ENDOCRINE DISRUPTERS AND FETAL AND CHILD HEALTH OUTCOMES

RESULTS FROM THE GENERATION R STUDY

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Paris Santé-Femmes Conference

25-01-2023

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Universitair Medisch Centrum Rotterdam

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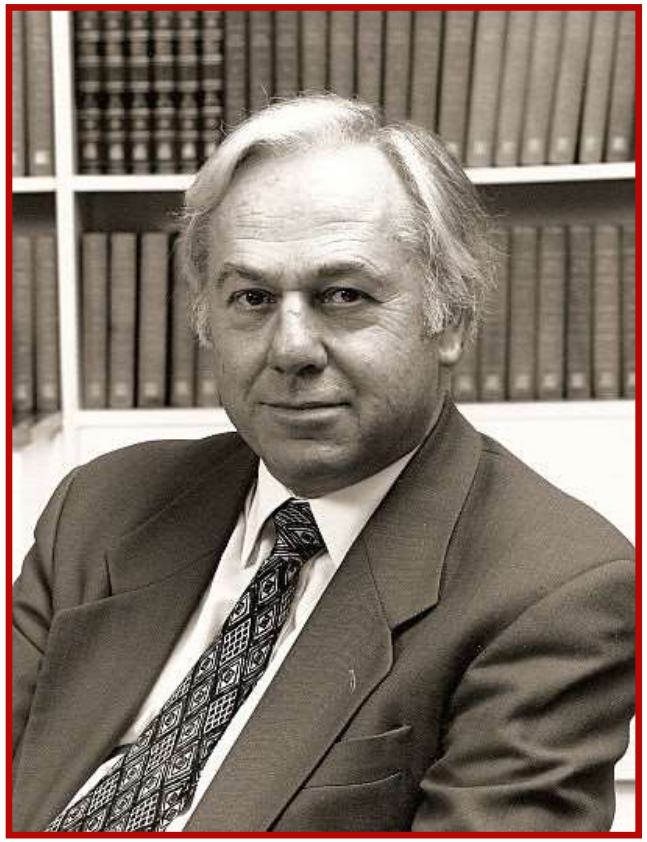
Barkers hypothesis

Developmental Origins of Health and Disease

“An adverse fetal or childhood environment during **critical periods** leads to permanent changes in organ structure or function and may have **detrimental effects on health** in later life”



DJ Barker, BMJ

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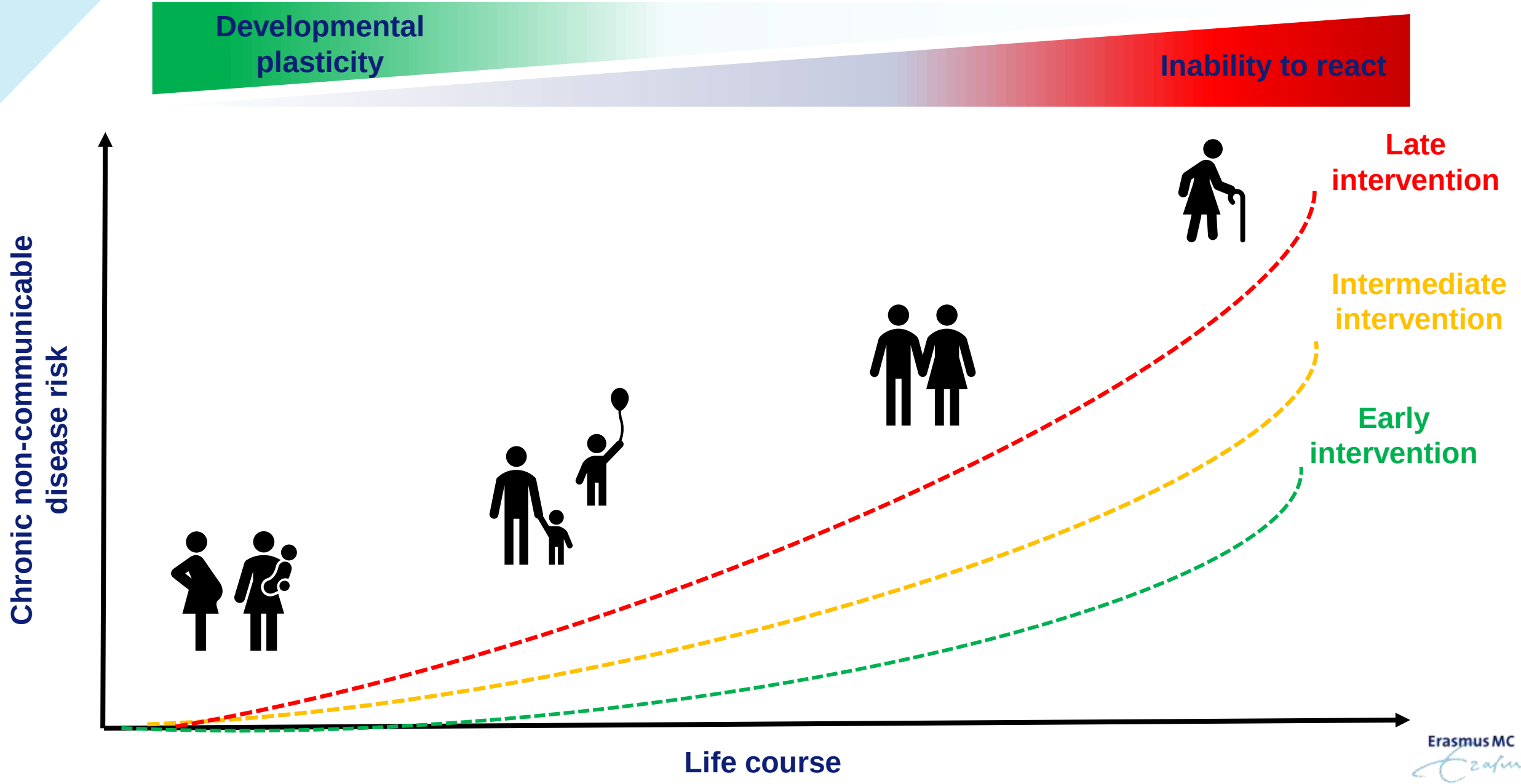
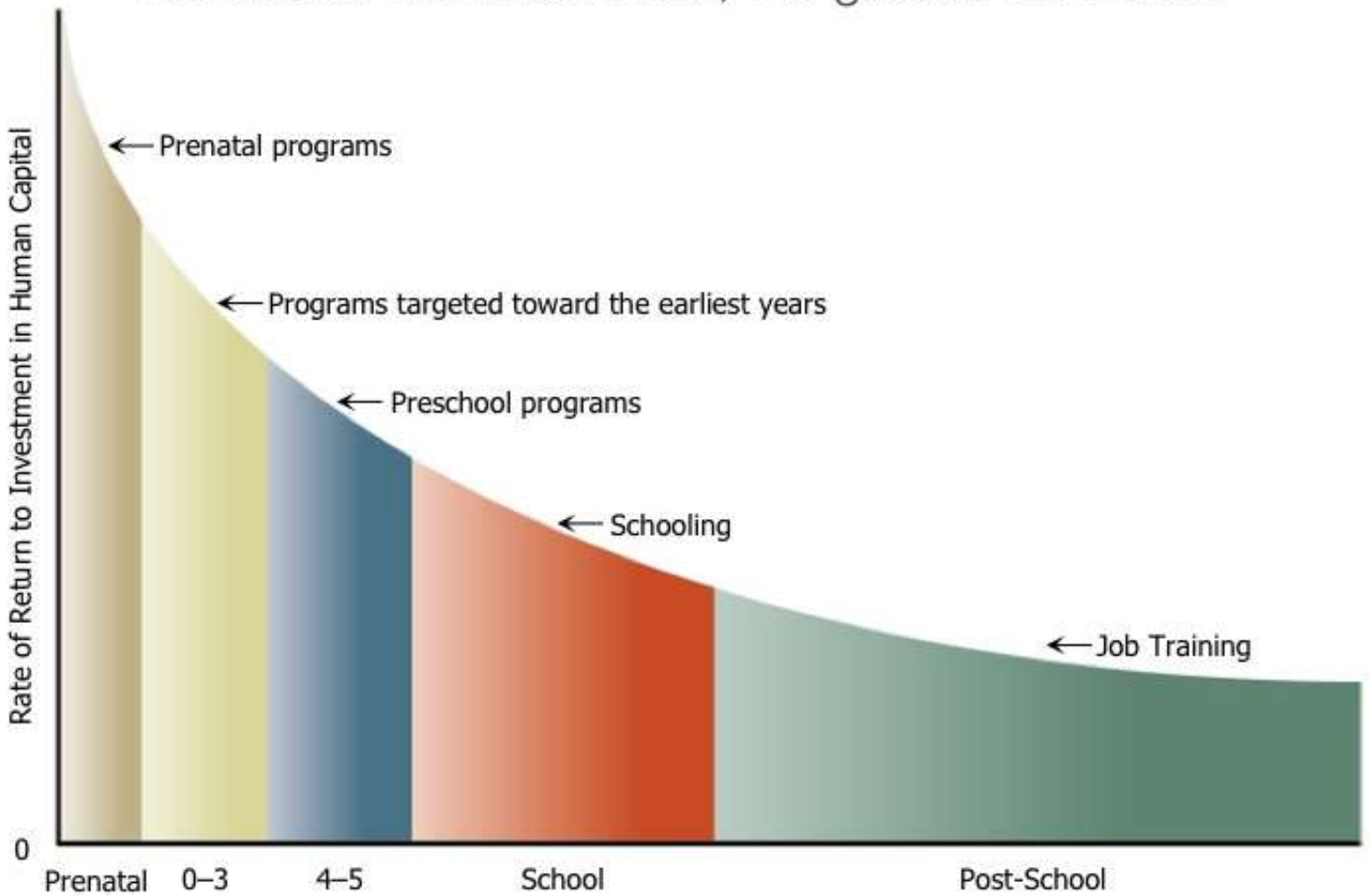

Developmental plasticity
Inability to react
Late intervention
Intermediate intervention
Early intervention
Chronic non-communicable disease risk
Life course

EARLY CHILDHOOD DEVELOPMENT IS A SMART INVESTMENT

The earlier the investment, the greater the return



Source: James Heckman, Nobel Laureate in Economics

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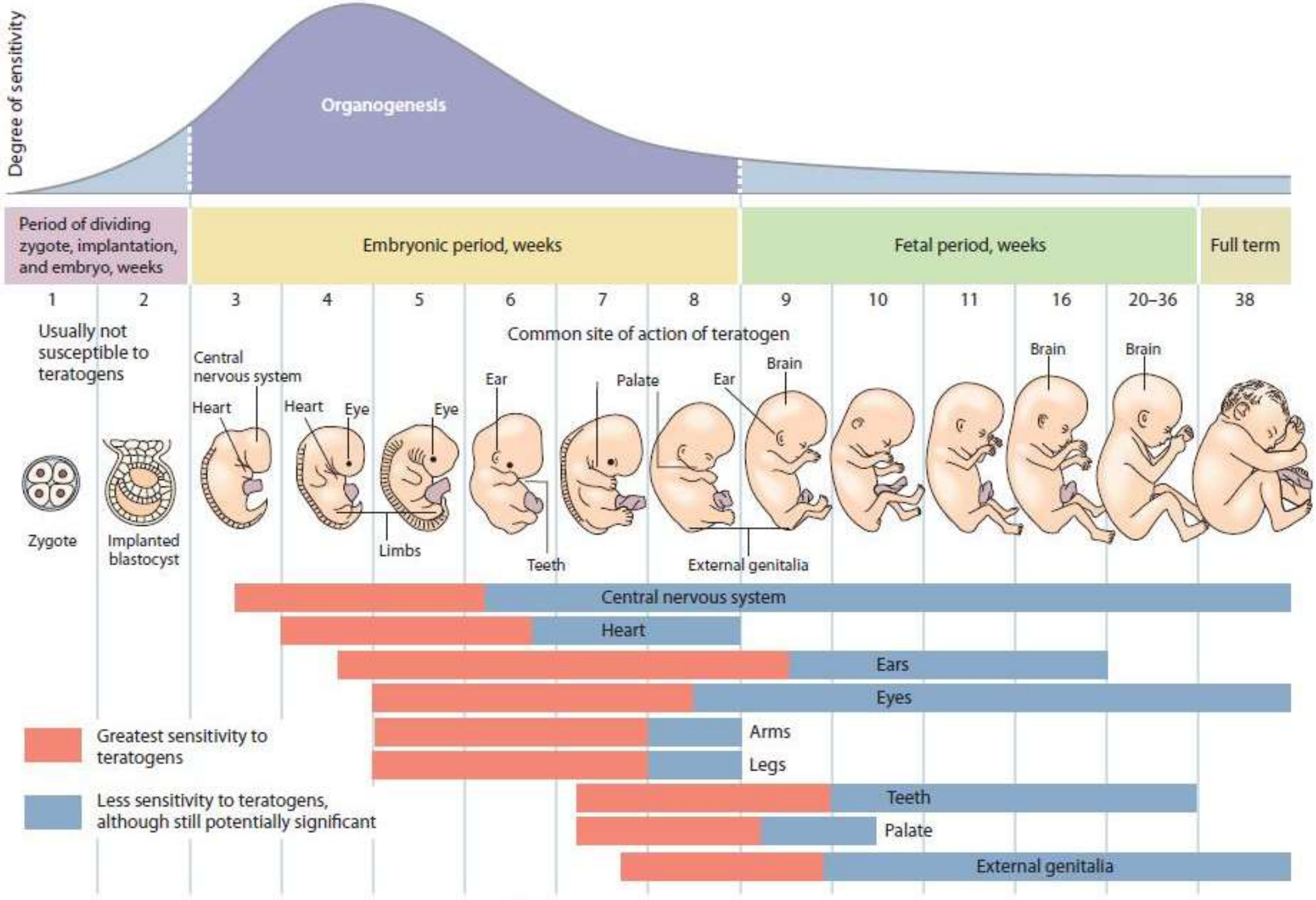
Degree of sensitivity
Organogenesis
Period of dividing zygote, implantation, and embryo, weeks
Embryonic period, weeks
Fetal period, weeks
Full term
1
2
3
4
5
6
7
8
9
10
11
16
20–36
38
Usually not susceptible to teratogens
Common site of action of teratogen
Central nervous system
Heart
Heart
Eye
Eye
Ear
Palate
Ear
Brain
Brain
Brain
Zygote
Implanted blastocyst
Limbs
Teeth
External genitalia
Central nervous system
Heart
Ears
Eyes
Arms
Legs
Teeth
Palate
External genitalia
Greatest sensitivity to teratogens
Less sensitivity to teratogens, although still potentially significant

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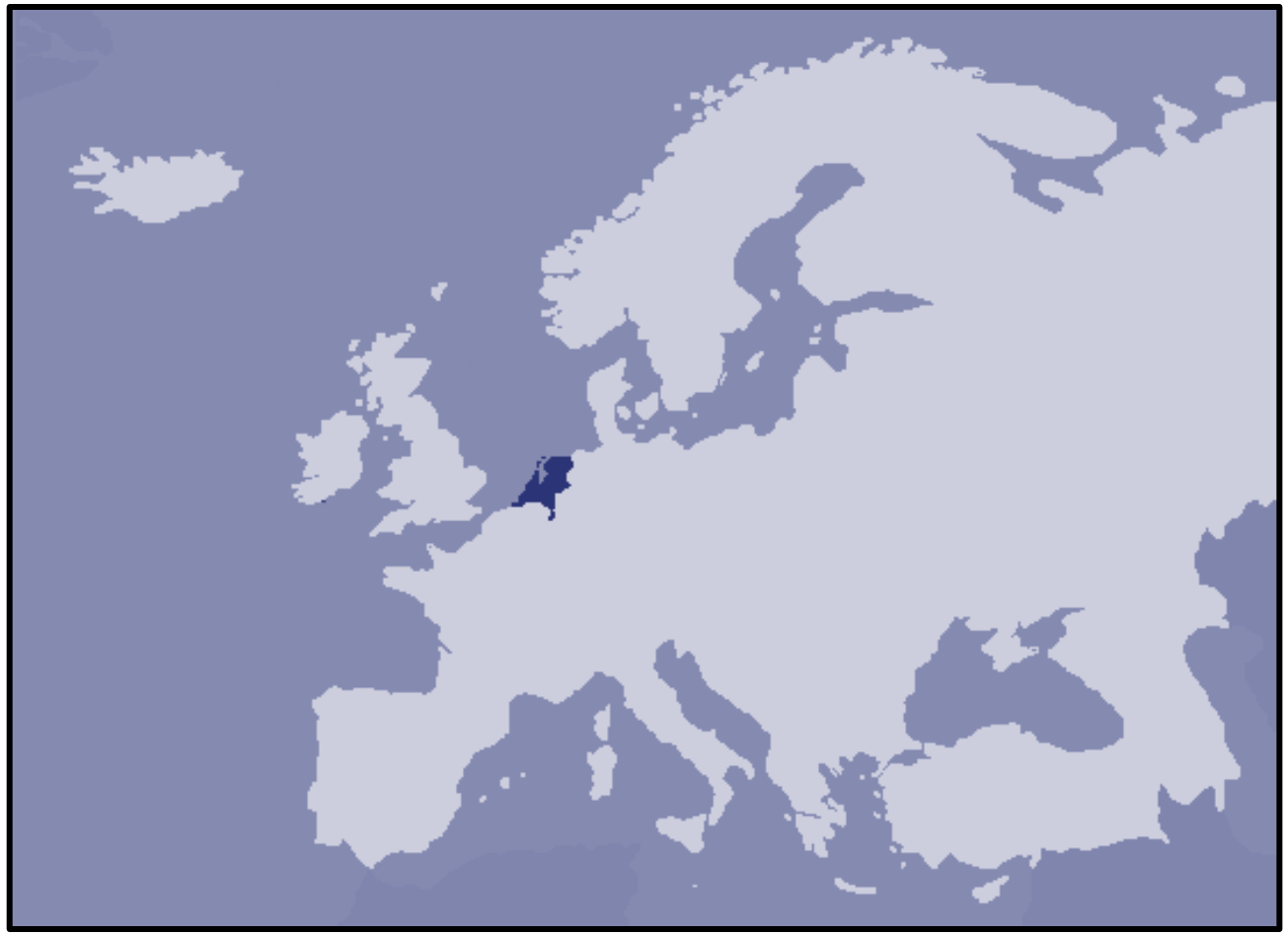
Generation R

- Observational cohort study
- 2001 - …
- 10.000 women and children
- Rotterdam, Netherlands



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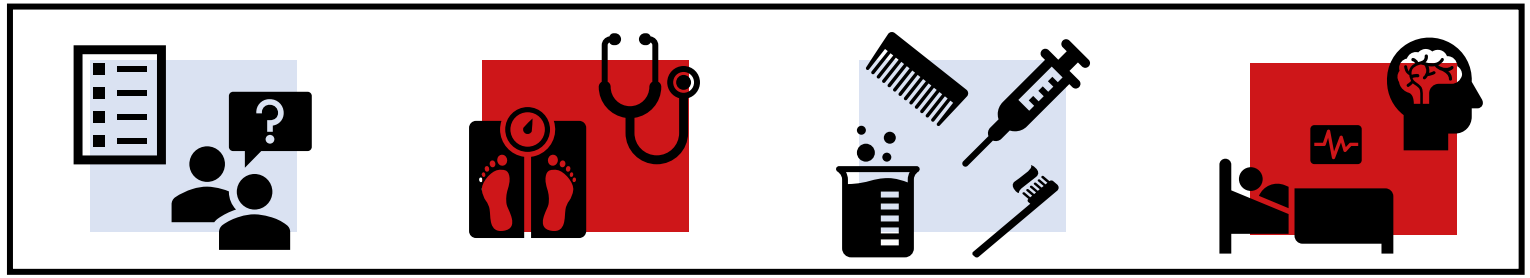

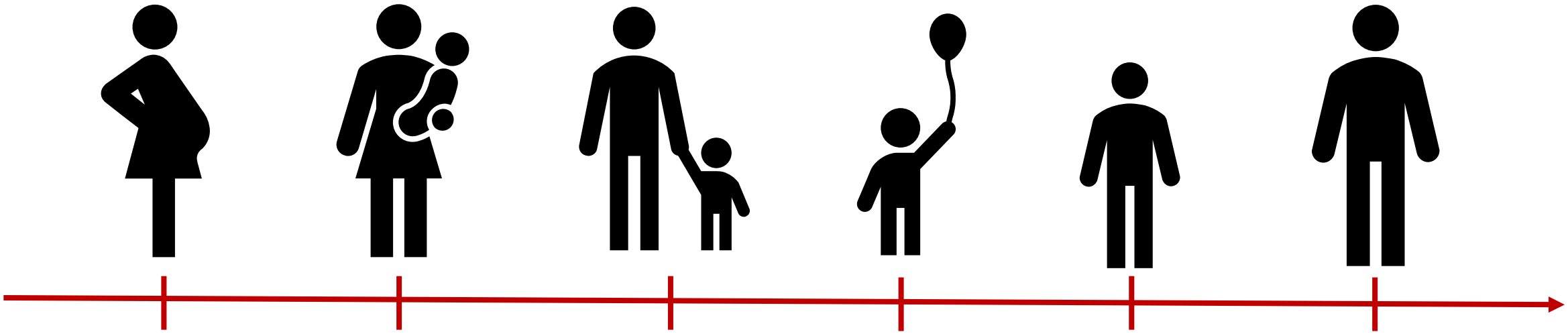

13 weeks GA

20 weeks GA

30 weeks GA

0-4 years

5 years

9 years

13 years

17 years

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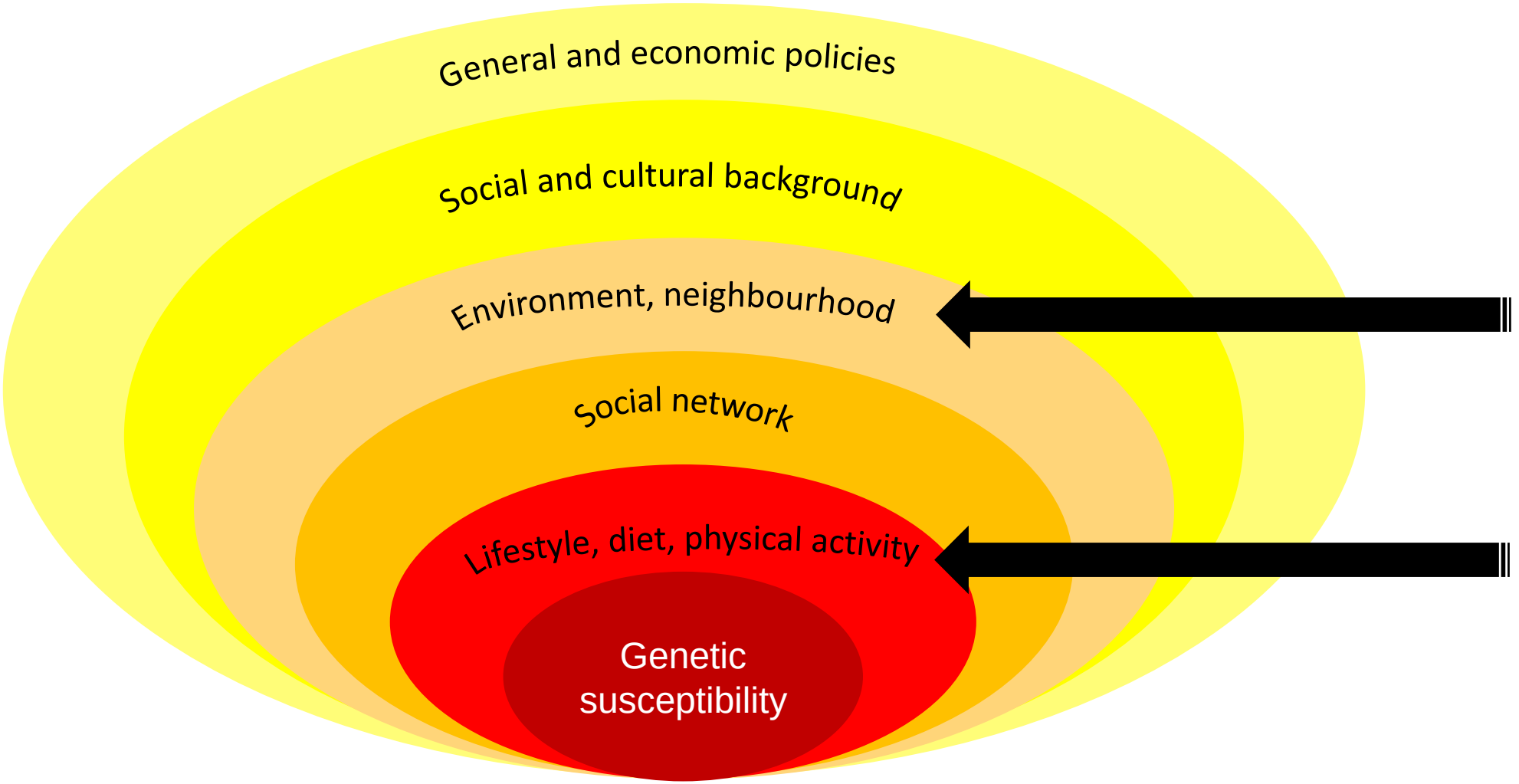
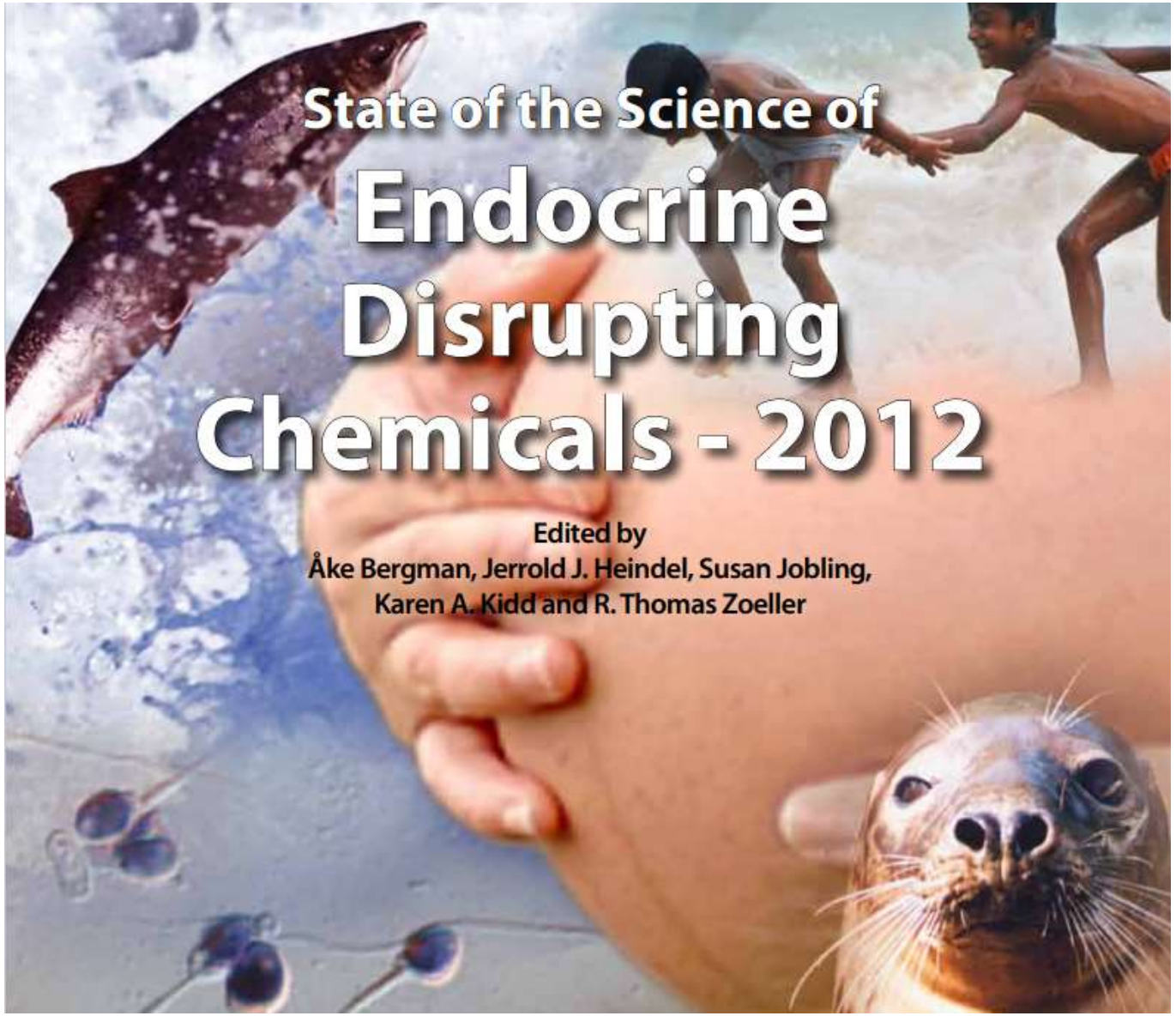

General and economic policies
Social and cultural background
Environment, neighbourhood
Social network
Lifestyle, diet, physical activity
Genetic susceptibility



1972-2012:
Serving People and the Planet

World Health Organization

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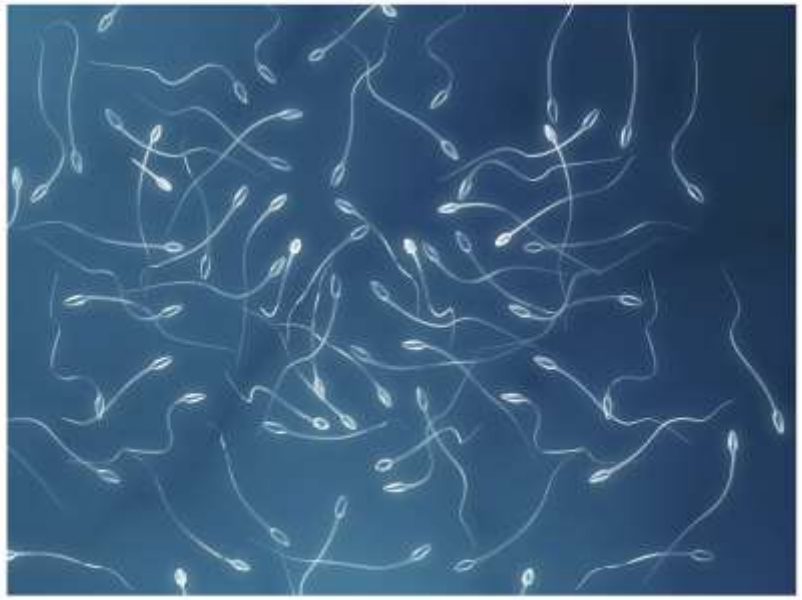
The New York Times

What Are Sperm Telling Us?

Scientists are concerned by falling sperm counts and declining egg quality. Endocrine-disrupting chemicals may be the problem.

Feb. 20, 2021



Chemicals used in packaging may play role in 100,000 US deaths a year – study

Phthalates, also found in consumer goods, may contribute to loss of life among older Americans costing US $40-47bn a year

Grossesse et perturbateurs endocriniens : de nouvelles données plaident pour la vigilance

Par Le Figaro avec AFP | Publié le 09/11/2022 à 17:12

Europe proposes drastic cuts of BPA, a hormone disruptor found in plastics and food

Food safety agency calls for 100,000-fold cut in dietary exposure to bisphenol A

16 FEB 2022 · 1:30 PM · BY ERIK STOKSTAD

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BISPHENOLS & PHTHALATES

- Non-persistent endocrine-disrupting chemicals
- Everyday products (plastic)
- General exposure increases
- Pass placental barrier!

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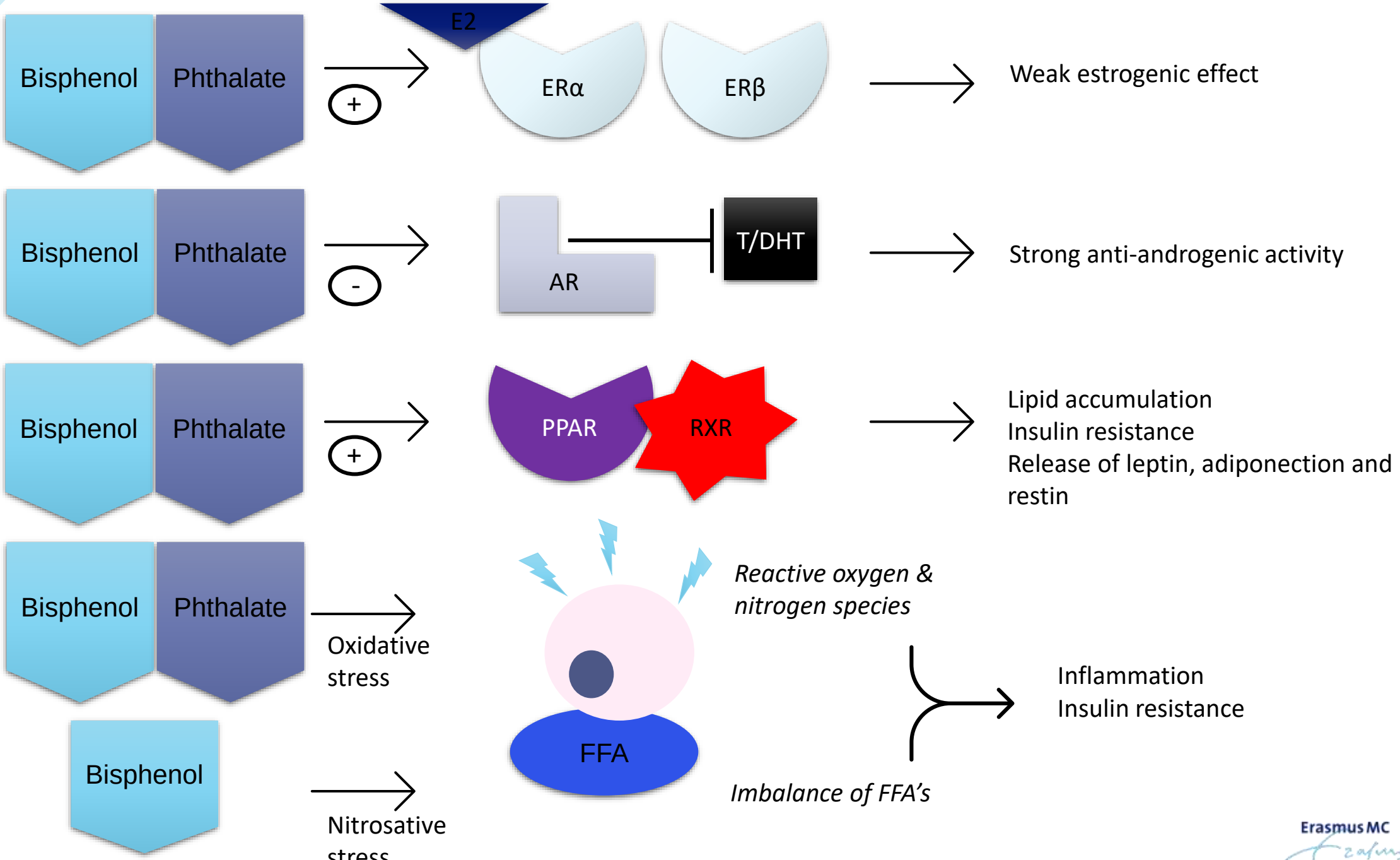
Bisphenol
Phthalate
+
E2
ERα
ERβ
Weak estrogenic effect
Bisphenol
Phthalate
-
AR
T/DHT
Strong anti-androgenic activity
Bisphenol
Phthalate
+
PPAR
RXR
Lipid accumulation
Insulin resistance
Release of leptin, adiponection and restin
Bisphenol
Phthalate
Oxidative stress
Bisphenol
Nitrosative stress
Reactive oxygen & nitrogen species
FFA
Imbalance of FFA's
Inflammation
Insulin resistance

PREVIOUS LITERATURE

- Animal studies: associated with cardiovascular, reproductive and neurocognitive health outcomes
- Adult exposure: associated with cardiovascular, reproductive and neurocognitive health outcomes
- DOHAD: studies on effects of fetal exposure lacking

WHAT IS THE ASSOCIATION OF MATERNAL EXPOSURE TO BISPHENOLS AND PHTHALATES IN PREGNANCY WITH FOETAL AND CHILD HEALTH OUTCOMES?

Generation R

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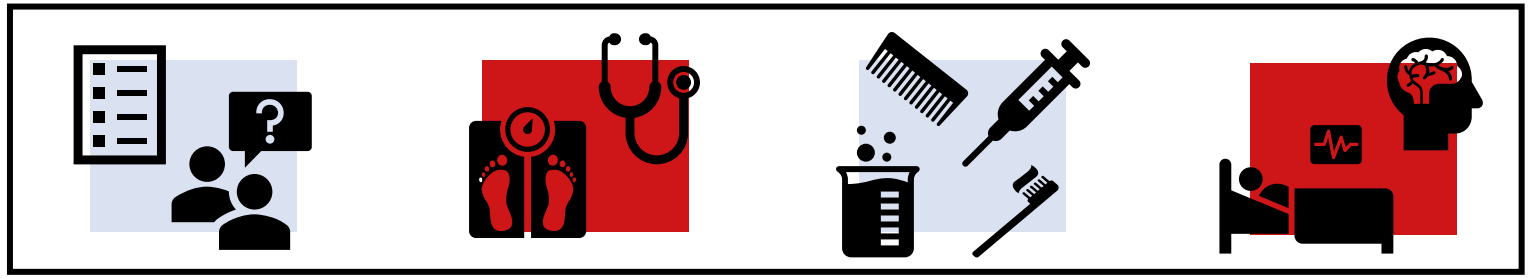

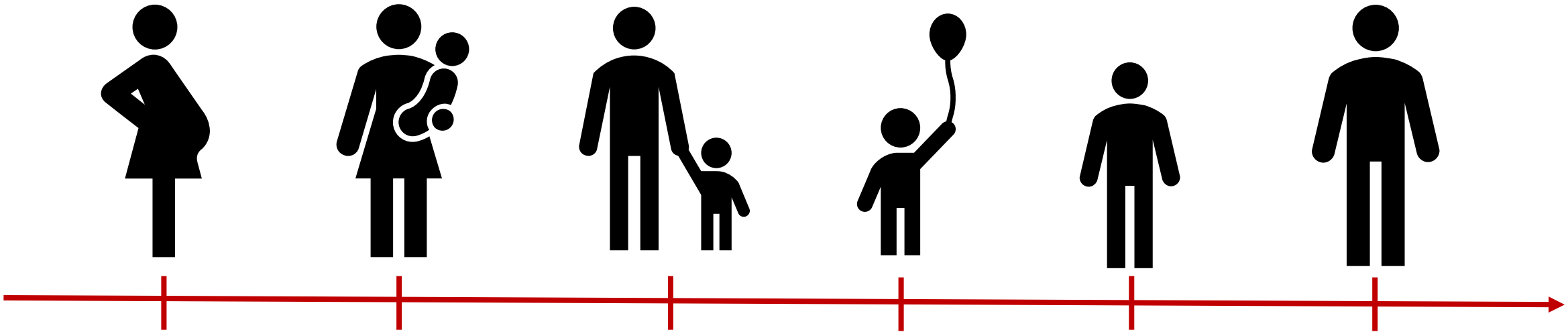

13 weeks GA

20 weeks GA

30 weeks GA

0-4 years

5 years

9 years

13 years

17 years

Bisphenols/phthalates N ±1400

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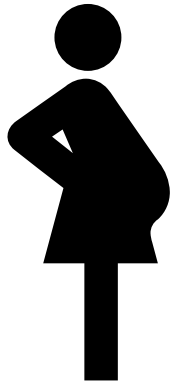
MATERNAL PREGNANCY HEALTH



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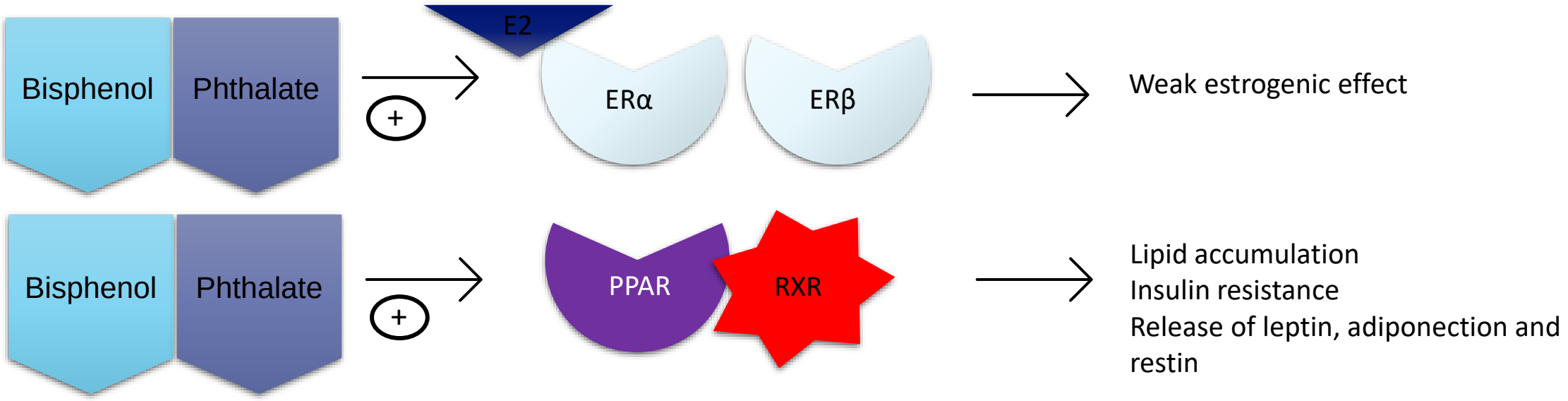
MATERNAL GESTATIONAL WEIGHT GAIN

- Both low and high maternal gestational weight gain → adverse birth and childhood outcomes
- Potential pathways of influence:



Source: Philips EM, Santos S, Steegers EAP, Asimakopoulos AG, Kannan K, Trasande L, Jaddoe VWV. Maternal bisphenol and phthalate urine concentrations and weight gain during pregnancy. Environ Int. 2020 Feb;135:105342.

Table 3

Associations of early and mid-pregnancy bisphenol and phthalate urine concentrations with gestational weight gain (n = 1,213).

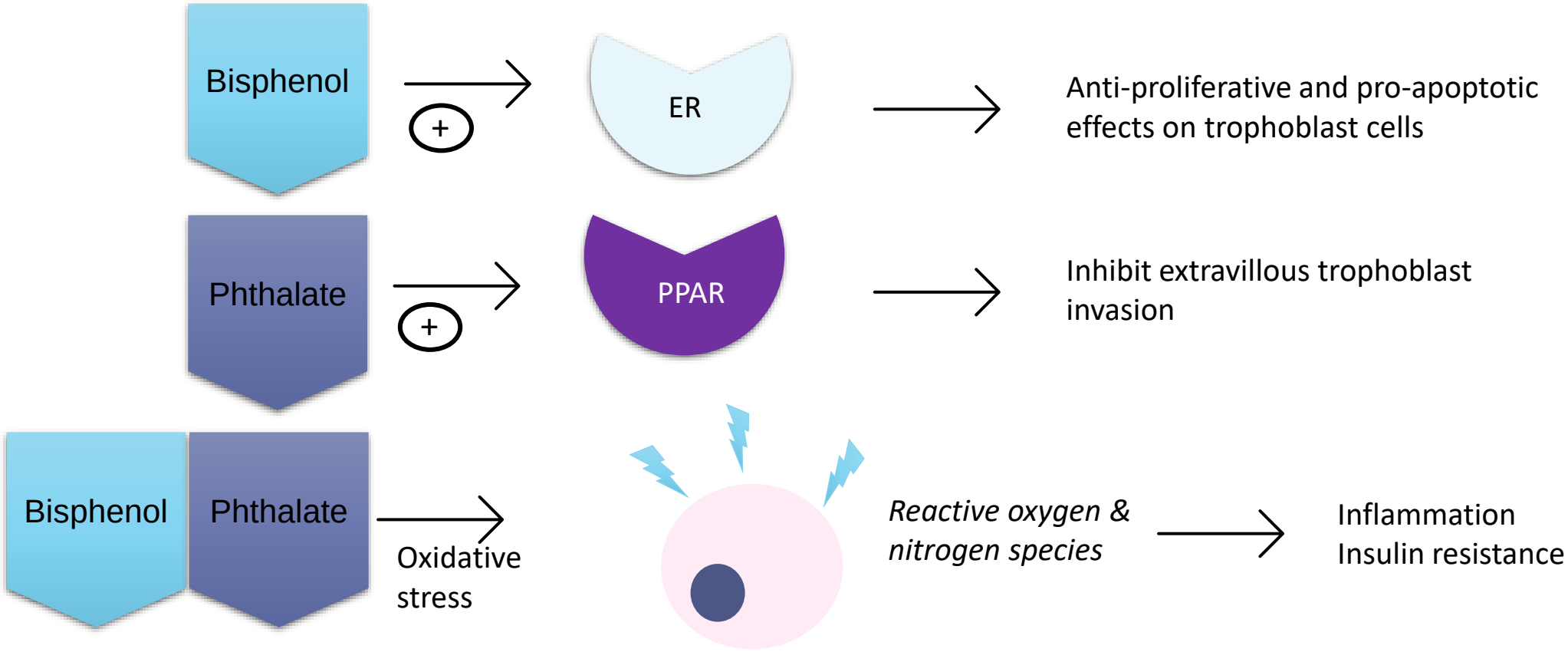
	Gestational weight gain (grams) Early to mid-pregnancy, (95% Confidence Interval) (n = 1,205)	Mid- to late pregnancy, (95% Confidence Interval) (n = 1,207)[1]	Late pregnancy to total, (95% Confidence Interval) (n = 819)[1]	Total (95% Confidence Interval) (n = 823)[1]
Early pregnancy (< 18 weeks)				
Total bisphenols	0 (−98, 98)	−218 (−334, −102) * †	−82 (−261, 98)	−354 (−641, −68)*
Bisphenol A	17 (−66, 100)	−132 (−231, −34)* †	−54 (−205, 98)	−125 (−367, 117)
Bisphenol S[2]	−26 (−97, 44)	−76 (−160, 7)	−41 (−169, 87)	−261 (−466, −56)*
Phthalic acid	32 (−84, 147)	−139 (−277, 0)	−131 (−334, 71)	−50 (−375, 274)
LMW phthalate metabolites	63 (−33, 159)	−110 (−230, 9)	−196 (−375, −17)*	−191 (−478, 96)
HMW phthalate metabolites	13 (−113, 140)	−133 (−285, 18)	−175 (−411, 61)	−268 (−646, 111)
DEHP metabolites	24 (−100, 147)	−122 (−270, 27)	−183 (−413, 47)	−259 (−627, 109)
DNOP metabolites	40 (−83, 162)	−176 (−324, −29)*	−218 (−436, −1)*	−319 (−666, 29)
Mid-pregnancy (18–25 weeks)				
Total bisphenols	–	−119 (−251, 14)	161 (−35, 356)	143 (−168, 453)
Bisphenol A	–	−112 (−238, 14)	151 (−36, 338)	147 (−150, 444)
Bisphenol S	–	–	–	–
Phthalic acid	–	−125 (−271, 21)	217 (−6, 440)	33 (−323, 389)
LMW phthalate metabolites	–	−86 (−221, 49)	145 (−56, 346)	60 (−262, 381)
HMW phthalate metabolites	–	−149 (−304, 5)	112 (−129, 353)	−30 (−415, 354)
DEHP metabolites	–	−140 (−292, 11)	156 (−81, 393)	64 (−315, 444)
DNOP metabolites	–	−68 (−235, 99)	96 (−149, 342)	−112 (−505, 280)

Estimates are based on multivariate regression analyses. Increases are per log unit increase in early and mid-pregnancy urinary Total bisphenols/BPA/BPS/Phthalic acid/LMW/HMW/DEHP/DNOP metabolite concentrations per gram creatinine. All models are adjusted for maternal age, maternal pre-pregnancy BMI, daily dietary caloric intake, parity, ethnicity, education, maternal smoking, maternal alcohol, and folic acid supplementation. In total, 1,213 women are included in the analyses in this table. Due to random nonresponse, not all women had available information about all the weights.

MATERNAL HEMODYNAMICS

Placenta: balance of factors. Endocrine disruptors might disrupt this balance → hypertensive disorders pregnancy

Potential pathways of influence:



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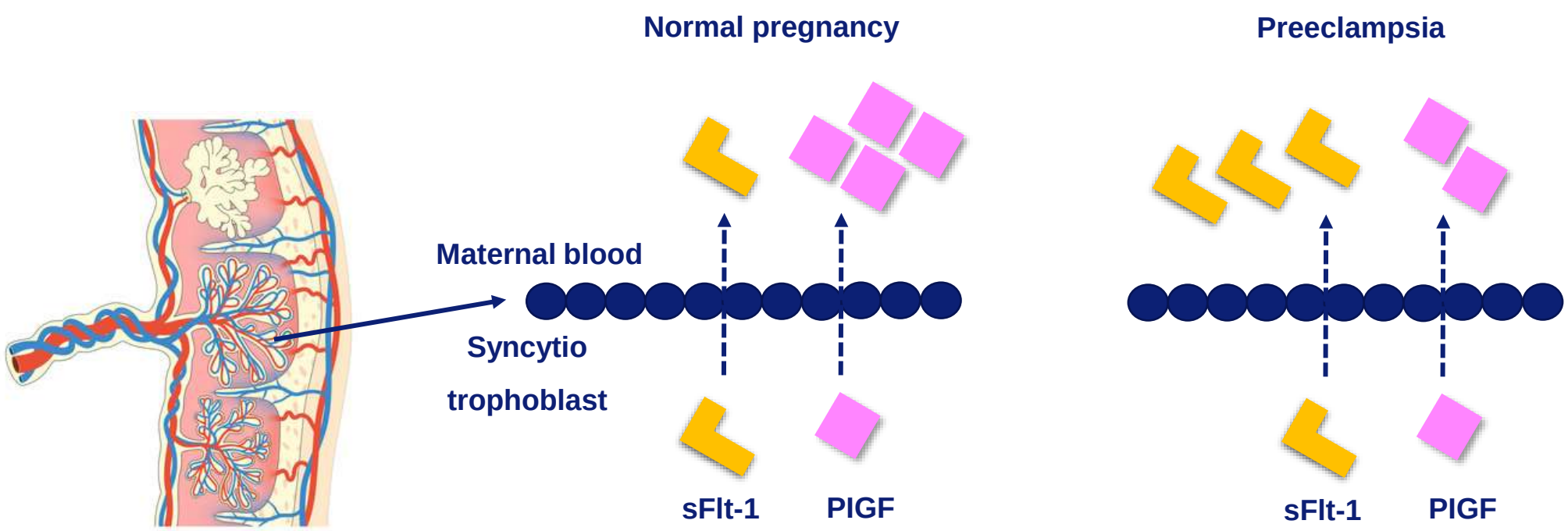
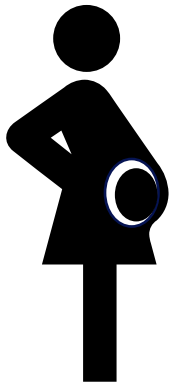


Phthalates

- ↑early pregnancy high-molecular-weight phthalate → ↑ sFlt and sFlt:PlGF ratio <18 weeks
- ↑early pregnancy low-molecular-weight phthalate → ↑ PlGF 18-25 weeks

Source: Philips EM, Trasande L, Kahn LG, Gaillard R, Steegers EAP, Jaddoe VWV. Early pregnancy bisphenol and phthalate metabolite levels, maternal hemodynamics and gestational hypertensive disorders. Hum Reprod. 2019 Feb 1;34(2):365-373.

FOETAL DEVELOPMENT



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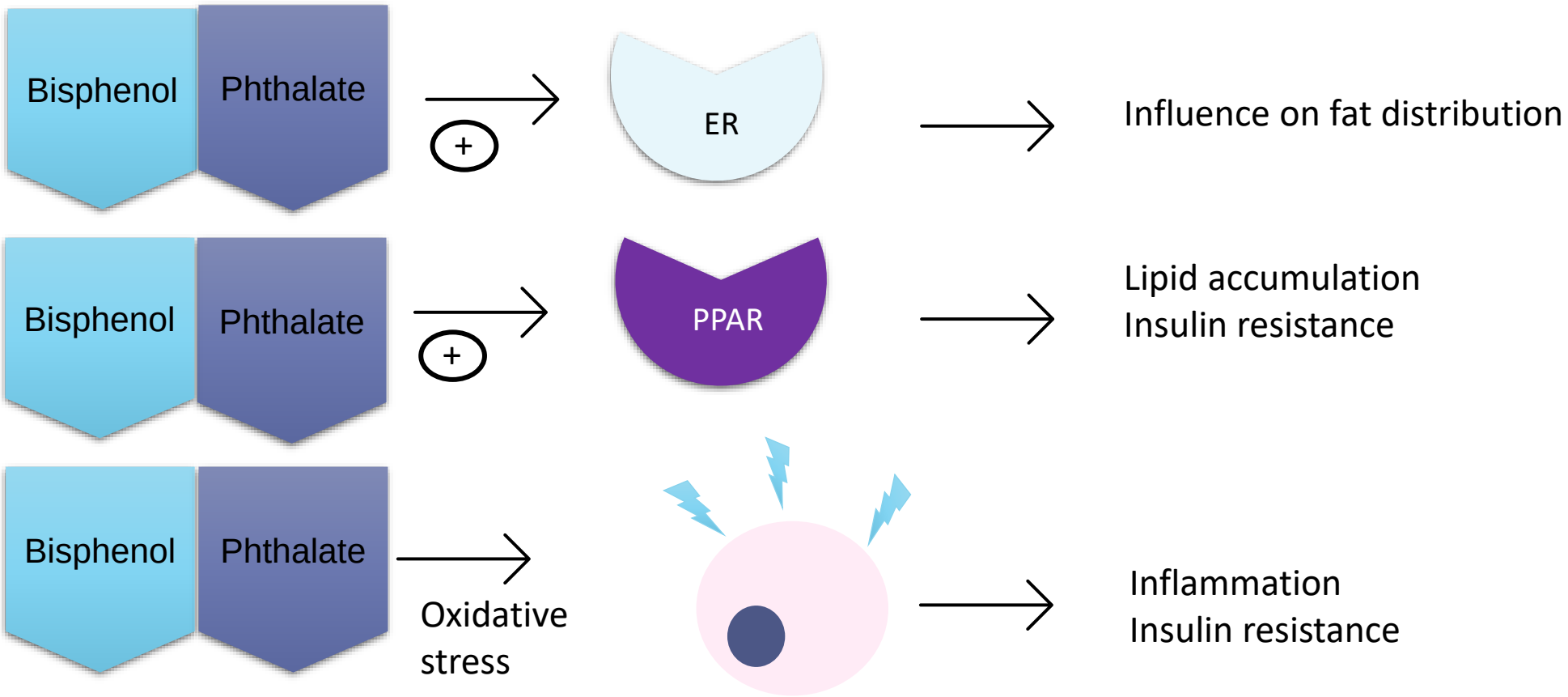
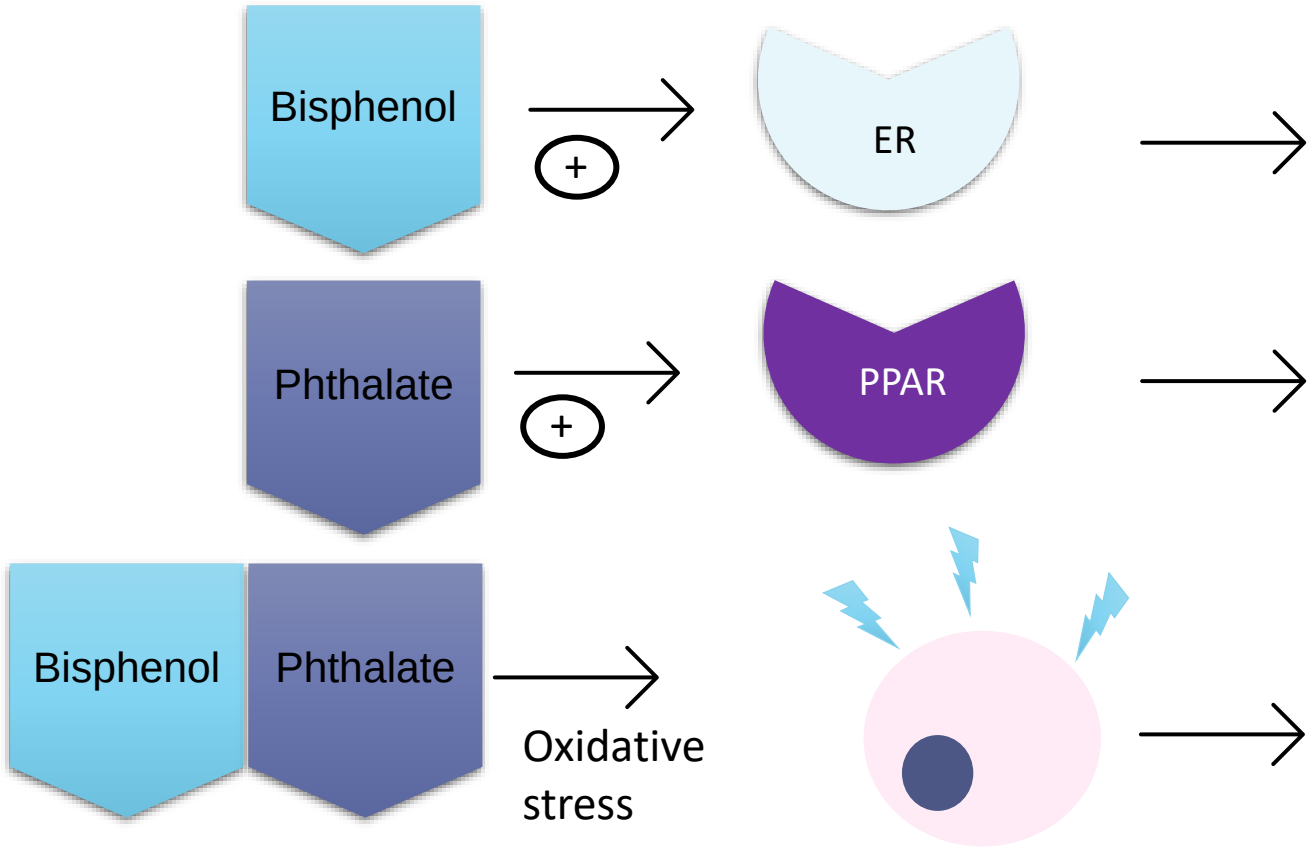
FETAL GROWTH – DIRECT EFFECT



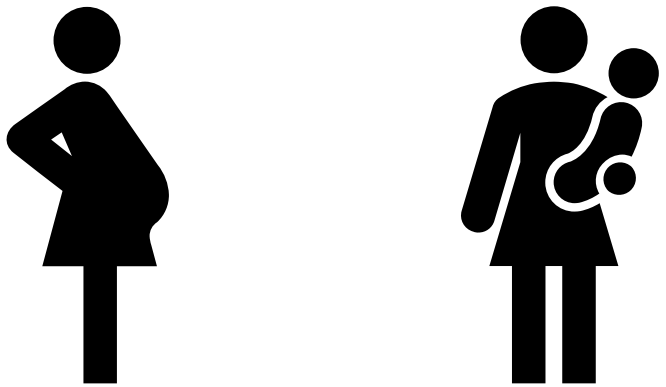
FETAL GROWTH – EFFECT PLACENTA



- Anti-proliferative and pro-apoptotic effects on trophoblast cells
- Inhibit extravillous trophoblast invasion
- Inflammation
- Insulin resistance

13wks: crown-rump-length
20 and 30wks: Fetal weight
Head circumference

Birthweight
Birth length
Head circumference



13 weeks GA

20 weeks GA

30 weeks GA

0 years

Bisphenols/phthalates

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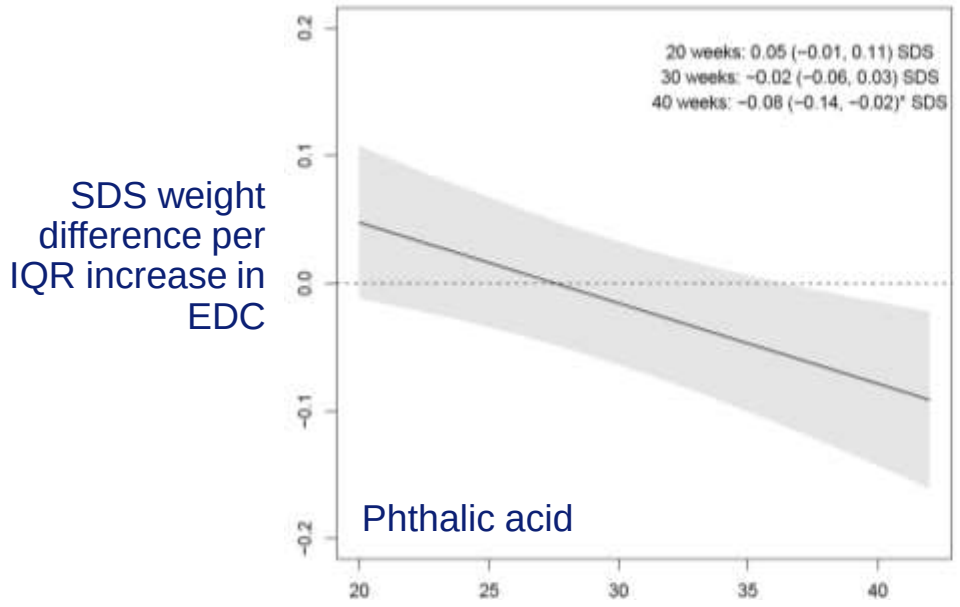
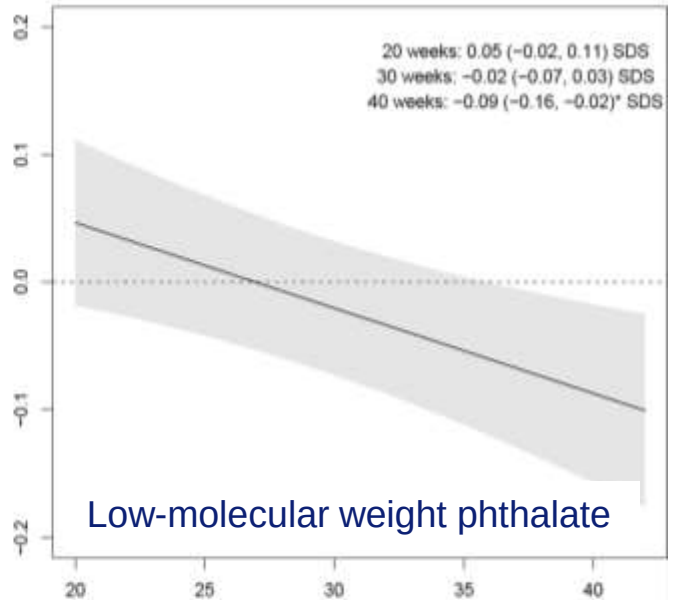
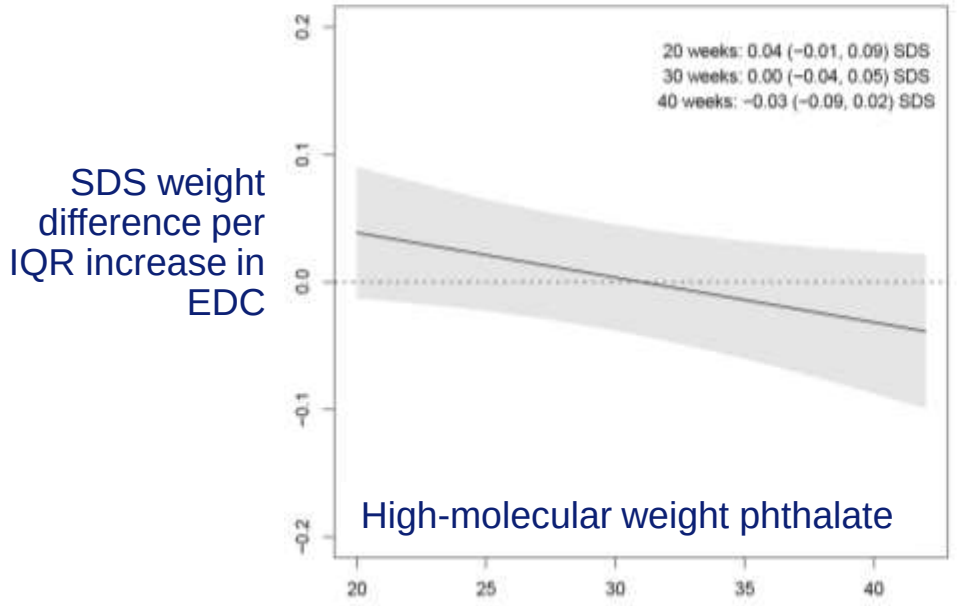
FETAL GROWTH

- ↑ phthalates → ↓ weight across gestation
- Associations stronger as pregnancy progressed







Source: Santos S, Sol CM, van Zwol-Janssens C, Philips EM, Asimakopoulos AG, Martinez-Moral MP, Kannan K, Jaddoe VWV, Trasande L. Maternal phthalate urine concentrations, fetal growth and adverse birth outcomes. A population-based prospective cohort study. Environ Int. 2021 Jun;151:106443

FETAL GROWTH

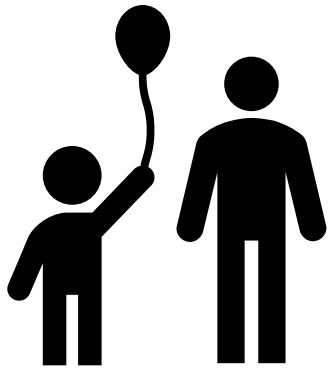
Bisphenols

- ↑pregnancy-averaged bisphenol S → ↑fetal head circumference across pregnancy
- ↑bisphenol S 1st trimester → ↑head circumference 1st and 3rd trimester
- ↑ bisphenol S 1st trimester → ↑fetal weight at birth
- ↑ bisphenol S 1st trimester → ↓risk on small-for-gestational-age

- No consistent associations of bisphenol A or F

Source: Sol CM, van Zwol-Janssens C, Philips EM, Asimakopoulos AG, Martinez-Moral MP, Kannan K, Jaddoe VWV, Trasande L, Santos S. Maternal bisphenol urine concentrations, fetal growth and adverse birth outcomes: A population-based prospective cohort. Environ Health. 2021 May 15;20(1):60.

CHILD REPRODUCTIVE DEVELOPMENT



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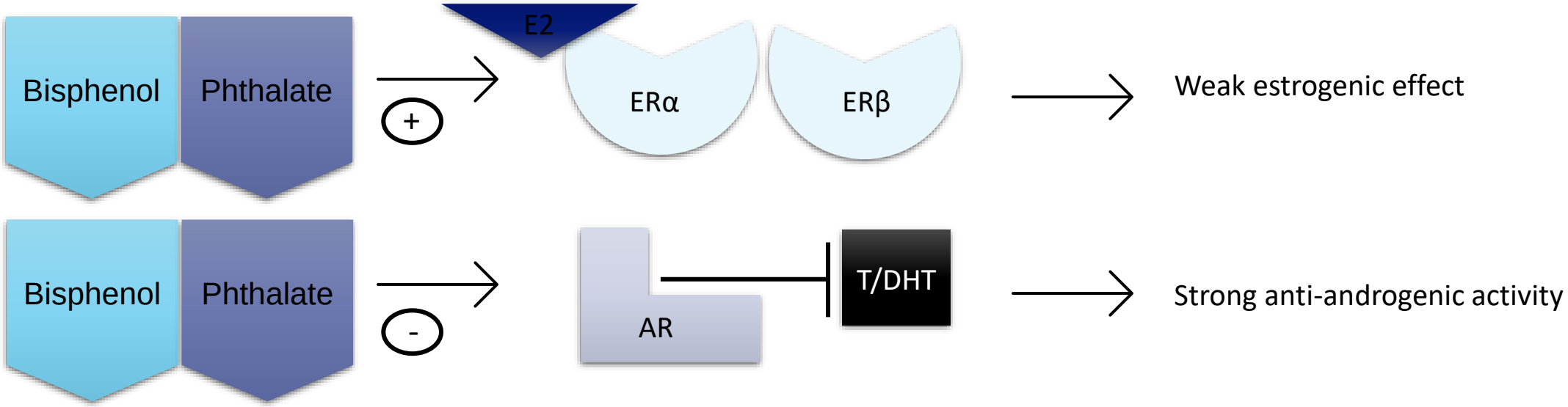
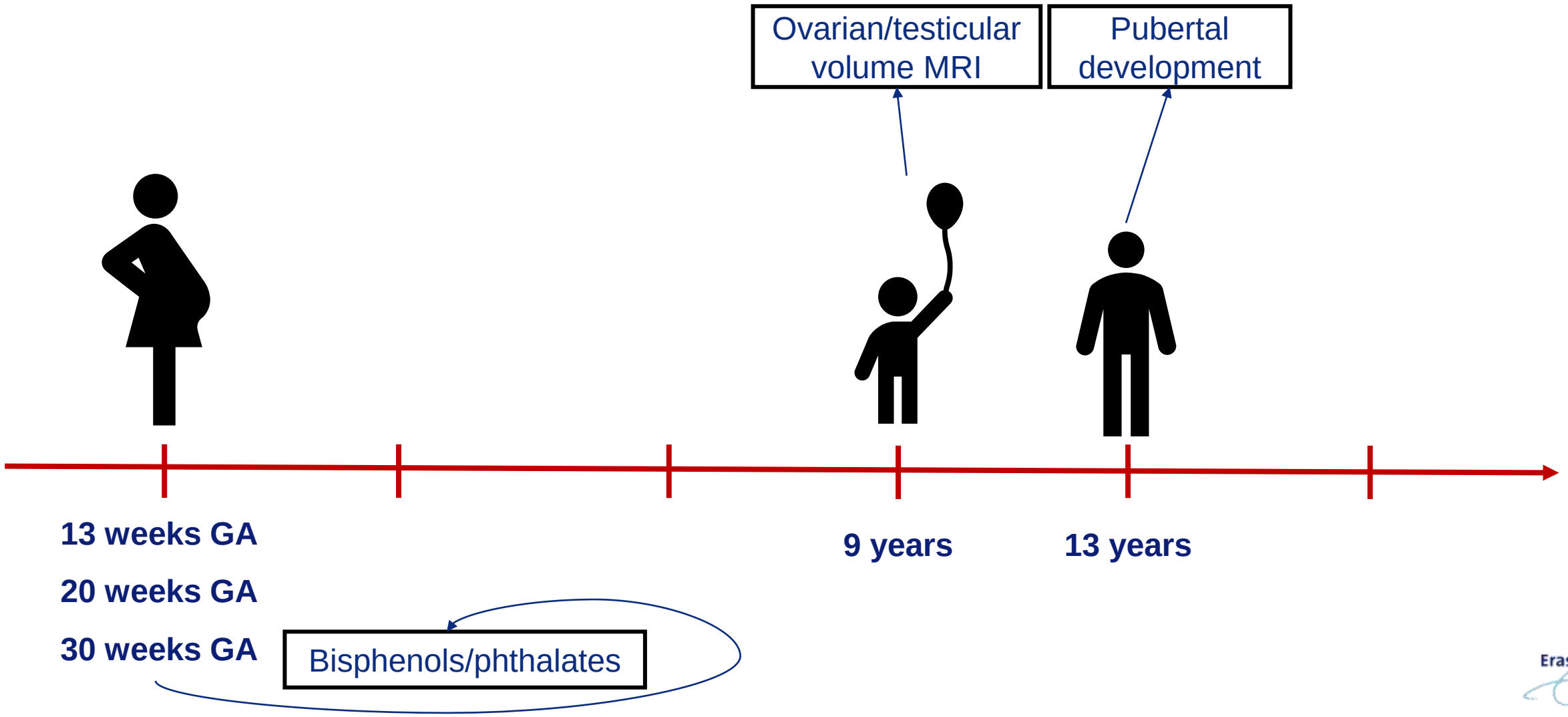
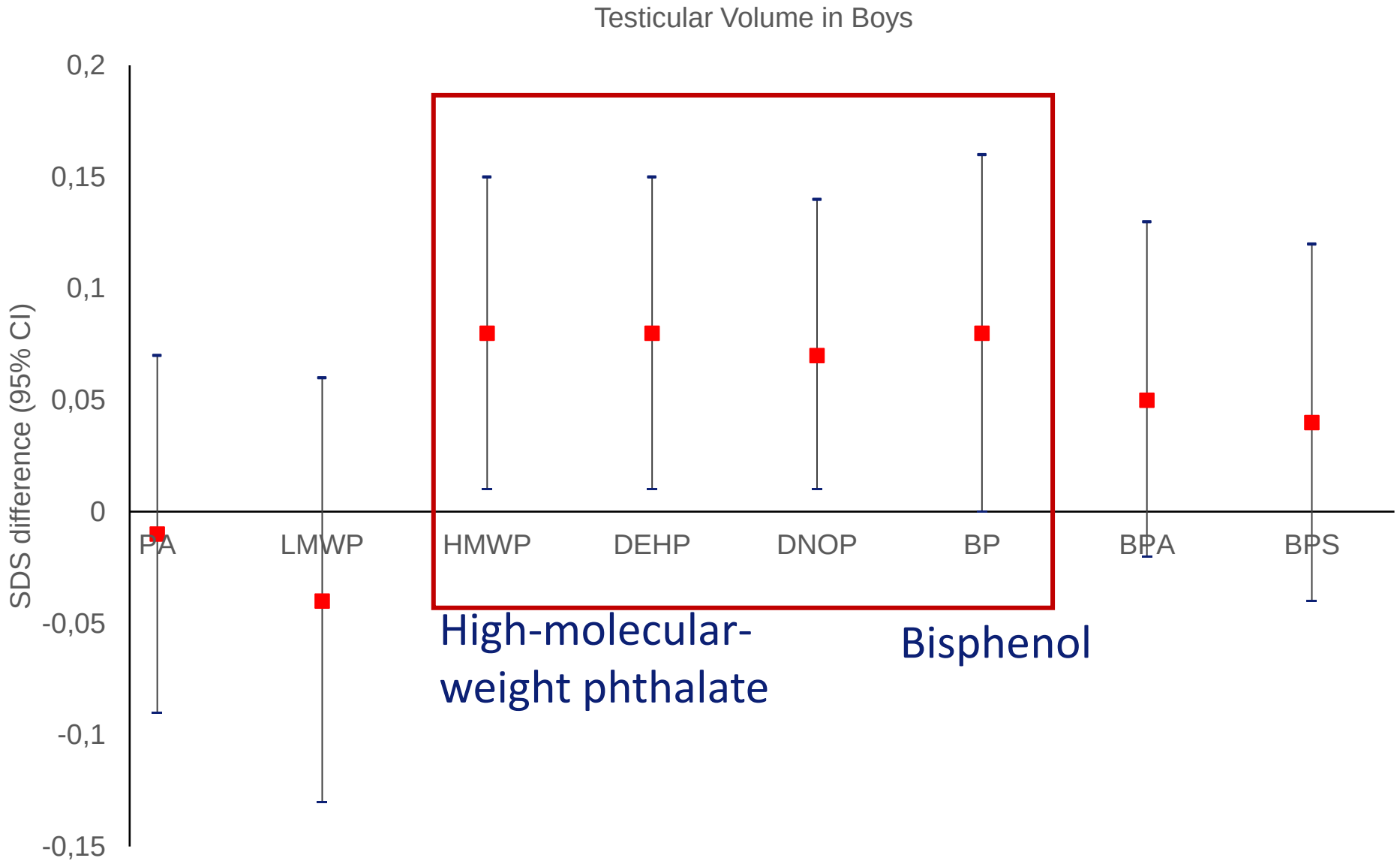
REPRODUCTIVE DEVELOPMENT




Ovarian/testicular volume MRI
Pubertal development
13 weeks GA
20 weeks GA
30 weeks GA
9 years
13 years
Bisphenols/phthalates

Boys 10yr



Source: Blaauwendraad SM, Jaddoe VW, Santos S, Kannan K, Dohle GR, Trasande L, Gaillard R. Associations of maternal urinary bisphenol and phthalate concentrations with offspring reproductive development. Environ Pollut. 2022 Sep 15;309:119745.

CHILD PUBERTAL DEVELOPMENT

Boys:

- ↑pregnancy averaged phthalic acid → faster genital development 13 yr
- ↑pregnancy averaged bisphenol A → faster pubic hair development 13 yr

Girls:

- ↑pregnancy averaged high-molecular weight phthalate → faster pubic hair development 13 yr

SUMMARY ENDOCRINE DISRUPTORS

- Developmental origins of health and disease
- Bipshenols and phthlates endocrine-disrupting chemicals
- Maternal
  - Bisphenols and phthalates → decreased gestational weight gain
  - Phthalates → unfavourable sLFT:PIGF ratio (hemodynamics)
- Fetus:
  - Phthalates → decreased fetal growth
  - Bisphenols → increased fetal growth
- Children:
  - Bisphenols and phthalates → faster pubertal development

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IMPORTANT CONSIDERATIONS

- Endocrine disruptors: long-term health effects
- Economic consequences
- Ethics of use
- Policy on a global level
  - EU some restrictions, less than other continents
- Clinical implication: be aware and inform patients

FUTURE RESEARCH

- Repeat research in large multi-ethnic populations

Our future focus → effect of environmental exposures on:

- Morbidity and mortality in adulthood
- Effects over generations

- Fertility
- Parental health before pregnancy

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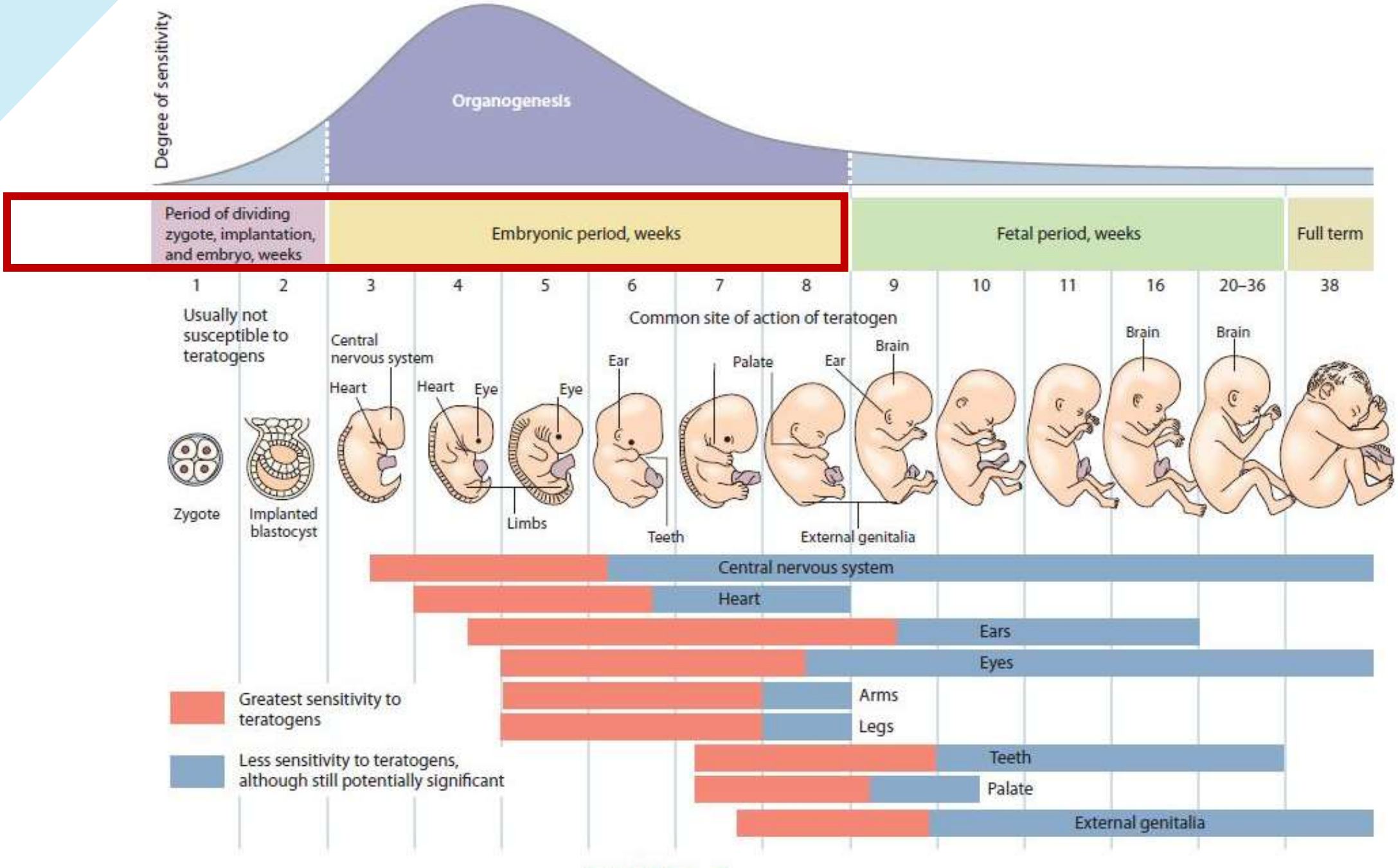
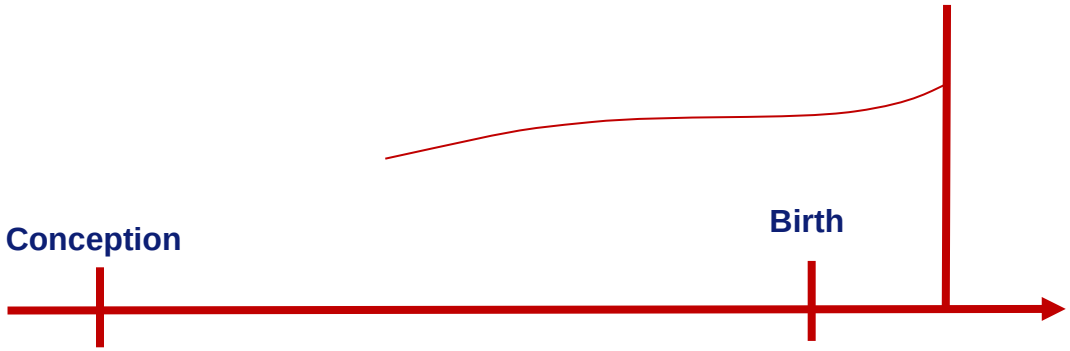
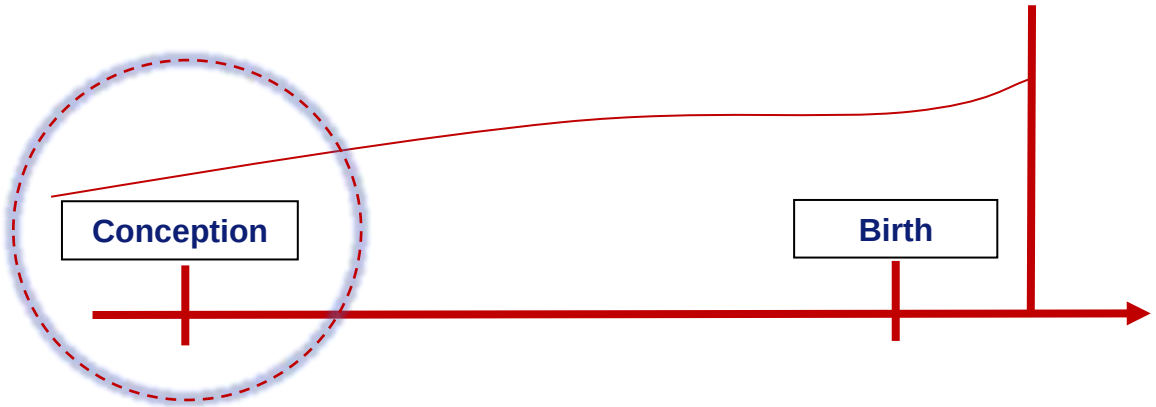

Degree of sensitivity
Organogenesis
Period of dividing zygote, implantation, and embryo, weeks
Embryonic period, weeks
Fetal period, weeks
Full term
1
2
3
4
5
6
7
8
9
10
11
16
20–36
38
Usually not susceptible to teratogens
Common site of action of teratogen
Central nervous system
Heart
Heart
Eye
Eye
Ear
Palate
Ear
Brain
Brain
Brain
Zygote
Implanted blastocyst
Limbs
Teeth
External genitalia
Central nervous system
Heart
Ears
Eyes
Arms
Legs
Teeth
Palate
External genitalia
Greatest sensitivity to teratogens
Less sensitivity to teratogens, although still potentially significant

Generation R



Generation R Next



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Participating mothers and children

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Erasmus University Rotterdam

Erasmus MC Universitair Medisch Centrum Rotterdam

Diabetes Fonds

erc

NIH National Institutes of Health

ZonMw

NWO Nederlandse Organisatie voor Wetenschappelijk Onderzoek

THANK YOU FOR YOUR ATTENTION

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