Examining Associations between Perinatal and Postnatal Risk Factors for Childhood Obesity Using Sibling Comparisons

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Abstract

Background: One of the major criticisms of observational studies examining risk factors for childhood obesity is unmeasured confounding. We examined the associations between breastfeeding initiation, cesarean delivery, prenatal smoking, and gestational diabetes mellitus (GDM) with childhood obesity using both a traditional observational approach and a sibling-pair design with family fixed effects.

Methods: We used data from the Linked the Collecting Electronic Nutrition Trajectory Data Using e-Records of Youth (CENTURY) Study, a clinical database created through the linkage of well-child visits with children's birth certificates, with obesity measured at 2 ($N=55,058$) and 5 ($N=43,894$) years of age. We conducted three sets of regression models: (1) full sample to examine the adjusted association between each risk factor and obesity with clustering by family; (2) rerun only among siblings with clustering by family; and (3) fixed effects analysis among siblings.

Results: Across risk factors, 30%–39% of children had siblings. In the full sample, breastfeeding initiation was associated with a lower BMI z-score, while cesarean delivery and smoking during pregnancy were associated with a higher BMI z-score. Effect sizes were consistent in models with siblings only. However, in the fixed effects models, the coefficients attenuated and were no longer significant for each of these risk factors. We found no association between GDM and child BMI z-score in any of the models. Results were consistent for childhood obesity as a dichotomous measure and at 5 years of age.

Conclusions: Our findings suggest that unmeasured genetic, environmental, and familial factors are likely confounding associations between breastfeeding, cesarean delivery, prenatal smoking, and GDM with childhood obesity in observational studies.

Keywords: breastfeeding; cesarean delivery; gestational diabetes; siblings; smoking

Introduction

As 13.9% of 2- to 5-year olds and 18.4% of 6- to 11-year olds were obese in 2015–2016,¹ identifying preventable risk factors is essential to curbing rising rates across childhood. An increasing body of evidence based on observational studies has demonstrated a higher risk of childhood obesity associated with maternal smoking during pregnancy,^{2–4} cesarean delivery,^{3,5,6} and gestational diabetes mellitus (GDM).^{3,7,8} Despite some conflicting research, studies have also reported that breastfeeding is

associated with a lower risk of childhood obesity.^{3,9,10} Furthermore, biological mechanisms exist, which could potentially increase^{11–13} or decrease¹⁴ risk for later obesity. While each of these risk factors is modifiable and plausible, results from traditional observational studies produce associations, but do not prove causation. Although randomized controlled trials may be considered the gold standard study design, they are not feasible in most cases, and alternative study methodologies can be utilized to provide insight into causation.

One of the major criticisms of observational studies is unmeasured confounding. In the United States, both

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childhood obesity and its perinatal and postnatal risk factors are socially patterned. Children from more disadvantaged households, including less educated and younger mothers, are more likely to be obese.¹⁵ In contrast, mothers from more advantaged households are more likely to engage in positive health behaviors during pregnancy, including a lower proportion of women who smoke,¹⁶ and are more likely to start and continue breastfeeding.¹⁷ Whether these risk factors are causally associated with obesity or appear significant due to the social patterning remains unknown. Furthermore, a significant association may also result from residual confounding by not fully accounting for genetic, environmental, and familial factors.^{18,19}

Sibling pair comparisons, an alternative study methodology, allow for the partial control of perinatal and postnatal environment, in addition to shared genetics, and produce a less confounded estimate.^{18–20} This within-family analysis compares associations between discordant siblings. Attenuation or elimination of any association from the between-family analysis compared to the within-family analysis suggests that the association is confounded by unmeasured genetic, environmental, and familial factors. Associations that remain in within-family analyses would then be more likely attributed to the exposure itself, implying causation.

Given the challenge of identifying datasets with a sufficient number of siblings, there has been limited childhood obesity research using within-family analyses. We found seven studies that used sibling analyses to examine the effects of breastfeeding initiation and duration on later obesity, with inconsistent results across cohorts.^{21–27} We identified two studies using a within-family analysis that examined the association between cesarean delivery and obesity outcomes, with one finding evidence for an increased risk²⁸ and the other reporting no effect.²⁹ A recent review of five studies using sibling data found evidence for a dose–response relationship between the number of cigarettes a mother smoked daily during pregnancy and offspring BMI z-score, suggesting the association may be independent of confounding factors.³⁰ An additional study also found that prenatal exposure to maternal smoking increased offspring BMI z-score within sibling pairs.³¹ Within-family studies of Pima Indians first documented the increased risk of obesity with exposure to GDM.³² These results are consistent with a study that also found the GDM exposure increased later BMI within male siblings.³³

The results from sibling studies remain inconclusive for the causal effects of breastfeeding, cesarean delivery, and GDM on childhood obesity, with some evidence for an increased risk of maternal smoking during pregnancy. Using a new database created through the linkage of well-child visits to children's birth certificates, we examined the associations between breastfeeding initiation, cesarean delivery, prenatal smoking, and GDM with childhood obesity using both a traditional observational approach and a sibling-pair design with family fixed effects.

Methods

We used data from the Linked the Collecting Electronic Nutrition Trajectory Data Using e-Records of Youth (CENTURY) Study, a longitudinal clinical database created through the linkage of well-child visits with each child's Massachusetts birth certificate. The development of the Linked CENTURY Study has been described elsewhere.³⁴ In summary, the CENTURY Study, an existing clinical database at Atrius Health in eastern Massachusetts with data on 306,147 children from 1980 to 2008,³⁵ was linked to birth certificate data using an algorithm that compared the child's name and date of birth and the mother's date of birth. Overall, 74% of the CENTURY cohort was matched. Each child was linked to his/her mother using insurance information and siblings were identified with a common family identifier. As sample size of children in the Linked CENTURY Study decreased with their age, we focused this analysis on children 2 ($N=55,058$) and 5 ($N=43,894$) years of age.³⁴

Institutional Review Board approval for the Linked CENTURY Study was obtained from Boston College, Harvard Pilgrim Health Care, Massachusetts Department of Public Health, and the Massachusetts General Hospital for Children.

Outcome Measures

We extracted height and weight data from electronic health records collected at well-child visits. Medical assistants measured height and weight according to the written protocol of Atrius Health-affiliated health centers. Weight was measured to the nearest 0.25 lb on a pediatric scale and height was measured standing.³⁴ We calculated BMI as weight in kilograms divided by height in meters squared. Our primary outcome was age- and sex-specific BMI z-scores based on the CDC growth charts.³⁶ We also generated age- and sex-specific BMI percentiles to create a dichotomous measure of childhood obesity, defined as a BMI ≥ 95 th percentile for age and sex.³⁶ Obesity outcomes at age 2 included children who were ≥ 2 and <3 years of age and outcomes at age 5 included children who were ≥ 5 and <6 years of age.

Perinatal and Postnatal Risk Factors

Our four perinatal and postnatal risk factors were derived from the birth certificate.³⁴ The hospital recorded whether the mother was breastfeeding at the time of discharge, which was used as an indicator of breastfeeding initiation (yes/no). The hospital also recorded the mode of delivery, which we dichotomized into cesarean versus no. Mothers self-reported the average number of cigarettes they smoked daily during pregnancy, which we dichotomized into yes (≥ 1 cigarette/day) versus no (none). The hospital recorded whether the mother had GDM, which we dichotomized into yes/no. The Massachusetts birth certificate collected data on breastfeeding and cesarean delivery

from 1987 onward, maternal smoking from 1992 onward, and GDM from 1996 onward.

Sociodemographic Information

From the electronic health record, we obtained information on the child's sex (male or female) and derived an indicator of the number of children in the household (1, 2, 3, or 4+) based on the number of children with a common family identifier. On the birth certificate, mothers reported their race and ethnicity (White, Hispanic, Black, Asian, or Other), age (13–19, 20–24, 25–29, 30–34, 35–39, or 40+ years), educational attainment (elementary, high school, college, or 5+ years of college), marital status (married or not married), and the hospital recorded the year of birth (1987–2006).

Statistical Analysis

As the perinatal and postnatal risk factors were introduced on the birth certificate over time, sample sizes vary across analyses to maximize the number of children included. For each perinatal and postnatal risk factor, we present descriptive statistics on the proportion with that risk factor, children with obesity at age 2, and the average child BMI *z*-score at age 2 overall and according to the presence of siblings. We next describe the sociodemographic characteristics of childhood obesity at age 2 as well as across risk factors.

We conducted three sets of models to rigorously examine the potential causal associations between perinatal and postnatal risk factors and childhood obesity outcomes. To illustrate, to study the exposure of breastfeeding initiation, the first model included the full sample to examine the association between breastfeeding initiation and child BMI *z*-scores adjusted for child sex, maternal race/ethnicity, education, age, marital status, number of children in the household, year of birth, and the presence of multiple siblings per family by clustering on the family identifier. This is the traditional observational model used to test the associations between risk factors and childhood obesity, while controlling for confounding factors. While <0.2% of children had missing data for race/ethnicity, education, or age across perinatal and postnatal risk factors, missing values were coded so all children were retained in analyses.

The second model included only siblings (≥ 2 children per family) and was adjusted for the same covariates, including clustering on the family identifier. While this approach is similar to the first model, it is repeated among siblings only to compare effects between the full sample and sibling sample. We used generalized estimating equations in the first two models to account for the non-independence of observations in each family.^{37 38}

The third model was a fixed effects analysis among siblings adjusted for the same covariates, except that sibling order was included rather than number of siblings. Maternal race/ethnicity was dropped from the model as it did not vary within families. This model compared asso-

ciations between breastfeeding initiation and child BMI scores among siblings with differing outcomes and controlled for unmeasured genetic, environmental, and familial factors.^{18,19} Within-family analyses use mothers as their own controls, thereby creating a less biased estimate and providing insight into a potential causal association between breastfeeding initiation and childhood obesity.

Subsequently, we conducted the same set of analyses with childhood obesity as a dichotomous outcome. As the third model examined associations only between siblings with differing outcomes, the samples are smaller because sibling sets with the same outcome (*i.e.*, both obese or not) were excluded. We repeated these sets of models for the remaining three perinatal and postnatal risk factors.

We repeated this series of analyses for children with data available at 5 years of age. We performed data analyses using Stata statistical software version 15.1 (StataCorp, College Station, TX).

Results

Overall, ~6% of children in the Linked CENTURY Study were obese at 2 years of age, increasing to over 12% at 5 years of age (Table 1 and Supplementary Table S1). Across perinatal and postnatal risk factors, 30%–39% of children had siblings in the dataset.

Over three-quarters of mothers initiated breastfeeding, nearly one-quarter of children were delivered by cesarean section, 5% of mothers reported smoking during pregnancy, and 4% of mothers had GDM (Table 1). These risk factors were also socially patterned such that there were significant differences according to maternal race/ethnicity, education, age, and marital status (Table 2). Trends also revealed that breastfeeding initiation, cesarean delivery, and GDM increased across years, while smoking during pregnancy decreased.

The prevalence of childhood obesity and perinatal and postnatal risk factors varied across sociodemographic characteristics (Table 2). Obesity was socially patterned with a higher proportion among children whose mothers identified as Hispanic, Black, and Other race/ethnicity compared to children of White and Asian mothers. Obesity prevalence was also higher among children whose mothers had lower levels of education, were younger, and were not married compared to their respective counterparts.

The three sets of models presented in Table 3 illustrate between family associations across the full sample and among siblings only, and within-family associations among siblings. In the full sample, breastfeeding initiation was associated with a lower BMI *z*-score, while cesarean delivery and smoking during pregnancy were associated with a higher BMI *z*-score. Effect sizes were consistent in models with siblings only. However, in the fixed effects models, the coefficients attenuated and were no longer significant for each of these three risk factors. We found no association between GDM and child BMI *z*-score in any of the three models.

Table 1. Sample Characteristics across Perinatal and Postnatal Risk Factors with Childhood Obesity Outcomes at Two Years of Age

Characteristic	Total N (%)	Siblings in dataset	
		No N (%)	Yes N (%)
Breastfeeding initiation	N=55,058	N=33,603	N=21,455
% Initiated breastfeeding	42,995 (78.1)	25,810 (76.8)	17,185 (80.1)
% Obesity	3226 (5.9)	2028 (6.0)	1198 (5.6)
BMI z-score (SD)	-0.13 (1.19)	-0.14 (1.21)	-0.12 (1.17)
Cesarean delivery	N=54,980	N=33,541	N=21,439
% Had cesarean delivery	12,941 (23.5)	8561 (25.5)	4380 (20.4)
% Obesity	3231 (5.9)	2027 (6.0)	1204 (5.6)
BMI z-score (SD)	-0.13 (1.19)	-0.14 (1.21)	-0.12 (1.17)
Smoking during pregnancy	N=41,936	N=26,896	N=15,040
% Smoked during pregnancy	2059 (4.9)	1598 (5.9)	461 (3.1)
% Obesity	2458 (5.9)	1632 (6.1)	826 (5.5)
BMI z-score (SD)	-0.13 (1.19)	-0.13 (1.21)	-0.12 (1.17)
Gestational diabetes	N=31,501	N=21,412	N=10,089
% Had gestational diabetes	1160 (3.7)	865 (4.0)	295 (2.9)
% Obesity	1801 (5.7)	1305 (6.1)	496 (4.9)
BMI z-score (SD)	-0.13 (1.18)	-0.13 (1.20)	-0.13 (1.14)

SD, standard deviation.

Results were similar in models with childhood obesity as a dichotomous measure. In the full sample, breastfeeding initiation was associated with a lower risk of childhood obesity, while cesarean delivery and smoking during pregnancy were associated with a higher risk. Associations were consistent in the siblings only analyses. In the fixed effects models, sample sizes reduced as the number of discordant sibling sets was much smaller than the full sibling sample. We found that associations across all risk factors attenuated toward the null and were no longer significant. We found no association between GDM and childhood obesity in any of the three models.

Both sets of analyses were repeated for children at 5 years of age. While sample sizes were lower at age 5, the number of discordant sibling sets increased. We found similar social patterning of childhood obesity and across perinatal and postnatal risk factors at age 5 (Supplementary Table S2). Associations were consistent with our findings

at age 2 for breastfeeding initiation, cesarean delivery, and smoking during pregnancy (Supplementary Table S3). In the full and sibling models, breastfeeding initiation was associated with a lower BMI z-score and reduced obesity risk, while cesarean delivery and smoking during pregnancy were associated with a higher BMI z-score and increased obesity risk at age 5. We also found that GDM was associated with a higher BMI z-score and increased risk for obesity at age 5. However, in the fixed effects models, associations with breastfeeding initiation, cesarean delivery, and GDM attenuated and were no longer significant. While in the fixed effects model, smoking during pregnancy was not associated with BMI z-score at age 5, it reduced the risk for childhood obesity (Supplementary Table S3).

Discussion

Using the Linked CENTURY Study, we exploited clinically measured height and weight data linked to children's birth certificates to examine the associations of four perinatal and postnatal risk factors with childhood obesity using a sibling-pair design. In between-family analyses, similar to traditional observational studies, we found that exposures to cesarean delivery, smoking during pregnancy, and GDM (at age 5 years only) increased children's risk for obesity, while breastfeeding was protective; however, these associations attenuated and were no longer significant in within-family analyses. Our findings suggest that unmeasured genetic, environmental, and familial factors are likely confounding these relationships in observational studies. While numerous reasons exist to encourage women not to smoke during pregnancy, not have a cesarean delivery unless medically indicated, to prevent GDM, and to start breastfeeding postpartum, we found that preventing childhood obesity may not be one of them.

Our findings contribute to the small body of literature using sibling-pair designs to test risk factors for obesity across the life course. Within-family studies examining the association between breastfeeding and obesity have been conducted across the largest number of cohorts, with three studies finding that breastfeeding was protective^{23,26,27} and four studies finding no effect.^{21,22,24,25} While the recent review by Albers et al.,³⁰ which combined data from five studies, and one more recent study,³¹ concluded that smoking during pregnancy increased risk for obesity, we found no evidence of associations between prenatal smoking and childhood obesity at age 2 or 5. More studies are needed to examine associations between cesarean delivery^{28,29} and GDM^{32,33} with childhood obesity. In research across all risk factors, some studies used fixed effects models,^{21-23,33,39} while others compared between-family and within-family estimates.^{24-28,31,32,40} We previously used the Linked CENTURY Study to examine the relationship between cesarean delivery and BMI z-scores at 5 years of age by decomposing the total association into

Table 2. Characteristics Associated with Perinatal and Postnatal Risk Factors and Childhood Obesity at Two Years of Age

Characteristic	% Obesity (N = 55,058)	% Initiated breastfeeding (N = 55,058)	% Had cesarean section (N = 54,980)	% Smoked during pregnancy (N = 41,936)	% Had gestational diabetes (N = 31,501)
Child sex, %					
Male	6.1	78.7	24.9	4.9	3.6
Female	5.6	77.5	22.1	5.0	3.7
Maternal race/ethnicity, %					
White	5.1	78.0	23.6	5.8	3.0
Hispanic	11.6	79.3	22.9	3.6	4.2
Black	8.1	75.0	23.9	3.7	4.7
Asian	4.2	84.0	22.6	0.6	7.1
Other	8.2	81.2	22.0	3.5	4.2
Maternal education, %					
Elementary	13.5	55.6	17.4	8.6	7.6
High school	7.2	65.7	23.5	9.9	3.4
College	5.3	81.0	24.4	3.2	3.9
5+ Years of college	4.8	92.1	21.0	0.9	3.2
Maternal age (years), %					
13–19	7.8	53.4	14.8	12.7	0.6
20–24	8.1	62.7	17.2	12.1	1.4
25–29	6.3	73.9	20.9	6.1	3.2
30–34	5.1	81.5	24.0	3.8	3.7
35–39	5.3	85.7	27.8	2.6	4.7
40+	5.5	88.1	33.4	2.4	6.2
Marital status, %					
Married	5.3	81.4	24.1	3.0	3.8
Not married	8.7	62.1	21.0	13.9	3.1
Number of children in household, %					
1	6.0	76.8	25.5	5.9	4.0
2	5.6	80.4	21.5	3.2	3.1
3	5.6	78.4	17.6	2.6	2.1
4+	5.7	83.5	11.7	2.2	3.6
Child year of birth (grouped), %					
1987–1990	5.9	69.3	21.1	—	—
1991–1995	6.2	75.4	18.5	7.0	—
1996–2000	7.1	77.1	21.2	5.6	3.5
2001–2003	5.5	82.4	26.3	3.8	3.5
2004–2006	4.6	86.7	31.5	3.2	4.0

Table 3. Models of the Associations between Perinatal and Postnatal Risk Factors with Childhood Obesity Outcomes at Two Years of Age									
	Breastfeeding initiation			Cesarean delivery			Smoking during pregnancy		
	N	β (95% CI)		N	β (95% CI)		N	β (95% CI)	
BMI z-score									
Full sample, adjusted ^a	55,058	−0.06 (−0.09 to −0.04)		54,980	0.08 (0.06 to 0.10)		41,936	0.18 (0.12–0.23)	
Siblings, adjusted ^{a,b}	21,455	−0.06 (−0.10 to −0.02)		21,439	0.08 (0.04 to 0.13)		15,040	0.22 (0.10–0.33)	
Siblings, fixed effects ^c	21,455	−0.04 (−0.10 to 0.03)		21,439	−0.03 (−0.11 to 0.04)		15,040	−0.00 (−0.19 to 0.19)	
		OR (95% CI)			OR (95% CI)			OR (95% CI)	
Obesity (BMI ≥95th vs. <95th)									
Full sample, adjusted ^a	55,058	0.80 (0.73 to 0.87)		54,980	1.26 (1.16 to 1.37)		41,921	1.54 (1.31 to 1.80)	
Siblings, adjusted ^{a,b}	21,455	0.80 (0.69 to 0.92)		21,439	1.33 (1.16 to 1.54)		15,027	1.69 (1.20 to 2.38)	
Siblings, fixed effects ^c	2260	0.97 (0.72 to 1.32)		2263	1.23 (0.87 to 1.74)		1523	0.79 (0.32 to 1.92)	
In the breastfeeding analysis, there were 1006 sibling sets (2260 individuals), in which there was variability in childhood obesity. In the cesarean delivery analysis, there were 1008 sibling sets (2263 individuals). In the smoking analysis, there were 693 sibling sets (1523 individuals). In the gestational diabetes analysis, there were 409 sibling sets (876 individuals).									
^a Model was adjusted for the presence of multiple siblings per family and included the following covariates: child sex, maternal race/ethnicity, maternal education, maternal age, marital status, number of children in household, and child year of birth.									
^b Conducted among a subsample of families with one or more siblings.									
^c Fixed effects model was fit among siblings with discordant outcomes and included the following covariates: child sex, maternal education, maternal age, marital status, sibling order, child year of birth.									
OR, odds ratio; CI, confidence interval.									

within- and between-family components.²⁹ We found no association in the within-family component and concluded that the significant between-family association was likely due to unmeasured confounding. In contrast, we utilized family fixed effects models in this study, which compare discordant siblings within mothers and models are adjusted for differing characteristics between siblings.

Despite the strengths of sibling-pair designs over traditional observational studies, challenges remain. Although the Linked CENTURY Study contained data on over 57,000 children from 44,000 families at age 2, the number of discordant siblings reduced the sample significantly. For example, we found there were 2263 children within 1007 sibling sets with discordance in childhood obesity at age 2. As sample sizes reduce, the power to detect effects also diminishes. There is the potential that null findings in sibling pair studies may be a result of insufficient discordant siblings rather than true null associations. A further limitation of sibling pair studies is that siblings may have varying exposures or outcomes for reasons that were not recorded and thus we could not account for them in our analysis. For example, one sibling may not be breastfed for a medical reason, such as a birth defect, which may or may not increase a child's risk for obesity independent of breastfeeding. Therefore, it is essential to consider potential reasons why there may be differences in exposure status between siblings, and whether the order of exposures or outcomes may systematically vary across pregnancies.

While the Linked CENTURY Study benefits from clinically measured obesity data and nearly complete sociodemographic information, there are limitations. While cesarean delivery, GDM, and breastfeeding were recorded by hospital staff, mothers' self-reported smoking during pregnancy has been shown to underestimate smoking compared to postpartum surveys.⁴¹ We were also able to examine breastfeeding initiation only, as duration data are not available on the birth certificate. Other perinatal risk factors for childhood obesity have been identified in the literature, including prepregnancy BMI and gestational weight gain,^{42,43} but this information was not recorded on the birth certificate or during well-child visits during our study period. In the Linked CENTURY Study, some siblings may not be biological as families were constructed based on a common family identifier. While we estimate that the proportion of nonbiological siblings is small, sibling sets with nonbiological siblings would still control for shared environmental and familial factors, but not shared genetics. Finally, since the Linked CENTURY Study was derived from a clinical database and our analyses focused on families with siblings, the results may not be generalizable to the broader population of young children.

By comparing associations from between-family analyses in traditional observational studies to associations from sibling pair analyses, our results contribute to the continuing discussions about the causal associations between breastfeeding, cesarean delivery, smoking during

pregnancy, and GDM with childhood obesity. Prevention research needs to move beyond traditional observational studies and embrace alternative study designs to help tease apart causation from correlation. As preventing childhood obesity is easier than treating childhood obesity, identifying causal mechanisms can help inform clinical and public health recommendations and interventions to improve population health.

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Author Disclosure Statement

No competing financial interests exist.

Supplementary Material

Supplementary Tables S1–S3

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