



# Otyłość u dzieci - profilaktyka i leczenie

2 - 3 lutego 2024, Warszawa



INSTYTUT „POMNIK-CENTRUM ZDROWIA DZIECKA”

## Programowanie metaboliczne

**Dariusz Grusfeld**

Klinika Neonatologii, Patologii i Intensywnej Terapii Noworodka i Niemowlęcia

(DOHaD)

The developmental origins of chronic adult disease

DJP Barker

MRC Environmental Epidemiology Unit, University of Southampton, United Kingdom



J Econ Perspect 2011; 25(3): 153-172. doi:10.1257/jep.25.3.153

Killing Me Softly: The Fetal Origins Hypothesis\*

Douglas Almond and Janet Currie



- płód jest "chroniony przed uszkodzeniami z powodu niedożywienia matki" [Susser i Stein, 1994]
- kobietom w ciąży mówiono, że „mogą śmiało zapalić papierosa i wypić kilka drinków” [Landro, 2010]
- około połowa amerykańskich matek zgłaszała palenie w ciąży w 1960 roku [Aizer i Stroud, 2009]

Wczesny stres/separacja → problemy behavioralne

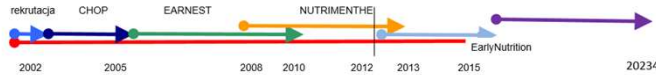
Effects of Early-Life Stress on the Brain and Behaviors: Implications of Early Maternal Separation in Rodents

Brain and Behavior

Effect of early life stress on anxiety and depressive behaviors in adolescent mice

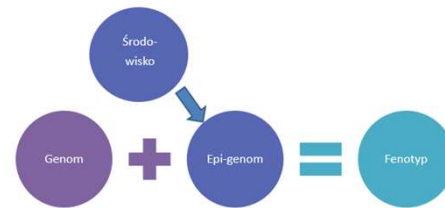
Early life stress induces submissive behavior in adult rats

EU Childhood Obesity Study  
obserwacja kohorty



Partners

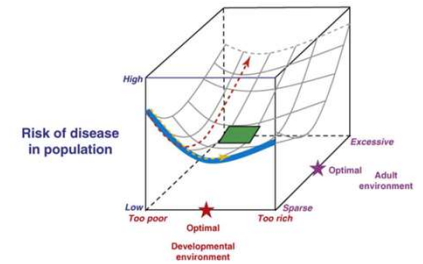
1. LMU-Monachium
2. URV - Tarragona i Reus
3. UNIMI - Mediolan
4. IP CZD - Warszawa
5. ULB - Bruksela i Liege



Lowest risk for human population: optimal developmental environment and living in adult environment on low side of mid-range

Improvement of developmental environment, resulting in reduced disease risk

Transition from poor to richer adult environment produces small reduction but then increases disease risk considerably



# (DOHaD)

## The developmental origins of chronic adult disease

DJP Barker

*MRC Environmental Epidemiology Unit, University of Southampton, United Kingdom*



## Killing Me Softly: The Fetal Origins Hypothesis\*

Douglas Almond and Janet Currie



Every doctor in private practice was asked:  
—family physicians, surgeons, specialists...  
doctors in every branch of medicine—  
“What cigarette do you smoke?”

According to a recent Nationwide survey:  
**More Doctors  
Smoke Camels**  
than any other cigarette!

Not a guess, not just a trend...but an actual fact based on the statements of doctors themselves to 3 nationally known independent research organizations.

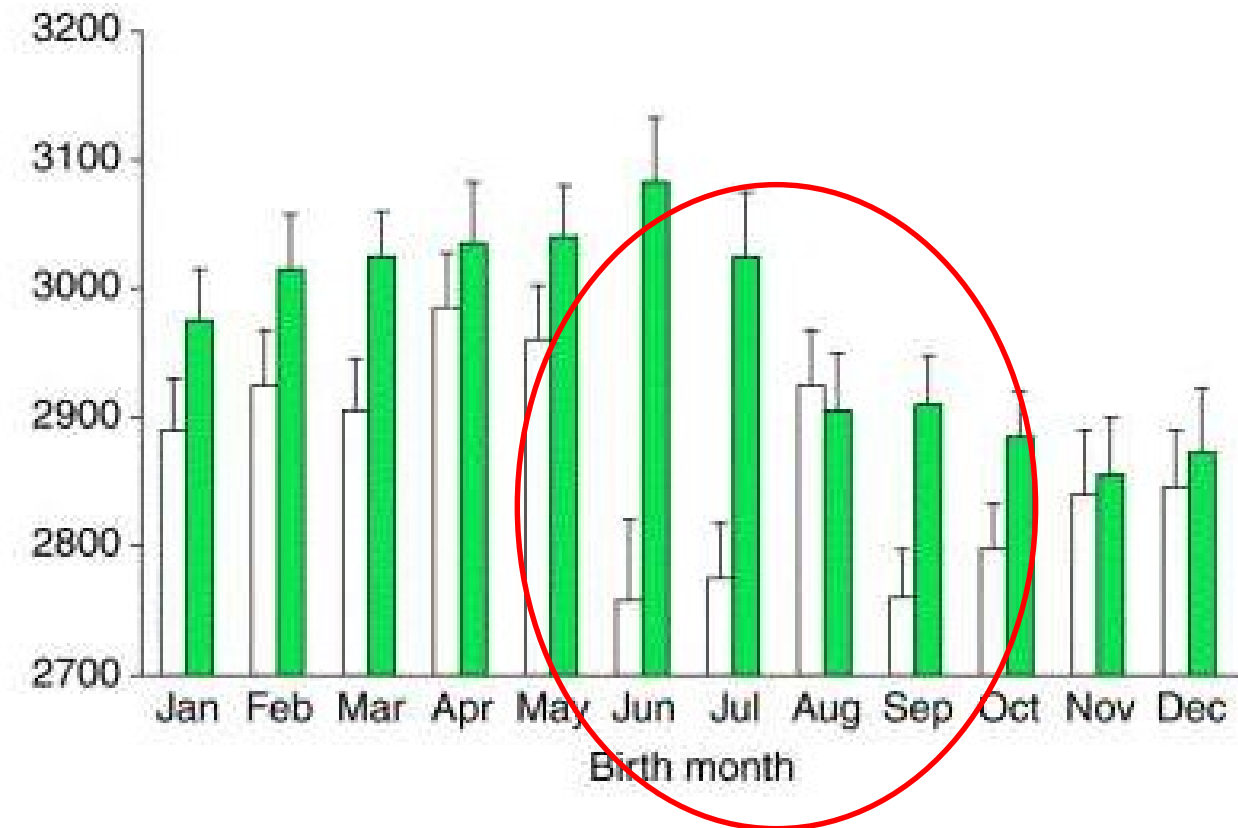
Yes, your doctor was asked...along with thousands and thousands of other doctors from Maine to California...  
And they've named their choice—the brand that more doctors named as their smoke is Camel! Three nationally known independent research organizations found this to be a fact.  
Nothing unusual about it. Doctors smoke for pleasure just like the rest of us. They appreciate, just as you, a mildness that's cool and easy on the throat. They too enjoy the full, rich flavor of expertly blended coastier tobaccos. And they named Camels...more of them named Camels than any other brand. Next time you buy cigarettes, try Camels.

envisoningtheamericandream.com

- płód jest "chroniony przez uszkodzeniami z powod niedożywienia matki" [Susser i Stein, 1994]
- kobietom w ciąży mówiono, że „mogą śmiało zapalić papierosa wypić kilka drinków” [Landro, 2010]
- około połowa amerykańskich matek zgłaszała palenie w ciąży 1960 roku [Aizer i Strou 2009]

# Early development, survival and reproduction in humans

Virpi Lummaa and Tim Clutton-Brock



- Gambia, n = 2047, 28 wiosek, 1989–1994.
- pora roku w chwili porodu vs. masa urodzeniowa
- deszczowy sezon (czerwiec–październik) wiąże się ze spadkiem m. ur.
- wysokoenergetyczna suplementacja (20 tygodni przed porodem) ↑ m. ur.

Lummaa, Virpi & Clutton-Brock, Tim. (2002)

## WEIGHT IN INFANCY AND DEATH FROM ISCHAEMIC HEART DISEASE

D. J. P. BARKER  
C. OSMOND

P. D. WINTER  
B. MARGETTS

S. J. SIMMONDS

MRC Environmental Epidemiology Unit, University of  
Southampton, Southampton General Hospital, Southampton  
SO9 4XY

n=5654

Hertfordshire, UK (1911 – 1930)

↑ ryzyko zgonu z powodu choroby  
wieńcowej

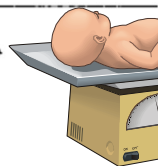
↑ ciśnienie tętnicze

↑ ryzyko T2D

↓ m. ur. →

Weight (pounds)	Cause of death		
	Ischaemic heart disease	Chronic obstructive lung disease	Lung cancer
<i>One year old</i>			
≤ 18 (n = 324)	111 (37)*	129 (6)	98 (11)
19–20 (n = 971)	81 (76)	86 (11)	99 (31)
21–22 (n = 1850)	98 (163)	41 (9)	87 (48)
23–24 (n = 1464)	71 (98)	61 (11)	57 (26)
25–26 (n = 769)	68 (49)	52 (5)	97 (23)
≥ 27 (n = 276)	42 (11)	29 (1)	70 (6)
<i>Birthweight</i>			
≤ 5.5 (n = 251)	104 (25)	93 (3)	113 (9)
6–6.5 (n = 752)	77 (51)	59 (5)	101 (22)
7–7.5 (n = 1598)	90 (129)	75 (14)	68 (32)
8–8.5 (n = 1757)	85 (141)	50 (11)	85 (47)
9–9.5 (n = 868)	62 (53)	69 (8)	67 (19)
≥ 10 (n = 428)	81 (35)	33 (2)	109 (16)
<b>Total (n = 5654)</b>	<b>82 (434)</b>	<b>61 (43)</b>	<b>83 (145)</b>

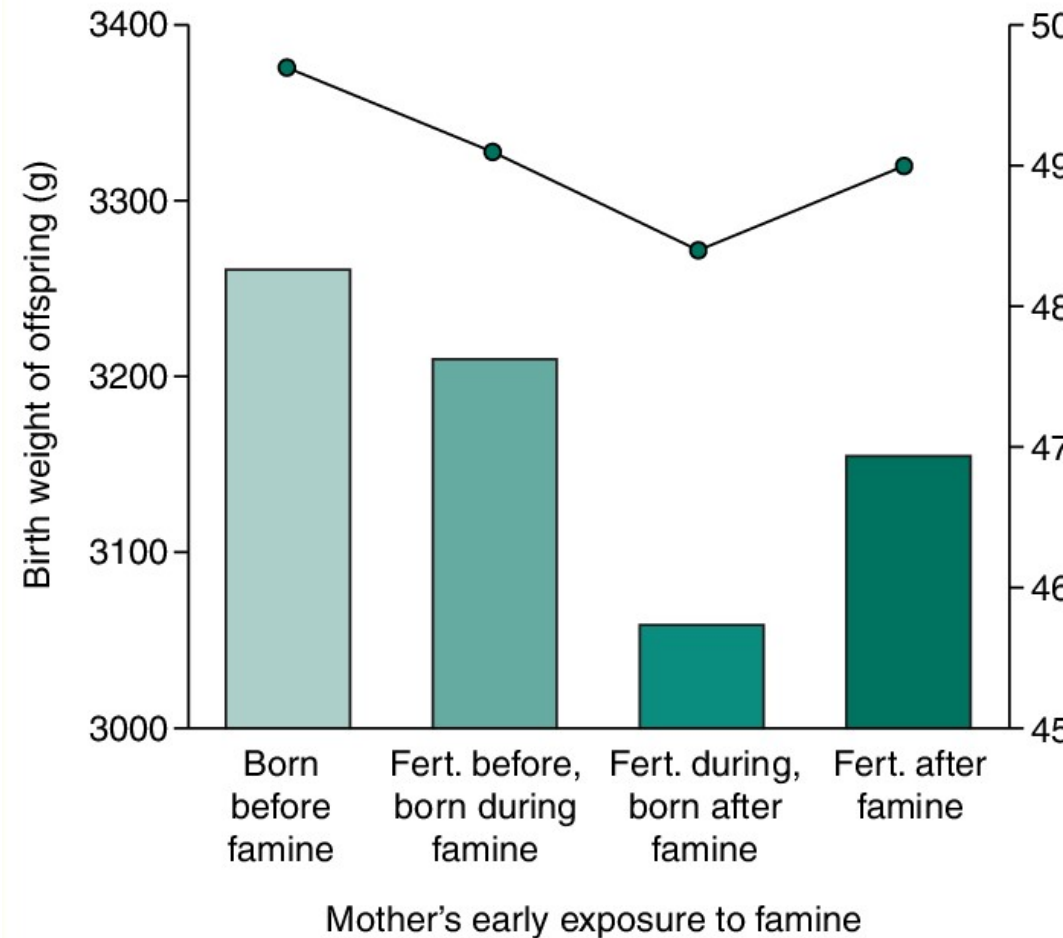
\*Number of deaths in parentheses. 2.2 pounds = 1 kg.



# Dutch Famine Birth Cohort Study - 1944-1945

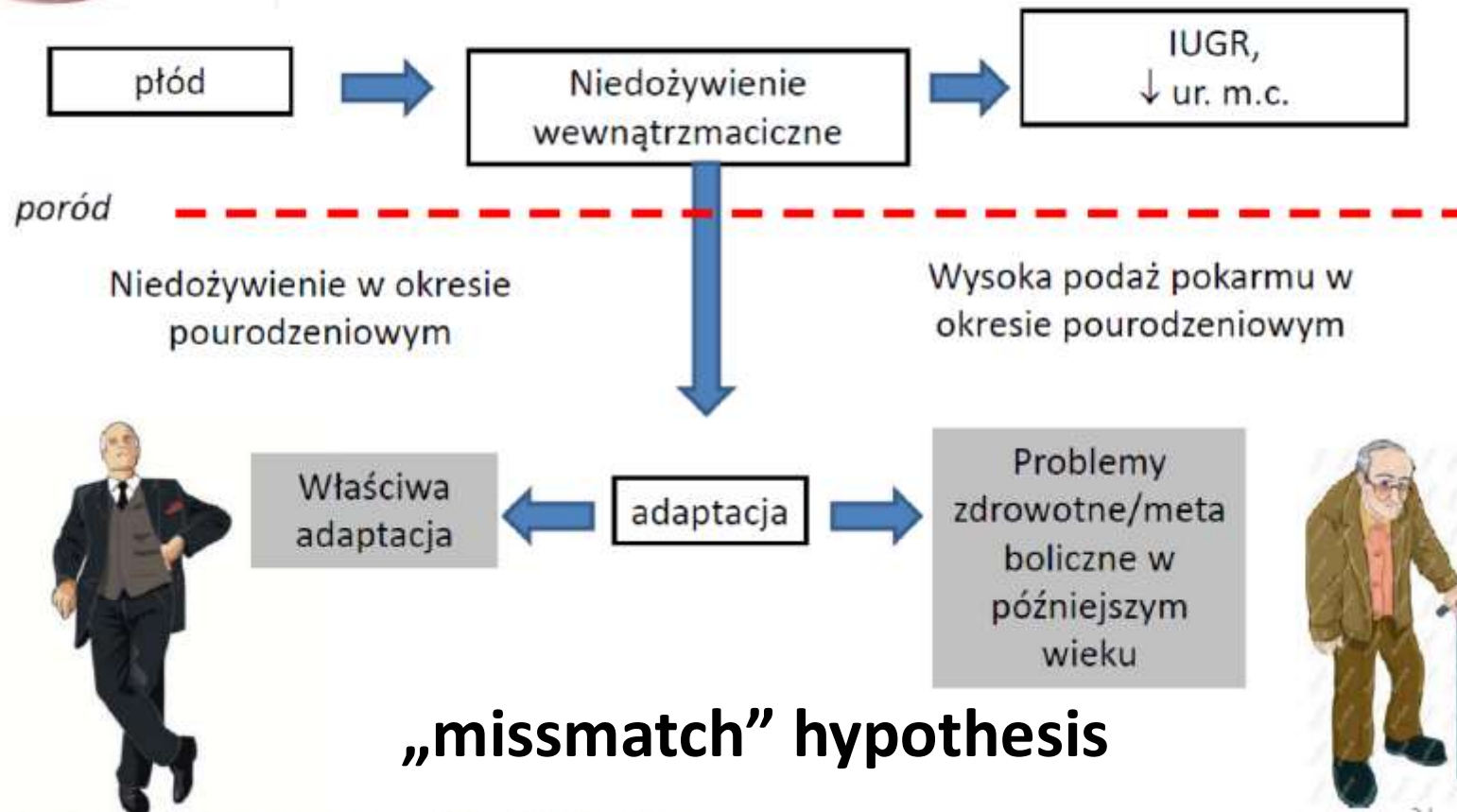
1944-1945; n ≈ 900 osób; ok. 50 r.ż.

- ↑ ciśnienie tętnicze,
- ↑ choroby wieńcowej (OR = 3.0),
- ↑ **cukrzycy insulino-niezależnej**,
- ↑ ryzyko otyłości,
- nieprawidłowy cholesterol
- 2x częściej schizofrenia w wieku dorosłym





## „Thrifty phenotype” hypothesis

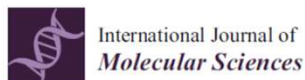


## „mismatch” hypothesis

Langley- Evans SC. Proc Nutr Soc. 2006; 65:97-105



# Wczesny stres/separacja → problemy behawioralne



Review

## Effects of Early-Life Stress on the Brain and Behaviors: Implications of Early Maternal Separation in Rodents

Mayumi Nishi

Department of Anatomy and Cell Biology, Nara Medical University, Kashihara 634-8521, Japan; nmayumi@naramed-u.ac.jp; Tel.: +81-744-29-8822; Fax: +81-744-29-7199

Received: 13 August 2020; Accepted: 25 September 2020; Published: 29 September 2020



## Brain and Behavior

Open Access

ORIGINAL RESEARCH | Open Access |

## Effect of early life stress on anxiety and depressive behaviors in adolescent mice

Ting He, Chen Guo, Chunlian Wang, Chunrong Hu, Huanxin Chen

First published: 21 January 2020 | <https://doi.org/10.1002/brb3.1526> | Citations: 29



## Behavioural Brain Research

Volume 372, 17 October 2019, 112025



Research report

## Early life stress induces submissive behavior in adult rats

[Dmitry Frank](#)<sup>a 1</sup> , [Alexander Zlotnik](#)<sup>a 1</sup> , [Ora Kofman](#)<sup>b</sup>

REVIEW ARTICLE

# Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis

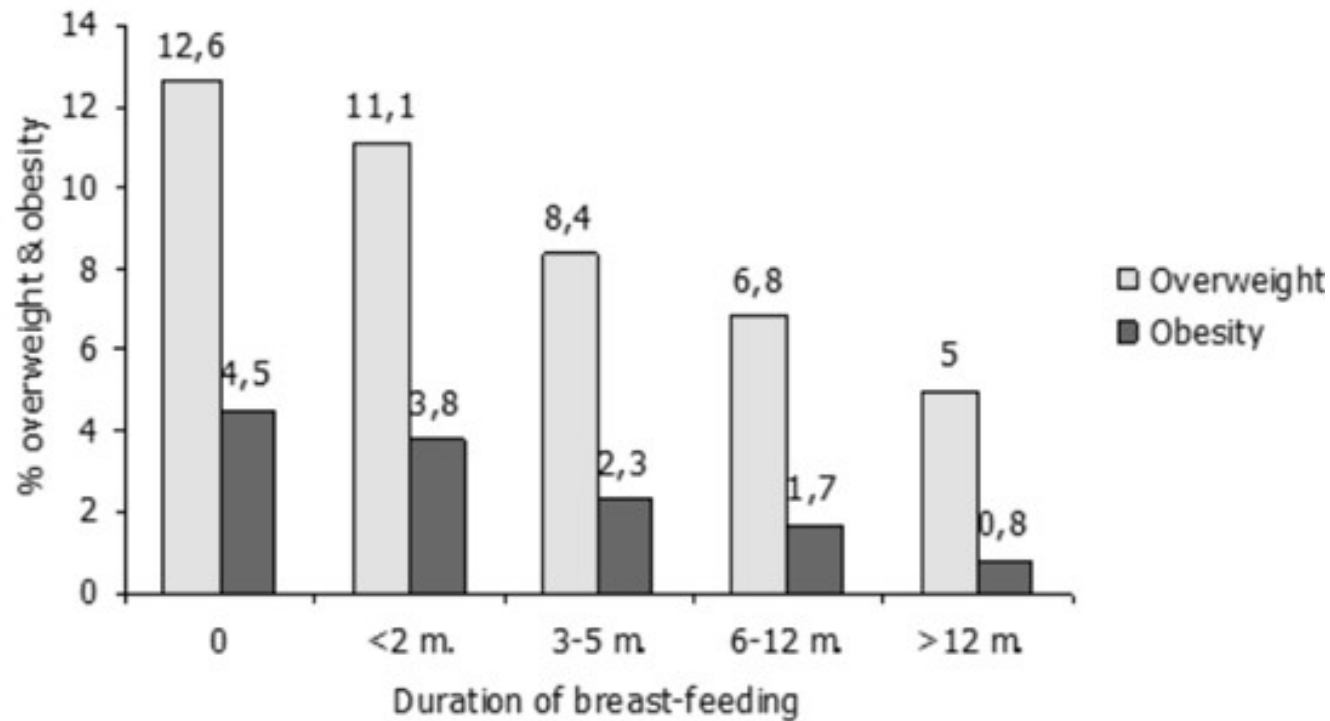
Bernardo L. Horta (blhorta@gmail.com), Christian Loret de Mola, Cesar G. Victora

5 Pooled effects of each outcome, from all studies and from those deemed to be of higher scientific quality

Outcome	All studies		Large sample size and control for confounding *		Large sample size, control for confounding* and recall <3	
	N	Pooled effect (95% confidence interval)	N	Pooled effect (95% confidence interval)	N	Pooled effect (95% confidence interval)
total blood cholesterol (mmol/L)	46	-0.01 (-0.05; 0.02)	9	0.00 (-0.02; 0.02)	5	0.01 (-0.02; 0.04)
systolic blood pressure (mmHg)	43	-0.80 (-1.17; -0.43)	9	-0.35 (-0.96; 0.27)	7	-0.48 (-1.21; 0.25)
diastolic blood pressure (mmHg)	38	-0.24 (-0.50; 0.02)	7	0.01 (-0.41; 0.42)	5	-0.03 (-0.61; 0.55)
ratio for overweight/obesity	113	0.74 (0.70; 0.78)	23	0.87 (0.81; 0.94)	11	0.87 (0.76; 0.98)
ratio for type-2 diabetes	11	0.65 (0.49; 0.86)	3	0.76 (0.40; 1.47)		**

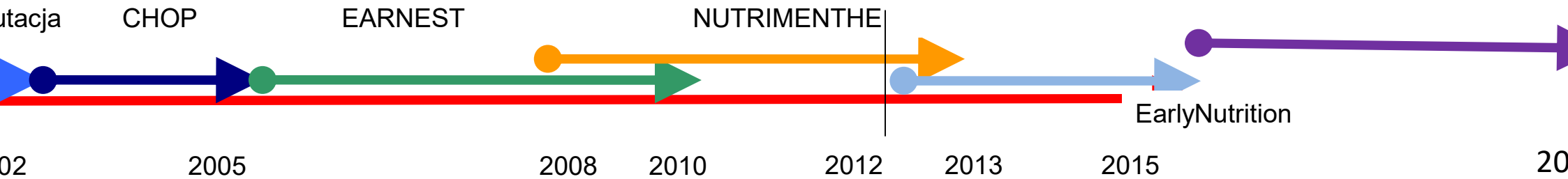
# Wpływ karmienia naturalnego na otyłość

n = 13 000; 5-6 r.ż.



# EU Childhood Obesity Study

## obserwacja kohorty



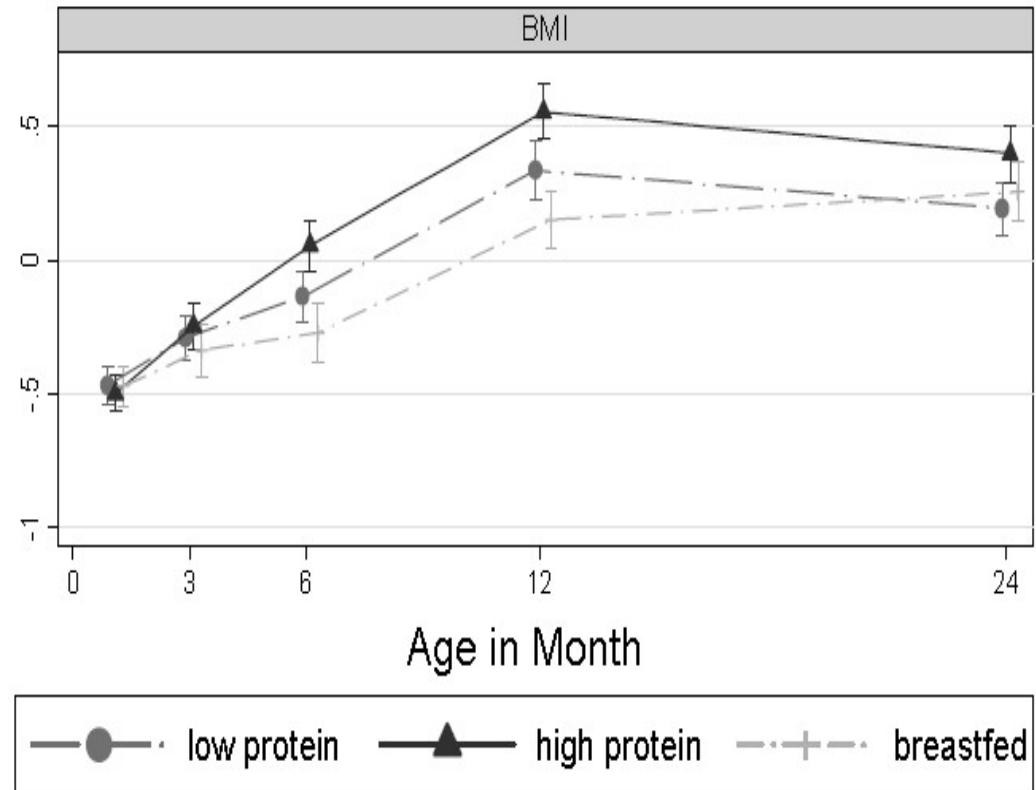
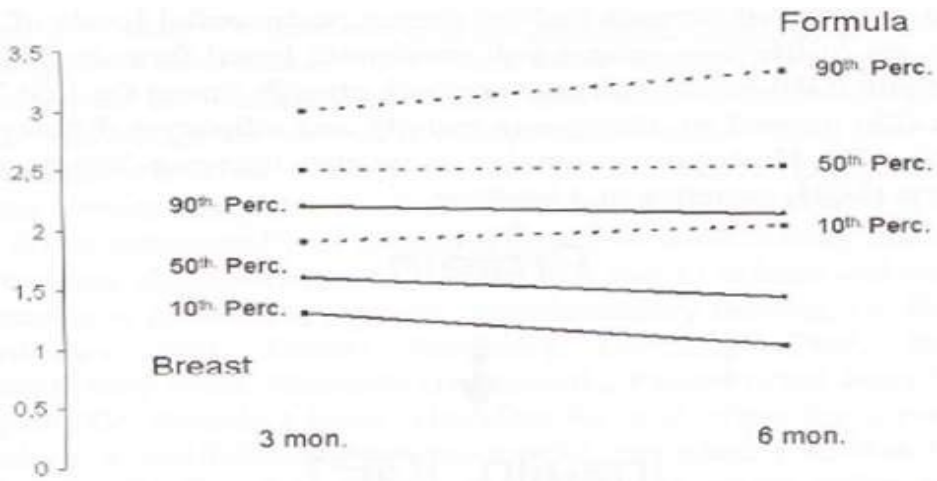
### Partners

1. LMU-Monachium
2. URV – Tarragona i Reus
3. UNIMI – Mediolan
4. IP CZD - Warszawa
5. ULB – Bruksela i Liege



# „Early protein hypothesis”

## EU Childhood Obesity Project (CHOP)



Niemowlęta karmione sztucznie otrzymują więcej białka

**BMI w 2 r.ż.**

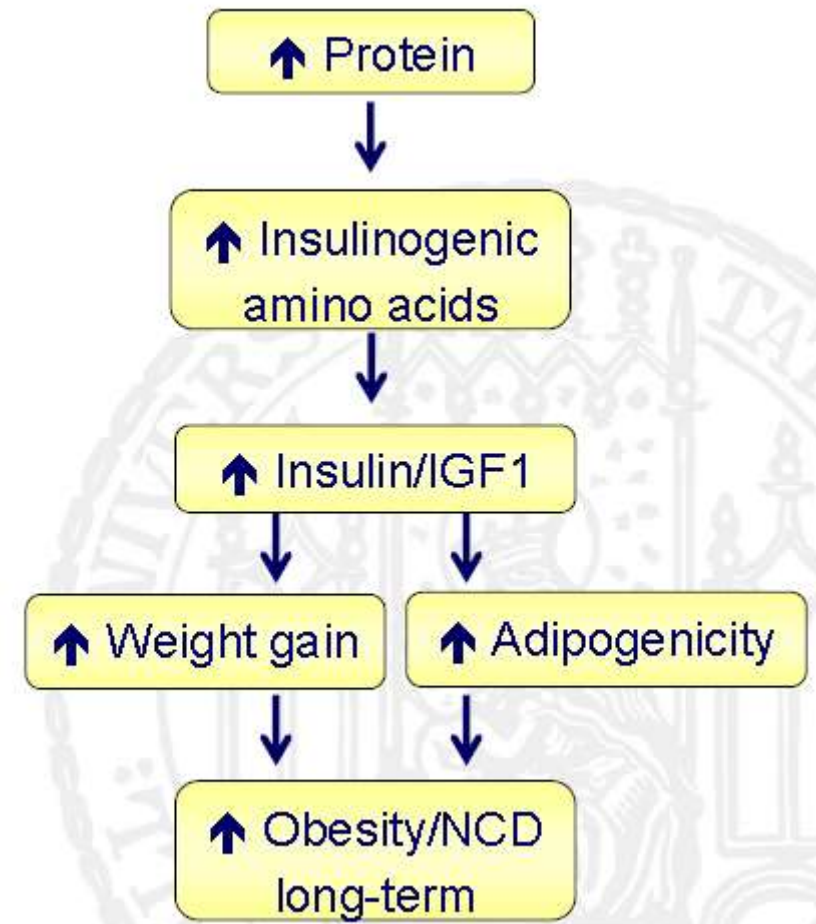
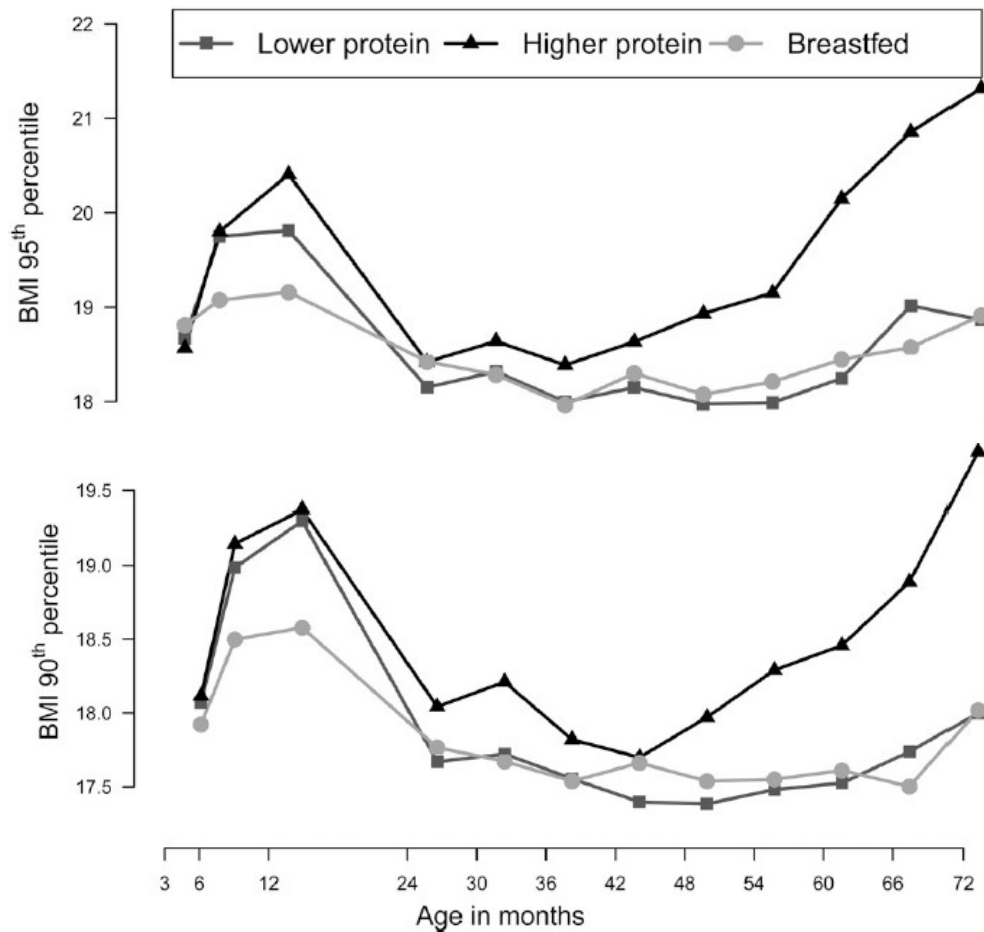
\*Alexy, U. Ann Nutr Metab 1999

\*Koletzko B, von Kries R, Closa R, Gruszfeld D, Dobrzanska A, Sengier A. Am J Clin Nutr. 2009

# Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial<sup>1-5</sup>

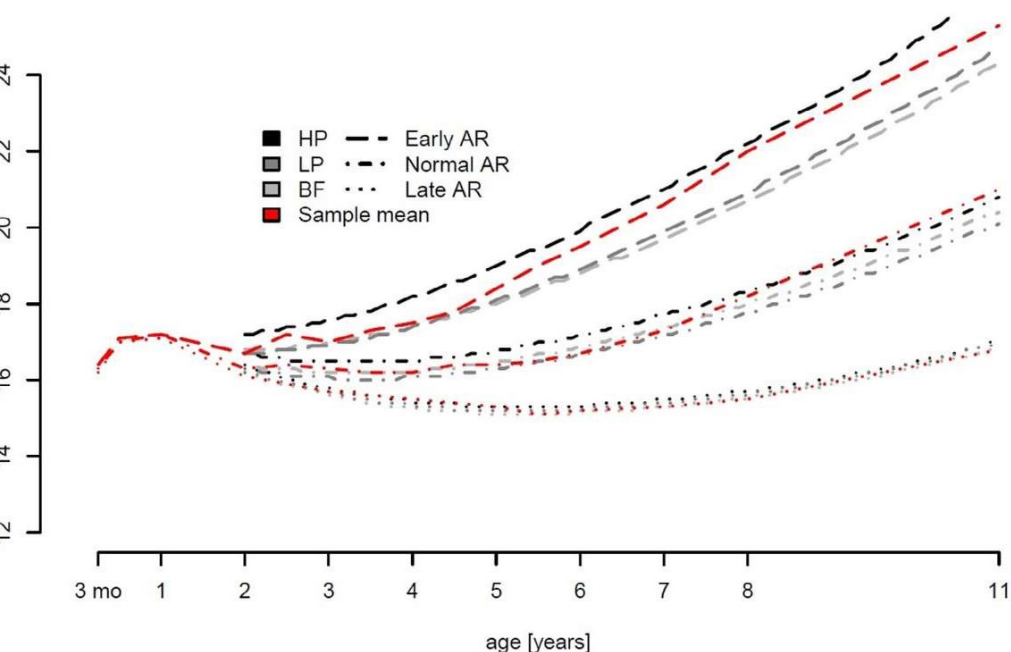


Martina Weber, Veit Grote, Ricardo Closa-Monasterolo, Joaquín Escribano, Jean-Paul Langhendries, Elena Dain, Marcello Giovannini, Elvira Verduci, Dariusz Gruszfeld, Piotr Socha, and Berthold Koletzko for The European Childhood Obesity Trial Study Group



Differential protein intake in the first year and its effects on adiposity rebound and obesity throughout childhood: 11 years follow-up of a randomized controlled trial

Michael Totszauer, Joaquin Escribano, Ricardo Closa-Monasterolo, Veronica Luque, Elvira Verduci, Josep M. Dominguez, Jean-Paul Langhendries, Françoise Martin, Annick Xhonneux, Dariusz Gruszfeld, Veronika Kuchta, Veit Grote, Berthold Koletzko on behalf of the European Childhood Obesity Trial Study Group ... See fewer authors



- karmienie mieszanką HP vs LP



- wyższa trajektoria BMI do 11. r.ż.
- „adiposity rebound”

Totszauer M et al.. Pediatr Obes. 2022

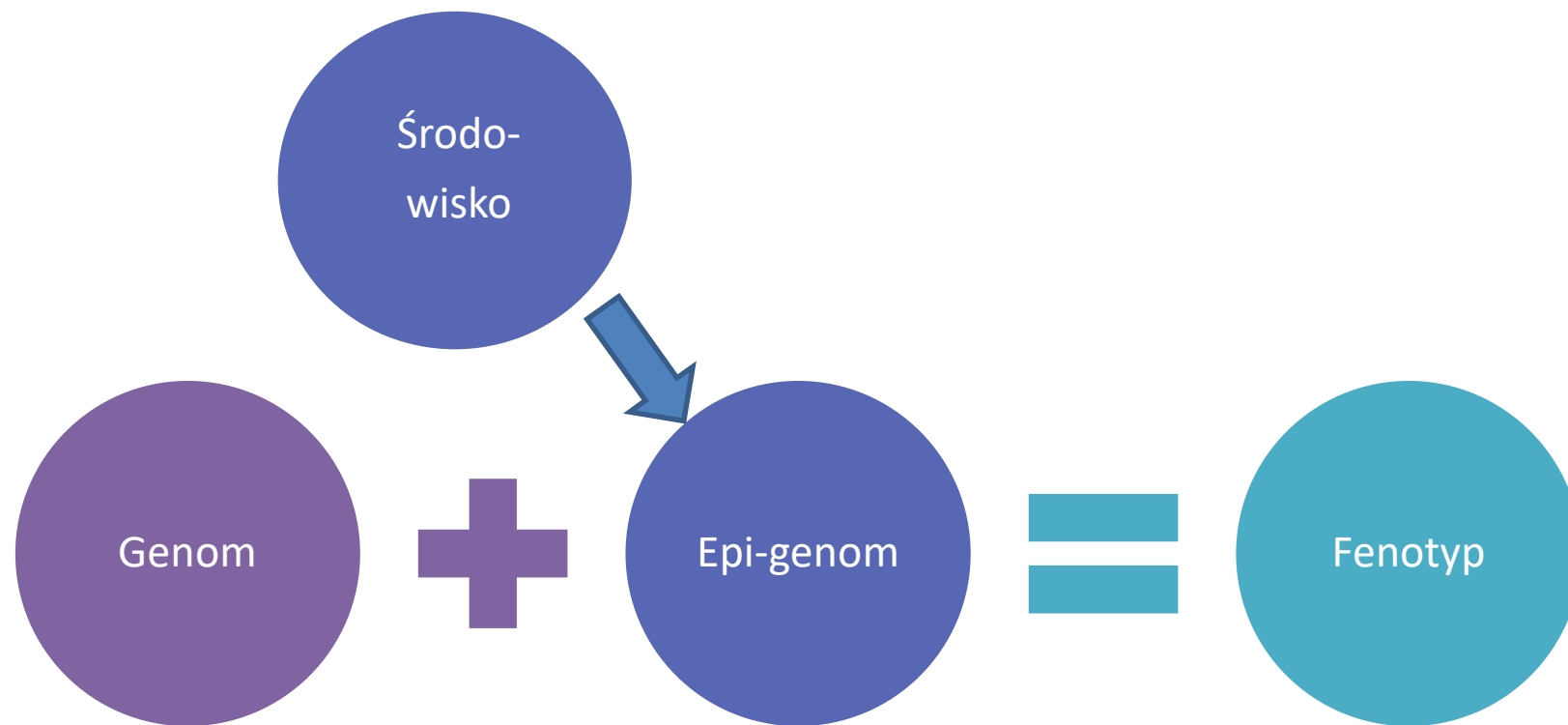
# Zalecenia podaży białka

Tabela 1. Zalecana zawartość białka w mleku początkowym oraz mleku następnym

Zalecenia	Rok	Mieszanki początkowe na bazie mleka krowiego	Mieszanki następne na bazie mleka krowiego
Dyrektywy Komisji Europejskiej	1991 <sup>31</sup>	1,8-3,0 g/100 kcal	2,25-4,5 g/100 kcal
	2006 <sup>32</sup>	1,8-3,0 g/100 kcal	1,8-3,5 g/100 kcal
	2016 <sup>33</sup>	1,8-2,5 g/100 kcal	1,8-2,5 g/100 kcal
Europejski Urząd ds. Bezpieczeństwa Żywności (EFSA)	2017 <sup>34</sup>		1,6-2,5 g/100 kcal*

Minimalna zawartość białka bliższa zawartości w mleku kobiecym



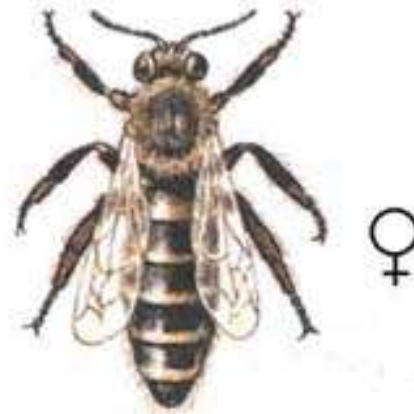




robotnica



truteń

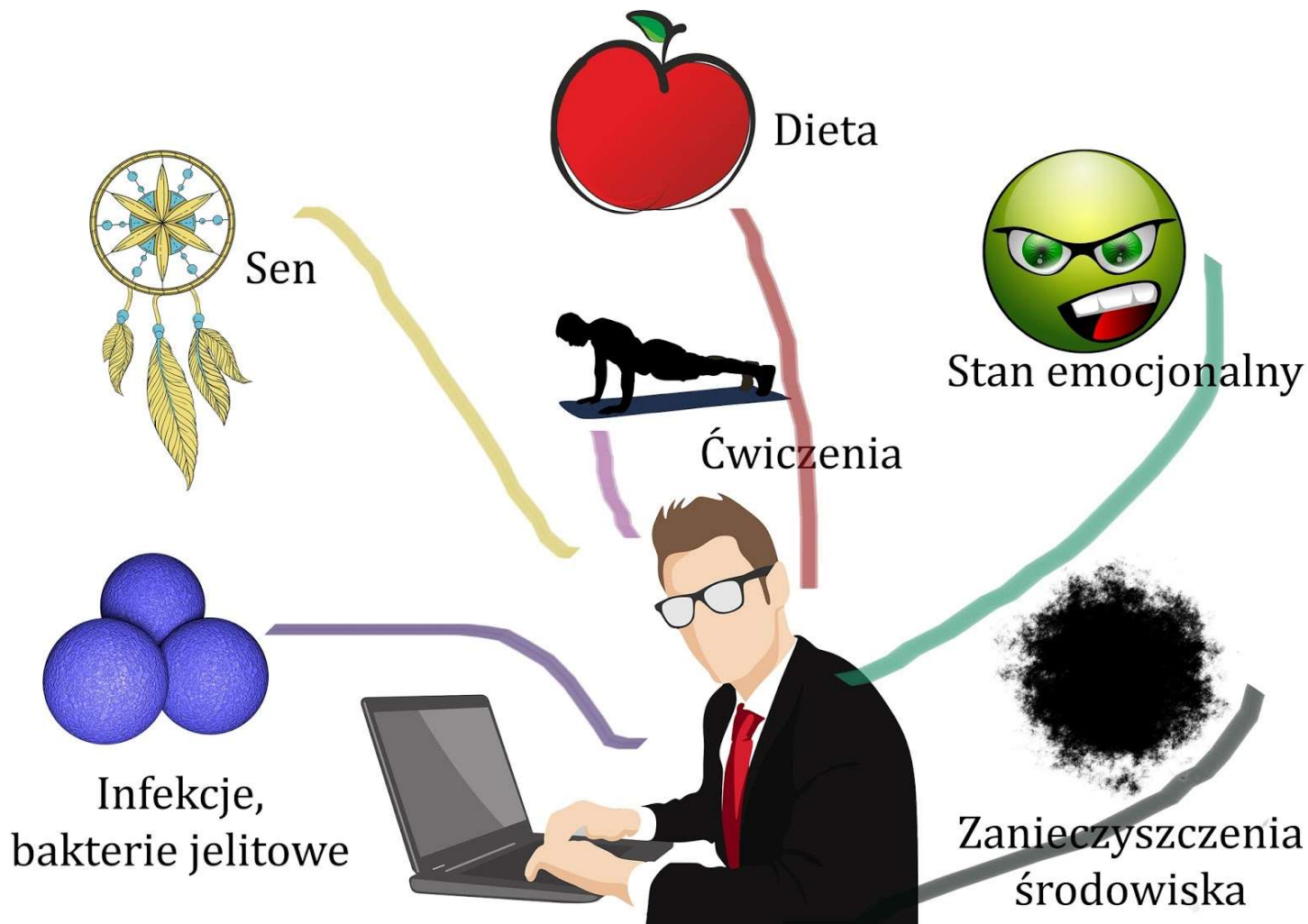


królowa

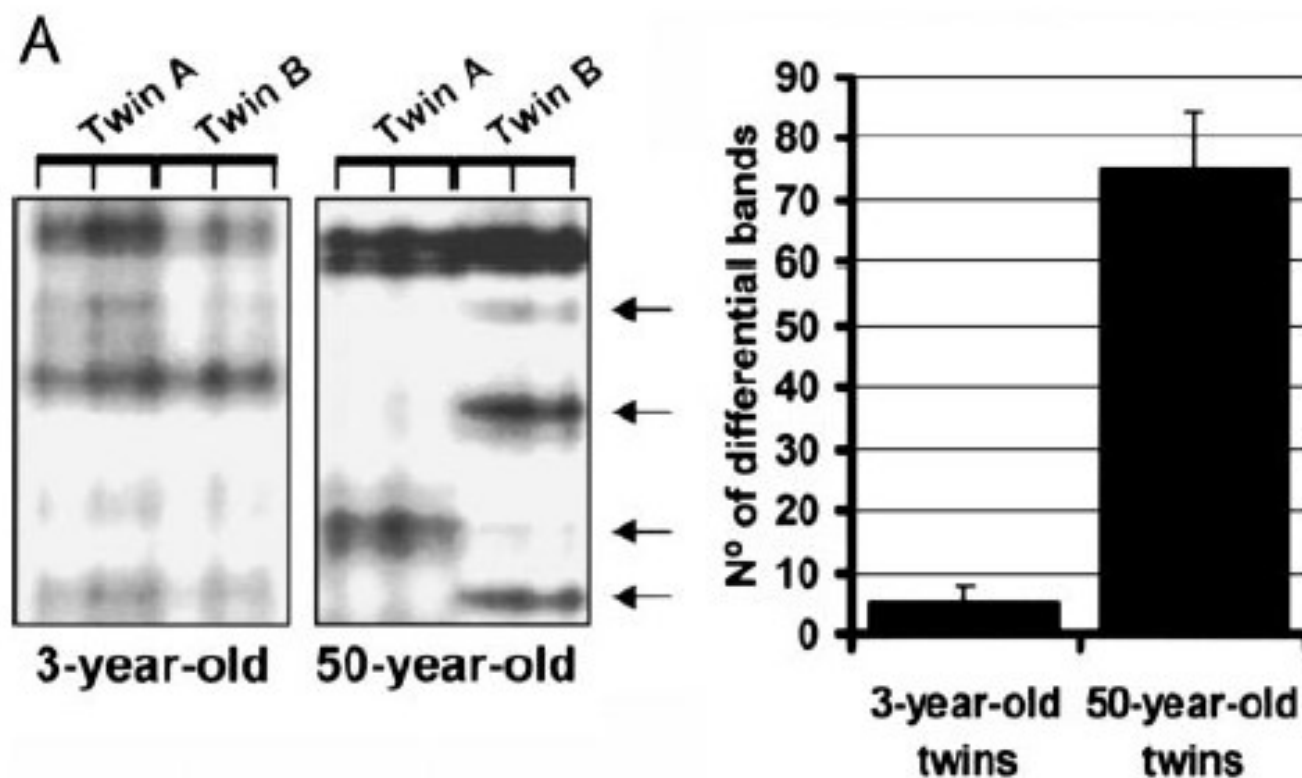
onal Control of Reproductive Status in Honeybees via DNA Methylation. R. Kucharski, J. Maleszka, Science 28 March



# Czynniki modyfikujące metylację DNA



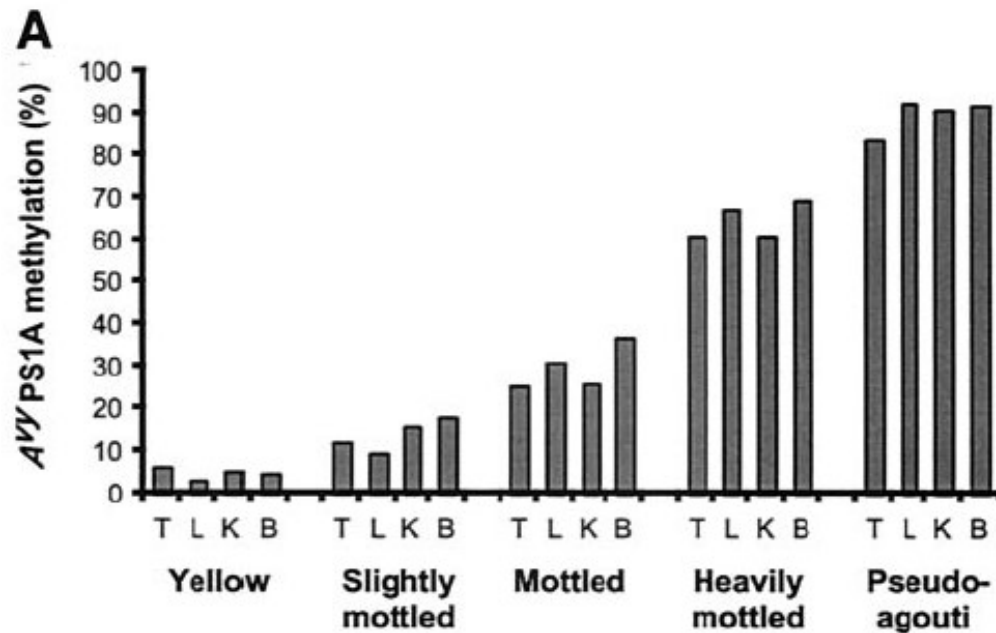
- bliźnięta jednojajowe - metylacja



Fraga MF. Epigenetic differences arise during the lifetime of monozygotic twins. Proc Natl Acad Sci U S A. 2005



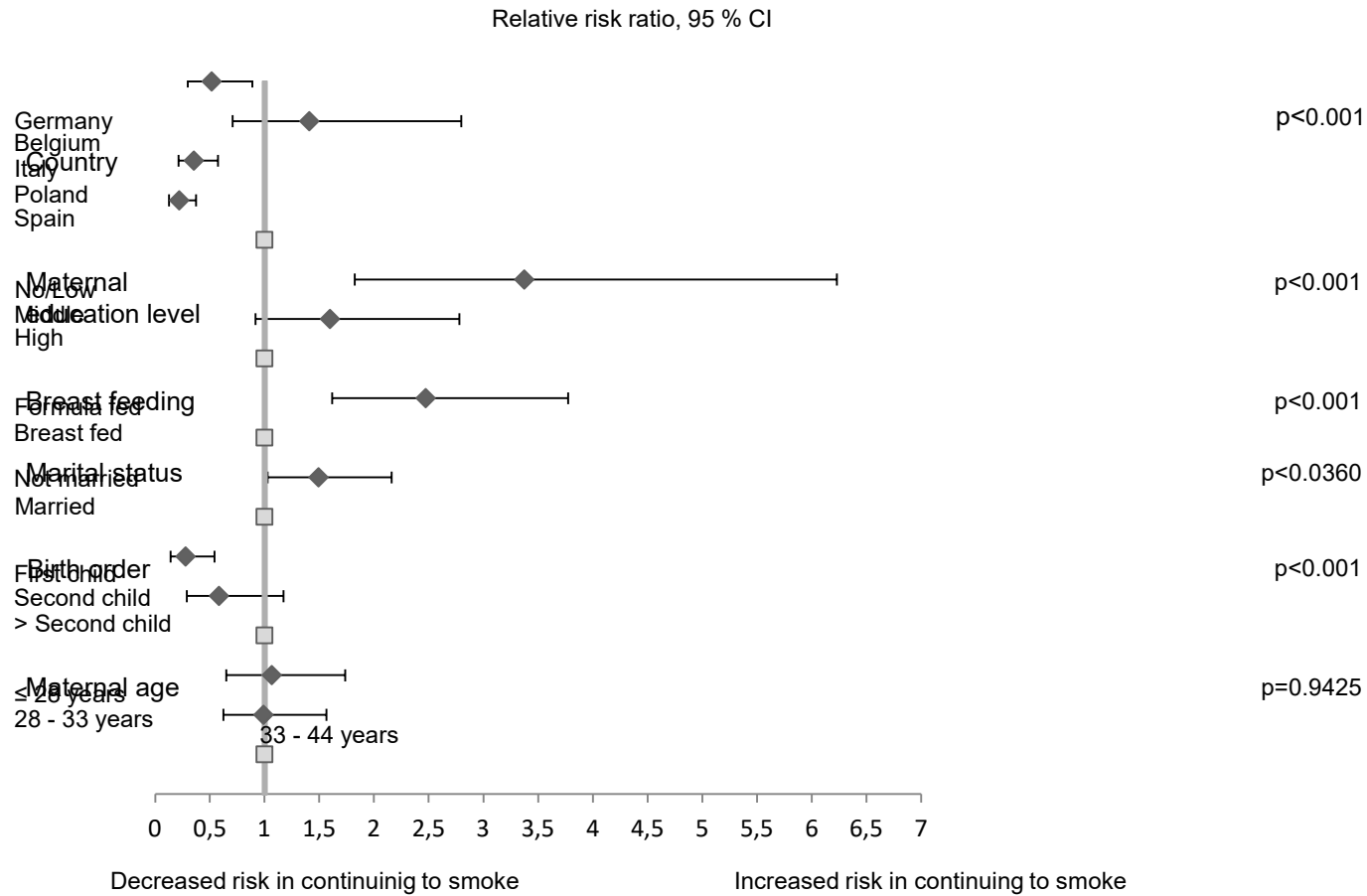
Yellow      Slightly mottled      Mottled      Heavily mottled      Pseudo-agouti



- Dieta bogata w substancje zwiększające metylację DNA (m.in. kw. foliowy, witaminę B12)

Waterland RA, Jirtle RL. Mol Cell Biol. 2003

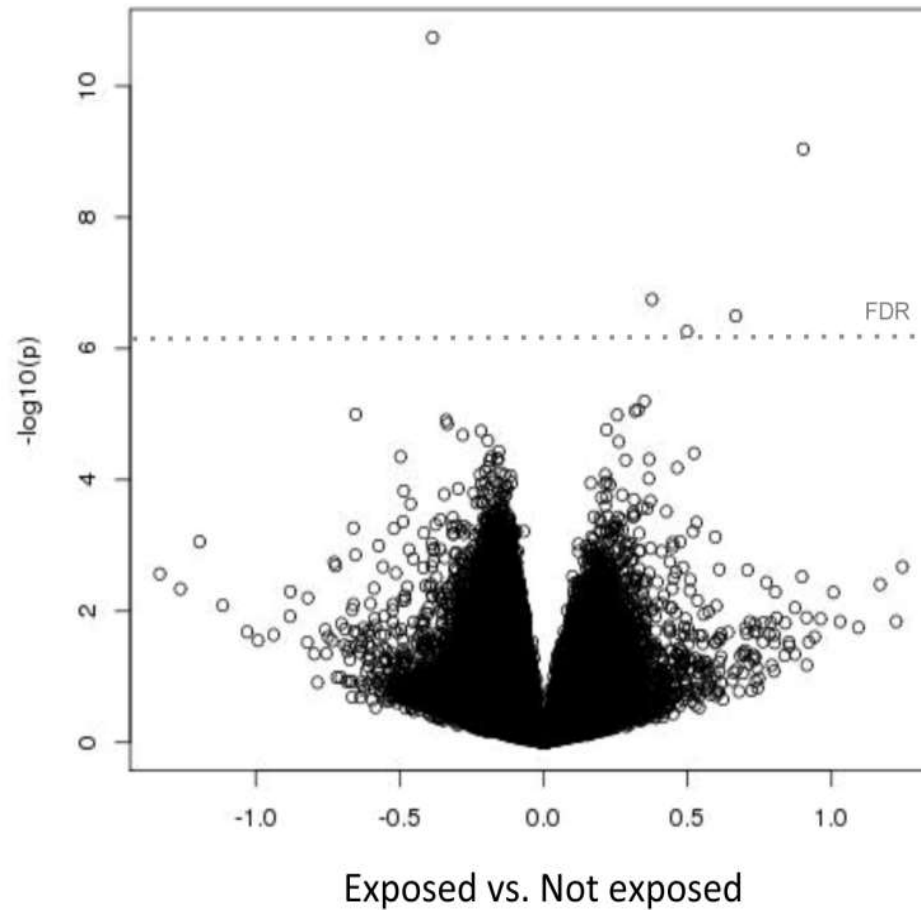
# Palenie w ciąży



# Wpływ na epigenom



A



- n=366; CHOP study cohort;
- ocena metylacji w wieku 5.5 roku



Rzehak P, Socha P, Gruszfeld D, Koletzko B. PLoS One. 2016

# Pregnancy And Childhood Epigenetic Consortium

MAS - w 2 punktach czasowych:  
p urodzeniu (21 cohorts,  $N = 9358$ )  
dzieci 1–11 letnich (12 cohorts,  $N = 3610$ )

związek między DNAm a porą roku w dniu urodzenia:  
(efekt czasowy)

zmienność w zależności od szerokości geograficznej  
(efekt przestrzenny).



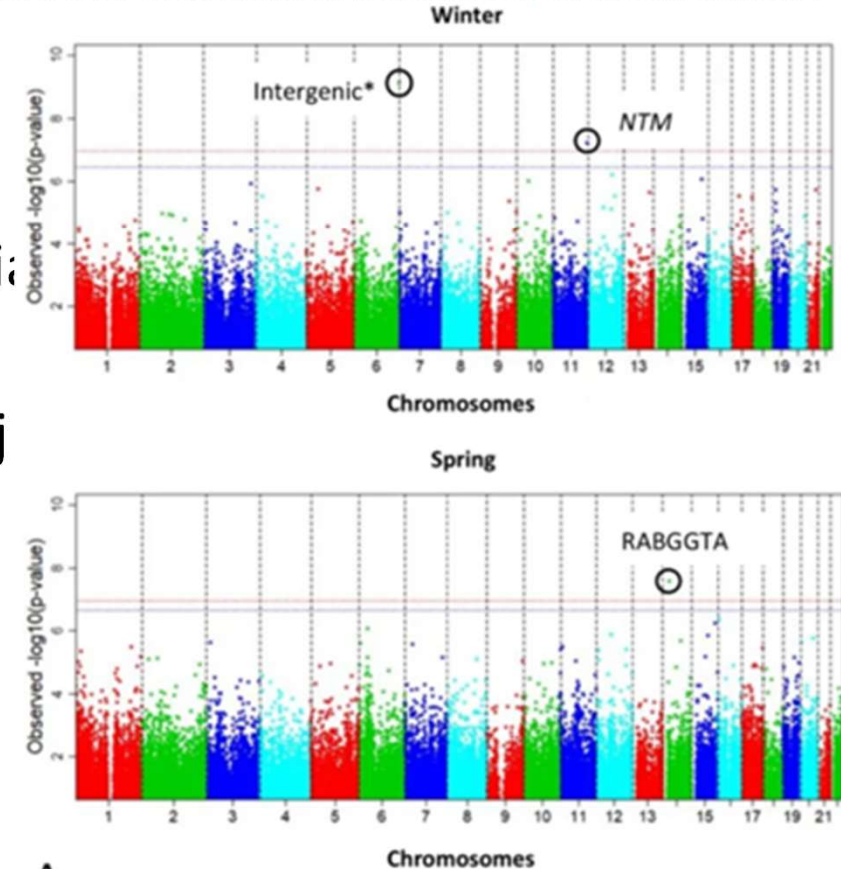
wpływ pory roku w dniu urodzenia na efekty  
zdrowotne w wieku dorosłym (?)

RESEARCH

Open Access

## Analysis of DNA methylation at birth and in childhood reveals changes associated with season of birth and latitude

Latha Kadalayil<sup>1,2</sup>, Md. Zahangir Alam<sup>2,3</sup>, Cory Haley White<sup>4</sup>, Akram Ghantous<sup>5</sup>, Esther Walton<sup>6†</sup>, Olena Gruzieva<sup>7,8</sup>, Simon Kebede Merid<sup>8</sup>, Ashish Kumar<sup>9</sup>, Ritu P. Roy<sup>10,11</sup>, Olivia Solomon<sup>12</sup>, Karen Huen<sup>12</sup>, Brenda Eskenazi<sup>12</sup>, Peter Rzehak<sup>13</sup>, Veit Grote<sup>13</sup>, Jean-Paul Langhendries<sup>14</sup>, Elvira Verduci<sup>15</sup>, Natalia Ferre<sup>16</sup>, Darek Gruszfeld<sup>17</sup>, Lu Gao<sup>18</sup>, Weihua Guan<sup>19</sup>, Xuehuo Zeng<sup>20</sup>, Enrique F. Schisterman<sup>21</sup>, John F. Dou<sup>22</sup>,



A



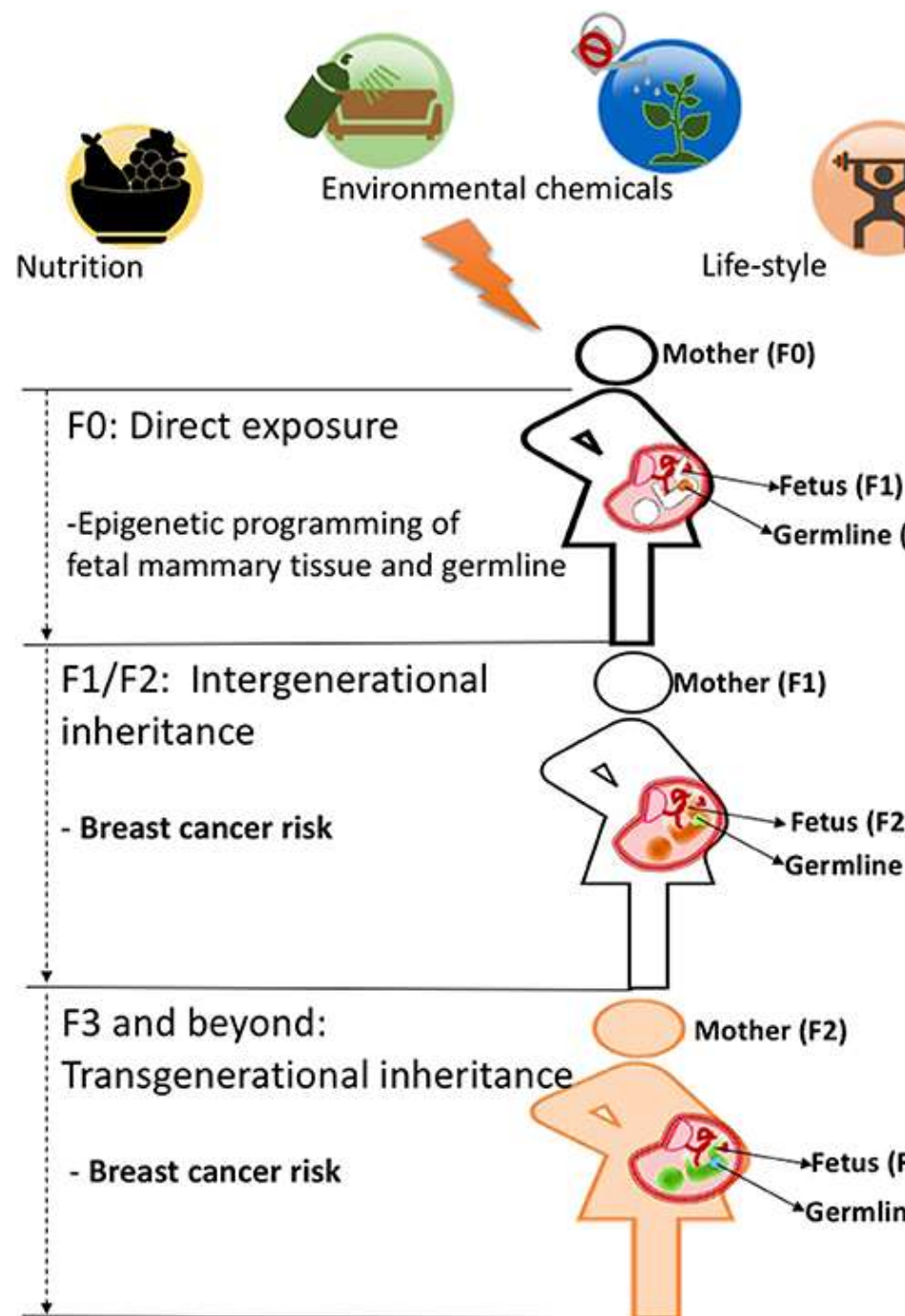


# Diet and Transgenerational Epigenetic Inheritance of Breast Cancer: The Role of the Paternal Germline

Raquel Santana da Cruz, Elaine Chen, Megan Smith, Jaedus Bates and Sonia de Assis\*†

Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC, United States

da Cruz RS et al..Front Nutr. 2020





Lowest risk for human population: optimal developmental environment and living in adult environment on low side of mid-range

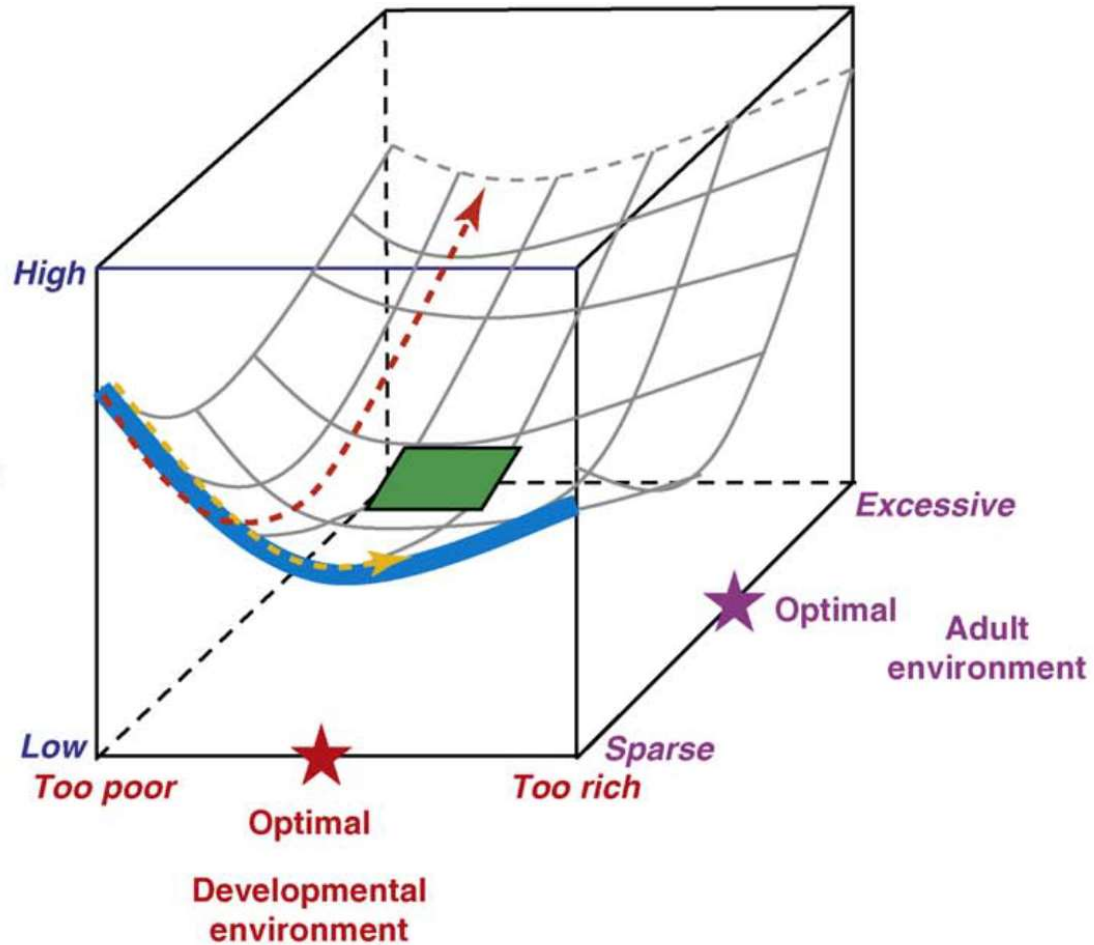


Improvement of developmental environment, resulting in reduced disease risk



Transition from poor to richer adult environment produces small reduction but then increases disease risk considerably

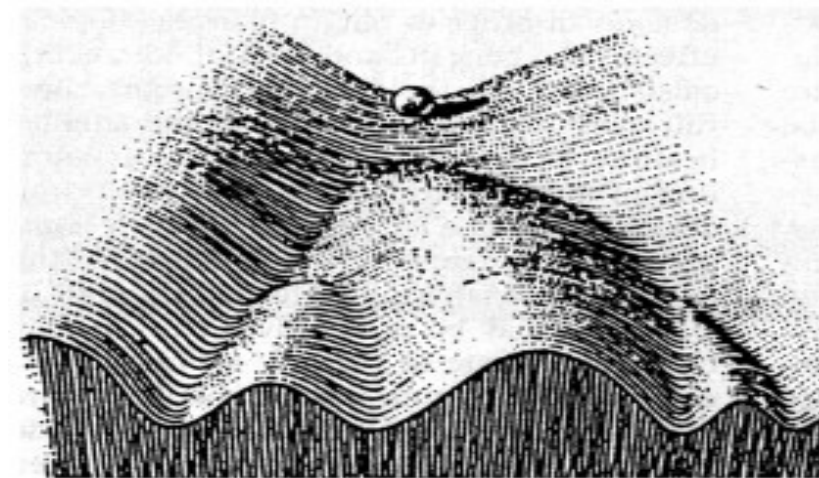
Risk of disease in population



# Take home message...

czynniki działające w okresie  
„krytycznym” wpływają na ryzyko  
późniejszych chorób [**David Barker**]

rodowisko tylko częściowo determinuje  
ryzyko przyszłej choroby – daje też  
szansę na jej zahamowanie? [**DG**]



Waddington's book *The Strategy of the Genes* (Allen and Unwin, 1957)