Département femme-mère-enfant

UNIL | Université de Lausanne

DIABETES PREVENTION… STARTS IN MUMMY'S BELLY

Pr Jardena Puder

28.09.2023

Interdisciplinary GDM Group Lausanne

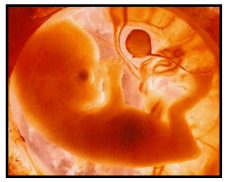
Clinical care and research for mother and infant

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE (**DOHAD**)

Conception 1000 DAYS 2nd birthday

2nd hits

Adulthood





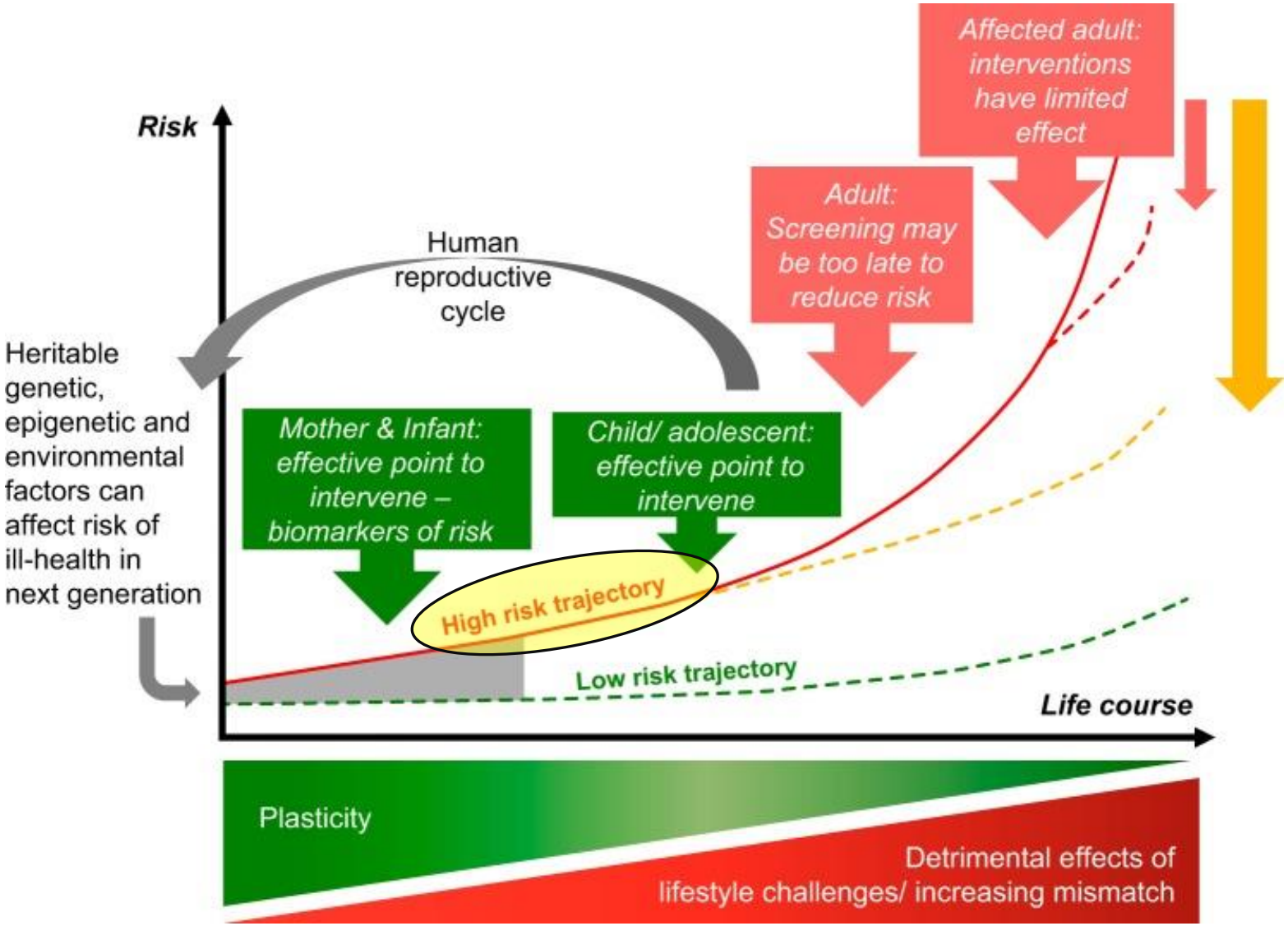
Normal variations in nutrition, stress, environmental toxicants exposure,

Periconceptional & perinatal disorders and interventions:
Preterm birth, Intra-uterine growth restriction, Maternal diabetes/overweight, C-section, ART

Nutrition,
Taste development
Microbiome
Stress
Toxicants

Non Communicable Diseases:
Hypertension,
Kidney disease
Diabesity
Cancer
Broncho-pulmonary disease
Infertility
Neuro-psychic vulnerability,
Senescence…

Epigenetic changes: DNA methylation, histones deacetylation/ methylation, phosphorylation, ncRNA



Hanson MA, Physiolog Reviews 14

TRANSGENERATIONAL APPROACH/LIFE TRAJECTORY EXAMPLE OBESITY

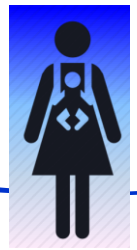
Genetic

Epigenetic risk:

« Intrauterine programming »

Family lifestyle

Parental guidance



→Starting early gives higher return on investment

But when is « early »…..?

Pregnancy, preconception?

MENU IN THE BELLY

- Nutrition
- Obesity
- GDM
- Stress
- Interventions (not Metformin)

DEVELOPMENTAL PROGRAMMING OF SIGNALING PATHWAYS FOR ENERGY HOMEOSTASIS, APPETITE REGULATION AND METABOLISM

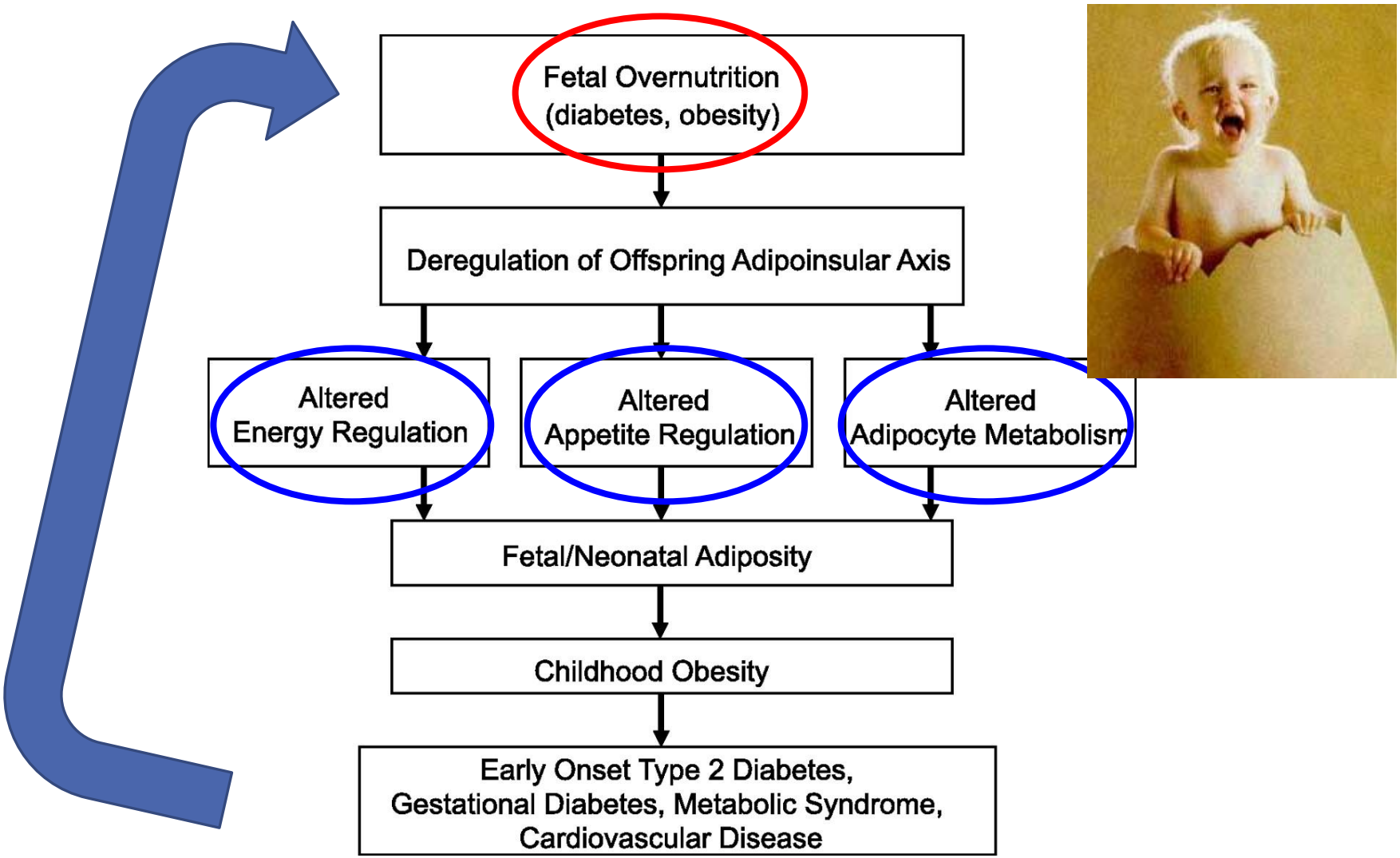
Before and during pregnancy

- Different maternal diets → programming of the offspring, also at the level of hypothalamus.
- Choice and timing of maternal diet exposure → effects on phenotypes, often gender-specific.
- Studies with little or no weight gain in mothers still on high caloric diet → strong effects on offspring phenotype.

- ❑ Altered hypothalamic gene expression
- ❑ Altered regulation in response to fasting
- ❑ Hyperphagia
- ❑ Disturbed glucose homeostasis, beta-cell number (D/O)
- ❑ Mass & fonction of adipocytes (stem cell lineages, D/O)
- ❑ Microbiota, Mitochondria (D/O)

Dearden L, Frontiers in Neuroendocrinology 2015
Agarwal P, 2018

HYPERALIMENTATION IN PREGNANCY



Dabelea D , Crume T, Diabetes 11
Curham , Circulation 1996

FETAL MALNUTRITION
(MALNUTRITION OR POOR PLACENTAL FUNCTION)

Mal- or undernutrition

↓

"Programming" of glucose-insulin metabolism
Epigenetic changes (also IGF-1), IUGR

↙ ↘

Low post-natal nutrition
High energy expenditure
Normal weight or lean adult

↓

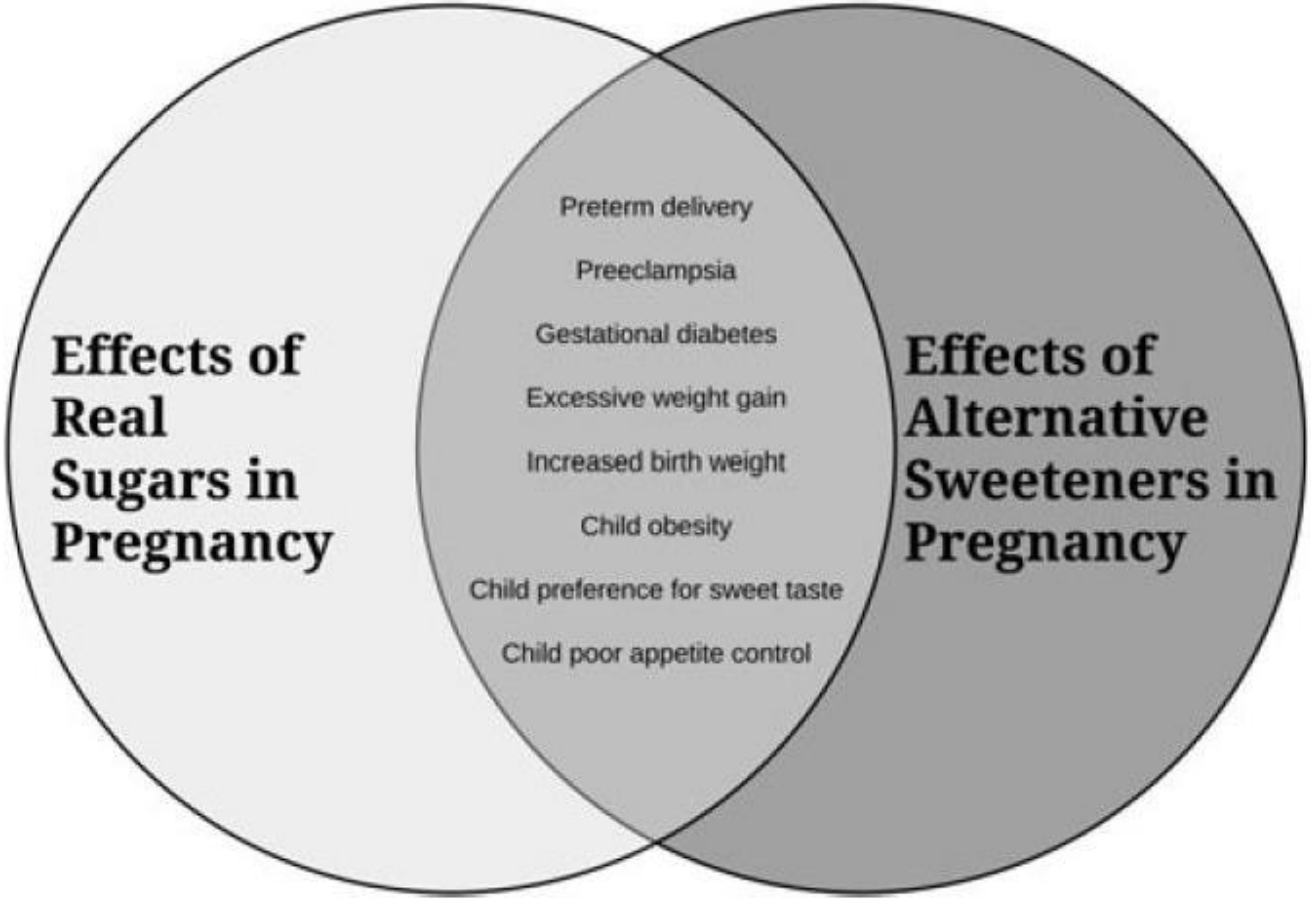
No diabetes

Excess nutritional intake
Obese adult
Low energy expenditure

↓

Insulin resistance, DM2
Metabolic syndrome

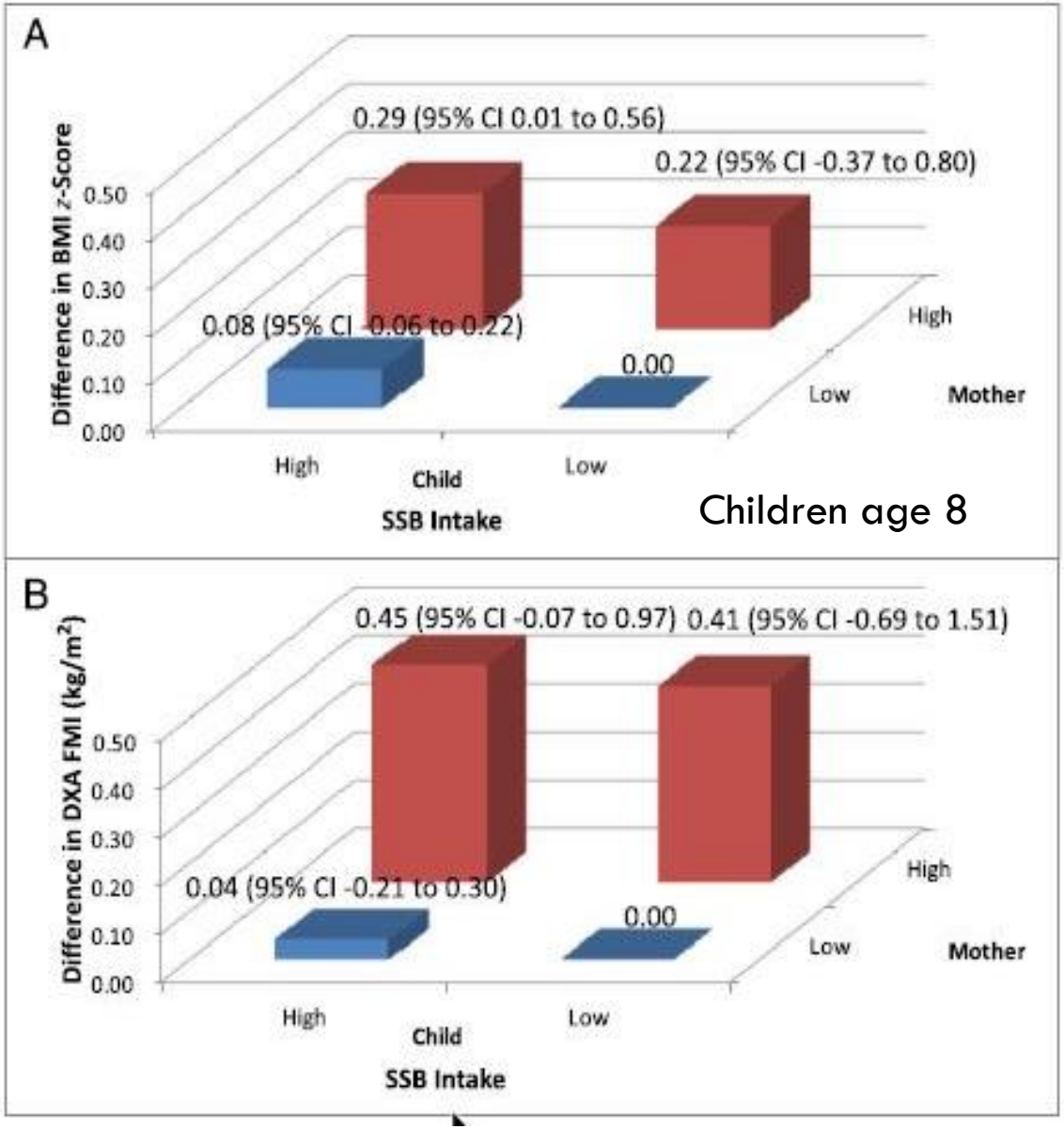
GLUCOSE/SUCROSE/FRUCTOSE AND ARTIFICIAL SWEETENERS: «SECOND HAND SUGAR EFFECT»



Excess sugar intake and artificial sweeteners in pregnancy (and even pre-conception…) have an impact on maternal and offspring health. Often independent of total energy intake and other confounders

Goran MI; Proceedings Nutrition Society 2018

SUGAR-SWEETENED BEVERAGES (SSB)



Children age 8

SSB mother in pregnancy &
SSB children age 8

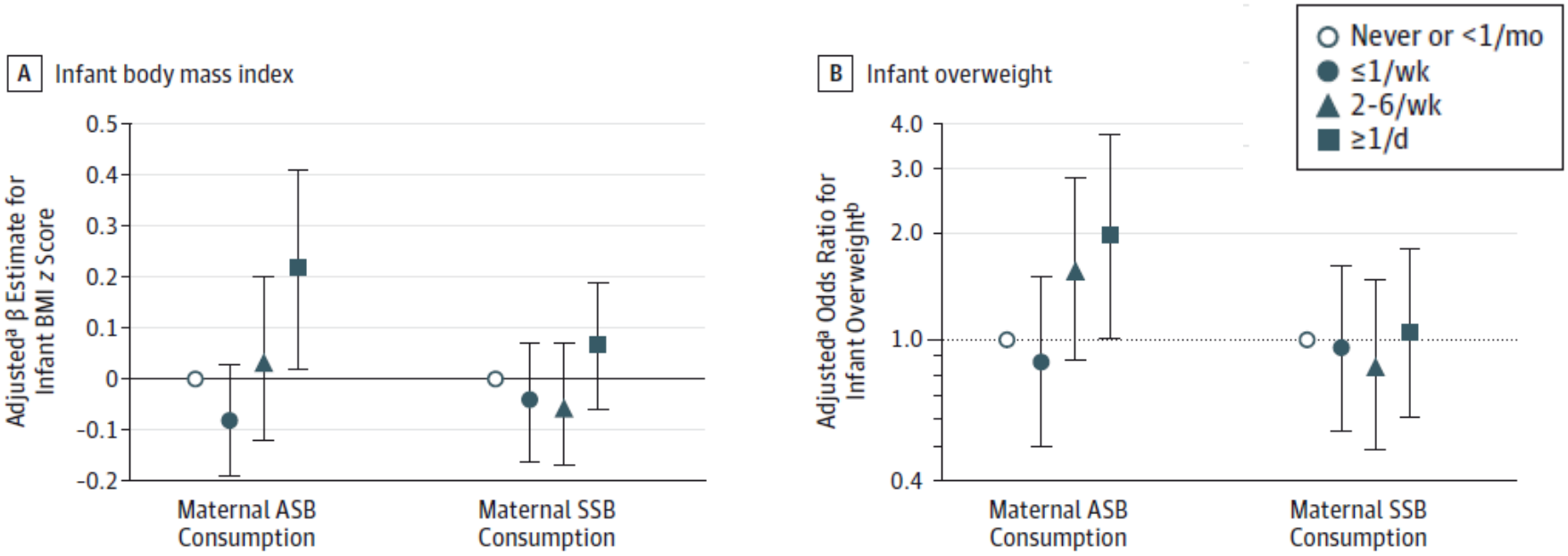
< 2 vs ≥ 2 servings/d 2ème T vs
0.5 vs 0.5 servings/wk child SSB

Association of the combination of maternal second-trimester (<2 vs ≥2 servings per day) and child (<0.5 vs ≥0.5 servings per week) intake of SSBs with BMI *z* score, A, and DXA FMI, B, in midchildhood. Low mother/low child is the referent group. Estimates are adjusted for maternal age, race and/or ethnicity, education, smoking, parity, and prepregnancy BMI; household income; and child age and sex. Data are from 1078 mother-child pairs participating in Project Viva. *N* = 272 low mother/low child, *N* = 720 low mother/high child, *N* = 13 high mother/low child, and *N* = 73 high mother/high child.

GillmanMW, Pediatrics 17

ARTIFICIAL SWEETENERS AND BODY COMPOSITION

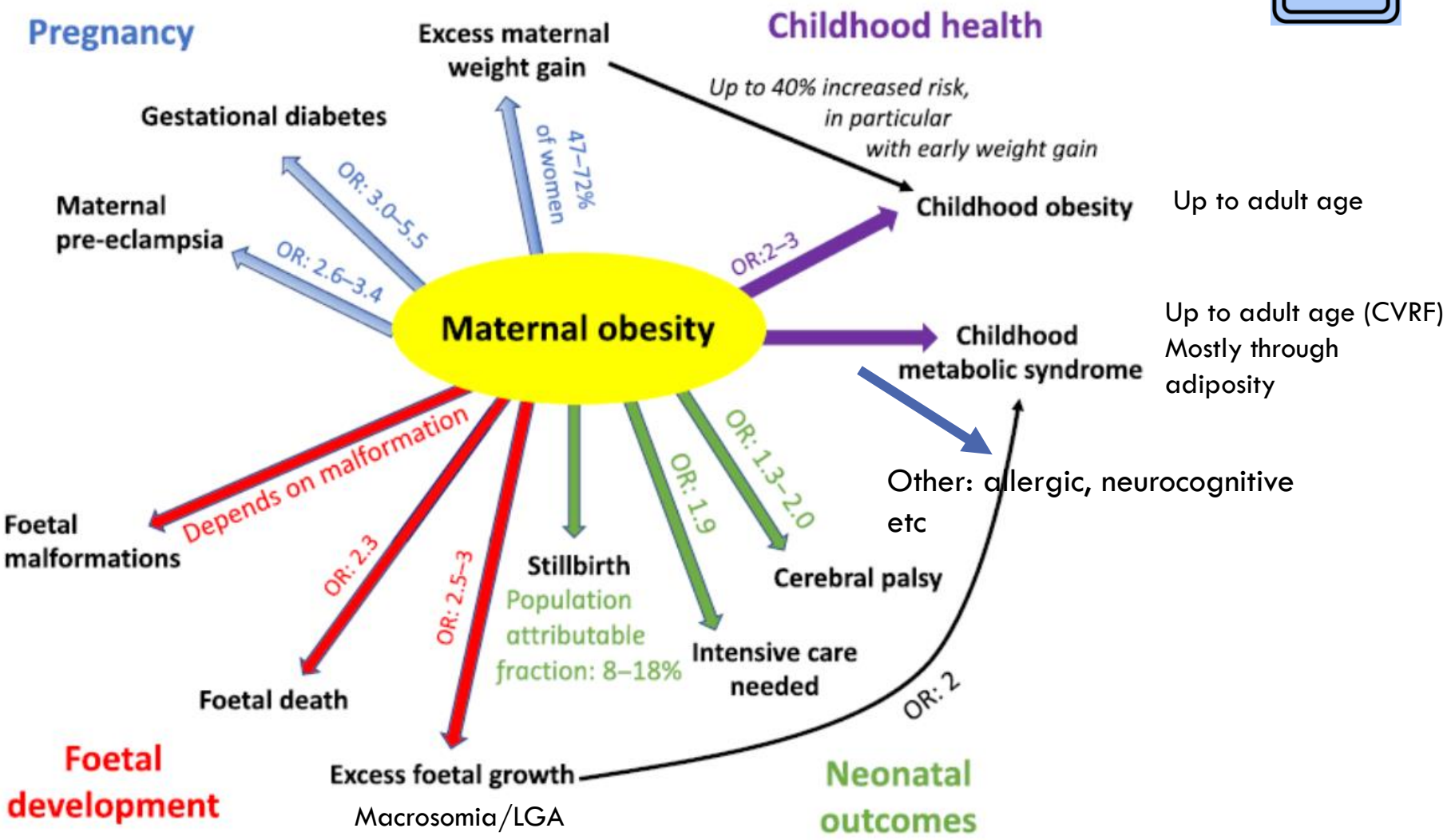
Maternal consumption of artifical sweeteners and sweet beverages and offspring body composition at 1 year



Size: 1 can (12 oz=350 ml)

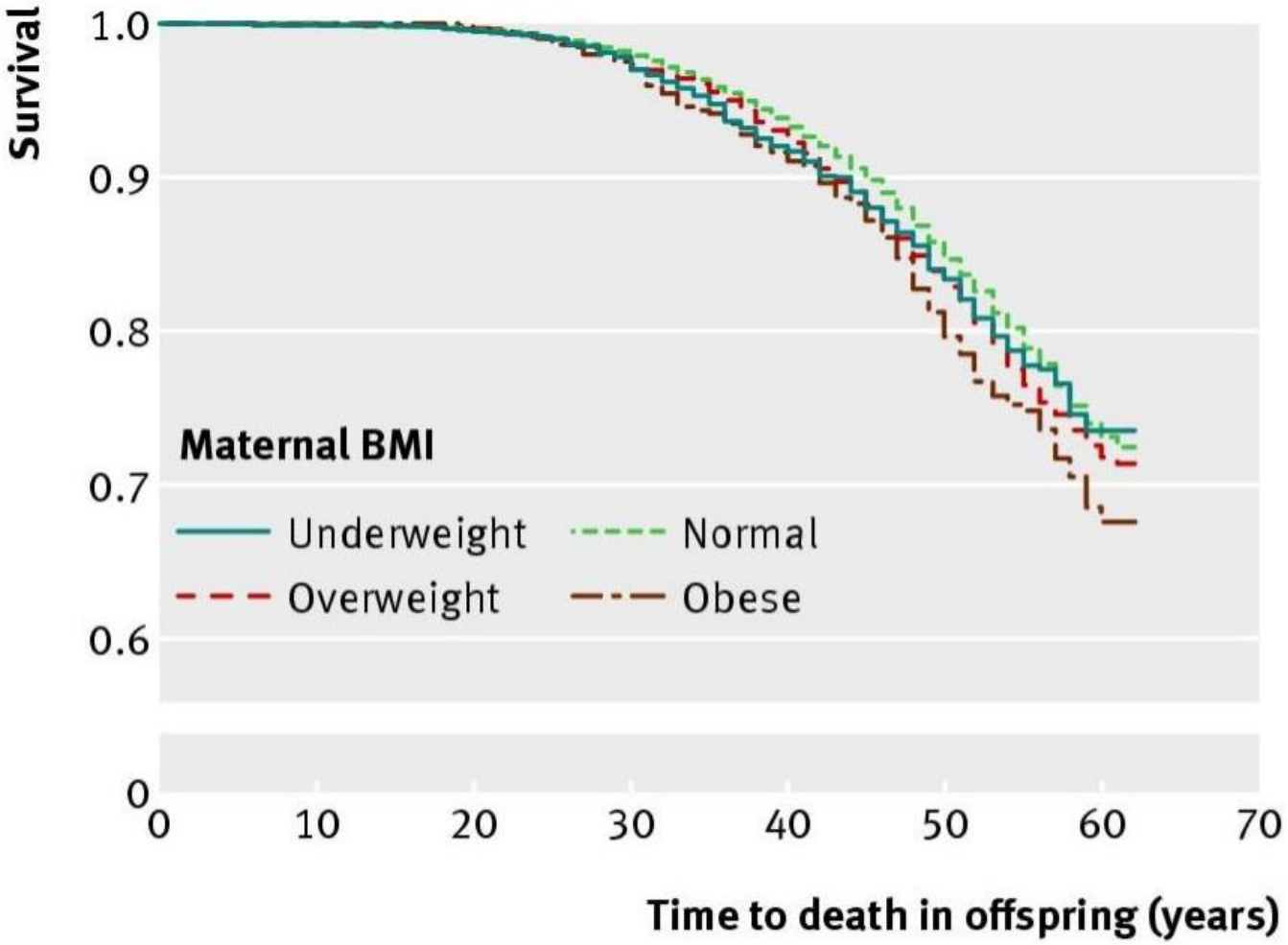
Azad M, *JAMA Pediatr.* 2016

MATERNAL OBESITY



Mitanchez D, Acta Paediatrica 18

MATERNAL OBESITY AND OFFSPRING MORTALITY

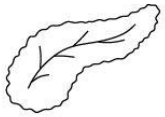
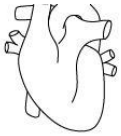


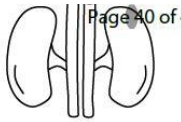
Death rates in offspring according to maternal BMI category Reynolds RM, BMJ 2013

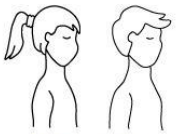
OB: All-cause mortality is 35% increased. Hosp for CV event: 29% increased

MATERNAL OBESITY: PATHWAYS FOR THE METABOLIC OFFSPRING HEALTH



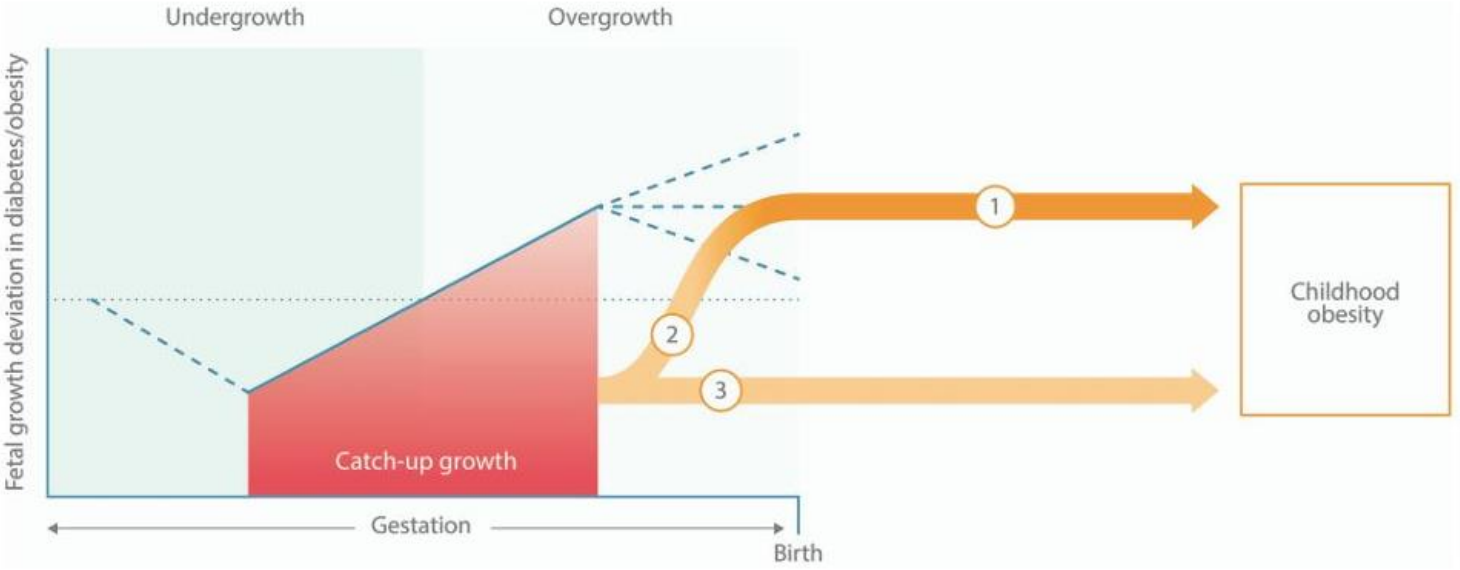





 Humans	Macrosomia Obesity ↑ Fat mass	n/a	Insulin resistance ↑ risk of type 2 diabetes	Subclinical fetal cardiac dysfunction ↑ risk of CVD	Hypertension Altered vascular structure	Impaired kidney development ↑ risk of chronic kidney disease
 Animal models	↑ Body weight ↑ Fat mass Adipocyte hypertrophy Impaired adipocyte proliferation Altered WAT metabolism ↑ WAT inflammation	Hyperphagia Altered hypothalamic appetite regulation Hypothalamic leptin resistance	Hyperinsulinaemia Glucose intolerance Peripheral insulin resistance β-cell dysfunction	Cardiac dysfunction Cardiac hypertrophy ↑ cardiac inflammation ↑ cardiac oxidative stress ↑ cardiac fibrosis Altered cardiac metabolism ↑ cardiac susceptibility to damage	Hypertension Altered vascular structure Altered response to vasoactive signals ↑ baroreflex set point	↓ renal function Altered renal structure ↑ kidney inflammatio ↑ kidney fibrosis ↑ kidney oxidative stress ↑ kidney susceptibilit to damage

Inzani I, 2023

GROWTH PATTERN IN MATERNAL OBESITY, GDM AND DM1: INTRAUTERINE CATCH-UP

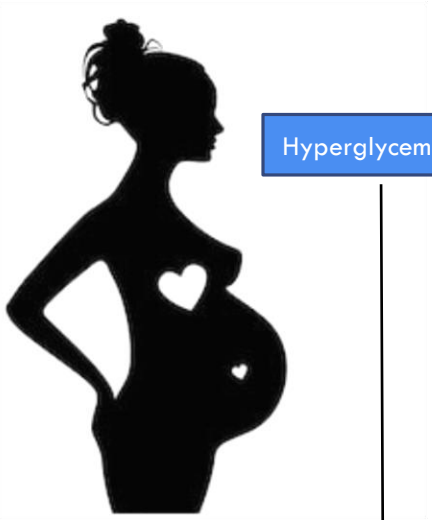


ARTICLE HIGHLIGHTS

- Longitudinal studies with serial measurements of fetal growth from early to late pregnancy in women with obesity, gestational diabetes mellitus, or type 1 diabetes identified similar fetal growth patterns in these conditions.
- Compared with that in healthy pregnancies, the fetal growth pattern in pregnancies complicated by obesity or diabetes is characterized by reduced growth in early pregnancy and fetal overgrowth in late pregnancy.
- The shift from growth reduction to overgrowth in pregnancies of women with obesity or diabetes implies a period of intrauterine catch-up growth.
- The intrauterine catch-up growth may constitute a risk factor for childhood obesity, and this calls for further investigation.

Van Poppel M, Diabetes Care 2[illegible]

SHORT-TERM RISKS OF PREEXISTING DM/GDM



Hyperglycemia

Fetal hyperglycemia

Chronic hypoxia

Asphyxia ↑

Pulmonary hypertension

Fetal EPO ↑

HKR ↑

Hyperbilirubinemia

Cardiomyopathy

Thromboembolic complications

Macrosomia

Cesarean sections

Transient Tachypnoa Neonate

Beta cell hyperplasia

Birth trauma

Prematurity/ Preeclampsia

Hyperinsulinemia

Glucosuria

Neonatal hypoglycemia

Surfactant ↓

RDS

Fetal magnesium ↓

Marcoux S, Diabetes Care 2022

Bankole T, Nutrients 2022

CONSEQUENCES FOR THE CHILD

Diabetes in pregnancy

Gestational diabetes

- Cardiomyopathy
- Congenital malformations
- Increased adiposity
- Macrosomia /LGA
- Prematurity
- Cesarean sections
- Asphyxia ↑
- Neonatal hypoglycemia
- Birth trauma
- Respiratory problems
- Hyper bilirubinemia
- Obesity
- Pre-/Diabetes
- Hyperten sion
- Cognitive
- Cancer

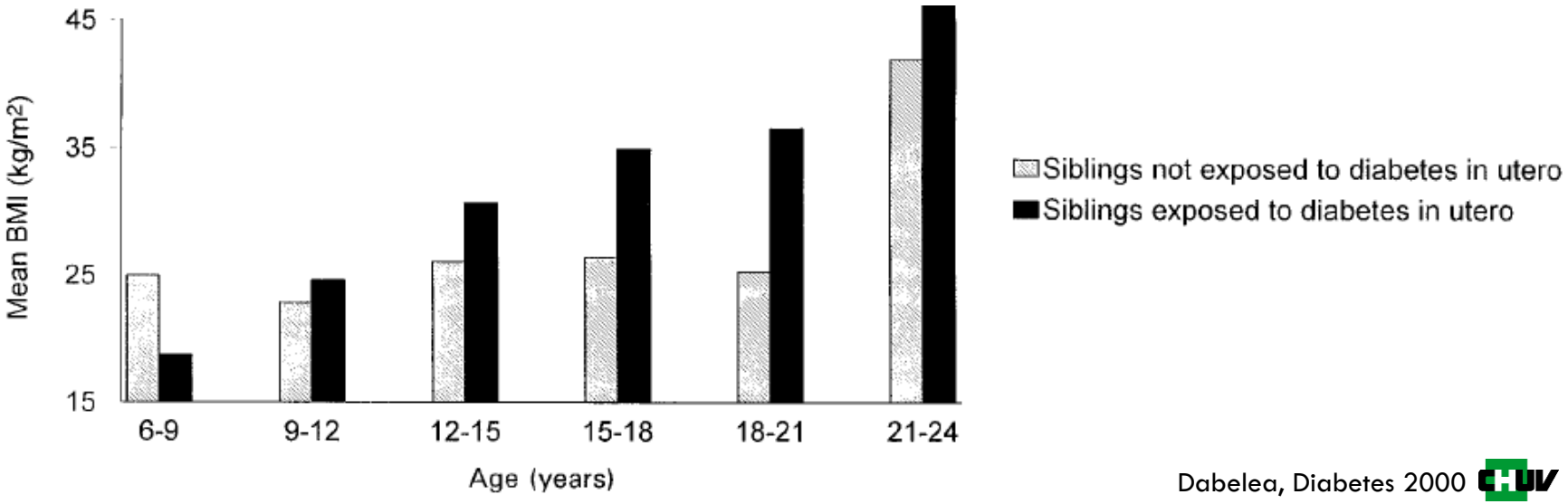
Marcoux S, Diabetes Care 2022
Bankole T, Nutrients 2022

TRYING TO ANSWER: GENETIC OR EPIGENETIC ? INTRAUTERINE EXPOSURE TO GDM

Average BMI of siblings exposed and unexposed to the diabetic intrauterine environment (> 90% GDM) by 3-year age groups

Exposed sibling:

Risk for DM: O.R. 3.7 (p=0.02)



Dabelea, Diabetes 2000

GDM: LONG TERM - IMPACT

In children 10-14 years (HAPO study)

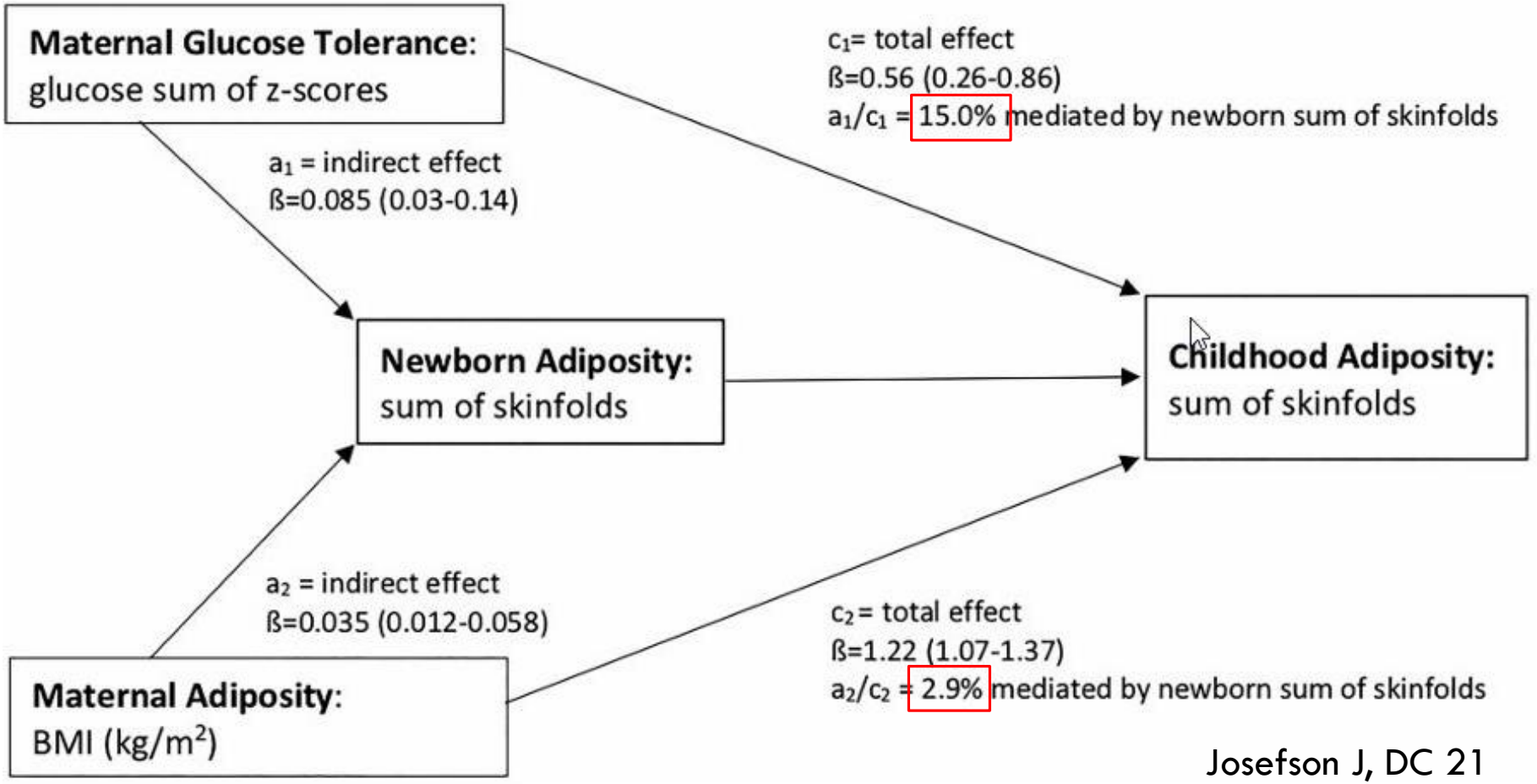
➔ **Maternal hyperglycemia linearly correlated** with increased **body fat** and incidence of **obesity** (after adjustment for maternal BMI during pregnancy).

In young adults (offspring of GDM women treated with dietary measures)

➔The risk of overweight was **doubled** compared to offspring from the base population, while the risk of **metabolic syndrome was 4 times higher** and the risk of **pre-diabetes/diabetes up to 8 times higher** (after adjustment for confounding factors).

Lowe Jr WL, Diabetologia. 2019

GDM AND/OR OBESITY?

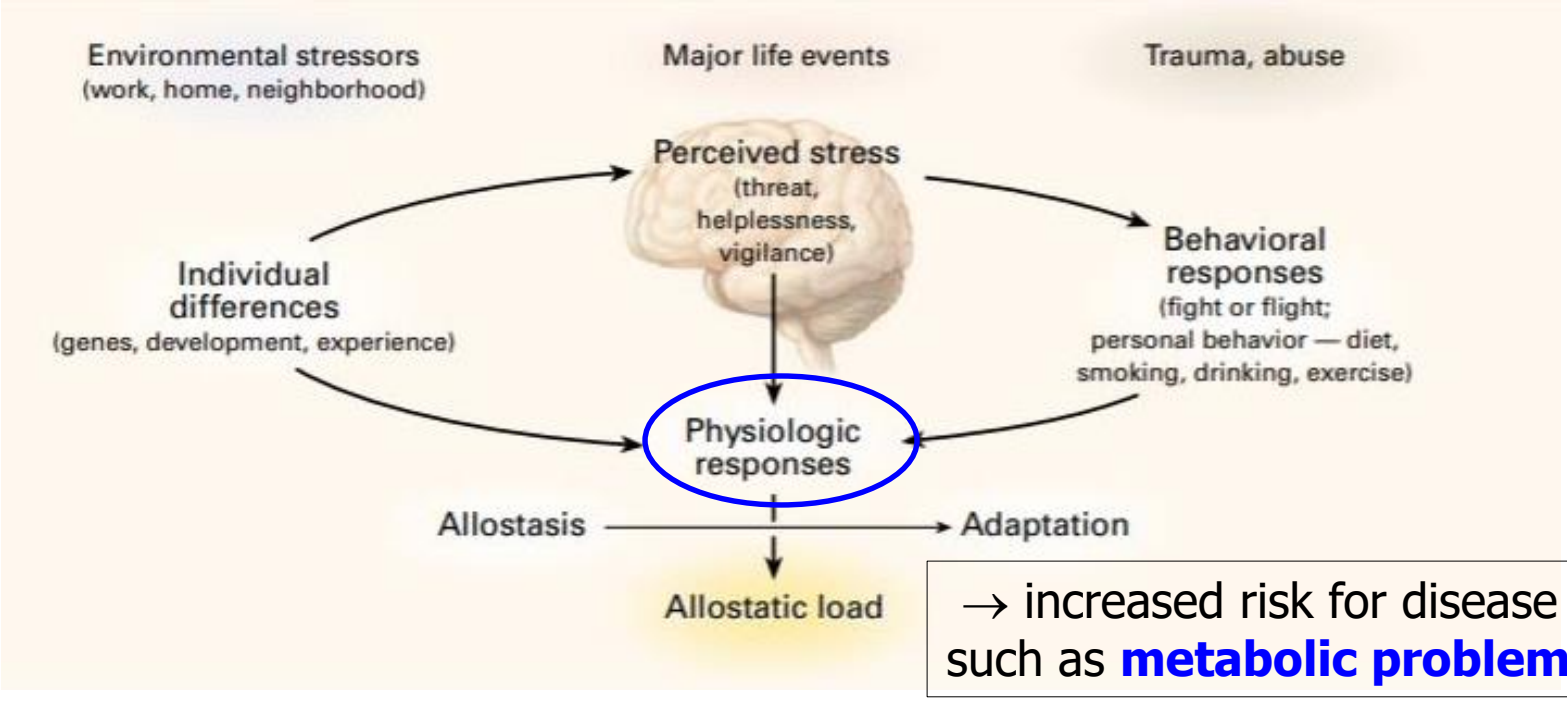


Josefson J, DC 21

ROLE OF MATERNAL STRESS

What is the role of maternal stress?

STRESS SYSTEM IN THE HUMAN BODY



→ increased risk for disease such as **metabolic problems**

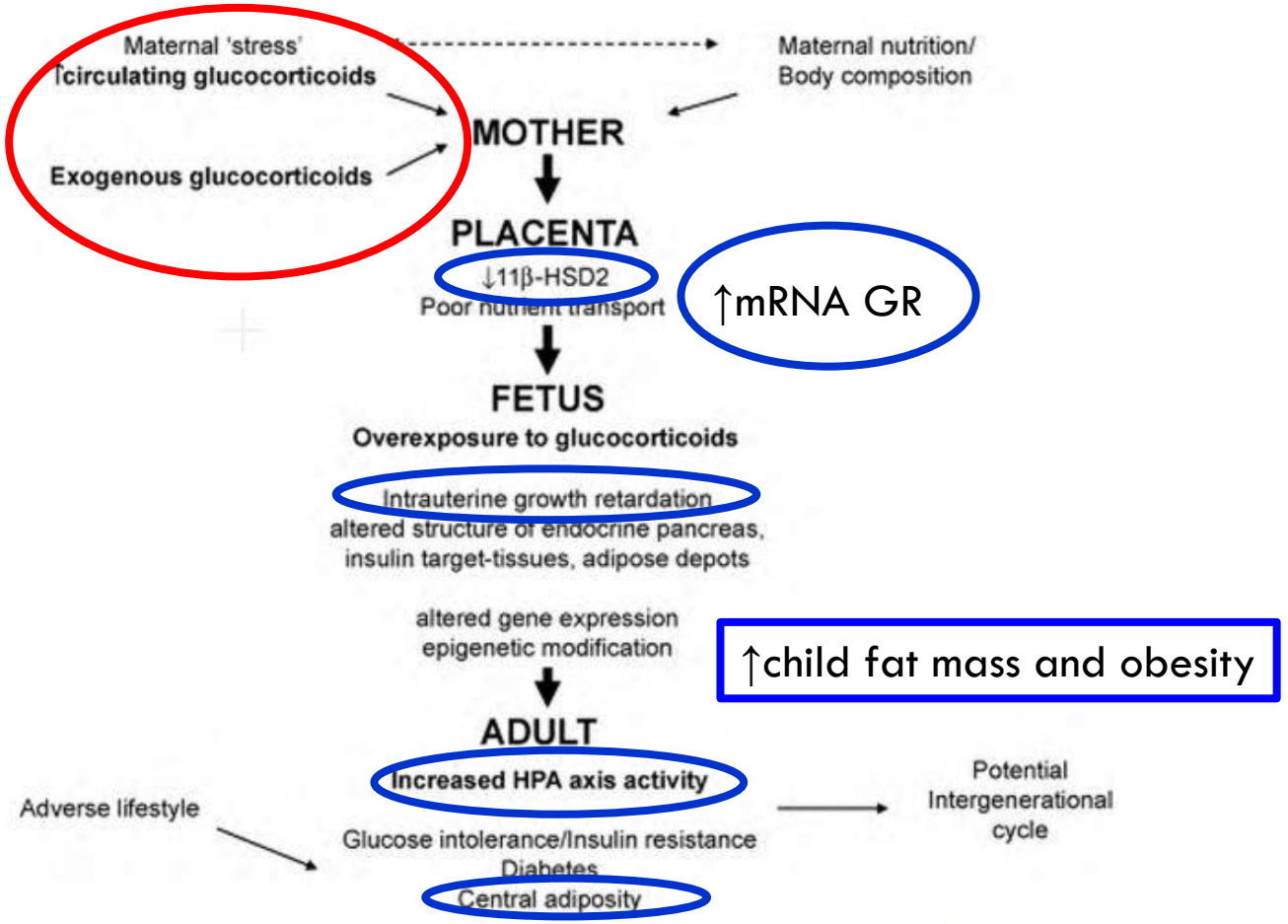
Most common allostatic physiological stress responses:

Hypothalamic-pituitary-adrenal axis (HPA)
→glucocorticoids (cortisol)

Autonomic nervous system
→ Catecholamines epinephrine (adrenaline) and norepinephrine

Silverman M. , 2014
Mc Ewen B, NEJM, 1998

STRESS AND GLUCOCORTICOIDS AND PROGRAMMATION



Salivary cortisol (especially in 2nd T) correlates with later childhood obesity (age 2-16)

Reynolds RM, Journal of Steroid Biochemistry & Molecular Biology 2010

WHAT CAN WE DO ? IN UTERO

- Treatment, even of mild GDM, helps to reduce birth weight and macrosomia (> 4kg; eg Crowther 10 % vs 21%)
- At 4- to 5-years-old, only small differences between treated and untreated mild GDM
- Chrononutritional and sleep hygiene intervention in GDM, no impact on LGA
- Most lifestyle intervention that decrease gestational weight gain also decrease LGA (large for gestational age), but not all efficient
- Early GDM treatment in high-risk GDM: 23% less LGA, but more SGA

Crowther C, NEJM 2005
Gillman M, DC 2010
Messika A, AJOG MFM 2022
Simmons D, NEJM 2023

EARLY FACTORS

Weng: Meta-analysis/systematic review

(30 prospective studies up to age 2)

- Maternal overweight and excessive gestational weight gain
- Maternal smoking during pregnancy
- High birth weight
- Rapid and early weight gain
- Short sleep duration

Increased risk of

Overweight/obesity in children

- Breastfeeding
- Late introduction of solid foods

Are moderately protective against

Weng S, Arch Dis Child 2012
Uwaezuoke, Clin Med Insights Pediatr 2017
Li L, Journal of Pediatrics and Child Health 2017
Baidal J, Am J Prev Med 16

canton de vaud

CHUV

NUMBER OF EARLY RISK FACTORS AND OW/OB AT AGE 6

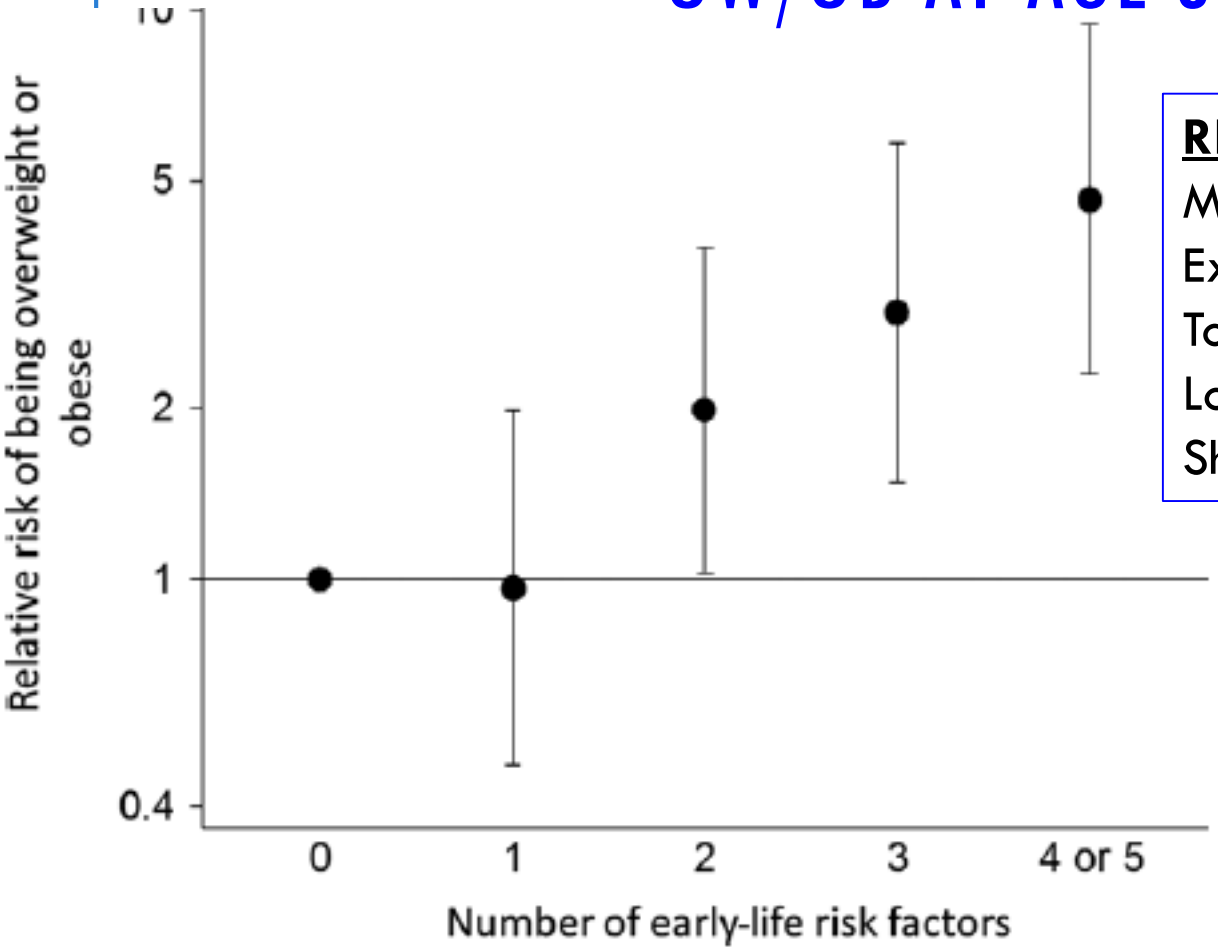


Figure 1 Relative risk (95% CI) of being overweight or obese at 6 years of age (International Obesity Task Force), according to number of early-life risk factors. Data adjusted for child's gestational age at birth, maternal height, education, parity and age at child's birth (Robinson *et al.* 2015).

RF:

Maternal obesity

Excessive gestational weight gain

Tobacco in pregnancy

Low maternal vitamin D level

Short breastfeeding duration

Robinson SM; Nutrition Bulletin 2017

Robinson S, AJCN 2015

INTERVENTIONS FOR THE CHILD

In children, protective factors include:

- Breastfeeding
- Later introduction of dietary diversification (6 months)
- Reduced consumption of sweetened beverages
- Increased physical activity
- Recognition of hunger signals

Dugas C, Obes Facts 2017
Verga MC, Nutrients 2022

THANK YOU FOR YOUR ATTENTION !

EARLY FACTORS

Weng: Meta-analysis/systematic review

(30 prospective studies up to age 2)

- Maternal overweight and excessive gestational weight gain
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Weng S, Arch Dis Child 2012
Uwaezuoke, Clin Med Insights Pediatr 2017
Li L, Journal of Pediatrics and Child Health 2017
Baidal J, Am J Prev Med 16

canton de vaud

CHUV

EARLY FACTORS (2)

Avon study , UK. Outcome: Obesity at age 7 years (900 children)

8 of 25 putative risk factors were associated with risk of obesity:

- **Parental obesity** (both parents: adjusted OR 10.44)
- Very early (at 43 months) body mass index or **rebound** adiposity (15)
- More than **8 hours of TV watching per week** at age 3 (1.55)
- **Catch-up growth** (2.60)
- **Z-score for weight** at 8 months (3.13) and 18 months (2.65)
- **Weight gain** in the first year (1.06, 1.02 to 1.10 per 100 g increase);
- **Birth weight**, per 100 g (1.05)
- **Low** (< 10.5 hours) **sleep duration** at age 3 (1.45)

Reilly JJ, BMJ 2005

NUMBER OF EARLY RISK FACTORS AND OW/OB AT AGE 6

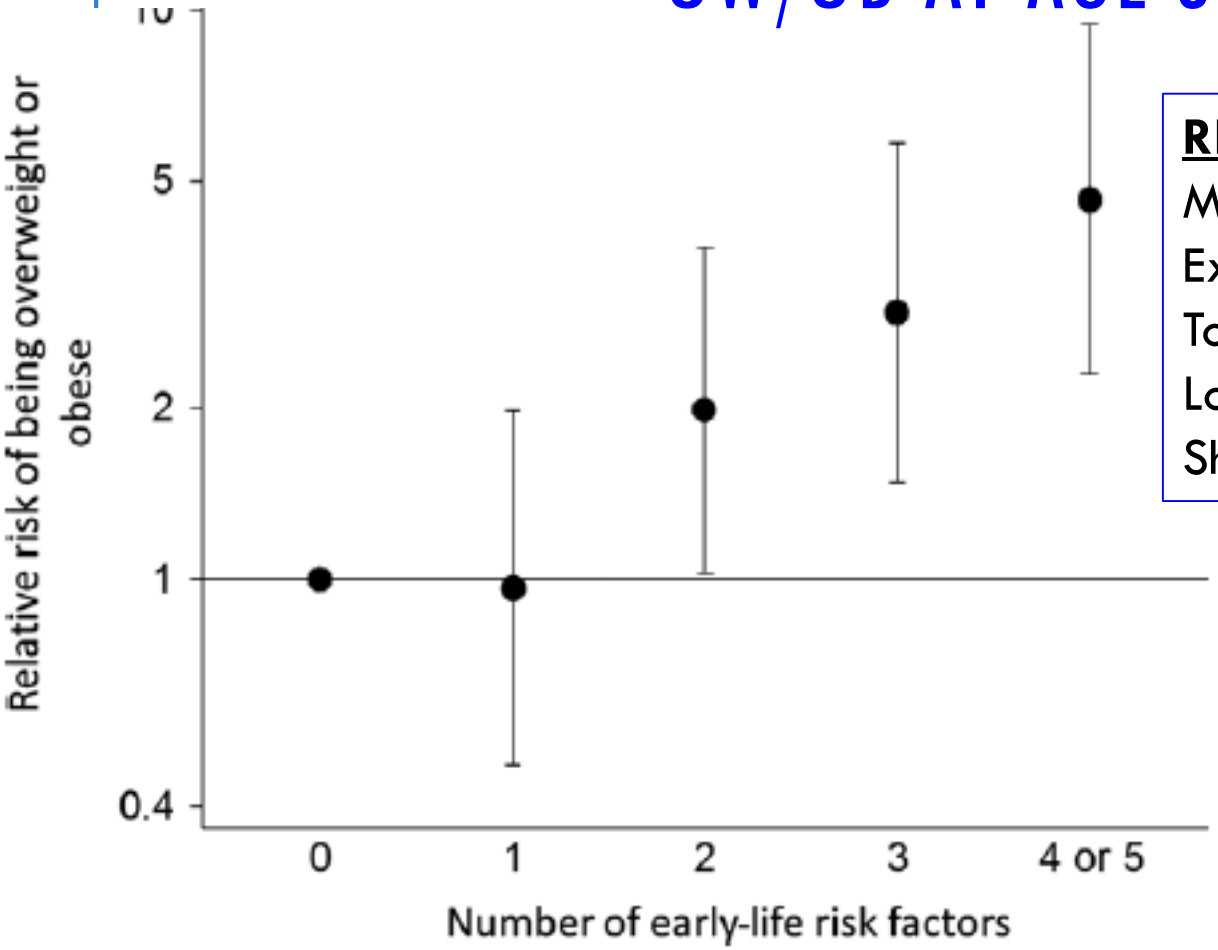


Figure 1 Relative risk (95% CI) of being overweight or obese at 6 years of age (International Obesity Task Force), according to number of early-life risk factors. Data adjusted for child's gestational age at birth, maternal height, education, parity and age at child's birth (Robinson *et al.* 2015).

RF:

Maternal obesity

Excessive gestational weight gain

Tobacco in pregnancy

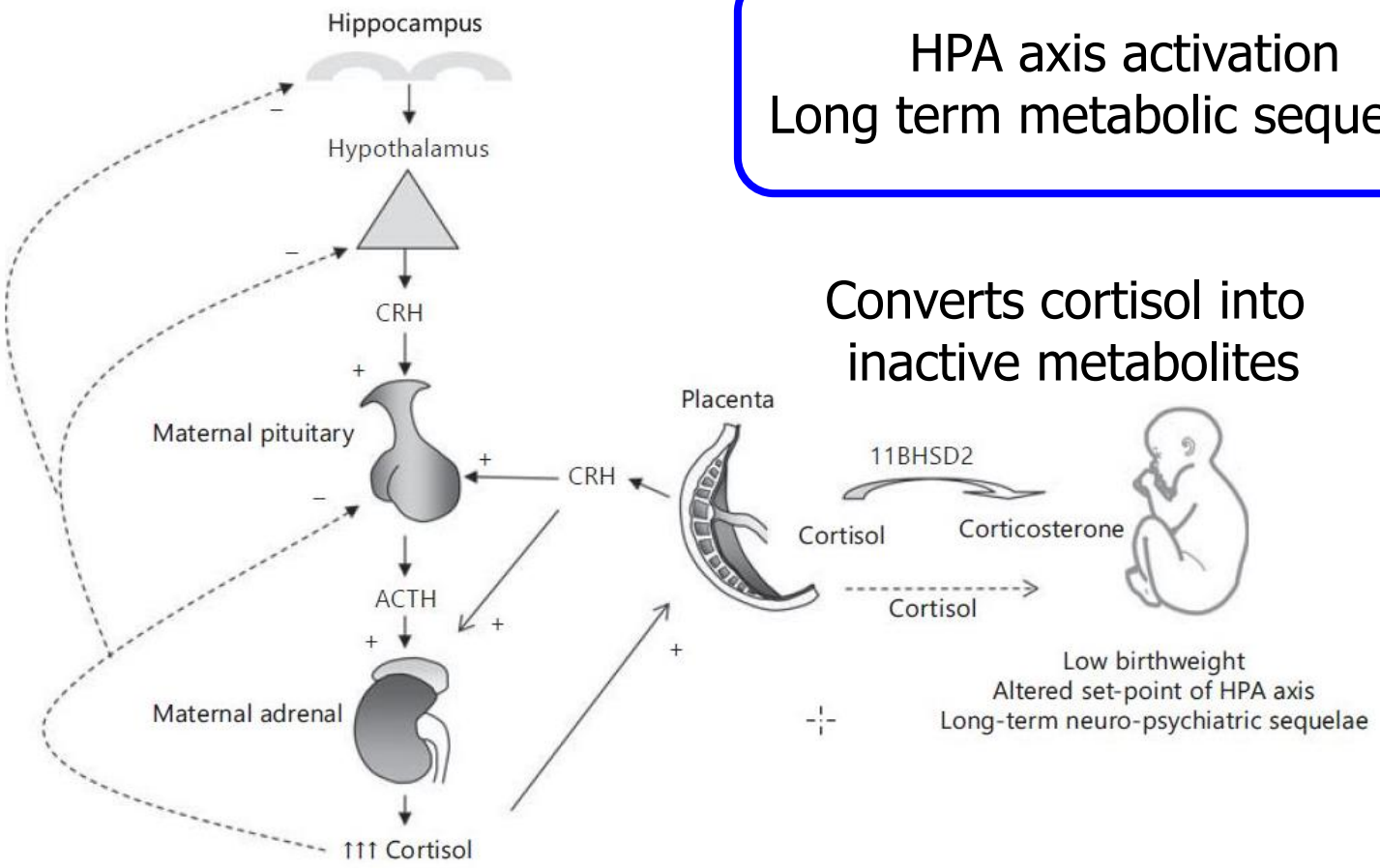
Low maternal vitamin D level

Short breastfeeding duration

Robinson SM; Nutrition Bulletin 2017

Robinson S, AJCN 2015

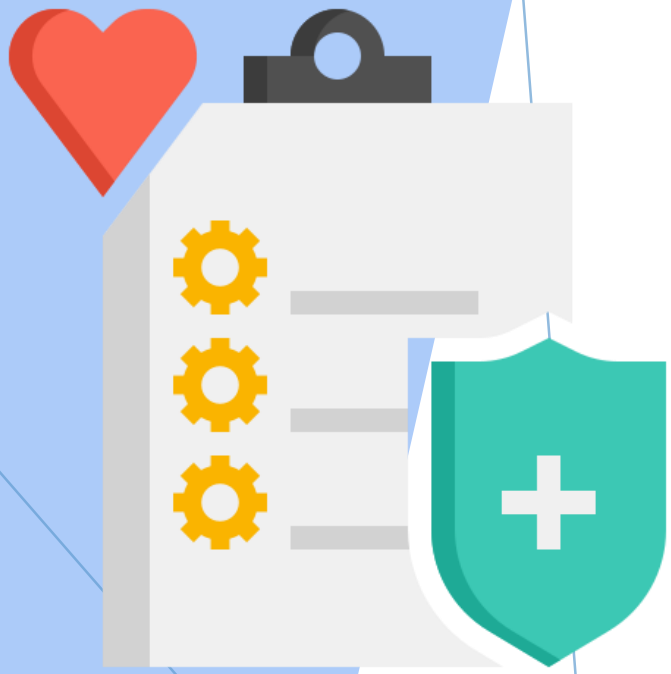
MATERNAL STRESS, HPA AXIS AND FETAL OUTCOMES



HPA axis activation
Long term metabolic sequelae

Converts cortisol into inactive metabolites

Duthie L, Neuroendo 13
Reynolds R; PNEC 13



HOW CAN THESE RISKS BE PREVENTED?

EARLY CHILDHOOD INTERVENTIONS

- Often start around 1 or 4 months and observe the results at 1-2 years. Some start in pregnancy
- Themes/messages: "breast is best", "only water in my cup", "I eat a variety of fruits and vegetables every day", hunger/satiety, distress, calming strategies, sleep

- Clinical, individual or group or "home visits"
- Results: often lower BMI, difference in behavior.
- Not all effective...

Paul I, BMC Pediatrics 2014 & Obesity 2011
Wen LM, BMJ 2012
Daniels LA, BMC Public Health 2009,
Int J Obesity 2012, Pediatrics 2013
Blake-Lamb, Am J Prev Med 16

EXAMPLE EFFECTIVE WEIGHT INTERVENTION

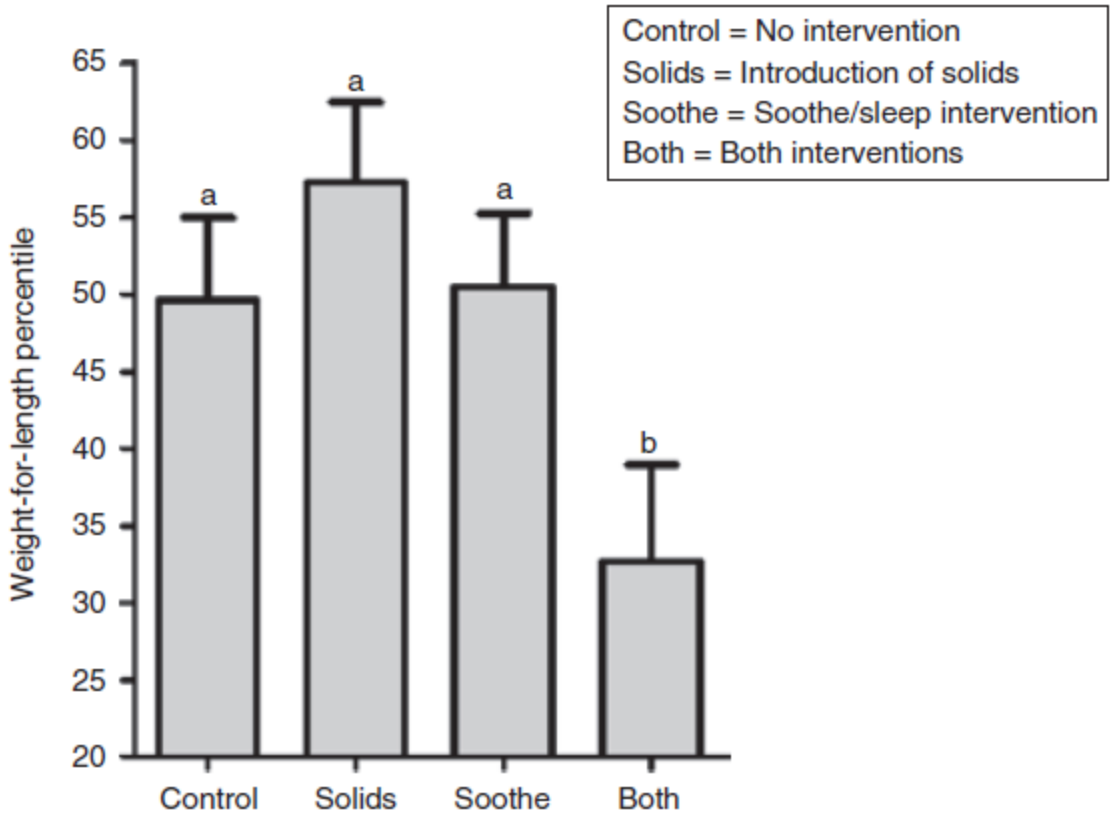
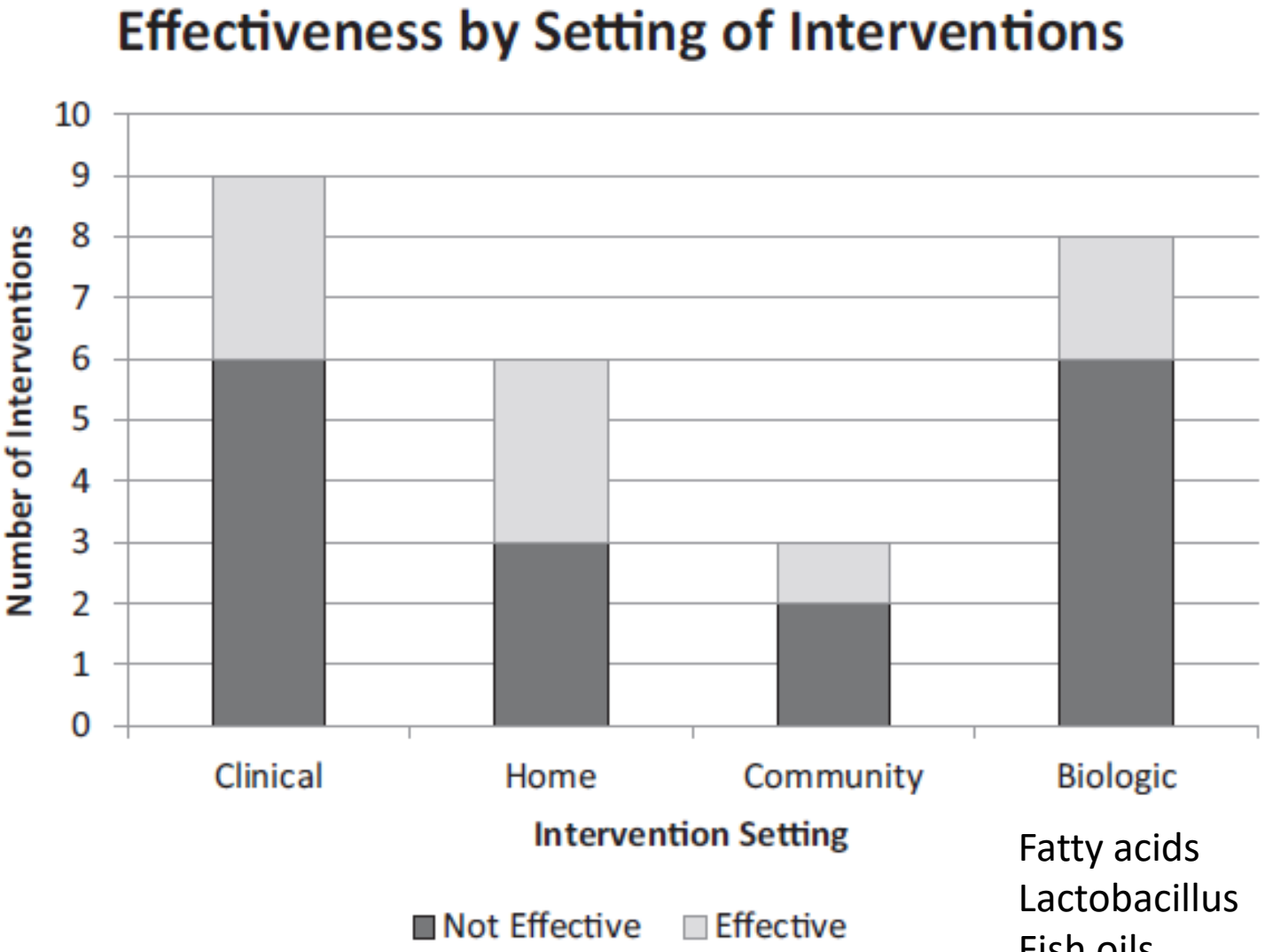


Figure 1 Study group weight-for-length percentiles at 1 year (both interventions group vs. other three groups; $P = 0.009$).

Paul I, Obesity 2011



Fatty acids
Lactobacillus
Fish oils
*Infant formula (proteins)

Blake-Lamb, Am J Prev Med 16

FACTORS RELATED TO THE INCREASE IN PEDIATRIC OBESITY

TREATMENT OF MILD GDM

Treatment, even of mild GDM, helps to reduce birth weight and macrosomia (> 4kg; eg Crowther 10 % vs 21%)

At birth, prevalence of macrosomia (birth weight >or=4,000 g) was 5.3% among the 94 children whose mothers were in the intervention group, and 21.9% among the 105 children in the routine care control group. At 4- to 5-years-old, mean (SD) BMI Z score was 0.49 (1.20) in intervention children and 0.41 (1.40) among controls. The difference between treatment groups was 0.08 (95% CI -0.29 to 0.44), an estimate minimally changed by adjustment for maternal race, parity, age, and socio-economic index (0.08 [-0.29 to 0.45]). Evaluating BMI >or=85th percentile rather than continuous BMI Z score gave similarly null results.

Conclusions: Although treatment of GDM substantially reduced macrosomia at birth, it did not result in a change in BMI at age 4- to 5-years-old.

Chrononutritional and sleep hygiene intervention in GDM, no impact on LGA

Early GDM treatment in high-risk GDM: 23% less LGA, but more SGA

Crowther C, NEJM 2005
Gillman M, DC 2010
Messika A, AJOG MFM 20
Simmons D, NEJM 2023

MATERNAL MACRONUTRIENT INTAKE AND INTRAABDOMINAL OFFSPRING FAT

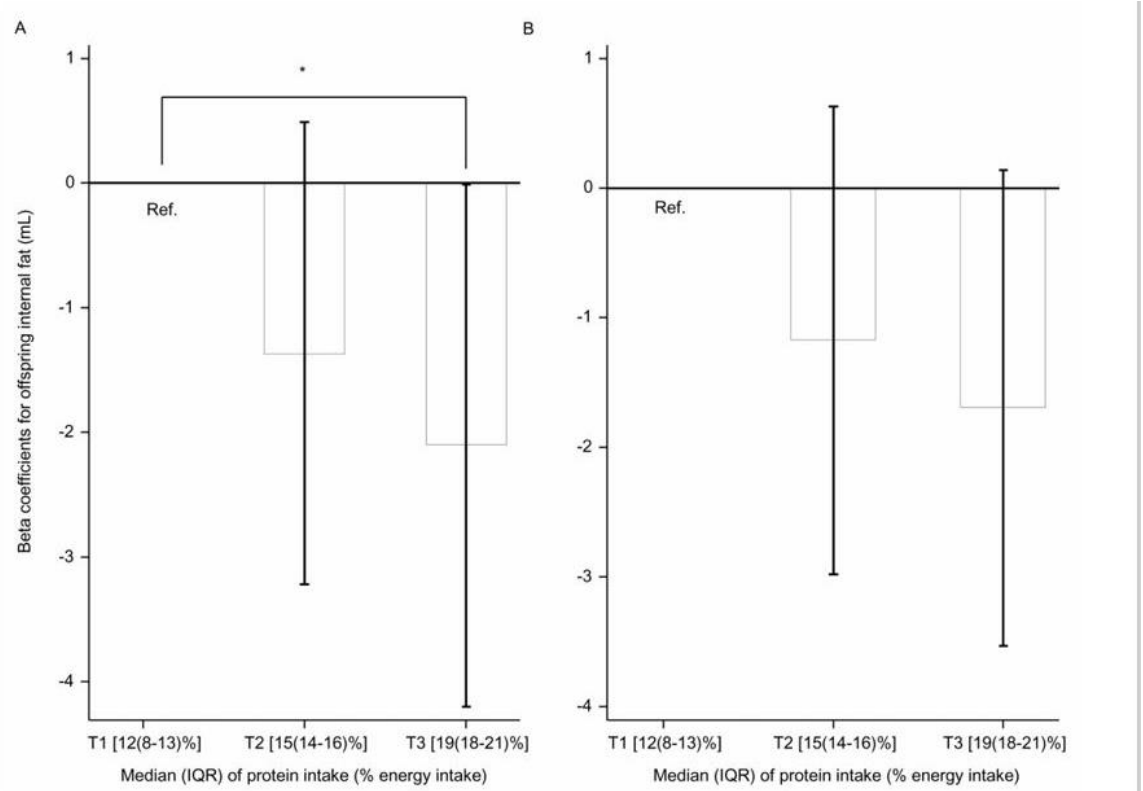
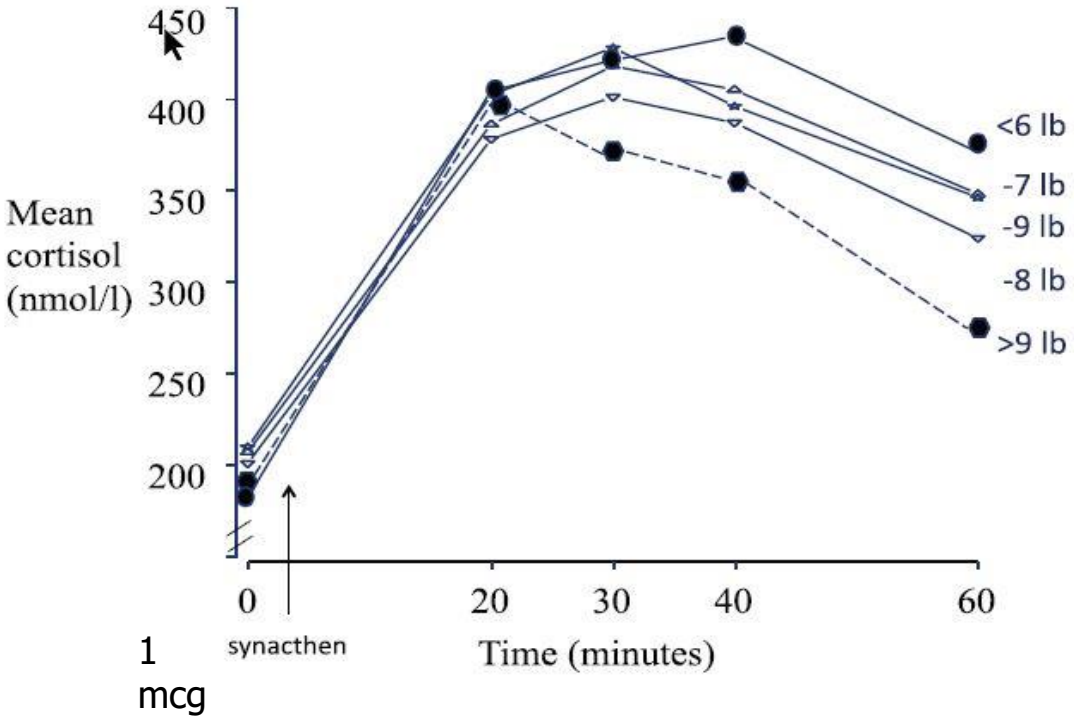


Figure 1.
Associations of protein to fat (A) or protein to carbohydrate (B) substitutions in maternal diets with neonatal abdominal internal fat by tertile of maternal protein energy intake in the GUSTO study (n= 320). Values on the x axes are medians (IQRs), n= 106 (T1, lowest) or

A: Protein to fat
B: Protein to carb

Chen L, J Nutrients 2016

BIRTH WEIGHT AND STRESS REACTIVITY UP TO ADULT AGE



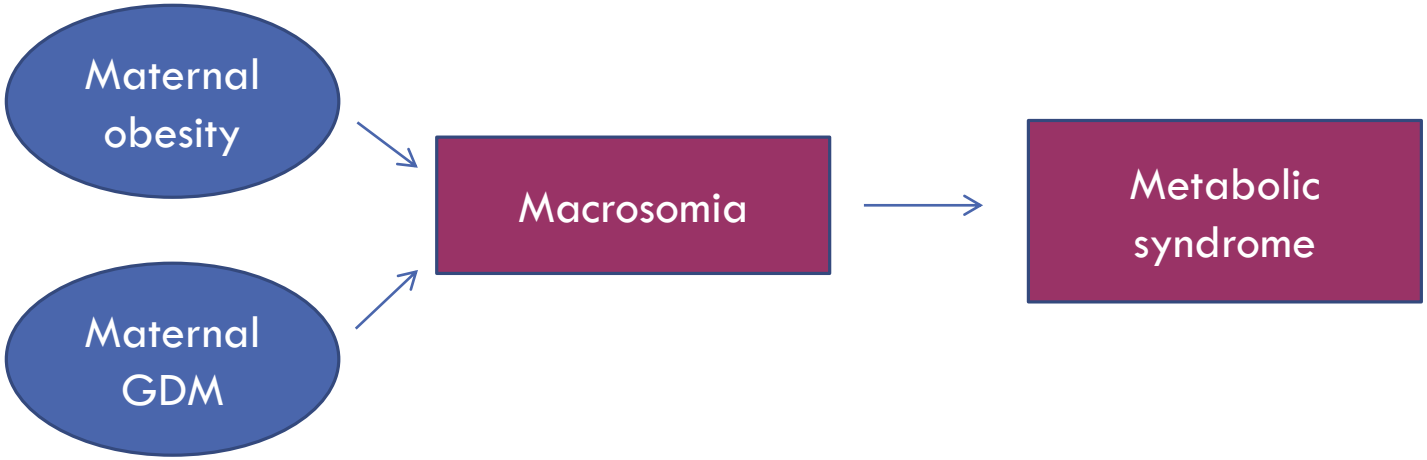
Overshooting in acute stress response in adults with low birthweight

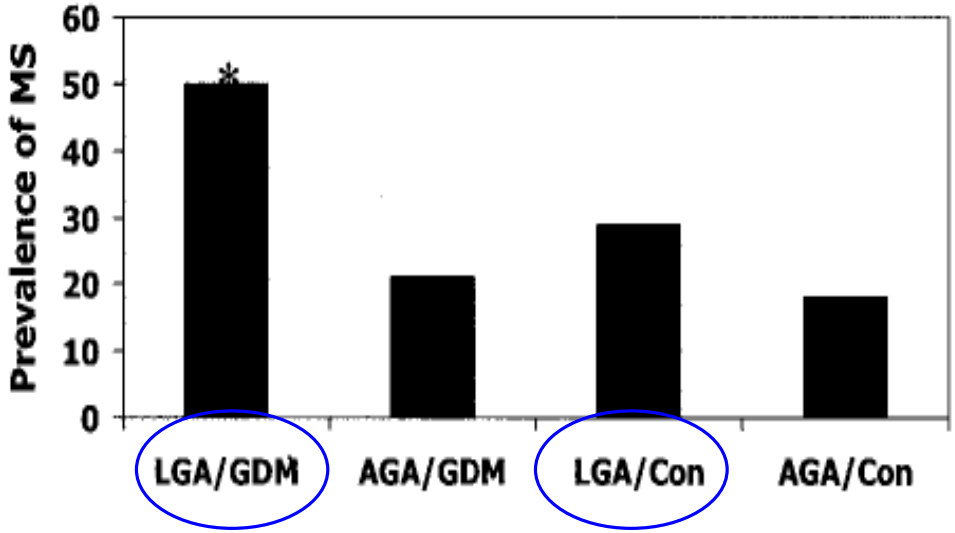
Need the «right amount» of reactivity…. !

Also differences in fasting glucose & childhood BMI

Reynolds R; PNEC 13

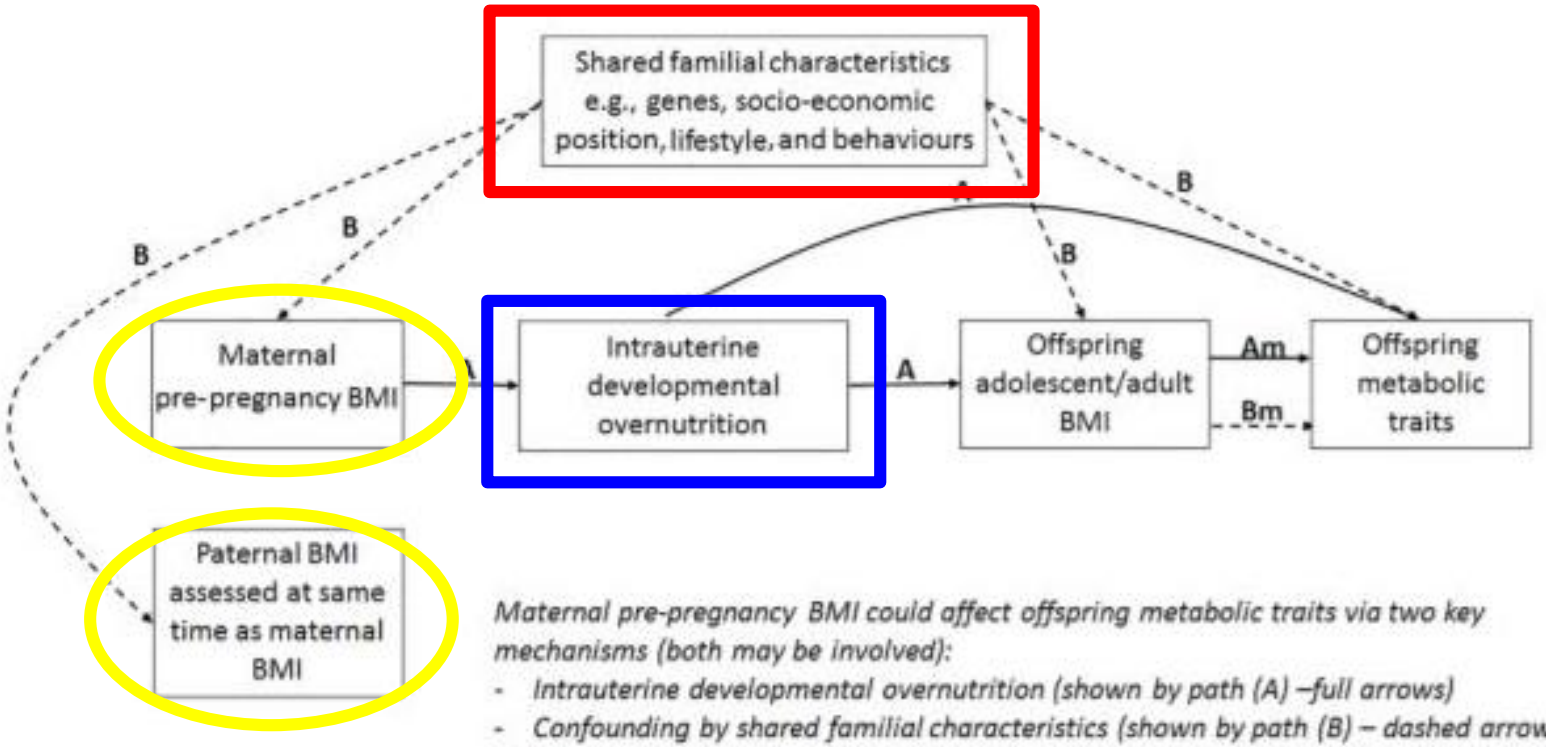
LONG-TERM RISKS OF GDM FOR CHILDREN AGED 6-11 YEARS





Boney C Pediatrics 05
Vohr BR, J Matern Fetal Neonatal Med 08

PEDIATRIC OBESITY



Maternal pre-pregnancy BMI could affect offspring metabolic traits via two key mechanisms (both may be involved):

- *Intrauterine developmental overnutrition (shown by path (A) –full arrows)*
- *Confounding by shared familial characteristics (shown by path (B) – dashed arrows)*

These are not mutually exclusive and either could be mediated via offspring's own BMI (shown by (Am) and (Bm))

Our findings primarily support path B, including Bm (i.e., that the association is largely driven by shared familial characteristics that influence parental and offspring BMI)

Santos-Ferreira D PLOS Medicine 17

RISQUE LIÉ AU DG POUR L'ENFANT LONG TERME

Relation DG et obésité pédiatrique

- Présent à la naissance
- Présent (obésité et obésité centrale) à 6-14 ans et à l'adolescence (incluant RI, indépendant de IMC mère et enfant)

Prévalence augmentée de diabète de type 2 (10-22 ans): (allaitement: effet protecteur)

- OR 6 pour DM mère pendant grossesse (>90% DG)
- OR 3 pour obésité mère pendant grossesse (médiateur: IMC de l'enfant)

HAPO, Lowe JAMA 2018
Crume TL-EPOCH, 6-13 ans, Diabetologia 11, Mayer-Davis E, DC 07
Pettitt D- HAPO, 2 ans, Diabetes Care 10, Silverman BL, 7-8 ans, Diabetes 91
Dabelea D, DC 08, Pettitt DJ, 5-24 ans- Pima, Diabetes 91, Grunnet L, DC 2017

SHORT TERM

The intrauterine environment can affect the fetal programming and future health of the offspring of mothers with GDM.

Pregnancies with GDM have an increased risk of adverse perinatal outcomes, such as :

- Large for gestational age (LGA)
- Increased adiposity
- Birth trauma
- Respiratory distress syndrome
- Postnatal hypoglycemia

LONG TERM

In childhood or adulthood:

- Altered insulin resistance and insulin secretion
- Increased obesity
- Pre-diabetes and DM2

SHORT TERM

The intrauterine environment can affect the fetal programming and future health of the offspring of mothers with GDM.

Pregnancies with GDM have an increased risk of adverse perinatal outcomes, such as :

- High weight for gestational age
- Increased adiposity
- Birth trauma
- Respiratory distress syndrome
- Postnatal hypoglycemia

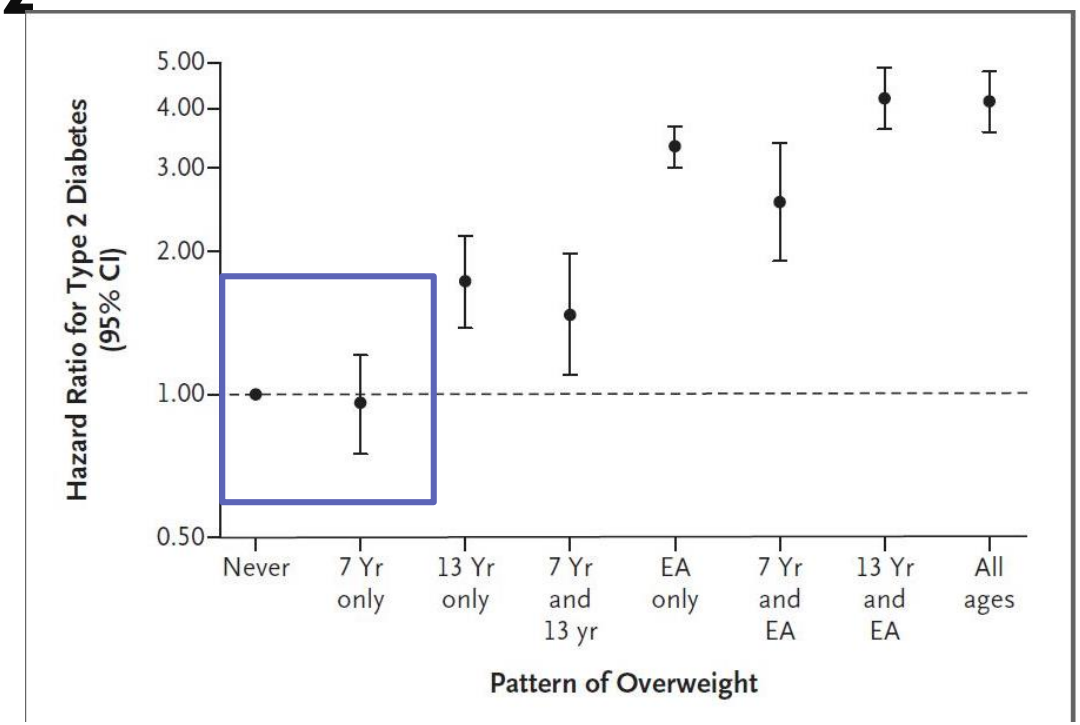
LONG TERM - LITERATURE

In children aged 10-14 years (HAPO study), maternal hyperglycemia was linearly correlated with increased body fat and incidence of obesity, even after adjustment for maternal BMI during pregnancy.

Similarly, in young adults who were offspring of women with GDM and treated with dietary management measures, the risk of overweight was doubled compared to offspring from the base population, while the risk of metabolic syndrome was 4 times higher and the risk of pre-diabetes/diabetes up to 8 times higher, after adjustment for confounding factors.

Some preliminary studies also reveal a possible link between GDM or hyperglycaemia during pregnancy and a future increased risk of cancers or autism in children, partly mediated by the mother's BMI.

CHANGEMENT DE SURPOIDS DURANT ENFANCE ET ÂGE ADULTE ET RISQUE DE DIABÈTE DE TYPE 2



Overweight at 7, 13 years of age or early adulthood was positively associated with the risk of type 2 diabetes; **Men who had had remission of overweight before the age of 13 years had a risk of having type 2 diabetes diagnosed at 30 to 60 years of age that was similar to that among men who had never been overweight** As compared with men who had never been overweight, men who had been overweight at 7 and 13 years of age but not during early adulthood had a higher risk of type 2 diabetes (HR 1.5), but their risk was lower than that among men with persistent overweight (HR 4). An increase in body-mass index between 7 years of age and early adulthood was associated with an increased risk of type 2 diabetes, even among men whose weight had been normal at 7 years of age.

Bjerregaard L, NEJM 18

AUTISM

Possible link between GDM or hyperglycaemia during pregnancy and an increased risk of **autism (ASD) in children**, partly mediated by the mother's BMI.

<u>Maternal hyperglycemia:</u>

Hypoxia/depleted oxygen supply to the fetus ➔ impaired neurodevelopment ➔ ASD ↑.

↑ free-radical production and impaired antioxidation ➔ oxidative stress in the cord blood and placental tissue. Known association between oxidative stress and ASD.

Epigenetic modification may also be implicated in the pathogenesis of ASD.

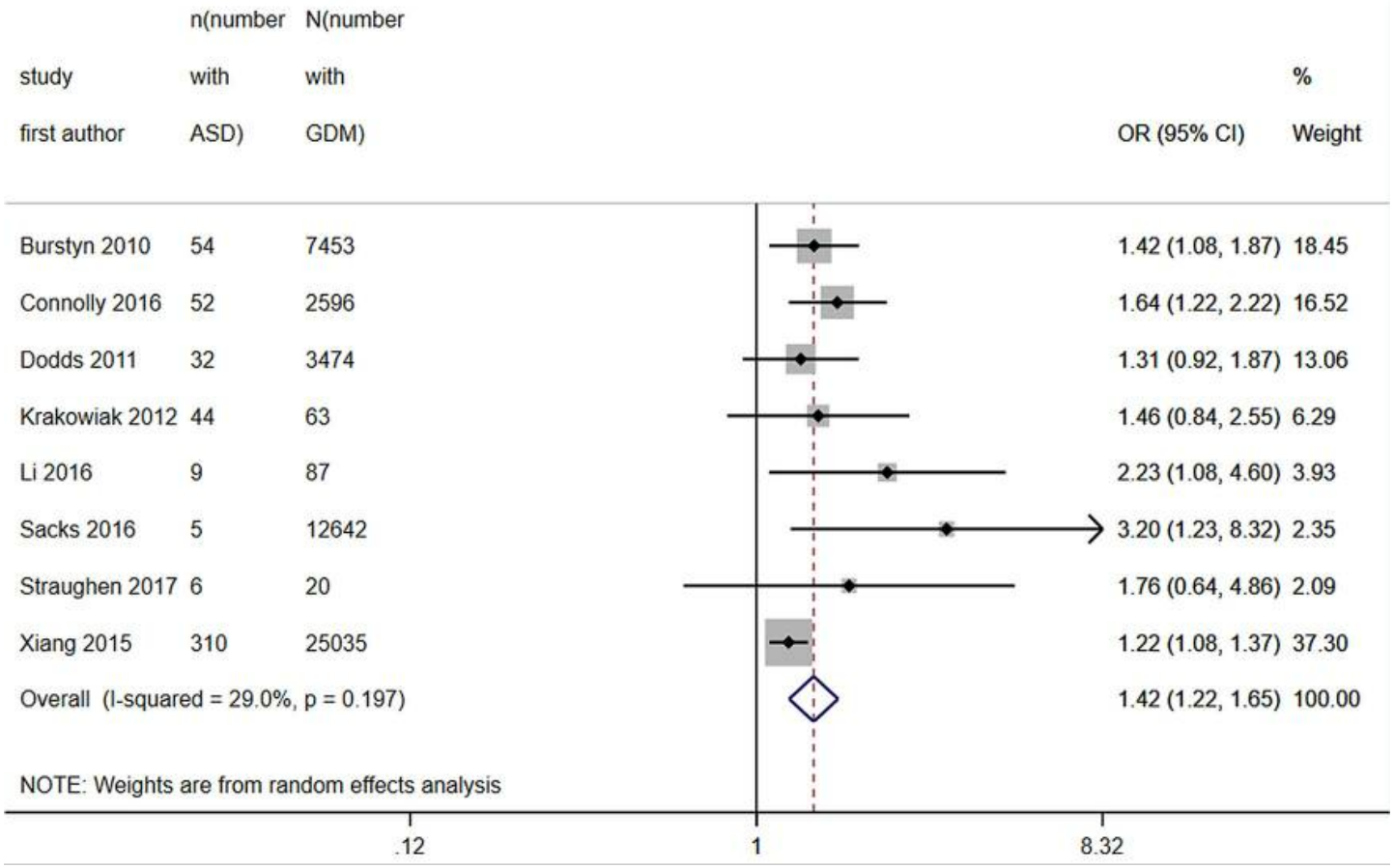
May be mediating factors such as pre-eclampsia or infants born large for gestational age.

Rowland J, Sci Rep 2021

Xu G, J Autism Dev Disord, 2014

AUTISM

On meta-analysis there was an increased risk of ASD (OR 1.42; 95% CI 1.22, 1.65)



Rowland J, Sci Rep 2021
Wang C, Medicine, 2017
Hongquan W, Medicine 2018
Xu G, J Autism Dev Disord, 2014

APPROCHE TRANSGÉNÉRATIONNEL/TRAJECTOIRE DE VIE:
EXEMPLE OBÉSITÉ

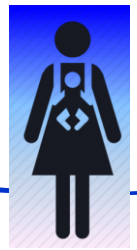
Génétique

Epigenetique:

Programmation intrautérine

Mode de vie famille

Guidance parentale

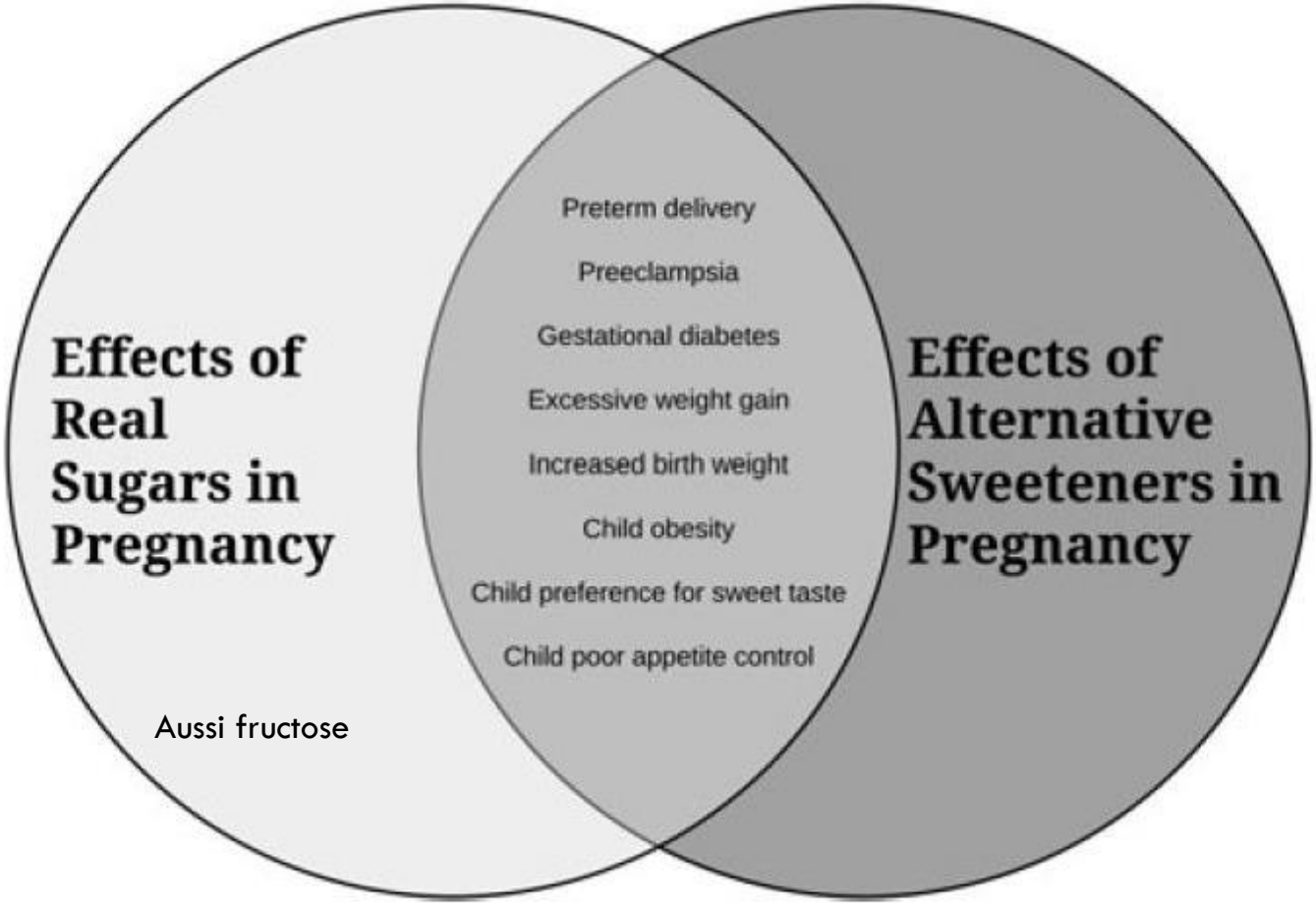


→Commencer tôt! → retour sur investissement

Mais, c'est quand « tôt »…..?

Grossesse, pré-conception?

SUCRE DANS LA GROSSESSE ET SANTÉ



Comment la consommation d'un excès de sucres et les édulcorants alternatifs pendant la grossesse ont un impact sur la santé maternelle et de l'enfant.

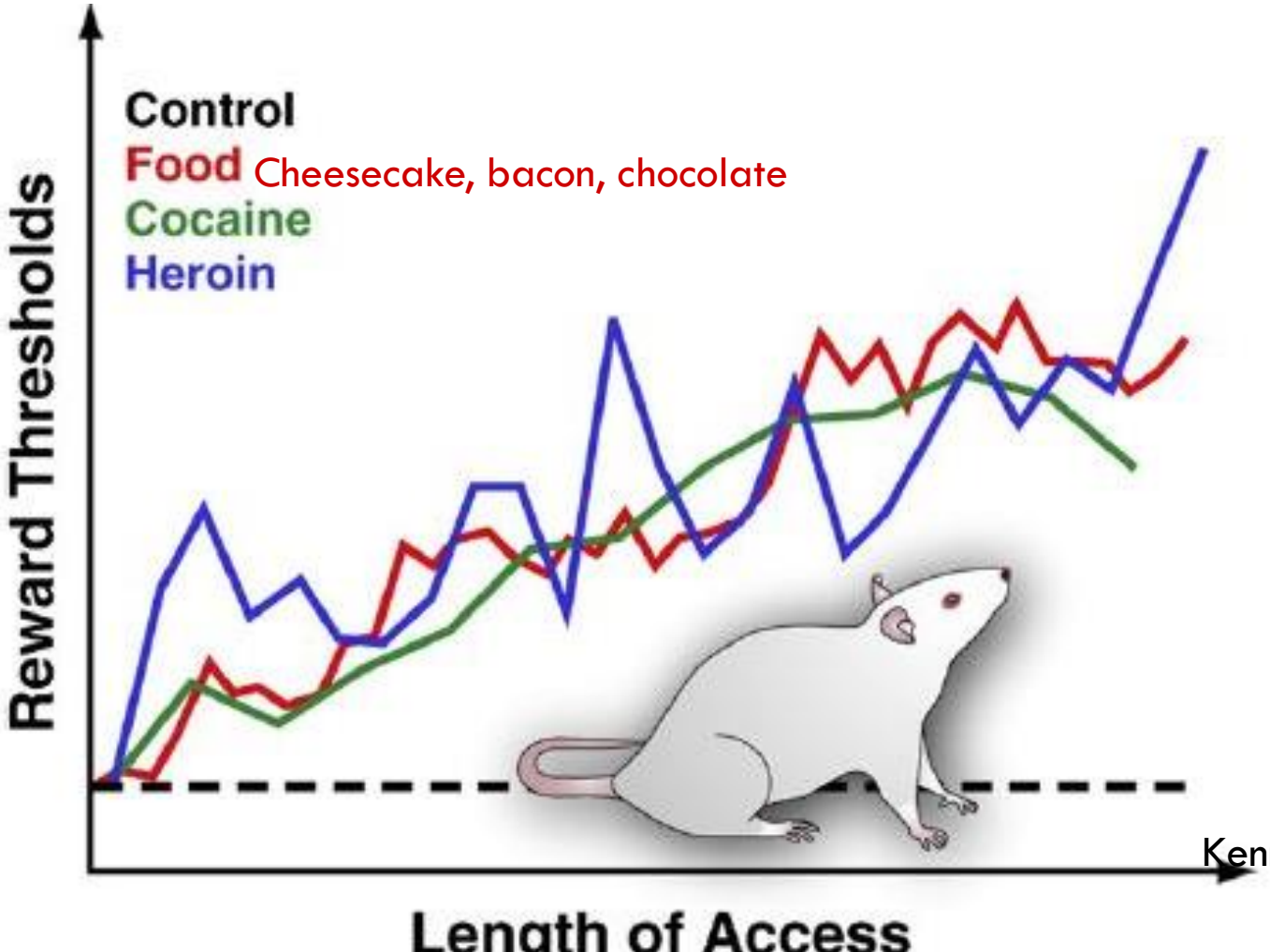
Goran MI; Proceedings Nutrition Society 2018

PRÉVENTION PRIMAIRE

SURTOUT ENFANTS « À RISQUE »

(GÉNÉTIQUE/ÉPIGÉNÉTIQUE)

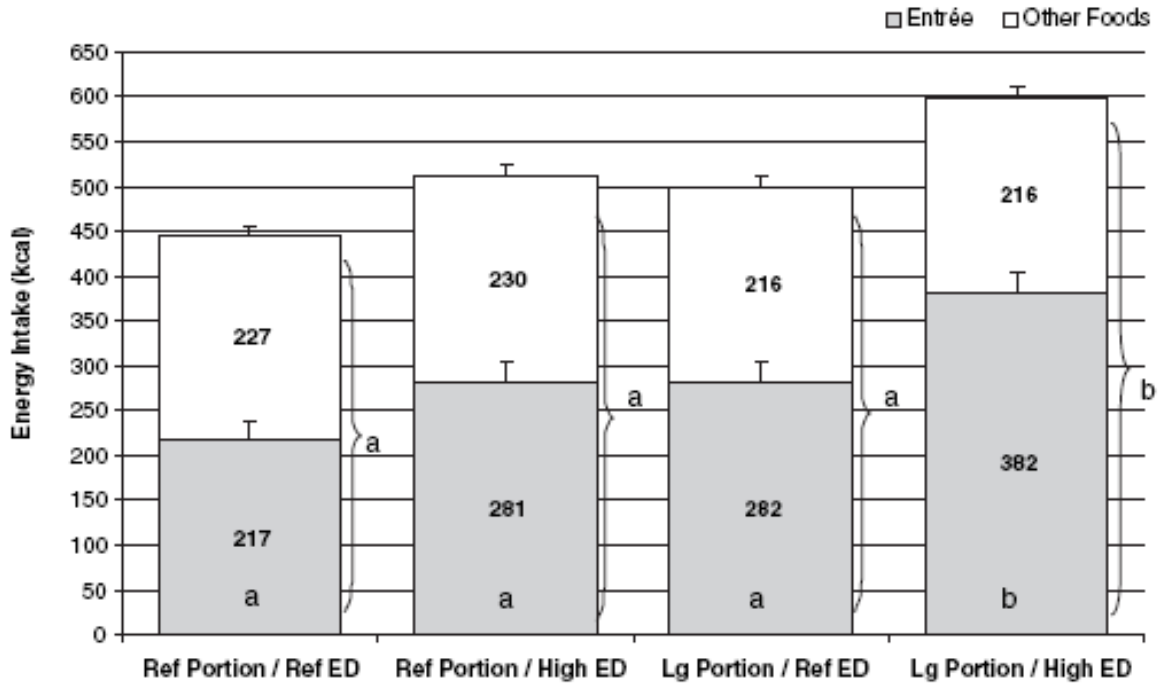
ALIMENTATION ET SYSTÈME DE RÉCOMPENSE



Kenny P, Neuron 11

L'OFFRE ET LA TAILLE DES PORTIONS INFLUENCE LE COMPORTEMENT (NUTRITIONNEL) DÈS L'ENFANCE

La taille et la densité énergétique des portions offertes en apéritif influencent les apports énergétiques de l'enfant au repas. Clairement à l'âge de 5-6 ans, probablement même plus jeune.



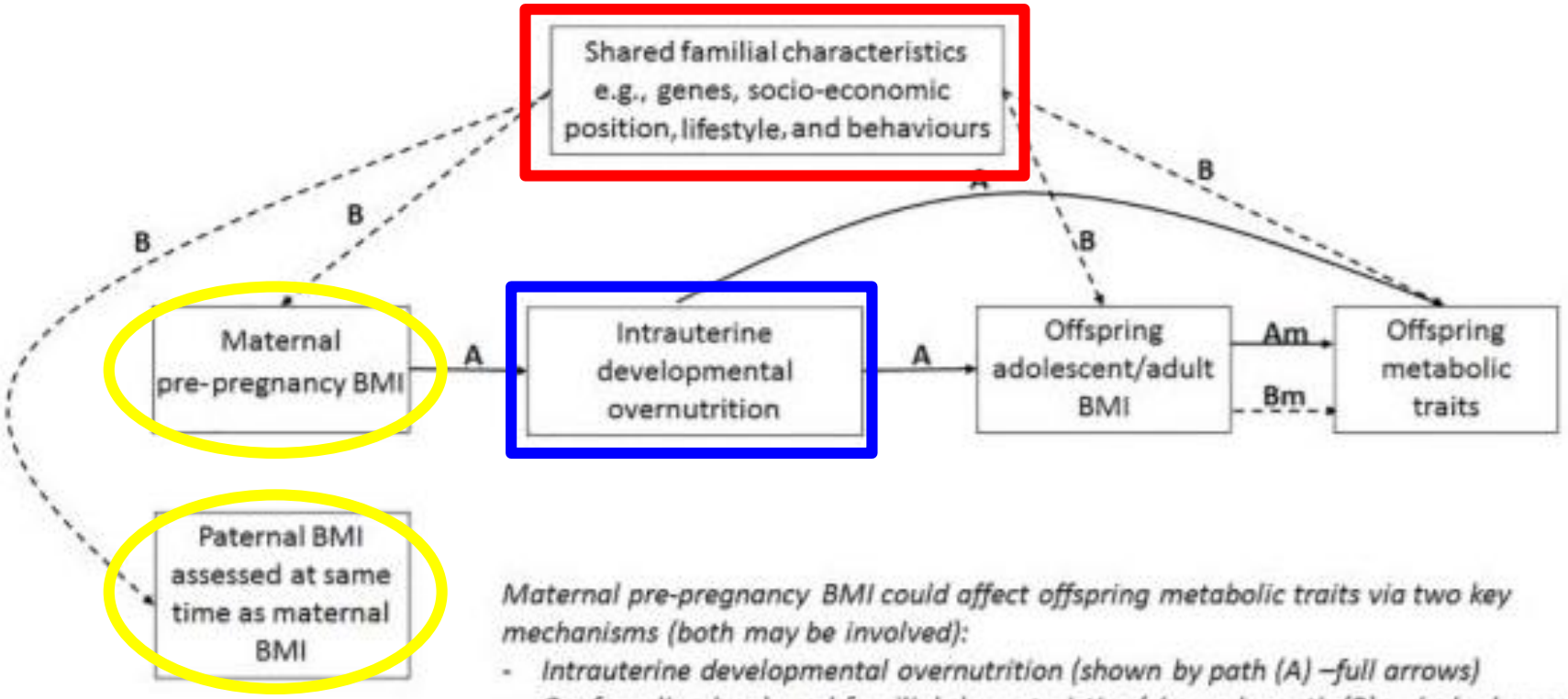
↑ ED

↑ S

↑ED& ↑S

Fischer JO Am J Clin Nutr 07
Fischer JO Obesity 07

OBÉSITÉ PÉDIATRIQUE: CONCEPT



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Santos-Ferreira D PLOS Medicine 17

« DÉVELOPPEMENT DU COMPORTEMENT ET PRÉFÉRENCE ALIMENTAIRE » - INTERACTIONS RÉCIPROQUES

Offering
Model/portray
Pressure

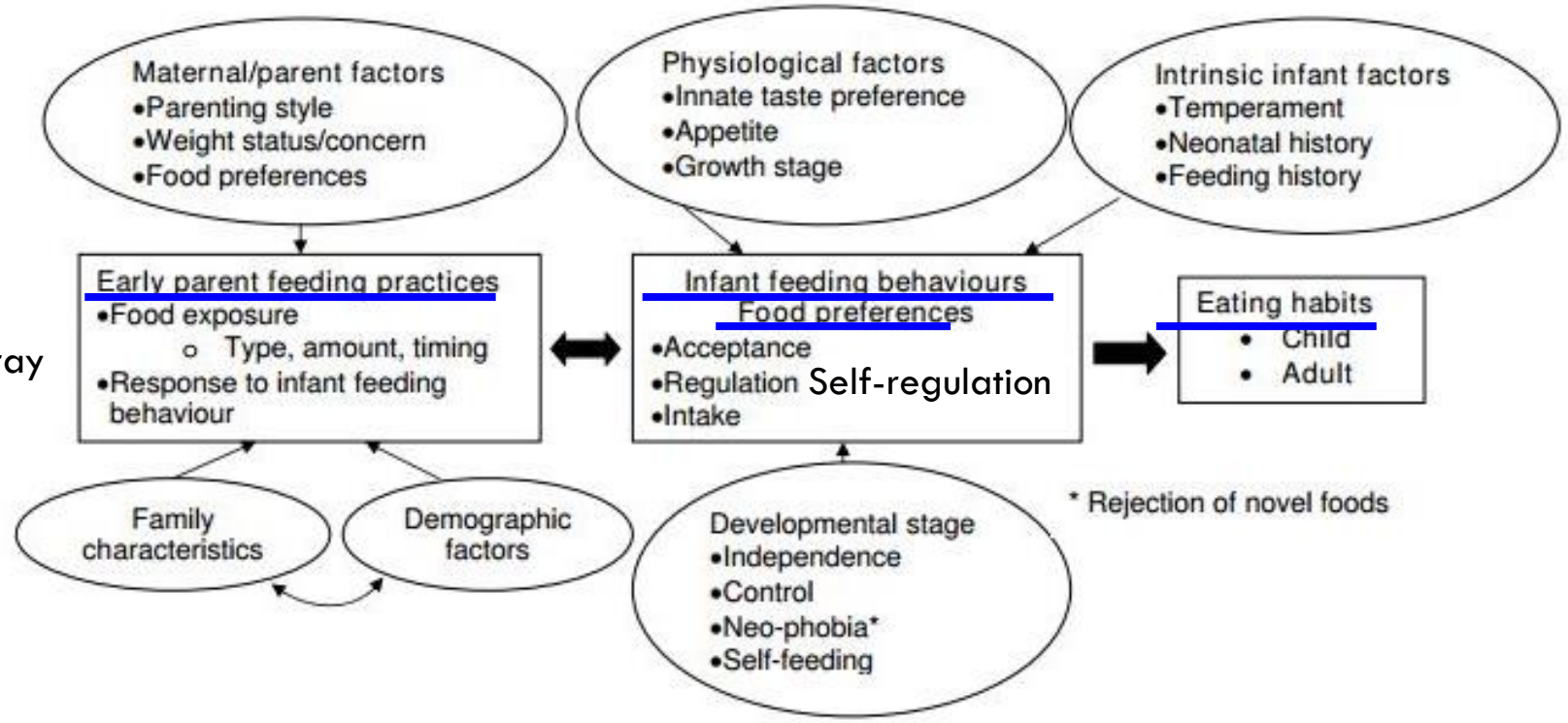


Figure 1
Key factors that influence the reciprocal relationships between parent feeding practices and infant feeding behaviour.

BMC Public Health, 2009
Alvarez-Pitti, Nutrients, 2020

L'ÂGE DE L'ALIMENTATION PRINCIPALEMENT NOCTURNE À L'ÂGE DE 1 AN EST ASSOCIÉ À UN GAIN D'ADIPOSITÉ ET UN RISQUE D'OT À L'ÂGE DE 2 ANS

Même apport calorique (apport plus élevé en graisses)

OR ajusté 2.78

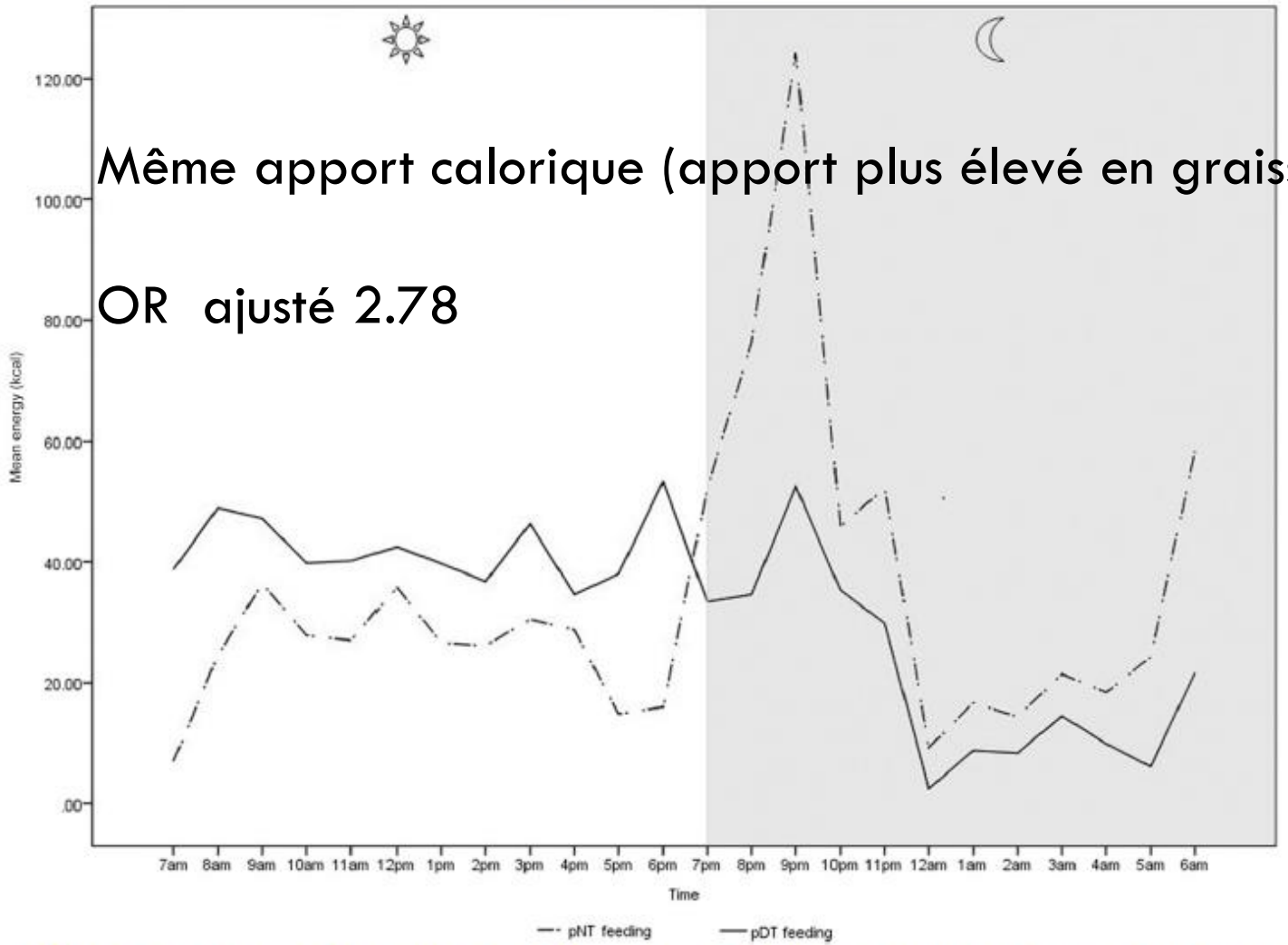


FIGURE 1 Mean 24-h energy-consumption patterns at age 12 mo for pNT-feeding infants (n = 67) and pDT-feeding infants (n = 282). Descriptive statistics were performed to calculate the mean energy at each time interval. pNT, predominantly nighttime; pDT, predominantly daytime.

Cheng T, AJCN 16

ALIMENTATION PRÉCOCE POUR DES ENFANTS À RISQUE D'HYPOGLYCÉMIE

- Alimentation précoce du nouveau-né:
  - enfant souvent réveillé pour être nourri, sans faim
  - conditions pas optimales pour mise au sein
- moins de lait maternel ingéré (compléments de 1xDM10% ensuite lait artificiel)
- stimulation moindre de la production de lait maternel

➢ **Opter à contribuer à préserver :**

- **l'allaitement maternel**
- **les mécanismes internes de la régulation de l'appétit**
- **et limiter la suralimentation**

GÉNÉTIQUE ET STYLE DE VIE SUR QUOI POURRAIT-ON AGIR PLUS FACILEMENT ?

Héritabilité
(*) Moins que 50%
* Autour de 50%
** Plus que 50%

***Manger en absence de faim, après un repas**

****Vitesse d'ingestion**

Compensation calorique (après des charges haut et bas en calories, « régulation »)/ ****sentiment de satieté**

*-****« Réactivité des signaux alimentaires »/Plaisir de manger (aussi: vue, odeurs des aliments, salivation devant aliments etc)**

***Néophobie**

***Récompense alimentaire/récompense**

***Prise alimentaire liée aux émotions/détresse**

(*)**Prise alimentaire/préférences alimentaires (énergie)**

Sommeil (*) durée -** initiation et maintenance

(*)-*****activité physique**

Carnell & Wardle Appetite 2009
Faith M, Hum Hered 13
Gemini: Llewellyn C Am J Clin Nutr 10
FTO: Wardle J, Int J Obes 09

EXEMPLE INTERVENTION ET POIDS

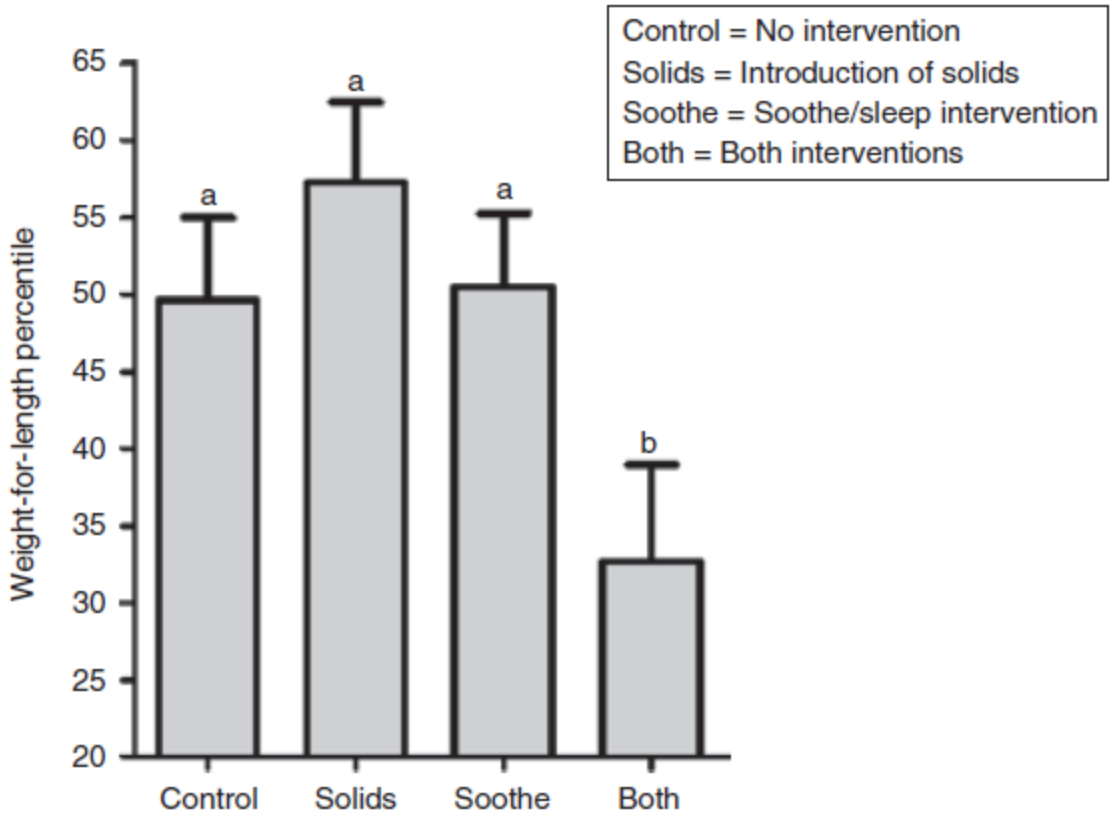


Figure 1 Study group weight-for-length percentiles at 1 year (both interventions group vs. other three groups; $P = 0.009$).

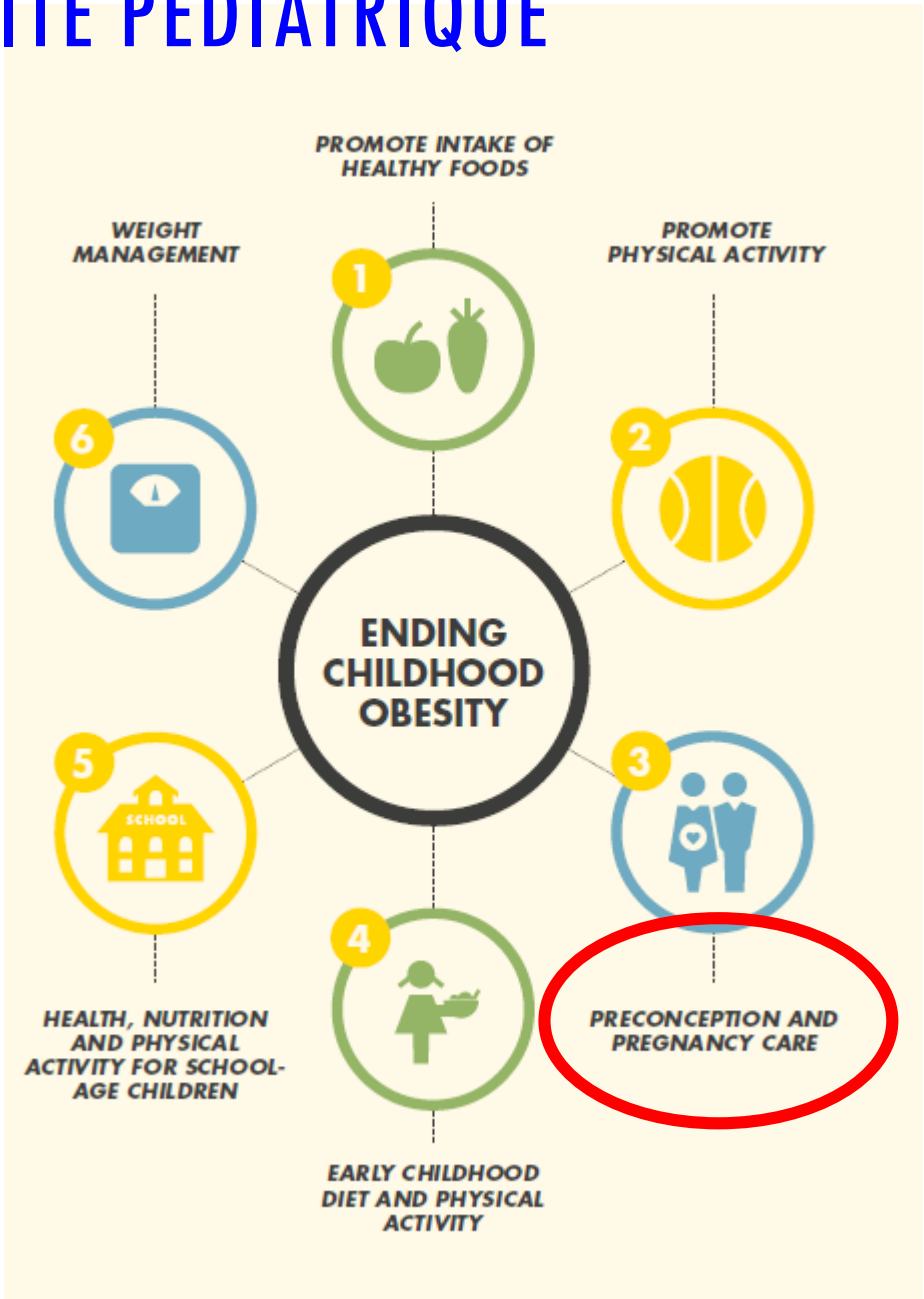
Paul I, Obesity 2011

CONSÉQUENCES À LONG TERME POUR L'ENFANT CONCERNANT …

- …l'obésité pédiatrique
- …le comportement alimentaire, homéostase, régulation appétit
- Effets des différents sucres durant la grossesse
- …le développement cognitive et moteur, paralysie cérébrale, spina bifida, ADHD, autisme
- …immunité, allergies, asthme, (infections)

- (pas: macrosomie, hypoglycémies, prématurité, mortalité perinatale, etc)
- Souvent: études observationnelles → residual confounding?

OMS: OBÉSITÉ PÉDIATRIQUE



PROGRAMMATION DÉVELOPPEMENTALE DES VOIES DE SIGNALISATION DE L'HOMÉOSTASE D'ÉNERGIE, DE LA REGULATION DE L'APPÉTIT ET DU MÉTABOLISME

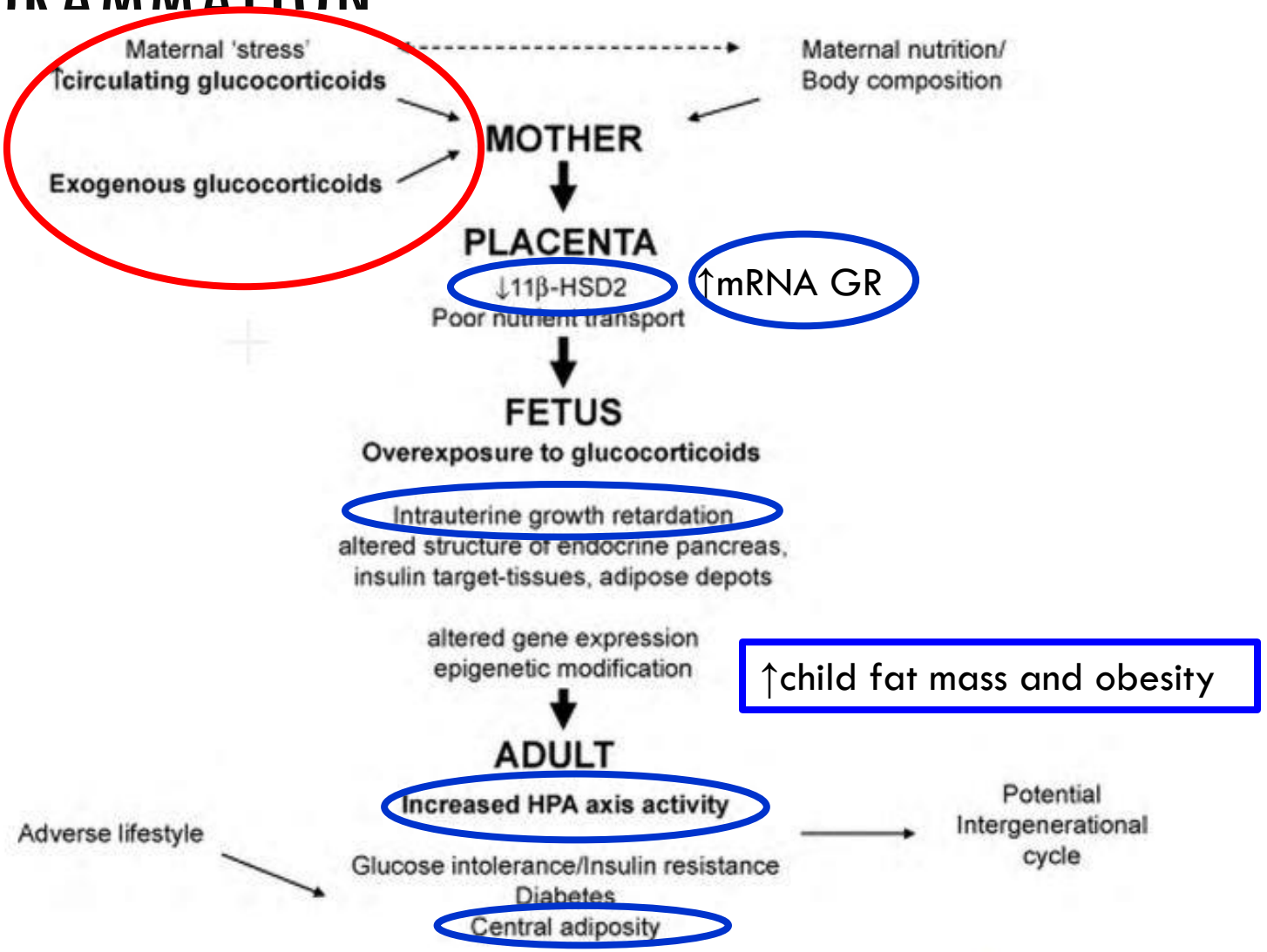
Pre- and during gestation

- Different maternal diets → hypothalamic programming in offspring.
- Choice and timing exposure of maternal diet → effects on offspring phenotypes, often sex specific.
- Studies with little or even no weight gain in dams that are consuming a calorie- rich diet still → in strong offspring phenotypes.

- ❑ Altered hypothalamic gene expression
- ❑ Altered regulation in response to fasting
- ❑ Hyperphagia
- ❑ Disrupted glucose homeostasis

Dearden L, Frontiers in Neuroendocrinology, 2015

STRESS ET GLUCOCORTICOIDES ET PROGRAMMATION



Salivary cortisol (especially in 2nd T) correlates with later childhood obesity (age 2-16)

Fig. 1. R… osure of the de… sulin target ti… esity. Adverse lifestyle factors in adulthood may contribute to the development of diabetes and obesity. These findings are potentially transmittable to the next generation leading to an intergenerational cycle of low birthweight, obesity and diabetes (11-βHSD2—11 beta hydroxysteroid dehydrogenase type 2 and HPA—hypothalamic–pituitary–adrenal).

Reynolds RM, Journal of Steroid Biochemistry & Molecular Biology 2010

OBÉSITÉ PÉDIATRIQUE: MAIS….

- 3 large cohorts (ALPSAC, 2 Finish): Profilings of offspring (adult age) circulating lipids, lipoproteins, metabolites by high-throughput NMR metabolomics
- 1 and 2-stage individual participant data analysis (IPD) with paternal BMI as negative control

→increasing maternal and paternal BMI adverse cardio-metabolic profile in offspring. Only slightly stronger association with maternal BMI

→ ↔ other studies, animal «mechanistic» studies. Paternal : preconception impact ??

Sørensen, AJCN 16
Santos-Ferreira D PLOS Medicine 17

OBÉSITÉ ET DÉVELOPPEMENT COGNITIVE ET MOTEUR

- Review: Most studies supported an adverse association between maternal pre-pregnancy obesity and childhood **cognitive development**.
- Negative correlation between pre-pregnancy maternal obesity and child **IQ in several studies, including poorer motor, spatial, and verbal skills**
- Possibly U-shaped
- A few studies also demonstrated a negative association between the maternal obesity and **gross motor function** in children (5 of 10), but not with fine motor function.
- Causality or due to confounder effects?
- Epigenetic mecanisms not very clear and not thoroughly studied, especially in humans

Adane AA, IJO 16
Contu L, Int. J. Mol. Sci. 2017

OBÉSITÉ ET DÉVELOPPEMENT COGNITIVE

Some helpful point to determine causality:

- Few studies: Associations with between maternal pre-pregnancy obesity, but not paternal obesity with cognitive development (or much less strong)
- Four large studies found significantly impaired child cognitive development after extensive confounder adjustment
- a large study in siblings varied in their exposure to maternal obesity, also confirmed the adverse effect of maternal pre-pregnancy obesity on the children's IQ score.

OBÉSITÉ ET DÉVELOPPEMENT COGNITIVE

- Potential pathways identified:
  - High concentration of nutrients (fatty acids, glucose)
  - Hormones (leptin, insulin)
  - Inflammatory mediators (interleukins, TNF)
  - Maternal obesity complications (GDM, hypertensive disorders, Apgar < 7 at 5', preeclampsia, preterm, periventricular leukomalacia, etc)
  - Oxidative stress
  - BDNF signaling
  - Abnormal development of neuronal circuitry, fetal hippocampal development
  - DNA methylation levels of folic acid, co-factor in the production of the principle methyl donor methionine, are decreased in the amniotic fluid of obese pregnant women

Adane AA, IJO 16
Contu L, Int. J. Mol. Sci. 2017
Godfrey K, Lancet Diab & Endo 2017

IMC ET PARALYSIE CÉRÉBRALE

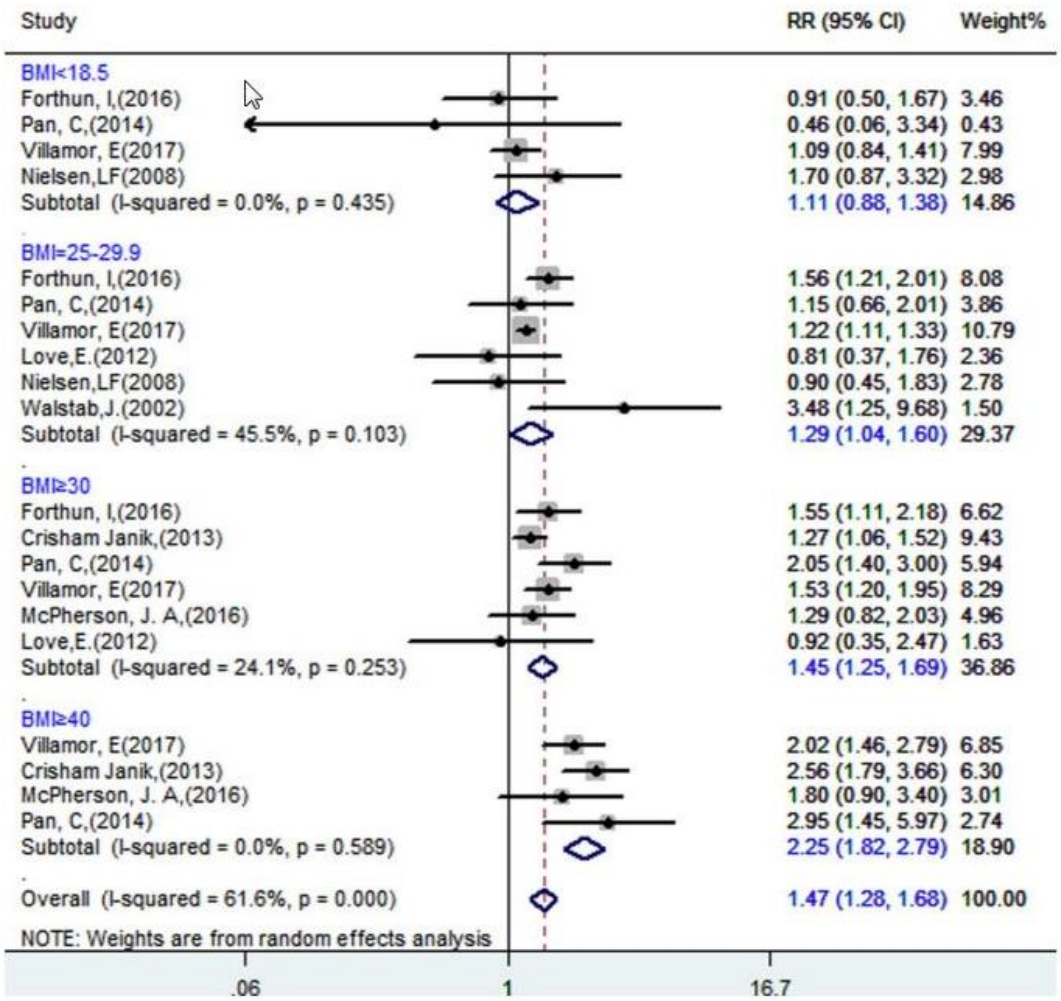


Fig 2. Forest plot of pooled analyses of maternal underweight, overweight, obesity or obesity III and CP in offspring, adjusted for several potentially confounding variables.

Xiao D, PLOS One 18

MALFORMATIONS

The increased risk of foetal malformations in obese pregnant women has been reviewed in detail. Studies showed that obesity doubled the risk of neural tube defects, especially spina bifida, increased the risk of cardiovascular malformations and limb abnormalities by 30%, the risk of a cleft lip and, or, palate by 20% and anorectal atresia and hydrocephalus by 50–70% (27,28). Maternal obesity has also been associated with about a twofold increased risk of omphalocele and diaphragmatic hernia (29). Conversely,

Mitanchez D, Acta Paediatrica 18

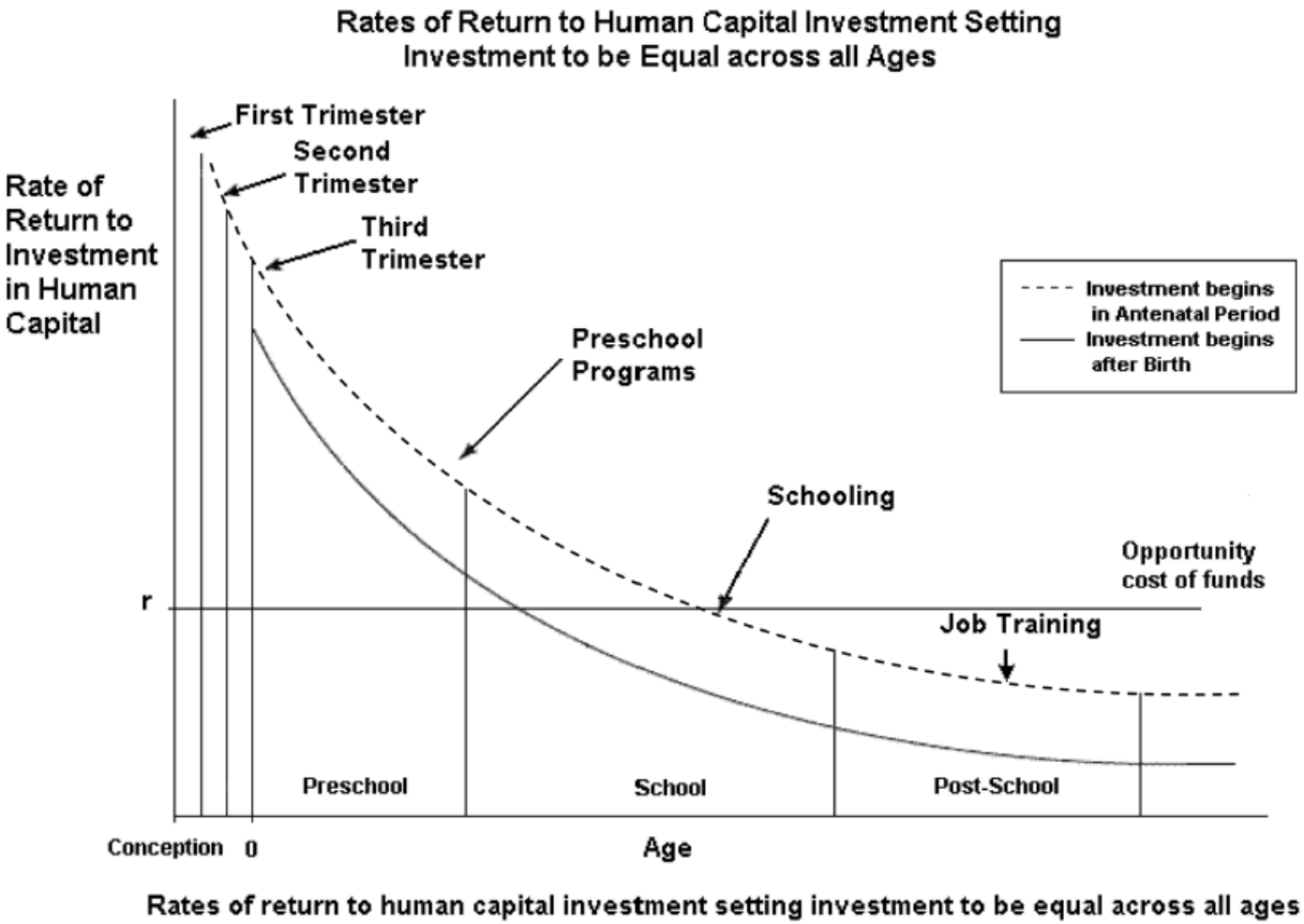
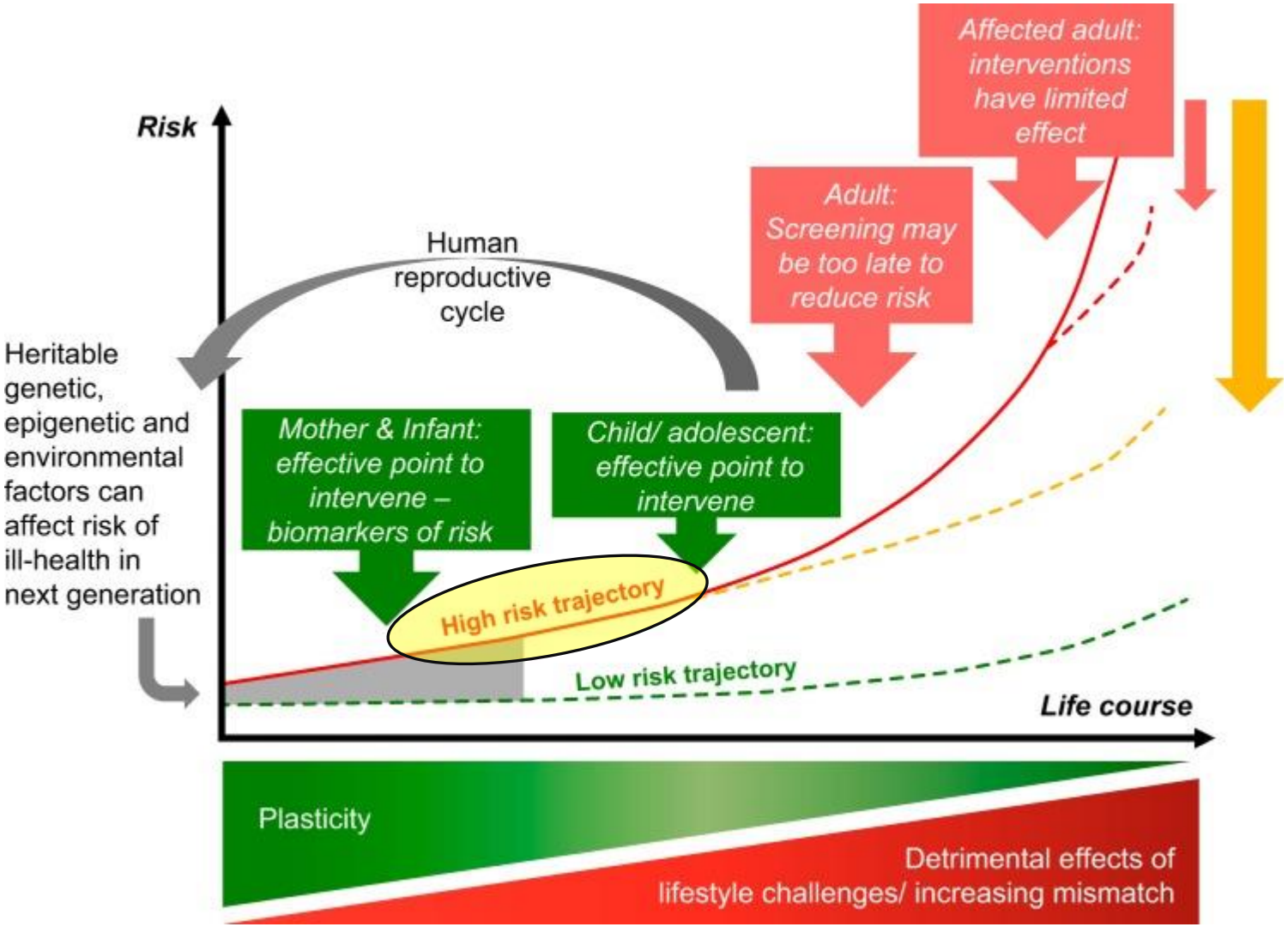


Figure 2.
Source: Carneiro and Heckman, 2003.



Hanson MA, Physiolog Reviews 14

FACTEURS PRÉCOCES IV
FACTEURS DE RISQUE PLUS « INNÉS »/GÉNÉTIQUE

Héritabilité
(*) Moins que 50%
* Autour de 50%
** Plus que 50%

*Manger en absence de faim, après un repas

**Vitesse d'ingestion

Compensation calorique (après des charges haut et bas en calories, « régulation »)/ **sentiment de satieté

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PROGRAMMATION DÉVELOPPEMENTALE DES VOIES DE SIGNALISATION DE L'HOMÉOSTASE D'ÉNERGIE, DE LA RÉGULATION DE L'APPÉTIT ET DU MÉTABOLISME

Avant-propos de la journée

- Différents régimes maternels → programmation hypothalamique de la progéniture.
- Choix and moment d'exposition de l'alimentation maternelle → effets sur les phénotypes, souvent spécifique au sexe.
- Etudes avec peu ou même pas de prise de poids chez les mères qui ont encore un régime riche en calories → fort effets sur le phénotype de la progéniture

- ❑ Expression génétique hypothalamique modifiée
- ❑ Régulation modifiée en réponse au jeûne
- ❑ Hyperphagie
- ❑ Homéostasie du glucose preturbée

Dearden L, Frontiers in Neuroendocrinology, 2015

HYPERALIMENTATION PENDANT LA GROSSESSE

Animaux et humains:

Obésité maternelle → enfants:

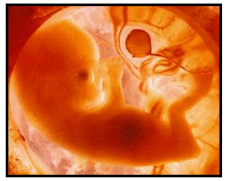
- Peut changer la programmation des voies de la **balance énergétique et comportement alimentaire** (expression hypothalamique de la leptin, etc), la régulation de l'appétit et ainsi amener à une **hyperphagie persistante**.
- Peut changer la **masse et fonction d'adipocytes**
- Changements aussi dans microbiota

DEVELOPMENTAL PROGRAMMING & THE DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE (DOHAD)

Conception 1000 DAYS 2nd birthday

2nd hits

Adulthood





Normal variations in nutrition, stress, environmental toxicants exposure,

Periconceptional & perinatal disorders and interventions:
Preterm birth, Intra-uterine growth restriction, Maternal diabetes/overweight, C-section, ART

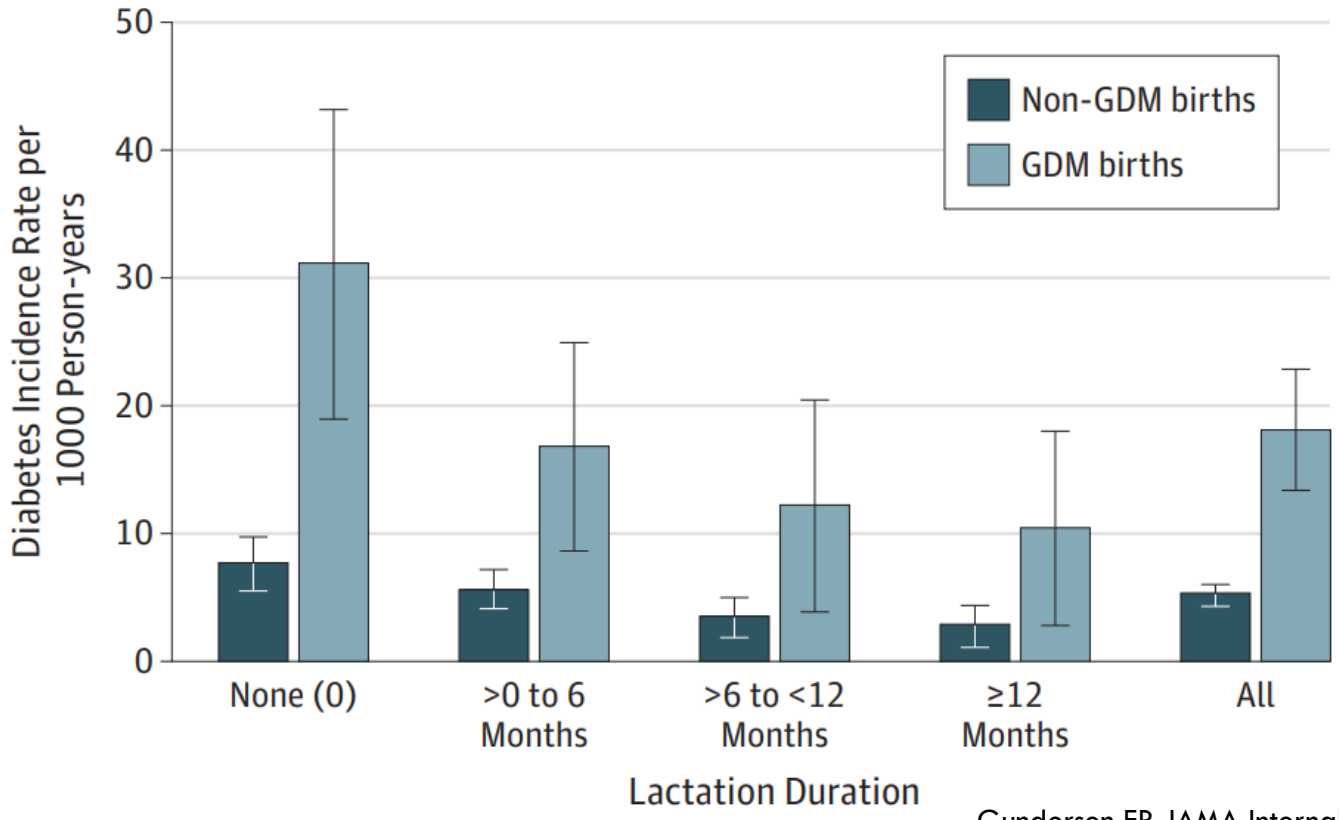
Nutrition, Taste development Microbiome **Stress Toxicants**

Non Communicable Diseases: Hypertension, Kidney disease Diabesity Cancer Broncho-pulmonary disease Infertility Neuro-psychic vulnerability, Senescence…

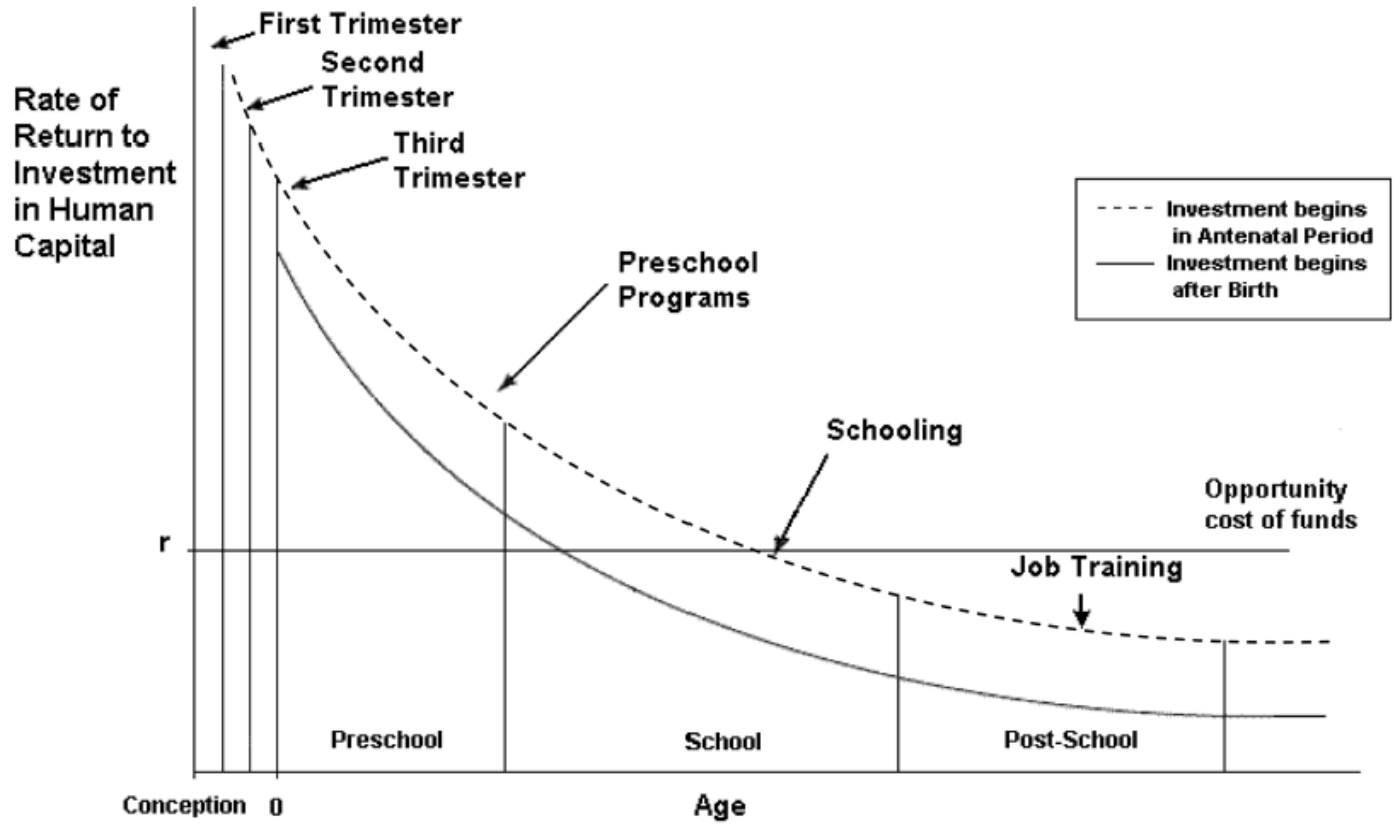
Epigenetic changes: DNA methylation, histones deacetylation/ methylation, phosphorylation, miRNA

GDM AND METABOLIC SYNDROME IN THE MOTHER - EFFECT OF BREASTFEEDING

Figure. Incidence Rates of Diabetes Mellitus Among Lactation Duration Categories Stratified by GD Status in Women



Gunderson EP, JAMA Internal Medicine, 18

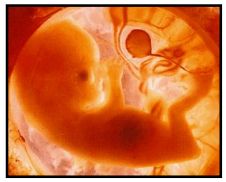


Rates of return to human capital investment setting investment to be equal across all ages

Source: Carneiro and Heckman, 2003.

Developmental origins of health and disease **(DOHaD)**

Conception 1000 DAYS 2nd birthday | 2nd hits | Adulthood





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Nutrition,
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Stress
Toxicants

Non Communicable Diseases:
Hypertension,
Kidney disease
Diabesity
Cancer
Broncho-pulmonary disease
Infertility
Neuro-psychic vulnerability,
Senescence…

Epigenetic changes: DNA methylation, histones deacetylation/ methylation, phosphorylation, ncRNA