

**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**

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## **ABSTRACT**

**Objective:** To determine whether childbearing increases the incidence of type 2 diabetes mellitus after accounting for preconception glycemia and gestational glucose intolerance.

**Research Design and Methods:** Prospective, biracial cohort examined up to five times from 1985-2006 in the multi-center, U.S. population-based Coronary Artery Risk Development in Young Adults Study. The analysis included 2,408 women (1,226 black, 1,182 white) who were aged 18-30 years, free of diabetes and had a fasting plasma glucose <126 mg/dl at baseline. Incident diabetes was by self-report, diabetes medication use, fasting plasma glucose  $\geq$ 126 mg/dl, and/or post 2-hr oral glucose load  $\geq$ 200 mg/dl. Time-dependent interim birth groups were 0 births, and 1+births with or without gestational diabetes mellitus (GDM) stratified by baseline parity. Complementary log-log models estimated relative hazards of incident diabetes by interim births adjusted for age, race, family history of diabetes, and baseline covariates (fasting plasma glucose, BMI, education, smoking and physical activity).

**Results:** Of 193 incident diabetes cases in 42,782 person-yrs (4.5 cases/1,000 person-yrs), 84 (44%) had 1+interim births. Among nulliparas at baseline, incident rates (95%CI) per 1,000 person-yrs were 3.2 (2.4-4.1) for 0 births, 2.9 (1.8-3.9) for 1+births without GDM, and 18.4 (10.9-25.9) for 1+births with GDM; adjusted relative hazards (95%CI) were 0.9 (0.6-1.4) for 1+births without GDM and 3.8 (2.2-6.6) for 1+births with GDM versus 0 births.

**Conclusions:** Childbearing did not elevate diabetes incidence among those with normal glucose tolerance during pregnancy (without GDM). Gestational diabetes conferred the highest risk of developing diabetes independent of family history of diabetes and preconception glycemia and obesity.

Journal Subject Heads: Incidence, Diabetes Mellitus, Epidemiology, Parity, Pregnancy, Women's Health, Gestational diabetes, Prospective cohort studies, Obesity, Longitudinal

Evidence that childbearing is associated with future development of type 2 diabetes in women remains conflicting.(1-12) Both nulliparity and multiparity have been associated with higher fasting glucose and insulin levels independent of body size among nondiabetic women. (6-8,13,14) In early cross-sectional and retrospective studies, grand multiparity ( $\geq 5$  births) was associated with higher rates of diabetes in women over 45, unadjusted for age, body size and socioeconomic status (SES).(1,2) In later population-based, cross-sectional studies controlling for age, obesity, and SES, the association between lifetime parity and prevalent diabetes was direct in three(9-11), and null in three.(3,4,6) Two studies of indigenous groups with high rates of type 2 diabetes reported inverse associations.(8,12) In a prospective study of 113,000 white women aged 30-55 years, the direct association between lifetime parity and incidence of self-reported diabetes was abolished after adjustment for age and obesity, with minimal confounding by family history of diabetes.(5)

Two limitations of all studies are that preconception glycemia was not measured and prevalence of glucose intolerance during pregnancy was unknown. Women who develop gestational diabetes mellitus (GDM), have an elevated risk of developing type 2 diabetes,(15-18) with subsequent weight gain and pregnancies apparently contributing to future risk(18). Residual confounding by GDM status and preconception hyperglycemia would tend to overestimate the association. Conversely, obesity, insulin resistance, and/or the polycystic ovarian syndrome may cause infertility (i.e., nulliparity) that would tend to underestimate of the association.

Conflicting evidence for an association between childbearing and development of diabetes may result from several factors. First, temporality of diabetes onset relative to pregnancy cannot be ascertained from previous studies whether cross-sectional or prospective in design because preconception glycemia had not been measured to rule out

overt diabetes before pregnancy. Secondly, overweight status, which is in the causal pathway to type 2 diabetes and is twice as likely after a first birth compared with no births(19), was ascertained subsequent to the childbearing years in the majority of subjects. Lastly, GDM status was not available in previous studies, except one that excluded women with GDM (5), because universal screening was not performed until the mid 1980s.

We prospectively investigated the natural course of childbearing in a biracial (black and white), population-based cohort of 2,408 U.S. women, aged 18-30 years, who were free of diabetes and normoglycemic at baseline in 1985-86, and had measurements of fasting glycemia and/or glucose tolerance during 20 years of follow-up. We estimated population-based incidence rates of type 2 diabetes across interim birth groups by GDM status and parity at baseline. The study sought to determine whether having one or more births versus none was associated with higher incidence of type 2 diabetes independent of family history of diabetes, race, preconception (baseline) fasting glycemia and obesity, age, socio-demographic and behavioral attributes, as well as GDM status. Finally, we assessed whether changes in physical activity and weight attenuated the associations.

#### **METHODS:**

The Coronary Artery Risk Development in Young Adults (CARDIA) Study is a multi-center, observational, population-based, longitudinal cohort study designed to describe the development of risk for coronary heart disease in young black and white men and women.(20,21) Participants were recruited from four geographic areas: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. In 1985-1986, 5,115 subjects (2,787 women; 53% black) aged 18-30 years were enrolled. Retention rates were 86, 81, 79, 74 and 72 percent of the surviving cohort at 5, 7, 10, 15 and 20 years after baseline.(22,23)

*Sample Selection Criteria:*

Of 2,787 women, we excluded those at baseline with type 1 or type 2 diabetes mellitus (DM) and/or a fasting plasma glucose  $\geq 126$  mg/dl (n=41), with a hysterectomy or removal of both ovaries (n=24), who were currently pregnant (n=7), or missing fasting plasma glucose, socio-demographic or behavioral covariates (n=127). We also excluded women who had not attended at least one follow-up exam (n=180) in years 5, 7, 10, 15 or 20. Women excluded were more likely to be smokers, unmarried, less educated, have a higher body mass index, and of black race than the analytic sample of 2,408 women (1,226 black, 1,182 white); 86 percent of the original cohort. Fasting plasma glucose measurements were obtained at baseline and follow-up years 7, 10, 15 and 20. For the five exams, fasting plasma glucose measurements were available for 1,083 (45%) for all five exams, 613 (25%) for four exams, 367 (15%) for three exams, and 227 (9%) for two exams. Institutional Review Boards at each participating study center approved the study. Written, informed consent was obtained from subjects for all study procedures.

*Data Collection Methods:*

Participants were asked to fast for at least 8-hours prior to each examination and fasting blood samples were drawn in the morning(24). Procedures followed in collection and storage of plasma samples as well as laboratory quality control procedures have been reported in detail elsewhere(24). Fasting plasma glucose was determined at Linco Research Inc. using the hexokinase-ultraviolet method(25).

**Definition of Cases of Incident DM**

Incident cases of DM after baseline were identified by elevated fasting plasma glucose levels in years 7, 10, 15 or 20, and current use of diabetes medications (insulin or oral hypoglycemics) or self-report of diabetes outside of pregnancy in years 5, 7, 10, 15 or 20. We administered the 2-hour 75 gram oral glucose tolerance tests (OGTT) to 1,229 and 1,398 women in years 10 and 20,

respectively. We defined incident DM cases by 1997 ADA criteria(26) for fasting plasma glucose (FPG) $\geq 126$  mg/dl, and/or 2-hour plasma glucose $\geq 200$  mg/dl after a 75-g oral glucose load (2-hr PG). Fasting plasma glucose levels became elevated ( $\geq 126$  mg/dl) for 101 women during the 20-year follow-up period. Fifteen women had abnormal two-hr PG tests in year 10 and 31 women in year 20. For DM cases identified by self-report only also reporting a pregnancy with diabetes since the previous exam, we conservatively classified their pregnancies as without GDM (n=9) because we could not determine whether diagnosis of diabetes had occurred before or after these pregnancies.

All incident DM cases were identified among non-pregnant women and are primarily type 2 DM based on the epidemiology of diabetes. Of 269 women currently pregnant or lactating at one or more follow-up exams, only one who was lactating at year 7, was classified as an incident DM case (fasting glucose value of 297 mg/dl). Otherwise, 223 (83%) attended at least one subsequent exam in the non-pregnant or non-lactating state with all fasting plasma glucose values below 126 mg/dl (range 57-112 mg/dl). Women with and without subsequent exams in the non-pregnant or non-lactating state had similar percentages with GDM (10.8% vs. 10.9%).

**Baseline Parity and Time-Dependent Interim Birth Groups by GDM Status:**

Participants were asked at each exam whether they were currently pregnant or breastfeeding, number pregnancies including abortions, miscarriages and live or stillbirths, duration of each gestation, and dates of deliveries. We classified pregnancies ending in miscarriages, abortions and/or those less than 20 weeks gestation as pregnancy losses, and those 20 weeks or longer as interim births. Number of interim births was defined as the cumulative number of births since baseline within each specific time interval ending in years 5, 7, 10, 15 and 20. At each exam, women were asked whether they ever had diabetes and if the diabetes was only during their pregnancies. In year

10, women reported whether they had diabetes during each previous pregnancy (before and after baseline).

Parity groups at baseline were defined as nulliparous (no live births >20 weeks) and parous (1 or more live births >20 weeks) prior to baseline. We classified women into time-dependent interim birth groups, no births (0 births) and one or more interim births (1+births), and by ever having a birth with GDM. Women transitioned from the baseline parity groups (nulliparous or parous) through each specific time interval into interim birth groups. A change from 0 births to 1+interim births was maintained through the end of follow-up. GDM status was maintained for future time intervals whether or not there was a subsequent birth with or without GDM.

Interim birth groups irrespective of baseline parity include: 0 interim births without GDM, 0 interim births with GDM (before baseline), 1+interim births without GDM, and 1+interim births with GDM. We further subdivided these groups by baseline parity (Figure 1). Nulliparas transitioned within three groups: 0 interim births (referent), 1+interim births without GDM, and 1+interim births with GDM. Women parous at baseline transitioned within two groups: 0 or 1+interim births without GDM, and 0 or 1+interim births with GDM. We combined 0 and 1+interim births for women parous at baseline because DM incidence rates were similar.

We 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 as ever having GDM was 100 percent (20 of 20), and specificity was 92 percent (134 of 145).

#### **Definition of Family History of Diabetes:**

Positive family history of diabetes is defined as report of one or more first degree relatives (i.e., father, mother or siblings) with diabetes for first degree family members at one or more exams in years 0, 5 and 10. The variable is fixed and covered any family history of diabetes during follow-up.

#### **Other Covariates:**

Certified technicians obtained weight, height and waist circumference (waist girth) measurements according to a standardized protocol(27). 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. Waist circumference was measured to the nearest 0.5 cm at the minimal abdominal girth(28). Body mass index (BMI) was computed as weight in kilograms divided by squared height in meters(29).

Socio-demographic and behavioral data [medication use, alcohol intake (ml/day), cigarette smoking, education, employment status, marital status, oral contraceptive (OC) use and physical activity] were collected at each exam using self- and interviewer-administered questionnaires. We categorized variables as: smoking; never, former, or current, years of education 12 or less, 13-15, and 16 or more, marital status; never married, widowed, divorced or separated, or married, employment; full-time, part-time or not employed outside the home, OC use; never, past, or current, and alcohol intake (mL/d); none, 1-15, 15-30, and >30. Assessments of daily physical activity were obtained using the interviewer-administered CARDIA Physical Activity History assessment at each exam(30). Physical activity scores were divided into quartiles because of skewedness of the data (data not shown). Dietary intake during the previous month was assessed using the CARDIA Dietary History administered by a trained interviewer at baseline(31). We examined daily dietary intakes of energy (kJ/d), total fat, protein, and carbohydrate as percentages of kilocalories, and total fiber as g/d/100 kcal.

#### **Statistical Methods:**

Preliminary analyses involved description of race, baseline and follow-up characteristics by DM case status. Baseline characteristics included age, parity, fasting plasma glucose, BMI, height, waist girth, dietary intake (fiber g/d/100 kcal, %kcal CHO,

%kcal Fat), alcohol intake, cigarette smoking, education, marital status, employment status, physical activity, and OC use. Follow-up characteristics included family history of diabetes and GDM status. Chi-square tests were used to assess associations of DM cases status across categories of race, socio-demographics, behaviors, family history of diabetes, and GDM status. Multiple linear regression methods (analysis of variance) were used to assess baseline differences in continuous variables among interim birth groups by DM case status. P-values were obtained from two-sided tests (significance < 0.05). Wilcoxon-rank sum test was used to assess differences in alcohol intake categories and physical activity quartiles.

We calculated the cumulative incidence of diabetes within each time interval (0-5, >5-7, >7-10, >10-15, >15-20 years) by dividing new cases of DM during each interval by the number of women at risk of diabetes at the end of the interval (Table 2). We estimated the incidence rates (IR) and 95% confidence intervals (95%CI) by dividing new cases of diabetes by the person-time for individuals observed. Incidence rates for interim birth groups were stratified by baseline parity groups and family history of diabetes (Table 3).

Because DM status was only determined at the CARDIA exams, the exact time of diabetes onset for a woman free of DM and diagnosed at a subsequent exam is unknown. We accounted for interval-censored data using the method of Prentice and Gloeckler(32) to provide point and interval estimates of the relative hazard of DM 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. Relative hazard ratios for incidence of DM were estimated for time dependent interim birth groups with nulliparas as the referent group.

We estimated RHs for interim birth groups from multivariate models. We examined potential confounders, race, age, study center, baseline covariates (BMI,

fasting plasma glucose, waist girth, behavioral, socio-demographic), and family history of diabetes. We also examined pregnancy losses, smoking, and OC use as time-dependent potential confounders. Covariates were introduced into the regression models in specified order by type of potential confounder; biological, socio-demographic and behavioral, based on a priori hypotheses. We examined race, BMI, family history of diabetes and smoking as effect modifiers in the association between interim births and incidence of DM through introduction of corresponding cross-product terms. Potential mediators of this association, changes in weight, waist girth, and physical activity from baseline to the end-of-follow-up, were also examined.

From these analyses, multivariate adjusted models were formed by forward stepwise addition of covariates. We added family history of diabetes, baseline fasting plasma glucose, and then, race, age, and baseline BMI. Fully adjusted model included these covariates plus baseline education, smoking and physical activity. In subsequent models, we separately added time-dependent changes in physical activity, weight gain, and waist girth.

## **RESULTS**

Among 2,408 women in our sample followed for 42,782 person-years, we identified 193 incident cases of DM yielding an incidence rate of 4.5 per 1,000 person-years. Among incident cases, 39 were ascertained by self-report only, 43 by diabetes medication use with or without DM self-report, and 111 by FPG  $\geq$  126 mg/dl and/or 2-hr PG  $\geq$  200 mg/dl. Incident DM cases (Table 1) were characterized by black race, family history of diabetes, and GDM. At baseline, DM cases were less educated, and had higher parity, BMI, fasting plasma glucose, and waist girth. Moreover, they also consumed more energy from carbohydrate and less alcohol, and were less physically active.

In our sample, 1,218 women (50% black, 50% white) had one or more interim births, and 149 (12%) had at least one birth

with GDM. Of the 193 DM cases, 84 (44%) had one or more interim births. Time from last birth until the end of follow-up averaged 119 (3.9-240) months for DM cases versus 123 (2.5-236) months for non-cases. Among nulliparas at baseline, crude incident rates (IR) per 1,000 person-yrs (95%CI) were 3.2 (2.4-4.1) for 0 births, 2.9 (1.8-3.9) for 1+births without GDM, and 18.4 (10.9-25.9) for 1+births with GDM. Among parous at baseline, IRs (95%CI) were 4.9 (3.8-6.1) for 0 or 1+births without GDM, and 17.9 (10.0-25.8) for 0 or 1+births with GDM.

Incidence of DM increased across all interim birth groups during 20 years (Table 2). The largest number of cases occurred between years 15 and 20 compared with earlier intervals. Cumulative incidence of DM among individuals at risk in these intervals ranged from 0.2-6.2 percent for 0 births without GDM, 4.2-38.5 for 0 births with GDM (before baseline), 0-3.4 percent for 1+births without GDM, and 0-16.8 percent for 1+births with GDM.

We examined the crude IR of DM for interim birth groups by family history of diabetes and parity at baseline (Table 3). Rates are similar for women nulliparous and parous at baseline by family history of diabetes and GDM status. The rates were lowest for nulliparas with 1+interim births without GDM and no family history of diabetes, intermediate for 1+interim births without GDM and a family history of diabetes, and highest for 1+interim births with GDM and a family history of diabetes. Crude IRs were 20 per 1,000 person-years among women with only one GDM birth and 18 per 1,000 person-years among women with one or more births prior to or subsequent to a GDM birth.

Relative hazards (RH) for DM was highest among women who ever had a GDM pregnancy whether before baseline or in an interim birth (Table 4). Adjustment for family history of diabetes attenuated RHs of DM among interim birth groups. Inclusion of baseline fasting plasma glucose minimally attenuated the RHs. Control for confounding by race, age, and baseline BMI moderately strengthened RHs of DM to 3.5 among

nulliparas at baseline who had 1+interim births with GDM. In the fully adjusted model, compared with 0 interim births, DM risk was nearly fourfold higher among nulliparas at baseline who had 1+interim births with GDM. One or more interim births without GDM was not associated with risk of DM. Among women parous at baseline, fully adjusted RHs for DM was similar to nulliparas at baseline, although weaker; DM risk was about threefold higher for those ever having a birth with GDM (0 or 1+interim births with GDM), and not associated with 0 or 1+interim births without GDM. Exclusion of 39 incident DM cases identified by self-report only strengthened associations in nulliparas at baseline; RH for DM was 5.1, 95%CI:2.9-9.1 for 1+births with GDM and 1.0, 95%CI:0.6-1.6 for 1+births without GDM compared with 0 births.

There was no evidence of effect modification by race, BMI, smoking and family history of diabetes in the association of interim births and incidence of diabetes (all interaction p-values>.30). Family history of diabetes conferred a more than twofold higher risk of diabetes (RH=2.4, 95%CI:1.8-3.2) independent of number of interim births and other covariates.

Compared with women with no births, having one or more births resulted in greater weight gain ( $p<.05$ ) and increased waist girth ( $p<.001$ ). Mean (SD) was: 12.9 (14.1), 14.3 (13.5) and 15.9 (13.1) for weight gain (kg), and 11.9 (11.4), 14.0 (10.8) and 16.4 (9.8) for waist girth (cm) among 0 interim births, 1+interim births without GDM and 1+interim births with GDM, respectively. Despite the greater weight gain and waist girth increase in women who gave birth, controlling for changes in body weight had minimal impact, while adding increased waist girth modestly attenuated the associations among nulliparas at baseline. Change in physical activity added separately to these models had little influence on RH for DM.

## **DISCUSSION**

Key strengths of this prospective study are: verification that women were free of diabetes at baseline based on actual measurements of fasting plasma glucose,

and collection of multiple fasting plasma glucose measurements at 3 to 7-year intervals and 2-hour oral glucose tolerance test results 10 and 20 years later to identify incident cases of diabetes. Moreover, these same measurements were available for a referent group of nulliparous women during the same interval. Finally, we validated GDM status and examined risks for this group separately. Our study overcomes weaknesses of previous studies that may have led to inconsistent findings(1-12), by controlling for preconception glycemia and obesity, preserving the temporality of pregnancy and diabetes, and estimating the risks separately for women with and without gestational diabetes.

Our findings show that childbearing does not increase the incidence of diabetes as long as women never developed GDM; their risk was similar to nulliparous women. In fact, the trend was for a non-significant lower risk of diabetes among ever parous women compared with women remaining nulliparous, which moved closer to one after adjustment for BMI, age and race. A small subset of nulliparas may have infertility secondary to insulin resistance and obesity which could explain why the risk was slightly higher in this group. In a prior prospective study, the Nurse's Health Study, BMI was measured primarily subsequent to childbearing years(5), which may have underestimated the association by ignoring the excess risk of overweight due to childbearing.

Secondly, having one or more GDM pregnancies conferred a fourfold higher risk of developing diabetes independent of preconception fasting glycemia, family history of diabetes and other risk factors. The incidence rate of diabetes was 300% higher for women with previous GDM compared with nulliparas, or women who had one or more births without GDM. The validity of our estimates is strongest for primiparas during our study years, because fasting plasma glucose levels helped to rule out diabetes before pregnancies, and preserved the temporality of the exposure (pregnancy) before specific risk factor changes and

disease onset. Our study also found that development of diabetes was associated with increased central obesity especially among women who reported GDM for an interim birth. Decreased physical activity and higher weight gain had a minimal impact on risk.

Healthy pregnancy is a temporary, diabetogenic state where hyperinsulinemia shifts fuel metabolism toward accentuated excursions in pre- and post-prandial glycemia. Gestational hormones promote insulin resistance and pancreatic beta-cell proliferation to achieve the 1.5 times higher insulin secretion needed to maintain maternal euglycemia(33,34). Failure of beta-cells to meet the greater demands for insulin production results in gestational glucose intolerance. Usually, the metabolic profile returns to the normal preconception state shortly after delivery. In earlier studies of women unscreened for GDM, multiparas (5 or more births) had higher plasma glucose and insulin levels as well as prevalence of diabetes. This evidence raised the possibility that repeated pregnancies had lasting adverse effects on glucose tolerance apart from obesity (6-8,13,14) and beta-cell function deteriorated to a threshold level with intermittent demands for greater insulin production(11). In our cohort, among 40 women (3%) with four or more births within the 20-year period, one developed diabetes.

Women with a history of GDM comprise a high-risk group for future development of primarily type 2 DM. Based on current diagnostic criteria(26), it is estimated that 5-10% of women will be diagnosed with type 2 DM within six months of GDM delivery and another 10-15% will develop type 2 DM within the subsequent 1-2 years(35-41). Among women with previous GDM, having a subsequent birth was associated with a threefold greater risk of developing type 2 DM independent of weight gain in one study(18), but not another (42). Our sample of women with GDM and subsequent births was too small to adequately assess the association with number of births.

Limitations of our study include diabetes cases identified by a single elevated fasting and/or 2-hour post-glucose load test result,

39 diabetes cases ascertained by self-report only, GDM pregnancies by self-report, and the variable time period from exams to conception. Although our study lacked prospective data on infertility, we controlled for family history of diabetes and baseline fasting glycemia to reduce confounding from nulliparity due to infertility. Infertility cases due to associated diagnoses (e.g., obesity, insulin resistance) are likely to be few and would bias our results toward the null.

Strengths of our study that enhance the validity of our findings are the high cohort retention rate over 20 years of follow-up (72%), availability of fasting plasma glucose at baseline for 100 percent and at least three measurements after baseline (3 to 7-year intervals) for 86 percent of the analytic sample. Thus, women in our cohort were likely to be free of diabetes before conception. Other strengths are measurements of preconception obesity, and a variety of socio-demographic and behavioral attributes to examine potential confounding.

We conclude that pregnancy does not have an adverse impact on women's future risk of diabetes, despite greater gains in overall and central adiposity(43). The fourfold higher risk of diabetes for an interim

birth with GDM did not vary by family history of diabetes. Our findings provide evidence that pregnancy in which GDM develops may unmask a predisposition to develop type 2 DM after delivery rather than cause type 2 DM. However, we cannot completely rule out the possibility that pregnancy hastens development of type 2 DM. Underlying defects in glucose homeostasis are likely to contribute to gestational diabetes mellitus, the strongest predictor of future diabetes among women of childbearing age. Identification of risk profiles for women who are most susceptible to the physiological stress of pregnancy may guide development of screening protocols to target preconception, prenatal and postpartum interventions in high-risk groups to prevent diabetes.

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References

- (1) Pyke DA. Parity and the incidence of diabetes. *Lancet*. 1956;270:818-820.
- (2) O'Sullivan JB, Gordon T. Childbearing and diabetes mellitus. United States-1960-1962. *Vital Health Stat* 11. 1966;1-19.
- (3) Boyko EJ. The effect of parity on the later development of diabetes. *N Engl J Med*. 1990;322:1320.
- (4) Collins VR, Dowse GK, Zimmet PZ. Evidence against association between parity and NIDDM from five population groups. *Diabetes Care*. 1991;14:975-981.
- (5) Manson JE, Rimm EB, Colditz GA, Stampfer, M.J., Willett, W.C., Arky, R.A.; Rosner, B. Hennekens, C.H.; Speizer, F.E. Parity and incidence of non-insulin-dependent diabetes mellitus. *Am J Med*. 1992;93:13-18.
- (6) Alderman BW, Marshall JA, Boyko EJ, Markham KA, Baxter J, Hamman RF. Reproductive history, glucose tolerance, and NIDDM in Hispanic and non-Hispanic white women. The San Luis Valley Diabetes Study. *Diabetes Care*. 1993;16:1557-1564.
- (7) Cowan LD, Go OT, Howard BV, Devereux, R.B.; Pettitt, D.J.; Fabsitz, R.R.; Lee, E.T.; Welty, T.K. Parity, postmenopausal estrogen use, and cardiovascular disease risk factors in American Indian women: the Strong Heart Study. *J Womens Health*. 1997;6:441-449.
- (8) Charles MA, Pettitt DJ, McCance DR, Hanson RL, Bennett PH, Knowler WC. Gravidity, obesity, and non-insulin-dependent diabetes among Pima Indian women. *Am J Med*. 1994;97:250-255.
- (9) Dawson SI, Smith WC, Watson MS, Wilson, B.J., Prescott, G.J., Campbell, D. Hannaford, P. A cohort study of reproductive risk factors, weight and weight change and the development of diabetes mellitus. *Diabetes Obes Metab*. 2003;5:244-250.
- (10) Martin FI, Hopper JL, Dean B, Campbell DG, Hammond P. Glucose tolerance and mortality in diabetes mellitus in Maltese-born residents of Victoria. *Med J Aust*. 1984;141:93-97.
- (11) Kritz-Silverstein D, Barrett-Connor E, Wingard DL. The effect of parity on the later development of non-insulin-dependent diabetes mellitus or impaired glucose tolerance. *N Engl J Med*. 1989;321:1214-1219.
- (12) Hanley AJ, McKeown-Eyssen G, Harris SB, Hegele, R.A., Wolever, T.M., Kwan, J., Zinman, B. Association of parity with risk of type 2 diabetes and related metabolic disorders. *Diabetes Care*. 2002;25:690-695.
- (13) Humphries KH, Westendorp IC, Bots ML, Spinelli, J.J., Carere, R.G., Hofman, A., Witteman, J.C. Parity and carotid artery atherosclerosis in elderly women: The Rotterdam Study. *Stroke*. 2001;32:2259-2264.
- (14) Kritz-Silverstein D, Barrett-Connor E, Wingard DL, Friedlander NJ. Relation of

- pregnancy history to insulin levels in older, nondiabetic women. *Am J Epidemiol.* 1994;140:375-382.
- (15) Metzger BE, Cho NH, Roston SM, Radvany R. Prepregnancy weight and antepartum insulin secretion predict glucose tolerance five years after gestational diabetes mellitus. *Diabetes Care.* 1993;16:1598-1605.
  - (16) Mestman JH, Anderson GV, Guadalupe V. Follow-up study of 360 subjects with abnormal carbohydrate metabolism during pregnancy. *Obstet Gynecol.* 1972;39:421-425.
  - (17) O'Sullivan JB. Body weight and subsequent diabetes mellitus. *JAMA.* 1982;248:949-952.
  - (18) Peters RK, Kjos SL, Xiang A, Buchanan TA. Long-term diabetogenic effect of single pregnancy in women with previous gestational diabetes mellitus. *Lancet.* 1996;347:227-230.
  - (19) Gunderson EP, Quesenberry CP, Jr., Lewis CE, Tsai AL, Sternfeld B., Smith, West D., Sidney, S. Development of overweight associated with childbearing depends on smoking habit: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Obes Res.* 2004;12:2041-2053.
  - (20) Cutter GR, Burke GL, Dyer AR, Friedman G.D, Hilner, J.E., Hughes G.H, Hulley S.B, Jacobs D.R., Jr., Liu K, Manolio T.A. Cardiovascular risk factors in young adults. The CARDIA baseline monograph. *Control Clin Trials.* 1991;12:1S-77S.
  - (21) Friedman GD, Cutter GR, Donahue RP, Hughes G.H., Hulley S.B, Jacobs D.R., Jr., Liu K, Savage P.J. CARDIA: study design, recruitment, and some characteristics of the examined subjects. *J Clin Epidemiol.* 1988;41:1105-1116.
  - (22) Lewis CE, Jacobs DR, Jr., McCreath H et al. 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.* 2000;151:1172-1181.
  - (23) Steffen LM, Kroenke CH, Yu X, Pereira, M.A., Slattery, M.L., Van Horn, L., Gross, M.D., Jacobs, D.R., 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.* 2005;82:1169-1177.
  - (24) Bild DE, Jacobs DR, Liu K, Williams O.D, Hilner J.E, Perkins L.L, Marcovina S.M.; Hulley S.B. Seven-year trends in plasma low-density-lipoprotein-cholesterol in young adults: the CARDIA Study. *Ann Epidemiol.* 1996;6:235-245.
  - (25) Slein MW, Cori GT, Cori CF. A comparative study of hexokinase from yeast and animal tissues. *J Biol Chem.* 1950;186:763-780.
  - (26) Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20:1183-1197.
  - (27) 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*. 1997;87:635-642.
- (28) 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*. 1994;271:1747-1751.
- (29) Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. The Evidence Report. 1998. Washington, D.C., National Institutes of Health, National Heart, Lung, and Blood Institute.
- (30) Anderssen N, Jacobs DR, Jr., Sidney S, Bild D.E, Sternfeld B, Slattery M.L, 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*. 1996;143:351-362.
- (31) McDonald A, Van Horn L, Slattery M, Hilner J, Bragg C, Caan B, Jacobs,D.,Jr., Liu K, Hubert H, Gernhofer N. The CARDIA dietary history: development, implementation, and evaluation. *J Am Diet Assoc*. 1991;91:1104-1112.
- (32) Prentice R, Gloeckler L. Regression analysis of grouped survival data with application to breast cancer data. *Biometrics*. 1978;34:57-67.
- (33) Desoye G, Schweditsch MO, Pfeiffer KP, Zechner R, Kostner GM. Correlation of hormones with lipid and lipoprotein levels during normal pregnancy and postpartum. *J Clin Endocrinol Metab*. 1987;64:704-712.
- (34) Ledoux F, Genest J, Nowaczynski W, Kuchel O, Lebel M. Plasma progesterone and aldosterone in pregnancy. *Can Med Assoc J*. 1975;112:943-947.
- (35) Pallardo F, Herranz L, Garcia-Ingelmo T, Grande C, Martin-Vaquero P, Janez M, Gonzalez A. Early postpartum metabolic assessment in women with prior gestational diabetes. *Diabetes Care*. 1999;22:1053-1058.
- (36) Pallardo LF, Herranz L, Martin-Vaquero P, Garcia-Ingelmo T, Grande C, Janez M. Impaired fasting glucose and impaired glucose tolerance in women with prior gestational diabetes are associated with a different cardiovascular profile. *Diabetes Care*. 2003;26:2318-2322.
- (37) Conway DL, Langer O. Effects of new criteria for type 2 diabetes on the rate of postpartum glucose intolerance in women with gestational diabetes. *Am J Obstet Gynecol*. 1999;181:610-614.
- (38) Schaefer-Graf UM, Buchanan TA, Xiang AH, Peters RK, Kjos SL. Clinical predictors for a high risk for the development of diabetes mellitus in the early puerperium in women with recent gestational diabetes mellitus. *Am J Obstet Gynecol*. 2002;186:751-756.
- (39) Aberg AE, Jonsson EK, Eskilsson I, Landin-Olsson M, Frid AH. Predictive factors of developing diabetes mellitus in women with gestational diabetes. *Acta Obstet Gynecol Scand*. 2002;81:11-16.

- (40) Buchanan TA, Xiang AH, Kjos SL, Trigo E, Lee WP, Peters RK. Antepartum predictors of the development of type 2 diabetes in Latino women 11-26 months after pregnancies complicated by gestational diabetes. *Diabetes*. 1999;48:2430-2436.
- (41) Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 2002;25:1862-1868.
- (42) Albareda M, Caballero A, Badell G, Piquer,S., Ortiz,A., De Leiva,A., Corcoy,R. Diabetes and abnormal glucose tolerance in women with previous gestational diabetes. *Diabetes Care*. 2003;26:1199-1205.
- (43) Gunderson EP, Murtaugh MA, Lewis CE, Quesenberry CP, West DS, Sidney S. Excess gains in weight and waist circumference associated with childbearing: The Coronary Artery Risk Development in Young Adults Study (CARDIA). *Int J Obes Relat Metab Disord*. 2004;28:525-535.

**Table 1:** Baseline Characteristics, Race, Family History of Diabetes, GDM Status by Incident DM

Variable	DM Incident Case (n=193)	Non-Case (n=2,215)	
	n (%)		p-value
Race: Black	142 (74)	1,084 (49)	<.001
<b>At Baseline:</b>			
Parity (Nulliparous)	105 (54)	1448 (65)	0.002
Education (high school or less)	89 (46)	795 (36)	<.001
OC use (current)	41 (21)	573 (26)	0.009
Marital Status (married)	57 (30)	527 (24)	0.19
Smoker (current)	65 (34)	619 (28)	0.23
	mean (SD)		p-value
Age (y)	25.3 ( 3.7)	24.9 ( 3.7)	0.10
BMI (kg/m)	29.7 ( 7.4)	24 ( 5.2)	<.001
Waist Girth (cm)	85.2 (16.4)	73 (10.3)	<.001
Fasting plasma glucose (mg/dl)	83.7 ( 9.7)	79.6 ( 7.6)	<.001
% Kcal as CHO	48.5 ( 7.9)	46.9 ( 7.4)	0.007
% Kcal as Fat	37 ( 6.3)	37.4 ( 6.2)	0.42
Alcohol Intake (ml/day) †	0.0 ( 7.3)	2.4 ( 9.6)	0.01
Physical activity score †	223.0 ( 280.0)	292.0 ( 322.0)	<.001
<b>During Follow-up:</b>			
	n (%)		p-value
Family history of Diabetes	114 (59)	604 (27)	<.001
GDM status (ever) including baseline	43 (22)	130 ( 6)	<.001
GDM status, interim births only	32 (17)	117 ( 5)	<.001

OC = oral contraceptives, GDM = gestational diabetes mellitus, DM = diabetes mellitus, CHO = carbohydrate, BMI = body mass index. † median (range) Kruskal-Wallis test.

**Table 2:** New cases of DM (n) divided by number of individuals at risk (N) for each interval after Baseline by Interim Birth Groups stratified by GDM status.

Years, Follow-up	No. of new cases of DM / no. of individuals at risk				
	Year 5	Year 7	Year 10	Year 15	Year 20
Interim Birth Groups	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
0 Births without GDM	3/1748 (0.2)	8/1518 (0.5)	18/1254 (1.4)	17/1010 (1.7)	53/859 (6.2)
0 Births with GDM (before baseline)	1/24 (4.2)	1/23 (4.4)	2/20 (10.0)	1/18 (5.6)	5/13 (38.5)
1+ Births without GDM	0/581 (0.0)	4/715 (0.6)	9/858 (1.1)	10/904 (1.1)	28/820 (3.4)
1+ Births with GDM	0/55 (0.0)	1/87 (1.2)	6/115 (5.2)	7/126 (5.6)	19/113 (16.8)
Total	4/2408 (0.2)	14/2343 (0.6)	35/2247 (1.6)	35/2058 (1.7)	105/1805 (5.8)

Fasting plasma glucose was not available at year 5

2-hr OGTTs were administered at years 10 and 20

DM = diabetes mellitus

GDM = gestational diabetes mellitus

**Table 3:** Unadjusted Incidence Rates (IR) of DM and 95% CI Limits by Number of Interim Births for Baseline Parity Groups Stratified by Family History of Diabetes.

Baseline Parity Groups	Incident cases of DM, per 1000 person-yrs, Incidence Rates (IR) and 95% CI Limits							
	No Family History of Diabetes				Family History of Diabetes			
Number of Interim Births:	n	Person yrs	IR	Lower, Upper limits	n	Person-yrs	IR	Lower, Upper limits
<u>Nulliparous at baseline</u>								
0 Births	25	12,337	2.0	1.2, 2.8	28	4,165	6.7	4.2, 9.2
1+ Births without GDM	9	7,294	1.2	0.4, 2.0	20	2,835	7.1	4.0, 10.1
1+ Births with GDM	10	747	13.4	5.1, 21.7	13	506	25.7	11.7, 39.7
<u>Parous at Baseline</u>								
0 or 1+ Births without GDM	28	9,223	3.0	1.9, 4.2	40	4,558	8.8	6.1, 11.5
0 or 1+ Births with GDM	7	556	12.6	3.3, 21.9	13	561	23.2	10.6, 35.8

DM = diabetes mellitus

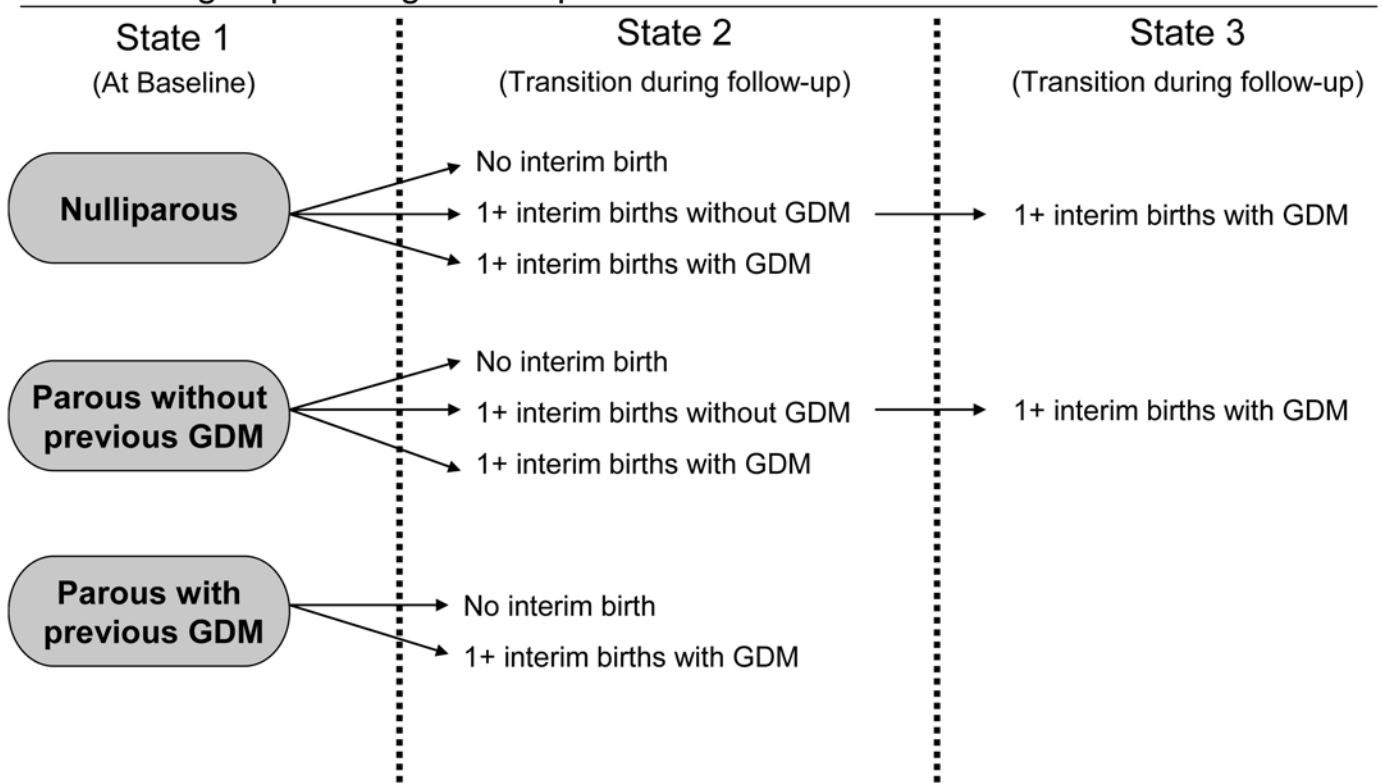
GDM = gestational diabetes mellitus

**Table 4:** Unadjusted and Multivariable adjusted RH (95%CI) for DM among Interim Birth Groups by GDM Status and Stratified by Baseline Parity Groups

Interim Birth Groups Stratified By Baseline Parity Groups	Unadjusted	Family history of diabetes	Family history of diabetes, baseline fasting plasma glucose	Family history of diabetes, baseline fasting plasma glucose, BMI, age, race	Fully Adjusted All previous covariates + baseline education, smoking, physical activity	Fully Adjusted + physical activity change (mediator)	Fully Adjusted + weight change (mediator)	Fully Adjusted + waist girth change (mediator)
Nulliparous at baseline								
0 Births (referent) (n=737)	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
1+ Births without GDM (n=720)	0.7 (0.5-1.1)	0.7 (0.5-1.1)	0.7 (0.5-1.1)	0.9 (0.6-1.3)	0.9 (0.6-1.4)	0.8 (0.5-1.3)	0.8 (0.5-1.3)	0.8 (0.5-1.2)
1+ Births with GDM (n=96)	3.7 (2.2-6.4)	3.1 (1.8-5.4)	3.0 (1.8-5.2)	3.5 (2.0-6.0)	3.8 (2.2-6.6)	3.7 (2.1-6.4)	3.8 (2.2-6.6)	3.4 (2.0-6.0)
Parous at Baseline								
0 or 1+ Births without GDM (n=778)	1.4 (1.0-1.9)	1.2 (0.9-1.8)	1.2 (0.9-1.8)	0.9 (0.6-1.3)	0.8 (0.5-1.2)	0.8 (0.5-1.1)	0.8 (0.5-1.1)	0.8 (0.5-1.1)
0 or 1+ Births with GDM (n=77)	4.8 (2.9-8.2)	3.7 (2.2-6.3)	3.5 (2.0-5.9)	3.2 (1.9-5.5)	2.9 (1.7-5.0)	2.7 (1.5-4.7)	2.7 (1.6-4.7)	2.6 (1.5-4.5)

DM = diabetes mellitus, GDM = gestational diabetes mellitus

**Figure 1:** Description of transitions from baseline parity groups into interim birth groups during follow-up.



The figure shows possible sequences of joint parity and GDM status (ignoring which exam transition occurred in). In terms of sequential states, the only allowable transitions are from State 1 to State 2 and from State 2 to State 3. State 1 is always at baseline, States 2 and 3 always during follow-up. Each transition can occur at any examination, except that GDM is an absorbing state (always henceforth classified as GDM after first having had it, even though a subsequent birth might be free of GDM) and nulliparous with no interim birth does not allow GDM.