Duration of Lactation and Incidence of Type 2 Diabetes

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Duration of Lactation and Incidence of Type 2 Diabetes

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Context Lactation is associated with improved glucose and insulin homeostasis, independent of weight change.

Objective To evaluate the association between lactation history and incidence of type 2 diabetes.

Design, Setting, and Participants Prospective observational cohort study of 83 585 parous women in the Nurses' Health Study (NHS) and retrospective observational cohort study of 73 418 parous women in the Nurses' Health Study II (NHS II).

Main Outcome Measure Incident cases of type 2 diabetes mellitus.

Results In the NHS, 5145 cases of type 2 diabetes were diagnosed during 1 239 709 person-years of follow-up between 1986 and 2002, and in the NHS II, 1132 cases were diagnosed during 778 876 person-years of follow-up between 1989 and 2001. Among parous women, increasing duration of lactation was associated with a reduced risk of type 2 diabetes. For each additional year of lactation, women with a birth in the prior 15 years had a decrease in the risk of diabetes of 15% (95% confidence interval, 1%-27%) among NHS participants and of 14% (95% confidence interval, 7%-21%) among NHS II participants, controlling for current body mass index and other relevant risk factors for type 2 diabetes.

Conclusions Longer duration of breastfeeding was associated with reduced incidence of type 2 diabetes in 2 large US cohorts of women. Lactation may reduce risk of type 2 diabetes in young and middle-aged women by improving glucose homeostasis.

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TYPE 2 DIABETES MELLITUS AFfects about 9 million adult women in the United States.[1] The disease and its complications impose a considerable burden on the health care system, absorbing $1 of every $10 spent on health care.[2] Multiple lifestyle factors, including diet, exercise, and obesity, are associated with risk of diabetes.[3]

Lactation imposes a substantial metabolic burden on mothers, with an increased energy requirement of approximately 480 kcal/d.[4] Both human studies[5-7] and animal models[8,9] have demonstrated improved insulin sensitivity and glucose tolerance during lactation compared with nonlactating mothers who served as controls. These differences were independent of weight change. Some studies have also suggested increased weight loss among lactating mothers in the postpartum period,[10-14] although recent findings suggest otherwise.[15] These findings suggest that maternal lactation may reduce future risk of type 2 diabetes.

Although several studies have examined the effects of lactation on glucose metabolism, no study, to our knowledge, has examined the association between maternal lactation and type 2 diabetes risk. We therefore studied the association between lactation history and development of type 2 diabetes in the 2 Nurses' Health Studies.

METHODS

The Nurses' Health Studies consist of 2 large cohorts enrolled in prospective, longitudinal studies of women's health (TABLE 1). The Nurses' Health Study (NHS) was initiated in 1976 and enrolled 121 700 women from 11 states. Participants were between 30 and 55 years of age at baseline, and each woman completed a detailed baseline questionnaire regarding diseases and health-related topics. Every 2 years, participants completed follow-up questionnaires regarding medical diagnoses and health-related topics, including pregnancy history, diet, exercise, and smoking.[16]

The second cohort, the Nurses' Health Study II (NHS II), began in 1989, enrolling 116 671 women from 14 states. Participants were between 25 and 42 years of age and completed a similar baseline questionnaire as well as biennial follow-up questionnaires.

Assessment of Lactation History

Women in the NHS reported parity at baseline in 1976 and incident pregnan-

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cies on biennial questionnaires. Lactation history was assessed once, in 1986, when women were asked to report total lifetime duration of lactation for all pregnancies as a categorical variable. Using the midpoints for each reporting category, we calculated total months of lactation for use in our models of lactation as a continuous variable.

In the NHS II, women reported the number of pregnancies lasting more than 6 months at baseline and on each biennial questionnaire. Lactation history was assessed 3 times. In 1993, participants reported total lifetime lactation. In 1997, a more detailed questionnaire assessed lactation history for the first 4 children, reporting duration as a categorical variable. Women with more than 4 children also reported total additional months of breastfeeding. Women reporting additional births after 1997 were asked to complete a similar detailed breastfeeding questionnaire in 2003. Information on parity was used to derive retrospectively each participant's total cumulative lactation at each 2-year interval. For example, consider a woman with 3 children who reported duration of lactation for each birth in 1997. On the 1989 baseline questionnaire, she reported 2 previous pregnancies lasting more than 6 months, so her lifetime lactation in 1989 was retrospectively calculated as the sum of the durations she reported in 1997 for her first and second children. She reported a third birth in 1993, so her lifetime lactation for 1993 was calculated as the sum of the durations of lactation for all 3 children, and it was updated in the analysis at that point.

Total duration of lactation was calculated based on the number of months after birth that the participant reported stopping breastfeeding altogether. Using the 1997 and 2003 NHS II data, we were also able to calculate duration of exclusive lactation, based on the reported timing of introduction of formula or solid food.

Ascertainment of Type 2 Diabetes Mellitus

Women who reported the diagnosis of diabetes on any biennial questionnaire completed a supplemental form with questions about symptoms, diagnostic tests, and hypoglycemic therapy. A case of diabetes was confirmed if a woman reported 1 of the following: (1) 1 or more classic symptoms (ie, excessive thirst, polyuria, weight loss, or hunger) plus either a fasting glucose level of 140 mg/dL (7.8 mmol/L) or more or random plasma glucose level of 200 mg/dL (11.1 mmol/L) or more; (2) at least 2 instances of elevated plasma glucose concentration (fasting glucose ≥140 mg/dL, random plasma glucose ≥200 mg/dL, or oral glucose tolerance test ≥200 mg/dL after 2 hours) on different occasions in the absence of symptoms; or (3) treatment with insulin or an oral hypoglycemic medication. These criteria are consistent with those of the National Diabetes Data Group.[17] To validate the study's diagnostic criteria, a random sample of 84 participants classified as having type 2 diabetes were asked to release medical records for review. Seventy-one agreed to participate and 62 charts were obtained. An endocrinologist blinded to the information reported on the supplemental questionnaire reviewed the charts and confirmed the diagnosis of type 2 diabetes in 61 of the 62 women.[18]

Table 1. Comparison of Nurses' Health Study and Nurses' Health Study II Cohorts

	Nurses' Health Study	Nurses' Health Study II
Total number of participants	121 700	116 671
Year of birth	1921-1945	1946-1965
Timing of questionnaires	Every 2 years, beginning in 1976	Every 2 years, beginning in 1989
Assessment		
Lactation	1986: "How many months in total (all births combined) did you breastfeed?" Response options: did not breastfeed, <1, 1-3, 4-6, 7-11, 12-17, 18-23, 24-35, 36-47, ≥48, cannot remember	1993: "How many months in total (all births combined) did you breastfeed?" Response options: did not breastfeed, <1, 1-3, 4-6, 7-11, 12-17, 18-23, 24-35, 36-47, ≥48, cannot remember 1997: For each of first 4 pregnancies, detailed questions regarding return of menses, use of medication to suppress lactation, timing of introduction of infant formula/solid food, pumping, more than 6 h at night without breastfeeding (response options: 0-2, 3, 4-5, 6-7, 8-11, or ≥12 mo), and cessation of breastfeeding (response options: 1-2, 3-5, 6-8, 9-11, 12-18, or ≥19 months) 2003: Supplemental questionnaire sent to women reporting births since 1997; same information gathered as on 1997 lactation questionnaire
Pregnancies	Baseline parity in 1976, additional pregnancies reported in 1978, 1980, 1982, 1984	Baseline parity in 1989, additional pregnancies reported every 2 y thereafter
Weight	Baseline weight in 1976, update on weight every 2 y thereafter	Baseline weight in 1989, update on weight every 2 y thereafter
Weight at age 18 y	1980	1989
Diabetes	Assessed on questionnaires every 2 y, confirmed by supplemental questionnaire	Assessed on questionnaires every 2 y, confirmed by supplemental questionnaire
Gestational diabetes	Not assessed	Assessed on questionnaires every 2 y

The criteria for diagnosis of diabetes changed in 1997, when a fasting glucose level of 126 mg/dL (7.0 mmol/L) or higher was made the diagnostic threshold.[19] A fasting glucose level of 126 mg/dL or more was used for confirmation of cases diagnosed in 1997 or later.

Ascertainment of Gestational Diabetes

Women in the NHS II were asked to report the diagnosis of gestational diabetes on each biennial questionnaire. To validate the study's diagnostic criteria,[20] 422 participants completed a detailed questionnaire, and 92% corroborated their diagnosis. A review of medical records for 120 of these women confirmed definite or probable gestational diabetes in 94%. To assess screening for gestational diabetes, a random sample of 100 study participants was surveyed, of whom 83% reported undergoing a 50-g, 1-hour glucose challenge test. Gestational diabetes history was not assessed in the NHS cohort.

Measurement of Covariates

Women enrolled in both the NHS and NHS II completed detailed food frequency questionnaires every 4 years. The reproducibility and validity of these questionnaires are described elsewhere.[21,22] A dietary score with a range of 1 to 5 was calculated for each woman based on her quintile of intake of cereal fiber, polyunsaturated fat, *trans*-fat, and glycemic load. The higher the score, the lower the dietary risk. This dietary score and its association with type 2 diabetes have been described in detail elsewhere.[3]

Physical activity was assessed by calculating total hours per week engaged in a specified list of moderate to vigorous activities. The reproducibility and validity of self-reported physical activity are described elsewhere.[23] Physical activity data were collected in the NHS in 1986, 1988, 1992, 1994, 1996, 1998, and 2000 and in the NHS II in 1989, 1991, 1997, and 1999.

In their baseline enrollment survey, women reported their current height and weight. Weight at age 18 years was reported in 1980 in the NHS and in 1989 in the NHS II. In each biennial questionnaire, women reported their current weight. Women reported past and current smoking history on each biennial questionnaire. Family history of diabetes was reported in the NHS in 1982 and 1988 and in the NHS II in 1989 and 1997.

Statistical Analysis

The hazard ratio (HR) for type 2 diabetes by lactation history was assessed using a Cox proportional hazards model. Proportionality of hazards was evaluated by visual examination of associations across intervals of time. Women contributed person-years from 1986 in the NHS and 1989 in the NHS II until diagnosis of diabetes, death, or study end date. In the NHS, we examined incident cases of diabetes from 1986, when the youngest women in our cohort were 40 years old, to 2002, excluding women who were nulliparous (n=8683) or had a history of diabetes in 1986 (n=2286). The primary NHS II analysis uses data from the 1997 and 2003 lactation questions, examining incident diabetes from 1989 to 2001, excluding women with a history of diabetes at baseline in 1989 (n=517) or who were nulliparous during the study period (n=23 097). Women who were nulliparous in 1989 entered the analysis after their first birth.

Lifetime lactation history among parous women was stratified into 6 groups: None (referent), more than 0 to 3 months, more than 3 months to 6 months, more than 6 months to 11 months, more than 11 months to 23 months, and more than 23 months. In the NHS, lactation information was used from the 1986 questionnaire. In the NHS II analysis, lactation history was derived from self-reported pregnancies assessed every 2 years and lactation reports in 1997 and 2003. Lifetime duration was updated every 2 years. Because our data were reported categorically, we modeled our primary analysis using categorical variables. Linear trend was assessed using midpoints of lactation categories. In our analysis of HR per year of lactation, we used the midpoints of reporting categories to calculate total lifetime lactation because this was the closest approximation of the original reported duration. Two-sided *P* values are reported for trends, and 95% confidence intervals (CIs) are reported for HR estimates.

All models were age-adjusted. Potential confounders, including parity, body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) at age 18 years, diet, physical activity, family history of diabetes, and smoking status, were included in the multivariate model. We included in our multivariate models only covariates that were a priori possible risk factors for type 2 diabetes to avoid potential overfitting of our model. Diet, physical activity, parity, and smoking status were updated at 2-year intervals. Because current BMI could be a confounder or an intermediate variable, we conducted multivariate analyses with and without adjusting for current BMI updated with each questionnaire cycle.

Body mass index was modeled as a continuous variable, while BMI at age 18 years (normal, <25; overweight, 25-30; obese, >30), diet score (quintiles 1-5), moderate to vigorous physical activity (<1, 1 to <2, 2 to <4, 4 to <7, or ≥7 h/wk), birth weight of the participant (<5.5 lb or ≥5.5 lb [2.5 kg]), parity (1, 2, 3, 4, or ≥5 births), multivitamin use (yes or no), and smoking status (never, past, or current 1-14, 15-24, or ≥25 cigarettes/d) were modeled as categorical variables.

A stratified analysis was performed to determine whether the association between lactation and type 2 diabetes was affected by interval since last birth. Women contributed person-years to the "recent birth" subgroup (last birth <15 years ago) until 15 years after their last reported pregnancy, after which they contributed person-time to the "no recent birth" subgroup. A cutoff of 15 years was selected to split cases of new-onset diabetes evenly in the 2 cohorts. To assess whether menopausal status affected the association between time since last birth and diabetes risk, we

added a cross-product term to the proportional hazards model.

To assess whether parity modified the relationship between duration of lactation and type 2 diabetes, we calculated the HR per year of lactation stratified by number of births. Statistical interaction was evaluated by adding a cross-product term to the regression model. We also compared the effect of exclusive breastfeeding vs total duration of breastfeeding on diabetes risk and, among women who never breastfed, we assessed whether using medication to suppress lactation was associated with subsequent risk of diabetes. To assess possible effect modification by gestational diabetes, we conducted an analysis of the NHS II cohort stratified by whether women ever reported a diagnosis of gestational diabetes.

In a secondary analysis, we derived a propensity score by regressing lactation (<1 year vs ≥1 year) on a multitude of lifestyle factors. We examined the association between lactation and diabetes risk including the propensity score in the Cox proportional hazards model.

Participants with missing baseline information on parity (NHS, n=1622; NHS II, n=0), duration of lactation (NHS, n=17 924; NHS II, n=19 099), or age at last birth (NHS, n=7594; NHS II, n=0) were excluded from the analysis. For the other covariates, including current BMI, BMI at age 18 years, diet, physical activity, birth weight of participant, smoking status, and multivitamin use, a "missing" indicator was created.

All analyses were performed using SAS software, version 8.2 (SAS Institute Inc, Cary, NC). The study was approved by the Institutional Review Board of the Brigham and Women's Hospital; completion of the self-administered questionnaire was considered to imply informed consent.

RESULTS

In the NHS cohort, 83 585 parous women reported lifetime duration of lactation; of these, 64% had ever breastfed. In the NHS II cohort, 73 418 parous women reported duration of lactation, and 85% had ever breastfed. In both cohorts, higher parity was associated with longer lifetime duration of breastfeeding. Women who breastfed for longer periods were also less likely to have a family history of diabetes or to be smokers (**TABLES 2** and **3**). In NHS II, longer duration of lactation was associated with a lower-risk dietary score, greater frequency of multivitamin use, and a somewhat lower mean BMI at age 18 years and at baseline in 1989 (Table 3).

In the NHS cohort, 5145 incident cases of type 2 diabetes were documented during 1 239 709 person-years of follow-up between 1986 and 2002. In the NHS II cohort, 1132 incident cases of type 2 diabetes were documented during 778 876 person-years of follow-up between 1989 and 2001.

In the NHS, women who had ever breastfed had a covariate-adjusted HR for type 2 diabetes of 0.97 (95% CI, 0.91-1.02) compared with women who never breastfed. There was a modest but statistically significant inverse association between duration of lactation and risk of type 2 diabetes (**TABLE 4**). In the multivariate-adjusted model including

Table 2. Age-Standardized Baseline Characteristics of Parous Women in the Nurses' Health Study in 1986, by Duration of Lactation*

Characteristics	Duration of Lactation, mo					
	None	>0 to 3	>3 to 6	>6 to 11	>11 to 23	>23
No. of person-years of follow-up	445 120	289 493	148 130	121 771	151 501	83 694
Age, mean, y	52.6	53.6	52.3	51.5	51.1	50.7
Body mass index, mean†						
At baseline	25.1	25.2	24.9	24.9	25.0	25.4
At age 18 y	21.3	21.3	21.2	21.2	21.2	21.2
Family history of diabetes						
Maternal	12.9	13.1	11.7	11.3	11.4	10.5
Paternal	9.9	10.8	9.6	9.8	9.8	9.4
Participant <5.5 lb (<2.5 kg) at birth	7.6	7.5	6.6	7.2	6.9	6.6
Dietary score, mean‡	3.0	3.2	3.0	3.1	3.0	3.0
Moderate to vigorous exercise, h/wk, mean	1.7	1.8	2.0	2.0	2.1	2.1
Parity						
1 Child	10.7	8.1	7.6	4.5	1.5	0.9
2 Children	34.4	31.1	32.4	31.8	23.8	8.2
≥3 Children	54.9	60.8	60.0	63.7	74.7	90.9
Smoking history						
Never	39.3	42.9	43.5	46.9	50.1	55.8
Past	35.0	35.6	34.5	33.8	33.0	29.7
Current	25.6	21.3	21.8	19.1	16.7	14.2
Multivitamin use	29.0	39.9	31.7	35.1	33.6	31.5

*Data are presented as percentages unless otherwise indicated and are directly standardized in years to the age distribution of the Nurses' Health Study.
†Body mass index was calculated as weight in kilograms divided by the square of height in meters.
‡Intakes of *trans*-fat and cereal fiber, ratio of polyunsaturated fat to saturated fat, and glycemic load were divided into quintiles. Each participant was then assigned a dietary score for each nutrient based on her quintile of intake, with a higher score representing a lower risk. The 4 scores were summed and the mean composite score is presented herein.

Table 3. Age-Standardized Baseline Characteristics of Parous Women in the Nurses' Health Study II in 1989, by Duration of Lactation*

Characteristics	Cumulative Duration of Lactation, mo, as of 1999					
	None	>0 to 3	>3 to 6	>6 to 11	>11 to 23	>23
No. of person-years of follow-up	123 444	94 150	78 394	142 140	182 115	158 633
Age, mean, y	36.7	35.3	35.1	35.1	34.9	34.8
Body mass index, mean†						
At baseline	24.5	24.7	24.1	23.9	23.6	23.3
At age 18 y	21.3	21.4	21.2	21.0	20.9	20.8
History of gestational diabetes	4.4	5.5	4.9	4.7	5.4	5.9
Family history of diabetes						
Maternal	8.3	7.8	7.0	6.4	6.2	5.8
Paternal	10.4	9.8	9.1	8.5	8.5	8.0
Participant <5.5 lb (<2.5 kg) at birth	7.6	6.6	6.7	6.6	6.1	6.0
Dietary score in 1991, mean‡	2.7	2.8	2.9	3.0	3.0	3.1
Moderate to vigorous exercise, h/wk, mean	3.3	3.0	3.3	3.3	3.3	3.2
Parity in 1999						
1 Child	27.2	23.2	31.6	21.0	8.9	0.0
2 Children	51.7	54.7	47.0	59.8	52.3	32.9
≥3 Children	21.1	22.1	21.4	19.2	38.8	67.1
Smoking history						
Never	61.2	63.3	62.6	64.5	67.7	72.5
Past	20.6	21.5	22.2	23.2	23.1	21.5
Current	18.2	15.2	14.9	12.2	9.1	5.9
Multivitamin use	36.9	40.9	43.9	45.3	47.5	52.4

*Data are presented as percentages unless otherwise indicated and are directly standardized in years to the age distribution of the Nurses' Health Study II.
†Body mass index was calculated as weight in kilograms divided by the square of height in meters.
‡Intakes of *trans*-fat and cereal fiber, ratio of polyunsaturated fat to saturated fat, and glycemic load were divided into quintiles. Each participant was then assigned a dietary score for each nutrient based on her quintile of intake, with a higher score representing a lower risk. The 4 scores were summed and the mean composite score is presented herein.

Table 4. Hazard Ratios for Type 2 Diabetes, Parous Women Only*

	Cumulative Duration of Lactation, mo						*P* Value for Trend*	HR per Additional Year of Lactation
	None	>0 to 3	>3 to 6	>6 to 11	>11 to 23	>23		
Nurses' Health Study†								
No. of cases	1943	1247	622	458	562	313		
Person-years of follow-up	445 120	289 493	148 130	121 771	151 501	83 694		
Age-adjusted HR (95% CI)	1.00	0.96 (0.90-1.04)	0.97 (0.89-1.07)	0.88 (0.79-0.97)	0.87 (0.79-0.96)	0.89 (0.79-1.01)	.001	0.95 (0.92-0.99)
Covariate-adjusted HR (95% CI)§	1.00	0.97 (0.91-1.05)	1.03 (0.94-1.13)	0.93 (0.84-1.04)	0.91 (0.83-1.00)	0.91 (0.80-1.03)	.02	0.96 (0.93-1.00)
Covariate-adjusted HR (95% CI), including current BMI§	1.00	0.98 (0.91-1.05)	1.03 (0.94-1.13)	0.96 (0.87-1.06)	0.92 (0.84-1.02)	0.88 (0.78-1.00)	.02	0.96 (0.92-0.99)
Nurses' Health Study II‡								
No. of cases	265	197	114	185	224	147		
Person-years of follow-up	123 444	94 150	78 394	142 140	182 115	158 633		
Age-adjusted HR (95% CI)	1.00	1.15 (0.95-1.38)	0.85 (0.68-1.06)	0.74 (0.62-0.90)	0.69 (0.57-0.82)	0.49 (0.40-0.60)	<.001	0.79 (0.74-0.84)
Covariate-adjusted HR (95% CI)§	1.00	1.09 (0.91-1.32)	0.90 (0.72-1.13)	0.86 (0.71-1.04)	0.83 (0.69-1.00)	0.58 (0.47-0.73)	<.001	0.84 (0.78-0.89)
Covariate-adjusted HR (95% CI), including current BMI§	1.00	1.04 (0.86-1.26)	0.91 (0.73-1.14)	0.87 (0.72-1.06)	0.88 (0.74-1.06)	0.67 (0.54-0.84)	<.001	0.88 (0.82-0.94)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
**P* value for trend across categories, based on category midpoint.
†Nurses' Health Study: prospective analysis using cases from 1986 to 2002.
‡Nurses' Health Study II: retrospective analysis using lactation data from 1997 and 2003, cases from 1989 to 2001, parous women only.
§Adjusted for parity, BMI at age 18 years, dietary score quintile, physical activity, family history of diabetes, smoking status, birth weight of participant, and multivitamin use.

current BMI, each additional year of lactation was associated with an HR of 0.96 (95% CI, 0.92-0.99) for type 2 diabetes. Among women who had ever breastfed in the NHS II, the covariate-adjusted HR for type 2 diabetes was 0.90 (95% CI, 0.77-1.04). Each year of lactation was associated with a covariate-adjusted HR of 0.84 (95% CI, 0.78-0.89). When BMI was added to this model, the HR was 0.88 (95% CI, 0.82-0.94) for each additional year of lactation.

In the secondary analysis, we compared women with less than 1 year of lifetime lactation with those with more than 1 year of lifetime lactation, then added a propensity score of independent predictors of diabetes development. In the NHS, the covariate-adjusted HR of type 2 diabetes for those who breastfed for more than 1 year was 0.92 (95% CI, 0.85-0.99); adding the propensity score yielded an HR of 0.87 (95% CI, 0.79-0.95). In the NHS II, the covariate-adjusted HR of type 2 diabetes was 0.78 (95% CI, 0.68-0.90), and adding the propensity score to the model yielded an HR of 0.80 (95% CI, 0.68-0.93). To assess whether the trend we observed in the NHS II reflected recall bias, we conducted a separate, prospective analysis of cases of diabetes between 1993 and 2001, using lactation data obtained in 1993. This analysis showed a similar trend, with a covariate-adjusted HR per year of lactation of 0.91 (95% CI, 0.84-0.98).

In analyses restricted to women who reported a birth in the past 15 years, we found covariate-adjusted HRs for diabetes of 0.85 (95% CI, 0.73-0.99) in the NHS and 0.86 (95% CI, 0.79-0.93) in the NHS II per additional year of breastfeeding (TABLE 5). In contrast, among women who reported their last birth more than 15 years ago, there was no association between duration of lactation and type 2 diabetes in the NHS II (covariate-adjusted HR per-year lactation, 0.96; 95% CI, 0.86-1.08) and a substantially reduced association in the NHS (covariate-adjusted HR per year of lactation, 0.96; 95% CI, 0.93-1.00). We did not have sufficient statistical power to subdivide time since last birth into shorter segments. When we added a cross-product term for menopausal status and recent birth, there was not a significant interaction in the NHS ($P=.32$) or the NHS II ($P=.54$).

The age-adjusted HR per year of lactation decreased with increasing parity (TABLE 6). There was no statistically significant interaction between parity and lactation in the NHS ($P=.10$) or the NHS II ($P=.68$). In a categorical analysis of women with only 1 birth, there was no association between lactation and diabetes for less than 6 months of breastfeeding, but there was a significant inverse association in the 6- to 11-month (age-adjusted HR, 0.68; 95% CI, 0.46-0.99) and 11- to 23-month (age-adjusted HR, 0.56; 95% CI, 0.34-0.93) lactation categories.

Detailed lactation data in the NHS II cohort allowed us to compare the effects of exclusive vs total breastfeeding. In models controlling for age and parity, each year of lifetime exclusive breastfeeding was associated with an HR

Table 5. Hazard Ratios for Type 2 Diabetes, Parous Women Only, in Analyses Restricted to Women Reporting a Birth in the Past 15 Years

	Cumulative Duration of Lactation, mo						*P* Value for Trend*	HR per Additional Year of Lactation
	None	>0 to 3	>3 to 6	>6 to 11	>11 to 23	>23		
Nurses' Health Study†								
No. of cases	68	30	18	18	28	24		
Person-years of follow-up	23 419	12 400	8669	9415	15 251	15 023		
Age-adjusted HR (95% CI)	1.00	0.76 (0.48-1.18)	0.76 (0.45-1.31)	0.61 (0.35-1.05)	0.63 (0.40-0.99)	0.41 (0.25-0.67)	<.001	0.80 (0.70-0.93)
Covariate-adjusted HR (95% CI)§	1.00	0.68 (0.42-1.09)	0.67 (0.39-1.18)	0.61 (0.34-1.08)	0.67 (0.42-1.08)	0.44 (0.26-0.74)	.008	0.84 (0.73-0.98)
Covariate-adjusted HR (95% CI), including current BMI§	1.00	0.72 (0.44-1.18)	0.74 (0.42-1.32)	0.64 (0.35-1.17)	0.70 (0.42-1.15)	0.47 (0.27-0.81)	.02	0.85 (0.73-0.99)
Nurses' Health Study II‡								
No. of cases	117	116	69	112	147	110		
Person-years of follow-up	72 041	70 354	62 386	116 228	155 323	143 430		
Age-adjusted HR (95% CI)	1.00	1.07 (0.83-1.39)	0.73 (0.54-0.99)	0.62 (0.48-0.81)	0.57 (0.44-0.72)	0.40 (0.31-0.53)	<.001	0.76 (0.70-0.82)
Covariate-adjusted HR (95% CI)§	1.00	1.03 (0.80-1.35)	0.78 (0.57-1.06)	0.76 (0.58-0.99)	0.76 (0.59-0.98)	0.53 (0.40-0.70)	<.001	0.82 (0.76-0.89)
Covariate-adjusted HR (95% CI), including current BMI§	1.00	0.98 (0.75-1.28)	0.76 (0.55-1.03)	0.74 (0.56-0.96)	0.81 (0.62-1.04)	0.59 (0.44-0.79)	<.001	0.86 (0.79-0.93)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
*P value for trend across categories, based on category midpoint.
†Nurses' Health Study: prospective analysis using cases from 1986 to 2002.
‡Nurses' Health Study II: retrospective analysis using lactation data from 1997 and 2003, cases from 1989 to 2001, parous women only.
§Adjusted for parity, BMI at age 18 years, dietary score quintile, physical activity, family history of diabetes, smoking status, birth weight of participant, and multivitamin use.

for type 2 diabetes of 0.63 (95% CI, 0.54-0.73), while each year of total breastfeeding was associated with an HR of 0.76 (95% CI, 0.71-0.81). Use of medication to suppress lactation was associated with an increased risk of type 2 diabetes compared with women who never breastfed but did not use such medication (covariate-adjusted HR, 1.46; 95% CI, 1.06-2.01).

Women with a history of gestational diabetes had a markedly increased risk of type 2 diabetes in the NHS II cohort, with 624 cases per 100 000 person-years compared with 118 cases per 100 000 person-years among those without such a history. We conducted a stratified analysis to assess whether gestational diabetes history modified the effect of lactation on diabetes risk. In the group never diagnosed with gestational diabetes, each additional year of lactation was associated with a covariate-adjusted HR of 0.84 (95% CI, 0.78-0.91) (TABLE 7). Lactation had no effect on diabetes risk in the gestational diabetes group, with a covariate-adjusted HR of 0.96 (95% CI, 0.84-1.09) per additional year of lactation.

COMMENT

In these analyses of 2 large prospective cohorts, we found that duration of lactation was inversely associated with risk of type 2 diabetes in young and middle-aged women, independent of other diabetes risk factors, including body mass index, diet, exercise, and smoking status. This association appeared to wane with time since last birth.

We chose to report our findings as risk reduction per year of lactation because the American Academy of Pediatrics recommends that mothers breastfeed their infants for at least 1 year.[24]

Our study population is composed of registered nurses, and breastfeeding rates in our study are similar to US rates among other women with advanced educational degrees. In the National Center for Health Statistics' National Survey of Family Growth, reported rates of breastfeeding among women with a bachelor's degree or

Table 6. Age-Adjusted HRs for Type 2 Diabetes, Stratified by Parity, in the Nurses' Health Study II*

Parity	Person-Years of Follow-up	No. of Cases	Age-Adjusted HR per Year of Lactation (95% CI)
1	160 822	250	0.56 (0.41-0.77)
2	378 437	532	0.76 (0.68-0.85)
3	180 920	248	0.76 (0.68-0.86)
4	46 573	74	0.85 (0.73-0.99)
≥5	12 125	28	0.77 (0.62-0.95)

Abbreviations: CI, confidence interval; HR, hazard ratio.
*Retrospective analysis using lactation data from 1997 and 2003, cases from 1989 to 2001.

Table 7. Hazard Ratios for Type 2 Diabetes, Parous Women Only, in the Nurses' Health Study II, Stratified by a History of Gestational Diabetes*

	Cumulative Duration of Lactation, mo						*P* Value for Trend†	HR per Additional Year of Lactation
	None	>0 to 3	>3 to 6	>6 to 11	>11 to 23	>23		
Never had gestational diabetes								
No. of cases	226	153	85	150	156	96		
Person-years of follow-up	118 105	88 597	73 986	134 822	171 737	149 031		
Age-adjusted HR (95% CI)	1.00	1.09 (0.89-1.34)	0.78 (0.61-1.01)	0.75 (0.61-0.92)	0.59 (0.48-0.73)	0.40 (0.31-0.51)	<.001	0.73 (0.68-0.79)
Covariate-adjusted HR (95% CI)‡	1.00	1.05 (0.85-1.29)	0.82 (0.64-1.06)	0.87 (0.70-1.07)	0.73 (0.59-0.90)	0.50 (0.39-0.66)	<.001	0.80 (0.74-0.86)
Covariate-adjusted HR (95% CI), including current BMI‡	1.00	1.00 (0.81-1.24)	0.80 (0.62-1.04)	0.86 (0.70-1.07)	0.77 (0.62-0.95)	0.58 (0.45-0.75)	<.001	0.84 (0.78-0.91)
Ever had gestational diabetes								
No. of cases	39	44	29	35	68	51		
Person-years of follow-up	5339	5553	4408	7318	10 378	9602		
Age-adjusted HR (95% CI)	1.00	1.26 (0.80-1.98)	0.98 (0.59-1.64)	0.71 (0.44-1.14)	0.94 (0.62-1.42)	0.72 (0.46-1.12)	.05	0.90 (0.81-1.01)
Covariate-adjusted HR (95% CI)‡	1.00	1.12 (0.70-1.80)	1.11 (0.66-1.88)	0.75 (0.45-1.23)	1.02 (0.66-1.57)	0.74 (0.45-1.20)	.20	0.89 (0.78-1.00)
Covariate-adjusted HR (95% CI), including current BMI‡	1.00	1.18 (0.72-1.93)	1.30 (0.75-2.25)	0.89 (0.53-1.49)	1.19 (0.76-1.87)	0.97 (0.58-1.61)	.85	0.96 (0.84-1.09)

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.
*Retrospective analysis using lactation data from 1997 and 2003, cases from 1989 to 2001. Women who ever reported having gestational diabetes were classified as having a history of gestational diabetes.
†*P* value for trend across categories, based on category midpoint.
‡Adjusted for parity, BMI at age 18 years, dietary score quintile, physical activity, family history of diabetes, smoking status, birth weight of mother, and multivitamin use.

higher ranged from 65.5% for births from 1972-1974 to 80.6% for births from 1993-1994.[25] In our cohorts, 64% of women in the NHS and 85% of women in the NHS II had ever breastfed. In 2003, 70.9% of women in the general US population reported ever breastfeeding after their most recent birth.[26]

One of the major concerns of our analysis was whether body mass index acts as a confounder or intermediate of the association between breastfeeding and diabetes. Numerous studies have suggested that obesity and insulin resistance at the time of delivery are associated with decreased breastfeeding initiation and duration.[27-33] In the NHS II cohort, higher BMI at age 18 years was associated with shorter duration of breastfeeding, and in both cohorts, duration of lactation was inversely associated with family history of diabetes. Gestational diabetes was not associated with duration of lactation. Nevertheless, adjustment for family history and BMI at age 18 years did not substantially diminish the inverse association between lactation and risk of type 2 diabetes, suggesting that the association we observed was not an artifact of pregravid or pregnancy obesity and its associated insulin resistance. However, stratification by history of gestational diabetes revealed that in this high-risk group of women, lactation did not affect risk of subsequent type 2 diabetes.

Lactation could protect against diabetes if it facilitates postpartum weight loss. Adjustment for updated BMI modestly diminished the association between breastfeeding duration and diabetes, but it remained statistically significant in both cohorts. A previous prospective analysis of postpartum weight loss in the NHS II cohort indicated a modest weight gain in nonobese primiparous women who breastfed.[15] This suggests that weight changes during lactation play a minor role in determining risk of type 2 diabetes in our population. Other studies of lactation and postpartum weight loss have yielded conflicting results.[10-13]

The decreased risk of type 2 diabetes associated with breastfeeding may also reflect differences in other health behaviors that we might not have been able to completely control for in our analyses, leading to residual or unmeasured confounding. The decision to breastfeed involves multiple cultural and socioeconomic factors. Breastfeeding for a prolonged period requires the support of family and employers. In both of our cohorts, women who breastfed for longer durations were less likely to have ever smoked. Nevertheless, controlling for markers of a healthy lifestyle, including diet, exercise, smoking history, and multivitamin use, did not materially alter the association of breastfeeding with diabetes, and the association remained unchanged using a propensity analysis. This suggests that confounding is unlikely to explain the association observed.

One of this study's strengths is that we used 2 cohorts to test the research hypothesis. The results in both cohorts consistently indicated a reduction in the incidence of type 2 diabetes with increasing duration of lactation. The small differences in the strength of the associations in the 2 cohorts could be due to differences in the assessment of lactation, differences in the statistical analysis, or random measurement error.

Recall bias has to be considered in the NHS II analysis. We elected to use lactation data collected in 1997 and 2003 for a retrospective analysis because it provided much more detailed information on each woman's breastfeeding history, and it allowed us to update our exposure. A separate prospective analysis using data on lactation collected in 1993 confirmed our findings. Moreover, our analysis in the NHS cohort was prospective, and the multivariate-adjusted HR for women with a birth in the previous 15 years paralleled our findings in the retrospective analysis for the NHS II.

When we assessed the impact of lactation on diabetes risk among women with a history of gestational diabetes, we failed to find any effect. This may reflect the fact that women in this group face a dramatically elevated type 2 diabetes risk, which may be fairly resistant to lifestyle changes. Notably, in our multivariate model, neither exercise nor diet affected diabetes risk among women with a prior history of gestational diabetes. The only significant predictors were BMI at age 18 years, current BMI, and family history of diabetes.

To our knowledge, no previous studies have examined the long-term association between lactation and subsequent development of type 2 diabetes. In the postpartum period, breastfeeding is known to decrease insulin resistance. In a rat model, Burnol et al[8] found that on day 12 of lactation, blood glucose levels were reduced 20% and insulin levels were reduced 35% compared with nonlactating rats. Jones et al[9] noted a 12-fold increase in insulin uptake by the mammary glands in the lactating rat, as well as a marked decrease in the plasma half-life of insulin.

Human studies suggest that lactation affects insulin and glucose homeostasis. Kjos et al[5] studied glucose tolerance in 809 primarily Latina women previously diagnosed as having gestational diabetes. In follow-up testing at 4 to 12 postpartum weeks, lactation was associated with improved glucose tolerance, fasting glucose, and total area under the glucose tolerance curve. In an analysis stratified by use of insulin during pregnancy, fasting glucose levels were significantly lower in the lactating group but other parameters were no longer significant.

A smaller study by McManus et al[6] assessed postpartum metabolic markers in 26 white women (14 lactating and 12 nonlactating) with gestational diabetes. At 3 postpartum months, there were no significant differences in insulin sensitivity, glucose effectiveness, or visceral or subcutaneous fat. The lactating group did have a higher disposition index, indicating more efficient pancreatic B-cell function.

Butte et al[7] found significant differences in metabolic parameters between nondiabetic lactating and nonlactating women at 3 and 6 postpartum

months, independent of body mass index. In the lactating group, insulin levels and insulin-glucose ratios were significantly lower and carbohydrate use was higher. Total energy expenditure was also significantly higher in the lactating group.

Our data on exclusive breastfeeding and duration stratified by parity suggest that the length and intensity of breastfeeding with each pregnancy affect the association with diabetes risk. We found that each year of exclusive breastfeeding was associated with a greater risk reduction than total breastfeeding. This may reflect the greater metabolic burden imposed by exclusive breastfeeding. We also found that longer durations of breastfeeding per pregnancy were associated with a greater benefit, with 1 year's lactation for 1 child resulting in a 44% reduction in age-adjusted risk, compared with 1 year's lactation between 2 children resulting in a 24% reduction in risk. It appears from our analysis of primiparous women that the beneficial association begins to accrue after 6 months of lactation. These data suggest that sustained lactation-associated metabolic changes have more profound effects on diabetes risk.

It is interesting to note that artificial suppression of lactation was associated with an increased risk of diabetes, raising the possibility that interfering in the hormonal changes involved in lactation may have significant metabolic consequences. Animal data lend tentative support to this hypothesis. Denis et al[34] assessed patterns of dietary intake and leptin homeostasis in rats. They found that administering bromocriptine to lactating dams decreased milk production, but it did not restore normal food intake or patterns of leptin release. In contrast, weaning by removing pups from the nest reestablished normal physiologic function. It is possible that use of bromocriptine to suppress lactation in postpartum women may also disrupt mechanisms of appetite regulation. Alternatively, a woman's decision to use medication to prevent lactation could be associated with other health behaviors that might increase her risk of type 2 diabetes, although the association was not altered by controlling for multiple known risk factors.

Changes in pituitary function may affect diabetes risk in women who have breastfed. Lactation suppresses gonadotropin levels, causing lactation-induced amenorrhea, and breastfeeding may influence other pituitary hormones. In a randomized trial, de Zegher et al[35] showed that lactating women had a decreased response to growth hormone–releasing peptide, especially in the immediate postpartum period. Lactation may also induce long-term changes in the hypothalamic-pituitary axis. Lankarani-Fard et al[36] found that postmenopausal women who had breastfed for more than 1 year had significantly higher fasting cortisol levels. Further studies are needed to characterize the association between lactation history and pituitary function.

Although several studies suggest that lactation may improve glucose homeostasis, the groups were not randomized, and it is possible that unsuccessful lactation is a marker for glucose intolerance or behaviors that affect glucose homeostasis. Further study of postpartum glucose metabolism and lactation will be needed to better characterize the effects of breastfeeding on glucose homeostasis.

In conclusion, increased duration of breastfeeding was associated with reduced risk of type 2 diabetes in 2 large cohorts of women. Together with clinical evidence of improved glucose homeostasis in lactating women, these data suggest that lactation may reduce the risk of type 2 diabetes in young and middle-aged women. Further clinical studies are needed to confirm this finding and to elucidate the physiologic mechanisms for an inverse association between duration of breastfeeding and risk of type 2 diabetes.

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Study concept and design: Stuebe, Rich-Edwards, Willett, Manson, Michels.
Acquisition of data: Rich-Edwards, Manson, Michels.
Analysis and interpretation of data: Stuebe, Rich-Edwards, Willett, Manson, Michels.
Drafting of the manuscript: Stuebe.
Critical revision of the manuscript for important intellectual content: Rich-Edwards, Willett, Manson, Michels.
Statistical analysis: Stuebe, Rich-Edwards, Willett, Michels.
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Narration is as much part of human nature as breath and the circulation of the blood.
—A. S. Byatt (1936-)

