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Preface

In the present Nutrition and Growth Yearbook, an international group of experts in nutrition, metabolism, gastroenterology, endocrinology, and auxology joined together to select for our readers some of the important manuscripts published between July 1, 2018, and June 30, 2019, dealing with issues related to children's growth, especially those manuscripts that deal with the interaction between nutrition and growth.

Children's growth is a common concern to all health care providers treating neonates, infants, toddlers, children, and adolescents. Defining the best nutrition for healthy and active children as well as for those who suffer from acute or chronic disease, considering subgroups defined by age or other relevant determinants, is relevant to the child, his care givers, and to health care providers dealing with the pediatric age group.

In this Yearbook, associate editors tried to choose manuscripts published during the last year that provided a significant contribution to our knowledge base. They looked for manuscripts that they believe are important and informative and wrote their comments on each of them aiming to highlight lessons that can be learnt.

We are sure there are more important studies and apologize that, because of lack of space, we could not include all of them.

We hope that this book will help all subspecialties of health care providers in the pediatric age group to get updated on some of the key issues dealt with in these manuscripts. We encourage readers to review the full manuscripts that are of interest to them whenever possible.

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World Rev Nutr Diet. Basel, Karger, 2020, vol 120, pp 1–19 (DOI: 10.1159/000503648)

The Physiology and Mechanism of Growth

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Introduction

In the present chapter, an international group of endocrinologists were trying to select some of the most important manuscripts dealing with the physiology of growth published in the period July 1, 2019, to June 2019. We specially looked for manuscripts that shed more light on the already known mechanisms related to linear growth and those dealing with the interaction between nutrition and growth. We probably missed some important manuscripts that we did not find or could not include in our chapter because of lack of space. In our comments, we tried to explain the reasons for selecting the specific manuscripts and to highlight our own personal conclusion drawn from them. We encourage the reader to read the full manuscript whenever possible.

Key articles reviewed for this chapter

The effect of a high-calorie diet on bone growth is mediated by the insulin receptor

Wu S, Zhang Y, De Luca F

Bone 2019;122:166–175

Effects of dairy product consumption on height and bone mineral content in children: a systematic review of controlled trials

de Lamas C, de Castro MJ, Gil-Campos M, Gil Á, Couce ML, Leis R

Adv Nutr 2019;10(suppl_2):S88–S96

Mechanisms by which sialylated milk oligosaccharides impact bone biology in a gnotobiotic mouse model of infant undernutrition

Cowardin CA, Ahern PP, Kung VL, Hibberd MC, Cheng J, Guruge J, Sundaresan V, Head RD, Barile D, Mills DA, Barratt MJ, Huq S, Ahmed T, Gordon JI

Proc Natl Acad Sci USA 2019;116:11988–11996

Plasma C-type natriuretic peptide: emerging applications in disorders of skeletal growth

Espiner E, Prickett T, Olney R

Horm Res Paediatr 2018;90:345–357

ASB20123: a novel C-type natriuretic peptide derivative for treatment of growth failure and dwarfism

Morozumi N, Yotsumoto T, Yamaki A, Yoshikiyo K, Yoshida S, Nakamura R, Jindo T, Furuya M, Maeda H, Minamitake Y, Kangawa K

PLoS One 2019;14:e0212680

Exogenous C-type natriuretic peptide restores normal growth and prevents early growth plate closure in its deficient rats

Hirota K, Furuya M, Morozumi N, Yoshikiyo K, Yotsumoto T, Jindo T, Nakamura R, Murakami K, Ueda Y, Hanada T, Sade H, Yoshida S, Enomoto K, Kanai Y, Yamauchi I, Yamashita T, Ueda-Sakane Y, Fujii T, Yasoda A, Inagaki N

PLoS One 2018;13:e0204172

Prospective study of growth and bone mass in Swedish children treated with the modified Atkins diet

Svedlund A, Hallböök T, Magnusson P, Dahlgren J, Swolin-Eide D

Eur J Paediatr Neurol 2019;23:629–638

Epiphyseal growth plate architecture is unaffected by early postnatal activation of the expression of R992C collagen II mutant

Fertala J, Arita M, Steplewski A, Arnold WV, Fertala A

Bone 2018;112:42–50

Rapid early increase in body mass index is associated with impaired longitudinal growth in children with cystic fibrosis

Hak S, Arets HGM, van der Ent CK, van der Kamp HJ

Pediatric Pulmonology 2019;54:1209–1215

Bone mass development is sensitive to insulin resistance in adolescent boys

Rønne MS, Heidemann M, Lylloff L, Schou AJ, Tarp J, Bugge A, Laursen JO, Jørgensen NR, Husby S, Wedderkopp N, Mølgaard C

Bone 2019;122:1–7

Growth pattern of infants with gastroschisis in the neonatal period

Hall NJ, Drewett M, Burge DM, Eaton S

Clin Nutr ESPEN 2019:32:82–87

Skeletal disproportion in glucocorticoid-treated boys with Duchenne muscular dystrophy

Kao KT, Joseph S, Capaldi N, Brown S, Di Marco M, Dunne J, Horrocks I, Shepherd S, Ahmed S, Wong SC

Eur J Pediatr 2019:178:633–640

Antibiotic perturbation of gut microbiota dysregulates osteoimmune cross talk in postpubertal skeletal development

Hathaway-Schrader JD, Steinkamp HM, Chavez MB, Poulides NA, Kirkpatrick JE, Chew ME, Huang E, Alekseyenko AV, Aguirre JI, Novince CM

Am J Pathol 2019;89:370–390

High prevalence of growth plate gene variants in children with familial short stature treated with growth hormone

Plachy L, Strakova V, Elblova L, Obermannova B, Kolouskova S, Snajderova M, Zemkova D, Dusatkova P, Sumnik Z, Lebl J, Pruhova S

J Clin Endocrinol Metab 2019;104:4273–4281

Cartilage-targeted insulin-like growth factor 1 treatment to promote longitudinal bone growth

Lui JC, Colbert M, Cheung CSF, Ad M, Lee A, Zhu [3], Barnes KM, Dimitrov DS, Baron J

Mol Ther 2019;27:673–680

Impact of the Ketogenic diet on linear growth in children: a single-center retrospective analysis of 34 cases

Ferraris C, Guglielmetti M, Pasca L3, De Giorgis V, Ferraro OE, Brambilla I, Leone A, De Amicis R, Bertoli S, Veggiotti P, Tagliabue A

Nutrients 2019;11:1442

The effect of a high-calorie diet on bone growth is mediated by the insulin receptor

Wu S[1,2], Zhang Y[2], De Luca F[1]

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Bone 2019;122:166–175

Background: Obese children grow faster than their normal-weight peers. Insulin resistance and hyperinsulinemia have been associated with obesity-related growth acceleration.

Methods: To determine whether obesity-associated hyperinsulinemia promotes bone growth by activating the insulin receptor (IR) in the growth plate, we generated $^{TamCart}IR^{flox/flox}$ mice. The injection of 4 doses of tamoxifen in these mice (beginning at postnatal day 5th with 2 days interval between injections) resulted in the IR gene excision exclusively in the cartilage. $^{TamCart}IR^{flox/flox}$ tamoxifen-treated mice (KO mice) and their $IR^{flox/flox}$ control littermates (C mice) at 3 weeks of age were exposed to a standard or hypercaloric (high-fat) diet for 4 weeks.

Results: At the end of study, C and KO mice fed with a high-fat diet exhibited greater weight gain than the respective strains fed with a standard diet. Body and tibial growth and growth plate height of C mice fed with high-fat diet were greater than those of standard-diet-fed C mice; however, no difference was observed between KO mice fed with standard or high-fat diet with respect to body and tibial growth and growth plate height. Circulating levels of insulin, insulin-like growth factor (IGF)-1 and leptin were significantly higher in C and KO mice exposed to high-fat diet compared to those in the same strain exposed to standard diet. Increased phosphorylation of Akt (one of the intracellular mediators of insulin action in bone) in the growth plate of C mice on high-fat diet (compared to those on standard diet) suggests that high-fat-mediated increased circulating insulin levels may directly affect growth plate function and bone growth. High-fat diet was not associated with any change of Akt phosphorylation in KO mice. In addition, in vitro studies in cultured primary chondrocytes revealed that Akt mediates the stimulatory effects of insulin on chondrocyte proliferation and differentiation.

Conclusions: In conclusion, the activation of the IR in the growth plate of mice fed with a hypercaloric diet stimulates skeletal growth and growth plate chondrogenesis.

Comments Insulin resistance and hyperinsulinemia are suggested to be important mechanisms involved in accelerated longitudinal growth in childhood obesity [1]. Role of insulin receptor (IR) at the growth plate, as an IGF-independent mechanism promoting growth, was studied in mice with isolated excision of the IR gene in cartilage. Both in vivo and in vitro data support this hypothesis. Namely, following a hypercaloric diet that results in insulin resistance and hyperinsulinism, growth at the level of growth plate was not increased in mice with a knockout of IR in comparison to controls. In addition, it was determined that in cultured primary chondrocytes, Akt mediates the stimulatory effects of insulin on chondrocyte proliferation and differentiation. Studies in humans are needed to further establish signaling through the IR as the mechanism involved in accelerated longitudinal growth in childhood obesity [2]. Unraveling IGF-independent mechanisms involved in bone growth is important for the development of novel therapeutic strategies in individuals with dysfunctional IGF signaling pathway and short stature.

Effects of Dairy Product Consumption on Height and Bone Mineral Content in Children: A Systematic Review of Controlled Trials

de Lamas C[1,2,3,4,5], de Castro MJ[4,5,6], Gil-Campos M[2,3], Gil Á[3,7,8], Couce ML[1,4,5,6], Leis R[1,3,4,5]

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Adv Nutr 2019;10(suppl_2):S88–S96

Background: There is a physiological basis for the roles of selected nutrients, especially proteins, calcium, and vitamin D, in growth and development, which are at a maximum during the pediatric period. Milk and dairy products are particularly rich in this group of nutrients.

Methods: The present systematic review summarizes the available evidence relating dairy product intake with linear growth and bone mineral content in childhood and adolescence.

A search was conducted in the MEDLINE (via PubMed) and SCOPUS databases following preferred reporting items for systematic reviews and meta-analyses guidelines and included intervention-controlled clinical trials with dairy products in children from January 1, 1926 to June 30, 2018. The risk of bias for each study was assessed using the Cochrane methodology.

Results: The number of study participants, the type of study and doses, the major outcomes, and the key results of the 13 articles included in the review are reported.

Conclusions: The present systematic review shows that supplementing the usual diet with dairy products significantly increases bone mineral content during childhood. However, the results regarding a possible relation between dairy product consumption and linear growth are inconclusive.

Mechanisms by which sialylated milk oligosaccharides impact bone biology in a gnotobiotic mouse model of infant undernutrition

Cowardin CA[1,2], Ahern PP[1,2], Kung VL[1,2], Hibberd MC[1,2], Cheng J[1,2], Guruge JL[1,2], Sundaresan V[1,2], Head RD[3,4], Barile D[5,6], Mills DA[5,6], Barratt MJ[1,2], Huq S[7], Ahmed T[7], Gordon JI[1,2]

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Proc Natl Acad Sci USA 2019;116:11988–11996

Background: Undernutrition in children is a pressing global health problem, manifested in part by impaired linear growth (stunting). Current nutritional interventions have been largely ineffective in overcoming stunting, emphasizing the need to obtain better understanding of its underlying

causes. Treating Bangladeshi children with severe acute malnutrition with therapeutic foods reduced plasma levels of a biomarker of osteoclastic activity without affecting biomarkers of osteoblastic activity or improving their severe stunting.

Methods: To characterize interactions among the gut microbiota, human milk oligosaccharides (HMOs), and osteoclast and osteoblast biology, young germ-free mice were colonized with cultured bacterial strains from a 6-month-old stunted infant and fed a diet mimicking that consumed by the donor population. Adding purified bovine sialylated milk oligosaccharides (S-BMO) with structures similar to those in human milk to this diet increased femoral trabecular bone volume and cortical thickness, reduced osteoclasts and their bone marrow progenitors, and altered regulators of osteoclastogenesis and mediators of Th2 responses. Comparisons of germ-free and colonized mice revealed S-BMO-dependent and microbiota-dependent increases in cecal levels of succinate, increased numbers of small intestinal tuft cells, and evidence for activation of a succinate-induced tuft cell signaling pathway linked to Th2 immune responses. A prominent fucosylated human milk oligosaccharide, 2'-fucosyllactose, failed to elicit these changes in bone biology, highlighting the structural specificity of the S-BMO effects. These results underscore the need to further characterize the balance between, and determinants of, osteoclastic and osteoblastic activity in stunted infants/children, and suggest that certain milk oligosaccharides may have therapeutic utility in this setting.

Comments Understanding mechanisms associated with childhood undernutrition and growth stunting is of paramount importance in the planning of successful and safe nutritional interventions. As discussed in extent in this systematic review, dairy product supplementation of diet has an important influence on bone mineral content in childhood; the effect on linear growth is, however, still debated [3].

In another study, the role of milk oligosaccharides on osteoclast and osteoblast biology was studied in experimental animals, as it was proposed from the epidemiological part of the study that alteration of the osteoclastic activity by nutritional intervention could improve decreased linear growth. Sialylated milk oligosaccharides with structures similar to those in human milk were found to increase femoral trabecular bone volume and cortical thickness, reduced osteoclasts and their bone marrow progenitors, and altered regulators of osteoclastogenesis and mediators of Th2 responses in these mice. These data shed important insights into the mechanisms of bone remodeling and growth and could have an important influence on the composition of foods used in nutritional interventions [4].

Plasma C-Type Natriuretic Peptide: Emerging Applications in Disorders of Skeletal Growth

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Horm Res Paediatr 2018;90:345–357

Abstract: Although studies in experimental animals show that blood levels of C-type natriuretic peptide (CNP) and its bioinactive aminoterminal propeptide (NTproCNP) are potential biomarkers of long bone growth, a lack of suitable assays and appropriate reference ranges has limited the application of CNP measurements in clinical practice. Plasma concentrations of the processed product of proCNP, NTproCNP – and to a lesser extent CNP itself – correlate with concurrent

height velocity throughout all phases of normal skeletal growth, as well as during interventions known to affect skeletal growth in children. Since a change in levels precedes a measurable change in height velocity during interventions, measuring NTproCNP may have predictive value in clinical practice. Findings from a variety of genetic disorders affecting CNP signaling suggest that plasma concentrations of both peptides may be helpful in diagnosis, provided factors such as concurrent height velocity, feedback regulation of CNP, and differential changes in peptide clearance are considered when interpreting values. An improved understanding of factors affecting plasma levels, and the availability of commercial kits enabling accurate measurement using small volumes of plasma, can be expected to facilitate potential applications in growth disorders including genetic causes -affecting the CNP signaling pathway.

ASB20123: A novel C-type natriuretic peptide derivative for treatment of growth failure and dwarfism

Morozumi N[1], Yotsumoto T[1,2], Yamaki A[1,2], Yoshikiyo K[1,2], Yoshida S[1,2], Nakamura R[1,2], Jindo T[1,2], Furuya M[1], Maeda H[1,2], Minamitake Y[1], Kangawa K[3]

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PLoS One 2019;14:e0212680

Background: C-type natriuretic peptide (CNP) and its receptor natriuretic peptide receptor B (NPR-B) are physiological potent positive regulators of endochondral bone growth; therefore, the CNP/NPR-B signaling pathway is one of the most promising therapeutic targets for treating growth failure and dwarfism.

Methods: In this article, we summarized the pharmacological properties of a novel CNP analog peptide ASB20123 as a therapeutic agent for short stature.

Results: ASB20123, one of the CNP/ghrelin chimeric peptides, is composed of CNP (1–22) and human ghrelin (12–28, E17D). Compared to CNP (1–22), ASB20123 showed similar agonist activity for NPR-B and improved biokinetics with a longer plasma half-life in rats. In addition, the distribution of ASB20123 to the cartilage was higher than that of CNP (1–22) after single subcutaneous (sc) injection to mice. These results suggested that the C-terminal part of ghrelin, which has clusters of basic amino acid residues and a BX7B motif, might contribute to the retention of ASB20123 in the extracellular matrix of the growth plate. Multiple sc doses of ASB20123 potently stimulated skeletal growth in rats in a dose-dependent manner, and sc infusion was more effective than bolus injection at the same dose. Our data indicated that high plasma levels of ASB20123 would not necessarily be required for bone growth acceleration.

Conclusions: Thus, pharmaceutical formulation approaches for sustained-release dosage forms to allow chronic exposure to ASB20123 might be suitable to ensure drug effectiveness and safety.

Exogenous C-type natriuretic peptide restores normal growth and prevents early growth plate closure in its deficient rats

Hirota K[1], Furuya M[2,3], Morozumi N[2], Yoshikiyo K[2], Yotsumoto T[2], Jindo T[2], Nakamura R[2], Murakami K[1], Ueda Y[1], Hanada T[2], Sade H[2], Yoshida S[2], Enomoto K[2], Kanai Y[1], Yamauchi I[1], Yamashita T[1], Ueda-Sakane Y[1], Fujii T[1], Yasoda A[1], Inagaki N[1]

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PLoS One 2018;13:e0204172

Background: Signaling by C-type natriuretic peptide (CNP) and its receptor, natriuretic peptide receptor-B, is a pivotal stimulator of endochondral bone growth. We recently developed CNP knockout (KO) rats that exhibit impaired skeletal growth with early growth plate closure. In the current study, we further characterized the phenotype and growth plate morphology in CNP-KO rats, and the effects of exogenous CNP in rats.

Methods: We used CNP-53, an endogenous form of CNP consisting of 53 amino acids, and administered it for four weeks by continuous subcutaneous infusion at 0.15 or 0.5 mg/kg/day to 4-week old CNP-KO and littermate wild type (WT) rats.

Results: We demonstrated that CNP-KO rats were useful as a reproducible animal model for skeletal dysplasia, due to their impairment in endochondral bone growth. There was no significant difference in plasma bone-turnover markers between the CNP-KO and WT rats. At eight weeks of age, growth plate closure was observed in the distal end of the tibia and the calcaneus of CNP-KO rats. Continuous subcutaneous infusion of CNP-53 significantly, and in a dose-dependent manner, stimulated skeletal growth in CNP-KO and WT rats, with CNP-KO rats being more sensitive to the treatment. CNP-53 also normalized the length of long bones and the growth plate thickness, and prevented growth plate closure in the CNP-KO rats. Using organ culture experiment of fetal rat tibia, gene set enrichment analysis indicated that CNP might have a negative influence on mitogen activated protein kinase signaling cascades in chondrocyte.

Conclusions: Our results indicated that CNP-KO rats might be a valuable animal model for investigating growth plate physiology and the mechanism of growth plate closure, and that CNP-53, or its analog, may have the potential to promote growth and to prevent early growth plate closure in the short stature.

Comments

Several manuscripts reported on the use of plasma C-type natriuretic peptide (CNP) as a potential therapeutic and/or diagnostic tool in growth failure including achondroplasia. CNP and its bioinactive aminoterminal propeptide (NTproCNP) are potential biomarkers of long bone growth. However, lack of suitable assays and appropriate reference ranges limits the application of CNP measurements in clinical practice, for example, predicting height velocity during interventions known to affect skeletal growth in children [5]. Therapeutic use of CNP-53, an endogenous form of CNP consisting of 53 amino acids, was studied in CNP knockout rats. Continuous subcutaneous infusion of CNP-53 significantly, and in a dose-dependent manner, stimulated skeletal growth. It normalized the length of long bones and the growth plate thickness and prevented growth plate closure. These data suggest that CNP-53, or its analog, may have the potential to promote growth and to prevent early growth plate closure in the short stature [6]. Another novel therapeutic agent for skeletal growth, a chimeric peptide composed of CNP (1–22) and human ghrelin (12–28, E17D), was studied. Especially, sc infusion stimulated skeletal growth in rats. Authors propose

that pharmaceutical formulation approaches for sustained-release dosage forms to allow chronic exposure to ASB20123 might be suitable to ensure drug effectiveness and safety [7]. These studies provide alternative approaches to achondroplasia treatment that is already in the final clinical trial phases [8].

Prospective study of growth and bone mass in Swedish children treated with the modified Atkins diet

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Background: The modified Atkins diet (MAD) is a less restrictive treatment option than the ketogenic diet (KD) for intractable epilepsy and some metabolic conditions. Prolonged KD treatment may decrease bone mineralization and affect linear growth; however, long-term studies of MAD treatment are lacking. This study was designed to assess growth, body composition, and bone mass in children on MAD treatment for 24 months.

Methods: Thirty-eight patients, mean age (SD) 6.1 years (4.8 years), 21 girls, with intractable epilepsy ($n = 22$), glucose transporter type 1 deficiency syndrome ($n = 7$), or pyruvate dehydrogenase complex deficiency ($n = 9$) were included. Body weight, height, body mass index, bone mass, and laboratory tests (calcium, phosphorus, magnesium, alkaline phosphatase, cholesterol, 25-hydroxyvitamin D, insulin-like growth factor-I and insulin-like growth factor binding protein 3) were assessed at baseline and after 24 months of MAD treatment.

Results: Approximately 50% of the patients responded with >50% seizure reduction. Weight and height standard deviation score were stable over 24 months, whereas median (min – max) body mass index standard deviation score increased from 0.2 (–3.3 to 4.5) to 0.7 (–0.9 to 2.6), $p < 0.005$. No effects were observed for bone mass (total body, lumbar spine and hip) or fat mass.

Conclusions: The MAD was efficient in reducing seizures, and no negative effect was observed on longitudinal growth or bone mass after MAD treatment for 24 months.

Comments Safety is an important factor influencing the use of diets. Appropriate linear growth and increased weight are prime indicators of health in growing children. Decreased linear growth caused by dieting would limit its usefulness in most children. To this effect, a study in children with epilepsy, glucose transporter type 1 deficiency syndrome, or pyruvate dehydrogenase complex deficiency, receiving MAD (a less restrictive treatment option than the KD) as a part of their treatment, was undertaken. Reassuringly, no negative effect was observed on longitudinal growth or bone mass after 24 months of diet in this population. Nevertheless, further studies with longer duration of treatment and larger cohorts are needed to determine its safety in growing children [9, 10].

Epiphyseal growth plate architecture is unaffected by early postnatal activation of the expression of R992C collagen II mutant

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Spondyloepiphyseal dysplasia (SED) exemplifies a group of heritable diseases caused by mutations in collagenous proteins of the skeletal system. Its main feature is altered skeletal growth. Pathomechanisms of SED include: changes in the stability of collagen II molecules, inability to form proper collagen fibrils, excessive intracellular retention of mutant molecules, and endoplasmic reticulum stress. The complexity of this pathomechanism presents a challenge for designing therapies for SED.

Our earlier research tested whether such therapies only succeed when applied during a limited window of development. Here, employing an inducible mouse model of SED caused by the R992C mutation in collagen II, we corroborate our earlier observations that a therapy must be applied at the prenatal or early postnatal stages of skeletal growth in order to be successful. Moreover, we demonstrate that blocking the expression of the R992C collagen II mutant at the early prenatal stages leads to long-term positive effects. Although, we could not precisely mark the start of the expression of the mutant, these effects are not significantly changed by switching on the mutant production at the early postnatal stages.

By demonstrating the need for early therapeutic interventions, our study provides, for the first time, empirically-based directions for designing effective therapies for SED and, quite likely, for other skeletal dysplasias caused by mutations in key macromolecules of the skeletal system.

Comments Studying mechanisms involved in rare bone dysplasias not only is important from the perspective of a specific bone disease but also may be applied for diagnostic and therapeutic procedure in other diseases of altered skeletal growth [11]. In the present study, timing of therapy during an individual's development was studied. In an animal model, it was determined as successful in the long term only if it is applied at the prenatal or early postnatal stages of skeletal growth [12]. Confirming an early initiation of treatment might be of importance also in other disorders of skeletal growth, affecting not only planning of timing and modes of treatment administration but also very early diagnosis.

Rapid early increase in body mass index is associated with impaired longitudinal growth in children with cystic fibrosis

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Pediatric Pulmonology 2019;54:1209–1215

Background: Growth failure and short stature is a common consequence of children and adolescents with cystic fibrosis (CF). Previous studies have documented associations between short stat-

ure and clinical outcomes, including reduced life expectancy. It was previously thought that the underlying aetiology of growth failure in CF is due to reduced food intake/absorption and concurrent increased energy losses. More recent studies demonstrate that growth failure and poor pubertal growth spurt is still observed in contemporary cohorts of children and adolescents with CF. Recent reports also document that obesity is also seen in the CF clinic, which may be a reflection of the obesitogenic environment we live in or the over-aggressive management of nutrition. There are very few longitudinal studies of linear growth and body mass index (BMI) in CF. The aim of this study was to evaluate stature in a cohort of Dutch children with CF diagnosed clinically (born between 1997 and 2001) from 0.5 until 18 years. The secondary aim was to evaluate the associations of increase in BMI between 1 and 6 years, lung function and CF-related diabetes.

Methods: A retrospective study from one single centre. All subjects were diagnosed clinically and not via newborn screening. Subjects were excluded if there was another significant co-morbidity, missing height data during follow-up. All subjects had reached adult height-defined as increase in height of <0.2 cm over at least 6 months.

Results: Height deficits were observed at presentation in both boys and girls even after accounting for parental height (target height), which increased following diagnosis. In boys, height for age minus target height Z-scores declined during puberty, leading to reduction in adult height corresponding to 4 cm lower ($p = 0.001$) than the healthy population. In girls, height for age minus target height Z-scores declined briefly after age 8 years but increased subsequently, with adult height of only 2 cm lower ($p = 0.22$) than the healthy population. Low BMI Z-scores were observed for both boys and girls only in the first year of life. The presence of CF-related diabetes and pulmonary function were not associated with adult height. Increase in BMI Z-scores between 1 and 6 years were associated with adult height in boys (Model $R^2 = 0.176$, $r = -0.420$, $p = 0.0230$ and girls (Model $R^2 = 0.217$, $r = -0.466$, $p = 0.0019$).

Conclusion: Adult height deficits were still observed in boys with CF despite improvement in clinical care. Associations between increase in BMI in infancy/early childhood and adult height in CF should be addressed in future studies.

Comments In this longitudinal retrospective study, the authors document that height deficits may still be observed in males with cystic fibrosis (CF). The gender difference for growth failure has also been shown in another group of childhood chronic disease, inflammatory bowel disease (Gupta et al. Inflamm Bowel Dis 2011;17:2318–2325; Mason et al. Horm Res Pediatr 2015;83:45–54), and this should be addressed in future studies in CF that include disease severity. Whilst statistical significant adult height deficits were documented in males with CF in this current study, it is encouraging to note that the magnitude of height deficit is only 4 cm (although the authors did not report 95% CI for the height deficit). Long-term adult height data in children with CF identified from newborn screening are now needed. The authors speculate that increase in body mass index (BMI) in infancy/early childhood may lead to increased production of adrenal androgens with associated earlier onset of puberty and therefore reduction in adult height. The associations reported in this study were obtained from univariate analysis which only explained approximately 18 and 22% of variation in adult height of males and females. Such a hypothesis needs to be proven in future studies, which take into account disease severity and nutritional status/management strategies. An alternative explanation could be that those children with more severe disease and/or nutritional issues were managed with aggressive nutritional management leading to greater increase in BMI. Optimal nutritional management in CF and impact on all health outcomes including linear growth and pulmonary function require further studies.

Bone mass development is sensitive to insulin resistance in adolescent boys

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Background: Existing data shows that insulin may exert an osteogenic effect on bone but the relationship maybe different depending on underlying body composition. Recent studies demonstrate that osteocalcin a bone specific non-collagen protein secreted by osteoblast may influence glucose metabolism and increase insulin sensitivity. The aim of this study was to evaluate the association between insulin resistance measured by the homeostasis model of insulin resistance (HOMA-IR) and dual energy absorptiometry (DXA) bone mass in healthy children. The secondary aim was to identify if body composition, physical activity or osteocalcin may influence the association between insulin resistance and bone mass in healthy children.

Methods: Data from a 6 year longitudinal study, The Childhood Health Activity and Motor Performance School Study, Denmark (CHAMPS-study, DK) with a total of 562 healthy children (277 boys) aged between 6 and 11 years were included in this study. Subjects were included if a baseline DXA and at least one follow-up DXA together with a fasting blood sample were obtained. Fasting blood samples were analysed for glucose, insulin and osteocalcin. Physical activity was measured by accelerometers worn at least for 7 days. Maturity was defined as number of years from age at peak height velocity based on previous published equations.

Results: Mean age of subjects at baseline was 9.6 years (range 7.7–12.0 years). At baseline, 16.4% were overweight and 3.4% were obese. At follow-up, HOMA-IR was negatively associated with DXA total body less head bone mineral content (TBLH-BMC) after adjusting for maturity, sex, height and DXA bone area ($p < 0.0001$). A sex difference was identified, including in stratified analysis where HOMA-IR was negatively associated with DXA TBLH-BMC only in boys ($\beta = -31.4$, $p < 0.001$). Additional adjustment for weight, DXA %fat, physical activity and osteocalcin showed similar associations between HOMA-IR and DXA TBLH-BMC (boys: β –29.3, $p < 0.0001$; girls: β –1.5, p = ns).

Conclusion: In a large cohort of healthy children and adolescents, measure of insulin sensitivity with HOMA-IR was inversely associated with DXA bone mineral content, following adjustment for numerous co-variates, including physical activity and osteocalcin. This relationship however was only present in boys.

Comments In this cohort of healthy children, insulin sensitivity measured by homeostasis model of insulin resistance was inversely associated with dual energy absorptiometry bone mass. The intriguing association present only in boys needs to be explored in further studies. It is unclear whether this association or the strength of this association is dif-

ferent in children with normal body mass index and those who are overweight and obese, given that insulin levels and homeostasis model of insulin resistance were generally in the "normal" ranges in this study. In addition, the interaction of nutritional intake should be explored in further studies.

Growth pattern of infants with gastroschisis in the neonatal period

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Clin Nutr ESPEN 2019:32:82–87

Background: Gastroschisis is a congenital abdominal wall defect, with evidence of intestinal failure in the early neonatal period requiring supportive parenteral nutrition for weeks to months. There is however limited information on growth of infants with gastroschisis.

Methods: This study is a retrospective review of all infants with gastroschisis managed in a single neonatal surgical unit over a 4-year period. Weight at birth, 10 days post-natal (±1 day), last day of any amount of parenteral nutrition, at discharge and at outpatient follow-up were converted to Z-scores. During the period of review, parenteral nutrition policy did not change. This consisted of starting parenteral nutrition at day 2–3 (providing 100–120 kcal/day in a volume of 150 mL/kg/day). All infants were kept nil by mouth until clinical evidence of intestinal motility, whereby enteral feeds were introduced. Results were reported as mean (SD).

Results: A total of 64 infants with gastroschisis were managed in the centre during the study period, and 61 (30 males) were included in this present study (3 excluded as were initially managed in another neonatal surgical unit). Mean gestation at birth was 36.0 (2.3), mean birth weight was 2.36 kg (0.54) and mean birth weight Z-score of –0.87 (0.85). Five infants did not receive any parenteral nutrition but the rest received parenteral nutrition until a mean of 29.8 days (21.3). Mean weight Z-scores fell to –1.19 (0.92) at day 10 with a nadir of weight Z scores of –2.24 (1.13) at day 71. Discharge weight Z score was significantly lower than birth weight Z-scores (Mean difference 0.84, $p < 0.0001$) and at time of stopping parenteral nutrition (Mean difference 0.48, $p < 0.0001$). Weight pattern during parenteral nutrition showed that weight Z-score fell during the first 10 days of life, with progressive increase and stabilised after 25 days of age. Weight fell following discontinuation of parenteral nutrition but stabilised approximately 30 days after.

Conclusion: This study demonstrated that despite nutritional support with parenteral nutrition, infants with gastroschisis show poor weight gain. Factors associated with weight gain and the long-term consequences should be evaluated in future studies.

Comments This interesting report showed that current contemporary nutritional support maybe inadequate for weight gain in infants with gastroschisis. In particular, poor weight gain or weight loss appears to be common at the time of transition from parenteral nutrition to enteral feeds. Research into different nutritional support of these infants is now needed. Longer term follow-up including data on linear growth is also needed.

Skeletal disproportion in glucocorticoid-treated boys with Duchenne muscular dystrophy

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Background: Boys with Duchenne muscular dystrophy (DMD) are treated with long term high dose oral glucocorticoid from approximately 4–5 years, and continued to adulthood. As a result, severe growth failure and short stature are commonly seen. Significant obesity is also a problem in paediatric DMD especially at the time of loss of ambulation. Small studies in children with hemiplegic cerebral palsy showed that lower leg length maybe present. The aim of the study is to evaluate body proportions in boys with DMD treated with GC.

Methods: Thirty boys with DMD on glucocorticoid therapy were compared with 30 healthy aged matched children (matched to within 6 months) recruited locally. Body segments and total height were measured using dual energy absorptiometry (DXA) total body images performed on Lunar Prodigy DXA scanner. Results were reported as median (range).

Results: All boys with DMD have been on oral glucocorticoid for a duration of 7.1 years (1.3 to 15.2). Height Z-score was significantly lower in boys with DMD compared with controls ($p < 0.0001$) and body mass index Z-score was significantly higher ($p < 0.0001$). Fifty seven percent of controls where pre-pubertal whereas 87% of boys with DMD were pre-pubertal. Height of boys with DMD was 10.7 cm (95% CI −17.1 to −4.3) lower than healthy controls after adjusting for pubertal status. Median percentage difference of sitting height in boys with DMD compared with controls was 6.5% lower (range −24 to +6.7%), whereas median percentage difference of leg length in boys with DMD in comparison with controls was 13% lower (range −46 to +13%). Median percentage difference in femur length in DMD compared with controls was 12% lower (range −41 to +19%) and median percentage difference in tibial length in DMD compared to controls was 23% lower (range −53 to +9.4%). Similarly, greater reduction of distal long bone of the upper limb was also observed in boys with DMD.

Conclusion: Boys with DMD on glucocorticoid therapy had evidence of skeletal disproportion with relatively shorter leg length and greater reduction in distal long bones. The underlying aetiology of this skeletal disproportion is currently unclear.

Comments Glucocorticoid excess is not known to be associated with skeletal disproportion, although there are hardly any studies in any childhood chronic condition of glucocorticoid excess. This study utilized a method of evaluating body proportions and bone lengths using DXA total body images and opens up the opportunity to evaluate stature and bone lengths in children with immobility. Previous studies show that short stature is relatively common in boys with Duchenne muscular dystrophy (DMD) even prior to treatment with glucocorticoid when these boys are still ambulant (approximately 25% with height Z-scores lesser than −2.0). The authors raise the possibility of an inherent growth disorder associated with DMD. Obesity is a common occurrence in DMD especially during childhood and in those on glucocorticoid therapy. The interaction of obesity and nutritional intake on linear growth, stature, and body proportions should be studied in future research.

Antibiotic perturbation of gut microbiota dysregulates osteoimmune cross talk in postpubertal skeletal development

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Background: Recent research show that host gut microbiota may have an influence on pathological states of the gastrointestinal tract and also impact on distant organs (e.g., liver, brain, heart and skeleton). Throughout the lifespan, various lifestyle factors may lead to changes in gut microbiota, which includes medications like antibiotics. Pro-inflammatory immune states can suppress osteoblastic bone formation and increase bone resorption. Antibiotic administration has been shown to lead to disruption of gut microbiota leading to a pro-inflammatory hyperimmune state. The osteoimmune mechanism linking antibiotic and skeletal development is unclear. The aim of this study was to investigate the effect of antibiotic disruption of gut microbiota in mice (C57BL/6 strain) from 6 to 12 weeks.

Methods: Mice were administered antibiotics (vancomycin, imipenem/cliastin and neomycin) or vehicle in drinking water from 6 to 12 weeks. Mice were euthanized at 12 weeks of age. MicroCT and histomorphometry (static and dynamic) of tibia were performed.

Results: Antibiotic therapy led to reduction in bacterial load in male and female mice but composition changes were sex dependent. Male mice treated with antibiotics showed significant increase in α-protobacteria and γ-proteobacteria but decrease in Bacteroidetes. On the other hand, female mice treated with antibiotics showed significant increase in α-proteobacteria and decrease in Bacteroidetes and Firmicutes. Trabecular microarchitecture deficits were observed in mice treated with antibiotics at 12 weeks, with greater deficits in male mice. Antibiotic treated mice did not show any evidence of growth impairment (tibia length, growth plate chondrocyte height and zone morphology). Static and dynamic studies of bone formation on histomorphometry did not show any abnormalities in osteoblastogenesis. However, histomorphometric studies of osteoclastogenesis with TRAP-stained proximal tibia showed increased osteoclast size and number. Increased systemic inflammation was observed with antibiotic administration in the mice (increased tumour necrosis factor and chemokines, CCL3). In addition, changes in adaptive and innate immune cells were also noted in mesenteric lymph nodes and spleen.

Conclusion: This study demonstrated that broad spectrum antibiotic administration led to disruption of gut microbiota composition altering host immune response which in turn modulates the developing skeleton. Deficits in trabecular microarchitecture and increased osteoclastogenesis were observed with no impairment in linear growth.

Comments This current study extends work that show that antibiotic perturbation of gut microbiota can influence bone mass by demonstrating that the potential mechanism is via alteration in systemic and local osteoimmune processes. The sex differences in alteration in gut microbiota and bone mass are intriguing and suggest the possible influ-

ence of sex steroid. The clinical implications of these results remain to be seen. In groups of children with chronic disorders requiring long-term treatment with prophylactic antibiotics, this maybe another mechanism of abnormalities in bone development.

High prevalence of growth plate gene variants in children with familial short stature treated with growth hormone

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Context: Familial short stature (FSS) is a term describing a growth disorder that is vertically transmitted. Milder forms may result from the combined effect of multiple genes; more severe short stature is suggestive of a monogenic condition. The etiology of most FSS cases has not been thoroughly elucidated to date.

Objectives: To identify the genetic etiology of severe FSS in children treated with growth hormone (GH) because of the diagnosis of small for gestational age or GH deficiency (SGA/GHD).

Design, Settings and Patients: Of 736 children treated with GH because of GHD/SGA, 33 with severe FSS (life-minimum height –2.5 SD or less in both the patient and shorter parent) were included in the study. The genetic etiology was known in 5 of 33 children prior to the study (ACAN [in 2], NF1, PTPN11, and SOS1). In the remaining 28 of 33, whole-exome sequencing was performed. The results were evaluated using American College of Medical Genetics and Genomics standards and guidelines.

Results: In 30 of 33 children (90%), we found at least one variant with potential clinical significance in genes known to affect growth. A genetic cause was elucidated in 17 of 33 (52%). Of these children, variants in growth plate-related genes were found in 9 of 17 (COL2A1, COL11A1, and ACAN [all in 2], FLNB, FGFR3, and insulin-like growth factor (IGF) 1R), and IGF-associated proteins were affected in 2 of 17 (IGFALS and HMGA2). In the remaining 6 of 17, the discovered genetic mechanisms were miscellaneous (TRHR, MBTPS2, GHSR, NF1, PTPN11, and SOS1).

Conclusions: Single-gene variants are frequent among families with severe FSS, with variants affecting the growth plate being the most prevalent.

Comments In the present study, the authors aimed to identify the genetic etiology of severe familial short stature (FSS). They classified short child (height ≤2 SD) as having FSS if at least one of his/her parents is also short (height ≤2 SD). They defined severe FSS if both the child and the shorter parent had height below –2.5 SD. It is true that more and more cases with idiopathic short stature actually are identified as suffering from different genetic variants of genes responsible for key processes that occur within the growth plate during the linear growth process. Several familial cases were already described in the literature. The surprise finding of the present manuscript is the fact that 30/33 (90%) of the children with severe FSS enrolled to the study were found to have at least one variant with potential clinical significance genes known to affect growth. It is almost like we can delete the term idiopathic familial severe short stature from our textbook and lists of potential diagnosis in our clinical practice since most cases (90%)

are not idiopathic anymore. I think it is too early to do that, and more studies in different centers and geographical areas are needed to confirm that very important and interesting finding.

Cartilage-targeted insulin-like growth factor-1 treatment to promote longitudinal bone growth

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Recombinant human growth hormone (GH) is commonly used to treat short stature in children. However, GH treatment has limited efficacy, particularly in severe, non-GH-deficient conditions such as chondrodysplasias, and potential off-target effects. Because short stature results from decreased growth plate chondrogenesis, we developed a cartilage-targeting single-chain human antibody fragment (CaAb) aiming to deliver therapeutic molecules to the growth plate, thereby increasing treatment efficacy while minimizing adverse effects on other tissues. To this end, we created fusion proteins of these CaAbs conjugated with insulin-like growth factor 1 (IGF-1), an endocrine and/or paracrine factor that positively regulates chondrogenesis. These CaAb-IGF-1 fusion proteins retained both cartilage binding and IGF-1 biological activity, and they were able to stimulate bone growth in an organ culture system. Using a GH-deficient (lit) mouse model, we found that subcutaneous injections of these CaAb-IGF-1 fusion proteins increased overall growth plate height without increasing proliferation in kidney cortical cells, suggesting on-target efficacy at the growth plate and less off-target effect on the kidney than IGF-1 alone. Alternate-day injections of these fusion proteins, unlike IGF-1 alone, were sufficient to produce a therapeutic effect. Our findings provide proof of principle that targeting therapeutics to growth plate cartilage can potentially improve treatment for childhood growth disorders.

Comments The authors developed an elegant and unique way to specifically deliver insulin-like growth factor (IGF)-1 to the growth plate. They also showed that the IGF-1 indeed increased growth plate and did not have an effect on other tissues (kidney). It is an important study indeed. Target-specific therapy is the desire of every physician in every specialty of medicine. Currently, physicians treating children with severe short stature with either growth hormone or IGF-1 are constantly concerned with the possible off-target short- and long-term undesired side effects. Frequently, pediatric endocrinologists treating children with GH have to consider reducing an effective dose because of too high systemic levels of IGF-1 and the concern of potential theoretical future malignancy. The described innovation of delivering the IGF-1 specifically to the growth plate where its action is needed paves the way to other targeted therapeutic options to be delivered specifically to the growth plate.

Impact of the ketogenic diet on linear growth in children: a single-center retrospective analysis of 34 cases

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Nutrients 2019;11:1442

Abstract: Data on the impact of the ketogenic diet (KD) on children's growth remain controversial. Here, we retrospectively investigated the occurrence of linear growth retardation in 34 children (47% males; age range: 2–17 years) diagnosed with drug-resistant epilepsy ($n = 14$) or glucose transporter type 1 deficiency syndrome ($n = 20$) who had been treated with the KD for 12 months. The general characteristics of children with and without growth retardation were also compared. All participants received a full-calorie, traditional KD supplemented with vitamins, minerals, and citrate. Most children (80%; 11/14 in the drug-resistant epilepsy subgroup and 16/20 in the glucose transporter type 1 deficiency syndrome subgroup) treated with the KD did not show growth retardation at 12 months. Although participants with and without delay of growth did not differ in terms of baseline clinical characteristics, dietary prescriptions, or supplementation patterns, marked ketosis at 12 months tended to occur more frequently in the latter group. Altogether, our results indicate that growth retardation may occur in a minority of children treated with the KD. However, further research is required to identify children at risk and to clarify how increased ketones levels may affect endocrine pathways regulating growth during KD administration.

Comments Even after the present study, the question "does ketogenic diet interfere with children's growth?" remains without a proper answer. The prospective nature of this study: mixed population, number of patients in each group, and the different age groups as well as the Tanner stage, make it difficult to draw definite conclusions from the results. So, I agree with the authors that prospective big studies are needed to answer this important question and not just for patients with drug-resistant epilepsy or glucose transporter type 1 deficiency syndrome. Many children in the world are trying different degrees of ketogenic diets for off-labeled indications, and their caregivers should know what it does to their growth during childhood and adolescence.

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Obesity, Metabolic Syndrome, and Nutrition

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Introduction

Childhood obesity has become a major worldwide health concern. During the last 30 years, the number of obese children and adolescents has significantly increased across most countries [1]. Childhood obesity tracks into adulthood with detrimental effects on health. The most common cause of obesity in children is a positive energy balance due to caloric intake in excess of caloric expenditure combined with a genetic predisposition for weight gain.

Given the long-term adverse sequelae of childhood obesity, identification of factors related to childhood obesity is warranted. A growing body of evidence suggests that the increased risk for childhood obesity is associated with early-life factors, such as the pregnancy period and the nutrition during the first years of life. Insights on the potential impact of maternal diet during early life on childhood adiposity have been provided by one of the studies reviewed below.

It is acknowledged that rapid or excess weight gain during the first 2 years of life is associated with a higher risk of being overweight or obese in later childhood [2].

Human milk is considered ideal and appropriate as the only food for the first 6 months of life, since it contains a variety of components essential for infant growth, development, and well-being, for example, vitamins, minerals, carbohydrates, amino acids, proteins, hormones, growth factors, and antimicrobial factors. Thus, breastfeeding may promote healthy growth trajectories during infancy, and the role of exclusive breastfeeding duration in eating behavior is presented. Exclusive breastfeeding in ear-

ly infancy may also promote a healthier lipid profile in late adolescence through mechanisms unrelated to adiposity, implicating its potential long-term benefits for cardiovascular health.

However, the extent to which breastfeeding is protective against later-life obesity is debated. Inconsistent associations between breastfeeding and infant obesity risk could be related to variations in human milk composition. Human milk is a dynamic and complex substance that delivers a milieu of hormones and other bioactive components. One of the studies reviewed below indicated that individual bioactive components of human milk may regulate different compartments of infant weight gain separately. The detection of appetite regulators in human milk and their association to offspring anthropometry and growth can represent another piece of the puzzle of the functions of human milk.

In infants fed with formula, the type of the formula can have a direct impact on early rapid weight gain. One of the reviewed studies highlights the role of infants in the feeding dynamic.

In particular, the differences in satiation properties and difference in energy intake and early rapid weight gain when healthy infants are fed different types of infant formulas, while isocaloric, differ in free amino acids and protein content.

Patterns of dietary habits and the type of food consumption during childhood may also be of relevance for an unfavorable development of body composition and may have consequences extending into adulthood. Some studies reported that consumption of fast food can have an adverse impact on the development of body composition during the primary school years and that adding sugars to foods that are commonly perceived as healthy may impact the adherence to healthy dietary guidelines and increase in adiposity risk as well.

Consumption of low-calorie sweeteners has increased in children, predominantly in the form of low-calorie sweetened beverages. Evidence from previous randomized controlled trials does not clearly support the intended benefits of non-nutritive sweeteners for weight management, and observational data suggest that low-calorie sweetened beverages consumption in children, with or without concomitant sugary beverage consumption, is associated with higher energy, carbohydrate, and sugar intakes compared with water.

Children with obesity are prone to develop obesity-related comorbidities. One of the comorbidities is non-alcoholic fatty liver disease (NAFLD). The role of nutrition and diet in the development of NAFLD is still not fully understood. One study presented in this chapter suggests that a sugar-rich diet might contribute to the development of early stages of NAFLD in overweight children and that moderate dietary counseling might improve the metabolic status of overweight children with NAFLD.

Finally, research over the last decade has demonstrated that the microbes that colonize the human gut may play key contributory roles in the pathogenesis of obesity. Gut microbes are known to have symbiotic relationship with the host and play a role in maintaining health and metabolic homeostasis, including production of a diverse

array of metabolites. Dysbiosis is associated with the promotion or aggravation of chronic metabolic diseases, including obesity and type 2 diabetes. Recent data provide evidence supporting a causative role of maternal obesity-associated infant dysbiosis in childhood obesity and NAFLD.

This chapter reviews a selection of notable articles published between July 2018 and June 2019, focusing on the relation between nutrition, obesity, and metabolic obesity comorbidities in childhood and young adulthood. This selection of articles indicates the range and intensity of the continuing efforts being made by researchers worldwide to confront the epidemic of childhood obesity.

Key articles reviewed for this chapter

Maternal Diet during Early Life and Risk of Childhood Obesity

Association between maternal adherence to healthy lifestyle practices and risk of obesity in offspring: results from two prospective cohort studies of mother-child pairs in the United States

Dhana K, Haines J, Liu G, Zhang C, Wang X, Field AE, Chavarro JE, Sun Q

BMJ 2018;362:k2486

Breastfeeding and Nutrition during Early Life and Risk of Childhood Obesity and Metabolic Comorbidities

Duration of exclusive breastfeeding may be related to eating behaviour and dietary intake in obesity prone normal weight young children

Specht IO, Rohde JF, Olsen NJ, Heitmann BL

PLoS One 2018;13:e0200388

Breastfeeding in infancy and lipid profile in adolescence

Hui LL Kwok MK, Nelson EAS, Lee SL, Leung GM, Schooling CM

Pediatrics 2019;143:e20183075

Bioactive components in human milk are differentially associated with rates of lean and fat mass deposition in infants of mothers with normal vs. elevated BMI

Young BE, Levek C, Reynolds RM, Rudolph MC, MacLean P, Hernandez TL, Friedman JE, Krebs NF

Pediatr Obes 2018;13:598–606

Satiety factors oleoylethanolamide, stearoylethanolamide, and palmitoylethanolamide in mother's milk are strongly associated with infant weight at four months of age-data from the Odense child cohort

Bruun S, Gouveia-Figueira S, Domellöf M, Husby S, Neergaard Jacobsen L, Michaelsen KF, Fowler CJ, Zachariassen G

Nutrients 2018;10:1747

Exposure to improved nutrition from conception to age 2 years and adult cardiometabolic disease risk: a modelling study

Ford ND, Behrman JR, Hoddinott JF, Maluccio JA, Martorell R, Ramirez-Zea M, Stein AD

Lancet Glob Health 2018;6:e875–e884

Early rapid weight gain among formula-fed infants: Impact of formula type and maternal feeding styles

Mennella JA, Papas MA, Reiter AR, Stallings VA, Trabulsi JC

Pediatr Obes 2019;14:12503

Nutrition during Childhood and Risk of Childhood Obesity and Obesity Related Comorbidities

Dietary patterns in primary school are of prospective relevance for the development of body composition in two German pediatric populations

Wolters M, Joslowski G, Plachta-Danielzik S, Standl M, Müller MJ, Ahrens W, Buyken AE

Nutrients 2018;5;10:1442

The effect of an extra piece of fruit or vegetables at school on weight status in two generations: 14 years follow-up of the fruit and vegetables makes the marks study

Stea TH, Tveter ET, Te Velde SJ, Vik FN, Klepp KI, Bere E

PLoS One 2018;13:e0205498

The impact of adding sugars to milk and fruit on adiposity and diet quality in children: A cross-sectional and longitudinal analysis of the identification and prevention of dietary- and lifestyle-induced health effects in children and infants (IDEFICS) study

Dello Russo M, Ahrens W, De Henauw S, Eiben G, Hebestreit A, Kourides Y, Lissner L, Molnar D, Moreno LA, Pala V, Veidebaum T, Siani A, Russo P and on behalf of the IDEFICS Consortium

Nutrients 2018;10:1350

Clustering of multiple energy balance-related behaviors in school children and its association with overweight and obesity-WHO European childhood obesity surveillance initiative (COSI 2015–2017)

Bel-Serrat S, Ojeda-Rodríguez A, Heinen MM, Buoncristiano M, Abdrakhmanova S, Duleva V, Sant'Angelo V, Fijałkowska A, Hejgaard T, Huidumac C, Hyska J, Kujundzic E, Milanović SM, Ovezmyradova G, Pérez-Farinós N, Petrauskiene A, Rito AI, Shengelia L, Braunerová RT, Rutter H, Murrin CM, Kelleher CC, Breda J

Nutrients 2019;11:511

Consumption of low-calorie sweetened beverages is associated with higher total energy and sugar intake among children, NHANES 2011–2016

Sylvetsky AC, Figueroa J, Zimmerman T, Swithers SE, Welsh JA

Pediatr Obes 2019;14:e12535

Non-alcoholic fatty liver disease in overweight children: role of fructose intake and dietary pattern

Nier A, Brandt A, Conzelmann IB, Özel Y, Bergheim I

Nutrients 2018;10:1329

A randomized control trial of the impact of LCPUFA-ω3 supplementation on body weight and insulin resistance in pubertal children with obesity

López-Alarcón M, Inda-Icaza P, Márquez-Maldonado MC, Armenta-Álvarez A, Barbosa-Cortés L, Maldonado-Hernández J, Piña-Aguero M, Barradas-Vázquez A, Núñez-García BA, Rodríguez-Cruz M, Fernández JR

Pediatr Obes 2019;14:12499

The Intestinal Microbiota and their Relation to Metabolic Programming

The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD

Soderborg TK, Clark SE, Mulligan CE, Janssen RC, Babcock L, Ir D, Young B, Kriebs N, Lemas DJ, Johnson LK, Weir T, Lenz LL, Frank DN, Hernandez TL, Kuhn KA, D'Alessandro A, Barbour LA, El Kasmi KC, Friedman JE

Nat Commun 2018;9:4462

Maternal Diet During Early Life and Risk of Childhood Obesity

Association between maternal adherence to healthy lifestyle practices and risk of obesity in offspring: results from two prospective cohort studies of mother-child pairs in the United States

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BMJ 2018;362:k2486

Objective: To examine the association between an overall maternal healthy lifestyle (characterized by a healthy body mass index, high quality diet, regular exercise, no smoking, and light to moderate alcohol intake) and the risk of developing obesity in offspring.
Design: Prospective cohort studies of mother-child pairs.
Setting: Nurses' Health Study II (NHSII) and Growing Up Today Study (GUTS) in the United States.
Participants: 24,289 GUTS participants aged 9–14 years at baseline who were free of obesity and born to 16,945 NHSII women.
Main Outcome Measure: Obesity in childhood and adolescence, defined by age and sex specific cutoff points from the International Obesity Task Force. Risk of offspring obesity was evaluated by

multivariable log-binomial regression models with generalized estimating equations and an exchangeable correlation structure.

Results: 1,282 (5.3%) offspring became obese during a median of 5 years of follow-up. Risk of incident obesity was lower among offspring whose mothers maintained a healthy body mass index of 18.5–24.9 (relative risk 0.44, 95% confidence interval 0.39–0.50), engaged in at least 150 min/week of moderate/vigorous physical activities (0.79, 0.69–0.91), did not smoke (0.69, 0.56–0.86), and consumed alcohol in moderation (1.0–14.9 g/day; 0.88, 0.79–0.99), compared with the rest. Maternal high quality diet (top 40% of the Alternate Healthy Eating Index 2010 diet score) was not significantly associated with the risk of obesity in offspring (0.97, 0.83–1.12). When all healthy lifestyle factors were considered simultaneously, offspring of women who adhered to all 5 low risk lifestyle factors had a 75% lower risk of obesity than offspring of mothers who did not adhere to any low risk factor (0.25, 0.14–0.47). This association was similar across sex and age groups and persisted in subgroups of children with various risk profiles defined by factors such as pregnancy complications, birth weight, gestational age, and gestational weight gain. Children's lifestyle did not significantly account for the association between maternal lifestyle and offspring obesity risk, but when both mothers and offspring adhered to a healthy lifestyle, the risk of developing obesity fell further (0.18, 0.09–0.37).

Conclusion: Our study indicates that adherence to a healthy lifestyle in mothers during their offspring's childhood and adolescence is associated with a substantially reduced risk of obesity in the children. These findings highlight the potential benefits of implementing family or parental based multifactorial interventions to curb the risk of childhood obesity.

Comments

Identifying modifiable risk factors for the prevention of childhood obesity has become a public health priority. Previous studies have shown that children's lifestyle choices are largely influenced by their mothers, and maternal behaviors are also associated with offspring's body mass index [3, 4]. Therefore, maternal lifestyle choices could exert health effects among offspring, probably through modulating the living environment and lifestyle of children.

This large study demonstrated that offspring of women adhering to an overall healthy lifestyle had a substantially lower risk of obesity than children of mothers who did not practice these lifestyle choices. Offspring of women who adhered to 5 low-risk lifestyle factors (high-quality diet, normal body weight, regular physical activities, light to moderate intake of alcohol, and non-smoking) had a 75% lower risk of developing incident obesity than children of mothers who did not adhere to any of the low-risk lifestyle factors. The risk of incident offspring obesity was 82% lower when both mothers and their offspring followed a healthy lifestyle. These associations were independent of other established and potential risk factors of childhood obesity and persisted among participants who had different baseline risk profiles defined by pregnancy complications and other maternal factors.

We have to remember that a maternal healthy lifestyle can have an impact both on the intra-uterine metabolic environment that is important for the prenatal fetal programming and can prevent obesity and metabolic comorbidities in the next generations [5, 6] and also on the children's lifestyle choices.

The strengths of the study are the large sample size, the detailed information of lifestyle factors in both mothers and offspring, and its prospective study design with long-term follow-up, which allowed to examine the impact of maternal factors before the occurrence of offspring obesity in childhood and adolescence.

The study is limited by the self-reported data of the lifestyle characteristics, including children's lifestyle assessments (patients with obesity tend to under-report their energy intake and over-report their amount of physical activities) and body weight

of mothers and their offspring, which are known to be subject to measurement errors.

Second, the participants belonged to the Nurses' Health Study II (NHSII) and Growing Up Today Study (GUTS) that are relatively of homogeneous socioeconomic status. Therefore, it can limit the generalizability of the findings to other populations with different socioeconomic status. Also, the study only examined maternal lifestyle, and the potentially crucial role of paternal lifestyle in the development of obesity in offspring was not investigated.

Overall, the study results highlight the potentially critical role of maternal lifestyle choices in the etiology of childhood obesity and show that adherence to a healthy lifestyle in both mothers and their children can result in an even further reduction in the risk of offspring obesity.

Breastfeeding and Nutrition During Early Life and Risk of Childhood Obesity and Metabolic Comorbidities

Duration of exclusive breastfeeding may be related to eating behaviour and dietary intake in obesity prone normal weight young children

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PLoS One 2018;13:e0200388

Abstract: Infants who are breastfed are introduced to a variety of flavours from the maternal milk, and thus the transition from maternal milk to complementary foods may be easier for these children. The aim of this study was to investigate if duration of exclusive breastfeeding was associated with pickiness or dietary intake of vegetables, fruit, starchy foods or sugar sweetened beverages among obesity prone normal weight children aged 2–6 years. This cohort study was based on data from the Healthy Start primary intervention study, the Danish Medical Birth registry and the Danish Health Visitor's Child Health Database. Infant feeding was registered by health nurses while home-visiting the mother and child up to 4 times within the first year. Information on eating behaviour and diet intake at age 2–6 years was obtained by parents. Crude and adjusted logistic and general linear regression models were used to investigate associations. A total of 236 children had complete information on all variables. Data showed lower odds of picky eating behaviour when exclusively breastfed until age 4–5 months compared to exclusively breastfed for 0–1 months (OR 0.35, 95 CI 0.16; 0.76, $p = 0.008$). In the crude analysis only, exclusively breastfed until age 6–10 months was associated with a higher daily intake of vegetables ($p = 0.04$). This study suggests that exclusive breastfeeding duration seems to influence pickiness and may contribute to facilitate the consumption of more vegetables in later childhood in obesity prone normal weight children.

Comments Food preferences by children are developed from early infancy. Infants who are breastfed are introduced to a variety of flavors from the maternal milk. Some studies have shown an association between duration of breastfeeding and a lower degree of pickiness in childhood.

This observation is confirmed in this study, as there was a lower odd of picky eating behavior when exclusively breastfed until age 4 ± 5 months as compared to exclusively breastfed for 0 ± 1 month. Some studies have also suggested 6 months of exclusive breastfeeding, the WHO recommendation, to be a threshold for not developing pickiness [7]. The presence of picky eating behavior is relevant for future health as prolonged picky eating has been associated with the development of obesity. Due to the exposure to a variety of flavors, complementary feeding seems also easier for children being exclusively breastfed compared to formula-fed children.

Some previous studies observed that children who were breastfed for a short duration or exclusively formula-fed infants tended to eat a less healthy diet in later childhood. In this study, exclusively breastfed until age 6 ± 10 months was associated with a higher daily intake of vegetables in the crude analysis, but not in the adjusted model. Contribution of breastfeeding to a high acceptance of vegetables consumption would be an important added value, as to increase vegetables intake later during childhood is one of the most difficult tasks in terms of eating behavior modification.

Breastfeeding in infancy and lipid profile in adolescence

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Objective: Breast milk has higher cholesterol than formula. Infants who are breastfed have different cholesterol synthesis and metabolism in infancy than infants who are formula fed. Little is known as to whether breastfeeding is associated with subsequent lipid profile, independent of adiposity. We assessed the association of breastfeeding in early infancy with lipid profile and adiposity at ~17.5 years in a setting where exclusive breastfeeding is not associated with higher socioeconomic position.

Methods: We used multivariable linear regression with multiple imputation and inverse probability weighting to examine the associations of contemporaneously reported feeding in the first 3 months of life (exclusive breastfeeding [7.5%], mixed feeding [40%], or always formula feeding [52%]) with lipids and adiposity at ~17.5 years in 3,261 participants in the Hong Kong Chinese birth cohort children of 1997, adjusting for sex, birth weight, gestational weeks, parity, pregnancy characteristics, parents' highest education, mother's place of birth, and age at follow-up.

Results: Exclusive breastfeeding, but not mixed feeding at 0–3 months, compared with formula feeding was associated with lower total cholesterol and low-density lipoprotein cholesterol but not with high-density lipoprotein cholesterol at ~17.5 years. BMI and fat percentage measured by bioimpedance did not differ by type of infant feeding.

Conclusions: Exclusive breastfeeding in early infancy may promote a healthier lipid profile in late adolescence through mechanisms unrelated to adiposity, implicating its potential long-term benefits for cardiovascular health.

Comments

High plasma concentrations of cholesterol are a principal risk factor for atherogenesis and thus a major cause of cardiovascular disease. Animal and epidemiological evidence suggest that exposures acting in early life may play a role in cardiovascular disease risk, and infant nutrition is one early-life factor that has generated much interest amongst life course researchers in recent years.

Breast milk has higher cholesterol than formula [8]. Infants who are breastfed have different cholesterol synthesis and metabolism in infancy than infants who are formula fed, with higher plasma cholesterol and less endogenous cholesterol synthesis in those who are breastfed [9].

Such early changes in cholesterol metabolism may program subsequent cholesterol homeostasis and lipid profile in adulthood.

This study reveals that the impact of breastfeeding on lipids is independent of adiposity because being exclusively breastfed was not associated with a lower BMI or fat percentage, suggesting that the long-term impact of exclusive breastfeeding in early infancy could be independent of mediating pathways related to adiposity.

Potential mechanisms could involve changes in the expression of 3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase and LDL receptors. The genetic variant related to expression of HMG-CoA reductase (rs12916 in HMGCR) is associated with LDL-C but not with HDL-C, whereas genetic variants related to LDL receptors (rs11613352 [LRP1], rs3136441 [LRP4], and rs11206510 [PCSK4]) are associated with changes in both LDL-C and HDL-C.

Thus, the observation of the study that lower LDL-C, but not lower HDL-C, in individuals who are exclusively breastfed appears to be more consistent with the role of HMG-CoA reductase in the programing effect of early cholesterol exposure, if any. Such a programing effect may explain the change in lipid profile but not in markers of adiposity by type of infant feeding observed here.

However, evidence is still lacking as to whether such a change in synthesis or metabolism of cholesterol in the neonatal period persists beyond weaning and into adulthood. Whether other differences between breast and formula milk (e.g., a higher phytosterol, protein, or galactose level in formula milk) could program lipid metabolism requires further research to elucidate.

The strengths of the study include the large number of patients included, the long-term follow-up, and the setting of the study where exclusive breastfeeding is not associated with higher socioeconomic position (which is also linked to better health).

The study is limited by the lack of data about maternal lipid profile that also may have an impact on maternal diet and breast milk. Also, there is a lack of information on diet after early infancy and on whether types of solid food given after weaning differed by mode of infant feeding. A higher proportion of participants who were exclusively breastfed had later solid food introduction, so we cannot rule out the possibility that the association of early infant feeding with lipids is due to subsequent dietary factors and that early exposure to breast milk has an effect on dietary behavior in later life (behavioral programming).

In conclusion, here we have another potential benefit of breastfeeding, and therefore, it should be advocated, when possible, as the preferred method of feeding in early life.

Bioactive components in human milk are differentially associated with rates of lean and fat mass deposition in infants of mothers with normal versus elevated BMI

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Pediatr Obes 2018;13:598–606

This manuscript is also discussed in Chapter 7 by Larnkjær et al., page 141.

Objective: To model breastfed infant growth and body composition patterns over the first 4 months with multiple bioactive components of human milk (HM) and clinical factors (including maternal BMI status), which are related to growth.

Methods: Longitudinal observation of infant growth and body composition from 0 to 4 months among 41 predominantly breastfed infants (25 mothers of Normal-weight and 16 mothers with overweight/obesity). Fasted morning HM samples were collected at 5 time-points. Macronutrients, leptin, adiponectin, ghrelin, insulin, cytokines and n-6:n-3 esterified fatty acid ratio were measured. Infant weight-for-length Z-score (WLZ) trajectory, fat-free mass (FFM) gain, fat mass gain and %fat gain were modelled controlling for clinical covariates.

Results: HM insulin negatively associated with WLZ trajectory among infants of NW mothers ($p = 0.028$), but not associated with WLZ trajectory among infants of OW/Ob mothers. HM glucose ($p < 0.001$) was associated with slower rates of infant FFM gain. Infants of mothers with OW/Ob exhibited slower rates of FFM gain. HM protein, adiponectin and insulin concentrations, and n-6:n-3 ratio were all significant predictors in the model of infant fat mass gain ($p < 0.03$). Any amount of formula supplementation was associated with faster fat gain ($p = 0.002$). The model of %fat gain was similar to that of fat mass gain, excepting HM adiponectin was not a significant covariate, and a trend for maternal OW/Ob to correlate with faster %fat gain ($p = 0.056$).

Conclusions: Bioactive components in HM may contribute to regulation of partitioning of body composition, and these contributions may differ between mothers of normal-weight versus with OW/Ob.

Comments

This study suggests that specific components present in human milk may contribute differently to the way that breastfed infants partition free-fat mass (FFM) versus fat mass. This effect may differ depending on maternal weight status. Specifically, human milk protein, n-6:n-3 ratio, and insulin may contribute to adiposity, while human milk glucose may contribute to accumulation of lean mass.

The study strength is its longitudinal design but is limited by the small sample size.

The study data suggest that breastfeeding and human milk may mitigate the risk imposed by in utero exposure to maternal overweight and obesity, strengthening recommendations for exclusive breastfeeding, especially in infants at risk for later obesity.

Satiety factors oleoylethanolamide, stearoylethanolamide, and palmitoylethanolamide in mother's milk are strongly associated with infant weight at four months of age-data from the Odense child cohort

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Abstract: Regulation of appetite and food intake is partly regulated by N-acylethanolamine lipids oleoylethanolamide (OEA), stearoylethanolamide (SEA), and palmitoylethanolamide (PEA), which induce satiety through endogenous formation in the small intestine upon feeding, but also when orally or systemic administered. OEA, SEA, and PEA are present in human milk, and we hypothesized that the content of OEA, SEA, and PEA in mother's milk differed for infants being heavy (high weight-for-age Z-score [WAZ]) or light (low WAZ) at time of milk sample collection. Ultra-high performance liquid chromatography-mass spectrometry was used to determine the concentration of OEA, SEA, and PEA in milk samples collected 4 months postpartum from mothers to high (n = 50) or low (n = 50) WAZ infants. Associations between OEA, SEA, and PEA concentration and infant anthropometry at 4 months of age as well as growth from birth were investigated using linear and logistic regression analyses, adjusted for birth weight, early infant formula supplementation, and maternal pre-pregnancy body mass index. Mean OEA, SEA, and PEA concentrations were lower in the high compared to the low WAZ group (all $p < 0.02$), and a higher concentration of SEA was associated with lower anthropometric measures, e.g., triceps skinfold thickness (mm; β –2.235, 95% CI –4.04 to –0.43, $p = 0.016$), and weight gain per day since birth (g; β –8.169, 95% CI –15.26 to –1.08, $p = 0.024$). This raises the possibility, that the content of satiety factors OEA, SEA, and PEA in human milk may affect infant growth.

Comments

Human milk contains a variety of components essential for infant growth, development, and well-being, for example, vitamins, minerals, carbohydrates, amino acids, proteins, hormones, growth factors, and antimicrobial factors.

N-acylethanolamine (NAE) lipids, oleoylethanolamide (OEA), stearoylethanolamide (SEA), and palmitoylethanolamide (PEA) were also detected in both human and animal milk [10]. These components were identified as players in the regulation of appetite and food intake [11].

The fact that orally administered OEA (and to some extent SEA and PEA) exert some of the same effects as endogenous OEA raises the possibility that the presence of these lipids in human milk plays a role in the regulation of appetite and food intake in breastfed infants.

Indeed, in this study, based on human milk samples collected at 4 months of age, there were statistically significant differences in the concentrations between mothers to infants with a low weight-for-age Z-score (WAZ) and mothers to infants with a high

WAZ at the time of the milk sample collection. The low WAZ group had a higher concentration of satiety factors OEA, PEA, and SEA compared to the high WAZ group. Even after adjustment for maternal pre-pregnancy BMI, birth weight, and supplementation with infant formula within breastfeeding establishment, a lower concentration of OEA, SEA, and PEA was associated with a higher weight gain since birth.

However, we must remember that human milk is a dynamic and complex substance that delivers a milieu of hormones and other bioactive components that support infant development. Many other individual components within human milk can modulate weight regulation including leptin, adiponectin, insulin, cytokines, and fatty acids [12]. The interplay between these components and NAE lipids may improve our understanding of different patterns of weight gain and growth in exclusively breastfed infants.

Exposure to improved nutrition from conception to age 2 years and adult cardiometabolic disease risk: a modelling study

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Background: Low-income and middle-income countries with populations that are chronically undernourished in early life are undergoing a nutrition transition and are experiencing an epidemic of cardiometabolic disease. These dual burdens are thought to be causally related; therefore, the extent to which improvements in early-life nutrition can offset adult-onset disease is important. The aim of this study was to examine whether improvement of protein-energy nutrition from conception to age 2 years can attenuate the risk of cardiometabolic disease.

Methods: We followed up a cohort of 2,392 individuals born between January 1, 1962, and February 28, 1977, in 4 villages in Guatemala who had participated in a cluster-randomised protein-energy nutritional supplementation (Atole) trial. Of 1,661 participants available for follow-up from February 26, 2015, to April 29, 2017, we studied 684 women and 455 men. We assessed cardiometabolic disease risk at ages 37–54 years using anthropometry, fasting and post-challenge glucose, fasting lipid concentrations, and blood pressure. We used generalised linear and logistic regression modelling to estimate the effect of Atole from conception to age 2 years (the first 1,000 days) on cardiometabolic disease risk.

Findings: Exposure to Atole from conception to age 2 years was associated with increased fatness (body-mass index [1.29 kg/m^2, 95% CI 0.08 to 2.50], body fat [1.73%, 0.20 to 3.26], and obesity [OR 1.94, 1.11 to 3.40]), diastolic blood pressure (1.59 mm Hg, –0.74 to 3.92), and blood lipids (total cholesterol [10.10 mg/dL, 0.80 to 19.40] and non-HDL cholesterol [10.41 mg/dL, 1.51 to 19.31]), reduced post-challenge glucose (–5·84 mg/dL, –12.51 to 0.83), and reduced odds of diabetes (odds ratio 0.46, 0.21 to 0.97). We found stratum heterogeneity by sex in pooled models for non-HDL cholesterol (4.34 mg/dL, 95% CI –6.86 to 15.55 for women vs. 19.84 mg/dL, 5.86 to 33.82 for men) and post-challenge glucose (–0.19 mg/dL, –8.63 to 8.24 for women vs. –13.10 mg/dL, –23.64 to

–2·56 for men). *P* values for interaction of sex and exposure to Atole from conception to age 2 years were 0·09 and 0·04, respectively.

Interpretation: Improved protein-energy nutrition from conception to the 2nd birthday reduced the odds of diabetes at ages 37–54 years; however, this protein-energy supplementation also increased the risk of obesity and several obesity-related conditions. Our findings suggest a mixed ability of protein-energy nutritional supplementation in early life to prevent adult cardiometabolic disease incidence in the context of high childhood stunting and high adult overweight and obesity.

Comments

Inadequate nutrition and impaired development in utero and during early life are thought to increase the risk of cardiometabolic disease in adulthood [13].

This study examined the effect of a nutritional supplementation intervention from conception to age 2 years (the first 1,000 days) on cardiometabolic disease risk in midlife.

Using experimental data from a longitudinal cohort with more than 40 years of follow-up, the authors reported a beneficial and detrimental effect of a protein-energy nutritional supplement (Atole) from conception to age 2 years on the cardiometabolic disease risk profile in Guatemalan adults. Exposure to Atole increased adiposity and caused a more atherogenic blood-lipid profile (total cholesterol and non-HDL cholesterol), but it had a strong inverse association with diabetes that was not mediated through measures of adiposity. Overall, the evidence from this cohort suggests that protein-energy nutritional supplementation has mixed ability to offset the incidence of adult cardiometabolic disease in contexts of chronic childhood undernutrition and obesogenic adult environments.

The strengths of the study include its long-term follow-up and the large number of participants.

The study findings worth the efforts trying to develop a different nutritional supplementation for the first 1,000 days of life that not only decrease the risk of diabetes but also can improve the atherogenic profile.

Early rapid weight gain among formula-fed infants: Impact of formula type and maternal feeding styles

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Background: What and how infants are fed are considered important determinants for the risk factor of early rapid gain weight.

Objectives: We conducted secondary analyses on data from a randomized clinical trial, wherein infants randomized to feed cow milk formula had double the incidence of early rapid weight gain than those fed extensively hydrolyzed protein formula, to determine whether maternal feeding styles had independent effects or interactive effects with infant formula type on early rapid weight gain.

Methods: Anthropometry and feeding patterning (number of daily formula feeds) were measured monthly, and maternal feeding styles were measured at 0.5, 3.5, and 4.5 months. Longitudinal models were fitted using generalized estimating equations and separate logistic models conducted.

Results: The treatment groups did not differ in formula feeding patterning or in maternal feeding styles, which were stable across the first 4.5 months. Feeding styles had no significant effects on early rapid weight gain and did not interact with formula group. However, type of infant formula had a direct and independent impact on early rapid weight gain ($p = 0.003$).
Conclusions: The type of infant formula had a differential impact on early rapid weight gain independent of maternal feeding style, highlighting the self-regulatory capabilities of infants.

Comments

This study demonstrates that neither maternal feeding styles nor how often mothers fed their infants formula per day had independent effects or interactive effects with the type of infant formula on whether infants gained weight rapidly during this time period. Instead, an independent determinant for early weight gain was the type of formula (cow milk formula [CMF] or extensively hydrolyzed protein infant formula [EHF]) the infant was fed.

The infant formulas were identical in calories (66.7 kcal/100 mL) and contained no added prebiotics or probiotics. The major differentiator of the formulas was the form of protein: CMF contains mainly intact proteins, whereas the protein in EHF consists of small-molecular-weight peptides, and its free amino acid (FAA) content was substantially higher compared with CMF.

Compared with infants randomized to feed EHF from 2 weeks of age, those randomized to feed an isocaloric CMF ingested more formula per feed, more kilocalories (kcal) of formula per day, and more kcal/kg body weight per day during the first months of life, resulting in more energy available for deposition and a greater proportion who were early rapid weight gainers. Neither infant formula intake nor rapid weight gain during these early months of life was related to the feeding styles of the mothers. Thus, the consistence of the formula had the major impact on weight gain.

A previous randomized controlled trial [14] evaluated the impact of these 2 types of infant formula (CMF and EHF) on growth and energy balance and demonstrated that CMF infants had significantly higher weight, but not length z scores than did EHF infants, and this persisted after solid foods complemented the formula diet. Early differences in energy intake and fecal loss, yielding greater energy available for deposition among CMF infants, contributed to the differential weight gain patterns, without significant differences between the formula treatment groups in total energy expenditure or sleeping energy expenditure. Moreover, the higher levels of FAA and small peptides found in EHF, when compared to CMF, are known satiation signals and modulators of gastroduodenal motor functioning, and they can signal satiation sooner and satiate on lower volumes of EHF than CMF [14].

The strengths of the study include its randomized controlled design and the fact that the infants of both groups were exclusively fed by the formula during the first 4.5 months postpartum when formula provided the vast majority of the energy intake. Furthermore, the repeated measure of maternal feeding styles and feeding patterning allows to characterize the stability of maternal feeding style traits and patterning of formula feeding and to determine whether either has independent effects or interacts with the type of formula and on how rapidly infants gain weight during the early life period.

Dietary patterns in primary school are of prospective relevance for the development of body composition in two German pediatric populations

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Abstract: This study performed comparative analyses in 2 pediatric cohorts to identify dietary patterns during primary school years and examined their relevance to body composition development. Nutritional and anthropometric data at the beginning of primary school and 2 or 4 years later were available from 298 and 372 participants of IDEFICS-Germany (Identification and prevention of Dietary-induced and lifestyle-induced health Effects In Children and infants Study) and the KOPS (Kiel Obesity Prevention Study) cohort, respectively. Principal component analyses (PCA) and reduced rank regression (RRR) were used to identify dietary patterns at baseline and patterns of change in food group intake during primary school years. RRR extracted patterns explaining variations in changes in body mass index (BMI), fat mass index (FMI), and waist-to-height-ratio (WtHR). Associations between pattern adherence and excess gain in BMI, FMI, or WtHR (>75th percentile) during primary school years were examined using logistic regression. Among PCA patterns, only a change towards a more Mediterranean food choice during primary school years were associated with a favorable body composition development in IDEFICS-Germany ($p < 0.05$). In KOPS, RRR patterns characterized by a frequent consumption of fast foods or starchy carbohydrate foods were consistently associated with an excess gain in BMI and WtHR (all $p < 0.005$). In IDEFICS-Germany, excess gain in BMI, FMI, and WtHR were predicted by a frequent consumption of nuts, meat, and pizza at baseline and a decrease in the consumption frequency of protein sources and snack carbohydrates during primary school years (all $p < 0.01$). The study confirms an adverse impact of fast food consumption on body composition during primary school years. Combinations of protein and carbohydrate sources deserve further investigation.

Comments Consumption of some food groups and nutrients has been independently associated to excess adiposity in children. However, the independent effects were not very strong. More and more studies are considering dietary patterns, that is, the frequent combination of some foods in the diet of certain individuals. In order to identify dietary patterns, different methods are available.

The most widely used method is principal component analysis. In this study, reduced rank regression (RRR) was also used. Obtained results were different in IDEFICS-Germany and KOPS and they were also different depending on the method used to derive dietary patterns.

In IDEFICS-Germany, a change toward a more Mediterranean food choice, identified using PCA, during primary school years, were associated with a favorable body composition development; however, in KOPS, a pattern characterized by consumption of fast foods or starchy carbohydrate foods, identified using RRR, was associated with an excess gain in BMI and WtHR.

Until now, few studies examined the prospective association of dietary patterns and body composition and most of them were performed in adolescents. Such studies often consider BMI alone; however, considering other adiposity-specific measures such as fat mass or waist circumference is, therefore, recommended.

In a previous study, considering the complete IDEFICS sample, from 8 European countries, and using cluster analysis as the method to identify dietary patterns, it was observed that children consistently showing a processed dietary pattern or changing from a processed pattern to a sweet pattern presented the most unfavorable changes in fat mass and abdominal fat [15].

Further exploration of changes in children's diet over time may help to identify changes in dietary patterns and/or children changing their dietary patterns, thus allowing a better understanding of the impact of diet on body composition.

The effect of an extra piece of fruit or vegetables at school on weight status in two generations – 14 years follow-up of the Fruit and Vegetables Makes the Marks study

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Background: The obesity epidemic presents a major public health challenge, and a poor diet quality has been identified as one of the most important contributing factors. Whereas a sufficient fruit and vegetable consumption has been associated with several positive health outcomes, the long-term effect on overweight and obesity is unclear. Thus, the aims of this study were to investigate if one year with free school fruit had any effect on weight status 14 years later, and if it affected the birth weight of the participants' children.

Methods: In 2001, 10–12-year old Norwegian children, received one year of free school fruit in the intervention study "Fruits and Vegetables Make the Marks" (FVMM) and in 2016, a total of 1,081 participants of 2,049 eligible responded to a follow-up survey. Multilevel logistic regression was used to investigate if one year of free school fruit was associated with weight status and with birthweight status of the offspring. The analyses were adjusted for gender, educational level, and the offspring analysis also for parents' weight status, and the nested design (child/parent).

Results: The odds ratios of being overweight (OR 0.93, 95% CI 0.70–1.24) or having a child with high or low birth weight (OR 0.52, 95% CI 0.21–1.30) in the intervention group compared to the control group were not statistically significant, 14 years after the intervention period.

Conclusions: One year of free school fruit did not have an effect on weight status on the participants or birth weight of their offspring, 14 years after the intervention period. Although, results from the present study contribute to fill the knowledge gaps concerning long-term effects of public health efforts on weight status, more follow-up studies with larger samples are warranted.

Comments Fruits and vegetables have low energy and high water and fiber composition and its consumption has been associated with a reduced risk of excess adiposity. A systematic review and meta-analysis have reported that intervention programs are able to increase fruits consumption by 0.24 portions per day [16].

In general, only a limited proportion of intervention studies trying to increase fruits and vegetables consumption report follow-up effects for more than a year after the intervention period. This study considers a follow-up of 14 years after the intervention period and weight status of the participants as the main outcome. The study does not observe a significant association with weight status of the participants or the birth weight of their offspring.

The main limitation of this study is that baseline measures of weight and height and the subsequent measures of participants' weight and height and birth weight of their children were self-reported. To explain the lack of a significant association, it should be considered the intervention lasted for 1 year, but 14 years before the outcomes were measured.

Future studies should assess whether interventions for more than 1 year may have a positive effect on weight status later in life. In any case, it should be considered that promoting healthy lifestyle habits, including increased consumption of fruits and vegetables, from early ages is important for effective prevention and treatment programs.

The impact of adding sugars to milk and fruit on adiposity and diet quality in children: A cross-sectional and longitudinal analysis of the identification and prevention of dietary- and lifestyle-induced health effects in children and infants (IDEFICS) study

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Abstract: Sugar, particularly as free sugars or sugar-sweetened beverages, significantly contributes to total energy intake, and, possibly, to increased body weight. Excessive consumption may be considered as a proxy of poor diet quality. However, no previous studies evaluated the association between the habit of adding sugars to "healthy" foods, such as plain milk and fresh fruit, and indicators of adiposity and/or dietary quality in children. To answer to these research questions, we Panalysed the European cohort of children participating in the IDEFICS study.

Anthropometric variables, frequency of consumption of sugars added to milk and fruit (SAMF), and scores of adherence to healthy dietary pattern (HDAS) were assessed at baseline in 9,829 children stratified according to age and sex. From this cohort, 6,929 children were investigated again after 2 years follow-up. At baseline, a direct association between SAMF categories and adiposity indexes was observed only in children aged 6–<10 years, while the lower frequency of SAMF consumption was significantly associated with a higher HDAS. At the 2-year follow-up, children with higher baseline SAMF consumption showed significantly higher increases in all the anthropometric variables measured, with the exception of girls 6–<10 years old. The inverse association between SAMF categories and HDAS was still present at the 2 years follow-up in all age and sex groups. Our results suggest that the habit to adding sugars to foods that are commonly perceived as healthy may impact the adherence to healthy dietary guidelines and increase in adiposity risk as well.

Comments

Given the potential negative impact of a high added sugar intake, the WHO recently recommended that, for avoiding obesity development, the consumption of free or added sugars should not exceed 10% of total daily energy intake. Despite this recommendation, added sugars are still widely present in the diet of infants, children, and adolescents. In order to reduce added sugars consumption, it is important to know the main sources of their intake in children.

In most studies, soft drinks and fruit-based drinks accounted for the greatest proportion of the added sugars intake, followed by milk products and sweet bakery products [17]. In European children, <20% of children were within the recommended intake of 10% of energy from free sugars. The habit of adding sugars to foods that are commonly perceived as healthy, such as yoghurt, milk, or fruits, may impact negatively the adherence to a healthy dietary pattern.

High added sugar intake has been associated with increased obesity risk and fat deposition in the liver, contributing to dyslipidemia, high blood pressure, insulin resistance, and cardiometabolic risk.

Several studies investigated the association of the consumption of ready-to-drink flavored milk beverages with energy intake and obesity. This is the first study evaluating the association between the habit of adding sugars to "healthy" foods, such as plain milk and fresh fruits, and indicators of adiposity and dietary quality. In the 2-year follow-up, children with higher baseline intake of sugars added to milk and fruits showed significantly higher increases in all the anthropometric variables measured, with the exception of girls 6–<10 years old. Therefore, it seems especially important to reduce children's intake of free sugars, focusing in certain foods and food groups and also on the sugar added to foods that are considered healthy, like fruits, milk, and milk products, such as yogurt.

Clustering of multiple energy balance-related behaviors in school children and its association with overweight and obesity-WHO European childhood obesity surveillance initiative (COSI 2015–2017)

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Abstract: It is unclear how dietary, physical activity and sedentary behaviors co-occur in school-aged children. We investigated the clustering of energy balance-related behaviors and whether the identified clusters were associated with weight status. Participants were 6- to 9-year-old children (n = 63,215, 49.9% girls) from 19 countries participating in the fourth round (2015/2017) of the World Health Organization (WHO) European Childhood Obesity Surveillance Initiative. Energy balance-related behaviors were parentally reported. Weight and height were objectively measured. We performed cluster analysis separately per group of countries (North Europe, East Europe, South Europe/Mediterranean countries and West-Central Asia). Seven clusters were identified in each group. Healthier clusters were common across groups. The pattern of distribution of healthy and unhealthy behaviors within each cluster was group specific. Associations between the clustering of energy balance-related behaviors and weight status varied per group. In South Europe/Mediterranean countries and East Europe, all or most of the cluster solutions were associated with higher risk of overweight/obesity when compared with the cluster "Physically active and healthy diet." Few or no associations were observed in North Europe and West-Central Asia, respectively. These findings support the hypothesis that unfavorable weight status is associated with a particular combination of energy balance-related behavior patterns, but only in some groups of countries.

Comments Low fruits and vegetables intake, consumption of high energy-dense/low nutrient-dense foods, low physical activity levels, and high sedentary time have been independently associated with obesity in children. However, the combined effect of these behaviors in relation with obesity development has been scarcely investigated.

Healthy and unhealthy behaviors seem to co-exist in the same groups of children. The most adequate method to assess the combined effect of behaviors of different nature is cluster analysis. Previous studies have investigated the clustering of energy balance-related behaviors and its association with childhood obesity.

However, studies assessing the association between behavior cluster patterns and obesity in children do not show consistent associations. One reason for this observation could be the different associations found in different geographic regions, as it is the case in different European regions in this study. In fact, in South Europe/Mediterranean countries and East Europe, most of the cluster solutions were associated with a higher risk of overweight/obesity when compared with the cluster "Physically active and healthy diet"; however, few associations were observed in North Europe and West-Central Asia. The applied methodology may also explain the lack of consistent results across the different regions. Behaviors were self-reported; for this reason, misclassification bias needs to be considered given that parentally reported measures are subject to possible misreporting of PA. Future studies should consider stronger methods to assess the target behaviors and longitudinal designs.

Obesity prevention programs should consider different key behavior messages, and future public health initiatives should target an increase in fruits and vegetables consumption and the time devoted to moderate vigorous physical activity and also to reduce high energy-dense/low nutrient-dense foods and the time devoted to sedentary behaviors [18].

Consumption of low-calorie sweetened beverages is associated with higher total energy and sugar intake among children, NHANES 2011–2016

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Objective: To examine associations between consumption of low-calorie sweetened beverages (LCSBs), sugar, and total energy intake in children in the United States.

Methods: We used 24-h dietary recalls from 7,026 children enrolled in the National Health and Nutrition Examination Survey (NHANES) 2011–2016 to assess energy and macronutrient intake among LCSB (≥4 oz LCSB, <4 oz SB), SB (≥4 oz SB, <4 oz LCSB), and LCSB + SB consumers (≥4 oz each) compared with water consumers (≥4 oz water, <4 oz LCSB and SBs). Sample weights and complex survey procedures were used for all analyses.

Results: Adjusting for body mass index (BMI) percentile, LCSB, SB, and LCSB + SB consumption was associated with 196, 312, and 450 more total calories and 15, 39, and 46 more grams of added sugar, which amounts to 60, 156, 184 more calories from added sugar, compared with water consumers ($p < 0.05$ for all pairwise comparisons). No differences in energy intake were observed between LCSB and SB consumers. (Correction added on 28 May 2019, after first online publication: In the preceding sentence, quantities of added sugar reported are in grams. The corresponding calories have also been specified in this version.)

Conclusions: These findings challenge the utility of LCSB for weight management in children and adolescents.

Comments

Extensive meta-analyses show that the risk from added sugars in beverages to weight gain and diabetes is very high. A reduction in the consumption of added sugars and sugar-sweetened beverages (SSBs) is a key focus of public health recommendations for a healthy diet among children. One approach to lower added sugar intake is to instead use low-calorie sweeteners (LCSs), which contain no or few calories.

Consumption of LCSs is increasing worldwide, with the most marked rise observed among children and adolescents. However, the extent to which LCS consumption is helpful or harmful for weight management is controversial, particularly when LCS consumption begins in childhood. While careful reviews and random controlled trials have not shown any adverse relationship of LCS on energy intake or increased consumption of sweet foods [19], several longitudinal cohort studies implicate LCS as a cause of increased weight and diabetes and other adverse cardiometabolic outcomes [20, 21].

The findings of the current study based on the NHANES 2011–2016 data demonstrate that child and adolescent consumers of LCS beverages, whether they are consumed alone or in combination with sugary beverage (SB), had higher energy, carbohydrate, total sugar, and added sugar intake compared with water consumers. Similar total daily energy intake was observed for LCS beverages consumers and SB consumers, and intakes of energy, carbohydrate, and sugar were consistently higher in combined LCS beverages + SB consumers compared with consumers of only LCS beverages or only SB. These data challenge whether LCS beverages are helpful for lowering sugar or energy intake and, rather, suggest that these may in fact promote higher consumption.

Several proposed physiologic mechanisms have been proposed to explain LCS beverages effects on energy and sugar intake and effects on body weight. These include LCS-induced promotion of appetite and energy intake by augmentation of insulin levels, failure to suppress ghrelin, alteration of the central reward response to carbohydrate ingestion, promotion of sweet taste preferences, and dysregulation of the predictive relationship between sweetness and calorie ingestion, leading to overconsumption [22]. Yet studies assessing effects of beverages with LCS compared with SSBs on child appetite report mixed findings. Some demonstrate that children completely compensate for the diluted energy content of LCS beverages by eating more solid food calories at subsequent meals compared with children administered SSBs, while others report a reduction in total energy intake with LCS beverages ingestion [23].

The current study is limited by the use of self-reported dietary intake data and relies on information collected during a single 24-h recall. Moreover, the analysis did not assess the quality of overall diet that may have a huge impact on body weight.

In summary, the results of the current study align with current recommendations that water, which is vital for all known forms of life, is the best alternative to SBs in children.

Non-alcoholic fatty liver disease in overweight children: role of fructose intake and dietary pattern

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Abstract: The role of nutrition and diet in the development of non-alcoholic fatty liver disease (NAFLD) is still not fully understood. In the present study, we determined if dietary pattern and markers of intestinal permeability differ between overweight children with and without NAFLD. In addition, in a feasibility study, we assessed the effect of a moderate dietary intervention only focusing on nutrients identified to differ between groups on markers of intestinal barrier function and health status. Anthropometric data, dietary intake, metabolic parameters, and markers of inflammation, as well as of intestinal permeability, were assessed in overweight children ($n = 89$, aged 5–9) and normal-weight healthy controls ($n = 36$, aged 5–9). Sixteen children suffered from early signs of NAFLD, for example, steatosis grade 1 as determined by ultrasound. Twelve children showing early signs of NAFLD were enrolled in the intervention study ($n = 6$ intervention, $n = 6$ control). Body mass index (BMI), BMI standard deviation score (BMI-SDS), and waist circumference were significantly higher in NAFLD children than in overweight children without NAFLD. Levels of bacterial endotoxin, lipopolysaccharide-binding protein (LBP), and proinflammatory markers like interleukin 6 (IL-6) and tumor necrosis factor α (TNFα) were also significantly higher in overweight children with NAFLD compared to those without. Total energy and carbohydrate intake were higher in NAFLD children than in those without. The higher carbohydrate intake mainly resulted from a higher total fructose and glucose intake derived from a significantly higher consumption of sugar-sweetened beverages. When counseling children with NAFLD regarding fructose intake (4 times, 30–60 min within 1 year; one one-on-one counseling and 3 group counselings), neither alanine aminotransferase (ALT) nor aspartate aminotransferase (AST) activity in serum changed; however, diastolic blood pressure ($p < 0.05$) and bacterial endotoxin levels ($p = 0.06$) decreased markedly in the intervention group after one year. Similar changes were not found in uncounseled children. Our results suggest that a sugar-rich diet might contribute to the development of early stages of NAFLD in overweight children, and that moderate dietary counseling might improve the metabolic status of overweight children with NAFLD.

Comments

As a result of the increasing prevalence of pediatric obesity, non-alcoholic fatty liver disease (NAFLD) has rapidly become the most common cause of chronic hepatopathies in children. NAFLD is a progressive disease that encompasses a spectrum of liver diseases, ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). Data related to survival in children are scarce, but data firmly associate NAFLD with higher risks of hepatic and non-hepatic morbidities and mortalities compared with the general population. More recently, the association between NAFLD and cardiovascular disease among children has increasingly been recognized. Considering the risk of progression of liver damage to cirrhosis and end-stage liver disease, in the last decades, scientific research in this field has been directed to the identification of pathogenetic mechanisms and possible therapeutic strategies for NAFLD.

Overweight and insulin resistance are among the key risk factors for the development of NAFLD; however, the question as to why some overweight individuals develop NAFLD and others do not is yet to be fully answered.

Although it is clear that glucose has important effects on obesity and other adverse health responses, it appears that fructose, when consumed at high levels, has additional adverse effects on increased liver fat, visceral fat, muscle fat, and triglycerides [24, 25].

Indeed, in the present study, overweight children with early signs of NAFLD had a significantly higher mean daily total energy intake when compared to overweight children without NAFLD (~250 kcal/day), which mainly seemed to result from a higher daily total fructose (free fructose and fructose derived from sucrose) and total glucose (free glucose and glucose derived from sucrose) intake originating from a markedly higher soft-drink and juice intake.

Results of the present study suggest that, in overweight children, very early stages of NAFLD are associated with higher body weight, greater waist circumference, and elevated proinflammatory cytokine levels, while markers of insulin resistance are not different. Therefore, the results of the present study preclude that an impaired glucose tolerance or insulin resistance contributes to the onset of NAFLD. Indeed, in adults and mouse models, it was shown that both fasting insulin and glucose levels can still be within the normal range in peripheral blood, while, in liver tissue, the expressions of insulin receptor and insulin receptor substrate were markedly lower [26]. Therefore, it could be that, such as in the present study, overweight children with NAFLD may have suffered from impairments of insulin signaling and glucose metabolism in liver tissue, while fasting glucose and insulin concentrations in peripheral blood were still within the normal range.

In this study, both bacterial endotoxin and lipopolysaccharide-binding protein (LBP) levels were significantly higher in overweight children with NAFLD than in those without, suggesting that alterations of intestinal barrier function and, subsequently, an increased translocation of bacterial endotoxin are critical in the development of NAFLD. This study also suggests that targeting sugar or fructose intake even with moderate measures may be beneficial for overall health status of overweight children with NAFLD.

However, the study is limited by the small sample size of the intervention group. Furthermore, no power calculation was performed to determine the number of subjects needed to be included for statistically significant outcomes. Thus, the characteristics of the feasibility study are rather explorative, and the effect of a moderate dietary intervention on metabolic and inflammatory markers needs to be assured in a larger randomized population.

Also, no valid data were available regarding nutritional intake and dietary pattern at the end of the intervention. Therefore, it is not clear if the beneficial effects on bacterial endotoxin levels found at the end of the study resulted from a change in fructose intake or dietary pattern or other factors. Furthermore, physical and sedentary activities were only acquired by questionnaires rather than activity monitors that are subject to report bias.

Finally, lifestyle modification and diet remain the mainstay of treatments of pediatric obesity and NAFLD, but with disappointing results because of the difficulty in obtaining sustained long-term results. The findings of this study call for design of larger randomized trials with a longer duration and follow-up that may give a better overview if targeting fructose intake may be beneficial for overall health status of overweight children with NAFLD.

A randomized control trial of the impact of LCPUFA-ω3 supplementation on body weight and insulin resistance in pubertal children with obesity

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Background: Paediatric obesity and insulin resistance (IR) are potentially reversible inflammatory conditions. Long chain polyunsaturated fatty acids omega-3 (LCPUFA-ω3) show anti-inflammatory and metabolic properties, but their clinical efficacy is unclear.

Objective: The objective of this study is to evaluate whether supplementation with LCPUFA-ω3 for 3 months reduces insulin resistance and weight to adolescents with obesity.

Methods: Double-blind trial of 366 adolescents with obesity randomly assigned to 1.2-g LCPUFA-ω3 (DO3) or 1-g sunflower oil (DP) daily for 3 months; both groups received an energy-restricted diet. Children attended monthly for anthropometric, dietary, and clinical measurements. Basal and final blood samples were obtained to measure metabolic markers and erythrocytes fatty acids. Regression models were used for analysis.

Results: A total of 119 DO3 and 126 DP children completed follow-up. At baseline, 92% of children presented IR, 66% hypertriglyceridemia, 37% low-grade inflammation, and 32% metabolic syndrome. Despite erythrocytes LCPUFA-ω3 increased more in DO3 (Median differences = 0.984 w/w%; 95 IC = 0.47, 1.53, $p < 0.001$), body weight, insulin, and HOMA changed similarly in both groups at the end of intervention. Adjusting for basal values, changes in weight, insulin, and HOMA was not related with supplementation.

Conclusions: Supplementation with LCPUFA-ω3 does not affect body weight or insulin in adolescents with obesity.

Comments

Both obesity and insulin resistance (IR) are potentially reversible, but the strategies used to reverse them have been disappointing; therefore, the search for effective therapies continues.

The pathophysiological events linking obesity with IR include augmented production of adipokines that generate oxidative stress, inflammation, and IR. Thus, the use of anti-inflammatory agents as adjuvants in the treatment of obesity seems appropriate.

Experimental studies have demonstrated that the long-chain polyunsaturated fatty acids omega-3 (LCPUFA-ω3), eicosapentaenoic (EPA), and docosahexaenoic (DHA) exert anti-inflammatory properties and stimulate the expression of genes involved in the metabolic pathways of insulin action [27], making them potential candidates in the treatment of obesity and IR, but their effectiveness is not well established.

LCPUFA-ω3 are increasingly being used in the prevention and management of several cardiovascular risk factors. LCPUFA-ω3 are effective modulators of the inflammation that accompanies several cardiometabolic abnormalities. Taking into consideration the pleiotropic nature of their actions, it can be concluded that dietary supplementation with LCPUFA-ω3 can lead to improvements in cardiometabolic health parameters.

A previous study [28] analyzed the effect of supplementation with LCPUFA-ω3 on adipokine concentration and IR of prepubertal and pubertal children, independent of weight loss. The researchers found that supplementation with n3-LCPUFA was a potential beneficial tool for the reduction of IR.

However, the results of the current study are disappointing, since it did not detect any effect of LCPUFA-ω3 supplementation on weight, insulin, or HOMA even after adjusting for their corresponding baseline values in children and adolescents who already have obesity and metabolic disturbances. Nevertheless, these results do not discount previous findings of the preventive effect of LCPUFAs-ω3 in healthy children or adolescents. We may speculate that LCPUFAs-ω3 has a protective role without a therapeutic effect. Therefore, LCPUFAs-ω3 supplementation does not reverse the already stabilized IR as seen in obese children but may provide other metabolic benefits.

The strengths of this study are the design of a double-blind, randomized, placebo-controlled, parallel study and the inclusion of a large number of participants.

The Intestinal Microbiota and their Relation to Metabolic Programming

The gut microbiota in infants of obese mothers increases inflammation and susceptibility to NAFLD

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Abstract: Maternal obesity is associated with increased risk for offspring obesity and non-alcoholic fatty liver disease (NAFLD), but the causal drivers of this association are unclear. Early colonization

of the infant gut by microbes plays a critical role in establishing immunity and metabolic function. Here, we compare germ-free mice colonized with stool microbes (MB) from 2-week-old infants born to obese (Inf-ObMB) or normal-weight (Inf-NWMB) mothers. Inf-ObMB-colonized mice demonstrate increased hepatic gene expression for endoplasmic reticulum stress and innate immunity together with histological signs of periportal inflammation, a histological pattern more commonly reported in pediatric cases of NAFLD. Inf-ObMB mice show increased intestinal permeability, reduced macrophage phagocytosis, and dampened cytokine production suggestive of impaired macrophage function. Furthermore, exposure to a Western-style diet in Inf-ObMB mice promotes excess weight gain and accelerates NAFLD. Overall, these results provide functional evidence supporting a causative role of maternal obesity-associated infant dysbiosis in childhood obesity and NAFLD.

Comments

Evidence in rodents, humans, and non-human primates support the scientific evidence that exposure to maternal obesity or high-fat diet during pregnancy creates a long-lasting metabolic signature on the infant innate immune system and the juvenile microbiota, which predisposes the offspring to obesity and metabolic disease.

Alteration of the early infant gut microbiome has been correlated with the development of childhood obesity. This is likely to be due to complex interactions between mode of delivery, antibiotic use, maternal diet, components of breastfeeding, and a network of regulatory events involving both the innate and adaptive immune systems within the infant host. Each of these factors are critical for informing microbiome development and can affect immune signaling, toxin release, and metabolic signals, including short-chain fatty acids and bile acids, that regulate appetite, metabolism, and inflammation. Clinical data also support correlations between pediatric obesity, non-alcoholic fatty liver disease (NAFLD), and gut dysbiosis [29].

The current study is the first experimental evidence to support the hypothesis that changes in the gut microbiome in infants born to obese mothers directly initiate obesity and NAFLD pathways. The study evaluated infants born to normal weight (NW) and obese (Ob) mothers; these infants were born vaginally, exclusively breastfed, and were without exposure to antibiotics after delivery.

By using germ-free (GF) mice, the researchers investigate the hypothesis that early gut dysbiosis noted in 2-week-old infants born to Ob mothers cause metabolic and inflammatory changes characteristic of obesity and NAFLD. Their results demonstrate that altered gut microbiota in 2-week-old infants born to Ob mothers induced changes in intestinal permeability and hepatic metabolism, including inflammation and a dysfunctional macrophage phenotype in in the liver and bone marrow cells of GF mice that might be causal factors underlying the increased transmission of obesity and NAFLD risk in children born to Ob mothers. These mice were predisposed to accelerated weight gain and the development of fatty liver following exposure to a Western-style diet (WSD).

Mice colonized with stool microbes from infants born to obese mothers (Inf-ObMB) had increased hepatic endoplasmic reticulum stress, hepatic inflammation, and liver macrophage accumulation, consistent with the concept that Inf-ObMB provokes an inflammatory microenvironment in the livers of these mice. Inf-ObMB colonized mice showed also histological evidence for increased periportal inflammation that is seen also in humans with advanced forms of pediatric NAFLD and features of the metabolic syndrome, suggesting that it has clinical relevance as an early manifestation of leaky gut.

Other important findings of this study were a significant increase in bile acid (BA) levels in feces from Inf-ObMB mice and the evidence of reduced gut barrier gene expres-

sion and increased intestinal permeability, as has been reported in children with established NAFLD [30]. The findings also indicate that a macrophage dysfunction, in addition to other consequences of dysbiosis on liver inflammation, accelerates steatosis and weight gain when exposed to WSD.

The strengths of the study include the study cohort of infants was relatively a homogenous group (infants who were born vaginally, exclusively breastfed, and were without exposure to antibiotics after delivery) that allowed exclusion of confounding factors that may impact the gut microbiota and bias the results. Also, the design of pooling infant stool samples allowed to create one inoculum for each round of colonization treatment group. Although it might have limited the variability seen between individual infants at this stage of development, the microbiota compositions of the Inf-NWMB and Inf-ObMB mice at 21 days post-gavage were significantly different and consistent with the major compositional differences in the NW and Ob infant donor stool. This, along with the replication of the findings with 3 rounds of colonization using unique pools of stool for each round, strengthens the likelihood that the results are relevant for a larger human infant population.

In conclusion, maternal obesity dramatically increases the long-term risk for obesity in the next generation partially by altering the offspring gut microbiome. Therefore, pregnancy and lactation may be critical periods at which to aim primary prevention to break the obesity cycle.

Future studies utilizing interventional strategy as changes in maternal diet and the use of pre/probiotics, as well as understanding their bioactive metabolites that might prevent metabolic perturbations, are needed to modify the epidemic of childhood obesity and NAFLD risk in infants born to obese mothers.

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Turck D, Shamir R, Koletzko B, Phillip M (eds): Nutrition and Growth: Yearbook 2020.
World Rev Nutr Diet. Basel, Karger, 2020, vol 120, pp 48–60 (DOI: 10.1159/000503649)

Epigenetics, Nutrition, and Growth

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Introduction

Both human growth and the response to diet, for example, the absorption and metabolism of certain nutrients, are modulated by genetic variation. Although rare monogenetic causes of obesity have been identified, the results of genome-wide association studies have demonstrated only relatively modest effects on human growth, body mass, and obesity risk. Likewise, sizeable nutrigenetic interaction effects have only been demonstrated for some nutrients so far, for example, folic acid and polyunsaturated fatty acids. It has been proposed that epigenetic effects may account for some of the unexplained heritability of common phenotypes and particularly for the lasting effects of exposure to environmental cues in early life on later health, performance, and disease risks (early metabolic programming of lifelong health). Epigenetic modifications of the genome are hereditary cell characteristics not determined by DNA sequence but by biochemical DNA changes, including histone modification, DNA methylation, or noncoding RNAs. Thereby, epigenetic modifications determine the accessibility of DNA to a variety of transcription and other regulatory factors and determine the activity state of underlying DNA code, that is, they can modify gene expression and hence function. Epigenetic profiles of individual cells can also act as memory of environmental exposure, particularly in early life with a high susceptibility to inducing epigenetic changes, allowing a cell to maintain its specific properties after each cell division. Most human studies to data have applied assessment of cytosine methylation given that commercial chips for high-throughput epigenome-wide analyses are available. The major challenge for such studies is not the biochemical analysis but rather the complex bioinformatic exploration of the resulting very large datasets. Some first studies have explored the potential relations of epigenetics, nutrition, and growth.

Key articles reviewed for this chapter

DNA methylation changes related to nutritional deprivation: a genome-wide analysis of population and in vitro data

He Y, de Witte LD, Houtepen LC, Nispeling DM, Xu Z, Yu Q, Yu Y, Hol EM, Kahn RS, Boks MP

Clin Epigenetics 2019;11:80

A randomized controlled trial of folic acid intervention in pregnancy highlights a putative methylation-regulated control element at ZFP57

Irwin RE, Thursby SJ, Ondičová M, Pentieva K, McNulty H, Richmond RC, Caffrey A, Lees-Murdock DJ, McLaughlin M, Cassidy T, Suderman M, Relton CL, Walsh CP

Clin Epigenetics 2019;11:31

A low glycaemic index diet in pregnancy induces DNA methylation variation in blood of newborns: results from the ROLO randomised controlled trial

Geraghty AA, Sexton-Oates A, O'Brien EC, Alberdi G, Fransquet P, Saffery R

Nutrients 2018;10:455

DNA methylation of imprinted genes at birth is associated with child weight status at birth, 1 year, and 3 years

Gonzalez-Nahm S, Mendez MA, Benjamin-Neelon SE, Murphy SK, Hogan VK, Rowley DL, Hoyo C

Clin Epigenetics 2018;10:90

Fetal growth is associated with CpG methylation in the P2 promoter of the insulin-like growth factor-1 gene

Le Stunff C, Castell AL, Todd N, Mille C, Belot MP, Frament N, Brailly-Tabard S, Benachi A, Fradin D, Bougnères P

Clin Epigenetics 2018;10:57 (Correction to: Fetal growth is associated with CpG methylation in the P2 promoter of the insulin-like growth factor-1 gene. *Clin Epigenetics 2018;10:74*)

Meta-analysis of epigenome-wide association studies in neonates reveals widespread differential DNA methylation associated with birthweight

Küpers LK, Monnereau C, Sharp GC, Yousefi P, Salas LA, Ghantous A, Page CM, Reese SE, Wilcox AJ, Czamara D, Starling AP, Novoloaca A, Lent S, Roy R, Hoyo C, Breton CV, Allard C, Just AC, Bakulski KM, Holloway JW, Everson TM, Xu CJ, Huang RC, van der Plaat DA, Wielscher M, Merid SK, Ullemar V, Rezwan FI, Lahti J, van Dongen J, Langie SAS, Richardson TG, Magnus MC, Nohr EA, Xu Z, Duijts L, Zhao S, Zhang W, Plusquin M, DeMeo DL, Solomon O, Heimovaara JH, Jima DD, Gao L, Bustamante M, Perron P, Wright RO, Hertz-Picciotto I, Zhang H, Karagas MR, Gehring U, Marsit CJ, Beilin LJ, Vonk JM, Jarvelin MR, Bergström A, Örtqvist AK, Ewart S, Villa PM, Moore SE, Willemsen G, Standaert ARL, Håberg SE, Sørensen TIA, Taylor JA, Räikkönen K, Yang IV, Kechris K, Nawrot TS, Silver MJ, Gong YY, Richiardi L, Kogevinas M, Litonjua AA, Eskenazi B, Huen K, Mbarek H, Maguire RL, Dwyer T, Vrijheid M, Bouchard L, Baccarelli AA, Croen LA, Karmaus W, Anderson D, de Vries M, Sebert S, Kere J, Karlsson R, Arshad SH, Hämäläinen E, Routledge MN, Boomsma DI, Feinberg AP, Newschaffer CJ, Govarts E, Moisse M, Fallin MD, Melén E, Prentice AM, Kajantie E, Almqvist C, Oken E, Dabelea D, Boezen HM, Melton PE, Wright RJ, Koppelman GH, Trevisi L, Hivert MF, Sunyer J, Munthe-Kaas MC, Murphy SK, Corpeleijn E, Wiemels J, Holland N, Herceg Z, Binder EB, Davey Smith G, Jaddoe VWV, Lie RT, Nystad W, London SJ, Lawlor DA, Relton CL, Snieder H, Felix JF

Nat Commun 2019;10:1893

ExtraUterine Growth Restriction in preterm infants: growth patterns, nutrition, and epigenetic markers. A pilot study

Tozzi MG, Moscuzza F, Michelucci A, Lorenzoni F, Cosini C, Ciantelli M, Ghirri P

Front Pediatr 2018;6:408

Phthalate exposures, DNA methylation and adiposity in Mexican children through adolescence

Bowman A, Peterson KE, Dolinoy DC, Meeker JD, Sánchez BN, Mercado-Garcia A, Téllez-Rojo MM, Goodrich JM

Front Public Health 2019;7:162

DNA methylation changes related to nutritional deprivation: a genome-wide analysis of population and in vitro data

He Y[1,4], de Witte LD[1,2], Houtepen LC[1], Nispeling DM[1], Xu Z[1], Yu Q[3], Yu Y[3], Hol EM[4,5], Kahn RS[1,2], Boks MP[1]

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Background: DNA methylation has recently been identified as a mediator between in utero famine exposure and a range of metabolic and psychiatric traits. However, genome-wide analyses are scarce and cross-sectional analyses are hampered by many potential confounding factors. Moreover, causal relations are hard to identify due to the lack of controlled experimental designs. In the current study, we therefore combined a comprehensive assessment of genome-wide DNA methylation differences in people exposed to the great Chinese famine in utero with an in vitro study in which we deprived fibroblasts of nutrition.

Methods: We compared whole blood DNA methylation differences between 25 individuals in utero exposed to famine and 54 healthy control individuals using the HumanMethylation450 platform. In vitro, we analyzed DNA methylation changes in 10 fibroblast cultures that were nutritionally deprived for 72 h by withholding fetal bovine serum.

Results: We identified 3 differentially methylated regions in 4 genes (ENO2, ZNF226, CCDC51, and TMA7) that were related to famine exposure in both analyses. Pathway analysis with data from both Chinese famine samples and fibroblasts highlighted the nervous system and neurogenesis pathways as the most affected by nutritional deprivation.

Conclusions: The combination of cross-sectional and experimental data provides indications that biological adaptation to famine leads to DNA methylation changes in genes involved in the central nervous system.

Comments This small exploratory pilot study analyzed whole blood DNA from 25 Chinese subjects whose mothers were exposed to famine in pregnancy. A weakness of the publication is that the approach to selecting this subgroup from the total originally included study population and the details of exposure and clinical characteristics of this subgroup are not reported. Hypomethylation of 3 differentially methylated regions in 4 gene promoters were reported with a statistical significance level of 1%. The genes involved relate to nervous system development. The sample size is very small, and the numerous statistical tests performed were not adjusted for multiple testing. Therefore, the results need to be interpreted with caution and considered as hypothesis raising, with a need for replicating the observations in larger studies.

A randomized controlled trial of folic acid intervention in pregnancy highlights a putative methylation-regulated control element at ZFP57

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Background: Maternal blood folate concentrations during pregnancy have been previously linked with DNA methylation patterns, but this has been done predominantly through observational studies. We showed recently in an epigenetic analysis of the first randomized controlled trial of folic acid (FA) supplementation specifically in the second and third trimesters (the EpiFASSTT trial) that methylation at some imprinted genes was altered in cord blood samples in response to treatment. Here, we report on epigenome-wide screening using the Illumina EPIC array (~850,000 sites) in these same samples (n = 86).

Results: The top-ranked differentially methylated promoter region (DMR) showed a gain in methylation with FA and was located upstream of the imprint regulator ZFP57. Differences in methylation in cord blood between placebo and FA treatment groups at this DMR were verified using pyrosequencing. The DMR also gains methylation in maternal blood in response to FA supplementation. We also found evidence of differential methylation at this region in an independent randomized controlled trial cohort, the AFAST trial. By altering methylation at this region in 2 model systems in vitro, we further demonstrated that it was associated with ZFP57 transcription levels.

Conclusions: These results strengthen the link between FA supplementation during later pregnancy and epigenetic changes and identify a novel mechanism for regulation of ZFP57.

Comments This is one of the few analyses of DNA methylation effects available so far from a randomized controlled clinical intervention trial. One hundred and ninety pregnant women were randomized to receive in the second and third trimester of pregnancy until child birth either 400 mg folic acid (FA) per day or placebo. In 86 newborn infants born to these mothers, cord blood cells were obtained and DNA methylation analyses were performed with a chip covering 850,000 CpG sites. Statistical analysis with a chosen significance level of 5% showed numerous sites to have group differences in the de-

gree of methylation, but unfortunately, an analysis of results corrected for multiple testing is not reported. Among the top 1,000 sites ranked for *p* levels, about 2/3 showed hypomethylation with FA supplementation and 1/3 hypermethylation. The authors highlight increased methylation of the imprint regulator ZFP57 in the offspring of women randomized to FA. Due to the limitations in statistical analyses, these results should be interpreted with some caution until reconfirmed in further studies.

A low glycaemic index diet in pregnancy induces DNA methylation variation in blood of newborns: results from the ROLO randomised controlled trial

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Abstract: The epigenetic profile of the developing fetus is sensitive to environmental influence. Maternal diet has been shown to influence DNA methylation patterns in offspring, but research in humans is limited. We investigated the impact of a low glycaemic index dietary intervention during pregnancy on offspring DNA methylation patterns using a genome-wide methylation approach. Sixty neonates were selected from the ROLO (Randomised cOntrol trial of LOw glycaemic index diet to prevent macrosomia) study: 30 neonates from the low glycaemic index intervention arm and 30 from the control, whose mothers received no specific dietary advice. DNA methylation was investigated in 771,484 CpG sites in free DNA from cord blood serum. Principal component analysis and linear regression were carried out comparing the intervention and control groups. Gene clustering and pathway analysis were also explored. Widespread variation was identified in the newborns exposed to the dietary intervention, accounting for 11% of the total level of DNA methylation variation within the dataset. No association was found with maternal early-pregnancy body mass index, infant sex, or birthweight. Pathway analysis identified common influences of the intervention on gene clusters plausibly linked to pathways targeted by the intervention, including cardiac and immune functioning. Analysis in 60 additional samples from the ROLO study failed to replicate the original findings. Using a modest-sized discovery sample, we identified preliminary evidence of differential methylation in progeny of mothers exposed to a dietary intervention during pregnancy.

Comments This is another one of the very few analyses of DNA methylation effects available so far from randomized controlled clinical intervention trials. A high-risk group of pregnant women who had delivered a macrosomic infant in a preceding pregnancy were randomized to receive no intervention or a dietary education session delivered by a trained dietician for a duration of about 2 h. The focus of the training was on preferential choice of foods with a low glycemic index and reducing the intake of foods with a high glycemic index. Written information was also provided, and the messages were reinforced in a second session with the dietician held between 28 and 34 weeks of gestation. In the overall trial, the intervention did not achieve any significant difference between the 2 groups in infant birth weight, birth weight centile, or ponderal index. However, women in the intervention arm had significantly less gestational weight gain (mean difference –1.3 kg) and a lower rate of glucose intolerance (21 vs. 28%). In a sub-

group of 30 infants each from the 2 intervention arms, circulating cell-free DNA was extracted from frozen cord blood serum and analyzed for DNA methylation with a chip covering 850,000 CpG sites. Data were evaluated with principle component and linear regression analyses adjusted for confounders, and the Benjamin-Hochberg false discovery rate was applied to adjust for multiple testing. The results indicate preliminary evidence for widespread but subtle changes of differentially methylated regions in the neonatal genome in response to the dietary intervention in their mothers during pregnancy. Methylation was not associated with maternal body weight or body mass index nor with neonatal birth weight. In a further subset of another 60 infants, methylation of 3 candidate genes using the Sequenom Mass Array technology was attempted, but here the initial findings could not be confirmed. The data indicate the real potential that diet in pregnancy may modulate epigenetic signaling in the offspring, which might impact child outcome. This should prompt further work in this promising area.

DNA methylation of imprinted genes at birth is associated with child weight status at birth, 1 year, and 3 years

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Background: This study assessed the associations between 9 differentially methylated regions of imprinted genes in DNA derived from umbilical cord blood leukocytes in males and females and (1) birth weight for gestational age *z* score, (2) weight-for-length *z* score at 1 year, and (3) body mass index (BMI) *z* score at 3 years.

Methods: We conducted multiple linear regression in $n = 567$ infants at birth, $n = 288$ children at 1 year, and $n = 294$ children at 3 years from the Newborn Epigenetics Study. We stratified by sex and adjusted for race/ethnicity, maternal education, maternal pre-pregnancy BMI, prenatal smoking, maternal age, gestational age, and paternal race. We also conducted analysis restricting to infants not born small for gestational age.

Results: We found an association between higher methylation of the sequences regulating paternally expressed gene 10 and anthropometric *z* scores at 1 year ($\beta = 0.84$; 95% CI = 0.34–1.33; $p = 0.001$) and 3 years ($\beta = 1.03$; 95% CI = 0.37–1.69; p value = 0.003) in males only. Higher methylation of the differentially methylated region regulating mesoderm-specific transcript was associated with lower anthropometric *z* scores in females at 1 year ($\beta = -1.03$; 95% CI –1.60 to –0.45; p value = 0.001) and 3 years ($\beta = -1.11$; 95% CI –1.98 to –0.24; p value = 0.01). These associations persisted when we restricted to infants not born small for gestational age.

Conclusion: Our data support a sex-specific association between altered methylation and weight status in early life. These methylation marks can contribute to the compendium of epigenetically regulated regions detectable at birth, influencing obesity in childhood. Larger studies are required to confirm these findings.

Comments This study associated DNA methylation in cord blood white cells with birth weight in more than 500 newborn infants and with weight at 1 and 3 years of age in close to 300 children, respectively. Methylation of paternally expressed gene 10 (PEG10) was associated with anthropometric measures at 1 and 3 years only in boys but not in girls. These data are of interest in that they suggest a potential sex-specific effect of DNA methylation on body mass index and potentially on obesity risk, which could provide the potential for sex-specific, targeted obesity prevention strategies in the future. More inside into exposures that might affect these methylation effects would be most valuable.

Fetal growth is associated with CpG methylation in the P2 promoter of the insulin-like growth factor-1 gene

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Correction to: Fetal growth is associated with CpG methylation in the P2 promoter of the insulin-like growth factor-1 gene.
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Background: There are many reasons to think that epigenetics is a key determinant of fetal growth variability across the normal population. Since insulin-like growth factor-1 (IGF-1) and INS genes are major determinants of intrauterine growth, we examined the methylation of selected CpGs located in the regulatory region of these 2 genes.
Methods: Cord blood was sampled in 159 newborns born to mothers prospectively followed during their pregnancy. A 142-item questionnaire was filled by mothers at inclusion, during the last trimester of the pregnancy and at the delivery. The methylation of selected CpGs located in the promoters of the IGF-1 and INS genes was measured in cord blood mononuclear cells collected at birth using bisulfite-PCR-pyrosequencing.
Results: Methylation at *IGF-1* CpG-137 correlated negatively with birth length ($r = 0.27$, $p = 3.5 \times 10^{-4}$). The same effect size was found after adjustment for maternal age, parity, and smoking: a 10% increase in CpG-137 methylation was associated with a decrease of length by 0.23 SDS.
Conclusion: The current results suggest that the methylation of *IGF-1* CpG-137 contributes to the individual variation of fetal growth by regulating *IGF-1* expression in fetal tissues.

Comments This study in a sample of 159 infants born in France explored DNA methylation in a promoter of the insulin-like growth factor-1 (IGF-1) gene and found an association of increased methylation with reduced neonatal length at birth. The effect size was not large, with an increase of CPG methylation from 40 to 70% associated with reduced length by about half a standard deviation. Nonetheless, the data suggest the exciting potential that increased methylation of this IGF1-P2 promoter may significantly impact on fetal growth, which should certainly motivate further exploration of the underlying pathways.

Meta-analysis of epigenome-wide association studies in neonates reveals widespread differential DNA methylation associated with birthweight

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Abstract: Birthweight is associated with health outcomes across the life course, DNA methylation may be an underlying mechanism. In this meta-analysis of epigenome-wide association studies of 8,825 neonates from 24 birth cohorts in the Pregnancy And Childhood Epigenetics Consortium, we find that DNA methylation in neonatal blood is associated with birthweight at 914 sites, with a difference in birthweight ranging from –183 to 178 g per 10% increase in methylation ($P_{Bonferroni} < 1.06 \times 10^{-7}$). In additional analyses in 7,278 participants, <1.3% of birthweight-associated differential methylation is also observed in childhood and adolescence, but not adulthood. Birthweight-related CpGs overlap with some Bonferroni-significant CpGs that were previously reported to be related to maternal smoking (55/914, $p = 6.12 \times 10^{-74}$) and body mass index in pregnancy (3/914, $p = 1.13 \times 10^{-3}$), but not with those related to folate levels in pregnancy. Whether the associations that we observe are causal or explained by confounding or fetal growth influencing DNA methylation (i.e., reverse causality) requires further research.

Comments This is a very impressive and well-performed, huge data analysis that combined data of epigenome-wide association studies in almost 9,000 newborn infants from a large number of birth cohorts, based on the established collaboration of the Pregnancy and Childhood Epigenetic consortium. DNA methylation in neonatal blood cells showed an association with birth weight at more than 900 genome sites, with some very large effect sizes: a 10% change in the degree of methylation modified birth rate by as much as up to 180 g upward and downward, respectively. These results indicate that environmental cues might markedly affect birth weight via epigenetic mechanisms. Future needs should explore which environmental cues may be of key relevance and whether the associations might reflect causal relationships.

ExtraUterine Growth Restriction in preterm infants: growth patterns, nutrition, and epigenetic markers. A pilot study

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Background/Aims: IntraUterine and ExtraUterine growth restriction (EUGR) may induce reprogramming mechanisms, finalized to survive before and after birth. Nutritional factors and other environmental signals could regulate gene expression through epigenetic modification, but the molecular mechanisms involved are not yet well understood. Epigenetic mechanisms could be considered as a bridge between environmental stimuli and long-lasting phenotype, acquired during the intrauterine life and the first weeks of life. Our aim was to investigate the relationship between growth patterns, nutritional determinants, and epigenetic pathways.

Methods: We enrolled 38 newborns admitted to neonatal intensive care unit at University Hospital of Pisa. Gestational age at birth was <34 weeks and post-menstrual age was 36–42 weeks at discharge. We excluded infants with malformations or clinical syndromes. EUGR was defined as the reduction in weight z score between birth and discharge >1 SD. We also evaluated DNA methylation of imprinting centre 1 (IC1) at birth and at discharge.

Results: We observed a decrease in SD of weight and head circumference mainly during the first weeks of life. We found a correlation between EUGR for weight and for head circumference and an increased

IC1 methylation ($p = 0.018$ and $p = 0.0028$, respectively). We observed a relationship between reduced protein and lipid intake and IC1 hypermethylation ($p = 0.009$ and $p = 0.043$, respectively).
Conclusion: IC1 hypermethylation could be a reprogramming mechanism to promote a catch-up growth, by means of an increased Insulin-like growth factor 2 expression, that may have potential effects on metabolic homeostasis later in life.

Comments This study in a small and somewhat heterogeneous group of 38 preterm infants from one neonatal intensive care in Italy determined methylation of an imprinting control region regulating the insulin growth factor-2 gene expression. There was no association with birth weight, but increased methylation was associated with a greater proportion of children who showed a reduction in weight z-score between birth and discharge by >1 SD. Increased methylation at this site was also inversely related to both dietary protein and lipid intake. However, statistical analysis was performed at the 5% significant level without any correction for multiple testing. Therefore, the observations need to be regarded with caution. Larger studies aiming at replication would appear highly desirable.

Phthalate exposures, DNA methylation and adiposity in Mexican children through adolescence

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Abstract: Phthalates are a class of endocrine disrupting chemicals with near ubiquitous exposure to populations around the world. Phthalates have been associated with children's adiposity in previous studies, though discrepancies exist across studies that may be due to timing of exposure or outcome assessment and population differences (i.e., genetics, other confounders). DNA methylation, an epigenetic modification involved in gene regulation, may mediate the effects of early life phthalate exposures on health outcomes. This study aims to evaluate the mediating effect of DNA methylation at growth-related genes on the association between phthalate exposure and repeat measures of adiposity (body mass index [BMI]-for-age z-score, waist circumference, and skinfolds thickness) in Mexican children. Urinary phthalate metabolite concentrations were quantified in mothers at each of the 3 trimesters of pregnancy and in children at the first peri-adolescent study visit. Blood leukocyte DNA methylation at *H19* and *HSD11B2* was quantified during the first peri-adolescent visit, and adiposity was measured at the first visit and again ~3 years later among participants ($n = 109$ boys, 114 girls) from the Early Life Exposure in Mexico to Environmental Toxicants project. Associations between phthalates or DNA methylation and repeat outcome measures were assessed separately in boys and girls using generalized estimating equation models including

covariates (urinary specific gravity, maternal education, and child's age). Sobel tests were used to assess DNA methylation as a mediator in models adjusting for the same covariates. Associations between phthalates and adiposity varied by phthalate and timing of exposure. Early gestation MBP, MIBP, and MBzP were associated with adiposity among girls. For example, among girls first trimester maternal urine concentrations of MIBP were associated with increases in skinfold thickness, BMI-for-age, and waist circumference ($p < 0.01$). Second trimester and adolescent MBzP were associated with adiposity among boys in opposite directions. In girls, *H19* methylation was positively associated with skinfold thickness. No significant mediation of phthalate exposure on adiposity by DNA methylation of *H19* or *HSD11B2* was observed (Sobel $p > 0.05$). However, the mediation analysis was underpowered to detect small to medium effect sizes, and the role of DNA methylation as a mediator between phthalates and outcomes merits further study.

Comments The authors explored the hypothesis that phthalates, widespread industrial plasticizers and additives with endocrine disruption properties DNA methylation, might induce epigenetic modifications that exert effects on childhood obesity. In a subsample of 109 boys and 114 girls from a Mexican longitudinal other-child cohort study up to the age of 14 years, and many of them also with follow-up to age 17 years, phthalates were measured in maternal and child urine samples by liquid chromatography triple mass spectrometry. DNA methylation was determined in DNA extracted from children's whole blood samples collected at an age between 8 and 14 years. While some phthalate measures in mothers and children were associated with measures of child obesity and adiposity, no significant mediation effects for DNA methylation were detected for the association between phthalates and outcomes in the total study sample, but there non-significant for DNA methylation as a mediator between phthalate exposure and adiposity in the Sobel test for non-zero mediation. These observations indicate the potential of exploring epigenetics as a mediator influencing susceptibility to effects from toxicant exposures, which should be tested in larger studies with greater statistical power.

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Term and Preterm Infants

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Introduction

For term infants, the review addressed several issues. Five articles on infant formula [1–5] are discussed. Three of them relate to the relationship between the composition/consumption of infant formula and health outcomes later in life [1–3]; 2 of them review the evidence on the supplementation of beta-palmitate in infant formula [4] and the role of hydrolyzed rice protein formulas in infant feeding [5]. Two additional papers are devoted to probiotics, a field where the gap between basic research and clinical practice has been constantly growing over the years. A Cochrane systematic review summarizes the available data on the use of probiotics in colicky infants, a very challenging issue for pediatricians and parents [6]. New data on the restoration of normal microbiota composition in antibiotic-treated and cesarean infants are provided [7]. The influence of pregnancy and infant feeding on the intestinal microbiome is also covered [8]. The impact of complementary feeding on allergic disorders has been systematically reviewed by an expert group from the United States [9]. The main message is to confirm that the introduction of complementary foods should not be different between infants at risk or not at risk for allergy. Preliminary data show that an early introduction of egg and peanut could even be beneficial to infants with a strong family history of allergy. Another paper suggests an influence of the timing of introduction of complementary feeding on infant sleep [10]. The last 3 articles on term infants demonstrate that the use of young child formula is one of the means to better cover the nutritional needs of young children (1–3 years), especially iron and vitamin D [11–13].

For preterm infants, the focus of last year's chapter has been on types of feeding. This year we will address 2 main issues. Both issues are important as they are related to the

actual provision of nutrients to the child, not only what is offered but also whether it is tolerated. Many observational studies have shown that undernutrition and poor growth affect neurodevelopmental and other long-term outcomes. This has been summarized in the review of Ong et al. in an elegant way. Undernutrition might be caused by a reduced or imbalanced nutrient offer or that the amount that is administered is adequate in itself but just does not reach the systemic circulation of the infant. Prevention of undernutrition is one thing; the question that also surfaces nowadays is whether additional nutrient supply beyond the stage of undernutrition proves to be beneficial. Four articles for which we were granted permission to discuss at this Yearbook are presented on this topic [14–17]. The other issue that will be addressed is on tolerance. Three articles are discussed [18–20]. The number of articles on this topic resembles the emphasis that is placed on reaching full enteral feeds as soon as possible. The reduction in time that indwelling catheters are in place, with subsequent higher risks not only of infection but also of suboptimal feeding and hepatic disturbances, is the underlying cause of the interest. In addition, when own mothers milk can be the major source of food, the risk for necrotizing enterocolitis and possibly septicemia can be reduced. It may also be of help of increasing neurocognitive development as this remains to be at risk for preterm infants, despite major advances in perinatal care.

Key articles reviewed for this chapter

Term Infants

Randomized controlled trial of iron-fortified versus low-iron infant formula: Developmental outcomes at 16 years

Gahagan S, Delker E, Blanco E, Burrows R, Lozoff B

J Pediatr 2019;212:124–130

Association of infant formula composition and anthropometry at 4 years: Follow-up of a randomized controlled trial (BeMIM study)

Fleddermann M, Demmelmair H, Hellmuth C, Grote V, Trisic B, Nikolic T, Koletzko B

PLoS One 2018;13:e0199859

Consumption of soy-based infant formula is not associated with early onset of puberty

Sinai T, Ben-Avraham S, Guelmann-Mizrahi I, Goldberg MR, Naugolni L, Askapa G Katz Y, Rachmiel M

Eur J Nutr 2019;58:681–687

Palm oil and beta-palmitate in infant formula: a position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition

Bronsky J, Campoy C, Embleton N, Fewtrell M, Fidler Mis N, Gerasimidis K, Hojsak I, Hulst J, Indrio F, Lapillonne A, Molgaard C, Moltu SJ, Verduci E, Vora R, Domellöf M; ESPGHAN Committee on Nutrition

J Pediatr Gastroenterol Nutr 2019;68:742–760

Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of cow's milk protein allergy

Bocquet A, Dupont C, Chouraqui JP, Darmaun D, Feillet F, Frelut ML, Girardet JP, Hankard R, Lapillonne A, Rozé JC, Simeoni U, Turck D, Briend A; Committee on Nutrition of the French Society of Pediatrics (CNSFP)

Arch Pediatr 2019;26:238–246

Probiotics to prevent infantile colic

Ong TG, Gordon M, Banks SSC, Thomas MR, Akobeng AK

Cochrane Database of Systematic Reviews 2019;3:CD012473

Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants

Korpela K, Salonen A, Vepsäläinen O, Suomalainen M, Kolmeder C, Varjosalo M, Miettinen S, Kukkonen K, Savilahti E, Kuitunen M, de Vos WM

Microbiome 2018;6:182

Diet during pregnancy and infancy and the infant intestinal microbiome

Savage JH, Lee-Sarwar KA, Sordillo JE, Lange NE, Zhou Y, O'Connor GT, Sandel M, Bacharier LB, Zeiger R, Sodergren E, Weinstock GM, Gold DR, Weiss ST, Litonjua AA

J Pediatr 2018;203:47–54

Complementary feeding and food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis: a systematic review

Obbagy JE, English LK, WongYP, Butte NF, Dewey KG, Fleischer DM, Fox MK, Greer FR, Krebs NF, Scanlon KS, Stoody EE

Am J Clin Nutr 2019;109(suppl):890S–934S

Association of early introduction of solids with infant sleep: a secondary analysis of a randomized clinical trial

Perkin MR, Bahnson HT, Logan K, Marrs T, Radulovic S, Craven J, Flohr C, Lack G

JAMA Pediatr 2018;172:e180739

Compared with cow milk, a growing-up milk increases vitamin D and iron status in healthy children at 2 years of age: The Growing-Up Milk-Lite (GUMLi) randomized controlled trial

Lovell AL, Davies PSW, Hill RJ, Milne T, Matsuyama M, Jiang Y, Chen RX, Wouldes TA, Heath ALM, Grant CC, Wall CR

J Nutr 2018;148:1570–1579

A comparison of the effect of a Growing Up Milk-Lite v. cow's milk on longitudinal dietary patterns and nutrient intakes in children aged 12–23 months: the Growing Up Milk-Lite randomized controlled trial

Lovell AL, Davies PSW, Hill RJ, Milne T, Matsuyama M, Jiang Y, Chen RX, Grant CC, Wall CR

Br J Nutr 2019;121:678–687

A multicenter, double-blind, randomized, placebo-controlled trial to evaluate the effect of consuming Growing Up Milk "Lite" on body composition in children aged 12–23 months

Wall CR, Hill RJ, Lovell AL, Matsuyama M, Milne T, Grant CC, Jiang Y, Chen RX, Wouldes TA, Davies PSW

Am J Clin Nutr 2019;109:576–585

Preterm Infants

Supplementing Enteral Intake

Improved lung function at age 6 in children born very preterm and fed extra protein post-discharge

Toftlund LH, Agertoft L, Halken S, Zachariassen G

Pediatr Allergy Immunol 2019;30:47–54

Neurodevelopmental outcome of nutritional intervention in newborn infants at risk of neurodevelopmental impairment: the Dolphin neonatal double-blind randomized controlled trial

Andrew MJ, Parr JR, Montague-Johnson C, Laler K, Holmes J, Baker B, Sullivan PB

Dev Med Child Neurol 2018;60:897–905

Improved outcomes in preterm infants fed a nonacidified liquid human milk fortifier: a prospective randomized clinical trial

Schanler RJ, Groh-Wargo SL, Barrett-Reis B, White RD, Ahmad KA, Oliver J, Baggs G, Williams L, Adamkin D

J Pediatr 2018;202:31–37.e2

Commencing nutrient supplements before full enteral feed volume achievement is beneficial for moderately preterm to late preterm low birth weight babies: a prospective, observational study

Fan WQ, Gan A, Crane O

Nutrients 2018;10:1340

Gastric Residuals

Effect of gastric residual evaluation on enteral Intake in extremely preterm infants: a randomized clinical trial

Parker LA, Weaver M, Murgas Torrazza RJ, Shuster J, Li N, Krueger C, Neu J

JAMA Pediatr 2019;173:534–543

Gastric residual volume in feeding advancement in preterm infants (GRIP Study): a randomized trial

Singh B, Rochow N, Chessell L, Wilson J, Cunningham K, Fusch C, Dutta S, Thomas S

J Pediatr 2018;200:79–83.e1

Gastric residual volumes versus abdominal girth measurement in assessment of feed tolerance in preterm neonates: a randomized controlled trial

Thomas S, Nesargi S, Roshan P, Raju R, Mathew S, Sheeja P, Rao S

Adv Neonatal Care 2018;18:E13–E19

Term Infants

Randomized controlled trial of iron-fortified versus low-iron infant formula: developmental outcomes at 16 years

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Background: The objective of the study was to test differences in cognitive outcomes among adolescents randomly assigned previously as infants to iron-fortified formula or low-iron formula as part of an iron deficiency anemia (IDA) prevention trial.

Methods: Infants were recruited from community clinics in low- to middle-income neighborhoods in Santiago, Chile. Entrance criteria included term, singleton infants; birth weight of ≥3.0 kg; and no major congenital anomalies, perinatal complications, phototherapy, hospitalization >5 days, chronic illness, or IDA at 6 months. Six-month-old infants were randomized to iron-fortified (12 mg/L) or low-iron (2.3 mg/L) formula for 6 months. At 16 years of age, cognitive ability, visual perceptual ability, visual memory, and achievement in math, vocabulary, and comprehension were assessed, using standardized measures. We compared differences in developmental test scores according to randomization group.

Results: At the follow-up assessment, the 405 participants averaged 16.2 years of age and 46% were male. Those randomized to iron-fortified formula had lower scores than those randomized to low-iron formula for visual memory, arithmetic achievement, and reading comprehension achievement. For visual motor integration, there was an interaction with baseline infancy hemoglobin, such that the iron-fortified group outperformed the low-iron group when 6-month hemoglobin was low and underperformed when 6-month hemoglobin was high.

Conclusion: Adolescents who received iron-fortified formula as infants from 6 to 12 months of age at levels recommended in the US had poorer cognitive outcomes compared with those who received a low-iron formula. The prevention of IDA in infancy is important for brain development. However, the optimal level of iron supplementation in infancy is unclear.

Comments

Iron deficiency anemia (IDA) is a global public health problem considered the most common and widespread nutritional disorder in the world. IDA in infancy is associated with negative health outcomes, including poorer cognitive, motor, and socioemotional development. The optimal level of iron fortification is controversial. There is increasing concern on iron neurotoxicity in infant and on the deleterious effects of iron exposure in early life on brain aging and neurodegenerative disease outcomes. The American Academy of Pediatrics Committee on Nutrition recommends that formula-fed infants receive formula containing 10–12 mg/L of iron, whereas the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition recommends lower concentrations of iron in infant formula, that is, 4–7 mg/L. The European Union Commission delegated Regulation of September 25, 2015, on the essential composition of infant (IF) and follow-on formula (FOF) set an iron content of 2–8 and 4–13 mg/L for IF and FOF, respectively.

The Santiago Longitudinal Study was designed to evaluate the behavioral and developmental effects of preventing IDA in infancy. Enrollment occurred between 1991 and 1994. Infants who were already taking ≥1 bottle of milk or formula per day (≥250 mL) were randomly assigned to iron-fortified or low-iron formula from 6 to 12 months of age. At 12 months, 835 infants completed the randomized controlled trial: 430 randomized to iron-fortified formula and 405 randomized to low-iron formula [1]. At the end of the trial, 19% of infants randomized to iron-fortified formula were iron deficient and 2.8% had IDA. Among those randomized to a low-iron formula, 35% were iron deficient and 3.8% had IDA.

At 16 years of age, outcomes were assessed in 49% of the infancy sample ($n = 405$). There was no significant difference in attrition by randomization group. Infancy background characteristics (i.e., age, sex, SES, HOME environment, formula intake, maternal age, IQ, and education) were similar in those assessed at 16 years compared with those not assessed. There were no statistically significant group differences in the hematologic or iron status measures at 16 years of age. The adolescent sample differed from the infancy sample in the proportion of males assessed (46 vs. 53% in infancy; $p < 0.05$). Furthermore, maternal IQ was slightly higher in those assessed compared with those not assessed (mean [SD] IQ 84.5 [0.5] vs. 83.1 [0.5]; $p = 0.04$). Sex and maternal IQ were adjusted for in all analyses. These differences illustrate the limitations of follow-up studies of randomized controlled trials, which should be considered as observational, thereby making it impossible to draw any causal relationship. However, the Santiago Longitudinal Study is the only study comparing iron-fortified formula with low-iron formula in humans. The results of this follow-up study do not question iron supplementation in IF and FOF. They point out the need for further research on the optimal level of iron fortification. With regard to iron supplementation in IF and FOF, the "more the better" is obviously not adequate.

Association of infant formula composition and anthropometry at 4 years: Follow-up of a randomized controlled trial (BeMIM study)

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Background: The relationships between nutrition, metabolic response, early growth and later body weight have been investigated in human studies. The aim of this follow-up study was to assess the long-term effect of infant feeding on growth and to study whether the infant metabolome at the age of 4 months might predict anthropometry at 4 years of age.

Methods: The Belgrade-Munich infant milk trial was a randomized controlled trial in which healthy term infants received either a protein-reduced infant formula (1.89 g protein/100 kcal) containing alphalactalbumin enriched whey and long-chain polyunsaturated fatty acids, or a standard formula (2.2 g protein/100 kcal) without long-chain polyunsaturated fatty acids, focusing on safety and suitability. Non-randomized breastfed infants were used as a reference group. Of the 259 infants that completed the Belgrade-Munich infant milk trial study at the age of 4 months (anthropometry assessment and blood sampling), 187 children participated in a follow-up visit at 4 years of age. Anthropometry including weight, standing height, head circumference, and percent body fat was determined using skinfolds (triceps, subscapular) and bioelectrical impedance analysis. Plasma metabolite concentration, collected in samples at the age of 4 months, was measured using flow-injection tandem mass spectrometry. A linear regression model was applied to estimate the associations between each metabolite and growth with metabolites as an independent variable.

Results: At 4 years of age, there were no significant group differences in anthropometry and body composition between formula groups. Six metabolites (Asn, Lys, Met, Phe, Trp, Tyr) measured at 4 months of age were significantly associated with changes in weight-for-age z-score between 1 and 4 months of age and BMI-for-age z-score (Tyr only), after adjustment for feeding group. No correlation was found between measured metabolites and long-term growth (up to 4 years of age). No long-term effects of early growth patterns were shown on anthropometry at 4 years of age.

Conclusion: The composition of infant formula influences the metabolic profile and early growth, while long-term programming effects were not observed in this study.

Comments

The association between both rapid weight gain and high protein intake in infancy and increased risk for overweight and obesity later in life is well known. However, there is yet no firm evidence from the available data that this relationship is causal. The influence of protein quality on longitudinal changes in body composition is less clear. This follow-up study was able to recruit at the age of 4 years 124 of the 213 infants randomized in the 2 IF groups, that is, an attrition rate of 42%. The study population at 4 years of age differed from the original study population with respect to age of mothers at delivery and percentage of mothers smoking during pregnancy. This is a limitation of the study which in any case should be considered as observational. This study found no evidence that the quality of the protein intake had an impact on the growth pattern assessed at 4 years of age. In addition, this study did not suggest an influence of early protein intake and growth from birth to 4 months of age on anthropometry at 4 years of age. It contradicts the observation by Weber et al. [2], showing

an association between early protein intake and weight gain and the risk for overweight and obesity at 6 years of age.
It is still to be demonstrated that the use of low-protein infant formula early in life plays a role on the risk for overweight and obesity later in life. However, there is no need to give a protein intake far beyond the protein needs in infancy.

Consumption of soy-based infant formula is not associated with early onset of puberty

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Background: The use of soy products is common in young children with cow milk allergy (CMA). The aim was to examine prospectively the association between infantile consumption of soy-based formula, growth parameters and early pubertal signs, in comparison to cow milk-based formula.
Methods: A nested case-control study was conducted, selected from a cohort of infants prospectively followed from birth until the age of 3 years for eating habits and the development of IgE-mediated CMA. Infants who consumed only soy-based formula were included in the soy group. The control group was randomly selected from those without IgE-CMA and not receiving soy formula. Study participants were reevaluated between ages 7.8 and 10.5 years by an interview, nutritional intake by 3 days diaries, and height, weight, and pubertal signs by physical examination.
Results: The soy-fed group included 29 participants (17 males), median age 8.92 years (interquartile range 8.21–9.42). The control group included 60 participants (27 males), median age 8.99 years (interquartile range 8.35–9.42). The groups had comparable height and BMI z scores (–0.17 ± 1.08 vs. –0.16 ± 1.01, $p = 0.96$, and 0.67 ± 1.01 vs. 0.53 ± 1.02, $p = 0.56$, for soy and control groups, respectively). Four (3 males and 1 female) from the soy-group (13.8%) and 8 females from the control-group (13.3%) had early pubertal signs ($p = 0.95$). No association was detected between puberty and infantile nutrition, after controlling for BMI and family data. No association with puberty or differences between groups were found in current daily consumption of soy, micronutrients, energy, carbohydrates, fat, and protein.
Conclusions: This is the first prospective, physical examination-based study, demonstrating no association between infantile soy-based formula consumption and both growth and puberty parameters.

Comments Phytoestrogens represent a broad group of plant-derived compounds of nonsteroidal structure that have weak estrogen activity. They are present in beans in general and soybeans in particular. Lignans and isoflavones are the major classes of phytoestrogens of interest from a nutritional and health perspective. The main compounds contained in soy protein-based foods are isoflavones that can bind to estrogen receptors, interact with enzyme systems influencing estrogenic activity, and exert weak estrogenic activity. Infant formulas based on soy protein isolates

contain relatively high concentrations of isoflavones, and more information is needed on potential long-term effects of phytoestrogens. There are several reports of a positive association between soy formula exposure and sexual development. A three-fold increase in the number of patients with premature thelarche seen between 1978 and 1981 in Puerto Rico led to further investigation in a case – control study [3]. Onset of thelarche before 2 years of age was significantly associated with consumption of soy protein isolate-based infant formula and of various meats. A study was performed in the United States with telephone interviews in 811 adults aged 20–34 years who had participated as infants during the years 1965–1978 in clinical trials with soy protein-based or cow's milk protein infant formula (n = 248; 120 males) [4]. Women-fed soy formula in infancy experienced a slightly but significantly longer duration of menstrual bleeding (by 0.37 days), with no difference in self-assessed intensity of menstrual flow. They also reported greater discomfort with menstruation (unadjusted relative risk for extreme discomfort vs. no or mild pain, 1.77; 95% CI 1.04–3.00). In a study from Israel, breast development in the first 2 years of life was associated with the use of soy infant formulas [5]. High-serum isoflavones concentrations were associated with the risk of precocious puberty in Korean girls, but their source was not obligatory from food intake [6]. Conversely, Andres et al. [7] observed no difference in ultrasonographic measures of breast bud, uterus, ovaries, prostate, and testes, in a group of 100 prepubertal children studied at 5 years of age, of whom a third were fed soy-based formula during infancy.

This study of Sinai et al. is the first prospective study, including real-time infantile data regarding both feeding habits and birth parameters, in conjunction with a physical examination and a face-to-face interview at the age of early pubertal onset. In addition, various factors known to play a role in the timing of onset of puberty (e.g., family history of early puberty, prenatal growth, obesity, nutritional habits, and physical activity) were accounted for in the study. The main weakness of the study is the small sample size (29 participants in the soy-fed group and 60 participants in the control group). The authors observed that soy consumption was not associated with early onset of secondary pubertal signs. There is a need for a large multicenter study to further assess whether or not soy protein formula should still be considered as an endocrine disruptor. In the meantime, the recommendations published in 2006 by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition to avoid the use of soy-protein formula in the first 6 months of life seem to remain appropriate [8].

Palm oil and beta-palmitate in infant formula: A position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition Committee on Nutrition

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Background: Palm oil (PO) is used in infant formulas in order to achieve palmitic acid (PA) levels similar to those in human milk. PA in PO is esterified predominantly at the SN-1,3 position of triacylglycerol, and infant formulas are now available in which a greater proportion of PA is in the SN-2 position (typical configuration in human milk). As there are some concerns about the use of PO, we aimed to review literature on health effects of PO and SN-2-palmitate in infant formulas.
Methods: PubMed and Cochrane Database of Systematic Reviews were systematically searched for relevant studies on possible beneficial effects or harms of either PO or SN-2-palmitate in infant formula on various health outcomes.
Results: We identified 12 relevant studies using PO and 21 studies using SN-2-palmitate. Published studies have variable methodology, subject characteristics, and some are underpowered for the key outcomes. PO is associated with harder stools and SN-2-palmitate use may lead to softer stool consistency. Bone effects seem to be short-lasting. For some outcomes (infant colic, faecal microbiota, lipid metabolism), the number of studies is very limited and summary evidence inconclusive. Growth of infants is not influenced. There are no studies published on the effect on markers of later diseases.
Conclusion: There is insufficient evidence to suggest that PO should be avoided as a source of fat in infant formulas for health reasons. Inclusion of high SN-2-palmitate fat blend in infant formulas may have short-term effects on stool consistency but cannot be considered essential.

Comments This is a position paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition (ESPGHAN CoN). The

systematic review performed by ESPGHAN CoN was able to appraise the available studies and to draw sound conclusions. It allows also to better estimate the possible gaps between the scientific evidence and the claims made by the manufacturers. Triacylglycerols (TAGs) in breast milk provide 45–55% of the energy intake of breast-fed infants as well as essential fatty acids and other lipids that play important roles in optimal development. Palmitate constitutes about 25% of the fatty acids of breast milk TAGs, and approximately 70% of this is at the sn-2 position. Inversely, palmitate in most infant formulas is predominantly at the sn-1 and sn-3 positions of the TAG backbone. This difference in TAG structure is of importance in palmitic acid (PA) and total lipid absorption. The pancreatic lipase – colipase system is highly selective for the sn-1 and sn-3 TAG positions, resulting in the generation of 2 free fatty acids and an sn-2 monoacylglycerol. All sn-2 monoacylglycerols are well absorbed as are saturated fatty acids of chain length <14 carbons and all unsaturated fatty acids. However, free long-chain saturated fatty acids, such as PA, form calcium soaps that are insoluble at body temperature and are excreted in the feces. Thus, PA absorption is greater in breast-fed infants than in formula-fed infants. The percentage of fed calcium that is also absorbed is greater in breast-fed than in formula-fed infants; fecal calcium – palmitate soaps are associated with hard stools, and this may, at least in part, explain the greater stool softness in breast-fed infants as compared to formula-fed infants.

A very recent randomized controlled trial including 488 infants from birth to 4 months of age not reviewed by ESPGHAN CoN demonstrated that feeding infant formulas with increased levels of sn-2 palmitate (respectively, 43 and 51% of the lipid content) and a concomitant decrease in sn-1 and sn-3 palmitate: (1) supports normal infant growth, (2) results in softer stools during the first 2 months of life, (3) increases bone mineral content at 4 months of age, and (4) is well tolerated. Thus, feeding formulas containing high sn-2 palmitate is safe and provides positive outcomes to infants in terms of stool consistency and bone mineralization during the first 4 months of life [9]. As stated by ESPGHAN CoN, there is insufficient evidence to suggest that palm oil should be avoided as a source of fat in infant formulas for health reasons. Inclusion of high SN-2-palmitate fat blend in infant formulas may have short-term effects on stool consistency because of reduced formation of calcium soaps but cannot be considered essential.

Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of cow's milk protein allergy

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Background: Foods for special medical purposes with a protein fraction made of hydrolyzed rice protein (HRP) are on the market in Europe since the 2000s for the treatment of cow's milk protein allergy (CMPA).

Methods: A PubMed search was performed with the objective to find studies regarding the efficacy and safety of HRP formulas (HRPFs). Eleven clinical trials on HRPFs in infants were identified and ranked according to the level of evidence of the Oxford Centre for Evidence-based Medicine (CRBM).

Results: HRPFs are proposed as a plant-based alternative to cow's milk protein-based extensively hydrolyzed formulas beside the soy protein formulas whose use in CMPA is controversial. HRPFs do not contain phytoestrogens and are derived from non genetically modified rice. HRPFs are strictly plant-based apart from the addition of vitamin D_3 (cholelecalciferol). As the aminoacid content of rice proteins differs from that of human milk proteins, the protein quality of these formulas is improved by supplementation with free lysine, threonine, and tryptophan. The consumption of HRPFs has risen: for example, in France, HRPFS account for 4.9% in volume of all formulas for children aged 0–3 years. Several studies have shown the adequacy of HRPFs in treating CMPA. They ensure satisfactory growth from the 1st weeks of life for infants and toddlers, both in healthy children and in those with CMPA.

Conclusion: HRPFs can be used to treat children with CMPA either straightaway or in second intention in cases of poor tolerance to cow's milk protein-based extensively hydrolyzed formulas for organoleptic reasons or for lack of efficacy. In France, the cost of HRPFs is close to that of regular infant or follow-on formulas.

Comments Rice protein allergy is rare in Western countries. Rice is considered the least allergenic cereal because it triggers undesirable reactions in <1% of children with allergies. Rice proteins can be the cause of the non-IgE-mediated food protein-induced enterocolitis (FPIES) but more rarely than cow's milk or soy proteins. The diagnosis delay and symptom severity are greater than for cow's milk protein allergy (CMPA). Children with rice-induced FPIES are more likely to develop the same syndrome with other foods (oats, barley, wheat, and other noncereal foods) than children whose FPIES was caused by cow's milk or soy. HRP formulas (HRPFs) are not available in many countries, while they are widely used in others such as Italy, Spain, and France.

Evidence from clinical trials published to date shows that HRPFs are a feasible treatment option in children with CMPA, either in first intention or in case of palatability issues with cow's milk protein-based extensively hydrolyzed formulas (CMP-eHFs). HRPFs allow a satisfactory growth from birth through the first few years of life in healthy children as well as in children suffering from CMPA. Such conclusions are, however, valid only for the products reported in the studies reviewed. Another aspect of HRPFs is a relatively low cost compared to CMP-eHFs. No data are available to draw any conclusions on the use of HRPFs in cases of allergy to CMP-eHFs, which today require the use of amino acid formulas. On the other hand, it is not currently possible to conclude on the influence of the formula used to treat infants with CMPA on the duration of the CMPA.

Inorganic arsenic intake is likely to affect long-term health. It should be kept in mind that high concentrations are found in some rice-based foods and drinks widely used in infants and young children. In order to reduce exposure, ESPGHAN CoN recommended in 2015 that rice drinks for infants and young children should be avoided and that, for all of the rice products, strict regulation should be enforced regarding arsenic content [10]. Since 2016 (EU 2015/1006 of June 25, 2015), the maximum level of inorganic arsenic for rice intended to produce foodstuffs for children under 3 years of age is 0.10 mg/kg (a limit twice as low as that for white rice) [11].

The CNSFP reiterates in this review paper its 2012 recommendations: HRPFs can be considered as an alternative to CMP-eHF as a first-line treatment for infants with CMPA because of their effectiveness, in terms of allergic symptoms and nutritional adequacy, their palatability, and their lower cost. HRPFs may therefore represent an option, either as a first intention regimen for a child with CMPA or as second intention if CMP-eHFs are either not accepted or poorly accepted for organoleptic reasons.

Probiotics to prevent infantile colic

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Background: Infantile colic is typically defined as full-force crying for at least 3 h/day, on at least 3 days/week, for at least 3 weeks. Infantile colic affects a large number of infants and their families worldwide. Its symptoms are broad and general, and while not indicative of disease, may represent a serious underlying condition in a small percentage of infants who may need a medical assessment. Probiotics are live microorganisms that alter the microflora of the host and provide beneficial health effects. The most common probiotics used are of *Lactobacillus*, *Bifidobacterium* and *Streptococcus*. There is growing evidence to suggest that intestinal flora in colicky infants differ from those in healthy infants, and it is suggested that probiotics can redress this balance and provide a healthier intestinal microbiota landscape. The low cost and easy availability of probiotics makes them a potential prophylactic solution to reduce the incidence and prevalence of infantile colic. The aim of the systematic review was to evaluate the efficacy and safety of prophylactic probiotics in preventing or reducing severity of infantile colic.

Methods: In January 2018 we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, 10 other databases and 2 trials registers. In addition, we handsearched the abstracts of relevant meetings, searched reference lists, ran citation searches of included studies, and contacted authors and experts in the field, including the manufacturers of probiotics, to identify unpublished trials. Randomised control trials of newborn infants <1 month of age without the diagnosis of infantile colic at recruitment were selected. We included any probiotic, alone or in combination with a prebiotic (also known as synbiotics), versus no intervention, another intervention(s) or placebo, where the focus of the study was the effect of the intervention on infantile colic. We used standard methodological procedures of Cochrane.

Results: Our search yielded 3,284 records, and of these, we selected 21 reports for full-text review. Six studies with 1,886 participants met our inclusion criteria, comparing probiotics with placebo. Two studies examined *Lactobacillus reuteri* DSM, 2 examined multi-strain probiotics, one examined *Lactobacillus rhamnosus*, and one examined *Lactobacillus paracasei* and *Bifidobacterium animalis*. Two studies began probiotics during pregnancy and continued administering them to the baby after birth. We considered the risk of bias for randomisation as low for all 6 trials; for allocation concealment as low in 2 studies and unclear in 4 others. All studies were blinded, and at low risk of attrition and reporting bias. A random-effects meta-analysis of 3 studies (1,148 participants) found no difference between the groups in relation to occurrence of new cases of colic: risk ratio 0.46, 95% CI 0.18–1.19; low-certainty evidence; I^2 = 72%. A random-effects meta-analysis of all 6 studies (1,851 participants) found no difference between the groups in relation to serious adverse effects (risk ratio 1.02, 95% CI 0.14–7.21; low-certainty evidence; I^2 not calculable (only 4 serious events for one comparison, 2 in each group: meconium plug obstruction, patent ductus arteriosus and neonatal hepatitis). A random-effects meta-analysis of 3 studies (707 participants) found a mean difference (MD) of –32.57 minutes per day (95% CI –55.60 to –9.54; low-certainty evidence; I^2 = 93%) in crying time at study end in favour of probiotics. A subgroup analysis of the most studied agent, *Lactobacillus reuteri*, showed a reduction of 44.26 minutes in daily crying with a random effects model (95% CI –66.6 to –21.9; I^2 = 92%), in favour of probiotics.

Conclusion: There is no clear evidence that probiotics are more effective than placebo at preventing infantile colic; however, daily crying time appeared to reduce with probiotic use compared to placebo. There were no clear differences in adverse effects. We are limited in our ability to draw conclusions by the certainty of the evidence, which we assessed as being low across all 3 outcomes, meaning that we are not confident that these results would not change with the addition of further research.

Comments

Infantile colic is defined as periods of inconsolable, unexplained, and incessant crying in a seemingly healthy infant that leads to exhausted, frustrated, and concerned parents seeking to comfort their child. These episodes often occur in the evening. Colic has been included under functional gastrointestinal disorders (Rome IV diagnostic criteria), and the definition has been expanded to include paroxysms of irritability and fussiness for at least 1 week in an infant who has no failure to thrive. This condition appears to be more frequent in the first 6 weeks of life, occurring in up to 25% of newborns depending on geography and definitions employed, with prevalence often peaking at that point. Episodes of colic usually resolve by 3–4 months of age. However, about 5% of colicky, crying infants have a serious, underlying medical problem, including cow's milk protein allergy, gastroesophageal reflux disease, or lactose intolerance. Any treatment that may improve the infant's condition is of course more than welcome by parents. The results of this Cochrane review are of paramount importance, avoiding an excessive and expansive use of probiotics that is not supported by the available scientific evidence. Health claims made by manufacturers on the use of probiotics in general and in colicky infants in particular need to be considered with great caution.

Probiotic supplementation restores normal microbiota composition and function in antibiotic-treated and in caesarean-born infants

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Background: Infants born by caesarean section or receiving antibiotics are at increased risk of developing metabolic, inflammatory and immunological diseases, potentially due to disruption of normal gut microbiota at a critical developmental time window.
Methods: We investigated whether probiotic supplementation could ameliorate the effects of antibiotic use or caesarean birth on infant microbiota in a double blind, placebo-controlled randomized clinical trial. Mothers were given a multispecies probiotic, consisting of Bifidobacterium breve Bb99 (Bp99 2×10^8 CFU), Propionibacterium freundenreichii subsp. shermanii JS (2×10^9 CFU), Lactobacillus rhamnosus Lc705 (5×10^9 CFU) and Lactobacillus rhamnosus GG (5×10^9 CFU; $n = 168$ breastfed and 31 formula-fed), or placebo supplement ($n = 201$ breastfed and 22 formula-fed) during pregnancy, and the infants were given the same supplement. Faecal samples of the infants were collected at 3 months and analyzed using taxonomic, metagenomic and metaproteomic approaches.
Results: The probiotic supplement had a strong overall impact on the microbiota composition, but the effect depended on the infant's diet. Only breastfed infants showed the expected increase in Bifidobacteria and reduction in Proteobacteria and Clostridia. In the placebo group, both birth mode and antibiotic use were significantly associated with altered microbiota composition and function, particularly reduced Bifidobacterium abundance. In the probiotic group, the effects of antibiotics and birth mode were either completely eliminated or reduced.
Conclusion: The results indicate that it is possible to correct undesired changes in microbiota composition and function caused by antibiotic treatments or caesarean birth by supplementing infants with a probiotic mixture together with at least partial breastfeeding.

Comments Microbial colonization of the infant gut plays an important role in later health. In healthy newborns, the gut microbiome composition experiences longitudinal changes until the age of 2–3 years, when an adult-like anaerobic pattern is acquired. Perturbations in the microbiome are associated later in life with susceptibility to autoimmune diseases, such as diabetes, inflammatory bowel disease, and atopy, and to overweight and obesity. Colonization of the infant gut is a complex process dependent on multiple overlapping factors, including age, mode of delivery, type of feeding, presence of siblings or pets, and environmental exposures as geographical location or farm exposure [12]. As an example, cesarean section and the use of antibiotics in the neonatal period and early infancy are strongly associated with a significant gut microbiota disruption, usually named as dysbiosis. Conversely, breast milk keeps the microbiota in a state characterized by low diversity and *Bifidobacte-*

rium domination, which is likely to be beneficial for child health. The study explores a further step in this fascinating research area, namely, a therapeutic approach using probiotics in mothers and infants during a 6-month period from birth in order to switch from an unfavorable microbiota linked to C-section and/or antibiotic treatment to a more desirable microbiota. In addition, infants were further supplemented daily with 0.8 g galacto-oligosaccharides. The results of this well-designed study are very encouraging. They show that the effect of the supplementation with oligosaccharides was dependent on concomitant breatsfeeding, at least partial. The optimal duration of such a probiotic supplementation has to be established. A treatment duration of at least 3 months may be appropriate since the microbiota imbalance in infants born by C-section was restored by daily probiotic supplementation by the age of 3 months.

Diet during pregnancy and infancy and the infant intestinal microbiome

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Background: To determine the association between diet during pregnancy and infancy, including breastfeeding versus formula feeding, solid food introduction, and the infant intestinal microbiome.
Methods: Infants participating in the Vitamin D Antenatal Asthma Reduction Trial were included in this study (n = 323). Maternal and infant diets were assessed by questionnaire. Infant stool samples were collected at age 3–6 months. Stool sequencing was performed using the Roche 454 platform. Analyses were stratified by race/ethnicity.
Results: Breastfeeding, compared with formula feeding, was independently associated with infant intestinal microbial diversity. Breastfeeding also had the most consistent associations with individual taxa that have been previously linked to early-life diet and health outcomes (e.g., *Bifidobacterium*). Maternal diet during pregnancy and solid food introduction were less associated with the infant gut microbiome than breastfeeding status. We found evidence of a possible interaction between breastfeeding and child race/ethnicity on microbial composition.
Conclusions: Breastfeeding versus formula feeding is the dietary factor that is most consistently independently associated with the infant intestinal microbiome. The relationship between breastfeeding status and intestinal microbiome composition varies by child race/ethnicity. Future studies will need to investigate factors, including genomic factors, which may influence the response of the microbiome to diet.

Comments Prenatal diet influences the risk of infant and child allergy. For instance, the Mediterranean diet during pregnancy has been associated with a reduced risk of both persistent and atopic wheeze and atopy in children at 6.5 years old. High meat consumption during pregnancy is associated with an increased risk of wheeze in the first year of life, while maternal dairy intake is associated with a reduced risk of infantile wheeze. Little is known about the actual mechanisms by which maternal diet affects children's health. Maternal diet may influence the infant gut microbiome through vertical transfer of maternal microbes to infants during vaginal delivery and breastfeeding. Diet during infancy is associated with health and disease outcomes and with the infant's intestinal microbiome. Short-term diets composed solely of either plant or animal foods have been shown to alter the human gut microbiome. In addition, studies in humans and humanized gnotobiotic mice show that diets with reduced carbohydrates, or high in polysaccharides, alter gut microbiome composition. There are few data on the relationship between maternal diet and the developing infant gut microbiome. One study observed that fruit and dairy intake of the mother during pregnancy was associated with the gut microbial composition [13].

The present study confirms the major role of breatsfeeding in the modulation of the intestinal microbiota in young infants. More information is needed to know whether the influence of breatsfeeding on the microbiota persists beyond 3–6 months of age. The reasons why race/ethnicity has an impact on infant's intestinal microbiota need further investigation. It should also be emphasized that the main weakness of this study is the fact that the included infants had a family history (father and/or mother) of asthma or allergy that may have an impact on the child microbiome. All of the data observed by Savage in this manuscript should be replicated by other investigators.

Complementary feeding and food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis: a systematic review

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Background: Nutrition during infancy and toddlerhood may influence health and disease prevention across the life span. Complementary feeding (CF) starts when human milk or infant formula is complemented by other foods and beverages, beginning during infancy and continuing to age 24 months. The aim of this study was to describe systematic reviews conducted for the USDA and the Department of Health and Human Services Pregnancy and Birth to 24 months Project to answer the following question: What is the relationship between the timing of the introduction of complementary foods and beverages (CFBs), or types and amounts of CFBs consumed, and the development of food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis?

Methods: The literature was searched using 4 databases (CINAHL, Cochrane, Embase, PubMed) to identify articles published from January 1980 to February 2017 that met predetermined inclusion criteria. For each study, data were extracted and risk of bias was assessed. The evidence was qualitatively synthesized to develop a conclusion statement, and the strength of the evidence was graded.
Results: Thirty-one included articles addressed the timing of CFB introduction, and 47 articles addressed the types and amounts of CFBs consumed.
Conclusion: Moderate evidence suggests that there is no relationship between the age at which CF first begins and the risk of developing food allergy, atopic dermatitis/eczema, or childhood asthma. Limited to strong evidence, depending on the specific food, suggests that introducing allergenic foods in the first year of life (after 4 months) does not increase the risk of food allergy and atopic dermatitis/eczema but may prevent peanut and egg allergy. There is not enough evidence to determine a relationship between diet diversity or dietary patterns and atopic disease. Research is needed to address gaps and limitations in the evidence on CF and atopic disease, including research that uses valid and reliable diagnostic measures and accounts for key confounders and potential reverse causality.

Comments

The influence of the timing of introduction of complementary foods on the occurrence and/or severity of atopic diseases is a controversial issue. Over the last 50 years, guidelines have changed several times moving from an early introduction, that is, < 2–3 months to a later introduction, that is, >6 months, with different advice in infants at risk and not at risk of allergy. Very few data were available to support these guidelines. More studies on complementary feeding are now published, even if most of them are observational and therefore do not allow to prove a causal relationship between time of introduction and health outcomes. The National Institute of Allergy and Infectious Diseases estimates that ~5% of children and ~4% of adults in the United States have ≥1 food allergies and that ~30% of the US population has atopic dermatitis. In addition, the CDC estimates that ~8% of Americans have asthma and an additional 8% have allergic rhinitis. Therefore, understanding the relationship between dietary intake during infancy and toddlerhood and atopic disease is of public health importance. An important consideration in the evaluation of the effect or association between the timing of introduction of complementary foods (CFs) and an atopic-disease-related outcome is reverse causality that may be either due to the presence of an atopic family history, on the one hand, and due to the presence of allergic symptoms before the introduction of CFs, on the other hand. In both cases, parents may decide to anticipate or postpone the introduction of CFs (depending on feeding recommendations given), while, at the same time, these children may already be at a higher risk of developing the disease, independent of the timing of introduction of CFs. Eczema and asthma-like symptoms are the most frequently investigated end points in prospective observational studies, while symptomatic food allergy was the most investigated end point in the randomized controlled trials.

Association of early introduction of solids with infant sleep: A secondary analysis of a randomized clinical trial

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Background: WHO recommends exclusive breastfeeding for 6 months. However, 75% of British mothers introduce solids before 5 months and 26% report infant waking at night as influencing this decision. The objective of the study was to determine whether early introduction of solids influences infant sleep.

Methods: The Enquiring About Tolerance (EAT) study was a population-based randomized clinical trial conducted from January 15, 2008, to August 31, 2015, that included 1,303 exclusively breastfed 3-month-old infants from England and Wales. Clinical visits took place at St Thomas' Hospital, London, England, and the trial studied the early introduction of solids into the infant diet from age 3 months. The early introduction group (EIG) continued to breastfeed while non allergenic and then 6 allergenic foods were introduced. The standard introduction group (SIG) followed British infant feeding guidelines (i.e., exclusive breastfeeding to around age 6 months and to avoid any food consumption during this period). Secondary analysis of an a priori secondary outcome of the effect of early food introduction on infant sleep using the standardized Brief Infant Sleep Questionnaire.

Results: Of the 1,303 infants who were enrolled in the Enquiring about Tolerance study, 1,225 participants (94%) completed the final 3-year questionnaire (618 SIG [95%] and 607 EIG [93%]). Randomization was effective and there were no significant baseline differences between the 2 groups. Following the early introduction of solids, infants in the EIG slept significantly longer and woke significantly less frequently than infants in the SIG. Differences between the 2 groups peaked at age 6 months. At this point, in the intention-to-treat analysis infants in the EIG slept for 16.6 (95% CI 7.8–25.4) minutes longer per night and their night waking frequency had decreased from 2.01 to 1.74 wakings per night. Most clinically important, very serious sleep problems, which were significantly associated with maternal quality of life, were reported significantly more frequently in the SIG than in the EIG (OR 1.8; 95% CI 1.22–2.61).

Conclusions: In a randomized clinical trial, the early introduction of solids into the infant's diet was associated with longer sleep duration, less frequent waking at night, and a reduction in reported very serious sleep problems.

Comments Infant sleep is an important issue for parents. It is a common belief that introducing complementary foods may help infants sleep better. In this ancillary study of the well-known enquiring about tolerance randomized controlled trial [14], infants introduced to CFs at 3–4 months of age slept on average about 7 min longer during the night (95% CI 2 to about 13 min) over the whole course of the study from birth to 3 years of age. Infants introduced to CFs at 3–4 months of age were also reported to have fewer night wakings (mean % difference: 9.1 [95% CI 4–14%]). The infants introduced to CFs at 3–4 months of age also showed lower odds of both "very serious" and "small" sleep problems (as perceived by the parents when answering the question "do you consider your child's sleep as a problem?"), in comparison to infants introduced to CFs at 6 months of age (OR 0.83 [95% CI 0.71–0.95] and 0.55 [0.38–0.82], respectively). It is worth men-

tioning that the severity of sleep problems was based on the perception of the parents. The observed differences in sleep duration or night wakings in this study were small in relation to an overall nighttime sleep duration of around 10–11 h at 6 months of age. They are very unlikely to be of biological relevance. Few data on the relationship between introduction of complementary feeding and infant sleep are available. The study by Bainbridge et al. [15] in which rice cereal was added to formula in the bottle in exclusively formula-fed infants at 4 vs. 6 months of age showed that infants receiving the rice cereal at 4 months slept on average 60 min longer during the night at 6 months of age (95% CI 34–154 min). This was assessed as the time that had passed between the last bottle at night and the first in the morning. The result was not statistically significant. However, the study population included 38 infants only, and thus the trial was most likely underpowered for this outcome. Three prospective studies at high risk of bias showed (1) either a longer night sleep duration [16], that is, on average 12 min at 9 and 18 months for those introduced to CFs at ≤3 vs. >3 months of age; (2) a shorter 24-h sleep duration [17], that is, on average about 24 min at 1 year and 13 min at 2 years for those introduced to CFs at ≤4 vs. >4 months of age; (3) no association between the timing of introduction of CFs and 24-h sleep duration at 6 months of age [17] or with sleep time in breastfed infants at 9 months of age [18]. The conclusion from the literature is that there is no evidence that the time of introduction of complementary foods has a relevant influence on the infant's sleep pattern.

Compared with cow milk, a growing-up milk increases vitamin D and iron status in healthy children at 2 years of age: The Growing-Up Milk-Lite (GUMLi) randomized controlled trial

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Background: Iron deficiency and vitamin D deficiency are significant pediatric health issues in New Zealand and Australia and remain prevalent micronutrient deficiencies in young children globally. We aimed to investigate the effect of a micronutrient-fortified, reduced-energy growing-up milk (GUMLi) compared with cow milk (CM) consumed for 1 year on dietary iron and vitamin D intakes and the status of New Zealand and Australian children at 2 years of age.

Methods: The GUMLi Trial was a multicenter, double-blind, randomized controlled trial in 160 healthy 1-year-old New Zealand and Australian children conducted in 2015–2017. Participants were randomly assigned 1:1 to receive GUMLi (1.7 mg Fe/100 mL; 1.3 μg cholecalciferol/100 mL) or CM (0.02 mg Fe/100 mL; 0.06 μg cholecalciferol/100 mL) for 12 months. Secondary outcomes, reported here, included change in dietary iron and vitamin D intakes, iron status, and 25-hy-

droxyvitamin D concentrations from blood samples at age 2 years. All regression models were adjusted for baseline outcome and study center.

Results: GUMLi was a large contributor to dietary intakes of iron and vitamin D after 12 months when compared with intakes from food and CM. The adjusted mean difference between groups for serum ferritin concentrations was 17.8 μg/L (95% CI 13.6–22.0 μg/L; $p < 0.0001$), and for 25-hydroxyvitamin D it was 16.6 nmol/L (95% CI 9.9–23.3 nmol/L; $p < 0.0001$). After 12 months, ID was present in 16 (24%) participants in the CM group and 5 (7%) participants in the GUMLi group ($p = 0.009$), and the prevalence of vitamin D deficiency in the CM group increased to 14% ($n = 10$) and decreased to 3% ($n = 2$; $p = 0.03$) in the GUMLi group.

Conclusion: In comparison with CM, GUMLi significantly improved dietary iron and vitamin D intakes and the iron and vitamin D status of healthy children at 2 years of age.

A comparison of the effect of a Growing Up Milk-Lite (GUMLi) vs. cow's milk on longitudinal dietary patterns and nutrient intakes in children aged 12–23 months: the GUMLi randomised controlled trial

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Background: The second year of life is a period of nutritional vulnerability. We aimed to investigate the dietary patterns and nutrient intakes from 1 to 2 years of age during the 12-month follow-up period of the Growing Up Milk - Lite (GUMLi) trial.

Methods: The GUMLi trial was a multi-centre, double blinded, randomised controlled trial of 160 healthy 1-year-old children in Auckland, New Zealand and Brisbane, Australia. Dietary intakes were collected at baseline, 3, 6, 9 and 12 months post-randomisation, using a validated FFQ. Dietary patterns were identified using principal component analysis of the frequency of food item consumption per day. The effect of the intervention on dietary patterns and intake of 11 nutrients over the duration of the trial were investigated using random effects mixed models. A total of 3 dietary patterns were identified at baseline: "junk/snack foods," "healthy/guideline foods" and "breast milk/formula."

Results: A significant group difference was observed in "breast milk/formula" dietary pattern z scores at 12 months post-randomisation, where those in the GUMLi group loaded more positively on this pattern, suggesting more frequent consumption of breast milk. No difference was seen in the other 2 dietary patterns. Significant intervention effects were seen on nutrient intake between the GUMLi (intervention) and cows' milk (control) groups, with lower protein and vitamin B12, and higher Fe, vitamin D, vitamin C and Zn intake in the GUMLi (intervention) group.

Conclusion: The consumption of GUMLi did not affect dietary patterns, however, GUMLi participants had lower protein intake and higher Fe, vitamins D and C and Zn intake at 2 years of age.

A multicenter, double-blind, randomized, placebo-controlled trial to evaluate the effect of consuming Growing Up Milk "Lite" on body composition in children aged 12–23 months

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Background: Growing Up Milk (GUM) was developed to assist young children in meeting their nutritional requirements during the second year of life. However, there is limited evidence that GUM improves nutritional status and growth in young children. To evaluate the effect of consuming Growing Up Milk "Lite" (GUMLi; reduced protein with synbiotics and micronutrients added) compared with standard cow milk as part of a whole diet for 1 year on body composition at 2 years of age.

Methods: GUMLi Trial was a multicenter, double-blind, randomized placebo-controlled trial conducted in Auckland and Brisbane. Healthy 1-year-old were recruited and randomly assigned to receive either GUMLi or standard cow milk for 12 months as part of a whole diet. The primary outcome was percentage body fat at 2 years of age measured by bioelectrical impedance. All regression models adjusted for baseline outcome and study center.

Results: 160 children (80 per arm) were randomly assigned, and 134 (67 per arm) were included in the modified intention-to-treat analyses. The mean percentage body fat at 12 months was 23.3% (SD 7.9) in the GUMLi group and 25.7% (SD 7.2) in the cow milk group. After adjusting for baseline outcome and study location, the estimated mean difference in percentage body fat between the intervention and control at 12 months was –2.19% (95% CI –4.24 to –0.15; $p = 0.036$). Per-protocol analysis showed a similar effect (mean difference: –2.09%; 95% CI –4.16 to –0.03; $p = 0.047$). Both fat mass and the fat mass index were significantly lower in the GUMLi group at 12 months than in the cow milk group.

Conclusions: At 2 years of age, children who consumed a GUM with a lower protein content than cow milk over 12 months had a lower percentage of body fat.

Comments Early childhood (1–3 years of age) is a period of rapid growth and development, with a gain of approximately 25% in height and 50% in weight occurring during this period. While milk remains a major food, this is a transition period from weaning foods toward a family diet, rendering children vulnerable to nutrient inadequacy. Taking into account the available evidence, the European Food Safety Authority considered, in 2013, that dietary intakes of alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), iron, vitamin D, and iodine (in some European countries) are low in infants and young children living in Europe, when compared to the dietary reference values [19]. European Food Safety Authority, therefore, proposed to pay particular attention to ensur-

ing an appropriate supply of ALA, DHA, iron, vitamin D, and iodine in infants and young children with inadequate, or at risk of inadequate, status of these nutrients [19]. More recently, the French Nutri-Bébé survey, covering 1,035 infants (<1 year) and young children (1–3 years) who were not breastfed at the time of the survey, revealed a high intake of protein, sodium, and vitamin A and a low intake of fat, ALA, DHA, iron, vitamin D, and vitamin E [20, 21]. These inadequacies were attributed to the early weaning and/or abandonment of milk formula, as well as to the consumption of an unbalanced diet with excessive use of semi-skimmed cow's milk and meals intended for adults [20, 21]. Young Child Formula (YCF, so called "Growing-Up Milk"), an alternative to cow's milk (CM) or breast milk for children 1–3 years of age, are marketed as products specifically formulated for the nutritional needs of young children aged 1–3 years [22]. They are fortified with several nutrients, including iron, vitamin D, and essential fatty acids, and they contain less protein, saturated fat, and sodium than CM. YCFs have been widely available in many countries since the early 90s. Previously classified as foods intended for a particular nutritional use (so-called "dietetic foods") since July 2016, they have been considered common foods, fortified with certain nutrients and targeting a specific subgroup of the population (young children). There is no specific regulation on the essential composition of YCFs worldwide, including the EU. The ESPGHAN Committee on Nutrition considered, after reviewing the literature, that there were limited data on the nutrient intakes of young children consuming YCF and the potential role of YCF in their diets [23]. Therefore, in a recent position paper, the Committee considered it of interest to determine whether YCF intake could correct (and to what extent) some of these deficits, as compared to CM.

The 3 abovementioned studies from New Zealand are therefore welcome to better understand what may be the role of YCFs to cover nutritional needs of young children aged 1–3 years. The supplementation of a YCF with vitamin D and iron allows to increase the status of these 2 nutrients as compared to cow's milk in healthy children aged 2 years. Interestingly, a lower percentage of body fat was observed in 2-year-old children consuming a low-protein YCF. Finally, the consumption of a reduced protein YCF fortified with iron and vitamin D did not affect dietary patterns compared with consumption of an unfortified CM. YCF allows the most frequent nutritional inadequacies observed in several countries to be overcome, especially iron and vitamin D. YCF consumption can also improve the intake of protein and sodium. The results of these 3 studies from New Zealand study could lead to consider, with caution, the potential consequences of an unbalanced diet associated with low YCF consumption in terms of the risk of overweight, iron deficiency, and hypertension.

While nutrient imbalance is common in many countries, complementary feeding regimens differ and are determined by tradition, empirical behaviors, and availability of foods, including the capacity to afford YCF. As a result, no universal instructions can be formulated. The advice of health professionals must be adapted to each family and child, taking into account the quality of their diet. The use of YCF is not a necessity if the diet provided is balanced as recommended, considering the possible nutrient deficits in each country. However, YCF is a useful tool to compensate, at least partially, for the gap between expectations and reality.

Supplementing enteral intake

Improved lung function at age 6 in children born very preterm and fed extra protein post-discharge

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Background: In very preterm-born children, alveolar maturation is challenged and lung function is often compromised during childhood. So far, very few studies have focused on type of early nutrition and lung function in children born preterm.
Methods: This study is a 6 years follow-up of 281 very preterm-born infants with a gestational age <32 + 0 weeks. Infants breastfed at discharge from hospital were randomized to unfortified (UHM) or fortified (FHM) mother's (human) milk, whereas those not breastfed received a preterm formula (PF). The intervention lasted until 4 months corrected age. At 6 years of age fractional exhaled nitric oxide (FeNO), airway resistance and occlusion measurements with reversibility were performed. Data on predisposition to asthma and allergy as well as possible allergic symptoms of the child were obtained with questionnaires.
Results: Outcome data was fully or partially available on 160 (66.9%) of 239 children. This included 49 (30.6%) children fed UHM, 58 (36.3%) fed FHM and 53 (33.1%) fed PF. Successful FeNO measurements were obtained in 119 (74.4%) children and airway resistance measurements in 160. FeNO results were not significantly different between feeding groups. Children fed a protein-enriched diet (FMH/PF) had the lowest, for example, best, airway resistance; FHM-fed had lower values than UHM-fed ($p = 0.042$) before, and PF-fed had significantly lower values than UHM-fed after beta-2-agonist inhalation ($p = 0.050$). The tendency of lower airway resistance when protein enriched were the same in gender-specific analyses. In SGA children, the same tendency was found between PF- and UHM-fed ($p = 0.007$ before and $p = 0.046$ after beta-2-agonist inhalation). All values were within reference limits.
Conclusions: Lung function in very preterm-born children may improve when fed a protein-enriched nutrition post-discharge.

Comments Due to immaturity, respiratory support, oxidative stress, and possibly undernutrition, preterm infants may develop lung damage and sometimes bronchopulmonary dysplasia. Bronchopulmonary dysplasia is in itself a significant risk factor of a disturbed neurocognitive development [24]. The lung damage obtained during the neonatal phase extends frequently to the school age range [25, 26], and a higher asthma incidence is associated with lower gestational age [27]. The use of a high-density formula in infants with chronic lung disease in the postnatal phase did not improve growth or respiratory outcome, despite a small increase in total energy and protein intake [28]. In the present study, the authors wanted to determine whether the type of post-discharge nutrition affects lung function in 6-year-old children born very preterm by

measuring airway resistance and fractional exhaled nitric oxide (a non-invasive method to screen for airway inflammation in asthma). In this multicenter Danish trial, 320 very preterm infants were included to receive unfortified human milk, fortified human milk, or preterm formula from discharge to 4 months corrected age. Children with BPD and diseases influencing nutritional status such as necrotizing enterocolitis, chromosomal anomalies, and intraventricular hemorrhage were excluded. At age 6 years, 119–160 children were tested. Regardless of feeding group, no significant differences between feeding groups were observed. Despite earlier research showing a clear effect of preterm birth on lung function at later age, this study showed that lung function, expressed by airway resistance, was within normal range within all groups. In addition, hardly any significant differences were seen between the feeding groups. This may indicate 3 things:

1 The differences between feeding groups were too small to detect an effect of the intervention.
2 The window of modulating an effect is before the intervention started (i.e. impact is possible at the direct postnatal phase)
3 Immediate postnatal nutritional support in Denmark at around 2005 was already of such a level that lung function in the studied "healthy" preterm infants was not influenced by modest changes following discharge.

Neurodevelopmental outcome of nutritional intervention in newborn infants at risk of neurodevelopmental impairment: the Dolphin neonatal double-blind randomized controlled trial

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Aim: To investigate whether neonates at risk for neurodevelopmental impairment have improved neurodevelopment after docosahexaenoic acid, choline, and uridine-5-monophosphate supplementation versus controls.
Method: Recruitment was from UK neonatal units. Eligible for inclusion were infants born at <31 weeks' gestation with a weight less than the ninth centile; infants born at <31 weeks' gestation with a grade II or higher intraventricular haemorrhage/preterm white matter injury; infants born between 31 and 40 weeks' gestation plus 28 days with a grade II or higher intraventricular haemorrhage/preterm white matter injury, moderate or severe hypoxic-ischaemic encephalopathy, or defined neuroimaging abnormalities. Treatment/control supplementation was for 2 years (double-blind, randomized, controlled design). Infants were stratified according to sex, gestation, and brain injury severity. Primary outcome was cognitive composite score of the Bayley Scales of Infant Development, Third Edition (Bayley-III at 24 months). Secondary outcomes were language composite score of the Bayley-III, motor composite score of the Bayley-III, and Vineland Adaptive Behaviour Scales, Second Edition score.
Results: Sixty-two neonates were recruited, 59 were randomized (34 males, 25 females). Fifty-3 started supplementation. Most families found supplementation acceptable. The treatment group cognitive composite score-Bayley-III scores were non-significantly higher than controls (mean score difference at 24 months: 9.0; 95% CI –0.2 to 18.2). Language and Vineland Adaptive Behaviour Scales, Second Edition scores, but not motor score, were non-significantly higher in the treatment group.

Interpretation: Most families found supplementation feasible. Improved neurodevelopmental outcomes in the treatment group were not statistically significant. A larger multicentre trial exploration is warranted.

Comments

This specific trial focusses on the supplementation of docosahexaenoic acid (DHA), choline, and UMP, supplementation in neonates with neurodevelopmental impairment risk factors. The study population included noenates being born very preterm, small for gestational age infants, but also on infants born between 31 and 40 weeks any brain damage. The only study that targeted a similar population was conducted by Dabydeen et al. [29] published in 2008. They conducted a prospective, double-blind, and randomized, 2-stage group sequential study and controlled for gestation, gender, and brain lesion. Neonates with perinatal brain damage were randomly allocated to receive either a high- (120% recommended average intake) or average (100% recommended average intake) energy and protein diet. The study began at term and continued for 12 months. That study was terminated when 16 subjects had completed the protocol because the predetermined stopping criterion of >1 SD difference in occipitofrontal circumference at 12 months' corrected age in those receiving the higher-energy and -protein diet had been demonstrated. Axonal diameters in the corticospinal tract, length, and weight were also significantly increased. They concluded that infants with significant perinatal brain damage have increased nutritional requirements in the first postnatal year and suggest that decreased postnatal brain growth may exacerbate their impairment. No study has been published since then. The present study does not provide more energy and protein but adds a specific mixture (DHA, choline and UMP, a pyrimidine) aimed to enhance the production of phosphatidylcholine, which is the most abundant brain phospholipid. In addition, DHA, choline, and uridine supplementation synergistically increases rodent brain phospholipids, synaptic components, functional brain connectivity, and cognitive performance [30]. Power calculation beforehand revealed that in total 48 infants should be included, with an additional 12 as a result of anticipated loss to follow-up.

Although the results were not statistically significantly different, there was a better score in the children who received the supplementation, Bayley composite score was 9 points (nonsignificant) higher. Disappointing as this may seem, these results as well as those obtained in the trial by Dabydeen indicate that there is a potential in additional nutritional support of especially vulnerable newborns. However, the observed improvement in Bayley-III for treated infants should be replicated in a larger trial, before this will have important implications for the treatment of infants at risk of neurological impairment.

Improved outcomes in preterm infants fed a nonacidified liquid human milk fortifier: a prospective randomized clinical trial

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Objective: To compare growth, feeding tolerance, and clinical and biochemical evaluations in human milk-fed preterm infants randomized to receive either an acidified or a nonacidified liquid human milk fortifier.

Study Design: This prospective, controlled, parallel, multicenter growth and tolerance study included 164 preterm infants (≤32 weeks of gestation, birth weight 700–1,500 g) who were randomized to acidified or nonacidified liquid human milk fortifier from study day 1, the first day of fortification, through study day 29 or until hospital discharge.

Results: There was no difference in the primary outcome of weight gain from study days 1 to 29 (acidified liquid human milk fortifier, 16.4 ± 0.4 g/kg/day; nonacidified liquid human milk fortifier, 16.9 ± 0.4 g/kg/day). However, in both the intention-to-treat and the protocol evaluable analyses, infants fed nonacidified liquid human milk fortifier had significantly greater weight gain from study days 1 to 15 (17.9 vs. 15.2 g/kg/day; $p = 0.001$). Infants fed with acidified liquid human milk fortifier received more protein (4.26 vs. 4.11 g/kg/day, $p = 0.0099$) yet had lower blood urea nitrogen values ($p = 0.010$). The group fed acidified liquid human milk fortifier had more vomiting (10.3 vs. 2.4%; $p = 0.018$), gastric residuals (12.8 vs. 3.7%; $p = 0.022$), and metabolic acidosis (27 vs. 5%; $p < 0.001$) in the intention-to-treat analysis and more abdominal distension (14.0 vs. 1.7%; $p = 0.015$) in the protocol evaluable analysis.

Conclusions: Infants fed an acidified liquid human milk fortifier had higher rates of metabolic acidosis and poor feeding tolerance compared with infants fed a nonacidified liquid human milk fortifier. Initial weight gain was poorer with the acidified liquid human milk fortifier.

Comments

The use of human milk fortifiers is widespread in neonatal units around the world. In some countries, such as the United States, liquid fortifiers are used. This was the resultant of several cases of infant infection and death from Cronobacter sakazakii sepsis using powdered formula and led the FDA to ban powered formulas or fortifiers [31]. In order to achieve sterility, liquid fortifiers can be acidified or treated with heat. Acidification of the fortifier will reduce the pH of the feeding with possible disadvantages. The disadvantage of any liquid fortifier is the replacement of a certain volume of own mother's milk, thereby reducing the amount of potential beneficial bioactive factors that are not been added by the fortifier. Fourteen sites participated in this nonblinded study, with a primary outcome of weight gain during the first 4 weeks of supplementation that started whenever the infants reached an intake of 80 mL/kg/day. In total, 160 infants participated in the intention to treat analysis; no differences were identified in the primary outcome of weight gain from study days 1 to 29 between the acidified or nonacidified liquid human milk fortifier groups in either the ITT analysis (effect size, –0.6 ± 0.6 g/kg/day) or protocol evaluable analysis (effect size, –0.8 ± 0.5 g/kg/day). Post hoc analyses did reveal some differences, for example, during the first 2 weeks and in

groups with large amounts of donor milk or other feedings, all in favor of the nonacidic fortifier. However, other important determinants showed detrimental effects of the use of an acidic fortifier (pH and vomiting episodes). These results, together with data from other trials [32, 33], indicate that whenever nonacidic fortifiers are available, those should be used. The question whether fortifiers should be used at all is again out there. The most recent Cochrane meta-analysis, with 1,071 infants included, reached the following conclusion: "Limited available data do not provide strong evidence that feeding preterm infants with multi-nutrient fortified breast milk compared with unfortified breast milk affects important outcomes, except that it leads to slightly increased in-hospital growth rates" [34]. Therefore, long-term results are warranted.

Commencing nutrient supplements before full enteral feed volume achievement is beneficial for moderately preterm to late preterm low birth weight babies: a prospective, observational study

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Abstract: The aim of this study was to observe after following a routine change in the feeding protocol whether the earlier introduction of nutrient supplements improved nutritional outcomes in moderately preterm to late preterm low birth weight (LBW) babies. In this prospective observational study, LBW babies between 31 and 39-weeks' gestation admitted to a Special Care Nursery were assigned to 2 groups (F80, $n = 45$, F160, $n = 42$) upon commencing nutrient supplement at total fluid intake achievement of 80 or 160 mL/kg/day. Outcomes included weight, protein intake, biochemical markers, feeding intolerance, and length of stay. F80 nutrient supplements commenced before F160 (2.8 vs. 6.7 days, $p < 0.0001$) and lasted longer (15.2 vs. 12.2 days, $p < 0.03$). Weight gain velocity and length of stay were similar. F80 mean protein intake during the first 10 days was higher (3.38 vs. 2.74 g/kg/day, $p < 0.0001$). There were fewer infants with protein intake <3 g/kg/day in the F80 group (8 vs. 65%, $p < 0001$). F80 babies regained birthweight almost 2 days earlier (7.5 vs. 9.4 days, $p < 0.01$). Weight gain Z-scores revealed an attenuation of the trend towards lower weight percentiles in the F80 group. Feeding intolerance was decreased for F80 (24.4 vs. 47.6%, $p < 0.03$). There were no adverse outcomes. Earlier nutrient supplementation for LBW babies lifts mean protein intake to above 3 g/kg/day and reduces both the duration of post-birth weight loss and incidence of feeding intolerance.

Comments The previous study started fortifying human milk at an intake of 80 mL/kg/day, but the studied infants were all below a gestational age of 32 weeks. The present study addresses a much larger population, namely, those born between 31 and 39 weeks of gestation. The resultant of the earlier start of fortification was predictable; slightly higher weight gain and faster time to regain birth weight. Moreover, it was not associated with any negative outcome, including tolerance. Although the number of infants studied was relatively small, there are only a few studies addressing this group. So, the conclusion is that there is a modest benefit, and no downsides to start fortifying own mother's milk at an intake of 80 mL/kg/day as can be done routinely in infants at lower gestational ages.

Effect of gastric residual evaluation on enteral intake in extremely preterm infants: a randomized clinical trial

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JAMA Pediatr 2019;173:534–543

Importance: Evaluating prefeed gastric residuals is considered routine care but has little supporting evidence.

Objective: To determine the effect of omitting prefeed gastric residual evaluation on nutritional outcomes in extremely preterm infants.

Design, Setting, and Participants: This single-center randomized clinical trial compared the omission of gastric residual evaluation with prefeed gastric residual evaluation. Infants were recruited from a level 4 neonatal intensive care unit and were enrolled from October 17, 2013, to October 8, 2016, and then followed up for 6 weeks after birth. Eligible participants were infants born at 32 or fewer weeks' gestation with a birth weight of 1,250 g or less; they were enrolled within 72 h after birth and within 24 h after feeding initiation. All participants (n = 143) were included in the modified intent-to-treat analysis, which was conducted from March to July 2018.

Interventions: The residual group underwent prefeed gastric residual evaluation; the no residual group did not. Feeding decisions were made according to nutritional guidelines, and infants received only human milk.

Main Outcomes and Measures: The primary outcome was weekly enteral nutrition intake in mL/kg for 6 weeks after birth.

Results: Of 143 infants, 74 (51.7%) were randomized to undergo gastric residual evaluation (residual group) and 69 (48.3%) to omitted gastric residual evaluation (no residual group). The residual group comprised an even number of male and female infants (37 [50.0%]) with a mean (SD) gestational age of 27.1 (2.4) weeks and a mean (SD) birth weight of 888.8 (206.6) grams, whereas the no residual group had more male infants (36 [52.17%]), a mean (SD) gestational age of 27 (1.2) weeks, and a mean (SD) birth weight of 915.2 (180) g. The no residual group had feedings that advanced more quickly compared with the residual group (mean weekly increase, 20.7 vs. 17.9 mL/kg/day; p = 0.02) and consumed more feedings at weeks 5 (137.2 [95% CI 128.6–145.8]; p = 0.03) and 6 (141.6 [95% CI 133.2–150.0]; p = 0.03). Among the secondary outcomes, the no residual group had higher mean estimated log weights (7.01 [95% CI 6.99–7.02] vs. 6.98 [95% CI 6.97–7.00]; p = 0.03), had fewer episodes of abdominal distention (0.59 [95% CI 0.34–1.01] vs. 1.79 [95% CI 1.27–2.53]; p = 0.001), and were discharged 8 days earlier (4.21 [95% CI, 4.14–4.28] vs. 4.28 [95% CI, 4.19–4.36]; p = 0.01). Odds for necrotizing enterocolitis (0.058 [95% CI 0.018–0.190] vs. 0.026 [95% CI 0.006–0.109]), death (0.004 [95% CI 0.0003–0.046] vs. 0.012 [95% CI 0.001–0.131]), late-onset sepsis (0.970 [95% CI 0.67–1.40] vs. 1.38 [95% CI 0.97–1.94]), and ventilator-associated pneumonia (0.084 [95% CI 0.033–0.214] vs. 0.056 [95% CI 0.019–0.168]) were similar between groups.

Conclusions and Relevance: Among extremely preterm infants, the omission of gastric residual evaluation increased the delivery of enteral nutrition as well as improved weight gain and led to earlier hospital discharge; these results may translate into evidence-based practice.

Gastric residual volume in feeding advancement in preterm infants (GRIP Study): a randomized trial

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J Pediatr 2018;200:79–83.e1

Objective: To evaluate the effect of not relying on prefeeding gastric residual volumes (GRV) to guide feeding advancement on the time to reach full feeding volumes in preterm infants, compared with routine measurement of GRV. We hypothesized that not measuring prefeeding GRV can shorten the time to reach full feeds.

Study Design: In this single-center, randomized, controlled trial, we included gavage fed preterm infants with birth weights (BW) 1,500–2,000 g who were enrolled within 48 h of birth. Exclusion criteria were major congenital malformations, asphyxia, and BW below the third percentile. In the study group, the GRV was measured only in the presence of bloody aspirates, vomiting, or an abnormal abdominal examination. In the control group, GRV was assessed routinely, and feeding advancement was based on the GRV. The primary outcome was the time to reach feeding volumes of 120 mL/kg/day. Secondary outcomes were time to regain BW, episodes of feeding interruptions, sepsis, and necrotizing enterocolitis.

Results: Eighty-seven infants were enrolled. There were no differences between the study and control groups with respect to time to reach full feeds (6 days [95% CI 5.5–6.5] vs. 5 days [95% CI 4.5–5.5]; $p = 0.82$), time to regain BW, episodes of feeding interruptions, or sepsis. Two infants in the control group developed necrotizing enterocolitis.

Conclusions: Avoiding routine assessment of GRV before feeding advancement did not shorten the time to reach full feeds in preterm infants with BW between 1,500 and 2,000 g.

Comments

The presence of large or greenish gastric residual volume (GRV) often triggers bedside staff to withhold or decrease the volume of subsequent feeds. Fear for NEC, although causality or associations are never proven, is usually the common ground for such a clinical decision. Two well-designed trials have appeared last year questioning the validity of measuring gastric residuals routinely in infants at the neonatal intensive cares. The results seem contradictory at first glance. Whereas Parker et al. found a positive effect of not measuring residuals, Singh et al. did not find any advantage in clinical outcomes. Both were single-center studies, but the infants they included were quite different. Healthy preterm infants, with a mean gestational age of 32 weeks and a birth weight of 1,750 g (Singh et al.), are a different population than preterm infants with a mean gestational age of 27 weeks and a birth weight of approximately 900 g (Parker et al.). Other studies, Torrazza et al. and Riskin et al. found also clinical benefits without apparent risks with a no – residual measurement regime [35, 36]. Studies by Mihatsch et al. [37] and Shulman et al. [38] concluded that GRV were unreliable predictors of feeding intolerance and the attainment of full enteral feeds and that increased GRV is not predictive of NEC. So together these studies indicate that there seems no benefit of measuring residuals. If anything, there might be a benefit in not measuring residuals in smaller infants. Besides, the time saved by not measuring residuals may also reduce the costs of nursing.

Gastric residual volumes versus abdominal girth measurement in assessment of feed tolerance in preterm neonates: a randomized controlled trial

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Adv Neonatal Care 2018;18:E13–E19

Background: Preterm neonates often have feed intolerance that needs to be differentiated from necrotizing enterocolitis. Gastric residual volumes (GRV) are used to assess feed tolerance but with little scientific basis.

Purpose: To compare prefeed aspiration for GRV and prefeed measurement of abdominal girth (AG) in the time taken to reach full feeds in preterm infants.

Methods: This was a randomized controlled trial. Infants with a gestational age of 27–37 weeks and birth weight of 750–2,000 g, who required gavage feeds for at least 48 h, were included. Infants were randomized into 2 groups: infants in the AG group had only prefeed AG measured. Those in the GRV group had prefeed gastric aspiration obtained for the assessment of GRV. The primary outcome was time to reach full enteral feeds at 150 mL/kg/day, tolerated for at least 24 h. Secondary outcomes were duration of hospital stay, need for parenteral nutrition, episodes of feed intolerance, number of feeds withheld, and sepsis.

Results: Infants in the AG group reached full feeds earlier than infants in the GRV group (6 vs. 9.5 days; $p = 0.04$). No significant differences were found between the 2 groups with regard to secondary outcomes.

Implications for Practice: Our research suggests that measurement of AG without assessment of GRV enables preterm neonates to reach full feeds faster than checking for GRV.

Implications for Research: Abdominal girth measurement as a marker for feed tolerance needs to be studied in infants <750 g and <26 weeks of gestation.

Comments Again, this study questioned the validity of measuring gastric residuals routinely. There results were in a similar direction as those of Parker et al., discussed earlier. The number of infants included was slightly above 100, with a mean gestational age of 31 weeks and a birth weight of 1,300 g. As a safety net, the researchers added the measurement of abdominal girth in the routine practice. This was well appreciated by the nurses. Measurement of abdominal girth only without checking gastric residual volume enabled preterm neonates to reach full feeds faster than routinely checking for residuals.

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Cognition

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Introduction

This chapter includes articles published in the area of nutrition and cognition from July 1, 2018, up to June 30, 2019. Pregnancy, infancy, and early childhood are crucial periods for neurodevelopment and are influenced by several factors. During these critical phases, nutrients and energy requirements of mothers and their offspring should be ensured to permit optimal brain growth as well as cognitive outcomes throughout life. Accordingly, all the articles that have been selected fall into four categories connected with later neurocognitive performance in the offspring: (1) Breastfeeding, with 2 observational studies, (2) Fatty Acids, including 2 RCT and 1 observational study, (3) a new paragraph, Holistic Approach, with 2 observational studies and 2 reviews, respectively, focusing on the role of socioeconomics conditions, environmental factors, and maternal stress up to the ingestion of amniotic fluid, and (4) Nutrients in pregnancy, with a selection of 10 studies, mostly observational, with a few systematic reviews and 1 RCT design from a major developing country. Comments following the abstracts are included for each of the 4 sections.

Key articles reviewed for this chapter

Breastfeeding

Is breast feeding associated with offspring IQ at age 5? Findings from prospective cohort: lifestyle during pregnancy study

Strøm M, Mortensen EL, Kesmodel US, Halldorsson T, Olsen J, Olsen SF

BMJ Open 2019;9:e023134

Nutrients or nursing? Understanding how breast milk feeding affects child cognition

Pang WW, Tan PT, Cai S, Fok D, Chua MC, Lim SB, Shek LP, Chan SY, Tan KH, Yap F, Gluckman PD, Godfrey KM, Meaney MJ, Broekman BFP, Kramer MS, Chong YS, Rifkin-Graboi A

Eur J Nutr 2019. Doi 10.1007/s00394–019–01929–2 [Epub ahead of print]

Fatty Acids

The effect of Atlantic salmon consumption on the cognitive performance of preschool children: A randomized controlled trial

Demmelmair H, Øyen J, Pickert T, Rauh-Pfeiffer A, Stormark KM, Graff IE, Lie Ø, Kjellevold M, Koletzko B

Clin Nutr 2018. Doi 10.1016/j.clnu.2018.11.031 [Epub ahead of print]

Fatty fish intake and the effect on mental health and sleep in preschool children in FINS-KIDS, a randomized controlled trial

Hysing M, Kvestad I, Kjellevold M, Kolden Midtbø L, Graff IE, Lie Ø, Hurum H, Stormark KM, Øyen J

Nutrients 2018;10:1478

Whole blood n-3 fatty acids are associated with executive function in 2–6-year-old Northern Ghanaian children

Adjepong M, Yakah W, Harris WS, Annan RA, Pontifex MB, Fenton JI

J Nutr Biochem 2018;57:287–293

Holistic Approach

Low socioeconomic status and severe obesity are linked to poor cognitive performance in Malaysian children

Poh BK, Lee ST, Yeo GS, Tang KC, Noor Afifah AR, Siti Hanisa A, Parikh P, Wong JE, Ng ALO and on behalf of the SEANUTS Study Group

BMC Public Health 2019;19(suppl 4):541

Sociodemographic, nutritional, and environmental factors are associated with cognitive performance among Orang Asli children in Malaysia

Murtaza SF, Gan WY, Sulaiman N, Mohd Shariff Z, Ismail SIF

PLoS One 2019;14:e0219841

The interplay between nutrition and stress in pregnancy: implications for fetal programming of brain development

Lindsay KL, Buss C, Wadhwa PD, Entringer S

Biol Psychiatry 2019;85:135–149

You are what you (first) eat

Buchanan KL, Bohórquez DV

Front Hum Neurosci 2018;12:323

Nutrients in Pregnancy

The importance of maternal folate status for brain development and function of offspring

Naninck EFG, Stijger PC, Brouwer-Brolsma EM

Adv Nutr 2019;10:502–519

Prenatal air pollution and childhood IQ: Preliminary evidence of effect modification by folate

Loftus CT, Hazlehurst MF, Szpiro AA, Ni Y, Tylavsky FA, Bush NR, Sathyanarayana S, Carroll KN, Karr CJ, LeWinn KZ

Environ Res 2019;176:108505

Maternal Iodine Status is Associated with Offspring Language Skills in Infancy and Toddlerhood

Markhus MW, Dahl L, Moe V, Abel MH, Brantsæter AL, Øyen J, Meltzer HM, Stormark KM, Graff IE, Smith L, Kjellevold M

Nutrients 2018;10:1270

Association of maternal iodine status with child IQ: a meta-analysis of individual-participant data

Levie D, Korevaar TIM, Bath SC, Murcia M, Dineva M, Llop S, Espada M, van Herwaarden AE, de Rijke YB, Ibarluzea JM, Sunyer J, Tiemeier H, Rayman MP, Guxens M, Peeters RP

J Clin Endocrinol Metab 2019;104:5957–5967

Maternal dietary intake of polyunsaturated fatty acids modifies association between prenatal DDT exposure and child neurodevelopment: A cohort study

Ogaz-González R, Mérida-Ortega Á, Torres-Sánchez L, Schnaas L, Hernández-Alcaraz C, Cebrián ME, Rothenberg SJ, García-Hernández RM, López-Carrillo L

Environ Pollut 2018;238:698–705

The impact of docosahexaenoic acid supplementation during pregnancy and lactation on neurodevelopment of the offspring in India (DHANI): trial protocol

Khandelwal S, Swamy MK, Patil K, Kondal D, Chaudhry M, Gupta R, Divan G, Kamate M, Ramakrishnan L, Bellad MB, Gan A, Kodkany BS, Martorell R, Srinath Reddy K, Prabhakaran D, Ramakrishnan U, Tandon N, Stein AD

BMC Pediatr 2018;18:261

Associations between vitamin D status in pregnancy and offspring neurodevelopment: a systematic literature review

Janbek J, Specht IO, Heitmann BL

Nutr Rev 2019;77:330–349

Maternal selenium status and neuropsychological development in Spanish preschool children

Amorós R, Murcia M, González L, Rebagliato M, Iñiguez C, Lopez-Espinosa MJ, Vioque J, Broberg K, Ballester F, Llop S

Environ Res 2018;166:215–222

Prenatal selenium status, neonatal cerebellum measures and child neurodevelopment at the age of 18 months

Močenić I, Kolić I, Nišević JR, Belančić A, Tratnik JS, Mazej D, Falnoga I, Vlašić-Cicvarić I, Štimac T, Špirić Z, Horvat M Prpić I

Environ Res 2019;176:108529

Maternal copper status and neuropsychological development in infants and preschool children

Amorós R, Murcia M, González L, Soler-Blasco R, Rebagliato M, Iñiguez C, Carrasco P, Vioque J, Broberg K, Levi M, Lopez-Espinosa MJ, Ballester F, Llop S

Int J Hyg Environ Health 2019;222:503–512

Breastfeeding

Is breast feeding associated with offspring IQ at age 5? Findings from prospective cohort: lifestyle during pregnancy study

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BMJ Open 2019;9:e023134

Objective: Breast feeding is associated with health benefits for both mother and child, but many studies focusing on neurodevelopment have lacked information on important confounders and few randomised trials exist. Our objective was to examine the influence of breast feeding on child IQ at 5 years of age while taking maternal IQ and other relevant factors into account.
Design: Prospective observational study.

Setting: Population-based birth cohort in Denmark.
Participants: We used data from The Lifestyle During Pregnancy Study 1,782 mother-child pairs sampled from the Danish National Birth Cohort (n = 101,042).
Outcome Measures: Child IQ was assessed at age 5 years by the Wechsler Primary and Preschool Scales of Intelligence-Revised. On the same occasion maternal intelligence was assessed by Wechsler Adult Intelligence Scale and Raven's Standard Progressive Matrices. Exposure data on duration of breast feeding (n = 1,385) were extracted from telephone interviews conducted when the child was 6 and 18 months, and analyses were weighted by relevant sampling fractions.
Results: In multivariable linear regression analyses adjusted for potential confounders breast feeding was associated with child IQ at 5 years (categorical χ^2 test for overall association p = 0.03). Compared with children who were breast fed ≤1 month, children breast fed for 2–3, 4–6, 7–9 and 10 or more months had 3.06 (95% CI 0.39 to 5.72), 2.03 (95% CI –0.38 to 4.44), 3.53 (95% CI 1.18 to 5.87) and 3.28 (95% CI 0.88 to 5.67) points higher IQ after adjustment for core confounders, respectively. There was no dose-response relation and further analyses indicated that the main difference in IQ was between breast feeding ≤1 month versus >1 month.
Conclusions: Breastfeeding duration of 1 month or shorter compared with longer periods was associated with approximately three points lower IQ, but there was no evidence of a dose-response relation in this prospective birth cohort, where we were able to adjust for some of the most critical confounders, including maternal intelligence.

Nutrients or nursing? Understanding how breast milk feeding affects child cognition

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Purpose: To explore the associations between type of milk feeding (the "nutrients") and mode of breast milk feeding (the "nursing") with child cognition.

Methods: Healthy children from the GUSTO (Growing Up in Singapore Toward healthy Outcomes) cohort participated in repeated neurodevelopmental assessments between 6 and 54 months. For "nutrients", we compared children exclusively bottle-fed according to type of milk received: formula only (n = 296) vs some/all breast milk (n = 73). For "nursing," we included only children who were fully fed breast milk, comparing those fed directly at the breast (n = 59) versus those fed partially/completely by bottle (n = 63).
Results: Compared to infants fed formula only, those who were bottle-fed breast milk demonstrated significantly better cognitive performance on both the Bayley Scales of Infant and Toddler Development (Third Edition) at 2 years [adjusted mean difference (95% CI) 1.36 (0.32, 2.40)], and on the Kaufman Brief Intelligence Test (Second Edition) at 4.5 years [7.59 (1.20, 13.99)]. Children bottle-fed breast milk also demonstrated better gross motor skills at 2 years than those fed formula [1.60 (0.09, 3.10)]. Among infants fully fed breast milk, those fed directly at the breast scored higher on several memory tasks compared to children bottle-fed breast milk, including the deferred imitation task at 6 months [0.67 (0.02, 1.32)] and relational binding tasks at 6 [0.41 (0.07, 0.74)], 41 [0.67 (0.04, 1.29)] and 54 [0.12 (0.01, 0.22)] months.
Conclusions: Our findings suggest that nutrients in breast milk may improve general child cognition, while nursing infants directly at the breast may influence memory.

Comments In these two studies, from different geographic settings (Denmark and Singapore, respectively), the authors try to disentangle from population cross-over designs the role of possible confounders on the proverbial association between breastfeeding and/or human milk and optimal neurofunctional development. The first study, while accounting for several confounders (maternal intelligence quotient, IQ, at first), does not show any dose–response relationship as continuous variable in terms of progressively longer breastfeeding duration and higher IQ scores. The only recorded difference has been found for breastfeeding ≤1 month (lower IQ) and >1 month (higher IQ), raising questions on the potential role of post-natal factors not considered within the survey. The Singapore study had the opportunity to focus on three categories, formula-fed infants, infants fed only human milk at the breast, and infants fed only human milk but at least partially as expressed and given through a bottle as assessed at the age of 3 months. The 2 human milk-fed groups showed higher developmental scores when visited between 6 and 54 months. Those fed at the breast showed a further advantage in memory items, so allowing for the conclusive remarks at the question "Nutrients or nursing?" in terms of "nutrients in breast milk may improve general child cognition, while nursing infants directly at the breast may influence memory." The reasons of the relatively high rate of mothers giving their expressed milk by bottle (the 2 samples were comparable) are not detailed by the authors, just referring to a generic "preferred mean of administration in some cultures."

The effect of Atlantic salmon consumption on the cognitive performance of preschool children. A randomized controlled trial

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Background and Aims: Long chain polyunsaturated n-3 fatty acids (LC-PUFA) are of functional and structural importance for brain development. Observational studies have shown positive relations between fatty fish consumption and cognitive performance in children, but Results from intervention studies using supplementary n-3 LC-PUFA are conflicting. Salmon is a good source of n-3 LC-PUFA, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). We tested the hypothesis that an increased dietary salmon intake results in better cognitive outcomes than a meat based diet.

Methods: Children (n = 205, age 4–6 years) in this trial were individually randomized to eating meals containing farmed Atlantic salmon or meat three times weekly for 16 weeks. Pre- and post-intervention a cognitive test (Wechsler Preschool and Primary Scale of Intelligence, 3rd edition, WPPSI-III) and a fine-motor coordination test (Nine Hole Peg Test, 9-HPT) were performed. Biochemical analyses included glycerophospholipid fatty acid profiles in plasma and cheek cells, serum 25-hydroxyvitamin D, and urinary iodine concentration. Dietary intake before and during the study were determined using food frequency questionnaires.

Results: Intakes of EPA, DHA, vitamin D and iodine were higher in the salmon than the meat group, but on biomarker level only EPA and DHA increased significantly in the salmon group compared to the meat group ($p < 0.001$). In general linear models no significant differences between the intervention groups were found in the scale scores of the WPPSI-III tests and the 9-HPT. In analyses of the raw scores, the salmon group showed significantly better improvement in two of the eight raw scores compared to the meat group (symbol search $p = 0.038$, picture concepts $p = 0.047$).

Conclusions: Intake of farmed Atlantic salmon led to a greater increase of the raw scores of the picture concept and symbol search subtests, while in the six other subtests raw scores were not different between the groups. This might indicate a modest positive association of salmon intake with the performance of preschool children in some subtests evaluating fluid intelligence but does not suggest an influence on global IQ development.

Fatty fish intake and the effect on mental health and sleep in preschool children in FINS-KIDS, a randomized controlled trial

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Abstract: Mental health and sleep problems are prevalent in children during preschool years. The aim of the current study was to investigate if increased intake of fatty fish compared with meat improves mental health and sleep in four- to six-year-old children. The children (n = 232) in the two-armed randomized controlled trial, Fish Intervention Studies-KIDS (FINS-KIDS), were randomly assigned to lunch meals with fatty fish (herring/mackerel) or meat (chicken/lamb/beef) three times a week for 16 weeks. The fish and meat were weighed before and after the meals to record the exact consumption in grams (dietary compliance). Mental health problems were assessed by the strengths and difficulties questionnaire (SDQ) and sleep by parent report pre- and post-intervention. There was no significant statistical difference between changes in mental health and sleep for the fish eating group compared with the meat eating group, neither in the crude analysis nor after adjusting for intake of fish or meat (dietary compliance).

Comments Two nice randomized trials explored the effects on neurodevelopment (the first) and mental health and sleep problems (the second) of fatty fish (salmon and blue fish, respectively) 3 times per week, through 16 weeks each, in preschool children aged 4–6 years, in well-developed settings. The results are modest in the first case and negligible in the second, suggesting that in well-developed countries, the positive effects of n-3 LC-PUFA from natural sources in preschool years may be overcome by other factors or, alternatively, quite higher intakes should be needed for a meaningful effect.

Whole blood n-3 fatty acids are associated with executive function in 2–6-year-old Northern Ghanaian children

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Abstract: Several studies demonstrate the importance of essential fatty acids (EFAs), and the long chain polyunsaturated FA docosahexaenoic acid (DHA), on cognition and brain development. The objective of this study was to investigate the relationship between whole-blood FAs and executive function in children from Northern Ghana. A total of 307, 2-to-6-year-old children attempted the dimensional change card sort (DCCS) task to assess executive function, and dried blood spot samples were

collected and analyzed for FA content. Significant differences in mean % total whole-blood fatty acids were observed between children who could not follow directions on the DCCS test (49.8% of the sample) and those who could (50.2% of the sample). Positive associations with DCCS performance were observed for DHA ($\beta = 0.25$, $p = 0.06$), total *n*-3 ($\beta = 0.17$, $p = 0.06$) and dihomo-gamma-linolenic acid (DGLA; $\beta = 0.60$, $p = 0.06$). Children with the highest levels of total *n*-3 and DHA were three and four times, respectively, more likely to pass at least one condition of the DCCS test of executive function than those with the lowest DHA levels. The results of this study indicate an association between n-3 FAs and high-level cognitive processes in children two to six years of age, providing impetus for further studies into possible interventions to improve EFA status of children in developing countries.

Comments Preliminary observational studies showing associations between blood circulating levels of major LCPUFA (DHA/total n-3 and n-6 DHGLA, respectively) in 2–6 years growing children within a developing country and executive functions, suggesting major potential effects of dietary supplemental LCPUFA in poorer settings.

Holistic Approach

Low socioeconomic status and severe obesity are linked to poor cognitive performance in Malaysian children

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Background: Socioeconomic factors and nutritional status have been associated with childhood cognitive development. However, previous Malaysian studies had been conducted with small populations and had inconsistent results. Thus, this present study aims to determine the association between socioeconomic and nutritional status with cognitive performance in a nationally representative sample of Malaysian children.

Methods: A total of 2406 Malaysian children aged 5 to 12 years, who had participated in the South East Asian Nutrition Surveys (SEANUTS), were included in this study. Cognitive performance [non-verbal intelligence quotient (IQ)] was measured using Raven's Progressive Matrices, while socioeconomic characteristics were determined using parent-report questionnaires. Body mass index (BMI) was calculated using measured weight and height, while BMI-for-age Z-score (BAZ) and height-for-age Z-score (HAZ) were determined using WHO 2007 growth reference.

Results: Overall, about a third (35.0%) of the children had above average non-verbal IQ (high average: 110–119; superior: ≥120 and above), while only 12.2% were categorized as having low/borderline IQ (<80). Children with severe obesity (BAZ >3 SD), children from very low household income families and children whose parents had only up to primary level education had the highest prevalence of low/borderline non-verbal IQ, compared to their non-obese and higher socioeconomic

counterparts. Parental lack of education was associated with low/borderline/below average IQ [paternal, OR = 2.38 (95%CI 1.22, 4.62); maternal, OR = 2.64 (95% CI 1.32, 5.30)]. Children from the lowest income group were twice as likely to have low/borderline/below average IQ [OR = 2.01 (95% CI 1.16, 3.49)]. Children with severe obesity were twice as likely to have poor non-verbal IQ than children with normal BMI [OR = 2.28 (95% CI 1.23, 4.24)].

Conclusions: Children from disadvantaged backgrounds (that is those from very low-income families and those whose parents had primary education or lower) and children with severe obesity are more likely to have poor non-verbal IQ. Further studies to investigate the social and environmental factors linked to cognitive performance will provide deeper insights into the measures that can be taken to improve the cognitive performance of Malaysian children.

Sociodemographic, nutritional, and environmental factors are associated with cognitive performance among Orang Asli children in Malaysia

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Abstract: Children aged 2 to 6 years are in a crucial period of growth development, during which it is important for them to attain specific cognition related to concentration and attention so that they can perform well in school later in life. Various factors influence children's cognition during this crucial period. However, to date, only a limited number of studies have examined the cognitive performance of underprivileged children living in poverty, particularly indigenous children (also known as Orang Asli children in Malaysia). Therefore, this cross-sectional study aimed to determine the associations between sociodemographic factors, nutritional factors (body composition and hemoglobin), and environmental factors (home environment and parasitic infections) with cognitive performance among Orang Asli children in Negeri Sembilan, Malaysia. The participants were 269 children (51% boys, 49% girls) aged 2 to 6 years (M = 4.0, SD = 1.2 years) and their mothers, from 14 Orang Asli villages. Face-to-face interviews were conducted with the mothers, and the children's cognitive performance, operationalized as working memory index (WMI), processing speed index (PSI), and cognitive proficiency index (CPI), was assessed using the Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV). The children's weight and height were measured, and their blood and stool samples were collected to assess hemoglobin level and parasitic infections, respectively. Multiple linear regression analysis showed that the father's years of education ($\beta = 0.262–0.342$, $p < 0.05$), availability of learning materials at home ($\beta = 0.263–0.425$, $p < 0.05$), and responsiveness of the parent to the child ($\beta = 0.192–0.331$, $p < 0.05$) were consistently associated with all three cognitive indices (WMI, PSI, and CPI). A holistic approach involving parents, communities, and government agencies should be established to improve the cognitive performance of these underprivileged children.

Comments These 2 observational studies from the same developing country (Malaysia) show that associations between disadvantaged social backgrounds and nutritional conditions (from anemia to obesity) are closely linked to neurodevelopmental indices in children of either preschool and school years. On a practical standpoint, all the aspects need

attention when exploring children's conditions and planning public health interventions in these settings. Furthermore, the study offers a model of holistic approach to be applied also in well-developed and rich countries, from poorer ethnic communities to the prevention of chronic degenerative disorders in the local, economically more advantaged population, as shown in other recent studies [1].

The interplay between nutrition and stress in pregnancy: implications for fetal programming of brain development

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Abstract: Growing evidence supports an important role for the intrauterine environment in shaping fetal development and subsequent child health and disease risk. The fetal brain is particularly plastic, whereby even subtle changes in structure and function produced by in utero conditions can have long-term implications. Based on the consideration that conditions related to energy substrate and likelihood of survival to reproductive age are particularly salient drivers of fetal programming, maternal nutrition and stress represent the most commonly, but independently, studied factors in this context. However, the effects of maternal nutrition and stress are context dependent and may be moderated by one another. Studies examining the effects of the bidirectional nutrition-stress interplay in pregnancy on fetal programming of brain development are beginning to emerge in the literature. This review incorporates all currently available animal and human studies of this interplay and provides a synthesis and critical discussion of findings. Nine of the 10 studies included here assessed nutrition-stress interactions and offspring neurodevelopmental or brain development outcomes. Despite significant heterogeneity in study design and methodology, two broad patterns of results emerge to suggest that the effects of prenatal stress on various aspects of brain development may be mitigated by 1) higher fat diets or increased intake and/or status of specific dietary fats and 2) higher dietary intake or supplementation of targeted nutrients. The limitations of these studies are discussed, and recommendations are provided for future research to expand on this important area of fetal programming of brain development.

You are what you (first) eat

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Abstract: As far back as we can remember, we eat. In fact, we eat *before* we can remember. Our first meal is amniotic fluid. We swallow it during the first trimester of gestation, and with that, we expose our gut to a universe of molecules. These early molecules have a profound influence on gut and brain function. For example, the taste of the amniotic fluid changes based on the mother's diet. Indeed, recent findings

suggest that food preferences begin *in utero*. Likewise, a baby's first exposure to bacteria, previously thought to be during birth, appears to be *in utero* as well. And just as postnatal food and microbiota are implicated in brain function and dysfunction, prenatal nutrients and microbes may have a long-lasting impact on the development of the gut-brain neural circuits processing food, especially considering their plasticity during this vulnerable period. Here, we use current literature to put forward concepts needed to understand how the gut first meets the brain, and how this encounter may help us remember food.

Comments These 2 papers have been separated from the following section on Nutrients in Pregnancy since they deal with unusual aspects, within a more holistic and comprehensive approach to nutrition. The first paper explores the possible combined effects of maternal stress and nutritional factors on fetal programming of brain function. The second paper describes the potential role of nutrients dispersed in the amniotic fluid and eaten by the fetus on an early taste imprinting or influencing the gut-brain neural circuits in the offspring by means of the in utero exposure to bacteria affecting the development of the gut microbioma.

Nutrients IN Pregnancy

The importance of maternal folate status for brain development and function of offspring

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Abstract: The importance of an adequate periconceptional maternal folate status to prevent fetal neural tube defects has been well demonstrated and resulted in the recommendation for women to use folic acid supplements during the periconception period. The importance of maternal folate status for offspring neurodevelopment and brain health is less well described. We reviewed the current evidence linking maternal folate status before conception and during pregnancy with neurodevelopment and cognition of the offspring. We discuss both animal and human studies. Preclinical research revealed the importance of maternal folate status for several key processes required for normal neurodevelopment and brain functioning in the offspring, including DNA synthesis, regulation of gene expression, synthesis of phospholipids and neurotransmitters, and maintenance of healthy plasma homocysteine concentrations. Human observational studies are inconclusive; about half have shown a positive association between maternal folate status and cognitive performance of offspring. Whereas some studies suggest a positive association between maternal folate intake and cognition of offspring during childhood, data from interventional studies are too limited to conclude that there is a direct effect. Future preclinical studies are needed to help us characterize the behavioral effects, understand the underlying mechanisms, and to establish an optimal dosage and time window of folate supplementation. Moreover, more conclusive data from well-designed human observational studies and randomized controlled trials are needed to determine whether current recommendations for folic acid supplementation during pregnancy cover the needs for normal cognitive development in the offspring.

Prenatal air pollution and childhood IQ: Preliminary evidence of effect modification by folate

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Environ Res 2019;176:108505

Objectives: Animal studies suggest that air pollution is neurotoxic to a developing fetus, but evidence in humans is limited. We tested the hypothesis that higher air pollution is associated with lower child IQ and that effects vary by maternal and child characteristics, including prenatal nutrition.
Methods: We used prospective data collected from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood study. Outdoor pollutant exposure during pregnancy was predicted at geocoded home addresses using a validated national universal kriging model that combines ground-based monitoring data with an extensive database of land-use covariates. Distance to nearest major roadway was also used as a proxy for traffic-related pollution. Our primary outcome was full-scale IQ measured at age 4–6. In regression models, we adjusted for multiple determinants of child neurodevelopment and assessed interactions between air pollutants and child sex, race, socioeconomic status, reported nutrition, and maternal plasma folate in second trimester.
Results: In our analytic sample (n = 1,005) full-scale IQ averaged 2.5 points (95% CI: 0.1, 4.8) lower per 5 μg/m^3 higher prenatal PM_{10}, while no associations with nitrogen dioxide or road proximity were observed. Associations between PM_{10} and IQ were modified by maternal plasma folate ($p_{interaction}$ = 0.07). In the lowest folate quartile, IQ decreased 6.8 points (95% CI: 1.4, 12.3) per 5-unit increase in PM_{10}; no associations were observed in higher quartiles.
Conclusions: Our findings strengthen evidence that air pollution impairs fetal neurodevelopment and suggest a potentially important role of maternal folate in modifying these effects.

Maternal iodine status is associated with offspring language skills in infancy and toddlerhood

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Abstract: Inadequate iodine status affects the synthesis of the thyroid hormones and may impair brain development in fetal life. The aim of this study was to explore the association between maternal iodine status in pregnancy measured by urinary iodine concentration (UIC) and child neurodevelopment at

age 6, 12 and 18 months in a population-based cohort. In total, 1036 families from nine locations in Norway were enrolled in the little in Norway cohort. The present study includes $n = 851$ mother-child pairs with singleton pregnancies, no use of thyroid medication in pregnancy, no severe genetic disorder, data on exposure (UIC) in pregnancy and developmental outcomes (Bayley Scales of Infant and Toddler Development, third edition). Data collection also included general information from questionnaires. We examined associations between UIC (and use of iodine-containing supplements) and repeated measures of developmental outcomes using multivariable mixed models. The median UIC in pregnancy was 78 μg/L (IQR 46–130), classified as insufficient iodine intake according to the WHO. Eighteen percent reported use of iodine-containing multisupplements. A UIC below ~100 was associated with reduced receptive ($p = 0.025$) and expressive language skills ($p = 0.002$), but not with reduced cognitive or fine- and gross motor skills. Maternal use of iodine-containing supplements was associated with lower gross motor skills (b = −0.18, 95% CI = −0.33, −0.03, $p = 0.02$), but not with the other outcome measures. In conclusion, an insufficient iodine intake in pregnancy, reflected in a UIC below ~100 μg/L, was associated with lower infant language skills up to 18 months. The use of iodine-containing supplements was not associated with beneficial effects.

Association of maternal iodine status with child IQ: a meta-analysis of individual-participant data

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Context: While the consequences of severe iodine deficiency are beyond doubt, the effects of mild-to-moderate iodine deficiency in pregnancy on child neurodevelopment are less well established.
Objective: To study the association between maternal iodine status during pregnancy and child IQ and to identify vulnerable time-windows of exposure to suboptimal iodine availability.
Design: Meta-analysis of individual-participant data from three prospective population-based birth cohorts: Generation R (The Netherlands), INMA (Spain), and ALSPAC (United King-

dom); pregnant women were enrolled between 2002–2006, 2003–2008, and 1990–1992, respectively.
Setting: General community.
Participants: 6,180 mother-child pairs with measures of urinary iodine and creatinine concentrations in pregnancy and child IQ. Exclusion criteria were multiple pregnancy, fertility treatment, medication affecting the thyroid, and pre-existing thyroid disease.
Intervention(s): none.
Main Outcome Measure: Child non-verbal and verbal IQ assessed at 1.5–8 years of age.
Results: There was a positive curvilinear association of the urinary iodine-to-creatinine ratio (UI/Creat) with mean verbal IQ only. UI/Creat <150 μg/g was not associated with lower non-verbal IQ [−0.6 points, 95% CI −1.7 to 0.4, $p = 0.246$] or lower verbal IQ [−0.6, 95% CI −1.3 to 0.1, $p = 0.082$]. Stratified analyses showed that the association of UI/Creat with verbal IQ was only present up to 14 weeks of gestation.
Conclusions: Fetal brain development is vulnerable to mild-to-moderate iodine deficiency, particularly in the first trimester. Our results show that any potential randomized, controlled trial investigating the effect of iodine supplementation in mild-to-moderate iodine deficient women on child neurodevelopment, should start with supplementation not later than the first trimester.

Maternal dietary intake of polyunsaturated fatty acids modifies association between prenatal DDT exposure and child neurodevelopment: A cohort study

Ogaz-González R[1], Mérida-Ortega Á[1], Torres-Sánchez L[1], Schnaas L[2], Hernández-Alcaraz C[1], Cebrián ME[3], Rothenberg SJ[1], García-Hernández RM[3], López-Carrillo L[1]

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Environ Pollut 2018;238:698–705

Objectives: To assess whether maternal dietary intake of ω-3 and ω-6 during pregnancy modifies the association between exposure to DDE and child neurodevelopment from age 42–60 months.
Methods: Prospective cohort study with 142 mother–child pairs performed in Mexico. DDE serum levels were determined by electron capture gas chromatography. Dietary ω-3 and ω-6 intake was estimated by questionnaire. Child neurodevelopment was assessed by McCarthy Scales.
Results: Docosahexaenoic (DHA) fatty acid intake significantly modified the association between DDE and motor component: increased maternal DDE was associated with lower motor development in children whose mothers had lower DHA intake ($\beta_{log2DDE} = -1.25$; 95% CI: −2.62, 0.12), in contrast to the non-significant increase among children whose mothers had higher DHA intake ($\beta_{log2DDE\text{-}motor} = 0.50$; 95% CI: 0.55, 1.56). Likewise, arachidonic fatty acid (ARA) intake modified the association between DDE and memory component: increased maternal DDE was associated with a significantly larger reduction in the memory component in children whose mothers had lower ARA intake ($\beta_{log2DDE} = -1.31$; 95% CI: −2.29, −0.32) than children whose mothers had higher ARA intake ($\beta_{log2DDE\text{-}memory} = 0.17$; 95% CI: −0.78, 1.11).
Conclusions: Dietary intake of DHA and ARA during pregnancy may protect against child neurodevelopment damage associated with prenatal maternal DDE levels.

The impact of docosahexaenoic acid supplementation during pregnancy and lactation on neurodevelopment of the offspring in India (DHANI): trial protocol

Khandelwal S[1,2], Swamy MK[3], Patil K[3], Kondal D[1], Chaudhry M[1], Gupta R[1], Divan G[4], Kamate M[5], Ramakrishnan L[6], Bellad MB[3], Gan A[3], Kodkany BS[7], Martorell R[8], Srinath Reddy K[1], Prabhakaran D[1,2], Ramakrishnan U[8], Tandon N[6], Stein AD[8]

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BMC Pediatr 2018;18:261

Background: Evidence suggests a strong association between nutrition during the first 1,000 days (conception to 2 years of life) and cognitive development. Maternal docosahexaenoic acid (DHA) supplementation has been suggested to be linked with cognitive development of their offspring. DHA is a structural component of human brain and retina, and can be derived from marine algae, fatty fish and marine oils. Since Indian diets are largely devoid of such products, plasma DHA levels are low. We are testing the effect of pre- and post-natal DHA maternal supplementation in India on infant motor and mental development, anthropometry and morbidity patterns.
Methods: DHANI is a double-blinded, parallel group, randomized, placebo controlled trial supplementing 957 pregnant women aged 18–35 years from ≤20 weeks gestation through 6 months postpartum with 400 mg/d algal-derived DHA or placebo. Data on the participant's socio-demographic profile, anthropometric measurements and dietary intake are being recorded at baseline. The mother-infant dyads are followed through age 12 months. The primary outcome variable is infant motor and mental development quotient at 12 months of age evaluated by Development Assessment Scale in Indian Infants (DASII). Secondary outcomes are gestational age, APGAR scores, and infant anthropometry. Biochemical indices (blood and breast-milk) from mother-child dyads are being collected to estimate changes in DHA levels in response to supplementation. All analyses will follow the intent-to-treat principle. Two-sample *t* test will be used to test unadjusted difference in mean DASII score between placebo and DHA group. Adjusted analyses will be performed using multiple linear regression.
Discussion: Implications for maternal and child health and nutrition in India: DHANI is the first large pre- and post-natal maternal dietary supplementation trial in India. If the trial finds substantial benefit, it can serve as a learning to scale up the DHA intervention in the country.

Associations between vitamin D status in pregnancy and offspring neurodevelopment: a systematic literature review

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Nutr Rev 2019;77:330–349

Context: Vitamin D plays an important role in the development of the brain, which is one of the earliest fetal organs to develop. Results from epidemiological studies investigating associations be-

tween maternal levels of vitamin D during pregnancy and offspring neurodevelopment are mixed and inconclusive.

Objective: This systematic review of studies that examined vitamin D levels in pregnancy and offspring neurodevelopment used 3 specific domains-timing of exposure during pregnancy trimesters, neurodevelopmental outcomes, and offspring age at assessment of outcomes-to determine whether vitamin D status in pregnancy is associated with offspring neurodevelopment.

Data Source: A search of the Embase, PsychInfo, Scopus, and The Cochrane Library databases in September 2017 and February 2018 identified 844 articles, of which 46 were retrieved for full-text assessment.

Study Selection: Eligibility criteria were used to select studies. All authors examined the studies, and consensus was reached through discussion. Results were divided according to the 3 domains

Data Extraction: Authors examined the studies independently, and data from eligible studies were extracted using a modified version of the Cochrane data collection form. Using the modified Downs and Black checklist, 2 authors assessed the quality of the studies independently and were blinded to each other's assessment. Consensus was reached upon discussion and with the involvement of the third author.

Results: Fifteen observational studies were included. Vitamin D in pregnancy was associated with offspring language and motor skills in young children. Associations persisted into adolescence, and results were not dependent on the timing of vitamin D exposure during pregnancy. No supplementation studies were identified.

Conclusions: There is some evidence that low vitamin D status in pregnancy is associated with offspring language and motor development, particularly in young children.

Maternal selenium status and neuropsychological development in Spanish preschool children

Amorós R[1,2], Murcia M[3,4], González L[4], Rebagliato M[3,4], Iñiguez C[3,4,5], Lopez-Espinosa MJ[2,4], Vioque J[3,6], Broberg K[7], Ballester F[3,4], Llop S[3,4]

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Environ Res 2018;166:215–222

Background: The relationship between maternal selenium (Se) status and child neurodevelopment has been scarcely assessed. In a previous study we observed an inverse U-shaped association between maternal Se concentrations and infant neurodevelopment at 12 months of age. In this study, this non-linear association was explored at preschool age. The effect modification by breastfeeding, child's sex and cord blood mercury was also evaluated.

Methods: Study subjects were 490 mother-child pairs from the Spanish Childhood and Environment Project (INMA, 2003–2012). Child neuropsychological development was assessed at around 5 years of age by the McCarthy Scales of Children's Abilities (MSCA). Sociodemographic and dietary characteristics were collected by questionnaire at the first and third trimester of gestation and

at 5 years of age. Se was measured in serum samples by ICP-MS at the end of the first trimester of pregnancy (mean ± standard deviation (SD) = 12.4 ± 0.6 weeks of gestation).
Results: The mean ± SD of maternal serum Se concentrations was 79.9 ± 8.1 μg/L. In multivariate analysis, no linear association was found between Se concentrations and the nine MSCA scales. Generalized additive models indicated inverted U-shaped relationships between Se concentrations and the verbal and global memory scales. When assessing the influence of effect modifiers, breastfeeding played a role: the association between Se and neuropsychological development was inverted U-shaped for the quantitative, general cognitive, working memory, fine motor, global motor and executive function scales only for non-breastfed children.
Conclusion: Low and high maternal Se concentrations seem to be harmful for child neuropsychological development, however further studies should explore this non-linear relationship.

Prenatal selenium status, neonatal cerebellum measures and child neurodevelopment at the age of 18 months

Močenić I[1], Kolić I[2], Nišević JR[2,3], Belančić A[3], Tratnik JS[4], Mazej D[4], Falnoga I[4], Vlašić-Cicvarić I[5], Štimac T[3,6], Špirić Z[3,7], Horvat M[4], Prpić I[2,3]

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Environ Res 2019;176:108529

Objectives: The aim of this study was to evaluate the association of maternal blood selenium (Se) levels and cord blood Se levels with neonatal cerebellum measures and child neurodevelopment at the age of 18 months. Moreover, to investigate whether the neonatal cerebellum measures could be used as a potential biomarker for selenium homeostasis during pregnancy.
Study Group and Methods: The study population consisted of 205 mother-child pairs from Croatian Mother and Child Cohort. Maternal blood and cord blood were obtained at delivery and selenium level was analyzed by Inductively Coupled Plasma Mass Spectrometry. Cranial ultrasonography examination was performed on 49 newborns – cerebellum length and width have been measured. Neurodevelopmental assessment of cognitive, language and motor skills were conducted on 154 children, using The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), at the age of 18 months.
Results: The mean levels of selenium in maternal blood and cord blood were 92.6 ng/g and 97.0 ng/g, respectively. Maternal blood selenium levels were moderately and negatively correlated ($r = –0.372$; $p = 0.008$) with cerebellum length, while cord blood selenium levels were positively correlated with cerebellum width ($r = 0.613$; $p = 0.007$) among female children group. Maternal blood selenium levels were weakly and positively correlated ($r = 0.176$; $p = 0.029$) with child's cognitive abilities.
Conclusions: To the best of our knowledge, our study is the first one investigating the association between neonatal brain measures and selenium levels in mother-child pairs. Our results indicate that prenatal selenium intake correlated with cerebellum length and width measured by cranial ultrasonography. Hence, cerebellum may be used as a potential biomarker and a target "organ" for early detection of possible adverse effects of prenatal status to various micronutrients.

Maternal copper status and neuropsychological development in infants and preschool children

Amorós R[1], Murcia M[2,3], González L[2,4], Soler-Blasco R[2], Rebagliato M[2,4], Iñiguez C[2,3,5], Carrasco P[2,4], Vioque J[3,6], Broberg K[7], Levi M[7], Lopez-Espinosa MJ[2,3], Ballester F[2,3,8], Llop S[2,3]

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Int J Hyg Environ Health 2019;222:503–512

Introduction: Copper (Cu) is an essential element involved in biological processes; however, excessive Cu could be harmful because of its reactive nature. Very few studies have evaluated its potential neurotoxic effects. We aimed to evaluate the association between maternal Cu levels and children's neuropsychological development.

Methods: Study subjects were mother-child pairs from the Spanish INMA (i.e. Childhood and Environment) Project. Cu was measured by inductively coupled plasma mass spectrometry in serum samples taken at the first trimester of pregnancy (2003–2005). Neuropsychological development was assessed using the Bayley Scales of Infant Development (BSID) at 12 months (n = 651) and the McCarthy Scales of Children's Abilities (MSCA) at 5 years of age (n = 490). Covariates were obtained by questionnaires during pregnancy and childhood. Multivariate linear and non-linear models were built in order to study the association between maternal Cu and child neuropsychological development.

Results: The mean ± standard deviation of maternal Cu concentrations was 1,606 ± 272 µg/L. In the multivariate analysis, a negative linear association was found between maternal Cu concentrations and both the BSID mental scale (beta = –0.051; 95% confidence intervals [CI]: –0.102, –0.001) and the MSCA verbal scale (beta = –0.044; 95% CI: –0.094, 0.006). Boys obtained poorer scores than girls, with increasing Cu at 12 months (interaction p value = 0.040 for the mental scale and 0.074 for the psychomotor scale). This effect modification disappeared at 5 years of age. The association between Cu and the MSCA scores (verbal, perceptive performance, global memory and motor, general cognitive, and executive function scales) was negative for those children with lowest maternal iron concentrations (<938 µg/L).

Conclusion: The Cu concentrations observed in our study were within the reference range established for healthy pregnant women in previous studies. The results of this study contribute to the body of scientific knowledge with important information on the possible neurotoxic capability of Cu during pregnancy.

Comments We have selected 10 studies on hundreds of mother–child pairs focusing on the levels of specific micronutrients in pregnancy (from the first trimester onward) and neurodevelopmental outcomes at short, medium, and longer term. Most studies are observational, with a few systematic reviews, and just one RCT as protocol. The nutrients involved are mostly expected, that is, folate, iodine, LC-PUFA (inclusive of the RCT protocol from a developing country, India), selenium (2 studies per each element, respectively), and 2 reports concerning vitamin D and copper, respectively. We hereby describe the main findings per micronutrient.

Folate: Data suggest a positive link between sufficient maternal folate status and offspring cognitive function, but there is still insufficient support from human interventional studies to draw harsh conclusions. The effects of folate intakes higher than recommended remain to be clarified. The neuroprotective role of folate is furthermore suggested by the observation that maternal folate may modify the negative effects of air pollution at 4–6 years of age.
Iodine: Fetal brain development is vulnerable to mild-to-moderate iodine deficiency, particularly in the first trimester, and an insufficient iodine intake in pregnancy is associated with lower infant language skills up to 18 months. Any RCT with iodine supplementation should start not later than the first trimester.
LC-PUFA: a neuroprotective effect, similar to that described for folate, has been shown at 42–60 months for dietary intake of DHA and ARA during pregnancy and child neurodevelopment impairment associated with prenatal maternal DDE levels. An interesting RCT study protocol of DHA supplementation from ≤20 weeks gestation through 6 months postpartum with 400 mg/day algal-derived DHA or placebo comes from India, and the results will be very valuable to look at any effect in a transition country.
Vitamin D: A systematic review shows that low vitamin D levels, as early as the second trimester of pregnancy, may be related to adverse effects on language skills and motor development between 1 and 5 years of age. Associations may persist up to adolescence. We lack data from large, well-conducted RCT trials on the effects of vitamin D in pregnancy on offspring neurodevelopment and (even from observational studies) on associations with above-normal vitamin D levels in pregnancy.
Selenium: Lowest and highest maternal serum levels at the end of the first trimester of pregnancy have been associated with a less favorable neuropsychological development at 5 years but only in non-breastfed children. An association has been described between selenium in maternal blood and cord and neonatal cerebellum length and width at 1–3 days (cranial ultrasonography).
Copper: Higher maternal levels at 3 months pregnancy have been associated with lower scores at developmental scales at 1 and 5 years, thus suggesting a potential neurotoxicity of copper, possibly connected with its chemically reactive nature.
On the whole, this huge set of data shows an increasing interest in the field of the effects of micronutrients intake and/or status in pregnancy and neurodevelopmental aspects in the offspring, waiting for more results from large randomized trials, particularly from developing and transition countries.

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Turck D, Shamir R, Koletzko B, Phillip M (eds): Nutrition and Growth: Yearbook 2020.
World Rev Nutr Diet. Basel, Karger, 2020, vol 120, pp 114–133 (DOI: 10.1159/000503644)

Nutrition and Growth in Chronic Disease

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Introduction

Chronic disease during infancy childhood and adolescence can deeply affect the child's nutritional state, alter the full potential of growth, and modify body composition. Moreover, nutritional status can influence the disease course, complications, and outcomes. Growth impairment is a common feature of chronic diseases in children, resulting from numerous contributing factors that include chronic inflammation, poor or inadequate energy and nutrient intake, reduced physical activity, and high energy needs.

In this chapter, some leading articles published on peer-review journals over the last year are reviewed. The selected 10 articles represent various aspects of nutrition and growth in 5 major chronic diseases of childhood: inflammatory bowel disease, celiac disease, juvenile idiopathic arthritis, cystic fibrosis, and cerebral palsy. These articles were selected for their enhancement and amplification of current knowledge regarding aspects of pathophysiology, advanced nutritional evaluation, treatment strategies, and contemporary challenges regarding nutrition and growth in pediatric chronic diseases.

Key articles reviewed for this chapter

Inflammatory Bowel Disease

The reduction of faecal calprotectin during exclusive enteral nutrition is lost rapidly after food re-introduction

Logan M, Clark CM, Ijaz UZ, Gervais L, Duncan H, Garrick V, Curtis L, Buchanan E, Cardigan T, Armstrong L, Delahunty C, Flynn DM, Barclay AR, Tayler R, McDonald E, Milling S, Hansen RK, Gerasimidis K, Russell RK

Aliment Pharmacol Ther 2019;50:664–674

Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial

Levine A, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, Cohen S, Peleg S, Shamaly H, On A, Millman P, Abramas L, Ziv-Baran T, Grant S, Abitbol G, Dunn KA, Bielawski JP, Van Limbergen J

Gastroenterology 2019;157:440–450

Treatment of active Crohn's disease with an ordinary food-based diet that replicates exclusive enteral nutrition

Svolos V, Hansen R, Nichols B, Quince C, Ijaz UZ, Papadopoulou RT, Edwards CA, Watson D, Alghamdi A, Brejnrod A, Ansalone C, Duncan H, Gervais L, Tayler R, Salmond J, Bolognini D, Klopfleisch R, Gaya DR, Milling S, Russell RK, Gerasimidis K

Gastroenterology 2019;156:1354–1367

Celiac Disease

The relationship between body composition and a gluten free diet in children with celiac disease

Więch P, Chmiel Z, Bazaliński D, Sałacińska I, Bartosiewicz A, Mazur A, Korczowski B, Binkowska-Bury M, Dąbrowski M

Nutrients 2018;10:1817

Celiac Disease and Bone Health in Children and Adolescents: A Systematic Review and Meta-Analysis

Fedewa MV, Bentley JL, Higgins S, Kindler JM, Esco MR, MacDonald HV

J Clin Densitom 2019. pii: S1094-6950(19)30009-5. Doi 10.1016/j.jocd.2019.02.003 [Article in Press]

Juvenile Idiopathic Arthritis

Growth patterns in early juvenile idiopathic arthritis: Results from the Childhood Arthritis Prospective Study (CAPS)

McErlane F, Carrasco R, Kearsley-Fleet L, Baildam EM, Wedderburn LR, Foster HE, Ioannou Y, Chieng SEA, Davidson JE, Thomson W, Hyrich KL

Semin Arthritis Rheum 2018;48:53–60

Body composition and phase angle as an indicator of nutritional status in children with juvenile idiopathic arthritis

Więch P, Sałacińska I, Bazaliński D, Dąbrowski M

Pediatr Rheumatol 2018;16:82

Cystic Fibrosis

Early life growth patterns persist for 12 years and impact pulmonary outcomes in cystic fibrosis

Sanders DB, Zhang Z, Farrell PM, Lai HJ, on behalf of the Wisconsin CF Neonatal Screening Group

J Cyst Fibros 2018;17:528–535

Nutritional status and pulmonary outcome in children and young people with cystic fibrosis

Papalexopoulou N, Dassios TG, Lunt A, Bartlett F, Perrin F, Bossley CJ, Wyatt HA, Greenough A

Respir Med 2018;142:60–65

Cerebral Palsy

Food intake, nutritional status and gastrointestinal symptoms in children with cerebral palsy

Caramico-Favero DCO, Guedes ZCF, Morais MB

Arq Gastroenterol 2018;55:352–357

Inflammatory Bowel Disease

The reduction of faecal calprotectin during exclusive enteral nutrition is lost rapidly after food re-introduction

Logan M[1,2], Clark CM[2], Ijaz UZ[1], Gervais L[3], Duncan H[3], Garrick V[3], Curtis L[3], Buchanan E[3], Cardigan T[3], Armstrong L[4], Delahunty C[5], Flynn DM[3], Barclay AR[3], Tayler R[3], McDonald E[6], Milling S[6], Hansen RK[3], Gerasimidis K[2], Russell RK[3]

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Background: Faecal calprotectin decreases during exclusive enteral nutrition in children with active Crohn's disease. It is unknown how faecal calprotectin changes during food re-introduction and the influence of maintenance enteral nutrition.

Aims: To study changes to faecal calprotectin during exclusive enteral nutrition and at food reintroduction, and explore associations with maintenance enteral nutrition.

Methods: Children with Crohn's disease were followed during exclusive enteral nutrition and during food-reintroduction. Faecal calprotectin was measured before, at 33 and 54 days of exclusive enteral nutrition, and at 17, 52 and 72 days after food-reintroduction. Maintenance enteral nutrition use was recorded with estimated weight food diaries. Data are presented with medians and Q1:Q3.
Results: Sixty-six patients started exclusive enteral nutrition and 41 (62%) achieved clinical remission (weighted paediatric Crohn's disease activity index <12.5). Baseline faecal calprotectin (mg/kg) decreased after 4 and 8 weeks of exclusive enteral nutrition (Start: 1,433 [Q1: 946, Q3: 1,820] vs. 33 days: 844 [314, 1,438] vs. 54 days: 453 [165, 1,100]; $p < 0.001$). Within 17 days of food reintroduction, faecal calprotectin increased to 953 [Q1: 519, Q3: 1611] and by 52 days to 1,094 [660, 1,625] (both $p < 0.02$). Fifteen of 41 (37%) children in remission used maintenance enteral nutrition (333 kcal or 18% of energy intake). At 17 days of food reintroduction, faecal calprotectin was lower in maintenance enteral nutrition users than non-users (651 [Q1: 271, Q3: 1,781] vs. 1,238 [749, 2,102], $p = 0.049$) and correlated inversely with maintenance enteral nutrition volume (rho –0.573, $p = 0.041$), kcals (rho –0.584, $p = 0.036$) and % energy intake (rho –0.649, $p = 0.016$). Maintenance enteral nutrition use was not associated with longer periods of remission ($p = 0.7$). Faecal calprotectin at the end of exclusive enteral nutrition did not predict length of remission.
Conclusions: The effect of exclusive enteral nutrition on faecal calprotectin is diminished early during food reintroduction. Maintenance enteral nutrition at ~18% of energy intake is associated with a lower faecal calprotectin at the early phase of food reintroduction but is ineffective in maintaining longer term remission.

Comments Comments on this manuscript as well as the following paper (Levine et al.) are incorporated into the comments of the manuscript of Svolos et al.

Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial

Levine A[1], Wine E[2], Assa A[3,4], Sigall Boneh R[1], Shaoul R[5], Kori M[6], Cohen S[7], Peleg S[8], Shamaly H[9], On A[10], Millman P[11], Abramas L[1], Ziv-Baran T[4], Grant S[12,13], Abitbol G[14], Dunn KA[15], Bielawski JP[15], Van Limbergen J[13,16,17]

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Background and Aims: Exclusive enteral nutrition (EEN) is recommended for children with mild to moderate Crohn's disease (CD), but implementation is challenging. We compared EEN with the CD

exclusion diet (CDED), a whole-food diet coupled with partial enteral nutrition (PEN), designed to reduce exposure to dietary components that have adverse effects on the microbiome and intestinal barrier. ***Methods:*** We performed a 12-week prospective trial of children with mild to moderate CD. The children were randomly assigned to a group that received CDED plus 50% of calories from formula (Modulen, Nestlé) for 6 weeks (stage 1) followed by CDED with 25% PEN from weeks 7 to 12 (stage 2) ($n = 40$, group 1) or a group that received EEN for 6 weeks followed by a free diet with 25% PEN from weeks 7 to 12 ($n = 38$, group 2). Patients were evaluated at baseline and weeks 3, 6, and 12 and laboratory tests were performed; 16S ribosomal RNA gene (V4V5) sequencing was performed on stool samples. The primary endpoint was dietary tolerance. Secondary endpoints were intention to treat (ITT) remission at week 6 (pediatric CD activity index score below 10) and corticosteroid-free ITT sustained remission at week 12. ***Results:*** Four patients withdrew from the study because of intolerance by 48 h, 74 patients (mean age 14.2 ± 2.7 years) were included for remission analysis. The combination of CDED and PEN was tolerated in 39 children (97.5%), whereas EEN was tolerated by 28 children (73.6%) ($p = 0.002$; OR for tolerance of CDED and PEN, 13.92; 95% CI 1.68–115.14). At week 6, 30 (75%) of 40 children given CDED plus PEN were in corticosteroid-free remission versus 20 (59%) of 34 children given EEN ($p = 0.38$). At week 12, 28 (75.6%) of 37 children given CDED plus PEN were in corticosteroid-free remission compared with 14 (45.1%) of 31 children given EEN and then PEN ($p = 0.01$; OR for remission in children given CDED and PEN, 3.77; CI 1.34–10.59). In children given CDED plus PEN, corticosteroid-free remission was associated with sustained reductions in inflammation (based on serum level of C-reactive protein and fecal level of calprotectin) and fecal Proteobacteria. ***Conclusion:*** CDED plus PEN was better tolerated than EEN in children with mild to moderate CD. Both diets were effective in inducing remission by week 6. The combination CDED plus PEN induced sustained remission in a significantly higher proportion of patients than EEN, and produced changes in the fecal microbiome associated with remission. These data support use of CDED plus PEN to induce remission in children with CD.

Treatment of active Crohn's disease with an ordinary food-based diet that replicates exclusive enteral nutrition

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Background and Aims: Exclusive enteral nutrition (EEN) is the only established dietary treatment for Crohn's disease (CD), but its acceptability is limited. There is a need for novel dietary treatments for CD.

Methods: We evaluated the effects of an individualized food-based diet (CD-TREAT), with similar composition to EEN, on the gut microbiome, inflammation, and clinical response in a rat model, healthy adults, and children with relapsing CD. Twenty-five healthy adults randomly received EEN or CD-TREAT for 7 days, followed by a 14-day washout period, followed by the alternate diet. Fecal microbiome and metabolome were assessed before and after each diet. HLA-B7 and HLA-B27 transgenic rats with gut inflammation received EEN, CD-TREAT, or standard chow for 4 weeks. Fecal, luminal, and tissue microbiome, fecal metabolites, and gut inflammation were assessed. Five children with active CD activity received CD-TREAT and their clinical activity and calprotectin were evaluated after 8 weeks of treatment.
Results: For healthy adults, CD-TREAT was easier to comply with and more acceptable than EEN. CD-TREAT induced similar effects to EEN (EEN vs. CD-TREAT) on fecal microbiome composition, metabolome, mean total sulfide (increase 133.0 ± 80.5 vs. 54.3 ± 47.0 nmol/g), pH (increase 1.3 ± 0.5 vs. 0.9 ± 0.6), and the short-chain fatty acids (μmol/g) acetate (decrease 27.4 ± 22.6 vs. 21.6 ± 20.4), propionate (decrease 5.7 ± 7.8 vs. 5.2 ± 7.9), and butyrate (decrease 7.0 ± 7.4 vs. 10.2 ± 8.5). In the rat model, CD-TREAT and EEN produced similar changes in bacterial load (decrease 0.3 ± 0.3 $\log_{10}$ 16S rRNA gene copies per gram), short-chain fatty acids, microbiome, and ileitis severity (mean histopathology score decreases of 1.25 for EEN [$p = 0.015$] and 1.0 for CD-TREAT [$p = 0.044$] vs. chow). In children receiving CD-TREAT, 4 (80%) had a clinical response and 3 (60%) entered remission, with significant concurrent decreases in fecal calprotectin (mean decrease 918 ± 555 mg/kg; $p = 0.002$).
Conclusion: CD-TREAT replicates EEN changes in the microbiome, decreases gut inflammation, is well tolerated, and is potentially effective in patients with active CD.

Comments

The pathogenesis of Crohn's disease (CD) appears to involve alteration of the microbiome as well as a breakdown in barrier function with defective bacterial clearance. Over the last decade, there is a growing body of evidence suggesting that dietary factors may play a role in the generation of inflammation by modulating the microbiome, tight junctions, and mucous layer [1]. Treating active CD by modifying the patients' diet has long been one of the most desirable therapeutic strategies, but until 2019 there were no randomized controlled studies demonstrating the efficacy of dietary treatment in the management of CD.

Dietary therapy by means of exclusive enteral nutrition (EEN), which is a liquid-only formula diet consumed for 6–8 weeks, is a highly effective treatment for achieving clinical remission and is recommended as the first-line treatment for active luminal disease in children [2].

Isocaloric partial enteral nutrition (PEN) with exposure to food was not effective enough in inducing or maintaining remission in various previous studies [3, 4], suggesting that complete exclusion of food plays an important role in the success of EEN. The study of Logan et al. cited in this chapter reinforces the short-term effect of EEN on bowel inflammation as suggested by the rise in fecal calprotectin after food reintroduction. Notably, this study showed that the increase in fecal calprotectin, following EEN, occurs even more rapidly than previously recognized [5], with a significant increase within just 17 days of food reintroduction. The median daily rate of fecal calprotectin rise was evaluated as 20 mg/kg/day. PEN, which was practiced by 41% of patients after the period of EEN, was associated with a significantly lower fecal calprotectin levels compared to patients not using PEN. Despite this early positive effect, there was no significant difference in relapse rate at either 6 or 12 months post-EEN between patients with or without PEN supplementation. However, while previous studies aimed for PEN providing about 50% of daily amount of calories, the amount

of PEN consumed by patients in this cohort was relatively low, with a median of 18% of their total energy intake.

Nonetheless, the early rise in fecal calprotectin observed in this study after cessation of EEN highlights the potent role of early dietary inflammatory triggers within the early food reintroduction phase. This finding further supports the need for discovering other adjuvant dietary treatments with better tolerance and adherence profiles for long-term dietary management of CD.

The CD exclusion diet (CDED) is a whole-food diet coupled with PEN, designed to reduce exposure to dietary components, hypothesized to negatively affect the microbiome, intestinal barrier, and intestinal immunity, and was shown to be effective in remission induction in a non-randomized study in children and adults who failed biologic therapy [6]. The multinational randomized controlled trial of Levine et al. [1] compared both the tolerability and the efficacy of CDED with those of EEN in pediatric patients with active mild-to-moderate CD. The remarkable results of this study showed not only better tolerance for CDED coupled with PEN but also a superior sustained remission and reduction in inflammation by week 12, compared to the standard of care therapy with EEN. Fecal calprotectin was evaluated in this study as well, on top of the clinical markers. Both groups demonstrated similar drops in fecal calprotectin during the induction 6-week period with no significant differences, whereas in the CDED + PEN group, the calprotectin continued to decline between week 6 and week 12.

The major importance of this study is it being the first randomized controlled trial to demonstrate the non-inferiority of the specific whole-food diet coupled with PEN in achieving remission, compared to EEN. Second, the differences between the groups after week 6, during the period of food reintroduction in the EEN group, showed superiority of CDED + PEN in obtaining sustained remission and continued drop of calprotectin by week 12. The microbiome analysis revealed a different pattern between the groups: while in the CDED + PEN group the microbiome continued to change between week 6 and 12, the microbiome of the EEN group generally rebounded to pretreatment levels at week 12. This could provide a plausible pathophysiologic explanation to the results, supporting the theory that exclusion of dietary components by EEN or CDED reduces microbiota species that are associated with CD [7], with a rebound of the same proinflammatory microbiota patterns upon re-exposure to regular diet.

Despite its remarkable results, the study suffers from some major limitations: (1) From week 6, the CDED group received the CDED diet (active treatment) with very partial PEN (25%), while the control group received regular diet with very partial (25%) PEN leaving them with a disadvantage in treatment. (2) The lack of endoscopic evaluation, not allowing the determination of mucosal healing in any group, especially considering the fact that calprotectin levels remained elevated in many patients in this study. (3) The 40% remission at week 12 in the EEN group is significantly lower than the remission rate observed in EEN studies. (4) PEN is inferior to EEN but does have an effect on inducing remission. Thus, the contributing effect of the supplementation of PEN on top of the CDED itself is yet to be determined.

The CD treatment-with-eating diet (CD-TREAT) described by Svolos et al. is another development of ordinary food diet, which is based on the composition of EEN. As the authors state, this diet recreates EEN by the exclusion of certain dietary components (egg, gluten, lactose, and alcohol) and matching of others (macronutrients, vitamins, minerals, and fiber) as closely as possible using ordinary food. The diet was tested in mice, healthy adult volunteers, and 5 children with active CD. The main findings included similar effects to those of EEN on the gut microbiome and metabolome of the healthy participants; reduced ileitis in the rat model of disease; and clinical remission with a decrease in fecal

calprotectin in 3 of 5 children with active CD after 8 weeks of diet. The establishment of efficacy of CD-TREAT in patients with active CD requires replication in large clinical trials. Overall, a wide variability and sometimes contradiction exists across diets that are being tested for CD over the last few years. Paradoxically, even EEN that is the nutritional intervention with the strongest evidence for the induction of remission, contains emulsifiers, is commonly based on milk formula, and has a low amount of fibers – all of which are presumed to promote dysbiosis and proinflammatory state [8]. This fascinating era of nutritional research in inflammatory bowel diseases holds a promise for better and safer treatment strategies in the future together with better understanding of the disease pathophysiology and environmental interactions.

Celiac Disease

The Relationship between Body Composition and a Gluten Free Diet in Children with Celiac Disease

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Abstract: The primary and proven therapy, in cases of celiac disease (CD), is a rigorous gluten-free diet (GFD). However, there are reports of its negative effects in the form of nutritional deficiencies, obesity, and adverse changes in body composition. The study aimed to assess the impact of a GFD on the body composition of children with CD. In a case-controlled study (n = 41; mean age 10.81 y; SD = 3.96) children with CD, in various stages of treatment, underwent medical assessment. The control group consisted of healthy children and adolescents, strictly matched for gender and age in a 1:1 case-control manner. More than half of the examined children (n = 26) followed a GFD. CD children had significantly higher mean values of the fat free mass (FFM% = 80.68 vs. 76.66, p = 0.015), and total body water (TBW% = 65.22 vs. 60.47, p = 0.012), and lower mean values of the fat mass (FM% = 19.32 vs. 23.34, p = 0.015). Children who were on a GFD presented slightly higher, but not statistically significant, mean values of FM and FFM, than children who did not follow dietary recommendations (FM [kg] = 7.48 vs. 5.24, p = 0.064; FM% = 20.81 vs. 16.73, p = 0.087; FFM [kg] = 28.19 vs. 22.62, p = 0.110). After minimum 1 year of a GFD, CD children showed significantly higher values of FFM [kg] (p = 0.001), muscle mass (MM) [kg] (p < 0.001), TBW [L] (p < 0.001) and body cell mass (BCM) [kg] (p < 0.001). Furthermore, CD children who were on a GFD presented a significantly higher increase in weight (p = 0.034) and body mass index (BMI; p = 0.021). The children adhering to a GFD demonstrate a tendency towards higher indices of selected body composition components.

Comments Celiac disease (CeD) is an immune-mediated enteropathy, affecting genetically susceptible individuals upon dietary exposure to gluten peptides. The immune response

causes inflammatory damage to the intestinal mucosa, further evolving into villous atrophy and reduced absorptive and digestive capacity. Classical presentation of CeD can include symptoms of malabsorption, weight loss, failure to thrive, and delayed growth. The impact of CeD on different components of body composition had been assessed by several studies in the past, with conflicting results ranging between similar body composition compared to healthy controls [9, 10] and reduced fat mass and lean body mass compared to healthy controls [11, 12]. The main components reported to recover under gluten free diet (GFD) are the fat mass and body mass index (BMI) [13, 14].

There is a controversy regarding the long-term impact of GFD on nutritional status as well as body composition, with a concern regarding increased adiposity, high fat content of the diet, and nutritional imbalance in uncontrolled GFD [10, 15–17].

This study evaluated body composition of children with CeD, compared to case-controlled healthy children. Body composition was assessed using bioelectric impedance. Although relatively small scale, the findings of this study are interesting. Children with CeD had different patterns of body composition compared to healthy controls, mainly lower fat mass and fat mass percentage, on the expense of higher fat-free mass percentage and total body water percentage. These trends were further emphasized in the comparison of GFD noncompliant to compliant patients. Patients with CeD who were not compliant with GFD had lower fat mass and higher fat free mass compared to compliant patients, although these differences did not reach statistical significance (possibly due to the small sample size). These findings suggest that children with CeD, and especially those who are not treated with appropriate GFD, have reduced body energy reserves reflected by their low fat mass.

A subset of patients in this study were followed with subsequent measurements after a mean of 17 months. Of those, the small group of patients who did not adhere to GFD showed a decrease in their BMI compared to an increase in the group of patients that adhered to GFD, further demonstrating the negative impact of CeD on the nutritional status and body composition of these children.

During a mean of 17-month follow-up in this study, patients with CeD demonstrated an expected increase in weight, height, absolute fat mass, muscle mass, and fat-free mass. There were no significant changes in any of the relative values, expressed as percentage of body composition, during the follow-up. This important finding suggests that components of body composition can remain stable under the maintenance of GFD, although larger long-term studies, including follow-up into adulthood, are needed to better assess the impact of GFD on body composition overtime.

Celiac disease and bone health in children and adolescents: a systematic review and meta-analysis

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Context: Celiac disease is characterized by deficits in bone mineral accrual and longitudinal growth.
Objective: The purpose of this study was to determine the differences in bone health and stature among children and adolescents with celiac disease versus healthy controls.

Data Sources: Articles published before February 27, 2018 were located using searches of the Physical Education Index ($n = 186$), PubMed ($n = 180$), Scopus ($n = 3$), SPORTDiscus ($n = 3$), and Web of Science ($n = 4$).
Study Selection: Bone mineral content (BMC) and areal bone mineral density (aBMD) were assessed via dual-energy X-ray absorptiometry, and height was measured using a stadiometer.
Data Extraction: Effect sizes (ES) were calculated as follows: the mean difference of the celiac disease group and healthy control group, divided by the pooled standard deviation. The inverse variance weight was used to calculate the overall mean ES. Random-effects models were used to aggregate a mean ES, 95% CIs and to identify potential moderators.
Results: The results of 30 effects gathered from 12 studies published between 1996 and 2017 indicated BMC (ES –0.54, 95% CI –0.69 to –0.40; $p < 0.0001$) and aBMD (ES –0.72, 95% CI –0.96 to –0.47; $p < 0.0001$) were lower in youth with celiac disease.
Limitations: These results were limited to only cross-sectional and baseline data from longitudinal studies reporting BMC and BMD, however did not assess changes in bone health over time.
Conclusion: Children and adolescents with celiac disease have suboptimal bone health and shorter stature.

Comments

Bone health is known to be negatively affected by CeD in various ways. Intestinal malabsorption of micronutrients is a major determinant of poor bone mass accruement, with the reduction of calcium and vitamin D absorption causing an elevation in parathyroid hormone and further bone loss [18]. Other nonintestinal factors associated with bone injury are mainly the result of the increased production of proinflammatory cytokines causing bone turnover and remodeling imbalance [19]. The majority of evidence regarding reduced bone mass in CeD is based on adult studies, with estimated prevalence of osteopenia in one-third and osteoporosis in another one-third of the patients [20]. There is also a reported increased risk of fractures [21]. The presence of bone disease and osteopenia in young age is of great importance, given the critical period for bone mass accrual in childhood and adolescence, and the known impact of bone health in childhood tracking into adulthood [22, 23].

In this comprehensive study, Fedewa et al. performed a meta-analysis of published data regarding bone mineral content (BMC) and areal bone mineral density (aBMD) in newly diagnosed children and adolescents with CeD, compared to healthy controls. Twelve studies met their inclusion criteria for analysis. The pulled results from this meta-analysis indicated a significant reduction of BMC and aBMD in children and adolescents with CD compared to healthy controls, with a mean Hedge's effect size of –0.54 and –0.72, respectively ($p < 0.0001$). Notably, the finding of lower bone mass and density in children with CD was found to be stable regardless of the skeletal region assessed in the reported studies. A secondary outcome assessed in this analysis was the effect size of height and body weight that were found to be significantly lower in children with CeD compared to healthy controls (mean effect size for height = –0.79, 95% CI –1.11 to –0.47; mean effect size for body weight = –0.71, 95% CI –1.00 to 0.42; $p < 0.0001$). The close link between bone density and height in children [24] further emphasize the importance of acknowledging poor linear growth in pediatric patients with CeD.

The main limitation of this study is its cross-sectional nature and, therefore, the lack of data on long-term bone status and the effect of GFD on bone health. Nevertheless, the importance of this study is the incorporation and pooled analysis of data regarding bone health in children with CeD. These findings reinforce the importance of the negative ef-

fects of CeD on both growth and bone mass in young age. More high-quality, controlled, longitudinal studies are further needed to assess long-term changes in bone health in patients with CeD overtime.

Juvenile Idiopathic Arthritis

Growth patterns in early juvenile idiopathic arthritis: Results from the Childhood Arthritis Prospective Study (CAPS)

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Objectives: To investigate early vertical growth patterns and factors associated with poor growth in a modern inception cohort of UK children with juvenile idiopathic arthritis (JIA) using data from the Childhood Arthritis Prospective Study (CAPS).

Methods: A study period of 3 years was chosen. Children included in this analysis had a physician diagnosis of JIA and had height measurements available at both baseline and at 3 years of follow-up. Height is presented as z-scores calculated using World Health Organisation growth standards for age and gender. Growth over the 3-year period was assessed using change in z-score and height velocity. Univariable and multivariable linear regressions were used to identify factors associated with height z-score at baseline and change of height z-score at 3 years.

Results: 568 patients were included; 65% female, median baseline age 7.4 years (interquartile range [IQR] 3.6 to 11.2), median symptom duration at presentation 5.5 months (IQR 3.1 to 11.6). Height z-score decreased significantly from baseline to 3 years ($p \leq 0.0001$); baseline median height z-score was –0.02 (IQR –0.71 to 0.61), decreasing to –0.47 (IQR –1.12 to 0.24) at 3 years. Growth restriction, defined as change of height z-score ≤–0.5, was observed in 39% of patients. At 3 years, higher baseline height z-score was the strongest predictor for a negative change in height z-score (–0.3 per unit of baseline height z-score [95% CI –0.36 to –0.24], $p < 0.0001$).

Conclusions: Although overall height at 3 years after initial presentation to rheumatology is within the population norm, as a cohort, children with JIA experience a reduction of growth in height over

the first 3 years of disease. Late presentation to paediatric rheumatology services is associated with lower height at presentation. However, patients with the lowest height z scores at presentation were also the most likely to see an improvement at 3 years. The impact of JIA on growth patterns is important to children and families and this study provides useful new data to support informed clinical care.

Comments Juvenile idiopathic arthritis (JIA) is one of the most common chronic inflammatory connective tissue diseases in childhood, with significant morbidity and the development of disability over the disease course. Similar to any systemic chronic inflammatory illness, growth impairment is an important complication of JIA, affecting up to a third of JIA patients in early adulthood, dependent on the disease subtype [25]. The reasons for poor growth in JIA are multifactorial and may relate to the degree of systemic inflammation, poor appetite and suboptimal nutrition, and the use of corticosteroids.

In this current longitudinal multicenter study from UK, the authors investigated early growth patterns over the first 3 years of disease presentation in children. In this large cohort, nearly half of the patients were classified as oligoarthritis. Forty-four percent of the patients received systemic corticosteroids, and 21% received biologic therapy. The most notable finding in this study is the significant decrease in height z scores across all JIA subtypes over the first few years of disease, although most prominent in systemic JIA and psoriatic arthritis. BMI z-score did not change significantly at 3 years. Total time on oral or intravenous steroids during the 3-year period was significantly associated with decrease in height *z*-score. This association was observed even after adjusting for disease activity, strengthening the independent negative effects of corticosteroids on linear growth in children with JIA, going far beyond the simple association between use of steroid treatment and disease severity [26]. This study emphasizes that even in the era of biologic treatments, corticosteroid use is still common in JIA and that growth failure continues to be a major challenge in the treatment of these children. The identification of growth restriction developing early in the disease course merits the discussion regarding early aggressive treatment regiments to prevent irreversible growth delay with and compromised final height.

Body composition and phase angle as an indicator of nutritional status in children with juvenile idiopathic arthritis

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Background: Juvenile idiopathic arthritis (JIA) is the most common chronic, systemic autoimmune connective tissue disease diagnosed in children and adolescents. An important aspect of monitoring of children with JIA is a precise assessment of the nutritional status to identify children and adolescents at risk of malnutrition. The aim of the study was to assess the body composition and phase angle in children diagnosed with JIA in comparison to age and sex matched healthy children since there are scarce reports in paediatric patients.

Methods: A total of 46 children and adolescents aged 4–18 years, with JIA were included in the cross-sectional study. Controls were selected from the group of healthy children and adolescents. Children with diagnosed JIA and healthy children were strictly matched for age and gender. In both groups BIA with phase angle calculation was performed.
Results: Phase angle score was significantly lower in the study group compared to control group (5.45 ± 0.64 vs. 5.85 ± 0.80, $p = 0.010$). Also lower percentage of body cell mass (50.63 ± 3.46 vs. 52.70 ± 4.06, $p = 0.010$) and muscle mass (46.02 ± 6.32 vs. 49.53 ± 6.67, $p = 0.005$) were revealed. In the analysis of subtypes of JIA we found significant differences between children and adolescents with polyarthritis compared to control group, while no significant differences were found between patients with oligoarthritis and control group.
Conclusions: The obtained results indicate a higher risk of malnutrition in children and adolescents with JIA compared to healthy peers, predominantly in patients with polyarthritis.

Comments

As discussed earlier, there is an ongoing concern regarding nutritional status of children with chronic systemic inflammatory illnesses as JIA, with conflicting evidence regarding the disease effects on various aspects of growth and body composition. In this study, Wiech et al. assessed parameters of body composition and phase angle (PhA) in children with JIA, using bioelectrical impedance analysis (BIA). PhA is a derived measure of BIA, calculated from the resistance and reactance obtained by this tool, which has been recognized as a measure of nutritional status. PhA reflects body cell mass and is one of the best indicators of cell membrane function [27]. It is considered as a screening tool for the identification of risk patients with impaired nutritional and functional status [28]. In this current match-controlled study of children and adolescents with JIA, no significance differences were found in anthropometric parameters between study and control groups. Remarkably, the value of the PhA in children with JIA was significantly lower than in healthy controls. Parameters of muscle mass and body cell mass were also significantly lower in the JIA group compared to control. These significant differences between case and control groups were found only for polyarthritis and not oligoarthritis, probably reflecting the difference in systemic inflammatory effects between the disease subtypes (as was shown also in the previous article by McErlane et al.). This current study lacks stratification by pharmacological treatment and disease severity, which could have influenced the results, and in particular the discrepancies between the subgroups. Moreover, the use of BIA in the assessment of segmental components of body composition has its limitation (compared to dual-energy x-ray absorptiometry) and has been shown to underestimate fat mass and overestimate lean mass [29]. In children with chronic disease in particular, the reliability of BIA in the estimation of body composition may be limited [30].

Nonetheless, the significant differences reported in this study between children with JIA and controls indicate the need for close monitoring of nutritional status and body composition in the routine clinical practice of children with JIA. Also, it suggests a role for BIA and PhA in this process.

Early life growth patterns persist for 12 years and impact pulmonary outcomes in cystic fibrosis

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Background: In children with cystic fibrosis (CF), recovery from growth faltering within 2 years of diagnosis (Responders) is associated with better growth and less lung disease at age 6 years. This study examined whether these benefits are sustained through 12 years of age.
Methods: Longitudinal growth from 76 children with CF enrolled in the Wisconsin CF Neonatal Screening Project was examined and categorized into 5 groups: R12, R6, and R2, representing Responders who maintained growth improvement to age 12, 6, and 2 years, respectively, and I6 and N6, representing Non-responders whose growth did and did not improve during ages 2–6 years, respectively. Lung disease was evaluated by % predicted forced expiratory volume in one second (FEV1) and chest radiograph (CXR) scores.
Results: Sixty-two percent were Responders. Within this group, 47% were R12, 28% were R6, and 25% were R2. Among Non-responders, 76% were N6. CF children with meconium ileus (MI) had worse lung function and CXR scores compared to other CF children. Among 53 children with pancreatic insufficiency without MI, R12 had significantly better FEV1 (97–99% predicted) and CXR scores during ages 6–12 years than N6 (89–93% predicted). Both R6 and R2 experienced a decline in FEV1 by ages 10–12 years.
Conclusions: Early growth recovery in CF is critical, as malnutrition during infancy tends to persist and catch-up growth after age 2 years is difficult. The longer adequate growth was maintained after early growth recovery, the better the pulmonary outcomes at age 12 years.

Comments Comments on this manuscript are incorporated into the comments of the following manuscript of Papalexopoulou et al.

Nutritional status and pulmonary outcome in children and young people with cystic fibrosis

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Respir Med 2018;142:60–65

Background: Nutrition is closely related to mortality and pulmonary and respiratory muscle function in cystic fibrosis (CF) patients. We initially validated results from a bioelectrical impedance device against dual energy x-ray absorptiometry (DEXA). We then determined whether fat free mass assessed by a portable impedance device rather than body mass index (BMI) better correlated with pulmonary function, respiratory muscle strength and exercise capacity in CF patients.
Methods: Eighteen young people and adults (median age 19, range 12–39 years) with CF had dual energy X-ray absorptiometry and direct segmental multi-frequency impedance analysis. Body composition, pulmonary function, respiratory muscle function and exercise tolerance using the impedance device were measured in 29 young people with CF with median age 15 (range 12–19) years.
Main Findings: There was a significant correlation between impedance and absorptiometry results ($r^2 = 0.947$). Fat free mass correlated with the forced vital capacity z-score ($r = 0.442$, $p = 0.016$), maximal inspiratory pressure ($r = 0.451$, $p = 0.014$) and exercise tolerance ($r = 0.\ 707$, $p < 0.001$). BMI z-scores did not significantly correlate with pulmonary or respiratory muscle function. Subjects with a fat free mass z-score of ≤2 had a lower forced expiratory volume in 1 s z-score ($p = 0.007$), lower forced vital capacity z-score ($p = 0.001$), higher residual volume z-score ($p = 0.042$), lower maximal inspiratory pressure ($p = 0.039$), more days of intravenous antibiotics per year ($p = 0.016$) and a higher rate of chronic infections ($p = 0.006$).
Principal Conclusions: Fat-free mass measured by impedance correlated better with pulmonary and respiratory muscle function and exercise capacity than BMI.

Comments

Cystic fibrosis (CF) is strongly associated with poor nutritional status, resulting from various factors including nutrient malabsorption, high energy needs, energy losses, and chronic and recurrent inflammatory status. Advances in the acknowledgment of the positive effects of early interventions on nutritional state of these patients, along with the proven association between better nutritional status in early life and better lung function in later years, has led to the development of professional guidelines for nutritional management of patients with CF [31, 32].

Over the past decade, a significant improvement was observed in nutritional outcomes of infants diagnosed by newborn screening. A study from Brazil published last year [33] joins former publications from Europe [34], Australia [35] and the United States [36], reporting better nutritional status in infants diagnosed with CF by newborn screening.

The 2 current studies presented in this chapter represent the continuum challenge of nutritional care in CF beyond the period of infancy and the importance of maintaining adequate growth and nutrition during the life course of patients with the disease.

The publication of Sanders et al. reports a follow-up of their longitudinal responders study. In the original study, infants with CF were defined as "responders" by a recovery from malnutrition and growth faltering as indicated by catch-up weight gain to the level comparable to their birth weight z-score within 2 years of diagnosis [37]. Consecutive anthropometric measurements, as well as pulmonary functions, were further evaluated after 6 and 12 years. The results of this study showed that most of the responders maintained their growth improvement by12 years of age, while only a minority of the nonresponders improved growth by 6 years of age and none of them maintained the improvement by the age of 12 years. These results demonstrate that growth patterns established early in life tend to persist and determine subsequent growth trajectories and that early catch-up growth in infants with CF could be detrimental for later nutritional status. As for the pulmonary status, the responders groups had significantly better lung functions at each time point by 12 years of age, demonstrating the strong association between adequate growth and pulmonary outcomes.

Finally, the study of Papalexopoulou et al. highlights the fact that growth trajectories are not necessarily the most important anthropometric predictors of pulmonary function in patients with CF and rather emphasizes the importance of body composition and fat-free mass. Among 29 adolescents with CF (age range between 12 and 19 years), BMI z-score was not significantly correlated with any pulmonary function, respiratory muscle function, or exercise indices. Alternatively, fat-free mass index demonstrated a good positive correlation with all aforementioned pulmonary outcomes and exercise tolerance. Continuous comprehensive assessment of all aspects of nutritional status, along with body composition and functional parameters, are all important components in the long-term care of patients with CF.

Cerebral Palsy

Food intake, nutritional status and gastrointestinal symptoms in children with cerebral palsy

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Arq Gastroenterol 2018;55:352–357

Background: Cerebral palsy may be associated with comorbidities such as undernutrition, impaired growth and gastrointestinal symptoms. Children with cerebral palsy exhibit eating problems due to the effect on the anatomical and functional structures involved in the eating function resulting in malnutrition.

Objective: The aim of this study was to investigate the association between food intake, nutritional status and gastrointestinal symptoms in children with cerebral palsy.
Methods: Cross-sectional study that included 40 children with cerebral palsy (35 with spastic tetraparetic form and 5 with non-spastic choreoathetoid form of cerebral palsy, all requiring wheelchairs or bedridden) aged from 4 to 10 years. The dietary assessment with the parents was performed using the usual household food intake inquiry. Anthropometric data were collected. Gastrointestinal symptoms associated with deglutition disorders, gastroesophageal reflux and chronic constipation were also recorded.
Results: The median of height-for-age Z-score (–4.05) was lower ($p < 0.05$) than the median of weight-for-age (–3.29) and weight-for-height (–0.94). There was no statistical difference between weight-for-age and weight-for-height Z-scores. Three patients with cerebral palsy (7.5%) exhibited mild anemia, with normal ferritin levels in two. Symptoms of dysphagia, gastroesophageal reflux, and constipation were found in 82.5% ($n = 33$), 40.0% ($n = 16$), and 60.0% ($n = 24$) of the sample, respectively. The patients with symptoms of dysphagia exhibited lower daily energy (1,280.2 ± 454.8 vs. 1,890.3 ± 847.1 kcal, $p = 0.009$), carbohydrate (median: 170.9 g vs. 234.5 g, $p = 0.023$) and fluid intake (483.1 ± 294.9 vs. 992.9 ± 292.2 mL, $p = 0.001$). The patients with symptoms of gastrointestinal reflux exhibited greater daily fluid intake (720.0 ± 362.9 mL) than the patients without symptoms of gastroesophageal reflux (483.7 ± 320.0 mL, $p = 0.042$) and a greater height-for-age deficit (Z-score: –4.9 ± 1.7 vs. 3.7 ± 1.5, $p = 0.033$). The patients with symptoms of constipation exhibited lower daily dietary fiber (9.2 ± 4.3 vs. 12.3 ± 4.3 g, $p = 0.031$) and fluid (456.5 ± 283.1 vs. 741.1 ± 379.2 mL, $p = 0.013$) intake.
Conclusions: Children with cerebral palsy exhibited wide variability in food intake which may partially account for their severe impaired growth and malnutrition. Symptoms of dysphagia, gastroesophageal reflux, and constipation are associated with different food intake patterns. Therefore, nutritional intervention should be tailored considering the gastrointestinal symptoms and nutritional status.

Comments

Cerebral palsy (CP) is a chronic nonprogressive encephalopathy, with a wide variation in disease severity, patterns of motor involvement, and associated impairments [38]. The most prevalent digestive tract disorders associated with CP are dysphagia, gastroesophageal reflux disease, and constipation [39]. Malnutrition and impaired growth are prominent features of children with severe CP, resulting from multifactorial etiology that includes feeding difficulties, increased energy requirement due to spasticity and involuntary movements, and the high frequency of both recurrent infections and respiratory difficulties. There are many causes of feeding difficulties in children with CP, including primarily oropharyngeal incoordination, vomiting, early satiety, and communication defects [40]. The European Society for Pediatric Gastroenterology, Hepatology and Nutrition offers comprehensive guidelines for the management of the gastroenterological and nutritional problems in children with neurological impairment [41].

This current study reports a cross-sectional assessment of both food intake and anthropometric measurements, together with the presence of gastrointestinal symptoms of children with CP. The study population included 40 children with severe CP, all requiring wheelchairs or were bedridden. Anthropometry included patients' weight and estimated height based on tibia length, presented as z scores. Food intake was compared to the reference Recommended Dietary Allowance (RDA). The results showed severe stunting and wasting in this cohort, with height being the most profoundly affected measurement. Overall, the total energy intake was adequate to the estimated energy requirement for the majority of patients, and protein and carbohydrate intake were even above RDA in most patients. The important findings of this

study are the differences in food intake according to gastrointestinal symptoms. Symptoms of dysphagia, gastroesophageal reflux, and constipation were common in this cohort, each characterized by different nutritional pattern. Patients with dysphagia had significantly lower energy intake and lower fluid intake, which could probably be associated with difficulties in swallowing and the need for fluid thickening to prevent aspirations. Intakes of all macronutrient groups were also reduced, reflecting the challenge of feeding this group of severely ill CP patients. Symptoms of gastroesophageal reflux were mainly associated with increased fluid intake, which in our opinion could be related to the common use of nutritional formula as well as enteral feeding that was not assessed in this study. The finding of reduced fiber intake in patients with constipation could be associated with reversed causality, as reduced fiber content in the diet is assumed to be a contributing factor for the development of constipation, although the evidence in children is weak [42].

In spite of the limitations of this descriptive study, not allowing for causation analysis, the results shed light on the unique patterns of food intake and nutritional deficits in patients with severe CP presenting various gastrointestinal challenges. This calls for better awareness and adjustment of nutritional interventions for the specific difficulties experienced by this vulnerable population.

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Early Nutrition and Its Effect on Growth, Body Composition, and Later Obesity

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Introduction

Early nutrition and growth are important factors in the regulation of both early and long-term health, and many papers on this topic are published every year. For this chapter, we have included 16 papers, which we found of special interest published during the period from July 1, 2018, to June 30, 2019. We have divided them into 8 topics, which are shown in the box below.

In recent years, there has been an increasing interest in breast milk composition with many publications from both low- and middle-income countries and high-income countries. Many of these papers focus on growth and obesity and overall show that breast milk composition has a huge role to play. Furthermore, several papers have examined maternal factors determining breast milk composition. Many different components have been examined including macronutrient content, human milk oligosaccharides, hormones, micronutrients, immune factors, fatty acids, and other bioactive compounds. We have therefore included several papers assessing breast milk composition as well as discussing some of the other papers in the light of the interesting findings on breast milk composition.

The growth patterns in early infancy, including changes in body composition, are increasingly being shown to be influenced by feeding practices and to have long-term health effects. In recent years, multiple studies have examined infants experiencing rapid growth in early infancy, and there is convincing evidence that this is associated with an increased risk of overweight, obesity, and metabolic problems later in life. Recent studies are trying to explain further the details of and the mechanisms behind these associations, including the role of complementary feeding.

We have included a selection of what we find are the most interesting papers on the effects of early nutrition from the last year. Together with the chapters, on the same topics in the Yearbooks from 2016, 2017, 2018, and 2019, this gives a summary of what has happened within this field during recent years.

Key articles reviewed for this chapter

Rapid Early Weight Gain

Infant formula feeding practices associated with rapid weight gain: a systematic review

Appleton J, Russell CG, Laws R, Fowler C, Campbell K, Denny-Wilson E

Matern Child Nutr 2018;14:e12602

Infant feeding and weight gain: separating breast milk from breastfeeding and formula from food

Azad MB, Vehling L, Chan D, Klopp A, Nickel NC, McGavock JM, Becker AB, Mandhane PJ, Turvey SE, Moraes TJ, Taylor MS, Lefebvre DL, Sears MR, Subbarao P, on behalf of the CHILD Study Investigators

Pediatrics 2018;142:e20181092

Excessive weight gain followed by catch-down in exclusively breastfed infants: an exploratory study

Larsson MW, Lind MV, Larnkjær A, Due AP, Blom IC, Wells J, Lai CT, Mølgaard C, Geddes DT, Michaelsen KF

Nutrients 2018;10:1290

Breast Milk Composition and Body Composition

Carbohydrates in human milk and body composition of term infants during the first 12 months of lactation

Gridneva Z, Rea A, Tie WJ, Lai CT, Kugananthan S, Ward LC Murray K, Hartmann PE, Geddes DT

Nutrients 2019;11:1472

Bioactive components in human milk are differentially associated with rates of lean and fat mass deposition in infants of mothers with normal vs. elevated BMI

Young BE, Levek C, Reynolds RM, Rudolph MC, MacLean P, Hernandez TL, Friedman JE, Krebs NF

Pediatr Obes 2018;13:598–606

Human milk short-chain fatty acid composition is associated with adiposity outcomes in infants

Prentice PM, Schoemaker MH, Vervoort J, Hettinga K, Lambers TT, van Tol EAF, Acerini CL, Olga L, Petry CJ, Hughes IA, Koulman A, Ong KK, Dunger DB

J Nutr 2019;149:716–722

Duration of Breastfeeding and Growth

Duration of breastfeeding and early growth: a systematic review of current evidence

Patro-Gołąb B, Zalewski BM, Polaczek A, Szajewska H

Breastfeed Med 2019;14:218–229

Breastfeeding and Growth: Mothers with Obesity or Gestational Diabetes Mellitus

Breastfeeding and growth during infancy among offspring of mothers with gestational diabetes mellitus: a prospective cohort study

Gunderson EP, Greenspan LC, Faith MS, Hurston SR, Quesenberry CP Jr on behalf of the SWIFT Offspring Study Investigators

Pediatr Obes 2018;13:492–504

Mode of infant feeding, eating behaviour and anthropometry in infants at 6-months of age born to obese women: a secondary analysis of the UPBEAT trial

Patel N, Dalrymple KV, Briley AL, Pasupathy D, Seed PT, Flynn AC, Poston L and on behalf of the UPBEAT Consortium

BMC Pregnancy Childbirth 2018;18:355

Formula Feeding: Composition and Growth

Association of infant formula composition and anthropometry at 4 years: Follow-up of a randomized controlled trial (BeMIM study)

Fleddermann M, Demmelmair H, Hellmuth C, Grote V, Trisic B, Nikolic T, Koletzko B

PLoS One 2018;13:e0199859

Complementary Feeding: Age at Introduction, Growth, and Overweight

Early introduction of complementary foods and childhood overweight in breastfed and formula-fed infants in the Netherlands: the PIAMA birth cohort study

Pluymen LPM, Wijga AH, Gehring U, Koppelman GH, Smit HA, van Rossem L

Eur J Nutr 2018;57:1985–1993

Prospective associations of age at complementary feeding and exclusive breastfeeding duration with body mass index at 5–6 years within different risk groups

Sirkka O, Vrijkotte T, Halberstadt J, Abrahamse-Berkeveld M, Hoekstra T, Seidell J, Olthof M

Pediatr Obes 2018;13:522–529

Baby-Led Weaning

Baby-led complementary feeding: randomized controlled study

Dogan E, Yilmaz G, Caylan N, Turgut M, Gokcay G, Oguz MM

Pediatr Int 2018;60:1073–1080

Early Nutrition and Growth Faltering in Low-Income Countries

Association between breast milk intake at 9–10 months of age and growth and development among Malawian young children

Kumwenda C, Hemsworth J, Phuka J, Ashorn U, Arimond M, Maleta K, Prado EL, Haskell MJ, Dewey KG, Ashorn P

Matern Child Nutr 2018;14:e12582

Stunting, wasting and breast-feeding as correlates of body composition in Cambodian children at 6 and 15 months of age

Skau JKH, Grenov B, Chamnan C, Chea M, Wieringa FT, Dijkhuizen MA, Ritz C, Wells JC, Berger J, Filteau S, Roos N, Michaelsen K, Friis H

Br J Nutr 2019;121:688–698

Supplementation with lactoferrin and lysozyme ameliorates environmental enteric dysfunction: a double-blind, randomized, placebo-controlled trial

Cheng WD, Wold KJ, Bollinger LB, Ordiz MI, Shulman RJ, Maleta KM, Manary MJ, Trehan I

Am J Gastroenterol 2019;114:671–678

Rapid Early Weight Gain

Infant formula feeding practices associated with rapid weight gain: A systematic review

Appleton J[1,2], Russell CG[1], Laws R[3], Fowler C[1,4,5], Campbell K[3], Denny-Wilson E[1]

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Matern Child Nutr 2018;14:e12602

Excess or rapid weight gain during the first 2 years of life is associated with an increased risk of later childhood and adult overweight and obesity. When compared with breastfed infants, formula fed infants are more likely to experience excess or rapid weight gain, and this increased risk in formula fed infant populations may be due to a number of different mechanisms. These mechanisms include the nutrient composition of the formula and the way formula is prepared and provided to infants. This systematic literature review examines the association between formula feeding practice and excess or rapid weight gain. This review explores these different mechanisms and provides practical recommendations for best practice formula feeding to reduce rapid weight gain. Eighteen studies are included in this review. The findings are complicated by the challenges in study design and accuracy of measurements. Nevertheless, there are some potential recommendations for best practice formula feeding that

may reduce excess or rapid weight gain, such as providing formula with lower protein content, not adding cereals into bottles, not putting a baby to bed with a bottle, and not overfeeding formula. Although further well designed studies are required before more firm recommendations can be made.

Comments Comments on this manuscript are incorporated in those on the next manuscript (Azad et al.).

Infant feeding and weight gain: separating breast milk from breastfeeding and formula from food

Azad MB[1–3], Vehling L[1,2], Chan D[1,2], Klopp A[1,2], Nickel NC[2,4], McGavock JM[1,2], Becker AB[1,2], Mandhane PJ[5], Turvey SE[6,7], Moraes TJ[8], Taylor MS[3,9], Lefebvre DL[10], Sears MR[10], Subbarao P[8], on behalf of the CHILD Study Investigators

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Objectives: Studies addressing breastfeeding and obesity rarely document the method of breast milk feeding, type of supplementation, or feeding in hospital. We investigated these practices in the CHILD birth cohort.

Methods: Feeding was reported by mothers and documented from hospital records. Weight and BMI z scores (BMIzs) were measured at 12 months. Analyses controlled for maternal BMI and other confounders.

Results: Among 2,553 mother-infant dyads, 97% initiated breastfeeding, and the median breastfeeding duration was 11.0 months. Most infants (74%) received solids before 6 months. Among "exclusively breastfed" infants, 55% received some expressed breast milk, and 27% briefly received formula in hospital. Compared with exclusive direct breastfeeding at 3 months, all other feeding styles were associated with higher BMIzs: adjusted β +0.12 (95% CI 0.01–0.23) for some expressed milk, +0.28 (95% CI 0.16–0.39) for partial breastfeeding, and +0.45 (95% CI 0.30–0.59) for exclusive formula feeding. Brief formula supplementation in hospital did not alter these associations so long as exclusive breast-feeding was established and sustained for at least 3 months. Formula supplementation by 6 months was associated with higher BMIzs (adjusted β +0.25; 95% CI 0.13–0.38), whereas supplementation with solid foods was not. Results were similar for weight gain velocity.

Conclusions: Breastfeeding is inversely associated with weight gain velocity and BMI. These associations are dose dependent, partially diminished when breast milk is fed from a bottle, and substantially weakened by formula supplementation after the neonatal period.

Comments Many studies have shown that early rapid weight gain is associated with later overweight and obesity. Therefore, it is important to find out how early feeding is associated

with rapid early weight gain, which is the focus of the 2 papers by Appleton et al. [1] and Azad et al. [2] addressed here. Other papers in this chapter cover specific aspects of this topic: the association between duration of breastfeeding and growth and how age at introduction of complementary feeding is associated with growth and overweight.

The 2 papers, which are based on a systematic review and a large observational cohort study from Canada, confirm that formula feeding is associated with rapid weight gain. However, what these 2 papers add is how different practices of breastfeeding and formula feeding modify the association with rapid weight gain and thereby provide information that is valuable for guiding parents about optimal early nutrition that may reduce the risk of later overweight and obesity.

In the systematic review by Appleton et al. [1], they included studies focusing on how formula-feeding practices influence growth. The findings are well known, but they strengthen the evidence base behind recommendations on these aspects. The authors have also published an exploratory qualitative study on infant formula-feeding practice based on interviews with mothers from Australia. They concluded that there was a need for additional support for parents feeding their infants with formula [3]. Important aspects are the interpretation of infant cues and the amount of formula given to the infant. In that perspective, it is interesting that a recent paper tested the amount of formula powder parents added when preparing formula and found that 78% added more powder than recommended [4]. This resulted in an energy content 11% above recommendation, which may have an impact on risk of later overweight and obesity.

The cohort study from Canada also provides information, which is valuable when informing parents about optimal early feeding. The duration of breastfeeding was considerably longer in this cohort compared to many other studies. At 12 months, 43.5% were still breastfed, and at 24 months, it was 7.8%. The study confirms that breastfeeding duration was inversely associated with weight gain. The effect of duration of exclusive breastfeeding on weight gain is often analyzed without analyzing if termination of exclusive breastfeeding is due to introduction of formula or due to introduction of complementary feeding. Interestingly, in this study, infants partially breastfed at 6 months had a higher BMI at 12 months compared to exclusively breastfed infants, if the infants got formula, while infants partially breastfed were not different from exclusively breastfed infants, if the infants got complementary feeding and no infant formula. Under future directions, the authors mention that there is a need for studies analyzing body composition. In several of the papers included below, the effect of early nutrition on body composition is explored.

Excessive weight gain followed by catch-down in exclusively breastfed infants: an exploratory study

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Some infants experience excessive weight gain (EWG) during exclusive breastfeeding, but causes and consequences are unknown. The objective was to identify factors associated with early EWG. Infants

with EWG (HW-group) were examined at 5, 9 and 18 mo and compared to a breastfed group with normal weight gain (NW-group). Anthropometry, body composition, milk and blood samples, and milk intake were measured. Mean body-mass-index-for-age z-scores (BAZ) increased 1.93 from birth to 5 mo in the HW-group (n = 13) while the NW-group (n = 17) was unchanged (–0.01). The HW-group had 70% more fat mass at 5 mo, and then showed marked catch-down in BAZ from 5 to 18 mo (–0.84). Milk intake at 5–6 mo did not differ between the groups. In the HW-group, milk-leptin was lower at 5 mo and serum-leptin was considerably higher at 5 and 9 mo compared to the NW-group. Serum-leptin at 5 mo was positively associated with weight-for-age z-score (WAZ) and fat mass and negatively with WAZ change from 5 to 9 mo. In conclusion, breastfed infants with EWG had catch-down growth when other foods were introduced. Low milk-leptin in the HW-group may have stimulated appetite and milk intake when weight gain was high. High serum-leptin in the HW-group suggests early leptin resistance, which could impact cerebral regulation of energy intake. Larger studies are needed to confirm these results.

Comments In this study, we report basic data from a small cohort of infants with excessive weight gain during exclusive breastfeeding [5]. Our findings show a lower milk leptin at 5 months in the HW group, suggesting that this could stimulate appetite and milk intake. At 5 months, the milk intake was 15% higher in the HW group, but the difference was not significant. We find it likely that a key factor in the excessive weight gain was a considerably higher milk intake during the first months after birth. A limitation of the study is that we were not able to measure milk intake before the age of 5 months, when the excessive weight gain had leveled off and when the weight gain possibly was at the same level as in the NW group. We also found significant differences in the HMO pattern between the 2 groups, which was published recently [6]. Several HMOs have been associated with growth velocity in breastfed infants and a suggested mechanism is through a modification of the gut microbiota increasing the energy harvest. Milk and gut microbiota, milk lipid profile, and fecal short-chain fatty acids have been analyzed from this cohort, but data are not yet published.

Breast Milk Composition and Body Composition

Carbohydrates in Human Milk and Body Composition of Term Infants during the First 12 Months of Lactation

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Human milk (HM) carbohydrates may affect infant appetite regulation, breastfeeding patterns, and body composition (BC). We investigated relationships between concentrations/calculated daily intakes (CDI) of HM carbohydrates in first year postpartum and maternal/term infant BC, as well as breastfeeding parameters. BC of dyads (n = 20) was determined at 2, 5, 9, and/or 12 months post-

partum using ultrasound skinfolds (infants) and bioelectrical impedance spectroscopy (infants/mothers). Breastfeeding frequency, 24-h milk intake and total carbohydrates (TCH) and lactose were measured to calculate HM oligosaccharides (HMO) concentration and CDI of carbohydrates. Statistical analysis used linear regression/mixed effects models; results were adjusted for multiple comparisons. Higher TCH concentrations were associated with greater infant length, weight, fat-free mass (FFM), and FFM index (FFMI), and decreased fat mass (FM), FM index (FMI), %FM and FM/FFM ratio. Higher HMO concentrations were associated with greater infant FFM and FFMI, and decreased FMI, %FM, and FM/FFM ratio. Higher TCH CDI were associated with greater FM, FMI, %FM, and FM/FFM ratio, and decreased infant FFMI. Higher lactose CDI were associated with greater FM, FMI, %FM, and FM/FFM, ratio and decreased FFMI. Concentrations and intakes of HM carbohydrates differentially influence development of infant BC in the first 12 months post-partum, and may potentially influence risk of later obesity via modulation of BC.

Comments This paper is one of 3 recent publications based on a small study analyzing the association between composition of human milk and growth and body composition [7]. The other 2 publications focus on protein (casein and whey) and on adipokines (leptin and adiponectin) [8, 9]. Strengths of the studies are detailed measurements of infant growth and body composition during the first 12 months, and that 24-h milk intake was measured so that calculated daily intakes (CDI) of the nutrients were included in the analysis. In addition to the findings in the paper analyzing carbohydrate content, they found that HMO concentrations were positively associated with fat-free mass. It is interesting that CDI of lactose was positively associated with fat mass and negatively with fat-free mass. It has been suggested that a high content of lactose in breast milk will increase milk intake [10]. However, this is partly based on studies of weanling piglets where a higher lactose content in feeds increase both feed intake and weight gain [11]. In addition to providing more energy, a hypothesis is that lactose might provide a prebiotic effect on the microbiota that could increase energy utilization [11].

Bioactive components in human milk are differentially associated with rates of lean and fat mass deposition in infants of mothers with normal versus elevated BMI

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This manuscript is also discussed in Chapter 2 by Shalitin et al, page 29.

Objective: To model breastfed infant growth and body composition patterns over the first 4 months with multiple bioactive components of human milk (HM) and clinical factors (including maternal BMI status), which are related to growth.

Methods: Longitudinal observation of infant growth and body composition from 0 to 4 months among 41 predominantly breastfed infants (25 mothers of Normal-weight and 16 mothers with overweight/obesity). Fasted morning HM samples were collected at 5 time-points. Macronutrients, leptin, adiponectin, ghrelin, insulin, cytokines and *n*-6:*n*-3 esterified fatty acid ratio were measured. Infant weight-for-length Z-score (WLZ) trajectory, fat-free mass (FFM) gain, fat mass gain and %fat gain were modelled controlling for clinical covariates.
Results: HM insulin negatively associated with WLZ trajectory among infants of NW mothers (p = 0.028), but not associated with WLZ trajectory among infants of OW/Ob mothers. HM glucose ($p <$ 0.001) was associated with slower rates of infant FFM gain. Infants of mothers with OW/Ob exhibited slower rates of FFM gain. HM protein, adiponectin and insulin concentrations, and *n*-6:*n*-3 ratio were all significant predictors in the model of infant fat mass gain ($p < 0.03$). Any amount of formula supplementation was associated with faster fat gain (p = 0.002). The model of %fat gain was similar to that of fat mass gain, excepting HM adiponectin was not a significant covariate, and a trend for maternal OW/Ob to correlate with faster %fat gain (p = 0.056).
Conclusion: Bioactive components in HM may contribute to regulation of partitioning of body composition, and these contributions may differ between mothers of normal-weight vs. with OW/Ob.

Comments Comments on this manuscript are incorporated in those on the next manuscript (Prentice et al.).

Human milk short-chain fatty acid composition is associated with adiposity outcomes in infants

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Background: Presumed benefits of human milk (HM) in avoiding rapid infancy weight gain and later obesity could relate to its nutrient composition. However, data on breast milk composition and its relation with growth are sparse.
Objective: We investigated whether short-chain fatty acids (SCFAs), known to be present in HM and linked to energy metabolism, are associated with infancy anthropometrics.
Methods: In a prospective birth cohort, HM hindmilk samples were collected from 619 lactating mothers at 4–8 week postnatally (median [IQR] age: 33.9 [31.3–36.5] years, body mass index [BMI; kg/m^2]: 22.8 [20.9–25.2]). Their offspring, born at 40.1 (39.1–41.0) week gestation with weight 3.56 (3.22–3.87) kg and 51% male, were assessed with measurement of weight, length, and skinfold thickness at ages 3, 12, and 24 months, and transformed to age- and sex-adjusted z scores. HM SCFAs were measured by 1H-nuclear magnetic resonance spectroscopy (NMR) and GC-MS. Multivariable linear regression models were conducted to analyze the relations between NMR HM SCFAs and infancy growth parameters with adjustment for potential confounders.

Results: NMR peaks for HM butyrate, acetate, and formic acid, but not propionate, were detected. Butyrate peaks were 17.8% higher in HM from exclusively breastfeeding mothers than mixed-feeding mothers ($p = 0.003$). HM butyrate peak values were negatively associated with changes in infant weight (standardized B = –0.10, $p = 0.019$) and BMI (B = –0.10, $p = 0.018$) between 3 and 12 months, and negatively associated with BMI (B = –0.10, $p = 0.018$) and mean skinfold thickness (B = –0.10, $p = 0.049$) at age 12 months. HM formic acid peak values showed a consistent negative association with infant BMI at all time points (B < = –0.10, $p \leq 0.014$), whereas HM acetate was negatively associated with skinfold thickness at 3 months (B = –0.10, $p = 0.028$) and 24 months (B = –0.10, $p = 0.036$).
Conclusions: These results suggest that HM SCFAs play a beneficial role in weight gain and adiposity during infancy. Further knowledge of HM SCFA function may inform future strategies to support healthy growth.

Comments

Human breast milk contains multiple compounds that are associated with the growth and health of the infant [10]. Potentially, the composition of breast milk can have long-lasting programming effects for the infants. When examining breast milk composition, there are several methodological considerations to take into account. One of the major difficulties is getting comparable determinations of breast milk composition across studies, as there are large differences in sampling methods. For example, the fat content differs considerably between fore- and hindmilk, and there can be differences in the content of many substances in a small sample taken by hand expression and a sample from a full emptying of a breast with a milk pump. The content of milk components might also change during the day, as well as with the feeding state of the mother. Thus, standardized study protocols for measuring breast milk composition are needed in order to get comparable results. The 2 studies above examine many different compounds and associations with growth and adiposity [12, 13]. Both studies have quite complex findings regarding the association of bioactive compounds and growth.

The study by Young et al. [12] provides interesting insights into multiple interesting bioactive compounds in human milk. One of these compounds is insulin, which has been shown to be potentially important for infant growth [14]. However, the results are somewhat inconsistent across studies, but the authors provide an interesting hypothesis about the human milk insulin levels and growth. As they found that insulin levels are only associated with WLZ trajectories in infants of normal weight mothers (during pregnancy) and not in infants of overweight or obese mothers – there might be a fetal programming of the infants of overweight or obese mothers to be less responsive to human milk insulin. This would explain why insulin seems to be associated with growth in some populations and not in others. This is a very interesting aspect, which highlights that we need both large cohorts and experimental studies in order to get a good understanding of the biology behind these effects.

The study by Prentice et al. [13] examined short-chain fatty acids (SCFAs) as bioactive compounds in breast milk. This study is an expansion of the study the group published previously where they presented interesting results of the association between breast milk macronutrients and infant growth [15]. SCFAs are synthesized by the gut microbiota and can both act as an energy substrate for the microbiota or enter circulation where they may play a role in energy metabolism. This study showed that the SCFAs butyrate was associated with lower BMI and mean skinfold thickness at 12 months. Butyrate has been shown to be important in appetite regulation [16], and thus, the relationship with BMI and mean skinfold thickness at 12 months is intriguing. Furthermore, the authors show that butyrate concentrations were higher in the breast

milk of exclusively breastfeeding mothers compared to milk of mothers both breastfeeding and giving formula. Thus, future studies could investigate whether the link between butyrate, slower growth, and breastfeeding might be mediated by satiety cues in the infant. Furthermore, it should be explored how much the breast milk SCFAs contribute on top of the endogenously produced SCFAs, and whether or not breast milk is a prominent source of SCFAs for the infant.

These 2 studies also highlight that our understanding of the determinants of breast milk composition is thus far limited. However, we know that some substances in breast milk seem to be influenced by maternal factors. These include genes, maternal BMI, infant sex, parity, mode of delivery, and lifestyle factors such as nutrition, including the time of the last meal before sampling, and smoking [10]. However, some of these maternal factors are also related to infant growth, which can render it difficult to conclude about causality. Future large-scale studies are needed in order to get an overview of potential determinants of later overweight and obesity, both modifiable and nonmodifiable, as well as to establish reference levels for nutrients and bioactive compounds.

Duration of Breastfeeding and Growth

Duration of breastfeeding and early growth: a systematic review of current evidence

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Breastfeed Med 2019;14:218–229

Introduction: Growth patterns of breastfed and formula-fed infants differ, but the influence of breastfeeding duration on early growth remains unclear. The objective of this study is to evaluate current evidence on the association of exclusive and partial breastfeeding duration with different growth parameters during infancy.

Materials and Methods: In this systematic review, we searched MEDLINE, EMBASE, and additional sources from January 2011 until March 2018 to identify relevant cohort studies and randomized controlled trials (RCTs).

Results: Twenty studies that recruited infants from the general population were included. In the developed setting, exclusive breastfeeding duration was inversely associated with weight and length gain during infancy in observational studies. Longer duration of exclusive breastfeeding was also associated with an earlier peak in infant body mass index (BMI). Inconsistent results were observed for the associations of exclusive breastfeeding duration with other infant BMI characteristics. In an RCT conducted in Iceland, exclusive breastfeeding for 4 versus 6 months did not affect infant growth patterns. In the developing setting, conflicting findings on the associations of exclusive breastfeeding duration with infant weight and length parameters were shown in observational studies. Shorter partial breastfeeding duration was associated with higher weight gain during infancy, with limited or inconclusive data regarding other growth parameters.

Conclusions: Longer duration of exclusive and partial breastfeeding tended to be associated with slower growth rates during infancy in the developed setting only. These associations seem to be dose dependent and more pronounced in exclusively versus partially breastfed infants.

Comments This systematic review adds to and updates the existing literature showing that the longer an infant is exclusively and partially breastfed the slower they are growing [17]. The conclusion is that duration of breastfeeding "tended" to be associated with slower growth in high-income countries. The few studies from low- or middle-income countries found no association. It is of special interest that the only RCT in the review, where infants were randomized to start complementary feeding at 4 or 6 months, did not show an effect on growth [18]. Another approach to examine the association between breastfeeding and growth was used in a systematic review and meta-analysis by Giugliani et al. [19], where they looked at the effect of breastfeeding promotion interventions. Sixteen studies were included, of which 11 were from middle-income countries and only 2 from high-income countries, and 15 of the studies only followed growth until the age of 6 months or less. The overall conclusion of this review was that there were no effects of the interventions on weight and length and a small but significant negative effect on BMI or weight-for-height.

Breastfeeding and Growth: Mothers with Obesity or Gestational Diabetes Mellitus

Breastfeeding and growth during infancy among offspring of mothers with gestational diabetes mellitus: a prospective cohort study

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Background: Breastfeeding (BF) may protect against obesity and type 2 diabetes mellitus in children exposed to maternal diabetes in utero, but its effects on infant growth among this high-risk group have rarely been evaluated.
Objectives: The objective of this study was to evaluate BF intensity and duration in relation to infant growth from birth through 12 months among offspring of mothers with gestational diabetes mellitus (GDM).
Methods: Prospective cohort of 464 GDM mother-infant dyads (28% White, 36% Hispanic, 26% Asian, 8% Black, 2% other). Weight and length measured at birth, 6–9 weeks, 6 months and 12 months. Categorized as intensive BF or formula feeding (FF) groups at 6–9 weeks (study baseline), and intensity from birth through 12 months as Group 1: consistent exclusive/mostly FF, Group 2: transition from BF to FF within 3–9 months and Group 3: consistent exclusive/mostly BF. Multivariable mixed linear regression models estimated adjusted mean (95% confidence interval) change in z-scores; weight-for-length (WLZ), weight-for-age and length-for-age.
Results: Compared with intensive BF at 6–9 weeks, FF showed greater increases in WLZ-scores from 6 to 9 weeks to 6 months (+0.38 [0.13 to 0.62] vs. +0.02 [–0.15 to 0.19]; $p = 0.02$) and birth to 12 months (+1.11 [0.87 to 1.34] vs. +0.53 [0.37 to 0.69]; $p < 0.001$). For 12-month intensity and duration, Groups 2 and 3 had smaller WLZ-score increases than Group 1 from 6 to 9 weeks to 6 months

(–0.05 [–0.27 to 0.18] and +0.07 [–0.19 to 0.23] vs. +0.40 [0.15 to 0.64]; $p = 0.01$ and 0.07), and birth to 12 months (+0.60 [0.39 to 0.82] and +0.59 [0.33 to 0.85] vs. +0.97 [0.75 to 1.19]; $p < 0.05$).
Conclusions: Among offspring of mothers with GDM, high intensity BF from birth through 1 year is associated with slower infant ponderal growth and lower weight gain.

Comments Comments on this manuscript are incorporated in those on the next manuscript (Patel et al.).

Mode of infant feeding, eating behaviour and anthropometry in infants at 6-months of age born to obese women – a secondary analysis of the UPBEAT trial

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BMC Pregnancy Childbirth 2018;18:355

Background: Maternal obesity and rapid infant weight gain have been associated with increased risk of obesity in childhood. Breastfeeding is suggested to be protective against childhood obesity, but no previous study has addressed the potential benefit of breastfeeding as a preventive method of childhood obesity amongst obese women. The primary aim of this study was to assess the relationship between mode of feeding and body composition, growth and eating behaviours in 6-month-old infants of obese women who participated in UPBEAT; a multi-centre randomised controlled trial comparing a lifestyle intervention of diet and physical activity to standard care during pregnancy.
Methods: Three hundred and fifty-three mother and infant pairs attended a 6-months postpartum follow-up visit, during which they completed the Baby-Eating Behaviour Questionnaire, a parent-reported psychometric measure of appetite traits. Measures of infant body composition were also undertaken. As there was no effect of the antenatal intervention on infant feeding and appetite the study was treated as a cohort. Using regression analyses, we examined relationships between: (1) mode of feeding and body composition and growth; (2) mode of feeding and eating behaviour and (3) eating behaviour and body composition.
Results: Formula fed infants of obese women in comparison to those exclusively breastfed, demonstrated higher weight z-scores (mean difference 0.26; 95% CI 0.01–0.52), higher rate of weight gain (0.04; 0.00–0.07) and greater catch-up growth (2.48; 1.31–4.71). There was also a lower enjoyment of food ($p = 0.002$) amongst formula fed infants, following adjustment for confounders. Independent of the mode of feeding, a measure of infant appetite was associated with sum of skinfold thicknesses (β 0.66; 95% CI 0.12–1.21), calculated body fat percentage (0.83; 0.15–1.52), weight z-scores (0.21; 0.06–0.36) and catch-up growth (OR 1.98; 1.21–3.21).
Conclusion: In obese women, exclusive breastfeeding was protective against increasing weight z-scores and trajectories of weight gain in their 6-month old infants. Measures of general appetite in early infancy were associated with measures of adiposity, weight and catch up growth independent of cord blood leptin concentrations and mode of early feeding.

Comments Infants born to mothers with obesity or gestational diabetes mellitus (GDM) are considered to be a high-risk group for later development of obesity and type 2 diabetes. Therefore, preventive strategies in these groups are of high interest. The 2 studies mentioned

above show that breastfeeding is associated with a slower growth in the first 6–12 months of life and thus could be protective of later development of obesity and type 2 diabetes [20, 21]. This is in accordance with other studies in general populations where breastfeeding has also shown to be associated with slower growth and lower long-term obesity risk [17, 22].

However, some studies have shown that breast milk from mothers with obesity or GDM might be different in composition compared to breast milk from healthy normal weight mothers [23, 24]. This includes multiple differences, for example, in energy and micronutrient content [24], branched-chain amino acids [25], leptin [23], and immune factors [26]. Alterations in breast milk composition such as higher content of branched-chain amino acids might lead to an increase in growth stimuli. Thus, it has been speculated that breast milk from mothers with obesity/GDM could be composed in such a way that these infants have more rapid growth [27]. However, others have shown that higher values of immune factors associated with obesity, such as IL-6 and TNF-α, are associated with lower lean mass and weight gain [28]. However, the 2 published studies show that breastfeeding compared to formula feeding is still associated with lower growth rates. In future studies, it would be interesting to also include a normal weight/normoglycemic control group as a comparator and to include analysis of breast milk composition.

Interestingly, despite the higher growth rate in one of the studies, the formula-fed infants of obese mothers showed a lower enjoyment of food according to the Baby-Eating Behaviour Questionnaire, a finding requiring further exploration in how appetite and early feeding mode are related to weight gain.

Formula Feeding: Composition and Growth

Association of infant formula composition and anthropometry at 4 years: Follow-up of a randomized controlled trial (BeMIM study)

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The relationships between nutrition, metabolic response, early growth and later body weight have been investigated in human studies. The aim of this follow-up study was to assess the long-term effect of infant feeding on growth and to study whether the infant metabolome at the age of 4 months might predict anthropometry at 4 years of age. The Belgrade-Munich infant milk trial (BeMIM) was a randomized controlled trial in which healthy term infants received either a protein-reduced infant formula (1.89 g protein/100 kcal) containing alpha-lactalbumin enriched whey and long-chain polyunsaturated fatty acids (LC-PUFA), or a standard formula (2.2 g protein/100 kcal) without LC-PUFA, focusing on safety and suitability. Non-randomized breastfed infants were used as a reference group. Of the 259 infants that completed the BeMIM study at the age of 4 months (anthropometry assessment and blood sampling), 187 children participated in a follow-up visit at 4 years of age. Anthropometry including weight, standing height, head circumference, and percent body fat was determined using skinfolds (triceps, subscapular) and bioelectrical impedance analysis. Plasma metabolite con-

centration, collected in samples at the age of 4 months, was measured using flow-injection tandem mass spectrometry. A linear regression model was applied to estimate the associations between each metabolite and growth with metabolites as an independent variable. At 4 years of age, there were no significant group differences in anthropometry and body composition between formula groups. Six metabolites (Asn, Lys, Met, Phe, Trp, Tyr) measured at 4 months of age were significantly associated with changes in weight-for-age z-score between 1 to 4 months of age and BMI-for-age z-score (Tyr only), after adjustment for feeding group. No correlation was found between measured metabolites and long-term growth (up to 4 years of age). No long-term effects of early growth patterns were shown on anthropometry at 4 years of age. The composition of infant formula influences the metabolic profile and early growth, while long-term programming effects were not observed in this study.

Comments This is a 4-year follow-up of the BeMIM study published in 2014 [29]. The findings are a little surprising suggesting that the intake of the high-protein formula was not associated with higher BMI at age 4 years, as this has been reported in other controlled intervention studies like the CHOP study [30]. In the CHOP study, the high-protein formula group induced a higher weight gain already after 3 months [31], which was not the case in the BeMIM study, where there was a tendency to a higher weight gain (p = 0.06) and a significant higher length gain (p = 0.02) in the protein-reduced formula group [29]. One reason for these findings may be that the protein-reduced formula was enriched with both alpha-lactalbumin and LC-PUFA. In the original paper by Fleddermann et al. [32], these enrichments were mentioned as a possible reason for higher energetic efficiency (growth per energy intake). This study underlines that not only protein quantity but also quality may be important for growth stimulation and programming effects. Future studies should thus focus not only on the amount of protein but also on quality and content of functional proteins and peptides.

Complementary Feeding: Age at Introduction, Growth, and Overweight

Early introduction of complementary foods and childhood overweight in breastfed and formula-fed infants in the Netherlands: the PIAMA birth cohort study

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Eur J Nutr 2018;57:1985–1993

Purpose: To investigate whether early introduction of complementary foods (CF) is associated with an increased risk of overweight during childhood, and whether this association differs between formula-fed and breastfed infants.

Methods: We included 2,611 participants that were born at term from a Dutch population-based birth cohort (n = 3,963) designed to investigate the development of asthma and allergies. Parents kept records of their infant's age when CF were first introduced. Weight and height were parent reported yearly from age 1 to 8 years, and at ages 11, 14 and 17 years. We used multivariate generalized estimating equations analysis to investigate the association between timing of CF introduction (before 4 months versus at or after 4 months of age) and overweight at ages 1–17 years.
Results: Children with CF introduction before 4 months had higher odds of being overweight during childhood than children with CF introduction at or after 4 months (OR 1.32, 95% CI 1.19–1.47). This association was observed in formula-fed infants (OR 1.51, 95% CI 1.17–1.94) and breastfed infants (OR 1.32, 95% CI 1.19–1.47). The duration of breastfeeding modified the association between CF introduction and overweight: children breastfed for shorter than 4 months, but not children breastfed for 4 months or longer with CF introduction before 4 months had higher odds of being overweight (OR 1.37, 95% CI 1.19–1.57 and 1.07, 95% CI 0.87–1.32, respectively), compared to those with CF introduction at or after 4 months.
Conclusions: In children born at term, formula-fed infants and infants who were breastfed for shorter than 4 months, but not infants who were breastfed for 4 months or longer, had a higher risk of being overweight during childhood when being introduced to CF before 4 months of age.

Comments Comments on this manuscript are incorporated in those on the next manuscript (Sirkka et al.).

Prospective associations of age at complementary feeding and exclusive breastfeeding duration with body mass index at 5–6 years within different risk groups

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Pediatr Obes 2018;13:522–529

Background: Children with overweight or obesity are at risk for developing obesity in adulthood. Certain maternal characteristics, such as ethnicity, education, body mass index (BMI) or neighbourhood, are determinants for childhood overweight risk. There are large variations in how mothers differing in these characteristics feed their infants. Therefore, associations of age at complementary feeding, exclusive breast feeding duration with childhood overweight may differ in these groups. Understanding these associations would be essential to develop overweight prevention strategies.
Objectives: The objective of this study is to study the associations of age at complementary feeding, exclusive breastfeeding duration with BMI-standard deviation score (SDS) at 5–6 years within risk groups.
Methods: Using data from the Amsterdam Born Children and their Development study, a population-based birth cohort (n = 4,495), we formed groups of children at varying risk of overweight according to maternal characteristics of ethnicity, education, pre-pregnancy BMI and neighbourhood. Linear and logistic regression analyses were conducted.

Results: Complementary feeding after 5 months of age was associated with lower BMI-SDS in children of mothers of Dutch ethnicity (B –0.12; 95% CI –0.21 to –0.04), medium-level education (–0.19; –0.30 to –0.08), normal BMI (–0.08; –0.16 to –0.01) and high-risk neighbourhood (–0.16; –0.29 to –0.02). Compared with exclusive breastfeeding for <3 months, exclusive breastfeeding for ≥6 months was associated with lower BMI-SDS in groups of medium-level education (–0.28; 0.44 to –0.11), normal BMI (–0.18; –0.29 to –0.08) and medium-risk (–0.18; –0.33 to –0.04) and high-risk (–0.22; –0.42 to –0.02) neighbourhoods.

Conclusions: Associations between infant feeding practices and childhood BMI may differ between risk groups, implying that overweight prevention strategies should be group-specific.

Comments

It is well known that overweight and obesity in childhood may track into adulthood. As obesity in adulthood is difficult to reverse and is associated with risk of noncommunicable diseases such as hypertension, diabetes mellitus type II, and cardiovascular diseases, it is important to have strategies for the prevention of overweight already in childhood. The 2 Dutch studies investigate how timing of introduction of complementary feeding and duration of breastfeeding may affect later BMI and identify potential modifying factors [33, 34].

Pluymen et al. [33] examine if age when starting complementary feeding is associated with overweight throughout childhood (1–17 years) and if this is different between breastfed and formula-fed infants. Previous studies have shown conflicting results regarding the impact of infant feeding mode on how age of introduction of complementary feeding influence the risk of later overweight. Whereas Huh et al. [35] observed a protective effect of breastfeeding beyond 4 months, Moss et al. [36] and Sun et al. [37] found no difference between breastfed and formula-fed infants. In the study by Pluymen et al. [33], they observe the expected association between early introduction of complementary feeding (before 4 months) and overweight during childhood for both breastfed and formula-fed infants. However, breastfeeding beyond 4 months eliminated this unfavorable relation. Hence, it seems important to support breastfeeding also in respect to introducing complementary feeding, and the recommendation for the timing of introducing complementary feeding may differ between groups depending on infant-feeding mode. Future studies should investigate this further, and according to the study by Sirkka et al. [34], the impact of maternal factors should be investigated as well.

In the other Dutch study by Sirkka et al. [34], the associations between age of complementary feeding introduction and duration of exclusive breastfeeding on BMI at 5–6 years were examined according to different risk groups, that is, ethnicity, educational level, pre-pregnancy BMI, and neighborhoods [34]. Associations with BMI at 5–6 years differed between the different risk groups. For example, analyses between introduction of complementary feeding at ≥5 months of age and BMI at the age of 5–6 years showed a significant inverse association and a reduced risk for Dutch ethnicity but not for the other ethnicities. The authors conclude that interventions should be group specific. However, this will be difficult to address, as there was no overall clear pattern. However, they direct attention to an important challenge as complementary feeding is influenced by culture and traditions and therefore may differ between groups and be difficult to change. As discussed above, adherence to recommendations could be improved with special focus on relevant risk groups. Future studies may help to identify relevant risk groups and methods for targeting these groups.

Baby-led complementary feeding: Randomized controlled study

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Pediatr Int 2018;60:1073–1080

Background: Baby-led weaning (BLW) is an approach to introducing solid foods to infants that gives control of the feeding process to the infant. Anecdotal evidence suggests that BLW is becoming popular with parents, but scientific research is limited to a few publications. This study assessed growth, hematological parameters and iron intake in 6–12-month-old infants fed by traditional or baby-led complementary feeding.

Methods: We recruited 280 healthy 5–6-month-old infants allocated to a control (traditional spoon feeding [TSF]) group or an intervention (BLW) group in a randomized controlled trial. Infant growth, hematologic parameters and iron intake were evaluated at age 12 months.

Results: Infants in the TSF were significantly heavier than those in the BLW group. Mean weight in the BLW group was 10.4 ± 0.9 kg compared with 11.1 ± 0.5 kg in the TSF group. There was no statistically significant difference in the iron intake from complementary foods between the BLW (7.97 ± 1.37 mg/day) and TSF (7.90 ± 1.68 mg/day) participants who completed the diet records. Hematologic parameters were similar at 12 months. The incidence of choking reported in the weekly interviews was not different between the groups.

Conclusion: To the best of our knowledge, this is the first randomized -controlled study to have examined the impact of weaning method on iron intake, hematological parameters and growth in breast-fed infants. BLW can be an alternative complementary feeding type without increasing the risk of iron deficiency, choking or growth impairment.

Comments Baby-led weaning (BLW) is a relatively recent method used for the transition from infant feeding to family foods. The idea of the concept is that the infant is exposed to a range of foods and decides what and how much to eat, which might reduce overeating and strengthen self-regulation. Though BLW is becoming more popular, only a few studies have examined the effect on growth, nutrient intake, and safety compared to traditional complementary feeding. This randomized study shows that after about 6 months of intervention, the weight was significantly lower for BLW group compared to infants using traditional weaning practices at the age of 12 months [38]. However, there were no differences in length, head circumference, chocking, or iron intake between the groups. This is in accordance with other recent studies [39, 40] indicating that BLW is a safe approach enabling the infant to get sufficient nutrients to obtain normal growth in stature. An interesting aspect of BLW approach is the role of the self-regulation. The complementary feeding approach may have an impact on the development of satiety regulation, and BLW seems to regulate the food intake differently from the traditional weaning approach [41]. Analogous breastfeeding also enables the infant to self-regulate food intake and has

in some meta-analyses shown to have a protective, although small effect, against later obesity [22]. In future studies, it would therefore be interesting to examine the potential effect of BWL on later weight development to establish the long-term consequences of BLW.

Early Nutrition and Growth Faltering in Low-Income Countries

Association between breast milk intake at 9–10 months of age and growth and development among Malawian young children

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Matern Child Nutr 2018;14:e12582

World Health Organization recommends exclusive breastfeeding for infants for the first 6 months of life, followed by introduction of nutritious complementary foods alongside breastfeeding. Breast milk remains a significant source of nourishment in the second half of infancy and beyond; however, it is not clear whether more breast milk is always better. The present study was designed to determine the association between amount of breast milk intake at 9–10 months of age and infant growth and development by 12–28 month of age. The study was nested in a randomized controlled trial conducted in Malawi. Regression analysis was used to determine associations between breast milk intake and growth and development. Mean (SD) breast milk intake at 9–10 months of age was 752 (244) g/day. Mean (SD) length-for-age z-score at 12 months and change in length-for-age z-score between 12 and 18 months were –1.69 (1.0) and –0.17 (0.6), respectively. At 18 months, mean (SD) expressive vocabulary score was 32 (24) words and median (interquartile range) skills successfully performed for fine, gross, and overall motor skills were 21 (19–22), 18 (16–19), and 38 (26–40), respectively. Breast milk intake (g/day) was not associated with either growth or development. Proportion of total energy intake from breast milk was negatively associated with fine motor ($\beta = -0.18$, $p = 0.015$) but not other developmental scores in models adjusted for potential confounders. Among Malawian infants, neither breast milk intake nor percent of total energy intake from breast milk at 9–10 months was positively associated with subsequent growth between 12 and 18 months, or development at 18 months.

Comments Comments on this manuscript are incorporated in those on the next 2 manuscripts (Skau et al. and Cheng et al.).

Stunting, wasting and breast-feeding as correlates of body composition in Cambodian children at 6 and 15 months of age

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The study aimed at assessing stunting, wasting and breast-feeding as correlates of body composition in Cambodian children. As part of a nutrition trial (ISRCTN19918531), fat mass (FM) and fat-free mass (FFM) were measured using 2H dilution at 6 and 15 months of age. Of 419 infants enrolled, 98% were breastfed, 15% stunted and 4% wasted at 6 months. At 15 months, 78% were breastfed, 24% stunted and 11% wasted. Those not breastfed had lower FMI at 6 months but not at 15 months. Stunted children had lower FM at 6 months and lower FFM at 6 and 15 months compared with children with length-for-age z ≥0. Stunting was not associated with height-adjusted indexes fat mass index (FMI) or fat-free mass index (FFMI). Wasted children had lower FM, FFM, FMI and FFMI at 6 and 15 months compared with children with weight-for-length z (WLZ) ≥0. Generally, FFM and FFMI deficits increased with age, whereas FM and FMI deficits decreased, reflecting interactions between age and WLZ. For example, the FFM deficits were –0·99 (95% CI –1.26 to –0.72) kg at 6 months and –1.44 (95% CI –1.69 to –1.19) kg at 15 months (interaction, <0.05), while the FMI deficits were –2.12 (95% CI –2.53 to –1.72) kg/m^2 at 6 months and –1.32 (95% CI –1.77 to –0.87) kg/m^2 at 15 months (interaction, <0.05). This indicates that undernourished children preserve body fat at the detriment of fat-free tissue, which may have long-term consequences for health and working capacity.

Comments Comments on this manuscript are incorporated with those on the manuscripts above and below (Kumwenda et al. and Cheng et al.).

Supplementation with lactoferrin and lysozyme ameliorates environmental enteric dysfunction: A double-blind, randomized, placebo-controlled trial

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Introduction: Environmental enteric dysfunction (EED) predisposes children throughout the developing world to high rates of systemic exposure to enteric pathogens and stunting. Effective in-

terventions that treat or prevent EED may help children achieve their full physical and cognitive potential. The objective of this study is to test whether 2 components of breast milk would improve a biomarker of EED and linear growth during the second year of life.

Methods: A prospective, randomized, double-blind, placebo-controlled clinical trial among children aged 12–23 months was conducted in rural Malawi. The experimental group received a daily supplement of 1.5 g of lactoferrin and 0.2 g of lysozyme for 16 weeks. The primary outcome was an improvement in EED, as measured by the change in the percentage of ingested lactulose excreted into the urine (Δ%L).

Results: Among 214 children who completed the study, there was a significant difference in Δ%L between the control and experimental groups over 8 weeks (an increase of 0.23 vs. 0.14%, respectively; $p = 0.04$). However, this relative improvement was not as strongly sustained over the full 16 weeks of the study (an increase of 0.16 vs. 0.11%, respectively; $p = 0.17$). No difference in linear growth over this short period was observed. The experimental intervention group had significantly lower rates of hospitalization and the development of acute malnutrition during the course of the study (2.5 vs. 10.3%, relative risk 0.25; $p < 0.02$).

Discussion: Supplementation with lactoferrin and lysozyme in a population of agrarian children during the second year of life has a beneficial effect on gut health. This intervention also protected against hospitalization and the development of acute malnutrition, a finding with a significant clinical and public health importance. This finding should be pursued in larger studies with longer follow-up and optimized dosing.

Comments

Growth faltering during the first 2 years of life is widespread in low-income countries [42], and attempts to reverse the decline in height-for-age through breastfeeding promotion or nutrition interventions have only had no or small effects [19, 43]. The studies by Kumwenda et al. [44] and Cheng et al. [45] examined the effects of breastfeeding and nutrition interventions during the second half of infancy on growth and body composition.

Kumwenda et al. [44] investigated the associations between intake of breast milk at 9–10 months of age and growth at 12–18 months in children from rural Malawi. They found that breast milk intake, measured in g/day or calculated as percentage of total energy intake per day, was not associated with length-for-age Z (LAZ) at 12 months or change in LAZ from 12 to 18 months of age. The mean LAZ declined between 12 and 18 months of age despite high breastfeeding rate and the fact that mean energy intake was higher than the mean requirements of children at this age. The results are discussed and are in line with cited studies in both younger children and older children where no evidence of breastfeeding and growth was found in low-income countries. However, some breastfeeding studies mentioned in the paper did find positive associations between breastfeeding practices and growth. The strength of the current study is the quantitative measurement of breast milk intake using stable isotope technique and the relatively large sample size ($n = 358$).

In rural Cambodia, Skau et al. [46] found that although breastfeeding rates were high and all children received a daily dietary supplement, the stunting rate increased from 15 to 24% and wasting increased from 4 to 11% in young children from 6 to 15 months of age. Non-breastfed infants at 6 months had a lower fat mass index (FMI) than breastfed infants, suggesting that breastfeeding supports accretion of fat mass. However, the number of non-breastfed children at 6 months was very low, and the results should be interpreted with caution. Stunting was not associated with FMI or fat-free mass index (FFMI). This means that stunted children gained fat and fat-free tissue "in the same proportion to their length" as nonstunted children. However, there was a

differential effect of wasting on FMI and FFMI at 6 and 15 months of age. Deficits in FFMI increased with age, whereas FMI deficits decreased with age. This suggests that body fat is preserved at the expense of accretion of fat-free tissue during wasting (acute malnutrition). This could have long-term consequences, including reduced working capacity and higher risk of noncommunicable diseases. This study also used stable isotope technique to measure body composition.

Environmental enteric dysfunction (EED), a condition involving villus atrophy, intestinal inflammation, and increased gut permeability has been found to contribute to stunting [47]. Cheng et al. [45] investigated if EED could be reduced by giving lactoferrin and lysozyme to 12- to 23-month-old children. Human milk contains both lactoferrin and lysozyme, and the level used in the supplement was based on the estimated amounts a 12-month-old child would receive from breast milk. The supplement was given during the hunger season when EED was expected to increase. One biomarker, Δ%L (change in lactulose excreted into urine), was used to measure EED. There was a modest effect of the intervention on Δ%L after 8 weeks ($p = 0.04$), which was not maintained after 16 weeks ($p = 0.17$). As expected, there was no effect on linear growth during the short intervention period. The number of children being hospitalized or developing moderate acute malnutrition during the intervention was lower in the experimental group compared to the control group.

In conclusion, stunting is still a challenge with approximately 25% of children below 5 years being stunted [48]. Research investigating the underlying mechanisms of stunting is needed in order to develop interventions aiming at the prevention of stunting. Interventions focusing on improvements of gut health may be one of the ways forward.

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Malnutrition and Catch-Up Growth during Childhood and Puberty

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Introduction

Children in resource-poor settings are prone to malnutrition resulting from a suboptimal nutrition and various environmental hindrances. According to the 2019 joint report of UNICEF, WHO, and the World Bank on levels and trends in child malnutrition, we are far from a world free of malnutrition. Indeed, global rates remain alarmingly high. In 2018, an estimated 14 million children younger than 5 years (21.9%) were affected by stunting, and wasting continued to threaten the lives of an estimated 49 million (7.3%). The report revealed that insufficient progress has been made to reach the World Health Assembly targets set for 2025 and the Sustainable Development Goals set for 2030 [1].

It is becoming evident that in order to effectively prevent and treat childhood malnutrition in low- and middle-income countries, a combination of interventions in several disciplines is needed: nutritional, for both mother and child; environmental, including access to basic health, water, hygiene, and sanitation services; and indirectly, agricultural and financial [2]. The nutritional interventions must be multisectoral and sustainable over the long term, and many countries appear to be moving in the right direction [1].

The prevention and treatment of stunting and wasting also require an in-depth understanding of the mechanisms underlying their development. Extensive research has

been directed specifically at deciphering the intricate relationship between the gut microbiome and the occurrence of enteric dysfunction. Recent findings suggest that interventions directed at the gut microbiota may help in the treatment of malnourished children [3].

This chapter reviews the most recent data on childhood malnutrition and catch-up growth, published between July 1, 2018, and June 30, 2019, and addresses several topics:

1 Evaluation and assessment of malnutrition in childhood and adolescence.

An interesting review of the genetic contribution to the evolvement of malnutrition [4] and 2 reviews on adolescent malnutrition [5, 6]

2 Nutritional interventions to prevent and treat malnutrition in children.

Several Cochrane database systemic reviews of RCTs and quasi-RCTs [7–10] and several summaries of clinical trials [11–13], assessing the effectiveness of different nutritional intervention approaches in the prevention and treatment of malnutrition in young children.

3 The microbiome and childhood malnutrition.

Several reviews summarizing the interplay between the microbiome and malnutrition and potential strategies for modulating the gut microbiota during childhood as prevention and treatment strategies against undernutrition [14–16].

Key articles reviewed for this chapter

Evaluation and Assessment of Malnutrition in Childhood and Adolescence

Does malnutrition have a genetic component?

Duggal P, Petri WA Jr.

Annu Rev Genomics Hum Genet 2018;19:247–262

Perspective: challenges in use of adolescent anthropometry for understanding the burden of malnutrition

Tumilowicz A, Beal T, Neufeld LM, Frongillo EA

Adv Nutr 2019;10:563–575

Addressing knowledge gaps in adolescent nutrition: toward advancing public health and sustainable development

Canavan CR, Fawzi WW

Curr Dev Nutr 2019;3:nzz062

Nutritional Interventions to Prevent and Treat Malnutrition in Children

Preventive lipid-based nutrient supplements given with complementary foods to infants and young children 6–23 months of age for health, nutrition, and developmental outcomes

Das JK, Salam RA, Hadi YB, Sadiq Sheikh S, Bhutta AZ, Weise Prinzo Z, Bhutta ZA

Cochrane Database Syst Rev 2019;5:CD012611

Ready-to-Use Therapeutic Food (RUTF) for home-based nutritional rehabilitation of severe acute malnutrition in children from six months to five years of age

Schoonees A, Lombard MJ, Musekiwa A, Nel E, Volmink J

Cochrane Database Syst Rev 2019;5:CD009000

Community-based supplementary feeding for food insecure, vulnerable and malnourished populations: An overview of systematic reviews

Visser J, McLachlan MH, Maayan N, Garner P

Cochrane Database Syst Rev 2018;11:CD010578

Effectiveness of provision of animal-source foods for supporting optimal growth and development in children 6–59 months of age

Eaton JC, Rothpletz-Puglia P, Dreker MR, Iannotti L, Lutter C, Kaganda J, Rayco-Solon P

Cochrane Database Syst Rev 2019;2:CD012818

Consumption of animal-source protein is associated with improved height-for-age z scores in rural Malawian children aged 12–36 months

Kaimila Y, Divala O, Agapova SE, Stephenson KB, Thakwalakwa C, Trehan I, Manary MJ, Maleta KM

Nutrients 2019;11:480

Maximizing recovery and growth when treating moderate acute malnutrition with whey-containing supplements

Stobaugh H

Food Nutr Bull 2018;39(suppl 2):S30–S34

Higher levels of dairy result in improved physical outcomes: a synthesis of 3 randomized controlled trials in Guinea-Bissau comparing supplements with different levels of dairy ingredients among children 6–59 months, 5–19 year olds, and mothers in preschools, primary schools, and villages, and the implications for programs

Schlossman N

Food Nutr Bull 2018;39(suppl 2):S35–S44

The Microbiome and Childhood Malnutrition

Gut microbiota alterations and dietary modulation in childhood malnutrition: The role of short chain fatty acids

Pekmez CT, Dragsted LO, Brahe LK

Clin Nutr 2019;38:615–630

A sparse covarying unit that describes healthy and impaired human gut microbiota development

Raman AS, Gehrig JL, Venkatesh S, Chang HW, Hibberd MC, Subramanian S, Kang G, Bessong PO, Lima AAM, Kosek MN, Petri WA Jr., Rodionov DA, Arzamasov AA, Leyn SA, Osterman AL, Huq S, Mostafa I, Islam M, Mahfuz M, Haque R, Ahmed T, Barratt MJ, Gordon JI

Science 2019;365:140

Effects of microbiota-directed foods in gnotobiotic animals and undernourished children

Gehrig JL, Venkatesh S, Chang HW, Hibberd MC, Kung VL, Cheng J, Chen RY, Subramanian S, Cowardin CA, Meier MF, O'Donnell D, Talcott M, Spears LD, Semenkovich CF, Henrissat B, Giannone RJ, Hettich RL, Ilkayeva O, Muehlbauer M, Newgard CB, Sawyer C, Head RD, Rodionov DA, Arzamasov AA, Leyn SA, Osterman AL, Hossain MI, Islam M, Choudhury N, Sarker SA, Huq S, Mahmud I, Mostafa I, Mahfuz M, Barratt MJ, Ahmed T, Gordon JI

Science 2019;365:139

Evaluation and Assessment of Malnutrition in Childhood and Adolescence

Does malnutrition have a genetic component?

Duggal P[1], Petri WA Jr[2]

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Annu Rev Genomics Hum Genet 2018;19:247–262

Abstract: Malnutrition is a complex disorder, defined by an imbalance, excess, or deficiency of nutrient intake. The visible signs of malnutrition are stunted growth and wasting, but malnourished children are also more likely to have delays in neurocognitive development, vaccine failure, and susceptibility to infection. Despite malnutrition being a major global health problem, we do not yet understand the pathogenesis of this complex disorder. Although lack of food is a major contributor to childhood malnutrition, it is not the sole cause. The mother's prenatal nutritional status, enteric infections, and intestinal inflammation also contribute to the risk of childhood malnutrition and recovery. Here, we discuss another potential risk factor, host and maternal genetics that may play a role in the risk of malnutrition via several biological pathways. Understanding the genetic risks of malnutrition may help to identify ideal targets for intervention and treatment of malnutrition.

Comments Challenging the common assumption that malnutrition is an acquired condition, with a small, if any, contribution of the host, this review summarizes current data on genes that may be involved in the pathways leading to malnutrition. The genes mentioned have been shown to predispose or protect an individual from acquiring a specific micro- or macronutrient deficiency; to confer susceptibility to developing diarrhea by specific enteric infections; or may take part in the pathways leading to chronic en-

teric inflammation. If so, this could explain why some children are more prone to malnutrition and stunting and suggest new directions for the development of targeted nutritional interventions.

Perspective: challenges in use of adolescent anthropometry for understanding the burden of malnutrition

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Adv Nutr 2019;10:563–575

Abstract: Improving nutritional status during adolescence is an opportunity to improve the lives of this generation and the next. Estimating the burden of malnutrition at a population level is fundamental to targeting interventions and measuring progress over time, and for adolescents, we usually depend on survey data and the 2007 WHO Growth Reference to do so. There is substantial risk of misguided conclusions regarding adolescent prevalence estimates, however, when underlying methodological limitations of the indicators and reference are not adequately considered. We use national prevalence estimates among girls and young women 10–22 years of age from the 2014 State of Food Security and Nutrition in Bangladesh report as an example to demonstrate that determining the true prevalence of undernutrition, overweight, and obesity is complicated by racial/ethnic variation across populations in timing of the adolescent growth spurt, growth potential, and body build. Further challenging the task are inherent limitations of the body mass index as an indicator of thinness and adiposity, and cutoffs that poorly distinguish a well-nourished population from a malnourished one. We provide recommendations for adolescent nutrition policy and program decision-making, emphasizing the importance of (1) critically interpreting indicators and distributions by age when using the 2007 WHO Growth Reference; (2) examining what is happening before and after adolescence, when interpretation of anthropometry is more straightforward, as well as trends over time; and (3) complementing anthropometry with other information, particularly dietary intake. Finally, we advocate that nutrition researchers prioritize exploration of better methods to predict peak height velocity, for development of standardized indicators to measure dietary quality among adolescents, and for studies that will illuminate causal paths so that we can effectively improve adolescent dietary intake and nutritional status.

Addressing knowledge gaps in adolescent nutrition: toward advancing public health and sustainable development

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Curr Dev Nutr 2019;3:nzz062

Abstract: Adolescence marks a critical period of growth in the life course. Malnutrition among adolescents includes suboptimal dietary intake of macronutrients and micronutrients as well as overweight and obesity linked to poor dietary quality. We discuss adolescent nutrition and outline 3 knowledge gaps toward advancing adolescent health. First, micronutrient and macronutrient

supplements have significant potential to improve nutritional status, but information on the most effective implementation strategies is lacking. Second, food system interventions offer a promising avenue to improve access to healthy foods, and school settings may be an important entry point for improving diets. Third, nutrition programs should be combined with delayed pregnancy interventions for greatest impact given the adverse effects of early pregnancy on maternal and infant health and nutrition outcomes. Evidence-based solutions for adolescent nutritional supplementation, food system and dietary intake interventions, and integration with sexual and reproductive health strategies present crucial opportunities for improving adolescent health and well-being.

Comments Improving the nutritional status of adolescents and young adults may better their present life, their future life, and that of their offspring. However, we still need to overcome some major methodological issues when evaluating this age group. These perspectives outline the knowledge gaps and challenges in diagnosing malnutrition and stunting in adolescents and in designing future studies on and effective interventions for these diagnoses. First of all, data required for developing adolescent growth standards are missing, yet these do not seem feasible to conduct a prospective, multicenter observational reference study similar to the WHO MRGS in adolescents. Additionally, significant differences in timing of puberty and peak height velocity interfere with the interpretation of existing data. Late outcomes of adolescent undernutrition cannot be properly assessed through cross-sectional studies as some undernourished adolescents experience very late catch-up growth. And finally, the BMIZ and HAZ cutoffs for the definition of wasting and stunting are not aligned with adult cutoffs for these same conditions, making it impossible to compare data on prevalence from different age groups. The authors highlight the need to find better methods to predict peak height velocity for the sake of cross-sectional surveys and the need for studies that will clarify causal paths and true outcomes so that we can effectively assess the barriers and develop solutions.

Nutritional Interventions to Prevent and Treat Malnutrition in Children

Preventive lipid-based nutrient supplements given with complementary foods to infants and young children 6–23 months of age for health, nutrition, and developmental outcomes

Das JK[1], Salam RA[1], Hadi YB[2], Sadiq Sheikh S[1], Bhutta AZ[3], Weise Prinzo Z[4], Bhutta ZA[5,6]

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Cochrane Database Syst Rev 2019;5:CD012611

Background: One nutritional intervention advocated to prevent malnutrition among children is lipid-based nutrient supplements (LNS). LNS provide a range of vitamins and minerals, but unlike

most other micronutrient supplements, LNS also provide energy, protein and essential fatty acids. Alternative recipes and formulations to LNS include fortified blended foods (FBF), which are foods fortified with vitamins and minerals, and micronutrient powders (MNP), which are a combination of vitamins and minerals.

Objectives: To assess the effects and safety of preventive LNS given with complementary foods on health, nutrition and developmental outcomes of non-hospitalised infants and children 6–23 months of age, and whether or not they are more effective than other foods (including FBF or MNP).

This review did not assess the effects of LNS as supplementary foods or therapeutic foods in the management of moderate and severe acute malnutrition.

Search Methods: In October 2018, we searched CENTRAL, MEDLINE, Embase, 21 other databases and 2 trials registers for relevant studies. We also checked the reference lists of included studies and relevant reviews and contacted the authors of studies and other experts in the area for any ongoing and unpublished studies.

Selection Criteria: Randomised controlled trials (RCTs) and quasi-RCTs that evaluated the impact of LNS plus complementary foods given at point-of-use (for any dose, frequency, duration) to non-hospitalised infants and young children aged 6–23 months in stable or emergency settings and compared to no intervention, other supplementary foods (i.e. FBF), nutrition counselling or multiple micronutrient supplements or powders for point-of-use fortification of complementary foods.

Data Collection and Analysis: Two review authors independently screened studies for relevance and, for those studies included in the review, extracted data, assessed risk of bias and rated the quality of the evidence using the GRADE approach. We carried out statistical analysis using Review Manager software. We used a random-effects meta-analysis for combining data as the interventions differed significantly. We set out the main findings of the review in "Summary of findings" tables.

Main Results: Our search identified a total of 8,124 records, from which we included 17 studies (54 papers) with 23,200 children in the review. The included studies reported on one or more of the pre-specified primary outcomes, and 5 studies included multiple comparison groups.

Overall, the majority of trials were at low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias, but at high risk of bias for blinding of participants and personnel due to the nature of the intervention. Using the GRADE approach, we judged the quality of the evidence for most outcomes as low or moderate.

LNS+Complementary Feeding Compared with no Intervention: Thirteen studies compared LNS plus complementary feeding with no intervention. LNS plus complementary feeding reduced the prevalence of moderate stunting by 7% (risk ratio [RR] 0.93, 95% CI 0.880.98; nine studies, 13,372 participants; moderate-quality evidence), severe stunting by 15% (RR 0.85, 95% CI 0.74–0.98; 5 studies, 6151 participants; moderate-quality evidence), moderate wasting by 18% (RR 0.82, 95% CI 0.74–0.91; 8 studies; 13,172 participants; moderate-quality evidence), moderate underweight by 15% (RR 0.85, 95% CI 0.80–0.91; 8 studies, 13,073 participants; moderate-quality evidence), and anaemia by 21% (RR 0.79, 95% CI 0.69–0.90; 5 studies, 2,332 participants; low-quality evidence). There was no impact of LNS plus complementary feeding on severe wasting (RR 1.27, 95% CI 0.66–2.46; 3 studies, 2,329 participants) and severe underweight (RR 0.78, 95% CI 0.54–1.13; 2 studies, 1,729 participants).

Adverse effects did not differ between the groups (RR 0.86, 95% CI 0.74–1.01; 3 studies, 3,382 participants).

LNS+Complementary Feeding Compared with FBF: Five studies compared LNS plus complementary feeding with other FBF, including corn soy blend and UNIMIX. We pooled 4 of the 5 studies in meta-analyses and found that, when compared to other FBF, LNS plus complementary feeding significantly reduced the prevalence of moderate stunting (RR 0.89, 95% CI 0.82–0.97; 3 studies, 2,828 participants; moderate-quality evidence), moderate wasting (RR 0.79, 95% CI 0.65–0.97; 2

studies, 2,290 participants; moderate-quality evidence), and moderate underweight (RR 0.81, 95% CI 0.73–0.91; 2 studies, 2,280 participants; moderate quality evidence). We found no difference between LNS plus complementary feeding and FBF for severe stunting (RR 0.41, 95% CI 0.12–1.42; 2 studies, 729 participants; low-quality evidence), severe wasting (RR 0.64, 95% CI 0.19–2.81; 2 studies, 735 participants; moderate-quality evidence), and severe underweight (RR 1.23, 95% CI 0.67–2.25; 1 study, 173 participants; low quality evidence).

LNS+Complementary Feeding Compared with MNP: Four studies compared LNS plus complementary feeding with MNP. We pooled data from 3 of the 4 studies in meta-analyses and found that compared to MNP, LNS plus complementary feeding significantly reduced the prevalence of moderate underweight (RR 0.88, 95% CI 0.78–0.99; 2 studies, 2,004 participants; moderate-quality evidence) and anaemia (RR 0.38, 95% CI 0.21–0.68; 2 studies, 557 participants; low-quality evidence). There was no difference between LNS plus complementary feeding and MNP for moderate stunting (RR 0.92, 95% CI 0.82–1.02; 3 studies, 2,365 participants) and moderate wasting (RR 0.97, 95% CI 0.77–1.23; 2 studies, 2,004 participants).

Authors' Conclusions: The findings of this review suggest that LNS plus complementary feeding compared to no intervention is effective at improving growth outcomes and anaemia without adverse effects among children aged 6–23 months in low- and middle-income countries (LMIC) in Asia and Africa, and more effective if provided over a longer duration of time (over 12 months). Limited evidence also suggests that LNS plus complementary feeding is more effective than FBF and MNP at improving growth outcomes.

Comments

Supplementary feeding is a strategy for providing extra food to children beyond their regular home diets. There are several common types of supplementary feeding designed to manage and improve malnutrition. One type is lipid-based nutrient supplements (LNS), a family of products that supply energy derived mainly from lipids in addition to a range of micronutrients, proteins, and essential fatty acids. LNS are nutrient-dense, require no cooking before use, and can be stored for months even in warm conditions. Other types of supplements include fortified blended foods (FBF) that are composed of cereals mixed with other ingredients, such as whey, soy protein isolate, dried skimmed milk, sesame, cashews, and chickpea paste, fortified with vitamins and minerals, and multiple micronutrient powders (MNP), supplied as single-dose packets of vitamins and minerals in powder form that can be spread on any ready-to-eat semi-solid food.

In 2019, a Cochrane systematic review by Das et al. [7] suggested that LNS plus complementary feeding is a safe and effective intervention for improving growth outcomes and anemia in healthy, nonhospitalized children aged 6–23 months. The intervention seemed to be more effective if provided for longer than 1 year. Although the data comparing LNS plus complementary feeding with other nutritional interventions were sparse, the authors found limited evidence that intervention with LNS plus complementary feeding probably reduces moderate stunting, moderate wasting, and moderate underweight compared to FBF and is probably more effective than MNP at reducing moderate underweight and improving height and weight. They also provided several directions for future studies to fill research gaps in the field. These include analyses of the impact of LNS and other nutritional interventions on psychomotor and neurodevelopmental outcomes, comparison of different nutritional interventions (different products as well as nutrition education alone), and further investigations of the long-term impact of different nutritional interventions on growth and development.

Ready-to-Use Therapeutic Food (RUTF) for home-based nutritional rehabilitation of severe acute malnutrition in children from six months to five years of age

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Background: Management of severe acute malnutrition (SAM) in children comprises 2 potential phases: stabilisation and rehabilitation. During the initial stabilisation phase, children receive treatment for dehydration, electrolyte imbalances, intercurrent infections and other complications. In the rehabilitation phase (applicable to children presenting with uncomplicated SAM or those with complicated SAM after complications have been resolved), catch-up growth is the main focus and the recommended energy and protein requirements are much higher. In-hospital rehabilitation of children with SAM is not always desirable or practical – especially in rural settings – and home-based care can offer a better solution. Ready-to-use therapeutic food (RUTF) is a widely used option for home-based rehabilitation, but the findings of our previous review were inconclusive.

Objectives: To assess the effects of home-based RUTF used during the rehabilitation phase of SAM in children aged between 6 months and 5 years on recovery, relapse, mortality and rate of weight gain.

Search Methods: We searched the following databases in October 2018: CENTRAL, MEDLINE, Embase, 6 other databases and 3 trials registers. We ran separate searches for cost-effectiveness studies, contacted researchers and healthcare professionals in the field, and checked bibliographies of included studies and relevant reviews.

Selection Criteria: Randomised controlled trials (RCTs) and quasi-RCTs, where children aged between 6 months and 5 years with SAM were, during the rehabilitation phase, treated at home with RUTF compared to an alternative dietary approach, or with different regimens and formulations of RUTF compared to each other. We assessed recovery, deterioration or relapse and mortality as primary outcomes; and rate of weight gain, time to recovery, anthropometrical changes, cognitive development and function, adverse outcomes and acceptability as secondary outcomes.

Data Collection and Analysis: We screened for eligible studies, extracted data and assessed risk of bias of those included, independently and in duplicate. Where data allowed, we performed a random-effects meta-analysis using Review Manager 5, and investigated substantial heterogeneity through subgroup and sensitivity analyses. For the main outcomes, we evaluated the quality of the evidence using GRADE, and presented results in a 'Summary of findings' table per comparison.

Main Results: We included 15 eligible studies (n = 7,976; effective sample size = 6,630), four of which were cluster trials. Eight studies were conducted in Malawi, 4 in India, and 1 apiece in Kenya, Zambia, and Cambodia. Six studies received funding or donations from industry whereas 8 did not, and one study did not report the funding source. The overall risk of bias was high for 6 studies, unclear for 3 studies, and low for 6 studies. Among the 14 studies that contributed to meta-analyses, none (n = 5), some (n = 5) or all (n = 4) children were stabilised in hospital prior to commencement of the study. One small study included only children known to be HIV-infected, another study stratified the analysis for "recovery" according to HIV status, while the remaining studies included HIV-uninfected or untested children. Across all studies, the intervention lasted between 8 and 16 weeks. Only 5 studies followed up children postintervention (maximum of 6 months), and generally reported on a limited number of outcomes. We found 7 studies with 2,261 children comparing

home-based RUTF meeting the World Health Organization (WHO) recommendations for nutritional composition (referred to in this review as standard RUTF) with an alternative dietary approach (effective sample size = 1,964). RUTF probably improves recovery (risk ratio [RR] 1.33; 95% CI 1.16 to 1.54; 6 studies, 1,852 children; moderate-quality evidence), and may increase the rate of weight gain slightly (mean difference [MD] 1.12 g/kg/day, 95% CI 0.27 to 1.96; 4 studies, 1,450 children; low-quality evidence), but we do not know the effects on relapse (RR 0.55, 95% CI 0.30 to 1.01; 4 studies, 1,505 children; very low-quality evidence) and mortality (RR 1.05, 95% CI 0.51 to 2.16; 4 studies, 1,505 children; very low-quality evidence). Two quasi-randomised cluster trials compared standard, home-based RUTF meeting total daily nutritional requirements with a similar RUTF but given as a supplement to the usual diet (213 children; effective sample size = 210). Meta-analysis showed that standard.

RUTF meeting total daily nutritional requirements may improve recovery (RR 1.41, 95% CI 1.19 to 1.68; low quality evidence) and reduce relapse (RR 0.11, 95% CI 0.01 to 0.85; low-quality evidence), but the effects are unknown for mortality (RR 1.36, 95% CI 0.46 to 4.04; very low-quality evidence) and rate of weight gain (MD 1.21 g/kg/day, 95%CI – 0.74 to 3.16; very low-quality evidence).

Eight studies randomised 5,502 children (effective sample size = 4456) and compared standard home-based RUTF with RUTFs of alternative formulations (e.g., using locally available ingredients, containing less or no milk powder, containing specific fatty acids, or with added pre- and probiotics). For recovery, it made little or no difference whether standard or alternative formulation RUTF was used (RR 1.03, 95% CI 0.99 to 1.08; 6 studies, 4,188 children; high-quality evidence). Standard RUTF decreases relapse (RR 0.84, 95% CI 0.72 to 0.98; 6 studies, 4,188 children; high-quality evidence). However, it probably makes little or no difference to mortality (RR 1.00, 95% CI 0.80 to 1.24; 7 studies, 4,309 children; moderate-quality evidence) and may make little or no difference to the rate of weight gain (MD 0.11 g/kg/day, 95% CI −0.32 to 0.54; 6 studies, 3,807 children; low-quality evidence) whether standard or alternative formulation RUTF is used.

Authors' Conclusions: Compared to alternative dietary approaches, standard RUTF probably improves recovery and may increase rate of weight gain slightly, but the effects on relapse and mortality are unknown. Standard RUTF meeting total daily nutritional requirements may improve recovery and relapse compared to a similar RUTF given as a supplement to the usual diet, but the effects on mortality and rate of weight gain are not clear. When comparing RUTFs with different formulations, the current evidence does not favour a particular formulation, except for relapse, which is reduced with standard RUTF. Well-designed, adequately powered, pragmatic RCTs with standardized outcome measures, stratified by HIV status, and that include diarrhoea as an outcome, are needed.

Comments

Ready-to-use therapeutic food (RUTF) is a widely used strategy for home-based rehabilitation of children with severe acute malnutrition (SAM). The products are energy-dense and typically include milk powder, sugar, peanut butter, vegetable oil, vitamins, and minerals. They are usually made according to a standard composition defined by the WHO. RUTF may serve as complete nutrition that meets all the nutritional requirements of a child recovering from SAM or as a supplement to the usual family diet. It requires no preparation and has long shelf-life without refrigeration. RUTF is available as a homogenous paste for consumption by children as young as 6 months or as a solid product that can be soaked in clean, boiling water to form porridge for young infants or consumed as a biscuit by older children.

A Cochrane systematic review by Schoonees et al. [8] suggested that RUTF probably improves recovery from malnutrition and may increase the rate of weight gain compared to alternative dietary approaches. However, its effects on relapse and mortality are unknown. The authors emphasize several limitations of existing studies, namely,

absence of a clear definition of SAM, use of different outcome measures (such as recovery and anthropometric outcomes), and lack of data on adverse effects (such as diarrhea and allergic reactions), compliance, and cost-effectiveness.

Community-based supplementary feeding for food insecure, vulnerable and malnourished populations: An overview of systematic reviews

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Background: Supplementary feeding may help food insecure and vulnerable people by optimising the nutritional value and adequacy of the diet, improving quality of life and improving various health parameters of disadvantaged families. In low- and middle-income countries (LMIC), the problems supplementary feeding aims to address are entangled with poverty and deprivation, the programmes are expensive and delivery is complicated.

Objectives: (1) To summarize the evidence from systematic reviews of supplementary feeding for food insecure, vulnerable and malnourished populations, including children under 5 years of age, school-aged children, pregnant and lactating women, people with HIV or tuberculosis (or both), and older populations. (2) To describe and explore the effects of supplementary feeding given to people in these groups, and to describe the range of outcomes between reviews and range of effects in the different groups.

Methods: In January 2017, we searched the Cochrane Database of Systematic Reviews, MEDLINE, Embase and nine other databases. We included systematic reviews evaluating community-based supplementary feeding, and concerning food insecure, vulnerable and malnourished populations. Two review authors independently undertook selection of systematic reviews, data extraction and "Risk of bias" assessment. We assessed review quality using the AMSTAR tool, and used GRADEpro "Summary of findings" tables from each review to indicate the certainty of the evidence for the main comparisons. We summarised review findings in the text and reported the data for each outcome in additional tables. We also used forest plots to display results graphically.

Main Results: This overview included eight systematic reviews (with last search dates between May 2006 and February 2016). Seven were Cochrane Reviews evaluating interventions in pregnant women; children (aged from birth to 5 years) from LMIC; disadvantaged infants and young children (aged 3 months to 5 years); children with moderate acute malnutrition (MAM); disadvantaged school children; adults and children who were HIV positive or with active tuberculosis (with or without HIV). One was a non-Cochrane systematic review in older people with Alzheimer's disease. These reviews included 95 trials relevant to this overview, with the majority (74%) of participants from LMIC. The number of included participants varied between 91 and 7,940 adults, and 271 and more than 12,595 children. Trials included a wide array of nutritional interventions that varied in duration, frequency and format, with micronutrients often reported as cointerventions. Follow-up ranged from 6 weeks to 2 years; 3 trials investigated outcomes at 4–17 years of age. All reviews were rated as high quality (AMSTAR score between 8 and 11). The GRADE certainty ratings ranged from very low to moderate for individual comparisons, with the evidence often comprising only 1 or 2 small trials, thereby resulting in many underpowered analyses (too small to detect small but important differences). The main outcome categories reported across reviews were death, anthropometry (adults and children) and other markers of nutritional status, disease-related outcomes, neurocogni-

tive development and psychosocial outcomes, and adverse events. Mortality data were limited and underpowered in meta-analysis in all populations (children with MAM, in children with HIV, and in adults with tuberculosis) with the exception of balanced energy and protein supplementation in pregnancy, which may have reduced the risk of stillbirth (risk ratio [RR] 0.60, 95% CI 0.39–0.94; 5 trials, 3,408 women). Supplementation in pregnancy also improved infant birth weight (mean difference [MD] 40.96 g, 95% CI 4.66–77.26; 11 trials, 5,385 participants) and reduced risk of infants born small-for-gestational age (RR 0.79, 95% CI 0.69–0.90; 7 trials, 4,408 participants). These effects did not translate into demonstrable long-term benefits for children in terms of growth and neurocognitive development in the 1–2 trials reporting on longer-term outcomes. In one study (505 participants), high-protein supplementation was associated with increased risk of small-for-gestational age babies. Effects on growth in children were mixed. In children under 5 years of age from LMIC, one review found that supplementary feeding had a little or no effect on child growth; however, a more recent review in a similar population found that those who received food supplementation gained an average of 0.12 kg more in weight (MD 0.12 kg, 95% CI 0.05–0.18; 9 trials, 1,057 participants) and 0.27 cm more in height (MD 0.27 cm, 95% CI 0.07–0.48; 9 trials, 1,463 participants) than those who were not supplemented. Supplementary food was generally more effective for younger children (younger than 2 years of age) and for those who were poorer or less well-nourished. In children with MAM, the provision of specially formulated food improved their weight, weight-for-height z scores and other key outcomes such as recovery rate (by 29%), as well as reducing the number of participants dropping out (by 70%). In LMIC, school meals seemed to lead to small benefits for children, including improvements in weight z scores, especially in children from lower-income countries, height z scores, cognition or intelligence quotient tests, and maths and spelling performance. Supplementary feeding in adults who were HIV positive increased the daily energy and protein intake compared to nutritional counselling alone. Supplementation led to an initial improvement in weight gain or body mass index but did not seem to confer long-term benefit. In adults with tuberculosis, one small trial found a significant benefit on treatment completion and sputum conversion rate. There were also significant but modest benefits in terms of weight gain (up to 2.60 kg) during active tuberculosis. The one study included in the Alzheimer's disease review found that 3 months of daily oral nutritional supplements improved nutritional outcomes in the intervention group. There was little or no evidence regarding people's quality of life, adherence to treatment, attendance at clinic or the costs of supplementary feeding programmes.

Authors' Conclusions: Considering the current evidence base included, supplementary food effects are modest at best, with inconsistent and limited mortality evidence. The trials reflected in the reviews mostly reported on short-term outcomes and across the whole of the supplementation trial literature it appears important outcomes, such as quality of life and cost of programmes, are not systematically reported or summarized.

Comments Visser et al. [9] conducted a Cochrane database review of published systematic reviews to summarize the current evidence on the effectiveness of supplementary feeding for food-insecure, vulnerable, and malnourished populations, including children, pregnant and lactating women, people with HIV or tuberculosis, and the elderly. The main results relevant to the present chapter were mixed. In children under 5 years of age from low- and middle-income countries, supplementary feeding seems to have a small impact on growth. The benefits observed include weight and height gains, especially in younger children (<2 years old) and poorer or more undernourished children. Some benefit could also be seen in children with moderate acute malnutrition (MAM) in terms of weight gain, improvement of other growth outcomes, and recovery rate. In schoolchildren, school meals seemed to promote small improvements in weight, height, intelligence test scores, and school performance. The authors con-

clude that the current evidence-based data on the effectiveness of supplementary food are modest at best, and findings on mortality are inconsistent and limited. Most of the studies were short term and did not investigate adherence to treatment, quality of life, or costs. The authors emphasize that to address the complex and multidimensional nature of food insecurity and malnutrition, an integrated approach is needed, combining supplementary feeding with other interventions. They list several important aspects to be considered in the development of a nutrition-based program for the prevention and treatment of malnutrition. These include targeting participants who are undernourished and vulnerable; selecting the place of administration (on-site versus home) that will minimize leakage, promote adherence, and allow for proper supervision; providing sufficient energy and nutrients (at least 30% of the dietary reference intakes); and starting early (in infants and children) to optimize benefit.

Effectiveness of provision of animal-source foods for supporting optimal growth and development in children 6–59 months of age

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Background: Adequate nutrients early in life promote cognitive development and are critical for proper growth and functioning. The effect of individual nutrients consumed through food is often not the same as consuming the same nutrients in supplementary form due to "food synergy," the biological and chemical interrelations that occur between nutrients. Animal-source foods, such as eggs, meat, fish, and dairy, are energy dense and contain multiple micronutrients and essential fatty acids with high bioavailability. The benefits of animal-source foods may include higher food synergy relative to fortified foods as well as decreasing dependence on external suppliers of fortified foods.

Objectives: To assess the effectiveness of animal-source foods compared to any other feeding interventions or no intervention in improving growth and developmental outcomes in children aged 6–59 months.

Search Methods: We searched CENTRAL, MEDLINE, Embase, CINAHL, 18 other databases, and 3 trials registers up to August 2018. We also contacted authors and known experts in the field for assistance in identifying ongoing or unpublished data, and searched the reference lists of included studies and reviews, and websites of relevant organizations, for other studies that may not have been captured by our electronic searches.

Selection Criteria: We included randomized controlled trials and quasi-randomized controlled trials of any duration, where children between 5 and 59 months (6 years) of age were provided with an animal-source food (e.g., consumption of milk, meat, or eggs), prepared with any cooking method, compared with any intervention or no intervention.

Data Collection and Analysis: Two review authors independently assessed trial eligibility using prespecified criteria, extracted data, assessed risk of bias, and graded the quality of the evidence using the GRADE approach.

Main Results: Study characteristics – We included 6 studies that analyzed data from 3,036 children aged 5–50 months. The studies were conducted in China, the Democratic Republic of Congo, Ecuador, Guatemala, Pakistan, the USA, and Zambia, and lasted between 5 and 12 months. Three studies were funded, in part, by government entities; one study was supported by a nonprofit organization. Two studies did not report a funding source. Three studies compared the effects of feeding an animal-source food with a fortified (iron or iron and zinc), or unfortified cereal; two used a control group with no intervention; one compared a meat-based diet to a dairy-based diet. The types of animal-source foods tested included yogurt, eggs, cheese, lyophilized (freeze-dried) beef product, ground and frozen pork, puréed and jarred beef with gravy or pork, and powdered whey protein. We judged 4 studies to be at unclear risk of bias overall; 3 studies because they were funded by an industry with a plausible interest in the outcome of the intervention; and one study because there was insufficient information to assess 5 of the 7 bias "Risk of bias" domains. We judged 2 of the 6 studies to be at high risk of bias overall; one study because there was significant baseline imbalance in length-for-age z scores (LAZ) between groups and evidence of selective reporting; the other study because there was both a significant baseline imbalance in LAZ and weight-for-age z scores (WAZ) between groups, and a large-scale social media campaign that may have influenced care received at home in the control group.

Key Results: *– Animal-source foods versus cereal-based foods or no intervention*

Five studies (2,972 children) measured change in linear growth with either height-for-age z scores (HAZ) or LAZ. Three studies (592 children) reported a significant increase in HAZ and LAZ in the intervention group compared to the control group. Two studies (2,380 children) reported a decline in LAZ in both groups. In one study (1,062 children) there was no difference between the groups in the rate of decline; in the other (1,318 children) the decrease in LAZ was significantly smaller in the intervention group. Five studies (2,972 children) measured weight gain using WAZ. Three studies (592 children) reported a significant increase in WAZ in the intervention group compared to the control group. In 2 studies (2380 children), WAZ decreased in both groups. In one of these studies (1,318 children), the decrease in the intervention group was significantly smaller than in the control group. In the other study (1,062 children), there was no difference between the groups. Three studies (1,612 children) reported impacts on all-cause morbidity, but metrics were inconsistent between studies. One study with yogurt (402 children) reported a significant reduction in duration and incidence of diarrhea and upper respiratory infections in the intervention group. One study with eggs (148 children) reported a significant increase in the incidence of diarrhea in the intervention group, but this may have been due to cultural associations with eggs and gastrointestional problems. There were no other significant differences in fever, respiratory infections, or skin conditions between groups. The third study (1,062 children) found no differences between intervention and control groups across morbidity measures. No studies reported data on anemia.

Meat-based diet versus dairy-based diet. One study (64 children) measured change in LAZ and WAZ in infants fed either a meat-based diet or dairy-based diet. There was a significant increase in LAZ among infants consuming the meat-based diet and a significant decrease in LAZ among infants consuming a dairy-based diet. WAZ increased in both groups, with no significant difference between groups. The study did not assess all-cause morbidity or anemia.

Quality of the evidence. We rated the quality of the evidence as very low overall due to baseline imbalances between intervention and control groups, high heterogeneity in meta-analysis, and imprecision due to wide confidence intervals and inconsistent direction of effects. We have little confidence in the results; further research is likely to change the estimate of magnitude and direction of treatment effect.

Authors' Conclusion: Given the limited quality of the evidence, we are uncertain of the effects of the provision of animal-source food versus cereal products or no intervention on the growth or development of children. More adequately powered trials with deliberately selected animal-source foods are needed.

Consumption of animal-source protein is associated with improved height-for-age z scores in rural Malawian children aged 12–36 months

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Abstract: Linear growth faltering, caused by insufficient diet, recurrent infections and environmental enteric dysfunction (EED), continues to plague young children in low- and middle-income countries (LMICs). Diets in LMICs are primarily plant based, and thus have poor-quality protein and low levels of essential micronutrients. The aim of this study was to assess the association of the type and protein quality of food consumed with stunting, EED and acute malnutrition in children aged 6–36 months in Limera and Masenjere, 2 rural Southern Malawian communities. This is a secondary analysis of 2 randomized controlled trials that tested the effects of common bean and cowpea flour on stunting in children aged 6–36 months. We used data from 2 interactive 24-h dietary recalls conducted 12 weeks after enrolment into each trial. Food intakes were compared between the regions using chi-square and Student *t* test. There were 355 children that participated in the dietary recalls. The diets of children were of poor quality, but the children from Limera consumed more fish (54 vs. 35%, $p = 0.009$) and more bioavailable protein (26.0 ± 10.3 vs. 23.1 ± 8.1 g/day, $p = 0.018$, respectively) than children in Masenjere. Food type and protein quality were not associated with any of the outcomes except an association between animal protein consumption and improvement in height-for-age z scores in children aged 12–36 months ($p = 0.047$). These findings support the notion that animal-source food (ASF) consumption in this vulnerable population promotes linear growth.

Maximizing recovery and growth when treating moderate acute malnutrition with whey-containing supplements

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Food Nutr Bull 2018;39(suppl 2):S30–S34

Background: Much debate exists about the utility of dairy ingredients in the supplementary foods used to treat childhood moderate acute malnutrition (MAM).

Objective: To review the evidence regarding the effectiveness of dairy-containing supplements, particularly specially formulated foods containing whey permeate and whey protein concentrate, in treating children with MAM.

Methods: A summary of a conference presentation regarding an overview of current evidence behind the use of whey in supplementary foods, including results of a randomized double-blinded clinical effectiveness trial involving 2,259 Malawian children treated for MAM using either a soy ready-to-use supplementary food (RUSF) or a novel whey RUSF treatment.
Results: While the majority of the evidence base only suggests potential benefits of including whey in supplementary foods to treat MAM, a recent study specifically demonstrates that a whey RUSF produced superior recovery and growth outcomes in treating children with MAM when compared with a soy RUSF.
Conclusions: The use of whey ingredients has been shown to improve outcomes in the treatment of MAM; however, further research is needed to identify the ideal amount and type of dairy protein required to produce the best outcomes for the lowest cost.

Higher levels of dairy result in improved physical outcomes: a synthesis of 3 randomized controlled trials in Guinea-Bissau comparing supplements with different levels of dairy ingredients among children 6–59 months, 5–19 year olds, and mothers in preschools, primary schools, and villages, and the implications for programs

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Background: This article synthesizes the results of 3 cluster randomized controlled trials of dairy-containing ready-to-use supplementary foods (RUSFs) to treat malnutrition in primary schools, preschools and villages in Guinea-Bissau, one of the world's poorest countries. Together, these studies document widespread malnutrition across infants, young children, adolescents, and pregnant and lactating women and point to intervention options that were not previously presented.
Objective: To combine the evidence from the United States Department of Agriculture-funded pilot studies in Guinea-Bissau on the effects of dairy protein supplementation to gain a broader perspective on the role of dairy containing RUSFs in various age-groups, the importance of the mother-child dyad and family food dynamics for infant and child growth. Translate the results into action and the next generation of effective products.
Methods: A comparative analysis of data and synthesis of evidence from 3 published studies and ongoing research conducted by our team in Guinea-Bissau.
Results and Conclusions: Higher dairy supplements have the potential to achieve broad benefits for malnutrition, especially in mothers and early childhood (first 1,000 days and 36–59 months).

Higher levels of dairy protein also can prevent moderate acute malnutrition in children younger than 2 years, independent of the family food dynamic. Community-level nutrition behavior change education should target older children and adolescents at the community level and through the preschool/school platform.

Comments Both the quality and quantity of protein are known to be important for growth in children. Eggs, meat, fish, and dairy are good sources of high-quality proteins and contain multiple micronutrients and essential fatty acids with high bioavailability. Numerous studies have suggested that animal-source protein improves nutritional outcomes in

undernourished populations [17]. Several papers [10–13], including one Cochrane systematic review [10], published in the last year focused on the role of animal-source protein in the prevention and treatment of malnutrition in high-risk pediatric populations from low-income regions.

A Cochrane systematic review by Eaton et al. [10] compared the effectiveness of animal-source foods with any other feeding interventions or no intervention in improving growth and developmental outcomes in children aged 6–59 months. Of the 6 studies included, 5 (total 2,972 children) measured changes in linear growth and weight. Four studies reported a significant superiority for the animal-based intervention group compared to the control group in the changes of linear growth and weight, and one found no between-group differences. However, the authors rated the quality of the evidence as very low owing to baseline imbalances between the intervention and control groups and the high heterogeneity in the meta-analysis. As a result, they report little confidence in the results and highlight the need for more high-quality randomized control trials with deliberately selected animal-source foods.

A study by Kaimila et al. [11] assessed the association of the source and quality of nutritional protein with stunting, environmental enteric dysfunction (EED), and acute malnutrition in children aged 6–36 months residing in 2 rural Southern Malawian communities, Limera and Masenjere. The children from Limera consumed a higher amount of protein from animal sources (mainly fish), and this was found to be associated with better linear growth at ages 12–36 months. Overall, these results suggest that populations in regions characterized by higher consumption of animal-source proteins have lower rates of stunting, acute malnutrition, and EED than populations from areas with lower consumption of these foods, regardless of the level of nutrient intake and the quality of sanitation practices. Furthermore, although the children from Masenjere had a higher dietary diversity score and more of them met the minimum required dietary diversity compared to the children from Limera, their rate of stunting was higher. This observation suggests that the source of the protein may be more important than the diversity of the diet for improving anthropometric status. However, it contrasts with other studies reporting a positive association between higher dietary diversity and improved anthropometric outcomes [18–20]. Additional studies of this issue are warranted.

Milk and dairy products are known to be important for growth in children [21]. Both interventional and observational studies [21–24] have provided evidence that milk products positively affect linear growth. However, the exact mechanisms by which they do so remain unclear. Potential contributory factors are bioactive peptides found in milk proteins, insulin-like growth factor, and various minerals, including calcium and zinc [25]. The milk proteins whey and casein are very high-quality proteins and are rich in branched-chain amino acids (BCAA) [26]. BCAA are metabolized by muscle, promoting protein synthesis and reducing the need to break down lean tissue for energy. This is important in the recovery from acute malnutrition, in which one of the goals is to build lean tissue mass [26]. Milk proteins, especially whey, also exert several general health benefits via their enhancement of immune system responses [26]. Whey protein is particularly advantageous because it is water soluble, mixes easily, and is rapidly digested [27].

A recent randomized, double-blind controlled clinical trial by Stobaugh et al. [12, 28] studied the effectiveness of whey-based compared to soy-based ready-to-use supplementary food (RUSF) on recovery from MAM in 2,259 Malawian children. The total amount of protein provided by the soy-based RUSF was approximately 50% higher than that of the whey-based RUSF for each dose received. Nevertheless, compared to

the patients fed the soy-based RUSF, the whey-based RUSF group had a higher rate of recovery in addition to better secondary growth outcomes. Thus, although the whey-based RUSF contained less protein and energy than the soy-based RUSF, it was more effective in children with MAM.

These findings were supported in a recent paper by Schlossman [13] summarizing the results of 3 cluster randomized controlled studies of the effectiveness of dairy-based RUSF in preventing malnutrition in infants, young children, adolescents, and pregnant and lactating women. The studies were conducted in Guinea-Bissau, one of the world's poorest countries. Participants were recruited from preschools, schools, and village health centers and assigned to 2 intervention groups and a control group. The first intervention group received RUSF in which 15% of the protein was derived from dairy (whey), and the second group received RUSF in which 33% of the protein was derived from dairy (50% whey and 50% nonfat dry milk), with the balance of the protein from soy isolate. The nutritional profile of the RUSFs was otherwise identical. The control group did not receive RUSF. The authors found that the supplements higher in dairy protein had a potential to achieve broad benefits in the treatment and prevention of MAM in all the age groups studied, and especially in mothers and young children. Furthermore, intake of the higher dairy protein supplements was associated with fewer reported illnesses in children. According to these results, 15% protein from dairy is probably not enough. More research is needed to determine the optimal protein content for optimal physical as well as for cognitive development.

To conclude, this review of the 2018 published data on nutritional interventions for the prevention and treatment of malnutrition in children provides a comprehensive survey of the existing literature in the field. The Cochrane database studies (3 systematic reviews and 1 overview) [7–10] show that supplementary feeding is an effective strategy to prevent and treat malnutrition in young children from vulnerable populations. Specifically, the data suggest that effective and safe interventions for improving growth outcomes in malnourished young children should include LNS plus complementary feeding. Furthermore, RUTF improves recovery from malnutrition. The standard RUTF that meets the total daily nutritional requirements may be more effective for recovery than RUTF given as a supplement to the usual diet. Animal-source proteins and milk proteins improve nutritional outcomes in undernourished populations and are probably superior to other protein sources.

However, all the Cochrane systematic reviews listed several major limitations to the included studies and assigned most of them a low or moderate quality-of-evidence rating. The main limitations were a high risk of bias for blinding of participants and personnel owing to the nature of the intervention, report of only short-term outcomes, and failure to address some important outcome factors, such as compliance, adverse events, mortality, psychomotor and neurological development, quality of life, and cost. Furthermore, there was a large heterogeneity among the nutritional intervention protocols in terms of duration, format, and nutrient composition, precluding conclusions regarding specific supplementary foods or practices. Visser et al. [9], in their summary of Cochrane systematic reviews, called for new studies focusing on relevant and understudied outcomes, with follow-up over longer periods of time (>2 years). They emphasized the need for investigations of approaches that integrate supplementary feeding programs with other interventions to address the complex issues of malnutrition and food insecurity.

Gut microbiota alterations and dietary modulation in childhood malnutrition: The role of short chain fatty acids

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Abstract: The gut microbiome affects the health status of the host through different mechanisms and is associated with a wide variety of diseases. Both childhood undernutrition and obesity are linked to alterations in composition and functionality of the gut microbiome. One of the possible mechanisms underlying the interplay between microbiota and host metabolism is through appetite-regulating hormones (including leptin, ghrelin, glucagon-like peptide-1). Short-chain fatty acids, the end product of bacterial fermentation of non-digestible carbohydrates, might be able to alter energy harvest and metabolism through enteroendocrine cell signaling, adipogenesis and insulin-like growth factor-1 production. Elucidating these mechanisms may lead to development of new modulation practices of the gut microbiota as a potential prevention and treatment strategy for childhood malnutrition. The present overview will briefly outline the gut microbiota development in the early life, gut microbiota alterations in childhood undernutrition and obesity, and whether this relationship is causal. Further we will discuss possible underlying mechanisms in relation to the gut-brain axis and short chain fatty acids, and the potential of probiotics, prebiotics and synbiotics for modulating the gut microbiota during childhood as a prevention and treatment strategy against undernutrition and obesity.

Comments There is a bidirectional relationship between the microbiome and childhood malnutrition: undernutrition interferes with the maturation and diversity of the microbiome, while microbial dysbiosis adversely affects the host's susceptibility to enteric infection, chronic inflammation, and other important mechanisms related to weight gain and growth. One of the ways in which the gut microbiota may exert its effect on the host's nutritional status is by the production and utilization of short-chain fatty acids (SCFAs). This review focuses on the different pathways in which SCFAs could be involved: enteroendocrine signaling and appetite control; the IGF-1 axis; providing a source of energy for colonic cells; and helping to maintain the epithelial gut barrier. This review provides an interesting perspective on the interplay between the microbiome and malnutrition.

A sparse covarying unit that describes healthy and impaired human gut microbiota development

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Abstract: Characterizing the organization of the human gut microbiota is a formidable challenge given the number of possible interactions between its components. Using a statistical approach initially applied to financial markets, we measured temporally conserved covariance among bacterial taxa in the microbiota of healthy members of a Bangladeshi birth cohort sampled from 1 to 60 months of age. The results revealed an "ecogroup" of 15 covarying bacterial taxa that provide a concise description of microbiota development in healthy children from this and other low-income countries, and a means for monitoring community repair in undernourished children treated with therapeutic foods. Features of ecogroup population dynamics were recapitulated in gnotobiotic piglets as they transitioned from exclusive milk feeding to a fully weaned state consuming a representative Bangladeshi diet.

Comments Important cohort study from a low- and middle-income country defining the taxonomy of healthy microbiota in a cohort of healthy children (under 5 years of age) with no growth failure. The findings are comparable to those observed from microbiota maturation among healthy children in Peru. Given the importance of microbiome in health and growth and potential interventions, these findings help develop standards and criteria for monitoring and evaluation and potential benchmarks for defining uptake and change. The findings of the 15 co-varying bacterial taxa need to be validated through additional studies in Asia (such as the MalED cohort) and also compared with findings from Africa in cohorts with healthy children without growth failure.

Effects of microbiota-directed foods in gnotobiotic animals and undernourished children

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Abstract: To examine the contributions of impaired gut microbial community development to childhood undernutrition, we combined metabolomic and proteomic analyses of plasma samples with metagenomic analyses of fecal samples to characterize the biological state of Bangladeshi children with severe acute malnutrition (SAM) as they transitioned, after standard treatment, to moderate acute malnutrition (MAM) with persistent microbiota immaturity. Host and microbial effects of microbiota-directed complementary food (MDCF) prototypes targeting weaning-phase bacterial taxa underrepresented in SAM and MAM microbiota were characterized in gnotobiotic mice and gnotobiotic piglets colonized with age- and growth-discriminatory bacteria. A randomized, double-blind controlled feeding study identified a lead MDCF that changes the abundances of targeted bacteria and increases plasma biomarkers and mediators of growth, bone formation, neurodevelopment, and immune function in children with MAM.

Comments Landmark study from a cohort of Bangladeshi children with moderate acute malnutrition identifying and validating the benefit of diets that improved the microbiome (based on preidentified bacterial taxa in the same population and also among healthy children in Peru) and biomarkers of growth and immune function. The work was systematic in identifying types of diets that led to improvement and normalization of microbiota in gnotobiotic animals (mice and piglets) as well as molecular signals of improved

growth and immune function. When tested among a small cohort of 60 malnourished children in Bangladesh over a 1-month period, the diet (based on chickpea, banana, and soy and peanut flours) helped the microbiomes mature and improve the molecular signals for healthy growth. These important findings point the way for longer-term studies of dietary (and other) approaches to prevent growth failure and reduce enteropathy of malnutrition among young children in low- and middle-income countries.

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Pregnancy: Impact of Maternal Nutrition on Intrauterine Fetal Growth

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Introduction

This chapter of the Yearbook on Nutrition and Growth reviews major studies published between July 2019 and June 2019 addressing the issue of the influence of maternal nutrition during pregnancy on intrauterine fetal growth. For the current edition, we carefully selected human studies, mainly of prospective design, along with several animal studies dealing with the effect of maternal dietary patterns at different stages of pregnancy or the use of nutrient supplementations on fetal growth and metabolic programming. Hopefully, this chapter will assist clinicians, researchers, and other healthcare providers, who are involved in prenatal and postnatal care, to update their knowledge on the effect of various intervention options and their effect on fetal growth and development.

Key articles reviewed for this chapter

Human Studies

Dietary patterns before and during pregnancy and birth outcomes: a systematic review

Raghavan R, Dreibelbis C, Kingshipp BL, Wong YP, Abrams B, Gernand AD, Rasmussen KM, Siega-Riz AM, Stang J, Casavale KO, Spahn JM, Stoody EE

Am J Clin Nutr 2019;109(suppl 7):729S–756S

Development of a novel Periconceptual Nutrition Score (PENS) to examine the relationship between maternal dietary quality and fetal growth

Kennedy RAK, Turner MJ

Early Hum Dev 2019;132:6–12

A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the women first trial

Hambidge KM, Westcott JE, Garcés A, Figueroa L, Goudar SS, Dhaded SM, Pasha O, Ali SA, Tshefu A, Lokangaka A, Derman RJ, Goldenberg RL, Bose CL, Bauserman M, Koso-Thomas M, Thorsten VR, Sridhar A, Stolka K, Das A, McClure EM, Krebs NF

Am J Clin Nutr 2019;109:457–469

Role of maternal preconception nutrition on offspring growth and risk of stunting across the first 1,000 days in Vietnam: A prospective cohort study

Young MF, Nguyen PH, Gonzalez Casanova I, Addo OY, Tran LM, Nguyen S, Martorell R, Ramakrishnan U

PLoS One 2018;13:e0203201

Maternal fruit and vegetable or vitamin C consumption during pregnancy is associated with fetal growth and infant growth up to 6 months: results from the Korean Mothers and Children's Environmental Health (MOCEH) cohort study

Jang W, Kim H, Lee BE, Chang N

Nutr J 2018;17:105

The impact of restricted gestational weight gain by dietary intervention on fetal growth in women with gestational diabetes mellitus

Kurtzhals LL, Nørgaard SK, Secher AL, Nichum VL, Ronneby H, Tabor A, McIntyre HD, Damm P, Mathiesen ER

Diabetologia 2018;61:2528–2538

Animal Studies

Effects of high-fat diets on fetal growth in rodents: a systematic review

Christians JK, Lennie KI, Wild LK, Garcha R

Reprod Biol Endocrinol 2019;17:39

Evidence for liver energy metabolism programming in offspring subjected to intrauterine undernutrition during midgestation

Zhou X, Yang H, Yan Q, Ren A, Kong Z, Tang S, Han X, Tan Z, Salem AZM

Nutr Metab (Lond) 2019;16:20

Human Studies

Dietary patterns before and during pregnancy and birth outcomes: a systematic review

Raghavan R[1], Dreibelbis C[1], Kingshipp BL[1], Wong YP[2], Abrams B[3], Gernand AD[4], Rasmussen KM[5], Siega-Riz AM[6], Stang J[7], Casavale KO[8], Spahn JM[2], Stoody EE[2]

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Background: Maternal diet before and during pregnancy could influence fetal growth and birth outcomes. Objective: Two systematic reviews aimed to assess the relationships between dietary patterns before and during pregnancy and (1) gestational age at birth and (2) gestational age- and sex-specific birth weight.

Methods: Literature was searched from January, 1980 to January, 2017 in 9 databases including PubMed, Embase, and Cochrane. Two analysts independently screened articles using predetermined inclusion and exclusion criteria. Data were extracted from included articles and risk of bias was assessed. Data were synthesized qualitatively, a conclusion statement was drafted for each question, and evidence supporting each conclusion was graded.

Results: Of the 9,103 studies identified, 11 (representing 7 cohorts and 1 randomized controlled trial [RCT]) were included for gestational age and 21 (representing 19 cohorts and 2 RCTs) were included for birth weight. Limited but consistent evidence suggests that certain dietary patterns during pregnancy are associated with a lower risk of preterm birth and spontaneous preterm birth. These protective dietary patterns are higher in vegetables; fruits; whole grains; nuts, legumes, and seeds; and seafood (preterm birth, only), and lower in red and processed meats, and fried foods. Most of the research was conducted in healthy Caucasian women with access to health care. No conclusion can be drawn on the association between dietary patterns during pregnancy and birth weight outcomes. Although research is available, the ability to draw a conclusion is restricted by inconsistency in study findings, inadequate adjustment of birth weight for gestational age and sex, and variation in study design, dietary assessment methodology, and adjustment for key confounding factors. Insufficient evidence exists regarding dietary patterns before pregnancy for both outcomes.

Conclusions: Maternal dietary patterns may be associated with a lower preterm and spontaneous preterm birth risk. The association is unclear for birth weight outcomes.

Comments This is one of the largest and extensive systematic reviews published to diet addressing the question "what is the relationship between dietary patterns before and during pregnancy and gestational age- and sex-specific birth weight?" Methodologically, combining several studies to answer this question is not an easy task. Therefore, the definition of the exposure must be clear. In the current systematic review, studies without an adequate description of the dietary pattern or a valid comparator were excluded. Yet, one must realize when interrupting the results that even after applying these exclusion criteria, the studies that were included in final analysis were highly inconsistent across the body of evidence with 10/21 reporting no association between dietary patterns before or during pregnancy and birth weight outcomes and the remaining were inconsistent regarding the direction of the effect that was associated with various dietary patterns. The main take-home message should be that in order to assess the association of maternal diet on fetal growth, strict definitions should be applied in order be able to reach practical conclusions and implement them to official recommendations and guidelines.

Development of a novel Periconceptual Nutrition Score (PENS) to examine the relationship between maternal dietary quality and fetal growth

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Background: Maternal nutrition may influence intrauterine fetal development. To date, the relationship between contemporary European dietary guidelines and fetal growth has not been examined.

Aims: To develop a novel Periconceptual Nutrition Score (PENS) to assess maternal dietary quality in early pregnancy and examine its relationship with fetal growth.

Study Design: Women were recruited conveniently at their first clinic visit and completed a supervised 4-day retrospective diet history. The PENS was developed using European Food Safety Authority recommended dietary intakes for pregnancy. The relationship between PENS and fetal growth was examined.

Subjects: Women with a singleton pregnancy.

Outcome Measures: Birthweight, small for gestational age (SGA), neonatal head circumference.

Results and Conclusions: Of the 202 women, the mean age was 32.2 ± 5.0 years and 44.6% were nulliparas. The mean PENS was 9.4 ± 3.1. On multivariable regression, there was a positive relationship between the PENS and birthweight (beta = 45.3, 95% CI 14.8–75.9, $p = 0.002$) and neonatal head circumference (beta = 0.12, 95% CI 0.01–0.23, $p = 0.03$). Compared with the lowest PENS quartile, the mean birthweight was increased in the highest quartile (Mean difference 328 g, $p = 0.02$). The incidence of SGA was 16.4% ($n = 10/61$) in the lowest PENS quartile compared to 6.5% ($n = 9/139$) in the top 3 quartiles ($p = 0.03$). Thus, higher maternal dietary quality was associated with increased intrauterine fetal growth. The PENS is potentially useful in identifying

those women before or during pregnancy who may benefit from dietary interventions that may optimise fetal growth. It may also be useful in tracking maternal dietary quality during pregnancy.

Comments As opposed to many modified food frequency questionnaires (FFQ) currently used to evaluate the quality of maternal dietary intakes in the second half of pregnancy, the current study focuses on the periconceptual period. The scoring system used for this study has some clear advantages, mainly the fact that it is very easy to use. Women were classified as either those meeting or not meeting recommended daily intake guidelines for dietary macronutrients and micronutrients. The same approach can be used in future studies exploring associations of maternal diet and adverse pregnancy and long-term outcome. Yet, it is important to acknowledge some of the limitations of this method. The scoring system described in the study consisted of a total of 23 nutrients. If a woman met the recommendation for an individual nutrient, she received 1 point per recommendation meaning that all nutrients were given equal weight in the scoring system. This may be misleading as inadequate intake of vitamin A and fat or carbohydrates, for example, affected the score in a similar manner. In addition, although it may imply that higher PENS was associated with lower rate of SGA, no multivariable analysis was done so other confounders were not adjusted for. Therefore, further research is needed to validate the proposed scoring system.

A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the women first trial

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This manuscript is also discussed in Chapter 10 by Mwangome et al., page 207.

Background: Reported benefits of maternal nutrition supplements commenced during pregnancy in low-resource populations have typically been quite limited.

Objectives: This study tested the effects on newborn size, especially length, of commencing nutrition supplements for women in low-resource populations ≥3 mo before conception (Arm 1), compared with the same supplement commenced late in the first trimester of pregnancy (Arm 2) or not at all (control Arm 3).

Methods: Women first was a 3-arm individualized randomized controlled trial (RCT). The intervention was a lipid-based micronutrient supplement; a protein-energy supplement was also provided if maternal body mass index (kg/m^2) was <20 or gestational weight gain was less than recommenda-

tions. Study sites were in rural locations of the Democratic Republic of the Congo (DRC), Guatemala, India, and Pakistan. The primary outcome was length-for-age z score (LAZ), with all anthropometry obtained <48 h post delivery. Because gestational ages were unavailable in DRC, outcomes were determined for all 4 sites from WHO newborn standards (non-gestational-age-adjusted, NGAA) as well as INTERGROWTH-21st fetal standards (3 sites, gestational age-adjusted, GAA).
Results: A total of 7,387 nonpregnant women were randomly assigned, yielding 2,451 births with NGAA primary outcomes and 1,465 with GAA outcomes. Mean LAZ and other outcomes did not differ between Arm 1 and Arm 2 using either NGAA or GAA. Mean LAZ (NGAA) for Arm 1 was greater than for Arm 3 (effect size: +0.19; 95% CI 0.08–0.30, $p = 0.0008$). For GAA outcomes, rates of stunting and small-for-gestational-age were lower in Arm 1 than in Arm 3 (RR 0.69; 95% CI 0.49–0.98, $p = 0.0361$ and RR 0.78; 95% CI 0.70–0.88, $p < 0.001$, respectively). Rates of preterm birth did not differ among arms.
Conclusions: In low-resource populations, benefits on fetal growth-related birth outcomes were derived from nutrition supplements commenced before conception or late in the first trimester.

Comments Fetal stunning as expressed by low birth weight and growth that does meet the individual's potential is one of the main problems in obstetrics. Although preventing fetal growth restriction is universally important, it has a special role in low resource countries, as a good "starting point" is of most importance. From the high rate of stillbirth (2–3%) in the study cohort, one can understand that the study population is considered at very high risk. In the current study, a relatively simple intervention was shown have a beneficial impact on fetal growth-related birth outcomes. The 87–88% compliance rate represents mainly a dedicated work of the investigators and research teams, stressing the importance of monitoring compliance to treatment and interventions also in common practice by the caregivers. Yet, although the results are promising, it may not be applicable to other cohorts from middle- or high-resource populations.

Role of maternal preconception nutrition on offspring growth and risk of stunting across the first 1,000 days in Vietnam: a prospective cohort study

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Abstract: Growing evidence supports the role of preconception maternal nutritional status (PMNS) on birth outcomes; however, evidence of relationships with child growth are limited. We examined associations between PMNS (height, weight and body mass index-BMI) and offspring growth during the first 1,000 days. We used prospective cohort data from a randomized-controlled trial of preconception micronutrient supplementation in Vietnam, PRECONCEPT (n = 1,409). Poisson regression models were used to examine associations between PMNS and risk of offspring stunting (<–2 HAZ) at 2 years. We used path analytic models to examine associations with PMNS on fetal growth (ultrasound measurements) and offspring HAZ at birth and 2 years. All models were adjusted for child age, sex, gestational weight gain, education, socioeconomic status and treatment

group. A third of women had a preconception height <150 cm or weight <43 kg. Women with preconception height <150 cm or a weight <43 kg were at increased risk of having a stunted child at 2 years (incident risk ratio [IRR] 1.85, 95% CI 1.51–2.28; IRR 1.35, 95% CI 1.10–1.65, respectively). While the traditional low BMI cut-off (<18.5 kg/m^2) was not significant, lower BMI cut-offs (<17.5 or <18.0 kg/m^2) were significantly associated with 1.3 times increased risk of child stunting. In path models, PMNS were positively associated with fetal growth (ultrasound measurements) and offspring HAZ at birth and 2 years. For each 1 SD increase in maternal height and weight, offspring HAZ at 2 years increased by 0.30 SD and 0.23 SD, respectively. In conclusion, PMNS influences both offspring linear growth and risk of stunting across the first 1,000 days. These findings underscore the importance of expanding the scope of current policies and strategies to include the preconception period in order to reduce child stunting.

Comments In the current study, the association of maternal preconception maternal nutritional status (PMNS) and fetal growth was explored using a prospective randomized trial (secondary analysis). Maternal PMNS was positively associated with fetal growth. The study is important mainly due to its prospective design, which allowed the researchers to adjust to many potential confounders, including the infant's sex, maternal gestational weight gain, and more. The study was conducted in Vietnam and almost one-third of patients had low pregestational weight (<43 kg) or their height was <150 cm. It will be interesting to see if similar interventions (or even a modified one) can also be used in a western society with a more diverse population. The results of the current study join those of the previous study presented in this chapter (Hambidge et al.) in stressing the importance of the preconception period as a major determinant of future pregnancy outcome, and especially, fetal growth. Future research should focus on additional detailed prospective information on inflammation and environmental exposures (i.e., mycotoxins; household air pollution) and biomarkers of nutritional status to examine the direct and indirect effects and interactions with maternal nutritional status.

Maternal fruit and vegetable or vitamin C consumption during pregnancy is associated with fetal growth and infant growth up to 6 months: results from the Korean Mothers and Children's Environmental Health (MOCEH) cohort study

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Background: Based on data obtained from pregnant women who participated in the Mothers and Children's Environmental Health (MOCEH) study in South Korea, we aimed to determine whether maternal intake of fruits and vegetables or vitamin C is associated with fetal and infant growth.
Methods: A total of 1,138 Korean pregnant women at 12–28 weeks gestation with their infants were recruited as study participants for the MOCEH. Intake of fruits and vegetables or vitamin C during pregnancy was assessed by a 1-day 24-h recall method. Fetal biometry was determined by ultrasonography at late pregnancy. Infant weight and length were measured at birth and 6 months.

Results: A multiple regression analysis after adjusting for covariates showed that maternal intake of fruits and vegetables was positively associated with the biparietal diameter of the fetus and infant's weight from birth to 6 months. Also, maternal vitamin C intake was positively associated with the abdominal circumference of the fetus and infant birth length. In addition, there was a significant inverse relationship between consumption of fruits and vegetables (below the median compared to above the median of ≥519 g/day) and the risk of low growth (<25th percentile) of biparietal diameter (OR 2.220; 95% CI 1.153–4.274) and birth weight (OR 1.434; 95% CI 1.001–2.056). A significant inverse relationship also existed between vitamin C consumption (below vs above the estimated average requirement [EAR] of ≥85 mg/day) and the risk of low growth (<25th percentile) of birth weight (OR 1.470; 95% CI 1.011–2.139), weight from birth to 6 months (OR 1.520; 95% CI 1.066–2.165), and length at birth (OR 1.579; 95% CI 1.104–2.258).
Conclusions: An increased intake of fruits and vegetables or vitamin C at mid-pregnancy is associated with increased fetal growth and infant growth up to 6 months of age.

Comments Fruit and vegetables are considered as an excellent source of vitamin C. During pregnancy, vitamin C consumption has been shown to be positively associated with neonatal birth weight. The current study reaffirms the results of a few previous prospective cohort studies addressing this issue. The main advantages of the current report lie in the large cohort with >700 babies followed up to 6 months of age. Yet, it is important to emphasize that some of the outcome measures, for example, biparietal diameter <25th percentile, are not commonly used to assess outcomes related to abnormal intrauterine growth. Therefore, caution should be used in understanding the terminology of outcomes to better understand the impact of fruit and vegetables consumption on fetal growth. The researchers also investigated maternal oxidative stress (MDA level), following the hypothesis that it might partly explain the underlying reason for their results. Antioxidant defense systems are crucial for the protection of tissues, cells, and organs from damage related to oxidative stress. Therefore, an imbalance between increased oxidative stress and decreased antioxidant defense can adversely affect pregnancy outcomes, including suboptimal fetal growth.

The impact of restricted gestational weight gain by dietary intervention on fetal growth in women with gestational diabetes mellitus

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Diabetologia 2018;61:2528–2538

Abstract Aims/Hypothesis: We aimed to investigate the impact of maternal gestational weight gain (GWG) during dietary treatment on fetal growth in pregnancies complicated by gestational diabetes (GDM).

Methods: This was a retrospective cohort study of 382 women consecutively diagnosed with GDM before 34 weeks' gestation with live singleton births in our centre (Center for Pregnant Women with Diabetes, Rigshospitalet, Copenhagen, Denmark) between 2011 and 2017. The women were stratified into 3 groups according to restricted (53%), appropriate (16%) and excessive (31%) weekly GWG during dietary treatment (using the Institute of Medicine guidelines) to estimate compliance with an energy-restricted "diabetes diet" (6,000 kJ/day [1,434 kcal/day], with approximately 50% of energy intake coming from carbohydrates with a low glycaemic index, and a carbohydrate intake of 175 g/day). Insulin therapy was initiated if necessary, according to local clinical guidelines.

Results: Glucose tolerance, HbA1c, weekly GWG before dietary treatment (difference between weight at GDM diagnosis and prepregnancy weight, divided by the number of weeks) and SD score for fetal abdominal circumference were comparable across the 3 groups at diagnosis of GDM at 276 ± 51 weeks (gestation time is given as weeksdays). The women were followed for 100 ± 51 weeks, during which 54% received supplementary insulin therapy and the average (mean) GWG during dietary treatment was 0, 3 and 5 kg in the 3 groups, respectively. Excessive weekly GWG during dietary treatment, reflecting poor dietary adherence was associated with increasing HbA1c (p = 0.014) from diagnosis of GDM to late pregnancy and infants with a birthweight-SD score of 0.59 ± 1.6. In contrast, restricted weekly GWG during dietary treatment, reflecting strict dietary adherence, was associated with decreasing HbA1c (p = 0.001) from diagnosis of GDM to late pregnancy and infants with a birthweight-SD score of 0.15 ± 1.1, without increased prevalence of infants born small for gestational age. Excessive GWG during dietary treatment and late-pregnancy HbA1c were identified as potentially modifiable clinical predictors of infant birthweight-SD score (p = 0.02 for both variables) after correction for confounders.

Conclusions/Interpretation: Restricted GWG during dietary treatment was associated with healthier fetal growth in women with GDM. GWG during dietary treatment and late-pregnancy HbA1c were identified as potentially modifiable clinical predictors of infant birthweight-SD score.

Comments The rate of gestational diabetes mellitus is increasing worldwide. Although gestational diabetes mellitus is related to several maternal, fetal, and neonatal complications, one of the early signs of uncontrolled gestational diabetes mellitus is accelerated fetal growth in response to maternal hyperglycemia. The effect was noticed in both twins and singleton pregnancies. The main challenge with gestational diabetes mellitus is that the diagnosis is usually made late in the second trimester, and there is only little time to react in order to modify the risk for complications. In the current study, it was shown that restricted gestational weight gain during dietary treatment was associated with improved fetal growth in women with gestational diabetes mellitus. As opposed to prior studies addressing this issue, in the current one, data on weekly maternal gestational weight gain were available from before and after the diagnosis of gestational diabetes, so it was possible to assess the effect of an energy-restricted diet in the cohort. Some limitations of the study should be mentioned. There is a risk for bias as self-reported prepregnancy weight was used to calculate body mass index (BMI) and also gestational weight gain prior to intervention. In addition, the intervention was uniform for all women, but the compliance and adherence to treatment were not reported. Finally, no subgroup analysis was done according to maternal prepregnancy BMI; thus, it remains unclear if this intervention is uniformly effective or if there are subgroups in which it may be of better use.

Effects of high-fat diets on fetal growth in rodents: a systematic review

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Reprod Biol Endocrinol 2019;17:39

Background: Maternal nutrition during pregnancy has life-long consequences for offspring. However, the effects of maternal overnutrition and/ or obesity on fetal growth remain poorly understood, for example, it is not clear why birthweight is increased in some obese pregnancies but not in others. Maternal obesity is frequently studied using rodents on high-fat diets, but effects on fetal growth are inconsistent. The purpose of this review is to identify factors that contribute to reduced or increased fetal growth in rodent models of maternal overnutrition.

Methods: We searched Web of Science and screened 2,173 abstracts and 328 full texts for studies that fed mice or rats diets providing ~45% or ~60% calories from fat for 3 weeks or more prior to pregnancy. We identified 36 papers matching the search criteria that reported birthweight or fetal weight.

Results: Studies that fed 45% fat diets to mice or 60% fat diets to rats generally did not show effects on fetal growth. Feeding a 45% fat diet to rats generally reduced birth and fetal weight. Feeding mice a 60% fat diet for 4–9 weeks prior to pregnancy tended to increase in fetal growth, whereas feeding this diet for a longer period tended to reduce fetal growth.

Conclusions: The high-fat diets used most often with rodents do not closely match Western diets and frequently reduce fetal growth, which is not a typical feature of obese human pregnancies. Adoption of standard protocols that more accurately mimic effects on fetal growth observed in obese human pregnancies will improve translational impact in this field.

Comments The current study is an important systematic review dealing with the potential effects of high-fat diets on the growth of rodent fetuses. The results of the 36 selected studies have shown that not only that high-fat diet is not associated with accelerated fetal growth in rats, but also it generally reduced birth and fetal weight. The effect of high-fat diet was also related to the time period in which the pregnant (or prepregnant) rats were fed with longer period of exposure leading to reduced fetal growth. The results of the current study suggest that although animal studies are an important and even crucial aspect in understanding biological processes, applying the conclusions of animal studies on human subjects is inappropriate. It seems that the high-fat diets used most often with rodent studies are not similar match to Western diets. Thus, using protocols that more accurately mimic effects on fetal growth observed in obese human pregnancies will improve the conclusions that can be drown from animal studies and will assist in the planning of human studies in this field.

Evidence for liver energy metabolism programming in offspring subjected to intrauterine undernutrition during midgestation

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Background: Maternal undernutrition programs fetal energy homeostasis and increases the risk of metabolic disorders later in life. This study aimed to identify the signs of hepatic metabolic programming in utero and during the juvenile phase after intrauterine undernutrition during midgestation.

Methods: Fifty-three pregnant goats were assigned to the control (100% of the maintenance requirement) or restricted (60% of the maintenance requirement from day 45 to 100 of midgestation and realimentation thereafter) group to compare hepatic energy metabolism in the fetuses (day 100 of gestation) and kids (postnatal day 90).

Results: Undernutrition increased the glucagon concentration and hepatic hexokinase activity, decreased the body weight, liver weight and hepatic expression of G6PC, G6PD, and PGC1α mRNAs, and tended to decrease the hepatic glycogen content and ACOX1 mRNA level in the dams. Maternal undernutrition decreased the growth hormone (GH) and triglyceride concentrations, tended to decrease the body weight and hepatic hexokinase activity, increased the hepatic PCK1, PCK2 and PRKAA2 mRNAs levels and glucose-6-phosphatase activity, and tended to increase the hepatic PRKAB1 and CPT1α mRNAs levels in the male fetuses. In the restricted female fetuses, the hepatic hexokinase activity and G6PC mRNA level tended to be increased, but PKB1 mRNA expression was decreased and the ACACA, CPT1α, NR1H3 and STK11 mRNA levels tended to be decreased. Maternal undernutrition changed the hepatic metabolic profile and affected the metabolic pathway involved in amino acid, glycerophospholipid, bile acid, purine, and saccharide metabolism in the fetuses, but not the kids. Additionally, maternal undernutrition increased the concentrations of GH and cortisol, elevated the hepatic glucose-6-phosphate dehydrogenase activity, and tended to decrease the hepatic glycogen content in the male kids. No alterations in these variables were observed in the female kids.

Conclusions: Maternal undernutrition affects the metabolic status in a sex- and stage-specific manner by changing the metabolic profile, expression of genes involved in glucose homeostasis and enzyme activities in the liver of the fetuses. The changes in the hormone levels in the male fetuses and kids, but not the female offspring, represent a potential sign of metabolic programming.

Comments It is well known that the intrauterine environment may have long-term effects via epigenetic changes and fetal programming. The current study focused on different aspects of maternal undernutrition in offspring of pregnant goats including the effects at the level of circulating blood, hepatic metabolites, genes, and enzymes. Interestingly, maternal undernutrition changed the hepatic metabolic profile and affected

the metabolic pathway involved in amino acid, glycerophospholipid, bile acid, purine, and saccharide metabolism in the fetuses but not in the kids. This implies that the effect may be reversible with proper nutrition after birth. Of note, during the juvenile stage, the kids were not exposed to an overnutrition environment.

It is important to notice that the restricted arm in this study included 40% energy restriction and that the exposure began at mid-gestation. It would be interesting to explore different levels of malnutrition and the effect when it starts in various stages of pregnancy and during the preconception period. In addition, as differences were noted between males and females, investigating the sexual dimorphism of fetal programming in liver metabolism following a nutritional challenge is warranted, as also suggested by the authors.

Overall Commentary

Primary prevention remains one of the most effective strategies in medicine. The advantages of education for healthier lifestyle and other modifications is that not only it can positively affect pregnancy outcome and decrease long-term morbidity of the offspring, but it may also serve as a window of opportunity for future maternal well-being. Nevertheless, a balanced diet is merely a single component in the determinants of fetal/offspring growth and development, which is attenuated by genetic, demographic, behavioral, and other factors. Thus, maternal nutrition, like any other intervention, should be personalized in order to achieve its maximal benefit.

Disclosure Statement

The authors report no conflict of interest.

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Turck D, Shamir R, Koletzko B, Phillip M (eds): Nutrition and Growth: Yearbook 2020.
World Rev Nutr Diet. Basel, Karger, 2020, vol 120, pp 193–210 (DOI: 10.1159/000503651)

Stunting of Growth in Developing Countries

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Introduction

Globally, 149 million children are stunted (i.e., length-for-age Z score less than –2) and the rate of decline has been unacceptably slow. The burden of this problem is in southern Asia and sub-Saharan Africa, where many communities remain impoverished. Childhood stunting is an indicator of poor linear growth and chronic undernutrition and is associated with adverse health, developmental, and eventual socioeconomic consequences for the affected children. The international community has agreed that stunting is a global child health and nutrition priority. As a result, there has been a global impetus to design, evaluate, and implement interventions to address this problem and inform policy changes. The hope is that these strategies will accelerate progress towards the global nutrition target of a 40% reduction in under-5 stunting by 2025.

In this chapter, we have put together an interesting selection of recently published papers on stunting and growth covering diverse areas of research and the evolving perspectives. The mechanisms of stunting have remained elusive and this has slowed down the development of interventions. We therefore include recent data on studies that have evaluated pathways to or factors associated with stunting in greater detail. Evidence of the association of stunting with maternal mental health, wasting in children, and the role of enteropathogens are outlined. We also include the most recent data on the efficacy of interventions that have been tested to address stunting in early childhood in low- and middle-income countries. These interventions are primarily nutrition (maternal and child) interventions alone or combined with water, sanitation, and hygiene (WASH) strategies. The findings from these studies and the accompanying perspectives provide key research questions that need to be explored in future

research in this field. Finally, we have included some thought-provoking perspectives on whether the investments being made for the development of interventions to address stunting are somewhat misplaced, as stunting may not after all be the best marker of childhood undernutrition? These papers remind us the importance of continuing to refine our research agendas and questions with the emerging evidence, as we seek to address childhood undernutrition.

Key articles reviewed for this chapter

Pathways

Maternal common mental disorder as predictors of stunting among children aged 6–59 months in Western Ethiopia: a case-control study

Girma S, Fikadu T, Abdisa E

Int J Pediatr 2019;2019:4716482

The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016

Schoenbuchner SM, Dolan C, Mwangome M, Hall A, Richard SA, Wells JC, Khara T, Sonko B, Prentice AM, Moore SE

Am J Clin Nutr 2019;110:498–507

Use of quantitative molecular diagnostic methods to investigate the effect of enteropathogen infections on linear growth in children in low-resource settings: longitudinal analysis of results from the MAL-ED cohort study

Rogawski ET, Liu J, Platts-Mills JA, Kabir F, Lertsethtakarn P, Siguas M, Khan SS, Praharaj I, Murei A, Nshama R, Mujaga B, Havt A, Maciel IA, Operario DJ, Taniuchi M, Gratz J, Stroup SE, Roberts JH, Kalam A, Aziz F, Qureshi S, Islam MO, Sakpaisal P, Silapong S, Yori PP, Rajendiran R, Benny B, McGrath M, Seidman JC, Lang D, Gottlieb M, Guerrant RL, Lima AAM, Leite JP, Samie A, Bessong PO, Page N, Bodhidatta L, Mason C, Shrestha S, Kiwelu I, Mduma ER, Iqbal NT, Bhutta ZA, Ahmed T, Haque R, Kang G, Kosek MN, Houpt ER; MAL-ED Network Investigators

Lancet Glob Health 2018;6:e1319–e1328

Biomarkers of environmental enteric dysfunction and associations with child linear growth in rural Odisha, India (OR10-06-19)

Sinharoy S, Reese H, ClasenA T

Curr Dev Nutr 2019;3(suppl 1); nzz034.OR10-06-19, https://doi.org/10.1093/cdn/nzz034.OR10–06–19

Consequences

The aggregate income losses from childhood stunting and the returns to a nutrition intervention aimed at reducing stunting

Galasso E, Wagstaff A

Econ Hum Biol 2019;34:225–238

Lifetime economic impact of the burden of childhood stunting attributable to maternal psychosocial risk factors in 137 low/middle-income countries

Smith Fawzi MC, Andrews KG, Fink G, Danaei G, McCoy DC, Sudfeld CR, Peet ED, Cho J, Liu Y, Finlay JE, Ezzati M, Kaaya SF, Fawzi WW

BMJ Glob Health 2019;4:e001144

Water, Sanitation, and Hygiene

Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on child stunting and anaemia in rural Zimbabwe: a cluster-randomised trial

Humphrey JH, Mbuya MNN, Ntozini R, Moulton LH, Stoltzfus RJ, Tavengwa NV, Mutasa K, Majo F, Mutasa B, Mangwadu G, Chasokela CM, Chigumira A, Chasekwa B, Smith LE, Tielsch JM, Jones AD, Manges AR, Maluccio JA, Prendergast A for the Sanitation Hygiene Infant Nutrition Efficacy (SHINE) Trial Team

Lancet Glob Health 2019;7:e132–e147

The WASH benefits and SHINE trials. interpretation of findings on linear growth and diarrhoea and Implications for policy: perspective of the investigative teams (P10-136-19)

Humphrey J, Pickering A, Null C, Winch P, Mangwadu G, Arnold B, Prendergast A, Njenga S, Rahman M, Ntozini R, Benjamin-Chung J, Stewart C, Huda T, Moulton L, Colford J, Luby S

Curr Dev Nutr. 2019;3(suppl 1) nzz034.P10-136-19, https://doi.org/10.1093/cdn/nzz034.P10-136-19

Thresholds of socio-economic and environmental conditions necessary to escape from childhood malnutrition: a natural experiment in rural Gambia

Husseini M, Darboe MK, Moore SE, Nabwera HM, Prentice AM

BMC Med 2018;16:199

Environmental enteric dysfunction and child stunting

Budge S, Parker AH, Hutchings PT, Garbutt C

Nutr Rev 2019;77:240–253

Intervention

A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the women first trial

Hambidge KM, Westcott JE, Garcés A, Figueroa L, Goudar SS, Dhaded SM, Pasha O, Ali SA, Tshefu A, Lokangaka A, Derman RJ, Goldenberg RL, Bose CL, Bauserman M, Koso-Thomas M, Thorsten VR, Sridhar A, Stolka K, Das A, McClure EM, Krebs NF

Am J Clin Nutr 2019;109:457–469

PROCOMIDA, a food-assisted maternal and child health and nutrition program, reduces child stunting in Guatemala: a cluster-randomized controlled intervention trial

Olney DK, Leroy J, Bliznashka L, Ruel MT

J Nutr 2018;148:1493–1505

Perspective

Perspective: what does stunting really mean? A critical review of the evidence
Leroy JL, Frongillo EA
Adv Nutr 2019;10:196–204

Stunting, starvation and refeeding: a review of forgotten 19th and early 20th century literature
Hermanussen M, Bogin B, Scheffler C
Acta Paediatr 2018;107:1166–1176

Pathways

Maternal Common Mental Disorder as Predictors of Stunting among Children Aged 6–59 Months in Western Ethiopia: A Case-Control Study

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Background: Child malnutrition in low- and middle-income countries still continues to be an alarming. Africa and Asia bear the greatest share of all forms of malnutrition. The association between maternal common mental disorder and stunting has not been studied well even in developed countries; much less in developing countries and even the findings are conflicting. Thus, the purpose of the present research was to investigate the relationship of maternal common mental disorder and child stunting.
Methods: Institution based unmatched case-control study design was employed from March to April 2017. Two hundred thirty-four sampled children (78 cases and 156 controls) were randomly selected. Anthropometric measurements (height/length and weight) were taken by calibrated instruments. Maternal common mental disorder (CMD) was measured by using the locally validated Self-Reporting Questionnaire (SRQ-20). Data entry was done by Epi data version 3.1 and analysis was done by SPSS 21.0 statistical software.
Results: Finding of this study found out about three-fourths of cases (71.8%) and three-fourths of controls (69.9%) were residing in rural and urban areas, respectively. Regarding maternal common mental disorder, more than half of cases mother (53.8%) and more than one-tenth of controls mother (13.5%) were found to have common mental disorder. The study showed that children of mothers who had common mental disorder were found to be 3 times more likelihood of developing stunting than children whose mothers had not common mental disorder.
Conclusion and Recommendation: The study indicated that maternal common mental disorder was significantly associated with stunting. Therefore, emphasis should be given in preventing, managing, and maintaining maternal mental health in order to prevent stunting.

Comments Maternal CMD which is composed of depressive, anxiety and somatic symptoms is highly prevalent, and it is one of the major contributors to the global burden of disease in low- and middle-income countries (LMICs). Using a case-control design, the study aims to unravel the specific association between maternal CMD and stunting. This study found that children whose mothers had CMD were 3 times more likely to be stunted than children whose mothers had no CMD. These data further support the known link between maternal mental health and childhood undernutrition. A major challenge in this field is finding interventions that work and are scalable in LMICs.

The relationship between wasting and stunting: a retrospective cohort analysis of longitudinal data in Gambian children from 1976 to 2016

Schoenbuchner SM[1], Dolan C[2], Mwangome M[3], Hall A[4], Richard SA[5], Wells JC[6], Khara T[2], Sonko B[7], Prentice AM[7], Moore SE[7,8]

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Am J Clin Nutr 2019;110:498–507

Background: The etiologic relationship between wasting and stunting is poorly understood, largely because of a lack of high-quality longitudinal data from children at risk of undernutrition.
Objectives: The aim of this study was to describe the interrelationships between wasting and stunting in children aged <2 years.
Methods: This study involved a retrospective cohort analysis, based on growth-monitoring records spanning 4 decades from clinics in rural Gambia. Anthropometric data collected at scheduled infant welfare clinics were converted to z scores, comprising 64,342 observations on 5,160 subjects (median: 12 observations per individual). Children were defined as "wasted" if they had a weight-for-length z score less than –2 against the WHO reference and "stunted" if they had a length-for-age z score less than –2.
Results: Levels of wasting and stunting were high in this population, peaking at approximately (girls-boys) 12–18% at 10–12 months (wasted) and 37–39% at 24 months of age (stunted). Infants born at the start of the annual wet season (July-October) showed early growth faltering in weight-for-length z score, putting them at increased risk of subsequent stunting. Using time-lagged observations, being wasted was predictive of stunting (OR 3.2; 95% CI 2.7–3.9), even after accounting for current stunting. Boys were more likely to be wasted, stunted, and concurrently wasted and stunted than girls, as well as being more susceptible to seasonally driven growth deficits.
Conclusions: We provide evidence that stunting is in part a biological response to previous episodes of being wasted. This finding suggests that stunting may represent a deleterious form of adaptation to more overt undernutrition (wasting). This is important from a policy perspective as it suggests we are failing to recognize the importance of wasting simply because it tends to be more acute and treatable. These data suggest that stunted children are not just short children but are children who earlier were more seriously malnourished and who are survivors of a composite process.

Comments The relationship between wasting and stunting is poorly understood. In recent decades, the nutrition community has separated child wasting and stunting along the humanitarian/development divide resulting in different policies, programs, research, and funding for these 2 manifestations of child undernutrition. The rationale behind the conceptual separation of stunting and wasting in terms of etiology and programs has been questioned in a number of recent reviews and publications [1, 2]. Using longitudinal cohort data from Gambia, the study sought to describe the interrelationships between wasting and stunting in children. The data showed that being wasted was predictive of stunting (OR 3.2; 95% CI 2.7–3.9), even after accounting for current stunting, meaning that the effects of wasting may be longer term manifesting as slow linear growth. There are compelling reasons for both treatment and prevention interventions to consider them jointly and with awareness of the relation between them.

Use of quantitative molecular diagnostic methods to investigate the effect of enteropathogen infections on linear growth in children in low-resource settings: longitudinal analysis of results from the MAL-ED cohort study

Rogawski ET[1,2], Liu J[1], Platts-Mills JA[1], Kabir F[3], Lertsethtakarn P[4], Siguas M[5], Khan SS[6], Praharaj I[7], Murei A[8], Nshama R[9], Mujaga B[10], Havt A[11], Maciel IA[12], Operario DJ[1], Taniuchi M[1], Gratz J[1], Stroup SE[1], Roberts JH[2], Kalam A[3], Aziz F[3], Qureshi S[3], Islam MO[6], Sakpaisal P[4], Silapong S[4], Yori PP[5,13], Rajendiran R[7], Benny B[7], McGrath M[13,14], Seidman JC[14], Lang D[15], Gottlieb M[15], Guerrant RL[1], Lima AAM[11], Leite JP[12], Samie A[8], Bessong PO[8], Page N[16], Bodhidatta L[4], Mason C[4], Shrestha S[17,18], Kiwelu I[10], Mduma ER[9], Iqbal NT[3], Bhutta ZA[3], Ahmed T[6], Haque R[6], Kang G[7], Kosek MN[5,13], Houpt ER[1]; MAL-ED Network Investigators

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Lancet Glob Health 2018;6:e1319–e1328

Background: Optimum management of childhood diarrhoea in low-resource settings has been hampered by insufficient data on aetiology, burden, and associated clinical characteristics. We used quantitative diagnostic methods to reassess and refine estimates of diarrhoea aetiology from the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) cohort study.

Methods: We re-analysed stool specimens from the multisite MAL-ED cohort study of children aged 0–2 years done at eight locations (Dhaka, Bangladesh; Vellore, India; Bhaktapur, Nepal; Naushero Feroze, Pakistan; Venda, South Africa; Haydom, Tanzania; Fortaleza, Brazil; and Loreto, Peru), which included active surveillance for diarrhoea and routine non-diarrhoeal stool

collection. We used quantitative PCR to test for 29 enteropathogens, calculated population-level pathogen-specific attributable burdens, derived stringent quantitative cutoffs to identify aetiology for individual episodes, and created aetiology prediction scores using clinical characteristics.
Findings: We analysed 6,625 diarrhoeal and 30,968 non-diarrhoeal surveillance stools from 1,715 children. Overall, 64.9% of diarrhoea episodes (95% CI 62.6–71.2) could be attributed to an aetiology by quantitative PCR compared with 32.8% (30.8–38.7) using the original study microbiology. Viral diarrhoea (36.4% of overall incidence, 95% CI 33.6–39.5) was more common than bacterial (25.0%, 23.4–28.4) and parasitic diarrhoea (3.5%, 3.0–5.2). Ten pathogens accounted for 95·7% of attributable diarrhoea: Shigella (26.1 attributable episodes per 100 child-years, 95% CI 23.8–29.9), sapovirus (22.8, 18.9–27.5), rotavirus (20.7, 18.8–23.0), adenovirus 40/41 (19.0, 16.8–23.0), enterotoxigenic Escherichia coli (18.8, 16·5–23·8), norovirus (15.4, 13.5–20.1), astrovirus (15.0, 12.0–19.5), Campylobacter jejuni or C coli (12.1, 8.5–17.2), Cryptosporidium (5.8, 4.3–8.3), and typical enteropathogenic *E. coli* (5.4, 2.8–9.3). 86.2% of the attributable incidence for Shigella was non-dysenteric. A prediction score for shigellosis was more accurate (sensitivity 50.4% [95% CI 46.7–54.1], specificity 84.0% [83.0–84.9]) than current guidelines, which recommend treatment only of bloody diarrhoea to cover Shigella (sensitivity 14.5% [95% CI 12.1–17.3], specificity 96.5% [96.0–97.0]).
Interpretation: Quantitative molecular diagnostics improved estimates of pathogen-specific burdens of childhood diarrhoea in the community setting. Viral causes predominated, including a substantial burden of sapovirus; however, Shigella had the highest overall burden with a high incidence in the second year of life. These data could improve the management of diarrhoea in these low-resource settings.

Comments Diarrhea due to pathogens, such as Shigella and enterotoxigenic *Escherichia coli*, has been associated with poor height attainment and poor weight gain, respectively, whereas rotavirus has been shown to have little effect on ponderal or linear growth. The study analyzed stool samples from the Etiology, Risk Factors, and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED). This was a multisite longitudinal birth cohort that assessed the effect of enteric infections and other risk factors on linear growth [3]. In their analysis, they used PCR technique that has high sensitivity compared to culture and immunoassays methods previously used. Data showed that subclinical infections with bacteria had larger and more consistent associations with larger decrements in LAZ than those of viruses or protozoa. Shigella infection resulted in the largest population-level difference in LAZ. This suggests that focused strategies to reduce subclinical infection may contribute to reducing prevalence of stunting.

Biomarkers of environmental enteric dysfuction and associations with child linear growth in rural Odisha, India (OR10-06-19)

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Objectives: Intestinal dysfunction due to mucosal inflammation, known as environmental enteric dysfunction (EED), has been hypothesized to contribute to stunting in low- and middle-income countries (LMICs). Given that consensus is lacking on gold standard biomarkers for EED and on

relationships with child linear growth, we examined 3 biomarkers of EED and height-for-age z-score (HAZ) among children under age 5 years in rural Odisha, India.
Methods: We conducted a sub-study within Gram Vikas MANTRA, a matched cohort study of a household-level water and sanitation intervention in Odisha, India. We collected stool samples and anthropometry data for children under age 5 (n = 209) in 2 rounds (October 2016 – January 2017 and July – October 2017). We analyzed stool samples for 3 biomarkers of EED: myeloperoxidase (MPO), neopterin (NEO), and α1-anti-trypsin (AAT). We assessed correlations between values and used linear regression to analyze associations between each biomarker and HAZ. All analyses were adjusted for relevant covariates and village-level clustering.
Results: Mean HAZ for children under 5 in our sample population was –1.52 (SD 1.34). Median biomarker values (25th, 75th percentiles) were 1,052.71 ng/mL (682.76, 3,208.22) for MPO, 2,104.21 nmol/L (1,193.64, 3,490.10) for NEO, and 0.406 mg/g (229.44, 743.78) for AAT. Correlations between the biomarkers were relatively low, with the highest correlation (ρ = 0.45) between MPO and AAT. We observed an inverse association between MPO and HAZ (β = –0.000027, $p < 0.001$) but no association between NEO and HAZ (β = 0.000031, p = 0.46) or AAT and HAZ (β = –0.000072, p = 0.52).
Conclusions: In our sample population, median values for NEO and AAT were similar to those from other studies of children in LMICs. MPO had substantially lower values than in other reports but was still strongly associated with HAZ. Previous studies have produced conflicting evidence on relationships between each biomarker of EED and HAZ. Our results contribute evidence that intestinal inflammation may play an important role in growth faltering in young children, possibly through mucosal dysfunction. MPO is a major component of the primary granules in neutrophils and hence reflects luminal neutrophilic infiltration. Priorities for a future research agenda on EED and growth will be discussed.

Comments There is growing interest in understanding the role environmental enteric dysfunction (EED) plays in childhood malnutrition in order to inform interventions. However, as there is still no gold standard biomarker to support the diagnosis of EED, this study in India takes an interesting approach and examines the relationship of 3 different biomarkers of EED with stunting.

Consequences

The aggregate income losses from childhood stunting and the returns to a nutrition intervention aimed at reducing stunting

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We undertake 2 calculations, one for all developing countries, the other for 34 developing countries that together account for 90% of the world's stunted children. The first asks how much lower a country's per capita income is today as a result of having a fraction of its workforce been stunted in childhood. We use a development accounting framework, relying on micro-econometric estimates

of the effects of childhood stunting on adult wages through their effects on years of schooling, cognitive skills, and height, parsing out the relative contribution of each set of returns to avoid double counting. We estimate that, on average, the per capita income penalty from stunting is between 5–7%, depending on the assumption. In our second calculation we estimate the economic value and the costs associates with scaling up a package of nutrition interventions using the same methodology and set of assumptions used in the first calculation. We take a package of 10 nutrition interventions that has data on both effects and costs, and we estimate the rate-of-return to gradually introducing this program over a period of 10 years in 34 countries that together account for 90% of the world's stunted children. We estimate a rate-of-return of 12%, and a benefit-cost ratio of 5:1–6:1.

Comments The economic cost associated with childhood stunting has previously been estimated; however, the rate of return expected by the application of various nutrition interventions is less well understood and hardly estimated. The study applies a unique approach to estimate the rate of return that would be expected if interventions were to be applied. In one study, the rate of returns from a package of 10 nutrition interventions over a period of 10 years in 34 countries was estimated at 12%.

Lifetime economic impact of the burden of childhood stunting attributable to maternal psychosocial risk factors in 137 low/middle-income countries

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Introduction: The first 1,000 days of life is a period of great potential and vulnerability. In particular, physical growth of children can be affected by the lack of access to basic needs as well as psychosocial factors, such as maternal depression. The objectives of the present study are to: (1) quantify the burden of childhood stunting in low/middle-income countries attributable to psychosocial risk factors; and (2) estimate the related lifetime economic costs.

Methods: A comparative risk assessment analysis was performed with data from 137 low/middle-income countries throughout Asia, Latin America and the Caribbean, North Africa and the Middle East, and sub-Saharan Africa. The proportion of stunting prevalence, defined as less than –2 SDs from the median height for age according to the WHO Child Growth Standards, and the number of cases attributable to low maternal education, intimate partner violence (IPV), maternal depression and orphanhood were calculated. The joint effect of psychosocial risk factors on stunting was estimated. The economic impact, as reflected in the total future income losses per birth cohort, was examined.

Results: Approximately 7.2 million cases of stunting in low/middle-income countries were attributable to psychosocial factors. The leading risk factor was maternal depression with 3.2 million cases attributable. Maternal depression also demonstrated the greatest economic cost at USD 14.5 billion, followed by low maternal education (USD 10.0 billion) and IPV (USD 8.5 billion). The joint cost of these risk factors was USD 29.3 billion per birth cohort.
Conclusion: The cost of neglecting these psychosocial risk factors is significant. Improving access to formal secondary school education for girls may offset the risk of maternal depression, IPV and orphanhood. Focusing on maternal depression may play a key role in reducing the burden of stunting. Overall, addressing psychosocial factors among perinatal women can have a significant impact on child growth and well-being in the developing world.

Comments The burden of childhood stunting in low- and middle-income countries has previously been quantified. The contribution of food and water, sanitation, and hygiene (WASH) interventions to the prevention and treatment of childhood stunting has also been well documented. In this study, using a large dataset from 137 countries, maternal-related risk factors are highlighted and the cases attributed to these factors estimated. Specifically, maternal depression and low levels of education are strong predictors of stunting and demonstrated the greatest impact cost at USD 14.5 billion and USD 10.0 billion, respectively. These new data call for a shift in focus and expand intervention packages targeting stunting across the globe.

Water, Sanitation, and Hygiene

Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on child stunting and anaemia in rural Zimbabwe: a cluster-randomised trial

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Background: Child stunting reduces survival and impairs neurodevelopment. We tested the independent and combined effects of improved water, sanitation, and hygiene (WASH), and improved infant and young child feeding (IYCF) on stunting and anaemia in Zimbabwe.

Methods: We did a cluster-randomised, community-based, 2 × 2 factorial trial in 2 rural districts in Zimbabwe. Clusters were defined as the catchment area of between 1 and 4 village health workers employed by the Zimbabwe Ministry of Health and Child Care. Women were eligible for inclusion if they permanently lived in clusters and were confirmed pregnant. Clusters were randomly assigned (1:1:1:1) to standard of care (52 clusters), IYCF (20 g of a small-quantity lipid-based nutrient supplement per day from age 6 to 18 months plus complementary feeding counselling; 53 clusters), WASH (construction of a ventilated improved pit latrine, provision of 2 handwashing stations, liquid soap, chlorine, and play space plus hygiene counselling; 53 clusters), or IYCF plus WASH (53 clusters). A constrained randomisation technique was used to achieve balance across the groups for 14 variables related to geography, demography, water access, and community-level sanitation coverage. Masking of participants and fieldworkers was not possible. The primary outcomes were infant length-for-age Z score and haemoglobin concentrations at 18 months of age among children born to mothers who were HIV negative during pregnancy. These outcomes were analysed in the intention-to-treat population. We estimated the effects of the interventions by comparing the 2 IYCF groups with the 2 non-IYCF groups and the 2 WASH groups with the 2 non-WASH groups, except for outcomes that had an important statistical interaction between the interventions.

Findings: Between Nov 22, 2012, and March 27, 2015, 5,280 pregnant women were enrolled from 211 clusters. 3,686 children born to HIV-negative mothers were assessed at age 18 months (884 in the standard of care group from 52 clusters, 893 in the IYCF group from 53 clusters, 918 in the WASH group from 53 clusters, and 991 in the IYCF plus WASH group from 51 clusters). In the IYCF intervention groups, the mean length-for-age Z score was 0.16 (95% CI 0.08–0.23) higher and the mean haemoglobin concentration was 2.03 g/L (1.28–2.79) higher than those in the non-IYCF intervention groups. The IYCF intervention reduced the number of stunted children from 620 (35%) of 1,792 to 514 (27%) of 1,879, and the number of children with anaemia from 245 (13.9%) of 1,759 to 193 (10.5%) of 1,845. The WASH intervention had no effect on either primary outcome. Neither intervention reduced the prevalence of diarrhoea at 12 or 18 months. No trial-related serious adverse events, and only 3 trial-related adverse events, were reported.

Interpretation: Household-level elementary WASH interventions implemented in rural areas in low-income countries are unlikely to reduce stunting or anaemia and might not reduce diarrhoea. Implementation of these WASH interventions in combination with IYCF interventions is unlikely to reduce stunting or anaemia more than implementation of IYCF alone.

Comments This was a rigorously designed and implemented trial using improved water, sanitation, and hygiene (WASH) interventions, optimizing breastfeeding and complementary feeding strategies and play spaces for infants and toddlers in rural Zimbabwe. The WASH interventions had no effect on the length-for-age Z scores (LAZ) or anemia in children at 18 months of age. The feeding strategies resulted in a modest increase in LAZ of 0.16 and a 2 g/L increase in hemoglobin levels. The WASH strategies that they used in this trial did not appear to achieve the levels of environmental hygiene that are required to prevent infant and young child morbidities such as environmental enteric dysfunction that are involved in the causal pathways of childhood stunting and anemia.

The WASH benefits and SHINE trials. Interpretation of findings on linear growth and diarrhoea and implications for policy: perspective of the investigative teams (P10-136-19)

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Objectives: We recently completed 3 efficacy trials (Bangladesh, Kenya, Zimbabwe) testing the independent and combined effects of improved complementary feeding (CF) and intensive household water quality, sanitation, and hygiene (WASH) on child diarrhea and length-for-age-Z-score (LAZ) at 18–24 months. Intervention uptake was high. In all 3 trials: CF increased LAZ but WASH had no effect on LAZ. WASH reduced diarrhea in Bangladesh but not in Kenya or Zimbabwe. We present a synthesis of trial findings and their implications.
Methods: Reviews of the literature and reanalysis of trial data were conducted.
Results: WASH and stunting: Copious observational studies have demonstrated a strong association between household-level WASH and child LAZ. We conducted an observational analysis (nested birth cohort) from our control arms. In adjusted analyses of all 3 trials, having an improved latrine when the pregnant woman was enrolled was associated with ~0.2LAZ increase in her child at 18–24 months. The frequently reported association between household WASH indicators and child growth may be confounded and drawing causal inference misguided. WASH and diarrhea: Promoters visited intervention households 6 times per month in Bangladesh and monthly in Kenya and Zimbabwe. We conducted a systematic literature review: virtually all evidence that household water chlorination and handwashing reduce diarrhea comes from studies with daily to fortnightly intervention contact. In studies with follow-up after the trial ending, behaviors steeply declined and the effect on child diarrhea disappeared. Household water chlorination and handwashing promotion implemented through sporadic message delivery may not reduce child diarrhea. Enteropathogen transmission: Despite achieving substantial contrast between WASH and non-WASH households, children in the WASH arms still experienced high enteropathogen transmission, illustrating the recalcitrance of pervasive fecal contamination in rural low-income communities to even intense intervention.
Conclusions: Household WASH interventions are unlikely to reduce child stunting and may not reduce child diarrhea. We call for substantial investment in research to identify and in programming to deliver much more efficacious interventions.

Comments This was a useful perspective from the study team who conducted 3 cluster randomized trials to evaluate the efficacy of optimizing infant-feeding strategies and enhancing environmental hygiene (chlorinated water, improved sanitation and hygiene interventions, i.e., handwashing with soap, WASH) on linear growth and diarrhea in the infants, in 3 low- and middle-income countries (Bangladesh, Kenya, and Zimbabwe). The findings showed that WASH interventions alone had no effect on linear growth and only had an effect on diarrhea in Bangladesh where there was more intensive household follow-up. Combined breastfeeding and complementary feeding strategies had a small but significant increase on the mean length-for-age Z score by 0.13–0.25 in the initial analysis. Interestingly, a subanalysis showed a small but significant

effect on infant linear growth of about 0.2 LAZ scores when pregnant women had access to improved latrines. Their insights into the limitations of their interventions and study design provides a platform for future research on early childhood exposures to enteropathogens whose pathways were not sufficiently interrupted by the interventions in these trials. Evaluation of interventions that focus on the appropriate strategies for disposal of infant and domestic animal feces to ensure that infants and older children are not exposed to these environmental contaminants is warranted.

Thresholds of socio-economic and environmental conditions necessary to escape from childhood malnutrition: a natural experiment in rural Gambia

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Background: Childhood malnutrition remains highly prevalent in low-income countries, and a 40% reduction in under-5 year stunting is WHO's top Global Target 2025. Disappointingly, meta-analyses of intensive nutrition interventions reveal that they generally have low efficacy at improving growth. Unhygienic environments also contribute to growth failure, but large WASH Benefits and SHINE trials of improved water, sanitation and hygiene (WASH) recently reported no benefits to child growth.

Methods: To explore the thresholds of socio-economic status (SES) and living standards associated with malnutrition, we exploited a natural experiment in which the location of our research centre within a remote rural village created a wide diversity of wealth, education and housing conditions within the same ecological setting and with free health services to all. A composite SES score was generated by grading occupation, education, income, water and sanitation, and housing and families were allocated to 5 groups (SES1 = highest). SES ranged from very poor subsistence-farming villagers to post graduate staff with overseas training. Nutritional status at 24 m was obtained from clinic records for 230 children and expressed relative to WHO Growth Standards.

Results: Height-for-age (HAZ) and weight-for-age (WAZ) Z-scores were strongly predicted by SES group. HAZ varied from –0.67 to –2.23 ($p < 0.001$) and WAZ varied from –0.90 to –1.64 ($p < 0.001$), from SES1 to SES5, respectively. Weight-for-height (WHZ) showed no gradient. Children in SES1 showed greater dispersion so were further divided in a post hoc analysis. Children resident in Western housing on the research compound (SES1A) had HAZ = +0.68 and WAZ = +0.36. The residual gradient between those in SES1B and SES5 spanned only 0.65 Z-score for HAZ (–1.58 to –2.23) and was not significant for WAZ or WHZ.

Conclusions: The large difference in growth between children in SES1A living in Western-type housing and SES1B children living in the village, and the very shallow gradient between SES1B and SES5, implies a very high SES threshold before stunting and underweight will be eliminated. This may help to explain the lack of efficacy of the recent WASH interventions and points to the need for what is termed 'Transformative WASH'. Good quality housing, with piped water into the home, may be key to eliminating malnutrition.

Comments This observational study was conducted in a rural Gambian community that for nearly 4 decades has had free access to primary health care services and a nutrition supplementation/rehabilitation center. In addition, breastfeeding in the first 18–24 months is the norm. It was a small study of 230 children with detailed information on parental socioeconomic status. At 2 years, the height-for-age Z score (HAZ) was strongly associated with socioeconomic status. In addition, children who resided in Western-style housing where there was limited contact with domestic animals, in-door running water, and flushing toilets had significantly better HAZ. The authors emphasized the fact that addressing stunting will require high thresholds of socioeconomic development in poor communities in low resource settings for this to be achieved.

Environmental enteric dysfunction and child stunting

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Nutr Rev 2019;77:240–253

In 2017, an estimated 1 in every 4 (23%) children aged <5 years were stunted worldwide. With slow progress in stunting reduction in many regions and the realization that a large proportion of stunting is not due to insufficient diet or diarrhea alone, it remains that other factors must explain continued growth faltering. Environmental enteric dysfunction (EED), a subclinical state of intestinal inflammation, can occur in infants across the developing world and is proposed as an immediate causal factor connecting poor sanitation and stunting. A result of chronic pathogen exposure, EED presents multiple causal pathways, and as such the scope and sensitivity of traditional water, sanitation, and hygiene (WASH) interventions have possibly been unsubstantial. Although the definite pathogenesis of EED and the mechanism by which stunting occurs are yet to be defined, this paper reviews the existing literature surrounding the proposed pathology and transmission of EED in infants and considerations for nutrition and WASH interventions to improve linear growth worldwide.

Comments This review provides current insights into environmental enteric dysfunction (EED), a pervasive, subclinical condition that is a key factor in the causal pathway of stunting and poor neurodevelopmental outcomes among children in poor communities in low- and middle-income countries. Also, that EED is not amenable to the current water, sanitation, and hygiene (WASH) interventions which focus on reducing episodes of diarrhea, whereas stunting is only weakly associated with diarrhea. The review suggests that more holistic approaches that also address environmental contamination by domestic animals would be more successful at limiting pathogen exposure in children in these environments. In addition, it emphasizes that future research should test integrated WASH, nutrition, caregiver practices, and early child development interventions.

A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the women first trial

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This manuscript is also discussed in Chapter 9 by Yogev and Hiersch, page 185.

Background: Reported benefits of maternal nutrition supplements commenced during pregnancy in low-resource populations have typically been quite limited.

Objectives: This study tested the effects on newborn size, especially length, of commencing nutrition supplements for women in low-resource populations ≥3 months before conception (Arm 1), compared with the same supplement commenced late in the first trimester of pregnancy (Arm 2) or not at all (control Arm 3).

Methods: Women First was a 3-arm individualized randomized controlled trial (RCT). The intervention was a lipid-based micronutrient supplement; a protein-energy supplement was also provided if maternal body mass index (kg/m^2) was <20 or gestational weight gain was less than recommendations. Study sites were in rural locations of the Democratic Republic of the Congo (DRC), Guatemala, India, and Pakistan. The primary outcome was length-for-age z score (LAZ), with all anthropometry obtained <48 h post-delivery. Because gestational ages were unavailable in DRC, outcomes were determined for all 4 sites from WHO newborn standards (non-gestational-age-adjusted, NGAA) as well as INTERGROWTH-21st fetal standards (3 sites, gestational age-adjusted, GAA).

Results: A total of 7,387 non pregnant women were randomly assigned, yielding 2,451 births with NGAA primary outcomes and 1465 with GAA outcomes. Mean LAZ and other outcomes did not differ between Arm 1 and 2 using either NGAA or GAA. Mean LAZ (NGAA) for Arm 1 was greater than for Arm 3 (effect size: +0.19; 95% CI 0.08, 0.30, $p = 0.0008$). For GAA outcomes, rates of stunting and small-for-gestational-age were lower in Arm 1 than in Arm 3 (RR 0.69; 95% CI 0.49–0.98, $p = 0.0361$ and RR 0.78; 95% CI 0.70–0.88, $p < 0.001$, respectively). Rates of preterm birth did not differ among arms.

Conclusions: In low-resource populations, benefits on fetal growth-related birth outcomes were derived from nutrition supplements commenced before conception or late in the first trimester.

Comments Initiating nutrition supplements in the preconceptual period is a suggested strategy to correct maternal underweight and micronutrient deficiencies. In the women first

trial, nutritional supplements were given before conception and during pregnancy (second and third trimester) with the aim of reducing the prevalence of stunting at birth. From these data, supplementing women before conception or in the first trimester may be more beneficial than not supplementing women at all. These data call for strategies to improve women nutrition before conception that may coincide with a focus on adolescent nutrition.

PROCOMIDA, a food-assisted maternal and child health and nutrition program, reduces child stunting in Guatemala: a cluster-randomized controlled intervention trial

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Background: Food-assisted maternal and child health and nutrition (FA-MCHN) programs may foster child growth during the first 1,000 days (pregnancy and the first 2 years of a child's life), but evidence is scant.

Objective: We evaluated the impact of an FA-MCHN program, *PROCOMIDA*, on linear growth (stunting [length-for-age *z* score (LAZ) less than –2] and length-for-age difference [LAD]) among children aged 1–24 months. *PROCOMIDA* was implemented in Guatemala by Mercy Corps and was available to beneficiaries throughout the first 1,000 days.

Methods: We used a longitudinal, cluster-randomized controlled trial with groups varying in family ration sizes (full [FFR], reduced [RFR], and none [NFR]) and individual ration types provided to mothers (pregnancy to 6 mo postpartum) and children (6–24 months of age) [corn-soy blend (CSB), lipid-based nutrient supplement (LNS), micronutrient powder (MNP)]: (1) FFR + CSB (n = 576); (2) RFR + CSB (n = 575); (3) NFR + CSB (n = 542); (4) FFR + LNS (n = 550); (5) FFR + MNP (n = 587); (6) control (n = 574). Program impacts compared with control, and differential impacts between groups varying family ration size or individual ration type, were assessed through the use of linear mixed-effects models and post hoc simple effect tests (significant if $p < 0.05$).

Results: *PROCOMIDA* significantly reduced stunting at age 1 month in FFR + CSB, RFR + CSB, and FFR + MNP groups compared with control (5.05, 4.06, and 3.82 percentage points [pp], respectively). Stunting impact increased by age 24 months in FFR + CSB and FFR + MNP relative to control (impact = 11.1 and 6.5 pp at age 24 months, respectively). For CSB recipients, the FFR compared with RFR or NFR significantly reduced stunting (6.47–9.68 pp). CSB reduced stunting significantly more than LNS at age 24 months (8.12 pp).

Conclusions: FA-MCHN programs can reduce stunting during the first 1,000 days, even in relatively energy/food-secure populations. Large family rations with individual rations of CSB or MNP were most effective. The widening of impact as children age highlights the importance of intervening throughout the full first 1,000 days.

Comments There is a window of opportunity to correct stunting in the first 24 months of life. High-energy/protein food supplements given earlier in life may increase growth of stunted children. PROCOMIDA was a cluster randomized trial that aimed to prevent

childhood stunting by delivering sufficient food, promoting the adoption of optimal health, nutrition, hygiene practices, and improving the provision and utilization of preventive health services. The program managed to reduce prevalence of stunting at 24 months by 11.1% point in the intervention group receiving full family ration (FFR) + corn-soy blend (CSB) package. The findings add to existing knowledge that combining nutrition supplementation, hygiene, and access to health services with family food rations may have even better impact.

Perspective

Perspective: What Does stunting really mean? A critical review of the evidence

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The past decade has seen an unprecedented increase in attention to undernutrition, and drastically reducing child stunting has become a global development objective. The strong focus on linear growth retardation and stunting has enabled successful advocacy for nutrition, but with this focus has come some confusion and misunderstanding about the meaning of linear growth retardation and stunting among researchers, donors, and agencies active in nutrition. Motivated by the belief that a sharp focus will further accelerate progress in reducing undernutrition, we critically reviewed the evidence. The global attention to stunting is based on the premise that any intervention aimed at improving linear growth will subsequently lead to improvements in the correlates of linear growth retardation and stunting. Current evidence and understanding of mechanisms do not support this causal thinking, with 2 exceptions: linear growth retardation is a cause of difficult births and poor birth outcomes. Linear growth retardation is associated with (but does not cause) delayed child development, reduced earnings in adulthood, and chronic diseases. We thus propose distinguishing 2 distinctly different meanings of linear growth retardation and stunting. First, the association between linear growth retardation (or stunting) and other outcomes makes it a useful marker. Second, the causal links with difficult births and poor birth outcomes make linear growth retardation and stunting outcomes of intrinsic value. In many cases a focus on linear growth retardation and stunting is not necessary to improve the well-being of children; in many other cases, it is not sufficient to reach that goal; and for some outcomes, promoting linear growth is not the most cost-efficient strategy. We appeal to donors, program planners, and researchers to be specific in selecting nutrition outcomes and to target those outcomes directly.

Comments This interesting and thought-provoking write-up seeks to clear up the confusion and misunderstanding about what stunting really means among researchers, donors, and agencies active in nutrition.

Stunting, starvation and refeeding: a review of forgotten 19th and early 20th century literature

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Aim: To scrutinize to what extent modern ideas about nutrition effects on growth are supported by historic observations in European populations.
Method: We reviewed 19th and early 20th century paediatric journals in the Staatsbibliothek zu Berlin, the third largest European library with an almost complete collection of the German medical literature. During a 3-day visit, we inspected 15 bookshelf meters of literature not available in electronic format.
Results: Late 19th and early 20th century breastfed European infants and children, independent of social strata, grew far below World Health Organisation (WHO) standards and 15–30% of adequately-fed children would be classified as stunted by the WHO standards. Historic sources indicate that growth in height is largely independent of the extent and nature of the diet. Height catch-up after starvation was greater than catch-up reported in modern nutrition intervention studies and allowed for unimpaired adult height.
Conclusion: Historical studies are indispensable to understand why stunting does not equate with undernutrition and why modern diet interventions frequently fail to prevent stunting. Appropriateness and effect size of modern nutrition interventions on growth need revision.

Comments Using data from historical studies in Europe, this interesting review argues that stunting does not equate to undernutrition. They concluded that "the historic literature lacks evidence of a strong association between food, child growth and adult height." Therefore, focusing on modern diet interventions to address stunting diverts attention away from focusing on interventions that can truly address childhood undernutrition. They argue that the "upstream" factors including improvements in living conditions, food quality, and socioeconomic empowerment of communities are required for stunting to be addressed.

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