Duration of Lactation and Incidence of the Metabolic Syndrome in Women of Reproductive Age According to Gestational Diabetes Mellitus Status: A 20-Year Prospective Study in CARDIA (Coronary Artery Risk Development in Young Adults)

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OBJECTIVE—The objective of the study was to prospectively assess the association between lactation duration and incidence of the metabolic syndrome among women of reproductive age.

RESEARCH DESIGN AND METHODS—Participants were 1,399 women (39% black, aged 18–30 years) in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, an ongoing multicenter, population-based, prospective observational cohort study conducted in the U.S. Women were nulliparous and free of the metabolic syndrome at baseline (1985–1986) and before subsequent pregnancies, and reexamined 7, 10, 15, and/or 20 years after baseline. Incident metabolic syndrome case participants were identified according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria. Complementary log-log models estimated relative hazards of incident metabolic syndrome among time-dependent lactation duration categories by gestational diabetes mellitus (GDM) adjusted for age, race, study center, baseline covariates (BMI, metabolic syndrome components, education, smoking, physical activity), and time-dependent parity.

RESULTS—Among 704 parous women (620 non-GDM, 84 GDM), there were 120 incident metabolic syndrome case participants in 9,993 person-years (overall incidence rate 12.0 per 1,000 person-years; 10.8 for non-GDM, 22.1 for GDM). Increased lactation duration was associated with lower crude metabolic syndrome incidence rates from 0–1 month through >9 months ($P <$ 0.001). Fully adjusted relative hazards showed that risk reductions associated with longer lactation were stronger among GDM (relative hazard range 0.14–0.56; $P = 0.03$) than non-GDM groups (relative hazard range 0.44–0.61; $P = 0.03$).

CONCLUSIONS—Longer duration of lactation was associated with lower incidence of the metabolic syndrome years after weaning among women with a history of GDM and without GDM, controlling for preconception measurements, BMI, and sociodemographic and lifestyle traits. Lactation may have persistent favorable effects on women's cardiometabolic health. ***Diabetes*** **59:495–504, 2010**

Lactation has favorable effects on cardiometabolic risk factors in women with and without a history of gestational diabetes mellitus (GDM), a strong predictor of type 2 diabetes (1,2) and the metabolic syndrome after pregnancy (3). In the general population, lactating compared with nonlactating women exhibit a less atherogenic lipid profile (4) and lower blood glucose and insulin concentrations (5). Consistent with these findings, lactating women with recent GDM experience lower fasting plasma glucose and insulin levels, higher plasma HDL cholesterol levels, and 50% lower prevalence of type 2 diabetes at 12–16 weeks postpartum (6,7).

Yet, few studies have investigated whether lactation's favorable effects on cardiometabolic risk factors persist after weaning to protect women against future disease. The only study, to our knowledge, to measure changes from preconception to after weaning reported 6-mg/dl higher average HDL cholesterol levels among women who lactated for ≥3 months versus <3 months independent of preconception plasma HDL cholesterol levels and weight gain (8). Epidemiologic studies have reported weak to modest protective associations between lactation and disease risk in midlife to late life, including lower prevalence of the metabolic syndrome (9,10) or cardiovascular risk factors (11) and lower incidence of myocardial infarction (12) and type 2 diabetes (13). Yet, evidence is lacking that directly links risk factor changes that persist after weaning to subsequent disease onset, because disease status and lactation history were ascertained decades after pregnancy, and preconception and/or postweaning risk factor measurements were not available (9–13). Other limitations include classification of outcomes via self-report only (11–13), and failure to account for mediating or confounding effects of lifestyle habits during the reproductive years. Lastly, lactation duration in relation to disease risk has not been examined separately among women with a history of GDM, with the exception of one study reporting a null association with incident diabetes (13).

To our knowledge, studies have never examined lactation and incidence of the metabolic syndrome, or variation

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Received 11 August 2009 and accepted 8 November 2009. Published ahead of print at http://diabetes.diabetesjournals.org on 3 December 2009. DOI: 10.2337/db09-1197.

in disease risk by GDM status. To address these gaps, we prospectively examined whether increasing duration of lactation was associated with lower incidence of the metabolic syndrome during a 20-year period among women of childbearing age. We examined incidence rates for GDM and non-GDM pregnancies and controlled for preconception risk factor levels, sociodemographics, and follow-up behavioral attributes.

RESEARCH DESIGN AND METHODS

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a multicenter, longitudinal, population-based, observational study designed to describe the development of risk factors for coronary heart disease in young black (52%) and white adults recruited from four geographic areas in the U.S.: Birmingham, Alabama, Chicago, Illinois, Minneapolis, Minnesota, and Oakland, California. The study design, recruitment, methodology, and cohort characteristics have been previously described (14,15). In 1985–1986, baseline data were collected for 2,787 women aged 18–30 years. All metabolic syndrome components were measured at exams in years 0, 7, 10, 15, and 20. Retention rates were 81, 79, 74, and 72% of the surviving cohort (16,17). Institutional review boards at each participating study center approved the study. Written, informed consent was obtained from participants for all study procedures.

Sample selection criteria. Of 2,787 women enrolled at baseline, we excluded 1,008 women who were parous at baseline; 18 women currently pregnant or breastfeeding, pregnant within the past 3 months, or who reported a previous hysterectomy; 4 women with type 1 diabetes; and 92 women who met the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria for the metabolic syndrome at baseline (Fig. 1). Further, we excluded 213 women missing covariates or with incomplete information on all five components to ascertain the metabolic syndrome at baseline and for at least one follow-up exam, 11 primiparas who delivered a multifetal pregnancy during the first follow-up interval, and 42 women missing all lactation information. Biochemical measurements at exams (years 0, 7, 10, 15, and 20) from currently pregnant or lactating women were not used in the analysis. Among the sample of 1,399 nulliparas who were free of the metabolic syndrome at baseline, 695 women were classified as nulliparous during follow-up (677 never gave birth, 9 developed the metabolic syndrome prior to any births, and 9 had later multifetal births only). The data from 704 women who subsequently delivered at least one singleton, live birth during the 20-year period (1986–2006) were used to examine the association of lactation duration and incidence of the metabolic syndrome. These 704 women were more likely than the 695 who remained nulliparous to be married, were slightly younger and thinner, were not using oral contraceptives, and had lower diastolic blood pressure levels at baseline.

Data collection methods. Methodologies for data collection and venipuncture are described elsewhere (14,15,18). Briefly, women fasted prior to each exam, and reported the number of hours since their last intake of food or beverages prior to the blood sample drawn into a Vacutainer tube containing EDTA. Procedures followed in the collection and storage of plasma samples, laboratory quality-control procedures, and methodology for analysis of plasma triglycerides (TGs), HDL cholesterol, LDL cholesterol, and total cholesterol are described elsewhere (18,19). Serum glucose was measured at year 0 using the hexokinase ultraviolet method by American Bio-Science Laboratories (Van Nuys, CA) and at years 7, 10, 15, and 20 using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St. Louis, MO).

Blood pressure measurements. After an initial 5-min rest, blood pressure was measured three times at 1-min intervals. At the baseline and year-7, -10, and -15 follow-up exams, blood pressure was measured using the Hawksley (Lancing, Sussex, U.K.) random-zero sphygmomanometer; the first and fifth phase Korotkoff sounds were recorded (15). At the year-20 exam, blood pressure was measured with an automated sphygmomanometer (Omron HEM907XL oscillometer; Omron, Schaumburg, IL). The protocol specified the appropriate cuff size (small, medium, large, extra large) based on the upper arm circumference, which was measured by the blood pressure technician at the midpoint between the acromion and the olecranon. Omron values were recalibrated to corresponding random zero values based on a study of both measurement techniques in 903 participants at year 20, as estimated random zero systolic value = 3.74 + 0.96 × Omron systolic value, and estimated random zero diastolic value = 1.30 + 0.97 × Omron diastolic value.

Anthropometric measurements. Certified technicians obtained anthropometric measurements (weight, height, and waist circumference) at each exam according to standardized protocol (20). Body weight was measured to the nearest 0.2 kg using a calibrated balance beam scale in participants wearing light clothing. Height (without shoes) was measured to the nearest 0.5 cm using a vertical ruler, and waist circumference to the nearest 0.5 cm at the minimal abdominal girth (21). BMI was computed as weight in kilograms divided by squared height in meters.

Definition of the metabolic syndrome. Participants who developed the metabolic syndrome (incident cases) were identified at follow-up exams (years 7, 10, 15, and 20) using the NCEP ATP III criteria (22). The metabolic syndrome was defined as the presence of three of five characteristics: *1*) waist girth >88 cm, *2*) fasting TG ≥150 mg/dl, *3*) HDL cholesterol <50 mg/dl, *4*) systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg or treatment with antihypertensive medication, and *5*) fasting glucose ≥100 mg/dl or treatment with diabetes medication. Incident metabolic syndrome case participants were ascertained subsequent to births delivered since baseline among women free of the metabolic syndrome before pregnancy, and in the nonpregnant and nonlactating state at exams. Incident case participants were censored from subsequent time intervals, and births that occurred during those intervals were not included in the analysis.

Number of pregnancies and births. At each exam, women reported whether they were currently pregnant or lactating, number of pregnancies including abortions, miscarriages, and live or stillbirths since the previous exam, along with length(s) of gestation, multifetal gestation, dates of delivery(ies), and diabetes during pregnancy. Interim births were defined as singleton pregnancies of longer than 20 weeks of gestation that were conceived and delivered after baseline. We ascertained preexisting diabetes before pregnancy as distinct from GDM pregnancy based on biochemical (fasting and 2-h glucose levels) and medical history (1) data. We also validated self-report of GDM among 165 women for whom laboratory data were abstracted from medical records for 200 births between baseline and year 10. Sensitivity for classification by self-report as ever having GDM was 100% (20 of 20), and specificity was 92% (134 of 145).

We classified women into time-dependent interim birth groups during the follow-up period based on the cumulative number of singleton births and by GDM status: 0 births, one or more non-GDM births, or one or more GDM births within four intervals extending from baseline through years 7, 10, 15, and 20. Women transitioned from 0 births into one or more (1+) non-GDM or GDM birth groups within an interval, and group assignments remained for subsequent intervals, except when a GDM birth occurred after a non-GDM birth; then non-GDM would transition into the GDM group. Once classified with GDM, a woman remained in that category until the end of the follow-up regardless of GDM status for subsequent births.

Time-dependent parity (continuous covariate) was defined as the cumulative number of births since baseline and was updated at each exam through the end of follow-up.

Time-dependent lactation categories. Women reported the number of months of lactation for each pregnancy by choosing one of the following categories: none, <6 weeks, 6–11 weeks, 3–6 months, or >6 months. To calculate the duration of lactation across all births, we assigned the midpoint of the interval for each lactation category as follows: 21 days for <6 weeks, 66 days for 6–11 weeks, and 135 days for 3–6 months. For >6 months of lactation, we assigned a value of 210 days as the upper limit. Duration of lactation for each time interval was obtained by summing the number of days of lactation across all births within an interval. Total cumulative duration of lactation was updated for subsequent interval(s) by summing the duration for all prior intervals.

Time-dependent lactation categories were designated within non-GDM and GDM birth groups. Women were classified into one of four lactation groups for each time interval: 0–1 month, >1–5 months, 6–9 months and >9 months, representing the cumulative lactation duration for all births since baseline for the interval. Within non-GDM and GDM groups, the referent group was 0–1 month.

Other baseline and follow-up covariates. Sociodemographic, medical, and behavioral data (medication use, alcohol intake [ml/day], cigarette smoking, education, marital status, oral contraceptive use, physical activity) were collected at each exam using self- and interviewer-administered questionnaires. Baseline categorical variables were smoking (never, former, or current), years of education (12 or fewer, 13–15, and 16 or more), marital status (never married, widowed, divorced or separated, or married), and oral contraceptive use (never, past, or current). Medication use, including insulin, oral hypoglycemics, and antihypertensives, was self-reported. A positive family history of diabetes was based on report of one or more first-degree relatives (father, mother, or siblings) with diabetes at the examinations in years 0, 5, and 10.

We assessed daily physical activity at each examination using the interviewer-administered CARDIA Physical Activity History (23) to calculate physical activity scores (race-specific quartiles) that have correlated positively with symptom-limited graded treadmill exercise test duration (24). Time-

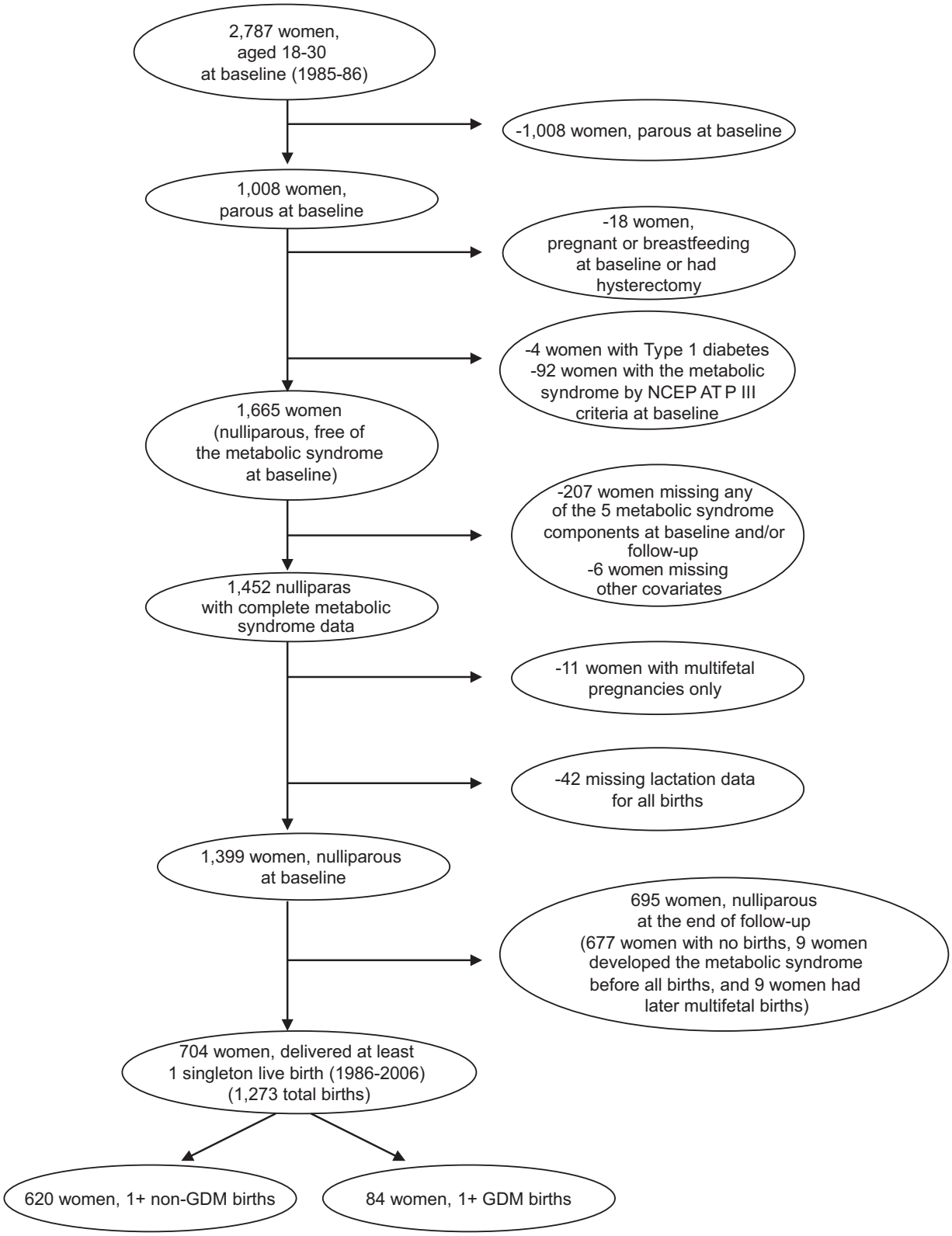


FIG. 1. Flow diagram for analytic sample selection: 704 women who were nulliparous, free of the metabolic syndrome, and aged 18–30 years at baseline (1985–1986) who delivered at least one singleton live birth during the 20-year follow-up period.

dependent covariates included physical activity, weight gain, cigarette smoking, oral contraceptive use, and parity groups for each follow-up time interval.

Statistical methods. Baseline and follow-up characteristics were described for outcome groups, and for the main effect, duration of lactation groups, by GDM status. We examined baseline characteristics: age, race, BMI, metabolic syndrome components (fasting plasma TG, HDL cholesterol, glucose levels, systolic and diastolic blood pressures, waist girth), diabetes, cigarette smoking, education, marital status, oral contraceptive use, alcohol, physical activity, and dietary intake. Follow-up characteristics included parity, family history of diabetes, and GDM status. χ^2 tests were used to assess associations with sociodemographic, medical history, study center, and behavioral categorical variables. t test statistics were used to assess the difference in continuous variables by incident metabolic syndrome. Multiple linear regression methods (ANOVA) were used to assess baseline differences in continuous

TABLE 1
Baseline characteristics (1985–1986), family history of diabetes, GDM status, and lactation duration among incident metabolic syndrome case participants and noncase participants (1986–2006)

Baseline characteristics	Incident metabolic syndrome case participants (n = 120)	Noncase participants (n = 584)	P*
Race (black)	67 (55.8)	212 (36.3)	<0.001
Education (high school or less)	41 (34.2)	148 (25.3)	0.06
Marital status (married)	22 (18.3)	99 (17.0)	0.64
Smoker (current)	27 (22.5)	125 (21.4)	0.90
Oral contraceptive use (current)	25 (20.8)	163 (27.9)	0.28
Family history of diabetes†	54 (45.0)	146 (25.0)	<0.001
Type 2 diabetes	1 (0.8)	1 (0.2)	0.31
GDM status (ever)†	23 (19.2)	61 (10.4)	0.007
Age (years)	23.8 ± 3.7	23.7 ± 3.6	0.75
BMI (kg/m^2)	26.8 ± 6.0	22.3 ± 3.5	<0.001
Waist girth (cm)	78.7 ± 12.1	69.1 ± 6.5	<0.001
Fasting			
Glucose (mg/dl)	82.1 ± 7.8	79 ± 7.1	<0.001
HDL cholesterol (mg/dl)	53.8 ± 13.1	58.2 ± 12.2	<0.001
TGs (mg/dl)	73.3 ± 37.7	61.2 ± 35.2	<0.001
Systolic blood pressure (mmHg)	110.5 ± 9.1	104.6 ± 8.6	<0.001
Diastolic blood pressure (mmHg)	68.5 ± 9.6	65.3 ± 8.7	<0.001
Dietary intake (% kJ)			
Fat	36.9 ± 6.3	37.1 ± 6.1	0.68
Saturated fat	13.9 ± 3.0	13.8 ± 3.0	0.83
Carbohydrate	47.4 ± 7.4	46.9 ± 7.4	0.50
Fiber (g)/1,000 kJ	0.54 ± 0.28	0.57 ± 0.28	0.29
Alcohol intake (ml/day)‡	2.4 (9.6)	2.4 (9.7)	0.53
Physical activity score‡	286.5 (281.0)	332.0 (339.5)	0.06
Lactation (months)†‡	2.6 (7.0)	7.0 (9.3)	<0.001

Data are n (%) or means ± SD. χ^2 test was used for categorical baseline characteristics; t test was used for continuous baseline characteristics. *Two-sided P value. †Ascertained during the 20-year follow-up period. ‡Median (interquartile range), Wilcoxon rank sum test.

variables (age, BMI, metabolic syndrome components, dietary intake) among duration of lactation groups. Wilcoxon rank sum and Kruskal-Wallis one-way tests were used to assess differences in alcohol intake and physical activity scores (median and interquartile range) due to skewing in the distributions. P values were obtained from two-sided tests (significance <0.05). Physical activity, weight gain, oral contraceptive use, parity, and smoking were examined as time-dependent covariates.

Metabolic syndrome incident case participants for each interval were categorized into time-dependent lactation categories and by GDM status during 20-year follow-up. To describe the pattern of new case participants over time, we calculated the cumulative incidence of metabolic syndrome (n/N, %) within each time interval (0–7, >7–10, >10–15, and >15–20 years) by dividing the number of incident case participants at the end of the interval by the number of women at risk of the metabolic syndrome at the beginning of the interval according to the lactation category and birth group assigned for that specific time interval. Women may transition into interim birth groups and longer lactation duration categories as parity and months of lactation increase through the end of follow-up.

We estimated unadjusted incidence rates of the metabolic syndrome for lactation groups by dividing the number of incident case participants of the metabolic syndrome by the person-time for individuals observed during the preceding intervals, then computed the exact 95% CIs. At each exam, women reported the number of births and months of lactation since the previous exam during follow-up. Person-time is contributed by each individual to a specific lactation category and interim birth group for the entire time interval during which they transitioned into a new category or birth group. During follow-up, women may contribute person-time to multiple lactation categories, and potentially to both non-GDM and GDM birth groups depending on whether non-GDM birth(s) preceded GDM birth(s) among successive intervals. Women remain in their group assignments through subsequent intervals unless additional births and/or months of lactation occur. For 23 births among a total of 1,273, lactation duration was missing and women had no previous births, so we assigned those births to the 0–1 month lactation category.

Because metabolic syndrome status was determined only at CARDIA exams, the exact failure time for a woman without the metabolic syndrome at a particular exam and identified with the metabolic syndrome at the subsequent exam is unknown. We accounted for interval-censored data using the method of Prentice and Gloeckler (25) to provide point and interval estimates of the relative hazard of metabolic syndrome associated with exposure. These estimates were obtained in the context of a generalized linear model for binary outcome with a complementary log-log link function. The hazard ratio for incidence of metabolic syndrome was estimated for lactation categories within GDM status groups at exams in years 7, 10, 15, and 20. Multivariable adjusted models (SAS version 9.1; SAS Institute, Cary, NC) included race, study center, time, baseline covariates (age, education, smoking), as well as the follow-up covariate, time-dependent parity, to account for differences in number of births across lactation categories (model 1). Next, we added other baseline covariates, BMI and all metabolic syndrome components, to model 1. To form the fully adjusted model, we then added baseline physical activity. Finally, we added time-dependent physical activity and weight gain, separately, as potential mediators of the lactation association by stepwise addition. Family history of diabetes and time-dependent smoking and oral contraceptive use had little impact on the results, and were not included in the fully adjusted model.

RESULTS

During 20 years, 704 participants without the metabolic syndrome before pregnancies delivered one or more singleton births (620 non-GDM, 84 GDM), and 695 women remained nulliparous. Among non-GDM and GDM groups, respectively, 252 (40%) and 21 (25%) women delivered one birth, 271 (44%) and 47 (56%) women delivered two births, and 97 (16%) and 16 (19%) women delivered three or more births during follow-up, for a total of 1,273 total births.

Among 704 parous women, there were 120 incident metabolic syndrome case participants in 9,993 person-years. The overall crude incidence rate was 12.0 case participants per 1,000 person-years (95% CI 10.0–14.3). Crude incidence rates were higher (P = 0.002) among women with GDM versus non-GDM pregnancies: 22.1 per 1,000 person-years (95% CI 14.1–33.0) and 10.8 per 1,000 person-years (95% CI 8.8–13.2), respectively. Among 695 nulliparas, there were 129 incident metabolic syndrome

TABLE 2
Baseline characteristics (1985–1986) and family history of diabetes for lactation categories stratified by GDM status (1986–2006)

Characteristics	Women with non-GDM births, lactation categories				
	0–1 month	>1–5 months	6–9 months	>9 months	*P**
n	157	157	152	154	
Race (black)	99 (63.1)	74 (47.1)	49 (32.2)	24 (15.6)	<0.001
Education (≤HS)	73 (46.5)	44 (28.0)	31 (20.4)	23 (14.9)	<0.001
Smoker (current)	42 (26.8)	40 (25.5)	22 (14.5)	20 (13.0)	0.001
Family history of diabetes	51 (32.5)	53 (33.8)	37 (24.3)	26 (16.9)	0.002
Age (years)	22.9 ± 3.6	23.6 ± 3.3	23.9 ± 3.7	24.5 ± 3.7	<0.001
BMI (kg/m^2)	24.2 ± 4.9	22.9 ± 4.0	22.6 ± 3.7	22.0 ± 3.1	<0.001
Waist girth (cm)	72.9 ± 9.0	70.3 ± 8.0	69.1 ± 7.3	69.3 ± 6.2	<0.001
Systolic blood pressure (mmHg)	106.1 ± 9.1	105.6 ± 8.5	106.1 ± 9.2	104.6 ± 9.2	0.41
Diastolic blood pressure (mmHg)	65.5 ± 8.7	65.4 ± 9.6	66.2 ± 8.8	65.9 ± 8.6	0.87
Fasting					
Glucose (mg/dl)	78.9 ± 7.5	78.9 ± 7.1	79.9 ± 6.5	79.5 ± 6.7	0.50
HDL cholesterol (mg/dl)	55.9 ± 12.2	57.8 ± 12.8	59.1 ± 11.7	58.4 ± 12.7	0.13
TGs (mg/dl)	66.7 ± 33.0	58.7 ± 23.4	59.0 ± 26.8	65.0 ± 54.2	0.11
Dietary intake (% kJ)					
Total fat	37.4 ± 6.5	37.9 ± 6.3	37.0 ± 5.2	35.4 ± 6.2	<0.01
Saturated fat	14.0 ± 3.1	14.0 ± 3.1	14.0 ± 2.7	13.1 ± 2.9	0.01
Carbohydrate	47.1 ± 8.1	46.3 ± 7.3	46.8 ± 6.6	48.0 ± 7.8	0.23
Fiber (g)/1,000 kJ	0.47 ± 0.26	0.55 ± 0.24	0.60 ± 0.26	0.66 ± 0.34	<0.001
Alcohol intake (ml/day)†	0.0 (7.6)	2.4 (9.5)	2.4 (9.7)	4.8 (12.1)	0.07
Physical activity score†	258.0 (280.0)	320.0 (317.0)	334.0 (382.0)	402.0 (362.0)	<0.001
	Women with GDM births, lactation categories				
	0–1 month	>1–5 months	6–9 months	>9 months	*P**
n	22	17	17	28	
Race (black)	16 (72.7)	7 (41.2)	4 (23.5)	6 (21.4)	0.001
Education (≤HS)	8 (36.4)	6 (35.3)	2 (11.8)	2 (7.1)	0.03
Smoker (current)	10 (45.5)	9 (52.9)	6 (35.3)	3 (10.7)	0.03
Family history of diabetes	11 (50.0)	3 (17.6)	6 (35.3)	13 (46.4)	0.16
Age (years)	22.8 ± 4.0	22.4 ± 3.7	24.2 ± 3.9	24.9 ± 3.6	0.10
BMI (kg/m^2)	27.0 ± 8.3	23.5 ± 4.5	23.9 ± 4.7	22.6 ± 4.1	0.05
Waist girth (cm)	79.5 ± 18.7	70.8 ± 7.8	72.1 ± 9.1	70.5 ± 8.2	0.05
Systolic blood pressure (mmHg)	108.4 ± 8.0	102.6 ± 7.7	103.3 ± 8.6	107.6 ± 10.4	0.10
Diastolic blood pressure (mmHg)	70.3 ± 7.3	60.4 ± 10.7	65.2 ± 7.0	68.7 ± 8.8	<0.01
Fasting					
Glucose (mg/dl)	80.0 ± 8.7	78.8 ± 10.8	81.8 ± 9.1	82.9 ± 9.2	0.48
HDL cholesterol (mg/dl)	52.7 ± 13.1	53.3 ± 12.7	56.9 ± 15.4	56.9 ± 11.7	0.59
TGs (mg/dl)	74.5 ± 25.9	70.6 ± 35.7	64.1 ± 30.0	70.0 ± 34.3	0.79
Dietary intake (% kJ)					
Total fat	37.3 ± 5.6	37.0 ± 3.3	40.4 ± 7.8	37.7 ± 5.6	0.29
Saturated fat	14.4 ± 2.8	14.0 ± 1.9	15.3 ± 4.5	13.8 ± 3.0	0.44
Carbohydrate	47.4 ± 6.7	46.3 ± 5.4	43.8 ± 8.8	46.2 ± 6.9	0.46
Fiber (g)/1,000 kJ	0.41 ± 0.16	0.48 ± 0.20	0.50 ± 0.22	0.62 ± 0.23	<0.01
Alcohol intake (ml/day)†	1.2 (7.6)	7.3 (18.4)	7.9 (15.2)	2.4 (8.6)	0.29
Physical activity score†	233.0 (297.0)	292.0 (153.0)	429.0 (334.0)	280.5 (309.0)	0.22

Data are *n* (%) or means ± SD. χ^2 test was used for categorical baseline characteristics; one-way ANOVA was used for continuous baseline characteristics. *Two-sided *P* value. †Median (interquartile range), Kruskal-Wallis test.

case participants in 11,590 person-years: incidence rate of 11.1 per 1,000 person-years (95% CI 9.3–13.2).

Compared with noncase participants, incident metabolic syndrome case participants (Table 1) differed in baseline characteristics including higher BMI, waist girth, fasting plasma glucose and TGs, and systolic and diastolic blood pressures as well as lower HDL cholesterol levels and physical activity scores. Incident metabolic syndrome case participants were also more likely to be black, to develop GDM, to have less education, to have a family history of diabetes, or to have a shorter duration of lactation.

Baseline characteristics differed among lactation categories (Table 2). Among the GDM group, lactation for 0–1 month compared with longer duration of lactation was associated with black race, less education, smoking, family history of diabetes, younger age, higher waist girth, BMI, fasting plasma TGs, total dietary fat and saturated fat intakes, and lower dietary fiber intake (g)/1,000 kJ. Lactation >9 months was associated with not smoking, older age, and higher physical activity score. Differences in baseline characteristics followed a similar pattern among lactation categories for the non-GDM group.

Incident metabolic syndrome case participants increased over time as the cohort aged (Table 3), with the greatest increase between years 15 and 20 compared with

TABLE 3
Cumulative incidence of the metabolic syndrome during follow-up intervals by GDM status and among duration of lactation categories (1986–2006)

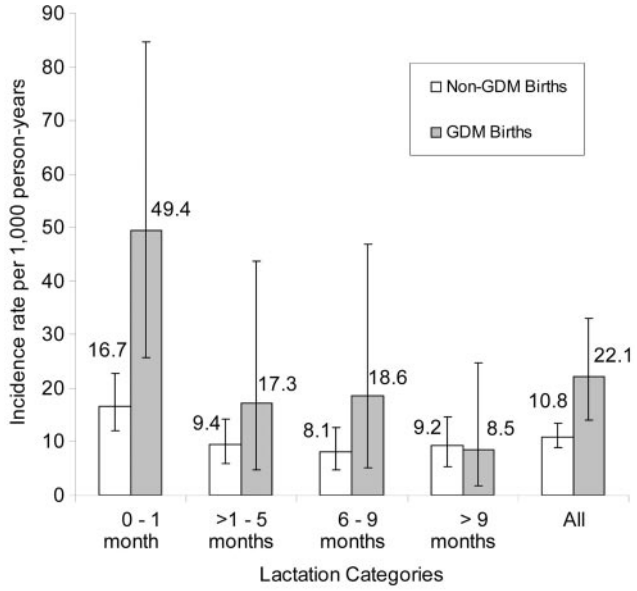
Duration of lactation	Year 0–7	Year >7–10	Year >10–15	Year >15–20
Non-GDM births (all)	8/382 (2.1)	13/463 (2.8)	30/515 (5.8)	46/463 (9.9)
0–1 month	5/143 (3.5)	6/147 (4.1)	14/124 (11.3)	15/93 (16.1)
>1–5 months	2/101 (2.0)	3/126 (2.4)	6/131 (4.6)	11/120 (9.2)
6–9 months	1/89 (1.1)	3/114 (2.6)	5/132 (3.8)	9/121 (7.4)
>9 months	0/49 (0.0)	1/76 (1.3)	5/128 (3.9)	11/129 (8.5)
GDM births (all)	6/43 (14.0)	5/53 (9.4)	3/61 (4.9)	9/55 (16.4)
0–1 month	4/16 (25.0)	2/12 (16.7)	1/10 (10.0)	5/9 (55.6)
>1–5 months	1/8 (12.5)	1/15 (6.7)	0/13 (0.0)	2/13 (15.4)
6–9 months	1/9 (11.1)	0/9 (0.0)	1/14 (7.1)	2/11 (18.2)
>9 months	0/10 (0.0)	2/17 (11.8)	1/24 (4.2)	0/22 (0.0)

Data shown are number of incident case participants of metabolic syndrome/number of individuals at risk within the specific interval (%).

the earliest interval. The cumulative incidence of the metabolic syndrome was highest for 0–1 month regardless of GDM status.

Incident metabolic syndrome case participants were more likely to develop new onset diabetes during follow-up: 19 (16%) of metabolic syndrome case participants and 16 (3%) of noncase participants ($P < 0.001$). Mean (SD) years since last birth were slightly fewer for metabolic syndrome case participants than noncase participants: 7.9 (5.0) and 9.2 (4.8), respectively ($P = 0.01$).

Crude incidence rates (number of case participants per 1,000 person-years) were higher for GDM than non-GDM groups across all lactation groups except for >9 months (Fig. 2). The incidence rates (95% CI) decreased with increasing duration of lactation: from 15.8 (11.3–21.5) to 9.2 (5.3–14.6) among the non-GDM group and from 49.4 (25.8–84.7) to 8.5 (1.8–24.8) among the GDM group. Overall, there was a sixfold lower crude incidence rate of the metabolic syndrome for >9 months versus 0–1 month



Metabolic Syndrome Case Participants by GDM Status:

Lactation Category:	0-1 month	>1-5 months	6-9 months	>9 months	All
Non-GDM, n	40	22	18	17	97
Person-years:	2,527	2,340	2,230	1,856	8,953
GDM, n	12	4	4	3	23
Person-years:	243	231	215	351	1,040

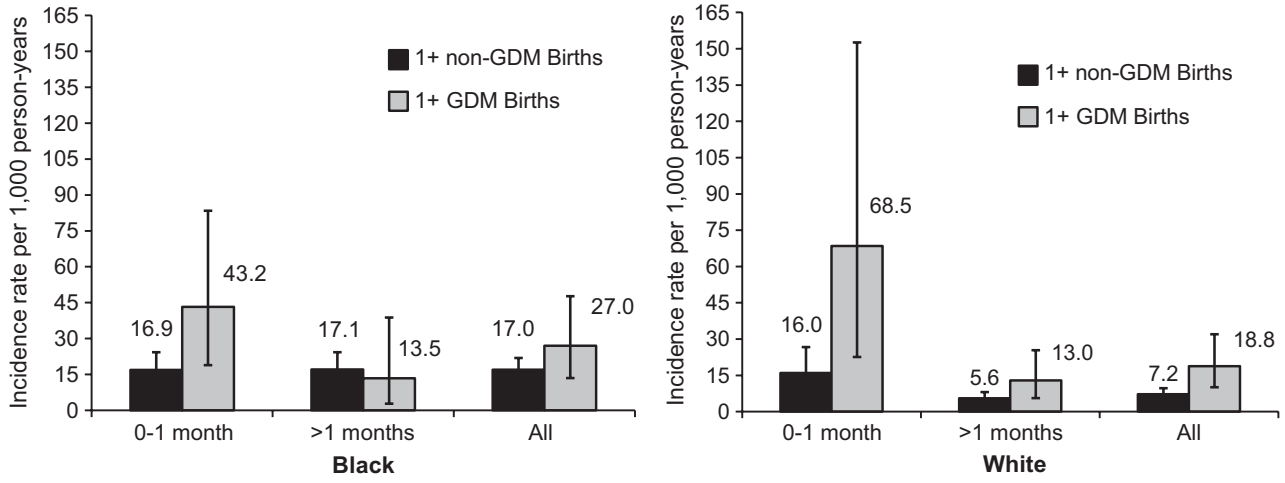
FIG. 2. Crude incidence rates (95% CIs) of the metabolic syndrome during 20 years of follow-up for lactation categories by GDM status.

of lactation among the GDM group, and a twofold lower incidence rate for the highest versus lowest duration of lactation among the non-GDM group. Within race groups, we examined crude incidence rates for >1 month versus 0–1 month of lactation, and found similar protective associations, except for blacks in the non-GDM group (Fig. 3). Median duration of lactation was shorter for blacks than whites (4.5 [interquartile range 4.8] vs. 7.0 months [9.2]; $P < 0.001$). Crude incidence rates for baseline BMI groups (<25, ≥25) were consistent with the race results (data not shown), including no difference in metabolic syndrome rates for >1 month and 0–1 month lactation categories among overweight women in the non-GDM group.

In multivariable models stratified by GDM status (Table 4), duration of lactation was inversely associated with the relative hazards of incident metabolic syndrome, from >1–5 months to >9 months compared with 0–1 month, with a stronger inverse association among GDM (relative hazard 0.11–0.24) than non-GDM groups (relative hazard 0.41–0.49) in unadjusted models (all $P < 0.001$). Adjustment for race, time-dependent parity, study center, and baseline covariates (age, education, smoking) attenuated relative hazards modestly, but a significant inverse association remained for GDM and non-GDM groups. In fully adjusted models, addition of baseline BMI, all metabolic syndrome components, and physical activity enhanced the graded inverse associations with longer lactation, remaining statistically significant for GDM and non-GDM groups (all $P = 0.03$). Addition of time-dependent physical activity during follow-up as a potential mediator revealed a stronger protective association among GDM (relative hazard 0.13–0.41; $P = 0.02$) than non-GDM groups (0.51–0.67; $P = 0.10$), whereas addition of weight gain in a separate model strengthened the association among women with GDM (0.09–0.49; $P = 0.01$).

DISCUSSION

Among women with and without GDM pregnancies, a longer cumulative duration of lactation was strongly protective, even after controlling for parity and baseline covariates, including components of the metabolic syndrome before pregnancy. For women with non-GDM pregnancies, there was a threshold effect with lactation >1 month conferring protection compared with 0–1 month. Among women with GDM pregnancies, we found a strong, graded inverse association of lactation with incidence of the metabolic syndrome, those with longest lactation



Race	Non-GDM		GDM	
	Duration of Lactation		Duration of Lactation	
	0-1 month	>1 months	0-1 month	>1 months
Black				
Cases, n	26	30	8	3
Person-yrs	1667	1,699	185	223
White				
Cases, n	14	27	4	8
Person-yrs	860	4,727	58	574
All				
Cases, n	40	57	12	11
Person-yrs	2,527	6.426	243	797

FIG. 3. Crude incidence rates (95% CIs) of the metabolic syndrome during 20 years of follow-up for lactation categories by GDM status (1986–2006) and race (black and white).

approaching the non-GDM incidence rate of the metabolic syndrome. The associations remained after controlling for mediators such as changes in physical activity or weight gain during follow-up, with a stronger protective association among the GDM group.

Associations were similar within race and BMI groups, especially for women with a history of GDM. However, black women had much shorter duration of lactation that limited our ability to fully assess the association of extended duration of lactation with disease risk. Overweight status was closely related to black race, and our sample size was too small to fully assess the separate effects. We did not observe significant interactions by number of singleton pregnancies because most women (84%) delivered only one or two pregnancies.

Epidemiologic studies examining lactation history and prevalence of the metabolic syndrome or cardiovascular disease (CVD) risk have not measured preconception risk factor levels or stratified by GDM status. Cross-sectional studies of primarily perimenopausal and postmenopausal women reported that lactation >1 month (9) or any lactation (10) was associated with 21–22% lower prevalence of the metabolic syndrome, and that lactation >12 months was associated with 9–20% lower prevalence of CVD risk factors, but not incidence of CVD (11). In studies of lactation and type 2 diabetes after GDM and non-GDM pregnancies, glucose levels before pregnancy were not measured (6,7,13). Longer lifetime lactation ≥4 months was associated with a 25% lower incidence of type 2 diabetes among white women, but not those with a history of GDM (13). In Latinas with previous GDM, findings on lactation and future diabetes risk were inconclusive, and duration was not assessed (26).

Our findings for women of reproductive age show a much stronger protective association for >1 month of lactation: lower incidence of the metabolic syndrome by 39–56% for non-GDM and by 44–86% for GDM groups. Because our sample included only nulliparas at baseline and preconception measurements of all metabolic syndrome components, we minimized confounding by preexisting conditions before pregnancy and lactation.

Our study's unique strengths include prospective collection of "preconception" measurements of the metabolic syndrome components to confirm that women were free of the metabolic syndrome before pregnancies, and stratification by GDM status. Metabolic syndrome components were measured at 3- to 7-year intervals before and after pregnancies over a 20-year period, thereby maintaining the temporality of the exposure (pregnancy and lactation duration) to new onset of metabolic syndrome. We also modeled lactation as a time-dependent main effect and controlled for multiple potential confounders including age, time-dependent parity, secular trends, sociodemographics, and behavioral attributes. The validity of our findings is enhanced by the population-based sample, high cohort retention rate over 20 years of follow-up, and measurement of all five metabolic syndrome components at baseline for 100% of the sample and for three or more follow-up visits for 72% of the sample. We also examined associations separately for black and white race groups, and found consistent associations.

Limitations include no data on lactation intensity, ascer-

TABLE 4
Unadjusted and multivariable adjusted relative hazards (95% CIs) of incident metabolic syndrome and duration of lactation categories by GDM status (1986–2006)

Models	1 or more non-GDM births, referent: 0–1 month lactation (n = 157)				1 or more GDM births, referent: 0–1 month lactation (n = 22)			
	Lactation duration				Lactation duration			
	>1–5 months	6–9 months	>9 months	P*	>1–5 months	6–9 months	>9 months	P*
n	157	152	154		17	17	28	
Unadjusted	0.49 (0.29–0.82)	0.40 (0.23–0.71)	0.41 (0.23–0.72)	<0.001	0.24 (0.08–0.75)	0.28 (0.09–0.86)	0.11 (0.03–0.39)	0.001
Model 1 = study center, race, baseline covariates (age, education, and smoking), and time-dependent parity†	0.54 (0.32–0.91)	0.49 (0.28–0.88)	0.54 (0.28–1.02)	0.03	0.33 (0.10–1.03)	0.34 (0.11–1.07)	0.14 (0.04–0.53)	0.01
Model 1 + baseline covariates: (BMI and all metabolic syndrome components)	0.63 (0.37–1.08)	0.52 (0.29–0.93)	0.45 (0.24–0.87)	0.04	0.54 (0.16–1.75)	0.37 (0.11–1.24)	0.14 (0.04–0.55)	0.03
Fully adjusted model = model 1 + baseline covariates (BMI, all metabolic syndrome components) and baseline physical activity	0.61 (0.36–1.05)	0.52 (0.29–0.93)	0.44 (0.23–0.84)	0.03	0.56 (0.17–1.82)	0.35 (0.11–1.16)	0.14 (0.04–0.55)	0.03
Fully adjusted model + time-dependent physical activity (mediator)	0.67 (0.39–1.16)	0.54 (0.30–0.98)	0.51 (0.26–0.98)	0.10	0.41 (0.12–1.35)	0.27 (0.08–0.90)	0.13 (0.03–0.52)	0.02
Fully adjusted model + time-dependent weight gain (mediator)	0.71 (0.41–1.24)	0.35 (0.19–0.65)	0.56 (0.29–1.09)	0.01	0.49 (0.15–1.64)	0.33 (0.09–1.14)	0.09 (0.02–0.37)	0.01

*Test of the overall association among lactation categories and incident metabolic syndrome within non-GDM and GDM birth groups. †Time-dependent parity (continuous covariate) is the cumulative total number of births since baseline for each time interval through the end of follow-up.

tainment of GDM by self-report, variable time intervals to conception and from delivery relative to CARDIA exams, and few higher order births. Our GDM validation study showed high sensitivity and specificity of GDM by self-report, and nondifferential misclassification would bias our findings toward the null. Women who lactated may have had healthier lifestyles than women who did not lactate, but we accounted for these traits as well as weight gain. Despite control for various behavioral and other potential confounders, residual confounding is always possible in observational studies.

One proposed mechanism through which lactation may influence cardiometabolic health is through greater weight loss. Although milk production increases maternal total energy expenditure by 15–25% (27,28), evidence for greater postpartum weight loss is equivocal (29). Prospective studies that measured maternal weights (not self-reported) before or during early pregnancy have generally reported lower postpartum weight retention at 1 year postpartum (30), more rapid loss approaching pregravid weight (31), or 1–2 kg greater weight losses within 3–6 months postpartum among lactating women (32). Yet, weight change did not explain the protective association between lactation and the metabolic syndrome in our study.

Another possibility is that lactation affects body composition and regional fat distribution. Well-nourished lactating women lose about 2 kg in total fat mass by 6 months postpartum based on magnetic resonance imaging (33) or mass spectrometry (34) and tend to mobilize more fat from the thigh than the trunk (33). In lactating American women, skinfold thickness was reduced in the suprailiac and subscapular regions, but increased in the triceps region (35). Yet, studies that compared lactating versus nonlactating women using dual-energy X-ray absorptiometry found greater declines in total body fat mass within 3–6 months postpartum (36) but no differences in mobilization of fat from leg, arm, and trunk regions (36,37). In 26 women with previous GDM, visceral fat mass via computed tomography at 3 months postpartum did not differ by lactation status (38). Longitudinal studies are needed to examine postpartum visceral fat changes in larger samples.

Acutely, lactogenesis has favorable effects on maternal cardiometabolic blood profiles, but few studies have adjusted for BMI, or measured postweaning levels. Lactating women had lower plasma TGs (39,40) and higher plasma HDL cholesterol levels and HDL cholesterol/total cholesterol ratios at 3–6 months postpartum unadjusted for BMI (4,41,42). They also had elevations in respiratory quotient and carbohydrate utilization consistent with preferential use of glucose (28). Moreover, lactating versus nonlactating women exhibited greater insulin sensitivity among GDM and non-GDM groups (5,38). In postweaning studies, plasma HDL cholesterol levels were higher with longer duration of lactation after accounting for preconception levels and weight gain (8), but lactation was not associated with plasma total cholesterol or other lipids (8,43).

In summary, longer duration of lactation was associated with lower incidence of the metabolic syndrome years after delivery and after weaning among women with non-GDM as well as GDM pregnancies. Lifestyle behaviors did not explain these associations. Lactation may ameliorate the increased risk of the metabolic syndrome associated with higher parity (30% per birth in non-GDM, 150% for GDM) (3). By contrast, other studies have not demonstrated clear benefits of lactation on future health of

women with a history of GDM. Our data provide strong evidence that lactation may have lasting favorable effects on metabolic risk profiles among women with a history of GDM who are most susceptible to developing metabolic diseases, as well as women without GDM. Further investigation is needed to elucidate the mechanisms through which lactation may influence women's cardiometabolic risk profiles, and whether lifestyle modifications, including lactation duration, may affect development of coronary heart disease and type 2 diabetes, particularly, among high-risk groups such as women with a history of GDM.

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (contracts nos. N01-HC-48047, N01-HC-48048, N01-HC-48049, N01-HC-48050, and N01-HC-95095 from the National Heart, Lung, and Blood Institute, and Career Development Award; Grant K01-DK-059944 from the National Institute of Diabetes and Digestive and Kidney Diseases) and a Research Award from the American Diabetes Association.

No potential conflicts of interest relevant to this article were reported.

Parts of this study were presented in oral abstract form at the 69th Scientific Sessions of the American Diabetes Association, New Orleans, Louisiana, 5–9 June 2009.

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