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The Association of Early Life Infant Feeding with Obesity Prevalence and Metabolic Changes among Offspring of Mothers with Gestational Diabetes Mellitus

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by

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Dedication

To my father, Dr. Bahman Vandyousefi, and

to the memory of my mother, Ms. Farideh Shams-Azaran.

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Abstract

The Association of Early Life Infant Feeding with Obesity Prevalence and Metabolic Changes Among Offspring of Mothers with Gestational Diabetes Mellitus

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Childhood obesity has become a serious health concern in the U.S., especially among Hispanic children.[1] Offspring born to mothers with gestational diabetes (GDM) are more likely to develop obesity, type 1 diabetes (T1D), type 2 diabetes (T2D), and other metabolic diseases later in life.[2,3] Many studies have shown that increased breastfeeding (BF) duration is linked to a lower prevalence of childhood overweight and obesity, diabetes, and the Metabolic Syndrome (MetS).[4-7] In addition, early exposure to sugar sweetened beverages (SSBs) is linked to increased obesity in youth[3]. However, few studies have examined how infant feeding impacts growth and obesity prevalence in offspring of mothers with GDM. Preliminary findings from the SWIFT cohort by Gunderson et al. showed that greater BF intensity and duration throughout the first 12 months of life was protective against ponderal

growth and weight gain among children of mothers with GDM.[8] To date, no study has examined how early life feeding in an exclusive GDM population impacts overweight and obesity, prediabetes, and MetS prevalence in children 1 to 19 years of age. Therefore, the overall goal of this analyses was to examine how early life feeding (i.e., BF duration and introduction to SSBs) impacts obesity, prediabetes, and MetS prevalence in offspring (1-19 years of age) of mothers with GDM.

The current research aims were from three different datasets all conducted in California: 1) Using a longitudinal study with over 300 Hispanic children (8-19 y) with overweight or obesity, where early life feeding was collected retrospectively, the effects of BF duration on MetS and prediabetes in offspring from mothers with and without GDM was assessed. 2) Using the LAC WIC 2014 survey with over 4,000 mothers with children (1-5 y), where early life infant feeding was collected retrospectively, the effects of exclusive BF and early introduction to SSBs on obesity prevalence in children born to mothers with and without GDM was assessed. 3) Using an ongoing prospective cohort of 1,035 postpartum women diagnosed with GDM during pregnancy, where the association of BF duration and intensity and early introduction to SSBs and fruit juice during the first year of life with subsequent overweight and obesity in children (2-5 y) was assessed.

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List of Abbreviations

AAP	The American Academy of Pediatrics
ADA	American Diabetes Association
AGA	Appropriate for Gestational Age
AT	Adipose Tissue
AV	Annual Visit
BF	Breastfeeding
BMI	Body Mass Index
CDC	Centers for Disease Prevention and Control
EBF	Exclusive Breastfeeding
FPG	Fasting Plasma Glucose
GDM	Gestational Diabetes Mellitus
HbA1c	Glycated Hemoglobin A1C
HDL	High-Density Lipoprotein Cholesterol
HMOs	Human Milk Oligosaccharides
IADPSG	International Association of Diabetes and Pregnancy Groups
ICC	Intraclass Correlation Coefficient
IDF	International Diabetes Federation
IGT	Impaired Glucose Tolerance
IHCL	Intrahepatocellular Lipid
LAZ	Length-for-Age Z Score
LGA	Large for Gestational Age
PYY	Protein Peptide YY
MetS	Metabolic Syndrome
MIHA	Maternal and Infant Health Assessment
NHW	Non-Hispanic White
NAFLD	Non-Alcoholic Fatty Liver Disease
OGTT	Oral Glucose Tolerance Test
RCT	Randomized Controlled Trial
SGA	Small for Gestational Age
SOLAR	Study of Latino Adolescents at Risk for Diabetes
SSB	Sugar Sweetened Beverages
SWIFT	Study of Women, Infant Feeding and Type 2 Diabetes after GDM
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
U.S.	United States
WAZ	Weight-for-Age Z-Scores
WHO	World Health Organization
WIC	Women, Infants, and Children
WLZ	Weight-for-Length Z-Scores

Chapter 1: Introduction and Review of Literature

HISPANICS -A HIGH-RISK POPULATION

As of 2017, there were 58.9 million people of Hispanic origin or 18.1% of the total population living in the United States (U.S.), making up the largest ethnic minority group.[9] Hispanics are one of the fastest growing ethnic minorities in the U.S. and they are estimated to make up 28% of the nation by 2060.[9] California has the nation's largest Hispanic population (15 million) among states and Hispanics comprise 39% of the state population with about 98% being of Mexican origin.[10] According to the World Health Organization (WHO), in 2014, over 41 million children under the age of five were either obese or overweight worldwide.[11] In the U.S., Hispanics are disproportionately affected by obesity, with around 40% of Hispanic youths (2-19 years of age), being overweight or obese (Body Mass Index (BMI) for Age ≥85th Percentile of the CDC Growth Charts), compared to 28.5% non-Hispanic white (NHW) youths. Approximately 9.4% of Hispanic infants (birth to 2 years of age) were obese with a BMI z score of $\geq 95^{th}$ percentile of CDC growth chart, compared to 6.6% NHW babies in 2012.[12] Moreover, Hispanic young children (2-5 years of age) had a higher rate (30%) of overweight or obesity, compared to NHWs.[13]

Hispanic youth have increased risk of obesity related metabolic disease, such as Type 2 Diabetes (T2D) and cardiovascular disease.[14-17] Goran et al. previously showed that over 30% of Hispanic children (8-19 years of age) have prediabetes and the metabolic syndrome (MetS).[16,18] Compared to NHWs, Hispanics have elevated levels of visceral adiposity, are insulin resistant, and exhibit early signs of β-cell dysfunction, all of which are linked to increased risk of T2D and cardiovascular disease.[19-21] The prevalence of T2D is 1.9 times higher in Hispanics compared to NHWs.[22] Hispanic pregnant women are affected by gestational diabetes mellitus (GDM) more than NHW mothers. The prevalence estimate of GDM in Asian/Pacific Islanders (16.3%) and Hispanics (12.1%) was higher than NHW pregnant women (6.8%) in 2010.[23] In addition, the likelihood of mortality from T2D in Hispanics is 50% more than NHWs.[24] While Hispanic women have the highest rates of BF initiation[25], they are more likely (33%) to provide formula supplementation as early as two days postpartum compared to other racial/ethnic groups in the U.S.[26] Compared with NHW mothers, Hispanic and African American mothers have lower rates of exclusive BF (EBF) and are more likely to introduce solid foods and sugar sweetened beverages (SSBs) before four months of age.[27]

GESTATIONAL DIABETES MELLITUS

GDM is one of the most common complications of pregnancy in women worldwide. American Diabetes Association (ADA) defines GDM as "any degree of glucose intolerance with onset or first recognition during pregnancy".[28] The International Association of Diabetes and Pregnancy Groups (IADPSG) recommends diagnosis of GDM based on having at least one abnormal value including fasting plasma glucose (FPG) $\geq$92 mg/dl, one-hour plasma glucose concentration $\geq$180 mg/dl, and two-hour plasma glucose concentration $\geq$153 mg/dl after a 75-gram oral glucose tolerance test (OGTT) in pregnant women.[29,30] Twenty five percent of pregnancies in Asia and 5% of U.K. pregnancies are affected by GDM.[31] While the true prevalence of GDM is unknown, depending on the population, approximately 1-14% of pregnant women are diagnosed with GDM annually in the U.S.[23,32,33] According to the Centers for Disease Prevention and Control (CDC), the average GDM prevalence rate among fifteen U.S. states was 9.2% in 2010.[23] Moreover, women of ethnic/racial minority groups in the U.S., especially Hispanic and Asian American subgroups, have consistently higher prevalence and risk of GDM, compared to NHW women.[32,34-41]

COMPLICATIONS OF GDM IN MOTHERS

GDM has been related to several short- and long-term complications for women diagnosed with GDM during pregnancy and their offspring.[42] Some of the main risk factors of GDM include early menarche[43,44], low pre-pregnancy levels of sex hormone-binding globulin (SHBG)[45], obesity and higher than normal BMI, T2D, history of macrosomia (birth weight >4 kg), weight gain between pregnancies, caesarian section, and multi-parity.[46-50] Untreated GDM throughout pregnancy is associated with higher rates of maternal morbidity.[51-54] Even mild hyperglycemia during pregnancy can adversely influence maternal health and is associated with a significantly higher risk of metabolic and hypertensive disorders later in life.[55] Research shows that women with GDM during pregnancy are more likely to have higher calorie intake, gain weight[44,56], and develop Non-Alcoholic Fatty Liver Disease (NAFLD)[57] following pregnancy compared to women without GDM. Though blood glucose level returns to normal in most women with GDM after delivery, they are still seven times more likely to develop T2D over their lifetime compared to women without GDM. [47,48,50,58-60] Many studies suggest that women with GDM, especially those who were obese prior to pregnancy, are at considerably higher risk of cardiovascular disease, compared to non-GDM women.[42,61-64] Oza-Frank and Gunderson reported that women diagnosed with GDM during pregnancy were less likely to breastfeed in the first hour postpartum and in the hospital[65], and more likely to have delayed onset of lactation >3 days postpartum.[66,67]

COMPLICATIONS OF GDM IN OFFSPRING

Children born to mothers with GDM are at high risk of perinatal morbidity and mortality and long-term complications.[51,68-70] A cohort of 796,346 French women, 57,629 of whom were mothers with GDM, found a 30% increase in the odds ratio (OR) for perinatal death in the GDM group compared to the non-GDM group.[71] Bone fracture, shoulder dystocia, born large for gestational age (LGA), and macrosomia are some of the severe perinatal consequences of *in utero* exposure to GDM.[3,31,70,72,73] Offspring born to mothers with GDM are also at increased lifelong risks for metabolic and cardiovascular diseases[74] and are more likely to develop impaired glucose tolerance and T2D, increased adiposity and obesity, and GDM (in female offspring) later in life.[51,68-70] A recent study of 970 mother-child dyads in China showed that offspring of mothers diagnosed with GDM had higher rates of abnormal glucose tolerance, overweight or obesity, and lower β-cell function compared to offspring of mothers without GDM, independent of pre-pregnancy weight, childhood obesity, or being born LGA.[75] Two studies on Chinese mothers and their offspring found that maternal GDM increased the cardiometabolic risk in early childhood

(7-10 years of age), but not at 15 years of age.[76,77] Similarly, a prospective, population-based birth cohort on 5,038 subjects in the U.K. found no clear association between maternal GDM and offspring cardiometabolic risk at a mean age of 15.5 years.[78]

There has been inconsistency in reports on the influence of GDM on childhood metabolic disease risk, particularly T2D, in different racial and ethnic groups, with some studies showing an association between intrauterine exposure to hyperglycemia in GDM offspring with impaired insulin sensitivity and secretion in adulthood[68,79,80] while others found no effect. Numerous studies have reported that offspring exposed to intrauterine GDM were at significant risk of developing MetS in childhood. A U.S. based study of 94 children of GDM mothers and 85 children of mothers without GDM (control) who were either large for gestational age (LGA; n= 84) or appropriate for gestational age (AGA; n= 95) and were evaluated at six, seven, nine, and 11 years, reported that LGA offspring born to mothers with GDM had about five times higher risk of MetS (≥3 components) at age 11 than non-GDM groups.[81]

It is well established that GDM throughout pregnancy is a contributing factor to childhood obesity.[82-86] A recent multinational cross-sectional study of 4,740 children reported a significant association between maternal GDM and increased odds of obesity and central obesity in children (9–11 years of age) in twelve countries including U.S.; however, these associations were not completely independent of maternal weight.[72] A study of 33,893 mothers and their offspring (birth-7 years of age) in the U.S. found that the odds of childhood obesity were 1.45-fold higher for children born to mothers with GDM versus without GDM.[87] Similarly, a retrospective study of 7,355 children (mean age of 5.8 years) born to mothers with GDM in Germany, found that the odds of childhood overweight (OR 1.81) and obesity (OR 2.80) were higher for offspring of mothers with GDM, compared to the non-GDM group.[88] The Northwestern University Diabetes in Pregnancy Study reported a dramatic increase in weight of children born to mothers with GDM after five years of age, and weight for age BMI >90th percentile by age eight in over 50% of the offspring of GDM mothers.[89] A prospective cohort study of 280,866 Swedish children born to mothers with GDM examined the impact of GDM on BMI in early adulthood and found that GDM was associated with greater mean BMI (average of 0.9 kg/m^2) in male offspring at age 18, compared to their brothers born prior to their mothers' GDM diagnoses.[90] Likewise, early findings of the longitudinal Pima Indian Study showed that the offspring of Pima Indian women with GDM had 40% higher rates of obesity at age 5–29 years than the offspring of women without GDM.[91]

The mechanisms by which the risk of obesity in offspring increases by intrauterine exposure to diabetes are not fully understood. Exposure to maternal diabetes is associated with excess fetal growth *in utero*, possibly due to fetal hormonal alterations and perturbations in fetal fat accretion. In a prospective longitudinal study, Logan et al. used MRI and spectroscopy to determine adipose tissue quantity and distribution and intrahepatocellular lipid (IHCL) content of 86 infants over the first 12 postnatal weeks and found that GDM offspring who were exclusively breastfed had significantly greater total adipose tissue volume and IHCL at 10 weeks than infants of non-GDM women.[92] Dabelea et al. found that exposure to maternal GDM *in utero* results in elevated leptin synthesis, hyperglycemia, and hyperinsulinemia in offspring. Moreover, maternal prenatal GDM may also influence and alter the expression of genes that direct the accumulation of body fat or related metabolism in a fetus.[93]

While there are numerous studies showing the impact of GDM on overweight or obesity prevalence in the offspring later in life, there are a few that failed to find a clear association between maternal GDM and obesity in offspring.[77,78,82,83,94] For example, Pettitt et al. found no significant relationship between maternal diabetes during pregnancy and BMI z-scores of children (two years of age) in the U.K.; however, this study included subjects with T2D and Type 1 Diabetes (T1D) and timing of maternal diabetes (before birth or after birth) and maternal age of diabetes diagnosis were adjusted as covariates.[94-96] The majority of the previous studies were conducted on non- Hispanic children <12 months or >5 years of age; therefore, the current study evaluated MetS, prediabetes, and childhood obesity prevalence in GDM offspring with a wide age range of children (1-19 years of age).

BREASTFEEDING

Breast milk has been regarded as the best food for infants to meet their daily nutrients and energy requirements.[97] The World Health Organization (WHO) defines BF in three different classifications including EBF (feeding infants exclusively with breast milk and no other liquids or solids), predominant (full) BF (receiving almost all the nutrients from breast milk but consumes some other liquids), and any BF (feeding with some breast milk during a day).[98] American Academy of Pediatrics and WHO both recommend initiation and continuation of EBF within one hour and for the first six months after birth, respectively.[98-100]

BF saves the lives of more than 800,000 children under the age of five years annually; however, most infants and children do not receive optimal feeding. For instance, only about 43% of infants (0-6 months of age) are exclusively breastfed worldwide[98]. According to the current CDC state wide BF report card[101], approximately 52% and 25% of infants in the U.S. were exclusively breastfed at 3- and 6-months of age in 2014-2015, respectively. Data from CDC describes that about 30% of mothers in southern U.S. states and 19% of mothers in western U.S. states completely stopped BF and/or pumping breast milk before one month postpartum.[102] The state of California had the highest rate (93%) of women who ever breastfed their infants in 2014. California had also longer rates of BF duration, with 56% and 25% of mothers exclusively breastfeeding for 3- and 6-months postpartum, respectively. However, according to the most recent reports from the Maternal and Infant Health Assessment (MIHA) survey in California, Hispanic and Asian/pacific islander minority groups had the lowest rates of EBF at 3- and 6-months after delivery, compared to Black and NHW groups in 2013-2014.[103] In the current study, we will examine how early life infant feeding (BF duration, introduction to SSBs/solids) affects childhood overweight and obesity prevalence in California.

Similarly, several researchers have shown that women with GDM are less likely to exclusively breastfeed in the first hour postpartum and more likely to formula feed their children in the hospital than women without GDM.[65-67,104-106] In the SWIFT cohort of women with GDM, insulin treatment during pregnancy was associated with delayed onset of lactogenesis.[67] Likewise, findings of the PRAM study that involved 72,755 women from 30 U.S. states and New York City showed that GDM women had lower BF initiation and continuation compared with non-GDM women.[106] In a cohort of 883 women diagnosed with GDM during pregnancy, Gunderson et al. found that women with GDM had shorter and less EBF (i.e., less lactation intensity) at 6-weeks post-delivery.[107] In addition, Nommsen-Rivers et al. found GDM to increase the likelihood of low milk supply (i.e., maternal nipple problems or difficulties with latching).[105] This study will assess how BF duration impacts childhood growth and obesity prevalence in offspring born to mothers with GDM.

BREASTFEEDING HEALTH BENEFITS FOR LACTATING MOTHERS

BF provides many health benefits for lactating mothers. Research shows that BF accelerates weight loss in lactating mothers and has protective effects against maternal obesity postpartum.[60,107-111] Widen et al. found that mothers who breastfed exclusively for longer duration gained less weight postpartum, compared to those who BF for shorter duration; however, they found no association between BF and body composition in lactating mothers.[112] In addition, several studies show that BF (any duration) significantly reduces rate of premenopausal breast cancer, ovarian cancer, obesity, T1D, T2D, and cardiovascular diseases and metabolic disease in mothers who breastfeed their infants, later in life.[2,113-117]

A prospective cohort study by Stuebe et al. found a strong association between longer total and exclusive BF duration and higher ghrelin and pancreatic Protein peptide YY (PYY) levels in lactating mothers at three years postpartum.[118] PYY is known for its role in metabolism and appetite regulation (i.e., appetite suppression) and its low levels is linked to obesity. Although high ghrelin stimulates hunger in the fasting state, PYY levels rise and ghrelin levels drop after feeding. In contrast, research shows that lower levels of ghrelin increase the risk for obesity, insulin resistance, hypertension, and T2D in the mother.[118-120] Finding of studies on health benefits of BF to both lactating GDM and non-GDM mothers are similar. Numerous studies by Gunderson et al. have consistently reported that higher lactation intensity is associated with decreased risk of T2D in the mother and improvements in maternal glucose tolerance, lipid profiles, and metabolic risk factor profiles during the postpartum period among women diagnosed with GDM throughout pregnancy.[49,60,107-109,121]

BREASTFEEDING AND OBESITY IN OFFSPRING

While BF has been shown to have numerous benefits to the lactating mothers, it has many long-term health benefits to the child. Children and young adults who were breastfed as babies are 20-50% less likely to become overweight or obese.[97,122-126] **Table 1** displays studies that have assessed the impact of BF on childhood obesity in offspring of both GDM and non-GDM mothers. Numerous studies have shown that lower BF duration and intensity increases the likelihood of overweight and obesity in children.[127-130] A cohort of 4,680 infants in the U.K. found that BF for longer than four months was independently associated with 6.8% lower growth velocity in children compared to those who were breastfed <4 months.[131] Likewise, a study of 915 mother-child dyads in the U.S. showed a significant association between exclusive BF for at least four months and smaller rate of increase in weight-for-length percentile of offspring at one year of age, compared to those who were BF <4 months or used formula, independent of maternal BMI.[132]

Similar studies reported that infants of mothers who did not receive breast milk grew faster from birth to six months of age than those whose mothers initiated BF, and those who breastfed ≥2 months[133] and ≥4 months.[131,134] Moreover, findings of the Western Australian Pregnancy Cohort Study indicated that cessation of exclusive BF <4 months was linked to significant increases in weight z-scores between birth and one year of age, early rapid growth at age three, and probability of exceeding the 95th percentile of weight from 1-8 years of age. Longer exclusive BF duration (>6 months) was also associated with significantly lower prevalence of overweight and obesity at 20 years of age.[135] Although there is increasing evidence that BF has a protective effect against obesity in offspring, the majority of these studies did not target exclusive GDM population and most just controlled for GDM status in their analyses.

The SWIFT cohort by Gunderson et al. showed that greater BF intensity and duration throughout the first 12 months of life is protective against ponderal growth and weight gain among children of mothers with GDM.[136] Another study of 382 mothers and their offspring (2-5 years of age) from the SWIFT Offspring Study in the U.S. by The SWIFT Offspring Investigators showed that higher BF intensity and duration was associated with lower odds of obesity in offspring exposed to GDM *in utero*.[137] A retrospective study of 2,295 children (2-4 years of age) of Hispanic mothers with GDM during pregnancy showed that offspring who were breastfed ≥12 months had a 72% decrease in obesity prevalence.[124] In a study of 324 GDM mothers and their children (2-8 years of age) in Germany, found that BF exclusively for at least three months reduced overweight prevalence by 40-50% in early childhood, after controlling for parental obesity and high birth weight.[85]

In contrast, a prospective cohort of 1,152 Asian women with GDM (n=181) in Singapore reported that offspring of mothers without GDM who were breastfed ≥4 months had slower growth rate from birth to 36 months of age than those who were not breastfed or BF <4 months; however, they did not find similar results in offspring of mothers with GDM. In the GDM offspring, greater breast milk intake was associated with accelerated weight gain and BMI in the first six months of age. Of note, this study did not examine factors such as adverse newborn health outcomes and early prematurity that may confound infant feeding and early growth velocity. Additionally, this study did not differentiate exclusive and predominant (full) BF groups, which might explain their conflicting findings.[138] Similarly, a study of 112 infants (birth-2 years of age) born to mothers with GDM showed a significant association between exclusive BF (any duration) and increased childhood relative body weight and blood glucose at two years of age; however, after adjustment for the volume of breast milk consumed during the first week of life, all these associations were eliminated.[139] Pettitt et al. found no significant association between maternal diabetes during pregnancy and BMI z-score of children at two years of age;

however, type of diabetes was adjusted as a covariate in their analysis and their findings were not exclusively on GDM.[94-96] The above conflicting studies highlight the need to further investigate the role that BF plays in obesity levels in GDM offspring. Thus, the current study will evaluate how BF impacts obesity prevalence and changes in adiposity in children born to mothers with GDM.

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
Aris et al.[138]	2016	retrospective	0-3 yrs.	1,152	Asian	Singapore	GDM vs. Non-GDM	Exclusive/predominant: – No BF –<4 mos. –≥4 mos.	–age –sex –ethnicity –parity –maternal age –maternal education –maternal BMI at 26-28 weeks-gestation –gestational age at delivery	– On chemotherapy, psychotropic drugs –With diabetes mellitus	BF≥4 months ~ accelerated • weight gain • growth velocity ➢ Opposite result for non-GDM
Bider-Canfield et al.[82]	2017	retrospective	2 yrs.	15,710	Multi	U.S.	GDM vs. Non-GDM	–Never BF –≥6 mos.	– sex –maternal age –parity –education –race/ethnicity –comorbidity –pre-pregnancy BMI –EGWG and GDM	Children of mothers with: –known type 1 diabetes –preexisting type 2 diabetes –polycystic ovarian syndrome	BF≥6 months ~ decreased • risk of childhood overweight at age 2 years
Crume et al.[140]	2012	retrospective	0-13 yrs.	493	Multi	U.S.	GDM vs. Non-GDM	–<6 mos. –≥6 mos.	–age –sex –race/ethnicity –current diet –physical activity levels	Unknown	BF≥6 breastmilk months ~ reduced • weight gain • overall body size • BMI growth velocity ➢ Similar result for GDM & non-GDM
Crume et al.[141]	2011	retrospective	6-13 yrs.	468	Multi	U.S.	GDM vs. Non-GDM	–<6 mos. –≥6 mos.	–age –sex –race/ethnicity –Tanner stage –age × Tanner interaction	Unknown	BF≥6 breastmilk months ~ lower • BMI • waist circumference • SAT level • VAT level ➢ Similar result for GDM & non-GDM

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
Davis et al.[142]	2007	retrospective	8-13 yrs.	240	Hispanic	U.S.	GDM vs. Non-GDM	–0-5.99 mos. –6-11.99 mos. –≥12 mos.	–age –sex –body composition –GDM –AIR (with dependent variable SI only)	–taking medications known to affect body composition –had syndromes or diseases known to affect body composition or fat distribution –had had any major illness at any time	– BF (any duration) no significant protective effects on: • Adiposity (total fat mass, total lean tissue mass, percent body fat, VAT, SAT) • T2D risk (fasting glucose, 2-h glucose, insulin dynamics (SI, AIR, and DI)) ➢ No GDM effect m,./23
Faith et al.[137]	2019	prospective	2-5 yr.	382	Multi	U.S.	GDM vs. Non-GDM	–<3 mos. –≥3 mos. –12 mos. combined	–race/ethnicity –gestational age at birth –maternal age –parity –education –pre-pregnancy BMI –total gestational weight gain (kg) –GDM treatment –gestational age at GDM diagnosis –weight-for-length z score infant diet	–had serious medical conditions (e.g., failure to thrive, physical impairment affecting feeding ability, chronic infectious disease, severe jaundice, or metabolic disorders)	– Lower intensity and shorter duration of BF ~ • Elevated infant soothability and activity temperament • Higher odds of later childhood obesity

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
Feig et al.[143]	2010	retrospective	1-15 yrs.	125	multi	Canada	Pre-GDM T2D (n=44) + T1D (n=81)	–BF at all –months exclusive BF –months total BF	–age –race/ethnicity –diabetes duration & type –parity –BF frequency –BF duration –maternal & child weight and height	–had no documented evidence of type 1 or type 2 diabetes before pregnancy	– BF >3.5 mos.~ decreased • the likelihood of obesity
Gunderson et al.[136]	2018	prospective	2-5 yr.	464	Multi	U.S.	GDM vs. Non-GDM	– Intensive BF or FF groups at 6–9 wks. (baseline) –Consistent exclusive/mostly FF –Transition from BF to FF within 3–9 mos. –Consistent exclusive/mostly BF	–race/ethnicity –gestational age at birth –maternal age –parity –education –pre-pregnancy BMI –total gestational weight gain (kg) –GDM treatment type –gestational age at GDM diagnosis	–had serious medical conditions (e.g., failure to thrive, physical impairment affecting feeding ability, chronic infectious disease, severe jaundice, or metabolic disorders)	– Higher intensity and longer duration of BF ~ • slower increases in ponderal growth • more favorable growth patterns • lower weight gain lower overall body adiposity
Kaul et al.[144]	2019	longitudinal	4-6 yrs.	81,226	Canadian	Canada	GDM vs. no diabetes vs. pre-existing diabetes	–Any BF<5 mos.	–maternal age –maternal ethnicity –urban residence –parity –pre-existing medical conditions –hypertensive disorders of pregnancy –delivery mode –household income	–SGA at birth –Women with medical conditions prior to pregnancy	Higher duration of BF~ • lower risk of being overweight/obese at 4-6 years of age. –No association between BF, and obesity in offspring born to mothers with diabetes
Plagemann et al.[145]	2002	prospective	2 yrs.	112	German	Germany	GDM (n=83) + T1D (n=29)	–Diabetic breast milk (DBM) vs.	–age –sex –birth weight –gestational age	–Women with diabetes –DBM volume 0.14 0.16	Higher volume of DBM ingested ~ higher • relative body weight

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
								–Nondiabetic banked donor breast milk (BBM) during the early neonatal	–type of maternal diabetes –maternal BMI	–BBM volume	• risk of overweight at 2 yrs. of age Higher volume of BBM ingested ~lower • body weight at follow-up • risk of childhood IGT
Rodekamp et al.[146]	2005	prospective	0-2 yrs.	112	German	Germany	GDM (n=83) + T1D (n=29)	BF = Diabetic breast milk (DBM) –Not BF –Solely BF –Partly BF	model I –age –sex –birth weight –gestational age –type of maternal diabetes –maternal BMI –maternal age model II –maternal blood glucose model III – DBM volume ingested model IV –BF duration	–Unknown	Exclusive BF ~ increased • risk of overweight • 120-min blood glucose model II: no relationship between GDM and the outcome ➢ Neither late neonatal DBM intake nor the duration of BF had an independent influence on childhood risk of overweight or IGT model III: no association
Shearer et al.[124]	2014	retrospective	2-4 yrs.	2,295	Hispanic	U.S.	GDM vs. Non-GDM	–No BF –≥1 to <6 mos. –6 to <12 mos. –≥12 mos.	–race/ethnicity –sex –birth weight –child's age in months –maternal BMI	–women with type 1 and type 2 diabetes –women unaware of their diabetes	– BF >12 months in the GDM group – any duration of BF in the non-GDM mothers ~ • reduce obesity levels

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
Schaefer -Graf et al.[85]	2006	retrospective	2-8 yrs.	324	German	Germany	GDM vs. Non-GDM	–Never BF –1-3 mos. –>3 mos.	–parental obesity –high birth	–Unknown	– BF >3 months ~ 40-50% childhood overweight – Never BF~ higher childhood overweight
Bell et al.[147]	2018	prospective	2-3 yrs.	953	Australian	Australia	n/a	–< 17 wks. –17 -25 wks. – 26-51 wks. – ≥52 wks.	–maternal age –level of education –country of birth –parity –pre-pregnancy BMI –delivery method –infant sex and birth weight	–intending to relocate within the next 12 months	• BF≥12 mos.~ • lower risk of being overweight/obese than those BF< 17 wks.
Davis et al.[126]	2012	retrospective	2-4 yrs.	1,438	Hispanic	U.S.	n/a	–No BF –1 wk. to <6 mos. –6 to <12 mos. –≥12 mos.	– mother's BMI – child's sex and age – type of milk most often consumed	– Unknown	– >12 months of BF duration ~ reduce obesity levels
Davis et al.[125]	2014	cross-sectional	2-4 yrs.	2,295	Hispanic	U.S.	n/a	–No BF –1 wk. to <6 mos. –6 to <12 mos. –≥12 mos.	– sex – race/ethnicity – age – mother's BMI – GDM status – birth weight	– ≤24 mos. – prematurity – LBW	– >12 months of BF duration ~ prevent obesity
Forbes et al.[148]	2018	prospective	0-12 mos.	1,087	Canadian	Canada	n/a	–EBF –Partial BF –No BF –FF –<3 mos. –≥3 mos. –<6 mos.	– race/ethnicity – infant sex – birth weight – maternal pre-pregnancy BMI – delivery mode – Parity	– Unknown	– Longer BF duration (partial and exclusive) ~ lower likelihood of obesity – FF

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
								–≥6 mos.	– GDM – smoking status – education		~Higher risk of overweight at 12 months
Gunnarsdottir et al.[133]	2009	prospective	0-1 yr.	154	Danish	Denmark Iceland	n/a	–0–2 mos. –3–4 mos. –≥5 mos.	– birth weight – country – duration of EBF	– preterm – neonatal diseases – malformation	– EBF ≤2 mos. ~ Weight gain (only 6-12 mos.)
Jwa et al.[149]	2014	prospective	1.5-8 yrs.	41,572	Asian	Japan	n/a	–1-2 mos. –3-5 mos. –≥6 mos.	– birth weight – sibling – maternal age – education – smoking status – education – income	– multiple birth – preterm deliveries – unknown gestational age – BF missing data	– BF (any duration) has a latent protective effect against childhood overweight and obesity
Johnson et al. [131]	2014	longitudinal	4-12 mos.	4680	British	U.K.	n/a	–No BF –birth - 1 wk. –1 wk. - 1 mo. –>1–2 mos. –>2–3 mos. –>3–4 mos. –<4 mos. –≥4 mos.	– age – sex – gestational age – maternal BMI – parity – age at weaning – smoking – socioeconomic status	– Unknown	– Longer BF (>4 months vs never) ~lower growth velocity – Later weaning (≥6 mos. vs <4 mos.) ~ lower – Growth velocity – Smaller size
Martin et al.[150]	2013	longitudinal	6-12 yrs.	13,879	Belarusian	Belarus	n/a	–<3 mos. –3-6 mos. –≥6 mos.	– n/a	– No BF intention – illnesses that contraindicate BF – preterm – LBW – Apgar score <5	– BF duration not ~obesity and IGF-1
Metzger et al.[151]	2010	longitudinal	0-19 yrs.	976	Multi	U.S.	n/a	–BF vs not-BF	– child's own lifestyle-related behaviors – parental BMI	– Unknown	– Longer BF ~ lower likelihood of obesity

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
McCrory & Layte[152]	2012	cross-sectional	9 yrs.	7,798	Irish	Ireland	n/a	– Never BF – ≤4 wks. – 5-8 wks. – 9-12 wks. – 13-25 wks. – ≥26 wks.	– socio-demographic factors – child's own lifestyle-related behaviors – parental BMI	– Unknown	– Longer BF ~ lower • likelihood of obesity
Novaes et al.[153]	2011	cross-sectional	6-10 yrs.	764	Brazilian	Brazil	n/a	BF: – 0 – <3 mos. – 3-5 mos. – 6-11 mos. – ≥12 mos. EBF: – 0 – <1 mo. – 1-3 mos. – 4-6 mos.	– sex – age – birth weight – gestational age – order of birth – siblings – type of school – physical activity – television time – diet – education – pregnancy weight gain – smoking	– with persistently high levels of systolic/diastolic BP – suspected for secondary hypertension	– Duration of BF was not ~ lower • risk of obesity • BMI
Ortega-Garcia[154]	2018	prospective	6 yrs.	315	Spanish	Spain	n/a	– EBF – Any BF – FF	– sex – birth weight – weight gain in first year of life – maternal age – pregestational maternal BMI – alcohol intake – smoking – nationality – education – family income – employment	– newborns admitted to the neonatal unit during the first 48 hours – a linguistic barrier	– Delayed FF~ lower • risk of obesity
Rzehak et al.[155]	2009	longitudinal	0-6 yrs.	7,643	German	Germany	n/a	– ≥4 mos. – Formula feeding – Mixed feeding	– study-center – socio-economic-status – maternal smoking	– LBW	– Infants fully-breastfed≥4mos. • gain less weight

Table 1. Breastfeeding and Obesity in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM Category	BF Categories	Adjusted Covariates	Exclusion Criteria	Outcomes for Offspring
Scott et al.[156]	2012	cross-sectional	9-16 yrs.	2,066	Australian	Australia	n/a	– 0 – <2 mos. – 2 to <4 mos. – 4 to <6 mos. – ≥6 mos.	– sex – age – birth weight – gestational age – education	– Unknown	– BF ≥6 mos. protective against later overweight and obesity
Sinigagli et al.[157]	2016	cross-sectional	0-2 yrs.	296	Puerto Rican	Puerto Rico	n/a	–BF in hospital –≤3 mos. –≤6 mos.	–age –sex –race/ethnicity –education	– <6 months of age – with any serious health condition that could alter normal feeding practices	BF practices was not ~ with • weight status – BF (any) ~ later introduction to SSBs
Tambalis et al.	2018	cross-sectional	8 yrs. and 15-25 yrs.	5,125	Greek	Greece	n/a	–EBF<1 mo. Vs. –1≤EBF≤5 mos. –EBF≥6 MOS.	– pre-pregnancy weight status – parity – education – nationality – gestational weight gain	– Unknown	– EBF ≥6 mos. ~ lower • Risk of overweight
Twells et al.[158]	2010	cross-sectional	4 yrs.	1,026	Canadian	Canada	n/a	– FF ≥3 mos. – mixed feeding ≥3 mos. – EBF ≥3 mos.	– sex – age – education – maternal smoking – pre/full term	– Unknown	– EBF to 3 months was protective of preschool obesity
Van Rossem et al.[159]	2010	prospective	3 yrs.	884	Multi	U.S.	n/a	– Never – any BF <6 mos. – partial BF ≥6 mos. – EBF ≥6 mos.	– sex – age – birth weight – race/ethnicity – education – smoking – maternal BMI – pregnancy weight gain	– gestational age at birth was <34 weeks	– EBF ≥6 mos. ~ lower • BMI z score • skinfold thicknesses • odds of obesity at age 3 years – Infant weight changes 0-6 mos. mediate associations of BF with BMI

BREASTFEEDING AND METABOLIC DISEASE IN OFFSPRING

The inverse association between BF and incident of T2D and metabolic disease has been found in numerous cohorts of lactating women and their offspring. **Table 2** highlights studies that have assessed the impact of BF on metabolic disease risk. BF (any duration) has been linked to lower risk of T1D, T2D, cardiovascular disease, and metabolic disease in both mothers and children later in life.[2,113-116] A recent systematic review by Binns et al. found that BF protects against the development of T1D in young adolescents and T2D in adults.[110] A study in the offspring of Pima Indian mothers found an association between exclusive BF and decreased risk for T2D in children and adolescents (10-39 years of age), after adjusting for maternal GDM.[160] Numerous literature reviews by Gunderson et al. reveal that research on the association between BF and lower risk of T2D is very limited in the offspring of mothers with GDM.[8,161-164]

To date, the only prospective study that assessed protective effects of BF on T2D in the GDM offspring used data from the cohort of Pima Indians and found that offspring of mothers with GDM (n=21) who were exclusively BF had lower prevalence of T2D, compared to those who were not breastfed or were bottle fed throughout their infancy; though, their results were not statistically significant.[160] While many of the studies mentioned in **Table 2** controlled for GDM or type of maternal diabetes during pregnancy, few examined the interaction of BF and GDM on glucose/insulin action in children. Therefore, the current study will examine the effect of BF on metabolic parameters in offspring with and without exposure to GDM population

Table 2. Breastfeeding and Metabolic Disease in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM	BF Categories	Adjusted covariates	Exclusion Criteria	Outcomes for GDM offspring
Davis et al.[142]	2007	Retrospective	8-13 yrs.	240	Hispanic	U.S.	GDM vs. Non-GDM	–0-5.99 mos. –6-11.99 mos. –≥12 mos.	– age – sex – body composition – GDM – AIR (with dependent variable SI only)	– with diabetes – taking medications known to affect body composition – had syndromes or diseases known to affect body composition or fat distribution – had any major illness at any time.	– BF (any duration) no significant protective effects on: • T2D risk (fasting glucose, 2-h glucose, insulin dynamics (SI, AIR, and DI)) • No GDM effect
Labayen et al.[115]	2012	Cross-sectional	9-10 yrs. 15-16 yrs.	704	European	Sweden; Estonia	n/a	– No BF – >1 mo. – 1 to <3 mos. – 3 to <6 mos. – ≥6 mos.	– country – sex – age – pubertal status – BMI/ fat mass/fat-free mass	– taking medications that might influence the results	– Exclusive BF≥6 months ~ with • less low- grade inflammation • lower CVD risk
Labayen et al.[116]	2012	Cross-sectional	9-10 yrs. 15-16 yrs.	1,996	European	Sweden; Estonia	– n/a	– <3 mos. – 3–6 mos. – >6 mos.	– country – sex – age – pubertal status – BMI/ fat mass/fat-free mass	– taking medications that might influence the results – had contraindications to any of the study procedures, including the maximal cycle-ergometer test	– Exclusive BF≥3 months~ • higher cardiorespirator y fitness • lower CVD risk later in life
Mayer-Davis[114]	2008	Case-control	10-21 yrs.	167	Multi	U.S.	Any DM	– Ever BF vs. – Never BF	– sex – age – race – family DM history – maternal attributes – child BMI z-score	– multiple births – gestational age<38 weeks – missing perinatal information	– BF is protective against • development of T2D in youth,

Table 2. Breastfeeding and Metabolic Disease in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM	BF Categories	Adjusted covariates	Exclusion Criteria	Outcomes for GDM offspring
Pettitt et al.[165]	1997	Longitudinal	10-39 yrs.	720	Pima Indians	U.S.	n/a	– EBF ≥2 mos. – EFF ≥2 mos. – Some BF ≥2 mos.	– age – sex – birthdate – parental diabetes – birthweight	– maternal diabetes during pregnancy	– Exclusive BF≥2 months~ • lower risk of T2D later in life
Pettitt et al.[166]	1998	Longitudinal	10-39 yrs.	572	Pima Indians	U.S.	GDM (n=21) vs. non-GDM (n=551)	– EBF ≥2 mos. – EFF ≥2 mos. – Some BF ≥2 mos.	– age – sex – parental diabetes – birthweight – maternal diabetes type	– unknown	– EBF≥2 months~ • lower risk of T2D in GDM offspring
Plagemann et al.[145]	2002	Prospective	2 yrs.	112	German	Germany	GDM (n=83) + T1D (n=29)	– Diabetic breast milk (DBM) vs. nondiabetic banked donor breast milk (BBM)	– age – sex – birth weight – gestational age – type of maternal diabetes – maternal BMI	– maternal diabetes	– Higher volume of DBM ~ • Reduced T2D risk • Increased childhood IGT risk
Rodekamp et al.[146]	2005	Prospective	0-2 yrs.	112	German	Germany	GDM (n=83) + T1D (n=29)	BF = Diabetic breast milk (DBM) –Not BF –Solely BF –Partly BF	<u>model I</u> – age – sex – birth weight – gestational age – type of maternal diabetes – maternal BMI – maternal age <u>model II</u> – maternal blood glucose <u>model III</u> – DBM volume ingested <u>model IV</u> – BF duration	– offspring of women without diabetes during pregnancy (type 1 diabetes and GDM)	– EBF ~ increased 120-min blood glucose <u>model III:</u> no association <u>model II:</u> no relationship between maternal blood glucose and the outcome – Neither late neonatal DBM intake nor BF duration had an independent influence on childhood risk of overweight or IGT

Table 2. Breastfeeding and Metabolic Disease in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM	BF Categories	Adjusted covariates	Exclusion Criteria	Outcomes for GDM offspring
Wong et al.[167]	2018	cross-sectional	3-6 yrs.	1,539	Canadian	Canada	n/a	–0-6 mos. – >6-12 mos. – >12-23 mos. – ≥24 mos.	– birth weight – child z height – child age – child sex – maternal age – maternal ethnicity – maternal education – family income – household smok e exposure – maternal or paternal history of cardiovascular disease or diabetes.	– Chronic conditions except asthma, severe development al delay, failure to thrive, gestational age of < 32 weeks	– Higher BF duration~ • lower cardiometabolic risk z score
Young et al.[168]	2002	Case-control	<18 yrs.	46	Canadian	Canada	GDM (n=22) + T1D (n=14) + none (n=10)	–BF >12 mos. vs never BF	– Age – sex-matched – type of maternal diabetes	– None	– BF>12 months~ • Decreased risk of T2D (in GDM and non-GDM) GDM~ • Increased risk of T2D

Early Introduction to Solids in GDM Offspring

Breast milk and formula will meet the nutritional requirements of infants up to age 6-months. After 6-months of age, solid foods are recommended to provide enough energy and adequate vitamins and iron.[169] The American Academy of Pediatrics (AAP) recommends initiation of solid and complementary foods no earlier than 4 months of age.[170] Early introduction to solids (<4 months of age) is associated with early exposure to pathogens and increased risk of developing obesity[171], T1D, and celiac disease.[172,173] On the other hand, delaying start of complementary foods until significantly later than six months of age may result in inadequate energy intake, iron deficiency, disinterest in solid foods, and consequently decelerated growth in children.[174] In a longitudinal cohort of 847 children (birth-3 years of age), the timing of solid food introduction to infants who were not breastfed or BF <4 months was associated with almost a six-fold increase in odds of obesity at three years of age.[175]

In addition, research shows that mothers who BF ≥4 months are less likely to introduce solids early.[173] A cohort of 2,907 infants reported that early introduction to solid foods was a risk factor for earlier cessation of BF, increased consumption of fatty or sugary foods, SSBs, and consequently obesity at one year of age.[169] Other studies also consistently shows that early intake of energy and macronutrients (i.e., fat, protein, carbohydrates) from nutrients other than breast milk or formula in early childhood (minimum of two years old) are linked to increased adiposity and childhood obesity.[176-178] **Table 3** includes studies that have assessed the influence of early introduction to solids on childhood obesity.

Although there is increasing evidence that early introduction to solids is associated with faster growth rate (increase weight and BMI changes) and higher prevalence of obesity in children, few studies have examined this in offspring born to mothers with GDM. In addition, the majority of studies examining the impact of BF on obesity or subsequent metabolic disease have not assessed the timing of introduction to solids or the type of solids concurrently. This study will examine the effects of BF and early introduction to SSBs and fruit juice, on obesity and metabolic parameters in predominantly Hispanic offspring, both those exposed to GDM and those not.

Table 3. Early Introduction to Solids in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM	BF Categories	Introduction to solids	Adjusted Covariates	Exclusion Criteria	Outcomes for offspring
Barrera et al.[171]	2016	longitudinal	6 yrs.	1,181	NHW	U.S.	n/a	–<4 mos. –≥4 mos.	–<4 mos. –4–<6 mos. –≥6 mos. –SSBs at 6 yrs.	–age –sex –birth weight –gestational age –maternal diabetes type –maternal BMI –education –income –pre-pregnancy BMI –marital status –parity –beverage intake frequency at 6 yrs.	–gestational age<35 weeks –weighing <5 lbs. –non-singleton	–Introduction to solids <4 ~ • obesity –Timing of introduction of solids was not ~ obesity at 6 yrs.
Bell et al.[147]	2018	prospective	2-3 yrs.	953	Australian	Australia	n/a	–<17 wks. –17-25 wks. – 26-51 wks. – ≥52 wks.	–<17 wks. –17 -25 wks. – ≥26 wks.	–maternal age –level of education –nationality –parity –pre-pregnancy BMI –maternal smoking –delivery method –infant sex –birth weight	–intending to relocate within the next 12 months	• BF≥12 mos.~ –lower risk of overweight/obesity than those BF< 17 wks. –Early introduction of solids was not associated with weight gain
Griffiths et al.[134]	2009	prospective	0-3 yrs.	10,533	British	U.K.	n/a	–No BF –<4 mos. –≥4 mos.	–<4 mos. –≥4 mos.	–socioeconomic status –Education –pre-pregnancy BMI –parity –smoking –height z-score	–Ethnic minority children –singletons from multiple conceptions –dual families –prematurity –missing data	–Longer BF ~ less weight gain –Early introduction of solids was not associated with faster weight gain

Table 3. Early Introduction to Solids in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM	BF Categories	Introduction to solids	Adjusted Covariates	Exclusion Criteria	Outcomes for offspring
Grummer-Strawn et al.[169]	2008	prospective	0-1 yr.	2,907	Multi	U.S.	n/a	–BF in hospital –<6 mos. –>6 mos.	–Solids: –<4 mos. –>4mos.	–age –race/ethnicity –education –income –parity –region	–no EBF through 16 wks. for the following reasons	Early intro to solids<4 mos. ~ • Early introduction to SSBs • BF cessation • Obesity prevalence
Hawkins et al.[179]	2009	cross-sectional	3 yrs.	13,172	Asian & British	U.K.	n/a	–Never –<4 mos. –≥4mos.	–<4 mos. –≥4mos.	–age –race/ethnicity –education –income –pre-pregnancy BMI	–the main respondent was not female –the partner respondent was not male –2 singletons	Introduction to solids <4mos. ~ Weight gain BF (>4 months vs never) ~lower Weight gain
Huh et al.[175]	2011	cross-sectional	3 yrs.	847	Multi	U.S.	n/a	–<4 mos. –≥4mos.	–<4 mos. –4 - 5 mos. –≥6mos.	–age –race/ethnicity –education –income –pre-pregnancy BMI –paternal BMI	–gestational age>22 weeks at the initial visit	Introduction to solids <4mos. ~ • weight gain x6 • increase in BMI z scores at 3 yrs. (in FF not BF infants) if the infant was breastfed, this was protective against the effects of introducing solids at 4 mos.
Jurado et al.[180]	2016	cross-sectional	2-4 yrs.	116	Mexican	Mexico	n/a	–<3 mos. –≥3 mos.	–<6 mos. –≥6 mos.	–unknown	–unknown	Introduction to solids <6 mos. & BF<3 mos. ~ • obesity

Table 3. Early Introduction to Solids in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM	BF Categories	Introduction to solids	Adjusted Covariates	Exclusion Criteria	Outcomes for offspring
Klag et al.[181]	2015	cross-sectional	0-1 yr.	438	Multi	U.S.	n/a	–<6 mos. –<12 mos.	–<4 mos. –4 to <6 mos. –≥6 mos.	–maternal race/ethnicity –WIC receipt –maternal smoking –maternal partner –maternal education level –maternal work/school –gestational age –BF duration	–Women whose medical record indicated their intention not to BF –prisoners –infant deaths	Longer BF~ with slower –growth Age at solids introduction was not ~ with growth
Moss et al.[182]	2013	longitudinal	2-4 yrs.	14,150	Multi	U.S.	n/a	–BF vs not-BF	–<4 mos. –4-5 mos. –≥6 mos.	–age –race/ethnicity –education –income –birth weight	– born to <16y old mothers –adopted –died prior to their first birthday –had parents who refused to participate – VLBW (<1,500 g) children	Longer BF and delay in intro to solids~ lower • likelihood of obesity
Sinigagli et al.[157]	2016	cross-sectional	0-2 yrs.	296	Puerto Rican	Puerto Rico	n/a	–BF in hospital –≤3 mos. –≤6 mos.	–any	–age –sex –race/ethnicity –education	– infants<6 mos. – infants or toddlers with any serious health condition that could alter normal feeding practices	BF practices or timing of introduction of beverages and solid foods were not ~ with • weight status BF (any) ~ later introduction to SSBs

Table 3. Early Introduction to Solids in Offspring

Authors	Year	Type	Age	N	Ethnicity	Location	GDM	BF Categories	Introduction to solids	Adjusted Covariates	Exclusion Criteria	Outcomes for offspring
Zheng et al.[183]	2015	prospective	0-6 yrs.	43,848	Asian	China	n/a	–Never vs. ever	–≤3 mos. –4-6 mos. –>6 mos.	–age –sex –birth weight –gestational age –delivery mode –weight gain during first 3 mos. –BF status –maternal age at birth –maternal BMI –educational –occupation	–gestational age (>44 weeks or <33 weeks) –birth weight (>5 kg or <1.5 kg) –BMI at 4-5 years of age (BMI z-score >5 or < 5)	–Introduction to solids <3 mos. ~ with greater • BMI z-score • higher risk of overweight (11%) • No significant ~ between timing of complementary feeding and obesity

EARLY INTRODUCTION TO SSBS IN GDM OFFSPRING

Mounting evidence points to sugar consumption in particular sugar-sweetened beverages (SSBs), as a key modifiable factor contributing to obesity and related metabolic disorders.[126-130,126,184-188] The Study of Latino Adolescents at Risk for Diabetes (SOLAR) cohort has consistently shown that high SSB intake is significantly related to adiposity and T2D risk factors in Hispanic adolescents (8-19 years of age).[189,190] Davis et al. found that the combination of BF ≥12 months and limited exposure to SSB intake was linked to a 65% reduction in obesity prevalence in 2,300 primarily Hispanic children (2-4 years of age) participating in Women, Infant, and Children (WIC) clinics in Los Angeles, CA.[191] In another separate cohort of 1,483 primarily Hispanic children (2-4 years of age) participating in WIC, children who were not breastfed and consumed ≥2 SSB per day, had 60% higher obesity rate compared to children breastfed for ≥12 months and had no SSB intake.[126]

Similarly, in a longitudinal study of low-income African American children (3–5 years of age), SSB intake was positively associated with 10-20% increase in the prevalence of obesity after two years.[192] **Table 4** includes studies that have examined the impact of early introduction to solids/beverages on childhood obesity. While some of the mentioned studies examined obesity prevalence in offspring of GDM, they did not examine the impact of early SSB intake on adiposity changes in Hispanic children (1 to 19 years of age) born to mothers with GDM. It is important to examine if and how GDM status impacts the effect of infant feeding on obesity prevalence in the offspring.

Table 4. Early Introduction to SSB

Authors	Year	Design	Age	N	Ethnicity	Location	GDM	BF Categories	Introduction to SSBs	Adjusted Covariates	Exclusion Criteria	Outcomes
Cantoral et al.[127]	2016	longitudinal	8-14 yrs.	227	Hispanic	Mexico	n/a	–≤12 mos. –>12 mos.	–SSBs –≤12 mos. –>12 mos.	–sex –any BF up to age 12 months –maternal obesity –concurrent age – non-SSB-energy intake –physical activity –TV time	–unknown	SSB ≤12 mos. ~ increased • odds of obesity • abdominal obesity • not enough BF>12 mos.
Davis et al.[126]	2012	cross-sectional	2-4 yrs.	1,438	Hispanic	U.S.	n/a	–No BF –1 wk. -<6 mos. –6 -<12 mos. –≥12 mos.	–No SSB –Mid SSB –High SSB	–mother's BMI –child's sex and age –type of milk most often consumed	–Non-Hispanic –preterm –age <2 and >4y	>12 months of BF duration and low SSB intake ~ reduce obesity levels
Davis et al.[125]	2014	cross-sectional	2-4 yrs.	2,295	Hispanic	U.S.	n/a	–No BF –1 wk. to <6 mos. –6 to <12 mos. –≥12 mos.	–No SSB –Mid SSB –High SSB	–gender –ethnicity –age –mother's BMI –GDM status –birth weight	–preterm –≤24 mos. –LBW	>12 months of BF duration and no SSB intake ~ prevent obesity
Faith et al.[137]	2019	prospective	2-5 yr.	382	Multi	U.S.	GDM vs. Non-GDM	–<3 mos. –≥3 mos. –12 mos. combined	–≤6 mos. –>6 mos.	–race/ethnicity –gestational age –maternal age –parity –education –pre-pregnancy BMI –total gestational weight gain (kg) –GDM treatment –gestational age at GDM diagnosis –weight-for-length z score at birth –infant diet	–serious medical conditions	– Lower intensity and shorter duration of BF and early SSB introduction ~ • Elevated infant soothability and activity temperament • Higher odds of later childhood obesity

Table 4. Early Introduction to SSB

Authors	Year	Design	Age	N	Ethnicity	Location	GDM	BF Categories	Introduction to SSBs	Adjusted Covariates	Exclusion Criteria	Outcomes
Grummer-Strawn et al.[169]	2008	prospective	0-1 yr.	2,907	Multi	U.S.	n/a	–BF in hospital –<6 mos. –>6 mos.	–<10 mos. –>10 mos.	–age –race/ethnicity –education –income –parity –region	–unknown	Early intro to solids<4 mos. ~ –BF cessation –Obesity prevalence
Gunderson et al.[137]	2019	prospective	2-5 yr.	382	Multi	U.S.	GDM vs. Non-GDM	–0-3 mos. –≥3mos.	–<6 mos. –≥6 mos.	– race/ethnicity – gestational age at birth – maternal age – parity – education – pre-pregnancy BMI – total gestational weight gain (kg) – gestational age at GDM diagnosis	–serious medical conditions	– Early intro to SSBs, shorter BF duration, and, elevated soothability ~ • Early childhood obesity

SUMMARY

Compared to other minority groups in the U.S., the pathway to obesity occurs much earlier in life among Hispanics, suggesting that early life feeding practices may be more critical for the health of Hispanic children.[193] Hispanic offspring born to mothers with GDM are more likely to develop obesity and T2D later in life. To date, little research has been conducted to assess how infant feeding (BF duration and introduction to SSBs) affects growth rate (weight and BMI changes) during the first year of life and adiposity changes and metabolic disease risk between 1-19 years of age in Hispanic offspring born to mothers diagnosed with GDM during pregnancy. Therefore, the overall goal of this study is to examine how early life infant feeding (BF duration and introduction to SSBs) impacts growth, obesity prevalence, and risk for subsequent metabolic diseases in Hispanic offspring exposed to GDM *in utero*.

For the first analysis (chapter 2), data from a longitudinal study with over 300 Hispanic youth (8–19 years of age) with an average of four annual inpatient and outpatient visits was used. Data on family history of diabetes, GDM of mothers, child's birth weight, BF duration were collected retrospectively at baseline and data on prediabetes and MetS were collected at each annual visit. The aim of this study (**Aim 1**) was to assess the associations of BF and GDM with the prevalence of MetS and prediabetes in Hispanic youth as they age (8-19 years). The hypothesis of Aim 1 was that BF for at least one month would be associated with lower odds of MetS and prediabetes in offspring born to mothers with and without GDM. For the second analysis (chapter 3), we used data from a cross-sectional study with over 4,000 mothers with children (1-5 years of age) participating in the WIC program in Los Angeles County, CA. Height and weight were measured on all children at their WIC clinic visits while GDM occurrence and early life feeding (EBF duration) were collected retrospectively and current SSBs intake of children was collected cross-sectionally via a survey. This study aimed (**Aim 2**) to examine the individual and interaction effects of exposure to GDM , EBF during the first year of life, and current SSB intake at 1-5 years of age on obesity and overweight prevalence. We hypothesized that EBF for at least six months and low SSB intake at 1-5 years of age would be associated with lower odds of overweight and obesity in children of mothers with and without GDM. For the third analysis (chapter 4), a prospective, observational cohort study followed 1,035 GDM mothers and their offspring from Kaiser Permanente Northern California (KPNC) hospital from 2008 to 2011. BF intensity and duration, and SSBs and 100% fruit juice exposure were collected during the first year of life and anthropometry data were retrieved from KPNC medical records. The third analysis aim (**Aim 3**) was to determine how early life modifiable factors (i.e., BF duration and intensity, and introduction to SSBs and 100% fruit juice during the first year of life) impact subsequent obesity prevalence in children aged 2-5 years who were exposed to maternal GDM. For this analysis we hypothesized that lower BF duration and intensity and early introduction to SSBs and 100% fruit juice (during the first year of life) would be associated with higher prevalence of overweight and obesity in children (2-5 years of age) of mothers with GDM.

Chapter 2: Association of Breastfeeding and Gestational Diabetes Mellitus with the Prevalence of Prediabetes and the Metabolic Syndrome in Offspring of Hispanic Mothers

Vandyousefi S, Goran MI, Gunderson EP, et al. Association of breastfeeding and gestational diabetes mellitus with the prevalence of prediabetes and the metabolic syndrome in offspring of hispanic mothers. *Pediatric Obesity.* 2019;14(7):e12515.[1]

ABSTRACT

The effects of breastfeeding (BF) on Metabolic Syndrome (MetS) and diabetes mellitus in children exposed to Gestational Diabetes Mellitus (GDM) in utero have rarely been evaluated. This study assessed BF and GDM in relation to the prevalence of prediabetes and MetS in Hispanic children and adolescents (8-19y). This is a longitudinal study with 229 Hispanic children (8-13y) with overweight/obesity, family history of diabetes, and an average of four annual visits (AV). Participants were categorized as: Never (negative for prediabetes/MetS at all AVs); ever (positive for prediabetes/MetS at any visit); intermittent (positive for prediabetes/MetS at 1-2 AVs); and persistent (positive for prediabetes/MetS

[1]SV and JD contributed to the acquisition of data, conceptualized the analysis plan, carried out the initial analyses, coordinated the interpretation of results, drafted the initial manuscript, and finalized the manuscript. MG conceptualized and designed the study, designed the data collection instruments, collected data, carried out the initial analyses, and critically reviewed and revised the manuscript. EP coordinated the interpretation of results and critically reviewed the manuscript for important intellectual content. All authors critically reviewed the manuscript for important intellectual content.

at ≥3 AVs). Compared to GDM offspring who were not BF (referent), GDM offspring who were BF had lower odds of persistent prediabetes (OR=0.18, 95%CI:0.04-0.82, p=0.02) and MetS (OR=0.10, 95%CI:0.02-0.55, p=0.008). Compared to referent group, non-GDM offspring who were BF, and non-GDM offspring not BF had lower odds of persistent prediabetes (OR=0.10, 95%CI:0.03-0.39, p=0.001; OR=0.05, 95%CI:0.01-0.11, p<0.001) and MetS (OR=0.14, 95%CI:0.04-0.59, p=0.01; OR=0.04, 95%CI:0.01-0.11, p<0.001). These results show BF is protective against prediabetes and MetS in offspring regardless of GDM status.

INTRODUCTION

Prediabetes is a condition defined as having higher than normal levels of fasting plasma glucose (FPG), oral glucose tolerance test (OGTT) 2 hour blood glucose, glycated hemoglobin (HbA1c), or a combination of these, but not high enough to be diagnosed as type 2 diabetes[194]. In the United States (U.S.), the prevalence of prediabetes among adolescent population (12-19 years of age) ranges from 15 to 47% [195]. Early onset of prediabetes during childhood increases risk of type 2 diabetes , the metabolic syndrome (MetS)[196], and cardiovascular disease later in life. According to the SEARCH for Diabetes in Youth study, the prevalence of type 2 diabetes among adolescents younger than 20 years of age, 50% of whom being Hispanics, is estimated to increase four-fold over the next 30 years[197].

The Metabolic Syndrome (MetS) is a condition described as having at least three of the following cardiometabolic risk factors: abdominal obesity, hypertriglyceridemia, hyperglycemia, hypertension, and low high-density lipoprotein (HDL) cholesterol[198]. Over 30% of U.S. adults had MetS in 2012[199]. Approximately 5% of adolescents and 30% of children who had obesity were diagnosed with MetS in 2010[200]. Hispanics have the highest prevalence of MetS compared to other racial/ethnic groups in the U.S.[201]. In addition, Hispanic youth have increased risk of obesity-related metabolic diseases, such as type 2 diabetes and cardiovascular disease[202,203]. Goran et al. previously showed that over 30% of Hispanic children and adolescents (8-19 years of age) have prediabetes and MetS[16,18].

Gestational Diabetes Mellitus (GDM), defined as "any degree of glucose intolerance with onset or first recognition during pregnancy", is one of the most common metabolic complications of pregnancy worldwide[28]. According to the International Diabetes Federation (IDF), GDM impacted one in seven births in 2017[204]. In the U.S., the prevalence of women with GDM was 7.6% between 2007 and 2014[205]. Children born to mothers with GDM are more likely to develop prediabetes, MetS, and increased adiposity later in life[206,207]. A longitudinal cohort of 6-11 year old children showed that GDM offspring who were large for gestational age (LGA) had 3-5 times higher prevalence of MetS than non-GDM children born appropriate for gestational age[81]. Another study of 168 Danish offspring born to mothers with GDM found that GDM offspring had a six-fold increased risk of prediabetes (17%) compared to non-GDM offspring (3%)[208]. Women of ethnic minority groups in the U.S., especially Hispanics, have consistently higher prevalence and risk of GDM, compared to non-Hispanic white (NHW) women[34,39,40]. Hispanics (9.3%) and Mexican Americans (9.9%) had higher prevalence of GDM compared to NHWs (7.0%) in the U.S between 2007-2014[205].

Breast milk has been regarded as the best food for infants to meet their daily nutrients and energy requirements. Breastfeeding (BF) saves the lives of more than 800,000 children under the age of five years annually; however, most infants and children do not receive optimal feeding[98]. The American Academy of Pediatrics and the World Health Organization (WHO) both recommend initiation and continuation of exclusive BF (feeding infants exclusively with breast milk and no other liquids or solids) within one hour and six months after birth, respectively[98,99]. According to the current Centers for Disease Control and Prevention (CDC) BF Report Card[101], approximately 52% and 25% of infants in the U.S. were exclusively breastfed at 3- and 6-months of age in 2014-2015, respectively. Data from CDC shows that approximately 30% of mothers in southern U.S. states and 19% of mothers in western U.S. states completely stopped BF and/or pumping breast milk in 2014[102]. Compared with NHW mothers, Hispanic and African American mothers have lower rates of exclusive BF[27].

A few studies have shown that women with GDM throughout pregnancy compared to those without GDM are less likely to exclusively breastfeed in the first hour postpartum, are more likely to formula feed their children, and have delayed onset of lactation mainly due to diabetes, insulin treatment, and obesity[67,209]. Numerous retrospective studies have reported the inverse association between BF history (any duration) and risk factors associated with MetS such as hyperglycemia, high blood pressure, obesity, cardiovascular disease, type 2 diabetes, and metabolic diseases in both mothers and children later in life[2]. However, research on the association between BF and lower risk of diabetes and MetS is limited in offspring of mothers with GDM[162]. In addition, research suggests that BF may decrease the prevalence of MetS, although not all findings are consistent[210,211].

To date, no study has examined the association between BF and GDM status on prevalence of MetS and prediabetes in young children, particularly in a high-risk Hispanic population. Therefore, this study aims to assess the effects of BF and GDM on the prevalence of MetS and prediabetes in Hispanic children and adolescents as they age (8-

19 years). This study hypothesized that a history of BF for at least one month will be associated with decreased MetS and prediabetes risk in older children of mothers reporting previous GDM or no GDM.

METHODS

The design, data collection procedures, and findings of the University of Southern California longitudinal SOLAR (Study of Latino Adolescents at Risk for Diabetes) cohort have been previously described in detail[212]. The present analyses included 229 children (enrolled at ages 8-13 years), with an average of four annual inpatient and outpatient visits (range of 2-7 visits). According to IDF, "MetS should not be diagnosed in children younger than 10 years"[213]; therefore, 198 children (10-19 years of age) who had complete MetS parameters for at least three annual visits were evaluated for persistence of MetS. Data was collected between 2004-2013. Participants were recruited from Los Angeles County, CA and met the following inclusion criteria: 1) age 8 to 13 years at baseline, 2) family history of type 2 diabetes in at least one parent, grandparent, or sibling determined by parental self-report, 3) Hispanic origin (all four grandparents of Hispanic origin as determined by parental self-report), and 4) body mass index (BMI) ≥85th percentile for age and sex based on CDC growth charts[214].

Participants taking any medications known to affect fat distribution, body composition, insulin action, or insulin secretion and those diagnosed with diseases that may influence insulin action and secretion such as lipoatrophic diabetes and cystic fibrosis, or body composition and fat distribution such as Cushing and Down syndromes were excluded from the study. SOLAR was approved by the Institutional Review Board of the University of Southern California. Informed written consent and assent were obtained from both parents and children, respectively, before testing commenced.

Anthropometrics and Adiposity Measures

A licensed pediatric health-care provider performed a detailed physical exam where Tanner staging was determined using established guidelines[215,216]. Height, weight and waist circumference (at the umbilicus) were measured to the nearest 0.1 cm, 0.1 kg and 0.1 cm, respectively. Blood pressure was taken in the sitting position and measures were repeated rapidly in triplicate at each annual visit[18]. BMI and BMI z-scores were determined by using the EPII 2000 software (version 1.1; CDC, Atlanta, GA, USA). Total body fat and soft lean tissue were measured by dual-energy X-ray absorptiometry (DXA) with the use of a Hologic QDR 4500W (Hologic, Bedford, MA, USA).

Oral Glucose Tolerance Test

After an overnight fast, a 2-hour OGTT was administered with a dose of 1.75 g glucose/kg body weight (to a maximum of 75 g). Blood samples were assayed for glucose and insulin after five minutes (fasting state), and two hours (relative to glucose ingestion).

Assays

Glucose from the OGTT was analyzed on a Dimension Clinical Chemistry system using an in vitro hexokinase method (Dade Behring, Deerfield, IL). Glucose was assayed in duplicate on a Yellow Springs Instrument 2700 Analyzer (Yellow Springs Instrument; Yellow Springs, OH) using the glucose oxidase method. Fasting blood samples were also measured for triglycerides, and total and HDL cholesterol using the Vitros chemistry DT slides (Johnson and Johnson Clinical Diagnostics Inc., Rochester, NY).

GDM and BF Measures

Data on family history of diabetes, maternal GDM status, child's birth weight, BF initiation and duration were assessed at baseline via parental self-administered questionnaires. In the current study, BF duration was analyzed as categorical variables (i.e., "No BF Group" who were breastfed 0 or < 1 month vs. "BF Group" who were breastfed ≥ 1 month). Children were divided into four categories based on GDM and BF: 1) mothers without GDM and were breastfed (i.e.; "non-GDM, BF"), 2) mothers without GDM and were not breastfed (i.e.; "non-GDM, no-BF"), 3) mothers with GDM and were breastfed (i.e.; "GDM, BF"), and 4) mothers without GDM and were not breastfed (i.e.; "GDM, no-BF").

Definition of MetS

To date, no standard definition of MetS for children/adolescents has been established[213]. For this analysis, MetS was categorized using a definition proposed by Cruz et al.[14] that applies pediatric cutoffs to the Adult Treatment Panel III definition[217]. MetS was defined as having at least three of the following risk factors: abdominal obesity (waist circumference ≥90th percentile for age, sex, and Hispanic ethnicity from NHANES III data), elevated blood pressure (systolic or diastolic blood pressure >90th percentile adjusted for height, age, and sex), low HDL cholesterol (HDL cholesterol ≤10th for age and sex), hypertriglyceridemia (triglycerides ≥90th percentile of age and sex), and impaired glucose tolerance (IGT). Participants with MetS were classified into four groups[18]: "NEVER (negative for MetS at all annual visits); EVER (positive for MetS at any annual visits); INTERMITTENT (positive for MetS at 1 or 2 annual visits); and PERSISTENT (positive for MetS at ≥3 annual visits)".

Definition of Prediabetes

Prediabetes was defined according to American Diabetes Association (ADA) diagnostic criteria, as FPG levels between 100 and 125 mg/dL (between 5.6 and 6.9 mmol/L) and /or IGT, 2-hour plasma glucose value of at least 140 and less than 200mg/dl, and/or HbA1c values between 5.7–6.4% (39–47 mmol/mol.)[194]. Similar to MetS, participants with prediabetes were classified into four groups: "NEVER (negative for prediabetes at all annual visits); EVER (positive for prediabetes at any annual visits); INTERMITTENT (positive for prediabetes at 1 or 2 annual visits); PERSISTENT (positive for prediabetes at ≥3 annual visits)".

Statistical Analysis

Summary statistics, graphical analyses, and frequency distributions were used to describe the data. Descriptive statistics (i.e., mean, standard deviation, range, median and quartiles, histograms and Q-Q plots) assessed the distribution of the data. First, t-tests and chi-square analyses were performed to assess differences in baseline and physical characteristics between GDM and non-GDM offspring. Next, multinomial logistic regressions evaluated the effects of BF, GDM, and BF-GDM interaction on the prevalence of MetS and prediabetes over time with sex, Tanner stage, age, total body fat percentage, and birth weight as covariates. All analyses were performed using SAS version 9.4 (SAS, North Carolina, USA). A *p* value of 0.05 was used to denote significance.

RESULTS

Of the 229 children, 26% (n=60) of children were exposed to GDM *in utero* and 57% (n=130) were breastfed for at least one month. **Table 5** displays baseline descriptive characteristics of the GDM and non-GDM participants. GDM offspring compared to non-GDM offspring had higher birthweight at baseline. There were no differences in age, sex, Tanner stage, overweight/obesity prevalence, breastfeeding status, and MetS prevalence between GDM and non-GDM participants at baseline. Approximately 60% were male with an average age of 11 years at baseline, and 80.1% had obesity. Fifty-seven percent were breastfed for ≥ 1 month, with an average duration of 5.2 ± 7.5 months. Approximately 25% had MetS at baseline. GDM offspring compared to non-GDM offspring had a higher prevalence of prediabetes at baseline (~58% vs. 33%, *p*=0.03).

Tables 6 and **7** compare baseline physical and metabolic characteristics of the participants with their prediabetes and MetS status (i.e.; never, ever, intermittent, and persistent), respectively. There were no differences in age, sex, Tanner stage, and birthweight of the participants at baseline and their prediabetes and MetS status at the latest visit. There were significant differences between weight, waist circumference, total body fat, and overweight/obesity prevalence at baseline and MetS categories (**Table 7**). However, this result was attenuated for the prediabetes groups (**Table 6)**. There were significant differences between GDM status (i.e.; being born to GDM vs. non-GDM mothers), BF status, BF duration, and fasting blood glucose level at baseline and prediabetes and MetS categories at the latest visit.

Table 5. Comparison of baseline physical and metabolic characteristics between GDM and non-GDM offspring

Variable[a]	Total (n=229)	Non-GDM (n=169)	GDM (n=60)	*P*-value[b]
Male, n (%)	131.0 (57.2)	106.0 (58.6)	25.0 (52.1)	0.42
Age (years)	11.1 ± 1.6	11.0 ± 1.6	11.1 ± 1.6	0.40
Birth weight (kg)	3.7 ± 0.9	3.5 ± 0.9	3.9 ± 0.9	**0.03**
Weight (kg)	71.7 ± 19.7	69.8 ± 17.9	75.2 ± 23.0	0.06
Waist circumference (cm)	92.3 ± 13.5	91.1 ± 13.1	93.4 ± 14.9	0.19
Total body fat (kg)	29.1 ± 11.4	26.9 ± 10.1	31.2 ± 12.9	0.48
Tanner stage, n (%)				
1- 3	157.0 (68.6)	118.0 (69.9)	39.0 (64.7)	0.87
4-5	72.0 (31.4)	51.0 (30.1)	21.0 (35.3)	
Overweight/obese status, n (%)				
Overweight (>85th-<95th percentile)	44.0 (19.2)	32.0 (18.9)	12.0 (20.6)	0.46
Obese (≥95th percentile)	185.0 (80.1)	137.0 (81.1)	48.0 (79.4)	
Breastfeeding status, n (%)				
<1 month	99.0 (43.2)	68.0 (40.2)	31.0 (50.9)	0.08
≥1 month	130.0 (56.8)	101.0 (59.8)	29.0 (49.1)	
BF duration (months)	5.2 ± 7.5	5.4 ± 7.8	4.6 ± 7.2	0.59
FPG (mg/dL)	92.4 ± 6.7	91.7 ± 6.2	93.1 ± 7.9	0.81
Metabolic Syndrome, n (%)	57.0 (24.9)	42.0 (25.0)	15.0 (25.5)	0.24
Prediabetes, n (%)	91.0 (39.7)	56.0 (33.3)	35.0 (57.6)	**0.003**

[a] Values are mean ± SD unless otherwise stated.
[b] t-tests and chi-square tests were run to assess difference in means or % between non-GDM and GDM groups.
Significant *p*-values (< 0.05) are bolded.
GDM: Gestational Diabetes Mellitus

Table 6. Comparison of baseline physical and metabolic characteristics by prediabetes (PreDM) groups at the latest visit

Variable[a]	Never PreDM (n=109)	Ever PreDM (n=120)	Intermittent PreDM (n=61)	Persistent PreDM (n=59)	*P*-value[b]
Male, n (%)	61.0 (56.0)	70.0 (58.3)	33.0 (54.1)	37.0 (62.7)	0.59
Age (years)	11.2 ± 1.7	11.0 ± 1.8	11.0 ± 1.8	11.0 ± 1.7	0.86
Birth weight (kg)	3.7 ± 0.9	3.6 ± 0.7	3.6 ± 0.7	3.5 ± 0.8	0.40
Weight (kg)	65.9 ± 19.9	64.6 ± 20.0	62.5 ± 16.2	66.7 ± 23.2	0.45
Waist circumference (cm)	88.9 ± 14.6	88.6 ± 12.5	87.9 ± 11.0	89.4 ± 13.9	0.82
Total body fat (kg)	25.4 ± 10.7	25.3 ± 10.2	24.2 ± 8.3	26.4 ± 11.8	0.52
Tanner stage, n (%)					
1- 3	81.0 (74.3)	98.0 (81.7)	52.0 (85.2)	46.0 (78.0)	0.16
4-5	28.0 (25.7)	22.0 (18.3)	9.0 (14.8)	13.0 (22.0)	
Overweight/obese status, n (%)					
Overweight (>85th-<95th percentile)	24.0 (22.0)	16.0 (13.3)	6.0 (9.8)	10.0 (16.9)	0.13
Obese (≥95th percentile)	84.0 (77.1)	104.0 (86.7)	55.0 (90.2)	49.0 (83.1)	
GDM[*] status, n (%)					
Non-GDM	97.0 (89.0)	84.0 (70.0)	48.0 (78.7)	36.0 (61.0)	**0.001**
GDM	12.0 (11.0)	36.0 (30.0)	13.0 (21.3)	23.0 (39.0)	
Breastfeeding status, n (%)					
<1 month	32.0 (29.4)	64.0 (53.3)	30.0 (49.2)	34.0 (57.6)	**0.001**
≥1 month	77.0 (70.6)	56.0 (46.7)	31.0 (50.8)	25.0 (42.4)	
BF duration (months)	6.7 ± 8.6	4.0 ± 6.4	3.4 ± 5.6	4.5 ± 7.1	**0.02**
FPG (mg/dL)	92.8 ± 6.1	94.5 ± 7.5	93.2 ± 7.3	95.8 ± 7.5	**0.03**

[a] Values are mean ± SD unless otherwise stated.
[b] ANOVA test was run to assess difference in means or % between metabolic outcomes and baseline variables.
[*] Significant *p*-values (< 0.05) are bolded.

Table 7. Comparison of baseline physical and metabolic characteristics by Metabolic Syndrome (MetS) groups at the latest visit

Variable[a]	Never MetS (n=117)	Ever MetS (n= 81)	Intermittent MetS (n=47)	Persistent MetS (n=34)	*P*-value[b]
Male, n (%)	60.0 (51.3)	49.0 (60.0)	29.0 (61.7)	20.0 (58.8)	0.29
Age (years)	11.2 ± 1.7	11.0 ± 1.8	11.0 ± 1.8	11.0 ± 1.5	0.45
Birth weight (kg)	3.7 ± 0.7	3.5 ± 0.9	3.5 ± 0.7	3.6 ± 1.0	0.71
Weight (kg)	63.7 ± 19.9	66.9 ± 19.3	66.9 ± 19.8	64.5 ± 18.8	**0.04**
Waist circumference (cm)	87.4 ± 13.5	90.1 ± 13.3	91.1 ± 13.3	89.1 ± 13.3	**0.00**
Total body fat (kg)	24.5 ± 10.5	26.1 ± 10.6	26.1 ± 10.5	26.1 ± 10.6	**0.004**
Tanner stage, n (%)					
1- 3	88.0 (75.2)	64.0 (79.0)	37.0 (78.7)	27.0 (79.4)	0.53
4-5	29.0 (24.8)	17.0 (20.0)	10.0 (21.3)	7.0 (20.6)	
Overweight/obese status, n (%)					
Overweight (>85th-<95th percentile)	26.0 (22.2)	11.0 (13.6)	4.0 (8.5)	7.0 (20.6)	**0.001**
Obese (≥95th percentile)	91.0 (77.8)	70.0 (86.4)	43.0 (91.5)	27.0 (79.4)	
GDM status, n (%)					
Non-GDM	95.0 (81.2)	58.0 (71.6)	35.0 (74.5)	23.0 (67.6)	**0.001**
GDM	22.0 (18.8)	23.0 (28.4)	12.0 (25.5)	11.0 (32.4)	
Breastfeeding status, n (%)					
<1 month	29.0 (24.8)	53.0 (65.4)	31.0 (66.0)	22.0 (64.7)	**0.001**
≥1 month	88.0 (75.2)	28.0 (34.6)	16.0 (34.0)	12.0 (35.3)	
BF duration (months)	7.1 ± 8.1	3.0 ± 5.9	2.5 ± 5.4	3.5 ± 6.3	**0.002**
FPG (mg/dL)	91.2 ± 4.8	95.6 ± 6.4	95.7 ± 6.2	95.4 ± 6.6	**0.048**

[a] Values are mean ± SD unless otherwise stated.
[b] ANOVA test was run to assess difference in means or % between metabolic outcomes and baseline variables.
[*] Significant *p*-values (< 0.05) are bolded.

Results from the multinomial logistic regression for prevalence of prediabetes are shown in **Table 8**. Of the 229 children, 27% and 26% had intermittent and persistent prediabetes across time, respectively. Males had three times higher persistent prediabetes than females (*p*=0.04). Total body percent fat, and Tanner stage did not differ across intermittent and persistent prediabetes groups. However, odds of ever prediabetes was four times higher for those in Tanner stage 4-5 than those in Tanner stage 1-3 (*p*<0.001). Age of the participants with ever prediabetes was significantly higher than those who never had prediabetes. GDM offspring compared to non-GDM offspring had approximately four, two and a half, and six times higher odds of ever, intermittent, and persistent prediabetes, respectively (*p*=0.0002; *p*=0.03; *p*<0.001). Children who were breastfed for at least one month had significantly lower odds of ever, intermittent, and persistent (*p*=0.0009; *p*=0.001; *p*=0.002) than those who were never breastfed or breastfed for less than one month.

There was an overall significant BF-GDM interaction on the prevalence of prediabetes (*p*=0.04). "GDM, no-BF" group was entered in the model as the referent group for Bonferroni post hoc comparisons and all prediabetes groups were compared to the "never prediabetes" group. Compared to the referent group, "non-GDM, BF" group had lower odds of ever prediabetes (OR=0.07, 95%CI: 0.02-0.24, *p*<0.0001), intermittent prediabetes (OR=0.12, 95%CI: 0.03-0.49, *p*=0.003), and persistent prediabetes (OR=0.04, 95%CI: 0.01-0.11, *p*<0.001). Compared to the referent group, "non-GDM, no BF" group had lower odds of ever and persistent prediabetes (OR=0.10, 95%CI: 0.03-0.39, *p*=0.001;

OR=0.10, 95%CI: 0.03-0.39, *p*=0.001); however, the prevalence of intermittent prediabetes was not significant for the mentioned group.

Among GDM offspring, those who were breastfed compared to those not breastfed had lower odds of persistent prediabetes (OR=0.10, 95%CI: 0.03-0.41, *p*=0.02); however, this result was attenuated for the prevalence of intermittent prediabetes. Among non-GDM offspring, those who were breastfed compared to those not breastfed had lower odds of intermittent prediabetes (OR=0.23, 95%CI: 0.10-0.54, *p*<0.001) and persistent prediabetes (OR=0.29, 95%CI: 0.06-0.28, *p*=0.01). **Figure 1** displays the results in terms of frequency of prediabetes within all GDM-BF groups.

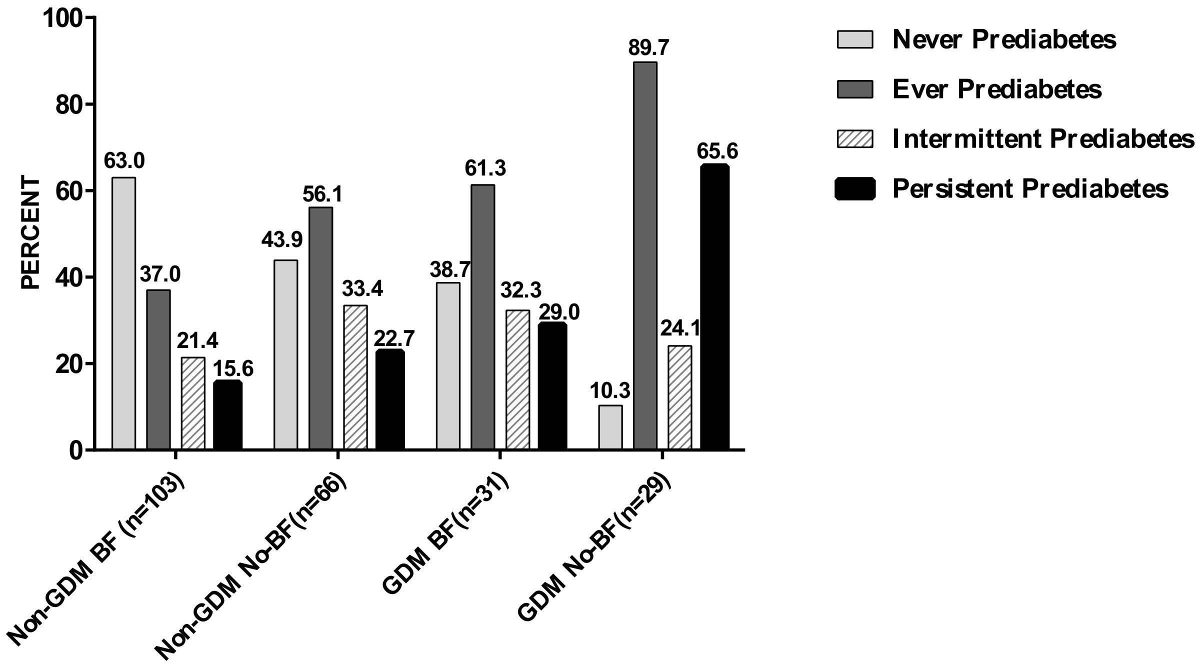

Figure 1. Frequency of each type of prediabetes by BF- GDM groups.

Never=negative for prediabetes at all annual visits; Ever = positive for prediabetes at any visit; Intermittent=positive for prediabetes at 1 or 2 visits; Persistent=positive for prediabetes at ≥ 3 annual visits.

Table 8. Logistic multinomial regression of physical and early life predictors on the prevalence of ever, intermittent, and persistent prediabetes

Predictors	**Ever Prediabetes (n=120)**		**Intermittent Prediabetes (n=61)**		**Persistent Prediabetes (n=59)**	
	***P*[a]**	**OR[b] (95% CI)**	***P*[a]**	**OR[b] (95% CI)**	***P*[a]**	**OR[b] (95% CI)**
Covariate Adjusted Additive Model for GDM and BF Status Separate						
GDM						
No	Referent	1.00	-----	1.00	-----	1.00
Yes	**0.0002**	3.67 (1.87, 7.20)	**0.03**	2.40 (1.09, 5.29)	**<0.001**	5.60 (2.59, 12.06)
Breastfeeding (BF)						
No	Referent	1.00	-----	1.00	-----	1.00
Yes	**0.0009**	0.38 (0.22, 0.67)	**0.002**	0.29 (0.13, 0.61)	**0.001**	0.26 (0.11, 0.58)
Covariate Adjusted GDM Groups Stratified by BF Status						
GDM, no BF	Referent	1.00	-----	1.00	-----	1.00
GDM, BF	**0.01**	0.15 (0.03, 0.67)	0.59	0.63 (0.11, 1.99)	**0.02**	0.18 (0.04, 0.82)
Non-GDM, no BF	**0.001**	0.10 (0.03, 0.41)	0.35	0.50 (0.12, 2.13)	**0.001**	0.10 (0.03, 0.39)
Non-GDM, BF	**<0.0001**	0.07 (0.02, 0.24)	**0.003**	0.12 (0.03, 0.49)	**<0.001**	0.05 (0.01, 0.11)
Sex						
Female	Referent	1.00	-----	1.00	-----	1.00
Male	0.05	1.84 (0.99, 3.43)	0.45	1.44 (0.56, 3.62)	**0.04**	2.98 (1.05, 8.45)
Total Body % Fat	0.23	1.03 (0.98, 1.08)	0.28	1.03 (0.98, 1.09)	0.36	1.03 (0.97, 1.09)
Birthweight	0.06	0.66 (0.43, 1.03)	0.43	0.81 (0.48, 1.38)	**0.01**	0.47 (0.26, 0.85)
Age	**0.01**	1.31 (0.98, 1.58)	**0.02**	1.23 (1.02, 1.54)	**0.03**	1.27 (0.99, 1.62)
Tanner						
1-3	Referent	1.00	-----	1.00	-----	1.00
4-5	**<0.001**	3.91 (1.97, 7.79)	0.05	1.71 (0.48, 6.06)	0.41	3.18 (0.77, 13.21)

[a] Significant *P*-values (< 0.05) are bolded
[b] OR: Odds Ratio, *p*-value for interaction = 0.04

Results from the multinomial logistic regressions for prevalence of MetS are shown in **Table 9**. Of the subsample of 198 offspring who were assessed for MetS, 58% never had MetS, 25% and 17% had intermittent and persistent MetS, respectively. Males had about three times higher odds of intermittent and any type of MetS (p=0.04; p=0.01) and five times higher odds of persistent MetS than females (p=0.004). Birthweight, age, and Tanner stage did not differ between MetS groups. Compared to offspring who had never had MetS, those with ever or persistent MetS had higher total body fat percentage (p=0.009; p=0.002). GDM offspring compared to non-GDM offspring had approximately four, three and a half, and six times higher odds of ever, intermittent, and persistent MetS, respectively (p=0.002; p=0.01; p=0.001). Children who were breastfed for at least one month had lower odds of ever, intermittent, and persistent MetS (p<0.001) than those who were never breastfed or breastfed for less than one month.

There was an overall significant BF-GDM interaction on the prevalence of MetS (p=0.03). Compared to "GDM, no BF" group (referent), "non-GDM, BF" group, had significantly lower odds of ever MetS (OR=0.02, 95%CI: 0.03-0.41, p<0.0001), intermittent MetS (OR=0.03, 95%CI: 0.01-0.10, p<0.001), and persistent MetS (OR=0.04, 95%CI: 0.01-0.11, p<0.001). "Non-GDM, no BF" group had lower odds of persistent MetS (OR=0.14, 95%CI: 0.04-0.59, p= 0.01) compared to the "GDM, no BF" group; however, this result was attenuated for the prevalence of intermittent MetS. Among GDM offspring, those who were BF compared to those not BF had lower odds of intermittent and persistent MetS (OR=0.12, 95%CI: 0.02-0.75, p=0.02; OR=0.10, 95%CI: 0.02-0.55, p=0.008).

Table 9. Logistic multinomial regression of physical and early life predictors on the prevalence of ever, intermittent, and persistent MetS rate

Predictors	Ever MetS (n= 81)		Intermittent MetS (n=47)		Persistent MetS (n=34)	
	***P*[a]**	**OR[b] (95% CI)**	***P*[a]**	**OR[b] (95% CI)**	***P*[a]**	**OR[b] (95% CI)**
<u>Covariate Adjusted Additive Model for GDM and BF Status Separate</u>						
GDM						
No	Referent	1.00	-----	1.00	-----	1.00
Yes	**0.002**	4.29 (1.73,10.64)	**0.01**	3.47 (1.29, 9.38)	**0.001**	5.72 (2.01, 13.29)
Breastfeeding (BF)						
No	Referent	1.00	-----	1.00	-----	1.00
Yes	**<0.001**	0.05 (0.02, 0.09)	**<0.001**	0.06 (0.02, 0.18)	**<0.001**	0.08 (0.03, 0.21)
<u>Covariate Adjusted GDM Groups Stratified by BF Status</u>						
GDM, no BF	Referent	1.00	-----	1.00	-----	1.00
GDM, BF	**0.01**	0.18 (0.05, 0.72)	**0.02**	0.12 (0.02, 0.75)	**0.008**	0.10 (0.02, 0.55)
Non-GDM, no BF	0.67	0.76 (0.22, 2.67)	0.81	0.88 (0.18, 4.13)	**0.01**	0.14 (0.04, 0.59)
Non-GDM, BF	**<0.0001**	0.02 (0.03, 0.41)	**<0.001**	0.03 (0.01, 0.10)	**<0.001**	0.04 (0.01, 0.11)
Sex						
Female	Referent	1.00	-----	1.00	-----	1.00
Male	**0.01**	3.02 (1.25, 7.27)	**0.04**	2.80 (1.04, 5.08)	**0.004**	5.18 (2.67, 9.93)
Total Body % Fat	**0.009**	1.11 (1.03, 1.19)	0.12	1.07 (0.98, 1.17)	**0.002**	1.17 (1.06, 1.29)
Birthweight	0.26	0.72 (0.41, 1.26)	0.49	0.81 (0.44, 1.49)	0.08	0.55 (0.28, 1.08)
Age	0.48	0.91 (0.69, 1.19)	0.12	0.79 (0.59, 1.05)	0.24	1.22 (0.87, 1.70)
Tanner						
1-3	Referent	1.00	-----	1.00	-----	1.00
4-5	0.92	1.05 (0.38, 2.84)	0.40	1.79 (0.53, 2.58)	0.80	1.18 (0.41, 2.73)

[a] Significant *p*-values (< 0.05) are bolded
[b] OR: Odds Ratio, *p*-value for interaction = 0.03

Among non-GDM offspring, those BF compared to those not BF had significantly lower odds of ever, intermittent, and persistent MetS, respectively (OR=0.18, 95%CI: 0.05-0.72, p=0.01; OR=0.12, 95%CI: 0.02-0.75, p=0.02; OR=0.10, 95%CI:0.02-0.55, p=0.008). **Figure 2** displays the frequency of MetS within all GDM-BF groups.

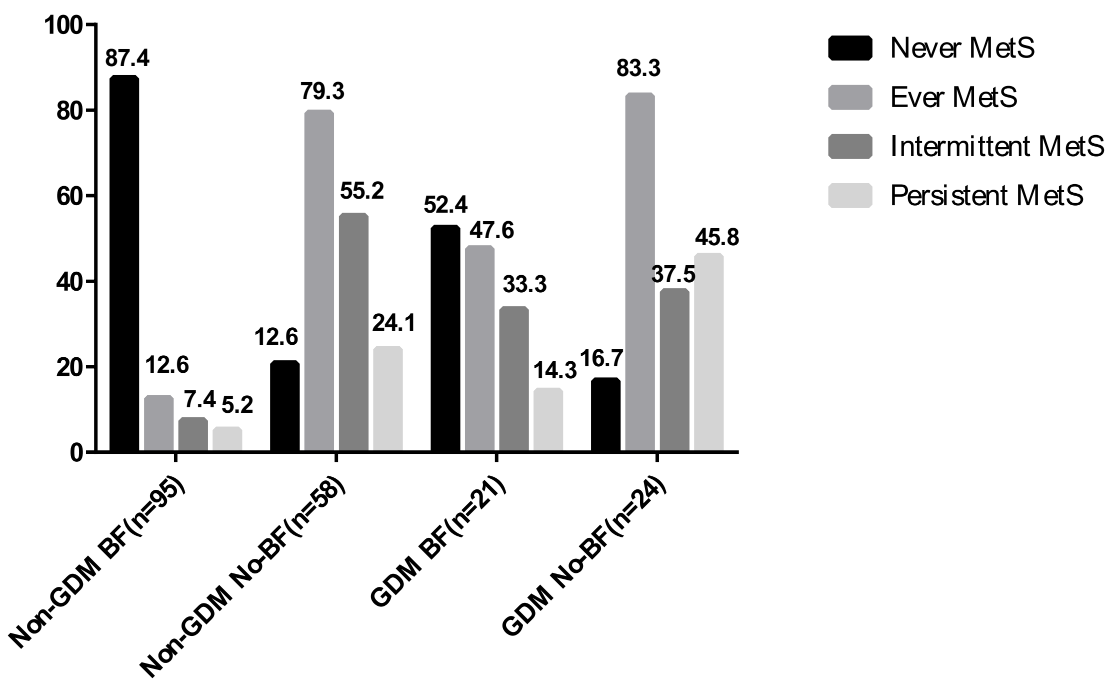

Figure 2. Frequency of each type of MetS by BF- GDM groups.

Never=negative for MetS at all annual visits; Ever = positive for MetS at any visit; Intermittent=positive for MetS at 1 or 2 visits; Persistent=positive for MetS at ≥ 3 annual visits.

DISCUSSION

This study examined the impact of BF and GDM across time on MetS and prediabetes in Hispanic offspring born to mothers with and without GDM. Although research shows that BF has a protective effect on diminishing development of MetS and prediabetes in offspring, there have been conflicting findings and much less is known about this protective effect of BF on children born to mothers with GDM. Additionally, no previous studies have examined the persistence of MetS and prediabetes in Hispanic offspring exposed to GDM *in utero* longitudinally. This longitudinal study shows that BF has a protective effect on the prevalence of ever and persistent MetS and prediabetes in both GDM and non-GDM offspring.

It is well established that GDM throughout pregnancy is a contributing factor to prediabetes and type 2 diabetes in women. While many of the mentioned studies controlled for GDM or type of maternal diabetes during pregnancy, few have actually examined the interaction of BF and GDM on glucose/insulin action in children[164]. A prospective cohort of Pima Indians assessed protective effects of BF on type 2 diabetes in GDM offspring and found that offspring of mothers with GDM (n=21) who were exclusively breastfed had lower prevalence of Type 2 Diabetes, compared to those who were not breastfed or were bottle-fed throughout their infancy; however, their results were not statistically significant[165]. The only longitudinal study with quality measurements, and quantitative assessment of breastmilk intake was conducted by Gunderson et al. and showed that greater BF intensity and duration throughout the first 12 months of life was protective against ponderal growth and weight gain among children of mothers with GDM.[136]

Another study of offspring born to mothers with GDM (n=29) and Type 1 Diabetes (n=83) in Berlin showed that breastfed children of mothers with diabetes had higher risk of developing overweight and IGT at two years of age than breastfed offspring of mothers without diabetes.[218] Their conflicting findings may be due to the heterogeneity of maternal type of diabetes and early assessment for prediabetes and overweight in children at or younger than two years of age, which is less predictive of overweight and prediabetes status at older ages. Findings of this study show that BF has a protective effect on the prevalence of intermittent prediabetes in non-GDM offspring and persistent prediabetes in GDM offspring across time.

While studies show that BF decreases the risks associated with MetS in children and adolescents, research on the association between BF and MetS is limited and inconclusive[210]. A recent systematic review of studies that examined the relationship between BF and MetS reported that of 11 studies, seven found significant inverse relationships between BF and MetS and four studies found no significant associations. One cross-sectional study with 1,770 children and adolescents (7-17 years of age) in China, found an inverse association between BF and prevalence of MetS. In contrast, a retrospective study by Yakubov et al. with 123 children and adolescents (3-18 years of age) in Israel showed that BF had no protective effect on the prevalence of MetS. However, this study included very young children where MetS might not have yet manifested, which may explain their non-significant findings. In addition, the IDF does not suggest MetS diagnosis in children younger than 10 years of age. Of note, all of the above studies were conducted outside the U.S. and no study has examined the persistence of MetS in offspring born to mothers with GDM, or in a high-risk Hispanic population. This study found an inverse association between BF and the prevalence of ever, intermittent, and persistent MetS in both GDM and non-GDM Hispanic older children.[210]

The mechanisms by which the risk of MetS and diabetes in offspring increases by intrauterine exposure to diabetes are not fully understood. Exposure to GDM is associated with excess fetal growth and overnutrition *in utero*, possibly due to hormonal perturbations and alterations in expression of genes that direct the accumulation of body fat or related metabolism in fetus. Research shows that exposure to maternal diabetes *in utero* results in hyperglycemia, hyperinsulinemia, and leptin resistance in offspring.[219] Consequently, exposure to high glucose and insulin concentrations increases levels of fatty acids, glucocorticoids, inflammation, and radicals of oxygen species (ROS) in the maternal-fetal placenta. Increased intrauterine insulin along with generated ROSs can cause altered β-cell differentiation, insulin resistance, and consequently increased risk of prediabetes and type 2 diabetes in offspring later in life. Additionally, increased ROSs in placenta can alter gene expression and metabolic programming of several organs including heart, liver, kidneys, and muscles that can lead to altered insulin signaling pathway, reduced bioavailable nitric oxide, vascular stiffness, and diastolic dysfunction triggering hypertension and development of MetS in those who were born to mothers with GDM throughout adulthood.[219]

Very little is understood about the composition of breast milk in mothers with GDM, and the precise mechanisms underlying the potential protective effect of BF on diabetes and MetS is still unclear. It is believed that exposure to overnutrition and high glucose levels in breast milk of women with diabetes during pregnancy may increase obesity and metabolic disease risk in offspring later in life. A plausible assumption is that GDM may alter the abundance and composition of free human milk oligosaccharides (HMOs), the highest constituent in breast milk after fat and carbohydrates, and glycosylation of protective proteins in milk.[220,221]

Infants do not have the necessary enzymes for digestion of HMOs; therefore, they remain undigested and will be consumed by specific infant gut microbiota members, which may alter metabolic programming and growth and development of offspring later in life. A few studies have shown that the glycosylation of protective proteins in milk is lower in women with GDM compared to those without GDM. However, no differences were found between the total HMOs and their composition in breast milk of women with and without GDM.[222] Although a few researchers have shown that breast milk from women with glucose intolerance would have adverse effects on health outcomes in children, neither the literature nor these findings support this.[136] In summary, the association between BF and health outcomes in offspring born to GDM mothers remains uncertain and further research is needed to investigate the effects of these alterations on offspring health outcomes.[222]

There are several limitations of the current study to consider. The study sample included only Hispanic children with overweight or obesity and with a family history of type 2 diabetes; therefore, the results may not be generalizable to Hispanic children of normal weight and other ethnic/racial populations. Replication of this study using non-homogenous populations is warranted. This study also did not account for GDM mothers receiving treatment, and the severity of the GDM was not known. In addition, GDM status was self-reported and was not confirmed with medical records; however, validity research has shown self-reported GDM status to be accurate with 94% of self-reported GDM cases confirmed by a physician.[223] This study did not assess maternal or paternal BMI, parity, gestational weight gain, or type of delivery mode (i.e., C-section vs. vaginal birth) for this study, all of which play a role in subsequent obesity and metabolic disease risk in the offspring. Other limitations are that BF was assessed retrospectively and since little information on BF was collected, exclusive BF could not be assessed. The sample size for

GDM offspring is rather small (n=60) and not enough to examine the various effects of breastfeeding duration groups on health outcomes; however, each subject had an average of four annual visits with sophisticated adiposity and metabolic testing, which somewhat offsets this limitation.

In conclusion, childhood prevalence of MetS and prediabetes is rising in the U.S., especially among Hispanic children and adolescents. This is the first longitudinal study to examine the association between BF and the prevalence of metabolic syndrome and prediabetes in Hispanic youth with overweight or obesity across puberty. These findings highlight the need to encourage mothers diagnosed with GDM during pregnancy to breastfeed for at least one month. Breastfeeding is one of the vital modifiable approaches that can have a profound effect on reducing the persistence of the metabolic syndrome and prediabetes during adulthood. Continued longitudinal analyses using more precise and valid measures such as exclusivity of BF in relation to metabolic syndrome and prediabetes are warranted, especially in high risk populations.

Chapter 3: Association of Breastfeeding and Early Exposure to Sugar-Sweetened Beverages with Obesity Prevalence in Offspring Born to Mothers with and without Gestational Diabetes Mellitus

Vandyousefi S, Whaley SE, Widen EM, et al. Association of breastfeeding and early exposure to sugar-sweetened beverages with obesity prevalence in offspring born to mothers with and without gestational diabetes mellitus. *Pediatric Obesity.* 2019:e12569.[2]

ABSTRACT

The relationship of Gestational Diabetes Mellitus (GDM), exclusive breastfeeding (EBF), and sugar-sweetened beverages (SSBs) on obesity prevalence in children has rarely been evaluated. This study examined the association of GDM status, EBF, and SSB with obesity prevalence in children (1-5 years of age). Data is from the 2014 Los Angeles County WIC Survey, which included 3,707 mothers and their children (1-5 years of age). Compared to GDM offspring who were not EBF, GDM offspring who were EBF had lower odds of obesity, as did non-GDM offspring who were and were not EBF. Compared to GDM offspring with high SSB intake (>3 servings/day) and no EBF, GDM offspring with high SSB intake and EBF did not have lower odds of obesity, whereas those with GDM, low SSB (≤1 serving/day), and EBF had lower odds of

[2]SV and JD contributed to the acquisition of data, conceptualized the analysis plan, carried out the initial analyses, coordinated the interpretation of results, drafted the initial manuscript, and finalized the manuscript. SW collected data, carried out the initial analyses, and critically reviewed and revised the manuscript for important intellectual content. All authors critically reviewed the manuscript for important intellectual content.

obesity. Using non-GDM, EBF and low SSB as referent, non- GDM offspring who were not EBF, with either high or low SSB, had approximately a 4-fold increase in odds of obesity. In GDM offspring, EBF is only associated with lower obesity levels if SSB intake is also low, whereas EBF is protective against obesity in non-GDM offspring regardless of high or low SSBs intake.

Keywords: Gestational diabetes mellitus, exclusive breastfeeding, sugar sweetened beverages, obesity

INTRODUCTION

Childhood obesity has become a serious health concern in the United States (U.S.) especially among Hispanic children. In 2015–2016, obesity impacted 18.5% of U.S. children and adolescents (2-19 years of age), 13.9% of whom were preschool-aged children (2–5 years of age).[224,225] In addition, 12.3% of 3-23 months old infants enrolled in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) in 2014 had high weight-for-length[226]. Hispanic children and infants have the highest obesity prevalence and weight-for-length among all racial/ethnic groups, respectively.[224,226] Many prenatal and early life factors such as *in utero* exposure to Gestational Diabetes Mellitus (GDM), and early life infant feeding may contribute to higher weight gain, obesity, and related metabolic complications in children.[7,227]

GDM, defined as "any degree of glucose intolerance with onset or first recognition during pregnancy", is one of the most common metabolic complications of pregnancy worldwide.[28] In 2017, one in seven women were diagnosed with GDM.[204] Hispanic women had consistently higher prevalence and risk of GDM (9.3%) than non-Hispanic white (NHW) women (7.0%) in the U.S. between 2007-2014.[205] Intrauterine exposure to GDM is known as one of the contributing factors to childhood obesity in offspring.[228] Several researchers have shown that women with GDM are less likely to exclusively breastfeed in the first hour postpartum and more likely to formula feed their children in the hospital than women without GDM.[105,106]

Breast milk has been recognized as the best food for infants to meet their daily nutrients and energy requirements for the first six months after birth.[98] Numerous studies have shown that lower breast feeding (BF) duration and intensity increases the likelihood of overweight and obesity in children.[97,125,142] While exclusive BF (EBF), feeding infants exclusively with breast milk and no other liquids or solids, for at least six months after birth is recommended[98,99], only about 25% of U.S. infants were exclusively breastfed for 6-months in 2014-2015.[101] Hispanics and African Americans have lower rates of EBF than NHW mothers in the U.S.[27] There is increasing evidence that BF has a protective effect against obesity in offspring; however, the impact of EBF in offspring exposed to GDM is not well studied or understood.

Mounting evidence points to sugar consumption, in particular sugar-sweetened beverages (SSBs), as a key modifiable factor contributing to obesity and related metabolic disorders.[126-129] A few studies have reported that children who were breastfed and had limited exposure to SSBs had lower obesity prevalence compared to those not breastfed and had higher intake of SSBs.[126,191] While some of the mentioned studies controlled for GDM status, these studies did not examine the interaction effect of GDM with early SSBs intake in children (1-5 years of age) on obesity prevalence. To date, no study has examined the relationships of EBF, SSBs intake, and GDM status on obesity prevalence in offspring (1-5 years of age). Therefore, the goal of this study was to examine the individual and interaction effects of EBF, SSB intake, and GDM status on obesity prevalence. The current study hypothesized that GDM, EBF, and SSBs would be independently associated with lower odds of obesity in offspring, and that there would be an interaction between these three factors, with the lowest prevalence of obesity in the group with no GDM, EBF, and low SSB intake.

METHODS

Data for this study are from the 2014 Los Angeles County (LAC) WIC Survey, the triennial WIC household survey adapted from the 2005 LAC Health Survey[229], which was designed to assess health-related information, early life infant feeding, and home and community indicators of support for women, infants, and children under age five residing in LAC.[230] Data on maternal GDM status, child's birth weight, EBF, and frequency of SSBs intake were collected via a parental telephone survey.[231] Although the 2014 survey of LAC WIC parents' questionnaire included 127 questions, the current study analyzed data on questions related to early life infant feeding practices of offspring, GDM status, demographics, ethnic and racial background of the child, and obesity measures.[232]

For this study, eligible participants were: 1) biological mother of a child enrolled in the WIC program, 2) delivered a full-term baby (excluded if delivered a premature or low birth weight), and 3) completed the infant feeding survey questions. If a family reported more than one WIC eligible child, then data were collected based on the child with the most recent birthdate[125]. Overall 5,000 women and their children (prenatal women through 5-year-olds) participated in LAC WIC 2014 however, this study only included 3,707 children (1-5 years of age) and about 470 (or approximately 13%) of them were born to mothers with GDM.[124] About 1,300 participants were excluded from the current analysis because they were pregnant with no children, had infants younger than one year of age, or had missing data.

GDM and Early Life Feeding Measures

The current study examined EBF, defined as feeding infants exclusively with breast milk and no other liquids or solids, for at least six months after birth. The following survey questions were asked from the mothers to determine EBF duration: "How old was your child the first time (he) (she) was given formula?", "Are you currently breast-feeding your child?", "How old was your child when you completely stopped breastfeeding (him/her)?", and "How old was your child the first time (he/she) was given anything besides breast milk? This includes formula, baby food, juice, cow's milk, sugar water or anything else you fed your baby." Responses for the last question were: "less than one week, one week but less than one month, one month but less than three months, three months but less than six months, at six months, or have you not fed your baby anything besides breast milk, more than six months".

GDM status was analyzed as categorical variables (i.e., "no GDM" who were born to mothers without GDM vs. "GDM" who were born to mothers with GDM). To analyze GDM-BF interaction, children were divided into four categories based on GDM and EBF status: 1) mothers without GDM who EBF (i.e.; "non-GDM, EBF"), 2) mothers without GDM who did not EBF (i.e.; "non-GDM, no-EBF"), 3) mothers with GDM who EBF (i.e.; "GDM, EBF"), and 4) mothers without GDM who did not EBF (i.e.; "GDM, no-EBF").

SSBs variable included all SSBs (excluding 100% fruit juice, diet sodas, and sugar-free drinks) and chocolate or flavored milk. SSBs frequency of intake was divided into tertiles to create three equal groups as categorical variables (i.e.; low SSB (≤1 serving/day), medium SSB (>1 and ≤3 servings/day), and high SSB (>3 servings/day)).[232] This dietary screener was previously tested to assess reliability and validity of sweetened foods and beverages intake among children (2-4 years of age) against three 24-hour recalls in a subsample of 70 primarily Hispanic mothers.[233] Intraclass Correlation Coefficient (ICC) for total SSB (excluding milk, chocolate milk, and 100% fruit juice) yielded to 0.7 (i.e. moderate agreement) and for chocolate or sweetened milk yielded to 0.84 (i.e. substantial agreement). Spearman's rank Correlations Coefficient (SCC) for total SSB (excluding milk, chocolate milk, and 100% fruit juice) yielded to 0.46 (i.e. moderate) and for chocolate or sweetened milk yielded to 0.57 (i.e. strong).

Anthropometrics

To overcome the challenges of accurately assessing a young child's height and weight in a phone survey, survey records were linked to WIC administrative data to obtain accurate anthropometric data for the target children. Children were weighed and measured every six months by WIC staff. Height, weight, and BMI measurements of children aged 2-5 years obtained by WIC staff were previously validated against the standard measurements taken by research staff. Sensitivity and specificity of WIC BMI percentile classifications (i.e., overweight/obese versus underweight/normal) were high at 86% and 92%, respectively, indicating that WIC staff can accurately measure anthropometrics.[234]

Definition of Obesity

Infants (1-2 years of age) with weight-for-height ≥97.7th percentile were classified as high weight-for-length.[235] Children (2-5 years of age) were classified as subjects with obesity if their BMI- for-age was ≥95th percentile, with overweight if their BMI- for-age was ≥85th percentile[236] and at risk of overweight if their BMI- for-age was ≥75th percentile.

Statistical Analysis

Summary statistics, graphical analyses, and frequency distributions were used to describe the data. Descriptive statistics (i.e., mean, standard deviation, range, median and quartiles, histograms and Q-Q plots) assessed the distribution of the data. First, t-tests and chi-square analyses were performed to assess differences in baseline and physical characteristics between GDM and non-GDM offspring. Next, binary logistic regressions evaluated the individual and interaction effects of BF, GDM, SSBs intake on the prevalence of obesity while controlling the following covariates: child's age, sex, and race/ethnicity. The dependent variable was obese status, i.e., children with obesity (either high weight-for-length for 1-2 y or BMI percentile≥95th for 2-5 y) were compared to non-obese children. If the interactions with GDM were significant, then the group with the least desirable condition was selected as the referent group for Bonferroni post hoc comparisons (i.e., GDM offspring who were not EBF and high SSBs intake). All analyses were performed using SAS version 9.4 (SAS, North Carolina, USA). A *p* value of 0.05 was used to denote significance.

RESULTS

A total of 3,707 children (1-5 years of age) were eligible for this analysis. Of these participants, 3,310 had complete data on all variables. About 81% of the participants were of Hispanic origin, 13% (n=470) were exposed to GDM *in utero*, 27% (n=924) were exclusively breastfed for at least six months, and 23% (n=865) were high SSBs consumers. Physical characteristics, GDM status, EBF, and overweight and obesity rates of the participants are shown in **Table 10**. There were no differences in age and sex between GDM and non-GDM participants. Half of the children were male with an average age of three years at the time their mother was surveyed. Although GDM offspring had higher birthweight, this difference was not significant. Non-GDM offspring were taller than those born to mothers with GDM (*p*=0.05). Hispanics had significantly higher rates of GDM (*p*=0.007) compared to other ethnicities. Compared to non-GDM offspring, GDM offspring had similar rates of EBF (25% vs. 27%; *p*=0.13) but had higher rates of obesity (18% vs. 29%; *p*<0.0001). Consumption of SSBs did not differ between the two groups.

Results from the logistic regression for obesity prevalence are shown in **Table 11**. Nineteen percent of children had either high weight-for-length (BMI percentile≥97.7th percentile; 1-2 years of age) or obesity (BMI for age percentile≥95th; 2-5 years of age). Males were more likely to have obesity than females. However, there were no differences between males and females with BMI-for-age ≥85 and 75th percentiles. Birthweight and age were not significant in the model. Hispanics, 1-5 year of age and 2-5 years of age, were 62% and 46% more likely to have obesity compared to NHW children (both p<0.01). Results were consistent with those with overweight and at risk of overweight. GDM offspring compared to non-GDM offspring (both 1-5 years of age and 2-5 years of age) were more likely to have obesity (OR=1.72 95%CI 1.36-2.19, p<0.0001; OR=2.47, 95%CI 1.73-3.54, p<0.0001). Similarly, 2-5 years old children who were exposed to GDM *in utero* were more likely to have BMI- for-age ≥85th and 75th percentiles than non-GDM offspring (OR=2.0 95%CI 1.55-2.70, p<0.0001; OR=1.67, 95%CI 1.27-2.19, p<0.0001).

Table 10. Comparison of physical characteristics between GDM and non-GDM children participating at LAC WIC

Variable[a]	**Total (n=3,707)**	**Non-GDM (n=3,237)**	**GDM (n=470)**	***P*-value**[b]
Male, n (%)	1,906.0 (51.4)	1,662.0 (51.3)	244.0 (51.9)	0.84
Age (years)	2.9 ± 1.2	2.9 ± 1.2	2.9 ± 1.2	0.07
Birth weight (kg)	3.4 ± 1.8	3.3 ± 1.6	3.5 ± 2.0	0.11
Weight (kg)	13.8 ± 3.9	13.8 ± 3.8	13.7 ± 4.1	0.52
Height (cm)	88.8 ± 12.2	88.9 ± 12.2	87.7 ± 12.4	0.05
Child's ethnicity				
Hispanics	3,011.0 (81.2)	2,602.0 (80.4)	409.0 (87.0)	**0.007**
Non-Hispanic White	122.0 (3.3)	112.0 (3.5)	10.0 (2.1)	
African–American	255.0 (6.9)	233.0 (7.2)	22.0 (4.7)	
Asian Pacific Islander	88.0 (2.4)	76.0 (2.3)	12.0 (2.6)	
Other	231.0 (6.2)	214.0 (6.6)	17.0 (3.6)	
Overweight/obesity status, n (%)				
1-2 years of age:				
High weight-for-length ≥987.7[h] percentile	236.0 (24.2)	199.0 (24.1)	37.0 (28.5)	0.27
2-5 years of age:				
At risk (≥75th-<85th percentile)	326.0 (12.6)	230.0 (10.1)	41.0 (12.9)	**<0.0001**
Overweight (≥85th-<95th percentile)	372.0 (14.4)	325.0 (14.3)	47.0 (14.8)	
Obesity (≥95th percentile)	502.0 (19.4)	410.0 (18.0)	92.0 (28.9)	
Exclusive breastfeeding status, n (%)				
<6 months	2,505.0 (72.6)	2,195.0 (72.8)	322.0 (74.8)	0.13
≥6 months	946.0 (27.4)	820.0 (27.2)	126.0 (25.2)	
SSBs frequency intake				
SSB≤ 1 serving/day	1,184.0 (31.9)	1,032.0 (31.9)	152.0 (32.3)	0.24
1<SSB≤3 serving/day	1,579.0 (42.6)	1,373.0 (42.4)	206.0 (43.8)	
SSB> 3 serving/day	865.0 (23.3)	765.0 (23.6)	100.0 (21.3)	

GDM = Gestational Diabetes Mellitus; SSBs = Sugar Sweetened Beverages
[a] Values are mean ± SD unless otherwise stated.
[b] t-tests and chi-square tests were run to assess difference in means or % between non-GDM and GDM groups. Significant P-values (<0.05) are bolded.

Table 11. Logistic regression of physical and early life predictors on the prevalence of obesity- Main Effects

	1-5 Years of Age (n=3,310)		2-5 Years of Age (n=2,427)					
	Obesity[a]		BMI Percentile≥95th		BMI Percentile≥85th		BMI Percentile≥75th	
Variables	***P*[b]**	**OR[c] (95% CI)**	***P*[b]**	**OR[c] (95% CI)**	***P*[b]**	**OR[c] (95% CI)**	***P*[b]**	**OR[c] (95% CI)**
Sex								
Female	Referent	1.00	-----	1.00	-----	1.00	-----	1.00
Male	**0.02**	1.21(1.01, 1.40)	**0.04**	1.22 (1.00, 1.48)	**0.67**	1.04 (0.87, 1.23)	**0.92**	0.99 (0.85, 1.17)
Age	0.14	0.95 (0.89, 1.02)	0.07	1.15 (1.03, 1.29)	0.05	1.19 (1.07, 1.31)	0.07	1.16 (1.05, 1.37)
Race								
Non-Hispanics	Referent	1.00	-----	1.00	-----	1.00	-----	1.00
Hispanics	**0.0002**	1.62 (0.99, 1.04)	**0.007**	1.46 (1.11, 1.94)	**0.001**	1.51 (1.18, 1.93)	**0.02**	1.29 (1.03, 1.61)
GDM								
No	Referent	1.00	-----	1.00	-----	1.00	-----	1.00
Yes	**<0.0001**	1.72 (1.36, 2.19)	**<0.0001**	2.47 (1.73, 3.54)	**<0.0001**	2.05 (1.55, 2.70)	**<0.0001**	1.67 (1.27, 2.19)
Exclusive Breastfeeding (EBF)								
No EBF (<6 mos.)	Referent	1.00	-----	1.00	-----	1.00	-----	1.00
EBF (≥ 6 mos.)	**<0.0001**	0.39 (0.31, 0.49)	**<0.0001**	0.40 (0.28, 0.58)	**0.001**	0.63 (0.48, 0.83)	**0.007**	0.69 (0.52, 0.90)
SSBs Intake	**0.03**	-----	**0.04**	-----	**0.44**	-----	**0.51**	-----
SSB> 3serving/day	Referent	1.00	-----	1.00	-----	-----	-----	-----
1<SSB≤3serving/day	0.68	0.78 (0.25, 2.47)	0.66	0.76 (0.23, 2.53)	0.66	-----	-----	-----
SSB≤ 1 serving/day	**0.04**	0.22 (0.05, 0.92)	0.09	0.26 (0.05, 1.28)	0.09	-----	-----	-----

[a]Obesity =High weight-for-length/ BMI Percentile≥97.7th (1-2 y) + BMI Percentile≥95th (2-5 y)
[b]Significant *p*-values (<0.05) are bolded
[c]OR: Odds Ratio

Children (1-5 years of age and 2-5 years of age) who were EBF had lower odds of obesity than those who were not EBF (OR=0.39, 95%CI 0.31-0.49, $p<0.0001$; OR=0.40, 95% CI 0.28-0.58, $p<0.0001$). SSBs intake was independently associated with obesity prevalence in both age categories ($p=0.03$ and $p=0.04$). However, there were no significant association between SSBs intake and having BMI- for-age ≥85th and 75th percentiles. Children 1-5 years of age who were low SSB consumers (≤1 SSB serving/day) compared to high SSB consumers (>3 SSB servings/day) had lower odds of obesity (OR=0.22, 95% CI 0.05-0.92, $p=0.04$), whereas the Bonferroni comparison was attenuated to a trend for children 2-5 year of age.

There was an overall significant EBF-GDM interaction on the prevalence of obesity among 1-5 years old ($p=0.03$) and 2-5 years old children ($p=0.04$). However, the interaction effect was attenuated to a trend for 2-5-year-old children with overweight and at risk of overweight. In 1-5-year olds, compared to GDM children who were not EBF (referent), GDM children who were EBF had lower odds of obesity (OR=0.56, 95% CI 0.33-0.95, $p=0.03$). Compared to GDM children not EBF, non-GDM children who were EBF or not EBF both had lower odds of obesity prevalence (OR=0.65, 95%CI 0.50-0.85, $p=0.001$; OR=0.21, 95%CI 0.15-0.30, $p<0.0001$). In the 2-5-year-old children, compared to GDM children not EBF, GDM children who were EBF had lower odds of obesity (OR=0.57, 95% CI 0.33-0.99, $p=0.04$). Compared to the referent group, non-GDM children who were EBF or not EBF both had lower odds of obesity prevalence (OR=0.54, 95% CI 0.40-0.73, $p<0.001$ and OR=0.17, 95% CI 0.11-0.25, $p<0.0001$). **Figure 3** displays the odds of obesity by EBF-GDM groups among all 1-5-year-old children.

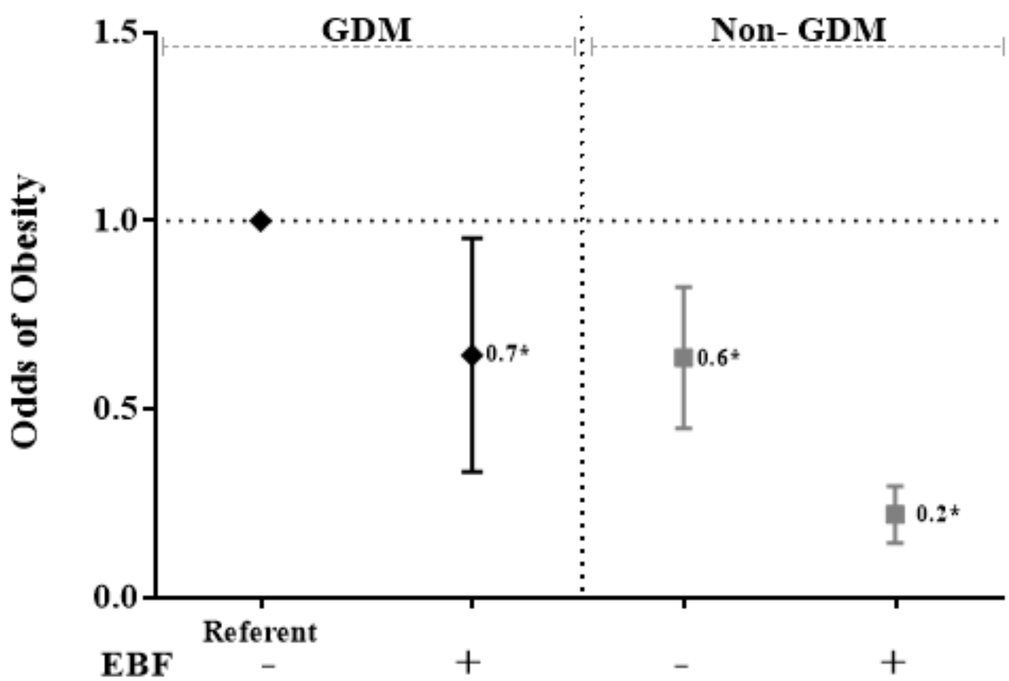

Figure 3. Obesity prevalence among 1-5 years old children by GDM-EBF groups
*Significantly lower odds compared to referent

The current study found no significant GDM-SSBs interaction on the prevalence of obesity among 1-5 years old (*p*=0.26) and 2-5 years old children (*p*=0.97). However, there was a significant GDM-EBF-SSBs interaction on obesity prevalence among 1-5-year olds (*p*=0.02). This relationship was attenuated for all 2-5 years old groups (*p*>0.05). Bonferroni post-hoc comparisons for GDM-EBF and GDM-EBF-SSBs interactions are further displayed in **Table 12**.

Table 12. Logistic regression of physical and early life predictors on the prevalence of obesity-Interaction Effects

Predictors	**1-5 Years of Age (n=3,310)**		**2-5 Years of Age (n=2,427)**	
	Obesity[a]		**BMI Percentile≥95th**	
	***P*[b]**	**OR[c] (95% CI)**	***P*[b]**	**OR[c] (95% CI)**
GDM-EBF Interaction	**0.03**	-----	**0.02**	-----
GDM, No EBF	Referent	1.00	-----	1.00
GDM, EBF	**0.03**	0.56 (0.33, 0.95)	**0.04**	0.57 (0.33, 0.99)
Non-GDM, No EBF	**0.001**	0.65 (0.50, 0.85)	**<0.001**	0.54 (0.40, 0.73)
Non-GDM, EBF	**<0.0001**	0.21 (0.15, 0.30)	**<0.0001**	0.17 (0.11, 0.25)
GDM-SSBs Interaction	0.26	-----	0.97	-----
GDM-EBF-SSBs Interactions	**0.02**	-----	0.14	-----
Non-GDM, EBF, Low SSB	Referent	1.00	-----	-----
Non-GDM, EBF, High SSB	**0.001**	1.77 (0.93-3.37)	-----	-----
Non-GDM, No EBF, Low SSB	**<0.0001**	3.62 (2.16-6.05)	-----	-----
Non-GDM, No EBF, High SSB	**<0.0001**	3.83 (2.26-6.48)	-----	-----
GDM, EBF, Low SSB	Referent	1.00	-----	-----
GDM, EBF, High SSB	**0.03**	4.77 (1.55- 8.60)	-----	-----
GDM, No EBF, Low SSB	**0.01**	4.33 (1.42- 8.07)	-----	-----
GDM, No EBF, High SSB	**0.01**	4.38 (1.39- 8.16)	-----	-----

[a]Obesity =High weight-for-length/ BMI Percentile≥97.7th (1-2 y) + BMI Percentile≥95th (2-5 y)
[b]Significant *P*-values (<0.05) are bolded
[c]OR: Odds Ratio

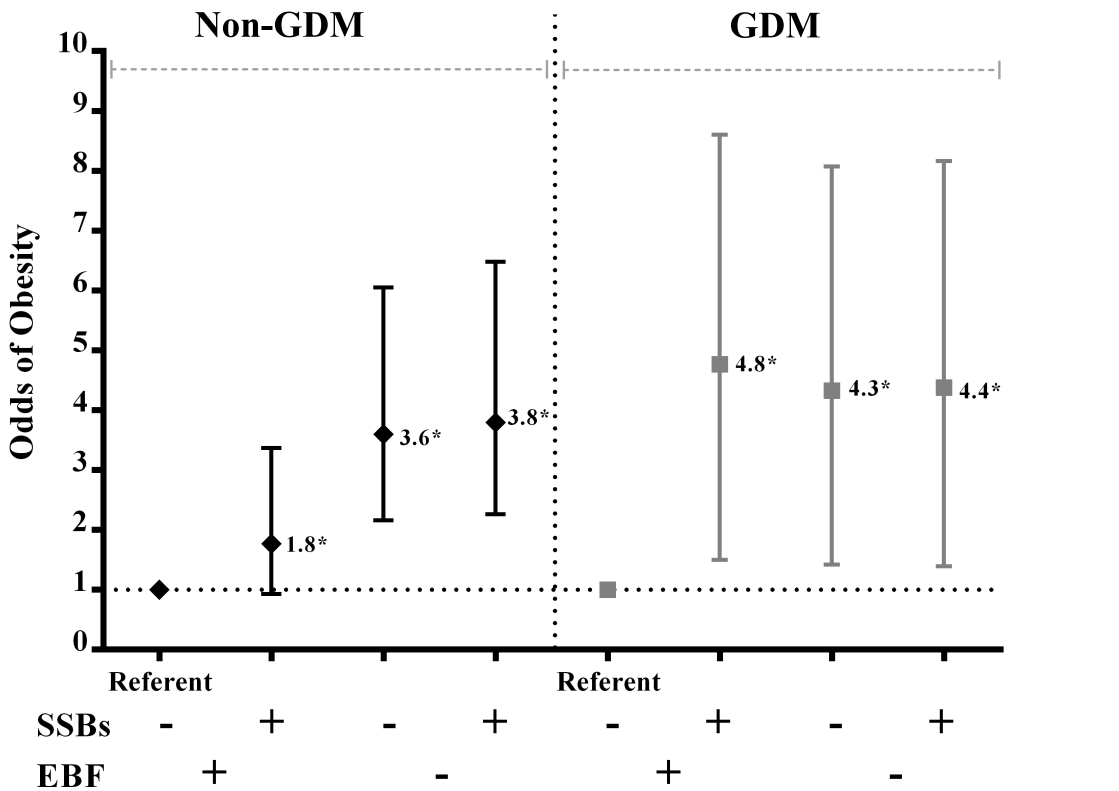

Figure 4. Obesity prevalence among 1-5 years old children by GDM-EBF-SSBs groups
*Significantly lower odds compared to referent

In the 1-5-year-old children, compared to GDM offspring, with low SSBs intake, and who were EBF (referent), those who were GDM, with high SSBs intake and who were EBF had approximately a five-fold increase in odds of obesity (OR=4.77, 95%CI 1.55-8.60, *p*=0.03). Compared to the GDM referent group, GDM offspring who were not EBF with low and high SSBs intake had 4.3- and 4.4-times higher odds of obesity, respectively (OR=4.33, 95%CI 1.42- 8.07, *p*=0.01; OR=4.38, 95%CI 1.39- 8.16, *p*=0.01). Using non-GDM, EBF and low SSB as referent, those who were not EBF, with either high or low SSBs had approximately a 4-fold increase in odds of obesity (OR=3.62, 95%CI: 2.16-6.05, *p*<0.0001; OR=3.83, 95%CI: 2.26-6.48, *p*<0.0001). Compared to the non-GDM referent group, those who were EBF and had high SSBs intake had 77% higher odds of obesity (OR=1.77, 95%CI 0.93-3.37, *p*=0.001). **Figure 4** exhibits the odds of obesity by EBF-GDM-SSBs groups among all 1-5-year-old children.

DISCUSSION

This study replicated numerous studies before, showing that being exposed to GDM *in utero* is a contributing factor to childhood obesity.[82,83,86] A study of 33,893 mothers and their offspring (birth-7 years of age) in the U.S. found that the odds of childhood obesity were 1.45-fold higher for children born to mothers with GDM versus without GDM.[87] Similarly, a retrospective study of 7,355 children (mean age of 5.8 years) born to mothers with GDM in Germany found that the odds of childhood overweight (OR=1.81) and obesity (OR= 2.80) were higher for offspring of mothers with GDM, compared to non-GDM group.[88] The current study found that GDM offspring had 1.72 times higher odds of obesity than non-GDM offspring.

The mechanisms by which the risk of obesity in offspring increases by intrauterine exposure to diabetes are not fully understood. Exposure to maternal diabetes is associated with excess fetal growth in utero, possibly due to fetal hormonal alterations and perturbations in fetal fat accretion. Dabelea et al.[93] found that exposure to maternal GDM in utero results in elevated leptin synthesis, hyperglycemia, and hyperinsulinemia in offspring. Moreover, maternal prenatal GDM may also influence and alter the expression of genes that direct the accumulation of body fat or related metabolism in fetus.[93]

The current study found a significant interaction effect of GDM and EBF on obesity prevalence, and showed that within GDM offspring, those who were EBF compared to those not EBF had 44% lower odds of obesity prevalence. Our results are consistent with the findings of other studies. A clinical cohort of 15,710 mothers and their offspring in the U.S. found an inverse association between breastfeeding and childhood overweight in two-year-old children who were breastfed for at least six months regardless of GDM status of their mothers. Although GDM was not independently associated with childhood overweight, it had no effect on the inverse relationship of BF with overweight prevalence when included in the model.[82] Of note, the above study examined only overweight status of two-year-old children without differentiating EBF from mixed BF. A retrospective study of 2,295 children (2-4 years of age) of Hispanic mothers with GDM during pregnancy showed that offspring who were breastfed for at least 12 months had a 72% decrease in obesity prevalence.[124] The only longitudinal study with quantitative assessment of breastmilk intake was conducted by Gunderson et al. and showed that greater BF intensity and duration throughout the first 12 months of life was protective against ponderal growth and weight gain among children (birth-12 months of age) of mothers with GDM.[136]

In contrast to the current findings and findings of the above studies, a prospective cohort of 1,152 Asian women with GDM (n=181) in Singapore reported that offspring of mothers without GDM who were breastfed for at least four months had slower growth rate from birth to 36 months of age than those who were not breastfed or were BF for less than four months; however, they did not find similar results in offspring of mothers with GDM[138]. In the GDM offspring, greater breast milk intake was associated with accelerated weight gain and BMI in the first six months of age. Of note, this study did not differentiate exclusive and predominant (full) BF groups, which might explain their conflicting findings. Similarly, a study of 112 infants (0-2 years of age) born to mothers with GDM by Rodekamp et al. showed a significant association between EBF (any duration) and increased childhood relative body weight and blood glucose at two years of age; however, after adjustment for the volume of breast milk consumed during the first week of life, all these associations were eliminated.[139]

Research is sparse on the relationship among GDM status, EBF, and childhood obesity and very little is understood about the composition of breast milk in women with diabetes during pregnancy. In a prospective longitudinal study, Logan et al. used MRI and spectroscopy to determine adipose tissue (AT) quantity and distribution and intrahepatocellular lipid (IHCL) content of 86 infants over the first 12 postnatal weeks and found that GDM offspring who were EBF had significantly greater total AT volume at 10 weeks than infants of non-GDM women. However, they found no significant differences between AT distribution and IHCL content of GDM and non-GDM groups at 11 days or 10 weeks postpartum.[92] Human milk oligosaccharide (HMOs) are one of the key components in human milk that may protect against chronic diseases. Although evidence linking HMOs to childhood obesity is inconclusive, HMOs are known to serve as a fuel for human milk microbiota and help develop healthy gut microbiome in breastfed infants. The gut microbiota affects regulation of the expression of genes that are involved in fat metabolism and deposition and is linked to reduced obesity rates in children.[237] No differences between the total HMOs in breast milk of women with and without GDM has been reported.[222] Therefore, it is unknown whether milk of mothers with GDM can be protective against obesity in offspring and more research on other components such as leptin and insulin levels in the breast milk of women with GDM is required.

The current study findings are consistent with other studies and showed that children (1-5 years of age) who were EBF for at least six months and had low SSBs intake (i.e.; ≤ 1 serving per day) had lower odds of obesity than those with high SSBs intake (i.e.; >3 servings per day) regardless of GDM status of their mothers throughout pregnancy. In a 10-year longitudinal cohort of over 200 Hispanic adolescents as they traverse through puberty (8-19 years of age), high SSBs intake had consistently been linked to increased adiposity and type 2 diabetes risk factors.[189,190] Davis et al. found that the combination of BF ≥12 months and limited exposure to SSBs intake was linked to a 65% reduction in obesity prevalence in 2,300 primarily Hispanic children (2-4 years of age) participating in WIC clinics in Los Angeles, CA.[191] In another separate cohort of 1,483 primarily Hispanic children (2-4 years of age) participating in WIC, children who were not breastfed and consumed ≥2 SSBs per day had 60% higher obesity rates compared to children breastfed for ≥12 months and had no SSBs intake.[126] Similarly, in a longitudinal study of low-income African American children (3–5 years of age), SSBs intake was positively associated with 10-20% increase in the prevalence of obesity after two years.[192]

Of note, all of the above studies simply controlled for GDM status of mothers and did not examine the interaction of SSB, GDM, and EBF. To our knowledge, this is the first study that has examined the relationship among GDM status, EBF, and early exposure to

SSBs and their independent associations with obesity prevalence in children (1-5 years of age). Our results showed a significant GDM-EBF-SSBs interaction. In non-GDM offspring (1-5 years of age), EBF was protective against odds of obesity in both high and low SSBs consumers; however, EBF was more protective against obesity in low SSBs consumers. In GDM offspring, EBF was only protective against obesity when SSBs intake was low. Surprisingly, GDM offspring that were EBF and had high SSBs consumption, had similar 4- to 5-fold increase in odds of obesity compared to those not EBF with either low or high SSBs intake. These results suggest that interventions should focus on the combined protective effects of EBF and low SSBs intake particularly in GDM offspring.

There are several limitations of the current study to consider. The study sample included predominantly Hispanic participants; therefore, the findings may not be applicable to other populations. Replication of this study using heterogenous populations are warranted. Another limitation of the current study is that height and weight of some of the participants were measured several months apart from their interview date; therefore, BMI status may not be reflective of their BMI at the date of the interview. However, EBF was retrospectively collected on children 1-5 years of age, and height and weight measures were collected on the children at a later visit, when the child was between the ages 1-5 years. The current study also did not account for GDM mothers receiving treatment, and the severity of the GDM was not known. The current study did not assess maternal or paternal BMI, parity, or type of delivery mode for this study, all of which play a role in subsequent obesity and metabolic disease risk in the offspring. In addition, GDM status was self-reported and was not confirmed with medical records; however, validity research has shown self-reported GDM status to be accurate with 94% of self-reported GDM cases confirmed by a physician.[223]

This is the first study, to our knowledge, that assessed the interaction effects of EBF, SSBs intake, and GDM on the prevalence of obesity in predominantly Hispanic children. This study found that exposure to GDM and high SSB intake are independently associated with higher risk of obesity whereas EBF is independently associated with lower risk of obesity. This study also found that within GDM offspring, EBF is only associated with lower obesity levels if SSB intake is also low, whereas EBF is protective against obesity in non-GDM offspring regardless of high or low SSBs intake. These findings highlight the need for interventions targeting mothers with and without GDM to focus on promoting EBF and limiting SSBs intake in their children during the first years of life. Although EBF was associated with lower adds of obesity in offspring exposed to GDM *in utero*, this study suggests that the combination of EBF and low SSBs intake is still needed to combat childhood obesity.

Chapter 4: Independent Associations of Breastfeeding, and Sugar-Sweetened Beverages and 100% Fruit Juice During the First Year of Life with Subsequent Overweight and Obesity in Young Children Exposed to Gestational Diabetes Mellitus *in utero*

Vandyousefi S, Davis JN et al. Independent Associations of Breastfeeding, and Sugar-Sweetened Beverages and 100% Fruit Juice During the First Year of Life with Subsequent Overweight and Obesity in Young Children Exposed to Gestational Diabetes Mellitus in utero. *Diabetes Care*. (in Review).[3]

ABSTRACT

This prospective study assessed the relation of breastfeeding (BF) measures and sugar-sweetened beverages (SSBs) and fruit juice intake during the first year of life to subsequent overweight and obesity among young children (ages 2-5y) exposed to gestational diabetes (GDM) *in utero*. The analysis utilized data from the Study of Women, Infant Feeding and Type 2 Diabetes after GDM (SWIFT), a prospective, observational cohort of 1,035 women with GDM who delivered ≥35 weeks gestation (2008-2011) and attended in-person research visits annually from 6-9 weeks through 2 y postpartum. Mothers completed

[3] SV, JD and EP contributed to the acquisition of data, conceptualized the analysis plan, carried out the initial analyses, coordinated the interpretation of results, drafted the initial manuscript, and finalized the manuscript. EP collected data, carried out the initial analyses, and critically reviewed and revised the manuscript for important intellectual content. All authors critically reviewed the manuscript for important intellectual content.

monthly mailed surveys on breastfeeding and infant diet from birth to 1 y including intake of SSB, fruit juice, or No SSB/juice. Anthropometry and health at birth and 2-5 y (2013-2016) were obtained from electronic health records (n=845). Logistic regression models estimated adjusted odds ratios (aOR) and (95%CI) for infant diet intake with child (2-5 y) overweight (BMI $\geq 85^{th}$ to $<95^{th}$) or obesity (BMI$\leq 95^{th}$ percentile) adjusted for covariates (maternal age, BMI, GDM severity, income, race/ethnicity, newborn outcomes). Of 845 GDM infants, there were 52% male, 30% Hispanic, 23% Non-Hispanic White and 37% Asian, 60% BF≥6 mos., and 17% had SSB, and 51% had 100% fruit juice during the first year. Compared to normal weight children, those with obesity had shorter BF duration (6.1 vs 9.4 mos.; all $p<0.0001$) and were more likely to drink SSBs (26% vs 16%) and fruit juice (58% vs 50%); (all $p=0.007$). Breastfeeding duration and SSB and fruit juice intake were each independently associated with child obesity (all $p<0.05$). Compared to those BF≥6 mos. and with no SSB, those BF≥6 months with SSBs and Any fruit juice, had three- and 4-fold higher odds of obesity, respectively (aOR=2.9 95%CI:1.1-7.3; $p=0.03$, and aOR=3.6; 95%CI:1.2-11.5; $p=0.02$). Those BF<6 mos. with Any SSB and Any juice intake were 5- and 7.5-fold more likely to have obesity (aOR=4.6; 95%CI:1.9-11.8; $p=0.001$, and aOR=7.5, 95%CI:2.7-21.1, $p<0.0001$). This is the first study to prospectively evaluate BF and SSB and fruit juice intake during infancy in relation to subsequent weight status among children of GDM mothers. Longer BF and avoidance of SSB and fruit juice in early life may ameliorate future obesity in this high-risk population.

Keywords: Gestational diabetes mellitus, breastfeeding, infant diet, Sugar-Sweetened Beverages, 100% Fruit Juice, childhood obesity, Body Mass Index

INTRODUCTION

In the United States (U.S.), the prevalence of childhood obesity has increased and become a major health issue. Nearly one in five children and adolescents in U.S. are affected by obesity. In 2015-2016, the prevalence of overweight and obesity among U.S. children and adolescents (2-19 years of age) was 16.6% and 18.5%, respectively, about 14% of them being young children (2–5 years of age) with obesity.[1,238] Many prenatal effects like intrauterine exposure to gestational diabetes mellitus (GDM) as well as early life factors such as limited breastfeeding (BF) status, early age of introduction to complementary foods, or intake of sugar sweetened beverages (SSB) intake or fruit juice during infancy may contribute to higher weight gain, obesity, and metabolic complications among children.[7,125,136,137,239,240]

GDM, defined as "any degree of glucose intolerance with onset or first recognition during pregnancy", is one of the most common metabolic complications of pregnancy, affecting 2-10% of all pregnant women annually in the U.S.,[28] and up to 28% worldwide depending on population characteristics.[241] Elevated blood glucose in women with GDM passes through the placenta, increasing the blood glucose and insulin levels in their fetuses. Consequently, the fetus receives more energy than their requirements for growth, and therefore develop higher fat stores than those of mothers without GDM. There is also mounting evidence that intrauterine exposure to GDM may impact the fetal programming of obesity and metabolic disorders in offspring.[242] Therefore, offspring born to mothers with GDM have higher risk of being born with macrosomia and developing obesity later in life.[243] Although many studies have reported that offspring born to mothers with GDM are more likely to develop obesity and have accelerated BMI growth later in life [206,228,244], only a few studies, including those conducted by this lab, have prospectively assessed the infant growth[136,138,245] or weight status among young children aged 2-5 years exposed to GDM *in utero*.[137,240]

One of the factors decreasing risk of childhood obesity is feeding infants with breast milk. Breast milk has been recognized as the best source of nutrients for infants. Research shows that BF lowers the risk of obesity later in life by 26 percent.[136] While EBF for the first six months of a child's life is recommended [98,99], only about 25% of U.S. infants are EBF for 6-months [101] Women with GDM are less likely to EBF in the first hour postpartum and more likely to formula feed their children in the hospital than women without GDM [105,106]. A recent study by Gunderson et al. reported an inverse association between BF intensity and duration and infant ponderal growth and weight gain from birth to one year among GDM offspring.[136] Early exposure to SSBs and pure fruit juice are postnatal factors that may increase the risk of obesity in children. Considerable amount of calories (7.3% of total caloric intake) in the diet of U.S. children comes from SSBs.[246] In 2011-2014, about 63% of U.S. children and adolescents (2-19 years of age) consumed at least one SSB per day.[246] Intake of SSBs during infancy tracks into childhood, particularly consuming at least one SSB per day at age six years.[247] Findings are inconsistent with regard to early exposure to 100% fruit juice and obesity.[248]

The current study is the first to prospectively assess BF duration and intensity as well as SSBs and 100% fruit juice intake from birth through the first year of life in relation to subsequent weight status among children exposed to GDM in utero. (2-5) In this exclusively GDM study sample, the analysis accounts for glucose intolerance severity, perinatal outcomes, and sociodemographic as well as numerous early life factors known to affect child body weight and growth. Therefore, the overall study goal is to examine how early life modifiable factors (i.e., BF duration and intensity, and introduction to SSBs and 100% fruit juice) impact subsequent obesity prevalence in children aged 2-5 years who were exposed to maternal GDM.

METHODS

The study subjects were mother-infant pairs enrolled in the Study of Women, Infant Feeding and Type 2 Diabetes after GDM (SWIFT), a prospective, observational cohort of 1,035 women (20-45 years of age) diagnosed with GDM who were recruited during pregnancy and delivered a pregnancy of ≥35 weeks' gestation at a Kaiser Permanente Northern California (KPNC) hospital from 2008 to 2011. KPNC participants represent the diverse racial and ethnic groups in California. The SWIFT Study utilized quantitative methods by Piper et al.[249] to assess BF intensity and duration, and evaluate fetal and postnatal life exposures (i.e., severity of maternal glucose intolerance, gestational age, newborn health outcomes, infant diet and complementary feeding). SWIFT mothers consented to three in-person research visits from 6-9 weeks through two years postpartum and completed feeding diaries and monthly mailed surveys on infant diet, including BF intensity/duration, SSB, fruit juice and food intake from birth to one year. Maternal and neonatal health outcomes, maternal glucose tolerance severity (i.e., 3- hour oral glucose tolerance test, gestational age at diagnosis of GDM, GDM treatment), gestational weight gain, infant birth weight, and weights and heights in children at ages 2-5 years (2013-2016) were obtained from electronic health records (n=845).

Women were eligible to participate in the SWIFT study if they: 1) were 20-45 years old at delivery, 2) delivered a singleton, live birth ≥35 weeks gestation 3) diagnosed with GDM, 4) had no history of diabetes or other serious medical conditions (e.g., failure to thrive, physical impairment affecting feeding ability, chronic infectious disease, severe jaundice, or metabolic disorders), 5) their clinical medical and delivery records from the KPNC were available, 6) had no further pregnancy plan for the next two years, 7) were not on any medications that alter results of their blood glucose test, and 8) were able to speak English or Spanish. Eligibility criteria to participate in the SWIFT study was also based on infant feeding practices and intentions. At baseline (6-9 weeks postpartum), mothers with GDM were equally distributed into the two infant feeding groups including: 1) intensive lactation (breast milk only or <6 oz. per day of formula supplementation within 6-9 weeks postpartum, and intention to continue BF intensively for at least four months postpartum) and 2)intensive formula feeding (FF) (no breast milk or at least 14 oz. of formula per day for the first four months post-delivery) groups.[245,250]

This study utilized dietary data collected from birth to 1 year of age: a) interviewer-administered questionnaires at in-person visits, recorded feeding diaries, and monthly mailed questionnaires to report the frequency of BF and FF, including daily amounts of formula fed, and introduction of solids, type and amounts, introduction of fruit juice, sweetened beverages, water and other beverages, and type of beverage and amount of that beverage; b) anthropometric measures of weight and length at birth; and c) anthropometric measurements from pediatric well-child health plan visits from 2-5 years of age from electronic medical records.

Infant Feeding Measures

The SWIFT study selected mothers who reported they were currently exclusively or mostly BF (<6 oz. formula per 24 hours), or exclusively or mostly FF (>14 oz. formula per 24 hours) at 4-6 weeks postpartum and intending to continue at these same levels for four months[15]. At enrollment at 6-9 weeks postpartum (study baseline), some women who later transitioned to higher amounts of formula feeding were included in the study. BF duration (total months) was evaluated as a continuous variable and categorized as never BF, BF <6 months, and BF ≥6 months. In addition, type and quantity of first complementary foods, fruit juice, and SSBs were categorized by age at initiation for infants. Intake of beverages other than milk feeds was categorized as ever consuming SSB, 100% Juice, or No SSB/No Juice from birth to 1 year of age during infancy.

Standardized Clinical Anthropometric Measurements at ages 2 to 5 years

Clinical measurements of neonates were obtained in the supine position, including weight and length, and the size at birth was calculated from KPNC population percentiles.[251] Children were measured in a standing position with heels against a wall, and weight using a digital scale at ages 2 to 5 years, and these measurements were obtained from the electronic medical records.[252-254] Weight and heights were used to calculate BMI and categorized as normal, overweight or obese based on the CDC growth percentiles.[255]

Statistical Analysis

Summary statistics, graphical analyses, and frequency distributions were used to describe the data. Descriptive statistics (i.e., mean, SD, range, median and quartiles, histograms and Q-Q plots) assessed the distribution of the data. All analyses were performed with SAS version 9.4 (SAS, North Carolina, USA). Significance was denoted at $p<0.05$. Multinomial logistic regression models estimated odds ratio (95%CI) for infant diet (BF duration, intensity, and SSB intake) among the child BMI status categories (normal weight=<85th BMI percentile; overweight weight ≥85^{th}-<95^{th} BMI percentile; and ≥ 95^{th} BMI percentile) based on the CDC growth standards for children ages 2 to 5 years. The models estimated adjusted ORs accounting for potential confounders including race/ethnicity, parity (Primiparous vs. Multiparous), WIC participation, education level of mother (years of formal schooling), severity of prenatal glucose intolerance (3-hr 100g OGTT sum of z-scores for glucose at fasting, 1 hr., 2 hr. and 3 hr.), GDM treatment type (diet modification only vs. oral hypoglycemic agents or insulin), gestational age at diagnosis of GDM, and child age at BMI measurement.

RESULTS

Descriptive Statistics and Correlates

A total of 845 infants of the SWIFT mothers had dietary intake assessments during the first year of life, and weight and height measurements available in the KPNC health records at ages 2-5 years to calculate BMI percentiles; 13% of the children had the measurements for BMI available at age 4 years or older. About 23% of infants were Non-Hispanic White, 30% of Hispanic origin, 37% Asian, and 10% were from other races. **Table 13** shows maternal characteristics among BMI categories for GDM exposed children. Maternal age, smoking at baseline, and type of GDM treatment, gestational weight gain, and parity did not differ among the child BMI categories. Children with obesity had mothers with significantly higher pre-pregnancy BMI (p<0.0001), increased GDM severity (prenatal 3-hr 100 g OGTT sum of z-scores) (p=0.002), and lower level of education (p<0.0001) than mothers of normal- and overweight children. Additionally, children with obesity compared to children with normal weight and overweight had a significantly earlier gestational age at maternal GDM diagnosis (mean (SD) gestational age, 23.2 (8.7) weeks vs 25.9 (6.7) and 25.7 (6.7) weeks; p= 0.006) and were more likely to participate in the Special Supplemental Nutrition Program for Women, Infants, and Children (43% vs 28% and 22% ; p<0.0001).

Table 13. Maternal characteristics among young children aged 2 to 5 years exposed to GDM *in utero*.

Maternal Characteristics[a]	All n=845	Child BMI Categories at Ages 2 to 5 Years: Normal < 85th percentile n=647	Overweight 85th to <95th percentile n=107	Obesity ≥95th percentile n=91	P-value[b]
Maternal Age (years)	33.4 ± 4.9	33.5 ± 4.8	33.3 ± 4.4	32.7 ± 5.5	0.12
Education (years)	14.9 ± 2.9	15.1 ± 2.9	14.6 ± 2.7	13.6 ± 2.7	**<0.0001**
Race/ethnicity, n (%)					
Non-Hispanic White	196 (23)	150 (24)	29 (28)	17 (19)	**0.002**
Non-Hispanic Black	68 (8)	47 (8)	8 (7)	13 (14)	
Hispanic	251 (30)	173 (27)	40 (39)	38 (41)	
Asian	313 (37)	263 (40)	28 (25)	22 (24)	
Other	17 (2)	14 (2)	2 (2)	1 (1)	
WIC recipient n (%)	211 (25)	142 (22)	29 (28)	40 (43)	**<0.0001**
Pre-pregnancy BMI kg/m^2	29.5 ± 7.2	28.5 ± 6.8	31.7 ± 8.3	33.4 ± 6.9	**<0.0001**
Pre-pregnancy weight status, n (%)					
BMI < 25 kg/m^2	269 (32)	236 (36)	22 (22)	11 (12)	**<0.0001**
25 kg/m^2 ≤BMI< 30 kg/m^2	247 (29)	197 (30)	33 (31)	17 (19)	
BMI ≥ 30 kg/m^2	329 (39)	214 (33)	52 (48)	63 (69)	
Prenatal 3-hr OGTT z-score	0.0 ± 2.7	-0.1 ± 2.6	-0.4 ± 2.4	0.9 ± 3.6	**0.002**
GDM Treatment Type, n (%)					
Diet only	593 (70)	459 (71)	75 (70)	59 (65)	0.45
Oral hypoglycemic agents	227 (27)	167 (26)	29 (28)	31 (34)	
Insulin	25 (3)	20 (3)	2 (2)	1 (1)	
Gestational age at GDM Diagnosis (weeks)	25.5 ± 7.0	25.7 ± 6.7	25.9 ± 6.7	23.2 ± 8.5	**0.006**
Gestational weight gain (kg)	10.5 ± 6.9	10.6 ± 6.3	10.2 ± 9.1	10.1 ± 7.5	0.80
Parity, n (%) birth order					
Primiparous	325 (38)	240 (38)	48 (45)	33 (36)	0.29
Multiparous	520 (62)	407 (63)	59 (55)	58 (64)	

Table 13. Maternal characteristics among young children aged 2 to 5 years exposed to GDM *in utero*.

Maternal Characteristics[a]	All n=845	Child BMI Categories at Ages 2 to 5 Years			
		Normal < 85th percentile n=647	Overweight 85th to <95th percentile n=107	Obesity ≥95th percentile n=91	P-value[b]
Gestational weight gain relative to IOM					
Below IOM	279 (33)	221 (34)	34 (32)	24 (26)	0.32
Within IOM	274 (32)	214 (33)	31 (29)	29 (32)	
Above IOM	292 (35)	212 (32)	42 (40)	38 (42)	
Infant feeding intention score	7.3 ± 1.1	7.3 ± 1.1	7.3 ± 1.0	7.3 ± 1.1	0.92
Smoking Status at baseline, n (%)					
Current	28 (3)	9 (3)	4 (4)	5 (6)	0.18
Past (Pre-conception)	146 (17)	107 (17)	26 (23)	13 (14)	
Never	671 (79)	521 (80)	77 (73)	73 (80)	

[a] Values are mean ± SD unless otherwise stated.
[b] t-tests and chi-square tests were run to assess difference in means or % between non-GDM and GDM groups. Significant *p*-values (<0.05) are bolded.

Physical characteristics, BF duration and intensity scores, and overweight and obesity prevalence of children are shown in **Table 14**. There were no significant differences in child age at the BMI measurement, sex, age of initiation of solids and complementary foods, infant feeding intention score, and parity among normal weight participants and children with overweight and obesity. About half of the children were male with an average age of three years at the time of BMI measurement. Compared to normal weight, offspring with overweight and obesity had significantly higher birthweight (3.3 vs. 3.7 and 3.5 kg.; $p<0.0001$) and birth length (50.4 vs. 51 and 51 cm; $p=0.01$). Compared to other ethnicities/races, Hispanics had significantly higher rates of overweight (39%) and obesity (41%) ($p=0.002$). Children with obesity were more likely to be large-for-gestational age (LGA) compared to those with overweight and normal weight (44% vs. 25% and 17%; $p<0.0001$). Participants were breastfed for an average of nine months.

All children were exposed to GDM *in utero*, and 60% (n=504) were breastfed for at least six months, and 17% (n=141) reported any SSB intake before the first year of life, and 51% (n=436) reported any 100% juice intake the first year of life. Compared to children with normal and overweight, children with obesity were breastfed for significantly shorter period (9.4 and 8.5 vs. 6.1 months; $p<0.0001$). Children with obesity had significantly lower rates of being breastfed for at least six months compared to those with normal- and over-weight (40% vs 60% and 62%; $p=0.0002$). Compared to offspring with normal-and over-weight, children with obesity had higher rates of SSBs (26% vs. 16% and 18%) and 100% fruit juice (58% vs. 50% and 53%) consumption (all $p=0.007$). Among offspring with obesity, rate of SSBs and 100% fruit juice consumers was significantly higher than those with no SSBs or 100% fruit juice intake (26% and 58% vs. 16%; *p*=0.007). Additionally, offspring with obesity had significantly lower rates of being exclusively/mostly breastfed and higher rates of exclusively/mostly being formula fed than children with normal-and over-weight (**Table 14**; all *p*=0.02).

Table 14. Infant characteristics among young children aged 2 to 5 years exposed to GDM *in utero*.

Infant Characteristics[a]	All n=845	Child BMI Categories at Ages 2 to 5 Years: Normal <85th percentile n=647	Overweight 85th to <95th percentile n=107	Obesity ≥95th percentile n=91	P-value[b]
Infant sex, n (%)					
Male	438 (52)	334 (52)	53 (52)	51 (56)	0.80
Birth weight (g)	3396 ±502	3337 ±492	3532 ±504	3645 ±477	**<0.0001**
Birth length (cm)	50.5 ±2.4	50.4 ±2.5	50.9 ±2.3	51.0 ±2.3	**0.01**
Size-for-Gestational Age					
Large (LGA)	181 (21)	114 (17)	27 (25)	40 (44)	**<0.0001**
Appropriate (AGA)	645 (77)	515 (80)	79 (74)	51 (56)	
Small (SGA)	19 (2)	18 (3)	1 (1)	0 (0)	
Gestational age (weeks)	39.0 ±1.2	39.0 ±1.2	39.2 ±1.0	39.1 ±1.2	0.23
Child age at the BMI measurement (months)	40.6 ±6.2	40.5 ±6.2	40.5 ±6.1	40.9 ±6.4	0.82
Gestational age, n (%)					
35-36 weeks	42 (5)	36 (5)	3 (3)	3 (3)	0.22
37-39 weeks	597 (71)	464 (72)	74 (68)	59 (66)	
40 weeks or more	206 (24)	147 (23)	30 (29)	29 (31)	
Birth weight, n (%)					
1,500 – 2,499 g	25 (3)	24 (4)	1 (1)	0 (0)	**0.0002**
2,500 – 2,999 g	155 (18)	131 (20)	17 (16)	7 (8)	
3,000 – 3,999 g	571 (68)	435 (67)	73 (68)	63 (69)	
4,000 g – 4,499 g	75 (9)	45 (7)	12 (11)	18 (20)	
4,500 g or more	19 (2)	12 (2)	4 (4)	3 (3)	
Breastfeeding duration 2 groups					
< 6 months	341 (40)	243 (38)	43 (40)	55 (60)	**0.0002**
≥ 6 months	504 (60)	404 (62)	64 (60)	36 (40)	
Breastfeeding intensity groups at 6-9 weeks					
Exclusively Breast Feeding	185 (22)	150 (23)	25 (23)	10 (11)	**0.0206**
Mostly Breast Feeding	344 (41)	270 (42)	42 (39)	32 (35)	
Mostly Formula Feeding	178 (21)	131 (20)	22 (20)	25 (27)	
Exclusively Formula Feeding	138 (16)	96 (15)	18 (18)	24 (27)	

Table 14. Infant characteristics among young children aged 2 to 5 years exposed to GDM *in utero*.

Infant Characteristics[a]	All n=845	Child BMI Categories at Ages 2 to 5 Years: Normal <85th percentile n=647	Overweight 85th to <95th percentile n=107	Obesity ≥95th percentile n=91	P-value[b]
Breastfeeding Intensity and Duration sum of ratios (Birth to 6 months)	3.9 ± 2.3	3.9 ± 2.2	3.7 ± 2.2	2.8 ± 2.3	**<0.0001**
Breastfeeding Intensity and Duration sum of ratios (Birth to 12 months)	6.0 ± 4.6	6.4 ± 4.6	5.5 ± 4.2	4.2 ± 4.3	**<0.0001**
Breastfeeding Intensity and Duration sum of ratios (Birth to 12 months), Groups					
Score < 3	308 (37)	218 (33)	39 (36)	51 (56)	**0.0002**
Score ≥ 3	537 (63)	429 (67)	68 (64)	40 (44)	
Score < 6	447 (53)	319 (49)	62 (56)	66 (72)	**<0.0001**
Score ≥ 6	398 (47)	328 (51)	45 (44)	25 (28)	
Score < 9	522 (64)	395 (60)	80 (74)	72 (79)	**0.0002**
Score ≥ 9	293 (36)	252 (40)	27 (26)	19 (21)	
Beverage feeding					
Sugar Sweetened Liquids ever	141 (17)	99 (16)	19 (18)	23 (26)	**0.007**
100% Fruit Juice	436 (51)	326 (50)	57 (53)	53 (58)	
None	268 (32)	222 (34)	31 (29)	15 (16)	
Initiation of solid foods					
≤ 4 months (Early)	133 (16)	97 (15)	16 (15)	20 (22)	0.24
> 4 months (Later)	712 (84)	550 (85)	91 (85)	71 (78)	
≤ 6 months (Early)	657 (78)	497 (77)	84 (78)	76 (83)	0.43
> 6 months (Later)	188 (22)	150 (23)	23 (22)	15 (17)	

[a] Values are mean ± SD unless otherwise stated.
[b] t-tests and chi-square tests were run to assess difference in means or % between non-GDM and GDM groups.
Significant *p*-values (<0.05) are bolded.

Logistic Regression Analyses

Results from the multinomial logistic regression are shown in **Table 15**. Variables such as child age and sex that did not vary among all three BMI categories were not included in the model. Thirteen percent (n=107) of children were overweight (≥95th BMI percentile) and 11% (n=91) had obesity (≥95th BM percentile). Compared to normal weight children, children with overweight or obesity had higher odds of being born LGA (OR=1.61, 95%CI 1.03-1.19, *p*=0.04; OR=3.46, 95%CI 2.24-5.26, *p*<0.0001). Hispanics were 59% and 68% more likely to have overweight and obesity compared to NHW children (both *p*<0.05). BF duration and intensity scores were inversely associated with obesity prevalence in children 2-5 years of age (all *p*<0.01). Compared to normal weight offspring who were breastfed for at least six months, children who were breastfed for shorter than six months had significantly higher odds of obesity (OR=2.33, 95%CI 1.48-3.67, *p*=0.0008). However, there were no significant differences between the BF groups in children with overweight compared to normal weight offspring. Greater breastfeeding intensity and duration (12-month combined) score was linked to lower odds of overweight and obesity, independent of covariates (*p*=0.009, *p*=0.003). Children who had obesity and overweight had 3.46- and 1.6-times higher odds of being born LGA than normal weight children (OR=3.46, 95%CI 2.24-5.26, *p*<0.0001; OR=1.61, 95%CI 1.03-2.54, *p*=0.04).

There was an overall significant association between beverage intake and BMI percentiles in the model (*p*=0.03). Both SSBs and unsweetened 100% juice intakes were independently associated with higher odds of obesity in children (OR=3.00, 95%CI 1.48-6.00, *p*=0.002 and OR=2.24, 95%CI 1.23-4.10; *p*=0.008). However, these associations were attenuated to trends for offspring with BMI- for-age ≥85th to 95th percentiles. There was an overall significant relationship between the stratified beverage and BF intake and odds of overweight and obesity in the model (p=0.03). Compared to normal weight children who were breastfed for at least six months and had no SSBs intake (referent), offspring who were BF and had unsweetened 100% juice and SSBs intake had three and four folds higher odds of obesity (OR=3.19, 95%CI 1.07-9.53, p=0.03; OR=3.67, p=0.02 and 95%CI 1.18-11.45, p=0.02). Compared to the referent group, children who were BF<6months or not BF and had no SSBs or 100% juice intake had three times higher odds of obesity (OR=2.85, 95% CI 1.11-7.29, p=0.03). Compared to normal weight children who were breastfed with no SSBs or 100% juice intake, those who were not breastfed or were breastfed for shorter than six months with any SSBs and 100% juice intake were five and eight times more likely to have obesity (OR=4.63, 95%CI 1.82-11.80, p=0.001; OR=7.53, 95%CI 2.68-21.10, p<0.0001). **Figure 5** displays the odds of obesity by BF-Beverage groups among all children (2-5 years of age) exposed to GDM *in utero*.

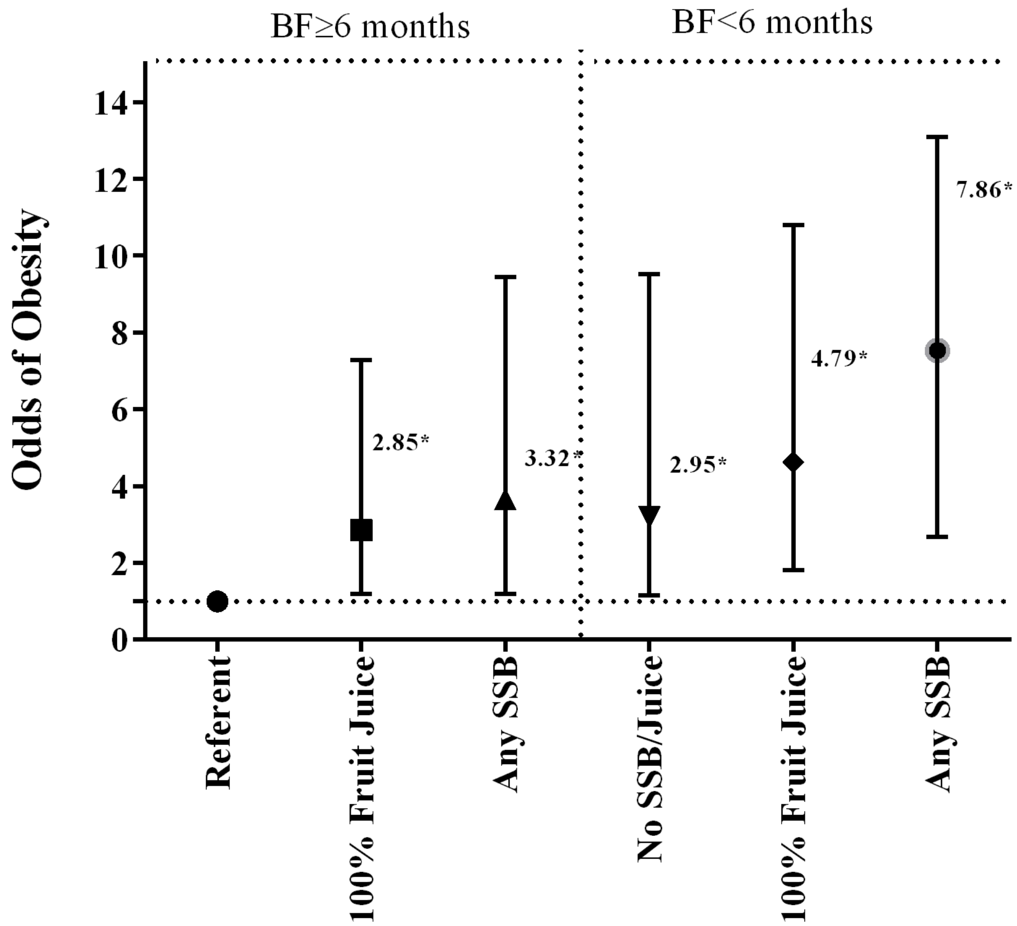

Figure 5. Obesity prevalence among 2-5 years old children by BF-SSBs groups
*Significantly lower odds compared to referent

Table 15. Logistic multinomial regression of prenatal and early postnatal influences on the subsequent prevalence of obesity in children aged 2 to 5 years exposed to GDM *in utero*

Variables	**Overall P**	Child BMI Categories at Ages 2 to 5 Years: Overweight (85th to <95th%tile) *P*[a]	Overweight OR[b] (95% CI)	Obesity (≥95th%tile) *P*[a]	Obesity OR[b] (95% CI)
Breastfeeding Duration (BF) categories	**0.001**				
BF (≥6 months)		Referent	1.00	-----	1.00
Short BF (<6 months)		0.69	1.09 (0.72,1.66)	**0.0008**	2.33 (1.48, 3.67)
Breastfeeding Intensity and Duration Score Sum of 12 Monthly Ratios (Birth to 12 months of age)					
Score ≥ 6	**0.0005**	Referent	1.00	-----	1.00
Score < 6		0.32	1.38 (0.91, 2.10)	**0.0004**	2.45 (1.50, 4.10)
Score ≥ 9	**0.007**	Referent	1.00	-----	1.00
Score < 9		**0.007**	1.89 (1.18, 3.02)	**0.002**	2.35 (1.36, 4.07)
Beverage Feeding (Birth to 1 year)	**0.03**				
No SSB/Juice		Referent	1.00	-----	1.00
SSB Ever		0.33	1.36 (0.72, 2.52)	**0.002**	3.00 (1.48, 6.00)
100% Fruit Juice Only		0.36	1.24 (0.77, 2.00)	**0.008**	2.24 (1.23, 4.10)
Covariate Adjusted SSBs Groups Stratified by BF Status					
Race/Ethnicity, n (%)	**0.02**				
None-Hispanics		Referent	1.00	-----	1.00
Hispanics		**0.04**	1.59 (1.03, 2.45)	**0.03**	1.68 (1.05, 2.67)
Prenatal 3-hr 100 g OGTT sum of z-scores	**0.006**	0.41	0.96 (1.03, 1.19)	**0.02**	1.11 (1.01, 1.17)
Size-for-Gestational Age	**<0.0001**	0.03			
Appropriate (AGA)/ Small (SGA)		Referent	1.00	-----	1.00
Large (LGA)		**0.04**	1.61 (1.03, 2.54)	**<0.0001**	3.46 (2.24, 5.26)
Maternal Gestational Weight Gain (kg)	0.80	0.55	0.99 (0.96, 1.02)	0.14	0.97 (0.94, 1.01)
Gestational age at GDM diagnosis (weeks)	**0.006**	0.66	1.01 (0.97-1.04)	**0.003**	0.95 (0.93, 0.98)
BF-SSB Groups (Intake Ever Birth to 1 year)	**0.03**				
BF, No SSB/Juice		Referent	1.00	-----	1.00
BF, Pure Juice		0.57	1.26 (0.57, 2.77)	**0.03**	2.85 (1.11,7.29)
BF, SSB Ever		0.40	1.43 (0.62, 3.26)	**0.02**	3.67 (1.18, 11.45)
Short BF, No SSB/Juice		0.39	1.29 (0.71, 2.35)	**0.03**	3.19 (1.07, 9.53)
Short BF, Pure Juice		0.47	1.26 (0.66, 2.43)	**0.001**	4.63 (1.82, 11.80)
Short BF, SSB Ever		0.44	1.37 (0.58, 3.26)	**<0.0001**	7.53 (2.68, 21.10)

[a]Significant *P*-values (<0.05) are bolded; [b]OR: Odds Ratio; The following covariates were used in the regression model: Child sex/ethnicity, prenatal 3-hr 100 g OGTT sum of z-scores, size-for-gestational age, and gestational age at GDM diagnosis.

DISCUSSION

This prospective study of infants of mothers with GDM is the first prospective study to show SSB and 100% fruit juice intakes during the first year of life were independently associated with increased obesity risk at 2-5 years of age whereas higher BF duration (≥ 6months) and intensity (score>9) were independently associated with decreased risk of obesity in GDM offspring. Our findings show that low BF duration and intensity score and high SSBs and 100% fruit juice intake in infancy were 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 to GDM *in utero*. This finding was consistent with those of the SWIFT Offspring Investigators.[137] A previous analysis of 382 SWIFT children (2-5 years of age) by the SWIFT Offspring Investigators showed that higher BF intensity and duration were associated with lower odds of obesity in GDM offspring. Although many studies including the current study have reported an inverse association between exclusive BF (EBF) and body mass index (BMI) and excessive weight gain later in life [256], the evidence for the association of BF and SSBs intake with slower infant growth is sparse and majority of the studies that have assessed such association are retrospective and rely on recall of BF duration. The only prospective study that has found a protective association is the SWIFT offspring study by Gunderson et al. They showed in the SWIFT cohort that greater BF intensity and duration were associated with slower ponderal growth and less weight gain from birth to one year among infants of mothers with GDM.[136]

Our main finding was that compared to children who were breastfed for at least six months and had no SSBs or 100% fruit juice intake (referent) during the first year of life, offspring who were breastfed for at least six months and consumed 100% fruit juice and SSBs in infancy had 2.9 and 3.7 times higher odds of obesity at 2-5 years of age. Odds ratios were about 1.5 times higher for those who were breastfed for shorter than six months. Findings of the current study were consistent with a recent cross-sectional study of 3,707 mothers and their children (1-5 years of age) participating in WIC clinics in Los Angeles, CA in regard to association of BF duration and SSBs intake with obesity prevalence. The above study assessed the association of EBF during the first year of life and SSBs intake at age 1-5 years with obesity prevalence in offspring born to mothers with and without GDM and showed that offspring who were BF exclusively for at least six months and had no current SSBs intake had lower odds of high-weight- for-length (1-<2 years of age) and obesity (2-5 years of age) than those EBF≥6 months with high SSBs intake (i.e.; >3 servings per day) regardless of GDM status of their mothers throughout pregnancy.[240] Of note, the above study was a cross-sectional study that assessed the mentioned association with obesity status in much younger children born to healthy (n=3,237) and GDM (n=470) mothers and did not account for SSBs during the first year of life nor did they control for GDM severity, gestational weight gain, gestational age at GDM diagnosis, and infant size at birth. Also, the BF intensity score and 100% fruit juice intake during the first year of life were not included in the mentioned study. Strengths of the current SWIFT study include the meticulous methods of diet assessment of GDM offspring during the first year of life, including quantitative methods of BF intensity measurement[249], the very wellcharacterized fetal life exposure, large sample size, racial/ethnic diversity of participants, prospective design and longitudinal follow up of outcomes, and comprehensive covariates including GDM severity, gestational weight gain, infant size at birth, gestational age at GDM diagnosis, and prenatal 3-hr 100 g OGTT sum of z-scores.[137]

While research shows that BF is linked to lower obesity prevalence in offspring, only a few studies have shown the impact of BF in offspring exposed to GDM[7,136,240] and the mechanism behind this association has not been well studied. Human milk oligosaccharide (HMOs) serve as a fuel for microbiota in human milk and therefore breastfed infants develop healthier gut microbiome than formula fed children because of consumption of human milk microbiota, which is linked to reduced obesity risk in children.[237] It is still unknown whether human milk *constituents* such as HMOs, leptin, insulin, and other hormones and nutrients in milk of mothers particularly those with GDM play a role in reducing obesity rates in offspring and more research is warranted.

The current study is the first prospective study to examine the association between 100% fruit juice intake during the first year of life and obesity status in GDM exposed children (2-5 years of age). Children who were BF for at least six months and had 100% fruit juice intake during the first year of life had about three times higher odds of obesity than those with no intake of SSBs 100% fruit juice. Research on the 100% fruit juice intake during the first year of life with future obesity prevalence is sparse and the current findings on early exposure to 100% fruit juice and obesity are inconclusive[257-259] with some studies linking 100% fruit juice to increased BMI *z* score at age 1-6 years [248], while other studies found no association between 100% fruit juice intake and obesity in children.[260] A meta-analysis of 4,657 articles reported that eight prospective cohort studies with 34, 470 children (1-18 years of age) found an associations between 100% fruit juice (6-8 oz./day) consumption and BMI *z* score controlling for total energy intake only in children ages 1 to 6 years. However, the mentioned association was not clinically significant.[248] In contrast, a systematic review of the literature that were published during 1995-2013 reported that majority of the studies did not find a significant association between 100% fruit juice intake and weight and adiposity in children. [260] However, the above studies did not examine the independent and additive associations of BF duration and intensity scores with SSBs and 100% fruit juice intake during the first year of life on obesity status. Nor did the above studies target an exclusive GDM population, while controlling for GDM severity, gestational weight gain, and gestational age at GDM diagnosis.

There are a few limitations of the current study to consider. The current study did not include observational or physiological measures of breastfeeding. Residual confounding associated with measurement error for beverage and dietary intake covariates may have affected results. Also the current study was conducted in California[101], which is a state with higher BF rates than other areas in the United States. Another limitation is that pre-pregnancy maternal BMI was self-reported, and evidence shows that Hispanic adults underreport overweight/obesity prevalence by 4.1-5.1%[261]. However, this study did not use self-reported anthropometrics, and heights and weights of children were measured by trained staff.

In conclusion, findings of this study highlight the need for interventions targeting women with GDM to focus on promoting higher BF duration and intensity and lower SSBs and 100% fruit juice in diet of their children during the first years of life. In conclusion, this study suggests that the combination of BF and no SSBs and 100% fruit juice intake should be warranted to combat childhood obesity specially in offspring exposed to intrauterine GDM.

Chapter 5: Conclusions and Public Health Implications

This research is one of the first to examine the independent and interaction effects of Gestational Diabetes Mellitus (GDM), Breastfeeding (BF), both exclusive and any BF, duration and intensity, and SSBs and 100% fruit juice intake on weight gain, obesity, prediabetes, and MetS prevalence in children from birth to 19 years of age who were born to mothers with GDM versus non-GDM population. Specifically, this dissertation examined: 1) the independent and interaction effects of GDM and BF duration (≥1month vs <1month) on the prevalence of prediabetes and MetS in Hispanic children (8 to 19 years of age) born to mothers with and without GDM; 2) the independent and interaction effects of GDM, exclusive BF duration (≥6 months vs. <6months), and SSBs intake (i.e.; low SSB (≤1 serving/day), medium SSB (>1 and ≤3 servings/day), and high SSB (>3 servings/day)) with offspring's high weight-for-length BMI percentile rate at 12 months through two years of age and overweight and obesity prevalence among at 2-5 years of age; and 3) the prospective relationship between early life infant feeding (BF duration (≥6 months vs. <6months) and intensity score (≥9 vs. <9), and introduction to SSBs (Any SSBs/juice vs. 100% fruit Juice vs. No SSBs/juice) on overweight and obesity prevalence among GDM offspring at 2-5 years of age.

The first analysis from the SOLAR cohort (Chapter 2) found that BF for at least one month was associated with lower odds of ever and persistent MetS and prediabetes in both GDM and non-GDM offspring. Only a few studies have shown an independent association between GDM and abnormal glucose tolerance and cardio metabolic risk[75,77,262] in children and the current study was the first to assess the association between BF and GDM status on the prevalence of the Metabolic Syndrome (MetS) and prediabetes in young children (8-19 years), particularly in a high-risk Hispanic population. Finding from this study fill a gap in the literature by assessing the mentioned association in offspring exposed to GDM *in utero*. Of note, the majority of studies that assessed the mentioned association, including the current study, were not collected in a longitudinal and prospective setting, had small sample sizes in homogenous populations, did not control for GDM severity and other maternal and prenatal factors affecting prediabetes and MetS risk in offspring. In addition, most of the studies collected self-reported data in a retrospective design. Therefore, further large-scale prospective longitudinal interventions are warranted to draw a firm conclusion.

The second analysis (chapter 3) showed that GDM and high SSBs intake were independently associated with higher odds of high weight for length in offspring 1-<2 years of age and obesity at 2-5 years of age, whereas, EBF for at least six months was linked to lower odds of high weight for length in offspring ≤12 months to <2 years of age and obesity at 2-5 years of age. Findings of this study were consistent with previous studies.[263] Of note, the previous and current studies were not longitudinal prospective cohorts, did not account for SSBs during the first year of life nor did they control for GDM severity, gestational weight gain, gestational age at GDM diagnosis. Our third analysis (chapter 4) findings were consistent with our previous findings, showing that higher BF duration (≥6months) and intensity score (≥9) were associated with decreased odds of future obesity whereas SSBs and 100% fruit juice intake during the first year of life, were independently associated with higher obesity risk at 2-5 years of age in children exposed to GDM *in utero*. Our third study is one of the first prospective studies that assessed the mentioned association in an exclusive GDM population accounting for GDM severity, maternal age at GDM diagnosis, and gestational weight gain. However, our third analysis was not a longitudinal research and did not have a non-GDM control group.

There is debate and question about whether breast milk of mothers with GDM and early exposure to SSBs and 100% fruit juice affect health outcomes in offspring. Findings of this dissertation help clarify the answer to this question and support the current recommendations regarding the beneficial effects of breast milk and its components on health of children compared to other foods including formula, SSBs, Juice, and solid foods in GDM offspring. Although several studies including the current research findings indicate that BF regardless of GDM status of mothers reduce risk of many health complications in mothers and their children[7,136,162,240,264], there are many factors that may impact a mother's decision in regard to BF. Difficulties of BF may be higher for women with GDM because of delayed onset of lactogenesis and medical management of mothers and their newborns.[60] One of the main barriers of BF is lack of knowledge about protective impact of BF on health of children. Unfortunately, many women in the U.S. are uncertain about what to expect with BF and are not aware of BF techniques. Although there are several BF campaigns and programs that encourage women to breastfeed, majority of them only provide written educational materials as their source of information.[265] It is important to conduct more effective programs that provide more effective BF education and involvement to influence their attitudes about BF.

Numerous interventions have been conducted globally to increase BF rate and duration, provide practical, psychological, and direct supports to mothers on how to breastfeed and overcome BF barriers. There are numerous types of interventions to promote exclusive BF rates including educational, home and family support, in-person group classes, professional and peer support, one-on-one counseling, telephone, electronic, and web-based counseling and education, and community interventions. There are also BF tracker applications that mothers can download and use, which help mothers to keep track of BF and learn more about BF. All types of interventions may be delivered before, during, and after pregnancy. There is strong evidence that BF promotion interventions have been successful in increasing BF initiation, duration, and exclusivity. A meta-analysis of 7,201 randomized controlled trials (RCTs) showed that educational interventions on BF that were thoroughly explained to women, were more effective than routine guidance from the health service on BF.[266] An intervention study conducted in Australia examined the effectiveness of an internet-based EBF rate promotion, reported that internet-based intervention programs were successful at increasing EBF rate in women who had hard time BF their child.[267] A quasi-experimental study examined the effectiveness of a family-centered BF education program on encouraging EBF up to six months and improving attitude and knowledge of women's and their families reported that the intervention group was more likely to EBF, had higher family support, and had improved knowledge level of bf than the control group.[268] A systematic review of 23,977 suggested a concurrent involvement of interventions including health systems, home and family, and the community environment to improve BF rate, duration, and continuation.[269]

A systematic review and meta-analysis of 27 RCTs including 36,051 mothers suggested that considering a multicomponent intervention improves effectiveness of the BF promotion programs.[270] Although research shows that BF interventions have been successful in promoting EBF initiation, duration, and continuation rates in women, none of them have targeted the high-risk pregnant groups including women with GDM and other complications during pregnancy who experience more difficulties BF[60] and may need more support to breastfeed their child. Considering barriers of BF and our findings in regard to the important role BF plays in lowering the risk of childhood obesity and other metabolic disease in offspring of women who had GDM during pregnancy, there is a need for interventions promoting EBF in high-risk groups GDM women are warranted.

When conducting interventions with GDM mothers, it is important to recruit mothers before or at their GDM diagnosis to help control their GDM by providing education and guidance on healthy diet and BF to control their GDM and prepare them for a successful BF experience. Barriers to consider with interventions to promote BF are social norms and employment of mothers. Mother's employment is one of the leading barriers for early weaning and stopping BF. It is recommended that organizations and workplaces to provide maternity leave and increase the number of on-site rooms for BF. Additionally, countries adopting legislation reflecting the provisions of the *International Code of Marketing of Breast-milk Substitutes* (WHO Code), which is "an international health policy framework for BF promotion", have higher BF rates. Of note, U.S. was one of the two countries that refused to implement the provisions of the code and enact legislation.[271] A legal action is needed to overcome these barriers and improve BF rate nationwide. Health care professionals including obstetrician-gynecologists, registered dietitians, nurses, pediatricians, and other providers of maternal and child care also play an important role with regard to promoting and supporting women's decisions about BF.

The current dissertation found that offspring who had high SSBs intake and 100% fruit juice had higher odds of obesity. Toddlers and young children have the highest fruit juice intake among all age groups in U.S. and most U.S. children exceed the recommended limits for added sugars in the diet and a large portion of their daily calorie comes from SSBs and 100% fruit juice. [246] Higher weight gain and BMI z score in SSBs consumers is mainly due to increased total calorie intake from high sugar content, mainly fructose, in SSBs.[239,272-274] Also, research shows that SSBs and high sugar snacks are less satiating than intake of protein or fat, therefore, children who have high intake of SSBs feel hungrier and consequently have higher total calorie intake than children who do not drink SSBs.[275] Increased SSBs consumption among U.S. children has become a concern and there are controversies on banning of the sale of large-volume servings of SSBs. A few U.S. cities have started adding taxes, up to two cents per ounce, on SSBs in order to lower consumer demand for SSBs and help improve purchasing healthier food.[276]

Although drinking 100% juice is recommended as a healthy beverage option, there has been a lot of controversy about intake of 100% fruit juice and obesity in children.[248,257-259] Our findings did not support this recommendation and instead we agree with Wojcicki et al.'s recommendation on that the U.S. Department of Agriculture's Child and Adult Food Care Program to promote the elimination of 100% fruit juice to reduce the prevalence of childhood obesity.[259] We support the American Academy of Pediatrics' recommendation in regard to not introducing any SSBs or 100% juice to diet of infants younger than one year of age, maximum of 4 ounces per day 100% juice products for 1-3 years old children, and 4-6 ounces for children ages 4-6 years.[277] Considering the adverse health outcomes of SSBs and how rates of SSBs intake among young children are increasing, there is a need for interventions that target reducing SSBs consumption. Numerous interventions including educational and behavioral interventions (campaigns, workshops, and advertising), price increase and taxation on SSBs, limiting the availability of SSBs at schools, restaurants, and stores, promoting healthy beverages and water intake, labeling and added sugar reduction, and policy and environmental changes have been some of the principal strategies targeting SSBs intake reduction.[278,279]

Although there are several proposed interventions to decrease SSBs consumption, strength and availability of evidence supporting these interventions varies. A systematic review and meta-analysis of 12 school-based and four community- and home-based interventions found a moderate effectiveness of educational and behavioral interventions on reducing SSB intake among children aged 4 to 16 years.[280] Another systematic review and meta-analysis of 90 RCTs reported that public health interventions particularly nutritional education/counseling interventions were moderately effective at decreasing SSBs and increasing water intakes in children. In addition, behavioral interventions within the home environment had greater effects on decreasing SSBs intake in children than school-based interventions.[281] A couple of systematic review studies found little evidence that water promotion interventions reduce SSB intake.[281,282] Of note, there is no strong evidence on effectiveness of SSB intake reduction strategies in young children, highlighting the need to conduct interventions targeting SSB reduction in mothers of young (birth-2 y) children.

In summary, higher breastfeeding intensity and duration and lower SSBs decreases childhood obesity, diabetes, and metabolic syndrome in offspring exposed to GDM. Findings of this research highlight the need to encourage mothers diagnosed with gestational diabetes during pregnancy to breastfeed their children for at least six months or longer and to not expose their toddlers to sugar sweetened beverages intake. These are two highly modifiable infant and child feeding approaches that can have profound effects on decreasing obesity rates and related metabolic disease risk in high-risk populations.

Chapter 6: Future Plans and Avenues of Research

Starting in the Fall of 2019, I will begin a postdoctoral position in Nutrition. I am the process of interviewing for several postdoctoral fellows at various accredited universities and hope to accept an offer in the next month. As a postdoctoral fellow, I am interested in conducting research on current nutrition issues, especially maternal, prenatal, and early life nutrition, as well as familiarizing myself with other related research areas. I am interested in expanding my exploration into how different factors like dietary intake, environmental, and public health factors impact obesity and other related complications across all age groups. I am also interested in examining how dietary related behaviors impact obesity, diabetes, and related metabolic diseases risk in youth. I would also like to obtain more training and knowledge on how to conduct controlled feeding trials. My goal is to expand my research, analytical, and grant writing skills, which will help me achieve my goals of becoming a tenure-track faculty member in Nutrition or related field at a research-intensive university. I wish to work in academia where I would have the opportunity to teach nutritional courses, provide mentorship to my own research team, and mentor students.

During my doctoral studies, I have gained some experience in writing grants and have been awarded two small pilot grants. The first grant titled "Austin School Gardens: Assessing the landscape of gardening schools around Austin" was funded by the City of Austin, Office of Sustainability and the second pilot grant was funded by the Academy of Nutrition and Dietetics "Pilot Study: Behavioral, Environmental, and Policy Factors Influencing Childhood Obesity". The pilot grant from the Academy of Nutrition and

Dietetics was to collect data from WIC clinics across the Austin area and examine the association of behavioral, environmental, and policy factors with childhood obesity among Hispanic youth. I am the process of data analyses for this study and will prepare a manuscript reporting these findings during Fall 2019.

In addition, I have gained ample project management experience. For the garden-based pilot study listed above, I developed the surveys, trained UT undergraduate students in data collection procedures, and supervised all data collection. The results of this study will be published in a manuscript as well as part of a City of Austin report, that will then be used to inform city policy. I have also served as a wet lab manager on a large NIH funded trial (PI: Davis), which involved creating protocols for blood processing, and supervising and training many students and staff on these procedures, overseeing lab safety, and assisting with anthropometric measurements. Beyond these project management experiences, I have mentored an Honors in Advanced Nutritional Sciences undergraduate student on her thesis project, which included training the student in data analysis, manuscript preparation, and thesis writing. I am currently working on a manuscript using baseline data from over 3,000 Hispanic youth (7-11 years of age) to examine the effects of cooking and gardening attitudes and self-efficacy on dietary intake using NDS-R 24-hour diet recalls. By the time I graduate, I will have up to four first author publications, ten co-authored publications, along with advanced analytical skills, expertise using NDS-R software, and experience analyzing large nutritional datasets.

All of my above experiences and trainings has shaped my research interests and I would love to expand my background in maternal, prenatal, and childhood nutrition by evaluating how several factors including dietary factors (i.e. micro- and macronutrients intake), sociodemographic (i.e. age, sex, language and immigration), socioeconomic status (i.e., food insecurity, income, and education), epigenetic (gut and vaginal microbiome), mode of delivery, and exposure to environmental pollutants and toxicants like bisphenol A can impact health outcome in mothers and their children. I would like to pursue further research on the role that family members specially fathers can play to support and encourage their wives/partners to breastfeed their child. Moreover, there is a need to further investigate the compositions of breast milk (i.e. HMOs, leptin, and insulin levels) specially milk of mothers with GDM and their influence on health outcomes in children. Additionally, considering the increased intake of SSBs specially among children and adolescence, I would like to design an intervention that helps decreases rate of SSBs intake and promotes healthy beverages such as water and aqua frescas consumption across all age groups. I would also like to study more about the effectiveness of taxation on SSBs and how researchers and health care professionals can collaborate with the state legislatures and politicians to eliminate availability of SSBs at daycares and schools and eventually help promote drinking healthy beverages instead.

My goal is to pursue a postdoctoral position that would expand my current experience in maternal, prenatal, and early life nutrition while additionally obtaining skills in areas such as public health nutrition and epidemiology, longitudinal study design and dietary feeding trials, use of the National Health and Nutrition Examination Survey (NHANES) and the National Collaborative on Childhood Obesity Research (NCCOR). Ultimately, I would like to join a multidisciplinary research team and collaborate with pediatricians, obstetrics and gynecology physicians, dietitians, nurses, psychiatrists, psychologists, and epidemiologists to work on projects that combine more expertise and disciplines in this field and lead to creative and high impact research. By working with a multidisciplinary research team, I would be able identify different barriers of BF promotion and SSBs intake reduction and consequently design an effective intervention that applies dietary, physiological, epidemiological, and psychological aspects of BF, SSBs intake, and health outcomes in children and adults. By incorporating my knowledge of nutrition and epidemiology and future collaborations with other health care professionals , hopefully I will be able to lead my own research team as a tenure-track professor at a prestigious university and help our society to understand how dietary choices and other factors can impact health outcomes later in life.

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