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BIOTICS AND LIPIDS IN THE F1000 DAYS: A UNIQUE WINDOW OF OPPORTUNITY TO SHAPE THE FUTURE

Congress report



Contents

Biotics & Lipids in the F1000 Days: A Unique Window of Opportunity to Shape the Future

BY PROF. **BERTHOLD KOLETZKO**

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Nutrition in the first 1,000 days is important for long term health. There are increasingly more observational and randomized controlled trials, with longer term follow up, highlighting the link between diet in pregnancy and early childhood with metabolic response and subsequent health outcomes.

There are 2 major health challenges that children face today:

1) The increased burden of non-communicable diseases (NCDs)*

2) The increased disparity of health

NCDs are the cause of 90% of deaths, and 85% of the years lived with a disability in Europe today.[1]

Malnutrition is the leading cause for the global loss of disability-adjusted life in years; overweight, dietary risk and malnutrition combined contribute more than high blood pressure, smoking and dysglycemia.[1] The window of opportunity to improve long term health outcomes is during the sensitive time of developmental plasticity during the first 1,000 days of pregnancy and the first 2 years of life.

Growth rate is rapid during the first 1,000 days and in particular, the immune system and brain, have an extremely fast growth rate during the last part of pregnancy and early childhood. The opportunity is not only for metabolic health (such as obesity), but also in modifying immunity and related disorders and brain development. Only by understanding the different mechanisms, will we be able to have more targeted, and more effective interventions.

*Noncommunicable diseases (NCDs), also known as chronic diseases, tend to be of long duration and are the result of a combination of genetic, physiological, environmental and behavioural factors. The main types of NCD are cardiovascular diseases (such as heart attacks and stroke), cancers, chronic respiratory diseases (such as chronic obstructive pulmonary disease and asthma) and diabetes.

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Next Generation Biotics: Pre-, Post- and Postbiotics, What Do We Know?

BY PROF. **HANIA SZAJEWSKA**

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Exclusive breastfeeding for around 6 months is a desirable goal, but partial breastfeeding, as well as breastfeeding for shorter periods of time are valuable.[2]

Micro, macronutrients, and components with bioactivity in breastmilk are often discussed. The overly simplistic approach to analysing single, mostly nutritive components in human milk is insufficient to understand the contribution of either individual components or the matrix within which they exist to both maternal and child health.[3]

Exclusive breastfeeding rates until 6 months of age are currently around 41%. The World Health Assembly 2025 target is to reach 50%.[4] However, there will always will be a need for human milk substitutes, no matter how successful the promotion of breastfeeding may be. There are no safety concerns regarding growth and adverse effects of human milk substitutes, but there are known differences between breastfed and formula-fed infants with respect to short- and long-term health outcomes. One such difference is the difference in the gut microbiota composition, especially Bifidobacterium.[5]

The composition of the gut microbiota changes throughout life, particularly in early life this is important. There are many factors influencing neonatal colonization such as duration of gestation (i.e., preterm delivery), mode of delivery (i.e., being born by cesarean section), mode of feeding (i.e., no breastfeeding), environment (i.e., spending time in the NICU), use of medication (i.e., antibiotics) which can all lead to the dysbiosis of the gut microbiota.

Dysbiosis is the disturbance of the number and function of gut microbiota. The use of “biotics” could be a strategy to modulate gut microbiota.

There have been 4 expert consensus papers on biotics by the International Scientific Association of Probiotics and Prebiotics (ISAPP) addressing each of the following:

1) Probiotics[6]
2) Prebiotics[7]
3) Synbiotics[8]
4) Postbiotics[9]

Probiotics

Probiotics are living microorganisms that, when administered in adequate amounts, confer a health benefit to the host.[6] However, there are differences in the health benefits they bring, depending on the genus, species, and strain; dose, safety, quality, and evidence.

ESPGHAN calls for mandatory, quality-control procedures for specific clinical situations, and for the use in vulnerable populations such as, infants and children.[10] The most appropriate probiotic differs per population and situation. Professionals should support patients to make the appropriate choice for their situation.

Nowadays, it is quite common that infant formulas are supplemented with probiotics aimed at supporting a healthy infant microbiome.

In the systematic review of Skorka et al., 2017,[12] there were fewer antibiotic prescriptions given to children who had been fed with a probiotic-supplement infant formula. The intake of antibiotics can have several adverse effects on gut microbiota. An association of the use of antibiotics in early life with several distinct health conditions with childhood onset exist; interventions to reduce the use of antibiotics are worth considering.[13]

In conclusion,

- the administration of currently evaluated probiotic-supplemented infant formulas does not raise safety concerns with regards to growth and adverse outcomes,
- the efficacy and safety should be considered for each probiotic(s)-supplemented formula separately, and
- some favourable clinical effects are possible.[11, 12]

Prebiotics

Prebiotics are substrates that are selectively utilized by host microorganisms conferring a health benefit.[7] There are lots of examples of prebiotics, and the most superior are human milk oligosaccharides (HMOS).

The differences in gut microbiota between breastfed and non-breastfed infants are likely to be due to HMOS that are naturally present in breastmilk. HMOS have no nutritive value for the infant but have functions such as antimicrobial and antiviral activity, mucosal barrier maturations, modulation of pathogen recognition, and other effects on immune function.[14]

There is a wealth of data on specific HMOS in breastmilk with specific health outcomes, although the data is not always consistent.[15, 16, 17, 18, 19, 20] The progress in biotechnology made some HMOs available as ingredient for infant formulas i.e., 2'-FL, LNnT and more recently LNT, 3'-FL, 3'-SL, 6'-SL.

It may be important to differentiate between HMOS naturally occurring in human breastmilk and biotechnologically produced HMOs, which may be identical to HMOS in breastmilk but do not originate from breastmilk. There is currently no consensus on what to call biotechnologically produced HMOs.

Over 50% of infant formulas now contain prebiotics and around 33% contain galacto-oligosaccharides (GOS) and/or fructo-oligosaccharides (FOS).[11, 12]

In conclusion,

- the administration of currently evaluated prebiotic supplemented infant formula does not raise safety concerns regarding growth and adverse effects,
- the efficacy and safety should be considered for each distinct prebiotic(s)-supplemented formula,
- non-clinical outcomes can include higher stool colony counts of Bifidobacterium, increased short chain fatty acids (SCFA) concentrations, reduced faecal pH, and
- A favourable clinical benefit is a stool softening effect, observed in some infants.[21]

Synbiotics

Synbiotics are a mixture comprising living microorganisms and substrate(s) (i.e., prebiotics) that are selectively utilized by host microorganisms and that confers a health benefit on the host.[8]

A systematic review of synbiotics given to mothers of infants born by cesarean section already during their pregnancy and/or lactation, showed that most interventions increased the level of Bifidobacterium in the newborns' gut microbiota. Consequently, this resulted in Bifidobacterium levels in cesarean-delivered newborns close to that of vaginally delivered newborns. The effect was more evident in breastfed infants when the intervention took place soon after birth. In most studies, changes in the microbiota composition continued after the end of the inventions.[22]

In a systematic review and meta-analysis on amino acid formulas for children with cow's milk protein allergy (CMPA) the effects of the supplemented synbiotics included an increased percentage of Bifidobacterium in the gut microbiota, lower rates of infections, and in one study, the reduced use of medication including antibiotics.[23]

Postbiotics

The definition of postbiotics is a preparation of inanimate microorganisms and/or their components that confers a health benefit on the host.[9] This includes components such as cell fragments, metabolites such as lactic acid, SCFAs, bacteriocins and enzymes.

If components are purified, they are not considered postbiotics, and they will have their own chemical names.

A recent systematic review on infant formula with postbiotics found that there were 11 randomised controlled trials (RCTs) that investigated infant formula supplemented with postbiotics. Ten studies used a formula fermented with Bifidobacterium breve C50 and Streptococcus thermophilus (BB/ST) and one study was fermented with L paracasei CBA L74. The review concluded that all 11 infant formulas with postbiotics evaluated were safe and well tolerated. However, no firm conclusion could be reached regarding the clinical effects and benefit of one formula over another, especially as different methods of fermentation (partial and full) were used between the studies.[24] A recent study showed that faecal sIgA concentrations at 4 months were in the group whose formula was supplemented with postbiotics higher and more similar to the concentrations found in the breastfed reference group, than in the control group.[25]

Overall, the summary of findings for the use of infant formula with postbiotics are:

- they are safe and well tolerated,
- support adequate growth,
- improve gut function,
- micronutrient composition and its activity is closer to that seen in breastfed infants
- functionality of each formula must be evaluated separately because they have various ingredients added.

Final Remarks for infant formula with pro-, pre-, syn and/or postbiotics

- There appears to be no safety concerns with regards to growth and adverse effects, and formulas are well tolerated
- There are some favourable, non-clinical effects including a gut microbiota composition similar to that of breastfed infants
- There are some favourable clinical effects including a reduction of the use of antibiotics use in some studies
- Not all biotics are the same. Each needs to be evaluated separately
- Even if the best evidence is available, it does not automatically lead to improved health outcomes

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Next Generation Lipids: New Evidence to Support Healthy Growth and Weight Development in the F1000 Days

BY PROF. **ANITA HOKKEN-KOELEGA**

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Breastfeeding is the preferred nutrition for infants and confers many health benefits for mothers and their infants. Breastfeeding is associated with a decreased risk for overweight, metabolic syndrome and lower blood pressure in childhood.[26, 27, 28, 29]

These long-term beneficial effects of breastfeeding may originate from differences in early life body composition development, which is known as metabolic programming. There is a critical window for infant growth. Breastfed infants have a differential growth pattern, with a slower weight for age and weight for length gain than non-breastfed infants.[30, 31, 32] Additionally, breastfeeding of healthy, term-born infants between 0-3 months is associated with a specific adiposity development pattern characterized by subcutaneous fat deposition rather than visceral fat deposition.[33] The underlying mechanisms of how breastfeeding confers its benefits are multifactorial, including socio-demographic behavioral and biological aspects.[34]

Although fat provides around 50% of the energy in human milk with most of this fat composed of triglycerides, there has been little attention given to the lipid content and quality of breastmilk as a potential mechanism. There are major differences in the lipid quality between breastmilk and infant formula.[35] Human milk fat globules have a unique structure; they have a mode diameter of about 4µm and a biological tri-layer with a native membrane comprising of phospholipids, glycolipids, proteins, and cholesterol. The lipid droplets in breastmilk and infant formula differ; standard infant formula has lipid droplets that are much smaller, about 0.5µm in mode diameter than human milk fat globules.[36] Approximately 0.2-2% of the total fat in human milk is made up of phospholipids and it has been shown that the cow's milk derived biological, native membrane (MFGM) might have beneficial properties for children, and has been added to some infant milk formulas. These MFGM fragments, however, are not coating the lipid droplets as in human milk, but are dispersed in the formula emulsion.

Recently, a novel infant milk formula (IMF) concept (Concept IMF) was developed with a different lipid architecture, Nuturis®, comprising larger lipid droplets (approximately 3-5µm in mode diameter) and a phospholipid coating. The Concept IMF lipid droplets showed a thin interface composed of a mixture of phospholipids, proteins, and cholesterol originating from (cow) milk fat globule membrane, which has been suggested to have potential biological functions in infants.[37] Clinical and preclinical studies have indicated that compared to a standard formula, the Concept IMF was shown to:

- alter in vitro lipid digestion kinetics,[38]
- affect postprandial lipid response in healthy adult men,[39]

- prevent excessive fat mass accumulation and adverse metabolic outcomes in murine nutritional program models,[40, 41]
- have a lasting programming impact on short-term memory tasks during adolescence and adulthood in mice.[42]

After positive results obtained with the Concept IMF in preclinical and proof of concept studies, the hypothesis was formulated that the physical properties of the new Concept IMF would contribute to differences in infant development by:

- having a fat delivery format closer to human breastmilk,
- evoking physiological responses closer to human breastmilk,
- following an early growth trajectory closer to breastfed infants,
- having long-term metabolic outcomes closer to that seen in breastfed infants.

However, at first the safety and suitability of the Concept IMF was to be confirmed. The MERCURIUS study[43] was a randomised, controlled, double-blind, equivalence trial to investigate the effects of the Concept IMF on growth, tolerance, and safety in healthy, term infants in four countries: Netherlands, Belgium, France, and Singapore.

The primary objective was to investigate equivalence in weight gain from randomisation until the age of 17 weeks. The secondary objectives were to investigate evidence of other growth parameters until the age of 17 weeks, assess gastrointestinal tolerance and safety until the age of 17 weeks and to explore efficacy in weight gain at 12 months.

Both Control and Concept IMF were isocaloric (66kcal/100ml) and contained protein (1.3g/100ml), lipids (3.4g/100ml), scGOS/lcFOS prebiotic mixture (9:1, 0.8g/100ml). The key differences between the study IMFs were the following: 1) the size of their lipid droplets, 2) the coating of their lipid droplets, and 3) the origin of their lipid sources. The Control IMF was a vegetable oil–based standard IMF containing lipid droplets with a volume-based mode diameter of 0.5µm. The Concept IMF contained a mixture of vegetable (52%) and dairy lipids (48%), including milk phospholipids, introducing a 3-fold increase of sn-2 palmitic acid compared with the Control IMF (36% compared with 12% of total palmitic acid). The lipid droplets in the Concept IMF had a volume-based mode diameter of 3–5µm and an interface predominantly composed of milk phospholipids following an adapted production process.

The MERCURIUS study demonstrated that the Concept IMF was safe, well-tolerated and supported an adequate growth in healthy infants, Subsequently, the infants were followed up to childhood.[43] The objectives of the MERCURIUS follow up study (NTR5538) were to explore whether exposure to the Concept IMF during the first four months of life:

- impacts body mass index (BMI) trajectory up to 5 years of age,
- impacts blood pressure (BP) at 5 years of age,
- impacts neurocognitive outcomes at 5 years of age.

The BMI for age z-score of both formula groups lay between -1 and +1 SD throughout the study which is an indication for both formulas to support an adequate growth. However, from infancy onwards, the BMI of the Concept IMF group was highly similar to the breastfed reference group.

In contrast, the Control IMF group showed higher BMI values differing between +0.5SD and +0.2SD between 1 and 5 years of age. Moreover, during the first year of life, a critical window of development, the Control group showed an increase in BMI z score close to +1SD, much higher than that observed in the Concept IMF and Breastfed group (+0.3 to + 0.4SD). It is of importance to note that the effect size of these differences are considered to be of clinical relevance, i.e. potentially associated with a higher risk for development of later life overweight risk.

There is a critical window in the first four months of life for programming later adverse effects. If you analyse the results in the per protocol data set, the BMI z score trajectory of the infants in the Concept IMF group did not increase during this window; this is similar to the breastfed infants. Conversely, the Control IMF group BMI z score clearly showed an increase during the first four months.

The analysis of weight for age z score, did not reveal significant differences between the three groups. However, the length for age z score was significantly higher in the Concept IMF group at 12 months of age. This might be important because children who have a better length have a better health profile later in life.

At 5 years of age, the Concept IMF group had a substantially lower diastolic blood pressure (BP, (mmHg), -4.30 (-7.29, -1.31), P = 0.005 and lower arterial BP (mmHg), -3.67 (-6.46, -0.89), P=0.010, than the Control IMF group. In addition, there was a trend towards a lower probability of elevated BP (including hypertension) for children fed the Concept IMF vs. the Control IMF in early life (OR 0.38 [98%CI, 0.13, 1.07], P=0.066. These observed lower BP in childhood may track to adolescence and adulthood, which is of relevance given the fact that adults with lower BP have a better cardiovascular health profile.

Concluding remarks

Marked differences in lipid quality exist between human milk and infant formula milk including the lipid composition and lipid droplet structure (size and coating).[36] The MERCURIUS study is the first clinical investigation into the long-term impact of lipid droplet characteristics in IMF on growth and metabolic development of healthy term infants.

The data suggests that early life exposure to an innovative Concept IMF with large, milk phospholipid coated lipid droplets containing dairy lipids:

- leads to childhood BMI trajectories closer to breastfeeding reference group,
- results in lower childhood BP; lowering the risk of elevated BP.

Further research under the SOPHIA SATURN trial (CCMO NL64048.078.18) has been initiated to confirm these findings and unravel the potential impact on body composition and metabolic development.

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MERCURIUS CLINICAL STUDY:
SHORT TERM OUTCOMES AND LONG-TERM BENEFITS

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Introduction

Exclusive breast milk is the preferred feeding for infants and provides a complete supply of nutrients to support growth and development in early life.

Breast milk is rich in lipids, important for growth, brain and cognitive development, as well as gastrointestinal and immune function[1-3].

Compared to breast milk, the lipid droplets in standard infant formula are smaller, lack a milkfat globule membrane and may differ in overall lipid composition and triglyceride structure[4].

Danone Nutricia Research has developed a unique concept infant formula with large, milk phospholipid coated lipid droplets (mode diameter 3-5 µm; NUTURIS®) which brings the structural and functional properties of infant formula closer to those of breastmilk[4].

BREAST MILK LIPID DROPLETS have a volume-based mode diameter of 4 µm[4].

STANDARD INFANT FORMULA LIPID DROPLETS have a volume-based mode diameter of ~0.5 µm[4].

CONCEPT INFANT FORMULA LIPID DROPLETS have a mode diameter of 3-5 µm; NUTURIS®[4].

In breastmilk, lipids are incorporated into large droplets surrounded by a complex triple-layer membrane (Milk Fat Globule Membrane)[4].

Due to the normal process of infant formula production, the natural fat droplets do not remain intact and the MFGM is disrupted[4].

Nuturis® brings the structure of the lipid droplets closer to breast milk[4].

Mercurius study: **A randomised, controlled, double-blind trial to investigate the effects of a new infant formula on growth, tolerance and safety in healthy term infants**[6]

(registered in the Dutch Trial Register as NTR3683)

4 countries:

Study groups:
- Concept group n=115 — Concept infant formula
- Control group n=108 — Control infant formula
- Reference group n=88 — Breastfed infants

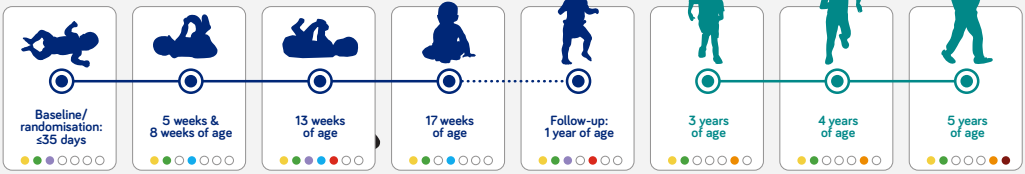
The primary objective:
To investigate equivalence of weight gain from randomisation until the age of 17 weeks.

Secondary objectives:
1. To investigate equivalence of other growth parameters until the age of 17 weeks
2. To assess gastrointestinal tolerance and safety until the age of 17 weeks
3. To investigate efficacy in weight gain at 12 months

Both Concept and Control formulas were isocaloric (66 kcal/100 ml) and contained:
- ✔ **Protein** (1.3 g/100 mL)
- ✔ **Lipids** (3.4 g/100 mL)
- ✔ **scGOS/lcFOS prebiotic mixture** (9:1, 0.8 g/100 mL)

The differences between formulas were:
- Concept formula contained vegetable (52%) and dairy lipids (48%) & 3-fold increase of sn-2 palmitic acid.
- Control formula contained small lipid droplets with vegetable oils (no dairy lipids).

INFANTS WERE FULLY FORMULA FED (EITHER CONTROL OR CONCEPT) UNTIL 17 WEEKS OF AGE:



Legend				
	Anthropometric parameters	Stool samples	Blood sample	Blood pressure
	Adverse Events (AEs)	GI symptoms & Stool consistency (7-d period preceding each visit)	Cognitive performance	

FOLLOW-UP STUDY (NTR5538)

Objectives were to evaluate whether early life exposure to the Concept infant formula

1. Impacts BMI trajectory up to 5 years of age 2. Has an impact on blood pressure at 5 years of age* 3. Impacts neurocognitive outcomes at 5 years of age

Conclusions

Formula with NUTURIS® is safe, well tolerated, and supports an adequate growth in healthy infants.

Equivalence in daily weight gain vs. Control formula at 4 months of age.

No relevant differences in number, severity or relatedness of adverse events.

Concept formula group had stool consistency closer to the Breastfed group.

Formula with NUTURIS® may result in a BMI trajectory close to that observed in breastfed infants.

Compared to Control, children in the Concept group had a lower BMI (statistically significant at 1 year of age).

Compared to Breastfed, children in the Control group had a higher BMI up to 5 years of age.

Compared to Breastfed, the BMI trajectory in Concept group was highly similar up to 5 years.

Formula with NUTURIS® might result in reduced childhood blood pressure.

Compared to Control:
- Children in the Concept group had a lower diastolic and arterial blood pressure at 5 years of age (all within healthy ranges).
- A lower percentage of children in the Concept group had elevated blood pressure.
- A lower percentage of children in the Concept group had hypertension, similar to breastfed infants.

Formula with NUTURIS® may improve cognitive outcomes of infants during early childhood, bringing them closer to the performance of breastfed infants.

Compared to Control, children in the Concept group had a higher DCCS score (executive function test, NIH Toolbox Early Childhood Cognition Battery®) and closer to the Breastfed group at 5 years of age.

LONG-TERM, FOLLOW-UP PERIOD

*Literature indicates that there is a direct relationship between childhood blood pressure and hypertension and the metabolic syndrome in adulthood

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