J Epidemiol 2001; 30 : 15 -23***

- ***Maternal diet is one main of the regulators on DNA stability and phenotypic adaption, influencing on methylation and acetylation of epigenetic mechanisms***




**Cetin et al., Curr Opin Clin Nutr Metab Care, 2013**

# Phenotype changes and maternal-fetal nutrition



# (2) Genetic and Epigenetic links – Fetal Programming

- Early embriogenesis, DNA undergoes demethylation and remethylation, that involves some genes as of maternal or paternal origin for subsequent inactivation,affecting many genes regulating fetal and placental growth.

***Reik W, Dean W, Walter J  Science 2001; 293: 1089-1093***

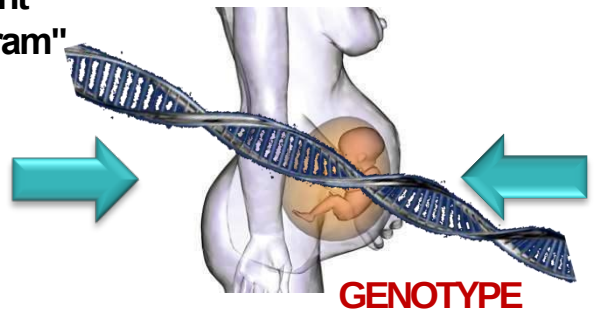
. Intrauterine environment affects to epigenetic mechanism establishing fetal genotype that may result in an incressed subceptibility to chronic disease in adulthood.

***Waterland RA, Jirtle RL.  Nutrition 2004; 20 : 63-6-***

# Fetal Programming

## Affects of pre- and post-natal environment

Preset development
"Epigenetic Program"



GENOTYPE

Epigenetic programming/ geneexpression by in-utero environment

Maternal diet (folate, PUFA,, antioxydants, etc…)

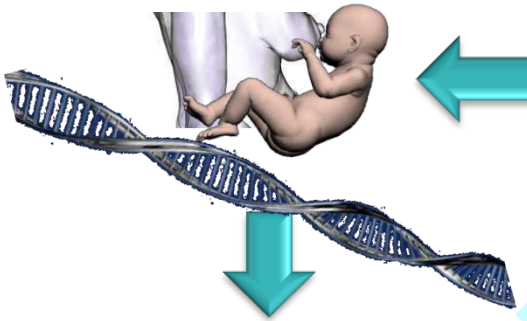
Microbial exposure

Other exposures (i.e. smoking & air pollution)

"Adaptive "development in genotype and epigenetics / early developmental programming

BIRTH

"Adaptive / Mistmath" development in established epigenetics



Epigenetic changes by postnatal environment

Colonisation

Infant diet (inc. breastfeeding)

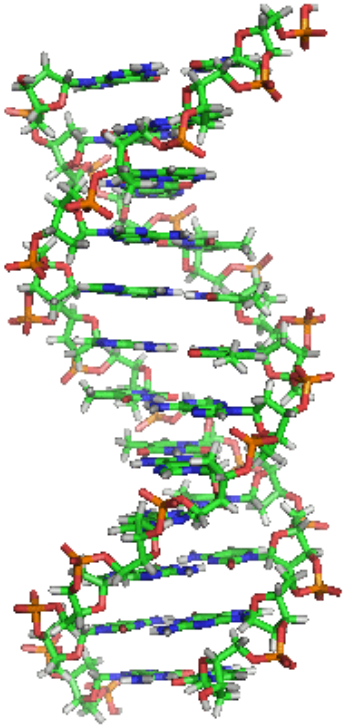
Smoking,air pollution other posnatal influence

PHENOTYPE

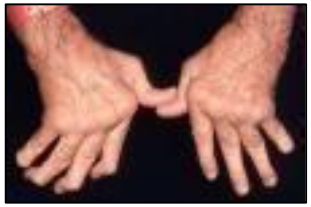
(Martino and Prescott, Allergy 2009)

# Fetal programming afects to health and chronic diseases in later life

**Fetal environment affects to established epigenetics, developping genotype - early life programming - leading to program a large number of metabolic and physiological genes, may affect to health and adult chronic díseases**

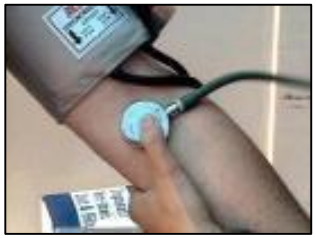


# Fetal programming – Origin of adult diseases

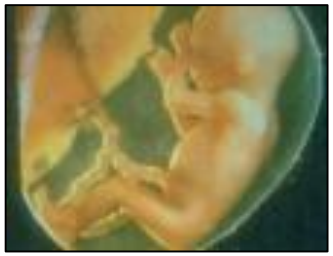


Rheumstic arthritis

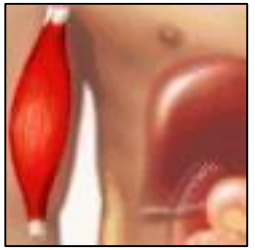
Obesity



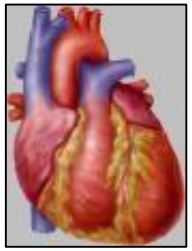
Hypertension



Early developmental programming



Diabetes mellitus



Ischemic heart disease

Strocke

# (3) Thrifty phenotype and adaptive response

- Theo “thrifty phenotype” hypothesis first proposed by Hales and Barker 1992. Undernutrition in pregnant,the fetus reduces insulin secretion and increases peripheral ínsulin resistance, thus directing more glucose to the brain and heart,less to tissues as skeletal muscle.

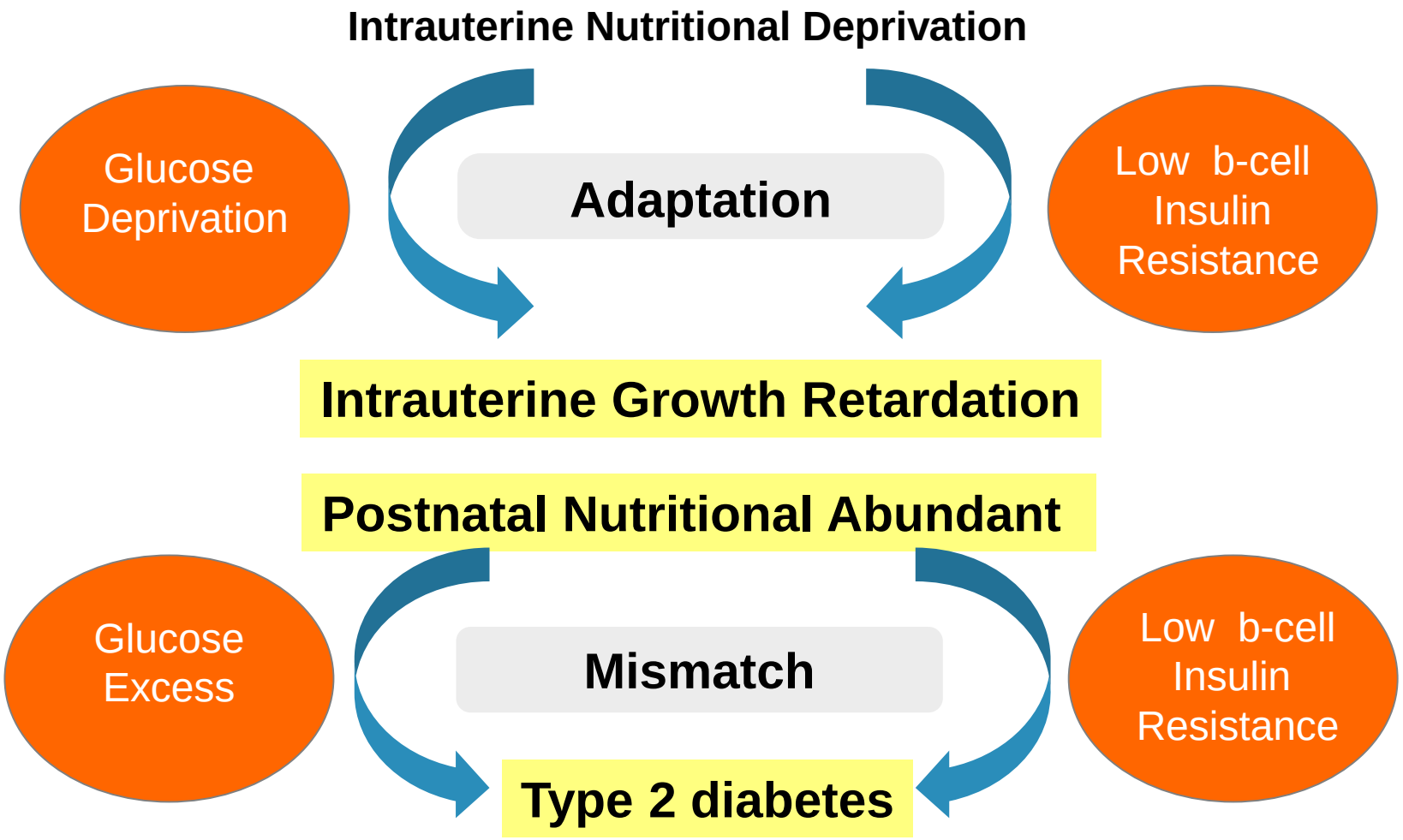
***Hales CN, Barker DJ.. Diabettologia 1992* ;35:595-601.**

- When nutrient is abundant in posnatal, this pancreatic beta-cell defect and peripheral insulin resistance, then cause glucose intolerance and diabetes.

***Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker DJ.***

***Diabetologia 2003;46:190-194.***

# “The Thrifty Phenotype” Hypothesis



# (4) Glucocorticoids

- Intrauterine glucocorticoid exposure leads to reduce numbers of glucocorricoid receptors in hypothalamus, affecting to hypothalamo-pituitary-adrenal axis after birth, contributing to increased blood pressure and glucose intolerance in offspring.

  ***Secki JR. Eur J Endocrinolog 2004; 152: U49-U62.***

- Babies born small tend to have higher plasma cortisol, lower activity of 11beta hydroxysteroid hydrogenase type 2 in placentas.

  ***Phillips DI. Diabetologia 1996; 39 :1119-1122.***

- Repeated administration of betamethasone or dexamethasone during pregnancy has been associated with reduced size at birth

  ***Thorp JA, Jone PG, Knox E, Clark RH. Obstet. Gynecol. 2012;99: 102-108***

.

# (5) Fetal Insulin hypothesis

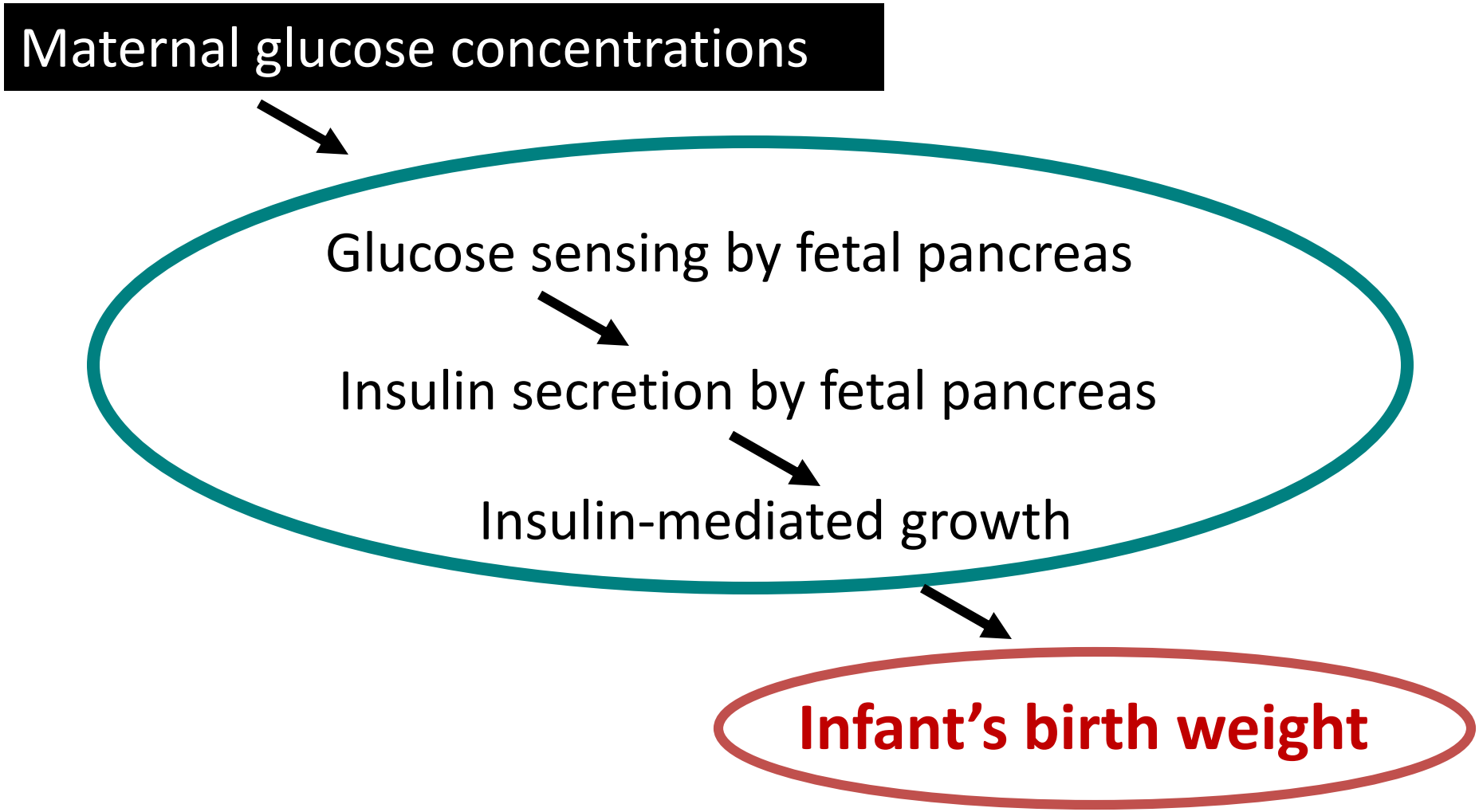
. The relation between small size at birth and impaired glucose tolerance in adult can explaine by inherited deficits in insulin secretion or action

***Hatterlay AT, Tooke JE. Lancet 1999; 353:1788-1792.***

- Insulin is an important regulator of fetal growth, impaired insulin secretion would have impaired growth before birth and would also go to have impaired glucose tolerancr in adulthood.

***Day IN, Chen XH, Gaunt TP, et al. J Endocrinol Metab 2004; 89 : 5568-5576***

# Fetal Insulin Hypothesis



# (6) Intergenerational Effects

- Adverse events during pregnancy can affect not only the offspring of that pregnancy but also the next generation. The birthweight of the mother is related to the birthweight of her children.

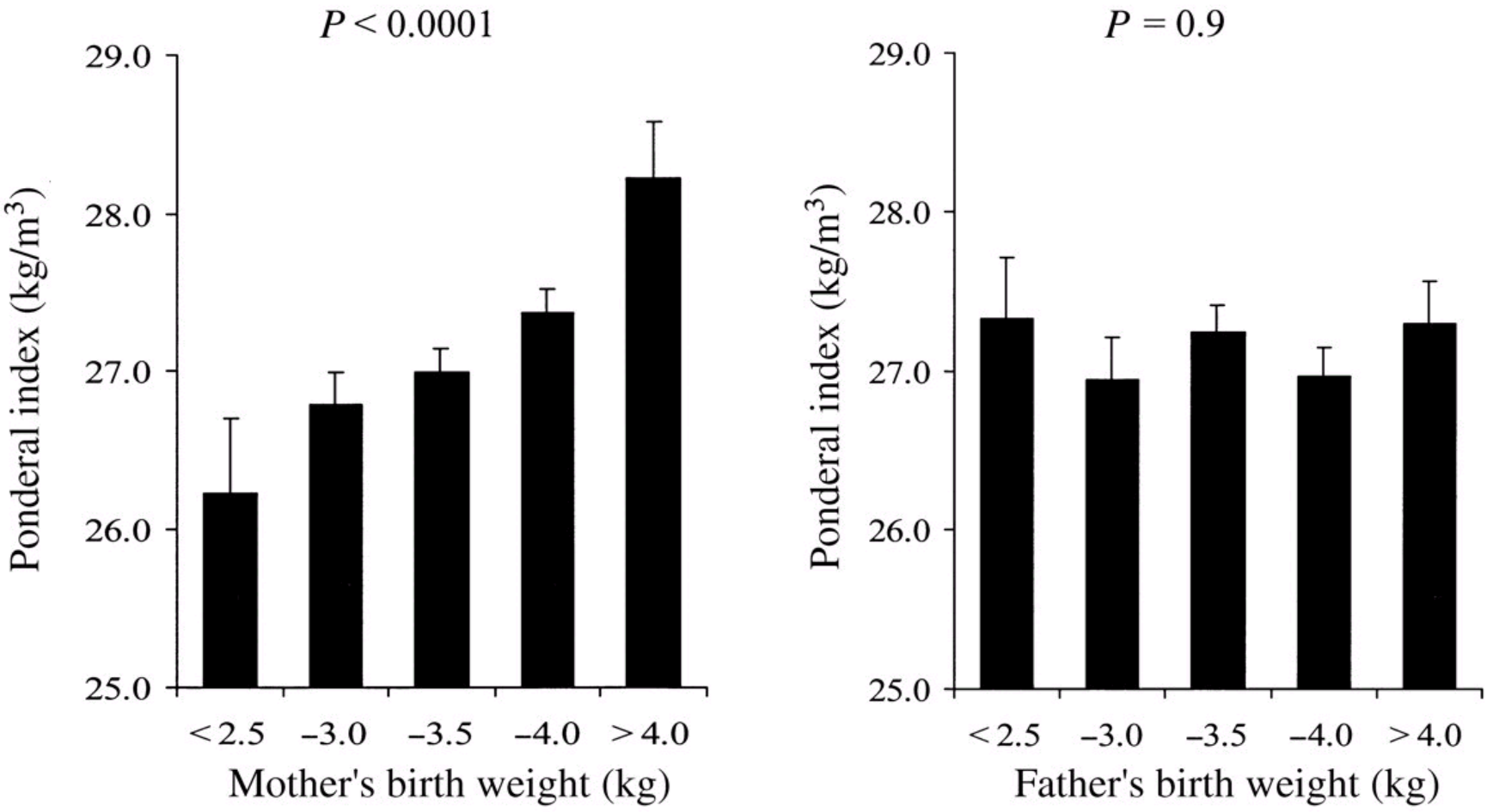
  ***Klebanoff MA, Klaubard BI, Kesel SS, Berendes HW. JAMA, 1984: 252 : 2423-2427***

- There are possible explanations for intergenerational effects on birthweight :

  + Hormonal environment of the uterus of undernourishhed mothers who were small at birth have reduced uterine and ovarian size . That smaller uterine size may impose a greater “maternal constrained “on the fetus, thereby reducing in growth .

  + Any epigenetic changes to the genome may be passed on to second generation.

  ***Ibanez L, Potau N, Enriquez G, de Zegher F. Pediatr Res. 2000; 47 : 575-577]***

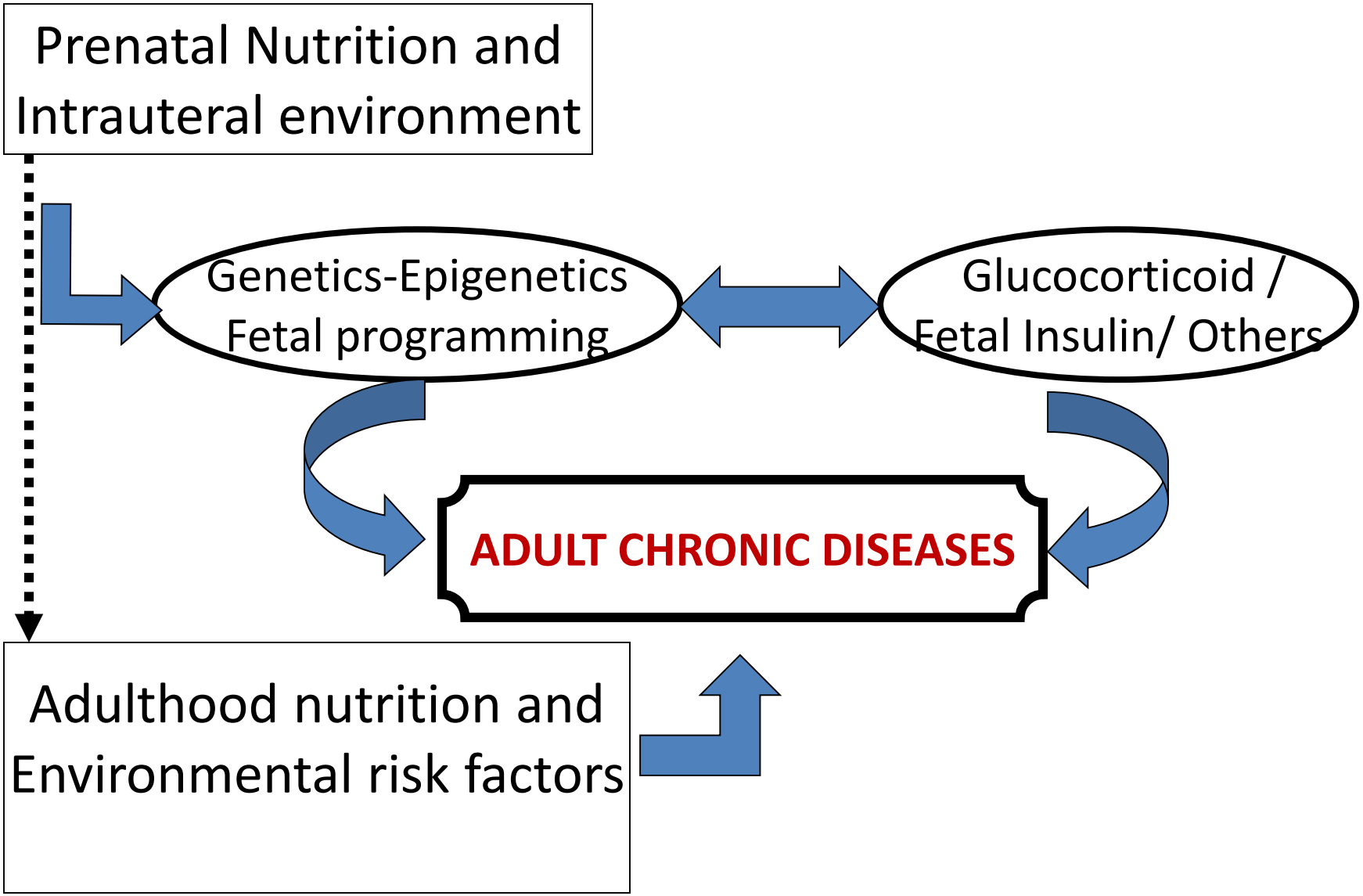



**Godfrey KM, Barker DJP, Robinson S, Osmond C**

.

**Br J Obstet Gynaecol 1997;104:663–7**

# Integrating mechanisms



## PREVENTION OF ADULT DISEASE ORIGINIZED FROM FETAL

***Prevention of low birth weight is crucial***

- Some factors associated with the occurence of low birth weight :
  - Maternal stress
  - Poor nutrition
  - Smoking
  - Drug abuse
  - Depression
  - Domestic violence
  - Poverty
  - Adverse living environment
  - Social exclusion
- These factors contribute in sustained levels of adrenalin leading in poor growth and permanent physiological changes.

## *Nutritional care for pregnant women → Prevention of adult diseases*

**Maternal diet, together with placental function, determines the umbilical nutrient composition, effecting to fetal growth and development.**

# CONCLUSIONS

**FETAL ORIGIN OF ADULT DISEASE is widely accepted.**

**Large number of studies determined that.**

**MECHANISMS : Altered fetal nutrition, Epigenetic -- Genetic links & Fetal programming, Thrifty phenotype, Glucocorticoid exposure and Integrated mechaníms**

**PREVENTION : All risk factors of low birth weight eliminate and nutrition care for pregnants are crucial in prevention of number adult chronic diseases**

***THE FIRST NINE MONTHS SHAPE THE REST OF YOUR LÌFE***

***THANK YOU VERY MUCH***


***Last words***

***FATE/DESTINY = EARLY LIFE PROGRAMMING IN FETAL ?***