Parity and Risk of Type 2 Diabetes

The Atherosclerosis Risk in Communities study

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OBJECTIVE — While high parity is hypothesized to be associated with insulin resistance and type 2 diabetes, few studies have examined this association in diverse racial samples or geographical areas. Our objectives were to estimate the magnitude of association between parity and diabetes and to determine if higher parity is predictive of future risk of diabetes.

RESEARCH DESIGN AND METHODS — This was a population-based, prospective cohort study of 7,024 Caucasian and African-American women from the Atherosclerosis Risk in Communities study, a prospective epidemiological study of men and women aged 45–64 years, with 9 years of follow-up. Incident diabetes was defined by the 1997 American Diabetes Association diagnostic criteria. Parity was defined as the number of live births (no live births [nulliparity], one to two live births, three to four live births, and five or more live births [grandmultiparity]). Parity and risk of diabetes was estimated for 754 incident cases of diabetes with Cox proportional hazard regression models, adjusting for sociodemographic, clinical, and lifestyle factors and inflammatory markers.

RESULTS — Incidence rates were highest among women with five or more live births (23/1,000 person-years [95% CI 20.3–26.7]) and lowest among women with one to two live births (11/1,000 person-years [9.6–12.5]). Adjustment indicated that much of the risk was due to sociodemographic factors and higher obesity, but after adjustment for all covariates, grandmultiparity (five or more) was still associated with a 27% increased risk for diabetes (hazard ratio 1.27 [95% CI 1.02–1.57]).

CONCLUSIONS — Grandmultiparity is predictive of future risk of diabetes after adjustment for confounders.

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There is growing interest in the effect of childbearing on the development of chronic medical conditions, including cardiovascular disease (1) and diabetes (2–4). Earlier investigations have suggested that parity, particularly five or more live births, might be associated with diabetes (2,4,5), whereas other investigations have found no association (6–8). Potential mechanisms include the influence of multiple pregnancies on postpartum weight retention (9,10) and development of obesity (6,7,11) or the influence of multiple exposures to the metabolic changes of pregnancy (2), including impaired insulin sensitivity and central obesity (12), both of which parallel the mechanisms underlying the development of diabetes. Other studies (5,13,14) suggest that nulliparity (no live births) may be associated with diabetes. Potential mechanisms include underlying insulin resistance and β-cell dysfunction (5) related to infertility and pregnancy loss (15).

While these studies offer important, useful information, the effect of parity on diabetes is not completely understood. Prior studies are relatively limited to one geographical region (4,8) or population (7,14). While some studies have adjusted for measures of obesity, fewer studies have adjusted for potentially modifiable lifestyle factors, such as physical activity and caloric intake (7), and limited laboratory data, such as markers of obesity or inflammation (5,16), have been presented. It is important for clinicians to be aware of potential associations between childbearing and diabetes in order to counsel women about potential long-term consequences of the metabolic and lifestyle changes associated with pregnancy (17).

The Atherosclerosis Risk in Communities (ARIC) study is a community-based cohort of men and women with currently 9 years of follow-up (18). Our goal was to determine the relation of parity with diabetes, accounting for the contribution of sociodemographic, clinical, and physiologic factors using a longitudinal approach. Our hypothesis was that parity is independently associated with diabetes. The study objectives were to *1*) determine the incidence of diabetes across parity groups in a community-based sample, *2*) describe the association between parity and established risk factors for diabetes, and *3*) determine whether parity is independently associated and predictive of diabetes after adjustment for sociodemographic and clinical factors and measures of inflammation.

RESEARCH DESIGN AND METHODS

— We conducted a longitudinal analysis of data from the ARIC study to examine the presence and strength of an association between parity and diabetes in a sample of African-American and Caucasian women. This study was approved by the institutional review boards of each participating institution.

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Abbreviations: ARIC, Atherosclerosis Risk in Communities.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Baseline demographic, behavioral, clinical, and physiological characteristics of 7,024 adult women by parity*

Characteristics	Never pregnant*	Parity†				*P*
		Women with prior pregnancies and the number of live births				
		No live births‡	1–2 live births	3–4 live births	≥5 live births§	
n	442	112	2,630	2,609	1,231	
Age (years)	54.1 ± 5.9	54.8 ± 5.9	53.2 ± 5.8	53.3 ± 5.5	54.4 ± 5.2	<0.01
African American (%)	17	46	19	21	48	<0.01
High school education or less (%)	11	22	14	17	40	<0.01
Annual household income <$16K (%)	19	26	17	19	43	<0.01
Caloric intake (kcal/day)	1,440 ± 541	1,522 ± 489	1,486 ± 538	1,501 ± 525	1,529 ± 550	0.03
Leisure-time physical activity score	2.37 ± 0.75	2.39 ± 0.73	2.38 ± 0.78	2.36 ± 0.77	2.23 ± 0.69	<0.01
Current/former/never smoker (%)	24/25/51	25/37/38	26/23/51	22/25/53	24/19/57	<0.01
Ever taken birth control pills (%)	28	36	47	52	44	<0.01
Menopausal (%)	71	76	68	68	78	<0.01
Ever used hormone replacement (%)	38	43	38	37	32	<0.01
Family history of diabetes (%)	12	13	13	14	13	0.61
BMI (kg/m^2)	26.1 ± 5.5	27.2 ± 5.5	26.3 ± 5.4	27.3 ± 5.5	29.3 ± 6.3	<0.01
Waist circumference	91.5 ± 14.8	94.1 ± 15.3	91.5 ± 14.1	93.5 ± 14.5	98.2 ± 15.7	0.01
Leukocyte count (cells/ml)	5.8 ± 1.7	6.0 ± 1.9	5.9 ± 1.8	5.9 ± 1.9	5.8 ± 1.9	0.07
Fibrinogen levels (mg/dl)	305 ± 62	306 ± 71	300 ± 60	300 ± 60	311 ± 67	<0.01
Glucose (mmol/l)	5.3 ± 0.5	5.4 ± 0.5	5.3 ± 0.5	5.4 ± 0.5	5.5 ± 0.5	<0.01

Data are means ± SD unless otherwise indicated. For continuous variables, the *P* value is from ANOVA; for categorical variables, the *P* value is from the χ^2 test. *Women who reported never being pregnant; †number of live births; ‡women who reported prior pregnancies but no live births; §grandmultiparity.

The ARIC study is a prospective, population-based study of 15,792 adult men and women, aged 45–64 years, who were recruited between 1986 and 1989 from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; and surburban Minneapolis, Minnesota (18). Baseline examinations were conducted between 1986 and 1989 (visit 1), with follow-up and clinic visits every 3 years (1990–1992 [visit 2], 1993–1995 [visit 3], and 1996–1998 [visit 4]), for a total of 9 years of follow-up. Response rates for the second, third, and fourth follow-ups were 93, 86, and 81%, respectively. We limited our analysis to Caucasian and African-American women (n = 8,579) due to small numbers of women in other racial groups. Participants who had diabetes at baseline (n = 1,096) and never returned for follow-up (n = 436) or whose information on parity was missing (n = 23) were excluded. The final sample size for the analysis was 7,024 women.

Exposure

The independent variable, parity, was defined as the total number of live births and was based on data collected at entry into the study. We classified parity into four categories: no live births (nulliparity), one to two live births, three to four live births, and five or more live births (grandmultiparity). We did not include spontaneous miscarriages or pregnancy terminations. We also constructed an additional category, nulligravida, for women who reported that they had never been pregnant and had not undergone any type of delivery.

Outcome: type 2 diabetes

Individuals were classified as having diabetes based on the 1997 American Diabetes Association criteria (19): *1*) a reported history of physician-diagnosed diabetes, *2*) current use of antidiabetes medications, or *3*) fasting serum glucose levels ≥126 mg/dl and nonfasting serum glucose levels ≥200 mg/dl. Individuals without diabetes at study entry who subsequently met any of these criteria at visits 2, 3, or 4 were considered to have incident diabetes.

Covariates

Race was based on self-report at the time of recruitment. Education was categorized as ≤12 or >12 years. Low income was defined as an annual household income of <$16,000. A positive family history for diabetes was recorded at study entry if at least one of the subjects' biological parents had been diagnosed with diabetes. Leisure-time physical activity was assessed by interview using a questionnaire developed by Baecke et al. (20). A physical activity index was then derived at baseline, which ranged from 1 (low activ-

Table 2—*Incidence rate of diabetes by childbearing categories, the ARIC study, 1986–1998*

Incidence rate of type 2 diabetes	Never pregnant*	Parity†			
		No live births	1–2 live births	3–4 live births	≥5 live births
Number of incident diabetes	29	16	224	280	205
Incidence rate per 1,000 person-years (95% CI)	8.4 (5.8–12.0)	19.8 (12.1–32.3)	11.0 (9.6–12.5)	13.8 (12.3–15.6)	23.3 (20.3–26.7)

*Women who reported never being pregnant; †number of live births among women who reported prior pregnancies.

Table 3—*RHs (95% CI) of diabetes over 9 years of follow-up by category of parity for 7,024 women, the ARIC study*

		Parity			
Adjustments	Never pregnant	No live births*	1–2 live births (reference)	3–4 live births	≥5 live births†
Model 1: unadjusted	0.77 (0.52–1.13)	1.78 (1.07–2.96)‡	1.0	1.26 (1.06–1.50)‡	2.10 (1.73–2.53)‡
Model 2: sociodemographics	0.77 (0.51–1.14)	1.41 (0.85–2.35)	1.0	1.23 (1.03–1.47)‡	1.44 (1.18–1.77)‡
Model 3: model 2 factors + lifestyle behaviors	0.80 (0.54–1.20)	1.48 (0.89–2.46)	1.0	1.26 (1.05–1.50)‡	1.46 (1.19–1.80)‡
Model 4: model 3 factors + reproductive factors	0.82 (0.55–1.22)	1.39 (0.82–2.35)	1.0	1.18 (0.98–1.42)	1.42 (1.15–1.76)‡
Model 5: model 4 factors + waist circumference and BMI	0.79 (0.53–1.18)	1.31 (0.77–2.22)	1.0	1.11 (0.92–1.34)	1.24 (1.00–1.53)‡
Model 6: model 5 factors + markers of inflammation§	0.80 (0.54–1.20)	1.31 (0.77–2.23)	1.0	1.11 (0.92–1.34)	1.27 (1.02–1.57)‡

Model 2: adjusted for age, center, race, income, education, and family history of diabetes. Model 3: adjusted for age, center, race, income, education, smoking, family history of diabetes, caloric intake, and physical activity score. Model 4: adjusted for age, center, race, income, education, smoking, family history of diabetes, caloric intake, physical activity score, menopause status, age at menopause, ever use of birth control pills, and ever use of hormone replacement therapy. Model 5: adjusted for age, center, race, income, education, smoking, family history of diabetes, caloric intake, physical activity score, menopause status, age at menopause, ever use of birth control pills, ever use of hormone replacement therapy, waist circumference, and BMI. Model 6: adjusted for age, center, race, income, education, smoking, family history of diabetes, caloric intake, physical activity score, menopause status, ever use of birth control pills, ever use of hormone replacement therapy, waist circumference, BMI, fibrinogen levels, and leukocyte count. *No live births, nulliparity; †≥5 live births, grandmultiparity. ‡$P < 0.05$. §Fibrinogen and leukocyte count.

ity) to 5 (high activity). Self-reported smoking status was based on a 12-item questionnaire, which classified subjects as current, ever, or never smokers. Total caloric intake was based on a modified 66-item food frequency questionnaire designed by Willett et al. (21). Reproductive health–related variables were collected through a standardized interview and included menopausal status and use of hormones or birth control pills. Anthropometry was performed in the fasting state (21).

Laboratory measurements

Participants were asked to fast for 12 h, and actual fasting times were recorded. Blood was collected in serum separator and EDTA tubes, processed, stored, and analyzed according to previously published protocols (22).

Statistical analysis

The incidence rate was defined as the number of women who had newly developed diabetes during the 9-year follow-up divided by person-years. The timing of the onset of diabetes was linearly interpolated between visits as described elsewhere (23). Incidence of diabetes during 9 years of follow-up was also determined for each category of childbearing: never pregnant, pregnant but no live births, one to two lives births, three to four live births, and five or more live births. CIs for incidence rates were calculated under the assumptions of the Poisson distributions. The distribution of participant characteristics, lifestyle behaviors, and inflammatory markers across childbearing groups at baseline were compared using χ^2 for categorical variables and ANOVA for continuous variables.

To explore whether parity at baseline was associated with development of diabetes in the future, we conducted a prospective analysis of women without diabetes at baseline using Cox proportional hazards regression analysis. We developed a series of models adjusting for potential confounders and estimated the relative hazard (RH) of developing diabetes for each of the four parity groups and for women with no history of pregnancies. Covariates were added to the model in a stepwise fashion: first sociodemographic and familial factors (age, study center, race, income, education level, and family history of diabetes), then lifestyle-related factors (total caloric intake, current smoking, and physical activity index), then reproductive health–related factors (menopause, age at menopause, ever user of birth control pills, and ever user of hormone replacement therapy), then BMI, and then, finally, inflammatory markers (fibrinogen level and leukocyte count).

We also developed proportional hazards regression models stratified by race, education, income, and BMI categories (underweight/normal, ≤24.9 kg/m^2; overweight, 25–29.9 kg/m^2; and obese, ≥30 kg/m^2). P values <0.05 were considered significant. All analyses were performed by SAS version 9.1 (24).

RESULTS — Women with five or more live births or no live births were older, more likely to be African-American, more likely to have a high-school education or less, and more likely to have an annual household income of <$16,000 ($P < 0.001$) relative to their counterparts in other childbearing categories (Table 1). Women with five or more live births and women with no live births had lower leisure-time physical activity scores, higher waist circumference, higher BMI, and higher fibrinogen levels. Leukocyte count was not statistically significantly different among all parity groups. Average glucose levels at baseline were higher among women with no live births and five or more live births compared with women with one to two live births.

Incidence of type 2 diabetes

Over 9 years of follow-up, there were 224, 280, and 205 incident cases of type 2 diabetes among women with one to two live births, three to four live births, and five or more live births, respectively (Table 2). Approximately 44% of the sample was diagnosed with type 2 diabetes by a clinician. Incidence rates ranged from 11.0/1,000 person-years (95% CI 9.6–12.5) in women with one to two live births to 13.8/1,000 person-years (12.3–15.6) in women with three to four live births, and 23.3/1,000 person-years (20.3–26.7) in women with five or more live births. The

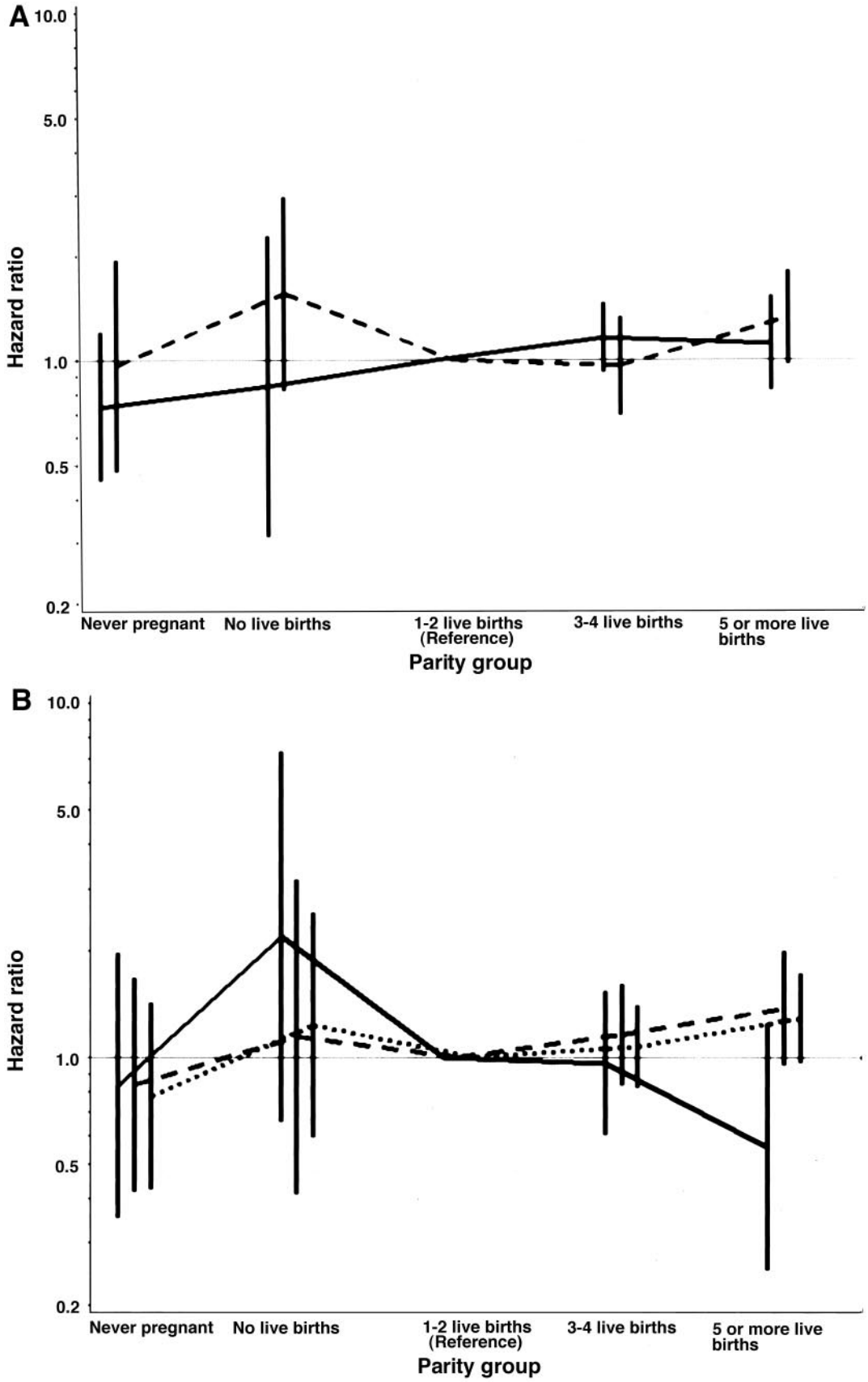

Figure 1—*The association of parity with incident type 2 diabetes among racial subgroups* (A) *and categories of BMI* (B). A*: Dotted line represents African-American women and solid line represents Caucasian women. Vertical line represent 95% CIs.* B*: Solid line represents normal/underweight, dotted line represents overweight, and dashed line represents obesity.*

incidence of diabetes among women with prior pregnancies but no live births was 19.8/1,000 person-years (12.1–32.3).

Parity and incident diabetes

After adjustment for sociodemographic factors, women with five or more live births had a 44% increased rate of developing diabetes compared with women with one to two live births (RH 1.44 [95% CI 1.18–1.77]) (Table 3). After the addition of lifestyle factors, five or more live births were still associated with the risk of diabetes. The association between five or more live births and diabetes was attenuated but remained significant after an additional adjustment for BMI and waist circumference (RH 1.24 [1.00–1.53]). In the fully adjusted model, including markers of inflammation, women with five or more live births had a 27% increased rate of developing diabetes compared with women with one to two live births (RH 1.27 [1.02–1.57]).

Further adjustment for time-dependent variables (income, smoking status, waist circumference, BMI, caloric intake, sports index, and leukocyte count) did not change the RHs of development of diabetes in any parity group compared with women with one to two live births.

Figure 1 shows the association of parity with type 2 diabetes stratified by race and BMI subgroups. The hazard ratio for developing type 2 diabetes was similar between African-American and Caucasian women for each parity category (Fig. 1*A*) and for each BMI category (Fig. 1*B*). There were no significant interactions with educational or income levels (data not shown).

CONCLUSIONS — We estimated the magnitude of association of parity with diabetes and identified behavioral, clinical, and laboratory factors that might account, in part, for the association of parity with diabetes. We then described the independent association between parity and diabetes, adjusting for covariates.

There are several possible mechanisms to explain the association between parity and type 2 diabetes. First, women of higher parity have a higher caloric intake and lower physical activity than women of lower parity. These sedentary lifestyle behaviors can lead to higher BMI, insulin resistance, and development of diabetes (10,25). In our study population, women of higher parity had a higher mean BMI and waist circumference at baseline than women of lower parity. Thus, postpartum weight retention with multiple births coupled with a sedentary lifestyle among highly parous women may also lead to diabetes. These findings suggest the need to further explore patterns of postpartum weight retention. Incorporating effective educational initiatives focused on nutrition and physical activity into standard prenatal and postnatal care may be a reasonable strategy to promote healthy lifestyle behaviors among women.

Second, socioeconomic status might lead to both higher parity and risk of diabetes. Both income and education were strong confounders of the association between parity and diabetes in our study. The addition of these variables to the multivariable models markedly attenuated the association between parity and diabetes. Lower socioeconomic status is associated with higher parity and can also affect lifestyle behaviors and risk of diabetes.

Third, we explored the role of inflammation as a possible connection between parity and diabetes risk. Other research indicates that fibrinogen levels (26) and white blood cell counts (27) can be related to incident diabetes and obesity, respectively. In our study population, higher parity was associated with an increase in these inflammatory markers. Higher parity may lead to obesity or weight retention, as evidenced by a concurrent rise in inflammatory markers and development of diabetes. Also, it may be that some of the association of inflammation with parity is explained by socioeconomic factors (28).

While some investigators propose that hormone levels might heighten insulin sensitivity (29), others propose that hormones might adversely affect insulin resistance and increase the risk of diabetes (30). Our findings do not support menopausal status, oral contraceptive use, or hormonal use as potential mediators of the association between parity and diabetes.

Our study has several strengths. The ARIC study is a large sample of individuals in which there was a standardized method of identifying incident diabetes for up to 9 years of follow-up. Because there are standardized measures of exposures, outcomes, behavioral factors, and laboratory measures (e.g., inflammatory markers) used at each recruitment site in an observational study design, the ARIC study provides an opportunity to examine potential mechanisms of the association between parity and diabetes.

There are also limitations to this study. Our results may have limited generalizability to other racial groups with higher rates of diabetes, such as Native Americans. We did not have data on pregnancy-related confounders, such as a history of gestational diabetes, gestational weight gain, or postpartum weight retention. Because most practitioners did not practice universal screening at the time of ARIC study recruitment, data on gestational diabetes was not ascertained. Women with prior gestational diabetes are known to be at high risk for the development of type 2 diabetes. Also, we did not have information on breast-feeding practices, which may affect the incidence of type 2 diabetes (31). Data on these parameters could broaden our understanding of the association between childbearing and lifestyle behaviors related to diabetes. Because we were unable to discern between nonlive births due to spontaneous miscarriage and intrauterine fetal death, we could not characterize potential pathways between parity and diabetes based on nonlive birth pregnancy outcomes.

The main implication of our study is that the association of pregnancy with development of diabetes, whether through biological mechanisms or lifestyle behaviors, deserves further study. After adjustment for all covariates, grandmultiparity is associated with a higher risk of diabetes. While further study is warranted, this work suggests the need for physicians to discuss the potential long-term effects of pregnancy to their patients. Our study serves as a basis for additional longitudinal studies of young women in which specific pregnancy-related weight gain measures, lifestyle factors, and changes in socioeconomic status can be prospectively measured. Additional studies should also include laboratory measures of insulin resistance, glucose tolerance, and adiposity as women progress through their reproductive years.

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