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Prevention of Obesity in Infancy and Early Childhood: A National Institutes of Health Workshop

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Abstract

Addressing the childhood obesity epidemic continues to be a challenge. Given that once obesity develops, it is likely to persist, there has been an increasing focus on prevention at earlier stages of the life course. Research to develop and implement effective prevention and intervention strategies in the first two years of life has been limited. In Fall 2013 the National Institute of Diabetes and Digestive and Kidney Diseases convened a multidisciplinary workshop to summarize the current state of knowledge regarding the prevention of infant and early childhood obesity and to identify research gaps and opportunities. The questions addressed included: 1.) What is known regarding risk for excess weight gain in infancy and early childhood; 2.) What is known regarding interventions that are promising or have been shown to be efficacious; 3.) What are the challenges and opportunities in implementing and evaluating behavioral interventions for parents and other caregivers, and their young children? This report summarizes the workshop presentations and discussion, including identification of high priority topics for further research.

Background

The most recent national estimates indicate that 8.1% of infants and toddlers have a weight-for-length greater than the 95th percentile, with sociodemographic disparities detectable by age 2 years.[1] Most obesity intervention trials in childhood have focused on school-age

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children. However, given that once obesity develops it is likely to persist, there has been an increasing focus on prevention at earlier stages of the life course.

Research to develop and implement effective prevention and intervention strategies in the first two years of life has been limited. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) convened a multidisciplinary workshop of more than 100 researchers in Fall 2013[2] to provide the scientific background to inform the research needed to prevent excessive weight gain in early life (see eSupplement for list of speakers). The importance of the prenatal period was briefly reviewed, but the workshop specifically targeted the birth to 24 months period, as it was felt that this developmental period has the most pressing gaps in knowledge. The workshop content and structure was developed by a multidisciplinary planning committee, and was necessarily focused on a limited number of topics. Speakers were asked to discuss studies beyond their own work and to broadly identify research gaps and opportunities, but were not asked to provide a broad and systematic review of the literature on included topics. The following questions were addressed: 1.) What is known regarding risk for excess weight gain in infancy and early childhood; 2.) What is known regarding interventions that are promising or have been shown to be efficacious; 3.) What are the challenges and opportunities in implementing and evaluating behavioral interventions for parents and other caregivers, and their young children?

Growth References and Definitions

The World Health Organization (WHO) Growth charts are recommended as the standard against which infant growth from birth to 24 months is clinically evaluated. This recommendation is based on the fact that, unlike the US Centers for Disease Control and Prevention (CDC) growth charts that were constructed from cross-sections of the population drawn from a range of US samples of children with relatively broad inclusion criteria, these charts are constructed based on frequently collected longitudinal data from healthy children in 6 different countries fed under optimal circumstances. There are several challenges introduced by using these curves for research, however, and the CDC makes no specific recommendations regarding whether the CDC or WHO curves should be used for research purposes. There is no straightforward solution for how to examine growth patterns from pre- to post-24 months of age (when one might switch from WHO to CDC growth charts). The thresholds for defining “overweight” or “obesity” remain in debate and differ between the two sets of growth curves. Furthermore, while the WHO curves provide body mass index (BMI) standards from birth to 24 months, the CDC curves do not. There is ongoing debate regarding the use of BMI as an indicator of adiposity in infancy.

Most research addressing infant weight gain and obesity risk has focused only on weight and length. Infant growth involves not only changes in weight and length but dramatic changes in body composition (i.e., fat, water, protein, and minerals[3]). These changes in body composition remain nearly entirely unexplored in relation to infant and early childhood obesity. Meta-analysis indicates differences in fat free mass and fat mass between formula- and breast- fed infants that vary by age in the first 12 months of life,[4] and do not map onto observed differences in patterns of linear growth and overall weight gain in a straightforward way. There are a number of methodologies that may be used to assess infant body composition, including isotope dilution, bioelectrical impedance or spectroscopy, air-displacement plethysmography, dual-energy X-ray absorptiometry, whole body counting, and magnetic resonance imaging. There are strengths and limitations to each of these approaches, and data regarding reliability and validity continue to emerge. A particular challenge is the measurement of body composition between ages 6 and 24 months, when children are unlikely to remain calm and still during assessment, which also precludes use of air displacement plethysmography in this age range. The development of non-invasive, low burden, and valid approaches to measurement of body composition in this age range including methods suitable for population studies, is an important research need.

Critical Developmental Periods

Observational data has repeatedly described an association of maternal pre-pregnancy weight[5] and gestational weight gain[6] with offspring overweight. Randomized controlled trials (RCTs) have provided some evidence that altering maternal gestational weight gain can alter fetal growth, but have also demonstrated the difficulty of altering gestational weight gain, and longer-term outcomes of the offspring are not yet available.[7] The role of the perinatal period becomes more complex when considering that during the era when childhood obesity prevalence has increased, birth weights have declined.[8] Much work remains to understand causal mechanisms and RCTs that shape the intrauterine environment and include long-term follow up of the offspring are needed.

Associations between rapid weight gain in infancy and subsequent obesity are well established,[9–11] but the underlying mechanisms and any causal associations remain unclear. Well-recognized genetic alleles for obesity risk later in the life course have been linked to rapid infant weight gain,[12,13] and twin studies suggest shared genetic influences on infant appetite and rate of weight gain.[14] However, these genetic alleles accounted for only a small amount of the variance in infant body mass index.[13] The epigenome as a modulator of genetic expression is increasingly believed to be a critical factor in the regulation of growth. Epigenetic processes such as DNA methylation and histone modifications during key developmental periods can modulate gene transcription and have long-term effects. Greater methylation of specific genes prenatally predicted more than 25% of the variance in adiposity in later childhood,[15] with subsequent investigations documenting differences in gene expression.[16] Identification of novel epigenomic biomarkers of childhood obesity risk and their mechanisms is an active area of research.

Emerging evidence also supports the hypothesis that placental leptin prevents rapid infant weight gain; some have hypothesized that tolerance develops and ultimately higher leptin levels predict faster adiposity gain.[17–19] The microbiome is also receiving increasing attention. The infant's microbiome comes largely from the mother [20] and differs by mode of delivery (vaginal vs. cesarean).[21] Studies inoculating germ-free mice with microbiota from human twin pairs discordant for obesity show that fat mass as well as obesity-related metabolic factors were transmissible, but modified by diet.[22] There are also emerging data that use of antibiotics in infancy is associated with modestly higher BMI later in childhood, possibly acting through alterations in the microbiota.[23] Further research that includes longitudinal stool and other biosample collection and utilizes metagenomic and metabolomic approaches is needed.

Physical Activity and Sedentary Behavior

Little is known about the normal range of physical activity and sedentary behavior in infancy and its relationship to energy balance. In infancy, physical activity occurs in short intermittent bursts,[24] and increases in the first months of life.[25] Accurate measurement of infant activity remains a major challenge, although recent work has successfully used accelerometry.[25,26] The evidence linking motor behaviors in infancy with adiposity is limited and observational.[27,28] There have been no published RCTs evaluating the effect of a physical activity intervention in infancy on increasing accelerometery-measured physical activity or preventing obesity. As yet untested strategies that may hold promise based on observational studies or interventions with children with developmental disabilities include prone positioning,[29] reinforced kicking,[30] and treadmill stepping.[31]

Sleep

Observational studies provide evidence for a link between short sleep duration and adiposity in children.[32] There continues to be debate, however, regarding the association in infancy. While some studies have reported inverse associations between sleep duration and adiposity in infancy,[33,34] others have had null findings[35,36] and at least one RCT of an infant sleep intervention did not have an effect on future overweight.[37] Although a number of studies provide evidence of underlying biological mechanisms later in the lifespan,[38] this type of work is lacking in infancy. In addition, most studies have focused on sleep duration. There is a need to examine the association of other features of sleep, such as quality, consolidation, or timing, with obesity risk in infancy. These features include timing (e.g., circadian rhythms), consolidation (e.g., frequency of nighttime awakenings), regularity (i.e., variability day to day), ecology (e.g., feeding during nighttime awakenings) as well as sleep disordered breathing. The irregular nature of infant sleep poses measurement challenges and studies are needed to assess both sleep duration and quality using validated, objective measures such as actigraphy. There is good evidence for the efficacy of behavioral interventions in improving features of sleep in infancy,[39–42] but RCTs testing the effects of these interventions on future adiposity are lacking.

Nutrition and Feeding Behavior

Breastfeeding is the gold standard for infant nutrition and has been shown to have a number of health benefits. Breastfeeding promotion as a target for obesity prevention in infancy and early childhood has received substantial attention and a great deal of study in the last decade. Observational studies in primarily white, middle-income, European and US populations have shown an association between breastfeeding and a reduced prevalence of obesity in meta-analysis,[43,44] and plausible mechanisms have been proposed.[45,46] However, in a large cluster-randomized clinical trial there was no effect of breastfeeding on body mass index in later childhood.[47] When infants are fed formula that is more similar in protein content to breastmilk (i.e., lower vs. higher protein), their weight-for-length at age 24 months does not differ from breastfed infants,[45] suggesting the importance of understanding the composition of the diet to which breastfeeding is being compared before drawing conclusions. Overall, the evidence for breastfeeding promotion as a robust obesity prevention strategy is currently lacking[48] and research examining additional nutritional strategies for obesity prevention is needed.

Formula-fed infants are larger than breastfed infants by the end of the first year of life.[49] The mechanism is posited to be both behavioral (e.g., overriding infants' ability to adjust intake in response to satiety) as well as due to differences in the composition of formula as compared to breastmilk. Evidence for the importance of milk composition comes from studies comparing formulas of differing composition. For example, infants consuming protein hydrolysate formula, as compared to cows' milk formula, are satiated sooner and have more normative (less excessive) rates of weight gain.[50] The mechanism of effect is currently unknown, but hypothesized to be related to differences in free glutamate (which is abundant in human breast milk), which may act as a satiety signal. In fact, the addition of glutamate to cow's milk formula has been shown to reduce infant intake.[51] A recent large RCT showed that lower protein formula (which was most similar in protein content to breastmilk) was associated with lower rates of weight gain.[45] Furthermore, bottle use, regardless of whether the content is formula or expressed breast milk, is associated with increased likelihood of "emptying" the bottle[46] and greater rate of weight gain,[52] presumably due to overriding satiety. Observational studies have shown links between bottle use and obesity,[53,54] but an RCT reducing bottle use showed no effect on adiposity.[55] In summary, breastmilk or formula composition, the mode of delivery of each, and their mechanisms of effect on infant growth is an important area for research. Understanding behavioral and physiologic phenotypes that may contribute to individual differences in intake, including appetite and food preference, may also lead to more effective interventions.

The early introduction of solid foods has been a popular target for interventions to date, but ongoing study has provided inconsistent evidence to support a robust association with obesity risk in the short- or long-term.[56,57] Very little is known regarding how differing macronutrient composition of complementary foods affect infant growth. The timing and composition of complementary feeding in shaping growth trajectories is an area in need of substantial additional research.

The development of infants' flavor preferences has received substantial research attention on the premise that food preferences are the primary predictor of children's intake[58], and dietary preferences established in childhood persist.[59] Flavor preferences (preference for sweet and dislike for bitter) are detectable at birth[60] but are also malleable. Greater exposure -- even prenatal exposure via transmission of the mother's diet in the amniotic fluid -- leads to greater infant liking of the flavors in the mother's diet.[61] Although there is a relatively large body of research examining the ontogeny of flavor preferences in infancy and early childhood, there is no evidence base for strategies to change the trajectory of the development of these flavor preferences. Infant food selection is also influenced by their observations of others. Others' behavior influences how much children eat, which foods children like, and which foods they select.[62] Furthermore, characteristics of the food-eating model shape infants' eating behavior, such that individuals who are more familiar are more powerful models.[63] Social and cognitive influences on infant food selection and eating behavior remain nearly entirely unexamined as they may relate to obesity risk.

Emotional and Behavioral Regulation and the Dyadic Feeding Interaction

Temperament is a modifiable but relatively enduring child characteristic that includes constitutional differences in reactivity and self-regulation. A number of studies have linked features of infant temperament (e.g., greater negative reactivity and less self- regulatory capacity) with more rapid weight gain in infancy, though findings are mixed with several large cohort studies reporting null findings.[64] Infant negative emotionality is associated with greater weight gain, and this association is explained at least partially by the use of feeding to soothe the infant.[65] Potentially modifiable aspects of parenting and feeding that are associated with food intake and child weight status include lack of sensitivity to infant feeding cues, rigid controls in feeding, lack of structure and routines, and indulgent feeding.[66] In a preliminary RCT, a multicomponent intervention that taught parents strategies for soothing the infant that did not involve food, prolonging infant sleep duration, recognizing infant hunger and satiety cues, delaying introduction of solid foods, and encouraging acceptance of new foods through repeated exposure Resulted in lower weight-for-length percentiles at age 1 year.[67]

Feeding practices are shaped by maternal beliefs and values that are embedded in complex cultural, biological systems,[68] and these beliefs and values are often at odds with nutritional guidance provided by health care providers.[69] Qualitative work has described infant feeding styles: Laissez-Faire, Pressuring/controlling, Restrictive/controlling, Responsive, and Indulgent.[70] There remains a lack of evidence, however, to support these feeding styles as causes of excessive infant weight gain. Ongoing work in this area and improved understanding of maternal motivations for their feeding styles will be important for the development of effective interventions.

Design Issues and Challenges to Trial Implementation

Several recently published or ongoing studies have begun to intervene in infancy and early childhood to prevent obesity.[71–73] Most studies have focused on infant feeding, particularly promoting breastfeeding initiation, prolonged duration, and exclusivity. More recent studies have targeted risk factors other than feeding, such as sleep [67,74] duration and health literacy.[75] In the United States, population-level measures could be tested within existing government-funded infrastructure systems, such as Women's Infants and Children's, infant home visiting, or child care programs. The potential causal role of infant child care experience (duration, structure and features reflecting quality) is understudied and poorly understood. These contexts have not been the venue for many RCT's however, which is likely a missed opportunity.

Many of the existing studies in infancy and early childhood share challenges in their design and implementation. As with most clinical trials, recruitment and retention is a challenge. Ensuring that study participants reflect the sociodemographic profile of United States infants will also be critical, particularly since this population is characterized by a high prevalence of poverty and non-white or Hispanic race/ethnicity. Other challenges include a lack of robust and valid outcome measures in infancy, an insufficient evidence base for intervention components, and perhaps, too much focus on behavioral targets with a weak evidence base, such as promoting breastfeeding, delaying introduction of solids, or avoiding pressuring the infant to eat.. The long-term risks and benefits of reducing the rate of infant weight gain by restricting infant dietary intake or changing the composition of infant formula are unknown.[45]

Discussion

Over the course of the workshop, the investigators collectively identified a number of research needs. The major deficiencies in the knowledge about obesity prevention in infancy and early childhood are summarized in Table 1. Overall, there was consensus that interventions that shape parenting behaviors to promote routines, healthy sleep patterns, and appropriate and responsive feeding practices may hold promise. Given the public health urgency of the current obesity epidemic and clinical demand for straightforward behavioral interventions that work, continued development, refinement, and testing of these types of interventions is important. However, it is also clear that there are substantial gaps in knowledge regarding underlying mechanisms.

In summary, fundamental knowledge regarding basic behavioral and biological mechanisms of obesity development during infancy and early childhood is lacking. Researchers from a range of disciplines who can bring expertise to the challenges in the field are needed and multi-disciplinary approaches employing the latest emerging methodologies will be essential.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Knowledge Gaps and Research Needs Related to Obesity Prevention in Infancy and Early Childhood

Area of Knowledge Gap	Research Need
Interpretation of infant weight and length against reference standards	• Studies examining short-and long-term health consequences of different thresholds for defining "overweight" or "obese" on the CDC or WHO infant growth charts • Studies examining the validity of body mass index as a measure of adiposity in infancy
Infant body composition	• Methods of assessing infant body composition between 6–24 months that are feasible and low-risk, including methods suitable for population studies • Studies examining infant body composition as a predictor of future outcomes, as an outcome of prenatal and early life influences, and as a mediator of links between risk factors and future obesity risk
Intrauterine determinants	• Studies examining mechanisms relating intrauterine risk factors with offspring obesity, particularly employing a systems biology approach
Rapid infant weight gain	• Studies examining patterns of weight gain and growth trajectories associated with risk for obesity development and other metabolic outcomes •Studies identifying modifiable behavioral, social-contextual, and biological determinants of rapid infant weight gain
Physical activity	• Methods for measuring physical activity and sedentary behavior • Naturalistic observational studies that document normal development of physical activity and its correlates • Studies examining whether differences in physical activity patterns, sedentary behaviors, and motor development cause differences in infant growth.
Sleep	• Studies identifying behavioral, biological, and social- contextual mediators specific to infancy • Studies that extend the conceptualization of sleep beyond sleep duration, to include sleep quality, timing, consolidation, and others • Development and validation of methods to measure sleep in infants and young children
Role of feeding "vessel" in shaping intake	• Studies examining reduction in bottle use or alteration in milk flow as a strategy for moderation of intake or obesity prevention, including investigation of mechanism of effect
Food preferences and appetitive behaviors in infants	• Studies examining effect of improving maternal diet during pregnancy on child food preference and dietary outcomes • Studies identifying mechanisms by which infants develop food preferences • Studies that identify how individual differences in infant/child appetite and food preference contribute to obesity development or treatment response
Formula and breastmilk composition	• Studies identifying the mechanism underlying differences in growth patterns based on milk or formula composition • Studies that examine the role of macronutrient composition and presence or absence of pre- and pro-biotics in different infant formulas on infant growth • Studies investigating the impact of breastmilk composition on infant growth
Complementary feeding	•Studies that examine moderators of the effects of timing of complementary feeding on infant growth and studies with longer follow up periods • Studies examining the effects of differing macro-and micro-nutrient compositions of complementary foods, the volume of food at each feeding, or the order of presentation of different foods and flavors
Social cognitive contributors to infant eating behavior	• Studies identifying how social information (e.g., behavior of siblings or parents) influences infant food choices and eating behavior. • Studies examining how television and other media exposures may exert social influences to shape infant eating behavior
Methods for characterization of behavioral phenotypes	• Development and validation of methods to assess infant/child behavioral factors that may contribute to obesity risk, such as appetite, food preference, temperament, learning, and other attributes
Infant emotional and behavioral regulation	• Studies that examine the mechanisms linking infant emotional and behavioral regulation to rapid weight gain • Studies of the dyadic features of the feeding interaction and their association with infant growth, including development and validation of methods for assessing child-caregiver interactions • Studies that identify how individual differences in behavioral phenotypes such as temperament and self-regulation contribute to obesity development or treatment response
Maternal feeding values and beliefs	• Studies examining maternal values and belief systems regarding infant feeding, how these shape feeding practices, and how these differ across sociodemographic and cultural groups • Studies delineating parental/caregiver feeding styles, their correlates, and determining their causal role in shaping infant growth
Emerging Risk Factors	• Studies investigating the impact of the hormonal milieu, microbiome, or epigenetic modifications on infant growth and risk for obesity development