Childhood obesity is a major worldwide health concern, widely recognized as a risk factor for the development of cardiometabolic comorbidities. Known to affect its occurrence are genetic, environmental, lifestyle, and behavioral factors. Although its prevalence is increasing [1], a recent study reported stabilization of this trend, especially in developed countries [2].

A growing body of evidence suggests that the increased risk for childhood obesity is associated with early-life factors, such as pregnancy weight gain, birth weight, rapid postnatal growth, and gestational diabetes.

In an evaluation of the relationship between breastfeeding during the first 6 months of life and body mass index (BMI) in infancy and subsequent childhood, there were contradictory findings regarding a long-lasting association.

Age at adiposity rebound is a predictor of subsequent changes in BMI pattern, an earlier age being associated with increased risk of overweight. One of the studies assessed the association between breastfeeding and BMI development trajectories from age 2 to 16 years.

Emerging evidence suggests that nutrition during early life may have consequences extending into adulthood. "Early Nutrition", an international research project, has provided up-to-date evidence of the effects of early nutrition on metabolic programming and their consequent health impacts. This report presents current standards, recommendations, guidelines, and regulations on nutrition in healthy term infants and children aged 1–3 years.

Other studies evaluated the associations between dietary intake of fatty acids and fiber during infancy, as well as infant circadian feeding patterns and measures of growth, adiposity, and cardiometabolic health during childhood.
The intestinal microbiota and antibiotic use have been also identified as potential modulators of early metabolic programming and development of obesity. Considerable numbers of children and adolescents are being diagnosed with metabolic syndrome (MetS), a cluster of risk factors including abdominal fatness, hypertension, dyslipidemia, and insulin resistance, all of which increase the risk of diabetes and cardiovascular disease (CVD). One report indicates that healthy eating practices during childhood may help prevent such disturbances and reduce later CVD mortality.

Other studies assessed the effect of vitamin D supplementation on BMI and inflammatory biomarkers in obese and overweight young subjects. The relatively new techniques of brain imaging have also been used to evaluate the brain’s response to food and its association with body weight. Since the energy balance is regulated by a multifaceted system of physiological signals influencing energy intake and expenditure, any variability in the brain’s response to food may be partially explained by differences in levels of metabolically active tissues throughout the body, including fat-free mass (FFM) and fat mass (FM). One study used functional magnetic resonance imaging (fMRI) to evaluate the hypothesis that the body composition of children is related to the response of the brain to food images varying in energy density (ED). Yet another study used fMRI to examine potential developmental differences in the responses of children and adults to unhealthy food (UF) cues and to determine how these responses relate to weight status.

This chapter reviews a selection of notable articles published between July 2016 and June 2017, focusing on the relation between nutrition, obesity, and MetS in childhood and young adulthood. This selection of articles published in the course of a single year indicates the range and intensity of the continuing efforts being made by researchers worldwide to confront the problem of childhood obesity.

Key articles reviewed for this chapter

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

Predictors of infant body composition at 5 months of age: the Healthy Start Study
Sauder KA, Kaar JL, Starling AP, Ringham BM, Glueck DH, Dabelea D
*J Pediatr* 2017;183:94–99.e1

Targeting sleep, food, and activity in infants for obesity prevention: an RCT
*Pediatrics* 2017;139:pii:e20162037
Age at adiposity rebound and body mass index trajectory from early childhood to adolescence; differences by breastfeeding and maternal immigration background
Besharat Pour M, Bergström A, Bottai M, Magnusson J, Kull I, Moradi T
*Pediatr Obes* 2017;12:75–84

**Nutrition of infants and young children (one to three years) and its effect on later health: a systematic review of current recommendations (Early Nutrition project)**
*Crit Rev Food Sci Nutr* 2017;57:489–500

**Intake of different types of fatty acids in infancy is not associated with growth, adiposity, or cardiometabolic health up to 6 years of age**
Stroobant W, Braun KV, Kiefte-de Jong JC, Moll HA, Jaddoe VW, Brouwer IA, Franco OH, Voortman T
*J Nutr* 2017;147:413–420

**Associations between dietary fiber intake in infancy and cardiometabolic health at school age: the Generation R study**
vан Gijssel RM, Braun KV, Kiefte-de Jong JC, Jaddoe VW, Franco OH, Voortman T
*Nutrients* 2016;8:531

**Predominantly nighttime feeding and weight outcomes in infants**

**The Intestinal Microbiota and Eating Practices and their Relation to Metabolic Programming**

**Childhood BMI in relation to microbiota in infancy and lifetime antibiotic use**
Korpela K, Zijsmans MA, Kuitunen M, Kukkonen K, Savilahti E, Salonen A, de Weerth C, de Vos WM
*Microbiome* 2017;5:26

**Associations between school meal-induced dietary changes and metabolic syndrome markers in 8- to 11-year-old Danish children**

**The Association Between Vitamin D and Inflammatory Biomarkers in Obese and Overweight Subjects**

**The effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects: a systematic review with meta-analysis**
Jamka M, Woźniiewicz M, Walkowiak J, Bogdański P, Jeszka J, Stelmach-Mardas M
*Eur J Nutr* 2016;55:2163–2176
Predictors of infant body composition at 5 months of age: the Healthy Start Study
Sauder KA, Kaar JL, Starling AP, Ringham BM, Glueck DH, Dabelea D
1Department of Pediatrics, University of Colorado School of Medicine, Aurora, CO, USA;
2Department of Epidemiology, Colorado School of Public Health, Aurora, CO, USA
J Pediatr 2017;183:94–99.e1

Background: Intrauterine exposure to maternal obesity is associated with increased obesity in offspring across the lifespan. Greater maternal pre-pregnant BMI and gestational weight gain are both associated with greater offspring body size and adiposity at birth. However, the degree to which these associations persist into the postnatal period has not been properly investigated. The main purpose of this analysis was to evaluate whether maternal pre-pregnant BMI, gestational weight gain, and breastfeeding exclusivity are associated independently with offspring body size and composition at 5 months of age. In addition, the analysis also aimed to determine whether these effects are independent of body composition at birth and early infant growth.
Methods: Women from obstetric clinics were recruited in early pregnancy. Data of 640 mother/offspring pairs from early pregnancy through approximately 5 months of age were collected. Offspring body composition was assessed with air displacement plethysmography at birth and approximately at 5 months of age. Linear regression analyses examined associations between predictors and FFM, FM, and percent FM (adiposity) at approximately 5 months. Secondary models were further adjusted for body composition at birth and rapid infant growth.

Results: Greater pre-pregnant BMI and gestational weight gain were associated with greater FFM at approximately 5 months of age, but not after adjustment for FFM at birth. Greater gestational weight gain was also associated with greater FM at approximately 5 months of age, independent of FM at birth and rapid infant growth, although this did not translate to increased adiposity. Greater percent time of exclusive breastfeeding was associated with lower FFM (−311 g; *p* < 0.001), greater FM (+224 g; *p* < 0.001), and greater adiposity (+3.51%; *p* < 0.001). Compared with offspring of non-Hispanic white mothers, offspring of Hispanic mothers had greater adiposity (+2.72%; *p* < 0.001) and offspring of non-Hispanic black mothers had lower adiposity (−1.93%; *p* < 0.001). Greater adiposity at birth suggested greater adiposity at approximately 5 months of age, independent of infant feeding and rapid infant growth.

Conclusions: There are clear differences in infant body composition by demographic, perinatal, and infant feeding characteristics, although data also show that increased adiposity at birth persists through approximately 5 months of age. These findings warrant further research into implications of differences in infant body composition.

Comments

Body composition in early life influences the development of obesity during childhood and adolescence. Therefore, it is important to adequately determine body composition during the first months of life. In a similar study in 203 healthy term infants, longitudinal body composition was also investigated. Changes in body fat % occurred mainly in the first 3 months of life, supporting the concept of a critical window for adiposity development in the first 3 months of life [3]. Appetite-regulating hormones play a role in the regulation of food intake and might thus influence body composition. In 197 healthy term infants, leptin, ghrelin, and insulin were associated with FM percentage or its changes during the first 6 months of life. Formula-fed infants had a different profile of appetite-regulating hormones than breastfed infants, suggesting that lower levels of ghrelin, leptin, and insulin in breastfed infants contribute to the protective role of breastfeeding against obesity development [4]. Higher cord blood leptin was also associated with slower weight gain during infancy, and this association was driven by lower increases in adiposity, at least in early infancy [5].

Targeting sleep, food, and activity in infants for obesity prevention: an RCT

Taylor BJ1, Gray AR2, Galland BC3, Heath AM4, Lawrence J3, Sayers RM3, Cameron S5, Hanna M3, Dale K3, Coppell KJ5, Taylor RW5

Departments of 1the Dean, Dunedin School of Medicine, 2Preventive and Social Medicine, 3Women’s and Children’s Health, 4Human Nutrition, and 5Medicine, University of Otago, Dunedin, New Zealand

*Pediatrics* 2017;139 pii:e20162037

Background: Obesity prevention studies, implemented in early life, concentrated on changing nutrition and activity in infants, with relatively little success. Although sleep is strongly associated with weight in observational research, few interventions have investigated the effectiveness of sleep modification for obesity prevention.
The aim of the study was to determine whether a conventional approach (food, activity, and breastfeeding (FAB) intervention), and/or an indirect approach (sleep intervention), to obesity prevention would result in lower BMI at 2 years of age compared with standard care.

**Methods:** This community-based, 2-year randomized controlled trial (RCT), allocated 802 pregnant women (≥16 years, <34 weeks' gestation) to 4 arms: control (usual care), FAB, sleep, and their combination (FAB and sleep). All groups received standard child care. FAB participants received additional support (8 contacts) promoting breastfeeding, healthy eating, and physical activity (antenatal-18 months). Sleep participants received 2 sessions (antenatal, 3 weeks) targeting prevention of sleep problems, as well as a sleep treatment program if requested (6–24 months). Combination participants received both interventions (9 contacts). BMI was measured at 24 months by researchers blinded to group allocation, and secondary outcomes (diet, physical activity, sleep) were assessed by using a questionnaire or accelerometry at multiple time points.

**Results:** At 2 years, 686 women remained in the study (86%). No significant intervention effect was observed for BMI at 24 months \( (p = 0.086) \), but there was an overall group effect for the prevalence of obesity \( (p = 0.027) \). Exploratory analyses found a protective effect for obesity among those receiving “sleep intervention” (sleep and combination compared with FAB and control: OR 0.54 [95% CI 0.35–0.82]). No effect was observed for “FAB intervention” (FAB and combination compared with sleep and control: OR 1.20 [95% CI 0.80–1.81]).

**Conclusions:** A well-developed food and activity intervention did not seem to affect children’s weight status. However, further research on more intensive or longer running sleep interventions is warranted.

**Comments**

Short sleep duration has been found to be associated with overweight and obesity in childhood. In 7,867 children aged 2–9 years, a dose-dependent inverse association between sleep duration and overweight was observed; after adjustment by geographical location, the association remained significant for sleeping less than 9 h per night \( (OR 2.22; 99\% CI 1.64–3.02) \) [6]. The IDEFICS intervention was based on the intervention mapping approach identifying 6 target behaviors, including ensuring adequate sleep duration. Nocturnal sleep duration of 11/10 h or more in pre-school/school children was achieved by 37.9% of the studied sample [7]. The sleep component of the intervention did not lead to clinically relevant changes in sleep duration [8]; however, adherence to physical activity, TV, and sleep recommendations was the main driver reducing the chance of being overweight during the 2 years follow-up [9]. Behavioral interventions targeting mothers and young children as the one presented in the current study, can be delivered inexpensively and not requiring specialized training. They could help prevent the development of obesity in infants and children; however, more research is needed, with focus on sleep determinants such as sleep knowledge, practices, and related environment.
Age at adiposity rebound and body mass index trajectory from early childhood to adolescence; differences by breastfeeding and maternal immigration background

Besharat Pour M1, Bergström A1, Bottai M2, Magnusson J1, Kull I1,2,4, Moradi T1,5

1Institute of Environmental Medicine, Division of Epidemiology, Karolinska Institutet, Stockholm, Sweden; 2Institute of Environmental Medicine, Unit of Biostatistics, Karolinska Institutet, Stockholm, Sweden; 3Department of Clinical Science and Education, Stockholm South General Hospital, Karolinska Institutet, Stockholm, Sweden; 4Sachs’ Children and Youth Hospital, Stockholm South General Hospital, Stockholm, Sweden; 5Centre for Epidemiology and Community Medicine, Stockholm County Council, Stockholm, Sweden

Pediatr Obes 2017;12:75–84

Background: Overweight children follow a higher BMI trajectory compared to their normal weight peers. During infancy, BMI rapidly increases after birth and peaks at 12 months of age, then gradually decreases until 6 years; literature has found that BMI nadir typically occurs within the range of 3–8 years of age. Thereafter, BMI starts a second phase of increase that will continue towards adulthood BMI. This paper aims to assess associations between breastfeeding and maternal immigration background and BMI development trajectories from age 2 to 16 years.

Methods: A cohort of children born in Stockholm during 1994 to 1996 was followed from age 2 to 16 years, with repeated measurements of height and weight at a maximum of 8-time points. The final study population included 2,278 children with complete information on breastfeeding, maternal country of birth, and BMI at least in 2-time points from 2 to 16 years of age. Age 2 years as start of follow-up was chosen to ensure temporal relationship between exposure and outcome. Children were categorized by breastfeeding status during the first 6 months of life into 3 groups of never/short (exclusive breastfeeding <2 weeks), partial (exclusive breastfeeding 2 weeks to <6 months), and exclusively breastfeeding (exclusive breastfeeding ≥6 months). Based on maternal country of birth, children were divided into 2 groups – offspring of Swedish mothers and of foreign born mothers (immigrant mothers). Foreign born mothers were from 61 countries. BMI trajectories and age at adiposity rebound were estimated using mixed-effects linear models.

Results: BMI trajectories were different by breastfeeding and maternal immigration status (p value <0.0001). Compared with exclusively breastfed counterparts, never/short breastfed children of Swedish mothers had a higher BMI trajectory, whereas never/short breastfed children of immigrant mothers followed a lower BMI trajectory. The estimated age at adiposity rebound ranged from 48 to 59 months. Ages at adiposity rebound were earlier for higher BMI trajectories regardless of maternal immigration background.

Conclusions: Differences in BMI trajectories and age at adiposity rebound between offspring of immigrant and of Swedish mothers suggest a lack of beneficial association between breastfeeding and long-term BMI development among children of immigrant mothers. Given the relation between long-term BMI development and risk of overweight/obesity, these differences challenge the notion that exclusive breastfeeding is always beneficial for children’s BMI development and subsequent risk of overweight/obesity.

Comments: Early adiposity rebound, when BMI rises after reaching a nadir, has been suggested as a predictor of later obesity. Therefore, adiposity rebound is considered as a suitable time period for childhood obesity prevention. Breastfeeding for longer than 4 months seems to be a protective behavior against later obesity development. In a retrospective cohort study that included 1,812 children born
in 2004, with follow-up until they were 8 years of age, breastfeeding during the first 6 months of life was not associated with a delay in the age of the adiposity rebound [10]. Concerning population differences in adiposity rebound, there is little information on this issue. There is also little information on whether childhood physical development in other populations differs from western populations. For instance, obese Japanese children developed adiposity rebound earlier than non-obese Japanese children, similar to those in Western countries reported in the literature [11]. In any case, these results highlight the importance of monitoring childhood growth so as to help identify children with early adiposity rebound who would be at risk of developing obesity later in life.

**Nutrition of infants and young children (one to three years) and its effect on later health: a systematic review of current recommendations (Early Nutrition project)**


1Department of Pediatrics, The Medical University of Warsaw, Warsaw, Poland; 2Department of Pediatrics, VU University Medical Center Amsterdam, Amsterdam, The Netherlands; 3Department of Pediatric Gastroenterology, La Fe University Hospital, Valencia, Spain; 4Division of Metabolic and Nutritional Medicine, Dr. von Hauner Children’s Hospital, University of Munich Medical Centre, Klinikum d. Univ. München, München, Germany; 5Department of Pediatrics, Emma Children’s Hospital, Amsterdam Medical Center, Amsterdam, The Netherlands

*Crit Rev Food Sci Nutr* 2017;57:489–500

**Background:** Evidence suggesting that nutrition early in life has consequences even in adulthood has emerged in recent decades. Nutrition-related chronic diseases, such as CVDs, obesity, type 2 diabetes, osteoporosis or some forms of cancer, have been linked to maternal and early infant nutrition. Nutrition in early life may influence metabolic programming and therefore the development of diseases later in life.

The aim of this article is to summarize, by performing a systematic review, current standards, recommendations, guidelines, and regulations (hereafter, referred to as documents) on the nutrition of children up to 3 years of age. The authors place a special emphasis on available studies on long-term effects of early nutrition, such as the risk of CVDs, hypertension, overweight, obesity, MetS, diabetes, or glucose intolerance.

**Methods:** MEDLINE, selected databases, and websites were searched for documents published between 2008 and January 2013. Only English language documents developed by and recognized by international and national societies and organizations were included. Position papers, scientific reports, and commentaries were also considered for inclusion.

**Results:** Almost 2,500 records were screened. A total of 156 publications that required further full text evaluation were identified. Forty-two documents met the inclusion criteria. The strongest and most consistent evidence for a protective, long-term effect was documented for breastfeeding. There is a consistency across the guidelines that exclusive breastfeeding for around 6 months is a desirable goal. Partial breastfeeding as well as breastfeeding for shorter periods of time are also valuable. In general, complementary food should be introduced into the infant diet within the range of 4 to 6 months of age.

Also, limiting the intake of sodium and rapidly absorbed carbohydrates, use of a specific meal pattern, reducing the consumption of saturated fatty acids (SFAs) by replacing them with polyunsatu-
rated fatty acids (PUFAs), and lowering the intake of trans-fatty acids, seems beneficial. Many documents did not evaluate long-term outcomes of interest, or reported insufficient or imprecise data. Inconsistency in recommendations for some outcomes and research gaps were identified.

**Conclusions:** The reported findings may serve as a helpful tool in planning further research, preventive actions against important diet-related diseases, and guidelines improvement.

**Comments**

There are many aspects related with nutrition in early life that could influence the development of some conditions during childhood or even in adulthood [12]. The body of evidence is still limited but sufficient in some areas. In most of the cases, there are recommendations with scarce scientific support. For a health professional interested in the topic, it is difficult to have a clear idea of the situation. For this reason, the current paper is important, as it compiles the available recommendations and their scientific background.

As stated in the abstract, the strongest and most consistent evidence for a protective, long-term effect of early nutrition was documented for breastfeeding. In the identified documents, several of them did not assess long-term outcomes or included insufficient data to justify the conclusions and the quality of evidence used to prepare the guidelines was not assessed. Some discrepancies in recommendations were also identified.

Another important value of this systematic review is the identification of research gaps in the literature that should support the development of further research projects. It was identified that current evidence on the long-term effects of early nutrition is based mainly on associations and not causality. Therefore, well designed and properly conducted RCTs, using strong clinical outcome measures and with relevant inclusion/exclusion criteria and adequate sample sizes should be used in the future.

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**Intake of different types of fatty acids in infancy is not associated with growth, adiposity, or cardiometabolic health up to 6 years of age**

Stroobant W¹, Braun KV¹, Kieffe-de Jong JC¹,², Moll HA³, Jaddoe VW¹,³, Brouwer IA⁴, Franco OH¹, Voortman T⁵

¹Departments of Epidemiology and Pediatrics, Erasmus Medical Center, University Medical Center, Rotterdam, The Netherlands; ²Leiden University College, The Hague, The Netherlands; ³Department of Health Sciences, Vrije Universiteit, Amsterdam, The Netherlands

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**Background:** The development of cardiometabolic risk factors begins early in life. Studies in adults indicate that a lower saturated and higher unsaturated fat intake is associated with a lower risk of MetS and CVDs. However, studies on fat intake in relation to cardiometabolic health during childhood are scarce.

The objective of this study was to examine the association between the intake of different types of fatty acids in early childhood and body composition and cardiometabolic health at 6 years of age in a prospective cohort study.

**Methods:** This study was conducted in 2,927 children participating in the Generation R study, a multi-ethnic, prospective, population-based cohort from fetal life onward in Rotterdam, The Netherlands. To determine their child’s dietary intake, mothers completed a semi-quantitative food frequency questionnaire. Food intake was assessed when the children had a median age of 12.9 months (95%, range 12.2–18.9 months). Children’s total fat intake and intakes of SFAs, monounsaturated fatty acids (MUFAs), and PUFAs were estimated as percentage of total energy intake. Children’s height and weight up to age 6 years...
were repeatedly measured. At 6 years of age, body fat percentage with a DXA scanner, diastolic and systolic blood pressure, and serum insulin, triacylglycerol, and high density lipoprotein (HDL)-cholesterol were measured. These outcomes were combined into a cardiometabolic risk factor score. Associations of FA intake with repeated measures of height, weight, and BMI by using linear mixed models and with cardiometabolic outcomes by using linear regression models, adjusting for sociodemographic and lifestyle factors and taking into account macronutrient substitution effects were examined.

**Results:** In multivariable models, no associations of a higher intake of total fat or SFAs, MUFAs, or PUFAs with growth, adiposity, or cardiometabolic health when fat was consumed at the expense of carbohydrates were observed. In subsequent models, there were also no associations observed for higher MUFA or PUFA intakes at the expense of SFAs with any of the outcomes. Results did not differ by sex, ethnicity, age, or birth weight.

**Conclusion:** The results of this study did not support the hypothesis that intake of different types of FAs are associated with adiposity or cardiometabolic health among children.

**Comments**

In the adult literature, there is controversy about the effect of different macronutrients intake on obesity and other cardiovascular risk factors. This is even more so in children and adolescents, as there is scarce information in that respect. Recently, the focus is mainly on protein and free sugars intake [13]; however, there are some previous studies showing the potential effect of dietary fat intake in the development of obesity. In the STRIP study, 1,062 children were randomly assigned to an intervention group receiving biannual fat-oriented dietary counseling or to a control group at 7 months of age. The children who were overweight at 13 years of age gained more weight than their normal-weight peers by the age of 2 or 3 years onward, and girls became overweight by the age of 5 years, whereas boys only after 8 years of age; however, the intervention had no effect on the examined growth parameters [14]. In the same study, the decrease in total and saturated fat intakes in the intervention group had a positive effect on the insulin resistance index in children aged 9 years [15]. Overall, there is no consistent information on the role of total fat intake or either different fatty acids intake in relation to obesity or related cardiometabolic complications in children and adolescents. Future studies should be performed using robust methods to assess the dietary intake or biomarkers of their intake alone or a combination of both.

**Associations between dietary fiber intake in infancy and cardiometabolic health at school age: the Generation R study**

van Gijssel RM1, 2, Braun KV3, Kiefte-de Jong JC4, 5, Jaddoe VW6–8, Franco OH9, Voortman T10

1The Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands; 2The Generation R Study Group, Erasmus MC, University Medical Center, Rotterdam The Netherlands; 3Department of Global Public Health, Leiden University, The Hague, The Netherlands; 4The Department of Pediatrics, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

*Nutrients* 2016;8:531

**Background:** In adults, dietary fiber intake is beneficial for various aspects of cardiometabolic health, such as lower insulin and cholesterol concentrations and lower blood pressure. However, whether this already occurs in early childhood is unclear.
**Aim:** The aim was to assess if there are associations between dietary fiber intake in infancy and cardiometabolic health in children.

**Methods:** Population-based cohort in Rotterdam, The Netherlands. Information on dietary fiber intake at a median age of 12.9 months was collected using a food-frequency questionnaire in 2,032 children. The population for analysis ranged from 1,314 to 1,995 children, per cardiometabolic outcome. The total dietary fiber intake was calculated using the Dutch Food Composition database (NEVO, Netherlands Voedingsstoffenbestand), where dietary fiber is defined as plant cell wall components that are not digestible by human digestive enzymes. Dietary fiber was adjusted for energy intake using the residual method. At a median age of 5.9 years, children visited the hospital, where they were examined. As a primary outcome, cardiometabolic risk factors including body fat percentage, high-density lipoprotein cholesterol, insulin and triglyceride concentrations, and diastolic and systolic blood pressure were used. These variables were expressed in age- and sex-specific standard deviation scores, and the total score was computed.

**Results:** In models adjusted for several parental and child covariates, a higher dietary fiber intake was associated with a lower cardiometabolic risk factor score. Cardiometabolic factors were observed individually, 1 g/day higher energy-adjusted dietary fiber intake was associated with 0.026 SDS higher HDL-cholesterol (95% CI 0.009–0.042), and 0.020 SDS lower triglycerides (95% CI –0.037 to –0.003), but not with body fat, insulin, or blood pressure. Results were similar for dietary fiber with and without adjustment for energy intake.

**Conclusions:** The observed findings suggest that higher dietary fiber intake in infancy may be associated with better cardiometabolic health in later childhood.

**Comments**

Another player when assessing the potential role of nutrients in the development of obesity and related cardiometabolic disorders during childhood is dietary fiber. However, there is also scarce information in this regard, just coming from cross-sectional studies. In a cross-sectional study in Danish children aged 8–11, dietary whole-grain and fiber intakes were not associated with the FM index but were inversely associated with serum insulin concentrations [16]. In adolescents, energy-adjusted water-soluble fiber and water insoluble fiber were positively associated with body fat percentage, waist to height ratio, and low-density lipoprotein cholesterol, while energy-adjusted water-soluble fiber was inversely associated with serum fasting glucose [17]. Further studies, especially well designed clinical trials are necessary to confirm the beneficial effects of total dietary fiber and its different types in terms of obesity development and related metabolic conditions in children and adolescents.
Predominantly nighttime feeding and weight outcomes in infants

Cheng TS1, Loy SL3, 5, Toh JY1, Cheung YB4, 8, Chan JK2, 3, 5, Godfrey KM9, 10, Gluckman PD7, 11, Saw SM12, Chong YS7, 13, Lee YS7, 14, Lek N1, 5, Chong MF6, 14, Yap F1, 5, 15

Departments of 1 Pediatrics and 2 Reproductive Medicine and 3 KK Research Center, KK Women’s and Children’s Hospital, Singapore; 4 Center for Quantitative Medicine, 5 Duke-NUS Medical School, Singapore; 6 Clinical Nutrition Research Center, 7 Singapore Institute for Clinical Sciences, Agency for Science, Technology and Research, Singapore; 8 Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital, Tampere, Finland; 9 Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK; 10 National Institute for Health Research Southampton Biomedical Research Center, University of Southampton and University Hospital Southampton National Health Service Foundation Trust, Southampton, UK; 11 Liggins Institute, University of Auckland, Auckland, New Zealand; 12 Saw Swee Hock School of Public Health and Departments of 13 Obstetrics and Gynaecology and 14 Pediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore; 15 Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

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This manuscript is also discussed in Chapter 6, pages 111–128.

**Background:** The influence of circadian feeding patterns on weight outcomes has been shown in animal and human studies but not in very young children. Adults who consumed greater energy in the evening tend to be overweight or obese.

The study aimed to assess the association between infant’s circadian feeding patterns at 12 months of age and the subsequent growth and weight status after 1 year.

**Methods:** Mothers from the ongoing prospective mother-offspring cohort study GUSTO (Growing Up in Singapore Towards Healthy Outcomes) in Singapore were included. A total of 349 mothers answered a 24-h dietary recall administered by trained clinical staff with the use of a 5-stage, multiple-pass interviewing technique to record food intakes and feeding times of the mothers’ children on the previous day, when the infants had 12 months of age. Mothers were also asked whether the assessed infant food intakes were typical or atypical compared with those on other unrecorded days. Predominantly daytime (07.00–18.59; \( n = 282 \)) and predominantly nighttime (19.00–06.59; \( n = 67 \)) feeding infants were defined by whether daytime energy intake was >50% or <50% of total energy intake. BMI-for-age z scores were computed using the World Health Organization (WHO) Child Growth Standards 2006 to determine changes in BMI-for-age z scores from 12 to 24 months of age and weight status at 24 months of age. Multivariable linear and logistic regression analyses were performed.

**Results:** Compared with predominantly daytime feeding, predominantly nighttime feeding was associated with a higher BMI-for-age z scores gain from 12 to 24 months of age (adjusted \( \beta = 0.38; 95\% \text{ CI} 0.11–0.65; p = 0.006 \)) and increased risk of becoming overweight at 24 months of age (adjusted OR 2.78; 95% CI 1.11–6.97; \( p = 0.029 \)) with adjustments for maternal age, education, ethnicity, monthly household income, parity, infant BMI-for-age z scores at 12 months of age, feeding mode in the first 6 months of life, and total daily energy intake.

**Conclusions:** The study suggests that the role of daily distribution of energy consumption in weight regulation begins in infancy. The feeding of infants predominantly during nighttime hours was associated with adiposity gain and risk of overweight in early childhood. The inclusion of advice on the appropriate feeding time may be considered when implementing strategies to prevent childhood obesity.

**Comments** Food consumption timing is a new issue in infant nutrition. In adults, unusual feeding time may produce a disruption of the circadian system with further unhealthy conse-
quences. Taking into account that feeding is the source of energy for adipose tissue, the time of feeding, particularly for high-energy content meals seems to be a relevant question for the development of obesity from childhood. These findings may be justified by the presence of an active circadian clock in different organs related to food intake; this is the case for stomach, intestine, pancreas or liver [18].

In a study in pregnant women, predominantly nighttime feeding was associated with higher fasting glucose concentrations in lean but not in overweight women; this finding suggests that the effect of timing of maternal feeding on glucose homeostasis may be dependent of adiposity [19]. Also, in a prospective birth cohort study assessing dietary intakes of 12-months-old infants and their respective feeding times using a 24-hours dietary recall, the timing of feeding at 12 months was associated with daily energy and macronutrient intakes, and feeding mode during early infancy [20]. No other study assessed the relationship between timing of infant feeding and later obesity development. Despite the very scarce literature on the issue in infants, children or adolescents, it seems there are different patterns of energy intake during the day and they could influence later obesity development and metabolism.

The Intestinal Microbiota and Eating Practices and their Relation to Metabolic Programming

**Childhood BMI in relation to microbiota in infancy and lifetime antibiotic use**

Korpela K1, Zijlmans MA2, Kuitunen M3, Kukkonen K4, Savilahti E3, Salonen A1, de Weerth C2, de Vos WM1, 5

1 Immunobiology Research Program, Department of Bacteriology and Immunology, University of Helsinki, Helsinki, Finland; 2 Department of Developmental Psychology, Behavioural Science Institute, Radboud University Nijmegen, Nijmegen, The Netherlands; 3 Children’s Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland; 4 Skin and Allergy Hospital, Department of Paediatrics, Helsinki University Central Hospital, Helsinki, Finland; 5 Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands

*Microbiome* 2017;5:26

**Background:** The intestinal microbiota and use of antibiotic have been identified as potential modulators of early metabolic programming and weight development. The aim was to assess if the early microbiota composition is associated with later BMI, and if the use of antibiotic modifies this association.

**Methods:** The fecal microbiota composition at 3 months and the BMI (calculated by measurements of weight and height) at 5–6 years were analyzed in 2 cohorts of healthy children born vaginally at term in The Netherlands (n = 87) and Finland (n = 75). Records of lifetime antibiotic use were obtained.

**Results:** The microbiota compositions differed clearly between the countries. The background variables: country, birth weight, breastfeeding duration, and total lifetime antibiotic use explained 11% of the BMI variation. The only significant contributor to BMI was birth weight (p < 0.001). Antibiotic use had a nearly significant positive association with BMI (p = 0.06). Children with a low rela-
The intestinal microbiota of infants is predictive of later BMI and may serve as an early indicator of obesity risk. The influence on BMI appears to depend on later antibiotic use.

Comments

The establishment of the gut microbial population in the neonate is a complex process that may involve interactions between the maternal and fetal genes and environment. These interactions may begin before birth and progress through multiple stages under the influence of various internal factors, such as the early decline in the abundance of oxygen in the gut that influences the balance of aerobes and anaerobes, and external factors such as diet [25]. Vaginally delivered neonates have larger populations of Bacteroides and Bifidobacteria species than those born by C-section [26] that have been reported to persist for months to years [25]. The observations that increased Bacteroidetes populations are present in both obese children and children born by C-section [27] suggest that the infant microbiome may contribute to the subsequent increased risk of obesity in children [28] and young adults [29] delivered by C-section. Similarly, maternal exposure to antibiotics in late pregnancy or exposure in early infancy are associated with decreased bacterial diversity of the first stool of the neonate, reduced abundance of lactobacilli and bifidobacteria in the infant gut, and an approximately 80% increased risk of childhood obesity [30].

The current study demonstrated that the intestinal microbiota of infants is predictive of later BMI and may serve as an early indicator of obesity risk, but only if these infants received several courses of antibiotics.

Identification of factors that increase the risk of excessive weight gain can help promote preventive strategies. The microbiota may represent a biomarker for assessing individual risks of excessive weight gain, and is a likely candidate for metabolic programming of infants. Moreover, the aggressive hands-on approach of prescribing antibiotics in early life has to also consider the long-term outcome of the risk of becoming obese.
Associations between school meal-induced dietary changes and metabolic syndrome markers in 8- to 11-year-old Danish children

Damsgaard CT¹, Ritz C¹, Dalskov S-T¹, Landberg R²,³, Stark KD⁴, Biltoft-Jensen A⁵, Tetens I⁵, Astrup A¹, Michaelsen KF¹, Lauritzen L¹

¹Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Frederiksberg, Denmark; ²Department of Food Science, Swedish University of Agricultural Sciences, Uppsala, Sweden; ³Nutritional Epidemiology Unit, Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; ⁴Department of Kinesiology, University of Waterloo, Waterloo, ON, Canada; ⁵Division of Nutrition, National Food Institute, Technical University of Denmark, Søborg, Denmark


Background: Consumption of meals rich in fish, vegetables, and potatoes with reduced intakes of fat can improve the blood pressure, homeostatic model assessment insulin resistance (HOMA-IR), and plasma triacylglycerol.

The aim of the present study was to evaluate whether intake of key dietary components of Nordic school meals are associated with MetS markers during 6-month intervention.

Methods: Data from 7-day dietary records and measurements of blood pressure, waist circumference, android/total FM assessed by dual-energy X-ray absorptiometry, whole-blood docosahexaenoic acid (DHA, 22:6n-3), an indicator of fish intake, and fasting blood MetS markers were collected at baseline, 3 and 6 months from children (n = 523). These parameters were analyzed in linear mixed-effects models adjusted for puberty, growth, and fasting.

Results: Whole-blood DHA was negatively associated with HOMA-IR (p < 0.001) and triacylglycerol (p < 0.0001). Potato intake was positively associated with waist circumference (p < 0.01). Intakes of whole-grain, dietary fiber, protein, and fat were not associated with any of the MetS markers.

Conclusions: DHA in whole-blood was the main diet-related predictor of the beneficial effects of the school meals on MetS markers.

Comments

The school food environment, including when and where children obtain food and the types of options available during the school day, plays an important role in children’s consumption patterns. Thus, childhood obesity prevention efforts often focus on altering the school food environment as a mechanism for improving student dietary intake. Healthy eating practices during childhood may also help prevent metabolic disturbances and reduce later CVD mortality.

Children from most Western populations have low consumption of fish and coarse vegetables and thereby eat few dietary fibers and too much sugar and saturated fat, relative to dietary guidelines. Nordic diets rich in fish, fruits, berries, vegetables, whole-grains, and nuts have been shown to improve CVD risk factors and have been associated with reduced mortality in adults [31]. Increased intake of n-3 long-chain polyunsaturated fatty acids and reduced intake of saturated fat can improve the blood pressure, insulin sensitivity, and lipid profile [32], and vegetable intake has been associated with reduced risk of MetS in adults.

Danish children get 40–45% of their daily energy intake in school and in after-school centers that offer the opportunity to test the impact of healthy diets on cardiometabolic health in children. This study found that insulin resistance and plasma triacylglycerol were inversely associated with whole-blood DHA. Surprisingly, neither intakes of whole-grain, dietary fiber, protein or fat were associated with the MetS markers.
Therefore, fish and n-3 long-chain polyunsaturated fatty acids are key components in a healthy diet with potential for prevention of MetS from childhood. One of the study limitation is that the diet assessment was based on dietary recordings, that is subject to both imprecision and inaccuracy, including selective under- and over-reporting, especially in children. Another limitation is the generalization of the study results, since in many countries fish consumption by children is much lower than in the Danish population. However, it suggests that school can offer a good opportunity of nutritional intervention to improve the metabolic outcome by healthier food consumption.

The Association Between Vitamin D and Inflammatory Biomarkers in Obese and Overweight Subjects

The effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects: a systematic review with meta-analysis

Jamka M1, Woźniewicz M1, Walkowiak J2, Bogdański P3, Jeszka J1, Stelmach-Mardas M2,4
1Department of Human Nutrition and Hygiene, Poznan University of Life Sciences, Poznan, Poland; 2Department of Paediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poznan, Poland; 3Department of Education and Obesity Treatment and Metabolic Disorders, Poznan University of Medical Sciences, Poznan, Poland; 4Department of Epidemiology, German Institute of Human Nutrition, Potsdam-Rehbrücke, Nuthetal, Germany

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Background: Obesity is strongly associated with a low-grade chronic inflammation. There is an inverse association between vitamin D level and total body fat and visceral obesity. Vitamin D can also play a role in immune activation and inflammation. The aim of the current review was to assess the effect of vitamin D supplementation on selected inflammatory biomarkers in obese and overweight subjects.

Methods: The search process was based on the selection of publications of RCTs in the databases of: PubMed, Web of knowledge, Scopus, the Cochrane Library, and Embase. The study quality was assessed by a 9-point scoring with high-quality study defined by a threshold of ≥7 points. Thirteen RCTs, consisting of 1,955 overweight and obese subjects (mean age range 13.6–71.7 years), were included. Changes in the concentration of 25-hydroxyvitamin D (25\[OH\]D), C-reactive protein, tumor necrosis factor-α, and interleukin-6 were assessed.

Results: The baseline levels of 25OHD suggested common vitamin D deficiency or insufficiency in the analyzed population. Vitamin D supplementation increased the plasma concentrations of 25OHD in each of the intervention groups achieving the mean levels of 20.1–80.0 ng/mL. The findings of this meta-analysis did not show statistically significant impact of vitamin D supplementation on selected pro-inflammatory cytokines (tumor necrosis factor-α and interleukin-6) and C-reactive protein.

Conclusions: The current findings suggest that vitamin D supplementation does not have a significant influence on changes in the levels of common inflammatory biomarkers in obese and overweight subjects.
Vitamin D deficiency and cardiometabolic risk factors are common in obese adolescents. Observational studies demonstrate an inverse relationship among serum 25OHD and obesity, insulin resistance, and inflammatory cytokines. Therefore, a systematic review based on RCTs to examine the association between oral vitamin D supplementation and circulating inflammatory biomarkers of overweight/obese subjects is essential. However, the current meta-analysis is limited by the small number of available studies concerning the described topic with limited number of participants. Additionally, the combined supplementation with vitamin D and calcium makes the effect difficult to distinguish between those 2 components. Furthermore, the dose of supplied vitamin D in the analyzed studies and the duration of the supplementation were different and could influence the full interpretation of the collected data. No information was available on long-term changes in cytokine levels in obese and overweight subjects that could strongly support the merit of vitamin D supplementation. Thus, RCTs with long-term follow-up should be applied for future investigations to give a better answer.

Relation between milk-fat percentage, vitamin D, and BMI z score in early childhood

Vanderhout SM1–3, Birken CS4–6, Parkin PC4–6, Lebovic G3, 6, Chen Y3, O’Connor DL3, Maguire JL1–6
TARGet Kids! Collaboration

1Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada; 2Department of Paediatrics, and 3Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Ontario, Canada; 4Department of Paediatrics, and 5Division of Paediatric Medicine and the Paediatric Outcomes Research Team, The Hospital for Sick Children, Toronto, Ontario, Canada; 6Child Health Evaluative Sciences, The Hospital for Sick Children, Peter Gilgan Centre for Research and Learning, Toronto, Ontario, Canada

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Background: Recommendations for children older than 2 years advice reduced milk-fat consumption to reduce childhood obesity. The objectives of the current cross-sectional study were: to explore the association between milk-fat percentage and both BMI z score (zBMI) and venous 25(OH)D, and to assess whether milk volume consumed modified this relation.

Methods: Healthy children aged 12–72 months were recruited from 9 primary health care practices within The Applied Research Group for Kids (TARGet Kids!) research group in Toronto, Canada. A linear regression analysis was used to examine the relation between milk-fat percentage and child 25(OH)D and zBMI concurrently.

Results: Among the included children (n = 2,745) there was a positive association between milk-fat percentage and 25(OH)D (p = 0.006) and a negative association with the zBMI (p < 0.0001). Participants who drank whole milk had a 5.4-nmol/L (95% CI 4.32–6.54) higher median 25(OH)D concentration and a 0.72 lower (95% CI 0.68–0.76) zBMI score than children who drank 1% milk. The consumed milk volume modified the effect of milk-fat percentage on 25(OH)D (p = 0.003) but not on zBMI (p = 0.77).

Conclusions: Whole milk consumption among healthy young children was associated with higher vitamin D stores and lower BMI.
Fortified cow milk is a contributor of vitamin D and dietary fat in children. Current guidelines for cow’s milk consumption in children older than age 2 years suggest 1 or 2% milk to reduce the risk of obesity. Given that milk is the main dietary source of vitamin D in young children and that vitamin D is fat soluble, it was logical to hypothesize that 25(OH)D concentration may be positively associated with the fat content of milk. Since the current study demonstrated that whole milk consumption among healthy young children was associated with higher vitamin D stores, current guidelines may have the paradoxical effect of limiting 25(OH)D concentration, and consumption of milk with higher fat content may be helpful in optimizing both vitamin D stores and adiposity.

The limitations of this study include: the cross-sectional design, in which causality and its direction cannot be established between the exposure and outcomes. Data collection for milk consumption was reported by parents, which may be subject to recall bias, and 56% of the children in the study regularly consumed a vitamin D-containing supplement.

Longitudinal and intervention studies are needed to confirm the current findings and examine clinical outcomes related to both serum 25(OH)D concentrations and adiposity in children.

**Vitamin D supplementation trial in infancy: body composition effects at 3 years of age in a prospective follow-up study from Montréal**

Hazell TJ\(^1\), Gallo S\(^2\), Vanstone CA\(^3\), Agellon S\(^3\), Rodd C\(^4\), Weiler HA\(^3\)

\(^1\)Department of Kinesiology and Physical Education, Wilfrid Laurier University, Waterloo, ON, Canada; \(^2\)Department of Nutrition and Food Studies, George Mason University, Fairfax, VI, USA; \(^3\)School of Dietetics and Human Nutrition, McGill University, Montréal, QC, Canada; \(^4\)Winnipeg Children’s Hospital, University of Manitoba, Winnipeg, MB, Canada

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**Background:** Circulating 25(OH)D concentrations positively associate with lean body composition in adolescents. Whether vitamin D positively relates to lean body composition in younger children is unknown. Addressing this knowledge gap could improve the understanding of the nutritional and environmental factors associated with healthy growth and body composition from birth to early childhood. The aim was to evaluate how vitamin D supplementation in infancy affects the body composition at 3 years of age.

**Methods:** This report is an observational follow-up of children 3 years of age that participated in a double-blind randomized trial of one-month-old healthy, breastfed infants (\(n = 132\)) randomly assigned to receive oral vitamin D\(_3\) supplements of 400, 800, 1,200, or 1,600 IU/day during the first year of life. Body composition was measured using dual-energy X-ray absorptiometry and plasma 25(OH)D concentrations by liquid chromatography tandem mass spectrometry.

**Results:** Anthropometry, body composition, diet, activity, and demographics were similar across dosage groups at 3 years. The mean 25(OH)D concentration from 1 month to 3 years was higher (\(p < 0.001\)) in the 1,200 IU group than in the 800 and 400 IU groups. Children with 25(OH)D concentrations >75 nmol/L had lower FM (\(~450\) g; \(p = 0.049\)). In multiple linear regression, mean 25(OH)D was associated with lean mass percent (\(p = 0.042\)), FM (\(p = 0.048\)), and body fat percentage (\(p = 0.045\)).
**Conclusions:** While there were no differences in vitamin D status or body composition at 3-year across the different vitamin D dosage groups, this study provides novel findings that suggest higher plasma 25(OH)D concentrations early in life being associated with leaner body composition.

**Comments**
The possible mechanism for the importance of vitamin D to a leaner body composition is not fully understood. There is a large body of growing evidence showing that dairy products, calcium, and vitamin D intake play a role in the regulation of body FM [33]. Data also indicate that vitamin D may increase the lean body mass and inhibit the development of adipocytes. These effects of vitamin D may be mediated by 1,25(OH)2D3 or via suppression of PTH [34]. It has been suggested that high levels of 1α,25-dihydroxyvitamin D and iPTH can modulate intracellular Ca++ concentrations, so increasing Ca++ flux to adiposities, which stimulate fatty acid synthase, may increase lipogenesis and inhibit lipolysis [35]. Evidence implies that high calcium and/or vitamin D intakes can repress fatty acid synthase by decreasing intracellular Ca++ in adiposities [36].
The limitation of the present study is that all children receiving at least 400 IU/day of vitamin from 1 to 12 months likely contributed to the very good vitamin D status >50 nmol/L and precluded studying children with lower vitamin D status. Overall, data of the present study suggest that children with higher vitamin D status over their first 3 years have a leaner body composition and that efforts to achieve healthy status targets should be made through ensuring adequate dietary or supplemental vitamin D intakes. However, more research is certainly warranted to establish how 25(OH)D contributes to a leaner body composition.

**Brain Imaging and Brain Response to Food**

**Developmental differences in the brain response to unhealthy food cues: an fMRI study of children and adults**

van Meer F1,2, van der Laan LN1,2, Charbonnier L1,2, Viergever MA1,2, Adan RA2, Smeets PA1–3 on behalf of the I. Family Consortium

1Image Sciences Institute and 2University Medical Center Utrecht, Utrecht, Netherlands; 3Division of Human Nutrition, Wageningen University and Research Centre, Wageningen, The Netherlands


**Background:** In modern societies, there is an abundance of food cues that may promote overconsumption. In light of the current rise in childhood obesity, it is crucial to investigate the neural mechanisms underlying food selection and overconsumption in children. Food selection is mainly guided by the visual system, and the sight of food leads to an array of responses ranging from preparation for food ingestion (cephalic-phase responses) to the desire to eat and hedonic evaluation. Brain areas most consistently activated by food viewing in children correspond with the appetitive brain network and largely overlap with those found in adults. However, children may not activate areas important for inhibitory control. Children may be particularly susceptible to food cues because their brain is still developing.
The aim was to examine potential developmental differences in children’s and adults’ responses to food cues, and to determine how these responses relate to weight status.

**Methods:** The study included children aged 10–12 years (n = 27) and adults aged 32–52 years (n = 32). fMRI was performed during a food-viewing task in which UF and healthy food (HF) pictures were presented.

**Results:** In children, there was a stronger response to UF than to HF pictures in the right temporal/occipital gyri and left precentral gyrus. Children with a higher BMI had lower activation in the bilateral dorsolateral prefrontal cortex while viewing unhealthy compared with HFs.

In adults, there was a stronger response to UF than to HF pictures in the bilateral middle occipital gyrus and the right calcarine sulcus. There were no correlations between brain activation in the UF > HF contrast and BMI.

Children had a stronger response to UFs compared with HFs than adults in the left precentral gyrus. When including healthiness ratings, liking ratings, hunger ratings, time since last meal, or Tanner stages as covariates in the fMRI analyses, the clusters found did not change. The difference between children and adults remained the same when only the parents of the included children were considered in the analysis.

**Conclusions:** Children activated the left precentral gyrus more than adults did in response to UF compared with HF pictures. Furthermore, children with a higher BMI had lower activation in the bilateral left dorsolateral prefrontal cortex while viewing UFs compared with HFs.

This study demonstrated that children have stronger activation than adults in brain sites implicated in motivation in response to UFs, with decreased activation in inhibitory areas in children with higher BMIs. This suggests that children who are overweight may have less control over their motivational responses toward foods.

**Comments**

In the field of functional neuroimaging, food stimuli, in comparison with non-food objects, activate occipital, limbic and paralimbic, and prefrontal areas. By far the most widely used technique in this research field is fMRI. This neuroimaging method measures the change in blood flow (indicated by the blood oxygen level-dependent [BOLD] signal) that is related to the neural activity in the human brain. fMRI has a number of advantages over other imaging modalities used in behavioral neuroscience: unlike nuclear techniques, it is entirely noninvasive, and its spatial resolution is much better than that achieved by magnetoencephalography and electroencephalography; furthermore, it has sufficient temporal resolution to observe patterns of neuronal activity in the entire brain in few seconds.

Functional neuroimaging studies examining brain activation in response to food images have identified brain regions related to both reward (limbic and paralimbic regions) and cognitive control (prefrontal cortices) in children [37, 38].

The finding of this study indicates that children are more susceptible to UF cues than adults, especially if they are overweight. This calls for better protection of children from targeted food marketing to prevent the overconsumption of UFs.

However, to better assess the effect of age on UF and HF cue reactivity, the results should be reproduced in a longitudinal fMRI study. Future studies should ideally take into account food intake as well to be able to clarify the link between food-cue reactivity and dietary behavior.
Brain response to images of food varying in energy density is associated with body composition in 7- to 10-year-old children: results of an exploratory study

Fearnbach SN1, English LK1, Lasschuijt M2, Wilson SJ3, Savage JS1, Fisher JO4, Rolls BJ1, Keller KL1, 5

1Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA; 2Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands; 3Department of Psychology, The Pennsylvania State University, University Park, PA, USA; 4Center for Obesity Research and Education, Department of Social and Behavioral Sciences, Temple University, Philadelphia, PA, USA; 5Department of Food Science, The Pennsylvania State University, University Park, PA, USA

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Background: Energy balance is regulated by a complex system of peripheral and central physiological signals that rise from compartments of adipose and lean tissue, as well as the gastrointestinal tract and accessory organs, to influence energy intake and expenditure. It is not known whether the effects of FM and FFM on energy balance are mediated by processes in appetite-regulating centers of the brain. Variability in the brain’s response to food could partially be explained by differences in levels of metabolically active tissues (FM and FFM) throughout the body. The aim of this study was to determine the association between children’s body composition, compartmentalized into FFM and FM, and brain activation in response to images of food that vary by ED, a measure of energy content per weight of food.

Methods: This was a cross-sectional study with a community-based sample of 36 children aged 7–10 years. The body composition was measured using bioelectrical impedance. Brain response to High (>1.5 kcal/g) and Low (<1.5 kcal/g) ED food images, and control images were measured by fMRI.

Multi-subject random effects general linear model and 2-factor repeated measures analysis of variance were used to test for the main effects of ED (high ED vs. low ED) in a priori defined brain regions of interest previously implicated in energy homeostasis and reward processing. Pearson’s correlations were then calculated between activation in these regions for various contrasts (high ED-low ED, high ED-control, low ED-control) and child body composition (FFM index, FM index, % body fat (BF)).

Results: Across the whole sample, BOLD activation was greater for high ED foods relative to low ED foods in the left thalamus (p < 0.05), which functions in sensory processing. BOLD activation for high ED relative to low ED foods in the right substantia nigra was positively correlated with children’s FFM index (p = 0.01). Thus, greater amounts of lean body mass were associated with greater BOLD activation for higher ED foods in a region of the brain involved with dopamine signaling and reward. This association was unaffected after controlling for BMIz (p < 0.05) and for children’s rated liking or wanting of high ED or low ED food images (p < 0.05). There was a trend in the direction of a negative association between the response to low ED foods in the right substantia nigra and both FM index and %BF.

Conclusions: The findings demonstrated a significant effect of ED on the thalamus (e.g., sensory processing) such that high ED foods elicited greater BOLD activation than low ED foods. However, there was heterogeneity in children’s brain responses to food stimuli, such that not all children responded in the same direction or with the same magnitude. Overall, FFM but not FM, was positively associated with BOLD activation for high ED foods in a reward region of the brain, the substantia nigra. FFM is an appetitive driver. These results confirm that brain response to foods varying in energy content is related to measures of child body composition.
Previous studies in adolescents and adults have demonstrated that FFM is the best predictor of meal size and daily energy intake [39, 40]. These effects on intake are attributed to the fact that FFM is the largest contributor to resting metabolic rate, and therefore total daily energy expenditure [41]. However, the underlying mechanism for how FFM affects appetite-regulating centers in the brain is not clear. The present results suggest that increases in FFM are associated with an increased reward response to high ED foods relative to low ED foods. Therefore, children with greater FFM have greater energy requirements, which may partly explain increased responsiveness to higher calorie foods relative to lower calorie options. However, body fat was not associated with the activation for high ED foods, which suggest that greater adiposity may be related to a reduced reward response to low ED food images. The direction of a negative association between the response to low ED foods in the right substantia nigra and both FMI and %BF suggest that as adiposity increases, children may be less responsive to healthier, low-calorie foods. It is important to evaluate this question further across a range of body weights to determine the generalizability of these findings.

The study limitations include the small sample size, the cross-sectional design in a homogenous sample of predominantly lean children that does not allow us to know whether these results are generalizable to other populations, or whether activation in these brain areas is a cause or a consequence of differences in body composition. It is possible that the relationship is bidirectional.

Future studies should determine whether these individual differences in brain activity can explain variability in actual eating behavior, and whether they are related to changes in children's weight status over time.

References


