Early nutrition programming of long-term health: fact or fiction?

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EARLYNUTRITION
Long-term effects of early nutrition on later health
project-earlynutrition.eu

Dr. von Haunersches Kinderspital

Disclosures

- Berthold Koletzko is a member of the National Breastfeeding Committee and tends to be biased towards breastfeeding.
- The Ludwig-Maximilians-University of Munich, Germany and the speaker have received support for scientific and educational activities by companies that market nutrition products for infants and children, including Abbott, Baxter, B. Braun, Dairy Goat Cooperative, Danone, Fresenius Kabi, Fonterra, Hipp, Mead Johnson, Nestlé, and Yakult, predominantly as part of publically funded research projects with support of the European Commission or German governmental research support.
- None of these have had any influence the content and conclusions of this presentation.

Early developmental programming of adult health: first 1000 days

During limited time periods of early development/ plasticity, nutrition and other factors induce lasting effects on physiology, function, health and disease risks.

Retrospective epidemiology: birthweight associated with later health

beginbeforebirth.org

How good is the evidence?
Only retrospective association, or more?

EARLYNUTRITION
Long-term effects of early nutrition on later health

Long term effects of early nutrition on later health (2012-2017) FP7-289346-*EarlyNutrition*

www.project-earlynutrition.eu

Research Budget
11.1 Mio€/≈14 Mio$
Co-ordination: Hauner Children's, U of Munich

36 research institutions, 16 countries, 3 continents

This project receives funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement n° 289346

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Metabolic modulators

Sensitive time windows of pre- and postnatal development

Cytogenesis

Organogenesis

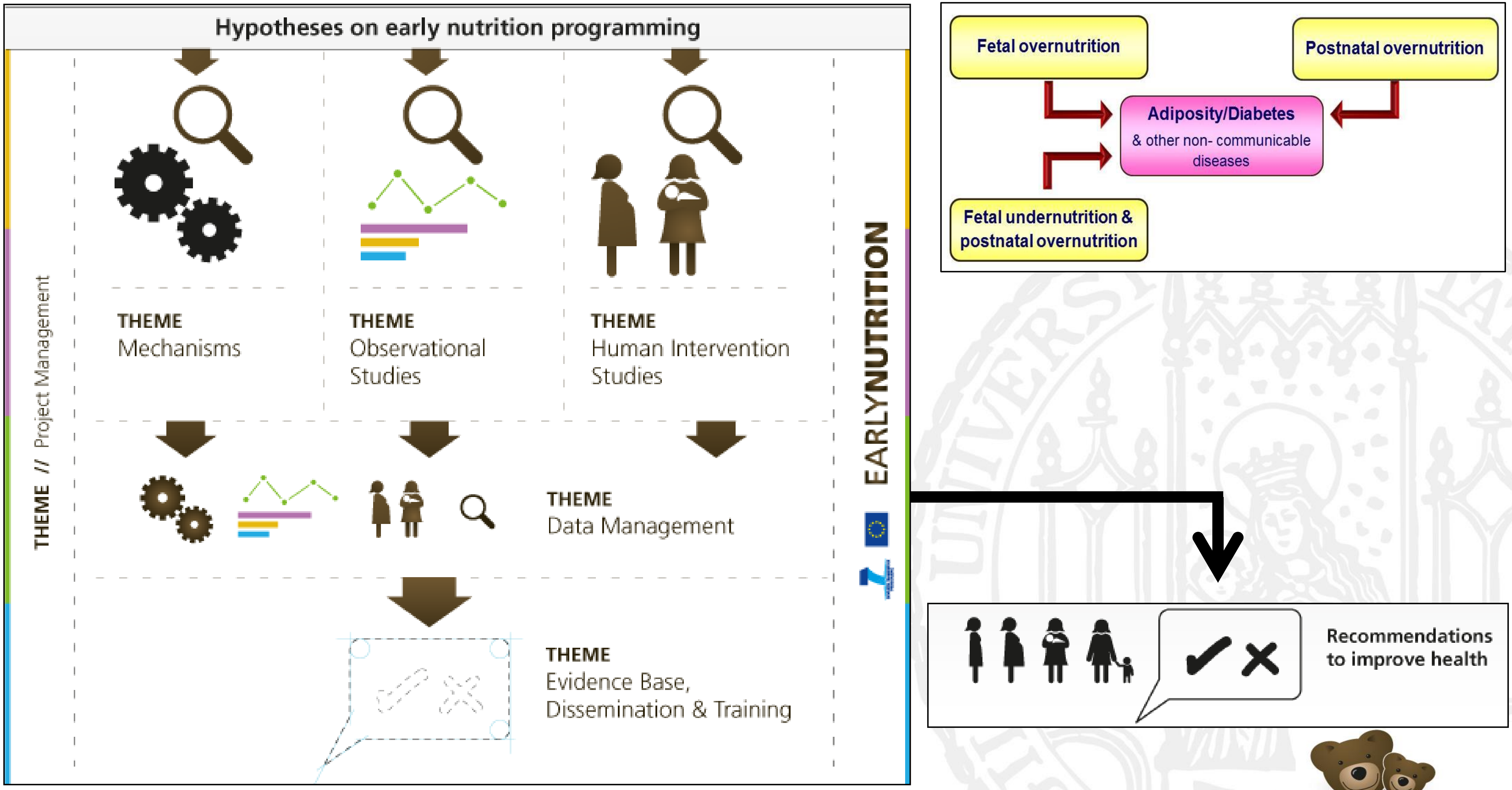
Metabolism Endocrine

Gene expression

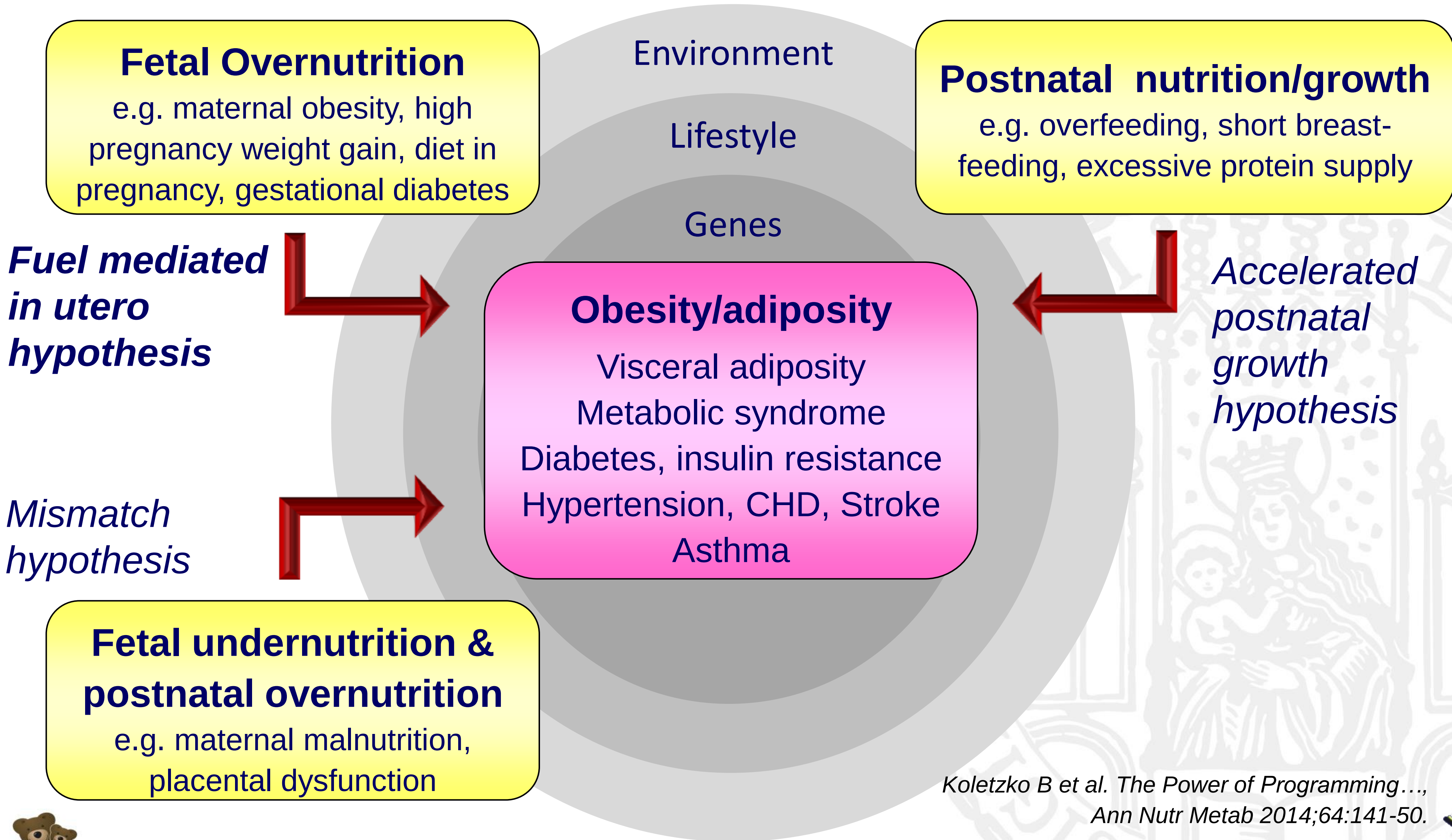
Early metabolic programming of lifelong health

Koletzko B et al. The Power of Programming …, Ann Nutr Metab 2014;64:141-50.

The *EarlyNutrition* Project



Programming of obesity & assoc. diseases



Koletzko B et al. The Power of Programming…, Ann Nutr Metab 2014;64:141-50.

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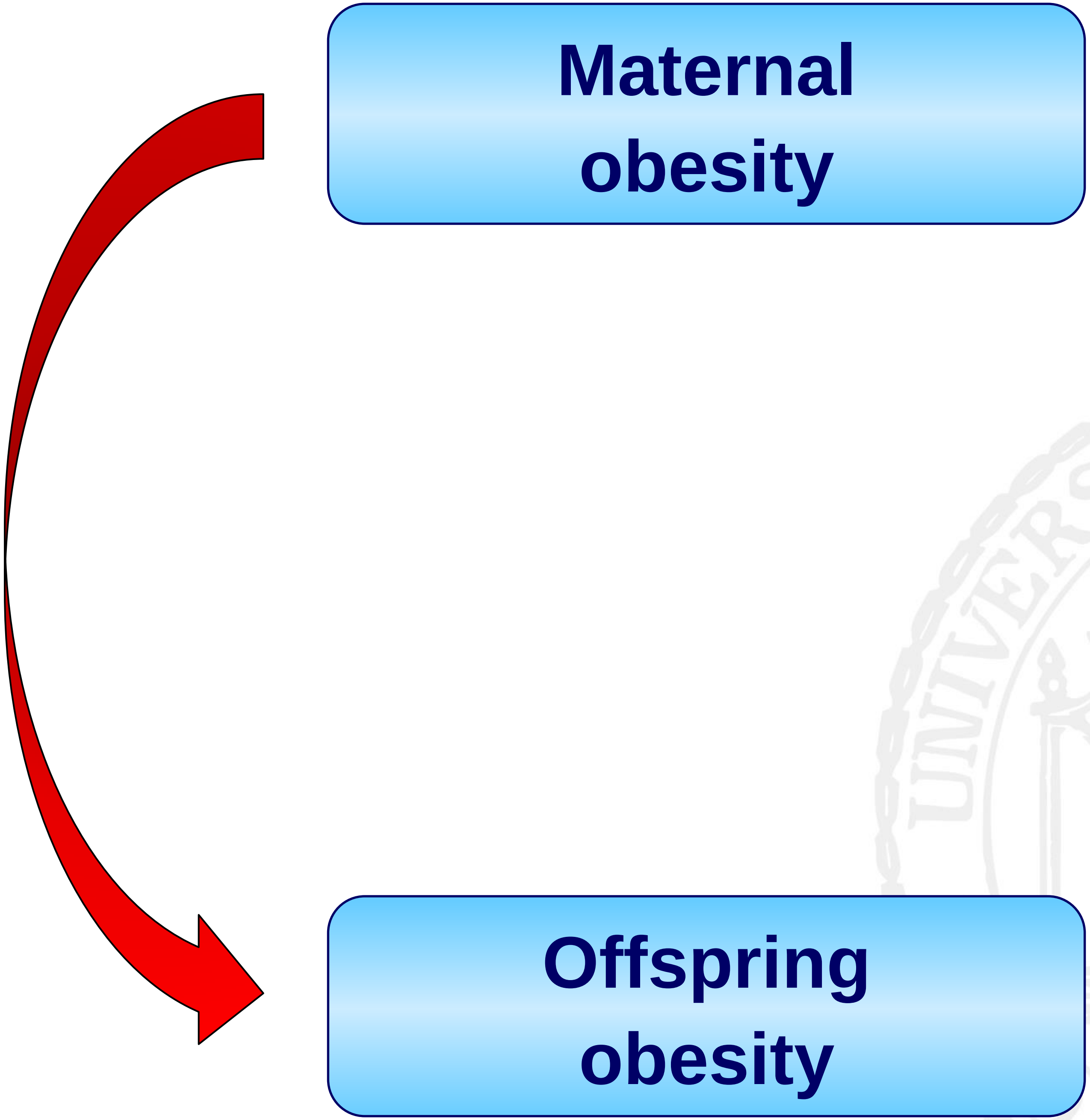

Maternal obesity
Offspring obesity

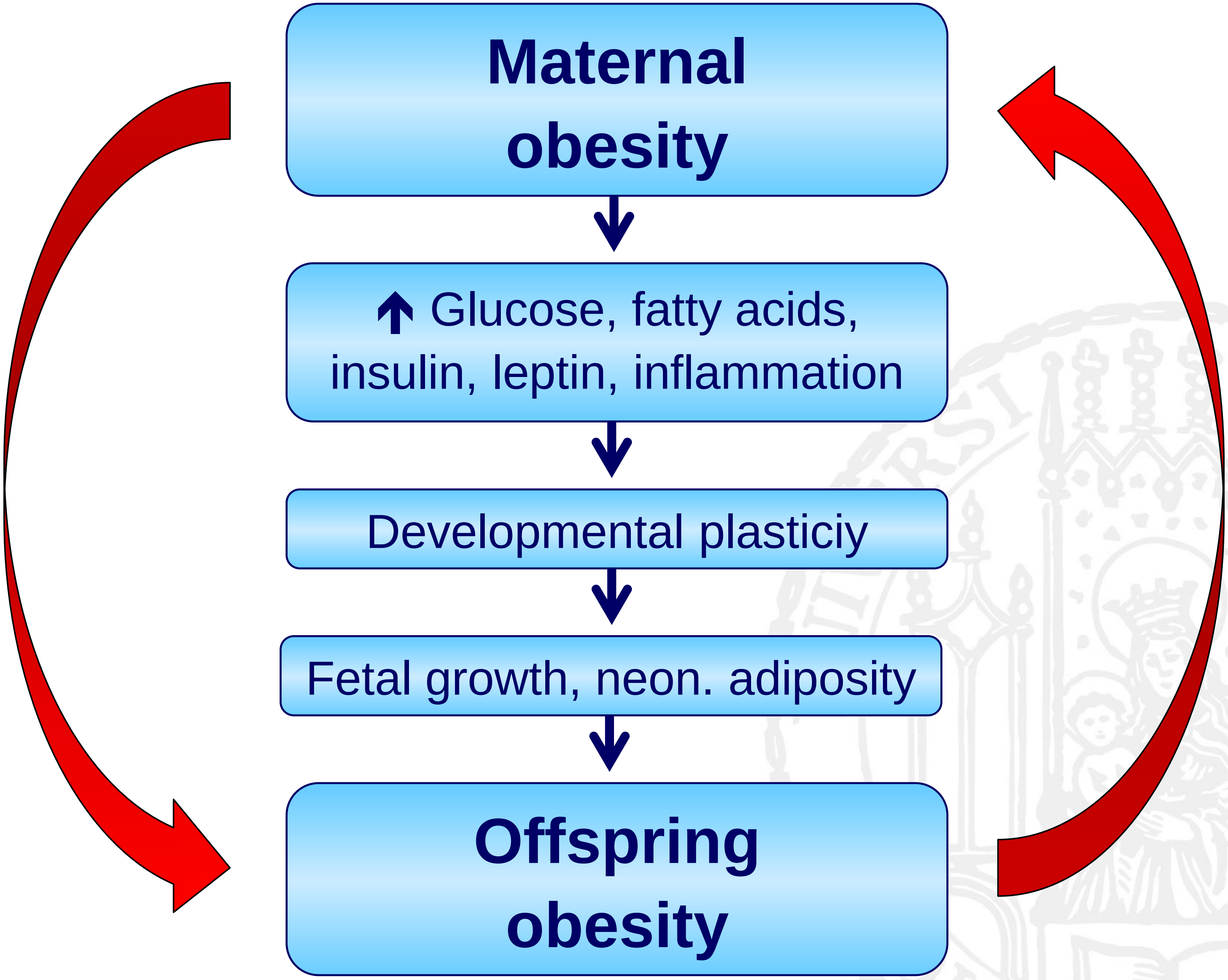
Maternal obesity

↑ Glucose, fatty acids, insulin, leptin, inflammation

Developmental plasticiy

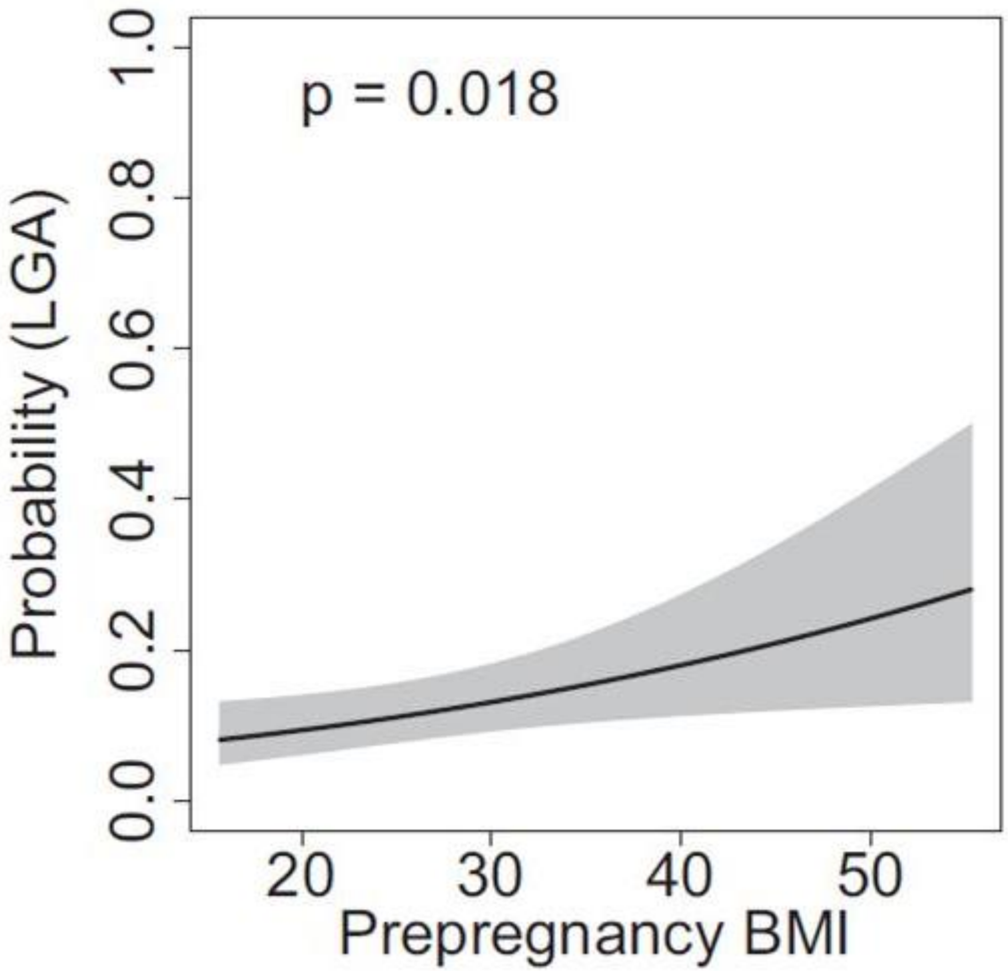
Fetal growth, neon. adiposity

Offspring obesity


Maternal obesity
↑ Glucose, fatty acids, insulin, leptin, inflammation
Developmental plasticiy
Fetal growth, neon. adiposity
Offspring obesity

High maternal prepregnancy BMI increases the risk of large for date infant

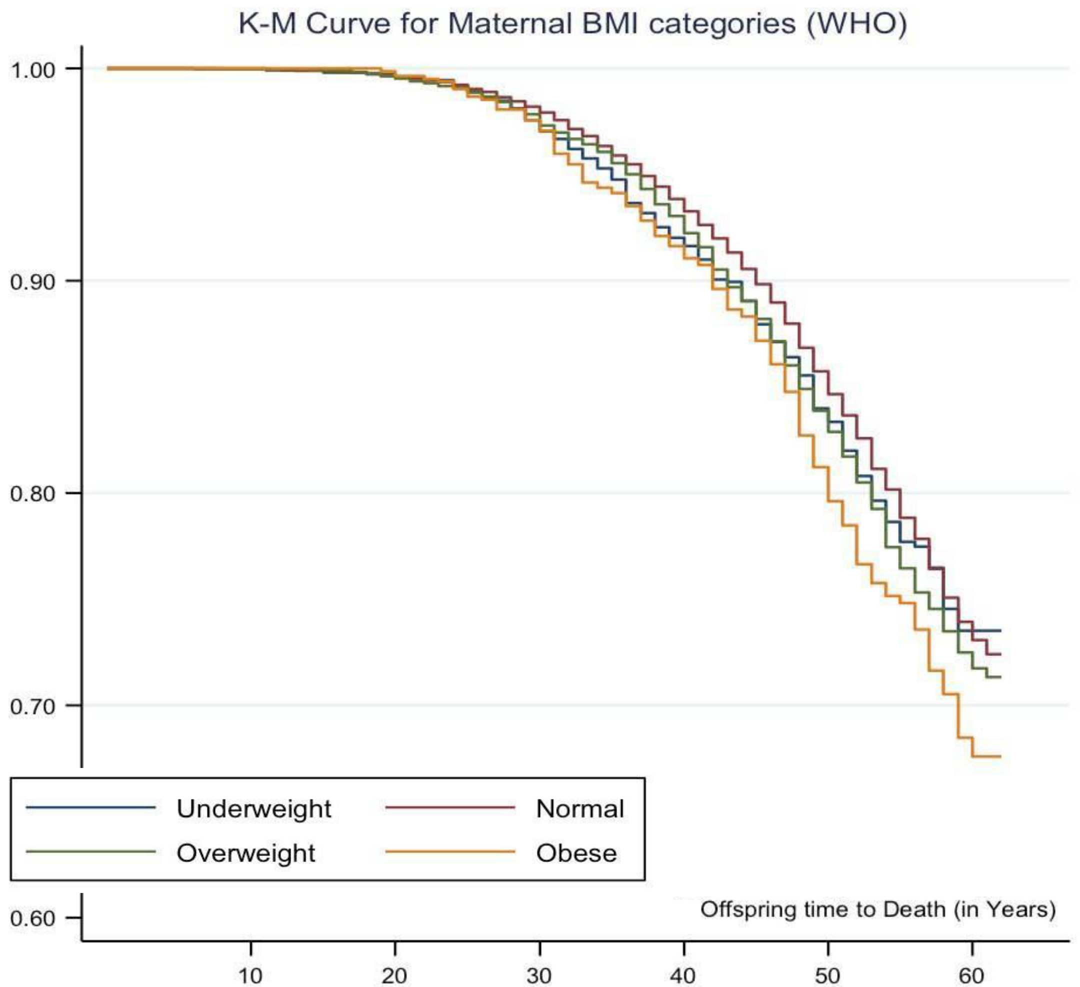
1250 women, USA, untreated mild glucose intolerance



Stuebe 2012.

Maternal obesity in pregnancy and premature offspring mortality from CVD

37 709 Scottish people with birth records from 1950, follow-up of 1 323 275 person years



Systematic review & meta-analysis
Reynolds et al, BMJ 2013

Prenatal intervention possible

- RCT in 2212 pregnant women, BMI≥25, South Australia
- Standard care, or counseling (3 x face to face, 3 x phone) on balanced diet, limiting refined CHO and SAFA, and increased physical activity
- No significant effect on LGA (primary outcome, RR 0.90)
- Reduced birthweight <4000 g (RR 0.81, p=0.03, NNT 28)

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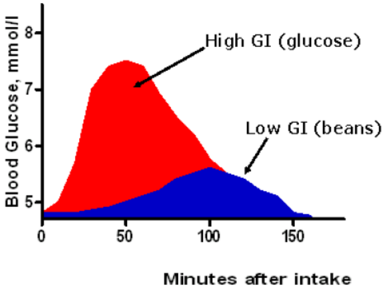
Long-term effects of early nutrition on later health

Diet



Physical activity

http://www.sportundschwangerschaft.de/

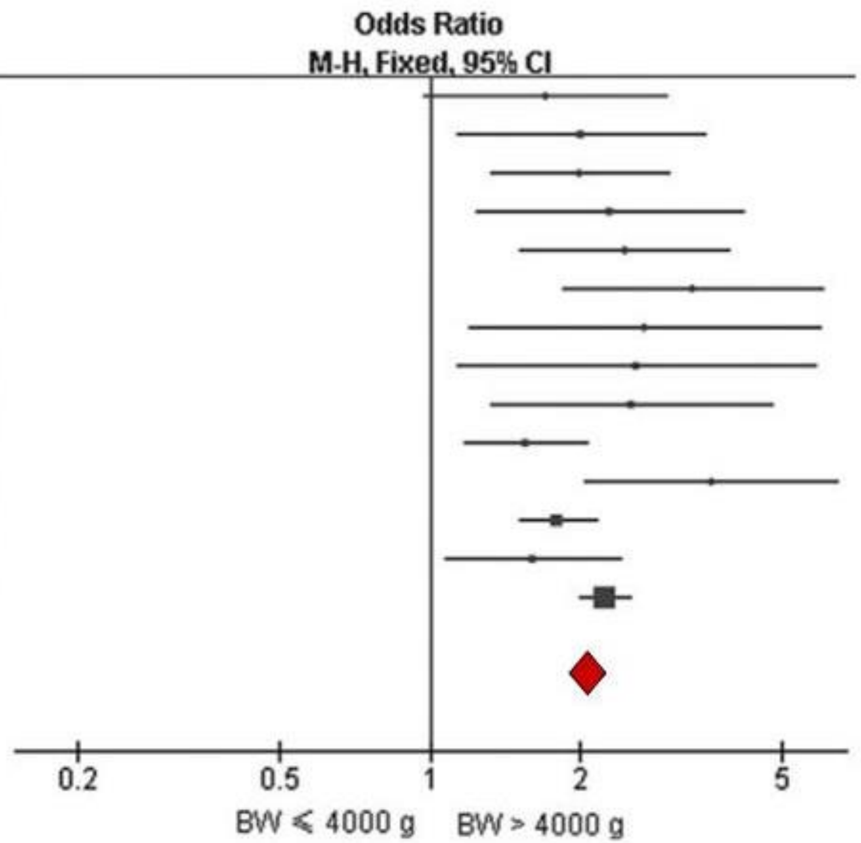
BMJ 2014;348:g1285 doi: 10.1136/bmj.g1285 (Published 10 February 2014)

Birthweight >4 kg doubles: 2x adult obesity

Systematic review & meta-analysis

	BW > 4000 g		BW ≤ 4000 g			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Che 2010	16	142	106	1526	2.2%	1.70 [0.98, 2.97]
Gu 2003	16	163	69	1336	1.9%	2.00 [1.13, 3.53]
He (a) 2000	74	114	388	805	4.7%	1.99 [1.32, 2.99]
He (b) 2005	14	143	57	1256	1.5%	2.28 [1.24, 4.21]
Hirschler 2008	28	95	136	932	2.5%	2.45 [1.52, 3.94]
Li 2007	36	141	20	214	1.6%	3.33 [1.83, 6.04]
Lu 2008	8	52	52	819	0.7%	2.68 [1.20, 5.99]
Mao 2007	21	30	115	242	1.1%	2.58 [1.13, 5.85]
Monteiro 2003	13	81	70	992	1.2%	2.52 [1.33, 4.78]
Ruan 2009	82	260	488	2135	10.0%	1.55 [1.17, 2.06]
Shi 2007	54	75	80	193	1.7%	3.63 [2.03, 6.49]
Wang 2009	179	1537	640	9360	22.0%	1.80 [1.51, 2.14]
Yang 2009	72	120	290	601	5.3%	1.61 [1.08, 2.40]
Zhang 2009	456	1977	1642	13875	43.6%	2.23 [1.99, 2.51]
Total (95% CI)		**4930**		**34286**	**100.0%**	**2.07 [1.91, 2.24]**
Total events	1069		4153			

Heterogeneity: Chi² = 17.87, df = 13 (P = 0.16); I² = 27%
Test for overall effect: Z = 17.75 (P < 0.00001)



Yu et al 2011.

Birthweight >4kg: high risk for later obesity

Early Childhood Longitudinal Study, 7738 children, USA

Birth-weight	n	Obesity (%) at age (yrs)		
		5.6	9.1	14.1
2.5-<4 kg	6035	11.2	17.8	19.4
≥4 kg	915	22.5	26.3	31.2

Birthweight >4 kg = 12% of the population,
but >36% of the obese children at age 14 yrs

Cunningham SA et al, NEJM 2014; 370:403-11.

Pregnancy: current advice

- Aim at normal body weight prior to conception
- Avoid excessive weight gain in pregnancy
- Maintain normal physical activity, moderate level sports
- Increase energy intake only by 10% until end of pregnancy
- Avoid high glycaemic load diet

Koletzko B et al. German national consensus recommendations on nutrition and lifestyle in pregnancy. Ann Nutr Metab. 2013;63:311-22. doi: 10.1159/000358398

Programming of obesity & assoc. diseases

Fetal Overnutrition
e.g. maternal obesity, high pregnancy weight gain, diet in pregnancy, gestational diabetes

Fuel mediated in utero hypothesis

Environment

Lifestyle

Genes

Postnatal nutrition/growth
e.g. overfeeding, short breast-feeding, excessive protein supply

Accelerated postnatal growth hypothesis

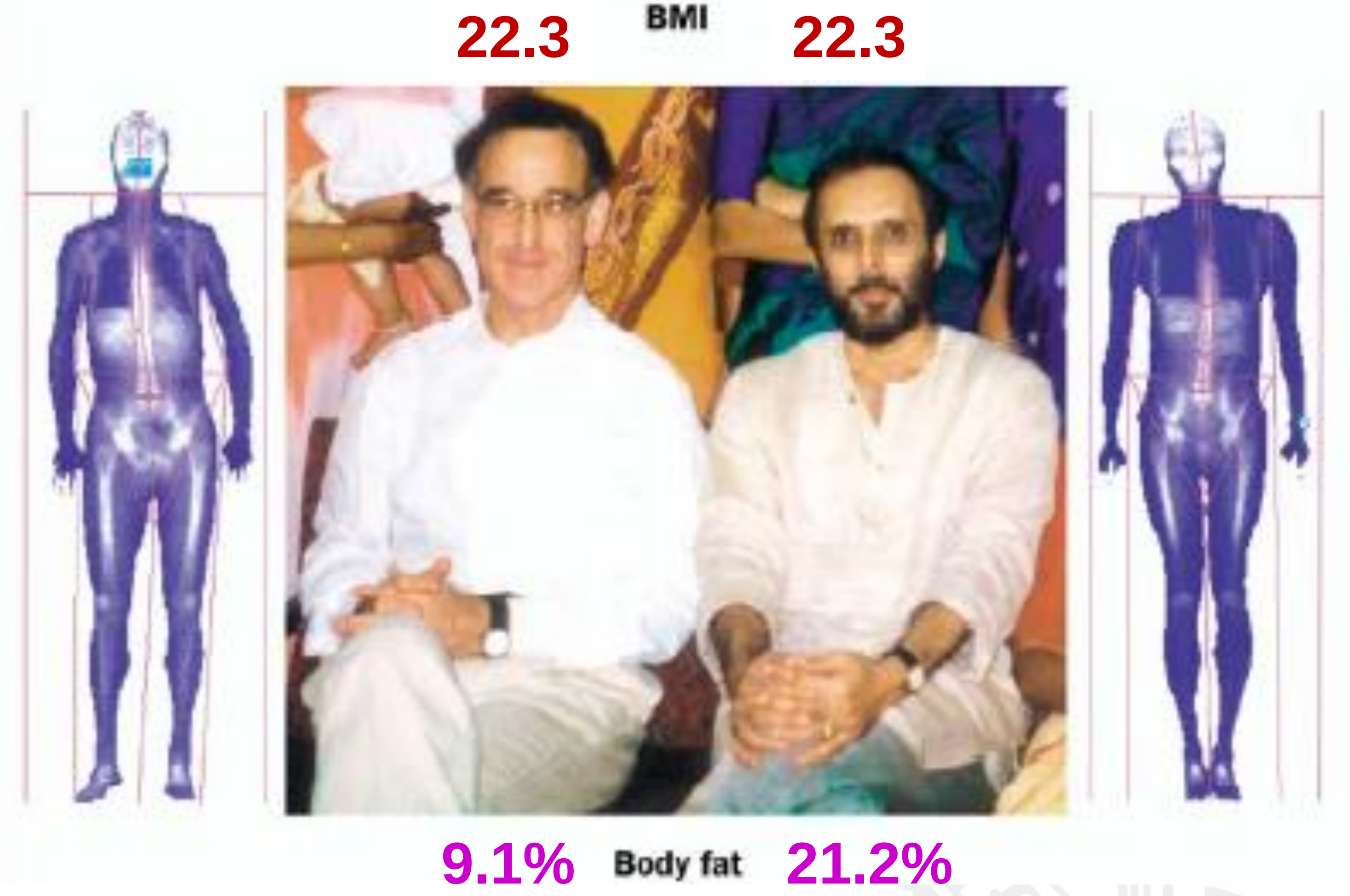
Obesity/adiposity
Visceral adiposity
Metabolic syndrome
Diabetes, insulin resistance
Hypertension, CHD, Stroke
Asthma

Mismatch hypothesis

Fetal undernutrition & postnatal overnutrition
e.g. maternal malnutrition, placental dysfunction

Koletzko B et al. The Power of Programming…, Ann Nutr Metab 2014;64:141-50.

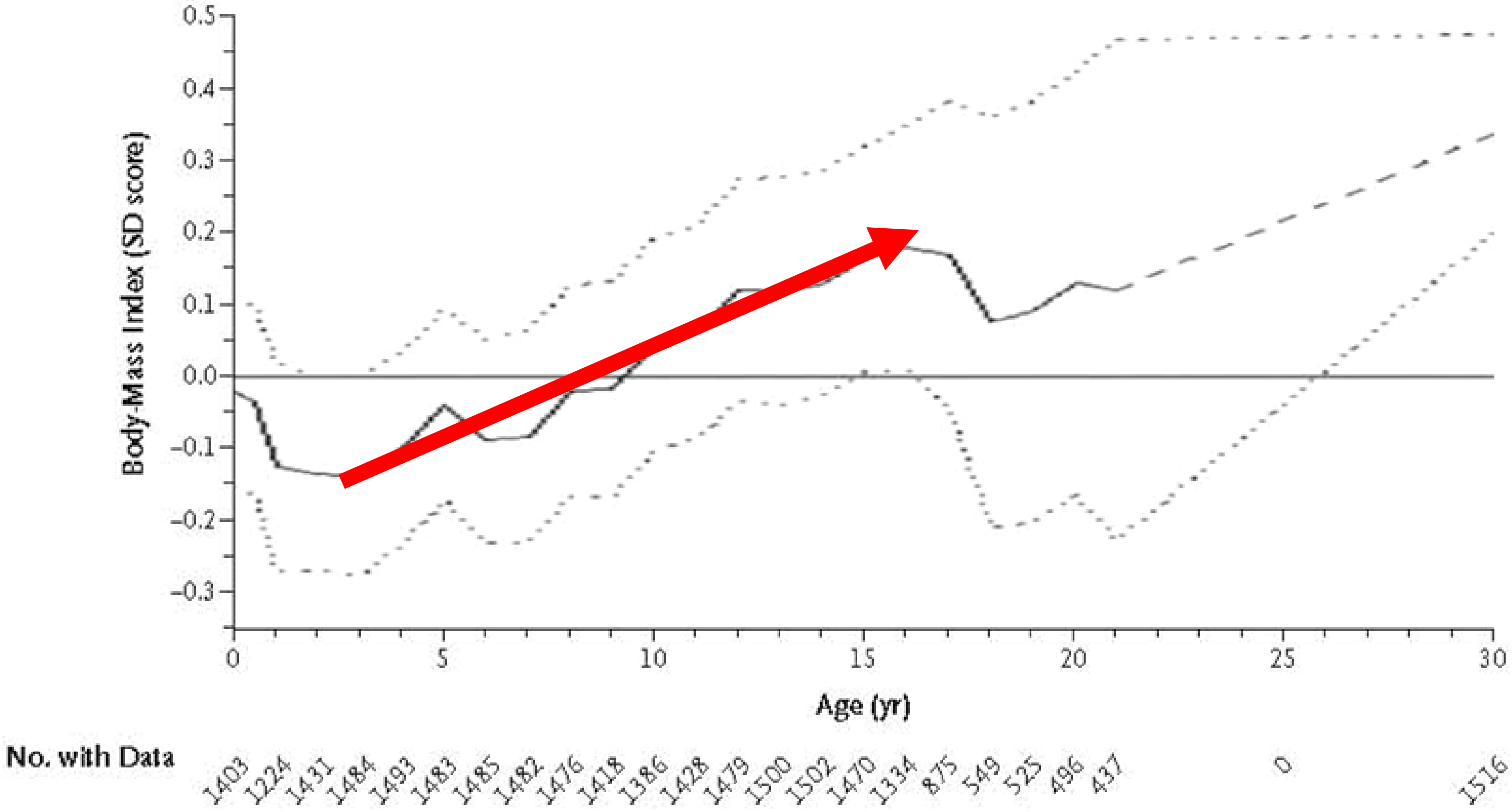
Mismatch of slow pre-natal and fast postnatal growth



Yajnik & Yudkin, Lancet 2004;363:163.

Low initial weight followed by rapid child growth predisposes to later NCD

⇨ High risk of diabetes, obesity, cardiovascular disease



1492 men and women aged 26 to 32 years, measures at birth and every 3-6 months through infancy, childhood, and adolescence in a prospective, population-based study *Bhargava et al, NEJM 2004.*

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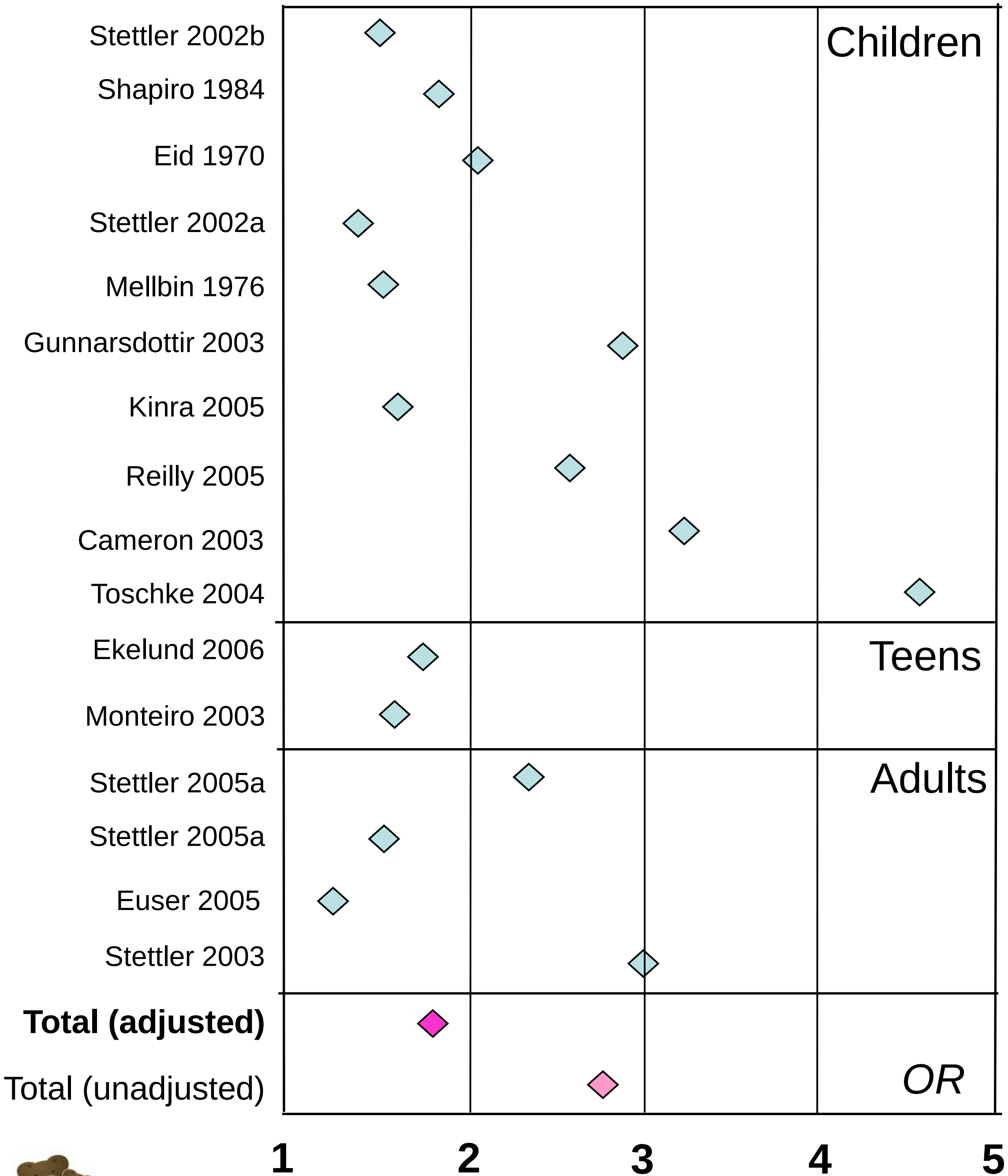


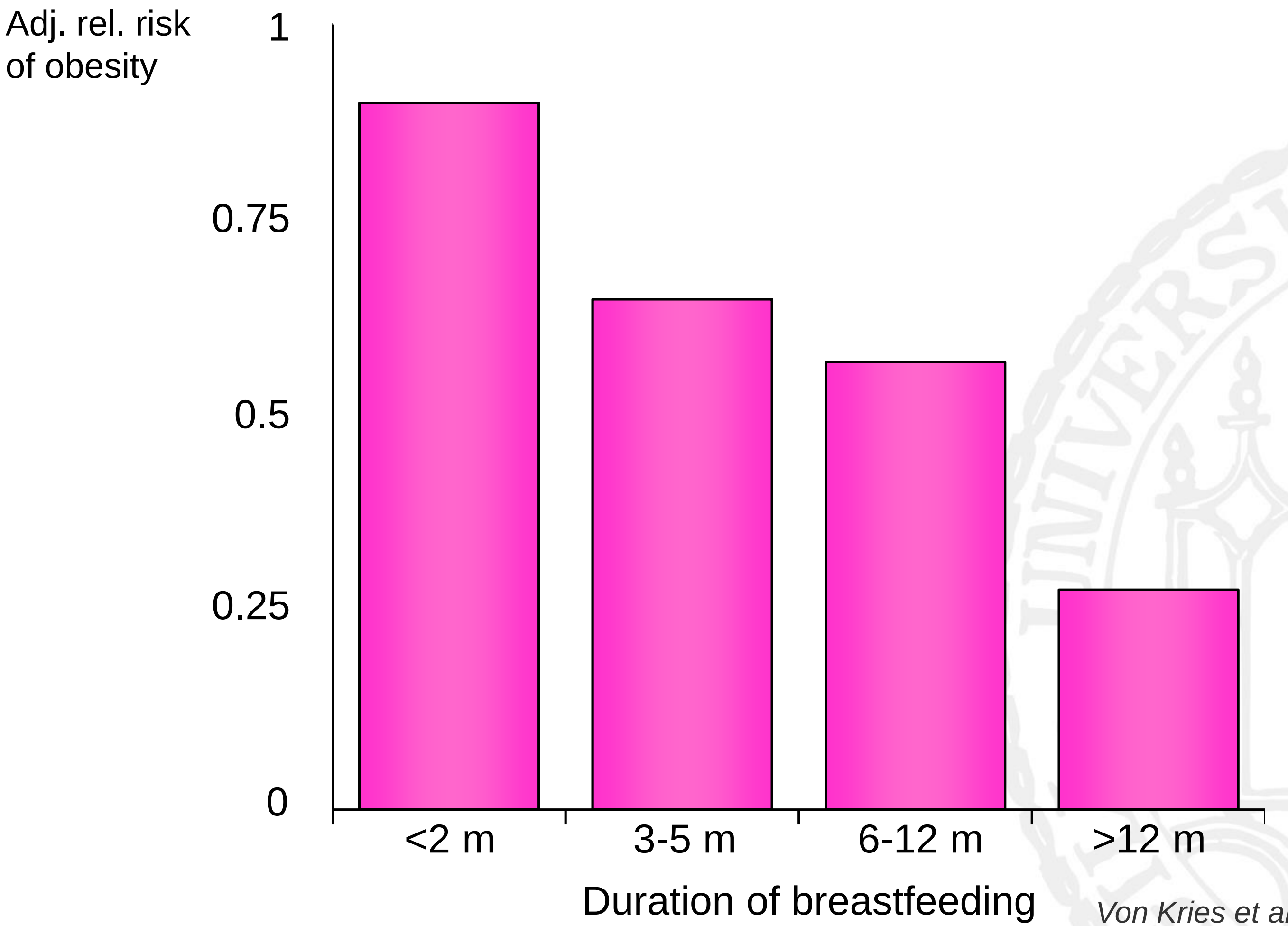
High weight gain in the 1st. & 2nd. year of life: increased obesity risk to adulthood

Brands B, Koletzko B.
Early nutrition and long-term obesity risk:
opportunities for paediatric prevention.
Monatsschr Kinderheilkd 2012;160:1096–1102.
Modified from Adair LS 2008.

Rapid early growth: nutrition or other factors?

„She is still hungry, even though I stuffed worms into her all day."

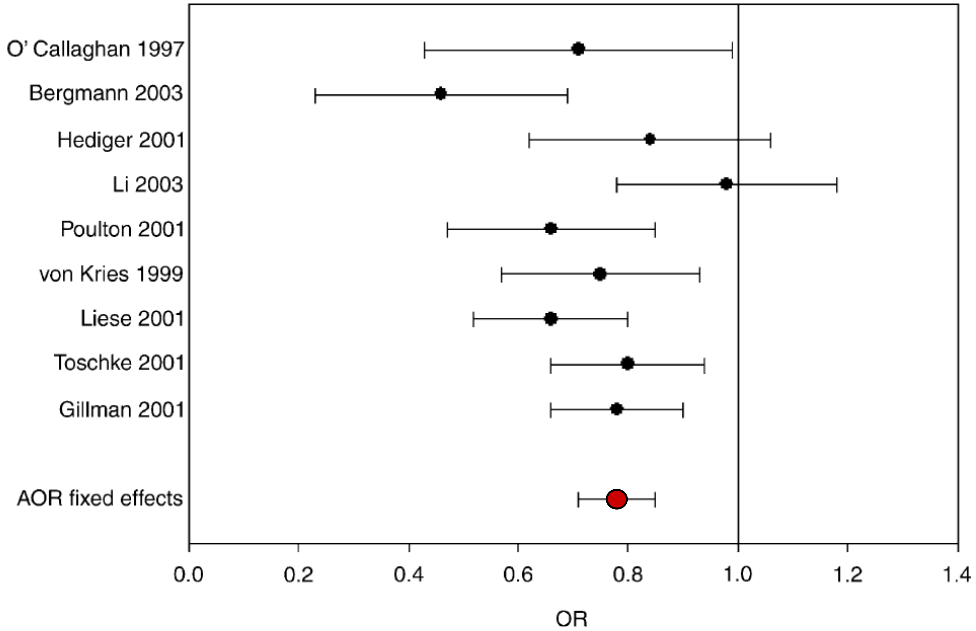
Longer breastfeeding ⇨ less obesity in >9000 children at school entry *(Bavaria, Germany)*



Von Kries et al. Brit Med J 1999,319:147-50
Koletzko et al. Ann Nutr Metab 2014;65:99–107

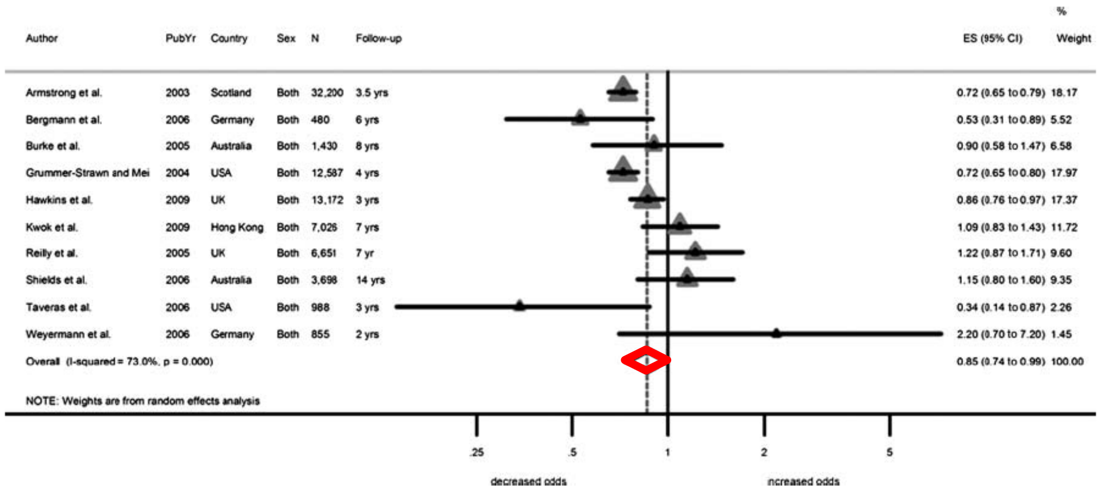
Breastfeeding ⇒ less obesity later

Early meta-analysis: 22% less obesity



Arenz S et al. Int J Obes Relat Metab Disord 2004; 28:1247–56

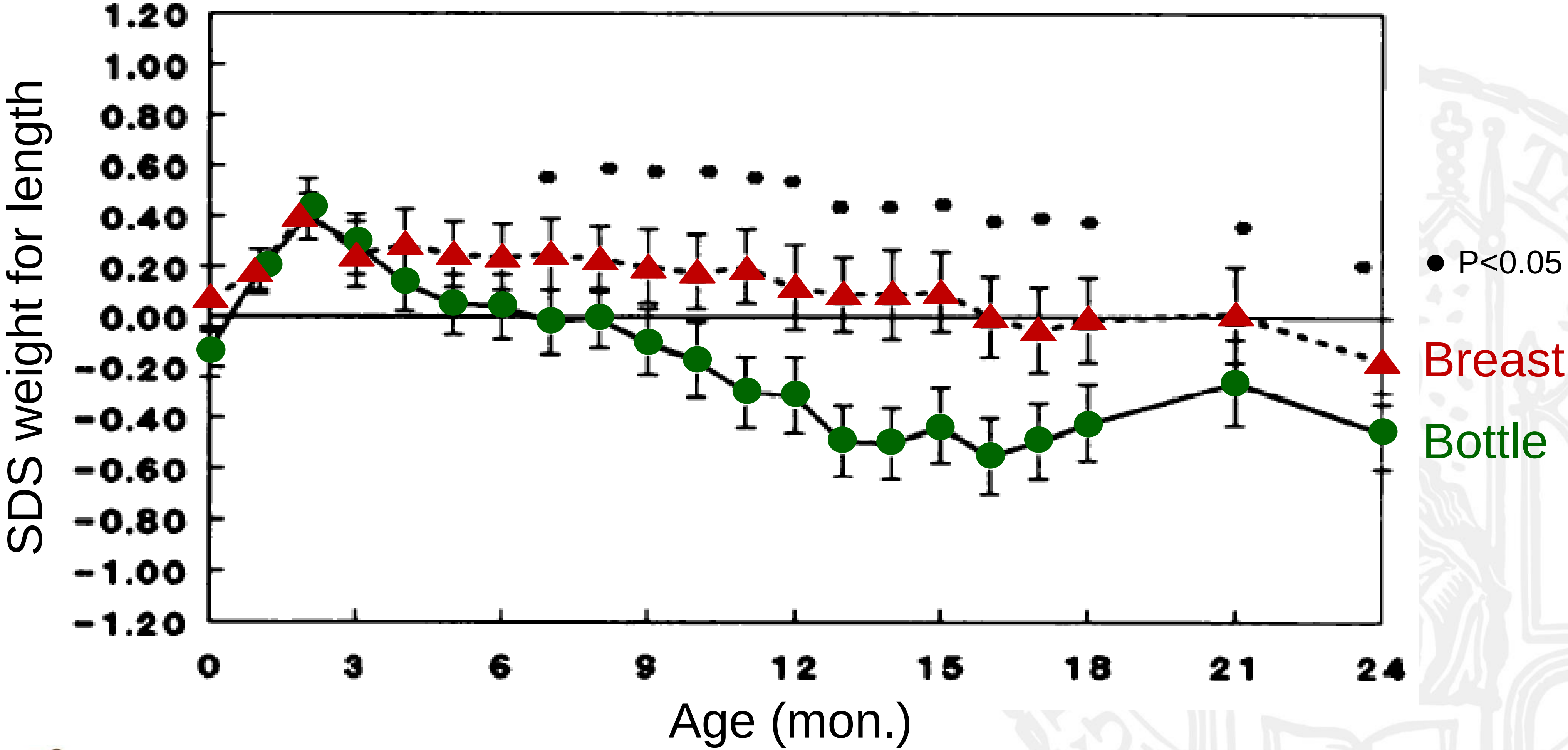
Recent meta-analysis: 15% less obesity



Weng S et al. Arch Dis Child 2012;97:1019–1026

Weight (SDS) in breast or bottle fed infants

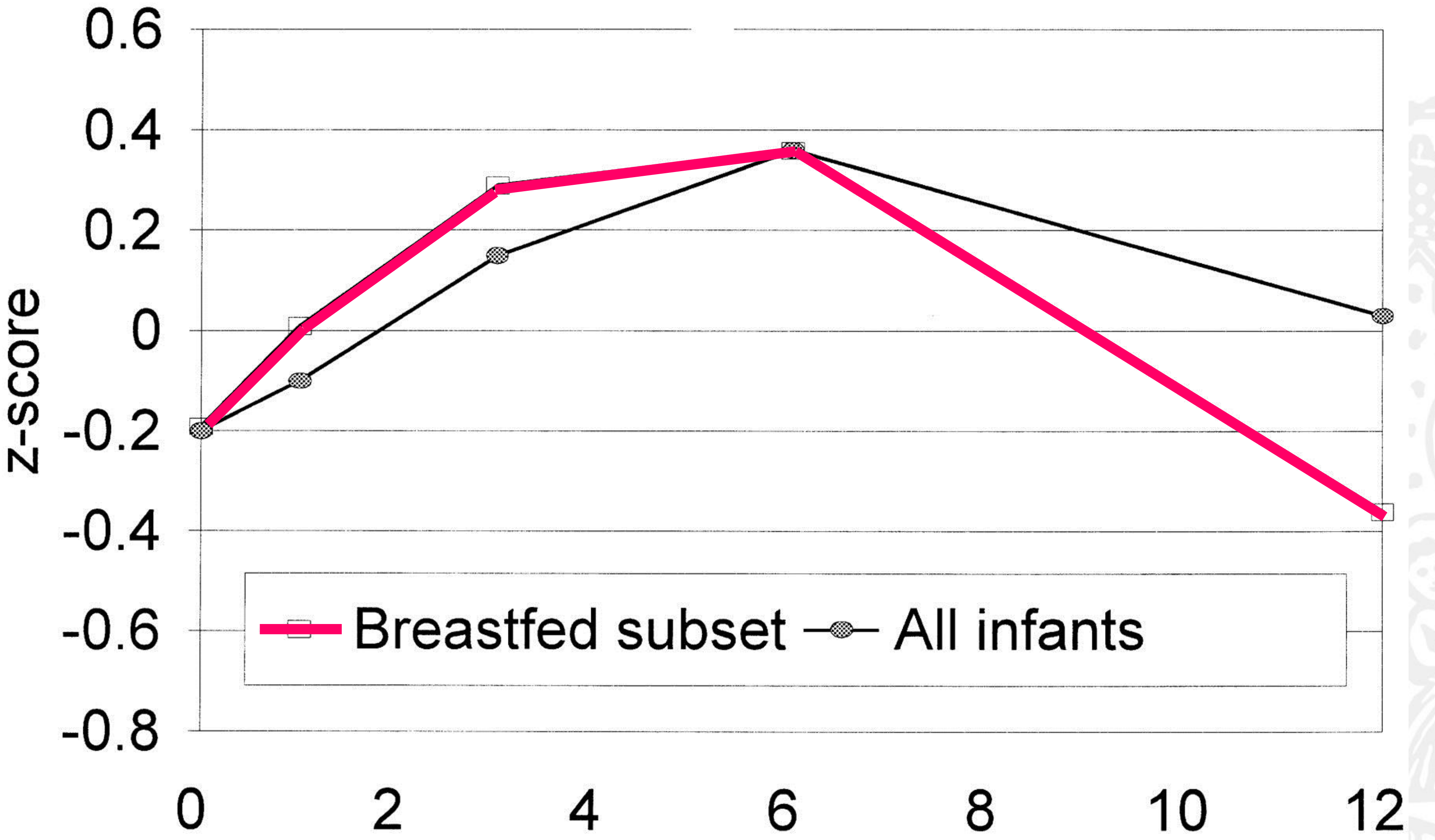
Darling Study, California, USA: 87 breast or bottle fed babies

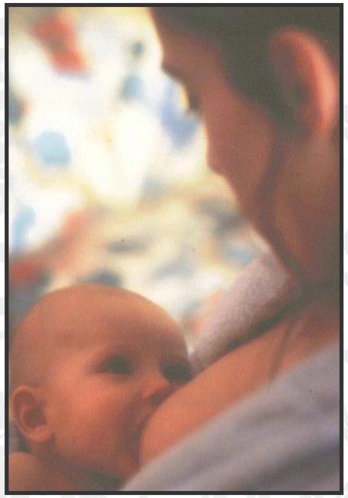


Dewey et al , AJCN 1993.

Growth differs in breastfed and in bottle fed infants

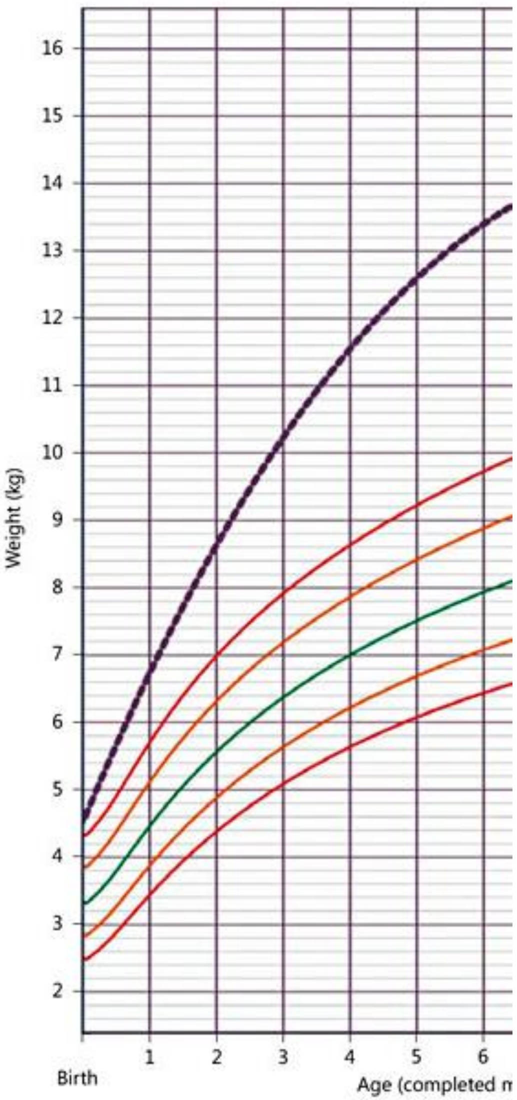
5,304 Brazilian infants predominantly breast or bottle fed followed prospect. from birth to 12 mon.





Victora et al, J Nutr 1998;128:1134-8

Can breastfeeding induce obesity?



Annals of Nutrition & Metabolism

Ann Nutr Metab 2014;64:271–275
DOI: 10.1159/000365033

Excessive Weight Gain during Full Breast-Feeding

Maria Grunewald Christian Hellmuth Hans Demmelmair Berthold Koletzko

Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children's Hospital, Ludwig Maximilian University of Munich, Munich, Germany

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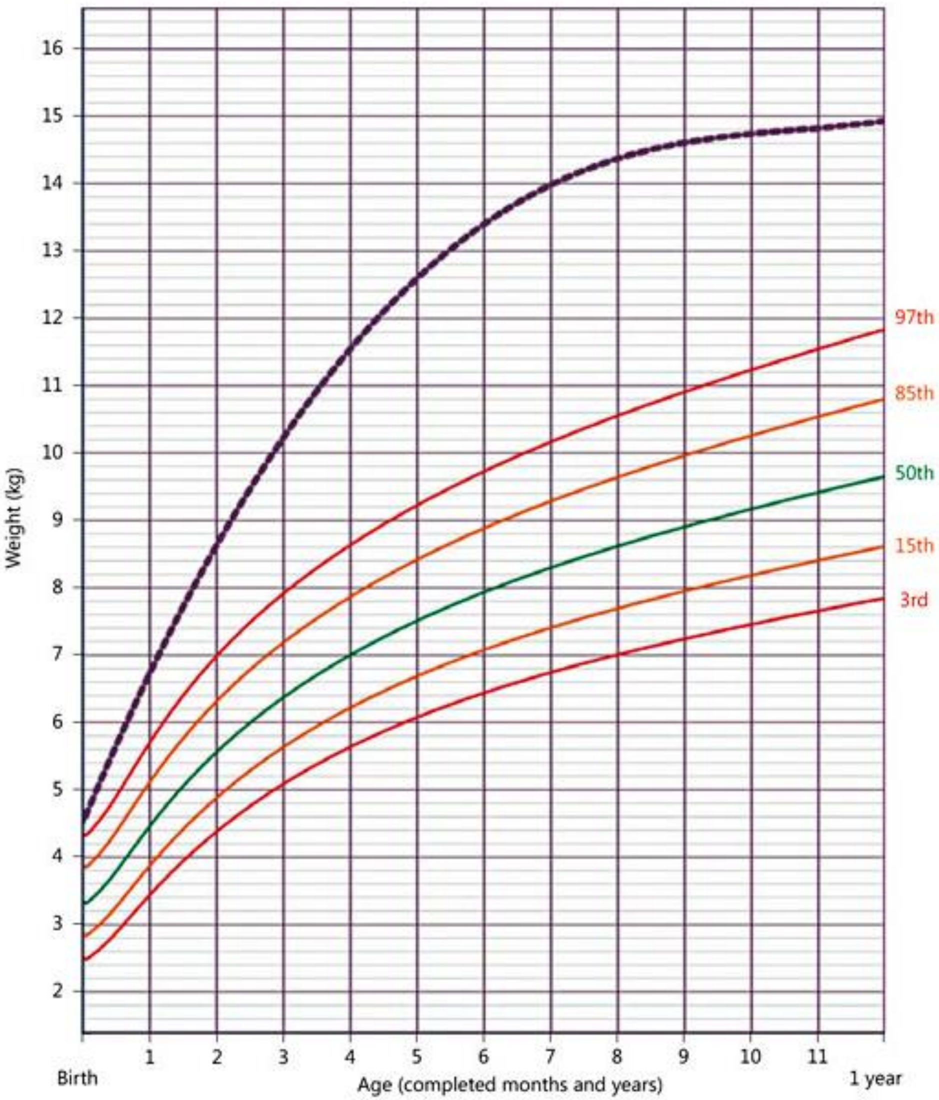

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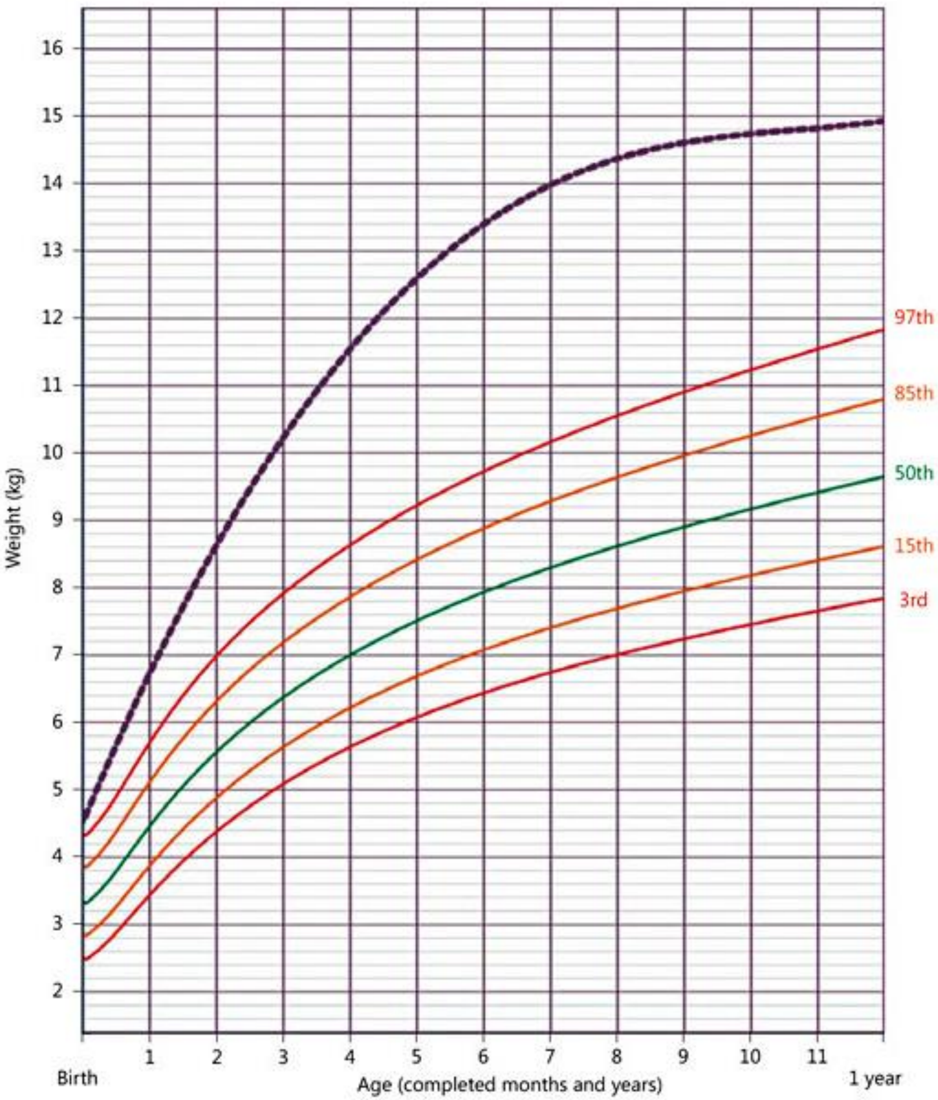

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Breast milk at 1 yr. lactation:

Protein	1.3 g/dl
Reference	0.8 g/dL

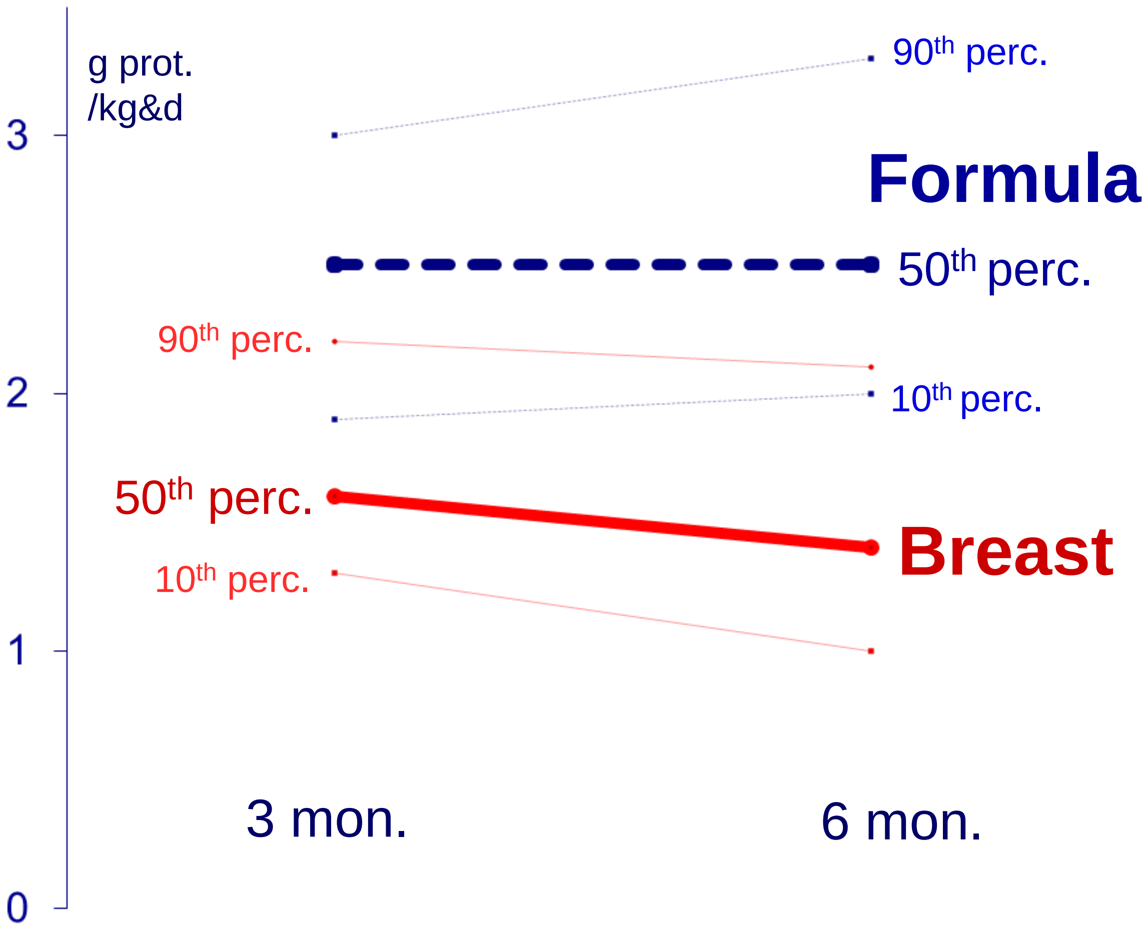
Does breastfeeding protect, and how?

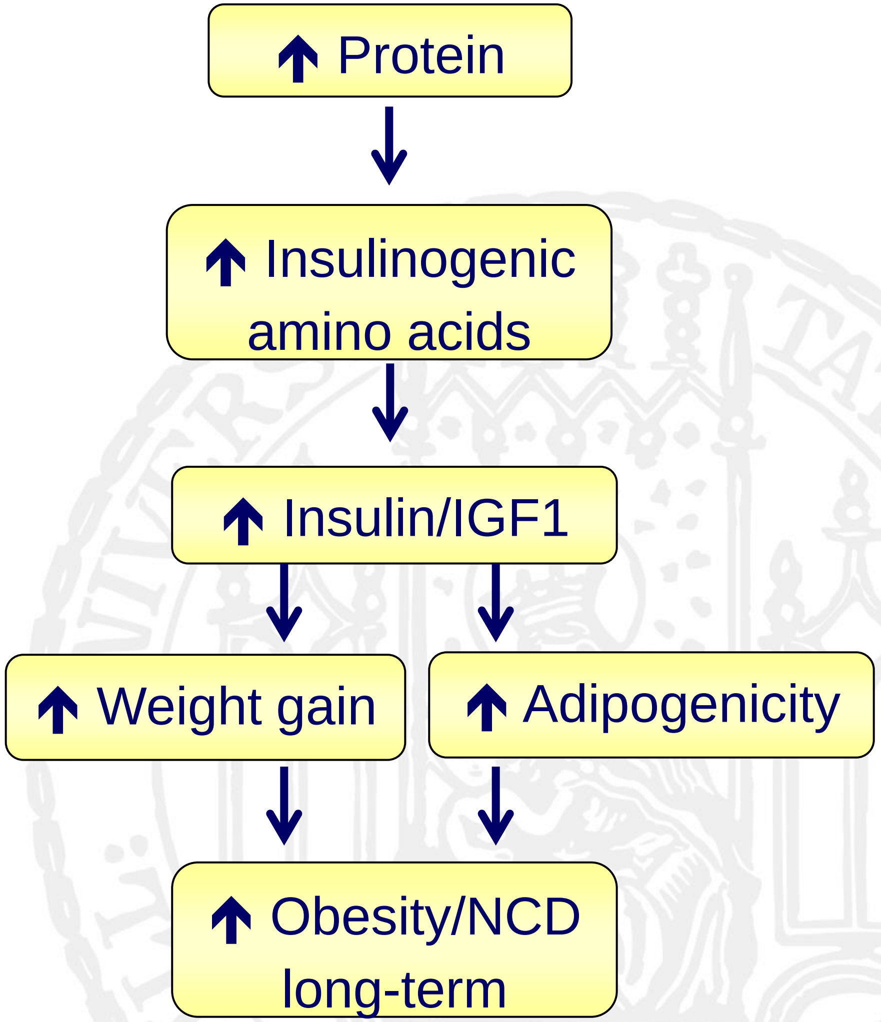
Early Protein Hypothesis

Excessive protein intake in infancy promotes high early weight gain and later obesity

Does early protein intake matter?

Far higher protein suppy with conv. formula than breast milk





Alexy et al, Ann Nutr Metab 1999;43:14-22.

Koletzko et al, Am J Clin Nutr 2011;94:2036-43S.

RCT: Childhood obesity project (CHOP)

1678 healthy term infants enrolled in 5 EU countries: Belgium, Germany, Italy, Poland, Spain

Weight/length at 6 y:

Breast fed

Protein: 1.2 g/dL

Breast fed 61.4%

Bottle

↑ Protein

IF 2.05 g/dL, FOF 1.6 g/dL

Doubly blind randomised

Bottle

↓ Protein

Bottle fed 60.4%

IF 1.25 g/dL, FOF 3.2 g/dL

Intervention

No intervention, follow-up

0 | 1 yr. | 2 yrs. | 6 yrs.

Koletzko et al, Am J Clin Nutr 2009;89:1836-45. Weber et al, Am J Clin Nutr. 2014;99:1041-51.

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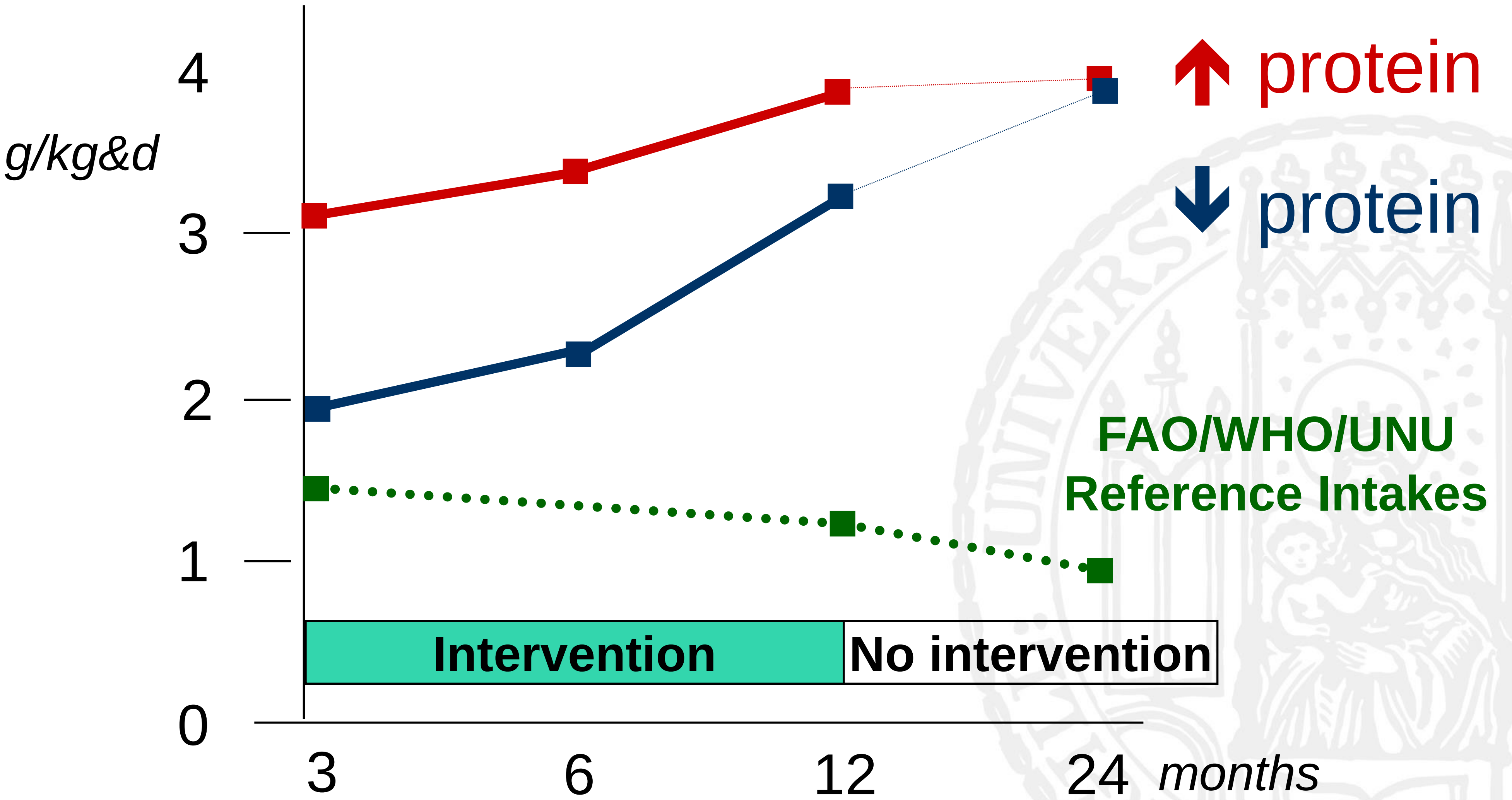
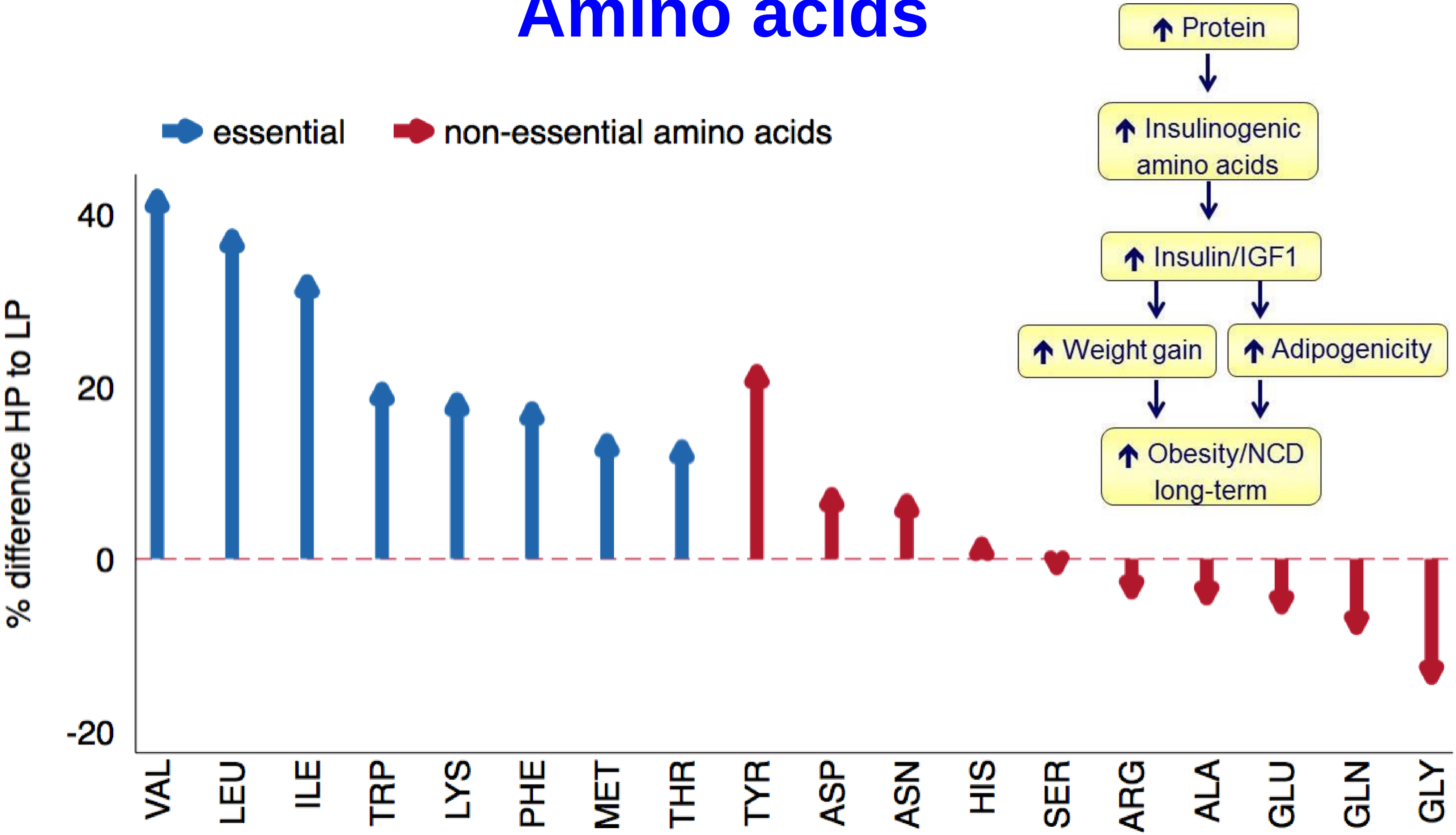
Protein Intake



Koletzko et al, Am J Clin Nutr 2009;89:1836-45.

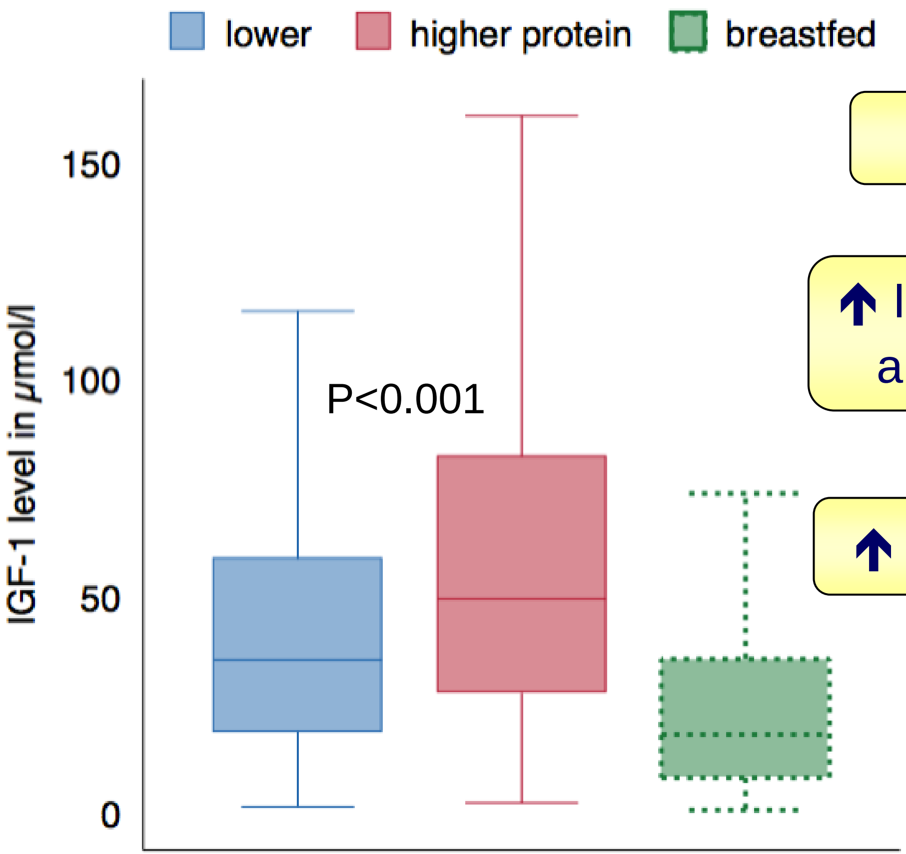
Amino acids



Socha et al, AJCN 2011;94:1776-84S.

Growth factors

IGF-1 (plasma)



↑ Protein

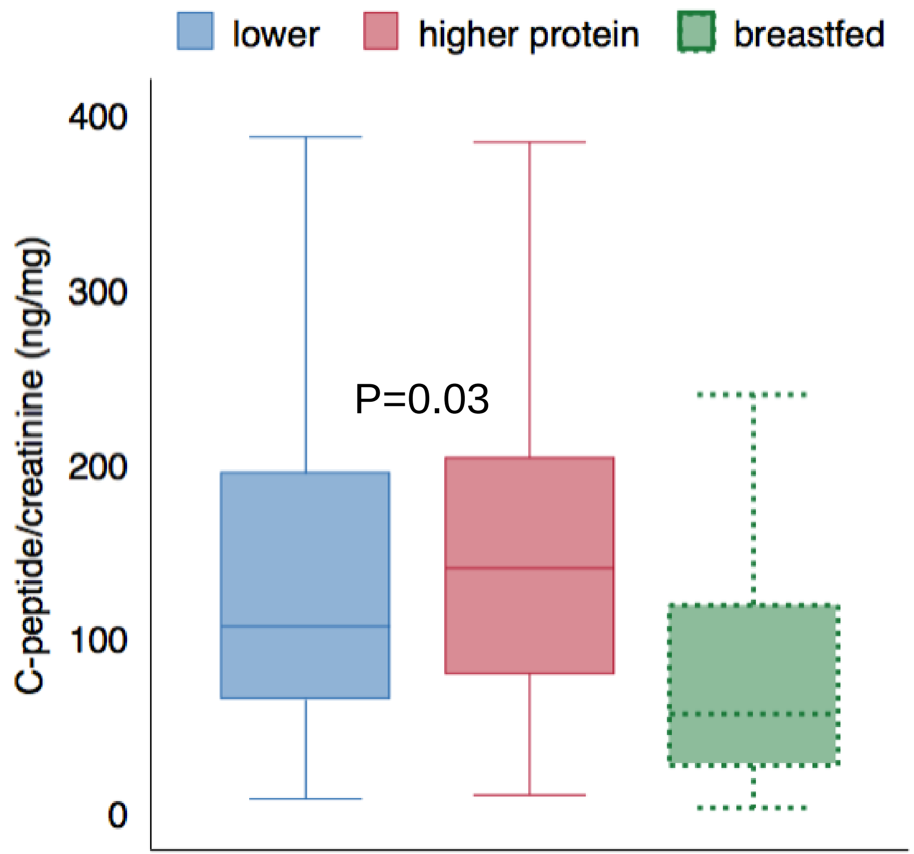
↓

↑ Insulinogenic amino acids

↓

↑ Insulin/IGF1

C-peptide/creatinine (urine)



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IGF-1 in infants: Genes, Gender or Gruel?

Explained variance (R^2) of IGF-1 axis related outcomes due to contributions from gender, genetic and nutritional variables

	Total IGF-1 (log10, R^2 in %)	**Free IGF-1** (log10, R^2 in %)	**IGF-BP3** (R^2 in %)	**IGF-1/IGF-BP3** (R^2 in %)
Gender only	1.5	2.0	1.2	1.1
Genetic only	3.8	3.6	0.78 *(n.s.)*	5.0

Characteristics of variants of the *IGF-1* and *IGFBP-3* genes.

Gene	dbSNPBuild 132	Position, bp	Location
IGF-1	rs6214	101,317,699	3′ UTR
	rs1520220	101,320,652	Intronic
	rs978458	101,326,369	Intronic
	rs7136446	101,362,645	Intronic
	rs10735380	101,368,366	Intronic
	rs2195239	101,380,832	Intronic
	rs35767	101,399,699	5′ near gene
	rs35766	101,404,603	5′ near gene
IGFBP-3	rs1496495	45,903,786	Intergenic
	rs6670	45,918,779	3′ UTR

Rzehak et al, Growth Horm IGF Res. 2013t;23:149-58.

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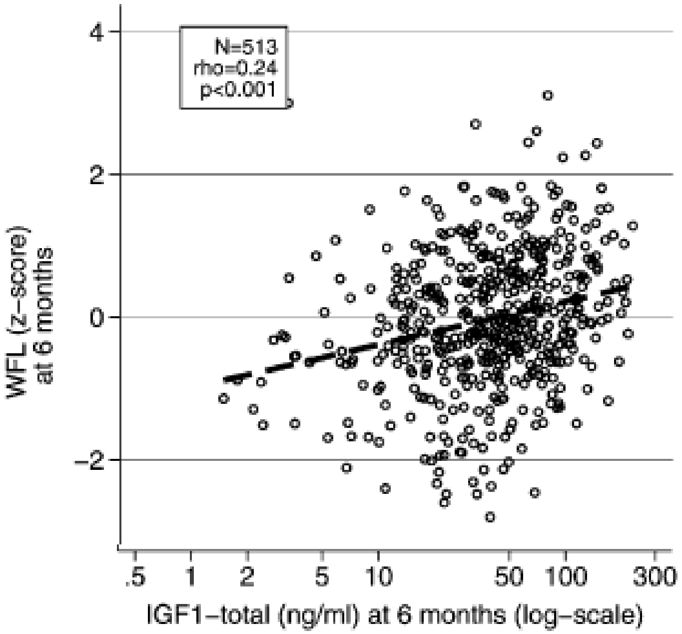
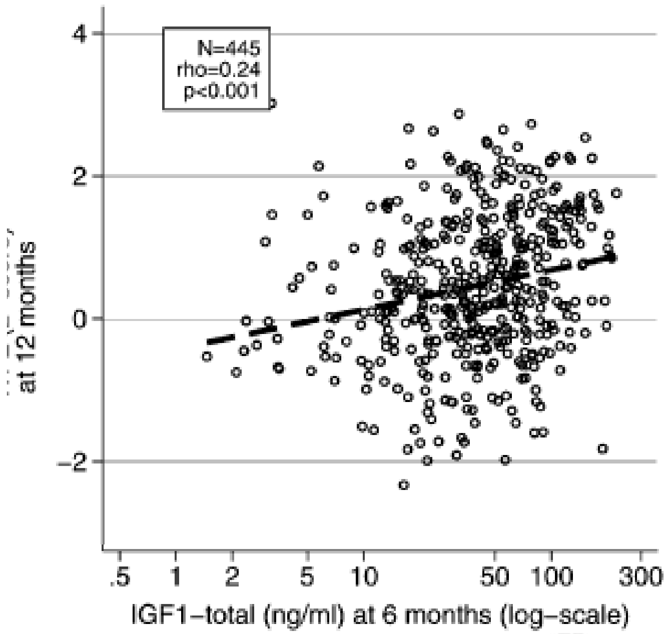
Serum IGF-1 predicts weight gain velocity

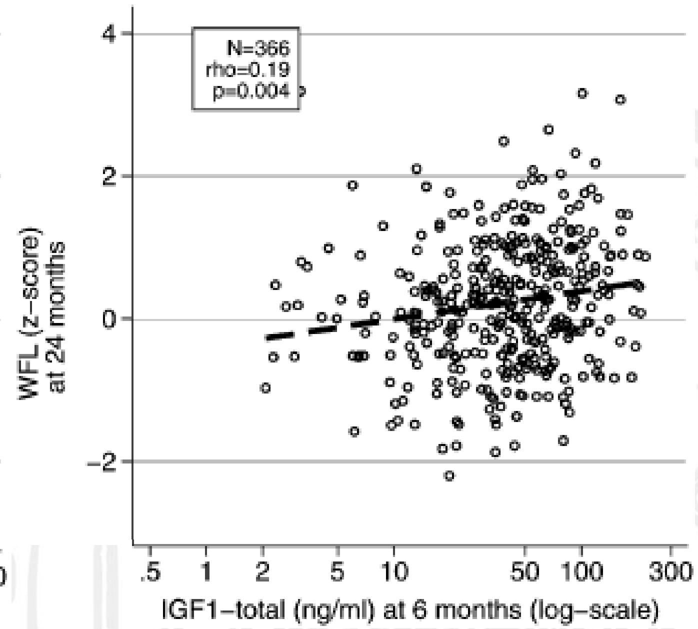
6 mon

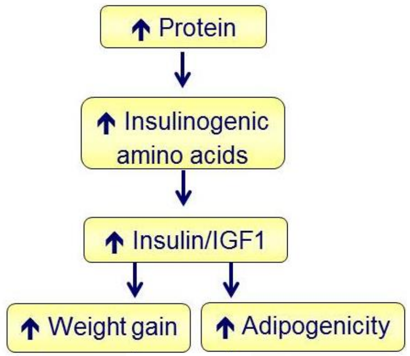


12 mon



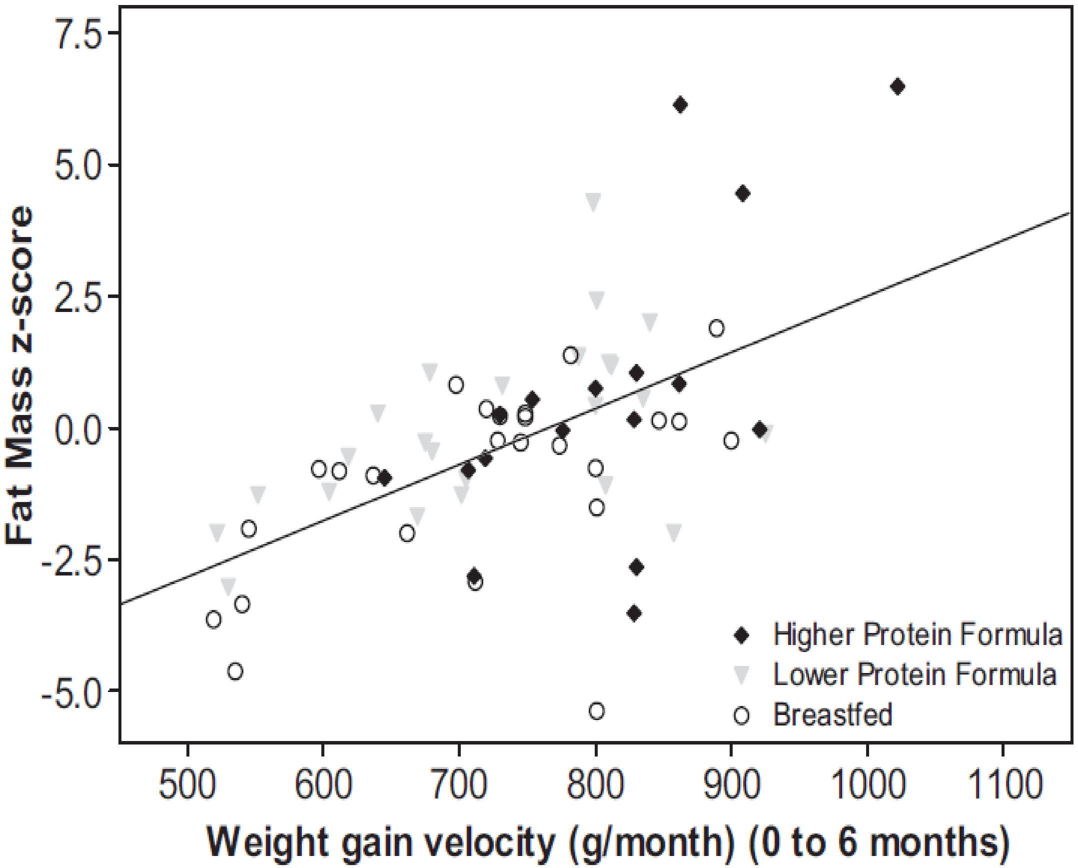
24 mon





Socha P et als. Am J Clin Nutr 2011;94:1776S–84..

Weight gain velocity ⇨ body fat mass
(isotope dilution method)

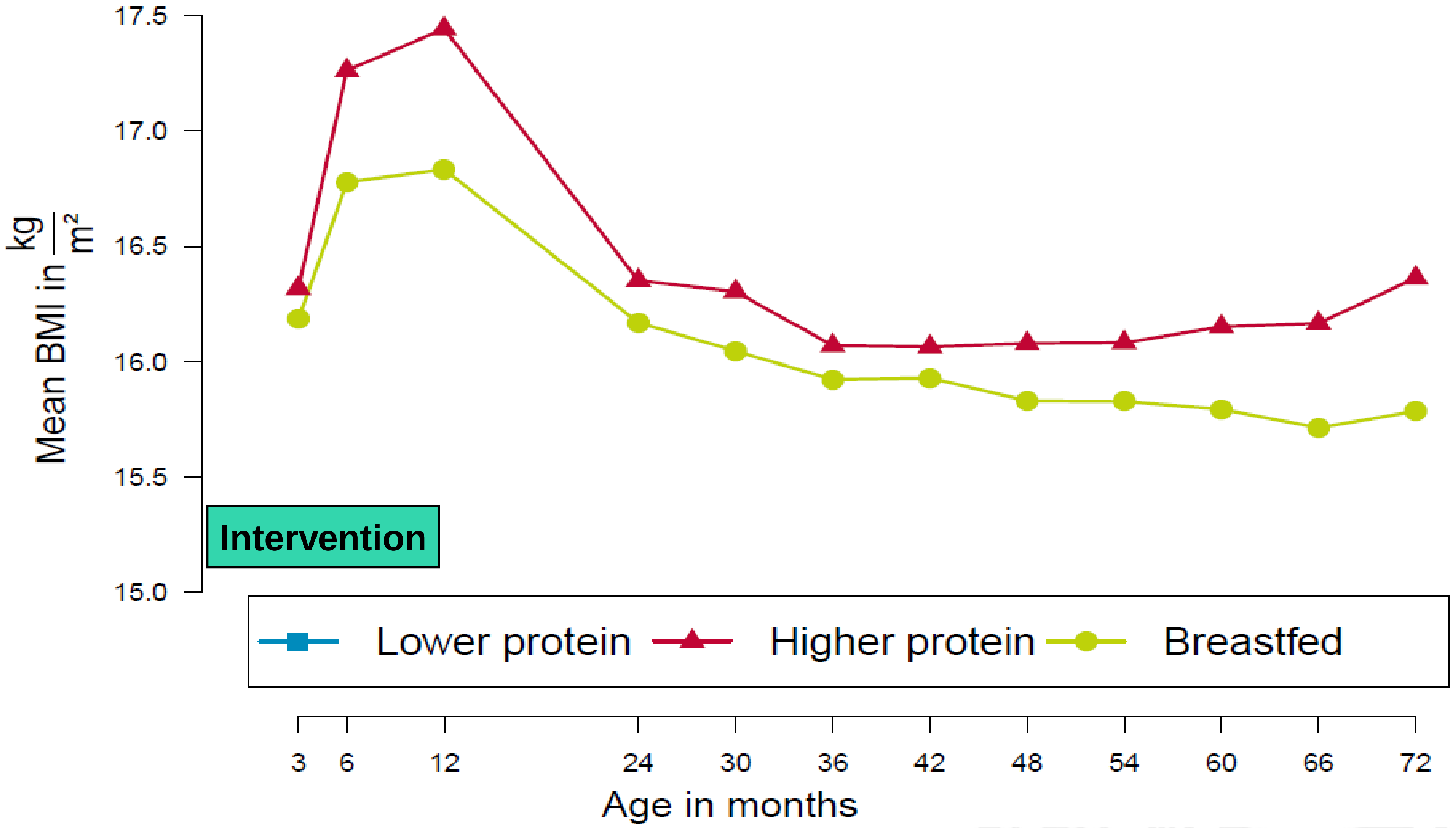


Weight and BMI vs. body fat mass
(Pearson r correlations)

	Fat mass z-score (Pearson r (P-value))	*Fat-free mass z-score (Pearson r (P-value))*
Anthropometry at 6 months		
Weight-for-length *z*-score	0.470 ($P<0.001$)	0.167 (0.180)
BMI *z*-score	0.475 ($P<0.001$)	0.160 (0.199)
Anthropometry at 12 months		
Weight-for-length *z*-score	0.374 ($P=0.002$)	0.168 (0.180)
BMI *z*-score	0.332 ($P=0.007$)	0.140 (0.267)
Anthropometry at 24 months		
Weight-for-length *z*-score	0.259 ($P<0.05$)	0.060 (0.641)
BMI *z*-score	0.247 ($P=0.051$)	0.039 (0.763)

Escribano J et al. Int J Obes 2012;36:548 -53.

Infant diet and BMI until early school age



Weber et al, Am J Clin Nutr 2014.

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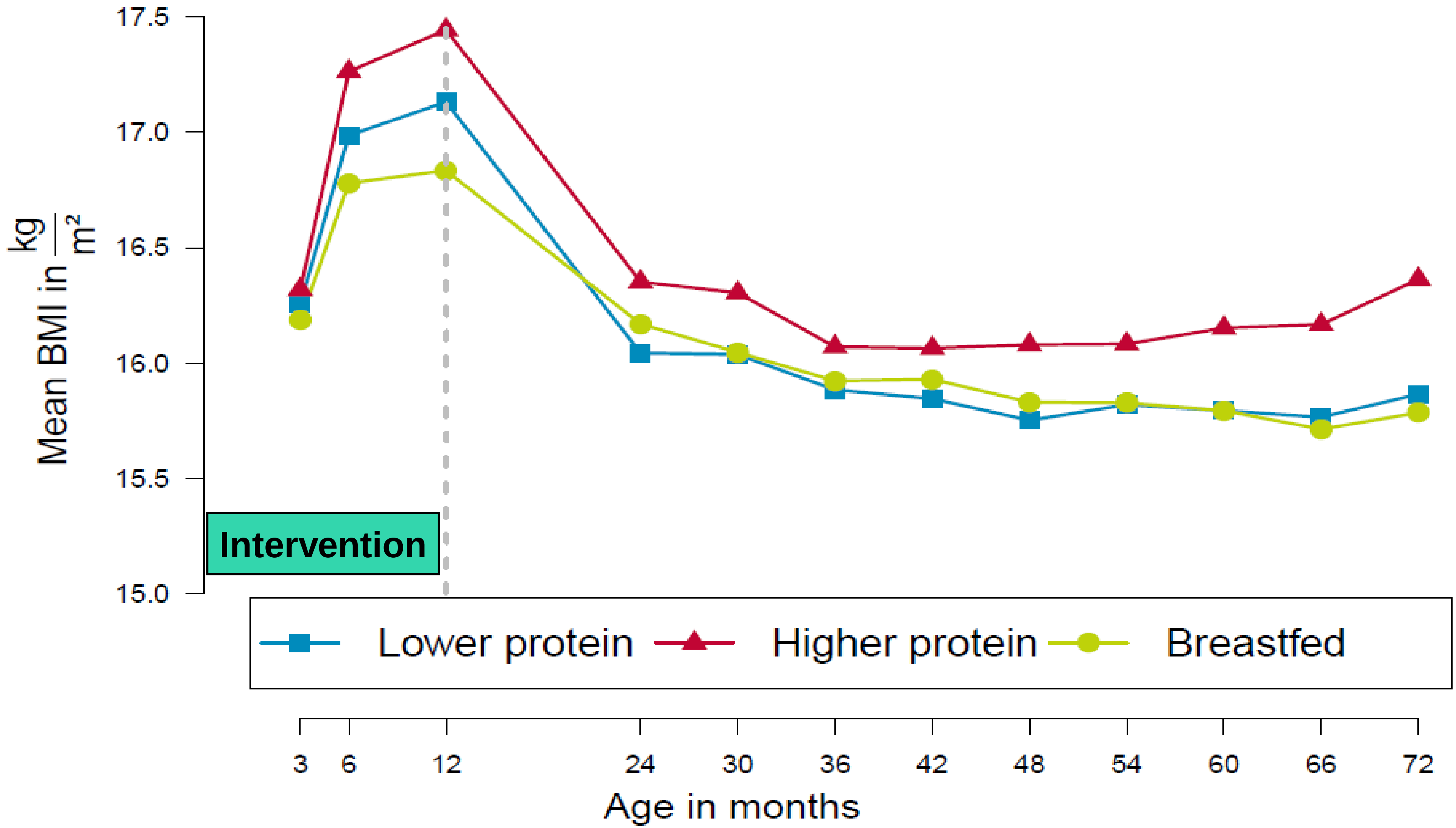
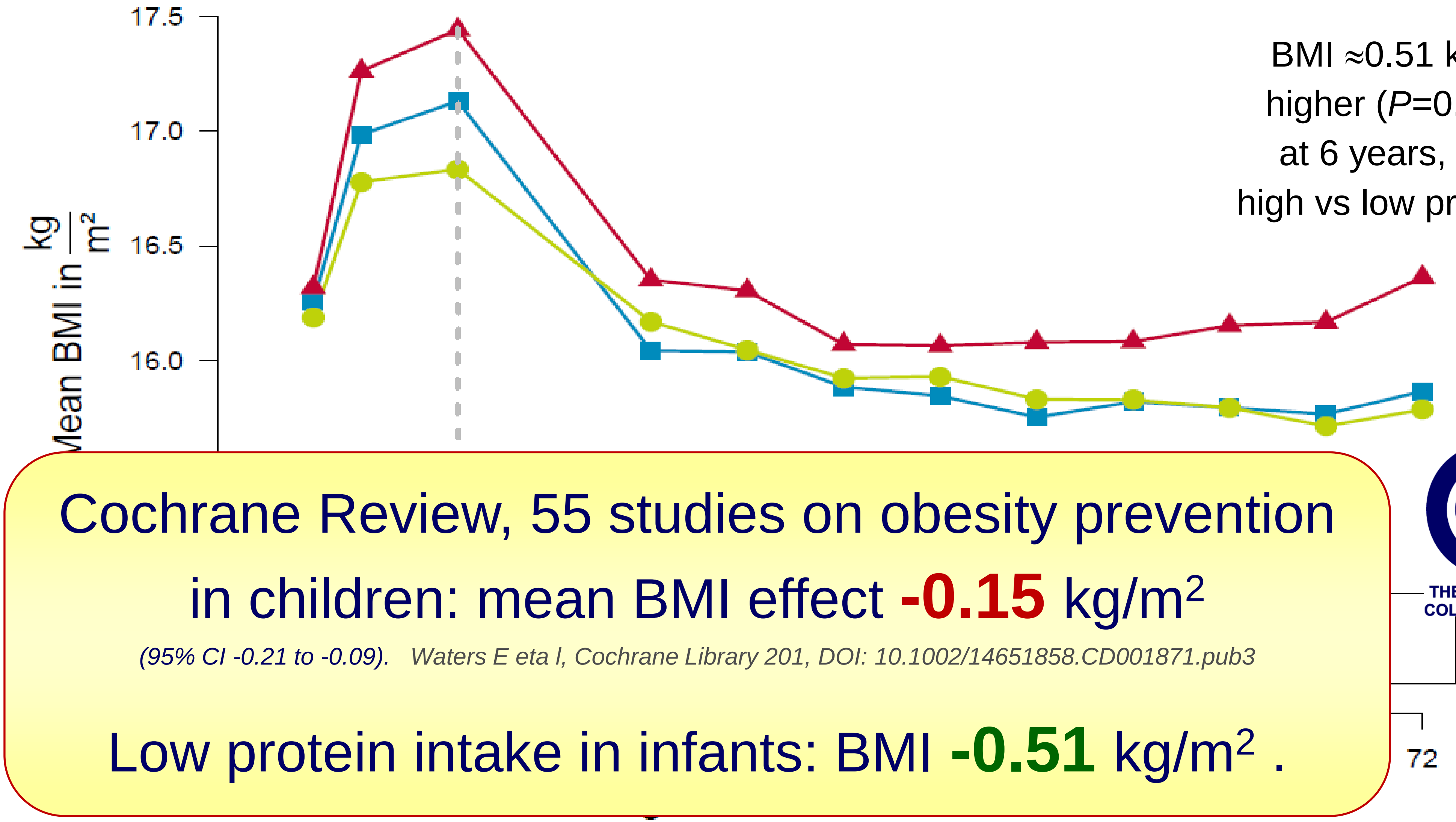


Weber et al, Am J Clin Nutr 2014.

Infant diet and BMI until early school age



BMI ≈0.51 kg/m² higher (*P*=0.009) at 6 years, early high vs low protein

Cochrane Review, 55 studies on obesity prevention in children: mean BMI effect **-0.15** kg/m²

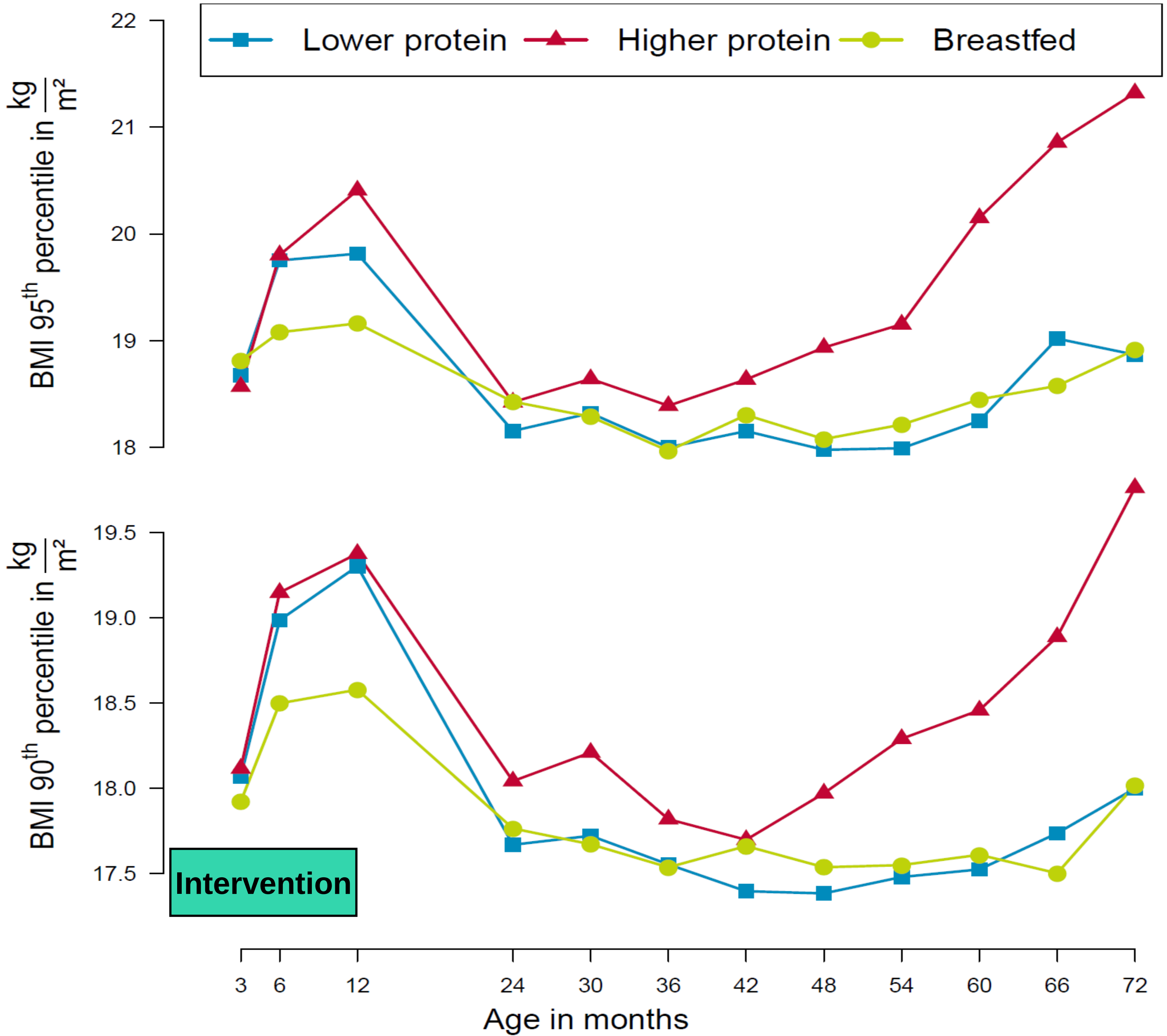
(95% CI -0.21 to -0.09). Waters E eta l, Cochrane Library 201, DOI: 10.1002/14651858.CD001871.pub3

THE COCHRANE COLLABORATION®

Low protein intake in infants: BMI **-0.51** kg/m² .

Weber et al, Am J Clin Nutr 2014.

Overweight and obesity until school age



BMI ≈2.5 kg/m² higher (P=0.014) at 95th. centile

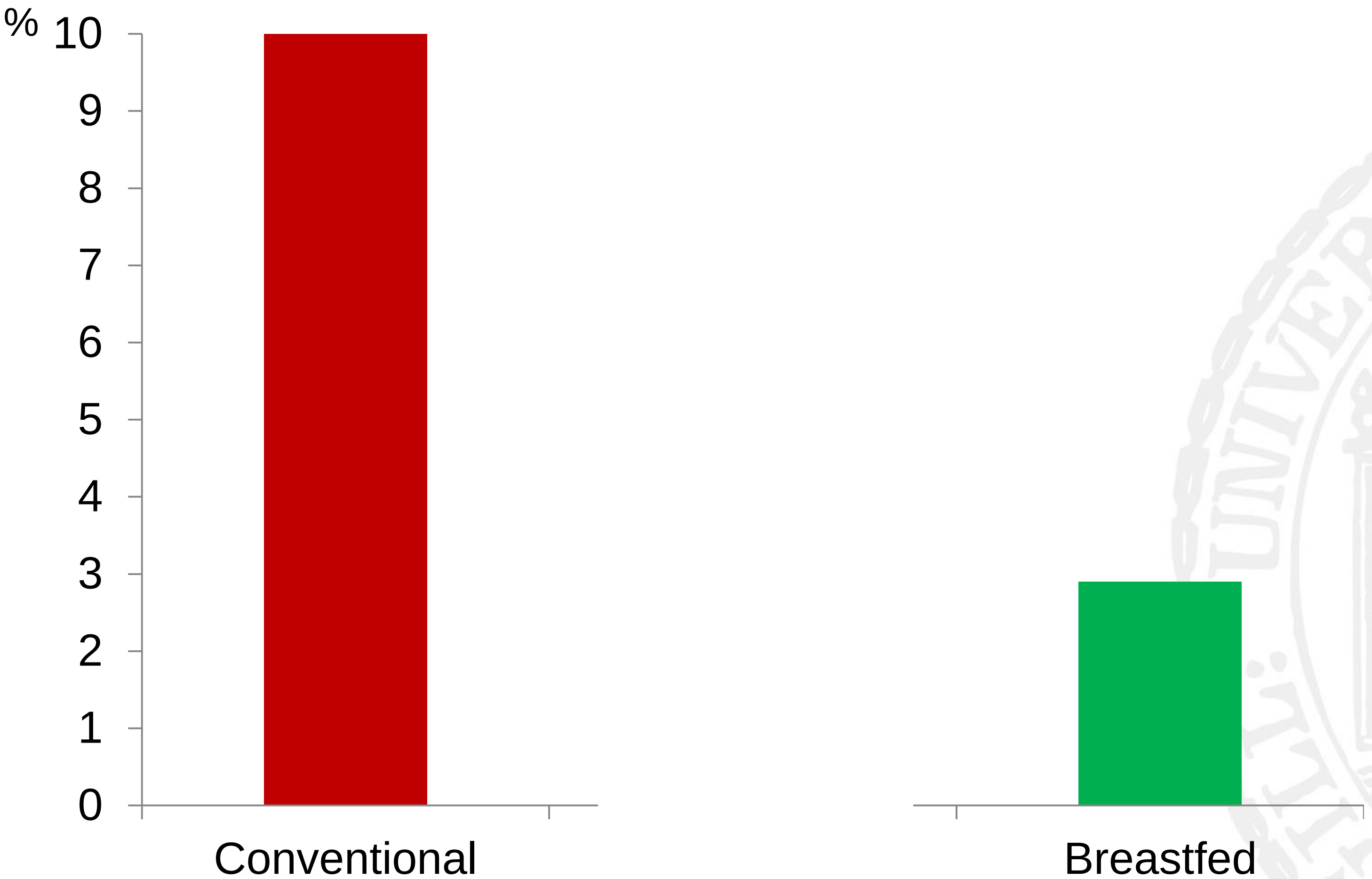
BMI ≈1.5 kg/m² higher (P=0.085) at 90th. centile

Weber et al, Am J Clin Nutr 2014.

↓ protein in infancy ⇨ ↓ obesity at 6 yrs.

RCT, Childhood Obesity Project (CHOP) Study, 1678 healthy term infants enrolled in 5 European countries

Obesity (%) at 6 years



Weber et al, Am J Clin Nutr. 2014;99:1041-51. doi: 10.3945/ajcn.113.064071.

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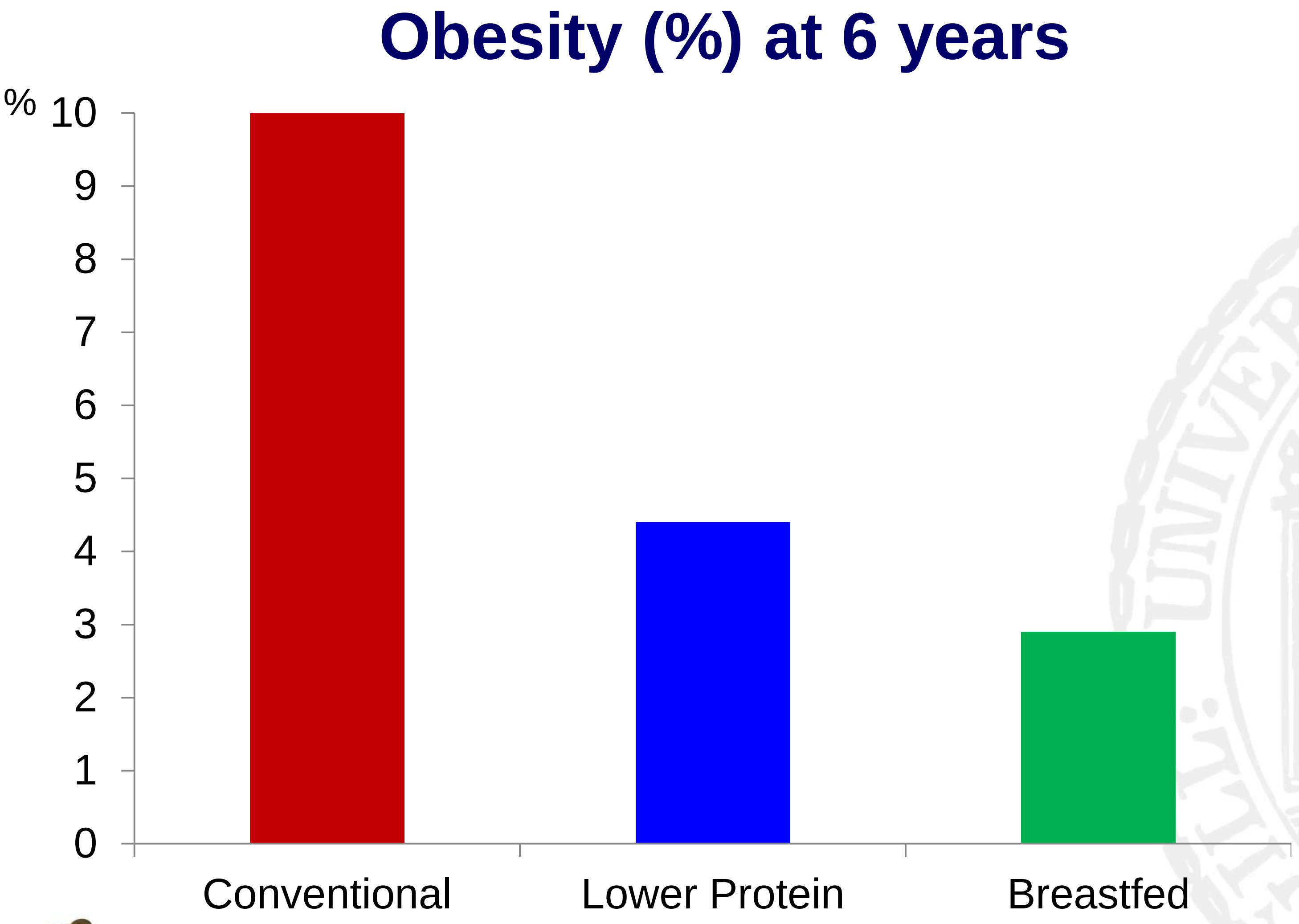

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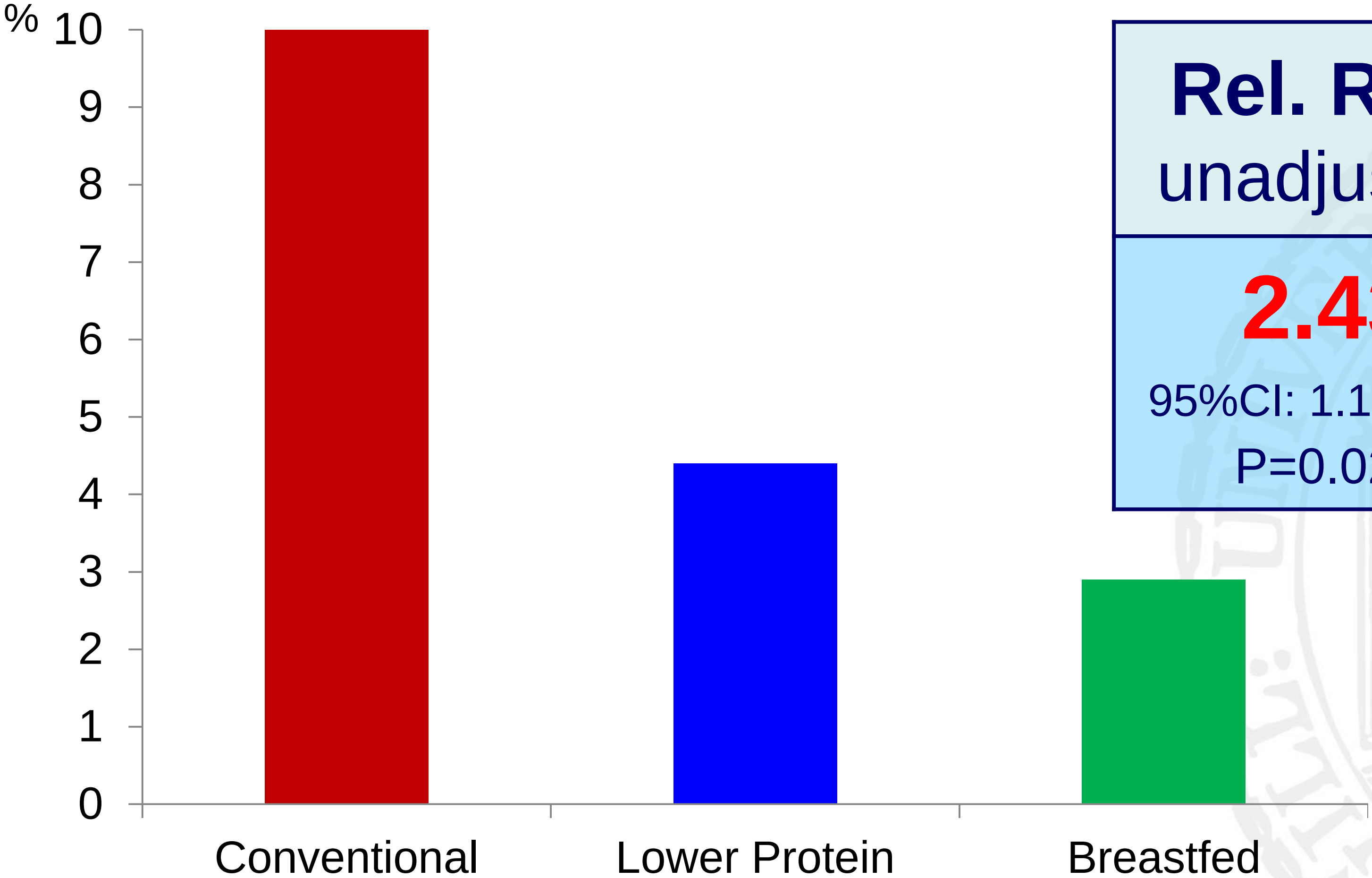


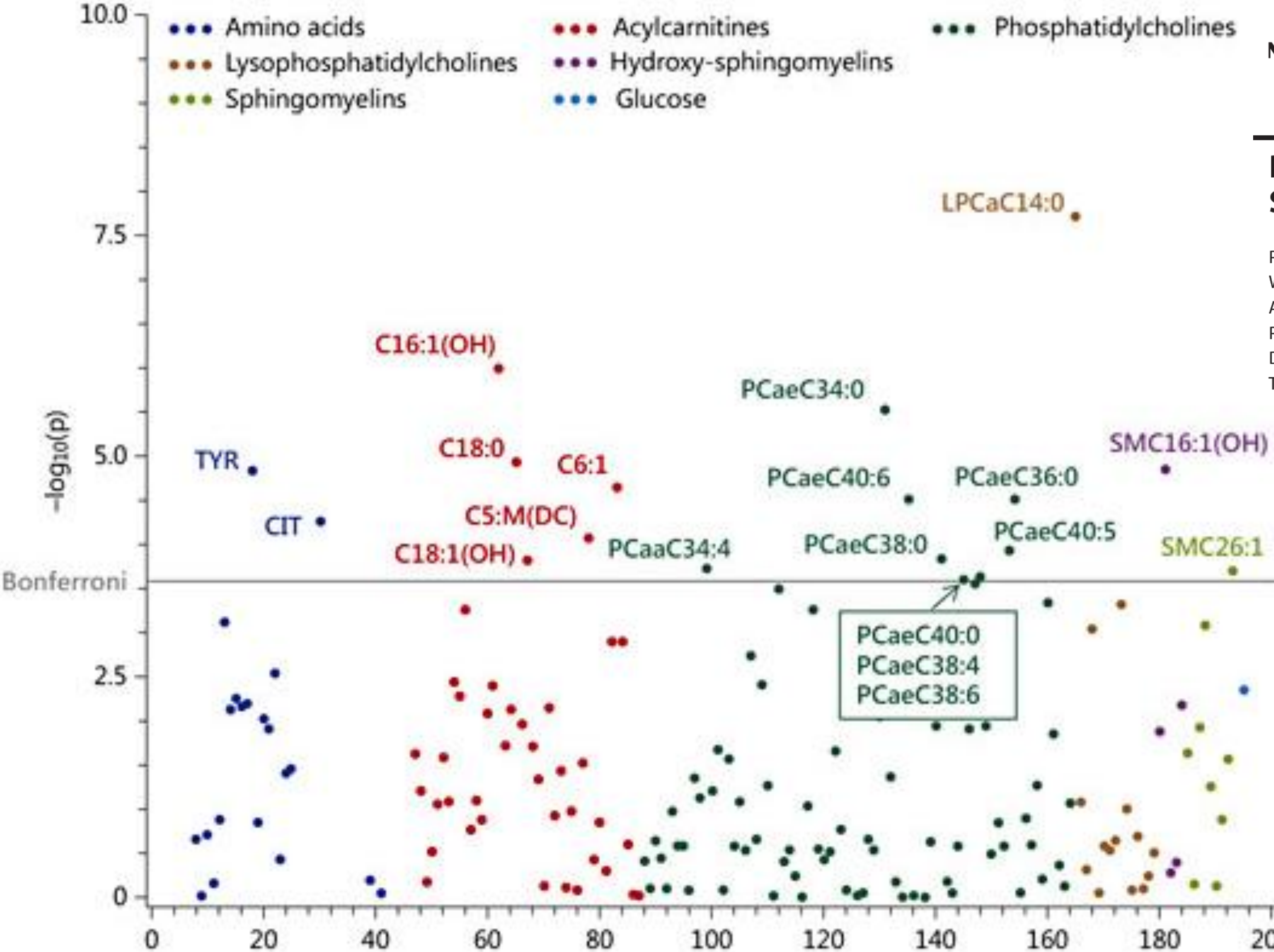
Rel. Risk unadjusted	Rel. Risk adjusted
2.43	**2.87**
95%CI: 1.12, 5.27	95%CI: 1.22, 6.75
P=0.024	P=0.016

Weber et al, Am J Clin Nutr. 2014;99:1041-51. doi: 10.3945/ajcn.113.064071.

Limit milk protein supply in infancy

- Breastfeeding reduces later obesity risk
  ⇨ **promote, protect & support breastfeeding**
- Avoid high protein supply
  - ⇨ Infants not (fully) breast fed**: infant formula with reduced protein**, but high protein quality
  - ⇨ All infants: **no cows‘ milk as a drink in infancy**

Metabolites predict Δ weight - birth to 6 months



Annals of Nutrition & Metabolism

Ann Nutr Metab 2014;64:294–303
DOI: 10.1159/000365037

Rapid Growth and Childhood Obesity Are Strongly Associated with LysoPC(14:0)

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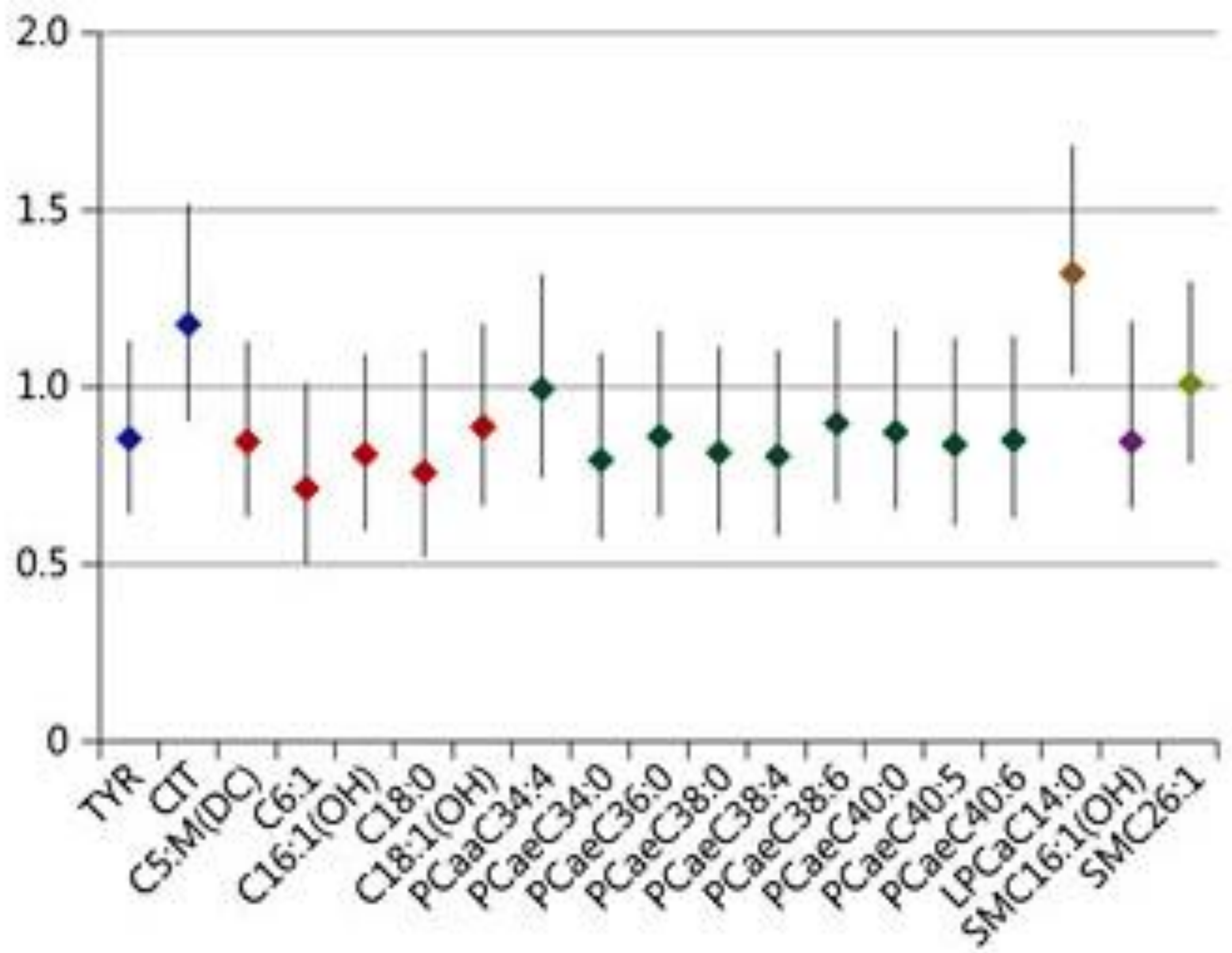

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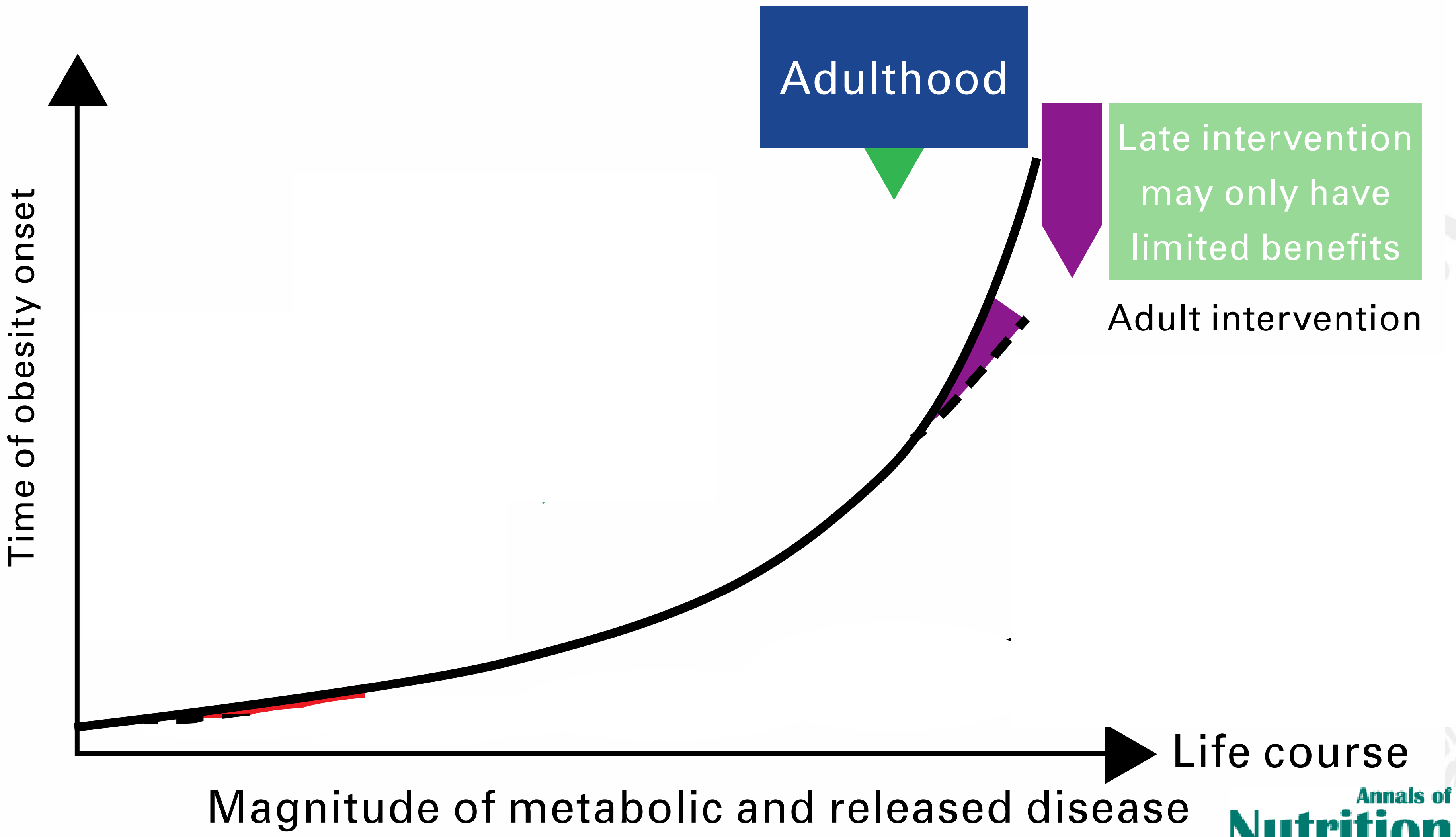
Great opportunities for health promotion



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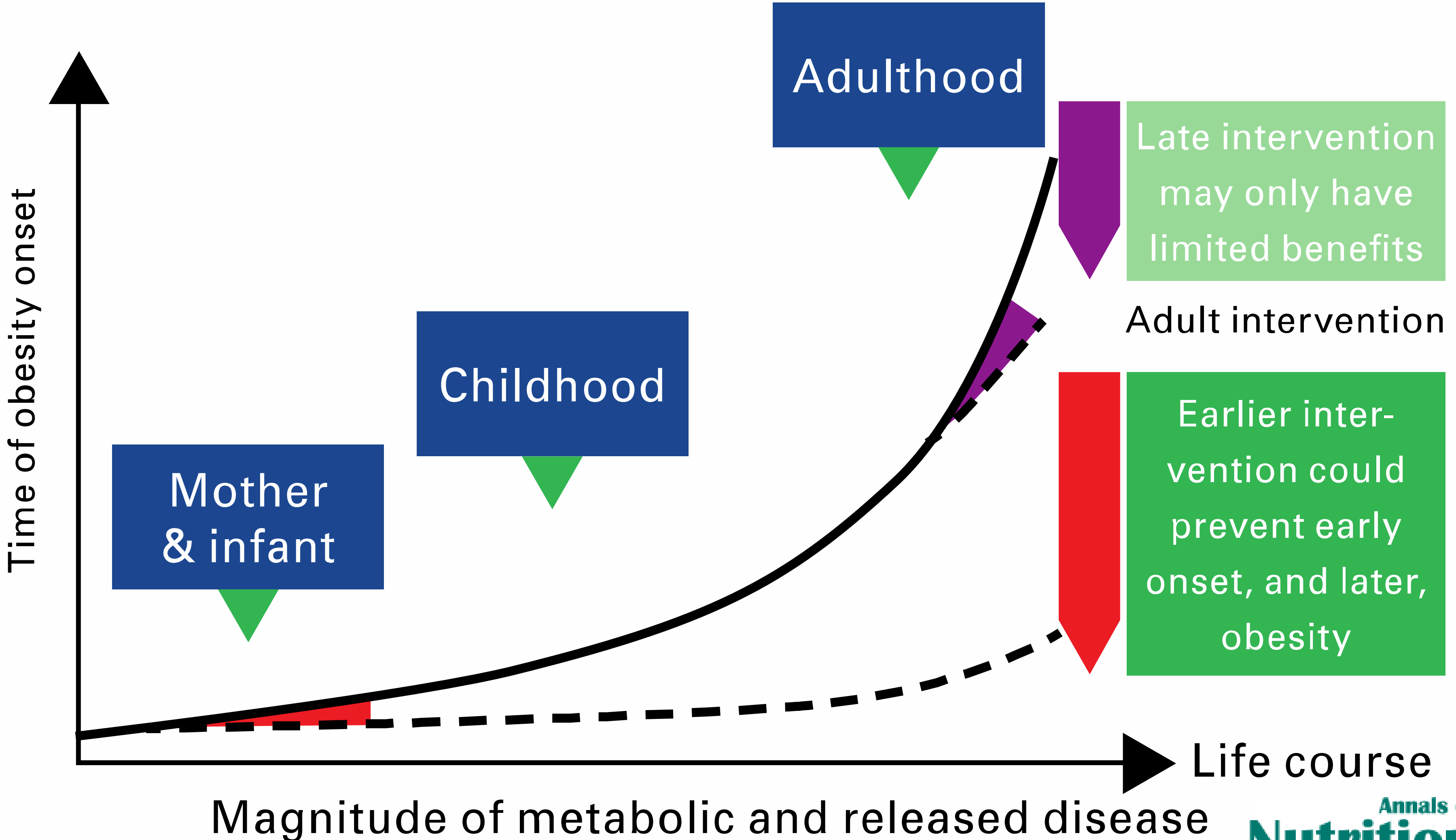

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Sincere thanks to funding bodies

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Long-term effects of early nutrition on later health

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Sincere thanks: to you for your kind attention, to participating subjects and families, and to fantastic colleagues and friends

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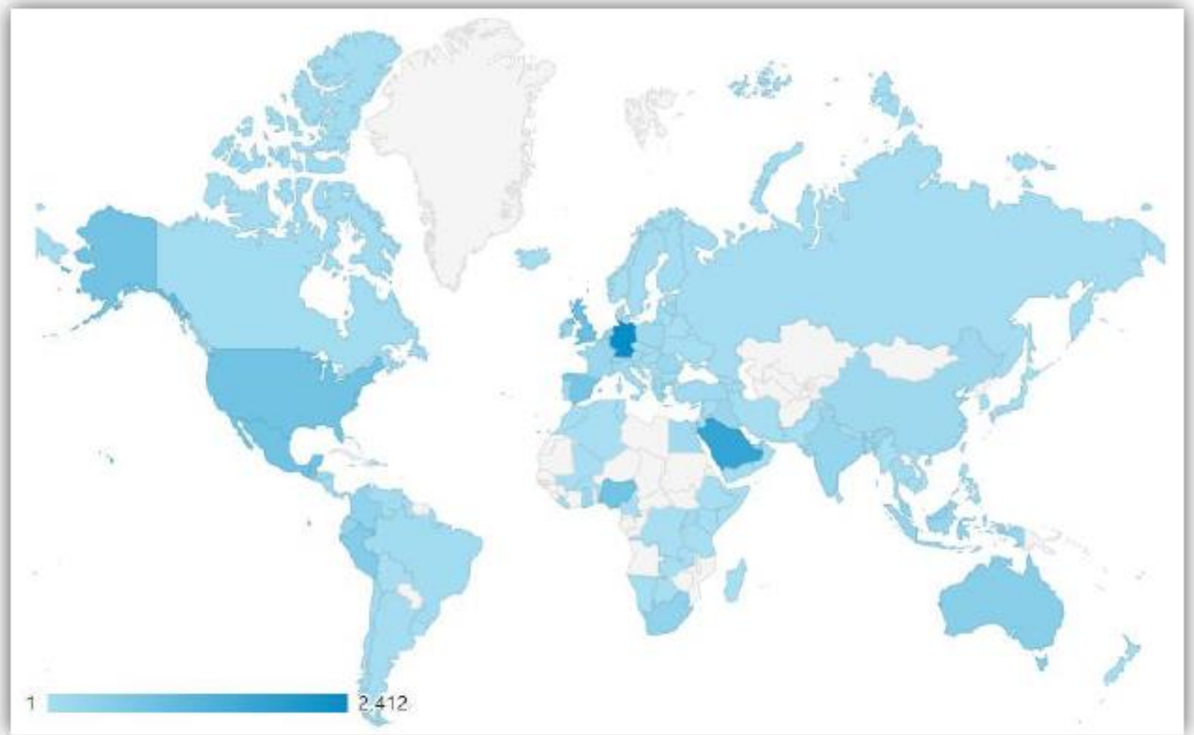

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