MATERNAL & NUTRITIONAL INFLUENCES ON PEDIATRIC CHRONIC DISEASE

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ABSTRACT

KATHERINE YONG WOJCIK: Maternal & Nutritional Influences on Pediatric Chronic Disease
(Under the direction of Melinda Beck)

Children are experiencing unprecedented levels of obesity, potentially complicating coexisting chronic conditions. Approximately 35% of American youth with type 1 diabetes (T1D) may also be overweight or obese. Although frequently associated with type 2 diabetes, excess weight is linked to heart disease and stroke, with negative implications for blood pressure that should not be ignored among T1D youth. Nearly 14% of these youth may already have ≥ 2 risk factors present for cardiovascular disease. Herein, a review of maternal influences on pediatric obesity revealed breastfeeding as slightly protective, while maternal overweight and smoking increased the risk. Breastfeeding may also protect against high blood pressure, a leading cause of stroke. Among a sample of T1D youth, no association between infant diet and hypertension was observed; important study limitations are noted. Such knowledge may inform future studies aimed at increasing efficacy of T1D self-management and quality of life.

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LIST OF ABBREVIATIONS

BMI = body mass index (kg/m^2)

BPA = bisphenol-A

CDC/DDT = Centers for Disease Control and Prevention, Division of Diabetes Translation

CVD = cardiovascular disease

DOHaD = developmental origins of health and disease

GDM = gestational diabetes

HLA = human leukocyte antigen

HTN = hypertension

IDH = Infant Diet History survey

IOM = Institute of Medicine

LBW = low birth weight

LCPUFA = long chain polyunsaturated fatty acid

LGA = large-for-gestational-age

MCTs = medium chain triglycerides

NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases

NIH = National Institutes of Health

NHANES = National Health and Nutrition Examination Survey

OR = odds ratio

PRAMS = Pregnancy Risk Assessment Monitoring System

RCT = randomized controlled trial

SEARCH = SEARCH for Diabetes in Youth Study

SGA = small-for-gestational-age

SNAS = SEARCH Nutrition Ancillary Study

T1D = type 1 diabetes

WHO = World Health Organization

BACKGROUND

Children are experiencing unprecedented levels of obesity, with about 30% estimated to be either overweight or obese,[1] potentially complicating coexisting chronic conditions. Although frequently associated with type 2 diabetes, about 35% of youth with type 1 diabetes (T1D) are also overweight or obese.[2] Excess weight in childhood predicts later obesity,[3-5] increases the severity of obesity experienced as an adult,[6] and increases risk of cardiovascular disease (CVD) [7,8] Moreover, nearly 14% of T1D youth may already have two or more risk factors for CVD present.[9] Hence, it is clear that excess weight should not be ignored among T1D youth, as it has negative implications for future blood pressure, stroke, and heart disease.

From a preventative standpoint, it is important to understand potential determinants of excess childhood weight gain; chapter 1 provides a broad overview of the maternal environmental factors thought to influence pediatric obesity. Exposure to breastfeeding offers numerous short[1011] and long term benefits[10,12] and may also offer some protection from future CVD. Under the concept of the developmental origins of human disease (DOHaD), the unique nutritional composition of breast milk may provide advantageous nutritional programming effects for vascular development and blood pressure through its differences in fatty acid profile and sodium content, compared to infant formulas.[12] Given the prevalence of excess weight and increased risk of CVD among youth with T1D, the aim of chapter 2 was to determine if exposure to breastfeeding might be protective for hypertension or elevated blood pressure in a sample of T1D youth. Such information may inform future interventions aimed at increasing efficacy of T1D self-management in youth, potentially decreasing future burden of CVD and increasing overall quality of life.

CHAPTER 1
MATERNAL DETERMINANTS OF CHILDHOOD OBESITY

INTRODUCTION

The mother's genetic background and her metabolic status and behavior before, during, and after pregnancy function as important determinants of obesity and related health outcomes in her child. A substantial body of research has explored the roles of maternal factors in childhood obesity-related outcomes; however, many questions remain as to how and when during development these factors exert their influence. Thus, priorities for either clinical or public health action to reduce the risk for childhood obesity are uncertain.

In this chapter, we discuss those maternal factors that appear to have the strongest influence on pediatric obesity: these include maternal weight status, breastfeeding, and smoking. Limited information on maternal dietary habits and physical activity is also presented. Some population subgroups may be more strongly influenced by these maternal factors than others. For example, African-American girls are at substantially greater risk of becoming obese earlier in life (nearly one-third in 2003–2006 National Health and Nutrition Examination Survey (NHANES)) than African-American boys or youth of other races and ethnicities. And compared to non-Hispanic white women, African-American women are at higher risk for being overweight at conception[13] and for developing gestational diabetes[14] and are less likely to breastfeed their offspring.[15] Similarly, Hispanic boys appear to be at greater risk of early obesity (more than 20% in 2003–2006 NHANES) than boys of other races and ethnicities, and Hispanic women are more likely to be overweight at conception than their non-Hispanic white counterparts.[13] Considering that genes and environment can have powerful interactions, maternal factors may be particularly strong within population subgroups at increased

risk. Throughout our discussion, it will be noted when maternal factors related to socioeconomic status, race and ethnicity, and cultural influences may be acting in concert. However, socioeconomic status and related topics will be discussed at greater length in other chapters of this book

MATERNAL WEIGHT STATUS

Obesity in children is associated with maternal overweight prior to, during, or after pregnancy. The potential public health impact of maternal weight status is quite high owing to the exceedingly high prevalence of overweight among women. Based on NHANES 2003–2004 data, the most recent reports available from the Centers for Disease Control and Prevention (CDC) reveal that approximately 33% of all adult women (≥20 years) in the United States are obese and nearly 62% of all adult women are overweight or obese.[16]

Pregravid Weight Status

One of the stronger predictors of childhood overweight is presence of overweight or obesity in the mother prior to pregnancy.[17] Maternal obesity may serve as a proxy for the child's genetic predisposition to obesity and/or for early fetal exposure to a biochemical environment altered by maternal overweight status.

Several studies have found pregravid obesity to be a consistently strong predictor of childhood obesity. For example, the odds ratios (ORs) of childhood obesity at 7 years of age were 1.38 with pregravid maternal overweight (Body Mass Index (BMI) = 26 - 29) and 2.56 with pregravid maternal obesity (BMI > 29); however, an interaction between maternal underweight status and maternal weight gain was also reported, as discussed later in this section.[18] In a study examining 2- to 14-year olds, the odds of obesity were 3.6 among children with mothers who were obese (BMI ≥30) prior to pregnancy compared to the referent group of children with non-obese mothers (BMI < 25).[17] When the same analysis was stratified by age (2- to 6-year olds, 7- to 10-year olds, and 11- to 14-year olds), the most dramatic increase in odds (OR: 5.7) was observed in the 7- to 10-year-old group.[17]

Among low income children, the odds ratios for obesity were 2.28 among 2-year olds, 3.06 among 3-year olds, and 3.07 among 4-year olds with obese mothers (BMI 30 - 39.9) compared to those with normal weight mothers (BMI 18.5 - 24.9).[19]

The impact of maternal obesity may extend through early adulthood; indeed, pregravid BMI has been related to higher adult BMI by age 20.[20] Yet conflicting evidence exists, as a recent study following children from birth to 5 years of age found that adjusting for prenatal factors including pregravid BMI accounted for some of the BMI Z-score differences in normal versus obese children; however, the effect was only observed until 24 months of age, having little or no further effect on BMI Z-score from 24 months to 5 years.[21]

The findings of this study are difficult to interpret; however, because maternal obesity is associated with births of large-for-gestational-age (LGA) babies, which is in turn a predictor of childhood obesity.[19,22-24] In an extensive review of maternal obesity, metabolism, and pregnancy outcomes conducted in 2006, obese women were more likely to have LGA/macrosomic infants.[23]

Does the father's weight function as a determinant of childhood weight gain? In one recent study, the odds of overweight in children at age 4.5 years were nearly two to three times higher in those with overweight or obese parents than in children with normal weight parents.[25] This effect was noted when maternal or paternal BMI was analyzed separately or in combination. Interestingly, same-sex parental BMI, mother-daughter or father-son, may also predict child obesity risk.[26]

In addition to maternal overweight or obesity, maternal underweight may also lead to child obesity if there is excess or inadequate gestational weight gain (see below) or rapid catch-up growth of the child during infancy and early childhood.[18,23]

Gestational Weight Gain

Excess gestational weight gain is associated with the birth of LGA infants (defined as birth weight ≥ 90th percentile for age).[22,27] Regardless of the woman's weight status prior to pregnancy,[27] excess gestational weight gain may double the risk of macrosomia, although much of this effect may

be attributable to gestational diabetes (GDM) status.[28,29] Key outcomes - high birth weight, LGA, and macrosomia - associated with excess gestational weight gain are, in turn, predictors of childhood obesity.[23,24,27,30,31] The impact of gestational weight gain may extend well into childhood, as suggested by the increase in odds of obesity at 7 years of age (OR: 1.48) in offspring of women with excess weight gain during pregnancy compared to women with recommended weight gain.[18] Despite the increasing body of evidence, a full understanding of the association of gestational weight gain with childhood obesity remains elusive due to complexities of gestational weight gain intertwined with issues of maternal obesity and GDM, which also have strong effects on the intrauterine environment, birth weight, and child obesity outcomes.

The impact of excess gestational weight gain may be most pronounced among underweight mothers. Maternal overweight and maternal obesity, compared to normal weight, each increased odds of childhood obesity at age 7 years (OR: 1.38 and 2.56, respectively), but a pronounced interaction (OR: 3.36) of low maternal BMI with excess gestational weight gain was reported when the model was adjusted for the child's sex, gestational age, first-born status, as well as the mother's race, maternal age, maternal prepregnancy BMI, smoking, and study site.[18]

The relationship between absolute gestational weight gain and higher birth weight is less clear among overweight and obese women than among normal weight women. This is because their preexisting weight status confers an increased risk of fetal macrosomia and childhood obesity even in the absence of excess gestational weight gain; alternatively, their relative gestational weight gain is less than that of normal weight women who gain equivalent amounts of excess weight during pregnancy.[27,30,32,33]

Even when gestational weight gain in overweight women is comparable to that in normal weight women, the overweight women have significantly heavier offspring.[33] It is possible (though not established) that overweight/obese mothers, even in the absence of pre-existing diabetes or GDM, transport excess glucose and fatty acids to the fetus and thereby contribute to fetal fat deposition.[24]

New Guidelines for Pregnancy Weight Gain in Overweight and Obese Women

During the past two decades in the United States, the rise in obesity rates occurred in parallel with increases in adverse maternal health and birth outcomes. Understandably, concerns were raised regarding excess gestational weight gain, particularly among the growing number of overweight and obese women. Indeed, analysis of trends from the Pregnancy Risk Assessment Monitoring System (PRAMS) showed substantial excess in weight gain during pregnancy among those classified as either overweight or obese. Previously, the guidelines for maternal weight gain formulated by the Institute of Medicine (IOM) were designed primarily to reduce the risk of intrauterine growth retardation. However, given recent findings, an update was released in May 2009. The new guidelines recommended that obese women lower their targeted weight gain (see Table 1.1 based on the 2009 IOM guidelines). The new recommendations highlight the importance of prepregnancy weight and gestational weight gain as determinants of metabolic outcome in the mother, fetus, and growing child.

Table 1.1 Total Pregnancy Weight Gain Recommendations by BMI Status

Prepregnancy BMI	*BMI*[a]	*Range of Recommended Total Weight Gain*
Underweight	<18.5	28 - 40
Normal weight	18.5 - 24.9	25 - 35
Overweight	25.0 - 29.9	15 - 25
Obese	≥ 30.0	11 - 20

[a]BMI calculation based on World Health Organization (WHO) Standards

Effects of Maternal Undernutrition

Maternal undernutrition, manifested as low prepregnancy BMI, inadequate gestational weight gain, or both, may negatively impact birth weight. The Dutch famine of 1944–1945 is an example of the relationship between inadequate maternal nutrition and its relationship to later obesity in the offspring. The timing of nutrient restriction was found to have important effects on birth weight and subsequent adiposity. Short-term nutrient restriction in the second and third trimesters resulted in

lower mean birth weight.[34] In contrast, nutrient restriction in early pregnancy resulted in higher mean infant birth weights when compared to infants of unexposed mothers.[35] If early trimester nutrient restriction increases birth weight, and high birth weight increases the risk of childhood obesity, then nutrient restriction early in pregnancy may contribute to the development of obesity in childhood.

More commonly, however, inadequate gestational weight gain results in small-for-gestational-age (SGA) or low-birth-weight (LBW) infants. Interestingly, low birth weight may be a risk factor for rapid weight gain in the first 5 months of life, which in turn may also increase childhood obesity risk. Rapid catch-up growth from age 1–7 years has also been linked to adult BMI.[21]

Postnatal Maternal Weight Status

It has been reported that women gaining the most weight while pregnant also experience increased postpartum weight retention.[36] Excess gestational weight gain has also been associated with long-term obesity in the mother.[37] This may predispose the mother to metabolic dysfunction or gestational diabetes in subsequent pregnancies, creating a vicious cycle that sustains the obesity epidemic. Thus, the failure to shed excess gestational weight gain could impact both future maternal BMI status and future offspring risk.

SMOKING

The relationship between maternal smoking and adverse outcomes such as intrauterine growth restriction, LBW, and SGA has been established through much research over the past four decades.[38-40] More recently, researchers have explored the relationship between smoking and childhood obesity. In one study, maternal smoking in early pregnancy was found to increase significantly the risk of obesity in 5-year-old children (OR: 5.04) compared with children whose mothers were either former smokers or never smokers during early pregnancy.[41] Other studies showed that maternal smoking during pregnancy significantly increased odds of BMI ≥95th percentile at 4.5

years (OR: 1.8).[25] Similar risks were noted at age 9-10 years (OR: 2.56).[41] Meta-analyses support the hypothesis that maternal smoking is related to increased risk of early childhood overweight and obesity.[42,43]

The vast majority of research to date collectively points in the same direction: that smoking increases risks of LBW and SGA, that LBW and SGA infants experience rapid postnatal catch-up growth with greater adiposity, and that each of these outcomes is associated with increased odds of childhood obesity. As noted by Oken et al., studies that reported the amount of maternal smoking in relation to childhood obesity provided evidence of a dose-response;[42] the prevalence of childhood obesity and the mean BMI and skinfold thickness at 5 years of age[44,45] correlated with the number of cigarettes smoked by the mother per day.

A recent study by McCowan et al. examined the effects of smoking cessation on gestational length and birth weight.[38] Among women who stopped smoking prior to 15 weeks of gestation, there was no increase in spontaneous preterm births or the number of children born SGA relative to non-smoking mothers. However, among women who continued to smoke, there was threefold increase in the number of preterm births and a 76% increase in the number of children born SGA.

The public health implications here are clear. Health professionals should continue to promote smoking cessation, particularly among women as a part of early prenatal care.

BREASTFEEDING

Breastfeeding is the optimal form of nutrition for infants; however, evidence to support its role in the prevention of childhood obesity remains controversial. Maternal behaviors that modulate the relationship between infant consumption of breast milk, duration of breastfeeding, and risk of childhood obesity are complex, and studies often fail to control effectively for confounding factors. Indeed, factors that may be considered confounders by some may be considered mediators by others. These include the rate and timing of weight gain in infancy in response to early feeding practices, and the co-occurrence of other health-promoting habits by the mother or the overall family. It has been

therefore difficult to determine if breastfeeding per se reduces the risks or severity of childhood obesity.

Nevertheless, meta-analyses largely support the hypothesis that breastfeeding reduces the odds of childhood obesity.[46-50] This is true if children who are breastfed exclusively are compared to formula-fed children (OR: 0.66)[49] or if children who were breastfed at any time are compared with non-breastfed subjects (OR: 0.78).[50] A recent meta-analysis showed a protective effect of breastfeeding among the larger studies (>1,500 participants) despite evidence for publication bias.[50]

Strong evidence for dose-response protection against development of child obesity with increased duration of breastfeeding is described in Harder's meta-analysis. Odds ratios were 0.81, 0.76, 0.67, and 0.68 for periods of breastfeeding ranging from 1 to 3 months, 4 to 6 months, 7 to 9 months, and >9 months, respectively. However, in most cases significant effects were not observed until children were breastfed for at least 3-6 months,[17,49,51,52] and at least one study reported an unexpected increased risk with breastfeeding duration <1 month compared to infants who never breastfed (OR: 1.36).[53] Another study reported that when formula was used with breastfeeding, a significant dose-response effect was not seen until 26 weeks.[54]

Since there are obvious ethical concerns in conducting randomized controlled trials (RCTs) of breastfeeding among infants, observational studies are the primary source of information. However, one study was conducted as a breastfeeding promotion intervention using RCT methods.[55] Researchers found no protective effect for breastfeeding compared to formula feeding, but the results should be interpreted with caution due to several methodological limitations. The study was conducted in a Belarusian population with very low obesity prevalence, the duration of breastfeeding did not exceed 3 months in the intervention group, and only 43% were breastfed exclusively.

If breastfeeding protects against childhood obesity, breastfeeding may also have beneficial effects on obesity-related health outcomes in childhood. From a case–control study, youth with type 2 diabetes were substantially less likely to have been breastfed as infants compared to their non-diabetic counterparts (unadjusted OR for the association of breastfeeding (ever versus never) and type 2

diabetes, 0.26).[49] Results were similar for non-Hispanic white, African-American, and Hispanic youth. The OR after adjusting for 12 potential confounders was 0.43.[49] When current BMI Z-score was added to the model, the OR was attenuated (OR: 0.82), suggesting possible mediation of the protective effect of breastfeeding through current childhood weight status.[49]

Exactly how breastfeeding confers protection, if any, is not well understood. Rapid weight gain in the first 4 months of life is associated with childhood obesity,[56] and breastfeeding has been associated with slower weight gain during the first 12 months of life.[57] Since bisphenol-A (BPA) has been implicated in the development of obesity through its role as an endocrine disruptor,[58] another possible mechanism is that exposure to endocrine disruptors through use of baby bottles containing BPA could be higher among formula-fed versus breastfed babies.

As discussed earlier, maternal prepregnancy overweight or obese status has been associated with an increased risk of childhood obesity. Due to the high energy cost of producing milk, breastfeeding may facilitate return to prepregnancy weight following delivery.[59] Therefore, the decision to breastfeed can play a role in determining the mother's future weight status, possibly influencing future offspring risk.

A variety of factors, including socioeconomic status and race/ethnicity, may influence the decision to breastfeed. Low maternal education or low income status was associated with lower rates of breastfeeding, and African-American infants were reported to have lower rates of breastfeeding compared to all other race/ethnicities. Some evidence of differential effects of breastfeeding has emerged, as studies of children whose mothers were white, black, or Hispanic reported that protection from childhood obesity was conferred only among children of white mothers.[54,60] The reasons for this remain unclear.

MATERNAL DIETARY HABITS AND PHYSICAL ACTIVITY

Interacting with breastfeeding are the physical activity and dietary habits of the mother. They are important contributors to the environment in which a child is raised. Maternal dietary habits will

directly influence breast milk fat and protein content, [59] and physical activity has the ability to indirectly influence breast milk nutrient content via its effects on energy balance and weight status. Maintaining a healthier weight and balanced dietary habits can lead to the production of breast milk containing a higher proportion of medium chain triglycerides (MCTs). Milk contains a higher proportion of MCTs when mammary tissue synthesizes fatty acids[61] rather than incorporating fatty acids released into blood from maternal fat stores; the latter are composed primarily of longer chain fatty acids and require bile for transport across intestinal cells. Infants have immature digestive systems and MCTs do not require bile acids for intestinal absorption; this is clearly advantageous in ensuring that the infant can meet caloric needs during the early and critical periods of development.

As a child transitions to solid foods, the dietary habits and activity patterns of the mother are likely to exert even more influence. Maternal dietary choices not only will affect the selection of foods available to the child but also will provide a means through which the child will watch and learn eating behaviors that may not be directly related to basic energy balance cues, such as satiety. Maternal activity patterns, including television viewing, [62] will shape the child's daily lifestyle. Maternal dietary and physical activity habits thus seem likely to be critical in the development of childhood obesity, yet a strong body of evidence examining their roles simply does not exist.

What has been studied are the roles played by parental education, income, and social environments, such as home and daycare, in modeling healthy behaviors and habits. Adolescents with mothers having graduate or professional degrees had lower odds of being very inactive (OR: 0.61) compared to adolescents with mothers having less education[63] and are less likely to be obese.

There is evidence showing that parental and peer modeling is crucial to early childhood development of healthy eating behaviors. Extensive research in this area has been conducted by Birch and colleagues. Among 3- to 5-year-old children, the strongest fat preferences and the highest fat intakes were observed among those with heavier parents.[64] In another study, children showing dislike for a particular vegetable began choosing the non-preferred vegetable when placed into an environment where peers were actively choosing and consuming the non-preferred vegetable.[65] In

young children, food preferences increase with familiarity, and Birch notes that current "availability of energy dense foods…provides an eating environment that fosters food preferences inconsistent with dietary guidelines, which can promote excess weight gain and obesity." [66]

Promotion of balanced dietary habits and increasing physical activity among children through a combination of parental and social context will remain important factors in reducing the alarming rates of overweight and obesity currently observed in developed countries.

OTHER INFLUENCES

Some interesting factors related in general to maternal lifestyle, such as the child's sleep duration, television watching, and computer screen time, have recently emerged as potential determinants of childhood obesity.

Short sleep duration has been associated with obesity via its association with a reduction in leptin and an increase in ghrelin, which may lead to hormonal disregulation of appetite and satiety controls.[67] In a study to identify early-life risk factors associated with childhood obesity in the United Kingdom, short sleep duration (<10.5 hours compared to >12 hours at age 3) and *television watching* (>8 hours/week at age 3) were associated with obesity at age 7 (OR: 1.45 and 1.55, respectively).[68] A recent meta-analysis examining short sleep duration and risk of obesity in children found an OR of 1.89 for short sleep duration (defined as either <10 or <10.5 hours except in one study which used <8 hours to classify short sleep duration).[69]

Since low-wage jobs usually involve long hours and a work schedule that may change week to week, maternal lifestyle as modified by low *socioeconomic status* may inhibit the establishment of both the mother's and the child's regular sleep patterns, adversely affecting the quality and duration of sleep. It must, however, be noted that the inverse correlation between sleep duration and obesity prevalence does not necessarily imply causation; no studies have shown that increasing sleep duration can reduce body weight.

The *birth weight of the mother and her early weight gain in childhood* were recently reported as predictive for next generation (her offspring's) birth weight as well as obesity risk.[70] Another study found that *grandparental obesity* may influence childhood obesity independent of parental obesity status.[71] Among children with normal weight parents, prevalence of childhood overweight was similarly elevated if the grandparents were obese (prevalence 17.4%, $p < 0.0001$) or if the grandparents had missing BMI status (16.9%, $p < 0.0001$).[71] These findings suggest that genetic factors exert a powerful influence on childhood weight gain.

SUMMARY

Maternal weight status, whether prepregnancy or postpartum, appears to be the strongest indicator of risk for childhood obesity. However, the offspring of underweight women gaining in excess of the IOM pregnancy weight gain guidelines also experienced a marked increase in risk of childhood obesity. Maternal weight is modifiable through increased physical activity and balanced dietary habits, but research associating maternal physical activity patterns with childhood risk of obesity is lacking. The evidence for breastfeeding remains inconclusive, but the available data suggest a modest benefit for protection against development of childhood obesity. Future studies must account fully for confounding factors such as maternal behavior, family habits/environment, and genetic inheritance.

Children inherently rely on adults to model appropriate behaviors. Hence, it is imperative that we gain a better understanding of high-risk factors through more research and translate that information into targeted public health interventions to empower parents and children alike to stop the obesity epidemic and improve the quality of life for generations to come.

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Pediatric Obesity: Etiology, Pathogenesis, and Treatment, Chapter 7 Maternal Determinants of Childhood Obesity: Weight Gain, Smoking, and Breastfeeding, 2010, pages 93-102, KY Wojcik and EJ Mayer-Davis.

CHAPTER 2
BREASTFEEDING AND HYPERTENSION AMONG YOUTH WITH TYPE 1 DIABETES IN THE UNITED STATES

INTRODUCTION

Adult high blood pressure, or hypertension (HTN), may be influenced by early life exposures such as breastfeeding.[72,73] HTN is a major risk factor for cardiovascular disease (CVD), which remains a leading cause of death in the United States and worldwide[74,75] and is known to track into adulthood from youth.[72,76] Youth with type 1 diabetes (T1D) may already be at increased risk for developing CVD, possibly earlier than non-diabetic youth, as 14% of T1D youth have been reported to have two or more CVD risk factors[77] and nearly 6% have elevated blood pressure, with those of minority race/ethnic backgrounds at greatest risk.[77,78] Even among these T1D youth, markers of insulin resistance have been associated with coronary artery calcification,[79] possibly contributing to the development of elevated blood pressure by reducing elasticity of arterial walls. Although frequently associated with type 2 diabetes, about 35% of youth with T1D are also overweight or obese.[2] This excess weight should not be ignored among T1D youth, as it may complicate their coexisting diabetes and has negative implications for blood pressure, stroke, and heart disease.

Under the concept of the developmental origins of human disease (DOHaD), nutritional programming of future blood pressure could be shaped by the unique composition of human milk , such as its fatty acid profile or low sodium content. [12] Long chain polyunsaturated fatty acids (LCPUFAs) are important structural components for all cell membranes (e.g. vascular endothelial cells), which may influence later blood pressure[80,81] and sodium is known to have a positive linear relationship with blood pressure.[82] In turn, these differences may influence imprinting of some permanent physiologic or anatomical change which affects one's ability to regulate blood pressure,

and reduce risk of HTN, over a lifetime.[12] Similarly, if breastfeeding serves as a proxy for maternal behaviors related to energy balance or which modify control of blood pressure (e.g. maternal regular exercise or high fresh fruit and vegetable intake), reducing potential for HTN, then behavioral imprinting may occur on the psyche, with similarly lasting effects carried through a lifetime, as a child learns how to eat and be fit through parental modeling.[66,83-85]

Further evidence of the association of breastfeeding and lower blood pressure comes from randomized trials. Among premature infants, breast milk consumption (either banked donor milk or mom's own) was protective against high blood pressure at 13-16 years of age.[86] In a randomized intervention trial designed to promote breastfeeding, no association was found between BP at 6.5yrs with either duration or exclusivity of breastfeeding;[87] however, all participants had already intended to breastfeed and variability of breastfeeding exposure may have been limited.

Given that these T1D youth may already have elevated blood pressure or other CVD risk factors present,[77-79] there may be negative impact on lifespan and future heart disease because of the earlier age at which these youth present with these risk factors. As such, investigating a potentially modifiable behavior, such as infant feeding practices in a high-risk population, may inform targeted public health messages and clinical guidance to improve long-term health outcomes of these high-risk youth. Therefore, the primary aim was to assess whether exposure to breastfeeding would be associated with decreased likelihood of HTN among T1D youth. Precision of the resulting estimates by definition of breastfeeding was also evaluated.

METHODS

Study Population. All data came from the SEARCH Nutrition Ancillary Study (SNAS), which aims to examine associations of nutritional factors with progression of β-cell failure and the presence of CVD risk factors among a subset of SEARCH for Diabetes in Youth (SEARCH) participants. SEARCH is an ongoing, multi-center, population-based observational study funded by the Centers for Disease Control and Prevention /Division of Diabetes Translation (CDC/DDT) and

National Institutes of Health/ National Institute of Diabetes and Digestive and Kidney Diseases (NIH/NIDDK), providing the most comprehensive data established in a large cohort of youth with diabetes. SEARCH study methods have been previously been detailed.[88] Briefly, all SEARCH subjects were from one of six clinical sites, had physician diagnosed diabetes mellitus, and were either prevalent cases <20 years of age in the year 2001 or were incident cases <20 years of age at diagnosis in 2002 -2005. All incident cases were eligible for participation in SNAS; for the prevalent cases, subjects eligible for the Prevalent Quality of Care survey in SEARCH were eligible for SNAS. Additionally among the prevalent cases, subjects of all ages and ethnicities who were age ≥10 years or who were of minority status and <10years were eligible; among those of non-Hispanic white race/ethnicity, who were also <10 years of age, a 10% sample was eligible due to budgetary considerations.

Definition of Hypertension Outcome. To account for differences in body size that occur as children and adolescents grow, HTN was based on average systolic blood pressure (SBP) or diastolic blood pressure (DBP) greater than or equal to age-, sex-, and height-specific 95th percentile, where blood pressure percentiles were based on normally distributed blood pressure data among healthy children. Subjects on hypertensive medication were not excluded from our analysis to be consistent with the literature,[82] as well as with other SEARCH publications. A very small number of individuals were on hypertensive medication or were missing information on hypertension (much less than 5% in both cases). Such small numbers of missing information are unlikely to affect the estimates and subjects with missing information for HTN were excluded from the analysis.

Definition of the Breastfeeding Exposure. Since the definition of breastfeeding exposure varies in the literature, analyses were conducted with three commonly used definitions of exposure to breastfeeding:

1. Ever breastfed (coded as yes or no) was used to reflect the potential biological effect which may be conferred with any exposure to breastfeeding

2. Categories of breastfeeding (coded as >0 to < 6 months, ≥ 6 months, or never breastfed) facilitated comparison with current guidelines for optimal infant feeding
3. Breastfeeding duration (number of months, as a continuous variable) was used to reflect both biological (length of time or ever/never) effects, as well as maternal behavioral factors, such as being health conscious. Breastfeeding duration as a continuous variable also improves power by reducing the loss of information that occurs with categorization. However, information on continuous duration was only available for the subset of subjects who had ever been breastfed. Therefore, both biological and behavioral effects may be represented, but no comparisons to subjects who were never breastfed can be made.

As part of SNAS, a retrospective Infant Diet History (IDH) survey was either self-administered (mail or web) or interviewer-administered (phone or in-person) based on the most convenient method to the participant. It was most commonly completed by the biological mother or an individual who had a major caregiver role in the subject's first year of life. In the survey, infant feeding while the SEARCH participant was in the hospital shortly after birth, as well as breast feeding, formula feeding, introduction of foods and beverages, and use of vitamins or other supplements during the first year of life were queried. The survey was offered to major caregivers of eligible subjects during regularly scheduled SEARCH visits (prevalent survey occasions, scheduled follow-up contacts for the 2002-2005 cohort). If the form was not returned, a phone follow-up was conducted. It is possible that variations in the quality of data may occur depending on the method of collection. As with dietary recalls, an interviewer who is well-trained in probing the subject to assist with accurate recall can provide enhanced quality and completeness for data collection. There were 3607 cases eligible to participate and 2317 (67%) completed the IDH survey. Reasons for non-participation in the IDH include refusals (n= 184), no contact (n=334), or passive refusal (n=772).

There was substantial variation in the length of time since infant feeding in the first year of life occurred, because timing of recall by the mother/primary caregiver was dependent upon the age

of the subject at the time of IDH survey completion. Maternal recall of breastfeeding (ever versus never) has been reported as both a valid and reliable means of assessment. However, measurement error from recall bias becomes apparent after longer periods of time,[89] whereas recall at 6 months does not differ significantly from prospectively collected infant feeding data. Specifically, significant differences in recall after more than 8yrs showed underestimation and recall at 14-15yrs showed overestimation.[89] Changes in the popularity of breastfeeding over time may have also influenced reporting practices.

Clinical and demographic characteristics. At the baseline visit in the parent SEARCH study, trained and certified research staff collected demographics (gender, race/ethnicity, maximum attained parental education) and clinical characteristics (age at onset, diabetes duration, %HbA1c, human leukocyte antigen (HLA), measured height, weight and blood pressure). Age and sex-specific Body Mass Index (BMI) Z-scores were calculated according to CDC standards, with overweight defined as ≥85th percentile and <95th percentile, and obesity as ≥95th percentile.

Statistical Methods. All statistical analyses were conducted with SAS software, version 9.2 (SAS Institute, Inc., Cary, North Carolina). Descriptive analyses examining differences in clinical, infant feeding, and general demographic characteristics by HTN status were assessed with t-tests and Pearson's chi square tests to detect differences between groups for continuous and categorical variables, respectively. A p-value<0.05 indicated significant differences between hypertension (yes/no) groups.

Because HLA risk genotype and minority race/ethnicity are known to differentially affect outcomes of both T1D and hypertension,[90,91] effect measure modification (EMM) in the context of breastfeeding and hypertension among a group of youth with T1D will be explored with stratified analyses and use of a chi-square test of homogeneity. A priori criteria defining presence of EMM are as follows: p<0.10 is a strong modifier, p=0.10-0.20 is a weak modifier and p>0.20 is not a modifier. Additionally, because of power limitations for stratified models, an interaction term will be included

during model fitting with a p-value <0.05 indicating when EMM may be present and determining if the associated interaction term should be retained in the full model.

Assessment for confounding by demographics (gender, race/ethnicity, maximum attained parental education, geographical site) and clinical characteristics (age at onset, diabetes duration) was evaluated by calculating the change in the estimated odds ratio (CoOR), where CoOR= crude OR/adjusted OR, followed by taking the natural log (ln) and finding the absolute value, denoted as |ln(CoOR)|. Presence of confounding was determined using criteria of $|\ln(\text{CoOR})| \geq 0.10$ and corresponding confounders were retained for adjustment in the full model.

Multivariate logistic regression was used to conduct the crude and adjusted cross-sectional analyses. To assess goodness-of-fit to the data , as covariates were added to the crude model, a likelihood ratio test was used with an a priori p-value<0.05 for determining if significant improvements in fitting the model to the data were achieved with sequentially adding in sets of covariates, such as demographics, or individual terms. If a significant association between the main exposure and outcome is observed, mediation by BMI z-score and insulin sensitivity will be considered. Precision of the resulting estimates, by definition of breastfeeding, was also assessed.

RESULTS

Mean age of these T1DM youth was 9±4 years, duration of diabetes at the first study visit was 25±34 months, HbA1c% was 7.9±1.6, SBP was 101±12mmHg, DBP was 64±10 mmHg, and only a small number were on hypertensive medication. Youth with hypertension were younger, had higher SBP and DBP, higher HbA1C, and were more likely to be obese (Table 2.1).

No association was observed between breastfeeding exposure and hypertension, regardless of the type of breastfeeding exposure (Table 2.2). No EMM by race/ethnicity, HLA risk, or parental education was observed (data not shown). Confounding by HLA and parental education was present, and retention of these terms in the models was further justified by the increased model fit observed with their inclusion (using likelihood ratio tests; data not shown).

Table 2.1 Characteristics* of youth with type 1 diabetes by hypertension status**

			Hypertension Status				
	ALL	n	Yes	n	No	n	p-value
Clinical Characteristics							
Diabetes Onset Age, years	8.63 ± 4.04	1819	7.32 ± 4.14	107	8.71 ± 4.01	1699	0.0005
Diabetes Duration, months	24.56 ± 34.45	1817	25.45 ± 34.08	107	24.59± 34.56	1697	0.80
No Hypertension Medication (%)	99	1805	97	106	99	1687	0.19
Blood Pressure, mmHg		1819		107		1699	
Systolic	100.96 ± 12.05		114.61 ± 12.27		100.17 ± 11.42		<0.0001
Diastolic	63.85 ± 10.18		76.55 ± 9.06		63.08 ± 9.69		<0.0001
% HbA1c	7.90 ± 1.56	1609	8.25 ± 1.91	80	7.89 ±1.54	1518	0.04
Infant Feeding Characteristics							
Ever Breastfed (%)		1811		107		1691	0.23
No	28		23		29		
Yes	72		77		71		
Infant Feeding Category (%)		1703		99		1596	0.12
Not Breastfed	30		25		30		
<6 months	28		37		28		
≥6 months	42		37		42		
Breastfeeding Duration, months	8.12 ± 7.40	1198	7.43 ± 8.38	74	8.17 ± 7.34	1119	0.41
General Characteristics							
Gender (%)		1819		107		1699	0.58
Female	51		49		51		
Male	49		51		49		
Race/Ethnicity (%)		1819		107		1699	0.15
White	64		56		64		
Black	13		14		13		
Hispanic	17		19		17		
Other	6		11		6		
Parental Education (%)		1811		105		1694	0.87
<High School	4		5		4		
High School Graduate	15		16		14		
Some College	34		35		34		
Bachelor's or more	47		44		48		
BMI (%)		1805		107		1695	0.0002
Underweight/Normal	64		50		65		
Overweight	22		23		22		
Obese	14		26		13		
HLA Risk Group (%)		1510		77		1423	0.48
High/Moderate	49		53		49		
Neutral/Low/Protective	51		47		51		
Clinical Site (%)		1819		107		1699	0.03
CA	14		19		13		
CO	29		30		39		
HI	5		6		4		
OH	18		8		19		
SC	15		11		15		
WA	19		26		19		

*Values are mean ± SD for all such values

**Total n varied with missing data according to characteristics; specific samples sizes are noted on the table.

Table 2.2 Breastfeeding and odds ratios for hypertension among youth with type 1 diabetes

	Odd Ratios (95% CI) for Hypertension			
	Adjusted odds ratio*	CLR**	Crude odds ratio	CLR
Ever vs Never Breastfed (n=1798)	1.37 (0.75, 2.51)	3.35	1.32 (0.84, 2.10)	2.50
Breastfed Category (n=1406)				
Not Breastfed (referent)	--		--	
< 6 months	1.72 (0.89, 3.34)	3.75	1.62 (0.96, 2.73)	2.85
≥ 6 months	1.18 (0.59, 2.33)	3.95	1.08 (0.64, 1.82)	2.83
Duration of breastfeeding (months; n= 1198)	0.99 (0.96, 1.03)	1.07	0.99 (0.95, 1.02)	1.07

*Includes gender, clinical site, race/ethnicity, parent education, diabetes onset age, diabetes duration, HLA risk group
** Confidence Limit Ratio (CLR) = upper limit/lower limit; values closer to ~1 represent more precise estimates

DISCUSSION

Breastfeeding has previously been suggested to play a role in nutritional programming for protection against later HTN via several potential mechanisms: lower sodium content, LCPUFA content, a small protective effect against obesity or by acting as a proxy measure of other maternal health modeling behaviors. In this ethnically diverse sample of youth with T1DM in the United States, no association between breastfeeding exposure (ever breastfed or duration of breastfeeding) and odds of hypertension was observed in either the unadjusted model or after adjustment for basic demographic and clinical characteristics.

One of the goals in examining models using the breastfeeding exposure in three different forms (ever/never, duration categories, continuous duration) was to better understand how the various coding techniques may impact the precision of the estimates provided. Although no association was found, differences in the precision of the crude and adjusted estimates were provided by calculating simple confidence limit ratios. This may reflect that caution should be used when choosing to categorize your data, given a discrete form is available. By nature, categories force loss of information from data. Although they can be quite helpful to improve the interpretability of results, as with BMI, it may be equally useful to observe the underlying and perhaps "true" nature of what the data have to offer.

Our findings tend to differ with the existing literature, where evidence of a modest association between breastfeeding and lower blood pressure (systolic and diastolic) later in life has

been found. Specifically, meta-analyses[12,72] indicate lower SBP (mean difference: -1.21 mmHg; 95%CI: -1.72, -0.70) and lower DBP (mean difference: -0.49 mmHg; 95%CI: -0.87, -0.11) among breastfed infants compared to bottle-fed infants.[12] Given the relatively small effect reported from meta-analyses, it is possible that breastfeeding may not confer enough protection or that its effects may not last as the child ages, given other socio-cultural and environmental factors which, through their effect on establishing diet and exercise habits, may play a larger role in the development of hypertension as the child gets older. Also, by transforming a continuous variable such as SBP or DBP into a dichotomous outcome variable, power to predict the outcome may be reduced, as cut points are often arbitrary, contributing to some of the information that is always lost with categorization of a continuous variable, which forces all the data within the chosen cut points to become more homogenous.

Construction of the breastfeeding exposure variable is largely based on study aim, type of infant feeding data collected, and sample size. Here, an "ever versus never" exposure variable was used to capture exposure to any breastfeeding during the first year of life. Since the "ever" breastfed variable reflects many different levels of breastfeeding exposure, this may not adequately capture the relevant amount of exposure needed to confer protection, therefore, we looked duration of breastfeeding as well, but were limited to only two categories (<6months or ≥6months) due to sample size. Perhaps a defined period of time being exposed as an infant to lower sodium or high LCPUFAs, or perhaps there is an interaction with both, to set the imprinting of physiological or anatomical changes in place. The timing of the window of plasticity, if it exists, is not well-understood and unlikely to be the same in every individual due to biological variation.

Limitations to this study include its observational, cross-sectional nature, which does not allow for any direct causal inference. Power to detect the outcome was limited, as only 6% of the sample had the hypertension outcome. However, despite these limitations, shorter duration of breastfeeding (<6months), race/ethnicity, clinical site, and duration of diabetes produced substantially different ORs from the crude and trended toward becoming predictors of the outcome. As previously

noted, duration of breastfeeding was limited to only two categories due to sample size, which may have reduced power to detect any dose-response or threshold effect. Because of the timing of administration of the questionnaire (it may have been many years since the subject was an infant) and with the recent resurgence in the popularity of breastfeeding, recall bias (systematic over-reporting due to recent popularity or random inaccurate reporting due to reliance on memory of prior behavior) may have occurred. This may affect not only how much true breastfeeding occurred, but may also reduce the accuracy of duration reported. In either case, our ability to observe the true effect of breastfeeding may have been limited. If all data had been collected by trained interviewers, careful probing may have reduced some of this potential measurement error in the data.

Because early nutrition is a potentially modifiable behavior to improve public health, nutrition in the first year of life continues to be important to advance our understanding of how nutritional programming may occur in humans. Recent evidence for programming of infant blood pressure by six months through randomized controlled intervention on maternal diet has been reported.[92] Evidence of metabolic programming also exists through animal models,[93] however replicating such studies in humans would be unethical, so we are usually limited to observational studies in order to understand the relationships that may exist between early life nutrition and later chronic disease. Future work using larger samples of data collected from ethnically diverse subjects prospectively followed from birth into adulthood with highly detailed infant feeding data may provide better insight. Even a small, protective effect of breastfeeding under the nutritional programming hypothesis may enhance our understanding of how elevated blood pressure, diabetes, obesity, and other metabolic disturbances develop, and provide meaningful targets for intervention, particularly as these morbidities are increasingly observed among younger, high-risk populations such as T1D youth.

CLOSING DISCUSSION / SUMMARY

Obesity continues to be a worldwide epidemic, even among children. Industrialized countries may be seeing a plateau in overall rates, but the developing world is seeing dramatic increases, adding to the already tremendous burden of obesity's prevalence. While research strives to identify behavioral factors that may be strategically targeted for impactful interventions, the complications arising from managing multiple chronic diseases will likely continue to increase the morbidities and mortality experienced from CVD, cancer, and diabetes, which are leading causes of death and are strongly associated with obesity.

Policy which addresses making the healthy choices the easy choices, in conjunction with efforts to improve accessibility to physical activity throughout the built environment, should be required and will go a long way toward improving the quality - and quantity - of years to be filled with rich life experiences for generations to come.

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