INTRAUTERINO PODRIJETLO KRONIČNIH BOLESTI

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Epidemiology

INFANT MORTALITY, CHILDHOOD NUTRITION, AND ISCHAEMIC HEART DISEASE IN ENGLAND AND WALES

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Summary Although the rise in ischaemic heart disease in England and Wales has been associated with increasing prosperity, mortality rates are highest in the least affluent areas. On division of the country into two hundred and twelve local authority areas a strong geographical relation was found between ischaemic heart disease mortality rates in 1968–78 and infant mortality in 1921–25. Of the twenty-four other common causes of death only bronchitis, stomach cancer, and rheumatic heart disease were similarly related to infant mortality. These diseases are associated with poor living conditions and mortality from them is declining. Ischaemic heart disease is strongly correlated with both neonatal and postneonatal mortality. It is suggested that poor nutrition in early life increases susceptibility to the effects of an affluent diet.

boroughs and urban districts), and rural areas within counties. Eighty-three towns were recognised as CBs before the 1974 reorganisation. Three of these became CBs after 1960 and in the analysis are classed as metropolitan boroughs. The London Government Act of 1963 defined thirty-three LBs: fifteen were aggregates of thirty-two former LBs; eighteen were previously urban areas of four counties adjacent to London and are classed as such in our analysis. There are fifty-eight counties but we included an additional county, Middlesex (metropolitan boroughs and urban districts only), which had been absorbed into London after the 1963 Act. In this paper England and Wales is therefore divided into two hundred and twelve local authority areas comprising eighty CBs, fifteen LBs, fifty-nine urban areas and fifty-eight rural areas.

We have divided the causes of infant deaths into five groups according to Woolf's[8] classification: congenital causes (Registrar General, 1921, short list nos 27, 28); bronchitis and pneumonia (18–19); infectious diseases (2–9, 13); diarrhoea (1, 22); and other. Because specific causes of infant death are recorded only from 1921, our analysis is based on the five years from 1921 to 1925. We have examined the relation between different causes of adult and infant death by age, sex, and geographical area using correlation coefficients and scatter plots. The coefficients are influenced by the numbers of deaths as well as by the strength of the relation. During 1921–25 there were 291 082 infant deaths, 127 796 in the first month of life (neonatal) and 163 286 thereafter (postneonatal). Death was attributed to congenital causes in 118 514, bronchitis and pneumonia in 61 770, infectious diseases in 20 668, diarrhoea in 31 147, and other reasons in 58 983. Calculations of rates for ischaemic heart disease during 1968–78 for ages thirty-five to seventy-four years, are based on 649 817 deaths in men and 273 017 in women: the average annual rates were 5722 deaths per million

WEIGHT IN INFANCY AND DEATH FROM ISCHAEMIC HEART DISEASE

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Summary Environmental influences that impair growth and development in early life may be risk factors for ischaemic heart disease. To test this hypothesis, 5654 men born during 1911–30 were traced. They were born in six districts of Hertfordshire, England, and their weights in infancy were recorded. 92·4% were breast fed. Men with the lowest weights at birth and at one year had the highest death rates from ischaemic heart disease. The standardised mortality ratios fell from 111 in men who weighed 18 pounds (8·2 kg) or less at one year to 42 in those who weighed 27 pounds (12·3 kg) or more. Measures that promote prenatal and postnatal growth may reduce deaths from ischaemic heart disease. Promotion of postnatal growth may be especially important in boys who weigh below 7·5 pounds (3·4 kg) at birth.

Introduction

THE known causes of ischaemic heart disease explain only part of the differences in risk between populations and between individuals, and do not explain why in Britain the highest rates of the disease are in the poorest areas and lowest income groups.[1,2] The geographical differences in death rates from ischaemic heart disease in England and Wales are related to differences in infant mortality seventy years ago.[3] This relation is with both neonatal mortality (deaths before one month of age) and post neonatal mortality (one month to one year).[4] Impaired growth and development in prenatal and early postnatal life may be an important risk factor for ischaemic heart disease. To investigate this hypothesis, we have studied death rates in men born in Hertfordshire during 1911–30, whose weights at birth and one year were recorded.

Subjects and Methods

The registration districts of Royston, Bishops Stortford, Ware, Hertford, Hatfield, and Barnet are grouped in east Hertfordshire. At the 1921 census most of the men were employed in agriculture or in trade and services.[5] There were no major industries. The combined population of the districts was 103 211. Infant mortality in the county was below the national average. In 1921–25 the rate was 49 deaths per 1000 births, 27 neonatal and 22 postneonatal.[6] The corresponding figures for England and Wales were 76, 33, and 43.

From 1911 the attending midwife was required to notify every birth to the county medical officer of health within thirty-six hours. Almost all births occurred at home. The name and address of the mother, the date of birth, and the birthweight were registered. The local health visitor recorded her observations on a form when she visited the home periodically throughout the first year. After a year the form was returned to the county health visitor and data were abstracted onto the register, including weight at one year and whether breast fed from birth, bottle fed, or both.

More deaths were expected in men than in women and men are more readily traced because they did not change their surnames. 17 464 boys were born alive in the six districts from 1911 to 1930. 1477 of them died during childhood. We excluded twins and triplets, leaving 15 664 singletons of whom 7991 had both birthweight and weight at one year recorded. Boys whose weights were recorded at ages other than one year but not at one year, were excluded. Weights were measured in pounds (2·2 pounds = 1 kg)

8663 © The Lancet Ltd, 1989

Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease

D J P Barker, C Osmond, J Golding, D Kuh, M E J Wadsworth

Abstract

In national samples of 9921 10 year olds and 3259 adults in Britain systolic blood pressure was inversely related to birth weight. The association was independent of gestational age and may therefore be attributed to reduced fetal growth. This suggests that the intrauterine environment influences blood pressure during adult life. It is further evidence that the geographical differences in average blood pressure and mortality from cardiovascular disease in Britain partly reflect past differences in the intrauterine environment.

Within England and Wales 10 year olds living in areas with high cardiovascular mortality were shorter and had higher resting pulse rates than those living in other areas. Their mothers were also shorter and had higher diastolic blood pressures. This suggests that there are persisting geographical differences in the childhood environment that predispose to differences in cardiovascular mortality.

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disease is more closely related to neonatal and maternal death rates in the past than to postneonatal rates.[6] This points to the importance of the environment during intrauterine rather than early postnatal life.

Blood pressure has been suggested as one link between the intrauterine environment and risk of cardiovascular disease.[6] We have therefore examined the relations among blood pressure, pulse rate, and intrauterine influences, as measured by birth weight, gestational period, mother's height, and mother's blood pressure. To do this we have used data from two large national samples, one of children aged 10 and another of adults aged 36.

We used geographical comparisons within England and Wales to examine the relation between intrauterine influences and cardiovascular disease. We compared geographical variations in mothers' heights and blood pressures, and in the birth weights of their children, with differences in cardiovascular mortality.

→ hipoteza o uvjetima života (socijalnim, ekonomskim, okolišnim, prehrambenim) kao ishodištu zdravlja i bolesti populacije (Kermack et al. 1934.)

→ Barker-serija epidemioloških studija o odnosu između perinatalnog ishoda i smrtnosti (1986-93.)

→ visoka geografska korelacija između neonatalnog mortaliteta i određenih bolesti odrasle dobi

→ povezanost između porođajne težine i smrtnosti od ishemijske bolesti srca

→ pothranjnost u trudnoći važan uzrok kroničnih bolesti odrasle dobi

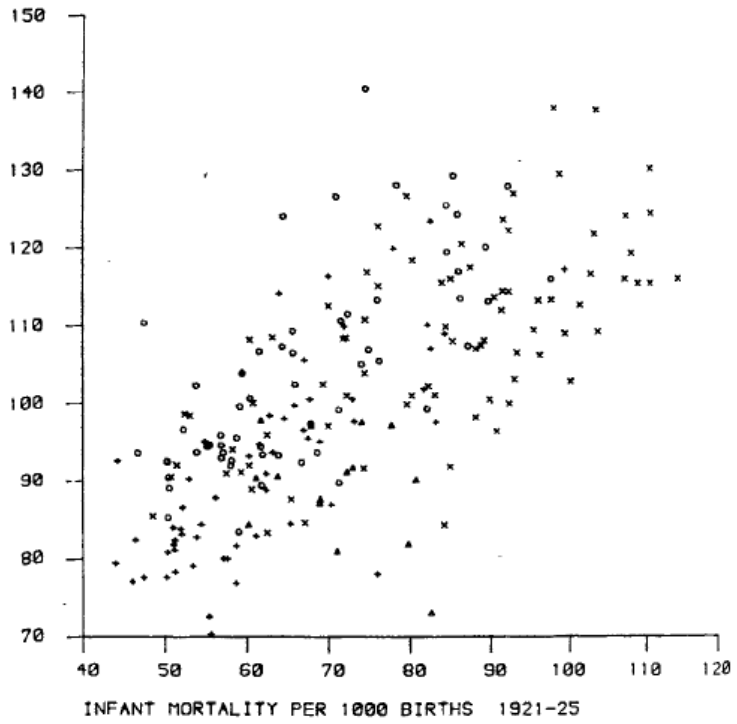


Fig 1—SMRs for ischaemic heart disease in 1968–78 at ages 35–74, men and infant mortality per 1000 births in 1921–25 in the 212 areas of England and Wales.

(X = CBs, Δ = LBs, ○ = urban areas, + = rural areas).

BARKER'S HIPOTHESIS

HIPOTEZA FETALNE OSNOVE KRONIČNIH BOLESTI ODRASLE DOBI

POTHRANJENOST TIJEKOM TRUDNOĆE

→→ važan rani uzročnik kardiovaskularnih/metaboličkih bolesti odrasle dobi

←**fetalno programiranje**
→→trajna promjena strukture/funkcije/metabolizma

FETALNO PROGRAMIRANJE

Fetal programming/imprinting

1. **EMBRIONALNO RAZDOBLJE (1.tr.)→intenzivan rast, stanična hiperplazija**
2. **FETALNO RAZDOBLJE (2.tr.) → stanična hiperplazija/hipertrofija**
3. **FETALNO RAZDOBLJE (3.tr.) → stanična hipertrofija/sazrijevanje organskih sustava**

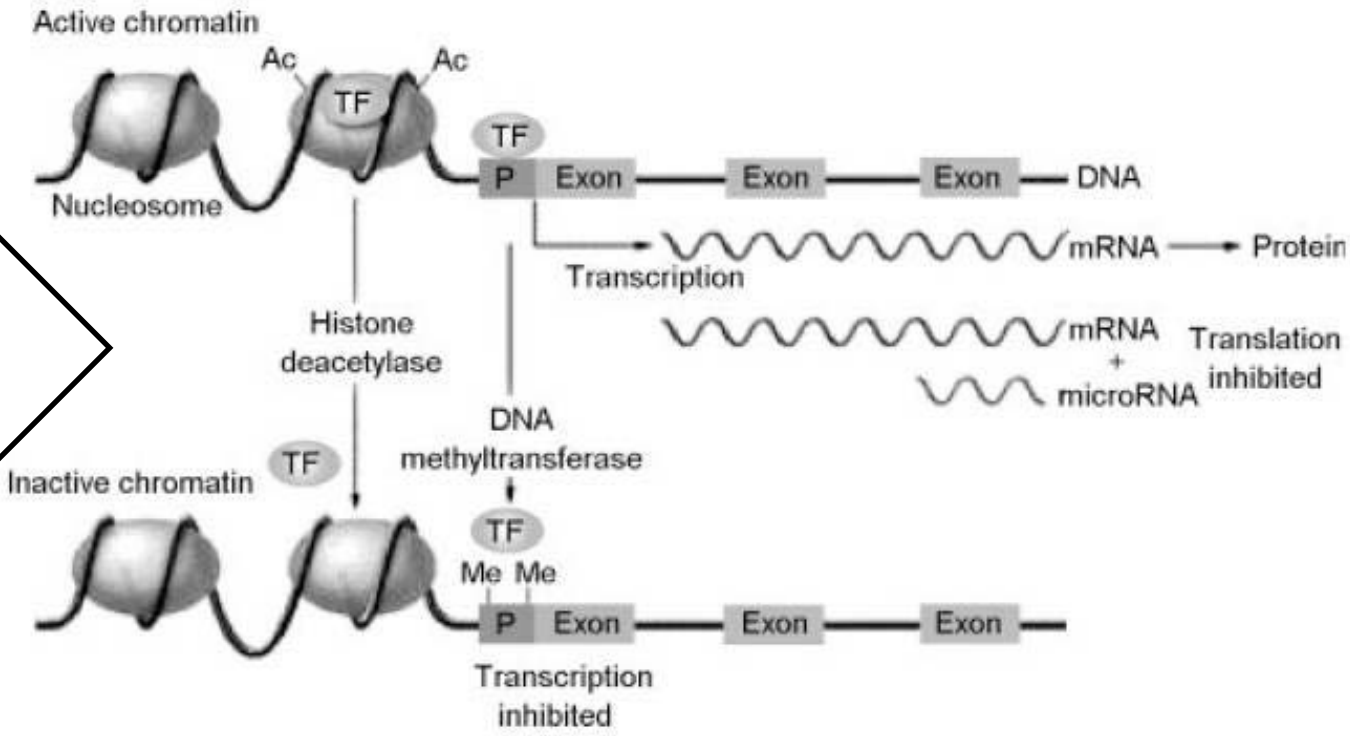
KLJUČNI TRENUTAK RASTA I RAZVOJA

INTARUTERINI STIMULUS/INZULT

PROMIJENJENA EKSPRESIJA FETALNOG GENOMA (EPIGENETSKA MODIFIKACIJA)

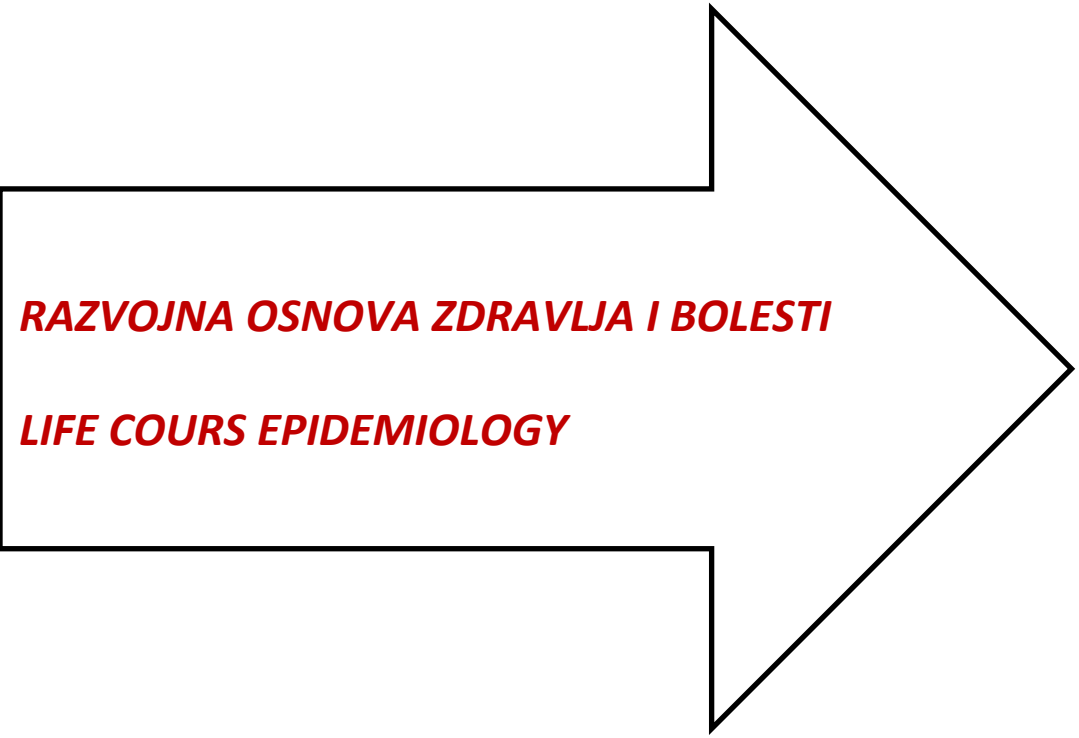
PROMIJENJENA FIZIOLOŠKA FUNKCIJA/ STRUKTURA

EPIGENETSKA MODIFIKACIJA



GENETSKA OSNOVA **INTRAUTERINI UVJETI**

EPIGENETSKA MODIFIKACIJA



RAZVOJNA OSNOVA ZDRAVLJA I BOLESTI

LIFE COURS EPIDEMIOLOGY

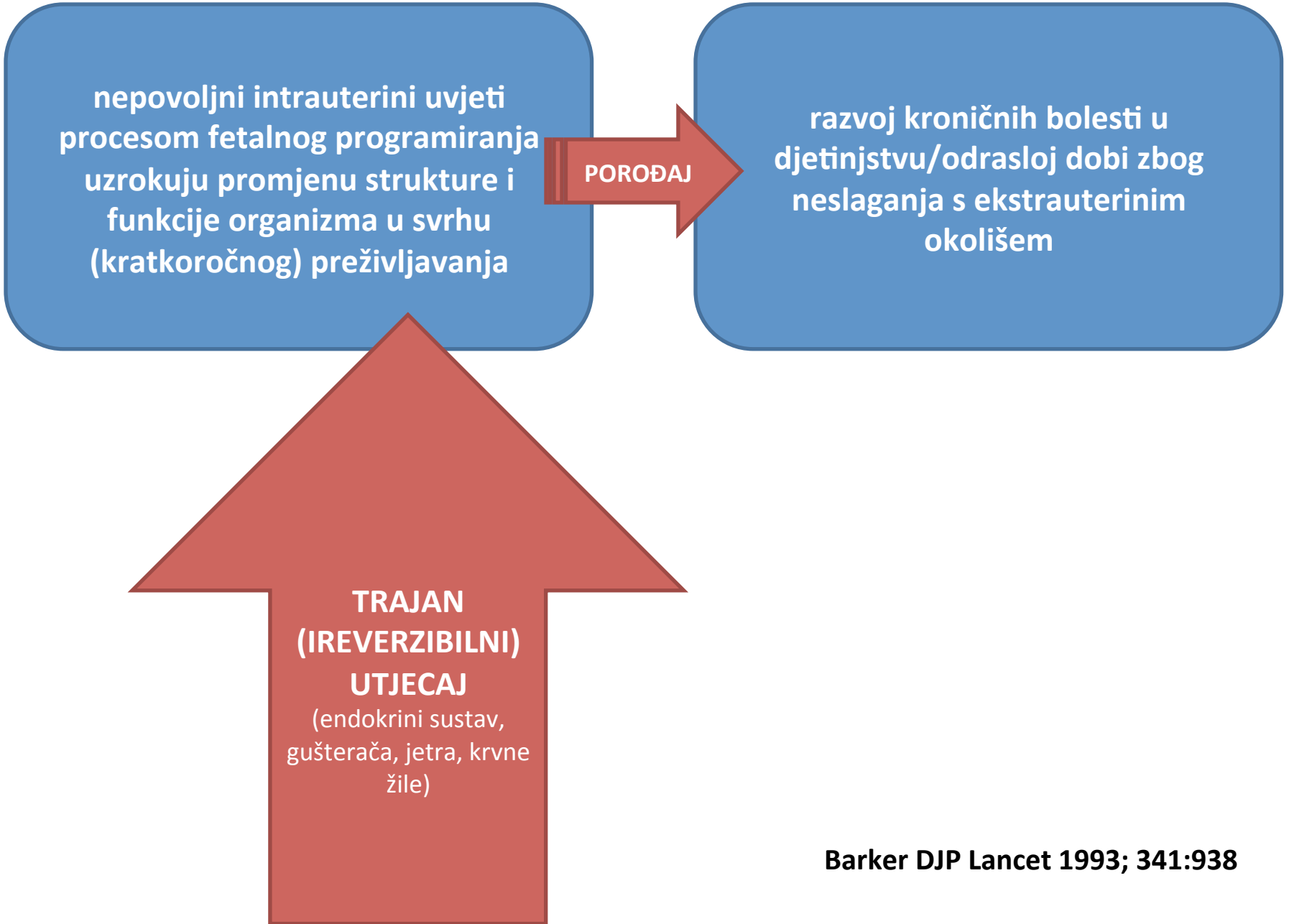
"...health conditions at any point in life are influenced by experience over a person's life from conception on..."

(Gluckman et al.,2010)
(Ben-Shlomo & Kuh, 2012)

Pokusi na životinjama→
pothranjenost/drugi utjecaji koji ometaju rast u kritičnim trenucima razvoja

fetalno programiranje
(endokrini sustav, jetra, gušterača, krvne žile)

Winick M, J. Nutr 1966; 89:300.
Hahn P, J Nutr 1984; 114:1231.
Barker DJP Lancet 1993; 341:938



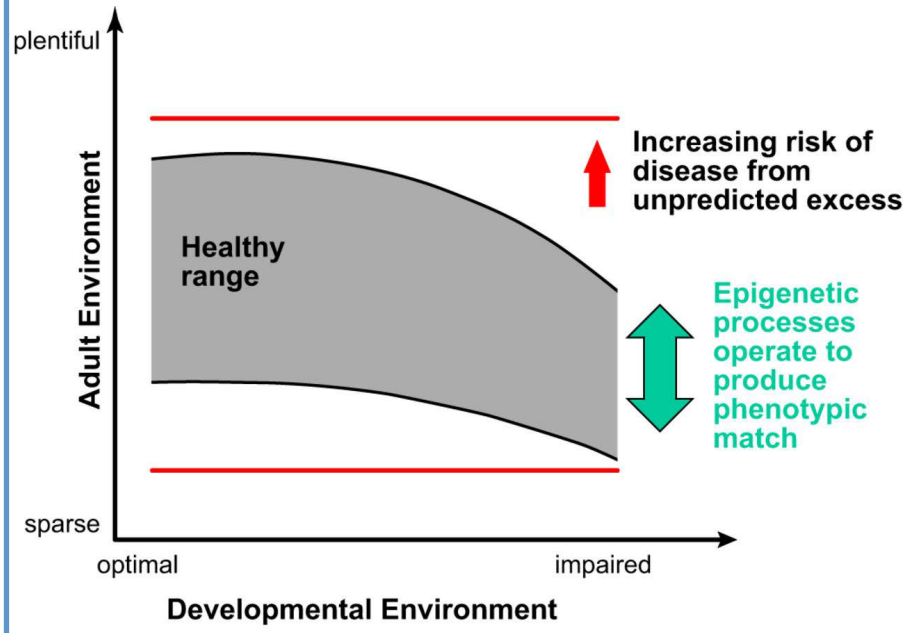
Barker DJP Lancet 1993; 341:938

Living with the past: evolution, develpoment and patterns of disease. Gluckman PD, Science 2004; 305:1733-1736

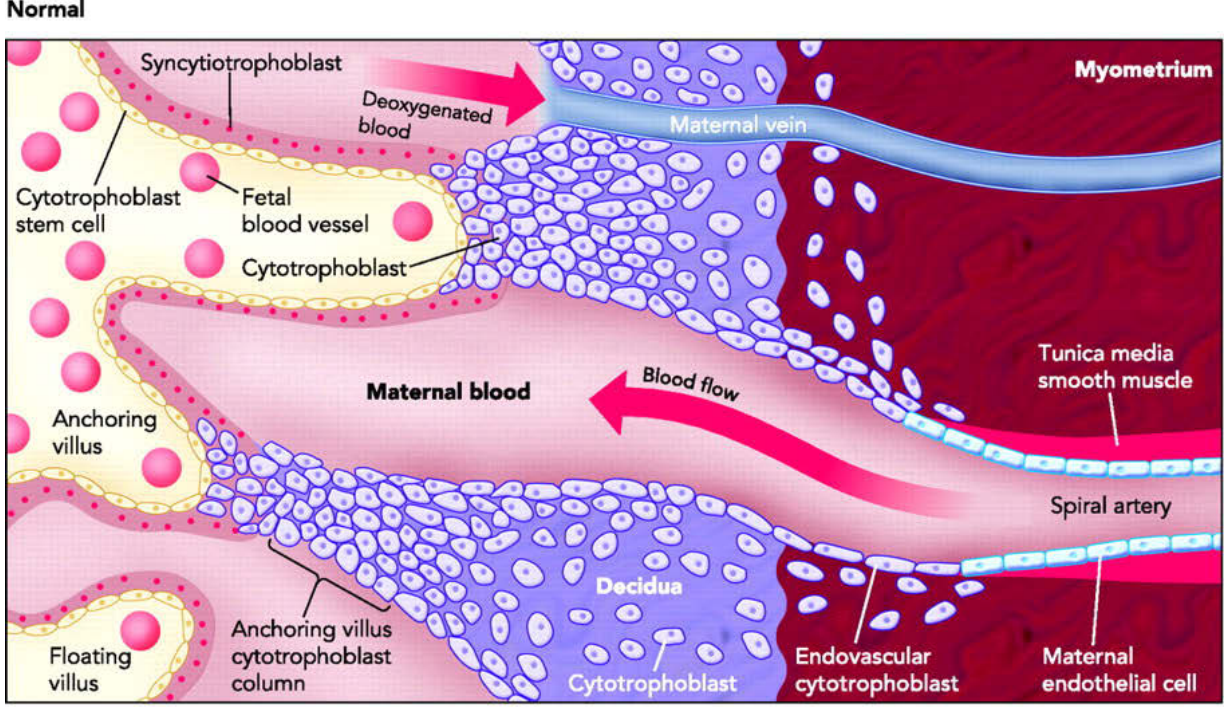
TEORIJA RAZVOJNE PLASTIČNOSTI

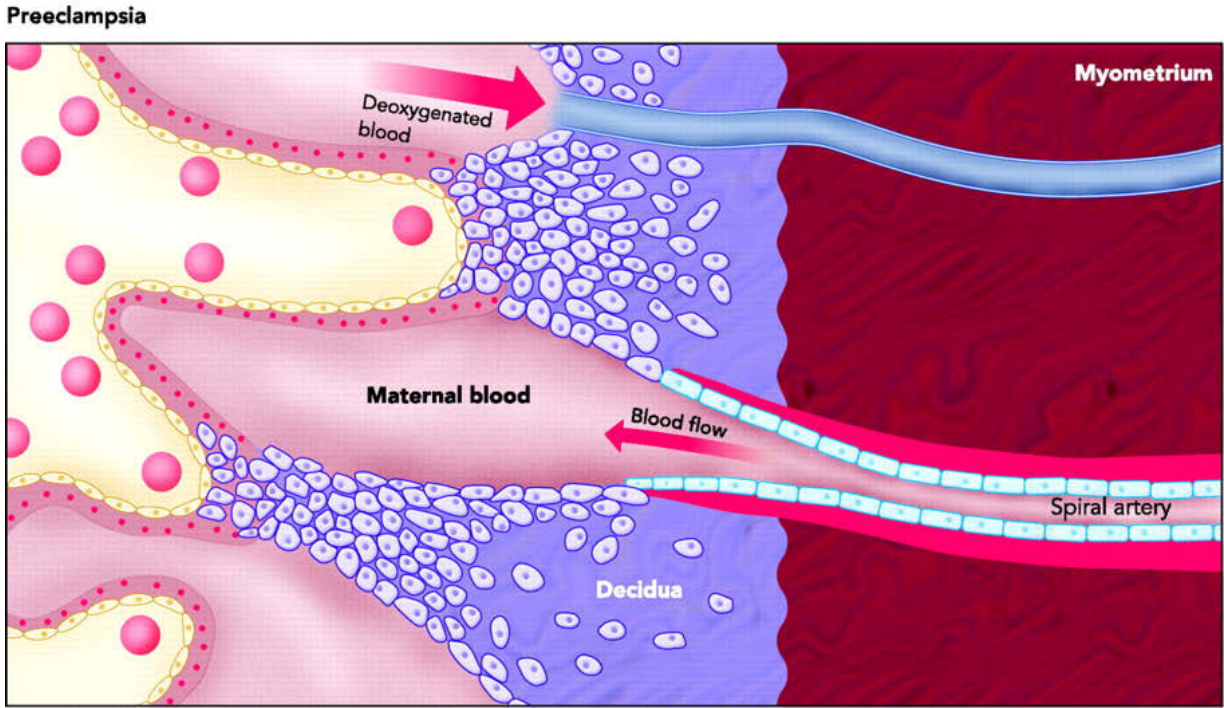
→cilj epigenetskog procesa-potaknuti gensku ekspresiju na stvaranje fenotipa koji je u skladu sa kasnijom okolinom
→u slučaju slaganja-zdravlje
→u slučaju neslaganja-smanjena mogućnost prilagodbe na zahtjeve okoline -porast rizika od razvoja bolesti

→ →STUPANJ NESLAGANJE ODREĐUJE PODLOŽNOST BOLESTI



1. POTHRANJENOST U TRUDNOĆI





Placental vascular dysfunction
Increased impedance umbilical artery

↓

Impaired fetal growth

↓

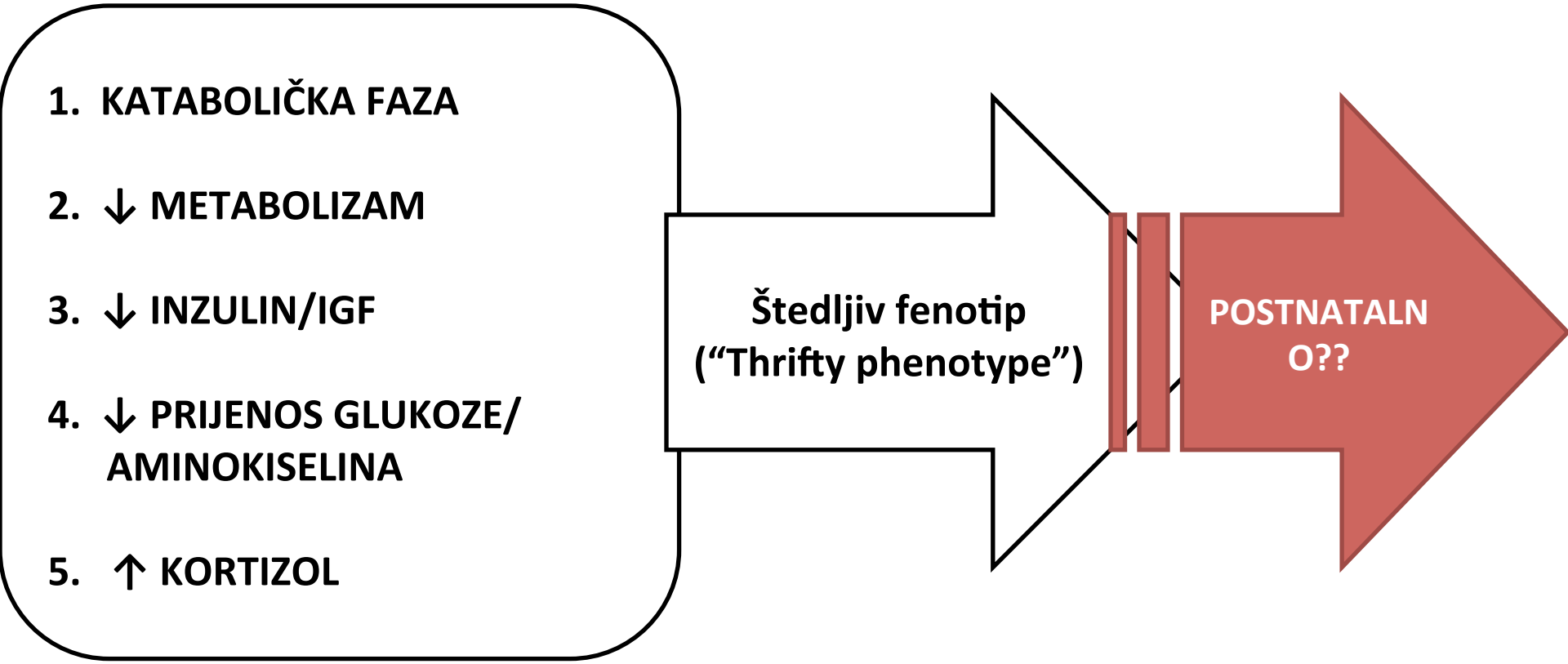
Decreased impedance fetal middle cerebral artery (ie, increased blood flow)
Shunting of blood from peripheral arterial beds to vital fetal organs and placenta
Decreasing amniotic fluid volume

↓

Further increases in umbilical artery impedance with diminished, then absent, then reversed end diastolic flow
Abnormal venous Doppler
- Reversed flow in the fetal inferior vena cava
- Decreased or reversed flow in the ductus venosus during late diastole

Decreased fetal heart rate variability
Nonreassuring tests of fetal well-being
- Nonreactive nonstress test
- Low biophysical profile score (reduction or loss of fetal breathing, movement, and tone)

Spontaneous late decelerations


1. KATABOLIČKA FAZA
2. ↓ METABOLIZAM
3. ↓ INZULIN/IGF
4. ↓ PRIJENOS GLUKOZE/ AMINOKISELINA
5. ↑ KORTIZOL
Štedljiv fenotip ("Thrifty phenotype")
POSTNATALNO??

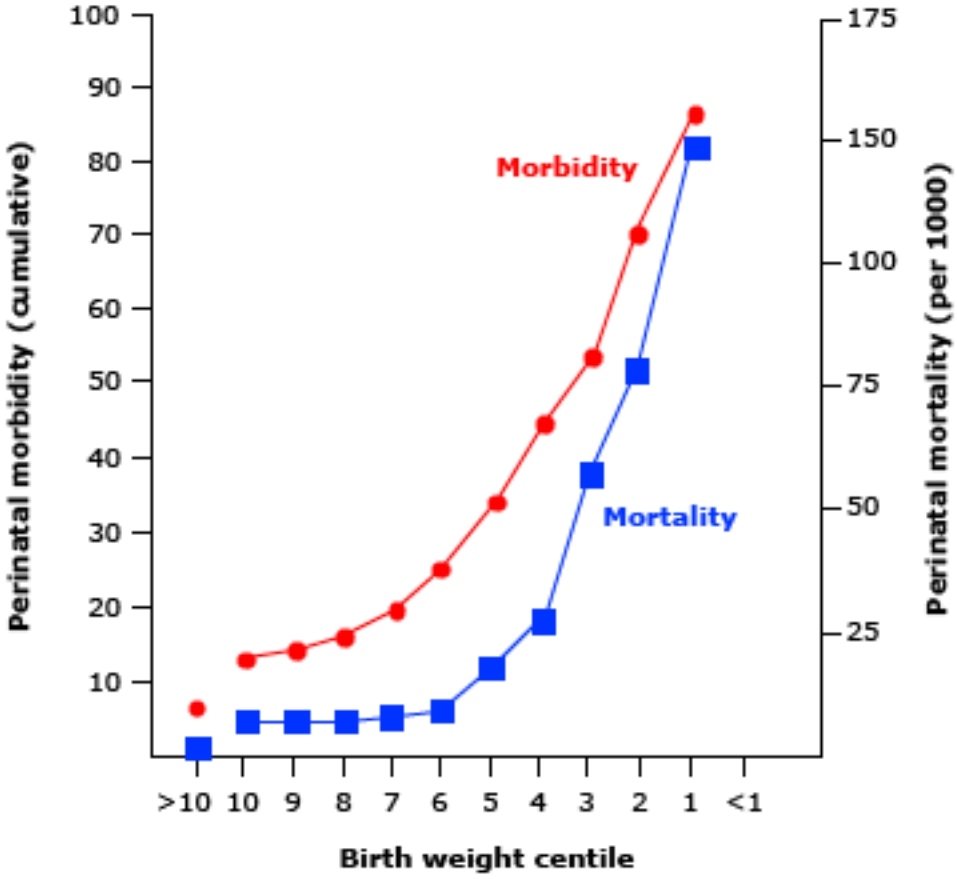
RAZVOJNA PLASTIČNOST I KASNIJE BOLESTI

→neodogovarajuća prehrana majke doprinosi razvoju štedljivog fenotipa ("thrifty fenotyp")

→ odgovor fetusa u razvoju=obrana od neposredne nepovoljne okoline (IUGR, reducirana skeletna masa, smanjen br. nefrona, neurona)

→ nakon porođaja javlja se problem zbog novih okolišnih čimbenika i trajno promijenjene građe i funkcije tijela

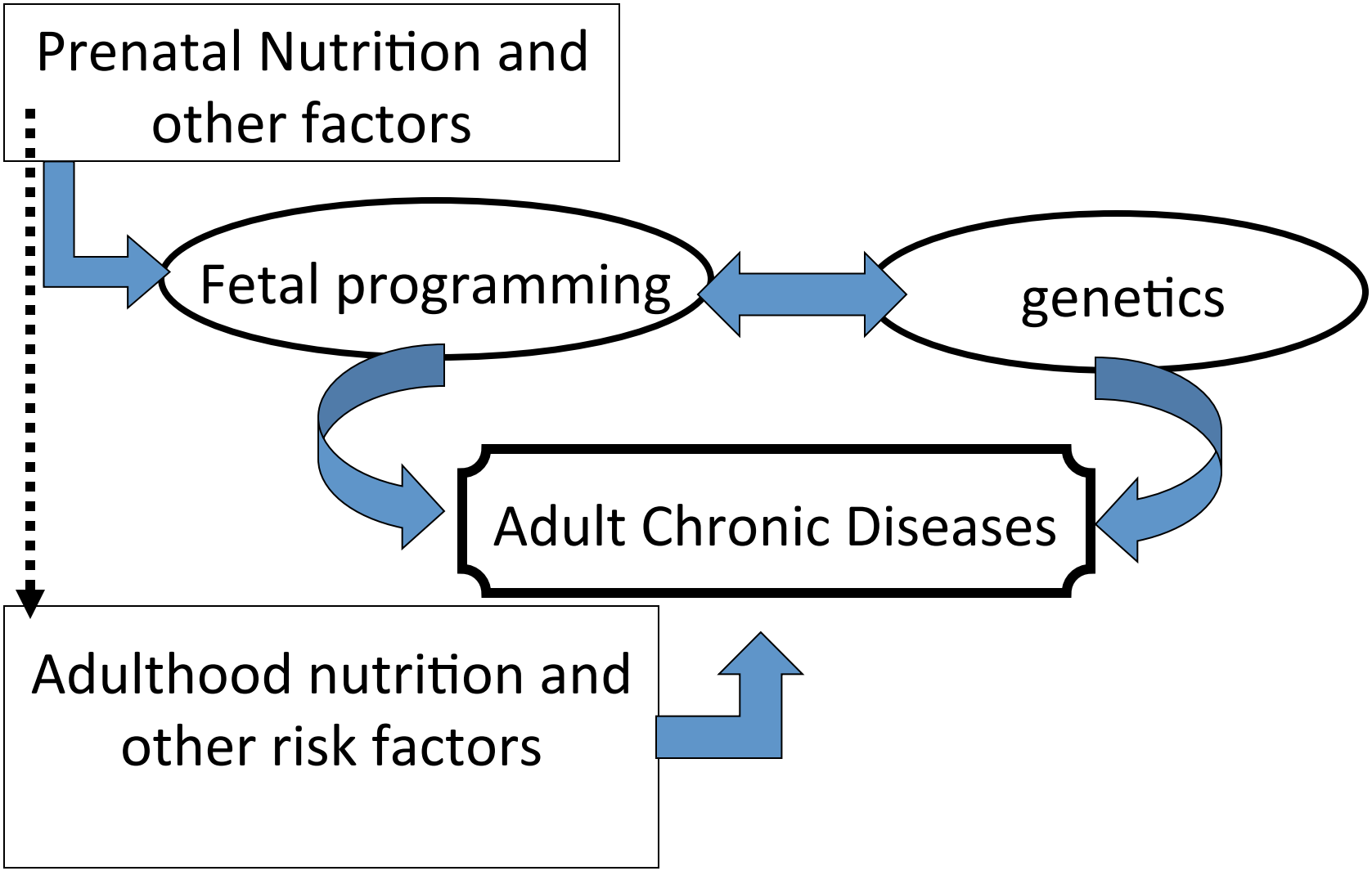
Perinatal morbidity and mortality in fetuses with intrauterine growth restriction

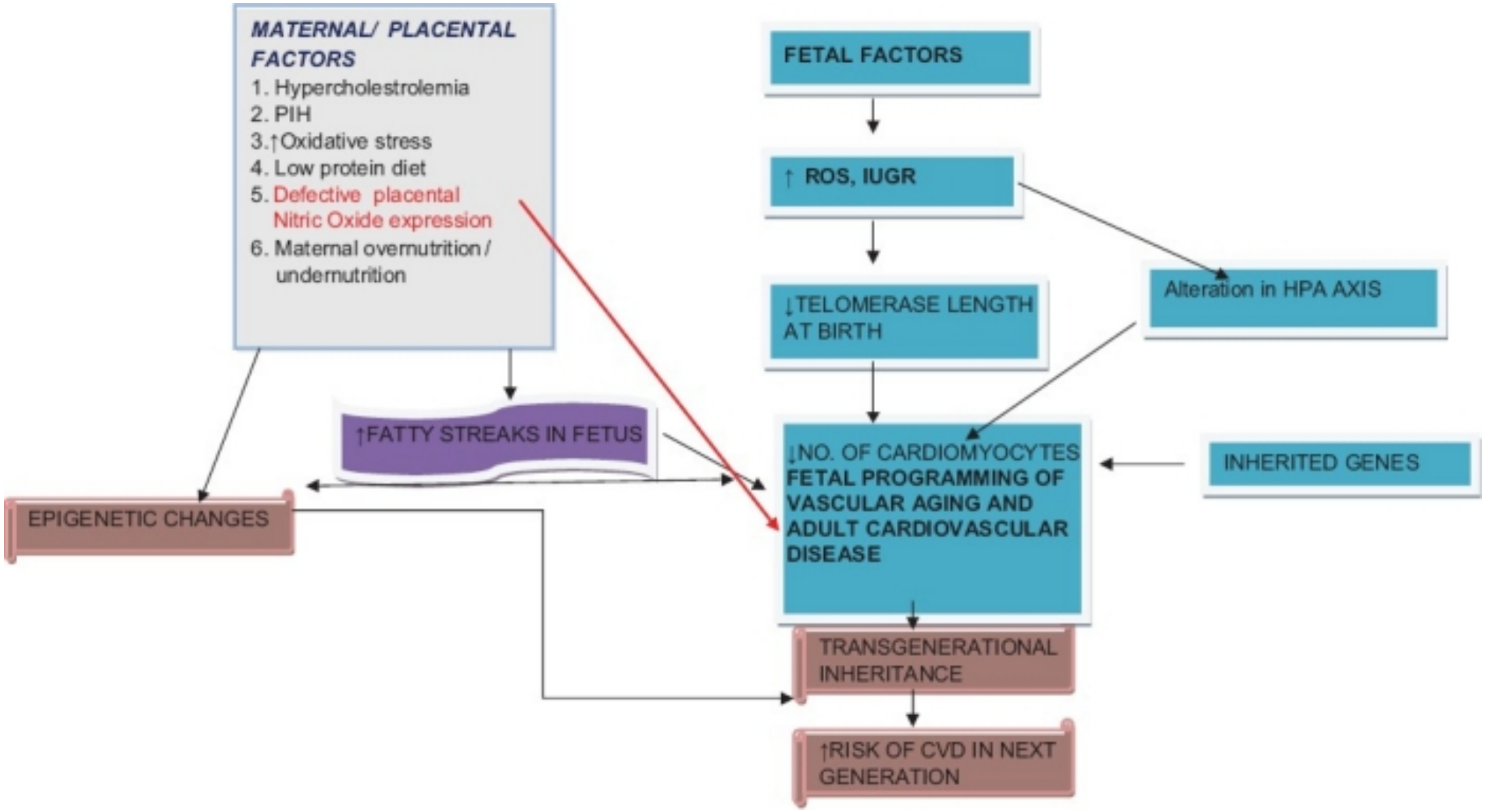


Data from: Manning FA. Intrauterine growth retardation. In: Fetal Medicine: Principles and Practice, Appleton & Lange, Norwalk, CT 1995. p.312.

UpToDate®

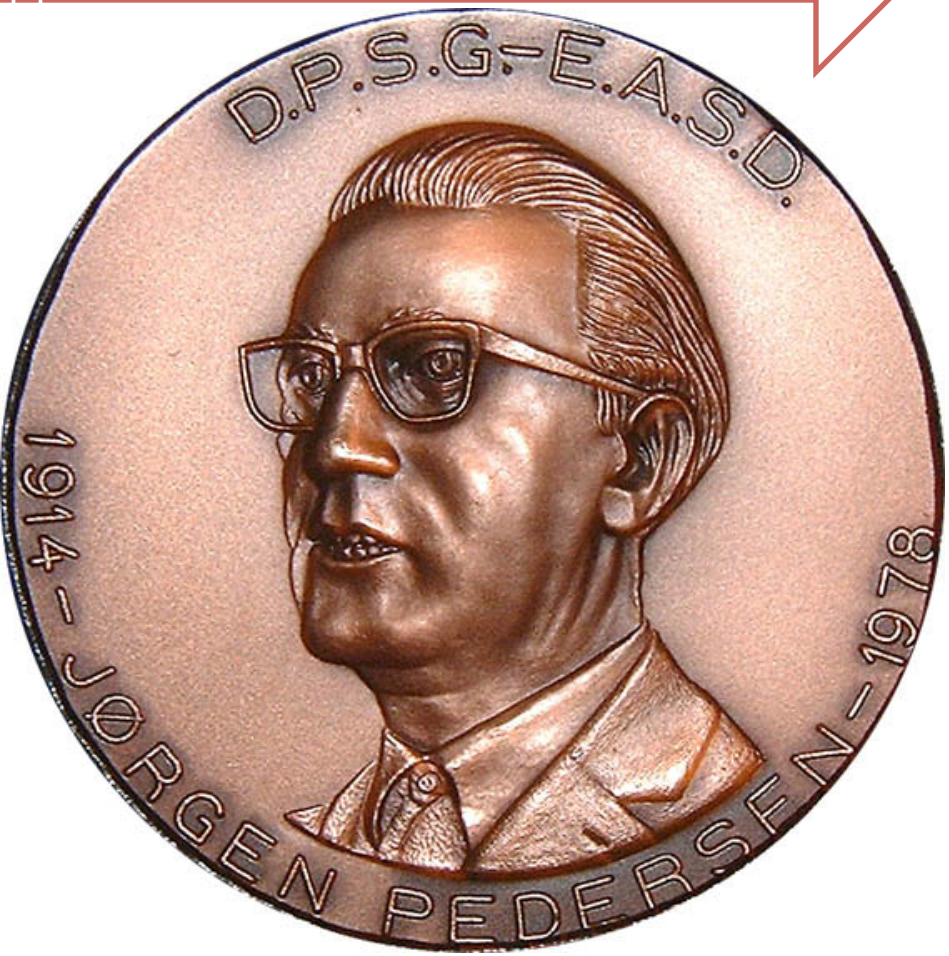
Integrating hypotheses

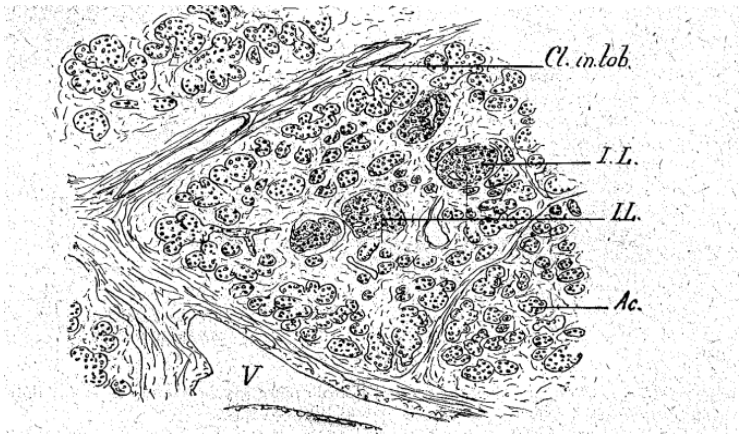


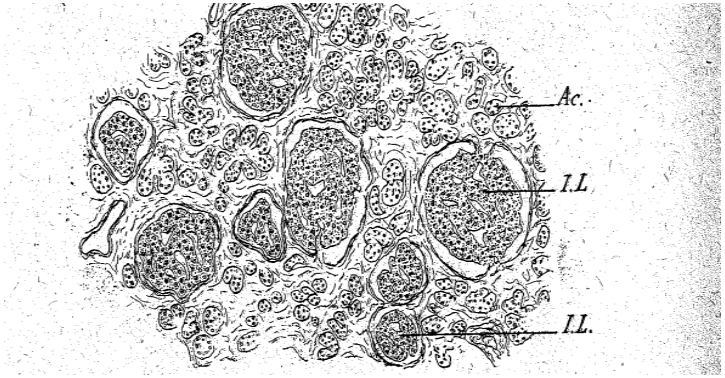

MATERNAL/ PLACENTAL FACTORS
1. Hypercholestrolemia
2. PIH
3.↑Oxidative stress
4. Low protein diet
5. Defective placental Nitric Oxide expression
6. Maternal overnutrition / undernutrition
FETAL FACTORS
↑ ROS, IUGR
↓TELOMERASE LENGTH AT BIRTH
Alteration in HPA AXIS
↑FATTY STREAKS IN FETUS
↓NO. OF CARDIOMYOCYTES
FETAL PROGRAMMING OF VASCULAR AGING AND ADULT CARDIOVASCULAR DISEASE
INHERITED GENES
EPIGENETIC CHANGES
TRANSGENERATIONAL INHERITANCE
↑RISK OF CVD IN NEXT GENERATION

JORGEN PEDERSENOVA HIPOTEZA: Jorgen Pedersen: 2. izd, 1977, str. 211

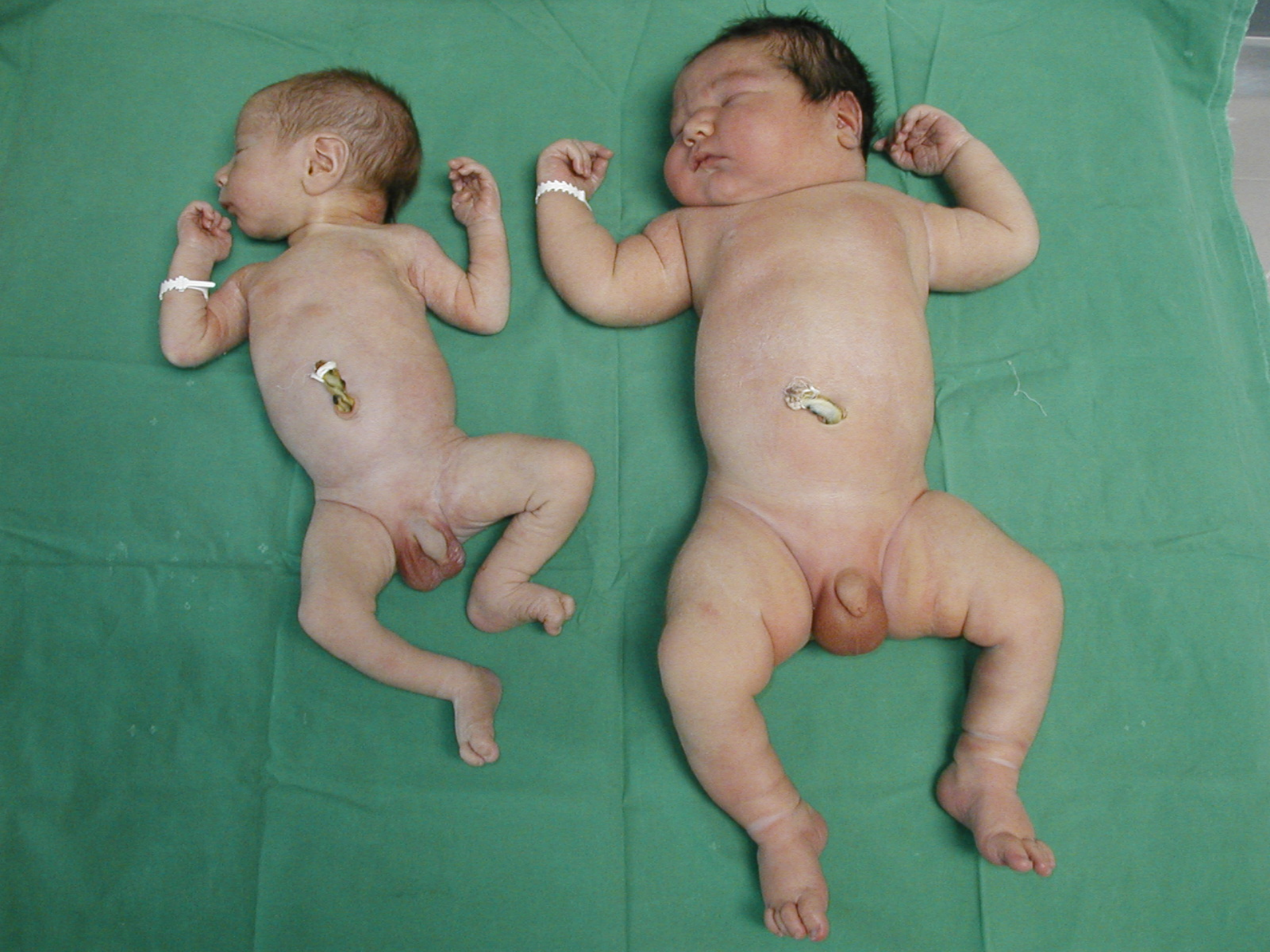
2. "OBILJE" U TRUDNOĆI







"….maternal hyperglycemia results in fetal hyperglycemia and, hence, in hypertrophy of fetal islet tissue with insulin hypersecretion."



Diabetic Pregnancy
Study Group
EASD

→HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, et al Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 200 8:1991.

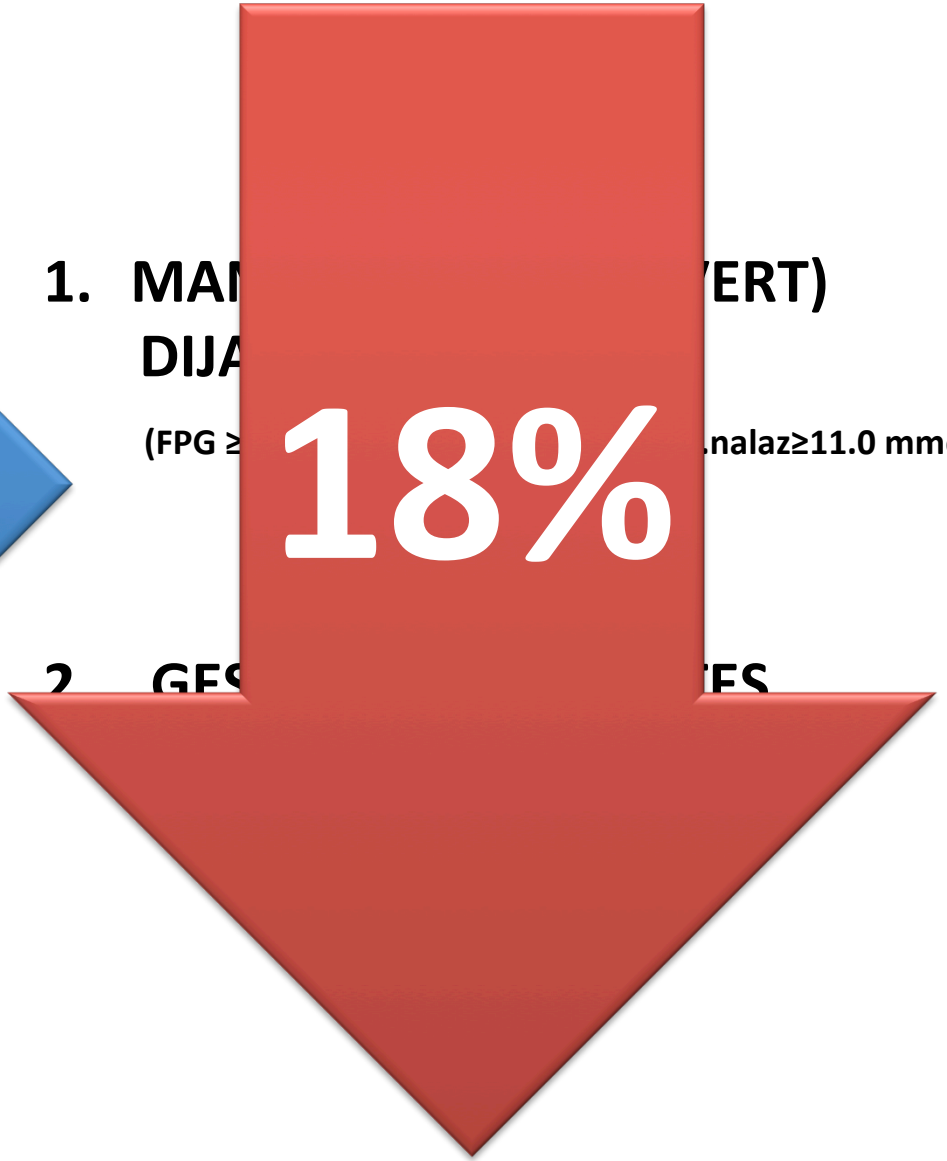
"continuous relation

najbolji suvremeni epigenetski eksperiment

→International Association of Diabetes and Pregnancy Study Groups C sus Panel, Metzger BE, Gabbe SG, et al. International association of diabet and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010; 33:676.

GESTACIJSKI DIJABETES

→dijabetes koji se prvi put dijagnosticira u trudnoći



1. MA ERT)
   DIJA
   (FPG ≥ nalaz≥11.0 mmol/l
2. GES ES

→ oštećena tolerancija glukoze u osobnoj anamnezi ili gestacijski dijabetes u prethodnoj trudnoći

→ dijabetes melitus u obiteljskoj anamnezi (1. rod)

→ tjelesna masa prije trudnoće ≥ 110% idealne tjelesne mase ili BMI>30 kg/m2, značajan dobitak na masi u adolescenciji ili između trudnoća ili značajan dobitak na masi u trudno

90%

→ neobjašnjeni perinatalni gubitak ili malformirano če opstetričkoj anamnezi

→ porođajna težina majke >4100 g ili <2700 g

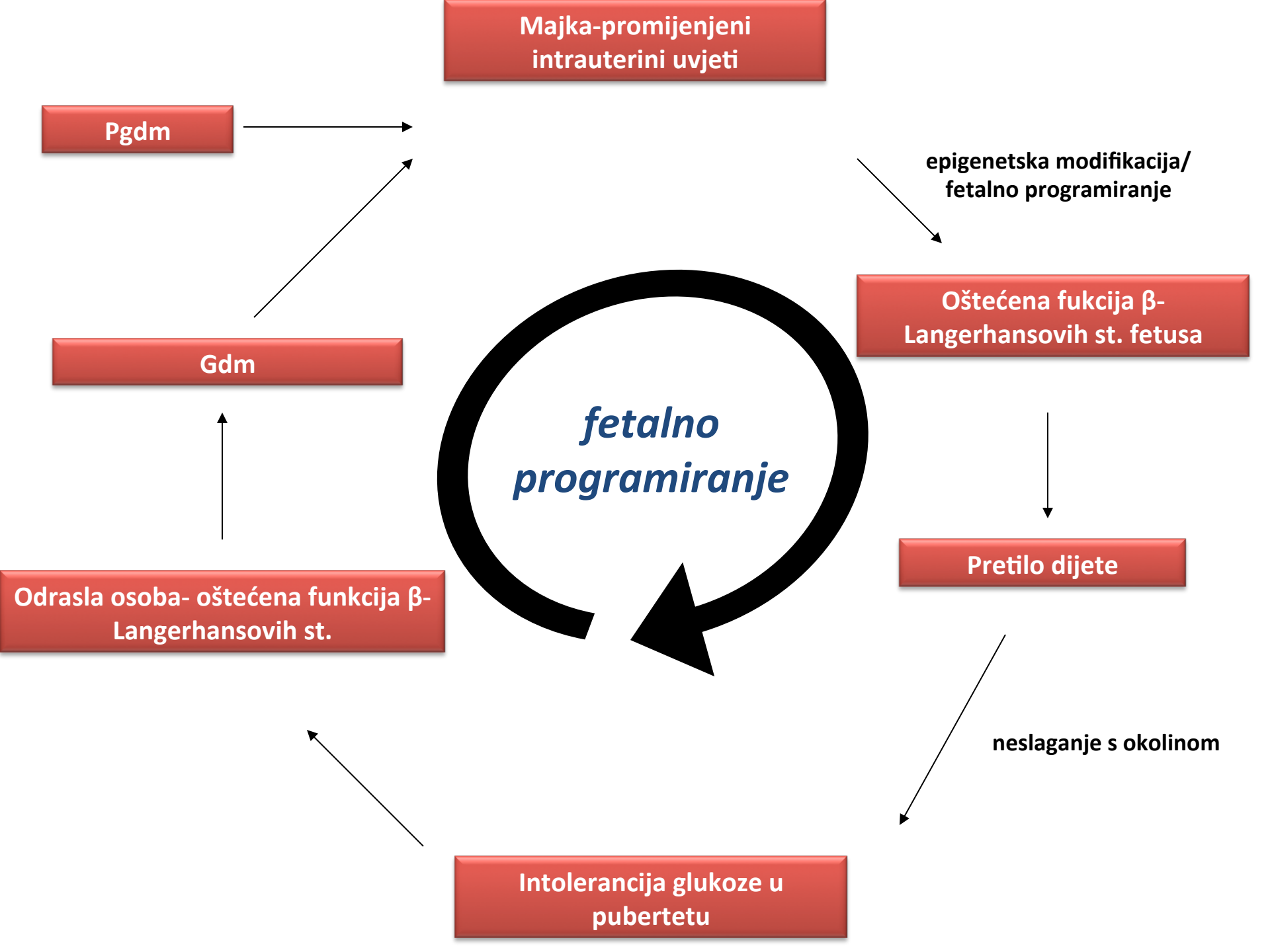
→ glikozurija na prvoj kontroli u trdnoći

→ metabolički sindrom, PCOS, liječenje glukokortikoidima, hipertenzija

Solomon CG, Willett WC, Carey VJ, et al. A prospective study of pregravid determinants of gestational diabetes mellitus. JAMA 1997; 278:1078.

1. **MAKROSOMIJA /LGA**)
2. **POLIHIDRAMNIJ**
3. **PREEKLAMPSIJA**
4. **FETALNA ORGANOMEGALIJA** (hepatomegalija, kardiomegalija)
5. **MATERNALNA/FETALNA POROĐAJNA TRAUMA** (operativno dovršenje trudnoće, shoulder distocija, oštećenja brahijalnog pleksusa, fraktura ključne kosti, razdori porođajnog kanala)
6. **OPERATIVNO DOVRŠENJE POROĐAJA**
7. **PERINATALNI MORTALITET**
8. **INTRAUTERINA SMRT**
9. **NEONATALNI MORBIDITET** (hipoglikemija, hiperbilirubinemija, hipokalcemija, eritremija, RDS)
10. **DUGOROČNI MORBIDITET (pretilost, IGT, metabolički sindrom kod potomstva; DM-II**, ateroskleroza, glomerulopatija, patološka retinalna angiogeneza kod majke)

“continuous relationship between glucose concentration and fetal growth/adverse fetal outcome”


Majka-promijenjeni intrauterini uvjeti
Pgdm
epigenetska modifikacija/ fetalno programiranje
Oštećena fukcija β-Langerhansovih st. fetusa
Gdm
fetalno programiranje
Pretilo dijete
Odrasla osoba- oštećena funkcija β-Langerhansovih st.
neslaganje s okolinom
Intolerancija glukoze u pubertetu

FETALNA OSNOVA BOLESTI

Fetal programming/imprinting

1. Kardiovaskularne bolesti
2. Kronične bubrežne bolesti
3. Tip 2 šećerne bolesti
4. Dislipidemija
5. Metabolički sindrom
6. Respiratorne bolesti
7. Imunološki poremećaji
8. Koagulacijski sustav
9. Zloćudne bolesti
10. Psihijatrijski poremećaji

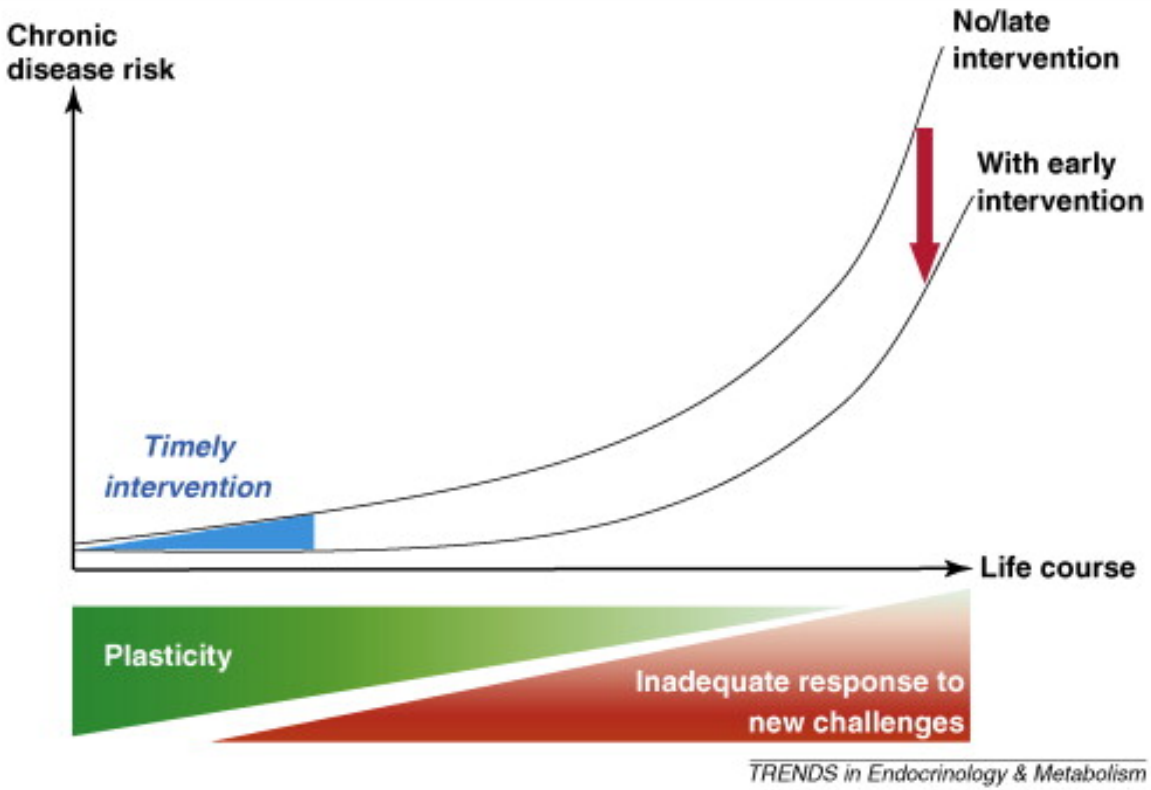
***"...programmed during the early stages of fetal development and are manifested at a far later stage**, when there is an added impact of lifestyle and other conventional acquired environmental risk factors that interact with the genetic factors..."*

KNOW WHAT, NOW WHAT??

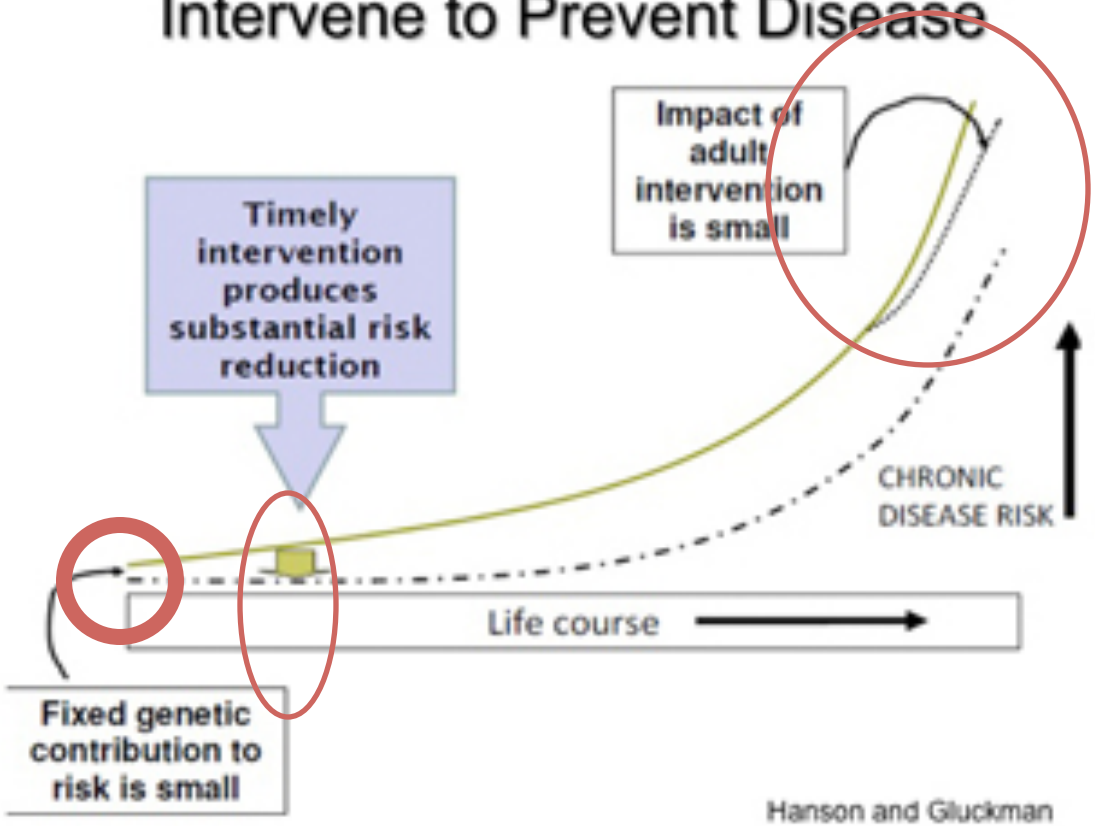
1. **Prijekoncepcijska obrada** (BMI, RR, guk, lipidogram...)

2. **Adekvatna prehrana**

3. **Rano prepoznavanje i liječenje komplikacija**


Chronic
disease risk
No/late
intervention
With early
intervention
Timely
intervention
Life course
Plasticity
Inadequate response to
new challenges
TRENDS in Endocrinology & Metabolism

Development is Most Important Time to Intervene to Prevent Disease



Hanson and Gluckman

OCTOBER 4, 2010

Environment Special:
The oceans—why 70% of our planet is in danger

The Facebook Movie:
The secret history of social networking

TIME

How the first nine months shape the rest of your life

The new science of fetal origins

BY ANNIE MURPHY PAUL

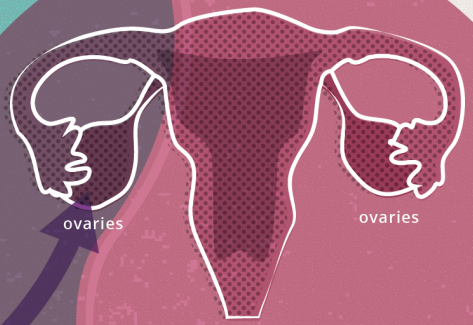
www.time.com

EXERCISE

HEALTHY DIET

LOW STRESS

Mother



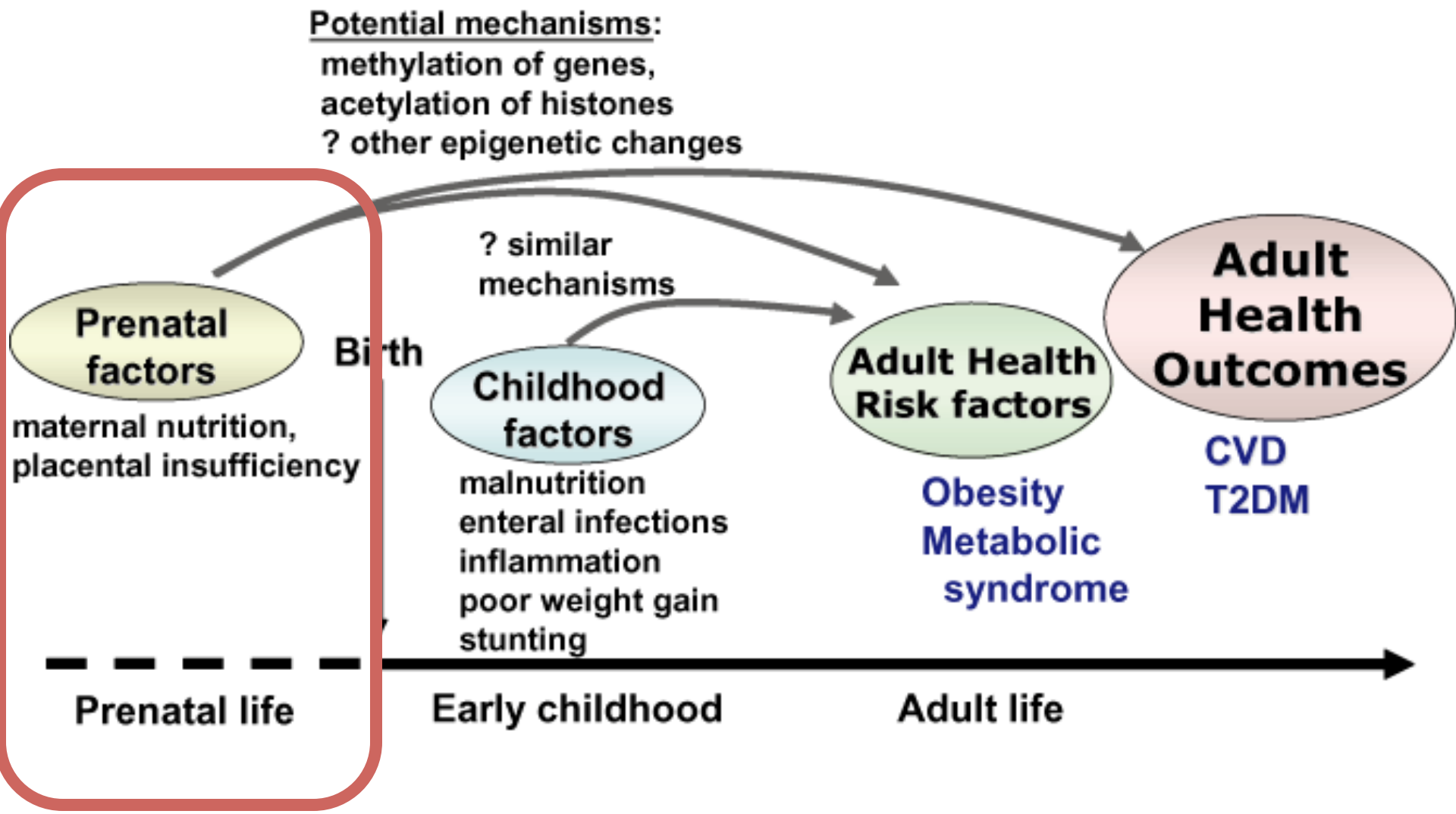
Future Grandchild

The eggs that may someday become the grandchild are developed inside the daughter while she is still in the womb within the mother. The eggs are nourished by the diet and environment of the mother.

Daughter

When you are pregnant, you are also pregnant with your grandchild.

betterthefuture.org


Potential mechanisms:
methylation of genes,
acetylation of histones
? other epigenetic changes
? similar
mechanisms
Prenatal
factors
maternal nutrition,
placental insufficiency
Birth
Childhood
factors
malnutrition
enteral infections
inflammation
poor weight gain
stunting
Adult Health
Risk factors
Obesity
Metabolic
syndrome
Adult
Health
Outcomes
CVD
T2DM
Prenatal life
Early childhood
Adult life