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# Lactation Duration and Midlife Atherosclerosis

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## Abstract

**Objective—**To evaluate lactation duration in relation to subsequent atherosclerosis in women during midlife.

**Methods—**The Coronary Artery Risk Development in Young Adults (CARDIA) study is multi-center prospective cohort that enrolled 2,787 women in 1985-1986 (ages 18-30, 52% Black, 48% White), of whom 2,014 (72%) attended the 20-year follow-up examination in 2005-2006. We selected 846 women (46% Black) without heart disease or diabetes at baseline who delivered one or more times after the baseline evaluation, had cardiometabolic risk factors measured at baseline, and had maximum common carotid intima-media thickness (mm) measured at the 20-year follow-up examination in 2005-2006. Lactation duration was summed across all postbaseline births for each woman and (n, women) categorized as: 0 to <1 month (n=262), 1 to <6 months (n=210), 6 to <10 months (n=169) and ≥10 months (n=205). Multiple linear regression models estimated mean common carotid intima-media thickness (95% CI) and mean differences among lactation duration groups compared with the 0 to <1 month group, adjusted for prepregnancy obesity, cardiometabolic status, parity, and other risk factors.

**Results—**Lactation duration had a graded inverse association with common carotid intima-media thickness; mean differences between ≥10 months vs. 0 to <1 month ranged from −0.062 mm for unadjusted models (p-trend<0.001) to −0.029 mm for models fully adjusted for prepregnancy BMI and cardiometabolic risk factors, parity, smoking, and sociodemographics (p-trend=0.010). Stepwise addition of potential mediators (BMI, systolic blood pressure at the 20-year follow-up

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examination) modestly attenuated the lactation and common carotid intima-media thickness association to −0.027 and −0.023 mm (p-trend=0.019 and 0.054).

**Conclusions—**Shorter lactation duration is associated with subclinical atherosclerosis. independent of prepregnancy cardiometabolic risk factors and traditional risk factors. The magnitude of differences in carotid artery intima-media thickness may represent greater vascular aging. Lactation may have long-term benefits that lower cardiovascular disease risk in women.

## Graphical Abstract

**Precis:** Lactation may lower the risk of atherosclerosis, a subclinical marker of heart disease in women.

## Introduction

Heart disease is the leading cause of death in U.S. women.(1) The importance of weight control, healthful dietary habits and adequate physical activity are recognized as key components of cardiovascular disease (CVD) prevention. Lactation history has been linked with reduced risk of myocardial infarction, hypertension, type 2 diabetes, and the metabolic syndrome in women during mid to late life.(2-5) However, studies have never measured CVD risk factors proximate to pregnancies, and rely on recall of lactation and self-report of CVD events or risk factors. Reverse causation (i.e., favorable cardiometabolic profiles and lower BMI cause longer lactation duration) remains a potential explanation for retrospective study findings.

Carotid artery intima media thickness is a measure of subclinical atherosclerosis, and a strong predictor of future heart disease and stroke, particularly in women.(6) Cross-sectional studies of lactation and carotid artery intima-media thickness have not revealed an association between the two.(7;8) However, the odds of aortic and coronary artery calcification were higher,(7) and lumen and adventitial sections of the carotid arteries (8) were smaller in women who never breastfed compared with women with 3 or more months of cumulative breastfeeding across.

No studies of CVD have considered risk factors that delay lactogenesis, (9) such as insulin resistance, obesity and gestational diabetes mellitus (GDM) and may be subject to reverse causation. One exception is the 20-year Coronary Artery Risk Development in Young Adults (CARDIA) study that measured prepregnancy risk factors through biochemical testing at 2 to 5-year intervals before and after pregnancies.(5) In CARDIA, lactation duration was associated with lower incidence of the metabolic syndrome independent of prepregnancy cardiometabolic risk factors, sociodemographics, lifestyle behaviors and weight gain.(5) Thus, we hypothesized that longer lactation duration would show a graded protective association with subclinical atherosclerosis in midlife, independent of prepregnancy cardiometabolic status, perinatal outcomes, lifestyle behaviors and follow up characteristics.

## Materials and Methods

The CARDIA Study is a population-based, multi-center, longitudinal, observational study examining the trends and determinants of coronary heart disease risk factors in young black

and white men and women. In 1985-1986, 5,115 participants (2,787 women) aged 18-30 years (52% Black, 48% White) were recruited from four geographic areas in the U.S.: Birmingham, Alabama, Chicago, Illinois, Minneapolis, Minnesota, and Oakland, California. Participants attended in-person exams every two to 5 years for measurements of blood pressure, anthropometry, biochemical parameters, sociodemographics, medical conditions and medications, and lifestyle behaviors. In women enrolled in CARDIA, we also assessed reproductive history, detailed pregnancy course and outcomes at each exam. Retention rates at follow-up exams 7, 10, 15, and 20 years later (2005-2006) were 81%, 79%, 74% and 72% of the surviving cohort, respectively. Institutional Review Boards at each participating study center approved the study. Written, informed consent was obtained from subjects for all procedures and for this current analysis.

Of 2,787 women enrolled in 1985-1986 (baseline), 2,014 (72%) attended the examination 20 years later in 2005-2006. After exclusions (Figure 1) the final analytic sample included 846 women without heart disease or overt diabetes before pregnancy, who delivered at least once after baseline (total of 1,535 births from 1986-2006), had common carotid intima-media thickness measured in 2005-2006, and reported lactation duration. Those excluded had less education, higher BMI, and higher percentage of Black race. Methodologies for data collection and venipuncture are described elsewhere.(10) Briefly, women fasted prior to each examination, and reported the number of hours since their last intake of food or beverages prior to the blood sample draw. Procedures for collection and storage of plasma and serum samples, laboratory quality control procedures, and methodology for analysis of plasma lipids lipoproteins, glucose, and insulin,(11) and calculation of the homeostatic model assessment of insulin resistance (HOMA-IR) have been previously described.(12) Pre-pregnancy risk factors were obtained at baseline. HOMA-IR = $(G_0 \times I_0) / 22.5$ and $G_0$ = fasting glucose, and $I_0$ = fasting insulin.

After an initial 5-minute rest, blood pressure was measured 3 times at one minute intervals, and the second and third values averaged. From Year 0 to 15, blood pressure was measured using the Hawksley (Lancing, Sussex, UK) random-zero sphygmomanometer; the first and fifth phase Korotkoff sounds were recorded. At Year 20, blood pressure was measured with an automated sphygmomanometer (Omron HEM907XL oscillometer, Omron Corp., Schaumburg, IL) via a standardized protocol. Omron values were recalibrated to corresponding random zero values based on measurement techniques in 903 participants, as estimated random zero systolic value = [3.74 + 0.96*Omron systolic value] and estimated random zero diastolic value =[1.30 + 0.97*Omron diastolic value].

Certified technicians measured weight, height and waist circumference at each examination according to standardized protocol using calibrated research equipment as previously described. (10) Body mass index (BMI) was computed as weight in kilograms divided by squared height in meters.

The metabolic syndrome was ascertained by the National Cholesterol Education Program (NCEP ATP-III) criteria: the presence of 3 of 5 characteristics (waist girth>88 cm, fasting triglycerides ≥ 150 mg/dL, HDL-cholesterol<50 mg/dL, blood pressures ≥ 130 or ≥ 85 mm Hg or treatment with anti-hypertensive medication, fasting glucose ≥ 100 mg/dL, or

treatment with diabetes medication), and incident diabetes was assessed by fasting serum glucose ≥ 126 mg/dL, two-hour serum glucose ≥ 200 mg/dL, and/or self-report of diabetes and medication treatment in examination years 0, 7, 10, 15 and 20.

The common carotid intima-media thickness was measured at 20 years post-baseline (June 2005- August 2006) when women were between the ages of 38-50 years. High-resolution B-mode ultrasound was used to acquire a longitudinal image of the common carotid arterial wall thickness, 2 images of the carotid artery bulb, and 2 images of the internal carotid artery above the bulb on the right and left sides.(13) These images of the common carotid artery were obtained according to a standard protocol using the GE-Logiq-700 (Issaquoah, Ill) with a high-resolution M12L transducer operating at a frequency of 13 MHz. Measurements of the maximal carotid intima-media thickness were made at a central reading center by readers blinded to all clinical information. The maximum intima-media thickness of the common carotid (mm) was defined as the mean of the carotid intima-media thickness of the near and far walls on both the left and right sides, with 1 to 4 measurements available for the common carotid and 1 to 8 for the carotid artery bulb and internal carotid artery. The common carotid intima-media thickness measure was analyzed as a continuous measure. This measure has shown the strongest correlation with CVD risk factors in CARDIA.(13) Any atherosclerotic plaque (measured in Year 20) was included as part of the intima media and a note was made about the extent of stenosis that existed anywhere in the right or left carotid artery.(13)

At each examination, participants reported whether they were currently pregnant or lactating, number of pregnancies and births since their last examination, and how they ended (abortion, miscarriage, and live or stillbirths), dates of delivery(ies), pregnancy complications [i.e., hypertensive disorders of pregnancy (hypertension during gestation with or without proteinuria), gestational diabetes mellitus (GDM), preterm birth (PTB) < 37 weeks gestation], perinatal outcomes including gestational age, infant birth weight and Cesarean-section delivery. Parity is defined as number of births beyond 20 weeks ofgestation. Time (years) from baseline to the first pregnancy and from the last birth to the Year 20 examination were calculated from dates of delivery. Validation of self-report of GDM based on prenatal medical record abstraction had a sensitivity for self-report of 100% and specificity of 92%.(14) Self-report of preterm births had sensitivity and specificity of 84% and 89%, respectively. Hypertensive disorders of pregnancy were over-reported by women; low sensitivity (40%) with high specificity (90%).

Women reported lactation duration for each birth at examination years 7, 10, 15 and 20 based on the following categories: none, <6 weeks, 6-11 weeks, 3-6 months, or >6 months. To calculate total lactation duration across all post-baseline births, we assigned the midpoint for each lactation category: 21 days for <6 weeks, 66 days for 6-11 weeks, 135 days for 3-6 months, and 210 days as the upper limit for >6 months. We summed the number of days of lactation across all births to estimate the overall duration of lactation for each woman. The overall duration (months) was next divided into four categories (n, women) to evenly distribute the analytic sample, as well as represent clinically relevant periods of lactation: 0 to<1 month (n=262), 1 to<6 months (n=210), 6 to<10 months (n=169) and ≥10 months (n=205).

Socio-demographics and behavioral data [alcohol intake (ml/day), cigarette smoking (pack-years), education, marital status, oral contraceptive (OC) use, physical activity score] were collected at each examination using self- and interviewer-administered questionnaires. The CARDIA Physical Activity History (15) provided physical activity scores that correlate positively with symptom-limited graded treadmill exercise test duration. Women also reported menopausal status, medication use and medical history [hypertension, heart disease, diabetes, and medications (diabetes, lipid-lowering, hormone replacement or hormonal contraceptives). Family history of diabetes and heart disease for one or more first degree relatives (father, mother or siblings) was reported at examinations in years 0, 5, 10 and 20.

Differences in characteristics at baseline and follow up among lactation categories were assessed using chi-square statistics for categorical variables (clinic site, race, education, perinatal outcomes, medication use, medical history), and by comparison of means for continuous variables using F-tests (fasting plasma lipids and glucose, age, BMI, HOMA-IR, systolic and diastolic blood pressures). Median and interquartile ranges were reported for alcohol intake, physical activity, age at first birth and time since last birth to account for skewing in the data. All p-values are for two-sided tests with statistical significance at <0.05. Trend p-values were obtained by ordering lactation categories from shortest to longest duration.

Linear regression models evaluated unadjusted and adjusted mean (95%CI) maximum common carotid intima-media thickness among lactation categories using procedures from SAS for Windows 9.1.3 (SAS Institute Inc., Cary, NC, USA). Evaluation of potential confounders was based on *a priori* hypotheses for prepregnancy measures [BMI, HDL-C, blood pressure, HOMA-IR], parity, education, age, number of post-baseline births, race, smoking, and time since last birth. Covariates were not included if they were not associated with common carotid intima-media thickness independent of the other model covariates [statistical significance level *p-value* >0.05]. Adjusted models were devised by stepwise addition of prepregnancy risk factors, and then addition of other covariates. We evaluated change in weight (BMI at Year 20) and blood pressure as potential mediators (i.e., on the causal pathway) in the association. Effect modification of the lactation duration and common carotid intima-media thickness association by race, number of births, and time since last birth were evaluated by introduction of cross-product terms for additive interaction (significance *p-value* <0.10). None of the interaction terms reached statistical significance.

## Results

The sample of 846 CARDIA women (46% Black) had a mean age of 24 years (range 18-30 years), 72% were nulliparous at baseline (1985-86), and gave birth to 1,535 children during the 20-year follow up period. Crude mean (95%CI) for maximum common carotid intima-media thickness (mm) was thicker for Black than White women; 0.801 (0.791–0.812) and 0.729 (0.719–0.738), respectively (p-value<0.001). Shorter lactation duration was associated with Black race, nulliparity, younger age, higher prepregnancy BMI and HOMA-IR, and lower prepregnancy plasma HDL-cholesterol and physical activity score (Table 1; All p-values<0.05). By the 20-year follow-up examination (Table 2), lactation duration was positively associated with plasma HDL-cholesterol, and inversely associated with BMI,

diastolic and systolic blood pressure (SBP), fasting serum glucose, HOMA-IR, incident type 2 DM, hypertension and the metabolic syndrome. Lactation duration was also positively associated with attained education and physical activity levels. The presence of atherosclerotic plaques at Year 20 (Figure 2) was associated with shorter lactation duration in crude and covariate adjusted analyses (prepregnancy BMI, HDL-C and SBP, age, smoking, parity; Trend p-value=0.0504).

In multivariable linear regression models (Table 3), lactation duration displayed a graded inverse association with mean maximum common carotid intima-media thickness (mm); group differences versus referent (0 to 1 months) in unadjusted models ranged from −0.034 to −0.062 (Trend p-value<0.001). Adjustment for covariates that met the study criteria as confounders (age, race, baseline parity, number of post-baseline births) resulted in attenuation of group differences to −0.021 to −0.033 (Trend p-value=0.002). Addition of other risk factors [prepregnancy SBP, BMI, HDL-C and HOMA-IR, education, smoking] resulted in minimal attenuation of these estimates by 10%, although the graded association became less pronounced (Trend p-value=0.010).

Adjustment for pregnancy complications, history of hypertension outside of pregnancy, medical conditions, time interval since last birth, oral contraceptive use, and fasting blood lipids had minimal impact on model estimates. However, stepwise addition of potential mediators (BMI and SBP at Year 20) of the lactation association with common carotid intima-media thickness resulted in modest attenuation of the group differences that remained statistically significant or was near statistical significance independent of attained BMI and SBP during the 20-year follow up (Trend p-value=0.019 and 0.050, respectively).

## Discussion

Our findings from this longitudinal study support the hypothesis that greater lactation duration has persistent effects that reduce the risk of early subclinical atherosclerosis in women during midlife. Most importantly, the graded inverse association between lactation duration and early atherosclerosis remained after adjustment for prepregnancy cardiometabolic risk factors (i.e., systolic BP, BMI, HDL-C, HOMA-IR), and smoking habit, providing evidence against reverse causation. We also found that changes in risk factors mediated the lactation association with subclinical atherosclerosis, including elevations in blood pressure and weight gain from baseline to the Year 20 examination (average 12 years from last delivery). These robust findings provide insight into the pathways through which lactation may affect the maternal vasculature and influence CVD risk.

Our findings contrast with null findings from two cross-sectional studies of 297 peri- or post-menopausal women aged 45-58 years,(7) and 607 premenopausal women within 4-12 years post-delivery.(8) These studies categorized lifetime lactation history across all births (i.e., breastfeeding all children for at least 3 months, some, or never), but did not assess overall duration. A consistent pattern of breastfeeding across all births was associated with lower risk of coronary artery calcification, and larger lumen and adventitial mean diameters of the vasculature compared to never breastfeeding, but no difference in common carotid intima-media thickness.(7;8) The absence of longitudinal biochemical data collection during

the perinatal period may contribute to unmeasured confounding from pre-existing maternal risk profiles that resulted in null findings.

Our study is consistent with previous reports of lower risk of self-reported hypertension and CVD related to longer lactation, including 23% reduction in risk of myocardial infarction.(3) Previous studies had limited power to examine graded associations with common carotid intima-media thickness, lacked perinatal risk factor measurements, self-reported CVD events, and had low rates of extended breastfeeding (i.e., 70% reported duration <6 months) that may limit their relevance to contemporary cohorts.

Physiological effects of lactogenesis on maternal cardiovascular function include the release of the neuro-peptide, oxytocin, associated with decreased maternal blood pressure and stress responses.(16;17) In humans, oxytocin has both anti-stress and blood pressure-lowering effects in some but not all studies.(18;19) One cross-sectional study reported higher maternal blood pressure, but lower heart rate during breastfeeding compared with bottle-feeding.(20) Our findings that higher BMI and SBP at Year 20 mediated the association provide evidence that lactation may reduce atherosclerosis through favorable effects on adiposity and blood vessels.

Previous epidemiologic studies(21-24) report mixed findings with regard to the longer-term effects of breastfeeding on blood pressure levels, or hypertensive disorders in women. These findings include inverse associations with average systolic and diastolic blood pressure,(22) or no association.(23) Two studies of hypertension outcomes(21)(24) reported inverse associations with lifetime lactation . However, these studies obtained a single measurement of blood pressure many years post-delivery, and did not assess gestational hypertensive disorders or perinatal risk status.(25) These studies did not assess cardiometabolic risk factors before, during or soon after pregnancy.

Strengths of our analysis include the prospective design with repeated measurements of cardiometabolic risk factors before pregnancy, and recall of pregnancy complications and lactation duration within 3 months to 4 years postpartum (maximum of 6 years), as well as measurements of prepregnancy cardiometabolic risk factors (blood pressure, obesity and metabolic status) that may delay lactogenesis(9) to minimize reverse causation. We controlled for confounding from social and cultural determinants of breastfeeding by adjustment for age, race, education, and smoking that cluster with healthful lifestyle. History of GDM and PTB were very accurately reported by CARDIA women.

Limitations of our study include the variable time intervals for measurements of blood pressure and other risk factors in relation to pregnancies, missing common carotid intima-media thickness measurements for 8% of women who attended the Year 20 exam, and the fact that hypertensive disorders of pregnancy were over-reported by women as noted in other epidemiologic studies.(26) However, time interval before the first birth or after the last birth did not confound or modify the lactation and common carotid intima-media thickness association. Although this study measured common carotid intima-media thickness only once at 20 years post-baseline, the young age at baseline (mean 24 years), and control for prepregnancy cardiometabolic risk factors, and lifestyle behaviors minimized confounding

due to pre-existing metabolic risk factors. Lactation duration per birth was limited to a maximum of 6 months due to the method of data collection.

Pregnancy imposes greater demands on the cardiovascular system, including persistent effects on CVD risk factors and vascular remodeling in women. Lactation may be crucial to return of maternal physiologic and metabolic systems to the prepregnancy state. Lactating women exhibit less atherogenic blood lipid profiles, greater insulin sensitivity, and less inflammation compared to non-lactating women.(5;27;28) Longer-term effects of lactation that persist post-weaning have been reported for various cardiometabolic risk factors.(5;28) For example, we previously reported 6 mg/dl higher HDL-C levels with 3 months or more of lactation,(28) and lower incidence of the metabolic syndrome among CARDIA women with and without a history of GDM independent of prepregnancy metabolic syndrome components, and other risk factors.(5) Given the strong inverse association between plasma HCL-C and CVD risk,(29) the biochemical evidence supports lactation's role in preventing atherosclerosis and carotid artery plaque formation. .

Suboptimal lactation may adversely affect maternal health and increases health care costs. (30) U.S. breastfeeding rates have increased dramatically during the past 50 years, but are still well below current recommendations that breastfeeding should continue for at least one year. Currently, 79% of U.S. women initiate lactation, but by 6months the rate drops to 49% and by one year to 26%.(31) Thus, improving lactation duration has great potential for a positive impact on women's health and health care cost savings. The CARDIA study provides strong evidence that lactation reduces future subclinical atherosclerosis by accounting for biochemical and clinical risk factors that preceded pregnancy, and lifestyle behaviors. Higher common carotid intima-media thickness in our study corresponds to 3-5 years of vascular aging(32) for suboptimal lactation.

If the persistent beneficial effects of lactation are substantiated, then breastfeeding may not only be seen as an important behavior to preserve child health, but may represent a unique opportunity for prevention of cardiovascular diseases in women.

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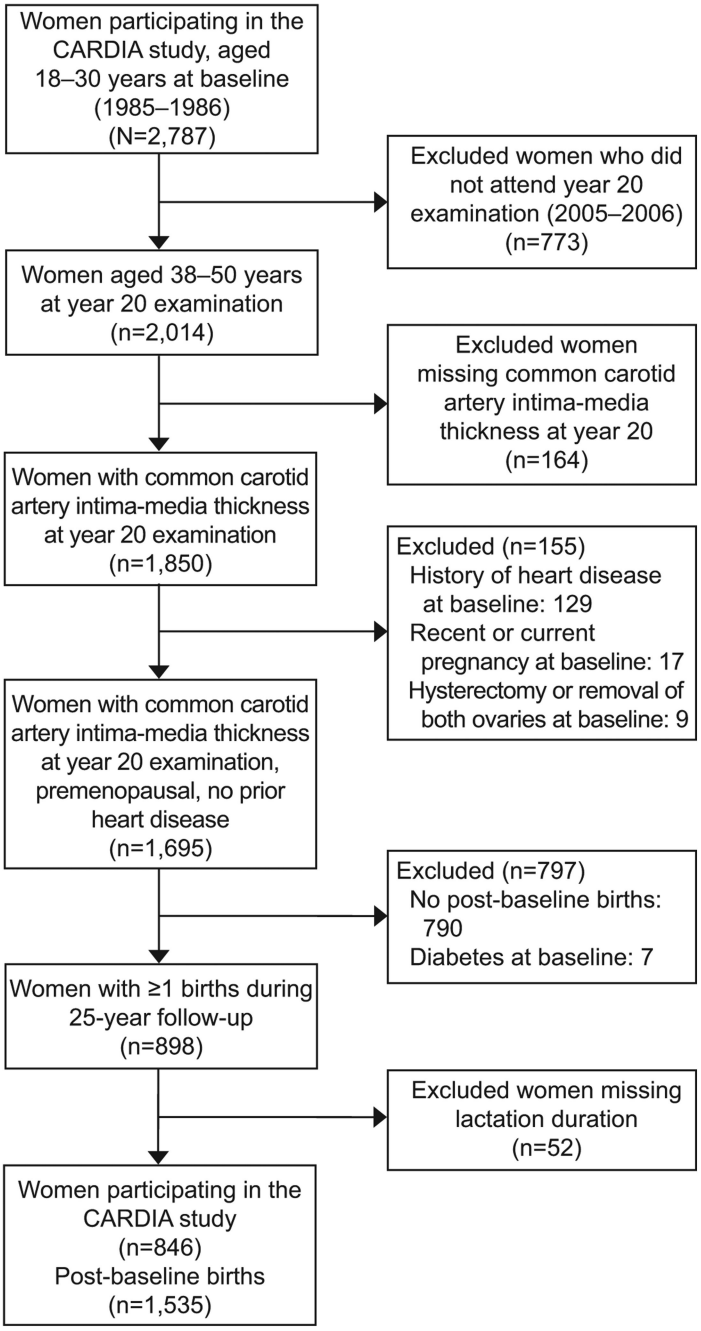


**Figure 1.**

Sample: Women participating in the CARDIAs study who were 18–30 years at baseline with no history of heart disease (1985–1986), common carotid intima-media thickness measurements at the year 20 examination (2005-2006), one or more post-baseline births, and reported lactation duration. CARDIA, Coronary Artery Risk Development in Young Adults.

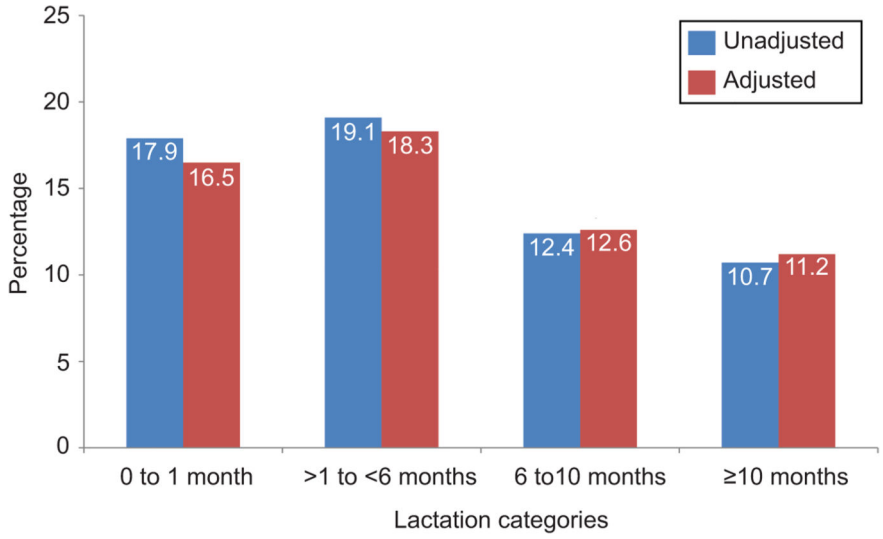


**Figure 2.**

Percentage of women with carotid artery atherosclerotic plaques present at year 20 (2005–2006) by lactation duration categories (n=846); *P*=.045 for unadjusted, and *P*=.050 for trend adjusted for prepregnancy body mass index, HDL-cholesterol and systolic blood pressure, age, smoking status, and parity.

**Table 1**

Baseline Characteristics (1985-1986) for 846 Coronary Artery Risk Development in Young Adults Women by Lactation Duration Categories for Postbaseline births (n=1,535).

| | Lactation Duration Categories | | | | |
|---|---|---|---|---|---|
| **Baseline Characteristics** | **0 to 1 month (n=262)** | **>1 to < 6 months (n=210)** | **6 to <10 months (n=169)** | **≥10 months (n=205)** | **Overall p-value** |
| N (%) | | | | | |
| Race (Black) | 189 (72) | 98 (47) | 56 (33) | 43 (21) | <0.001 |
| Parity Groups | | | | | <0.001 |
| Nulliparous (0) | 138 (53) | 161 (77) | 129 (76) | 179 (87) | |
| Primiparous (1) | 86 (33) | 34 (16) | 22 (13) | 18 (9) | |
| Multiparous (2 or more) | 38 (15) | 15 (7) | 18 (11) | 8 (4) | |
| Center: Alabama | 82 (31) | 45 (21) | 27 (16) | 39 (19) | 0.003 |
| Chicago | 75 (29) | 57 (27) | 48 (28) | 54 (26) | |
| Minneapolis | 38 (15) | 37 (18) | 31 (18) | 50 (24) | |
| Oakland | 67 (26) | 71 (34) | 63 (37) | 62 (30) | |
| Pre-pregnancy, Mean (SD) | | | | | |
| Age (y) | 24 (4) | 24 (4) | 25 (4) | 24 (4) | 0.002 |
| BMI (kg/m$^2$) | 25 (5) | 23 (4) | 23 (4) | 23 (4) | <0.001 |
| Waist girth (cm) | 75 (10) | 71 (8) | 70 (8) | 72 (9) | <0.001 |
| Blood Pressure (mm Hg) | | | | | |
| Systolic | 106 (9) | 105 (9) | 105 (9) | 105 (8) | 0.10 |
| Diastolic | 67 (9) | 66 () | 66 (8) | 66 (8) | 0.62 |
| Fasting Plasma (mg/dL) | | | | | |
| Triglycerides | 69 (36) | 63 (51) | 64 (33) | 62 (27) | 0.15 |
| HDL-Cholesterol | 54 (12) | 58 (13) | 57 (13) | 57 (12) | 0.001 |
| LDL-Cholesterol | 110 (31) | 110 (30) | 105 (28) | 110 (27) | 0.24 |
| Total Cholesterol | 177 (33) | 180 (32) | 175 (30) | 179 (30) | 0.39 |
| Fasting Serum Glucose (mg/dL) | 79 (9) | 81 (7) | 79 (7) | 80 (8) | 0.21 |
| HOMA-IR | 2.4 (1.7) | 1.9 (1.2) | 1.7 (1.1) | 2.1 (1.8) | <.001 |

Missing values for baseline variables;N= 19 fasting plasma TG, HDL-C, or Total Cholesterol N = 27 fasting serum glucose, N =29 HOMA-IR

**Table 2**

Follow-up Characteristics (2005-2006) and Pregnancy Outcomes for 846 Coronary Artery Risk Development in Young Adults Women according to Lactation Duration Categories for Post-baseline births (n=1,535).

| Follow-up Characteristics | Lactation Duration Categories | | | | |
|---|---|---|---|---|---|
| | 0 to 1 month (n=262) | >1-<6 months (n=210) | 6 to <10 months (n=169) | ≥10 months (n=205) | Overall p-value |
| Sociodemographics/Lifestyle Behaviors: | | | | | |
| Age at Year 20 exam, Mean (SD) | 44 (4) | 44 (4) | 45 (4) | 45 (4) | 0.001 |
| Education (High school or less), N (%) | 60 (23) | 16 (8) | 8 (5) | 9 (4) | <0.001 |
| Physical activity score, Median (IQR) | 144 (248) | 228 (358) | 237.0 (298.0) | 292 (319) | <0.001 |
| Smoking (pack-years), Mean (SD) | 5 (9) | 3 (8) | 2 (4) | 3 (6) | <0.001 |
| Smoker (ever), N (%) | 136 (52) | 92 (44) | 65 (38) | 79 (39) | 0.01 |
| Reproductive, N (%): | | | | | |
| Current Oral contraceptive use | 27 (13) | 25 (14) | 16 (11) | 29 (17) | 0.45 |
| Postmenopausal | 54 (21) | 44 (21) | 31 (18) | 30 (15) | 0.31 |
| Post-baseline Births (>Y0 to Y20), N (%): | | | | | <.001 |
| 1 birth | 140 (53) | 124 (59) | 72 (43) | 16 (8) | |
| 2 births | 85 (32) | 66 (31) | 76 (44) | 116 (57) | |
| 3 or more births | 37 (14) | 20 (10) | 22 (13) | 73 (36) | |
| Pregnancy Timing | | | | | |
| Age at First birth post-baseline (yrs), Mean (SD) | 29 (5) | 32 (5) | 32 (4) | 32 (5) | <0.001 |
| Age at Last birth post-baseline (yrs) Mean (SD) | 31 (5) | 34 (4) | 36 (4) | 34 (5) | <0.001 |
| Time from Y0 to first birth (yrs) Median (IQR) | 4 (5) | 6 ( 7) | 6 (7) | 6 (6) | <0.001 |
| Time from last birth to Y20 exam (yrs) Median (IQR) | 14 (6) | 12 (7) | 11 (6) | 9 (7) | <0.001 |
| Pregnancy Outcomes, N (%): | | | | | |
| GDM History | 228 (87) | 184 (88) | 147 (87) | 174 (85) | 0.86 |
| Hypertensive disorders of pregnancy | 86 (33) | 67 (32) | 51 (30) | 77 (38) | 0.45 |
| Preterm birth (ever) | 55 (21) | 36 (17) | 24 (15) | 32 (16) | 0.29 |
| Cesarean-section delivery | 87 (33) | 60 (29) | 48 (28) | 58 (28) | 0.58 |
| Anthropometry, Mean (SD): | | | | | |
| BMI (kg/m$^2$) | 32 (8) | 28 (7) | 27 (6) | 29 (8) | <0.001 |
| Waist circumference (cm) | 92 (15) | 85 (14) | 82 (13) | 87 (16) | <0.001 |

| Follow-up Characteristics | Lactation Duration Categories | | | | |
|---|---|---|---|---|---|
| | 0 to 1 month (n=262) | >1-<6 months (n=210) | 6 to <10 months (n=169) | ≥10 months (n=205) | Overall p-value |
| Weight gain (Y0 to Y20) | 19 (14) | 14 (14) | 12 (11) | 16 (15) | <0.001 |
| Weight gain (kg) per year to 1st birth | 0.8 (2.3) | 0.7 (1.6) | 0.5 (1.5) | 0.7 (1.5) | <0.001 |
| Blood Pressure (mm Hg), Mean (SD) | | | | | |
| Systolic | 117 (17) | 108 (11) | 108 (14) | 112 (13) | <0.001 |
| Diastolic | 75 (12) | 68 (10) | 67 (10) | 71 (11) | <0.001 |
| Fasting (mg/dL), Mean (SD) | | | | | |
| Plasma Triglycerides | 96 (56) | 86 (47) | 89 (48) | 91 (48) | 0.25 |
| Plasma HDL-Cholesterol | 56 (17) | 62 (17) | 61 (16) | 60 (16) | 0.008 |
| Plasma LDL-Cholesterol | 107 (30) | 110 (27) | 104 (28) | 109 (29) | 0.20 |
| Plasma Total Cholesterol | 182 (32) | 189 (30) | 183 (31) | 187 (31) | 0.09 |
| Serum Glucose (mg/dL) | 99 (32) | 92 (13) | 90 (11) | 94 (18) | <0.001 |
| HOMA-IR, Mean (SD) | 4.5 (3.4) | 3.3 (2.8) | 3.0 (1.8) | 3.8 (2.7) | <0.001 |
| Disease Status, N (%): | | | | | |
| Family History of Heart Disease | 46 (18) | 41 (20) | 37 (22) | 45 (22) | 0.60 |
| Hypertension (ever) | 96 (37) | 40 (19) | 21 (12) | 26 (13) | <0.001 |
| Lipid-lowering medication (ever) | 11 (4) | 13 (6) | 4 (2) | 9 (4) | 0.35 |
| Incident Diabetes (post-delivery to Y20) | 34 (13) | 20 (10) | 10 (6) | 8 (4) | 0.003 |
| Metabolic syndrome (Y0 to Y20) | 31 (12) | 19 (9) | 8 (5) | 11 (5) | 0.02 |

† Kruskal-Wallis test; Y0 = Baseline exam; Y20 = Year 20 exam. Missing values for variables: N=27 fasting serum glucose, insulin, HOMA-IR or fasting plasma lipids;

**Table 3**

Unadjusted and Adjusted Means (95%CI) for Maximum Common Carotid Artery Intima-Media Thickness (mm) by Lactation Duration Categories among (n=846) Coronary Artery Risk Development in Young Adults Women with One or More Post-baseline Births after Year 0 (baseline) through Year 20 (1986-2006).

| | Lactation Duration Categories | | | | | Difference in Mean Intima-Media Thickness (95% CI) Between Groups relative to referent | | |
|---|---|---|---|---|---|---|---|---|
| **Models** | **0 to 1 months (referent; n=262)** | **>1 to <6 months (n=210)** | **6 to <10 months (n=169)** | **≥10 months (n=205)** | **Trend p-value** | **>1 to <6 months vs. 0 to 1 month** | **6 to <10 months vs. 0 to 1 month** | **≥10 months vs. 0 to 1 month** |
| 0 | 0.795 (0.782, 0.808) | 0.761 (0.747, 0.776) | 0.747 (0.730, 0.763) | 0.733 (0.718, 0.747) | <.001 | −0.034** (−0.053, −0.014) | −0.048** (−0.069, −0.027) | −0.062** (−0.082, −0.043) |
| 1 | 0.783 (0.770, 0.796) | 0.762 (0.748, 0.776) | 0.759 (0.744, 0.774) | 0.751 (0.735, 0.766) | 0.002 | −0.021 (−0.040, −0.003) | −0.024 (−0.045, −0.004) | −0.033* (−0.054, −0.012) |
| 2 | 0.776 (0.761, 0.790) | 0.757 (0.740, 0.773) | 0.757 (0.739, 0.775) | 0.746 (0.728, 0.765) | 0.010 | −0.019 (−0.038, 0.000) | −0.019 (−0.040, 0.001) | −0.029* (−0.051, −0.008) |
| 3 | 0.773 (0.759, 0.787) | 0.755 (0.739, 0.772) | 0.756 (0.738, 0.774) | 0.746 (0.728, 0.765) | 0.019 | −0.018 (−0.036, 0.001) | −0.017 (−0.037, 0.003) | −0.027* (−0.048, −0.006) |
| 4 | 0.769 (0.755, 0.783) | 0.754 (0.738, 0.770) | 0.757 (0.739, 0.775) | 0.747 (0.729, 0.765) | 0.054 | −0.015 (−0.034, 0.003) | −0.012 (−0.032, 0.008) | −0.023 (−0.044, −0.002) |

Pair-wise comparison to the referent group

Model 0: Unadjusted model,

Model 1: Model 0 adjusted for age, race, baseline parity, and number of post-baseline births during 20 years (since Year 0 to year 20),

Model 2: Model 1 + [prepregnancy (Year 0) SBP, BMI, HDL-C and HOMA-IR] + maximum education and smoking pack-years through Year 20,

Model 3: Model 2 + BMI at Year 20 (potential mediator) to evaluate change in BMI (i.e., weight change),

Model 4: Model 3 + Systolic blood pressure (SBP) at Year 20 (potential mediator) to evaluate change in SBP.

* p-values<0.05

** p-values<0.01