

**Diabetes Care**



**Lifetime Duration of Breastfeeding and Cardiovascular Risk in Women With Type 2 Diabetes or a History of Gestational Diabetes: Findings From Two Large Prospective Cohorts**

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- Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among people with type 2 diabetes and accounts for >75% of hospitalizations and >50% of all deaths .

The American Heart Association embraces primordial prevention to avoid the development of CVD risk factors, as treating manifest clinical risk factors is not equivalent to avoiding them because the risk of CVD remains elevated even with optimal treatment.

**Type 2 diabetes** is associated with up to **50% higher** relative **CVD risk** in women compared with men .

In addition to type 2 diabetes, the onset or recognition of diabetes for the first time in pregnancy (gestational diabetes mellitus [GDM]) confers higher risk for CVD . GDM affects 5–10% of pregnancies in the U.S. alone and is a cardiovascular risk factor even among women who do not develop type 2 diabetes Thus, it is important to identify early modifiable determinants of CVD risk specific for these high-risk women.

**Breastfeeding** provides short-term and long-term health benefits to women and children.

In mothers, breastfeeding is associated with decreased risks of breast and ovarian cancers , type 2 diabetes, CVD , and all-cause and cause-specific mortality .

Exclusive breastfeeding is recommended by the World Health Organization (WHO) for the first 6 months of life and continued breastfeeding for at least first 2 years of life, with complementary foods being introduced at 6 months postpartum .

However, <50% of postpartum women worldwide breastfeed according to WHO recommendations.

Whether breastfeeding as a modifiable risk factor is associated with lower CVD risk in the high-risk population of women with type 2 diabetes or GDM history has not been investigated so far.

To address these knowledge gaps, we assessed the association of lifetime duration of breastfeeding and CVD risk among women with diabetes in two large U.S. cohorts, the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II).

Additionally, we examined the relationship of total and exclusive breastfeeding duration with CVD risk among women with prior GDM in NHS II.

## **RESEARCH DESIGN AND METHODS**

The analysis was conducted in two ongoing prospective cohort studies.

The NHS was initiated in 1976 and included 121,701 female nurses aged 30–55 years.

The NHS II was established in 1989 recruiting 116,429 female U.S. nurses aged 25–42 years. In both cohorts, mailed questionnaires were administered biennially to assess reproductive and lifestyle factors and health status, with follow-up rates >90%.

For analyses among women with type 2 diabetes, we included parous women who reported physician-diagnosed type 2 diabetes on any questionnaire between 1986 (retrospective breastfeeding report across all pregnancies) and 2016 in the NHS and between 1989 and 2017 in the NHS II.



Type 2 diabetes could be diagnosed before or after pregnancies but had to be diagnosed before the CVD event. GDM was defined as glucose intolerance with onset or first recognition during pregnancy.

The population for analysis among women with prior GDM comprised NHS II participants who reported a history of GDM in 1989 or were diagnosed with GDM during the follow-up pregnancies.

After exclusion of nulliparous participants, participants with prevalent CVD or cancer at baseline, without breastfeeding data, missing date of birth, who never returned followup questionnaires, the analytical samples comprised 9,606 NHS and 5,540 NHS II nurses with type 2 diabetes, and 4,537 NHS II nurses with prior GDM.

Type 2 diabetes subsequently developed in 505 women (11%) with prior GDM and available breastfeeding data, and stratified analyses according to interim diabetes status were performed among women with prior GDM.

## **Assessment of Breastfeeding**

In the NHS, breastfeeding history was assessed once, in 1986, when most of the women had completed their reproductive life span and were asked to report the total lifetime duration of breastfeeding cumulatively for all pregnancies as a categorical variable: cannot remember, did not breastfeed, <1, 1–3, 4–6, 7–11, 12–17, 18–23, 24–35, 36–47, or ≥48 months.

Participants in the NHS II reported their breastfeeding duration in three follow-up questionnaires.

The sample size in some of the categories was small, we redefined the categories of cumulative breastfeeding in both cohorts as follows: 0 months, 1–6 months, 7–18 months, and >18 months prior to analyses.

Categories of lifetime total duration of exclusive breastfeeding were defined as 0 months, 1–6 months, 7–12 months, and >12 months. Previous studies have demonstrated that both self-reported breastfeeding initiation and duration are highly reliable .

**The primary outcome** was major CVD, defined as a combined end point of nonfatal or fatal myocardial infarction (MI), stroke, coronary artery bypass graft (CABG) surgery, or percutaneous coronary intervention (PCI). The following **secondary outcomes** were assessed: total coronary heart disease (CHD), comprising fatal, nonfatal MI, and CABG surgery; and total stroke, including fatal and nonfatal stroke cases (ischemic, hemorrhagic, and undetermined subtypes).

When a participant (or family members of deceased participants) reported an incident event, permission was obtained to examine their medical records by physicians who were blinded to the participant risk-factor status. For each end point, the month and year of diagnosis were recorded as the diagnosis date.

## **Statistical Analyses**

Descriptive analyses were conducted for baseline characteristics according to breastfeeding duration among parous women by standardizing to participants' age distribution.

We applied time-dependent Cox proportional hazards regression models to estimate the adjusted hazard ratios (aHRs) and 95% CIs for the associations between lifetime total breastfeeding duration and risk of CVD in both cohorts, jointly stratified by age in years at the start of follow-up and calendar years of the current questionnaire cycle that were equivalent due to the way we structured the data and formulated the Cox models.

we examined the associations between breastfeeding duration as a continuous variable (per 6 months of breastfeeding) and risk of CVD.

Person-time was calculated from the return date of the questionnaire in which the type 2 diabetes or GDM diagnosis was first reported until CVD onset, death, or end of the follow-up, whichever occurred first. End of the follow-up was June 2016 for NHS and June 2017 for NHS II participants.

Multivariable Cox models were initially adjusted for age (strata).

Model 2 was additionally adjusted for race/ethnicity (non-Hispanic White or other), age at first birth (12–24, 25–29, 30–34, ≥35 years), prepregnancy BMI (<25, 26–30, >30 kg/m<sup>2</sup>), parental history of CVD <60 years of age (yes/no), and time-varying variables of smoking status (ever/never smoker), physical activity, and alcohol intake.

Stratified analyses were performed to assess the effect modification by family history of CVD, smoking status, parity (one or two or more) and menopausal status(postmenopausal vs. premenopausal) across women's reproductive life span.



All data were analyzed using SAS 9.4 for UNIX (SAS Institute), and a two-sided P value of  $<0.05$  was considered statistically significant in all analyses.

# RESULTS

The baseline age-standardized characteristics of 15,146 parous NHS and NHS II participants with type 2 diabetes and 4,537 NHS II participants with prior GDM according to breastfeeding duration are shown in Table 1.

In total, 6,339 (41.9%), 3,265 (21.6%), 3,197 (21.1%), and 2,345 (15.5%) women with diabetes breastfed for a cumulative total of 0, 1–6, 7–18, and ≥18 months, respectively.

Among women with prior GDM, the corresponding distribution for breastfeeding duration was 17.6%, 17.7%, 34.1%, and 30.5%.

In both cohorts, the number of live births and physical activity tended to increase, and the prevalence of smoking tended to decrease with a longer duration of breastfeeding.

A total of 1,159 CVD events(7.7%) were documented among women with type 2 diabetes during 188,874.4 person-years of follow-up. Among 4,537 NHS II participants with a GDM history, 132 (2.9%) experienced at least one CVD event during 100,217.9 person-years of follow up.

**Table 1—Characteristics of NHS and NHS II participants with type 2 diabetes or a history of GDM according to quantiles of lifetime duration of breastfeeding**

	Lifetime duration of breastfeeding, months			
	0	1–6	7–18	>18
<b>NHS-type 2 diabetes (<i>n</i> = 9,606)</b>	<i>n</i> = 4,873	<i>n</i> = 2,222	<i>n</i> = 1,526	<i>n</i> = 985
Age, years*	66.1 (8.45)	66.2 (8.44)	65.7 (8.05)	65.0 (8.36)
Age at first birth, years*	32.9 (22.9)	26.4 (10.9)	26.3 (9.94)	26.9 (12.5)
BMI (kg/m <sup>2</sup> ) at age 18	22.0 (3.58)	21.8 (3.4)	21.7 (3.14)	21.6 (3.03)
White, %	92	92	93	92
Family history of CVD, %	23	22	25	22
Ever smoking, %	59	57	53	44
Parity, <i>n</i>	3.02 (1.46)	3.16 (1.52)	3.25 (1.3)	4.15 (1.68)
Physical activity, MET-h/week	14.7 (21.8)	15.5 (21.2)	16.1 (19.7)	17.2 (21.3)
Alcohol intake, g/day	2.66 (6.90)	3.05 (8.04)	3.67 (9.07)	2.79 (7.12)
<b>NHS II-type 2 diabetes (<i>n</i> = 5,540)</b>	<i>n</i> = 1,466	<i>n</i> = 1,043	<i>n</i> = 1,671	<i>n</i> = 1,360
Age, years*	52.8 (7.54)	52.1 (7.41)	52.4 (7.23)	53.1 (7.13)
Age at first birth, years*	25.0 (5.12)	26.1 (5.14)	26.2 (4.61)	25.9 (4.08)
BMI (kg/m <sup>2</sup> ) at age 18	22.6 (4.47)	22.7 (4.47)	22.1 (3.93)	21.9 (3.65)
White, %	90	88	91	93
Family history of CVD, %	34	33	33	32
Ever smoking, %	41	42	36	32
Parity, <i>n</i>	1.98 (0.81)	1.96 (0.85)	2.20 (0.78)	2.88 (1.00)
Physical activity, MET-h/week	15.4 (22.6)	15.1 (23.5)	17.3 (23.0)	19.2 (26.0)
Alcohol intake, g/day	2.64 (5.76)	3.39 (7.39)	3.73 (7.18)	3.64 (8.12)
<b>NHS II-GDM (<i>n</i> = 4,537)</b>	<i>n</i> = 800	<i>n</i> = 803	<i>n</i> = 1,549	<i>n</i> = 1,385
Age, years*	32.2 (4.87)	32.5 (4.81)	32.2 (4.75)	32.9 (4.76)
Age at first birth, years*	27.2 (5.16)	28.5 (5.35)	28.0 (4.91)	26.6 (4.40)
BMI (kg/m <sup>2</sup> ) at age 18	22.1 (4.68)	21.6 (3.94)	21.1 (3.39)	20.8 (3.08)
White, %	91	89	91	93
Family history of CVD, %	21	18	18	17
Ever smoking, %	38	38	33	29
Parity, <i>n</i>	1.92 (0.87)	1.77 (0.85)	2.01 (0.85)	2.80 (1.12)
Physical activity, MET-h/week	16.4 (22.6)	16.4 (20.8)	17.1 (23.9)	17.6 (21.0)
Alcohol intake, g/day	1.93 (4.46)	2.34 (5.24)	2.41 (5.07)	2.10 (4.77)

Values are means (SD) for continuous variables and percentages for categorical variables and are standardized to the age distribution of the study population. Characteristics are presented at type 2 diabetes or GDM onset, unless otherwise specified. \*Not age-adjusted.

A longer lifetime duration of breastfeeding was associated with lower CVD risk in women with type 2 diabetes (Table 2).

Compared with women who never breastfed, women cumulatively breastfeeding >18 months had 32% lower CVD and 38% lower CHD risks in the pooled cohorts.

When breastfeeding duration was treated as a continuous variable per 6-month increase, the association remained: pooled adjusted aHRs were 0.94 (95% CI 0.91–0.98) for CVD and 0.93 (95% CI 0.88–0.97) for CHD.

No association with stroke was observed in either of the cohorts.



**Table 2—Associations between lifetime duration of breastfeeding and incident cardiovascular disease in NHS and NHS II participants with type 2 diabetes**

	Lifetime duration of breastfeeding, months				<i>P</i> -trend	Continuous, per 6 months
	0	1–6	7–18	>18		
<b>NHS-type 2 diabetes (<i>n</i> = 9,606)</b>						
Total CVD ( <i>n</i> cases/ <i>n</i> total)*	480/4,873	215/2,222	144/1,526	70/985		
Model 1	Reference	0.92 (0.78–1.09)	1.00 (0.82–1.22)	0.73 (0.56–0.95)	0.04	0.95 (0.91–1.00)
Model 2	Reference	0.93 (0.78–1.11)	1.02 (0.83–1.24)	0.75 (0.57–0.99)	0.08	0.96 (0.92–1.00)
CHD ( <i>n</i> cases/ <i>n</i> total)*	277/4,873	110/2,222	79/1,526	35/985		
Model 1	Reference	0.82 (0.65–1.04)	0.95 (0.73–1.24)	0.66 (0.46–0.95)	0.05	0.94 (0.88–1.00)
Model 2	Reference	0.84 (0.66–1.06)	0.98 (0.75–1.28)	0.68 (0.47–0.99)	0.09	0.95 (0.89–1.01)
Stroke ( <i>n</i> cases/ <i>n</i> total)*	206/4,873	108/2,222	67/1,526	36/985		
Model 1	Reference	1.07 (0.83–1.37)	1.06 (0.79–1.43)	0.83 (0.57–1.22)	0.39	0.97 (0.91–1.04)
Model 2	Reference	1.06 (0.82–1.37)	1.08 (0.80–1.45)	0.86 (0.58–1.26)	0.49	0.98 (0.92–1.04)
<b>NHS II-type 2 diabetes (<i>n</i> = 5,540)</b>						
Total CVD ( <i>n</i> cases/ <i>n</i> total)*	95/1,466	52/1,043	64/1,671	39/1,360		
Model 1	Reference	0.83 (0.57–1.20)	0.61 (0.43–0.86)	0.52 (0.35–0.78)	0.001	0.89 (0.83–0.95)
Model 2	Reference	0.83 (0.57–1.20)	0.61 (0.43–0.88)	0.55 (0.36–0.82)	0.003	0.90 (0.83–0.96)
CHD ( <i>n</i> cases/ <i>n</i> total)*	74/1,466	40/1,043	44/1,671	32/1,360		
Model 1	Reference	0.87 (0.57–1.32)	0.54 (0.36–0.82)	0.54 (0.34–0.83)	0.004	0.89 (0.82–0.96)
Model 2	Reference	0.85 (0.56–1.30)	0.54 (0.36–0.83)	0.54 (0.34–0.84)	0.006	0.89 (0.82–0.96)
Stroke ( <i>n</i> cases/ <i>n</i> total)*	21/1,466	13/1,043	21/1,671	7/1,360		
Model 1	Reference	0.82 (0.38–1.74)	0.86 (0.45–1.67)	0.46 (0.19–1.13)	0.11	0.89 (0.76–1.03)
Model 2	Reference	0.89 (0.40–1.96)	0.90 (0.44–1.80)	0.50 (0.20–1.25)	0.15	0.89 (0.76–1.04)
<b>Pooled results (<i>n</i> = 15,146)</b>						
Total CVD ( <i>n</i> cases/ <i>n</i> total)*	575/6,339	267/3,265	208/3,197	109/2,345		
Model 1	Reference	0.90 (0.77–1.06)	0.88 (0.74–1.05)	0.66 (0.53–0.82)	0.0005	0.94 (0.90–0.97)
Model 2	Reference	0.91 (0.78–1.07)	0.90 (0.75–1.07)	0.68 (0.54–0.85)	0.002	0.94 (0.91–0.98)
CHD ( <i>n</i> cases/ <i>n</i> total)*	351/6,339	150/3,265	123/3,197	67/2,345		
Model 1	Reference	0.83 (0.68–1.02)	0.80 (0.64–1.00)	0.61 (0.46–0.80)	0.0009	0.92 (0.88–0.97)
Model 2	Reference	0.84 (0.68–1.03)	0.82 (0.66–1.03)	0.62 (0.46–0.83)	0.002	0.93 (0.88–0.97)
Stroke ( <i>n</i> cases/ <i>n</i> total)*	227/6,339	121/3,265	88/3,197	43/2,345		
Model 1	Reference	1.04 (0.82–1.32)	1.03 (0.78–1.34)	0.76 (0.54–1.08)	0.16	0.96 (0.90–1.02)
Model 2	Reference	1.04 (0.82–1.33)	1.05 (0.79–1.38)	0.79 (0.55–1.13)	0.23	0.96 (0.91–1.02)

There were 9,606 NHS participants and 5,540 NHS II participants with type 2 diabetes who contributed 127,174.8 and 61,699.6 person-years of follow-up, respectively. Model 1 is adjusted for age (strata). Model 2 is model 1 plus ethnicity, smoking at baseline, prepregnancy BMI, physical activity, family history of CVD, age at first birth, alcohol intake, and duration of type 2 diabetes. \*Total CVD includes MI, stroke, CABG surgery, or PCI. Total CHD includes MI, CABG surgery, and PCI. Stroke includes ischemic and hemorrhagic stroke.

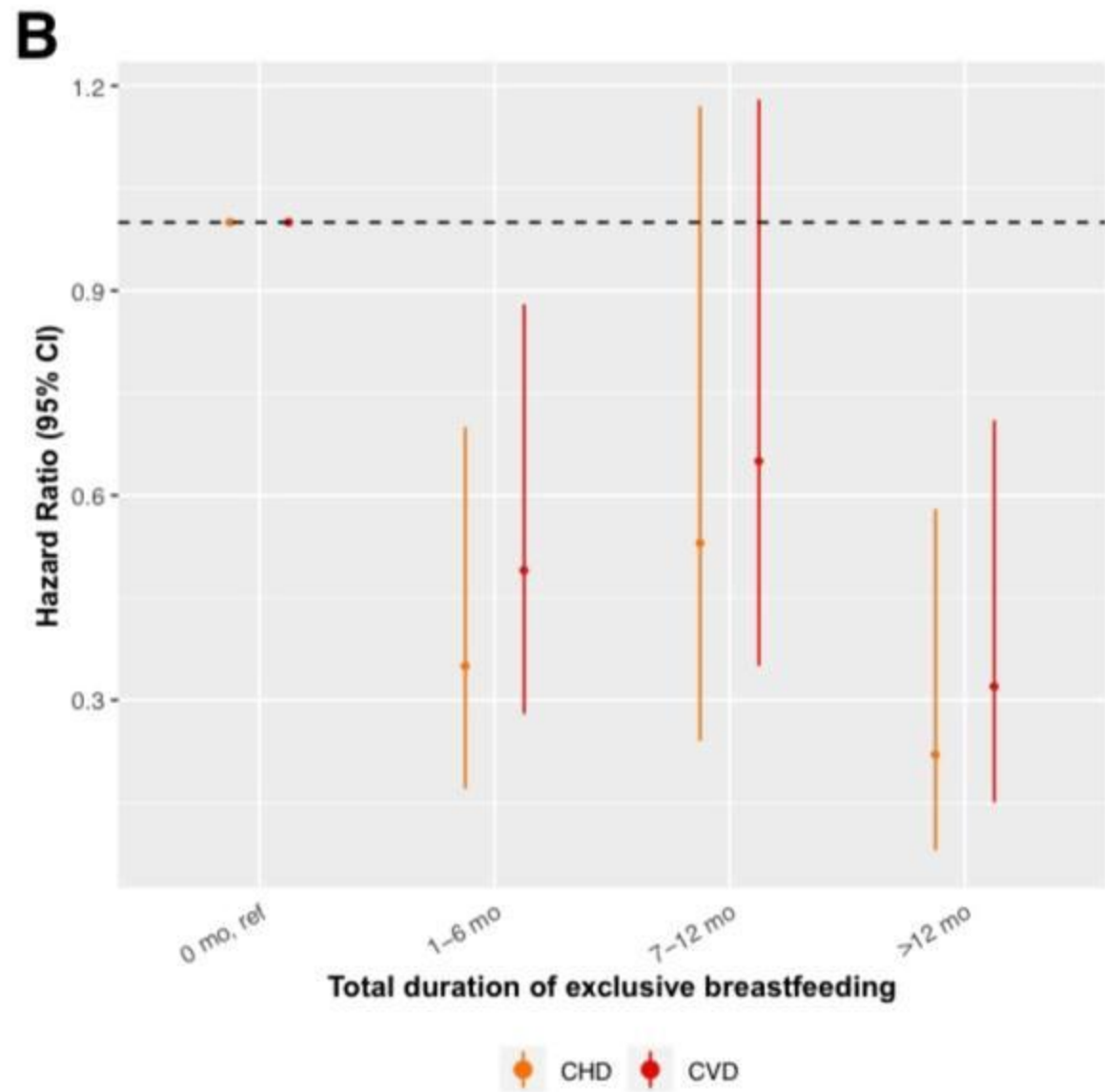
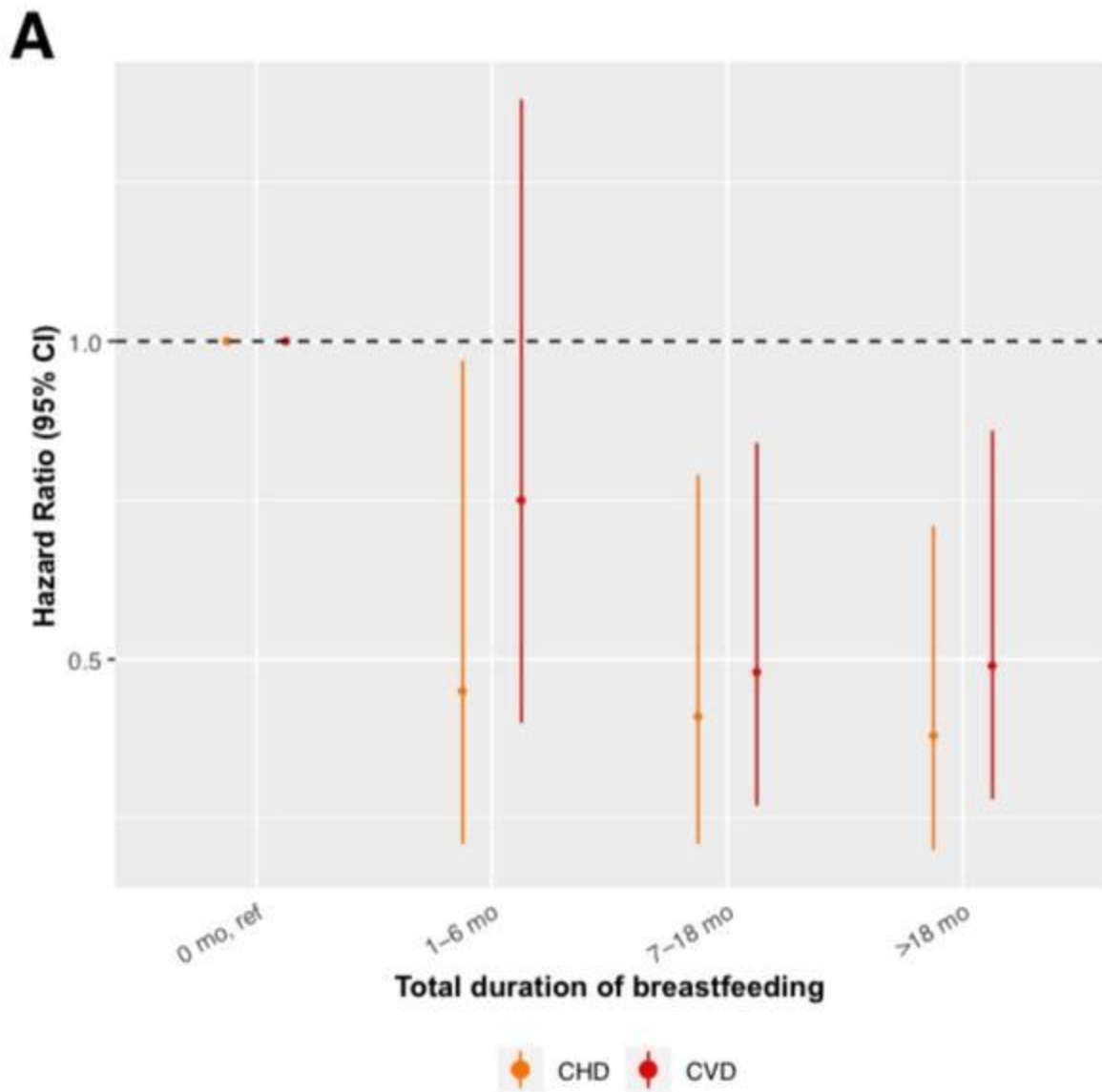


Compared with parous women who never breastfed, those with a cumulative breastfeeding duration >18 months had a 51% lower risk of incident CVD (aHR 0.49 [95% CI 0.28–0.86], P-trend = 0.02 across quintiles of cumulative breastfeeding) and a 62% lower risk of CHD (aHR 0.38 [95% CI 0.20–0.71], P-trend =0.02)

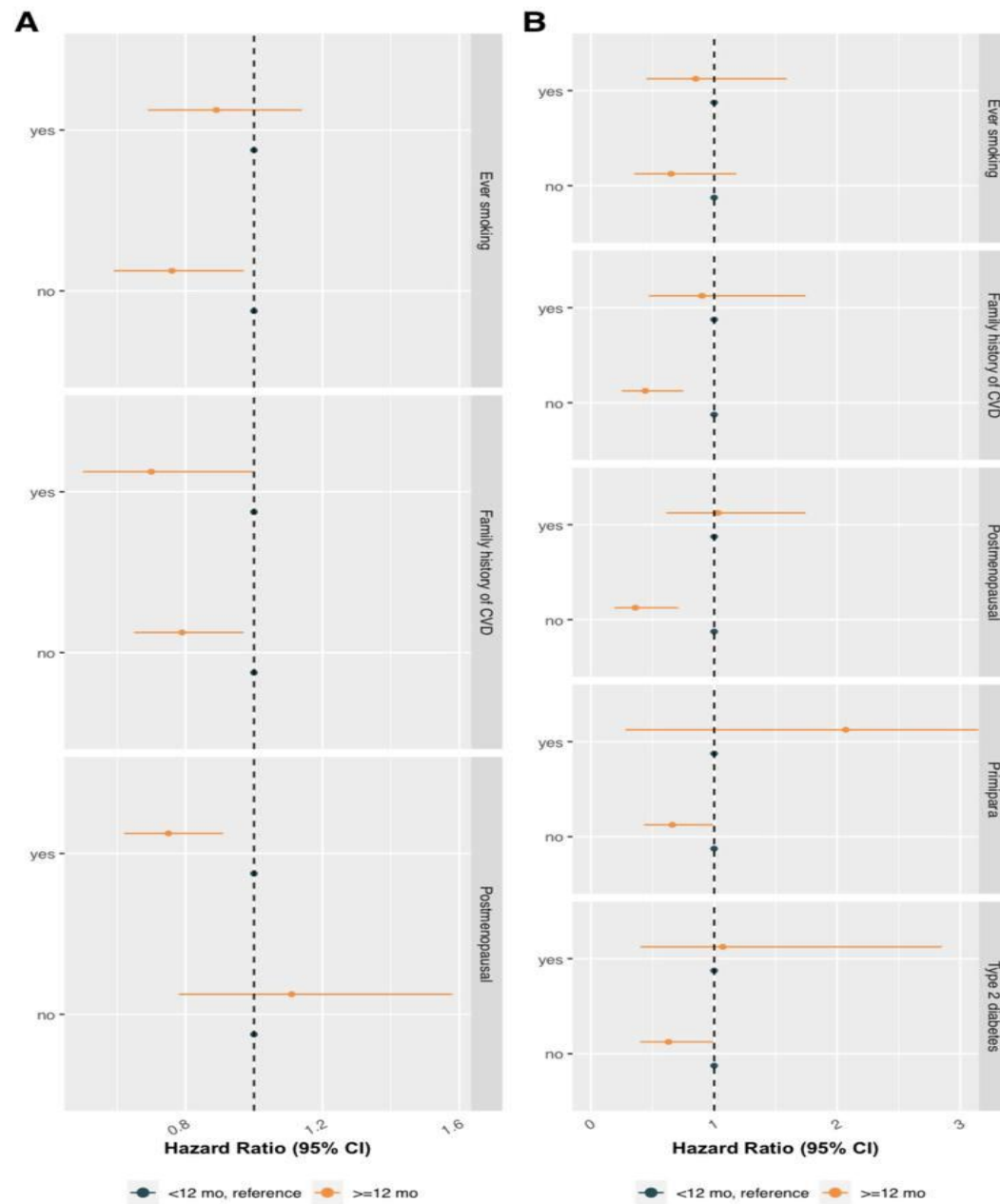
The analysis for stroke (n = 43 cases) showed an aHR of 0.90 (95% CI 0.74–1.08) per additional 6 months in total duration of breastfeeding, and an aHR of 0.78(95% CI 0.23–2.67) when comparing the extreme categories of breastfeeding duration (P-trend = 0.25; data not shown)

Longer duration of exclusive breastfeeding versus **no** breastfeeding was associated with an even lower risk of CVD and CHD among women with GDM (aHR 0.79[95% CI 0.67–0.94] for incident CVD and aHR 0.72 [95% CI 0.57–0.89] for incident CHD per 6-month increase in exclusive breastfeeding)

Similar to analyses with total duration of breastfeeding, no significant association was observed between the duration of exclusive breastfeeding and stroke (data not shown).



**Figure 1**—Associations between lifetime duration of breastfeeding, exclusive breastfeeding, and incident CVD in NHS II participants with a GDM history ( $n = 4,537$ ). CVD includes MI, stroke, CABG surgery, or PCI. CHD includes MI, CABG surgery, and PCI. Models are adjusted for age (strata), ethnicity, smoking at index GDM, prepregnancy BMI, physical activity at index GDM pregnancy, family history of CVD, age at first birth, and alcohol intake.



**Figure 2**—Stratified analyses by major CVD risk factors among NHS and NHS II women with type 2 diabetes or prior GDM. Subgroup analyses among NHS and NHS II female participants with type 2 diabetes (pooled HRs with 95% CI from both cohorts) (A) and NHS II participants with prior GDM (B) for the risk of composite CVD in relation to lifetime duration of breastfeeding (dichotomized, <12 months [reference] vs.  $\geq 12$  months), stratified by risk factors at baseline or across reproductive life span.

## **CONCLUSIONS**

In two large prospective cohorts of women at high risk for CVD involving 15,146 women with type 2 diabetes and 4,537 women with a GDM history, we found that longer lifetime duration of breastfeeding was inversely associated with CVD risk, independent of other cardiovascular risk factors, including BMI, family history of CVD, physical activity, alcohol intake, and socioeconomic and smoking status.

Among women with prior GDM, this inverse association persisted even in women who did not develop interim type 2 diabetes, and an even stronger inverse association was observed between duration of exclusive breastfeeding and CVD risk.



On the one hand, breastfeeding favorably influences carbohydrate and lipid metabolism by mobilizing stored fat, reestablishing glucose homeostasis , and improving insulin secretion through increased b-cell proliferation and reduced oxidative stress in b-cells .

In population based human studies, breastfeeding is associated with improved glucose metabolism and pancreatic b-cell function, more favorable lipid and inflammatory profiles , and greater weight loss and lower risk of metabolic disease, although data linking breastfeeding with long-term weight change in human populations are mixed.

In our study, we did not observe any substantial differences in long-term weight change between the categories of total lifetime breastfeeding duration or any meaningful attenuation of the association between breastfeeding duration and CVD risk after accounting for BMI change during the follow-up.

Thus, breastfeeding may be particularly beneficial for the prevention of early-onset (premenopausal) CVD in this population.

Another possible mechanism through which breastfeeding may contribute to lower CVD risk is oxytocin, a crucial hormone for ejecting breast milk.

**Oxytocin** has recently been demonstrated to exert several beneficial effects on the cardiovascular system, including blood pressure–lowering effects, vasodilatation, glucoselowering actions, antioxidant effects, inhibition of inflammation, and lowering of fat mass.

Breastfeeding may also modify cardiovascular risk through changes in stress response, with breastfeeding being associated with lower autonomic responses to stressors

In conclusion, in the current study comprising 15,146 parous women with type 2 diabetes from two large prospective cohorts and 4,537 women with a GDM history, we found significantly lower CVD rates among women who had ever breastfed, and women who cumulatively breastfed for >18 months experienced the lowest CVD risk.

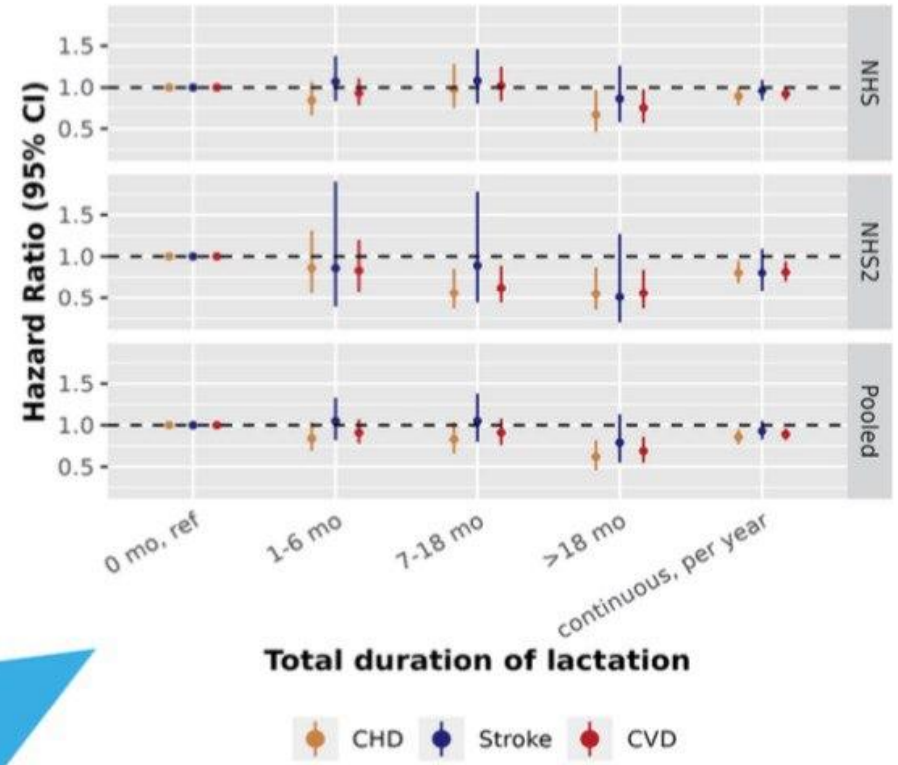
Our findings strengthen and expand the evidence of lifelong benefits from breastfeeding to parous populations of women at high risk for CVD complications, such as women with type 2 diabetes or GDM, where breastfeeding might mitigate the excess risk of CVD associated with diabetes in women. **The findings underscore the need for greater efforts to promote breastfeeding as a primary prevention strategy in high-risk women.**



# Lifetime duration of breastfeeding and CVD risk in women with type 2 diabetes or a history of GDM

15,146 parous women with T2D from NHS and NHS II with 188,874 person-years of follow-up

4,537 parous women with prior GDM from NHS II with 100,218 person-years of follow-up



**Longer duration of breastfeeding is associated with lower CVD risk in women with type 2 diabetes or GDM**

CVD: cardiovascular disease, CHD: coronary heart disease, T2D: type 2 diabetes, GDM: gestational diabetes mellitus, NHS: Nurses' Health Study, NHS II: Nurses' Health Study II



*Thank you*