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Obesity and Metabolic Disorders in Childhood

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EDITOR'S NOTE

The world of Medicine has made great advances since its early days. In recent years we have had the privilege of witnessing developments in understanding the pathogenesis of many of the diseases burdening humankind. It is frustrating, though, to realize that most of this up-to-date knowledge does not reach its natural recipients, who are specialist in each specialty working in daily practice. Thus, we believe that the need for an informative journal is obvious and self-explanatory.

For this reason, CCM fills the gap in continuing medical education to benefit every day clinical practice, by publishing this innovative series of Current Views. In every issue, readers will find a review article and several summary articles. *Current Views in Pediatric Nutrition* was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the CCM editorial team based on an ongoing review of the international literature, and articles are selected for review and citation on the basis of their relevance to clinical practice.

Current Views in Pediatric Nutrition provides specialists with an attractive means of continuing medical education that demonstrates the best of critical thinking and is a source of, and a catalyst for, new ideas and learning. The editors and medical advisors at CCM have made every effort to search the international literature to present the most current, interesting and cutting edge articles, in order to make *Current Views in Pediatric Nutrition* a respected and useful tool of physicians with one aim: to provide a good service to their patients. For this issue, we have retrieved information from several well respected peer reviewed journals:

Am J Clin Nutr.
Ann Nutr Metab
Br J Nutr.
Foods.
Front Neuroendocrinol
Front Pediatr.
Gut Microbes.
J Allergy Clin Immunol Pract.
J Pediatr (Rio J)
J Pediatr Gastroenterol Nutr.
J Pediatr.
Neonatology.
Neuroimage.
Nutrients.
Nutrition.
Pediatrics.
PLoS One.
Prev Med.
Trends Microbiol.

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Editorial Board Members

A Note from the Regional Editors

Progress in Pediatric Nutrition has continued at a spectacular pace culminating in a rapid surge in the number of increasingly precise articles on information about the assessment of growth, the nutritional status assessment and feeding guidelines, biochemical evaluation of nutritional status, infant nutrition, enteral nutrition, parenteral nutrition, nutritional management in health as well as in disease for pediatric residents powered by research. The cumulative knowledge of the complexities of Pediatric Nutrition continues to be the foundation of new advances across the clinical care continuum.

Discoveries in the fields of metabolism, genomics and immunology have been particularly fruitful and have firmly established two new pillars of clinical care. These exciting fields of research also show immense promise for the future. Furthermore, Clinical Medical Societies have been updating their Guidelines of Pediatric Nutrition.

Current Views in Pediatric Nutrition was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the Regional Editors based on an ongoing review of the international literature, and articles are selected and then summarized for citation and review on the basis of their relevance to clinical practice.

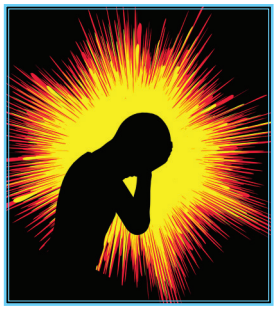
Current Views in Pediatric Nutrition mainly caters to the needs of the professionals, researchers, clinical practitioners and medical practitioners in the field of Pediatrics. Our content covers topics that advance clinical practice, and tackle issues related to global Pediatrics. The Regional Editorial Board's aim is to include the most complete and reliable sources of information and discoveries ongoing in Pediatrics and Nutrition research and treatment. The Regional Editors work as a distinguished team of experts to ensure the highest standards of selection. All relevant articles in the international literature are carefully considered and once selected all materials are promptly processed and published.

The stringency of selecting and voting on state of the art articles was done by our respected Regional Editorial team members who are listed within the journal. Our fundamental purpose is to advance clinically-relevant knowledge of Pediatric Nutrition, and improve the outcome of prevention, diagnosis and treatment of pediatric disease.

In this fourh issue, due to the spectacular developments seen lately, original research articles, early reports and review articles covering key points, potential pitfalls, and management algorithms which allow for rapid-reference, and link with the latest evidence, related to infant formula, cow's milk allergy and dietary interventions covering the major professional society guidelines and recommendations for clinical practice have been included.

We believe that the readers will find many topics of interest related to their everyday practice.

The Regional Editorial Board



Obesity and Metabolic Disorders in Childhood

Introduction

It has been estimated that 4% to 23% of children worldwide are overweight or obesity. The prevalence of childhood obesity has been increasing dramatically during the past 4 decades, both in developed and developing countries.[1,2] As reported by the World Health Organization (WHO), the number of overweight infants and children in Europe rose steadily from 1990 to 2008, and the proportion of overweight and obesity in childhood increased by 47.1% between 1980 and 2013 worldwide.[3,4]

Childhood obesity leads to short- and long-term problems of physical, social, and emotional health.[4] Obese children are highly prone to becoming obese in adulthood, and this long time-span puts subjects at high risk for developing severe comorbidities such as the metabolic syndrome (MS), type 2 diabetes mellitus (T2DM), cardiovascular disease, ischemic stroke and several types of cancer in adults; however, socioeconomic status and unmeasured lifestyle factors may confound these observational associations.[1,4,5,6]

The insidious effects of metabolic disease and the limited treatments to prevent the long-term morbidities of metabolic syndrome on cardiovascular disease (CVD) make obesity a threat to both child and adult health.[7]

Prenatal, infant, childhood predictors of adult obesity

Obesity is simply defined by the extra-accumulation of fat in the adipose tissues due to either excess caloric intake, reduced energy expenditure, or both. In mammals, white adipose tissue (WAT) accumulates such extra calories in the form of triglycerides, while brown adipose tissue (BAT) burns the fat to produce heat in maintaining body temperature. WAT

is the major culprit in the pathogenesis of obesity, as it accumulates fat/triglycerides and keeps expanding; while BAT consumes fat to produce heat, thus combating obesity.[8]

Prenatal risk factors are associated with increased risk for obesity later in life. A relationship has been shown between maternal BMI, maternal smoking and maternal weight gain during pregnancy and adult obesity. Maternal obesity affects peri-conception events such as oocyte and embryo quality. Intrauterine growth restriction with early catch-up growth during infancy is related to the development of central adiposity and the risk of cardiovascular disease.[4]

The condition of high BMI in childhood predisposes to obesity in adulthood and increased risks for obesity-related morbidities and mortality in adulthood, and this risk rises with age. In a systematic review including 34 studies, the effects of childhood obesity on the cardiovascular system is confirmed by the strong association between obesity (BMI > 85th or 95th centiles) and several cardiovascular risk factors (i.e., dyslipidemia, high blood pressure, abnormalities in left ventricular mass or function, abnormalities in endothelial function, hyperinsulinemia, or insulin resistance).[4]

In the Kaunas cardiovascular risk cohort study with over 35 years of follow-up, an increased childhood BMI and skinfold thicknesses is associated with an increased risk of developing adult obesity, hyperglycemia or T2DM, MS, and an elevated level of high-sensitivity C reactive protein (CRP). By contrast, childhood obesity does not influence arterial hypertension and serum levels of triglycerides and high-density lipoprotein (HDL) cholesterol. Moreover, an increased odds of the overall mentioned risk factors is observed when BMI is increased from childhood to adulthood.[9]

Although it is well recognized that early-onset obesity is associated with an increased risk for developing metabolic and cardiovascular disease, there is still debate about the utility of MS as a cardiovascular predictor in children and adolescents. Population-based studies highlight that the presence of MS during adolescence is not predictive of adult MS and T2DM or increased carotid intima-media thickness (cIMT).[4,10]

While cardiovascular risk associated with childhood BMI and MS has been shown to be reversible in the case of obesity and MS recovery, childhood low-density lipoprotein (LDL) cholesterol, blood pressure and, in particular, a triglyceride/high-density lipoprotein (HDL) ratio < 3 are associated with adult cardiovascular risk, irrespective of their tracking into adulthood.[4,11]

Among risk factors predisposing to the development of MS in childhood, genetic factors, low birth weight, and early adiposity rebound may all contribute to a child's future risk. Several other risk factors have been emerging as potential predictors of MS at a general population level. Among lifestyle risk factors, infrequent fruit consumption and low physical activity in childhood are associated with accelerated 6-year IMT progression in adulthood.[4]

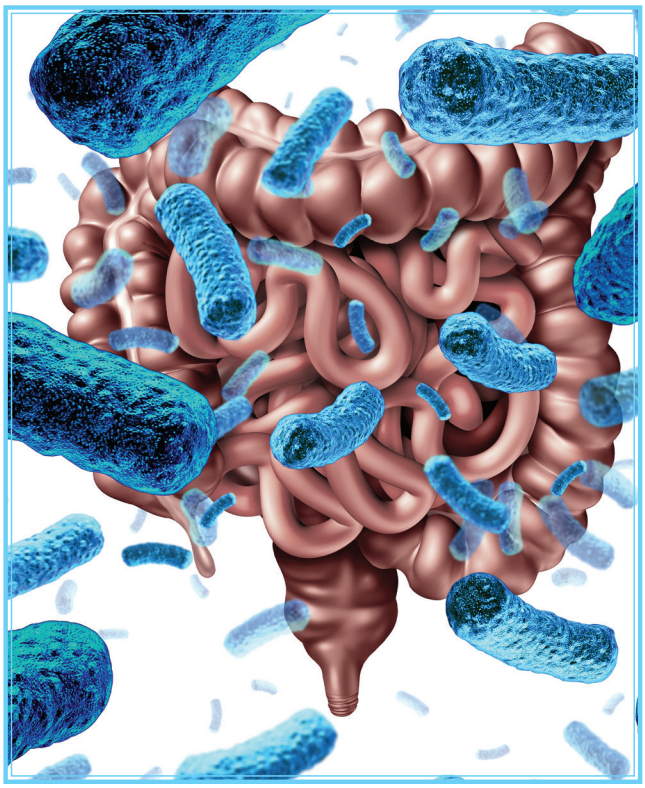
Metabolic inflammation in childhood obesity

In the setting of obesity, codependent interactions between metabolism and inflammation have been observed in the prenatal environment, infancy, early childhood, and adolescence.[7]

Emerging evidence indicates that immune cells and adipocytes interact to regulate metabolic functions that impact obesity. In general, to fight with infections or other threats, immune cells disperse energy to release cytokines and cell proliferation by consuming glucose and other sources of energy from the body.[8,12] However, upon surplus energy situations, adipocytes also start releasing inflammatory cytokines that bi-directionally influence the functions of adipose tissue resident immune cells such as macrophages. In these conditions, adipocytes do not function properly and cause different forms of cellular stress which activate the inflammatory signaling pathways, which in turn cause insulin resistance in adipocytes.[8,13]

Pro-inflammatory cascades within adipocytes are required for adipogenesis and adipocyte hypertrophy with high-fat diet (HFD) challenge.[8,14] With chronic obesity, leukocytes within adipose tissue generate a sustained pro-inflammatory tone that has negative effects on adipocyte insulin sensitivity and contributes to systemic insulin resistance. Adipose tissue leukocytes such as eosinophils and innate lymphoid cells interact with ATMs in the lean state to maintain homeostasis and counteract the pro-inflammatory signals.[8,15]

While many preclinical studies have examined the effects of obesity on inflammation in prenatal and early postnatal periods, there are limited basic studies assessing the effects of childhood and adolescent obesity on life-long disease risk.[8] Overweight and obese children as young as 3 years of age demonstrate elevations in CRP and absolute neutrophil counts.[16] Several studies have shown that elevated white blood cell (WBC) counts in obese children track into adult-



hood and correlate with the number of metabolic syndrome components.[8]

In children, these inflammatory biomarkers are strongly associated with adiposity, and in severely obese adolescents the risk of elevated CRP, impaired fasting glucose, and hypertension increase in concert with increased BMI.[17,18] Protective factors such as adiponectin have been shown to have a similar decrease with increasing BMI and increased CRP.[8]

Obesity has lifelong effects on metabolism and immune system activation that may have multiple starting points from the prenatal period through adolescence. The existing data suggest that whenever it is initiated in children, many features of inflammation persist through adulthood. Weight reduction in children can normalize inflammatory markers.[7]

Gut microbiome and childhood obesity

Microbiota studies have underlined the role of dysbiosis in developing several metabolic disorders like obesity, diabetes and immune-related disorders like asthma. During the early years of life, the intestinal microbiome is relatively dynamic, and these initial dwellers have a key impact on the host health throughout life. Thus, it is important to understand the factors that influence and modify the microbiome at various stages of life for an individual, with an emphasis on early life.[19,20] These efforts will lead to the development of disease-specific biomarkers that can be used potentially for diagnostics and eventually to design treatment strategies. The gut microbiome can play a key role in the immune-adipocyte interactions regulating obesity. Studies over the past decade have confirmed that the gut microbiome is not only associated with obesity but is also a causative factor, having the ability to increase its risk.[8]

Gut microbiome, immune, and metabolic (MIM) cells, including adipocytes, closely interact and regulate functions of each other, which can impact obesity pathology. While the role of the MIM axis in obesity is emerging considerably in context to adulthood obesity, its role in childhood obesity is not well developed.[8]

Overall maternal health is crucial for the risk of obesity in offspring later in life. Factors including maternal obesity, diabetes, malnutrition, medications, and lifestyle (during, before, and after pregnancy) can impact the offspring's MIM axis.[21] Almost two-thirds of American child-bearing aged women have obesity.[22] Maternal obesity and diabetes are known to pose high risks of developing these ailments in their children.[8,23]

Human studies demonstrated that the offspring from mothers with peripartum or intrapartum obesity/overweight are more likely to have obesity/overweight. Infants of mothers with less gestational weight gain (GWG) have lower fat mass, while offspring with excessive GWG have greater fat mass.[24] The microbiome is significantly less diverse in children from mothers with obesity, demonstrating that environmental factors like microbiome may contribute to human childhood obesity.[8,25]

Antibiotic use during infancy increases the risk of obesity by inducing microbiome dysbiosis.[26] Compared to older children and adults, the microbiome of the infant is much more sensitive to antibiotic-induced alterations. Specifically, infants struggle to replenish bacteria that have been killed by antibiotics.

Stark et al. found that antibiotic exposure in early life significantly increases the risk of early childhood obesity regardless of the strength or type of antibiotic, and longer exposure increases this risk.[27] Another study demonstrated that specifically the number of antibiotic courses – rather than mere exposure – during childhood determines the risk

of childhood obesity, where children having at least four course of antibiotics had significant increases in the risk of childhood obesity.[8,28]

Cardiometabolic characteristics of obese children with NAFLD

Previous studies have shown certain differences in the metabolic characteristics between non-alcoholic fatty liver disease (NAFLD) children and simple obese children, especially in Western countries. A study in Norway reported NAFLD children had significantly lower insulin-like growth factor 1 standard deviation score (IGF-1 SDS), higher BMI, homeostasis model insulin resistance index (HOMA-I), and uric acid (UA) than simple obese children, and IGF-1, BMI, HOMA-IR, and UA were useful markers of NAFLD in obese children and adolescents.[29] As newly established component of metabolic syndrome, UA served as a predictor for NAFLD as well. A meta-analysis showed that higher UA levels led to an increased risk of metabolic syndrome, and showed a linear dose-response relationship. Furthermore, they also showed a causal relationship between UA and childhood NAFLD.[29,30,31]

Genetic determinants in children obesity

During intrauterine life, several factors such as maternal and paternal genes, maternal BMI, maternal smoking, maternal alcohol consumption, maternal drug use, exercise during pregnancy, and birth weight, vary depending on the epigenetics of an individual, and can predispose to obesity and other phenotypes during later stage of life.[4]

As a multifactorial disease, obesity in children is associated with both genetic determinants and environmental factors. In this sense, genetic polymorphisms have been evaluated in obesity, and it is thought that approximately 65% of the variation in obesity is genetic.[32] However, genetic factors alone cannot explain the rise in the prevalence of this disease: the gene-environment interaction has been suggested as an important factor in the development of obesity.[32,33]

Dietary intake of methyl groups (choline, methionine, genistein and folate) during critical periods of developmental stages alters promoter DNA and histone methylation, thereby resulting in lifelong changes in gene expression, and alteration of the epigenome towards obesity in adulthood.[4]

DNA methylation Studies about DNA methylation in childhood obesity are incipient when compared with adult obesity. The understanding of DNA methylation in children is especially important, since evidence shows that the patterns of methylation established in early life are persistent.[34] In addition, factors that can alter gene expression and DNA methylation, such as comorbidities and smoking, do not occur or have minimal impact in children and teenagers.[3235]

Leptin The adipokine leptin has been extensively studied since its discovery. This protein acts in the central nervous system and plays important roles in the regulation of metabolism and in satiety. Higher levels of this protein are observed in individuals with obesity when compared with lean ones, both in children and in adults.[36,37] Several studies have shown that the leptin (*LEP*) promoter in the blood, saliva, and cord blood is hypomethylated in children with obesity, and this state is negatively correlated with body weight, adiposity, and metabolic profile. Methylation of the leptin receptor (*LEPR*) gene was also assessed in children, although no associations were observed between methylation and measures related to obesity.[32,38]

Insulin-like growth factor 2/long noncoding RNA H19 (IGF2/H19) Children with obesity who were not breastfed in their first year of life presented a higher mean methylation at the differentially methylated region (DMR) when compared with lean children who had also never been breastfed. For the three CpGs located upstream of the exon 3 in the *IGF2* gene, there were no associations of the methylation at these CpGs with body weight or breastfeeding status. The increase in the levels of methylation in the *IGF2* P3 promoter was associated with higher serum concentrations of triglycerides, C reactive protein, and triglycerides/high density lipoprotein (HDL) ratio in children.[32]

Epigenome-wide studies in childhood obesity, despite the variability, frequently identify differentially methylated CpGs in genes implicated with lipid metabolism and adipogenesis, insulin action, embryonic development, cancer, and immune regulation.

The investigation of methylation profile across a wide range of sample types needs to be further explored and compared; the precise maternal and paternal influence upon children's adiposity, body weight, and methylation needs to be better addressed; variables, such as participants' age, must be controlled more strictly; well as longer longitudinal studies should be performed.[32]

It is difficult to address all the progressive mechanisms that lead to the long-term adverse effects of childhood or adolescent obesity on cerebrovascular and cardiovascular diseases and accidents in adulthood. Early obesity occurring in childhood may expose subjects to the long-term effects of metabolic disturbances with further consequences during adulthood.[4]

Lifestyle interventions

The importance of the early identification of children at risk of developing MS, and subsequently progressing to T2DM and cardiovascular disease in later life must not be underestimated. Current initiatives include school-based programs addressing physical activity and diet, which have been conducted with mixed success in reducing adiposity.[4]

Schools are regarded as a suitable setting for implementing obesity and related disease prevention programs, as they provide continuous and intensive contact with children, regardless of their ethnicity or socio economic status. However, the main issues concerning physical activity and nutrition arise in school children.[39,40]

Costa-Urrutia et al developed a school-based multi-component intervention program which included 60-min physical activity conducted five days a week, a health education workshop once a week, a meal serving program at the school five days a week and parent involvement activities to treat and prevent overweight, diabetes and cardiovascular risk in schoolchildren. The intervention program was applied in six urban (Mestizo ethnic group) and indigenous (Seri and Yaqui ethnic groups) primary schools for 12 weeks. A total of 320 children aged 4–12 years participated in intervention program; 203 under Treatment 1 [health education and parent involvement – (PAHEPI) program] and 117, only from Mestizo groups, under Treatment 2 (PAHEPI+ school meals). For BMI, cardiovascular and diabetes factors, pairwise comparisons of values at baseline and after treatments were done using Wilcoxon signed rank test. Generalized linear models were applied to assess the intervention effect by age, sex and nutritional status in relation to ethnicity and treatment.[39]

The Mestizo groups showed improvements in TG and GL. Nevertheless, children under T2 showed improvements in almost all outcomes, except for TG which showed no differences and slightly increased $HbA1_C$. HDL decreased significantly and LDL increased under T1; however, LDL decreased under T2 but we did not observe positive changes in HDL. It suggests that physical activity along with an education and school meals is effective for improving LDL in the short term, but improvements in HDL may take longer than 12 weeks. The intervention was successful in reducing cardiovascular risk factors (TC and TG), and BMI in children with overweight and obesity.[39]

Effective treatment of obesity in children and adolescents traditionally requires frequent in-person contact, and it is often limited by low participant engagement. Mobile health tools may offer alternative models that enhance participant engagement.[41] Cueto et al enrolled a total of 1120 participants in the mobile app–based health coaching and behavior change program for weight management analyses. Among overweight and obese children using a mobile app–based health coaching and behavior change program, increased en-

gagement was associated with longer voluntary commitment periods, and increased number of coaching sessions was associated with decreased weight status.[39]

Monzani et al validated "skipping breakfast" as a marker of risk of overweight/obese (OW/OB). The "chrono-nutrition" has been investigated within the context of obesity since studies have shown that eating at the "wrong" time of day can induce weight gain, despite a similar caloric intake. The length of night fasting, the presence of time-restricted feeding, the composition of nutrients of the last meal before sleeping, the chronotype of individuals, the food timing behaviors of parents and sibling should be all investigated with respect to breakfast skipping or not in further studies to reduce residual confounders beyond sleeping habits, daily food quality and physical activity data supporting skipping breakfast as a potential "marker" of lifestyle behaviors in children and adolescents that promote OW/OB and metabolic diseases.[42]

Obesity prevention

Early infant weight development influences metabolic regulation later in life. For the prevention of obesity and metabolic diseases, it is important to understand the underlying mechanisms in detail. High maternal and low cord blood leptin levels are associated with a higher BMI-SDS gain in the first year of life. Maternal leptin levels are influenced by prepregnancy BMI and weight gain during pregnancy. Cord blood leptin concentrations are influenced by sex as well as maternal moderate-intensity physical activity during the third trimester.

An active maternal lifestyle, maternal BMI, and the weight gain during pregnancy may indirectly influence an infant's change in BMI-SDS during the first year, partly explained by its influence on leptin levels. In terms of obesity prevention, it is important to focus on infant weight development in the first year, taking potential influencing factors, such as maternal lifestyle and anthropometry, into account.[43]

Appropriate algorithms specific for childhood obesity are needed to allow more realistic predictions of intervention effects. Only recently such an algorithm has been proposed in adults to estimate the weight outcomes of clinical health interventions accounting for compensatory changes in energy intake or expenditure.[4]

Conclusion and future perspectives

Obesity is the main manifestation of metabolic syndrome. Obese children are more likely to develop cardiovascular disease, diabetes, metabolic syndrome, fatty liver, and insulin resistance, causing higher casualty.

As obesity has become a worldwide problem, researchers have naturally searched to discover causative factors that could be modulated to improve this issue. Early life factors seem to play a large role in imprinting risk factors for future overweight and obesity. Thus, it has become crucial to analyze maternal, prenatal, infant, and childhood decisions made that could impact the child's health, as early life overweight and obesity lead to significantly increased risk of persistent obesity in adulthood, contributing to the current obesity epidemic. Some of the important factors that could significantly alter the risk of childhood obesity include maternal health, use of antibiotics in both mother and children, and birth and feeding methods.[8]

Unhealthy diets, increasingly sedentary lifestyles and genetic/epigenetic variants play a role in the persistence of obesity in adulthood. Health promotion programs/agencies should consider these factors as reasonable targets to reduce the risk of adult obesity.[4]

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Infant Formula

Underestimated Risks of Infantile Infectious Disease from the Caregiver's Typical Handling Practices of Infant Formula[1]

Cho TJ, Hwang JY, Kim HW, Kim YK, Il Kwon J, Kim YJ, Lee KW, Kim SA, Rhee MS. Sci Rep. 2019 Jul 5;9(1):9799. doi: 10.1038/s41598-019-46181-0.

Infants have a developmentally premature immune system and gastrointestinal tract, which raises the possibility of bacterial infection when exposed to contaminated foods. Clinical cases of foodborne illness in infants have been linked to powdered infant formula (PIF) contaminated with pathogens, especially *Cronobacter sakazakii*, *Salmonella enterica*, and *Staphylococcus aureus* for several decades. Although bacterial contamination in PIF has been reported and extrinsic contamination during the handling of PIF has been believed to cause bacterial infections in infants, the route of bacterial transmission is not yet fully understood.

In this study, Cho et al revealed novel route of pathogen transfer through hand - spoon - PIF unexpectedly occurred by even typical practices of caregivers, handling of PIF and storage of feeding-spoon in PIF container. Hand-spoon-PIF contamination route was simulated to analyze the transfer and subsequent survival of pathogens.

Major pathogens associated with infantile fatal diseases (*Cronobacter sakazakii*, *Salmonella enterica*, *Staphylococcus aureus*) were readily transmitted to PIF from skin (3-6log CFU/hand) via spoons following long-term survival of transferred pathogens (3 weeks; use-by date of PIF) as the excessive level of infectious dose, highlighting direct onset of diseases. The authors found that low bacterial load on skin (ca. 1log CFU/hand) could prevent cross-contamination of PIF, however, at least 72h survival of transferred pathogen on spoons demonstrated the probability on re-contamination of PIF.

Research on the cross-contamination between surfaces has revealed that the transfer of bacteria varies due to the difficulty of managing environmental factors. To minimize differences between laboratory experiments and real-life conditions, the authors conducted a simulative analysis of experimental conditions that could affect the results (i.e. surface properties of skin, contact time of skin with spoon, pressure of hand for holding spoon were strictly controlled).

The study findings imply the following: (1) bacterial transfer from hands to PIF via utensils occurred readily, and the risk of cross-contamination was strongly dependent on the bacterial load on hands; (2) survival of transferred pathogens was dependent on the type of bacteria; (3) long-term survival of pathogens on spoons and in PIF represents a direct hazard to infants; (4) transmission of pathogens from extrinsic contamination routes should be considered for quantitative microbiological risk assessment (QMRA); and (5) storage of spoons in PIF containers should be avoided to prevent re-contamination of transferred pathogens on food contact surfaces.

Analysis of bacterial survival revealed that unhygienic practices by the caregivers not only caused cross-contamination, but also resulted in the long-term survival of pathogens in PIF (up to 3 weeks, use-by date suggested by manufacturers). Cross-contamination of pathogens in PIF highlights the risk of infection to infants continually exposed via feeding.

This is the first study to investigate the cross-contamination of utensils in contact with powdered-foods. The authors concluded that bacterial load on hands is the key determinant of pathogen transfer and the extent of risk are species-dependent. These evidential results redefine risk of caregivers' practices and facilitate incorporation of cross-contamination into risk-assessment as underestimated route of infection.

Unintentional Error in Formula Preparation and its Simulated Impact on Infant Weight and Adiposity[2]

Altazan AD, Gilmore LA, Guo J, et al. Pediatr Obes. 2019 Jul 26:e12564. doi: 10.1111/ijpo.12564.

Diet and feeding practices early in life impact risk for childhood obesity and chronic diseases in adulthood such as obesity, diabetes, and cardiovascular disease. The World Health Organization (WHO) and the American Academy of Pediatrics recommend exclusive breastfeeding until 6 months of age; however, over 80% of infants in the United States receive infant formula in addition to human milk as the sole source of nutrition prior to their sixth-month birthday. Weight gain in infancy has increased and became a public health issue and is likely due to feeding behaviors. No studies have considered the ability of adults to accurately dispense infant formula powder and to understand the implication of formula dispensing on weight gain or adiposity.

Altazan et al aimed to test the accuracy of individuals to dispense infant formula as compared with recommended serving sizes and to estimate the effect of dispensing inaccuracy on infant growth. Inlight of this goal, fifty-three adults dispensed infant formula powder for three servings of 2, 4, 6, and 8 fl oz bottles, in random order. The weight of dispensed infant formula powder was compared with the recommended serving size weight on the nutrition label. A novel mathematical model was used to estimate the impact of formula dispensing on infant weight and adiposity.

The authors found that 90% of bottles (20 of 636) prepared contained the recommended amount of infant formula powder. Three percent were underdispensed, and 78% of bottles were overdispensed, resulting in 11% additional infant formula powder. Mathematical modelling feeding 11% above energy requirements exclusively for 6 months for male and female infants suggested infants at the 50th percentile for weight at birth would reach the 75th percentile with increased adiposity by 6 months.

This cross-sectional study provides compelling observational evidence as to the potential prevalence and magnitude of overdispensing of infant formula powder and its impact on weight gain in infants fed infant formula partially or solely. Despite food intake early in life being fairly universal, there is a discordance of infant growth between formula-fed and breastfed infants.

Fortunately, the US Food and Drug Administration (FDA) mandate strict instructions for labelling on infant formula, including instructions on dispensing infant formula powder and bottle preparation using pictographs. This study uncovers the potential for providing infants with meals containing additional infant formula unintentionally due to overdispensing infant formula powder and provides new explanation for accelerated weight gain trajectories in formula-fed infants.

In summary, inaccurate measurement of infant formula powder and overdispensing, which is highly prevalent, may contribute to rapid weight gain and increased adiposity in formula-fed infants.

Use of Partially Hydrolysed Formula in Infancy and Incidence of Eczema, Respiratory Symptoms or Food Allergies in Toddlers from the ELFE Cohort[3]

Davisse-Paturet C, Raherison C, Adel-Patient K, Divaret-Chauveau, Bois C, Dufourg MN, Lioret S, Charles MA, de Lauzon-Guillain B. Pediatr Allergy Immunol. 2019 Sep;30(6):614-623. doi: 10.1111/pai.13094.

Current guidelines on infant feeding recommend exclusive breastfeeding for the first 6 months of life or at least 4 months, and introduction of complementary foods not before 4 months but not delayed after 6 months, even for allergenic foods. Although the overall benefits of breastfeeding on children's health and development are clearly established, its specific benefit for allergy prevention remains controversial.

Partially hydrolyzed formulas (pHF) are recommended in non-breastfed infants with familial history of allergy to prevent allergy development. However, recent meta-analysis does not provide strong support for their protective effect. In this context, the aim of this study was to examine the associations between the use of pHF in infancy, in real-life conditions of use, and the incidence of eczema, respiratory symptoms, or FA in toddlerhood, with a particular focus on infant formula with a HA label.

In light of this goal, Davisse-Patyuret et al, conducted an analysis based on data from the nationwide ELFE (Etude Longitudinale Française depuis l'Enfance) study, including children born in 2011 in 320 participating maternity units in mainland France.

Infant feeding (breast milk only, partially hydrolyzed formula with [pHF-HA] or without a hypoallergenic label [pHF-non-HA], and non-hydrolyzed formula [Nhf]) was reported at 2 months. Eczema, FA, and respiratory symptoms such as wheezing and asthma were reported at 2 months, 1 year, and 2 years. Infants with prior FA at 2 months were excluded from analyses.

The authors found that, among 11 720 infants, those who received only breast milk at 2 months were at lower risk of eczema at 1 year than those who received nHF (OR[95% CI] = 0.78[0.65-0.94] in non-at-risk infants; 0.86[0.75-0.98] in at-risk infants). The use of pHF-HA, compared with nHF, at 2 months was related to higher risk of wheezing at 1 year in at-risk infants (1.68[1.24-2.28]) and higher risk of FA at 2 years both in non-at-risk infants (3.78[1.52-9.41]) and in at-risk infants (2.31[1.36-3.94]).

In analyses restricted on whey-based pHF, regardless of HA label, findings were consistent with those from the main analyses, suggesting that the type of hydrolyzed proteins used in infant formulas was not the main determinant of the association.

Regarding the protective effect on allergic diseases of protein hydrolysis in infant formula, the German Infant Nutritional Intervention (GINI), conducted among at-risk children, showed a lower risk of atopic dermatitis during the first 3 years of life among the children who received a whey-based pHF in their first 4 months, compared to those receiving nHF, but did not highlight any protective effect on other allergic manifestation (allergic urticaria, FA with manifestation in the gastrointestinal tract, or asthma).

In this nationwide study, the authors concluded that pHF-HA use was not associated with a lower risk of any of the studied outcomes. By contrary, it was associated with a higher risk of wheezing and FA. The authors consider that this should be confirmed in further studies.

Ketogenic Diet & Epilepsy

The Ketogenic Diet for Super-Refractory Status Epilepticus Patients in Intensive Care Units[4]

Park EG, Lee J, Lee J. Brain Dev. 2019 May;41(5):420–427. doi: 10.1016/j.braindev.2018.12.007.

Super-refractory status epilepticus (SRSE) is one of the most challenging issues in intensive care units (ICUs) in that it is associated with high morbidity and mortality. The ketonic diet (KD), a high-fat, low-carbohydrate, and low-protein diet that mimics the fasting state, has been proved to be effective for intractable epilepsy, and recent reports suggest that the KD can also be useful as an acute treatment for SRSE in both adults and children. However, the use of the diet as therapy can be complicated by concomitant medical problems specific to critically ill patients.

In this study, Park et al aimed to describe their experience of the KD for SRSE patients in ICUs. They retrospectively reviewed the medical records of 16 patients (10 males, 6 females) with SRSE who were treated with the KD in the ICUs at Samsung Medical Center from July 2005 to July 2017.

The median age of seizure onset was 8 years (interquartile range 5-13.5). Prior to diet initiation, the patients were in convulsive or non-convulsive SRSE for a median of 23 days (range, 3-420). According to the authors' findings, the median time to achieve ketosis was 3 days (range, 2-6). The KD was continued for a median of 2.1 months (range, 0.1-15.8). Of the 16 patients, nine (56.3%) achieved seizure freedom, six (37.5%) reported >50% seizure reduction, and one (6.2%) had <50% seizure improvement after the KD.

There was no significant change in the number of antiepileptic drugs. The most commonly encountered complication during the KD was gastrointestinal disturbance.

Fifteen of 16 patients (93.8%) were followed for a median of 19 months (range, 3–85) after discharge. The remaining

patient was 14-year-old female who had been hospitalized for long periods because of uncontrolled seizures. After she began KD, she experienced a 50% reduction in seizure frequency at three days and had 75% improvement by the end of the first month. During follow-up, complete seizure control was achieved in 6 of 15 patients (40%), three of whom were performing well in school with no need for assistance with activities of daily living.

This study revealed that the KD played an essential role in cutting off continuous infusion of anesthetic agents or controlling seizures in more than half of patients (56.3%). The KD was also helpful for weaning from mechanical ventilation in six of eight patients (75%). Because prolonged coma therapy or ventilatory support, unremitting seizures, and use of a number of AEDs may increase the risk of serious infection or critical multiorgan dysfunction, the KD can serve as an alternative strategy to treat SRSE patients in ICUs.

Based on their experience, the researchers in this study indicated that the KD is an effective alternative therapeutic strategy for SRSE patients in ICUs with adequate efficacy and safety in reducing seizure frequency and weaning from prolonged mechanical ventilation, although functional outcome was not favorable for most patients. Close monitoring and preventive management of potential adverse effects are critical elements for success with the KD in patients with SRSE.

Cow's Milk Allergies

Association of Blood Eosinophilia and Vitamin D Insufficiency in Young Infants with Cow Milk Allergy[5]

Li J, Mei X, Cai X, Zhuo Y, Zhang L, Guo H, Yang H, Yang G. Asia Pac J Clin Nutr. 2019;28(3):550-557. doi: 10.6133/apjcn.201909_28(3).0014.

Cow milk allergy (CMA) is the most common food allergic disease in infants, especially those under 6 months. The incidence rate of CMA in children of one year or younger was estimated at 2% to 6%. The symptoms vary but include diarrhea and/or bloody stool due to intestinal inflammation caused by cow milk protein (CMP). Vitamin D plays a critical role in regulating intestinal inflammation. Li et al investigated the roles of vitamin D in cow milk allergy. In light of this aim, fifty-six young infants with cow milk allergy were enrolled. The serum 25-hydroxyvitamin D (25OHD), total and specific IgE, circulating regulatory T lymphocytes, and blood eosinophil counts were determined.

The serum 25OHD in cow milk allergy and age-matched infants were similar (68.3±38.9 nmol/L versus 72.9±33.1 nmol/L, p>0.05), 71% Cow milk allergy infants (40/56) had serum 25OHD lower than 75 nmol/L compared to 66% (37/56) in the controls. The cow milk allergy infants with 25OHD lower than 75 nmol/L had persistent blood eosinophilia and delayed resolution of symptoms after cow milk elimination compared to those with 25OHD above 75 nmol/L (odd ratio 3.7, 95% CI 1.1-12.6, p<0.05). The serum 25OHD inversely correlated with blood eosinophil counts after cow milk elimination (r=-0.37, p<0.01). Cow milk allergy infants with 25OHD lower than 50 nmol/L (vitamin D deficiency, n = 22) were in general at younger

age (1.6±0.6 months) compared to infants with insufficient (50-75 nmol/L) or normal (≥75 nmol/L) group (4.3±1.2 and 4.6±0.9 months, respectively, $p<0.001$).

Vitamin D has multiple biological effects, and may directly or indirectly affects the blood eosinophils of CMA infants. Eosinophils are major innate immune cells and play important roles in maintaining gut homeostasis and inflammation. Blood eosinophil level is often increased in allergic diseases and has been used as a marker for monitoring the process of allergic disorders in clinical settings.

Consistent with these findings, the authors revealed that low serum vitamin D is associated with persistent blood eosinophilia and symptoms in young cow milk allergy infants.

Cow's Milk Allergy: Immunomodulation by Dietary Intervention[6]

D'Auria E, Salvatore S, Pozzi E, Mantegazza C, Sartorio MUA, Pensabene L, Baldassarre ME, Agosti M, Vandenplas Y, Zuccotti G. Nutrients. 2019 Jun 21;11(6). pii: E1399. doi: 10.3390/nu11061399.

A growing body of evidence suggests a close relationship between immunoinflammation and gastrointestinal (GI) motility triggered by dietary antigens. Cow's milk (CM) free diets and in particular extensive hydrolyzed formulas may reduce gastrointestinal (GI) symptoms due to both immune mechanisms and motility alterations, such as reduced gastric emptying time.

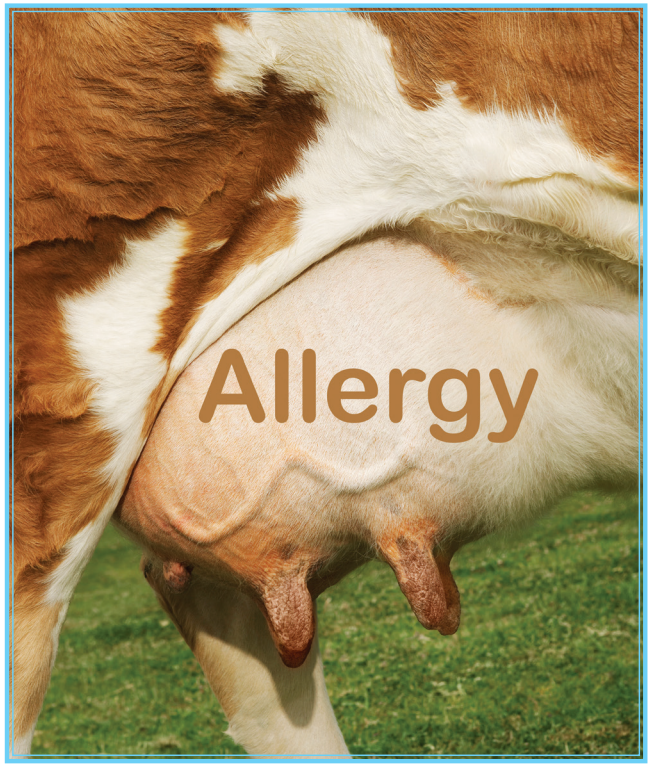
Cow's milk proteins cause allergic symptoms in 2% to 3% of all infants. In these individuals, the physiological mechanism of tolerance is broken with subsequent possible sensitization to antigens, which can lead eventually to allergic responses. Protein hydrolysates have been recognized as a potent source of bioactive peptides. They may act locally, e.g., in the gut, by modulating the intestinal microbiota, thereby playing a role in inducing oral tolerance to milk proteins

The current review aimed to provide an overview of different aspects of immune modulation by dietary intervention in cow's milk allergy (CMA). D'Auria et al focused on pathogenetic mechanisms of different CMA related disorders, e.g., gastroesophageal reflux and eosinophilic esophagitis, highlighting the role of dietary management on innate and adaptive immune systems.

The diagnosis of CMA in patients with GI symptoms is often challenging because of the delayed type of allergic reaction and the absence of specific diagnostic tests: Skin prick or serum specific IgE are usually negative, while atopy patch tests have shown conflicting data. Hence, elimination diet followed by an oral open or double blind standardized challenge, in infants or older children is the recommended test to diagnose CMA.

The traditional dietary management of CMA has greatly changed in the last years, moving from a passive approach, consisting of an elimination diet to relieve symptoms, to a "proactive" one, meaning the possibility to actively modulate the immune system. Thus, new insights into the role of hydrolysates and baked milk in immunomodulation are addressed here.

Hydrolysates have been demonstrated as capable of reducing the gut intestinal permeability in ex vivo models. The improved barrier function may decrease the antigen uptake and the antigen contact with the intestinal immune cells in the lamina propria, which may lead to a reduction in allergic symptoms.



More recent evidence, however, suggests that hydrolyzed peptides also have an active role in modulating the immune system through different mechanisms both in children with CMA and in those at risk of developing CMA.

Many cohort and retrospective studies have hypothesized that CMA resolution occurs more rapidly in cases of regular baked milk assumption. However, since cow's milk tolerance can spontaneously occur in the first years of life, studies without a control group could not explain whether the faster tolerance observed is due to real immune modulation via a baked product, or by a milder phenotype of those patients.

Additionally, nutritional components, such as pre- and probiotics, may target the immune system via microbiota, offering a possible road map for new CMA prevention and treatment strategies.

A recent multicenter double-blind randomized controlled trial investigated the effects of an amino acid-based formula (AAF), including fructo-oligosaccharides, and the probiotic strain, *Bifidobacterium breve* M-16V, in 35 infants with suspected non-IgE-mediated CMA. After 8 weeks of diet, the median percentage of Bifidobacteria was significantly ($p < 0.001$) higher in the test group than in the 36 control subjects fed non-supplemented AAF (35.4% vs. 9.7%), whereas *Eubacterium rectale/Clostridium coccoides* group in feces was lower (9.5% vs. 24.2%) and similar to that detected in breastfed infants (55% and 6.5%, respectively).

In conclusion, much has changed in recent years in food allergy management, moving from a one-size approach to a personalized one, associated with the specific food allergy phenotype. While different protein hydrolysates seem able to modulate the immune system, the few in vivo data, although promising, do not allow us to draw conclusions on their effect on tolerance achievement. The heterogeneity among the studies currently limit one's ability to compare the results and to recommend the routine use of prebiotics and probiotics for prevention and treatment of CMA.

Gastrointestinal Disorders

Nutritional Status and Food Intake in Pediatric Patients with Inflammatory Bowel Disease at Diagnosis Significantly Differs from Healthy Controls[7]

Sila S, Trivić I, Pavić AM, Niseteo T, Kolaček S, Hojsak I. Eur J Pediatr. 2019 Aug 17. doi: 10.1007/s00431-019-03443-3.

In inflammatory bowel disease (IBD), malnutrition is a well-recognized condition, especially in children with Crohn's disease (CD) in whom linear growth failure often precedes gastrointestinal symptoms and around two-thirds of them are underweight at the time of diagnosis. Sila et al considered that the relationship between the nutritional status and dietary intake in pediatric-onset inflammatory bowel disease are complex and need to be further explored. Therefore, they have assessed anthropometric measures, body composition, and dietary intake of newly diagnosed pediatric patients, and compared them with healthy controls.

The authors conducted a prospective cross-sectional study including newly diagnosed patients with inflammatory bowel disease (n = 89) and healthy controls (n = 159). Information about food consumption was obtained at the time of diagnosis for all included patients.

With regard to the energy intake, the authors found that the mean energy intake was significantly lower in healthy controls compared to patients with ulcerative colitis (UC), but not in patients with Crohn's disease (CD). Intake of all macronutrients, dietary fiber, and calcium was significantly lower in patients with ulcerative colitis, whereas the only intake of animal protein, fruit, and calcium differed significantly in patients with Crohn's disease. There were no significant differences in the body fat percentage between patients with ulcerative colitis or Crohn's disease vs. controls; however, lean mass-for-age z-scores were significantly lower

in patients with both diseases in comparison to controls.

The authors found a significant difference in anthropometric measurements and lean mass between CD and UC patients vs. healthy controls. Despite having lower BMI-for-age z-scores compared to healthy controls, both CD and UC patients had significantly lower z-scores for lean body mass while having the same body fat percentage. That clearly confirms that BMI is not an ideal marker of body composition in children with IBD.

The authors concluded that food intake of newly diagnosed pediatric patients with inflammatory bowel disease significantly differed from healthy controls. Altered anthropometry and body composition are present already at the time of diagnosis. This study showed significantly lower intake of energy, macronutrients, and various micronutrients in patients with ulcerative colitis compared to healthy controls, while patients with Crohn's disease have a lower intake of fruits, calcium, and animal protein at diagnosis.

How Does One Choose the Appropriate Pharmacotherapy for Pediatric Patients with Functional Dyspepsia?[8]

Manini ML, Camilleri M. Expert Opin Pharmacother. 2019 Aug 6:1-4. doi: 10.1080/14656566.2019.1650021.

Definition, prevalence, and impact of pediatric functional dyspepsia

Dyspepsia in Greek means bad digestion. Functional dyspepsia (FD) refers to upper gastrointestinal (GI) symptoms (including epigastric pain or burning sensation, early satiety, and postprandial fullness) that are unrelated to bowel movements and are unrelated to another etiology to explain these symptoms. Rome criteria are used in adults and children to diagnose functional GI disorders (FGID), including FD. The criteria for the diagnosis of FD have evolved over time; Rome IV identified, for the first time, epigastric pain syndrome (EPS) and postprandial distress syndrome (PDS) as two subtypes of FD in children, as recognized in adults. Symptoms have to be present at least 4 days per month for 2 months to diagnose FD. PDS is defined as postprandial fullness/early satiation that interferes with completion of a meal and could be associated with upper abdominal bloating or nausea. EPS is a pain or burning sensation localized to the epigastrium that can be induced or relieved by ingestion of a meal and can occur while fasting. FD in children can be associated with significant morbidity, and symptoms can have a negative impact on the child's quality of life (QOL), negatively affecting school attendance.

Etiology and pathophysiology of pediatric functional dyspepsia

Pathophysiological features include altered upper GI motility, mucosal disturbances, and visceral hypersensitivity, with psychosocial stressors and mood disorders altering and modulating the severity of symptoms. Indirect and direct evidence suggests that acid hypersecretion is not a feature of recurrent abdominal pain, but this may not reflect EPS.

Abnormalities in gastric sensory and motor function may be helpful in managing patients and guiding therapy, but they do not necessarily classify patients into the clinically recognized subgroups of FD, as there is significant overlap in the pathophysiology between the FD subgroups of EPS and PDS.

Expert opinion

In this review, M. Louai Manini and Michael Camilleri indicate that when symptoms are moderate in severity, with increased frequency, but with no significant impact on QOL, a 4-6 week trial of a proton pump inhibitor (PPI) or H2 receptor antagonist (H2RA) is reasonable.

Combination therapy addressing symptoms (i.e. nausea), pain, abnormal gastric function, and psychological therapy may be required in patients with refractory symptoms.

Measurements of gastric motor and sensory functions are helpful in guiding pharmacological therapy.

Metabolic Disorders

Paternal Impact on the Life Course Development of Obesity and Type 2 Diabetes in the Offspring[9]

Gemma C. Sharp, Debbie A. Lawlor. Diabetologia. 2019 Oct;62(10):1802-1810. doi: 10.1007/s00125-019-4919-9.

The aetiologies of obesity and type 2 diabetes are incredibly complex, but the potential role of paternal influences remains relatively understudied. A better understanding of paternal influences on offspring risk of obesity and type 2 diabetes could have profound implications for public health, clinical practice and society.

In this review, Gemma C. Sharp and Debbie A. Lawlor outlined potential biological and social mechanisms through which fathers might exert an impact on the health of their offspring. They also presented a systematically compiled overview of the current evidence linking paternal factors to offspring development of obesity and type 2 diabetes throughout the life course.

Most studies taken into consideration by the authors did not explore the biological or social mechanisms through which fathers might influence obesity and type 2 diabetes risk in offspring, but identification and clarification of such mechanisms would be one way to strengthen causal inference.

A better understanding of paternal influences on offspring risk of obesity and type 2 diabetes could have profound implications for public health, clinical practice and society. There are multiple possible mechanisms through which paternal exposures might influence offspring health and development. Although evidence is accumulating to support paternal associations with offspring outcomes, more high-quality research is needed

to overcome specific methodological challenges and provide stronger causal evidence.

Early-Life Factors Contributing to Type 1 Diabetes[10]

Craig ME, Kim KW, Isaacs SR, Penno MA, Hamilton-Williams E, Couper JJ, Rawlinson WD. Diabetologia. 2019 Oct;62(10):1823-1834. doi: 10.1007/s00125-019-4942-x.

The incidence of type 1 diabetes has increased since the mid-twentieth century at a rate that is too rapid to be attributed to genetic predisposition alone. While the disease can occur at any age, mounting evidence from longitudinal cohort studies of at-risk children indicate that type 1 diabetes associated autoantibodies can be present from the first year of life, and that those who develop type 1 diabetes at a young age have a more aggressive form of the disease. This corroborates the hypothesis that environmental exposures in early life contribute to type 1 diabetes risk, whether related to maternal influences on the fetus during pregnancy, neonatal factors or later effects during infancy and early childhood.

Studies to date show a range of environmental triggers acting at different time points, suggesting a multifactorial model of genetic and environmental factors in the pathogenesis of type 1 diabetes, which integrally involves a dialogue between the immune system and pancreatic beta cells.

Dietary factors, including early introduction of cow's milk protein, overall dairy intake and early or late introduction of gluten, have long been implicated in the development of islet autoimmunity (IA) and type 1 diabetes, potentially through a mechanistic role; these dietary factors may act as antigenic triggers of autoimmunity or as co-factors in the context of gut infection and/or inflammation.

Breastfeeding may have a weak protective effect on type 1 diabetes risk, while use of an extensively hydrolyzed formula does not. Additionally, exposure to being overweight pre-conception, both in utero and postnatally, is associated with increased risk of type 1 diabetes. Epidemiological, clinical and pathological studies in humans support a role for viral infections, particularly enteroviruses, in type 1 diabetes, but definitive proof is lacking. The role of the early microbiome and its perturbations in islet autoimmunity and type 1 diabetes is the subject of investigation in ongoing cohort studies.

While incidence rates for type 1 diabetes are highest in Scandinavia/Northern Europe, the load of type 1 diabetes cases globally includes regions that have not been comprehensively studied, such as the Middle East, Africa, Asia and South America. For interventions aimed at primary, secondary and tertiary prevention of type 1 diabetes to be successful, understanding the heterogeneity of type 1 diabetes is essential.

Understanding the interactions between environmental exposures and the human genome and metagenome, particularly across ethnically diverse populations, will be critical for the development of future strategies for primary prevention of type 1 diabetes.

Association of Infant Temperament with Subsequent Obesity in Young Children of Mothers with Gestational Diabetes Mellitus[11]

Faith MS, Hittner JB, Hurston SR, Yin J, Greenspan LC, Quesenberry CP Jr, Gunderson EP; SWIFT Offspring Study Investigators. JAMA Pediatr. 2019 May 1;173(5):424-433. doi: 10.1001/jamapediatrics.2018.5199.

Infant temperament is associated with excess weight gain or childhood obesity risk in samples of healthy individuals, although the evidence has been inconsistent. In this study, Faith et al worked on the hypothesis that infant temperament

may be associated with early childhood obesity risk among offspring of mothers with gestational diabetes mellitus. No prior research has examined this topic among children exposed to gestational diabetes mellitus (GDM) in utero.

The authors aimed to prospectively evaluate infant temperament in association with overweight and obesity status at ages 2 to 5 years among children born to mothers who experienced GDM. This prospective cohort study took place at Kaiser Permanente Northern California medical centers. The researchers studied singleton infants delivered at 35 weeks' gestational age or later to mothers who had been diagnosed with GDM. Data were collected from 2009 to 2016, and data analysis occurred from June 2017 to October 2018.

The primary exposures in the child's first year were soothability, distress to limitations, and activity aspects of temperament, as assessed by a validated questionnaire. Modifiable covariates in the child's first year included breastfeeding intensity and duration monthly ratio scores, along with the timing of the introduction of sugary beverages and complementary foods.

The primary outcome was child overweight and obesity status, assessed at ages 2 to 5 years. Weight status categories were classified based on age-specific and sex-specific BMI percentiles. Multinomial logistic regression models estimated adjusted odds ratios and 95% CIs for infants whose temperaments were measured at 6 to 9 weeks of age and categorized as elevated (≥75th percentile) or not elevated in the 3 domains. The authors controlled for nonmodifiable and modifiable covariates across models.

A total of 382 mother-infant pairs participated, including 130 infants (34.0%) who were non-Hispanic white, 126 infants (33.0%) who were Hispanic, 96 infants (25.1%) who were Asian, 26 infants (6.8%) who were non-Hispanic black, and 4 infants (1.1%) who were of other races/ethnicities. In descriptive analyses, elevated infant soothability and activity temperaments were associated with the early introduction of 100% fruit juice and/or sugar-sweetened beverages (at ages <6 months) and shorter breastfeeding duration (from 0 to <3 months), while elevated distress to limitations was associated with early introduction of complementary foods (at ages <4 months). Elevated soothability consistently was associated with a higher odds of later childhood obesity, with adjusted odds ratios across models ranging from 2.22

(95% CI, 1.04-4.73) to 2.54 (95% CI, 1.28-5.03). Greater breastfeeding intensity and duration (12-month combined) score was associated with lower odds of obesity, independent of infant temperament and other covariates.

The main finding of this study revealed that a high soothability temperament in infancy was associated with a 2.2-fold to 2.5-fold increased odds of future obesity at 2 to 5 years of age in children exposed in utero to GDM. This finding was consistent, remaining significant in the context of multiple nonmodifiable and modifiable obesity risk factors.

According to the authors analysis, associations between distress to limitations (DTL) and activity temperaments with risk of future obesity were null (in the main analyses) and/or inconsistent (in the post hoc analyses). This may reflect factors specific to infants of mothers with GDM or other methodological factors and should be reexamined in future research.

The authors concluded that, among this high-risk population of infants, elevated soothability was associated with early childhood obesity risk, perhaps in part because caregivers use sugary drinks to assuage infants. Soothability temperament may be a novel screening target for early obesity prevention interventions involving responsive feeding and emotion regulation.

Neonatology

Sensorineural Hearing Loss in Newborns Hospitalized in Neonatal Intensive Care Unit: An Observational Study[12]

Stadio AD, Molini E, Gambacorta V, et al. Int Tinnitus J. 2019 Jan 1;23(1):31-36. doi: 10.5935/0946-5448.20190006.

Sensorineural Hearing Loss (SNHL) in newborns represents a common condition with serious effects on the ability to develop speech, language and social skills. The prevalence of SNHL ranges from 1 to 3 per thousand newborns. Children hospitalized in Neonatal Intensive Care Units (NICU) present an increased risk for SNHL due to prematurity, hypoxia-ischemia, hyperventilation, low birth weight and the use of ototoxic drugs.

In this study, Stadio et al aimed to assess the prevalence of SNHL in newborns hospitalized in a NICU using Transient Evoked Otoacoustic Emissions (TEOAE) and Automated Auditory Brainstem Responses (A-ABR) and analyze the associated risk factors. In this context, a sample of 153 newborns hospitalized in NICU underwent TEOAE, A-ABR and clinical ABR to evaluate the presence of hearing deficits. Prevalence of SNHL was calculated and odds ratio for specific risk factors was measured.

According to the authors' finding, one-hundred fifteen babies (86.7%) presented normal hearing at TEOAE and A-ABR. Fifteen children had a REFER response at TEOAE and a PASS response at A-ABR. Twenty-five children (16.3%) had a REFER A-ABR and were addressed to clinical ABR. A diagnosis of SNHL was made in 12 (7.8%) newborns. An increased risk of SNHL was observed in preterm children <28 weeks (p=0.0135), in children with neurological disorders (p=0.02), that underwent surgery (p=0.0002), affected from premature retinopathy (p=0.0006), craniofacial malformation (p=0.007) and that had sepsis

(p=0.04).

Additional risk factors for SNHL in the sample studied were a maternal disease during pregnancy (p=0.0011), cesarean delivery (p<0.0001) and a twin pregnancy (p<0.0001). SNHL in newborns was correlated with hospitalization in NICU.

Most of the children included in this study presented prematurity, a common reason of admission to NICU; this was equally present in children with SNHL and in normal hearing population but children with hearing loss had a slightly lower mean gestational age (28 weeks) compared to normal hearing children (31-32 weeks). The researchers did not observe an increased prevalence of SNHL in babies hospitalized in NICU over five days, that underwent to antibiotics treatment and that presented a low weight at birth.

In conclusion, SNHL in newborns was correlated with hospitalization in NICU. The early diagnosis and intervention in children with hearing loss at <6 months of age led to significantly better outcomes for speech and language development compared to non-treated children

Although universal newborn hearing screening programs allowed early identification of children with hearing loss, a specific attention should be dedicated to children hospitalized in NICU, in which an accurate early audiological evaluation associated to a rigorous clinical medical collection of data is always necessary due to the higher risk of SNHL.

Effect of Early Childhood Development Interventions Implemented by Primary Care Providers Commencing in the Neonatal Period to Improve Cognitive Outcomes in Children Aged 0-23 Months: Protocol for A Systematic Review and Meta-Analysis[13]

Edmond KM, Strobel NA, Adams C, McAullay D. Syst Rev. 2019 Aug 30;8(1):224. doi: 10.1186/s13643-019-1142-1.

Impacts of early childhood development (ECD) interventions (such as fostering attachment and responsiveness through communication, play and stimulation) are well known. Globally, there is increasing recognition of the importance of the 'golden' minutes, hours and days after birth for infant health and development. However, only one systematic review has examined ECD interventions implemented in the neonatal period (0-27 days), and this review only assessed interventions implemented by specialized providers. Primary care providers have many potential contacts with mothers and infants throughout the neonatal period. However, it is unclear how many research studies or programmes have examined the effectiveness of ECD interventions commencing in the neonatal period and which methods were used. To date, there has been no systematic review of the effect of ECD interventions delivered by primary care providers commencing in the neonatal period.

Edmond et al conducted a systematic review of the effect of ECD interventions implemented by primary care providers in the neonatal period. The authors assessed effects by timing and number ('dose') of contacts with primary care providers. Subgroup assessment included effects in disadvantaged infants such as those born with low birth weight and to mothers with mental health disorders. The authors also assessed effects in low- and high-income countries and by type of care provider.

The primary outcome was cognitive status in children aged 0-23 months as measured using standardized scales. Secondary outcomes included other child neurodevelopment domains (speech, language, fine motor, gross motor, social, emotional, behavior, executive functioning, adaptive functioning) in children aged 0-23 months. Effects on maternal mental health were also assessed between 0-23 months postpartum.

Databases such as MEDLINE (OVID), PsycINFO (OVID), EMBASE (OVID), CINAHL, Cochrane Library, WHO databases and reference lists of papers were searched for relevant articles. The researchers included only randomized controlled trials. A narrative synthesis for all outcomes will be reported. Meta-analyses will be performed where exposures and outcomes are sufficiently homogeneous. Guidelines for PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) will be followed.

Primary care coverage is high in the early days after

birth, even in low-income countries and disadvantaged populations, but then 'drops out' with estimates ranging from 80-100% coverage in the early neonatal period to 10-20% by the third month of life. Despite these data, there is little evidence about the effectiveness of current primary care service models in improving quality of neurodevelopmental care in the neonatal period from 0-27 days of life.

Neonatal care is especially medicalized. Information about ECD interventions delivered by nurses, midwives, community health workers and frontline 'on the ground' workers, and simple interventions and support is particularly needed.

This review appears to be the first to be conducted in this area. The findings will be an important resource for policymakers, primary care providers and researchers who work with young infants in primary care settings.

Congenital scars: a rare presentation of neonatal lupus[14]

Khurana A, Maria A, Sardana K, Shukla A, Gupta A. Arch Dis Child Fetal Neonatal Ed. 2019 Jul 30. pii: fetalneonatal-2019-317141. doi: 10.1136/archdischild-2019-317141.

A 6-hour-old baby weighing 2.68 kg, born to an apparently healthy first gravida, presented with erythematous and hyperpigmented, linear to irregular, depressed scars all over the body most prominently on the face, trunk and upper limbs, noticed right at birth.

Possible causes of congenital scars include in utero varicella/herpes, aplasia cutis variants, cutis marmorata telangiectatica congenita and microphthalmia with linear skin defects.

Neonatal lupus erythematosus (LE) typically presents with an annular scaly rash, predominantly over the head and upper trunk, the mean age of presentation being 6 weeks.

The presence of predominantly atrophic lesions at birth, is an unusual presentation that it is rarely described in literature. However, it is important to consider this rare presentation for the prognostic implications it has for the baby and the mother.

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