JAMA | Original Investigation

Association of Gestational Diabetes With Maternal Disorders of Glucose Metabolism and Childhood Adiposity

William L. Lowe Jr, MD; Denise M. Scholtens, PhD; Lynn P. Lowe, PhD; Alan Kuang, MS; Michael Nodzenski, MS; Octavious Talbot, MS; Patrick M. Catalano, MD; Barbara Linder, MD, PhD; Wendy J. Brickman, MD; Peter Clayton, MD; Chaicharn Deerochanawong, MD; Jill Hamilton, MD; Jami L. Josefson, MD, MS; Michele Lashley, MBBS, DM; Jean M. Lawrence, ScD; Yael Lebenthal, MD; Ronald Ma, MB, BChir, FRCP; Michael Maresh, MD, FRCOG; David McCance, MD; Wing Hung Tam, MD; David A. Sacks, MD; Alan R. Dyer, PhD; Boyd E. Metzger, MD; for the HAPO Follow-up Study Cooperative Research Group

IMPORTANCE The sequelae of gestational diabetes (GD) by contemporary criteria that diagnose approximately twice as many women as previously used criteria are unclear.

OBJECTIVE To examine associations of GD with maternal glucose metabolism and childhood adiposity 10 to 14 years' postpartum.

DESIGN, SETTING, AND PARTICIPANTS The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study established associations of glucose levels during pregnancy with perinatal outcomes and the follow-up study evaluated the long-term outcomes (4697 mothers and 4832 children; study visits occurred between February 13, 2013, and December 13, 2016).

EXPOSURES Gestational diabetes was defined post hoc using criteria from the International Association of Diabetes and Pregnancy Study Groups consisting of 1 or more of the following 75-g oral glucose tolerance test results (fasting plasma glucose ≥92 mg/dL; 1-hour plasma glucose level ≥180 mg/dL; 2-hour plasma glucose level ≥153 mg/dL).

MAIN OUTCOMES AND MEASURES Primary maternal outcome: a disorder of glucose metabolism (composite of type 2 diabetes or prediabetes). Primary outcome for children: being overweight or obese; secondary outcomes: obesity, body fat percentage, waist circumference, and sum of skinfolds (>85th percentile for latter 3 outcomes).

RESULTS The analytic cohort included 4697 mothers (mean [SD] age, 41.7 [5.7] years) and 4832 children (mean [SD] age, 11.4 [1.2] years; 51.0% male). The median duration of follow-up was 11.4 years. The criteria for GD were met by 14.3% (672/4697) of mothers overall and by 14.1% (683/4832) of mothers of participating children. Among mothers with GD, 52.2% (346/663) developed a disorder of glucose metabolism vs 20.1% (791/3946) of mothers without GD (odds ratio [OR], 3.44 [95% CI, 2.85 to 4.14]; risk difference [RD], 25.7% [95% CI, 21.7% to 29.7%]). Among children of mothers with GD, 39.5% (269/681) were overweight or obese and 19.1% (130/681) were obese vs 28.6% (1172/4094) and 9.9% (405/4094), respectively, for children of mothers without GD. Adjusted for maternal body mass index during pregnancy, the OR was 1.21 (95% CI, 1.00 to 1.46) for children who were overweight or obese and the RD was 3.7% (95% CI, −0.16% to 7.5%); the OR was 1.58 (95% CI, 1.24 to 2.01) for children who were obese and the RD was 5.0% (95% CI, 2.0% to 8.0%); the OR was 1.35 (95% CI, 1.08 to 1.68) for body fat percentage and the RD was 4.2% (95% CI, 0.9% to 7.4%); the OR was 1.34 (95% CI, 1.08 to 1.67) for waist circumference and the RD was 4.1% (95% CI, 0.8% to 7.3%); and the OR was 1.57 (95% CI, 1.27 to 1.95) for sum of skinfolds and the RD was 6.5% (95% CI, 3.1% to 9.9%).

CONCLUSIONS AND RELEVANCE Among women with GD identified by contemporary criteria compared with those without it, GD was significantly associated with a higher maternal risk for a disorder of glucose metabolism during long-term follow-up after pregnancy. Among children of mothers with GD vs those without it, the difference in childhood overweight or obesity defined by body mass index cutoffs was not statistically significant; however, additional measures of childhood adiposity may be relevant in interpreting the study findings.

JAMA. 2018;320(10):1005-1016. doi:10.1001/jama.2018.11628

Supplemental content

CME Quiz at jamanetwork.com/learning

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The collaborator members of the HAPO Follow-up Study Cooperative Research Group are listed at the end of this article.

Corresponding Author: Boyd E. Metzger, MD, Northwestern University Feinberg School of Medicine, Endocrinology, 300 E Superior, Ste 12-703, Chicago, IL 60611 (bem@northwestern.edu).

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study recruited a large, multinational, racially and ethnically diverse cohort of women.[1] The HAPO Study demonstrated that pregnant women who had glucose levels during a 2-hour 75-g oral glucose tolerance test lower than those diagnostic of diabetes were associated with adverse pregnancy outcomes along a continuum.[1] Based on the HAPO Study and other studies, new criteria for the diagnosis of gestational diabetes were proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG)[2] and adopted by the World Health Organization and others.[3,4] The HAPO Follow-up Study examined associations of gestational diabetes (identified post hoc using the IADPSG criteria) with the long-term outcomes of mothers and children.

The Carpenter-Coustan criteria[5] are typically used to diagnose gestational diabetes in the United States. This stepwise screening approach begins with a 50-g glucose challenge test, then a 3-hour 100-g oral glucose tolerance test, and has glucose cutoffs similar to the IADPSG cutoffs. However, the Carpenter-Coustan criteria require 2 abnormal glucose values over 3 hours compared with 1 abnormal value required by the IADPSG criteria during a 2-hour 75-g oral glucose tolerance test. Approximately twice as many women are diagnosed with gestational diabetes using the IADPSG criteria compared with the Carpenter-Coustan criteria.[6] Whether women meeting the IADPSG criteria for gestational diabetes and their offspring are at risk for long-term adverse outcomes is unclear.

The primary objectives of this study were to assess whether in utero exposure to untreated gestational diabetes (defined post hoc using the IADPSG criteria) was associated with long-term risk of a disorder of glucose metabolism among mothers and greater adiposity among their children 10 to 14 years' postpartum.

Key Points

Question Is gestational diabetes diagnosed with contemporary criteria associated with long-term risks for a disorder of glucose metabolism in mothers and greater adiposity in children?

Findings In this international multiethnic cohort study of 4697 women and 4832 children followed up for a median of 11.4 years, gestational diabetes defined post hoc was significantly associated with maternal development of a disorder of glucose metabolism (composite of type 2 diabetes or prediabetes; odds ratio, 3.44). Gestational diabetes was not significantly associated with the composite outcome of childhood overweight or obesity.

Meaning Gestational diabetes defined by criteria that identify a larger group of women was associated with a maternal disorder of glucose metabolism.

Methods

The study protocol was approved by each center's institutional review board. Mothers gave written informed consent and, at sites that required it, children assented. An external observational study monitoring board oversaw the study. The HAPO Study was a population-based study and women underwent a 75-g oral glucose tolerance test at approximately 28 weeks' gestation as described.[1] Fasting plasma glucose level and 1-hour and 2-hour plasma glucose levels were measured.

Results for the oral glucose tolerance test were not known by the caregivers or the participants unless (1) the fasting plasma glucose level was greater than 105 mg/dL (>5.8 mmol/L), (2) the 2-hour plasma glucose level was greater than 200 mg/dL (>11.1 mmol/L), (3) both of these occurred, (4) either measure yielded a plasma glucose level of less than 45 mg/dL (<2.5 mmol/L), or (5) at 34 to 37 weeks' gestation, the random plasma glucose level was 160 mg/dL or greater (≥8.9 mmol/L).[1]

A total of 427 participants (1.8%) were informed of their results based on reaching the fasting plasma glucose level threshold, the 2-hour plasma glucose threshold, or both. The remaining participants were not treated because they did not meet any of these criteria and they were not informed of their glucose tolerance test results.

Height, weight, and blood pressure were measured using standard procedures. Demographic and lifestyle characteristics were collected via questionnaire and parity via medical record abstraction. The HAPO Study included women from multiple racial/ethnic groups according to self-report using prespecified categories to describe the study population, ensure broad applicability of the results, and adjust for potential confounding by race/ethnicity due to differences in gestational diabetes or outcome frequencies if not sufficiently modeled by study site (field center).

Participants

The participants for this study were examined between February 13, 2013, and December 13, 2016, at 10 of 15 field centers based on demonstration of feasibility by the field center to recontact and recruit participants. Eligibility criteria included: (1) remaining blind to the results of the oral glucose tolerance test, (2) gestational age at delivery of 37 weeks or greater, and (3) having no major fetal or neonatal malformations or death.

Multiple attempts were made to contact eligible participants through various means approved by local institutional review boards. Screening questionnaires were completed by eligible mothers by telephone to ascertain willingness to participate and confirm eligibility.

Study Visit

During the study visit (additional details appear in eFigures 1 and 2 in the Supplement), height was measured twice without shoes to the nearest 0.5 cm with a stadiometer (if results differed by >1.0 cm, height was measured a third time). Similarly, weight was measured twice using a calibrated scale to the nearest 0.1 kg and again if results differed by more than 0.5 kg. Waist circumference was measured twice at the iliac crest to the nearest 0.1 cm and again if results differed by more than 1.0 cm.

Skin folds (triceps, subscapular, suprailiac) were measured twice with calibrated calipers (Harpenden) to the nearest 0.1 mm (if results differed by >1.0 mm, they were measured a third time). Body fat percentage was measured by air displacement plethysmography (BOD POD; Cosmed). Blood pressure was measured using a calibrated electronic device (Omron 705) 3 times after sitting for 5 minutes with 1-minute to 2-minute intervals between measurements. The mean of the second and third blood pressure measurements was used for the analysis.

In children, Tanner staging was performed by trained individuals using breast or areolar development or testicular volume (Prader orchidometer). The mothers provided their daughter's menstrual status via questionnaire.

The mothers underwent a 2-hour 75-g oral glucose tolerance test following an 8-hour overnight fast. Nonfasting blood samples were obtained from participants who reported having diabetes that was being treated with oral medication or insulin. The blood samples were processed and stored at −80°C at the field center until shipment to the central laboratory. The 11 mothers who reported being positive for HIV or having hepatitis B or C did not have their blood sampled.

Age, race/ethnicity, family history of diabetes in first-degree relatives, the number of subsequent pregnancies since the HAPO Study, smoking status, and alcohol consumption were collected by questionnaire.

Laboratory Measurements

Glucose was measured at the clinical chemistry laboratory of Northwestern Memorial Hospital using Beckman-Coulter SYNCHRON LX analyzers. Blinded duplicate samples were assayed several weeks apart and coefficients of variation were calculated within pairs for a random subset of 10%. The mean coefficient of variation was 1.4% for fasting plasma glucose and 1.5% for 2-hour plasma glucose. To exclude type 1 diabetes, serum anti-GAD65, serum anti-insulin, serum anti-ZnT8, and serum anti-IA-2 antibodies were measured at the Barbara Davis Center for all mothers with self-reported treated diabetes or with a new diagnosis of diabetes.

Primary and Secondary Outcomes

The primary maternal outcome was a disorder of glucose metabolism (composite of type 2 diabetes or prediabetes), with prediabetes based on an impaired plasma fasting glucose level, an impaired glucose tolerance test result, or both. Type 2 diabetes and prediabetes also were examined individually as prespecified secondary outcomes. Type 2 diabetes was determined by self-reported treated diabetes or fasting plasma glucose level of 126 mg/dL or greater (≥7.0 mmol/L), 2-hour plasma glucose level of 200 mg/dL or greater (≥11.1 mmol/L), or both, during the oral glucose tolerance test at the study visit. There were 4 mothers with diabetes who were excluded based on antibodies consistent with type 1 diabetes.[7] Prediabetes was defined as a fasting plasma glucose level between 100 and 125 mg/dL (5.6-6.9 mmol/L), a 2-hour plasma glucose level between 140 and 199 mg/dL (7.8-11.0 mmol/L), or both.[8]

The primary outcome for children of being overweight or obese was defined by age- and sex-specific body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) cutoffs from the International Obesity Task Force (IOTF) and using Asian-specific cutoffs for Asian children and international cutoffs for all others.[9] Prespecified secondary adiposity outcomes were examined to evaluate the robustness of the primary outcome results for children and included IOTF-defined obesity and body fat percentage, waist circumference, and sum of skinfolds (>85th percentile for latter 3 outcomes). The 85th percentiles were estimated by quantile regression in the HAPO Follow-up Study data set and were adjusted for age, sex, and field center. Body mass index, body fat percentage, waist circumference, and sum of skinfolds also were assessed as continuous outcomes.

Primary Independent Variable

The primary independent variable was gestational diabetes during the pregnancy while enrolled in the HAPO Study, defined post hoc using IADPSG criteria and consists of 1 or more of the following 75-g oral glucose tolerance test results: fasting plasma glucose level of 92 mg/dL or greater (≥5.1 mmol/L), 1-hour plasma glucose level of 180 mg/dL or greater (≥10.0 mmol/L), 2-hour plasma glucose level of 153 mg/dL or greater (≥8.5 mmol/L).[2]

Statistical Analyses

This study was powered to detect associations of gestational diabetes with childhood measures of adiposity during 10 to 14 years of follow-up. A target sample size of 7000 mother-child pairs was specified, anticipating 300 mother-child pairs at the Chicago, Illinois, and Cleveland, Ohio, field centers and 800 mother-child pairs at the other field centers. Based on the results of the HAPO Study, it was assumed that 16% of participating mothers would have had gestational diabetes using the IADPSG criteria.

Estimating that 25% of children of mothers without gestational diabetes would be overweight or obese, a sample size of 5632 was required to detect an odds ratio (OR) of 1.30 with 90% power for a 2-sided type I error rate of 5%.[10-12] Correlation between gestational diabetes and other model variables[13] observed in the HAPO Study and anticipated for the follow-up study motivated a 10% increase in the planned sample size.

Therefore, based on inclusion of the variables in this study, the total sample size was estimated at 6195. However, due to the uncertainty regarding the frequency of overweight or obesity, the recruitment goal was set as 7000 mother-child pairs. The study was not powered to examine sex-specific associations.

The statistical power for maternal outcomes was evaluated a priori. For the least frequent outcome of type 2 diabetes,[14] the conservative estimate that 2.5% of women with gestational diabetes and 1% of women without gestational diabetes would develop type 2 diabetes yielded an OR of 2.54 and required a sample size of 6156 for 90% power at a 2-sided type I error rate of 5%. A 10% increase in the sample size to account for the correlation between gestational diabetes and other model variables indicated a sample size of 6772, which confirmed 7000 as the recruitment goal.

Data were summarized using frequencies and counts for categorical variables and means and standard deviations for continuous variables. All data were compared by maternal gestational diabetes status. The summary statistics during pregnancy were compared for eligible mothers and for mothers of eligible children who did or did not participate with weighted summaries for nonparticipants to account for varying participation rates at field centers. Histograms and box plots were examined to determine the shape of the distributions and to identify potential outliers. Multiple logistic regression was used to estimate the ORs and 95% CIs for dichotomous outcomes and modified least-squares regression with Huber-White robust standard errors was used to estimate risk differences with 95% CIs.[15]

Multiple linear regression was used for continuous outcomes to estimate the adjusted mean differences with 95% CIs. Two-sided $P < .05$ was used for evaluating statistical significance for the primary outcomes of a disorder of glucose metabolism among mothers and overweight or obesity among children.

In a post hoc analysis, the Bonferroni correction was applied to take into account the multiple comparisons involved in evaluating the secondary outcomes; therefore, $P < .025$ was used for evaluating statistical significance for the 2 secondary outcomes in mothers and $P < .0125$ was used for the 4 secondary outcomes in children. The statistical analyses were conducted using R version 3.4.1 (R Foundation for Statistical Computing).[16]

Multiple models were considered for all outcomes and the independent variables were identified according to the study design, known potential confounders, and the adjustments used for the analyses in the HAPO Study.[1] Colinearity was evaluated using pairwise correlations. Logistic regression model fit was measured using the C statistic and confirmed by the Hosmer-Lemeshow goodness-of-fit test.[17] Linear regression model fit was assessed by scatter plots of residuals vs fitted values, histograms and qqplots of residuals, and DFbeta statistics. Adjusted R^2 values were used to gauge variability explained in linear models.

Maternal Outcomes

For the maternal outcomes, the covariate adjustments made by model were as follows for model 1: field center; model 2: model 1 plus the following maternal variables at oral glucose tolerance test during pregnancy: age, height, BMI, family history of diabetes in first-degree relatives, mean arterial pressure, smoking status (yes or no), alcohol consumption (yes or no), parity (0, ≥1), and gestational age; model 3: model 1 plus 2 of the maternal variables at oral glucose tolerance test during pregnancy from model 2 (parity [0, ≥1] and gestational age), plus maternal variables at follow-up (age, height, BMI, family history of diabetes in first-degree relatives, mean arterial pressure, smoking status [yes or no]), alcohol consumption [yes or no]), and the No. of pregnancies subsequent to birth during the HAPO Study (child 0, 1, ≥2).

Outcomes for Children

For the outcomes of the children, the covariate adjustments made by model were as follows for model 1: age, sex, and field center; model 2: model 1 plus child pubertal status (Tanner stage 1, 2/3, 4/5 and sex × Tanner stage interaction); model 3: model 2 plus the maternal variables at oral glucose tolerance test during pregnancy of age, height, family history of diabetes in first-degree relatives, mean arterial pressure, parity (0, ≥1), smoking status (yes or no), alcohol consumption (yes or no), and gestational age; model 4: model 3 plus maternal BMI at oral glucose tolerance test during pregnancy.

For the overweight or obesity outcome and the obesity outcome, which were defined using the IOTF criteria with sex- and age-specific definitions, adjustment was made for field center only in model 1. For the outcomes of body fat percentage, waist circumference, and sum of skinfolds (>85th percentile for each outcome), model 1 was unadjusted because the 85th percentiles included age, sex, and field center in their definition.

Multiple Imputation and Exploratory Analyses

Multiple imputation under a missing at random assumption[18,19] using the Mice R package[20] was used in the analyses to model the outcomes for children to account for missing data for Tanner stage and included measured levels of estradiol, testosterone, and serum hormone-binding globulin (additional details appear in the eMethods in the Supplement). Exploratory analyses were conducted using χ^2 tests to evaluate unadjusted associations between gestational diabetes defined by the Carpenter-Coustan criteria vs the IADPSG criteria and outcome frequencies.

Results

Participants

Of 15 812 eligible mother-child pairs (eTable 1 in the Supplement), 9322 were screened to confirm eligibility and willingness to participate. From these, 4834 children and 4747 mothers completed all or part of the study visit, representing 69.1% and 67.8% of the 7000 target, respectively (eFigures 3 and 4 in the Supplement).

One child was excluded for inadequate fasting and another child for inability to complete the protocol due to autism, leaving 4832 children (mean [SD] age, 11.4 [1.2] years; 51.0% male) for the analyses. Of these, 4821 had at least 1 physical measurement and 4775 had BMI measurements that were analyzed to determine overweight or obesity status.

Data from 49 mothers were excluded for previous bariatric surgery and from another mother for cancer treatment, leaving 4697 mothers (mean [SD] age, 41.7 [5.7] years) for the analyses. Of these, 4609 had glucose measurements or self-reported treated type 2 diabetes and were included in the analyses for the maternal glucose outcomes. The median duration of follow-up was 11.4 years (interquartile range, 10.6-12.2 years).

For participating mothers and children whose data were analyzed, missing data ranged from 0% to 1.5% for model variables, and most variables had complete data (100%). Only Tanner stage had substantial missingness; 15.2% of girls and 36.3% of boys lacked a trained assessment.

The characteristics of participating mothers overall and by gestational diabetes status appear in **Table 1** (data for race/ethnicity by field center appear in eTables 2 and 3 in the Supplement). Overall, 14.3% (672/4697) of participating mothers had gestational diabetes, which was lower than the 16% anticipated during study planning. For the 672 participating mothers with gestational diabetes, 345 (51.3%) met fasting plasma glucose level criteria, 344 (51.2%) met 1-hour plasma glucose level criteria, and 239 (35.6%) met 2-hour plasma glucose level criteria. The characteristics of the participating children also appear in Table 1.

The characteristics of the mothers (during the HAPO Study) of the participating children in the follow-up study appear in eTable 4 in the Supplement. At the oral glucose tolerance test during the HAPO Study pregnancy, mothers with gestational diabetes were older, weighed more, and had higher BMIs, mean arterial pressures, and glucose concentrations compared with mothers without gestational diabetes.

At the follow-up study visit, mothers with gestational diabetes had higher BMIs and more frequent family histories of diabetes in first-degree relatives. The BMIs of mothers in both groups during this follow-up study were similar to their BMIs during the original HAPO Study visit at 28 weeks' gestation, suggesting weight gain subsequent to the pregnancy during the HAPO Study. The offspring of all mothers in the study were of similar age and height at follow-up; however, the offspring of mothers with gestational diabetes were heavier than the offspring of mothers without gestational diabetes.

Among women who participated in this follow-up study, the mean age during the HAPO Study was 30.1 years and the frequency of gestational diabetes was 14.3% compared with 29.1 years and 16.3%, respectively, among those women who did not participate (unable to contact or declined) (Table 1). The mean age of the mothers of the children who participated in the follow-up study was 29.9 years and the frequency of gestational diabetes was 14.1% (683 of 4832 mothers) compared with 29.1 years and 16.4%, respectively, among mothers of the children who did not participate (eTable 4 in the Supplement). The mean BMI, fasting plasma glucose level, 1-hour plasma glucose level, and 2-hour plasma glucose level during the HAPO Study oral glucose tolerance test and race/ethnicity were similar between groups.

Model Diagnostics

The Hosmer-Lemeshow *P* values for the logistic regression models ranged from .35 to .99 for the outcomes of mothers and .13 to .99 for the outcomes of children, indicating reasonable model fit. Colinearity was not a concern because the pairwise correlations ranged from 0 to 0.20 for the model covariates. Residual plots confirmed linear modeling assumptions and DFbeta statistics indicated no observations of undue influence.

The C statistics for the logistic regression models ranged from 0.61 to 0.86 for the outcomes of mothers and increased across models 1 through 3, suggesting better model fit for the outcomes of mothers with covariate adjustments.

The C statistics were lowest for model 1 for the outcomes of children (as low as 0.50). The model fit improved for models 2 and 3 for the outcomes of children, with the highest C statistics ranging from 0.68 to 0.74 in model 4. The R^2 values ranged from 0.05 to 0.28 for continuous outcomes for children and increased across models 1 through 4, suggesting improved fit for the adjusted models.

Gestational Diabetes Status and Maternal Outcomes

Primary Outcome

The data for the association of gestational diabetes with a maternal disorder of glucose metabolism at follow-up appear in **Table 2.** Overall, 52.2% (346/663) of mothers with gestational diabetes developed a disorder of glucose metabolism compared with 20.1% (791/3946) of mothers without gestational diabetes. The OR was 3.57 (95% CI, 2.98-4.29) for model 2. The OR was 3.44 (95% CI, 2.85-4.14) for model 3, which adjusted for maternal variables at follow-up, and the risk difference was 25.7% (95% CI, 21.7%-29.7%). These differences were consistent with higher outcome frequencies among mothers with gestational diabetes.

Secondary Outcomes

The secondary maternal outcomes included type 2 diabetes and prediabetes assessed using criteria from the American Diabetes Association at follow-up. A total of 134 women had type 2 diabetes; 43 self-reported type 2 diabetes and were receiving treatment and 91 were newly diagnosed at the follow-up study visit. Of 4475 mothers without type 2 diabetes and with sufficient blood sampling for analysis, 1003 had prediabetes.

Among mothers with gestational diabetes, 10.7% (71/663) had type 2 diabetes and 41.5% (275/663) had prediabetes compared with 1.6% (63/3946) and 18.4% (728/3946), respectively, among mothers without gestational diabetes. The observed frequencies for type 2 diabetes were higher than the estimate of 2.5% used in sample size calculations among mothers with gestational diabetes and the estimate of 1% among mothers without gestational diabetes.

For type 2 diabetes, the OR was 5.38 (95% CI, 3.68-7.86) for model 2 and the OR was 5.44 (95% CI, 3.68-8.08) for model 3. For prediabetes, the OR was 3.18 (95% CI, 2.63-3.85) for model 2 and the OR was 3.07 (95% CI, 2.53-3.73) for model 3. The risk differences were consistent and there were higher outcome frequencies among mothers with gestational diabetes for model 3 (type 2 diabetes: 7.3% [95% CI, 5.0%-9.6%]; prediabetes: 22.8% [95% CI, 18.6%-27.0%]).

Gestational Diabetes Status and Outcomes for Children

Primary Outcome

Among children whose mothers had gestational diabetes, 39.5% (269/681) were overweight or obese compared with 28.6% (1172/4094) of children whose mothers did not have gestational diabetes (**Table 3**). These percentages were higher than the estimates used for study planning. Gestational diabetes was positively associated with childhood overweight or obesity (model 1), with slight attenuation after adjusting for Tanner stage and maternal variables during pregnancy (models 2 and 3) (Table 3). In model 4, after adjustment for maternal BMI during pregnancy, the association with

Table 1. Participant and Nonparticipant Characteristics During the HAPO Study and the Follow-up Study

Characteristic	All Participants	Mother With Gestational Diabetes[a]	Mother Without Gestational Diabetes	Nonparticipants[b]
Mothers During HAPO Study				
Mothers, No. (%)	4697 (100)	672 (14.3)	4025 (85.7)	11 115[c]
Age at oral glucose tolerance test, mean (SD), y	30.1 (5.6)	31.9 (5.3)	29.8 (5.6)	29.1 (5.3)
Height, mean (SD), cm	161.7 (6.8)	161.0 (7.0)	161.8 (6.8)	161.5 (6.3)
Weight, mean (SD), kg	71.7 (13.7)	77.1 (15.1)	70.9 (13.3)	72.0 (13.5)
Body mass index, mean (SD)[d]	27.4 (4.8)	29.7 (5.2)	27.0 (4.6)	27.6 (4.8)
Mean arterial pressure, mean (SD), mm Hg	80.4 (7.9)	83.4 (7.7)	79.9 (7.9)	80.8 (7.8)
Fasting plasma glucose level, mean (SD), mg/dL	81.0 (6.6)	88.9 (7.6)	79.7 (5.4)	81.3 (6.5)
1-h plasma glucose level, mean (SD), mg/dL	133.3 (30.2)	173.0 (28.8)	126.7 (24.9)	133.1 (29.9)
2-h plasma glucose level, mean (SD), mg/dL	110.5 (23.1)	137.2 (26.7)	106.1 (19.1)	110.7 (22.7)
Gestational age at oral glucose tolerance test, mean (SD), wk	27.7 (1.7)	27.9 (1.7)	27.7 (1.7)	27.8 (1.5)
Race/ethnicity, No. (%)				
Non-Hispanic white	2213 (47.1)	270 (40.2)	1943 (48.3)	46.8[e]
Hispanic	488 (10.4)	108 (16.1)	380 (9.4)	9.6[e]
Non-Hispanic black	735 (15.6)	82 (12.2)	653 (16.2)	15.5[e]
Asian	1174 (25.0)	196 (29.2)	978 (24.3)	25.7[e]
Other[f]	87 (1.9)	16 (2.4)	71 (1.8)	2.5[e]
Prenatal alcohol consumption, No. (%)	243 (5.2)	42 (6.2)	201 (5.0)	6.7[e]
Prenatal smoker, No. (%)	402 (8.6)	56 (8.3)	346 (8.6)	8.2[e]
Parity (any prior delivery ≥20 wk), No. (%)	2422 (51.6)	383 (57.0)	2039 (50.7)	49.6[e]
Family history of diabetes, No. (%)	1057 (22.5)	203 (30.2)	854 (21.2)	21.3[e]
Family history of hypertension, No. (%)	1802 (38.4)	287 (42.7)	1515 (37.6)	36.6[e]
Mothers During HAPO Follow-up Study				
Age, mean (SD), y	41.7 (5.7)	43.6 (5.4)	41.4 (5.7)	
Height, mean (SD), cm	161.6 (6.5)	160.6 (6.8)	161.7 (6.5)	
Weight, mean (SD), kg	70.6 (17.0)	74.7 (18.0)	69.9 (16.8)	
Body mass index, mean (SD)[d]	27.0 (6.2)	28.9 (6.5)	26.7 (6.0)	
Fasting plasma glucose level, mean (SD), mg/dL	92.2 (12.6)	99.1 (22.2)	91.0 (9.8)	
2-h plasma glucose level, mean (SD), mg/dL	113.5 (35.8)	134.8 (52.5)	110.1 (30.9)	
Family history of diabetes, No. (%)	1981 (42.2)	362 (53.9)	1619 (40.2)	
Family history of hypertension, No. (%)	3175 (67.6)	476 (70.8)	2699 (67.1)	
Children During HAPO Follow-up Study				
Children, No. (%)	4832 (100)	683 (14.1)	4149 (85.9)	
Age, mean (SD), y	11.4 (1.2)	11.5 (1.2)	11.4 (1.2)	
Height, mean (SD), cm	148.6 (10.2)	149.4 (9.8)	148.4 (10.3)	
Weight, mean (SD), kg	43.2 (13.3)	45.9 (14.2)	42.8 (13.1)	
Male sex, No. (%)	2465 (51.0)	361 (52.9)	2104 (50.7)	
Tanner stage for girls, No. (%)[g]				
1	381 (19.0)	48 (17.1)	333 (19.3)	
2/3	853 (42.5)	123 (43.9)	730 (42.2)	
4/5	774 (38.5)	109 (38.9)	665 (38.5)	
Tanner stage for boys, No. (%)[g]				
1	565 (36.0)	70 (30.7)	495 (36.9)	
2/3	726 (46.2)	111 (48.7)	615 (45.8)	
4/5	279 (17.8)	47 (20.6)	232 (17.3)	

Abbreviation: HAPO, Hyperglycemia and Adverse Pregnancy Outcome.

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

[a] Defined by International Association of Diabetes and Pregnancy Study Groups criteria as ≥1 of the following results from a 75-g oral glucose tolerance test (1) ≥92 mg/dL for fasting plasma glucose level, (2) ≥180 mg/dL for 1-hour plasma glucose level, or (3) ≥153 mg/dL for 2-hour plasma glucose level.

[b] Weighted by the number of participants at each field center.

[c] Of this cohort, 16.3% had gestational diabetes.

[d] Calculated as weight in kilograms divided by height in meters squared.

[e] These are weighted percentages.

[f] Included Native American/Alaskan Native at US field centers, First Nation in Toronto, Ontario, Canada, and self-identified as other at all field centers.

[g] Assesses pubertal status; a higher stage number represents greater physical maturity.

Table 2. Association of Gestational Diabetes With Maternal Glucose Outcomes in Follow-up Study

Model	No. of Mothers/Total No. (%)[a]		Risk Difference, % (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	C Statistic
	Mother With Gestational Diabetes	Mother Without Gestational Diabetes					
Primary Maternal Outcome: A Disorder of Glucose Metabolism							
Composite of type 2 diabetes or prediabetes[b]	346/663 (52.2)	791/3946 (20.1)					
Model 1[c]			31.7 (27.7-35.7)	<.001	4.33 (3.64-5.16)	<.001	0.62
Model 2[d]			27.3 (23.3-31.4)	<.001	3.57 (2.98-4.29)	<.001	0.71
Model 3[e]			25.7 (21.7-29.7)	<.001	3.44 (2.85-4.14)	<.001	0.74
Secondary Maternal Glucose Outcomes[f]							
Type 2 diabetes[b]	71/663 (10.7)	63/3946 (1.6)					
Model 1[c]			9.1 (6.7-11.5)	<.001	7.63 (5.33-10.95)	<.001	0.73
Model 2[d]			7.8 (5.5-10.1)	<.001	5.38 (3.68-7.86)	<.001	0.82
Model 3[e]			7.3 (5.0-9.6)	<.001	5.44 (3.68-8.08)	<.001	0.86
Prediabetes[b]	275/663 (41.5)	728/3946 (18.4)					
Model 1[c]			27.2 (23.0-31.4)	<.001	3.72 (3.09-4.47)	<.001	0.61
Model 2[d]			24.0 (19.7-28.2)	<.001	3.18 (2.63-3.85)	<.001	0.69
Model 3[e]			22.8 (18.6-27.0)	<.001	3.07 (2.53-3.73)	<.001	0.72

[a] International Association of Diabetes and Pregnancy Study Groups criteria were used to identify gestational diabetes post hoc. American Diabetes Association criteria were used to identify prediabetes and a disorder of glucose metabolism during follow-up.

[b] Type 2 diabetes was defined as self-reported diabetes or fasting plasma glucose level of 126 mg/dL or greater, 2-hour glucose level of 200 mg/dL or greater, or having both of these. Prediabetes was defined as fasting plasma glucose level between 100 and 125 mg/dL, 2-hour plasma glucose between 140 and 199 mg/dL, or having both of these.

[c] Adjusted for field center.

[d] Adjusted for model 1 plus the following maternal variables at oral glucose tolerance test during pregnancy: age, height, body mass index, family history of diabetes in first-degree relatives, mean arterial pressure, smoking status (yes or no), alcohol consumption (yes or no), parity (0, ≥1), and gestational age.

[e] Adjusted for model 1, plus 2 of the maternal variables at oral glucose tolerance test during pregnancy from model 2 (parity [0, ≥1] and gestational age), plus maternal variables at follow-up (age, height, body mass index, family history of diabetes in first-degree relatives, mean arterial pressure, smoking status [yes or no]), alcohol consumption [yes or no]), and the No. of pregnancies subsequent to birth during the Hyperglycemia and Adverse Pregnancy Outcome study (child 0, 1, ≥2).

[f] $P < .025$ was used for evaluating statistical significance for the 2 secondary outcomes in mothers.

overweight or obesity was no longer statistically significant (OR, 1.21 [95% CI, 1.00 to 1.46]; risk difference, 3.7% [95% CI, −0.16% to 7.5%]).

Secondary Outcomes

Among children whose mothers had gestational diabetes, 19.1% (130/681) were obese compared with 9.9% (405/4094) of children whose mothers did not have gestational diabetes. A higher percentage of offspring of mothers who had gestational diabetes had values for body fat percentage, waist circumference, and sum of skinfolds that were in the 85th percentile or greater.

Gestational diabetes was positively associated with these outcomes (model 1), with slight attenuation after adjusting for Tanner stage and maternal variables during pregnancy (models 2 and 3) (Table 3). In model 4 (fully adjusted model), the OR was 1.58 (95% CI, 1.24-2.01) and the risk difference was 5.0% (95% CI, 2.0%-8.0%) for obesity; the OR was 1.35 (95% CI, 1.08-1.68) and the risk difference was 4.2% (95% CI, 0.9%-7.4%) for body fat percentage; the OR was 1.34 (95% CI, 1.08-1.67) and the risk difference was 4.1% (95% CI, 0.8%-7.3%) for waist circumference; and the OR was 1.57 (95% CI, 1.27-1.95) and the risk difference was 6.5% (95% CI, 3.1%-9.9%) for the sum of skinfolds (>85th percentile for latter 3 outcomes).

Compared with the offspring of mothers without gestational diabetes, the offspring of mothers with gestational diabetes had higher BMIs, body fat percentages, waist circumferences, and sum of skinfolds. The adjusted mean differences for the continuous measures of child adiposity were significantly higher in models 1 through 3 among children of mothers with gestational diabetes compared with children of mothers without gestational diabetes (Table 3).

In model 4, these differences were attenuated after adjusting for maternal BMI during pregnancy; however, all variables except BMI remained significant. The adjusted mean differences among the offspring of mothers with gestational diabetes vs the offspring of mothers without gestational diabetes were 0.26 (95% CI, −0.06 to 0.57) for BMI, 1.05 (95% CI, 0.24 to 1.85) for body fat percentage, 1.28 (95% CI, 0.43 to 2.14) cm for waist circumference, and 2.52 (95% CI, 0.82 to 4.22) mm for sum of skinfolds.

IADPSG vs Carpenter-Coustan Criteria for Gestational Diabetes

The diagnosis of gestational diabetes using the Carpenter-Coustan criteria requires 2 abnormal glucose values: a fasting plasma glucose level greater than 95 mg/dL, a 1-hour plasma glucose level greater than 180 mg/dL, a 2-hour plasma glucose level greater than 155 mg/dL, or a 3-hour plasma glucose level greater than 140 mg/dL. This study was not designed to compare women with vs without gestational diabetes defined by the Carpenter-Coustan criteria.

Table 3. Association of Gestational Diabetes With Measures of Adiposity Among Children in Follow-up Study

Model	No. of Children/Total No. (%)		Risk Difference, % (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value	C Statistic	Mean (SD)		Adjusted Mean Difference (95% CI)	*P* Value	Adjusted R^2
	Mother With Gestational Diabetes[a]	Mother Without Gestational Diabetes						Mother With Gestational Diabetes[a]	Mother Without Gestational Diabetes			
Primary Outcome for Children												
Overweight or obesity[b]	269/681 (39.5)	1172/4094 (28.6)										
Model 1[c]			8.9 (5.0 to 12.8)	<.001	1.51 (1.27 to 1.80)	<.001	0.59					
Model 2[d]			9.0 (5.2 to 12.8)	<.001	1.53 (1.28 to 1.83)	<.001	0.66					
Model 3[e]			7.5 (3.7 to 11.4)	<.001	1.44 (1.20 to 1.72)	<.001	0.69					
Model 4[f]			3.7 (−0.16 to 7.5)	.06	1.21 (1.00 to 1.46)	.05	0.74					
Secondary Outcomes for Children[g]												
Obesity[b]	130/681 (19.1)	405/4094 (9.9)						20.3 (4.7)[h]	19.1 (4.2)[h]			
Model 1[c]			7.9 (4.9 to 11.0)	<.001	1.96 (1.56 to 2.44)	<.001	0.64			0.88 (0.54 to 1.21)[h]	<.001	0.12
Model 2[d]			8.1 (5.1 to 11.1)	<.001	1.98 (1.58 to 2.49)	<.001	0.70			0.89 (0.57 to 1.22)[h]	<.001	0.17
Model 3[e]			7.2 (4.2 to 10.3)	<.001	1.84 (1.46 to 2.33)	<.001	0.73			0.72 (0.39 to 1.05)[h]	<.001	0.19
Model 4[f]			5.0 (2.0 to 8.0)	.001	1.58 (1.24 to 2.01)	<.001	0.78			0.26 (−0.06 to 0.57)[h]	.11	0.27
Body fat %[i,j]	145/669 (21.7)	553/3989 (13.9)						23.8 (11.2)	20.7 (10.3)			
Model 1[k]			7.8 (4.5 to 11.1)	<.001	1.72 (1.40 to 2.11)	<.001	0.50			2.31 (1.48 to 3.14)	<.001	0.08
Model 2[d]			7.6 (4.3 to 10.8)	<.001	1.71 (1.39 to 2.11)	<.001	0.54			2.31 (1.50 to 3.12)	<.001	0.12
Model 3[e]			6.4 (3.1 to 9.7)	<.001	1.57 (1.27 to 1.95)	<.001	0.64			1.90 (1.08 to 2.72)	<.001	0.14
Model 4[f]			4.2 (0.9 to 7.4)	.01	1.35 (1.08 to 1.68)	.007	0.68			1.05 (0.24 to 1.85)	.01	0.18
Waist circumference[j]	147/679 (21.7)	571/4113 (13.9)						73.2 (13.1)[l]	69.8 (11.7)[l]			
Model 1[k]			7.8 (4.5 to 11.0)	<.001	1.71 (1.40 to 2.09)	<.001	0.50			2.87 (1.98 to 3.77)[l]	<.001	0.16
Model 2[d]			7.8 (4.6 to 11.0)	<.001	1.72 (1.40 to 2.11)	<.001	0.54			2.87 (1.99 to 3.74)[l]	<.001	0.20
Model 3[e]			6.5 (3.2 to 9.8)	<.001	1.58 (1.28 to 1.96)	<.001	0.64			2.40 (1.51 to 3.28)[l]	<.001	0.22
Model 4[f]			4.1 (0.8 to 7.3)	.02	1.34 (1.08 to 1.67)	.009	0.69			1.28 (0.43 to 2.14)[l]	.003	0.28
Sum of skinfolds[j]	153/664 (23.0)	553/4039 (13.7)						44.0 (23.8)[m]	38.4 (20.9)[m]			
Model 1[k]			9.4 (6.0 to 12.7)	<.001	1.89 (1.54 to 2.30)	<.001	0.50			4.76 (3.03 to 6.49)[m]	<.001	0.05
Model 2[d]			9.7 (6.3 to 13.0)	<.001	1.94 (1.58 to 2.37)	<.001	0.53			5.16 (3.45 to 6.88)[m]	<.001	0.08
Model 3[e]			8.7 (5.3 to 12.1)	<.001	1.80 (1.46 to 2.23)	<.001	0.64			4.34 (2.60 to 6.08)[m]	<.001	0.10
Model 4[f]			6.5 (3.1 to 9.9)	<.001	1.57 (1.27 to 1.95)	<.001	0.68			2.52 (0.82 to 4.22)[m]	.004	0.15

[a] Defined by International Association of Diabetes and Pregnancy Study Groups criteria as ≥1 of the following results from a 75-g oral glucose tolerance test (1) ≥92 mg/dL for fasting plasma glucose level, (2) ≥180 mg/dL for 1-hour plasma glucose level, or (3) ≥153 mg/dL for 2-hour plasma glucose level.

[b] Used International Obesity Task Force definition with body mass index–based cutoffs specific to sex and the child's age in months.

[c] Adjusted for field center only because the International Obesity Task Force included age and sex in the definition.

[d] Adjusted for model 1 plus child pubertal status (Tanner stage 1, 2/3, 4/5 and sex × Tanner stage interaction).

[e] Adjusted for model 2 plus the following maternal variables at oral glucose tolerance test during pregnancy: age, height, family history of diabetes in first-degree relatives, mean arterial pressure, parity (0, ≥1), smoking status (yes or no), alcohol consumption (yes or no), and gestational age.

[f] Adjusted for model 3 plus maternal body mass index at oral glucose tolerance test during pregnancy.

[g] $P < .0125$ was used for evaluating statistical significance for the secondary adiposity outcomes in children.

[h] These data are for body mass index, which was calculated as weight in kilograms divided by height in meters squared.

[i] Assessed by air displacement plethysmography using the BOD POD (Cosmed).

[j] Outcome ranked as being >85th percentile. The percentile was determined using quantile regression that was adjusted for age, sex, and field center.

[k] Unadjusted because the 85th percentiles included age, sex, and field center in their definition.

[l] These data are for the waist circumference (measured at the iliac crest) and are expressed in centimeters.

[m] These data are expressed in millimeters.

Table 4. Exploratory Analyses of Outcome Frequencies[a]

	No./Total No. (%)		
	Mothers With Gestational Diabetes		
	Defined Using IADPSG Criteria[b]	Defined Using Carpenter-Coustan Criteria[6,c]	Mothers Without Gestational Diabetes
Glucose Outcomes for Mothers			
Prediabetes[d]	200/508 (39.4)	75/155 (48.4)	728/3945 (18.5)
Type 2 diabetes[e]	40/508 (7.9)	31/155 (20.0)	63/3945 (1.6)
Disorder of glucose metabolism[d,e]	240/508 (47.2)	106/155 (68.4)	791/3945 (20.0)
Adiposity Outcomes for Children			
Overweight or obesity[f]	192/522 (36.8)	77/159 (48.4)	1172/4094 (28.6)
Obesity[f]	91/522 (17.4)	39/159 (24.5)	405/4095 (9.9)
Body fat % >85th percentile[g,h]	100/511 (19.6)	45/158 (28.5)	553/3990 (13.9)
Waist circumference >85th percentile[h]	108/519 (20.8)	39/160 (24.4)	571/4114 (13.9)
Sum of skinfolds >85th percentile[h]	110/510 (21.6)	43/154 (27.9)	553/4039 (13.7)

[a] All χ^2_2 tests for the post hoc evaluations of the outcomes across the 3 groups yielded $P < .001$ for all outcomes.

[b] The International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria are ≥1 of the following results from a 75-g oral glucose tolerance test (1) ≥92 mg/dL for fasting plasma glucose level, (2) ≥180 mg/dL for 1-hour plasma glucose level, or (3) ≥153 mg/dL for 2-hour plasma glucose level.

[c] Requires 2 abnormal glucose values: a fasting plasma glucose level >95 mg/dL, a 1-hour plasma glucose level >180 mg/dL, a 2-hour plasma glucose level >155 mg/dL, or a 3-hour plasma glucose level >140 mg/dL.

[d] Defined as fasting plasma glucose level between 100 and 125 mg/dL, 2-hour plasma glucose between 140 and 199 mg/dL, or having both of these.

[e] Defined as self-reported diabetes or fasting plasma glucose level of ≥126 mg/dL, 2-hour glucose level of ≥200 mg/dL, or having both of these.

[f] Used International Obesity Task Force definition with body mass index–based cutoffs specific to sex and the child's age in months.

[g] Assessed by air displacement plethysmography using the BOD POD (Cosmed).

[h] Determined using quantile regression adjusted for age, sex, and field center.

However, exploratory analyses were conducted using χ^2 tests to compare the outcome frequencies for different groups. The mothers who had 2 to 3 glucose values that were at or above the Carpenter-Coustan thresholds were identified as having Carpenter-Coustan gestational diabetes. The outcome frequencies for mothers and children were progressively higher across those mothers without gestational diabetes, those with IADPSG-defined gestational diabetes (ie, met IADPSG but not Carpenter-Coustan criteria), and those with Carpenter-Coustan–defined gestational diabetes ($P < .001$ for all outcomes; **Table 4**).

Discussion

This study demonstrated that untreated gestational diabetes (identified post hoc using the IADPSG criteria) was associated with a higher risk for a maternal disorder of glucose metabolism 10 to 14 years' postpartum. The association of gestational diabetes with childhood overweight or obesity was not statistically significant; however, other childhood adiposity measures may be relevant for interpreting the study findings.

The IADPSG criteria for gestational diabetes, which were established based on glucose levels associated with adverse pregnancy outcomes in the HAPO Study and in other studies, identify a larger group of mothers than the Carpenter-Coustan criteria. In the United States, prevalence of gestational diabetes was 7.4% using the Carpenter-Coustan criteria during a period similar to the HAPO Study.[21] In contrast, gestational diabetes prevalence in the HAPO Study was 17.8% using the IADPSG criteria and the prevalence ranged from 15.5% to 25.5% in the North American HAPO Study field centers.[22]

In this follow-up study, more than twice as many mothers with IADPSG-defined gestational diabetes compared with mothers with Carpenter-Coustan–defined gestational diabetes (ie, 240 vs 106) developed a disorder of glucose metabolism and there were similar findings for the adiposity outcomes for children. Gestational diabetes according to the Carpenter-Coustan criteria as defined in this study was linked to higher outcome risks. However, the risks for the large group of women meeting the IADPSG-defined criteria for gestational diabetes were substantial and cannot be ignored from a public health perspective.

Gestational diabetes is a risk factor for type 2 diabetes. A meta-analysis of 20 studies that were performed prior to the development of the IADPSG criteria and that used varied criteria to diagnose gestational diabetes demonstrated that women with a history of gestational diabetes had a higher risk of developing type 2 diabetes compared with women with a normoglycemic pregnancy (relative risk, 7.43).[23] The risk factors for progression to type 2 diabetes include maternal age, prepartum and postpartum BMI, family history of type 2 diabetes, receipt of insulin for gestational diabetes, and fasting glucose level during pregnancy.[6,24-26] This study demonstrated that a larger population of women with lesser degrees of hyperglycemia (ie, IADPSG-defined gestational diabetes) were at risk for progression to prediabetes and type 2 diabetes.

The IADPSG criteria for diagnosing gestational diabetes were developed based on adverse pregnancy outcomes,

including higher newborn adiposity, which is a risk factor for childhood adiposity.[27] The current follow-up study demonstrated that IADPSG-defined gestational diabetes was associated with childhood obesity as well as direct measures of child adiposity (eg, sum of skinfolds, body fat percentage). These associations were stronger than the associations with BMI, likely reflecting contributions of both fat and lean body mass to BMI.

The higher prevalence of obesity among women with gestational diabetes confounds the association of gestational diabetes with childhood obesity.[28] Higher maternal BMI is associated with higher childhood adiposity through shared genetics, familial lifestyle and environmental factors, and the intrauterine environment.[29] Adjusting for maternal BMI attenuated the associations between gestational diabetes and childhood obesity in earlier studies,[30,31] therefore raising the question whether the association of gestational diabetes with childhood adiposity is independent of maternal BMI. In this study, adjusting for maternal BMI attenuated observed associations of gestational diabetes with measures of childhood adiposity, but multiple associations remained significant, demonstrating that gestational diabetes was associated with these measures independent of maternal BMI. This was consistent with the independent and additive effects of maternal obesity and gestational diabetes on newborn adiposity outcomes in the HAPO Study.[32]

Whether an association of gestational diabetes with newborn and childhood outcomes is mediated solely through glucose or mixed nutrients, as proposed by Freinkel,[33] remains to be determined. However, recent metabolomics studies performed within the HAPO Study and within other cohorts support the concept that mixed nutrients (eg, sugars, lipids, and amino acids) contribute to associations of maternal hyperglycemia with newborn outcomes.[34,35]

This study had several strengths. The participants of the HAPO Study had an oral glucose tolerance test during pregnancy and, in this blinded observational follow-up study, none were prospectively diagnosed with gestational diabetes. Therefore, treatment was not a confounding factor for maternal and child outcomes. In addition, the racial/ethnic diversity of the participants make the findings broadly applicable.

For childhood outcomes in this prospective study, pubertal status was determined and adiposity was characterized using standardized procedures via multiple methods. This study also addressed limitations of previous studies examining the association of gestational diabetes with childhood adiposity, including lack of complete data on glucose values during pregnancy, maternal BMI, and childhood measures of age-adjusted BMI.[30,36-40]

Limitations

This study had several limitations. First, the proportion of participants who met IADPSG criteria for gestational diabetes and participated in this study was lower than in all eligible participants.

Second, this study used maternal BMI collected at the time of the oral glucose tolerance test during pregnancy, not pregestational BMI, because objectively measured prepregnancy weight was not available in the HAPO Study. However, for the 4452 mothers of child participants who self-reported prepregnancy BMI during the HAPO Study, the correlation between prepregnancy BMI and BMI during the HAPO Study was 0.92.

Third, during the HAPO Study, 1.8% of participants with oral glucose tolerance test values higher than predefined thresholds during pregnancy were unblinded and excluded from the primary analyses of the HAPO Study and from this follow-up study.[22] This subgroup likely would have included mothers with higher outcome frequencies for type 2 diabetes and prediabetes at the time of this follow-up study and children at the highest risk of overweight or obesity; therefore, the reported associations may be underestimates.

Fourth, beyond family history, paternal data were not available. Fifth, recruitment was lower than expected. The prespecified recruitment target was 7000 mother-child pairs; recruitment totals were 67.8% for women and 69.1% for children. The characteristics of all mothers during pregnancy (regardless of participation) were similar; however, social, behavioral, or other differences between participants and nonparticipants that may have confounded associations of gestational diabetes with outcome frequencies cannot be ruled out. Sixth, maternal hemoglobin A_{1c} levels at follow-up were not used. Seventh, detailed data on postnatal lifestyle that affects childhood adiposity were not available.

Conclusions

Among women with gestational diabetes identified by contemporary criteria compared with those without it, gestational diabetes was significantly associated with a higher maternal risk for a disorder of glucose metabolism during long-term follow-up after pregnancy. Among children of mothers with gestational diabetes vs those without it, the difference in childhood overweight or obesity defined by body mass index cutoffs was not statistically significant; however, additional measures of childhood adiposity may be relevant in interpreting the study findings.

ARTICLE INFORMATION

Accepted for Publication: July 23, 2018.

Author Affiliations: Northwestern University Feinberg School of Medicine, Chicago, Illinois (W. L. Lowe, Scholtens, L. P. Lowe, Kuang, Nodzenski, Talbot, Brickman, Josefson, Dyer, Metzger); MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio (Catalano); National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland (Linder); Ann and Robert H. Lurie Children's Hospital, Chicago, Illinois (Brickman, Josefson); Royal Manchester Children's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, School of Medical Sciences, Faculty of Biology, Medicine, and Health, University of Manchester, Manchester, England (Clayton); Rajavithi Hospital, Bangkok, Thailand (Deerochanawong); Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada (Hamilton); Queen Elizabeth Hospital, School of Clinical Medicine and Research, University of the West Indies, Barbados (Lashley); Kaiser Permanente of Southern California, Pasadena (Lawrence, Sacks); Jesse Z. and Sara Lea Shafer

Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel (Lebenthal); Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong, China (Ma, Tam); St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, England (Maresh); Royal Victoria Hospital, Belfast, Ireland (McCance).

Author Contributions: Drs Scholtens and Metzger had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs W. Lowe Jr and Scholtens contributed equally to this work.
Concept and design: W. Lowe, Scholtens, L. Lowe, Catalano, Linder, Deerochanawong, Josefson, Ma, McCance, Tam, Dyer, Metzger.
Acquisition, analysis, or interpretation of data: W. Lowe, Scholtens, L. Lowe, Kuang, Nodzenski, Talbot, Catalano, Linder, Brickman, Clayton, Deerochanawong, Hamilton, Josefson, Lashley, Lawrence, Lebenthal, Ma, Maresh, McCance, Sacks, Dyer, Metzger.
Drafting of the manuscript: W. Lowe, Scholtens, L. Lowe, Talbot, Catalano, Hamilton, Ma, Maresh, McCance, Dyer, Metzger.
Critical revision of the manuscript for important intellectual content: W. Lowe, Scholtens, L. Lowe, Kuang, Nodzenski, Catalano, Linder, Brickman, Clayton, Deerochanawong, Hamilton, Josefson, Lashley, Lawrence, Lebenthal, Ma, Maresh, McCance, Tam, Sacks, Dyer, Metzger.
Statistical analysis: Scholtens, L. Lowe, Kuang, Nodzenski, Talbot.
Obtained funding: L. Lowe, Ma, Metzger.
Administrative, technical, or material support: W. Lowe, L. Lowe, Catalano, Linder, Deerochanawong, Josefson, Lashley, Tam, Metzger.
Supervision: L. Lowe, Catalano, Brickman, Deerochanawong, Hamilton, Lawrence, Ma, Maresh, Tam, Metzger.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr W. Lowe Jr reported receiving grant support from the National Institutes of Health and the Endocrine Fellows Foundation. Dr Ma reported receiving grant support from AstraZeneca, Bayer, and Pfizer; and speaker's fees from Boehringer Ingelheim and Takeda. No other disclosures were reported.

Funding/Support: The HAPO Follow-up Study was funded by grant 1U01DK094830 from the National Institute of Diabetes and Digestive and Kidney Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The HAPO Study was funded by grants R01-HD-34242 and R01-HD-34243 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development. The HAPO Follow-up Study data were collected and managed using REDCap electronic data capture tools hosted at Northwestern University Feinberg School of Medicine. REDCap is supported at Feinberg School of Medicine by the Northwestern University Clinical and Translational Science Institute. The research reported in this article was supported, in part, by grant UL1TR001422 from the National Center for Advancing Translational Sciences, National Institutes of Health.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Dr Linder (National Institutes of Health) was a participating member of the study steering committee and the writing group for this article because of the cooperative funding agreement. She was involved in the design of the study but not the conduct of the study; she was not involved in the collection, management, and analysis of the data; and she was involved in the preparation, review, and approval of the manuscript and the decision to submit the manuscript for publication.

Group Information: The collaborator members of the HAPO Follow-up Study Cooperative Research Group by field center are: *Bangkok, Thailand*: C. Deerochanawong, T. Tanaphonpoonsuk (Rajavithi Hospital) and S. Binratkaew, U. Chotigeat, W. Manyam (Queen Sirikit National Institute of Child Health); *Barbados*: M. Forde, A. Greenidge, K. Neblett, P. M. Lashley, D. Walcott (Queen Elizabeth Hospital, School of Clinical Medicine and Research, University of the West Indies); *Belfast, Ireland*: K. Corry, L. Francis, J. Irwin, A. Langan, D. R. McCance, M. Mousavi (Belfast Health and Social Care Trust) and I. S. Young (Queen's University); *Bellflower, California*: J. Gutierrez, J. Jimenez, J. M. Lawrence, D. A. Sacks, H. S. Takhar, E. Tanton (Kaiser Permanente of Southern California); *Chicago, Illinois*: W. J. Brickman, J. Howard, J. L. Josefson, L. Miller (Ann and Robert H. Lurie Children's Hospital and Northwestern University Feinberg School of Medicine); *Cleveland, Ohio*: J. Bjaloncik, P. M. Catalano, A. Davis, K. Koontz, L. Presley, S. Smith, A. Tyhulski (MetroHealth Medical Center and Case Western Reserve University); *Hong Kong, China*: A. Li, R. C. Ma, R. Ozaki, W. H. Tam, M. Wong, C. Yuen (Chinese University of Hong Kong and Prince of Wales Hospital); *Manchester, England*: P. E. Clayton, A. Khan, A. Vyas (Royal Manchester Children's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Healthy Sciences Centre and School of Medical Sciences, Faculty of Biology, Medicine, and Health, University of Manchester) and M. Maresh (St Mary's Hospital, Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Sciences Centre); *Petah-Tikva, Isreal*: H. Benzaquen, N. Glickman, A. Hamou, O. Hermon, O. Horesh, Y. Keren, S. Shalitin (Schneider Children's Medical Center of Israel) and Y. Lebenthal (Jesse Z. and Sara Lea Shafer Institute for Endocrinology and Diabetes, National Center for Childhood Diabetes, Schneider Children's Medical Center of Israel, Sackler Faculty of Medicine, Tel Aviv University); and *Toronto, Ontario, Canada*: K. Cordeiro, J. Hamilton, H. Y. Nguyen, S. Steele (Hospital for Sick Children, University of Toronto). *Coordinating Center:* Northwestern University Feinberg School of Medicine (F. Chen, A. R. Dyer, W. Huang, A. Kuang, M. Jimenez, L. P. Lowe, W. L. Lowe Jr, B. E. Metzger, M. Nodzenski, A. Reisetter, D. Scholtens, O. Talbot, P. Yim). *Consultants*: D. Dunger, A. Thomas. *National Institute of Diabetes and Digestive and Kidney Diseases:* M. Horlick, B. Linder, A. Unalp-Arida. *Eunice Kennedy Shriver National Institute of Child Health and Human Development*: G. Grave.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Additional Contributions: We are grateful for all the mothers and children who participated in the HAPO Study and the HAPO Follow-up Study.

REFERENCES

1. Metzger BE, Lowe LP, Dyer AR, et al; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*. 2008; 358(19):1991-2002. doi:10.1056/NEJMoa0707943

2. Metzger BE, Gabbe SG, Persson B, et al; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*. 2010;33(3):676-682. doi:10.2337/dc09-1848

3. World Health Organization. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. *Diabetes Res Clin Pract*. 2014;103(3):341-363. doi:10.1016/j.diabres.2013.10.012

4. International Diabetes Federation. *IDF Diabetes Atlas*. Brussels, Belgium: International Diabetes Federation; 2017.

5. Committee on Practice Bulletins—Obstetrics. Practice Bulletin No. 180: gestational diabetes mellitus. *Obstet Gynecol*. 2017;130(1):e17-e37. doi:10.1097/AOG.0000000000002159

6. Coustan DR, Carpenter MW, O'Sullivan PS, Carr SR. Gestational diabetes: predictors of subsequent disordered glucose metabolism. *Am J Obstet Gynecol*. 1993;168(4):1139-1144. doi:10.1016/0002-9378(93)90358-P

7. Regnell SE, Lernmark Å. Early prediction of autoimmune (type 1) diabetes. *Diabetologia*. 2017; 60(8):1370-1381. doi:10.1007/s00125-017-4308-1

8. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2014;37(suppl 1):S81-S90. doi:10.2337/dc14-S081

9. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. *Pediatr Obes*. 2012;7(4): 284-294. doi:10.1111/j.2047-6310.2012.00064.x

10. Gillman MW, Rifas-Shiman S, Berkey CS, Field AE, Colditz GA. Maternal gestational diabetes, birth weight, and adolescent obesity. *Pediatrics*. 2003;111 (3):e221-e226. doi:10.1542/peds.111.3.e221

11. Hillier TA, Pedula KL, Schmidt MM, Mullen JA, Charles MA, Pettitt DJ. Childhood obesity and metabolic imprinting: the ongoing effects of maternal hyperglycemia. *Diabetes Care*. 2007;30 (9):2287-2292. doi:10.2337/dc06-2361

12. Lawlor DA, Fraser A, Lindsay RS, et al. Association of existing diabetes, gestational diabetes and glycosuria in pregnancy with macrosomia and offspring body mass index, waist and fat mass in later childhood: findings from a prospective pregnancy cohort. *Diabetologia*. 2010; 53(1):89-97. doi:10.1007/s00125-009-1560-z

13. Hsieh FY, Bloch DA, Larsen MD. A simple method of sample size calculation for linear and logistic regression. *Stat Med*. 1998;17(14):1623-1634. doi:10.1002/(SICI)1097-0258(19980730)17:14<1623::AID-SIM871>3.0.CO;2-S

14. Carr DB, Newton KM, Utzschneider KM, et al. Modestly elevated glucose levels during pregnancy are associated with a higher risk of future diabetes among women without gestational diabetes mellitus. *Diabetes Care*. 2008;31(5):1037-1039. doi:10.2337/dc07-1957

15. Cheung YB. A modified least-squares regression approach to the estimation of risk difference. *Am J Epidemiol*. 2007;166(11):1337-1344. doi:10.1093/aje/kwm223

16. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2016.

17. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York: Wiley; 2013. doi:10.1002/9781118548387

18. White IR, Daniel R, Royston P. Avoiding bias due to perfect prediction in multiple imputation of incomplete categorical variables. *Comput Stat Data Anal*. 2010;54(10):2267-2275. doi:10.1016/j.csda.2010.04.005

19. Rubin DB. *Multiple imputation for nonresponse in surveys*. New York: Wiley; 1987. doi:10.1002/9780470316696

20. Van Buuren S, Groothuis-Oudshoorn K. mice: multivariate imputation by chained equations in R. *J Stat Softw*. 2011;45(3):1-67. doi:10.18637/jss.v045.i03

21. Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999-2005. *Diabetes Care*. 2008;31(5):899-904. doi:10.2337/dc07-2345

22. Sacks DA, Hadden DR, Maresh M, et al; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Diabetes Care*. 2012;35(3):526-528. doi:10.2337/dc11-1641

23. Bellamy L, Casas JP, Hingorani AD, Williams D. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet*. 2009;373(9677):1773-1779. doi:10.1016/S0140-6736(09)60731-5

24. Catalano PM, Vargo KM, Bernstein IM, Amini SB. Incidence and risk factors associated with abnormal postpartum glucose tolerance in women with gestational diabetes. *Am J Obstet Gynecol*. 1991;165(4 Pt 1):914-919. doi:10.1016/0002-9378(91)90438-W

25. Löbner K, Knopff A, Baumgarten A, et al. Predictors of postpartum diabetes in women with gestational diabetes mellitus. *Diabetes*. 2006;55(3):792-797. doi:10.2337/diabetes.55.03.06.db05-0746

26. Bao W, Yeung E, Tobias DK, et al. Long-term risk of type 2 diabetes mellitus in relation to BMI and weight change among women with a history of gestational diabetes mellitus: a prospective cohort study. *Diabetologia*. 2015;58(6):1212-1219. doi:10.1007/s00125-015-3537-4

27. Dabelea D, Crume T. Maternal environment and the transgenerational cycle of obesity and diabetes. *Diabetes*. 2011;60(7):1849-1855. doi:10.2337/db11-0400

28. Buchanan TA, Xiang AH. Gestational diabetes mellitus. *J Clin Invest*. 2005;115(3):485-491. doi:10.1172/JCI200524531

29. Lakshman R, Elks CE, Ong KK. Childhood obesity. *Circulation*. 2012;126(14):1770-1779. doi:10.1161/CIRCULATIONAHA.111.047738

30. Philipps LH, Santhakumaran S, Gale C, et al. The diabetic pregnancy and offspring BMI in childhood: a systematic review and meta-analysis. *Diabetologia*. 2011;54(8):1957-1966. doi:10.1007/s00125-011-2180-y

31. Zhao P, Liu E, Qiao Y, et al; ISCOLE Research Group. Maternal gestational diabetes and childhood obesity at age 9-11: results of a multinational study. *Diabetologia*. 2016;59(11):2339-2348. doi:10.1007/s00125-016-4062-9

32. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes*. 2009;58(2):453-459. doi:10.2337/db08-1112

33. Freinkel N. Banting lecture 1980: of pregnancy and progeny. *Diabetes*. 1980;29(12):1023-1035. doi:10.2337/diab.29.12.1023

34. Scholtens DM, Bain JR, Reisetter AC, et al; HAPO Study Cooperative Research Group. Metabolic Networks and Metabolites Underlie Associations Between Maternal Glucose During Pregnancy and Newborn Size at Birth. *Diabetes*. 2016;65(7):2039-2050. doi:10.2337/db15-1748

35. McCabe CF, Perng W. Metabolomics of Diabetes in Pregnancy. *Curr Diab Rep*. 2017;17(8):57. doi:10.1007/s11892-017-0890-3

36. Tam WH, Ma RC, Yang X, et al. Glucose intolerance and cardiometabolic risk in children exposed to maternal gestational diabetes mellitus in utero. *Pediatrics*. 2008;122(6):1229-1234. doi:10.1542/peds.2008-0158

37. Catalano PM, Farrell K, Thomas A, et al. Perinatal risk factors for childhood obesity and metabolic dysregulation. *Am J Clin Nutr*. 2009;90(5):1303-1313. doi:10.3945/ajcn.2008.27416

38. Kim SY, England JL, Sharma JA, Njoroge T. Gestational diabetes mellitus and risk of childhood overweight and obesity in offspring: a systematic review. *Exp Diabetes Res*. 2011;2011:541308. doi:10.1155/2011/541308

39. Kim SY, Sharma AJ, Callaghan WM. Gestational diabetes and childhood obesity: what is the link? *Curr Opin Obstet Gynecol*. 2012;24(6):376-381. doi:10.1097/GCO.0b013e328359f0f4

40. Donovan LE, Cundy T. Does exposure to hyperglycaemia in utero increase the risk of obesity and diabetes in the offspring? A critical reappraisal. *Diabet Med*. 2015;32(3):295-304. doi:10.1111/dme.12625