



CHAPTER 2: CAUSES OF OBESITY

Part 2: **Fetal and Infant Origins of Obesity**

References:

1. Peter G. Kopelman, Ian D. Caterson, William H. Dietz - Clinical Obesity in Adults and Children 4e-Wiley-Blackwell (2022): **Main reference**
2. Child health matters: A life course perspective. Available from: https://www.researchgate.net/publication/348620529_Child_health_matters_A_life_course_perspective [accessed Oct 13 2024].
3. https://sph.uth.edu/research/centers/dell/webinars/11.03.2020_fetal_origins.pdf
4. Other studies cited throughout the slides

Outline

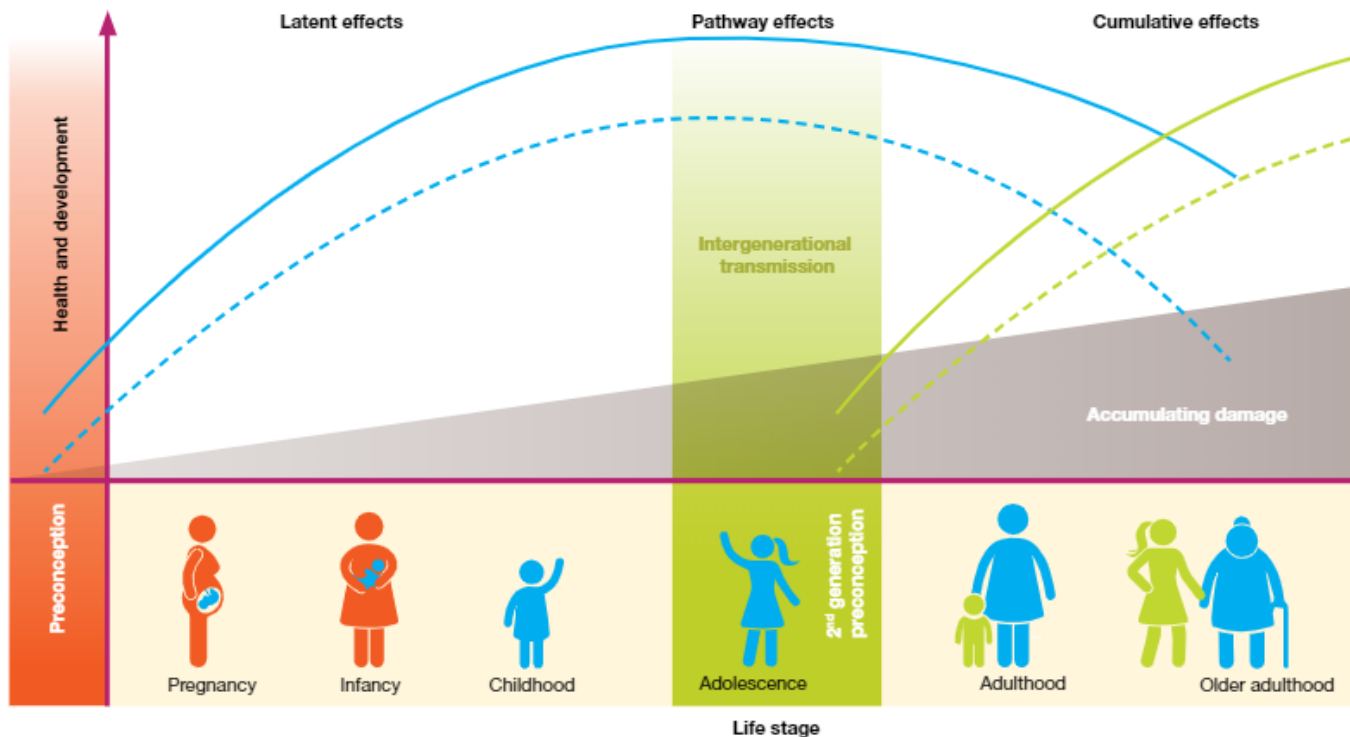
In this part, we will aim to:

1. Understand the importance of considering a **life course perspective** to understanding obesity
2. Developmental **risk factors** of obesity
3. **Biology** and Mechanisms
4. **Implications**



Introduction

- Multiple streams of evidence suggest that **exposures occurring in early life**, including prenatally and even pre-conceptionally, contribute to obesity trends



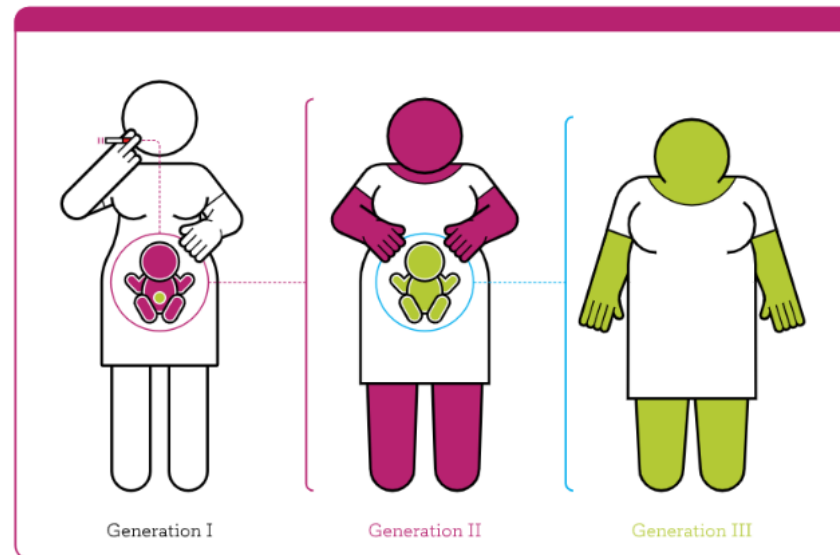
1. A Life Course Perspective

- There is substantial evidence to suggest that **early life nutrition** and experiences play a pivotal role in the progression towards adult obesity
- Life course perspective recognizes the complex interaction between our **biology** and **environmental** cues
- **First 1000 days:**
 - The development of physiological systems are influenced by the environmental and genetic elements during this critical window
 - This stage is particularly plastic and sensitive: Environmental exposures may have a stronger and potentially lifelong effect on structure and functioning.



A Life Course Perspective

- The framework highlights the intergenerational transmission of health and disease that starts early –even preconception.
- For example: Tobacco use during pregnancy impact across three generations

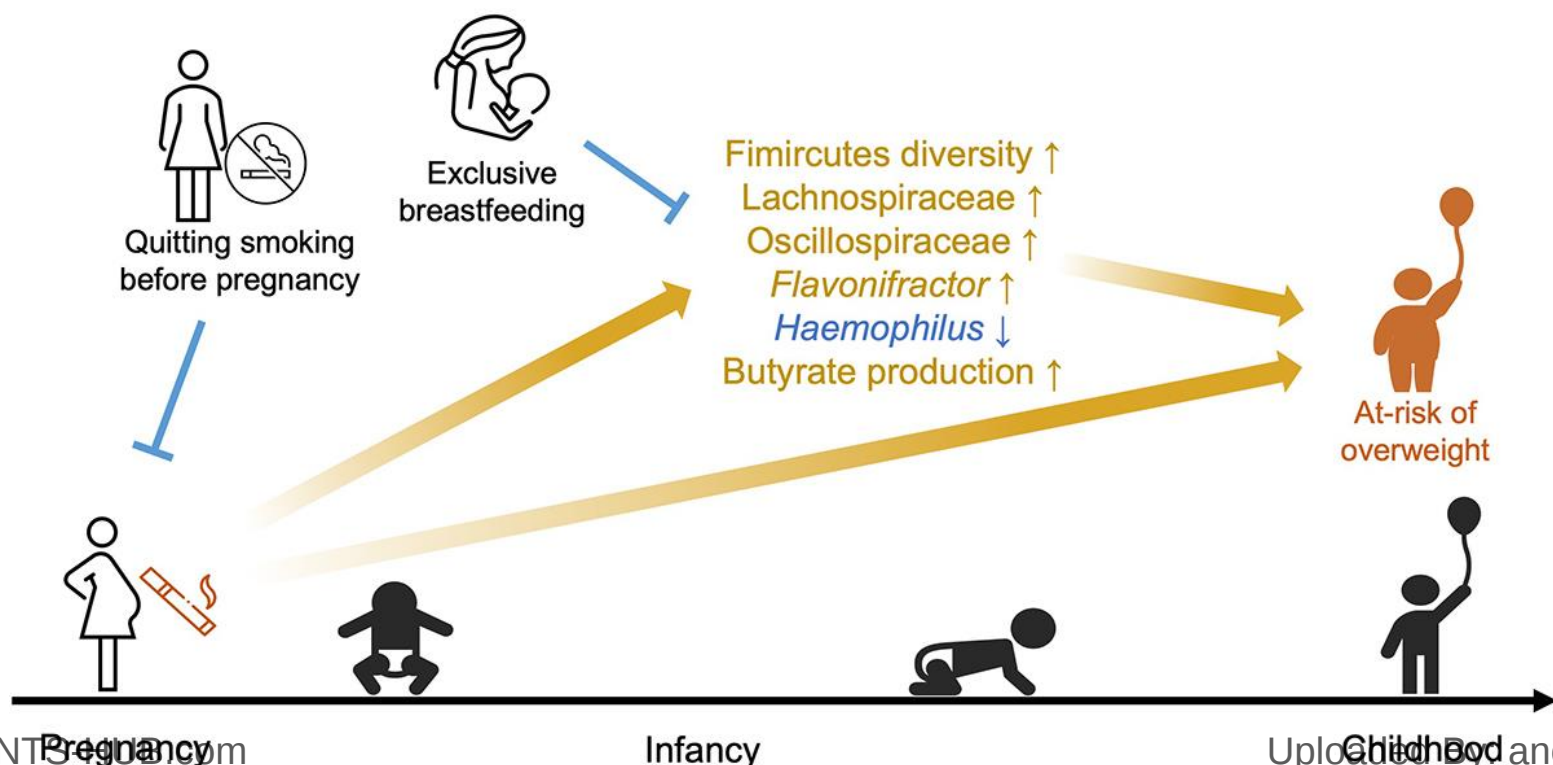


Maternal smoking during pregnancy increases the risk of gut microbiome-associated childhood overweight and obesity

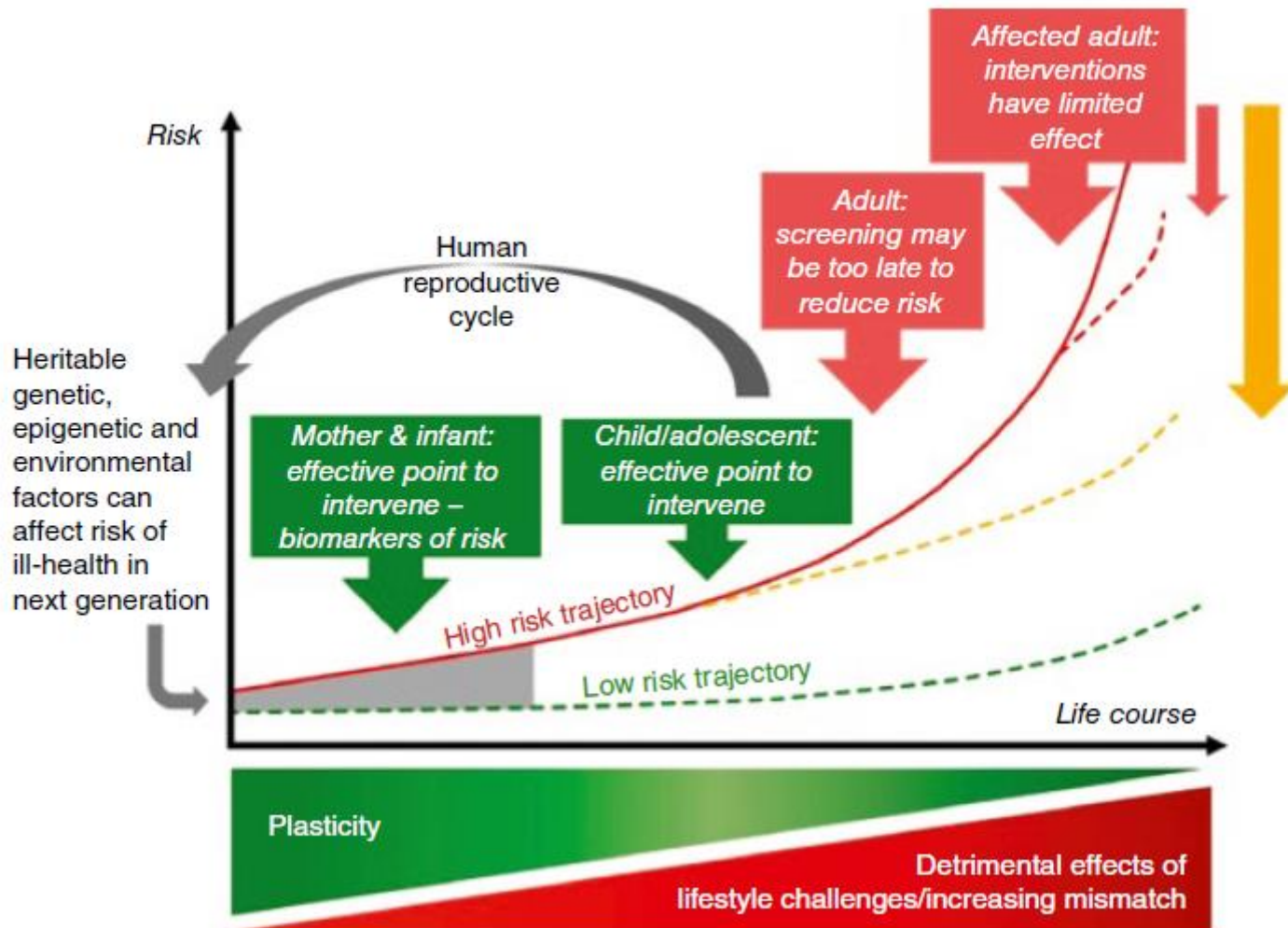
Ye Peng , Hein M Tun  , Siew C Ng, Hogan Kok-Fung Wai, Xi Zhang, Jaclyn Parks, ...show all

Article: 2323234 | Received 14 Sep 2023, Accepted 21 Feb 2024, Published online: 04 Mar 2024

 Cite this article  <https://doi.org/10.1080/19490976.2024.2323234>

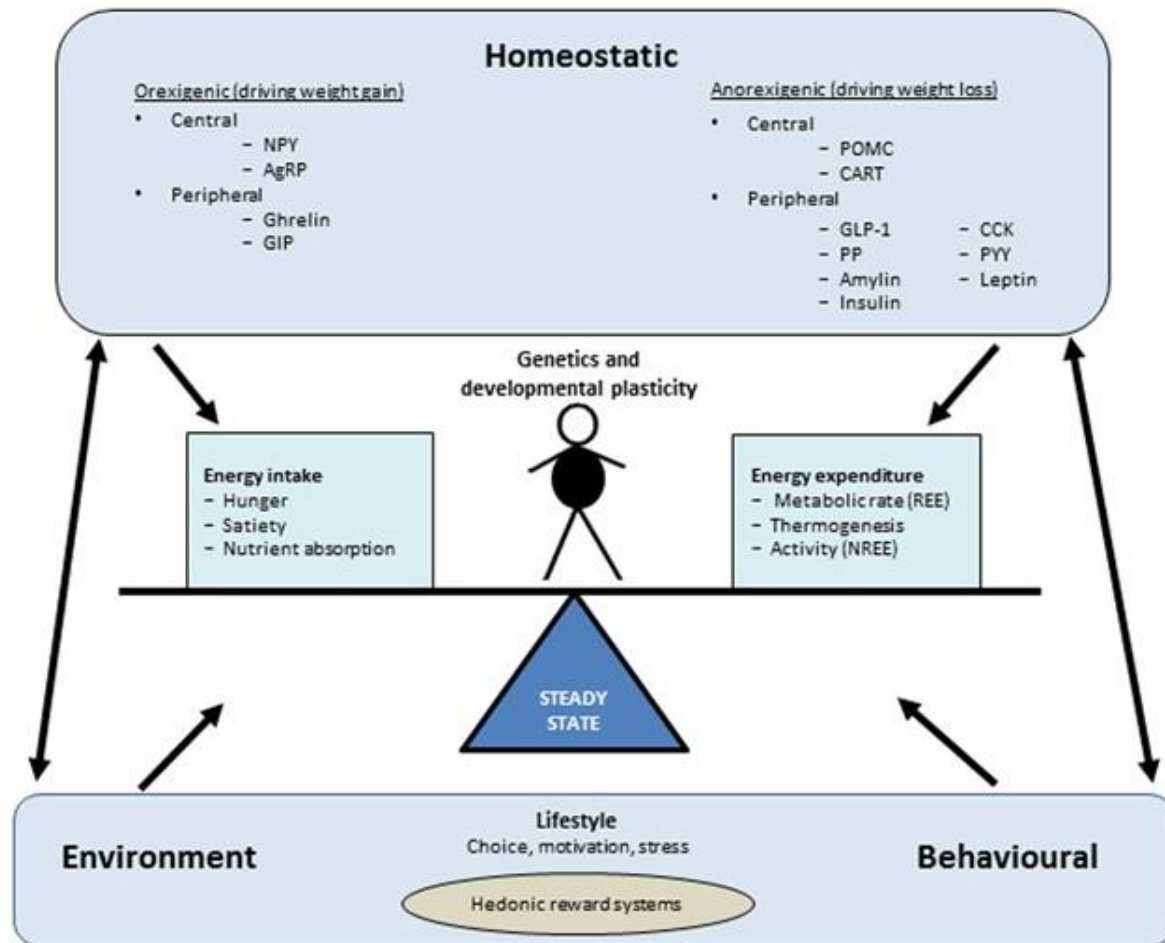


Life-course view of NCDs



2. Developmental Risk Factors

- Once established, obesity is **stubbornly resilient to reversal**, even in childhood.
- This likely results from entrenched habits, environmental influences, & **physiologic set-points**.



Greenway, F. Physiological adaptations to weight loss and factors favouring weight regain. *Int J Obes* **39**, 1188–1196 (2015).

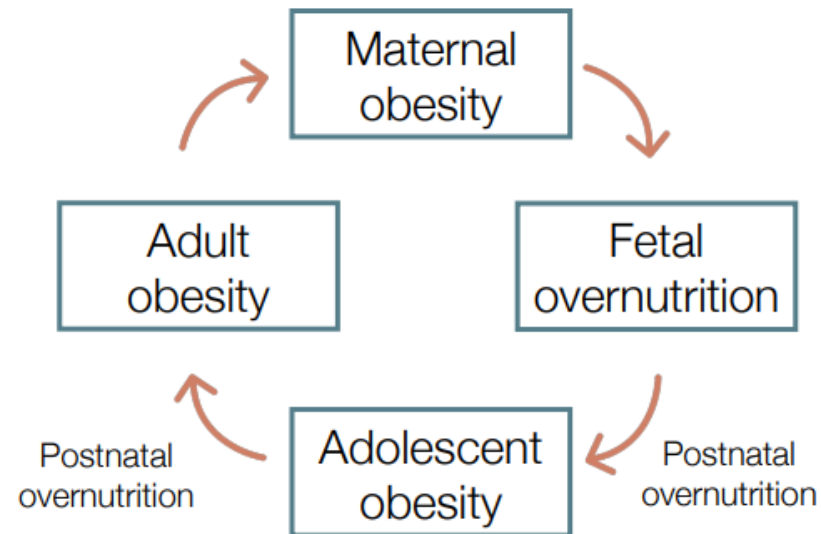
<https://doi.org/10.1038/ijo.2015.59>

2. Developmental Risk Factors

- Obesogenic risk factors discussed here include:
 - I. Maternal overnutrition and diet
 - II. Environmental Chemicals
 - III. Infant growth and diet

Maternal overnutrition

- Maternal **overweight/obesity**
 - Higher weight entering pregnancy are strong predictors of excess offspring weight at birth and childhood
 - Genetics?
 - Children born to mothers after bariatric surgery have lower obesity risk compared with siblings.
- Gestational **weight gain**
 - Greater gain predicts offspring obesity (independent of pre-pregnancy weight)
- Exposure to pre-gestational or **gestational diabetes** mellitus also predicts offspring obesity risk.



Gestational diabetes and childhood obesity

- Maternal **obesity** is an important risk factor for gestational diabetes mellitus; women who are obese or severely obese before pregnancy are four and eight times more likely to develop gestational diabetes mellitus, respectively, compared with normal weight women
- Maternal **insulin resistance** and corresponding **hyperglycemia** can result in fetal hyperinsulinemia, which can lead to increased adiposity
- Excessive adiposity at birth can affect the long-term adiposity of the offspring

Long-term effect?

[Medicina \(Kaunas\)](#). 2023 Mar; 59(3): 455.

Published online 2023 Feb 24. doi: [10.3390/medicina59030455](https://doi.org/10.3390/medicina59030455)

PMCID: PMC10051905

PMID: [36984456](https://pubmed.ncbi.nlm.nih.gov/36984456/)

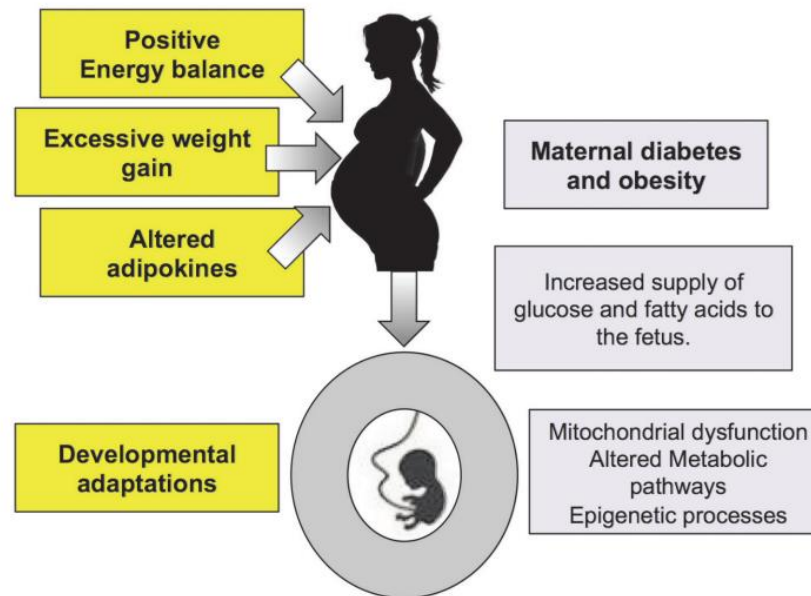
Maternal Gestational Diabetes Is Associated with High Risk of Childhood Overweight and Obesity: A Cross-Sectional Study in Pre-School Children Aged 2–5 Years

Multivariate logistic regression analysis for evaluating whether maternal gestational diabetes mellitus was independently related to sociodemographic and anthropometric characteristics and perinatal outcomes after adjusting for multiple confounding factors.

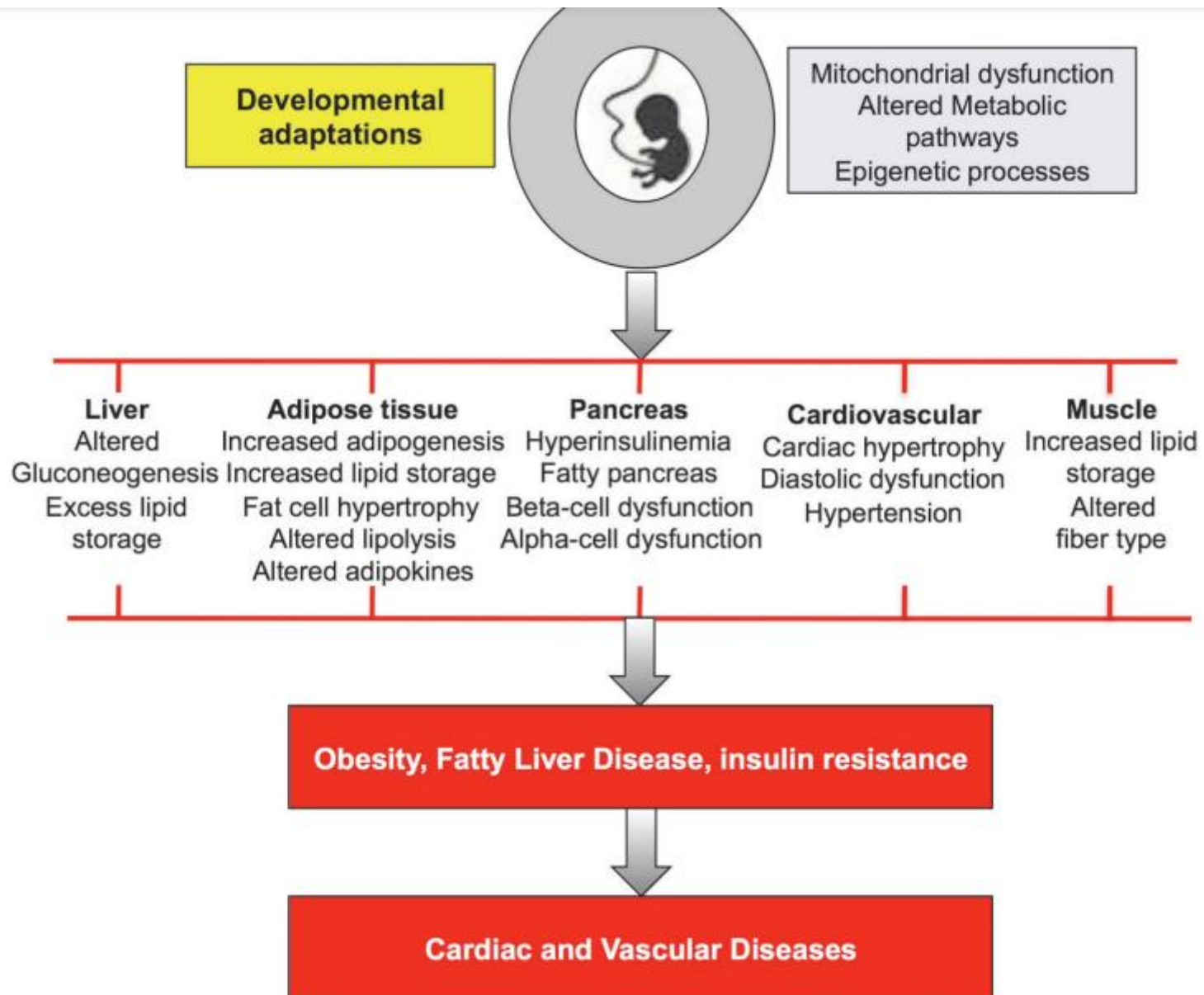
Characteristics	Gestational Diabetes Mellitus	
	OR * (95% CI **)	p-Value
Children BMI status (Normal weight/overweight or obese)	2.13 (1.94–2.31)	p = 0.0006
Children gender (Male/female)	1.27 (0.88–1.69)	p = 0.0050
Maternal age (Below/over mean value) at the time of pregnancy	1.29 (0.92–1.64)	p = 0.0027
Maternal pre-pregnancy BMI status (Underweight and normal weigh/overweight and obese)	1.30 (0.79–1.92)	p = 0.0326
Maternal education level (Below/over mean value)	0.97 (0.22–1.87)	p = 0.8502
Family economic status (Low or medium/high)	0.89 (0.24–1.71)	p = 0.2147
Smoking habits (No/yes)	1.54 (1.16–1.97)	p = 0.0204
Parity (Nulliparity/multiparity)	1.26 (0.69–1.80)	p = 0.2813
Maternal gestational weigh gain (Below/over mean value)	1.40 (0.61–2.12)	p = 0.3172
Preterm birth (No/yes)	1.77 (1.41–2.16)	p = 0.0135
Maternal gestational hypertension (No/yes)	1.14 (0.43–1.96)	p = 0.3804
Exclusive breastfeeding (No/yes)	1.31 (0.86–1.89)	p = 0.0932
Childbirth weight (Low or normal/high)	1.19 (0.52–1.91))	p = 0.4311

Maternal overnutrition

- These three factors are associated with **excess macronutrient status** → delivery of excess nutrients to the fetus.



Influence of maternal overnutrition and gestational diabetes on the programming of metabolic health outcomes in the offspring: experimental evidence¹ Troy J. Pereira, Brittany L. Moyce, Stephanie M. Kereliuk, and Vernon W. Dolinsky



Maternal overnutrition

- What about **early-life undernutrition**?
 - “Higher risk for developing obesity, hyperinsulinemia, and hyperleptinemia, especially in the presence of a high- fat diet after” weaning.

Maternal undernutrition

Stress

"Predictive adaptive response"
secondary to reduced nutrient availability in utero

Long-term obesity risk

Maternal overnutrition

**Maternal/
Gestational diabetes**

Pathological response
secondary to excess nutrient availability in utero

The metabolic conditioning of obesity: A review of the pathogenesis of obesity and the epigenetic pathways that “program” obesity from conception. October 2022 [Frontiers in Endocrinology](#) 13:1032491
doi: [10.3389/fendo.2022.1032491](#)

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From the The **Dutch Famine Study**

- “Children exposed to **nutrient deprivation** in the first two trimesters, were programmed for increased responsiveness to caloric cues, cravings, or appetite due to insufficient energy substrate availability during the critical development period of the hypothalamus”

The metabolic conditioning of obesity: A review of the pathogenesis of obesity and the epigenetic pathways that “program” obesity from conception. October 2022 [Frontiers in Endocrinology](#) 13:1032491
•DOI: [10.3389/fendo.2022.1032491](#)

Maternal diet

- **Sugary beverage** intake and child adiposity:
 - Each additional serving per day of sugary drinks consumed by mothers during pregnancy was associated with higher child BMI z scores (0.07 units), fat mass index (0.15 kg/m²), and waist circumference (0.65 cm).
- Maternal **Mediterranean dietary patterns**
 - Higher MDS was associated with lower BMI
 - For each 3- point increment in the MDS, offspring BMI z- score was lower by 0.14 units, waist circumference by 0.39 cm, and the sum of skin- fold thicknesses by 0.63 mm.

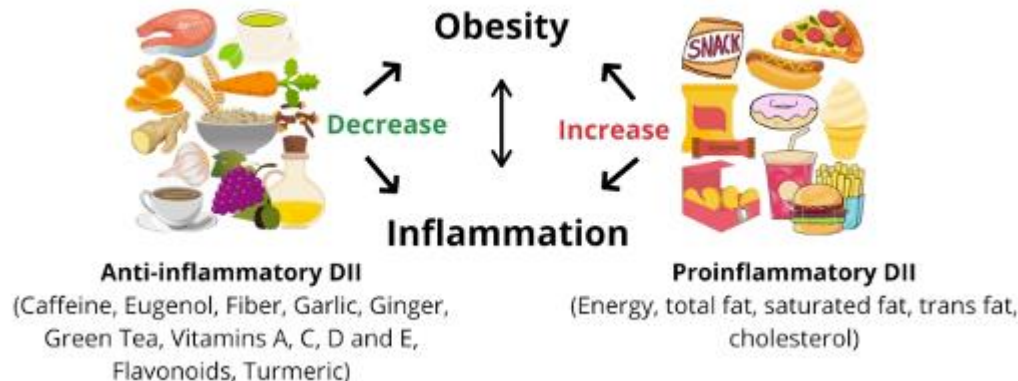
For your reference: **Mediterranean dietary score (MDS)**

Questions	Criteria for 1 point
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥ 4 tbsp
3. How many vegetable servings do you consume per day? (1 serving : 200 g [consider side dishes as half a serving])	≥ 2 (≥ 1 portion raw or as a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥ 3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	< 1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	< 1
7. How many sweet or carbonated beverages do you drink per day?	< 1
8. How much wine do you drink per week?	≥ 7 glasses
9. How many servings of legumes do you consume per week? (1 serving : 150 g)	≥ 3
10. How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥ 3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	< 3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥ 3
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)?	≥ 2

doi:10.1371/journal.pone.0043134.t001

Maternal diet

- One mechanism that can explain this is via increasing systemic **inflammation**.
- A high Dietary Inflammatory Index (DII)TM during pregnancy and early childhood is associated with higher waist circumference in all children and higher BMI in boys



Dietary inflammatory index and its relation to the pathophysiological aspects of obesity: a narrative review. Roseli Neves de Mello ORCID logo, Bárbara Paixão de Gois ORCID logo, Ana Claudia Pelissari Kravchychyn ORCID logo, Ana Raimunda Dâmaso ORCID logo, Maria Aderuza Horst ORCID logo, Glaucia Carielo Lima ORCID logo, Flávia Campos Corgosinho ORCID logo

Maternal diet

- **Healthy Eating Index** for assessing diet quality shows increased neonatal **adiposity**, but not birth weight, with poor diet quality. This is independent of maternal BMI

Components	Maximum Score	Maximum score criteria	Criteria for zero score
1. Total fruit (includes fruit juice)	5	≥ 0.8 cup per 1000 kcal	No fruit or juice
2. Whole fruit (includes all forms except juice)	5	≥ 0.4 cup per 1000 kcal	No whole fruit
3. Total vegetables	5	≥ 1.1 cup per 1000 kcal	No vegetables
4. Greens and beans	5	≥ 0.2 cup per 1000 kcal	No dark green vegetables or legumes
5. Whole grains	10	≥ 40 g per 1000 kcal	No whole grains
6. Dairy	10	≥ 1.3 cup per 1000 kcal	No dairy
7. Total protein foods	5	≥ 70 g per 1000 kcal	No protein foods
8. Seafood and plant proteins	5	≥ 20 g per 1000 kcal	No seafood or plant protein
9. Fatty acids	10	$(PUFAs + MUFAs) / SFAs \geq 2.5$	$(PUFAs + MUFAs) / SFAs \leq 1.2$
10. Refined grains	10	≤ 50 g per 1000 kcal	≥ 120 g per 1000 kcal
11. Sodium	10	≤ 1.1 g per 1000 kcal	≥ 2 g per 1000 kcal
12. Empty calories	20	$\leq 19\%$ of energy	$\geq 50\%$ of energy

PUFAs polyunsaturated fatty acids, MUFAs monounsaturated fatty acids, SFAs saturated fatty acids

- Nutrition quality is just as important as weight gain and BMI

Environmental chemicals

- **Environmental obesogens**: organic and inorganic pollutants of human and natural origin
- Prenatal smoking causes reduced fetal growth, and has associations with later offspring obesity.
- Maternal smoking during pregnancy conferred 50% increased odds of offspring obesity across an age range of 3–33 years.
- 238,340 mother–child- pairs: a **linear positive association** was observed between the number of cigarettes smoked and offspring overweight for up to 15 cigarettes per day.

Again ...

Research paper

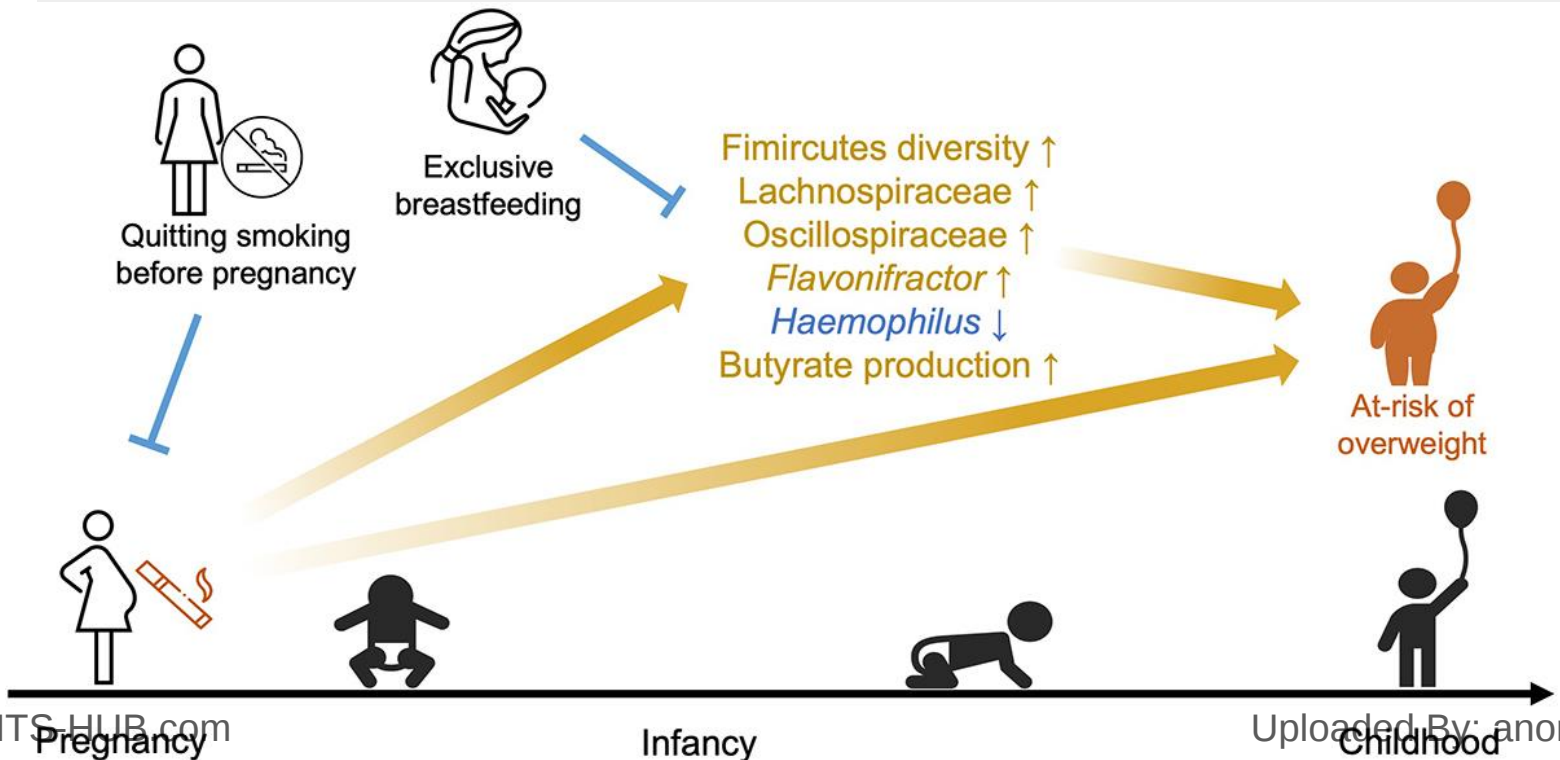
Maternal smoking during pregnancy increases the risk of gut microbiome-associated childhood overweight and obesity

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 Cite this article  <https://doi.org/10.1080/19490976.2024.2323234>

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Environmental chemicals

- Per- and polyfluorinated substances (PFAS): man- made fluorinated chemicals used in stain- resistant and water- resistant coatings for textiles, non- stick cookware, food containers, floor polish, fire- fighting foam, and industrial surfactants: results in **bioaccumulation** and persistence in human tissues for years.
- These chemicals can cross the placenta.
- Greater prenatal exposure was associated with a decrement in birth weight, and weight gain or obesity in children and adults.

Infant growth patterns and timing

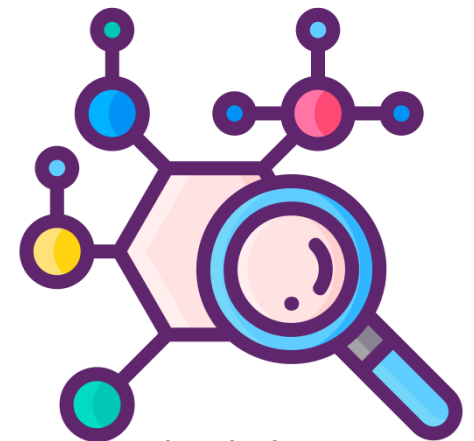
- **Accelerated weight gain** during the first weeks or months of life is associated with higher BMI or obesity later in life.
- The true explanations are as yet unclear. In addition, the apparent cardiometabolic harms of rapid infant weight gain need to be balanced against its potential benefit for neurocognitive out-comes, especially in babies born preterm.

Infant diet quality and eating behaviors

- Breastfeeding was associated with a significantly reduced risk of obesity in children (AOR 0.78).
- A dose- response effect between breastfeeding duration and reduced risk of childhood obesity.
- However, There is conflicting evidence.

3. Biology and mechanisms

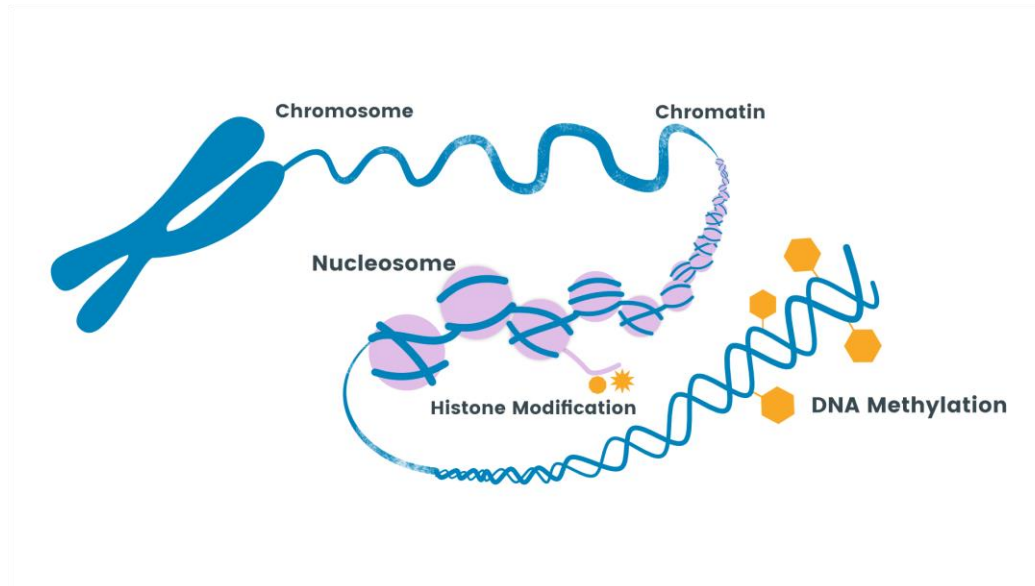
- There are extensive studies addressing the potential relationship between events in early life and long- term health
- However, limited understanding of the mechanisms by which this may arise



3. Biology and mechanisms

Epigenetics

- Epigenetics: mechanisms that alter gene activity without changing the DNA sequence.
- In newborns, maternal BMI was associated with small methylation variation at various sites throughout the genome.
- Cord blood DNA methylation & maternal smoking explaining 12–19% birth weight reduction



3. Biology and mechanisms

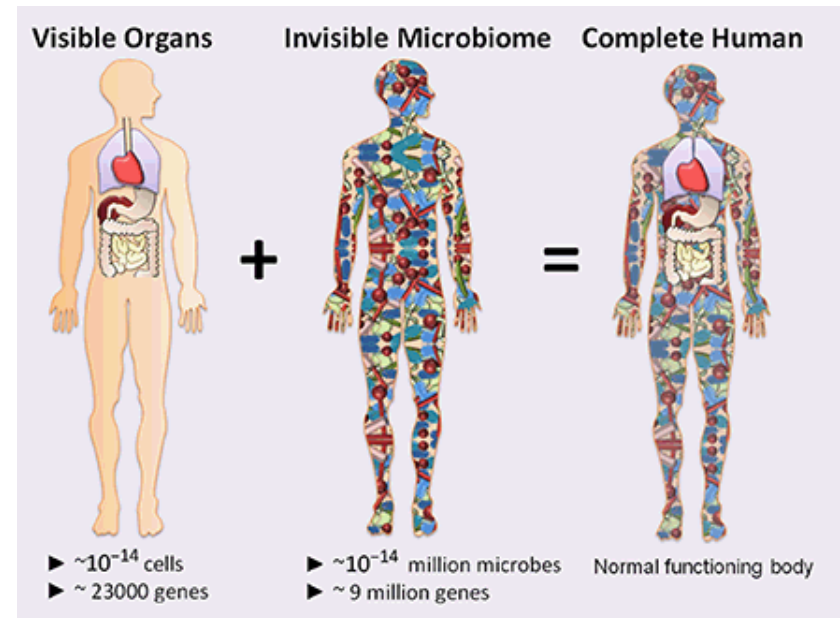
Mediating metabolic factors

- Glucose, leptin, ghrelin, and insulin can all be regulated by diet.
- High or low levels exposures during critical periods of development could provide mechanisms by which nutrition could impact on later obesity risk.

3. Biology and mechanisms

Gut microbiota

- The role of the gut microbiota in influencing obesity risk is much debated.
- Points to discuss:
 - Cesarean versus vaginal delivery.
 - Antibiotic exposure during the first year of life
 - Effect size?



4. Implications

- Strong evidence has identified a number of early life experiences that predict later obesity risk.
- However, let us consider the **confounding factors** here and the difficulties of **experimental study designs**.
- We should think of many of these factors as **risk markers** rather than **causal risk factors**.

Implications

- We can use this knowledge to identify children at higher risk for subsequent obesity, to promote interventions than can direct trajectories
- Support policies that help limit exposures to likely **obesogens**: smoke- free public spaces, smoking cessation efforts, restricting sugary beverages, reducing exposures to toxic chemicals.