The Developmental Origins of Health and Disease (DOHaD)

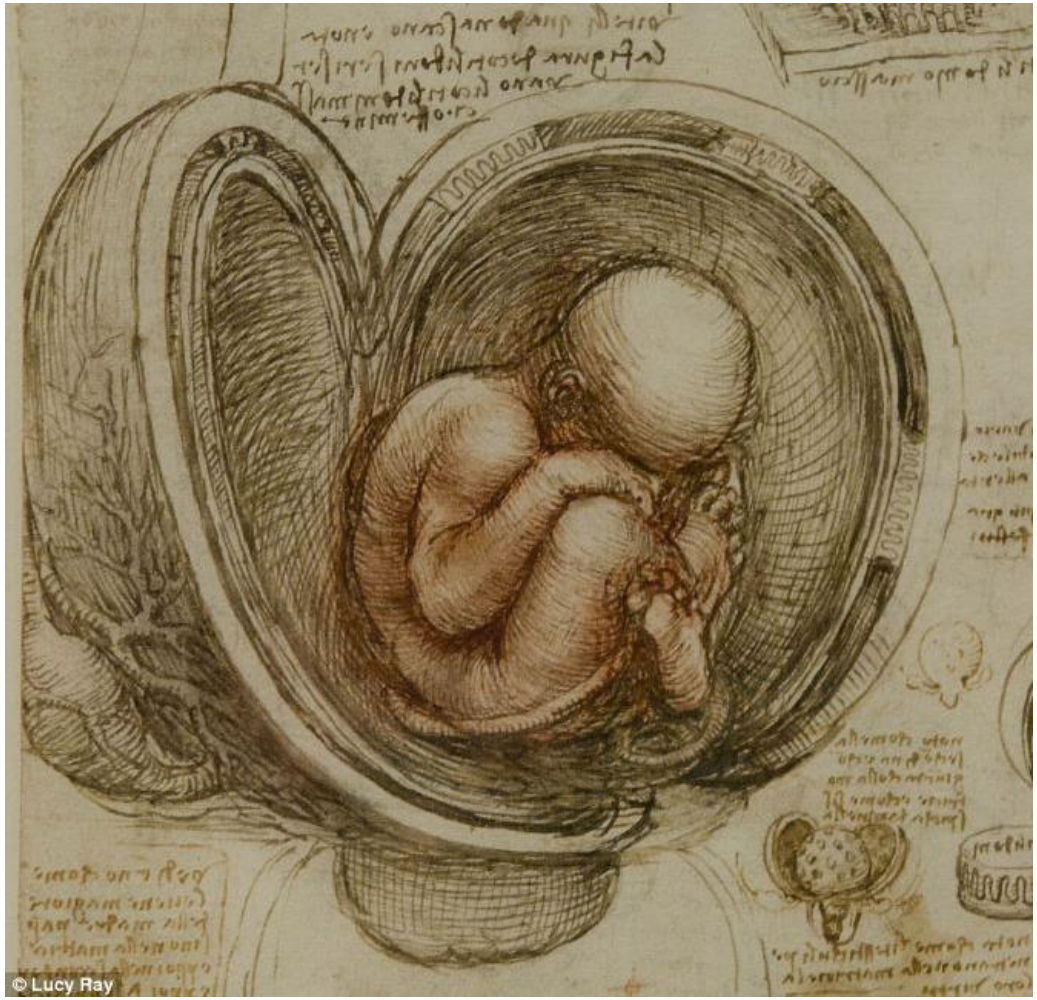
Maribel Casas

BRN Seminar - 27 Novembre 2018

ISGlobal
Institut de Salut Global Barcelona

Institució CERCA
Centres de Recerca de Catalunya

The origins of DOHaD...

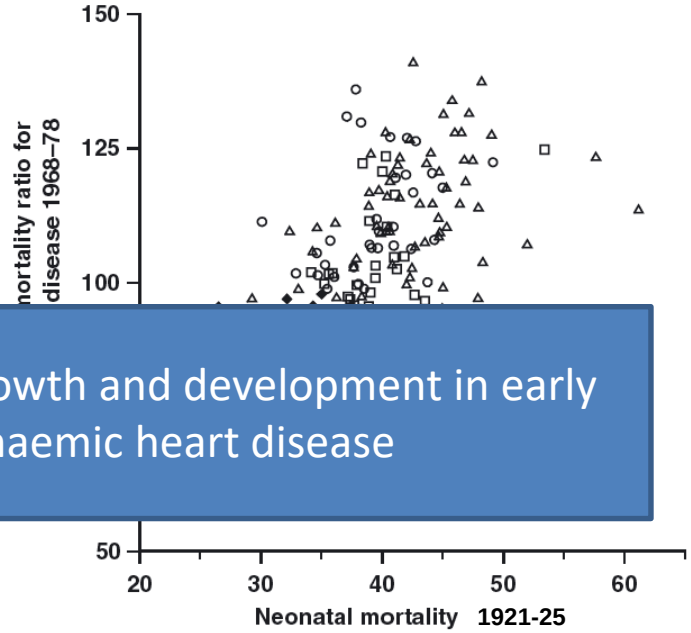


80's | Coronary Heart Disease Mortality

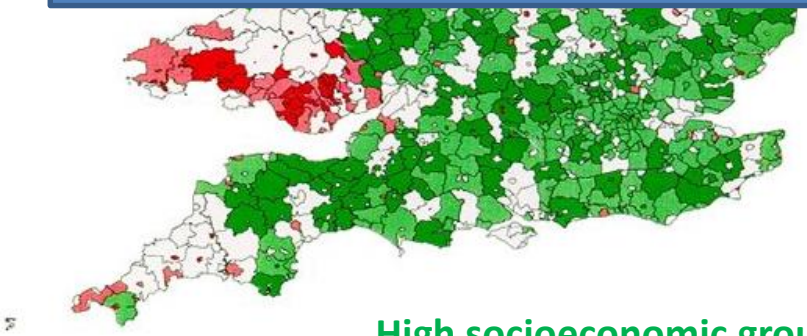
England and Wales 1968-1979 | Ecological study – population data

Most deprived areas

Less deprived areas



Environmental influences that impair growth and development in early life may be risk factors for ischaemic heart disease



High socioeconomic groups

Low socioeconomic groups

TABLE I—CORRELATION OF CAUSE OF DEATH (SMRS*) AT AGES 35–74 YEARS IN BOTH SEXES AND INFANT MORTALITY RATES

Cause of death	ICD no, 8th revision	Correlation coefficient
Ischaemic heart disease	410–414	0·73
Bronchitis	490–492	0·82
Stomach cancer	151	0·79
Rheumatic heart disease	393–398	0·72
Stroke	431–438	0·54
Lung cancer	162	0·46

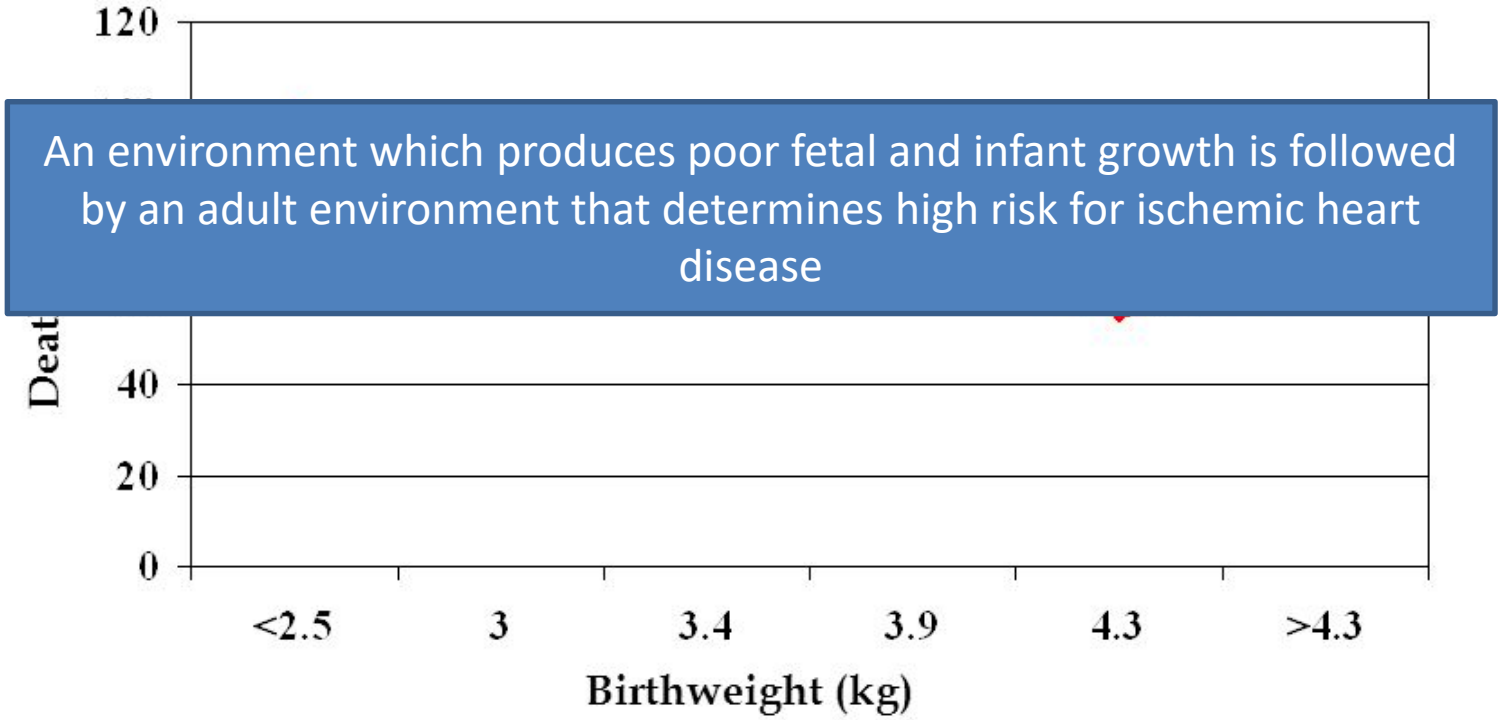
*Standardised mortality ratios.

Barker et al, Lancet 1986

80's | Coronary Heart Disease Mortality

England and Wales | Cohort study – individual data

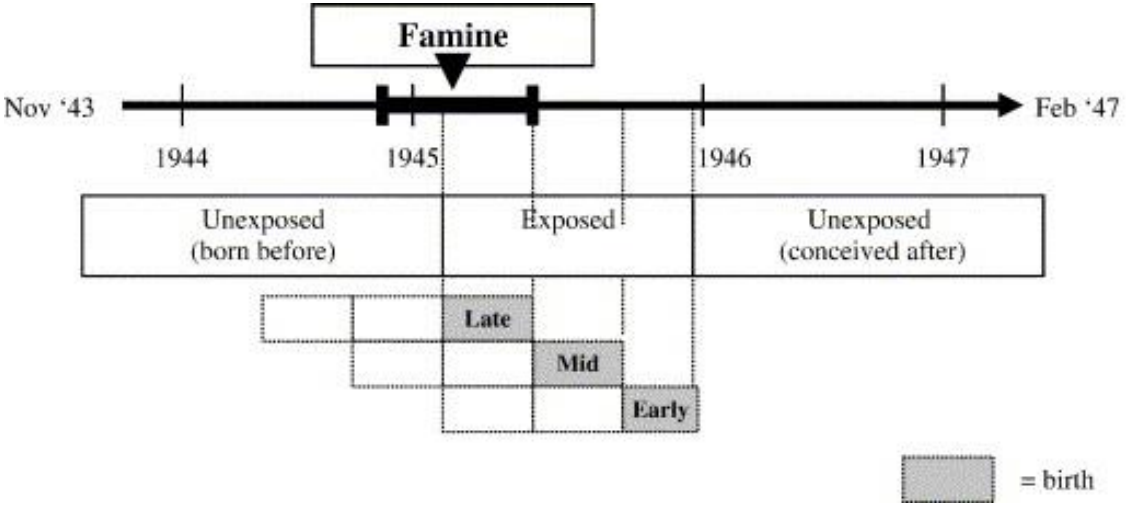
- 5654 men born during 1911-1930
- Information on birth weights and deaths from ischeamic heart disease

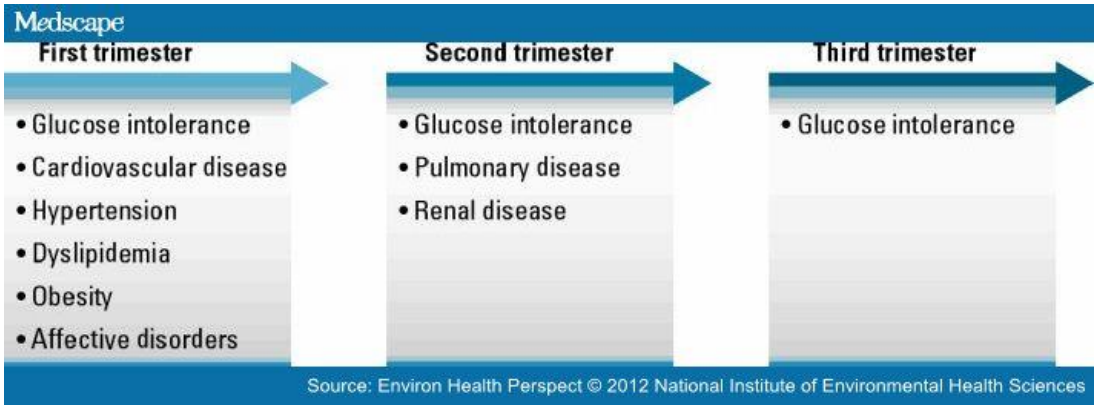


An environment which produces poor fetal and infant growth is followed by an adult environment that determines high risk for ischemic heart disease

Barker et al, Lancet 1989

1944-45 | The Dutch Famine





The Dutch Hunger Winter Study publications

Exposure to the Dutch Famine (1944-45) during gestation and phenotypes later in life

Glucose tolerance in adults after prenatal exposure to famine

A C J Ravelli, J H P van der Meulen, R P J Michels, C Osmond, D J P Barker, C N Hales, O P Bleker

(Lancet 1998)

Obesity at the age of 50 y in men and women exposed to famine prenatally[1–3]

(AJCN 1999)

Anita CJ Ravelli, Jan HP van der Meulen, Clive Osmond, David JP Barker, and Otto P Bleker

Early onset of coronary artery disease after prenatal exposure to the Dutch famine[1–3]

(AJCN 2006)

Rebecca C Painter, Susanne R de Rooij, Patrick M Bossuyt, Timothy A Simmers, Clive Osmond, David J Barker, Otto P Bleker, and Tessa J Roseboom

Lipid profiles in middle-aged men and women after famine exposure during gestation: the Dutch Hunger Winter Families Study[1–4]

(AJCN 2009)

LH Lumey, Aryeh D Stein, Henry S Kahn, and JA Romijn

Arch Gen Psychiatry. 1996 Jan;53(1):25-31.

Schizophrenia after prenatal famine. Further evidence.

Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, Gorman JM.

Department of Psychiatry, Columbia University, New York, NY, USA.

Atopy, lung function, and obstructive airways disease after prenatal exposure to famine

(Thorax 2009)

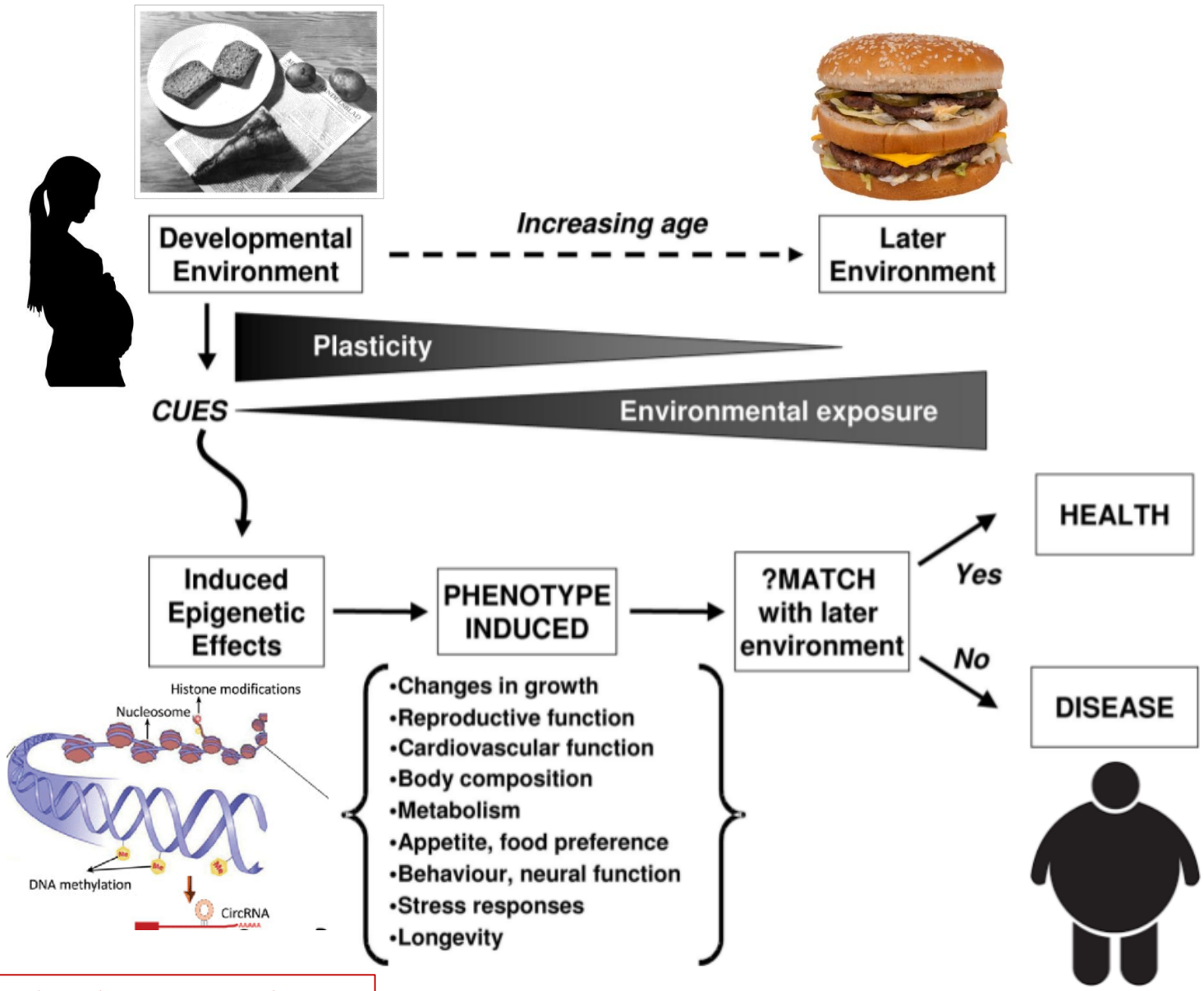
C E Lopuhaä, T J Roseboom, C Osmond, D J P Barker, A C J Ravelli, O P Bleker, J S van der Zee, J H P van der Meulen

Persistent epigenetic differences associated with prenatal exposure to famine in humans

Bastiaan T. Heijmans[a,1,2], Elmar W. Tobi[a,2], Aryeh D. Stein[b], Hein Putter[c], Gerard J. Blauw[d], Ezra S. Susser[e,f], P. Eline

Prenatal Famine and Genetic Variation Are Independently and Additively Associated with DNA Methylation at Regulatory Loci within *IGF2/H19*

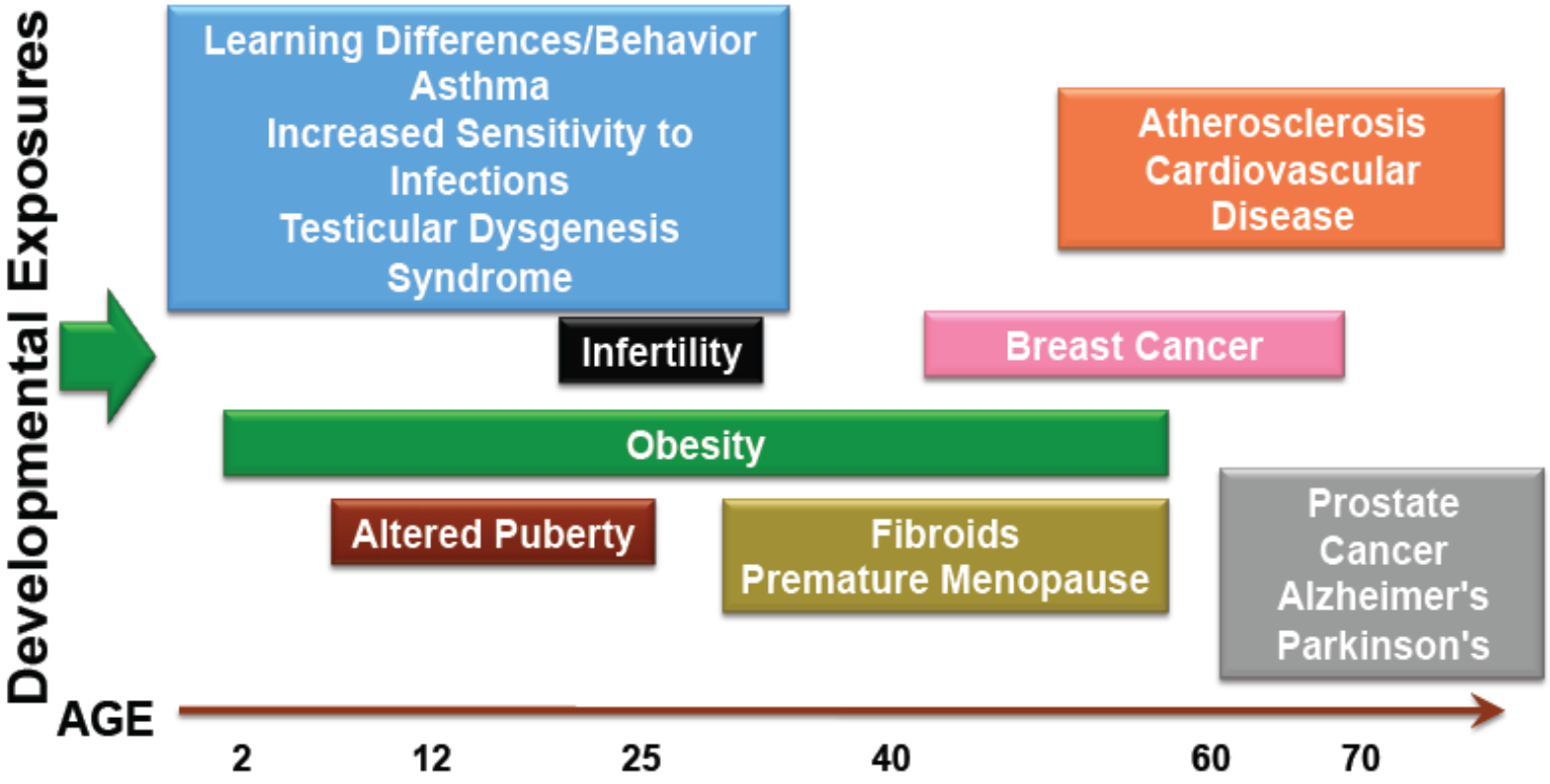
The Dutch Famine – Epigenetic changes

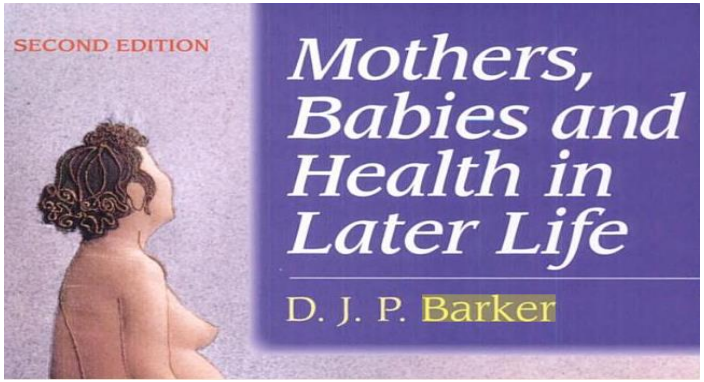


Godfrey et al, Pediatric Research 2007

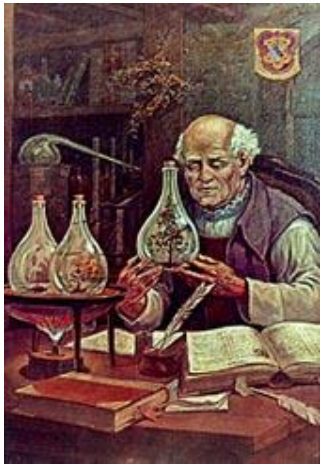
Exposures during critical fetal and infant periods lead to developmental adaptations, which predispose individuals to development of NCD in later life.

Examples of Developmental Origins of Health and Disease (DOHAD)





…from "the ***dose*** makes the poison"
to "the ***timing*** makes the poison"

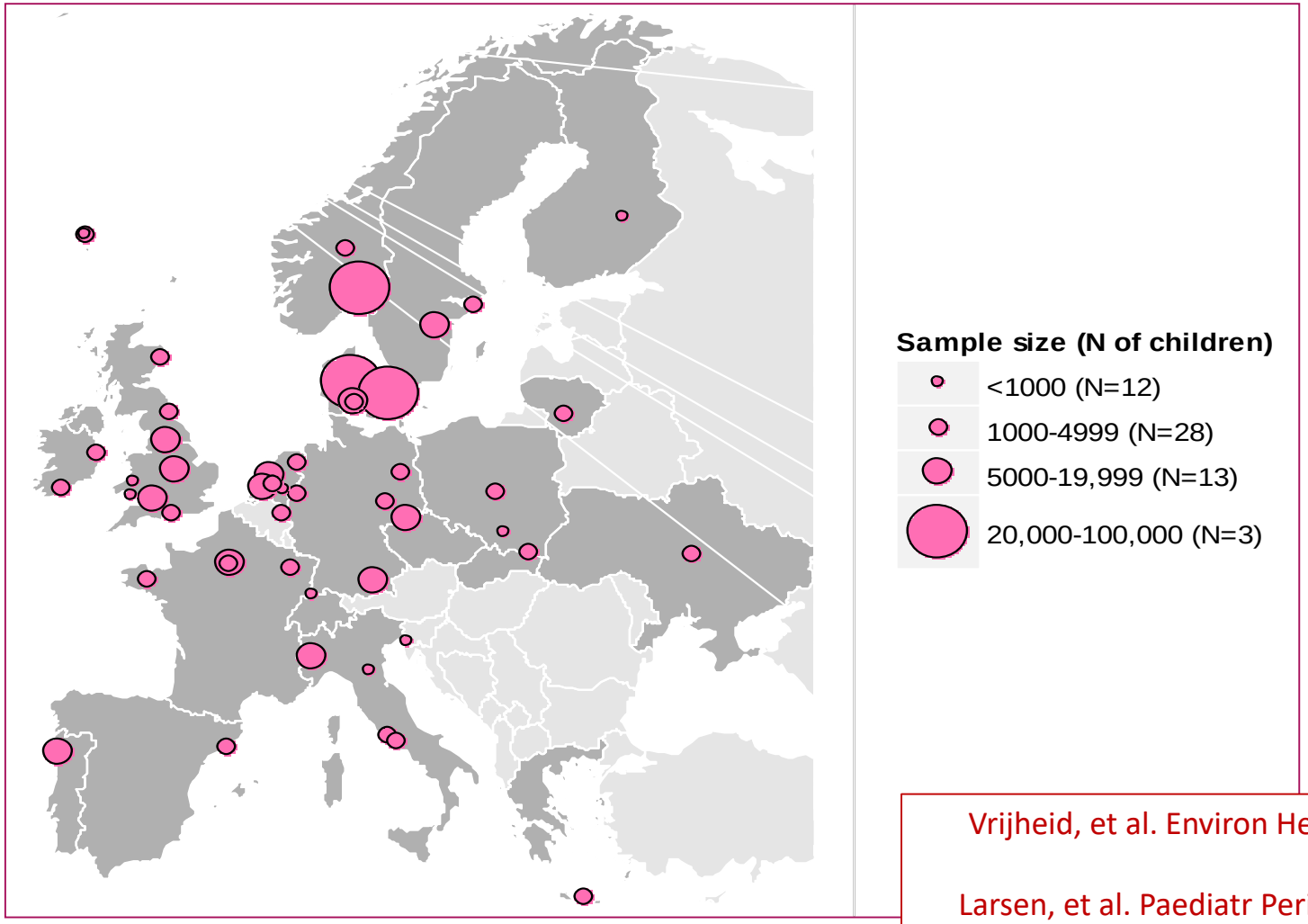


Developmental Origins of Health and Diseases - Barker, 1980's

In *utero* and early postnatal stressors, including environmental contaminant exposures, can permanently change the body's structure, physiology, and metabolism, predisposing individuals to the development of serious chronic pathologies later in life.

More than 70 birth cohorts, following more than 500,000 children and parents

Inventory: www.birthcohorts.net



Vrijheid, et al. Environ Health Perspect 2011

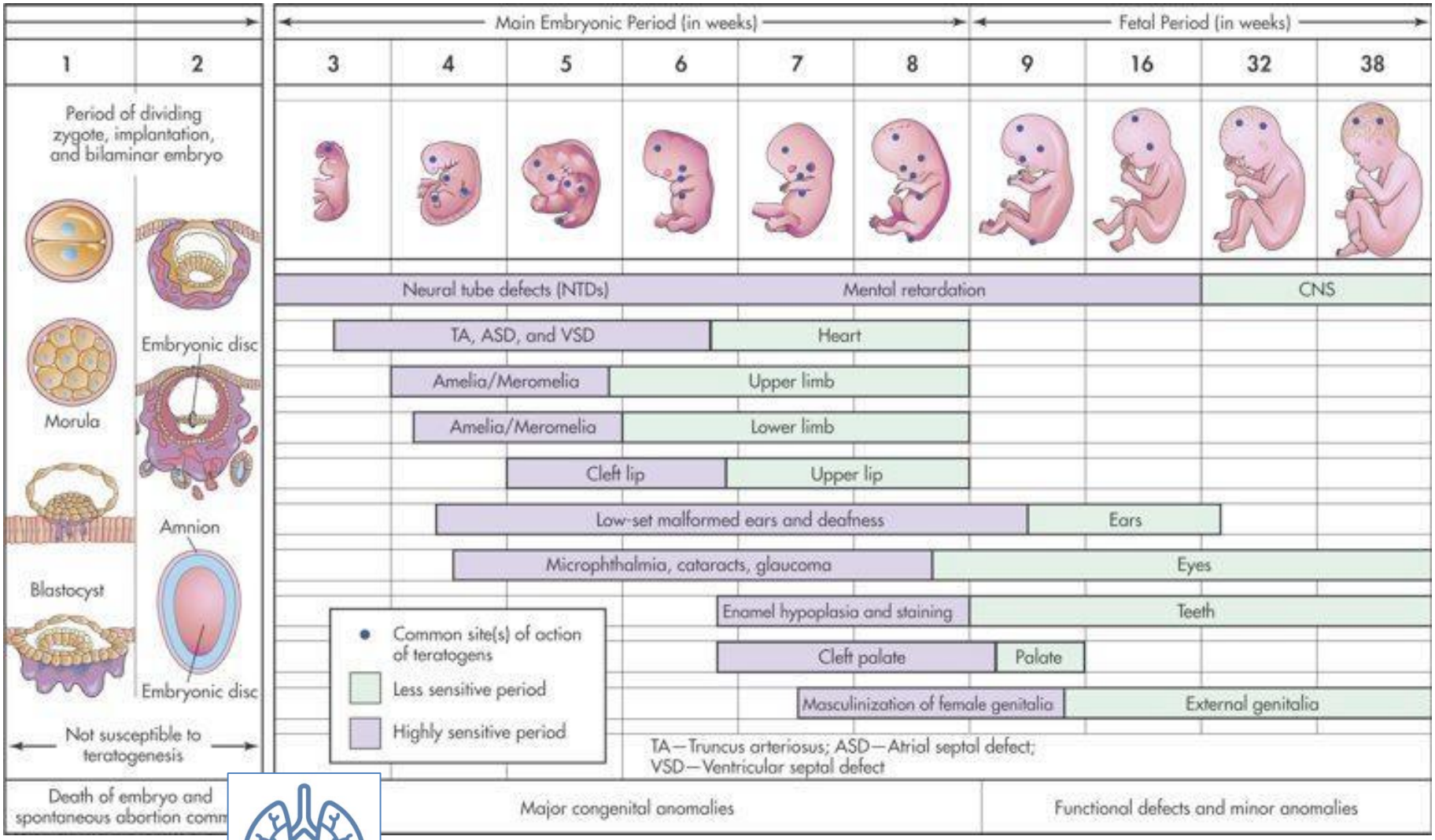
Larsen, et al. Paediatr Perinat Epidemiol 2013

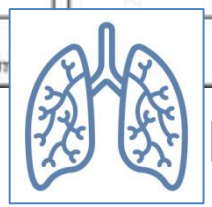
Children are not little adults

Why are children more vulnerable to environmental exposures?

- They breathe faster and inhale a greater proportion of air.
- The metabolism is faster and the consumption of food and liquid is proportionally greater.
- Excretion of toxics is slower compared to adults.
- After birth many systems are still very susceptible.
- Exposures at the beginning of life can affect years later – and they have more years than adults to develop a disease.
- They have exclusive routes of exposure: placenta, maternal milk, exclusive behavior (mouth, floor, etc.).

Critical periods during pregnancy



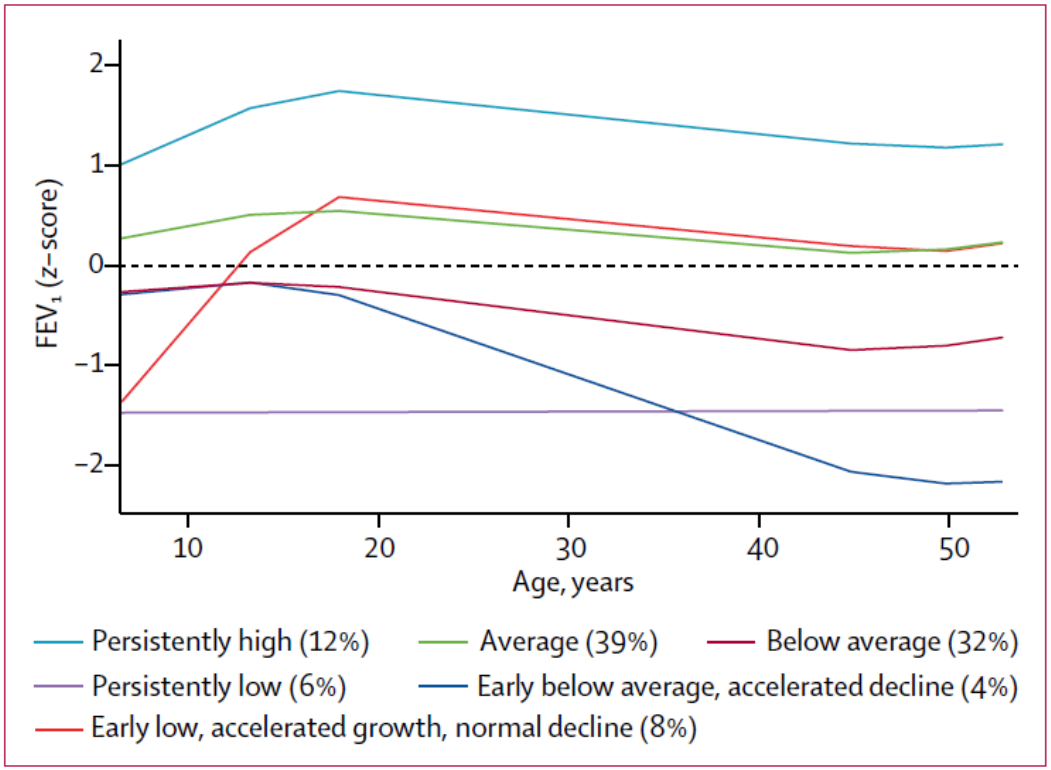


Lung

Which are the determinants of lung function development?

Why is important to study the determinants of lung function development?

Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life



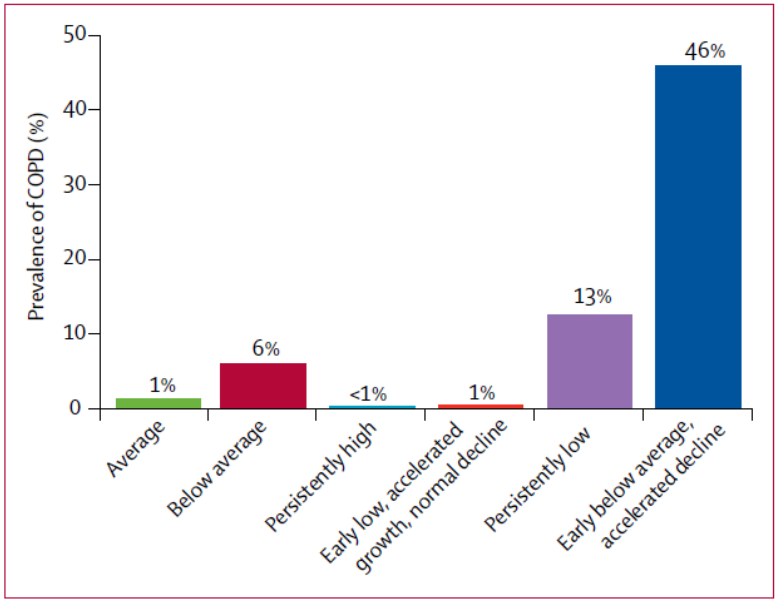
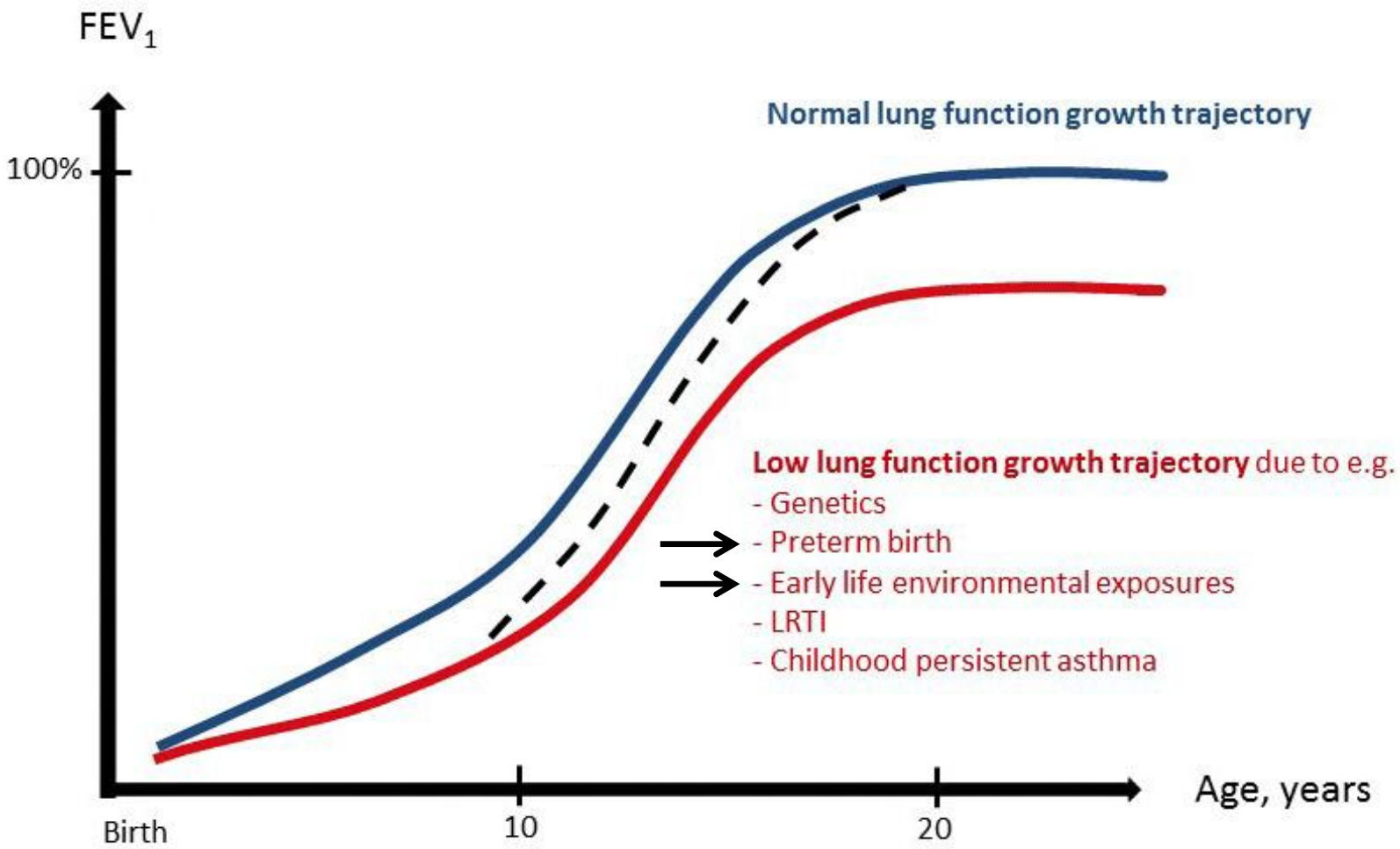


Figure 2: **Prevalence of COPD among six lung function trajectories at 53 years**
COPD=chronic obstructive pulmonary disease.

Bui et al, Lancet 2018

Determinants of lung function development

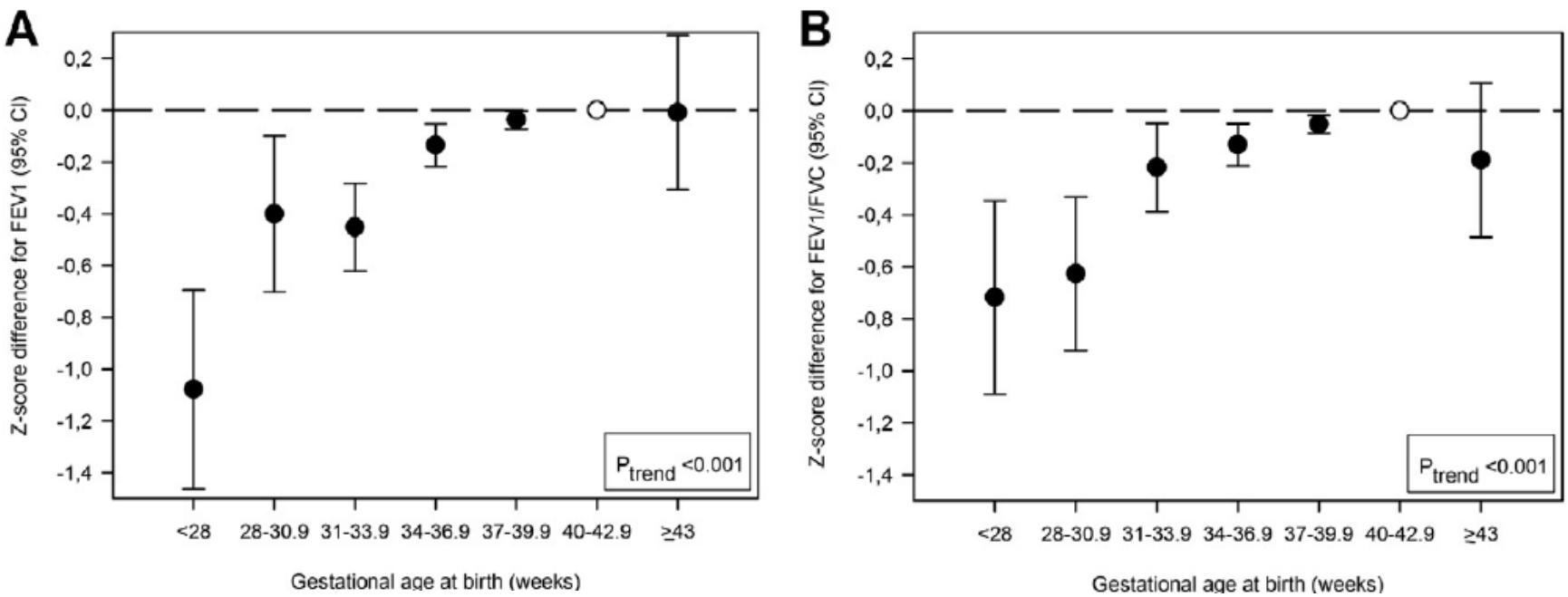


Mélen and Guerra, F1000Res 2017

Preterm birth

Early growth characteristics and the risk of reduced lung function and asthma: A meta-analysis of 25,000 children

Gestational age → Lung function (4-19 years)



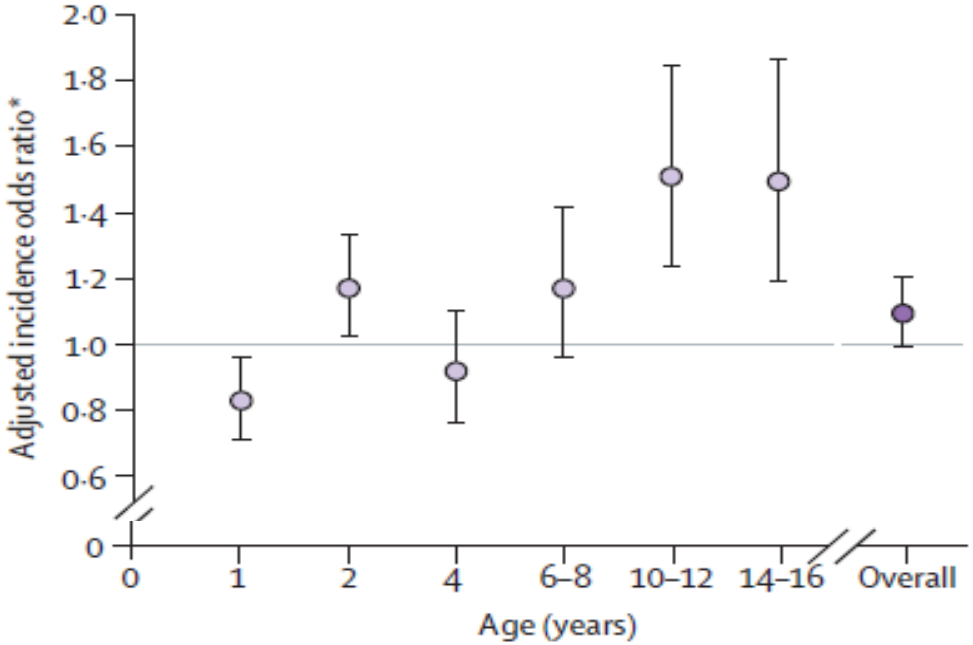
Den Dekker et al, JACI 2015

Early life environmental exposures – Air pollution

BAMSE, PIAMA, GINI-LISA birth cohorts

N=14,126 children 14-16 years

1.13 incidence odds ratio of incident asthma per 10 µg/m^3 increase prenatal NO_2

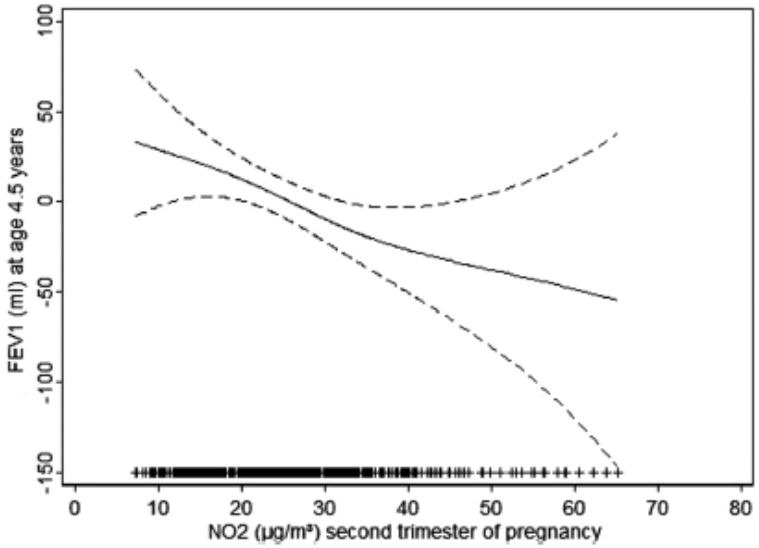


Gehring et al, Lancet Respiratory Medicine 2015

INMA birth cohort

N=620 children 4 years

−28 mL for an interquartile range increase of prenatal NO_2



Morales et al, Thorax 2014

Exposure to persistent pesticides

INMA n=255-406

Wheeze

DDE conti

Quartiles

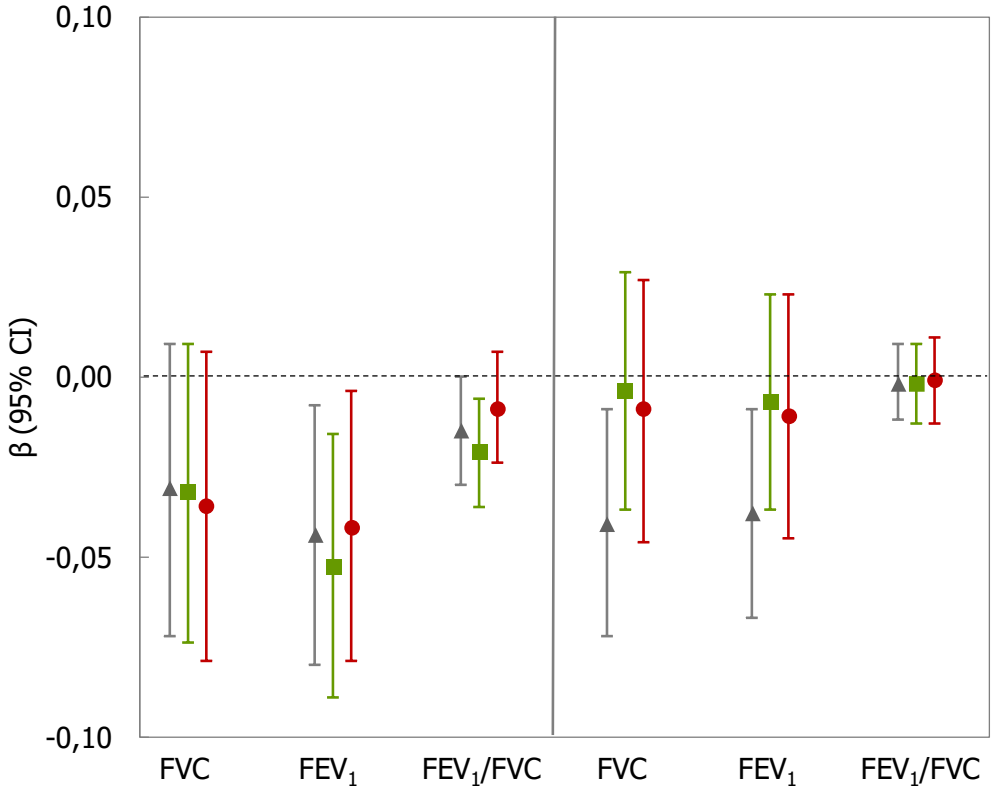
<0.57

0.57-1.0

1.03-1.9

>1.90

Sunyer



First quartile: reference

▲ Second quartile
4 years: 0.14-0.23 ng/mL
7 years: 0.17-0.28 ng/mL

■ Third quartile
4 years: 0.23-0.34 ng/mL
7 years: 0.28-0.50 ng/mL

● Fourth quartile
4 years: >0.34 ng/mL
7 years: >0.50 ng/mL

Abellan et al, in preparation

1.15)
1.09)
1.07)
1.08)

1.07)
1.10)
1.29)

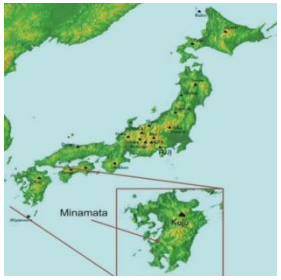
1.08)
1.06)

Atopy 6.5y	0.97 (0.80, 1.20)	1.10 (0.81, 1.51)	0.99 (0.92, 1.07)

Gascon et al, Environment International 2014

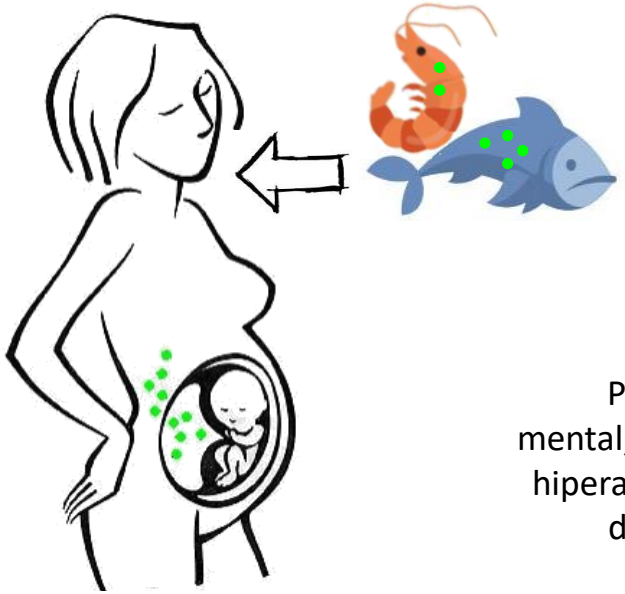
1956: MINAMATA

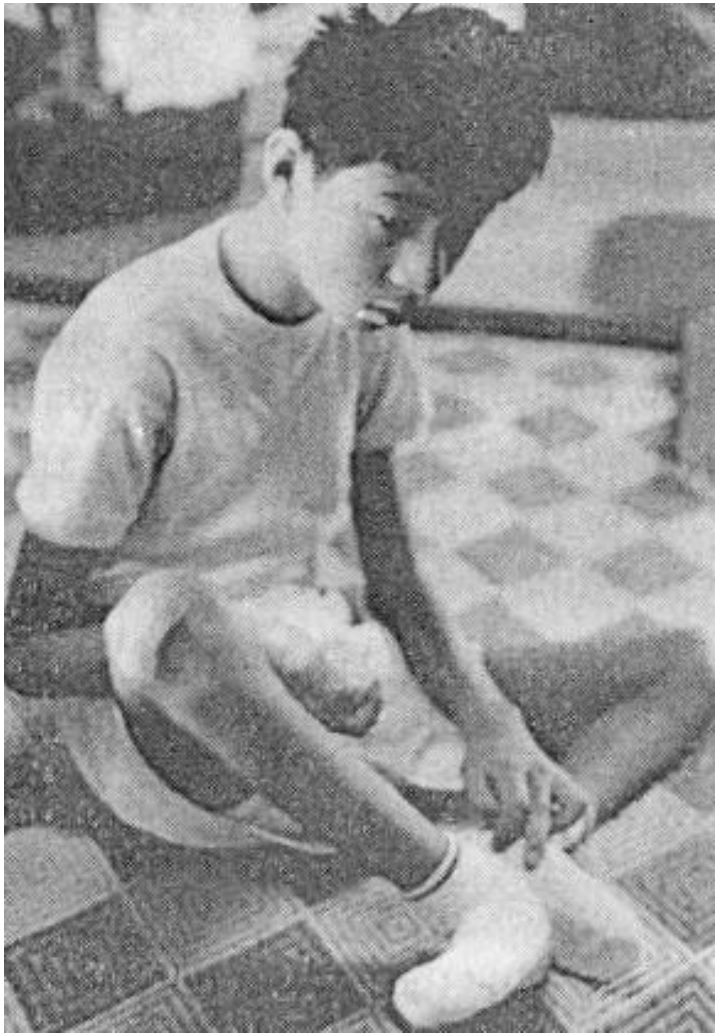
- Grans abocaments de metilmercuri procedents de la producció d'acetaldehid (1932-1968)
- Bioacumulació en peixos i marisc
- 1956: epidèmia del SNC:
  - Més de 2,000 víctimes reconegudes
  - Fins a 10,000 indemnitzades
- Animals domèstics símptomes semblants



1956: MINAMATA

- Grans concentracions de mercuri a l'aigua i als cabells
- Nens que no havien menjat mai peix → malaltia congènita
- El metilmercuri bloqueja la síntesi de l'hormona tiroïdal: **trastorns hormonals**





Noi de 14 anys:
Paràlisi cerebral, deficiència mental, incoordinació, nistagmus, hiperactivitat, malformacions als dits i a la columna vertebral