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Lactation Duration and Progression to Diabetes in Women Across the Childbearing Years
The 30-Year CARDIA Study

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IMPORTANCE Lactation duration has shown weak protective associations with incident diabetes (3%-15% lower incidence per year of lactation) in older women based solely on self-report of diabetes, studies initiated beyond the reproductive period are vulnerable to unmeasured confounding or reverse causation from antecedent biochemical risk status, perinatal outcomes, and behaviors across the childbearing years.

OBJECTIVE To evaluate the association between lactation and progression to diabetes using biochemical testing both before and after pregnancy and accounting for prepregnancy cardiometabolic measures, gestational diabetes (GD), and lifestyle behaviors.

DESIGN, SETTING, AND PARTICIPANTS For this US multicenter, community-based 30-year prospective cohort study, there were 1238 women from the Coronary Artery Risk Development in Young Adults (CARDIA) study of young black and white women ages 18 to 30 years without diabetes at baseline (1985-1986) who had 1 or more live births after baseline, reported lactation duration, and were screened for diabetes up to 7 times during 30 years after baseline (1986-2016).

EXPOSURES Time-dependent lactation duration categories (none, >0 to 6 months, >6 to <12 months, and ≥12 months) across all births since baseline through 30 years.

MAIN OUTCOMES AND MEASURES Diabetes incidence rates per 1000 person-years and adjusted relative hazards (RH) with corresponding 95% CIs, as well as proportional hazards regression models adjusted for biochemical, sociodemographic, and reproductive risk factors, as well as family history of diabetes, lifestyle, and weight change during follow-up.

RESULTS Overall 1238 women were included in this analysis (mean [SD] age, 24.2 [3.7] years; 615 black women). There were 182 incident diabetes cases during 27 598 person-years for an overall incidence rate of 6.6 cases per 1000 person-years (95% CI, 5.6-7.6); and rates for women with GD and without GD were 18.0 (95% CI, 13.3-22.8) and 5.1 (95% CI, 4.2-6.0), respectively (*P* for difference < .001). Lactation duration showed a strong, graded inverse association with diabetes incidence: adjusted RH for more than 0 to 6 months, 0.75 (95% CI, 0.51-1.09); more than 6 months to less than 12 months, 0.52 (95% CI, 0.31-0.87), and 12 months or more 0.53 (0.29-0.98) vs none (0 days) (*P* for trend = .01). There was no evidence of effect modification by race, GD, or parity.

CONCLUSIONS AND RELEVANCE This study provides longitudinal biochemical evidence that lactation duration is independently associated with lower incidence of diabetes. Further investigation is required to elucidate mechanisms that may explain this relationship.

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Supplemental content

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Normal pregnancy is an insulin-resistant state characterized by intensified fluctuations in maternal fasting and postprandial glycemia, hypertriglyceridemia, and increased insulin secretion.[1] Lactation rapidly lowers maternal circulating triglycerides and glucose, lessens insulin secretion, and mobilizes adipose tissue stores.[2-4] Some longitudinal evidence shows that more favorable metabolic profiles persist postweaning,[5] despite minimal or no weight loss,[6] but biochemical evidence that directly links lactation with long-term diabetes risk is unavailable. Large, prospective epidemiologic studies of middle-aged or older women of northern European or Asian ancestry showed weak to modest relative reductions in diabetes risk of 3% to 15% per year of lactation,[7,8] or 20% for 6 or more months of lactation.[9] All studies relied on self-report of diabetes without biochemical testing or other assessments across the childbearing years or beyond.[7-9] Furthermore, none considered gestational diabetes (GD), a strong risk factor for type 2 diabetes in young women,[10-12] although a retrospective subanalysis among women reporting GD after incident diabetes found no association.[7] Thus, risk estimates may be biased away from the null owing to unmeasured confounding or reverse causation from cardiometabolic risk factors, GD status, perinatal outcomes, and differences in lactation duration among older vs younger women, or biased toward the null by exclusion of high-risk younger women who had transitioned to diabetes many years prior to study baseline. The lack of longitudinal biochemical testing, older age of study participants at baseline, and the inability to evaluate antecedent biochemical and perinatal parameters, including GD status, diminish the validity for this entire body of evidence.

One prospective study[13] of women with GD found that increasing lactation intensity and duration were associated with 34% to 57% lower 2-year incidence of diabetes (*P* for trend = .01) from annual oral glucose tolerance tests. This is the only study to account for reverse causation and confounding from prepregnancy obesity, gestational metabolism, perinatal outcomes, sociodemographics, and postdelivery lifestyle behaviors.[13]

To overcome the limitations of previous studies among mostly older women, we prospectively evaluated progression to diabetes among young black and white women during the 30-year Coronary Artery Risk Development Study in Young Adults (CARDIA) study (NCT00005130). CARDIA conducted multiple assessments of glucose tolerance and other risk factors up to 7 times from prepregnancy to postweaning across the childbearing years. The prospective biochemical assessments enhance validity given that randomization to either breast or formula feeding is not desirable or feasible. We hypothesized that lactation duration is associated strongly with lower incidence of diabetes in women through midlife.

Key Points

Question Is the protective association between lactation duration and progression to diabetes supported by a biochemical evidence basis?

Findings Among young white and black women in this observational 30-year study, increasing lactation duration was associated with a strong, graded 25% to 47% relative reduction in the incidence of diabetes even after accounting for prepregnancy biochemical measures, clinical and demographic risk factors, gestational diabetes, lifestyle behaviors, and weight gain that prior studies did not address.

Meaning This study provides evidence to support the hypothesis that lactation may lower risk of diabetes in women; these findings open new avenues into mechanisms leading to glucose intolerance.

Methods

The US multicenter CARDIA study examines the trends and correlates of cardiovascular disease risk in young black and white men and women. The CARDIA study enrolled 5115 adults aged 18 to 30 years from 1985 to 1986 (2787 women; 52% black and 48% white) using community-based sampling from 4 geographic areas in the United States: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. The study design, recruitment, methodology, and characteristics are described elsewhere.[14] Retention was 81%, 79%, 74%, 72%, 72% and 71% of the surviving cohort at 7, 10, 15, 20, 25, and 30 years since baseline, respectively. Institutional review boards at each participating study center (University of Alabama at Birmingham, Northwestern University, University of Minnesota, and Kaiser Permanente Northern California) approved the study. Written informed consent was obtained from participants for all study procedures.

Selection Criteria

Of 2787 women enrolled, we excluded 41 with diabetes, 24 with a hysterectomy or bilateral oophorectomy, and 5 who were pregnant or lactating at baseline. We also excluded 2 women who developed diabetes before their first postbaseline birth, 154 without any follow-up, and 1196 without postbaseline births (eFigure 1 in the Supplement). Of 1365 women without diabetes who attended 1 or more follow-up examinations, 127 (9.3%) had missing lactation duration data. The analysis included 1238 women (n = 615 black [50.0%]) without diabetes before pregnancy who delivered 2302 live born infants after baseline. Women excluded were less educated, had higher body mass index (BMI; calculated as weight in kilograms divided by height in meters squared), and were more likely of black race.

Data Collection

Data collected included trained and certified staff-assessed medical and clinical attributes; sociodemographics and lifestyle behaviors at in-person examinations using standardized methodologies; calibrated equipment; and interviewer and self-administered questionnaires. Procedures for venipuncture, laboratory quality control, and biochemical assays are detailed elsewhere.[15] We used the homeostasis model assessment index (HOMA-IR) to estimate insulin resistance,[16] and the NCEP-ATP III (National Cholesterol Education Program Adult Treatment Panel III) criteria for the metabolic syndrome.[17]

Incident Diabetes

We defined incident diabetes as self-report of diabetes with medication treatment or elevated fasting or 2-hour postload serum glucose from the 75 g oral glucose tolerance tests and/or glycated hemoglobin consistent (fasting glucose measured at examinations in years 0, 7, 10, 15, 20, 25, or 30; oral glucose tolerance tests in years 15, 20, 25, or 30; and glycated hemoglobin in years 20, 25, or 30) based on the American Diabetes Association diagnostic criteria for diabetes: fasting glucose, 126 mg/dL or greater; 2-hour glucose, 200 mg/dL or greater; and/or glycated hemoglobin, 6.5% or greater (48 mmol/mol).[18]

Time-Dependent Parity (Postbaseline Births) and GD

At each examination, women reported current pregnancy or lactation, number of pregnancies and births since the last examination, pregnancy outcomes (abortion, miscarriage, and live or stillbirths, dates of deliveries, gestational ages, infant birth weight, hypertension with or without proteinuria, GD, preterm birth, and mode of delivery). Parity at baseline was defined as number of pregnancies 20 weeks' gestation or more. Time-dependent parity and GD variables indicate the number of live births since baseline by GD status and are updated at each study examination. We validated GD history by medical record abstraction of discharge diagnoses and laboratory tests for 165 women (200 pregnancies). Self-report of GD had high sensitivity (100%) and specificity (92%) confirmed by oral glucose tolerance laboratory results based on the Carpenter and Coustan criteria.[19] Preterm birth (<37 weeks) was reported with high sensitivity and specificity of 84% and 89%, respectively. Hypertensive disorders of pregnancy were overreported by women and had low sensitivity (40%) but high specificity (90%).[20] We distinguished GD from overt diabetes based on the CARDIA Study questionnaires, dates of self-report of diabetes diagnosis with medication treatment, and biochemical test results at study examinations as previously described.[21]

Time-Dependent Lactation Duration

Women reported lactation duration at year 7 for all previous birth(s) and for each birth at subsequent examinations. For a "yes" that they had breastfed the child, women selected 1 of these categories: less than 6 weeks, 6 to 11 weeks, 3 to 6 months, or 6 months or more. To calculate duration, we assigned the midpoint of each lactation category to each birth: 21 days for less than 6 weeks; 66 days for 6 to 11 weeks; 135 days for 3 to 6 months; and 210 days as the upper limit for 6 months or more (except women currently lactating, who were assigned a maximum of 650 days). Then, we summed lactation duration (days) across all births. Time-dependent lactation categories were updated at each examination year as births occurred. Women were assigned into relevant categories: none (n = 322 [26.0%]); more than 0 to 6 months (n = 418 [33.8%]); more than 6 months to less than 12 months (n = 268 [21.6%]); and 12 months or more (n = 230 [18.6%]) across examinations through the end of follow-up.

Other Covariates

At each examination, women reported sociodemographics and lifestyle behaviors (alcohol intake, cigarette smoking, physical activity), as well as prior medical history (hypertension, heart disease, diabetes), and medication use. Women also reported menopausal status and family history of diabetes. The CARDIA Diet History questionnaire[22] assessed dietary intake at baseline, and years 7 and 20. We calculated an a priori diet quality score, an index of plant-based food patterns, as described in detail elsewhere.[23] We averaged the scores from the 3 examinations. The CARDIA Physical Activity History questionnaire estimated a physical activity score that correlates positively with the symptom-limited graded treadmill exercise test duration.[24] We configured physical activity as time-dependent race-specific quartiles.

Statistical Analysis

We assessed differences in baseline and follow-up characteristics among lactation categories and by incident diabetes using χ^2 statistics for categorical variables and using analysis of variance for continuous variables. Median and interquartile ranges were reported for alcohol intake, HOMA-IR, weight change, and physical activity score for skewed distributions, with differences across lactation categories and by incident diabetes assessed with the Kruskal-Wallis test; *P* values were obtained from 2-sided tests (significance, <.05). All analyses were performed using SAS version 9.3 (SAS Institute, Inc).

We identified incident diabetes cases between consecutive examinations (0-7, >7 to 10, >10 to 15, >15 to 20, >20 to 25, >25 to 30 years), and estimated incidence rates and 95% CIs for diabetes among lactation categories by dividing the number of incident cases by the person-time across preceding intervals. Person-time is contributed by each individual for the entire time interval within the lactation category. Women may contribute person-time to multiple lactation categories moving across time until the end of follow-up (ie, last examination year 7 to year 30 or onset of incident diabetes). Because diabetes onset was only determined at CARDIA examinations, the exact failure time for a woman without diabetes at a particular examination and onset of diabetes at the subsequent examination is unknown. We calculated point and interval estimates of relative hazards ratio (RH) and 95% CI for incidence of diabetes among lactation duration categories accounting for interval-censored data using the Prentice and Gloeckler[25] proportional hazards regression model. Adjusted models included covariables: examination years (time), race, family history of diabetes, baseline age, fasting glucose, BMI and waist circumference, time-dependent GD, parity and physical activity, and dietary quality score. Trend *P* values were generated from models of continuous time-dependent lactation duration. We evaluated potential confounders based on a priori hypotheses for selected baseline (BMI, fasting blood glucose and lipids, HOMA-IR, blood pressure, sociodemographics), and follow-up (smoking, dietary quality, physical activity, hypertension, medication use, and pregnancy outcomes) covariates. We evaluated median weight change as a time-dependent dichotomous covariate. Covariates were not included if they were not associated with incident diabetes independent of other model covariates or did not alter 1 or more coefficients for lactation by at least 10% after addition of covariates. We formally tested effect modification of the lactation-

diabetes association by race, baseline BMI, GD status, and parity by introduction of cross-product terms (*P* value significance, <.10).

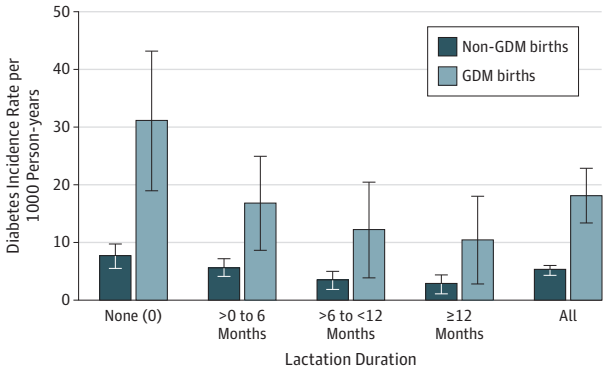
Results

Of 1238 women (n = 615 black [50.0%] and n = 623 white [50.0%]) without diabetes before pregnancies who delivered 1 or more singleton births (n = 2302) after baseline, 155 (12.5%) reported GD status for postbaseline births within a mean (SD) follow-up time of 24.7 (6.6) years. There were 182 incident cases of diabetes (median age, 47 years) in 27 598 person-years for an overall incidence rate of 6.6 cases per 1000 person-years (95% CI, 5.6-7.6), with 132 cases (73.0%) in 13 369 person-years for black women, and 50 cases in 14 229 person-years for white women. Diabetes incidence per 1000 person-years was higher in black women (9.9; 95% CI, 8.2-11.6), than white women (3.5; 95% CI, 2.5-4.5) (*P* for differences <.001). Diabetes incidence per 1000 person-years was alsohigher for women with GD than women without GD (non-GD) groups: 18.0 (95% CI, 13.3-22.8) and 5.1 (95% CI, 4.2-6.0), respectively (*P* for difference <.001) (**Figure**; **Table 1**). For GD and non-GD groups, lactation duration was inversely associated with diabetes incidence, with lowest incidences for lactation more than 12 months (all *P* for trend = .02). Eighty-six percent of incident cases of diabetes occurred from 15 to 30 years postbaseline, whereas 93% of the postbaseline births occurred prior to 15 years postbaseline.

At baseline, women who later developed diabetes (**Table 2**) were more likely to be black, multiparous, reach menarche earlier, and had higher BMI, waist circumference, fasting glucose and triglycerides, HOMA-IR and blood pressure, and lower high-density lipoprotein cholesterol, physical activity, and diet quality scores. At follow-up, women who later developed diabetes had higher parity, weight gain and decrements in physical activity, shorter lactation duration, and lower diet quality, and a higher percentage were unmarried, treated for hyperlipidemia and hypertension, developed GD, gestational hypertension or metabolic syndrome, and had a family history of diabetes (**Table 3**).

Baseline characteristics were similar across the lactation categories (eTable 1 in the Supplement). All biochemical parameters fell within normal ranges, reflecting their young age (18-30 years) and good health, but the absolute differences across lactation categories were small. However, at baseline, women who never lactated (none) tended to be slightly younger, nulliparous, black race, or smokers; had slightly lower

Figure. Incidence Rates of Diabetes Mellitus Among Lactation Duration Categories Stratified by GD Status in Women



Crude incidence rates and corresponding 95% CIs (whiskers) of diabetes in black and white women enrolled in the Coronary Artery Risk Development in Young Adults trial subsequent to postbaseline births and lactation during 30 years of follow-up (1986-2016). The incidence rates of diabetes (cases per 1000 person-years) were based on systematic testing up to 7 times and were stratified by GD status for postbaseline births. The entire sample comprised 1238 women (GD = 155; non-GD = 1083), and overall *P* < .001 (*P* for trend for women with GD = .02; *P* for trend for women without GD = .001). See Table 1 for further data. GD indicates gestational diabetes.

Table 1. Incidence Rates of Diabetes Among Lactation Categories

	Lactation Duration Categories[a]				
GD Status	None	>0 to 6 Months	>6 to <12 Months	≥12 Months	All
Women without GD (n = 1083)					
Cases of diabetes, No.	49	49	18	10	126
Person-years	6506	8866	5367	3753	24 492
Incidence rate per 1000 person-years (exact 95% CI)	7.5 (5.4-9.6)	5.5 (4.0-7.1)	3.4 (1.8-4.9)	2.7 (1.0-4.3)	5.1 (4.2-6.0)
Women with GD (n = 155)					
Cases of diabetes, No.	25	16	8	7	56
Person-years	805	957	663	681	3106
Incidence rate per 1000 person-years (exact 95% CI)	31.1 (18.9-43.2)	16.7 (8.5-24.9)	12.1 (3.7-20.4)	10.3 (2.7-17.9)	18.0 (13.3-22.8)
All women (n = 1238)					
Cases of diabetes, No.	74	65	26	17	182
Person-years	7311	9823	6030	4434	27 598
Incidence rate per 1000 person-years (exact 95% CI)	10.1 (7.8-12.4)	6.6 (5.0-8.2)	4.3 (2.7-6.0)	3.8 (2.0-5.7)	6.6 (5.6-7.6)

Abbreviations: GD, gestational diabetes.

[a] For for lactation duration categories, the number of incident cases per 1000 person-years for all women was 1238, stratified by GD status; women with 1 or more GD births, 155; and women without GD births, 1083 (overall association for lactation duration and incident diabetes, *P* < .001; among women with GD, *P* for trend = .001; and among women without GD *P* for trend = .02).

Table 2. Baseline Characteristics by Incident Diabetes During 30 Years From 1986 to 2016 Among Women Without Diabetes Before 1 or More Live Births Since the Baseline CARDIA Examination[a]

Baseline Characteristics	No. (%)		P Value
	Incident Diabetes (n = 182)	No Diabetes (n = 1056)	
Black race/ethnicity	132 (73)	483 (46)	<.001
Parity			
Nulliparas (0 births)	110 (60)	742 (70)	.01
Primiparas (1 birth)	52 (29)	204 (19)	
Multiparas (2 or more births)	20 (11)	110 (10)	
Married	44 (24)	273 (26)	.22
Smoker (current or past)	60 (33)	259 (25)	.05
Metabolic syndrome at baseline	3 (2)	2 (0.2)	.03
Age, mean (SD), y	24.2 (3.7)	24.0 (3.7)	.55
Age at menarche, mean (SD), y	12.3 (1.7)	12.7 (1.6)	.003
Body mass index, mean (SD), kg/m^2	27.5 (6.8)	23.1 (4.4)	<.001
Waist circumference, mean (SD), cm	80.3 (14.3)	71.1 (8.7)	<.001
Blood Pressure, mean (SD), mm Hg			
Systolic	108.6 (9.7)	105.2 (8.9)	<.001
Diastolic	67.8 (8.9)	65.5 (8.5)	.001
Fasting glucose, mean (SD), mg/dL	82.0 (9.3)	78.9 (7.4)	<.001
Cholesterol, mean (SD), mg/dL			
High-density lipoprotein	52.6 (13.5)	56.8 (12.5)	<.001
Low-density lipoprotein	110.2 (31.2)	107.7 (29.8)	.31
Total	176.7 (32.5)	177.3 (32.2)	.84
Triglycerides, mean (SD), mg/dL	69.6 (32.9)	64.0 (34.5)	.04
Dietary intake, mean (SD) for % kcal			
Energy from carbohydrate	47 (7)	47 (8)	.81
Energy from fat	38 (6)	37 (6)	.22
Diet Quality score, mean (SD)[b]	61.3 (12.7)	64.7 (13.6)	.002
HOMA-IR, median (IQR)[c]	2.5 (2.5)	1.7 (1.2)	<.001
Crude fiber intake, median (IQR) g/1000 kcal	2 (1)	2 (1)	.12
Alcohol intake, median (IQR), mL/d[c]	0.0 (7.9)	2.4 (9.6)	.18
Physical activity score, median (IQR)[c]	221 (268)	306 (330)	<.001

Abbreviations: HOMA-IR, homeostatic model assessment–insulin resistance; IQR, interquartile range.

[a] This analysis included 1238 women and 2302 births.

[b] A priori Diet Quality score was obtained at baseline (year 0).

[c] Data for fasting serum glucose levels at year 0 were available for 1223 participants; year 7 prior to diabetes for 10 participants; and missing for 5 participants (Kruskal-Wallis test).

mean plasma high-density lipoprotein cholesterol, dietary fiber intake, physical activity, and dietary quality; and slightly higher dietary fat intake, BMI, waist circumference, low-density lipoprotein cholesterol, and HOMA-IR. During follow-up (eTable 2 in the Supplement), the no lactation group (none) had lower education and diet quality, higher prevalence of the metabolic syndrome; treatment for hypertension, and a family history of diabetes; and greater weight gain. Mean weight change during follow-up among lactation categories was similar among women with or without incident diabetes (*P* for interaction = .99) (eFigure 2 in the Supplement).

In multivariate models stratified by GD status, graded inverse lower RH of incident diabetes with time-dependent lactation categories were slightly stronger among GD than non-GD groups (data not shown). In multivariate models stratified by race, these graded inverse associations were similar among black women and white women (data not shown) but did not reach statistical significance. Adjusted RHs for incident diabetes in models with continuous months of lactation were similar by race (eTable 3 in the Supplement) and by GD status but reached statistical significance for women with GD (data not shown). There was no evidence of effect modification by race, baseline BMI, GD, or parity (*P* values >.16; Figure). Based on these analyses, we combined race and GD groups into a single Cox proportional hazards model (**Table 4**). In unadjusted models, increasing time-dependent categories of lactation duration were strongly associated with lower incidence of diabetes (*P* for trend <.001; Table 4). Addition of a priori confounders (race, prepregnancy BMI, waist circumference, fasting blood glucose or HOMA-IR, age, time-dependent parity and GD status, family history of diabetes) moderately attenuated associations, but they remained statistically significant (*P* for trend = .01; Table 4). Addition of lifestyle behaviors during follow-up (ie, quartiles of dietary quality score and time-dependent physical activity) had minimal impact on RHs. Addition of time-dependent weight change strengthened these graded protective associations with estimates of 25% to 47% lower relative risk of incident diabetes (fully adjusted RHs range from 0.75 to 0.53; *P* for trend = .01). Other characteristics (eg, medical conditions, fasting lipids,

Table 3. Characteristics by Incident Diabetes From 1986 to 2016 Among Women Without Diabetes Before 1 or More Live Births During Follow-up[a]

Follow-Up (Up to Year 30) Characteristics	Incident Diabetes (n = 182)	No Diabetes (n = 1056)	*P* Value
Education (high school or less), No. (%)	27 (15)	133 (13)	<.001
Marital Status (married), No. (%)	94 (54)	595 (61)	.10
Postmenopausal status, No. (%)	75 (41)	609 (58)	<.001
Pregnancy Outcomes, No. (%)			
1 Postbaseline birth	92 (50)	417 (39)	.003
2 Postbaseline births	69 (38)	421 (40)	
≥3 Postbaseline births	21 (12)	218 (21)	
Gestational diabetes mellitus, No. (%)	56 (31)	99 (9)	<.001
Gestational hypertensive disorder, No. (%)	73 (40)	233 (22)	<.001
Preterm birth (<37 weeks gestation), No. (%)	38 (21)	188 (18)	.29
Cesarean birth, No. (%)	61 (34)	307 (29)	.23
Medical conditions/medication use, No. (%)			
Antihypertensive medications	85 (47)	244 (23)	<.001
Lipid-lowering medications	74 (41)	115 (11)	<.001
Incident metabolic syndrome	79 (43)	82 (8)	<.001
Family history of diabetes	127 (70)	435 (41)	<.001
Social/clinical risk factors, mean (SD)			
Age, y	46.3 (7.1)	51.4 (7.1)	<.001
Body mass index[b]	37.2 (8.6)	29.3 (7.4)	<.001
Waist circumference, cm	104.9 (16.2)	88.7 (15.6)	<.001
Weight change, kg	27.0 (27.4)	16.8 (15.7)	<.001
Smoking, pack-years	5.4 (9.3)	3.7 (7.6)	.007
Dietary Quality score[c]	64.1 (10.1)	67.6 (11.8)	<.001
Weight change, median (IQR), kg[d]	24.6 (21.8)	14.4 (20.2)	<.001
Physical activity change, median (IQR)[d]	−78.0 (256.0)	−61.5 (323.0)	.67
Alcohol intake, median (IQR), mL/d[d]	0.0 (2.7)	2.4 (12.1)	<.001
Lactation duration, median (IQR), months[d]	1.4 (5.1)	4.4 (8.5)	<.001

Abbreviations: IQR, interquartile range.

[a] This analysis included 1238 women and 2302 births.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] A priori Dietary Quality score average of scores from years 0, 7, and 20.

[d] Kruskal-Wallis test.

Table 4. Unadjusted and Adjusted Relative Hazards of Incident Diabetes During Follow-up From 1986 to 2016 Among Lactation Duration Categories

Multivariate Models	Time-Dependent Lactation Duration Categories, Adjusted Relative Hazard (95% CI)				*P* Value for Trend[a]
	None (n = 322)	>0 to 6 mo (n = 418)	>6 to <12 mo (n = 268)	≥12 mo (n = 230)	
Model 1 Unadjusted	1 [Reference]	0.60 (0.43-0.83)	0.36 (0.23-0.57)	0.29 (0.17-0.49)	<.001
Model 2 (model 1 plus adjustment for race time-dependent parity and GD status during follow-up)	1 [Reference]	0.74 (0.53-1.04)	0.55 (0.34-0.87)	0.45 (0.26-0.80)	.003
Model 3 (model 2 plus age, baseline covariates [body mass index,[b] waist circumference, and fasting glucose[c]], and familiy history of diabetes)	1 [Reference]	0.84 (0.60-1.20)	0.56 (0.35-0.91)	0.50 (0.27-0.90)	.006
Model 4 (model 3 plus time-dependent physical activity score[d] and Diet Quality score[e] during follow-up)	1 [Reference]	0.81 (0.56-1.19)	0.53 (0.31-0.88)	0.53 (0.29-0.98)	.01
Model 5 (model 4 plus time-dependent weight change[f] during follow-up)	1 [Reference]	0.75 (0.51-1.09)	0.52 (0.31-0.87)	0.53 (0.29-0.98)	.01

Abbreviation: GD, gestational diabetes.

[a] No evidence of effect modification by race, GD status, or parity groups.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Fasting serum glucose at baseline (year 0); there was missing data for 5 participants, and 10 participants had fasting glucose from year 7 before diabetes onset (all values at year 7 <100 mg/dL).

[d] Quartiles for time-dependent physical activity score for race-specific quartiles were evaluated as the average of scores from years 0, 7, and 20 (19 women were missing follow-up physical activity score).

[e] Quartiles for the a priori Diet Quality score were evaluated as the average of scores from years 0, 7, and 20 (10 women were missing average Diet Quality score).

[f] Time-dependent weight change equals weight change above the median vs at or below from baseline through the end of follow-up.

antilipid lowering or hypertensive medication use, pregnancy complications) did not materially affect the estimates. A sensitivity analysis of 848 women who were nulliparous at baseline showed even stronger relative risk reductions in incident diabetes associated with increasing lactation duration that remained statistically significant

(eTable 3 in the Supplement). The fully adjusted RHs range from 0.66 to 0.44 for lactation duration from more than 0 through 6 months to 12 months or more (*P* for trend = .02).

For the full sample of 1238 women, models with continuous months of lactation yielded consistent lower RHs of incident diabetes in unadjusted and adjusted race-stratified models and combined models (eTable 4 in the Supplement). Finally, unadjusted and adjusted RHs (95% CIs) of incident diabetes for covariates, race, family history of diabetes, and prepregnancy BMI, showed attenuation in fully adjusted models but stable RHs for GD status (eFigure 3 in the Supplement).

Discussion

The US community-based CARDIA study provides a biochemical basis for strong, graded inverse associations between lactation duration and incidence of diabetes in women of childbearing age. The graded risk reduction ranged from 25% for 6 months or less to 47% for 6 or more months of lactation. Importantly, these estimates were adjusted for key potential confounders and took into account reverse causation from antecedent risk factors across the childbearing years that previous studies had been unable to address,[7-9] except 1 study of women with recent GD.[13] Overall, we found an excess risk of incident diabetes associated with no lactation compared with 12 or more months of lactation that was 2.08% per year higher among women with a history of GD and 0.48% per year higher among women without a history of GD.

Our findings in young black and white women are consistent with studies in high-risk women with GD that re-screened women systematically for diabetes after pregnancy. Among 1010 women with recent GD, lactation intensity and duration were associated with a strong, graded 36% to 57% lower 2-year incidence of diabetes after accounting for gestational metabolic status, prepregnancy obesity, perinatal outcomes, and lifestyle behaviors.[13] This strong graded, protective association is strikingly similar in magnitude to our 30-year follow-up risk reduction in healthy CARDIA women (ie, 2-fold higher risk with no lactation). Among 264 women with GD, lactation for 3 months or longer was associated with 45% lower 15-year incidence of diabetes,[26] but this study validity is reduced by unmeasured confounding from perinatal outcomes, lifestyle behaviors, or weight changes that were not evaluated.

Meta-analyses of lactation and diabetes incidence or prevalence have yielded protective summary estimates of 9% to 11% per year of lactation. This weaker association may be related to 2 decades older age at baseline (median, 47-52 years) compared with women who participated in CARDIA (median, 24 years), incomplete ascertainment of incident diabetes by self-report compared with regular screening, or unknown GD history.[7-9] One meta-analysis[10] evaluated 6 studies (3 prospective, 2 cross-sectional, and 1 in GD) yielding a summary estimate for diabetes risk of 0.91 (95% CI, 0.86-0.96) for each additional year of lactation. The heterogeneity of outcomes and participant risk status undermines its validity. A second meta-analysis[9] of only prospective studies estimated a pooled relative hazards of 0.89 (95% CI, 0.82-0.97) for 6 to 11 months of lactation vs none, based primarily on older US white nurses and Asian women.[7,8] One study[9] found a 20% lower incidence for 6 months of lactation, but had limited statistical power related to longer lacation and nonsignificant findings after controlling for BMI at baseline.

Self-report of disease status may be reasonable to investigate breast cancer and heart disease that have long latency periods, but progressive deterioration in glucose intolerance is optimally detected via regular biochemical screening. Moreover, GD history, a major risk factor for type 2 diabetes in young women,[11] and other perinatal outcomes were not evaluated in the prospective studies of lactation.[7-9] For example, parity has been directly associated with diabetes, but prospective studies that accounted for prepregnancy metabolic risk and GD status,[21] or that excluded women with a history of GD,[27] showed null associations.

Black women have both higher diabetes prevalence and lower breastfeeding initiation and duration than white women. Type 2 diabetes affects 1.9% of US women of childbearing age (20-39 years) with a 6-fold higher prevalence in black (4.7%) than white women (0.8%).[28] In CARDIA, diabetes incidence was 3-fold higher for black compared with white women, as expected from national estimates. Although 41.0% of black women vs 11.0% of white women had never breastfed a child, the protective association between lactation duration and diabetes risk did not differ by race. This consistency across race groups provides strong evidence that lactation may protect against diabetes via biological mechanisms rather than cultural or social factors. Moreover, CARDIA is a community-based cohort of healthy young adults recruited from suburban and urban centers enhancing its generalizability.

Several mechanisms are plausible to explain the lower risk of diabetes associated with lactation duration. Lactating women have lower circulating glucose in both fasting and postabsorptive states,[29] as well as lower insulin secretion,[4,30] despite increased glucose production rates.[4] About 50 g of glucose per 24 hours is diverted into the mammary gland for milk synthesis via non-insulin mediated pathways.[2] These processes for milk production have been associated with lower basal and glucose-stimulated β-cell secretory activity for a standardized glucose load and beneficial effects that unload the pancreatic β-cells.[3] Higher basal and sporadic increased prolactin levels in lactating women may preserve pancreatic β-cell mass and function.[31] In mice, lactating vs nonlactating animals showed greater pancreatic β-cell proliferation.[32] Studies in pregnant women indicate that lactogenic hormones, such as prolactin, may influence future diabetes risk in women.[33] Lactation requires greater energy expenditure (additional 300 kcal per day)[34] and mobilizes adipose tissue, including regional subcutaneous stores,[35] or visceral depots,[36] although potential effects on body composition[37] or postpartum weight loss (1 to 2 kg for exclusive lactation) are minimal.[6] The Diabetes Prevention Program found a 5 kg greater weight loss owing to physical activity reduced incidence of diabetes by 58%.[38] Yet, weight loss did not explain our 47% lower relative hazards of incident diabetes for more than 6 months of lactation.

Obesity before pregnancy and insulin treatment of GD have been associated with delayed lactogenesis.[39,40] It has been hypothesized that heightened insulin resistance may interfere with timely lactogenesis after delivery.[41] However, overweight or obese women are also more likely to experience medical complications and adverse perinatal outcomes that can disrupt early breastfeeding initiation.[42] Heavier women have been found to report more limited access to breastfeeding education and support[43] or may hold unrealistic expectations about weight loss that negatively affect breastfeeding duration.[44] In our study, the strong protective association between lactation and incident diabetes remained even after accounting for prepregnancy metabolic status, obesity, and perinatal outcomes, and the associations became stronger in a sensitivity analysis limited to women who were nulliparous at baseline.

Strengths and Limitations

The study strengths include the biracial cohort, longitudinal serial biochemical assessments from before to after pregnancies and postweaning, standardized diabetes screening almost every 5 years for 30 years (retention, 71%), and control for prepregnancy cardiometabolic risk, lifestyle behaviors, and GD history to minimize reverse causation. All previous prospective studies enrolled women many years to decades after pregnancies and did not conduct any assessments during the childbearing period.

Limitations include the variable timing of assessments in relation to pregnancies and self-report of pregnancy complications. However, GD and other perinatal outcomes were accurately reported. We relied on self-report of lactation and recall post-delivery (within ≤4 years for 88% of births), which may be a limitation, but studies indicate that women are able to accurately recall duration up to 20 years later.[45,46] Because lactation duration was obtained for a maximum of 6 months for each birth, we could not determine absolute duration. However, CARDIA reflects contemporary breastfeeding practices with 78% of births occurring between 1985 and 1995, when only 20% of US women breastfed at 6 months. Thus, our lactation categories closely approximate actual duration. Women who lactated longer may have had better health habits that determined lower risk of diabetes. However, metabolic status before pregnancy was similar among lactation categories, and we controlled for time-varying weight change and lifestyle behaviors within race groups to address these differences, but they had little impact. The similar protective associations among black and white women, despite differences in obesity, based on our stratified analyses of lactation support the associations. Although this study is not a randomized trial, our study evaluated reverse causation and potential confounding by characteristics antecedent to lactation and diabetes onset, especially biochemical measures before lactation that have not been available in previous studies.

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists recommend breastfeeding for 1 year, but 70% of women in high or middle income countries do not achieve this duration.[47,48] In the United States, only 55% are still breastfeeding at 6 months, which drops to 33% at 1 year postpartum.[49] Black women are less likely to breastfeed regardless of socioeconomic status or body size,[50] and only 35% breastfeed for 6 months, indicating cultural barriers to breastfeeding.[49] These racial disparities in breastfeeding adversely affect both maternal and child health outcomes.[51] Declining breastfeeding rates are reported in nations transitioning to higher economic levels,[52] particularly South Asia, which is at the center of the worldwide diabetes epidemic. Suboptimal lactation has been linked to substantially higher health care costs related to preventable diseases such as heart disease and cancer, according to a cost-benefit analysis.[53] For diabetes, cost savings were much lower,[53] because all studies focused on older women,[10] and few included any younger women. Breastfeeding offers numerous other health benefits to both mother and child, including reduction in childhood infectious diseases, asthma and type 2 diabetes,[54] as well as lower risk of breast and ovarian cancer in women.[12,55]

Conclusions

Our findings may have implications for social policies to extend paid maternity leave to achieve higher intensity and longer duration of breastfeeding. Second, increased allocation of health care resources to increase breastfeeding rates through the first year postdelivery may be offset by lower health care costs associated with prevention of chronic disease in women. It is also imperative to improve breastfeeding practices to interrupt the transgenerational transmission of obesity-related diseases. Lactation is a natural biological process with the enormous potential to provide long-term benefits to maternal health, but has been underappreciated as a potential key strategy for early primary prevention of metabolic diseases in women across the childbearing years and beyond.

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Study concept and design: Gunderson, Lewis, Gross, Jacobs.
Acquisition, analysis, or interpretation of data: Gunderson, Lewis, Lin, Sorel, Sidney, Jacobs, Shikany, Quesenberry.
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