Childhood Obesity and Metabolic Imprinting

The ongoing effects of maternal hyperglycemia

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OBJECTIVE — The purpose of this study was to determine how the range of measured maternal glycemia in pregnancy relates to risk of obesity in childhood.

RESEARCH DESIGN AND METHODS — Universal gestational diabetes mellitus (GDM) screening (a 50-g glucose challenge test [GCT]) was performed in two regions (Northwest and Hawaii) of a large diverse HMO during 1995–2000, and GDM was diagnosed/treated using a 3-h 100-g oral glucose tolerance test (OGTT) and National Diabetes Data Group (NDDG) criteria. Measured weight in offspring (n = 9,439) was ascertained 5–7 years later to calculate sex-specific weight-for-age percentiles using U.S. norms (1963–1994 standard) and then classified by maternal positive GCT (1 h ≥ 7.8 mmol/l) and OGTT results (1 or ≥2 of the 4 time points abnormal: fasting, 1 h, 2 h, or 3 h by Carpenter and Coustan and NDDG criteria).

RESULTS — There was a positive trend for increasing childhood obesity at age 5–7 years ($P <$ 0.0001; 85th and 95th percentiles) across the range of increasing maternal glucose screen values, which remained after adjustment for potential confounders including maternal weight gain, maternal age, parity, ethnicity, and birth weight. The risk of childhood obesity in offspring of mothers with GDM by NDDG criteria (treated) was attenuated compared with the risks for the groups with lesser degrees of hyperglycemia (untreated). The relationships were similar among Caucasians and non-Caucasians. Stratification by birth weight also revealed these effects in children of normal birth weight (≤4,000 g).

CONCLUSIONS — Our results in a multiethnic U.S. population suggest that increasing hyperglycemia in pregnancy is associated with an increased risk of childhood obesity. More research is needed to determine whether treatment of GDM may be a modifiable risk factor for childhood obesity.

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Diabetes in pregnancy is associated with an increased rate of offspring childhood obesity, impaired glucose tolerance, and type 2 diabetes (1–7). The strongest single risk factor for obesity in Pima Indian children is exposure in utero to maternal diabetes, independent of maternal obesity and birth weight (3,4,8). Pettitt et al. (9) found an overall linear association between maternal glucose concentration (2-h glucose on the 75-g oral glucose tolerance test [OGTT]) and obesity in their offspring in Pima Indians, with the effect being most pronounced for a 2-h post-OGTT level ≥ 7.8 mmol/l. Some, but not all, studies in populations other than Pima Indians reported an association of gestational diabetes mellitus (GDM) with increased obesity in offspring (7,10–12).

With normal growth, children's weight rises in proportion to height at an average age of 6 years. This period, called adiposity rebound (13–15), is thought to be a critical time of risk for adult obesity: obesity in this childhood period strongly predicts adult obesity (16–19).

We sought to determine whether increasing hyperglycemia in pregnancy, ranging from normal to GDM, is related to childhood obesity in offspring during the typical period of adiposity rebound in a diverse population. We tested our hypotheses among 9,439 women in a large multiethnic U.S. population universally screened for GDM, whose children had weight measured between ages 5 and 7 years. This established universal two-step GDM screening program (50-g glucose challenge test [GCT]; if positive, then a diagnostic OGTT) allows us to evaluate a large number of offspring whose mothers' glucose intolerance ranged from a normal GCT to GDM, diagnosed by old (treated) and current (untreated) criteria during the study period.

RESEARCH DESIGN AND METHODS

— The study population was drawn from a combined membership of >650,000 in two Kaiser Permanente regions: Hawaii (KPH) and Northwest (KPNW). Memberships of both regions are ~20% of the general populations of the areas and reflect their demographic/sociographic characteristics. In Hawaii, low-income individuals enroll under the State Health Insurance Plan for Medicaid and comprise ~10% of the state and KPH population. During the study period, KPNW served ~8% of Medicaid members through the Oregon Health Plan, a population demographically similar to the area population (20). All members in both regions have access to medically nec-

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Abbreviations: EMR, electronic medical record; GCT, glucose challenge test; GDM, gestational diabetes mellitus; KPH, Kaiser Permanante Hawaii; KPNW, Kaiser Permanante Northwest; NDDG, National Diabetes Data Group; OGTT, oral glucose tolerance test.

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

essary services from Kaiser Permanente or by referral from their primary care physician.

Both KPH and KPNW maintain administrative and clinical electronic databases on inpatient admissions, pharmacy dispenses, chronic disease registries, laboratory tests, and outside claims/referrals. All databases are linked through each member's unique health record number. Both regions also have ongoing validated diabetes registries (21), so women with preexisting diabetes can be excluded from analyses. The institutional review boards of both Kaiser Permanente regions and the State of Hawaii Department of Health approved this study.

Glucose testing and GDM diagnosis

Both KPH and KPNW universally screen for GDM, initially using a 50-g, 1-h GCT. Women who fail this screening at a level >11.1 mmol/l are assumed to have GDM and not tested further. Those remaining who fail the GCT (≥7.8 mmol/l) then receive the 100-g, 3-h OGTT. For women screened more than once during pregnancy, we used the latest test.

Both the National Diabetes Data Group (NDDG) and Carpenter and Coustan criteria for GDM diagnosis require that ≥2 of the 4 possible time points measured with the 100-g OGTT are positive, although they have different threshold cutoffs. Relevant to this analysis, during 1995–2000, Kaiser Permanente used the NDDG criteria to diagnose and treat GDM, allowing us to also assess potential differences in outcomes with treatment. Therefore, those meeting the NDDG criteria were likely to be treated with diet or diet/insulin, but those meeting only the Carpenter and Coustan criteria were likely to not be treated. We have thus calculated GDM using both criteria sets. The NDDG criteria require the ≥2 values to exceed these thresholds: fasting ≥5.8 mmol/l; 1 h ≥10.5 mmol/l; 2 h ≥9.2 mmol/l; and 3 h ≥8.0 mmol/l (22,23). The more recent Carpenter and Coustan criteria have these lower thresholds: fasting ≥5.3 mmol/l; 1 h ≥10 mmol/l; 2 h ≥8.6 mmol/l; and 3 h ≥7.8 mmol/l (22,24).

Sample selection

We identified 27,560 singleton births at KPH and KPNW during 1995–2000 (15,002 from KPH for 1995–2000; 12,558 from KPNW for 1995–1999). Mothers with preexisting diabetes (n = 261) were excluded from analysis (elevated A1C, provider-diagnosed diabetes, or in regional diabetes registry), leaving a pool of 27,229 without preexisting diabetes. As both regions universally screen for GDM, we had available laboratory measurements for 26,211 women (96% screening rate). Of the 26,211 women, 9,439 children had Kaiser Permanente membership at age 5–7 years postpartum and had measured weight data in the electronic medical record (EMR) at age 5–7 years; these 9,439 mother-child pairs are the final group included in the analysis. Importantly, these 9,439 mother-child pairs did not differ from the excluded mother-child pairs (whose children did not remain members/have measured weight at age 5–7 years) by category of maternal glucose screening (i.e., percent normal, positive GCT with normal OGTT, one abnormal value on an OGGT, and GDM by Carpenter and Coustan and NDDG criteria). They also did not differ by offspring sex or maternal weight gain in pregnancy. Those children who remained members tended to have less macrosomia at birth (12 vs. 13%, P = 0.031) and were less likely to be Caucasian (44 vs. 51% Caucasian, $P < 0.0001$), and their mothers were generally older (28.6 vs. 27.4 years, $P < 0.001$) and were less likely to be nulliparous (43 vs. 44%, $P = 0.01$). Thus, the final sample was reasonably representative of the original sample.

Classification of childhood obesity

Obesity was classified as age- and sex-specific percentiles for both BMI and weight, based on U.S. Centers for Disease Control and Prevention criteria (with the normative reference range of 1964–1990, when U.S. children were typically more lean) (25), and all outcomes were assessed with both BMI and weight percentiles.

At KPNW, all children with measured weight had a measured height to calculate BMI. However, at KPH, a large proportion had only measured weight (2,309 of 5,841 [40%]) available in the EMR, partly because KPH transitioned to several outpatient EMR systems during our data collection period and in some cases because a child had a visit for illness during which only weight was measured (e.g., to calculate antibiotic dosing). As these children without height measures also represented a large proportion of children whose mothers had GDM with elevated fasting levels on the OGTT (37 of the 117 in Hawaii), we thought the potential bias to analyses would be greater by requiring height to assess obesity with BMI. Therefore, we present weight percentiles as our primary analysis, after confirming that results were similar with BMI percentiles with the same Centers for Disease Control and Prevention normative database (25).

Classification of ethnicity and other covariates

Ethnicity classification was based on the mother's reported race on the official birth certificates in her state. As per state algorithms for classifying race, if the mother reports being any part Native Hawaiian, ethnicity is classified as Native Hawaiian. If she did not list Native Hawaiian, but a non-Caucasian race, then we classified the child into that group. Race was classified as Caucasian only if no other race/ethnicity was reported.

Maternal age, infant sex, and birth weight were recorded in the EMRs. State birth certificate records validated birth weight and also provided mother's reported parity and pregnancy weight gain.

Statistical analyses

We conducted all statistical analyses using the SAS Statistical Analysis System (version 6.12; SAS Institute, Cary, NC). We assessed the relationship between GCT quartiles and childhood weight and then stratified maternal glucose screening results into five categories: *1*) normal GCT (referent group); *2*) positive GCT and normal OGTT; *3*) one abnormal value on the OGTT by either NDDG or Carpenter and Coustan criteria (≥2 abnormalities are required to diagnose GDM by either criteria set); *4*) GDM by the lower Carpenter and Coustan criteria; and *5*) GDM by NDDG criteria (during the study period this is the GDM treated group).

We first conducted all analyses for KPH and KPNW separately, both overall by region and for the Caucasian subgroups, to confirm that results were similar between the two regions. Because results were consistent, our final analyses are combined for both regions. We also assessed relationships among various ethnic subgroups to confirm that results were similar before we combined them into one non-Caucasian category.

We used t tests, a Pearson χ^2 test, and Mantel-Haenszel χ^2 tests to evaluate univariate relationships with potential confounders and child weight. Excessive pregnancy weight gain is a strong independent predictor of macrosomia (26) and ranged markedly from 0 to 98 lb (median 30.0 lb). Therefore, we assessed the

Table 1—*Characteristics of the 9,439 mother-child pairs*

Maternal age at screen	
<18 years	260 (2.7)
18–25 years	2,821 (29.9)
26–30 years	2,187 (23.2)
31–35 years	2,830 (30.0)
≥36 years	1,341 (14.2)
Parity†	
0	4,019 (42.6)
1	3,155 (33.4)
2	1,429 (15.1)
≥3	821 (8.7)
Unknown	15 (0.2)
Maternal weight gain	
0–24 lb	2,014 (21.3)
25–31 lb	2,078 (22.0)
32–40 lb	1,866 (19.8)
≥41 lb	1,480 (15.7)
Unknown	2,001 (21.2)
Ethnicity	
Caucasian	4,103 (43.5)
Hawaiian	2,056 (21.8)
Filipino	1,235 (13.1)
Japanese	571 (6.1)
Pacific Islander (other than Hawaiian or Samoan)	345 (3.7)
Chinese	249 (2.6)
Hispanic	209 (2.2)
African American	180 (1.9)
Samoan	169 (1.8)
Other*	322 (3.4)
Birth weight >4,000 g	1,147 (12.2)
Sex of baby female	4,618 (48.9)

Data are *n* (%). *Other includes Korean (98), Puerto Rican (58), Native American (54), Vietnamese (39), other categories (60), and unknown (13). †Prior to current pregnancy.

relationship between maternal weight gain and childhood weight initially by quartiles. The risk of childhood obesity increased significantly with the highest quartile of maternal weight gain (>40 lb), and thus we dichotomized maternal weight gain (>40 lb) for the multivariate analyses.

We used a Pearson χ^2 test to analyze univariate associations and multiple logistic regression to calculate odds ratios and CIs adjusted for other covariates. All of the statistical tests that we report are two sided; the term statistically significant implies $P < 0.05$.

RESULTS — Table 1 presents characteristics of the multiethnic 9,439 mother-child pairs.

Childhood obesity based on mother's GCT and OGTT results in pregnancy

Table 2 presents the prevalence and risk of childhood obesity (defined as >85th and >95th percentiles of age- and sex-adjusted weight to U.S. populations norms of 1963–1994) associated with maternal GDM screening results during pregnancy. The highest quartile of hyperglycemia on the GCT was associated with a significantly higher level of childhood obesity compared with the referent lowest quartile ($P_{trend} < 0.0001$ for both >85th and >95th percentiles) (Table 2).

When the range of glycemia, including those requiring a OGTT, was evaluated in categories relative to those with a normal GCT, an increasing level of hyperglycemia in pregnancy was associated with a greater risk of childhood obesity ($P_{trend} < 0.0001$ for both >85th and >95th percentiles) (Table 2). However, only those with an abnormal OGTT differed significantly from the normal GCT group in risk for childhood obesity (Table 2). This significant trend for increasing childhood obesity associated with increasing maternal hyperglycemia remained after multivariate adjustment for maternal age, parity, pregnancy weight gain, ethnicity, macrosomia at birth, and infant's sex (Table 2). Importantly, the increased risk of childhood obesity with maternal GDM by NDDG criteria (which was treated) was not significant after multivariate adjustment, whereas the risk of all other levels of hyperglycemia based on ≥1 abnormal OGTT values remained significant (Table 2).

Increasing maternal glycemic level was associated with a greater prevalence of macrosomia (>4,000 g, $P < 0.0001$). As some of the effect of increasing maternal hyperglycemia on future childhood obesity could operate through increasing macrosomia, we also assessed models stratified by macrosomia. Interestingly, the relationship of increasing maternal hyperglycemia and associated increased childhood obesity was significant only among children who were not macrosomic at birth (Table 3) (see also details in the online appendix available at http://dx.doi.org/10.2337/dc06-2361). In contrast, the children who were macrosomic at birth had a higher prevalence of childhood obesity irrespective of maternal glycemic level. However, the interaction

Table 2—*Prevalence and risk of childhood obesity at age 5–7 years, stratified by mother's glycemia while pregnant*

Maternal glucose scale with screening for GDM by GCT and OGTT	*n*	Child's weight >85th percentile*		Child's weight >95th percentile*	
		Prevalence (%)†	OR (95% CI)‡§	Prevalence (%)†	OR (95% CI)‡§
Women with normal GCT (quartiles)	7,609				
43–94 mg/dl	1,987	21.6	Reference	10.3	Reference
95–108 mg/dl	1,953	23.6	1.09 (0.92–1.29)	12.0	1.15 (0.92–1.44)
109–121 mg/dl	1,801	23.3	0.99 (0.83–1.17)	13.4	1.20 (0.96–1.50)
122–140 mg/dl	1,868	25.5	**1.22 (1.03–1.45)**	13.2	**1.28 (1.02–1.60)**
Women with GCT/OGTT	9,439				
Normal GCT	7,609	23.5	Reference	12.2	Reference
+GCT, normal OGTT	999	23.3	0.98 (0.81–1.17)	12.8	0.97 (0.77–1.24)
+GCT, 1 abnormal C&C or NDDG	288	26.7	**1.37 (1.01–1.84)**	15.3	1.30 (0.89–1.90)
+GCT, GDM-C&C	173	34.7	**1.89 (1.30–2.76)**	20.2	**1.82 (1.15–2.88)**
+GCT,GDM-NDDG; treated	370	27.8	1.29 (0.85–1.97)	17.3	1.38 (0.84–2.27)

*Sex-specific weight-for-age percentiles based on U.S. norms (1963–1994 standard) (25). †$P_{trend} < 0.0001$ in both stratified GCT and GCT/OGTT group analyses. ‡Adjusted for maternal age, parity, weight gain during pregnancy, ethnicity, macrosomia at birth (>4,000 g), and sex of child; significant values are bolded. §For multivariate analyses only, the final sample sizes were 6,071 total women with normal GCT and 7,428 women with GCT/OGTT, because of missing self-reported weight gain and parity data; the smallest subgroup for the multivariate analysis remained women with +GCT; GDM-C&C ($n = 124$). +GCT, 1-h 50-g glucose challenge test >7.7 mmol/l (140 mg/dl); OGTT, 100-g glucose tolerance test; GDM, ≥2 values exceed the threshold by Carpenter and Coustan (C&C) or NDDG criteria (22).

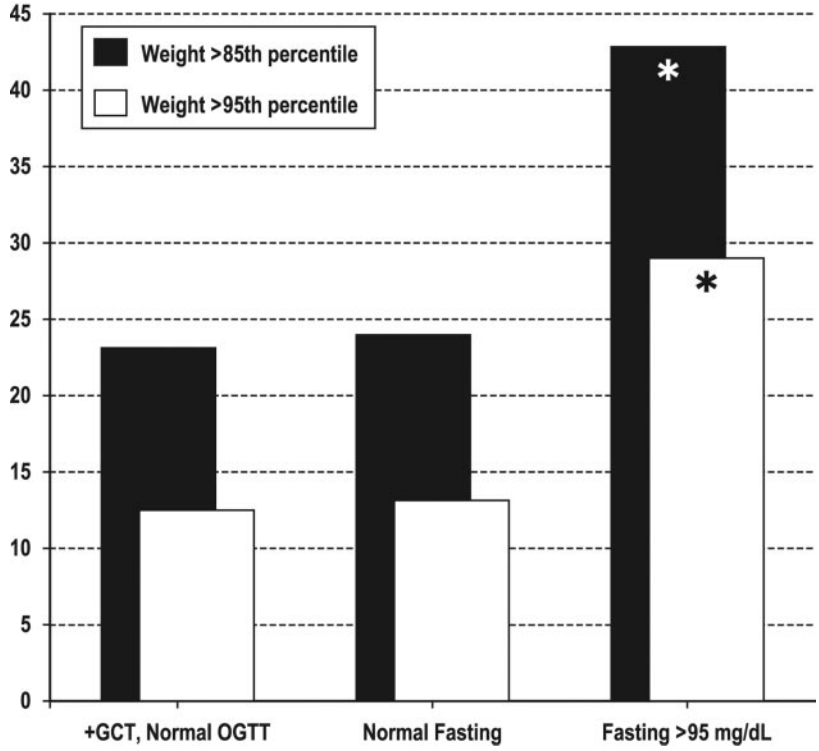

Figure 1—*Relationship of fasting maternal hyperglycemia in pregnancy with childhood obesity at age 5–7 years, among the subsample with abnormal GCT and complete follow-up OGTT results: 1) GCT >140 mg/dl (7.7 mmol/l) but follow-up OGTT normal at all 4 time points (fasting, 1 h, 2 h, and 3 h post-OGTT) by Carpenter and Coustan criteria (22,24) (*n *= 731); 2) normal fasting glucose (≤95 mg/dl [5.3 mmol/l]) but ≥1 Carpenter and Coustan postprandial values equaled or exceeded on OGTT (*n *= 547); and 3) elevated fasting glucose (>95 mg/dl [*n *= 184]) on OGTT and 0, 1, or 2 Carpenter and Coustan postprandial values equaled or exceeded. Categories 2 and 3 are stratified on the basis of fasting glucose on the OGTT irrespective of whether the woman met the criteria for GDM (2 of 4 values exceeded by either Carpenter and Coustan or NDDG criteria).*

between maternal glucose levels and birth weight was not significant in the multivariate model. Further, the relationship between maternal glycemia and child weight was not different when birth weight was excluded from the model.

Childhood obesity based on mother's fasting glucose on an OGTT

We did a subgroup analysis in offspring of women who had an abnormal GCT and a subsequent OGTT, stratifying by fasting results on the OGTT (Carpenter and Coustan criteria) irrespective of whether at least two abnormalities were present on the OGTT (and thus GDM was diagnosed). The risk of childhood obesity at age 5–7 years was nearly double in those children whose mothers had an elevated fasting glucose of >5.3 mmol/l (95 mg/dl) on the OGTT compared with those whose mothers had normal fasting glucose but other abnormal post-OGTT values ($P < 0.0001$) (Fig. 1). Results were similar when women with GDM by the NDDG criteria (treated) were excluded (data not shown).

CONCLUSIONS — Among 9,439 mother-child pairs in a diverse U.S. population universally screened for GDM, we found that an increasing hyperglycemia level in pregnancy is associated with increased future risk of obesity in their children at age 5–7 years. Importantly, our results suggest that this risk is modifiable by treating GDM, as obesity risk was attenuated and no longer significant after multivariate adjustment in the treated GDM group. To our knowledge, this is the first study of a population besides Pima Indians to evaluate childhood obesity with the complete range of hyperglycemia in pregnancy.

Our results also suggest that "metabolic imprinting" of the future child for obesity occurs with ≥1 abnormalities on a OGTT and that fasting hyperglycemia in particular is an important predictor of future childhood obesity. The concept of metabolic imprinting in women and animal models of diabetes has previously been eloquently demonstrated; i.e., the altered metabolic milieu of diabetes in pregnancy increases the offspring's risk of obesity and type 2 diabetes more than would be predicted from genetics alone (2,3,9,27–31). The strongest single risk factor for obesity in Pima Indian children is maternal diabetes in utero, independent of maternal obesity and birth weight (3,4,8). Offspring of mothers with diabetes have up to a 10-fold increased risk of becoming obese during childhood and adolescence and developing impaired glucose tolerance as adolescents (5,7,32). Pettitt et al. (1) found that by age 20–24 years, 45% of offspring of diabetic mothers had developed type 2 diabetes in the Pima Indian population, compared with 8.6% of offspring of pre-diabetic women (mothers developed type 2 diabetes postpartum), and only 1.4% of offspring had developed type 2 diabetes by age 20–24 years if their mothers had not had GDM or later type 2 diabetes.

Prior literature reports are less clear on the degree to which obesity occurs in the offspring of women with GDM (versus preexisting type 1 or type 2 diabetes) in other ethnic groups (7,10–12,18). Among a multiethnic population of nearly 10,000 mother-child pairs in whom maternal glucose was measured as part of a universal screening program, we found that GDM in pregnancy was associated with increased obesity in children who were examined at age 5–7 years.

Macrosomia is both a recognized short-term obesity complication of diabetes in pregnancy and an independent risk factor for future childhood obesity (7,33). Treatment of GDM dramatically reduces the rate of macrosomia (34,35), but it is unclear whether treatment might also reduce the child's future risk of obesity. Our stratified findings based on macrosomia (≤4,000 vs. >4,000 g) revealed a significant relationship with increasing maternal hyperglycemia and childhood obesity only among children whose weight was normal at birth. Moreover, among this normal group, treatment of GDM (diagnosed by NDDG) resulted in childhood obesity rates closer to those of offspring of mothers with normal glucose tolerance.

These results suggest that treatment of GDM may reduce childhood obesity rates and by metabolic mechanisms other than macrosomia. Our results are consistent with the earlier results of Pettitt et al. (8) who found that even among infants

with normal birth weight, diabetes during pregnancy increased the risk of childhood obesity over that for offspring whose mothers did not have GDM (this effect was also not seen in the macrosomia group). It is also notable that in their sentinel randomized, controlled trial of GDM treatment more than four decades ago, O'Sullivan et al. (35) found the greatest relative reduction in macrosomia among women who were normal weight (although the overall prevalence of macrosomia was highest in overweight mothers).

In addition to our findings that increasing maternal hyperglycemia is associated with future childhood obesity risk, we found that fasting hyperglycemia in particular is associated with future childhood obesity risk. Langer et al. (36) assessed perinatal outcomes in a secondary analysis of a randomized trial of women who needed GDM treatment (glyburide versus insulin) and found that the proportion of large-for–gestational age infants was double among mothers with elevated fasting hyperglycemia on the screening OGTT irrespective of treatment group (18% large-for–gestational age infants in mothers with fasting glucose >95 mg/dl vs. 8–9% in both treatment groups with fasting OGTT ≤95 mg/dl). Together, these findings suggest that fasting hyperglycemia is an important risk factor for immediate and long-term obesity risk in offspring. This suggestion needs to be tested further.

Our study has important strengths. The population is a large multiethnic U.S. sample of nearly 10,000 mother-child pairs in which universal GDM screening was performed, and the children were prospectively followed and assessed for obesity 5–7 years after birth. Measurement of birth weight and other potential confounders such as ethnicity and maternal age and weight gain are also strengths. Additionally, we were able to determine that the relationships observed between hyperglycemia in pregnancy and childhood obesity were consistent among differing ethnic groups as we report in detail for the entire population.

Our study also has limitations. We were limited to evaluating a subsample of the birth cohort who remained members to have measured weight at age 5–7 years. However, change in membership would probably be random loss to follow-up and, as detailed under RESEARCH DESIGN AND METHODS, those children who remained members were remarkably similar to those who did not. Moreover, there were no differences in the distribution of maternal hyperglycemia between the two groups. Thus, a significant bias from losses to follow-up is unlikely. Because the outpatient EMR was just beginning for KPNW during the initial study period and was not in place at KPH, we do not have access to mothers' prepregnancy weights. Thus, we cannot determine how prior maternal obesity may have contributed to the hyperglycemia observed in pregnancy or mediated the childhood outcomes. However, we were able to adjust for weight gain in pregnancy (reported on the birth certificates) and birth weight, both independent predictors of childhood obesity in our analysis, and the relationships we observed were independent of both of these weight variables. Moreover, multivariate results were remarkably similar in effect size to the unadjusted results that did not account for weight differences. Finally, our classification of maternal hyperglycemia is based on GDM screening results at one time point in pregnancy; multiple measures of glycemia are not available for the population.

In summary, among a large multiethnic U.S. population we found that increasing hyperglycemia in pregnancy and fasting hyperglycemia, in particular, are associated with an increased risk of childhood obesity. This risk was present in Caucasians as well as in other high-risk ethnic groups and even among children of normal birth weight. These results suggest that metabolic imprinting of the child for future obesity occurs in women with GDM (not only in those with preexisting diabetes), and, thus, GDM screening might have long-term benefits to offspring. They also suggest that GDM treatment may decrease the risk of childhood obesity and provide an additional reason for screening for GDM in pregnancy. More research is needed to determine whether treatment of maternal GDM may be a modifiable risk factor for childhood obesity.

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