

Association pour l'Information et la Recherche
sur le maladies rénales Génétiques - Suisse
30 avril 2016

Projet de recherche: épigénétique et maladies rénales

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Pour l'équipe du Laboratoire DOHaD

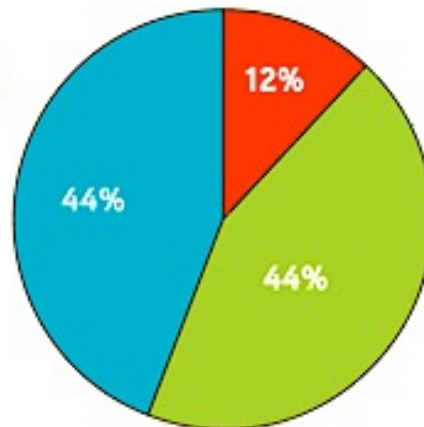
Service de pédiatrie, DMCP

CHUV & FBM/UNIL

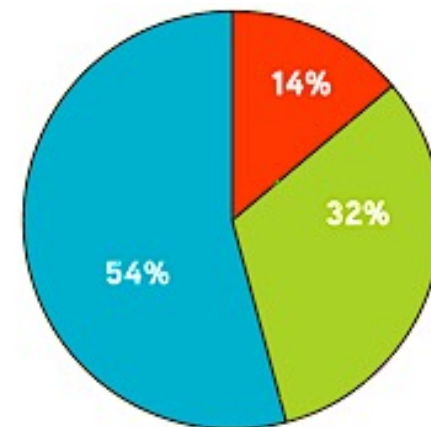
Lausanne

The growing burden of noncommunicable diseases (cardiovascular disease, obesity, diabetes,...)

Low- and
Middle-Income
Countries

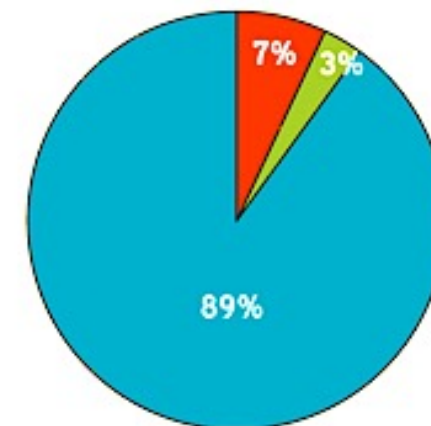
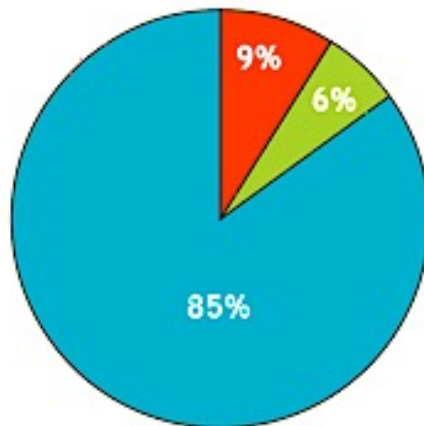


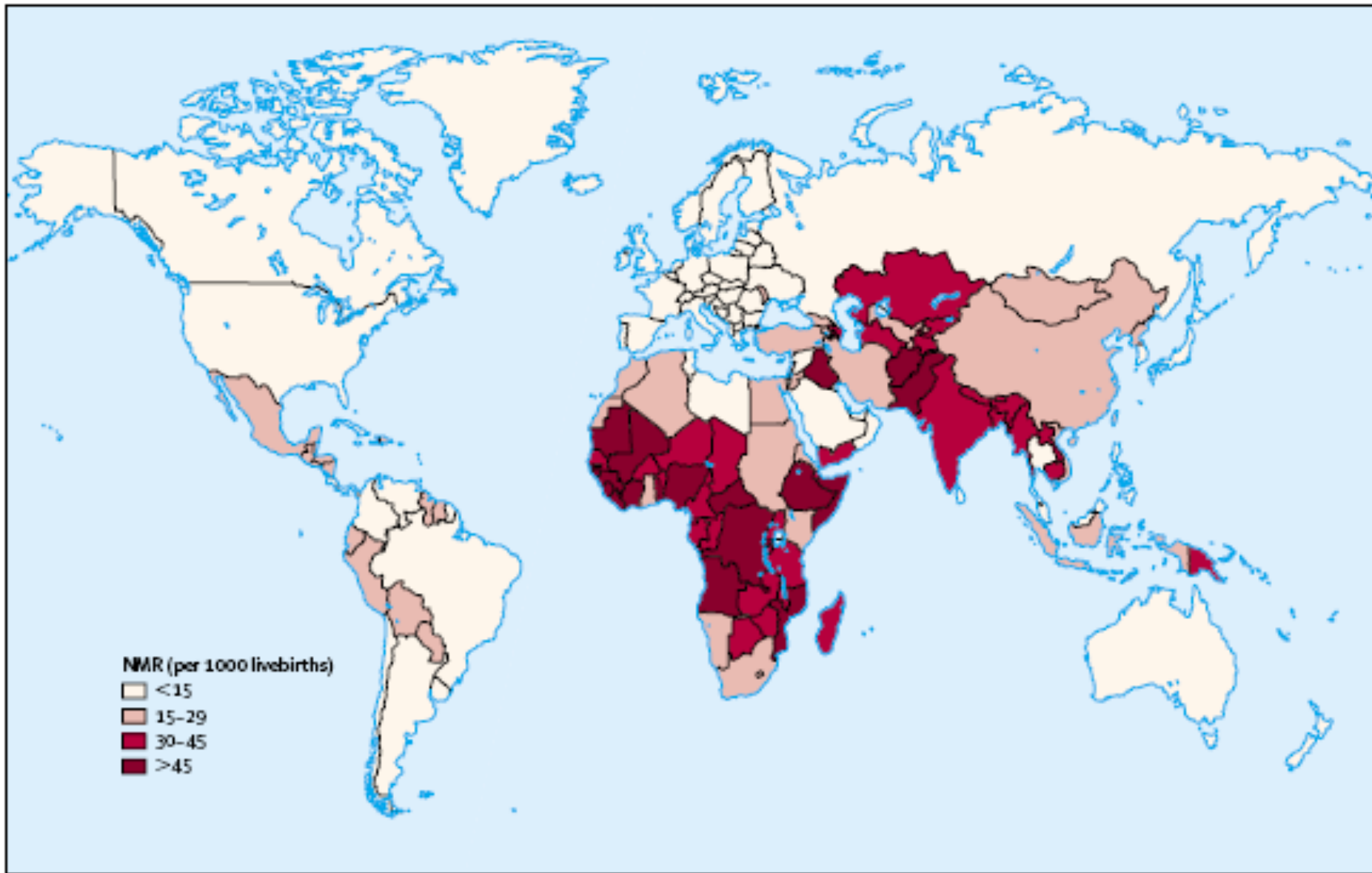
2002



2030

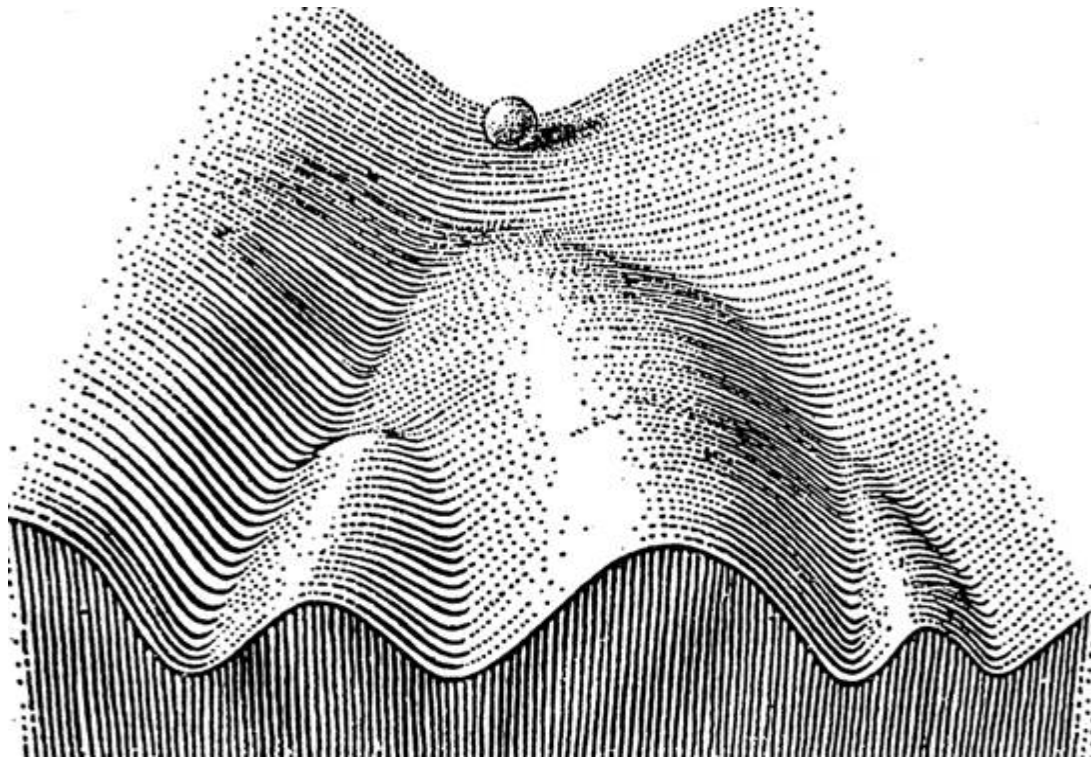
High-Income
Countries





Neonatal Mortality
70%: associated with low birth weight

Epigenetic Landscape and Biological Development: How the environment affects genes regulation and development



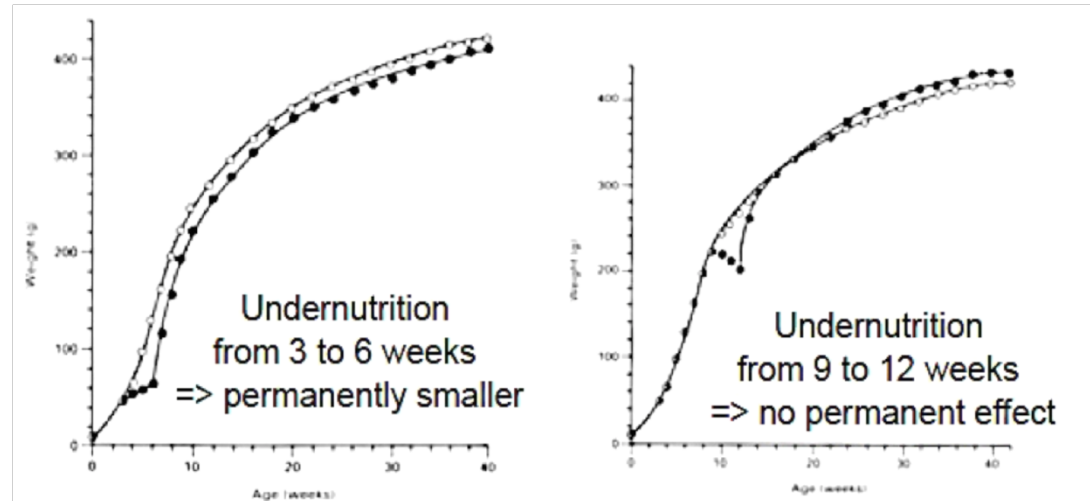
C Waddington

Developmental programming:

A process by which a stimulus applied during a critical period of sensitivity during development exerts not only short term, but lifelong effects

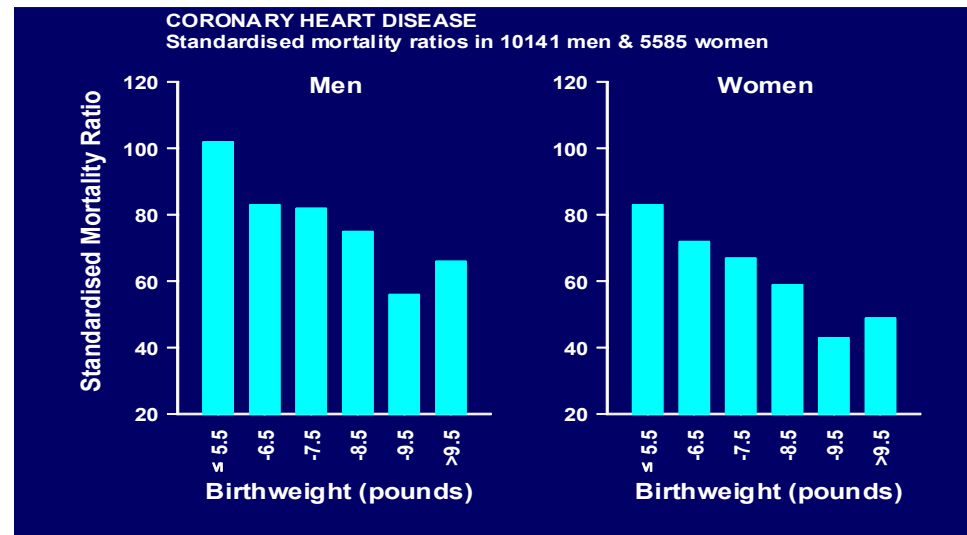
The effect of finite periods of undernutrition at different ages on the composition and the subsequent development of the rat

Widdowson & Mc Cance, Proc. Roy Soc London 1966

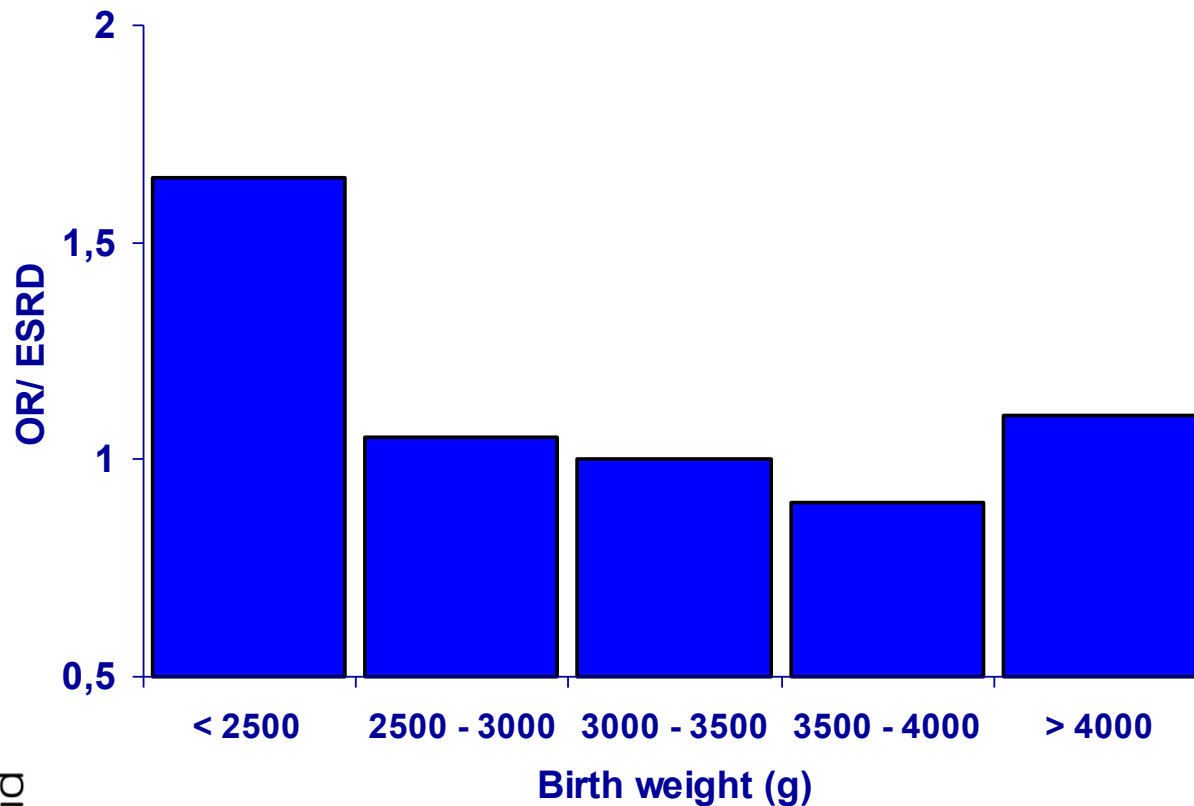


The effect of birth weight on the mortality ratio of coronary heart disease in human

Barker et al, Lancet 1989

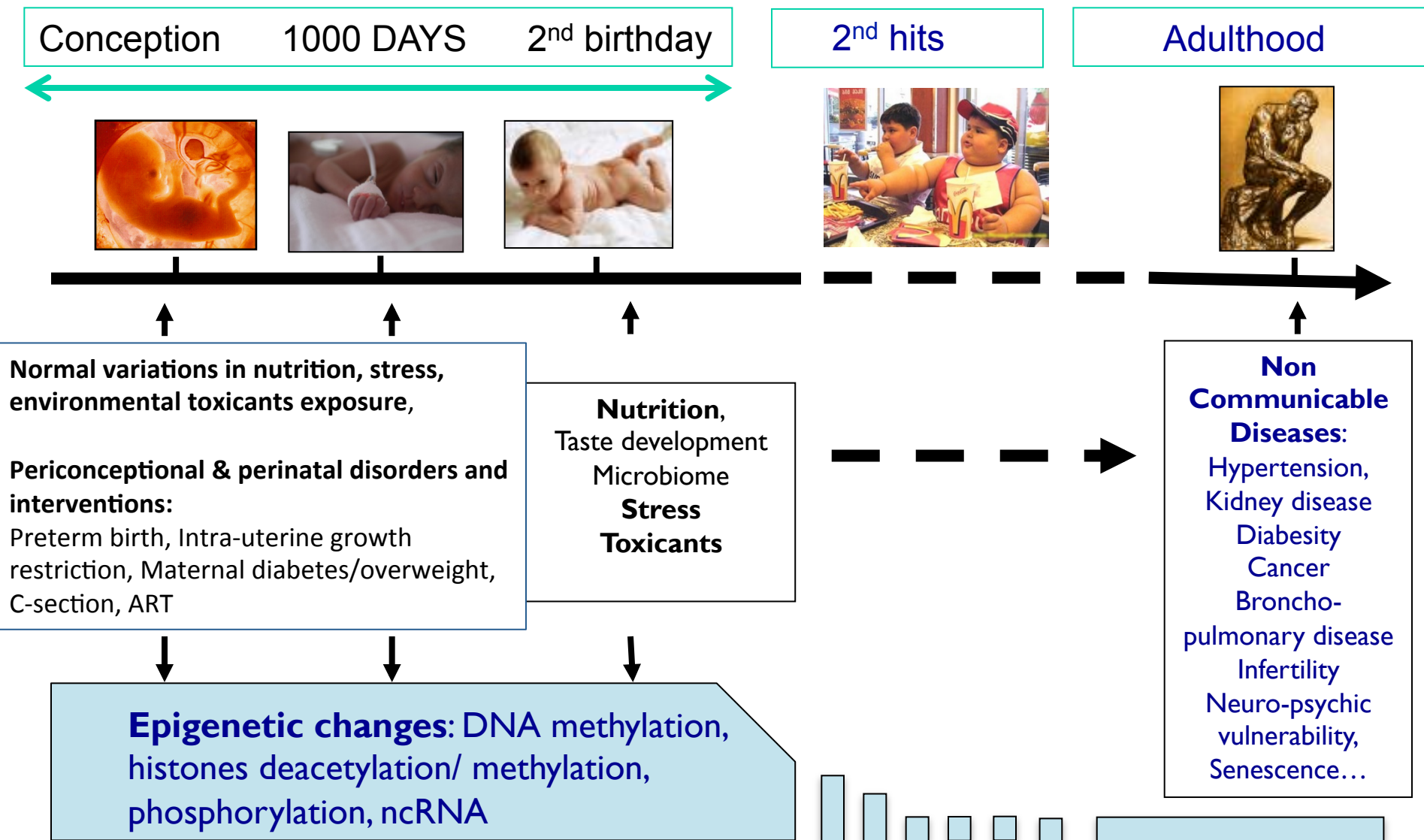


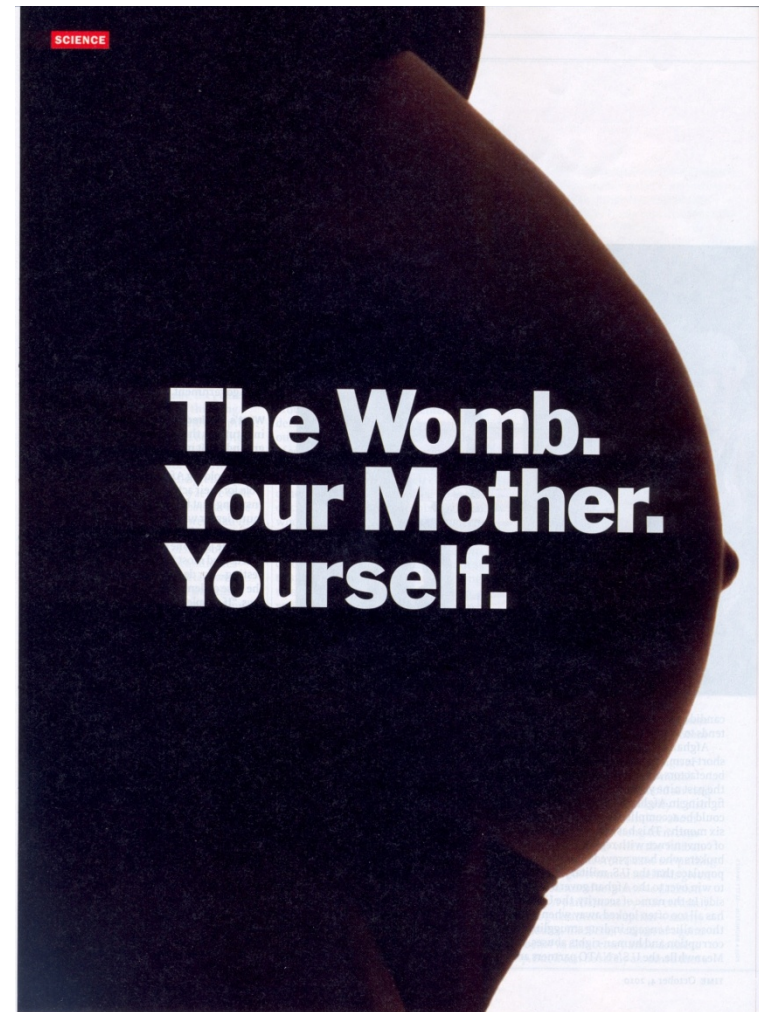
Insuffisance rénale terminale (IRT): corrélation au poids de naissance



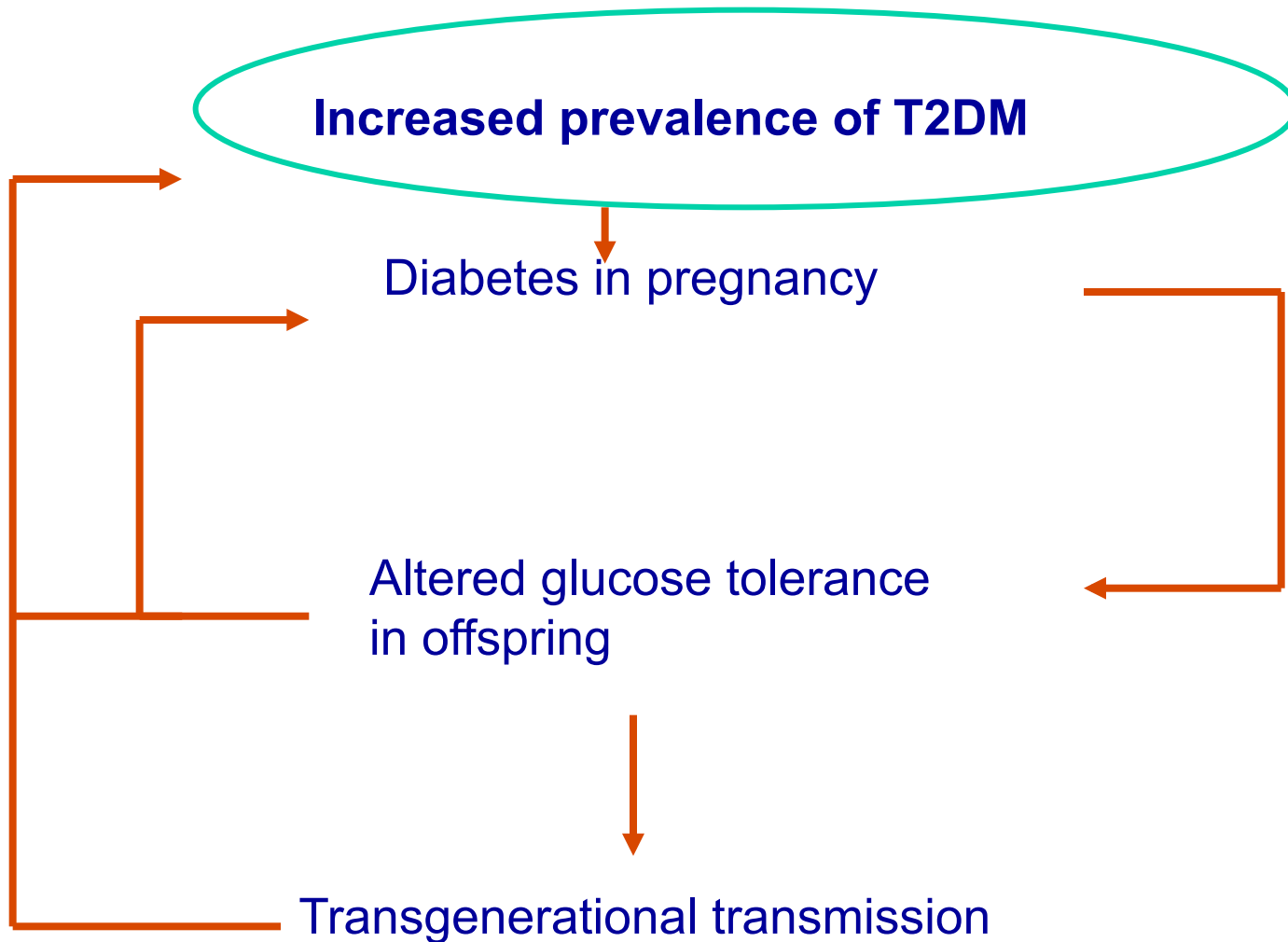
Case-control study
Patients = 1230
Controls = 2460

Developmental « programming » & The Developmental Origins of Health and Disease (DOHaD)





The amplifying effect of the cycle of reproduction: Worldwide Type 2 Diabetes Mellitus Epidemic

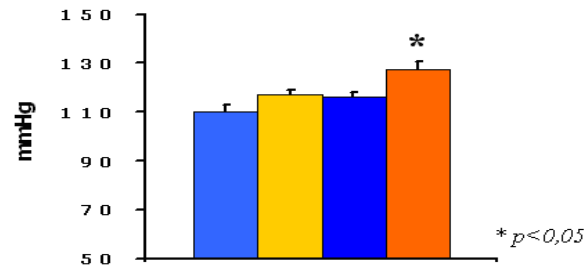


Kidney: Developmental Programming of Hypertension and of Renal Function: Low maternal protein diet, IUGR & effect of postnatal overfeeding (OF)

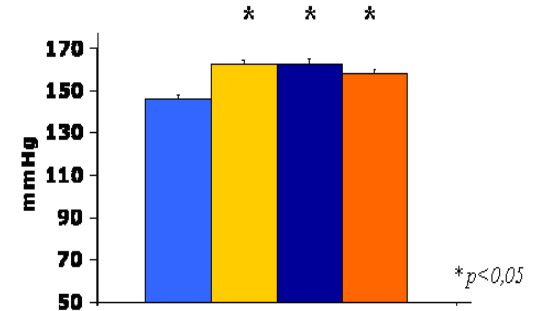


■ Controls
■ IUGR
■ OF
■ IUGR + OF

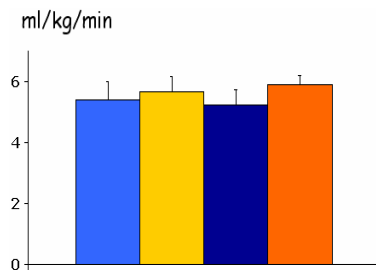
Systolic ABP 1 month



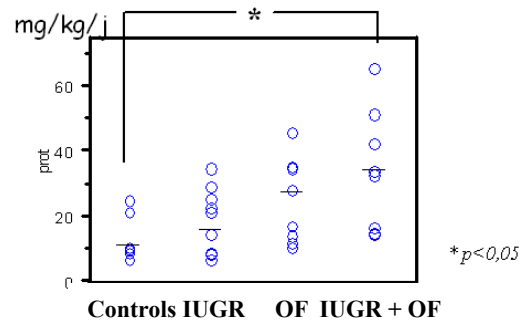
Systolic ABP 4 months



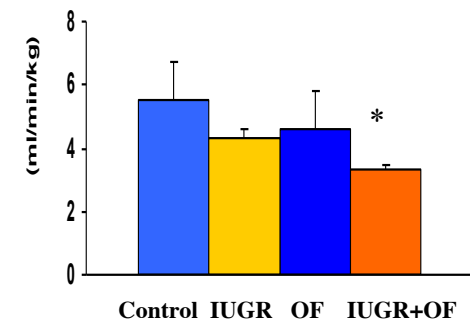
CCr 4 months



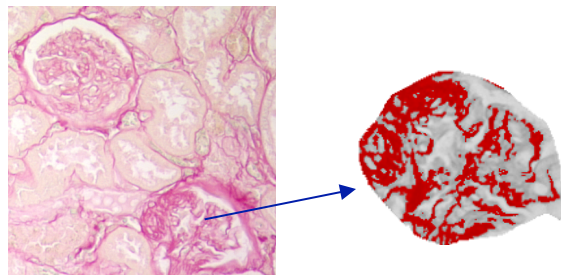
Proteinuria 4 months



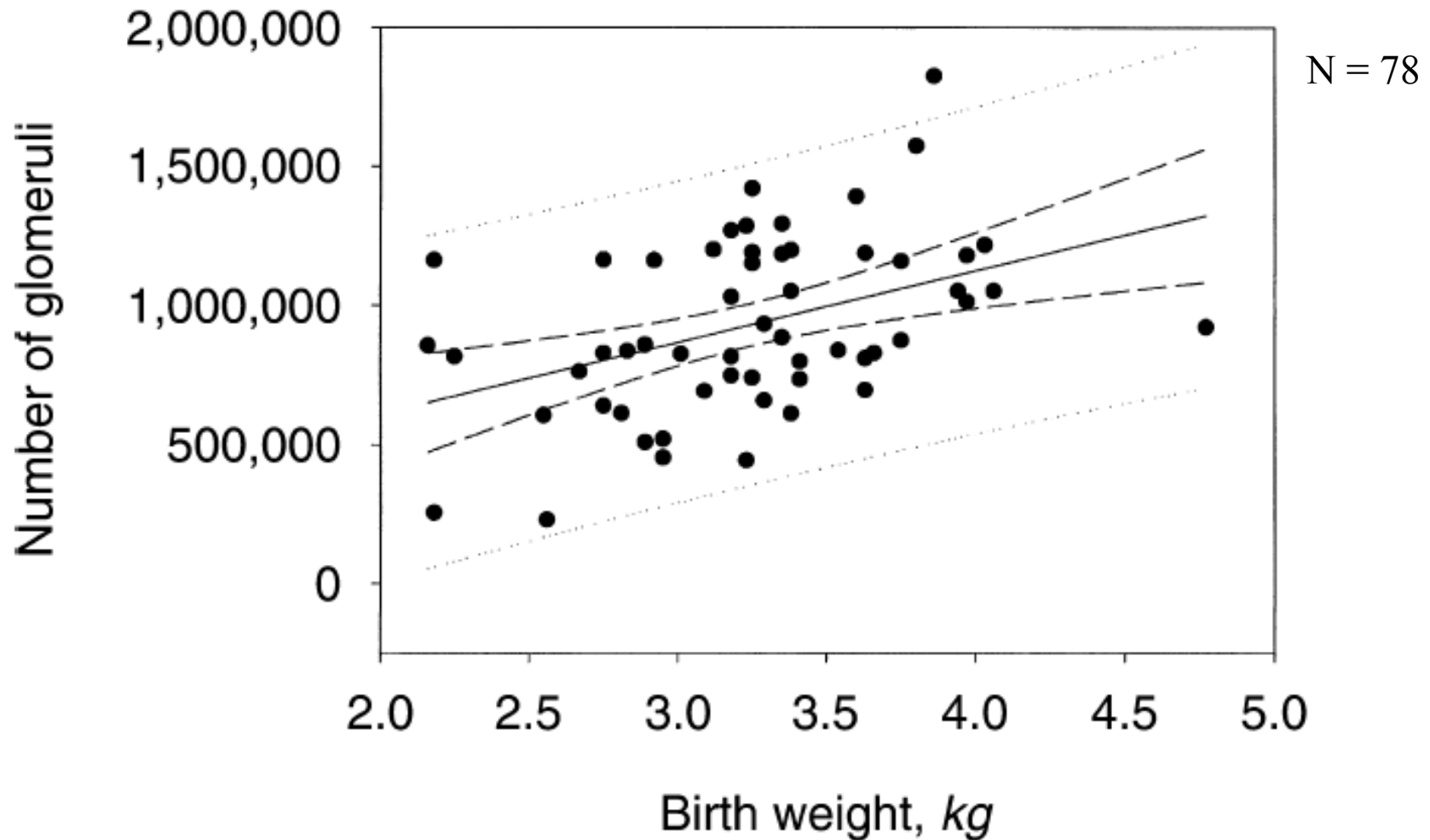
CCr 12 months (males)



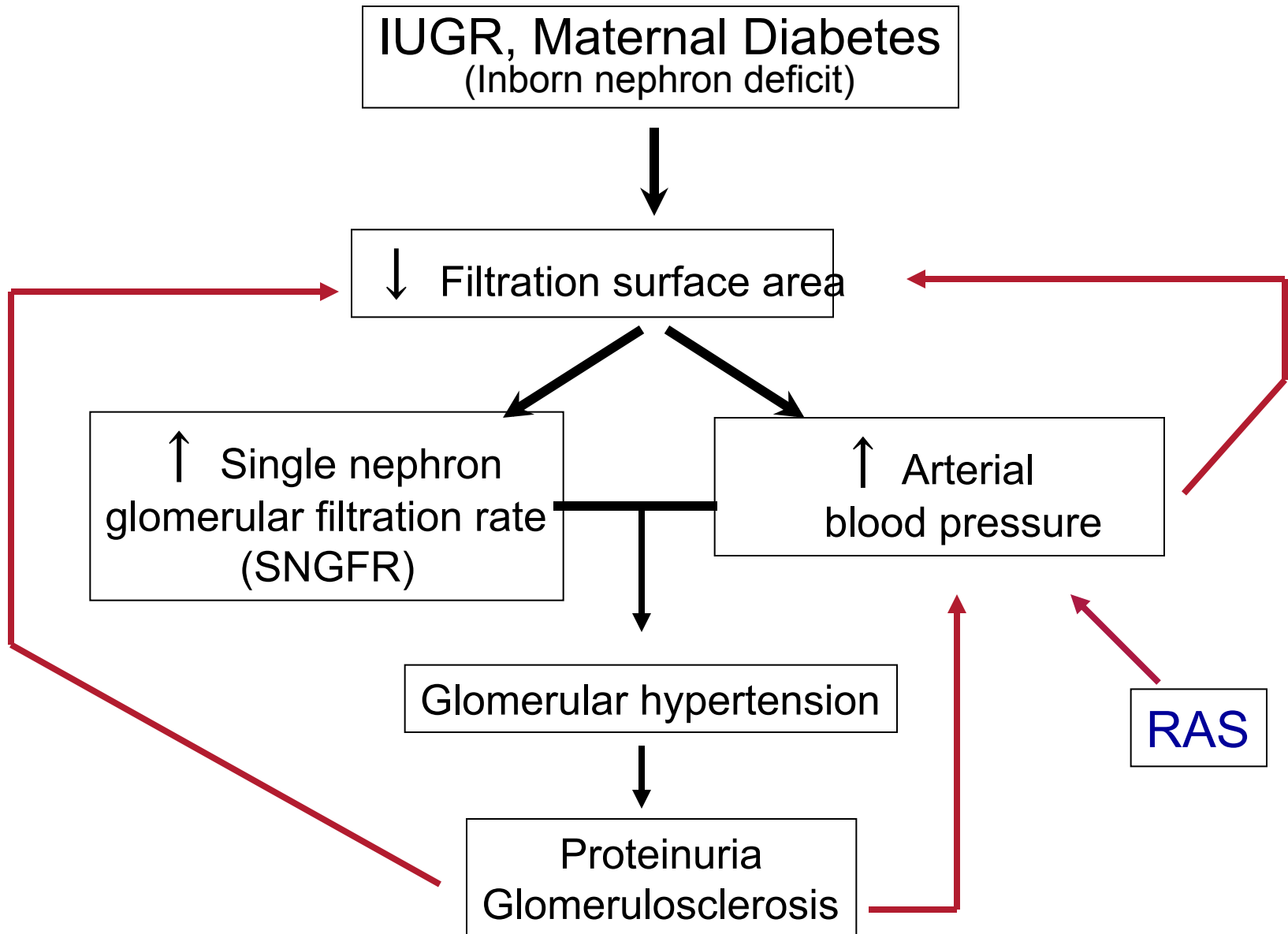
Glomerular sclerosis

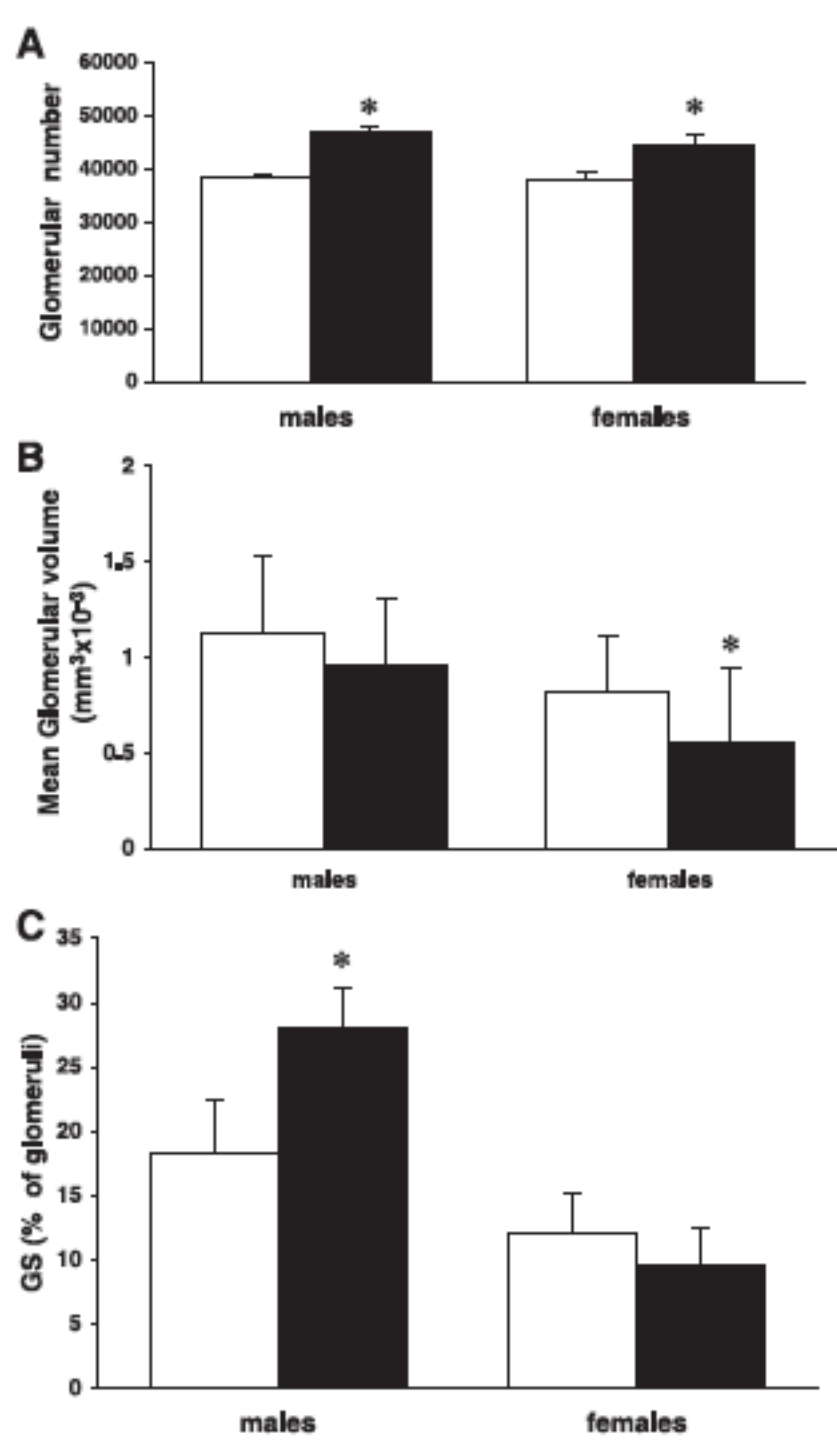


Nephron number endowment



Hypertension and Renal Damage: Effects of high protein intakes



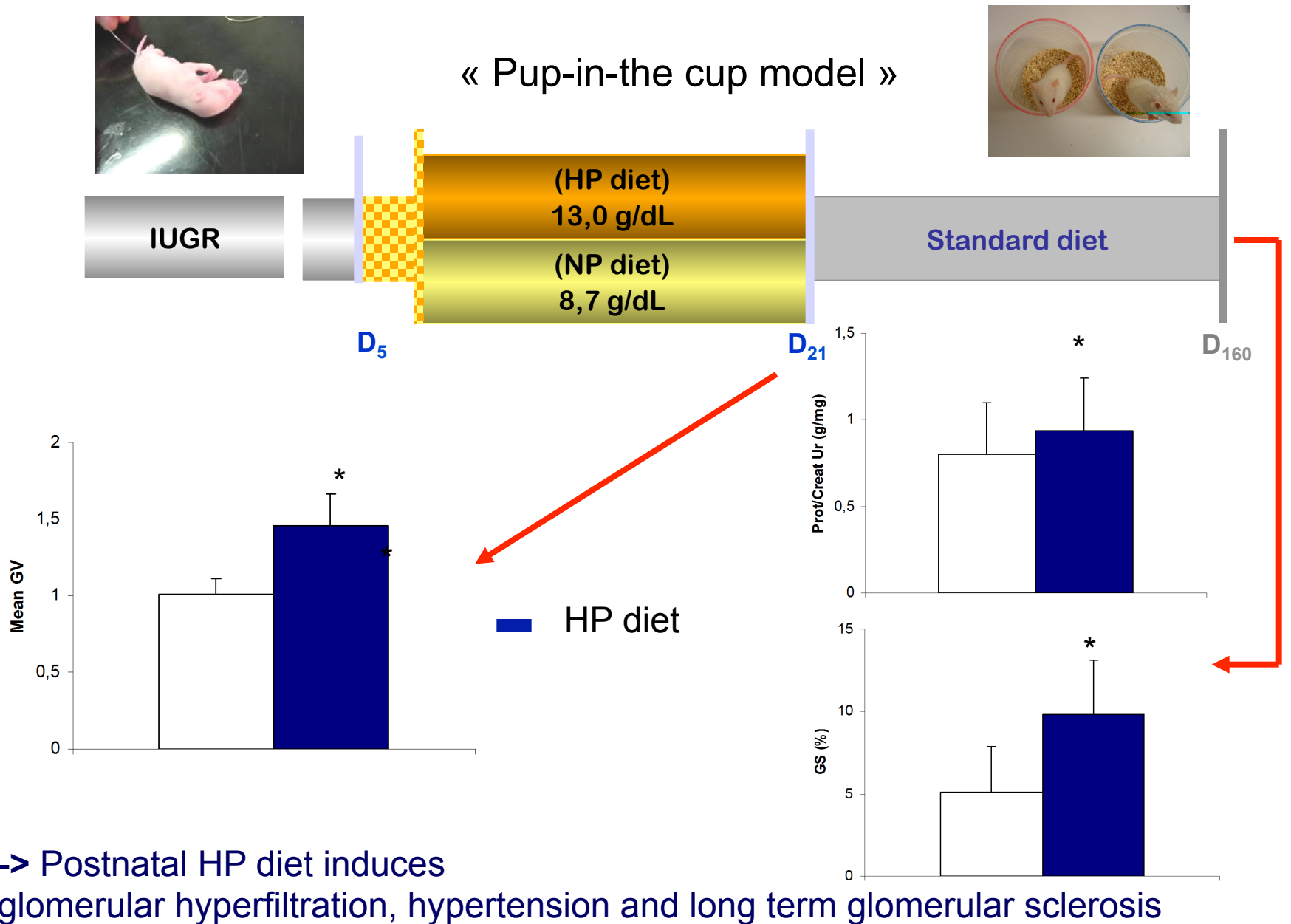


Is low nephron number preventable?

Effect of postnatal over (breast-)feeding
on normal rat pups kidneys:
Increases glomerular number
but reduces glomerular volume;
leads to glomerular sclerosis in males

Boubred et al Am J Physiol 2007

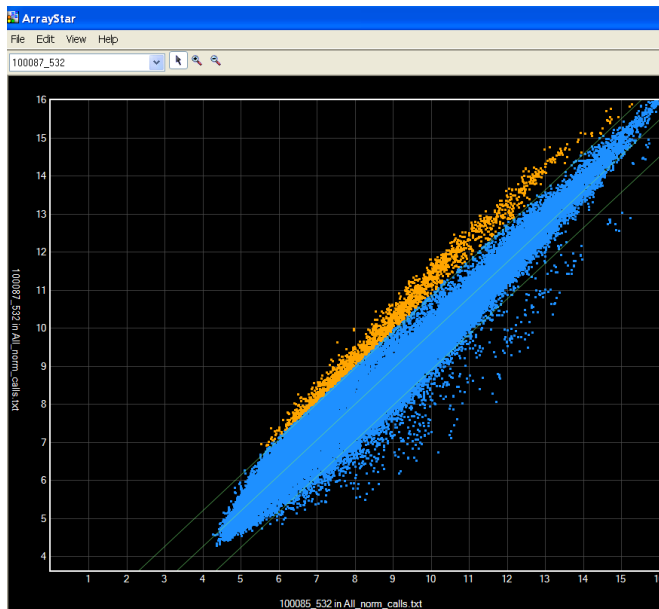
Kidney: Effect of Postnatal High Protein Diet in IUGR Rat Pups



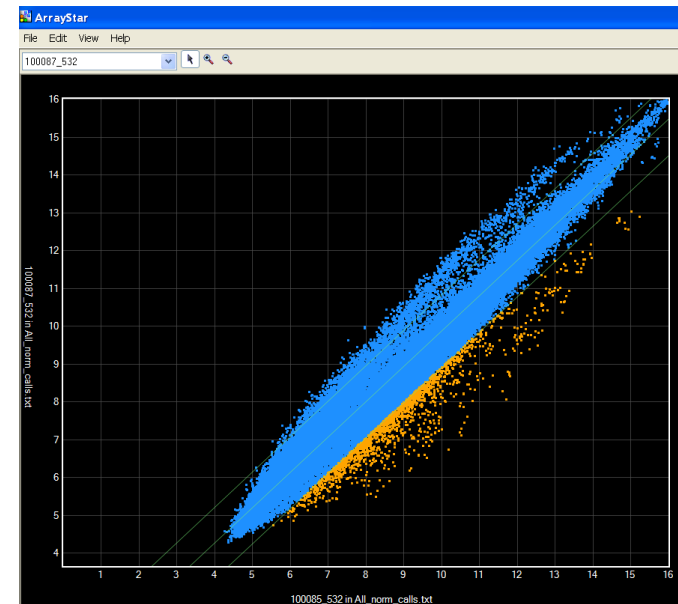
Intrauterine growth restricted (IUGR) neonatal rats: transcriptome analysis

IUGR vs control rats

➤ 1800 transcripts altered over 2 X



➤ 760 up-regulated



➤ 1040 down-regulated

IUGR kidneys

IUGR-gene expression profiles: Kidney

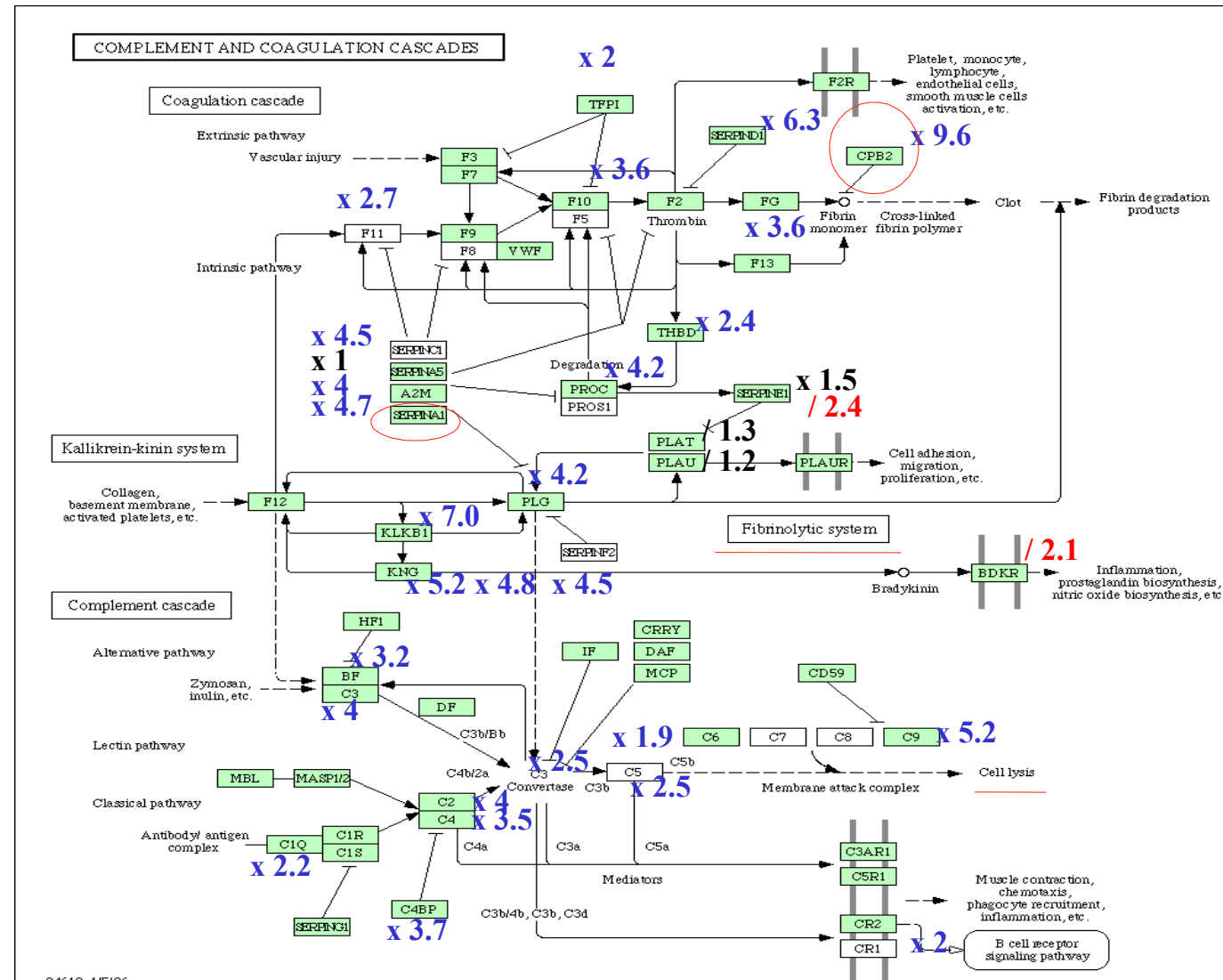
Massive alteration of coagulation genes:

- ## 1: Pro-thrombotic event:

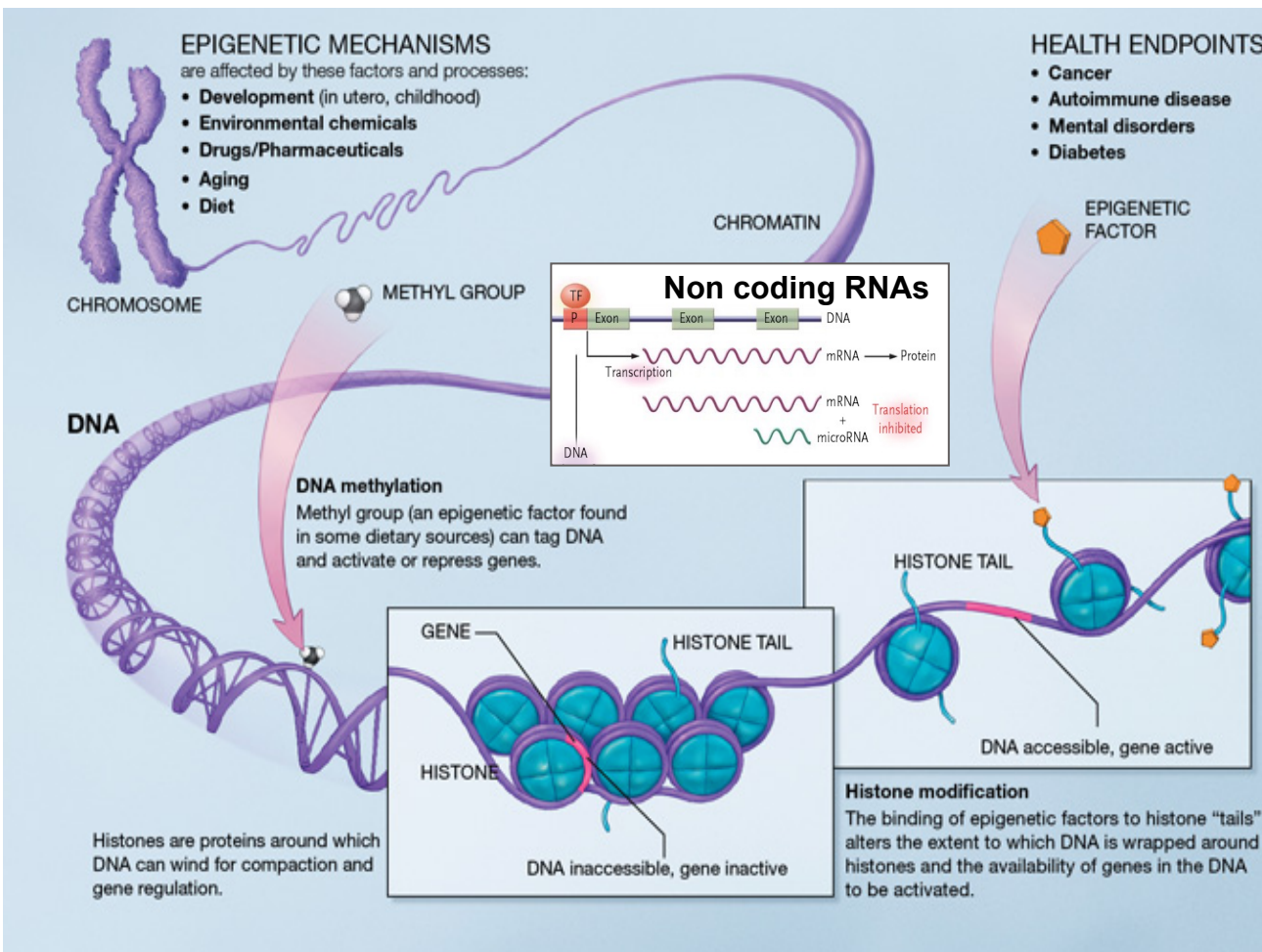
- CPB2
- SERPINA1

- 2: inflammatory process:
- strong activation of kinin kallikrein system

- ### 3: Cell lysis:
- Strong activation of Complement cascade



Epigenetics: a long lasting, heritable molecular translation of early genome-environment interactions, in the absence of gene sequence alteration



Royal gelly fed bees

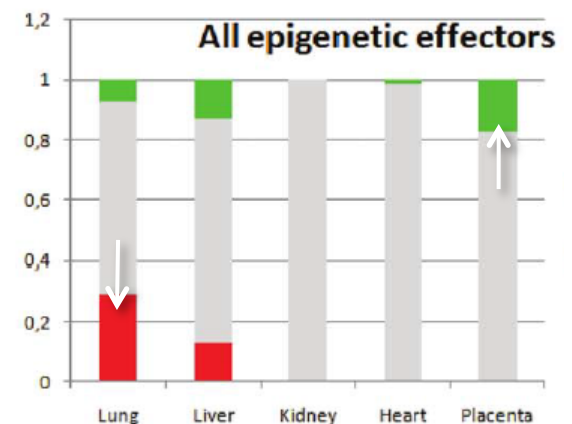
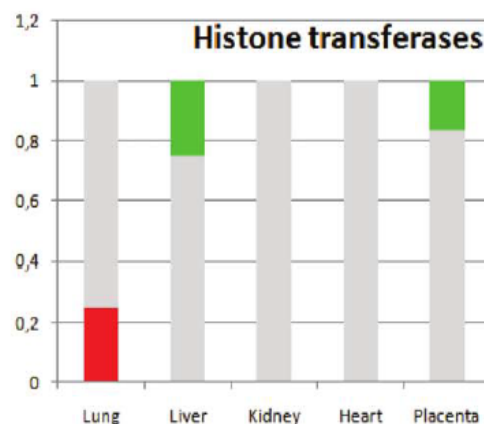
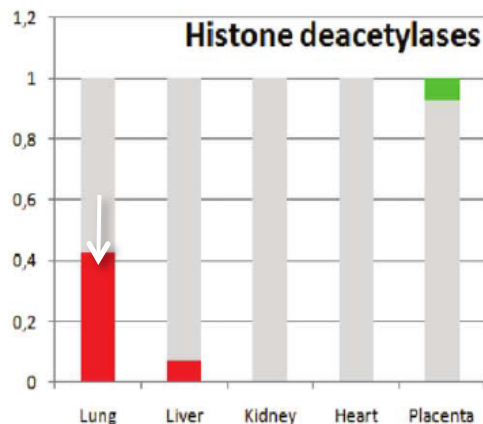
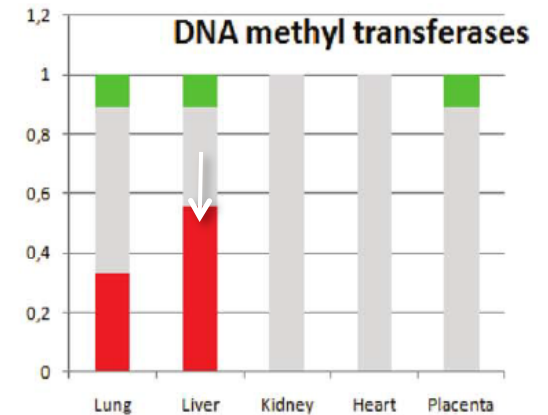
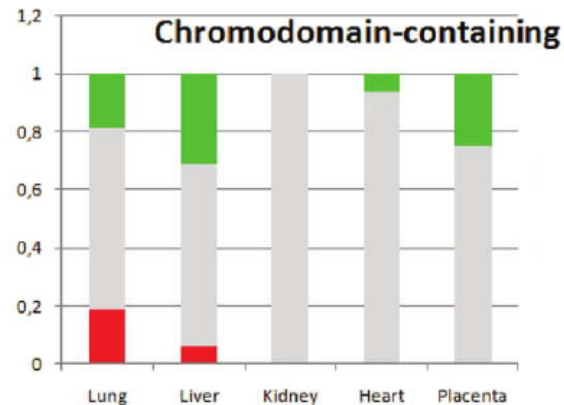
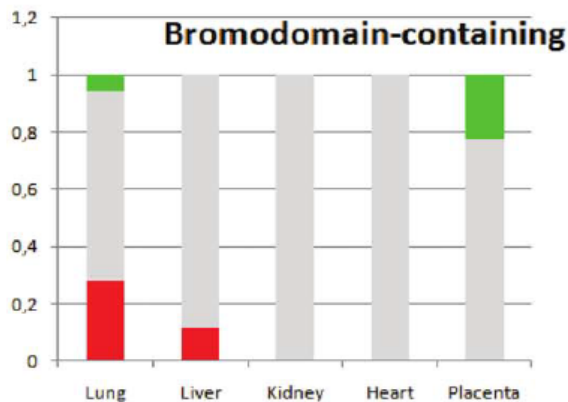


become bigger,
live longer
and are fertile.

Epigenetic effectors: IUGR rats

Analysis of specific groups of genes : epigenetic regulators

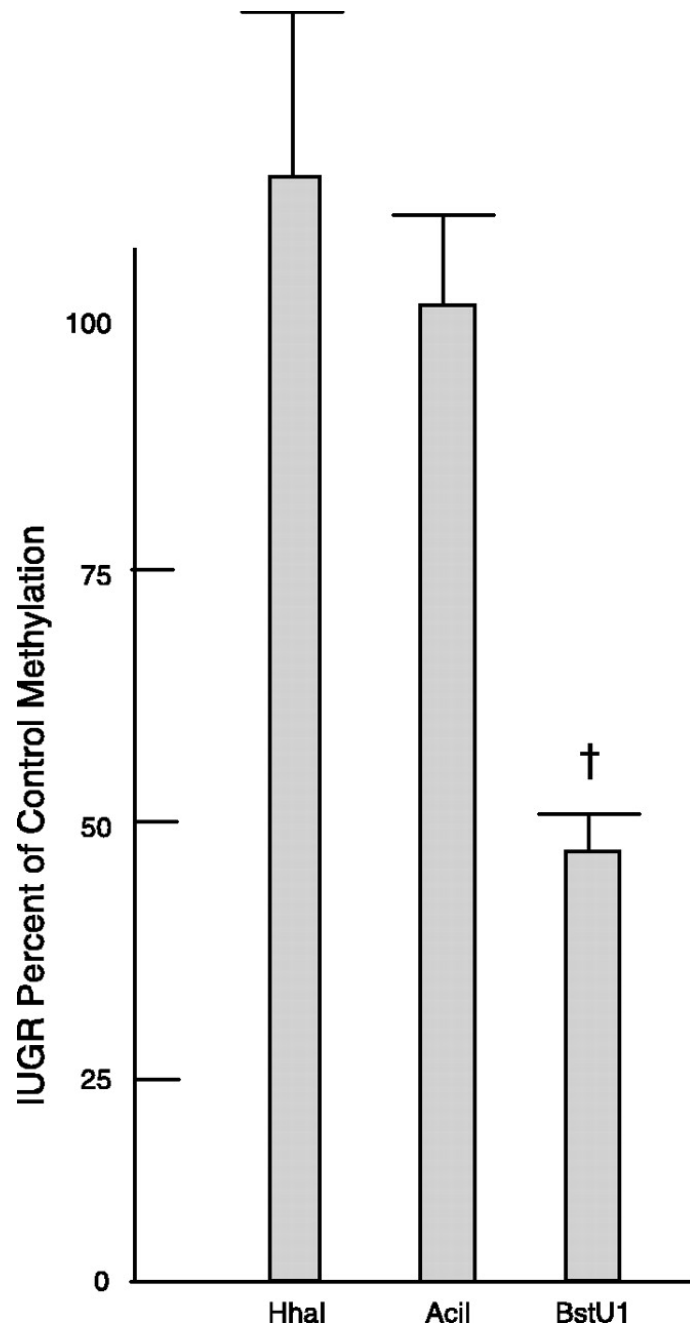
Buffat et al, PLoS Genet 2011



■ Up-regulated

■ Unchanged

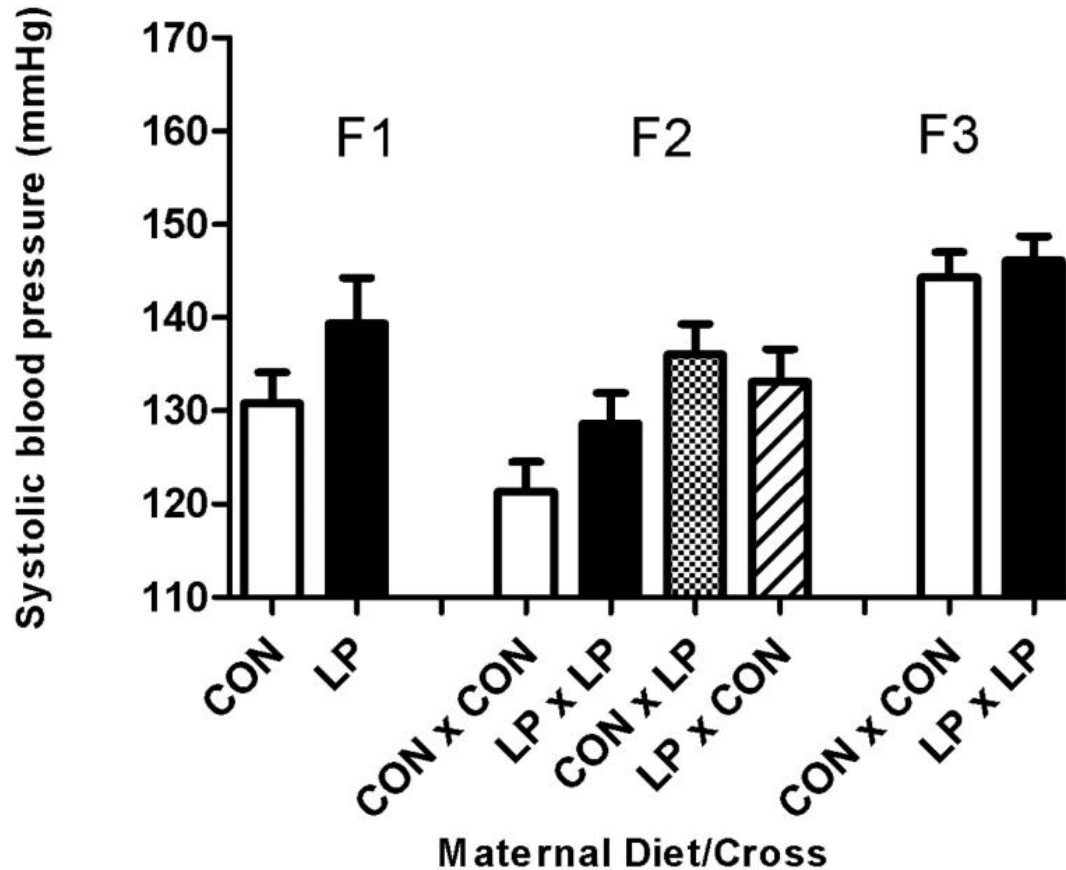
■ Down-regulated



Apoptosis and p53 gene methylation In IUGR rat kidney

Pham et al, Am J Physiol 2003;285:R962

Intergenerational programming of impaired nephrogenesis



Environnement précoce

Exposition à des stress
nutritionnels, toxiques, psychosociaux,...

impact

Épigénome

Marques et machinerie
épigénétiques
(archive des impacts
environnementaux)

Flexible, dynamique
tout au long de la vie

Activation
ou
inhibition

Génome

Séquence ADN
Gènes
Immuable
(sauf cancer)

Expression
des gènes

Protéines

Structure et
fonctions
des organes
Altérations qui
peuvent
être irréversibles

Phénotype

Sensibilité à des
comportements
et à des
environnements

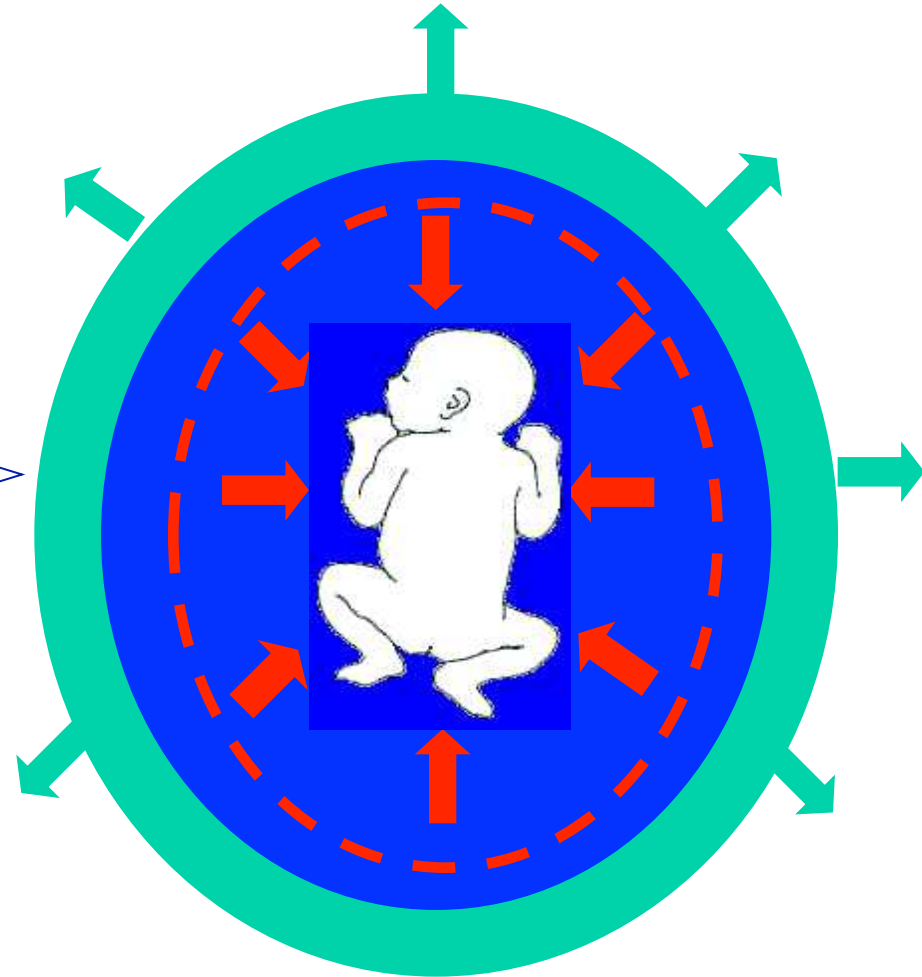
Developmental programming and plasticity: Early adaptive predictive responses and later mismatch

Environment: **-**



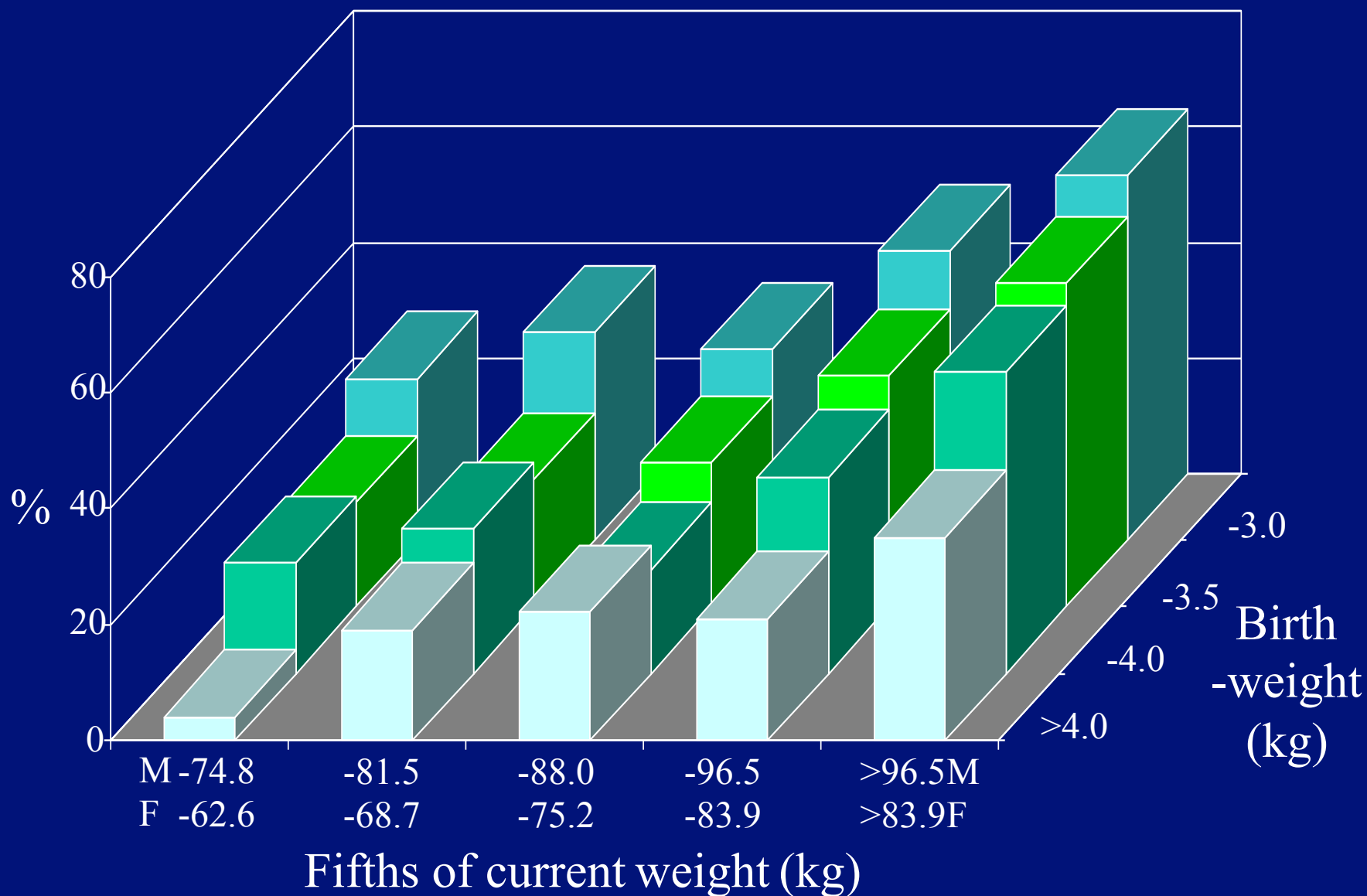
**Fetal life and
early infancy**

Environment: **+**



Later development

Prevalence of hypertension



**Capital fonctionnel
d'un organe**

Différents effets de
l'environnement
au cours
du développement
de l'organe

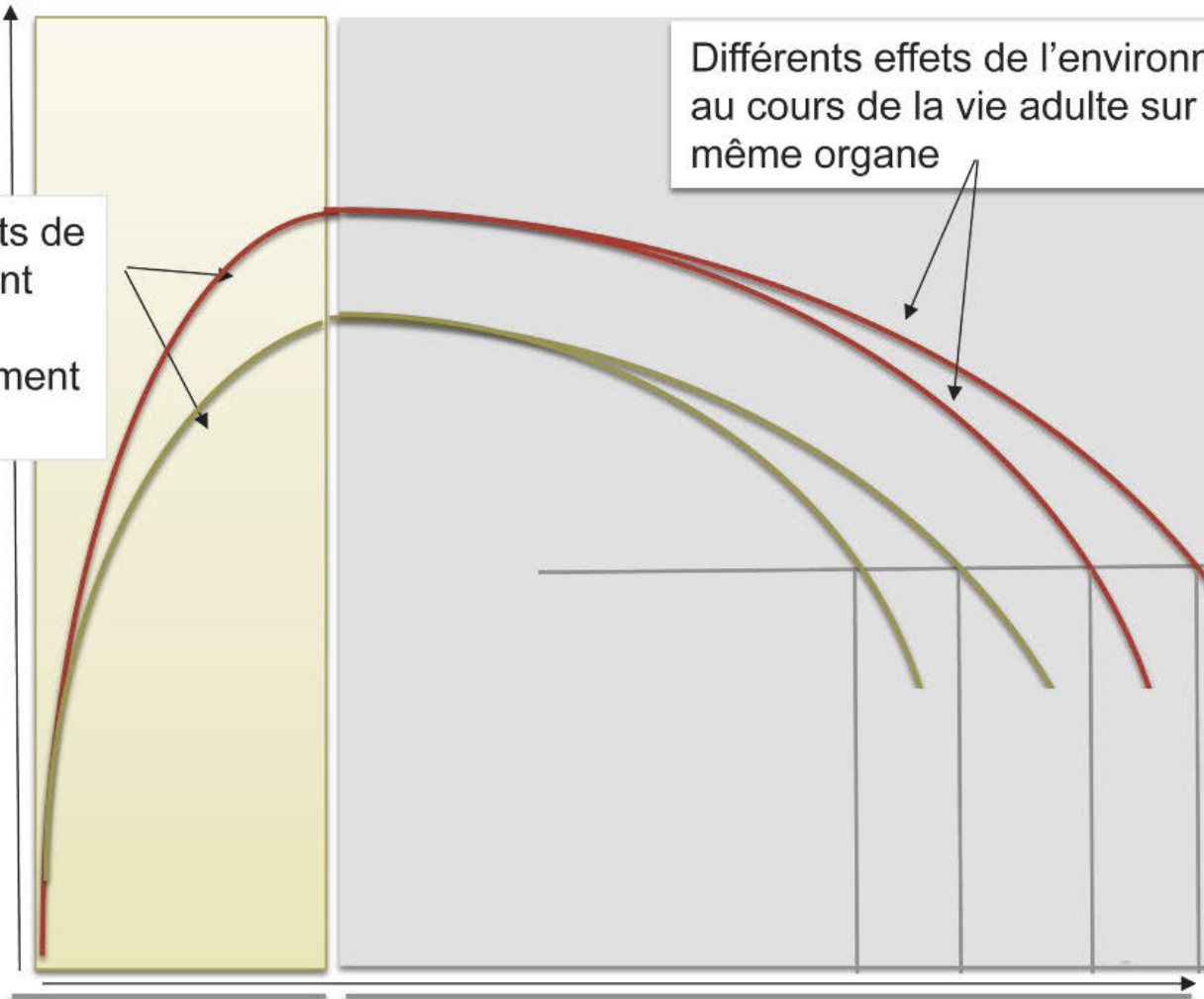
Différents effets de l'environnement
au cours de la vie adulte sur un
même organe

Niveau d'apparition
des symptômes de
la maladie

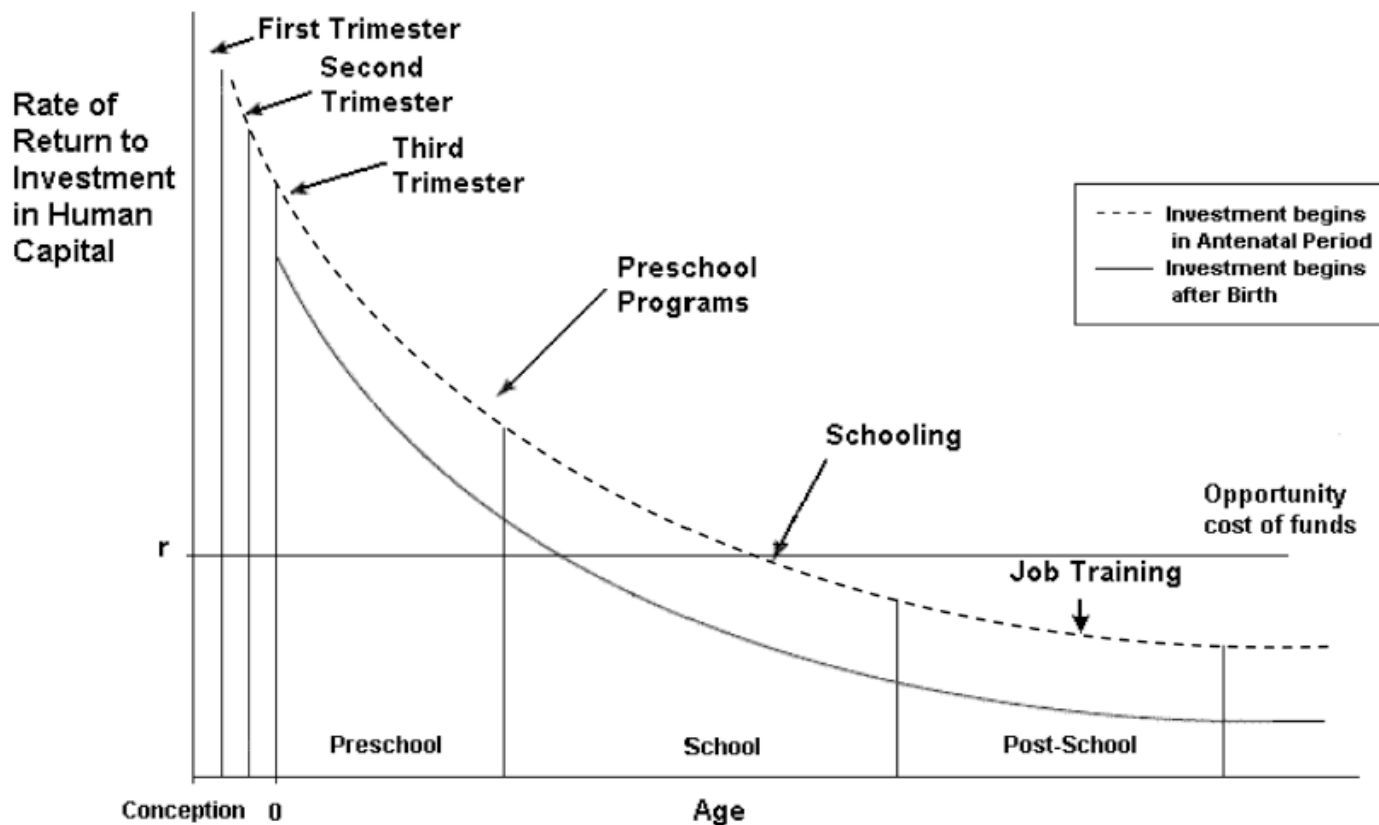
Période de
développement
de l'organe

Phase de déclin du capital
fonctionnel de l'organe

**Âge de
l'individu**



Rates of Return to Human Capital Investment Setting Investment to be Equal across all Ages



Rates of return to human capital investment setting investment to be equal across all ages

Source: Carneiro and Heckman, 2003.

Conclusions

- Le risque d'insuffisance rénale chronique à l'âge adulte a des origines précoces, au cours du développement, lié à l'exposition aux facteurs environnementaux affectant celui-ci (stress, nutrition, contaminants toxiques, mode de vie) et à la transmission intergénérationnelle de marques épigénétiques.
- Des programmes de recherche sont nécessaires pour identifier des biomarqueurs performants et repérer les sujets à risque, et des cibles thérapeutiques potentielles.
- Des stratégies de prévention précoce, orientées vers les mères, enfants, et futurs parents sont nécessaires pour interrompre l'incidence croissante de l'insuffisance rénale chronique et des maladies non transmissibles.

**1,000
DAYS**

"Improving nutrition for mothers and children is one of the most cost-effective and impactful tools we have for poverty alleviation and sustainable development."

— May, 2012

Learn More →

Leaders' Declaration

G7 Summit

7-8 June 2015



G7 GERMANY

2015 | Schloss Elmau

***« We affirm a life-long approach with
A focus on the nutrition of women
of reproductive age, pregnant women,
nursing mothers and children under five,
with particular attention to the first 1000
days from pregnancy to a child's second
birthday. »***