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The Importance of Achieving Healthy Growth in Infants & Children with Cow Milk Allergy:

The Role of Amino Acid-Based Formulas

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Disclosures

- Nutricia's speakers bureau

The opinions expressed by the speaker are independent of Nutricia North America

Upon completion, you should be able to:

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1. Define adequate and faltering growth in the infant and child population.
2. Discuss the impact cow milk allergy can have on growth.
3. Describe the role of amino acid-based formulas in the management and growth of infants and children with cow milk allergy.
4. Summarize the clinical evidence behind the use of amino acid-based formulas in achieving normal and catch-up growth.
5. Explain the clinical evidence for the components of amino acid-based formulas.

Normal growth in children age ≤2 years of age is based on WHO infant growth standards

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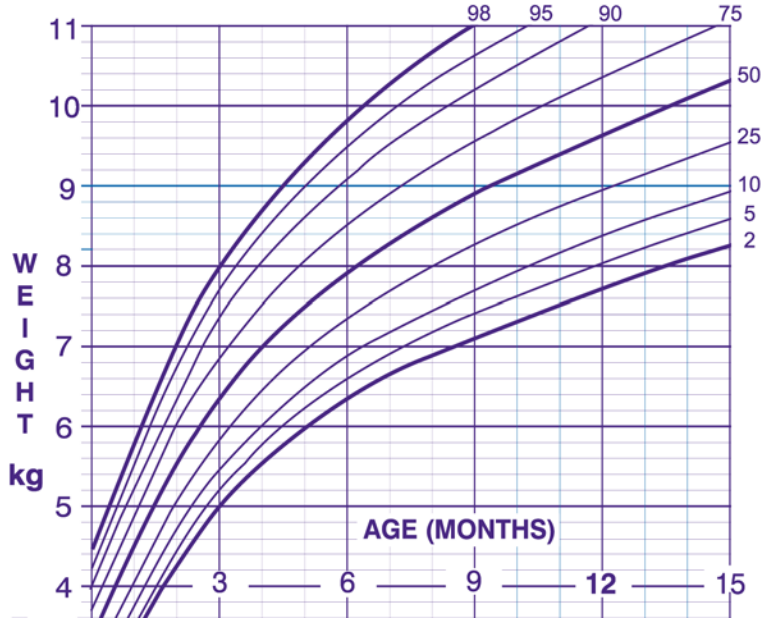
- Based on WHO 2006 infant 'growth standard'
- WHO Multicenter Growth Reference Study (MGRS)
- Criteria:
  - Exclusive breastfeeding x 4 months
  - Complementary foods by 4-6 months
  - Breastfeeding x 12 months
- Growth in children age 2 – 20 years is monitored using CDC 2000 growth reference charts



Growth of breastfed infants is the ‘standard’

- Formula-fed infants grow differently from breastfed infants
- WHO: 0–3 m breastfed infants gained weight slightly faster
- CDC: 3-24 m formula-fed infants grew faster and gained more weight

Grummer-Strawn, et al. MMWR Recomm Rep. 2010;59:1-15.

The WHO definition of malnutrition addresses three conditions

Malnutrition refers to deficiencies, excesses, or imbalances in a person's intake of energy and/or nutrients. It addresses 3 broad groups of conditions:

I. **Undernutrition**: wasting (low weight-for-height), stunting (low height-for-age) and/or underweight (low weight-for-age)

II. **Micronutrient-related malnutrition**: micronutrient deficiencies (a lack of important vitamins and minerals) or micronutrient excess

III. **Overweight, obesity and diet-related noncommunicable diseases:** increased risk for heart disease, stroke, diabetes and some cancers

https://www.who.int/news-room/fact-sheets/detail/malnutrition. Accessed May 5, 2019.

The first 1000 days are critical in human development

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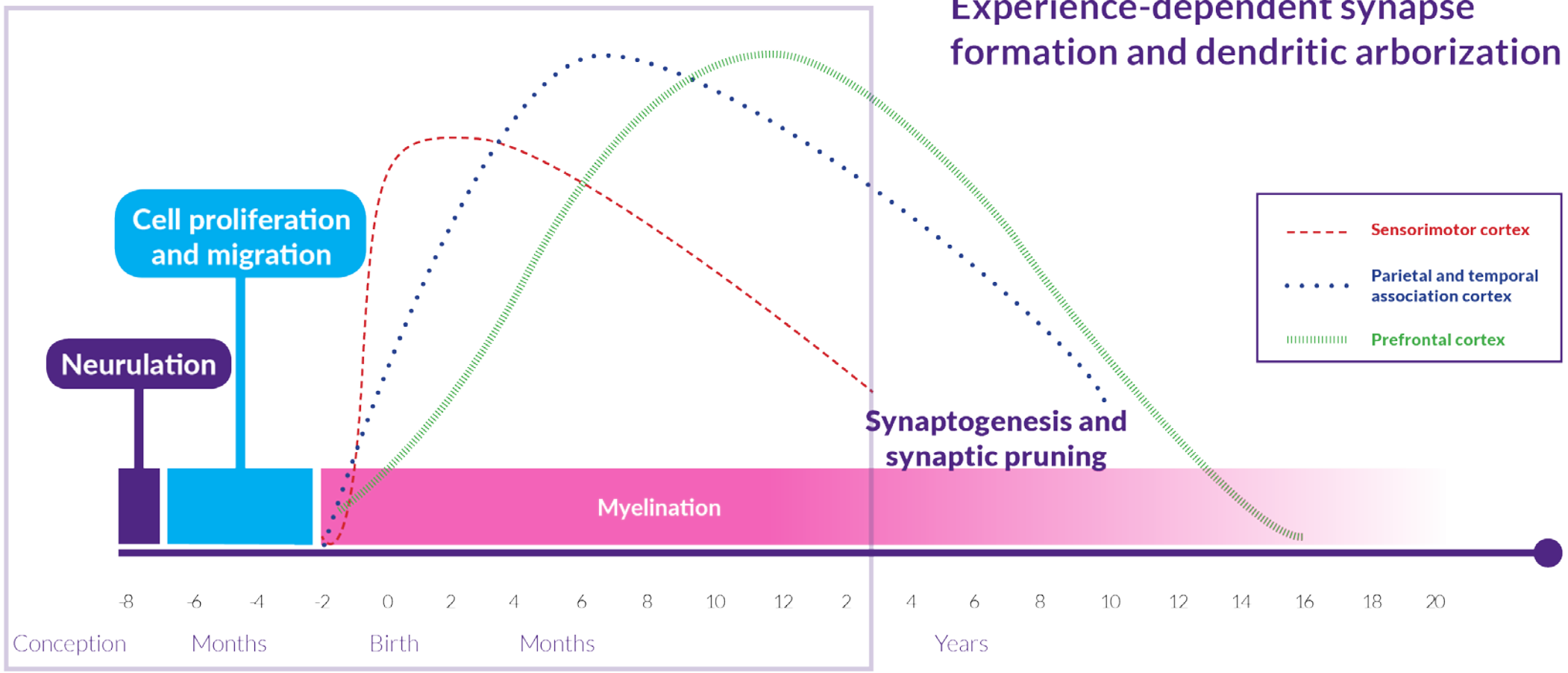
Developmental course of human brain development



Adapted from Casey et al, 2005.

1. Casey, et al. Trends Cogn Sci. 2005;9:104-10. **2.** Schwarzenberg, et al. Pediatrics. 2018;141.

Normal growth includes developing a healthy gut microbiome

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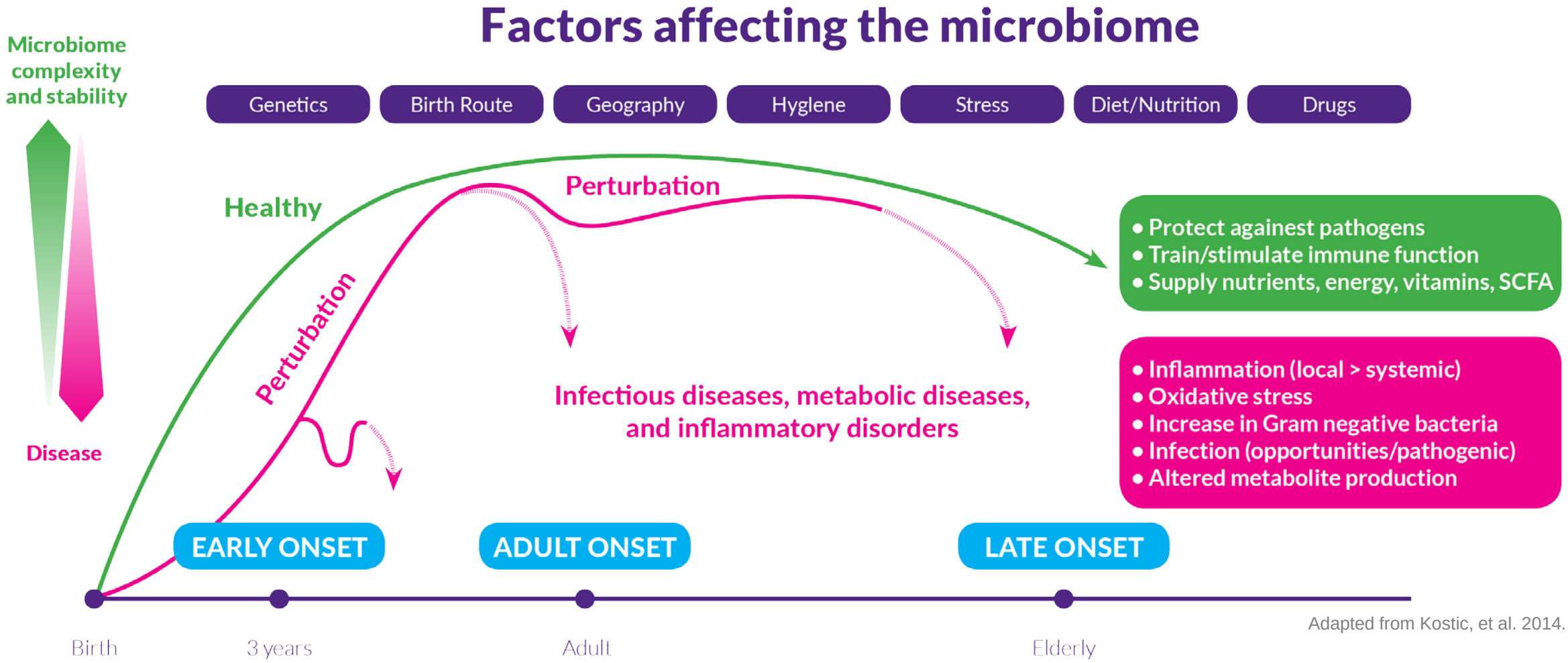

Adapted from Kostic, et al. 2014.

Kostic, et al. Gastroenterology 2014;146:1489-99.

There are 5 domains involved in nutrition assessment

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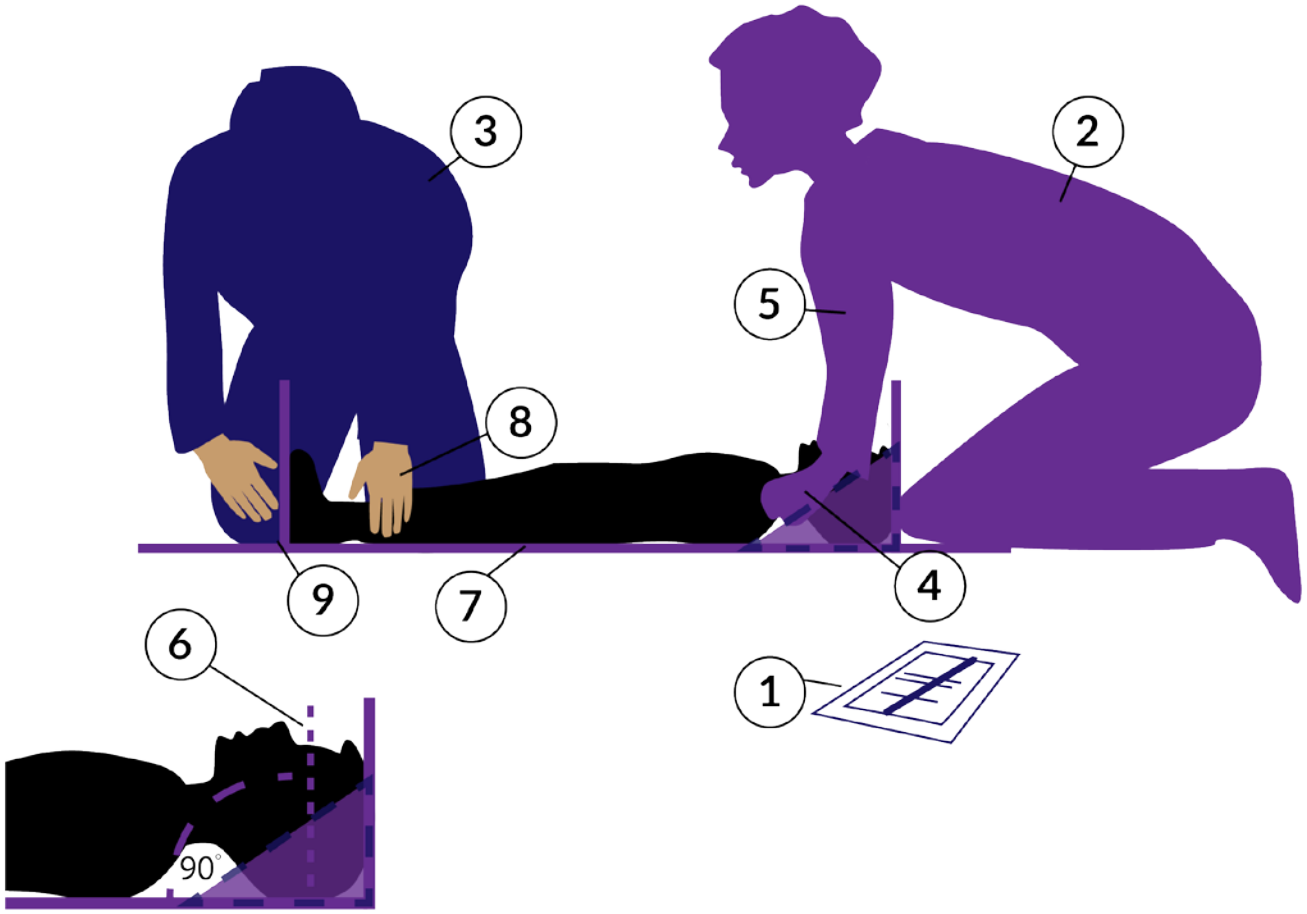
Domain	Assessment	Variables
A	Anthropometric variables	Weight, length/height, head circumference, BMI, growth charts, z-scores
B	Dynamism of growth	Z-score difference ≥0.67 is significant
C	Duration of growth/nutrition abnormalities	Acute (<3 months) Chronic (>3 months)
D	Etiology/pathogenesis of growth/nutrition abnormalities	Dietary intakes and mechanism of nutrition imbalance
E	Impact of growth/nutrition abnormalities on functional and development	

1. Mehta, et al. JPEN J Parenter Enter Nutr. 2013;37:460-81. 2. Monteiro, et al. Obes Rev. 2005;6:143-54.

Certain anthropometric techniques should be followed

Length ≤ 2 years of age:



1. Questionnaire and pencil on clipboard on floor or ground
2. Assistant on knees
3. Measurer on knees
4. Hands cupped over ears; head against base of board
5. Arms comfortably straight
6. Line of sight perpendicular to base of board
7. Child flat on board
8. Hand on knees or shins; legs straight
9. Feet flat against footpiece

Adapted from The Open University, Nutrition Module.

http://www.open.edu/openlearnworks/mod/oucontent/view.php?id=318&printable=1. Accessed May 5, 2019.

Certain anthropometric techniques should be followed

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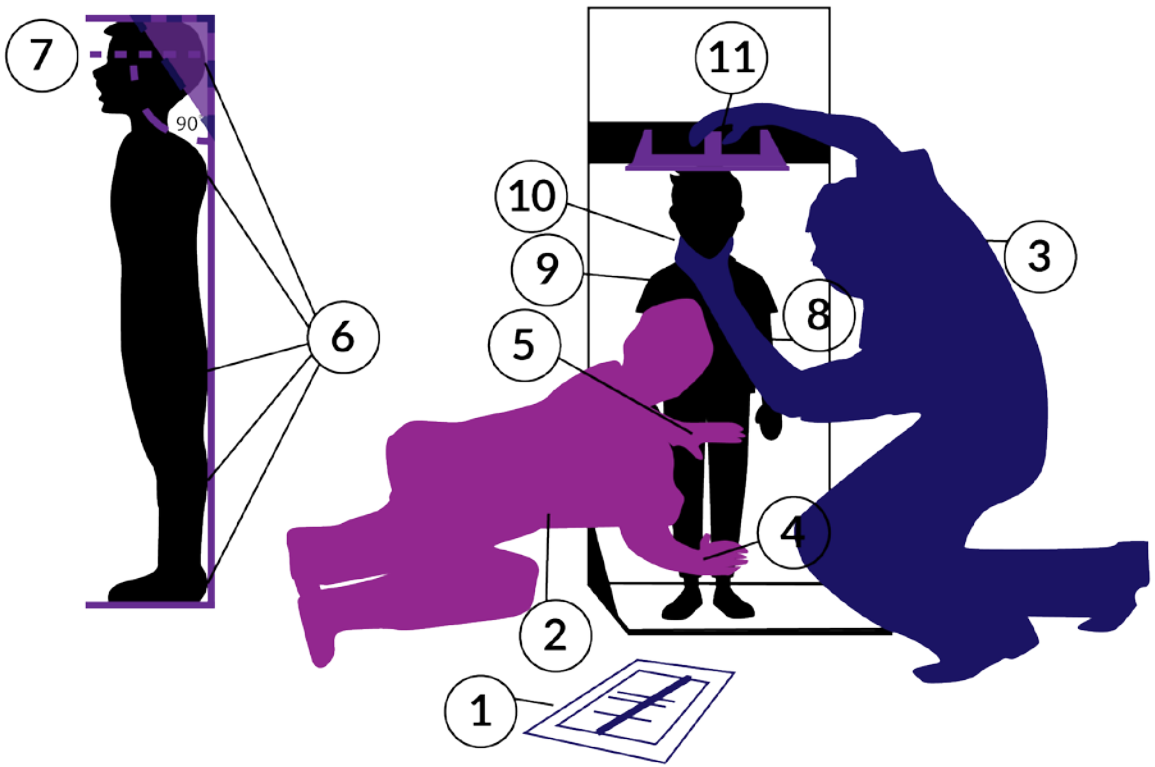
Height > 2 years of age:



1. Questionnaire and pencil on clipboard on floor or ground
2. Assistant on knees
3. Measurer on knees
4. Right hand on shins; heels against back and base of board
5. Left hand on knees; knees together against board
6. Body flat against board
7. Line of sight
8. Hands at side
9. Shoulders level
10. Hand on chin
11. Headpiece firmly on head

Adapted from The Open University, Nutrition Module.

http://www.open.edu/openlearnworks/mod/oucontent/view.php?id=318&printable=1. Accessed May 5, 2019.

Certain anthropometric techniques should be followed

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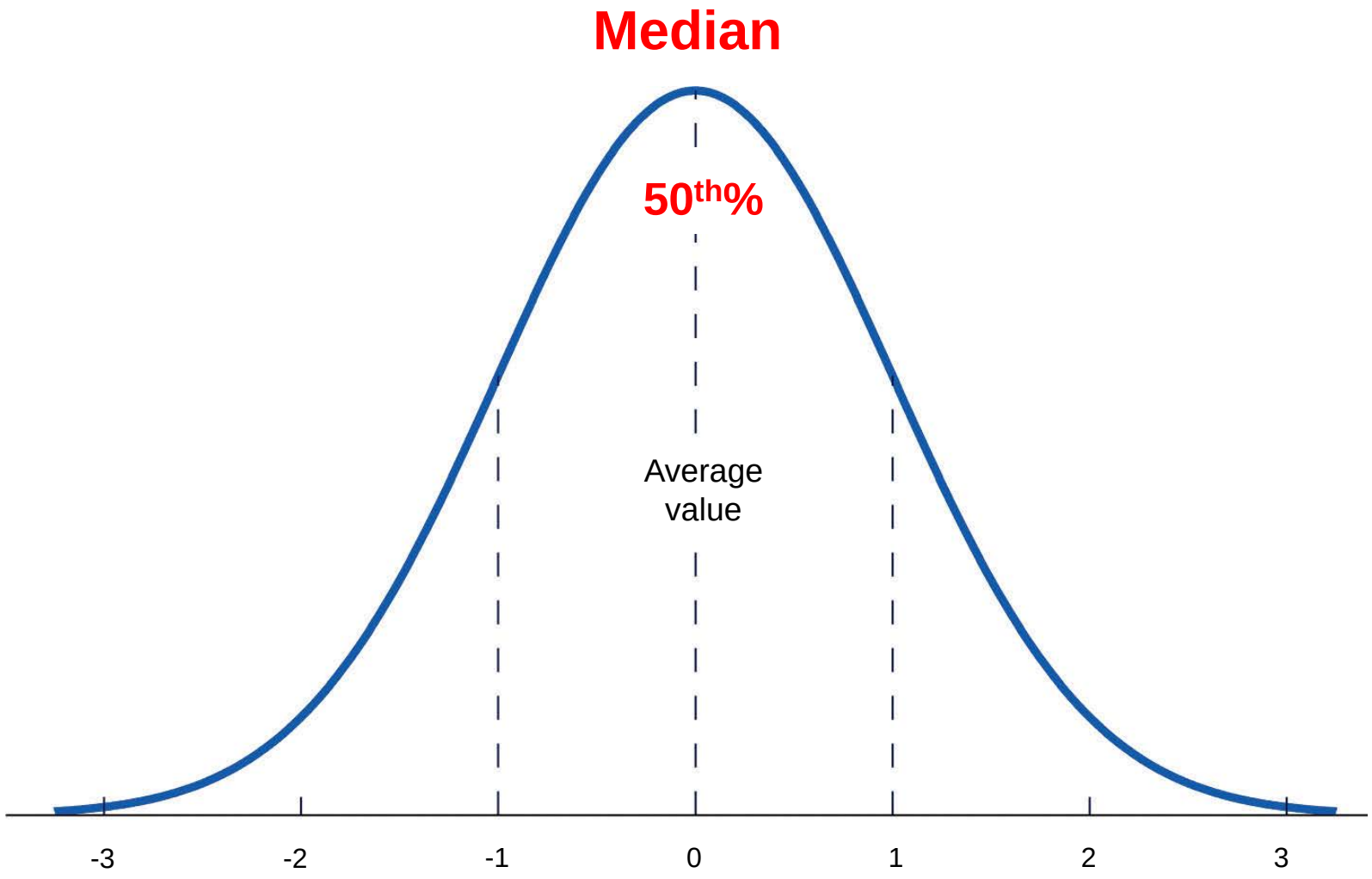
Head circumference ≤ 3 years of age:

There are differences in percentiles vs. Z-scores



Z-scores can be used to classify malnutrition

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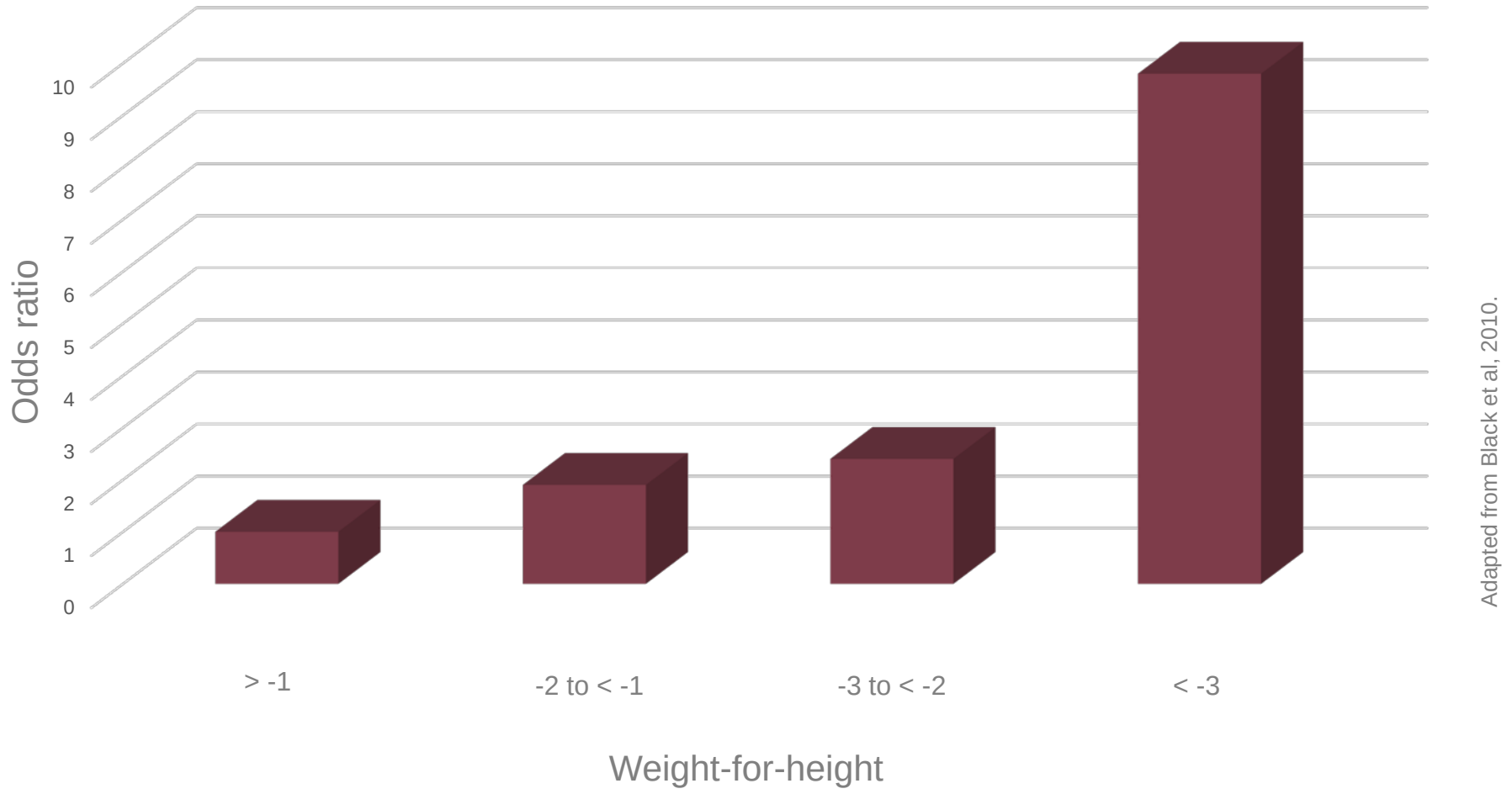
PERCENTILE	Z-SCORE	WEIGHT	WT-FOR-LENGTH/ BMI	LENGTH/HEIGHT
≥97th	≥2.0	Overweight	Obesity	Very tall
85th – 97th	1.0 to 2.0	Normal	Overweight	Normal
50th	0	Normal	Normal	Normal
3th – 16th	-2.0 to -1.0	Normal	Mild malnutrition	Normal
<3rd	-3.0 to -2.0	Moderate underweight	Moderate malnutrition	Moderate stunting
<<3rd	<-3.0	Severe underweight (acute/chronic)	Severe malnutrition (acute)	Severe stunting

Severe malnutrition is associated with mortality risk



Black, et al. Lancet. 2010;375:1969-87.

Cow milk allergy (CMA) is a common food allergy in infants

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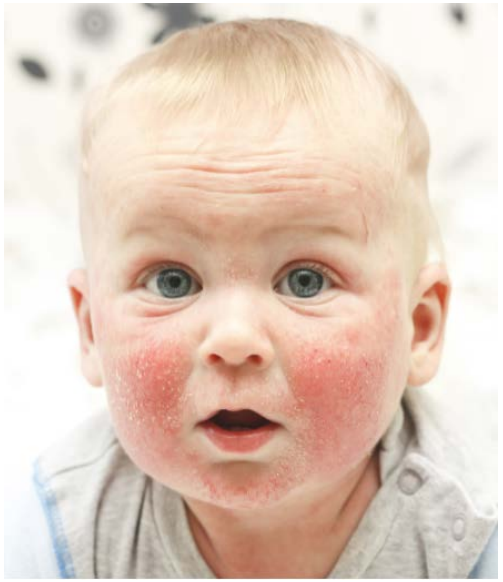
- Prevalence of CMA ranges from 2-3% of infants
- 53% of infants with food allergies have CMA
- Mechanism:
  - IgE-mediated
  - Non-IgE-mediated
  - Mixed
- Symptoms may be general or involve different organ systems:
  - Skin
  - Gastrointestinal tract
  - Respiratory tract
- Involvement of ≥ 2 organ systems increases the probability of CMA diagnosis



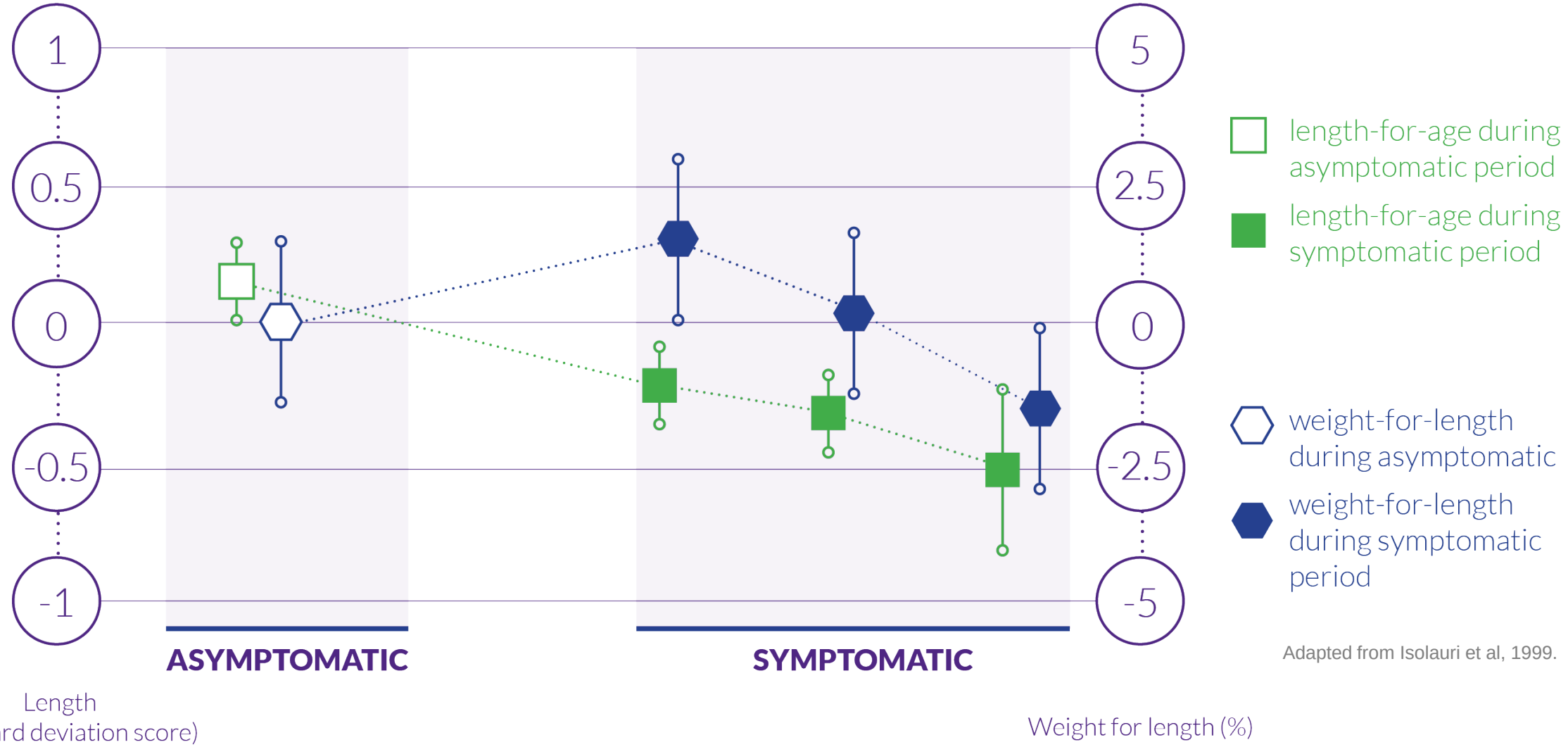
1. Warren, et al. Ann Allergy Asthma Immunol. 2018;121:S13. 2. Hill, et al. Clin Exp Allergy. 2007;37:808-22. 3. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9.

Clinical manifestations of CMA vary

	Immediate onset 1 – 4 hrs (IgE–mediated)	Later onset >12 h – several days (Non-IgE-mediated)
Skin (5-90%)	Angioedema, urticaria, atopic dermatitis/eczema	Atopic dermatitis/eczema, contact rash
Respiratory (20-30%)	Rhinoconjuctivitis, asthma (wheeze, cough), laryngeal edema, otitis media with effusion (eustachian dysfunction)	Pulmonary hemosiderosis (Heiner's syndrome)
Digestive (32-60%)	Oral allergy syndrome, nausea/vomiting, colic, diarrhea	Anorexia, abdominal pain, refusal to feed, frequent regurgitation, eosinophilic esophagitis, enterocolitis syndrome, colitis, protein losing enteropathy, FPIES, failure to thrive
General (0.8 – 9%)	Anaphylaxis, shock with metabolic acidosis: FPIES (non-IgE mediated)	Anemia, irritability, sleeplessness

1. Host, et al. Pediatr Allergy Immunol. 2002;13 Suppl 15:23-8. 2. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9.

Poor growth can occur during symptomatic CMA



Adapted from Isolauri et al, 1999.

Isolauri, et al. J Pediatr. 1999;134:27-32.

Malnutrition may occur through various mechanisms in CMA

Symptom	Mechanism
Inadequate intake	Dysphagia, feeding aversions, cricopharyngeal spasm, food refusal, gastroesophageal reflux (GER), vomiting, food impaction, restricted diets
Malabsorption	Milk protein enterocolitis, enteropathy, protein losing enteropathy, failure to thrive, weight loss
Feeding intolerance	Vomiting, diarrhea, meal-related chest and abdominal pain
General	Colic, sleeplessness, anemia

1. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. 2. Host, et al. Pediatr Allergy Immunol. 2002;13 Suppl 15:23-8.

An algorithm should be followed when diagnosing CMA

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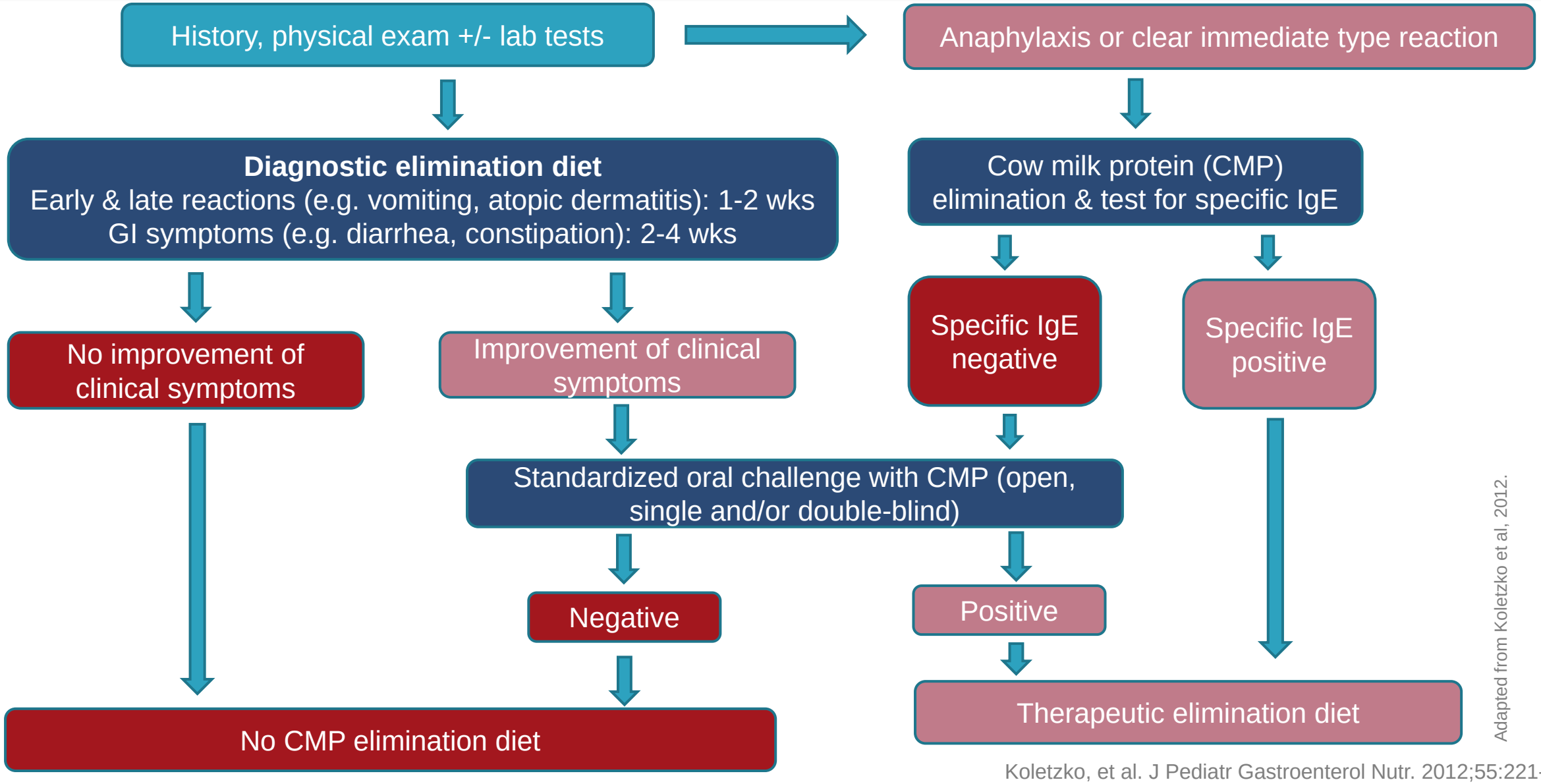

Adapted from Koletzko et al, 2012.

Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9.

Infants with complicated CMA may require amino acid-based formula (AAF)

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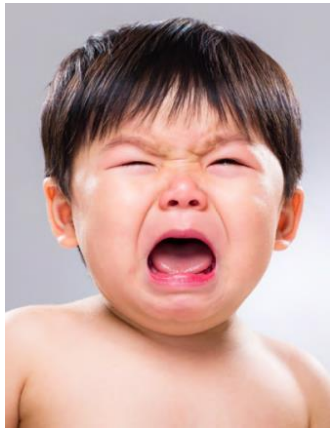
- Breastfed infants: Maternal elimination diet may be required. Should be under the supervision of a health care professional.
  - Milk (dairy) and all milk products
- Non-breastfed infants: Change to extensively hydrolyzed formula (eHF)
- 2-10% of infants with uncomplicated CMA will not tolerate eHF thus require AAF
- 40% of infants and children with complicated CMA require AAF



1. Hill, et al. Clin Exp Allergy. 2007;37:808-22. 2. Koletzko, et al. J Pediatr Gastroenterol Nutr. 2012;55:221-9.

There are several indications for use of AAF for infants and children with CMA

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- Anaphylaxis
- Symptoms not fully resolved on eHF
- Faltering growth
- Requirement for multiple food eliminations
- Symptoms while breastfeeding
- Severe eczema
- Severe gastrointestinal symptoms
- Eosinophilic esophagitis (EoE)
- Food protein-induced enterocolitis syndrome (FPIES)

1. Fiocchi, et al. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125. 2. Meyer, et al. J Allergy Clin Immunol Pract. 2018;6:383-99.

There are regulatory requirements in place for all infant formulas in the US

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- Must have been demonstrated to support growth with a well-controlled growth monitoring study
- Specific nutrient specifications must be followed
- Other requirements including but not limited to labeling & good manufacturing practices

1. U.S. National Archives and Records Administration. 21CFR106.96. 2018. 2. U.S. National Archives and Records Administration. 21CFR107.100. 2018.

AAFs resolve symptoms and promote adequate growth

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Reference	Population/diagnosis	Intervention	Growth & symptom outcomes

Isolauri et al, J Peds 1995	• Breastfed/formula-fed infants
	• Age: 5.5 ± 1.5 mo
	• Atopic dermatitis/eczema
	• CMA, (+)DBPC challenge
	• N = 45
		Breast milk/formula → AAF vs. eHF
		
		Follow-up x 9 mo
			• AAF fed (n = 23)
			• Relative weight:
			  • ↑ 6% compared to baseline
			• LAZ:
			  • -0.3±0.4 → ~0.7±0.3
			• SCORAD: Δ p = 0.0001

Isolauri et al, J Peds 1999	• Breastfed infants • Age: 6 ± 4 mo • Atopic dermatitis/eczema • Faltering growth • N = 100	Breast milk → AAF	• Pre Rx: LAZ, -0.5±0.29 • Post Rx: LAZ 0.12±0.24 p = 0.006 • SCORAD: Δ p = 0.001
Hill et al, J Peds 1999	• Infants w/ hx CMA • Age: 7.3±0.76 mo • Rx eHF c/o irritability, vomiting, diarrhea, atopic dermatitis • N = 18	Soy or eHF → AAF Follow-up x 3 years	Significant FTT: • Pre Rx: WAZ, -2.4 • Post Rx: WAZ,-0.4 • Symptoms: ↓

1. Isolauri, et al. J Pediatr. 1995;127:550-7.2. Isolauri, et al. J Pediatr. 1999;134:27-32. 3. Hill, et al. J Pediatr. 1999;135:118-21.

AAFs resolve symptoms and promote adequate growth

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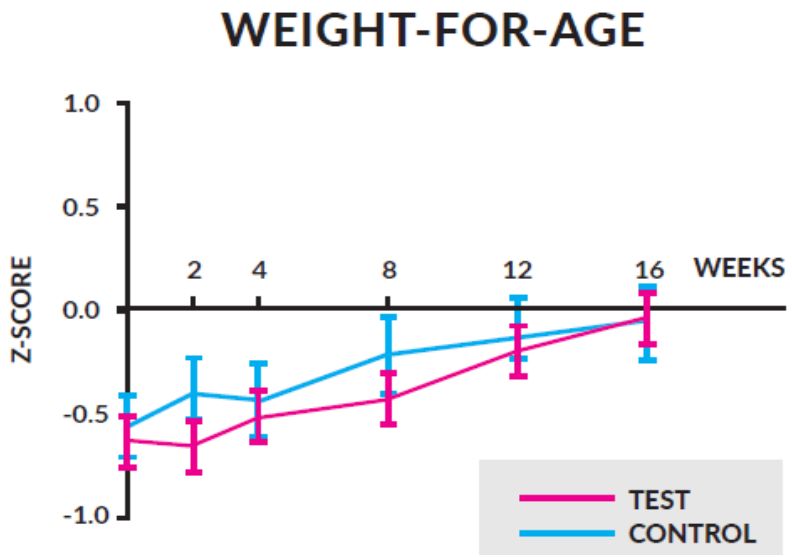
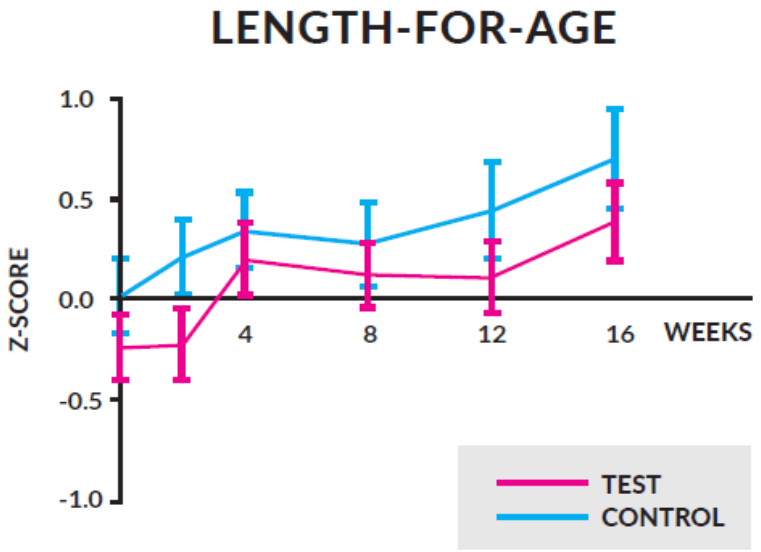
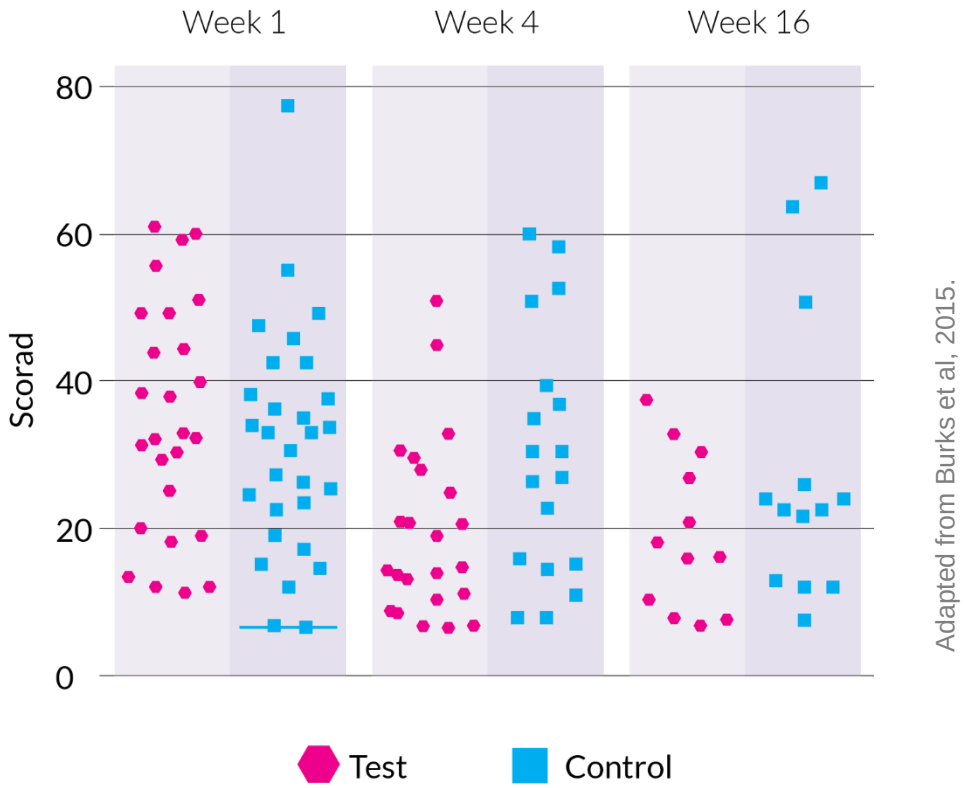
Reference	Population/diagnosis	Intervention	Growth & symptom outcomes
De Boissieu et al, J Peds 2002	• Infants hx CMA • Age: 5.3±3.8 m • Persistent sx on eHF • N = 52	eHF → AAF	• Pre Rx: WAZ: -1.04 ±1.45 • Post Rx: WAZ, -0.02 ±1.16 p < 0.001
Burks et al, Peds Allerg Immunol 2015	• Infants w/ confirmed IgE or non-IgE-mediated CMA • Age: 4.58±2.45 m • (+) DBPC challenge • (+) SPT > 6 mm • N = 110	Randomized to: AAF + DHA/ARA (control group) vs. AAF + DHA/ARA + synbiotics (test group) x 16 weeks	• Baseline: Similar WAZ, LAZ, HCZ • 16 weeks: Both groups improved in WAZ: +0.147 • No group differences in rate of WAZ, LAZ & HCZ • SCORAD: ↓ in both

1. de Boissieu, et al. J Pediatr. 2002;141:271-3. 2. Burks, et al. Pediatr Allergy Immunol. 2015;26:316-22.

Growth and symptom resolution outcomes of AAF + specific synbiotics vs. AAF







Adapted from Burks et al, 2015.

- AAF + synbiotics had similar growth outcomes as AAF

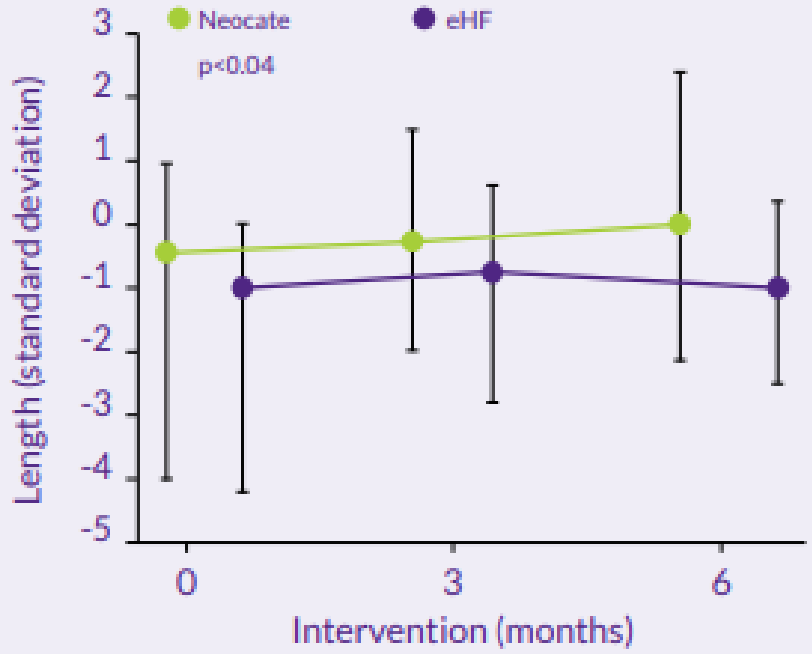
Burks, et al. Pediatr Allergy Immunol. 2015;26:316-22.

Growth outcomes on AAF vs. eHF are similar

	AAF (n=42)	eHF (n=31)	p-value
Gender (F/M)	13/29	11/20	NS
Age (months)	5.5	5.7	NS
Total IgE (kU/l)	16.0	30.0	NS
Specific IgE to CM positive	22 (52%	15 (48%)	NS
SCORAD	18.5	14.7	NS
Family hx of atopy	36 (86%)	26 (84%)	NS

Patient background data at time of trial entry

Length data during management with eHF versus AAF (median and standard deviation range)

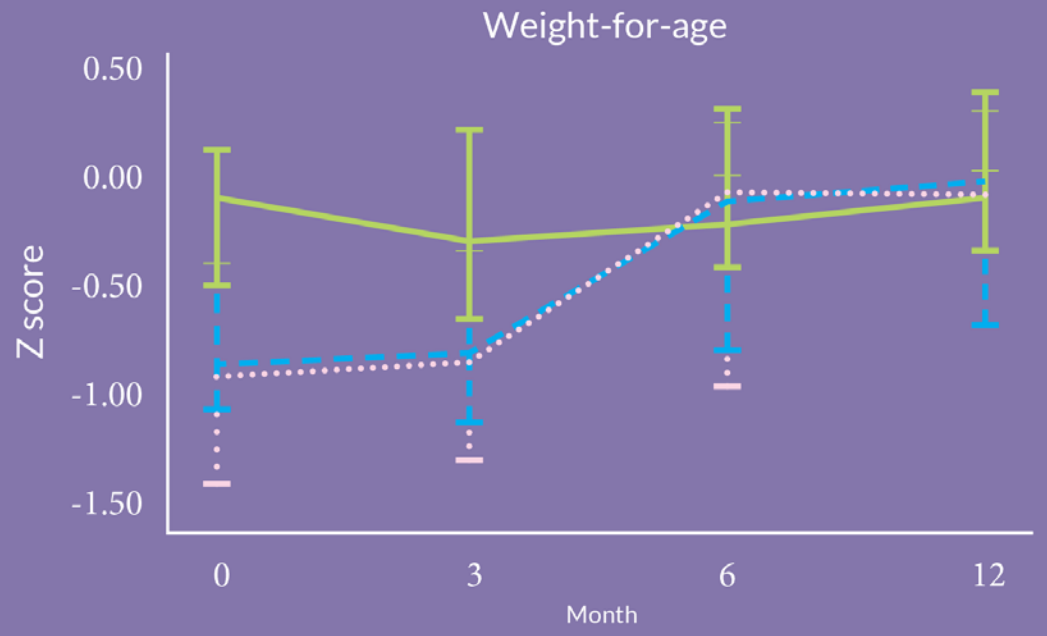


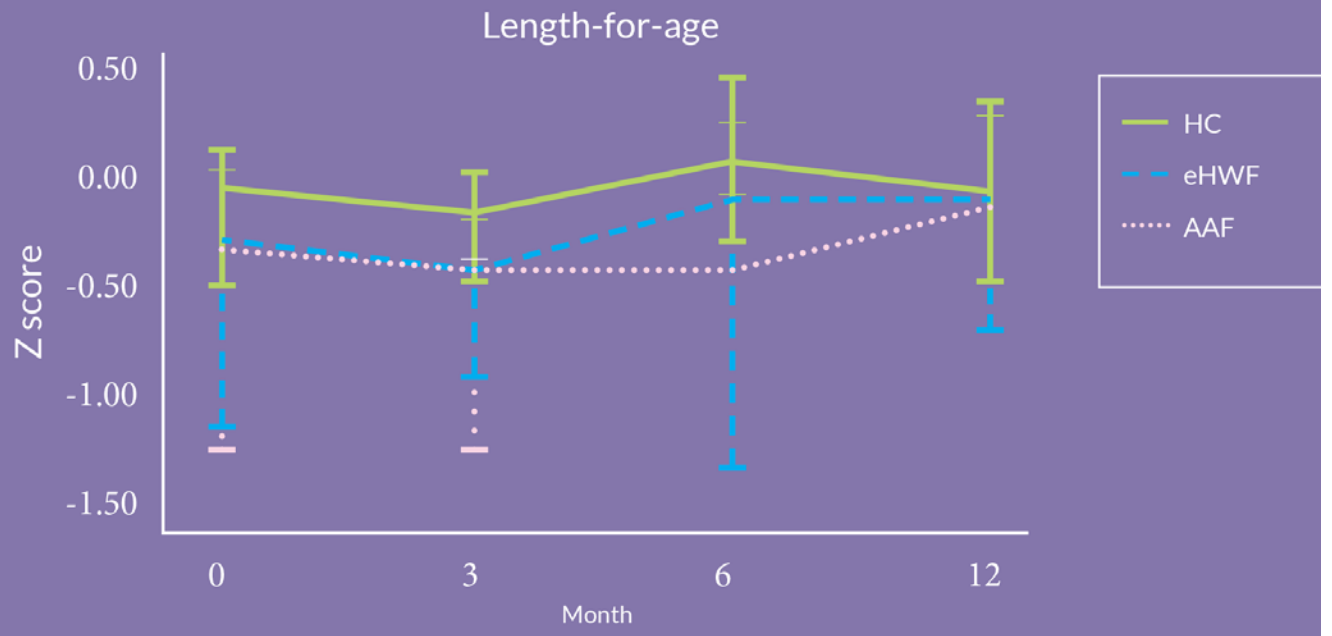
Adapted from Niggemann, et al. 2001.

Niggemann, et al. Pediatr Allergy Immunol. 2001;12:78-82.

AAF promotes normal growth comparable to healthy infants

	Subjects with CMA managed with AAF (n=21)	Subjects with CMA managed with eHWF (n=19)
Male, n (%)	13 (61.9)	11 (57.9)
Age, mo (±SD)	6.5 (1.5)	7 (1.7)
Duration of breastfeeding, mo (±SD)	4.3 (1.6)	5 (2)
Age of weaning, mo (±SD)	4.9 (0.9)	5.3 (0.6)

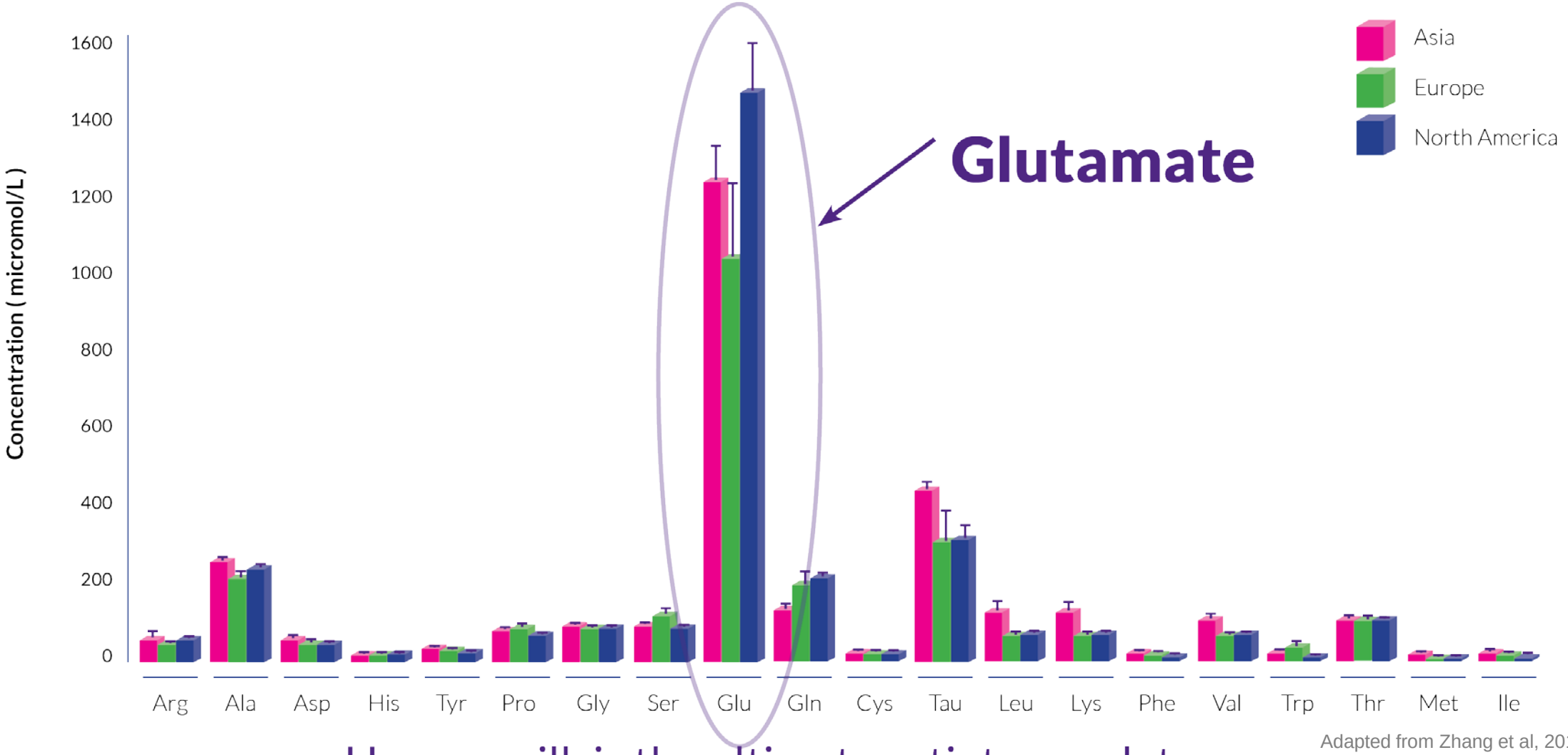




Adapted from Berni Canani et al, 2017.

Berni Canani, et al. J Pediatr Gastroenterol Nutr. 2017;64:632-8.

Free amino acids are present in breast milk



Adapted from Zhang et al, 2013.

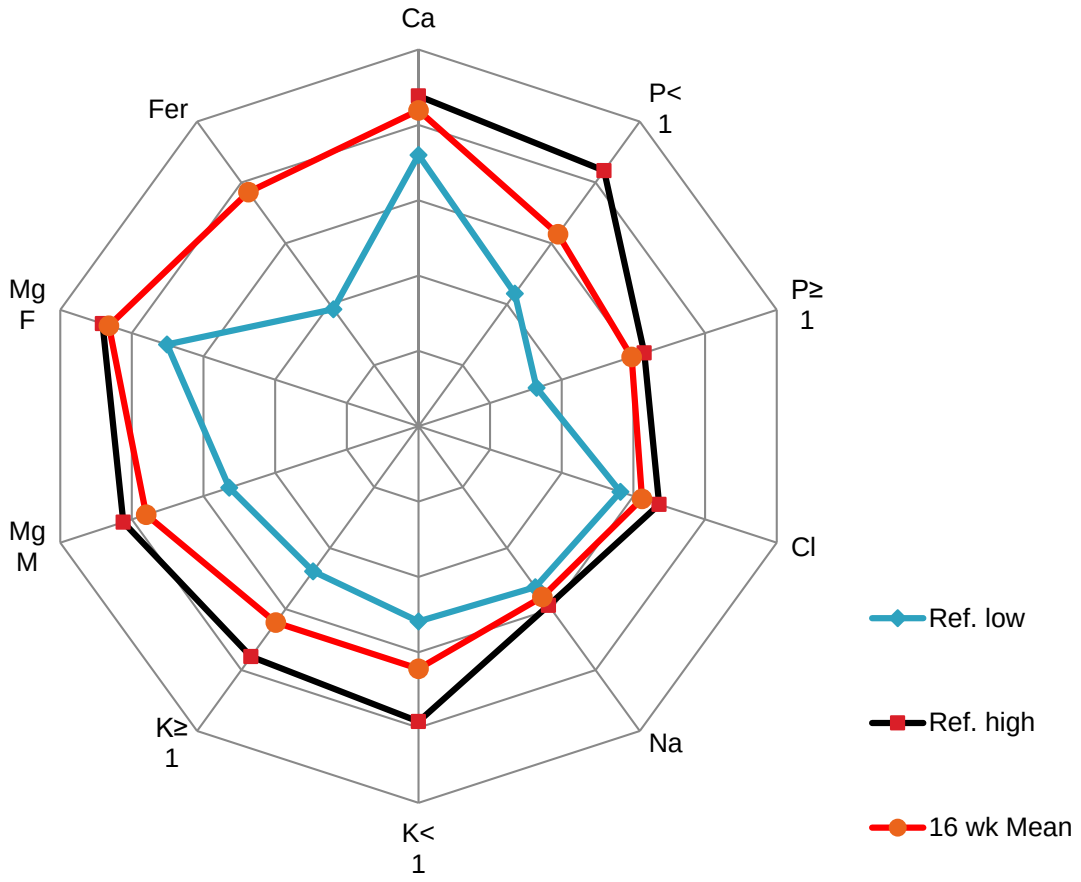
Human milk is the ultimate satiety regulator

1. Zhang, et al. Nutrients. 2013;5:4800-21. 2. Agostoni, et al. J Pediatr Gastroenterol Nutr. 2000;31:508-12.

Adequate mineral status is maintained by infants with CMA consuming AAF

Mean blood chemistry parameters after 16 weeks on AAF (n = 66) and number of subjects with mineral status below the reference range.

Mineral	Reference range	After 16 weeks on AAF, Mean ± SD
Calcium (Ca), mmol/L	2.25-2.74	2.62 ± 0.14
Phosphorus <1 y (P<1), mmol/L	1.36-2.62	1.97 ± 0.20
Phosphorus ≥1 y (P≥1), mmol/L	1.03-1.97	1.86 ± 0.24
Chloride (Cl), mmol/L	94-112	104 ± 2.3
Sodium (Na), mmol/L	132-147	140 ± 2.3
Potassium <1 y (K<1), mmol/L	3.7-5.6	4.6 ± 0.29
Potassium ≥1 y (K≥1), mmol/L	3.4-5.4	4.6 ± 0.48
Magnesium Male ≥30 d (Mg M), mmol/L	0.66-1.03	0.95 ± 0.07
Magnesium Female ≥30 d (Mg F), mmol/L	0.78-0.98	0.96 ± 0.07
Ferritin (Fer), mcg/L	≥12	24 ± 18



Harvey, et al. J Pediatr Gastroenterol Nutr. 2017;65:346-9.

Establishing a balanced gut microbiota in early life is important

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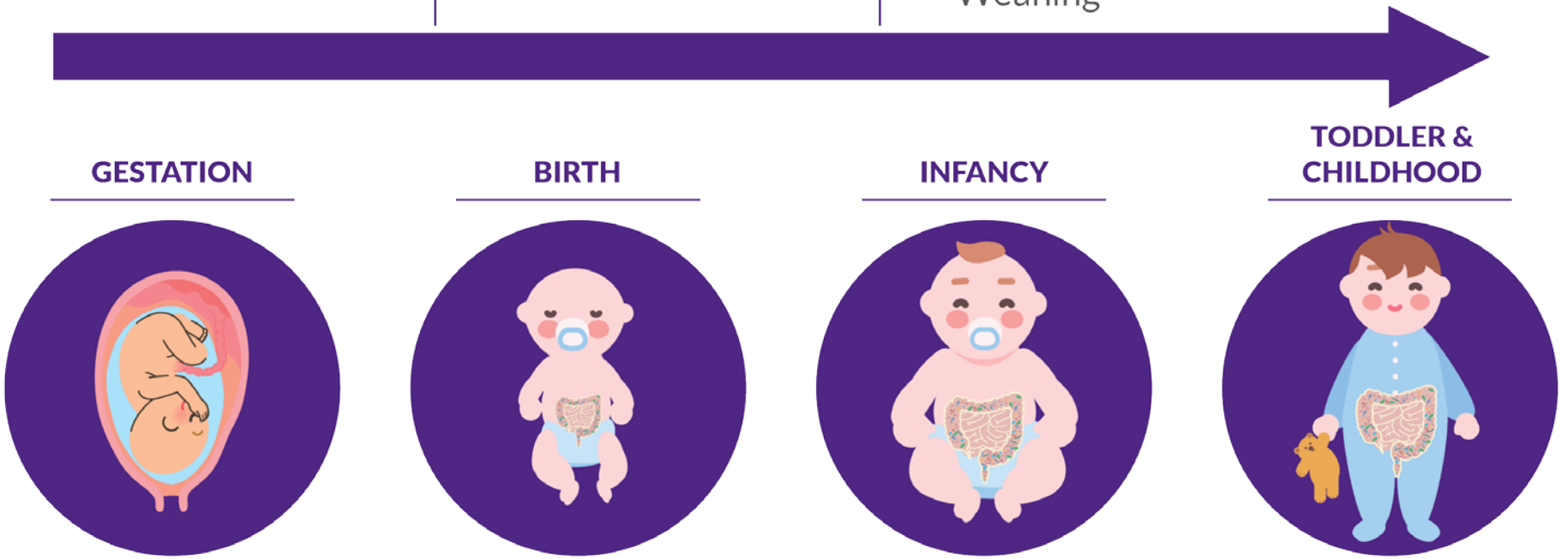
Window of opportunity for microbiota modulation

Prenatal factors:
Placenta

Neonatal factors:
Mode of delivery
Gestational age

Neonatal factors:
Feeding: breast milk vs. formula
Geographical location
Family members
Host interactions
Maternal diet
Weaning



Adapted from Milani et al, 2017.

Milani, et al. Microbiol Mol Biol Rev. 2017;81:e00036-17.

Microbe contact begins in utero and through breast milk

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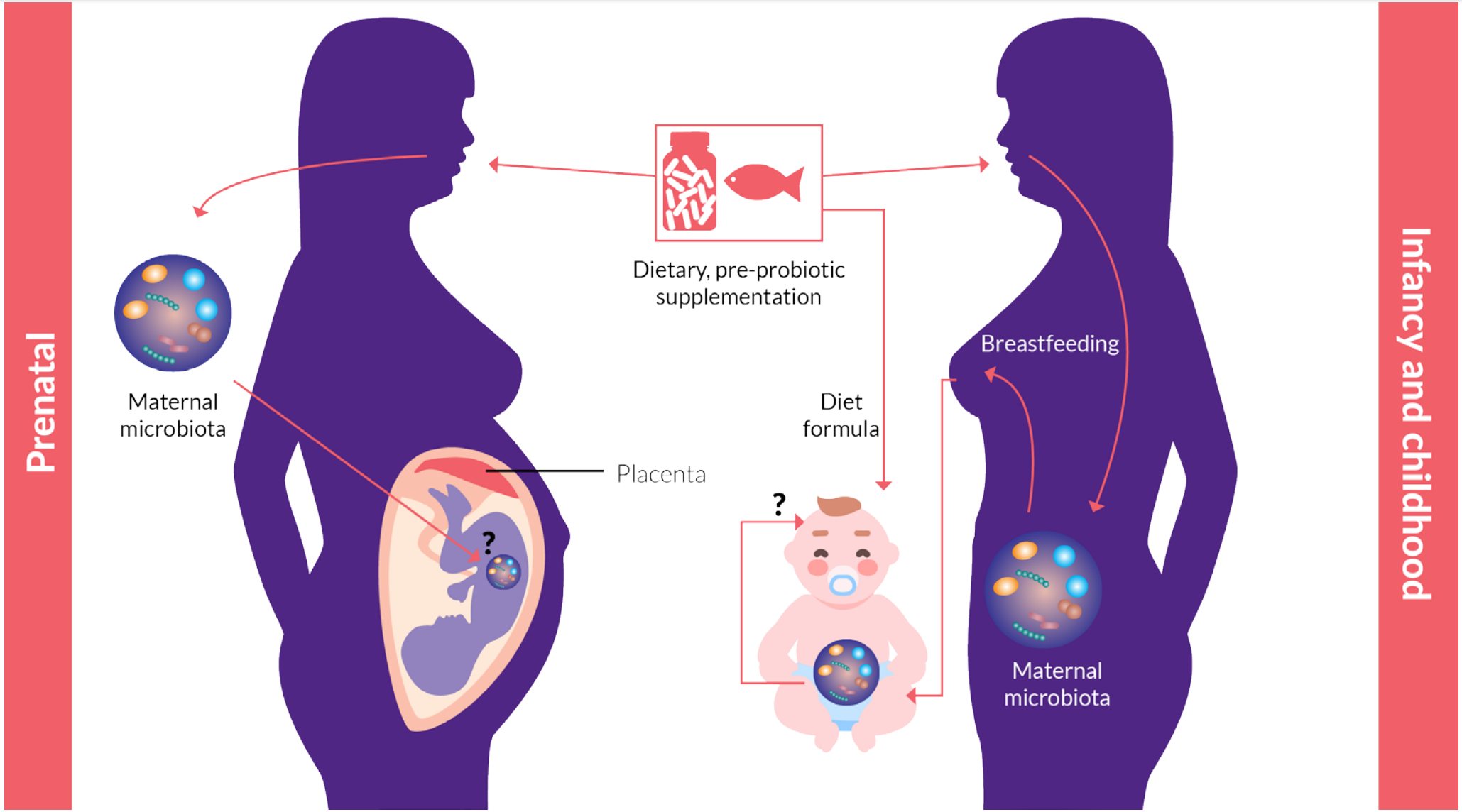
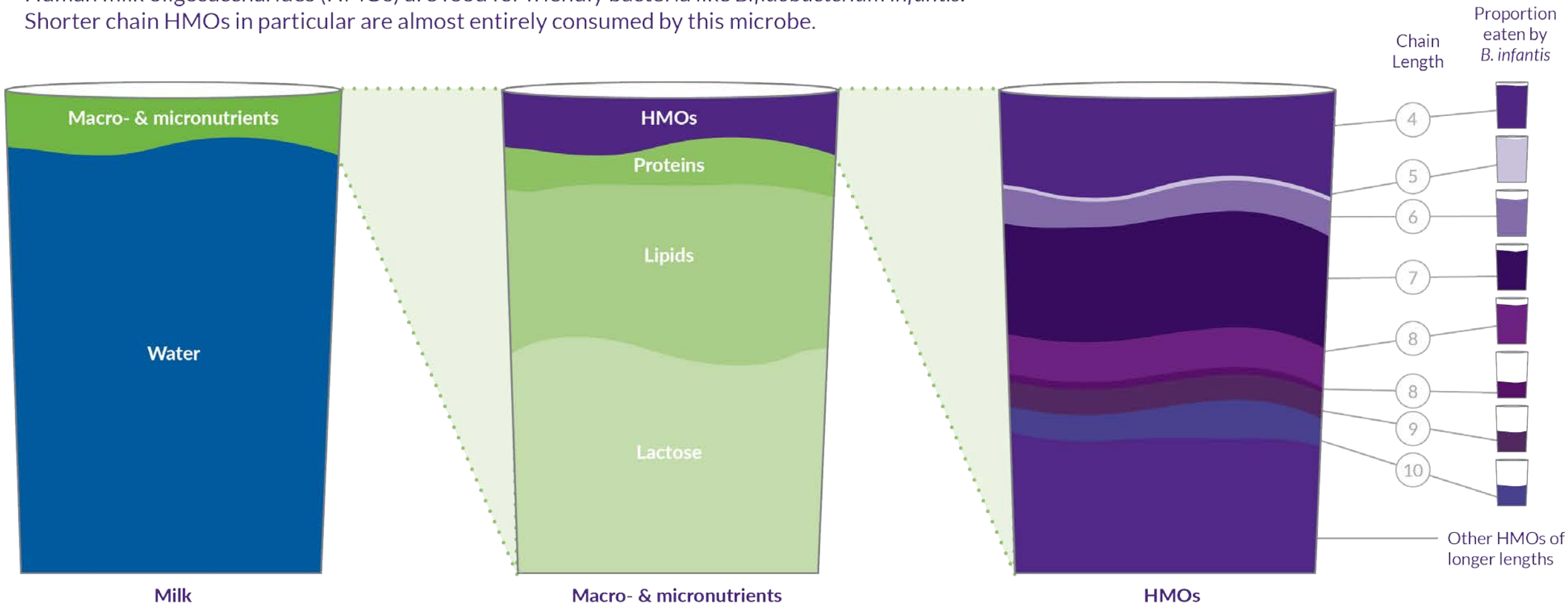


Adapted from Borre et al, 2014.

Borre, et al. Trends Mol Med. 2014;20:509-18.

Human milk is the ultimate synbiotic

Human milk oligosaccharides (HMOs) are food for friendly bacteria like *Bifidobacterium infantis*.
Shorter chain HMOs in particular are almost entirely consumed by this microbe.



Adapted from Petherick, 2010.

Petherick. Nature 2010;468:S5-7.

AAF with specific synbiotics aims to eliminate allergens for active management of cow milk allergy

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Maximal allergen elimination

- Hypoallergenic formula
- 100% free amino acids
- 0 -12 months

+

Helps to address underlying gut dysbiosis

- **scFOS / lcFOS** (9:1 ratio)
  - 0.63g / 100 ml
  - No GOS (to avoid cow milk protein contamination)
- ***Bifidobacterium breve* M-16V**
  - 10^8 CFU/g powder
  - Processed in a milk-protein free environment

AAF + specific synbiotics promotes sustained bifidobacteria growth and reduces *Eubacterium / Clostridia*, similar to breastfed infants

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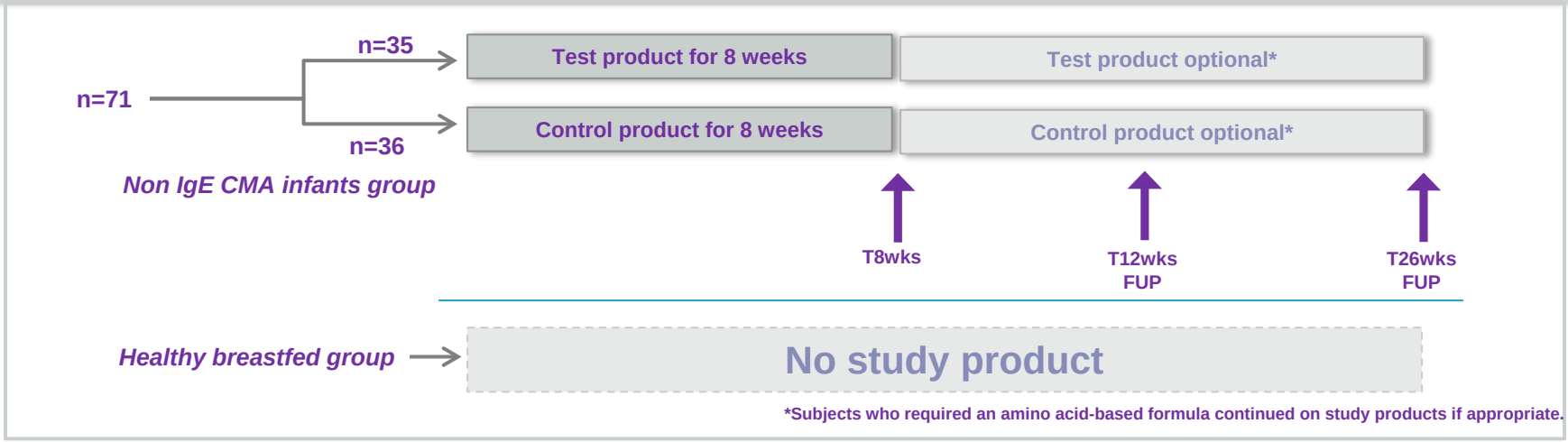
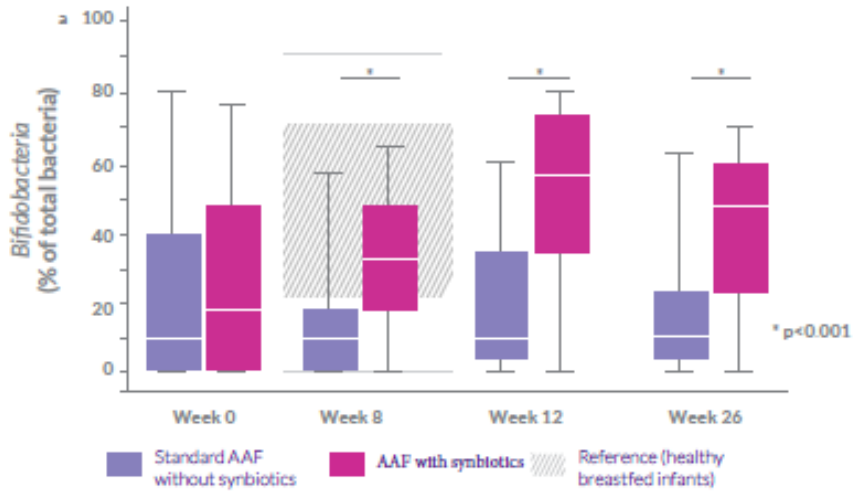
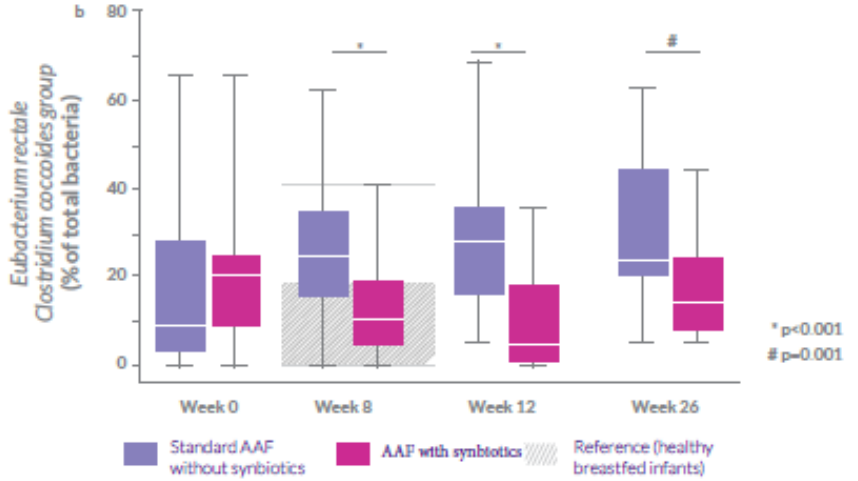


Bifidobacterium species in fecal microbiota



E. rectale / C. coccoides cluster in fecal microbiota



Fox, et al. Clin Transl Allergy. 2019;9:5.

Key takeaways

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- The standard for healthy growth is based on healthy breastfed infants
- Growth should be assessed and monitored using z-scores
- Growth deficits should be addressed as early as possible to optimize long-term outcomes
- Infants and children with CMA are at risk of faltering growth, particularly poor linear growth
- Delayed dietary intervention is a major risk factor for malnutrition in infants and children with CMA

Key takeaways (continued)

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AAF is recommended where there is faltering growth in CMA, arising from eHF failure, severe gastrointestinal symptoms and multiple food allergy

AAF reverses symptoms of persistent/complicated CMA

Extensive, published evidence-based studies on AAF have been carried out over the last 25 years demonstrating efficacy in achieving normal and catch-up growth

AAF supports adequate mineral status in infants with CMA

AAF with synbiotics reverses dysbiosis in children with CMA and supports an intestinal microbiota similar to breastfed infants

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Thank you!

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