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Duration of lactation and incidence of myocardial infarction in middle-to-late adulthood

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Abstract

Objective—We assessed the relation between duration of lactation and maternal incident myocardial infarction.

Study Design—Prospective cohort study of 89,326 parous women in the Nurses' Health Study.

Results—During 1,350,965 person-years of follow-up, 2540 cases of coronary heart disease were diagnosed. Compared with parous women who had never breastfed, women who had breastfed for a lifetime total of ≥ 2 years had 37% lower risk of coronary heart disease (95% CI

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Location where study was conducted: Members of the Nurses' Health Study were recruited in 1976 from California, Connecticut, Florida, Maryland, Massachusetts, Michigan, New Jersey, New York, Ohio, Pennsylvania and Texas.

Prior presentation

Preliminary findings were presented at the Society for Maternal Fetal Medicine, San Francisco, California, February 8-10, 2007.

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23–49%, p for trend <0.001), adjusting for age, parity and stillbirth history. With additional adjustment for early-adult adiposity, parental history, and lifestyle factors, women who had breastfed for a lifetime total of ≥ 2 years had a 23% lower risk of coronary heart disease (95% CI 6–38%, p for trend = 0.02) than women who had never breastfed.

Conclusions—In a large, prospective cohort, long duration of lactation was associated with a reduced risk of coronary heart disease.

Keywords

Epidemiology; Lactation; Myocardial Infarction

Introduction

Heart disease remains the leading cause of death for women in the US¹. Multiple lifestyle factors contribute to heart disease risk. In addition, hypertension, high cholesterol and diabetes increase the risk for myocardial infarction.

Both animal and human studies suggest that lactation may alter maternal glucose and lipid homeostasis and affect blood pressure regulation. Animal studies suggest that lactation has significant effects on lipid homeostasis², and breastfeeding women have lower triglyceride³ and higher HDL cholesterol⁴ levels. Moreover, both animal models^{5, 6} and human studies^{7–9} indicate that lactation reduces blood pressure and heart rate.

While these studies document metabolic differences during breastfeeding, epidemiologic data suggest these changes may persist after weaning. In a recent large cohort study, each year of cumulative lactation was associated with a 15% reduction in a woman's risk of developing type 2 diabetes in the 15 years after giving birth¹⁰. Other recent studies have found lactation to be positively associated with HDL cholesterol levels¹¹, and inversely associated with hypertension¹² and the metabolic syndrome¹³. Collectively, these data suggest that lactation may impact cardiovascular disease risk.

Although several authors have examined the effects of lactation on risk factors for cardiovascular disease, to our knowledge no study has examined the association between lactation and cardiovascular events. We therefore studied the association between lactation history and incident fatal and nonfatal myocardial infarction in the Nurses' Health Study.

Materials and Methods

The Nurses' Health Study (NHS) began in 1976, enrolling 121,700 women from 11 states for a longitudinal, prospective study of women's health. At baseline, participants were between 30 and 55 years of age, and each woman completed a detailed questionnaire regarding medical diagnoses, lifestyle, reproductive and other variables. Every 2 years, participants completed follow-up questionnaires regarding medical diagnoses and health-related topics¹⁴.

Assessment of Reproductive and Lactation History

Women in the NHS reported baseline parity in 1976 and incident pregnancies on biennial questionnaires. In 1976, women also reported the number of pregnancies lasting six months or more that ended in a stillbirth. Lactation history was assessed once, in 1986, when women reported total duration of lactation for all pregnancies as a categorical variable. At that time, the youngest women in the cohort were 40 years of age, and only 75 births were reported after 1986.

Ascertainment of Myocardial Infarction

In our study, we assessed incident cases of nonfatal myocardial infarction (MI) and mortality due to coronary heart disease from 1986 to 2002. Women who reported a nonfatal myocardial infarction were asked to release medical records. Physicians blinded to the participant's questionnaire reviewed records to confirm the diagnosis. Confirmed cases met World Health Organization criteria for myocardial infarction: symptoms associated with diagnostic electrocardiographic changes or elevations in cardiac enzymes. Deaths were ascertained from state death records, the national death index, the subject's family, or postal authority reports. Cause of death was determined from hospital records or autopsy, when available. Fatal coronary disease was defined as fatal MI if it was confirmed by hospital records or autopsy, if coronary disease was listed as the cause of death on the death certificate and was the underlying and most plausible cause, and if evidence of previous coronary disease was available. We coded an event as "probable" if the participant reported an infarction that required a hospitalization and was corroborated by a letter or telephone interview but for which hospital records were not obtained. Analyses limited to cases of confirmed coronary heart disease were similar to analyses based on confirmed and probable coronary heart disease; thus, we examined both confirmed and probable cases.

Ascertainment of covariates

Women who reported the diagnosis of diabetes on any biennial questionnaire were asked to complete a supplemental form with questions about symptoms, diagnostic tests, and hypoglycemic therapy. Diagnostic criteria and validation for diabetes are reviewed in detail elsewhere¹⁰. Diagnoses of angina, hypertension, or high cholesterol and history of coronary bypass graft surgery were reported on biennial questionnaires. Validation of self-reported hypertension and hypercholesterolemia has been reported elsewhere¹⁵.

Dietary information was collected through detailed food-frequency questionnaires every 4 years. The reproducibility and validity of these questionnaires are described elsewhere^{16, 17}. We calculated a diet score of 1 to 5 for each woman based on her quintile of intake of cereal fiber, polyunsaturated fat, trans fat (inverse), and glycemic load (inverse). The higher the score, the better the woman's dietary risk profile¹⁸. For this analysis, we used data on alcohol consumption reported in 1984, 1986, 1990, 1994, and 1998 and used data on aspirin use reported in 1984 and on each questionnaire from 1988 to 2000. We assessed multivitamin use as reported on each questionnaire from 1986 to 2000.

We assessed physical activity as reported on questionnaires in 1986, 1988, 1992, 1994, 1996, 1998, and 2000. From these data, we calculated 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 elsewhere¹⁹.

Women reported their current height and weight in the baseline enrollment survey in 1976, and they reported weight at age 18 in 1980. Weight was reassessed with each biennial questionnaire. Self-reported weights are highly correlated with measured weights in our cohort ($r=0.96$)²⁰. Women reported past and current smoking history on each biennial questionnaire. Parental history of diabetes was reported in NHS in 1982 and 1988, and parental history of MI before age 60 was reported in 1976 and 1984. Women also provided information on socioeconomic status. At baseline, each participant reported her parents' employment when she was 16 years of age, providing a measure of childhood SES. On the 1992 questionnaire, participants reported educational degrees earned, marital status, and their spouse's highest level of education.

Statistical analysis

The relative risk of MI by lactation history was assessed using a Cox proportional hazards model. We evaluated proportionality of hazards by assessing the interaction between lactation duration category and time since last birth. Women contributed person-years from 1986, when lactation duration was ascertained, until diagnosis of myocardial infarction, death, or study end date. We examined incident cases of MI from 1986, when cohort members were age 40 to 65 years, to 2002, at which point they were age 56 to 81 years. Month and year of diagnosis was determined by chart review or participant report. We excluded subjects who were nulliparous (n=7443) or for whom information on parity (n=2775) or duration of lactation (n=17,685) was missing. Parity and baseline body mass index among women missing lactation data were similar to those for whom lactation data was available. We further excluded parous women who had reported only stillbirths (n=210) or had a history of MI (n=517), angina (n=3572), or coronary artery bypass graft (n=148) before 1986.

Lifetime lactation history among parous women was stratified into six groups: none (referent), >0–3 months, >3–6 months, >6–11 months, >11–23 months, and >23 months. Because our data were reported categorically, we used categorical variables to model our primary analysis. We used midpoints of lactation categories to assess linear trend. A value of 24 months was assigned to participants with >23 months lactation. Two-sided p-values are reported for trends, and 95% confidence intervals are reported for hazard ratio estimates.

All models were age-adjusted and included parity and whether the participant had reported any stillbirths. In our adjusted model, we included coronary risk factors and lifestyle factors. To adjust for coronary disease risk, we included participant birth weight, parental history of MI, and body mass index (BMI) at age 18. To adjust for lifestyle factors, we also included dietary score quintile, exercise (hours per week), smoking status, multivitamin use, postmenopausal hormone use, aspirin use, and alcohol consumption. To assess whether socioeconomic status confounded the association between breastfeeding and myocardial infarction, we further adjusted for parental occupation, participant degrees earned, marital status and partner's education. We hypothesized that lactation may impact cardiovascular risk through its effects on hypertension, diabetes, hyperlipidemia and body mass index. To test this hypothesis, we added these intermediates to our covariate-adjusted model to assess whether their inclusion attenuated the observed association.

We only included covariates in our multivariate models that were a priori suspected risk factors for MI to avoid overfitting. Diet, physical activity, parity, diabetes, hypertension, high cholesterol, current BMI, and smoking status were updated at 2-year intervals.

BMI was modeled as a continuous variable, while BMI at age 18 (normal < 25, overweight $25 \leq 30$, obese > 30), diet score (quintiles 1–5), hours per week of moderate to vigorous physical activity (< 1, 1 to < 2, 2 to < 4, 4 to < 7, ≥ 7), birth weight (< 5.5 lbs, ≥ 5.5 lbs), parity (1, 2, 3, 4, ≥ 5 births), multivitamin use (yes, no), aspirin use (yes, no), alcohol consumption (0, 0.1–4.9, 5.0–14.9, ≥ 15.0 g/day), and smoking status (never, past, current 1–4, 5–14, 15–24, 25–34, 35–44, and ≥ 45 cigarettes/day) were modeled as categorical variables.

In previous work relating duration of lactation to risk of type 2 diabetes¹⁰, we observed an attenuation of the association with increasing time since last birth. To assess whether the association between lactation and myocardial infarction risk also diminished with time since last birth, we performed a stratified analysis. Women were divided into two groups, those with a birth in the previous 30 years and those without a birth in the previous 30 years. We

used a cutoff of 30 years to split incident cases of MI evenly. To test for differences in the effects of lactation by parity, we added an interaction term to the covariate-adjusted model.

For subjects with missing data on covariates, we created a missing indicator variable. We used this approach for subjects lacking data on current BMI, BMI at age 18, diet, physical activity, birth weight of subject, smoking status, postmenopausal hormone use, aspirin use, alcohol consumption, and multivitamin use. To assess the impact of missing data on our results, we performed a sensitivity analysis limited to participants with complete covariate data.

The Institutional Review Board of the Brigham and Women's Hospital approved the study.

Results

A total of 89,326 parous women reported lifetime duration of lactation and were eligible for the study. Of these, 63% had ever breastfed. One percent of women reported breastfeeding for 48 months or more, which was the longest duration category assessed. As expected, higher parity was associated with longer duration of lactation. Women who breastfed for longer periods of time were less likely to report a diagnosis of hypertension, high cholesterol, or diabetes, to report a parental history of MI, to have ever smoked, and to be postmenopausal in 1986 (Table 1).

During the study period, 2,540 incident cases of MI or death due to coronary heart disease were diagnosed during 1,350,965 person-years of follow-up. In the model adjusting for age, parity, and history of stillbirth (Table 2), >23 months of lifetime lactation was associated with a hazard ratio (HR) of 0.63 (95% CI, 0.51–0.77) for incident MI, compared with women who had never breastfed (p for trend < 0.001). When coronary and lifestyle risk factors were added to the model, we found an HR of 0.77 (95% CI, 0.62–0.94) for women with >23 months of lifetime lactation (p for trend = 0.02). When we included measures of childhood and adult socioeconomic status in our analysis, the association between with >23 months of lifetime lactation and myocardial infarction remained unchanged (HR: 0.77, 95% CI 0.62–0.96). Similarly, when we excluded participants with missing covariate data, the point estimate for >23 months of lifetime lactation was unchanged (HR: 0.78, 95% CI 0.62–0.99).

We used an interaction term between time since last birth and duration category to test for proportionality of hazards and found no significant effect modification (p = 0.77) in our multivariate-adjusted model.

Women who had breastfed for >1 year had a coronary and lifestyle-covariate adjusted risk of 0.87 (95% CI 0.77–0.98) compared with women who had never breastfed. The interaction between lactation duration and parity was not significant (log likelihood test p = 0.21). The small numbers of cases in analyses stratified by parity did not allow us to distinguish between the effects of long lactation for a single pregnancy vs. shorter durations for multiple pregnancies. Adding potential intermediates, including hypertension, diabetes, hypercholesterolemia and BMI, to the model resulted in an HR of 0.80 (95% CI, 0.65–0.98) for the group with longest duration of lactation (p for trend=0.06).

As we had hypothesized, stratifying the population by time since last birth revealed a stronger association between lactation and MI in the 30 years after a woman's last birth (Table 3). For women without a birth in the previous 30 years, we found no association between lactation and MI, with a multivariate HR of 0.93 (95% CI, 0.79–1.11) for ≥ 1 year of lactation, compared with women who had never breastfed. Among women with a birth in the previous 30 years, those who breastfed for ≥ 1 year had a covariate-adjusted HR of 0.80

(95% CI 0.66–0.97) compared with those who had never breastfed. Among women with a birth in the previous 30 years, those who breastfed for >23 months had a covariate-adjusted HR of 0.66 (95% CI, 0.49–0.89) for incident MI or coronary disease death, compared with women who had never breastfed.

Comment

In this analysis of a large prospective cohort, we found an inverse association between long duration of lactation and myocardial infarction, independent of known risk factors for cardiovascular disease, including obesity at age 18, parental history of MI, smoking, exercise, diet, aspirin use, alcohol consumption, hormone use, and menopausal status.

Breastfeeding rates in our study population are comparable with contemporary rates in the United States. All of our study participants were registered nurses, and 63% had ever breastfed. More than 10% of the cohort reported a birth in each year from 1954 to 1968, a period during which overall rates of breastfeeding were declining, from about 70% in 1951 to about 30% in 1966²¹. In 2005, 73% of US women had ever breastfed, 39% were still breastfeeding at 6 months, and 20% were breastfeeding at 1 year²². These data suggest that, at current breastfeeding rates, a substantial number of US women of childbearing age who give birth to two or more children will breastfeed for ≥ 2 years.

Our findings must be interpreted in the context of the study design. All observational studies are subject to confounding, and studies of breastfeeding are particularly challenging in this regard. Animal data and human studies have linked obesity and insulin resistance to difficulties with breastfeeding, suggesting that shortened lactation could be a marker for an aberrant metabolic profile^{23, 24}. Successful, prolonged breastfeeding depends on a wide range of factors, from a woman's choice to begin nursing to the support she receives from her birth attendant, her infant's pediatrician, her family, and her employer. A woman whose circumstances allow prolonged breastfeeding may live in a less stressful environment and thus face a lower risk of cardiovascular disease. Secular trends in breastfeeding duration, diet, exercise, and other health behaviors may also affect our results. Of note, all participants in our study are registered nurses, and 97 percent are Caucasian, so confounding by race or socio-economic status is less likely than in a more diverse cohort. Moreover, when we adjusted for parental occupation, education, partner's education and marital status, the effect was minimal, making it unlikely that other unmeasured SES variables explain the observed association.

Misclassification is also a potential concern, because lifetime lactation history was self-reported. Promislow and colleagues²⁵ examined maternal recall of breastfeeding duration among women ages 69 to 79. The authors compared self-reported duration with prospectively recorded menstrual diaries collected between 1940 and 1966. They observed an overall correlation of 0.55, with a mean difference between recorded and recalled duration of 0 (SD 2.7) months, indicating misclassification, but no overall recall bias. Moreover, they found that women with shorter durations tended to over-report, while women with longer durations tended to underreport. If such misclassification occurred in our cohort, it would bias our results toward the null. Nevertheless, we observed a substantial, statistically significant association between more than 2 years of lifetime breastfeeding and incident myocardial infarction.

Notably, we observed a stronger protective association for women who breastfed for >23 months, suggesting either a threshold effect or substantial differences between this group and those with shorter durations of lactation. When we adjusted for multiple coronary risk and lifestyle factors, the inverse association between long duration of breastfeeding and MI

was diminished, but the association remained significant, suggesting that other mechanisms also play a role.

Our findings are consistent with and extend those from earlier reports linking reproductive history to cardiovascular disease risk. Several authors have reported an increased risk of coronary heart disease among women with high parity^{26, 27}, although results are mixed^{28–30} and may be confounded by socioeconomic status³¹. Pre-eclampsia and stillbirth^{32, 33} have also been linked to subsequent cardiovascular risk. Both animal and human studies suggest biologically plausible mechanisms for an association between lactation and coronary heart disease. Lactation influences carbohydrate and lipid metabolism, and oxytocin has been linked to regulation of blood pressure and cardiovascular function.

Studies in animal models^{34, 35} and lactating women³⁶ show that lactation is associated with decreased postpartum insulin resistance, lower insulin-glucose ratios, and increased carbohydrate utilization. Differences in lactation physiology among rodents, ruminants and humans limit extrapolation of animal data to humans³⁷; however, epidemiologic studies suggest that human lactation is associated with beneficial long-term changes in glucose metabolism. In a previous analysis in the Nurses' Health Studies, we found that lifetime lactation was inversely associated with incident type 2 diabetes¹⁰, and a recent study of middle-aged women found an inverse association between lactation and the metabolic syndrome¹³. The association of lactation with incident diabetes among women with gestational diabetes is less clear^{38, 39}.

Both animal and human studies suggest that lactation affects lipid metabolism⁴⁰. In the rat, lipids accumulate in adipose tissue during pregnancy and are mobilized during lactation through local lipoprotein lipase activity^{41, 42}. Moreover, lactating rats have reduced visceral fat stores⁴³, smaller adipose cells, and reduced peripheral levels of lipoprotein lipase⁴⁴ compared with nonlactating animals. Differences in regional adipose tissue activity during pregnancy and lactation have also been observed in humans⁴⁵. These data suggest that women who do not lactate may have greater difficulty mobilizing fat stores after delivery, although data linking lactation with long term adiposity in human populations are mixed⁴⁶.

Pregnancy is also associated with a physiologic increase in serum triglycerides and total cholesterol. These changes resolve more rapidly in women who breastfeed than in those who do not³. Lactating women also have higher levels of HDL cholesterol and apolipoprotein AI than their nonlactating counterparts^{4, 38, 47}. In a recent prospective cohort study, Gunderson et al¹¹ reported that these favorable changes in lipid metabolism persist after weaning, suggesting that lactation has a lasting effect on maternal metabolism.

Lactation may also modify cardiovascular risk through changes in stress response. A recent study found a modest protective association between lactation history and incident hypertension¹². Animal studies suggest that oxytocin, which is released during milk let-down, may affect blood-pressure regulation. Petersson et al.⁴⁸ found that oxytocin administration produced decreases in blood pressure in rats that persisted for weeks after discontinuation, despite the drug's brief half-life. The authors postulate that oxytocin administration leads to long-term changes in central regulatory pathways. Similarly, observational studies^{7, 49–52} suggest that nursing mothers have diminished autonomic responses to stressors.

These observations suggest an important role for lactation in women's health. Fat stores accumulate during pregnancy, assuring that the mother will have adequate resources to compensate for variations in local food supply during the neonatal period⁵³. If these resources are not mobilized during lactation, women may accumulate adipose tissue, and pregnancy-associated metabolic changes may persist for a longer period of time. We

speculate that this impaired resetting of postpartum physiology may contribute to long-term disease risk. Further studies will be needed to test this hypothesis.

In conclusion, we have identified a novel association between greater than two years of lifetime lactation and myocardial infarction risk in a large, prospective cohort. This association persists after controlling for multiple lifestyle factors. Studies of metabolic risk profiles among contemporary women are needed to delineate further the relation between lactation and cardiovascular disease risk.

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Table 1

Age-standardized* baseline characteristics of parous women in the Nurses' Health Study in 1986, by duration of lactation (in % unless indicated otherwise)

	Duration of Lactation (months)				
	None	> 0-3	> 3-6	> 6-11	> 11-23
Number of person-years	25.4	25.4	25.1	25.1	25.2
Body mass index, mean	25.4	25.4	25.1	25.1	25.2
Body mass index age 18, mean	21.4	21.4	21.3	21.2	21.2
Hypertension	23.3	22.5	21.6	20.3	19.7
High cholesterol	7.3	7.2	7.8	7.0	6.7
Type 2 diabetes	2.1	1.9	1.7	1.6	1.7
Parental history of myocardial infarction prior to age 60	18.4	18.1	17.5	17.4	16.8
Subject < 5.5 lbs at birth	7.4	7.7	6.6	7.2	7.0
Moderate to vigorous exercise (mean hrs per week)	1.9	1.8	2.1	2.1	2.2
Mean Diet Score [†]					
Parity	2.9	3.2	3.0	3.1	3.0
1 child	11.2	8.3	7.7	4.7	1.5
2 children	34.2	31.0	32.6	31.9	23.8
≥3 children	54.6	60.7	59.8	63.4	74.7
History of stillbirth	3.4	3.2	3.2	3.0	3.1
Smoking history [‡]					
Never smoker	39.6	43.0	43.6	47.0	50.0
Past smoker	34.5	35.5	34.1	33.6	32.9
Current smoker	25.8	21.4	22.0	19.2	16.9
Menopausal	54.0	56.7	52.6	50.2	49.3
Hormone replacement therapy [§]					
Never	25.4	25.7	22.6	22.9	22.9
Past	11.8	12.9	11.7	10.9	10.1
Current	12.3	14.7	13.9	13.1	12.7
Multivitamin use	33.8	41.1	38.7	40.4	39.9
Aspirin use, > 1 tablet/wk	63.7	69.9	65.1	65.9	65.6

	Duration of Lactation (months)				
	None	> 0–3	> 3–6	> 6–11	> 11–23
No alcohol use	24.1	30.2	21.8	24.5	24.6
	26.5				

* Directly standardized in years to the age distribution of NHS

[†] Intakes of trans fat and cereal fiber, ratio of polyunsaturated-fat to saturated fat, and glycemic load were divided into quintiles. Each woman was then assigned a diet score for each nutrient based on her quintile of intake, with a higher score representing a lower risk. The four scores were summed, and the mean composite score is presented here.

[‡] Does not total 100% due to missing data. Covariate data were missing for the following proportions: BMI at age 18, 13.1%; physical activity, 2.8%; diet score, 6.7%; smoking, 1.1%; participant birth weight, 32.7%; multivitamin use, 5.7%; postmenopausal hormone use, 9.3%; alcohol use, 6.7%; aspirin use, 2.2%.

[§] Percentage of full study cohort

Table 2

Incident myocardial infarction and duration of lactation among parous women in the Nurses' Health Study: Prospective analysis using cases from 1986 to 2002; all models adjusted for age, parity, and history of stillbirth.

Cumulative duration of lactation (months)	None	> 0-3	> 3-6	> 6-11	> 11-23	>23	P for trend
No of cases	1,037	627	304	224	241	107	
Person-years	494,667	306,669	161,586	132,492	164,746	90,805	
Age, parity and stillbirth-adjusted HR (95% CI)	1.0 (ref)	0.90 (0.81 – 0.99)	0.91 (0.8 – 1.03)	0.88 (0.76 – 1.02)	0.77 (0.67 – 0.89)	0.63 (0.51 – 0.77)	<.0001
Multivariate-adjusted HR (95% CI)*	1.0 (ref)	1.01 (0.91 – 1.11)	1 (0.88 – 1.14)	1.02 (0.88 – 1.18)	0.93 (0.8 – 1.07)	0.77 (0.62 – 0.94)	0.02

* Hazard ratio (HR) and 95% CI adjusted for age, parity, history of stillbirth, BMI at age 18, birth weight of subject, parental history of myocardial infarction before age 60, diet quintile, physical activity, smoking, menopausal status, and use of aspirin, alcohol, multivitamins, and postmenopausal hormones.

Table 3

Incident myocardial infarction and duration of lactation, stratified by time since last birth among parous women in the Nurses' Health Study: Prospective analysis using cases from 1986 to 2002; all models adjusted for age, parity, and history of stillbirth.

Cumulative duration of lactation (months)		None	> 0-3	> 3-6	> 6-11	> 11-23	> 23	P for trend
No birth in last 30 years								
No of cases		616	426	186	130	133	54	
Person-years		211,951	146,625	67,250	49,338	54,082	21,443	
Age, parity and stillbirth-adjusted HR (95% CI)		1.0 (ref)	0.96 (0.85 – 1.09)	0.94 (0.79 – 1.11)	0.91 (0.75 – 1.1)	0.82 (0.68 – 0.99)	0.77 (0.58 – 1.02)	0.01
Multivariate-adjusted HR (95% CI)*		1.0 (ref)	1.04 (0.92 – 1.18)	1.02 (0.86 – 1.21)	1.02 (0.84 – 1.24)	0.95 (0.78 – 1.15)	0.90 (0.67 – 1.19)	0.33
Birth in last 30 years								
No of cases		421	201	118	94	108	53	
Person-years		282,716	160,044	94,336	83,155	110,663	69,362	
Age, parity and stillbirth-adjusted HR (95% CI)		1.0 (ref)	0.81 (0.69 – 0.96)	0.87 (0.71 – 1.07)	0.81 (0.65 – 1.02)	0.71 (0.57 – 0.88)	0.50 (0.37 – 0.67)	<0.001
Multivariate-adjusted HR (95% CI)*		1.0 (ref)	0.94 (0.79 – 1.12)	0.98 (0.8 – 1.21)	0.96 (0.76 – 1.21)	0.89 (0.71 – 1.1)	0.66 (0.49 – 0.89)	0.02

* Hazard ratio (HR) and 95% CI adjusted for age, parity, history of stillbirth, BMI at age 18, birth weight of subject, parental history of myocardial infarction before age 60, diet quintile, physical activity, smoking, menopausal status, and use of aspirin, alcohol, multivitamins, and postmenopausal hormones.