EARLYNUTRITION
Long-term effects of early nutrition on later health

PROVEN BENEFITS OF NUTRITIONAL MODIFICATIONS OF PATTERNS OF GROWTH.

Power of Programming, Munich 2016
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PROVEN BENEFITS OF NUTRITIONAL MODIFICATIONS OF PATTERNS OF GROWTH

This presentation is about:

- Proven benefits → potential benefits
- Nutritional modifications → early nutrition:
  - **1. Protein concentration in infant formula**
  - **2. Duration of breastfeeding (BF)**
- Benefits → obesity risk
- Patterns of growth – whenever feasible

QUESTIONS to be answered:

- How infant feeding (protein content in infant formula and BF duration) affect early growth?
- Can early growth predict later obesity?
- What is the link between protein content in infant formula and BF duration and later obesity?

Protein Concentration in Milk Formula, Growth, and Later Risk of Obesity: A Systematic Review

High early protein intake

in excess of metabolic requirements

↓

Stimulation of the secretion of insulin and IGF1

↓

Enhanced weight gain in infancy

Increased risk of later obesity

Patro-Gołąb B, Zalewski BM, Kouwenhoven SM, et al.; J Nutr. 2016

Objective

To investigate current evidence on the effects of **infant formulas and follow-on formulas with different protein concentrations** on infants and children's growth, body composition, and later risk of overweight and obesity.

Methods

- A **systematic review** of randomized controlled trials (RCTs)

- Electronic databases searched up to Nov 2014:

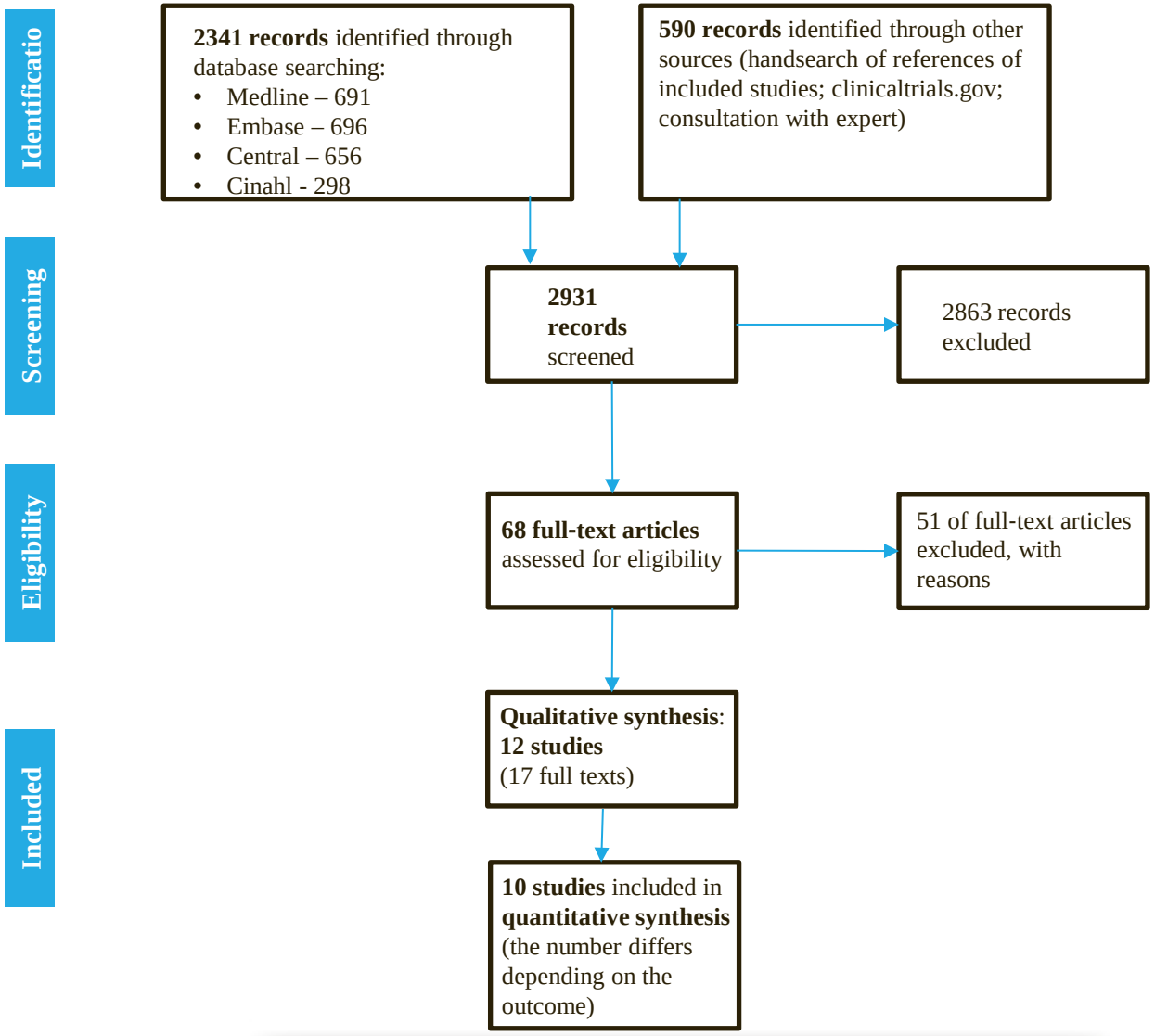
  - Medline
  - Embase
  - Cochrane Library
  - Cumulative Index to Nursing and Allied Health Literature (CINAHL)

Methods

Eligibilty criteria:

- **Population**: infants and children aged 0–3 y representing the general population
- **Intervention**: cow milk–based infant formulas with variations in protein concentration
- **Comparison**: lower-protein cow milk–based formulas (as defined by the authors)
- **Outcomes**: growth, overweight, obesity, and body composition

Results - flow diagram of the study selection process



Results

Protein concentration range in lower-protein formula vs higher-protein formula groups, respectively:

1.1 to 2.1 *vs* 1.5 to 3.2 g/100 mL

Results – growth

Outcomes assessed at different time points in different studies:

- BMI, BMI z-score
- Mean weight, weight z-scores, weight gain
- Mean length/height, length gain
- Head circumference, head circumference gain
- Weight-for-length z scores
- Other…

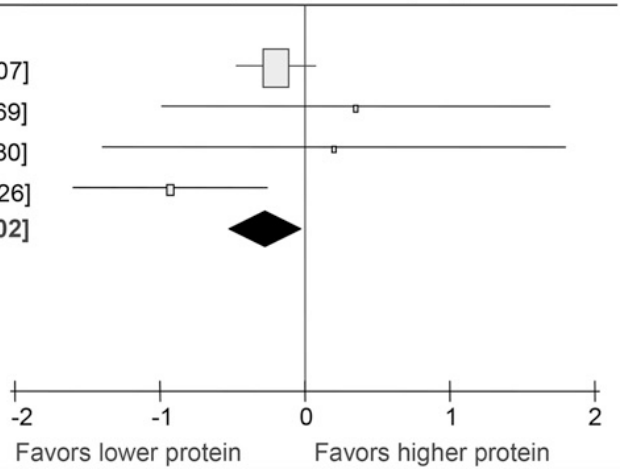
Results – linear growth

Transient effect on mean length at 3 mo in a meta-analysis of 4 studies

Study or Subgroup	Lower protein Mean [cm]	SD	Total	Higher protein Mean [cm]	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
3 months								
CHOP study*	60.43	2.02	454	60.63	2.17	451	80.8%	-0.20 [-0.47, 0.07]
Picone 1989 (F11 + F13)^ (22)	60.55	2.08	20	60.2	1.58	10	3.4%	0.35 [-0.99, 1.69]
Räihä 1986 (24)	59.9	1.87	10	59.7	1.77	10	2.4%	0.20 [-1.40, 1.80]
Szajewska 1993 (F2.2 + F2.2)^ (18)	62.04	0.95	14	62.97	1.23	29	13.5%	-0.93 [-1.60, -0.26]
Subtotal (95% CI)			**498**			**500**	**100.0%**	**-0.27 [-0.52, -0.02]**

Heterogeneity: Chi² = 5.13, df = 3 (P = 0.16); I² = 42%

Test for overall effect: Z = 2.16 (P = 0.03)



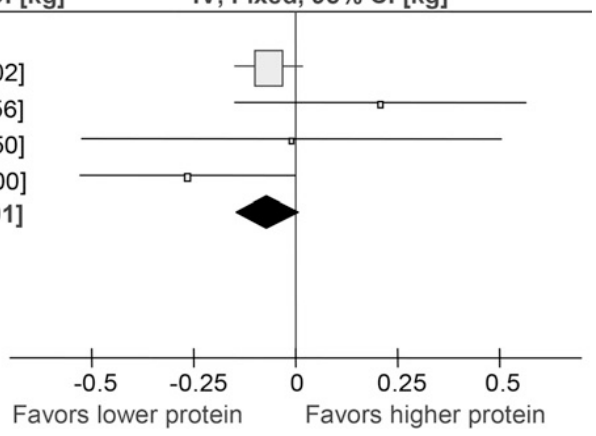
Results – weight

- **Mean weight – 12 RCTs**
  - **Lower in lower-protein group from 6 to 12 mo of age**
  - **No significant differences <6 mo of age**
- **Mean weight gain – 9 RCTs**
  - **no statistically significant differences up to 12 mo of age**

	Lower protein			Higher protein				Mean Difference	Mean Difference
Study or Subgroup	Mean [kg]	SD	Total	Mean [kg]	SD	Total	Weight	IV, Fixed, 95% CI [kg]	IV, Fixed, 95% CI [kg]
3 months									
CHOP study*	5.942	0.62	454	6.01	0.652	451	84.8%	-0.07 [-0.15, 0.02]	
Picone 1989 (F11 + F13)^ (22)	5.872	0.638	20	5.66	0.357	10	4.6%	0.21 [-0.15, 0.56]	
Räihä 1986 (24)	5.79	0.534	10	5.8	0.632	10	2.2%	-0.01 [-0.52, 0.50]	
Szajewska 1993 (F2.2 +F2.2)^ (18)	6.244	0.350	14	6.51	0.52	29	8.4%	-0.27 [-0.53, -0.00]	
Subtotal (95% CI)			498			500	100.0%	**-0.07 [-0.15, 0.01]**	

Heterogeneity: Chi² = 4.50, df = 3 (P = 0.21); I² = 33%

Test for overall effect: Z = 1.77 (P = 0.08)



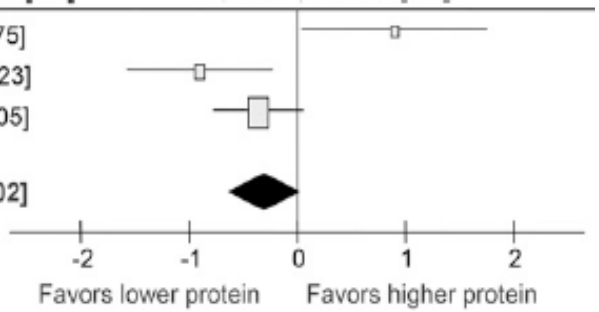
Results – head circumference

- **Head circumference - 5 RCTs**
  - **Inconsistent results**
- **Head circumference gain – 2 RCTs**
  - **Similar growth rate in both study groups**

Study or Subgroup	Lower protein group Mean [cm]	SD	Total	Higher protein group Mean [cm]	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI [cm]
Picone 1989 (F11 + F13)^ (22)	41	1.41	20	40.1	0.95	10	14.5%	0.90 [0.05, 1.75]
Räihä 1986 (24)	40.2	0.7	10	41.1	0.82	10	23.6%	-0.90 [-1.57, -0.23]
Szajewska 1993 (F2.2 + F2.2)^ (18)	40.6	0.45	14	40.96	0.93	29	61.9%	-0.36 [-0.77, 0.05]
Total (95% CI)			44			49	100.0%	-0.31 [-0.63, 0.02]

Heterogeneity: Chi² = 10.77, df = 2 (P = 0.005); I² = 81%

Test for overall effect: Z = 1.84 (P = 0.07)



Results - BMI

Mean BMI – 2 RCTs

- **No significant differences in mean BMI assessed <6 mo** of age reported

- **Lower BMI at 12 mo of age and later** (24 mo, and 6y) in children fed lower-protein infant formula (1 large RCT)

Results – overweight, obesity

- Only 1 RCT (Childhood Obesity Program, the CHOP study; n = 448)

- The risk of becoming obese at the age of 6 y significantly lower in the lower-protein formula group

RR 0.44; 95% CI: 0.21, 0.91

Conclusions

- **The evidence is insufficient to firmly assess the effects of reducing the protein concentration in infant formulas on long-term outcomes.**

- **Reducing the protein concentration in infant formulas appears as promising intervention for reducing the risk of overweight and obesity in children.**

- **More studies replicating effects on long-term health outcomes are needed.**

Effect of dietary protein on plasma insulin-like growth factor-1, growth, and body composition in healthy term infants: a randomised, double-blind, controlled trial (Early Protein and Obesity in Childhood (EPOCH) study).

Putet G, Labaune JM, Mace K, Steenhout P, Grathwohl D, Raverot V, Morel Y, Picaud JC.

Br J Nutr. 2016;115:271-84.

Protein and growth – EPOCH study

- **Aim**: to determine the effects of formula with different protein content on IGF-1 concentrations and growth.
- **Study design:** RCT
- **Population:** Healthy term infants, N=154

- **Intervention/Comparison**:

  Formula containing **1·8 g** *vs* **2·7 g protein/418·4 kJ** (100 kcal) exclusively for the first 4 mo of life.

Putet G et. al. Br J Nutr. 2016;115:271-84.

EPOCH study – RESULTS

- **The IGF-1 concentrations**:
  - **similar in lower and higher protein groups** at 4 mo

- **Lower anthropometric parameters in lower protein group** during the first 60 mo of life.
- Significant differences for:
  - head circumference (2 to 60 mo),
  - body weight at 4 and 6 mo
  - length at 9, 12 and 36 mo of age.

Putet G et. al. Br J Nutr. 2016;115:271-84

EPOCH study - CONCLUSIONS

- Increased **protein intake did not affect the IGF-1 concentration during the first 12 months of life.**

- **The effect on length and head circumference growth** suggests the role of other factors in determining growth velocity.

Putet G et. al. Br J Nutr. 2016;115:271-84

BREASTFEEDING and obesity

Plausible mechanisms of protective effect of BF against obesity:

- The role of hormones present in breast milk (leptin, adiponectin, ghrelin) in determining long-term appetite signalling.
- Better self-regulation of energy intake than in bottle-fed infants.
- Infant formulae contain more protein than breast milk.
- **Infant growth patterns**

Gillman MW; Int J Epidemiol. 2011

BREATSFEEDING duration and growth - what is known?

Two systematic reviews – search date 2011

Kramer et al.

- **No deficits have been demonstrated in growth** among infants exclusively BF for 6 months or longer

Hornell et al.

- **Slower weight gain** during the 2nd half of the first year, when exclusive BF for longer than 4 months

•*Hörnell A et al.. Food Nutr Res. 2013;57.*
•*Kramer MS et al.. Cochrane Database Syst Rev. 2012;(8):CD003517.*

Current evidence on BF duration and growth: a systematic review

AIM:

To systematically evaluate current evidence on the associations between duration of exclusive BF or any BF and growth in infancy.

- A **systematic review** of cohort studies, RCTs

- Electronic databases searched from Jan 2011 – Aug 2016:

  - Medline
  - Embase

BF duration and growth - Methods

Eligibilty criteria:

- **Population**: infants representing the general population
- **Exposure**: BF of any duration and pattern
- **Comparison**: different duration of BF
- **Outcomes**: growth parameters during the 1st year of life

BF duration and growth - RESULTS

- **3115 records** screened
- **16 studies** included

- **Population**
  - 11 studies - developed countries
  - 4 studies - developing countries
  - 1 study – mixed population

- **Risk of bias** assessed with the use of Newcastle-Ottawa scale
  - varying among the studies (ascertainment of exposure, outcome assessment, completeness of follow up)

Duration of exclusive BF

STUDY	SETTING	OUTCOMES	RESULTS
Agarwal	India n=71	Mean length and weight gain (0-18mo)	**Inverse association** (from 8 mo onwards)
Betoko	France n= 1239	WFA, LFA, WFL z-scores changes (0-4 mo)	**Inverse association**, statistically significant only for LFA
de Hoog	Netherlands n= 2998	Δ SDS for weight, length and WFL (4 weeks-6 mo)	**Inverse association**
Jensen	Denmark n=311	BMI growth curves (14 d - 19 mo)	Positive association with earlier peak in infant BMI and a lower prepeak velocity
Jonsdottir	Iceland n=119	WFA , LFA, BMI and HC z-scores (0-38 mo)	**No effects of EBF for 4 vs 6 mo** on the growth pattern
Kattula	India, n=497	Monthly height and weight gain (up till 2y)	**Inverse association**, but it was not statistically significant for weight gain
Queiroz	Brazilia n=489	Mean LFA z-scores during 1st y of life	**Positive association with linear growth**
Woo	USA, China, Mexico, n=365	WFA, LFA, BMI z-socres at 1y	**Inverse association with WFA**, but not LFA or BMI z-scores

WFA – Weight for age; LFA -lenght for age; HC – head circumference

Duration of any BF

- **12 cohort studies**
- **Setting**: developed countries (10 studies)

- **Linear growth**
  - **inverse association** in 5 studies, transient effect (3-6 mo) in 1 study
- **Weight gain / weight gain trajectory**
  - **inverse association** in 9 studies, transient effect (3-6 mo) in 1 study
- **BMI / BMI trajectories**
  - **inverse association** with higher BMI trajectories in 1 study, and with BMI z-scores - 2 studies
  - no effect in 1 study

BF duration and growth – CONCLUSIONS

Duration of EBF

- Length gain - inverse association in the majority of observational studies (but not in a single RCT)
- Weight gain, BMI - inconsistent results

Duration of any BF

- Consistent evidence for inverse association with different growth parameters in almost all studies

BF duration and growth

Infant Feeding and Growth

Can We Answer the Causal Question?

Michael S. Kramer,[a,b] Erica E. M. Moodie,[b] and Robert W. Platt[a,b]

Kramer et al.; Epidemiology. 2012 Nov;23(6):790-4.

Growth in infancy and later obesity

EARLY RAPID WEIGHT GAIN is associated with increased subsequent obesity risk

Being big or growing fast: systematic review of size and growth in infancy and later obesity

Janis Baird, David Fisher, Patricia Lucas, Jos Kleijnen, Helen Roberts, Catherine Law

Rapid growth in infancy and childhood and obesity in later life – a systematic review

. Monteiro[1] and C. G. Victora[2]

OPEN ACCESS Freely available online PLOS | ONE

Systematic Examination of Infant Size and Growth Metrics as Risk Factors for Overweight in Young Adulthood

Andrew O. Odegaard[1]*, Audrey C. Choh[2], Ramzi W. Nahhas[2], Bradford Towne[2], Stefan A. Czerwinski[2], Ellen W. Demerath[1]

1 Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota, United States c
Research Center, Boonshoft School of Medicine, Wright State University, Dayton, Ohio, United States of America

Rapid infancy weight gain and subsequent obesity: Systematic reviews and hopeful suggestions

KEN K. ONG[1,2] & RUTH J. F. LOOS[1]

Nutritional interventions or exposures in infants and children aged up to 3 years and their effects on subsequent risk of overweight, obesity and body fat: a systematic review of systematic reviews

B. Patro-Gołąb, B. M. Zalewski, M. Kołodziej, S. Kouwenhoven, L. Poston, K. M. Godfrey, B. Koletzko, J. B. van Goudoever, and H. Szajewska

Obesity Reviews 2016; doi: 10.1111/obr.12476

BREATSFEEDING and obesity – Systematic review of systematic reviews

9 systematic reviews

- A consistent association of BF with a modest reduction in later risk of overweight and obesity, but residual confounding cannot be excluded.
- **No conclusive evidence that exclusive BF, regardless of its duration, has a strong protective effect** on the later risk of overweight and obesity.
- **Some indications that BF of very short duration has a lesser protective effect than BF of longer duration**, although residual confounding cannot be excluded.

Patro-Gołąb & Zalewski et al.; Obesity Reviews 2016; doi: 10.1111/obr.12476

Conclusions

How infant feeding affect early growth?

- **Protein concentration in infant formula**
  - Some alterations in early growth reported
  - Inconsistent results between the studies
  - More high quality RCTs needed

- **BF duration**
  - Some evidence that longer duration of BF is protective against growth acceleration in weight and length
  - Residual confounding cannot be excluded

Conclusions

Can early growth predict later obesity?

- Rapid weight gain from 0-2 y associated with increased risk of later obesity

What is the link between protein content in infant formula, BF duration and later risk of obesity?

- Lowering the protein concentration in infant formulas - promising intervention
- BF of very short duration - some indications of lesser protective effect

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Thank you for your attention!

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