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# Duration of Lactation and Incidence of the Metabolic Syndrome in Women of Reproductive Age According to Gestational Diabetes Mellitus Status: A 20-Year Prospective Study in CARDIA—The Coronary Artery Risk Development in Young Adults Study

**Short Running Title:** Lactation and Incident Metabolic Syndrome by GDM Status

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*Objective(s):* To prospectively assess the association between lactation duration and incidence of the metabolic syndrome (MetS) among women of reproductive age.

*Research Design and Methods:* Participants were 1,399 women (39% black, aged 18-30) in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, an ongoing multi-center, population-based, prospective observational cohort study conducted in the United States. Women were nulliparous and free of the MetS at baseline (1985-86) and before subsequent pregnancies, and re-examined 7, 10, 15 and/or 20 years after baseline. Incident MetS cases were identified according to NCEP ATP III criteria. Complementary log-log models estimated relative hazards of incident MetS among time-dependent lactation duration categories by gestational diabetes mellitus (GDM) adjusted for age, race, study center, baseline covariates (BMI, MetS components, education, smoking, physical activity) and time-dependent parity.

*Results:* Among 704 parous women (620 non-GDM, 84 GDM), there were 120 incident MetS cases in 9,993 person-years (overall incidence rate 12.0 per 1,000 person-years;10.8 for non-GDM, 22.1 for GDM). Increasing lactation duration was associated with lower crude MetS incidence rates from 0-1 month through >9 months ($p<0.001$). Fully adjusted relative hazards showed that risk reductions associated with longer lactation were stronger among GDM (RHs range:0.14 to 0.56;$p=0.03$) than non-GDM groups(RHs range:0.44 to 0.61;$p=0.03$).

*Conclusions:* Longer duration of lactation was associated with lower incidence of the metabolic syndrome years post-weaning among women with a history of GDM and without GDM controlling for preconception measurements, BMI, socio-demographic and lifestyle traits. Lactation may have persistent favorable effects on women's cardiometabolic health.

Lactation has favorable effects on cardiometabolic risk factors in women with and without a history of gestational diabetes mellitus(GDM), a strong predictor of type 2 diabetes (1;2) and the metabolic syndrome following pregnancy.(3) In the general population, lactating compared with non-lactating women exhibit a less atherogenic lipid profile,(4) and lower blood glucose and insulin concentrations.(5) Consistent with these findings, lactating women with recent GDM experience lower fasting plasma glucose and insulin levels, higher plasma high-density lipoprotein cholesterol(HDL-C) levels, and 50% lower prevalence of type 2 diabetes at 12-16 weeks postpartum.(6;7)

Yet, few studies have investigated whether lactation's favorable effects on cardiometabolic risk factors persist post-weaning to protect women against future disease. The only study, to our knowledge, to measure changes from preconception to post-weaning reported 6 mg/dl higher average HDL-C levels among women who lactated for ≥3 months versus <3 months independent of preconception plasma HDL-C levels and weight gain.(8) Epidemiologic studies have reported weak to modest protective associations between lactation and disease risk in mid to late life including lower prevalence of the metabolic syndrome(9;10) or cardiovascular risk factors,(11) and lower incidence of myocardial infarction(12) and type 2 diabetes.(13) Yet, evidence is lacking that directly links risk factor changes that persist post-weaning to subsequent disease onset, because disease status and lactation history were ascertained decades after pregnancy, and preconception and/or post-weaning risk factor measurements were not available.(9-13) Other limitations include classification of outcomes via self-report only(11-13), and failure to account for mediating or confounding effects of lifestyle habits during the reproductive years. Lastly, lactation duration in relation to disease risk has not been examined separately among women with a history of GDM, albeit one study reporting a null association with incident diabetes.(13)

To our knowledge, studies have never examined lactation and incidence of the metabolic syndrome, or variation in disease risk by GDM status. To address these gaps, we prospectively examined whether increasing duration of lactation was associated with lower incidence of the metabolic syndrome during a 20-year period among women of childbearing age. We examined incidence rates for GDM and non-GDM pregnancies and controlled for preconception risk factor levels, socio-demographics, and follow-up behavioral attributes.

## METHODS

The CARDIA Study is a multi-center, longitudinal, population-based, observational study designed to describe the development of risk factors for coronary heart disease in young black (52%) and white adults recruited from four geographic areas in the U.S.: Birmingham, Alabama, Chicago, Illinois, Minneapolis, Minnesota, and Oakland, California. The study design, recruitment, methodology, and cohort characteristics have been previously described.(14;15) In 1985-1986, baseline data was collected for 2,787 women aged 18-30 years. All metabolic syndrome components were measured at exams in years 0, 7, 10, 15 and 20. Retention rates were 81, 79, 74 and 72% of the surviving cohort.(16;17) Institutional Review Boards at each participating study center approved the study. Written, informed consent was obtained from participants for all study procedures.

**Sample Selection Criteria:** Of 2,787 women enrolled at baseline, we excluded 1,008 women who were parous at baseline, 18 women currently pregnant or breastfeeding, pregnant within the past 3 months, or who reported a previous hysterectomy, 4 women with type 1 diabetes, and 92 who met the NCEP ATP III criteria for the metabolic syndrome (MetS) at baseline (Figure 1). Further, we excluded 213 women missing covariates or with incomplete information on all five components to ascertain the MetS at baseline and for at least one follow-up exam, 11 primiparas who delivered a multi-fetal pregnancy during the first follow-up interval, and 42 women missing all lactation information. Biochemical measurements at exams (years 0, 7, 10, 15, 20) from currently pregnant or lactating women were not utilized in the analysis. Among the sample of 1,399 nulliparas who were free of the MetS at baseline, 695 women were classified as nulliparous during follow-up, (677 never gave birth, 9 developed the MetS prior to any births, and 9 had later multi-fetal births only). The data from 704 women who subsequently delivered at least one singleton, live birth during the 20-year period (1986-2006) were used to examine the association of lactation duration and incidence of the MetS. These 704 women were more likely than the 695 who remained nulliparous to be married, slightly younger and thinner, not using oral contraceptives, and had lower diastolic blood pressure levels at baseline.

**Data Collection Methods:** Methodologies for data collection and venipuncture are described elsewhere.(14;15;18) Briefly, women fasted prior to each exam, and reported the number of hours since their last intake of food or beverages prior to the blood sample drawn into a Vacutainer tube containing ethylenediaminetetraacetic acid (EDTA). Procedures followed in the collection and storage of plasma samples, laboratory quality control procedures, and methodology for analysis of plasma triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC), glucose, and insulin are described elsewhere. (18;19)

**Blood Pressure Measurements***:* After an initial 5-minute rest, blood pressure was measured 3 times at one minute intervals. At the baseline and year 7, 10 and 15 follow-up exams, blood pressure was measured using the Hawksley (Lancing, Sussex,UK) random-zero sphygmomanometer; the first and fifth phase Korotkoff sounds were recorded.(15) At the year 20 exam, blood pressure was measured with an automated sphygmomanometer (Omron HEM907XL oscillometer, Omron Corp., Schaumburg,IL). The protocol specified the appropriate cuff size (small, medium, large, extra large) based on the upper arm circumference, which was measured by the blood pressure technician at the midpoint between the acromion and the olecranon. Omron values were recalibrated to corresponding random zero values based on a study of both measurement techniques in 903 participants at year 20, 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.

**Anthropometric Measurements:** Certified technicians obtained anthropometric measurements (weight, height and waist circumference) at each exam according to standardized protocol.(20) Body weight was measured to the nearest 0.2 kg using a calibrated balance beam scale in participants wearing light clothing. Height(without shoes) was measured to the nearest 0.5 cm using a vertical ruler, and waist circumference to the nearest 0.5 cm at the minimal abdominal girth.(21) Body mass index (BMI) was computed as weight in

kilograms divided by squared height in meters.

**Definition of the Metabolic Syndrome:** Incident (new) cases of the MetS were identified at follow-up exams (years 7, 10, 15, 20) using the National Cholesterol Education Program (NCEP ATP III) criteria (22): MetS defined as the presence of 3 of 5 characteristics (waist girth>88 cm, fasting TG ≥150 mg/dL, HDL-C<50 mg/dL, blood pressure≥130 or≥85 mm Hg or treatment with anti-hypertensive medication, fasting glucose≥100 mg/dL or treatment with diabetes medication). Incident MetS cases were ascertained subsequent to births delivered since baseline among women free of the MetS before pregnancy, and in the non-pregnant and non-lactating state at exams. Incident cases were censored from subsequent time intervals, and births that occurred during those intervals were not included in the analysis.

**Number of Pregnancies and Births:** At each exam, women reported whether they were currently pregnant or lactating, number of pregnancies including abortions, miscarriages, and live or stillbirths since the previous exam along with length(s) of gestation, multi-fetal gestation, dates of delivery(ies), and diabetes during pregnancy. Interim ~~B~~births were defined as singleton pregnancies of longer than 20 weeks gestation that were conceived and delivered after baseline. We ascertained pre-existing diabetes before pregnancy as distinct from GDM pregnancy based on biochemical (fasting and 2 hour glucose levels) and medical history data.(1) We also validated self-report of GDM among 165 women for whom laboratory data were abstracted from medical records for 200 births between baseline and year 10. Sensitivity for classification by self-report as ever having GDM was 100% (20 of 20), and specificity was 92% (134 of 145).

We classified women into time-dependent interim birth groups based on the cumulative number of singleton births and by GDM status: 0 births, 1 or more non-GDM births, or 1 or more GDM births within four intervals extending from baseline through years 7, 10, 15 and 20. Women transitioned from 0 births into one or more (1+) non-GDM or GDM birth groups within an interval and group assignments remained for subsequent intervals, except when a GDM birth occurred after a non-GDM birth, then non-GDM would transition into the GDM group. Once classified with GDM, a woman remained in that category until the end of the follow-up regardless of GDM status for subsequent births.

Time-dependent parity (continuous covariate) was defined as the cumulative number of births since baseline and was updated at each exam through the end of follow-up.

**Time-dependent Lactation Categories:** Women reported the number of months of lactation for each pregnancy by choosing one of the following categories: none,<6 weeks, 6-11 weeks, 3-6 months, or >6 months. To calculate the duration of lactation across all births, we assigned the midpoint of the interval for each lactation category as follows: 21 days for <6 weeks, 66 days for 6-11 weeks, and 135 days for 3-6 months. For >6 months of lactation, we assigned a value of 210 days as the upper limit. Duration of lactation for each time interval was obtained by summing the number of days of lactation across all births within an interval. Total cumulative duration of lactation was updated for subsequent interval(s) by summing the duration for all prior intervals.

Time-dependent lactation categories were designated within non-GDM and GDM birth groups. Women were classified into one of four lactation groups for each time interval: 0 to 1 month, >1 to 5 months, 6 to 9

months and >9 months, representing the cumulative lactation duration for all births since baseline for the interval. Within non-GDM and GDM groups, the referent group was 0 to 1 month.

**Other Baseline and Follow-up Covariates***:* Socio-demographic, medical and behavioral data [medication use, alcohol intake (ml/day), cigarette smoking, education, marital, oral contraceptive (OC) use, physical activity] were collected at each exam using self- and interviewer-administered questionnaires. Baseline categorical variables were smoking (never, former, or current), years of education (12 or less, 13 to 15, and 16 or more), marital status (never married, widowed, divorced or separated, or married), and OC use (never, past, or current). Medication use including insulin, oral hypoglycemics and anti-hypertensives was self-reported. A positive family history of diabetes was based on report of one or more first degree relatives (father, mother or siblings) with diabetes at the examinations in years 0, 5, and 10.

We assessed daily physical activity at each examination using the interviewer-administered CARDIA Physical Activity History (23) to calculate physical activity scores (race-specific quartiles) which have correlated positively with symptom-limited graded treadmill exercise test duration.(24) Time-dependent covariates included physical activity, weight gain, cigarette smoking, OC use and parity groups for each follow-up time interval.

**Statistical Methods:**Baseline and follow-up characteristics were described for outcome groups, and for the main effect, duration of lactation groups, by GDM status. We examined baseline characteristics: age, race, BMI, MetS components (fasting plasma TG, HDL-C, glucose levels, systolic and diastolic blood pressures, waist girth), diabetes, cigarette smoking, education, marital status, OC use, alcohol, physical activity, and dietary intake. Follow-up characteristics included parity, family history of diabetes, and GDM status. Chi-square tests were used to assess associations with socio-demographic, medical history, study center and behavioral categorical variables. T-test statistics were used to assess the difference in continuous variables by incident MetS. Multiple linear regression methods (analysis of variance) were used to assess baseline differences in continuous variables (age, BMI, MetS components, dietary intake) among duration of lactation groups. Wilcoxon rank sum and Kruskal Wallis one-way tests were used to assess differences in alcohol intake and physical activity scores (median and inter-quartile range) due to skewedness in the distributions. P-values were obtained from two-sided tests (significance <0.05). Physical activity, weight gain, OC use, parity, and smoking were examined as time-dependent covariates.

MetS incident cases for each interval were categorized into time-dependent lactation categories and by GDM status during 20-year follow-up. To describe the pattern of new cases over time, we calculated the ~~C~~cumulative incidence of MetS (n/N, %) within each time interval (0-7, >7-10, >10-15, >15-20 years) by dividing the number of incident cases at the end of the interval by the number of women at risk of the MetS at the beginning of the interval according to the lactation category and birth group assigned for that specific time interval. Women may transition into interim birth groups and longer lactation duration categories as parity and months of lactation increase through the end of follow-up.

We estimated unadjusted incidence rates (IR) of the MetS for lactation groups by dividing the number of incident cases of the MetS by the person-time for individuals observed during the preceding intervals, ~~and~~ then computed the exact 95% confidence intervals (CI). At each exam, women

reported the number of births and months of lactation since the previous exam during follow-up. Person-time is contributed by each individual to a specific lactation category and interim birth group for the entire time interval during which they transitioned into a new category or birth group. During follow-up, women may contribute person-time to multiple lactation categories, and potentially to both non-GDM and GDM birth groups depending on whether non-GDM birth(s) preceded GDM birth(s) among successive intervals. Women remain in their group assignments through subsequent intervals unless additional births and/or months of lactation occur. For 23 births among a total of 1,273, lactation duration was missing and women had no previous births, so we assigned those births to the 0 to 1 month lactation category.

Because MetS status was only determined at CARDIA exams, the exact failure time for a woman without the MetS at a particular exam and identified with the MetS at the subsequent exam is unknown. We accounted for interval-censored data using the method of Prentice and Gloeckler (25) to provide point and interval estimates of the relative hazard of MetS associated with exposure. These estimates were obtained in the context of a generalized linear model for binary outcome with a complementary log-log link function. The hazard ratio for incidence of MetS was estimated for lactation categories within GDM status groups at exams in years 7, 10, 15 and 20. Multivariable adjusted models (SAS version 9.1; SAS Institute Inc., Cary, North Carolina) included race, study center, time, baseline covariates (age, education, smoking) as well as the follow-up covariate, time-dependent parity, to account for differences in number of births across lactation categories (Model 1). Next, we added other baseline covariates, BMI and all MetS components, to Model 1. ,–To form the fully adjusted model, we then added baseline physical activity. Finally, we added time-dependent physical activity and weight gain, separately, as potential mediators of the lactation association by stepwise addition. Family history of diabetes and time-dependent smoking and OC use had little impact on the results, and were not included in the fully adjusted model.

## RESULTS

During 20 years, 704 women without the MetS before pregnancies delivered one or more singleton births (620 non-GDM, 84 GDM), and 695 women remained nulliparous. Among non-GDM and GDM groups, respectively, 252(40%) and 21(25%) women delivered one birth, 271(44%) and 47(56%) women delivered two births, and 97(16%) and 16(19%) women delivered three or more births during follow-up; 1,273 total births.

Among 704 parous women, there were 120 incident MetS cases in 9,993 person-years. The overall crude incidence rate was 12.0 cases per 1,000 person-years (95%CI: 10.0,14.3). Crude incidence rates were higher($p=0.002$) among women with GDM versus non-GDM pregnancies; 22.1 per 1,000 person-years (95%CI:14.1,33.0) and 10.8 per 1,000 person-years (95%CI:8.8, 13.2), respectively. Among 695 nulliparas, there were 129 incident MetS cases in 11,590 person-years; incidence rate of 11.1 per 1,000 person-years (95% CI:9.3,13.2).

Compared with non-cases, incident MetS cases (Table 1) differed in baseline characteristics including higher BMI, waist girth, fasting plasma glucose and triglycerides, and systolic and diastolic blood pressures as well as lower HDL-C levels and physical activity scores. Incident MetS cases were also more likely to be of black race, to develop GDM, to have less education, a family history of diabetes, or shorter duration of lactation.

Baseline characteristics differed among lactation categories (Table 2). Among

the GDM group, lactation for 0 to 1 month compared to longer duration of lactation was associated with black race, less education, smoking, family history of diabetes, younger age, higher waist girth, BMI, fasting plasma triglycerides, and total dietary fat and saturated fat intakes, and lower dietary fiber intake (g)/1000 KJ. Lactation >9 months was associated with not smoking, older age and higher physical activity score. Differences in baseline characteristics followed a similar pattern among lactation categories for the non-GDM group.

Incident MetS cases increased over time as the cohort aged (Table 3) with the greatest increase between years 15 and 20 compared with the earliest interval. The cumulative incidence of the MetS was highest for 0 to 1 month of lactation regardless of GDM status.

Incident MetS cases were more likely to develop new onset diabetes during follow-up;19 (16%) of MetS cases and 16 (3%) of non-cases(p<.001). Mean (SD) years since last birth were slightly less for MetS cases than non-cases; 7.9 (5.0) and 9.2 (4.8), respectively, (p=.01).

Crude incidence rates (number of cases per 1,000 person-years) were higher for GDM than non-GDM groups across all lactation groups except for >9 months (Figure ~~1~~ 2). The incidence rates (IR, 95%CI) decreased with increasing duration of lactation; from 15.8 (95%CI:11.3,21.5) to 9.2 (95%CI:5.3,14.6) among the non-GDM group, and 49.4 (95%CI:25.8,84.7) to 8.5 (95%CI: 1.8,24.8) among the GDM group. Overall, there was a sixfold lower crude IR of the MetS for >9 months versus 0 to 1 month of lactation among the GDM group, and a twofold lower IR for the highest versus lowest duration of lactation among the non-GDM group. Within race groups, we examined crude incidence rates for >1 month versus 0 to 1 month of lactation, and found similar protective associations, except for blacks in the non-GDM group (Figure ~~2~~ 3). Median duration of lactation was shorter for blacks than whites [4.5 (interquartile range 4.8) versus 7.0 months (interquartile range 9.2);p<.001]. Crude incidence rates for baseline BMI groups (<25, ≥ 25) were consistent with the race results (data not shown), including no difference in MetS rates for >1 month and 0 to 1 month lactation categories among overweight women in the non-GDM group.

In multivariable models stratified by GDM status (Table 4), duration of lactation was inversely associated with the relative hazards (RH) of incident MetS; from >1 to 5 months to >9 months compared with 0 to 1 month; with a stronger inverse association among GDM (RHs of 0.11 to 0.24) than non-GDM groups (RHs of 0.41 to 0.49) in unadjusted models (all p<0.001). Adjustment for race, time-dependent parity, study center and baseline covariates (age, education, smoking) attenuated RHs modestly, but a significant inverse association remained for GDM and non-GDM groups. In fully adjusted models, addition of baseline BMI, all MetS components and physical activity enhanced the graded inverse associations with longer lactation, remaining statistically significant for GDM and non-GDM groups (all p=.03). Addition of time-dependent physical activity during follow-up as a potential mediator revealed a stronger protective association among GDM (RHs of 0.13 to 0.41;p=0.02) than non-GDM groups (RHs of 0.51 to 0.67;p=0.10), while addition of weight gain in a separate model strengthened the association among women with GDM (RHs of 0.09 to 0.49;p=0.01).

## DISCUSSION

Among women with and without GDM pregnancies, a longer cumulative duration of lactation was strongly protective, even after controlling for parity and baseline covariates, including components of the

metabolic syndrome before pregnancy. For women with non-GDM pregnancies, there was a threshold effect with lactation >1 month conferring protection compared with 0 to 1 month. Among women with GDM pregnancies, we found a strong, graded inverse association of lactation with incidence of the metabolic syndrome; those with longest lactation approaching the non-GDM incidence rate of the metabolic syndrome. The associations remained after controlling for mediators such as changes in physical activity or weight gain during follow-up, with a stronger protective association among the GDM group.

Associations were similar within race and BMI groups, especially for women with a history of GDM. However, black women had much shorter duration of lactation which limited our ability to fully assess the association of extended duration of lactation with disease risk. Overweight status was closely related to black race, and our sample size was too small to fully assess the separate effects. We did not observe significant interactions by number of singleton pregnancies because most women (84%) delivered only one or two pregnancies.

Epidemiologic studies examining lactation history and prevalence of the metabolic syndrome or CVD risk have not measured preconception risk factor levels or stratified by GDM status. Cross-sectional studies of primarily peri- and postmenopausal women reported that lactation >1 month (9) or any lactation(10) was associated with 21-22% lower prevalence of the metabolic syndrome, and that lactation >12 months was associated with 9-20% lower prevalence of CVD risk factors, but not incidence of CVD.(11) In studies of lactation and type 2 diabetes after GDM and non-GDM pregnancies, glucose levels before pregnancy were not measured.(6;7;13) Longer lifetime lactation ≥4 months was associated with a 25% lower incidence of type 2 diabetes among white women, but not those with a history of GDM.(13) In Latinas with previous GDM, findings on lactation and future diabetes risk were inconclusive, and duration was not assessed.(26)

Our findings for women of reproductive age show a much stronger protective association for >1 month of lactation; lower incidence of the metabolic syndrome by 39-56% for non-GDM and by 44-86% for GDM groups. Because our sample included only nulliparas at baseline and preconception measurements of all metabolic syndrome components, we minimized confounding by pre-existing conditions before pregnancy and lactation.

Our study's unique strengths include prospective collection of "preconception" measurements of the metabolic syndrome components to confirm that women were free of the metabolic syndrome before pregnancies, and stratification by GDM status. Metabolic syndrome components were measured at 3 to 7-year intervals before and after pregnancies over a 20-year period, thereby maintaining the temporality of the exposure (pregnancy and lactation duration) to new onset of metabolic syndrome. We also modeled lactation as a time-dependent main effect and controlled for multiple potential confounders including age, time-dependent parity, secular trends, socio-demographics and behavioral attributes. The validity of our findings is enhanced by the population-based sample, high cohort retention rate over 20 years of follow-up, and measurement of all five metabolic syndrome components at baseline for 100% of the sample and for three or more follow-up visits for 72% of the sample. We also examined associations separately for black and white race groups, and found consistent associations.

Limitations include no data on lactation intensity, ascertainment of GDM by self-report, variable time intervals to

conception and from delivery relative to CARDIA exams, and few higher order births. Our GDM validation study showed high sensitivity and specificity of GDM by self-report, and non-differential misclassification would bias our findings toward the null. Women who lactated may have had healthier lifestyles than women who did not lactate, but we accounted for these traits as well as weight gain. Despite control for various behavioral and other potential confounders, residual confounding is always possible in observational studies.

One proposed mechanism through which lactation may influence cardiometabolic health is through greater weight loss. Although milk production increases maternal total energy expenditure by 15-25%,(27;28) evidence for greater postpartum weight loss is equivocal.(29) Prospective studies that measured maternal weights (not self-reported) before or during early pregnancy have generally reported lower postpartum weight retention at one year postpartum,(30) more rapid loss approaching pregravid weight,(31) or 1-2 kg greater weight losses within 3-6 months postpartum among lactating women.(32) Yet, weight change did not explain the protective association between lactation and the metabolic syndrome in our study.

Another possibility is that lactation affects body composition and regional fat distribution. Well-nourished lactating women lose about 2 kg in total fat mass by 6 months postpartum based on magnetic resonance imaging,(33) or mass spectrometry,(34) and tend to mobilize more fat from the thigh than the trunk.(33) In lactating American women, skinfold thickness was reduced in the suprailiac and subscapular regions, but increased in the triceps region.(35) Yet, studies that compared lactating versus non-lactating women using dual-energy X-ray absorptiometry (DXA) found greater declines in total body fat mass within 3-6 months postpartum,(36) but no differences in mobilization of fat from leg, arm and trunk regions.(36;37) In 26 women with previous GDM, visceral fat mass via computed tomography at 3 months postpartum did not differ by lactation status.(38) Longitudinal studies are needed to examine postpartum visceral fat changes in larger samples.

Acutely, lactogenesis has favorable effects on maternal cardiometabolic blood profiles, but few studies have adjusted for BMI, or measured post-weaning levels. Lactating women had lower plasma triglycerides,(39;40) and higher plasma HDL-C levels and HDL-C: total cholesterol ratios at 3-6 months postpartum unadjusted for BMI.(4;41;42) They also had elevations in respiratory quotient and carbohydrate utilization consistent with preferential use of glucose.(28) Moreover, lactating versus non-lactating women exhibited greater insulin sensitivity among GDM and non-GDM groups.(5;38) In post-weaning studies, plasma HDL-C levels were higher adjusted for preconception levels and weight gain,(8) but not plasma total cholesterol or other lipids.(8;43)

In summary, longer duration of lactation was associated with lower incidence of the metabolic syndrome years after delivery and post-weaning among women with non-GDM as well as GDM pregnancies. Lifestyle behaviors did not explain these associations. Lactation may ameliorate the increased risk of the metabolic syndrome associated with higher parity (30% per birth in non-GDM, 150% for GDM).(3) By contrast, other studies have not demonstrated clear benefits of lactation on future health of women with a history of GDM. Our data provide strong evidence that lactation may have lasting favorable effects on metabolic risk profiles among women with a history of GDM who are most susceptible to developing

metabolic diseases, as well as women without GDM. Further investigation is needed to elucidate the mechanisms through which lactation may influence women's cardiometabolic risk profiles, and whether lifestyle modifications, including lactation duration, may affect development of coronary heart disease and type 2 diabetes, particularly, among high-risk groups such as women with a history of GDM.

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**REFERENCES**


1. Gunderson,EP, Lewis,CE, Tsai,AL, Chiang,V, Carnethon,M, Quesenberry,CP, Jr., Sidney,S: A 20-Year Prospective Study of Childbearing and Incidence of Diabetes Mellitus in Young Women Controlling for Glycemia before Conception: The Coronary Artery Risk Development in Young Adults Study. *Diabetes* 56:2990-2996, 2007
2. Kim,C, Newton,KM, Knopp,RH: Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care* 25:1862-1868, 2002
3. Gunderson,EP, Jacobs,DR, Jr., Chiang,V, Lewis,CE, Tsai,A, Quesenberry,CP, Jr., Sidney,S: Childbearing is associated with higher incidence of the metabolic syndrome among women of reproductive age controlling for measurements before pregnancy: the CARDIA study. *Am.J.Obstet.Gynecol.* 201(2):177.e1-9, 2009
4. Knopp,RH, Walden,CE, Wahl,PW, Bergelin,R, Chapman,M, Irvine,S, Albers,JJ: Effect of postpartum lactation on lipoprotein lipids and apoproteins. *J.Clin.Endocrinol.Metab* 60:542-547, 1985
5. Tigas,S, Sunehag,A, Haymond,MW: Metabolic adaptation to feeding and fasting during lactation in humans. *J.Clin.Endocrinol.Metab* 87:302-307, 2002
6. Kjos,SL, Henry,O, Lee,RM, Buchanan,TA, Mishell,DR, Jr.: The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. *Obstet.Gynecol.* 82:451-455, 1993
7. Lenz,S, Kuhl,C, Hornnes,PJ, Hagen,C: Influence of lactation on oral glucose tolerance in the puerperium. *Acta Endocrinol.(Copenh)* 98:428-431, 1981
8. Gunderson,EP, Lewis,CE, Wei,GS, Whitmer,RA, Quesenberry,CP, Sidney,S: Lactation and changes in maternal metabolic risk factors. *Obstet.Gynecol.* 109:729-738, 2007
9. Cohen,A, Pieper,CF, Brown,AJ, Bastian,LA: Number of children and risk of metabolic syndrome in women. *J.Womens Health (Larchmt.)* 15:763-773, 2006
10. Ram,KT, Bobby,P, Hailpern,SM, Lo,JC, Schocken,M, Skurnick,J, Santoro,N: Duration of lactation is associated with lower prevalence of the metabolic syndrome in midlife--SWAN, the study of women's health across the nation. *Am.J.Obstet.Gynecol.* 198:268-6, 2008
11. Schwarz,EB, Ray,RM, Stuebe,AM, Allison,MA, Ness,RB, Freiberg,MS, Cauley,JA: Duration of lactation and risk factors for maternal cardiovascular disease. *Obstet.Gynecol.* 113:974-982, 2009
12. Stuebe,AM, Michels,KB, Willett,WC, Manson,JE, Rexrode,K, Rich-Edwards,JW: Duration of lactation and incidence of myocardial infarction in middle to late adulthood. *Am.J.Obstet.Gynecol.* 2008
13. Stuebe,AM, Rich-Edwards,JW, Willett,WC, Manson,JE, Michels,KB: Duration of lactation and incidence of type 2 diabetes. *JAMA* 294:2601-2610, 2005
14. Cutter,GR, Burke,GL, Dyer,AR, Friedman,GD, Hilner,JE, Hughes,GH, Hulley,SB, Jacobs,DR, Jr., Liu,K, Manolio,TA, .: Cardiovascular risk factors in young adults. The CARDIA baseline monograph. *Control Clin.Trials* 12:1S-77S, 1991
15. Friedman,GD, Cutter,GR, Donahue,RP, Hughes,GH, Hulley,SB, Jacobs,DR, Jr., Liu,K, Savage,PJ: CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J.Clin.Epidemiol.* 41:1105-1116, 1988
16. Lewis,CE, Jacobs,DR, Jr., McCreath,H, Kiefe,CI, Schreiner,PJ, Smith,DE, Williams,OD: Weight gain continues in the 1990s: 10-year trends in weight and overweight from the

CARDIA study. Coronary Artery Risk Development in Young Adults. *Am.J.Epidemiol.* 151:1172-1181, 2000

17. Steffen,LM, Kroenke,CH, Yu,X, Pereira,MA, Slattery,ML, Van Horn,L, Gross,MD, Jacobs,DR, Jr.: Associations of plant food, dairy product, and meat intakes with 15-y incidence of elevated blood pressure in young black and white adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am.J.Clin.Nutr.* 82:1169-1177, 2005
18. Bild,DE, Jacobs,DR, Liu,K, Williams,OD, Hilner,JE, Perkins,LL, Marcovina,SM, Hulley,SB: Seven-year trends in plasma low-density-lipoprotein-cholesterol in young adults: the CARDIA Study. *Ann.Epidemiol.* 6:235-245, 1996
19. Lewis,CE, Funkhouser,E, Raczynski,JM, Sidney,S, Bild,DE, Howard,BV: Adverse effect of pregnancy on high density lipoprotein (HDL) cholesterol in young adult women. The CARDIA Study. Coronary Artery Risk Development in Young Adults. *Am.J.Epidemiol.* 144:247-254, 1996
20. Lewis,CE, Smith,DE, Wallace,DD, Williams,OD, Bild,DE, Jacobs,DR, Jr.: Seven-year trends in body weight and associations with lifestyle and behavioral characteristics in black and white young adults: the CARDIA study. *Am.J.Public Health* 87:635-642, 1997
21. Smith,DE, Lewis,CE, Caveny,JL, Perkins,LL, Burke,GL, Bild,DE: Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. *JAMA* 271:1747-1751, 1994
22. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 285:2486-2497, 2001
23. Anderssen,N, Jacobs,DR, Jr., Sidney,S, Bild,DE, Sternfeld,B, Slattery,ML, Hannan,P: Change and secular trends in physical activity patterns in young adults: a seven-year longitudinal follow-up in the Coronary Artery Risk Development in Young Adults Study (CARDIA). *Am.J.Epidemiol.* 143:351-362, 1996
24. Sidney,S, Haskell,WL, Crow,R, Sternfeld,B, Oberman,A, Armstrong,MA, Cutter,GR, Jacobs,DR, Savage,PJ, Van Horn,L: Symptom-limited graded treadmill exercise testing in young adults in the CARDIA study. *Med.Sci.Sports Exerc.* 24:177-183, 1992
25. Prentice,R, Gloeckler,L: Regression analysis of grouped survival data with application to breast cancer data. *Biometrics* 34:57-67, 1978
26. Gunderson,EP: Breastfeeding after gestational diabetes pregnancy: subsequent obesity and type 2 diabetes in women and their offspring. *Diabetes Care* 30 Suppl 2:S161-S168, 2007
27. Dewey,KG: Energy and protein requirements during lactation. *Annu.Rev.Nutr.* 17:19-36, 1997
28. Butte,NF, Hopkinson,JM, Mehta,N, Moon,JK, Smith,EO: Adjustments in energy expenditure and substrate utilization during late pregnancy and lactation. *Am.J.Clin.Nutr.* 69:299-307, 1999
29. Fraser,AB, Grimes,DA: Effect of lactation on maternal body weight: a systematic review. *Obstet.Gynecol.Surv.* 58:265-269, 2003
30. Janney,CA, Zhang,D, Sowers,M: Lactation and weight retention. *Am.J.Clin.Nutr.* 66:1116-1124, 1997
31. Kramer,FM, Stunkard,AJ, Marshall,KA, McKinney,S, Liebschutz,J: Breast-feeding reduces maternal lower-body fat. *J.Am.Diet.Assoc.* 93:429-433, 1993

32. Dewey,KG, Heinig,MJ, Nommsen,LA: Maternal weight-loss patterns during prolonged lactation. *Am.J.Clin.Nutr.* 58:162-166, 1993
33. Sohlstrom,A, Forsum,E: Changes in adipose tissue volume and distribution during reproduction in Swedish women as assessed by magnetic resonance imaging. *Am.J.Clin.Nutr.* 61:287-295, 1995
34. Sadurskis,A, Kabir,N, Wager,J, Forsum,E: Energy metabolism, body composition, and milk production in healthy Swedish women during lactation. *Am.J.Clin.Nutr.* 48:44-49, 1988
35. Brewer,MM, Bates,MR, Vannoy,LP: Postpartum changes in maternal weight and body fat depots in lactating vs nonlactating women. *Am.J.Clin.Nutr.* 49:259-265, 1989
36. Butte,NF, Hopkinson,JM: Body composition changes during lactation are highly variable among women. *J.Nutr.* 128:381S-385S, 1998
37. Wosje,KS, Kalkwarf,HJ: Lactation, weaning, and calcium supplementation: effects on body composition in postpartum women. *Am.J.Clin.Nutr.* 80:423-429, 2004
38. McManus,RM, Cunningham,I, Watson,A, Harker,L, Finegood,DT: Beta-cell function and visceral fat in lactating women with a history of gestational diabetes. *Metabolism* 50:715-719, 2001
39. Darmady,JM, Postle,AD: Lipid metabolism in pregnancy. *Br.J.Obstet.Gynaecol.* 89:211-215, 1982
40. Qureshi,IA, Xi,XR, Limbu,YR, Bin,HY, Chen,MI: Hyperlipidaemia during normal pregnancy, parturition and lactation. *Ann.Acad.Med.Singapore* 28:217-221, 1999
41. Erkkola,R, Viikari,J, Irjala,K, Solakivi-Jaakkola,T: One-year follow-up of lipoprotein metabolism after pregnancy. *Biol.Res.Pregnancy.Perinatol.* 7:47-51, 1986
42. Knopp,RH, Bergelin,RO, Wahl,PW, Walden,CE: Effects of pregnancy, postpartum lactation, and oral contraceptive use on the lipoprotein cholesterol/triglyceride ratio. *Metabolism* 34:893-899, 1985
43. Kallio,MJ, Siimes,MA, Perheentupa,J, Salmenpera,L, Miettinen,TA: Serum cholesterol and lipoprotein concentrations in mothers during and after prolonged exclusive lactation. *Metabolism* 41:1327-1330, 1992

Table 1: Baseline Characteristics (1985-86), Family History of Diabetes, GDM status and Lactation Duration Among Incident Metabolic Syndrome (MetS) Cases and Non-cases (1986-2006).

| **Baseline characteristics** | **MetS Incident Case (n=120)** | **Non-case (n=584)** | p-value‡ |
|---|---|---|---|
| | n (%) | n (%) | |
| Race (Black) | 67 (55.8) | 212 (36.3) | <.001 |
| Education (high school or less) | 41 (34.2) | 148 (25.3) | 0.06 |
| Marital Status (married) | 22 (18.3) | 99 (17.0) | 0.64 |
| Smoker (current) | 27 (22.5) | 125 (21.4) | 0.90 |
| OC use (current) | 25 (20.8) | 163 (27.9) | 0.28 |
| Family history of diabetes £ | 54 (45.0) | 146 (25.0) | <.001 |
| Type 2 Diabetes mellitus | 1 (0.8) | 1 (0.2) | .31 |
| GDM status (ever) £ | 23 (19.2) | 61 (10.4) | 0.007 |
| | Mean (SD) | Mean (SD) | |
| Age (y) | 23.8 ( 3.7) | 23.7 ( 3.6) | 0.75 |
| BMI ($kg/m^2$) | 26.8 ( 6.0) | 22.3 ( 3.5) | <.001 |
| Waist girth (cm) | 78.7 (12.1) | 69.1 ( 6.5) | <.001 |
| Fasting plasma: | | | |
| Glucose (mg/dl) | 82.1 ( 7.8) | 79 ( 7.1) | <.001 |
| HDL-C (mg/dl) | 53.8 (13.1) | 58.2 (12.2) | <.001 |
| Triglycerides (mg/dl) | 73.3 (37.7) | 61.2 (35.2) | <.001 |
| Systolic blood pressure (mm Hg) | 110.5 ( 9.1) | 104.6 ( 8.6) | <.001 |
| Diastolic blood pressure (mm Hg) | 68.5 ( 9.6) | 65.3 ( 8.7) | <.001 |
| Dietary Intake (% KJs): | | | |
| Fat | 36.9 ( 6.3) | 37.1 ( 6.1) | 0.68 |
| Saturated Fat | 13.9 ( 3.0) | 13.8 ( 3.0) | 0.83 |
| Carbohydrate | 47.4 ( 7.4) | 46.9 ( 7.4) | 0.50 |
| Fiber (g)/1000 KJ | 0.54 (0.28) | 0.57 (0.28) | 0.29 |
| Alcohol intake (ml/day) † | 2.4 ( 9.6) | 2.4 ( 9.7) | 0.53 |
| Physical activity score† | 286.5 (281.0) | 332.0 (339.5) | 0.06 |
| Lactation (months) † £ | 2.6 ( 7.0) | 7.0 ( 9.3) | <.001 |

† median (inter-quartile range), Wilcoxon Rank Sum test
‡ two-sided p-value. Chi-square test was used for categorical baseline characteristics;
T-test was used for continuous baseline characteristics.
£ ascertained during the 20-year follow-up period

Table 2. Baseline Characteristics (1985-1986) and Family History of Diabetes for Lactation Categories Stratified by GDM Status (1986-2006).

| Characteristics | Women with Non-GDM Births Lactation Categories | | | | |
|---|---|---|---|---|---|
| | 0 to 1 month (n=157) | >1 to 5 months (n=157) | 6 to 9 months (n=152) | >9 months (n=154) | p-value‡ |
| | | | n (%) | | |
| Race (Black) | 99 ( 63.1) | 74 ( 47.1) | 49 ( 32.2) | 24 ( 15.6) | <.001 |
| Education (<=HS) | 73 ( 46.5) | 44 ( 28.0) | 31 ( 20.4) | 23 ( 14.9) | <.001 |
| Smoker (current) | 42 ( 26.8) | 40 ( 25.5) | 22 ( 14.5) | 20 ( 13.0) | 0.001 |
| Family history of diabetes | 51 ( 32.5) | 53 ( 33.8) | 37 ( 24.3) | 26 ( 16.9) | 0.002 |
| | | | mean (SD) | | |
| Age (y) | 22.9 (3.6) | 23.6 (3.3) | 23.9 (3.7) | 24.5 (3.7) | <.001 |
| BMI (kg/m$^2$) | 24.2 (4.9) | 22.9 (4.0) | 22.6 (3.7) | 22.0 (3.1) | <.001 |
| Waist girth (cm) | 72.9 (9.0) | 70.3 (8.0) | 69.1 (7.3) | 69.3 (6.2) | <.001 |
| Systolic blood pressure (mm Hg) | 106.1 (9.1) | 105.6 (8.5) | 106.1 (9.2) | 104.6 (9.2) | 0.41 |
| Diastolic blood pressure (mm Hg) | 65.5 (8.7) | 65.4 (9.6) | 66.2 (8.8) | 65.9 (8.6) | 0.87 |
| Fasting plasma: | | | | | |
| Glucose (mg/dl) | 78.9 (7.5) | 78.9 (7.1) | 79.9 (6.5) | 79.5 (6.7) | 0.50 |
| HDL-C (mg/dl) | 55.9 (12.2) | 57.8 (12.8) | 59.1 (11.7) | 58.4 (12.7) | 0.13 |
| Triglycerides (mg/dl) | 66.7 (33.0) | 58.7 (23.4) | 59.0 (26.8) | 65.0 (54.2) | 0.11 |
| Dietary intake (%KJ as) | | | | | |
| Total Fat | 37.4 (6.5) | 37.9 (6.3) | 37.0 (5.2) | 35.4 (6.2) | <.01 |
| Saturated Fat | 14.0 (3.1) | 14.0 (3.1) | 14.0 (2.7) | 13.1 (2.9) | 0.01 |
| Carbohydrate | 47.1 (8.1) | 46.3 (7.3) | 46.8 (6.6) | 48.0 (7.8) | 0.23 |
| Fiber (g)/1000 KJ | 0.47 (0.26) | 0.55 (0.24) | 0.60 (0.26) | 0.66 (0.34) | <.001 |
| Alcohol Intake (ml/day)† | 0.0 (7.6) | 2.4 (9.5) | 2.4 (9.7) | 4.8 (12.1) | 0.07 |
| Physical activity score† | 258.0 (280.0) | 320.0 (317.0) | 334.0 (382.0) | 402.0 (362.0) | <.001 |

| Characteristics | Women with GDM Births Lactation Categories | | | | |
|---|---|---|---|---|---|
| | 0 to 1 month (n=22) | >1 to 5 months (n=17) | 6 to 9 months (n=17) | >9 months (n=28) | p-value‡ |
| Race (Black) | 16 ( 72.7) | 7 ( 41.2) | 4 ( 23.5) | 6 ( 21.4) | 0.001 |
| Education (<=HS) | 8 ( 36.4) | 6 ( 35.3) | 2 ( 11.8) | 2 ( 7.1) | 0.03 |
| Smoker (current) | 10 ( 45.5) | 9 ( 52.9) | 6 ( 35.3) | 3 ( 10.7) | 0.03 |
| Family history of diabetes | 11 ( 50.0) | 3 ( 17.6) | 6 ( 35.3) | 13 ( 46.4) | 0.16 |
| | | | mean (SD) | | |
| Age (y) | 22.8 (4.0) | 22.4 (3.7) | 24.2 (3.9) | 24.9 (3.6) | 0.10 |
| BMI (kg/m$^2$) | 27.0 (8.3) | 23.5 (4.5) | 23.9 (4.7) | 22.6 (4.1) | 0.05 |
| Waist girth (cm) | 79.5 (18.7) | 70.8 (7.8) | 72.1 (9.1) | 70.5 (8.2) | 0.05 |

| | | | | | |
|---|---|---|---|---|---|
| Systolic blood pressure (mm Hg) | 108.4 (8.0) | 102.6 (7.7) | 103.3 (8.6) | 107.6 (10.4) | 0.10 |
| Diastolic blood pressure (mm Hg) | 70.3 (7.3) | 60.4 (10.7) | 65.2 (7.0) | 68.7 (8.8) | <.01 |
| Fasting plasma: | | | | | |
| Glucose (mg/dl) | 80.0 (8.7) | 78.8 (10.8) | 81.8 (9.1) | 82.9 (9.2) | 0.48 |
| HDL-C (mg/dl) | 52.7 (13.1) | 53.3 (12.7) | 56.9 (15.4) | 56.9 (11.7) | 0.59 |
| Triglycerides (mg/dl) | 74.5 (25.9) | 70.6 (35.7) | 64.1 (30.0) | 70.0 (34.3) | 0.79 |
| Dietary intake (%KJ as) | | | | | |
| Total Fat | 37.3 (5.6) | 37.0 (3.3) | 40.4 (7.8) | 37.7 (5.6) | 0.29 |
| Saturated Fat | 14.4 (2.8) | 14.0 (1.9) | 15.3 (4.5) | 13.8 (3.0) | 0.44 |
| Carbohydrate | 47.4 (6.7) | 46.3 (5.4) | 43.8 (8.8) | 46.2 (6.9) | 0.46 |
| Fiber (g)/1000 KJ | 0.41 (0.16) | 0.48 (0.20) | 0.50 (0.22) | 0.62 (0.23) | <.01 |
| Alcohol Intake (ml/day)† | 1.2 ( 7.6) | 7.3 (18.4) | 7.9 (15.2) | 2.4 ( 8.6) | 0.29 |
| Physical activity score† | 233.0 (297.0) | 292.0 (153.0) | 429.0 (334.0) | 280.5 (309.0) | 0.22 |

† median (inter-quartile range), Kruskal Wallis test. ‡ two-sided p-value.
Chi-square test was used for categorical baseline characteristics;
One way ANOVA was used for continuous baseline characteristics.

Table 3. Cumulative Incidence of the Metabolic Syndrome during Follow-up Intervals by GDM status and among Duration of Lactation Categories (1986-2006).

| | Number of incident cases of Metabolic Syndrome / number of individuals at risk within the specific interval | | | |
|---|---|---|---|---|
| **Intervals:** | Year 0 to 7 | Year >7 to 10 | Year >10 to 15 | Year>15 to 20 |
| Duration of Lactation Categories By GDM status | n/N (%) | n/N (%) | n/N (%) | n/N (%) |
| **Non-GDM Births (all)** | 8/382 (2.1) | 13/463 (2.8) | 30/515 (5.8) | 46/463 (9.9) |
| Lactation Duration: | | | | |
| 0 to 1 month | 5/143 ( 3.5) | 6/147 ( 4.1) | 14/124 (11.3) | 15/93 (16.1) |
| >1 to 5 months | 2/101 ( 2.0) | 3/126 ( 2.4) | 6/131 ( 4.6) | 11/120 ( 9.2) |
| 6 to 9 months | 1/89 ( 1.1) | 3/114 ( 2.6) | 5/132 ( 3.8) | 9/121 ( 7.4) |
| >9 months | 0/49 ( 0.0) | 1/76 ( 1.3) | 5/128 ( 3.9) | 11/129 ( 8.5) |
| **GDM Births (all)** | 6/43 (14.0) | 5/53 (9.4) | 3/61 (4.9) | 9/55 (16.4) |
| Lactation Duration: | | | | |
| 0 to 1 month | 4/16 (25.0) | 2/12 (16.7) | 1/10 (10.0) | 5/9 (55.6) |
| >1 to 5 months | 1/8 (12.5) | 1/15 ( 6.7) | 0/13 ( 0.0) | 2/13 (15.4) |
| 6 to 9 months | 1/9 (11.1) | 0/9 ( 0.0) | 1/14 ( 7.1) | 2/11 (18.2) |
| >9 months | 0/10 ( 0.0) | 2/17 (11.8) | 1/24 ( 4.2) | 0/22 ( 0.0) |

GDM = gestational diabetes mellitus

Table 4: Unadjusted and Multivariable Adjusted Relative Hazards (95% Confidence Interval) of Incident Metabolic Syndrome (MetS) and Duration of Lactation Categories by GDM Status (1986-2006).

| GDM status and Lactation duration: | 1 or more Non-GDM Births<br>Referent: 0 to 1 month lactation (n=157) | | | | 1 or more GDM Births<br>Referent: 0 to 1 month lactation (n=22) | | | |
|---|---|---|---|---|---|---|---|---|
| Models**Error! Bookmark not defined.** | >1-5 months (n=157) | 6-9 months (n=152) | >9 months (n=154) | p-value* | >1-5 months (n=17) | 6-9 months (n=17) | >9 months (n=28) | p-value* |
| Unadjusted | 0.49 (0.29-0.82) | 0.40 (0.23-0.71) | 0.41 (0.23-0.72) | <0.001 | 0.24 (0.08-0.75) | 0.28 (0.09-0.86) | 0.11 (0.03-0.39) | 0.001 |
| Model 1 = study center, race, baseline covariates (age, education and smoking) and time-dependent parity† | 0.54 (0.32-0.91) | 0.49 (0.28-0.88) | 0.54 (0.28-1.02) | 0.03 | 0.33 (0.10-1.03) | 0.34 (0.11-1.07) | 0.14 (0.04-0.53) | 0.01 |
| Model 1 + baseline covariates: (BMI and all MetS components) | 0.63 (0.37-1.08) | 0.52 (0.29-0.93) | 0.45 (0.24-0.87) | 0.04 | 0.54 (0.16-1.75) | 0.37 (0.11-1.24) | 0.14 (0.04-0.55) | 0.03 |
| Fully Adjusted Model = Model 1 + baseline covariates:(BMI, all MetS components) and baseline physical activity | 0.61 (0.36-1.05) | 0.52 (0.29-0.93) | 0.44 (0.23-0.84) | 0.03 | 0.56 (0.17-1.82) | 0.35 (0.11-1.16) | 0.14 (0.04-0.55) | 0.03 |
| Fully Adjusted Model + time-dependent physical activity (mediator) | 0.67 (0.39-1.16) | 0.54 (0.30-0.98) | 0.51 (0.26-0.98) | 0.10 | 0.41 (0.12-1.35) | 0.27 (0.08-0.90) | 0.13 (0.03-0.52) | 0.02 |
| Fully Adjusted Model + time-dependent weight gain (mediator) | 0.71 (0.41-1.24) | 0.35 (0.19-0.65) | 0.56 (0.29-1.09) | 0.01 | 0.49 (0.15-1.64) | 0.33 (0.09-1.14) | 0.09 (0.02-0.37) | 0.01 |

* test of the overall association among lactation categories and incident metabolic syndrome within non-GDM and GDM birth groups.
† Time-dependent parity (continuous covariate) is the cumulative total number of births since baseline for each time interval through the end of follow-up.

**Figure Legends:**

Figure 1: Flow diagram for Analytic Sample Selection: 704 women who were nulliparous, free of the Metabolic Syndrome (MetS) and aged 18-30 years at baseline (1985-1986) who delivered at least one singleton live birth during the 20-year follow-up period.

Figure 2: Crude Incidence Rates (95% Confidence Intervals) of the Metabolic Syndrome during 20 Years of Follow-up for Lactation Categories by GDM Status

Figure 3: Crude Incidence Rates (95% Confidence Intervals) of the Metabolic Syndrome during 20 Years of Follow-up for Lactation Categories by GDM Status (1986-2006) and Race (black and white).

Figure 1. Flow diagram for analytic sample selection: 704 women who were nulliparous, free of the Metabolic Syndrome (MetS) and aged 18-30 years at baseline (1985-1986) who delivered at least one singleton live birth during the 20- year follow-up period.

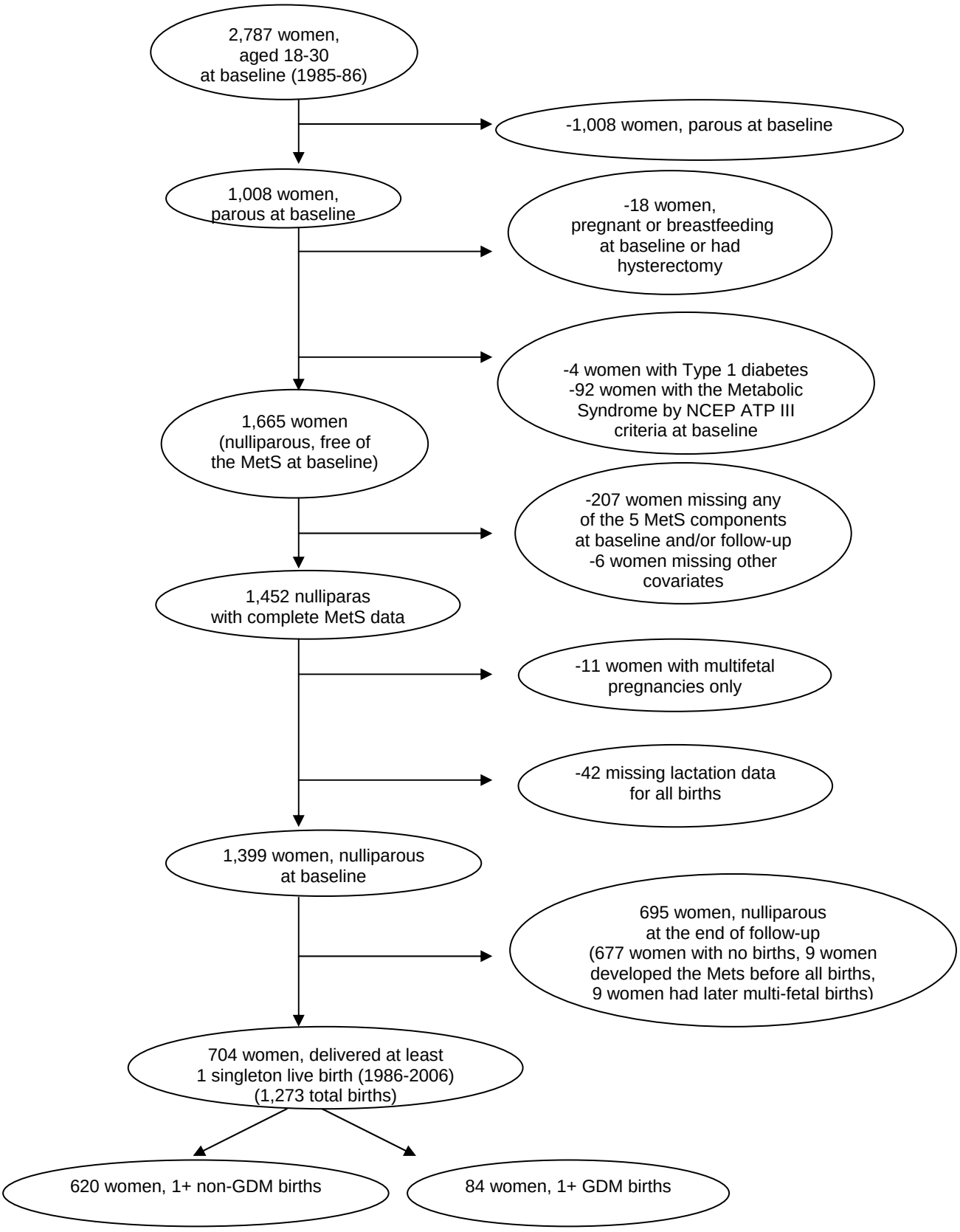
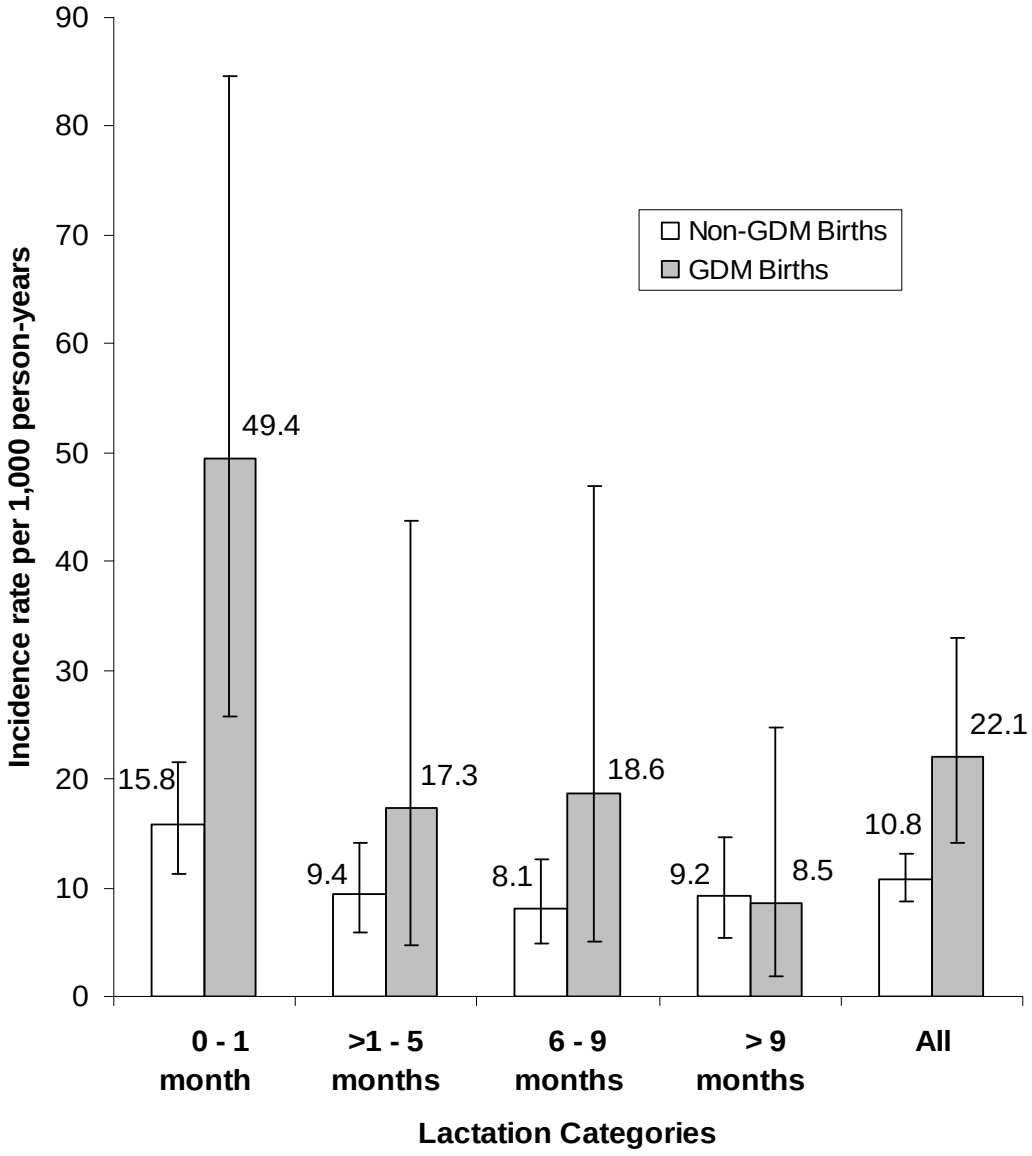
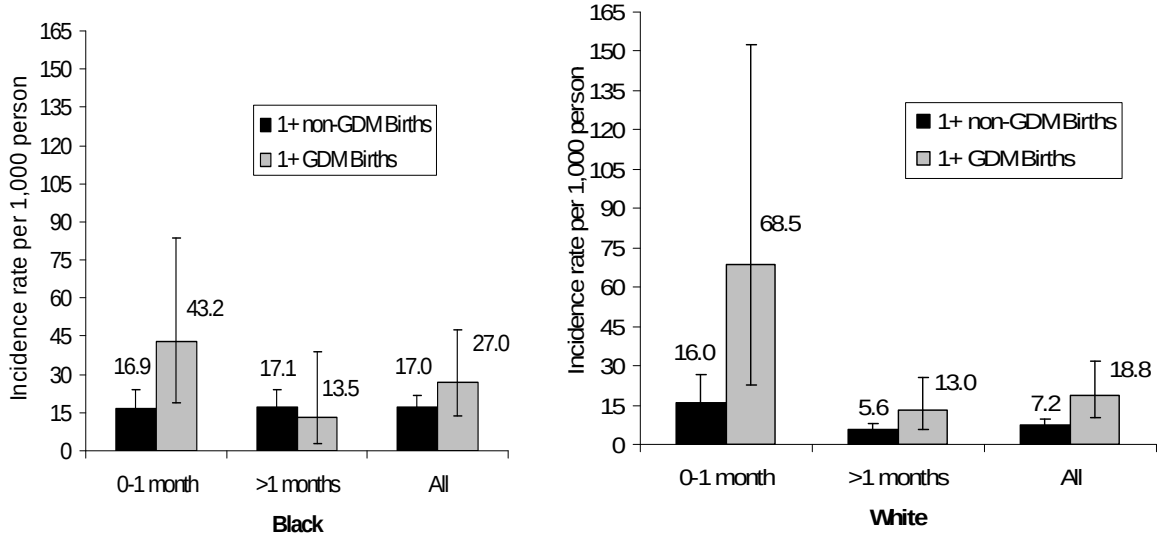


Figure 2: Crude Incidence Rates (95% Confidence Intervals) of the Metabolic Syndrome during 20 Years of Follow-up for Lactation Categories by GDM Status (1986-2006).




| Metabolic Syndrome Cases: | | | | | |
|---|---|---|---|---|---|
| Non-GDM, n | 40 | 22 | 18 | 17 | 97 |
| Person-years: | 2,527 | 2,340 | 2,230 | 1,856 | 8,953 |
| | | | | | |
| GDM, n | 12 | 4 | 4 | 3 | 23 |
| Person-years: | 243 | 231 | 215 | 351 | 1,040 |

Figure 3: Crude Incidence Rates (95% Confidence Intervals) of the Metabolic Syndrome during 20 Years of Follow-up for Lactation Categories by GDM Status (1986-2006) and Race (black and white).




| Race | Non-GDM Duration of Lactation | | GDM Duration of Lactation | |
|---|---|---|---|---|
| | 0-1 month | >1 months | 0-1 month | >1 months |
| **Black** | | | | |
| Cases, n | 26 | 30 | 8 | 3 |
| Person-yrs | 1667 | 1,699 | 185 | 223 |
| **White** | | | | |
| Cases, n | 14 | 27 | 4 | 8 |
| Person-yrs | 860 | 4,727 | 58 | 574 |
| **All** | | | | |
| Cases, n | 40 | 57 | 12 | 11 |
| Person-yrs | 2,527 | 6.426 | 243 | 797 |