Breast-Feeding and Type 2 Diabetes in the Youth of Three Ethnic Groups

The SEARCH for Diabetes in Youth Case-Control Study

Elizabeth J. Mayer-Davis, phd[1]
Dana Dabelea, md, phd[2]
Archana Pande Lamichhane, ms[1]
Ralph B. D'Agostino, Jr., phd[3]
Angela D. Liese, phd[1]
Joan Thomas, ms[1]
Robert E. McKeown, phd[1]
Richard F. Hamman, md[2]

OBJECTIVE — To evaluate the hypothesis that breast-feeding is associated with reduced type 2 diabetes among African-American, Hispanic, and non-Hispanic white youth, mediated in part by current weight status.

RESEARCH DESIGN AND METHODS — The SEARCH Case-Control Study, an ancillary study to SEARCH for Diabetes in Youth, was conducted in two of six SEARCH clinical sites. Eighty youth with type 2 diabetes aged 10–21 years were included. Nondiabetic control participants were recruited from primary care provider offices (n = 167). Breast-feeding information was recalled by biological mothers.

RESULTS — Prevalence (%) of breast-feeding (any duration) was lower among youth with type 2 diabetes than among control subjects (19.5 vs. 27.1 for African Americans, 50.0 vs. 83.8 for Hispanics, and 39.1 vs. 77.6 for non-Hispanic whites). The overall crude odds ratio for the association of breast-feeding (ever versus never) and type 2 diabetes was 0.26 (95% CI 0.15–0.46). Results were similar by race/ethnic group (P value for interaction = 0.17). The odds ratio for the association after adjusting for 12 potential confounders was 0.43 (0.19–0.99). When current BMI z-score was added to the model, the odds ratio was attenuated (0.82 [0.30–2.30]), suggesting possible mediation through current childhood weight status. Analyses that incorporated duration of breast-feeding, adjusted for potential confounders, provided evidence for dose response (test for trend, P value <0.0001), even after inclusion of BMI z-score.

CONCLUSIONS — Breast-feeding appears to be protective against development of type 2 diabetes in youth, mediated in part by current weight status in childhood.

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Dramatic increases in childhood obesity (1) and the emergence of type 2 diabetes in youth (2,3) motivate research to identify lifestyle approaches to primary prevention of both conditions. Among adults, breast-feeding in infancy has been associated with reduced risk of type 2 diabetes (4), but little is known regarding the potential beneficial effect of breast-feeding on the development of type 2 diabetes in adolescence. Studies in young Native American populations have shown that individuals with type 2 diabetes were less likely to have been breast-fed as infants compared with those without type 2 diabetes (5,6). However, this finding has not been replicated in other populations.

The biologic plausibility for a protective effect of breast-feeding against type 2 diabetes in youth lies primarily in the potential for breast-feeding to reduce the risk for childhood obesity. Recent meta-analyses, primarily drawing from white populations, concluded that having been breast-fed is associated with a 13–22% reduced odds for overweight or obesity in childhood or later in life (7,8), in a dose-dependent fashion (9). On the other hand, in a study of >73,000 low-income white and black children (10), breast-feeding was protective against obesity at age 4 years only among the offspring of white mothers. Further, analysis based on duration of breast-feeding showed a protective dose-response relationship with the risk of overweight only among non-Hispanic white subjects (11). A recent study of Latino youth at high risk for diabetes showed no association of breast-feeding with adiposity or measures of glucose and insulin metabolism (12); thus, differential effects of breast-feeding according to race/ethnicity may exist.

Using a case-control design, we hypothesized that youth with type 2 diabetes would be less likely to have been breast-fed compared with nondiabetic control youth and that this finding would be consistent across three race/ethnic groups of non-Hispanic whites, African Americans, and Hispanics and independent of maternal diabetes status. Further, we explored whether current BMI would account for any of the observed protective association.

RESEARCH DESIGN AND METHODS

— The SEARCH Case-Control (SEARCH CC) study is an ancillary study to SEARCH for Diabetes in Youth, conducted at two of six SEARCH clinical sites. A detailed description of SEARCH study methods has been published (13). SEARCH is a multicenter study that began conducting population-based ascertainment of nongestational cases of diagnosed diabetes in youth aged <20 years in 2001 for prevalent cases and continuing with ascertainment of incident cases through the present.

SEARCH CC case inclusion

In the Colorado and South Carolina SEARCH sites, diabetes cases were iden-

From the [1]Center for Research in Nutrition and Health Disparities and Epidemiology and Biostatistics, University of South Carolina, Columbia, South Carolina; the [2]Department of Preventive Medicine and Biometrics, University of Colorado School of Medicine, Denver, Colorado; and the [3]Department of Public Health Sciences, Wake Forest University School of Medicine, Winston Salem, North Carolina.

Address correspondence and reprint requests to Elizabeth Mayer-Davis, University of South Carolina, Center for Research in Nutrition and Health Disparities, 2718 Middleburg Dr., Columbia, SC 29208. E-mail: ejmayer@gwm.sc.edu.

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Abbreviations: SEARCH CC, SEARCH Case-Control.

tified in selected counties in both states for 2001 prevalent cases and statewide in subsequent years for incident cases, using a network of health care providers including pediatric endocrinologists, hospitals, and other providers. Case subjects were considered valid if they were diagnosed by a health care provider. Type of diabetes was based on provider diagnosis. Using Health Insurance Portability and Accountability Act–compliant procedures, youth with diabetes identified by the SEARCH recruiting network were asked to complete a brief survey and were then invited to the SEARCH study visit, which involved questionnaires, a brief physical examination, and laboratory measurements.

Between July 2003 and March 2006, SEARCH case subjects aged ≥10 years who attended the SEARCH in-person study visit were invited to participate in the SEARCH CC study. Data collection unique to the SEARCH CC study included a perinatal questionnaire completed by the biological mother. Overall, of 228 youth with provider-diagnosed type 2 diabetes who were invited to participate in the SEARCH CC study, a total of 119 participated. The most common reason for nonparticipation by SEARCH case subjects in the SEARCH CC ancillary study was unwillingness or inability to attend an additional visit within the SEARCH CC study time window.

SEARCH CC control inclusion

Because all SEARCH cases of physician-diagnosed diabetes arose from health care provider offices, we recruited control subjects from primary care offices in the same geographic areas. Within the South Carolina and Colorado clinical sites, control subjects were overrecruited with respect to minority race/ethnicity (African Americans and Hispanics) relative to non-Hispanic white subjects, considering sex and age (10–12, 13–15, 16–18, and ≥19 years). For defined periods of time, participating primary care offices provided an initial study brochure, and patients and their parent or guardian were asked to complete a one-page information form and an indication of permission for study staff to contact them regarding participation in the study. The SEARCH CC study staff contacted those interested in learning more about the study and recruited participants accordingly. Of 1,203 information forms returned by participating practices, 881 (73.2%) indicated interest in learning about the study, of whom 41 were ineligible, 233 later refused explicitly, 389 could not be successfully contacted ("passive refusals"), and 218 participated in the SEARCH CC study by the close of the data collection period. All control subjects were confirmed to be nondiabetic by fasting glucose values obtained as part of the SEARCH CC study visit. The overrecruitment of minority youth yielded higher proportions of both African-American (28.7%) and Hispanic (18.6%) control subjects who were intermediate between the 2002 U.S. Census for South Carolina and Colorado (African Americans, 20.3%; Hispanics, 14.8%) and the case distribution (African Americans, 51.3%; Hispanics, 20%), thus providing adequate numbers of youth within each race/ethnic group for statistical analyses.

Variable measurement

Breast-feeding history was queried from the biological mother, including duration of breast-feeding and timing of introduction of formula and other foods and beverages. Two measures of breast-feeding exposure were generated: breast-feeding (yes/no) and duration of breast-feeding.

The biological mother also reported maternal diabetes status during her pregnancy with the case or control subject, prepregnancy height and weight, maternal smoking and alcohol use during pregnancy and lactation, birth weight and length, and approximate gestational age. Family history of diabetes was obtained by interview regarding biological parents, including diabetes in the biological mother that was diagnosed after delivery of the case or control subjects, and grandparents.

Standardized physical examinations were conducted by trained and certified study staff. Height and weight measurements were used to calculate BMI (kg/m^2). Age- and sex-specific BMI z-scores were derived based on the Centers for Disease Control and Prevention national standards, and weight status categories were assigned as overweight for individuals in the 85th to 95th percentile and obese for those greater than the 95th percentile (14).

Before implementation of the protocol, the study was reviewed and approved by the local institutional review boards that had jurisdiction over the local study population. Before the study visit, written informed consent was obtained for case and control subjects according to the guidelines established by the local institutional review board from subjects who were aged ≥18 years or from the parent or guardian if the subject was aged <18 years. Written assent was also obtained from the subjects who were aged <18 years as governed by local institutional review boards.

Final subject inclusion and exclusion

The present analyses included 80 youth with type 2 diabetes and 167 nondiabetic control youth, after the exclusion of individuals with missing interview results, multiple births, gestational age <38 weeks or missing perinatal information.

Statistical methods

Logistic regression was used to generate unadjusted and adjusted odds ratios and 95% CIs for the association of breast-feeding with type 2 diabetes. An interaction term between breast-feeding and race/ethnicity was used to evaluate whether the association differed according to the race/ethnicity. To address potential confounding, two models were developed. First, a partially adjusted model included design variables (clinical site location, age, sex, and race/ethnicity) and covariates that were found to be statistically significantly associated with both case/control status and breast-feeding (yes/no). Second, a fully adjusted model included all variables from the partially adjusted model, plus additional variables that could logically address potential residual confounding. Current weight status (BMI z-score) was added to the adjusted models to evaluate potential mediation of the association between breast-feeding and type 2 diabetes by obesity. Test for trend was conducted across three categories of breast-feeding.

RESULTS — Unadjusted characteristics of case and control subjects are shown in Table 1. Of note, 31.3% of youth with type 2 diabetes were breast-fed, compared with 63.5% of nondiabetic control youth, and duration of breast-feeding was longer among control than case subjects ($P < 0.0001$). Current BMI z-score was higher among case compared with control subjects ($P < 0.0001$).

Among control subjects, youth who were breast-fed had lower BMI z-scores than those who were not breast-fed (BMI z-score [means ± SD] 0.5 ± 1.1 vs. 1.3 ± 1.1, respectively; $P < 0.001$). A similar pattern was seen among youth with type 2 diabetes, but the BMI z-score difference

Table 1—*Characteristics of youth with type 2 diabetes and nondiabetic control subjects: the SEARCH CC study, 2003–2006*

Variables	Provider-diagnosed type 2 diabetes	Control subjects	*P* value
n	80	167	
Breast-feeding (%)			
Yes	31.3	63.5	<0.0001
Duration of breast-feeding (%)			
Never breast-fed	68.7	36.5	
<6 months	15.0	30.0	
≥6 months	13.7	33.5	<0.0001
Missing	2.5	0.0	
Sex (%)*			
Female	65.0	61.7	
Race/ethnicity (%)*			
Non-Hispanic white	28.8	50.9	
Non-Hispanic black	51.3	28.7	
Hispanic	20.0	18.6	
Missing	0.0	1.8	
Location (%)			
South Carolina	65.0	43.7	0.0017
Birth weight (%)			
Low birth weight (<2,500 g)	10.0	3.6	
Normal birth weight (≥2,500 g)	90.0	94.6	0.0456
Missing	0.0	1.8	
Maternal diabetes (%)			
Yes	21.3	4.8	
No	77.5	94.6	<0.0001
Missing	1.3	0.6	
Family history of diabetes (%)			
Yes	86.3	55.1	
No	13.7	43.1	<0.0001
Missing	0.0	1.8	
Maternal age (%)			
<35 years	91.3	88.0	
≥35 years	8.8	11.4	0.5194
Missing	0.0	0.6	
Maternal prepregnancy BMI (%)			
Overweight	45.0	27.0	
Normal	41.3	69.5	0.0004
Missing	13.8	3.6	
Maternal education (%)			
Less than high school	13.8	6.6	
High school graduate and more	86.3	92.2	0.0690
Missing	0.0	1.2	
Maternal smoking during pregnancy (%)			
Yes	12.5	9.6	
No	86.3	89.8	0.4732
Missing	1.3	0.6	
Maternal alcohol consumption during pregnancy (%)			
Yes	1.3	16.8	
No	98.8	82.6	0.0004
Missing	0.0	0.6	
Age*	15.7 ± 2.7	14.5 ± 2.8	
BMI z-score	2.1 ± 0.7	0.8 ± 1.1	<0.0001

Data are percent or means ± SD. *Statistical testing not done as a result of overrecruitment of control subjects based on race/ethnicity, sex, and age.

did not reach statistical significance (BMI z-score 1.9 ± 0.9 vs. 2.2 ± 0.5, respectively; $P = 0.10$).

Lower odds of being breast-fed in infancy were observed among type 2 diabetic case subjects compared with control subjects (Fig. 1) (unadjusted odds ratio for African Americans 0.65 [95% CI 0.24–1.77]; for Hispanics 0.19 [0.05–0.76]); for non-Hispanic whites 0.18 [0.07–0.49]). No difference in the association of breast-feeding and case-control status was observed according to race/ethnicity (*P* value for interaction = 0.17).

As shown in Table 2, a partially adjusted model included eight variables that were statistically significantly associated with both case-control status and breast-feeding. This model attenuated the original unadjusted odds ratio for breast-feeding (yes/no) of 0.27 (95% CI 0.14–0.50) to an adjusted odds ratio of 0.37 (0.17–0.83), using the all subjects ' covariate data available. Adjustment for an additional four covariates further attenuated the odds ratio to 0.43 (0.19–0.99). Consistent with the possibility of mediation of this association by childhood obesity, the addition of the subjects' current BMI z-score attenuated the odds ratio to 0.82 and the 95% CI included the null value. Because of the amount of missing data for covariates (~25 subjects), Table 2 also displays unadjusted results in the sample of individuals for whom all covariate data were present. Results were very similar compared with unadjusted results in the full sample.

Evaluation of dose response is displayed in Table 2, based on the breast-feeding duration. Before inclusion of the BMI z-score in the model, a protective association was observed for both low (<6 months) and high (≥6 months) breast-feeding duration, with the strongest protective association observed for the high breast-feeding duration. Inclusion of BMI z-scores specifically attenuated the odds ratio for low breast-feeding duration from 0.49 (95% CI 0.18–1.32) to 1.20 (0.36–3.98), while the odds ratio estimate for high breast-feeding score was only slightly changed. The test for linear trend, using the breast-feeding duration as an ordinal variable, was highly statistically significant in this BMI z-score–adjusted model ($P < 0.0001$).

CONCLUSIONS — Findings provide evidence for a protective association of breast-feeding against the development of type 2 diabetes in youth in a dose-

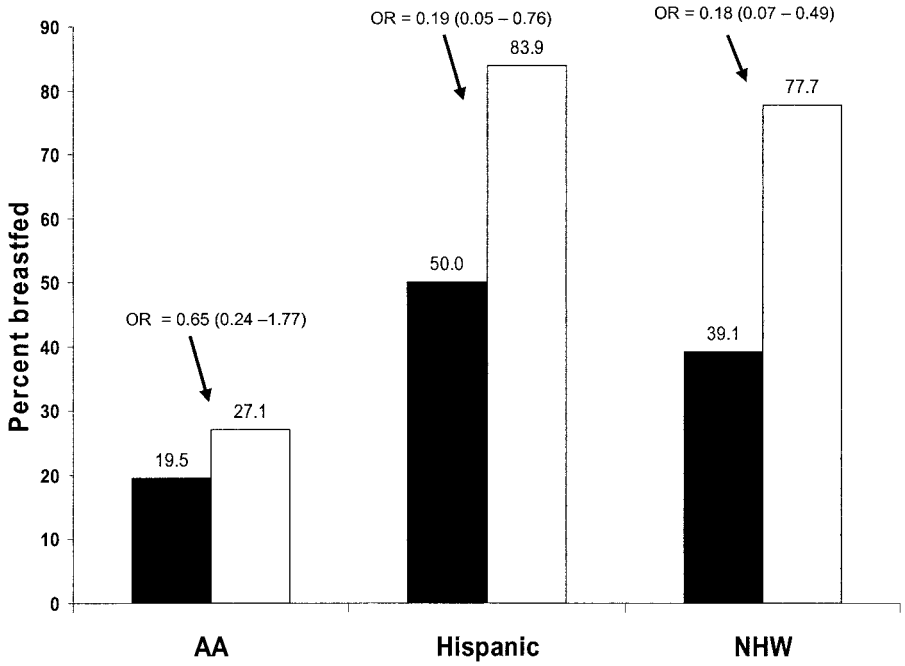

Figure 1—*Percent of youth ever breast-fed and odds ratio for breast-feeding history (ever versus never breast-fed) by case-control status and race/ethnicity: the SEARCH CC study, 2003–2006.* ■*, type 2 diabetes;* □*, control.*

response fashion, independent of other potentially confounding variables. Attenuation of the odds ratios when BMI z-score was added to the models were consistent with a causal pathway in which breast-feeding may lower the risk for childhood overweight, which may in turn reduce risk for type 2 diabetes. Even with multiple potential confounders accounted for, a statistically significant trend ($P < 0.0001$) for breast-feeding duration was observed that was not fully accounted for by current weight status in childhood.

The protective association of breast-feeding in relation to type 2 diabetes was observed for all race/ethnicity categories, with higher proportions of breast-fed infants with lower risk of diabetes, and the statistical test for interaction by race/ethnicity was not statistically significant. It is possible that insufficient sample size precluded detection of a statistically significant interaction in which breast-feeding was associated with type 2 diabetes case status less strongly among African Americans than among non-Hispanic whites or Hispanics. There are at least three possible reasons for the non-significant odds ratio within the African-American subgroup other than sample size. First, the proportion of African-American youth who were breast-fed was markedly lower compared with either non-Hispanic white or Hispanic youth, for both case and control subjects, with only 27% of control subjects having been breast-fed. Thus, a "floor effect" occurred such that to obtain a comparable odds ratio to that seen in non-Hispanic whites (of 0.18), the percent of African-American case youth who were breast-fed would have needed to be 6.3%. Second, it is possible that contributors to type 2 diabetes that are unrelated to breast-feeding are more prominent among African-American youth than among youth in other race/ethnic groups; therefore, breast-feeding may have lesser impact on risk for type 2 diabetes. Third, breast-feeding may have a lesser impact on current childhood obesity in African-American youth compared with other race/ethnic groups. Further research in larger samples is required to better understand potential race/ethnic differences, or lack thereof, in associations of breast-feeding and type 2 diabetes.

Previous studies have documented a lower prevalence of breast-feeding among African-American infants than among infants of other race/ethnicities (15) and among infants of families with low income and with low maternal education (15). These characteristics were considered as potential confounding variables in the present analyses, yet the finding of a protective association of breast-feeding against type 2 diabetes in youth remained. Therefore, targeting population subgroups at relatively high risk both for type 2 diabetes and low prevalence of breast-feeding, including African-American, low-income, and low-education populations, may offer an important opportunity for primary prevention of type 2 diabetes.

Maternal diabetes is a strong risk factor for diabetes (16). Potentially deleterious effects of breast-feeding in very early life of offspring by mothers with diabetes have been reported, including increased adiposity (17). In contrast, Mayer-Davis et al. (18) showed a protective effect of breast-feeding on childhood weight status that was comparable across maternal diabetes and obesity status. In the present study, we did not have a sufficient sample size to allow evaluation of potential effect modification according to maternal diabetes status; however, statistical adjustment for maternal diabetes status was done so that findings reflect associations independent of maternal diabetes status.

We hypothesized that analyses would yield evidence that current child weight status mediated, at least in part, any observed protective association of breast-feeding with type 2 diabetes. Potential causal mechanisms for an association of breast-feeding with a reduction in childhood obesity include satiety signaling in response to nutritional composition of breast milk (19) and overfeeding among bottle-fed infants who exhibit significantly higher plasma insulin levels and a prolonged insulin response (20) compared with breast-fed infants. Although inclusion of current BMI z-scores attenuated the association of breast-feeding with type 2 diabetes, a statistically significant protective dose-response association was still observed (test for trend, $P < 0.0001$) (Table 2, unadjusted, partially adjusted, and fully adjusted models).

We can only speculate regarding potential mechanisms other than weight status that would account for a protective association between breast-feeding and type 2 diabetes. Various environmental toxins, particularly endocrine-disrupting chemicals, have recently been postulated as contributors to obesity and related metabolic disorders (21). These include bisphenol-A, which has been widely incorporated into plastic products including infant feeding bottles (22,23) and which has been associated with both reduced pancreatic β-cell function and insulin resistance (24).

Development of type 2 diabetes re-

Table 2—*Association of the breast-feeding (ever versus never and duration) with type 2 diabetes case versus control status: the SEARCH CC study, 2003–2006*

Breast-feeding (Ever/never)	Without BMI z-score	With BMI z-score
Unadjusted model (all available data)	0.26 (0.15–0.46) (n = 247)	0.57 (0.29–1.13) (n = 243)
Unadjusted model (restricted to subjects with no missing covariate data)	0.27 (0.14–0.50) (n = 220)	0.59 (0.29–1.21) (n = 217)
Partially adjusted model (restricted to subjects with no missing covariate data)*	0.37 (0.17–0.83) (n = 220)	0.58 (0.23–1.45) (n = 217)
Fully adjusted model (restricted to subjects with no missing covariate data)†	0.43 (0.19–0.99) (n = 220)	0.82 (0.30–2.30) (n = 217)
Breast-feeding duration‡		
Unadjusted model (all available data)	(n = 245)	(n = 241)
Never	Referent	Referent
<6 months	0.26 (0.13–0.55)	0.62 (0.26–1.46)
≥6 months	0.22 (0.10–0.46)	0.44 (0.18–1.07)
Unadjusted model (restricted to subjects with no missing covariate data)	(n = 219)	(n = 216)
Never	Referent	Referent
<6 months	0.30 (0.14–0.65)	0.72 (0.30–1.74)
≥6 months	0.21 (0.09–0.48)	0.43 (0.17–1.11)
Partially adjusted model (restricted to subjects with no missing covariate data)*	(n = 219)	(n = 216)
Never	Referent	Referent
<6 months	0.44 (0.17–1.13)	0.88 (0.29–2.69)
≥ 6 months	0.24 (0.09–0.70)	0.26 (0.08–0.90)
Fully adjusted model (restricted to subjects with no missing covariate data)†	(n = 219)	(n = 216)
Never	Referent	Referent
<6 months	0.49 (0.18–1.32)	1.20 (0.36–3.98)
≥6 months	0.30 (0.10–0.86)	0.39 (0.10–1.45)

Data are odds ratio (95% CI). *Adjusted for location, race, sex, age, birth weight, family history of diabetes, maternal prepregnancy BMI, and maternal alcohol consumption during pregnancy. †Adjusted for location, race, sex, age, birth weight, maternal diabetes status during pregnancy, family history of diabetes, education, maternal age, maternal prepregnancy BMI, maternal alcohol and smoking during pregnancy. ‡P value for trend <0.0001 for all models of breast-feeding duration. Note: Number of case and control subjects for the different sample sizes used in the analyses: n = 247: case subjects = 80, control subjects = 167; n = 243: case subjects = 77, control subjects = 166; n = 220: case subjects = 68, control subjects = 152); n = 217: case subjects = 65, control subjects = 152; n = 245: case subjects = 78, control subjects = 167; n = 241: case subjects = 75, control subjects = 166; n = 219: case subjects = 67, control subjects = 152; n = 216: case subjects = 64, control subjects = 152.

quires inadequate insulin secretion relative to insulin resistance; thus, we considered possible mechanisms for protection by breast-feeding related to insulin secretion. Vitamins E (25) and D (26) have been associated with improved β-cell function. However, both vitamins E and D are likely to be provided in sufficient quantity in infant formula (27,28). Nitrate exposure may have a negative impact on the β-cell resulting in development of diabetes (29). It is possible that increased intake of tap water, mixed with formula powders, increases nitrate exposure in formula-fed infants compared with breast-fed infants.

Study limitations

Although studies of breast-feeding and childhood obesity have been criticized on the basis of residual confounding, a recent report of discordant sibships demonstrated that residual confounding related to familial health habits was unlikely, in at least one relatively small study population (30). In the present analyses, inclusion of 12 potentially confounding variables reflective of maternal characteristics, socioeconomic factors, and child characteristics attenuated the odds ratio for the association of breast-feeding and type 2 diabetes; however, statistical significance was retained. Thus, it seems unlikely that residual confounding accounts for the present results.

Selection bias and recall bias are of potential concern. Selection bias would require that the odds of breast-feeding were different in individuals who did, versus those who did not, participate and that this difference varied between case and control subjects. Figure 1 shows breast-feeding prevalence within race/ethnic control groups that are quite similar to those reported from the general population (15,31). Thus, although we cannot rule out selection bias, these findings suggest that selection bias was unlikely to have substantially biased the present findings.

For recall bias to substantially bias the estimate of the odds ratio, the biological mothers of case and control subjects would need to have under- or overestimated breast-feeding differentially and in a dose-response fashion. Breast-feeding is not a commonly known risk factor for type 2 diabetes in youth; thus, it seems rather unlikely that case mothers would differentially underreport this exposure. Also, we included both case subjects with prevalent diabetes in the year 2001 and those with clinical diabetes diagnosis in the year 2002 or later. None of the case subjects were seen for their SEARCH visit at the actual time of clinical diagnosis, which could have biased recall of health habits differentially, compared with recall at a point in time well after clinical diagnosis. Only 17% of case subjects were seen <3 months from diagnosis. Still, we adjusted for diabetes duration in the fully adjusted models to further address the issue of potential bias related to disease duration. Finally, maternal recall of both breast-feeding and (to a lesser extent) duration of breast-feeding has been shown to be accurate even after long periods of time (32).

In summary, breast-feeding may be protective against development of type 2

diabetes in youth regardless of race/ethnicity and mediated in part by current weight status in childhood. Further work is needed to confirm this finding and to evaluate both obesity-related and obesity-independent mechanisms. In the meantime, given other well-established reasons for breast-feeding, renewed efforts to encourage breast-feeding in populations at high risk for type 2 diabetes may be useful.

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