Obesity and Weight Regulation

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We have been very happy to get 3,380 papers out of our established search strategy in PubMed and have selected 21 papers which in our mind have been the most exciting ones. The highlights in this year's chapter are publications about stabilization or even decline in obesity prevalence rates in children in several countries, several new mutations for monogenic obesity in children, new clinical data on the relevance of brown adipose tissue in humans, and the finding that previously described associations between breastfeeding and lower risk of obesity later in life may be subject to confounding factors and publication bias. Thus, the present *Yearbook* chapter on obesity and weight regulation covers again a broad research area with some new developments which we think have the potential for a future breakthrough.

New data on incidence and prevalence

Incidence of childhood obesity in the United States

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Background: The prevalence and trends of overweight and obesity in the USA are well known but there are little data about its incidence. This study aimed to report on national data regarding the incidence of obesity among elementary schoolchildren in the USA.

Methods: Measured data of a representative prospective cohort ($n = 7,738$ in kindergarten 1998) from the Early Childhood Longitudinal Study were analyzed. Between 1998 and 2007, trained assessors measured weight and height at 7 time points. Non-obese participants at baseline ($n = 6,807$) were followed for 50,396 person-years. CDC growth charts were used to classify overweight and obesity. The incidence of obesity was calculated on the basis of the follow-up data for the non-obese children at baseline. Furthermore, the cumulative incidence (>9 years) and the incidence density (cases per person-years) were estimated.

Results: At baseline, 12.4% of the children (mean age 5.6 years) were defined as obese and another 14.9% as overweight. The follow-up evaluation in 8th grade (mean age 14.1 years) showed 20.8% being obese and 17.0% being overweight. Between kindergarten and the period between the 5th and 8th grade, a decrease in annual incidence could be observed from 5.4 to 1.7%. Overweight children at baseline had a fourfold higher risk to become obese compared with normal-weight children (31.8 vs. 7.9% cumulative incidence). Nearly half of the children who became obese within the course of the study had been overweight at baseline.

Conclusions: Incidence of obesity between the ages 5 and 14 years occurred more likely among younger children, especially those who were overweight in kindergarten.

The present study reports on an important issue which may provide insights into the nature of the obesity epidemic. Examining obesity incidence could help to define critical vulnerable ages and risk groups. 45.3% of all the incident obesity cases that occurred between the ages 5 and 14 years arose in those 14.9% who were overweight as 5-year-olds. The authors describe a much higher annual incidence of obesity during kindergarten among children who entered the kindergarten overweight compared to normal-weight children (19.7 vs. 2.4%). Furthermore, normal-weight kindergartners had a four times lower risk of becoming obese by the age of 14 compared to overweight kindergart-

ners. With increasing age the high incidence of obesity among children who were overweight in kindergarten decreased. The here shown estimates are in accordance with nationally representative data regarding the trend of obesity prevalence in the USA published by Ogden et al. [1]. In 2009 and 2010 the authors found a higher prevalence among elementary schoolchildren compared to the obesity prevalence among all children (18.0 vs. 16.9%). Regarding the risk of obesity development, factors established before birth and during the first 5 years of life have been shown to be important. Sub-analyses revealed that more than one third of high birth weight children and almost half of children (45.3%) who were overweight at kindergarten entry became obese adolescents. In children who were large at birth the incidence of obesity was described as 36% between the age of 5 and 14 years. A strong relationship between obesity risk and body weight and eating patterns early in life was mentioned by Baidal et al. [2]. To target the risk of becoming obese in later childhood, the authors speculate that obesity-prevention efforts could be effective if they focus on children who are overweight at the age of 5 years. Because of the findings and because many of the processes leading to obesity start in early life, further research is important with respect to data on incidence before adolescence.

Prevalence of childhood and adult obesity in the United States, 2011–2012

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Background: Despite no increase in obesity prevalence in the USA between 2003–2004 and 2009–2010, the rates remain at a high level with more than one third of adults and 17% of youth being obese. This report gives the most recent data on childhood obesity, shows trend analyses over time (2003–2012), and estimates obesity development in adults in the USA.

Methods: For the recent analysis, measured data on weight and height or recumbent length were collected in 9,120 NHANES participants in 2011–2012. Obesity trends were analyzed with 5 time periods between 2003–2004 and 2011–2012 using existing nationally representative NHANES data. CDC growth charts were used to define overweight and obesity among children and adolescents aged 2–19 years. Obesity in adults ≥ 20 years was defined as a BMI ≥ 30 .

Results: Overall, no significant change could be observed between 2003–2004 and 2011–2012. Currently (in 2011–2012), obesity was present in 16.9% (14.9–19.2%) of 2- to 19-years-olds and 34.9% (32.0–37.9%) of adults. 8.1% (5.8–11.1%) of infants and toddlers showed a high weight for recumbent length. Subgroup analyses showed that the obesity prevalence in pre-schoolchildren (2–5 years) significantly decreased (from 13.9 to 8.4%; $p = 0.03$) whereas the obesity prevalence in older women (≥ 60 years) significantly increased (from 31.5 to 38.1%; $p = 0.006$) during the survey period.

Conclusions: Because the obesity prevalence remains high, a continued surveillance is important regardless of the desirable development of no significant rise in obesity prevalence between 2003–2004 and 2011–2012 among youth or adults.

This paper reports the most recent data on obesity prevalence in the USA. Between 2003–2004 and 2009–2010 a first leveling off in US obesity prevalence had been described, but also a still high level in prevalence [3]. However, it should be noted that extreme obesity is still increasing [4]. A stabilization or even decline in obesity prevalence in children could also be observed in other developed countries [5]. Our group has postulated a cumulative effect of public health programs for obesity prevention resulting, for example, in an increase in physical activity and a decline in television viewing and in the consumption of sugar-sweetened soft drinks by children as possible reasons for this joyful development [6]. Regarding public health efforts on obesity, the US Department of Agriculture implemented regulations for food packages in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) [7, 8], state- and community-based interventions were funded by the CDC [9] and numerous reports and recommendations were issued by the Institute of Medicine [10], the US Surgeon General [11], and the White House [12]. On the basis of the experience from the last 10–15 years, the focus on public health programs aiming at reducing obesity-promoting lifestyles might be the more effective approach to combat obesity compared to individually based approaches. Further studies are needed.

Loss of function of the melanocortin 2 receptor accessory protein 2 is associated with mammalian obesity

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Science 2013;341:275–278

Background: Accessory proteins can modulate trafficking of G protein-coupled receptors as well as ligand binding and signaling. *Mrap2* and *Mc4r* mRNAs are co-expressed in cells of the paraventricular nucleus of the hypothalamus in mice. Therefore, it was hypothesized that *Mrap2* might modulate signaling through *Mc4r*.

Methods: The physiological role of brain-expressed melanocortin 2 receptor accessory protein 2 (MRAP2) was characterized in mice with a large panel of experiments. In addition, a cohort of humans with severe early-onset obesity was screened for variants in *MRAP2*.

Results: Whole-body as well as brain-specific targeted deletion of MRAP2 in mice resulted in severe obesity at a young age. MRAP2 interacts directly with melanocortin 4 receptor (*Mc4r*), enhancing *Mc4r*-mediated generation of the second messenger cyclic adenosine monophosphate. Sequencing of the coding region and intron/exon boundaries of *MRAP2* in obese and control individuals from the genetics of obesity study cohort [13] and the Swedish obese children's cohort [14] brought up four rare heterozygous variants. Only one of these variants, however, is clearly disruptive.

Conclusions: This sophisticated study shows that global or brain-specific inactivation of MRAP2 results in obesity in mice and that rare heterozygous variants in *MRAP2* are associated with early-onset obesity in humans.

Membrane-expressed G protein-coupled receptors (GPCRs) modulate cellular responses to several physiological stimuli. Recent data show that accessory proteins can interact with GPCR function. For example, an accessory protein for melanocortin 2 receptor (MC2R) is required for its trafficking to the surface of adrenal cells and for signaling in response to ACTH. In humans it has been shown that the loss of MC2R as well as the loss of MRAP results in severe resistance to ACTH and in glucocorticoid deficiency [15, 16].

The phenotype of *Mrap2*-null mice comprises normal birth weight and normal postnatal weight gain, but the development of extreme obesity during later life on a regular *ad libitum* diet. Heterozygous mice were significantly heavier than wild-type animals. Even when fed with the same amount of chow under controlled conditions, null-mice gained more weight than did wild-type mice. Only late in life was a subtle increase in cumulative food-intake observed in null animals as compared with control animals. This means that the onset of obesity precedes hyperphagia in mice.

Furthermore, it was asked whether the deletion of *Mrap2* causes obesity in part by altering signaling through centrally expressed *Mc4r*. Brain-specific targeted deletion of *Mrap2* led to the same phenotype as shown for whole-body *Mrap2* deletion. Furthermore, *Mrap2* deficiency led to a less severe obesity than *Mc4r* deficiency. In a heterologous system of CHO cells, the authors showed that MRAP2 enhances MC4R-mediated generation of cAMP suggesting that *Mrap2* disruption alters MC4R signaling and that this mechanism might partially explain the development of obesity. However, the exact mechanisms by which MRAP2 exerts its effects on the regulation of energy homeostasis remain to be firmly established.

In the same volume of *Science*, Sebag et al. [17] reported that the zebrafish ortholog of *Mrap2* similarly affects the zebrafish MC4R signaling. The evolutionary conservation and consequences of loss of MRAP2 function supports its importance in vertebrate biology.

Loss-of-function mutations in *SIM1* contribute to obesity and Prader-Willi-like features

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Background: Obesity is a feature of *SIM1* haploinsufficiency in mice. In humans with Prader-Willi syndrome, abnormalities in chromosome 6q16, a region that includes *SIM1*, have been reported. *SIM1* involvement in the development of obesity in humans however has not yet been demonstrated.

Methods: *SIM1* was sequenced in 44 children with Prader-Willi-like syndrome features and in controls. In heterologous systems the functional effects of identified *SIM1* variants were investigated.

Results: Four rare variants in *SIM1* were identified in the children with Prader-Willi-like syndrome features. In addition, 4 other rare variants in *SIM1* were identified in 7 extremely obese adults. Three mutations showed strong loss-of-function effects. These mutations were also associated with a high intra-family risk for obesity. The variants with mild or no functional effects were not associated with obesity within families.

Conclusions: These clinical and in vitro data show a consistent link between *SIM1* loss of function and severe obesity in man.

Rare variants in single-minded 1 (*SIM1*) are associated with severe obesity

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J Clin Invest 2013;123:3042–3050

Background: Obesity is a feature of *Sim1* haploinsufficiency in mice. In humans with Prader-Willi syndrome, abnormalities in chromosome 6q16, a region that includes *SIM1*, have been reported. *SIM1* involvement in the development of obesity in humans however has not yet been demonstrated.

Methods: The coding region of *SIM1* was sequenced in 2,100 patients with severe early-onset obesity and in 1,680 controls. Functional assays were performed in stably transfected cells to investigate the activation of a *SIM1*-responsive reporter gene.

Results: Thirteen different heterozygous variants in *SIM1* were identified in 28 unrelated severely obese patients. Nine of these 13 variants showed functional impairment in the in vitro studies. These variants also co-segregated with obesity in extended family studies, however with variable penetrance.

Conclusions: Rare variants in *SIM1* are associated with severe obesity and should be considered in patients with hyperphagic obesity of early onset.

Single-minded 1 (*SIM1*) is a basic helix-loop-helix transcription factor involved in the development and function of the paraventricular nucleus (PVN) of the hypothalamus, a region that plays a critical role in energy homeostasis. Whereas *Sim1* homozygous null mice die in the perinatal period and have abnormal hypothalamic architecture, *Sim1* heterozygous mice survive and develop severe obesity associated with increased food intake. Interestingly, *Mc4r* mRNA levels in the PVN are significantly reduced in *Sim1*^{+/-} mice. The response of melanotan II, a potent melanocortin receptor agonist, is blunted in these mice, suggesting that *SIM1* lies downstream of MC4R [18].

Patients with chromosomal deletions involving 6q14–q21, a region that encompasses several genes including *SIM1*, have been reported to develop early-onset obesity and developmental delay. Some reports suggest a phenotypic overlap with the Prader-Willi syndrome.

The results of both studies show that in human *SIM1* variants, which also exhibit reduced activity in a heterologous in vitro cell system, provide strong evidence that this transcription factor is an important factor for the regulation of food intake and energy homeostasis by interacting with the central melanocortin signaling. The precise mechanisms and the direct transcriptional targets of *SIM1* have

yet to be established. Interestingly, the necdin protein (NDN) which is believed to be involved in the Prader-Willi syndrome [19] regulates the activity of the SIM1:ARNT₂ dimer. This finding supports a possible role of *SIM1* in Prader-Willi-like syndrome.

Pseudohypoparathyroidism as a model of obesity and insulin resistance

Energy expenditure in obese children with pseudohypoparathyroidism type 1a

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Background: Early-onset obesity is a typical feature of pseudohypoparathyroidism (PHP-1a). Whole-body energy homeostasis has not yet been investigated in these patients in order to find a link to increased weight gain.

Methods: Whole-room indirect calorimetry was applied to determine resting energy expenditure (REE) as well as the thermogenic effect of a high-fat meal in 6 patients with PHP-1a and 21 obese individuals as controls.

Results: REE in children with PHP-1a was significantly reduced as compared to controls: adjusted for fat-free mass individuals with PHP-1a expended 346.4 kcal/day less than controls as REE. Also the thermogenic effect of food tended to be lower in PHP-1a individuals as compared to obese controls.

Conclusions: The reduced REE measured in PHP-1a children may contribute to the development of obesity. In addition, PHP-1a individuals show also a tendency of abnormal diet-induced thermogenesis in response to a high-fat meal.

Reduced insulin sensitivity in adults with pseudohypoparathyroidism type 1a

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Background: Severe obesity as well as insulin resistance are clinical features of the disruption of the G_sα maternal allele in mice, whereas early-onset obesity is a clinical feature in patients with PHP-1a. So far, insulin sensitivity and glucose metabolism have not been systematically characterized in individuals with PHP-1a.

Methods: Eight patients with PHP-1a and 24 subjects matched for age, gender and percentage body fat participated in the study. Insulin sensitivity, β-cell function, energy expenditure, and sympathetic nervous system activity were investigated.

Results: Insulin sensitivity (measured by an intravenous glucose tolerance test as well as during a mixed meal) and β-cell function (measured by the disposition index) tended to be lower in PHP-1a patients as compared to controls. Resting energy expenditure (EE), total EE, meal-induced thermogenesis, and 24-hour urinary catecholamine excretion were not different between the groups.

Conclusions: The results of this study indicate that adults with PHP-1a are more resistant to insulin compared with their matched controls. This finding may contribute to an earlier onset of glucose intolerance and diabetes in these patients.

The stimulatory G-protein α unit (G_sα) mediates hormone-stimulated, receptor-stimulated intracellular cAMP formation. Patients with PHP-1a are characterized by early-onset obesity and resistance to multiple hormones including PTH, TSH, GH-RH, and gonadotropins in their respective target tissues

due to maternal mutations in the tissue-specific imprinted gene $G_{5\alpha}$ (*GNAS*). These patients develop severe obesity early in life. Interestingly, patients with inherited *GNAS* mutations on the inactive paternal allele do not develop obesity more than the general population [20].

Patients with maternally inherited mutations in $G_{5\alpha}$ develop the clinical phenotype of PHP-1a including classic Albright hereditary osteodystrophy (short stature, brachydactyly, subcutaneous ossifications, and cognitive impairment) as well as multi-hormone resistance. Patients with a paternally inherited $G_{5\alpha}$ mutation, termed pseudopseudohypoparathyroidism, have only a mild form of the Albright hereditary osteodystrophy and no multi-hormone resistance syndrome.

Concerning the observed rapid weight gain the following possible explanations have been debated: abnormal function of MC4R, subclinical hypothyroidism, growth hormone deficiency, and reduced sympathetic nervous system activity.

The two above-mentioned studies improved our understanding of the pathophysiology of PHP-1a in several aspects. Shoemaker et al. report the first study to measure energy expenditure in patients with PHP-1a. The clearly decreased REE in the absence of hyperphagia explains in part the rapid weight gain seen in children with PHP-1a. Interestingly, their findings are supported by findings in mice with a brain-specific *gnas* knockdown disruption of the maternal allele with decreased REE compared with animals where the paternal allele was disrupted. The authors discussed several similarities between the resulting obesity phenotype and obesity due to mutations in *MC4R* as there is reduced REE and reduced thermogenesis induced by a meal. This difference in thermogenic effect of food has however been only demonstrated in mice.

Muniyappa et al. report the first study of systemic insulin sensitivity and β -cell function in PHP-1a patients as compared to controls. The cohort with PHP-1a was less insulin-sensitive and tended to have impaired pancreatic β -cell function. These findings may contribute to the high incidence of glucose intolerance and diabetes observed in patients with PHP-1a. Their findings are inconsistent with results in a mouse model of PHP-1a in which glucose intolerance and insulin resistance develop even before the onset of obesity. The finding of lower β -cell function in PHP-1a patients might be due to a $G_{5\alpha}$ -mediated defect of incretin such as GLP-1 and GIP in β cells. It would be intriguing for future studies to investigate the incretin effect of GLP-1 administration on insulin secretion in subjects with PHP-1a.

There are important differences between these two studies in their findings relating to REE. These differences may indicate that during the developmental period of childhood more significant metabolic differences can be observed than in adulthood. Accordingly, it should be noted that the phenotype obesity is usually more severe in children than in adults with PHP-1a. In summary, these two studies improved our knowledge about the role of $G_{5\alpha}$ function in energy expenditure, insulin sensitivity, and β -cell function on the basis of sophisticated investigations in patients with PHP-1a.

Obesity as a late effect of cancer treatment in childhood and adolescence

Obesity in pediatric ALL survivors: a meta-analysis

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Background: In recent years, obesity has been increasingly recognized as a potential late effect of treatment for pediatric acute lymphoblastic leukemia (ALL). Although most available studies report increased prevalence of overweight and obesity in pediatric ALL survivors, there is heterogeneity in the available data regarding rates of obesity and risk factors for the development of obesity (i.e. gender, age at treatment, treatment modalities).

Methods: All papers indexed in MEDLINE from its inception through January 2013 were searched and papers were included in the meta-analysis if they enrolled at least 10 survivors of pediatric ALL who

were diagnosed before age 21 years, assessed prevalence of overweight and obesity or reported anthropometric measures of weight status (BMI, BMI z-score, BMI percentile, or percentage body fat measured by DXA), and compared obesity among ALL survivors to reference populations (either growth references or external control groups). For quality assessment of the included studies, a modified Newcastle-Ottawa Scale was used. Summary BMI z-scores were obtained from the study data using an inverse variance random-effects model. Subgroup meta-analyses were performed to explore associations between patient characteristics, treatment modalities and obesity. Robustness of findings of the meta-analyses was assessed by a set of sensitivity analyses and between-study heterogeneity was assessed by using Cochran's Q statistic.

Results: Meta-analysis included 47 studies reporting on 9,223 survivors of pediatric ALL. Prevalence of overweight/obesity exceeded 40% in 11 studies reporting data on survivors <5 years post-treatment, ranged between 29 and 69% in survivors 5–9 years post-treatment (14 studies), and ranged between 34 and 46% in five studies evaluating survivors ≥10 years post-treatment. Twenty studies provided data for BMI z-score in a total of 1,742 patients. Mean BMI z-score in this sample was 0.83 (95% CI 0.60, 1.60), corresponding to the 80th BMI percentile. Subgroup meta-analyses demonstrated no significant effect of gender, age at diagnosis, and cranial radiation therapy on BMI z-score or prevalence rate of overweight and obesity in ALL survivors.

Conclusions: Overweight and obesity are prevalent sequelae of ALL in children and adolescents. Regular screening for unfavorable weight changes and obesity-associated co-morbidities is therefore a mandatory component of long-term follow-up care for survivors of pediatric ALL.

The chances of successful treatment of cancer in childhood and adolescence have improved dramatically over the last three decades. The current 5-year overall survival rate for all childhood cancers is 81%, is up to 88% for acute lymphoblastic leukemias (ALL) and exceeds 95% for those under the age of 15 years with Hodgkin's lymphoma [21]. These excellent survival rates are a result of aggressive, combined modality therapies (multi-agent chemotherapy, surgery, radiotherapy, intensified supportive care). Unfortunately, these treatments are associated with long-term toxicities, which often become apparent only years or even decades after discontinuation. Data from the Childhood Cancer Survivor Study (CCSS) demonstrates that 73% of long-term survivors of childhood cancers are affected by one or more chronic health conditions during the course of 30 years of follow-up [22]. Chronic health conditions and impaired quality of life affect a growing and aging population of long-term survivors. In 2003, more than 270,000 survivors of childhood cancer were living in the USA, equivalent to 1:640 of 20- to 39 year-olds [23]. Survivors of cancers in childhood and adolescence are frequently affected by endocrine late effects because of the high vulnerability of the endocrine system to the effects of certain cytostatic agents and radiotherapy. The prevalence of endocrine disorders in adolescents and young adults surviving a childhood cancer is >20% in CCSS data [24], and is up to 40% in published case series [25].

The current meta-analysis by Zhang et al. highlights the importance of overweight and obesity in survivors of childhood ALL, which still is an underdiagnosed treatment-related late effect. Their meta-analysis not only confirms the high prevalence of overweight and obesity in ALL survivors, but also underscores the need for regular screening of all pediatric ALL survivors for the development of obesity during long-term follow-up regardless of specific risk factors (e.g. treatment exposures). In the most comprehensive review to date, Zhang et al. also deliver a concise description of the areas of uncertainty. Published data comes from observational studies in heterogeneous populations with heterogeneous therapeutic exposures often using differing definitions of overweight and obesity. Therefore it is unsurprising that currently very little is known on the mechanisms leading to obesity in childhood ALL survivors. Furthermore, data on the lifelong risk for obesity and associated co-morbidities in long-term survivors are missing. Additional research is needed not only to adapt and optimize follow-up protocols, but also to develop effective strategies for obesity prevention in childhood cancer survivors.

Brain responses to food logos in obese and healthy-weight children

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Background: Food advertising is a powerful factor contributing to the high childhood obesity rates. Studies suggest that exposure to TV commercials is associated with brand preference and obesity risk [26, 27].

Methods: Brain activation to viewing familiar food versus non-food brand labels was compared in 10 normal-weight (mean BMI 50th percentile) and 10 obese (mean BMI 97.9th percentile) children aged 10–14 years. Self-control was assessed using a standardized questionnaire.

Results: Compared with the healthy-weight children, obese children reported higher impulsivity (13.2 vs. 8.4, $p = 0.036$). In response to the food labels, they showed less activation in the middle frontal and temporal, yet more activation in the post-central gyrus and midbrain. In response to the non-food labels, they showed increased activation in the thalamus, inferior frontal gyrus, insula and cuneus. When contrasting food versus non-food items they showed less activation in the inferior and middle frontal, superior temporal, parahippocampal, and insular cortex ($p < 0.1$). Overall, this pattern is consistent with decreased activation in areas involved in cognitive control yet increased activation in reward areas specifically in response to the food labels.

Conclusions: Obese children may be more vulnerable to the effects of food advertising.

In this well-designed study, the authors compare two conditions (viewing of food versus non-food labels) and their contrast in healthy-weight versus obese children. They link the decreased activation in centers of cognitive control to the also observed higher impulsivity in obese children and they postulate increased vulnerability to food advertisements. It is interesting that obese compared to healthy-weight subjects showed overall higher activation in response to the non-food items, but generally lower responses to food labels. This opens the door to speculations whether the impaired impulse control is specifically food-related. However, this is not assessed in this study and contradicts previous findings [28].

Breastfeeding: no influence on weight or body fat

Effects of promoting longer-term and exclusive breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: a randomized trial

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Background: It is assumed that children who were not breastfed are at greater risk for being overweight and obese later in life. This assumption is supported by results of observation studies, but until now no randomized trial has been performed to test the hypothesis that longer duration and exclusivity of breastfeeding prevent the development of obesity later in life.

Methods: A cluster-randomized controlled trial in 31 Belarusian maternity hospitals and their affected clinics was performed (PROBIT study). The maternity hospitals and clinics were randomized into two groups: breastfeeding promotion intervention modelled on the WHO/UNICEF Baby-Friendly Hospital Initiative (experimental group; $n = 16$) or usual practice (control group; $n = 15$). At baseline (between 1996 and 1997) 17,046 breastfeeding mother-infant pairs were enrolled in the study. At follow-up

(between January 2008 and December 2010) 13,879 children (median age 11.5 years) and their mothers were examined. Anthropometric parameters (BMI, fat and fat-free mass index (FMI, FFMI), percent body fat, waist circumferences, triceps and subscapular skinfold thickness) in children were measured and whole-blood IGF-I levels were measured in finger-prick spot samples of whole blood. Overweight in children was defined as being between the 85th and 94th percentiles and obesity as being in or above the 95th percentile based on Centers for Disease and Control and Prevention (CDC) 2000 reference data.

Results: At baseline and at follow-up examination, no differences in sociodemographic and potential confounding factors were observed between the experimental group and control group. Increased breastfeeding and exclusive breastfeeding duration was observed in the experimental versus control group. The cluster-adjusted mean differences in anthropometric parameters and IGF-I concentrations in 11.5-year-old children between the experimental and control group were: 0.19 (−0.09, −0.46) for BMI, 0.12 (−0.03, −0.28) for FMI, 0.04 (−0.11, −0.18) for FFMI, 0.47% (−0.11, −1.05) for body fat, 0.30 cm (−1.41, −2.01) for waist circumference, −0.07 mm (−1.71, −1.57) for triceps, −0.02 (−0.79, −0.75) for subscapular skinfold thickness and −0.02 SDs (−0.12, −0.08) for IGF-I. The cluster-adjusted odds ratio for overweight was 1.18 (95% CI 0.97–1.41) and 1.17 (95% CI 0.97–1.41) for obesity in the experimental versus control group.

Conclusions: This cluster-randomized trial investigated the hypothesis that longer and exclusivity of breastfeeding prevent the development of obesity in later life. The intervention increased the duration and exclusivity of breastfeeding significantly but had no significant effect on anthropometric parameters or IGF-I levels in 11.5-year-old children. In summary, an improvement in duration and exclusivity of breastfeeding did not prevent overweight or obesity in children at the age of 11.5 years.

Systematic reviews of published observational studies concluded that children who were breastfed have a lower risk for later obesity [29–31]. However, a quantitative review of published and unpublished observational studies by Owen et al. [32] observed a null effect of breastfeeding on the prevalence of obesity later in life after adjustment for important confounders. Owen et al. concluded that the previously described protective effect of breastfeeding on later obesity may be explained by confounding factors. One limitation of observational studies is the impossibility of identifying a causal relationship between breastfeeding and a lower risk of obesity later in life, which can only be shown by a randomized controlled trial (RCT). Martin et al. report the first cluster-randomized trial (PROBIT, Promotion of Breastfeeding Intervention Trial) to investigate the effects of an intervention, to promote increased duration and exclusivity of breastfeeding, on overweight prevalence and IGF-1 levels in children at the age of 11.5 years. No effect on the prevalence of overweight or on IGF-1 levels in children at the age of 11.5 years was found. The authors described that similar results had already been observed in these children at age 6.5 years [33].

The findings from this cluster-randomized trial give for the first time evidence that an improved duration and exclusivity of breastfeeding did not prevent the development of overweight later in life. The results of this study support the hypothesis that previously described associations between breastfeeding and lower risk of obesity later in life may be subject to confounding and publication bias. Nevertheless the promotion of breastfeeding should be fostered, because breastfeeding has numerous other health advantages for the mother and child.

Resveratrol improves adipose insulin signaling and reduces the inflammatory response in adipose tissue of rhesus monkeys on high-fat, high-sugar diet

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Cell Metab 2013;18:533–545

Background: Resveratrol, a polyphenolic natural compound, has been linked to anti-inflammatory and antidiabetic effects. Studies in obese humans have demonstrated that a short-term supplementation with resveratrol had beneficial effects on insulin sensitivity and metabolic parameters. The aim of this study was to investigate the effects of a 2-year administration of resveratrol in a non-human primate model.

Methods: Adult male rhesus monkeys received a control diet or a high-fat, high-sugar (HFS) diet with or without daily administration of resveratrol (80 mg/day for the first year, 480 mg/day in the second year). Endocrine and metabolic parameters were monitored.

Results: Gene array analyses revealed that the supplementation with resveratrol opposed the HFS diet-induced changes, specifically inflammation-related functions, in adipose tissue. Resveratrol led to an increase in the number of small fat cells and *Sirt1* expression, and inhibited NF- κ B activation in visceral adipose tissue. Serum obtained from resveratrol-treated monkeys exerted anti-inflammatory effects and improved insulin sensitivity in 3T3-L1 adipocytes.

Conclusions: The findings suggest that the chronic administration of resveratrol leads to beneficial metabolic and anti-inflammatory effects.

Resveratrol is a small pleiotropic molecule apparently exerting health-beneficial actions including anticancer, anti-inflammatory and antioxidant effects. It has gained considerable attention because it extended the lifespan in several laboratory organisms including yeast, *Drosophila melanogaster*, or *Caenorhabditis elegans* by mimicking caloric restriction [34, 35]. Interestingly, resveratrol has also been implicated in the French paradox: despite a diet rich in saturated fats, French people have a low incidence of coronary heart disease. This finding has been linked to the moderate consumption of red wine, which contains considerable amounts of resveratrol [36].

Another study recently published in *JAMA* has thrown oil on the fire of long ongoing, controversial discussions whether dietary resveratrol concentrations would have any implications on health. The InCHIANTI Study (Invecchiare in Chianti, aging in the Chianti area) enrolled 783 participants aged 65 years and older and followed them for 9 years. The aim of the study was to elucidate if resveratrol levels achieved by normal diet were connected to cardiovascular disease, cancer, and death. 24-Hour urine collections were performed to determine the levels of resveratrol and its breakdown products. To make a long study short, no association was found between urinary resveratrol metabolites and health outcomes and the authors concluded that dietary resveratrol from Western diets does not have a substantial influence on inflammation, cardiovascular disease, cancer, and longevity in community-dwelling older adults [37].

However, dietary supplementation with resveratrol has proven beneficial effects, specifically improving insulin sensitivity and metabolic parameters [38]. Therefore, studies investigating the safety and outcome of long-term resveratrol supplementation – like the one reported here by de Cabo's group – are important to understand whether taking resveratrol as a pill is recommendable.

Childhood craniopharyngioma: hypothalamus-sparing surgery decreases the risk of obesity

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J Clin Endocrinol Metab 2013;98:2376–2382

Background: Craniopharyngioma accounts for about 7% of brain tumors in children. Its high local recurrence rate has led surgeons to perform extensive surgery in the past. More recently, severe side effects such as hypothalamic damage and the associated decrease in quality of life have informed the more conservative approach of limited surgery to minimize hypothalamic damage. This approach may decrease the occurrence of extreme obesity at the expense of needing radiotherapy to complete the treatment [39, 40].

Methods: Based at a pediatric teaching hospital in Paris, the authors compared weight gain and local recurrence rates after extensive resection surgery (ERS) in a retrospective cohort (1985–2002, 37 boys, 23 girls, median age 8 years) and hypothalamus-sparing surgery (HSS) in a prospective cohort (2002–2010, 38 boys, 27 girls, median age 9.3 years). In the prospective cohort, an established algorithm including surgical approach and potential radiotherapy was applied to minimize hypothalamic damage [41]. Data were collected before and in intervals after surgery.

Results: Mean BMI z-score before surgery did not differ between the two cohorts (0.756 after ERS vs. 0.747 after HSS; $p = 0.528$). At any time after surgery, mean BMI z-score was significantly lower after HSS (e.g. 1.89 vs. 2.92 SD, $p = 0.004$ at 1 year). At the last follow-up, the HSS cohort had a significantly lower prevalence of severe obesity (28 vs. 54%, $p < 0.05$). In addition, patients in the HSS cohort demonstrated lower rates of corticotrophin deficiency (71 vs. 98%, $p < 0.001$), hypogonadotropic hypogonadism (79 vs. 98%, $p = 0.006$) and diabetes insipidus (82 vs. 98%, $p = 0.002$). In a multivariate analysis, preoperative hypothalamic involvement and hypothalamus-sparing surgery independently predicted the presence of severe obesity at the last follow-up. The mean number of surgical procedures did not differ between the two cohorts.

Conclusions: Hypothalamus-sparing surgery decreases the occurrence of severe obesity without increasing the local recurrence rate.

By analyzing two historical childhood craniopharyngioma cohorts treated by the same highly experienced surgical team, these authors show that limited surgery adapted to the degree of tumor spread and highly respectful of the hypothalamus, followed by adjuvant radiotherapy, does not lead to an increased rate of recurrence, decreases the risk of severe weight gain and partially decreases the prevalence of endocrine deficiencies. As pointed out by the authors, a limitation of this study is the retrospective design, resulting in widely different follow-up times of 103 versus 33 months, which might affect the validity of results on recurrence rates. However, most relapses of craniopharyngioma occur during the first 3 years after surgery. A randomized side-to-side comparison is desirable but would be difficult to perform ethically.

Differential methylation in glucoregulatory genes of offspring born before versus after maternal gastrointestinal bypass surgery

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Background: Obesity prevalence in mothers of child-bearing age is increasing. Positive associations have been observed between maternal pre-pregnancy BMI values and offspring adiposity and adverse cardio-metabolic traits. Alongside genetic factors and shared postnatal environmental factors, epigenetic changes could mediate these associations. In a Canadian sibling cohort, the impact of maternal gastrointestinal bypass surgery on methylation levels of genes of cardiometabolic pathways in children born before maternal surgery (BMS) or after maternal bariatric gastrointestinal bypass surgery (AMS) were compared.

Methods: In a sibling cohort of 25 BMS children and 25 AMS siblings (age 2–25 years) of 20 unrelated mothers (34–51 years), the methylation and expression levels of genes involved in cardiometabolic pathways were compared. Maternal presurgical data were obtained from medical records. Outcome maternal and offspring anthropometric parameters were measured between July and October 2010 in the Quebec Heart and Lung Institute or a regional hospital and a fasting blood sample was taken. Plasma concentrations of lipid, glucose and insulin were measured. The HOMA-IR index was calculated ($\text{glucose} \times \text{insulin}/22.5$). Differential methylation analysis was conducted and links between gene methylation and expression levels were assessed by correlating genomic findings with plasma markers of insulin resistance.

Results: Compared to AMS children, BMS children had higher weight, height, waist and hip girth after the adjustment for sex and puberty. Lower fasting insulin levels, HOMA-IR index and blood pressure were observed in AMS versus BMS children. Differences in methylation levels between BMS and AMS children were described in a total of 5,698 genes, including several genes related to autoimmune diseases, pancreas disorders, diabetes mellitus and disorders of glucose metabolism. Gene methylation levels, gene expression and plasma markers of insulin resistance were significantly interrelated. These associations were consistent with the observed metabolic improvements in AMS versus BMS children which may reflect changes in methylation levels in genes involved in diabetes-related cardiometabolic pathways in these children.

Conclusions: An effective treatment of a maternal phenotype is durably detectable in the methylome and transcriptome of their offspring.

This unique sibling study has highly important relevance to the investigations of epigenetics and gene function mechanisms in the fetal programming of long-life diseases. Interesting findings of this sibling cohort were already published in 2006. It was shown that AMS offspring had a lower prevalence of obesity, greater insulin sensitivity, and less hypertension and dyslipidemia than BMS offspring [42]. Improvements in cardiometabolic risk factors were also described in a further cohort of 49 mothers with biliopancreatic diversion bariatric surgery and their 54 BMS or 75 AMS offspring (2.5–26 years). The authors hypothesized that an improved intrauterine environment in children born AMS versus BMS could explain these findings [43]. The current analysis of the Canadian sibling cohort gives further support to this hypothesis. In 5,698 genes, different methylation levels between children born BMS versus AMS were observed. Highly interestingly was the observation that the gene methylation levels, gene expression and plasma markers of insulin resistance were correlated. The authors concluded that these correlations were consistent with the observed metabolic improvements in AMS versus BMS born children and they suggested that genes involved in diabetes-related cardiometabolic pathways are relevant.

The findings of this clinical study are unique and add to the body of evidence that the intrauterine milieu plays an important role in the development of metabolic disorder later in life. Additionally, these results indicate the importance of optimal BMI values in women at child-bearing age for offspring health.

Brown fat activation mediates cold-induced thermogenesis in adult humans in response to a mild decrease in ambient temperature

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Background: The contribution of brown adipose tissue (BAT) to the energy balance in humans upon cold exposure has not been completely established. The objective of this study was to investigate the impact of BAT on cold-induced thermogenesis (CIT).

Methods: In this single-blind, randomized crossover intervention study, CIT and BAT activation was assessed in 31 healthy volunteers. Overnight EE measurement in a whole-room indirect calorimeter at either 24 or 19°C (cold exposure) was followed by an ¹⁸F-fluorodesoxyglucose-PET scan. After 36 h, volunteers crossed over to the alternate study temperature under identical conditions.

Results: In comparison to 24°C, exposure to 19°C increased BAT activity ($10.5 \pm 11.1\%$, $p < 0.001$) paralleled with increased EE ($5.3 \pm 5.9\%$, $p < 0.001$), indicating CIT response. Multi-regression analysis revealed that a difference in BAT activity ($p < 0.001$), age ($p = 0.01$), and gender ($p = 0.037$) were independent contributors to individual variability of CIT.

Conclusions: Small reductions in ambient temperature are sufficient to increase human BAT activity, which correlates with individual CIT response. The enhancement of cold-induced BAT stimulation may represent a novel environmental strategy in obesity treatment.

Since the discovery of active brown adipose tissue (BAT) in adults [44–46], it has been repeatedly demonstrated that the activity of BAT negatively correlates with BMI and fat percentage, pointing to a role of BAT on body weight regulation [45, 47, 48]. However, the contribution of BAT activity to cold-induced thermogenesis (CIT) has not been resolved yet. Former studies using PET/CT after cold exposure performed intense cooling to maximize the effect sizes, which potentially can confound the assessment of BAT impact on CIT due to shivering.

The authors of this study thus used mild cold exposure (19 vs. 24°C, overnight) to characterize the relationship between BAT activity and CIT. Despite this moderate exposure, they found an induction in BAT activity upon cold exposure which was paralleled by an increase of energy expenditure (EE) by 5.3%. Moreover, BAT activation decreased with age and was also dependent on sex (higher in women), confirming findings from retrospective PET/CT studies.

These results suggest that even moderate reduction in temperature, which can be easily achieved by air conditioning, can increase BAT activity. Is this moderate cold challenge relevant in terms of body weight regulation? When extrapolating their data to a period of 12 months, the authors calculated that the increase in EE upon cold exposure would be equivalent to 20 days of fasting. This effect might even be further accelerated in subjects chronically exposed to cold. This question has been elaborated on in the following studies.

Cold acclimation recruits human brown fat and increases non-shivering thermogenesis

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Background: Active brown adipose tissue (BAT) has been recently found in humans. This study investigates whether activation and recruitment of BAT can be targeted to counteract obesity.

Methods: Subjects (n = 17) were acclimated to mild cold (15–16°C) 2–6 h daily for 10 consecutive days. BAT activity was assessed by positron emission tomography (PET). Biopsies of skeletal muscle and subcutaneous adipose tissue were obtained. Visual analogue scales were used to assess subjective sensation, thermal comfort and shivering.

Results: BAT activity as well as non-shivering thermogenesis (NST) was increased upon 10-day cold acclimation without showing any sex differences in presence or activity of BAT before or after cold acclimation. As judged by respiration measurements in permeabilized fibers and isolated mitochondria, there was no significant contribution of skeletal muscle mitochondrial uncoupling to the increase in NST. No induction of markers of brown/beige adipose tissue could be observed in subcutaneous adipose tissue upon cold acclimation. In line with the physiological observations, subjects reported warmer environment, higher comfort in the cold and less shivering after cold acclimation.

Conclusions: Repeated intermittent cold exposure leads to recruitment of BAT and increase in NST and thus might be used to increase energy expenditure to counteract obesity.

Increased brown adipose tissue oxidative capacity in cold-acclimated humans

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Background: Recent human studies have revealed that brown adipose tissue (BAT) has thermogenic potential in adults and plays a role in glucose and fatty acid clearance under acute mild cold exposure. Conversely, it has been suggested that BAT metabolism is defective in obesity and type 2 diabetes, pointing to pathological and therapeutic implications. Although phenotypic flexibility of BAT upon chronic cold exposure has been shown in mammals, not much is known about the metabolic plasticity of this tissue in humans.

Methods: Six men were acclimated to cold (10°C) 2 h daily for 4 weeks (5 days/week), using a liquid-conditioned suit. Prior and following 4 weeks of cold acclimation, shivering intensity, BAT oxidative metabolism, glucose uptake and volume were assessed using electromyography and positron emission tomography with ^{11}C -acetate and ^{18}F -fluorodesoxyglucose under controlled acute cold exposure.

Results: Cold acclimation for 4 weeks led to a 45% increase in BAT volume (from 66 ± 30 to 95 ± 28 ml, $p < 0.05$) and a 2.2-fold increase in cold-induced total BAT oxidative metabolism (from 0.725 ± 0.300 to 1.591 ± 0.326 ml·s $^{-1}$, $p < 0.05$). Shivering intensity was not significantly different between pre- and post-acclimation (2.1 ± 0.7 vs. $2.0 \pm 0.5\%$ MVC, respectively). Fractional glucose uptake in BAT increased post-acclimation (from 0.035 ± 0.014 to 0.048 ± 0.012 min $^{-1}$) while net glucose uptake trended towards an increase as well (from 163 ± 60 to 209 ± 50 nmol·g $^{-1}$ ·min $^{-1}$).

Conclusions: This study demonstrates that total BAT volume of activity increases significantly as a result of cold acclimation. Moreover, change in BAT mass is paralleled by an increase in BAT oxidative capacity. Therefore, the contribution of BAT to non-shivering thermogenesis must necessarily increase during cold acclimation in humans.

These two studies elegantly demonstrate the recruitment process of brown adipose tissue (BAT) upon acclimation to moderate cold. Until recently, the only evidence suggesting that chronic cold exposure induces an increase in BAT recruitment in vivo in adult humans came from a study 30 years ago which described a greater presence of multilocular adipocytes in Finnish outdoor workers compared to indoor workers [49]. The two studies discussed here (and the study of Yoneshiro et al. [50] discussed below) can be seen as milestones in the investigation of BAT recruitment upon chronic cold exposure in humans. In the first study, subjects were acclimatized to mild cold (15–16°C) for 6 h/day for 10 days. Afterwards, they were exposed to an individualized cooling protocol using a water-cooled suit. In order to exclude effects of shivering on energy expenditure during acute cold exposure, the temperature was adjusted to a degree slightly above the temperature where shivering occurred. The authors showed that both BAT activity and BAT volume increased after cold acclimation, paralleled by an increase in non-shivering thermogenesis (NST). As assessed by respiration measurements in isolated skeletal muscle mitochondria, a participation of skeletal muscle on NST could be ruled out. Interestingly, the

physiological changes after cold acclimation were also reflected by subjective temperature sensing of the subjects.

The second study performed a similar approach. Subjects ($n = 6$) were acclimatized to cold for 4 weeks and then acutely exposed to cold, while measuring BAT glucose uptake and tissue oxidation rate by PET/CT scans. Cold acclimation led to a significant increase in BAT volume as well as an increase in the oxidative metabolism of BAT, which was accompanied by a reduction in blood glucose levels. This indicates a role of BAT in the clearance of glucose which has been already shown in mice [51].

These studies provide further arguments that cold could be used as a simple and tolerable treatment strategy to reduce body weight by targeting BAT. The direct role of cold-induced BAT activity on weight regulation and the potential occurrence of behavioral or metabolic compensatory mechanisms in humans should be addressed in future studies.

Recruited brown adipose tissue as an antiobesity agent in humans

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J Clin Invest 2013;123:3404–3408

Background: Brown adipose tissue (BAT) uses intracellular lipid stores to produce heat upon cold exposure which also has an impact on energy metabolism. BAT mass decreases with age thereby pronouncing age-dependent accumulation of body fat in humans. Thus, BAT may play a role in reducing body fat stores.

Methods: Healthy male volunteers ($n = 51$) underwent PET/CT scans after acute 2 h cold exposure at 19°C. Resting EE was analyzed before and after cold exposure using a respiratory gas analyzer. 22 subjects with undetectable or low BAT activity were randomly divided into two groups: one was exposed to cold daily (2 h/day) within a 6-week time period, the other retained usual lifestyles without cold exposure. Effects of capsinoids on BAT activity was tested in a randomized, single-blinded, placebo-controlled crossover trial including 10 subjects with low or undetectable BAT activity.

Results: Acute cold exposure increased energy expenditure. There was a strong correlation between BAT activity and cold-induced increments of EE ('cold-induced thermogenesis', CIT), independent of age and fat-free mass. Cold acclimation for 6 weeks led to a parallel increase in BAT activity and CIT accompanied by a decrease in body fat mass. Changes in BAT activity and body fat mass were negatively correlated. Daily ingestion of capsinoids similarly increased CIT in subjects with low BAT activity before treatment.

Conclusions: BAT can be recruited even in individuals with low BAT activity, thereby contributing to body fat reduction.

The prevalence of brown adipose tissue (BAT) varies between adults and declines with age [44, 45, 48]. Previous reports from the same group indicate that the body fat content of subjects without detectable BAT increased with age, while it remained relatively stable in subjects with detectable BAT activity [52]. This suggests that the decline of BAT activity with age facilitates an acceleration of body fat accumulation. Yoneshiro et al. hypothesized that a reactivation of BAT may be protective against obesity and related co-morbidities.

Subjects with no or low BAT activity ($n = 32$) were taken to two different treatment strategies: participants were either exposed daily to mild cold (17°C) for 6 weeks or received oral capsinoids capsules daily for the same time period. Capsinoids are non-pungent derivatives of capsaicin and are usually found in chili pepper. The same group has recently demonstrated that capsinoids activate BAT through the sympathetic nervous system via stimulation of transient receptor potential (TRP) channels [52]. In the present study, both cold exposure and capsinoid treatment increased BAT activity which was paralleled by a reduction on body fat content in the cold-exposed subjects.

These findings show that BAT can be recruited even in subjects who had completely lost their BAT activity. It points to an enormous plasticity of BAT in humans. Moreover, the authors show that capsinoids may be a convenient treatment alternative to daily cold exposure to increase BAT activity in order to combat the onset of obesity. It would be interesting to see if these treatments – either cold exposure or capsinoids – are also effective in body weight reduction in obese patients. Such studies will surely be reported in the near future.

Ontogeny of taste preferences: basic biology and implications for health

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Background: A major challenge of health initiatives attempting to change the behavior of children and adolescents is that neither children/adolescents nor adults comply with such recommendations. A critical question in this respect is how strong are biological drivers of food acceptance during infancy and childhood, and how do the influences of early-life experiences interact with inherent plasticity of the chemical senses to mold preferences for foods.

Methods: This review summarizes research articles on the topic of ontogeny of taste preferences related to basic biology and human health.

Results: Children have natural food preferences (they prefer sweet and salty tastes while rejecting bitter tastes). From a biological point of view, children do not favor 'healthy recommendations' of low sugar, low sodium, and vegetable-rich diets. By contrast, children are vulnerable to the current food environment of foods high in salt and refined sugars. However, results of studies show that early life sensory experiences can shape these preferences and may go a long way to promote healthy eating.

Conclusions: The challenge faced by parents and caregivers to modify the diets of children by reducing added sugars and salt seems to be charged by a strong biological basis. Such understanding emphasizes the need for new strategies to change children's diet.

This review highlights results from clinical studies that show there are strong biological drives for food acceptance and consumption during infancy and childhood. However, there are also clinical data with convincing evidence that early-life experiences can interact with this basic biological background and are able to mold preferences for foods.

The review comprises four parts. In the first part, studies showing the importance of early-life experiences are summarized. The second part summarizes data on the biology of the chemical senses (sweet, salt, bitter). The third part puts together results from studies showing the effects of early taste preferences including first food, amniotic fluid and mother's milk. Finally the last part tries to translate these findings into evidence-based strategies for food and vegetable acceptance during infancy.

Evidence-based prevention

School-based obesity prevention programs: a meta-analysis of randomized controlled trials

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Obesity (Silver Spring) 2013;21:2422–2428

Background: School-based prevention programs have been implemented to reduce childhood obesity. A lack of consistency in effectiveness was reported in a systematic review covering school-based studies until 2006. The aim of the present systematic review and meta-analysis was to give an update including studies until January 2012.

Methods: To review school-based studies through to January 2012, the methodology of literature research was adopted from the earlier systematic review of Kamath et al. in 2008 covering RCTs until 2006.

Results: The results from 32 school-based prevention studies ($n = 52,109$) showed a mild effect regarding BMI reduction compared to the control groups. Although there was no statistically significant difference between children and teenager interventions, those in children showed significant effects com

pared to controls, while those in teenagers did not. Comprehensive intervention programs with a duration of more than 1 year showed the largest effects, particularly among children. Effective program components included the provision of information on nutrition and physical activity, change in attitudes, behavior monitoring, modification of the environment, involvement of parents, increase in physical activity and improvement of diet.

Conclusions: With longer durations, greater comprehensiveness and the inclusion of parents, recent school-based prevention programs can achieve a mild reduction in BMI in children.

Childhood obesity is a major health problem worldwide. The decrease in physical activity and the over-consumption of energy-dense food are considered the main reasons for the obesity epidemic [53]. Because the number of research studies in obesity prevention has increased in the past years, regular literature updates are needed. The present meta-analysis of RCTs shows significant but mild effects of school-based obesity prevention programs on BMI reduction. This improvement was primarily true for children, but not for teenagers. The findings from earlier reviews showed inconsistent effects on BMI [54–59]. The effectiveness of prevention programs is influenced by many factors. First, long-term interventions are more effective than short-term interventions [56, 57], as confirmed by the present meta-analysis. Second, the authors found that programs that combined different intervention components (i.e. nutritional training and promoting physical activity) were most effective in reducing BMI in children. It has been shown that such combination is important for long-term efficacy [54, 57, 60]. For example, most study participants will return to their initial weight within 1–5 years after completing the program if the intervention focused only on altering eating habits alone without a regular regime of physical activity [61]. Third, the involvement of parents was associated with greater program success. In general, parents play a critical role in preventing obesity. For instance, parents are more likely to make healthy eating choices for their children if they have better knowledge about healthy nutrition [62].

School-based intervention programs can reach most children and teenagers, and also their parents. But, if the environmental conditions are not consistent with the intervention goals, the best school-based intervention will not be effective in inducing BMI changes [57]. There are a limited number of studies which have investigated BMI changes in teenagers in a school-based intervention program. Most available studies reported no effective BMI reduction [63, 64]. More work is needed to develop and testing school-based interventions for teenagers and further studies should clarify what interventions work and in which populations.

Systematic review of community-based childhood obesity prevention studies

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Pediatrics 2013;132:e201–e210

Background: There is an increasing body of literature regarding studies on community-based childhood obesity prevention. The aim of this study was to systematically review community-based prevention programs for obese children in the USA and other high-income countries.

Methods: The medical literature databases Medline, Embase, PsychInfo, CINAHL, clinicaltrials.gov, and the Cochrane Library were searched for relevant English-language studies. Inclusion criteria were: the implementation in the community setting; follow-up of at least 1 year, and a comparison group. Title scan, and abstract and full-article reviews were conducted by two independent reviewers. For data abstraction, each article was examined twice.

Results: After reviewing 601 full articles, 9 community-based studies were included (5 RCTs and 4 non-RCTs). The selected studies had different settings: community only ($n = 1$), community and school ($n = 3$), and community and at least 1 other setting such as the home ($n = 5$). Almost half of the studies ($n = 4$) reported desirable changes in BMI or BMI z-score. Significant improvements in behavioral outcomes (i.e. physical activity, vegetable intake) were reported by two studies.

Conclusions: Combined community-based obesity prevention programs that include a school component are moderately effective at preventing overweight or obesity. To gain more insights into the effectiveness of such interventions, more research studies using consistent methods are needed.

Despite the observed leveling off in obesity prevalence in pediatric populations, obesity prevention remains a priority because the current prevalence is high. Communities are important settings for obesity prevention because many drivers of positive energy balance (i.e. too much energy or too little expenditure) are found in the environment [65–67]. The 2012 Institute of Medicine report on obesity prevention recommends a comprehensive approach that includes the community [10]. Obesity prevention programs that cover the community-setting have markedly increased in number in recent years. Nine relevant studies were identified, of which four reported desirable and significant changes in BMI or BMI z-score [68–71]. Effective programs had longer durations, they focused on younger children (middle school or younger), they included multiple intervention components, and they were delivered in other settings than just the community. In conclusion, regarding weight gain prevention in children, combined interventions implemented in multiple settings may have larger effects than single-component interventions located in the community only. As a limitation, the considerable heterogeneity across the study designs, methodologies, settings, and interventions contributed to the inconsistent findings. Because of such heterogeneity, robust conclusions on the impact of community-based childhood obesity prevention programs are not yet possible. Further research is needed.

Systematic review of home-based childhood obesity prevention studies

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Background: Childhood obesity is a major public health concern. The family and home environment significantly influence the obesity risk behaviors, mainly of young children. Studies focusing on home-based obesity prevention are scarce and their effectiveness is uncertain. Examining the evidence base for the effectiveness of obesity prevention programs with a home setting was the aim of this systematic review.

Methods: The medical literature databases Medline, Embase, PsychInfo, CINAHL, clinicaltrials.gov, and the Cochrane Library were used to search relevant literature from inception through August 11, 2012. Inclusion criteria were: experimental and natural experimental studies on children with a home setting and follow-up of at least 1 year which reported on weight-related outcomes. Study screening and data extraction was performed by two independent reviewers. The quantity, quality, and consistency of interventions targeting diet, physical activity (PA), or both for obesity prevention were graded giving the strength of evidence.

Results: After reviewing 601 full articles, 6 home-based studies were included. The selected studies used different intervention approaches: combined diet and PA (n = 3), diet only (n = 1), primary care combined with consumer health informatics components (n = 1), and combined intervention with school and community components (n = 1). Beneficial effects on fruit/vegetable intake and sedentary behaviors were observed with combined interventions. Regarding weight outcomes, no significant effects were reported.

Conclusions: Overall, there is insufficient evidence to draw conclusions about the effectiveness of home-based interventions targeting diet. There is currently a low strength of evidence for the effectiveness of combined home-based interventions for obesity prevention. Additional research is needed to investigate further components including parenting strategies and environmental modification in the home setting.

The child's diet and physical behavior is significantly influenced by the family and home environment [72, 73]. This is particularly true for young children [74–76]. Overweight children are more likely to be affected by adverse physical and psychosocial health outcomes and become obese adults, therefore obesity prevention in early life is highly important. This study reports a valuable summary of the evidence on home-based interventions. The authors identified six home-based childhood obesity prevention studies conducted in high-income countries. Weight-related outcomes were unaffected and statistically significant benefits on fruit/vegetable intake or sedentary behaviors were observed in only three studies [77–79]. Overall, the strength of evidence is low because of the few available data, and the considerable heterogeneity in populations, approaches, outcomes, measurement tools among studies. For these reasons, a quantitative systematic synthesis of the literature was not possible. The small sample sizes, small intervention duration and intensity, and the inclusion of studies

that did not primarily aim to prevent obesity may have also contributed to the lack of treatment effect observed. Longer intervention durations and/or greater intensity of intervention dose may be necessary to examine the impact of home-based interventions on weight-related outcomes. As seen for community-based interventions (reviewed above), home-based programs could be an effective component of wider behavior change interventions that also include components delivered in other settings (e.g. school community, primary care setting). Without systematically addressing the child's food and physical environment, the impact of interventions that target only individual behavior change may be attenuated in terms of obesity prevention. More research is needed to fully evaluate the impact of home-based obesity prevention programs, in particular studies integrating parenting and addressing important environmental sources of influence.

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