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*

*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*

*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
*Nutrients* 2018; 10; 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 mark study
Stea TH, Tveter ET, Te Velde SJ, Vik FN, Klepp KI, Bere E

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 (IDFICS) study
*Nutrients* 2018; 10:1350

*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
**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

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


*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**


*Nat Commun* 2018; 9:4462
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.

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**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.
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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Pediatrics 2019;143:e20183075

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.

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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 programming effect of early cholesterol exposure, if any. Such a programming 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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Nutrients 2018;10:1747

Abstract: Regulation of appetite and food intake is partly regulated by N-acyl ethanolamine 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 systemically 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.

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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-acyl ethanolamine (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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Lancet Glob Health 2018;6:e875–e884

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/m², 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...
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.

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**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.
**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**

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*Nutrients* 2018;5:10:1442

**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.

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**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.

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**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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*PLoS One 2018;13:e0205498*

**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.

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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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Nutrients 2018;10:1350

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.

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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.

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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.

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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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Pediatr Obes 2019;14:12535

Objective: To examine associations between consumption of low-calorie sweetened beverages (LC-SBs), 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.

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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 SSBs 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 (TNFa) 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.

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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Pediatr Obes 2019;14:12499

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.

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 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.

References


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Obesity, Metabolic Syndrome, and Nutrition